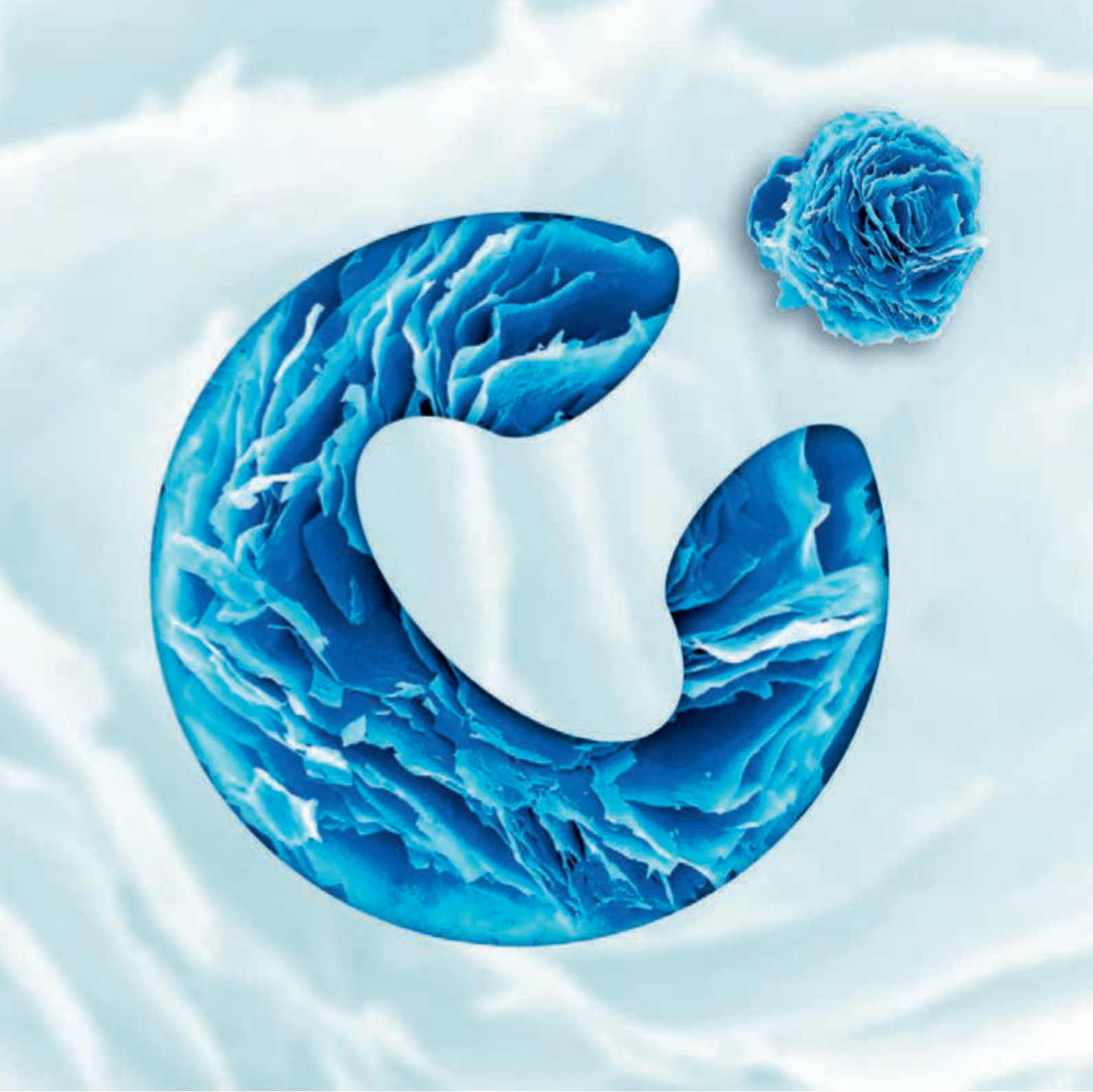

Max Planck Institute of Colloids and Interfaces

REPORT 2017-2018

MAX-PLANCK-GESELLSCHAFT

Mikro-Blüte: Hierarchische Selbstanordnung von metallorganischen Nanoschicht-Blütenblättern zu einer mesokristallinen Mikrorose

Micro-Blooming: Hierarchical self-assembly of metalorganic nanosheet petals towards mesocrystal micro-rose

Max Planck Institute of Colloids and Interfaces

RESEARCH REPORT 2017–2018

Imprint

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Address: Science Park Potsdam-Golm, Am Mühlenberg 1, 14476 Potsdam
Phone: +49 (0) 331/567-7814
Fax: +49 (0) 331/567-7875
Email: info@mpikg.mpg.de
Internet: www.mpikg.mpg.de
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Theory & Bio-Systems

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Vorwort

„Die beste Methode die Zukunft vorherzusagen besteht darin, sie zu erfinden." (Alan Kay)

Das Max-Planck-Institut für Kolloid- und Grenzflächenforschung (MPIKG) wurde 1992 als eines der ersten Max-Planck-Institute in den neuen Bundesländern gegründet und hat sich seitdem zu einer weltweit führenden Forschungsinstitution entwickelt. Das Institut bezog 1999 ein neues Gebäude im Potsdam Science Park.

Die Kolloid- und Grenzflächenforschung beschäftigt sich mit sehr kleinen Strukturen im Nano- und Mikrometerbereich. Einerseits handelt es sich dabei um eine „Welt der versteckten Dimensionen", andererseits bestimmen diese winzigen Strukturen die Eigenschaften von Materialien und Biosystemen auf mesoskopischen und makroskopischen Skalen. Ein quantitatives Verständnis der Nanostrukturen bildet deshalb die Grundlage, um neuartige Impfstoffe, intelligente Wirkstoffträger und Mikrokompartimente sowie adaptive Biomaterialien zu entwickeln. Dazu ist ein interdisziplinärer Zugang notwendig, der (bio)chemische Synthese und biomimetische Materialwissenschaften mit physikalisch-chemischer Analyse und Charakterisierung sowie theoretischer Modellierung verknüpft.

Das MPIKG wird kollegial geleitet und gliedert sich seit der Emeritierung von Helmuth Möhwald im Jahre 2014 in die vier Abteilungen „Biomolekulare Systeme" (Peter Seeberger), „Kolloidchemie" (Markus Antonietti), „Biomaterialien" (Peter Fratzl) und „Theorie & Bio-Systeme" (Reinhard Lipowsky) sowie die Max-Planck-Forschungsgruppe „Mechano(bio)chemie" (Kerstin Blank). Das Institut hat zur Zeit etwa 400 Mitarbeiter mit einem Frauenanteil von 45 %.

Die Mission des Instituts besteht darin, mit wissenschaftlicher Exzellenz eine Brücke von Molekülen zu vielskaligen Materialien und Biosystemen zu schlagen und dabei den wissenschaftlichen Nachwuchs bestmöglichst zu fördern. Tatsächlich sind inzwischen etwa 300 ehemalige Mitarbeiter/innen auf Professuren an in- und ausländische Universitäten berufen worden.

Forschungsschwerpunkte

Die Nano- und Mikrostrukturen, die am MPIKG erforscht werden, sind aus noch kleineren atomaren und molekularen Bausteinen aufgebaut. Die Synthese und der Zusammenbau dieser Bausteine nutzt das Prinzip der Selbstorganisation aus: Man stellt die äußeren Bedingungen so ein, dass sich die Bausteine „von selbst" miteinander verbinden und größere Strukturen aufbauen. Die beiden Abteilungen „Biomolekulare Systeme" und „Kolloidchemie" beschäftigen sich schwerpunktmäßig mit diesem Systemaufbau.

In der Abteilung „Biomolekulare Systeme" werden maßgeschneiderte Zuckermoleküle mit einer vorgegebenen Sequenz synthetisiert und mit anderen molekularen Gruppen verknüpft. Diese komplexen Kohlehydrate können andere Kohlehydrate sowie Proteine und Antikörper an ihrem molekularen Aufbau erkennen und diskriminieren, ein Prozess, der mit Hilfe sogenannter Glyco-Chips systematisch untersucht wird. Ein langfristiges Ziel ist dabei die Entwicklung von Impfstoffen auf Zuckerbasis.

Fotos: G. Gnaudschun

Die Abteilung „Kolloidchemie“ setzt verschiedenartige Makromoleküle ein, um daraus mesoskopische Verbundsysteme und Hybridmaterialien mit unterschiedlicher Architektur aufzubauen. Der Schwerpunkt liegt dabei auf der gezielten Kodierung von Strukturbildung und Selbstorganisation, d. h. die Moleküle enthalten bestimmte Muster, die die Strukturbildung steuern und die Zielstruktur weitgehend festlegen. Ein langfristiges Thema ist die Spaltung von Wasser mit Hilfe von Sonnenlicht. Für diesen Prozess wurde mit einem neuartigen Kohlenstoffnitrit-Polymer ein vielversprechender Katalysator gefunden.

Nano- und Mikrostrukturen sind hierarchisch aufgebaut. Besonders eindrucksvolle Beispiele für diesen „verschachtelten“ Systemaufbau finden sich in mineralisierten Geweben, wie Knochen, Zähnen oder Muschelschalen, sowie in Pflanzen und deren Zellwänden. Diese Systeme werden in der Abteilung „Biomaterialien“ mit physikalischen Methoden erforscht. Dabei wird auch die Methode der fokusierten Synchrotronstrahlung eingesetzt, die es erlaubt, die Struktur von Mikrodomänen des Materials mit atomarer Auflösung sichtbar zu machen. Im Zentrum des Interesses stehen die Struktur-Funktions-Beziehungen dieser natürlichen Materialien, insbesondere ihre außergewöhnlichen mechanischen Eigenschaften, die sich ständig wechselnden äußeren Bedingungen anpassen. Das vielskalige Verhalten von biomimetischen und biologischen Systemen wird auch in der Abteilung „Theorie & Bio-Systeme“ untersucht. Aktuelle Schwerpunkte sind biomolekulare Maschinen sowie biomimetische Membranen und deren Wechselwirkung mit Nanopartikeln. Zur Abteilung gehören auch mehrere experimentelle Arbeitsgruppen, die Lipid-Vesikel und deren „multiresponsive“ Verhalten untersuchen. Die theoretischen und experimentellen Aktivitäten verfolgen das langfristige Ziel, die grundlegenden Mechanismen und generellen Prinzipien aufzuklären, die die Selbstorganisation von Bio-Systemen im Nanobereich bestimmen.

Die Max-Planck-Forschungsgruppe „Mechano(bio)chemie“ untersucht den Einfluss von Kräften auf die Struktur und Funktion von Molekülen und Materialien. Aktuelle Schwerpunkte sind molekulare Kraftsensoren, Kräfte in polymeren Materialien sowie die Integration von Kraftmessung und Fluoreszenzdetektion. Diese verschiedenen Forschungsaktivitäten werden im Hauptteil dieses Berichts sehr viel ausführlicher beschrieben. Dieser Hauptteil ist nach den Abteilungen des Instituts gegliedert und setzt sich aus den Forschungsberichten der einzelnen Arbeitsgruppen zusammen.

Weitere Informationen über das MPIKG finden Sie unter http://www.mpikg.mpg.de

Ich danke allen Kollegen/innen und Mitarbeiter/innen des MPIKGs, unserem wissenschaftlichen Beirat, unserem Kuratorium sowie der Leitung der Max-Planck-Gesellschaft für ihre tatkräftige Unterstützung während der letzten beiden Jahre.

Markus Antonietti
Managing Director 2017–2018

von links:
Markus Antonietti, Kerstin Blank, Peter H. Seeberger, Peter Fratzl, Reinhard Lipowsky

Preface

„The best way to predict the future is to invent it."
(Alan Kay)

The Max Planck Institute of Colloids and Interfaces (MPICI) was founded in 1992 as one of the first Max Planck Institutes in the new states of Germany and soon became a world leading research institution. In 1999, the MPICI moved to a new building in the Potsdam Science Park.

Colloids and interfaces consist of very small and ultrathin structures with linear dimensions between nanometers and micrometers. On the one hand, these nanostructures represent a „world of hidden dimensions". On the other hand, these small structures determine the properties and functions of much larger systems and materials. Therefore, a quantitative understanding of these structures provides the knowledge base to develop novel vaccines, intelligent drug delivery systems and microcompartments as well as adaptive materials. Such a deeper understanding can only arise from an interdisciplinary approach that combines (bio)chemical synthesis and biomimetic materials with physical analysis and characterization as well as theoretical modelling.

After the retirement of Helmuth Möhwald in 2014, the MPICI consists of the four Departments „Biomolecular Systems" (Peter Seeberger), „Colloid Chemistry" (Markus Antonietti), „Biomaterials" (Peter Fratzl) and „Theory & Bio-Systems" (Reinhard Lipowsky) as well as of the Max Planck Reserch Group „Mechano(bio)chemistry" (Kerstin Blank). The institute has currently about 400 associates with a 45 percentage of women.

The mission of the MPICI is to bridge the gap between molecules and multiscale materials and biosystems through excellence in science and via the support of young scientists. In fact, about 300 former associates have taken up professorships or equivalent positions at universities in Germany and Europe.

Focus Areas of Research

The nano- and microstructures investigated at the MPICI are built up from even smaller atomic and molecular building blocks. The synthesis and assembly of atomic and molecular building blocks is primarily based on self-assembly and self-organization. When placed into an appropriate environment, the building blocks assemble „by themselves" into well-defined larger structures. These structure formation processes represent the focus areas of the two Departments „Biomolecular Systems" and „Colloid Chemistry".

The Department „Biomolecular Systems" synthesizes and designs sugar molecules and carbohydrates with welldefined and fine-tuned architectures. These complex macromolecules are able to specifically recognize and distinguish other macromolecules such as proteins and antibodies, a process that is studied by immobilizing the molecules on so-called glycochips. A long-term goal of this research is to develop new vaccines based on the fine-tuned sugar molecules. In the Department „Colloid Chemistry", a variety of macromolecules is used in order to construct mesoscopic compound systems and hybrid materials. One important aspect of this activity is the molecular encoding of self-assembly and self-organization by specific molecular groups that guide these processes towards a certain target structure. A long-term target is water cleavage by sunlight, which can be achieved by polymeric carbon nitride, a promising new catalyst.

Nano- and microstructures are built up in a hierarchical fashion. Particularly impressive examples for this „nested" system architecture is found in mineralized tissues such as bone, teeth, and seashells as well as in plants and their cell walls. These systems are studied in the Department „Biomaterials" using a variety of experimental characterization methods. One particularly powerful method is microfocussed synchrotron radiation, by which one can determine the structure of micrometer domains with atomic resolution and determine the structure-function relationships of these natural materials. One important aspect are their extraordinary mechanical properties, which can adapt to changing environmental conditions. The multiscale behavior of biomimetic and biological systems is also investigated in the Department „Theory & Bio-

Systems". Current focus areas are biomolecular machines as well as biomimetic membranes and their interactions with nanoparticles. The department includes several experimental research groups that study lipid vesicles and their multiresponsive behavior. The long-term goal of these theoretical and experimental activities is to elucidate the fundamental principles and generic mechanisms, that govern the self-organization of biomimetic and biological systems in the nanoregime.

The Max Planck Research Group „Mechano(bio)chemistry" investigates the influence of mechanical forces on the structure and function of molecules and materials. Current focus areas are molecular force sensors, forces in polymeric networks, as well as the integration of mechanical and optical material characterization techniques.

The different research activities mentioned above will be described in much more detail in the main body of this report, which is organized according to the departments of the MPICI. Each department consists of several research groups, which will present their research results obtained during the past two years.

More information about the MPICI can be found at http://www.mpikg.mpg.de/en

I take this opportunity to thank all of my colleagues and associates at the MPICI, our scientific advisory board and our board of trustees for their active support during the past two years. Last but not least, I am grateful to our president and to our vice-president for their continuous support of our institute.

Markus Antonietti
Managing Director 2017–2018

Helmuth Möhwald

Prof. Dr. Dr. h. c. Helmuth Möhwald war einer der weltweit einflussreichsten Wissenschaftler auf dem Gebiet der physikalischen Chemie von weicher Materie. Er forschte an den Eigenschaften von Membranschichten und ähnlichen zweidimensionalen Systemen. Diese Art von Grenzflächen hat eine zentrale Bedeutung für biologische Systeme, zum Beispiel als Zellmembranen, Vesikel oder auch als kleine Behälter für den Transport von Wirkstoffen in unserem Körper. Weiche Grenzflächenschichten eignen sich aber auch für Materialsysteme, die Licht in chemische Signale umsetzen können oder selbstheilende Eigenschaften besitzen.

Helmuth Möhwald, am 19. Januar 1946 in Goldenöls (Zlatá Olešnice, Tschechien) geboren, studierte Physik in Göttingen und verbrachte dann zwei Jahre bei IBM in San José in Kalifornien. Nach seiner Habilitation über funktionelle organische Kristalle an der Universität Ulm verbrachte er zunächst zwei Jahre als Forscher in der Industrie (Dornier Systeme, Friedrichshafen), bevor er eine außerordentliche Professur am Lehrstuhl für Biophysik der Technischen Universität München annahm. Dort arbeitete er sieben Jahre lang im Umfeld des Doyens der deutschen Biophysik, Professor Erich Sackmann, mit dem ihn zeitlebens eine enge Freundschaft verband. Dieser interessante Werdegang machte Möhwald zu einem Grenzgänger zwischen den Disziplinen der Physik, Chemie und Biologie. Obwohl er immer großen Wert auf die grundlegende Bedeutung seiner Forschungsthemen legte, waren ihm praktische Anwendungen nicht fremd. Eine große Zahl von Patenten und industriellen Umsetzungen seiner Forschungsarbeiten sowie auch einige aus seiner Arbeitsgruppe hervorgegangene Start-ups zeugen davon.

Im Jahr 1987 erfolgte der Ruf auf den Lehrstuhl für physikalische Chemie der Universität Mainz, und fünf Jahre später wurde Möhwald einer von drei Gründungsdirektoren des Max-Planck-Instituts für Kolloid- und Grenzflächenforschung in Potsdam. Dieses Institut war eine der ersten Neugründungen von Max-Planck-Instituten in den neuen Bundesländern kurz nach der Wiedervereinigung Deutschlands. Möhwald hat sich beim Aufbau dieses Instituts große Verdienste erworben. Besonders kamen ihm dabei sein strategischer Weitblick und sein herausragendes Engagement für den wissenschaftlichen Nachwuchs zugute. Nach nur wenigen Jahren war das Potsdamer Institut weltweit sichtbar, und das gilt besonders auch für die von Möhwald geleitete Abteilung zur Grenzflächenforschung. Insbesondere seine Arbeiten an mikrometergroßen Hohlkugeln aus Polyelektrolyten erregten große Aufmerksamkeit – die entsprechenden Arbeiten werden immer noch tausendfach zitiert. Er befasste sich sehr erfolgreich mit der Struktur komplexer Grenzflächen (Amphiphile, Peptide, Proteine, Polymere, Cluster, Partikel) oder auch mit der Frage, wie sich chemische Reaktionen oder Kristallisationsvorgänge verändern, wenn sie in kleinen Hohlräumen stattfinden. Er entwickelte schaltbare Mikrokapseln, die – durch Licht oder pH-Wert getriggert – Wirkstoffe freisetzen. In den letzten Jahren befasste er sich auch mit der Beeinflussung von chemischen Reaktionen durch Ultraschall. Insgesamt gehört Möhwald zu den höchstzitierten Wissenschaftlern in der physikalischen Chemie mit heute mehr als 140 Arbeiten, die einhundertmal oder öfter zitiert wurden. 2014 emeritierte er als Direktor am Max-Planck-Institut für Kolloid- und Grenzflächenforschung.

Eine besondere Liebe von Helmuth Möhwald galt dem Fußball, und seit vielen Jahren wird im Wissenschaftspark Potsdam-Golm ein von ihm initiiertes Turnier zwischen den ansässigen Forschungseinrichtungen der Max-Planck- und der Fraunhofer-Gesellschaft ausgetragen. Dieses Turnier wird nun unter dem Titel „Helmuth-Möhwald-Cup“ weitergeführt.

Möhwald war Vorbild und Mentor für viele jüngere Kollegen und mehrere Generationen von Nachwuchswissenschaftlern. Ich selbst verdanke ihm viele Ratschläge und Kontaktanbahnungen in den ersten Jahren, nachdem ich als ein weiterer Direktor ans Max-Planck-Institut gewechselt war. Ungezählte ehemalige Mitarbeiter seiner Potsdamer Abteilung bekleiden Professorenstellen auf der ganzen Welt. Er war Honorarprofessor an der Universität Potsdam, wo die meisten seiner Doktoranden in der Chemie oder Physik promovierten. Sehr früh schon widmete er sich der Förderung der Zusammenarbeit mit China, insbesondere durch die Ausbildung von Nachwuchs aus diesem Land. Ab 2001 unterhielt er mehrere Gastprofessuren an zuletzt insgesamt acht chinesischen Universitäten und Instituten.

Möhwald erhielt für seine wissenschaftlichen Leistungen eine große Zahl von Auszeichnungen wie eine Ehrendoktorwürde der Universität Montpellier und Preise der American Chemical Society, der Königlich Spanischen Gesellschaft für Chemie, der Deutschen und der Europäischen Kolloid-Gesellschaft sowie den Gay-Lussac-Preis für deutsch-französische wissenschaftliche Zusammenarbeit. Noch kurz vor seinem Tod wurde ihm im Jahr 2017 der Preis als distinguished scientist der Chinesischen Akademie der Wissenschaften verliehen. Er war Mitglied der Academia Europaea und seit 2004 auch korrespondierendes Mitglied im Ausland der Österreichischen Akademie der Wissenschaften.

Am 27. März 2018 verstarb Helmuth Möhwald viel zu früh im Alter von 72 Jahren. Die Auszeichnung für seine Lebensleistung durch die Internationale Vereinigung der Kolloid- und Grenzflächenforscher (IACIS) konnte ihm auf der Jahrestagung in Rotterdam im Mai 2018 nur noch posthum verliehen werden. Neben seiner Frau und seiner Tochter widmete er sich in den letzten Jahren vor allem seinen Kooperationen mit Kollegen in Frankreich und mit vielen seiner Schüler in der Welt. Er hatte noch viel vor. Wir trauern um einen großartigen Wissenschaftler, Kollegen, Freund und Mentor.

Peter Fratzl

Helmuth Möhwald

Prof. Dr. Dr. h. c. Helmuth Möhwald was one of the world's most influential scientists in physical chemistry of soft matter. He investigated the properties of membrane layers and similar two-dimensional systems. This type of interfaces is of central importance for biological systems, for example as cell membranes, vesicles or as small containers for the transport of active substances in our body. Soft interface layers are also suitable for material systems that can convert light into chemical signals or have self-healing properties.

Helmuth Möhwald, born on 19 January 1946 in Goldenöls (Zlatá Olešnice, Czech Republic), studied physics in Göttingen and then spent two years at IBM in San José, California. After his habilitation on functional organic crystals at the University of Ulm, he initially spent two years as an industrial researcher (Dornier Systeme, Friedrichshafen) before accepting an associate professorship at the Department of Biophysics at the Technical University of Munich. There he worked for seven years in the environment of the doyen of German biophysics, Professor Erich Sackmann, with whom he had a close friendship throughout his life. This interesting career made Möhwald a commuter between the disciplines of physics, chemistry and biology. Although he always put great emphasis on the fundamental importance of his research, he was also familiar with practical applications. A large number of patents and industrial applications, as well as a few start-ups originated from his department.

In 1987 he was appointed Chair for Physical Chemistry at the University of Mainz, and five years later Möhwald became one of the three founding directors of the Max Planck Institute of Colloids and Interfaces in Potsdam. The institute was one of the first Max Planck Institutes in the new federal states, shortly after the reunification of Germany. Möhwald greatly contributed to build this research institution. In particular, the institute benefited from his strategic vision and his outstanding commitment to young scientists. After just a few years, the Institute was globally visible, in particular also the Department of Interfaces headed by Helmuth Möhwald. Especially his work on multifunctional polyelectrolyte-based micro- and nanocapsules attracted much attention – the corresponding work continues to be cited thousands of times. He was very successful in studying the structure of complex interfaces (amphiphiles, peptides, proteins, polymers, clusters, particles), or how chemical reactions or crystallization processes change when they occur in small confinements. He developed switchable microcapsules that – triggered by light or pH – are able to release drugs. In recent years, he carried out research on the influence of ultrasound on chemical reactions. Overall, Helmuth Möhwald is one of the most highly cited scientists in physical chemistry, today with more than 140 papers cited hundred times or more. 2014 he retired as Director of the Max Planck Institute of Colloids and Interfaces.

Helmuth Möhwald had a particular passion for soccer He initiated a tournament between the research institutions of the Max Planck Society and the Fraunhofer Society in the Science Park Potsdam-Golm, which has been taking place annually for many years. This tournament is now continued as „Helmuth Möhwald Cup".

Möhwald was a role model and mentor for many younger colleagues and several generations of junior researchers. I myself owe him a great deal of advice and contacts in the first few years after I joined the Institute as director of the Biomaterials department. Countless former employees of his Interface department hold professorships all over the world. He was an honorary professor at the University of Potsdam, where most of his doctoral students were defending their PhD in chemistry or physics. Very early, he devoted himself to encouraging cooperation with China, in particular by training young scientists from this country. From 2001, he held visiting professorships at as many as eight Chinese universities and institutes.

Möhwald received a large number of awards for his scientific achievements, including an honorary doctorate from the University of Montpellier and prizes from the American Chemical Society, the Royal Spanish Society for Chemistry, the German and European Colloid Society and the Gay Lussac Prize for Franco-German scientific cooperation. Shortly before his death in 2017, he was awarded the prize as distinguished scientist by the Chinese Academy of Sciences. He was a member of the Academia Europaea and since 2004 also a corresponding foreign member of the Austrian Academy of Sciences.

On March 27, 2018 Helmuth Möhwald died much too early at the age of 72 years. The award for his lifetime achievements by the International Association of Colloids and Interfacial Researchers (IACIS) had to be awarded to him posthumously at the annual meeting in Rotterdam in May 2018. In the last few years he devoted himself to his wife and daughter and to his collaborations with colleagues in France and with many of his students all over the world. He still had many projects for the future. We are mourning for a great scientist, colleague, friend and mentor.

Peter Fratzl

Das Institut in Zahlen

Haushalt

Im Jahr 2018 konsolidierte sich der Haushalt des Institutes leicht über dem Niveau der Jahre 2013/14. Die Jahre 2015 (Bezug des Erweiterungsbaus) und 2016 (Beschaffung dringend notwendiger Großgeräte) stellten für das Institut jeweils Ausnahmesituationen dar. Auch das Jahr 2017 ist durch den von der Generalverwaltung vorgegebenen erweiterten Investitionsrahmen aller Max-Planck-Institute noch einmal in finanzieller Sicht hervorzuheben. Der Haushalt **(Abb. 1)** weist daher von 2015-2017 einen ungewöhnlichen Zuwachs auf. Bereinigt um diese außerordentlichen Ausgaben kann man erkennen, dass die institutionelle Förderung etwa nur leicht gestiegen ist, der Anteil der Drittmittel bis 2017 aber signifikant schrumpfte **(Abb. 2)**. Dies liegt vor allem daran, dass mehrere Projekte, gefördert durch den European Research Council (ERC) und auch normale EU-Projekte, ausliefen und sich zudem der Anteil der Förderung durch das Bundesministerium für Bildung und Forschung (BMBF) reduzierte. Dies konnte nicht vollständig durch die erhöhte Förderung durch die Deutsche Forschungsgemeinschaft (DFG) kompensiert werden. Anwendungsnahe Projekte wurden nicht mit entsprechender Förderung durch EU oder BMBF weitergeführt, sondern bevorzugt in Ausgründungen übernommen. Seit 2018 steigt der Anteil der bewilligten Projektanträge langsam wieder.

Wenn man den um die erhöhten Investitionen bereinigten Institutshaushalt von etwa 22 Mio. Euro als Maßstab nimmt, beträgt der Drittmittelanteil am Haushalt 18.75% (4.1 Mio Euro). Die Struktur der Ausgaben **(Abb. 3)**, ist gekennzeichnet durch einen starken Anstieg der Personalausgaben für jüngere Wissenschaftler. Alle jüngeren Wissenschaftler/innen wurden durch die Umstellung von Stipendien auf Förderverträge auf institutsfinanzierte Stellen transferiert.

Abb. 1

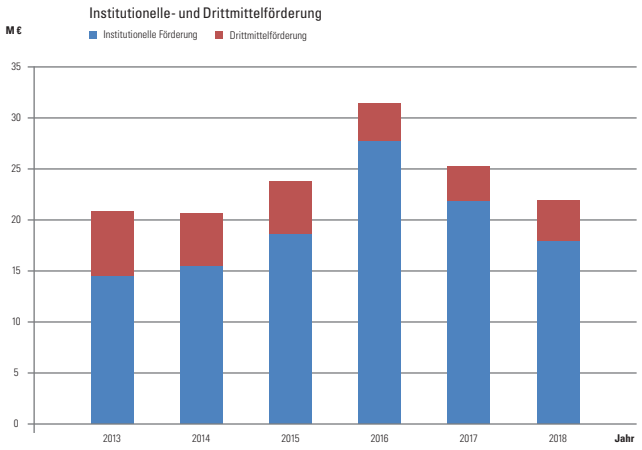
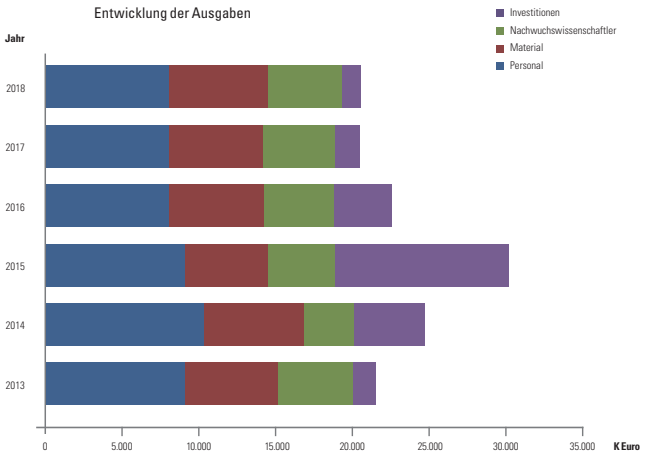


Abb. 3



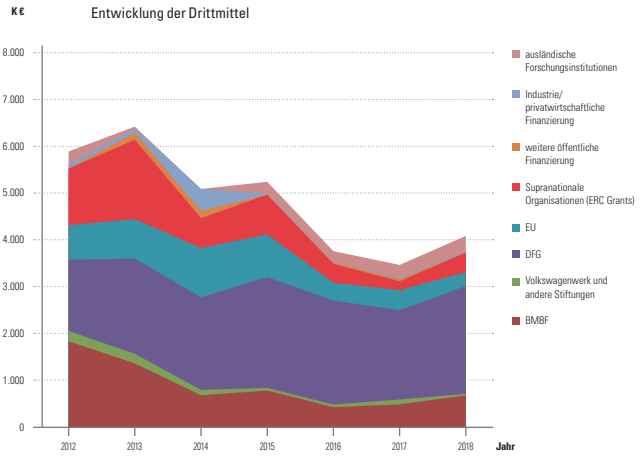


Abb. 2

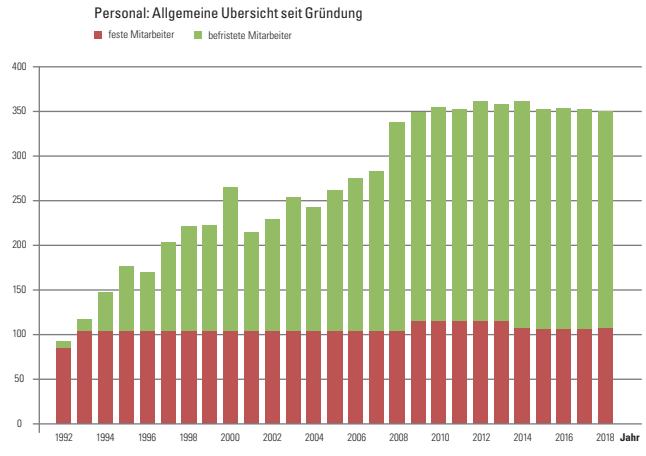


Abb. 4

Personal

Die Anzahl am Institut beschäftigter Personen blieb in den letzten Jahren konstant wie auch die Zahl der Mitarbeiter auf Haushaltsstellen (**Abb. 4**). Während die administrativen und technischen Mitarbeiter fast ausschließlich permanente Stellen besitzen, ist es bei den Wissenschaftlern genau umgekehrt. Neben den Direktoren sind weniger als zehn Wissenschaftler permanent beschäftigt. Dieses zeichnet die gewünschte hohe Fluktuation im Wissenschaftsbereich aus, da sich das Institut als Brutstätte erfolgreicher Forscher versteht, die ein neues Gebiet aufgreifen und dann ihre Arbeit an anderer Stelle in Forschung oder Industrie fortsetzen.

Bei den Postdoktoranden sank die Zahl von durchschnittlich 90 auf etwa 80 in den letzten beiden Jahren, mit einem weit überwiegenden Anteil an Ausländern **(Abb. 5)**. Die Zahl der Doktoranden aus dem Inland reduzierte sich weiter signifikant, so dass die Gesamtzahl an Doktoranden auf etwa 80 sank. Hier ist das Verhältnis von ausländischen zu inländischen Doktoranden etwa 2/1. Die geringere Anzahl an Postdocs und Doktoranden ist der Umstellung der MPG von Stipendien auf Förderverträge geschuldet.

Insgesamt liegt der Anteil ausländischer Gäste bei etwa 47% mit einer großen Mehrheit im wissenschaftlichen und einer sehr kleinen Minderheit im technischen und administrativen Bereich.

Die Nationalitätenverteilung hat sich in den letzten Jahren nur gering verschoben. Der Anteil der Gäste aus dem europäischen Ausland beträgt annähernd 50%, wobei der Anteil Westeuropäer sich im Vergleich zu dem der Osteuropäer weiter erhöhte. Der Anteil der Inder und der Chinesen sank leicht, der der Amerikaner stieg etwas, und auch der Anteil von Wissenschaftlern aus dem Nahen Osten erhöhte sich. **(Abb. 6)**.

Die Geschlechterverteilung spiegelt eine allgemeine Situation wieder: Während bei den Doktoranden die Geschlechter etwa gleich vertreten sind, befinden sich die promovierten männlichen Wissenschaftler in einer deutlichen Mehrzahl **(Abb. 6 und 7)**. Der unterschiedliche Anteil unter den Stipendiaten sollte dabei nicht besonders gewertet werden, da an Max-Planck-Instituten seit 2015 nur in Ausnahmefällen Stipendien vergeben werden, deren Anteil also in Zukunft fast verschwinden wird.

Abb. 5

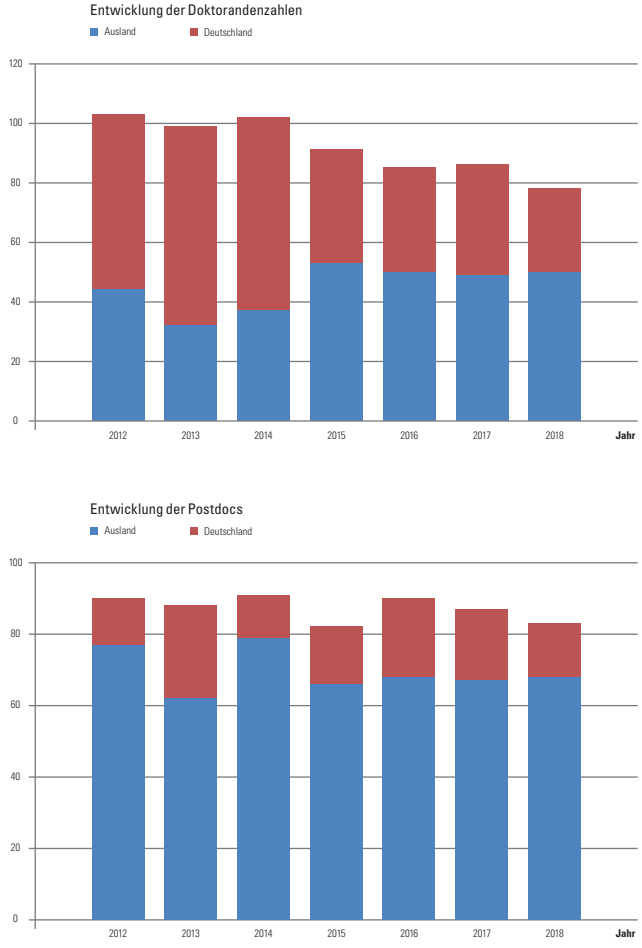
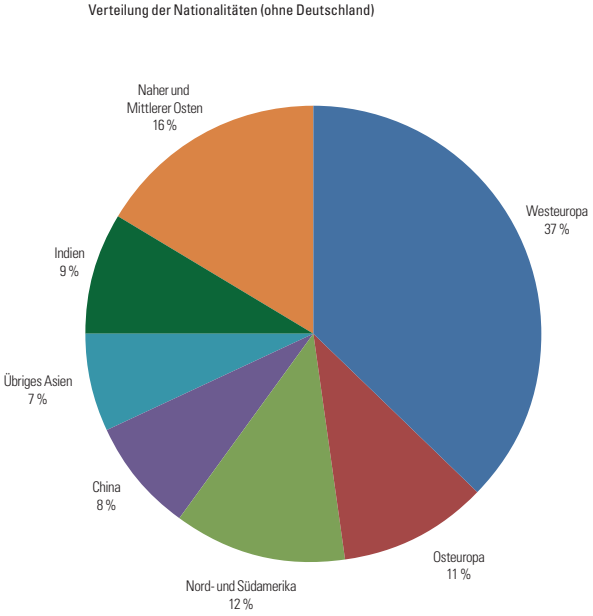


Abb. 6



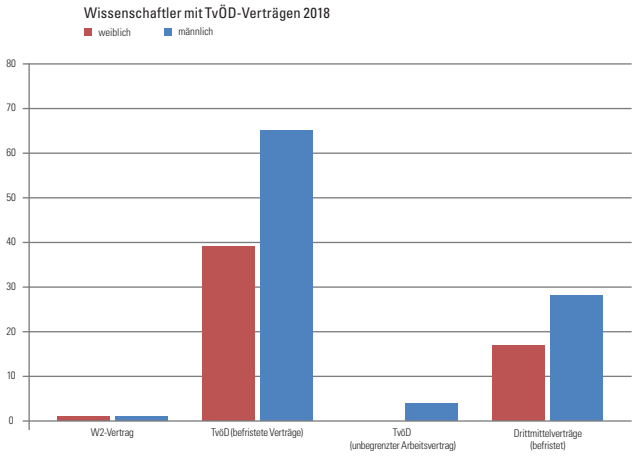
Wissenschaftliche Ergebnisse und deren Einfluss

Die Zahl der Publikationen beträgt seit zehn Jahren um die 350 pro Jahr **(Abb. 8)**. Diese Publikationen werden im Durchschnitt mehr als 45 mal zitiert. Das MPIKG muss keinen Vergleich mit einer Einheit ähnlicher Größe weltweit scheuen. Es beweist, dass das MPIKG, das mit Absicht nicht den klassischen Trends der Kolloid- und Grenzflächenforschung folgte, viele Entwicklungen in diesem Gebiet erst etabliert hat. Dieses sehen offenbar auch viele junge Wissenschaftler so, die am MPIKG forschen und die sich auch gern an ihre erfolgreiche Zeit in Potsdam erinnern. Dieses schlägt sich ebenfalls in den Rankings der Humboldt-Stiftung nieder, bei denen das MPIKG in den letzten Jahren einen Podestplatz einnahm, weit vor erheblich größeren Max-Planck-Instituten oder Forschungszentren.

Wichtiger als Zitationen und Publikationen ist jedoch der Wissenstransfer durch Köpfe, und dies geschieht durch die Ausbildung junger Wissenschaftler auf verschiedenen Stufen ihrer Karriere. Deren Qualität ist nur mit großer Verzögerung anhand ihrer Karrieren zu erfassen und kaum zu quantifizieren. Die Zahl der ehemaligen Mitarbeiter auf Professorenstellen oder äquivalenten Stellen im akademischen Bereich dürfte mittlerweile bei etwa 300 liegen.

Wenn man bedenkt, dass etwa 25 Doktoranden und 50 Postdoktoranden jährlich das MPIKG verlassen, kann man davon ausgehen, dass dieser Wissenstransfer erheblich zur Weiterentwicklung des Gebiets beiträgt. Dies ist insbesondere dann der Fall, wenn es gelang, diese Wissenschaftler für die Kolloid- und Grenzflächenforschung zu begeistern, und wir erhielten viele Rückmeldungen, dass dies gelungen ist.

Abb. 7



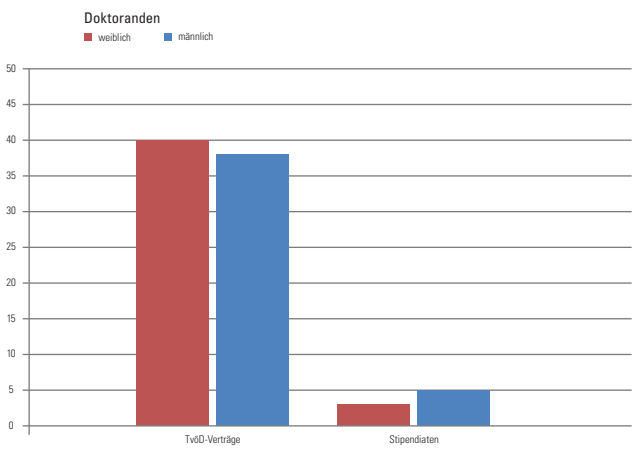
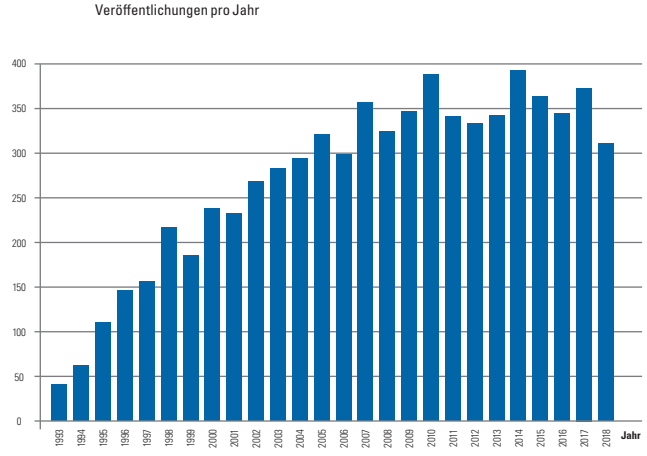
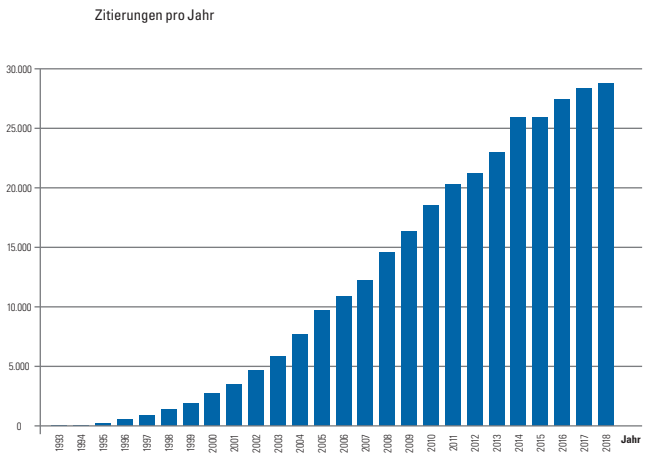


Abb. 8





The Institute in Numbers

Budget

In 2018, the Institute's budget was slightly above the level of 2013/14. The years 2015 (moving into the extension building) and 2016 (procurement of urgently needed large-scale facilities) were exceptional for the institute. 2017 has to be emphasized in financial terms by the extended investment framework that was set by the administrative headquarters of the Max Planck Society. Therefore the budget **(Fig. 1)** shows an unusual increase from 2015 to 2017. Adjusted for these extraordinary expenses it can be seen that institutional funding has risen only slightly, but the amount of third party funding was decreased significantly in 2017 **(Fig. 2)**. This is due particularly to the fact that several projects, funded by the European Research Council (ERC) and just normal EU projects expired and the proportion of funding by the Federal Ministry of Education and Research (BMBF) has decreased. This could have not be compensated completely by the increased funding by the German Research Foundation (DFG). In addition, application-related projects did not get further appropriate funding by the EU or the BMBF, but lead into spin-offs. Since 2018 the proportion of approved project applications is rising again. Taking the institutional budget of around EUR 22 million adjusted for the increased investment as the benchmark, the share of third-party funds in the budget is at 18.75% (EUR 4.1 Mio.). The expenses are characterized by **(Fig. 3)**, an enormous increase in personnel costs for younger researchers. All young scientists got employment contracts instead of scholarships. The institute pays these employees directly from its own financial resources now.

Fig. 1

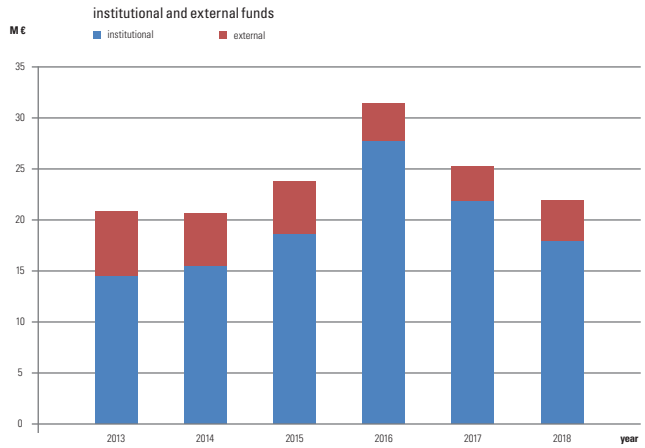


Fig. 2

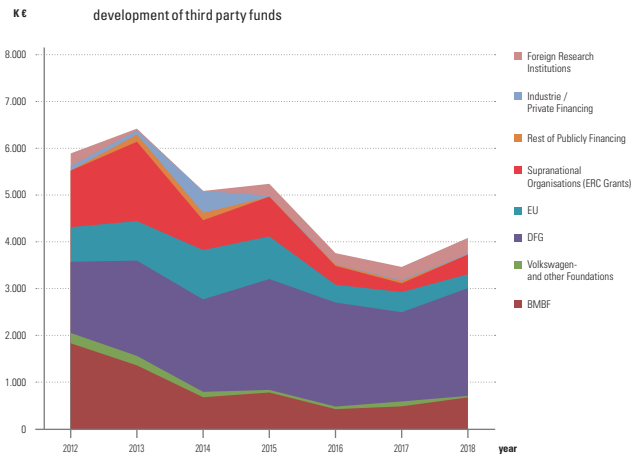


Fig. 3

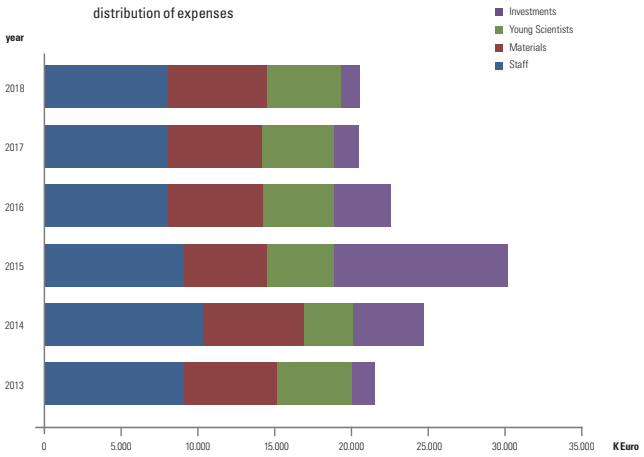
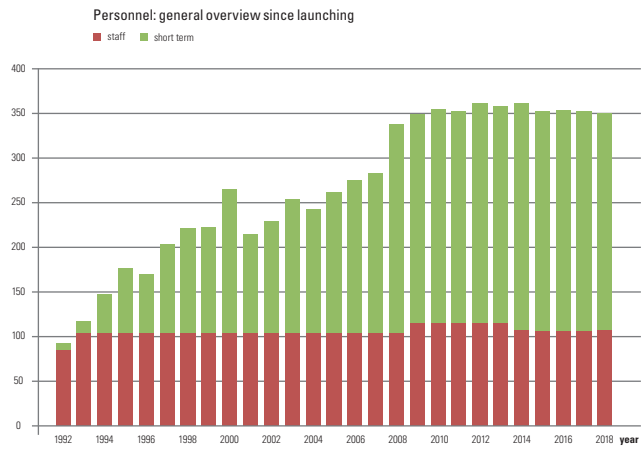


Fig. 4



Personnel

The number of employees has remained roughly stable in recent years, the number of employees within the institute's budget too **(Fig. 4)**. While nearly all of the administrative and technical staff have permanent jobs, it is the opposite case within the scientific community. Apart from the directors, less than ten scientists hold permanent positions. The Max Planck Institutes generally have high rates of employee turnover as the institutes see themselves as hotbeds for successful scientists that open up new fields of research and then continue their career in academia or industry elsewhere.

The number of postdocs decreased from an average of 90 to about 80 in the last two years. The vast majority are foreigners **(Fig. 5)**. The number of doctoral students from Germany continued to decline significantly, bringing the total number of doctoral students down to about 80. Here, the ratio of foreign to domestic doctoral students is about 2/1. The lower number of postdocs and doctoral students results from the fact that the Max Planck Society changed from scholarships to employment contracts. Overall, the proportion of foreign staff members is about 47%, with a large majority in the scientific and a very small minority in the technical and administrative field.

The distribution of nationalities has shifted only slightly in recent years. The proportion of guests from other European countries is approximately 50%, with the proportion of Western Europeans still increasing compared to that of Eastern Europeans. The proportion of Indians and Chinese decreased slightly, that of the Americans rose slightly. The proportion of Middle Eastern scientists also increased. **(Fig. 6)**.

The gender distribution reflects a general situation: While the gender ratio among doctoral students is approximately equal, the number of male postdoctoral researchers is in the clear majority **(Fig. 7)**. Apart from this, there should be no special consideration to the varying proportion of fellows. The Max Planck Institutes only rarely awarded scholarships since 2015, so their share will almost disappear in the future.

Fig. 5

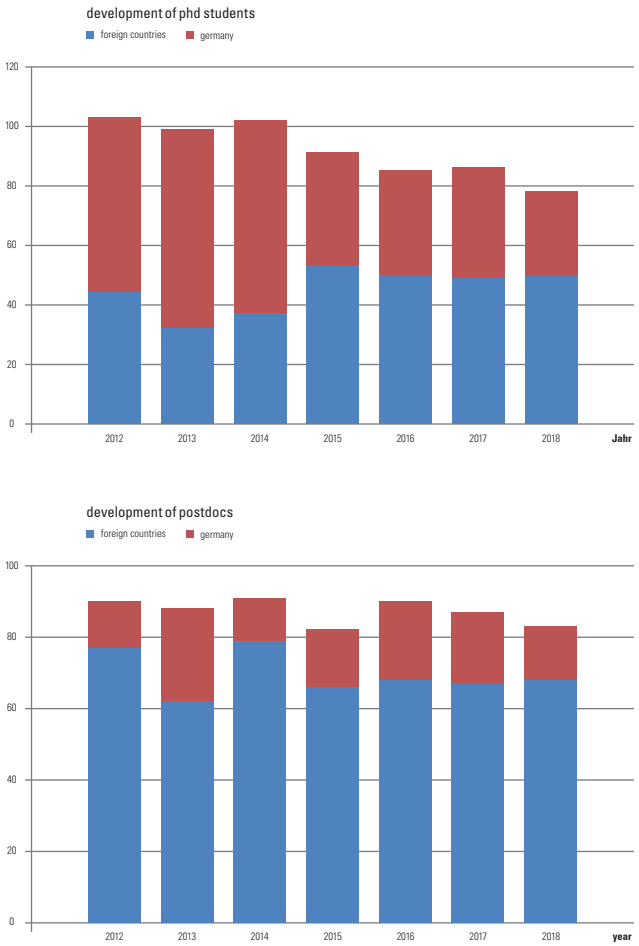
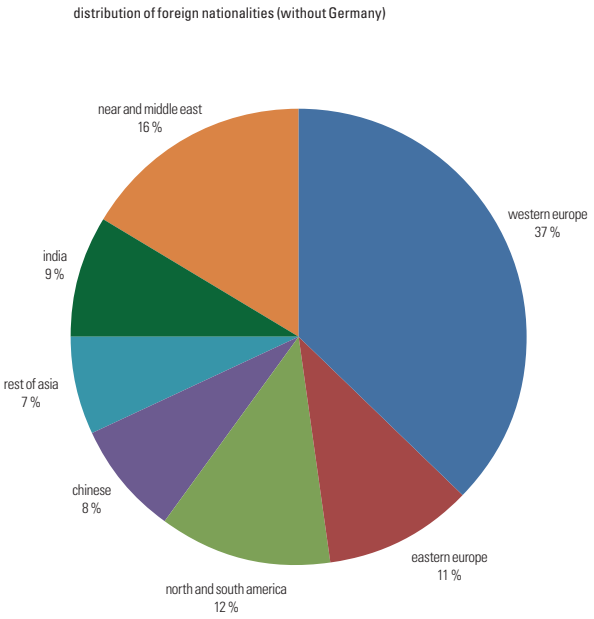


Fig. 6

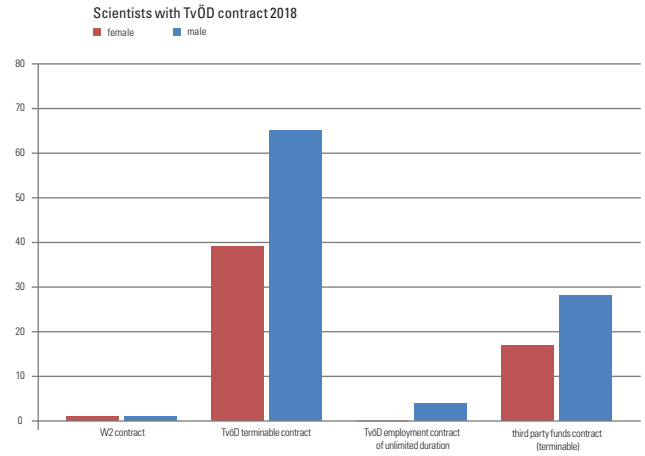


Scientific Output and Impact

The number of publications has been about 350 per year for ten years. **(Fig. 8)**. These publications are cited on average more than 45 times. The MPICI does not have to shun any comparison with a unit of similar size worldwide. It proves that the Insitute, which deliberately did not follow the classic trends in colloid and interface science, has been the first to establish many developments in this field. Many young scientists who are doing research at the MPICI and who also like to remember their successful time in Potsdam apparently see this. This is also reflected in the rankings of the Humboldt Foundation, where the Institute has taken a podium in recent years, ahead of much larger Max Planck Institutes or research institutions.

More important than citations and publications, however, is the knowledge transfer by minds, and this is done through the training of young scientists at various stages of their careers. Their quality can only be grasped with great delay on the basis of their careers and can hardly be quantified. The number of former employees at professorships or equivalent positions in the academic field should now be around 300. Considering that around 25 PhD students and 50 postdocs leave the MPICI each year, it can be assumed that this transfer of knowledge significantly contributes to the further development of the area. This is particularly the case when these scientists have been inspired by colloid and interface science, and we have received much feedback that this has been achieved.

Fig. 7



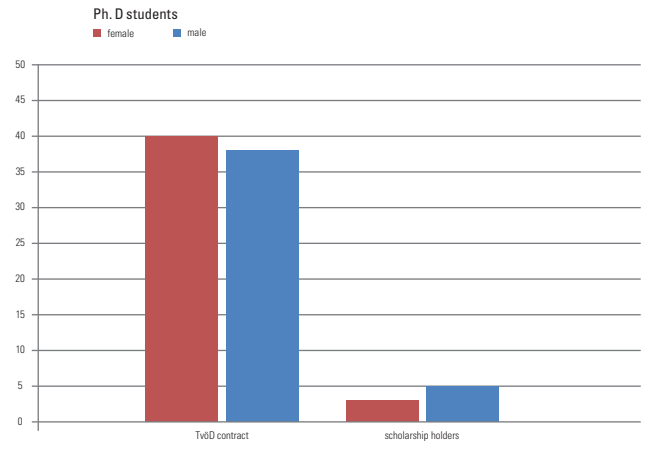
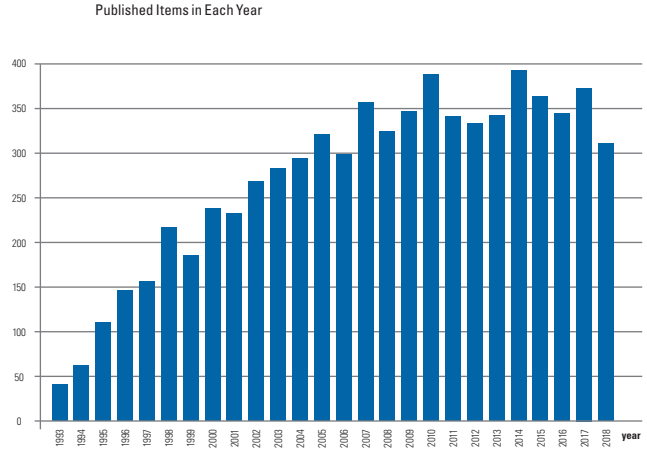
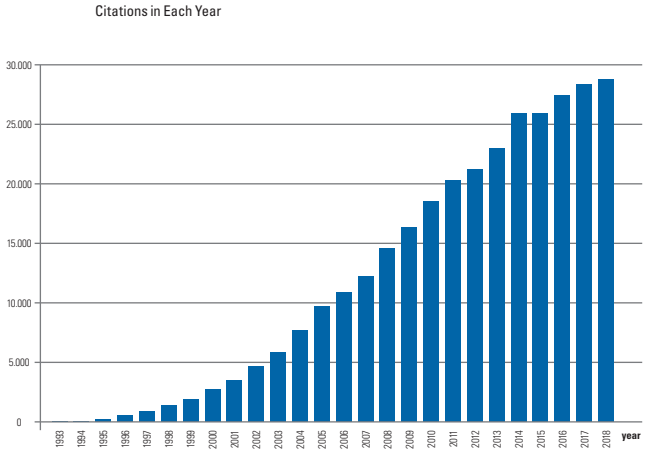


Fig. 8





Das Forschungsprogramm des Max-Planck-Instituts für Kolloid- und Grenzflächenforschung (MPIKG)

Vision und Mission

Kolloide sind winzige Bausteine, die grundlegende Einheiten von lebenden Organismen und vielen nützlichen Materialien darstellen. Das Verständnis ihres Aufbaus sowie ihre erfolgreiche Synthese, erlaubt die Lösung drängender Probleme u.a. in den Bereichen Gesundheit, Energie und Werkstoffe.

Das MPIKG beschäftigt sich deshalb primär mit den fundamentalen wissenschaftlichen Problemen von Kolloiden und deren Grenzflächen. Die wissenschaftliche Vision des Instituts ist auf zwei Kernbereiche ausgelegt: Zum einen auf das Herstellen, Visualisieren, Messen und das Verständnis dieser Bausteine und zum anderen auf deren vielfältige Wechselwirkungen und Anordnungen (**Abb. 1**). Unsere Forschung umfasst daher sowohl biologische und medizinische Fragestellungen als auch Materialien und deren verschiedenste Anwendungen. Die bioinspirierte Materialforschung schlägt dabei die Brücke zwischen den beiden Ausrichtungen, indem sie Materialstrukturen, die in der Natur vorkommen, in Konzepte für technische Materialien übersetzt.

Abb.1: Wissenschaftliche Strategie des MPIKG

Wir wollen dabei wissenschaftliche Exzellenz mit außergewöhnlichem Engagement in der Betreuung und Unterstützung von jungen WissenschaftlerInnen kombinieren. Unsere Mission ist es, eine Brücke von Molekülen zu mehrskaligen Materialien und Biosystemen zu schlagen und dabei Nachwuchswissenschaftlerlnnen bestmöglich zu fördern.

Das MPI für Kolloid- und Grenzflächenforschung nimmt, 25 Jahre nach seiner Gründung, eine führende Rolle in verschiedenen innovativen Wissenschaftsfeldern ein. Diese Forschungsgebiete – geordnet von kleinen zu größer werdenden Objekten – reichen von der Synthese, Charakterisierung und theoretischen Beschreibung von Kohlehydraten, Proteinen und Lipiden über funktionalisierte Nanopartikel und Hybridmaterialien, der Selbstorganisation von komplexen Grenzflächen und Mehrkomponentenmembranen bis hin zu hierarchischen Biomaterialien basierend auf Polysacchariden, Proteinen oder mineralisierten Geweben, wie Knochen und Zähnen. In all diesen Bereichen bürgt der Name des MPIKG für Exzellenz in der Grundlagenforschung.

Das Institut verfolgt zwei generelle Strategien, um seine Spitzenposition in diesem Bereich zu festigen und weiter auszubauen: (i) Es identifiziert und wählt fortwährend neue interdisziplinäre Forschungsthemen, die eine höchstmögliche Relevanz für die Wissenschaft und Gesellschaft aufweisen; (ii) es ist sehr aktiv in der Ausbildung von DoktorandInnen und der Förderung junger WissenschaftlerInnen. So wird das MPIKG zum idealen Ausgangspunkt für erfolgreiche akademische Karrieren.

In den letzten Jahren wurden insbesondere Themen, welche unmittelbar mit biomimetischen und biologischen Systemen verknüpft sind, in die Forschungsarbeit aufgenommen. So gibt es vier neue Schwerpunktgebiete:

- Erkennung von Biopolymeren
- Photoinduzierte molekulare Prozesse
- Zellähnliche Systeme und Prozesse
- Gewebeähnliche Systeme und Prozesse

Diese Forschungsbereiche finden sich auch als Themenschwerpunkte in der neuen Internationalen Max Planck Research School über „Multiscale Bio-Systems: Von der molekularen Erkennung zum mesoskopischen Transport". Das Graduiertenprogramm startete 2013, wird in einer zweiten Förderperiode bis 2025 gefördert. Ein besseres Verständnis von vielskaligen Biosystemen ist dabei Grundlage für eine Vielzahl möglicher Anwendungen wie z.B. der Entwicklung von intelligenten Wirkstoffträgern und Biomaterialien.

Interdisziplinäre Expertise

Die komplexe und vielfältige Welt der Kolloide und Grenzflächen bietet eine große Anzahl an räumlichen und zeitlichen Organisationseinheiten, welche von molekularen bis hin zu mesoskopischen Skalen reichen. Für eine umfassende Untersuchung dieser Systeme und Prozesse bieten die einzelnen Abteilungen des Instituts eine komplementäre Methodik und Fachkenntnis in den Bereichen Chemie, Biochemie, Physik, Materialwissenschaften und Theorie. Die Abteilungen „Biomolekulare Systeme" (Seeberger) und „Kolloidchemie" (Antonietti) besitzen spezielle Expertise bei der chemischen Synthese von Molekülen und Materialien. Die Abteilung „Biomaterialien" (Fratzl) fokussiert ihre Arbeit dagegen auf die strukturelle Analyse und physikalische Charakterisierung dieser Systeme. Wenn es um das Verständnis und die Modellierung geht, ist die Abteilung „Theorie & Bio-Systeme" federführend.

Nach der Gründung der Abteilung „Biomaterialien" unter Peter Fratzl im Jahr 2003 und der Abteilung „Biomolekulare Systeme" unter Peter H. Seeberger im Jahr 2008 wurde 2014 eine neue unabhängige Max-Planck-Forschungsgruppe zum Thema „Mechano(bio)chemie" (Kerstin Blank) etabliert.

Langfristige Ziele

Jede Abteilung des MPIKG hat sich langfristig anspruchsvolle Ziele gesetzt: Die Abteilung von Peter Seeberger untersucht die Rolle von komplexen Kohlehydraten, die fast alle Zellen umhüllen. Grundlegende Einsichten haben auf Kohlehydraten basierende Impfstoffkandidaten hervorgebracht. Die ForscherInnen um Markus Antonietti sind auf dem Weg enzymähnliche Nanokatalysatoren und die künstliche Photosynthese zu entwickeln und so grüne Energiegewinnung und -speicherung zu ermöglichen. Im Mittelpunkt der Abteilung von Peter Fratzl stehen das Verständnis und die Nachahmung von natürlichen auf Proteinen oder Polysacchariden basierenden Materialen, von Pflanzenbewegung sowie von Knochenwachstum und -heilung. Das Verständnis und die Überwindung der Komplexitäts-Lücke zwischen künstlichen und natürlichen Systemen ist ein langfristiges Thema in der Abteilung von Reinhard Lipowsky. Schließlich beschäftigt sich die Gruppe um Kerstin Blank mit dem Einfluss mechanischer Kräfte auf Moleküle und Materialien.

Neue Forschungsperspektiven

Während der letzten Jahre haben sich einige neue zukunftsweisende Forschungsgebiete herauskristallisiert. Bei der molekularen Erkennung von Kohlehydraten handelt es sich um ein Arbeitsgebiet aus der Abteilung Seeberger, welches aber mit aktuellen Untersuchungen aus den Abteilungen Antonietti und Lipowsky Schnittmengen aufweist. Die Forschung in diesem Kernbereich basiert im Wesentlichen auf der Synthese von Polysacchariden und Kohlehydraten, die eine sehr definierte molekulare Architektur besitzen (Seeberger). Diese Kohlehydrate werden sowohl an Nanopartikeln (Antonietti) als auch an Lipid-Doppelschichten (Lipowsky) verankert. Diese Systeme können mit verschiedenen experimentellen und theoretischen Methoden untersucht werden, wobei eine hohe räumliche und zeitliche Auflösung angestrebt wird. Fotoinduzierte molekulare Prozesse sind ein Fokus der Abteilung Antonietti, wobei es hier gemeinsame Interessen mit den Abteilungen Seeberger und Lipowsky gibt. Ein neuer Katalysator auf der Basis von Kohlenstoff und Stickstoff wurde 2007 vorgestellt und wird nun weiterentwickelt bzw. optimiert (Abt. Antonietti). Andere fotoinduzierte Prozesse beinhalten die Entwicklung völlig neuartiger organisch-chemischer Reaktionskaskaden mit höchster Einfachheit und exzellenten Ausbeuten (Seeberger, Antonietti), und fotoinduzierte konformative Änderungen von supramolekularen Strukturen (Lipowsky).

Biomolekulare Maschinen, die molekulare Lasten transportieren oder Informationen verarbeiten, sind ein Schwerpunkt der Abteilung Lipowsky. Aktuelle Themenbereiche sind dabei der kooperative Lastentransport durch Teams von molekularen Motoren, die Krafterzeugung durch Filamente und die Proteinsynthese durch Ribosomen. Verwandte Thematiken werden in der Abteilung Fratzl und der Blank-Gruppe bearbeitet, wie z.B. die molekulare mechanische Wechselwirkung von Zellen mit ihrer extrazellulären Umgebung. Ein weiteres aktuelles Thema der Abteilung Lipowsky sind asymmetrische Doppelschicht-Membranen sowie der Einschluss von Nanoteilchen durch derartige Membranen.

Biomimetische Bewegung und Gewebewachstum sind Kernthemen innerhalb der Abteilung Fratzl. Formänderungen in Geweben werden durch die Erzeugung von ungleichmäßigen, internen Belastungen ausgelöst. Diese werden durch die Wasseraufnahme in Zellwänden und durch Zellproliferation in Knochen und Hautgewebe erzeugt (Fratzl). Weiterführende Studien dieser belastungsauslösenden Prozesse werden mittels mehrskaliger Computersimulationen durchgeführt (Lipowsky). Auf diese Weise wird das Ziel verfolgt, die zu Grunde liegenden molekularen Mechanismen aufzudecken. Auch dies steht in einem engen Zusammenhang mit Untersuchungen in der Blank-Gruppe, die sich mit mechanischen Struktur-Funktions-Beziehungen von protein-basierten Materialbausteinen beschäftigt.

Programme für Doktorandinnen und Doktoranden

Ein starkes Engagement für die Ausbildung von DoktorandInnen ist Markenzeichen unseres Instituts. Die erste Max Planck Research School (IMPRS) über „Biomimetische Systeme“ wurde über zwölf Jahre erfolgreich betrieben und beendete ihre Arbeit im Herbst 2012. Die zweite IMPRS über „Multiscale Bio-Systems“ begann ihre Arbeit 2013 und ist bis 2025 bewilligt. Hauptziel der IMPRS ist es, dass die teilnehmenden DoktorandInnen effizient und erfolgreich an einem zukunftsweisenden Forschungsprojekt arbeiten können, und das unter Erlernen verschiedener Disziplinen. Darüber hinaus ist das MPIKG auch noch in weiteren Graduiertenschulen aktiv: Diese sind das DFG-Graduiertenkolleg “Self-Assembled Soft Matter Nano-Structures at Interfaces“, koordiniert von der TU Berlin, die Berlin-Brandenburg School for Regenerative Therapies (BSRT), koordiniert von der Charité – Universitätsmedizin Berlin, die SALSA, School of Analytical Sciences Adlershof, koordiniert von der Humboldt-Universität zu Berlin das ZIBI, Zentrum für Infektionsbiologie und Immunologie, koordiniert von der FU Berlin und das Graduiertenkolleg 2046 „Parasiteninfektionen: von experimentellen Modellen zu natürlichen Systemen“, ebenfalls koordiniert von der FU Berlin.

Förderung von jungen WissenschaftlerInnen

Das Institut ist und war schon immer ein guter Nährboden für junge WissenschaftlerInnen, die eine akademische Karriere anstreben. Viele der früheren MitarbeiterInnen und Postdocs sind jetzt ProfessorInnen an deutschen oder ausländischen Universitäten. Während der letzten zehn Jahre haben ca. 300 frühere ArbeitsgruppenleiterInnen, Doktoranden und Wissenschaftler Spitzenpositionen eingenommen, die vergleichbar mit den deutschen W3 oder W2 Professuren sind. In der neuen IMPRS über „Multiscale Bio-Systems“ sind alle ArbeitsgruppenleiterInnen des MPIKG, die an verwandten Themen arbeiten, Mitglieder der erweiterten Fakultät der Schule und nehmen an der Auswahl und Zulassung der StudentInnen teil.

Gesellschaftliche Relevanz

Viele Forschungsaktivitäten am MPIKG haben -als Grundlagenforschung- potentielle Anwendungen in verschiedenen Technologie-Feldern und haben das Potenzial die Lebensqualität der Menschheit nachhaltig zu verbessern. Die Entwicklung von Impfstoffen auf der Basis von Kohlenhydraten und die Möglichkeit große Mengen dieser Moleküle zu produzieren, ist vielversprechend und wegweisend für die Prävention von bakteriellen Infektionen wie Krankenhauskeimen aber auch Parasitenerkrankungen wie Malaria. Diese Impfstoffe sind speziell für Entwicklungsländer sehr bedeutsam. Funktionelle Nanopartikel und Materialien können für die Erzeugung und Speicherung von Energie und für neue Methoden der CO_2-Bindung eingesetzt werden. Darüber hinaus besitzen diese Systeme ein breites Anwendungsspektrum in Bezug auf den intelligenten Wirkstofftransport, da sie die molekulare Erkennung und Bewegung mit der gezielten Wirkstofffreigabe kombinieren. Am Institut werden Biosysteme untersucht, die in Zukunft zu neuen Materialkonzepten führen werden, die auf bioinspirierten Designs basieren oder zur Geweberegeneration beitragen. Schließlich wird unsere Gesellschaft sehr stark von den jungen WissenschaftlerInnen profitieren, die ihre breite interdisziplinäre Ausbildung am MPIKG erhalten haben und das Institut verlassen, um ihr Wissen in anderen Wissenschafts- und Ingenieurbereichen anzuwenden.

Markus Antonietti, Peter Fratzl, Reinhard Lipowsky,
Peter H. Seeberger

The Research Program of the Max Planck Institute of Colloids and Interfaces (MPICI)

Vision and Mission

Colloids are small building blocks that are often basic units of living organisms and of many natural and man-made materials. Mastering colloid synthesis and assembly will solve urgent problems in health and energy as well as many other important areas. The research program of the MPICI addresses fundamental scientific problems of such colloids and of the interfaces between them. Thus, the scientific vision of the institute is focused on two areas: to lead the effort in making, visualizing, measuring and understanding these nanoscale building blocks, as well as to control their interactions and assembly (see **Fig. 1**). Our research includes biological or medical questions, as well as materials with their very diverse applications. Bioinspired materials research is bridging between the two directions, translating material structures found in nature into design concepts for engineering materials.

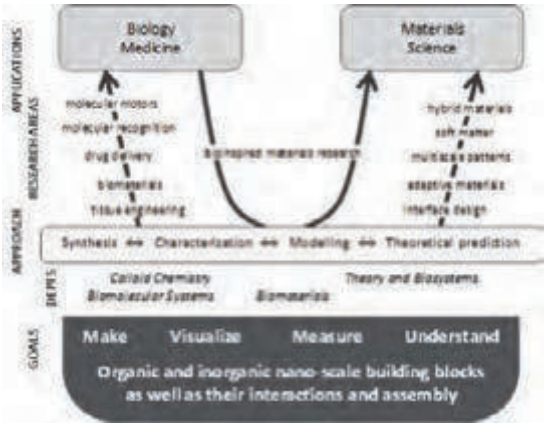


Fig. 1: Scientific strategy of the MPICI

We therefore intend to combine scientific excellence with exceptional commitment to mentoring and supporting young scientists. Our mission is: Bridging the gap between molecules and multiscale materials and biosystems through excellence in science and via the support of young scientists.

The MPI of Colloids and Interfaces (MPICI), 25 years after its foundation, has attained a leading position in several innovative fields of research. These areas – ordered from small to increasingly larger objects – include the synthesis, characterization and theoretical description of carbohydrates, proteins and lipids, through functionalized nanoparticles and hybrid materials, the self-organization of complex interfaces and multi-component membranes up to hierarchical biomaterials based on polysaccharides, proteins or mineralized tissues, such as bone and teeth. In all of these areas, the name of the MPICI serves as a trademark for excellence.

The MPICI pursues two general strategies in order to maintain and strengthen its leading role in these fields: (i) The MPICI constantly identifies and selects new interdisciplinary research topics with the highest potential impact on science and society; and (ii) the MPICI is very active in the training of graduate students and the support of young scientists and, thus, continues to be a hotbed for academic careers.

In the last few years, especially topics which directly relate to biomimetic and biological systems have been taken up. Four new focus areas are:

- Recognition of Biopolymers
- Photo-induced Molecular Processes
- Cell-like Systems and Processes
- Tissue-like Systems and Processes

These areas are also pursued in the framework of the International Max Planck Research School on "Multiscale Bio-Systems": From molecular recognition to mesoscopic transport": This graduate program started in 2013 and is funded until 2025. An improved understanding of multiscale bio-systems also provides the knowledge base for many possible applications such as the development of intelligent drug carriers and biomaterials.

Interdisciplinary Expertise

The complex and versatile world of colloids and interfaces provides many levels of spatial and temporal organization, from molecular to mesoscopic scales. In order to address these multiscale systems and processes, the departments at the MPI provide complementary methodology and core expertise from chemistry, biochemistry, physics, materials science, and theory. The departments of "Biomolecular Systems" (Seeberger) and "Colloid Chemistry" (Antonietti) have their core expertise in the chemical synthesis of molecules and materials. The department of "Biomaterials" (Fratzl) focusses on structural analysis and physical characterization. The department of "Theory & Bio-Systems" (Lipowsky) provides expertise in theory and modeling. After establishing the Fratzl department on "Biomaterials" in 2003 and the Seeberger department on "Biomolecular Systems" in 2008, a new independent Max Planck Research Group on "Mechano(bio)chemistry" (Kerstin Blank) has been established in 2014.

Long-term Objectives
Each department of the MPICI sets itself challenging long-term objectives. The Seeberger department characterizes the complex mixture of carbohydrates, which surround practically all cells. These fundamental observations have resulted in candidates for carbohydrate based vaccines. The Antonietti department is establishing enzyme-like nanocatalysts and artificial photosynthesis as key milestones for green energy production and chemical conversion reactions. The Fratzl department aims to understand and mimic polysaccharide and protein based materials, with the goal of unravelling the processes determining plant motility and bone tissue growth and healing. The Lipowsky department aims to investigate and bridge the complexity gap between artificial and natural biosystems. Last but not least, the Blank group elucidates the influence of mechanical forces on molecules and materials.

New Focus Areas
During the last couple of years, several new focus areas have emerged at the MPI: Molecular recognition of carbohydrates is a focus area of the Seeberger department, with overlapping interests of the Antonietti and Lipowsky departments. Research in this core area is based on the synthesis of polysaccharides and carbohydrates with a well-defined molecular architecture (Seeberger). These carbohydrates are then anchored to nanoparticles (Antonietti), and lipid bilayers (Lipowsky). In this way, they become accessible to experimental and computational methods that probe these systems with high spatial and temporal resolution.

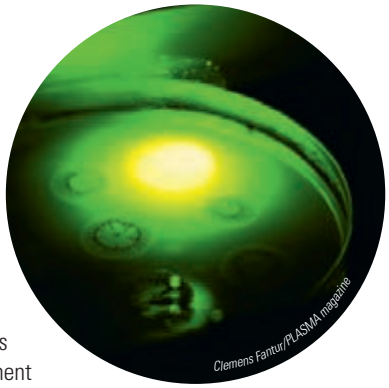
Photo-induced molecular processes are a focus area of the Antonietti department, with overlapping interests of the Seeberger and Lipowsky departments. A new type of catalyst based on carbon and nitrogen has been introduced about ten years ago and will be further developed and optimized (Antonietti). Other photo-induced processes include the development of fundamentally new reaction cascades for organic chemistry (Seeberger, Antonietti), and photoinduced conformational changes of supramolecular assemblies (Lipowsky).

Biomolecular machines that transport molecular cargo or process nanoscale information is a focus area of the Lipowsky department, with overlapping interests of the Fratzl department and the Blank group. Current topics include the cooperative cargo transport by motor teams, the force generation by filaments and the protein synthesis by ribosomes. A related theme is treated in the Blank group and the Fratzl department where mechanical interactions between cells and the extracellular environment are analyzed. The Lipowsky department puts another focus on asymmetric bilayer membranes and their interactions with nanoparticles.

Biomimetic actuation and growth of tissues are focus areas of the Fratzl department, with overlapping interests of the Lipowsky department. Shape changes in tissues are caused by the generation of non-uniform, internal stresses. These stresses are generated by water absorption in the cell walls of plant tissues and by cell proliferation in bone or skin tissues (Fratzl). The ongoing experimental studies of these stress-generating processes are also addressed by multiscale computer simulations in order to elucidate the underlying molecular mechanisms (Lipowsky). These observations are in line with projects in the Blank group, which aim at elucidating structure-function relationships of protein-based materials components.

Graduate Programs
The MPICI will continue its strong commitment to the training of graduate students. The first International Max Planck Research School (IMPRS) on "Biomimetic Systems" has been successfully operated for twelve years until fall 2012. The second IMPRS on "Multiscale Bio-Systems" has started in 2013, and its first funding period will last until 2019. The new school covers the new focus areas of the MPICI as described above. The main objective of the IMPRS curriculum is to enable the participating doctoral students to work on their research projects, which are at the forefront of current research, in an efficient and fruitful manner. In addition, the MPICI participates in the following graduate schools: International Research Training Group on "Self-assembled Soft Matter Nano-Structures at Interfaces (coordinated by the TU Berlin), the "Berlin-Brandenburg School of Regenerative Therapies" (coordinated by the Charité Hospital, Berlin), SALSA, the Graduate School of Analytical Sciences Adlershof (coordinated by the Humboldt University Berlin), the Center of Infection Biology and Immunity (ZIBI) (coordinated by the FU Berlin) as well as the Research Training Group 2046 „Parasite Infections: From Experimental Models to Natural Systems" (coordinated by the FU Berlin).

Support of Young Scientists
The MPICI will continue to be a hotbed for young scientists who pursue a higher career in academia. A large number of former associates, graduate students and postdocs are now professors at German or foreign universities. In particular, during the last ten years, at least 300 former junior scientists of the MPICI have taken up offers for professorships that are equivalent to German W3 or W2 positions. Many of these research group leaders were teaching in the framework of the old IMPRS on "Biomimetic Systems". In the new IMPRS on "Multiscale Bio-Systems", all research group leaders, who work on topics related to the school, are members of the school's associate faculty and take part in the recruitment and admission of the students.



Potential Applications and Impact on Society as a Whole

Many research activities at the MPICI have applications that will be useful and beneficial for research in other disciplines and for society as a whole. The development of vaccines based on carbohydrates, in connection with the possibility to produce large amounts of these molecules, are very promising for the prevention of bacterial infections (e.g. hospital germs) of parasitic (not parasitical!) diseases (e.g. Malaria). These vaccines are particularly beneficial for developing countries. Functionalized nanoparticles and materials can be used for improved photoinduced cleavage of water and for new methods of CO_2 fixation. Likewise, these systems have a wide range of applications in the context of smart drug delivery systems, which combine molecular recognition and activation with triggered drug release. In the latter context, the interactions of nanoparticles with cell membranes play a decisive role. The bio-systems studied at the MPICI are also likely to lead to new materials concepts based on bio-inspired designs as well as new concepts for material-supported tissue regeneration. Finally, the society as a whole will strongly benefit from the many young scientists that have received a broad interdisciplinary training at the MPICI and leave the institute in order to apply their knowledge in other branches of science and engineering.

Markus Antonietti, Peter Fratzl, Reinhard Lipowsky, Peter H. Seeberger

Wissenschaftliche Beziehungen

Das Max-Planck-Institut für Kolloid- und Grenzflächenforschung (MPIKG) unterhält intensive Kooperationen mit Universitäten und Forschungsinstituten auf regionaler, nationaler und internationaler Ebene.

Regionale Kooperationen

Zwischen dem Max-Planck-Institut für Kolloid- und Grenzflächenforschung (MPIKG) und der Universität Potsdam besteht seit Institutsgründung eine intensive und gute Zusammenarbeit. Alle vier aktiven Direktoren sind Honorarprofessoren an der Universität Potsdam. Dies spiegelt sich in einer intensiven Lehrtätigkeit sowohl in Bereichen des Grundstudiums als auch in den Wahlpflichtfächern wider. Prof. Fratzl und Prof. Lipowsky sind zudem Honorarprofessoren an der Humboldt-Universität zu Berlin und Prof. Seeberger an der Freien Universität Berlin. Darüber hinaus wurden 2005 Prof. Jürgen Rabe (Institut für Physik, Humboldt-Universität zu Berlin) und 2017 Prof. Joanna Aizenberg (Amy Smith Berylson Professor of Materials Science at Harvard's School of Engineering and Applied Sciences) sowie Prof. Dr. Ulrich S. Schubert (Friedrich-Schiller-Universität Jena) als auswärtige wissenschaftliche Mitglieder an das MPI für Kolloid- und Grenzflächenforschung berufen.

Zusätzlich dazu gibt es Kooperationsvereinbarungen mit dem Helmholtz-Zentrum Berlin für Materialien und Energie (HZB) über die gemeinsame Nutzung von Neutronenstreuinstumenten und Synchrotron-Beamlines sowie mit der Bundesanstalt für Materialforschung und -prüfung (BAM) über die Betreibung einer Mikrofokus-Beamline.

