

Max Planck Institute of Colloids and Interfaces

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**Max Planck Institute
of Colloids and Interfaces**

RESEARCH REPORT 2013-2014

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Vorwort



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Helmuth Möhwald,
Kerstin Blank,
Reinhard Lipowsky

Kolloide sind sehr kleine Partikel im Größenbereich zwischen Nano- und Mikrometern. Objekte dieser Dimension sind die Bausteine, aus denen Organismen zusammengesetzt sind. Sie sind aber auch wesentliche Bestandteile von Materialien, Lacken oder Emulsionen, die oft deren mechanische, optische oder magnetische Eigenschaften bestimmen. Die allgemeine Zielsetzung im Max-Planck-Institut für Kolloid- und Grenzflächenforschung (MPIKG) ist es, unser Verständnis von Kolloiden und deren Zusammenwirken durch Erforschung der Synthese, durch physikochemische Charakterisierung sowie durch theoretische Beschreibung zu verbessern. Auf Grund der geringen Größe ihrer Bestandteile besitzen Materialien oder Organismen, die aus einer Assemblierung von Kolloiden bestehen, eine besonders große Grenzfläche zwischen eben diesen Komponenten. Viele der makroskopischen Eigenschaften werden deshalb auch durch die Natur der Grenzflächen bestimmt. Das vertiefte Verständnis von kolloidalen Strukturen und deren Grenzflächen stellt daher eine Basis für Entdeckungen und Innovationen im Bereich neuer Materialien und neuer medizinischen Behandlungen dar.

Das Max-Planck-Institut für Kolloid- und Grenzflächenforschung wurde 1992 gegründet und befindet sich seit 1999 im Wissenschaftspark Potsdam-Golm in Potsdam, der Hauptstadt von Brandenburg. Das Institut besteht aus vier Abteilungen, die die vielversprechendsten Aspekte der Forschung an Kolloiden und Grenzflächen betrachten, sowie aus einer Max-Planck-Forschungsgruppe zur Mechano(Bio)Chemie (Kerstin Blank).

Zwei Abteilungen befassen sich primär mit chemischer Synthese: Die Abteilung Kolloidchemie (Markus Antonietti) ist bekannt für die Chemie von Systemen, wobei eine breite Palette von Makromolekülen synthetisiert wird, um mesoskopische Verbundsysteme und Hybridmaterialien herzustellen. In letzter Zeit gelangen Durchbrüche in der Synthese funktionaler kohlenstoffbasierter Materialien auf Basis von erneuerbaren Ressourcen. Die Abteilung für Biomolekulare Systeme (Peter Seeberger) ist Vorreiter bei der Synthese von Poly-

sacchariden mit kontrollierter molekularer Struktur. Diese komplexen Makromoleküle sind in der Lage, andere lebenswichtige Moleküle wie Proteine oder Antikörper zu erkennen und von anderen zu unterscheiden. Ein längerfristiges Ziel dieser Forschungsarbeit ist die Entwicklung von neuen Impfstoffen, basierend auf Zuckermolekülen.

Die anderen beiden Abteilungen verfolgen einen physikbasierten Ansatz. Die Abteilung Biomaterialien (Peter Fratzl) setzt den Schwerpunkt in der experimentellen Charakterisierung, die Abteilung Theorie & Bio-Systeme (Reinhard Lipowsky) in der theoretischen Beschreibung. Die Forschung der Abteilung Biomaterialien konzentriert sich auf mehrskalige Strukturen von biologischen Materialien wie Knochen, Zähnen, Muscheln, dem Panzer von Arthropoden oder Pflanzenstengeln. Die Struktur und Funktion dieser Materialien in ihrem natürlichen Kontext zu verstehen, hilft uns bei der Entwicklung neuer Konzepte für bioinspirierte Materialien. Dadurch ergeben sich auch bessere Ansätze in der Knochenregeneration sowie bei der Diagnose und Behandlung von Knochenkrankheiten wie der Osteoporose. Theoretische Studien in der Abteilung Theorie & Bio-Systeme betrachten derzeit vor allem molekulare Maschinen sowie auch Biomembranen und Vesikel, die zum Teil auch mittels optischer Mikroskope experimentell studiert werden. Das langfristige Ziel dieser Forschungsaktivitäten ist es, die fundamentalen Prinzipien und die allgemeinen Regeln aufzuklären, auf Grund derer die Selbstorganisation von biomimetischen und biologischen Systemen im Nanometerbereich erfolgt.

Die Max-Planck-Forschungsgruppe Mechano(Bio)Chemie entwickelt Strategien, um Kräfte zu messen, die in biologischen Systemen auf Moleküle aufgebracht werden.

Ein wichtiges Ziel dabei ist es, besser verstehen zu lernen, wie biologische Prozesse durch mechanische Signale moduliert werden. Schließlich betreibt einer der Gründungsdirektoren des Institutes, ehemals Direktor der Abteilung Grenzflä-

Das MPIKG unterhält engen Kontakt zu allen Universitäten in Potsdam und Berlin, zum Beispiel durch die Teilnahme an mehreren Großprojekten im Rahmen der Deutschen Exzellenzinitiative. Das Institut betreibt auch eine Graduiertenschule (International Max Planck Research School on „Multiscale Bio-Systems“) in Kooperationen mit

Peter Fratzl,
Geschäftsführender Direktor 2013-14

Preface

Colloids are small particles in the size range between nanometers and microns. Objects of this size are the building blocks of all living organisms but they also represent essential components in materials, paints, emulsions and define their mechanical, optical, magnetic or other functional properties. The overall goal of the Max Planck Institute of Colloids and Interfaces (MPICI) is to improve our understanding of colloids and of their assembly through synthesis, physico-chemical characterization and theoretical description. Due to the small size of their constituents, materials or organisms based on the assembly of colloids contain exceptionally large amounts of interface between the building blocks, and many macroscopic properties may also be determined by the nature of these interfaces. Such improved understanding will be the basis for further discoveries and innovations in the areas of new materials and of new biomedical treatments.

The institute was founded in 1992 and established 1999 in the Potsdam-Golm Science Park located in Potsdam, the capital of Brandenburg. It is based on four Departments covering most promising aspects of colloid and interface science, as well as on a Max Planck Research Group on Mechano(Bio)Chemistry (Kerstin Blank).

Two departments are mainly addressing chemical synthesis: the Department of Colloid Chemistry (Markus Antonietti) is well-known for its research of the “chemistry of system design”, fabricating a variety of macromolecules to construct mesoscopic composite systems and hybrid materials. Recent breakthroughs relate to the synthesis of functional carbon-based materials from renewable resources. The Department of Biomolecular Systems (Peter Seeberger) is

pioneering the synthesis of polysaccharides with controlled molecular structure. These complex macromolecules are able to specifically recognize other macromolecules such as proteins and antibodies. A long-term goal of this research is to develop novel vaccines based on such sugar molecules.

The two other departments take a physics-based approach with an emphasis on experimental characterization in the Department of Biomaterials (Peter Fratzl) or on theoretical description in the Department of Theory and Bio-Systems (Reinhard Lipowsky). Research in the Department of Biomaterials focusses on the multi-scale structure of biological materials, such as bone, teeth, sea shells, arthropod carapaces or plant bodies. Understanding the function of these materials in their natural context leads to new concepts for bioinspired materials, as well as contributes to develop better approaches in bone regeneration and in the diagnosis and treatment of bone diseases, such as osteoporosis. Theoretical investigations in the department Theory & Bio-Systems currently address molecular machines as well as bio-membranes and vesicles that are also studied experimentally using optical microscopy. The long-term goal of these research activities is to elucidate the fundamental principles and generic mechanisms that govern the self-organization of biomimetic and biological systems in the nano-regime.

The Max Planck Research Group on Mechano(Bio)Chemistry develops strategies for sensing forces applied to molecules in complex biological systems. The long-term goal is to improve our understanding of how biological processes are modulated by mechanical signals. Finally, one of the founding directors of the institute, former



director of the Department of Interfaces and now emeritus (Helmuth Möhwald) continues research on soft nanostructures, such as monolayers of organic molecules and multilayers and capsules of positively and negatively charged polymers.

These and other research activities carried out in the last two years will be described in more detail in the main body of this report, which is structured according to the research groups within all departments of the MPICI. In the years 2013-14, the Department of Peter Seeberger was still provisionally located in Berlin-Dahlem within buildings of the Freie Universität Berlin. During these years, an additional wing was added to the building of the Institute in Golm, which was finished in the first half of 2015. Thus this Department will be finally able to move to the Golm Campus in summer 2015. In addition to new labs for this department, the construction also provides common laboratory space which will house improved nuclear magnetic resonance facilities as well as a new transmission electron microscope. These major investments will complement the wide range of physical and chemical characterization tools in the Institute that comprise among others a x-ray scattering and diffraction beam-line, combined with Raman spectroscopy, installed at the BESSY II synchrotron source in Berlin.

The MPICI has strong ties to all universities in Potsdam and Berlin, for example participating in several large projects in the framework of the German excellence initiative. It also runs the International Max Planck Research School on "Multiscale Bio-Systems" for the education of graduate students, together with several universities and the Fraunhofer Institute for Cell Therapy and Immunology IZI in the Potsdam-Golm Science Park. Members of the MPICI are involved in many teaching activities with the partner universities, and training of young scientists is one of the priorities in the institute. More than 50 former group leaders of the MPICI have now taken up professorships in Germany and abroad. The institute is highly visible internationally and regularly takes one of the first positions in the ranking by the Humboldt Foundation. The success of the MPICI is primarily due to the creativity, the hard work and the collaborative spirit of all its members. I sincerely thank them all for their contribution. We are all very grateful for the advice from our scientific advisory board, for the support by the Max Society and its various bodies, by our board of trustees and for the large number of wonderful collaborations that we could enjoy with scientists all over the world.

Peter Fratzl,
Managing Director 2013-14



Das Institut in Zahlen

Personal

Die während der letzten Jahre stabile Zahl von insgesamt 360 Mitarbeitern (**Abb.1**), von 100 Doktoranden (**Abb.2**) und von 90 Postdoktoranden (**Abb.3**) belegen, dass die Schrumpfung der Abteilung Grenzflächen durch den Aufbau der Abteilung Biomolekulare Systeme in etwa kompensiert wurde. Eine weitere Expansion wurde durch die (nicht) vorhandene Laborfläche limitiert. Diese Begrenzung wird nun bei Bezug des Erweiterungsbaus entfallen. Der Anteil der Ausländer unter den Postdoktoranden betrug konstant etwa 85%, während dieser Anteil unter den Doktoranden auf unter knapp 40% fiel.

Relativ informativ ist der Blick auf die Altersverteilung. Diese weist ein Maximum unter 30 Jahren bei den Doktoranden und etwas über 30 Jahren bei den Postdoktoranden auf (**Abb.4**). Bei den technischen und administrativen Mitarbeitern ist diese Verteilung relativ gleichmäßig. Bei den erfahreneren

Postdoktoranden und Gruppenleitern weist die Altersverteilung ein Maximum um 35 Jahre auf. Dies spiegelt wider, dass für diese Gruppe die Arbeit an dem Institut ein wesentlicher Karriereschritt ist. Dass der Schritt erfolgreich war, belegt die hohe Zahl an ehemaligen Mitarbeitern, die eine Lebenszeitprofessur erlangt haben.

Insgesamt sind 42% der Mitarbeiter Ausländer, und unter diesen kommt ein zeitlich konstanter Anteil von etwa 50% aus Europa. Der Anteil der Chinesen ging etwas zurück, während der der Indier anstieg (**Abb.5**).

Haushalt

Der Haushalt lag über die letzten Jahre stabil bei etwas über 20 Mio. Euro, wobei jedoch der Drittmittelanteil auf etwas unter 25% abfiel. (**Abb.6**) Dieses wird verständlich, wenn man sich die Aufteilung der Drittmittel auf die verschiedenen

Fig. 1

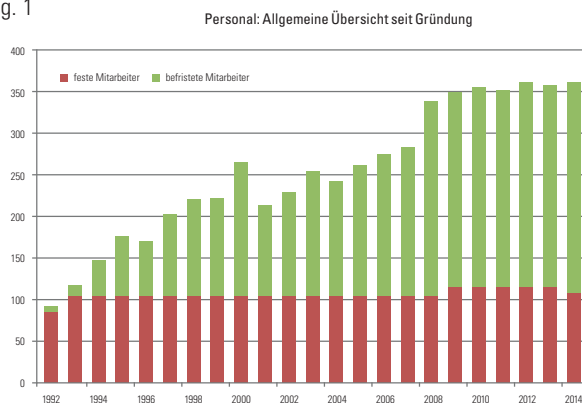


Fig. 3

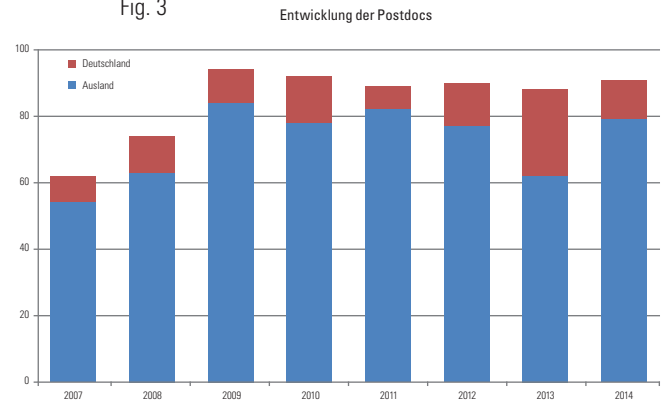


Fig. 2

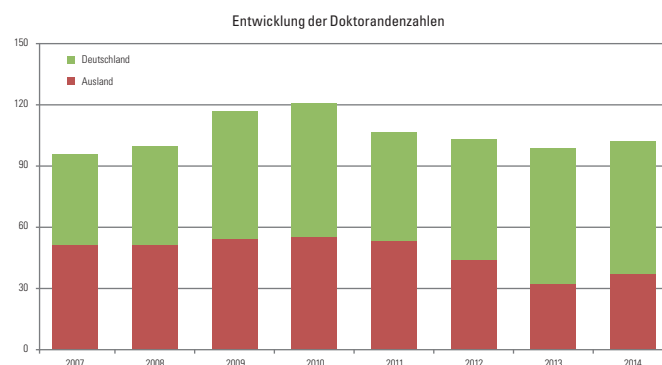
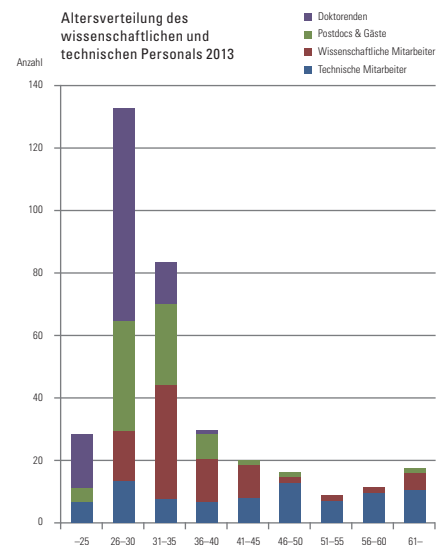


Fig. 4



Drittmittelgeber ansieht. (Abb.7) Es gibt einen starken Abfall der Mittel vom BMBF (Bundesministerium für Bildung und Forschung), da verschiedene Projekte der Abteilungen Grenzflächen und Biomolekulare Systeme ausliefen. Gleichzeitig wurden zwar neue Projekte genehmigt, waren aber noch nicht ausgabenwirksam. Ein weiterer großer Abfall entstand bei der Förderung durch das ERC (European Research Council), da größere Projekte erwartungsgemäß beendet, aber noch keine neuen Projekte genehmigt wurden. Diese Rückgänge der Förderung konnten nicht vollständig durch Zuwächse der Drittmittel von der EU und von der DFG (Deutsche Forschungsgemeinschaft) kompensiert werden, so dass insgesamt ein Rückgang von 15% entstand. Wie für ein Institut der Grundlagenforschung zu erwarten, gibt es zwar direkte Industrieförderung, aber deren Anteil am Gesamthaushalt liegt nur bei etwa 2%.

Interessant ist auch der Blick auf die Gesamtausgaben (Abb.8). Diese liegen für die Stammebelegschaft bei etwas unter 40% mit steigender Tendenz. Die Investitionen betragen etwa 10% mit einem Maximum 2009 bei Aufbau der Abteilung Biomolekulare Systeme. Sie werden in diesem und im nächsten Jahr stark steigen wegen des Bezugs des Erweiterungsbaus. Der Anteil der Förderung von Nachwuchswissenschaftlern liegt bei konstant etwa 23%, und er lässt sich offenbar nicht leicht steigern. Andererseits besteht die Hälfte dieses Anteils aus Stipendienmitteln. Die Gremien der MPG haben beschlossen, diese Stipendien durch normale Arbeitsverträge zu ersetzen ohne äquivalente Kompensation im Haushalt. Die Konsequenz wird eine sinkende Zahl der Nachwuchswissenschaftler sein, eine Verringerung deren Kosten oder vielleicht eine noch unklare andere Lösung.

Fig. 5

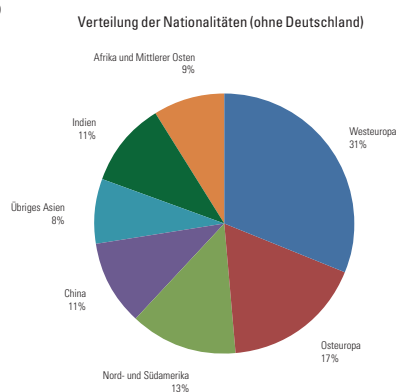


Fig. 6

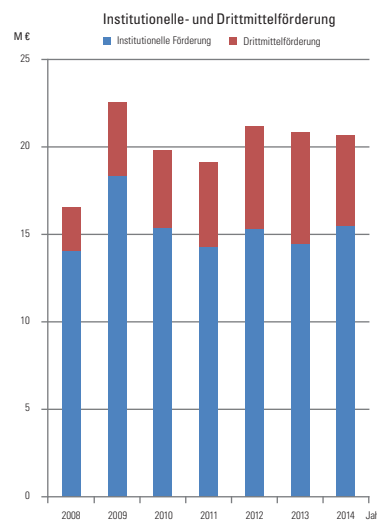


Fig. 7

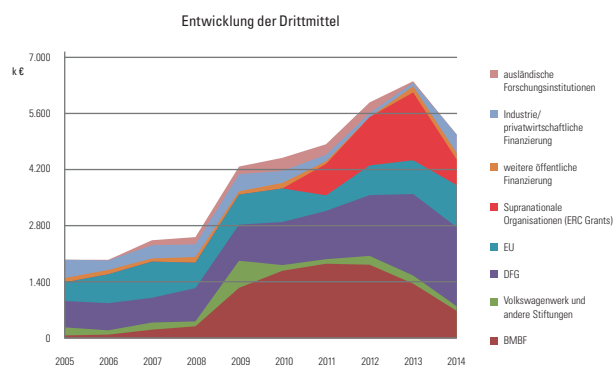
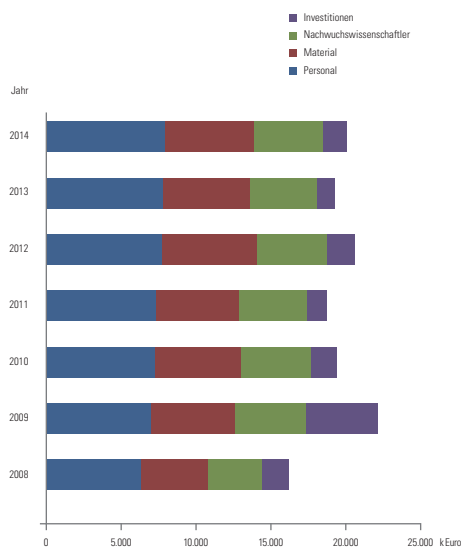


Fig. 8



Wissenschaftliche Ergebnisse und deren Einfluss

Das wichtigste Ergebnis eines Instituts sind gut ausgebildete Mitarbeiter, denen es gelingt, im Anschluss an die Arbeit im Institut eine Karriere im akademischen Umfeld, in der Industrie oder der Verwaltung aufzubauen. Im Mittel werden etwa fünf Mitarbeiter jährlich auf Professuren oder vergleichbare Stellen berufen, 25-30 Doktoranden werden promoviert und etwa 50 Postdoktoranden wechseln auf neue Stellen. Deren Verbleib ist statistisch schwerer zu erfassen, aber wir schätzen, dass mittlerweile mehr als 300 ehemalige Mitarbeiter auf Professuren berufen wurden.

Schwer zu erfassen sind auch die Publikationen des Instituts, deren Zahl mittlerweile oberhalb 11.000 liegt. Daher beziehen sich die Zahlen der **Abb. 9a** nur auf den Kernbereich des Web of Science (WoS). **Abb. 9a** zeigt, dass die Zahl der Veröffentlichungen konstant bei etwa 350 liegt. Das entspricht etwa der Zahl der Mitarbeiter. Dies ist nicht sehr viel für ein Institut, das für sich beansprucht, Weltspitze zu sein. Der Einfluss der Arbeiten (**Abb. 9b**), gemessen an den Zitationen, ist

jedoch überragend und braucht den Vergleich nicht zu scheuen mit einer Institution ähnlicher Größe weltweit. Es ist auch offenbar, dass der Einfluss dieses relativ jungen Instituts weiter stark zunimmt. Das MPIKG beschritt also Forschungsrichtungen, denen andere folgten, und diese Funktion als Trendsetter wird hoffentlich weiter anhalten. Die hohen Zitationszahlen sind vermutlich ein wesentlicher Grund, weshalb viele junge Wissenschaftler versuchen, als Gast oder als längerfristiger Mitarbeiter am Institut zu arbeiten. Daher belegt das Institut in Rankings wie dem der Humboldt-Stiftung auch regelmäßig einen der ersten drei Plätze, weit vor erheblich größeren Einrichtungen.

Auf der anderen Seite basieren diese Zahlen natürlich auf der Quantität der Zitationen, und nicht notwendigerweise auf der Qualität. Da letztere nur schwer auszuwerten ist, ist der Leser dieses Berichts aufgerufen, dies herauszufinden. Er wird hoffentlich zu dem Schluss kommen, dass sich die Qualität unserer Forschung ebenfalls auf einem Top-Level befindet.

Fig. 9a

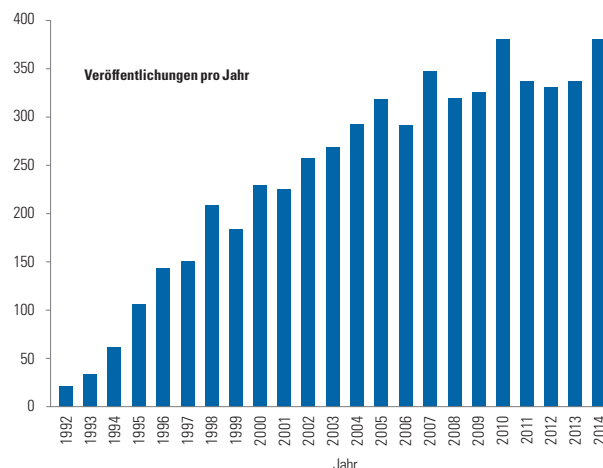
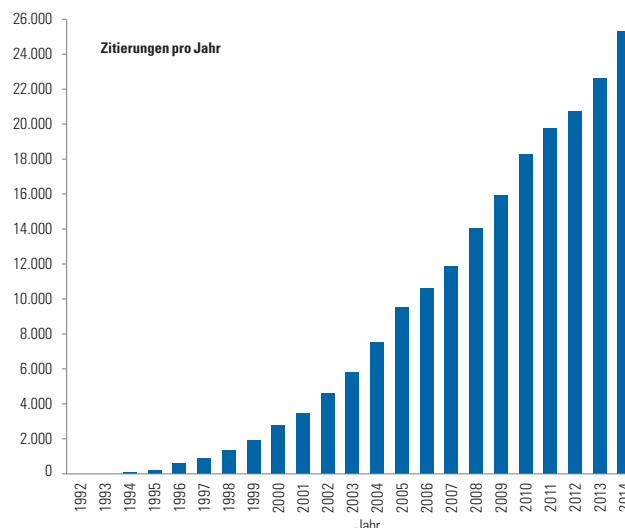


Fig. 9b



The Institute in Numbers

Personnell:

The stable number around 360 of total institute's members (**Fig.1**), of about 100 PhD students (**Fig.2**) and of about 90 postdocs (**Fig.3**) indicates that the downsizing of the Department of Interfaces has been mostly compensated by the build-up of the Department of Biomolecular Systems.

Further expansion was above all limited by lab space, and this will now be removed after moving into the extension of the building. The fraction of foreigners among the postdocs has remained above 85%, whereas their fraction among the graduate students has dropped to slightly below 40%. Rather instructive is the age distribution, peaking below 30 years for the PhD students, and slightly above 30 years for the postdocs. (**Fig.4**)

For the technical staff the age is rather evenly distributed. The age of staff scientists peaks around 35 years, which reflects the fact that most of them work in the institute as part of a step in their career. This has been really the case, as is reflected in this report and apparent from the many former co-workers now on tenured professor positions worldwide. Overall 42 % of the institute's members are foreigners, and among them the fraction of nearly 50% from Europe has remained stable over the years. The fraction of Chinese has been slightly decreasing, and instead that of Indians has increased to a similar level. (**Fig.5**)

Fig. 1

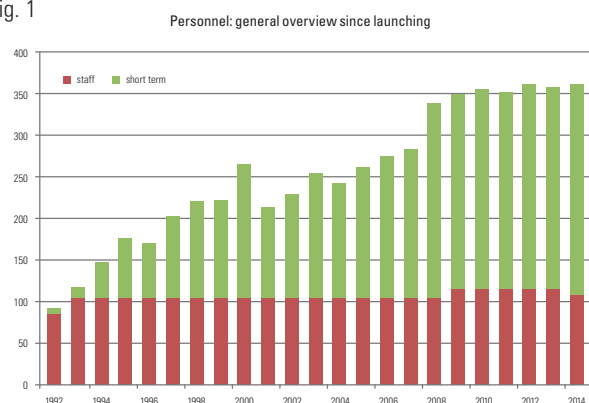


Fig. 3

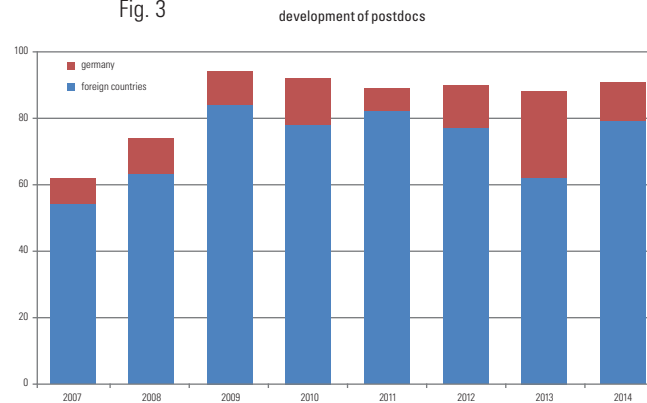


Fig. 2

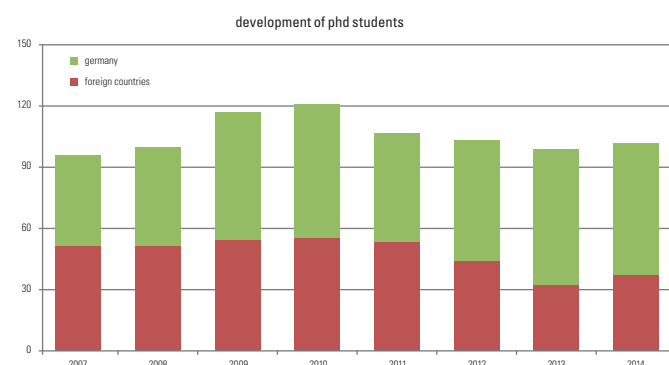
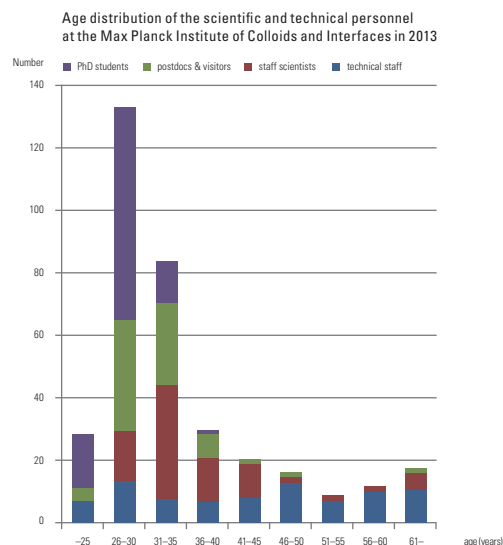


Fig. 4



Budget: The budget has remained stable slightly above 20 million Euro, but the fraction of external funding has decreased below 25 %. (**Fig.6**) The latter can be understood looking at the different funding sources (**Fig.7**). There is a strong decrease of funding from the BMBF (federal ministry of education and research), which on one hand is due to the phasing out of projects from the departments of Interfaces and Biomolecular Systems. New projects from BMBF have been granted, but these have just started and hence do not appear in the statistics based on expenses. Another major decay is from ERC funding and these major grants have been terminated as expected, but new ones have not yet been granted. These decreases in funding have not been fully compensated by the increased amount granted from European Union and from DFG (German Research Council), thus causing an overall 15 % decrease of the external funding. As to be expected for an institute with a basic sci-

ence mission the direct industry funding is existing but on a level around 2 % of the total budget.

It is rather instructive to look at the structure of the expenses. (**Fig.8**) The expenses for staff have increased, but remained slightly below 40%. Investments have been fluctuating around 10 % with some peak upon start up of the Biomolecular Systems Department, and they will again peak this and next year with the move into the new premises. The budget for young scientists has been remaining around 23 %, and obviously there are not many ways to increase this fraction. However, about half of this budget is for stipends and the central administration has decided that these stipends should be replaced by full contracts without equivalent compensation. The consequences will be removal of the number of young scientists or an overall reduction of their costs, and hopefully there will be solutions with times passing by.

Fig. 5

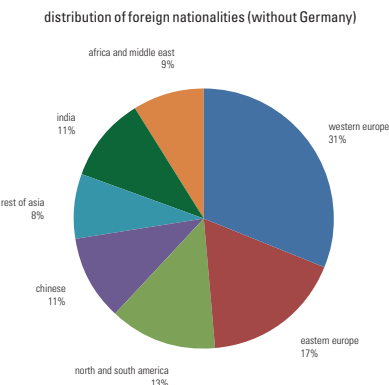


Fig. 6

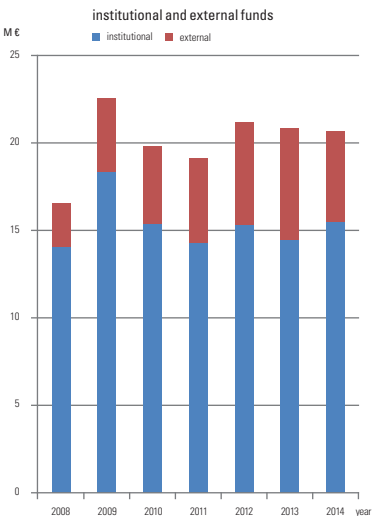


Fig. 7

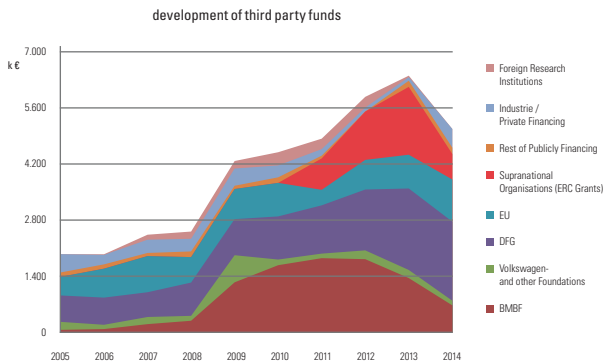
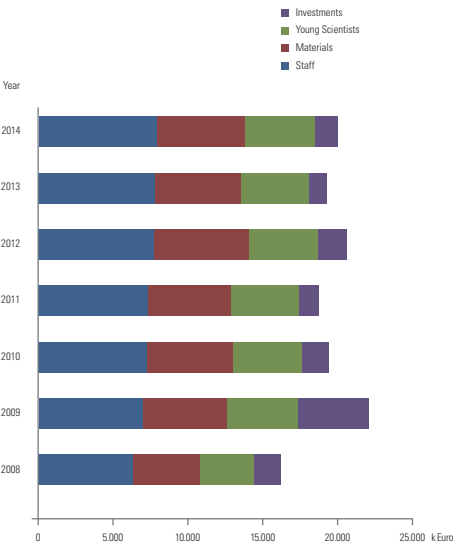


Fig. 8



Scientific Results and Impact:

The most important results of the institute are well trained people that managed to advance a career in science , industry or administration, following their work here. Typically 5 persons per year left on professor positions or equivalent, 25-30 PhD students received their degrees, and about 50 postdocs left on new positions. Their further destination is statistically difficult to assess, but we estimate that the network of former co-workers now on professor positions meanwhile exceeds 300 persons.

It is also more difficult to assess all publications, as they exceed 11.000 in the Web of Science WoS, hence the statistics below confines to the core data in the WoS. As **Fig.9a** shows the number of annual publications fluctuates around 350. This number , almost equal to that of employees, is not extraordinarily high for an institute that claims to be world top.

However, their impact in terms of annual citations is outstanding and does not have to fear a comparison with a similarly sized research unit world -wide. It is obvious, that the impact of this rather young institute is dramatically increasing with time (**Fig.9b**). Apparently we have set trends , that many others have followed, and hopefully this feature as trendsetter will remain. These numbers on impact are presumably also one of the main reasons, why many young scientists seek to join the institute with a stipend or as guest or as employee, and this is also why the institute typically is at least among the top 3 in the ranking of the Humboldt foundation, ahead of many much larger institutes.

On the other hand these numbers are based on impact, not necessarily on quality. As the latter is more difficult to assess we ask the reader of this report to look inside to hopefully find out that also quality is at a top level.

Fig. 9a

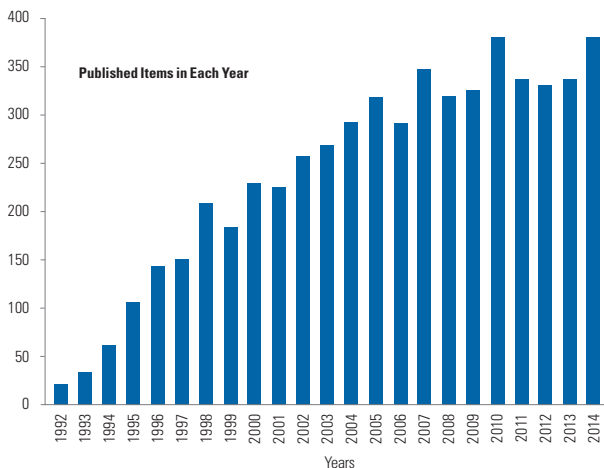
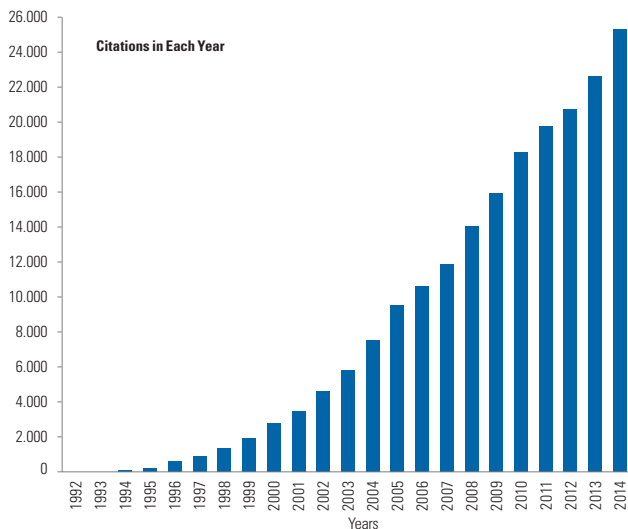


Fig. 9b



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

Vision und Mission

Kolloide sind winzige Bausteine, welche die grundlegenden Einheiten von lebenden Organismen und vielen nützlichen Materialien bilden. Das Verständnis des Aufbaus sowie die erfolgreiche Synthese dieser kleinen Teilchen könnten in Zukunft helfen, drängende Probleme u.a. in den Bereichen Gesundheit, Energie und Transport zu lösen. Das Forschungsprogramm des MPIKG beschäftigt sich deshalb auch 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 winzigen organischen und anorganischen Bausteine und zum anderen auf deren vielfältige Wechselwirkungen und Anordnungen (**Abb.1**). Unsere Grundlagenforschung untersucht 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.

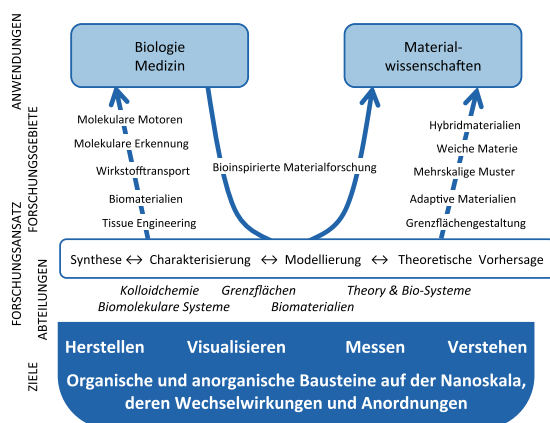


Abb. 1: Wissenschaftliche Strategie des MPIKG

Dies ist aber nur möglich durch die Kombination von wissenschaftlicher Exzellenz und außergewöhnlichem Engagement, die vor allen Dingen in die Betreuung und Unterstützung von jungen WissenschaftlerInnen fließen. Unsere Mission ist es, mit wissenschaftlicher Exzellenz eine Brücke von Molekülen zu mehrskaligen Materialien und Biosystemen zu schlagen und dabei NachwuchswissenschaftlerInnen bestmöglich zu fördern.

Das MPI für Kolloid- und Grenzflächenforschung nimmt bereits jetzt eine führende Rolle in verschiedenen innovativen Wissenschaftsfeldern ein. Diese Forschungsgebiete –

geordnet von kleinen nach größer werdenden Objekten – reichen von der Synthese, Charakterisierung und theoretischen Beschreibung von Oligosacchariden und Kohlehydraten über funktionalisierte Nanopartikel und Hybridmaterialien, Polyelektrolyt-Multischichten, 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 ausgewiesene Expertise.

Das Institut verfolgt zwei generelle Strategien um seine Spitzenposition in diesem Bereich zu etablieren 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: Molekulare Erkennung von Kohlehydraten, fotoinduzierte molekulare Prozesse, Transportprozesse und Informationsverarbeitung durch molekulare Maschinen und biomimetische Bewegungssysteme. Diese Forschungsbereiche finden sich auch als Themen-Schwerpunkte in der neuen Internationalen Max Planck Research School über „Multiscale Bio-Systems: Von der molekularen Erkennung zum mesoskopischen Transport“. Das Graduiertenprogramm startete 2013 und wird in einer ersten Förderperiode bis zum Jahr 2019 gefördert.

Ein besseres Verständnis von mehrskaligen Biosystemen ist dabei Wissensgrundlage 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 vielskaligen Systeme und Prozesse bieten die einzelnen Abteilungen des Instituts eine komplementäre Methodik und Fachkenntnis in den Bereichen Chemie, 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) und die Emeritusgruppe „Grenzflächen“ (Möhwald) fokussieren 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.

Während des letzten Jahrzehnts hat das Institut seine Aktivitäten auf dem Gebiet der Biosysteme mit der Gründung der Abteilung „Biomaterialien“ unter Peter Fratzl im Jahr 2003 und der Abteilung „Biomolekulare Systeme“ unter Peter H. Seeberger im Jahr 2008 stark erweitert. Um diese Aktivitäten zu verstärken und zu erweitern wurde 2014 eine neue unabhängige Max-Planck-Forschungsgruppe über „Mechano(bio)chemie (Blank)“ etabliert. Ferner verfolgt das MPIKG weiterhin das Ziel, eine fünfte Abteilung einzurichten.

Langfristige Ziele

Jede Abteilung des MPIKG hat sich langfristig anspruchsvolle Ziele gesetzt: Die Seeberger-Abteilung charakterisiert die komplexen Kohlehydratmischungen in der Glycocalix von eukariotischen und prokariotischen Zellen. Auf diese Weise sollen auf Kohlehydrate basierende Impfstoffe hergestellt werden. Die WissenschaftlerInnen um Markus Antonietti sind auf dem Weg enzymähnliche Nanokatalysatoren und die künstliche Photosynthese zu entwickeln und so einen Meilenstein für die grüne Energiegewinnung zu setzen. Im Mittelpunkt der Abteilung von Peter Fratzl stehen das Verständnis und die Nachahmung von Pflanzenbewegung und Knochenwachstum. 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. Hierzu zählen vor allen Dingen die molekulare Erkennung von Kohlehydraten, fotoinduzierte molekulare Prozesse, Transport und Informationsverarbeitung durch molekulare Maschinen sowie biomimetische Bewegungssysteme.

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 (Abt. Seeberger). Diese Kohlehydrate werden sowohl an Nanopartikeln (Abt. Antonietti), Lipid-Monoschichten (Emeritusgruppe Möhwald) als auch an Lipid-Dop-

pelschichten (Abt. 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. Die größte Herausforderung für die fotoinduzierte Aufspaltung von Wasser ist es geeignete Katalysatoren zu finden. Ein neuer Katalysator auf synthetischer Polymerbasis wurde erst kürzlich vorgestellt und wird nun weiter entwickelt bzw. optimiert (Abt. Antonietti). Andere fotoinduzierte Prozesse beinhalten die Synthese von Polymeren unter Zuhilfenahme von beschleunigenden Radikalen (Abt. Seeberger, Abt. Antonietti), die fotoinduzierte Durchdringung von Polyelektrolytkapseln (Emeritusgruppe Möhwald) und fotoinduzierte konformelle Änderungen von supramolekularen Strukturen (Abt. 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. 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 (Abt. Fratzl). Weiterführende Studien dieser belastungsauslösenden Prozesse werden mittels mehrskaligen Computersimulationen durchgeführt (Abt. Lipowsky). Auf diese Weise wird das Ziel verfolgt, die zu Grunde liegenden molekularen Mechanismen aufzudecken.

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. Die erste Förderperiode wurde kürzlich von 2013-2019 bewilligt. Die

Schule integriert die zuletzt genannten Kernbereiche der einzelnen Abteilungen in ihr Programm. Hauptziel der IMPRS ist es, dass die teilnehmenden DoktorandInnen effizient und erfolgreich an einem zukunftsweisenden Forschungsprojekt arbeiten können. Für die interdisziplinäre Forschung an mehrskaligen Systemen müssen die DoktorandInnen verschiedene unterschiedliche Disziplinen erlernen. Ferner sollen sie befähigt werden, das Wesentliche aus der hohen Anzahl an wissenschaftlicher Literatur zu extrahieren und auf die verschiedenen Bereiche anzuwenden. Die Ausbildung ist auch für BewerberInnen interessant, die eine nichtakademische Karriere anstreben: beispielsweise in der Pharmazie, den Bioingenieurwissenschaften und der Medizin. Darüber hinaus ist das MPIKG auch noch in drei weiteren Graduiertenschulen aktiv: Das 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 und die SALSA, School of Analytical Sciences Adlershof, koordiniert von der Humboldt-Universität zu Berlin.

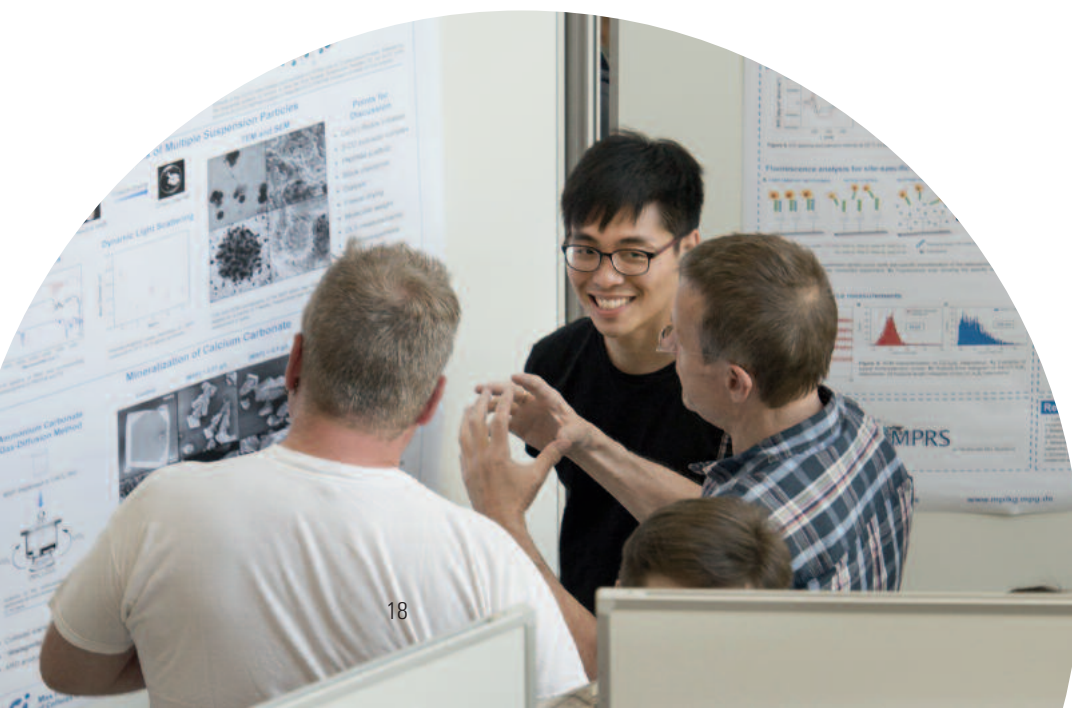
Förderung von jungen WissenschaftlerInnen

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 etwa 40 frühere ArbeitsgruppenleiterInnen Spitzenpositionen eingenommen, die vergleichbar sind mit den deutschen W3 oder W2 Professuren. Die meisten dieser WissenschaftlerInnen haben zuvor innerhalb des Netzwerks der alten IMPRS über „Biomimetische Systeme“ unterrichtet. 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 potentielle Anwendungen in verschiedenen Technologie-Feldern und könnten die Lebensqualität unserer Gesellschaft nachhaltig verbessern. Die Entwicklung von Impfstoffen auf der Basis von Kohlenwasserstoffen und die Möglichkeit große Mengen dieser Moleküle zu produzieren, ist vielversprechend und wegweisend für die Prävention von Tropenkrankheiten wie Malaria oder Leishmaniose. Diese Impfstoffe sind speziell für Entwicklungsländer sehr bedeutsam. Funktionelle Nanopartikel und Materialien können dagegen für die verbesserte foto-induzierte Aufspaltung von Wasser und für neue Methoden der CO₂-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. Dabei spielt die Wechselwirkung von Nanopartikeln mit Zellmembranen eine zentrale Rolle. Ferner könnten selbstreparierende Beschichtungen entscheidend dazu beitragen, den Materialverbrauch zu verringern, indem sie helfen Korrosion und bakteriellen Bewuchs zu vermeiden. Biosysteme, die am Institut untersucht werden, werden in Zukunft zu neuen Materialkonzepten führen, die auf bioinspirierten Designs basieren oder zur Organregeneration 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,
Helmuth Möhwald,
Peter H. Seeberger



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

Vision and Mission

Colloids are small building blocks which constitute the basic units of living organisms and of many useful materials. Mastering their synthesis and assembly will solve urgent problems in health, energy, transport and many other important areas. The research strategy of the MPICI is to address fundamental scientific problems relating to colloids and to the interfaces between them. Thus the scientific vision of the institute is to lead the effort in making, visualizing, measuring and understanding these organic and inorganic nano-scale building blocks, as well as their interaction and assembly (see Fig. 1). This is guiding our basic scientific research related to biological or medical questions, as well as to materials for various applications. Bio-inspired materials research is bridging between the two directions by translating materials structures found in nature into concepts for engineering materials.

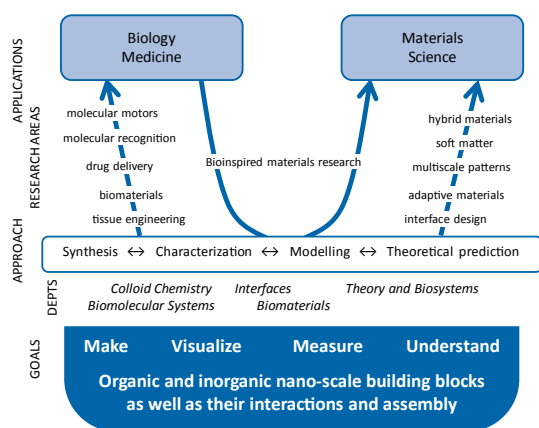


Fig. 1: Scientific strategy of the MPICI

To achieve these goals, we are convinced that scientific excellence must be combined with an exceptional commitment to mentoring and supporting young scientists.

Thus, our mission statement is: **Bridging the gap between molecules and multiscale materials and bio-systems through excellence in science and by the support of young scientists.**

Over the last years the MPI of Colloids and Interfaces (MPICI) has attained a leadership position in several cutting edge research areas within the field of colloids and interfaces. These areas – ordered from smaller to increasingly larger objects – include the synthesis, characterization and theoret-

ical description of oligosaccharides and carbohydrates, of functionalized nanoparticles and hybrid materials, of polyelectrolyte multilayers, the self-organization of complex interfaces and multi-component membranes, as well as 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.

The MPICI pursues two general strategies in order to keep and strengthen its leading role in the field: (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.

Recently, several new topics related to biomimetic and biological systems have been taken up. Four new focus areas are: molecular recognition of carbohydrates, photo-induced molecular processes, transport processes based on molecular motors, and biomimetic actuation and motility. These areas are also pursued in the framework of the new International Max Planck Research School on "Multiscale Bio-Systems": From molecular recognition to mesoscopic transport" which started in 2013 and will be funded, during its first funding period, until 2019.

An improved understanding of multiscale bio-systems 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, physics, and materials science. 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) and the Emeritus Group on "Interfaces" (Möhwald) focus on structural analysis and physical characterization. The department of "Theory & Bio-Systems" (Lipowsky) provides expertise in theory and modeling. During the last decade, the MPICI has strongly enhanced its activities on bio-systems by establishing the Fratzl department on "Biomaterials" in 2003 and the Seeberger depart-



ment on “Biomolecular Systems” in 2008. In order to strengthen and expand its core expertise, the new independent Max Planck Research Group on “Mechano(bio)chemistry” (Blank) has been established in 2014. Moreover, the MPICI has the long-term goal to establish a fifth department to cover related areas.

Long-term Objectives

Each department of the MPICI pursues challenging long-term objectives. The Seeberger department characterizes the complex mixture of carbohydrates in the glycocalix of eukaryotic and prokaryotic cells in order to develop carbohydrate based vaccines. The Antonietti department wants to establish enzyme-like nanocatalysts and artificial photosynthesis as milestones for green energy production. The Fratzl department wants to understand and mimic plant motility and bone tissue growth. The Lipowsky department wants to understand and bridge the complexity gap between artificial and natural bio-systems, an activity that is now popularized under the buzz word “Synthetic Biology”. The Blank group wants to elucidate 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, photo-induced molecular processes, transport by molecular motors, as well as biomimetic actuation and motility.

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 (Dept. Seeberger). These carbohydrates are then anchored to nanoparticles (Dept. Antonietti), lipid monolayers (Emeritus Group Möhwald), and lipid bilayers (Dept. Lipowsky). In this way, they become amenable 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. The main challenge for the photo-induced cleavage of water is to find appropriate catalysts. A new type of catalyst

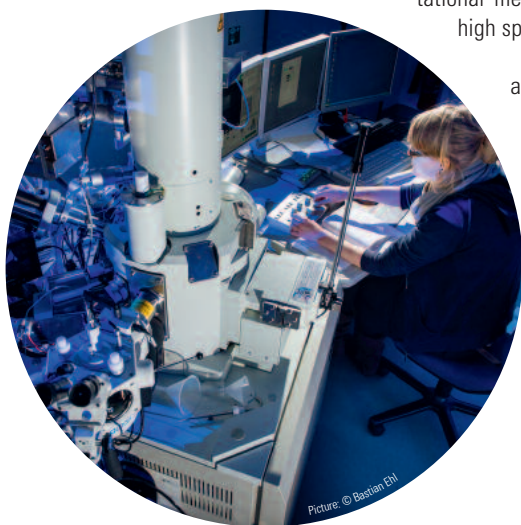
based on a synthetic polymer has been recently introduced and will be further developed and optimized (Dept. Antonietti). Other photo-induced processes include the synthesis of polymers using snowballing radical generation (Dept. Seeberger, Dept. Antonietti), photo-induced permeation of polyelectrolyte capsules (Emeritus Group Möhwald), and photo-induced conformational changes of supramolecular assemblies (Dept. 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. Another focus area of the Lipowsky department are asymmetric bilayer membranes and their interactions with nanoparticles.

Biomimetic actuation and growth of tissues is a focus area 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 (Dept. Fratzl). The ongoing experimental studies of these stress-generating processes are also addressed by multi-scale computer simulations in order to elucidate the underlying molecular mechanisms (Dept. Lipowsky).

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 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 order to participate in the interdisciplinary research area of multiscale bio-systems, doctoral students must learn the different languages as used in these different disciplines and need to understand how to extract useful information from the vast scientific literature that is published in these disciplines. The training will also be useful for doctoral students, who intend to pursue a career outside academia in pharmacology, bioengineering, and medicine. In addition, the MPICI partici-





pates in three other graduate schools: The 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), and the "School of Analytical Sciences Adlershof" (coordinated by the Humboldt University Berlin).

Support of Young Scientists

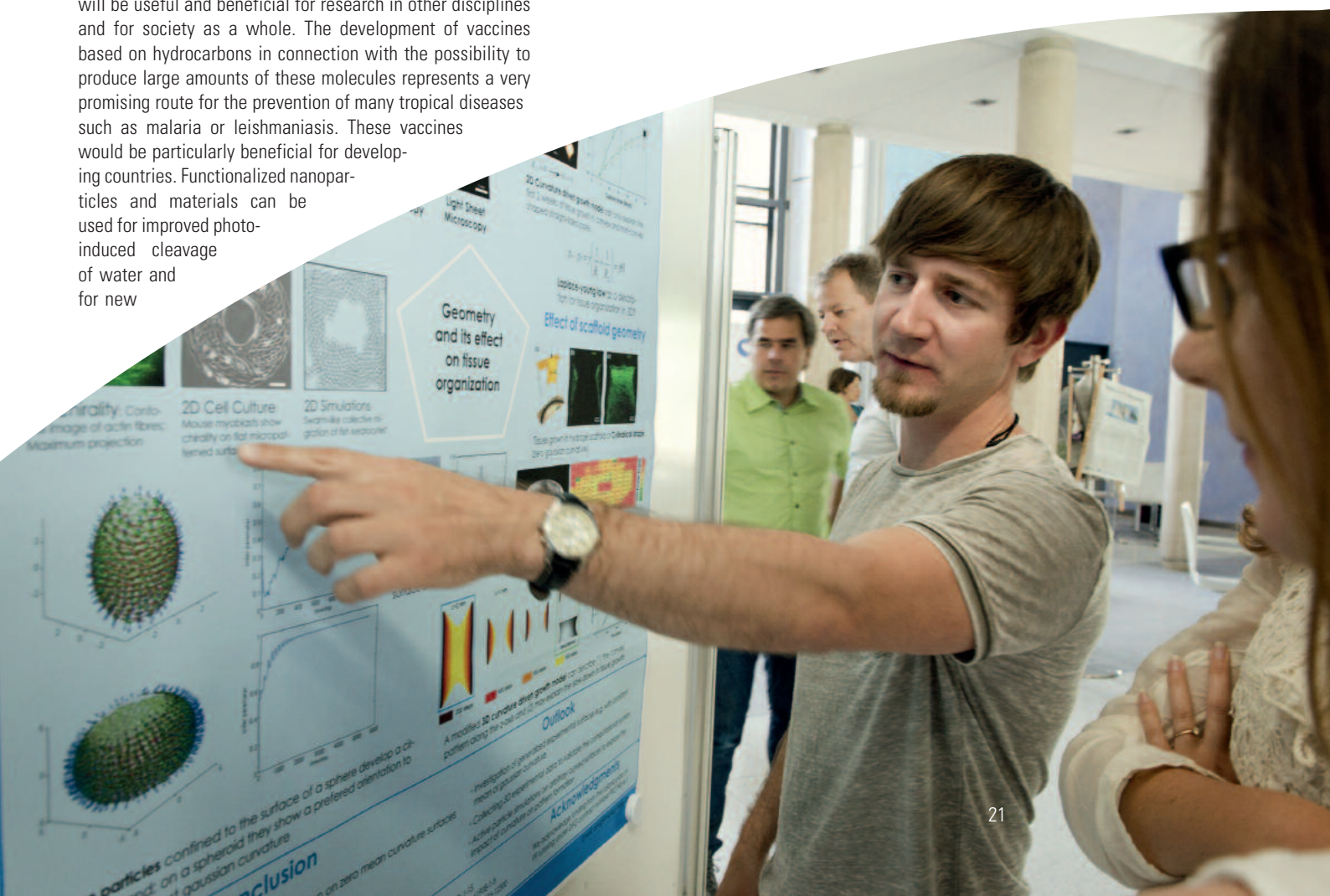
The MPICI will continue to be a hotbed for young scientists who pursue a career in academia. A large number of former associates and postdocs are now professors at German or foreign universities. In particular, during the last ten years, about 40 former research group leaders of the MPICI have taken up offers for professorships that are equivalent to German W3 or W2 positions. Most 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 hydrocarbons in connection with the possibility to produce large amounts of these molecules represents a very promising route for the prevention of many tropical diseases such as malaria or leishmaniasis. These vaccines would be particularly beneficial for developing countries. Functionalized nanoparticles and materials can be used for improved photo-induced cleavage of water and for new

methods of CO₂ 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. Self-repairing coatings may lead to less materials consumption by avoiding corrosion and bio-fouling. 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 organ 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,
Helmuth Möhwald,
Peter H. Seeberger



Wissenschaftliche Beziehungen

Nationale 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 und der Direktor (em.) sind Honorarprofessoren an der Universität Potsdam. Dies spiegelt sich in einer intensiven Lehrtätigkeit sowohl in Bereichen des Grundstudiums als auch in den Wahlpflichtfächern wieder. Prof. Fratzl und Prof. Lipowsky sind zudem Honorarprofessoren an der Humboldt Universität zu Berlin und Prof. Seeberger an der Freien Universität Berlin. Darüber hinaus wurde Prof. Rabe vom Institut für Physik der Humboldt-Universität 2005 als Auswärtiges Wissenschaftliches Mitglied an das MPI für Kolloid- und Grenzflächenforschung berufen.