Das MPIKG, die Universität Potsdam, die Humboldt-Universität zu Berlin und die Freie Universität Berlin arbeiten eng im Rahmen der International Max-Planck Research School (IMPRS) on „Multiscale Bio-Systems" zusammen. Die Aktivitäten über biomimetische Systeme wurden zunächst durch die gemeinsam vom Institut und der Universität Potsdam im Jahr 2000 ins Leben gerufene International Max Planck Research School (IMPRS) on „Biomimetic Systems" komplettiert, entscheidend gestärkt und unterstützt. Im Oktober 2012 lief die zwölfjährige Förderung für die Schule aus. Ab Juni 2013 hat die neue International Max- Planck Research School (IMPRS) on „Multiscale Bio-Systems" ihre Arbeit aufgenommen. Diese befasst sich mit dem hierarchischen Aufbau von Biosystemen im Nanometer- und Mikrometerbereich und wird bis 2025 gefördert. Sprecher ist Professor Reinhard Lipowsky.

Ferner beteiligt sich das Institut an weiteren Graduiertenschulen:

- International Research Training Group on "Self-assembled Soft Matter Nano-Structures at Interfaces (koordiniert von der TU Berlin)
- „Berlin-Brandenburg School of Regenerative Therapies" (koordiniert von der Charité, Berlin)
- SALSA, the Graduate School of Analytical Sciences Adlershof (koordiniert von der Humboldt-Universität zu Berlin)
- ZIBI Graduate School, Center of Infection Biology and Immunity (koordiniert von der FU Berlin)
- Graduiertenkolleg 2046 „Parasiteninfektionen: von experimentellen Modellen zu natürlichen Systemen" (koordiniert von der FU Berlin)

Das MPIKG ist ebenfalls involviert in die von der Deutschen Forschungsgemeinschaft (DFG) geförderten „Sonderforschungsbereiche" (SFB):

- SFB1340 „In vivo Visualisierung der pathologisch veränderten Extrazellulärmatrix "Matrix in Vision"", koordiniert von der Charité Berlin
- SFB1114 „Skalenkaskaden in komplexen Systemen", koordiniert von der FU Berlin
- SFB TR84 „Angeborene Immunität der Lunge: Mechanismen des Pathogenangriffs und der Wirtsabwehr in der Pneumonie", koordiniert von der Charité Berlin

Im Projekt »Glyco3Display« kreiert ein Team des Fraunhofer-Institut für Zelltherapie und Immunologie (IZI) gemeinsam mit dem Max-Planck-Institut für Kolloid- und Grenzflächenforschung eine neue Stoffgruppe, die als innovatives mikrobielles Agens fungieren könnte. So könnten Rezeptoren so blockiert werden, dass Krankheitserreger nicht mehr in der Lage sind, an menschliche Zellen anzudocken und sie zu infizieren.

Ebenfalls beteiligt ist das MPIKG am vom Bundesministerium für Bildung und Forschung (BMBF) finanzierten Berlin-Brandenburger Zentrums für Regenerative Therapien (BCRT) sowie am Exzellenzcluster „Matters of Activity. Image Space Material" (P. Fratzl ist Co-Sprecher), welcher primär an der Humboldt-Universität zu Berlin angesiedelt ist.

Das Institut ist auch Teil des Forschungsverbundes „Unifying Systems in Catalysis (UniSysCat) – Katalyse-Netzwerke verstehen und nutzen lernen". Dieser neue von der Technischen Universität Berlin beantragte Exzellenzcluster kann auf zehn Jahre hervorragende Arbeit von „Unifying Concepts in Catalysis" (UniCat) aufbauen, dem Vorgängercluster aus der Exzellenzinitiative, an dem das MPIKG ebenfalls beteiligt war.

Nationale und Internationale Kooperationen

Im Rahmen von europäischen Förderprogrammen, laufen zurzeit drei EU-Projekte innerhalb des EU-Rahmenprogramms „HORIZON2020", davon ein ERC Starting Grant.

Das Institut ist Teil des Forschungsnetzwerks MaxSynBio, welches Anfang 2014 seine Arbeit aufgenommen hat. Die Max-Planck-Gesellschaft bündelt hier ihre Kompetenzen im Bereich der synthetischen Biologie. Insgesamt neun Max-Planck-Institute beteiligen sich daran. MaxSynBio wird vom Bundesministerium für Bildung und Forschung (BMBF) und von der Max-Planck-Gesellschaft über einen Gesamtzeitraum von sechs Jahren gefördert.

Darüber hinaus ist das MPIKG Mitglied des Projektes „Big-Data Driven Materials Science (BiGmax) unter der Federführung des Fritz-Haber-Institutes in Berlin sowie des Projekts MaxWater unter der Federführung des MPI für Polymerforschung in Mainz, beide gefördert durch die Max-Planck-Gesellschaft.

Des Weiteren ist das Institut gemeinsam mit dem Max-Planck-Institut für molekulare Physiologie in Dortmund und dem Riken Advanced Science Institute (ASI) in Wako federführend beteiligt am RIKEN-Max Planck Joint Research Center for Systems Chemical Biology. Beide Forschungseinrichtungen schaffen damit eine Plattform, auf der sie Wissen, Erfahrungen und Infrastruktur sowie neue Methoden und Techniken im Bereich der chemischen Systembiologie bündeln.

Das Institute of Technology, Varanasi (Indien) und das MPIKG haben zudem 2017 eine Deutsch-Indische Max-Planck-Partnergruppe ins Leben gerufen. Die Partnergruppe beschäftigt sich insbesondere mit dem Einsatz der automatisierten Zuckersynthese bei zuckerbasierten marinen Naturstoffen. Hierbei soll das Potenzial für die Entwicklung von neuartigen Materialien und die Verwendung im medizinischen Bereich ausgelotet werden.

Das „Max Planck-NTU Joint Laboratory for Artificial Senses" ist eine gemeinsame Einrichtung der Nanyang Technological University, Singapur (NTU Singapur) und des MPIKG. Innovative Forschungsaktivitäten im Bereich der künstlichen Sensorik werden hier gebündelt und sollen z.B. in der Robotik und im modernen Gesundheitswesen ihren Einsatz finden.

Darüber hinaus gibt es gemeinsame Labors und internationale Partnergruppen mit dem National Laboratory for Physical Sciences at Microscale (CAS) in Hefei, China; der Fuzhou University, China, der Zheijiang University/ Hangzhou sowie der Jiao Tong University/Shanghai. Intensive Projektkooperationen gibt es im Bereich von molekularen Bio-Systemen insbesondere mit dem Weizmann Institute/Israel, der ETH Zürich, und dem Burnham Institute for Medical Research.

Bilaterale- und Kooperationsprojekte bestehen zurzeit unter der Förderung der European Space Agency (ESA), der Deutschen Forschungsgemeinschaft (DFG), der German Israel Foundation (GIF) for Scientific Research and Development, mit Belgien, China, Frankreich, Griechenland, Großbritannien, Irland, Italien, Israel, Niederlande, Russland, Schweiz, und den USA.

In enger Zusammenarbeit mit dem Ludwig-Boltzmann Institut für Osteologie in Wien (Österreich) wird an klinisch orientierter Knochenforschung gearbeitet.

Industriekooperationen, Verwertungsverträge, Ausgründungen

Das Institut hält gegenwärtig 39 Patente.

Im Zeitraum von 1993–2018 erfolgten folgende Ausgründungen: Capsulution Nanoscience AG, Colloid GmbH, Nanocraft GmbH, Nanolytics, Optrel, Riegler & Kirstein, Sinterface, Oxidion GmbH, Carbon Solutions GmbH, Glycouniverse, Artemiflow, Vaxxilon, and Fluxpharm.

Wissenschaftliche Beziehungen
Editorial Boards

Unsere Wissenschaftler fungieren als Gutachter und Berater von fachspezifischen Zeitschriften und Journalen. In der folgenden Liste sind nur die Wissenschaftler angeführt, die entweder Herausgeber oder Mitglied eines Editorial Boards sind. Des Weiteren informieren wir Sie über Mitgliedschaften in Fachbeiräten.

Editorial Boards und Editorial Advisory Boards:

- ACS Chemical Biology (P. H. Seeberger)
- Advanced Engineering Materials (P. Fratzl)
- Advanced Functional Materials (P. Fratzl)
- Advanced Healthcare Materials (P. Fratzl)
- Advances in Carbohydrate Chemistry and Biochemistry (P. H. Seeberger)
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- Bioinspiration & Biomimetics (P. Fratzl)
- Biophysical Reviews and Letters (K. G. Blank)
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- Bioorganic & Medicinal Chemistry (P. H. Seeberger)
- Calcified Tissue International (P. Fratzl)
- ChemBioChem (P. H. Seeberger)
- Chemistry of Materials (M. Antonietti)
- Colloid & Polymer Science (M. Antonietti)
- Current Opinion in Chemical Biology (P. H. Seeberger)
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- Frontiers in Molecular Biosciences (K.G. Blank)
- Journal of Biotechnology (P. H. Seeberger)
- Journal of Carbohydrate Chemistry (P. H. Seeberger)
- Journal of Flow Chemistry (P. H. Seeberger)
- Journal of Structural Biology (P. Fratzl)
- Journal of Statistical Physics (R. Lipowsky)
- Langmuir (M. Antonietti)
- Macromolecular Biosciences (P. H. Seeberger)
- Macromolecular Journals of Wiley-VCH (M. Antonietti)
- Materials Chemistry (M. Antonietti)
- Materials Horizons (M. Antonietti)
- New Journal of Chemistry (M. Antonietti)
- Journal of Rheology (M. Antonietti)
- PeerJ (K. G. Blank)
- PLOS ONE (K. G. Blank)
- Polymer (M. Antonietti)
- Progress in Polymer Science (M. Antonietti)
- Review in Molecular Biotechnology (M. Antonietti)
- Science Magazine (P. Fratzl)
- Soft Matter (M. Antonietti)

Fachbeirat:

- Alberta Ingenuity Centre for Carbohydrate Science, Canada (P. H. Seeberger)
- B-Cube Dresden, (P. Fratzl, Scientific Advisory Board, Chair)
- Behnken-Berger-Stiftung, Berlin (P. Fratzl, Board of Trustees)
- Chinese Academy of Sciences Institute of Nanosciences (M. Antonietti, Scientific Advisory Board)
- CIC biomaGUNE, San Sebastian, Spain (P. H. Seeberger)
- Dutch Catalysis Excellence Cluster (M. Antonietti, Evaluation Board)
- IdEx Bordeaux (Initiative of Excellence of Bordeaux (M. Antonietti, Scientific Advisory Board)
- Institute for Science & Technology Austria (P. Fratzl, Scientific Advisory Board, Chair)
- Leibniz Institute of Polymer Research Dresden (P. Fratzl, Board of Trustees)
- Massachusetts Institute of Technology (MIT), Cambridge, MA, USA (P. Fratzl, Corporation Visiting Committee)
- Matters of Activity, Excellence Cluster (Co-spokes person)
- National Science and Technology Development Agency (NSTDA), Thailand (M. Antonietti, International Advisory Committee)
- National Nanotechnology Center (NANOTEC), Thailand (M. Antonietti, Scientific Advisory Board)
- PolyMat San Sebastian (M. Antonietti, Scientific Advisory Board)
- Projekthaus NanoBioMater, University Stuttgart (P. Fratzl, Advisory Board)
- Ray Jaime I Committee (M. Antonietti, Advisory Board)
- WYSS Institute for Bioinspired Engineering at Harvard
- University (P. Fratzl, Scientific Advisory Board)

Scientific Relations

The MPICI is collaborating intensively with universities and research institutes at the regional, national, and international level. Some of these collaborations will be highlighted in the following subsections.

Regional Networks
At regional level, formal cooperation agreements have been signed with the University of Potsdam in 1995 and the Humboldt University Berlin in 2005. Markus Antonietti and Peter H. Seeberger are honorary professors at the University of Potsdam, Prof. Peter Fratzl and Prof. Reinhard Lipowsky at both universities, and Prof. Peter Seeberger is an honorary professor at the Free University of Berlin. Prof. Jürgen Rabe (Physics Department, Humboldt University) is an external scientific member of the MPICI since 2005, Prof. Joanna Aizenberg (Amy Smith Berylson Professor of Materials Science at Harvard's School of Engineering and Applied Sciences) and Prof. Ulrich S. Schubert (Faculty of Chemistry and Earth Sciences Friedrich-Schiller-Universität Jena) are external scientific members since 2017.

Additional cooperation agreements exist with the Helmholtz Center of Materials and Energy (former Hahn Meitner Institute and BESSY) about the joint operation of neutron scattering instruments and synchrotron x-ray beamlines, and with the Federal Institute for Materials Research and Testing (BAM) for running a microfocus beamline.

The MPIKG, the University of Potsdam, the Humboldt University and the Free University Berlin closely collaborate in the framework of the International Max Planck Research School. The first International Max Planck Research School (IMPRS) on „Biomimetic Systems" has been successfully operated for twelve years until fall 2012. The second IMPRS on „Multiscale Bio-Systems" has started in 2013, and its funding will last until 2025. The school is focussing on hierarchical structures of bio-systems on supramolecular and mesoscopic scales between a few nanometers and many micrometers. The speaker of the school is Reinhard Lipowsky.

In addition, the MPICI participates in other graduate schools:

- International Research Training Group on "Self-assembled Soft Matter Nano-Structures at Interfaces (coordinated by the TU Berlin),
- „Berlin-Brandenburg School of Regenerative Therapies" (coordinated by the Charité Hospital, Berlin),
- SALSA, the Graduate School of Analytical Sciences Adlershof (coordinated by the Humboldt University Berlin),
- ZIBI Graduate School, Center of Infection Biology and Immunity (ZIBI) (coordinated by the FU Berlin)
- Research Training Group 2046 "Parasite Infections: From Experimental Models to Natural Systems" (coordinated by the FU Berlin)

The MPICI takes part in several collaborative research centers („Sonderforschungsbereiche" SFB) of the German Research Foundation (DFG):

- SFB 1340: In vivo Visualization of Extracellular Matrix Pathology „Matrix in Vision", coordinated by Charité Medical School
- SFB 1114: Scaling Cascades in Complex Systems, coordinated by the Free University
- Transregio SFB-TR 84 "Innate Immunity of the Lung: Mechanisms of Pathogen Attack and Host Defence in Pneumonia", coordinated by Charité Medical School

In the "Glyco3Display" project, a team from the Fraunhofer Institute for Cell Therapy and Immunology (IZI), in collaboration with the Max Planck Institute for Colloids and Interfaces, is creating a new group of substances that could act as an innovative antimicrobial agent. Thus, receptors could be blocked so that pathogens are no longer able to dock on human cells and infect them.

Apart from this, the MPICI participates in the Berlin-Brandenburg Center for Regenerative Therapies (BCRT) and in the Cluster of Excellence "Matters of Activity. Image Space Material" (where P. Fratzl is co-spokesperson), which is primarily located at the Humboldt University of Berlin.

The Cluster of Excellence "Unifying Systems in Catalysis (UniSysCat) – How to Understand and Utilize Networks in Catalysis" is another important project. Headed by the Technical University Berlin, it can build on ten years of outstanding work by UniCat, the previous cluster of the Excellence Initiative. Here the MPICI was already participating.

National and International Collaborations
Within the European framework program "HORIZON2020", the institute is involved in three projects, including one ERC Starting Grant.

Furthermore, the MPICI is a member of the research consortium MaxSynBio. This is dedicated to Synthetic Biology and funded by the Max Planck Society and the Federal Ministry of Education and Research. Research groups from nine Max Planck Institutes across Germany, as well as the Department of Theology of the Friedrich Alexander University Erlangen-Nuremberg, are involved. The project started 2014 and will run for six years.

Moreover the institute is also a member of the project „Big-Data Driven Materials Science (BiGmax) coordinated by the Fritz Haber Institute in Berlin and the project MaxWater coordinated by the MPI for Polymer Research in Mainz, both funded by the Max Planck Society.

Together with the Max Planck Institute of Molecular Physiology in Dortmund and the Riken Advanced Science Institute (ASI) in Wako, the MPICI is a principle partner of the RIKEN-Max Planck Joint Research Center for Chemical Systems Biology.

The research center promotes the more effective use of research resources as well as information and technology in the field of chemical systems biology.

In 2017, the Indian Institute of Technology (BHU)-Varanasi and the MPICI have entered into a research collaboration. The Indo-German Max Planck Partner group is focusing on the use of carbohydrate synthesis to unravel the potency of carbohydrate marine natural products as materials and for medical uses.

Nanyang Technological University, Singapore (NTU Singapore) and the MPICI have launched the „Max Planck-NTU Joint Laboratory for Artificial Senses" in 2019 to conduct research in artificial senses and develop innovative robotics and healthcare solutions.

Moreover "Joint laboratories" and international partner groups have been established with the National Laboratory for Physical Sciences at Microscale (CAS) in Hefei, China; with the Fuzhou University, China, with the Zheijiang University/Hangzhou, as well as with the Jiao Tong University/Shanghai. Project cooperation in the area of molecular biosystems is, among many others, cultivated with the Weizmann Institute/Israel, the ETH Zürich, and the Burnham Institute for Medical Research.

In addition to the collaborations described, a number of collaborations also exist, which are for example funded by the European Space Agency (ESA), the German Research Foundation (DFG), German Israel Foundation (GIF) for Scientific Research and Development as well as the involvement of the national funding agencies of Belgium, Commonwealth of Independent States (CIS), China, France, Greece, Ireland, Italy, Israel, the Netherlands, Switzerland, UK and the USA.

Clinically oriented bone research is carried out in close collaboration with the Ludwig Boltzmann Institute of Osteology in Vienna (Austria).

Industrial Cooperations, Patents and Spin-Offs
At present the MPICI maintains 39 patents.

In the time period from 1993 to 2018, the following spin-offs have been launched: Capsulution Nanoscience AG, Colloid GmbH, NanocraftGmbH, Nanolytics, Optrel, Riegler & Kirstein, Sinterface, Oxidion GmbH, Carbon Solutions GmbH, Glycouniverse, Artemiflow, Vaxxilon, and Fluxpharm.

Editorial and Advisory Boards
MPICI scientists serve as editors, reviewers and advisors for many journals. In the following only activities as editor or editorial board member are listed. In addition, a list of advisory board memberships can be found.

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- Advanced Engineering Materials (P. Fratzl)
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- Journal of Flow Chemistry (P. H. Seeberger)
- Journal of Structural Biology (P. Fratzl)
- Journal of Statistical Physics (R. Lipowsky)
- Langmuir (M. Antonietti)
- Macromolecular Biosciences (P. H. Seeberger)
- Macromolecular Journals of Wiley-VCH (M. Antonietti)
- Materials Chemistry (M. Antonietti)
- Materials Horizons (M. Antonietti)
- New Journal of Chemistry (M. Antonietti)
- Journal of Rheology (M. Antonietti)
- PeerJ (K. G. Blank)
- PLOS ONE (K. G. Blank)
- Polymer (M. Antonietti)
- Progress in Polymer Science (M. Antonietti)
- Review in Molecular Biotechnology (M. Antonietti)
- Science Magazine (P. Fratzl)
- Soft Matter (M. Antonietti)

Advisory Boards:

- Alberta Ingenuity Centre for Carbohydrate Science, Canada (P. H. Seeberger)
- B-Cube Dresden, (P. Fratzl, Scientific Advisory Board, Chair)
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- CIC biomaGUNE, San Sebastian, Spain (P. H. Seeberger)
- Dutch Catalysis Excellence Cluster (M. Antonietti, Evaluation Board)
- IdEx Bordeaux (Initiative of Excellence of Bordeaux) (M. Antonietti, Scientific Advisory Board)
- Institute for Science & Technology Austria (P. Fratzl, Scientific Advisory Board, Chair)
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- PolyMat San Sebastian (M. Antonietti, Scientific Advisory Board)
- Projekthaus NanoBioMater, University Stuttgart (P. Fratzl, Advisory Board)
- Ray Jaime I Committee (M. Antonietti, Advisory Board)
- WYSS Institute for Bioinspired Engeneering at Harvard University (P. Fratzl, Scientific Advisory Board)

Internationale Max Planck Research School (IMPRS) on Multiscale Bio-Systems

In Zusammenarbeit mit der Universität Potsdam, der Freien Universität Berlin, der Humboldt Universität Berlin und dem Fraunhofer Institut für Zelltherapie und Immunologie IZI hat das MPIKG im Jahr 2013 eine neue IMPRS zum Thema „Multiscale Bio-Systems" etabliert. Der Sprecher der Schule ist Prof R. Lipowsky, der Vize-Sprecher ist Prof R. Seckler und der Koordinator ist Dr. A. Valleriani. Das Graduiertenprogramm vermittelt grundlegende Kenntnisse über Biosysteme in Makromolekülen und wässrigen Lösungen, über molekulare Erkennung zwischen den Grundbausteinen, freie Energieübertragung bei molekularen Maschinen sowie Strukturbildung und Transport in Zellen und Geweben. Diese Forschungsaktivitäten konzentrieren sich auf vier Kernbereiche: Molekulare Erkennung von Biopolymeren, Photoinduzierte molekulare Prozesse, zellähnliche Systeme und Prozesse sowie gewebeähnliche Systeme und Prozesse. Ein Hauptziel der IMPRS ist ein quantitatives Verständnis der Prozesse auf supramolekularer und mesoskopischer Ebene im Größenbereich zwischen einigen Nanometern und vielen Mikrometern. Der interdisziplinäre Ansatz verbindet bottom-up und top-down Ansätze, die von verschiedenen Gruppen in Theorie und experimenteller Biophysik, in Physik und Kolloidchemie sowie in Biochemie und Molekularbiologie verfolgt werden.

Rahmenbedingungen

Das englischsprachige Doktorandenprogramm bietet aktuelle Themen interdisziplinärer Forschung und wurde für bis 2025 genehmigt. Hauptverantwortlicher der Schule ist das Max-Planck-Institut für Kolloid- und Grenzflächenforschung. Im Einklang mit den allgemeinen Regeln der IMPRS kommt weniger als die Hälfte der zugelassenen Studenten aus Deutschland. In den Jahren von 2013 bis 2018 sind circa 1.800 Bewerbungen eingegangen, aus denen 42 Doktoranden ausgewählt wurden, 15 von ihnen aus Deutschland, der Rest aus 13 anderen Ländern. Die Auswahl der Studenten findet in einem dreistufigen Verfahren statt, bei dem die Kandidaten sich zuerst auf ein Projekt bewerben, das von zwei oder mehr Fakultätsmitgliedern angeboten wird. In der zweiten Stufe wird eine Auswahl von Bewerbern zu Interviews mit den Fakultätsmitgliedern eingeladen. In einem dritten Schritt müssen die besten Bewerber den IMPRS-Lenkungsausschuss und ihre Betreuer überzeugen, um einen Doktorandenvertrag zubekommen.

Lehrprogramm

Jeder Doktorand arbeitet an einem Projekt unter Aufsicht eines „Dissertationskommitees", das aus mindestens drei Betreuern besteht, welche sich regelmäßig mit dem Doktoranden treffen, um seine Fortschritte und eventuelle Änderungen des Projekts zu besprechen. Die IMPRS organisiert zwei Workshops im Jahr, zu denen sich alle Gruppen treffen um über ihre jeweiligen Projekte zu diskutieren und sich auszutauschen. Vorträge der Doktoranden und viel Zeit während der Poster-Präsentationen erlauben es jedem, persönlich mit den Doktoranden und ihren Betreuern zu sprechen.

Sie bietet auch eine Vielzahl von Veranstaltungen zu Soft Skills – von Workshops zum wissenschaftlichen Schreiben, über Übungen zu Präsentationstechniken bis hin zu Deutschkursen und Vorträgen zu Karriereperspektiven in Kollaboration mit den Universitäten und der lokalen Startup Academy in Golm.

Das Graduiertenprogramm bietet auch Semesterkurse an, wo einzelne Themengebiete vertieft werden. Bis zum Wintersemester 2018/19 gab es 61 solcher Kurse, in denen Themengebiete von Biochemie bis statistischer Physik behandelt wurden, um die Kluft zwischen den einzelnen Teildisziplinen zu überbrücken. Gruppenleiter, Nachwuchsgruppenleiter und Professoren des MPIKG, der Universität Potsdam, der FU Berlin, der HU Berlin nehmen an dem Programm teil und bieten Training und Mentoring an.

Weitere Informationen finden Sie unter:
imprs.mpikg.mpg.de

Reinhard Lipowsky und Angelo Valleriani

International Max Planck Research School (IMPRS) on Multiscale Bio-Systems

In collaboration with the University of Potsdam, the Free University Berlin, the Humboldt University Berlin, and the Fraunhofer Institute for Cell Therapy and Immunology IZI, the MPICI now offers a new IMPRS on "Multiscale Bio-Systems".The speaker of the school is R. Lipowsky, the vice-speaker is R. Seckler, and the coordinator is A. Valleriani. The new IMPRS started its training activities in the winter semester 2013/2014. The IMPRS addresses the fundamental levels of Biosystems as provided by macromolecules in aqueous solutions, molecular recognition between these building blocks, free energy transduction by molecular machines as well as structure formation and transport in cells and tissues. The research activities are focused on four core areas: Molecular recognition of biopolymers, Photo-induced molecular processes, Cell-like systems and processes, Tissue-like systems and processes. One general objective is to understand, in a quantitative manner, how the processes on supramolecular and mesoscopic scales between a few nanometers and many micrometers arise from the structure and dynamics of the molecular building blocks. The interdisciplinary research combines bottom-up with top-down approaches, which are pursued by several groups from theoretical and experimental biophysics, from physical and colloid chemistry as well as from biochemistry and molecular biology.

General Framework

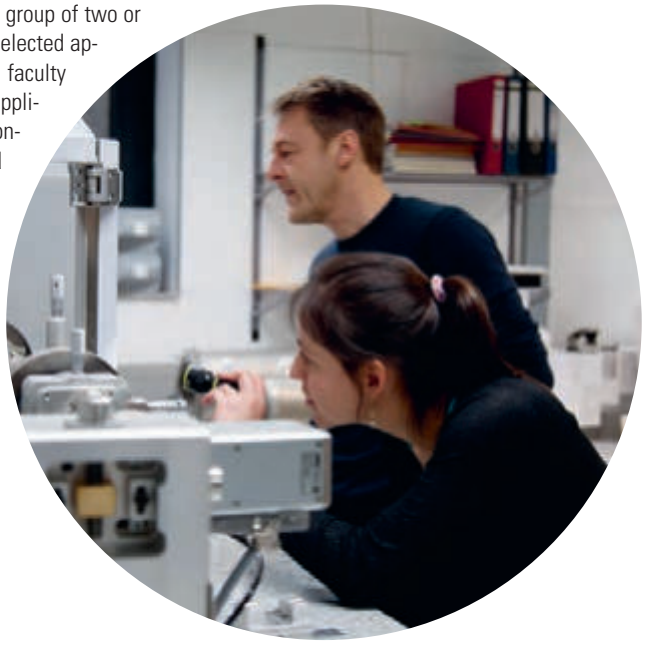
The English-speaking doctoral program offers cutting-edge, interdisciplinary research and has been approved until 2025. Headquarter of the school is the MPI of Colloids and Interfaces. In line with the general rules for all IMPRS, less than half of the admitted students can be from Germany. In the years from 2013 to 2018, we have received about 1.800 applications and recruited 42 doctoral students, 15 from Germany and the rest from 13 different countries. The recruitment of new students is based on a three-step procedure, in which applicants first apply for a project proposed by a group of two or more faculty members. In a second stage, selected applicants are invited for an interview by the faculty members,who evaluate the quality of each applicant. Finally, those candidates who have convinced the IMPRS steering committee and their future supervisors receive an offer.

Research Training Activities

Every doctoral student works on a project under the supervisionof a Thesis Committee composed of at least three persons, who meet regularly to discuss progresses and adjustments of the project. The school organizes two workshops per year, where all groups meet and discuss about each of the current projects. Talks by the doctoral students and plenty of time during the poster session allow anybody to personally discuss with the doctoral students and their supervisors. The school offers a variety of soft skills events, including workshops on scientific writing, presentation skills, German language courses as well as lectures on career possibilities in collaboration with the Universities and with the local StartUp Academy in Golm. The school also offers semester courses to cover broad topics in depth. Until the winter semester 2018/19, the school has offered 61 courses, covering topics from biochemistry to statistical physics, in order to bridge the gap between different disciplines. Group leaders, junior group leaders and professors of the Max Planck Institute of Colloids and Interfaces, Potsdam University, FU Berlin, HU Berlin participate in the program and offer training and mentorship.

For further information see:
imprs.mpikg.mpg.de

Reinhard Lipowsky and Angelo Valleriani



Presse- und Öffentlichkeitsarbeit

Das Max-Planck-Institut für Kolloid- und Grenzflächenforschung informiert innerhalb seiner Presse- und Öffentlichkeitsarbeit über die wissenschaftlichen Innovationen am Institut und deren Ergebnisse in Lehre, Forschung und Anwendung. Auf diese Weise möchten wir ein eigenständiges, positives Image und Vertrauen schaffen. Gleichzeitig soll dazu beigetragen werden eine Brücke von der Lehr- und Forschungsstätte in die Öffentlichkeit zu schlagen, aktuelle Impulse aufzunehmen, neue Ideen zu finden und umzusetzen. Ein Hauptziel ist es, unsere aktuelle Forschung in das Bewusstsein der allgemeinen Öffentlichkeit, der Politik, der Presse, unserer KooperationspartnerInnen, zukünftiger StudentInnen, ehemaliger Institutsangehöriger sowie der internen Gemeinschaft zu bringen. Aufmerksamkeit und Interesse für die Wissenschaft und damit letztendlich Akzeptanz, Sympathie und Vertrauen zu gewinnen, gehören zu unseren wichtigsten Anliegen.

Fach- und Publikumsjournalisten werden über das aktuelle Geschehen mit Hilfe von fundierten Nachrichten und Hintergrundwissen informiert. Regelmäßig veröffentlichen wir unseren Zweijahresbericht, Presse-Informationen, beantworten Presseanfragen und halten zu den Medienvertretern persönlichen Kontakt. Neben der klassischen Pressearbeit stellt die Konzeption, Organisation und Durchführung von Veranstaltungen den zweiten Tätigkeitsschwerpunkt des Referats dar.

Auf den Wurzeln zweier Institute der ehemaligen Akademie der Wissenschaften gegründet, gibt es das Max-Planck-Institut für Kolloid- und Grenzflächenforschung schon mehr als 25 Jahre lang in Brandenburg. Am bundesweiten Max-Planck-Tag, wurde dieses Jubiläum am 14. September 2018 gebührend gefeiert.

Ein weiterer Höhepunkt war der Potsdamer Tag der Wissenschaften, der am 13. Mai 2017 im Wissenschaftspark Potsdam-Golm durchgeführt wurde. In über 200 Einzelveranstaltungen präsentierten sich 40 Hochschulen und Forschungseinrichtungen aus Brandenburg und luden ein, die Brandenburgische Wissenschaftslandschaft kennenzulernen. Von 13 bis 20 Uhr hatten die rund 15.000 Besucher die Möglichkeit, hinter die Kulissen der interdisziplinären und internationalen Grundlagenforschung und angewandten Wissenschaften zu schauen.

Darüber hinaus werden am Institut Führungen für Interessierte, insbesondere für Schulklassen, sowie Vorträge an den Schulen selbst organisiert. Das Institut beteiligt sich ebenfalls jedes Jahr am „Zukunftstag für Mädchen und Jungen im Land Brandenburg“. Ehemalige Mitarbeiter des Max-Planck-Instituts für Kolloid- und Grenzflächenforschung arbeiten auf der ganzen Welt. Sie sind in der Wissenschaft, Wirtschaft und Verwaltung tätig, beeinflussen Entwicklungen und zukünftige Strukturen – Grund genug, alljährlich ein Ehemaligentreffen zu veranstalten, welches über die „Trends in Colloids and Interface Science“ informiert.

Der Internetauftritt, aber auch die interne Kommunikation stellen zudem weitere wichtige Bereiche der Öffentlichkeitsarbeit dar. Wir sehen es als Aufgabe an, die Bedeutung der Grundlagenforschung und der zukünftigen Entwicklungen in der Kolloid- und Grenzflächenforschung an die breite Öffentlichkeit zu transportieren. Entdecken Sie auf den folgenden Seiten, dass Wissenschaft faszinierend, kreativ und fesselnd ist! Sollten Sie bei auftretenden Fragen unsere Hilfe benötigen, unterstützen wir Sie jederzeit gern.

Katja Schulze
Presse- und Öffentlichkeitsarbeit
katja.schulze@mpikg.mpg.de

Press and Public Relations

Press and Public Relations at the Max Planck Institute of Colloids and Interfaces serve as the interface between scientists' work and the public. We inform you about the research results, and want to create an independent, positive image and thus trust in scientific work. Simultaneously we try to bridge the gap between research institution and general public and hence get new impetus and ideas. We promote the perception of our research among the community, the press, government, corporate partners, prospective students, alumni and our own internal community. It is a matter of great importance that not only the scientific community but in fact anyone interested in modern science should have the opportunity to get an idea about the aims of our institute. Attention, interest and finally trust in science must be one of our most important concerns. Therefore we inform journalists with profound news and background knowledge about current research. To pursue this task press releases are edited, brochures – such as this Report – are published and distributed on request and informal support is provided whenever necessary.

Besides classical Press and Public Relations the complete conception, organization and realization of events is a second core theme.

Based on the roots of two former institutes of the Academy of Sciences the Max Planck Institute of Colloids and Interfaces now exists for more than than 25 years in Brandenburg. On this occasion, we celebrated our anniversary at the nationwide Max Planck Day on September 14th, 2018.

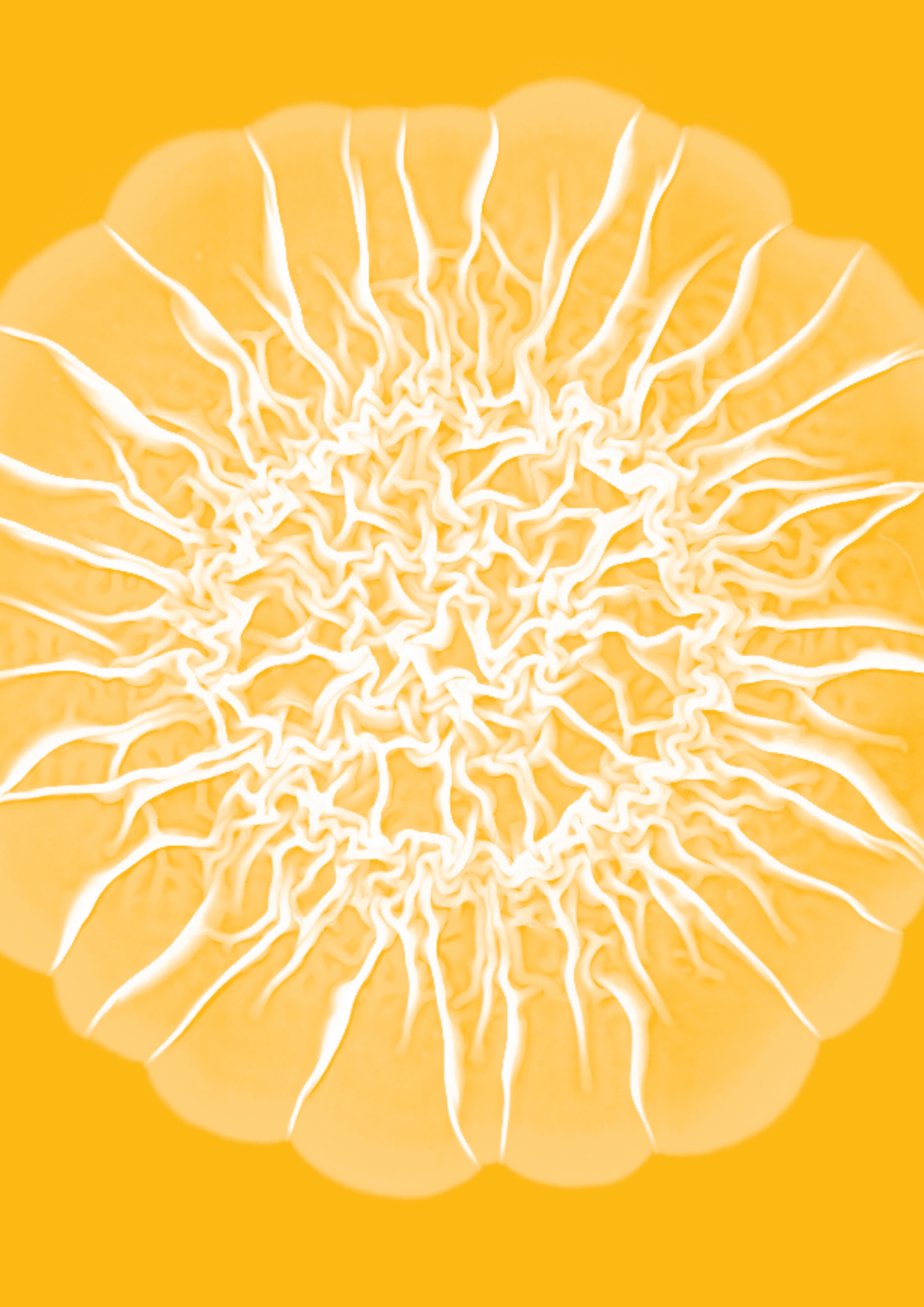
Another highlight was the "Potsdame Day of Science" which took place on May 13th, 2017 in the Potsdam-Golm Science Park. 40 universities and research institutes from Brandenburg presented themselves with more than 200 individual events. From 1 pm to 8 pm about 15.000 visitors took the chance to look behind the scenes of interdisciplinary and international basic science as well as applied science.

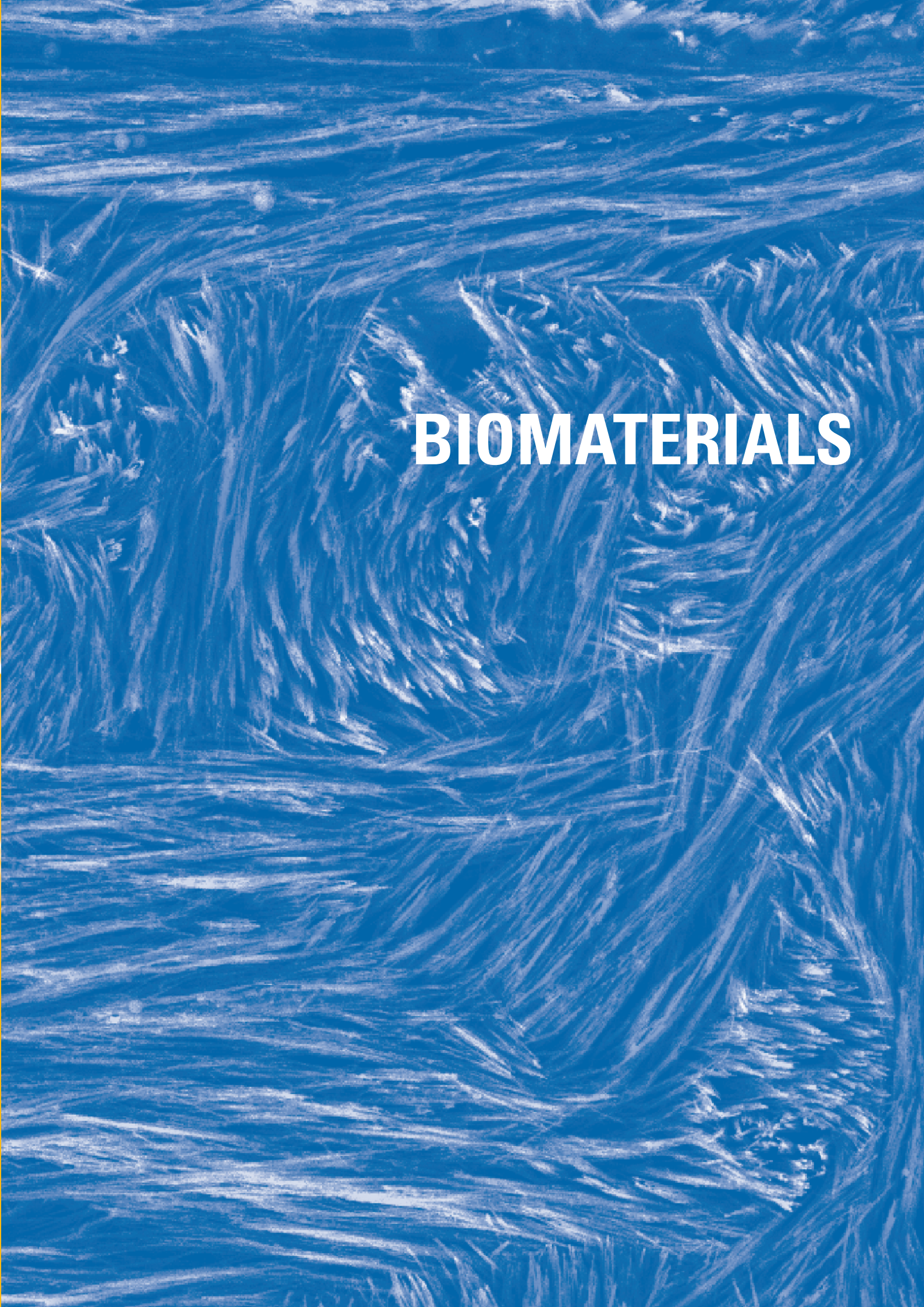
Moreover, the institute takes part in the „Zukunftstag für Mädchen und Jungen im Land Brandenburg" every year.

Former members of the Max Planck Institute of Colloids and Interfaces work around the world. They are employed in science, business and administration, influence developments and future structures. Reason enough to organize together with the "Freunde der Kolloid- und Grenzflächenforschung e.V." an annual alumni meeting, which informs about the „Trends in Colloids and Interface Science". This forum enables alumni to stay in touch with other alumni, their department and the institute at large, providing both personal and professional benefits.

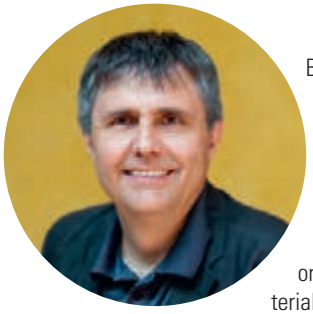
But also the internet presence and the internal communication are additional important fields within Press and Public Relations. We try to create awareness for the role of basic research in general, especially with regard to future developments in colloid and interface science. We also seek to show that the world of science and technology is fascinating, challenging, varied and rewarding. Within these pages you can find the latest news from the institute as well as a more in depth look at our research. If you have any further questions, please contact us. We are pleased to help you.

Katja Schulze
Press and Public Relations
katja.schulze@mpikg.mpg.de




BIOMATERIALS

DEPARTMENT OF BIOMATERIALS



Peter Fratzl
13.09.1958
1980: Diploma (Ingénieur Diplômé de l'Ecole Polytechnique, Paris)
1983: PhD, Physics (University of Vienna)
1981–1985: Research Scientist (Austrian Academy of Sciences, Vienna; Laboratoire Leon Brillouin, Saclay, France); Visiting Research Fellow (Hahn Meitner Institute, Berlin; New York University)
1986–1998: Assistant and Associate Professor (Institute for Materials Physics of the University of Vienna, Austria)
1988 and 1989: Visiting Professor (Rutgers University, New Jersey, USA)
1991: Habilitation, Solid State Physics (University of Vienna)
Since 1993: Associated member (Ludwig Boltzmann Institute of Osteology, Vienna).
1993-1994: Visiting Research Fellow (Heriot-Watt University, Edinburgh)
1997: Visiting Professor, (Physics Department of the University of Munich)
1998–2003: Chair of Metal Physics (University Leoben, Austria)
Director (Erich Schmid Institute for Materials Science of the Austrian Academy of Sciences)
Since 2003: Director, Department of Biomaterials (Max Planck Institute of Colloid and Interfaces, Potsdam-Golm)
Since 2004: Honorary Professor of Physics at Humboldt University Berlin
Since 2009: Honorary Professor (Physics of Biomaterials) at the Potsdam University, Fellow of the Materials Research Society, Member of the Austrian Academy of Sciences, the Academy of Science and Literature Mainz, ACATECH as well as the Berlin-Brandenburg Academy of Sciences)
Since 2017: Chair of the Chemistry/Physics/Engineering Section of the Max Planck Society

Biological Materials Science is the overall research field covered by the Department. This encompasses research on the structure and behavior of biological materials with an emphasis on biological or biomedical questions. It also includes research to uncover principles by which engineering problems were solved by organisms through evolution. Examples are materials combining stiffness and fracture resistance or providing capabilities for sensing, self-healing or shape-change. Many types of natural materials are addressed in the Department. They are generally based on natural polymers, such as cellulose, chitin or protein (collagen and others) as well as minerals in some cases.

This research is carried out by scientifically independent research groups with diverse backgrounds including mathematics, physics, chemistry, materials science, physical chemistry, biochemistry, wood science, botany and zoology. The group leaders were assembled based on their scientific excellence and their capability of collaborating – where needed – with the other groups in the department as well as with its director who contributes his expertise in general materials science, x-ray scattering and mechanical modeling. This strategy is outlined in **Fig. 1** which shows two arrows, from the study of biological materials to bio-inspired materials and to medical applications. This figure also mentions all the research groups that are submitting reports on the following pages. In comparison to the last report (2015–16), several groups moved to different endeavors: Matt Harrington took a professor position at McGill University, Montreal, Canada; Katja Skorb moved to a professor position in St. Petersburg, Russia and John Dunlop took a chair of physics at the University of Salzburg in Austria. Igor Zlotnikov is now heading a BMBF research group at TU Dresden, Wouter Habraken moved to a career in teaching and Reinhard Miller went into retirement. Damien Faivre is present in this volume with a report, although he moved in 2018 to a position at the CEA Research Center in Cadarache, France. Finally two new research groups are now present in the Department: Cécile Bidan joined as a group leader to work on bacterial biofilms; Amaia Cipitria won an Emmy Noether Group Award from the German Research Foundation (DFG) to work on materials science aspects of cancer cell dormancy.

While the research work in the Department has always been interdisciplinary within the sciences (mostly physics, chemistry, biology and engineering), steps have been taken in the last years to address materials issues in an even wider perspective, including also various disciplines from humanities and from design (Gestaltung). This mainly happened through an initiative of the director who participated in the Excellence Cluster "Image-Knowledge-Gestaltung" at Humboldt University as principle investigator and, in the last two years, as one of the spokespersons. The goal was to establish an interdisciplinary laboratory (see also **Fig. 1**) where issues of joint interest between disciplines can be discussed. This led to the definition of a new Cluster Initiative "Matters of Activity" that was granted starting 2019. Peter Fratzl is principal investigator and one of the spokespersons and four of the group leaders are involved as associated investigators: Michaela Eder, Mason Dean, Cécile Bidan and Richard Weinkamer. The general goal of this Cluster that involves science, humanities and design disciplines is to develop a new culture of the material (see below).

Natural Materials Based on Proteins, Lipids, Polysaccharides

Yael Politi studies the structure, properties and bio-synthesis of the cuticle of arthropods and insects, such as spiders or locusts. This cuticle supports a variety of tools and sensory devices that are essential for the survival of the animal. The fiber architecture of the cuticle as well as its composite character comprising chitin, protein and water are key for its functionality.

Michaela Eder works with her research group primarily on cellulose-based biological materials, such as wood and certain seed capsules that open with changing air humidity or temperature. These capsules are particularly interesting because they represent models for shape-changing polymeric materials potentially useful in soft robotics.

Emanuel Schneck runs an Emmy-Noether group (supported by DFG) on the physics of biomolecular interfaces. The research addresses interaction between membranes and with biomolecules. He makes use of x-ray and neutron reflectivity studies as well as numerical modeling.

Although Matt Harrington left already in 2016 to take a professorship in Canada, several PhD-students stayed at the Max Planck Institute to finish their work, mainly supervised by him through electronic media and by the MPI-director. Results were published on structure and properties of the byssus fibers by which different sea shells attach to rocks **[1]**, as well as polymeric materials inspired by them **[2, 3]**. Another recent work concentrated on the origins of the supercontraction of silk fibers with hydration, a collaboration with Admir Masic, another former Department member now at MIT **[4]**.

Biomineralized Tissues

Mason Dean studies cartilaginous skeletal elements of sharks and rays and, in particular, the formation, structure and mechanical performance of tesserae, mineralized tiles covering all skeletal elements. He reports recent work showing that these tesserae not only consist of mineralized cartilage based on collagen type II and proteoglycans but also contain collagen type I, which is typical for mammalian bone but is not expected to exist in cartilage.

Damien Faivre has been heading until 2018 a group focusing on magnetotactic bacteria and the synthesis and application of magnetic nanoparticles. He is also interested in magnetic microswimmers and in other types of biomineralization (not based on magnetite). He recently moved to the CEA research center in Cadarache, France.

Luca Bertinetti reports on the structure of biogenic mineral crystals and the transformation of transient amorphous phases into crystalline structures. The role of water in biological materials (with and without mineral) is an important part of this research.

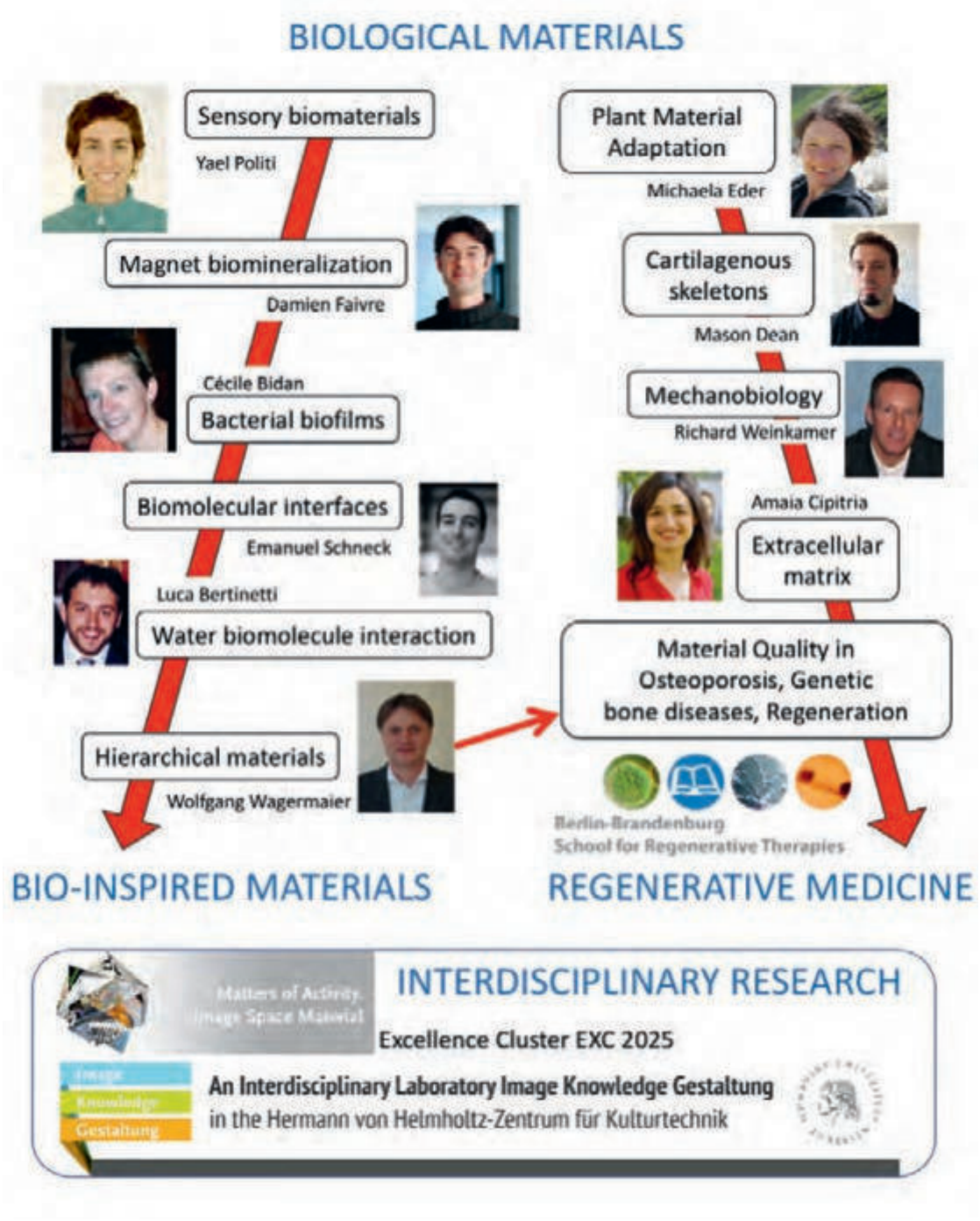


Fig. 1: Research strategy of the Biomaterials Department. A network of research groups covers a variety of topics starting with the analysis of (hierarchical) structure and properties of biological materials, based on proteins, polysaccharides and/or mineral in connection to their biological function as well as their biosynthesis. This research is pushed either towards the development of new bio-inspired material concepts (left arrow) or towards biomedical applications (right arrow). Within the Excellence Cluster "Image Knowledge Gestaltung" (2012-2018) and the follow-up Cluster "Matters of Activity" (2019 onwards), this research is also put into a wider interdisciplinary context including science, engineering, humanities and design disciplines. All research group leaders mentioned in this picture are submitting their independent research report in this book.

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Richard Weinkamer uses primarily numerical modeling tools to study the response of biological tissues to mechanical stimulation. Osteocyte networks in bone are currently in the focus of the research in his group.

Wolfgang Wagermaier studies the mineralization of the callus appearing during bone healing and carries out research on the structure and properties of bio-inspired materials.

Other recent work on biomineralized tissue was done in collaboration with the Ludwig Boltzmann Institute in Vienna Austria, studying a mouse model for brittle bone disease **[5]**, as well as with Paul Zaslansky, an alumni of the Department now at Charité Berlin, on bone development through an analysis by micro-computed x-ray tomography **[6, 7]**. Together with the Humboldt Award Winner F. Dieter Fischer from Montanuniversität Leoben (Austria), we modeled the propagation of cracks in lamellar bone **[8]**. A very surprising result was obtained by two visiting scientists at the Institute, Yannicke Dauphin from Paris and Emil Zolotoyabko from the Technion in Haifa, Israel. While it is a paradigm in mineralogy that the visible faces of a mineral crystal reflect its crystallographic structure, it turns out that some sea shells use biological control to generate a "fake" orientation of calcite crystals where the crystallographic planes are oriented perpendicular to what one would expect from the visible shape of the calcite prisms **[9]**. One of the highlights in the area of biomineralization was the discovery of an entirely new crystalline (hydrated) calcium carbonate phase **[10]**.

Cell-material Interactions

Two new group leaders in the Department are addressing this topic from very different angles.

Cécile Bidan, a former PhD-student in the Department, returned as group leader after several years of postdoc in Netherlands, USA and France. In the past, she has been studying mammalian tissue growth in confined geometries and the influence of substrate curvature on tissue formation. In her new group she now focusses on bacterial biofilms and on the interplay between substrate properties and film morphology development, in particular wrinkling.

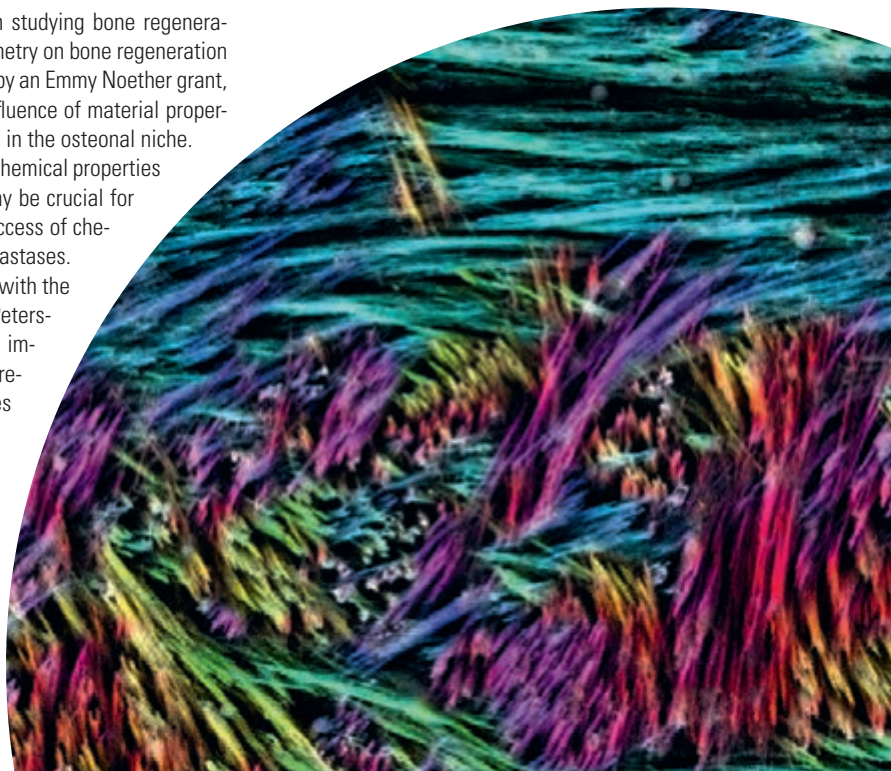
Amaia Cipitria has experience in studying bone regeneration and the impact of scaffold geometry on bone regeneration using engineered tissues. Financed by an Emmy Noether grant, she recently started to study the influence of material properties on the dormancy of cancer cells in the osteonal niche. The hypothesis is that physical and chemical properties of the material hosting the cells may be crucial for dormancy and, therefore, for the success of chemotherapies to remediate bone metastases.

Other work done in collaboration with the alumna Katja Skorb (now in St. Petersburg) relates to the modification of implant surfaces using ultrasound to create specific roughness that influences biological tissue growth **[11, 12]**.

Methodological Approaches

Our experimental approach is based on multi-method imaging where different probes are used to image the same specimen. This provides information on different features of the materials such as micro-structure, chemical composition, or mechanical properties in a position-resolved manner with micron-range resolution. We are currently developing and using multi-method characterization approaches combining x-ray tomography; scanning electron microscopy and scanning x-ray diffraction as well as spectroscopic imaging to characterize micro- and nanostructure and many levels of structural hierarchy (see also report by *W. Wagermaier*). We use nano-indentation as well as acoustic microscopy to estimate local mechanical properties. With modulus mapping techniques it is possible to push the lateral resolution of mechanical characterization into the nanometer range **[13]**. The strength of this multi-method approach is that the different parameters measured on the same specimen can be correlated at the local level with micron (or even smaller)-scale spatial resolution. In addition to our dedicated beamline end station for scanning small- and wide-angle scattering and fluorescence spectroscopy that is operated at the synchrotron BESSY at the Helmholtz Zentrum Berlin, we now started an new emphasis on electron microscopy. In addition to transmission electron microscopy where the institute (specifically the Department of Colloid Chemistry) is running a new facility, the Department of Biomaterials started an operation for (cryo)-focused ion beam 3D electron imaging (see report by *Luca Bertinetti*). This is an extremely promising technique which has the potential to revolutionize our understanding of cell and tissue structure, in particular mineralized tissues.

These characterization approaches are accompanied by a significant effort in mathematical modeling, which is always closely tied to the experimental work in the department. Typically, modeling and experimentation go hand in hand with the research projects (see the report by *Richard Weinkamer*).



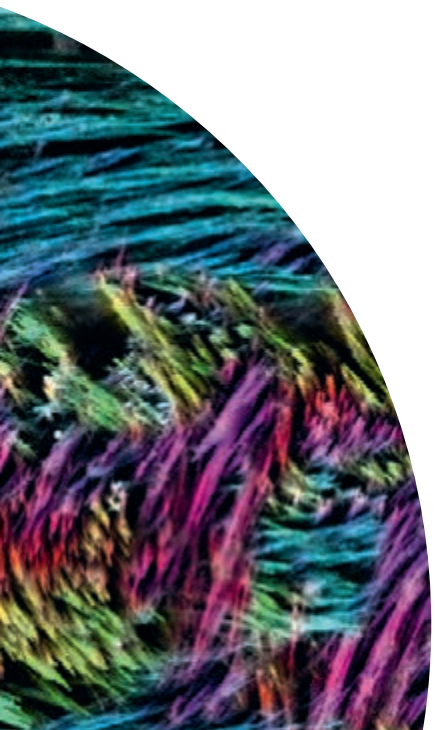
A New Culture of the Material

The classical concept that materials are a passive support for the activity of technical devices is currently challenged by research on active materials that are responsive or adaptive, which regenerate or allow shape changes. This poses challenging questions in many disciplines from science to humanites and design. The potential of collaborating with humanities and design disciplines in this research was originally explored by the Cluster of Excellence "Image-Knowledge-Gestaltung" supported by the German Science Foundation (DFG) at Humboldt University Berlin. During this period from 2012 to 2018, it was possible to develop this interaction that led to a number of exciting results such as joined books and a very successful exhibition ("+ultra – gestaltung schafft wissen" at Gropiusbau, Berlin, November 2016). The English version of the catalogue for this exhibition was published in 2017 **[14]**. This finally led to the application for a new excellence cluster "matters of activity" that started in January 2019.

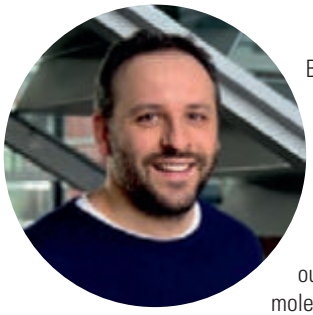
The general idea is that the future of digital industrial applications will require materials that are no longer passive components of active devices, but become themselves operational as carriers of information. Indeed, information stored in smart materials that are responsive and even adaptive does not need to be centrally processed which would be both too time and energy consuming. This is analogous to natural systems where every activity is distributed over many length scales, from molecules to tissues, organs and the whole organism, and where information is processed both in the periphery and centrally in the brain. The excellence cluster aims at addressing this issue in a completely interdisciplinary fashion, including scientific, historical and design perspectives. The goal is to develop a new culture of the material. https://www.matters-of-activity.hu-berlin.de/en

All in all, the majority of the research in the Department of Biomaterials involves collaborations – within the Department, with other Departments in the Institute and with many outside partners around the world to whom we all extend our sincere gratitude for cultivating and fostering such wonderful partnerships.

Peter Fratzl
Director of the Department of Biomaterials



Structure and Dynamics of Forming Tissues



Luca Bertinetti
03.09.1975
1994–2001: Master of of Science (110/110 cum Laude) majoring in Materials Science (University of Torino, Italy)
2002–2005: Doctoral Thesis (Chemistry): Nanomaterials for biomedical applications: synthesis and surface characterization. (University of Torino, Italy)
2006–2009: Research Technician in charge of the Electron Microscopy research line of the Structural and Functional Materials Group of the IPM Department of the Torino University, Italy
2010–2016: Independent researcher, Department of Biomaterials, Max Planck Institute of Colloids and Interfaces.
Since 2017: Research Group Leader Department of Biomaterials, Max Planck Institute of Colloids and Interfaces.

Biological materials and tissues are based on basic building blocks which are organized at various hierarchical levels. Their organization at the different scales, as well as their interactions with water and ions result from thousands of years of evolution and are often crucial to the attainment of their functions. In our group, we focus on the molecular and supramolecular principles and processes underlying the biological production of materials (both mineralized and unmineralized) and the attainment of such functionalities. In this respect, we are interested, on the one hand, in solvent mediated molecular and long-range interactions that are responsible for the chemical/colloidal and mechanical properties of biological materials as well as for their synthesis and self-assembly into 3D complex structures, and, on the other hand, in understanding strategies and processes of transport and selective/local precipitation of inorganic materials within living tissues. In the past two years, these themes have been investigated in our group through the following topics: 1) the role of water in the structure and stability of amorphous calcium carbonate, ACC (with M. Alberic, Z. Zou and Y Politi of the Biomaterials department and L. Addadi and S. Weiner of the Weizmann institute of Science, Rehovot, Israel); 2) water and water-mediated interactions in collagen-based tissues and plant secondary cell walls (with A. Masic, Massachussets Institute of Technology, USA and T. Zemb, ICSM, Insitut de Chémie separative de Marcoule, France, Kerstin Blank form the Mechano-biochemistry group and E. Schneck of the Biomaterials department). Also, the past two years have been devoted to the development of workflows to prepare, image and analyze tomographic datasets of living tissues in order to investigate the cellular machinery and processes underlying the deposition of biological materials.

Formation, Structure and Stability of ACC

The use of amorphous precursors has been recognized as a common strategy employed by many organisms across various phyla to build biominerals. ACC, which is a hydrated amorphous phase, is surprisingly widespread in biological systems where it is found in two forms: transient and stabilized. Biogenic transient ACCs are short lived precursor phases and have been shown to generally dehydrate prior to crystallization. Also, they have been suggested to have a different local structure than stable ACCs which, on the other hand, were shown to contain organic as well as inorganic additives. Despite previous extensive research has shown that the structure and composition are related to the endurance of the mineral phase, it is still not fully understood what are the key to ACC stabilization and the mechanisms that control its crystallization. In our work, we addressed the structural, compositional and thermodynamics aspects linked to the formation and the stabilization of synthetic ACC as a model to understand the biogenic system. First, we have investigated the stability of Ca^{2+} and CO_3^{2-} solutions showing that a liquid-liquid phase boundary, which likely delineates a spinodal region, exists and behind this boundary the unstable solution undergoes a rapid and uncontrolled un-mixing process that leads to the formation of a liquid enriched in ions from which finally amorphous calcium carbonate particles form **[1]**. Interestingly, the presence of biologically relevant inorganic cations affects only little the position of the phase boundary while phosphate ions move it to lower concentrations **[2]**.

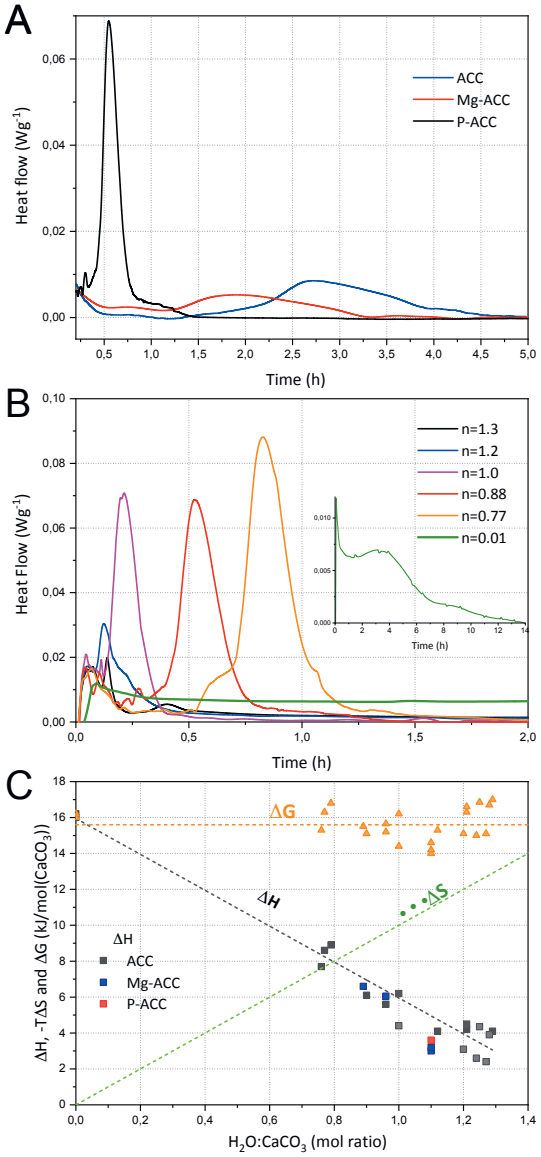


*Fig. 1: Heat flow evolution during crystallization induced by humidity of A) ACC with traces of inorganic ions and B) differently hydrated pure ACC·nH2O. C) ΔH, –T·ΔS (estimated), and ΔG with respect to calcite of ACC with different hydration levels at T = 25 °C **[3]**.*

The different ACC precipitated from solution (pure and with additives) exhibit similar initial short- and medium-range order but the presence of additives delays the onset of crystallization as well as the time required for its completion **(Fig. 1) [3]**. The water content of ACC dramatically affects the kinetic stabilization of the mineral as water controls ion mobility within the solid. In fact, as we have shown using total scattering tech-

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niques **[4]**, all H_2O molecule are bound, in ACC, to carbonate ions and therefore they are key to structural rearrangement during dehydration. Because of these strong interactions with ions, the nature of water in ACC is very different from bulk liquid water, as demonstrated by quasi-elastic neutron scattering **[5]** and, in fact, water also determines the energetic landscape of amorphous carbonate phases **(Fig. 1)**. While exploring the effect of hydration on the thermodynamics of calcium carbonates, we discovered that, at very high hydrations (more than 6 water/$CaCO_3$), ACC can be so unstable to undergo a reentrant transformation first to Ikaite ($CaCO_3{\cdot}6H_2O$) and then back to a less hydrated amorphous phase **[6]**. The ensemble of our results contributes significantly to the description of structural, dynamic and thermodynamic aspects of ACC that are critical to understand the behavior of biogenic amorphous carbonates and the strategies put in place by biological systems to control the precipitation and the crystallization of ACC.

Water and Water-mediated Interactions in Biological Materials

Water plays a key role not only in determining many of the chemico-physical properties of inorganic compounds but also in regulating structure and mechanics of organic building blocks of biological materials and tissues as well as their interactions with ions in solution. This is the case for instance in wood, where, thanks to the development of an ab-initio equation of state for the wood-water system, we could describe cell walls composition-dependent ions specifics effects in plant tissues, which is a technologically relevant problem in wood sciences **[7–8]**. Another molecule which strongly relies on interactions with water to accomplish its functions is collagen, which is the most abundant protein in mammals' tissues and presents complex structural motives at several different scale lengths. In collaboration with A. Masic we developed a multi-technical approach which combines x-ray scattering fluorescence and vibrational spectroscopies **[9]** for in-situ multi-scale analysis of biological materials. With this approach, we could study the effect of water on highly ordered collagen based tissues like tendon and skin **[10]**. Lately, we started investigating collagen model peptides to unveil the molecular changes underlying hydration and dehydration of the triple helices which have been shown to contribute crucially to the mechanics of the collagen molecule.

3D Imaging of Forming Tissues

In the past 2 years, we established a full pipeline from sample preparation to image acquisition and analysis of relatively large tomographic volumes of biological materials and tissues with nanometric resolution. The main technique employed to acquire the volumes is focussed ion beam/scanning electron microscopy (FIB/SEM) based serial block-surface imaging (SSI), both at room temperature and in cryogenic conditions. This technique bridges the gap between the typical scale length of light microscopy (for which the resolution is often diffraction limited) and that of transmission electron microscopy (that offers sub-nm resolution, but is very limited in the size of investigated volumes). FIB-SEM SSI allows to collect volumes up to $(100\mu m)^3$ at a resolution that can go down to 3–5 nm and represents therefore an ideal tool to characterise cells and cell organelles (which are typically in the µm size) and their relationships with the building blocks of the biological materials they produce (that can span several length scales from a few nm to several tents of µm). Using this technique, we started studying the mineralisation of collagen-based tissues (bone and mineralising tendons), the re-growth of spines in sea urchins and the mineralisation in marine algae **(Fig. 2)**, the production and assembly of chitin fibers in Locust (in collaboration with Y. Politi), the dynamic of the formation of the cuticle granules in mussel threads (in collaboration with M. Harrington).

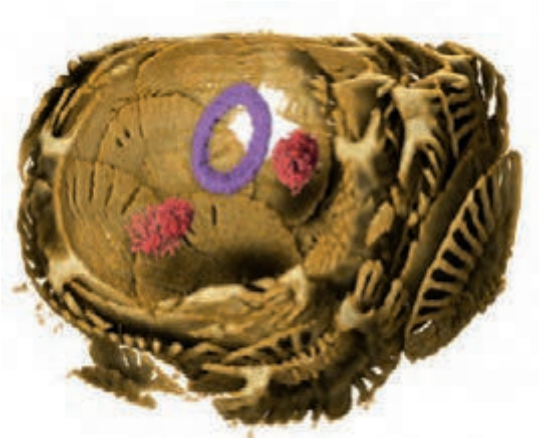

Fig. 2: 3D rendering of an E. huxleyi cell from a cryo-FIB-SEM image series, showing the extracellular coccosphere (yellow), the intracellular calcium pools (red) likely involved in the intracellular growth of the coccolth (purple).

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bertinetti@mpikg.mpg.de

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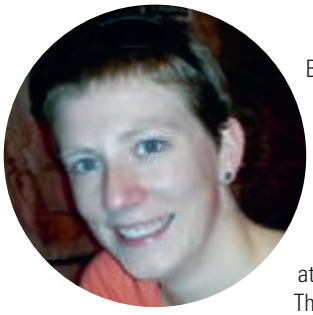
Principles of Matrix Architecture in Biofilms



Cécile Bidan
Date of Birth: 02.07.1986
2006–2009: Engineering / Master's Degree in Materials Science
School for Electrochemistry Electrometallurgy (PHELMA) Grenoble INP, France
2009–2012: PhD Student in Biophysics
Geometric control of tissue growth and organization.
Max Planck Institute of Colloids and Interfaces
2013–2014: Postdoctoral Scientist
Groningen University, Department of Molecular Pharmacology & Harvard Medical School, Beth Israel Deaconess Medical Center
2014–2017: Postdoctoral Scientist
Laboratory for Interdisciplinary Physics (LIPhy), University Grenoble-Alpes, CNRS
Since 10/2017: Research Group Leader
Department of Biomaterials, Max Planck Institute of Colloids and Interfaces

Biological tissues are complex 3D structures that form as cellular organisms get embedded in a matrix of self-produced and organized fibrous biopolymers **[1]**. The architecture of such biological materials ensures both their physical and biological functions. Abnormal structural changes in tissues are often associated with dysfunction or pathogenesis **[2]**.

The general interest of our research group is to clarify the biophysical principles guiding tissue architecture during morphogenesis, with the ultimate goal to provide new physics-based strategies to tune tissue functions. In particular, we focus on the architecture of biofilms, which are microbial tissue-like complex 3D structures made of fibrous biopolymers produced by bacteria. Indeed, these adhesive living systems are known for their consequences on human health and antibiotics resistance, but they can also impair industrial processes by developing into pipelines. Understanding how biofilms are built will help to design new strategies to prevent their formation and favour their elimination.

Earlier Research on Mammalian Soft Tissues

To explore the architectural principles of biofilm formation, we will take inspiration from top-down approaches common in materials science and which I previously used during my PhD in the former group *Biomimetic Actuation and Tissue Growth* led by J. Dunlop.

Our aim was to understand the influence of mechanical boundary conditions on bone-like tissue growth and organisation **[3]**. For this, we cultured bone cells in macro-pores of different shapes and showed that the geometry of a surface strongly influences both tissue growth kinetics and extracellular matrix organization **[4]**. Indeed, geometry sets the boundary conditions of the mechanical environment that cells probe via mechanosensing, and respond to by assembling an extracellular matrix network aligned with the mechanical tensions (**[5]**, **Fig. 1**).

In a collaborative work with A. Cipitria (previously at the Julius Wolf Institute, now leading the group *Extracellular Matrix in Disease and Regeneration* in the Biomaterials department **[6]**), we contributed with our 3D computational model of curvature-driven growth **[7]** to demonstrate that the geometrical cues of a scaffold – in particular surface curvature – determine bone soft tissue formation and collagen organisation *in vivo* **(Fig. 2)**.

Motivated by our recent research, P. Kollmannsberger (former member of the Biomaterials department), initiated a project in V. Vogel's lab (ETH Zürich) to clarify the role of mechanics in tissue growth. He used skin cells naturally sensitive to mechanical tension (primary human dermal fibroblasts turning into myofibroblasts) to show that i) cellular tension, ii) matrix tension, iii) cell proliferation and iv) muscle like markers were upregulated at the growth front of skin tissue grown in macro-pores of square geometries **([8], Fig. 3)**.

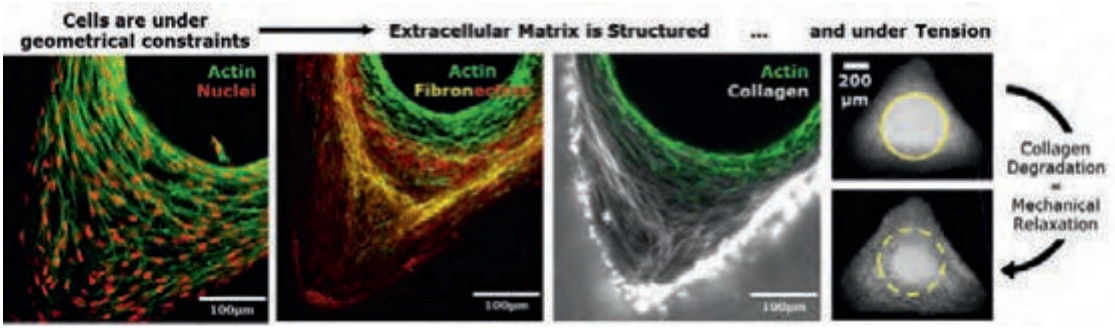


Fig. 1: The geometry of a surface influences both cells and extracellular matrix organization (5), mainly through mechanical forces that are transferred from the cells to the matrix fibres. (please display Fig1 on 2 columns)

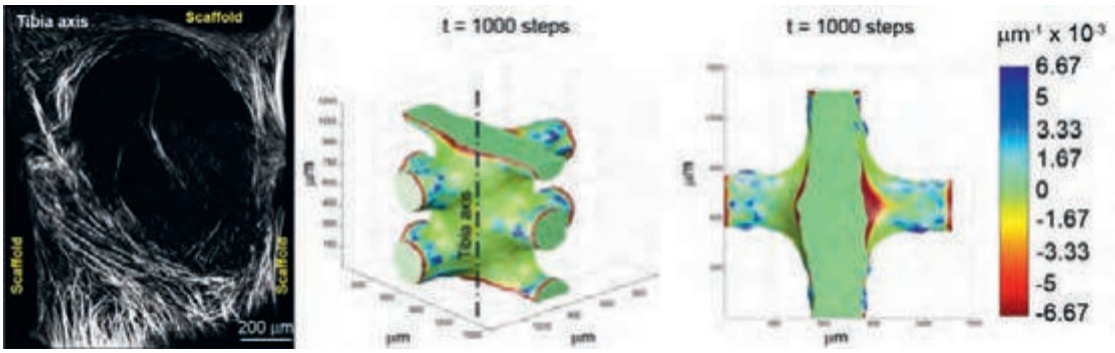


*Fig. 2: Our 3D model of curvature-driven growth (7) was applied to the complex surface of scaffolds before implantation in sheep tibia. The simulations predicted similar growth patterns of soft tissue as those observed in the scaffolds during the in vivo experiments **[6]**.*

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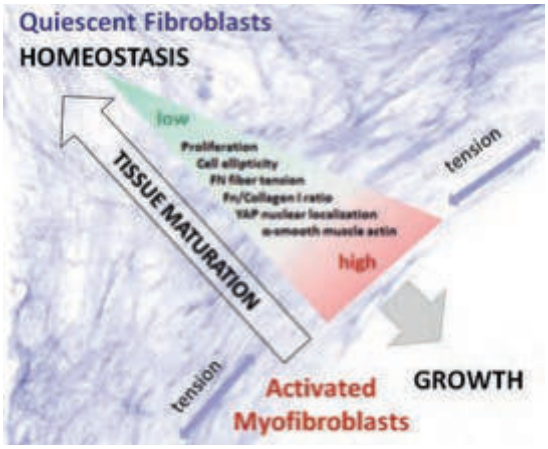

*Fig. 3: Myofibroblast-to-fibroblast transition illustrates how the highly tensed growth front rich in myofibroblasts drives tissue growth, and how myofibroblasts revert to quiescent fibroblasts as the tissue matures **[8]**.*

Pursuing similar studies on capillary bridges with non-zero Gaussian curvature surfaces, the group recently demonstrated that bone-like tissue behaves like a viscous fluid, which shape is determined by surface tension. The same work also revealed that the cells embedded in such tissue spontaneously acquire a long range organisation reminiscent of liquid crystals **([9], Fig. 4)**

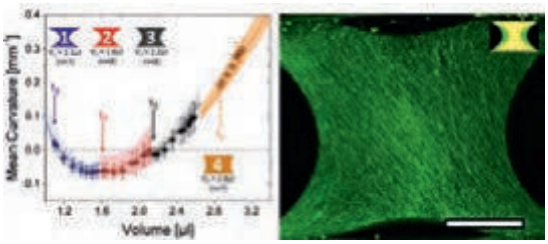

Fig. 4: When constrained by curved surfaces, bone-like tissue (experimental points) behaves like a liquid (theoretical lines). The cells embedded in such tissue spontaneously acquire a long range organisation into chiral structures.

This background in soft tissue research inspired the approaches that will be implemented by our new research group to investigate how bacteria design and structure their extracellular matrix into biofilms. Our efforts will now focus on the mechanisms enabling the complex 3D architecture of such microbial tissues to effectively match the physical constraints of their host surface and fulfil mechanical and biological functions associated with their protective role.

Biophysical Study of Biofilm Morphogenesis

Growing single droplets of *E.coli* bacteria on a nutritive substrate gives rise to large 3D biofilms with complex morphologies. To study how bacteria orchestrate biomass production and localized wrinkling of the resulting tissue, we established experimental setups and live-imaging protocols to monitor biofilm formation. Computational tools for image analysis have been adapted to quantify biofilm growth from time-lapse data.

We have shown that rigorous characterizations of the complex 3D morphology of biofilms will be possible by combining micro X-ray computed tomography (µCT), 3D reconstruction and surface quantification **(Fig. 5)**. In collaboration with the mathematician D. Fischer (Montan University Leoben), we aim at coupling our experiments with modelling approaches to assess the role of physical and mechanical principles in the process of biofilm formation.

Fig. 5: A biofilm (stereomicroscopy in inset) was scanned by µCT and reconstructed to quantify the unfolded surface.

Amyloid and cellulose fibres are two major components of the extracellular matrix, which play a key role in the mechanical properties and thus the protective function of *E.coli* biofilms. Together with the microbiology research group of Regine Hengge (HU Berlin), we aim at clarifying the assembly and organization process of these fibres into large structures using quantitative structural analyses. With this project, we have been involved in writing the proposal for the DFG excellence cluster "Matters of Activity – Image Space Material", recently granted. Our collaboration is at the basis of the setting "Woven architectures in Microbial Biofilms" and will be brought into broader perspectives of bio-inspired materials through interactions with architects and designers. In order to quantify matrix distribution and orientation in flat and wrinkled regions of biofilms, we will first have to meet the challenges of handling slimy biofilms, developing well controlled sample preparation techniques and producing standard samples made of purified matrix components.

Influence of Physical Cues

As for many other biological materials, we expect biofilm growth and architecture to be affected by physical cues of the environment. For example, we propose to investigate the role of surface geometry on biofilm morphogenesis. Besides adding insights into the principles of matrix architecture, studying biofilm growth on various geometries will find more relevance in Nature, where biofilms rarely grow on flat surfaces.

Finally, we envisage to take advantage of our experience in designing tools for mechanical stimulation of living systems **[10]** to explore the effects of a dynamic mechanical environment on biofilm formation together with the group Mechano(Bio)Chemistry of K. Blank.

C. Bidan, S. Ehrig, B. Large, C. Pilz, B. Schulze
bidan@mpikg.mpg.de

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Extracellular Matrix in Disease and Regeneration

Amaia Cipitria
01.05.1980
1998–2004: M.Eng. in Mechanical Engineering
University of Navarra, Spain
Master thesis at Alstom Power, Switzerland
2004–2008: Ph.D. in Materials Science and Metallurgy
University of Cambridge, UK
Doctoral Thesis: Sintering of plasma-sprayed thermal barrier coatings for gas turbines.
2009: Postdoctoral Scientist
Queensland University of Technology, Australia
2009–2010: Postdoctoral Scientist
Julius Wolff Institute, Charité – Universitätsmedizin Berlin, Germany
2011–2017: Principal Investigator
Julius Wolff Institute, Charité – Universitätsmedizin Berlin, Germany
Since 09/2017: Emmy Noether Research Group Leader
Department of Biomaterials, Max Planck Institute of Colloids and Interfaces, Germany

The cell microenvironment or cell niche includes the extracellular matrix (ECM), biochemical factors and neighboring cells, and the interaction between these three regulates cell function **[1]**. Biomaterial scaffolds and hydrogels allow independent control of biochemical and biophysical properties and have contributed to the understanding of how cells sense these cues in tissue regeneration. Materials science approaches have also been used to investigate different steps in cancer progression, such as tumor growth, invasion or metastasis. The first section of this report presents the work on biomaterial physical cues and regeneration conducted with the Julius Wolff Institute, Charité, Berlin. The second section discusses the progress and aims of the Emmy Noether group, to understand the role of biophysical mechanisms in cancer dormancy and bone metastasis.

Scaffold Curvature-mediated Biomineralization

Substrate geometry influences cell behavior and tissue formation *in vitro*, yet little is known regarding how this translates to an *in vivo* scenario. We used clinically relevant bone regeneration experiments to study how the scaffold mean surface curvature guides collagen fiber organization and subsequent mineralization *in vivo* **[2]**. Soft tissue formation followed a curvature-driven growth model. Geometrical constraints imposed by this endogenous soft matrix lead to a non-standard form of biomineralization, whereby the pre-existing organic matrix was mineralized without collagen remodeling and without an intermediate cartilage ossification phase. Micro- and nanoscale analysis allowed quantitative characterization of the continuous soft-hard tissue interface **(Fig. 1)**. These findings on *in vivo* tissue growth under geometric confinement provide fundamental knowledge on scaffold design for musculoskeletal tissue engineering.

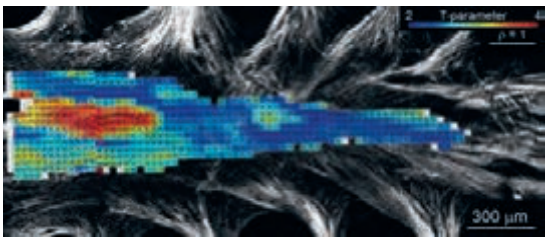

Fig. 1: Quantitative characterization of the continuous soft tissue-to-bone tissue microstructure visualized by second-harmonic generation imaging and synchrotron small angle X-ray scattering.

Covalently Crosslinked Alginate Hydrogels with Tunable Mechanical and Degradation Properties

Degradability is of fundamental importance in regeneration and cell or drug delivery. Calcium crosslinked alginate hydrogels with a stiffness optimized for osteogenic differentiation were used for the regeneration of critical sized bone defects **[4]**. While a trend was observed for hydrogel stiffness influencing bone formation, this effect was insufficient for complete healing. One possible limitation was the fact that ionically crosslinked gels exhibit an uncontrolled degradation via diffusion of crosslinking Ca^{2+} ions as a function of the ionic strength of the environment, and therefore the mechanical cues were not maintained in time.

To overcome this limitation, we developed an alginate-based material system with two different types of covalent crosslinking and degradation modes. The first one involves oxidizing and adding norbornene or tetrazine functional groups to the polymer backbone. When combined, these species crosslink spontaneously via Diels-Alder click chemistry resulting in a hydrolytically-degradable product **[5]**. The second one necessitates the design of peptide crosslinkers that can be recognized and cleaved by native enzymes. When these crosslinkers are mixed with norbornene-modified alginate and exposed to UV light, an enzymatically-degradable hydrogel is formed by thiol-ene reaction. In both cases, mechanical and degradation properties could be tuned, and high viability of 3D encapsulated cells was confirmed. *In vivo* tissue infiltration was shown to occur only in materials designed to degrade, not in non-degradable controls **[5]**.

Patterned Alginate-based Hydrogels

The two orthogonal crosslinking modes described above could then be combined. Taking advantage of the fact that one occurs spontaneously and the other relies on UV light for initiation, more sophisticated patterned biomaterials could be formed via photomasks. We have fabricated hydrogels with patterns in stiffness, degradability and biomolecule presentation and started to explore the effect on cells in 2D and 3D. One example is the spatial control of 2D cell attachment via the immobilization of a thiol-coupled RGD cell adhesion peptide **(Fig. 2)**.

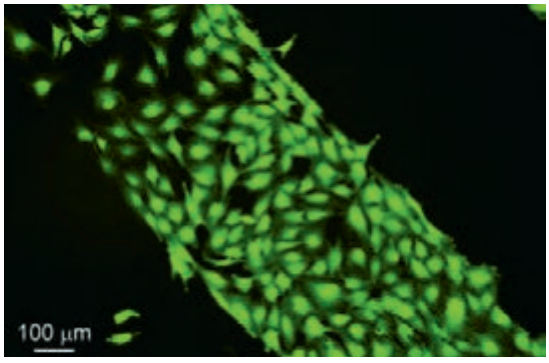

Fig. 2: Patterns in thiol-coupled RGD cell adhesion peptide are formed by exposing to UV through a photomask and result in spatial control of cell adhesion.

Extracellular Matrix Biophysical Cues in Cancer Dormancy and Bone Metastasis

Breast cancer is one of the leading causes of cancer-associated deaths among women worldwide. Breast cancer often metastasizes to bone, which can occur even 10 years following tumor resection. This implies that cancer cells can undergo a dormancy phase. Three mechanisms have been identified: (i) dormancy of solitary cells, (ii) angiogenic tumor dormancy (cell division balanced by apoptosis) and (iii) immunosurveillance **[6]**. In dor-

mancy of solitary cells the interaction with the microenvironment is pivotal. However, the role of ECM biophysical cues in dormancy and reactivation is poorly understood, in part due to a lack of appropriate *in vitro* and *in vivo* models.

The goal of our Emmy Noether research group is to contribute to the understanding of how biophysical mechanisms regulate cell-matrix interaction in cancer dormancy and bone metastasis, by (i) synthesizing biomimetic cell microenvironments and (ii) developing characterization and imaging methods to study the early metastatic and dormant niche *in vivo*. The knowledge gained from the synthetic systems will guide the characterization of the native tissue, while the *in vivo* observations will feed back to the design of the synthetic microenvironments **(Fig. 3)**.

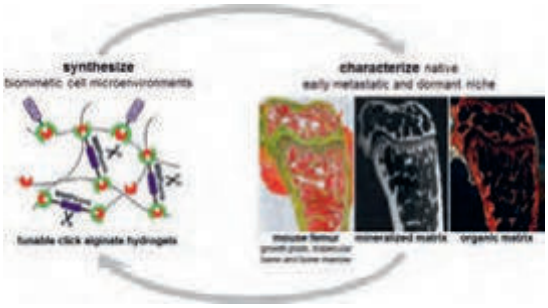

Fig. 3: Feedback loop between synthetic microenvironments, based on alginate hydrogels with tuneable mechanical, adhesion and degradation properties, and in vivo observations of the early metastatic and dormant niche.

Fluorescence-ubiquitination-cell-cycle-indicator

As dormancy is in essence an exit from the cell cycle, we genetically modified the MDA-MB-231 highly metastatic breast cancer cell line with the fluorescent ubiquitination cell cycle indicator (FUCCI) **[7]** through lentiviral transduction, in order to track the cell cycle phases **(Fig. 4)**. Briefly, mCherry fluorescent protein is fused to the cell cycle regulator cdt1, while mVenus fluorescent protein is fused to cell cycle regulator geminin. During the G1 phase of the cell cycle, geminin is degraded, leaving only cdt1 tagged with mCherry emitting red fluorescence within the nuclei. In the S/G2/M phases, cdt1 is degraded, resulting in geminin emitting green fluorescence.

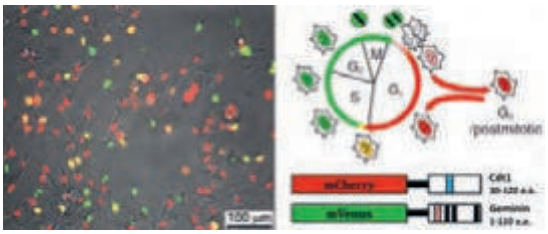

Fig. 4: Successful generation of FUCCI-modified MDA-MB-231 cell line, where the cells express mCherry in the G1 phase and mVenus in the S/G2/M phase of the cell cycle.

Synthetic Biomimetic Cell Microenvironments

Non-degradable norbornene-modified alginate hydrogels with different degrees of crosslinking densities were chosen to mimic confined environments experienced by disseminated cancer cells within the bone marrow. The degree of norbornene functionalization of the alginate polymer was determined by nuclear magnetic resonance, while mechanical properties were assessed with rheology. Upon encapsulation, FUCCI MDA-MB-231 cell cycle dynamics can be investigated quantitatively in real-time within hydrogels of different biophysical properties **(Fig. 5)**.

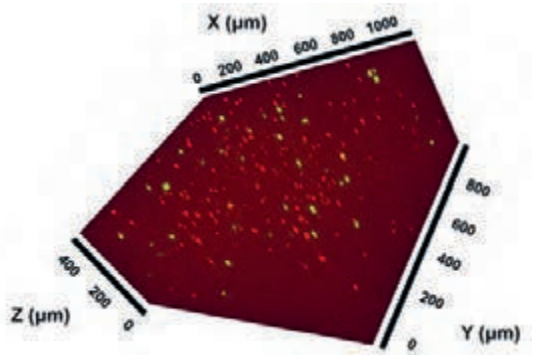

Fig. 5: Fluorescence image of FUCCI MDA-MB-231 cells encapsulated in a 3D hydrogel after 1 day of seeding.

Bone Ultrastructural Characterization of Humanized Mouse Models

In collaboration with Prof. Dietmar Hutmacher, we investigate the bone ultrastructure in humanized mouse models. These models aim to create human-like bone physiology in a mouse for the study of bone metastasis. We applied a correlative imaging methodology that combined 2D immuno-histology to detect human specific markers, with 3D imaging techniques from mm to submicron scale. We characterized quantitative differences between regions of positive and negative expression of human specific-markers. By doing so, we will provide a platform to quantify the degree of bone 'humanization' in humanized mice and, hence, a method to continue to improve humanized animal models for pre-clinical research.

A. Cipitria, S. Bakhshandeh, D.S. Garske, I. Moreno, J. Steffen, H. Taieb, S. Young, A. Lueckgen (Charité)
amaia.cipitria@mpikg.mpg.de

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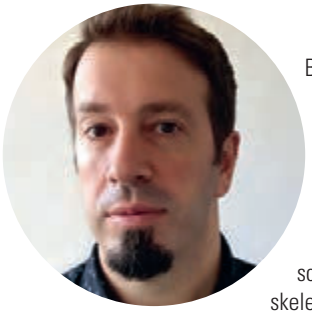
Evolutionary Perspectives on Vertebrate Hard Tissues



Mason Dean
17.1.1975
1993–1997: Bachelor's in Biology (Marine Biology conc.); Duke University (Durham, North Carolina, USA)
1999–2003: M.S. in Zoology; University of South Florida (Tampa, Florida, USA)
2003–2009: Ph.D. in Ecology & Evolutionary Biology; University of California (Irvine, California, USA)
2009–2011: Alexander von Humboldt Fellow, Dept. Biomaterials, MPIKG, Potsdam
2011–2017: Independent Researcher and HFSP workgroup leader, Dept. Biomaterials, MPIKG, Potsdam
Since 2017: Group Leader, Dept. Biomaterials, MPIKG, Potsdam

Biomaterials and engineering approaches to biology research often necessarily favor resolution over scope, meaning that studies of skeletal materials are rarely rooted in broader contexts that consider tissue diversity and evolution. This is reflected in introductory biology and anatomy textbooks which, when describing the architecture and structure of animal skeletons, typically focus only on the few bone and cartilage types found in humans. In reality, cartilage and bone are far more diverse in the animal kingdom, particularly within fishes, where cartilage and bone types exist that are characterized by features that are anomalous or even pathological in humans. Our group investigates principles of organization in skeletal tissue structure, development and function, from tissues up to whole skeletons. By rooting our studies in the ecologies of the animals and in comparisons with better-known skeletal tissues, we demonstrate a rich variety in the anatomy and function of skeletons that could not be appreciated from human tissues alone. As fishes occupy a huge range of habitats, exhibit extensive morphological diversity, and represent ~55% of all vertebrate species, they offer unparalleled opportunity for defining and understanding the true diversity of form-function relationships in cartilage and bone.

What can tissue biodiversity teach us?

Cartilaginous fishes (sharks and rays) provide particularly intriguing models for skeletal biology research in being the only vertebrates with cartilage skeletons as adults. The cartilage resembles humans' in structure and composition, yet with distinct characteristics (e.g. longevity and capacity for mineral regulation) suggesting untapped potential for cartilage and cell biology research. Our recent investigation of collagens patterning this tissue showed that rather than being comprised purely of the collagen typical for mammal cartilage, shark and ray cartilage also possesses a defined layer of bone-like collagen **[1]**. The cartilage- and bone-like tissues abut inside the mineralized crust of the skeleton **(Fig. 1)**, resulting in a tissue interface oddly similar to those in human joints, where bone and cartilage jostle for position during growth. Furthermore, we found that the mineralizing cartilage does not exhibit all of the steps thought necessary to calcify cartilage **[1–2]**, arguing that either some factors considered vital to mineralization actually aren't or that evolution has arrived on more than one way to mineralize cartilage. We further this research currently with study of other cartilaginous fishes, to catalogue features and processes universal to all cartilages, thereby facilitating understanding of the roots of observed differences, particularly those relevant to cartilage health.

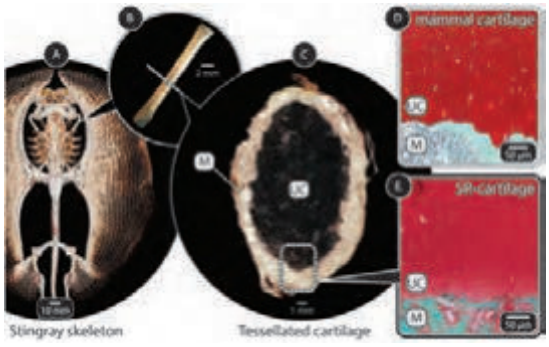


Fig. 1: Shark and ray (SR) skeletons comprise large amounts of unmineralized cartilage (UC) with an outer layer of mineralization (M), forming blocks called tesserae. The similarities and differences we demonstrate between this tissue and mammal cartilage, argue it can be a useful model for understanding cartilage and its interaction with bone.

How do skeletal tissues manage damage?

Our skeletons support our long lives because they are changeable: bone is capable of altering its material composition and architecture to better manage loads. In contrast to bone, mammal cartilage is incapable of the responsive 'modeling' process, making the lifespans and high activity of cartilaginous fishes (sharks and rays) particularly counterintuitive. In our investigations of cartilaginous fish skeletal structure, we have found several novel tissues associated with damaged areas, apparently involved in with stabilizing injured tissues **[3–4] (Fig. 2)**. While this supports the idea that cartilage is universally incapable of complete repair, it indicates that cartilaginous fish cartilage does have an ability to respond to insult and therefore could prove a useful comparative model for degenerative joint diseases, such as osteoarthritis.

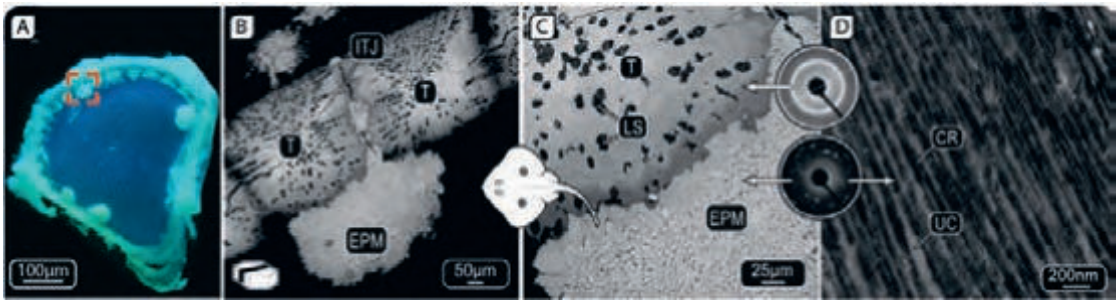


Fig. 2: Aberrant skeletal mineralization (endophytic masses, EPM) in a skate shows distinct ultrastructure/crystallography from tesserae (T). ***[3]***

How are structure and function linked?

Understanding the mechanical biology of skeletons – how they respond to both usual and unusual loads – demands knowledge of the role of the skeletal material. Digital and physical modeling can be an effective method for gaining a foothold in this, in that they allow controlled exploration of the effects of structure on function. Shark and ray cartilage is particularly tractable for form-function modeling, in that it comprises several relatively discrete tissues, arranged in layers. Of particular interest to our group is the hard, outer crust of the skeleton, which is broken into small, geometric tiles (*tesserae;* **Fig. 1**) and believed to be the source of the impressive mechanical properties of shark and ray cartilage. Working from high-resolution CT data and using a module built in collaboration with David Knoetel and Daniel Baum at the Zuse Institute Berlin, we can quantify the shapes and sizes of the many thousands of tiles on a piece of skeleton, in order to help dissect the construction laws governing this tessellated system **[5] (Fig. 3A)**. These data, paired with our fine-scale structure **[1–2]** and material property data then act as the starting points for our models of tissue mechanics. For example, analytical models of 2d tiled arrays – where tissue geometries and material properties were varied in a range around those measured in real tesserae – indicate that the stiffness of the material can be controlled by adjusting the ratio of joint-to-tile material properties and by changing tile shape **[6] (Fig. 3B)**. These results demonstrate that the properties of the tissue composite can be tuned by adjusting simple aspects of the subunits (i.e. the tesserae), suggesting promising avenues for the manufacture of lightweight, manmade composites. We are exploring the performance of more complicated, bio-realistic tessellations (e.g. three-dimensional and less uniform tilings) to better understand these relationships. In parallel, we are also developing techniques to facilitate 3D printing nearly directly from CT scan data and for printing and combining multiple materials into integrated structures (e.g. involving complex arrangements of both soft and hard materials) **[7–8]**. These can aid flexible hypothesis-testing for biological research (e.g. modeling diverse morphologies for form-function study) **[7]**, but also expedite 3D printing for medical applications, for example via the building of patient-specific anatomical models **[8]**.

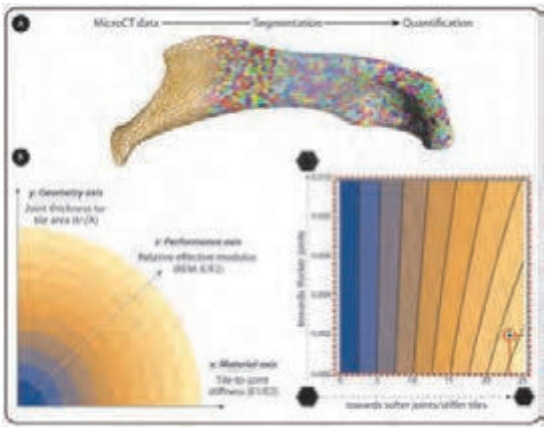


Fig. 3: From the biological system to models of function. Starting from microCT data of whole skeletal elements, our developed workflow isolates and maps the patterns of tesserae on the skeleton, allowing quantification of their arrangements and morphometry (Fig. 3A) ***[5]****. These shape data, paired with our material data are then fed into models of tessellated patterns, allowing the construction of performance 'landscapes' (Fig. 3B), with the warmer colors representing higher overall effective stiffness (REM) of the material. From these simulations, the performance of the biological system (red lines) can be compared to hypothetical alternate constructions to examine the optimization of the biological system for function* ***[6]****.*

M. Dean, A.K. Jayasankar, J. Chaumel, R. Seidel, C. Liu
mason.dean@mpikg.mpg.de

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Plant Material Adaptation

Michaela Eder
1972
2003: Diploma in Wood Science and Technology (BOKU – University of Natural Resources and Applied Life Sciences, Vienna, Austria)
2007: Doctoral Thesis: Structure, properties and function of single wood fibres of Norway Spruce (Picea abies [L] Karst.) (BOKU, Vienna, Austria)
2007–2011: Postdoctoral Scientist Department of Biomaterials, Max Planck Institute of Colloids and Interfaces.
Since 09/2011: Research Group Leader, Department of Biomaterials, Max Planck Institute of Colloids and Interfaces

Characteristic for plant cells is that they are encased by a cell wall, a composite of cellulose, hemicelluloses, pectins and sometimes lignin. The cell wall is an essential material to form tissues, organs and the whole plant body. In the group Plant Material Adaptation we are mainly interested in cell wall based materials and their functionality for the plant organism but also for potential use and applications.

Besides investigating cell wall structure and mechanics of different tissues **[1]** we started to include ecological aspects in our research **[2]**. Particularly suitable systems are plants of the native Australian genus Banksia, since they typically grow in an "old" ecosystem, without any soil renewal, providing for the plants very stable ecological conditions over long periods. We are particularly interested in the seed storing structures of Banksias which can remain on the plant for up to 15 years, even though they consist of dead tissue only. The triggers for opening are often high temperatures, caused by bush fires, a component of the natural Australian landscape since millions of years. As a consequence, vegetation has adapted to these natural harsh conditions and developed strategies for re-establishment after fire such as resprouting and/or germination from seeds **(Fig. 1)**.

Fig. 1: Resprouting plants and plants regenerating from seeds after a fire in Western Australia. Burnt plants contain many open seed pods.

In the genus Banksia both strategies are common and in many cases plants accumulate a seed bank in the canopy: the showy flower spikes (inflorescences) of Banksias contain up to several thousand flowers; some of them get pollinated and develop into follicles (photograph in **Fig. 2**) on a cone (infructescence). Each follicle contains one or two winged seeds with a separator in-between. The follicle valves consist of three layers: endocarp, mesocarp and exocarp. Endocarp and mesocarp form a bilayer with each layer having different directional swelling properties, similar to pine scales. However, movement of the bilayer does not occur upon drying during maturation since many species accumulate seeds after maturity instead of releasing them. This plant trait of seed accumulation for several years is termed "serotiny". However, different levels of serotiny exist, even within one species.

Banksia attenuata – Follicle Opening Depends on Geographic Location

Banksia attenuata is the most widely distributed Banksia species in Western Australia (distribution shown in green in **Fig. 2**). Within its distribution range soil types, temperature ranges and rainfall differ and it has been reported by Cowling and Lamont in 1983 that the level of serotiny, which describes the proportion of closed follicles, changes within the species along the coast from south to north. Based on this study we collected mature infructescences (dead tissue) at five sampling sites from Perth to Eneabba (black dots in the map) and found that the opening temperature gradually changed from ~54 °C in the South to ~72 °C in the North.

Fig. 2: Distribution range of B. attenuata (green). Black dots show sampling sites. Infructescences with mainly closed follicles are typical in the North whereas southern cones contain both open and closed follicles.

To understand both the long-term stability of the seed pods, the temperature-triggered opening and the protection of the seeds during fires we applied numerous materials characterization methods at different length scales (eg. micro computed tomography, microscopy, X-ray scattering, spectroscopic methods). The availability of follicles of one species with different opening temperatures as well as a range of different species facilitated the understanding of the multifunctional follicle material.

Long-term Stability of Seed Pods

Raman experiments on follicles of *B. serrata*, *B. candolleana* and *B. attenuata* of different collection sites were performed to determine the melting temperature of the wax, which connects the two follicle halves (**Fig. 3**, junction zone). The melting temperature was 45–55 °C for all samples **[3]**, which is below the opening temperature of most follicles **(Fig. 3)**. This is a hint that the wax might act as a sealing agent for small cracks and contributes to the integrity of the follicle and seed viability and persistence for many years, since temperatures of 45–55 °C can be reached on warm summer days in the field.

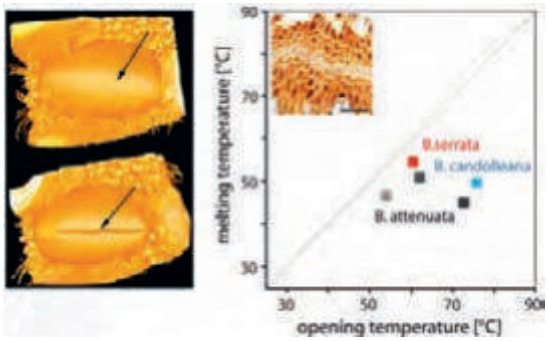

Fig. 3: Black arrows on the CT scans point to the junction zone which consists of interdigitating cells (micrograph, scalebar 100 µm) and a wax in between. Melting temperatures of the wax are below the determined opening temperatures (diagram).

Temperature-triggered Follicle Opening

To understand the mechanism underlying the temperature triggered opening of the follicles heating experiments were performed on *B. attenuata* follicles of different sampling sites inside a µCT scanner. The aim was to identify the area of initial opening which turned out to be the junction zone (**Fig. 3**, black arrows). Since wax melting occurs below the opening temperature we excluded the wax being the "sensor". Analysis of follicle geometry revealed differences in internal follicle curvature which can explain higher dimensional stability of northern follicles. With increasing temperature the inner resistance layer (endocarp) of the follicle softens and internal stresses are released, leading to the initial opening **[2]**.

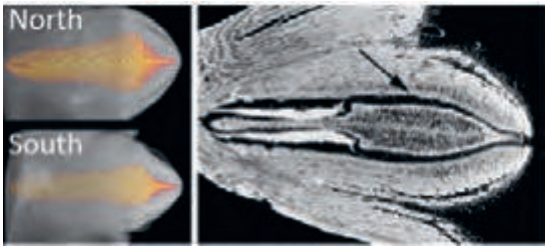

Fig. 4: Internal follicle geometry was segmented on µCT data and shows differences between northern and southern follicles. Arrow in the right µCT scan points to the resistance layer (endocarp) which softens upon increasing temperatures and allows release of internal stresses, leading to initial opening.

Heat Protection of Seeds During Fire

For long-term species survival it is critical that seeds are protected from heat. In burning experiments (180 seconds, ~450 °C on follicle surface) we could show that maximum seed temperatures do not exceed 95 °C. This is achieved by the multicomponent system consisting of the two valves, the porous separator and an air layer surrounding the seeds. Experiments on follicles with different sizes (*B. prionotes*, *B. candolleana* and *B. serrata*) showed that the arrangement of the components determines the heat transfer rate more than the individual tissue properties. A strong embedment of follicles in the central rachis of the infructescence can compensate for thin follicle valves **[4]**.

Water Fueled 2nd Opening

Initial temperature triggered opening is not sufficient for seed release, instead the follicles need wetting and drying cycles for further opening which activates the endocarp – mesocarp bilayer **[5, 6]**. By exposing the follicles to different wetting conditions we were able to show that the total amount of water uptake determines how much the follicle opens upon a subsequent drying step. This mechanism seems to ensure that seeds are only shed into an environment ensuring availability of water for germination.

Banksia Follicles - Multifunctional Polymeric Composites

Banksia follicles are an excellent example for long-term stability of a purely polymeric material, properties highly desirable for plant-based materials for buildings and/or constructions. Furthermore, the 2-step triggered opening provides inspiration for self-sensing, moving and actuating materials and systems. Since this multifunctional material consists only of a few basic building blocks, namely cellulose, hemicelluloses, lignin, tannins and waxes **[5]**, recycling and sustainable material use seem to be much easier compared to multi-component composites.

Besides learning for future material use our research leads to a better understanding of seed release in natural ecosystems. This knowledge could be beneficial for predicting effects of changing climate on plant communities but also for planning land management activities such as controlled burns.

M. Eder, J. Huss, F. Reppe, H. Taieb, S. Weichold, C. Wenig, G. Wienskol
michaela.eder@mpikg.mpg.de

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MOLECULAR BIOMIMETICS AND MAGNETS BIOMINERALIZATION

From Magnetite to Calcite

Damien Faivre
03.10.1977
2001: Master, fundamental and applied geochemistry (Institute of Earth Physics and University Denis Diderot, Paris) Thesis: Effect of formation conditions on the geochemical properties of magnetite nanocrystals
2004: PhD, fundamental and applied geochemistry (University Denis Diderot, Paris)Thesis: Kinetics, mineralogy, and isotopic properties of magnetite nanoparticles formed at low temperature: Implication for the determination of biogenicity criterion
2005–2007: PostDoc (MagnetoLab, Max Planck Institute of Marine Microbiology, Bremen, Germany)
Since 2007: Group Leader Biomaterials Department, (Max Planck Institute of Colloids and Interfaces, Potsdam)
2011–2015: ERC Group Leader
Since 2014: Privatdozent (Institute of Chemistry, University Potsdam)
Since 2018: Group Leader, Institute of Biosciences and Biotechnologies of Aix-Marseille, CEA Cadarache (France)

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Biomineralization is the process by which organisms form materials. These materials are as different as the function they fulfill. Examples encompass calcium phosphate in bones for mechanical support, calcium carbonate in sea shells for protection against predators and magnetic minerals for orientation. Over the years, it has become evident that the biological materials not only have outstanding properties when compared to man-made materials of similar composition but also that they are also formed under physiological conditions. Accordingly, materials scientists can learn from the design principle to produce engineered materials with reduced ecological footprints when compare to current state of the art techniques. In my group, we study the formation of these biological materials and their unmatched properties. We also test extracted principles to form similar materials synthetically with potential applications in biomedical research.

Biological Materials

Biomineralization is characteristically of primary importance for the biomineralizing organisms. The formed materials may even be vital for the organisms. Accordingly, it is for example impossible to turn off bone formation to study the associated mineralization pathway. In contrast, biomineralization in unicellular organisms can be turn on and off because the function of the materials there is not as primary as in the above mentioned case. In particular, coccolithophorid algae or magnetotactic bacteria survive and even live well when they are deprived from the main constituent building the mineral (Calcium for the former and Iron for the later). In addition, these organisms also play strategic geological roles for CO_2 fixation or in the Fe-cycle. In recent years, we have studied the mineral formation in these organisms by a variety of analytical approaches as described below. In addition, we have started to analyzed non-mineralized functional materials such as the teeth of the giant limpet **[1]**.

Calcite Biomineralization in Coccolithophores

Coccoliths **(Fig. 1)** are calcite crystals produced by coccolithophores, which are a group of unicellular algae representing a major part of the marine phytoplankton with potential effect on the geological sequestration of carbon dioxide. Each cell is surrounded by several coccoliths. The biological function of coccoliths is currently unclear. This work is based on a collaboration with the group of A. Scheffel from the neighboring Max Planck Institute of Molecular Plant Physiology.

The mechanism leading to the formation of the coccoliths has remained unclear; in particular the exact pathway followed by Calcium has remained elusive. We showed earlier that an intermediate phase might exist. Many organisms form minerals from such precursor phases but these remain challenging to identify. The connection of the identified Calcium–Phosphorus-rich pool to the mineralization process in particular remained to be unambiguously proven. We used Strontium to label the Calcium–Phosphorus-rich phase in the cells, and cryo X-ray absorption spectroscopy and analytical transmission electron microscopy to follow the Strontium within the algae. We demonstrated that the calcium used by the cells to build calcite indeed originated from the Calcium–Phosphorus-rich pool **[2]**.

In addition, using a combination of state-of-the-art cryoelectron and cryo soft X-ray microscopy, we demonstrated that the recently discovered Calcium-Phosphorus stores of coccolithophores were similar to the common Calcium storage organelles of noncalcifying organisms **[3]**. These results relate questions of environmental and evolutionary significance to a large body of physiological and molecular genetic findings of better-characterized organisms.

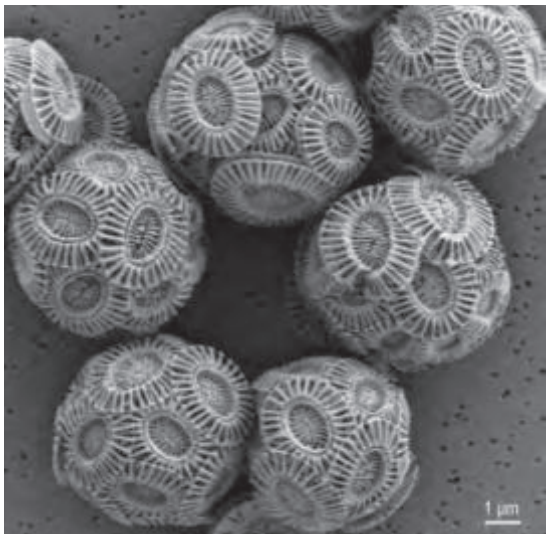

Fig. 1: SEM image of typical coccolithophore algae.

Magnetite Biomineralization in Magnetotactic Bacteria

Magnetotactic bacteria **(Fig. 2)** are a group of microorganisms that synthesize and organize magnetic nanoparticles called magnetosomes. The magnetosomes are membrane-enveloped magnetite (Fe_3O_4) or greigite (Fe_3S_4) nanoparticles that are supposed to help the cells navigating along the magnetic field lines of the Earth's magnetic field to reach their preferred conditions at the bottom of lakes / seas. One of our long-standing works has been to elucidate the chemical route by which magnetite is intracellularly formed. In our most recent study, we investigated the magnetosome organization and the potential applications of the bacteria.

We started by using simulations in collaboration with the group of S. Klumpp (Uni Göttingen) to study the assembly and the stability of magnetosome chains, which are constructed from particles attached to a filamentous structure. We showed that the filamentous backbone was crucial for the robust assembly of the magnetic particles into a linear chain, which in turn is key for the functionality of the chain in cellular orientation and magnetically directed swimming **[4]**. Our simulations underlined the dynamic nature of the magnetosome chain. More generally, they showed the rich complexity of self-assembly in systems with competing driving forces for alignment.

The bacteria have developed as a model for the understanding of how organization of magnetic nanoparticles can influence magnetic properties. We thus used ferromagnetic resonance spectroscopy combined with simulations to measure the magnetic anisotropies in species exhibiting different organizations **[5]**. In this way, we quantitatively characterized the magnetosome arrangement in both wild-type cells with aligned chains and *ΔmamJ* mutants, exhibiting magnetosome clusters.

Finally, we have studied a variety of potential application. For examples, we have shown that the bacteria can be used as transporter of drug to fight bacterial biofilms **[6]**. More surprisingly, the cells can also be used as remotely tunable photonic device **[7]**. We will continue to look for even less expected applications in the future.

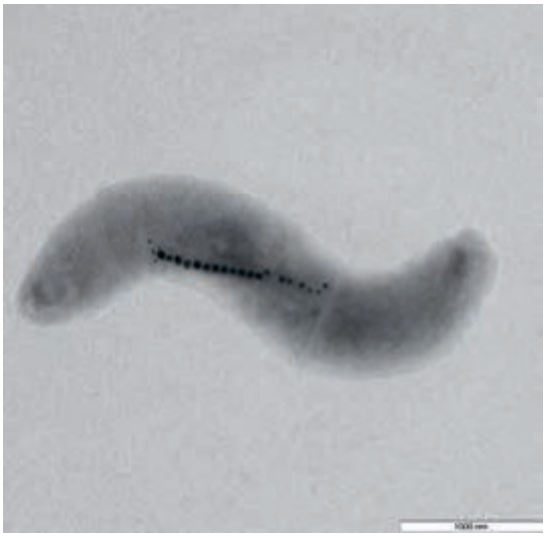

Fig. 2: TEM image of a typical magnetotactic bacterium and its characteristic magnetosome chain.

Biomimetic Systems

Reconstructing Biological Mineralization in the Beaker

The formation of intricately shaped crystalline minerals by organisms is orchestrated by specialized biomacromolecules. We had showed the role of the so-called baseplate in the concentration of calcium-rich particles reminiscent of coccoliths. In our most recent work, we reached the next step and achieved calcite mineralization **[8]**. In particular, we showed that the ioriginal calcium-rich phase could be mineralized into a thin film of single-crystalline calcite by the balanced addition of carbonate ions.

We also followed similar approaches for the mineralization and organization of iron oxides nanoparticles. In particular, we have used a simple polypeptide to control size and organization of magnetic nanoparticles **[9]**. Alternatively, we preferred a genetically-engineering approach to outperform simple biological organization as observed in the bacteria. Thereby, we could organize not only magnetite but also gold particles along a filament we additionally fluorescently marked to form a truly multifunctional materials **[10]**.

Random Synthetic Magnetic Swimmers

We finally profit from our expertise to synthesize and assemble nanoparticles to use these aggregates as steerable micro- to nanoswimmers **[11]**.

In contrast to previously designed magnetically actuated devices that all are of helicoidally- shaped, ours are of random morphology. This enabled us to particularly study the effect of shape and magnetization on the propelling properties **[12]**. We also compared the pattern formed by identical helical swimmers and by random-shaped ones **[13]**, showing that crystalline vs. amorphous patterns were respectively obtained.

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faivre@mpikg.mpg.de

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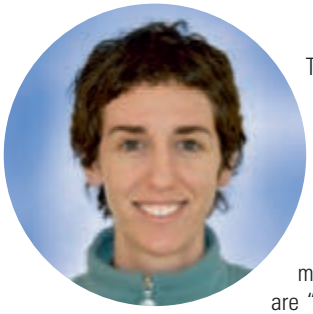
BIOLOGICAL CHITIN-BASED TOOLS AND SENSORS



Yael Politi
10.09.1976
1999–2001: Bachelor of Science majoring in Biology (with Honours) (Tel Aviv University, Tel Aviv, Israel)
2002–2004: MSc. Thesis: Transient amorphous calcium carbonate in sea urchin skeleton. (Weizmann Institute of Science, Rehovot, Israel)
2005–2009: Doctoral Thesis: The formation of transient amorphous calcium carbonate in biomineralization and its transformation into calcite. (Weizmann Institute of Science, Rehovot, Israel)
2009–2012: Postdoctoral Scientist Department of Biomaterials, Max Planck Institute of Colloids and Interfaces.
2009: Alexander von Humboldt Fellow
Since 07/2012: Research Group Leader, Department of Biomaterials, Max Planck Institute of Colloids and Interfaces

The arthropod cuticle is a fascinating multi-functional chitin-based composite material. Using simple building blocks, a narrow range of compositional modification but a wide range of structural organization motifs across multiple length scale (hierarchical organization), arthropods achieve an impressive variability in materials properties. Learning how biomaterials are "designed" and built bears implication for the synthesis of sustainable multifunctional materials.

The arthropod cuticle is made of chitin nano-fibers embedded in a protein matrix. The focus of the group "chitin based materials tools and sensors" is to investigate the relationships between the structure and properties of this composite material as well as elucidating cuticle formation mechanisms. These themes are investigated in this group through different topics: 1. Biological control over fiber orientation. Here we use a combination of scanning x-ray diffraction and high-resolution 3D imaging approach. The work is performed in collaboration with L. Bertinetti (MPIKG), Jan-Henning Dirks, Hochshule Bremen, Bremen, Germany) and Bernard Maussian (University of Nice Sophia Antipolis, Nice, France), 2. The relationship between structure and property in cuticular tools such as the spider fangs and claws and sensor auxiliary structures such as spider vibration sensitive slits sensors, hairs, compound eye cornea and more. The work is performed in collaboration with Friedrich Barth (Vienna university, Vieanna, Austria), Gerhard Scholtz (Humboldt university, Berlin, Germany) and Benny Ber-On (Gen Gurioun vuniversity, Beer-Shebba, Israel). The group also addresses the topic of biomineralization by studying synthetic systems as well as biomineral formation in marine organisms, mainly in sea urchins. This is done in collaboration with Emil Zolotoybako (Technion, Haifa, Israel) and Nadine Nassif (Sorbonne Universités, Paris, France).

Fiber Orientation Control in the Cuticle of the Desert Locust.

The fiber orientation in the cuticle has a large effect on the cuticle materials properties. But it is yet unknown how the control of fiber orientation is achieved during cuticle deposition. The cuticle is formed by epidermal cells which control the deposition of building blocks as well as the properties of the environment in which they are assembled **(Fig. 1)**. The three-dimensional structure of the cuticle exhibits ordered anisotropic organization similar to that of liquid crystals but it is fixed (solid) in its functional state. This has lead to the widely accepted hypothesis that the biological formation of the cuticle follows self-assembly of the bio-macromolecules into liquid ordered meso-phases. Evidence for or to the contrary of this hypothesis are, however, scarce despite its fundamental importance. We address this question studying cuticle deposition in *Locusta migratoria*, which shows daily cuticle growth layers of alternating chitin fiber arrangements. These vary between parallel ("day" cycle) and rotated plywood ("night") structures. Using cutting edge microscopy and 3D imaging along with quantitative x-ray scattering methods, we hope to shed light on this important question. Our results so far unravel an interplay between molecular self-assembly and active cellular control over fiber organization, but it is yet unclear to what extent and how these processes are orchestrated.

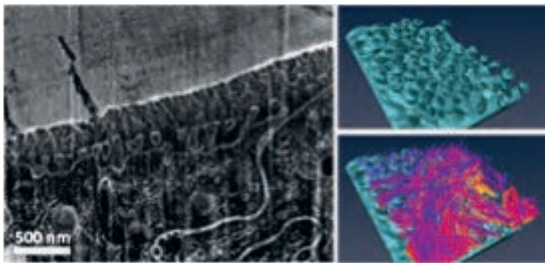


Fig. 1: cuticle deposition in L. migratoria. (left): the interface between epidermal cells (bottom) and the cuticle (top). The apical side of the epidermal cells forms microvilli from which chitin is synthesized and deposited in the "deposition zone" between the cells and the cuticle. (Right) upper panel: 3D reconstruction of the surface of the epidermal cells showing the lateral organization of the microvilli during night-type cuticle deposition. Bottom panel: the same cell surface with the freshly deposited chitin fibers in the deposition zone. Data is acquired in the "slice and view" method using FIB-SEM at room temperature with freeze-substituted cryo-fixed samples of locusts' tibiae.

Structure and Composition of Arthropod Cornea

The optical apparatus of each ommatidium (optical unit) of the compound eye of horseshoe crab, *Limulus poliphemus*, is made of cuticle material. In order to understand the optical mechanism of the cornea and lens (crystalline cone), we study the optical properties of the cuticluar cone and cornea structure and relate the findings to results from structural and compositional characterization. We show that compositional gradients as well as fiber architecture determine the optical properties of the cones, which in turn govern the light path and the optical mechanism.

Biomineralization

Biomineralization processes in living organisms result in the formation of skeletal elements with complex structures. Sea urchins build skeletal elements, which diffract X-ray as single crystals of calcite however they fracture like amorphous material and contain occluded organic molecules. The interrelation between calcite, amorphous calcium carbonate (ACC), and intracrystalline organics in adult sea urchin biominerals is however not yet clear. We studied this interplay in the spines and test plates of the *Paracentrotus lividus* sea urchins **(Fig. 3)**. Thermogravimetric analysis coupled with differential scanning calorimetry measurements, solid-state nuclear magnetic resonance (NMR), and high-resolution powder X-ray diffraction show that spines and test plates are composed of Mg-rich calcite, comprise about 1.2 to 1.6 wt % organics, 10 wt % of anhydrous ACC and less than 0.2 wt % of water. We proposed that anhydrous ACC originates from incomplete crystallization of a precursor ACC phase during spine and test plate formation and that it is associated with intracrystalline organics at the molecular level. Molecular interactions at organic/inorganic interfaces cause calcite lattice tensile type distortions. The latter are amplified during ACC crystallization and finally disap-

pear after heat-assisted destruction of the organic molecules. Following the stress evolution upon annealing we find that complete crystallization of ACC leads to the isotropy of residual stresses in all investigated skeletal parts.

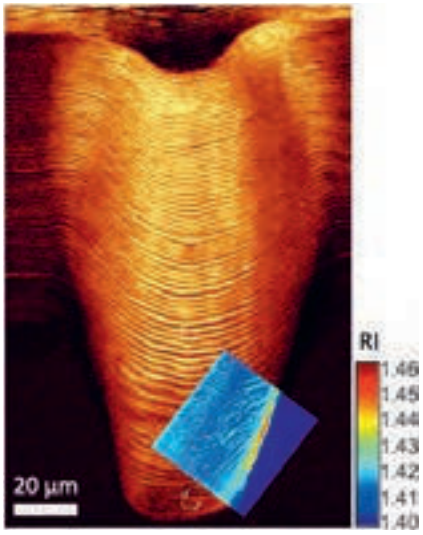


Fig. 2: Raman map of a single cone. The color scale shows the normalized intensity of the amide I peak) highlighting the chitin fiber orientation. Blue scale inset: Refractive Index (RI) mapping of the end of a cone using Holotomogrpahy. The RI follows primarily the chitin fiber orientation. In addition an out layer with increased RI is observed.

Not only sea urchins, but also many other organisms use amorphous calcium carbonate (ACC) and control its stability by various additives and water. We studied the effect of water and inorganic additives commonly found in biology on the dynamics of the structure of synthetic ACC during crystallization and on the energetics of this process. Total X-ray scattering and pair distribution function (PDF) analysis show that the short- and medium- range order of all studied ACC samples are similar; however, the use of *in situ* methodologies allowed us to follow small structural modifications that are otherwise overlooked. Isothermal calorimetry coupled with micro- gravimetric measurements show that the presence of Mg^{2+} and of PO_4^{3-} in ACC

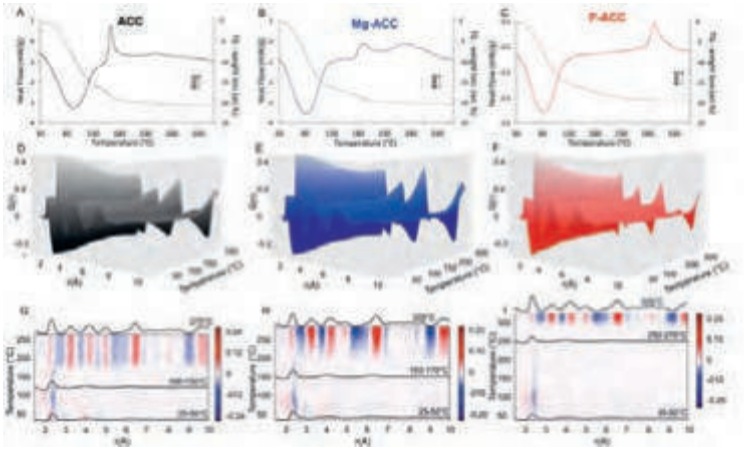


Fig. 4: TGA–DSC analysis of A) ACC, B) Mg-ACC, and C) P-ACC, PDF from in situ heating XRD measurements of D) ACC, E) Mg-ACC, and F) P-ACC and differential dPDF/dT maps of G) ACC, H) Mg-ACC, and I) P-ACC, averaged PDFs at selected temperatures are superimposed on the maps (black curves). For ACC, averaged PDFs between 25 and 50 °C (1.4 H2O), between 100 and 150 °C (0.4 H2O) and at 275 °C. For Mg-ACC, averaged PDFs between 25 and 50 °C (1.4 H2O), between 150 and 170 °C (0.2 H2O) and at 300 °C. For P-ACC, averaged PDFs between 35 and 50 °C (1.3 H2O), between 250 and 270 °C (0.4 H2O) and at 325 °C.).

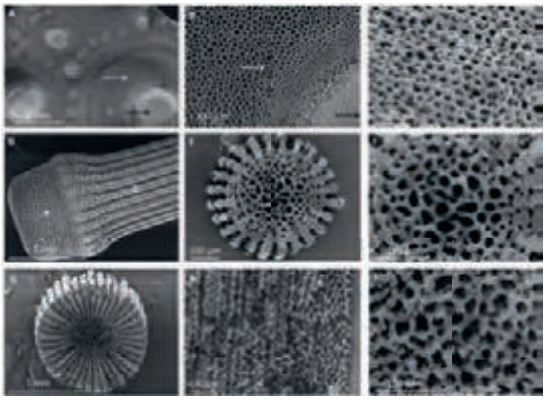


*Fig. 3: Scanning electron micrographs of the microstructure of sea urchin skeletal elements: (A) coronal plates with the tubercles (top of the tubercle: black arrow; base of the tubercle: white arrow); (B) high magnification of the tubercle; (C) cross-section of the coronal plate; (D) base (*) and shaft (Δ) of a small spine; (E) cross-section of the middle of the shaft of a small spine perpendicular to its long axis; (F) magnification of the inner stereom of (E); (G) cross-section of the middle of the shaft of a large spine perpendicular to its long axis; (H) cross-section along the long axis of the spines; (I) magnification of the inner stereom of (G). "Reprinted with permission from **[2]**. Copyright (2018) American Chemical Society."*

retards the crystallization whereas increased water content accelerates the transformation. Most interestingly, the enthalpy of ACC with respect to calcite appears to be independent of the additive concentration but it decreases with water content. The enthalpic contribution of water is compensated for by an equal and opposite entropic term leading to no correlation between ACC thermodynamic stability and its hydration level. We showed kinetic stabilization effect of inorganic additives and water **[1]** as well as organic additives **[3]**. Our results bear strong implications to the understanding of the biological control of mineral stability like in the sea urchin and other animals.

Y. Politi, R. Angermann, C. Goerdeler, O. Späker, B. Schonert, S. Sviben, M. Tadayon, A. Talib.
politi@mpikg.mpg.de

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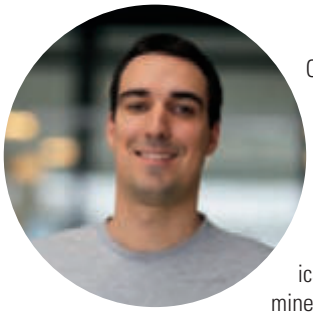
Physics of Biomolecular Interfaces



Emanuel Schneck
16.10.1979
2005: Diploma, Physics (Technical University of Munich) Thesis: Structure and Mechanics of Glycolipid Membrane Stacks studied by Specular and Off-Specular Neutron Scattering
2007: Research Stay, Institut Laue-Langevin (Grenoble, France)
2008: Research Stay, Kyoto University (Japan)
2010: PhD, Physics (University of Heidelberg), Thesis: Generic and Specific Roles of Saccharides at Cell and Bacteria Surfaces Revealed by Specular and Off-Specular X-Ray and Neutron Scattering
2010–2012: Post-Doctoral research, Technical University of Munich and Free University of Berlin
2012–2014: Marie-Curie Fellow, Institut Laue-Langevin (Grenoble, France)
Since 2014: Research Group Leader, Max Planck Institute of Colloids and Interfaces, Potsdam

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Cells and the biological organisms they form are constituted to a large fraction by functional biomolecular layers. The most prominent example are the biological membranes – only few nanometers in thickness – which have diverse functions in context with cell compartmentation and metabolism. It is the chemical characteristics of their surfaces that determine how the membranes interact with one another and with their surroundings, for example whether they spontaneously form multilamellar assemblies or whether they can be targeted by other molecules.

In our Emmy-Noether research group, supported by the German Research Foundation (DFG), we study the interaction of biological and technologically relevant soft interfaces with solutes (such as proteins) in their aqueous environment and also their mutual interaction in the aqueous milieu, with a specific focus on interactions involving biological membranes. One of our main goals is to understand the relation between membrane interactions and the molecular composition of membrane surfaces. In this context we are also interested in nature's strategies to control the interactions by adjusting the membrane composition.

X-Ray & Neutron Scattering Techniques and Complementary Computer Simulations

To address these questions, molecular-scale structural insight into the involved layers is required **[1, 2]**. In order to obtain such information, we prepare model systems of well-defined (bio-) molecular composition at solid/air, solid/water, liquid/water, and air/water interfaces and study them with various structure-sensitive techniques based on x-ray and neutron scattering **[3–11]**. In addition, we employ complementary methods, such as ellipsometry, calorimetry, tensiometry, and spectroscopy. Finally, computer simulations carried out in collaborations provide a means to interpret experimental results on a mechanistic level. To this end we have developed a simulation method that accurately accounts for the chemical potential of water between interacting surfaces, and which has recently led to a better understanding of the long-debated "hydration repulsion" between membranes **[12–14]**.

Molecular Conformations in Single and Interacting Bacteria Surfaces

The outer surfaces of Gram-negative bacteria are composed of lipopolysaccharide (LPS) molecules exposing oligo- and polysaccharides to the aqueous environment. This unique, structurally complex biological interface is of great scientific interest as it mediates the interaction of bacteria with antimicrobial agents as well as with neighboring bacteria in colonies and biofilms. Structural studies on LPS surfaces, however, have so far dealt almost exclusively with rough mutant LPS of reduced molecular complexity. With the help of neutron reflectometry, we investigate planar monolayers of wild-type LPS featuring strain-specific linear polysaccharides (so-called O-side chains) in the presence and absence of divalent cations and under controlled interaction conditions **(Fig. 1)**. The saccharide profiles are found to be bimodal, with dense internal oligosaccharides and more dilute, extended O-side chains **[6]**. The structure is significantly affected by a depletion of calcium: the lateral packing is reduced, and water appears to overlap with the hydrocarbon chain region. At the same time the internal oligosaccharides become more extended in the perpendicular direction. Both effects can be attributed to enhanced electrostatic repulsion in the absence of divalent cations and yield insight into the enhanced vulnerability of bacteria under these conditions. For interacting LPS monolayers we have established the pressure-distance curve and determined the distance-dependent saccharide conformation. The pressure-distance data are well described by the Alexander-de-Gennes model of interacting polymer brushes. The O-side chain conformation is nearly un-perturbed at the largest separation, with only a weak overlap at the midplane (**Fig. 1**). The corresponding central water fraction is above 90 %, suggesting the preservation of hydrodynamic pathways for small molecules **[6]**.

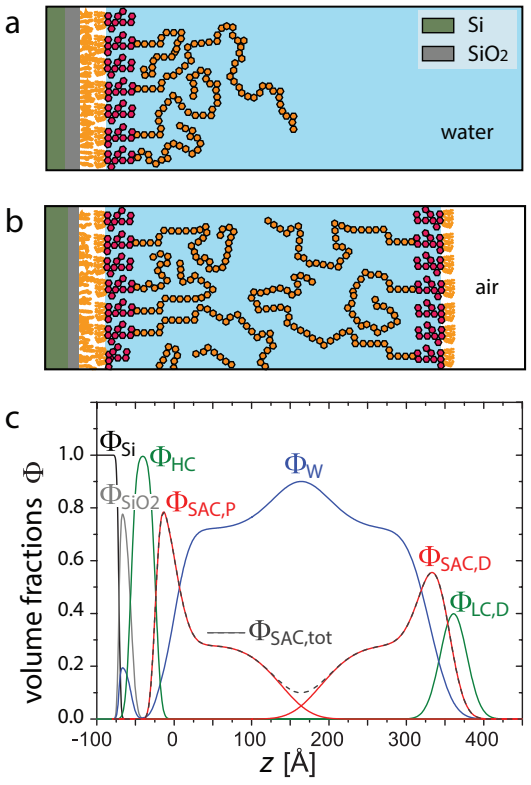

Fig. 1: (a and b) Schematic illustrations of one single and two interacting solid-supported LPS surfaces mimicking the outer surfaces of bacteria. (c) Volume fraction profiles of all chemical components as obtained by neutron reflectometry with contrast variation.

Stability of Membrane Stacks – A Matter of the Dipoles

Naturally occurring membrane stacks, such as the photosynthetically active thylakoids, exhibit high glycolipid contents. In contrast to the commonly studied phospholipids, glycolipids in their headgroups display many small electric dipoles in the form of OH groups instead of a single large dipole **(Fig. 2)**. This difference is determining for the spontaneous stack formation

of glycolipid membranes, as we have recently found out **[12]**. We have used atomistic molecular dynamics simulations **(Fig. 2)** to first reproduce experimentally obtained pressure-distance curves between phospho- and glycolipid membranes and to then analyze them. The analysis revealed that the physical mechanisms responsible for the strong short-range repulsion between phospholipid membranes are inoperative for the glycolipids, due to the architecture of their headgroups. The key aspect are the interactions between the lipid molecules and the water molecules. As a result, stack formation of glycolipid membranes is promoted **[12]**.

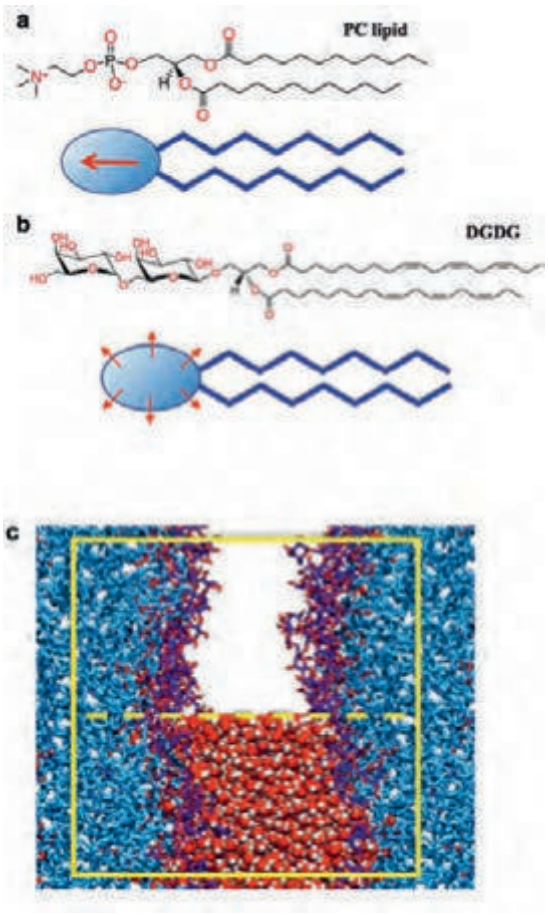

Fig. 2: Chemical structures of (a) a PC lipid with one large electric dipole and of (b) a glycolipid (here: DGDG) comprising multiple small electric dipoles in the form of OH groups. Both are schematically illustrated below the chemical structures. (c) Simulation snapshot of interacting DGDG membranes. The simulation box with periodic boundary conditions is indicated with a bright rectangle. For illustration, water molecules are only shown in the lower half of the box.

Protein Adsorption to Material Surfaces

The adsorption of proteins onto the surfaces of implants and drug delivery systems is commonly believed to be the initial step of harmful foreign body response in patients. In order to suppress undesired protein adsorption, artificial materials in biomedical applications are often functionalized with end-grafted hydrophilic polymer chains, so-called "polymer brushes". This approach, however, does not always lead to the results hoped for. With the help of neutron reflectometry, we obtain detailed insights into the adsorption characteristics of proteins out of human blood serum onto polymer-functionalized solid surfaces **[3, 4]**. It turns out that the brushes do not completely suppress protein adsorption **(Fig. 3)**. By contrast, certain blood proteins, whose identity is still unknown, do even accumulate within the brushes in the form of a so-called "ternary adsorption". These results challenge the common picture of the working principle of polymer brushes and suggest that it may have to do with the suppression of protein-protein recognition as secondary effect **[3]**.

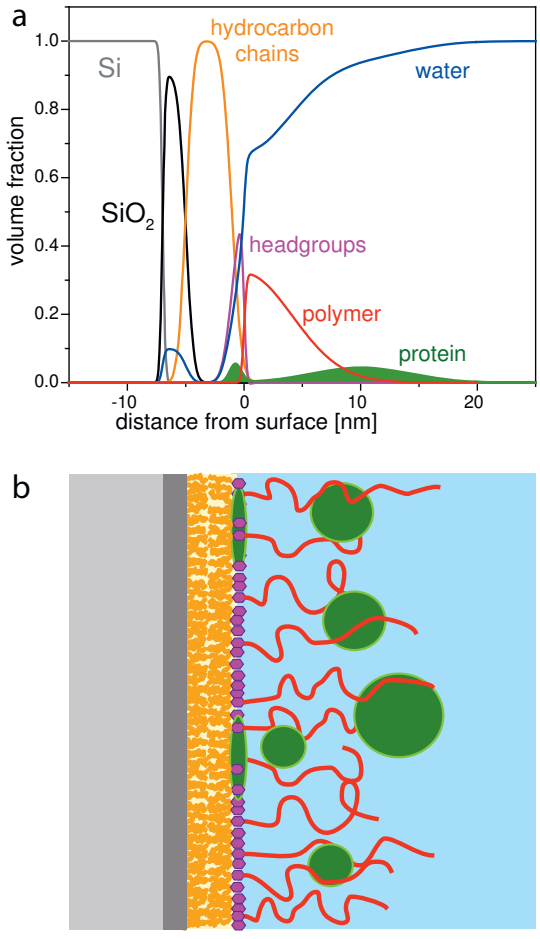

Fig. 3: (a) Spatial distribution of various chemical components after the adsorption of proteins onto a polymer-functionalized silicon surface. The distributions are obtained by neutron reflectometry with contrast variation. (b) Schematic illustration of the protein distribution in the polymer brush.

E. Schneck, G. R. Del Sorbo, G. Gochev, V. M. Latza, S. Micciulla, I. Rodriguez-Loureiro, E. Scoppola, C. Stefaniu, W. Zhang
schneck@mpikg.mpg.de

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Hierarchical Structure of Biological and Biomimetic Materials

Wolfgang Wagermaier
19.06.1974
2003–2006: PhD, Materials Science (MPI of Colloids and Interfaces, Potsdam and Montanuniversität Leoben)
Thesis: Synchrotron x-ray diffraction studies of nanoscale bone structure and deformation mechanisms
2007–2009: Postdoc, (GKSS Research Center, Center for Biomaterial Development, Teltow)
Since 2009: Group Leader (Max Planck Institute of Colloids and Interfaces, Potsdam)
2017: Habilitation in Materials Science (Technische Universität Berlin)

In our group, we combine various materials science approaches to answer biological questions in natural materials and to understand structure-function relations in biological and synthetic materials. One major aim is to elucidate biological processes and to transfer knowledge from natural materials to the design and optimization of man-made materials, such as polymer-based hybrid materials and nanostructured mineral-based materials.

In our research, bone serves as a typical hierarchically structured material with extraordinary mechanical properties. As a living organ, bone has the capability to adapt its shape and architecture to altered environmental conditions and to regenerate after injury. These biological processes are accompanied by changes in the material structure at each hierarchical level which can be studied by materials science methods. The research on bone is performed in collaboration with partners from the Shriners Hospital in Montreal, Canada and the Ludwig Boltzmann Institute of Osteology in Vienna, Austria.

Our main experimental methods are x-ray scattering (SAXS, WAXS), confocal laser scanning microscopy (CLSM), electron microscopy (EM) and micro-computed tomography (µCT). For x-ray scattering experiments, we use our laboratory sources as well as synchrotron radiation – the MPI µSpot beamline at BESSY II (Helmholtz-Zentrum Berlin für Materialien und Energie, Berlin Adlershof). This beamline is also equipped with a Raman microscopy setup for simultaneous measurements with SAXS, WAXS and Raman **[1]**.

Bone Healing

Bone has the ability to regenerate its structure and function after fracture by forming a bony callus around the gap to stabilize the bone. We investigated a mouse osteotomy model and analyzed newly formed callus tissue and mature lamellar bone in the cortex. This model exhibits three types of bone with different fibrillar organization: (i) woven, (ii) moderate lamellar and (iii) lamellar.

We demonstrated that woven bone differs strongly from lamellar bone regarding collagen fibril orientation as well as in amount, orientation and shape of mineral particles. The changes in the minerals are likely to contribute to the reduced mechanical competence of woven bone compared to lamellar bone. This may explain why over time many organisms replace less organized bone regions with more organized tissue **[2]**.

In addition, we investigated the osteocyte network in the bone healing model to elucidate the functionality of these bone cells **[3]**. Osteocytes are located in lacunae which are connected by narrow channels, namely canaliculi, to construct the osteocyte lacuno-canalicular network (LCN). Osteocytes are presumed to play a direct role in mineral homeostasis by resorbing and depositing bone mineral from their immediate vicinity. We characterized the LCN architecture and the mineral particle dimensions across different types of tissue. Compared to the cortex, the callus lacunae are more randomly distributed and many lacunae have few canaliculi, such as those located near highly mineralized cartilage islands **(Fig. 1)**. The correlations found between LCN architecture and mineral particle parameters may indicate an osteocytic influence on mineralization **[3]**.

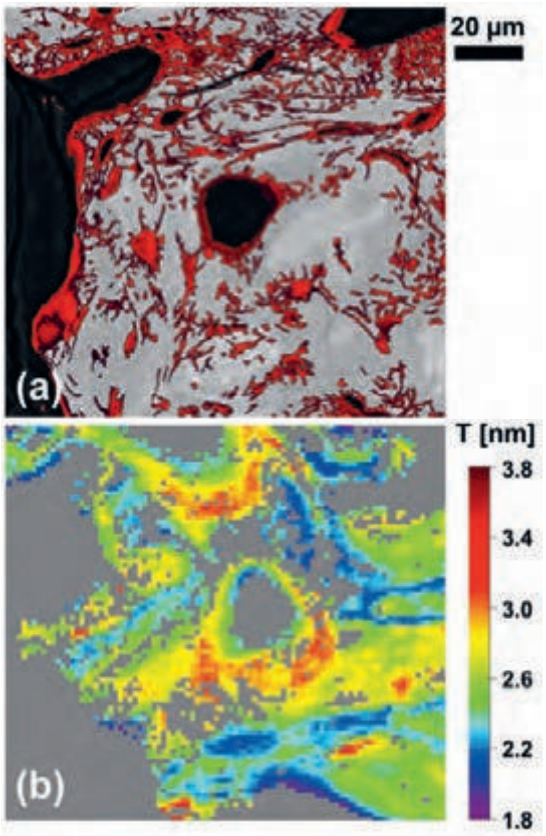

*Fig. 1: Bone healing visualized by a combination of high resolution x-ray scattering, quantitative backscattered electron microscopy and CLSM **[3]**: (a) backscattered electron microscopy image with overlaid (in red) data from CLSM showing the architecture of the LCN; (b) mineral particle thickness (T parameter in nm) measured by synchrotron SAXS from of the same area as shown in (a).*

Mineralization in Healthy and Diseased Bone

The material properties of diseased bone often differ from healthy bone due to altered mineralization processes. By comparing material properties between diseased and healthy bones through our multi-method approach, we could better understand the mechanisms lead to the bone disease.

Bone mineral nanoparticles are likely to influence the pathogenesis of skeletal metastasis in breast cancer. We found that bone regions associated with the initiation of metastasis contain less mature mineral particles and that mammary tumors enhance mineral particles immaturity in these regions even prior to secondary tumor formation **[4]**.

At the femoral neck of elderly people, there is an increasing amount of hypermineralized bone tissue which might increase the hip fracture risk. We found that this tissue had significantly thinner, shorter and more irregularly distributed mineral platelets compared to normal lamellar bone. This mineral alteration could contribute to the reduced fracture resistance of the femoral cortex **[5]**.

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Polymer-based Synthetic Materials

We explored structure-function relations in diverse nano-structured fibers, namely materials made from cellulose **[6]** as well as fibers from recombinant, synthetic proteins, inspired from spider silk **[7, 8]**. We showed how cellulose nano-fibrils with high aspect ratio can be efficiently aligned in extrusion to fibers, leading to increased modulus of toughness, Young's modulus and yield strength by increasing the extrusion capillary length, decreasing its diameter, and increasing the flow rate. Wide angle x-ray scattering confirmed that the enhanced mechanical properties are positively correlated with increased alignment. Our results suggest a possible pathway that can be integrated into a gel-spinning process to simultaneously acquire high stiffness, strength and toughness **[6]**.

We investigated the formation process of synthetic proteins inspired by spider silk. This type of protein has a three-block architecture consisting of two folded terminal domains and one mid-section consisting of a repetitive spider fibroin (spidroin) sequence. We showed how coacervates formed by liquid-liquid phase separations which serve to form materials from dilute solutions **[7, 8]**.

To elucidate the first steps of the formation process, we used *in situ* synchrotron x-ray scattering measurements of a drying droplet of recombinant spider silk and found that the amount and ordering of beta-sheet structures strongly depend on protein concentration, humidity and temperature **[8]**. This study might contribute to optimize the synthesis of new materials from solution and to determine properties of the final products at specific humidity levels and temperatures.

Hybrid materials exhibit a large interface between an inorganic phase and an organic matrix at the nanoscale. Such large interfaces are a main condition for enhanced mechanical properties in natural as well as synthetic materials. We investigated hybrid materials produced by collaborators from HU Berlin (Prof. Hans Börner). This model system is based on magnesium fluoride nanoparticles (MgF_2) embedded in a PEO matrix **[9]**. The interface between these phases consists of a peptide side adhering specifically to the inorganic surfaces of the nanoparticles and a PEO side which bonds well with the matrix. We showed that the mechanical properties of the composites could be increased with the amount of conjugate adhered to MgF_2 nanoparticles. Small angle X-ray scattering revealed that the hybrid material indeed primarily contains particles in the size of a few nanometers which in non-agglomerated form may greatly contribute to the improved mechanical performance **(Fig. 2) [9]**.

The Effect of Strontium Incorporation in Calcium Carbonate Microlens Arrays

By exploring fundamental formation and crystallization processes in a calcium carbonate-based microlens array (MLA) system, we aim to better understand general biomineralization processes. We produced thermodynamically stable, transparent microlens arrays by transforming an amorphous $CaCO_3$ phase into nano-crystalline calcite.

In a short review, we illustrated basic strategies to produce optical materials from $CaCO_3$ by manipulating the material structure and identified three main possibilities to make optical materials based on $CaCO_3$: (i) orienting the optical axis along the desired light propagation direction, (ii) stabilizing metastable phases, and (iii) producing nanocrystalline structures, which reduce birefringent properties **[10]**.

In our microlens model system, we currently perform crystallization experiments starting from strontium-rich amorphous calcium carbonate (ACC) to investigate the effect of incorporating ions into the calcite crystals. Thereby we follow two different routes: (i) in a high humidity environment at room temperature, and (ii) upon heating at 300 °C. In both cases, x-ray diffraction measurements revealed the formation of particular crystal phases with the ability to take up substantial amounts of strontium.

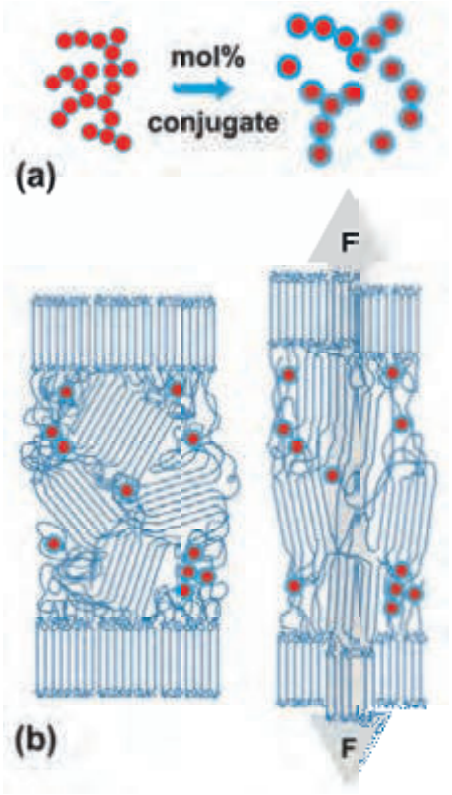

Fig. 2: Schematic illustration of the hybrid material made from PEO (light blue lines) and MgF_2 nanoparticles (red; surrounded by conjugate in light blue). (a) changes of the agglomeration behavior with increasing conjugate amount derived from the fractal dimension measured by SAXS. Conjugate suppresses the agglomeration of the MgF_2 nanoparticles. (b) deformation mechanism of PEO + MgF_2 nanoparticles with conjugate during applied tensile stress. Conjugate leads to a stabilization of the amorphous phase resulting in faster block-slip mechanisms as compared to a non-filled polymer.

W. Wagermaier, P. De Falco, A. Gjardy, C. Li, A. Roschger, V. Schemenz, I. Schmidt, S. Siegel, T. Tang, D. Werner, F. Zemke and I. Zenke
wolfgang.wagermaier@mpikg.mpg.de

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Mechanobiology

Richard Weinkamer
14.08.1967
1995: Diploma, Mathematics
(University of Vienna, Austria)
Thesis: The modular group: an investigation with methods of combinatorial group theory
1998: Research Stay
(Rutgers University, New Jersey, USA)
2000: PhD, Physics
(University of Vienna, Austria)
Thesis: Diffusion and diffusional phase transformations in binary alloys: Monte Carlo simulations of lattice models
2000–2003: Postdoctoral Scientist,
(Erich Schmid Institute of Materials Science, Leoben, Austria)
Since 2003: Group Leader
(Max Planck Institute of Colloids and Interfaces, Potsdam)
2012: Habilitation in Theoretical Physics
(Humboldt University, Berlin)
Thesis: Processes in living bone and the resulting structural changes – computational studies

Biological materials change their structure on very different time scales. In bone, cellular sensing and signaling responses occur in seconds, the first rapid incorporation of mineral (primary mineralization) into newly formed bone in days, the renewal of bone via remodeling in weeks, the healing after fracture in months, the deterioration of the bone material due to aging in years, and the evolutionary adaptation of the bone structure in millennia. Our research focus is how mechanical stimuli influence and regulate the different processes that result in structural changes and adaption in bone. A key player in these processes are osteocytes, the most abundant bone cells. Being completely encased in the mineralized bone matrix, these cells eluded systematic scientific investigations for a long time. Important for understanding their function is their organization in an intricate cell network, where the cell bodies are housed in lacunae and the cell processes in submicrometer thin channels called canaliculi. A promising research strategy is to study the connectome of this lacunocanalicular network (LCN) to clarify the multiple functions that are attributed to the osteocyte network. These functions include mechanosensation of a load-induced fluid flow through the canaliculi, the extraction and deposition of mineral from the surrounding bone using the large surface of the LCN, and signaling and transport of nutrients. A current research aim is, therefore, to establish a quantitative relation between the LCN architecture and parameters of bone health and disease.

Structural Network Analysis

The structure of the lacunocanalicular network was analyzed by a combination of staining the bone sample, imaging using confocal laser scanning microscopy and image analysis with a specifically developed software. The focus was first on osteons, the main building block of human cortical bone **(Fig. 2)**. For healthy adults a reference value for the density of the network was obtained with 74 km of network length within a cubic centimeter of cortical bone. Our interpretation of large areas in osteons without network is that with the death of osteocytes the surrounding network gets clogged **[1]**. A structural interdependence between canaliculi and fibrous collagen matrix could be demonstrated by a coalignment between the direction of lateral canaliculi (i.e., canaliculi not pointing towards the central Haversian canal of the osteon) and the preferred orientation of the collagen matrix **[2]**. While connectomics approaches are already well developed in neuroscience, a framework to relate the connectome of the LCN and the functionality of the network has still to be developed **[3]**. As first pioneering steps in this direction, we could show that important network properties are conserved independent of the species and the degree of order of the tissue organization (woven bone vs lamellar bone) **(Fig. 1)** suggesting the presence of a more universal self-organization process to form the cell network **[4]**.

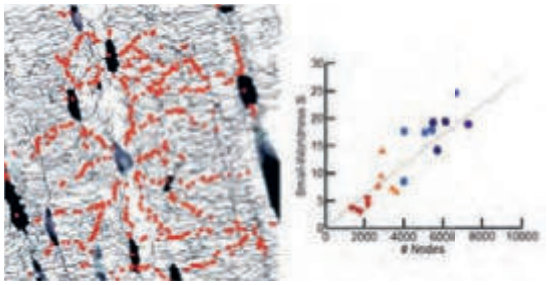

Fig. 1: Connectomics approach to characterize the lacunocanalicular network (LCN) in different species. Left, the LCN in ovine fibrolamellar bone with dark "blobs" marking the lacunae and the fine lines the canaliculi connecting the lacunae. With red dots nodes in the network are highlighted with a particularly high betweenness, i.e. many shortest paths connecting two nodes pass through these nodes. The lining up of these red dots indicate the existence of a kind of "highway system" in the LCN. Right, the parameter of small worldness, characterizing how efficient a network is in connecting distant nodes with as few edges as possible, is higher in fibrolamellar ovine bone (light and dark blue) compared to woven murine bone (red and orange) and depends roughly linear on the number of nodes in the network.

Towards a Functional Network Analysis

The availability of 3D structural data of the lacunocanalicular network provokes the question of how this data can be interpreted in terms of the multiple functions of the network. A widely accepted hypothesis explains the mechanosensitivity of bone due to a fluid flow through the network caused by the loading of the bones and a sensing of this flow by osteocytes. To analyze the influence of the intricate network structure on the fluid flow through the network, we investigated two different types of human osteons. Beside normal osteons, the fluid flow was specifically studied in a frequent sub-type of osteons – osteon-in-osteons – which are characterized by a ring-like zone of low network connectivity between the inner and outer part of these osteons. The calculated fluid velocity was 2.3 times higher in osteon-in-osteons compared to normal osteons. In particular, extended paths across the osteon of very high velocity were observed in osteon-in-osteons **(Fig. 2)**. Our analysis suggests that osteon-in-osteons have to be seen as significant contributors of mechanosensitivity in cortical bone, in particular in the low loading regime of daily activity. Currently the fluid flow analysis is applied to mouse tibiae, from which the recent sites of bone formation and resorption are known from *in vivo* microcomputed tomography imaging **[5]**.

Evidence is accumulating that the large surface of the LCN is used by the osteocytes to access the mineral in the surrounding bone matrix thereby contributing to mineral homeostasis. In a study on human osteons we spatially correlated the local density of the LCN with the mineral content at the same location in micrometer-sized volume elements. As the LCN-porosity lowers the local mineral content, a negative correlation between Ca content and network density was expected. However, the experiment revealed for 66 out of 71 osteons a positive correlation resulting in an average additional Ca loading of +1.13 fmol per µm of canalicular network, i.e. an accumulation of mineral has occurred at dense network regions **[6]**. Signifi-

cant differences found between individuals indicate that the extent of additional mineral loading by the network could be an important parameter for mineral homeostasis.

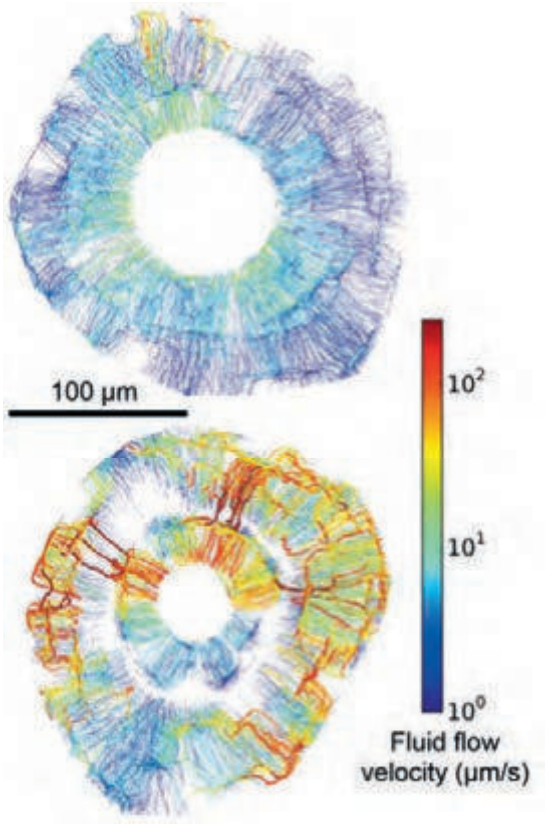

Fig. 2: Fluid flow through the lacunocanalicular network in different types of osteons in human cortical bone. On top a normal osteon with the Haversian canal in the center and most of the canaliculi oriented towards this central canal. At the bottom, an osteon-in-osteon, which is characterized by a low network connectivity between the outer and the inner osteon. Using circuit theory the fluid flow through the network was calculated. The fluid flow in osteon-in-osteons is more heterogeneous with very high flow velocities in connection with the few bridges connecting the inner and outer part of the osteon.

Mineralization Kinetics

Newly formed bone is unmineralized. Only with time mineral is incorporated into the collagen matrix. This mineralization process together with the remodeling of the bone results in a spatially heterogeneous distribution of the mineral content. This heterogeneity can be quantified experimentally by measuring the frequency distribution of mineral content, the bone mineral density distribution (BMDD). A simple mathematical model has been developed, which allows to connect the rate of incorporation of mineral, the rate of bone turnover and the shape of the BMDD **[7]**. This model was applied to test different hypotheses of late stages of the mineralization process, which are particularly challenging to access experimentally. Too abrupt stops of the mineralization process would lead to an additional peak in the BMDD or to a strongly asymmetric BMDD peak, two occurrences which are not observed experimentally. Consequently, we conclude that mineralization proceeds in humans slowly up to a calcium content greater than 30 wt% Ca **[8]**. In a second study we employed the model to explain the shift of the BMDD peak towards higher mineral content in cortical bone compared to trabecular bone. The analysis showed that the different turnover rate in the two bone types does not provide a sufficient explanation, but that the mineralization kinetics has to be different in cortical compared to trabecular bone.

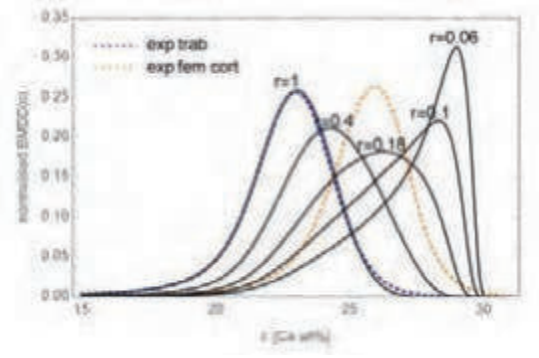

Fig. 3: Comparison between experimentally obtained bone mineralization density distributions (BMDDs) and model predictions. Measured BMDDs for trabecular (dashed blue) and cortical bone (dashed orange). The parameter r for the theoretical BMDDs denote the turnover rate with r=1 corresponding to a normal turnover rate in trabecular bone (i.e., turnover time equal to 5 years). For the late stage of mineralization it was assumed that a maximum Ca content of 30 wt% was attained slowly. None of the calculated BMDDs fit the experimental BMDD of cortical bone which suggests the conclusion that different turnover alone cannot explain differences in the BMDD between trabecular and cortical bone.