Die Aktivitäten über biomimetische Systeme wurden 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 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. Sprecher ist Professor Lipowsky.

Ferner beteiligt sich das Institut am Forschungsverbund „Unifying Concepts in Catalysis“ (UniCat), welcher im Rahmen der Exzellenzinitiative des Bundes und der Länder 2007 gegründet wurde und von der TU Berlin koordiniert wird. Prof. Antonietti ist hier seit 2009 Principal Investigator (PI). Über den SFB 765 „Multivalenz als chemisches Organisations- und Wirkprinzip“, das von der FU koordiniert wird, kooperiert es ferner mit der FU Berlin und dem Helmholtz-Zentrum Geestacht (Institut für Polymerforschung). Das Institut ist Mitglied des vom Bundesministerium für Bildung und Forschung (BMBF) finanzierten Berlin-Brandenburgischen Zentrums für Regenerative Therapien (BCRT) sowie der von der DFG-Exzellenzinitiative geförderten Graduiertenschule Berlin-Brandenburg School of Regenerative Therapies (BSRT). Darüber hinaus ist das MPIKG Partner des Exzellenzclusters „Image-Knowledge-Gestaltung“, welches von der Humboldt-Universität durchgeführt wird (P. Fratzl fungiert hier als PI sowie weitere Mitglieder der Abteilung Biomaterialien als assoziierte PIs). Zudem koordiniert Prof. Fratzl das DFG-Schwerpunktprogramm SPP 1420 „Biomimetische Materialforschung“, an dem mehr als zehn Universitäten so - wie Max-Planck-Institute beteiligt sind, das Bauprinzipien und Herstellung von neuartigen, hierarchisch strukturierten Materialien untersucht, die auf natürlichen Vorbildern basieren.

Großes Engagement gilt der Betreuung und dem Aufbau von Messplätzen an den Berliner Neutronen- und Synchrotronstrahlungsquellen sowie dem Deutschen Elektronen Synchrotron (DESY) in Hamburg. Das Institut kooperierte mit dem bisherigen Fraunhofer-Institut für Biomedizinische Technik IBMT und der Universität Potsdam von 2009 bis Ende 2014 in dem Projekt „Das Taschentuchlabor: Impulszentrum für Integrierte Bioanalyse“. Hier arbeiteten vierzehn Partner aus Wissenschaft und Industrie an der Entwicklung von neuartigen Biosensoren, mit denen Krankheitserreger sofort und

ohne komplizierte Aufreinigung detektiert werden können. Schließlich ist das Institut auch aktiv beteiligt an der International Graduate Research and Training Group on "Self-Assembled Soft Matter Nano-Structures at Interfaces", koordiniert von der TU Berlin

Internationale Kooperationen

Im Rahmen von europäischen Förderprogrammen, laufen zurzeit zwölf EU-Projekte innerhalb des 7. Rahmenprogramms und fünf innerhalb des EU-Rahmenprogramms „HORIZONT 2020“, davon ein ERC Advanced Grant und ein ERC Starting Grant. 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 neuen Riken-Max Planck-Joint Research Center. 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 Indian Institute of Science and Education Research (IISER), Pune und das Institut haben zudem 2011 eine Max-Planck Partnergruppe ins Leben gerufen. In diesem Gemeinschaftsprojekt sollen innovative Nanosysteme entwickelt und hergestellt werden, die helfen sollen, Krebs besser behandeln zu können.

Bilaterale- und Kooperationsprojekte bestehen zurzeit unter der Förderung der European Space Agency (ESA), der NATO, des Deutschen Akademischen Austausch Dienstes (DAAD), der Deutschen Forschungsgemeinschaft (DFG), der German Israel Foundation (GIF) for Scientific Research and Development, des National Institutes of Health (NIH), des Schweizer Nationalfonds, der Schweizerischen Eidgenossenschaft sowie der VW-Stiftung mit China, Frankreich, Griechenland, Großbritannien, Irland, Italien, Israel, Japan, Niederlande, Norwegen, Portugal, Polen, Russland, Schweiz, Schweden und Spanien und den USA. Darüber hinaus wird in enger Zusammenarbeit mit dem Ludwig-Boltzmann Institut für Osteologie in Wien (Österreich) an klinisch orientierter Knochenforschung gearbeitet. Ferner betreibt die Abteilung Grenzflächen seit 2008 ein „Laboratoire Européen Associé“ über „Sonochemie“ mit dem CEA-Institut für Separationschemie in Marcoule, das von der Abteilung Biomaterialien weitergeführt wird.

Verwertungsverträge, Ausgründungen

Das Institut hält gegenwärtig 18 Patente. Im Zeitraum von 1993-2015 erfolgten insgesamt neun Ausgründungen: ArtemiFlow, Capsulation Nanoscience AG, Colloid GmbH, GlycoUniverse, Nanocraft GmbH, Optrel, Riegler & Kirstein, Sin-terface und Vaxxilon AG.

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.

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Fachbeirat:

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- IdEx Bordeaux (Initiative of Excellence of Bordeaux (M. Antonietti, Scientific Advisory Board)
- Institute for Science & Technology Austria (P. Fratzl, Scientific Advisory Board)
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- Minerva Foundation, Centers Committee (P. Fratzl, Chair)
- National Science and Technology Development Agency (NSTDA), Thailand (M. Antonietti, International Advisory Committee)
- National Nanotechnology Center (NANOTEC), Thailand (M. Antonietti, Scientific Advisory Board)
- Pole Chimie Balard Montpellier (H. Möhwald)
- WYSS Institute for Bioinspired Engineering at Harvard University (P. Fratzl, Scientific Advisory Board)

Scientific Relations

National Co-operations

The Max Planck Institute of Colloids and Interfaces (MPICI) and the University Potsdam maintain since its foundation intense and well-connected research co-operations. All four active directors and the director emeritus hold Honorary Professorships at the University Potsdam which reflect intensive teaching in basic studies as well as in specialized subjects. In addition to this Prof. Fratzl and Prof. Lipowsky hold Honorary Professorships at the Humboldt University Berlin and Prof. Seeberger at the Free University Berlin. In 2005 Prof. Rabe of the Humboldt University Berlin (Institute of Physics) was appointed as Foreign Member of the Max Planck Institute of Colloids and Interfaces.

In order to support and enhance its activities on biomimetic systems, and to improve the training of young researchers in this emerging field, the MPICI had created the International Max Planck Research School (IMPRS) on Biomimetic Systems, followed by the new International Max Planck Research School (IMPRS) on "Multiscale Bio-Systems" which started in July 2013. The school is supported by the Max Planck Society and the partner universities, which are all Berlin Universities and the University Potsdam. The program lasts at least six years, but it can be extended up to twelve years, can take on up to 20 students every year and leads to a doctor's degree in physics, chemistry or biology.

The institute is also involved in the Cluster of Excellence "Unifying Concepts in Catalysis", which is coordinated by the Technical University Berlin. Since 2009 Prof. Antonietti has been principal investigator (PI) there. It was founded in 2007 within the framework of the Excellence Initiative launched by the German Federal and State Governments. Furthermore the MPICI cooperates in the SFB program 765 "Multivalent Display" coordinated by the Free University Berlin and the Institute of Polymer Research at the Helmholtz-Centre Geesthacht. It is also a member of the BMBF financed Berlin-Brandenburg Center for Regenerative Therapies (BCRT) and the Berlin-Brandenburg School of Regenerative Therapies (BSRT), funded by the Excellence Initiative of the DFG. The MPICI is partner of the excellence cluster "Image-Knowledge-Gestaltung" coordinated by the Humboldt University (with P. Fratzl as PI and several members of the Biomaterials Department as associated PIs). On top of this Prof. Fratzl coordinates the DFG priority program SPP 1420 "Biomimetic Materials Research", in which more than ten universities as well as Max Planck Institutes take part. The aim is to explore the possibility of generating new material classes of great potential by combining the degrees of freedom of hierarchical structuring inspired by nature with the variety of materials offered by engineering.

Big engagement required also the maintenance and build-up of beam-lines at the neutron- and synchrotron radiation sources in Berlin and the German electron synchrotron (DESY) in Hamburg. From 2009 till 2014 the institute also cooperated in the project "The Lab in a Hankie" – Impulse Centre for Integrated Bioanalysis with the former Fraunhofer Institute of Biomedical Engineering IBMT, the University Potsdam and others. The project aims at the development of

new biosensors for the direct detection of pathogens without complicated purification steps. Beyond that it takes part in the international graduate program "Self-Assembled Soft Matter Nano-Structures at Interfaces", together with the Berlin universities, which is funded by the DFG.

International Co-operations

Within the framework of European programs there are twelve EU projects within the 7th framework program and five within the EU framework program "HORIZON 2020", including one ERC Advanced Grant and one ERC Starting Grant. Furthermore the Institute is together with the Max Planck Institute of Molecular Physiology in Dortmund and the Riken Advanced Science Institute (ASI) in Wako principal partner of the new Riken Max Planck Joint Research Center. The new research center is able to promote the more effective use of research resources as well as information and technology in the field of systems chemical biology.

The Indian Institute of Science and Education Research (II SER), Pune and the Max Planck Institute (MPI) of Colloids and Interface, Germany have entered 2011 into a research collaboration to design and construct nanodevices to improve treatment of cancer. The Max Planck Partner Group is funded by the Department of Science & Technology, Govt. of India and the Max Planck Society, Germany.

Beyond the collaborations described there exist bilateral and co-operation projects under assistance of the European Space Agency (ESA), the NATO, the German Academic

Exchange Service (DAAD), the German Research Foundation (DFG), German Israel Foundation (GIF) for Scientific Research and Development, the National Institutes of Health (NIH), Swiss National Science Foundation (SNSF) and the VW-Foundation with Commonwealth of Independent States (CIS), China, France, Greece, Ireland, Italy, Israel, Japan, the Netherlands, Norway, Poland, Portugal, Switzerland, Sweden, United Kingdom (UK) and the USA. Clinically oriented bone research is carried out in close collaboration with the Ludwig Boltzmann Institute of Osteology in Vienna (Austria). Moreover the former Department of Interfaces has established a Laboratoire Européen Associé about „Sonochemistry". It is run since 2008 together with the CEA Institute of Separation Chemistry in Marcoule and continued with the Department Biomaterials

Application Contracts, Spin-Offs

At present the MPIKG upholds 18 patents. In the period from 1993-2015 nine spin-offs have been launched: ArtemiFlow, Capsulation Nanoscience AG, Colloid GmbH, GlycoUniverse, Nanocraft GmbH, Optrel, Riegler & Kirstein, Sinterface and Vaxxilon AG.

Editorial and Advisory Boards

Scientists serve as reviewers and advisors for many journals. Therefore listed are only activities as editor and member of an editorial board. Moreover you will find a list where you can find memberships in advisory boards.

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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 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. Die neue IMPRS nahm ihre Forschungs- und Ausbildungsaktivitäten im Wintersemester 2013/14 auf.

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 Gewebe. Diese Forschungsaktivitäten konzentrieren sich auf vier Kernbereiche: molekulare Erkennung von Kohlehydraten, Interaktion von Biomolekülen mit Licht, gerichtete intrazelluläre Prozesse und gerichtete Formveränderung von Geweben. 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 sechs Jahre genehmigt mit der Aussicht auf Verlängerung um weitere sechs Jahre. 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 2013 und 2014 sind mehr als 800 Bewerbungen eingegangen, aus denen 21 Doktoranden ausgewählt wurden, sieben 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 ein Stipendium zu bekommen.

Lehrprogramm

Jeder Doktorand arbeitet an einem Projekt unter Aufsicht eines „thesis committee“, 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 Posterpräsentationen erlauben es jedem, persönlich mit den Doktoranden und ihren Betreuern zu sprechen. Zusätzlich dazu organisiert die IMPRS eine Ringvorlesung, in der Fakultätsmitglieder der Schule und eingeladene Sprecher pädagogisch orientierte Vorlesungen halten, die alle vier Kernbereiche der Schule abdecken. Bisher hat die Schule 21 Vorlesungen in drei Semestern organisiert. Sie bietet auch eine Vielzahl von soft-skills Veranstaltungen, von Workshops zum wissenschaftlichen Schreiben, über Übungen zu Präsentationstechniken bis hin zu Deutschkursen und Vorträgen zu Karriereperspektiven. Das Graduiertenprogramm bietet auch Semesterkurse an, wo einzelne Themengebiete vertieft werden. Während der letzten drei Semester gab es 20 solche 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 und des Fraunhofer Instituts für Zelltherapie und Immunologie IZI 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 MPICl 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 carbohydrates, interaction of biomolecules with light, directed intracellular processes as well as directed shape changes of tissues. 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

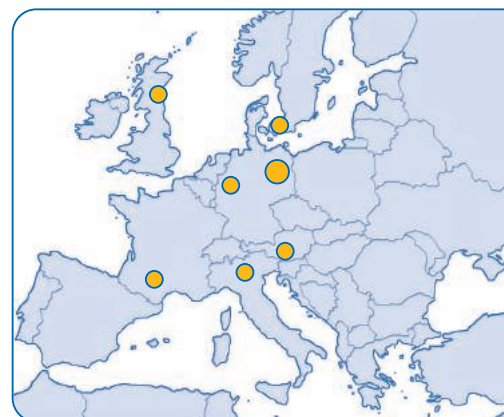
The English-speaking doctoral program offers cutting-edge, interdisciplinary research and has been approved for six years, with a possible extension for another six years. Headquarter of the school is the MPI of Colloids and Interfaces. In line with the general rules for all IMPRS, less than half of the admitted students can be from Germany. In the years 2013 and 2014, we have received more than 800 applications and recruited 21 doctoral students, seven from Germany and the rest from thirteen 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 supervision of 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. Furthermore, the school organizes a lecture series where faculty members of the school as well as invited speakers deliver pedagogically oriented lectures covering all four core areas of the school. So far, the school has organized 21 lectures in three semesters. 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. The school offers also semester courses to cover broad topics in depth. During the last three semesters, the school has offered 20 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, the Potsdam University, FU Berlin, HU Berlin, and the Fraunhofer Institute for Cell Therapy and Immunology IZI 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.

Der alle zwei Jahre stattfindende Tag der Offenen Türen im Wissenschaftspark Potsdam-Golm ist dabei einer unserer Höhepunkte. Gemeinsam mit den Max-Planck-Instituten für Gravitationsphysik und Molekulare Pflanzenphysiologie, den Fraunhofer-Instituten für Angewandte Polymerforschung IAP sowie für Zelltherapie und Immunologie IZI, dem Golm Innovationszentrum GO:IN sowie dem Brandenburgischen Landeshauptarchiv bieten wir interessierten Besuchern aller Altersklassen einen faszinierenden Einblick in die Forschung. Das vielfältige Programm mit Führungen, Experimenten, Vorträgen und Mitmach-Aktionen bietet Jung und Alt

Wissenschaft zum Anfassen und zahlreiche Möglichkeiten High-Tech-Technologien hautnah zu erleben und zu

begreifen. Der Tag der Offenen Türen 2014 fand am 6. September von 11.00-17.00 Uhr statt.

Ein weiterer Höhepunkt konnte am 28. März 2013 mit dem Richtfest für den Erweiterungsbau des Max-Planck-Instituts für Kolloid- und Grenzflächenforschung gefeiert werden. Das Gebäude mit modernsten Laboren und weiteren 2300 Quadratmeter Nutzfläche wird am 21. September 2015 eingeweiht. Das Institut gewinnt dadurch Platz für den Betrieb moderner Großgeräte, die Einrichtung von Nachwuchsgruppen wie auch für die Forschung von 100 weiteren Mitarbeitern.

In der seit März 2014 eröffneten Wissenschaftsetage im Potsdamer Bildungsforum zeigen Wissenschaftler der Region in der Ausstellung „Forschungsfenster“ auf 300 Quadratmeter Einblicke in ihre Arbeit. Auch das MPIKG ist mit dabei und beantwortet Fragen wie „Warum sind Knochen so belastbar?“ oder „Wie stabil kann Glas sein?“.

Anlässlich des zehnjährigen Bestehens der Berlin Declaration of Open Access trafen im November 2013 Berliner Schüler und Studenten den 16-jährigen Erfinder und Open Access-Fürsprecher Jack Andraka. Zusammen mit Nick Shockey (Right to Research Coalition) und Daniel Kolarich, Gruppenleiter am Max-Planck-Institut für Kolloid- und Grenzflächenforschung sprachen sie über die Notwendigkeit von Open Access in der Wissenschaft und erklärten wie dadurch jeder selbst zu einem Wissenschaftler werden kann.

Des Weiteren fand die Jahresversammlung der Max-Planck-Gesellschaft vom 5. bis 6. Juni 2013 in Potsdam statt. Rund 600 Gäste aus Wissenschaft, Politik und Wirtschaft, darunter mehrere Nobelpreisträger der Max-Planck-Gesellschaft nahmen daran teil. Für interessierte Besucher bot der Max-Planck-Campus eine Führung durch die Institute an. Das MPI für Kolloid- und Grenzflächenforschung gewährte dabei mit den Themen „Vorbild Natur: Von der Materialwissenschaft zur Medizin“ sowie „Funktionale Kunststoffe für Energie- und Trennanwendungen“ einen Blick ins Labor.

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 Girls' Day – dem Mädchenzukunftstag. 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
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Press and Public Relations

Press and Public Relations at the Max Planck Institute of Colloids and Interfaces serve as the interface between the 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. Beside classical Press and Public Relations the complete conception, organisation and realisation of events is a second core theme.

One of our highlights every two years is the Open Day, which is an interesting and fun-packed day, combining demonstrations of high-tech learning facilities with hands on activities for all age groups. The Open Day is held together with the Max Planck Institutes of Gravitational Physics and Molecular Plant Physiology, the Fraunhofer Institutes for Cell Therapy and Immunology IZI and for Biomedical Engineering IBMT, the Golm Innovation Center GO:IN and the Brandenburg Main State Archive. In 2014 it took place on September 6th from 11 a.m. till 5 p.m. On that day we offered lab tours, popular talks and scientific demonstrations providing an excellent opportunity for everybody to experience scientific activity at first hand.

Beside this the MPICl has celebrated the “topping out” of its extension building on March 28th 2014. The new building with most modern laboratories and further 2300 square meters space will be inaugurated on September 21st 2015. This is for immense importance as we gain space for large-scale facilities, for junior research groups as well as for the research of 100 additional employees.

Since March 2014 scientists from the region show in the newly opened Science Floor of the “Potsdamer Bildungsforum” their research. In the exhibition “Forschungsfenster”, with a total area of 300 square meters, the institute is also involved. There it answers questions such as “Why are bones so resistant?” or “How stable is glass?”.

In November 2013, on the occasion of the 10th anniversary of the Berlin declaration, Berlin High Schoolers and students met Jack Andraka, a 16-year-old inventor and Open Access advocate. Together with Nick Shockey, Right to Research Coalition, and Daniel Kolarich, group leader at the Max Planck Institute of Colloids and Interfaces they spoke about the necessity of Open Access in science and explained how it will enable everyone to be a scientist.

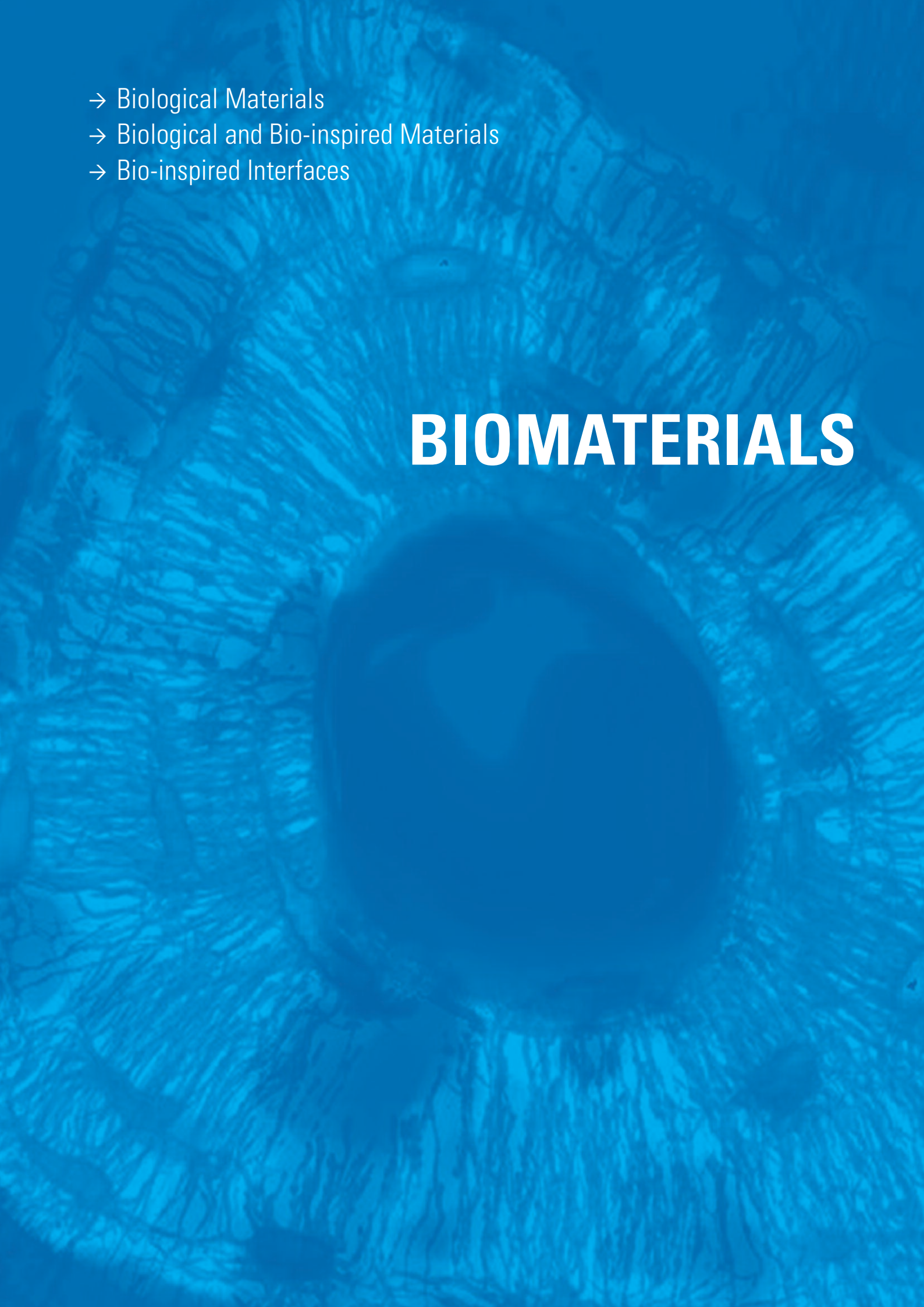
Furthermore the Annual Meeting of the Max Planck Society was held on June 5th and 6th 2013 in Potsdam. Around 600 guests were attending representing science, politics and industry, among them several of the Max Planck Society's Nobel laureates. For interested participants of the meeting the Max Planck Campus in Potsdam-Golm offered a guided tour. Under the motto „Look into the Lab” our institute presented topics such as “From material science to medicine” or “Functional synthetic materials for energy and separation applications”.

Beyond this tours through the institute as well as talks at schools are organized. Besides this the institute takes part in the Germany-wide campaign Girls'Day – Future Prospects for Girls every year. 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
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- Biological Materials
 - Biological and Bio-inspired Materials
 - Bio-inspired Interfaces

BIOMATERIALS

Research in the 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)

Biological Materials Science is the overarching research area of the Department. As schematically shown in figure 1 below, this research field connects materials science and biology in several interesting ways: First, biological or biomedical questions often require input by methods and approaches borrowed from physics, chemistry or materials science (red arrow on the left). One such example with far-reaching medical importance is the Department's research on bone material quality in osteoporosis and other skeletal diseases associated with bone fragility. Second, the diversity of natural organisms presents a unique opportunity to study naturally evolved solutions to typical materials engineering problems encountered by organisms. Examples are materials combining stiffness and fracture resistance or providing self-healing or self-actuating capabilities to skeletons, shells, hold-fast systems or protective capsules (green arrow on the right). This type of bioinspired research is an important component in the research by most of the groups in the Department. Third, it is essential to understand how cells interact with materials, both biogenic and artificial. Indeed, materials in contact with cells are often carrying (mechanical or chemical) signals for the cells and/or are being modified by them (blue connector in the center of the sketch). Of particular interest in several groups of the Department is the way in which cells interact mechanically with their environment.

To tackle such questions, members of the Department have very diverse scientific backgrounds, including mathematics, physics, chemistry, materials science, physical chemistry, biochemistry, wood science, botany, zoology and molecular biology.

The Department addresses Biological Materials Science through all three angles sketched in **Figure 1**. A number of research groups and staff scientists work independently but also in a collaborative way on these topics. **Figure 2** lists these individual research efforts along two lines (red arrows) starting from the analysis of biological materials with the goal to either provide new concepts for the materials sciences (left) or helping the understanding of biological or biomedical problems (right). The position of the various research groups on these arrows is, of course, only a rough attempt of classifying the diverse activities. Since all research group leaders and independent scientists submit their own report, only a brief summary of the research strategies will be given here, with a little more emphasis on the research work done outside these groups (mostly by the director with external partners).

The groups of *Matt Harrington* (a) and *Michaela Eder* (b) are shown on top of the pyramid in Figure 2. Both work primarily in elucidating structure function relations in biological materials, although Matt recently also started some activity in synthesizing bioinspired polymer-based materials. The emphasis in (a) is on protein-based materials with mechanical

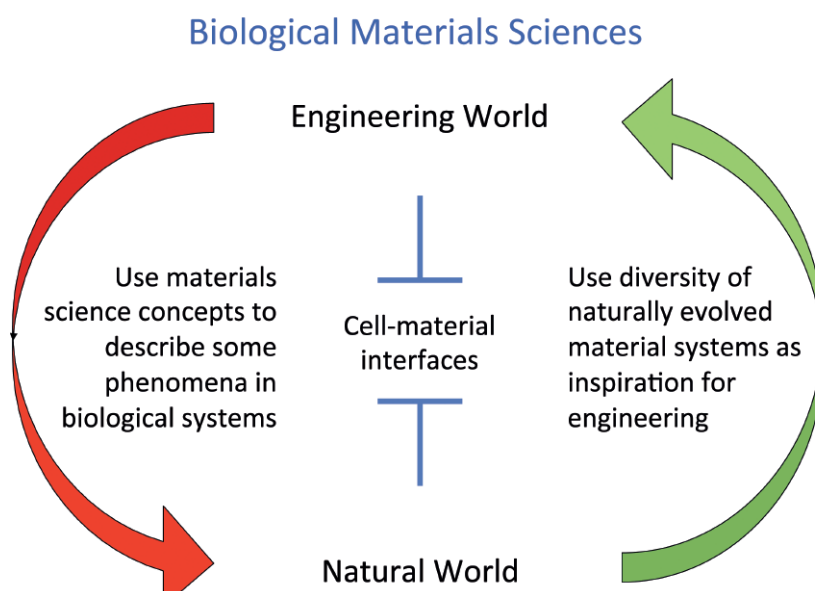


Figure 1

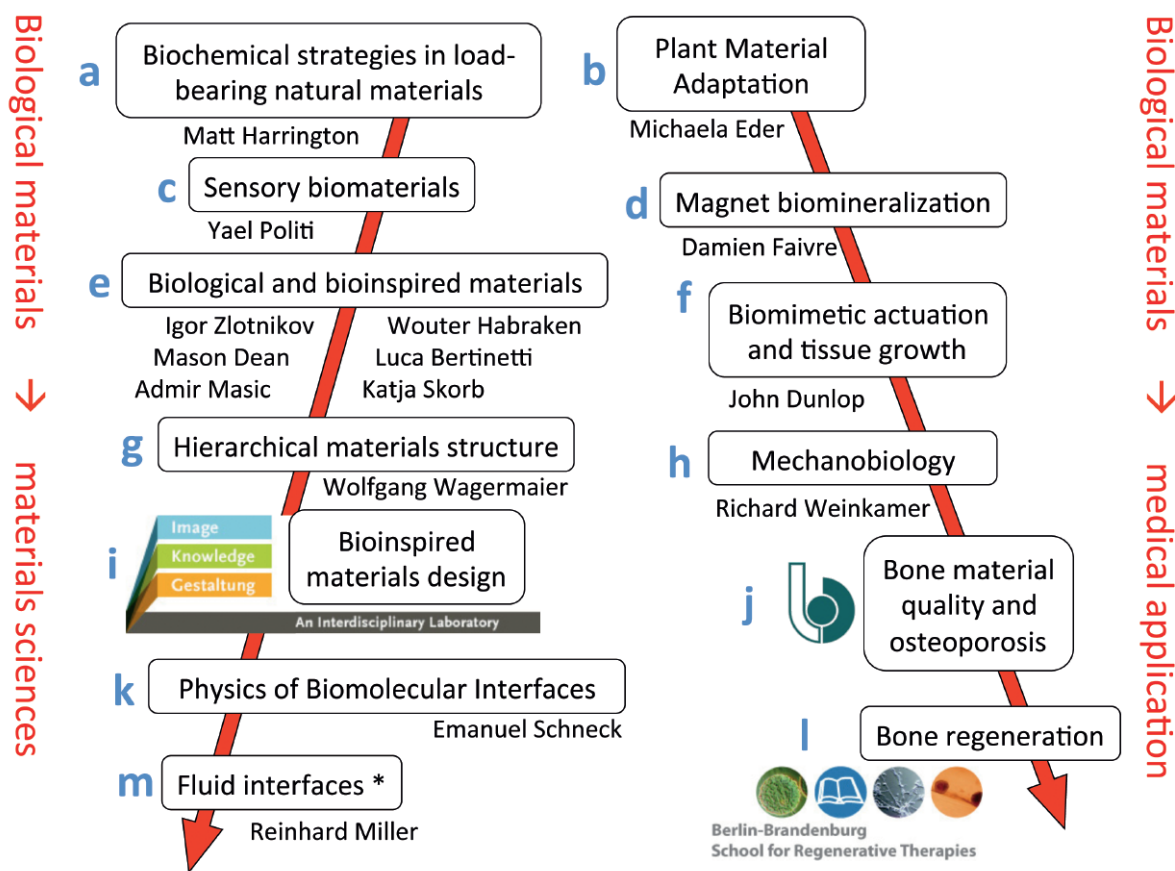


Figure 2: Research group structure, Department of Biomaterials.

function, such as the byssus threads of mussels who show an interesting self-healing behavior based on metal coordination bonds. Michaela's work (b) currently focusses on seed capsule materials. In particular, the follicles of *Banksia* need a bushfire and subsequent humid weather to release their seeds by a opening mechanism that does not require an active metabolism. Current research is elucidating the intricate material structure and composition that allows such behavior (see their reports).

Sensory biomaterials, especially located in the spider cuticle are at the center of *Yael Politi's* (c) research. Spiders cuticle is a composite material based on chitin and possesses ultrasensitive vibration sensors as well as venom fangs (effectively "injection needles") with very unusual engineering properties. This work both contributes to the better understanding of how arthropods may have evolved these capabilities, but also shows examples of high-performance materials that are interesting from the viewpoint of bio-inspired engineering (see her report and [1]).

Damien Faivre (d) is heading a research group entirely supported by an ERC-grant to him. The research topic gravitates around magnetic nanoparticles (mostly magnetite), their synthesis in bacteria and in vitro, as well as applications from nanorobotics to medical imaging (see his report).

Several independent researchers work on different problems related to biological or bioinspired materials (e), as described in their individual reports. *Luca Bertinetti* studies the interaction of water with cellulose and collagen; *Admir Masic* develops advanced in situ and in vivo spectroscopic imaging of biological tissues; *Igor Zlotnikov* focusses on structural and nanomechanical characterization of mineralized biomaterials; *Mason Dean* addresses evolutionary perspectives on vertebrate hard tissues; *Wouter Habraken* coordinates a 5-year collaborative project on the physical chemistry of amorphous minerals in living organisms (supported by the DIP-Program of the German Science Foundation), together with partners at the Weizmann Institute (Lia Addadi and colleagues); see his report and [2-4]; finally *Katja Skorb* started a program on generating smart systems by surface nanostructuring for bio-applications.

John Dunlop (f) is interested in the autonomous dynamical reconfiguration of materials systems. One line of research is to elucidate how growing tissue is able to sense and react to the curvature of the substrate in its growth behavior. He also studies self-actuating systems based on swelling honeycomb-like structures (see his report). This research may have important repercussions on (soft) robotics and on tissue engineering.

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The mechanobiology group (g) of *Richard Weinkamer* investigates the basis for the capability of bone to adapt to mechanical loads. A network of cells (osteocysts) buried inside the mineralized tissue is thought to control the mechanosensitivity of bone. Current research studies these networks both experimentally and by numerical modeling.

Emanuel Schneck (k) just started an Emmy-Noether group (supported by DFG) on the physics of biomolecular interfaces. The research addresses interaction between membranes and with biomolecules, making use of light and neutron reflectivity studies as well as numerical modeling (see his report).

Reinhard Miller (m), previously member of the Interface Department, moved into the Biomaterials Department after the retirement of Helmuth Möhwald. His research focusses on solution-air interfaces (see his report).

Three further topics are mentioned in Figure 2. First, there is a long-standing collaboration with the Ludwig Boltzmann Institute of Osteology in Vienna, Austria on clinically oriented research on bone diseases (j), such as osteoporosis and osteogenesis imperfecta (brittle bone disease). *Richard Weinkamer* and *Wolfgang Wagermaier* are both involved in this collaboration (see their reports). In addition, methodologies based on Raman imaging [5,6] and on acoustic microscopy [7] are being established for use in clinical studies. Mineral densities have been studied in a large pre-osteoporotic and osteoporotic patient cohort [8,9]. Finally, the behavior of osteoclasts was characterized in in-vitro studies [10].

The same two groups (as well as *John Dunlop*) are also involved in a consortium on bone regeneration (l) with the Berlin Brandenburg School of Regenerative Therapies (supported by the DFG Excellence initiative). The emphasis there is fundamental research on bone healing (see the report by *Wagermaier*), as well as on the interaction of regenerating bone with various types of implants [11-14].

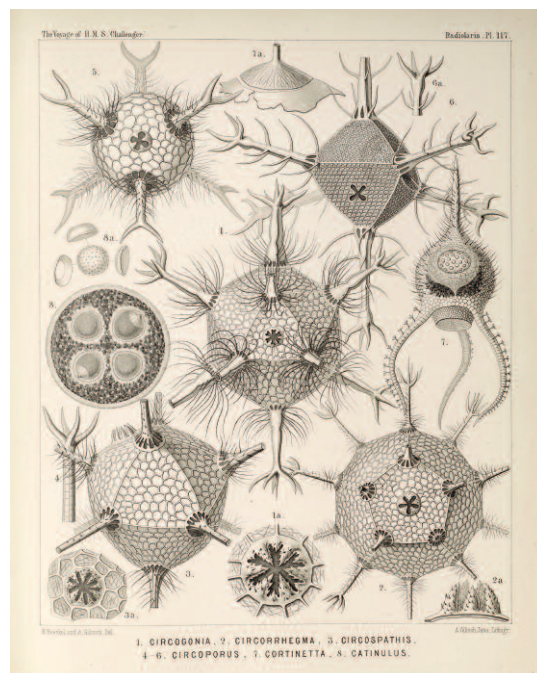


Figure 3: image from the report of the challenger expedition (Radiolaria)

Several researchers of the department of Biomaterials are involved in the Excellence Cluster "Image-Knowledge-Gestaltung" at the Humboldt University Berlin (i). Peter Fratzl is one of the PIs who participated in the definition of the cluster. The goal is highly interdisciplinary work between humanities, natural sciences, and also design and engineering, see <https://www.interdisciplinary-laboratory.hu-berlin.de/en/laboratory>. The Department is involved in several base projects including research on the significance of models in science and humanities, or on historical structures. The latter focusses on establishing a searchable data base collecting descriptions of organisms in historical texts, such as the reports on the challenger expedition 1872-76 (Fig. 3) in view of a potential use in bioinspired engineering. The strategy is to generate an ontology connecting engineering problems with natural solutions, as described in modern or historical biological literature.

Methodological approaches

Generally, the 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 to characterize micro- and nanostructure and many levels of structural hierarchy (see report by *Wolfgang Wagermaier*). We have established polarized and confocal Raman imaging to provide information on chemical composition and fiber orientation, which is now being combined in-situ with synchrotron x-ray scattering (see report by *Admir Masic*). We use nano-indentation as well as acoustic microscopy to estimate local mechanical properties. Currently, *Igor Zlotnikov* is establishing modulus mapping which pushes the lateral resolution of mechanical characterization into the nanometer range (see his report). 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. This facilitates the extraction of structure-property relationships even in extremely heterogeneous materials with hierarchical structure.

In a second type of approach, we study in situ changes in various materials (e.g. due to mechanical stress or to chemical or thermal processing) by time-resolved scattering or spectroscopy during mechanical deformation or thermal or hygroscopic treatment. This gives insight into the molecular and supramolecular mechanisms which are responsible for the noteworthy properties of these materials. In some cases, such measurements can be performed in the laboratory (e.g. with Raman or infrared spectroscopy or in the environmental scanning electron microscope), but in many cases synchrotron radiation is needed (e. g. for x-ray diffraction or small-angle scattering). A dedicated beamline end station for scanning small- and wide-angle scattering and fluorescence spectroscopy is operated at the synchrotron BESSY at the Helmholtz Zentrum Berlin. A particular challenge is related to the big amount of data generated in such experiments, which led us to head an effort in developing software for the online analysis of large x-ray scattering datasets [15].

These efforts are complemented 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 for example the reports by *John W.C. Dunlop* and *Richard Weinkamer*).

Visiting scholars

Several experienced scientists have been spending significant time in the Department. *Franz Dieter Fischer*, professor of mechanics at the Montanuniversität Leoben (Austria) recipient of the Alexander von Humboldt Award, came for many short visits, which helped advance the mathematical modeling of tissue growth in particular (see report by *J.W.C. Dunlop*) and was involved in theoretical research about the mechanical properties of biological hybrid materials [16]. *Hartmut Metzger* who arrived in the beginning of 2010 from the European Synchrotron Radiation Facilities (ESRF) brought many years of experience in x-ray diffraction, in particular with grazing incidence and using coherent beams, to our Department and, before retiring in 2013 he was involved in a number of projects utilizing synchrotron radiation such as the study of biological materials. *Emil Zolotoyabko*, professor of materials science at the Technion (Israel Institute of Technology) regularly spends several sabbatical months per year in the Department. He is involved in a wide range of projects by different research groups. *Yves Bréchet*, currently High Commissioner of nuclear and alternative energies for the French government received a Gay Lussac-Humboldt Award and is visiting our Department regularly since 2012. *Scott White*, professor at the University of Illinois at Urbana-Champaign received the Humboldt Research Award and was visiting the Department in 2013. His research is focused on developing self-healing and self-remodeling engineering materials. *Claudia Fischbach-Teschl*, professor at Cornell University spent half a year of her sabbatical in Golm during 2014, supported by the Humboldt Foundation. She is interested in the development of bone metastases from breast cancer and brought this new topic to the department of biomaterials, which lead to currently ongoing collaborative work. In addition to developing new collaborations, our visiting scholars play an important role in the mentoring of young scientists, and we are most grateful to them for this very important contribution.

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 positive and constructive partnerships.

Peter Fratzl

Director of the Department of Biomaterials

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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

We are interested in understanding functionality of plant materials in the context of their environment. Plant material can be defined as any material forming the plant body. The plant body is typically composed of different tissues, formed by cells. The cells - various shapes are possible – are encased by a polymeric cell wall made of pectins, hemicelluloses, lignin and cellulose, the most abundant polymer on earth. The arrangement of the long and stiff cellulose molecules which form so-called fibrils directly influences cell wall mechanics. Furthermore the interactions with the other cell wall substances, including water, play an important role for material performance.

Currently our research activities are focused mainly on two different plant materials: Banksia follicles and wood (**Fig. 1**).

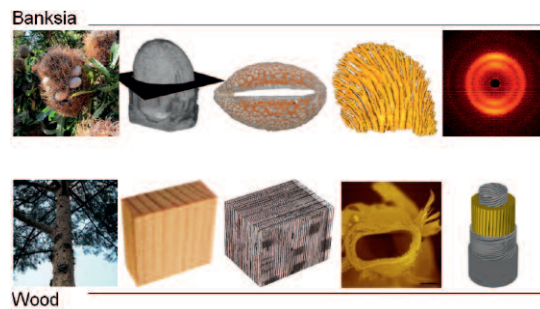


Fig. 1: Banksia follicles, characteristic structures at different length scales, left cm-level, right nm-level. Bottom row shows the structure of softwoods at different length scales.

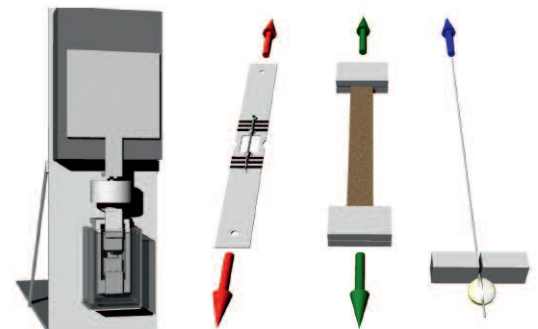
Banksia follicles are seed capsules that store seeds on the Banksia plants for up to 17 years before releasing them upon an environmental trigger which is in most cases fire. This trait is of particular advantage in environments with nutrient poor soils. The follicles are composed of dead polymeric tissue, and from a material science point of view are of particular interest concerning long-term stability/durability but also functionality when exposed to high temperatures. These properties are highly desirable when thinking about wood, a widely used (construction) material having drawbacks when it comes to fire retardancy, long-term resistance against weathering, microbial and insect attack. In contrast to the almost unknown material properties of Banksia follicles, wood of several tree species is very well studied, however still many open questions related to wood material properties, especially on smaller length scales, eg. at the cell wall level, remain. For these reasons it is a suitable material to establish/apply/verify (new) experimental micromechanical techniques to investigate plant material in detail and at the same time to contribute to a deeper understanding of the material wood.

In many cases micromechanical experiments are the method of choice in answering open questions. During the last years we were able to establish different experimental setups which allow us to test samples with different sizes and shapes as well as fragile and more robust materials **[1]**.

In the following both a brief summary about some of our micromechanical testing systems and research projects where we could contribute with our knowledge and techniques are given.

Experimental Micromechanical Testing

During the past years a variety of setups for the micromechanical characterization of biological, bio-inspired and other materials has been developed. **Fig. 2** shows schematically some available systems for tensile tests which allow us to test samples with various shapes and properties ranging from very fragile (eg. primary cell wall systems) to robust (eg. woody tissues). We are able to control temperature and humidity in the sample vicinity to account for the fact that mechanical properties of biological materials are typically humidity dependent. To allow monitoring changes during mechanical loading the systems can be combined with other techniques such as light and electron microscopy, Raman spectroscopy or synchrotron radiation. For tissues and samples that cannot be tested in tension, nanoindentation is often an appropriate alternative to characterize mechanical properties **[2]** and even there humidity control is possible now **[3]**.



*Fig. 2: Schematic drawing of a tensile tester which allows testing of samples immersed in a liquid in a glass cuvette (left). Foliar frame serving as a support for fragile samples (eg. *Arabidopsis hypocotyls* or wood cells), red arrows point in loading direction. Green arrows indicate the loading direction of a larger sample clamped between metal plates, alternatively glue can be used for more fragile specimens (eg. hydrogels or membranes **[4]**). Right: glass fibre with a droplet of glue, blue arrow indicates loading direction of fibre, 2 metal plates hold the glue droplet, the fibre can be pulled out of the glue and interfacial shear strength can be determined.*

The Dependence of the Mechanics of Wood Cell Walls on Environmental Conditions

It is well known that the arrangement of cellulose fibrils in wood cell walls significantly affects the mechanical properties of wood, especially the parallel alignment of microfibrils in the predominant S2 layer. By controlling cellulose fibril orientation the tree is able to modulate wood properties in order to react to environmental conditions. A high angle of the fibrils with respect to the longitudinal cell axis (the so-called microfibril angle, black lines in yellow cell wall layer, cartoon Fig. 1, bottom right) results in a more flexible materi-

al, low angles result in stiff material. As long as wood is the material of a living tree, the moisture content is above the so-called fibre saturation point. When wood is used as a material by mankind its moisture content is typically below the fibre saturation point and its properties are then highly dependent on the amount of water in the cell wall. In a recent review [2] we collected and summarized literature data on how the mechanical properties of wood cell walls change with microfibril angle and moisture (grey triangles in Fig. 3). To fill some missing data gaps we sampled wood from different locations in a tree (micrographs in Fig. 3) allowing us to investigate single wood fibres with different MFAs. By controlling relative humidity during the tensile test we were able to systematically describe changes in mechanical properties and could show that the influence of moisture on the tensile stiffness becomes larger with higher microfibril angles [5]. This work is a good example highlighting the mechanical role of the matrix polymers hemicelluloses and lignin in the cell wall, since in cells with higher microfibril angles the matrix substances experience higher stresses.

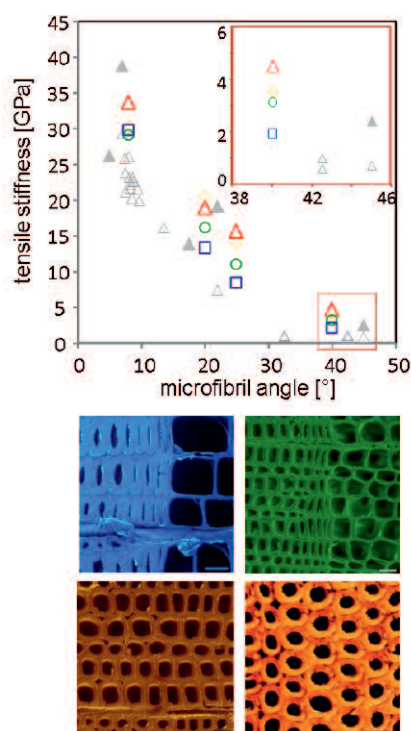


Fig. 3: Diagram showing tensile stiffness of single wood cells plotted against microfibril angle (each data point represents mean values of ~10-20 experiments). Grey symbols show data from literature (details can be found in [2]), white triangles represent data for wet fibres, filled triangles those tested under laboratory conditions (65%rh, 20°C). Coloured symbols represent data from new experiments, red triangles (5%rh), yellow square (50%rh), green circle (75%rh) and blue square (90%rh). SEM micrographs show the selected tissue types: blue adult wood, MFA=8°, green juvenile wood, MFA=20°, brown reaction wood from stem, MFA=25° and orange reaction wood from branch, MFA=40°. Scalebars 20µm.

Unfortunately tensile tests are – so far - only possible for single fibres longer than 0.7 mm. However, nanoindentation is a useful alternative which allows to control environmental conditions [3].

Bioinspiration: Interfacial Design of Glass Fibre-Reinforced Composites

Not only cellulose is an important mechanical component of the cell wall. Hemicelluloses are supposed to be the mediators between cellulose and lignin. Even though less stiff and much weaker than cellulose they play a major role in toughening cell walls. Toughness and in addition a fracture behaviour which is comparable to many biological materials are characteristics of particular importance for composite materials such as glass-fibre reinforced polymers. In a project with cooperation partners from the colloids department, the Universities of Bayreuth and Freiburg and the ITV Denkendorf [6] surfaces of glass fibres were modified to improve their interactions with the epoxy matrix. The whole process was inspired by the role of hemicelluloses in cell walls and realized by a so-called grafting-from and grafting-onto procedure. It has been shown in pull-out tests (Fig. 2) that the interfacial shear strength (determined in pull-out tests) can be controlled and modified by tailoring the interphase design (eg. grafting density).

Fibre reinforced composites are often used for high-performance applications. Especially for such applications a system which is able to report micro-damages in a reliable way is highly desirable. A group at the University of Basel coated glass fibres with a fluorescent protein-based mechanophore. When protein unfolding occurs upon damage the yellow fluorescence of the protein is lost. This signal can then be used as a damage sensor for microcracks. We were able to show that interfacial shear strength is comparable to native glass fibres and amino glass fibres which indicates that the protein coating does not affect the interfacial shear stress [7].

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BIOLOGICAL MATERIALS

Biochemical Strategies in Load-Bearing Natural Materials



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Biological organisms produce a variety of protein-based polymeric materials under environmentally benign conditions, which achieve an impressive range of industrially desirable properties – e.g., damage tolerance, self-healing, actuation, shape-memory and underwater adhesion. The primary research interest of this research group is to understand the biochemical, biophysical and structural underpinnings of such adaptive material behaviors, with the goal of applying extracted concepts to the design and synthesis of bio-engineered polymers with tailored properties. These aims are achieved through a multi-disciplinary approach consisting of three interdependent strategies: 1. Learn from nature 2. Characterize protein building blocks and 3. Synthesize tailored biopolymers. The self-healing fibers of the mussel byssus provide the primary model system studied in the group (**Fig. 1**).

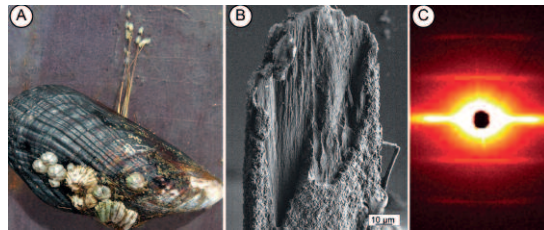


Fig. 1: In situ structural analysis of mussel byssal threads. A) Mussels attach to substrates with anchoring fibers known as byssal threads. B) Cryo-SEM image of byssal thread revealing a fibrous core surrounded by a thin protective layer. C) Small-angle X-ray pattern of the thread core indicates a highly organized semi-crystalline protein framework [1].

Learn from Nature

Learning from nature requires the in-depth characterization of structure-function relationships of protein-based biological materials. Byssal threads are stiff, tough, extensible and self-healing protein-based fibers produced by marine mussels that provide a secure attachment in seashore habitats. X-ray diffraction studies (**Fig. 1**) led by Stefanie Krauss (former postdoc) have revealed the importance of a semi-crystalline protein framework in the deformation and healing behavior of the byssus [1]. In particular, it was discovered that the elastic and reversible deformation of the framework is vital for re-uniting ruptured sacrificial bonds, whose recovery likely leads to self-healing behavior. Current work by Clemens Schmitt (PhD student) using advanced spectroscopic methods in collaboration with Yael Politi (Dept. of Biomaterials) indicates that the sacrificial bonds likely consist of metal coordination bonds primarily mediated by Histidine residues, whereas further X-ray diffraction work by Antje Reinecke (PhD student) suggests that reversible unfolding of specific folded protein structures contributes to the high extensibility of the threads.

In collaboration with several other groups, we have harnessed numerical and computer-based modeling in an attempt to understand the observed damage-tolerant mechanical behaviors of the byssus as well as similar biopolymers. In collaboration with the group of Markus Hartmann (Montanuniversität Leoben), Monte Carlo simulations of polymer chains with sacrificial bonding sites modeled after mussel byssal proteins provided several important insights into the intricacies of bond rupture and reformation under load, as well as the importance of bond topology in controlling the effective strength of sacrificial bonds [2, 3]. Additionally, a numerical model developed in collaboration with Peter Fratzl (Dept. of Biomaterials) and Dieter Fischer (Montanuniversität Leoben) was able to describe the pseudoelastic mechanical behavior of whelk egg capsules in terms of a classical phase transformation – leading to important mechanistic insights into the origin of the characteristic mechanical hysteresis of the material [4].

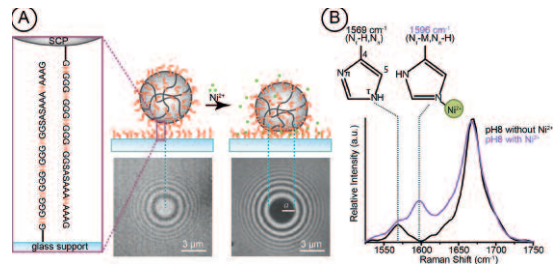


Fig. 2: Characterization of peptides based on His-rich domains (HRDs) of the preCols. A) Soft colloidal probe spectroscopy revealed a significant interaction between HRD peptide layers in the presence of metal ions, but not in their absence. B) Raman spectroscopic analysis revealed that the interaction is largely mediated through His-metal coordination bonding. Adapted from reference [5].

Characterize Protein Building Blocks

The primary building blocks contributing to the tensile mechanical behavior of mussel byssal threads are collagen-like proteins, known as the preCols. As mentioned, histidine amino acid residues concentrated in the terminal domains of preCols are believed to contribute to deformation and healing behavior by forming reversibly breakable metal coordination bonds. To test this hypothesis, Stephan Schmidt (former post-doc) and Antje Reinecke (PhD student), in collaboration with the group of Laura Hartmann (Dept. of Biomolecular Systems), investigated the metal-dependent mechanical behavior of peptide sequences derived from the His-rich domains of the mussel byssal preCols. Soft-colloidal probe force spectroscopy combined with Raman spectroscopy demonstrated the propensity of these peptides to form stable, yet reversibly breakable cross-links mediated by interactions by metal ions and histidine [5]. Notably, the PEG-based colloidal probes also exhibited increased stiffness in the presence of metal ions indicating the potential for such a strategy in reinforcing polymeric networks reversibly.

Synthesize Tailored Biopolymers

The principles extracted from studying the byssus and characterizing its building blocks – namely, the use of metal coordination interactions as robust and reversible cross-links – were integrated into a recombinant biopolymer through rational design of protein sequence. Specifically, in a project led by Elena Degtyar (Postdoc), metal-binding histidine residues were genetically engineered into the sequence of insect resilin, which was recombinantly expressed, purified and photo-cross-linked into biopolymeric thin films. Mechanical characterization of the thin films with AFM-based indentation indicated a nearly 800-fold increase in stiffness in the presence of Zn^{2+} ions compared with wild-type resilin, which was shown by spectroscopic means to arise at least in part from histidine-mediated metal coordination cross-links [6].

Mussel-Inspired Biomimetic Polymers

In continued collaboration with the group of Niels Holten-Andersen (MIT), we investigated mussel-inspired PEG-based hydrogels stabilized by metal coordination cross-links between various metal ions (e.g. Fe, V, Al) and 3,4-dihydroxyphenylalanine (DOPA), a post-translational modification of tyrosine found enriched in many byssus proteins [7]. Metal- and pH-dependent variations in the affinity of the ions for DOPA led to tunable mechanical properties of the hydrogels, which also display self-healing properties.

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After cellulose chitin is the second most abundant natural bio-macromolecule as it forms the main building block of all arthropod cuticles – the richest phyla in nature. Due to its widespread abundance and biocompatibility chitin is also extensively used in diverse industrial processes and has found various technological and medical applications

[1]. The study of chitin and chitin based materials therefore holds a promise for clever bio-inspired materials design.

The large diversity seen in the arthropod phylum is also reflected in an ample diversity of cuticular materials with different physical properties that serve many different biological functions forming the external skeleton, skin, sense organs and more. The cuticle can be described as a fiber reinforced composite material, where α -chitin crystallites tightly coated by a protein shell form the fibrous phase and the matrix is composed of a wide range of proteins [2]. The main goals of our group are to obtain basic understanding of the cuticular material and to gain insight into the structure-properties-function relations in specific organs such as cuticular tools (e.g. fangs, claws) and sensors. We work in close collaboration with Prof. Friedrich Barth, from the University of Vienna (Vienna, Austria) Prof. Vladimir Tsukruk from Georgia Institute of Technology (Atlanta, USA) and Prof. Emil Zolotoy-abco from the Technion Institute of technology (Haifa, Israel).

The current members of the group are Ms. Ana Licuco, Dr. Hanna Leemreize, Ms. Inga Hettrich, Dr. Marie Albéric, Dr. Osnat Younes-Metzler and Ms. Birgit Schonert.

Mechano-Sensing in Spiders

The spider cuticle is covered by numerous cuticular-sensors that react with remarkable sensitivity and specificity to a wide range of mechanical stimuli (medium flow, substrate vibration and cuticle strain) [2]. Filtering of background noise from relevant information occurs at the material/organ level which makes these structures appealing as models for the bio-inspired design of mechanoresponsive and adaptive nanostructured materials.

In order to exploit fundamental principles found in natural mechanoreceptors for bio-inspired materials, we focus on understanding the mechanism of mechanical signal detection, transmission and filtration for the spider slit biosensory system at the material level. We investigated the direct spatial correlation among cuticle morphology, hierarchical structural organization and micromechanical properties in spider metatarsal slit-sensor and the cuticular pad just in-front of it.