R. Weinkamer, J. Cheng, P. de Falco, J. Ferracci, C. Pilz, A. Roschger, A. van Tol
richard.weinkamer@mpikg.mpg.de

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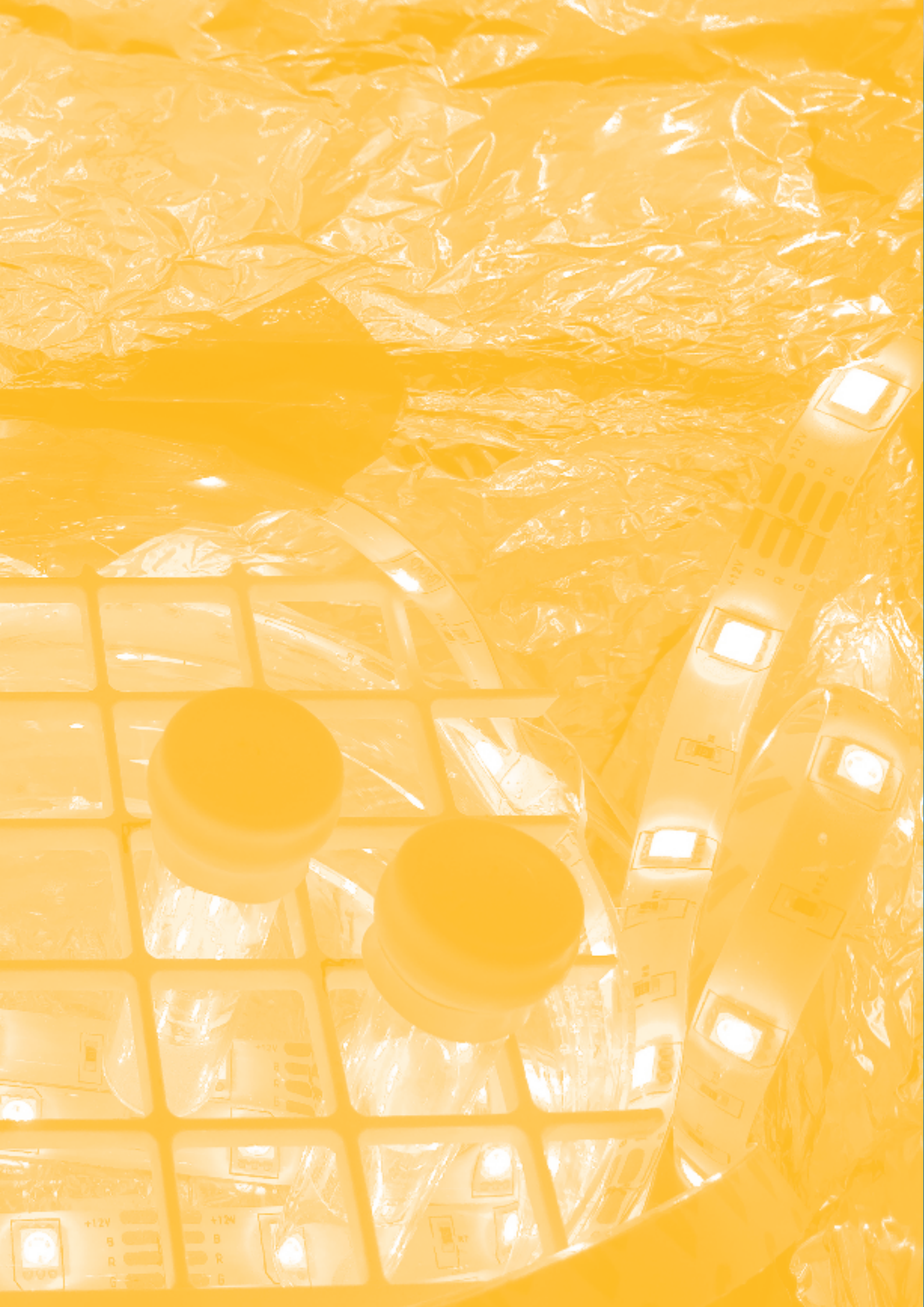

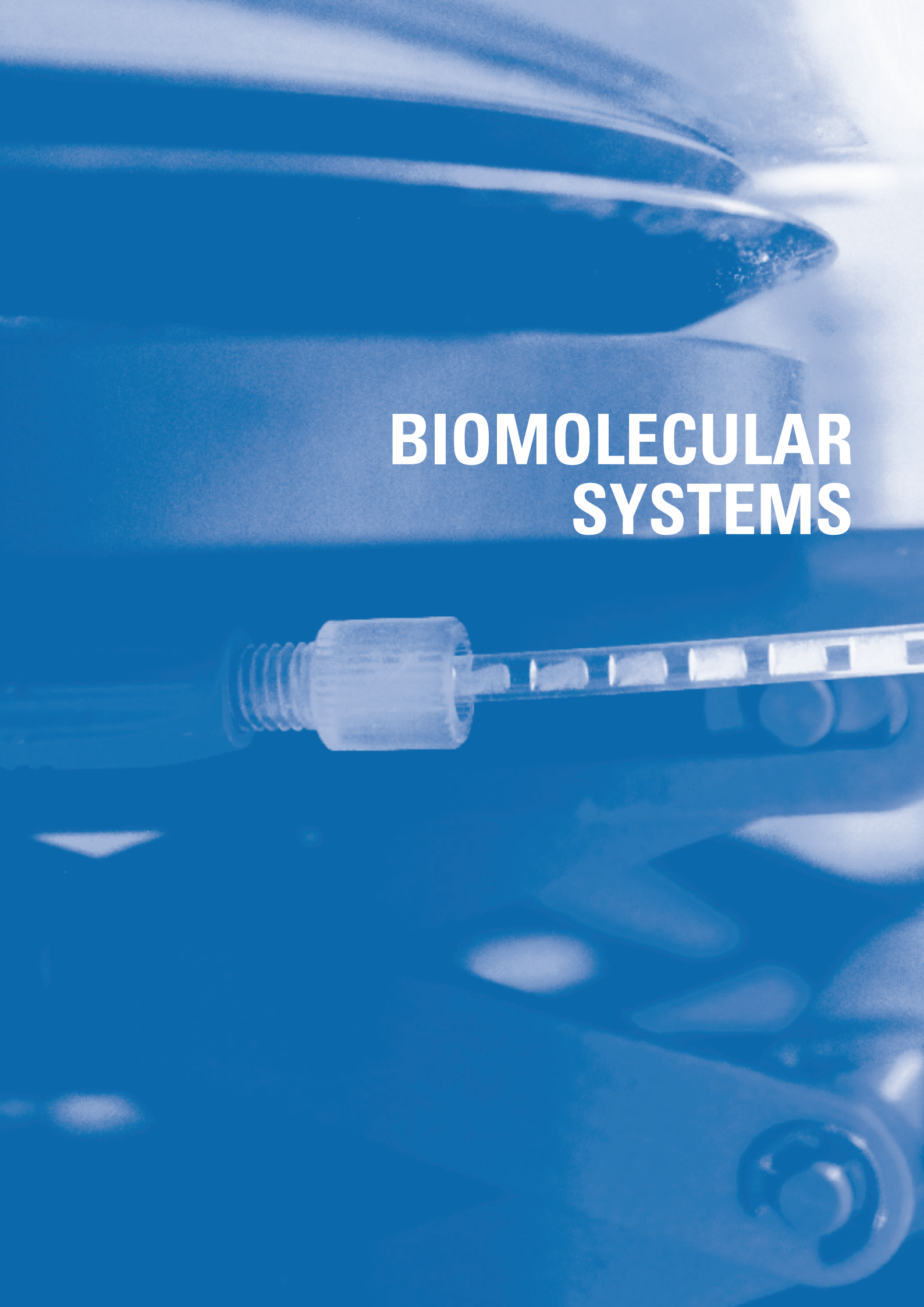

BIOMOLECULAR SYSTEMS

RESEARCH IN THE DEPARTMENT OF BIOMOLECULAR SYSTEMS

Peter H. Seeberger
14.11.1966
1989: B.S. (Univ. Erlangen-Nürnberg)
1995: PhD, Biochemistry
(Univ. of Colorado, Boulder)
1995–1997: Research Fellow (Memorial Sloan-Kettering Cancer Center)
1998–2003: Assistant and Associate Professor (Massachusetts Institute of Technology, MIT, Cambridge, USA)
2003–2009: Professor (ETH Zurich, Switzerland)
Since 2009: Director, Department for Biomolecular Systems
(Max Planck Institute for Colloids and Surfaces, Potsdam)

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The Department for Biomolecular Systems conducts research at the *interface of chemistry, engineering, biology, immunology, medicine and materials science*. The approach is trans-disciplinary and interactive between the groups in the department that cover different areas of expertise. The core focus are the glycosciences and the development of *synthetic methods* for the automated assembly of defined polysaccharides. The glycans serve as *chemical tools* that aid *biological investigations* into the fundamental roles complex carbohydrates play in biological processes that underlie disease. Insights into how the mammalian immune system recognizes oligosaccharides associated with various infectious diseases laid the foundation for *vaccine development* efforts concerned with the carbohydrate antigen and novel modes of presentation to the immune system.

The department has been operating at steady state. In the past two years, two group leaders left the department. Dr. Zoltan Konthur started a company and Dr. Ursula Neu moved as a Habilitand to Freie Universität Berlin. At the same time, four new group leaders joined the department. Dr. Martina Delbianco is now in charge of the "Polysaccharide Materials" group that was funded by a Minerva Fast Track Fellowship and raised a substantial Max-Planck-Fraunhofer grant. Dr. Oren Moscovitz was promoted to the position of group leader in 2018 and focuses on the development of nanobodies as binders for carbohydrates to diagnose and treat disease. The work in his group has already resulted in the spin-off company "Tacalyx" that received an A-Round of financing of 7 Mio € in 2019. Dr. Christian Roth joined the department in 2017 to replace Dr. Neu and add strength in X-ray crystallography studying carbohydrate-processing enzymes. Starting in 2018 Dr. Bartholomäus Pieber set up the "Catalysis Group" that closely collaborates with the Colloid Chemistry department by using semi-conducting materials originating from where and has received a Liebig Fellowship to support his group. Together, we are actively pursuing different questions in the glycosciences including the structure, function and biological role of sugars found on the surface of mammalian and bacterial cells particularly in the areas of immunology, biochemistry and human disease.

Our efforts in creating and understanding novel carbohydrate materials have grown significantly. Fueled by our ability to prepare polysaccharides as large as 100-mers, collaborations with the *Biomaterials Department* as well as the MPIs in Stuttgart and Bremen for structural investigations.

Continuous-flow chemistry has benefitted from a close collaboration with the Colloids Department that provide key catalysts for efficient transformations in the context of the synthesis of active pharmaceutical ingredients. The MPI in Magdeburg has been a close partner in developing methods for flow synthesis and purification.

Automated Glycan Assembly

AGA, our core technology has reached a new level of sophistication. With several home-built and one *Glyconeer 2.1* synthesizers and commercial building blocks in place we are developing even better instruments and methods.**[1]** Polysaccharides as long as 100-mers have been prepared using ever faster coupling cycles. **[2]** AGA is now a standard tool to prepare diverse sets of polysaccharides that enable investigations into new areas of biology as well as material sciences. Synthetic oligosaccharides have fueled our glycan microarray screening facility **[19]**, work with glycan nanoparticles, and collaborations to elucidate fundamental biological processes with the aid of X-ray crystallography. **[17]**

Synthetic Carbohydrate Vaccines

The medicinal chemistry approach to carbohydrate vaccine development has yielded fundamental insights into the interplay of bacterial polysaccharides and the mammalian immune system. A series of carbohydrate antigens present on serious bacterial pathogens including *Klebsiella pneumoniae* **[8]**, *Streptococcus pneumoniae* **[7, 9, 11, 18]** have been prepared and have been tested in challenge studies in experimental animals including mice, rabbits and pigs. Novel modes of formulation including carriers and adjuvants have given rise to attractive vaccine candidates for translation into humans.

Plant Carbohydrates

A polysaccharide-rich matrix constitutes the cell wall of all higher plants. Synthetic glycans are key tools for investigating plant cell walls, and automated glycan assembly was key to preparing 80 synthetic glycans. A synthetic plant glycan microarray has been key to investigating antibodies recognizing plant cell wall glycans and enzymes involved in the biosynthesis of the plant cell wall. The glycosynthase-catalyzed polymerization provided access to a series of artificial xylan polysaccharides with defined substitution patterns for structure-property relationship studies.

Carbohydrate Materials

The group uses AGA to prepare collections of related glycans, to establish structure-property correlations of polysaccharides. Different classes of polysaccharides were found to adopt fundamentally different conformations, such as helices or rod-like structures, that can be disrupted by single-site substitution. **[12]** This approach was followed to systematically manipulate hydrogen bonds and create novel tailor-made cellulose derivatives with drastically improved water solubility and affected aggregation behavior. Moreover, it was discovered that simple synthetic oligosaccharides self-assemble into nanostructures of varying morphologies. Well-defined differences in chain length, monomer modification, and aggregation methods yielded glycomaterials with distinct shapes and unexpected excitation-dependent intrinsic optical properties. **[20]**

GPI Group

The group investigates methods for the production of GPI-anchored proteins and glycoproteins and the application of GPI glycolipids as markers for the diagnosis of parasitic infections by protozoa. A bead-based detection of toxoplasmosis illustrates the potential of this approach over commercial methods for seroepidemiological studies. Three intein-mediated strategies to attach expressed proteins to synthetic GPIs were developed to prepare Thy-1 proteins and MSP-1 from *Plasmodium*

falciparum that induced the production of proinflammatory cytokines *in vitro*.

Glycoimmunology

The group develops specific and potent small molecules probes for glycan binding proteins fostered by a strong focus on biophysical techniques such as NMR and SPR **[2]**. A ligand for the C-type lectin receptor Langerin, serves as the basis for a novel delivery platform for skin-based vaccines in nanomedicine. Langerhans cells (LCs) are located in the epidermis, the upper layer of the skin. Human Langerin is a LC-restricted C-type lectin receptor. A small molecule ligand specific for this receptor is a mediator of antigen delivery via liposomal formulations. These nanoparticulate formulations can encapsulate toxins, small molecules and protein antigens and release their cargo intracellularly. These highly specific nanoparticles have the potential to build the basis for innovative delivery of vaccines via the skin.

Synthetic Array Technologies

Interdisciplinary research in physics, engineering, chemistry, biology, and computer science enables miniaturized high-throughput chemical syntheses. The group has developed laser-based microarray technology by combining state-of-the-art laser processing methods with a new matrix-based chemical synthesis strategy. An automated laser machine allows for fully automated production of peptide microarrays. A low budget variant makes this method available for almost every laboratory around the world. Peptide microarrays enable high-throughput disease diagnostics for malaria, dengue, and zika fever.

Carbohydrate Structure and Function

The group started at the end of 2017 dedicated to the structural and functional analysis of carbohydrate protein complexes, using x-ray crystallography. To build, remodel and degrade carbohydrate structures a multitude of different enzymes are used to achieve the challenging task. These carbohydrate active enzymes (CAZymes) have often exquisite regio- and stereospecificity, impossible to predict from sequence data alone. Currently, several potential glycoside hydrolases, involved in the degradation of the extracellular polysaccharide matrix of biofilms are under investigation, including different galactosaminogalactans and poly-α-1.4-galactosamine, found in biofilms of pathogenic fungi. Synthetic carbohydrate oligomers help to evaluate the specific substrate binding pattern of these hydrolases and the catalytic itinerary, defining the function of the enzymes.

Continuous Flow Chemistry

The Continuous Chemical Systems group have significantly advanced the utilization of solids and photochemistry for the production of active pharmaceutical ingredients. **[6]** Fully or partially heterogenous conditions in flow, whether, have traditionally been a severe limitation of the field, necessitating either elaborate chemical replacements or packed bed systems for their utilization. A new means of delivering and utilizing fully insoluble or partially soluble reagents into a flow stream was showcased using a photoredox decarboxylative fluorination. **[14]** The final stage of artemisinin production in the plant *Artemisia annua* is a photooxidation step. Using crude plant extract that contains multiple natural photocatalysts, the process is tenfold more efficient than using pure photocatalysts as reagents. This "artificial photosynthetic" process is the most efficient means of producing artemisinin to-date. **[13]**

Catalysis

The group develops materials and strategies for heterogeneous photocatalysis with a focus on carbon–heteroatom cross coupling reactions. The combination of graphitic carbon nitride, a heterogeneous organic semiconductor that absorbs visible light, and a homogeneous nickel catalyst was used for selective C–O and C–S bond formations. The organic semiconductor exhibits a broad substrate scope, is able to harvest green light, and can be recycled multiple times. *In situ* FTIR was used to track the reaction progress at different irradiation wavelengths and reaction scales. The team is currently studying the mechanism of these reactions and expands this synthetic strategy to other transformations.

Peter H. Seeberger
Director of the Department of Biomolecular Systems
peter.seeberger@mpikg.mpg.de

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Automated Glycan Assembly

The Seeberger group conceived the concept of automated glycans assembly in 1998 and since has been developing new methods to accelerate and generalize the method systematically.

Instrument Development.
With ten commercial Glyconeer 2.1® synthesizers in Europe, Asia and North America working, the group continues to improve all aspects of the automation process **[1]**. Three home-built synthesizers are used to accelerate the coupling cycles, to introduce new protocols and improve post-synthesis manipulations.

Polysaccharide Synthesis – the Basis for Material Science.
In the past two years, the largest oligosaccharide made in the department was a 50-mer **[2]** beating our own record 30-mer in 2013. The incorporation of a capping step into the coupling cycle greatly improved the yield (22% instead of 4% over 101 steps) and became possible since the overall coupling cycle was shortened **[3]** Fast AGA enabled the preparation of well-defined oligo- and polysaccharides resembling natural as well as unnatural structures. These synthetic glycans are ideal probes for the fundamental study of polysaccharides **(Fig. 1)**. According to molecular modelling simulations, different classes of polysaccharides adopt fundamentally different conformations that are drastically altered by single-site substitutions. Larger synthetic polysaccharides are obtained via a "LEGO"-like approach as a first step towards the production of tailor-made carbohydrate-based materials. **[4]**

Automated Synthesis of Self-Assembling Oligosaccharides.
Fully synthetic oligosaccharides allow for structural fine-tuning to adjust the material morphology. A series of modified oligomers was prepared to form nanospheres and other distinctive microstructures. These compounds show unique optical properties such as broad emission profiles and red edge excitation shift and may be useful for optical devices and nanotechnology. **[6]**

Automated Glycan Assembly of Lewis Type I and II Oligosaccharide Antigens.
Human blood group related glycan antigens are fucosylated (neo-)lactoseries oligosaccharides that play crucial roles in pathogenic processes. Lewis type-II-chain antigens mark the surface of cancer cells, but also are mediators of bacterial infections. Using a set of six monosaccharide building blocks, AGA provided quick access to a series of more than ten defined Lewis type-I and type-II antigens, including Le^x, Le^y, Le^a, Le^b and KH-1. Glycans with up to three α-fucose branches were assembled following a strictly linear approach and obtained in excellent stereoselectivity and purity **(Fig. 2)**.

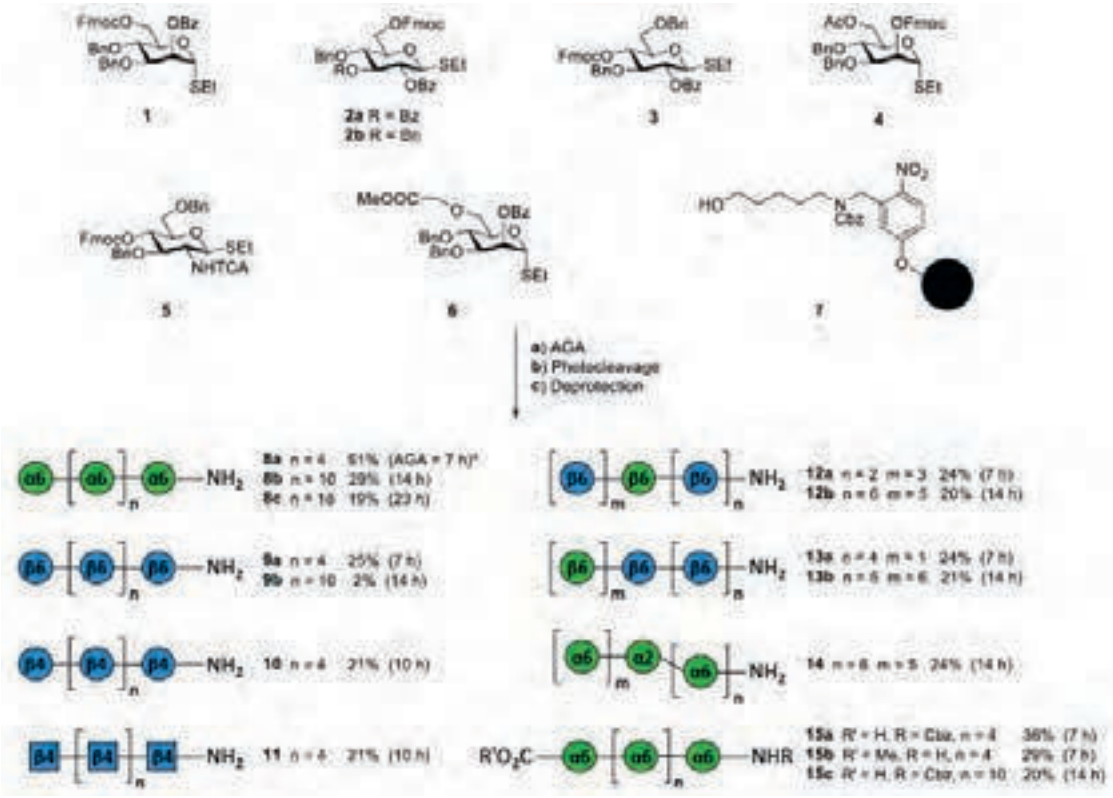

*Figure 1. AGA of oligo- and polysaccharides 8-15 using thioglycoside building blocks 1-6 and linker-functionalized polymer resin 7. *All reported reaction times are for AGA.*

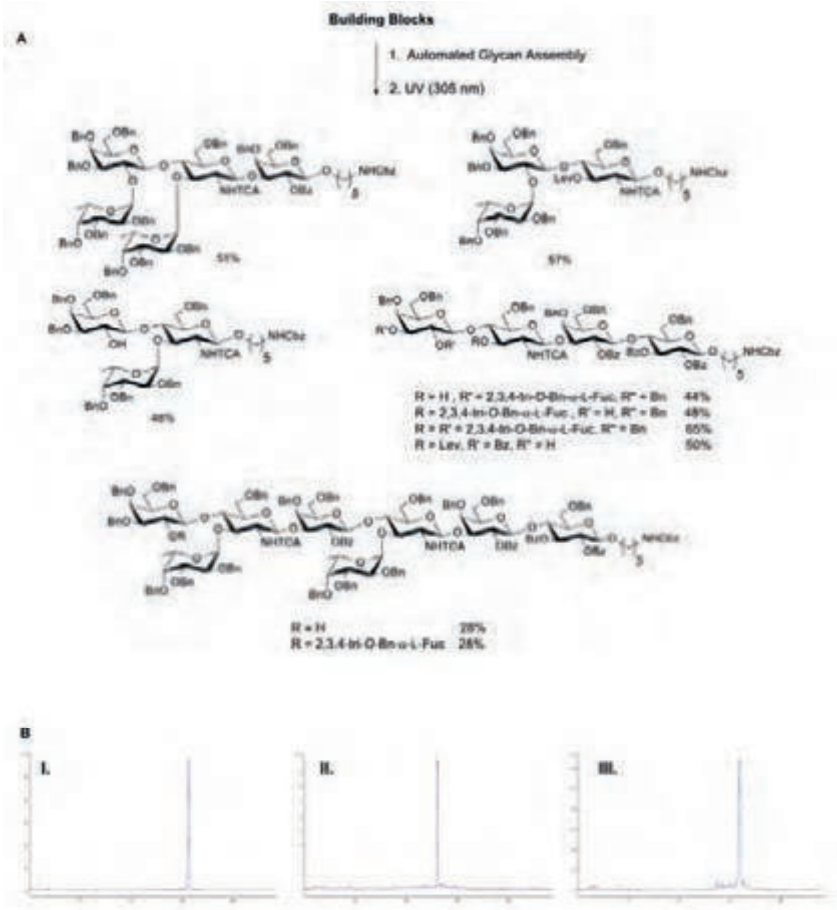

Figure 2. A) AGA of fully protected Lewis type-II oligosaccharides. B) analytical NP-HPLC of protected oligosaccharides Le^x (I.), Le^y (II.) and KH-1 (III.) after AGA and photo-induced cleavage from the resin.

Traceless Photolabile Linkers for AGA.

Cleavage from the solid support provided access to oligo- and polysaccharides with a spacer and amine group and yields were often lower than desired. Several new linkers were developed to access oligosaccharides with a free reducing end or an aminoalkyl spacer at the reducing end. The new linker enabled the convergent synthesis of an asymmetrically branched N-glycan octasaccharide and of pure laminarins. A new protocol for the global deprotection of oligosaccharides with free reducing end was developed. AGA using the new linkers enables access to glycans that can be converted into glycosylating agents to be used on block couplings. The glycans with a free reducing end are valuable standards for mass spectrometry and biological assays. **[9]**

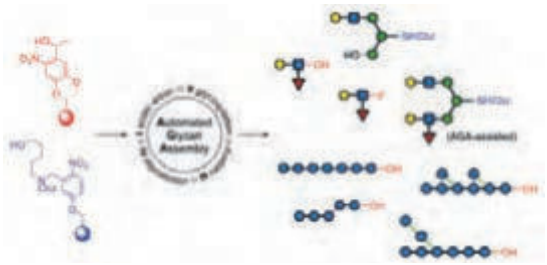

Figure 3. Novel photo-cleavable linkers for AGA.

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Anti-Bacterial Vaccines

The bacterial surface is covered by capsular polysaccharides (CPS). Induction of an immune response against isolated CPS is the basis of glycoconjugate vaccines that are highly successful. The vaccine group uses synthetic oligosaccharide antigens to understand all aspects of the immune response to glycans. The long-term goal is a detailed understanding of the factors that determine glycan immunogenicity and render a protective immune response in mammals. New vaccine carrier concepts, novel delivery systems, different adjuvants and routes of administration are currently being explored.

Streptococcus pneumoniae.

This pathogen has been a major focus for the group for several years. Recently, serotype 2 that is not in current vaccines **[1]** serotype 5 that is suffering from production problems **[2]** serotype 1 **[3]** and serotype 7F **[4]** were studied in detail. The medicinal chemistry approach to glycoconjugate vaccine development helped to improve the stability and immunogenicity of synthetic vaccine candidates leading to the induction of higher levels of specific protective antibodies. Subsequently, we showed that marketed CPS-based glycoconjugate vaccines can be improved by adding synthetic glycoconjugates representing serotypes that are not covered by existing vaccines. Combination of synthetic glycoconjugates with the licensed vaccines Prevnar13®(13-valent) and Synflorix®(10-valent) yields improved 15- and 13-valent conjugate vaccines in rabbits. A novel pentavalent semi-synthetic glycoconjugate vaccine containing five serotype antigens (sPCV5) elicited antibodies with strong *in vitro* opsonophagocytic activity. Synthetic oligosaccharides can be used in coformulation with both isolated polysaccharide glycoconjugates to expand protection from existing vaccines and each other to produce defined multivalent conjugated vaccines. **[5]**

Haemophilus influenzae serotype b (Hib).

The first glycoconjugate vaccine using isolated glycans was licensed to protect children from Hib infections. Still, a detailed understanding concerning the correlation between oligosaccharide chain length and the immune response towards the polyribosyl-ribitol-phosphate (PRP) capsular polysaccharide that surrounds Hib remained elusive. We demonstrated that an octasaccharide antigen containing four repeating disaccharide units resembles PRP polysaccharide in terms of immunogenicity and recognition by anti-Hib antibodies. Key to this discovery was the development of a modular synthesis that enabled access to oligosaccharides up to decamers. Conjugates of the synthetic antigens and the carrier protein CRM197 were employed in immunization studies in rabbits. **[6]**

Klebsiella pneumoniae.

Hospital acquired infections caused by carpabenem-resistant *Klebsiella pneumoniae* (CR-*Kp*) are problematic, with only a 50% average survival rate. At a time when antibiotics are becoming less effective, no vaccines to protect from this severe bacterial infection exist. We developed a convergent synthesis of the CPS hexasaccharide repeating unit and related sequences. Immunization with conjugates resulted in high titers of cross-reactive antibodies against CR-*Kp* CPS in mice and rabbits. **[7]**

By immunizing mice with protein-conjugated CR-*Kp* CPS our collaborator Prof. Fries produced monoclonal antibodies that protect in a murine intra-tracheal infection model. With the help of our glycan arrays, we were able to demonstrate that both mAbs bind to the same glycan epitope. These mAbs may provide life-saving passive immunotherapy and the glycan epitope is a potent vaccine target. **[8]**

Synthesis of Other Antigens

In addition to longer running programs, we are exploring potentially attractive targets that challenge our synthetic skills. The outer core octasaccharide of *Helicobacter pylori* was assembled using a synergistic glycosylation strategy. **[9]** The densely-functionalized *Plesiomonas shigelloides* Serotype 51 aminoglycoside trisaccharide antigen required the development of novel methodologies. **[10]**

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Synthesis of Antigens for Structure Determination.
Methicillin-resistant Staphylococcus aureus (MRSA) is a frequent cause of difficult-to-treat, often fatal human infections. Most humans have antibodies against *S. aureus*, but these are often not protective and vaccine development programs have failed. Many people carry *S. aureus* antibodies that targets wall teichoic acid (WTA), a poly-ribitol-phosphate (RboP) surface polymer modified with *N*-acetylglucosamine (GlcNAc). With the help of synthetic oligosaccharide antigens, a WTA glycosyltransferase, named TarP, was identified as a potential vaccine target. TarP is crucial for the capacity of *S. aureus* to evade human host defense. High-resolution structural analyses of TarP bound to WTA components explain the mechanism of altered ribitol-phosphate glycosylation and form a template for targeted inhibition of TarP. The study revealed a new immune evasion strategy of *S. aureus* based on reducing the immunogenicity of its dominant glycoantigen WTA. **[12]**

Glycan Array Screening Platform
Synthetic oligosaccharides covering diverse glycan structures found throughout nature including bacterial surface glycans, plant derived structures and cellular recognition motifs are the basis for the glycan array work in our group.
Our glycan array assays can be used for rapid screening to identify binding partners or evaluate the specificity of newly developed affinity probes. Tailor-made arrays can be printed to meet project needs including all quality controls. **[13]**

Peter H. Seeberger
Director of the Department of Biomolecular Systems
peter.seeberger@mpikg.mpg.de

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Synthetic Oligosaccharides to Understand Carbohydrates

Martina Delbianco
24.11.1987
2006–2009: Bachelor in Chemistry (110/110 with Honors), University of Milan, Italy
2009–2011: Master in Organic Chemistry (110/110 with Honors), University of Milan, Italy
2012–2014: Doctoral Thesis: Highly Emissive Eu(III) Probes for Biological Assays (Durham University, UK)
2015–2016: Postdoctoral Scientist, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces.
2017: Minerva Fast Track Fellow
Since 01/2018: Research Group Leader, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces

Polysaccharides are the most abundant organic materials in nature, yet correlations between their three-dimensional structure and macroscopic properties have not been established. Due to their ability to form a large number of hydrogen bonds, these biomolecules are ideal candidates for the formation of supramolecular structures **[1]**. However, the use of polysaccharide materials is limited by poor quality control and reproducibility, owing to the polydispersity of chain length and modifications. With automated glycan assembly **[2, 3]** we prepare well-defined oligo- and polysaccharides resembling natural as well as unnatural structures. These are ideal probes for the fundamental study of polysaccharides.
We follow two lines of investigation:

1. Analysis of the correlation between the chemical composition, the three dimensional structure and the properties of oligo- and polysaccharides. Particular focus is given to how a specific modification affects the overall properties of the molecule.
2. Development of novel carbohydrate-based materials, crucial for a better understanding of biological process as well as for the use of engineered platforms for biomedical applications.

Well-defined Oligo- and Polysaccharides as Ideal Probes for Structural Studies

Automated glycan assembly enables the preparation of well-defined oligo- and polysaccharides resembling natural as well as unnatural structures **[3]**. We prepared a series of related compounds, modified at specific positions of the chain, to shed light on how the modification patterns affect the polysaccharides' properties (i.e. three dimensional shape and aggregation behavior) **[4]**. Molecular modeling simulations and NMR analysis demonstrated that different classes of polysaccharides adopt fundamentally different conformations **(Fig. 1)**. While some polymers form helices, others adopt rod-like structures; such three dimensional structures are disrupted by single-site substitution.

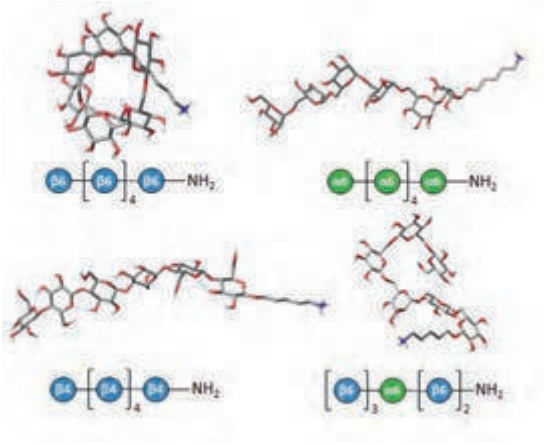

Fig. 1: Conformations of oligosaccharides obtained by molecular dynamics simulations illustrate a marked difference based on monosaccharide composition and connectivity.

Oligosaccharides Self-Assemble and Intrinsically Fluoresce

Simple peptides and nucleic acids can spontaneously self-assemble to form defined supramolecular patterns as materials for bionanotechnology applications. Natural polysaccharides, such as cellulose and chitin, have a strong tendency to aggregate in well-defined architectures with different physical properties and are key structural components in nature. Chemical modification tunes polysaccharide properties to create biocompatible, cheap, and renewable self-assembling materials for application in nanotechnology, optical components, drug delivery systems, and tissue engineering. While synthetic oligosaccharides should be able to self-assemble into tunable materials, this process has not been observed for structurally-defined oligosaccharides, as access to pure glycans has been challenging.

We demonstrated that simple synthetic oligosaccharides, ranging from dimers to hexamers, self-assemble into nanostructures of varying morphologies and fluoresce within the visible spectrum in an excitation-dependent manner **(Fig. 2)**. Well-defined differences in chain length, monomer modification, and aggregation methods yield glycomaterials with distinct shapes and properties. The excitation-dependent intrinsic fluorescence in a broad range within the visible spectrum illustrates their potential for use in optical devices and imaging applications.

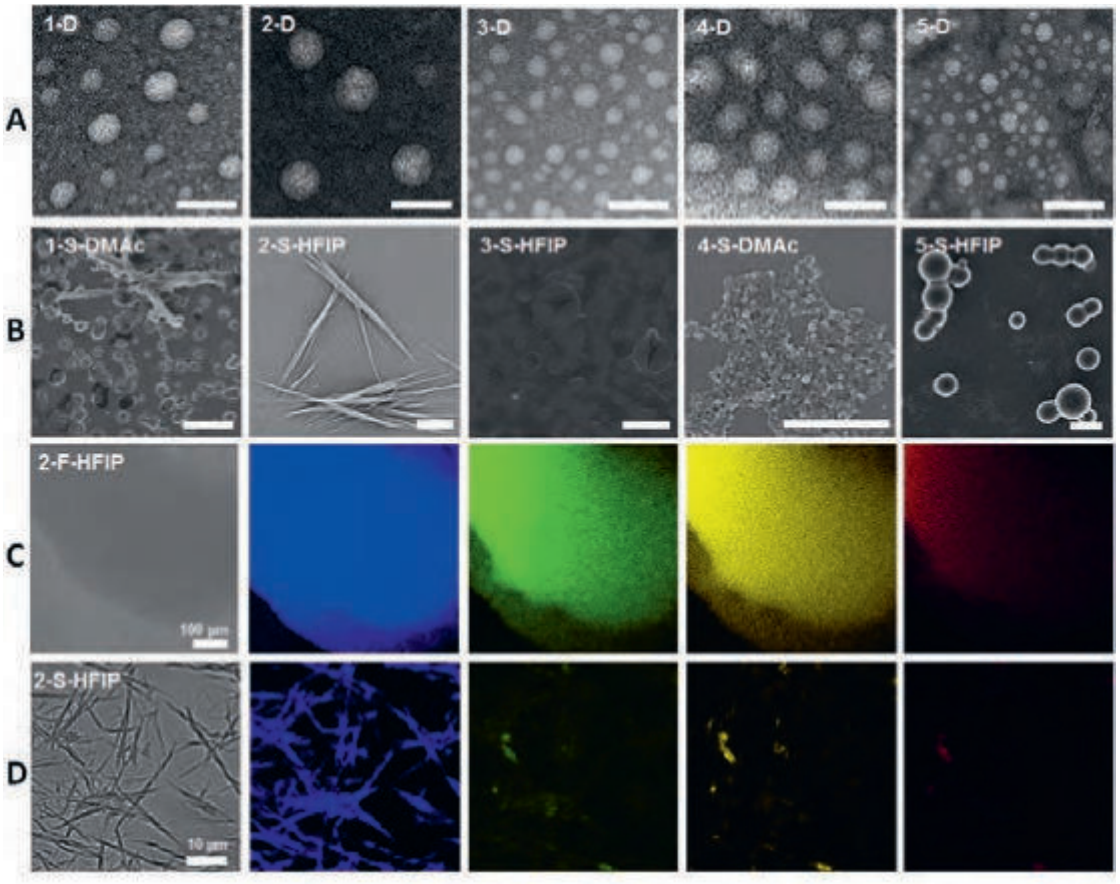

Fig. 2: Self-assembly of well-defined oligosaccharides: A) TEM images (scale bars: 100 nm) of samples prepared by dialysis method. B) SEM images (scale bars: 2 µm) of samples prepared by solvent-switch method. Confocal microscope images of disaccharide aggregates prepared by C) HFIP evaporation (scale bars: 100 µm) and D) solvent-switch (scale bars: 10 µm) in four different channels (blue(ex/em): 405/451 nm, green: 488/529 nm, yellow: 561/597 nm, and red: 633/709 nm).

Glyco3Dysplay

We create novel carbohydrate-based compounds by integrating glycan molecules with DNA-based structural scaffolds. A synthetic collection of glycans is displayed on DNA origami, generating multivalent tailored arrangements of defined glycan chains with single-nanometer spatial resolution. With this approach, we investigate fundamental questions regarding glycan conformation, and screen for medically relevant interactions with pathogen surface receptors in a combinatorial, high-throughput manner. Currently, we are exploiting our integrated screening pipeline to find novel diagnostics and anti-adhesive lead compounds against respiratory and enteric pathogens which minimize the risk of resistance development.

M. Delbianco, V. Bordoni, G. Fittolani, S. Gim, T. Tyrikos-Ergas, Y. Yu, Z. Zhao
Martina.delbianco@mpikg.mpg.de

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SYNTHETIC ARRAY TECHNOLOGIES

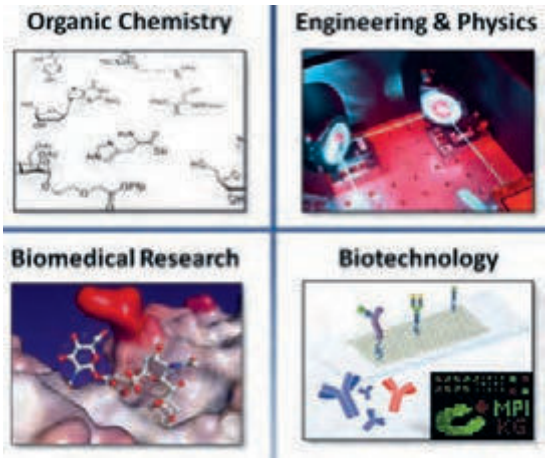
Laser Transfer for High-Throughput Research

Felix Löffler
26.07.1984
2004-2009: Physics Diploma, supplementary certificate in Biophysics University of Heidelberg, Germany
2009-2012: Doctoral Thesis, summa cum laude (highest honors) Kirchhoff Institute of Physics, University of Heidelberg, & German Cancer Research Center (DKFZ), Germany
2012-2013: Postdoctoral Scientist German Cancer Research Center (DKFZ), & Karlsruhe Institute of Technology, Germany
2014: Visiting Scholar, UC Berkeley, USA
2014-2016: Young Investigator Karlsruhe Institute of Technology, Germany
Since 2017: Research Group Leader Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces

High-throughput screenings of large chemical libraries with hundreds of thousands to millions of different molecules are established as a standard method in drug discovery. The screening of highly diverse and large chemical libraries for molecular interactions promises the discovery of new drug candidates or, in the case of peptide libraries, for example, the identification of new biomarkers for the development of diagnostics or vaccines. However, the costs for the synthesis of complex chemical substance libraries are very high, so that only larger pharmaceutical companies have this possibility. This prevents advancements in both, fundamental research, as well as applied research and development. Much better would be a method to cost-efficiently synthesize minute amounts of chemical compounds on demand and perform miniaturized and highly parallelized screens. Therefore, we develop novel technologies **[1]**, which offer unprecedented flexibility and miniaturization for the combinatorial synthesis of chemical compound libraries. With such tailor-made molecule libraries, we want to advance biomedical research and diagnostics.

Synthetic Array Technologies Group

Our highly interdisciplinary research focuses on the development of microarray technologies (biotechnology) and diagnostic applications of microarrays (biomedical research & bioinformatics). However, this requires major basic research efforts in laser processing (engineering & physics) and synthesis strategies (organic chemistry).



We strive to automate the high-throughput synthesis process by employing advanced robotics and mechanical engineering. This method allows for *in situ* solid phase synthesis of e.g. peptides and glycopeptides in the microarray format.

These arrays facilitate the investigation of many peptide-protein interactions in parallel, such as enzymatic glycosylation and mapping of epitopes for the development of therapeutic antibodies. Currently, we investigate biomedical applications utilizing this high-throughput approach to screen patients suffering from different infectious diseases.

Laser-Based Material Transfer

Our novel laser-based material transfer allows for high-precision deposition of tiny amounts (< 1 ng, < 50 nm thick) of all kinds of chemical building blocks, catalysts, activators, click chemistry components, scavengers, acids, and bases in – at room temperature – solid solvents. These nanometre thin solid polymer spots of exactly defined material amounts (*"polymer nanolayers"*) are flexibly patterned onto a synthesis slide, and can be also stacked on top of each other **(Fig. 1)**

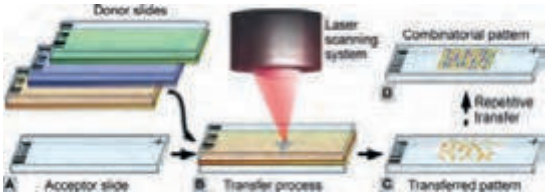


*Fig. 1: Principle of the combinatorial laser-induced forward transfer synthesis. In an automated laser transfer process, tiny solid material spots are rapidly transferred from a donor film to an acceptor surface, requiring only minute amounts of materials. The transfer is performed with different and easy-to-produce donor slides. Each donor slide bears a thin polymer film, embedding one type of monomer **[1]**.*

At the heart of the method are different donor glass slides, each of them covered with a thin layer of an inert polymer matrix material that embeds one kind of pre-activated chemical building block (*e.g., amino acids*). In addition, the matrix serves as a solvent, when it is heated and thereby becomes a viscous gel. The donor slide is placed onto a functionalized acceptor glass substrate. Next, a laser, directed by a 2d laser scanning system, transfers tiny material spots of exactly defined amounts to an acceptor slide at freely chosen areas, as shown in **Fig. 2**. Afterwards, additional donor slides are used to pattern the acceptor slide with many different materials, and at any desired combination. For a successful proof-of-principle, we used this multi-material, and – in z-direction – nanometre thin polymer layer patterning to synthesize a high-density array of 9-mer peptides.

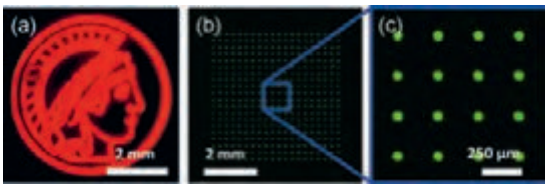


Fig. 2: Fluorescence scans of example transfers. Containing (a) Minerva, (b) 20 x 20 grid of fluorescent dye containing spots with 250 µm distance – spot size ~50 µm, (c) magnification.

Automated Array Synthesis

To achieve highest precision, reproducibility, and spot density, we built an automated setup (see **Fig. 3**) that reduces human interaction during the laser transfer and synthesis to a minimum.

The setup is controlled by a master computer, which is responsible for the robot movement, mechanical alignment, camera detection, laser activation, and time control for all actions: The donor slides are automatically placed on top of the acceptor slide and the laser receives a signal form the master to initiate the lasing process. Repeating these steps allows us to generate combinatorial patterns.

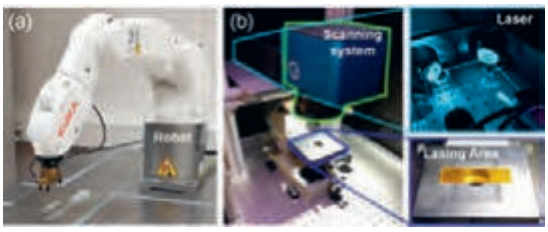


Fig. 3: Automation setup: (a) High precision robot for sample handling and automation, (b) laser transfer setup including scanning system, laser, and lasing area.

Diagnostics and Disease Research

Very effective vaccinations shield us from a lot of common infectious diseases. For instance, diphtheria was the major cause of death among children, before the immunization reached the public in the 1920s. It is known that vaccines protect us amongst others by inducing long-lived antibody producing cells. However, the precise mechanism of the immune response and the exact composition of antibodies elicited by vaccinations remain unclear. It has been shown in several studies that vaccinations against viruses can enhance other diseases by cross-reaction, or lead to antibody-dependent enhancement of the same disease. Therefore, there is an urgent need to elucidate the humoral immune response to a vaccination in detail.

High-density peptide arrays are an excellent means to profile antibody responses. Different protein intrinsic epitopes can be distinguished and additional insights are gained, when compared to assays involving the full-length protein. Distinct reactivities to specific epitopes within one protein may explain differences in published results, regarding immunity or susceptibility to diseases.

We applied our technology to investigate a number of different infectious diseases, such as lyme disease **[3]**, tetanus **[4]**, zika and dengue **[5]**, and malaria **[6]**.

Novel Diagnostic Malaria Biomarkers

After many years of exposure, people in malaria endemic areas develop a partial immunity, which protects against severe disease progression upon infection with the malaria pathogen *Plasmodium falciparum*. This immunity can be transferred to other people using serum antibodies. However, we do not exactly know which antibodies mediate this immunity or how such antibodies can be induced by a vaccine. Previous attempts to find such antibodies, or the corresponding vaccine-appropriate antigens, all used a range of recombinantly expressed *Plasmodium* proteins, which did not yet succeed in designing a potent vaccine. One reason might be that these approaches did not consider distinct protein intrinsic differences (i.e. peptides).

Thus, together with our international collaboration partners (Heidelberg University Hospital, Germany; BioInfoBank Institute, Poland; Centre de Recherche en Santé de Nouna, Burkina Faso), we used peptide arrays to analyze the naturally acquired antibody response against the malaria pathogen *Plasmodium falciparum* **[6]**.

We screened all peptides from twelve known vaccine candidates and a bioinformatical selection (see **Fig. 4**), which resulted in strong reactivities to epitopes derived from known vaccine candidates. Furthermore, we identified new immunogenic proteins/epitopes, which may serve as vaccine targets and new biomarkers.

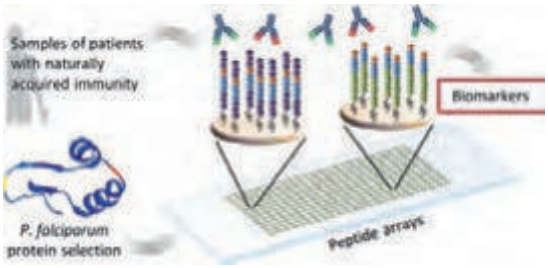


Fig. 4: Workflow – Profiling antibody responses of patients with naturally acquired malaria immunity using high-density peptide arrays **[6]**.

F. Loeffler, S. Eickelmann, J. Heidepriem, M. Mende, G. Paris, A. Tsouka, J. Zhang
felix.loeffler@mpikg.mpg.de

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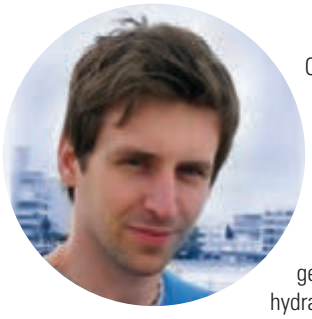
BIOMOLECULAR SYSTEMS

Synthetic Plant Carbohydrates



Fabian Pfrengle
26.11.1981
2001–2006: Diploma in Chemistry (with distinction) at the Freie Universität Berlin
2006–2010: Dissertation in Organic Chemistry (summa cum laude) at the Freie Universität Berlin,
Advisor: Professor Hans-Ulrich Reißig
2007–2009: Predoctoral fellowship of the Fonds der Chemischen Industrie (FCI)
2010–2013: Research Associate in the Department for Chemical Physiology at the Scripps Research Institute in La Jolla, USA,
Advisor: Professor James C. Paulson
2010–2012: Postdoctoral fellowship of the Deutscher Akademischer Austauschdienst (DAAD)
Since 09/2013: Group Leader in the Department of Biomolecular Systems at the Max Planck Institute of Colloids and Interfaces
2013–2015: Liebig fellowship of the Fonds der Chemischen Industrie (FCI)
Since 02/2015: Emmy Noether-program of the DFG

Carbohydrates play crucial roles in the life cycle of plants, both as structural components and as important players in signaling events and energy provision. As a food source, plant carbohydrates can provide beneficial effects on the human immune system, but constitute also abundant immune determinants on allergens. Despite the strong impact of plant carbohydrates on the bio-economy and human health, their chemical synthesis remains largely unexplored compared to the synthesis of mammalian and bacterial glycans. Our aim is to explore automated oligosaccharide synthesis and chemo-enzymatic methods for the generation of plant carbohydrate libraries as a powerful means for investigating their application in plant biology and materials science. The synthesized plant carbohydrates are applied in the characterization of monoclonal antibodies derived from cell wall polysaccharides, plant cell wall biosynthetic enzymes, and cell wall glycan-deconstructing enzymes as well as in the evaluation of materials properties. **[1]**

Automated Glycan Assembly of Plant Cell Wall Oligosaccharides

Automated glycan assembly is a technology that was introduced by Prof. Peter H. Seeberger in 2001. Using this technology, rapid access to collections of defined oligosaccharides is provided. We expanded our collection of plant cell wall oligosaccharides by automated glycan assembly **(Fig. 1)**.**[2–5]**

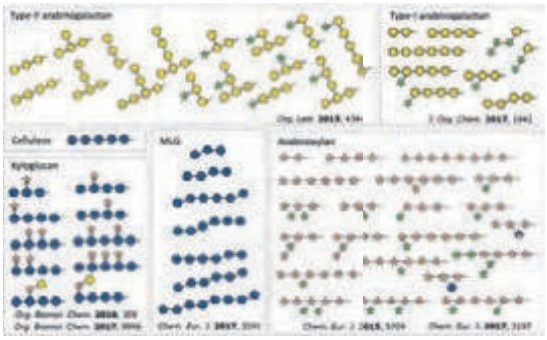


Fig. 1: Library of synthetic plant carbohydrates produced by the Synthetic Plants Carbohydrates Group.

Characterization of Cell Wall Glycan-Directed Antibodies with Synthetic Plant Carbohydrates

Researchers in plant cell wall biology rely on about 200 monoclonal antibodies for the localization of glycans in the plant cell wall. These antibodies were prepared by different laboratories worldwide through immunization of animals with poly- and oligosaccharide antigens extracted from the plant cell wall. With the help of these antibodies the occurrence and structure of cell wall glycans in different tissues and cell types can be analyzed using fluorescence microscopy. Due to a lack of pure and well-defined oligosaccharides, the binding specificities of these antibodies are insufficiently characterized and it is not possible to determine the exact molecular structure that is recognized by the antibodies. To enable a high-throughput screening of the antibodies for their binding specificities, we printed all prepared cell wall oligosaccharides, together with a number of additional synthetic glycans that we obtained from collaborators, as microarrays and incubated them with more than 200 of the cell wall glycan-directed antibodies **(Fig. 2)**.**[6–7]** We were able to determine the epitopes of 79 of these antibodies. These data are now an important resource for plant biologists to design their immunolocalization experiments.

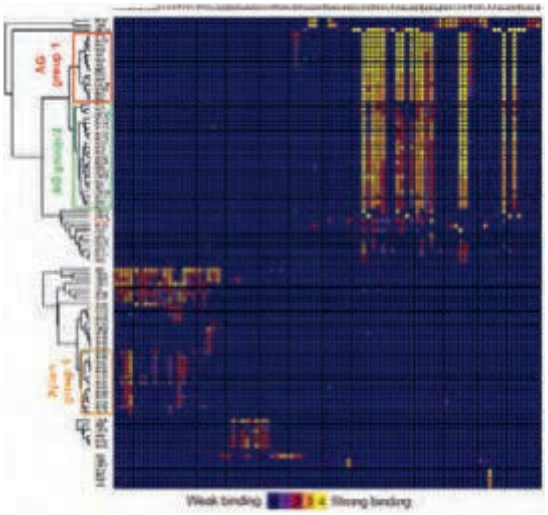


Fig. 2: Identification of epitopes of plant cell wall glycan-directed monoclonal antibodies (mAbs). Summarizing heatmap of the binding interactions between individual mAbs and synthetic glycans.

Incorporation of the Synthetic Oligosaccharides into Plant Cell Walls for Analysis of Endotransglycosylases

Endotransglycosylases are cell wall-remodeling enzymes that cleave glycosidic bonds in existing cell wall polysaccharides and re-connect them with the non-reducing end of other polysaccharide chains (e.g. newly biosynthesized). We focused on xyloglucan-endotransglycosylases (XETs) which are the best studied cell wall remodeling enzymes and play an important role in cell growth and cell division. They enable the incorporation of freshly synthesized xyloglucan into the plant cell wall and thus loosen the cellulose-xyloglucan network. We sought to shed light on the substrate specificities of these enzymes by investigating if the xyloglucan oligosaccharides prepared by automated glycan assembly are incorporated into the plant cell wall by the action of XETs or not. After attachment of fluorescein to the aminoalkyl linker of the synthesized oligosaccharides, we have incubated small pieces of plant material with the fluorescently labeled oligosaccharides and investigated any potential incorporation into the plant cell wall using fluorescence microscopy **(Fig. 3)**. In this way, it was possible to analyze the substrate specificity of the XETs in *Arabidopsis thaliana*, peas and beans. **[8]**

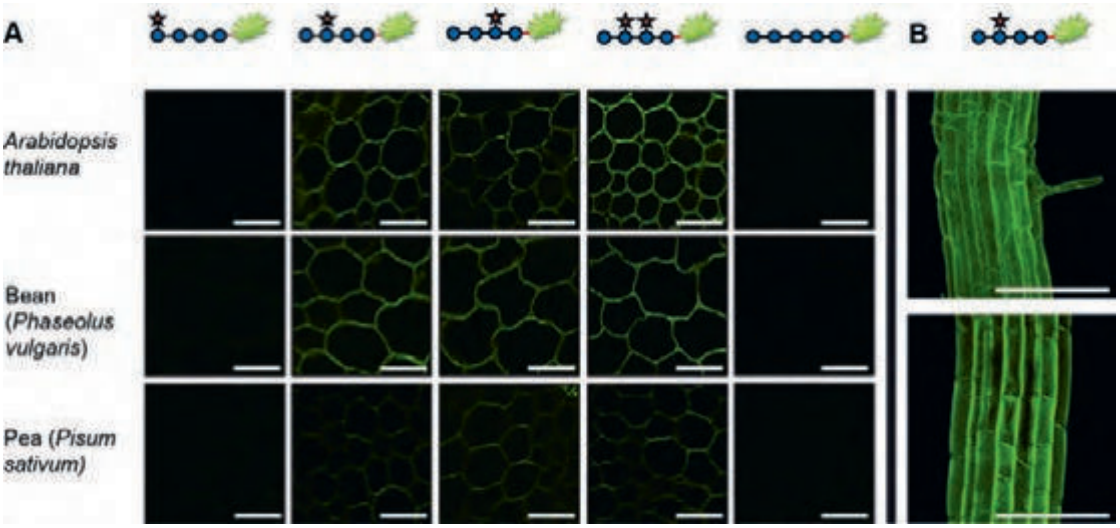


Fig. 3: Incorporation of synthetic xyloglucan oligosaccharides into plant cell walls assessed by fluorescence microscopy.

Chemo-enzymatic Synthesis of Artificial Xylan Polysaccharides with defined Substitution Patterns

Cellulose and xylan are the major polysaccharides in lignocellulosic biomass and thus promising renewable resources for the production of materials and fuels. While cellulose is regularly utilized for these purposes, the exploration of xylan is lagging behind due to its structural complexity. The molecular composition of xylans has a strong impact on their macroscopic properties. The discrete substitution pattern in xylan for example strongly affects the ability of xylan to bind to cellulose and thus determines the strength of plant material.

Well-defined molecular tools mimicking natural xylan polysaccharides have great potential for studying structure and properties of xylan, including its interaction with cellulose. Based on the synthetic strategy we have established for the synthesis of arabinoxylan oligosaccharides, we developed a chemo-enzymatic approach towards artificial arabinoxylan polysaccharides with systematically altered branching patterns. The polysaccharides were obtained by glycosynthase-catalyzed polymerization of glycosyl fluorides derived from seven different arabinoxylan oligosaccharides that were procured either synthetically or from a commercial source **(Fig. 4)**. **[9]**

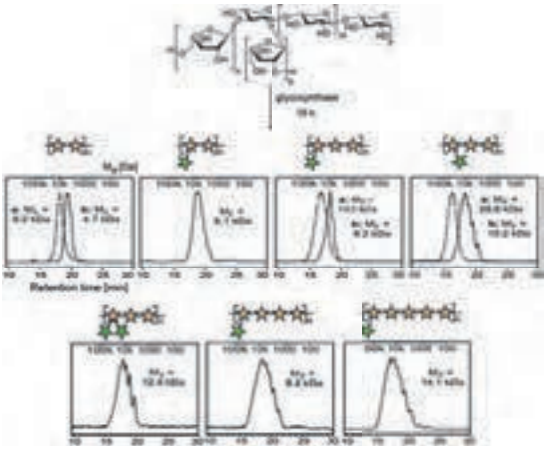


Fig. 4: Synthesis of artificial arabinoxylan polysaccharides by enzymatic polymerization of arabinoxylan oligosaccharide fluorides. The molecular mass distribution of the polysaccharide products is analyzed by high-pressure size-exclusion chromatography.

F. Pfrengle, A. Baryzewska, I. Alvarez Martinez, U. Osswald, C. Ruprecht
Fabian.Pfrengle@mpikg.mpg.de

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Chemistry and Biology of the Protein Glycosylation

Daniel Varón Silva
09.04.1974
1992–1998: Diploma in Chemistry, Department of Chemistry, National University of Colombia, Bogotá, Colombia
1998–2002: Research associate, Department of Chemistry, Colombian Immunology Institute Foundation, Bogotá, Colombia
2003–2007: PhD in Chemistry, Bioorganic Chemistry, University of Bayreuth, Bayreuth, Germany
2007–2008: Postdoctoral Fellow, Laboratory of Organic Chemistry, Swiss Federal Institute of Technology, Zurich, Switzerland
2009–2010: Postdoctoral Fellow, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces, Berlin, Germany
Since 06/2010: Group Leader, GPI and Glycoproteins group, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces, Berlin, Germany

Glycosylation is the most common post-translational modification of proteins. It involves the addition of carbohydrates to the side chains of amino acids such as asparagine (*N*-glycosylation), threonine and serine (*O*-glycosylation) or at the C-terminal residue (Glypiation) **(Fig. 1)**. The attached carbohydrates participate in diverse biological process by interacting with other biomolecules and cells or by influencing the properties of the protein **[1]**. Glycoproteins are naturally found as a mixture of glycoforms, proteins having identical amino acid sequence but different carbohydrate structure. Studies to identify the role carbohydrates on proteins are hampered by a difficult and low yielding isolation of pure glycoforms. To overcome this limitation, two strategies emerged as an alternative: the use of genetically manipulated cell lines and the synthesis of glycoproteins.

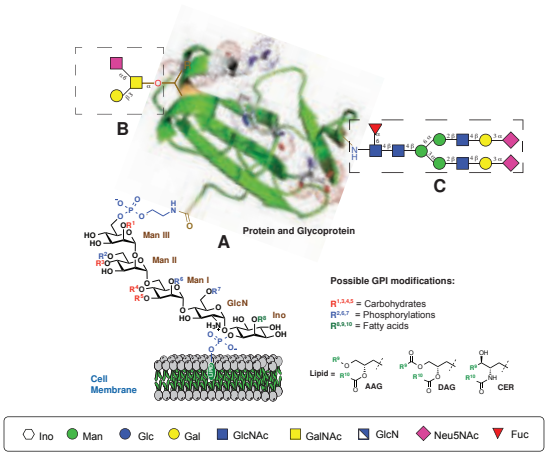

Fig. 1 Main Protein Glycosylations Found in Eukaryotes. A) Glypiation, B) O-glycosylation, and C) N-glycosylation

Semi-Synthesis of Homogeneous Glycoproteins

Most of the current strategies to produce well-defined glycoproteins involve either a combination of glycopeptide synthesis and expressed proteins fragments that are connected via ligation reactions, or chemoenzymatic processes to introduce a fully synthetic glycan to modified existing structures on full-length proteins.

The group has been working in developing semi-synthetic methodologies to glypiate proteins and to obtain glycopeptides having both *N*- and *O*-glycans that can used by a combination of strategies to get proteins with multiple and defined glycosylations.

The main limitation to obtain glycoproteins chemically is the need of pure glycans in good amounts, which require efficient synthetic strategies or purification methods. The group developed and optimized strategies for the synthesis of GPI glycolipids having saturated and unsaturated lipids and of GPIs for ligation reaction with peptides and proteins **[2–4]**. Furthermore, *N*-glycans have been obtained from natural sources and modified to obtain glycan building blocks for the synthesis of *N*-glycopeptides or their use as standards in MS-analysis **[5, 6]**.

Three strategies were established for the glypiation of proteins. They involved the use of fully or split inteins domains to generate active C-terminal protein thioesters **[4]**. These activated proteins are reacted with synthetic cysteine-containing GPIs to form a glypiated protein **(Fig. 2)**.

These methods differ in regard to protein solubility requirements, reaction rate, reaction setup and side product formation. Best results were obtained using split inteins in one-pot ligation (OPL). Using this strategy, model proteins and the naturally glypiated protein of the parasite Plasmodium falciparum were obtained and used to investigate the effect of the glypiation on the structure and activity of the protein. Characterization of the MSP1-GPI by circular dichroism (CD) showed that the global structure of the protein is not affected by the glycolipid. But, *in vitro* activation of isolated dendritic cells (DCs) using MSP1 with and without GPI showed a strong effect of the glycolipid, enhancing the production of the pro-inflammatory cytokines TNF-a and IL-12.

Considering to investigate the effect on the structure and activity of proteins of the common combination of glycosylation and glypiation, new methods have been explored to obtain the fully glycosylated CD59 and Thy-1 (or CD90) protein, two naturally glypiated and glycosylated proteins. Glycosylated protein fragments have been obtained using solid phase peptide synthesis and elongated using sequential ligation reactions. Glycans have been introduced using an Asn-*N*-acetylglucosamine unit for further trans-glycosylation process at the end of the synthesis using a mutated Endo M/A enzyme and different isolated and modified *N*-glycans donors **[6]**.

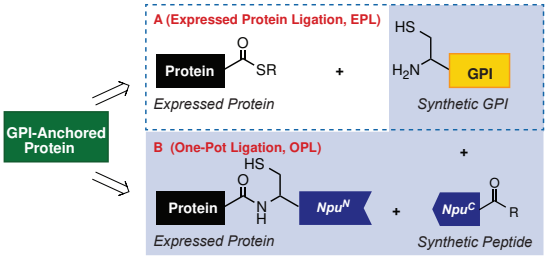

Fig. 2. Strategies for the Glypiation of Proteins.

Synthesis of *N*-Glycopeptide Standards

Determination of changes in the glycosylation profile of antibodies of patients has been postulated as a tool for developing precise diagnostic techniques for colon rectal cancer, the third type of cancer in Europe. In addition to the close correlation between the IgG glycan profile and the CRC stages, differences in IgG glycosylation profiles are observed for IgG subclasses containing slightly different amino acid sequences **[7]**.

Glycan analysis is a complicated and time-consuming process having limitations, especially for absolute quantification. Therefore, to use glycopeptide quantification for the development of CRC diagnostic methods on the basis of, it is essential to consider both the glycan and the peptide part and to use standards that match with respect to the glycan and peptide moieties **[6]**. To obtain the required amounts of glycopeptide standards with the desired peptide sequence and well-defined

glycosylation, a combination of chemical synthesis and enzymatic remodeling of glycans is a good alternative **(Fig. 3)**.

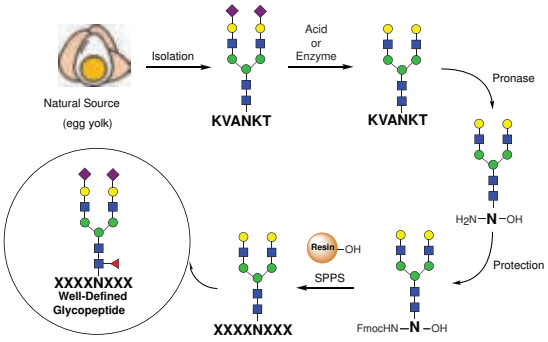

Fig. 3: Schematic representation for the synthesis of Nglycopeptides using isolated glycans

Starting with the synthesis of glycosylated Fmoc-protected asparagine building block for solid phase glycopeptide synthesis, a protocol for the isolation of a sialylglycopeptide (SGP) from egg yolk was established and used to obtain this glycopeptide in gram-scale. The isolated SGP was enzymatically and chemically modified to deliver a glycosyl asparagine building block, which has been efficiently used in chemical peptide synthesis to obtain various IgG Nglycopeptides. To expand the number of glycan structures, these glycopeptides were successfully isolated and modified with enzymes to deliver a series of standards having a differentiated glycan and peptide structure. By using this strategy, a library of 22 different glycopeptides was obtained. These glycopeptide library is now being used for the quantification of IgG glycosylation in CRC patients and in animal models.

Analysis of GPI-Glycolipids on Monolayers

The function of glypiated proteins (GPI-APs) is often associated with lipid rafts, also known as detergent-resistant domains. It is not clear the role of the glycan and lipid composition of GPIs in raft formation. Therefore, the clustering of GPI-APs in rafts has been mostly attributed to protein-protein interactions. Studies on the structural arrangement of GPIs in a model membrane has provided initial insight into the relationship between the glycolipid composition, especially of the glucosamine unit and its behavior in model membranes **[8]**. To expand this study to understand the role of the lipid chains, GPI fragments bearing linear, branched and unsaturated lipid chains were synthesized and evaluated towards the formation of substructures in monolayers at the water/air interface **(Fig. 4)**.

Four GPI fragments were synthesized containing the pseudodisaccharide glycan and a diacylglycerol bearing either saturated, unsaturated or branched fatty acids chains. GIXD patterns and contour plots of the monolayers depicted different substructures that depend on the lipid composition and the polar head group. The monolayer structures showed a correlation between an increase in the zwitterionic character of the glycolipid and a reduction in the flexibility of the head group of the GPI fragment. GPI fragments containing acetylated glucosamine were more flexible and demonstrated a reduced packing compared to the non-acetylated glycolipid. This confirmed the importance of this amine in the hydrogen bonding and formation of ordered structures in the membrane. The presence of branching and unsaturation at the lipid induces a similar effect and are responsible for the fluidity of the membrane. These findings suggest that the lipids play a crucial role in the organization of the GPIs in the membrane and are responsible for many cellular functions.

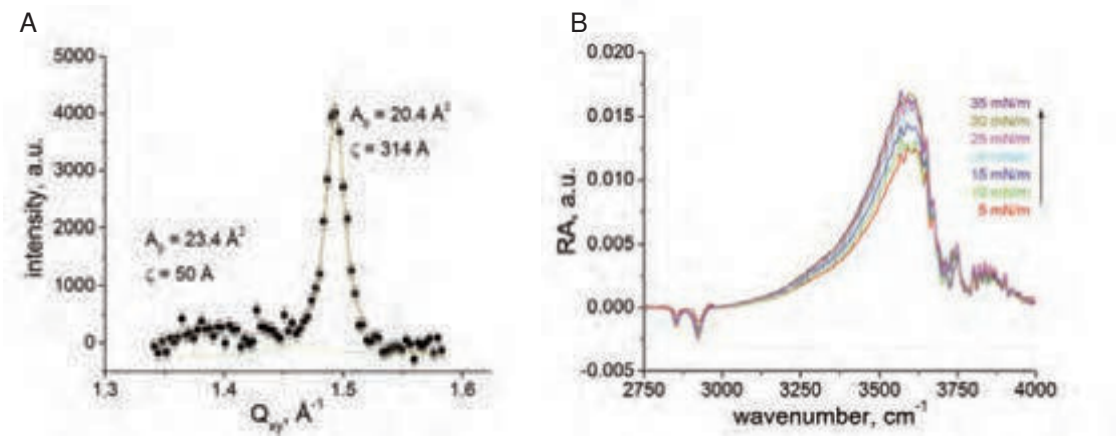

Fig. 4. Monolayers of GPI with unsaturated lipid at 20 °C. (A) GIXD pattern; (B) IRRAS spectra of OH stretching region at different lateral pressure

D. Varón Silva, R. Roller, A. Malik, H.-I. Oh, A. Rella, S.M. Pinzon Martin
daniel.varon@mpikg.mpg.de

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Controlled Conditions, Controlled Chemistry

Kerry Gilmore
10.06.1984
2002–2006: Bachelor of Science majoring in Chemistry
Bachelor of Science majoring in Biology (Roger Williams University, Bristol, RI, USA)
2006–2012: Doctoral Thesis: Cyclizations of Alkynes. (Department of Chemistry and Biochemistry, Florida State University. Tallahassee, Fl, USA)
2010: Fulbright Scholar
2012–2013: Postdoctoral Scientist Biomolecular Systems Department, Max Planck Institute of Colloids and Interfaces.
2014–2018: Group Leader, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces
since 2019: W-2 Research Group Leader, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces

Inarguably, the success of the vast majority of chemical transformations is reliant on the degree of control exhibited over a wide range of variables such as stoichiometry, temperature, reaction time, mixing, and exposure to light. Utilizing flow chemical techniques – where reagents are passed through a set of conditions via thin tubing as opposed to applying conditions to a round bottom flask – has allowed for achieving chemistries and efficiencies previously inaccessible. The modular nature of this technique has also facilitated the development of a novel means of chemical synthesis, which targets core functionalities as opposed to specific molecules, allowing for multiple derivatives to be produced with a single flow system.

At its core, the essential focus of an organic chemist's pursuits is control over molecules – whether this is expressed as regio- or chemoselectivity of functional group transformations, the formation and utilization of reactive intermediates, or precision in reaction conditions. For a number of applications, a significant increase in molecular and environmental (reaction conditions) control can be achieved using flow chemistry. This technique, where reagents are passed through tubing held at a precise set of conditions, is particularly advantageous in high temperature/pressure chemistries, multi-phasic systems (gas/liquid, liquid/liquid), very fast reactions, and photochemistry. We recently reviewed the field as a whole **[1]** and the specific challenges faced continuous multistep synthesis **[2]**.

Flow chemistry is modular in nature, allowing for its components (pumps, mixers, reactors, etc.) to be arranged in any number of combinations. This built-in flexibility has allowed for a wide variety of applications. In the last two years, our group has utilized this technique to probe two major branches of organic synthesis: methodology (developing new reactions and studying their mechanisms) and multi-step synthesis (continuous and semi-continuous processes to produce active pharmaceutical ingredients (APIs)). A selection of these works are discussed below.

Methodology

One of the most complex reactions in organic chemistry from a mechanistic perspective is the glycosylation reaction. This is due to the multitude of mechanistic pathways operating simultaneously, the unknown identity of the intermediates, and the extreme sensitivity to environmental conditions.

This presented the perfect exemplar for the development of a continuous flow platform for mechanistic investigations. Seven syringe pumps feed the reagents into a variable temperature microchip reactor, and the reaction output is analysed online by HPLC. Using this platform, more than 270 experiments were performed with a high degree of reproducibility. Judicious choice of both reagents and conditions allowed for the systematic exploration of the chemical space subset, and allowed for an empirical understanding of the variables influencing the stereochemical outcome **(Fig. 1)**. This knowledge allows for the design of conditions maximizing either the alpha or beta product **[3]**.

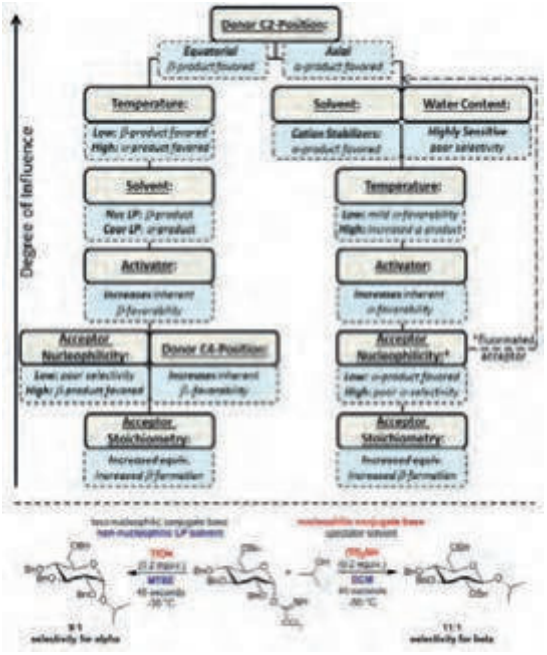

Fig. 1: A flow platform allowed for the rapid screening of glycosylation reactions to gain a fundamental understanding of how to control the stereochemical outcome.

Collaborative Efforts

Two collaborative efforts focused on the development of new methods for catalytic transformations (**Fig. 2**). With researchers from the University of Leipzig (Germany) and Ferrara (Italy), a lab-on-a-chip device was created featuring two distinct packed beds, allowing for both heterogeneous enantioselective organocatalysis and the subsequent chiral high-pressure liquid chromatographic separation **[4]**. With researchers from the University of Évora (Portugal), a palladium-catalyzed enantioselective cyclization was developed, allowing for the facile and scalable synthesis of benzofused cyclic chiral alcohols **[5]**.

Chemoselective Photoredox Couplings

We have extended our expertise of photoredox chemistries **[6]** and the alpha-functionalization of amines with the development of a chemoselective process to generate unprotected primary amines from carbonyls via the corresponding N-H imine. While imines can be rapidly (and reversibly) generated by reaction of ammonia and an aldehyde/ketone, the reduction potentials unfortunately favour reduction of the carbonyl **Fig. 3)**. However, in the presence of a suitable activator – either a proton or Lewis acid – the favourability shifts to allow for the selective reduction of the activated imine. This finding allowed for the development of methods to selectively generate a series of functionalized amines including vicinyl diamines, as well as the arylated and reduced products **[7]**.

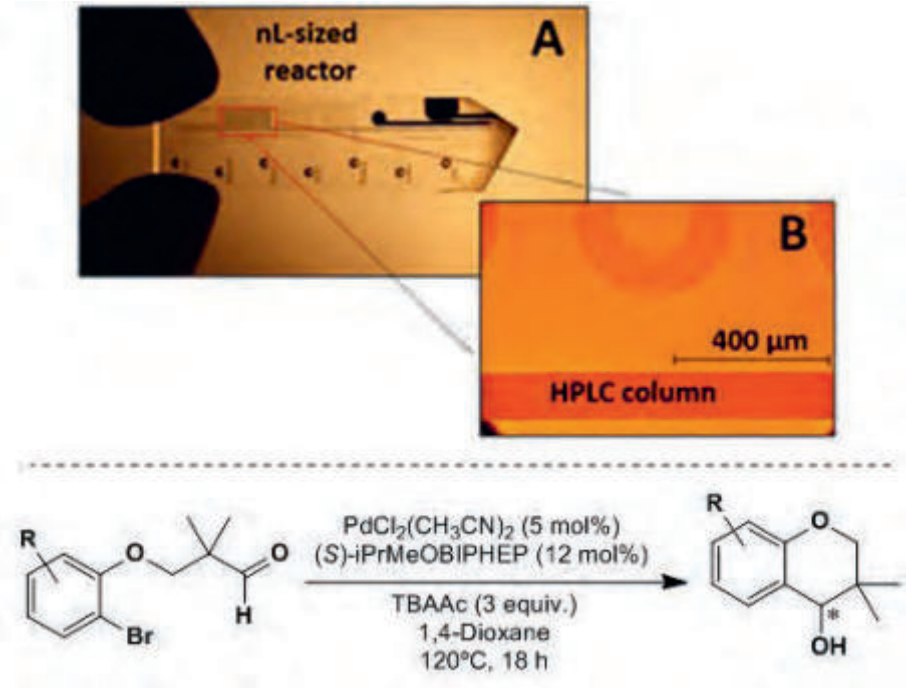

Fig. 2: Enantioselective catalytic processes were developed and studied in collaboration with external collaborators.

Accelerated Photosynthesis

Finally, our drive to better understand synthetic organic chemistry led to the re-evaluation of the method for synthesizing the anti-malarial active pharmaceutical ingredient artemisinin **[8]**. Previously we developed a means of converting the biological precursor dihydroartemisinic acid (DHAA) to artemisinin using singlet oxygen generated by the addition of a photocatalyst **[9]**. However, as this process occurs naturally as a non-enzymatic process, we reasoned that the plant must already contain the catalysts necessary for this transformation. As such, when the crude extract was exposed to the flow photooxidation conditions previously developed, we were delighted to find the green solution, which contains the green dye chlorophyll, efficiently converted DHAA into artemisinin. The process is so efficient that up to 100x the natural levels of DHAA can be transformed using this process.

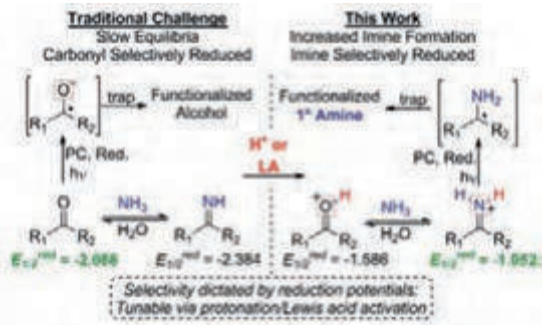

Fig. 3: Activated imines can be selectively reduced in the presence of an aldehyde/ketone using a photoredox catalyst, allowing for the facile synthesis of a range of a-functionalized primary amines.

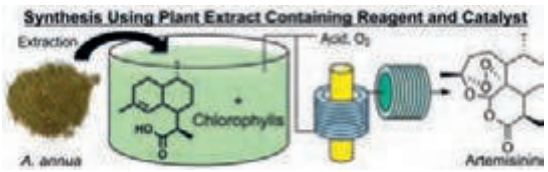

Fig. 4: A new approach towards synthesizing APIs, where naturally occurring catalysts are utilized in flow reactors to perform efficient chemical synthesis.

K. Gilmore, S. Chatterjee, M. Guidi, S. Moon
kerry.gilmore@mpikg.mpg.de

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Carbohydrates: Structure and Function

Christian Roth
17.04.1980
1999–2005: Diploma in Applied Sciences
(Technical University "Bergakademie" Freiberg, Germany)
2005–2013: Doctoral Thesis: Structural and functional characterisation of enzymes from microbial degradation pathways
(University Leipzig, Center for Biotechnology and Biomedicine. Leipzig, Germany)
2013–2017: Postdoctoral Scientist
The University of York, York Structural Biology Lab York, United Kingdom
2017–2018: Postdoctoral Scientist
Max Planck Institute of Colloids and Interfaces, Department of Biomolecular Systems
Since 09/2018: Research Group Leader, Max Planck Institute of Colloids and Interfaces, Department of Biomolecular Systems

Carbohydrates are one of the most important building blocks in nature and are involved in all important processes of life, for example cell signalling, nutrition or as building material for cell walls and other biomaterials. In contrast to DNA and proteins, there is no template based production of carbohydrate structures. Given the complexity of carbohydrate building blocks the diversity of carbohydrate structures is considerably higher. Indeed, calculations have shown that the possible combinations of a simple hexasaccharide exceeds 10^{12} **[1]**. Therefore, nature has dedicated a significant number of proteins for the synthesis, degradation and remodelling of carbohydrate structures. Sequence based methods have revealed a huge number of different carbohydrate active enzymes and carbohydrate binding modules, which are classified in different families and can be found in carbohydrate active enzyme database (CAZy) **[2]**. We want to shed light how enzymes and carbohydrate binding proteins interact with carbohydrates and what are the fundamental principles of this interaction. Furthermore we want to understand how the investigated enzymes achieve their catalytic activity and exquisite selectivity in respect of their regio- and stereoselectivity. To achieve these goals, we are using x-ray crystallography as main method of interrogation. The Carbohydrates Structure and Function group plans to contribute to the field of carbohydrate active enzymes and proteins on two major topics; Carbohydrate recognition and binding by antibodies as well as Glycoside hydrolases in biotechnology and medicine

Carbohydrate Recognition by Antibodies

Carbohydrates are an essential part of the outer surface of all cells in form of the glycocalyx and act as an identifier, which allows to distinguish different cells, for example bacterial cells or parasitic ones from host cells. Carbohydrates are an attractive target for antibody development due to their exposed localisation on the cell surface. Indeed several vaccines based on capsular polysaccharides from pathogenic bacteria are on the market. However often the exact antigen is not known, nor how antibodies recognize carbohydrates structures with high affinity and specificity. Furthermore, with the determination of different antibodies with a diverse range of ligands we want to establish if common motifs exist, which are exploited by antibodies for the recognition of carbohydrate structures. Currently, two groups in the Department: "Synthetic Vaccines", led by Prof. Seeberger and "Glycan Targeted Therapeutics" led by Dr. Moscovitz, are actively involved in the development of new carbohydrate targeting antibodies, covering multichain antibodies of the Ig-type as well as single chain antibodies. We collaborate with both groups to access a broad pool of different glycan targeting antibodies. Initially we have chosen a novel IgG type antibody (1H8) against the highly virulent *Streptococcus pneumoniae* Serotype 8 strain **[3]**. The minimal epitope and binding characteristics have been identified, but a detailed understanding how the antibody recognize and bind the antigen is unknown due to the lack of structural data. In collaboration with the Vaccine biology group we have produced sufficient amounts of antibody for subsequent structural studies. A workflow was established to convert the full length IgG in the corresponding FAB-fragment for crystallisation. High throughput crystallisation screens were carried out to identify initial crystallisation conditions, which have been refined to obtain crystals amenable for diffraction experiments. Data have been collected at the HZB Berlin synchrotron to a resolution of up to 3.0 Å. The phase problem could be solved and an initial model could be build **(Fig. 1a)**. We also started to work on single heavy chain antibodies, produced by cameloid species, often called nanobodies due to their small size. The nanobodies have been identified and initially characterized by the group of Dr. Moscovitz. Two nanobodies, one against a parasitic glycan structure and one against a plant structure have been chosen and produced in sufficient amounts in *Escherichia coli*. Crystallisation conditions have been identified using sparse matrix screening. For one nanobody single crystals have been obtained and data have been collected to a resolution of 2.0 Å. The structure of the nanobody has been determined and the potential antigen binding site identified **(Fig. 1b)**. The next steps will be to determine a structure with the antigen itself to reveal the molecular details of the antigen binding.

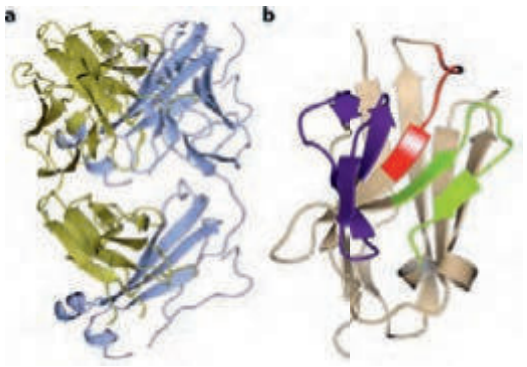

Fig. 1: Crystal structures of antibodies in ribbon representation a) Model of 1H8 derived FAB-fragment with lightchain in blue and heavy chain in sand. b) Structure of a nanobody with the antigen interacting elements coloured in red, purple and green the constant part is coloured in fawn.

Glycoside Hydrolases in Biotechnology and Medicine

Fungal cell wall targeting glycoside hydrolases are attractive enzymes to prevent fungal infection and adherence to surfaces, for example pipes or medical instruments. Whereas enzymes are known to target bacterial biofilms, attached fungal cell cluster are much harder to treat partly due to the unusual cell wall and biofilm components, including polygalactosamine **[4]**. Only one family of hydrolases (GH114) is currently known to target this polymer, however no structural and only limited functional information for this class is available. We have cloned and purified several members of GH114 family and obtained soluble protein for a homologue from *Thermotoga maritima* (Tm114). The protein could be purified and crystallised under several conditions. Several datasets have been collected up to a resolution of 2.5 Å. Several datasets showed pathologies but one dataset was suitable to solve the structure using Molecular Replacement **(Fig. 2)**.