The metatarsal lyriform organ of the Central American wandering spider *Cupiennius salei* is its most sensitive vibration detector. It is able to sense a wide range of vibration stimuli over four orders of magnitude in frequency between at least as low as 0.1 Hz and several kHz. Transmission of the vibrations to the slit organ is controlled by the cuticular pad. While the mechanism of high frequency stimulus transfer (above ca.40 Hz) is well understood and related to the vis-

coelastic properties of the pad's epicuticle [3], it was not yet clear how low frequency stimuli (<40 Hz) are transmitted. We recently [4] addressed this question using a variety of experimental techniques, such as, *in-situ* x-ray micro-computer tomography (μ CT) for 3D imaging (Fig. 1), x-ray scattering for structural analysis, and atomic force microscopy (AFM) and scanning electron microscopy (SEM) for surface imaging. We showed that large tarsal deflections (necessary for low frequency signal transmission) cause large deformation in the distal highly hydrated part of the pad. Beyond this region, an unusual sclerotized region serves as a supporting frame which resists the deformation and is displaced to push against the slits, with the displacement values considerably scaled down to only few micrometers. Importantly, we have shown how the organization of the chitin fibrils in 3D contributes to the mechanical properties and the performance of the pad under biologically relevant loads [4].

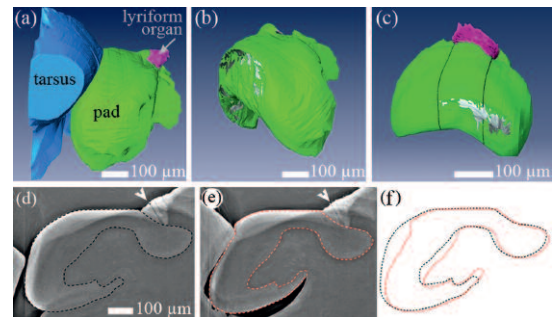


Fig. 1: (a) Surface rendering of the reconstructed μ CT data of the pad and tarsus during *in-situ* compression study. tarsus (blue), pad (green), slit-sensilla (pink). (b) 3D shape of the cuticular pad during compression extracted from (a). Grey regions at the distal side of the pad indicate the contact area with the tarsus. (c) 3D shape of the cuticular pad under load with a slight lateral component. Grey regions at the distal side of the pad indicate the contact area with the tarsus. (d-f) μ CT virtual slices of the sample in a-b sectioned in the sagittal plane in the center of the pad in relaxed (d) state (< 0°), and deflected by 9° (e). The dashed lines indicate the outline of the cuticular material of the pad. The white arrows indicate one slit of the metatarsal lyriform organ. (f) An overlay of the pad shape from (d) and (e).

Further research is focused now on the structure-properties of the slits organ it-self. In fact the exact mechanism of how the mechanical signal is transferred to the slits and from the slits to the nerve cells is still poorly understood. A better understanding of the slits structure, mechanical performance and how they behave under biological relevant loads is a key for deciphering their functional mechanism. We analyse slit compression during load from similar *in-situ* μ CT measurements and describe the 3D fiber orientation along the slits walls using nano-focused x-ray beam (Fig. 2). Unravelling the structural arrangement in such specialized structures may provide conceptual ideas for the design of new materials capable of controlling a technical sensor's specificity and selectivity, which is so typical of biological sensors.

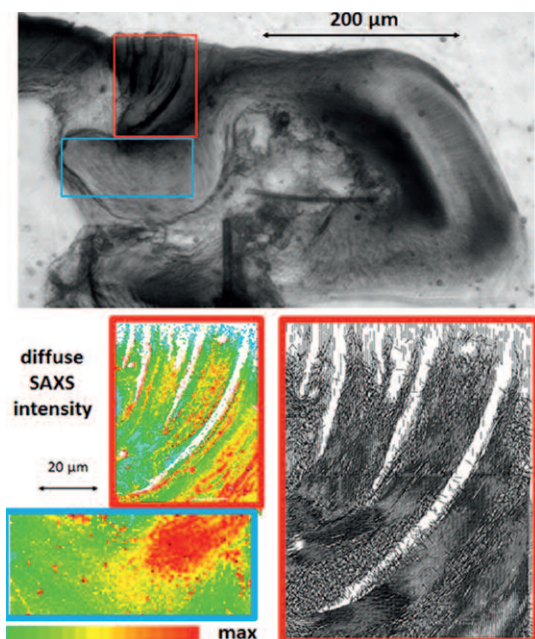


Fig. 2: left: light microscope image of a sagittal section (10 μm thickness) of the distal end of the metatarsus showing the slits and the pad. Red and Blue frames mark the measured regions. Middle: the scattering signal intensity from (110) peak reflection of chitin crystal and diffuse SAXS signal intensity at lowest measured scattering angles. Right: vector graphics showing the fiber orientation as extracted from azimuthal integration of the scattering data.

Multi-Scale Structural Gradients Analysis of the Spider Fang

The spider fang is a natural injection needle, hierarchically built from a complex composite material comprising multi-scale architectural gradients [5]. Considering its biomechanical function, the spider fang has to sustain significant mechanical loads. We analyzed [6] the macroscopic fang stiffness and damage resilience in view of its multi-scale architectural motifs using mechanical modeling based on experimental observations from previous work [5]. We first studied the macroscopic architecture of the fang and then proceeded to the material level. We applied experiment-based structural modelling of the fang, followed by analytical mechanical description and Finite-Element simulations and showed that the naturally evolved fang architecture results in highly adapted effective structural stiffness and damage resilience.

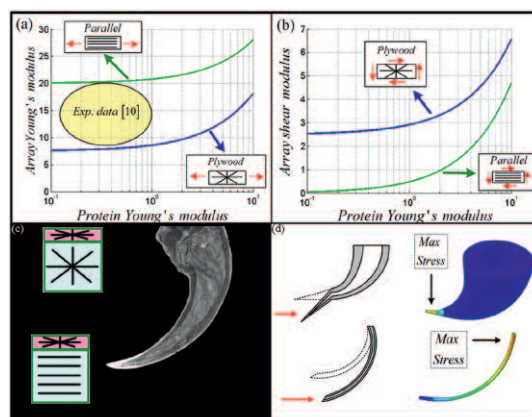


Fig. 3: Effect of the proteins' Young's modulus on the composite moduli. (a) Young's modulus and (b) shear modulus of parallel-fibred (green) and rotated-plywood (blue) fibril arrays, made from chitin fibrils (modulus ~ 100 GPa, volume fraction 0.2) and a protein matrix (range of moduli). The circle in (a) indicates the typical range of the experimental values (aFM). (c) distribution of fiber architecture along the fang: the external layer is always composed of rotated plywood (pink), while the internal layer is composed mostly of parallel fiber at the tip of the fang and rotated plywood at its base. (d) The effect of the fang macroscopic shape on the Von-Mises stress (kPa) distributions in the fang model.

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Evolutionary Perspectives on Vertebrate Hard Tissues



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Natural selection can act on multiple size scales in the evolution of skeletons, altering material, structure, and/or gross anatomy to affect how tissues respond to the demands of their environment. Yet, there is often a disconnect between our understandings of finescale material performance (e.g. how structure and composition relate to tissue mechanics), and the larger scale relationships between species-level anatomical variation and ecology (e.g. how skeletal structure relates to diet and behavior). The bridging of these hierarchical size scales and disciplines represents a grand challenge for biomaterials science, one we tackle through study of 'lower vertebrate' skeletal systems (particularly in fishes), using a rich network of interdisciplinary approaches that incorporate material science perspectives, as well as species' ecologies and evolutionary relationships.

How can Cartilage Perform like Bone?

Fish skeletal tissues are extremely diverse, with many species possessing cartilage and bone (similar to our skeletons), but also tissues that represent hybrids between these. These allow us to better understand form-function relationships in skeletal tissues in general, as well as the evolutionary pressures that shaped animal anatomy. In particular, we investigate the materials, structure and mechanics of mineralized shark cartilage, supported by a Human Frontier Science Program Young Investigator's grant between our department, the Wyss Institute for Biologically Inspired Engineering (Harvard University), and the Zuse Institute Berlin (ZIB). This interdisciplinary collaboration, supporting a variety of students and post docs, brings together high-resolution material property and ultrastructure data (MPIKG) with quantitative analyses of skeletal form (ZIB) to build bio-realistic and idealized 3d-printed models (Wyss) for hypothesis testing and comparison with mechanical testing data of native tissues [1-2]. By combining these structure-function studies with investigations into muscular anatomy, skeletal development and patterning [e.g. 3], we are learning fundamental design rules for this unique tissue, and layered, low-density composite materials in general.

Is Bone Still "Bone" if it Has no Cells?

Mammalian bone, unlike cartilage, is capable of repairing the microdamage it accumulates from daily use. The longevity of our skeletons depends on this 'remodelling', which has long been thought to rely on osteocytes (cells in bone) to sense when and where to repair. This paradigm is called into question by the skeletons of most bony fishes, which lack osteocytes (and therefore should be irresponsive to load and damage), and yet exhibit mechanical performance similar to mammalian bone [4]. We examine fish bone ultrastructure and mechanical properties in broad contexts, linking bone structure and mechanics to ecology, and comparing with bone from other taxa [4-6] (Fig. 1) to ask whether "bone" exhibits only a limited range of properties or is functionally and structurally diverse. Our results indicate a range of mechanical properties across vertebrate bone types and evi-

dence for remodelling even in 'anoosteocytic' fish bone, suggesting that there are unexplored principle regulators in bone mechanobiology beyond osteocytes, and that fishes represent ideal systems for bringing these to light.

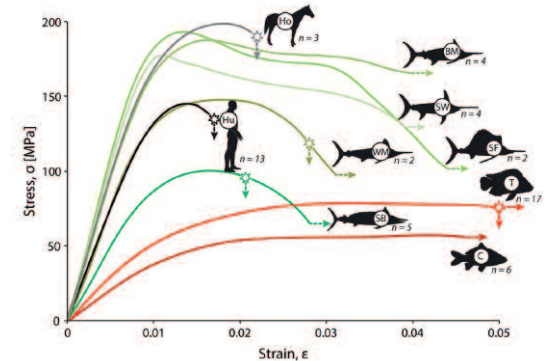


Fig. 1: Bending tests for bone beams from two mammals and seven fish species of different lineages, ecologies and tissue types. Stiffness is calculated from the initial, linear slope of the curve - whereas only some fish bone is as stiff as mammal bone (i.e. has a similar initial slope), all fish bone reaches considerably larger post-yield strains (i.e. deforms considerably before breaking). [6]

The mineralized skeletal tissues of fishes (e.g. bone, mineralized cartilage) are largely similar in composition to mammals' — a mix of water, apatitic mineral and collagen — yet our data show that they exhibit distinct structure and mechanics. Our studies help to clarify the origins, constraints and distribution of tissue types among taxa, also allowing deep understanding of form-function interactions in biological and manmade structural materials.

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Advanced *in situ* and *in vivo* Spectroscopic Imaging of Biological Tissues

Research at the interface between biology and materials science is leading to new discoveries that draw on the unique methodologies from each of these disciplines with potential applications in fields as diverse as bio-medicine, mechanical engineering, and energy conversion and storage. Complex biological materials, such as bone, silk or collagen fibers, often exhibit outstanding mechanical properties, a feature that can be directly related to their functional adaptations and interactions at multiple hierarchical length scales. Our research is focused on development of novel high performance *in situ* and *in vivo* characterization techniques that are able to overcome current research bottlenecks in the investigation of living tissues and complex hierarchically organized biological materials. These objectives are realized by implementing innovative techniques such as *in situ* multi-scale, simultaneous X-rays-Raman scattering (integrated at the μ -spot beamline at Helmholtz-Zentrum Berlin synchrotron facility), or *in vivo* simultaneous fluorescence-Raman chemical imaging platform (developed in collaboration with Mathieu Bennet and Damian Faivre (MPIKG)). The latter setup, for example, allowed for the unprecedented *in vivo* chemical characterization of the earliest stages of bone formation in genetically modified zebrafish larvae (in collaboration with Anat Akiva, Weizmann Institute, Israel, (Fig.1)), [1, 2]. In collaboration with A. Skirtach and H. Möhwald (MPIKG) we also developed a Surface Enhanced Raman Spectroscopy (SERS) platform, based on silica probes coated with single wall carbon nanotubes and gold nanoparticle aggregates, for sensing biomolecules inside living cells [3].

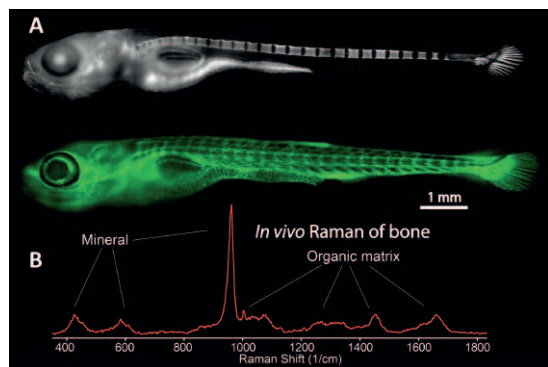


Fig. 1: Simultaneous fluorescence-Raman imaging of the early stages of bone formation in zebrafish larvae. (A) *In vivo* fluorescence image of the transgenic *tg(fli1:EGFP)* zebrafish skeletal (top) and circulatory (bottom) systems. (B) *In vivo* Raman spectrum of newly formed bone tissue.

One of the goals of our work is to elucidate precise structure-property relationships in collagen – a protein that is main component of tendons, bones, skin and other structural tissues in the body. In this context we developed methodologies to assess collagen 3D orientation in tissues [4, 5] (in collaboration with Kay Raum, Charité Hospital Berlin), water associated changes of the molecular and nanoscopic structural features in tendons [6, 7] (in collaboration with Markus Buehler, MIT, USA), as well as processes connected with the deterioration of the Dead Sea Scrolls [8] (in collaboration with Ira Rabin, BAM, Berlin). Recently, for example, we discovered the mechanisms of hydration-driven force generation in tendon collagen, revealing an unexpected and still unexplored active function of collagen fibrils [6].

The ultimate aim of our work is to collect complementary information regarding structural complexity and chemical composition in biological and biomimetic materials [9-14]. One such example is collaboration with James Weaver (Harvard University, USA), where, using sea urchin (*Strongylocentrotus franciscanus*) as a research model, we demonstrate a new set of high throughput, multi-spectral methods for the large scale characterization of mineralized biological materials (Fig. 2), [15].

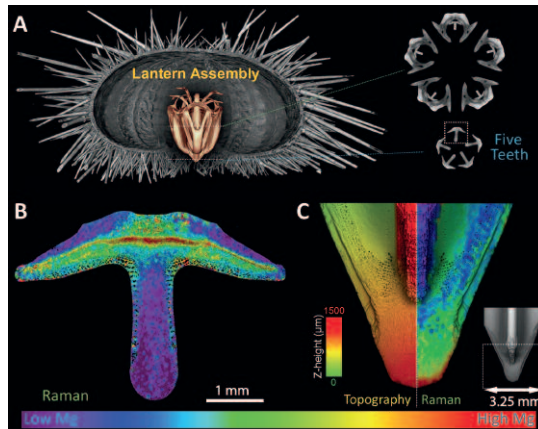


Fig. 2: Large area chemical imaging of magnesium content in the sea urchin tooth. (A) micro-CT reconstruction of an entire sea urchin with the highlighted feeding apparatus and the support ossicles for the 5 radially organized T-shaped teeth. Large area (B) and True Surface® (C) Raman chemical imaging of magnesium content in this multiphasic calcite composite. For details see ref. [15].

Using these approaches, in conjunction with whole animal micro-computed tomography studies, we have been able to spatially resolve micron and sub-micron structural features across macroscopic length scales on entire urchin tooth and correlate these complex morphological features with local variability in elemental composition.

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Mechanobiology



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In mechanobiology the structural changes of biological materials **[1]** as response to mechanical stimulation are studied. An important example is living bone with its many mechano-regulated processes. The mechanical performance of bone is the result of an intricate interaction between the cellular component of bone and the extracellular matrix.

One cell type – the osteocyte – is embedded in the mineralized bone material. Osteocytes make use of a network of small channels – so-called canaliculi – to connect with each other. The network of osteocytes is thought to sense the mechanical stimulation thereby controlling bone remodeling, a process which results in a continuous renewal of the bone material and allows for a structural adaptation of bone **[2]**. Evidence is accumulating that osteocytes also contribute to mineral homeostasis by dissolving mineral in their vicinity **[3]**.

The aim of the research group is to describe quantitatively how mechanical stimulation influences the process of bone remodeling, healing and mineralization. Since the mechanical stimulation depends on the mechanical properties of the bone itself, measurements of the bone quality are performed. The aim is pursued by an interplay between experimental characterization techniques and computational simulations, where quantification of experimental images often serves as a link.

Mechanobiology of Bone Remodeling

With the perspective to improve our understanding of the function of the osteocyte network, in a first step its topology was characterized. The osteocyte lacuno-canalicular network (OLCN) is imaged by staining with rhodamine, which enters into the porous network, followed by confocal laser scanning microscopy **[3]**. The 3-dimensional image data of the OLCN was skeletonized rendering the network topology (**Fig. 1**). The investigations focused on human osteons, the cylindrical building blocks of cortical bone formed during remodeling (**Fig. 2**). The density of the network in osteons was determined to be $0.071 \pm 0.013 \mu\text{m}/\mu\text{m}^3$ **[4]**. Within osteons the network density showed large variations, with extensive regions without network at all (**Fig. 2**). Most of the network is oriented radially towards the center of the osteon. More quantitatively, $64 \pm 1\%$ of the canalicular length has an angle smaller than 30° to the direction towards the osteon center, while the lateral network - defined by an orientation angle larger than 60° - comprises $16 \pm 1\%$. The orientation of these lateral canaliculi twists when moving along the direction of bone deposition towards the center of the osteon **[4]**. The lateral network can, therefore, be described by a twisted plywood model being coaligned with the orientation of the collagen matrix. The results of our investigation agree with the hypothesis that early osteocytes are involved in the alignment of the collagen matrix during bone formation. The regions without network raise the question, whether parts of the network get lost with time thereby reducing the mechano-sensitivity of bone.

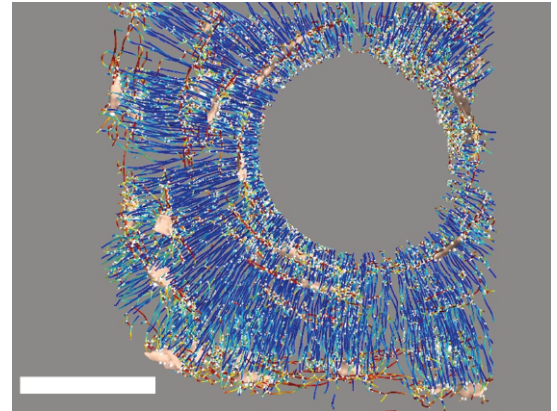


Fig. 1: Network of canaliculi in a human osteon obtained by confocal microscopy and advanced 3-dimensional image analysis. The color of canaliculi denotes their orientation (blue towards the center, red tangential to it). Pinkish objects mark the lacunae of the osteocytes and white balls locations where canaliculi meet; scale bar 50 μm .

Recent advances in experimental methodology allow monitoring bone remodeling in living animals. Using *in vivo* micro-computed tomography the amount and specific site of remodeled bone can be determined **[5]**. In animal experiments performed at the Julius Wolff Institute, Charité, (B. Willie, G. Duda) a controlled mechanical stimulation is applied to one leg of the mice, while the other serves as control. Evaluation of experimental data showed that mechanical stimulation acted stronger on enhancing bone formation than suppressing resorption. Comparison of animals of different age demonstrated that only the amount of bone forming surface could be increased by mechanical stimulation in old animals **[6]**. The spatial correlation between the local probabilities for bone formation/resorption and the local mechanical strains calculated using the Finite Element method **[7]** provided quantitative information of how the mechanical control of remodeling changes with age. A study performed with ETH Zürich indicated that mechanical stimulation can also speed up the mineralization process **[8]**, i.e. the incorporation of mineral in the collagen matrix after bone formation.

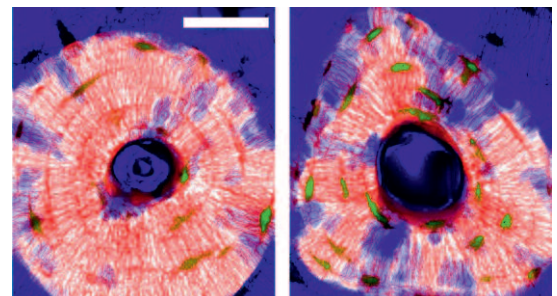


Fig. 2: The network of canaliculi in two different osteons. Osteocyte lacunae are shown in green. Areas without an accessible network are marked in blue; scale bar 50 μm . **[4]**

In a recent simulation study we questioned the common belief that mechanics helps to conserve the integrity of the network formed by trabecular bone (**Fig. 3**). The line of argumentation is that an “accidental” thinning of a trabecula due to a resorption event would result in a local increase of load, thereby activating bone deposition. Simulating a dynamic network structure undergoing remodeling, we could demonstrate that - in contrast to the argumentation above - mechano-regulated remodeling within a network-like architecture leads to local concentrations of thin trabeculae [9].

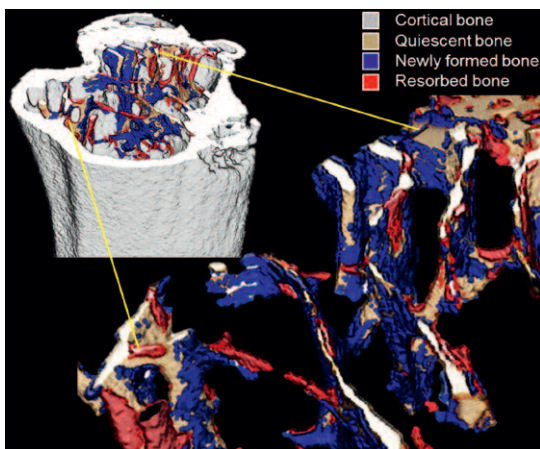


Fig. 3: Trabecular bone in the upper part of a mouse tibia, which was mechanically stimulated with a loading device. The alignment of two micro-CT scans taken at a time interval of 2 weeks allows the identification of regions on the surface of the bone, where bone was deposited (blue) or resorbed (red). [5]

Bone Material Quality

In a project performed together with LION corporation, Japan, the influence of type 2 diabetes on bone structure and properties have been studied. In two different mouse models of diabetes and healthy control mice, the investigations focused on the femur and the jaw bone since diabetes favors oral diseases. The quantitative analysis of the bone porosity showed that while in control mice the sizes of the osteocyte lacunae became smaller when comparing young to older animals, such a reduction in microporosity was not observed in the diabetic mice. This increased microporosity has to be considered as a contributing factor towards the reduced bone material quality with diabetes. The characterization of the size and alignment of mineral particles in the jaw bone of the mice were performed together with Wolfgang Wagermaier using synchrotron small-angle X-ray scattering (SAXS) (**Fig. 4**). On both, the buccal and lingual side, the particle thickness and length were decreasing in alveolar bone towards the tooth. In the animals with diabetes a trend towards smaller particle thicknesses was observed. Interesting was the detected structural asymmetry between the buccal and lingual side with often more than one preferred direction of the mineral particle orientation on the lingual side. This nanoarchitectural asymmetry of alveolar bone can be interpreted as the result of an asymmetric loading during mastication.

An efficient way to functionally characterize biological materials on the micrometer scale is by scanning acoustic microscopy (SAM). With this non-destructive method the spatial variation of bone stiffness in human osteons was estimated taking into account the full opening of the acoustic lens of the microscope. The additional information of the mass density allowed to separate the variation of the stiffness due to differences in mineral content from variations due to orientation effects of the fibrous collagen matrix [10].

Bone Regeneration and Healing

The formation of different tissues in the callus during secondary bone healing is at least partly influenced by mechanical stimuli. We used computer simulations to test the consequences of different hypotheses of the mechanobiological regulation at the cellular level on the tissue patterns formed during healing. The computational results were compared with an experiment on sheep. Our simulations showed that the amount and location of the cartilage formed at intermediate phases of healing are least robust with respect to the mechanobiological regulation [11]. Using a generic model of healing it was studied how the two pieces of a broken mechano-responsive material reconnect depending on the response of the material to mechanical stimulation [12]. These insights are important for the design of self-healing materials. Simulations of bone healing were also discussed in the Excellence Cluster “Image Knowledge Gestaltung” at Humboldt University as an example of how biological complexity compels model simplifications to perform predictive simulations [13].

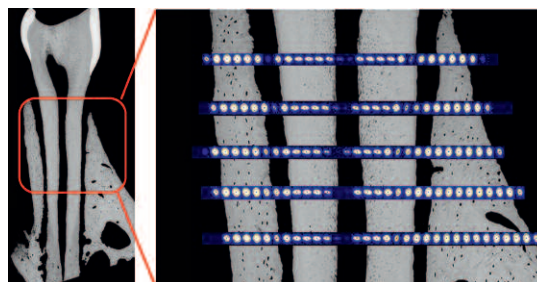


Fig. 4: Left, longitudinal cross-section through the first molar of a mouse showing the tooth anchored in alveolar bone with the buccal (lingual) side left (right). Right, synchrotron small angle X-ray scattering (SAXS) spectra were taken at every 30 µm. The more or less circular shape of the spectra provides information about the preferred orientation of the mineral particles in bone and tooth.

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Biomimetic Actuation and Tissue Growth



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Biological materials have remarkable property combinations arising through the exquisite control of their microstructures at multiple length scales [1, 2]. Perhaps one of their most interesting features is their ability to change their shape, form and internal structure through the processes of tissue growth, remodelling and swelling. As highlighted in the classic work of D'Arcy Thompson, these shape changes are often mediated by the physical environment of the tissues. The presence of external boundaries for example may constrain a swelling or growing tissue resulting in the development of internal stresses. On one hand such stresses may be sufficient to deform the boundaries, causing macroscopic shape changes, but on the other hand they may act as mechanical signals that are sensed by the cells further modifying their growth behaviour. Such mechanical signalling can act at large distances with respect to the size of a cell, and is thought to be a potential mechanism that allows tissues to organise in complex ways. An understanding of the physics of shape change in biology is thus fundamental to understand the genesis of complex multi-scale architectures in biological materials [1] with obvious applications in tissue engineering and medicine, and may also provide inspiration for the development of synthetic actuator systems. In this research group we focus on investigating the role of the geometry of external boundaries on the behaviour of growing and actuating (swelling) tissues, using combined experimental and theoretical approaches.

The Role of Geometry on Actuation

Many examples abound in the plant kingdom of natural actuators that change shape with changing humidity. Actuation arise due to differences in the swellabilities and the geometric arrangement of the constituent tissues. In the seed capsules of the ice-plant, which open to release seeds upon wetting, actuation is directed by the shape of the cells making up the active tissue [3] (with I. Burgert, ETH Zurich and L. Bertinetti). The flattened diamond-like cross sections of the cells converts isotropic swelling of the cell lumens to a strongly anisotropic swelling at the macroscopic tissue scale. Using finite element simulations and simple “ball-spring” models we could simulate the swelling behaviour of the diamond honeycomb-like structures found in the natural system [4]. Another outcome of these simulations is the realisation that by changing pore shape and tiling it is possible to control and modify macroscopic swelling behaviour giving expansion in arbitrary directions. Fig. 1 (top) shows the results of two finite element simulations of the expansion of a honeycomb made of “step-like” pores with two different arrangements: one expands only uniaxially, the other in almost pure shear (with Y. Bréchet, CEA). State of the art rapid prototyping methods allows physical models of these structures to be printed in 3D (Fig. 1 bottom) allowing for experimental validation of our theoretical approaches (with J. Weaver, Wyss Institute).

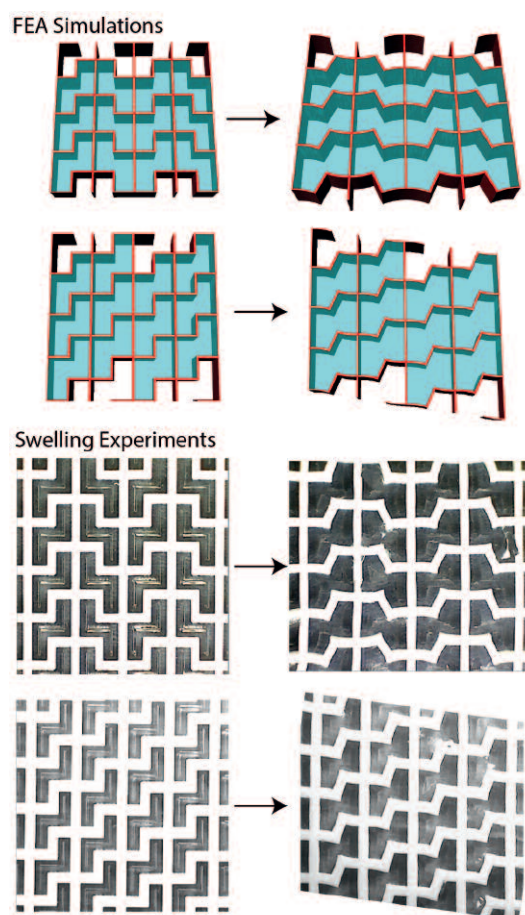


Fig. 1: Finite element simulations (above) and swelling experiments (below) to explore the role of cell shape and arrangement on the actuation of honeycombs

The group also collaborates with materials chemists to help understand the physics of polymer actuator systems. Even simple bilayers can reveal surprising results. The group of L. Ionov (Leibniz Institute of Polymer Research, Dresden) demonstrated that by controlling the time at which swelling occurs in different parts of a bilayer it is possible to fold them into complex 3D structures [5]. The group of J. Yuan (Colloid Department) have produced poly-ionic liquid membranes with gradients in cross-linking and porosity, which give rise to ultrafast bending responses to the presence of solvents [6]. By investigating the physics of these well defined synthetic systems we also hope to provide a useful basis in supporting the research of more complex natural actuators such as those studied in the group of M. Eder.

Geometry is also fundamental in controlling the unfolding of thin biological membranes. Together with T Stach (Humboldt Uni., Bild Wissen Gestaltung) we are exploring the 3D shape and function of the “filter house” of the tunicate, *Oikopleura dioica* (Fig. 2). This structure consists of a polysaccharide containing membrane produced around the animal’s head and inflated by the action of the animals tail. The house’s shape controls internal fluid flow, important for inflation, as well as concentration of the food particles for the animal.

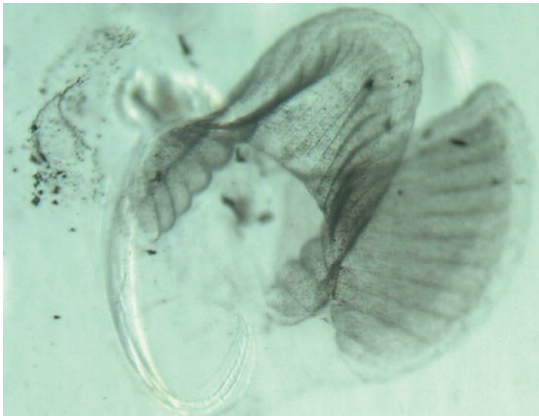


Fig 2: Image of the house of the tunicate *O. dioica*

The Role of Geometry on Tissue Growth

From previous research done in the group e.g. [7, 8] we have demonstrated the importance of substrate curvature on the rate of tissue formation in scaffolds. Within scaffolds with straight sided pores we observe that tissue grows on concave surfaces at a rate proportional to the local curvature. These pores only differ in their convex cross sections and show no significant difference (experimental and theoretical) between the total tissue growth rates. However when we test the model on non-convex cross sections for example cross-shaped pores we can accelerate the rate of tissue formation by a factor of two as confirmed experimentally [7]. Further extensions to the model now enable us to predict tissue growth in 3D [9]. We are now focussing on optimising the experimental conditions in order to observe the rate of tissue formation in 3D for arbitrarily curved and re-entrant surfaces. In order to understand the role of mechanics on growth we have also developed, more detailed continuum models for growth together with F. D. Fischer and co-workers at the Uni. Leoben [10]. These models demonstrate the importance of surface stress on the curvature response of tissue growth, and are now being extended to more realistic 3D geometries.

The majority of our work till now e.g. [7, 8] has focussed on observing the tissue produced by a bone-like cell line (MC3T3-E1). We have observed such response to curvature with fibroblasts, and in a collaboration with C. Werner (Max Bergmann Institute Dresden) it has been possible to show that human mesenchymal stem cells, are also able to sense and respond to large scale geometries as a function of differentiation state. Together with K. Skorb, we are also investigating the role of surface nanostructuring on tissue growth in 3D titanium scaffolds, being more realistic materials for load bearing tissue engineering applications.

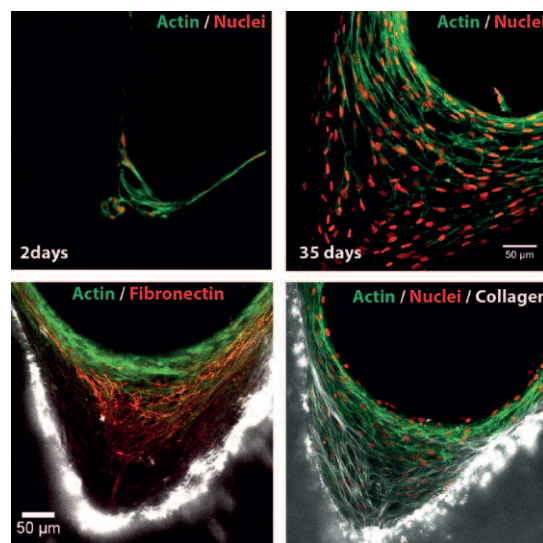


Fig. 3: Confocal microscopy images of tissues formed in the corners of triangular pores showing the role of geometric features on the organisation of tissue as it grows.

In addition to controlling the rate of growth, geometric constraints also influence the microstructure of tissues formed in the pores. This is illustrated in Fig. 3, which shows the orientation and distribution of actin stress fibres, nuclei and the extracellular matrix (ECM) proteins fibronectin and collagen within a pore. These experiments indicate that cells align with external geometric features, which in turn has a strong influence on ECM organisation (with A. Petersen (Julius Wolff Institute, Berlin), P. Kollmannsberger (ETH Zurich), and C. Bidan, (UJF Grenoble)).

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Magnetite Mineralization, Organization and Function



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In the conventional scientific classification, biology deals with the study of Life and living organisms whereas chemistry and physics deals with the constituents of matter and their dynamics. Materials science in turn combines engineering aspects to chemistry and physics and focuses on the structure-function relationship of materials. My group is putting genes on the menu of materials science: we perform interdisciplinary studies of biological materials.

Biological materials, the combination of biological components with inorganic parts such as bone and shells have indeed been used by humans for tens of thousands of years. These materials with remarkable properties are even more outstanding when we realize that they are formed under physiological conditions i.e. at ambient temperatures and pressures, and with commonplace constituents, which is not the case of typical engineered man-made materials. Nature thus not only provides inspiration for designing novel materials but also teaches us how to use soft molecules to structure and assemble simple building blocks into functional entities.

Biological Materials

Magnetotactic bacteria and their chain of magnetosomes represent a striking example of a simple organism that precisely controls the properties of individual building blocks together with their assembly at the nanometer-scale in order to form a functional entity (Fig. 1), [1].

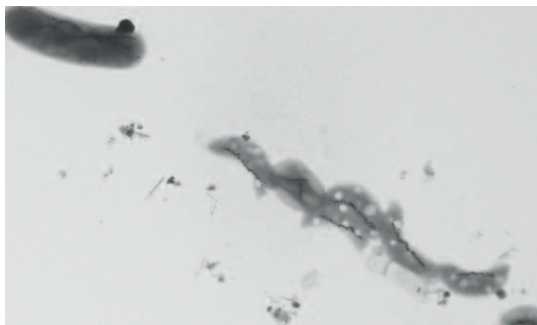


Fig. 1: a typical TEM image from magnetotactic bacteria extracted from a sediment. The magnetosomes are the electron-dense particles that are aligned and form chain(s) in the cells. Three different types of microorganisms are observed here. Image by C. Lefèvre.

Magnetosome's Magnetite Forms from Poorly Organized Minerals

The biomineralization of the mineral magnetite inside the magnetosome organelle is a process that is controlled at the cellular level [2]. The chemical route by which magnetite is formed intracellularly has been debated. We used X-ray absorption spectroscopy at cryogenic temperatures and transmission electron microscopy to characterize and spatially resolve the mechanism of biomineralization in magnetotactic bacteria [3]. We showed that magnetite forms through phase transformation from a highly disordered phosphate-rich ferric hydroxide phase, consistent with prokaryotic fer-

ritins, which is found outside the organelle. Then, a transient nanometric ferric (oxyhydr)oxide intermediate is observed within the magnetosome vesicles. This pathway remarkably resembles our results obtained on synthetic magnetite formation.

Magnetosome Chains are Mechanically Stable

Magnetotactic bacteria do not simply assemble magnetosomes in chain but also control the crystal orientation to form their cellular compass. We performed a texture analysis of aligned bacteria to show that the magnetite particles in the organelles are aligned along their easy axis of magnetization [4]. This axis is the [111] for isotropic magnetite (Fig. 2). However, some strains showed a texture along the [100] axis, which is associated with the hard axis of magnetization. We showed that the magnetosome produced by this strains are elongated in such a way that the easy axis also switch to this direction in this strain.

MamK is in particular a protein from the bacteria that forms a filament to which magnetosomes are attached by the MamJ protein. We showed that MamJ and MamK indeed interact in a host organism in vivo [5]. In addition, when fixing the cells in a gel and rotating strong magnetic field around them, we revealed that the MamK filament is mechanically stable and that it is certainly the interaction between MamJ and MamK that is first disrupted [6].

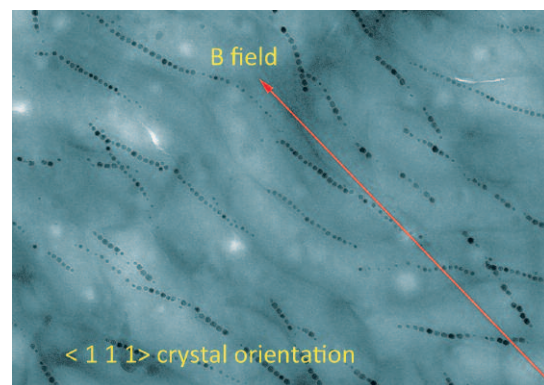


Fig. 2: false colour transmission electron microscopy image of aligned magnetotactic bacteria. The bacteria are aligned on the TEM grid by the application of a strong external magnetic field. For *Magnetospirillum gryphiswaldense*, the magnetosome crystals are oriented along the <1 1 1> crystallographic direction.

Microorganisms Swim with a Compass

Magnetotactic bacteria perform so-called magnetotaxis. They use the Earth's magnetic field together with chemical sensing to move towards favored habitats. We developed a multi-modal microscopy platform that permitted simultaneous fluorescence and high-speed imaging to map the physiological environment and record the cellular position. Combining this with aerotactic models, we characterized the magnetotaxis of *Magnetospirillum gryphiswaldense* as a function of the magnetic field [7]. We found that neither a ten-fold increase of the field strength nor a tilt of 45° results in a sig-

nificant change of the aerotaxis. However, when the field is zeroed or when its angle is tilted to 90°, the magneto-aerotaxis efficiency is drastically reduced. Our experimental evidence thus shows that this behavior is more complex than assumed in previous models.

We then studied the behavior of 12 magnetotactic strains when confronted to an inversion of the magnetic field direction [8]. We report six different behaviors that can be described as a combination of three distinct mechanisms, including the reported (di-)polar, axial, and a previously undescribed mechanism we named unipolar. We implement a model suggesting that the three magneto-aerotactic mechanisms are related to distinct oxygen sensing mechanisms that regulate the direction of cells.

Biomimetic Magnetite

Synthetic Magnetite Forms from Particulate Intermediate

The formation of crystalline materials is typically described by the nucleation and growth theory, where atoms or molecules assemble directly in and from solution. For many systems however, the formation of the stable mineral is preceded by intermediate phase(s), which seem to contradict the classical theory. Magnetite is a ferrimagnetic mineral with multiple applications for which the formation mechanism has remained unclear. We have developed a set-up for the controlled growth of magnetite particle *in vitro* [9]. We can reach average particle dimension of 50 nm, and thereby control the magnetic properties of the particles. We are able to synthetically reach particle size so far only attainable by biological synthesis.

We then studied the mechanism of such formation by cryogenic transmission electron microscopy [10]. We found that the nucleation and the growth of magnetite proceed through rapid agglomeration of nanometric primary particles and that no intermediate amorphous bulk precursor phase is involved. We demonstrate that these observations can be described within the framework of classical nucleation theory.

Finally, we studied the role of particular additive on the mechanism of magnetite formation. In particular, we showed that MamP, a protein from the magnetotactic bacteria can control the redox state of the iron and thereby enable the formation of magnetite from the sole Fe(II) under reducing condition [11].

Biomimetic Chains: Towards Hierarchy in a Semi-Synthetic System

Hierarchical structuring of single particles can lead to the formation of multifunctional materials. We are thus interested in the biomimetic arrangement of the magnetic particles we form *in vitro*. While studying the role of several additives, we found that a dedicated polypeptide was enabling the formation of a chain of magnetite nanoparticles (Fig. 3), certainly by controlling the particles size and thereby the magnetic interactions between particles [12].

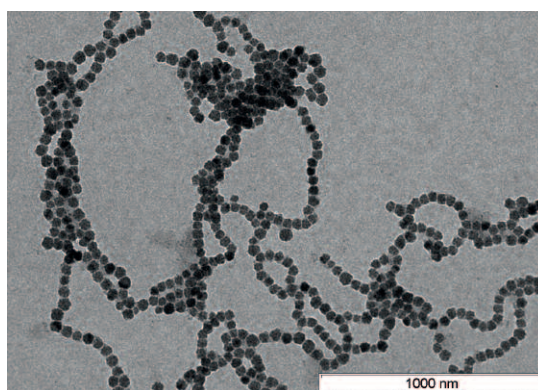


Fig. 3: Typical image of magnetite chain as observed when the synthesis is performed in the presence of polyarginine. Image by V. Reichel.

Random Synthetic Magnetic Swimmers

We finally used magnetic nanoparticles as building blocks to form carbon-coated magnetic aggregates. We show that we can select magnetically steerable nanopropellers from a set of these randomly shaped materials using weak homogeneous rotating magnetic fields [13]. Despite their arbitrary shape, all nanostructures propel parallel to the vector of rotation of the magnetic field. We use a simple theoretical model to find experimental conditions to select nanopropellers which are predominantly smaller than previously published ones.

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Water Interactions in Complex Biological Materials



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Natural materials are constituted by molecular/supramolecular building blocks, assembled at several hierarchical levels, which in most cases interact molecularly with water. From the point of view of a living organism, in an evolutionary perspective, a choice has to be made about how to tailor a material with respect to this interaction. In nature, a high variety of material's responses to water and changes in moisture content or environmental relative humidity can be observed. My main goal is to describe, from the molecular level upward, the effect of water "crowding" around the molecular components of some selected natural materials and to understand what molecular mechanisms are responsible for the observed responses. This understanding allows to extract biomimetic principles to be applied in several different fields, in particular for energy harvesting and conversion. To describe those interactions at the various hierarchical levels I use a multi-technique approach, developing environmental setups (in collaboration with many groups of the department, as for instance in [1]) allowing the control of temperature and water chemical potential (either from the gas phase or with osmotic stress techniques) and following the changes occurring in the materials from the molecular level (vibrational spectroscopies), to higher supramolecular levels (X-Ray scattering, electron microscopy), to the macroscopic size (micro-mechanical testing) possibly measuring molar free energies and enthalpy changes (through microgravimetric and calorimetric techniques) at the same time. The experimental data are then compared with thermodynamic and mechanical modeling of the considered material.

Energy Conversion in Plants Tissues

Many plants developed organs that, by controlling the organisation of their underlying tissues, can move or generate stresses in complex ways, which are powered by water sorption. Using a force balance approach, one can describe how chemical energy can be used to overcome the work of swelling for fibre reinforced polymeric composites and be used to accomplish mechanical work. This approach allows to establish the full thermodynamics of the actuation for non-living plant tissues [2]. For example, from mechanical testing experiments we could extract the free energy of water within the wood material (Fig. 1) that is lower than that of the bulk liquid water by about a seventh of a H-bond. This relatively large binding energy represents the "energy source" used by the tissues to generate large stresses.

On the other hand, other systems profit from very small entropic forces to generate large strains. This is the case for instance of the seed capsules of the ice plant that, thanks to a sophisticated design at various hierarchical level, can accomplish a full opening cycle by exploiting the entropy of dilution of a hydrophilic polymer that fills the keels cell compartments [3].

As actuation in these systems relies on solvent-materials interactions, in collaboration with prof. Thomas Zemb (ICSM Marcoule, France), we aim to quantitatively describe the thermodynamics of solvent related molecular forces existing between natural tissues' building blocks. Because of the structural and chemical complexity of the systems, it is crucial to take into consideration their geometry and the composition and account for the presence of electrolytes in solution as well.

Molecular Changes in Collagen-Based Tissues

Another system very sensitive to differences in water content is collagen. In this case, in collaboration with A. Masic, we aim to describe from the molecular to the macroscopic level the changes the collagen undergoes when its hydration state changes. In fact, applying osmotic pressure changes comparable to those occurring *in vivo*, the triple helix undergoes heterogeneous conformational changes and can generate a macroscopic tensile stress which comparable to that of the peak stress of human muscles [4]. This effect can be of extreme importance for processes occurring *in vivo*.

Development of Data Analysis Tools

Finally, I develop data analysis techniques to extract structural features of nanometric/molecular moieties from spectroscopic, scattering and imaging data [5-7].

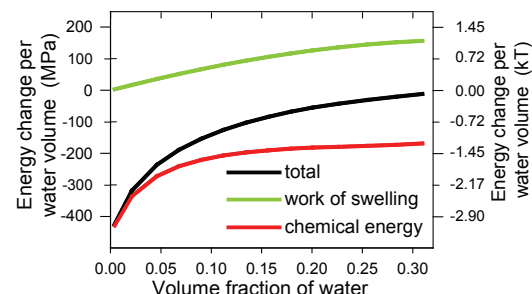


Fig. 1: Balance of energy densities for compression wood in *Piceas Abies*.

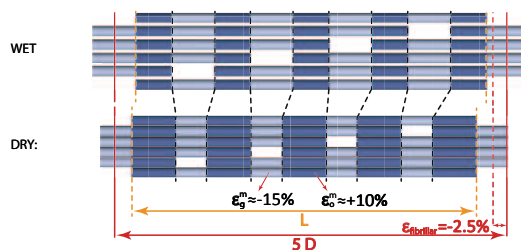


Fig. 2: Heterogeneous structural changes in collagen due to dehydration

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Synthesis and Thermodynamic Stability of Amorphous Minerals: Deeper Understanding of the Amorphous Precursor Route

Although the formation of crystals from solution is a well-described process for soluble salts, especially in the case of poorly to non-soluble salts like carbonates, phosphates and sulphates formation processes are complex and often involve an amorphous intermediate stage [1]. Interestingly, biology uses the same materials to form its complex mineralized structures, which are often composites of inorganic and organic origin with improved mechanical properties compared to the abiotic mineral. The amorphous precursor is prerequisite for the formation of these biominerals, as its properties can be easily manipulated by the presence of additives or by changing the physicochemical conditions of the local environment. By doing so, biology can choose where the amorphous precursor crystallizes and also in which type of mineral preferably it crystallizes into. However, also examples of stable amorphous minerals are known in biological records [2, 3].

As biological mineralization is complex, to retrieve more insight into the so-called amorphous precursor route, comparative laboratory studies are prerequisite where the influence of specific actuators on the formation, stability and transformation behavior of amorphous precursors is investigated. Until now mechanistic insights into these processes, however, are limited as the introduction of one specific actuator often changes more than one parameter. Additionally, to mimic biological mineralization also the interplay between different actuators need to be understood.

To enable a mechanistic evaluation, in our studies we directly focus on the intrinsic chemical, physical and morphological properties of the amorphous mineral itself as a translation step between external actuators and final outcome. As for this a high control over the synthesis is prerequisite [4], use is made of a state-of-the art titration equipment as well as numerous *in-situ* and *ex-situ* analysis techniques. Furthermore, in all steps of the research there is a close cooperation with Luca Bertinetti and Yael Politi (both MPI, Biomaterials) as well as the Department of Structural Biology of the Weizmann Institute of Science.

Particle Size Effect

Synthetic amorphous calcium carbonate (ACC) is always present as nanometer-sized spherical particles, and also in biology this morphology can be found [2, 3]. The size of these particles is variable, however, little is known about the consequences of the particle size. As one of the intrinsic properties of ACC, in our studies we investigate the effect of ACC particle size on its stability against crystallization and polymorph selection.

Additionally, we perform destabilization experiments using changing environments. By doing so, we retrieve additional insights into the effects of different kinetics and water on the crystallization mechanism. In these experiments use is made of ion-selective electrodes (in solution), an online synchrotron SAXS/WAXS setup and TGA/DSC analysis.

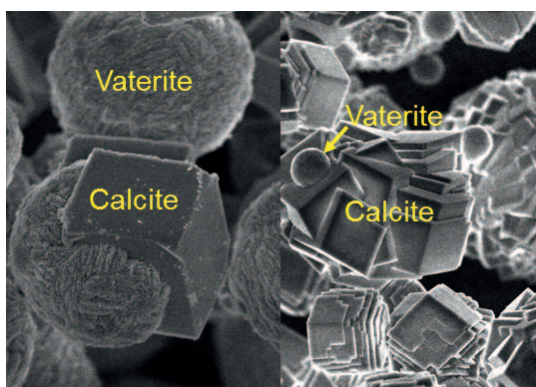


Fig. 1: SEM-images of crystallized products from ACC transformation in solution at 34°C (left) and 7°C (right) using exactly the same 200 nm sized ACC particles. Note especially the difference in crystal habit as well as in polymorph abundance of the rhombohedral calcite crystals and spherulitic aggregates of hexagonal vaterite crystals.

Effects of Mg^{2+} and PO_4^{3-}

Next to organic molecules, foreign ions like Mg^{2+} and PO_4^{3-} are commonly found inside biological calcium carbonate minerals [2], and have been observed to influence calcium carbonate mineralization *in vitro*. Similar as Mn^{2+} and Sr^{2+} , Mg^{2+} hereby enters the lattice of the final crystalline calcium carbonate polymorph (calcite), whereas PO_4^{3-} can be observed inside the amorphous precursor phase, but is expelled the moment the mineral crystallizes. Comparison of the effects of both commonly found impurities gives us insights into general mechanisms of additive controlled calcium carbonate mineralization.

Phase Behaviour

The mechanism at which amorphous calcium carbonate is formed is a hot topic of discussion, where lately numerous possible pathways have been described, but little experimental evidence is presented. By systematic synthesis of calcium carbonate mineral at controlled conditions, and analysis of the physicochemical properties of extracted material, in our studies we try to retrieve empirical information on the phase behaviour of amorphous calcium carbonate. Additionally, the role of previously described additives on the phase behaviour is investigated.

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Hierarchical Structure of Biological and Biomimetic Materials



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Biological materials are often an inspiring source for materials scientists developing new materials with specific functions and properties. In our group, we use combinations of materials science approaches to answer (i) biologically driven questions in natural materials and (ii) to understand structure-function relations in biological and synthetic materials. By this approach we aim to elucidate biological processes and to transfer knowledge from natural materials to the design of man-made materials, such as polymer-based hybrid materials and nanostructured mineral-based materials.

In our research, bone serves as a prototypical system for a hierarchically structured material with extraordinary mechanical properties [1]. Bone as a living organ has the capability to adapt to environmental conditions and to regenerate after injury. These processes are closely related with changes in the material structure at all size levels and can therefore be assessed indirectly by materials science methods. The research on bone is performed in cooperation with partners from the Julius Wolff Institute at the Charité in Berlin as well as the Ludwig Boltzmann Institute of Osteology in Vienna, Austria.

Our central experimental methods are X-ray scattering (SAXS, WAXS) [1,2], X-ray fluorescence (XRF), polarized light microscopy (PLM), confocal laser scanning microscopy (CLSM), electron microscopy, micro-computed tomography (μ CT) and nanoindentation (NI). For X-ray scattering experiments we use our lab sources as well as synchrotrons, in particular the MPI μ Spot beamline at BESSY II (Helmholtz-Zentrum Berlin für Materialien und Energie, Berlin Adlershof). To evaluate large data sets from synchrotron sources, we also develop tailored plug-in based software [3].

The Role of Osteocytes in Bone

Osteocytes are bone cells coordinating bone remodeling. We found that osteocytes are involved in mineral homeostasis and explored their impact on the bone material [4]. The osteocyte network in bone was visualized with CLSM and the nanoscopic bone mineral particle properties relative to the cell network were characterized using high resolution SAXS/WAXS techniques. Most of the mineral particles reside within less than a micrometer from the nearest cell network channel and mineral particle characteristics depend on the distance from the cell network.

Together with cooperation partners from the FU Berlin, we have been working on a synthesis of new staining molecules and explored their capacity to effectively stain and consequently visualize bones with varying porosity [5]. In a study on mouse bone we found that regions labeled with a commonly used calcein fluorochrome have lower mean mineral thickness and degree of mineral alignment [6]. Surprisingly, fluorochrome seems not only binding to mineralizing surfaces, but also alters mineral properties, stunting their growth.

Bone Healing

A fracture in bone results in a strong change of mechanical loading conditions at the site of injury, where a bony callus is formed. In fractured bone we found that primary bone formation was followed by secondary bone deposition with mineral particle sizes changing from on average short and thick to long and thin particles [7] (Fig. 1). Comparing healing in samples with a small and a large fracture gap, we found that the difference of geometry of the initial condition led to completely different mechanical situations. In the case of successful healing, a bony connection in the marrow space enabled a load transfer across the fracture gap promoting further healing. This is considered the essential step compared to critical healing (large gap size), which resulted in the formation of a bony closure at each bone end without a reunion (Fig. 1c and d).

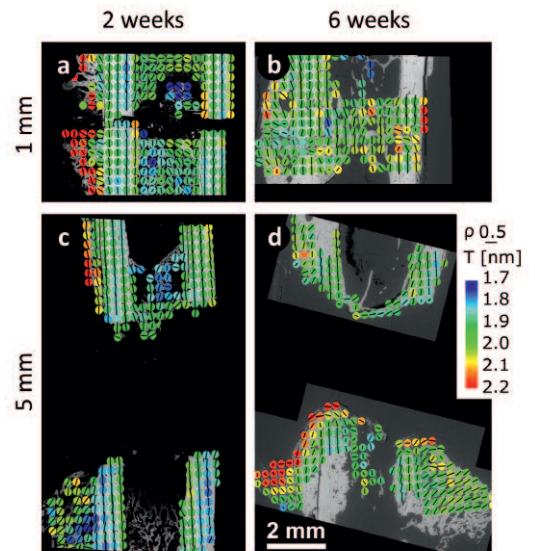


Fig. 1: Bone healing [7]. Results of SAXS measurements of normal (a and b) and critical (large gap size) (c and d) healing samples at two and six weeks after fracture. Color-coded measurement points represent the mean mineral particle thickness (T). The degree of orientation (ρ) and the predominant particle orientation are denoted by the length and orientation of the bar.

In addition, we investigated bone during healing by means of μ CT and different two-dimensional methods [8]. Together with visualization experts from Zuse Institute Berlin we developed an approach to assemble 2D data in a 3D μ CT reference frame.

With our multi-method approach we also studied osseointegration of zirconium and titanium implants by characterizing mineral particle characteristics [9]. We found that the bone material quality around zirconium implants is at least as good as for titanium.

Mineralization in Healthy and Diseased Bone

The course of bone mineralization is a crucial determinant influencing properties of healthy and diseased bone. The detailed mechanism by which calcium is deposited during mineralization and removed during resorption is largely unknown.

We studied medullary bone (bone in the central cavity of long bones in egg-laying birds) as a model system for rapid bone turnover rates as it is a calcium source for egg shell formation in hens (**Fig. 2a**) [10]. The microscopic and nanoscopic architecture of avian medullary bone material is rapidly changing during the daily egg-laying cycle. Additionally to the two known bone types (cortical and medullary bone) a third type (represented by a calcium halo) has been discovered, which may represent an intermediate phase during mineralization (**Fig. 2b and c**).

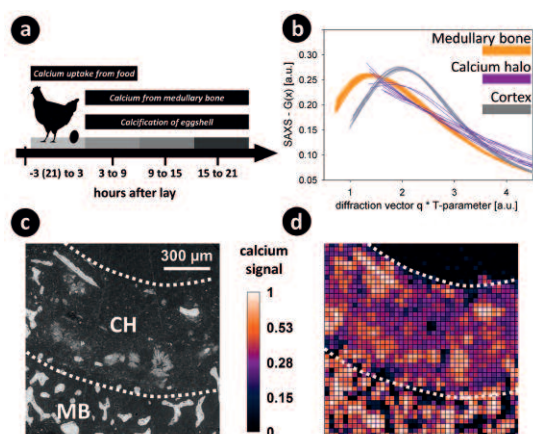


Fig. 2: Characterization of different bone types with SAXS and XRF: (a) processes during the 24h egg-laying cycle. (b) BSE micrograph showing medullary bone (MB) and a calcium halo (CH). (c) XRF mapping of the calcium concentration. High Ca concentrations are present adjacent to MB trabeculae [10].

Osteogenesis imperfecta (OI), also known as brittle bone disease, relates to a group of connective tissue disorders characterized by mutation in genes involved in collagen synthesis. Beside increased bone fragility, OI leads to low bone mass, impaired bone material properties and abnormally high bone matrix mineralization. We investigated mineral particle properties in human bone of children with OI type I and compared it with a control group. We found that the increase in mineral density in OI type I was not due to an increase in particle size, but due to an increase in the number of particles [11].

Hybrid Materials

Hybrid materials consist -like bone- at the nanoscale of an inorganic phase embedded in an organic matrix. With the aim of understanding structure-function relations and consequently tuning materials properties we elucidate deformation mechanisms in a material synthesized by cooperation partners at the HU Berlin. This hybrid material with nanometer-sized metal fluoride particles embedded in poly(ethylene oxide) is currently being investigated by a combination of SAXS/WAXS techniques and tensile testing experiments. The second hybrid material of interest is based on natural collagen extracted from turkey leg tendons as organic part infiltrated with different transition metals (Zn, Al and Ti) as inorganic part. In this study, we investigate the usability of turkey leg tendons as matrices for nanoparticle infiltration to modify materials properties.

Crystallization Patterns in Calcium Carbonate Microlens Arrays

Exploring fundamental formation and crystallization processes in tailored mineral-based materials can contribute to a deeper understanding of complicated biomineralization processes. We produced thermodynamically stable, transparent calcium carbonate-based microlens arrays (MLA) by transforming an amorphous CaCO_3 phase into nano-crystalline calcite (**Fig. 3a**) [12]. Structure and properties of crystallized MLA have been visualized by WAXS, polarized light and electron microscopy (**Fig. 3b and c**). The nano-crystallinity of the formed calcite minimized structural anisotropy and resulted in greatly reduced birefringent effects.

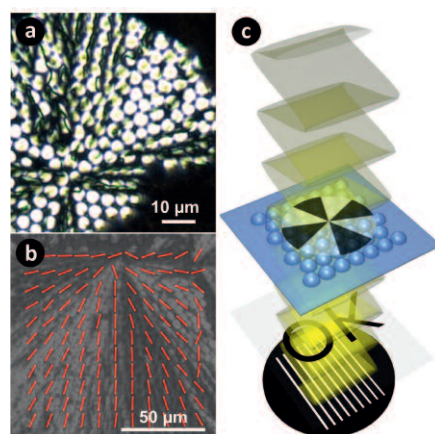


Fig. 3: Morphology and optical properties of crystallized CaCO_3 microlens arrays. (a) PLM image of the CaCO_3 microlens array showing spherulite-like patterns. (b) SEM image of crystallized microlens array with results from scanning WAXS: red bars indicate the crystallization direction. (c) Schematic illustration of the optical microscope setup to test birefringence and other optical properties: the incident light (yellow) passes the optical microscope polarizer, the glass slide with an "OK" symbol, the MLA and finally the analyzer [12].

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Structural and Nanomechanical Characterization



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Living organisms form complex mineralized biocomposites that perform a variety of essential functions. These biomaterials are often multifunctional, being responsible for not only mechanical strength, but also provide optical, magnetic or sensing capabilities. Many studies have emphasized the complexity of biochemical mechanisms in charge of the delicate equilibrium and interaction chemistry between inorganic precursors and macromolecular components leading to nucleation, assembly and growth of different biominerals. In contrast, mechanical and thermodynamic constraints, governing the microstructure formation, growth kinetics, morphology and mechanical properties of the mineralized tissue are much less understood. Therefore, we aim to address the fundamental question of how nature takes advantage of mechanical and thermodynamic principles to generate complex functional structures.

Thermodynamically Driven Mesostructure Formation in the Shell of *Pinna nobilis*:

We studied the structural evolution of the calcitic prismatic layer in *P. nobilis* by analogy to classical grain growth theories [1]. The microstructure of the layer was reproduced using high-resolution synchrotron-based microtomography, beamline ID19 in ESRF. Mainly, we focused on mean field considerations, where the growth kinetics of a single prism was described by an average behaviour of the entire prismatic layer, and topological considerations of space filling. As a result, we showed that the classical theories of normal grain growth and coarsening completely describe the growth process of the prismatic layer of *P. nobilis*, **Fig. 1**.

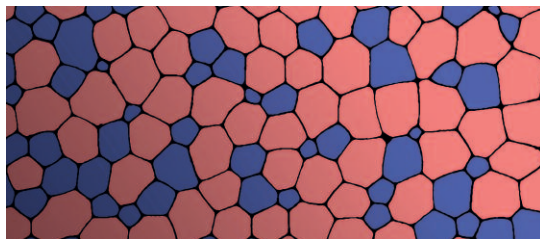


Fig. 1: 2D microtomography section perpendicular to the growth direction of the prismatic layer. Growing prisms are color-coded pink, shrinking prisms are color-coded blue.

This outcome supports the idea that the biological organism which regulates calcite growth is not controlling the shape evolution of the prisms beyond setting the thermodynamic boundary conditions. In addition to providing new insights into the way biogenic minerals are built, these results demonstrated that the prismatic layer of the mollusc shell is actually a textbook example for grain growth.

Environmentally-Controlled Static and Dynamic Mechanical Characterization on the Nanoscale:

Understanding the structure-to-function relationship in biological materials at the macroscopic level requires studies of all the hierarchical levels at many different length scales. Recent progress in applications of the nanoindentation equipment includes the nanoscale modulus mapping technique enabling to probe static and dynamic mechanical properties with high spatial resolution, **Fig. 2**.

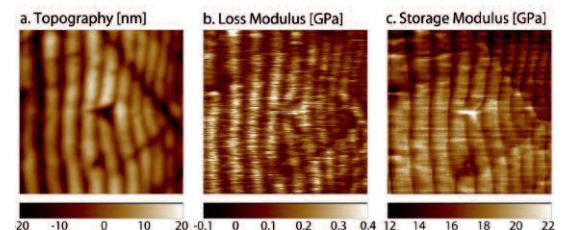


Fig. 2: Nanoscale modulus mapping of a chitin plywood structure in the exocuticle area of a tibia of the wandering spider, *Cupiennius salei*, produced on a cut parallel to tibia long axis: (a) – topography map; (b) – loss modulus map; (c) – storage modulus map. The maps size is 3x3 μm^2 .

Nanoindentation based instrumentation was initially developed for mechanical characterization of stiff and hard composite structures. Therefore, for correct evaluation of mechanical properties, its application on compliant and soft biocomposites requires adaptation of the experimental set-up and modification of the theory behind it. Our research was focused on implementing this technique in biomaterials research. We adapted the technique and combined it with reverse finite element analysis in order to determine the elastic moduli of nanometric inclusions even when embedded in a matrix which is 50 times stiffer [2]. Furthermore, we adjusted the theoretical backbone of this technique to fit to the analysis of relatively soft tissues [3]. Finally, because biological materials typically reside in humid environments in their natural condition and perform under a variety of relative humidities and temperatures, we successfully designed and realized experimental set-up allowing moisture and temperature dependent mechanical properties of the S2 layer of *Picea abies* wood cell walls to be exclusively and independently determined [4]. Currently, we are the only laboratory in the world able to routinely perform static and dynamic nanoindentation in controlled environment.

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Surface Nanostructuring for Bioapplications: Intelligent Smart Systems

Our focus is the surface nanoarchitecture which provides spatially and temporally defined control over the behaviour of biomolecules and cells at the solid-liquid interface [1].

Metal Surface Nanostructuring

As a fast and versatile methodology which provides controllable variation of surface topography and roughness by tuning the numerous synthetic parameters we use high intensity ultrasonic treatment for the formation of mesoporous surfaces [2]. Mesoporous surfaces are believed to be the most promising for the formation of surface encapsulation systems [3]. We also use titanium nanotubes slides obtained by electrochemical oxidation. By titanium surface nanostructuring we (J. Dunlop, Biomaterials, and P. Knaus, FU Berlin) aim to control the adhesion of cells to surface, as well as their behavior in terms of proliferation, migration and differentiation.

Surface Drug Depot

Methods for encapsulation, prolonged storage and controllable release were developed [3-4] and are in focus (with H. Möhwald, Emeritus Group Interfaces) [1]. Formation of stimuli responsive encapsulated systems are suggested via layer-by-layer assembly, mobile chemical bonding (hydrogen bonds, chemisorptions) and formation of special dynamic stoppers. The most essential advances of the systems presented are multifunctionality and responsiveness to a multitude of stimuli (Fig. 1).

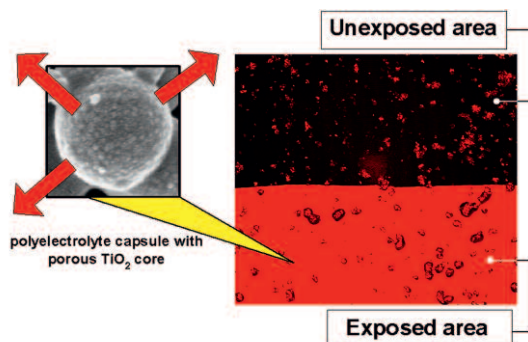


Fig. 1: Example of pH and light responsive surface capsules: micrograph of the edge of the laser beam trace at the surface containing polyelectrolyte capsules with titania core. The red area corresponds to spatial controlled release of Rhodamine 6G from the capsules.

Stimuli Sensitive Response

Stimuli responsive behavior, which is intrinsic to natural systems, is becoming a key requirement for advanced artificial materials and devices. Intelligent surfaces which are able to control the behavior of biomolecules and cells in both space and time are in focus in our group (with D.V. Andreeva, Univ. Bayreuth) [1-6]. External stimuli or internal stimuli can be used to alter surface properties. In particular, we decorate the surfaces with stimuli responsive layers. Thus, for example, we use as a pH-sensitive polymer layer commercial or sensitized by our partners (R. Haag, FU Berlin; M. Karg, Univ. Bayreuth) polymers, e.g. polyelectrolytes, biopolymers and bioinspired polymers, microgels, etc. For etch particular applications the system is require the individual nanostructuring. It is shown in Fig. 2 the nanostructuring of mesoporous metal sponge layer with pH responsive micelles [6] for self-regulation of *Lactic* bacteria adhesion. *Lactic* bacteria change pH via generation of lactic acid in their life cycle. The pH responsive micelles change their corona size and push of the bacteria from the surface.

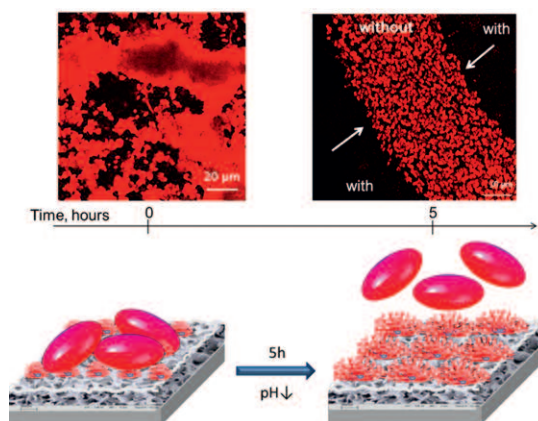


Fig. 2: Example of self-controllable responsive antifouling surface: confocal images of spatial controlled release of Lactic bacteria on patterned with pH responsive micelles mesoporous sponge surface.

The developed nanoengineered systems represent a generic technological tool, which opens numerous applications in chemical technology, biotechnology and bioanalytical chemistry, among them: self- and light-healing dynamic surfaces; anti-fouling surface; 'smart' supports for growing cells and tissues; controlled implant coatings; drug delivery systems; (bio-)sensors.

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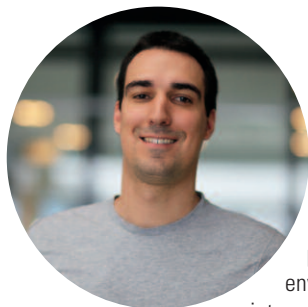
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Physics of Biomolecular Interfaces



Biological tissues and cells are composed of diverse functional units such as organelle membranes, protein complexes, and carbohydrate assemblies. The structural organization of these cellular constituents on the sub-micrometer scale is essential for their proper function and in the congested biological environment largely depends on the physical interactions between their surfaces.

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Molecular Interactions at Membrane Surfaces

In our Emmy-Noether research group, supported by the German Research Foundation (DFG), we study the physical mechanisms that govern the interaction of biological interfaces with their aqueous environment and also their mutual interaction in the aqueous milieu, with a specific focus on interactions involving biological membranes (see Fig. 1). Without regulation of these interactions by the organism essential cellular processes such as material transport or cell division would not be possible. 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 membrane compositions. To investigate interactions at biological interfaces we carry out experiments with model systems of well-defined biomolecular composition. Our primary tools are various x-ray and neutron scattering techniques, however we also employ complementary methods, such as ellipsometry, calorimetry, and spectroscopy techniques. In addition, computer simulations carried out in collaborations provide a means to interpret the experimental results on an atomic scale level.

X-Ray & Neutron Scattering Techniques and Complementary Computer Simulations

The research group *Physics of Biomolecular Interfaces* is the most recent research group in the Biomaterials department and was installed only in autumn 2014. Within the group leader's PhD project at Heidelberg University and a postdoctoral research project at the Institut Laue-Langevin (Grenoble France), funded by a Marie-Curie research grant by the European Commission, we have established a number of experimental strategies to create planar models of biological and biotechnologically relevant surfaces and to structurally investigate them by means of scattering techniques [1–4]. During a post-doctoral research project in soft-matter theory at Technical University of Munich and Free University of Berlin we have developed computer simulation methods that allow reproducing and mechanistically interpreting experimental results on surface interactions [5–6]. These simulations accurately account for the chemical potential of water between the surfaces and have lead to a better understanding of the long-debated “hydration repulsion” between membranes [6].

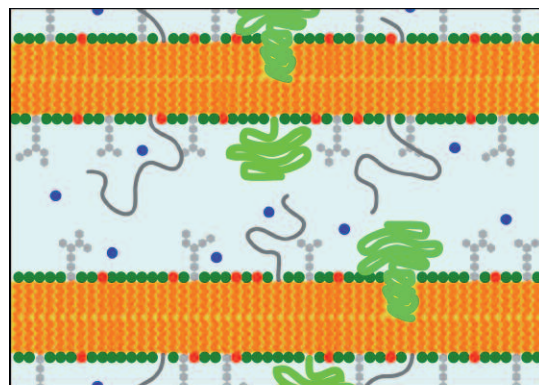


Fig. 1: Cartoon of two interacting biological membranes. Their surfaces display a variety of hydrophilic lipid moieties and membrane-bound macromolecules. The mutual interaction of membranes is governed by this molecular composition.

Protein Adsorption to Material Surfaces with Biocompatible Functionalization

In 2013/2014 we studied interactions between proteins and polymer brushes at solid/liquid interfaces. Protein adsorption to material surfaces causes problems in medical applications such as implanted biomedical devices (e.g., catheters or stents), as it can promote foreign-body reaction. A common approach to prevent undesired protein adsorption is to functionalize surfaces with hydrophilic polymer brushes, most frequently of poly[ethylene glycol] (PEG). However, the interaction of polymer brushes with proteins is not well understood. In particular, little is known about the mechanisms responsible for regularly observed “brush failure”, where protein adsorption arises despite brush functionalization. We have fabricated PEG brushes of well-defined grafting layer chemistry, polymer length, and polymer grafting density, and structurally investigated different modes of undesired protein adsorption using neutron reflectometry with contrast variation. This experimental technique yields matter density profiles perpendicular to the interface with sub-nanometer resolution. The brushes were created from amphiphilic lipo-polymers with PEG portions of defined lengths. They were first prepared as water-insoluble (so-called Langmuir-type) monolayers at an air/water interface and then transferred onto hydrophobically functionalized surfaces of planar silicon blocks at controlled lateral densities. Our results obtained after incubation with different types of proteins highlight the importance of the brush parameters [3] and the implications of PEG's reported but often neglected antigenicity [4].

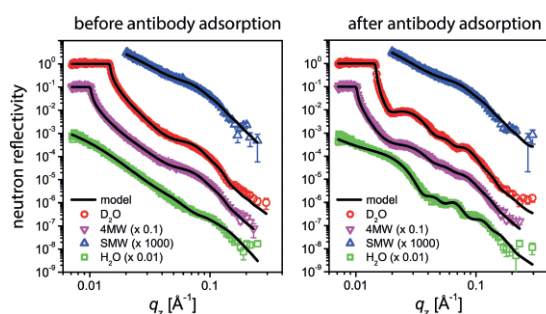


Fig. 2: Neutron reflectivity curves from a PEG brush in H_2O and D_2O as well as in H_2O/D_2O mixtures termed 4MW and SMW, before (left) and after (right) incubation with antiPEG IgG antibodies. Solid lines indicate the reflectivity model used to reconstruct the protein density profiles.

Fig. 2 shows a set of reflectivity curves from a PEG brush in aqueous solution before (left) and after (right) incubation with solutions of antiPEG IgG antibodies (Fig. 3 top), as are sometimes found in the human blood. The four curves in each panel correspond to four different “water contrasts” in neutron reflectometry, which are realized by mixing H_2O and D_2O in defined ratios. The adsorption of proteins leads to a number of additional features (in particular minima and maxima) in the reflectivity curves, from which the density profiles of the polymer brushes and adsorbed antibodies were reconstructed with the help of a suitable reflectivity model (solid lines in Fig. 2). The reconstructed protein density profiles (Fig. 3 middle) distinctly showed that the adsorption of antibodies occurred onto the brush itself, an adsorption mode termed “ternary adsorption” in the theoretical literature. Closer inspection revealed that the antibodies form dense layers and assume an inverted “Y” configuration (Fig. 3 bottom), indicating strong and specific protein/polymer interactions involving the binding regions on the F_{AB} segments [4]. In this configuration the antibodies display their F_C segment to the aqueous phase suggesting that foreign body reaction is promoted.

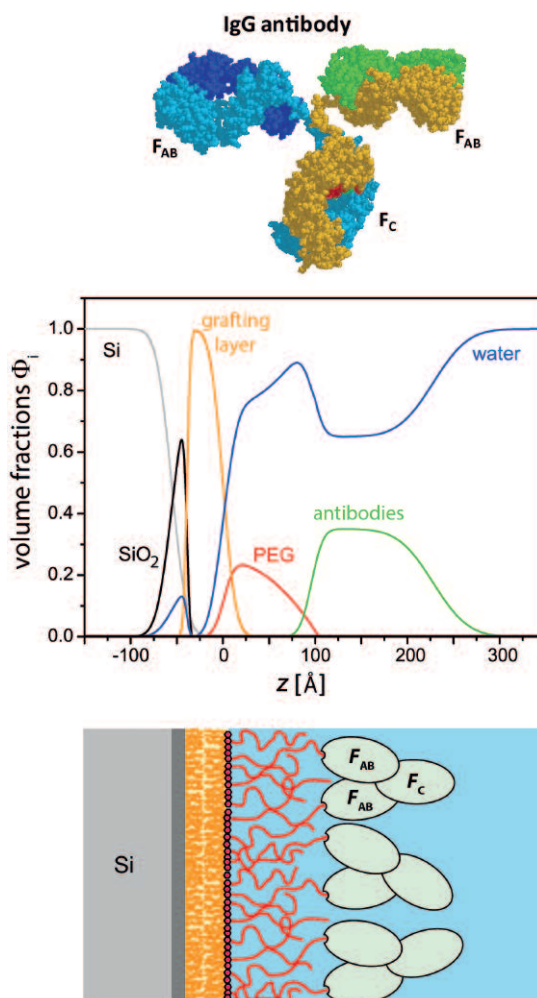


Fig. 3: (top) Structure of an IgG antibody. (middle) Density profiles of antiPEG IgG antibodies (Abs), PEG, and other compounds in the vicinity of the silicon/water interface as reconstructed from the reflectivity curves in Fig. 2. (bottom) Cartoon illustrating the interpretation of the density profiles.

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Mixed Protein-Surfactant Adsorption Layers



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Proteins are used in many applications due to the particular interfacial properties of their adsorption layers. Even more, mixtures of protein with low molecular weight surfactants allow tailoring the interfacial behavior such that optimum conditions can be provided for many industrial applications in food processing, pharmacology or cosmetics. The adsorption of surfactants influences the equilibrium and dynamic properties of liquid interfaces. This modified behavior depends on the nature of the surfactant. Proteins mixed with ionic surfactants form complexes with a higher surface activity due to the compensation of the charged groups in the protein and the addition of hydrophobicity by the surfactant's alkyl chains. In contrast, the addition of non-ionic surfactants to protein solutions leads only to weak hydrophobic interactions. The formation of such mixed adsorption layers was described so far mainly by a competitive adsorption mechanism. The non-ionic surfactants adsorb in competition to the proteins and at sufficiently high surfactant concentrations a replacement of the protein molecules from the interface can be observed.

Aggregate formation in the bulk of mixed solutions takes obviously place via hydrophobic interaction when the amount of added non-ionic surfactants is sufficiently high. In literature a number of studies show that this is true for protein concentrations above 10^{-4} mmol/l, and the results were discussed mainly in terms of dipole interactions of weakly charged hydrophilic groups in the protein molecules and the hydrophilic groups of the non-ionic surfactants.

In recent investigations we studied the dynamic surface tension and dilational surface rheology of protein solutions (β -lactoglobulin – BLG, β -casein – BCS) at very low concentrations mixed with very small amounts of non-ionic surfactants (dodecyl and tetradecyl dimethyl phosphine oxide – C_{12} DMPO, C_{14} DMPO, dodecanol – C_{10} OH and pentaerythritol decyl ether – C_{10} EO₅). The investigations were performed at surfactant concentrations between 10^{-8} and 10^{-4} mol/l, a range in which the used surfactants alone do not show any measurable adsorption effects. The protein concentrations were in the range between 10^{-9} and 10^{-7} mol/l.

Fig. 1 shows the dynamic surface tensions of an individual BCS solution (10^{-8} mol/l) in absence (curve 1) and in presence of different amounts of C_{12} DMPO. The measurements were done with the profile analysis tensiometer PAT using the buoyant bubble configuration. Even at very low C_{12} DMPO concentrations the dynamic and equilibrium surface tensions of the mixtures are significantly lower than those for the individual protein solution. Note, for concentrations below 10^{-6} mol/l the surfactant C_{12} DMPO alone does not show remarkable surface tension changes. For comparison, the same figure presents results of a 100 times higher BCS concentration (10^{-6} mol/l) with similar admixtures of C_{12} DMPO (see the three lower curves 9-11). At this BCS concentration the addition of the non-ionic surfactant does not affect the tension remarkably.

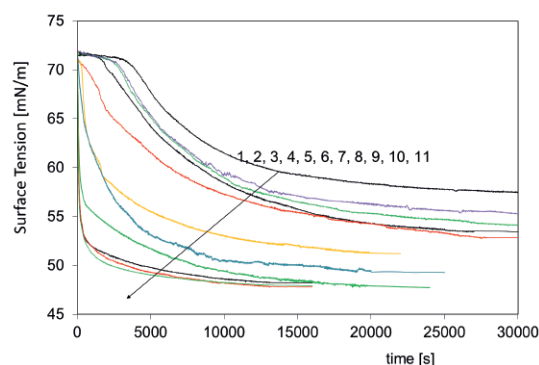


Fig. 1: Dynamic surface tension of 10^{-8} mol/l BCS solutions at different C_{12} DMPO concentrations: curve 1 - 0.0, curve 2 - 4×10^{-8} , curve 3 - 10^{-7} , curve 4 - 3×10^{-7} , curve 5 - 10^{-6} , curve 6 - 3×10^{-6} , curve 7 - 5×10^{-6} , curve 8 - 10^{-5} mol/l; and 10^{-6} mol/l BCS solutions at different amounts of added C_{12} DMPO (the concentrations are: curve 9 - 0.0, curve 10 - 10^{-7} mol/l, curve 11 - 10^{-5} mol/l); according to [1].

The equilibrium surface tension of pure BCS solution at the concentration of 10^{-5} mmol/l (horizontal dotted line) as well as the isotherms of mixtures with C_{12} DMPO and C_{14} DMPO as a function of the surfactant concentrations, are shown in **Fig. 2**. The results for the pure C_{12} DMPO and C_{14} DMPO solutions, also shown in this figure, can be well described by the Frumkin adsorption model (thin solid lines). Note, for the surfactants an intrinsic compressibility coefficient of the adsorption layer of $\epsilon = 0.003$ m/mN was considered.

The Fig. 2 contains also calculated surface tension isotherms for the mixed systems BCS/ C_{12} DMPO and BCS/ C_{14} DMPO at a fixed BCS concentration of 10^{-5} mmol/l using a classical Frumkin adsorption model for mixed adsorption layers (dashed lines, red for C_{12} DMPO and blue for C_{14} DMPO). As one can see, the calculated data are inconsistent with the experiments. In [2] a new approach was proposed to consider the presence of traces of non-ionic surfactants as a reason for the increase of the surface activity of the protein. For this a coefficient $k = 1 + a^* \cdot c_s$, c_s being a linear function of the surfactant concentration c_s was introduced to modify the adsorption activity constant for the protein (details see [2]). The solid lines in Fig. 2 confirm that such a model reflects the changes in the protein's effective surface activity very well.

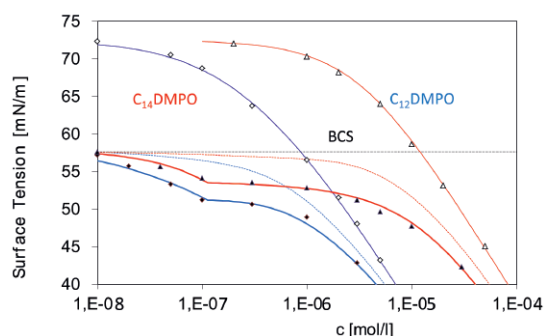


Fig. 2: Equilibrium surface tension isotherms for BCS+ C_{12} DMPO (\blacktriangle) and BCS+ C_{14} DMPO (\blacklozenge) mixtures at a BCS bulk concentration of 10^{-8} mol/l; (\triangle) and (\diamond) are the data for individual C_{12} DMPO and C_{14} DMPO solutions; the equilibrium surface tension of pure 10^{-8} mol/l BCS solution is given by the dotted horizontal line; the dashed lines were calculated with a Frumkin type adsorption model, the bold solid lines are calculated with the new thermodynamic approach; according to [2].

The variation of the 'effective' adsorption activity on the surfactant concentration in a certain concentration range could probably depend on the structure of the protein as well as on the kind of surfactant. The efficiency of the surfactant, expressed by the parameter a^* , is governed by the interaction between the polar groups of the surfactant molecules with the polar groups of the amino acids located in the protein structure. In [2] these effects for four non-ionic surfactants was discussed: C_{12} DMPO, C_{14} DMPO, C_{10} OH and C_{10} EO₅.

For a deeper understanding of the effect of non-ionic surfactants on the adsorption activity of proteins at very small amounts of added non-ionic surfactants, dilational viscoelasticity studies were performed. These properties are most sensitive to the composition of mixed adsorption layers and can reflect best the interactions between the components adsorbed at a liquid interface. The dependencies of the viscoelasticity modulus on the surfactant concentration at an oscillation frequency of 0.1 Hz for mixtures of BCS (again at a fixed concentration of 10^{-8} mol/l) with C_{12} DMPO are shown in Figs. 3 as example.

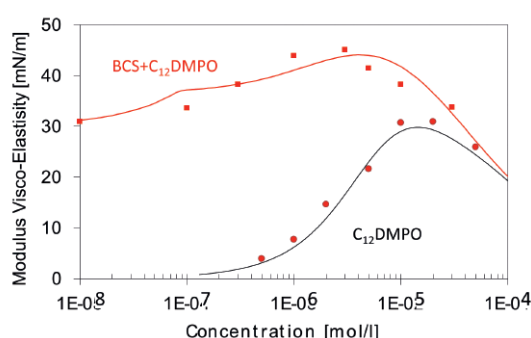


Fig. 3: Dependence of the visco-elasticity modulus for mixtures of a 10^{-8} mol/l BCS solution with C_{12} DMPO (\blacksquare) and for the individual C_{12} DMPO solutions (\bullet) on the surfactant concentration for an oscillation frequency of 0.1 Hz; the lines refer to the thermodynamic model discussed in the text; according to [3].

The results obtained for this mixture are similar to those for mixtures of the other three studied surfactants and also for the equivalent mixtures with the protein BLG. The obtained data can be interpreted very well and further confirm the quality of the new proposed model.

R. Miller, S.Faraji, G. Gochev, X.W. Hu, A. Javadi, T. Kairaliyeva, M. Karbaschi, J. Krägel, M. Lotfi, N. Moradi, N. Mucic, X.Y. Qiao, I. Retzlaff, S. Siegmund, A. Sharipova, M. Taeibi-Rahni, A. Tleuova, V. Ulaganathan, D. Vollhardt, J.Y. Won, R. Wüstneck

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- Continuous Chemical Systems
 - Glycoproteomics
 - Glycoimmunology
 - Synthetic Plant Carbohydrates
 - Structural Glycobiology
 - GPIS and Glycoproteins
 - Immunomics
 - Polymeric Biomimetics

BIOMOLECULAR SYSTEMS

Research in the Department of Biomolecular Systems



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2003-2009: Professor

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The Department for Biomolecular Systems conducts research at the **interface of chemistry, engineering, biology, immunology and medicine**. The approach is trans-disciplinary and interactive between the groups in the department that cover different areas of expertise. The core focus is the development of **synthetic methods** for the chemical synthesis of defined oligosaccharides. The compounds are the basis for **chemical tools** that aid **biological investigations** into the fundamental roles complex carbohydrates play in biological processes that underlie disease. Carbohydrate arrays greatly helped us to advance our understanding of **immunological aspects** of various infectious diseases. **Vaccine development** has resulted in innovation at all levels including the glycan portion, novel carriers, and novel modes of presentation to the immune system. Several glycoconjugate vaccine candidates have passed challenge studies in experimental animals and are being readied for human clinical trials in a spin-off company. Following an initial growth phase after the move from ETH Zurich in 2009, the department has reached a steady state. In 2014, four group leaders left the department. Dr. Laura Hartmann was promoted to W3 professor at the University of Düsseldorf after less than five years with us. Prof. Tyler McQuade left in 2013 after just one year with us after receiving an immensely attractive offer as program chief at the US Defense Agency Research Program Agency (DARPA) while holding a professorship at Florida State University. Dr. Kerry Gilmore assumed the position as leader of the continuous flow group after proving himself for one year as project leader of the same group in 2014. Dr. C. Anish left for a leadership position at a top vaccine company in Holland following a very productive phase of the vaccine biology group. Dr. Lepenies who worked with his glycoimmunology group on the role of glycans *in vivo* will leave for a W2 professorship in Hannover in 2015. Currently, we are actively seeking a glycoimmunologist to fill the void in this area.

Glycan sequencing and glycomics (Dr. Kolarich) helps to identify glycans of biological importance particularly on interfaces of the human body – skin and intestine. The synthesis and study of plant glycans is the focus of a new Emmy-Noether research group headed by Dr. Fabian Pfrengle. Our increased interest in establishing structure-function correlations of glycans is expanding. In addition to the Emmy-Noether group of Dr. C. Rademacher that is concerned with questions relating to structural immunology, in 2015 Dr. Ursula Neu will join our department to add strength in X-ray crystallography. 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.

Materials aspects related to carbohydrates are continuing to be pursued in the department particularly since we are now able to produce ever larger, structurally defined polysaccharides.

Continuous-flow chemistry has seen immense successes in part due to a close collaboration to the chemical engineers of the group of Prof. Seidel-Morgenstern at the MPI in Magdeburg. The development of novel concepts for the modular production of pharmaceutically active ingredients is currently a key focus for the group. The department is engaged in collaborations with the Colloid Department concerning the use of supported catalysts.

Automated Synthesis of Carbohydrates

Automated glycan assembly, our core technology has reached a new level of sophistication. After many years of systematic improvements, the synthesizer as well as most reagents have been commercialized via the spin-off company **GlycoUniverse**. At the same time, the variety and complexity of oligosaccharides has been increased and the type of linkages that are now accessible has been drastically expanded.

Automated glycan assembly is becoming more and more a standard tool to prepare ever longer polysaccharides that enable investigations into new areas of biology as well as material sciences.



The first commercial automated synthesizer GlycoUniverse 2.1 that was based on work in the Biomolecular Systems Department

Synthetic Tools for Glycobiology

Access to synthetic oligosaccharides has given rise to tools such as glycan microarrays, glycan nanoparticles, and radioactively labeled glycans. These tools are now commonly used by the glycobiologists in the department to elucidate fundamental processes such as the entry mechanism of parasites into host cells.

Synthetic Carbohydrate Vaccines

We have established a comprehensive program targeting the development of fully synthetic carbohydrate vaccines. The team of Dr. C. Pereira produced a host of antigens found on the surface of pathogenic bacteria. Conjugations of these antigens with carrier proteins and with self-adjuvanting glycolipids performed extremely well in immunological and functional studies in several disease models in experimental animals. Several constructs have now reached a mature stage that resulted in preparation of a spin off company that is expected to be launched in 2015 to advance the different synthetic vaccines into human clinical trials.

Carbohydrate-based Nanotechnology

The attachment of carbohydrates to the surface to nanoparticles has been expanded further in efforts to use glycosylated materials for disease monitoring as well as treatment. Stroke models in rats have been a focus of recent activities, while the attachment to silicon nanoparticles is gaining momentum.

Glycoimmunology

Carbohydrate recognition by C-type lectin receptors influences key functions of dendritic cells such as antigen presentation, cytokine release, and the expression of co-stimulatory molecules. Since all of these processes impact T cell priming and differentiation, CLR targeting is a means to orchestrate an initiated immune response. To identify immune stimulatory and immune modulatory CLR ligands, a screening platform has been developed, followed by *in vitro* and *in vivo* assays. The extracellular domains of different CLRs were expressed as fusion proteins and used in conjunction with the glycan array technology for high-throughput screening of lectin/carbohydrate interactions. Novel binding partners of CLRs were identified and interactions with known ligands confirmed. Carbohydrate-protein interactions were further characterized by surface plasmon resonance (SPR) measurements. This platform brings together CLR ligand identification and their immunologic evaluation. Hence, it is a highly useful tool for the functional analysis of CLR ligands

Carbohydrate-carbohydrate interactions

As part of the Collaborative Research Centre (SFB) 765 ("Multivalency as chemical organization and action principle"), we focus on the characterization of carbohydrate-carbohydrate interactions. Interactions between carbohydrates are even weaker than carbohydrate/lectin interactions, thus are often hardly measurable. In this context we focus on biophysical and biological analyses of interactions between the tumor-specific carbohydrate antigens GM3 and Gg3 as well as GB4 and GalGB4. Efforts to employ these multivalent carbohydrate interactions for cell-specific targeting and imaging are underway.

Continuous Flow Chemistry

After our pioneering efforts since the turn of the century, continuous flow chemistry has now reached a stage where not single reactions but rather entire systems are under investigation. Over the past three years, the production of artemisinin-based anti-malaria medications has been a key example to demonstrate the power of the approach. A general approach to create chemical assembly systems has resulted in modular methods to create multiple medications. Among other successes, access to a key anti-HIV medication in fewer steps and higher yield has been a major breakthrough. The group leader, Dr. Kerry Gilmore has added chemical engineers to the team in order to further automate reaction optimization and to more intricately integrate in-line analytical methods.

Peter H. Seeberger

Director of the Department of Biomeolecular Systems

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Development of Chemical Assembly Systems



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Chemical synthesis traditionally takes a linear approach, developing both chemistries and technologies to achieve novel and more efficient routes towards specific targets. In recent years, flow chemistry has emerged as a useful tool to aid in a chemist's pursuits, accessing advanced structures and active pharmaceutical ingredients (APIs) in both step-wise and multi-step processes. Conceptually, however, the field has not advanced, as multi-step synthetic processes remain target oriented. This group has introduced a novel paradigm in organic synthesis aimed at advancing this field: chemical assembly systems [1]. These systems consist of modular synthesis platforms [2-4], capable of being connected in an interchangeable fashion. This non-iterative approach to automated assembly manifests itself into three fields of study in our group: (1) the development of novel reaction modules allows us to perform detailed methodological studies, accessing transformations and selectivities not previously realized; (2) when individual units are linked together, continuous, multistep synthesis can be achieved targeting specific compounds with the goal of low-cost, high-efficiency syntheses; (3) individual modules can also be arranged interchangeably, with the goal of developing divergent synthesis systems which allow access to a wide breathe of chemical space.

Methodology

The development of novel reaction modules is the core of our philosophy. Reaction modules are developed in one of two mindsets: either as a method to achieve selectivity/reactivity unachievable in a batch setting or to provide a required transformation within a given synthetic setting. One area where we have made a considerable impact is the application of photochemistry in a continuous synthesis setting [5]. Specifically, in 2011 we developed a facile and reliable means of producing singlet oxygen photochemically in a flow reactor [2]. This allowed for the rapid examination of a variety of transformations including the ene reaction. This important process was utilized to provide the first continuous synthesis of an anti-malarial medicine Artemisinin [6, 7, Fig. 1]. The advantage of our developed reactor module as compared to previous photochemical set-ups is our ability to control the temperature down to -80°C , allowing us to control reactivity and achieve excellent selectivity. One example of this selectivity is that while secondary amines can be easily oxidized with singlet oxygen and trapped with a nucleophile, the corresponding primary amines instead give the product of oxidative coupling at room temperature. However, we have shown that at -50°C the desired aldimine can, for the first time, be efficiently trapped with a variety of nucleophiles [3,8]. We were also the first to introduce a visible light-mediated single electron transfer flow system [9], accomplishing a variety of transformations using a home built reactor (Fig. 1). Recently, we have developed a means of accomplishing carbonyl and imine reductions using inexpensive sodium borohydride

in flow [4]. While this common reagent has been used for decades in batch systems, only expensive, soluble reductants could be used in flow. This module was developed in the context of a divergent synthesis system, described below.

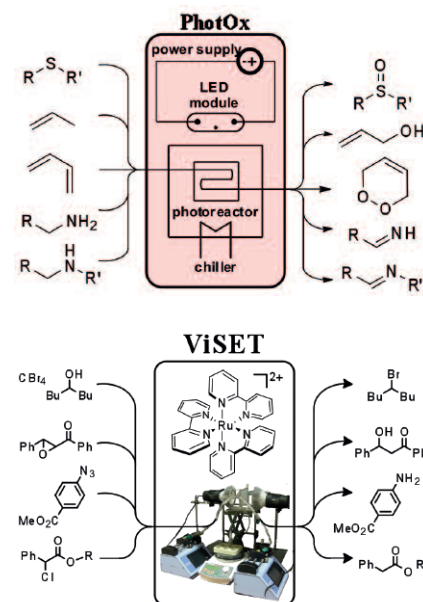


Fig. 1: Two examples of reaction modules which have been developed. These versatile, chemoselective units can be linked with others or used individually.

Target Oriented Synthesis

Continuous chemistry offers the inherent advantage of more efficient and less expensive production. With this in mind, this group, as well as others, have sought to develop continuous, multi-step syntheses for the production of active pharmaceutical medicines (APIs). By coupling our PhotOx module with a second reactor capable of an acid-catalyzed rearrangement, we were able to develop a synthetic process to produce artemisinin [6, 7]. This WHO-critical medicine is currently obtained via extraction from the plant *A. annua* and the price fluctuates so erratically that demand is often not met. While artemisinin is now also being produced in limited quantities in a biotech/chemical manner, our developed process will help to expand production by converting a current plant waste product, dihydroartemisinic acid, into artemisinin – increasing production and helping to stabilize prices (Fig. 2). We have also developed several other processes for the synthesis of other APIs, including the anti-obesity drug Rimona-bant as well as an upcoming publication featuring the short-est-ever synthesis of the HIV medicine Efavirenz [10].

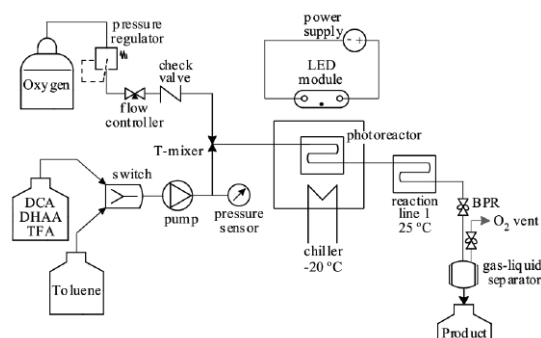


Fig. 2: Chemical engineering diagram for the developed continuous-flow process for the synthesis of artemisinin from the natural extract dihydroartemisinic acid (DHAA).

Systems Oriented Synthesis

The most efficient way to manufacture a given product, however, is not target oriented. Ideally, a process would be adaptable, divergent, and modular such that a variety of products can be made using a single system. While almost every other product worldwide is produced in this assembly line manner, pharmaceuticals are still produced in a stepwise batch manner, resulting in long production times and, critically, high costs. In 2014, we introduced a novel paradigm to organic synthesis, that of the chemical assembly systems (CAS). These processes rely on flow reaction modules, connected in series, to produce specific core structures. By modifying the reactants as well as the order of the reaction modules, a wide breadth of chemical space can be accessed in both a convergent and divergent manner. Two such systems have thus far been introduced [11, 12]. The first expands our synthetic efforts past artemisinin to the derivatives utilized in anti-malaria treatments (Fig 3). The major breakthrough was the development of a means of not only reducing artemisinin to dihydroartemisinin inexpensively [4], but the coupling of this step to the synthesis of the final substrates, something which was previously unrealized. Inline IR monitoring of the process allowed for real-time information regarding the quality and robustness of the process to be monitored. In collaboration with Prof. Seidel-Morgenstern at the MPI in Magdeburg, we coupled this system to a continuous purification module, allowing for the continuous production of medicines which exceed WHO/FDA quality standards [11].

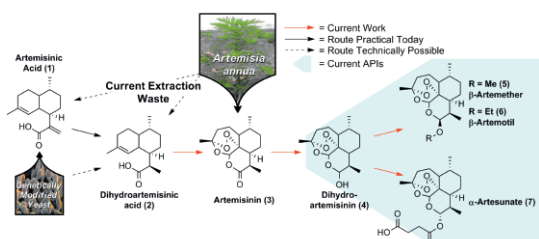


Fig. 3: A divergent chemical assembly system was developed to access all of the currently WHO-recommended treatments for malaria.

While a variety of medicines could be obtained using the above-described system, the structural diversity of the products obtained is low. We thus set out to develop a truly divergent system, where interchangeable modules allowed access to a wide breadth of structural classes. As such, a five-module system was developed, which could be connected in a several different combinations to access three different structural classes: β -amino acids, γ -lactams, and γ -amino acids (Fig 4). With judicious choices of starting materials, we were able to synthesize five different active pharmaceutical ingredients present in generic or patented medicines (Rolipram, Lyrica, Phenibut, Baclofen, Gabapentin) in good overall yields (49–75%). Importantly, neither purification nor modification of the reaction stream occurred between modules [12].

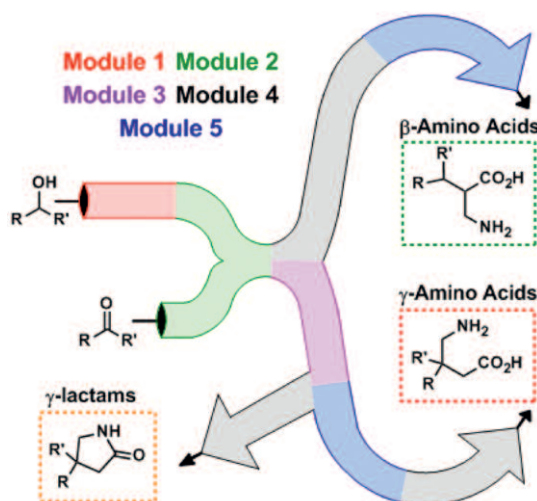


Fig. 4: A five module CAS was developed which accessed three structural classes of compounds. This system was used to produce five active pharmaceutical ingredients continuously in good overall yields.

This group attempts to advance the manner of which organic compounds are being produced through the development of chemical assembly systems. These flexible systems are comprised of flow reaction modules, which are developed either to fit a need within a given synthesis or as part of mechanistic investigations. We also utilize the inherent advantages of flow chemistry to devise alternate, more efficient syntheses of specific compounds, specifically medicines, with the aim of reducing both production time and cost.

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Opening the Doors Towards Automated In-Depth Glycan Sequencing



Glycoproteins are complex molecules where the DNA encoded protein sequence is further modified with specific sugar chains [1]. A sophisticated cellular network of various enzymes performs these complex modifications on the protein sequences in a non-template manner, making any predictions which set of glycans is present on a specific protein at a specific time point impossible. However, the specific

glycan structures present on particular cell surfaces and on specific proteins at a given time point are known to influence the functionalities of the respective cells & proteins, which becomes particularly important in the context of many major diseases. Despite the fact that a global change of glycosylation has been frequently reported in many different types of cancer and chronic inflammatory diseases such as inflammatory bowel diseases, the global impact of these dynamic glycosylation alterations are still largely not well understood – also due to the lack of reliable, sensitive and sufficiently selective methods to analyse specific glycosylation signatures within a single experiment from minute amount of clinical specimens. Within the Glycoproteomics group we are working on developing and automating methods for glycan and glycoprotein sequencing and applying these on clinically relevant challenges (Fig. 1).

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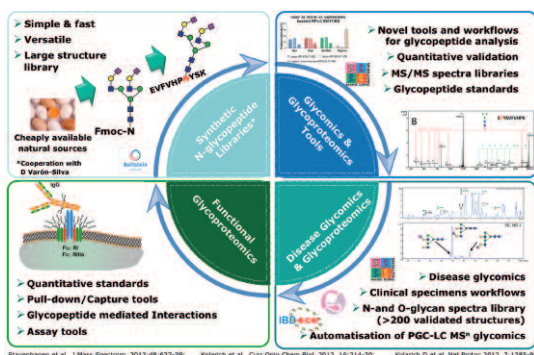


Fig. 1: Four major, interconnected research areas are followed within the glycoproteomics group in the efforts to sequence glycoconjugates.

The Technology Behind Mass Spectrometry Based Glycan Sequencing

Glycan structures are often built up by similar building blocks, however, in contrast to e.g. peptide or DNA oligomers, these different glycan building blocks can be linked either via different linkages (alpha or beta) or via different positions within a monosaccharide to form larger oligosaccharides. However, the type of linkage and its position influence the biological properties of these glycoconjugates, thus understanding the functional relevance of protein glycosylation requires accurate and selective methods for their sequencing.

Many of these glycoconjugates exhibit an exact similar chemical composition, making it difficult to separate and dis-

tinguish them by simple tandem Mass Spectrometry (MS/MS) approaches. Within the glycoproteomics group we are combining the selectivity benefits provided by porous graphitized carbon (PGC) liquid chromatography (LC) separation with the sensitivity and speed of MS/MS detection to separate, detect, characterise and relatively quantify such isobaric structure compounds (Fig. 2) [2,3].

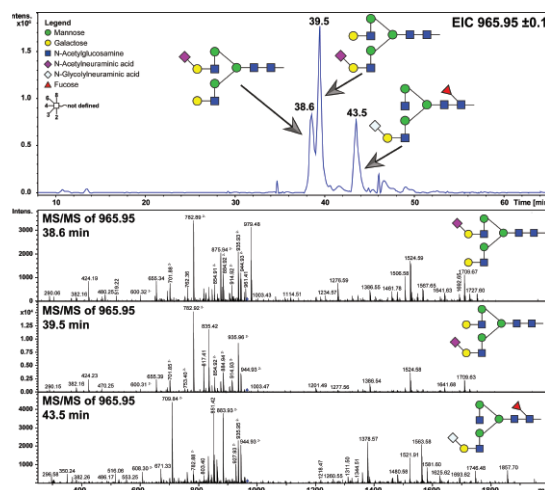


Fig. 2: Example for the separation and identification of an isobaric N-glycan present in porcine serum. Top: Extracted ion Chromatogram (EIC) showing the separation of the three N-glycans exhibiting exactly the same m/z value. Bottom spectra: Fingerprint tandem MS spectra allowing automated in depth structure assignment.

The Human Bowel N- and O-glycomes Show Specific Signatures

Chronic inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are affecting a large part of the society, but IBD onset and progression are comparably poorly understood. The colon mucosa is heavily glycosylated and lectins as well as glycan receptors were suggested to be involved in the aetiology of IBD. However, there is comparably little known about IBD related glycosylation. A step towards a better understanding of these diseases is the identification of disease specific glycosylation signatures by profiling large sample cohorts of colon tissue. Mucin glycosylation changes have been reported to occur over the entire healthy colon, but hardly any information is available on the bowel cell surface protein glycosylation.

As part of a larger EU-funded consortium (www.ibd-biom.eu) aiming to gain a better understanding of IBD onset and progression we are investigating bowel tissue specific glycosylation signatures. In order to identify disease specific global glycosylation features we first require a detailed map on the cell surface glycosylation of the colon, one of the largest organs of the human body. Using our PGC-LC ESI MS/MS based glycan sequencing platform we systematically analysed and deciphered N-glycan and O-glycan profiles of colon biopsies from IBD and control patients. From the biop-

sies which were taken from seven distinct positions between ileum and rectum the to date most comprehensive protein glycome map of the human bowel was established [4]. In each biopsy more than 150 individual N-glycan structures and a similar number of O-glycans could be identified and characterised. We could show that distinct differences in the occurrence of specific glycosylation features occurred in a region specific manner (an example for a single glycan feature is shown in Fig. 4). This data provides crucial step forward in the on-going glyco-marker screening as this information allows a better matching between different disease vs. control samples and disease specific features can be more accurately distinguished from region specific ones. A key achievement in this undertaking was the establishment of a distinct N- and O-glycan MS/MS spectra library database for semi-automated glycan structure annotation. These developments are currently being applied in the on-going analysis of a larger dataset derived from 500 patient and the comparable number of control samples.

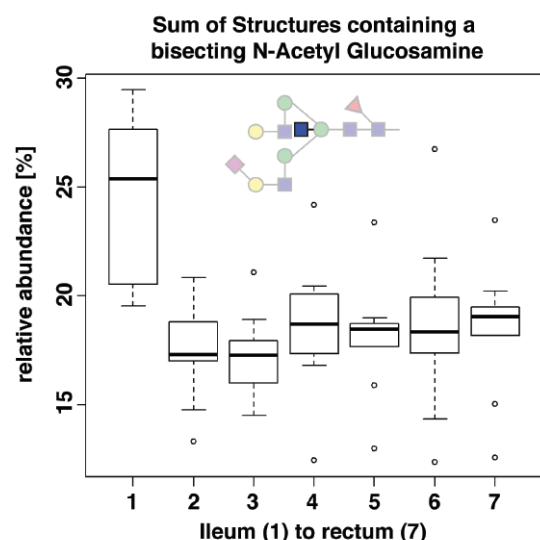


Fig. 4: Occurrence of N-glycans carrying a bisecting N-acetyl glucosamine residue. The presence of this glycan feature is significantly increased in the ileum part of the colon.

Accessing Disease Glyco-Signatures from FFPE Histopathological Specimens

In order to study the diagnostic and/or prognostic potential of disease induced glycosylation alterations access to well-characterised samples is a crucial factor. Nevertheless, the availability of such well-defined clinical specimens in sufficient numbers often represents a serious obstacle in glyco-biomarker analyses. Therefore we explored the possibility to use formalin-fixed paraffin-embedded (FFPE) clinical specimens as an attractive alternative for glyco-biomarker research, given that the glyco-epitopes remain unaltered and sufficient glycan amounts can be obtained from conventional FFPE tissue sections frequently used by pathologists.

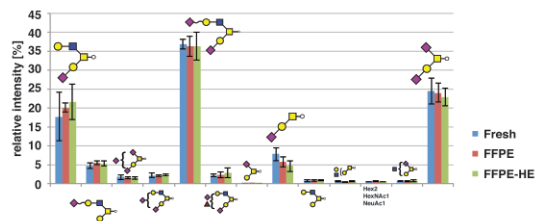


Fig. 3: O-glycan profiles obtained from different preparations of human hepatocellular carcinoma specimens from a single donor. No statistically relevant differences in the qualitative and relative quantitative presence of the identified O-glycans were detected between fresh tissue, FFPE and FFPE slides stained with hematoxylin (FFPE-HE).

Our recent efforts have allowed us to establish a workflow for an in-depth glycomic PGC-LC ESI MS/MS based profiling of both, N- and O-glycans from single FFPE tissue sections as thin as 3 μ m. We could show that unstained as well as hematoxylin and eosin (HE) stained FFPE tissue samples provide similar results and that these results are largely correlating to the data obtained from non-FFPE treated fresh material [5]. This enables us now to I) gain easier access to clinical specimens from FFPE storage repositories, II) easily obtain statistically significant numbers of clinical samples required for serious glyco-biomarker screening and III) work from specimens which have been evaluated by pathologists prior analysis.

Our recent developments represent an important step forward in the glycan sequencing of clinical samples, providing large datasets on the dynamics of disease induced glycosylation alterations. With this basic knowledge a better understanding on the functional aspects of protein glycosylation in health and disease will be achieved.

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C-type Lectin Receptors: Ligand Identification, Cell-Specific Targeting and Their Role in Infection and Inflammation



Research of the Glycoimmunology group focuses on lectins. Lectins are carbohydrate-binding proteins that display high specificities for certain sugar moieties. We are interested in a specific lectin superfamily, termed C-type lectin receptors (CLRs). In innate immunity, CLRs serve as pattern recognition receptors that recognize invading pathogens, thus they provide a first line of defense in the body.

CLRs are mainly expressed by antigen-presenting cells (APCs) such as dendritic cells and macrophages and often recognize carbohydrates in a Ca^{2+} -dependent manner. Engagement of CLRs by carbohydrate ligands may lead to APC activation, but may also dampen APC functions. Thus, CLRs are often crucial to initiate protective immune responses against pathogens, but they can also contribute to immune homeostasis (Fig. 1).

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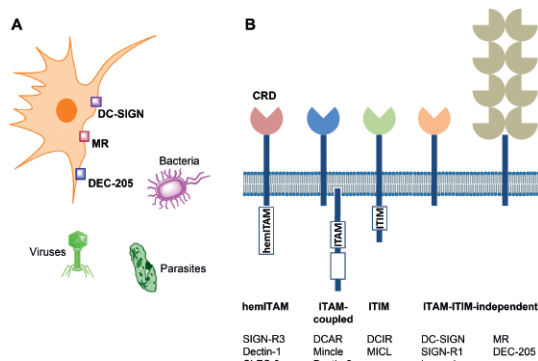


Fig. 1: Myeloid C-type lectin receptors (CLRs) in innate immunity. A, CLRs such as DC-SIGN, Mannose receptor (MR), or DEC-205 serve as pattern recognition receptors in innate immunity and bind to carbohydrates on pathogens such as bacteria, viruses, or parasites. B, Myeloid CLRs share one or more homologous carbohydrate-recognition domains (CRD) that bind to carbohydrates often in a Ca^{2+} -dependent manner. The signaling pathway elicited upon CLR engagement depends on the cytoplasmic signaling motif. Figure reprinted from [1] with permission from Elsevier.

One major goal of our group is to identify yet unknown CLR ligands on pathogens and to further characterize these novel CLR-pathogen interactions on the molecular level. In addition, we use distinct carbohydrate ligands to target CLRs on APCs for a cell-specific delivery of drugs and vaccine antigens. Finally, we are interested in the role of CLRs *in vivo*. To this end, we employ murine infection and autoimmunity models to unravel the contribution of specific CLRs to immunity against infections and to clarify their role in immune homeostasis.

CLR Targeting for Cell-Specific Drug Delivery and Immune Modulation

Numerous APC functions may be influenced by CLR targeting such as antigen uptake and presentation, cytokine production, and/or the expression of co-stimulatory molecules (Fig. 2). As a consequence, the ligand recognition by CLRs on APCs impacts the subsequent T cell activation and also affects the CD4^+ T cell differentiation into T cell subsets. Thus, CLR targeting is a means to shape an initiated immune response and may be exploited for immune modulatory therapies (Fig. 2).

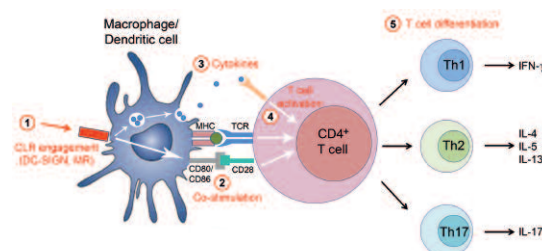


Fig. 2: CLR targeting as a means to shape an initiated immune response. Engagement of myeloid CLRs in innate immunity such as DC-SIGN or MR leads to receptor-mediated endocytosis (1). When an antigen is targeted to an antigen-presenting cell (APC), the antigen will be internalized, processed and presented by major histocompatibility complex (MHC) molecules to T cells. Moreover, signaling pathways may be provoked in APCs that lead to the expression of co-stimulatory molecules CD80/CD86 (2), and the production of cytokines (3). T cells recognize MHC-presented peptides through their T cell receptor (TCR) and are activated in the presence of a secondary, co-stimulatory signal mediated via the interaction of CD80/CD86 with CD28 (4). Cytokines released by APCs influence T cell differentiation and T cell effector functions (5). Figure reprinted from [1] with permission from Elsevier.

During the past years, the Glycoimmunology group has generated a comprehensive CLR library using eukaryotic expression systems. The library consists of so-called CLR-Fc fusion proteins in which the extracellular domain of each CLR is fused to the Fc part of human IgG1 molecules. By now, the library covers a high number of immunologically relevant CLRs. With the help of this library, we have identified several novel carbohydrate ligands of CLRs and have evaluated their potential for cell-specific antigen delivery and immune modulation. As a first step, the glycan array platform was used to screen for CLR-carbohydrate interactions (Fig. 3). To test whether the identified CLR ligands could be used for CLR targeting on APCs, selected carbohydrates were then coupled to the model antigen ovalbumin (OVA). The OVA neoglycoconjugates were used to stimulate APCs *in vitro* and were also employed for immunization studies *in vivo*. Indeed, the carbohydrate modification of OVA led to increased antigen targeting to APCs and impacted their cytokine profile as well as their antigen presentation capability [2, 3]. Hence, we have demonstrated that the platform developed in our group can be used to screen for CLR ligands and their potential for immune modulation.