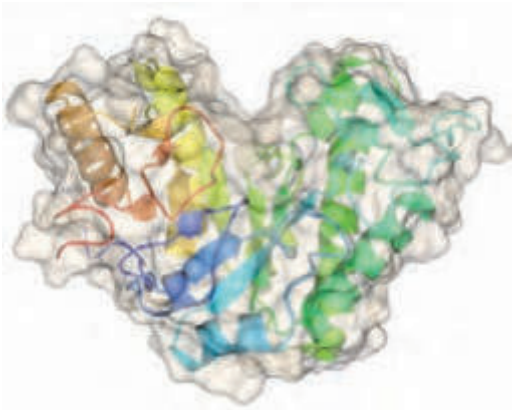

Fig. 2: Crystal structure of Tm114 in ribbon representation coloured from the N- to the C-terminus in blue to red. The Van der Waals surface is shown in beige.

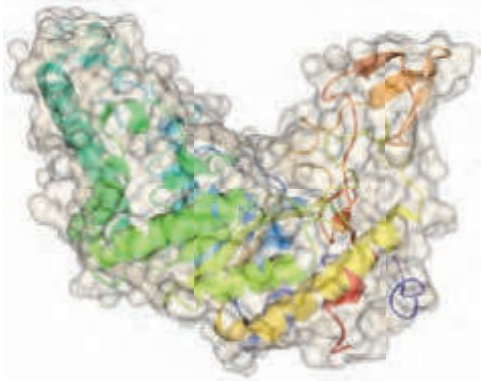

Fig. 3: Crystal structure of XynA xylan glycosynthase in ribbon representation coloured from the N- to the C-terminus in blue to red. The Van der Waals surface is shown in beige.

Glycosynthases for the Production of Plant Oligomers and Polymers:

All glycoside hydrolases have to some extend inherently the capability to catalyse the inverted reaction of the hydrolysis and form a glycosidic bond between two glycosides. This reaction is often referred to as transglycosylation. Whereas this is an unwanted side reaction in nature, it can be used to synthesize larger structures from inexpensive source material while using the exquisite stereo- and regioselectivity of the enzyme to generate the target structure. An extension of this concept led to the development of so called glycosynthases, inactive mutants of hydrolases but still able to bind the substrate and catalyse a reaction, if activated donors are used. We focus on the generation of new glycosynthases, for plant and yeast polymer structures for functional studies, in collaboration with the group of Dr. Pfrengle. The Pfrengle group has already shown, that the substitution pattern of arabinoxylans is crucial for the specific function in the context of the cell wall itself. **[5]** Furthermore, well defined oligomers and polymers are ideal substrates to probe the specificity of hydrolases and transferases involved in cell wall synthesis, degradation and remodelling. Currently a glycosynthase belonging to GH family 10 from *Geobacillus stearothermophilus* **[6]** was structurally characterised **(Fig. 3)**. Complex structures with different substrates will be the next step on the way to understand the observed product profile. Furthermore we have started to develop glycosynthases for the production of plant β-mannan. We have chosen the described β-mannase/synthase from *Cellovibrio japonicus* **[7]** as well a potential Cellulase/Mannase Cel5A from *T. maritima* as potential starting points to develop and improve mannan synthases. Both genes were cloned, and tested for protein production for subsequent assays for mannan synthase activity.

C. Roth, B. Boyraz, C. Lubahn, S. Almeida Dias Miranda, A-M. Tsirigoni
Christian.roth@mpikg.mpg.de

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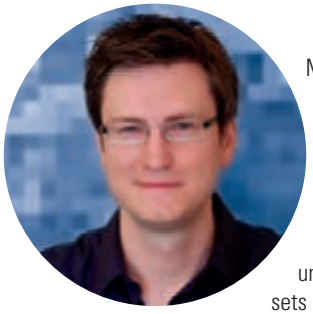
Ligand-based Targeted Delivery to C-type Lectin Receptors



Christoph Rademacher
05.05.1979
2001–2004: Bachelor Studies in "Molecular Biotechnology" at the University of Lübeck, Germany (with honours).
2004–2006: Master Studies in "Molecular Life Science" at the University of Lübeck, Germany (with honours)
2006–2009: Doctoral Thesis: "Investigations into Viral Entry Mechanisms and Carbohydrate-Protein Interactions using NMR" (summa cum laude, Prof. Dr. Thomas Peters, Institute of Chemistry, University of Lübeck, Germany)
2007–2009: PhD stipend from the Fonds der chemischen Industrie.
2009–2011: Postdoctoral training at Department of Chemical Physiology, The Scripps Research Institute with Prof. Dr. James C. Paulson (La Jolla, CA, USA).
2009–2011: EMBO Long-Term Fellowship
Since 11/2011: Research Group Leader, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces
2011–2012: Liebig Stipend from the Fonds der Chemischen Industrie
2012–2016: Emmy-Noether Young Research Group Leader
since 2017: ERC Starting Grant holder

Mammalian carbohydrate receptors are involved in cell migration, pathogen recognition, uptake and processing, and determine many aspects of cellular communication. In particular, a large number of carbohydrate receptors are found on cells of the innate immune system. Strikingly, many of these receptors are uniquely expressed on defined immune cell subsets allowing to specifically address these cells in their complex biological environment. Hence, these cells, initiators and regulators of an effective immune response, are attractive targets for the therapeutic modulation of the immune reaction.

Consequently, small molecule modulators of these carbohydrate-protein interactions would be beneficial for basic research and therapeutic intervention. Unfortunately, carbohydrate-binding sites are often rather featureless and flat and are therefore considered either challenging or undruggable, hampering the development of small molecule inhibitors. Additionally, only a limited number of high throughput screening attempts have been successful against this class of biomolecules. Our work is concerned with the development of glycan receptor-specific ligands primarily resulting from fragment-based screening approaches using biophysical assay such as ^{19}F NMR, STD NMR, HSQC NMR, and SPR **[1-5]**. These assays are complemented by in silico approaches as well as screening on chemical fragment microarrays and also by a recently developed cell-based assay that allowed screening our 900-member fragment library **[5]**. Based on these chemical probes resulting from fragment-based design, we explore basic immunological questions as well as applied aspects such as small molecule targeted delivery of stimulants to specific immune cell subsets.

CellFy: A Cell-based Fragment Screening Assay for the Identification of Novel Lectin Ligands

To complement the existing pipeline of technologies existing in the laboratory to for the identification of small molecules ligands for C-type lectins, we developed a fragment screening targeting receptors exposed on cell surfaces **[5]**.

In general, fragment-based drug discovery is a powerful complement to conventional methods for ligand identification, especially for difficult targets such as lectins. However, screening low molecular weight fragments usually requires highly sensitive biophysical methods due to the generally low affinity of the identified ligands. A cell-based fragment screening assay (cellFy) was developed that allows sensitive identification of fragment hits in a physiologically more relevant environment in contrast to isolated target screenings in solution. For this, a fluorescently labelled multivalent reporter was employed, enabling direct measurement of displacement by low molecular weight fragments. Two challenging targets were chosen to test the applicability of this novel assay. Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) and Langerin. A library of 900 members was screened and hits were validated using orthogonal assays, mainly from NMR spectroscopy. Additionally, since the assays is based on flow cytometric analysis, a multiplexed assay format was developed for simultaneous screening against multiple CLRs allowing a selectivity counterscreening. Overall, this sensitive cell-based fragment screening assay provides a powerful tool for rapid identification of bioactive fragments, even for difficult targets.

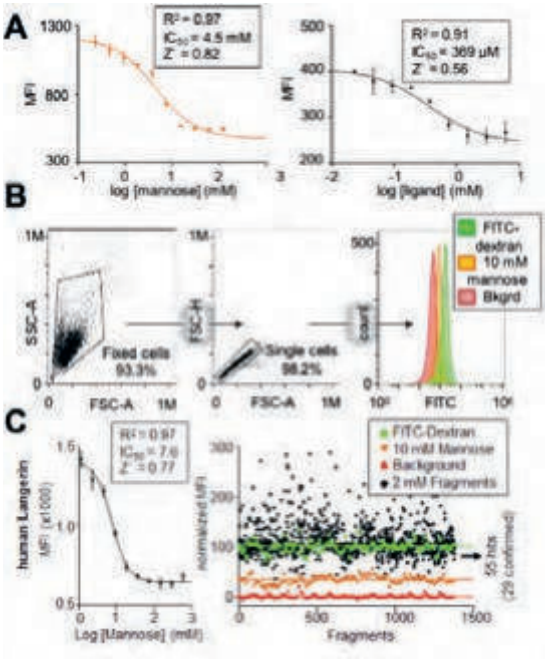


*Fig. 1: Cell-based fragment screening assay (cellFy). (A) A fluorescent reporter (FITC-dextran) is displaced from the cell surface in a flow cytometry experiment. (B) Raw experimental data from flow cytometry. (C) IC_{50} evaluation of mannose against Langerin and primary data from the screening of a fragment library **[5]**.*

Identification of Secondary Sites: DC-SIGN

In a continuation of our efforts to understand C-type lectin accessibility to drug-like molecules, a larger screening campaign against DC-SIGN was conducted **[3]**. DC-SIGN is a cell surface receptor for several pathogenic threats such as HIV, Ebola virus or Mycobacterium tuberculosis. Multiple attempts to develop inhibitors of the underlying carbohydrate–protein interactions have been undertaken in the past fifteen years. Still, drug-like DC-SIGN ligands are sparse, which is most likely owed to its hydrophilic, solvent-exposed carbohydrate binding site. In a parallel fragment screening against DC-SIGN, SPR and a reporter displacement assay complemented previous screenings using ^{19}F NMR **[1]** and chemical fragment microarrays **[2]**. Hit validation including SPR and ^{1}H-^{15}N HSQC NMR revealed that although no fragment bound in the primary carbohydrate site, five secondary sites are available to harbour drug-like molecules. In the context of druggability of the CLRs, this is an important finding, since it complements our previous findings for human Langerin, for which an allosteric network of communicating amino acids was described **[6]**. Here, the existence of secondary sites for DC-SIGN, shows how small molecules can be utilized to modulate the lectin function. Building on key in-

teractions of the reported fragment hits, these pockets will be targeted in future approaches to accelerate the development of DC-SIGN inhibitors.

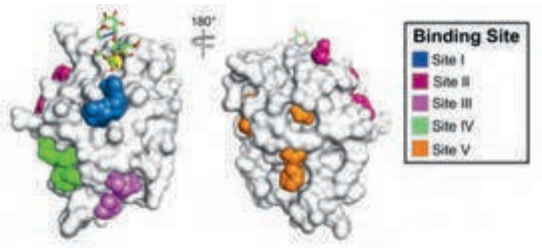


*Fig. 2: DC-SIGN harbors multiple binding sites for drug-like molecules as inferred from NMR studies and computational binding site assessment **[3].***

First Allosteric Inhibitor of a Mammalian Lectin

Having identified an allosteric network being present in human Langerin **[6]** and multiple secondary sites in its close relative DC-SIGN **[3]**, we expanded our work into allosteric modulators of mammalian lectin functions. To identify starting points for chemical probe development we chose the murine Langerin and used ^{1}H and ^{19}F NMR screening utilizing our 871-member drug-like fragment library. Subsequently, hits were validated by surface plasmon resonance and enzyme-linked lectin assay. Using structure-activity relationship studies and chemical synthesis, we identified thiazolopyrimidine derivatives with double-digit micromolar activity that displayed Langerin selectivity. Again, chemical fragment arrays **[2]** were crucial for the decision-making which compound series to expand with an elaborate SAR study. Moreover, based on ^{1}H-^{15}N HSQC NMR and competitive binding and inhibition experiments, we demonstrate that thiazolopyrimidines allosterically inhibit Langerin. To the best of our knowledge, this is the first report of drug-like allosteric inhibitors of a mammalian lectin.

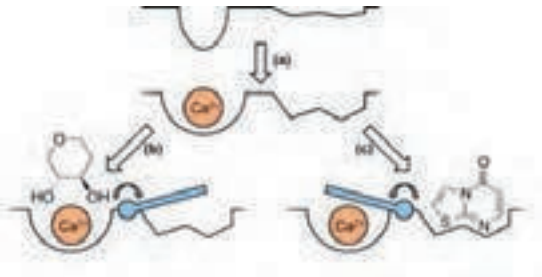


*Fig. 3: The first allosteric inhibitor of a mammalian lectin was discovered for murine Langerin **[4]**.*

Targeted Delivery of Liposomal Nanoparticles to Primary Human Langerhans Cells

To make use of the CLR ligands we have discovered, we envisioned to use them as targeting ligands to modulate immune cell functions, in particular Langerhans cells (LCs) **[7]**. LCs are a subset of dendritic cells residing in the epidermis of the human skin. As such, they are key mediators of immune regulation and have emerged as prime targets for novel transcutaneous cancer vaccines. Importantly, the induction of protective T cell immunity by these vaccines requires the efficient and specific delivery of both tumor-associated antigens and adjuvants. Langerhans cells uniquely express Langerin. We identified a specific, glycomimetic Langerin ligand following a heparin-inspired design strategy that integrated NMR spectroscopy and molecular docking. The conjugation of these glycomimetics to liposomes enabled the specific and efficient targeting of Langerhans cells in the human skin. This delivery platform provides superior versatility and scalability over antibody-based approaches and thus addresses current limitations of dendritic cell-based immunotherapies.

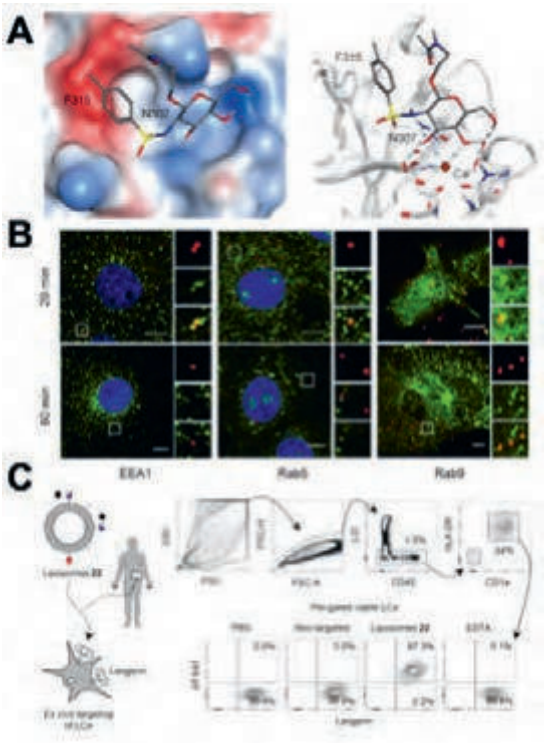


*Fig. 4: A targeted liposomal delivery system was developed to address human Langerhans cells. (A) A model of the targeting ligand in the receptor site was derived from NMR studies. (B) Confocal imaging and co-localization assays allowed deriving the spatial and temporal uptake of the targeted particles. (C) Targeted liposomes were exposed to epidermal cell suspensions and specific targeting of LCs was observed **[7]**.*

C. Rademacher, F. Fuchsberger, D. Kim, M. Rentzsch, E. Shanina, R. Wawrzinek, H. Zhang
Christoph.Rademacher@mpikg.mpg.de

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Noble-Metal-Free Heterogeneous Photocatalysis

Bartholomäus Pieber
05.02.1988
2006–2009: Bachelor of Science at the University of Graz and Graz University of Technology
2009–2011: Master of Science (with distinction) at the University of Graz and Graz University of Technology
2011–2015: Doctoral Thesis: "Organic Chemistry in Single- and Multiphase Continuous Flow Regimes" (with distinction, Prof. C. Oliver Kappe, Institute of Chemistry, University of Graz)
2016–2017: Postdoctoral Scientist, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces
Since 2018: Research Group Leader, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces
Since 2018: Liebig Fellowship of the Fonds der Chemischen Industrie (FCI)

Using light to accelerate chemical reactions is attractive since in contrast to conventional reagents, photons are traceless species which reduces purification time and costs. Traditionally, photochemical reactions were carried out using ultraviolet light for the direct excitation of substrates or reagents. The high energy often causes unselective reactions which are difficult to predict and control. As a result, photochemistry has largely remained a neglected technique in synthetic organic chemistry. This perception has changed with the development of photocatalysts (PC) that can be excited by visible light and subsequently initiate transformations via energy transfer (photosensitization) or single-electron transfer (photoredox) events **[1]**.

The vast majority of protocols involving photocatalysis are carried out using expensive, homogeneous ruthenium or iridium polypyridyl complexes such as $Ru(bpy)_3^{2+}$ **(Fig. 1)**. Although very powerful, homogeneous photocatalysis suffers from two main drawbacks. First, operationally these catalysts require tedious separation and purification procedures in order to recycle the catalytically active material, if possible at all. Second, long-term viability is clouded by high economic and environmental cost of acquiring the catalysts, as iridium is the rarest transition metal in the Earth's crust with ruthenium also among the least abundant.

Heterogeneous semiconductors are promising sustainable alternatives given their straightforward recycling strategies (e.g. filtration, centrifugation) and ease of preparation **(Fig. 1, B)**.

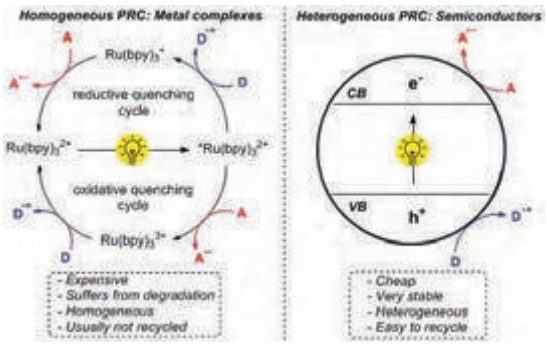

Fig. 1: Homogeneous versus heterogeneous visible light photocatalysis

Graphitic carbon nitrides (g-CN), a class of metal-free polymers, are among the most potent materials for heterogeneous photocatalysis **[2]**. Unlike the most widely studied semiconductor TiO_2, g-CN materials absorb light in the visible area. In general, g-CN polymers are easy to synthesize from readily available and cheap precursors, and exhibit a high thermal and chemical stability. The high potential of this purely organic semiconductor as a photocatalyst for sustainable organic synthesis is further supported by its recyclability and has recently been demonstrated for a range of photocatalytic transformations **[2]**.

The replacement of homogeneous noble-metal photocatalysts by tailored carbon nitrides is the prime goal of our research efforts. We focus not only on the development of new catalytic systems and dedicated technologies for efficient transformation to but also aim to understand their underlying mechanisms.

Photocatalytic Fluorinations

In a collaborative effort with researchers of the colloid department, we have recently discovered that g-CN can be indeed used to substitute ruthenium and iridium complexes by a g-CN derivative for the decarboxylative fluorination of phenoxyacetic acid and phenylacetic acid derivatives **(Fig. 2) [3]**. Moreover, it was found that the semiconducting material is an effective catalyst for the direct fluorination of benzylic C–H bonds **(Fig. 2)**, a transformation that has previously been catalyzed by organic photocatalysts via hydrogen atom or electron transfer processes. The synthetic potential is furthermore improved by the easy recycling routine upon filtration or centrifugation as well as the catalytic activity over time. Another important feature of these catalytic protocols lies in the short reaction time which is similar or even shorter than for the homogeneously catalyzed processes.

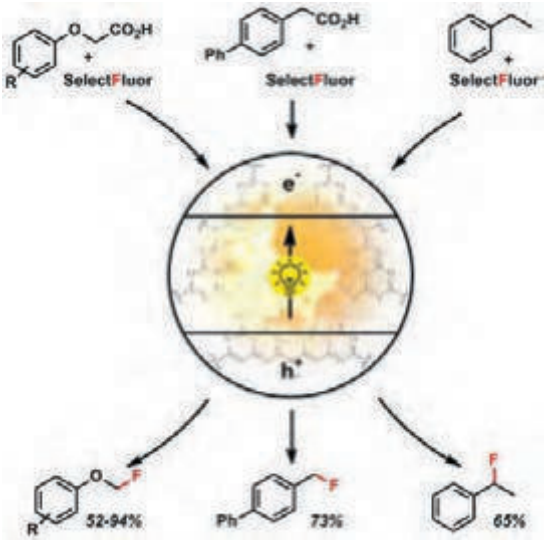

Fig. 2: Photocatalytic fluorinations using graphitic carbon nitride as heterogeneous catalyst.

Dual Catalytic Cross-Coupling Reactions

To date, palladium-catalyzed carbon-carbon and carbon-heteroatom cross-coupling reactions are among the most important reactions for constructing complex molecular scaffolds. Their substitution with first-row transition metals would not only lead to more economic and sustainable solutions but could also help our understanding of how nature constructs highly complex structures using earth-abundant metal species. Among those, nickel occupies a privileged position due to its fundamental properties such as the accessibility of N^{I} and N^{III} oxidation states through single electron processes. This electronic versatility in combination with Ir and Ru photoredox catalysis recently resulted in many cross-coupling protocols at mild conditions **[4]**. Combining the advantages of this dual catalytic strategy and recyclable, heterogeneous g-CN materials

led to a semi-heterogeneous approach **(Fig. 3) [5]**. Compared to iridium and ruthenium photocatalysts, the organic semiconductor is recyclable and can harvest a broader range of the visible light spectrum (up to ~600 nm) as shown by *in situ* FTIR analysis.

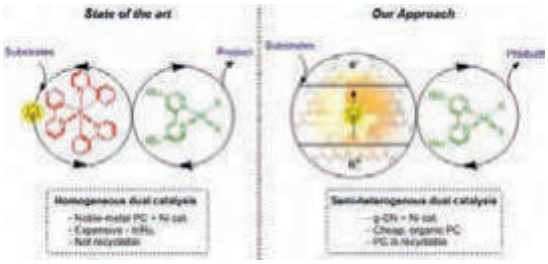

Fig. 3: Comparison of homogeneous and semi-heterogeneous dual Ni/photo(redox) catalysis.

Reaction Technology

Heterogeneous photocatalysts such as carbon nitrides are commonly employed in batch processes but are ill suited for continuous flow chemistry **[6]**. For thermal reactions, heterogeneous catalysts are typically used in packed bed reactors that cannot be penetrated by light and thus are not suitable for photocatalytic reactions involving solids. The development of serial micro-batch reactors (SMBRs) allow for the continuous use of solid materials together with liquids and gases in flow **(Fig. 4) [3]**. The system combines the advantages batch processing offers for heterogeneous materials with the benefits of flow photochemistry. This technology was utilized to intensify the selective and efficient fluorination protocols discussed above and gives access to sustainable and scalable heterogeneous photocatalysis.

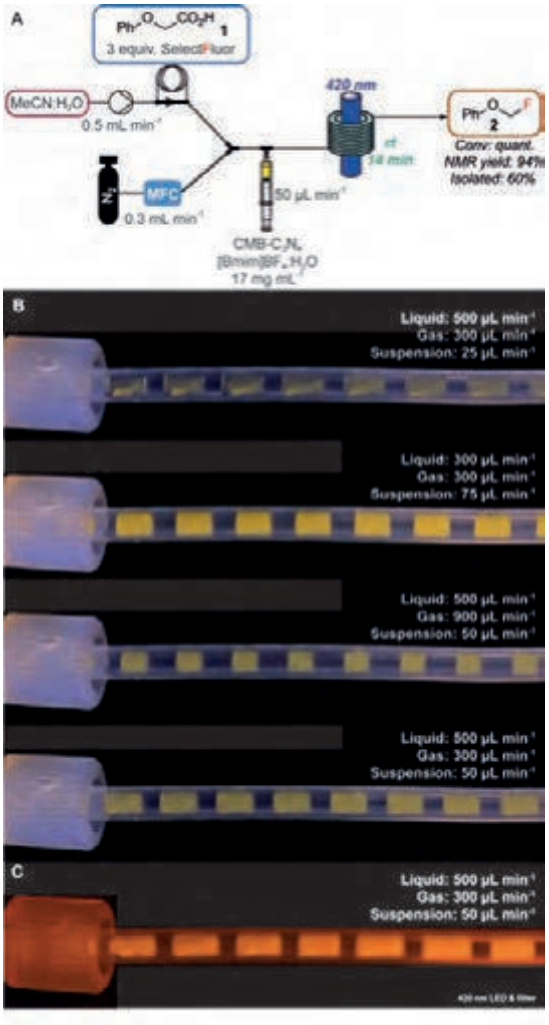

Fig. 4: Heterogeneous photoredox catalysis with CMB-C_3N_4 in SMBRs. (A) Decarboxylative fluorination of phenoxyacetic acid. (B) On the fly adjustment of reaction parameters. (C) Internal mixing results in a uniform, efficiently irradiated suspension (segments were irradiated with 420 nm LEDs and the picture was taken through a blue light filter).

B. Pieber, C. Cavedon, S. Gisbertz, S. Reischauer, A. Madani
bartholomaeus.pieber@mpikg.mpg.de

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FIGHTING CANCER USING GLYCAN BINDING SINGLE DOMAIN ANTIBODIES

Oren Moscovitz
31.01.1977
2001–2004: Bachelor of Science, Summa cum laude, Biomolecular biology, Bar Ilan University, Ramat-Gan, Israel
2005–2007: Master of Science, Biotechnology and Molecular Biology, The Hebrew University of Jerusalem, Jerusalem, Israel
2007–2013: Doctoral Thesis: Regulation of the 20S proteasome ubiquitin independent degradation pathway. Group of Prof. Michal Sharon, Department of Biological Chemistry, Weizmann Institute of Science, Rehovot, Israel
2013–2014: Postdoctoral researcher, Group of Prof. Michal Sharon, Department of Biological Chemistry, Weizmann Institute of Science, Rehovot, Israel
2014–2017: Alexander von Humboldt Fellow, Group of Prof. Juri Rappsilber, Department of Biotechnology, Technical University of Berlin, Germany
2017–2018: Postdoctoral researcher, Group of Prof. Peter H. Seeberger, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces, Berlin, Germany
Since 01/2018: Group Leader, "Glycan-Targeted Therapeutics", Group of Prof. Peter H. Seeberger, Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces, Berlin, Germany

Glycans are the predominant molecule on our cell surface and shape the initial cell-cell and cell-pathogen interactions upon first contact. Each and every cell in our body is covered by a thick and complex layer of glycans called the glycocalyx. Our glycocalyx is composed of glycan molecules that are attached to proteins, lipids or to other glycans.

The structural complexity of the glycans composing the glycocalyx is enormous and is the result of their unique biosynthesis pathway that directly and indirectly involves large parts of our genome.

Unlike the linear, template-driven synthesis of proteins from nucleic acids, the complex, branched and heterogeneous structures of glycans are formed by a network of interacting, and sometimes competing, enzymes. These enzymes work in concert to produce, activate and carry the different building blocks, assemble and modify the glycan chain, and finally couple the glycan to its right partner (a lipid, protein or another glycan). The unique synthesis pathway of glycans results in the immense number of different glycan structures that exceeds by orders of magnitude the number of proteins encoded by our genome.

The extraordinary heterogeneity of the glycome is the main reason why glycobiology in general and glycotherapy in particular, is lagging behind in the development of basic research tools that target specific glycan structures. Structural heterogeneity of native glycans caused great difficulties with isolating and characterizing specific naturally occurring glycans in sufficient amounts. Therefore, the ability to distinguish a specific glycan structure and elucidate its exact biological contribution was wishful thinking not so long ago.

This changed dramatically with the appearance of synthetic glycan assembly that enables us to access glycan structures which are simply unattainable from biological sources. To date, synthetic glycans are used for a diverse array of glycobiology applications from glycan arrays that elucidate different binding epitopes of glycan binding proteins **[1]** to glycan standards for glycomics which help to sort and identify complex serum samples **[2]**.

In my group we utilize synthetic glycans to develop glycan targeted compounds that are used for basic research as well as for therapeutic and diagnostic purposes. By using synthetic glycans immobilized on microarrays we identify specific glycan structures in order to better understand protein-glycan and glycan-glycan interactions in nature. These novel insights then contribute to the development of pharmaceuticals that target native glycan structures. Current work in my group focuses on development of anti-cancer therapeutics that target aberrant glycan structures which are expressed in different cancers.

Aberrant Glycans are Attractive Anti-Cancer Targets

The first report of aberrant glycosylation on cancer cells was 70 years ago **[3]**. Since then, extensive studies showed that appearance of aberrant glycosylations or Tumor Associated Carbohydrates Antigens (TACAs) serve as a hallmark of cancer. Aberrant glycan structures are expressed on the surface of cancer cells, coupled to membrane lipids and cell surface proteins. TACAs expression was correlated with most aspects of cancer biology. From cancer proliferation and tissue invasion, to metastasis, immune cell evasion, and even drug resistance. Interestingly, the exact mechanism through which TACAs expression governs different aspects of cancer biology is far from being fully understood. This is mainly due to lack of sufficient molecular tools that can recognize specific glycan epitopes.

TACAs can be divided into three categories **(Fig. 1)**: I) non-human TACAs that are consumed as part of our diets and get incorporated into the cancer cell glycocalyx (for example N-Glycolylneuraminic acid (Neu5Gc)). 2) Embryonic stem cell glycans that should not be expressed on differentiated cells but re-appear in malignant cells. 3) Overexpressed, truncated or aberrant glycan structures as a result of altered activity and/or expression levels of glycan-synthesizing enzymes

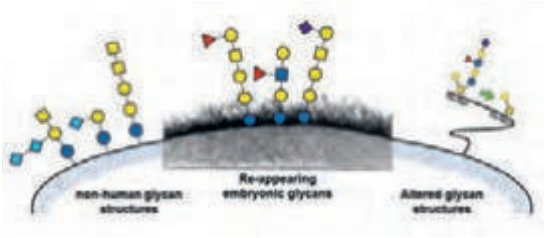

Fig. 1: Examples of the different types of tumor associated carbohydrates antigens (TACAs) groups that can be found on the glycocalyx of human cancer cells.

To date, it is clear that TACAs play a pivotal role in cancer biology. There is a continuous effort to identify novel TACAs and shed more light on TACAs involvement in the different malignant processes. Moreover, specific binding of TACAs adds a highly valuable diagnostic and therapeutic tool that can aid in our global war against cancer **[4]**.

Due to glycan heterogeneity, generating glycan binding antibodies is a relatively young field that started blooming mainly after synthetic and well-defined glycan structures were available. As a result, the number of highly specific anti-TACAs antibodies is low and is still far from fulfilling its full potential.

We aim to close the gap and provide tools that will broaden our understanding of the interplay between cancer biology and expression of specific TACAs structures. For that we use well defined synthetic glycans that are exploited in three consecutive steps: 1) Identification of biologically relevant TACAs structures using glycans immobilized on microarrays. 2) Animal immunization studies 3) Identification and isolation of specific high affinity TACAs-binding antibodies.

The monoclonal antibodies we develop in my group are unique Alpaca derived single domain antibodies, or "nanobodies".

Nanobodies are Nature's Magic Bullets

During late 80s and the following years, it was discovered that the Camelidae family (camels, llamas, alpacas, vicugnas), and also different cartilaginous fish (sharks and rays), produce special IgG3 antibodies. In addition to the classical heavy and light chain IgG1 molecules, these animals produce a unique kind of IgG3 lacking the light chain **(Fig. 2)**. The antigen-binding site in each of these unusual heavy chain antibodies (hcAbs) is formed only by a single domain, designated VHH or "nanobody" (Nb). As shaped by evolution, Nbs have higher stability and solubility compared to engineered single domain antibodies. In addition, due to their ultra-small size (~13kDa) and lack of a light chain, their antigen-binding interface evolved to be longer compared with conventional IgG1 antibodies **[5]**. As a result, Nbs are able to penetrate and bind unique and more concave epitopes that are simply inaccessible to classical antibodies.

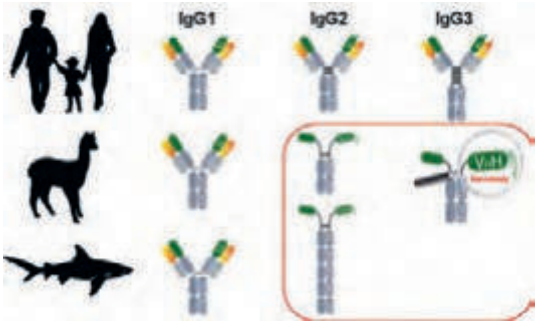

Fig. 2: Nbs are the recombinantly expressed antigen binding domain of unique heavy chain only antibodies found in members of the Camelidae family and several cartilaginous fish.

In addition, Nbs are a highly attractive tool as they can be easily engineered with a vast range of functionalization properties. Since Nbs are small monomeric proteins, the molecular engineering tools to functionalize and modify multivalency, specificity and/or effector molecules are already well established. Using basic cloning methods or site-specific labelling, Nbs can be modified as desired, either with fluorescent probes, radiotracers, or therapeutic drugs. Nbs can be expressed as monomers, dimers or higher oligomers to form several binding entities simultaneously. Importantly, the fused Nbs can have different specificities as part of a single multispecific chain. The multispecific chain is then able to simultaneously bind multiple antigens or different epitopes on a single antigen; an attractive property when heterogeneous glycan structures are targeted.

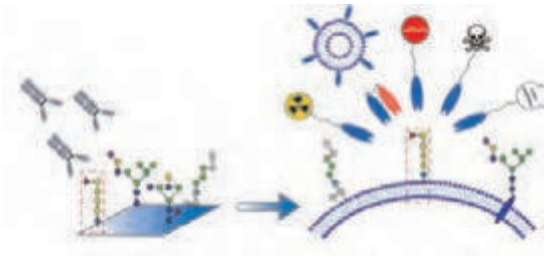

Fig. 3: Using synthetic glycan microarrays we can identify and isolate specific TACAs binding heavy chain antibodies. These antibodies are then developed into functionalized glycan targeting Nbs for basic research, therapeutics and diagnostics purposes.

Targeting Cancer Cells via TACAs Binding Nbs

As mentioned previously, we aim to develop tools that will broaden our understanding of the glycan code of cancer biology by targeting specific glycan epitopes. An example for our work is highlighted in **Fig. 3** which shows specific binding of Nbs to breast cancer cells. The Nbs recognize a unique glycan structure which is part of a larger TACAs family that is highly abundant on different cancers. These Nbs which were generated by immunizing an alpaca with a synthetic glycan can bind synthetic but also the native glycan on cancer cells with high affinity. Current work functionalizes these Nbs with anti-cancer drugs and radio tracer probes in order to further test them for diagnostic and therapeutic experiments in animal models towards clinical trials.

O. Moscovitz, S. Borowski, F. Goerdeler, S. Khilji, A. Peters, M. Zaslona
Oren.Moscovitz@mpikg.mpg.de

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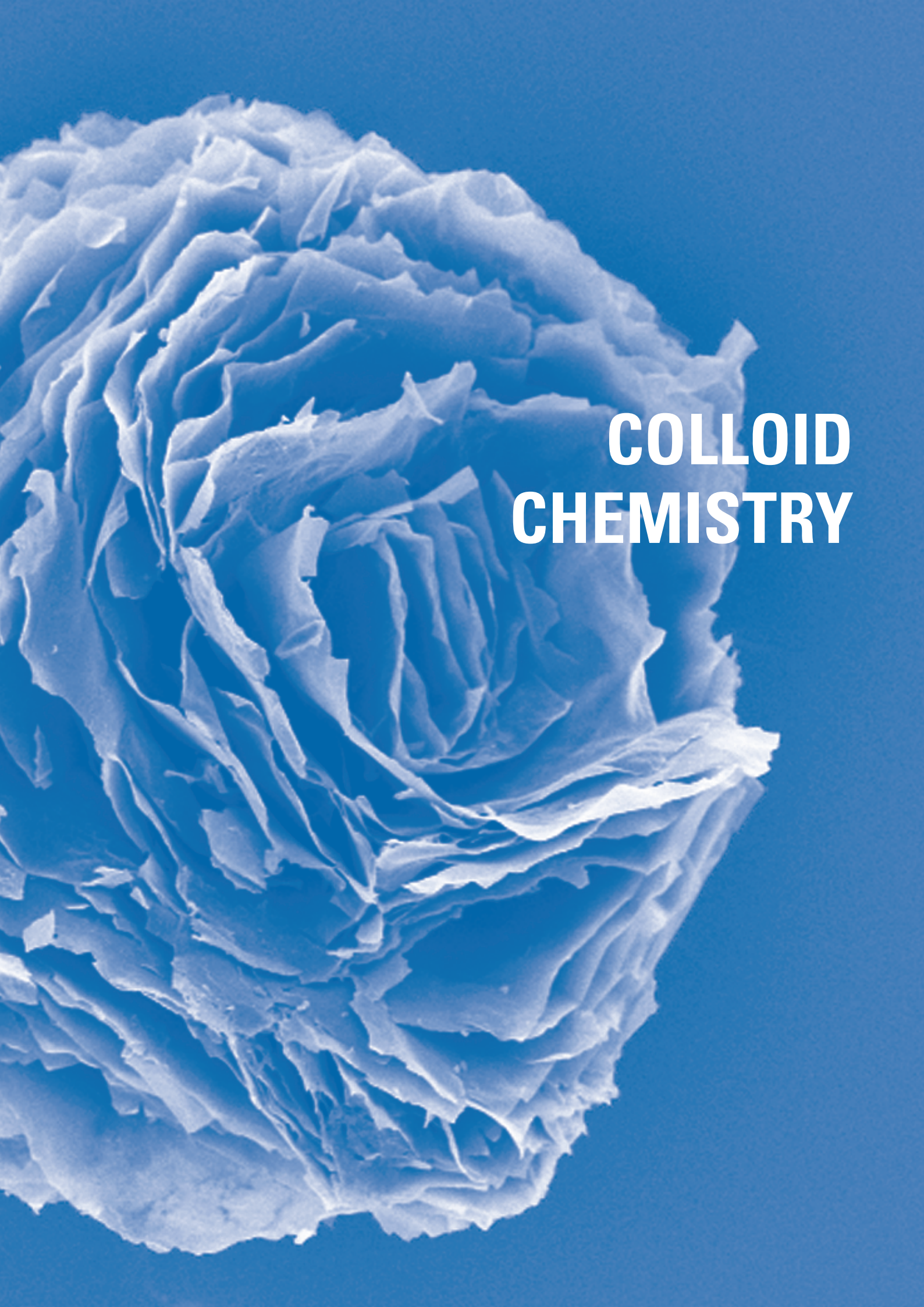


COLLOID CHEMISTRY

RESEARCH PERSPECTIVES OF THE DEPARTMENT OF COLLOID CHEMISTRY

Markus Antonietti
06.02.1960
1983: Diploma, Chemistry (University of Mainz)
Thesis: Bestimmung der Diffusion von photomarkiertem Polystyrol: spezielle Systeme, chemische und physikalischchemische Aspekte
1985: Doctorate for natural science (summa cum laude, University of Mainz
Thesis: Diffusion in topological constraint polymer melts with Prof. Dr. H. Sillescu
1990: Habilitation, Physical Chemistry (University of Mainz) Thesis: Microgels – Polymers with a special architecture
02/1991: Associate Professor (University of Mainz)
09/1991: Full Professor (Philipps University Marburg)
Since 1993: Director (Max Planck Institute of Colloids and Interfaces, Golm), Full Professor (University of Potsdam)

A) General Description of the Department

1. Management Principles and Scientific Profile

The overall size of the Department of Colloid Chemistry has decreased due to legal issues to about 65 people, however still covering a broad range of research topics. The effective constituting element of the scientific activities is the "project", a structure headed by a senior scientist involving a mixture of technicians, graduate students and post-docs (3 – 10 people). Projects are related to scientists, but usually have a temporal character of about 5 years. After this time, permanent scientists (including the director) have to redefine their profile to justify the allocation of resources. In the case of non-permanent scientists, the projects usually leave the department with the promotion of the scientist, i.e. the group leaders can continue their specific research in their new academic environment (usually as professors) without competition of the institute.

In the time of this report and following those rules, the serious changes of my department already running in the last three periods continues to take place. Dr. Klaus Tauer retired, while Dr. Nadja Tarakina took over the new AC-HRTEM laboratory from Dr. Marc Willinger who went to ETH Zürich.

It is fair to say that a majority of the group is now still in the early phase of higher academic profiling, making the following overview more concept that result oriented. This turnover of leading junior scientists is beyond typical and simple, and I would opt for some more stability after so many changes.

The following topics are currently explored within the department:

1.1 Novel Self Assembly Processes in Polymers
1.2 Next generation Electrochemistry materials
1.3 Modern Techniques of Colloid Analysis
1.4 Energy and Environmental Utilization of Carbon Nanomaterials
1.5 Colloid Chemistry for Green Chemistry, green polymers and Biorefining, Kitchen Lab
1.6 Artificial photosynthesis

The projects behind the headers are briefly explained below:

1.1 Novel Self Assembly Polymers

Amphiphilic polymers usually consist of components which dissolve in different media, e.g. a hydrophilic and a hydrophobic part, but this paradigm is proven to be incomplete. The newest observation in this direction is that also block copolymers without hydrophobic contrast can self-assemble to complex structures. Focal points of interest in this project group are:

- The aggregate formation and lyotropic liquid crystalline phase behavior of double hydrophilic block copolymers is examined in dependence of the molecular structure, the relative amount of the different components, as well as the secondary interactions between the structure forming bio-like blocks *(Dr. Bernhard Schmidt)*.
- Polymer Ionic Liquids 2.0: *Dr. Ryan Gutermann* followed Prof. Yuan in this very promising subject. He is currently synthesizing very powerful, selective alkylation agents based on novel PIL chemistry but also N- polycarbene chemistry to broaden the range of available polymer structures

1.2 Next Generation Electrochemistry Materials

Following the project house ENERCHEM which has ran out, our department continues to take a leading role in the field of energy materials. Hydrogen storage, better fuel cells, new energy cycles, new catalysts for more efficient energy conversion processes, novel batteries, ultra-capacitors, remote energy storage, all these topics are intimately connected with the control and design of materials nanostructure. Activities based in Golm include:

- Metal free organocatalysis and photocatalysis with porous organic semiconductors: Novel synthesis schemes towards carbonnitrides *(Dr. Oleksandr Savatieiev)*.
- The synthesis and characterization of high surface area functional carbons and their use for ionic liquid based supercapacitors and. supramolecular approaches towards C2N *(Dr. Martin Oschatz)*.
- New battery concepts such as the Magnesium battery rely on new solvent systems, and the corresponding new cathodes are based on surface binding instead of intercalation, all employing novel solvent/ conducting salt systems. All this –with a physicochemical perspective- is handled within the group of *Clemens Liedel*.

1.3 Modern Techniques of Colloid Analysis

All the work described is necessarily accompanied by a considerable amount of colloid analysis which includes fully commercial techniques, but also relies on the development of new techniques or methods of preparation and data handling. The developments in this area are currently mainly focused on electron microscopy:

- Special techniques of transmission and scanning electron microscopy on soft, structured matter which are run on the base of a central service group *(Dr. Nadja Tarakina, Dr. Jürgen Hartmann)*.
- Structure and composition of organic-inorganic interfaces *(Dr. Nadja Tarakina)*.

1.4 Energy and Environmental Utilization of Carbon Nanomaterials

The group of *Dr. Martin Oschatz* is a rather recent addition and for the first 3 years covered by a Liebig-Fellowship of the VCI. Dr. Oschatz combines his longstanding experience on porous carbon materials from the Kaskel/TU Dresden group with or own expertise in sustainable carbon synthesis. Projects include:

- Electrically induced gas sorption and gas separation in new materials, materials with unusually high selectivity for gas separation, co solvent effects in gas separation.
- Superstable and non-innocent catalytic supports for electrochemistry and classical heterogeneous catalysis.

1.5 Colloid Chemistry for Green Chemistry, Green Polymers and Biorefining; Kitchen Lab

Advanced materials chemistry is still mostly based on non-sustainable resources, and carbon neutral processes are to be invented for a fully sustainable society. Based on previous projects on hydrothermal carbonization, we carefully analyzed hydrothermal processes for the generation of value chemicals from biomass. These projects were first driven by my previous ERC Advanced Grant but now have reached practical matureness to handle it over to group leaders. This project platform includes

- Valorization of lignin via reductive hydrothermal splitting *(Markus Antonietti)*.
- Conversion of carbohydrates into lactic acid and other platform chemicals *(Dr. Majd al-Naji, Markus Antonietti)*.
- Next Generation Green Polymers based on sustainable monomers *(Dr. Bernhard Schmidt)*.

This projects move the department admittedly to upstream competence, but is expected to allow a new type of organic materials chemistry by new key components.

For outreach we run a so-called "Food-Lab" *(Dr. Valerio Molinari)* where typical cooking technologies are applied to the field of material synthesis. This is to be understood as the inversion of the principle of "molecular cuisine". Started as a save place for schoolkids and candidates of temporal chemistry ban, it quickly turned out as a fountain of fresh processing ideas and materials. The leader position of this lab is currently vacant, and I am head-hunting a appropriate candidate.

1.6 Artificial photosynthesis

The international joint laboratory on Artificial Photosynthesis was established in July 2008 between the Max-Planck Institute of Colloids and Interfaces (Prof. Markus Antonietti) and Fuzhou University. The lab is now lead by Prof. Dr. Xinchen Wang, former group leader of the MPI-CI. Natural photosynthesis, the process by which green plants are converting solar energy into chemical energy, has inspired the development of artificial versions of photosynthesis, i.e. (1) the splitting of water into hydrogen and oxygen, and (2) the conversion of carbon dioxide into organics via sunlight. This was recently also successfully supported by a DFG-NSFC binational project between the same partners

An important challenge in artificial photosynthesis is the development of catalysts that should be sufficiently efficient, stable, inexpensive, and capable of harvesting the abundant visible light in solar spectrum. There are many trials to establish stable systems for this purpose, mostly based on inorganic semiconductors with appropriately engineered band-gap. In our group we are investigating polymeric and organic-inorganic hybrid materials with controlled nanostructures as potential energy transducers for artificial photosynthesis for such applications as solar energy conversion, environmental purification, and organic synthesis.

- Melon, a carbon nitride polymer with graphitic structure, has turned out to be efficient for the direct splitting of water into oxygen and hydrogen. We improve the chemical structure of this polymer by copolymerization and textural control to improve light extinction and quantum efficiency of this process *(Dr. Oleksandr Savatieiev)*.
- New organic chemistry under photoredox conditions. A number of fellows is exploring the use of the as made catalysts for novel chemistry, such as photo-acetalization, Disulfide chemistry and Hantsch ester and thiamide synthesis. This is currently combined with the Seeberger department in a joint project on the future of chemical fine synthesis. *(Dr. Oleksandr Savatieiev)*

2. Future Perspective: the director's view for the next years

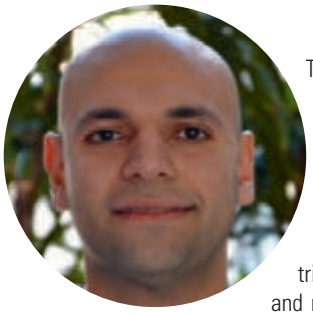
After losing most of my more senior scientists independent careers and one case of retirement, I use the opportunity for a redefinition and reorientation of the department. I will continue the restructuration to enter a period with more coordinated research and longer term goals, driven by the director and more tightly bound junior people.

Our trials to cooperate with the National Excellence Centre on Catalysis of the TU Berlin are to my opinion a big success, concerning the development of new catalytic materials and Solar Energy Usage Cascades. The new projects on "Energy Materials" and "Processes for the Raw Material Change" turned out to be very timely and secured my department in the last two years a leading European role in these activities. This is also nicely reflected in many invitations for plenary and main lectures and the overall bibliometric performance.

Due to the talents of the new people hired, we can also seriously strengthen work projects between the departments, among them the highly promising "flow chemistry" project together with the Seeberger department, where we bring in our heterogeneous catalysis knowledge and which are showcased some spectacular progress for synthetic chemistry.

The finalization of our new advanced electron microscopy lab with the new JEOL electron microscope and the hiring of Dr. Nadja Tarakina as a Senior Scientist will lead to increased cooperation with the Fratzl department. I expect here also a new project on quantitative locally resolved EELS to characterize organic semiconductors. Other potential projects which have found appropriate junior staff scientists in 2018/2019 are "carbon Q-dots" and "soil colloids".

Lignocellulosic Biomass for Sustainable Platform Chemicals using Heterogeneous Catalysis



Majd Al-Naji
24.10.1984
2002–2008: Bachelor of Science in applied Chemistry from Damascus University
2010–2013: Master of Science in Structural Chemistry and Spectroscopy (SCS) from the Institute of Chemical Technology at Universität Leipzig
2013–2017: Doctoral Thesis: Liquid-Phase Hydrogenation of Lignocellulosic Biomass-Derived Model Mixtures using Highly Efficient and Stable Supported Metal Catalysts in Institute of Chemical Technology at Universität Leipzig
01/17–12/17: Postdoctoral Scientist at Center for Surface Chemistry and Catalysis at KU Leuven
Since 01/2018: Postdoctoral Scientist at department of Colloid Chemistry, Max Planck Institute of Colloids and Interfaces

The associated resource stress and price volatility, as well as climate changing and polluting effects of our linear fossil based economy necessitates a transition towards a sustainable circular economy based on renewable biomass resources. However, biomass includes lignocellulose, lipids containing triglycerides from animal fats, vegetable origin and microalgae and turpentine streams. Of these, lignocellulosic biomass consists of cellulose, hemicellulose lignin and represents the most abundant and low cost one. In addition, lignocellulosic biomass multi-functionalities, *e.g.*, -OH, -C=O, -COOH and -R-O-R-, render its highly reactive nature and makes it a suitable source to replace fossil oils as platform chemicals. Valorization of lignocellulosic biomass process is greatly linked with utilization of heterogeneous catalysts. In this regard, a wide range of supported metal catalysts with bifunctionalties, *i.e.*, acid or base and metal function, were already applied. The upgrading of lignocellulosic biomass to fine chemicals and liquid transportation fuels has been achieved utilizing two approaches: i) the submission of entire lignocellulosic biomass to thermochemical processes or ii) the pre-treatment of lignocellulosic biomass followed by a biochemical or catalytic process. The scope of the *Biorefinery and Sustainable Chemistry Research Group* is to develop an integrated catalytic flow process for upgrading of lignocellulosic biomass (cellulose, hemicellulos and lignin) into variety of building block chemicals **(Fig. 1)**. **[1]**

Fig. 1: Routes for conversion of lignocellulosic biomass to platform chemicals via catalytic flow processes.

The *Biorefinery and Sustainable Chemistry Research Group* focuses on developing an integrated catalytic process to upgrade the cellulosic biomass-derived sugars such as fructose and glucose into 5-hydroxymethylfurfural (HMF) through hydrolysis **(Fig. 2)**. Later, the formed HMF is further hydrogenated towards 2,5-dimethylfuran (DMF), *cf.* **Fig. 2**. In this approach, acid catalyst was used to dehydrate the sugars to selectively produce HMF and levulinic acid (LA) with total yield of (80%). Afterwards, HMF was quantitatively hydrogenated over Ni catalyst supported on carbon hydrogenated to DMF. DMF is one of the most promising lignocellulosic biomass derivatives because it can be used directly as fuel or as a starting material for synthesizing different monomers, *e.g.*, *p*-xylene and 2,5-furandicarboxylic acid. **[2–4]**

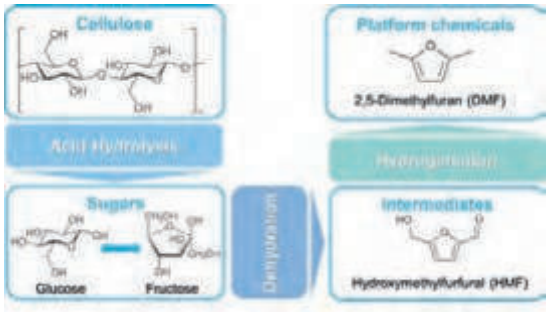


Fig. 2: An integrated catalytic process for valorization of cellulosic biomass into sugars which subsequently upgraded to HMF and DMF through dehydration and hydrogenation step.

At the *Biorefinery and Sustainable Chemistry Research Group* we successfully developed a green and unique approach for selective DMF upgrading (derived from HMF, *cf.* **Fig. 2**) to *p*-xylene in a flow system. This procedure includes Diels-Alder reaction between DMF and acrylic acid over an acid catalyst such as zeolite, at 473 K. With this method the complete conversion of DMF with an 80% yield of *p*-xylene was achieved **(Fig. 3)**.**[5]** Finally, *p*-xyelene can be simply converted to terphtalic acid via catalytic oxidation process to poly(ethylene terephthalate) (PET).

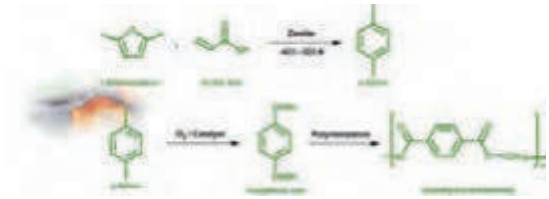


Fig. 3: Eco-friendly approach for synthesis of p-xylene from lignocellulosic biomass which can simply be upgraded to PET.

Besides HMF, levulinic acid (LA) is another very interesting compound which can be produced from sugars dehydration process. **[6]** In the Biorefinery and Sustainable Chemistry Research Group we are following two routes for upgrading LA into platform chemicals and liquid transportation fuels. One of the routes consists of converting LA in the presence of formic acid (FA) as a H_2 source to γ-valerolactone (GVL) and finally to pentanoic acid (PA) via subsequent dehydration and hydrogenation steps **(Fig. 4)**. **[6]** This route was applied in a flow system at 533 K and the complete conversion of LA was achieved. Furthermore, the final valuable mixture was formed as main products, *i.e.*, PA (yield = 75%) and GVL (yield = 25%).

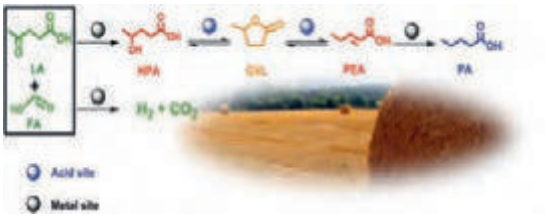


Fig. 4: Production of valeric biofuels through hydrogenation/dehydration step starting from LA to GVL and finally to PA.

The second route is devoted for upgrading LA to GVL (hydrogenation step), followed by α-methylenation reaction of GVL with formaldhyde to produce α-methylene-γ-valerolactove (MeGVL) over basic catalysts. MeGVL is a type of methacrylic monomer with potential applications similar to methyl methacrylate (MMA). This similarity gives MeGVL potential for an eco-friendly large scale production of poly(α-methylene-γ-valerolactone) (PMeGVL), which could substitute a series of fossil based high glass transition thermoplastics. **[7]**

In our group, we established a unique tandem heterogeneously-catalyzed flow process for MeGVL synthesis from cellulosic biomass-derived GVL in the present of trioxane as a formaldehyde source using basic Beta zeolite as catalyst, *cf.* **Fig. 5**.

Additionally, the polymerization of the synthesized MeGVL to PMeGVL was achieved through a green route by using visible-light and graphitic-carbon nitride (g-CN), *cf.* **Fig. 6**.

Fig. 5: The tandem route for MeGVL synthesis from GVL over basic zeolite in the presence of trioxane via α-methylenation reaction.

Fig. 6: Image showing the withdrawn sample after reaction (left), sample after polymerization reaction (middle) using g-CN via visible light induced free radical polymerization at ambient temperature and PMeGVL_S after filtration of g-CN and drying at 333 K (Right).

Lignin is one of the most important candidates for the procurement of renewable aromatics. The development of successful strategies for the production of building blocks from lignin implies the design of effective depolymerisation protocols. In this regard, kraft lignin was valorized towards wide range of monophenolics compounds **(Fig. 7)** over Ni catalyst supported on nitrogen-doped carbon (NDC). **[8, 9]**

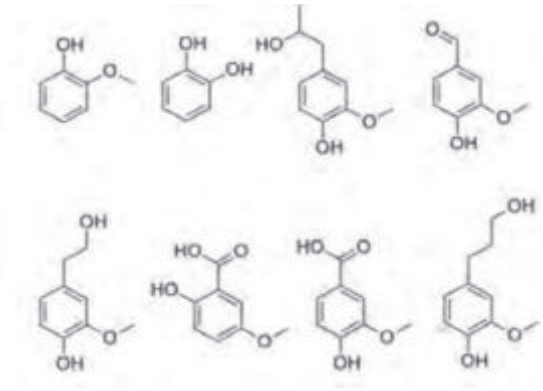


Fig. 7: Different phenolic monomers that can be produced from lignin depolymerization using Ni/NDC catalyst.

Ongoing research in our laboratory focus on the development of novel functional-tolerant catalysts, *e.g.* nanoparticles on highly stable supports (ZrO_2, CeO_2 and carbon nitride), nanozymes and acid/base catalysts and their use in an integrated flow process together with green solvents for lignocellulosic valorization towards value-added bio-based building blocks. Additional interest is on the implantation of nobel carbon-based catalyst in lignin depolymerization to produce lignin-oil and phenolic monomers.

M. AL-Naji, M. Bäumel, F. Brandi, J. Mendoza, I. Shekova
majd.al-naji@mpikg.mpg.de

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IONIC LIQUIDS AS REAGENTS AND POLYMERS

Synthesis and Design

Ryan Guterman
24.05.1988
2005–2010: Bachelor of Science (Honours) in Chemistry (University of Western Ontario, London, Canada)
2010–2015: Doctoral Thesis: Exploring the Chemistry of Phosphorus for Photopolymer Applications (University of Western Ontario, London, Canada)
2015–2017: Postdoctoral Scientist Department of Colloids, Max Planck Institute of Colloids and Interfaces
Since 01/2017: Research Group Leader, Department of Colloids, Max Planck Institute of Colloids and Interfaces

The birth of ionic liquids (ILs) as a distinct field of study arose out of the need for new compounds that exhibit unprecedented chemical or physical properties. This class of compound is defined in general terms as low-melting organic salts with melting points below 100 °C, or as salts displaying very wide and accessible liquid ranges. While at first glance this feature alone is neither evidently useful nor unique in its own right, the development of many modern technologies in the mid-20th century demanded such compounds to fulfill specific tasks. It is here in this context where the paradigm for ionic liquid research was first developed, which based its foundation on their high stability and resistance to bond forming/breaking. We seek to change this paradigm by imagining ionic liquids as chemical reagents or as polymers for material science applications. We shed the "staticness" associated with ionic liquids and instead explore their bond forming properties and how their incredible tailorizability can be used for this task.Through this approach we seek to discover fundamentally new chemistry, uncover latent reactivity, and solve problems in synthesis, biochemistry, and energy materials.

Ionic Liquids as Alkylating Agents

Alkylating agents are among the most widely used reagents in chemistry and are critical for the preparation of pharmaceuticals, natural products, biotechnology, and much more. Unfortunately they are also highly toxic and/or carcinogenic while simultaneously being volatile, thus increasing exposure during handling. Some examples include MeI, MeOTf, methane and methylsulfonate, which all must be handled with great care. An alkylator that is non-volatile, stable under handling conditions, and reactive towards nucleophiles would allow for their use in situations previously unthinkable for conventional alkylators. These include analytical devices, synthesizers, lab-on-chips, and others. Ionic liquids are non-volatile salts and are thus prime candidates for this task. Their tunable chemical structures would also allow for libraries of alkylators to be designed and a convenient approach to conjugate these molecules in to complex systems like biomolecules, polymers, materials, surfaces, and particles in a simple fashion. We (Ryan Guterman, Han Miao, and Vincenzo Alessandro Cataldo, Colloids) show that the 1,3-dialkyl-2-alkylthioimidazolium structure is capable of fulfilling all necessary criteria to achieve these goals **(Fig. 1) [1, 2]**. The key to their utility is the exclusive transfer of the S-alkyl moiety to a variety of different nucleophiles, leaving all other positions (R2-R5) untouched. This high level of specificity allows for derivatization at the nitrogen and alkenyl positions independently of its alkylation abilities, thus acting as a platform for further design. By fine-tuning the electrophilicity of the thioimidazolium cation reactivity can be controlled, with salts derived from caffeine possessing a rate constant ~1000x that of salts derived from imidazole for a given reaction.

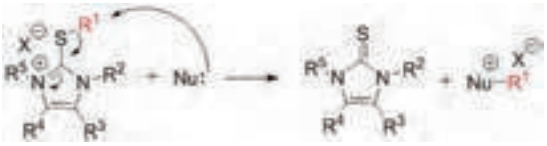

Fig. 1: The thioimidazolium cation as an alkylator.

Surprisingly the anion has a profound effect on the reactivity of these salts, with iodide salts possessing a rate constant 100x greater than salts with the bis(trifluoromethane)sulfonyimide (TFSI) anion. The iodide anion acts as a methyl "shuttle" at increased temperatures and increases the reaction rate. This process does not occur for TFSI because of its low nucleophilicty and demonstrates a unique feature of ionic liquid alkylators.

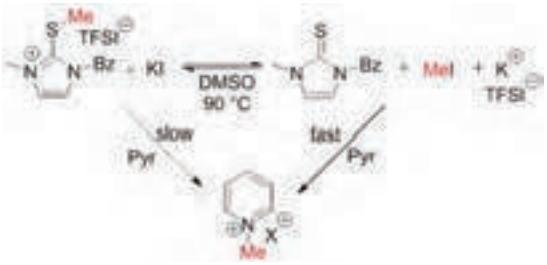

Fig. 2: Iodide-assited alkylation of an alkylating ionic liquid.

Polymeric Ionic Liquids as Binders in Electrochemical Devices

When ionic liquids are polymerized, they retain many of the useful characteristics of ionic liquids (such as conductivity and electrochemical stability) but have much improved processability and mechanical strength. One particularly useful feature of these charged polymers is their ability to coat surfaces, whether they are particles, nanosheets, or fibers composed of either carbon or metal alike. Such favourable interfacial cohesion between poly(ionic liquids) (PILS) and so many different types of materials has led to their recent use as binders in electrochemical devices. We (Ryan Guterman, Colloids, Alen Vizintin, NIC) have examined different linear and crosslinked particle PILs for use in lithium-sulfur batteries as cathode binders **[3]**. In comparison to commonly used polyvinylidenefluoride (PVdF), the charged binders performed as well if not better, with greater cycle capacities, a much higher initial discharge capacity, and a reduced degradation rate. We attribute these benefits to the polymeric ionic liquid's ability to absorb the negatively charged sulfides and prevent expansion-induced degradation by distributing the volume expansion more evenly. This is in stark contrast to PVdF, which prefers to demix with produced sulfides and lead to an uneven volume expansion within the cathode, causing failure. Crosslinked polymeric ionic liquids have the added benefit of not fully covering carbon within the cathode while allowing for better electrolyte flow and thus offers lower resistance.

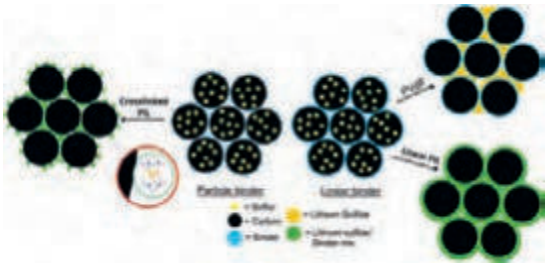

Fig. 3: Comparison of different binders in the cathode of a lithium-sulfur battery.

The binding properties of PILs were also examined for use in water splitting electrodes **[4]**. We (Ryan Guterman, Colloids, Ioannis Spannos, MPICEC) show that PIL can improve the cycling stability of NiCo oxide nanopowder catalyst under accelerated aging conditions. The PIL acts as a local membrane which protects and "glues" catalyst particles together, while being permeable to water and anions by anion-exchange. This is in contrast to some fluorinated binders commonly used for this application, which instead block active sights and do not allow and ion transport.

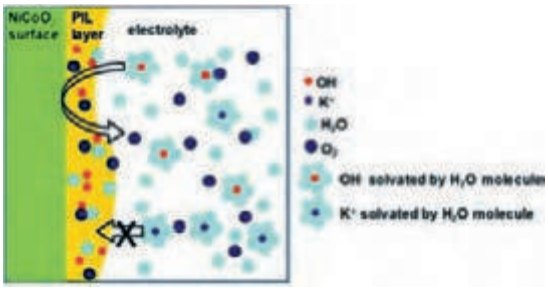

Fig. 4: PIL layer on the surface of a $NiCoO_2$ particle acting as a local membrane for ion transport.

Theophylline-derived PILs and NHC Formation for Silver Ion Stabilization

Natural products come in many shapes and varieties and are often produced on large scale either as part of a food product or resource. Xanthines in particular are among the most widely produced class of alkaloids on Earth, with caffeine from coffee and theophylline from chocolate topping the list. The use of these compounds as reagents for preparing useful materials would help to reduce reliance on petroleum and move towards a more sustainable approach to materials fabrication. We (Ryan Guterman and Han Miao, Colloids) have modified the theophylline molecule to undergo polymerization to fabricate the first alkaloid-derived PIL **[5]**. The useful chemical properties of the theophylline molecule is retained in the polymer and can be used to sequester silver ions to form crosslinked nanogels **[6]**. Silver oxide acts as a base and metalation reagent to crosslink polymer chains *via* a carbene. Depending on the reaction conditions, nanogels of different sizes were isolated, while at high concentrations silver nanoparticles were produced. In this way, the carbene-forming abilities of the polymer can be harnessed to create nanogels of different sizes.

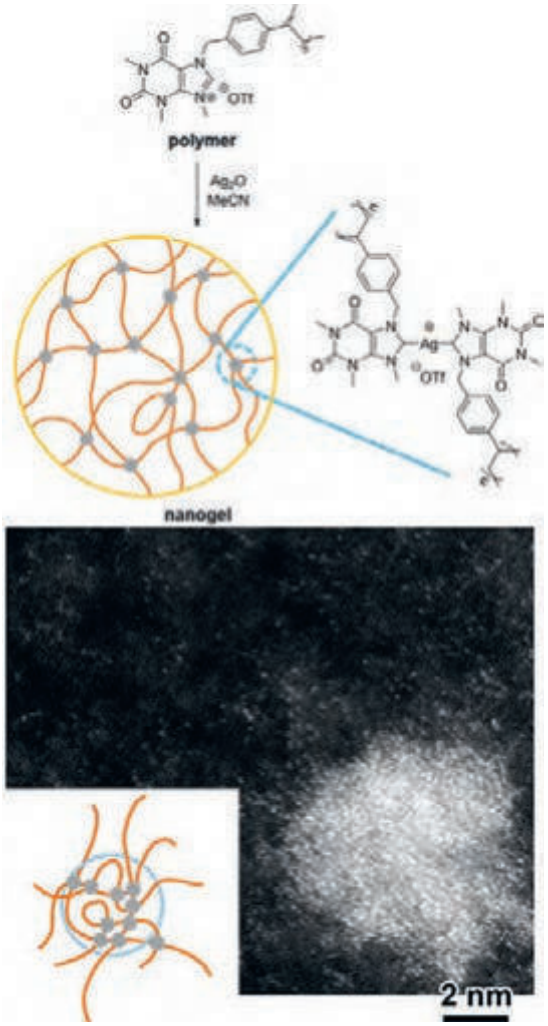

Fig. 5: (Top) Synthesis of nanogel from theophylline-derived PIL using Ag_2O. (Bottom) High-resolution STEM images a nanogel containing silver ion evenly distributed throughout the structure.

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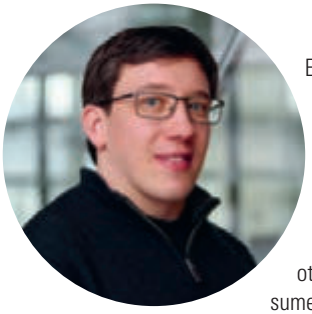
Benign Battery Materials based on Biopolymers and Ionic Liquids



Clemens Liedel
21.04.1984
2003–2008: Diploma, Chemistry (with honours, University of Bayreuth, Bayreuth, Germany)
2006–2010: Elite Study Program Macromolecular Science (University of Bayreuth, Bayreuth, Germany)
2008–2013: Doctoral Thesis, Chemistry: Towards Aligned Nanowires from Block Copolymer Templates (summa cum laude, RWTH Aachen University, Aachen, Germany)
2013–2015: Postdoctoral Research, Department of Materials Science and Engineering (Cornell University, Ithaca, NY, USA)
Since 07/2015: Research Group Leader, Department of Colloid Chemistry (Max Planck Institute of Colloids and Interfaces)

Energy storage has become one of the big challenges of modern society. On the one hand, in order to store energy which is gained in times of excess production, increasing development of renewable energy in the form of wind power or photovoltaic devices demands for powerful energy storage facilities. On the other hand, the global demand for mobile consumer electronics and electric vehicles implies the production of millions of batteries every day.

Batteries for high energy applications are nowadays usually based on the lithium ion technology. While promising higher capacity than conventional batteries, this technology however relies on dangerous and unsustainable resources like lithium and cobalt, respectively. Lithium, being highly reactive, may cause problems in case of accidents, as lithium fires cannot be extinguished by conventional means. The high performance electrolytes used in today's lithium ion batteries are furthermore thermally unstable and release highly toxic gases like hydrofluoric acid upon incineration. Cobalt, the major component of most lithium ion battery cathodes (approx. 10 g per smartphone), is rather unsustainable as half of the worldwide cobalt supplies are located in the Democratic Republic of Congo, often obtained by artisanal mining using child labour. Both constituents should be replaced by more benign alternatives in next generation high performance batteries.

Innovative possibilities to do so are investigated in this group. On the one hand, new electrolytes with enhanced stability and safety are being studied, with the emphasis on benign and sustainable synthesis methods and applications in post-lithium ion battery technologies. On the other hand, the group focusses on organic cathode materials which may be synthesized from bioresources and thus from renewable raw materials.

Ionic Liquid Electrolytes for Magnesium Batteries

Magnesium batteries are appealing candidates for next generation energy storage as they combine a high theoretic charge density with abundant worldwide raw material supplies and increased safety due to the excellent stability of magnesium metal. The stability is caused by the rapid formation of a thin protection layer once magnesium gets into contact with any substance that can easily be reduced, such as water vapour in the air. This protection mechanism however also prevents the use of many conventional electrolytes in magnesium batteries as even traces of electrochemically instable species react with and passivate the magnesium surface, resulting in battery failure.

In this regard, ionic liquids may be used as solvent species in magnesium batteries, as this class of designer liquids may be tuned regarding electrochemical and thermal stability, ionic conductivity, and viscosity. Some ionic liquids, especially those based on imidazolium cations, may furthermore be synthesized in benign reactions using green and sustainable starting materials, which improves the sustainability of magnesium batteries **[1]**.

In order to combine all advantages, a conventional ionic liquid can be transformed into a liquid with betaine character (stable positive and negative charge combined in one molecule, in the following denoted as zwitterionic liquid, ZIL). The resulting zwitterionic liquid exhibits reasonable thermal and electrochemical stability and surprisingly low viscosity **[2]**. Its comparably low molecular weight enables high mobility and consequently promises favourable applicability in electrolytes. In fact, an electrolyte consisting of magnesium borohydride dissolved in the ZIL is electrochemically stable and does not passivate magnesium metal electrodes. Magnesium can be reversibly electrodeposited and dissolved using this electrolyte and stainless steel or magnesium electrodes, which demonstrates the general eligibility of the electrolyte for magnesium batteries **[3]**. The ZIL together with its properties and electrochemical performance is highlighted in **Fig. 1**.

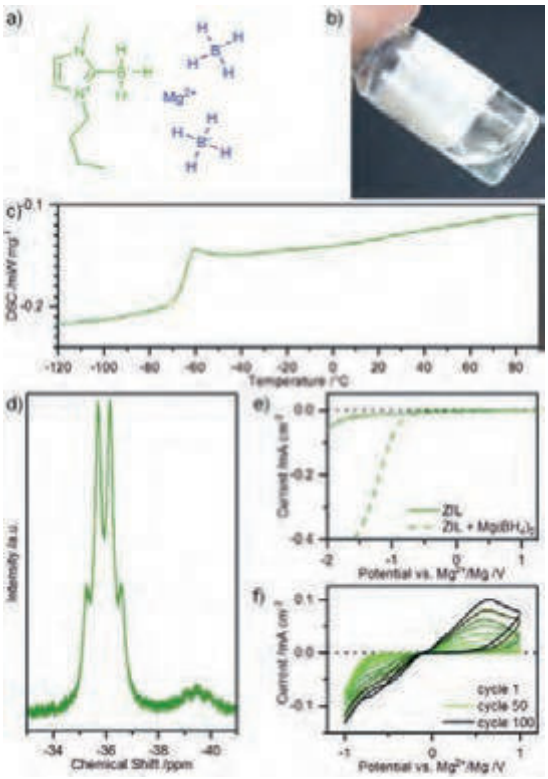


*Fig. 1: (a) Schematic structure of the electrolyte consisting of a zwitterionic liquid (green) and $Mg(BH_4)_2$ (blue). (b) Photo and (c) DSC curve of the ZIL. (d) ^{11}B NMR of the electrolyte measured in bulk at 60 °C, clearly showing signals of the borohydride group in the ZIL and the BH_4^- anion. (e) Linear sweep voltammograms of the ZIL and the electrolyte vs. a Mg reference electrode; the ZIL is stable, and Mg is electrodeposited significantly before electrochemical degradation occurs. (f) Cyclic voltammogram of the electrolyte system with increasing cycling from bright to dark showing reversible electrodeposition of magnesium **[2, 3]**.*

Biobased Hybrid Electrode Materials

Reversible redox reactions are omnipresent in biomaterials and crucial for essential processes in plants as well as animals. As these processes always proceed in the presence of water, the redox potential of such reactions is within the stability range of water and thus in the range of cathode materials for lithium

based batteries. Our group investigates this potential application by using naturally occurring molecules and such molecules that may easily be produced from natural resources as cathodes for future batteries. Challenges like solubility in electrolytes, bad charge transport to current collectors, and inhibited ion transport to the electrolyte are addressed. Using redox active polymers in combination with conductive additives often helps to resolve these challenges.

One prominent potentially redox active biopolymer is lignin: after electrochemical demethylation of methoxy functionalities, it can reversibly be oxidized and reduced. To facilitate charge transport and simultaneously increase charge storage, combinations with high surface area conductive carbon materials are advantageous **[4]**. Dissolution in the electrolyte is usually prevented by the incorporation of fluorinated binders. The use of such binders inherently decreases sustainability of the bioorganic hybrid electrodes because of the negative environmental impact of production and upon incineration (for example when treating battery waste after their end of use) of the electrodes.

In lignin based electrodes, binders may be omitted when lignin is cross-linked instead, leading to insoluble large aggregates. Such crosslinking may be performed by glyoxal during mild heat treatment **[5]**. Importantly, hybrid electrodes from lignin and high surface active carbon need to be composed before crosslinking in order to prevent formation of large insoluble crosslinked lignin particles with limited charge transfer properties to the conductive additive **(Fig. 2)**.

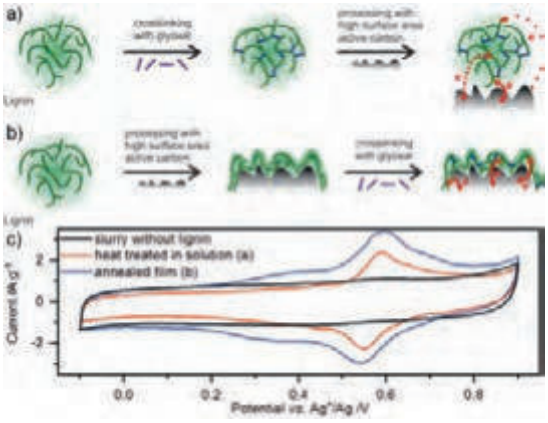


*Fig. 2: (a, b) Schematic illustration of the interaction between lignin (green) and carbon (black). If lignin is crosslinked by glyoxal (blue) before combining it with carbon, charge transport is hindered (a), while crosslinking after formation of the hybrid material facilitates charge transport (b). Cyclic voltammetry curves in (c) show that indeed charge storage is higher if crosslinking is performed by annealing the electrodes (b) compared to a situation in which crosslinked lignin particles together with carbon form the electrodes (a). A rectangular background shows the contribution of carbon (black) to charge storage **[5]**.*

Using such rather sustainable lignin based electrodes, approximately 80 mAh g^{-1} can be stored (at 0.2 A g^{-1} discharging rate). Biomolecules with a higher density of redox active groups than lignin can surpass this capacity significantly due to the relatively lower average molecular weight of redox active functionalities. In this regard, our group investigated electrode materials in which dopamine was copolymerized with pyrrole to include conductive properties, redox functionalities, and dopants into one polymer. After drying, rodlike insoluble colloidal polymer particles are obtained, caused by synergistic interactions between dopamine and pyrrole. Electrodes with these particles as active component can store up to 160 mAh g^{-1} in lithium half-cell experiments (at 0.1 A g^{-1} discharging rate) **[6]**. Despite at a slightly lower potential, this charge is comparable to state-of-the-art lithium ion battery cells. **Fig. 3** summarizes the results.

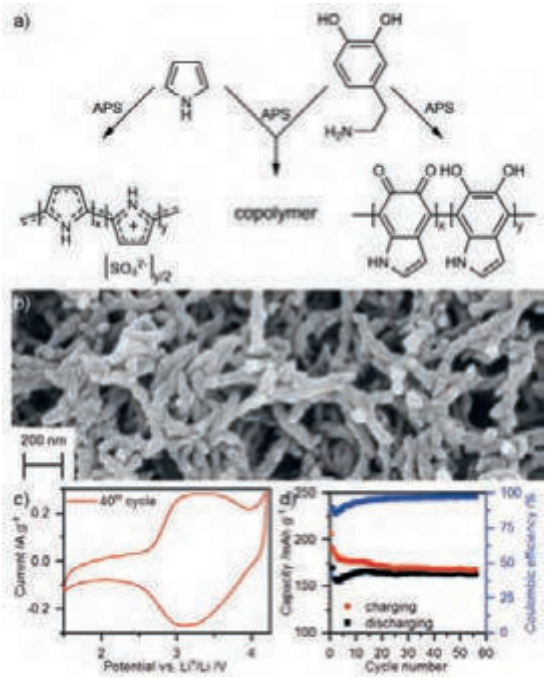


*Fig. 3: (a) Copolymerization of dopamine and pyrrole in the presence of ammonium persulfate leads to conjugated polymers with quinone and hydroquinone functionalities. (b) SEM image of the resulting structures. (c) The 40th cycle in cyclic voltammetry measurements of a copolymer electrode shows pronounced redox reactions in the range of 3 – 3.5 V vs. Li^+/Li. (d) Capacity and coulombic efficiency as calculated from galvanostatic charging/discharging experiments **[6]**.*

C. Liedel, J. Brandt, J. Hwang, I. Ilić
Clemens.Liedel@mpikg.mpg.de

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Functional Nanoporous Carbon-Based Materials in Energy and Environmental Applications

Martin Oschatz
28.05.1987
2006–2009: Bachelor of Science (Chemistry)
(Technische Universität Dresden, Germany)
2009–2011: Master of Science (Chemistry)
(Technische Universität Dresden, Germany)
2011–2015: Doctoral Thesis (summa cum laude): "New Routes Towards Nanoporous Carbon Materials for Electrochemical Energy Storage and Gas Adsorption"
(Technische Universität Dresden, Germany)
2013: Research Internship (supported by the DAAD)
"Carbon Materials for Electrochemcial Energy Storage in Supercapacitors"
(Georgia Institute of Technology, Atlanta, USA)
2015–2016: Postdoc (supported by the DAAD) "Tailoring and Modification of Nanostructured Catalyst Supports for Sustainable Production of Lower Olefins from Synthesis Gas"
(University of Utrecht, Utrecht, The Nethermalnds)
Since 11/2016: Research Group Leader (supported by a Liebig Fellowship of the German Chemical Industry Fund)
Colloid Chemistry Department,
Max Planck Institute of Colloids and Interfaces

The chemical element carbon can cover a very broad range of physicochemical properties. They are depending on the nature of the chemical bonds between the individual atoms. Diamond consists of sp^3 hybridized carbon atoms and is an optically transparent electrical insulator. It is the hardest material we know. In contrast, graphite which is built up by sp^2 hybridized carbon atoms is a soft material with black appearance and is a very good electron conductor. In many applications, control over the structure of carbon materials on the nanoscale is very important to make use of these attractive properties. In particular, sp^2-based carbon materials with internal pores with sizes in the nm-range provide specific surface areas as high as 2000 m^2/g and in some cases even higher. One result is that such carbons combine electric conductivity with a very high contact area to the mater surrounding it. This feature is highly required in many energy- and environmental applications in which such interface effects play a major role **[1]**. The research of this group is focused on the synthesis of carbon materials with defined porosity and atomic construction and their application as model compounds to investigate structure-performance relationships in applications which are relevant for energy and environment. The following fields are of particular interest. 1) The group investigates fundamental effects on the electrode-electrolyte interface in electrochemical energy storage devices (supercapacitors with ionic liquid electrolytes, sodium-ion battery anodes, and lithium-sulphur batteries). It is the major objective to explore new energy storage mechanisms to enable increase of the future energy density of these devices. Parts of this research are carried out in cooperation with the research groups of Prof. Volker Presser (Leibniz Institute for New Materials, Saarbrücken), Prof. Patrice Simon (Université Paul Sabatier, Toulouse), Dr. Jan Philipp Hofmann (Eindhoven University of Technology), Prof. Joachim Maier (Max Planck Institute for Solid State Research, Stuttgart), Markus Niederberger (ETH Zürich), and Prof. Matthias Ballauff (Helmholtz-Zentrum Berlin). 2) Another field of research is the interaction of carbon-based materials with gas molecules such as carbon dioxide, water vapor, and ammonia. A detailed understanding of the adsorption mechanism is not only important for the catalytic conversion of these substances but also for their selective removal from gas mixtures. In this field collaborations exist with the groups of Prof. Stefan Kaskel (Technical University Dresden), Prof. Arne Thomas (Technical University Berlin), Prof. Thomas Kühne (Paderborn University), Dr. Bernhard Schmidt, Dr. Nadja Tarakina, and Dr. Oleksandr Savatieiev (all Max Planck Institute of Colloids and Interfaces). 3) The nanoporous carbon-based materials (often doped with a substantial amount of heteroatoms) are used as metal-free catalysts and as catalyst support in oxidation and hydrogenation reactions. Electrocatalytic hydrogenation of carbon dioxide and nitrogen as well as chemocatalytic hydrogenation of carbon monoxide are investigated. This research is carried out in cooperation with the groups of Prof. Krijn P. de Jong (University of Utrecht), Dr. Haijun Jiao (Leibniz Institute for Catalysis, Rostock), and Dr. Daniel Varon Silva (Max Planck Institute of Colloids and Interfaces).

Electrochemical Energy Storage in Supercapacitors and Batteries

Electrode-electrolyte interfaces are of crucial importance for electrochemical energy storage devices. In contrast to batteries, the charge separation in so-called supercapacitors is based on the electrosorption of electrolyte ions on the surface of porous carbon electrodes. This leads to high power density (up to 10 kW/kg) and practically endless cycle-life of such devices but their energy density is significantly lower than in batteries (usually less than 10 Wh/kg). In order to realize supercapacitors with high energy density, the research of the group is focussed on the use of solvent-free ionic liquid (IL) electrolytes. ILs are room-temperature molten salts which can enable high energy supercapacitors due to their high electrochemical stability window. More importantly, by using salt-templated model carbon materials **(Fig. 1)** with tuneable porosity with and without nitrogen doping, our group has recently unraveled the contribution of ordering transitions in the ILs to the energy storage in such devices **[2, 3]**. Based on these findings, targeted improvement of the energy density can be achieved in the future by controlling the porosity (by templating) and by fine-tuning the electronic structure of the electrode materials (by heteroatom-doping and/or deposition of metal or metal oxide nanoparticles) **[4, 5]**.