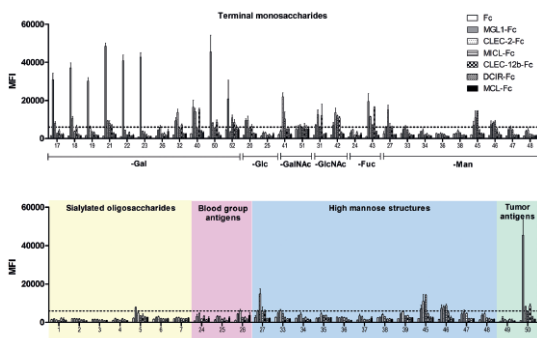


Fig. 3: Exemplary glycan array results for the CLR-Fc fusion proteins MGL-1-Fc, CLEC-2-Fc, MCL-Fc, CLEC-12b-Fc, DCIR-Fc, and MCL-Fc. The results are shown as mean fluorescence intensities (MFI) \pm SEM and are presented based on terminal monosaccharides recognized by the respective CLR-Fc fusion protein or based on the type of glycan structure. Figure reprinted from [2] with permission from Elsevier.

In a collaborative project with the MPI-DKTS in Magdeburg, we investigated how a differential glycosylation of influenza vaccine antigens impacted APC targeting and subsequent T cell activation [4]. We focused on influenza virus hemagglutinin (HA) since HA is the most abundant protein in the virus particle membrane and an essential component of most influenza vaccines. Indeed, HA glycosylation markedly impacted T cell activation *in vitro*. To analyze the impact of HA glycosylation *in vivo*, mice were immunized with the differentially glycosylated influenza virus variants. We observed a dramatic reduction in T cell activation and anti-HA antibody production when mice were immunized with the deglycosylated influenza virus variants. In conclusion, this study highlights the potential of “glyco-optimization” of antigens to increase their immunogenicity and to enhance vaccine potency.

Role of CLRs in Infection and Inflammation

A major focus of our work is the characterization of CLR functions *in vivo* in relevant murine models. Currently, we have established a number of CLR-deficient mouse lines and elucidate the role of specific CLRs in malaria as well as colitis models. In a recently published study, the contribution of the CLR Dendritic cell immunoreceptor (DCIR) to the pathogenesis of cerebral malaria was analyzed [5]. Using *Plasmodium berghei* ANKA infection of mice, we found a crucial role for DCIR in cerebral malaria induction. DCIR^{-/-} mice were protected from cerebral malaria and displayed markedly reduced leukocyte sequestration in the brain. Accordingly, DCIR^{-/-} mice exhibited decreased TNF- α serum levels as well as a modulated activation of CD4⁺ and CD8⁺ T cells in spleen. Thus, DCIR is essential for cerebral malaria induction highlighting the importance of CLRs for innate immunity during malaria.

We have also analyzed the function of CLRs in the regulation of intestinal immunity. For instance, we have investigated the role of the murine CLR SIGNR3 in colitis pathogenesis [6]. We found that SIGNR3 recognizes fungal species

present in commensal microbiota. To analyze whether the SIGNR3/fungi interactions influence intestinal immunity, the model of chemically induced colitis was employed. In this model, SIGNR3^{-/-} mice exhibited an increased weight loss accompanied by more severe clinical colitis symptoms compared to wild-type mice. The increased inflammation in SIGNR3^{-/-} mice was caused by higher cytokine levels such as TNF- α in colon. This finding indicates that CLRs are involved in intestinal immune homeostasis and that dysfunction in commensal recognition by specific CLRs may contribute to colitis. We also analyzed binding of two other poorly characterized members of the CLR family, the Macrophage-restricted C-type lectin (MCL) and the Dendritic cell immunoreceptor (DCIR) to microbiota [7]. Both CLRs bound to intestinal microbiota to a different extent and modulated the production of pro-inflammatory cytokines by APCs upon stimulation with heat-killed microbiota. In addition, these CLRs also impacted T cell responses in APC/T cell co-cultivation assays *in vitro*. However, MCL^{-/-} as well as DCIR^{-/-} mice exhibited only a slightly increased severity of disease in the murine model of chemically induced colitis compared to wild-type mice. The limited role of both CLRs *in vivo* may be due to cross-talk between different CLRs and partially redundant CLR functions in intestinal immunity. As a next step, we plan to investigate how multiple CLRs impact disease pathogenesis. Currently, we are also identifying distinct CLR ligands on commensal microbes.

The role of CLRs in antimicrobial immune responses seems to be evolutionarily conserved across species. Recently, we discovered that specific C-type lectins in the roundworm *Caenorhabditis elegans* are crucial for immunity during bacterial infection [8]. Thus, CLRs may contribute to pathogen recognition in species of many phylogenetic clades.

Multivalent Targeting Approaches

Carbohydrate-lectin interactions and – even more – carbohydrate-carbohydrate binding events generally display low affinities. Consequently, multivalent approaches are often needed to exploit these weak interactions for cell-specific targeting and imaging. Further targeting approaches of our group include liver-specific drug delivery by targeting the asialoglycoprotein receptor expressed by hepatocytes as well as antibiotics delivery to bacteria for antimicrobial treatment [9].

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SYNTHETIC PLANT CARBOHYDRATES

Synthesis of Plant Carbohydrates and their Biological Application



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Carbohydrates play crucial roles in the life cycle of plants, both as structural components and as important players in signaling events and energy provision [1]. 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 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 [2] and chemo-enzymatic methods [3] for the generation of plant carbohydrate libraries as a powerful means for investigating their application in plant biology and biomedical research. In particular, two types of plant carbohydrates are synthesized: polysaccharide fragments of the plant's cell wall and *N*-linked glycans of plant glycoproteins. The synthesized plant carbohydrates are applied in the characterization of monoclonal antibodies derived from cell wall polysaccharides and in the development of improved methods for allergy diagnosis. In addition, the polysaccharide fragments are evaluated for their immunostimulatory potential. Together, the synthetic plant carbohydrates will provide a new toolbox for studying the role of carbohydrates in plant biology and their interaction with human health.

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

A large amount of plant carbohydrates are located in the cell wall, which consists of a complex mixture of polysaccharides and other biopolymers assembled into a highly organized network that surrounds all cells. Many genes responsible for the biosynthesis of cell wall polysaccharides have been identified and detailed insight into the structure and function of plant cell wall polymers has been gained by high resolution imaging of cell wall microstructures [4]. Monoclonal antibodies directed toward plant polysaccharide antigens are used by plant biologists as powerful molecular probes to detect the structural elements of glycans in the cell wall. However, the precise molecular structures recognized by the antibodies are unknown. The goal of the project is to exploit automated solid-phase synthesis for the rapid assembly of plant carbohydrate libraries and their application in the epitope mapping of monoclonal antibodies.

One of the main components of plant cell wall polysaccharides is the hemicellulose xylan, the second most abundant polysaccharide in nature. Xylans are dietary carbohydrates in everyday food that can provide medicinal benefits including immunomodulatory, anti-tumor, and anti-microbial effects. In addition, xylans are potential resources for the production of food additives, cosmetics, and biofuels. Although the structure of xylans varies between plant species, they all possess a common backbone consisting of β -1,4-linked D-xylopyranoses. This backbone structure may be partially acetylated and substituted with L-arabinofuranosyl or D-(4-*O*-methyl) glucuronyl residues.

We produced a library of eleven oligoarabinoxylans of different complexity by automated solid-phase synthesis and printed the compounds as microarrays for probing a set of 31 anti-xylan monoclonal antibodies for binding. We observed specific binding of the antibodies to the synthetic oligoarabinoxylans and the binding epitopes of several antibodies were characterized (Fig. 1). This work will serve as a starting point for future studies where libraries of synthetic plant oligosaccharides are screened for the binding of cell wall glycan-directed antibodies, generating the essential information required for interpretation of immunolabeling studies of plant cell walls.

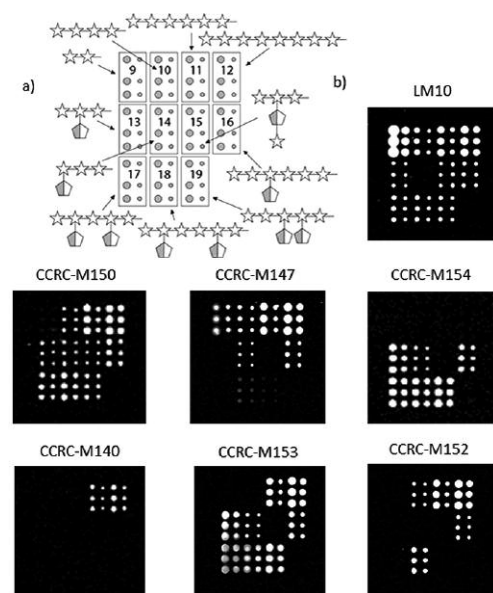


Fig. 1: Detection of oligoarabinoxylans by anti-xylan monoclonal antibodies (mAb): a) Printing pattern; b) Microarray scans. Representative scans of at least two independent experiments are shown. The intensity of the spots corresponds to the binding affinity of the respective mAb. The structures are drawn according to the CFG-nomenclature.

Evaluation of the Synthesized Polysaccharide Fragments for their Potential as Immunomodulators

Plant cell wall polysaccharides are important dietary carbohydrates in everyday food such as fruits and cereals. They are believed to exhibit beneficial therapeutic properties through modulation of innate immunity [5], but the molecular basis of their interaction with immune receptors remains largely unknown. We will evaluate synthetic polysaccharide fragments for their potential to stimulate immune cells. A long-term objective of the study is the identification of specific binding epitopes on immunomodulatory polysaccharides and of the receptors responsible for their recognition.

Chemo-Enzymatic Synthesis of Plant N-Glycans

Plants are not only an important part of the food chain, but can also cause pollen and food allergies [6]. Many or most of the plant-based allergens we inhale or ingest are glycosylated with oligosaccharides that are potentially immunogenic. *N*-Linked glycans in plant glycoproteins include similar glycans as found in animals but are of limited diversity and feature several unique modifications such as an additional xylose or fucose residue. We plan on synthesizing a collection of plant *N*-glycans by enzymatic carbohydrate synthesis for various biological applications.

Construction of a Plant Carbohydrate Microarray

Current carbohydrate microarrays are strongly biased towards mammalian glycans and do not contain large numbers of bacterial or plant-specific oligosaccharides [7]. To resolve this shortcoming, we will generate a comprehensive microarray containing synthetic plant carbohydrates. The microarray will be used for lectin binding studies, screening of the sera of allergy patients, and epitope mapping of monoclonal antibodies developed against plant cell wall polysaccharides (Fig. 2).

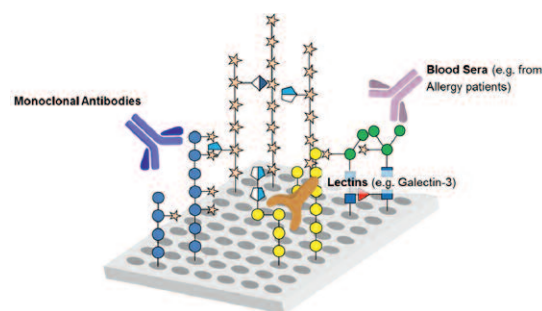


Fig. 2: Plant carbohydrate microarray for probing the binding specificities of monoclonal antibodies, antibodies from sera, and lectins.

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Specific C-type Lectin Receptor Ligands



Carbohydrates cover every living cell and are a central biomacromolecular building block of life. Cell surfaces are decorated with a large diversity of glycans and by that determine many fundamental processes such as embryonic development, cell-cell communication and regulation of the immune system.

Hence, it is not surprising to find glycan binding proteins in all organisms. Three major mammalian glycan binding protein families are important in immunobiology, namely Galectins, Siglecs and C-type lectin receptors (CTLRs). These lectins determine the response to incoming signals during pathogen recognition and killing, antigen processing, and tumor progression.

In particular, mammalian C-type lectin receptors have emerged as targets for immunomodulatory therapies. In contrast to their potential, the number of specific molecular probes modulating carbohydrate recognition by C-type lectin receptors is limited. The dendritic cell-specific intercellular adhesion molecules-3-grabbing non-integrin (DC-SIGN) is a well-studied CTLR and is expressed on dendritic cells and macrophages. A large array of pathogens such as *Mycobacterium tuberculosis*, *Leishmania*, hepatitis C virus, Ebola and HIV is recognized. For HIV, it was demonstrated that DC-SIGN promotes trans-infection of T cells and has since then drawn attention as a therapeutic target in anti-viral therapy [1]. Another CLTR of high interest is Langerin. This lectin is expressed on Langerhans cells and dendritic cells and promotes pathogen uptake and antigen presentation. Due to its restricted expression pattern it also resembles an attractive receptor for targeted immune stimulation and delivery.

The overall goal during the present and upcoming period is the development of specific and high-affinity CTLR ligands for chemical biology purposes. For this, orthogonal routes are followed: (i) fragment-based lead discovery, (ii) computer-aided structure-based design, and (iii) receptor-based NMR techniques.

Druggability Assessment of CTLRs and Fragment-Based Design of Novel Lectin Ligands

The development of small molecule modulators of biological processes is an expensive endeavor and target receptor selection should be done carefully. The term 'druggability' refers to the ability of a target protein to bind a small molecule drug with high affinity and specificity. Several techniques have evolved over the recent years for the prediction of druggability of proteins and resemble a valid starting point in many drug discovery campaigns. Conversely, low druggability scores have been found to be a good indicator for a high failure rate during later stages of development. Both, computational and experimentally derived predictors of druggability have been pursued to evaluate the potential of CTLRs.

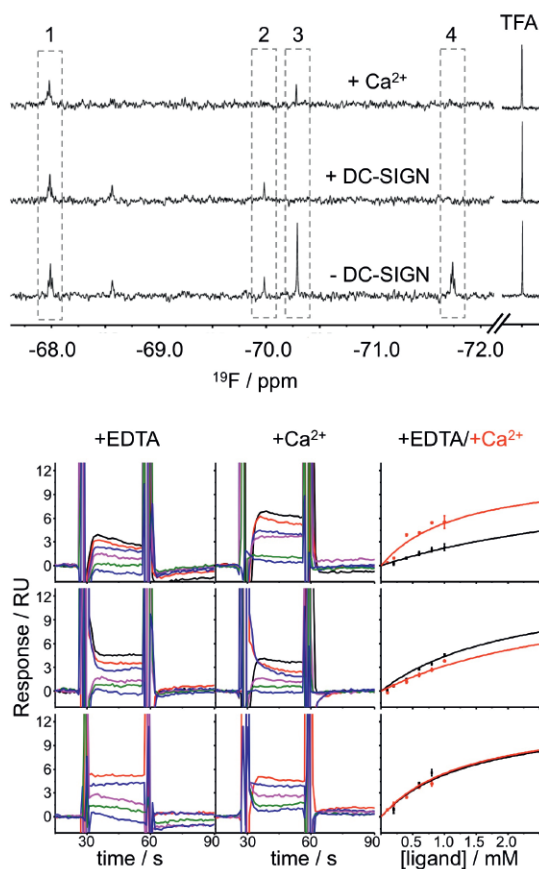


Fig. 1: Screening a fragment library against DC-SIGN. (upper) ¹⁹F NMR-based screening of a selected panel of fragments is shown in absence and presence of DC-SIGN and in presence of calcium as a competing ligand for CTLRs (from bottom to top). Disappearance of signals in presence of protein highlights binding of fragments. Re-appearance after addition of calcium suggests that these fragments bind close to the carbohydrate recognition site. (lower) Hit validation was performed using SPR spectroscopy. Here, data of three fragments are shown, exemplifying binders being affected by presence of calcium ions [2].

Computer-aided assessment of target druggability is an attractive method, as its resource requirements are limited. Scores can be deduced from available X-ray crystallographic data and many software tools are available to the community. These algorithms have a two-step process in common that first identifies binding sites and then scores their potential to bind a drug-like ligand. To predict the druggability of human CTLRs we compiled a set of 22 crystal structures and analyzed it using DogSiteScorer [3]. Many mammalian glycan binding proteins have shallow and feature-less binding sites and in accordance with previous computational evaluations of the druggability of lectins, CTLRs have been found to show only limited potential to recognized drug-like molecules [2].

Next, we pursued experimental validation of our findings. One experimental approach to assess the druggability

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of a target is screening of fragments of drug-like molecules. A diverse library of fragments ranging between 150 and 300 Da of molecular weight has been constructed and screened (**Fig. 1**). The advantage of using fragments instead of drug-like molecules is the large coverage of chemical space. It has been estimated that 1000 fragments can cover a similar chemical space as 10 trillion drug-sized molecules [4]. Fragments have an intrinsically low affinity for their targets, requesting sensitive biophysical screening techniques for detection. We chose NMR spectroscopy for the primary screen as it has a remarkably low false-positive rate. In particular, ^{19}F NMR turned out to be highly sensitive and enabled us to detect 10 to 16 % hits in the first round of screening against three human CLTR targets, namely DC-SIGN, Langerin and MCL. These hit rates are a good indicator for a high druggability of the lectin receptors. As ligand observed NMR techniques allow identifying hits from mixtures without deconvolution, these hit structures were directly advanced to an orthogonal validation screen using SPR spectroscopy (**Fig. 1**). Overall, our results highlight limitations of current *in silico* approaches to druggability assessment, in particular with regard to carbohydrate-binding proteins. At the same time, our data indicate that small molecule ligands for a larger panel of C-type lectin receptors can be developed and the biophysical screening resulted in several starting points for future design of specific CTLR ligands [2].

Computer-Aided Carbohydrate-Based Design of C-Type Lectin Ligands

The availability of a few X-ray structures of CTLRs provides opportunity for rational ligand design (**Fig 3**). We employed the co-crystal structure of a CTLR with its natural carbohydrate ligand to elucidate the potential of carbohydrate derivatives as lectin ligands. In general, compared to the number of members of the C-type lectin fold family, the structural information is rather sparse. Still, a few members of the subfamily of myeloid CTLRs have been characterized by X-ray crystallography and NMR spectroscopy. The resolution of these structures is of sufficiently high resolution allowing *in silico* methods to be used to aid the search for small molecular probes for these lectins. CTLRs that obey a calcium-mediated recognition of glycans share a shallow binding site (**Fig. 2**). This not only explains the intrinsically low affinity of these cell surface receptors for their glycan ligands, but also imposes a challenge to any rational design of high affinity ligands for these proteins.

To overcome this challenge, structure-based *in silico* design is combined with carbohydrate chemistry to generate focused libraries of carbohydrate derivatives. Molecular Operating Environment (MOE) was employed to evaluate a database of 40,000 commercially available building blocks as substituents on a carbohydrate scaffold. Moreover, a synthetic strategy for the preparation of the selected analogs was established. ^{19}F R_2 -filtered and ^1H saturation transfer difference nuclear magnetic resonance experiments were employed to determine the affinity and the bound conformation of the synthesized analogs.

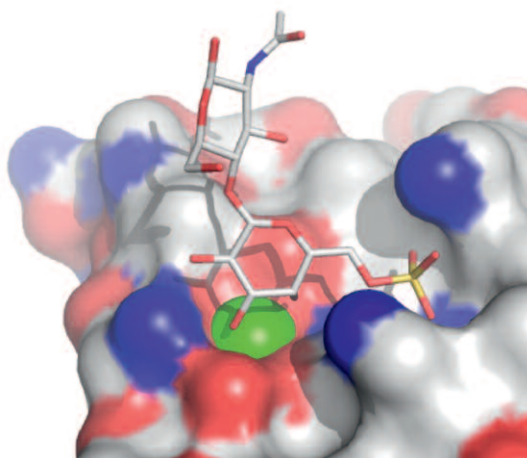


Fig. 2: Langerin in complex with a natural carbohydrate ligand. The 6'-sulfo-galactose moiety is coordinated by the central calcium ion (green) in the binding site of Langerin [5].

Studying C-Type Lectin Interactions with Complex Glycans by Biomolecular NMR Spectroscopy

To expand our understanding of CTLR structural biology, we began studying these receptors employing techniques from solution NMR spectroscopy in presence of their natural glycan ligands. Complex glycan structures have evolved as versatile regulators of many aspects of health and disease such as in immune cell recognition, development, hormone activity, tissue organization, and metastasis. In general, many functions of carbohydrates in a biological context are tightly coupled to their recognition by glycan binding proteins (GBPs). In the context of immune cell regulation, CLTR recognise self- as well as non-self glycan structures. Only the side-by-side analysis of the recognition process at atomic resolution and functional studies in a relevant biological environment provides means to fully elucidate a carbohydrate structure-function relationship. Therefore, we apply biophysical techniques, such as nuclear magnetic resonance (NMR) and combine the results with our insights from computational analysis. These data give rise to hypotheses that are under current investigations in the laboratory.

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Chemical Biology of Glycosylphosphatidylinositols



Many eukaryotic proteins are attached to the cell membrane using glycosylphosphatidylinositols anchors (GPIs). GPIs are characterized by a conserved core structure containing a glycan pseudo-pentasaccharide, a phosphoethanolamine unit and a phospholipid. However they are usually modified with phosphates, glycans and lipid chains in a cell type dependent form [1]. The lipid moiety is variable and may include diacylglycerol, alkylacylglycerol or a ceramide, with chains of different length and degree of unsaturation (Fig. 1).

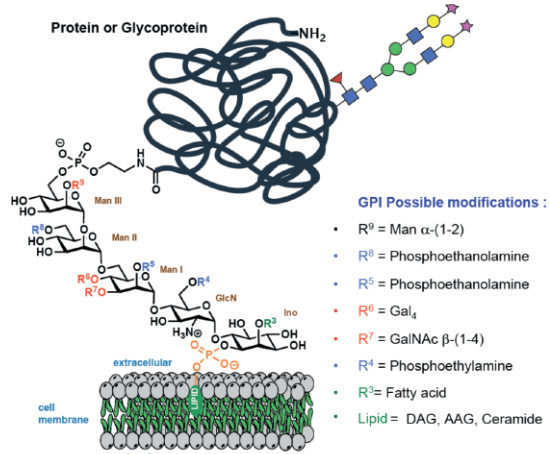


Fig. 1: Structure and possible modifications of GPI anchors. (DAG Diacylglycerol, AAG: Alkylacylglycerol)

The primary biological role of GPIs is to localize the attached molecules to the outer leaflet of the cell membrane [2]. However, different studies show that GPIs play a role in the association of anchored proteins with lipid rafts and are, thereby, involved in diverse processes such as regulation of innate immunity and protein trafficking among others [3].

Development of Strategies to obtain GPIs

Studies to evaluate the role of GPIs and the structure-function relationship rely on the availability of good amounts of homogeneous glycolipids. To address this need we developed a synthetic strategy to obtain well-defined GPIs [4]. Our strategy is based on modular assembly of common building blocks and relies on a fully orthogonal set of protecting groups. They enable the regioselective introduction of phosphodiester and efficient assembly of the glycans (Fig 2). This strategy was used to obtain different and structurally distinct GPIs and GPI derivatives for biological and biophysical evaluations.

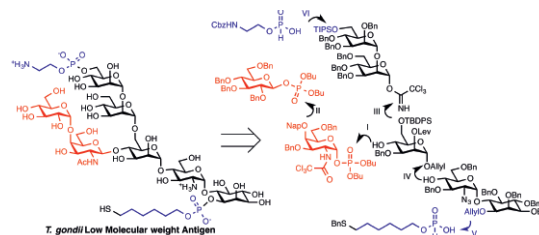


Fig. 2: Assembly sequence of the low molecular weight antigen from *T. gondii* using the general strategy.

The assembly sequence of the GPIs is dictated by the position of the protecting groups, which is kept constant across the set of common building blocks. The glycosylations are performed using similar coupling partners, making the reactions conditions transferable between different GPI syntheses [5].

GPI-Anchors as Diagnostic Tools

Protozoan parasites express highly amounts of non-protein-linked, free GPIs, and GPI-anchored proteins (GPI-APs) that may participate in the regulation of the host immune response during infections [6]. However, in most cases, the heterogeneity and difficult isolation of pure GPIs have limited the evaluation of their function.

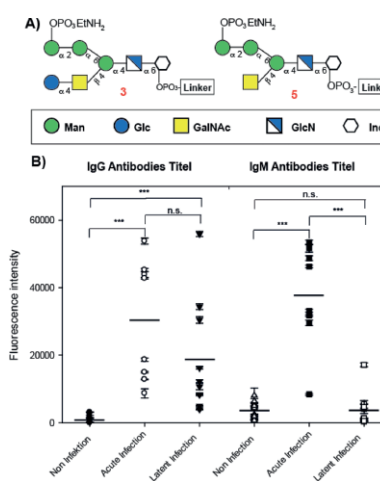


Fig. 3: Antibody levels determined by microarray analysis against LMA of *T. gondii* in sera samples from different toxoplasmosis stages. Black bars represent mean antibody levels

Two GPIs **3** and **5** of *T. gondii* and a series of GPI fragments either containing a single amine or thiol linker were synthesized and printed on epoxide modified glass slides (Figure 3A). The resulting GPI-microarray was incubated with reference sera of patients with acute or latent toxoplasmosis and with seronegative individuals.

The screening results showed that all sera from non-infected patients contained undetectable or low levels of IgG and IgM antibodies directed against the printed GPIs or their substructures. In contrast, all sera from patients diagnosed with an acute toxoplasmosis showed high levels of IgG and IgM antibodies recognizing the full GPI structure. The sera samples of latently infected patients showed an IgG antibody binding pattern and signal intensities that are comparable

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with analyses of sera from acutely infected humans (**Figure 3B**); however, the IgM levels were considerably low.

These results are in accordance with reports describing that the immune response against GPIs in *T. gondii* infected humans is mainly directed against the free GPI **3**. Based on these results, the GPI **3** of *T. gondii* emerged as a suitable biomarker for the diagnosis of different stages of toxoplasmosis. The IgG level against the GPI **3** can be used to distinguish non-infected from *T. gondii* infected humans whereas the concentration of IgM antibodies binding the same carbohydrate may serve to differentiate latent and acute toxoplasmosis [7].

Biophysical Studies with GPI-fragments

Insights into the behaviour of GPIs and GPI-APs in cell membranes could contribute to the understanding of the roles GPIs play in biological processes. In this context, to evaluate the participation of GPIs in the formation of microdomains in the cell membrane, it was performed a comparative analysis of the structural arrangement in a series of 2D model membranes of three GPI-fragments (monolayers formed at the air/water interface). This study demonstrates that increase in the size of the head groups of the fragments from **6** to **7** and then **8** results in an increase in the in-plane area per molecule, which causes increase in the tilt of the alkyl chains and increase in surface pressure required for the transition to a non-tilted phase. While the trends observed are in line with what is expected for such a series of GPI fragments, the addition of a GlcN moiety in compound **8** causes dramatic changes in the structure of the monolayers (**Fig. 4**) [8].

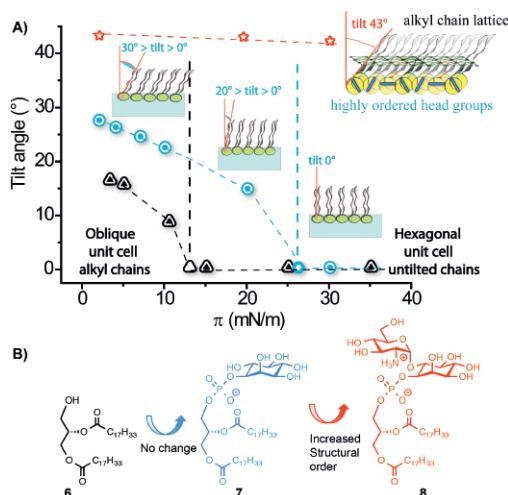


Fig. 4: (A) Comparative representation of the monolayer structural changes of three GPI-fragments (variation of the tilt angle of the alkyl chains (t) with the lateral surface pressure (p)) on PBS at 20 °C. (B) Chemical structures of the investigated GPI-fragments

Compounds **6** and **7** form ordered monolayers defined only by an alkyl chain lattice. In contrast, GPI-fragment **8** forms higher ordered monolayers characterized by two commensurate lattices: a lattice of the alkyl chains and a molecular lattice formed as a consequence of ordering of the head groups through interactions between glycans [9]. These interactions

are likely responsible for the partial segregation of GPI-fragment **8** when mixed with a liquid-disordered model membrane of POPC. When compound **8** is mixed with lipids that form ordered monolayer phases, such as **6** or **7**, hydrophobic interactions of the chains induce complete mixing of the two components. The mixed monolayers of **6** or **7** with **8** are homogenous with structures defined only by ordered alkyl chains and characterized by packing parameters of compounds without strong head group interactions. Further experiments to determine if this behaviour of **8** is applicable in real membranes and transferable to full GPIs are under process.

Synthesis of GPI-Anchored Proteins

To evaluate the effect of GPIs in the function and activity of GPI-anchored proteins, two protein splicing approaches have been used to attach synthetic GPIs to proteins: native chemical ligation (NCL) and protein trans-splicing (PTS).

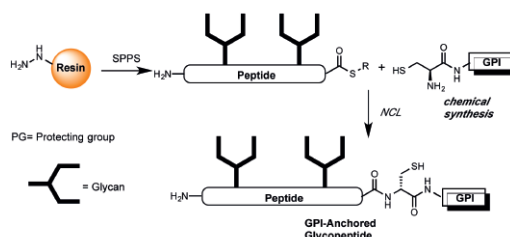


Fig. 5: Schematic representation for the synthesis of GPI-Anchored Glycoproteins

In the first strategy, GPIs containing a cysteine residue at Man III were obtained using the described strategy. To obtain the required protein thioesters, three proteins (GFP, IL-2 and PrP) fused at their C-termini to an intein domain were expressed in *E. coli* in optimized form. After establishing the best purification and folding conditions, the desired protein thioesters were formed. A NCL between the GPI and the protein delivered the GPI-APs. In the second strategy, a naturally split intein from *N. punctiforme* has been used [10]. In this strategy, the proteins are expressed as fusion proteins with the N-terminal fragment of the split intein and submitted to PTS with GPI molecules linked to the C-terminal fragment of the split intein. With the established methods we have synthesized GPI-anchored GFP and PrP.

Besides the GPI-APs, these strategies allow also the synthesis of GPI-anchored glycopeptides (**Fig. 5**). To introduce the carbohydrate to the peptides we accomplish the Lansbury aspartylation between a solid phase bound, an activated peptide and an amino sugar. After the cleavage of the peptide from the resin, a conversion to the glycopeptide thioester, a NCL is performed between the two synthetic molecules to generate a GPI-anchored glycopeptides. Initial results were obtained with small sugars, however we are developing new methods that allow the introduction of large oligosaccharides into the peptides and proteins.

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In Search of the Difference



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The immune system protects us from foreign substances or pathogens by eliciting an immune response generating specific antibodies. However, in a variety of diseases – especially autoimmune disorders – the immune system dysfunctions leading to self-reactive (auto)antibodies. In some cases, these antibodies can cause severe damage to the body, while in other cases their presence is seemingly without consequence. Our knowledge about their role in disease progression, whether being of significance or simply a bystander effect is rather vague.

The major interest of the Immunomics group centers on the investigation of antibody-antigen complexes in autoimmune disorders. The scientific focus of the group centres on the analysis of V(D)J recombination patterns in immunoglobulin repertoires in healthy individuals and autoimmune patients and the elucidation of autoantigenicity patterns in health and disease. The methodological portfolio includes the use of Next Generation Sequencing (NGS), Phage Display as well as Protein Array Technologies.

Immunoglobulin Repertoires of Health and Disease

Our goal is to explore whether there is a difference in the nature of how healthy individuals and autoimmune patients shape their antibody repertoires. The variety of immunoglobulin (Ig) paratopes for antigen recognition is a result of a V(D)J recombination mechanism in the heavy and the light chain of the antibody molecule, while a fast and efficient immune response is mediated by specific Ig-isotypes obtained through class switch recombination (CSR). Hence, we believe that it is not enough to analyse V(D)J recombination, but we need to address the effector function of an antibody encoded in the isotype as well, as it is of equal importance.

Since no adequate analytical tools were available to tackle this question, we have established a new method of yet unpaired sensitivity to amplify and sequence the expressed antibody repertoire of an individual. The method is based on V-gene independent amplification of rearranged immunoglobulin repertoires in combination with emulsion PCR to minimize primer- and PCR-induced bias. We first analysed the obtained sequences using the IMGT/High V-Quest online tool and developed a novel avenue of bioinformatic analysis based not only on information on V(D)J recombination but also on class-switch recombination of individual donors by incorporating isotype-specific analysis of the antibody sequences.

We sequenced the antibody repertoire of peripheral blood mononuclear cells from 14 healthy Caucasian donors of different age and gender. We found, that hierarchical clustering of the donors only according to the V(D)J recombination information revealed neither correlation by age nor gender. However, when CSR information was introduced into the analysis, for the first time, donors clustered hierarchically according to age. We could observe changes in Ig-isotype repertoires to be age-dependent indicating reduction of class-switch capability. This is in good agreement with recent findings suggesting that the dramatically reduced vaccination efficacy in elderly populations is not because of a lack of specific antibodies due to reduction of V(D)J recombination, but rather a problem in antibody titre and lacking specificity in the right immunoglobulin class to elicit response. Unexpected however is the fact that the decline of class-switch ability starts already relatively early. The age of fifty and beyond defines the onset of immune senescence **[1]**. We are now extending our analyses to immunoglobulin repertoires of autoimmune patients with rheumatoid arthritis (RA) in collaboration with the Department of Rheumatology and Clinical Immunology of the Charité. We are comparing this data set with that obtained of healthy individuals to see whether there is a difference in the nature of V(D)J recombination patterns between the antibody repertoires of healthy individuals and autoimmune patients.

Autoantigenicity Patterns in Health and Disease

Everybody has circulating self-reactive antibodies in their blood. Although individual repertoires of autoantibodies can significantly overlap, they differ between healthy and diseased individuals. Differential analysis can lead to the identification of biomarker sets that can clearly separate different autoimmune diseases or even allow subdiagnosis of patients within a certain disease. A current project centres on RA and is conducted in close collaboration with the Department of Rheumatology and Clinical Immunology of the Charité. Applying protein array technology, we were able to find specific autoantibody profiles, which allow discrimination between early stages of RA and systemic lupus erythematosus (SLE). With the ongoing downstream characterisation and evaluation of the biomarkers in a BMBF-funded project we now are exploring their diagnostic value. The biomarkers can possibly not only discriminate between early stage RA and SLE, but may possibly also serve as prognostic marker, i.e. give clues about the progression of RA in those patients possessing such autoantibodies.

We apply two complementary screening technologies for the discovery of autoantigenicity patterns, namely Protein Arrays and Phage Display. They comprise of different subsets of the human proteome and offer different means of selection. While most antigens on the array are denatured, the proteins on the bacteriophage surface are presented as folded structures. Our protein arrays consist of ~25.000 expression constructs of a human foetal brain cDNA library representing 2055 human genes in multiple copies. For phage display, we have now generated various versions of full-ORF libraries of 4452 genes applying the Gateway-technology. While the identity of each spot on the protein array is known, the phage display libraries require downstream processing. Selection is carried out in an iterative process based on affinity enrichment using patient-derived immunoglobulin fractions as selection targets. The identity of the enriched clones is revealed by NGS of the cDNA inserts. We have recently applied these screening technologies for the elucidation of autoantigenicity profiles of healthy donors, Multiple Sclerosis and Alzheimer's patients [2, 3].

Expression of Recombinant Biomolecules in *L. tarentolae*

Since most of the biological drugs marketed today are secretory proteins, novel routes of expression are of great interest to the biotech community [4]. Within the frameworks of a BMBF project, we have explored the use of the protozoa *Leishmania tarentolae*, as an expression host for secretory molecules. *L. tarentolae* is a eukaryotic protozoa which is easily cultured and has been reported to glycosylate proteins in a more human-like manner than for instance yeast. To investigate this, we have generated a vector series for optimized secretion/expression using recombinant antibody fragments as an example [5]. Additionally, we used these vectors for expression of bioactive human soluble amyloid precursor protein alpha (sAPPalpha) and analyzed its glycosylation pattern in cooperation with the glycoproteomics group (Dr. Daniel Kolarich). We could show for the first time that recombinantly expressed human protein in *L. tarentolae* can not only be N-glycosylated, but also O-glycosylated [6, 7]. Additionally, we have recently established a vector/strain combination, which allows the production of *in vivo* biotinylated recombinant molecules [8].

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Precision Glycopolymers



Sugar Mimetic Ligands

Sugars play an important role in various areas of science and our everyday life. They are an important energy source and thus part of our nutrition. In plants and insects, polysaccharides are used as materials e.g. to build up a chitin shell but they also play an important role in many industrial applications from detergents to paints to plastics. Another area where sugars are gaining more and more attention is medicine. Sugars play a key role in any kind of cell-cell-interaction e.g. during infection, tissue growth or cell signalling. Such interactions are most often mediated by the sugar acting as a ligand binding to a specific protein receptor. However, the specific binding of a sugar ligand to a protein receptor is not easily obtained, as the binding affinity of a sugar to a protein is usually very weak. Nature overcomes this problem by using the so-called multivalency effect where several sugar ligands bind to several receptors at the same time. While it is highly important to understand the principle of multivalency in order to learn more about the role of sugar ligands in biology and medicine, this also opens an opportunity for a new class of molecules – the sugar mimetic ligands. Through the covalent attachment of several sugar ligands to an artificial scaffold and thus their multivalent presentation, we can obtain a molecule having a much higher affinity than the single sugar ligand itself. One important class of such sugar mimetic ligands are the glycopolymers carrying multiple sugar ligands along a polymeric backbone.

Glycopolymers have a great potential for various applications in biomedicine and biotechnology e.g. as antibacterial or antiviral therapeutics due to their increased affinity and other positive attributes such as their ease of synthesis and prolonged stability. However, most glycopolymers so far are optimized empirically and little is known about what makes a glycopolymers a good sugar ligand mimetic and thus a potential candidate in biomedical applications. The major limitation is the ill-defined nature of classical synthetic polymers as they are always obtained as polydisperse samples and do not allow for a sequence control of monomers within the polymeric scaffold.

Solid Phase Polymer Synthesis

Therefore, we introduced a new approach towards monodisperse, sequence-defined glycooligo- and polymers [1]. The highly defined chemical structure of these so-called precision glycopolymers allows for detailed structure-property correlation studies. On the one hand, this will help to give new insights into the multivalent interactions of natural and sugar mimetic ligands and their role in cell-cell interactions. On the other hand, this will allow for the rational design and straightforward synthesis of novel glycopolymers for various applications especially in biomedicine and biotechnology. Our approach is based on the use of solid phase peptide synthesis [1,2]. However, instead of amino acids, we use especially designed dimer building blocks. Stepwise assembly of the building blocks on a solid support allows for the straightforward control over the monomer sequence and yields

monodisperse molecules (Fig. 1). The sugar ligands can be introduced in the same way, by covalent attachment to a functional side chain of one of the building blocks during solid phase synthesis (Fig. 1). Besides the exact control over the position of the sugar ligand on the precision glycooligomer scaffold, this also makes it possible to have the precise positioning of different sugars at different positions leading to so-called heteromultivalent glycooligomers [3].

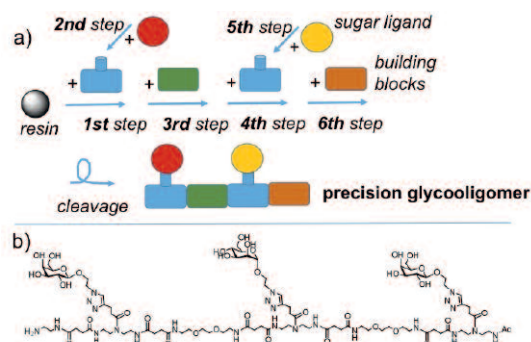


Fig. 1: a) Schematic presentation of the solid phase polymer synthesis of glycooligo-/polymers. The stepwise assembly of tailor-made building blocks on a solid support and their functionalization with sugar ligands allows for the synthesis of monodisperse sequence-controlled or so-called precision glycooligomers. b) example for a heteromultivalent glycooligomer [3].

Currently we are expanding our building block library introducing a variety of functional groups in the scaffold such as degradable moieties, switchable units [4] or charges [5]. Additionally, we can vary the architecture going from linear to branched [6] scaffolds as well as to peptidomimetic scaffolds with secondary structure motifs e.g. β -strands [7].

Fundamental Studies on Precision Glycopolymers Targeting Lectin Receptors

In order to obtain novel insights into the rational design of glycopolymers and the underlying concept of multivalency, we synthesized a series of glycooligomers varying the number, position and kind of sugar ligands as well as the chemical properties of the scaffold itself [1-3]. We have found that depending on the structure of the glycooligomer, different binding modes can be observed for sugar ligand/protein receptor complex formation (Fig. 2). Specifically, we have observed a strong influence of statistical rebinding, where a higher local density of sugar ligands leads to an increase in binding probability and thus overall binding affinity. Another important effect, so far often neglected for sugar mimetic ligands, are the steric contributions of all non-binding parts of the molecule. Non-binding parts e.g. of the scaffold or through non-binding sugar ligands attached to the scaffold can sterically shield binding pockets of the receptor and thus inhibit other ligands from binding on this site. This leads to an observed increase in binding affinity. Most of our structure-property correlation studies were performed with Concanavalin A (Fig. 2), a well-characterized lectin receptor, but we could show that these results are also transferrable to other

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2001-2004: Diplom majoring in Polymer Chemistry (Albert-Ludwigs-Universität Freiburg, Germany)

2004-2007: Doctoral Thesis: Synthesis of monodisperse, multifunctional poly(amidoamines) and their application as non-viral vectors for gene therapy (Max Planck Institute of Colloids and Interfaces, Department of Colloidal Chemistry, Golm, Germany)

2007-2009: Postdoctoral Scientist (Stanford University, Department of Chemical Engineering, Palo Alto, USA)

2009-2014: Emmy Noether research group leader (Max Planck Institute of Colloids and Interfaces, Department of Biomolecular Systems, Berlin/Golm, Germany)

2014: Habilitation in Polymer Chemistry: Precision Glycomacromolecules and Glycohydrogels: Synthesis and Applications in Biotechnology and Biomedicine. (Freie Universität Berlin, Germany)

Since 07/2014: W3-Professor for Macromolecular Chemistry (Heinrich-Heine-Universität Düsseldorf, Germany)

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lectin receptors such as PA-IL [4]. Ongoing projects further extend these systematic studies e.g. towards glycooligomers with varying architecture.

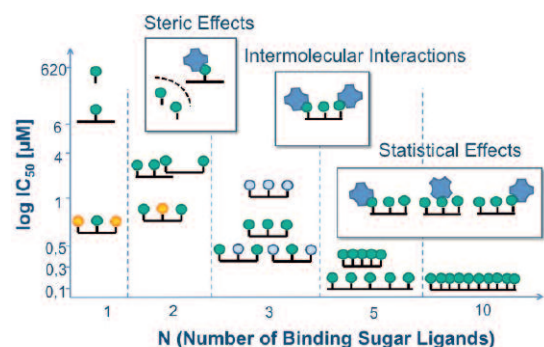


Fig. 2: Examples for different glycopolymers, their IC_{50} values and possible binding modes with ConA.

Glycopolymers in Biotechnology and Biomedicine

Especially for the transition from the fundamental studies towards the application of our precision glycooligomers in biotechnology and biomedicine, a key information is still missing. If we look at the ligand-receptor mediated contact of a bacteria and a cell, the glycooligomer has to compete with several ligand-receptor complexes at the cell-cell interface in order to inhibit the bacterial infection. However, this situation is not represented by any of the standard affinity assays mostly displaying one or both, ligand or receptor, in solution. Therefore, we developed a novel affinity assay mimicking more closely ligand-receptor complex formation between two surfaces and the inhibition of these complexes by sugar mimetic ligands [8,9].

The measuring principle is based on the adhesion and deformation of a hydrogel particle, a so-called soft colloidal probe (SCP), on a glass surface. Via reflection interference contrast microscopy (RICM), the contact area of the SCP on the surface can be detected and through a mathematical model (JKR-model) directly correlated to the adhesion energy. Here, the SCP is modified with a sugar ligand while the glass surface presents the protein receptor (Fig. 3). Through addition of increasing concentrations of an analyte in solution (e.g. a glycooligomer) and detection of the decreasing contact area, the half maximum inhibitory concentration (IC_{50} value) can be obtained. On the one hand, this set-up represents a simplistic model of cell-cell-contacts and allows for novel insights and systematic studies of ligand-receptor mediated adhesion at soft interfaces. On the other hand, this assay offers high sensitivity and specificity while using only simple and cost-efficient materials and equipment, e.g. in comparison to affinity assays based on surface plasmon resonance or isothermal calorimetry. In current projects, we therefore apply the SCP-RICM assay also to study other adhesion phenomena e.g. the self-healing of mussel-derived peptides [10].

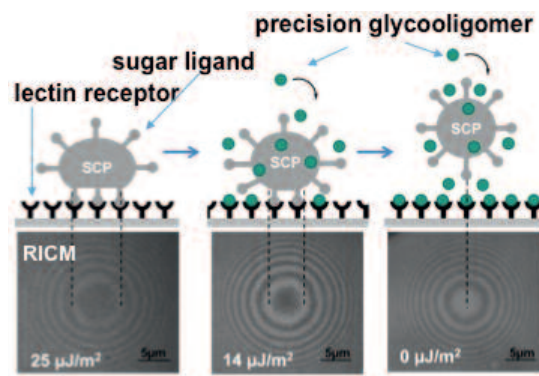


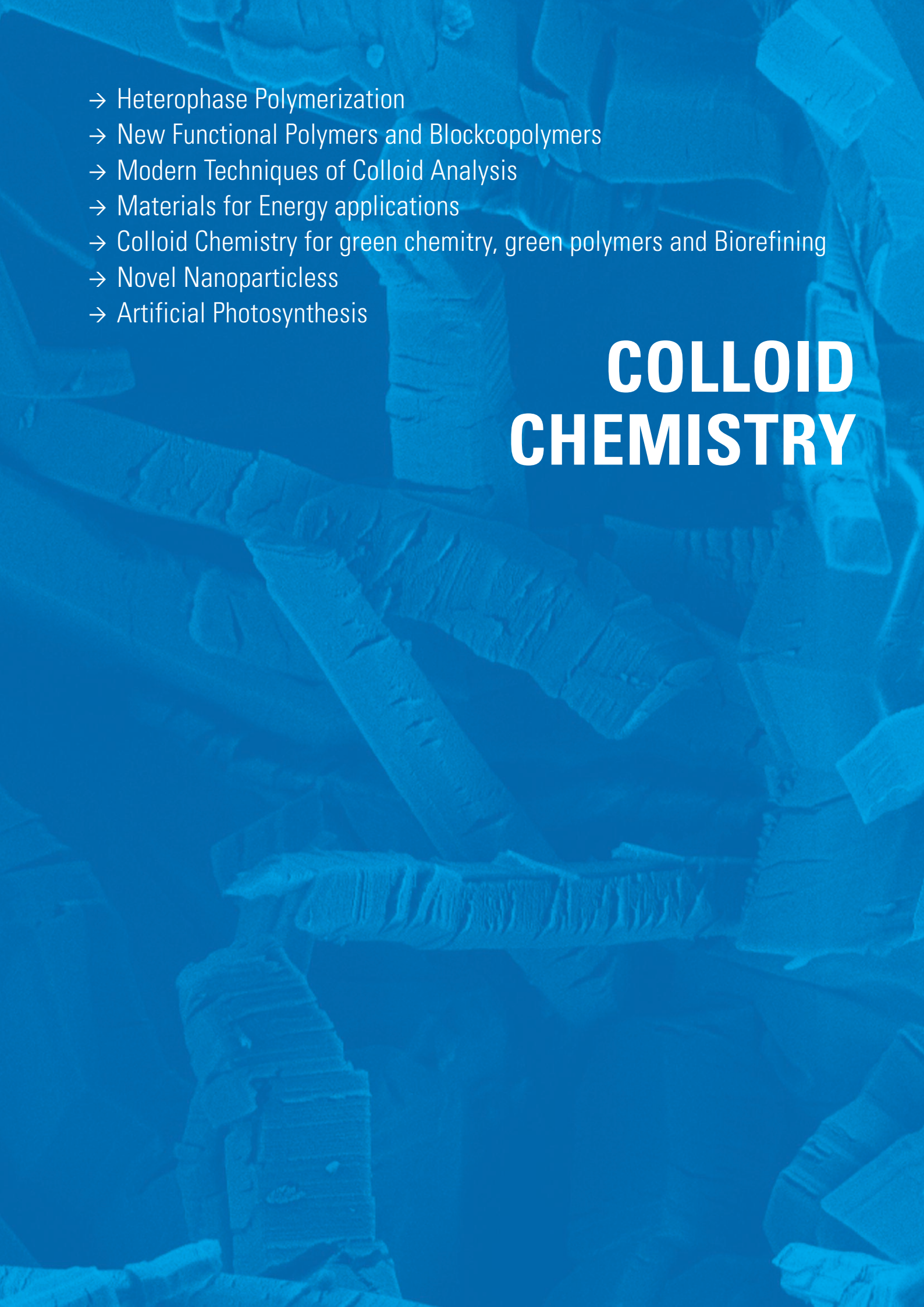
Fig. 3: Schematic presentation of the SCP-RICM assay [9].

The results obtained from the SCP-RICM assay of different precision glycooligomers, are currently compared with the inhibitory concentration of the glycooligomer ligands in bacterial growth assays. Besides their use in antibacterial therapy, glycooligomers have been applied for cell specific targeting, as multivalent scaffolds in vaccine development and are currently under investigation for their use in antiviral treatments (unpublished results).

Following the same synthetic strategies and using the results obtained from the bacterial inhibition studies, we also developed novel bacteria binding magnetic particles [11]. In contrast to the commercial system, the magnetic porous sugar-functionalized poly(ethylene glycol) particles (MAPOS) can bind more bacteria per particle and avoid non-specific interactions e.g. with serum proteins or other cells. MAPOS can therefore be used to isolate specific bacterial strains from solution e.g. in patients sample analysis.

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- Heterophase Polymerization
 - New Functional Polymers and Blockcopolymers
 - Modern Techniques of Colloid Analysis
 - Materials for Energy applications
 - Colloid Chemistry for green chemistry, green polymers and Biorefining
 - Novel Nanoparticless
 - Artificial Photosynthesis

COLLOID CHEMISTRY

Research in the Department of Colloid Chemistry



Scientific Profile

The overall size of the Department of Colloid Chemistry is currently about 70 people, 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 two periods continues to take place. Dr. Schlaad, a permanent staff member working with me for 15 years, just left for a Full Professorship of the University of Potsdam, Dr. Jens Weber got promoted to Professor and the Applied University of G rlitz-Zittau. Dr. Filipe Vilela was called for a Senior lectureship to Scotland, while Dr. Cristina Giordano is in the very last phases of completing her Habilitation.

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 report more idea that result oriented. This turnover of leading junior scientists is beyond typical and easy, but reflects the dynamic character of the department. The profile of the department has therefore continued to be reoriented, keeping only some of the old strongholds.

The following topics are currently explored within the department:

- Heterophase Polymerization
- New Functional Polymers and Blockcopolymers
- Modern Techniques of Colloid Analysis
- Materials for Energy applications
- Colloid Chemistry for green chemistry, green polymers and Biorefining
- Novel Nanoparticless
- Artificial Photosynthesis

The projects behind the headers are briefly explained below:

Heterophase Polymerization

The notation "Heterophase Polymerization" summarizes the techniques of suspension-, emulsion-, mini-, and microemulsion-polymerization as well as precipitation polymerization. Solvent is usually water, but heterophase polymerizations in inverse media are also examined. In all cases, the product is a polymer colloid or polymer nanoparticle. This class of techniques, although one of the eldest in polymer science, is still most actual, as it allows the production of high polymer containing formulations in water as an environment-friendly solvent and to address nanoparticles and nanostructures in industrial scale.

Central points of interest of the team working on heterophase polymerization are:

- Understand nucleation and particle formation for an optimal control of the particle; the experimental investigations are supplemented by theoretical and modelling descriptions (*Dr. Klaus Tauer*).
- Synthesis of complex polymer morphologies on a molecular level (synthesis of block & graft copolymers by emulsion polymerization) and on a colloidal level (core-shell latices, hollow spheres, colloidal superstructures) by a rational use of the particle interfaces and interface effects in heterophase polymerization (*Dr. Klaus Tauer*).

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1983: Diploma, Chemistry

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Thesis: Bestimmung der Diffusion von photomarkiertem Polystyrol: spezielle Systeme, chemische und physikalisch-chemische 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, G lm),

Full Professor (University of Potsdam)

New Functional Polymers and Blockcopolymers

Amphiphilic polymers consist of components which dissolve in different media, e.g. a hydrophilic and a hydrophobic part. Since we are able to adjust both components sensitively to the dispersion medium as well as to the dispersant, amphiphilic polymers allow the stabilization of unusual dispersion problems. 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 micelle 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*).
- Oligophenols are omnipresent in Nature, but less well used and examined in synthetic polymer chemistry. As polyphenols are strongly interacting with each other, with metals and with surfaces, we expect to discover "the fourth code" of polymeric secondary structure formation (*Dr. Bernhard Schmidt*).
- Polymer ionic liquids represent highly polarizable surfactants which enable to solve very complicated dispersion problems, e.g. nanocarbons in water. The synthesis and self-organization of those PILs is systematically explored (*Dr. Jiayin Yuan*).

Modern Techniques of Colloid Analysis

All the work described above 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 include:

- Special techniques of transmission and scanning electron microscopy on soft, structured matter which are run at the base of a central service group (*Dr. Jürgen Hartmann*).

Materials for Energy Applications

Following the project house ENERCHEM which has run out, our department continues to take a leading role in the field of energy materials. This was also appreciated by the creation of the MaxNet, which has started in 2014 and hosts some of the activities described below. Hydrogen storage, better fuel cells, new energy cycles, new catalysts for more efficient processes, methane activation, better batteries, ultra capacitors, remote energy storage, lightweight solar cells, all these topics are intimately connected with the control and design of materials nanostructure. Activities based in Golm include:

- New C/N-polymers and carbon materials to expand the property profile of carbon. Use of such materials as an electrode and electrocatalyst, both in batteries (metal/air, metal/sulfur) and in fuel cells. (*Dr. Tim Fellingner*).
- Metal free catalysis and photocatalysis with porous organic semiconductors: Novel synthesis schemes towards carbon nitrides (*Dr. Darya Dontsova*).
- Use of CN-materials for electrochemistry and photoelectrochemistry. Generation of new materials hybrid systems based on Ni and metalnitrides/metallcarbodiimides for hydrogen and oxygen generation (*Dr. Menny Shalom*).
- Superhigh surface area carbons and their use for supercapacitors, in-situ analysis of the charge storing process. Salt melt carbon synthesis and supramolecular approaches towards C₂N (*Dr. Nina Fechner*).

Colloid Chemistry for Green Chemistry, Green Polymers and Biorefining

Advanced materials chemistry is still mostly based on non-sustainable resources, leading to the so-called “element crisis”, e.g. the global depletion of Co, Ni, Ta, or In. 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 ERC Advanced Grant but now have reached practical maturity. This project platform includes

- Valorization of lignin via reductive hydrothermal splitting (a joint Max Planck-Fraunhofer project, *Dr. Davide Esposito* together with *Dr. Thomas Aicher/FHG*)
- Conversion of carbohydrates into lactic acid and other platform chemicals (*Dr. Davide Esposito*)
- Next Generation Green Polymers based on sustainable monomers (*Dr. Davide Esposito, Markus Antonietti, Dr. Bernhard Schmidt*)

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

De Novo Nanoparticles

Many materials, which are relevant for novel energy cycles and more efficient chemical reactions (catalysis) are not available as nanostructures (or their synthesis is not sustainable) so that “de novo” systems have to be designed from scratch.

- We develop new synthetic pathways towards special lead-based perovskite nanostructures for photovoltaics. (*Dr. Menny Shalom*)
- New cathode nanomaterials for the lithium battery are another target for novel nanostructures where progress will directly impact society (*Dr. Tim Fellingner*)
- Synthesis in interacting but not reactive salt melts is another way to unusual nanostructures (*Dr. Nina Fechner*)

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 (Prof. Xianzhi Fu). The lab is now lead by Dr. Xinchun 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.

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. Darya Dontsova*).
- Novel nanoparticles act as co-catalysts for both water oxidation and reduction to replace the non-sustainable Pt and Ru currently used. Functional carbon nanodots and carbon hybrids seem to be unexpected promising choices (*Dr. Darya Dontsova, Dr. Menny Shalom, Dr. Tim Fellingner*).

*Visions and Future Perspectives in the
Director's Perspective for the Next Years*

After losing most of my more senior scientists for independent careers, I used the opportunity for a redefinition and reorientation of the department. We completed the restructuring to enter a period with more coordinated research and longer term goals focused around the director and more tightly bound junior people. These people have already started (Dr. Feller, Dr. Esposito, Dr. Shalom, Dr. Fechner and Dr. Dontsova, in 2015: Dr. Schmidt) and are currently setting their corresponding profiles.

Our trials to cooperate with the National Excellence Centre on Catalysis of the TU Berlin are to my opinion in full bloom, concerning the development of new catalytic materials and Solar Energy Usage Cascades (together with TU Inorganic Chemistry, 2 joint BMBF projects are now completed). 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. We are also progressing with our activities to strengthen work projects between the departments, among them a "glycomaterials" project together with the Seeberger and the Fratzl department. Other potential projects which awaiting appropriate junior staff scientists are "gradient materials" and "soil colloids".

Markus Antonietti
Director of the Department
of Colloid Chemistry

Langmuir Monolayers as Model Systems in Biophysics, Colloid and Material Science



Monomolecular films at the air/water interface are interesting model systems in biophysics, colloid and material science [1]. But the early work with amphiphile monolayers was largely hampered by the absence of tools to investigate liquid interfaces with molecular and microscopic resolution [2, 3].

Meanwhile, many highly surface sensitive techniques can be applied to study interactions of dissolved biomolecules (DNA [4, 5], peptides [6, 7], enzymes) or nanoparticles with model membranes to contribute to a better understanding of structure-function relationships. Additionally, the structures of thin layers of peptides confined to the soft air/liquid interface have been investigated and compared with structures obtained in bulk. Exciting and unprecedented results have been obtained by discovering a highly-ordered two-dimensional structure of glycolipid monolayers. Using a novel hexayne amphiphile as a reactive, carbon-rich sibling of typical fatty acid ester amphiphiles that formed well-ordered self-assembled monolayers at the air-water interface, self-supporting sp²-rich carbon nanosheets have been prepared at room temperature. In this report, the main results of our work concerning peptidomimetics [8, 9], glycosylphosphatidylinositols [10, 11], and carbon nanosheets [12] will be described.

Selected Achievements

Precision Polymerfoldamers as Peptidomimetics

β^{3R6} -peptides (in cooperation with L. Hartmann, Department of Biomolecular Systems) have been studied in 2D and 3D in order to investigate their folding and aggregation behavior. Stable films of specifically designed oligomers can be formed on a buffer solution. All oligomers investigated contain a high amount of β -sheet-like structures, as seen by bands in the Amide I region between 1625 and 1645 cm⁻¹.

Two representative oligomers were selected for GIXD experiments as they form strands which do and do not aggregate, respectively. The short oligomer **7** exhibits Bragg peaks in the wide- as well as in the small-angle regions (Fig. 1). The weak Bragg peak at 1.327 Å⁻¹ (Fig. 1e) corresponds to the interstrand distance of 4.735 Å defined by the hydrogen bonds in crystalline β -sheets (proved by IRRAS experiments showing a band at 1635 cm⁻¹). The other oligomer (**11**) does not show the characteristic Bragg peak in this region in good agreement with IRRAS data showing the amide I band only at a high wavenumber of 1641 cm⁻¹. This non-aggregated strand structure is characterized by the lack of long-range correlation between the strands. Additionally, both layers exhibit two-dimensional smectic order (Bragg peaks in the small-angle region). The higher longitudinal order of oligomer **11** can be attributed to electrostatic repulsion, since both ends are positively charged in contrast to oligomer **7**. The determined long repeat distances are shorter than expected for elongated strands.

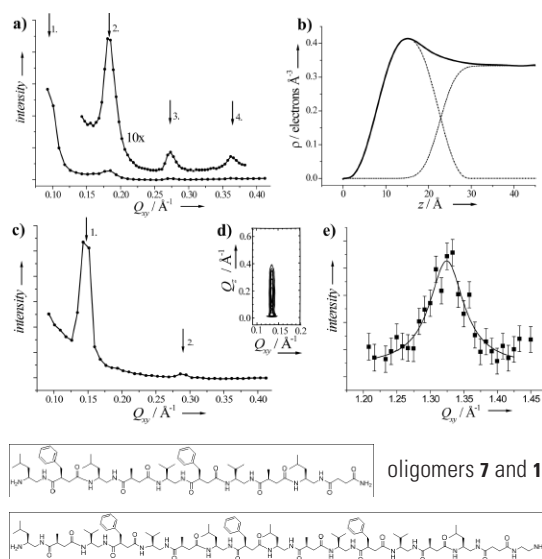


Fig. 1: a) Corrected X-ray intensities versus the in-plane scattering vector component Q_{xy} for **11**. b) Electron density profile $\rho(z)$ of **11** versus the vertical z coordinate. c) Corrected X-ray intensities versus the in-plane scattering vector component Q_{xy} for **7**. d) Contour plot of the corrected X-ray intensities as a function of in-plane (Q_{xy}) and out-of-plane (Q_z) scattering vector components of **7**. e) Corrected X-ray intensities versus the in-plane scattering vector component Q_{xy} for **7**. Note that the intensity of this Bragg peak is extremely small (large error bars). All experiments have been performed at the air/water interface at 20 °C and 20 mN/m.

Subgel Phase Structure in Monolayers of Glycosylphosphatidylinositol Glycolipids

Glycosylphosphatidylinositols (GPIs), natural complex glycolipids essential for a range of biological functions, are poorly understood with regard to their interactions and arrangements in cellular membranes. To evaluate the role of the head group in the 2D structure formation three GPI-fragments (Fig. 2A) bearing the same hydrophobic part but different head groups have been investigated (in cooperation with D. Varón Silva and P.H. Seeberger, Department of Biomolecular Systems). Condensed monolayers of simple GPI fragments are defined only by ordered alkyl chains. The monolayers of more complex fragments are additionally characterized by highly ordered head groups (Fig. 2B). Due to the strong H-bond network formed by the head groups, GPI-fragment **3** both segregates and induces order in a model membrane phospholipid (POPC) that mimics the liquid-disordered phase of cell membranes. We have shown that the strong van der Waals interactions between hydrophobic chains overcome the head group interactions and dominate the structure formation in mixtures of GPI-fragment **3** with lipids **1** and **2** that form condensed phases. This behaviour can be linked to the GPIs affinity for lipid rafts.

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Thesis: The parametric pump – a physical-chemical model of the active transport of ions in cells

1981: PhD, Physical Chemistry (Martin Luther University of Halle/S.)

Thesis: Einfluss der chemischen Struktur auf das thermische Phasen- und Mischungsverhalten binärer und ternärer Phospholipid-Wasser-Systeme

1987: Habilitation, Colloid Chemistry (Martin Luther University of Halle/S.)

Thesis: Untersuchungen zum Phasen- und Mischungsverhalten ausgewählter Phospholipid-Wasser-Systeme

1981-1982: Postdoc

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1982-1992: Research Scientist (Institute of Physical Chemistry, University of Halle/S.)

1992-1995: Research Scientist (Institute of Physical Chemistry, University of Mainz)

Since 1995: Group Leader (Max Planck Institute of Colloids and Interfaces, Potsdam)

Since 2009: apl. Professor, Physical Chemistry (University Potsdam)

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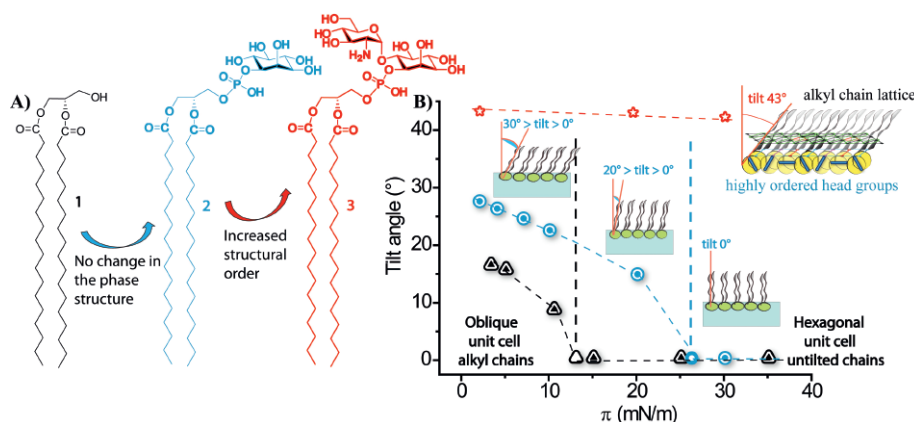


Fig. 2: A) Chemical structures of the three investigated GPI-fragments B) Comparative representation of the monolayer structural changes of the three GPI-fragments depicted by the variation of the tilt angle of the alkyl chains (t) with the lateral surface pressure (p) on PBS at 20 °C.

Functional Carbon Nanosheets

Carbon nanostructures including two-dimensionally extended nanosheets are promising components for technological applications, such as high performance composites, lithium storage, fuel cell technology, photovoltaics, or nanoelectronics. Chemical surface functionalization would render such structures better processable and more useful for tailored applications but is precluded by their thermolytic preparation. In cooperation with the group of H. Frauenrath (Ecole Polytechnique Fédérale de Lausanne, EPFL), a novel approach for the preparation of thin, two-dimensional carbon nanostructures with extended lateral dimensions based on the self-assembly and subsequent carbonization of a carbon-rich hexayne amphiphile at the air-water interface has been developed. The amphiphiles self-assembled into ordered monolayers which have been characterized by different experimental methods. The molecules form a distorted hexagonal 2D lattice ($a = 5.20 \text{ \AA}$, $b = 6.25 \text{ \AA}$, $c = 6.29 \text{ \AA}$ with spacings determined by the size of the hydrated polar head group. The hexayne

and dodecyl segments are closely packed and display tilt angles of 62.5° and 35.0° relative to the layer normal, respectively, resulting in an overall layer thickness of 2.6 nm. A detailed molecular model of the internal structure proved that the hexayne moieties were densely packed at π - π stacking distance, suitable for carbonization (carbon-carbon short contacts of 3.42–3.53 Å between acetylene carbons C1–C9 and C4'–C12' (along the a axis) and 3.60–3.78 Å between acetylene carbons C3–C8 and C7'–C12' (along the b axis) of neighboring molecules). The very tight packing of the hexayne segments within this less than 7 Å thick 'carbon precursor' sublayer was suitable for quantitative carbonization upon UV irradiation at room temperature (Fig. 3), producing sp^2 -rich carbon nanosheets with a microstructure that resembled 'amorphous carbon' materials typically obtained after annealing at temperatures of 800–1000 °C. Mechanically stable and rigid carbon films with a molecularly defined thickness of 1.9 nm and lateral dimensions on the order of centimeters have been produced. These thin carbon nanosheets with their hydrophilic surface functionalization proved to be useful as low background contrast substrates for high resolution TEM imaging of specimen deposited from aqueous media.

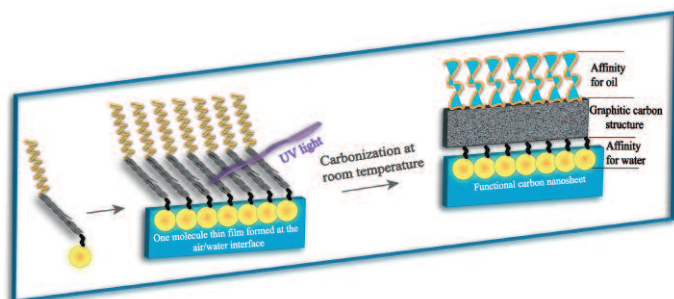


Fig. 3: The hexayne amphiphile was spread from a dilute chloroform solution onto the surface of Millipore water in a Langmuir trough. Compression leads to a stable and tightly packed layer composed of essentially three segments: the hydrophobic dodecyl chain, the carbon-rich hexayne sublayer and the polar head group. Mild carbonization by UV irradiation at room temperature resulted in quantitative carbonization of the oligoynes within minutes. The self-supporting carbon nanosheets with macroscopic lateral dimensions exhibited a molecularly defined thickness of 1.9 nm and an 'amorphous carbon' microstructure.

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Novel Approaches to Carbon Nitrides – Photocatalysts for Water Splitting



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Photocatalytic water splitting is an inexhaustible potential source of hydrogen which is the friendliest fuel to the environment. Hydrogen has the largest energy density and has recently emerged as a highly attractive alternative to depleting and expensive fossil fuels. However, photocatalytic water splitting requires large amount of input energy, and is still incompatible with existing energy generation technologies. Most of photocatalysts used for photocatalytic water reduction have disadvantages of absorbing only UV-light (e.g. TiO_2) which is only the minor fraction of solar light or suffer from photocorrosion. Graphitic carbon nitride based materials (having stoichiometry close to C_3N_4) represent a class of metal-free organic polymeric semiconductors that absorb the high energy part of visible light, and are typically prepared by thermal condensation of nitrogen-rich precursors, such as melamine, urea, cyanamide or dicyandiamide. However, products of bulk synthesis are characterized by low surface areas ($1\text{--}10\text{ m}^2/\text{g}$) and poor separation of photogenerated charge-carriers that leads to low reaction rates and quantum yields. Silica templates were previously used to prepare C_3N_4 with high ($\sim 200\text{ m}^2/\text{g}$) surface areas, but these had to be removed using toxic HF sources.

Our group works on 1) development of alternative safe methods to obtain C_3N_4 with high surface areas, 2) improvement of charge-separation in C_3N_4 by tailoring its chemical structure or creating an efficient semiconductor heterojunction, and 3) elaboration of new synthesis strategies to C_3N_4 .

Salt – Melt Assisted Synthesis

Running polymerization reactions in a suitable solvent may provide control over morphology, crystallinity and surface areas of the resulting polymers. Molten salts can potentially serve as high temperature solvents for condensation of C_3N_4 precursors if they have a suitable melting point, which is close to the onset of the first condensation step, and are dissolving C_3N_4 precursors and further reaction intermediates. Known examples are LiX/KX ($\text{X} = \text{Cl}, \text{Br}$) eutectics which are used to prepare crystalline poly(triazine imides)/ LiX (PTI/ LiX). We obtained different functional C_3N_4 -related composites by performing the condensation in eutectics containing divalent metal chlorides as a main component. Selection of metal (M^{2+}) influences the strength of the corresponding Lewis acid, MCl_2 ($\text{M} = \text{Zn}^{2+}, \text{Sn}^{2+}, \text{Co}^{2+}$), and in this way defines the interaction between the salts and precursors.

Condensation of melamine in **ZnCl_2 -containing eutectics** gives rise to novel PTI-based composites with the improved absorption in visible light range due to the formation of dyadic system between C_3N_4 and ZnO clusters or other Zn^{2+} containing species. Unlike LiX/KX ($\text{X} = \text{Cl}, \text{Br}$), ZnCl_2 being a *strong Lewis acid* plays a role of the reactive solvent during the synthesis, and binds strongly to the condensation intermediates. Adjustment of precursor concentration and a proper selection of the alkali metal chloride constituent of MCl/ZnCl_2 melt give a possibility to change the on-set of

phase demixing, tune the interactions strength between the condensation intermediates and the solvent and vary the solubility of the intermediates in the melt. Overall, one can direct the reaction from zinc cyanamide to both crystalline poly(triazine imides) or amorphous MOF-like hybrid materials (**Fig. 1**). The latter have surface areas up to $700\text{ m}^2/\text{g}$ and turned out to be interesting as highly performing CO_2 adsorbents [1]

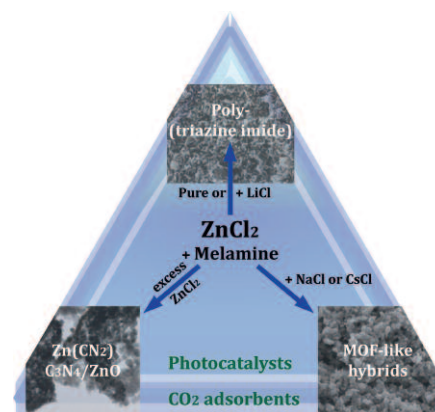


Fig. 1: Schematic illustration of possibilities provided by use of ZnCl_2 -eutectics for C_3N_4 synthesis.

SnO_2 /carbon nitride photocatalysts with surface areas up to $300\text{ m}^2/\text{g}$ were prepared by condensation of dicyandiamide in alkali metal chloride/ **SnCl_2 -containing salt melts** at $550\text{ }^\circ\text{C}$, without the use of hard templates. XPS, XRD and HR-TEM investigations showed that the obtained materials are composed of $5\text{--}10\text{ nm}$ SnO_2 nanoparticles deposited onto nanosheets set up from Sn-intercalated 1D-melon ribbons (**Fig. 2**). $\text{SnO}_2/\text{C}_3\text{N}_4$ composites are found to be highly efficient in the photocatalytic reactions, as exemplified by Rhodamine B degradation and water reduction (Pt is used as a co-catalyst). Under optimized synthesis conditions, these composites achieve hydrogen evolution rates more than two times higher than mesoporous graphitic carbon nitride (mpg- C_3N_4 , s. a. $\sim 200\text{ m}^2/\text{g}$) under visible light irradiation. In principle, this new method based on utilization of MCl/SnCl_2 salt melts as a reaction medium allows carrying out various polymerization reactions in the presence of the *mild Lewis acid* in the solution phase in a wide temperature range of $180\text{--}550\text{ }^\circ\text{C}$. Moreover, SnCl_2 eutectics are even suitable for post-synthesis modification of bulk carbon nitride to retaylor its morphology and greatly increase the surface area and photocatalytic activity [2].

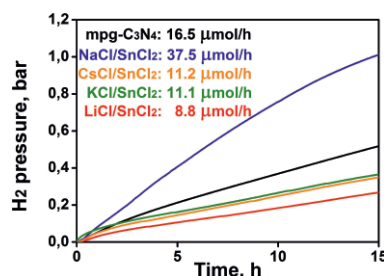
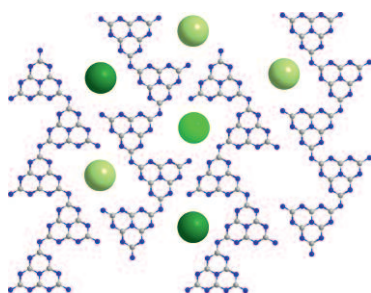


Fig. 2: Suggested structure of C_3N_4 prepared in $SnCl_2$ -salt melts (left); photocatalytic water reduction rates using SnO_2/C_3N_4 composites (right). Blue, grey and green spheres correspond to N, C and Sn atoms, respectively.

On its turn, eutectics containing $CoCl_2$, a weak Lewis acid, can serve as a reaction medium in single-step preparation of $Co(II, III)$ oxide/ C_3N_4 photocatalysts that show water oxidation efficiencies comparable to those of Co_3O_4 NP/ C_3N_4 composites prepared in 3 steps (Fig. 3). The chemical structure of C_3N_4 counterpart of composite can be conveniently adjusted by selection of second component of the salt melt, and alkali metal chlorides and $ZnCl_2$ give rise to PTI, while $SnCl_2$ results in melon polymers.

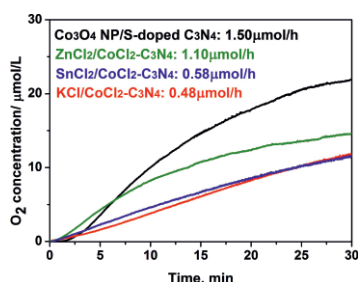


Fig. 3: Photocatalytic water oxidation by $CoOx/C_3N_4$ photocatalysts prepared in $CoCl_2$ -containing salt melts.

Complex-Templating Method

Complex templating method combines the advantages of hard template method and phenomenon of supramolecular complex formation between molecules with complementary hydrogen bonding. Here, $Al(NO_3)_3 \cdot 9H_2O$ was successfully used as a "green template" and a hydrogen-bonding partner of melamine simultaneously providing a distinct porosity and defined particle morphology to the resulting carbon nitrides. Surface areas of final products (up to $90 \text{ m}^2/\text{g}$) are several times lower than those provided by SiO_2 templates, still, the benefits of $Al(NO_3)_3 \cdot 9H_2O$ are low cost and easy removal of its decomposition products after the synthesis. The developed synthesis procedure resulted in up to 20 times increase of the photocatalytic activity in comparison to the reference graphitic carbon nitride. The factors responsible for such a high activity are increased surface area and pore volume, as well as improved charge separation achieved by smaller grain size of photocatalysts and in-situ created heterojunction between melamine- and complex-derived carbon nitride phases.

1,2,4-Triazoles as New C_3N_4 Precursors

We found that the pyrolysis of electron-rich, but hydrogen poor precursors, 3,5-diamino-1,2,4-triazole and 3-amino-1,2,4-triazole-5-thiol, in bulk and in $LiCl/KCl$ salt melt leads to the formation of carbon nitride materials with distinct linear, partially negatively charged, melon structure resembling the structure of emeraldine salts of polyaniline (Fig. 4) [3]. The acidic character of the precursor expressed as an ability to undergo the replacement of imine-nitrogen with alkali metal is partially preserved by the final carbon nitride structures giving rise to the improved optical absorption and emission properties. This also comes with different electronic and crystalline structures when compared to all previously reported carbon nitride materials. All of the products are thermodynamically able to reduce water, and photocatalysts prepared from 3-amino-1,2,4-triazole-5-thiol in $LiCl/KCl$ are 1.2 – 1.8 times more active than mpg- C_3N_4 in HER upon visible light irradiation. Such a high activity in spite of modest ($30 \text{ m}^2/\text{g}$ – $100 \text{ m}^2/\text{g}$) surface area of catalysts is attributed to the improved conductivity within the material and the resulting efficient charge separation of the photo-generated charge carriers.

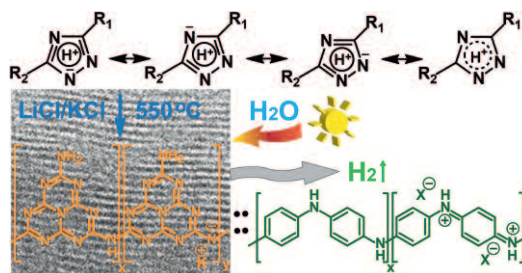


Fig. 4: Schematic illustration of preparation and photocatalytic properties of charged poly(heptazine imides) from substituted 1,2,4-triazoles.

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BIOMASS CONVERSION INTO BUILDING BLOCKS FOR COLLOIDS

Biorefinery and Sustainable Chemistry



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Modern society is still heavily dependent on fossil resources for the generation of fuels, chemicals and pharmaceuticals. Unfortunately the last decades have witnessed a constant depletion of traditional fossil resources and in addition the global use of non-renewable resources has been responsible for a constant increase in environmental pollution. In this scenario, modern society is facing the challenge to provide solutions for a sustainable and environmental friendly development. In the last decades, the scientific community has identified biomass and food waste as promising feedstocks for the generation of fuels and commodity chemicals. The valorization of renewable feedstocks in a biorefinery is analogous to that of classical refineries, which convert fossil resources (oil) into higher value products (fuels and chemicals). To date, examples of biorefineries for the production of energy (by thermal methods), or fuels (by biotechnological approaches) have appeared. Nevertheless, the selective generation of fine and platform chemicals from biomass using chemical strategies is still in its infancy, and its success will strongly depend on the development of efficient catalytic methodologies. The main objective of our group is the development of successful strategies for the upgrade of biomass into an array of valuable chemical for the generation of polymers and colloids. We are currently articulating our research around three major themes (**Fig. 1**): 1) the development of hydrothermal methods for biomass deconstruction, which enable the conversion of polysaccharides and lignin into an array of useful building blocks and platform chemicals; 2) the development of novel colloidal sustainable catalysts, to be evaluated during the catalytic upgrade of biomass derived substrates; 3) the synthesis of value-added products on the basis of sustainable building blocks that can be produced as the output of biorefinery conversion schemes.

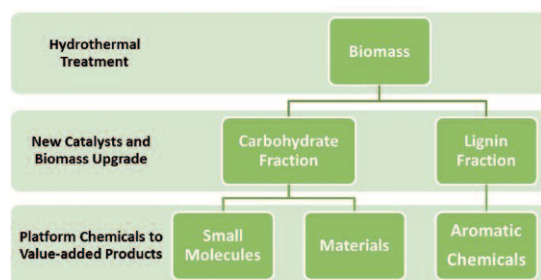


Fig. 1: Schematic Biorefinery

Hydrothermal Deconstruction of Biomass

Lignocellulosic materials are rather heterogeneous in nature and are mostly composed of polysaccharides, usually accounting for 60–80% of the weight, and lignin (15–30%). The entry step in a biomass conversion scheme should enable the separation of the carbohydrate portion of the biomass from the lignin one. In this regard, organosolv methods, which consist in the treatment of biomass with organic solvents at elevated temperatures, have found broad application. Nevertheless, this approach has been aimed at the sole isolation of the lignin fraction. In order to improve the efficiency of these kind of treatments, we designed a new methodology that allow for the simultaneous isolation of an upgraded polysaccharide fraction (**Fig 2**). We identified conditions for the alkaline hydrothermal treatment of sugars and biomass which are highly selective for the formation of lactic acid, a very important platform chemical for the preparation of biodegradable plastics [1]. This strategy has proven successful when applied to the conversion of raw biomass on a 40 grams scale. During the treatment of raw biomass, in addition to lactic acid, lignin could be isolated together with other organic acids, suggesting the possible use of this convenient method as entry point for new biorefinery schemes.



Fig. 2: A schematic representation of the hydrothermal deconstruction of biomass used to separate upgraded carbohydrate and lignin fractions ready for further processing or applications.

Besides alkaline treatments, complementary acidic hydrothermal methods, which usually results in the formation of C5 scaffolds, are also being explored. For instance, we optimized a method for the conversion of cellulose into levulinic acid, a very versatile platform chemical, which was subsequently hydrogenated with Raney-Nickel to afford γ -valerolactone, a green solvent with excellent properties as fuel additive [2]. The functionalization of γ -valerolactone via α -methylenation has further being pursued, in order to obtain a monomer suitable for radical or emulsion polymerization. The preparation of latex particles on the basis of such monomer are currently investigated in collaboration with the group of Dr. Tauer (Colloid Chemistry), and will showcase an integrated refinery scheme capable of converting lignocellulosic feedstock into added-value nanomaterials.

Catalysts Development

Many of the primary products of the hydrothermal treatments of biomass can be conveniently upgraded into different platform chemicals by straightforward catalytic transformations. Unfortunately, many of these processes are catalyzed by expensive and rare elements belonging to the platinum-group metals. In addition, supported catalysts are often accessed via time-consuming synthetic procedures, besides being subjected to leaching and passivation when in contact with real biomass hydrolysates. The use of inexpensive and abundant elements, for example iron and nickel, for the synthesis of heterogeneous catalysts on the basis of simple protocols can positively influence the production of sustainable chemicals from biomass. In this context, carbon supported metals have been successfully applied as catalysts in the field of hydrogenolysis and hydrogenation. With this in mind, carbon supported Ni-Fe alloys were prepared by simple impregnation of cellulose from biomass followed by carbothermal reduction [3]. This form of reductive treatment has proven ideal to generate carbon encapsulated nanoparticle as catalyst for the hydrogenolysis of biomass molecules, which are characterized by superior stability compared to the non-encapsulated commercial analogs. As an alternative approach, we are exploring the design and preparation of heterogeneous catalysts with precise tuning of the structure at the nanometer scale. We rely on the use of nitrides of non-rare metals. The hybridization of such materials with metal nanoparticles results in a completely new family of composites in which the activity of the metal is modulated by the electronic properties of the nitride support. For instance, we have recently showed how titanium nitride obtained as colloidal dispersion on amorphous or graphitic carbon can be efficiently used as support or promoter [4]. In fact, the carbon matrix of this compound was successively doped with nickel nanoparticles to obtain composites with a high reactivity for the hydrogenolysis of aryl ethers and lignin fragments.

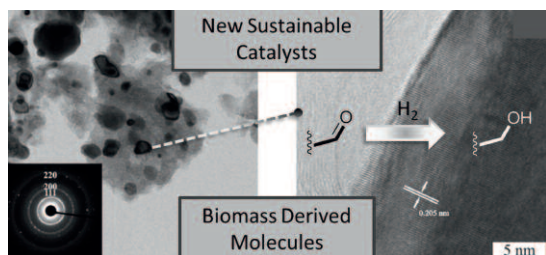


Fig. 3: Design of sustainable catalysts for the reductive upgrade of biomass molecules

New Value-Added Sustainable Chemicals

On the basis of the pool of molecules which can be obtained via biomass deconstruction, we design green strategies for the synthesis of sustainable building blocks and platform chemicals that find application in polymer and material sciences. One of our first goals in this direction was the development of green synthetic methods to access sustainable ionic liquids and imidazolium ions.



Fig. 3: New Value-added chemicals from biomass molecules

During the synthesis of lactic acid, pyruvaldehyde was identified as a valuable sustainable synthon [1]. We further exploited it to synthesize a library of disubstituted imidazolium ions in combination with natural amino acids by using a green modification of the Debus-Radziszewski synthesis [5]. The obtained compounds have proven as versatile building blocks for the preparations of task specific ionic liquids by simple acidification. Due to their functionalities, these compounds can find application in different areas, including the synthesis of poly(ionic-liquids) that we are exploring in collaboration with the group of Dr. Yuan (Colloid Chemistry). Additional studies on the reactivity of the bio-derived imidazolium ions are being conducted. As an example, we performed the hydrothermal decarboxylation of representative building blocks, which showed a great potential for the generation of a new family of ionic liquids exclusively derived from renewable precursors. Some of the so prepared ionic liquids have been exploited as reaction media for cross coupling reactions as well as cellulose and biomass dissolution [6, 7, 8].

Interestingly, imidazolium ions are common precursor of N-heterocyclic carbenes. On the basis of the substitution patterns derived from aminoacids, we are evaluating the possible use of the bio-derived imidazolium compounds as chelating N-heterocyclic carbenes for the generation of stable organometallic complexes. Alternatively, such compounds can be immobilized on solid supports and porous silicates to obtain heterogeneous-like ligands for different applications. Immobilization studies are being conducted in collaboration with the group of Prof. Hesemann (Université de Montpellier 2).

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RESEARCH COORDINATOR

Functional Carbon and Inorganic Materials via self-assembly



Scientific questions have become very complex mostly requiring close co-working of disciplines, research institutions and industry. However, such structures demand for careful communication and organization. Here, my task is built on our opinion that it is time for rethinking common ways of practice and the believe that affiliation to both science and communications infrastructure is essential.

Therefore, I decided to take the venture on this still emergent career path and operate as Research Coordinator employed by the MAXNET Energy.

Duties include the coordination of (internal) projects with the other partners of MAXNET Energy. Furthermore, in order to understand the needs and to stay active in the communication stream, I also work on my own research topics together with my small group, often in close collaboration with (international) partner institutions. This allows me to develop also my scientific profile which is also a prerequisite for an effective coordination of research.

A) Activities as a Research Coordinator

The MAXNET Energy pools knowledge and activities of eight different MPIs and tries to establish accelerated progress in the field of sustainable materials for energy conversion, more specifically with water splitting as main focus. Within these activities, I'm responsible for the communication and matching of projects between the partners and within our department. In addition my group is actively participating in the projects which deal with the fabrication and investigation of carbons as catalyst support and as thermoelectric materials, respectively.

Along another path, we strive to link the binary program between the University of California Santa Barbara (UCSB), USA and the MPG also to the MPI of Colloids and Interfaces eventually establishing our institute as one of the main partners. Here my group is synergistically working together with the chemical engineering department at UCSB with the goal to investigate carbons and occurring respective (surface)processes during energy storage using solid state nuclear magnet resonance (NMR) spectroscopy. In this regard the design of suitable carbon materials is crucial and we developed a supramolecular approach towards highly nitrogen containing carbons with the possibility for ^{13}C - and ^{15}N -isotope labelling. This eventually makes the investigation of these commonly hardly detectable materials possible.

Within the so-called "111-project", I coordinate scientific operations between the Institute of Chemistry of the Chinese Academy of Science, China and the MPI of Colloids and Interface. Here, projects are very diversified, yet all have in common the integral aspect of surface phenomena. One of the first started projects concentrate on photo-switchable nitrogen-containing carbon materials (hydrophilic-hydrophobic) for controlled electrostriction.

Upcoming duties will include the coordination of novel European training networks (ITNs) as well as a potential bigger industrial cooperation within the concepts of biorefinery.

B) Activities as Research Team Leader

My group aims to make use of rational and simple synthesis schemes towards functional porous materials. So far, especially salts turned out to be highly versatile alternatives for the generation of nanoporous structures. In this report, the examples of carbons, carbon composites and oxides will be shown.

A second way I intend to follow is the supramolecular approach where we currently make use of preorganization schemes mediated through strong but non-covalent and thus reversible interactions. Recent activities include the use of well-chosen precursors to generate pre-defined, more ordered and nanostructured carbons, metal coordination to design crystalline phenolic materials and new approaches towards the utilization of natural building blocks for the generation of porous materials with high degree of chemical surface functionality.

As my group just started recently, this report is more a description of future concepts while I can only present the most important results for the salt templating approach.

Nanoporous Carbons

Functional carbons and composites became recently some of the most useful and versatile materials as they possess a variety of important and adjustable properties while costs are rather low. The final materials properties can be influenced, besides others, on the molecular as well as morphological level and incorporation of heteroatoms such as nitrogen into the carbon lattice, metals or porosity turned out to be highly powerful. Here, not only the chemical but also physical properties can be altered e.g. electronic conductivity and (oxidation) stability eventually leading to increased (electro)catalytic activity. Until today the fundamental principles for these phenomena are still not clear, yet the interplay of electronic states, heteroatom incorporation and morphology are suspected to play key roles.[6]

Eventually, the development of more efficient and sustainable synthesis approaches for nanoporous materials is highly demanding.[5] However, besides the quest for convenient precursors, hard templating or activation processes still have to be applied. Major drawbacks are the use of hazardous chemicals for the template removal and multiple, rather energy consuming synthesis steps. In order to circumvent this, we invented a new tool called „salt templating“ allowing for the synthesis of a variety of porous material classes, e.g. functional carbons, carbon-based composites and oxides. [7, 3] The general concept is based on crosslinking of a precursor in the presence of a molten salt phase which simultaneously acts as solvent and template. This unique synthesis gives access to a wide variety of compositions, morphologies and porosities where the appropriate choice of salts controls the pore size, architecture on the nanoscale and particle size. The pore size can correspond to ion pairs, ion pair clusters and their geometric percolation structures (Fig. 1).

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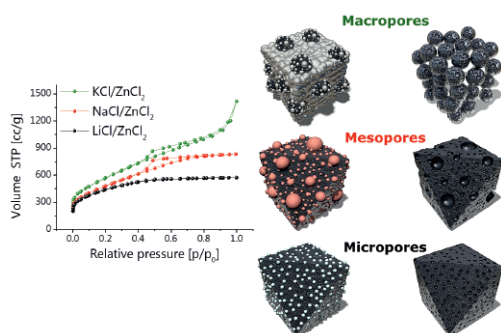


Fig. 1: Left: nitrogen sorption isotherms of carbons prepared with the same precursor but different template salts, (surface areas $2000 \text{ m}^2 \text{ g}^{-1}$; right: illustration of the different demixing processes during the synthesis leading to micropores (bottom), mesopores (middle) and porous spheres & macropores (top).

Contrary to current methods, it is possible to proceed in a single-step synthesis, while the porogen can easily be removed with water and in principal recovered afterwards for further use. Additionally, we were able to show that the final materials are, besides others, very suitable for energy storage and conversion.[1, 2]

Nanoporous Composites

Exemplarily shown for (but not restricted to) ionic liquids (IL) as precursors, the IL constitutes the nitrogen-doped carbon matrix and also acts as nitrogen source, here for metal nitride formation. After aqueous removal of the salt phase, e.g. vanadium nitride nanoparticles embedded in a nitrogen-doped carbon matrix with surface areas of up to $2400 \text{ m}^2 \text{ g}^{-1}$, are obtained (Fig. 2).

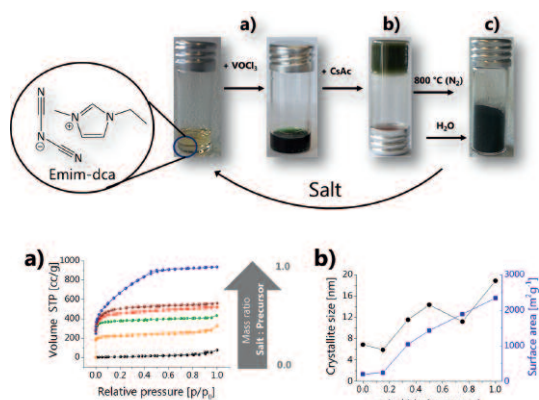


Fig. 2: top: a) addition of a vanadium precursor to the IL Emim-dca leads to a green complex, b) further addition of the template salt caesium acetate generates a glassy precursor, c) after heat treatment under inert atmosphere and aqueous removal of template salt highly porous vanadium nitride carbon composites are obtained. Bottom: a) increasing salt amounts result in increasing surface areas and pore sizes, b) surface area and vanadium nitride particle size in dependence on the salt amount.

Adding to the simplicity of the salt templating approach, it serves as a platform toward the rational design of nanoporous materials in a more sustainable fashion.

Nanoporous Oxide Powders and Aerogels

By exchanging the precursor, the broader application of salts for the synthesis of highly porous materials could be demonstrated, too. Here, the synthesis of porous oxides such as silicates and titania were tested for proof of principle even allowing for the synthesis of aerogels under ambient conditions (Fig. 3).[4, 8]

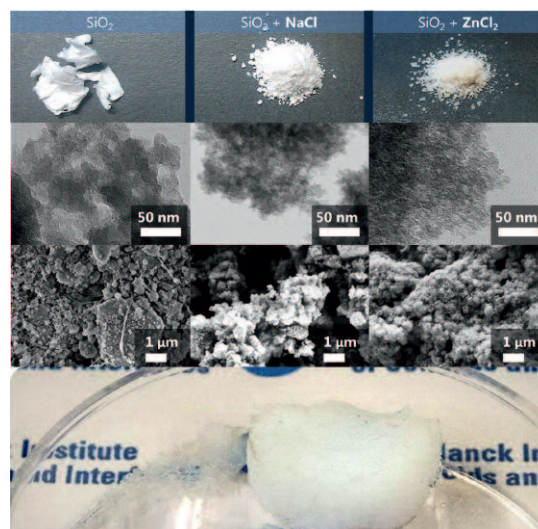


Fig. 3: Silicates synthesized without salt (left), with NaCl (middle) and ZnCl_2 (right). First row: macroscopic appearance, middle row: SEM, bottom row: TEM pictures. Bottom: photo of a silica aerogel synthesized in the presence of ZnCl_2 under ambient conditions.

It could be shown that similarly to the carbons and composites the salt nature and amount strongly influences the materials structures on the nanometer scale resulting in highly porous oxides.

Fine tuning of the process additionally allows for the synthesis of silica aerogels under ambient conditions, thus conventional supercritical CO_2 drying is not needed anymore (Fig. 3).

In general, the examples already shows the beauty and at the same time power of simple processes. My group aims to extend the demonstrated possibilities also with respect to processing such as porous film formation as well as preorganization. Especially with regard to carbons, we want to make use of the significant materials property changes due to differences on the molecular scale. For example, carbons can be conductors or semiconductors, and we believe that the right combination of different carbon families will allow for the fabrication of all-carbon composites. Furthermore, through rational choice and preorganization of functional groups we aim to generate materials with custom-made properties for energy storage and conversion.

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CARBON MATERIALS AND ELECTROCHEMICAL ENERGY APPLICATIONS

Teaching Catalysis to Carbon



Introduction

Carbon nanomaterials, due to their unique properties, are one of the most important materials in applications including adsorption, separation, energy conversion and storage [1]. The key-drawback in the synthesis is still the necessity of using templates and structure directing agents, which have to be pre-synthesized and/or removed in a separate step, to obtain porosity, high surface area or special shapes and morphologies. Moreover such carbonizations are typically carried out in solid-state transformations, which are inherently limited in their reorganizational dynamics. From an application point of view carbon materials, e.g. heteroatom-doped carbons are very promising, especially in the topical area of electrocatalysis, such as in the oxygen reduction/evolution reaction (ORR/OER). Recent reports suggest that increased Fermi levels may lead to improved electrocatalytic activity and stability [2]. As heterojunctions are a feasible way for modification of the electronic band structure, hybrid carbon-inorganic materials are a key target in this research.

Carbon and Carbon-Inorganic Hybrid Aerogels as Efficient Electrocatalysts

Previously, we reported on a novel one-step salt templating carbonization route using inorganic salt melts to prepare highly microporous nitrogen doped carbons with surface areas $>2000\text{m}^2\text{g}^{-1}$ [3]. The salt melts (e.g. eutectic KCl/ZnCl_2) act as solvents and porogens with a broad temperature window, in which microporous carbons and depending on the salt to precursor ratio also meso- and macroporous carbons can be obtained. Carbonizable ionic liquids are used as precursors as they form homogeneous melts with the inorganic salts as an essential requirement for a well-controlled process. In some recent work we optimized the synthesis conditions including the salt to precursor ratio and obtained highly porous and high surface area nitrogen doped carbon aerogels, which naturally possess a mass transport porosity, which is desired in electrocatalysis. The reaction scheme is shown in Fig. 1.

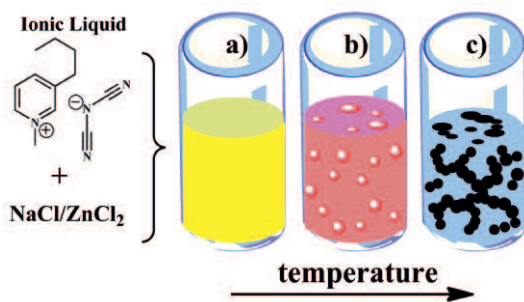


Fig. 1: Ionothermal Carbonization of Ionic Liquid in Inorganic Salt Melt

The carbon aerogels, synthesized with this easy-to-do procedure show very high mass activities in the important ORR and have equal performance like expensive platinum based commercial catalysts in the alkaline medium (Fig. 2) [4].

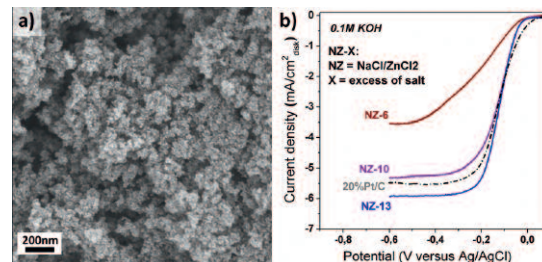


Fig. 2: a) SEM image of the N doped aerogel; b) ORR polarization curves in alkaline medium at 1600 rpm

In a similar approach we expanded this innovative synthetic approach towards non-noble metal containing hybrid materials, by using another ionic liquid precursor and in addition simple iron salts. The specific ionic liquids based carbon hardly undergoes carbothermal reduction even at temperatures as high as 850°C . Therefore, the iron ions remain homogeneously coordinated to the nitrogen doped carbon scaffold and together efficiently catalyze ORR with improved performances also in acidic medium [5].

Hybrid Materials Based on Heteroatom Doped Carbons as Bifunctional Mott-Schottky Catalysts

The heterojunction between two materials with different electronic properties leads to an exchange of electron density, which is accompanied with the bending of electronic bands. The resulting modified electronic properties of the junction can enhance catalytic properties, which is referred to as Mott-Schottky catalysis [6]. Recent reports suggest that the ORR process at nitrogen doped carbons is an outer sphere mechanism and that the position of the Fermi level is the key-descriptor for the activity. High potentials for OER, but also ORR give rise to carbon oxidation as a main issue with regard to the catalytic stability. A reduced energy of the valence band of heteroatom doped carbon should improve the critical oxidation stability. We recently reported on two novel carbon hybrid systems, where synergistic effects on the catalytic properties could be observed. In one example, we employed common filter paper, which is composed of cellulose as a sustainable carbon precursor and structural template at the same time. After infiltration with phenanthroline, and nickel acetate, followed by thermal treatment to 800°C , we obtained a porous nitrogen doped carbon scaffold with strongly attached and nitrogen-coordinated nickel/nickel oxide nanoparticles with the size of $\sim 14\text{nm}$. Interestingly the hybrid material shows increased catalytic activity towards OER as compared to the equivalent material without nitrogen binding sites. Coordination and strong attachment create heterojunctions, which favorably influence the electronic properties of the hybrid material leading to the enhanced catalytic performance.

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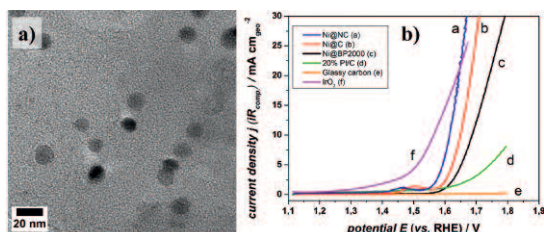


Fig. 3: a) TEM image of Ni@NC sample; b) OER performance of Ni@NC compared to a number of reference catalysts

In addition, the material is also an efficient hydrogen evolution catalyst and could be used for the construction of a symmetric electrolyzer with the theoretical efficiency of 68% at 10 mA cm⁻² [7]. In another example we generated cheap and sustainable porous carbon by employment of nanosized CaCO₃ as sacrificial template using dry pig blood powder as the carbon source. Inside the porous and heteroatom doped (N, S and P sites) we grew Co₃O₄ nanoparticles, which were well-dispersed and again strongly bound to the carbon backbone. Also in this case we found strong enhancement of the catalytic activity. Herein, the hybrid material performed better in ORR than the pure heteroatom doped carbon, but at the same time the performance in OER was also enhanced compared to Co₃O₄ bound to an undoped carbon (Fig. 4).

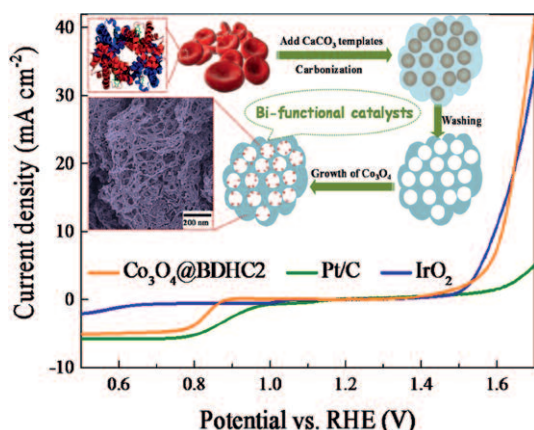


Fig. 4: Illustration of the preparation process and the electrocatalytic performance towards ORR and OER compared to reference catalysts

That means the heterojunction herein leads to synergistic enhancement of the catalytic activity of both compounds at the same time. This bifunctional catalyst could be used either in a fuel cell or in an electrolyzer mode [8].

Novel Ionothermal Carbon Superstructures

Continuing the research of the innovative and uncommon use of inorganic salt melts as reaction medium for carbonizations we recently had a break-through in terms of novel structure formations. We could observe the formation of vertically aligned graphene sheets performing carbonization of ionic liquids in molten zinc chloride and on the surface of nickel foam. For mechanistic considerations a blind experiment was performed. The ionic liquid precursor was wetted on the nickel foam and carbonized in absence of inorganic salt melt.

Instead of nanosheets we obtained bamboo-like carbon nanotubes. The synthesis scheme, as well as the results of the blind experiment and the interesting superstructure are illustrated in Fig. 5.

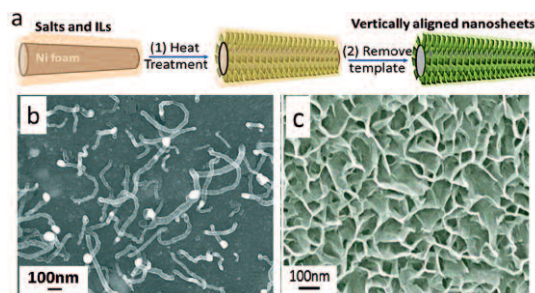


Fig. 5: a) Scheme of the synthesis process; b) SEM image of the blind experiment; c) SEM image of vertically aligned carbon nanosheets on a nickel foam

These results emphasize the importance of the nickel surface for heterogeneous nucleation and graphitization via the dissolution/precipitation mechanism, whereas the preferential growth of CNSs is aided by the presence of inorganic salt melt [9]. Further on, we introduced the first thermal carbonization approach directly in solution. We used molten ZnCl₂ at 550° C and directly pyrolyzed hot-injected common organic solvents like ethanol, acetone, DMSO, acetonitrile, ethylene glycole or pyridine. The combination of ionothermal synthesis and the hot-injection technique leads to novel solvent derived nanocarbons with three distinct morphologies: spherical, sheet-like and branched nanofibers.

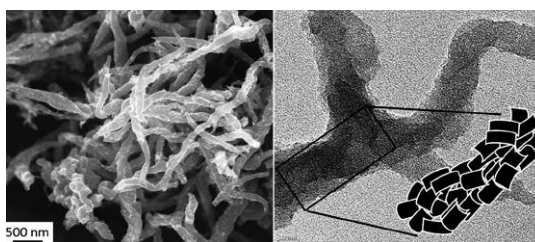


Fig. 6: Carbon after instant ionothermal carbonization of organic solvents

Contrary to possible extensive evaporation the solvents are carbonized quite efficiently, with sometimes surprising high yields. When heteroatom containing solvents were used, the doping levels reached up to 14 wt.% nitrogen and 13 wt.% sulfur. Like observed for other ionothermal carbonizations, in some cases high surface area solvent carbons (up to 1666 m²g⁻¹) were obtained. Importantly, the nanofibrous morphology was explained by vectorial alignment of nanographenes, which herein act as carbon nuclei (Fig. 6) [10]. Such oriented attachment mechanism was so far not reported for carbon, but is a well-known process in inorganic chemistry [11].

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Electron Microscopic Studies of Colloidal Systems and Interfaces



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Transmission electron microscopy and scanning electron microscopy are suitable techniques to investigate the morphological structure of synthetic polymeric and inorganic particles, emulsions, polymeric membranes, mesoporous carbon, interfaces and composite materials and naturally-grown biomaterials on the micro- and nanometer scale. The determination of structural parameters such as the size and size distribution of colloidal particle systems, the pore size of mesostructured networks, the shape and the spatial arrangement of nanoparticles and their crystallinity are in focus on our electron microscopic research. Using cryo-scanning electron microscopy the internal morphological structure of aqueous systems like concentrated water/oil emulsions can be characterized. Because of the organization of the institute, there are many closed co-operations between the electron microscopy group and other research groups. Some of the interesting results of electron microscopic investigations are presented in the following.

The synthesis of non-spherical particles made of hydrophobic polymers requires special actions and frequently multi-step procedures. However, to conclude from the observed shape in the dry state on electron micrographs to the real state in the aqueous dispersion is not always possible because amphiphilic particles can change shape, morphology, and size in the dispersed state in dependence on concentration and ionic strength. Due to their chemical structure, cyclodextrins appear promising reductants for the redox-initiation of aqueous heterophase polymerizations with ceric ions. Using β -cyclodextrin (β -CD) as reductant in the ceric ion redox initiation of aqueous heterophase polymerization of N-isopropylacrylamide leads to latex particles with unprecedented morphology [1]. In **Fig. 1a, b** the synthesized particles appear as a stable assembly of polystyrene particles linked together with poly (N-isopropylacrylamide) (PNIPAM). The size of the β -CD-PNIPAM - polystyrene clusters is in a range of 2-4 μm and the diameter of the spherical polystyrene particles inside the cluster is between 20 and 200 nm. Comparing the morphology of the cluster in the dried state similar to their structure in the presence of the aqueous phase in the cryo-fixed state, in both the polystyrene particles are bounded inside the β -CD - PNIPAM complex (**Fig. 1c**). The cryo-SEM micrograph (**Fig. 1d**) shows the anticipated 3D morphology of a cluster containing smaller polystyrene particles after freeze drying. A cluster that piles up on the fracture plane can be considered as lucky occurrence revealing, however, the 3D structure in the dispersed state. This new strategy for the synthesis of colloidal particles assemblies has a great potential for developments of new and so far unattainable colloidal morphologies.

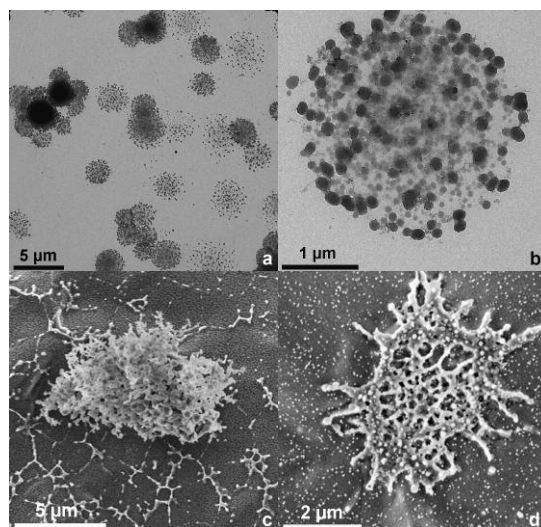


Fig. 1: Spherical assembly of primarily β -CD-PNIPAM - polystyrene clusters (a), the typical morphology of a single cluster (b) and a freeze-fractured (c) and a freeze-dried (d) β -CD -PNIPAM - polystyrene cluster of concentrated aqueous dispersion (solids content of 5 wt%).

Despite numerous methods that have been successfully applied for the fabrication of micro scaled carriers filled by hydrophobic substances, continuous efforts are made to develop new encapsulation techniques.

The ultrasonication technique is most promising for the simultaneous encapsulation of prepared emulsion droplets of a mixture of polymer solution and water-immiscible liquid. Microcapsule shells composed of polymer are synthesized at the interface between oil and the polymer solution.

Here, a new class of oil-filled microcontainers with core-shell morphology is presented, which can be prepared in one-step procedure by applying a low-frequency ultrasonic treatment [3].

A mixture of chitosan and xanthan gum was layered with nonaqueous liquids and exposed to high-intensity ultrasonication. Cross-linking of both polysaccharides due to chemical interactions between their amino, hydroxyl, and carboxyl functional groups is induced by high energy ultrasound treatment. It leads to the formation of a stable layer at the droplet surface and, subsequently, to the formation of permanent shells of microcontainers, loaded with different types of "oils", such as miglyol, soybean oil, hexane, cyclohexane, and toluene. By varying the soybean oil/water ratio (from 1:300 to 1:1.5, respectively) the size the containers is varying in a wide range (300 nm to 8000 nm) (**Fig. 2**). The thin external polymer shell covers the inner container core. The estimated thickness of the shell is 7-10 nm, which, however, is robust enough to keep the microcontainers stable during storage at 4°C for at least 6 months.

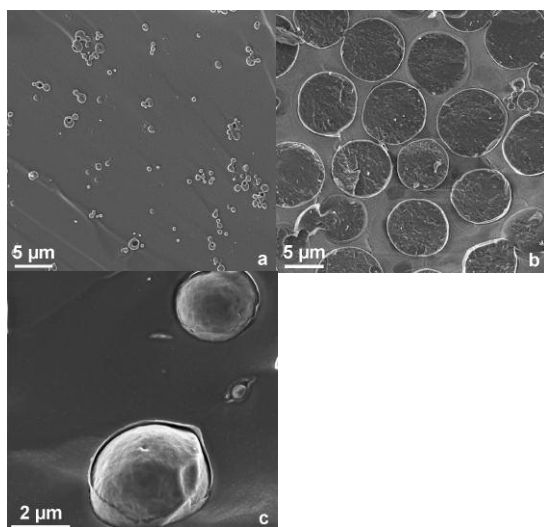


Fig. 2: Microcontainers with different size: (a) 1160 nm (PDI = 0.417), soybean oil/water ratio 1/60; (b) 7325 nm (PDI = 0.146), soybean oil/water ratio 1/1.5; and (c) containers with broken shells.

The used shell components-polysaccharides, chitosan, and xanthan gum are biocompatible, biodegradable, and lack allergenicity. These containers can be further modified upon demand with oppositely charged polyelectrolytes and/or particles.

High biocompatibility and biodegradability of proteins as material for the containers' buildup can be considered as benefits for their potential application.

The electrochemical conversion of the O^2 -/oxygen couple is important for the next-generation energy technologies including metal-air batteries and devices, which can be reversibly used as water electrolyzer and fuel cell [4]. Herein, we present a method that enables facile and scalable preparation of foam-like porous heteroatom doped carbon / Co_3O_4 nanoparticle hybrid materials using conventional blood powder (BP) as a unique carbon precursor and commercial $CaCO_3$ nanoparticles as template, with a particle size in the range of 10-100 nm with a narrow distribution.

During the solid state grinding the precursor and $CaCO_3$ template are successfully homogenized before the carbonization process. After carbonization Co_3O_4 nanoparticles were deposited onto the blood powder derived heteroatom doped carbon (BDHC) by a one-pot thermal deposition technique.

The utilization of nanosized $CaCO_3$ with a particle size of around 25 nm as a hard template/activating agent, it is interesting to find that highly porous BDHCs with variable morphologies can be obtained by changing the initial mass ratios of BP to $CaCO_3$.

For the initial ratio of BP: $CaCO_3$ = 2:1 (BDHC-2:1), the prepared carbon offers an interconnected mesoporous structure.

The spherical pore shape and pore size is similar to the particle size of the used $CaCO_3$ nanospheres. This indicates, that the $CaCO_3$ particles were embedded into the precursor matrix to act as hard templates for the generation of mesopores (Fig. 3a, b). When the relative amount of $CaCO_3$ was increased (BP: $CaCO_3$ = 1:1) a highly porous carbon (BDHC-1:1) with a foam-like morphology, composed of a fibrous network was found.

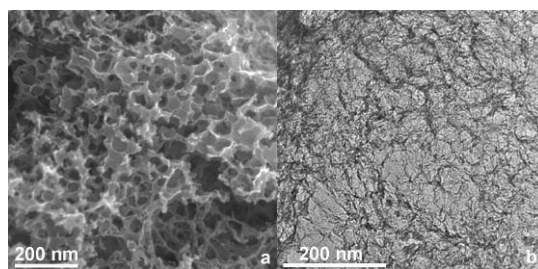


Fig. 3: Mesoporous morphology of BDHC-2:1; REM (a) and TEM (b)

Co_3O_4 nanoparticles with a size smaller than 10 nm and in the range of 20 nm to 40 nm were found for Co_3O_4 @BDHC2. Fig. 4 a, b shows bright-field and dark-field TEM micrographs recorded on the same area of the Co_3O_4 @BDHC2 sample. As can be seen in the dark-field image, the Co_3O_4 nanoparticles with bright contrast are uniformly embedded in the continuous foam-like carbon matrix.