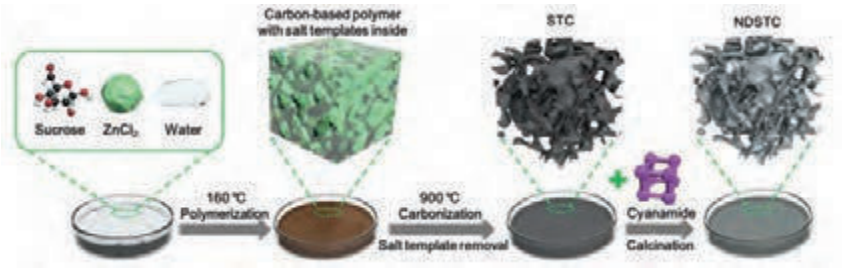

*Fig. 1: Synthesis of salt-templated carbon (STC) and nitrogen-doped salt-templated carbon (NDSTC) **[2]**.*

In the field of battery technology, sodium-ion batteries and lithium-sulphur batteries are interesting alternatives to established lithium-ion batteries due to the abundancy and sustainability of the elements involved in the electrochemical processes. The group uses composite materials combining the high electrical conductivity and specific surface area of nanoporous carbons and the high polarity (providing specific binding sites for sodium and lithium polysulphides) of heteroatom-doped carbons. For instance, electrode materials with high electric conductivity are produced with electrospinning. With these approaches, it is the final aim to decouple electron transport/

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storage from ion transport storage and by that establishing new principles in electrochemical energy storage. In the ideal case, such mechanisms would be based on all-carbon-based (composite) materials without the use of metals in both battery electrodes.

Fundamentals of Gas Adsorption on Nitrogen-Doped Carbon Materials

In addition to pores with sizes close to the dimensions of gas molecules, the introduction of specific binding sites in solid materials is a method to increase the interaction (i.e., the adsorption enthalpy) with the pore walls. For example, doping porous carbon materials with heteroatoms such as nitrogen is a widely established method to increase their affinity towards polar gases such as carbon dioxide, ammonia, or water vapour **[6]**. However, the chemical binding motives of such heteroatoms are usually not well-defined. The benefits for adsorption remain low and detailed structure-performance relationships are difficult to conclude.

The group uses controlled condensation of molecular precursors such as hexaazatriphenylene-hexacarbonitrile (HAT-CN) for the synthesis of nitrogen-doped carbon materials with C_2N composition **(Fig. 2)**. Nitrogen content and porosity can be controlled by the condensation temperature between 525 and 1000 °C. On the one side, the resulting materials show an atomic construction that is well-defined and dictated by the molecular precursor. On the other side, such C_2N materials stand out by high oxidation resistance and can thus be called "noble carbons" **[7, 8]**. As a result of the microporous structure and extremely polar character, their adsorption properties are not typical for carbon materials and rather characteristic for polar substances such as zeolites. In consequence, HAT-CN-derived carbon materials enable very selective carbon dioxide molecular sieving out of nitrogen which is very important for the removal of the greenhouse gas component from flue gas or its direct capture from air. In view of the absence of any metallic compound in these materials, this behaviour is remarkable.

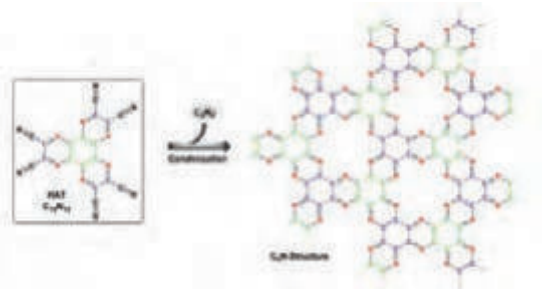

*Fig. 2: Synthesis of nitrogen-doped carbon materials with defined C_2N-type architecture by condensation of a preorganized hexaazatriphenylene-hexacarbonitrile precursor **[7]**.*

Application of Carbon Materials in Catalysis

Carbon materials are widely used as supports for metallic nanoparticles in heterogeneous catalysis. The group investigates the effect of carbon pore structure and heteroatom-doping on the properties of the resulting catalysts in gas phase hydrogenation of carbon monoxide (typically with carbon-supported iron catalysts) and oxidation of glucose with molecular oxygen in aqueous solution (typically with carbon-supported gold catalysts) **[9, 10]**. The pore structures and atomic constructions of the carbon supports have a strong influence on the size and oxidation state of the deposited metal or metal oxide nanoparticles and by that also on the properties of the resulting catalysts.

In addition to these rather traditional chemocatalytic fields, research on the electrocatalytic reduction of carbon dioxide and nitrogen is of particular interest. Traditional approaches for the conversion of these molecules require high temperatures and pressures. The application of an electric potential is a promising alternative for their catalytic conversion under mild conditions. On the one side, templated porous noble carbons are applied in order to stabilize single-site catalysts such as gold atoms or clusters **(Fig. 3)**. This can lead to novel schemes for activation of these molecules comparable to a frustrated Lewis-pair mechanism **[11]**. Furthermore, anion substitution in transition metal oxides was recently explored as another promising approach to create catalytically active sites for electrochemical conversion of nitrogen. On the other side, IL electrolytes are applied in these reactions as their ability to dissolve nitrogen and carbon dioxide is significantly higher than that of water. This can increase the efficiency of the catalysts.

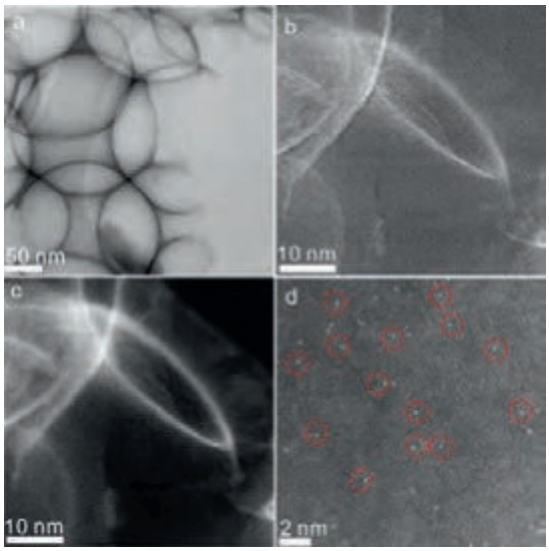

*Fig. 3: Transmission- and scanning transmission electron microscopy images of single-site gold catalysts supported on a nitrogen-doped carbon material with hierarchical pore architecture **[11]**.*

M. Oschatz, R. Yan, R. Walczak, I. Harmanli, F. Lai, Q. Qin, M. Perovic, K. Schutjajew, I. Below-Lutz, S. Lama
martin.oschatz@mpikg.mpg.de

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Potassium Poly(Heptazine imide) and Sustainable Organic Synthesis

Aleksandr Savateev
14.05.1989
2006–2010: Bachelor of Science majoring in Organic Chemistry and Technology of Organic Compounds (National Technical University of Ukraine "Kyiv Polytechnic Institute", Kyiv, Ukraine)
2010–2012: Master of Science majoring in Organic Chemistry and Technology of Organic Compounds (National Technical University of Ukraine "Kyiv Polytechnic Institute", Kyiv, Ukraine)
2012–2016: Doctoral Thesis: P,P- and P,N-bidentate phosphine ligands for metalocomplex catalysis (Institute of Organic Chemistry, Department of Chemistry of Organo-phosphorus compounds. Kyiv, Ukraine)
2015–2016: Postdoctoral Scientist at Colloid Chemistry Department, Max Planck Institute of Colloids and Interfaces
Since 01/2017: Research Group Leader, Colloid Chemistry Department, Max Planck Institute of Colloids and Interfaces

The problems related to the intensification of the industrial production, due to growing demand in energy and goods jeopardize the world that has been existing for millions of years. Our civilization relies on chemicals – organic and inorganic compounds that are used as pharmaceuticals, building blocks in material science, fuels, etc. We do not want to stop the progress that makes the modern life possible by shutting down every chemical plant. We want to decrease the impact on the environment by implementing energy and material efficient technologies that reckon with the principles of green chemistry.

Heterogenous photocatalysis has emerged as a rescue boat for our civilization, while *Innovative Heterogeneous Photocatalysis group* develops materials and applies these materials to produce fine chemicals and fuels in a sustainable way.

Combining the state-of-the-art knowledge in materials design, we have developed a carbon nitride based photocatalyst producing hydrogen from water, the greenest among all possible fuels, in unprecedented efficacy of light-to-hydrogen conversion 60%. **[1]**

The main advantage of the heterogeneous photocatalysis related to the production of fine organic compounds is that chemical reactions can be enabled without expensive and hazardous auxiliary reagents. **[2]**, **[3]** The primary material that we use in organic photocatalysis is potassium poly(heptazine imide) (K-PHI) **(Fig. 1)**.

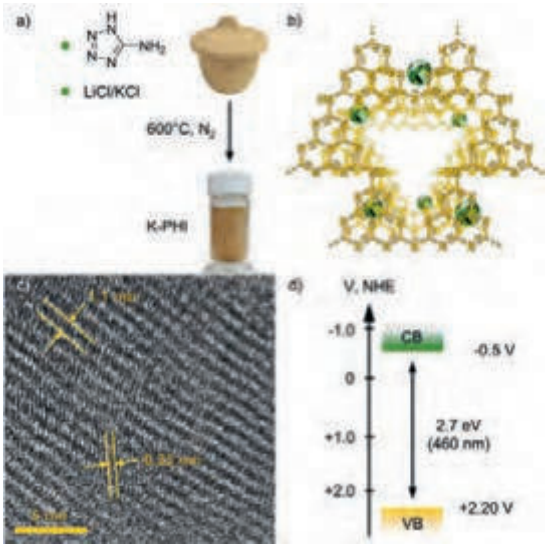

Fig.1: Synthesis (a), chemical structure (b), TEM image (c) and band structure of K-PHI (d).

This material is routinely prepared on a gram scale from 5-aminotetrazole in a highly polar solvent – eutectic LiCl/KCl mixture. **[4]** K-PHI is crystalline, thermally stable up to 400 °C, resistant to strong bases and oxidants.

The distinct feature of K-PHI is to form a long-lived tinted radical anion (K-PHI$^{\bullet-}$). K-PHI$^{\bullet-}$ is readily available photochemically using such electron donors as alcohols and amines under light irradiation or chemically using reductants such as metal hydrides, *n*-butyllithium, etc. The capacity of K-PHI reaches 1000 μmol electrons per gram of the material or 96 C g^{-1}. This value was determined by quenching K-PHI$^{\bullet-}$ with methylviologen (Fig.2). Given high stability of K-PHI$^{\bullet-}$, this charged radical is a key intermediate in all photocatalytic reactions presented below.

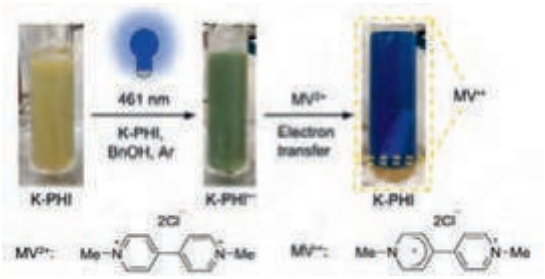

Fig. 2: Generation of K-PHI and quenching of K-PHI$^{\bullet-}$ with methylviologen.

K-PHI has optical band gap of 2.7 eV that corresponds to the photon energy 460 nm. The band structure of K-PHI and especially very positive potential of the valence band, +2.2 V vs. NHE, **(Fig. 1)**, makes the material suitable for activation of organic compounds that in general have quite high oxidation potential above +2.0 V vs. NHE by generating the respective radical cations. The radical cations are then trapped by the reagent of interest.

Combining K-PHI and blue photons, *Innovative Heterogeneous Photocatalysis group* has developed a series of photocatalytic processes using elemental sulphur as a reagent in organic synthesis. These reactions are divided into two groups – (1) those where elemental sulphur is used as a selective and mild terminal oxidant and is not incorporated into the product and (2) sulphur is upgraded to the organosulfur compounds.

The first set of organic reactions is represented by the selective oxidation of benzylalcohol to benzaldehyde **(Fig. 3)**. Aldehydes have commercial value. Selective oxidation of alcohols to aldehydes in organic synthesis usually is done by pyridinium-chlorochromate, which however is required in stoichiometric amount and after the reaction is converted to chromium waste.

Oxidation of benzylalcohol to benzaldehyde can be accomplished using O_2. In this case, selectivity of aldehyde formation is still low due to formation of carboxylic acids – the products of aldehydes overoxidation. Using K-PHI and elemental sulphur, we achieved close to 100% selectivity toward benzaldehyde along with conversion 91% **(Fig. 3)**. **[5]**

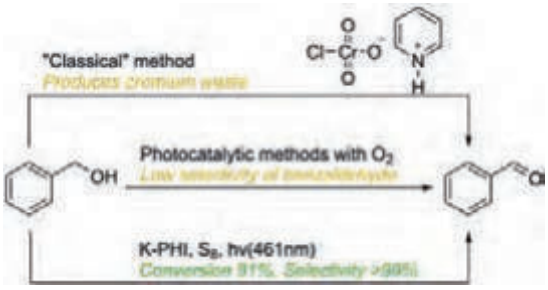

Fig. 3: Classical chemical and photocatalytic (using O_2 and S_8) methods of benzylalcohol oxidation to benzaldehyde.

Furthermore, we have shown that aldehydes, generated *in situ* from the corresponding alcohols, are readily coupled with acetoacetate and ammonia **(Fig. 4)**. **[5]**.

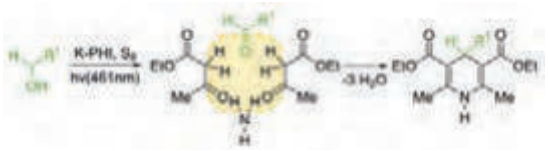

Fig. 4: Photo-Hantzsch pyridine synthesis.

Combining K-PHI and S_8 a series of hydrazones was converted into the corresponding 1,3,4-oxadiazoles **(Fig. 5)**. **[6]**.

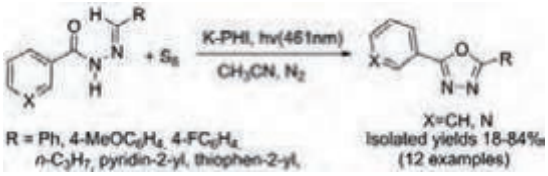

Fig. 5: Photocatalytic synthesis of 1,3,4-oxadiazoles.

Important to note, under similar conditions O_2 gave 1,3,4-oxadiazoles with low yields. This experiment substantiates higher selectivity of the reaction mediated by S_8 compared to O_2.

Two examples illustrate photocatalytic upgrade of elemental sulphur to value-added organic compounds – thioamides and substituted dibenzyldisulfanes.

In the former example thioamides were synthesized using oxidative coupling of two benzylamine molecules in the presence of S_8 **(Fig. 6)**. **[7]** Compared to the classical conditions, known as Kindler reaction, 130–150 °C, the photocatalytic approach requires only 70 °C and therefore makes the whole process more energy efficient.

C-H functionalization of hydrocarbons has a tremendous significance for industry, because it affords value-added chemicals from cheap and abundant reagents. Because of high thermodynamic stability of hydrocarbons, their C-H functionalization requires high temperature, reactive reagents or transition metals catalysts.

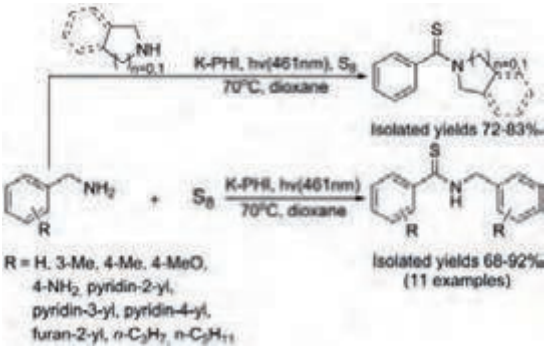

Fig. 6: Photo-Kindler reaction.

Due to highly positive valence band potential of K-PHI, +2.2 V vs. NHE, toluene can be oxidized to the radical cation and then trapped with appropriate reagent. If reaction is performed in the presence of convenient electron acceptors – oxygen or elemental sulphur, benzaldehyde or dibenzyldisulfide are produced respectively. Thus, a series of ring-substituted toluenes, *i.e.* methylarenes, was converted into the respective dibenzyldisulfanes with good to moderate isolated yields **(Fig. 7)**. **[8]**

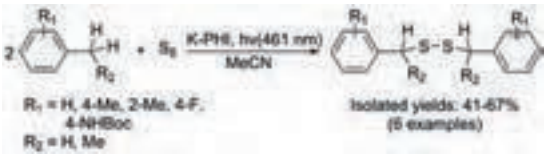

Fig. 7: Oxidaive thiolation of methylarenes.

The examples presented here afford important for chemical industry compounds, aldehydes, oxadiazoles, pyridines, thioamides and dibenzyldisulfanes, from simple molecules and a byproduct of oil refinery – elemental sulphur under mild conditions – visible light irradiation and room or slightly elevated temperature. Ongoing research suggests that potassium poly(heptazine imide) and related carbon nitride materials are powerful heterogenous photocatalysts. By tuning the reaction conditions and selecting appropriate electron mediator, practically any desired chemical reaction can be implemented.

A. Savateev, B. Kurpil, L. Li, Y. Markushyna, K. Otte, G. Zhang, Y. Zhao
oleksandr.savatieiev@mpikg.mpg.de

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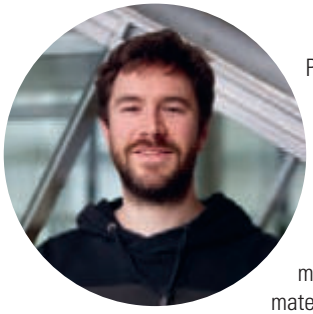
Novel Self-Assembly Polymers



Bernhard V.K.J. Schmidt
22.01.1984
2004-2009: Studies of Chemistry (Technical University Darmstadt, Germany) majoring in Macromolecular Chemistry
2009–2010: Internship (Supervisor: Dr. Lutz, Fraunhofer Institute for Applied Polymer Research Potsdam, Germany)
2010–2013: Doctoral Thesis: Novel Macromolecular Architectures via a Combination of Cyclodextrin Host/Guest Complexation and RAFT Polymerization (Supervisor: Prof. Barner-Kowollik, Karlsruhe Institute of Technology, Germany)
2013–2014: Postdoctoral Scientist as DAAD fellow (Supervisor: Prof. Hawker, Materials Research Laboratory, University of California, Santa Barbara, USA)
Since 01/2015: Research Group Leader, Department of Colloid Chemistry, Max Planck Institute of Colloids and Interfaces

Polymers give access to various colloidal structures as well as advanced materials. For example block copolymers can be utilized to form various nano- and micro structures in dispersion. Water-based crosslinked polymer networks, i.e. hydrogels, give access to various useful properties as soft and elastic materials. While polymers lead to remarkable materials properties and self-assemblies, precise polymer synthesis is the key to obtain defined polymers materials. In such a way, structure-property relationships can be studied and evaluated. Finally, an improvement of materials properties can be achieved as well as novel properties designed. In our work, we focus on water-based polymer systems as well as a combination of polymers and metal-organic frameworks (MOFs). Hence, self-assembly of double hydrophilic block copolymers (DHBCs) in aqueous solution is investigated with the aim to obtain permeable colloidal structures. Moreover, we study water-in-water emulsions as an avenue to novel capsule and compartmentalized polymer materials. In addition, novel hydrogels based on graphitic carbon nitride (g-CN) with remarkable mechanical properties are fabricated. Finally, we investigate ways to modulate the structures of MOFs via various strategies as well as catalysts for polymerization and organic reactions.

Double Hydrophilic Block Copolymer Self-Assembly

Self-assembly of amphiphilic block copolymers in water is a well-known strategy to obtain complex colloidal structures. In contrast, self-assembly of DHBCs in aqueous media is not based on interactions of hydrophobic blocks **[1]**. In the case of water-soluble homopolymers, aqueous biphasic systems can be generated from water-soluble homopolymers, where each homopolymer type is present in one of the aqueous phases. Such a phase separation is possible, when the concentration of the polymers is high enough and significant differences in the hydrophilicity of the homopolymers are present. In the case of a covalent connection of both homopolymers, i.e. a block copolymer, demixing on the microscopic scale is enabled.

Self-assembly of linear DHBCs leads to various structures in solution, e.g. particles **[2, 3]** or vesicles **[4]**. In order to study the effect of architecture on self-assembly, we attempted to utilize DHBCs with linear-brush architecture. Hence, a poly(saccharide), namely Pullulan (PuII), was coupled to poly(oligo ethylene glycol methacrylate) (POEGMA) to form a linear-brush block copolymer **(Fig. 1) [5]**. In the next step self-assembly was studied via dynamic light scattering (DLS) and cryo scanning electron microscopy (cryo-SEM). Interestingly, a significant difference in intensity weighted particle size distributions were observed depending on POEGMA chain length. For lower POEGMA chain lengths an improved particle formation was observed, which can be correlated with the change in polymer architecture. In a subsequent step, the formed particle structures were crosslinked via phosphate bridges to improve stability against dilution.

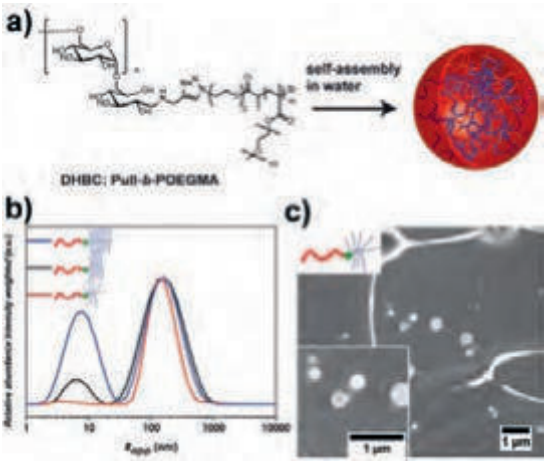


*Fig. 1: Self-assembly of PuII-b-POEGMA in water: a) Schematic overview, b) DLS at 25 °C with varying POEGMA chain length (13, 23 and 33 kg mol^{-1}) at a concentration of 1 wt.% and c) cryo-SEM of PuII$_{22k}$-b-POEGMA$_{13k}$ at 1 wt.% **[5]**.*

Water-in-water Emulsions

As already mentioned water-soluble homopolymers can form biphasic systems in water at high concentrations, which have found significant attention recently. Accordingly, it is possible to form emulsions in a completely aqueous system, yet only particles can be utilized as stabilizers due to the rather broad interface between the polymer containing aqueous phases.

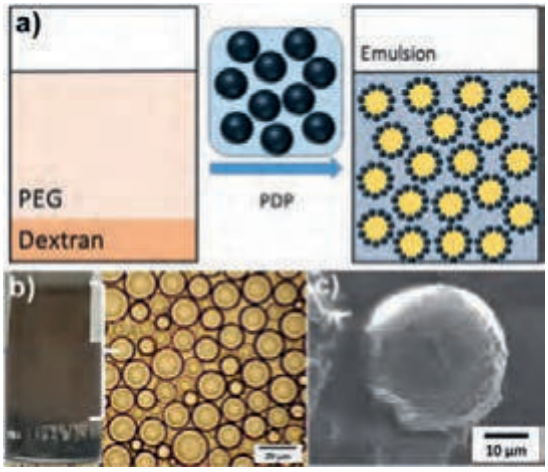


*Fig. 2: a) Schematic overview of PDP-based water-in-water emulsion formation, b) optical microscopy of dextran (3 wt.% in water) in PEO (7 wt.% in water) emulsion and c) corresponding cryo-SEM image **[6]**.*

To facilitate future applications in the biomedical field water-in-water emulsions were formed from biocompatible poly(ethylene oxide) (PEO), dextran and poly(dopamine) particles (PDP) **(Fig. 2) [6]**. The formed emulsions could be observed via optical microscopy and cryo-SEM as well as confocal laser scanning microscopy. In addition, the emulsions showed good stability over various weeks and could be demulsified via dilution or surfactant addition.

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To improve the stability against dilution, the Pickering stabilizers were crosslinked via addition of poly(acrylic acid) and amide formation. As the outer surface of the droplets was crosslinked to form colloidosomes, the emulsions could not be demulsified via dilution or surfactant addition anymore.

Carbon Nitride-based Hydrogels

The material g-CN is well-known for its photocatalytic activity under visible light that can be exploited in water splitting, CO_2 reduction or organic synthesis. Notably, it can be also utilized as radical initiator in polymer chemistry.

To form hydrogels, a dispersion of g-CN in water is mixed with monomer and crosslinker and irradiated with visible light **(Fig. 3)**. In such a way, hydrogels with remarkable mechanical properties are obtained as g-CN acts as reinforcer and crosslinker in addition to its initiation activity. For example, high storage moduli can be obtained as well as significant compressibility via various routes **[7, 8]**. For example a co-solvent was utilized to increase the amount of dispersed g-CN in order to improve mechanical properties.

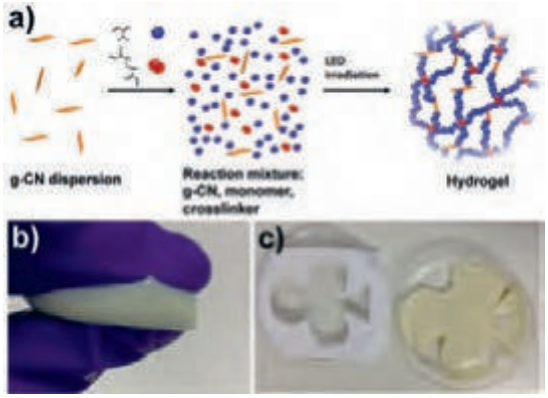

Fig. 3: a) Schematic overview of hydrogel formation, b) compressible g-CN hydrogel (>90 wt.% water) and c) patterned g-CN hydrogel via photomask **[8, 10]**.

Due to the light-mediated polymerization, patterned hydrogels can be obtained via photomasks **[8]**. Variation of g-CN surface chemistry via a photochemical addition reaction of functional molecules facilitated enhanced dispersibility in water and organic solvents as well **[9]**. Moreover, sulfonic acid functionalized g-CN enabled the formation of hydrogels with extreme compressibility amongst other properties like cut resistance and shock absorption **(Fig. 3) [10]**.

Metal-Organic Framework (Meso)crystal Design

MOFs provide porous networks with defined pore sizes and architectures. Moreover, the incorporation of carefully chosen metal ions endows MOFs with catalytic properties. One of the major topics in current MOF research is the formation of tailored crystal morphologies.

In order to form crystals with modified morphology, a DHBC, namely PEO-*b*-poly(methacrylic acid) (PEO-*b*-PMAA) was added to the MOF precursor molecules during MOF fabrication **(Fig. 4) [11]**. In such a way, hexagonal mesocrystals were obtained, which is a significantly different structure compared to the respective MOFs without DHBC addition.

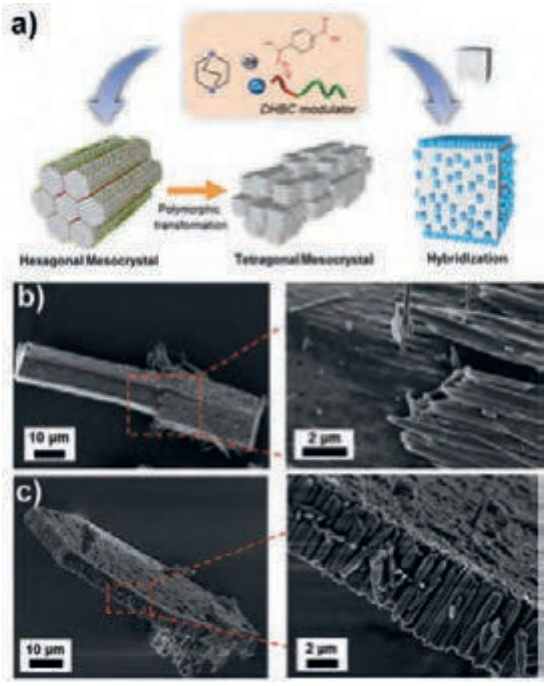

Fig. 4: a) Schematic overview of mesocrystal formation, b) obtained metal-organic mesocrystals (employing PEO_{68}-b-$PMAA_8$) and c) obtained metal-organic mesocrystals (employing PEO_{114}-b-$PMAA_{12}$) ***[11]***.

The mesocrystal formation occurs via a hierarchical assembly of individual nm-sized hexagonal rods, which leads to the formation of µm-sized hexagonal rods. Interestingly, the obtained mesocrystal morphology could be further tailored via the utilized block copolymer. The utilization of a longer PEO block led to the formation of hexagonal platelets consisting of individual hexagonal crystal rods. The MOF could be expanded easily via hybrid formation with other MOFs, e.g. including other metal ions. Moreover, the crystal structure could be changed after addition of protic solvent, which was utilized in another project to generate tailored MOF morphologies via solvent effects **[12]**.

B.V.K.J. Schmidt, Q. Cao, M. Gräwert, B. Kumru, A. Plucinski, M. Rasti, J. Zhang
Bernhard.schmidt@mpikg.mpg.de

[3] Willersinn, J., Schmidt, B.V.K.J.: Aqueous self-assembly of pullulan-b-poly(2-ethyl-2-oxazoline) double hydrophilic block copolymers. Journal of Polymer Science Part A: Polymer Chemistry. 55, 3757–3766 (2017).
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Electron Microscopy of Functional Materials

Nadezda V. Tarakina
12.09.1979
1996–2002: Bachelor and Master of Science, Chemistry (with Honour), Ural State University, Ekaterinburg, Russia
2002–2006: Doctoral Thesis: "Crystal structure of new compounds in the $AO–B_2O_5$ (A = Mn, Zn; B = Nb, Ta) system prepared by high-pressure/high-temperature synthesis,
(with Honour), Institute of Solid State Chemistry, Ural Branch of the Russian Academy of Sciences, Russia
2003–2004: Guest Ph.D. student at Stockholm University, Stockholm, Sweden
2006–2007: BELSPO Postdoctoral Scientist, University of Antwerp, Antwerp, Belgium
2007–2011: Senior researcher, Institute of Solid State Chemistry, Ural Branch of the Russian Academy of Sciences, Ekaterinburg, Russia
6/2009–8/2009: DAAD Guest Researcher, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany
6/2010–9/2010: Guest postdoctoral Scientist, University of Uppsala, Uppsala, Sweden
2011–2014: Akademische Rätin, Würzburg University, Würzburg, Germany
2014–2017: Experimental officer, Queen Mary University of London, London, UK
9/2017–11/2017: Postdoctoral Scientist, Fritz Haber Institute, MPG, Berlin, Germany
since 11/2017: Research group leader, Department of Colloid Chemistry, Max Planck Institute of Colloids and Interfaces, Potsdam, Germany

The installation of the new aberration-corrected (scanning) transmission electron microscope ((S)TEM) JEOL ARM-200F in September 2016 opened a broad range of new technical capabilities for studying materials at the nano/atomic scale, which was not available at MPIKG before. This state-of-the-art microscope, capable of a lattice resolution in the picometer range and permitting analyses of chemical compositions and electronic structures with an energy resolution down to 0.5 eV, not only enables to deliver completely new levels of data to support/service the needs of different departments at the institute, but also to re-think the research directions of the electron microscopy group in general. Two main topics that are closely linked together and related to scientific problems studied at MPIKG are currently in development in the electron microscopy group: (1) nanoscale characterisation of organic-inorganic interfaces and (2) understanding material formation at the nanoscale. It is worth pointing out that concepts and approaches developed in the context of one topic are beneficial for the other too.

Understanding Material Formation at the Nanoscale

There are several approaches through which the formation of materials can be studied with transmission electron microscopy (TEM). The most traditional way is to investigate final reaction products obtained at slightly different experimental conditions and compare them. This approach is particularly useful in situations where no other methods can provide insights into a material's structure, for example in the case of materials having a high concentration of disorder.

Synergy of X-ray Powder Diffraction and Transmission Electron Microscopy for Solving Structures of Highly Disordered Crystals

Finding an unambiguous structural solution of a highly defect/disordered system based only on X-ray powder diffraction data is often not possible. A realistic starting model for a structural refinement can only be built with input from other methods. Combining X-ray diffraction and advanced TEM is a powerful approach for solving crystal structures exhibiting high concentrations of defects and/or disorder. High-resolution TEM (HR-TEM) and annular dark-field scanning transmission electron microscopy (ADF-STEM) enable collecting crystallographic information on the nano-/atomic scale in direct space, while electron diffraction enables reconstructing a part of reciprocal space. These sets of TEM data can help to build an initial structural model for refining X-ray powder data, thus allowing to quantitatively describe disorder and to control and engineer defect states.

Using this approach we solved and refined the crystal structure of disordered poly(heptazine imide) potassium salt (K-PHI) and poly(heptazine imide) acid (H-PHI) **[1, 2]**. Both compounds were found to crystallize in hexagonal unit cells, sp.gr. *P*31*m* and *P*3, respectively. In the idealised K-PHI structure, heptazine units are stacked on top of each other so that continuous channels along the *c* direction are formed (AAAA stacking) where K atoms tend to sit closer to the centre of the channels (with a probability of 70%). The high degree of disorder is associated with (1) PHI layer stacking faults (in particular, the ideal AAAA sequence can be faulted, leading to local AABB, AB, ABC, … stackings) and (2) disorder in the distribution of K atoms (in particular, the probability to find K atoms in between channels at different positions is 20–25%).

During the ion exchange reaction of K^+ by H^+, while the main motif of the PHI-K structure is preserved, a rearrangement of the PHI layer sequences occurs. The AAAA sequence, which is dominant in PHI-K, changes to the AABB layer sequence in PHI-H, adjusting the alignment of negatively and positively charged centres. The ion exchange reaction generates even more turbostratic disorder. These two factors considerably reduce the photocatalitic activity of PHI-H compared to PHI-K. Similar structural changes were found during the formation of metal oxyhydroxides from corresponding salts, however the increase in turbostatic disorder positively influenced the reactivity and sorption properties of oxyhydroxides **[3]**.

Finding Order in Disorder. Electron Pair Distribution Function (PDF) and Beyond.

For amorphous phases very little information can be obtained from bulk diffraction techniques based on conventional crystallographic approaches. The Electron Microscopy group is exploring possibilities for studying short- and medium-range order in amorphous and nanocrystalline systems using electron pair distribution functions and cross-correlation approaches.

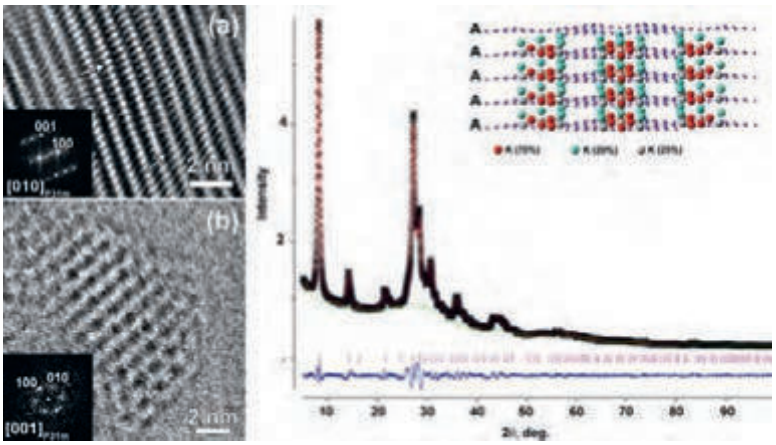

Fig. 1: HRTEM images of K-PHI taken along (a) the [010] and (b) the [001] directions in the structure with corresponding fast Fourier transform (FFT) in the insets. Observed (crosses), calculated (solid line) and difference (bottom) X-ray powder diffraction patterns of K-PHI; structural representation at the top right.

Ex situ/*in situ* Time-dependent Studies

A full understanding of real processes is only possible if we can monitor/observe them in real time. There are several *in situ* TEM studies of structural transformations, nucleation and growth of nanoparticles, particle assembly in real time at different temperatures (up to 1200 °C) and in liquid environments that we are conducting in collaboration with groups from the Colloid Chemistry and Biomolecular Systems departments and external collaborators. For example, as a part of the study of the effect of the manganese oxidation state on antiferromagnetic order in the $SrMn_{1-x}Sb_xO_3$ perovskite, we investigated the structural transition in $SrMn_{0.8}Sb_{0.2}O_3$ from a tetragonal to a cubic perovskite structure in situ. The transition occurs at both micro and sub-micron scales in a similar way and is associated with the displacements of oxygen atoms from general positions in the tetragonal unit cell to special positions in the cubic unit cell **[4]**. However, not all processes can be directly studied with TEM, for example the presence of vacuum can considerably influence carbonisation processes, while the "exit" of gas phases in the confined liquid holder restricts experiments in the liquid phase. For these reasons, *ex situ* time-dependent measurements are still relevant. As an example, we mention the study of CuH crystal formation, which allows obtaining Cu particles with a surface area several times higher than compared to nanoparticles obtained by conventional methods. To monitor crystal formation at different reaction stages with TEM, a drop of the reaction mixture was taken every 2 minutes and quenched and rapidly dried on a holey carbon grid. The *ex situ* time-dependent TEM study was complemented by *in situ* photon cross correlation spectroscopy. We showed that crystallization follows a non-classical mechanism. The nucleation of CuH particles can be described as a two–step process: (1) formation of colloidal droplets of slightly different density than the surrounding solution with chemical composition close to $Cu(H_2PO_2)_{2(aq)}$; (2) formation of small CuH (primary) particles inside the confined space of the droplets. Primary particles further increase in size via diffusion and/or surface reactions and merge into a network within the entire volume of the colloidal droplet, forming a porous rose-like shape structure **[5, 6]**. "Rose" structures agglomerate into chains. This non-classical crystallisation path leads to a network of 8.6 ± 2.9 nm particles within "rose petals" of 216.8 ± 53.4 nm. In air, CuH decomposes into hydrogen and Cu; hydrogen leaves the structure without changing the particles' morphology, further enhancing the total surface area.

Nanoscale Characterisation of Organic-inorganic Interfaces

The fact that the soft (organic) component of hybrid materials has poor electron-optical image contrast and is sensitive to ionizing radiation makes studying hybrid interfaces by conventional TEM challenging. Staining, which is used widely in biological samples, could be used to enhance the contrast of macromolecules, but it is very difficult to control and it degrades spatial resolution. The goal of our studies is to be able to image both soft and hard components of interfaces in their pristine state at the nanoscale (very often in liquid environment and ambient temperature) and to be able to understand their properties and formation mechanisms. We take part in the study of the assembly/dynamics of multi-functional hybrid polymer-magnetic nanoparticle composites in ionic liquids (ILs). Varying and optimizing the intermolecular forces between an IL and a polymer, as well as applying external magnetic fields, enables the construction of equilibrium hybrid nanostructure assemblies with tuneable mechanical and conductive properties.

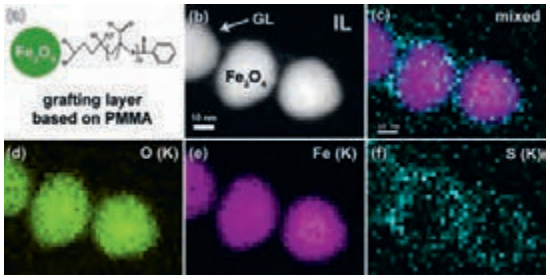

Fig. 3: (a) Representation of Fe_3O_4 and the grafting layer, (b) ADF-STEM image of the Fe_3O_4 grafted particles in ionic liquid, (c-f) EDX maps based on mixed, O(K), Fe(K) and S(K) signals, respectively ***[7]*** *.*

Using chemical contrast based on EDX signals, we are able to resolve the organic shell in the hybrid nanostructures in its pristine form in an IL inside a TEM at nanometer resolution, analyse different assemblies and obtain insights into the intermolecular forces driving particular types of assemblies.

Nadezda V. Tarakina, Tobias Heil
nadja.tarakina@mpikg.mpg.de

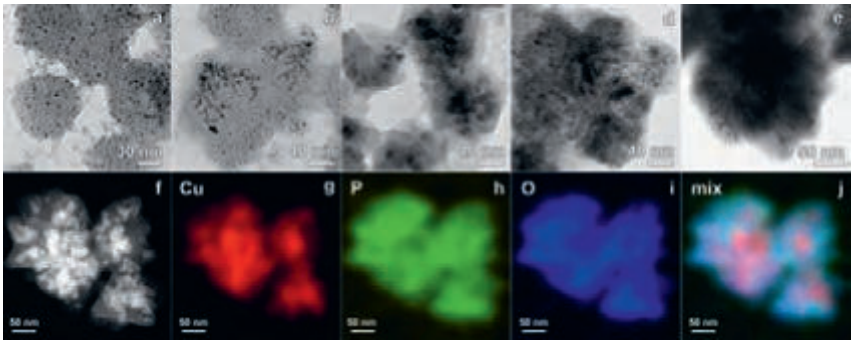

Fig. 2: (a-e) TEM images of CuH droplets at different reaction stages, (f) ADF-STEM image of a droplet with growing CuH particles after 7 minutes of the reaction (complementary to (c)), (g-j) EDX maps representing signal of Cu, P, O, and overlap of signals.

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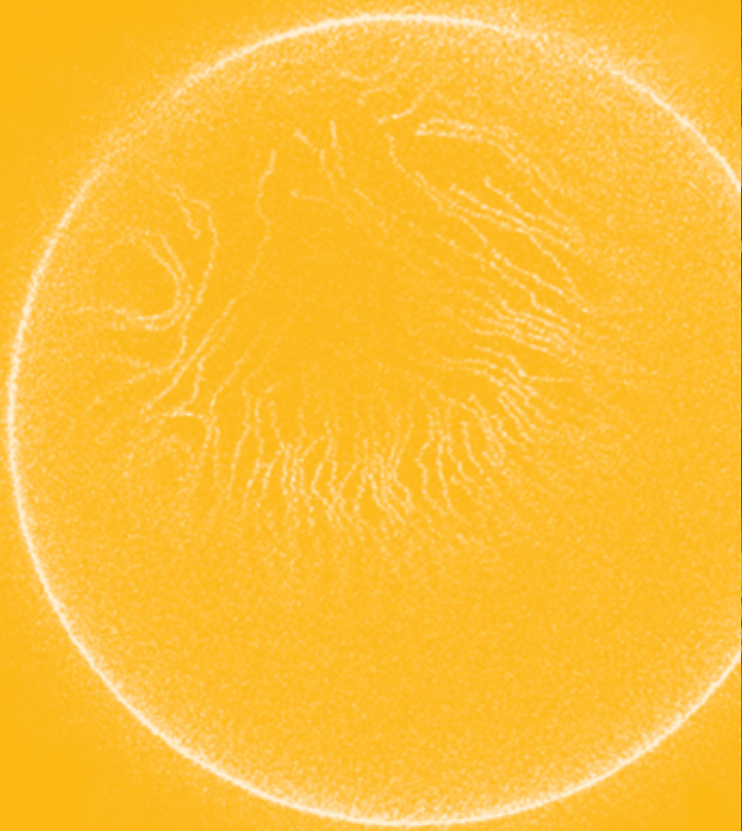


THEORY &
BIO-SYSTEMS

Research in the Department of Theory & Bio-Systems

"There is no falsification before the emergence of a better theory." Imre Lakatos

Reinhard Lipowsky
11.11.1953
1978: Diploma, Physics, (University of Heidelberg)
1982: PhD (Dr. rer. nat.), Physics (University of Munich)
1979-1984: Teaching Associate (University of Munich)
1984-1986: Research Associate (Cornell University)
1986-1988: Group leader (FZ Jülich)
1987: Habilitation, Theoretical Physics (University of Munich)
Thesis: Critical behavior of interfaces: Wetting, surface melting and related phenomena
1989-1990: Associate Professorship (University of Munich)
1990-1993: Full Professorship (University of Cologne), Director of the Division "Theory II" (FZ Jülich)
Since Nov 1993: Director (Max Planck Institute of Colloids and Interfaces, Potsdam)

The main objective of our research activities is to understand the hidden dimensions of self-organization and pattern formation in biomimetic and biological systems. The associates of the department form several research groups.

During the last two years, the research group leaders and topics were (in alphabetic order):

- Rumiana Dimova: Biophysics Lab (Exp);
- Andrea Grafmüller: Multiscale Simulations;
- Roland Knorr: Dynamics of Biomembranes (Exp);
- Markus Miettinen: High-fidelity Molecular Modeling
- Hans Riegler: Solid-Air Interfaces (Exp);
- Tom Robinson: Biomicrofluidic Systems (Exp);
- Sophia Rudorf: Biomolecular Processes;
- Mark Santer: Carbohydrates and Polysaccharides (until May 2019);
- Angelo Valleriani: Stochastic Processes;
- Ana Vila Verde: Soft Matter Simulations;
- Thomas Weikl: Proteins and Membranes.

The experimental group of Tom Robinson is an independent junior group, funded by the Max Planck Research Network in Synthetic Biology (MaxSynBio). The experimental group of Hans Riegler originally belonged to the former Interface Department of Helmuth Möhwald.

The main results of the different research groups are described in separate reports on the following pages. These reports are ordered in a bottom-up manner, i.e. from small to large length scales, and related to five research areas: Molecular Modeling, Biomolecular Processes, Proteins and Membranes, Membranes and Vesicles as well as Interfacial Processes. Here, these individual reports will be briefly summarized and a few results will be highlighted.

Molecular Modeling

The four research groups of Ana Vila Verde, Mark Santer, Andrea Grafmüller and Markus Miettinen studied the molecular dynamics of proteins, polysaccharides, and lipids. The Vila Verde group investigated the water dynamics around ions and amino acids. One focus during the last couple of years was on fluorinated amino acids and proteins. The Santer group worked on force field modularization for carbohydrate compounds (glycans). These force fields have been applied to GPI anchors in lipid membranes. The average orientation of the GPI-anchor was found to be perpendicular to the bilayer normal. The Grafmüller group has focused on long polysaccharide chains and optimized the corresponding force fields in order to obtain a reliable description for the osmotic pressure. It turned out that essentially all previous force fields failed in this respect. In addition, the atomistic model has been mapped onto a coarse-grained model that allows to simulate much longer chains. The Miettinen group is involved in NMRlipids, a collaborative effort of several groups to understand lipid bilayers. The group uses a detailed comparison between experiment and simulation to improve the force fields by data-driven calibration.

Biomolecular Processes

The two research groups of Sophia Rudorf and Angelo Valleriani use stochastic modelling to study biomolecular processes. The Rudorf group addressed the dependence of protein translation on EF-Tu concentration and codon optimization via synonymous substitution. Two doctoral projects of the Rudorf group addressed the entry of the nascent peptide chain into the ribosomal exit tunnel **(Fig. 1)** as well as post- and co-translational assembly of proteins. The Valleriani group focused on the ageing and degradation of biomolecules as well as on the information that one can deduce from ribosomal profiling or sequencing (Ribo-seq) data. These data can be used to estimate the local, codon-dependent speed of the ribosomes.

We also continued our study of cooperative cargo transport by teams of molecular motors. The theoretical challenge is to combine the stochastic stepping of the motors with their elastic coupling to the cargo. One issue that has been quite controversial for some time is whether motors from the same team share their overall load force equally. The simplest system to address this issue consists of two identical motors pulling the cargo in one direction and a third antagonistic motor that pulls in the opposite direction **(Fig. 2)**. This system is indeed characterized by equal force sharing. The same conclusion applies to N identical motors pulling against an optical trap (project of Mehmet Ucar).

Proteins and Membranes

The group of Thomas Weikl studied the interactions of proteins and other biomolecules, both in solution and anchored to membranes. Using multiscale modeling, the group analyzed the bonds between membrane-anchored receptors and liqands that are relevant for phagocytosis by macrophages. The analysis was based on experimental data obtained by Jan Steinkühler during his visit to the lab of Dennis Discher at UPenn. The detailed comparison between experiment and simulations revealed the cooperative nature of the receptor-ligand bond arising from nanoscale membrane fluctuations.

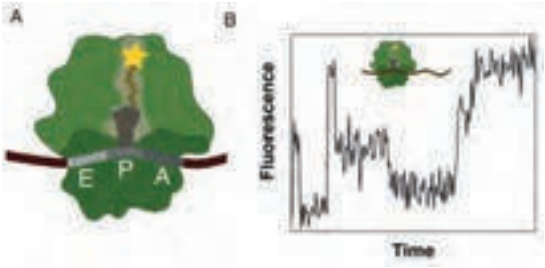

Fig. 1: Protein synthesis by ribosomes: (A) Nascent peptide chain (brown dots) within the exit tunnel (light grey), which is located above the P site of the ribosome (green). The first amino acid of the nascent chain is labeled with a fluorophore (yellow star) that probes the local interactions with the walls of the exit tunnel; (B) Putative fluorescence signal obtained from a growing chain as a function of time. In practise, only ensemble averages over many ribosomes can be measured and stochastic modeling is needed to interpret the data. ***[Haase ... Rudorf, Nucleic Acids Research, 2018]***

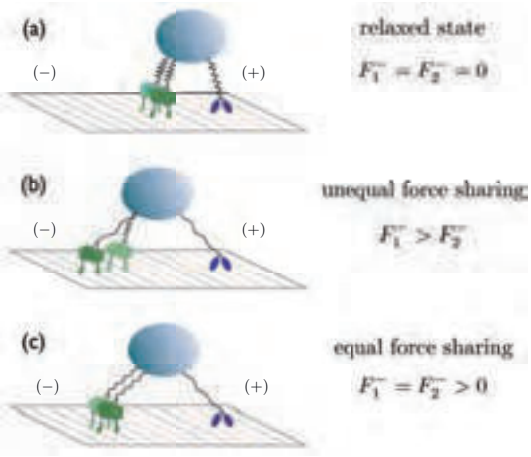

Fig. 2: A small team of two dynein motors (green) and a single kinesin motor (blue), elastically coupled to a cargo particle (grey). Both motors perform discrete steps of about 8 nm. The dyneins move preferentially to the left, the kinesin to the right, thereby changing the elastic force balance between the motors and the cargo. Starting from the relaxed state in (a), the most likely conformation exhibits equal force sharing between the two dyneins as in (c). ***[Ucar and Lipowsky, Scientific Reports, 2019]***

Membranes and Vesicles

The behavior of biomembranes and giant unilamellar vesicles (GUVs) has been addressed experimentally by the three groups of Rumiana Dimova, Roland Knorr and Tom Robinson. The Dimova group studied various mechanisms that lead to the generation of highly curved membrane segments. Furthermore, several analysis methods are now available by which we can deduce the spontaneous curvature from the observed GUV morphologies. One general method is based on pulling nanotubes by optical traps that are applied to membrane-bound beads **(Fig. 3)**.

The Knorr group focused on the interactions of membranes with biomolecular condensates, originally called membraneless organelles. These condensates form within living cells, are enriched in intrinsically disordered proteins, and behave like liquid droplets. When the condensates interact with giant vesicles, they undergo two distinct wetting transitions. In addition, in the partial wetting regime, the condensates mold the membranes by capillary forces and complete engulfment. The Robinson group has further developed microfluidic methods to produce giant unilamellar vesicles and designed microfluidic chips that can be used to manipulate vesicles and cells. The group has created nested membrane structures ("vesicles in vesicles"), encapsulated enzymatic reactions in vesicles, and studied cancer cells and bacteria encaged within microfluidic traps.

One intriguing aspect of membranes and vesicles is their morphological complexity. On the scale of tens of nanometers, simulations of molecular bilayers have revealed that spherical nanovesicles transform into many different shapes (project of Rikha Ghosh and Vahid Satarifard). This polymorphism reflects small variations in the assembly process of these vesicles that lead to different mechanical tensions within the two bilayer leaflets. Sufficiently different leaflet tensions generate lipid flip-flops between the two leaflets (project of Aparna Sreekumari). On the scale of several micrometers, the morphological complexity of giant unilamellar vesicles (GUVs) is obvious from their spontaneous tubulation. The nanotubes increase the robustness of the GUVs against mechanical preturbations **(Fig. 4)**. The GUV membranes also form a large variety of multi-sphere shapes that consist of (punctured) spheres connected by closed membrane necks (project of Tripta Bhatia). Furthermore, once a closed membrane neck has formed, a further increase of the spontaneous curvature generates constriction forces around this neck and a sufficiently large increase of this curvature leads to neck fission and vesicle division. Recent experimental studies have demonstrated that this division process can be induced in a controlled and quantitative manner by low densities of membrane-bound proteins (project of Jan Steinkühler).

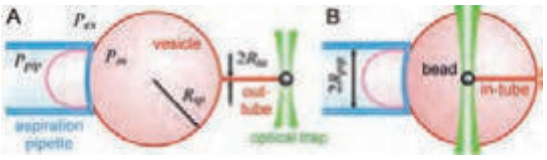

Fig. 3: An optical trap (green) is applied to a bead (black) that is attached to the membrane of a giant vesicle (pink). This bead can then be to pulled towards the exterior solution as in (A) or towards the interior solution as in (B), thereby generating out-tubes and in-tubes, respectively. Combining the results for both pulling directions, the fluid-elastic parameters of the vesicle membrane can be obtained irrespective of the membrane tension. ***[Dasgupta ... Dimova, PNAS, 2018]***

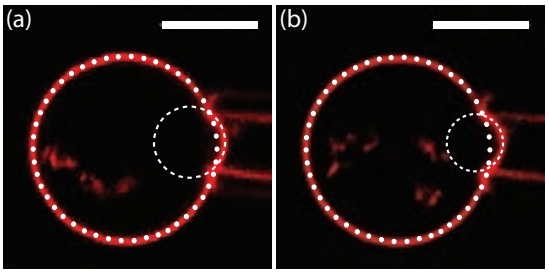

Fig. 4: Micropipette aspiration of a GUV (red with white dots) with membrane nanotubes (red) protruding into the vesicle interior. Increasing aspiration from (a) to (b) leads to the retraction of the nanotubes into the mother vesicle. The mechanical response of the vesicle is very similar to a liquid droplet with the interfacial tension replaced by the spontaneous membrane tension. ***[Bhatia ... Lipowsky, ACS Nano, 2018]***

Interfacial Processes

The group of Hans Riegler focused on the behavior of liquids with volatile components that form sessile drops and thin films at solid substrates. A variety of processes has been studied including the influence of Marangoni flow on the coalescence of sessile drops, the behavior of nanoparticles in thin films of volatile liquids, and the nucleation and growth of very long crystalline fibers built up from dipeptides.

International Max Planck Research Schools

The department of Theory & Bio-Systems was in charge of the International Max Planck Research School on "Multiscale Biosystems", which started its operation in July 2013 and, after a very positive evaluation in 2017, has been extended until 2025.

For additional information about research at the Department of Theory & Bio- Systems, see the subsequent reports and www.mpikg.mpg.de/th/

Reinhard Lipowsky
Head, Department of Theory & Bio-Systems

MOLECULAR MODELING

From Ionic Solutions to Interacting Proteins

Ana Vila Verde
20.08.1976
1994–1999: Undergraduate degree (5 years) in Teaching of Physics and Chemistry, University of Minho, Braga, Portugal
1999–2000: Teacher of physics and chemistry (António Feijó junior high school, Ponte de Lima, Portugal)
2000–2001: Teacher of physics and chemistry (Alcaides de Faria high school, Barcelos, Portugal)
2001–2005: Doctoral thesis: Optimization of minimal invasive dental laser ablation by mesoscopic modeling (Department of Physics, University of Minho, Braga, Portugal)
2005–2007: Post-doctoral researcher, Pennsylvania State University, Pennsylvania, USA
2007–2010: Post-doctoral researcher, FOM institute AMOLF, Amsterdam, The Netherlands
2010–2011: Post-doctoral researcher, University of Amsterdam, The Netherlands
2012–02/2014: Post-doctoral researcher, Department of Theory and Bio-systems, Max Planck Institute of Colloids and Interfaces
Since 03/2014: Research Group Leader, Department of Theory and Bio-systems, Max Planck Institute of Colloids and Interfaces

We use molecular simulations and classical, atomistic models to investigate biological soft matter. Ions are ubiquitous in biological systems, and critically affect biological function. To study biological systems in the presence of ions, we *developed parameters (force fields) for mono-* and *polyatomic* ions in various water models. A prevalent problem when developing ion force fields is ensuring internal consistency in the absence of equivalent experimental data for all the ions of interest. Internal consistency is indispensable to investigate why different ions affect system properties differently. To resolve this issue, we developed a hybrid experimental-*ab initio* parameterization approach.

Experiments with *fluorinated proteins* have demonstrated the potential of fluorination to tune protein properties, but the mechanisms by which this occurs remain unknown. The force field we created can now be used to gain molecular scale insight into these systems. We have clarified the molecular mechanisms behind changes in hydration free energies upon fluorination using an analytical solvation model.

Our studies of dimeric and trimeric coiled coils (CC) under shear load are revealing how their mechanical response depends on the length of the α-helices and the CC oligomerization state. We investigated these systems at low pulling speeds, necessitating simulation times in excess of 12 months. We obtain pull forces almost identical to the rupture forces measured in experiment. This proximity suggests that our simulations give unprecedented insight into the deformation mechanisms probed experimentally.

Interactions between Water, Ions and Proteins

It has been established for over a century that the identity of the ions forming a salt has a measurable impact on the properties of an aqueous electrolyte solution (e.g., water dynamics, solution structure) and on the behaviour of other solutes in solution (e.g., protein folding and aggregation). The molecular origin of ion-specific effects is still incompletely understood, in part because of the absence of classical force fields that correctly represent the interaction balance between all species. Force fields (as opposed to *ab initio* calculations) are indispensable to reach the large length- and timescales involved in many cases.

We have optimized ion force fields for both ion-ion and ion-water interactions as a step towards investigating a variety of problems. i) We developed a force field for the alkali, alkali earth and halide ions and the TIP5P water model, based on experimentally-determined hydration free energies and solution activity derivatives (a_{cc}) **[1]**. Although suitable ion parameters exist for other water models, a TIP5P-based force field is particularly desirable for simulations of saccharides. The state-of-the-art approach used to parameterize anion-cation interactions consists of attempting to reproduce a_{cc} at one or more concentrations. We show that this approach often leads to a huge number of possible parameters, and that other target properties are necessary to resolve this indetermination. Existing force-fields for mono- and divalent monoatomic ions – parameterized only against ion-water interactions – often over-estimate the number of ions in direct contact in solution; explicit parameterization of ion-ion interactions is essential. ii) We developed a set of parameters for the SO_4^{2-}, SO_3^{2-}, HPO_4^{2-}, $H_2PO_4^-$ ions, the methylated versions of these anions, and for acetate, compatible with the TIP3P water model typically used with the AMBER force field for proteins **[2]**. The interactions of these anions with positively charged amino acids and with Na^+ are explicitly parameterized, enabling the study of ion-specific effects in proteins. Our results show that existing force fields greatly overestimate interactions between negative amino acids and Na^+, as well as the strength of salt bridges in proteins. iii) More recently, we developed parameters that better represent the interaction between K^+ and acetate at molar concentrations. Such parameters are indispensable to investigate the mechanisms by which proteins remain functional at molar concentrations of KCl. These concentrations are found inside halophilic organisms, which thrive under external molar NaCl concentrations. Halophilic proteins – a recent topic of interest in the group – are of interest for the creation of biodevices (e.g., for H_2 production) that function in brine and in oceans.

Fluorinated Amino Acids and Proteins

Fluorinating – replacing C-H bonds by C-F bonds – the side chains of hydrophobic residues in proteins often improves the protein's thermal stability. Even though the intrinsic physicochemical properties of fluorine are well understood, the mechanisms by which fluorination alters protein properties are not. To investigate these issues we developed a force field for fluorinated amino acids. The force field is fully compatible with the widely used AMBER force field for proteins, but uses a non-standard parameterization of the amino acid charges because the standard procedure proved insufficient. With this force field we investigated how mono-, di- and trifluorination alter the hydration free energy (ΔG_{Hyd}) of amino acids with alkyl side chains.

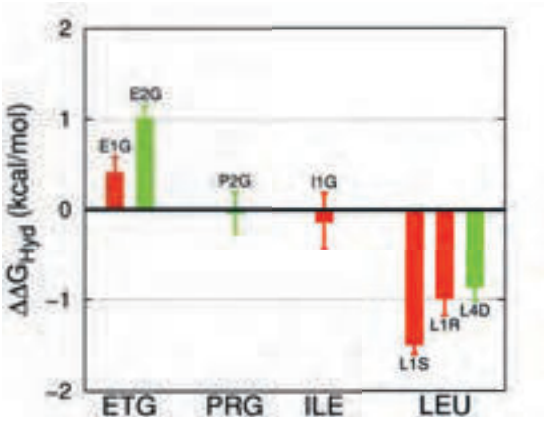

Fig. 1: $\Delta\Delta G_{Hyd}$ associated with mono-, di- and tetrafluorination of amino acids with alkyl side chains.

We predict that side chain fluorination alters the hydration free energy of amino acids in surprising ways: $\Delta\Delta G_{Hyd}$ strongly depends on the chirality and location of the fluorinated site and on the identity of the amino acid, as **Fig. 1** illustrates **[3, 4]**. Using a simple, analytical solvation model, we identify the mech-

anisms behind this dependence: there is a cost of introducing larger fluorine atoms, gains *and* costs associated with the higher polarity of fluorinated alkyl groups, and gains or costs from altering the number of backbone-water hydrogen bonds. For small molecules, it is often possible to predict the sign and even estimate the magnitude of $\Delta\Delta G_{Hyd}$ upon fluorination. In contrast, for complex molecules 'the devil is in the details': the contribution of each mechanism to $\Delta\Delta G_{Hyd}$ depends on conformational preferences and interactions between different parts of the molecule, *making commonly-used rules-of-thumb insufficient*. For example, monofluorination *does not* always make amino acids more hydrophilic; similar increases in the solvent-exposed surface area of different molecules do not imply that the molecules will experience similar increases in ΔG_{Hyd}.

Our results offer a road map to mechanistically understand how fluorination alters ΔG_{Hyd} of (bio)polymers and (bio)molecules. The solvation model we developed for amino acids can be used to interpret hydration free energies of other molecules containing the same functional groups, and extended to other functional groups. The solvation model is also directly relevant for proteins: together with short molecular dynamics simulations of proteins in the folded and unfolded ensembles, it can be used to gain quick insight into how fluorination-induced changes in protein-water interactions contribute to changes in the free energy of folding. We aim to extend the solvation model to include mechanisms by which fluorination alters intra-protein non-bonded interactions. This extension is necessary to understand how fluorination alters the thermal stability of proteins.

Mechanical Response of Coiled Coils under Tension

Coiled coils (CCs; **Fig. 2**) are protein motifs consisting of bundles of two or more α-helices. These motifs are present in circa 10% of natural proteins. Coiled-coils are thought to have chemical functions as well as mechanical or chemomechanical ones. We have investigated how the *mechanical* response of coiled coils is affected by helix length and by the multimerization state (dimeric or trimeric; 2CC or 3CC) of the coiled coil. Clarifying these issues is critical to understand the role of coiled coils with different multimerization states in biology. We investigated the mechanical response of coiled coils in shear load, by performing pulling simulations where one end of an α-helix is kept fixed and another one is pulled **(Fig. 2)**.

The simulation setup is analogous to atomic force microscopy (AFM) experiments. For 2CC, experiments were also performed in the group of K. Blank (MPIKG). In contrast with prior all-atom simulation studies of 2CCs, the plateau forces we detect in simulation (40 to 50 pN) at our lowest pull speed are very similar to the rupture forces (45-55 pN) detected in AFM experiments at the largest experimentally-accessible loading rate **[5]**. This similarity suggests that our simulations at the lowest pull speed (10^{-3} ns/ns) give unprecedented insight into the mechanism of coiled coil deformation and rupture in experiment. We find that 2CCs with longer helices have higher plateau forces, in agreement with experimental data that shows larger rupture forces for longer 2CCs **[5, 6]**. Dimeric and trimeric CCs have a similar force-extension dependence: in both cases, the CC initially deforms elastically and subsequently reaches a force plateau before the helices separate **[5, 7]**.

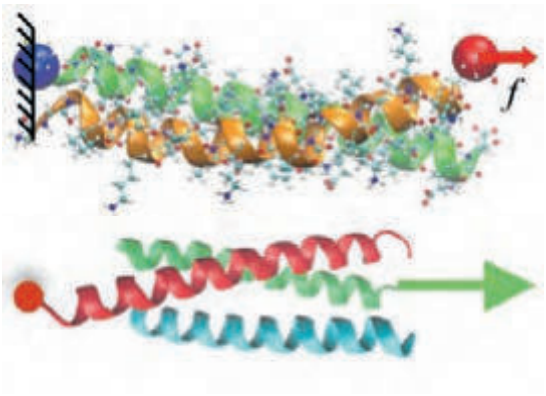

Fig. 2: Dimeric and trimeric CCs under a pulling force f.

The similarities between dimers and trimers are qualitative only, however. The trimer is both stronger and tougher than the dimer, withstanding higher forces (127 pN vs. 49 pN at v = 10^{-3} nm/ns) and dissipating up to five times more energy before rupture. The deformation mechanism of 3CC at all pull speeds is dominated by progressive helix unfolding. In contrast, at the lowest pull speeds, 2CC deforms by unfolding/refolding-assisted sliding. The additional helix in 3CC thus both determines the stability of the structure and affects the deformation mechanism, preventing helix sliding. The mechanical response of the CCs is not only sensitive to the oligomerization state but also to helix stability: preventing helix unfolding doubles the mechanical strength of 3CC, but decreases its toughness to half. Our results show that CC trimers expand the range of CC responses to an applied shear force. Altering the stability of individual helices against deformation emerges as one possible route towards fine-tuning this response, enabling the use of these motifs as nanomechanical building blocks. Future work by our group will investigate how the oligomerization state affects the mechanical response for other loading modes, and the general connection between thermodynamic stability, mechanical strength and toughness for each loading mode.

Ana Vila Verde, Ana Bergues Pupo, Hosein Geraili, Sadra Kashef Ol Gheta, Chuanfu Luo, João Robalo,
ana.vilaverde@mpikg.mpg.de

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The Sweet Battle with Water

Mark Santer
27.10.1971
2003: PhD in Physics at the University of Freiburg
2003–2006: Postdoc at the Institute of Microsystems Engineering, University of Freiburg. Group leader *Nanofluidics*
2006–2009: Employee at the Fraunhofer Institute of Mechanics of Materials (IWM), Freiburg
2010: Postdoc at the Theory Department, MPI for Colloids and Interfaces, Potsdam
From 09/2010: Group Leader *Carbohydrates and Polysaccharides* in the Department of Theory and Biosystems.

In nearly all organisms, a major portion of proteins and also lipids is modified with *glycans*, complex carbohydrate compounds that alter or enhance their function. The hydroxyl-rich sugars can fine-tune solubility or act as epitopes that are recognized by other proteins. Hydrogen bonding is naturally the major mechanism for a glycan to interact with other biomolecules, opposed by (de-)solvation forces. This highly non-trivial competition is the key to understand how glycan-specific binding and receptor sites must be tailored, which role a protein glycosylation should be attributed to or how glycolipids distribute in the plasma membrane. In recent computational studies we have made some progress along this way by taking the *synthetic route:* in our case studies the biomolecular systems were subject to systematic mutations or varied in complexity.

Slippery when Wet. Polysaccharides in Extended Binding Sites.

So-called tail spike proteins (TSPs) are the cutting tools of phages to locally hydrolyse and remove the protective O-Antigen polysaccharides of Gram-negative bacteria they infect. They bind oligosaccharide epitopes in extended sites close to catalytic residues. Affinity is largely generated by the multivalent action of hydrogen bridges **[1]**.

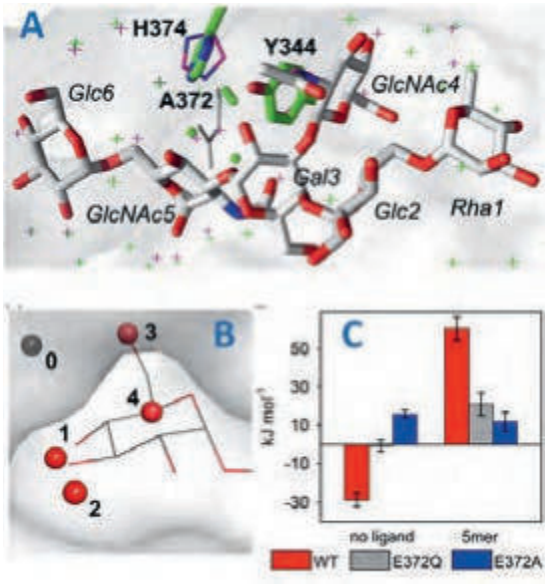

Fig. 1. (A) Hexamer (one repeat unit) of antigen polysaccharide O18A1 of E coli in the binding site of HK620 TSP. The glucose Glc6 to the left fills a cavity indicated in (B). For the pentamer of O18A the cavity is occupied by waters 1-4 (Glc6 indicated by sticks). Their affinity depends on both, mutation of HK620TSP (here shown for residue 372, glutamate) and whether the pentamer is present or not (C). For the mutation to alanine, two waters (green spheres in A) slip into the position of the carboxy group.

For the case of HK620TSP (*E. coli*) we could recently study an unusually large number of x-ray structures with a series of high-affinity mutants co-crystallized with two different O-Antigen polysaccharide fragments, a hexasaccharide from strain O18A1 and a pentamer from O18A, lacking the branching glucose of O18A1, see **Fig. 1**. Not only water expulsion from (leading to entropy-enthalpy compensation) or water condensation at the binding site could be elucidated in detail, but also some less obvious phenomenon: the affinity of surface waters does not only depend on the local protein environment, but also on the network of nearby surface waters they are part of. The effect of a local reordering of the water grid can propagate to other sites, as has explicitly been demonstrated for waters residing in a cavity that would otherwise host the branching glucose of O18A1, see **Fig. 1**. These waters are impacted by mutation of the somewhat remote residue 372 near the "gate" of the cavity.

Swimming and Diving. GPI-anchors as Lifesavers for Membrane Proteins

Approximately 1 % of all membrane bound proteins on eukaryotes is attached by so-called glycosylphosphatidyl-inositol (GPI-) anchors. At the C-terminus, the protein is connected to a phospholipid tail via a pseudo-pentasaccharide backbone and a phosphoethanolamine linker.

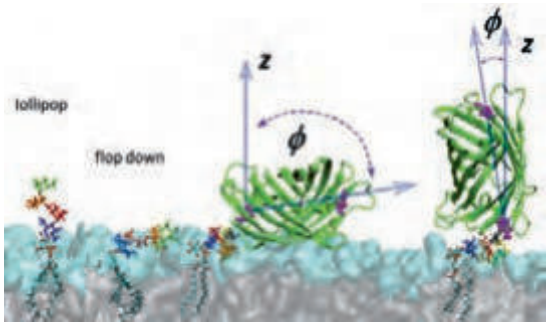

Fig. 2. Schematic view of free GPIs and GPI-anchored green fluorescent protein (GFP). The lipid bilayer leaflet (DMPC) has been stitched together for illustrative purposes from four independent simulation snapshots. Although the protein can explore a variety of orientations, the GFP barrel prefers to "sleep" on the head groups (flop down) most of the time, as shown by the central cartoon.

Why did nature invent such a complex anchoring device? We have created a modular molecular model by which GPIs can be build up incrementally starting from a simple phospho-inositol lipid. One of the insights gained is that the GPI is highly unlikely to function as a spacer as indicated by the "lollipop" in **Fig. 2** **[3]**. Already the free GPI glycan flops down onto the head group region and interacts extensively with it. This situation is essentially conserved even after the rather large GFP is attached: it explores a broad range of orientations but remains close to the bilayer surface. The phosphoethamolamine linker provides sufficient flexibility.

As a rule of thumb it is usually stated that the nature of the fatty acid tails determine which membrane domain a GPI anchored protein should associate with. This concept should carefully be reviewed: taking into account that the glycan part of the GPI can show drastic variations through the addition of side chains, the consequences of this heterogeneity on GPI distribution and trafficking must be explored.

Rafting and Floating: Selecting a Reaction Path.
The aqueous solvent plays an important role for biochemical reactions, as a reaction partner in hydrolytic cleavage or as a dielectric medium influencing the reaction pathway. Both aspects are important when questions about conformational selection arise: when an O-Antigen polysaccharide is initially caught by the TSP, does the latter bind the conformation of the epitope which is later found in the co-crystal? Or does efficient cleavage favor a tweaked version? To obtain an unbiased view on how the reaction pathway depends on conformation a combination of advanced simulation techniques is required involving path sampling techniques and hybrid quantum mechanical/molecular mechanics (QM/MM). Application of this methodology is subtle, and for now we have taken a first step and established a numerically efficient implementation using the thermal isomerization of azobenzene derivatives as a case study **[4]**, see **Fig. 3**.

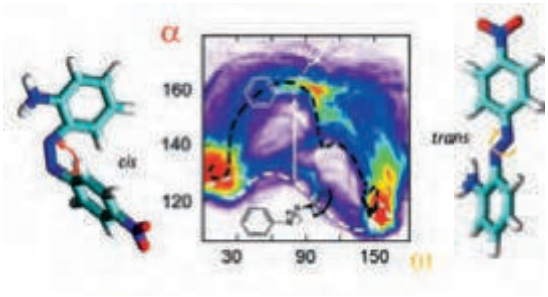

Fig. 3. Thermal isomerization of a push-pull azobenzene studied by sampling reaction paths connecting cis and trans isomers (red basins in the space of a and w angles) in vacuum. The expected isomerization path should proceed via inversion, indicated by the black dashed line, where the cis form initially flaps open by increasing a, and then carries out a pedal-like rotation in w. Even when forced to carry out a pure rotation initially (white dashed line), over many iterations, the path correctly evolves into inversion. Each new path is obtained from the preceding one by restarting with different initial velocities at some randomly chosen intermediate time.

One satisfactory result was that the MM solvent models exhibiting only static polarity were sufficient to capture a non-trivial phenomenon: the isomerization pathway of the push-pull derivative shown in **Fig. 3** correctly changed its nature from inversion (in unpolar toluene) to rotation (in rather polar DMSO).

M. Santer, P. Banerjee, S. Schimka, A. Chaimovich
mark.santer@mpikg.mpg.de

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Efficient Models for large Saccharide Systems

Andrea Grafmüller
18.08.1980
2000–2004: Master in Science (MSci), Physics, Queen Mary University of London
2004–2007: Doctoral Thesis: The Fusion of Membranes and Vesicles (Max Planck Institute for Colloids and Interfaces)
2007–2009: Postdoctoral Scientist, Department of Theory and Bio systems, Max Planck Institute of Colloids and Interfaces
2009–2010: Postdoctoral Scientist, University of Utah
2010–2011: Postdoctoral Scientist, University of Chicago
2011–2012: Research Scientist, Department of Theory and Bio systems, Max Planck Institute of Colloids and Interfaces
Since 2012: Research Group Leader, Department of Theory and Bio systems, Max Planck Institute of Colloids and Interfaces

Carbohydrates are abundant in nature and natural materials. Their function ranges from structural stability and energy storage to functions in the glycocalyx, the extracellular matrix, cell signaling and the molecular recognition of pathogens. They are also of considerable interest for various applications, owing to favorable properties such as biocompatibility, non-toxicity and bio-degradability. One polysaccharide of major interest for developing therapeutic hydrogels is chitosan, which is derived from chitin. The presence of a primary amine group on its glucosamine monomers provides a site for chemical modification with the purpose of fine-tuning the chitosan-hydrogel properties.

To understand the diverse properties of carbohydrates, increased efforts have been made recently to model their molecular properties. Interaction parameters for carbohydrates have been developed for several biomolecular molecular dynamics (MD) force fields **[1, 2]**. While some of these reproduce solution properties and hydration free energies well, they drastically underestimate osmotic pressure of carbohydrate solutions and produce the wrong trend with molecule size, which indicates overly attractive solute-solute interactions. Indeed, good agreement with experimental data can be achieved by reducing the solute-solute interaction strength **[3]**.

However, such models with atomistic resolution cannot reach, in many cases, the length and time scales of natural carbohydrate systems, necessitating the development of simplified coarse-grained (CG) models. One coarse-graining strategy that has been successfully applied to chitosan is to sample the polymer's conformational space based on the dihedral angles of the glycosidic bonds, which represent the most flexible degrees of freedom **[4]**. Another CG modelling procedure, that includes more detailed sugar-sugar interactions, generates the non-bonded interaction potentials based on the Force-Matching method, which aims to reproduce the forces sampled at atomistic resolution. Such a model can reproduce the structural data from the underlying atomistic systems very well, and it has been shown that interaction potentials can be transferred to systems with different polymer lengths or saccharide concentrations **[5]**. Here we describe the application of such a CG model to two quite different systems.

Efficient Osmotic Pressure Calculations

The osmotic pressure is a sensitive measure for the strength of molecular interactions, and has been a valuable tool for force-field evaluation and development. However, for carbohydrate solutions, these calculations are slow to converge, requiring µs simulations to obtain reliable osmotic pressure values even for simple molecules. For viscous solutions of linear oligosaccharides, convergence for molecules with more than 7 monomers could not be achieved at all within 4 µs simulation time. The high computational cost of measuring osmotic pressure makes the process of parameter scanning for force field parametrization very time consuming, and prevents the application of the method to systems involving larger and more complex molecules.

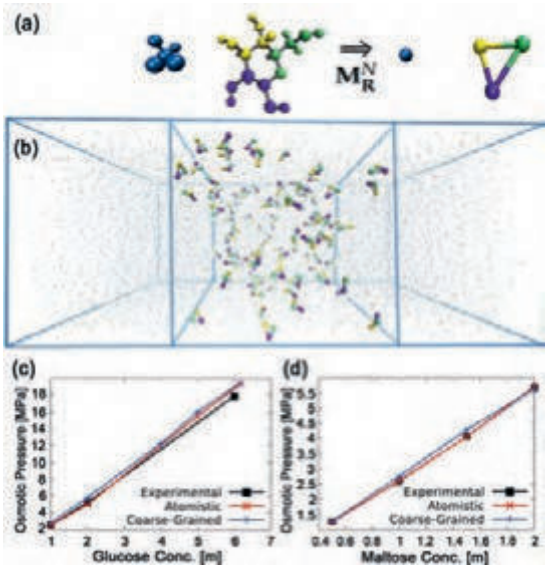

Fig. 1: CG simulations to measure the Osmotic Pressure: (a) CG mapping of one glucose and one water molecule; (b) simulation setup to measure the osmotic pressure in the CG glucose solution confined in the central region; (c) and (d) comparison of the osmotic pressure measured experimentally, with all-atom resolution and in the CG system for glucose (c) and maltose (d).

Because the osmotic pressure is calculated from the wall force acting on the sugar molecules and the CG procedure relies on reproducing the forces sampled in the atomistic system, it is in principle also possible, to measure the osmotic pressure in the CG system **[6]**. To be able to reproduce atomistic results, it was required to (i) treat solute-solute, solute-solvent and solvent-solvent interactions separately, (ii) use a large cutoff of 1.8 nm in the CG model and (iii) apply a distance dependent regularization function to avoid over-sensitivity to long range perturbations in the interactions. The CG model allows the use of a larger water bath, reducing boundary effects. As a result, excellent agreement between the osmotic pressure measured in the atomistic and CG systems is achieved, as shown for the examples in **Fig. 1c and d**.

The overall gain in computational efficiency in the CG setup is approximately a factor of 500. Instead of the 500 ns simulation time required for each data point of the atomistic system in **Fig. 1c and d**, converged osmotic pressure values are reached within 2ns in the CG system, due to the smoother energy landscape and faster dynamics. An additional factor of 2.4 per time-step is gained because the system has fewer degrees of freedom.

The sampling time at atomistic resolution to obtain reliable CG interaction potentials, i.e. 100 ns, is much shorter than what is required for converged osmotic pressure results, requires a smaller system, because no water bath is needed, and only needs to be performed at one concentration value. Thus this multiscale set-up for measuring the osmotic pressure can very efficiently scan the parameter space to include concentration dependent osmotic pressure data in the force-field parametrization process. In addition, the computational speedup of

this procedure will allow measuring the osmotic pressure of much larger molecules and longer branches, to gain a concise understanding of the factors governing molecular interaction strength and self-assembly in polysaccharide systems.

Hydrogel Structure for Chitosan Gels

Hydrogels prepared from chitosan or chemically modified chitosan polysaccharides have been widely proposed as optimal drug carriers. Optimizing type and degree of modification used to achieve the desired network structure and drug release profile is a complex process. We have therefore applied our CG model to characterize the structure of hydrogels formed by chitosan modified with hydrophobic acetyl, butanoyl, and heptanoyl moieties at different degrees of modification, χ **[7]**. Because the pattern of the substitutions on the polymers is not known and a tendency for the hydrophobic modifications to form clusters has been proposed, simulations were performed both with the modified monomers evenly spaced and clustered in small blocks of four.

In the simulations, the network structure is found to depend both on the type and the pattern of modification, changing from a network with a homogeneous distribution of chitosan chains to a heterogeneous structure with hydrophobic-rich clusters, which are connected by polymer strands and large pores. For the smaller acetyl modifications, the network remains homogeneous for both modification patterns the whole χ range up to $\chi = 50\%$ **(Fig. 2b and c)**. For butanoyl modified chitosan, a cluster-pore topology forms at high χ **(Fig. 2e)** while the onset of the transition depends markedly on the modification pattern, beginning at lower χ for block wise modifications.

Next, the diffusion through these network structures has been studied for two specific model drugs, doxorubicin (DOX) and gemcitabine (GEM) **(Fig. 2a)**, which were coarse grained using the same protocol. In all cases, GEM, which is small and hydrophilic, is only minimally slowed down by the interaction with the chitosan network. The diffusion of DOX molecules, which are larger and more hydrophobic, on the other hand, is significantly affected by interactions with the network. Interestingly, opposing trends for the diffusion coefficients with χ are found for acetyl and butanoyl modifications: diffusion decreases with increasing degree of acetylation, but notably increases with the degree of butanoyl modification.

These opposing trends for the different modifications result from the interplay of two mechanisms (i) hydrophobic interactions of DOX with the modifications and (ii) the changing network morphology: In acetylated-chitosan the network structure and pore sizes remain almost constant, so that the decrease in the diffusion is governed by the increasing number of hydrophobic interactions. In the butanoyl-chitosan networks the clusters and large pores **(Fig. 2e)** formed at high χ facilitate the motion of the molecules through the network and at the same time reduce hydrophobic contacts, as the modifications are wrapped by the hydrophilic backbone. Finally, for the diffusion of both drug molecules together, the diffusion trends are rather different than for the single drugs. The diffusion of DOX

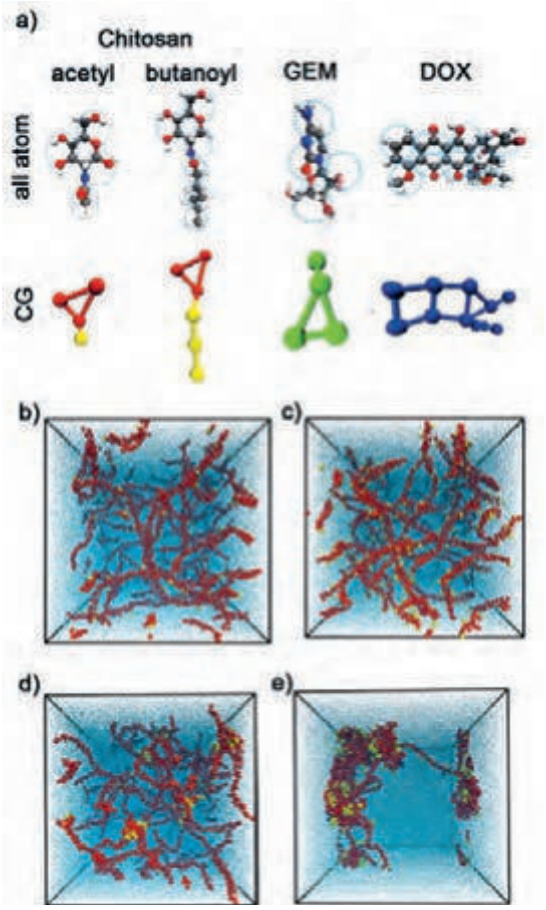

Fig. 2: Diffusion of drug molecules through chitosan networks; (a) CG mapping of acetylated and buanoated chitosan monomers, DOX and GEM; (b)-(e) chitosan hydrogels with blocky modification pattern for (a) 16% acetylation, (b) 50% acetylation, (c) 16 % butanoation, and (d) 32% butanoation.

is now almost constant across the entire range of χ for both acetyl- and butanoyl-chitosan, whereas the diffusion of GEM depends on the network indicating that drug-drug interactions can significantly affect their interactions with the network and drug release from the hydrogel.