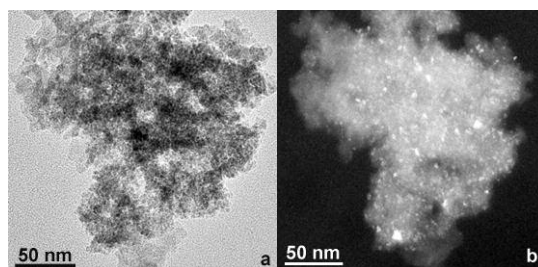


Fig. 4: TEM micrographs of Co_3O_4 nanoparticles in the BDHC2-system a) Bright-field and b) Dark-field imaging

The mesoporous fibrous network structure of the blood powder derived heteroatom doped carbon results from the concerted action of hard templating and activation using $CaCO_3$ nanoparticles. The high surface area and strongly heteroatom doped material features stable anchoring sites for the immobilization of Co_3O_4 , which greatly reduce the aggregation and growth of the decorated Co_3O_4 nanoparticles and improve the charge transfer between the two species [4].

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Materials for Renewable Energy Production



One of the promising technologies for future alternative energy sources is the direct conversion of sunlight into chemical and electrical energy by using photocatalysis or photoelectrochemical cells (PEC), respectively [1]. The greatest challenge in these fields is to develop new types of advanced materials with the desired electrical and optical properties that will replace the conventional raw materials that are

currently used. Photocatalysis has attracted great interest over the last decades, especially for its potential to produce clean and cheap renewable energy without dependence on fossil fuels and without carbon dioxide emission. Photocatalysis applications span from many fields such as: solar fuel production, water splitting, photo-degradation of pollutants, and catalysis of other chemical reactions, e.g. for the production of fine chemicals. The photocatalytic operation usually involves photoactive semiconductors, mostly the ones which consist of metal-based semiconductors like TiO_2 , ZnO , Fe_2O_3 , and many more. For efficient photocatalysis, the internal recombination rate of the charge carriers should be sufficiently low to allow electron/hole migration to the surface of the catalyst, in order to perform the desired reaction. In this system, the photocatalyst is dispersed within the desired solution, and under illumination the charges transfer to the solution and start the desired reaction (Fig. 1).

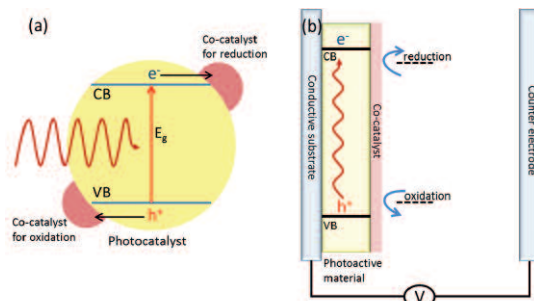


Fig. 1: Illustration of two photocatalysis systems

The second system is based on photo electrochemical cell (PEC) which is based on semiconductor-liquid junctions which can be relatively efficient with respect to the first system, due to improvement of charge separation under illumination. The PECs can be used in order to convert the solar radiation into chemical energy (i.e. water splitting) or to electric energy (i.e. solar cells). Typically for efficient photo (electro) catalysis, an additional co-catalyst, which is currently mostly based on noble metals, is needed in order to increase the wanted reaction activity and rate. Although in the last years a significant progress has been made in this field, it is still an essential task to find efficient and low cost materials as photoactive materials and co-catalysts. More importantly, it is necessary to gain a basic understanding of the physical properties and the fundamental operation mechanisms in this field.

Metal Free Carbon Nitride-Based Materials

While most of the research in this field is focused on metal based semiconductors (metal oxides, sulfides and nitrides) as photocatalysts, in the last years metal-free graphitic carbon nitride (C_3N_4) materials have attracted widespread attention due to their outstanding (electro)catalytic and photocatalytic activity.

Despite of the great progress in C_3N_4 synthesis, it is still a standard problem of C_3N_4 chemistry that only rather disorganized textures with small grain sizes are obtained. Therefore, it is essential to find new and simple synthetic pathways to form highly ordered structures of carbon nitride with controlled electronic, optical and catalytic properties.

Recently, this group used the supramolecular chemistry approach to synthesize well-defined structures of C_3N_4 such as hollow boxes, spheres and spherical macroscopic assemblies [2-4] with the possibility to control their photophysical and photocatalytic properties (Fig. 2). Supramolecular chemistry provides a great opportunity for the synthesis of nanostructured materials without any further templating techniques. The supramolecular approach includes the use of non-covalent interactions such as hydrogen bonding to form order between building blocks for the desired synthesis. Hydrogen bonds are very useful for controlling molecular self-assembly thanks to the reversibility, specificity, and directionality of this class of interactions. The structure of the final products can be controlled by choosing the appropriate monomers and solvents for the synthesis. The starting monomers will organize into different structures according to their ability to form hydrogen bonds in the given solvent and form ordered and stable aggregates which consecutively define the resulting materials.

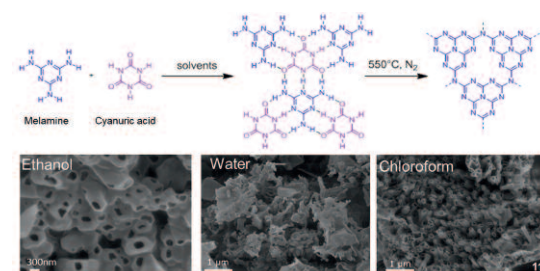


Fig. 2: A graphic presentation of hydrogen-bonded supramolecular complex and the resulting carbon nitride materials in different solvents

However, for photoelectrochemical applications a direct connection between C_3N_4 and the conductive substrates is needed. Due to the large particle size and the insolubility of C_3N_4 in most solvents, the use of common deposition techniques such as spin-coating and screen-printing results in poor coverage and conductivity. Therefore it is essential to find a new and simple synthetic pathway to grow C_3N_4 on different substrates. Using the supramolecular approach we were able to grow highly ordered carbon nitride structures on different substrates both in solid state and liquid-based growth [5-6].

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Thanks to the new deposition methods we were able to show, for the first time, the reduction of water to hydrogen using a metal-free C_3N_4 electrocatalyst. Moreover, we found that the C_3N_4 can act as an absorber and electron accepting layer in polymer solar cell which exhibits a remarkable open circuit voltage of 1 V.

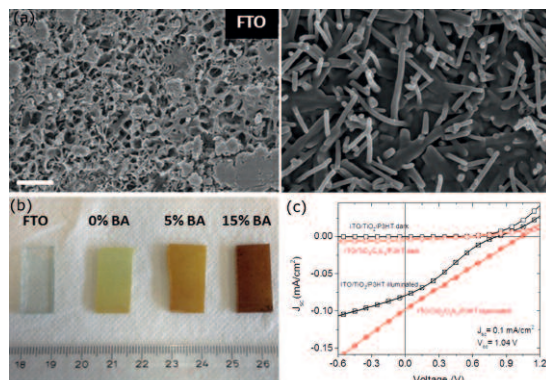


Fig. 3: (a) SEM images of carbon nitride deposited on FTO and glass. (b) Photograph of bare FTO and FTO with C_3N_4 films modified by different amounts of carbon. (c) J-V curves of $TiO_2/C_3N_4/P3HT$ and $TiO_2/P3HT$ solar cells measured in darkness and under 100 mW/cm² AM 1.5G illumination.

Non Noble Metals Based Materials for Energy Related Applications

An important topic of our group is the development of new, low cost and efficient materials as electro and co-catalysts for energy related applications (i.e. water splitting). Electrochemical water splitting to hydrogen (HER) and oxygen (OER) plays a growing role in the fabrication of alternative energy devices due to the need of clean and sustainable energy. Nickel-based materials have attracted enormous attention because of the flexible catalytic properties, along with low price and high abundance when compared to noble metals.

We developed a facile and easy synthesis of large-scale nanoporous, nickel based materials (Ni and Ni_3N), partly embedded in an amorphous matrix of a carbon-nitrogen material [7]. Moreover, we demonstrated the ability to dope these materials with other metals (Mn, Co and Fe). The obtained materials show remarkable performance in the electrochemical production of hydrogen both in terms of low overpotential and high current densities. In addition, we found that the electrochemical properties of Ni-based materials can be altered by simple annealing, resulting in the formation of metal oxides on the surface alongside an increase in surface area [8]. Consequently, after oxidation, the electrocatalysts demonstrate high activity in OER. In sum, the activity of the highly porous material can be easily tuned from HER to OER only by simple thermal treatment in air, leading to a 70% overall water splitting efficiency.

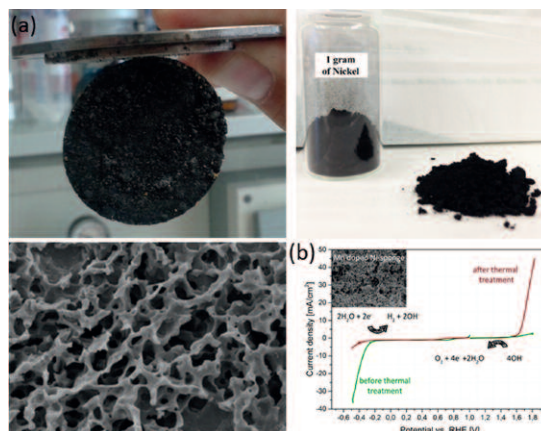


Fig. 4: (a) ~3g of sponge-like Ni that was prepared in one crucible (before and after grinding and washing with water) and the corresponding SEM image. (b) Linear sweep voltammetry of Ni-based material before and after surface activation which shows the HER and OER activity.

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Polymer Dispersions/Heterophase Polymerizations



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Despite the fact that the various heterophase polymerizations (HP) are centennial technologies, the formulation of general mechanistic aspects is still an unsolved issue. Better understanding of HP and educating students on this topic is of general scientific and economic interest and a goal that it is in the very core of the activities of our research. Amongst others the following results have been published 2013-14.

Colloidal Aspects of Heterophase Polymerization – Pressures, Polymers, Particles

The action of pressure during the different heterophase polymerizations is the common ground which allows a unified consideration. Besides the overall pressure which in a certain range can be controlled by the experimenter, the pressures dictated by the colloidal nature of the reaction system – the Laplace (P_L) and the swelling pressure (P_S) – are important. The importance of P_L and P_S on the events in the course of the reaction changes primarily in dependence on the composition of the droplets. **Fig. 1** summarizes our findings [1].

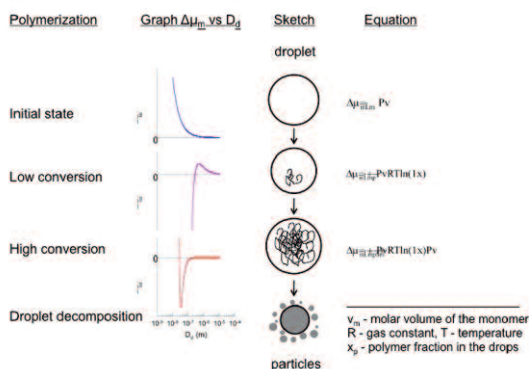


Fig. 1: Sketch how pressures influence HP initiated in monomer droplets; the middle part sketches the transition from a single monomer droplet (initial situation) to many polymer particles in the final dispersion; the equations on the right hand side show the contributions to the chemical potential of the droplets in the various states of the polymerization and the corresponding graphs on the left hand side illustrate the excess chemical potential ($\Delta\mu_m$) in dependence on the droplet size ($\Delta\delta$)

Heterophase Polymerization in the Presence of Monomer Droplets

There are two fundamentally different strategies to carry out heterophase polymerizations, either in the presence or absence of monomer droplets. Here we restrict the discussion to the situation where monomer drops are present prior to polymerization. Under such condition HP is a transition between different colloidal states (from emulsion to suspension) controlled by polymerization. The key issue in this context is the role of monomer droplets. Their size is an important parameter essentially governing the process [2]. Initiation inside the monomer drops happens with all initiators. It

happens more frequently the higher the solubility of the initiator in the monomer phase. Polymer formation causes a stabilization of the droplet against Ostwald ripening because the insolubility of the polymer in the aqueous phase counteracts the Laplace pressure (situation at low conversion of **Fig. 1**). Further increasing x_p leads to rising swelling pressure which causes a volume increase of the particles. The swelling pressure can be so strong that tiny droplets are expelled (situation at high conversion of **Fig. 1**). The fate of the expelled droplets depends strongly on the stabilizing conditions (properties and concentration of the stabilizer). Quite importantly with respect to generalization, these ideas are independent of the particular polymerization conditions as demonstrated experimentally [1]. However, the proportion of both the small and the large particles is controlled by the polymerization conditions, particularly by the nature of the initiator (hydrophobic or hydrophilic (**Fig. 2, 3**) for poly(vinyl alcohol) stabilizer). In each case a very specific morphology of the particles is observed, resembling colloidosomes – large cores covered by much smaller particles.

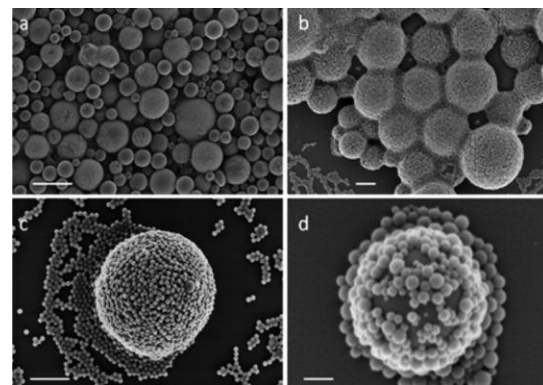


Fig. 2: SEM micrographs of PS particles made with hydrophobic initiators V65 (a, c) and BPO (b, d); the bar indicates 20 μm (a), 2 μm (b and c), 300 nm (d)

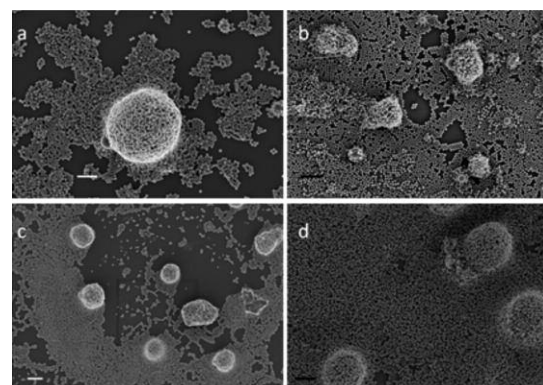


Fig. 3: SEM micrographs of PS particles made with hydrophilic initiators KPS (a), VA-086 (b), V501 (c), and V50 (d); the bar indicates 2 μm (a, b, d) and 3 μm (c)

How Much Weighs the Swelling Pressure

We developed a new method to follow (almost) isochoric swelling of gels by measuring the apparent weight increase after establishing the contact between the confined gel sample and the swelling agent [3]. The gel is located inside a confinement cell with porous walls which is completely immersed in an arbitrarily large pool of the swelling agent. The whole setup is placed on a scale with the confinement cell being tightly connected to an external reference point in a way that the force is redirected almost completely towards the scale. This arrangement permits easily to modify the conditions inside the reservoir of the swelling agent during the swelling process (Fig. 4). Moreover, this technically simple method allows quite convincingly illustrating the action of the chemical potential.

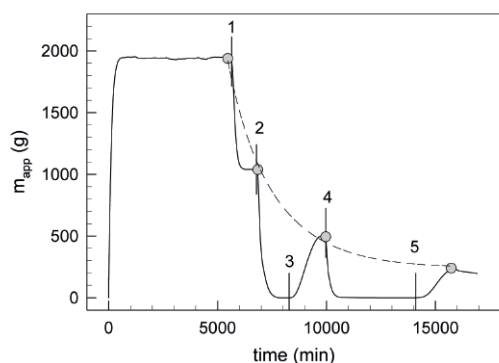
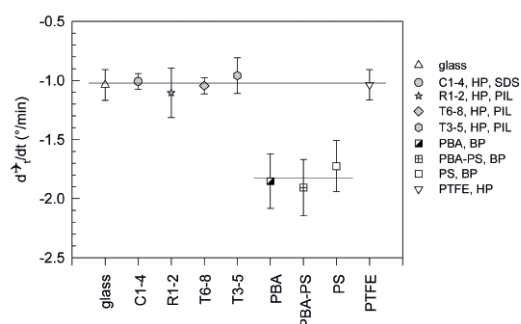


Fig. 4: Change of the apparent mass (m_{app}) of a PAA gel in pure water (from time 0 to point 1) and after alternating addition of sodium hydroxide solution and sulphuric acid; the amounts of base and acid added were adjusted to achieve after each addition a pH of about 13 and 1; the dashed line is a fit of the grey points and describes the response of the swollen gel under basic conditions on the ionic strength which increases from point 1 (pure water) to point 5 up to a value of about 5.5 M

The Wettability of Polymer Films Depends on the Polymerization Conditions

The polymerization conditions have a strong influence on the barrier properties of polymeric films. For a given copolymer composition, the recipe components of emulsion copolymer films clearly influence the initial static water contact angle, a measure of hydrophilicity. Common emulsifiers such as sodium dodecyl sulphate (SDS) cause lower contact angles than poly(ionic liquid) (PIL) dispersions which are a new class of stabilizers for heterophase polymerization [4, 5]. In contrast, the time-dependent properties of the water contact angle reflect the given hydrophilic/hydrophobic conditions during the polymerization. Water-born emulsion copolymers (the upper data points of Fig. 5) show a distinctly different time-dependence of the contact angle than bulk polymers (lower data points of Fig. 5) of the same molecular composition regardless of the initial static contact angle [6].



PBA - poly(butyl acrylate); PS - polystyrene; PBA-PS copolymer butyl acrylate - styrene; PTFE - polytetrafluoroethylene; C, R, T - PBA-PS samples; HP - heterophase polymerization in water; BP - bulk polymerization; SDS - sodium dodecylsulphate; PIL - poly(ionic liquid) dispersion

Fig. 5: Dependence of the rate of change of the initial water contact angle on the nature of the substrate

A New Morphology of Colloidal Particles – Multiple Suspension Particles (MSP)

A new class of colloidal polymeric particles consisting of polystyrene spheres grown in a poly(N-isopropyl acrylamide) precursor scaffold has been synthesized via redox-initiated heterophase polymerization [7]. The morphology and thermo-responsiveness of these assemblies are proven by electron microscopy investigations and temperature-dependent measurements of the change of both the speed of sound travelling through the dispersion and the hydrodynamic particle size. Electron microscopy (EM) micrographs (transmission and scanning EM as well as cryo-scanning EM) prove the existence of colloidal clusters when the freeze-dried copolymer is redispersed in pure water (Fig. 6). The clusters have a size of several micrometers, contain about 800 polystyrene particles with diameter below 100 nm, and show a highly reproducible thermo-responsive behaviour with a lower critical solution temperature corresponding to that of pure poly(N-isopropyl acrylamide).

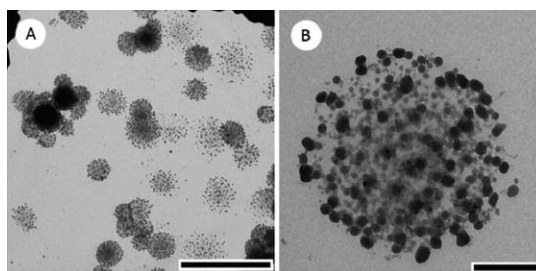


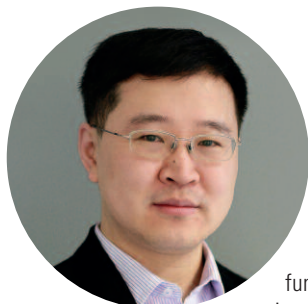
Fig. 6: TEM micrographs clarifying the particular morphology of β -CD – PNIPAM – polystyrene clusters; A – overview micrograph proving that the dispersion consists primarily of clusters and B – magnified micrograph illustrating a typical single cluster; the bars of micrograph A and B correspond to 10 and 1 μ m, respectively

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Poly(ionic liquid)s as Innovative Functional Polyelectrolytes



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Poly(ionic liquid)s (PILs), also named polymerized or polymeric ionic liquids, are the polymerization products of monomeric ionic liquids (ILs) [1]. The connection and accumulation of IL moieties through a polymeric backbone or framework builds up a macromolecular architecture featuring a high density of IL functionalities. As such, some of the unique properties and chemistry of ILs are synergistically combined with the general features of polymers, i.e. processibility, mechanical stability, chain dynamics, etc. As an extended class of conventional polyelectrolytes, numerous materials applications have been realized via the PILs route. This progress in turn motivates more activities in fundamental research of PILs in terms of chemical structure diversity and intrinsic structure-property relationship. Our group is dedicated to discovering new chemistry of PILs and studying their properties for applications in membrane technology, colloidal science, responsive materials, and carbon nanostructures.

PILs in Membrane Technology

Porous, especially nanoporous polymer membranes represent a multifunctional platform in both fundamental research and industry. In this regard, nanoporous polyelectrolyte membranes (NPMs) are particularly appealing because of the presence of charges and the high mechanical and chemical stability. However, currently no suitable fabrication method allows for large scale production of NPMs due to difficult processing associated with the water solubility and ionic feature of common polyelectrolytes. Our group introduced a facile, efficient route to achieve NPMs by exploiting electrostatic complexation between a cationic PIL and neutralized poly(acrylic acid) (PAA) [2]. Typically, a hydrophobic, water-insoluble PIL was mixed with PAA in a 1:1 equivalent molar ratio with regard to the repeating unit (Fig. 1). Both were fully dissolved in DMF to form a homogeneous solution [3]. This solution was then cast onto a glass plate, dried at 80 °C, and subsequently immersed in aqueous NH₃ solution. This procedure was applied to produce a large, freestanding membrane. SEM characterization proves that the 3D interconnected pores are 30-100 nm in size. Such membranes are structurally robust in various environments. Advantageously, this method produces not only traditional freestanding membranes but also functional coating. The membranes, when fabricated onto an optical fiber, serve as a highly sensitive, fast responsive fiber-optical pH sensor. This fabrication technique can be generalized to introduce pores from nano to micrometer range. When PAA is replaced by a multiacid compound, porous membranes with pore size of 0.2-3 μm were prepared, which could function as an ultrafast actuator in organic vapour [4].

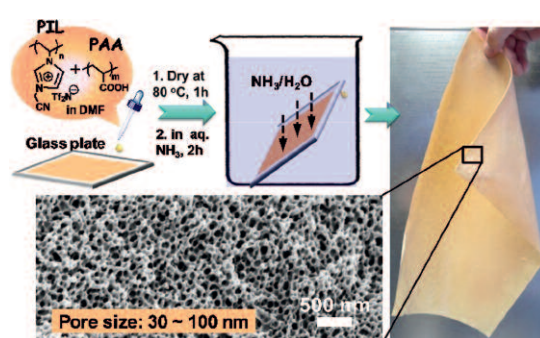


Fig. 1: Preparation scheme and a SEM image of a nanoporous polyelectrolyte membrane from a mixture solution of a cationic PIL and poly(acrylic acid) in DMF.

PILs as Stabilizer for Colloidal Systems

PILs are known as highly interfacial active materials, which bind to diverse surfaces. This function is useful for colloidal stabilization [5]. One example is dispersion of long, slender and flexible cellulose nanofibrils (CNFs) with diameters of 5-60 nm and lengths up to several micrometers. They are a class of renewable nanomaterials with outstanding properties, such as versatile chemical-modification capacity, low thermal expansion, excellent mechanical property, and a high aspect ratio. To achieve good material performance, CNFs need to be dispersed in solution. With the assistance of PILs, we were able to disperse CNFs in solvents at will via grafting PIL onto CNFs (Fig. 2). The dispersability can be readily tuned by exchanging the counter anion. Such omnidisperseable PIL/CNF hybrids served as mechanical reinforcing agent in porous membranes.

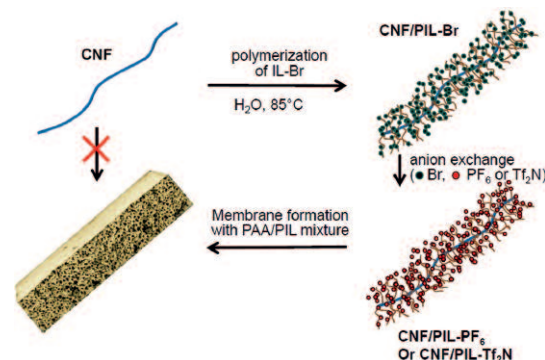


Fig. 2: Illustration of dispersion of CNFs via surface grafting of PIL onto CNFs (IL-Br: IL monomer with Br-), and the subsequent hybrid membrane preparation.

In parallel, we designed a specific PIL with a low glass transition temperature of -57 °C. It exhibits a rarely observed fluidic behaviour in bulk even at room temperature (RT), different from conventional polyelectrolytes. This property enables the PIL to act as a macromolecular solvent for various compounds, and simultaneously as stabilizer for colloid particle synthesis. The synergy in the solvation and stabilization is a striking character to downsize the *in situ* formed particles [6].

PILs as Thermoresponsive Polymers

Polymers with lower critical solution temperature (LCST) behaviours in solution have been widely investigated as “intelligent” materials [7]. However, fully-ionized polyelectrolyte homopolymers showing LCST behaviour have been ignored for a long time. We synthesized from an IL, tributyl-4-vinylbenzyl phosphonium pentanesulfonate (TVBP-C5S) the first cationic polyelectrolyte that undergoes a LCST-type phase transition in water [8]. Its phase transition occurs in a wide temperature range, showing dependence on polymer concentration and externally added salts. Anion exchange and salting-out effects are responsible for the flexible phase transition. Such a PIL is useful for nanoparticle stabilization and manipulation. As shown in Fig. 3 A, Au nanoparticles of 10 nm can be stabilized by poly(TVBP-C5S) in water at RT. Upon heating, the dispersion turns turbid due to precipitation of the poly(TVBP-C5S)-nanoparticle hybrid. Filtration through a membrane filter (0.2 µm in size) at this temperature yields a nanoparticle-free solution. Unlike conventional LCST-type polymers, the thermoresponsiveness of the hybrids can be readily abandoned by adding NaCl. NaCl addition replaces sulphate by Cl⁻, which shifts the transition temperature above 100°C. By this PIL, the thermoresponsiveness of gold nanoparticles in water can be rendered or cancelled at will. In addition, we also developed the first LCST-type polyelectrolytes from a Gemini dicationic IL [9].

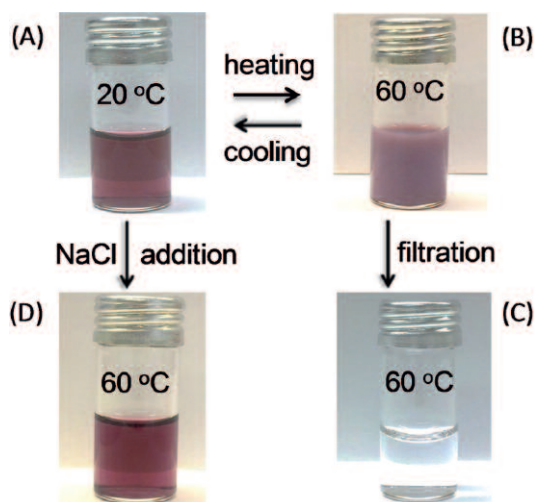


Fig. 3: Photographs of poly(TVBP-C5S) stabilized Au nanoparticles at (A) 20 °C, (B) 60 °C, (C) 60 °C after filtration, and (D) 60 °C in the presence of 0.2 M NaCl.

PILs as Carbon Precursor

Nitrogen doping of carbon nanostructures can improve the catalytic activity, oxidation resistance and electric conductivity. Recently, hollow carbon nanospheres, named “carbon nanobubbles” are one of the most intensively studied structures because of their intrinsic properties associated with the unique shape, such as high surface-to-volume ratio, high thermal and chemical stability, compartmentalized structure,

and low apparent density. We have focused on this specific structure in the last two years. As example, PIL nanoparticles were used as precursor and colloidal template to create ultra-small carbon nanobubbles (25-90 nm) with controlled dimension, variable nitrogen doping, superior aqueous dispersability, high conductivity, and a distinctive atomic graphitic order [10-11]. In a typical synthetic route (Fig. 4), silica nanocasting was conducted by dropwise addition of tetramethyl orthosilicate (TMOS) into an aqueous dispersion of PIL nanoparticles under vigorous stirring. In this way individual PIL nanoparticles were initially coated with a silica layer, and eventually trapped in compact silica. Pyrolysis of the PIL/silica hybrid at 1000° C under N₂ atmosphere *in situ* converts the PIL nanoparticles into isolated carbon nanobubbles. Subsequent removal of silica releases the carbon nanobubbles into aqueous solution. Uniquely the PIL nanoparticles played a triple role as a sacrificial template, carbon precursor and N source.

Besides using PIL nanoparticles as template, an alternative way to prepare hollow carbon spheres is to graft PIL chains onto the surface of silica nanoparticles, followed by carbonization and silica etching [12]. These nanobubbles were successfully applied in catalysis and electrochemistry (lithium ion batteries, oxygen reduction reaction in fuel cells), and served as inorganic stabilizers for carbon nanotubes. [10, 12, 13].

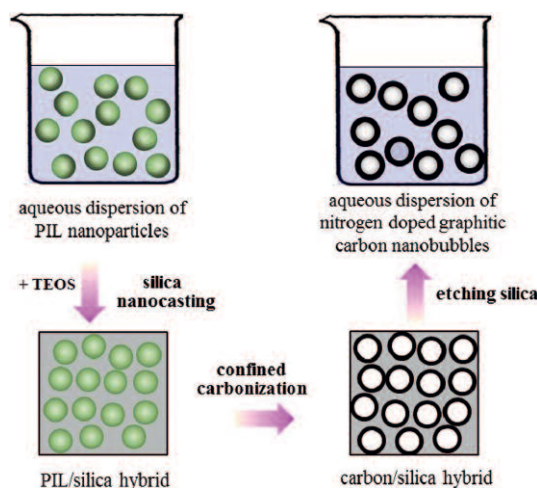


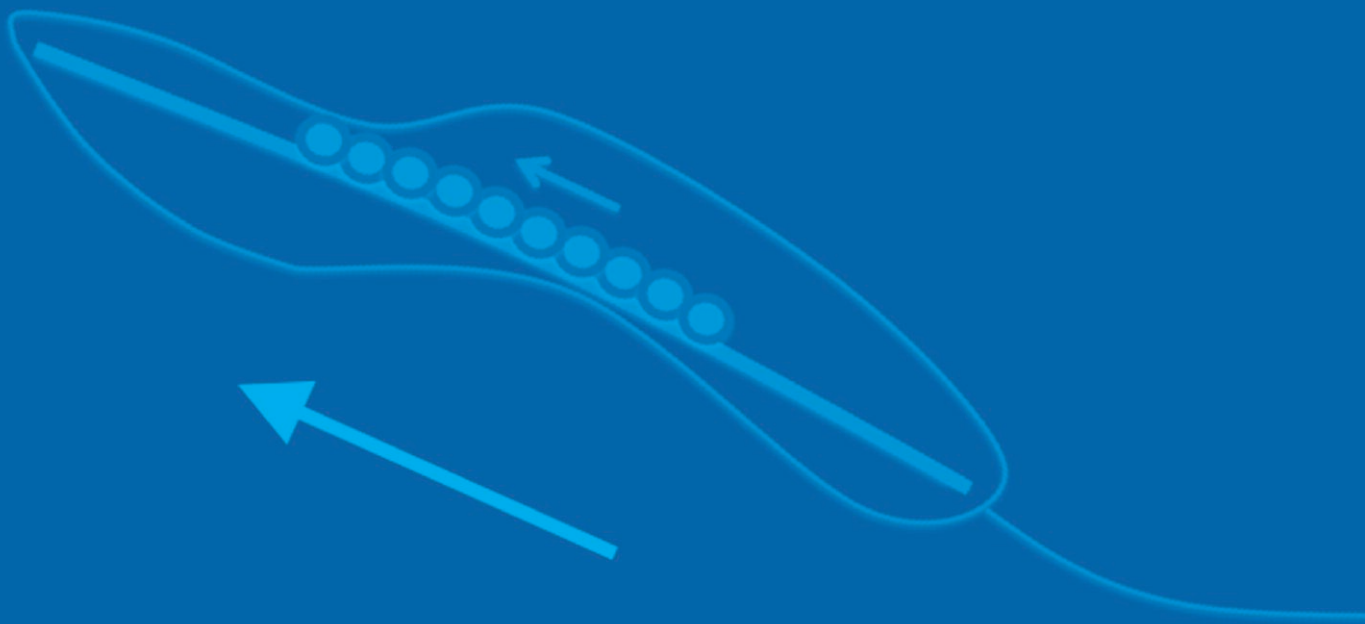
Fig. 4: Synthetic route to nitrogen-doped hollow carbon nanospheres via silica nanocasting technology through the PIL nanoparticles

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- Biopolymers
- Biomolecular Processes
- Membranes and Vesicles
- Interfacial Phenomena
- Complex Systems

THEORY & BIO-SYSTEMS



Research in the Department of Theory & Bio-Systems

„Das Ganze ist mehr als die Summe seiner Teile“ Aristoteles



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 molecular building blocks of these systems join „by themselves“ and form a variety of supermolecular assemblies, which then interact to produce even larger structures and networks.

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1986-1988: Group leader (FZ Jülich)

1987: Habilitation, Theoretical Physics

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Wetting, surface melting and related

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1989-1990: Associate Professorship

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The associates of the department form several research groups. At present, the research group leaders and topics are (in alphabetical order):

- Rumiana Dimova: Biophysics Lab;
- Andrea Grafmüller: Multiscale Simulations;
- Stefan Klumpp: Regulation of Bioprocesses;
- Hans Riegler: Solid-Air Interfaces (since 2014);
- Sophia Rudolf: Biomolecular Processes (since 2015);
- Mark Santer: Carbohydrates and Polysaccharides;
- Angelo Valleriani: Stochastic Processes;
- Ana Vila Verde: Soft Matter Simulations (since 2014);
- Thomas Weikl: Proteins and Membranes.

The main results of these 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: Biopolymers, Biomolecular Processes, Membranes and Vesicles, Interfacial Phenomena, and Complex Systems. In the following, the projects of these research groups will be briefly summarized and some additional projects will be highlighted.

Biopolymers

The smallest 'bio-systems' are aqueous solution as studied by *A. Vila Verde* who elucidated the effect of ions on the dynamics of water molecules. More recently, her group has started to address water dynamics near hydrophobic interfaces such as fluorinated amino acids and the interactions of anionic polymers with proteins. The group of *M. Santer* continued its studies of polysaccharides and glycans by molecular dynamics simulations. Two topics that have been investigated in some detail were the development of force fields for hybrid molecules such as the GPI-anchor involving lipids, oligosaccharides, and proteins as well as the cleavage of oligosaccharides by protein complexes of bacteriophages. *A. Grafmüller* and her group determined the effective interactions for coarse-grained descriptions of polysaccharides in order to address their materials properties. One important target is hemicellulose, which typically consists of more than 500 monomeric building blocks. The group of *T. Weikl* further elucidated the different pathways for the binding of protein molecules, induced-fit versus conformational selection, which differ in the temporal ordering of binding steps and conformational changes.

Biomolecular Processes

We continued our study of the multi-scale motility of molecular motors, which involves the chemomechanical coupling of single motors, cargo transport by teams of motors, and motor traffic of many cargo-motor complexes. The allosteric coupling between different subdomains of kinesin's motor domain has been investigated by atomistic molecular dynamics simulations (**Fig. 1**) and, was found to be strongly affected by the presence of tubulin. A new topic was protein synthesis by ribosomes for which a detailed Markov model has been developed and used to predict the transition rates *in vivo* from the measured *in-vitro* values (report of *S. Rudolf* and **Fig. 2**).

Membranes and Vesicles

The adhesion of membranes via specific receptor-ligand bonds is strongly affected by the membrane's nanoroughness (report of *T. Weikl*). A new experimental method has been developed to prepare multi-component membranes with a well-defined composition (report of *R. Dimova*). This method is important in order to determine the phase behavior of these membranes in a quantitative manner. Additional topics included the spontaneous and stable tubulation of vesicle membranes (**Fig. 3**), bilayer asymmetry arising from the adsorption of small molecules onto the two leaflets of the membranes (**Fig. 4**), and the strong influence of spontaneous curvature on the engulfment of nanoparticles by membranes (**Fig. 5**). The latter figure explains the instability of the completely engulfed state for particle radii that are smaller than the threshold value

$$\left[\frac{1}{R_w} + M'_{ms} - 2m \right]^{-1}$$

which depends on the adhesion length R_w , on the segment curvature M'_{ms} of the mother membrane, and on the spontaneous curvature of the membrane, m , which can be positive or negative.

Interfacial Phenomena

The group of *H. Riegler* continued its investigations of phase transitions and transport phenomena at solid-air interfaces. Two phenomena of interest were the melting of terraces of long chain alkanes at SiO₂-air interfaces and the heterogeneous nucleation on planar solid substrates with a regular array of nano-indents.

Complex Systems

A. Valleriani and coworkers applied stochastic modelling methods to the degradation of mRNA and studied the relations between the network structure of the Markov process and the distribution of first-passage times. The independent research group of *S. Klumpp* addressed the interplay of physical constraints and functional requirements in living systems. Two major topics were the interplay of gene expression and cell growth as well as bacterial motility. In the latter context, both the pili-based motility along surfaces and the movements of magnetotactic bacteria have been studied.

Biannual Series of Symposia

We continued our biannual series of topical symposia and organized a three-day symposium on 'Multiscale Motility of Molecular Motors' in 2013 as well as another three-day symposium, the 'Biomembrane Days 2014'.

International Max Planck Research Schools

The department of Theory & Bio-Systems was in charge of the new IMPRS on "Multiscale Biosystems", which started its operation in July 2013.

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

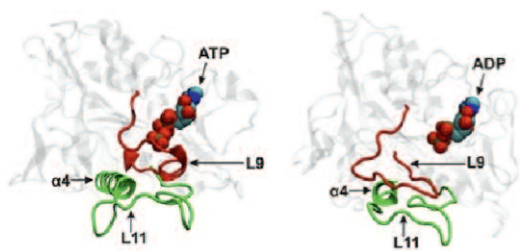


Fig. 1: Molecular Dynamics simulations of kinesin's motor domain attached to tubulin. Allosteric coupling between the nucleotide binding pocket (red) and the microtubule binding domain (green): (left) state with bound ATP; and (right) state after hydrolysis and phosphate release with bound ADP. During the release step, the L9 loop (red) undergoes a conformational change and rotates the $\alpha 4$ helix (green). [A. Kruka et al, PCCP **16**, 6189 (2014)]

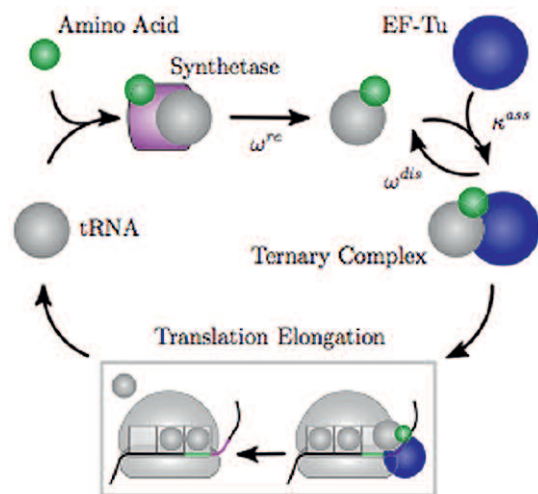


Fig. 2: Protein synthesis by ribosomes: Extended Markov process for translation elongation and its coupling to recharging of deacylated tRNA (upper left) and to ternary complex formation (upper right). This extended scheme is important in order to identify the different subpopulations of tRNA molecules in vivo. [S. Rudolf and R. Lipowsky, PLoS ONE in press]

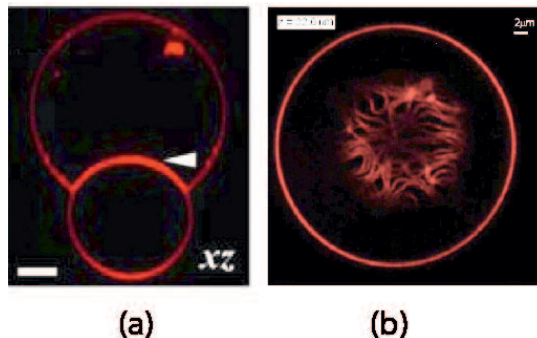


Fig. 3: Formation of many stable membrane nanotubes protruding into the interior of a vesicle enclosing two aqueous phase-separated droplets. The image in (b) corresponds to a confocal scan at the height of the white arrowhead in (a). [Y. Liu et al, to be submitted]

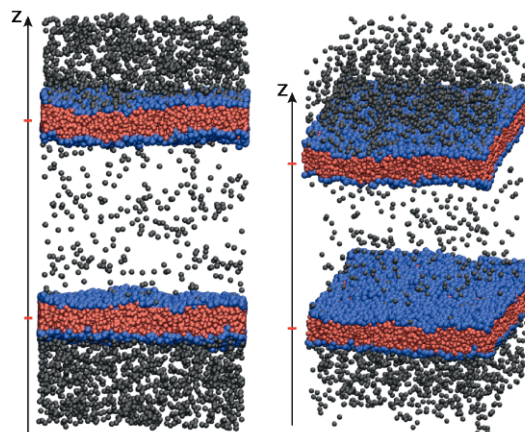


Fig. 4: Side view (left) and oblique view (right) of two lipid bilayers (blue-red), which separate two aqueous compartments. Both compartments contain adsorbate particles (gray) but with different concentrations. The adsorption of these particles onto the head group layers (blue) leads to asymmetric bilayers with a spontaneous curvature that can be as large as $1/(20 \text{ nm})$. [B. Rozycki and R. Lipowsky, J. Chem. Phys. **142**, 054101 (2015)]

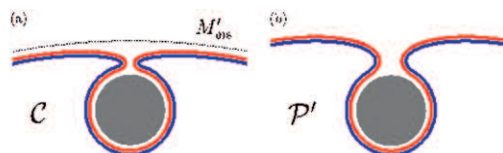


Fig. 5: Engulfment of nanoparticle (gray) by asymmetric bilayer membrane (blue/red): The completely engulfed state of the nanoparticle (left panel) is unstable and the membrane neck starts to open (right panel) if the particle size is smaller than a certain threshold size. [J. Agudo-Canalejo and R. Lipowsky, ACS Nano **9**, 3704 (2015)]

From Ionic Solutions to Interacting Proteins



The ability of biopolymers such as proteins to fulfil their biological function is determined by the balance between their intramolecular interactions, their interactions with natural or artificial ligands, water, free ions and other molecules in solution. Seemingly small changes to the protein or its environment – e.g., fluorinating a single protein alkyl group or sulphating a few amino acids in a ligand – often lead

to large alterations in protein properties. In this group we use molecular simulations to investigate interactions relevant for protein structure and function: we gain fundamental knowledge by investigating small model systems: 1) interactions between water and ions; 2) water at hydrophobic interfaces (with the experimental groups of R. Kramer Campen at the Fritz Haber Institute, Berlin, and Beate Koks at the Free University (FU), Berlin). We apply this knowledge in the study of biologically important protein systems: 3) interactions between anionic polymers and proteins (with the experimental groups of R. Haag, FU, and Peter Fratzl at this institute).

Interactions between Water and Ions

Reports from ultrafast pump-probe spectroscopy experiments suggest that densely charged ions such as magnesium and sulphate have a long-range effect on water dynamics: together, they slow down water rotation beyond what would be expected from an additive model. Similar experiments also indicate that even in 1:1 salts, monovalent cations affect the rotational dynamics of the water shell of their counterions. These claims defy evidence from other experiments and simulations, which suggest that the effect of anions and cations on water dynamics is limited to their first hydration shell and is largely additive. We address this on-going controversy by using atomistic molecular dynamics simulations and polarizable models to investigate the dynamics of rotation of hydroxyl groups in aqueous solutions containing ions with either high or low charge density: MgSO_4 and CsCl . These models are parameterized by us to reproduce both the free energy of hydration of single ions and the solution activity derivative at high concentration, thus being appropriate to gain insight into water dynamics at both low and high salt concentrations. Using these models, we calculate the average water reorientation autocorrelation function in solutions of CsCl or MgSO_4 at various concentrations. We find that MgSO_4 greatly slows down water dynamics whereas water is only minimally affected by the presence of CsCl . These trends qualitatively reproduce the experimental ones, confirming the soundness of the models. Examining the water rotational dynamics in subpopulations near static contact- or solvent-shared ion pairs, from separate simulations of isolated ion pairs, indicates that water rotation may be slower than, equal to or larger than that predicted by a simple additive model, for both $\text{Cs}^+ \dots \text{Cl}^-$ and $\text{Mg}^{2+} \dots \text{SO}_4^{2-}$ ion pairs. Large, supra-additive, slowdown, is observed only for water molecules directly bridging $\text{Mg}^{2+} \dots \text{SO}_4^{2-}$ solvent-shared ion pairs (Fig. 1).

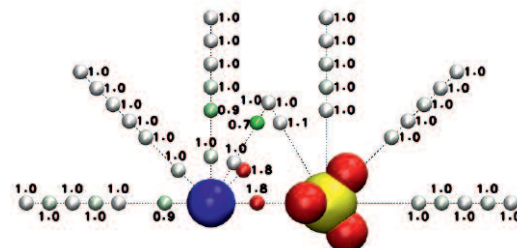


Fig. 1: Supra-additive factor for different water subpopulations around a MgSO_4 solvent-shared ion pair. Values >1 indicate supra-additive slowdown of water rotation.

To verify that the supra-additive slowdown observed in simulations of static ion pairs is not an artefact we build an analytical model to predict the average rotational dynamics in salt solutions, where the ions are free to move, from the contributions of water around static ion pairs. We find that the average water rotational dynamics in concentrated MgSO_4 solutions can indeed be predicted from the contributions of water near static ion pairs. On the other hand, at MgSO_4 concentrations close to the solubility limit, the supra-additive slowdown brought by ion pairs is insufficient to explain the extremely slow water dynamics in these solutions. Our results show that this extremely slow dynamics is associated with multi-ion clusters. Because non-additive effects are small for pairs of low charge density ions and these pairs have lifetimes comparable to the rotational dynamics of water, the standard additive picture holds for CsCl . These results clarify the molecular scale mechanism by which static properties of an electrolyte solution – number and type of ion pairs – will influence the solution dynamics, and show that supra-additive slowdown of solution dynamics at high concentrations may be expected when ions preferentially form solvent-shared ion pairs with life-times larger than the water reorientation dynamics [1]. Our results have direct implications for studies with proteins: they suggest that the dynamics of the water of hydration of proteins, thought to influence protein conformational dynamics and activity, may be modulated by the formation of solvent-shared ion pairs between the protein and densely charged ions.

Recent experimental studies probing the interface of aqueous salt solutions have suggested that anion-cation association at the interface is greatly altered relative to the bulk. The exact nature and magnitude of these changes is still unclear, though, largely because most experiments are sensitive to the interfacial water, but not to the ions. In the next stage of this project, we will use our models to investigate these outstanding questions.

Water at Hydrophobic Interfaces

Interfaces between water and non-polar functional groups are ubiquitous in biopolymers. These interfaces are at the origin of the hydrophobic effect which largely drives the self-

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assembly of biopolymers into stable structures. While the thermodynamic signature of hydrophobic interfaces is well known, the molecular details of water at hydrophobic interfaces and the molecular origin of the hydrophobic effect are still under study. The air/water interface is a useful model for this study because of its simplicity. Using atomistic molecular dynamics simulations, we characterize the orientation and dynamics of two subpopulations of OH groups belonging to water molecules at the air/water interface: those OH groups that donate a hydrogen bond (called “bonded”) and those that do not (called “free”) [2-3]. We found that free interfacial OH groups reorient in two distinct regimes: a fast regime from 0 to 1 ps and a slow regime thereafter. Qualitatively similar behavior was reported by others for free OH groups near extended hydrophobic surfaces. Our results clarify that the free OH groups are structurally and dynamically heterogeneous: longer lived free OH groups tend to point closer to the surface normal, have a narrower orientation distribution, and are closer to the vapor phase. Existing descriptions of extended hydrophobic interfaces focus on one of two aspects of these interfaces: the presence of free OH groups and of large density fluctuations. The connection between these two aspects is not yet clear. Our work shows that the net reorientation of bonded interfacial OH groups occurs at a rate similar to that of bulk water, which suggests that the molecular origin of the density fluctuations that are characteristic of extended hydrophobic interfaces lies with the free OH groups.

The knowledge gained on the air/water interface serves as the foundation for our on-going study of hydrophobic interfaces containing fluorinated alkyl groups. Inserting these groups into proteins is known to alter their properties, and those of their water of hydration, but at present no experimental or computational studies have directly investigated how the water of hydration of fluorinated alkyl groups differs from that at typical hydrophobic interfaces. A single experimental study has *indirectly* probed water dynamics near a fluorinated amino acid, with unusual results: water near fluorinated groups appears to have unusually slow dynamics. This work, which started in September 2014, will be done using all-atom models of small fluorinated analogues of alkanes and aliphatic amino acid side chains. We are in the process of developing those models.

Interactions between Anionic Polymers and Proteins

Selectins are well known for their role in the adhesion of leukocytes and platelets to the endothelium that takes place, e.g., during inflammation. Because of the important biological role played by selectins, much effort has been put into finding artificial ligands that effectively compete with the natural ones. The Haag group investigated the potential of dendrimeric polyglycerol (dPG) polymers functionalized with various anionic groups as possible inhibitors of the interaction between L-selectin (**Fig. 2**) and its natural ligands.

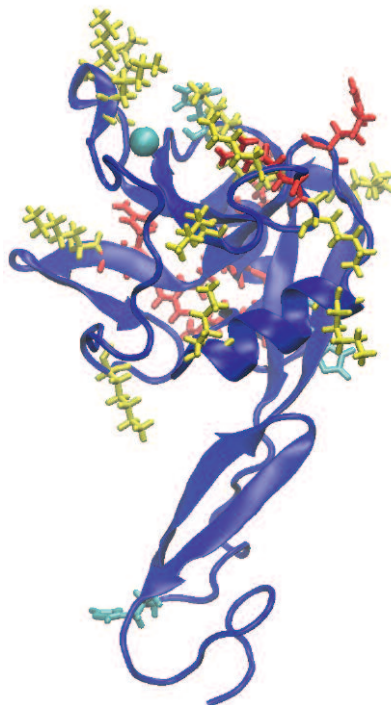


Fig. 2: L-selectin. The cationic amino acids are shown in stick representation.

They found that the affinity of dendrimers for selectins depends strongly on the nature of the anionic group, increasing in the order carboxylate < phosphate < phosphonate \approx sulfonate < bisphosphonate \lll sulfate. This anionic series cannot be understood in terms of simple considerations based on electrostatic interactions or the acidity of the anionic groups, but instead suggests that complex and competitive microscopic intermolecular and intramolecular interactions might play a role. The first stage of this project, which started in July 2014, consists of characterizing the *intrinsic* interactions between various anionic functional groups and positively charged amino acids, using small molecule analogues (e.g. methylphosphate or methylamine). This work is done using classical all-atom models and explicit water. Results from these simulations will be compared against those from *ab initio* calculations, to ensure the reliability of the classical models. In the next stage, we will use classical, atomistic models to investigate the interaction between selectin and triglycerol sulfate. Our results will be compared with experiments done in the Haag group, thus yielding both a stringent test of the quality of the models and molecular scale insight into multivalent interactions between a small, rigid, ligand and selectin.

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Glycans under the Computational Microscope



In virtually all organisms carbohydrate compounds (*glycans*) are involved to modify or enhance the function of many biomolecules [1]. The glycosylation of proteins and lipids in the extracellular matrix is important for initiating cell recognition, fine tuning inter-cell communication or establishing protective barriers. This heterogeneous functionality is provided by diversity in glycan composition and conformational flexibility [2]. Experimental insight into the interplay of these aspects at the molecular level is rather limited, and atomistic simulation techniques appear as a promising complementary approach. In our group we pursue two long-term case studies highlighting the essential aspects of the mutual interaction of carbohydrates, proteins and lipids. One of them, carried out in close collaboration with S. Barbirz (U. Potsdam), is related to the infection of the Gram-negative bacterium *Shigella flexneri* by phage Sf6, and clearly teaches us that understanding structure alone is not enough.

How do Phages Penetrate the Protective LPS Coat of Gram-Negative Bacteria?

Gram-negative bacteria protect themselves from phage invasion with a lipopolysaccharide (LPS) brush, see Fig. 1.

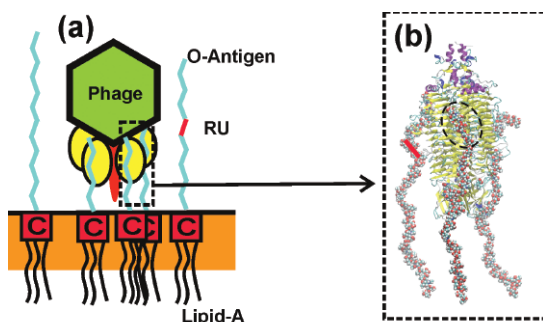


Fig. 1: (a) Schematic representation of a phage penetrating the outer LPS coat of a bacterium. The O-Antigen consists of tetrasaccharide repeat units (RU) (b) MD simulation snapshot where three O-Antigens of *Shigella flexneri* Serotype Y simultaneously attach to TSP Sf6. The dashed ellipse marks the location of a binding site that can host a 2RU (octasaccharide) fragment.

The so-called O-Antigen polysaccharide side chains normally form a repelling barrier, yet the phage's tail spike proteins (TSP) repeatedly target a specific 2RU fragment at a rather shallow binding site (Fig. 1b), cleave the chains by hydrolysis, and pave the way for DNA injection. We have recently carried out a numerical study of octasaccharides bound to Sf6 TSP, supported by detailed experimental evidence from X-ray diffraction (U. Gohlke, Max Delbrück Center Berlin), see Fig. 2, and NMR data (G. Widmalm, University of Stockholm) [3].

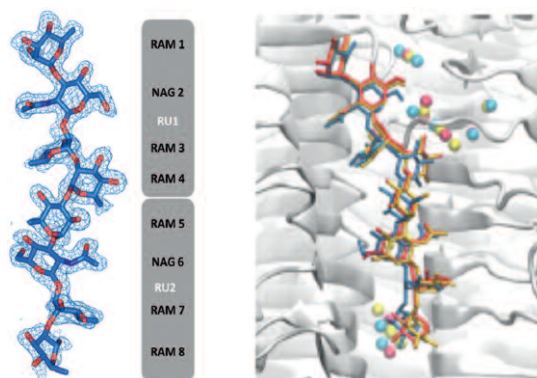


Fig. 2: Left: Stick representation of an O-Antigen octasaccharide placed within an iso-surface of the electron density map from X-ray analysis. Repeat units RU1 and RU2 consist of rhamnoses (RAM) and N-Acetylglucosamines (NAG). Right: superposition of the crystal structure (blue) and average structures of the Wild Type (red) and the E366A/D399A mutant (orange) inferred from simulations. Saturation transfer difference (STD) NMR data in solution support the binding mode shown.

The binding mode resembles the dominating solution conformation of the octasaccharide, although further numerical analysis shows that free fragments with more repeat units cannot be directly accommodated. As conveyed by Fig 1b, distortion, dynamics and conformational selection are essential aspects of the recognition process.

Our second case study, conducted in collaboration with D. Varón-Silva (Department of Biomolecular Systems, MPIKG) involves a special class of glycolipids. Here, the question in how far we can extrapolate the behavior of a larger glycan from a set of smaller fragments reappears.

The Nature of GPI Anchors

Many proteins are attached to the outer leaflet of a cell membrane by Glycosylphosphatidylinositol (GPI) anchors [1], see also Fig. 3(a). The carbohydrate part of the GPI, a linear pseudo-pentasaccharide backbone, is an invariant part of every GPI anchored protein. This short anchor segment determines how the protein interacts with the outer leaflet of the cell membrane. With a computational study, we can give insight into whether the backbone should be pictured as a spacer or rather establishes a close contact with the lipid headgroup region. It is important to realize that a GPI anchored protein consists of three different classes of biomolecules, the specificities of which usually are taken care of in independent lines of force field development. However, using corresponding force fields from the same family, we can create a reasonable hybrid representation, compare the scheme in Fig. 3(b) [5].

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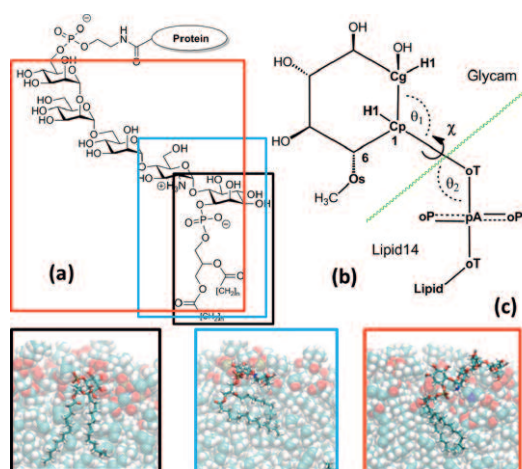


Fig. 3: (a) Chemical structure of a general GPI anchored protein; (b) scheme of the hybrid representation of the GPI anchor, the green wavy line indicates the transition from the GLYCAM (pertaining to carbohydrates) to the Lipid14 force field (optimized for lipids) of the Amber family, along with a few parameters requiring re-parameterization. (c) Simulation snapshots of the GPI fragments indicated in (a) with the hybrid model. Here, we chose palmitoyl lipid tails embedded in a POPC lipid bilayer (only one leaflet shown).