A. Grafmüller, V. Satarifard, A. Singhal, S. Wagle, T. Irmscher
gmueller@mpikg.mpg.de

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High-Fidelity Biomolecular Modelling

Markus Miettinen
21.11.1977
1997–2004: Master of Science (with distinction) in Bioinformation Technology (Helsinki University of Technology, Helsinki, Finland)
2005–2010: Doctor of Science in Theoretical and Computational Physics (Aalto University, Helsinki, Finland)
2005: Finnish Academy of Science and Letters Doctoral Fellow
2010–2012: Postdoctoral Scientist, Institute for Biology and Biochemistry, Potsdam University, Germany
2011–2012: EMBO Long-Term Fellow
2012–2016: Postdoctoral Scientist, Department of Physics, Free University Berlin, Berlin, Germany
2012–2015: VolkswagenStiftung Post-Doctoral Fellow
2016–2017: Postdoctoral Scientist, Department of Theory and Bio-Systems, Max Planck Institute of Colloids and Interfaces
Since 4/2017: Research Group Leader, Department of Theory and Bio-Systems, Max Planck Institute of Colloids and Interfaces

Many interesting molecular systems from chemistry, physics, and biology can be considered to be classical many-body systems. To describe their behaviour, no quantum mechanics is needed, but atoms and chemical bonds can be treated as objects of classical mechanics. In molecular dynamics (MD) simulations, the equations of motion governing the time evolution of such systems are solved numerically. The ever-continuing exponential growth in computing power has made MD a tool that, at its best, provides impressive 3D videos on the spatial and temporal functioning of biomolecules, facilitating discoveries such as the Tamiflu drug resistance of the H1N1 Swine Flu.

However, the usefulness of MD fully depends on the fidelity of the classical approximation, i.e., the underlying 'force field'. To this end, our group strives towards the ideal of truly faithful biomolecular MD, in which the positions and movements of atoms match reality as precisely as the most structurally-sensitive experimental methods (NMR spectroscopy and scattering) can measure. The critical assessment of MD against these experiments is crucial: It not only reveals the limits of applicability of our current force fields, but the critically vetted MD provides the best available intuitive interpretation of these typically hard to interpret experimental data. These themes we approach via three topics: 1) by an open science collaboration focused on lipid force fields (with O. H. S. Ollila, Uni. Helsinki, and the NMRlipids community of researchers worldwide), 2) by automatic data-driven calibration of biomolecular force fields, and 3) by calculation of nanoscale stress distributions across biomolecular systems from MD data (with R. Lipowsky).

NMRlipids – Open Collaboration to Understand Lipid Systems at Atomistic Resolution

Force field development is slowed down as long as only large research groups can afford to do it. To improve this situation, we borrow solutions from the highly successful open-source software community. Open online collaboration allows everyone in the field to participate, and the accuracy necessary for genuinely predictive force fields will be reached faster. In 2013, we (together with O. H. S. Ollila) founded NMRlipids, an open scientific collaboration project to understand the atomistic resolution structures of lipid systems by critically comparing MD to (mostly NMR) experimental data. The project is progressed through posts and comments in an open blog (nmrlipids.blogspot.fi) and on GitHub. The main results are also published in traditional peer reviewed scientific journals **[1–3]**; the list of authors is alphabetical. First, we tested 13 commonly used atomistic force fields, and found that the structure of the water-facing surface of phosphatidylcholine (PC) lipid membranes is incorrect in all of them **[1]**. We then demonstrated that one can directly compare ion binding affinities between MD and experiments via changes in the choline headgroup order parameters; and that sodium does not specifically bind to PC at sub-molar concentrations, despite the strong binding erroneously predicted by several force fields **[2]**. Moving to the phosphatidylserine (PS) lipids, we showed that all current force fields fail to capture the PS headgroup structure **(Fig. 1)**, and that their ion binding behaviour is qualitatively wrong **[3]**. Importantly, the NMRlipids project has collected and made available the largest open repository of MD trajectories in existence (zenodo.org/communities/nmrlipids), which can be used, e.g., for data mining, or as a training set for machine learning efforts.

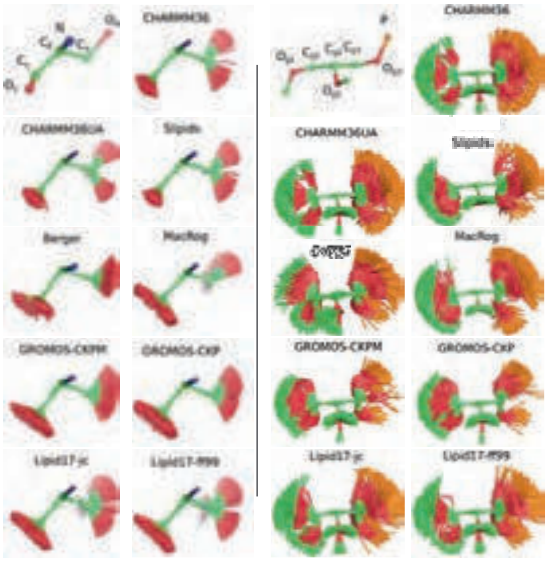

*Fig. 1: Overlayed snapshots of glycerol backbone (left) and PS headgroup (right) structures in different force fields **[3]**.*

Data-driven Calibration of Biomolecular Force Fields

As mentioned, all the current force fields are somewhat flawed **[1]**. Their improvement is held back by the obvious complexity of the problem of describing an inherently quantum system with classical mechanics; but also by old-fashioned approaches taken to tackle the problem, such as fine-tuning individual parameters based on chemical intuition. We work to harness powerful high-throughput approaches used in the field of Big Data to push MD towards realistic atomistic resolution. Our proof-of-concept application is lipids, however, we aim at an approach generalisable to any biomolecule. Our calibration tool is based on a combination of an evolutionary algorithm (covariance matrix adaptation evolution strategy) and an atomic-resolution experimental dataset (C-H order parameters measured with solid state NMR), see **Fig. 2A**. At each optimisation round ('generation'), a set of candidate solutions, each with their specific force field parameters (playing the role of 'genes'), are evaluated based on their ability to replicate the experimental data ('fitness'). As only the fittest candidates produce offspring, thus passing their (possibly mutated) genes on to the next generation, the population fitness on average improves. **Fig. 2B** demonstrates that we were able to improve one of the best existing lipid force fields, CHARMM36. Further refinement of our algorithm is currently ongoing to improve its usability. However, preliminary data indicate that our approach is capable of creating a force field that correctly reproduces the conformational ensemble of lipid bilayers.

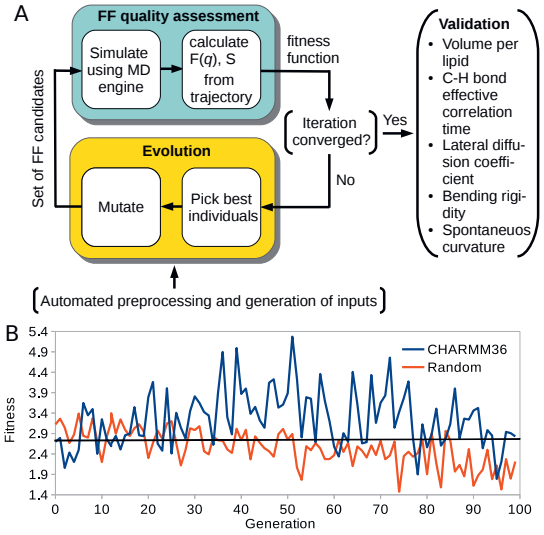

Fig. 2. A) Schematic of an evolutionary algorithm applied to optimization of lipid force fields. B) 100 generations of optimization, starting from the best available force field, CHARMM36. Evolutionary optimization of dihedral parameters improved the ability to describe the target data both when started from the original (blue) and random (red) dihedral parameters. Original parameters are clearly in a local minimum of the optimization landscape, from which one had to escape before improvement was possible.

Mechanical Stress at the Nanoscale

Local pressure – or stress – can be an excellent conceptual tool to understand and explain the behaviour and properties of biomolecular systems at nanoscale. Indeed, the local stress field is intimately connected to properties and concepts from elasticity theory, such as spontaneous curvature and bending rigidity. These provide both an intuitive understanding and a quantitative description of morphological events seen in living cells, such as vesicle formation, budding, and the shape a membrane adopts under given external conditions. In our group, we have used this connection to identify the natural state of compositionally asymmetric lipid membranes **[4]**, and to quantify the curvature generation of the glycolipid GM1 in phospholipid membranes **(Fig. 3)**.

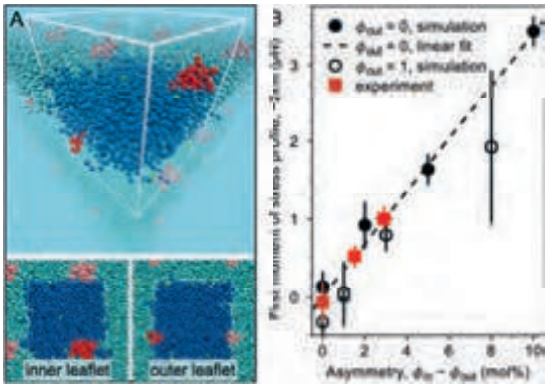

Fig. 3: A) Simulation snapshot of a large-headed GM1 lipid (red) embedded in a bilayer on small-headed POPC lipids (blue); light colours indicate periodic images. B) When plotted as a function of bilayer asymmetry, the calculated first moment of the lateral stress profile (black) matched the corresponding experimental measurement (red) quantitatively. ***[5]***

Intriguingly, however, the local stress itself remains a debated concept, and mutually contradictory approaches have been used on defining and calculating it. The most common definition (originally introduced by Irving and Kirkwood, and properly formalised by Schofield and Henderson) defines the local stress as a differential equation based on atom trajectories. This differential equation, however, lacks fundamental additional information, and its solution is thus not uniquely defined. Over the years, many solutions have been published, providing, however, only limited insight into the underlying conceptual issues. In our ongoing work, we have been able to connect the change in internal energy of a system due to a deformation with the solution of the said differential equation in such a way that the non-uniqueness does not manifest itself. Interestingly, a part of our solution indeed produces an entity resembling the Cauchy stress tensor of elasticity theory for very large systems. In addition, we have devised an algorithm to extract the elastic properties of any MD system, such as the bending rigidity and spontaneous curvature of biomembranes.

M. Miettinen, H. Antila, O. Schullian
Markus.Miettinen@mpikg.mpg.de

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Protein Synthesis in the Cell

Sophia Rudorf
12.02.1985
2004–2009: Diploma, Physics (University of Potsdam/LMU Munich); Thesis: Investigation of the Self Assembly of Monomolecular DNA-Lipid Complexes
2010–2015: PhD, Physics (MPI of Colloids and Interfaces); Thesis: Protein Synthesis By Ribosomes
Since 2015: Research Group Leader, Department of Theory and Bio-Systems, Max Planck Institute of Colloids and Interfaces

The synthesis of proteins is a fundamental task of all living cells because almost every cellular process is governed by proteins. To synthesize a protein, molecular machines called ribosomes use the genetic information stored in messenger RNAs (mRNAs). A mRNA consists of a sequence of codons, each of which codes for a specific amino acid. The ribosome reads the mRNA codon by codon and takes up the corresponding transfer RNAs (tRNAs) that carry the amino acids. This process is called translation. Our group studies translation at different levels from individual biochemical kinetic rates to cell-wide protein synthesis.

Inhibition of Protein Synthesis

The bacterial doc-phd toxin-antitoxin system has a strong influence on the rate of cell growth. The toxic protein Doc suppresses the growth rate by inhibiting the elongation factor EF-Tu, which is crucial for bacterial translation, see **Fig. 1**. Given that EF-Tu is one of the most abundant proteins in bacteria, it is astonishing that Doc is such an effective toxin. To find the origin of the high Doc efficiency, we study the effect of EF-Tu inhibition on protein synthesis within a recently established theoretical framework for bacterial translation **[1, 2]**. Surprisingly, we find a very sensitive dependence of the overall translation rate on EF-Tu abundance: a small decrease in EF-Tu concentration leads to a strong suppression of overall protein synthesis, despite the extremely high cellular abundance of the elongation factor **[3]**. We show that this ultrasensitivity is caused by imbalances in the interplay of different codons and tRNAs and can be observed for complex *in-vivo* protein synthesis as well as in simple artificial translation systems based on only two codons and their cognate tRNAs. Thus, the abundance of EF-Tu is a highly effective control variable for bacterial protein synthesis whereby the growth-inhibiting effect of Doc is strongly amplified.

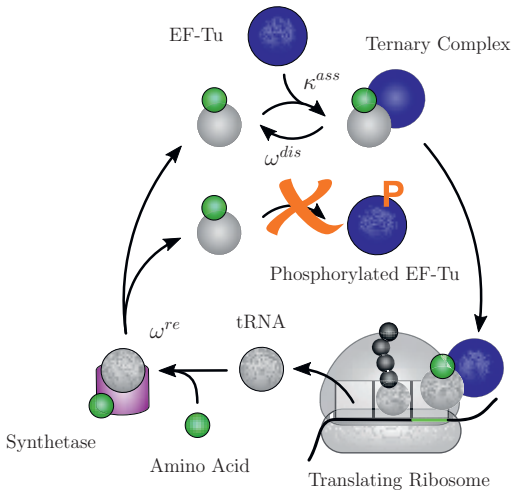


Fig. 1: After a tRNA is released from a ribosome, it binds to an aminoacyl tRNA synthetase that recharges the tRNA with its cognate amino acid. The recharged tRNA binds to elongation factor EF-Tu to form a ternary complex that delivers its amino acid to a translating ribosome (upper pathway). Translation may get inhibited in multiple ways by enzymes or antibiotics. For example, the toxin Doc phosphorylates EF-Tu molecules, which are then no longer able to bind aminoacylated tRNAs (lower pathway).

Position-dependent Translation Rates

During translation, the elongating nascent peptide chains traverse the ribosomes' exit tunnels. In collaboration with the department of Prof. Dr. Marina Rodnina from the Max Planck Institute for Biophysical Chemistry, we applied the stopped-flow method to monitor this co-translational movement via fluorescent probes attached to the N-termini of the nascent chains, see **Fig. 2**.

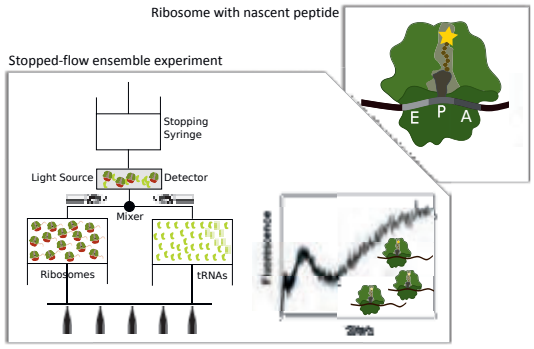
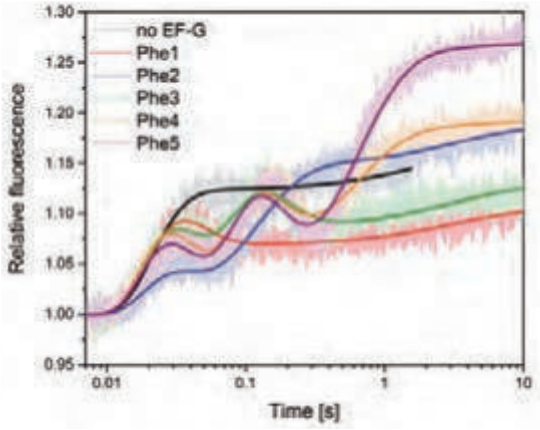


Fig. 2: Schematic drawing of a stopped-flow instrument to study translation by fluorescent probes. The syringe on the left is filled with a mixture of ribosomes and mRNAs, whereas the right syringe contains the tRNAs. Translation begins when both solutions are mixed. Progression of translation is monitored by a fluorescent signal emitted by fluorophores (yellow stars) attached to the N-termini of the elongating peptides. ***[4]***

Due to fluorophore quenching, the time-dependent fluorescence signal emitted by an individual peptide is determined by co-translational events, such as secondary structure formation and peptide-tunnel interactions. To obtain information on these individual events, the measured total fluorescence signal has to be decomposed into position-dependent intensities. To this end, we describe mRNA translation as a Markov process and assign a specific fluorescence intensity to each ribosomal state. **Fig. 3** shows measured time-dependent total fluorescence intensities for poly-phenylalanine peptides of different lengths in comparison to numerical results obtained by the evaluation of our model. Due to the complexity of the translation process and the resulting high dimensionality of the Markov model's parameter space, we apply model reduction and regularization methods to avoid overfitting and obtain non-ambiguous kinetic information about the process. Our final theoretical description provides a good representation of the biological process. We find that the N-terminus of poly-phenylalanine experiences major environmental changes, which occur primarily during early translation (first couple of amino acids). Surprisingly, our analysis revealed that codons at the 4th position are translated at a much slower rate than preceding or subsequent codons, see **Fig. 3 [4]**.



Codon Position	Translation rate $[s^{-1}]$
1^{st}	28 ± 3
2^{nd}	9 ± 0.5
3^{rd}	20 ± 2
4^{th}	2 ± 0.1
5^{th}	13 ± 1

Fig. 3: Fluorescence signal of poly-phenylalanine translation (transparent lines) obtained by stopped-flow experiments and signal as determined by our translation model (solid lines). Model fitting revealed a dramatic slow-down of translation at the 4th codon. ***[4]***

Complex Assembly of Protein Subunits

Organization, efficiency, and control of protein assembly from multiple subunits are subject of ongoing research. In collaboration with Roy Bar-Ziv and his group from the Weizmann Institute of Science in Israel, we study protein complex assembly by *in-vitro* translation experiments and computer simulations to assess the impact of various parameters of the assembly process on its dynamics. Our collaborators established a method for cell-free protein synthesis on biochips (Heyman et al, Nature Nanotechnology 2012). We analyze the experimental data using a Markov model including peptide synthesis, subunit assembly, and protein subunit and complex diffusion. With our model, we can evaluate for example how the positioning of the translation sites and the synthesis rates of the different protein subunits influences the assembly complex. We found that both parameters modulate the spatial distribution of the complexes on the biochip in a non-trivial manner, see **Fig. 4**.

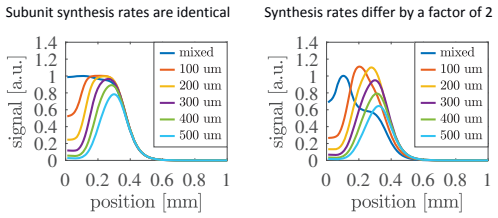


Fig. 4: The spatial distribution of protein complexes in a biochip of 1 mm length depends on the distance between the translation sites (see plot legends), and the synthesis rates of the subunits.

Furthermore, we developed an adapted version of our model to study post- and co-translational assembly processes *in vivo* in collaboration with the group of Günter Kramer (DKFZ/University of Heidelberg). In contrast to the widely accepted view that protein assembly is a post-translational process, recent experiments by our collaborators show that protein complexes can also assemble co-translationally, i.e., subunits may assemble *before* translation has finished (Yu-Wei Shieh et al., Science 2015). Our theory predicts that the dominance of co-translational assembly is a function of time and depends on the distance of the translation sites as well as on the protein subunit stabilities, see **Fig. 5**.

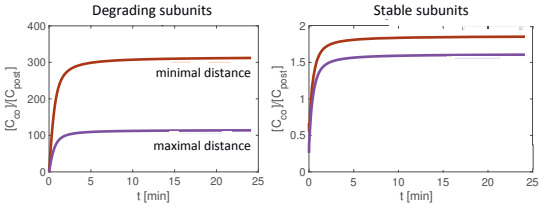


Fig. 5: Ratio of concentrations of co- and post-translationally assembled protein complexes as a function of time after start of synthesis. This ratio depends on subunit stability (left: low, right: high) and the distance of the translation sites (brown lines: overlapping, purple lines: maximally separated).

Optimization of Protein Translation Dynamics

Optimizing protein translation for synthetic gene expression is a complex task. In contrast to conventional approaches based on codon usages, we predict optimal sequences mainly based on translation speed and accuracy and confirm our optimization approach with proteome data from widely used prokaryotic, eukaryotic, and human expression systems **[5]**. We optimized and tested heterologous expression of two genes, *manA* and *ova* in *Salmonella Enterica serovar Typhimurium*, which showed a threefold increase in protein yield compared both to wild-type and commercially optimized sequences. Our multi-parameter algorithm cannot only be used for protein yield optimization but also for example to engineer attenuated viruses.

S. Rudorf, S. Förste, N. Haase
sophia.rudorf@mpikg.mpg.de

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BIOMOLECULAR PROCESSES

Data Analysis and RNA Biology

Angelo Valleriani
14.03.1966
1992: Diploma, Physics (University of Bologna)
Thesis: Conformal Invariance, Re normalization Group and Integrable Models in Two-Dimensional Quantum Field Theories
1996: PhD, High-Energy Physics (SISSA-ISAS, Trieste)
Thesis: Form Factors and Correlation Functions
1996–1998: Postdoc (Max Planck Institute for the Physics of Complex Systems, Dresden)
1998–2000: Postdoc (Max Planck Institute of Colloids and Interfaces, Potsdam)
Since 2000: Group Leader and IMPRS Coordinator, (Max Planck Institute of Colloids and Interfaces, Potsdam)

The group Stochastic Models in Complex and Biological Systems develops methods and models to study a variety of complex systems and performs analyses of experimental data. Examples include the random distribution of nuclei in cells **[1]**, protein and mRNA synthesis in yeast **[2]**, AFM data **[3]**, and the kinetics of viral/cell interaction **[4]**. The research of the group focuses on a set of topics that are in continuous development as summarized in the following.

Ageing and Degradation of Biological Macromolecules

The life of biological molecules is often determined by random encounters with other molecules. For instance, the messenger RNA (mRNA) in animal cells may get recruited by short RNA molecules called microRNA (miRNA), which then may either recruit some enzyme responsible for degradation or silence the mRNA and thus stabilize it **[5]**. To give another example, newly synthesized proteins may get incorporated into a larger protein complex thereby becoming stabilized or they may remain in the cell body as single molecules until some degradation enzyme starts their degradation **[6]**.

The different fates of molecules of the same species are expressed by the fact that the lifetime of such molecules is random. This randomness can be described via a probability distribution which is, in principle, specific for each species of mRNA or each species of protein.

Every time a molecule of interest, say a mRNA, interacts with another molecule in the cell, this interaction can make the degradation of the mRNA in the next units of time more or less likely. We would then say that the rate of degradation changes as a consequence of these encounters. These encounters can be considered as a new biochemical state for the mRNA and in general they tend to change the life expectancy of the molecule with its age. We will say that the molecule ages.

Ageing is related to the probability distribution of the lifetime. It is a well-known fact in probability theory that when the lifetime distribution is exponential there is no ageing. This is known as the memoryless property of the exponential distribution. When instead the lifetime probability is non-exponential ageing is taking place. Understanding the nature of the lifetime distribution means therefore to uncover the biochemical mechanisms of ageing and thus understanding the biochemistry of degradation. From the theoretical and mathematical point of view, one can provide a self-consistent description of the distribution of the number of molecules under a variety of general conditions **[7]**. Experimentally, however, only the average number of target molecules is observable. This kind of observation, which is based on degradation assays, provides data about the decay of the average number of molecules in time. We have shown that the average number of molecules decreases with time as

$$M(\Delta t \mid t_p) = \frac{\int_{\Delta t}^{\Delta t + t_p} (1\text{-}F(x))\,dx}{\int_0^{t_p} (1\text{-}F(x))\,dx} \qquad (1)$$

where *1-F(x)* is the survival probability until age *x*, t_p is the duration of pulse (or labelling) of the target molecule and Δt is the time of measurement after the pulse **[7]**. The analysis of these decay patterns requires special tools that make use of Markov chains to provide a mathematical basis for the lifetime probability function *F(x)* **[8]**. An example for the application of this method is provided in **Fig. 1**.

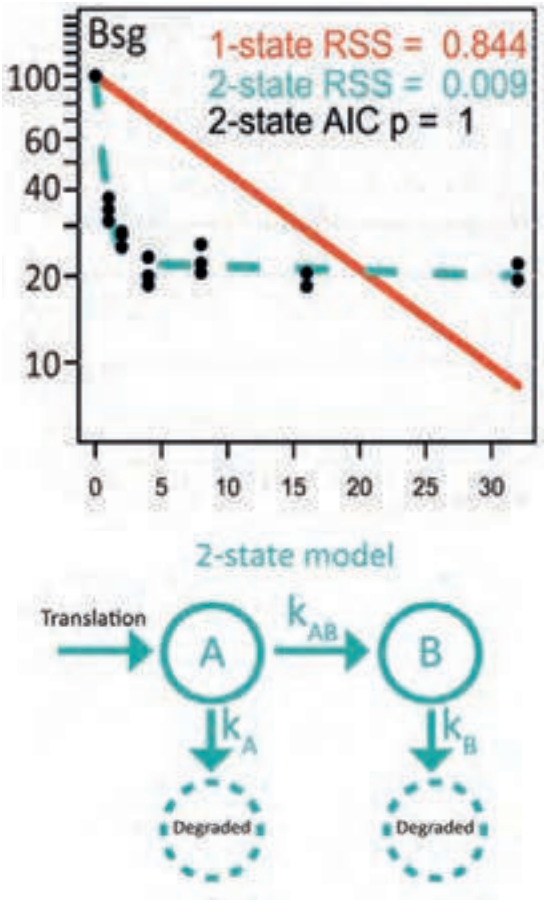

*Fig. 1: Analysis of protein decay **[6]**.*

There, in the upper plot, the dots are the experimental data for the decay of one exemplary protein in mice cells. The naïve exponential fit (red line) does a poor job to fit the data. The non-exponential fit with Eq. (1) instead works much better. The probability function is provided by the simple two-state Markov chain model shown in **Fig. 1** (bottom). In this model, the random time to go from state A to the degradation state represents the random lifetime of one molecule. The plot on the top of **Fig. 1** indicates that the proteins decay rate changes with the age of the protein. In fact, it indicates that the age-dependent degradation rate decreases to a constant as the molecule ages. This is probably due to the fact that at their early stage of life, proteins not yet included into a complex (in state A) are particularly easy targets of the degradation enzymes. In contrast, when proteins are included into the complex (in state B) they are protected and thus get stabilized.

Translational Control and Ribo-seq Data

Ribosomes initiate translation at the 5′ end (called 5′ UTR) of the mRNA. After encountering the start codon, they read the mRNA one codon per step and incorporate the amino acid encoded by that codon to elongate the peptide and eventually form the final protein **Fig. 2**. The ribosomes are complex molecular machines that visit a large set of biochemical and conformational states before making each step of translation.

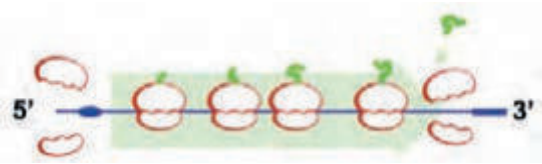

Fig. 2: A cartoon of translation. The ribosome starts at the 5′ UTR and moves left to right. Several ribosomes may translate the same mRNA molecule at the same time. When the ribosome reaches the 3′ end of the mRNA it disassembles and releases the protein in the cell.

This process is dominated by the availability of other molecules such as tRNA and elongation factors and it is subject to thermal fluctuations as well. Therefore, the peptide elongation rate is a stochastic process.

Fig. 3: Ribo-seq coverage profile for one specific mRNA made in 9 different and independent laboratories (from D. Chiarugi and A. Valleriani, in preparation).

As a consequence of the stochasticity of elongation, the speed of the ribosomes along the mRNA can change and may depend on the local features of the mRNA sequence. One powerful experimental method to investigate these changes in the elongation rate is the Ribo-seq method, which has been successfully applied to understand several aspects of translational control in E. coli **[9]**.

The Ribo-seq method allows extracting a picture of where the ribosomes are slower and faster along each specific mRNA, **Fig. 3**. There, we see that the Ribo-seq coverage of the same mRNA performed by 9 independent laboratories provides a clear picture of the strong variations of ribosome velocity along the mRNA as well as a clear evidence of the variation of the profiles across independent laboratories. A detailed statistical analysis of the reproducibility and reliability of the profile coverages is currently under preparation in a collaboration project with D. Chiarugi (Cambridge).

Despite the large variations in the coverage profile, it is still possible to investigate general properties of translating ribosomes by merging together the profiles of all genes in a given study. To this purpose, it is possible to see that one of the stochastic events in the elongation process is constituted by ribosome drop-off, namely a non-specific premature termination of translation.

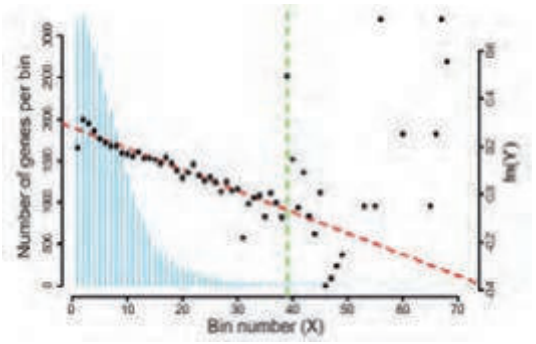

Fig. 4: Binned Ribo-seq data after merging the profiles from all genes in E. coli. One bin is 100 nucleotides. The slope of the red dotted line is 1.7×10^{-4} per codon **[10]**.

In **Fig. 4** the density of ribosomes decreases exponentially from left to right with a rate equal to the rate of ribosome drop-off. Investigation of this phenomenon on various other datasets revealed that the rate of drop-off depends on the growth conditions: under acute stress or starvation the rate of drop-off becomes particularly large. This indicates that bacteria tend to respond to stress by reducing the translation apparatus **[9, 10]**.

A. Valleriani
angelo.valleriani@mpikg.mpg.de

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Protein Binding and Membrane Adhesion

Thomas Weikl
01.04.1970
1996: Diploma, Physics
(Freie Universität Berlin)
Thesis: Interactions of rigid membrane inclusions
1999: PhD, Physics
(Max Planck Institute of Colloids and Interfaces, Potsdam)
Thesis: Adhesion of multicomponent membranes
2000–2002: Postdoc
(University of California, San Francisco)
Since 2002: Group Leader
(Max Planck Institute of Colloids and Interfaces, Potsdam)
2008: Habilitation, Physics
(University Potsdam)
Thesis: Transition states and loop closure principles in protein folding

Cooperative Binding of Proteins in Membrane Adhesion

Membrane-anchored receptor and ligand proteins can bind only if the membrane separation l at the site of the proteins is within an appropriate range. The binding constant of the receptors and ligands thus depends on the local separation l of the membranes, which varies along the membranes and in time because of thermally excited membrane shape fluctuations. Measurements of binding constants imply averages in space and time and therefore lead to an average binding constant K_{2D} = [RL]/[R][L], where [RL] is the average area concentration of bound receptor-ligand complexes, and [R] and [L] are the average area concentration of unbound receptors R and ligands L in the adhesion zone. Our simulations and theories indicate that this average binding constant can be understood as **[1, 2]**

$$K_{2D} = \int K_{2D}(l) P(l)\, dl \qquad (1)$$

where $K_{2D}(l)$ is the binding equilibrium constant as a function of the local membrane separation l, and P(l) is the distribution of local membrane separations that reflects the spatial and temporal variations of l. This general theory for K_{2D} implies cooperative binding: The initial binding of receptors and ligands smoothens the membranes and brings the membranes separation closer to the preferred separation of the receptors and ligands for binding, which both facilitates the formation of additional receptor-ligand complexes.

Our recent experiments and modeling of the binding of the "marker of self" protein CD47 to its binding partner SIRPα confirm the cooperative binding of membrane-anchored proteins **[1]**. In the experiments, CD47 anchored to giant vesicles generated from plasma membranes binds to SIRPα immobilized on a surface. In our multi-scale modeling approach, we have combined (i) simulations of the coarse-grained CD47-SIRPα

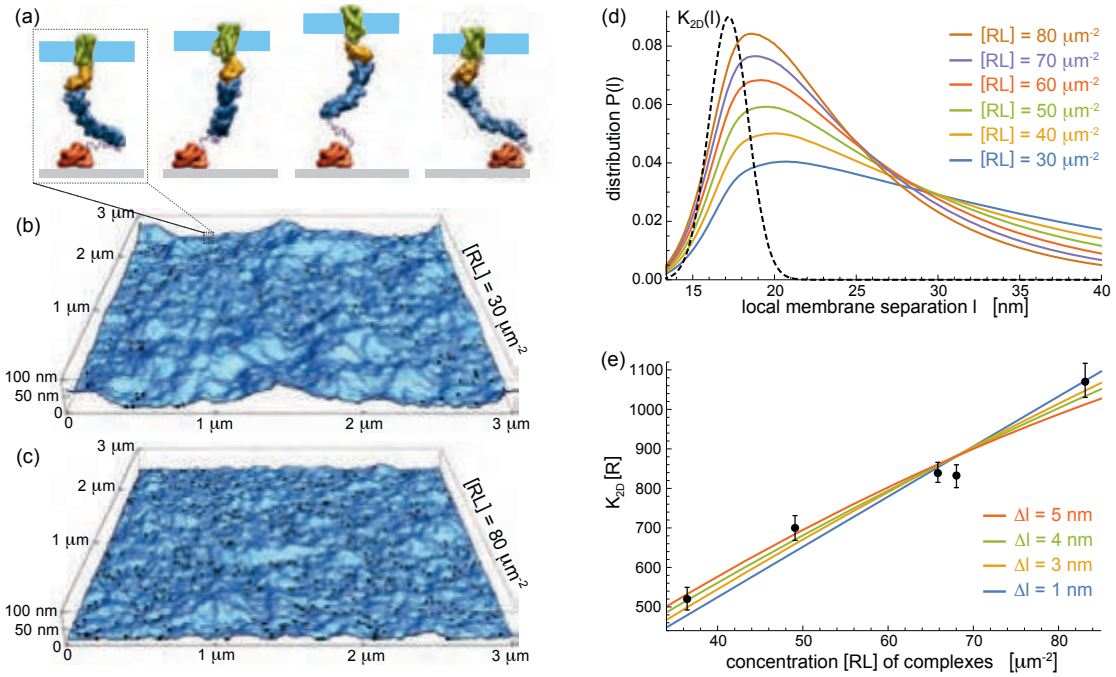

*Fig. 1: Multiscale modeling of CD47-SIRPα binding and comparison to experimental data **[1]**: (a) Snapshots from coarse-grained molecular simulations of a CD47-SIRPα complex. The separation between the membrane patch (light blue) and the substrate (grey) varies in the simulations mainly due to conformational changes of the unstructured linker that covalently connects SIRPα (blue) to substrate-bound GST (red). (b) and (c) Snapshots from simulations of adhering membrane segments with area 3×3 μm² for the concentrations [RL] = 30 μm⁻² and 80 μm⁻² of CD47- SIRPα complexes at the parameter value Δl = 4 nm of the repulsive membrane-substrate interactions. The repulsive interactions between the protein layer on the substrate and the membrane are taken into account by allowing only local separations $l > l_0 - \Delta l$ between the membrane patches and the substrate where l_0 is the preferred separation for binding. Each complex is represented by a black dot. The positions of the complexes are varied in the simulations. (d) Distributions P(l) of the local separation between membrane and substrate obtained from averaging over many membrane snapshots for Δl = 4 nm at various complex concentrations [RL]. The dashed black line represents the function $K_{2D}(l)$ (arbitrary units). (e) Binding constant K_{2D} as a function of complex concentration [RL] from experiments (data points) and modeling (lines) for different parameter values Δl of the repulsive membrane-substrate interactions. The modeling is based on Eq. (1) with $K_{2D}(l) = K_{max} \exp[-(l-l_0)^2/\sigma^2]$ and the fit values K_{max} = (956±24)/[R], (470±10)/[R], (378±8)/[R], and (326±8)/[R] for Δl = 1 nm, 3 nm, 4 nm, and 5 nm, respectively. The preferred separation l_0 =17.2 nm for binding and the standard deviation σ = 1.2 nm of $K_{2D}(l)$ are obtained from the coarse-grained molecular simulations in (a). The binding constant K_{2D} is given in units of the concentration [R] of unbound SIRPα. The effective spring constant of the bound complexes in (b) and (c) is $k_B T/\sigma^2$.*

complex (see **Fig. 1(a)**) to gain insights on $K_{2D}(l)$ and the effective spring constant of the complex, and (ii) simulations of large membrane segments adhering via CD47-SIRPα complexes, modeled as elastic springs (see **Fig. 1(b) and (c)**), to determine the distribution P(l) of local membrane separations.

The binding constant K_{2D} obtained from the experiments and multi-scale modeling increases with the bond concentration [RL] (see **Fig. 1(e)**), because the distributions P(l) narrow and shift towards the preferred binding separation l_0 with increasing [RL] (see **Fig. 1(d)**). The modeling results are in good agreement with the experimental data points for different values of the parameter Δl for the repulsive interactions between the membrane and the protein layer on the substrate (see **Fig. 1(e)**). We use a range of Δl values in the modeling because the thickness of the protein layer on the substrate is not precisely known. The strong increase of K_{2D} with [RL] reflects cooperative binding of CD47 and SIRPα. The binding cooperativity is mediated by membrane shape fluctuations, which are constrained by bound receptor-ligand complexes.

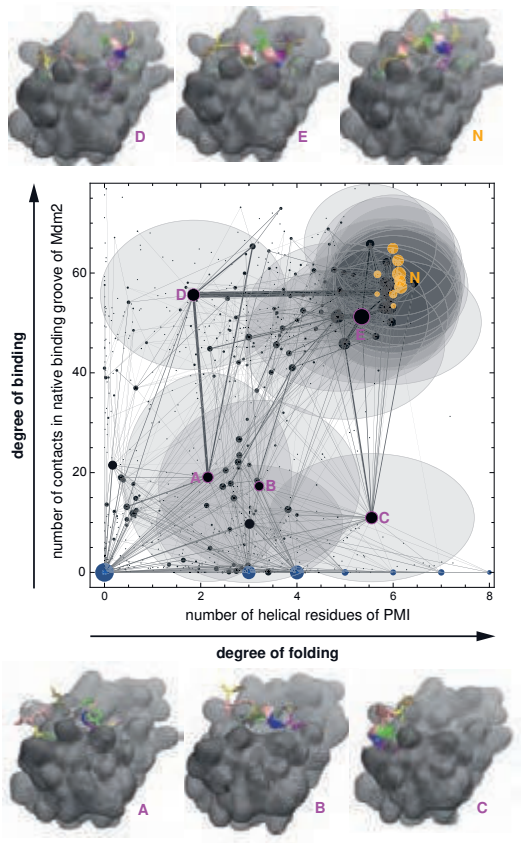

*Fig. 2: Two-dimensional representation of the reactive flux for the folding of PMI during binding to Mdm2 obtained in our Markov state modeling of atomistic simulations **[8]**. Each Markov state is represented by a disk with an area that is proportional to the reactive flux through the microstate. Unbound Markov states are shown in blue, and native-like bound Markov states in yellow. In this two-dimensional representation, the Markov states are positioned according to their average degrees of folding and binding. The degree of folding is quantified by the number of helical residues, and the degree of binding by the number of non-hydrogen-atom contacts of PMI with residues in the native Mdm2 binding groove. The gray ellipses represent the standard deviations of these degrees of folding and binding for the 25 Markov states with the largest reactive flux. The width of the lines that connect Markov states is proportional to the reactive flux between the states. In the structural representations of the selected six Markov states A, B, C, D, E, N with high reactive flux, a "main representant" that is closest to the average PMI coordinates of the Markov states is shown in color. In addition to the main representant, a cloud of 50 random PMI conformations is represented as gray thin curves with semitransparent spheres at the termini.*

Cooperative Adsorption of Nanoparticles to Membranes

Membrane-mediated cooperativity also arises in the adsorption of nanoparticles to membranes **[3, 4, 5, 6]**. The cooperativity results from attractive curvature-mediated interactions of the particles, which induce membrane curvature during adsorption. In general, indirect membrane-mediated interactions of proteins or particles can arise from local changes in the membrane curvature or fluctuations induced by the proteins or particles **[2]**.

Conformational Changes During Protein Binding

Unstructured proteins and peptides typically fold during binding to ligand proteins. A challenging problem is to identify the mechanism and kinetics of these binding-induced folding processes in experiments and atomistic simulations. Two mechanisms for the coupling of folding and binding are 'conformational selection' and 'induced fit'. In an induced-fit mechanism, folding occurs after binding and is apparently 'induced' by the binding process. In conformational selection, folding occurs prior to binding: the metastable folded state appears to be 'selected' for binding, and is stabilized in the bound complex.

The inhibitor peptide PMI folds into a helix during binding to the oncoprotein Mdm2. Our atomistic simulations and Markov state modeling **[7, 8]** indicate that the binding-induced folding of PMI is highly parallel and can occur along a multitude of pathways (see **Fig. 2**). Some pathways are induced-fit-like with binding occurring prior to PMI helix formation, while other pathways are conformational-selection-like with binding after helix formation. On the majority of pathways, however, binding is intricately coupled to folding, without clear temporal ordering. Overall, binding-induced folding of PMI does not fit into the classical picture of induced fit or conformational selection that implies a clear temporal ordering of binding and folding events. We have argued that this holds in general for binding-induced folding processes because binding and folding events in these processes likely occur on similar timescales and do exhibit the time-scale separation required for temporal ordering **[8]**.

T. Weikl, F. Bonazzi, B. Kav, P. R. Pandey, F. Paul, K. Ziolkowska
thomas.weikl@mpikg.mpg.de

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Morphological Complexity of Biomembranes

Reinhard Lipowsky
11.11.1953
1978: Diploma, Physics, (University of Heidelberg)
1982: PhD (Dr. rer. nat.), Physics (University of Munich)
1979-1984: Teaching Associate (University of Munich)
1984-1986: Research Associate (Cornell University)
1986-1988: Group leader (FZ Jülich)
1987: Habilitation, Theoretical Physics (University of Munich)
Thesis: Critical behavior of interfaces: Wetting, surface melting and related phenomena
1989-1990: Associate Professorship (University of Munich)
1990-1993: Full Professorship (University of Cologne), Director of the Division "Theory II" (FZ Jülich)
Since Nov 1993: Director (Max Planck Institute of Colloids and Interfaces, Potsdam)

Biomembranes consist of molecular bilayers with many lipid and protein components that form two-dimensional liquids. Because of their fluidity, the membranes can respond to different environmental cues by changing their local molecular composition as well as their shape and topology. During the last couple of years, we continued to study this morphological complexity in a systematic and quantitative manner, combining analytical theory and molecular simulations with experimental observations.

Curvature-elastic Properties of Tensionless Bilayers

In molecular simulations of bilayer membranes, the simplest geometry is provided by a planar bilayer that spans the simulation box and is subject to periodic boundary conditions. To determine the curvature-elastic properties of such bilayers from simulations, the bilayers have to be prepared in a state of sufficiently low membrane tension. The standard procedure to obtain such a 'tensionless' state is to match the number of membrane molecules with the lateral size of the simulation box. More precisely, one measures the stress profile across the bilayer and computes the bilayer tension by integrating this stress profile over the coordinate perpendicular to the bilayer. The bilayer tension changes sign for a certain lateral size of the simulation box, which defines the tensionless state of the membrane.

The most important curvature-elastic properties of fluid bilayers are their bending rigidity and their preferred or spontaneous curvature. We have recently determined both properties for bilayers with two lipid components, which differ in the size of their head groups. **[1]** The bending rigidity was found to depend on the lipid composition in a nonmonotonic manner whereas the spontaneous curvature showed a linear dependence on the compositional asymmetry between the two leaflets of the bilayer. The simulations also revealed that the bending rigidity κ can be expressed in terms of the area compress-ibility K_A and the membrane thickness ℓ_{me} via the simple relationship $\kappa = K_A \ell_{me}^2/48$. This latter relation, which we had previously obtained for one-component bilayers, has been criticized by other groups who claimed that the prefactor 1/48 should be replaced by 1/24. However, analyzing the spectrum of the bending undulations, we have now confirmed the factor 1/48 for all lipid compositions of the two-component bilayer. **[1]**

From Tensionless Bilayers to Tensionless Leaflets

Bilayer membranes consist of two leaflets (or monolayers). For the bilayers discussed in the previous paragraph, the lipid molecules did not undergo flip-flops, i.e., they did not move from one leaflet to the other on the time scales of the simulations. As a consequence, each leaflet contained a constant, 'quenched' number of lipids. What happens if one lipid component undergoes frequent flip-flops? It turns out that such flip-flops lead to a relaxed bilayer state in which *both leaflets are tensionless.* **[2]**

The bilayer tension Σ is equal to the sum of the two leaflet tensions, Σ_1 and Σ_2. The relation $\Sigma = \Sigma_1 + \Sigma_2$ implies that $\Sigma_1 = -\Sigma_2$ for vanishing bilayer tension $\Sigma = 0$. Thus, the two leaflet tensions have opposite signs but will, in general, have a nonzero value as long as the lipids do not undergo flip-flops. However, when the bilayer contains at least one lipid species that undergoes frequent flip-flops, a bilayer with vanishing bilayer tension $\Sigma = 0$ attains a relaxed state with vanishing leaflet tensions, $\Sigma_1 = \Sigma_2 = 0$.

A bilayer membrane resembles a thin film with two leaflet-water interfaces. It is intuitively appealing to assume that these two interfaces are governed by two interfacial tensions, Σ_{lw1} and Σ_{lw2}. The latter view implies that different leaflet-water tensions should generate a finite spontaneous curvature. Indeed, the combined interfacial free energy of the two leaflet-water interfaces can be reduced if the bilayer bulges towards the leaflet with the lower leaflet-water tension, thereby decreasing the area of the inter- face with the larger interfacial tension. **[3]** Based on this view, one would also expect that the spontaneous curvature vanishes for $\Sigma_{lw1} = \Sigma_{lw2}$. The latter expectation has been confirmed for the adsorption of small solutes onto the two leaflet-water interfaces. **[4]** However, for multi-component bilayers with a flip-flopping lipid species, the bilayer can aquire a significant spontaneous curvature even in the mechanically relaxed state with $\Sigma_1 = \Sigma_2 = 0$. **[2]**

Morphological Transformations of Spherical Nanovesicles

Lipid bilayers and biomembranes form nanovesicles with a diameter between 20 and 200 nm. Electron microscopy studies have shown that these vesicles can attain both spherical and non- spherical shapes. However, the insight obtained from electron microscopy studies of nanovesicle shapes is quite limited because the corresponding images provide only a single snapshot of each vesicle. In contrast, molecular dynamics simulations can monitor the morphologies of individual nanovesicles as we vary a certain control parameter such as the vesicle volume. Recently, we studied how nanovesicles respond to such changes in their volume. As a result, we found *that spherical nanovesicles can transform into a multitude of nonspherical shapes,* see **Fig. 1. [5]**

In this Figure, we display four spherical nanovesicles that enclose the same volume of water and have been assembled from the same total number N of lipids. However, the four spherical vesicles differ in the lipid numbers, N_1 and N_2, that are placed in their inner and outer leaflets, with $N_1 + N_2 = N$. As a consequence, the two leaflets of the vesicle membrane experience different leaflet tensions, Σ_1 and Σ_2, which act to stretch or compress these leaflets. As we reduce the volume of the spherical vesicles, the compressed leaflets prefer to expand whereas the stretched leaflets prefer to contract. Therefore, the surprising polymorphism displayed in **Fig. 1** arises from small variations of the assembly process.

Stability of Closed Membrane Necks

In **Fig. 1d**, the spherical nanovesicle is transformed into a dumbbell shape consisting of two (punctured) spheres that are connected by a closed membrane neck. Such dumbbell shapes with closed membrane necks are also observed for giant vesicles, i.e., on the scale of many micrometers, see **Fig. 2a**. If the membrane has a uniform composition, such membrane necks are governed by a relatively simple stability relation that can be expressed in terms of the spontaneous curvature m as well as the two radii R_l and R_s of the two spheres (the subscripts l and s stand for 'large' and 'small'). In **Fig. 1d** and **Fig. 2a,** both spheres of the two-sphere shapes have positive mean curvatures $M_l = 1/R_l > 0$ and $M_s = 1/R_s > 0$. In such a situation, the stability relation for the closed membrane neck has the form

$$m \geq \frac{1}{2}\,(M_l + M_s) \equiv M_{\rm ne} \qquad (1)$$

which defines the (effective) curvature $M_{\rm ne} > 0$ of the membrane neck. **[6]**

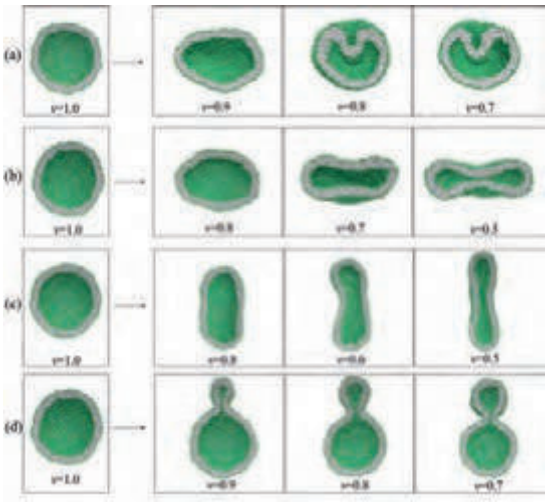

Fig. 1: Morphogical transformations of spherical nanovesicles: Each panel a–d displays a series of shapes that an individual vesicle attains when we decrease its volume v. In all four cases, we start with a spherical vesicle (leftmost snapshot, v = 1) that encloses the same volume of water. In addition, all four spherical vesicles are bounded by a lipid bilayer that is built up from the same total number of lipids but differ in the lipid numbers, that are assembled in their inner and outer leaflets. As a consequence, the spherical vesicles transform into very different shapes as we reduce their volumes to v < 1. **[5]**

Two-sphere shapes as in **Fig. 1d** and **Fig. 2a, d, e** with $M_l > 0$ and $M_s > 0$ can only form for positive spontaneous curvature. For negative spontaneous curvature, on the other hand, one obtains two-sphere shapes with two mean curvatures that have opposite signs, see **Fig. 2b, c**. In these cases, the spherical in-buds have negative mean curvature $M_s = -1/R_s$ and the neck curvature $M_{\rm ne}$ is negative as well.

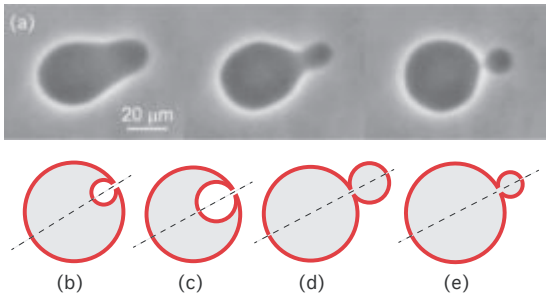

Fig. 2: (a) Giant unilamellar vesicle (GUV) that forms a spherical out-bud as observed by phase contrast microscopy. In the rightmost image, the spherical out-bud and the larger mother vesicle are connected by a closed membrane neck; and (b-e) Budded GUV shapes with closed membrane necks for different spontaneous curvatures, increasing from a large negative value in (b) to a large positive value in (e).

The two-spheres shapes in **Fig. 2** are stable within certain subregions of the twodimensional morphology diagram, which depends on two dimensionless parameters, the volume-to-area ratio v and the rescaled spontaneous curvature $mR_{\rm ve}$ with the vesicle size $R_{\rm ve} \equiv \sqrt{A}\,/(4\pi)$ defined in terms of the membrane area A. The stability regime for (1 + 1)-spheres with positive spontaneous curvature is displayed in **Fig. 3**. Within this stability regime, the geometry of the two-sphere vesicles is solely determined by the dimensionless volume-to-area ratio v. Therefore, the curvature $M_{\rm ne}$ of the closed membrane neck is also determined by v and is independent of the spontaneous curvature m, as implied by the inequality in equation (1).

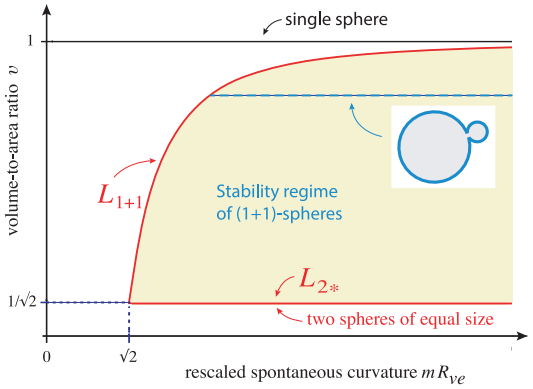

Fig. 3: Morphology diagram as a function of the rescaled spontaneous curvature $mR_{ve} > 0$ and the volume-to-area ratio v with $0 \leq v \leq 1$. The yellow region represents the stability regime for (1 + 1)-sphere morphologies. This stability regime is located between two lines of limit shapes denoted by L_{1+1} and L_{2*}. Along the line L_{2*}, the vesicle forms a (1 + 1)-sphere morphology consisting of two equally sized spheres. Within the yellow stability regime, the shapes depend only on v and not on mR_{ve}.

Stable Multi-sphere Morphologies of Vesicles

The two-sphere shapes displayed in **Fig. 2** represent the simplest examples of multi-sphere vesicles. Indeed, the theory of curvature elasticity predicts stable multi-sphere shapes consisting of an arbitrary number of (punctured) spheres connect-

ed by closed membrane necks. **[7, 6]** For uniform membranes, these multi-sphere shapes can involve only two types of spheres, large and small ones, with two different radii, R_l and R_s. This property follows from the shape equation for spheres as given by

$$\Delta P = 2\Sigma M_{\rm sp} + 4\kappa m^2 M_{\rm sp} - 4\kappa m M_{\rm sp}^2 \qquad (2)$$

and determines the mean curvature Msp of the sphere in terms of the pressure difference $\Delta P = P_{\rm in} - P_{\rm ex}$ between the interior and the exterior solution, the mechanical bilayer tension Σ, the bending rigidity κ, and the spontaneous curvature m. Because the shape equation as given by equation (2) is quadratic in the mean curvature $M_{\rm sp}$, it can have no, one, or two real solutions. Those parameters that lead to two real solutions describe multi-sphere shapes that have two different radii, R_l and $R_s \neq R_l$. The degenerate case with only one real solution implies that all spheres have the same radius, $R_l = R_s = R_*$. For each multi-sphere morphology consisting of N_l large and N_s small spheres, one again finds a certain stability regime within the two-dimensional morphology diagram. Different stability regimes corresponding to different numbers N_l and N_s overlap within the morphology diagram. As a consequence, the bending energies associated with these multi-sphere morphologies form a rugged energy landscape with many metastable states.

Some insight into this landscape can be obtained by a Gedankenexperiment in which we produce multi-sphere shapes with an increasing number of small spheres. To be specific, let us consider a spherical vesicle enclosed by a membrane with negative spontaneous curvature $m < 0$. When we reduce the volume of this vesicle, it can form a variable number N of small spheres, see **Fig. 4**.

The morphological complexity of multi-sphere shapes has been recently studied experimentally for giant unilamellar vesicles (GUVs) that were exposed to asymmetric solutions of two simple sugars, sucrose and glucose. When the interior solution contained only sucrose and the exterior solution only glucose, the vesicle membranes acquired a positive spontaneous curvature of about 1/μm. Some examples for the resulting multi-sphere morphologies are displayed in **Fig. 5**. **[8]** It is important to note that all of these morphologies involve at most two different radii, R_l and R_s, in agreement with the quadratic nature of the shape equation (2). One striking example for a multi-sphere shape that is built up from equally sized spheres with $R_s = R_l = R_*$ is displayed in **Fig. 5f**.

Mechanical and Spontaneous Tension of Membranes

Inspection of the shape equation (2) for spheres shows that it involves two different terms that are linear in the mean curvature $M_{\rm sp}$. The first linear term, $2\Sigma M_{\rm sp}$, is proportional to the mechanical tension Σ. The second linear term, $4\kappa m^2 M_{\rm sp}$ can be rewritten in the form $2\sigma M_{\rm sp}$ with the spontaneous tension $\sigma \equiv 2\kappa m^2$ which represents the intrinsic tension scale of curvature elasticity. **[3]** In contrast to the mechanical tension Σ, which is affected by the forces and constraints experienced by the vesicle membrane, the spontaneous tension is a material parameter that remains constant as the vesicle changes its shape. Defining the total membrane tension $\hat{\Sigma}$ as the sum of the mechanical and the spontaneous tension, the shape equation (2) attains the compact form $\Delta P = 2\hat{\Sigma} M_{\rm sp} - 4\kappa m M^2$ with the total membrane tension

$$\hat{\Sigma} \equiv \Sigma + \sigma = \Sigma + 2\kappa m^2. \qquad (3)$$

The spontaneous tension σ is proportional to m^2 and, thus, becomes large for large spontaneous curvatures m. In fact, when the spontaneous curvature m is large compared to the inverse vesicle size $1/R_{\rm ve}$, the total membrane tension is dominated by the spontaneous tension. In such a situation, osmotic deflation of a spherical vesicle with radius $R_{\rm ve}$ leads to a spherical mother vesicle with a reduced radius $R_{\rm mv} < R_{\rm ve}$ and to many membrane protrusions in the form of membrane nanotubes. The width of these nanotubes is of the order of $1/|m|$ and much smaller than the size $R_{\rm mv}$ of the mother vesicle. Long nanotubes have a cylindrical shape. **[9]** In the absence of external forces, the radius $R_{\rm cy}$ of this cylinder becomes equal to $1/(2|m|)$ for large spontaneous curvatures $|m|$. In this limit, the mechanical tension Σ behaves as $\Sigma \approx \pm(R_{\rm cy}/R_{\rm mv})\sigma$. **[3]** Therefore, the separation of length scales between the nanotube

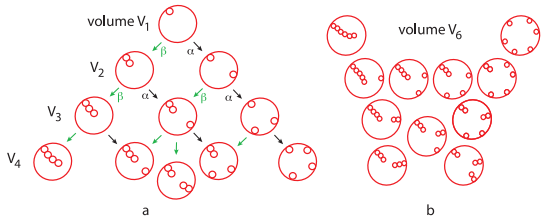

Fig. 4: Multi-sphere shapes that can be formed by a single vesicle for large negative spontaneous curvature and different vesicle volumes V_N with $V_N < V_{N-1}$. Starting from a spherical vesicle with volume V_0, a single in-bud is formed for volume $V_1 < V_0$. As the volume is reduced to $V_2 < V_1$, the existing in-bud can be transformed into an in-necklace consisting of two small spheres (left) or the membrane can form a second in-bud (right). For N ≥ 3, the vesicle can attain an increasing number of morphologies with N small in-spheres. ***[7]***

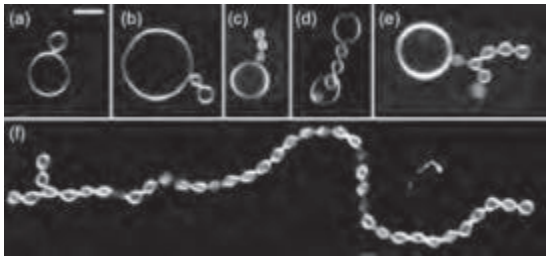

Fig. 5: Stable multi-sphere morphologies of GUVs consisting of large and small spheres as observed when the interior and exterior solution contained 234 mM sucrose and 234 mM glucose, respectively: (a) Large sphere connected to a single small sphere; (b) Large sphere connected to a linear necklace of two small spheres; (c) Large sphere with a linear necklace of three small spheres; (d) Two large spheres connected by a necklace of two small spheres; (e) Large sphere with a branched necklace consisting of seven small spheres; and (f) Branched necklace consisting of 39 spheres of equal size. The scale bar in (a) corresponds to 5 μm and applies to all images. ***[8]***

radius R_{cy}, which is of the order of 100 nm, and the radius R_{mv} of the spherical mother vesicle, which is of the order of 10 µm, implies that the mechanical tension Σ is much smaller than the spontaneous tension σ.

Increased Robustness of Tubulated Vesicles

The small mechanical tension of a tubulated vesicle reflects the reservoir of membrane area provided by the nanotubes. When the mother vesicle experiences some mechanical perturbations, it can adjust its area by exchanging membrane with the nanotubes. This increased robustness of tubulated vesicles against mechanical perturbations has been recently demonstrated for micropipette aspiration and osmotic inflation. **[10]**

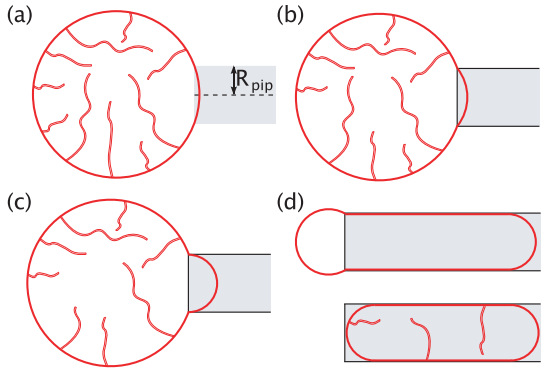

Fig. 6: Different stages for the aspiration process of a tubulated GUV (red) by a micropipette (grey) of radius R_{pip}: (a) The spherical mother vesicle comes into contact with the pipette; (b) With increasing suction pressure, some of the nanotubes are retracted and the mother vesicle develops a tongue that has the form of a spherical cap; (c) When the suction pressure reaches a critical value, the cap-like tongue becomes a hemisphere with radius R_{pip}, and the vesicle membrane starts to flow into the micropipette; and (d) Depending on the membrane area stored in the nanotubes, the vesicle motion stops as soon as all nanotubes have been retracted (d, top) or continues until the vesicle is completely aspirated into the pipette (d, bottom) ***[10]***

When a tubulated vesicle is aspirated by a micropipette, we can distinguish several stages of the process, see **Fig. 6**. During initial aspiration, the GUV extends a short membrane tongue into the micropipette. The initial tongue has the shape of a spherical cap with curvature radius R_{to}. When the mother vesicle comes into contact with the pipette as in **Fig. 6a**, the radius R_{to} of the tongue is equal to the radius R_{mv} of the mother vesicle. As the suction pressure $P_{ex} - P_{pip}$ increases, the tongue grows and its curvature radius decreases, see **Fig. 6b,** until the tongue attains a hemispherical shape and its radius becomes equal to the radius R_{pip} of the pipette, as in **Fig. 6c**. During this initial aspiration process, the suction pressure $P_{ex} - P_{pip}$ is balanced by the elastic couter pressure arising from the membrane deformation which implies **[10]**

$$P_{ex} - P_{pip} \approx 2\sigma \left(\frac{1}{R_{to}} - \frac{1}{R_{mv}} \right) \qquad (4)$$

as long as the tongue radius R_{to} is much larger than the width of the nanotubes. The suction pressure can be controlled experimentally whereas the radii of the tongue and the mother vesicle can be measured by optical microscopy. As a consequence, the spontaneous tension σ can be directly obtained from the relationship in equation (4). When the suction pressure is increased beyond the value at which the tongue become a hemisphere, the vesicle membrane starts to flow into the pipette, see **Fig. 6d**.

Spontaneous Curvature from Force-induced Tabulation

In the last couple of years, we have developed a variety of methods to determine the spontaneous curvature in a quantitative manner. One such method is based on force-induced tubulation of GUV membranes. **[3, 11, 12, 13]** The GUV is aspirated into a micropipette and an optical trap is used to pull a small, membrane-attached bead away from the GUV, thereby creating a cylindrical nanotube between the bead and the mother vesicle. The cylinder radius R_{cy} is necessarily much smaller than the radius R_{mv} of the mother vesicle. The force f acting onto the membrane-attached bead then satisfies the relationship **[3, 11]**

$$m + \frac{f}{4\pi\kappa} \approx \pm \left(\frac{\hat{\Sigma}}{2\kappa} \right)^{1/2} - \frac{1}{4R_{mv}} \quad \text{for large } R_{mv}/R_{cy} \qquad (5)$$

which involves the total, m-dependent membrane tension $\hat{\Sigma} = \Sigma + 2\kappa m^2$. The force f is taken to be positive and negative if it points towards the exterior and interior aqueous solution, respectively.

For certain parameter ranges, the total membrane tension $\hat{\Sigma}$ can be replaced by the aspiration tension as obtained from the Laplace equation for the spherical endcap of the fully aspirated membrane tongue. **[11]** Using this replacement, the relationship in equation (5) has been used to obtain the spontaneous curvatures of membranes that contain the glycolipid GM1 **[12]** or are exposed to asymmetric ionic conditions **[13]**, see the contribution of Rumiana Dimova in this biannual report.

Curvature-induced Division of Giant Vesicles

As described in the previous paragraphs, a variety of methods is now available to determine the spontaneous curvature of GUV membranes. What has been missing, however, is an experimental protocol that allows us to vary the spontaneous curvature in a controlled and quantitative manner. Such a protocol has now been developed based on the reversible binding of His-tagged GFP proteins to anchor-lipids within the GUV membranes. **[14]** When these membranes are exposed to a certain molar concentration of GFP in the exterior solution, they acquire a spontaneous curvature m that is found to be proportional to this concentration over a wide concentration range. Combining this controlled generation of spontaneous curvature with osmotic deflation, we have been able to transform spherical GUVs into dumbbell-shaped GUVs, consisting of two (punctured) spheres connected by a closed membrane neck, see the asymmetric and symmetric dumbbell shapes displayed in the panel II of **Fig. 7a** and **7b**. A further increase in the

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GFP concentration leads to the cleavage of the neck and to the division of the dumbbell-shaped GUV as shown in the rightmost panels of **Fig. 7**.

These experimental observations confirm the recent theoretical prediction that neck fission can be achieved by simply increasing the membrane's spontaneous curvature. More precisely, the spontaneous curvature m is predicted to generate a constriction force f around the neck as given by **[6]**

$$f = 8\pi\kappa\,(m - M_{\rm ne}) \qquad (6)$$

which is proportional to the difference $m - M_{\rm ne}$ between the spontaneous curvature m and the neck curvature $M_{\rm ne}$, defined in equation (1), as well as to the bending rigidity κ. For the GUV membranes shown in **Fig. 7**, the spontaneous curvature induced by the membrane-bound GFP generates constriction forces up to 80 pN, comparable to the largest constriction forces generated by specialized protein complexes that cleave the necks of cellular membranes. In contrast to the latter *in-vivo* systems, the synthetic biosystems described here are *chemically quite simple* and involve only lipid membranes and His-tagged proteins. Therefore, these biosystems provide an extendible module for the bottom-up approach to synthetic biology.

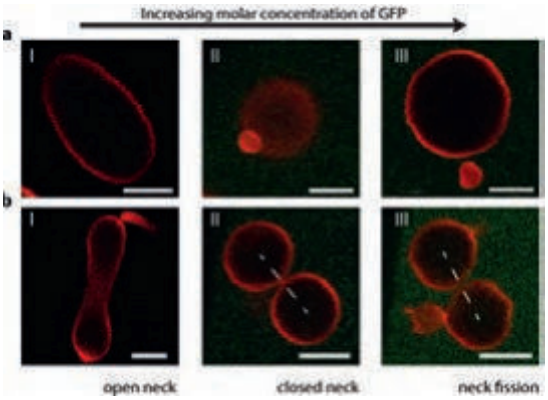

Fig. 7: Division of giant unilamellar vesicles (GUVs) (red) by increasing the molar concentration of green fluorescent protein (GFP) (green) in the exterior aqueous solution: (a) Asymmetric division into one large and one small daughter vesicle; (b) Symmetric division into two daughter vesicles of equal size. The division process starts, in the absence of GFP, from a prolate vesicle shape as displayed in I. Addition of GFP then transforms each GUV into two (punctured) spheres that are connected by a closed membrane neck as in II. A further increase in the GFP concentration leads to the cleavage of the neck and to the division of the GUV as shown in III. ***[14]***

Segmentation of Membranes

So far, we discussed membranes that have a spatially uniform composition and thus are characterized by spatially uniform tensions and curvature-elastic properties. However, membranes are often partitioned into different membrane segments (or two-dimensional compartments) that differ in their molecular composition. Such membrane segments can be formed by lipid phase separation, which leads to the coexistence of intramembrane domains, or by spatially nonuniform environments that lead to an ambience-induced segmentation of the membranes. Simple examples for the latter segmentation are provided by vesicle membranes in contact with substrate surfaces, nanoparticles, or liquid droplets.

The different membrane segments are characterized by different segment tensions. In the simplest case, we have only two different segments, say a and b, with surface areas A_a and A_b and segment tensions, Σ_a and Σ_b. The corresponding contribution to the free energy has the form $\Sigma_a A_a + \Sigma_b A_b = \Sigma_a A + (\Sigma_b - \Sigma_a)A_b$ with the total membrane area $A \equiv A_a + A_b$. To be specific, let A_a be the contact area of the membrane with an aqueous buffer and A_b the contact area with a certain condensed phase β corresponding, e.g., to a substrate surface, nanoparticle, or liquid droplet. In such a situation, the tension difference $\Sigma_b - \Sigma_a$ represents the adhesion free energy per unit area, W, between the membrane and the condensed phase β. **[15]**

Endocytosis of Rigid Nanoparticles

The endocytosis of rigid nanoparticles consists of three elementary steps as shown in **Fig. 8**: adhesion of the nanoparticle to the membrane; complete engulfment of the particle by the membrane; and fission of the particle-bound membrane segment from the rest of the membrane. It is quite remarkable that each of these steps is governed by a relatively simple curvature-dependent (in)stability relation. **[16, 17]**

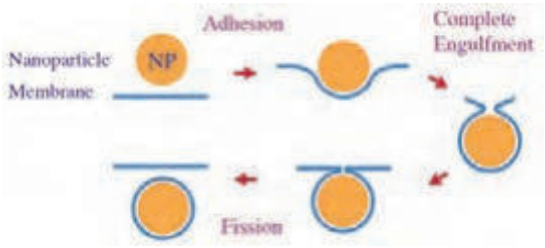

Fig. 8: Endocytosis of a rigid nanoparticle (NP) by a biomembrane consists of three steps: (i) Adhesion of the NP to the membrane; (ii) complete engulfment of the NP by the membrane, leading to the formation of a closed membrane neck that connects the particle-bound membrane segment with the unbound segment; and (iii) Fission of the membrane neck that releases the membrane-engulfed NP to the other side of the membrane.

One key parameter for these relations is provided by the adhesion length $R_W = \sqrt{2\kappa/|W|}$ which encodes the competition between membrane bending as governed by the bending rigidity κ and the membrane-surface adhesion as described by the adhesive strength $|W|$. The onset of adhesion for a nanoparticle with radius $R_{\rm pa}$, for example, requires that the membrane curvature M at the point of contact satisfies the instability relation **[16]**

$$M \le \frac{1}{R_W} - \frac{1}{R_{\rm pa}}\,. \qquad (7)$$

Similar relations have been derived for the stability of the completely engulfed state and for the constriction force of the closed membrane neck that now involves the adhesion length

R_W as well. Our theory has been further extended to determine the local and global free energy landscapes of nanoparticles at membranes **[17]** as well as the adhesion-induced fission of membranes by ESCRT proteins **[18]**.

Wetting and Molding of Membranes by Water-in-water Droplets

Water-in-water droplets are formed within water-in-water emulsions and aqueous two-phase systems, also known as aqueous biphasic systems. One example are PEG-dextran solutions that undergo aqueous phase separation when the weight fractions of the polymers exceed a few weight percent. Another example that has recently attracted a lot of interest are biomolecular condensates that form membraneless organelles within eukaryotic cells and behave like liquid droplets.

When the exterior aqueous solution of a giant vesicle undergoes phase separation, it can exhibit a variety of wetting morphologies as displayed in **Fig. 9**. **[15]** For partial wetting, the water-water interface and the membrane form a three-phase contact line that partitions the membrane into two distinct segments with different tensions and different curvature-elastic properties. On the nanometer scale, the capillary forces arising from the water-water interface lead to a smoothly curved membrane that forms an intrinsic contact angle with the interface. On the micrometer scale, the capillary forces deform the membrane segments into spherical caps with an apparent kink along the contact line as shown in **Fig. 9a**. A new computational method has been developed by which these piece-wise spherical vesicle shapes can be analyzed in a systematic manner. **[15]** This method has been applied to the morphologies of giant vesicles in contact with biomolecular condensates that are enriched in the FUS protein **[19]**, see the contribution of Roland Knorr in this biannual report.

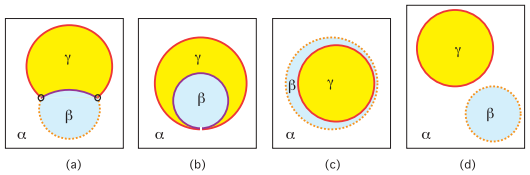

Fig. 9: Wetting morphologies arising from phase separation into two aqueous phases, α (white) and β (blue), outside a giant vesicle which is filled with the aqueous spectator phase γ. (a) Partial wetting of the vesicle membrane by α and β. The apparent kink at the contact line (black circles) reveals the capillary forces that the αβ interface exerts onto the vesicle membrane; (b) Complete engulfment of the β droplet by the vesicle membrane; (c) Complete wetting of the membrane by the β phase; and (d) Complete wetting by the α phase which is equivalent to complete dewetting of the β droplet. ***[15]***

When the droplets and vesicles have linear dimensions in the micrometer range, one can usually ignore the line tension of the contact line between the water-in-water interface and the vesicle membrane. However, when the phase separation leads to individual, well-separated droplets, it proceeds *via* nucleation and growth, starting from droplets with a linear dimension in the nanometer range. The interactions of such nanodroplets with membranes has been recently studied by molecular dynamics simulations. **[20]** These simulations revealed that the line tension of the contact line plays an important role for the membrane engulfment of nanodroplets and that this tension has a negative value for a wide range of parameters. This negative line tension causes the contact line and the associated membrane neck to close into an unusual, tight-lipped shape as depicted in **Fig. 10**. Such a tight-lipped membrane neck suppresses both thermally activated and protein-induced fission of the neck, implying a reduction in the cellular uptake of nanodroplets by pinocytosis and fluid-phase endocytosis.

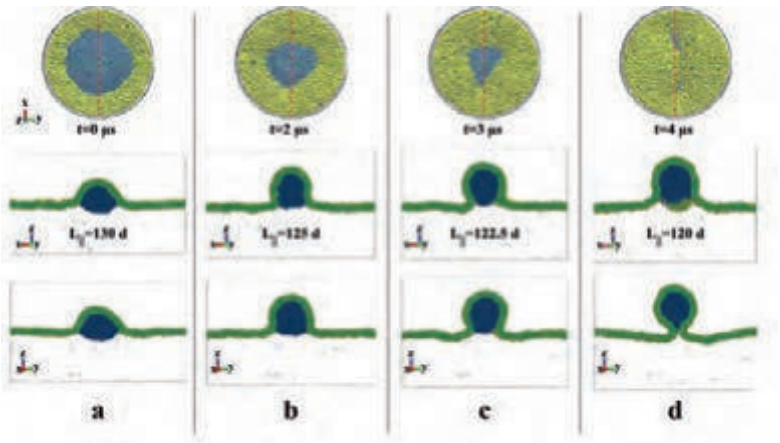

Fig. 10: Time-dependent engulfment of a nanodroplet (blue) by a bilayer membrane (green) from the initial time t = 0 in column (a) to the final time t = 4 μs in column (d). The engulfment process is driven by a reduction in the lateral box size $L_{||}$, for fixed volume of the simulation box, where the bead diameter d is of the order of 1 nm. The panels in the top row show bottom views of circular membrane segments (yellow-green) around the water-water interface (blue), separated by the contact line which is circular at t = 0, strongly non-circular after t = 3 μs, and has closed into a tight-lipped shape after t = 4 μs. ***[20]***

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Reshaping Membranes

Rumiana Dimova
06.04.1971
1991–1995: Master of Science in Theoretical Chemistry and Chemical Physics (Sofia University, Bulgaria)
1996–1997: Second Master of Science in Separation Processes in Industry and Environmental Protection (Sofia University, Bulgaria)
1997–1999: PhD with Doctoral Thesis: Hydrodynamic properties of model lipid membranes: study by means of optical trapping manipulation of particles. (Bordeaux University, Centre de Recherche Paul Pascal, Bordeaux, France)
2000–2001: Postdoctoral Scientist, Theory Department, Max Planck Institute of Colloids and Interfaces
Since 2001: Research Group Leader, Department of Theory and BioSystems, Max Planck Institute of Colloids and Interfaces
2012: Habilitation in Biophysics at Potsdam University
2014: Privatdozent in Biophysics at Potsdam University
2014: Emmy Noether distinction for women in physics (European Physical Society)
2016: Elected as Scientific Representative of Max Planck Institute of Colloids and Interfaces
2016/2017: Chair of the Membrane Structure and Assembly Subgroup of the Biophysical Society

Giant unilamellar vesicles (GUVs) represent a promising and extremely useful biomembrane system because they provide the possibility for systematic measurements of the membrane mechanics as a function of composition, surrounding media, and temperature **[1]**. In addition, they open the gate for the modular bottom-up assembly of artificial cells **[2–5]**. Presumably, their most important advantage over other model membrane systems is their cell-size dimensions and that the membrane response to external factors such as ions, (macro)molecules, hydrodynamic flows or electromagnetic fields can be directly observed under the microscope. In the last couple of years, we have dedicated significant effort to understand the mechanism of membrane reshaping and to quantitatively assess it using GUVs as a model membrane system.

Biological membranes are seldom flat but instead often exhibit strongly curved morphologies as exhibited by the shapes of cells and cellular organelles. Membrane deformations cost substantial energy and yet membrane shape transformations are ubiquitous during cellular and organelle functions. The preferred or *spontaneous curvature* of membranes is determined by the asymmetry across and within the bilayer, which can originate from the composition of the leaflets but also from their immediate environment in terms of solution composition, see **Fig. 1 [6]**. Any type of asymmetry across a membrane will influence its spontaneous curvature and thus the preferred membrane shape. In the last couple of years, employing GUVs as a workhorse, our group has focused on quantifying the effect of asymmetry imposed by ions, charged lipids and glycolipids, amphiphilic light-sensitive molecules and (bio) macromolecules.

Membrane Curvature Generated by Asymmetric Ionic Conditions

Considering the differences in the cytosolic and periplasmic solutions containing macromolecules and ions at various concentrations, we attempted to elucidate the changes in the mechanical properties of membranes exposed to asymmetric buffer conditions and the associated curvature generation **[7, 8]**. As a model system, we used GUVs exposed to distinct salt and sugar solutions on both sides of the membrane. We aspirated the GUVs into micropipettes and attached small beads to their membranes. An optical tweezer was used to exert a local force on a bead, thereby pulling out a membrane tube from the vesicle, see **Fig. 2**. This assay, developed in an earlier work **[9]**, allowed us to measure the spontaneous curvature and the bending rigidity of the bilayer in the presence of different ions and sugar across the membrane. At low sugar/salt (inside/out) concentrations, the membrane spontaneous curvature generated by NaCl and KCl is close to zero, but negative in the presence of LiCl. In the latter case, the membrane bulges away from the salt solution. At high sugar/salt conditions, the membranes were observed to become more flexible and the spontaneous curvature was enhanced to even more negative values, comparable to those generated by some proteins. Our findings reveal the reshaping role of alkali chlorides on biomembranes.

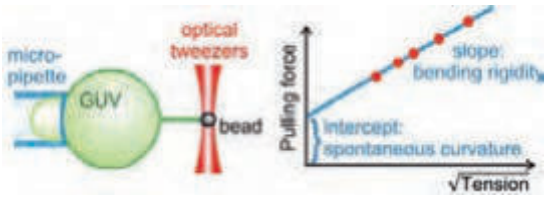

Fig. 2: Pulling a nanotube out of a GUV aspirated by a micropipette: (left) A sketch of the setup in which the optical tweezers pulls away a bead attached to the GUV, thereby forming a lipid nanotube. (right) Principle of measurement: from the pulling force assessed with the optical tweezers and from the membrane tension measured with the micropipette aspirating the GUV, one can deduce the spontaneous curvature and bending rigidity of the membrane.

Curvature Generation by a Glycolipid

We also investigated the reshaping role of the ganglioside GM1, which is present in neuronal membranes at elevated concentrations with an asymmetric spatial distribution. It is known to generate curvature and can be expected to strongly influence the neuron morphology. To elucidate these effects, we prepared GUVs with GM1 predominantly present in one leaflet of the membrane. Based on pulling inward and outward tubes **(Fig. 2)**, we assessed the membrane spontaneous curvature **[9]**. Using vesicle electroporation and fluorescence intensity analysis, we were able to quantify the GM1 asymmetry across the membrane and to subsequently estimate the local curvature generated by the molecule in the bilayer.

Deflated GUVs with asymmetric GM1 distribution exhibit nanotubes which can be outward or inward **(Fig. 3a–c)** depending on the predominant location of GM1 in the membrane leaflets. These nanotubes are stabilized by the membrane sponta-

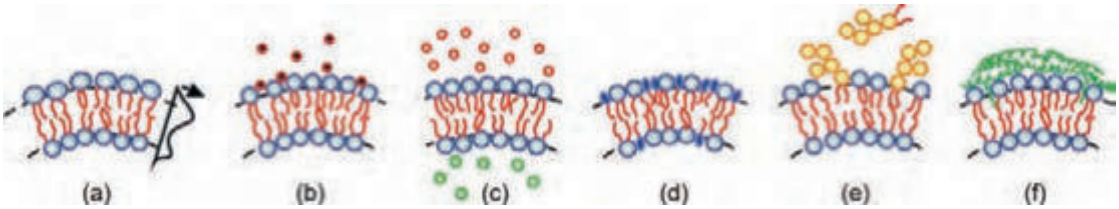

*Fig. 1: Sources of nonzero spontaneous curvature include: (a) Differences in the effective molecular area of constituting lipids in the bilayer, e.g. as a result of differences in hydration, pH or molecular structure; (b) Asymmetric ion distribution leading either to condensing or expanding one of the bilayer leaflets; (c) Asymmetric distribution of nonadsorbing particles or (bio)molecules of different sizes; (d) Amphiphilic molecules asymmetrically distributed in the membrane; (e) Partially water-soluble molecules (such as glycolipids or peripheral proteins) asymmetrically inserting in or desorbing from the membrane; (f) Asymmetrically inserted/anchored proteins with specific geometry **[6]**.*

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neous curvature acquired by the asymmetric distribution of GM1. They represent area reservoirs, which attribute increased robustness of tubulated vesicles as demonstrated with micropipette aspiration experiments **[10]**. GM1 is already known to play a crucial role in connection with receptor proteins. Our results on curvature generation and tubulation point to an additional important role of this ganglioside, namely in shaping neuronal membranes. We are currently investigating the effect of GM1 on the membrane stability when exposed to electric fields.

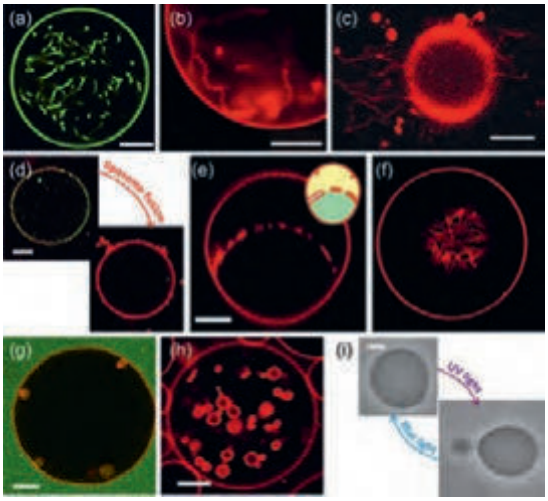

*Fig. 3: Reshaping membranes: generating nanotubes and buds in vesicles. (a-c) Cylindrical or necklace-like tubes can be spontaneously generated by asymmetric distribution of GM1 on the two membrane leaflets **[9, 10]**. Inward tubes (a, b) form upon desorption of GM1 from the outer leaflet and outer tubes (c) are produced when GM1 added externally inserts in the membrane. (d) Small outward buds and tubes are observed upon the fusion of small liposomes (red) with the GUV (initially green) because of the inherent area difference of the liposome leaflets **[12]**. (e, f) Inward tubes produced in vesicles loaded with aqueous two-phase systems result from the asymmetric adsorption of polymers onto the membrane **[15]**. The tubes adsorb to the two-phase interface: (e) side view with a sketch and (f) top view of the two-phase interface. (g, h) ESCRT-III proteins added externally trigger the formation of inward buds (g) and scission of these buds to form intraluminal vesicles (h) inside the GUVs **[16]**. (i) Vesicles doped with photoresponsive amphiphilic molecules undergo outward budding upon irradiation as the molecules inserted in the membrane undergo isomerization; the process is reversed upon blue-light irradiation **[17]**.*

Lipid Asymmetry can also Drive Tube Sprouting

One of the most popular protocols for preparing GUVs is electroformation **[1]**, where the bilayer swelling is enhanced by an externally applied electric field. We found that upon osmotic deflation, GUVs electroformed from charged and neutral lipids exhibit inward-pointing lipid nanotubes, suggesting negative spontaneous curvature of the membrane. This curvature generation results from the asymmetric distribution of the charged lipids in the two bilayer leaflets **[11]**.

Outward tubes and small buds were also observed to form when negatively-charged GUV membranes fuse with small positively charged liposomes (~100 nm), **Fig. 3d [12]**. Upon fusion, the leaflets of the GUV increase asymmetrically in area (the outer leaflet acquiring more lipids because of the area difference between the bilayer leaflets of the small liposomes), which induces a positive spontaneous curvature. In contrast, the membrane of neutral GUVs was observed to engulf the small liposomes, similarly to the behaviour observed for polyionic nanoparticles in contact with GUVs **[13, 14]**. However, this latter interaction resulted in destabilizing the GUV membrane.

Membrane Remodelling by Polymers, Amphiphilic Molecules and some Proteins

Tubulation can be triggered by the adsorption of polymers such a PEG. In the last couple of years, we have investigated GUVs loaded with solutions of PEG and dextran forming aqueous two-phase systems **[15]**. Tubes form even in the absence of phase separation and otherwise adsorb at the two-phase interface **(Fig. 3e, f)**.

Proteins are probably the most popular suspect when discussing the trigger for curvature generation in cells. We investigated the reshaping role of three ESCRT-III proteins. Our findings indicate that when sequentially added to the GUV exterior, they trigger inward budding followed by scission of the buds to intraluminal vesicles inside the GUV as shown in **Fig. 3g, h [16]**.

Outward budding as a result of membrane area increase can be achieved also by insertion of amphiphilic molecules which undergo photoisomerization under UV and visible light, **Fig. 3i [17, 18]**. The results show that exo- and endocytic events can be controlled by light and that these photoinduced processes provide an attractive method to change membrane area and morphology.

Biomembranes are constantly remodelled and in cells, these processes are controlled and modulated by an assortment of membrane proteins. Our work demonstrates that such remodelling can also be induced by a number of factors such as ions, charged lipids, glycolipids, (bio)macromolecules and amphiphilic photoresponsive molecules.

R. Dimova, M. Aleksanyan, Y. Avalos-Padilla, T. Bhatia, E. Ewins, V. Georgiev, M. Karimi, R. Lira, D. Roy, J. Steinkühler, Z. Zhao
dimova@mpikg.mpg.de

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MEMBRANES AND VESICLES

Dynamics of Bio-Membranes

Roland L. Knorr

1977

From 1997: University studies at the Friedrich-Schiller-University, Jena/ Germany majoring human nutrition

2004: Diploma thesis at the Dept. of Pharmaceutical Biology, Friedrich-Schiller-University, Jena/ Germany

2005: Analytical scientist in a biopharmaceutical company (IDT Biologika, Dessau/Germany)

2006: Scientist in a biotech startup (liposomal delivery, Novosom AG Halle/Germany)

2007–2010: Doctoral Thesis: Giant vesicles - influence of phase state, composition and electric pulses (Physical Biochemistry of the University Potsdam and Dept. of Theory and Biosystems, Max Planck Institute of Colloids and Interfaces)

2010/11: DFG Post-doc Fellow

2011–2016: Postdoctoral Scientist (Morphological transitions of biomembranes during autophagy; Dept. of Theory and Biosystems, MPI of Colloids and Interfaces)

Since 10/2016: Research Group Leader, Dept. of Theory and Biosystems, MPI of Colloids and Interfaces

Since 10/2018: Assistant Professor, Dept. Biochemistry and Molecular Biology, University of Tokyo

In the aqueous environment of living cells, a huge number of chemical reactions run in parallel. An essential trait of the cell is its capability to organize these reactions in space and time by compartmentalization. Compartments reduce the mutual interference of biochemical processes, allow to control and to optimize the respective physicochemical environments and to protect enzymes and proteins from degradation. Currently, membrane-bound and membrane-less compartments are distinguished.

Conventional organelles are compartments surrounded by biological membranes based on phospholipid bilayers and examples include the Endoplasmic Reticulum or the Golgi Apparatus. How membrane-bound organelles communicate with each other to give the right response to each stimulus they receive, how they coordinate the exchange of molecules via lipid vesicles, and how the shapes of organelles are regulated are fundamental questions in cell biology. Topological and morphological remodelling of membranes, for example, takes part in all vesicular transport pathways, as well as during autophagy **[1]**, viral infection, and cell division as well as in the dynamics of organelles such as mitochondria.

The formation of transient, fluid condensates by a process resembling liquid-liquid phase separation (LLPS) is a concept that is fast gaining widespread attention to explain how cells organize their contents without using membranes. Phase coexistence in cells often involves low affinity, multivalent interactions between molecules, for example, provided by proteins rich in intrinsically disordered regions. In cells, switching condensates formed by biomolecules between nucleation, growth, and dissolution require critical changes of specific physicochemical conditions such as protein and salt concentrations, temperature, and pH.

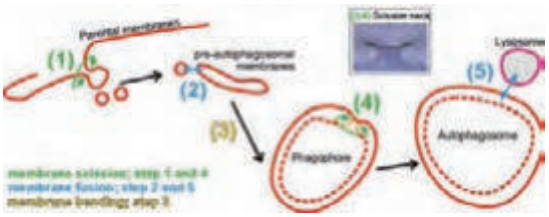

Fig. 1: Shape transformations of lipid membranes during autophagy. Autophagy is characterized by four topological transformations (two early ones and two late ones), with one morphological bending step in between.[1]

In this group, which was established in 2016, we investigate the dynamics of bio-membranes and bio-LLPS by focusing on three major topics: 1) Remodelling of membranes with focus on autophagy, 2) Interaction of membrane-bound organelles with biomolecular condensates, and 3) Formation and stability of biomolecular fluids. We aim for a quantitative understanding of shape changes by applying a diverse set of experimental methods at the interface between cell biology, protein and lipid biochemistry and -physics **[2, 3]**, typically in combination with theoretical approaches as developed in the department. We collaborate with various groups at the MPIKG, very closely with the labs of R. Dimova and T. Robinson.

1) Remodeling of Autophagic Membranes

Autophagy is an intracellular degradation system within eukaryotic cells whereby flexible double-membrane sheets isolate portions of the cell and deliver this cargo for degradation to lysosomes. Autophagy involves a large number of membrane shape transformations as illustrated in **Fig. 1** and is regulated by a great number of proteins which were identified by Yoshinori Ohsumi and coworkers. By a combination of theory and experiment, we clarified the mechanisms underlying autophagosomal size regulation and membrane closure, **[4–7] Fig. 1**. Currently, we focus on the question of how closed autophagosomes manage to reopen. With the aim to establish a synthetic tool to study autophagic membrane remodelling, we generated recently sheet-like, pre-autophagosomal membranes using fluid interfaces, **Fig. 2**.

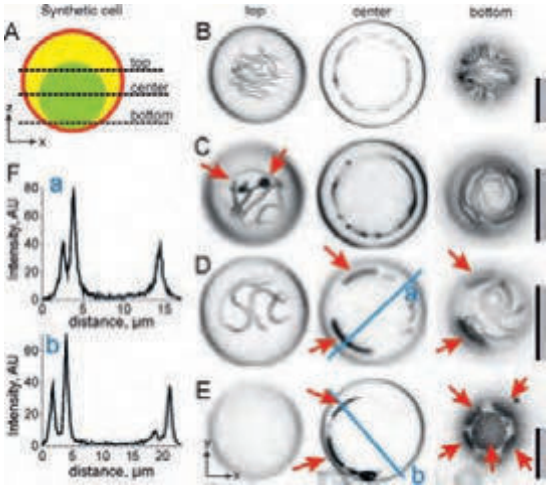

Fig. 2: Shape transformations of a nanotubular network into double-membrane sheets resembling pre-autophagosomal membranes. (A) Sketch of the setup and confocal sections shown in (B-E). (B) A tubular network without sheets is visible. (C) Sheets nucleate at the tubular network. (D) Two large sheets coexist with nanotubules. (E) Forming sheeted consumed nanotubules completely. The blue lines indicate the location of the line plots in (F) verifying the double-membrane nature of the sheets. The arrows highlight the circular sheets. Inverted confocal snapshots showing membrane fluorescence, scale bars 10 µm.

2) Interaction of Membrane-Bound Organelles with Biomolecular Condensates

In living cells, LLPS and the formation of liquid condensates proceed in an environment spatially crowded with membrane-bound organelles. Snapshots illustrating physical contacts between condensates and organelles in vivo have been published. However, the mechanisms of the droplet-membrane interaction have received little attention.

Our recent experimental and theoretical results suggest that biological liquids can switch their morphology on lipid mem-

branes between three different states depending on environmental conditions: 1) without contact to membranes (dewetting), 2) spatially restricted interaction with membranes (partial wetting); and 3) full coverage of the membrane by the droplet (complete wetting) **[8]**. These main morphologies are highlighted in **Fig. 3A, B**. In the dewetted state, droplets and vesicles are spherical but remodel mutually during partial or complete wetting, a process we call fluid-elastic scaffolding. The fundamental understanding of intracellular wetting processes we provide has important implications for cell biology as it will allow to specifically manipulate signalling pathways linking cyto- with nucleo-plasm, non-membrane-bound organelles with cellular membranes; **Fig. 3C**.

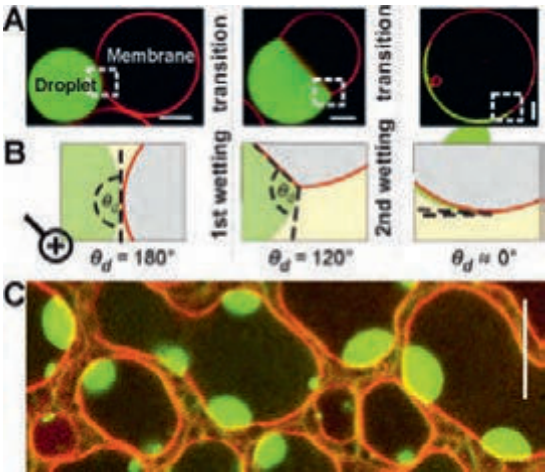

Fig. 3: Wetting transitions of condensates on biological membranes. (A) Three distinct wetting regimes can be distinguished in vitro; dewetting, partial wetting and complete wetting. (B) Schematics showing the three phase contact lines and the contact angles of the droplets. (C) Partial wetting in vivo: Condensates formed by seed storage proteins (green) wet the membrane of protein storage vacuoles (red) in maturating seeds of the plant Arabidopsis thaliana[9]. Scale bars: 5 µm

3) Large-Scale Phase Separation of the Cytosol

Molecularly crowded environments constitute conditions for phase separation and the formation of intracellular droplets. The separation of simple solutions with a few components into coexisting phases is well understood. However, we know very little about the behavior of complex biological solutions. Recently, we examined LLPS of such a complex solution and observed separation of the cytosol into two coexisting phases, **[9] Fig. 4**. Using optical microscopy, we analyzed the partitioning of macromolecules, vesicles, and microorganisms between the phases obtained, demonstrated the rapid exchange of molecules across the interface and verified the fluid state of the phases by monitoring the coalescence of cytosolic droplets. Quantitatively, the dynamics of the liquid-liquid phase separation of the cytosol and a simple aqueous (dextran/polyethylene glycol) two-phase system were found to be similar. Our results imply that the cytosol behaves like a biological two phase system where both phases occupy similar volume fractions. We argue that the proximity of intracellular solutions to coexistence lines is physiologically important, not only during hyperosmotic stresses but also for the development of dormant states such as seeds, **Fig. 3C**.

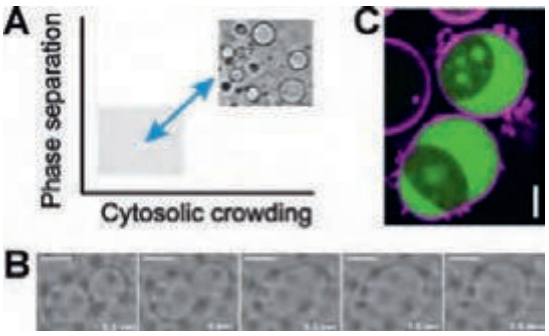

Fig. 4: Large scale phase separation of the cytosol. (A) Schematic of the experiments, (B) Coalescence of cytosolic droplets, (C) Coexisting cytosolic phases (both in different greens) in synthetic cells (membrane in purple)[9]. Scale bars: 5 µm

R.L. Knorr, C. Ferencz
Knorr@mpikg.mpg.de

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Microfluidics for Biomimetic Systems and Single-cell Analysis

Tom Robinson
17.06.1982
2001–2005: Master of Science in Physics (Imperial College, London, UK)
2006–2007: Master of Research in Chemical Biology (Institute of Chemical Biology, Imperial College, London, UK)
2007–2011: PhD in Chemistry (Departments of Chemistry and Physics, Imperial College, London, UK). Thesis: The Application of Multi-dimensional Fluorescence Imaging to Microfluidic Systems.
2011–2014: Postdoctoral research fellow (ETH, Zurich, Switzerland)
2014–2015: Postdoctoral research fellow in the group of Dr Rumiana Dimova (Department of Theory & Bio-systems, Max Planck Institute of Colloids and Interfaces)
Since 01/2016: Independent Research Group Leader, funded via the MaxSynBio (Department of Theory & Bio-systems, Max Planck Institute of Colloids and Interfaces)

Compartmentalisation is one of the key features to emerge from eukaryotic cell evolution. Their multi-compartment structure consisting of organelles ensures vital spatial separation of cellular functions and metabolic processes. To study this feature and other cellular processes, an increasingly common technique is to use artificial cells rather than biological cells **[1]**.

Our independent research group produces synthetic lipid vesicles and uses them as biomimetic systems. This engineering approach allows us to tune certain components, such as membrane composition and the aqueous environment in a highly controlled manner. We achieve a further level of control via microfluidic technology to produce and handle these delicate cell-sized objects. Currently, we use this combination of lipid vesicles and microfluidic technology to study enzymatic cascade reactions and membrane adhesion between multiple membrane compartments.

The group also uses microfluidic platforms to study biological cells at the single-cell level. Traditional bulk methods can result in loss of critical data from averaged data sets, but studies on individual cells can reveal hither to unknown properties and behaviours. For this reason, micro- posts and wells situated within microfluidics can isolate individual cells from a solution confining them in one spatial location for analysis. We currently apply this approach to bacterial cells to study their motility and to cancer cells to study dormancy. Cells can also be isolated at the single-cell level via encapsulation within lipid vesicles to investigate molecular uptake.

Biomimetic Vesicles in Microfluidic Systems

Producing GUVs with Microfluidics

A core technology in the group is microfluidics. These are small devices with micron-sized fluidic channels containing picolitre volume chambers. The use of microfluidic systems has exploded in the past 10 years with applications ranging from single-cell analysis to 'Lab-on-chip' in-the-field applications. A major challenge with giant unilamellar vesicles (GUVs) is the lack of size control and buffer composition offered by conventional production methods. While bulk emulsion-based methods do allow for a wide range of buffers there is little control over their size **[2]**. Our approach is to take advantage of microfluidics to produce them with a defined size and in any aqueous solution **[3]**. Double emulsion templates are created by microfluidic water-in-oil droplets at high-throughput rates, and the oil phase is later removed leaving highly mono-disperse GUVs **(Fig. 1)**. The encapsulation efficiencies are high, physiological salt concentrations can be used, and the sizes of the GUVs can be precisely tuned from 10 to 150 µm.

Microfluidic Handling of Vesicles

Microfluidic technology is used for the handling and analysis of lipid vesicles. This is traditionally performed in simple observation chambers and while easy to use, does not allow for rapid and homogeneous delivery of analytes to the GUVs. Moreover, tracking of single GUVs over time is non-trivial. Microfluidics, on the other hand, can overcome these challenges. **Fig. 2** shows how we engineer different microfluidic devices to capture and isolate specific numbers of vesicles. Once captured, the vesicles are stable for hours or days allowing tracking and analysis over time **[4]**. Moreover, flow control offers rapid and homogenous exchange of the surrounding solution and therefore to add/remove solutes which interact with the vesicle's membrane. Current systems have been successfully implemented in a number of different applications involving GUVs **[4–8]**, and recently we have developed a method to trap large collections of GUVs for high-throughput membrane studies **[9] (Fig. 2)**. Moreover, the device was used to investigate membrane-nanoparticle interactions in collaboration with the Department of Colloid Chemistry **[10]**. In the future, we envision its use to model cells in their natural environment using dense 3-D collections of vesicles as tissue mimicking systems.

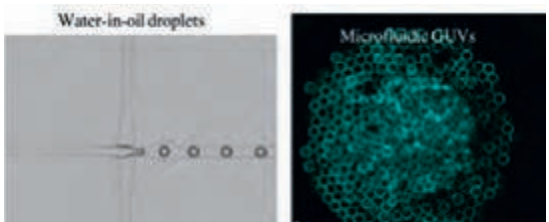

Fig. 1: A droplet-based microfluidic device to create water-in-oil-in-water double emulsions (left). After removal of oil, mono-disperse GUVs are created (right).

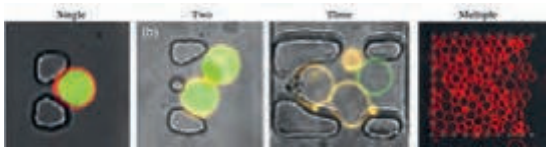

Fig. 2: Microfluidic devices designed to immobilise defined numbers of GUVs at specific locations.

Multi-compartment Vesicle Systems

Compartmentalisation within eukaryotes is advantageous for the segregation of different metabolic processes within the cell, but the large size of organelles can also hinder the diffusion of metabolites due to crowding. Specific membrane contact sites between organelles allow coordination of cellular activities by creating regions which favour exchange between compartments. For example, lipid transport proteins are localised to membrane-membrane contact sites. Even though is it vital for cellular function, spatial organisation of organelles is not well understood. To this end, our group is motivated to establish synthetic membrane-membrane adhesion within our multi-compartment systems with the aim of creating an artificial cell able to exhibit self-organisation of its internal structures. The challenge lies in encapsulating smaller vesicles within larger GUVs. We take advantage of the high-encapsulation efficiencies of emulsion-based methods **(Fig. 3)**. Once these multi-compartment vesicles are created, we use adhesive moieties for self-organisation and triggering of

morphological changes. Adhesion is mediated either by protein-protein or DNA-DNA interactions for reversibility, or using biotin-streptavidin interactions as shown in **Fig. 3**.

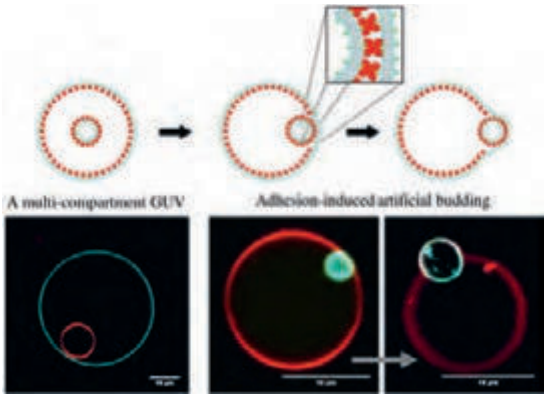

Fig. 3: Multi-compartment systems for self-organisation. Left: emulsion-based methods to encapsulate GUVs. Right: by functionalising the lipid head-groups adhesion events are induced leading to membrane budding.

Encapsulating Enzymatic Reactions

Many enzymatic pathways are confined to specific organelles or proceed between different organelles. The group currently has two running projects in this direction. The first project aims to dissect the role of compartmentalization of biosynthetic pathways in eukaryotes by studying the first steps of the biosynthesis of the molybdenum cofactor (Moco). In eukaryotes the first step for Moco biosynthesis is localised in the mitochondria and a stable intermediate is transported to the cytosol where all further steps proceed. We separate the steps using bacterial proteins (in collaboration with Prof. Leimkühler at the University of Potsdam) and encapsulate them into our vesicles. This enables studies of the transported intermediate in detail and will give insights into the role of mitochondria for Moco biosynthesis. The second project aims to build multi-compartmentalized systems designed to host a completely synthetic enzymatic reaction cascades making use of membrane proteins to transport reactants and products between the compartments **(Fig. 4)**. A key aspect is to build these compartments with different microenvironments i.e. buffers, pH, etc. in order to mimic the different intracellular conditions. The hope is that this system will allow modelling of the signalling cascades between organelles of a eukaryotic cell in a bottom-up approach.

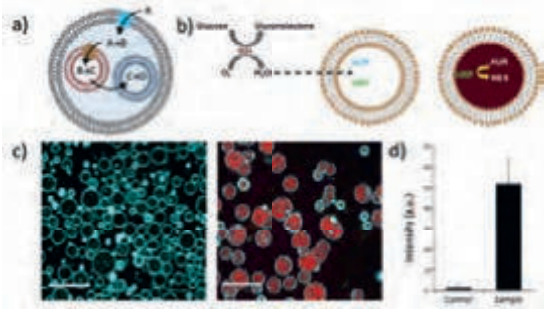

Fig. 4: a) Synthetic enzyme cascades. b) A two-enzyme coupled reaction in a single compartment. c) Images of control (left) and sample (right) containing enzyme HRP in the presence of glucose corresponding to b). Scale bars: 50 µm. d) Average fluorescence intensities within the GUVs.

Single-cell Analysis

Another topic explored within the Robinson lab is single-cell capture and analysis using microfluidic methods. **Fig. 5** shows the different strategies employed to isolate single cells. We use micro-fabricated structures to hydrodynamically capture the cells. From there we can take advantage of microfluidic flow control to add/remove (bio)chemical agents or to subject cells to different shear stresses. We currently have a number of projects on this topic in collaboration with the Department of Biomaterials.

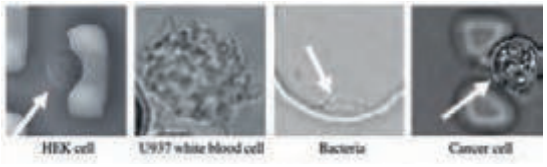

Fig. 5: Examples of different cells immobilized in different microfluidic structures.

Using Microfluidics to Investigate Cancer Dormancy

Breast cancer often metastasizes to bone, which can occur up to 10 years following tumour removal. This implies that cancer cells can undergo a dormancy phase. However, the mechanisms underlying cancer dormancy and reactivation and in particular the role of biophysical cues (pH, shear stress, osmotic pressure, CO_2) are poorly understood. Here the microfluidic approach is used to trap cells and precisely control changes in osmotic pressure and fluid flow at the single-cell level. Genetically modified cells with a cell cycle reporter allow us to detect and quantify the state and duration of the cell cycle. This project is in collaboration with Amaia Cipitria from the Department of Biomaterials funded via the IMRPS doctoral training school.

Liposomes and Microfluidics for Single-bacteria Studies

Understanding the behaviour of magnetotactic bacteria (MTB) both at the biological and physical level is not only important for basic research but has massive potential for novel drug delivery systems. Therefore, the Robinson lab has an on-going collaboration with Damien Faivre (Department of Biomaterials). One aspect focusses on confinement of the MTB within a defined volume – a unique feature afforded by microfluidics - and characterising their motility both experimentally and computationally. The aim is that an optimised model can be used to tune and predict the behaviour of these bacteria. Finally, we use GUVs to confine the MTB and iron uptake (for the formation of magnetosomes) is monitored via a fluorescence-based assay at the single-cell level. Current efforts are focussed on cell viability as well as optimising the detection assay. Future work will involve monitoring iron uptake rates as a function of magnetic fields, environment, and nutrient conditions.

T. Robinson, A. Moga, T. Hantke, T. Kirchhofer, N. Yandrapalli, J. Weinke, S. Shetty
tom.robinson@mpikg.mpg.de

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Evaporating Liquids at Planar Solid Substrates: Films and Droplets

Hans Riegler
29.01.1955
1986: PhD in Physics (Technical University, Munich)
1986–1988: Postdoc (Bell Laboratories)
1988–1994: Research Group Leader, Postdoc, Physical Chemistry Department (University of Mainz)
1995: Habilitation
Since 1994: Research Group Leader, Department of Interfaces (Max Planck Institute of Colloids and Interfaces)

Our research focusses on the behaviour of sessile drops and thin liquid films at planar interfaces, when the liquid contains volatile components. We investigate how the evaporation of the volatile components affects the shape of the drops and the wetting and rupture of thin liquid films. We study further the impact of the evaporation on the deposition of the nonvolatile liquid components. The investigations primarily focus on fundamental research aspects. Nevertheless, the studies are also relevant for applications. They provide for instance a better understanding of spin casting, a widely used process to form thin films on solid surfaces.

Evaporation and Coalescence of Sessile Drops

Sessile drops have a remarkably complicated evaporation behaviour. It is characterized by a larger evaporation rate near the contact line compared to the apex. This rate difference affects the shape of the drop, causes internal liquid flows, and can lead, for instance, to the well-known coffee ring effect. The behaviour becomes even more complicated for mixtures of liquids.

We have investigated the case of mixtures of two liquids with different volatilities and surface tensions. Evaporation leads to the enrichment of the less volatile component at the drop contact line. If this component has the lower surface tension, its peripheral enrichment results in a surface tension gradient towards the apex of the drop. This can cause a Marangoni flow away from the contact line. Thus a sessile drop with a quasistationary contact angle ("Marangoni contraction" **[1]**) may be observed for some time, even though each individual liquid component and their mixture completely wet the surface and eventually form a thin wetting layer.

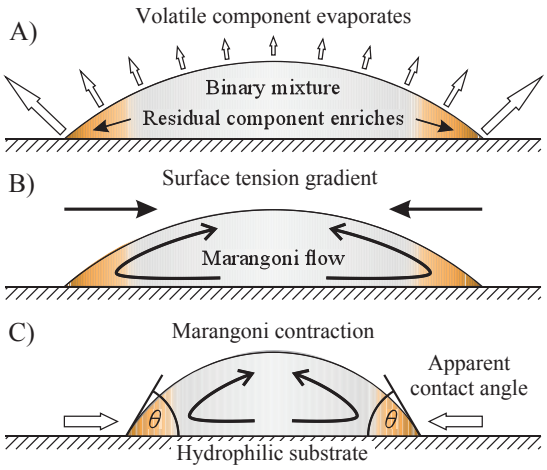

Fig. 1: Formation of a sessile drop with a quasistationary contact angle due to "Marangoni contraction" arising from the peripheral evaporative enrichment of one component.

We also investigated how the special evaporative behaviour of sessile drops affects the corrosive properties of these drops **[2]**. The impact of the Marangoni flow on the coalescence behaviour of two sessile drops has been used to investigate the fundamental research topic of "structured solvents". In this case the drops contained different liquids, which react with each other **[3]**.

Thin Planar Fims of Volatile Liquids Containing Nanoparticles

Individual nanoparticles embedded in molecularly thin films at planar substrates and the resulting film surface distortion (meniscus) adjacent to the nanoparticles was investigated by conventional optical reflection microscopy **(Fig. 2)**.

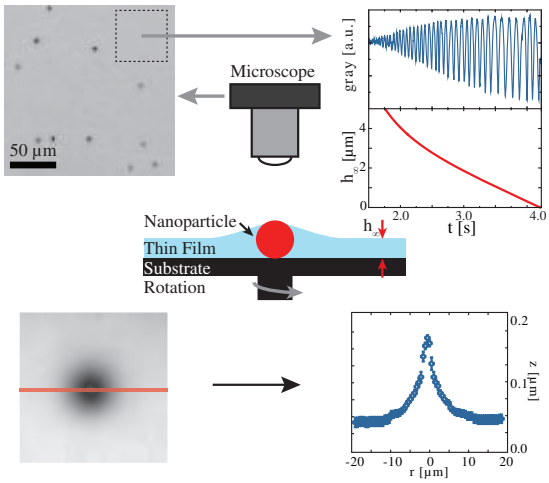

Fig. 2: Experimental setup to investigate the thinning of evaporating liquid films (in this case containing for instance individual nanoparticles). The temporary mean liquid film thickness is derived from the oscillation/variation of the mean reflected brightness (interferometry). Local deviations of the surface planarity modify locally the reflected intensity. This reveals the location of objects even much smaller than the Rayleigh diffraction limit (e.g., a nanoparticle).

In spite of their small size, the nanoparticles deform the fluid-fluid interface on the micrometer scale, a deformation that can be observed by optical microscopy **(Fig. 2)**. Thus the location of individual nanoparticles can be identified even if they are much smaller than the Rayleigh diffraction limit. The shape of the liquid meniscus was investigated in detail **[4]**. The configuration may possibly also be used to investigate biological systems (e.g., surface distortions in supported membranes caused by proteins or protein aggregates).

Thin Planar Fims of Mixtures of Volatile Liquids and Nonvolatile Polymers

Spin casting of mixtures of nonvolatile polymeric solutes dissolved in volatile solvents was studied experimentally and theoretically. The final solute coverage, time-resolved film thinning and the solvent evaporation, as well as the evolution of the solute concentration within the thinning film was investigated **[5]**. Various combinations of different polymers and different solvents were studied for a wide range of polymer concentrations and spin cast conditions. The findings were translated into a concise theoretical description of the process. It allows

to quantitatively predict the final solute coverage for polymer films with thicknesses up to several µm (see **Fig. 3**). The results are useful for an improved application of spin casting.

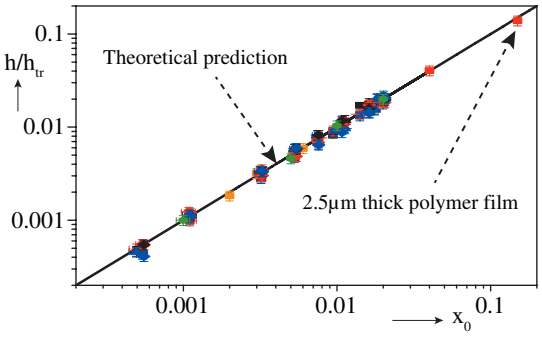

Fig. 3: Measured polymer film thicknesses (scaled to the so-called transition height h_{tr}) as a function of the initial polymer concentrations, x_0, compared to the theoretical prediction (full line).

Thin Planar Fims of Mixtures of Volatile Liquids and Nonvolatile Salts

The evaporative thinning behaviour of films of a volatile liquid solvent containing nonvolatile solutes (salts) has been investigated with time-resolved reflection microscopy **(Fig. 2)**. It is studied **(Fig. 4)** how the precipitation of the salt at the solid/liquid interface upon salt saturation (due to the evaporative loss of the solvent) initiates dewetting of the solvent film. The precipitates induce film rupture, whereas the pure solvents completely wet the substrate surface. A universal scenario is presented **[6]**, which relates the film rupture behaviour to the saturation limit of the salts.

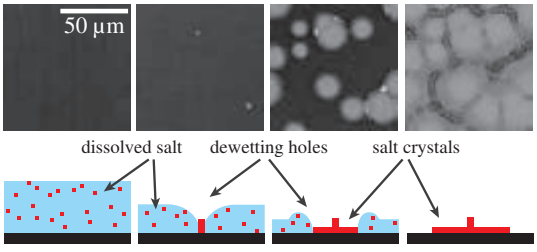

Fig. 4: Optical microscopy data and schematic showing how the growth of salt crystals leads to film rupture.

Immobilization of NPs and Nucleation Studies

A new preparation protocol to immobilize nanoparticles at surfaces through binding agents has been developed **[7]**. It has been found that the reversal of the sequence of a widely applied particle immobilization procedure strongly improves nanoparticle adhesion. The reason is the capillary-enhanced enrichment of the binding agent in the contact region between the particle and the substrate (see **Fig. 5**). The new protocol is widely applicable to different substrates, particles, and binding agents.

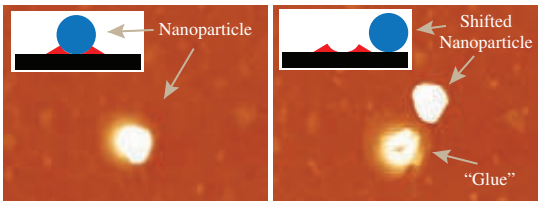

Fig. 5: Enrichment of the adhesion-promoting binding agent ("red glue") near the particle/substrate contact as demonstrated by an AFM study (left: nanoparticle located and fixed after application of the new immobilization protocol; right: binding agent found after the particle has been shifted away by an AFM tip).

In another study the controlled nucleation and growth of aggregates on prefrabricated arrays of active nucleation sites has been investigated **[8]**.

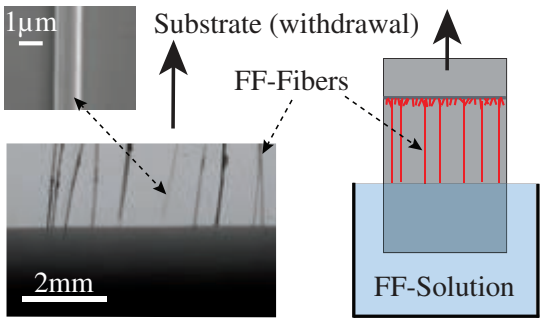

Fig. 6: Controlled growth of fibers of FF (diphenylalanine) by dip coating. The specific conditions near the contact line can be used to improve and modify the fiber growth.

Self-Assembly of Ultralong Aligned Dipeptide Single Crystals

A new and rather universal method for the controlled, fast fabrication of horizontally aligned single crystals from solution was developed **[9, 10]**. The focus was on the fabrication of fibers of FF (diphenylalanine). The approach uses the conventional dip coating technique with an important modification. With solvent mixtures the specific evaporation/composition conditions at the three phase contact line (see section on drop experiments) in combination with the resulting Marangoni flow affects the precipitation and crystal growth. It is demonstrated how this can be used to modify, control and improve the crystal growth.

H. Riegler, G. Chen, J. Danglad-Flores, S. Eickelmann, R. Perez-Garcia.
Hans.Riegler@mpikg.mpg.de

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MAX PLANCK RESEARCH GROUP

Coiled Coils as Molecular Force Sensors for Cell Biology and Materials Science

Kerstin G. Blank
01.02.1974
1996–2000: Diploma in Biotechnology University of Applied Sciences, Jena, Germany, Thesis: Protein engineering of antibody scFv-fragments as ligands for affinity chromatography
2003–2006: Doctoral thesis in Biophysics, Ludwig-Maximilians Universität, München, Germany Thesis: Molecular Force Sensors - Design, Characterization and Applications
2007: FEBS Postdoctoral Fellowship University of Strasbourg, France
2008: HFSP Postdoctoral Fellowship University of Leuven, Belgium
2009–2014: assistant professor Radboud University Nijmegen, The Netherlands
Since 07/2014: Max Planck Research Group Leader, Max Planck Institute of Colloids and Interfaces

Understanding the complex, multiscale mechanical interaction between cells and materials is one key goal that currently unites Biophysics, Cell Biology, Material Science and Medicine. It is well established that cells sense the mechanical properties of a material and physical material properties are now widely recognized as a design parameter in material development. Despite enormous progress in identifying the key molecular players in the cell, it has remained an open question how cells measure global material properties via localized receptor-ligand interactions **[1]**. Towards answering this key question, we are developing molecular force sensors (MFSs) that allow for measuring mechanical processes *in situ* and in real-time, both at the cell-material interface (2D) and inside a material (3D).

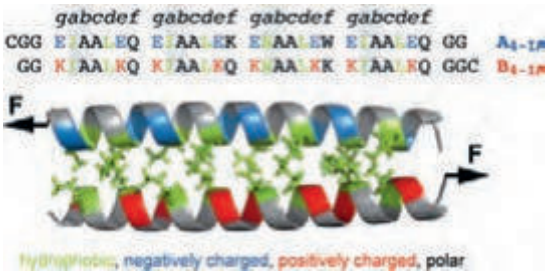

Fig. 1: Structure of the heterodimeric coiled coil $A_{4\text{-}IA}B_{4\text{-}IA}$. This superhelical structure is stabilized via hydrophobic amino acids located at specific positions (a and d). Other factors that stabilize the structure are ionic interactions (e and g) as well as the helix propensity of the individual helices. To apply force in the shear geometry, cysteine residues are located at specific termini.

These MFSs are based on structural elements found in extracellular matrix (ECM) proteins. In this report, we focus on coiled coils (CCs; **Fig. 1**), but also collagen mimetic triple helical structures are an interesting MFSs building block. In the last two years, our primary goal was to determine the sequence-structure-MECHANICS relationship of CCs and to establish a library of mechanically characterized and calibrated CC-based MFSs. While expanding this library, we have started with the development of CC-MFSs functionalized surfaces for 2D cell culture experiments. Moreover, we have introduced CCs as mechanoresponsive hydrogel crosslinks, which represents the first critical step towards the development of molecularly controlled, mechanosensitive and self-reporting ECM mimicking materials.

Coiled coils as molecular force sensors

In the last two years, we have gained detailed mechanistic insights into the mechanical response of CCs to shear forces **(Fig. 2a) [2–6]**. Using a combination of single-molecule force spectroscopy (SMFS) and molecular dynamics (MD) simulations (with Ana Vila Verde, Angelo Valleriani, Reinhard Lipowsky, MPICI) we have started with investigating CCs of different length **[2, 3]**. CC rupture (i.e. chain separation) follows a hierarchy of timescales. At very high loading rates (d*F*/dt), only accessible in simulations, the individual helices continuously uncoil from the points of force application. At intermediate loading rates (MD and SMFS), helix refolding becomes possible, which facilitates uncoiling-assisted sliding. At low loading rates (SMFS), uncoiling-assisted dissociation occurs once a sufficient amount of helical structure is uncoiled to render the remaining structure kinetically unstable. Uncoiling-assisted dissociation is the dominant chain separation mechanism for short CCs (see e.g. **Fig. 1**), where uncoiling small amounts of helical structure is already sufficient to dissociate the CC.

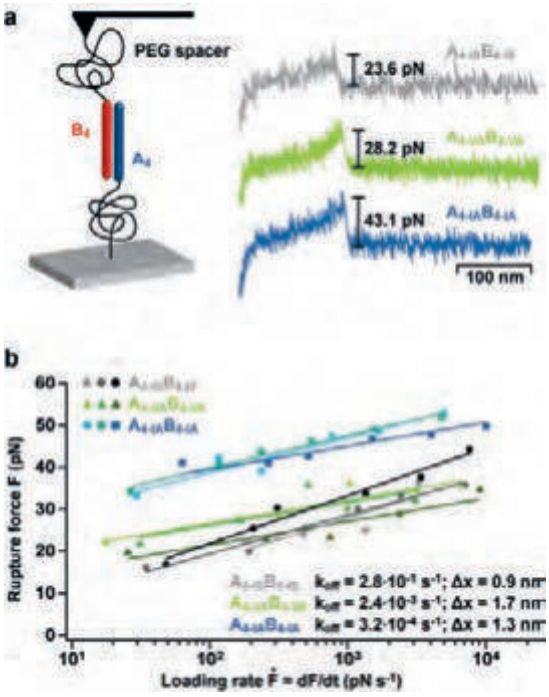

Fig. 2: Single-molecule force spectroscopy of heterodimeric CCs. a) Experimental setup and characteristic force extension curves of 3 different sequences. The sequences were designed to compare the effect of hydrophobic core packing (isoleucine (I) vs. valine (V) in position a) and helix propensity (alanine (A) vs. serine (S) in position b). b) Bell-Evans analysis of the different sequences to determine the dissociation rate k_{off} and the distance to the transition state Δx.

Knowledge of this fundamental mechanism has led to the question how helix propensity and hydrophobic core packing affect the CC response to shear forces. We thus introduced mutations to reduce the packing density in the hydrophobic core or the helix propensity **(Fig. 2)**. Both mutations reduced the thermodynamic stability; however, SMFS showed different effects on the underlying energy landscape **[4]**. A lower helix propensity decreased the barrier height (k_{off}) and the distance to the transition state (Δx). In contrast, the sequence with the less densely packed hydrophobic core showed an increase in Δx. Combined with the MD results, these additional mechanistic insights directly suggest that reinforcing the individual helices against uncoiling stabilizes the entire CC. Using covalent

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and dynamic staples, which bridge two adjacent helical turns, we were indeed able to increase the rupture force, depending on the number and position of the staple(s) **[5]** (with Matthew Harrington, MPICI, now McGill Montreal; David Fairlie, UQ Brisbane). Integrating all obtained results, we have established a small library of CCs with rupture forces in the range of 15–55 pN. Our next goal is to extend the force range towards higher rupture forces. Towards this goal, we have investigated a heterotrimeric sequence with MD simulations. The simulations predict significantly higher rupture forces for the CC trimer when compared to a structurally similar dimer **[6]**.

Molecular force sensors for cell biology

Using the current library of mechanically calibrated CCs, we have implemented first experiments to test the application potential of CC-based MFSs for measuring cell-generated traction forces. Similar to the SMFS experiments, one chain of the CC was immobilized to a glass surface while the second chain was equipped with the cell-adhesive peptide RGDS **(Fig. 3)**.

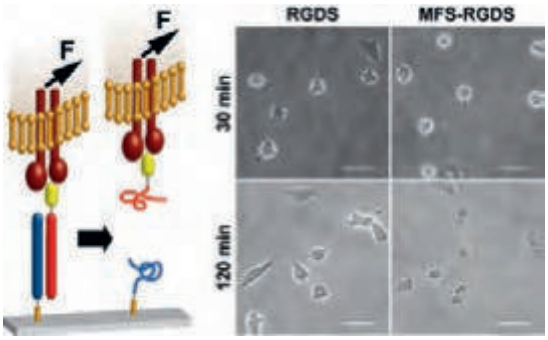

Fig. 3: CC-based MFSs for determining the threshold force of cell attachment. The CC $A_{4\text{-}IA}B_{4\text{-}IA}$ was functionalized with the cell-adhesive peptide RGDS (MFS-RGDS). Mouse fibroblasts are not able to stably attach to the MFS-RGDS functionalized surface over a two-hour time window. In contrast, stable attachment was observed when RGDS was covalently coupled to the surface (RGDS; positive control) Scale bar: 50 µm.

Preliminary results show that fibroblasts are indeed able to attach to MFS-RGDS functionalized surfaces (30 min); however, the tested CC $(A_{4\text{-}IA}B_{4\text{-}IA})$ was not able to maintain long-term cell growth. After two hours (120 min), the cells have ruptured a significant fraction of CCs so that the density of RGDS dropped below a critical threshold. In contrast, experiments with endothelial cells (obtained from a collaboration with Petra Knaus, FU Berlin **[7]**) showed a higher number of attached cells at the two-hour time point. This is a highly crucial result as it proves the biocompatibility of our MFS design as well as the potential of CC-based MFSs for sensitively discriminating cell-generated forces.

Molecular force sensors for material science

Towards ECM mimicking materials, we are utilizing the CCs as crosslinks for poly(ethylene glycol) (PEG)-based hydrogels. Using star-shaped PEG, we ensure that the contour length of each crosslinked chain is similar within the hydrogel. This yields a structurally controlled material where the mechanical properties of each building block are exactly described **(Fig. 4) [5, 8]**.

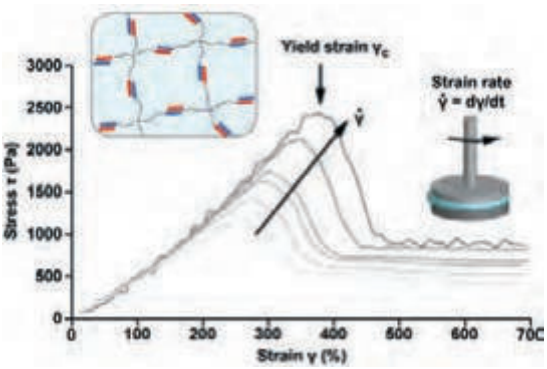

Fig. 4: CCs as mechanoresponsive hydrogel building blocks. Probing $A_{4\text{-}IA}B_{4\text{-}IA}$-crosslinked materials in the non-linear viscoelastic range reveals that the yield strain shifts to higher values when increasing the strain rate; a behaviour that is reminiscent of non-equilibrium bond rupture in SMFS.

Using bulk rheology, we have shown that material failure (i.e. CC rupture) is strain rate dependent. This suggests that crosslink rupture in the hydrogel can be described in a similar way as bond rupture in SMFS. In collaboration with Klaus Kroy (U Leipzig), we have developed a new model that allows us to quantitatively describe the hydrogel response and to extract single bond parameters. This is an excellent starting point for the further development of this hydrogel as a force-sensing material. Our final goal is to integrate a fluorescent readout (donor-acceptor pair reporting on CC rupture and self-healing). This will ultimately allow for observing local force distributions and force propagation pathways as well as material failure processes with unprecedented spatial and temporal resolution.

Additional projects

Other on-going projects involve (1) synthetic dendritic cells **[9–11]** (Carl Figdor, Radboud University Nijmegen), (2) single-molecule catalysis **[12–13]** (Alan Rowan, Radboud University Nijmegen), (3) mechanically reinforced hydrogels **[14]** (Bernhard Schmidt, MPICI), (4) sequence-structure-mechanics relationships of collagen (Luca Bertinetti, Emanuel Schneck, Peter Fratzl, MPICI), (5) protein-magnetite interactions **[15]** (Damien Faivre, MPICI, now CEA Cadarache) and (6) protein-chitin interactions (Yael Politi, MPICI).

K. G. Blank, Z. Atris, R. Dünnebacke, M. Göktas, E. Grad, A. Hahmann, A. Heilig, P. López García, J. Ruiz Rodriguez, A. Sanz de León, T. Schmitz, G. Song, A. Talib, I. Tunn, H. van Kan-Davelaar, R. Yaadav, J. Zhu
kerstin.blank@mpikg.mpg.de

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APPENDIX

Organigramm
Organization Chart

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- 3D Imaging of Forming Tissues/Dr. Luca Bertinetti
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  (Since October 2017 Full Professor in the Department of the Chemistry and Physics of Materials at the University Salzburg)
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BMBF	Biotechnologie2020+ Strukturvorhaben: MaxSynBio	Prof. Lipowsky TH	01.08.2017 – 31.07.2020	MPI für Dynamik komplexer technischer Systeme, Magdeburg MPI für Biochemie, Martinsried MPI für molekulare Physiologie, Dortmund Friedrich-Alexander-Universität, Erlangen MPI für molekulare Zellbiologie und Genetik, Dresden MPI für Polymerforschung, Mainz MPI für Intelligente Systeme, Stuttgart MPI für terrestrische Mikrobiologie, Marburg MPI für Dynamik und Selbstorganisation, Göttingen
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EU

Zuwendungs-geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
EU	Nanomedicine for target-specific imaging and treatment of atherothrombosis: development and initial clinical feasibility	Dr. Faivre BM	01.02.2013 – 31.01.2018	Institut National de la Sante et de la Recherche Medicale, Paris, France Assistance Publique - Hopizaux de Paris, Paris, France Inserm-Transfert SA, Paris, France Academic Medical Center, Amsterdam, The Netherlands Medical University of Graz, Clinical Institute for Medical and Chemical Laboratory Diagnosis, Graz, Austria Syddansk Universitet, Odense, Denamrk Universitätsklinikum Erlangen, Erlangen University of Twente, Enschede, Netherlands CEA-LETI, Commissariat à l'énergie atomiques et aux énergies alternatives, Paris, France CLINAM – European Foundation for Clinical Nanomedicine, Basel, Switzerland WizSoft, Tel Aviv, Israel nanoPET Pharma GmbH, Berlin Semmelweis University, Budapest, Hungary Bracco Imaging S.p.A., Milan, Italy Edinethics Ltd., Edinburgh, UK
EU	Systems Glycobiology of Gastric Cancer	Dr. Kolarich BMS	01.05.2013 – 30.04.2018	University of Gothenburg, Goeteborg, Sweden National Institute for Bioprocessing Research & Training, Dublin, Ireland Institute of Molecular Pathology and Immunology of the University of Porto, Porto, Portugal Swiss Institute of Bioinformatics, Geneva, Switzerland Umeå University, Umeå, Sweden University of Copenhagen, Copenhagen, Denmark OLINK AB, Uppsala, Sweden University of Siena, Siena, Italy Uppsala University, Uppsala, Sweden Syddansk Universitet, Odense, Denamrk Ariana Pharma SA, Paris, France
EU	Complex wetting phenomena	Dr. Miller GF	01.01.2014 – 31.12.2017	Technische Universität Darmstadt „Aristotle University of Thessaloniki, Greece Aristotle University of Thessaloniki, Greece „Hebrew University of Jerusalem, Israel Loughborough University, UK Universidad Complutense de Madrid, Spain Maria Curie-Sklodovska University, Lublin, Poland University of Twente, Enschede, Netherlands Evonik AG, Essen Unilever UK Central Resources Limited, London, UK

EU

Zuwendungs-geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
EU	Nanoporous Poly(Ionic Liquid) Membrane - NAPOLI	Dr. Yuan KC	01.03.2015 - 31.12.2017	
EU	Development of Selective Carbohydrate Immunomodulators Targeting C-type Lectin Receptors on Antigen Presenting Cells	Prof. Seeberger BMS	01.01.2015 - 31.12.2018	Asociacion Centro de Investigacion Cooperativa en Biomateilales – CIC biomaGUNE, Spanien Glycodiag, Chevilly, Frankreich Universita Degli Studi Di Milano, Italien Universite Joseph Fouruer Grenoble, Frankreich Agencia Estatel Consejo Superior de Investigaciones Cientificas, Madrid Stichting VU.VUMC, Amsterdam Deutsches Krebsforschungsinstitut, Heidelberg Universiteit Leiden, Niederlande Glycouniverse GmbH & Co. KGAA, Berlin The University of Manchester, UK DC4U, Bussum, Niederlande Midatech Biogune, Derio, Spanien
EU	Automated synthesis of S. pneumoniae 7F capsular polysaccharide repeating unit as candidate for conjugate vaccines	Prof. Seeberger BMS	01.04.2015 - 31.03.2017	
EU	High energy lithium sulphur cells and batteries	Prof. Antonietti KC	01.06.2015 - 31.05.2019	Kemijski Institut, Ljubljana, Slovenia Saft SAS, Bagnolet, France Centre National de la Recherche Scientifique, Paris, France Solvionic SA, Toulouse, France Chalmers University of Technology, Goeteborg, Sweden Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V., Münschen Picosun Oy, Espoo, Finnland Westfälische Wilhelms-Universität Münster Fundacio Institut de Recerca de L'Energia de Catalunya, Sant Adria De Besos, Spanien Accurec-Recycling GmbH, Mühlheim Tel Aviv University, Isreal Insitut National de L Environnement et des Risques Ineris, Verneuil En Halatte, Frankreich Peugeot Citroen Automobiles S.A., Velizy-Villacoublay, Frankreich
EU	Exploiting Glycosylation of Colorectal Cancer for the development of improved diagnostics and therapeutics	Dr. Varon Silva BMS	01.09.2015 - 31.08.2019	Academisch Ziekenhuis Leiden –Leids Universitair Medisch Centrum, Leiden, Netherlands Ludger Ltd, Abingdon, UK Genos Doo Za Vjestacenje I Analiz, Osijek, Coratia Centre National de la Recherche Scientifique, Paris, France Stichting VU.VUMC, Amsterdam Alma Mater Studiorum – Universita de Bologna, Italien Nova ID FCT – Associacao Para A Inovacao e Desenvolvimento Da DCF, Caparica, Portugal
EU	Nanoporous Poly(Ionic Liquid) Membrane - NAPOLI	Dr. Yuan KC	01.03.2015 - 31.12.2017	

DFG

Zuwendungs-geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
DFG	Stochastic modelling of protein synthesis by ribosomes	Prof. Lipowsky TH	12.06.2015-11.06.2018	
DFG	Mechanische Anpassung von Biomaterialien durch Protein-Metall-Komplexe	Dr. M. Harrington BM	01.01.2014-31.10.2018	
DFG Transregios	Funktionelle Biomaterialien zur Steuerung von Heilungs-sprozessen in Knochen- und Hautgewebe – vom Material zur Klinik	Prof. Seeberger BMS	01.07.2013-30.06.2017	Universitätsklinikum Leipzig Universität Leipzig Technische Universität Dresden Universitätsklinikum Dresden Helmholtz-Zentrum für Umweltforschung Leipzig-Halle Leibniz-Institut für Polymerforschung Dresden e. V. Innovent e. V., Jena
DFG	eScience-konforme Standards für die Morphologie	Prof. Fratzl BM	01.09.2014-30.08.2017	Zoologisches Forschungsmuseum Alexander Koenig (ZFMK) Leibniz-Zentrum für Biodiversität der Tiere (ZFMK) Museum für Naturkunde Leibniz-Institut für Evolutions- und Biodiversitätsforschung Universität Rostock Rheinische Friedrich-Wilhelms-Univer-sität Bonn
DFG	Magneto-Aerotaxis bei magnetotaktischen Bakterien	Dr. Faivre BM	01.10.2014-30.09.2019	
DFG	Magneto-Aerotaxis bei magnetotaktischen Bakterien	Dr. Faivre BM	ab 2019	
DFG	Magneto-Aerotaxis bei magnetotaktischen Bakterien	Dr. Klumpp TH	01.11.2014-31.10.2017	
DFG	Selbstheilende Metallopolymere: Vom biologischen Modell bis zu synthetischen Materialien	Dr. Harrington BM	01.07.2014-31.03.2018	Max-Planck-Institut für molekulare Pflanzenphysiologie, Potsdam
DFG Transregios	Verbesserte anti-Kohlenhydrat-basierte Impfstoffe durch gezielte Aktivierung des angeborenen Immunsystems	Prof. Seeberger BMS	01.07.2014-30.06.2018	Charité - Universitätsmedizin Berlin
DFG Transregios	Verbesserte anti-Kohlenhydrat-basierte Impfstoffe durch gezielte Aktivierung des angeborenen Immunsystems	Prof. Seeberger BMS	01.07.2018-30.06.2022	Charité - Universitätsmedizin Berlin
DFG	Skalenkaskaden in komplexen Systemen	Dr. Weikl TH	01.10.2014-30.09.2018	Freie Universität Berlin
DFG	Untersuchung des Ablaufes der Kalzitbiomineralisation in Coccolithophoriden	Dr. Faivre BM	01.09.2014-30.08.2017	
DFG Emmy-Noether-Programm	Die Physik der nicht-spezifischen Wechselwirkungen zwischen Biomembranen	Dr. Schneck BM	01.11.2014-31.12.2018	
DFG Emmy-Noether-Programm	Die Physik der nicht-spezifischen Wechselwirkungen zwischen Biomembranen	Dr. Schneck BM	01.11.2017-30.04.2019	
DFG Emmy-Noether-Programm	Die Physik der nicht-spezifischen Wechselwirkungen zwischen Biomembranen	Dr. Schneck BM	01.11.2018-31.10.2019	

DFG

Zuwendungs-geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
DFG	"Greigit oder Magnetit: Umwelt und genetische Faktoren, die die Biomineralisation in magnetotaktische Bakterien kontrollieren"	Dr. Faivre BM	01.04.2015-31.01.2019	
DFG	Gottfried Wilhelm Leibniz-Programm	Prof. Fratzl BM Dr. Dunlop BM Dr. Wagermaier BM Dr. Dean	01.09.2010-31.01.2019	5 Subprojekte am Institut
DFG	Exzellenzcluster UniCat: Unifying Concepts in Catalysis	Prof. Antonietti KC	01.11.2012-31.10.2017 01.10.2017 - 31.12.2018	Humboldt-Universität Berlin Freie Universität Berlin Universität Potsdam Fritz-Haber-Institut der Max-Planck-Gesellschaft Berlin
DFG	Synthese pflanzlicher Kohlenhydrate und ihre Anwendung in der Biologie	Dr. Pfrengle BMS	01.02.2015 - 30.06.2018	
DFG	Synthese pflanzlicher Kohlenhydrate und ihre Anwendung in der Biologie	Dr. Pfrengle BMS	01.02.2018 -	
DFG	ERA_Chemistry_Biomimetische Bindung und Organisation von Magnetit-Nanopartikeln	Dr. Faivre BM	23.02.2015-30.09.2019	
DFG	Aufklärung der Mechanismen der Chitin-Faser-Orientierung in Athropodenkutikula	Dr. Politi BM	09.07.2015-31.05.2019	Technische Universität Dresden Hochschule Bremen
DFG	Die Funktion des Osteozytennetzwerks und dessen Einfluss auf das Knochenmaterial	Dr. Weinkamer BM	10.08.2015-31.03.2020	
DFG	Die Funktion des Osteozytennetzwerks und dessen Einfluss auf das Knochenmaterial	Dr. Wagermaier BM	10.08.2015-31.12.2019	
DFG	Empirisches Verständnis von Glykosylierungsreaktionen	Prof. Seeberger BMS	02.07.2015-03.01.2019	
DFG	Neue chemische Werkzeuge zur Aufklärung der Kohlenhydratchemie	Prof. Seeberger BMS	01.01.2019-31.12.2021	
DFG	Strukturelle Glykobiologie der Wechselwirkungen von Viren mit bakteriellen Polysacchariden	Dr. Neu BMS	03.09.2015-30.06.2018	
DFG	Strukturelle Flexibilität des optischen Disigns der Arthropodencornea	Dr. Politi BM	12.11.2015-31.10.2021	Humboldt Universität Berlin
DFG	Multifunktionelle geschichtete Magentit Komposite	Dr. Faivre BM	16.12.2015-15.12.2017	Universität Konstanz Universität Erlangen Forschungszentrum Jülich GmbH
DFG	Chemische Modifikationen von Polyheptazinimid: Kohlenstoff-Stickstoffbasierte Halbleiter mit verbesserter Struktur und elektronischen Eigenschaften für die komplette Wasserspaltung und neue photokatalytische Reaktion	Prof. Antonietti KC	01.02.2017 - 31.01.2020	
DFG	Aufklärung des natürlichen Fabrikationsprozesses eines leistungsstarken biologischen Polymerfadens	Dr. Bertinetti BM	01.05.2017 - 30.04.2020	

DFG

Zuwendungs-geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
DFG	Molekulare Mechanismen hinter der Protein-Halotoleranz	Dr. Vila Verde TH	01.06.2018 - 31.05.2021	
DFG	Mikromechanik und Struktur-Funktions-Beziehungen in Mechanosensoren von Spinnen; Schlüssel zum Verständnis der Organleistung	Dr. Politi BM	01.06.2017 - 31.05.2020	Ben-Gurion University of Negev
DFG Emmy-Noether-Programm	Biophysikalische Signale der extrazellulären Matrix im Ruhezustand und der Knochenmetastase	Dr. Cipitria BM	01.10.2017 - 30.09.2020	
DFG	Aufnahme und Freigabe von Ladung durch den humanen Lektinrezeptor Langerin	Dr. Rademacher BMS	01.05.2018 - 30.04.2021	
DFG	Entwicklung von Nicht-Kohlenhydrat Glykomimetika für bakterielle Lektine	Dr. Rademacher BMS	01.02.2018 - 31.01.2021	k.A.
DFG	Organische Kathodenmaterialienfür Magnesiumbatterien	Dr. Liedel KC	01.03.2018 - 28.02.2021	
DFG	Dispersive Wechselwirkungen in flourinierten Biopolymeren	Dr. Vila Verde TH	01.04.2018 - 30.03.2021	k.A.
DFG	In vivo Visualisierung der pathologisch veränderten Extrazellulärmatrix “Matrix in Vision”	Prof. Seeberger BMS	01.07.2018 - 30.06.2022	Charité - Universitätsmedizin Berlin

Supranationale Einrichtungen

ESA/ESTEC	FOR ESA-MAP Soft Matter Dynamics	Dr. Miller BM	01.10.2015 - 31.12.2019	Deutsches Zentrum für Luft- und Raumfahrt, Köln Uiversite Paris-Sud Le Centre National de la Recherche Scientifique, Paris University of Liege, Belgien Aberystwyth University, Ceredigion, UK TeclisParc de Chancolan, Frankreich Trinity College, Dubin, Irland Universität Düsseldorf University Twente, Niederlande University of Rennes 1, Frankreich Universität Erlangen Duke University, Durham, UK CNR, Padova, Italien Research Committee AUTH, Thessaloniki, Griechenland IFP Energies nouvelles, Frankreich Loufakis Chemicals S.A., Griechenland Nestlé S.A., Vevey, Schweiz University of Pennsylvania, USA Moscow State University, Russland ESPCI Paris
HFSP Research Grant		Prof. Fratzl BM	01.09.2017 - 31.08.2020	Cornell University Weizmann Insitute

Stiftungen

Zuwendungs-geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
Körber-Stiftung	Körber-Preis 2007	Prof. Seeberger BMS	01.01.09.2007-	
GIF-German Israeli Foundation	Targeting Antibiotic Resistance of Bacteria with Self-Immolative Dendritic Prodrugs	Prof. Seeberger BMS	01.01.2015 - 30.06.2018	Tel Aviv University
GIF-German Israeli Foundation	Enantiselective mesoporous carbon based on chiral ionic liquids	Dr. Oschatz KC	01.01.2017 - 31.12.2019	Bar Ilan University
Lundbeck Foundation	Improved mechanical functionaltity of chitin based biological materials by inorganic fortification	Prof. Fratzl Hanna Leemreize BM	01.03.2016-31.01.2017	
Böhringer Ingelheim Stiftung	Fragment-based design of targeted delivery vehicles: High specificity through low affinity heteromultivalent interactions	Dr. Rademacher BMS	01.11.2016-31.10.2017	
DARPA	Radial Approach to the Automated Synthesis of Small Molecules	Dr. Gilmore BMS	01.09.2016-31.12.2018	
Novo Nordisk Fonden	Project “Draupnir”	Prof. Seeberger BMS	01.01.2018 - 30.06.2019	

Sonstige deutsche Forschungsfinanzierer

DAAD	Projektbezogener Personenaustausch mit Portugal	Dr. Kolarich BMS	2016-2017	Institute of Molecular Pathology and Imm, Portugal

Ausgewählte Veranstaltungen
Selected Events

2017

- **13. May Potsdam Science Day**
  Potsdam Science Park

- **27. April Zukunftstag für Mädchen und Jungen im Land Brandenburg**
  Max Planck Campus, Potsdam Science Park

- **28. May – 1. June 12th International Conference on the Chemistry and Biology of Mineralized Tissues (ICCMBT)**
  Kongresshotel Potsdam

- **16. June Alumni Meeting**
  MPI of Colloids and Interfaces

- **16. – 18. October Multiscale Mechanochemistry & Mechanobiology – From Molecular Mechanisms to Smart Materials**
  Harnack Haus, Berlin

- **27. – 28. November AESTHETICS get SYNTHETIC: 1ST KLAS WORKSHOP**
  Max Planck Campus, Potsdam Science Park

- **14. December Biomolecular Systems Day**
  MPI of Colloids and Interfaces

2018

- **19. – 22. March 4th Euro Bio-inspired Materials – International School and Conference on Biological Materials Science**
  Kongresshotel Potsdam

- **26. April Zukunftstag für Mädchen und Jungen im Land Brandenburg**
  Max Planck Campus, Potsdam Science Park

- **26. April Leibniz-Kolleg Potsdam: Künstliches Leben?**
  Universität Potsdam, Campus Am Neuen Palais

- **1. June Alumni Meeting**
  MPI of Colloids and Interfaces

- **2. – 4. July MaxSynBio Symposium Magdeburg 2018**
  Festung Mark Magdeburg

- **13. December Biomolecular Systems Day**
  MPI of Colloids and Interfaces

Wissenschaftliche Abschlüsse
Scientific Degrees

Bachelor Theses
Department of Biomolecular Systems

2018

Busmann, J.: Affinity of multivalent carriers affect Langerin internalization and eadosomal routing. Freie Universität Berlin.

Lühle, J.: In vitro validation of recombinant alpaca single domain antibodies targeting Plasmodium falciparum GPIs. Universität Potsdam.

Master Theses
Department of Biomolecular Systems

2017

Cazin, I.: Novel Heterogeneous Photoredox Transformations Using Organic Materials. Universität Zagreb.

Rentzsch, M.: Targeted Delivery to Langerin-expressing cells. Freie Universität Berlin.

2018

Fittolani, G.: Automated Glycan Assembly of Fluorinated Cellulose Oligosaccharides. Padova University.

Fortes Martin, R.: Synthesis of Carbohydrate Building Blocks for Automated Glycan Assembly. Freie Universität Berlin.

Frensemeier, K.: Title: Validation of recombinant camelid single domain antibodies targeting globo-series glycans on cancer cells. Freie Universität Berlin.

Heidepriem, J.: Expression und neuartiges High-Throughput-Screening der O-GlcNAc-Transferase mit Peptid-Arrays. Beuth Hochschule für Technik Berlin.

Tsouka, A.: High-Throughput Synthesis of Glycan and Peptide Microarrays. Freie Universität Berlin.

Department of Colloid Chemistry

2018

Schutjajew, K.: Phase Transitions of Ionic Liquids Confined in Charged Carbon Nanopores. Master Thesis, Freie Universität Berlin.

Perovic, M.: Illuminating the Principles of Partial Glucose Oxidation in Aqueous Solution with Molecular Oxygen Using Gold Catalysts on Carbonaceous Model Supports. Universität Potsdam.

Mechano(bio)chemistry

2017

Farhadi, D.: Klonierung, Expression und Charakterisierung des Magnetit-bindenden Proteins Mad10 aus Desulfamplus magnetovallimortis BW-1. Hochschule Niederrhein

Yaadav, R.: Single-molecule force spectroscopy of the N-terminal domain (NTD) of spider silk proteins. Amity University

2018

Schmitz, T.: Interaction of magnetosomal proteins with synthetic magnetite nanoparticles. Universität Ulm

PhD Theses
Department of Biomaterials

2017

Ehrig, S.: 3D curvature and its role on tissue organization. Universität Potsdam.

Ghaisari, S.: Anisotropy analysis of magnetic nanoparticles in magnetotactic bacteria. Universität Potsdam.

Reichel, V.: Bioinspired magnetite nanoparticles: A step forward to biomedical applications? Universität Potsdam.

Schöppler, V.: Material properties of Banksia follicles. Universität Potsdam.

Schrof, S.: Multimodal structural, compositional, and mechanical characterization of cortical bone on the micron scale. Humboldt-Universität zu Berlin.

Zhukova, Y.: Surface Nanostructuring for Cell and Tissue Growth. Freie Universität Berlin.

2018

Codutti, A.: Behavior of Magnetic Microswimmers: Simulations for Natural Swimmers and Synthetic Propellers. Universität Potsdam.

Jensen, A.: Structure and dynamics of amorphous carbonates related to biomineralization. Universität Potsdam.

Könnig, D.: Influence of Mechanical Boundary Conditions on Mechanical and Structural Properties of Regenerating Muskuloskeletal Tissues: An in Vitro Approach. Humboldt-Universität zu Berlin.

Rodriguez, I.: Structural characterization of single and interacting soft interfaces displaying brushes of synthetic or biomolecular polymers. Universität Potsdam.

Seidel, R.: Multi-scale, correlative structural and material characterization of the tiled skeletons of sharks and rays. HU Berlin/Museum of Natural History Berlin.

Pohl, A.: Shaping via binding: Do Mad proteins determine anisotropic growth of magnetite crystals? Universität Potsdam.

Department of Biomolecular Systems

2017

Bharate, P.: Automated Glycan Assembly of Oligomannose Glycans for Sensing Applications. Freie Universität Berlin.

Dallabernardina, P.: Automated Glycan Assembly of Hemicellulosic Oligosaccharides from the Plant Cell Wall. Freie Universität Berlin.

Garg, M.: Conformational Analysis and Applications in Diagnostic of Glycosylphosphatidylinositol Glycan Derivatives. Freie Universität Berlin.

Geißner, A.: Glycan Arrays: From Basic Glycobiology to Diagnostics and Vaccine Research. Freie Universität Berlin.

Grube, M.: Synthesis and biological evaluation of Glycosylphosphatidylinositols from Trypanasoma brucei. Freie Universität Berlin.

Michel, D.: Synthesis of homogeneous N-glycosylated- and GPI-anchored peptides for semi-synthesis of the prion protein. Freie Universität Berlin.

Plutschack, M. B.: Sustainable Oxidants for the Photooxidation of Organic Molecules in Flow. Freie Universität Berlin.

Schirmeister, F.: Development and Application of High Throughput Porous Graphitized Carbon Glycomics and In-Depth Glycoproteomics of Bacterial Flagellins. Freie Universität Berlin.

Wamhoff, E.-C.: Glycomimetic Langerin Ligands for Langerhans Cell Targeting. Freie Universität Berlin.

2018

Bartetzko, M.: Development of Synthetic Glycan Tools for Investigating Plant Cell Wall Pectins. Freie Universität Berlin.

Kononov, A.: Oligosaccharides Prepared by Automated Glycan Assembly as Basis for Structural Investigations of Carbohydrates. Freie Universität Berlin.

Roller, R.: Intein-Mediated Semi-Synthesis and Characterization of Glycosylphosphatidylinositol (GPI)-Anchored Proteins, Freie Universität Berlin.

Schultze, J.: Towards Langerhans cell immune modulation. Freie Universität Berlin.

Senf, D.: Synthesis of Arabinoxylan Oligo- and Polysaccharides from the Plant Cell Wall. Freie Universität Berlin.

Varela, S.: Carbohydrate-based Nanomaterials for Imaging and Drug Discovery. Freie Universität Berlin.

Xu, F.: Synthetic Oligosaccharides as Tools to Investigate Bacterial Capsular Polysaccharides and Teichoic Acids. Freie Universität Berlin.

Department of Colloid Chemistry

2017

Berthold, T.: Tannine für nachhaltige und funktionale Kohlenstoffmaterialien: Synthesestrategien und mögliche Anwendungen. Universität Potsdam.

Graglia, M.: Lignin Valorization: Extraction, Characterization and Applications. Universität Potsdam.

Jordan, T.: CxNy-Materials from Supramolecular Precursors for „All- Carbon" Composite Materials. Universität Potsdam.

Lin, H.: Acceleration and Amplification of Biomimetic Actuation: The Empty Pore Matters. Universität Potsdam.

Peh, E.: Calcium Carbonate Formation: Influence of various Interfacial Conditions. Universität Potsdam.

Vacogne, C. D.: New Synthetic Routes towards Well-Defined Polypeptides, Morphologies and Hydrogels. Universität Potsdam.

Wei, C.: On the Role of Monomer Drops and Swelling in Aqueous Heterophase Polymerization. Universität Potsdam.

Willersinn, J.: Self-Assembly of Double Hydrophilic Block Copolymers: Organized Particles and Vesicles Beyond Amphiphiles. Universität Potsdam.

Zhang, W.: Functional Poly(ionic liquid) Materials based on Poly(1,2,4- triazolium)s. Universität Potsdam.

2018

Braun, M.: Heterogeneous Catalysis for the Conversion of Fructose to Chemicals and Fuel in a Continuous Flow Process. Universität Potsdam.

Chaleawlert-Umpon, S.: Sustainable electrode materials based on lignin. Universität Potsdam.

Doriti, A.: Sustainable bio-based poly-N-glycines and polyesters. Universität Potsdam.

Lama, S.: Functionalization of Porous Carbon Materials with Heteroatoms and Application as Supports in Industrial Heterogeneous Catalysis. Universität Potsdam.

Lee, H.-C.: Toward Ultimate Control of Polymerization and Catalytic Property: A Combination of Metal-Organic Frameworks and ATRP. Universität Potsdam.

Li, L.: Preparation of novel photoactive materials: different pre-compositions, post-modifications and improved performance. Universität Potsdam.

Mani, C. M.: Functional Nanoporous Carbon-Based Materials derived from Oxocarbon-Metal Coordination Complexes. Universität Potsdam.

Tröger-Müller, S.: Truly Sustainable Imidazolium Ionics Towards Expanding Applicability in Next-Generation Batteries. Universität Potsdam.

Department of Theory & Bio-Systems

2017

Georgiev, V.: Light-induced transformations in biomembranes. Universität Potsdam.

Kashef Ol Gheta, S.: Developing Ion Parameters and Investigating Ion Specific Effects in Biological Systems. Freie Universität Berlin.

Kiani, B.: On Structural Properties of Magnetosome Chains. Universität Potsdam.

Muždalo, A.: Thermal cis→trans isomerization of azobenzenes studied by path sampling and QM/MM stochastic dynamics. Universität Potsdam.

Paul, F.:	Markov State Modeling of Binding and Conformational Changes of Proteins. Universität Potsdam.
Sauter, J.:	The Molecular Origin of Plant Cell Wall Swelling. Universität Potsdam.
Uçar, M. C.:	Elastic Interactions Between Antagonistic Molecular Motors. Universität Potsdam.

2018

Danglad-Flores, J. A.:	Quantitative Analysis of the Deposition of Nonvolatile Species on Planar Solid Substrates from Evaporative Thin Films. TU Berlin.
Eickelmann, S.:	Experimental Study of Liquid Interfaces with Compositional Gradients: Distortion & Rupture of Ultra-Thin Films and Other Effects. Universität Potsdam.
Perez Garcia, R.:	Controlled Deposition Fullerenes. TU Berlin.
Rey, U.:	Presynaptic biogenesis by axonal transport of lysosome-related vesicles. Freie Universität Berlin.
Robalo, J. R.:	Investigating the role of fluorinated amino acids on protein structure and function using simulation. Universität Potsdam.
Chen, G.:	Nanoparticles at Solid Interfaces. Universität Potsdam.

Habilitations

Department of Biomolecular Systems

2018

Varon Silva, D.:	Chemical Biology of Glycosylphosphatidylinositols and GPI-Anchored Molecules, Freie Universität Berlin.

Personalien
Appointments and Honors

Ehrungen/Mitgliedschaften/Honorarprofessuren
Honors/Memberships/Honorary Professorships

2017

Prof. Dr. Reinhard Lipowsky: Director of the Department of Theory & Bio-Systems received the Ostwald Preis of the German Colloid Society.

Prof. Dr. Peter H. Seeberger: Director of the Department of Biomolecular Systems received 2017 Stifterverband Science Prize.

Prof. Dr. Ulrich S. Schubert: Chair of Organic and Macromolecular Chemistry at the Friedrich-Schiller-University Jena, was appointed as External Scientific Member of the Max Planck Institute of Colloids and Interfaces.

Prof. Joanna Aizenberg: Amy Smith Berylson Professor of Materials Science at Harvard's School of Engineering and Applied Sciences, Co-Director of The Kavli Institute for Bionano Science and Technology, Professor of Chemistry and Chemical Biology at Harvard University and Core Faculty Member of the Wyss Institute for Biologically Inspired Engineering, was appointed as External Scientific Member of the Max Planck Institute of Colloids and Interfaces.

Dr. Jaime Agudo-Canalejo: Postdoc in the Department of Theory and Bio-Systems received the Otto-Hahn-Medal of the Max Planck Society.

Dr. Felix Bröcker: Postdoc in the Department of Biomolecular Systems, received the 11th Potsdam young scientist award.

Dr. Felix Löffler: Group Leader in the Department of Biomolecular Systems, received one of the BMBF NanoMatFutur grants 2017.

Dr. Martina Delbianco: Group Leader in the Department of Biomolecular Systems has been received a Minerva Fast Track Fellowship.

Dr. Benjamin Schumann: Postdoc in the Department of Biomolecular Systems received the Otto-Hahn-Medal of the Max Planck Society.

2018

Prof. Dr. Markus Antonietti: Director of the Department of Colloid Chemistry, was awarded the Order of Merit (First Class) of the Federal Republic of Germany for his outstanding accomplishments for the Potsdam Science Park.

Peter H. Seeberger: Director of the Department of Biomolecular Systems, was chosen by the British journal "Medicine Maker" to be among the TOP 25 most inspirational professionals in the category „Masters of Bench".

Peter H. Seeberger: Director of the Department of Biomolecular Systems, received the Ernst Hellmut Vits Award from the Society for the Advancement of the University of Münster.

Peter H. Seeberger: Director of the Department of Biomolecular Systems, received the Gusi Peace Price, given by the Gusi Peace Prize Foundation, based in Manila, Philippines.

Bartholomäus Pieber: Group Leader in the Department of Biomolecular Systems, received the „Brandenburg Post-Doc Award" of the Brandenburg Ministry of Science, Research and Cultural Affairs.

Bartholomäus Pieber: Group Leader in the Department of Biomolecular Systems, received the „Monatshefte der Chemie – Wissenschaftspreis 2018" of the Austrian Chemical Society.

Bartholomäus Pieber: Group Leader in the Department of Biomolecular Systems, received a Liebig Fellowship of the Fonds der chemischen Industrie (VCI).

Sophia Rudorf: Group Leader in the Department of Theory & Bio-Systems, received the special price in "Theoretical Biophysics" of the Leibniz-Kolleg Potsdam.

Bernhard V.K.J. Schmidt: Group Leader in the Department of Colloid Chemistry, received a Dr. Hermann Schnell Fellowship of the GDCh (Gesellschaft Deutscher Chemiker; German Chemical Society)

Dr. Sanja Sviben: Postdoc in the Department of Biomaterials received the Otto-Hahn-Medal of the Max Planck Society.

Ruf an eine Universität
Appointments

2017

Dr. John Dunlop: Group Leader in the Department of Biomaterials, accepted a position as Full Professor in the Department of the Chemistry and Physics of Materials at the University Salzburg.

Dr. Matt Harrington: Group Leader in the Department of Biomaterials accepted a position as Assistant Professor in the Department of Chemistry at the McGill University Montreal, Canada.

Dr. Katja Skorb: Independent Researcher in the Department of Biomaterials, accepted a position as Full Professor in the Laboratory of Solution Chemistry of Advanced Materials and Technologies (SCAMT) at the ITMO University St. Petersburg.

2018

Dr. Damien Faivre: Group Leader in the Department of Biomaterials, accepted a position as group leader at the CEA Cadarache, France.

Publications

Biomaterials 2017

Journal Article

Albéric, M., Dean, M. N., Gourrier, A., Wagermaier, W., Dunlop, J. W. C., Staude, A., Fratzl, P., Reiche, I. Relation between the Macroscopic Pattern of Elephant Ivory and Its Three-Dimensional Micro-Tubular Network. PLoS One 12, e0166671 (2017).

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Publications

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Orientierungskarten
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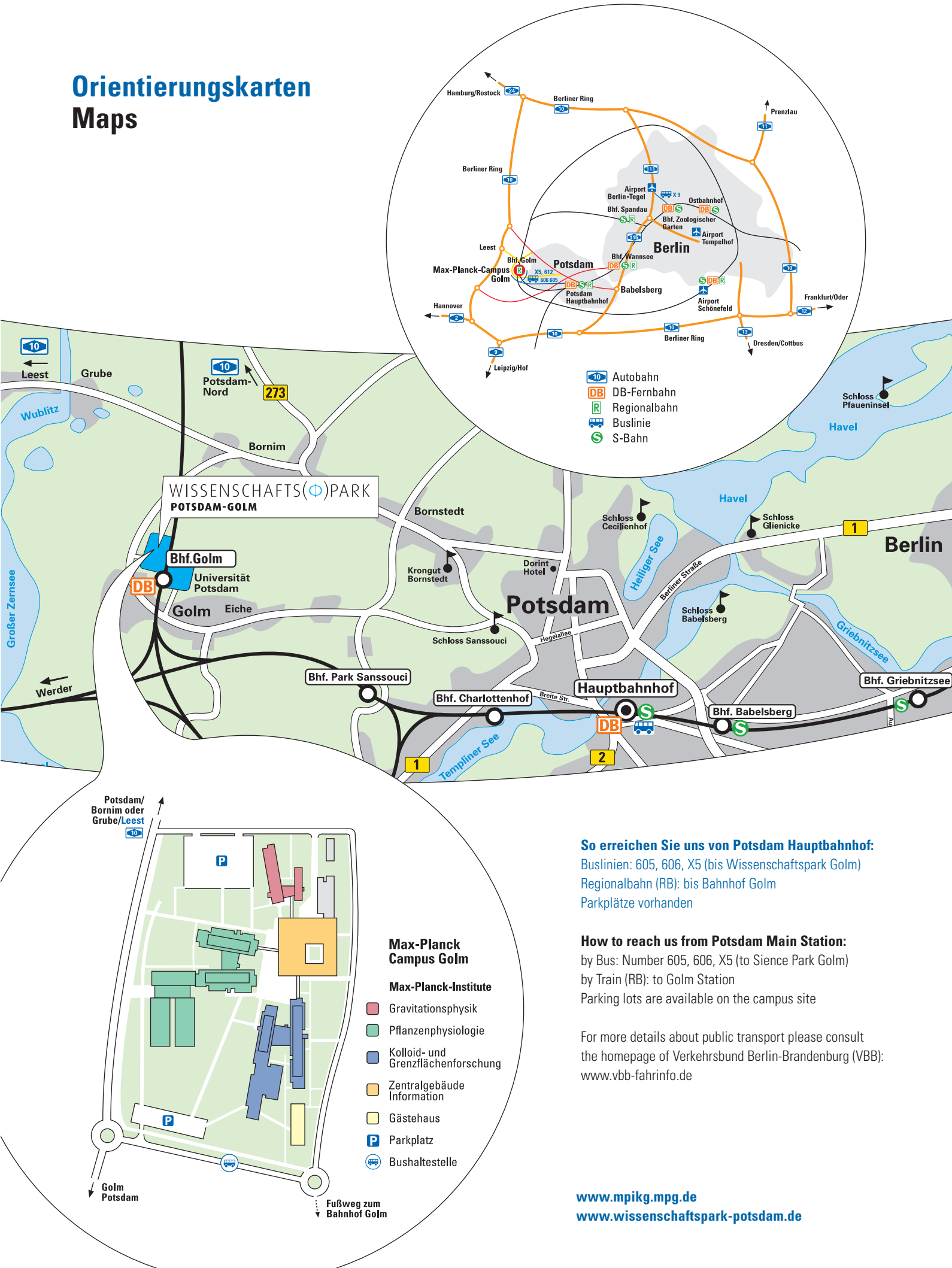

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