Although our previous studies of the isolated GPI backbone have suggested that it should be rather rigid (favoring the notion of a spacer), **Fig. 3** indicates that this does not exclude almost full embedding in the membrane headgroup region. The conformational preferences of the GPI backbone here are almost indistinguishable from those in isolation.

Conclusions.

Although continuous and important progress in the experimental setup and analysis of purified GPI systems has been made using, e.g., Langmuir monolayers [6], or glycan fragments as tagged molecules suitable for advanced NMR analysis [7], the *computational microscope* will remain an important device to visualize, e.g., a GPI anchor in a more natural environment. The same applies to the interaction of TSP with long O-Antigen chains. Numerically, however, we are facing a series of problems that require unconventional ideas. For instance, adequate conformational sampling of large glycans can be established in a hierarchical fashion, also including coarse-grain models. This allows us to treat rather long O-Antigen fragments [4]. In a similar way, employing a “grafting from” approach, the binding modes of O-Antigens at the TSP surface can be characterized [3]. The bound or embedded epitope is systematically grown into a larger structure, a strategy also successfully applied in the binding of multivalent glyco-oligomers to lectins [8]. The hybrid modeling of GPI anchors finally suggests a systematic “tuning” of the force field. Instead of relying on a postulated “best” set of parameters, we might be interested in how persistent simulation results are under admissible parameter changes, given the approximate nature of bio-molecular force fields in general.

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Multi-Scale Modelling of Natural Polysaccharides



Polysaccharides are among the most abundant polymers in nature and natural materials. In living organisms, the most common forms are related to structural stability or energy storage related. However, saccharides play many other important roles for instance as part of the glycocalyx, the extracellular matrix and the molecular recognition of pathogens, the extent of which has only just begun to emerge.

The basic building blocks of natural polysaccharides are simple sugars linked by glycosidic bonds to linear or branched chains, as shown in **Fig. 1**, which lead to a large variety of material properties. The diverse properties derive from the structure and hierarchical spatial organization in natural materials achieved by controlled self-assembly. The intrinsically multi-scale nature of these structures makes polysaccharides, like many biomolecules and biomaterials, challenging systems to model. While models with atomistic resolution can give a detailed picture of the molecular interactions [1] they often cannot reach the length and timescales required to sample larger biomolecules. Strategies to overcome these difficulties involve the use of simplified coarse-grained (CG) models, with fewer degrees of freedom as used in [2-4] to study membrane fusion, or enhanced sampling methods such as umbrella sampling [5, 6], or a combination of both [7]. Here we describe the application of these modelling strategies to two different natural polysaccharide systems.

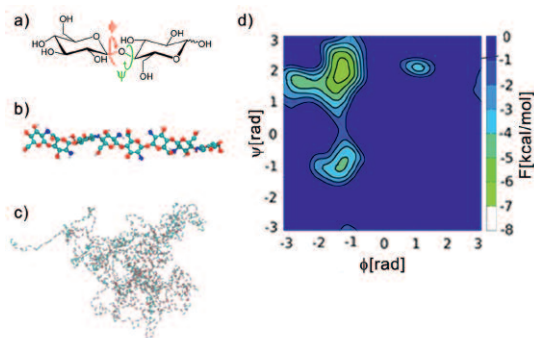


Fig. 1: (a) Chemical structure of cellobiose as a typical disaccharide. The flexible glycosidic torsion angles ϕ and ψ are highlighted; (b) all atom representation of a chitosan octamer; (c) coarse-grained representation of a chitosan polysaccharide with 1250 monomers and (d) free energy map for the conformations of the glycosidic angles in cellobiose, shown together with snapshots of the corresponding molecular conformations.

Hemicellulose Building Blocks

In many plant tissues, arrangement of crystalline cellulose fibrils embedded in a matrix of hemicelluloses polysaccharides enables the generation of reliable actuated movement [8], induced by the exceptional propensity for swelling of the hemicellulose matrix.

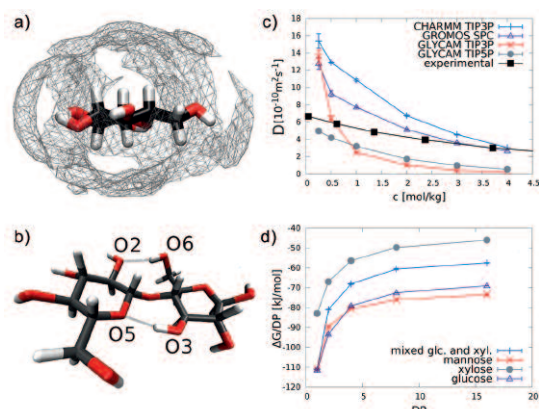


Fig. 2: Water interaction of Hemicellulose building blocks; (a) spatial distribution of water molecules around a glucose monomer. (b) intramolecular H-bond formation in cellobiose; (c) comparison of the concentration dependent diffusion coefficients for four common carbohydrate FFs with experimental data; (d) hydration free energy per monomer for short linear oligosaccharides.

All atom molecular dynamics (MD) simulations provide the means of gaining a concise understanding of local interactions of small polysaccharides with water, which are a key factor for the molecular origin of hemicellulose swelling. MD simulations rely on the accurate parametrization of the force field (FF). Since carbohydrate FFs are comparatively new and little experimental data is available, the performance of four common FFs with respect to their ability to reproduce the solution properties has been evaluated [9]. These properties include the aggregation numbers, diffusion coefficients, bulk density and the free energy of hydration of the saccharides in water.

All FFs except GLYCAM with TIP3P water, for which aggregation sets in at non-physically low concentrations of 0.5 mol kg^{-1} , show the correct trends for the aggregation and diffusion (**Fig. 2c**). As a result of the aggregation, GLYCAM-TIP3P does not lead to a reasonable dependence of the diffusion coefficients on the concentration of the sugar monomers. Inversely, at high concentrations, no FF except GLYCAM TIP3P shows aggregation. The best quantitative agreement with experimental data was found for the GLYCAM FF with TIP5P water.

Therefore, the GLYCAM TIP5P FF has been chosen to characterize the water interactions, H-bond formation both with water and within the molecule, solution properties, and solvation free energies of short segments of the most abundant hemicellulose backbone components. **Fig. 2d** shows the free energy of hydration per monomer for several such segments. The differences observed for different monomer types are almost entirely determined by the number of free hydroxyl groups, which form highly occupied H-bonds with water, resulting in the high water density regions in **Fig. 2a**. The ability to form intra-molecular H-bonds, such as in **Fig. 2b**, has a negligible effect for the short polysaccharides investigated here, because the occupancy of those H-bonds is much lower.

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Development of a Coarse Grained Model

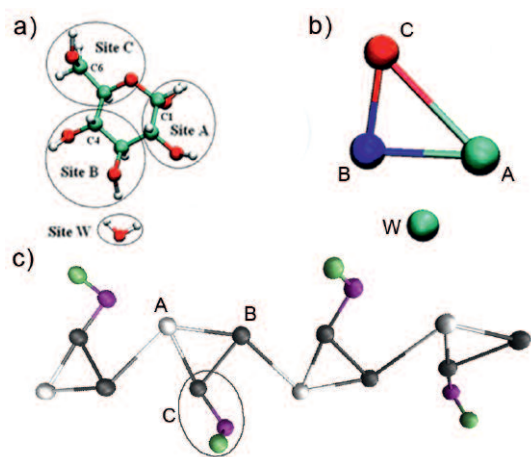


Fig. 3: CG mapping of a glucose monomer (a) all atom representation, indicating which atoms group into which CG site; (b) 3-site CG model; (c) 5-site CG model with higher resolution of the former C sites containing the C6 atom (purple & green).

Since a typical hemicellulose polysaccharide consists of more than 500 monomers, simulations with atomistic resolution of even a single molecule in water are not feasible. Therefore, we aim to develop CG models able to reproduce as much of the atomistic conformational features as possible.

After comparing several CG approaches, the best strategy for coarse-graining a solution of small oligosaccharides appears to be a hybrid method using Boltzmann inversion to parametrize bonded interactions while non-bonded interactions are constructed using the force matching procedure, which infers optimal CG interactions directly from the forces in the atomistic simulations. The CG model shown in **Fig. 3** uses three CG sites for each monomer and an explicit 1-site CG water, and is able to reproduce structural features of the saccharide solutions very successfully. The same strategy also works with implicit water for efficient simulations at constant water concentration.

In order to simulate large polymers, it is crucial to introduce transferable monosaccharide potentials from which longer polysaccharides can be constructed. However, the aggregation behavior of the CG system depends sensitively on coarse-graining parameters such as the cutoff radius used in the force matching procedure and the saccharide concentration, which differ for polymers of different length. This lack of transferability currently presents the greatest challenge for an accurate CG description. The most prominent differences in CG potentials are observed for the site containing the C6 atom. Therefore, a promising strategy is to use a higher resolution for the atoms contained in that site. In addition, methods to systematically adapt the force-matching cutoff radius, which determines how long range effects enter into the model, have to be investigated.

Chemical Potential of Water

The excess chemical potential of water μ_{ex} is a key parameter to predict the swelling behavior and water uptake for polysaccharide networks. To determine μ_{ex} a hybrid method combining Widom Test Particle Insertion and Bennet Acceptance Ratio was used. While this method yields reasonable results for all water models in pure water systems, in the saccharide solutions the “nobel” water leads to aggregation which perturbs the results significantly.

An alternative method to measure μ_{ex} directly is to confine the saccharides within a region of the simulation box with a potential mimicking a semipermeable membrane, and measuring the force on these virtual walls throughout the simulation. The latter method leads to a reasonable comparison between experimental values and simulation results for glucose solutions. An additional advantage is that, because it measures forces directly, it is straightforward to apply in the CG model, which was developed to closely mimic the forces in the atomistic model. First results for the glucose monomer solution show that the osmotic forces for the two spatial resolutions differ by at most 15%.

Polysaccharides for Biomimetic Materials

Their ready availability and versatile functionality make polysaccharides promising molecules for the development of functional materials. Many common biologically derived polysaccharides behave as polyelectrolytes and their conformation, charge density, and solubility depend strongly on pH and ionic strength of the system.

To gain a detailed understanding of the factors governing the properties of polysaccharides, we study their conformations based on the free energy landscapes of the glycosidic angles, the most flexible degrees of freedom. The free energy maps, for example shown in **Fig. 1d**, have been recorded using metadynamics MD simulations. In addition, steric repulsion between the stiff rings and, in the case of charged monomers, electrostatic interactions are taken into account. Conformations are sampled using Monte Carlo schemes for polymers. pH and ionic strength of the solution are included via protonation moves for the titratable sites, based on the intrinsic pK values of the monomers and the local electrostatic environment.

Such a relatively simple model is able to accurately predict polymer properties such as the radius of gyration, the persistence length, or the degree of protonation, for large polymers with over 1000 monomers and a large range of physic-chemical conditions.

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Protein Synthesis by Ribosomes



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The synthesis of proteins is a fundamental task of all living cells because almost every cellular process is governed by proteins. Every protein consists of at least one chain of amino acids. The concatenation of individual amino acids into peptide chains is achieved by molecular machines called ribosomes. To synthesize a protein, a ribosome uses the genetic information stored in the corresponding messenger RNA (mRNA). A mRNA consists of a sequence of codons, each of which codes for a specific tRNA and, thus, for a specific amino acid. Each amino acid is carried by a transfer RNA (tRNA) molecule. An aminoacylated tRNA and an elongation factor EF-Tu form a ternary complex that reaches the ribosome by diffusive motion. The ribosome reads the mRNA codon by codon and takes up the corresponding ternary complexes, see **Fig. 1**. This process is called translation elongation.

Protein Synthesis Proceeds with Variable Speed

Translation elongation is a nonuniform process with codon-specific elongation rates and error frequencies. This process has to meet conflicting requirements concerning speed and accuracy. On the one hand, protein synthesis must be fast enough to ensure doubling of protein mass within the time scale of cell division. On the other hand, translation must be very precise to avoid erroneous proteins that are often dysfunctional or even harmful to the cell. Therefore, perturbations that hamper or dysregulate protein synthesis can lead to all kinds of cellular defects and even to cell death, a well-known strategy to fight bacterial infections: Antibiotics kill microorganisms by blocking their protein synthesis. The speed and the accuracy of translation have direct influence, for example, on the folding dynamics of peptide chains and the functionality and abundance of the synthesized protein. It is therefore important to elucidate the underlying molecular mechanisms that influence the local and global speed and accuracy of translation. We developed and applied a new theoretical framework for the process of protein synthesis to address this question.

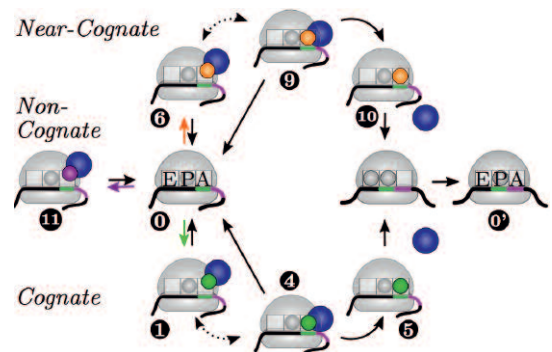


Fig. 1: Translation elongation cycle. The ribosome (gray dome) has three tRNA binding sites, the A, P, and E site. A ribosome that has just arrived at a new (green) codon of a mRNA (black-green-purple-black line) has an empty A site, whereas the P site is occupied by a tRNA (gray sphere) that is cognate or near-cognate to the preceding codon. Elongation factors (EF-Tu, large blue spheres) and tRNAs carrying amino acids (purple, orange, and green spheres) form ternary complexes. Cognate, as well as near-cognate or non-cognate ternary complexes can bind to the ribosome. Since the initial binding is not codon-specific, all ternary complexes unbind again from the internal binding site with the same dissociation rate. Alternatively, a cognate or near-cognate ternary complex can be recognized by the ribosome and is subsequently accommodated in the ribosomal A site. The new A-site tRNA is then further processed and shifted to the P site, while the ribosome translocates to the next (purple) codon. The former P-site tRNA has now reached the E site and dissociates from the ribosome. The numbers correspond to the states of the codon-specific Markov process shown in Fig. 2.

Protein Synthesis as a Markov Process

We describe translation as a Markov process to capture its stochastic nature, see **Fig. 2**. Our theory takes major aspects of in vivo protein synthesis into account: We distinguish between non-cognate, near-cognate and cognate ternary complexes, which compete for binding to the ribosome in a concentration-dependent manner. The concentrations of free ternary complexes are calculated from the total tRNA concentrations by considering the details of a tRNA life cycle. These concentrations determine the codon-specific elongation rates and error frequencies. Like many other cellular processes, translation is a complex multistep process with numerous individual transitions of the molecules involved, see **Figs. 1 and 2**. Our theory incorporates experimental data on the rates of these transitions obtained by Marina V. Rodnina and her co-workers, our collaborators from the Max Planck Institute for Biophysical Chemistry (Göttingen). All transition rates were measured in vitro because so far it is not possible to determine these rates in vivo. To bridge the gap between in vitro measurements and in vivo translation, we developed a method to predict in vivo rates from their in vitro values [1]. We introduced the kinetic distance, a new measure to quantitatively compare the kinetics of a process in different envi-

ronments, and predicted the in vivo rates by a constrained minimization of this kinetic distance. We found that nine out of twelve in vivo transition rates are similar to the measured in vitro rates, whereas the other three have considerably increased in vivo values. Closer analysis revealed that initial selection of ternary complexes and proofreading by the ribosome are much more reliable in vivo than in vitro, i.e., in vivo translation is less error-prone.

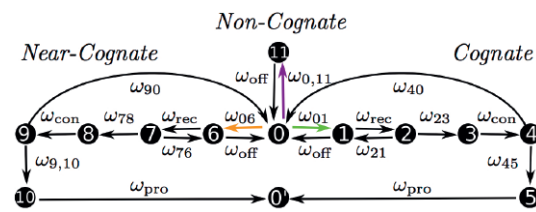


Fig. 2: Representation of translation as a codon-specific Markov process. For each codon c , the translation elongation cycle is represented by twelve states numbered from 0 to 11. The state (c|0) describes a ribosome with its A site at codon c and no initially bound tRNA. The states (c|1) - (c|5) represent the cognate branch for the decoding and full accommodation of a cognate tRNA. The states (c|6) - (c|10) belong to the near-cognate branch for the erroneous decoding of a near-cognate tRNA. The state (c|11) represents an initially bound non-cognate tRNA. An arrow from state i to state j indicates a transition with rate ω_{ij} . All rates of transitions between states are taken to be codon-independent, except for the binding rates of cognate, near-, and non-cognate ternary complexes (green, orange and purple arrows). State (c'|0') is attained by the ribosome after translocation to the next codon c' .

Protein Synthesis in Bacteria

We applied our theory to translation in *Escherichia coli* (E. coli) and studied various parametric dependencies of the translational speed and accuracy. We found that the overall speed of protein synthesis strongly depends on individual tRNA concentrations, see Fig. 3, and on the abundance of active ribosomes. Furthermore, the overall elongation rate exhibits a phase transition at low tRNA and at high ribosome concentrations. We also found that codon-specific elongation rates and error frequencies are considerably influenced by the overall codon usage in the cell, see Fig. 3 [2]. We focused on translation in E. coli because of the extensive database available for these cells. However, our theoretical framework is general and can be applied to all prokaryotic and eukaryotic cells. It can be used, for example, to study protein synthesis in human mitochondria, which are to some extent similar to bacteria, reflecting the endosymbiotic origin of these organelles. Our theoretical framework can also be applied to protein synthesis in eukaryotic cells to predict mutated codon sequences of individual genes that lead to an optimized gene expression in human cells and yeast in the context of protein-based vaccines.

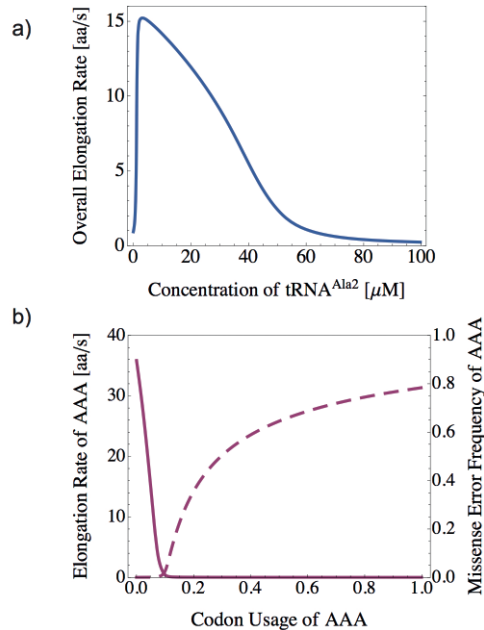


Fig. 3: Speed and accuracy of protein synthesis. (a) Influence of individual tRNA concentration on overall elongation rate. Only the concentration of $tRNA^{Ala2}$ was varied, while leaving the concentrations of all other tRNA species at their in vivo values. (b) Dependence on codon usage (relative frequency) of codon AAA for fixed ratios of the codon usages of all other codons. The concentration of free Lys-tRNA^{Lys} ternary complex decreases when the codon usage of one of its cognate codons, AAA, increases (not shown). This relationship leads to a decreasing elongation rate of codon AAA (solid line, left axis), and an increase in the near-cognate missense error frequency of AAA (dashed line, right axis).

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Protein Binding and Membrane Adhesion



Binding of Membrane-Anchored Proteins

Biological processes often involve the binding of proteins. These proteins are either soluble, i.e. free to diffuse throughout intracellular compartments or extracellular spaces, or are anchored to membranes that surround cells or cellular compartments. The membrane proteins are central for numerous biological processes but much less understood than soluble proteins since their structure and function is more difficult to assess in experiments. Key biological processes that are mediated by the binding of membrane-anchored proteins are the adhesion of cells and the adhesion of vesicles to cells or organelles in immune responses, tissue formation, cell signaling or intracellular transport. The adhesion processes depend sensitively on the binding constant of the membrane-anchored receptor and ligand proteins that mediate adhesion, but this constant is difficult to measure in experiments.

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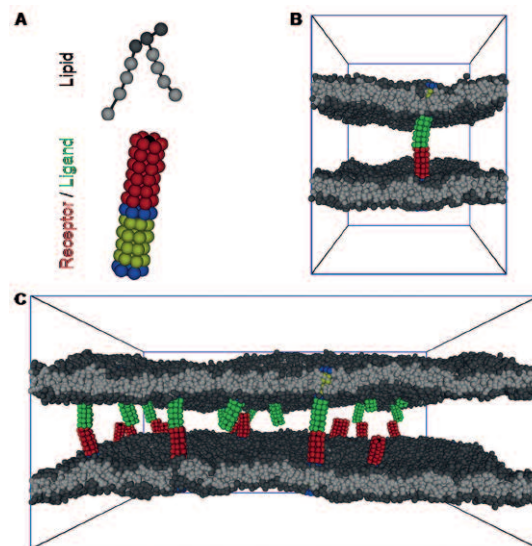


Fig. 1: (A) Coarse-grained structures of a lipid molecule and of a membrane-anchored receptor or ligand. (B) Simulation snapshot of two apposing membrane segments bound together by one receptor-ligand bond. (C) Larger membrane segments bound by many receptor-ligand bonds.

We have investigated the binding of membrane-anchored receptor and ligand proteins with molecular dynamics simulations (Fig. 1). These simulations indicate that the binding constant of the anchored proteins strongly decreases with the membrane roughness caused by thermally excited membrane shape fluctuations on nanoscales (Fig. 2). In addition, we have derived a theory that explains the roughness dependence of the binding constant for the anchored proteins from membrane confinement and that relates this constant to the binding constant of soluble proteins without membrane anchors. Since the binding constant of soluble proteins is readily accessible in experiments, our results provide a novel route to compute the binding constant of membrane-anchored receptor and ligand proteins [1].

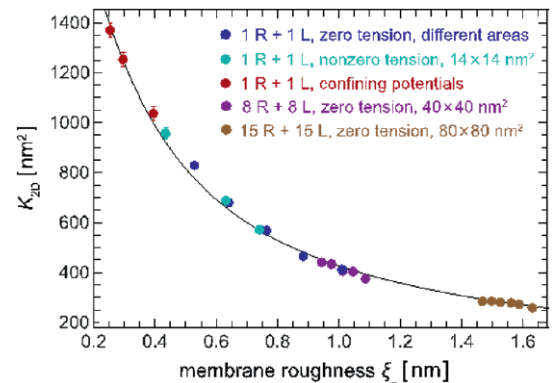


Fig. 2: Binding constant K_{20} for receptor-ligand binding as a function of membrane roughness of the two apposing membranes caused by thermally excited membrane shape fluctuations. The data points are from molecular dynamics simulations of a variety of membrane systems that differ in the number of receptors R and ligands L , the membrane area, or membrane tension. The red data points are from simulations with confining membrane potentials that strongly suppress shape fluctuations. All simulations are performed at an average separation of the membranes that is close to the optimal separation for binding at which the binding free energy is maximal.

Conformational Changes During Protein Binding

Protein binding often involves conformational changes [2,3]. Advanced NMR experiments indicate that these conformational changes can occur in the absence of ligand molecules (or with bound ligands), and that the ligands may 'select' protein conformations for binding (or unbinding). We have argued that this conformational selection requires transition times for ligand binding and unbinding that are small compared to the dwell times of proteins in different conformations, which is plausible for small ligand molecules [2]. Such a separation of timescales leads to a decoupling and temporal ordering of binding/unbinding events and conformational changes. We have proposed that conformational-selection and induced-change processes (such as induced fit) are two sides of the same coin, because the temporal ordering is reversed in binding and unbinding direction (Fig. 3). Conformational-selection processes can be characterized by a *conformational excitation* that occurs *prior* to a binding or unbinding event, while induced-change processes exhibit a characteristic *conformational relaxation* that occurs after a binding or unbinding event. The ordering of events can be determined from relaxation rates in mixing experiments, and from the conformational exchange rates measured in advanced NMR or single-molecule experiments [2]. For larger ligand molecules such as peptides, conformational changes and binding events can be intricately coupled and exhibit aspects of conformational-selection and induced-change processes in both binding and unbinding direction.

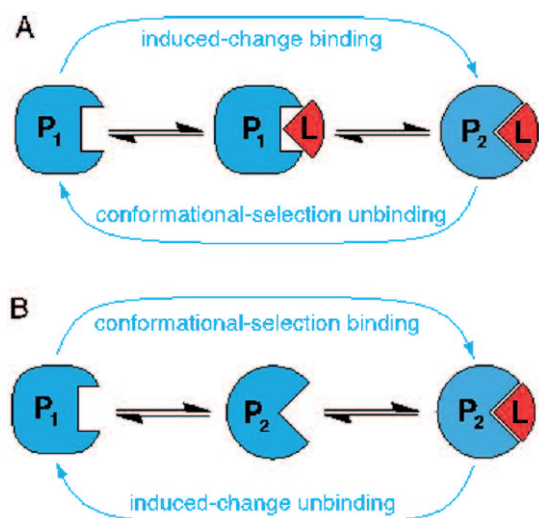


Fig. 3: Two different binding/unbinding pathways that connect the unbound ground state P_1 and bound ground state P_2L of a protein with two conformations 1 and 2. The intermediate states along these pathways are higher-energy, excited states: the state P_1L in (A) is higher in energy than the bound ground state P_2L , and the conformation P_2 in (B) is higher in energy than the unbound ground-state conformation P_1 . Along pathway (A), the conformational change occurs after the binding of the ligand molecule L , and is apparently 'induced' by this binding event. In the reverse direction from P_2L to P_1 , the conformational change occurs prior to the unbinding of the ligand. The ligand thus appears to 'select' the excited-state conformation P_1L for unbinding. Along pathway (B), the ligand binds via conformational selection, i.e. the conformational change occurs prior to ligand binding. In the reverse direction from P_2L to P_1 , the conformational change is induced by the unbinding of the ligand. The conformational transitions of the induced-change processes in (A) and (B) are relaxations into a ground state. The conformational changes of the conformational-selection processes, in contrast, are excitations.

Wrapping of Nanoparticles by Membranes

Advances in nanotechnology have led to an increasing interest in how nanoparticles interact with living organisms. To enter the cells or cell organelles of such organisms, nanoparticles have to cross biomembranes. This crossing requires the wrapping of the particles by the membrane and the subsequent fission of a membrane neck if the particles are larger than the membrane thickness and cannot permeate the membrane directly. In general, both wrapping and fission can either be passive, or can be actively driven or assisted by protein machineries that consume chemical energy. Passive wrapping can occur if the adhesive interaction between the nanoparticles and membranes is sufficiently strong to compensate for the cost of membrane bending [4].

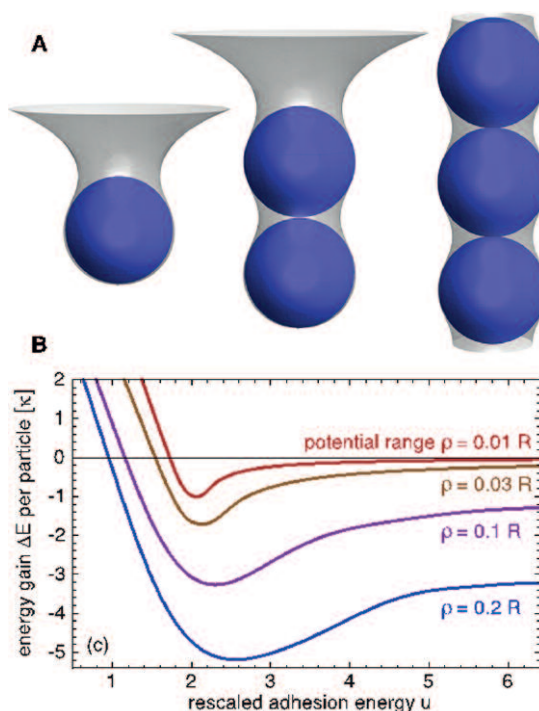


Fig. 4: (A) From left to right: A single particle wrapped by a membrane, two particles wrapped cooperatively in a membrane tube, and three central particles in a long tube. (B) Energy gain ΔE for the cooperative wrapping of particles in a long tube relative to their individual wrapping. The energy gain strongly depends on the range ρ of the particle-membrane adhesion potential, and on the rescaled adhesion energy $u = UR^2/\kappa$ where U is the adhesion energy per area and R is the particle radius. The bending rigidity κ of the membranes is of the order of $10 k_B T$.

Our recent Monte Carlo simulations of passive wrapping (reviewed in [4]) indicated the cooperative wrapping and internalization of spherical nanoparticles in tubular membrane structures. To understand the formation of these tubular structures, we have systematically investigated the energy gain of this cooperative wrapping by minimizing the energies of the rotationally symmetric shapes of the membrane tubes and of membrane segments wrapping single particles [5]. We have found that the energy gain for the cooperative wrapping of nanoparticles in membrane tubes relative to their individual wrapping as single particles strongly depends on the ratio ρ/R of the particle radius R and the range ρ of the particle-membrane adhesion potential (Fig. 4). For a potential range of the order of one nanometer, the cooperative wrapping in tubes is highly favorable for particles with a radius of tens of nanometers and intermediate adhesion energies, but not for particles that are significantly larger.

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Phase Separation in Multicomponent Membranes



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In recent years, the prevailing view of cell membrane structure has gradually evolved from the fluid mosaic model proposed by Singer and Nicolson to a heterogeneous membrane model with domains of lipids in the liquid-ordered (Lo) phase surrounded by lipids in the liquid-disordered (Ld) phase. The Lo domains (also called lipid rafts) are rich in cholesterol and saturated lipids, and are thought to play an important role in regulation of cell processes. To gain insight into the roles of individual membrane components, a variety of model membrane systems have been established, containing the lipid species of interest and exhibiting the richness of phase coexistence as in cell membranes. Giant unilamellar vesicles (GUVs) are a particularly practical biomimetic tool for displaying membrane behavior directly under the optical microscope [1, 2]. We employed these cell-sized biomimetic systems to study the phase state of membranes composed of ternary lipid mixtures [3, 4] and the influence of proteins such as cytochrome c adsorbing onto the membrane [5, 6].

Phase Diagrams of Ternary Lipid Mixtures

A typical phase diagram of a ternary lipid mixture is given by the Gibbs triangle in Fig. 1. It characterizes membranes composed of DOPC, an unsaturated lipid with a low melting temperature, sphingomyelin (SM), a high melting temperature lipid, and cholesterol (Chol). Each point in the Gibbs triangle represents a certain membrane composition. The corners and the borders of the triangle correspond to single- and two-component membranes, respectively. The membrane can exhibit Lo, Ld or solid (S) phase or their coexistence and the colored areas indicate such coexistence regions. The phase state of the membrane can be assessed from the domain shapes and mobility. Domains are visualized by incorporating a small fraction (<0.5 mol%) of fluorophores, which preferentially partition in certain phases.

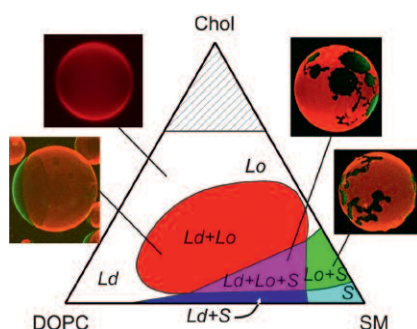


Fig. 1: Phase diagram of the ternary lipid mixture DOPC/SM/Chol at 23.5°C [3]. Tentative boundaries of one-, two-, and three-phase regions are shown. The hatched area indicates the solubility limit of cholesterol, above which no membrane is formed. The images illustrate vesicles with homogeneous or phase-separated membranes corresponding to certain regions of the phase diagram. The vesicles are around 30 μm in diameter.

Problems with Multicomponent Vesicles

Phase diagrams as in Fig. 1 can be determined by preparing and examining GUVs with membrane compositions that vary over the whole Gibbs triangle. However, vesicles from the same batch can have very different compositions depending on their individual history. For example, before observation, a phase-separated vesicle may have budded yielding two daughter vesicles with two compositions that both differ from the composition of the mother vesicle. Thus, vesicles both with and without domains can be detected in the same batch. Deviations in the vesicle composition in a batch can be well demonstrated by the distribution of the area fraction of one of the domain types. If all vesicles had the same composition, they should exhibit the same domain surface area fractions. However, the observed distribution of area fractions is often quite broad, see Fig. 2.

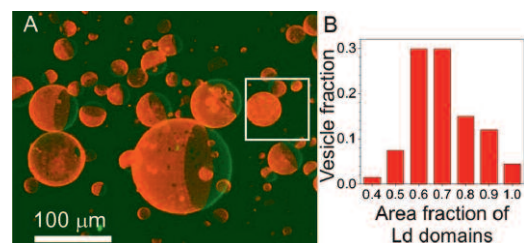


Fig. 2: Compositional inhomogeneity of vesicles prepared from mixture of 40/40/20 mol% DOPC/SM/Chol observed at 23°C. (A) 3D projections reconstructed from confocal series. Vesicles with this composition exhibit phase separation, as observed for all vesicles on the image except for the framed one. This vesicle has no domains. (B) Distribution of the area fraction of red (Ld) domains over a population of ~70 vesicles from the same batch [3].

To overcome this problem, we use an alternative method to obtain a specific vesicle composition: we produce vesicles with domains via electrofusion of two vesicles made of two different fully miscible lipid mixtures. After electrofusion, the lipids in the newly created vesicle redistribute as described by the phase diagram.

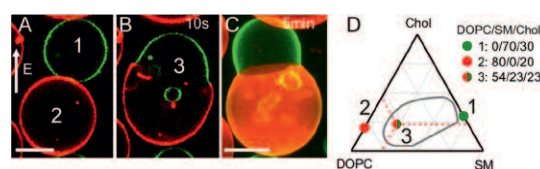


Fig. 3: Electrofusion of single- or two-component vesicles provides a novel protocol to create three-component vesicles with precisely controlled composition. (A–C) Fusion of two vesicles: confocal microscopy cross sections (A and B) and a 3D projection (C). Vesicles 1 and 2 were subjected to an electric pulse (400 kV/m, 150 μs ; arrow indicates the field direction) and fused to form vesicle 3 shown in B and C. The time after application of the electric pulse is indicated in the upper-right corners. (D) Compositions of the vesicles in the images. Scale bars correspond to 20 μm .

Tie-Line Determination

Knowing the boundaries of the coexistence regions in the phase diagram is not sufficient to characterize the composition of domains in a multicomponent vesicle. In order to determine the latter, we need to know the tie lines in the coexistence region. Locating these lines is challenging because the coexisting phases in the bilayer membrane cannot be physically isolated and then analyzed for chemical composition. We proposed a new method for locating the tie lines based on microscopy quantification of the domain surface areas in GUVs produced by the electrofusion of two- or single-component vesicles. Contrary to other approaches, this method allows for direct observation of the membrane behavior under the microscope, and easily provides many tie lines.

Domain surface areas obtained from the 3D confocal scans recorded right after electrofusion were used to calculate the composition of the fused vesicle. The method for tie-line determination is based on quantifying the domain areas in the obtained three-component vesicle after equilibration. By applying the lever rule, we can also predict the approximate location of the critical point by extrapolating a curve passing through the midpoints of the found tie lines, see Fig. 4.

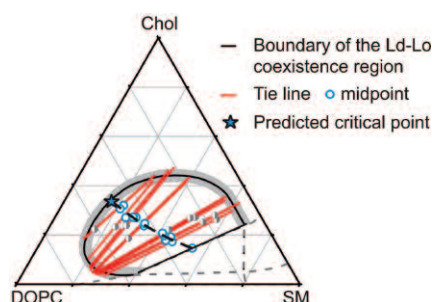


Fig. 4: Tie lines in the phase diagram DOPC/SM/Chol at 23°C [3]. Half-solid circles in gray indicate the compositions of the fused vesicles whose images were used to locate tie lines (red). The Ld-Lo coexistence region is indicated by the solid black curve shown with ± 2 mol % deviation in gray. The blue open circles indicate the midpoints of the found tie lines, and the dashed black curve serves as a guide to the eye to connect them. It is extrapolated to the boundary of the Ld-Lo coexistence region to predict the location of the critical point as indicated by the star.

Effect of Cytochrome C on the Membrane Phase State

Interactions of water-soluble proteins with membranes play an important role in many biological processes, such as signal transduction and transport processes. A good example for such a protein is cytochrome c (cyt c), a globular heme protein carrying approximately 4 effective positive charges. Upon adsorption to a membrane composed of negatively charged and neutral lipids, a positively charged protein may induce local changes in lipid composition. We used cyt c to address the effect of adsorption of a positively charged protein to negatively charged membranes with several fluid domains. First, we characterized GUVs composed of DOPG, a negatively

charged lipid, SM and cholesterol. Confocal microscopy was used to explore more than 70 different membrane compositions in the Gibbs triangle of the DOPG/SM/Chol mixture at room temperature and to locate the Ld-Lo coexistence region in the absence of cyt c, see area shaded in yellow in Fig. 5.

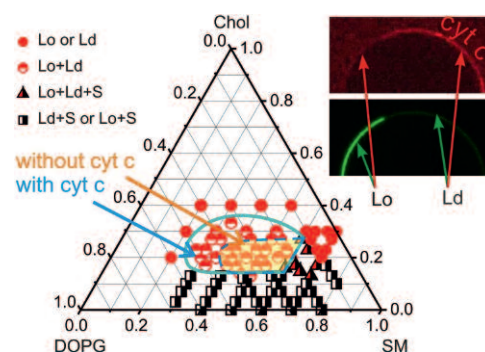


Fig. 5: Cyt expands the Ld-Lo coexistence region in the phase diagram of DOPG/SM/Chol at 23°C. The protein concentration was 0.56 μ M. The inset in the upper right corner shows that cyt c preferentially adsorbs to the Ld phase domain as demonstrated by cross section confocal images of a GUV (red and green channel) composed of a 40/40/20 mixture of DOPG/SM/Chol, with fluorescent lipid dye (green) partitioning predominantly in the Lo phase and labeled cyt c (red) adsorbing predominantly to the Ld phase [5, 6]

We then studied the influence of cyt c on the membrane phase behavior. Upon the addition of cyt c, the area of Ld domains (rich in charged DOPG) was found to increase. Apparently, the bound protein attracts more charged lipids to the liquid disordered domains where it predominantly binds (see inset in Fig. 5). In addition, the protein was found to induce micron-sized domains in membranes belonging to the single-fluid-phase region of the protein-free ternary mixture and, as a result, to expand the Ld-Lo coexistence region, see Fig. 5. The protein also induced vesicle leakage even at relatively low concentrations.

In eukaryotic cells under normal physiological conditions, cyt c is localized within the intermembrane space of mitochondria. Thus, during cell apoptosis when cyt c is released into the cytosol and adsorbs to intracellular membranes, it may strongly perturb the lipid distribution within these membranes and induce their leakage, thus, further enhancing the process of apoptosis.

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Phase Transitions and Transport Phenomena at Solid/Air-Interfaces



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We are interested in the impact of interfacial energy contributions on the phase behaviour of nano-size systems and how interfacial contributions affect volume flows (via surface Marangoni-flows).

Both of these phenomena are practically relevant. Phase transition processes of small/confined systems, in particular nucleation phenomena, are ubiquitous (from cloud formation to metallurgy). Liquid flows induced by surface tension gradients are for instance important in ink jet printing.

The nucleation studies are partly performed within an international graduate school (funded by DFG) in collaboration with universities in the Berlin area and partners in the US (NC State). Some of the Marangoni-flow activities occur in collaboration with French research groups (CEA, Saclay and ICSM, Marcoule).

Our research topics and collaborations are motivated by applications. But our research clearly focuses on a better fundamental understanding of the phenomena.

Melting/solidification of Nano Size Structures

We investigate how interfacial contributions affect the nucleation and phase transition behavior of small, confined systems (e.g., small islands on inert surfaces). As experimental systems for this topic, we use terraces (films/multilayers) of long chain alkanes at SiO_2/Air interfaces. The melting is imaged by interference-enhanced microscopy. The findings are analyzed analytically and by simulations.

Our main focus is on how the melting behavior of nano size aggregates is affected by the aggregate geometry (shape, faceting, grooves, edges, etc.) and by their wetting properties. The aim is an improved understanding of the melting process. Very little is known about this process because the emerging liquid phase has no memory of it (in contrast to the reverse solidification process).

First order phase transitions implicate the formation of an interface between the old and the new, emerging phase. This formation process usually causes a nucleation energy barrier for the transition. The nucleation is heterogeneous when the emerging phase is in contact with other (inert) phases in addition to the interface between old and new phase. The latter configuration lowers the energy barrier. If the topography between emerging phase and inert template is non-planar or if the solid is faceted with different interfacial energies, the impact on the nucleation barriers and on the nucleation paths depends on all these properties.

For melting, empirically in virtually all cases and for virtually all substances, no nucleation barrier is found.

It is commonly assumed that the liquid melt completely wets all solid facets, which would result in a vanishing nucleation barrier for all facets. This assumption has never been proven or tested. To explain the experimental findings it would suffice if melting starts locally i.e., if the nucleation barrier for melting is vanishing only locally or for specific facets/interfaces. Virtually every macroscopic systems has nano size geometrical features, which can serve as such "defects". Therefore nano-size systems with known wetta-

bilities and geometries are much better suited to investigate the melting process.

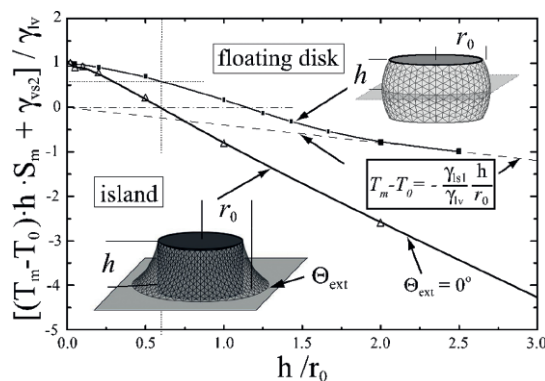


Fig. 1: Scaled shift of the melting temperatures (T_0 = bulk melting temperature) of floating disks and of round islands as a function of the ratio between height and radius, h/r_0 (S_m = melting entropy, γ = interface energies). For comparison also a typical "Gibbs-Thompson"-behavior ($T_m - T_0 \propto 1/h_0$) is shown. Small aggregates can even be overheated.

Our experimental and theoretical studies on small systems reveal details on the melting kinetics. We find for instance, nucleation barriers for the melting of real systems (alkane films) and a melting behavior that is very different from the commonly accepted, single-parameter "Gibbs-Thompson"-behavior ([1], Fig. 1).

Patterned Growth Induced by Heterogeneous Nucleation

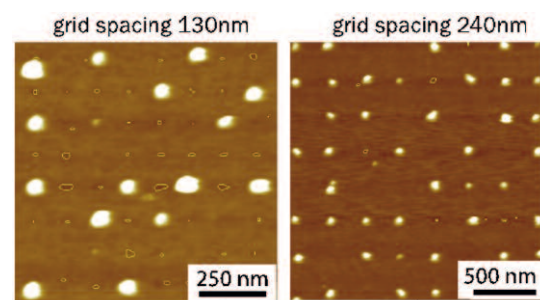


Fig. 2: AFM-image of regular arrangements of C60-aggregates on a regular rectangular 8×8 pattern of indents in a smooth planar substrate (SiO_2 , surface roughness less than 0.4nm). The indents have diameters of about 20nm. Their depth is less than 1nm.

Heterogeneous nucleation is investigated with planar solid substrates that are pre-structured with an array of nano-indents. Although the indents are very shallow, C60 aggregates that precipitate from solution during spin casting preferentially adsorb within the indents and thus replicate the pattern geometry (Fig. 2). This behaviour is not yet understood.

To gain better quantitative insight into the spatio-temporal evolution of the solute/solvent evolution during the film thinning, leading to the phenomena depicted in Fig 2, the spin casting process itself is analyzed theoretically [2] and experimentally (Fig. 3).

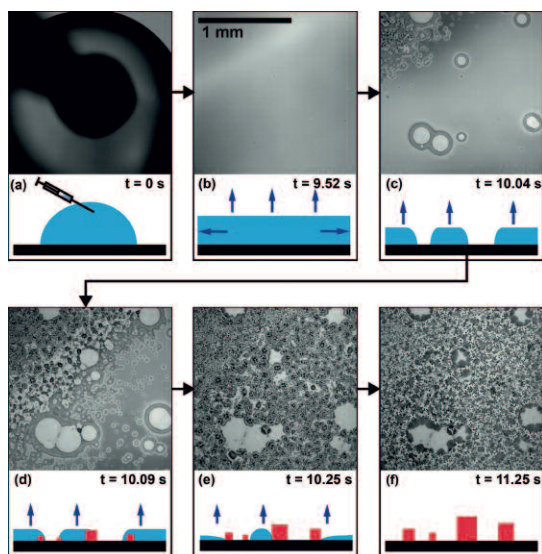


Fig. 3: On-line, time resolved optical imaging of film thinning, precipitation and dewetting during spin casting of mixture of volatile solvent and non-volatile solute (0.5M NaCl in H₂O).

In a related project we also investigate how nano-size interfacial features induce the local formation of gas bubbles within supersaturated solutions. We focus, in particular, on the unknown process how local gas enrichments eventually (trans)form into gas bubbles.

Drop-Drop Coalescence, Interfacial Flow and Drop Evaporation.

The coalescence of sessile droplets is governed by interfacial effects. Capillarity favours fast drop coalescence. With different liquids in both drops however, surface tension gradients may form in the region where the drops connect. The resulting Marangoni flows can unexpectedly cause a long delay of the drop coalescence. The main drop bodies remain separated while connected via a thin neck through which the drops exchange liquid. For simple liquids this phenomenon is meanwhile understood.

Currently we investigate the coalescence behaviour of drops containing different, reacting liquids, which can induce fascinating, self-organized pattern formation (Fig. 4).

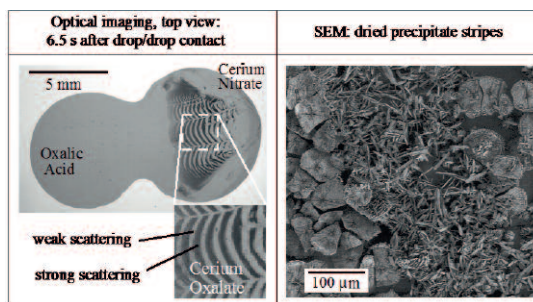


Fig. 4: Patterned precipitation of Cerium-Oxalate appearing during the coalescence of sessile drops with reacting liquids. The SEM images from the dry precipitate show that the stripes consist of different aggregate sizes.

In a related project we also investigate the evaporation behaviour of sessile drops from mixtures of liquids with different volatilities. This behaviour is complicated and not well understood because the locally heterogeneous evaporation flux from sessile drops induces spatio-temporal variations of the liquid composition (e. g., the selective enrichment of components at the drop perimeter) and leads to various interacting transport processes (Fig. 5).

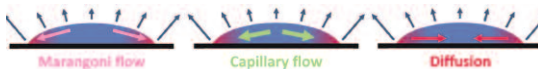


Fig. 5: In the case of complex fluids the locally heterogeneous evaporation flux of sessile drops (indicated by the different lengths of the arrows) can induce spatial constitutional variations and thus various (local) transport processes.

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Stochastic Processes in Biological Systems



Single-Molecule Modeling of mRNA Degradation

The control of the amount of messenger RNA (mRNA) is a key component of the regulatory apparatus of gene expression. Controlled transcription and degradation of mRNA guarantee the timely modulation of mRNA abundance during the lifetime of the cell and an appropriate response to external stimuli. Large experimental research efforts are devoted to uncovering which complex set of proteins and enzymes is responsible for the degradation of mRNA. Most of these studies approach the problem by formulating a single-molecule perspective according to which the mRNA consecutively binds to different complexes until final degradation eventually happens. The experimental studies are thus aimed at defining the interaction network of the target mRNA with these complexes. To achieve this purpose, very ingenious techniques are used to single out the relative strength of various protein complexes on the process of degradation. However, it is still not possible to experimentally monitor single mRNA molecules during the process of degradation. Indeed, all available experimental techniques just allow monitoring the decay pattern of the average amount of mRNA, which is the amount of mRNAs left after a certain time in the cell culture.

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Traditionally, decay patterns are either compared qualitatively, to decide which pattern decays faster than another, or are assumed to be exponential functions and fitted to deliver the rate of degradation. In both cases, no useful conclusion can be drawn about the underlying interaction network responsible for the degradation of the mRNA. Moreover, if there is a (complex) interaction network the decay pattern should not be exponential and it should contain some information about the structure of the network.

An extensive analysis of published data of mRNA decay patterns has convinced us that indeed only a fraction of the experimental patterns are exponential. This fact convinced us to develop a mathematical framework to relate the single-molecule viewpoint of mRNA decay with the bulk decay patterns that are experimentally accessible [1]. This mathematical approach is based on two complementary methods. On the one hand, a very general approach, technically close to survival data analysis, shows that non-exponential decay patterns are related to age-dependent degradation processes. On the other hand, by interpreting the degradation interaction network in terms of Markov chains it is possible to find the structure of the most parsimonious network compatible with data and thus derive both an explicit form of the lifetime distribution and of the age-dependent degradation rate.

Based on the first approach, we have been able to find a mathematical expression of the age-dependent degradation rate when ribosomes shield the mRNA against degradation factors [2]. The shielding process is known to happen in many organisms. In *E. coli*, in particular, it is easy to see this effect because of the short lifetime of the mRNA. Based on the Markov chain approach, we have been able to reconstruct the backbone of the interaction network with which miRNA mediates the degradation of its target mRNA [3]. In particular, through data analysis of various knock-down experiments in *drosophila*, we found out that the silencing complex miRISC interacts with the proteins NOT1 and PAN3 before recruiting the mRNA for deadenylation. This finding unveils a new aspect of the interaction network of miRNA-mediated degradation that was unknown before (see Fig. 1).

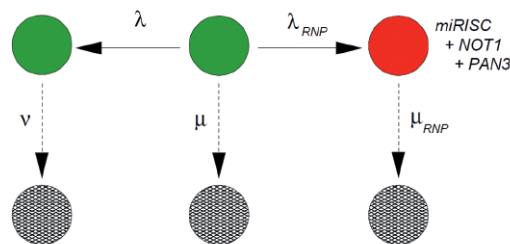


Fig. 1: The network of states responsible for the miRNA-mediated mRNA degradation. The green central dot represents the mRNA before the process of degradation starts. The red dot is the mRNA after having been recruited by miRISC bound to NOT1 and PAN3. According to our analysis [3], this is the most parsimonious network supported by the available data.

Structure and Properties of Complex Stochastic Networks

Many single-molecule processes, including mRNA degradation [3] and molecular motor movements [4], are successfully modelled as Markov chains on a network of states. In many cases, some of the interesting properties are expressed in terms of first passage time distributions. For instance the step duration of a kinesin molecule, the lifetime of a mRNA molecule, or the time until detachment from a filament are all technically computed as first-passage times or as absorption times. Sometimes, however, the structure of the underlying network is only partially known but first passage time measurements between two chosen states or configurations are available. Which kind of information about the underlying network of states is contained in the distribution of the first passage times? If we had the lifetime distribution of the mRNA, what would this tell us about the network of states underlying its controlled degradation? If we had the distributions of the duration of each kind of molecular motor steps, what would these tell us about the structure of the underlying chemomechanical network? In computer simulations of single-molecule transitions, if we had the first-passage time distributions of the visits to configuration B starting from configuration A, what would this tell us about the structure of the free-energy landscape between A and B?

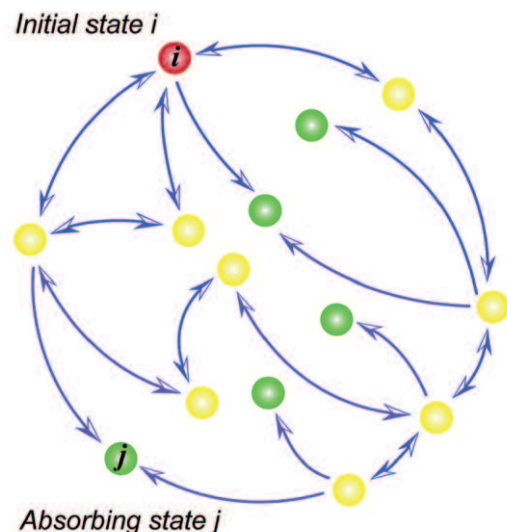


Fig. 2: A generic network of states for a Markov chain. The probability density of the first passage time from state i to state j has a short time behavior that grows linearly in time because the shortest path from i to j contains only one intermediate state [5].

In a work that generalizes an idea of Li and Kolomeisky (2013), we found out that for any general Markov chain on a network of states the first term of the Taylor series (dominating the short time behaviour) of the first-passage time density is necessarily an integer power of time. Using graph theory methods we then showed that this power is a linear function of the number of states along the shortest path(s) from the initial to the final state [5] (see Fig. 2). In particular, the power of the first term of the density will be zero only if there is a direct connection between the initial and the final state. Thus, as a tool to discover network structures, the fit of the early time behaviour of experimental first-passage time densities may reveal the number of intermediate states between two accessible states. A natural generalization in this context concerns an extension to semi-Markov chains, where the dwell times on the states can be assumed to be distributed according to a generalized Gamma density. Also in this case, the short time behaviour of the first passage time density reveals the number of intermediate states but some details of the dwell time distributions must also be known [6]. In complex networks there are usually many paths that join one state to another. Some of these paths are shorter than others but may be slow on average while other paths might be longer but faster on average. Which one of them characterizes the short time behaviour of the first-passage time density? In other terms, if we select transition paths according to which one is the fastest, are we also selecting for the most probable path? Not always. In fact, even if a path is highly improbable but shorter than any other path, there exists a time scale below which almost all realizations will occur through the shortest path [7].

When a process is conditioned to first pass through a state before another state is equivalent to a condition in the future outcome. Processes conditioned in their future outcome are very difficult to study because their properties are quite counterintuitive, as the example of the shortest path described above illustrates [7]. Mathematically, these conditioned processes are related to the original unconditioned process through a Doob-h transform, which essentially completely transforms all the rates of the original process. Among the strange properties produced by this transformation, there are new forms of time duality and balance relationship similar to detailed balance even when the process is not at equilibrium. The structural properties of the network of states that generate such time duality are a topic in current development in the field of Markov chains and their application [8].

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Regulation of Bio-Processes



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Biological processes must obey the laws of physics, but are also subject to functional requirements and shaped by the forces of evolution. Our group is interested in how functional requirements are implemented within the given physical constraints. To that end, we develop theoretical tools to describe complex regulatory systems and their coupling to the cellular context. Focusing on bacterial systems, we address these questions in two main areas, *gene regulation* and *cell growth* as well as *bacterial motility*. In both areas we build on our expertise on *molecular motors* and *machines*.

Gene Expression and Cell Growth

A long-term interest of the group is the unavoidable coupling of expression of any gene to the physiological state of the whole cell, through (among other things) the sharing of gene expression machinery. Exponentially proliferating bacteria provide a good model system to address these questions, as the physiological state of the cell can to a large extent be characterized by a single parameter, the cell's growth rate. We develop theoretical methods to describe such coupling and include growth-rate dependence into descriptions of gene circuits [1]. In addition, we study the effects of shared gene expression machinery, i.e. RNA polymerases, ribosomes and their associated factors.

In rapidly growing bacteria, ribosomes are a limiting commodity for the synthesis of proteins and, thus, cell growth. A striking demonstration of the link between ribosomes and growth is the linear relation between ribosome concentration and growth rate (Fig. 1). This relation reflects the autocatalytic activity of ribosomes that synthesize ribosomal proteins. We could recently show that the linear relation is consistent with a translation speed that is a function of the growth rate [2], reconciling two observations that were previously believed to be in disagreement. The modulation of the translation speed could be explained as resulting from a balance between the cost of making more ribosomes and the cost of making more elongation factors that are needed to speed up the ribosomes. Based on this analysis we concluded that the underlying allocation of resources is close to optimal. Moreover, our theoretical analysis also indicated that the cost associated with the translation speed arises from the slow diffusion of the large elongation factor complexes in the crowded cytoplasm.

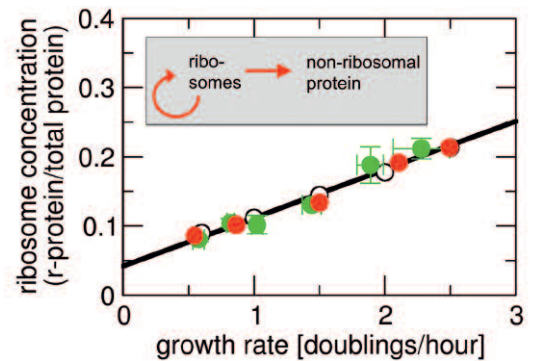


Fig. 1: A linear relation between cellular ribosome concentration and growth rate, here for the bacterium *Escherichia coli*, reflects the autocatalytic activity of ribosomes making ribosomal protein. Studying the allocation of ribosomes, toward making ribosomal proteins versus making factors affecting the speed of translation, provides a window into the economic principles of the cell [2].

Competition for gene expression machinery is also crucial in the case of sigma factors, proteins associated with RNA polymerases in bacteria. Sigma factors direct RNA polymerases to subclasses of genes and play an important role during the switch of gene expression programs in stress responses. During stress responses, genes under the control of different sigma factors become coupled and exhibit “passive control”, i.e. genes become up- or down-regulated indirectly because competing genes are actively regulated in the opposite direction. In particular, we found that type of control can be hypersensitive to changes in RNA polymerase core enzyme concentration, indicating a strong role in stress responses such as the stringent response [3].

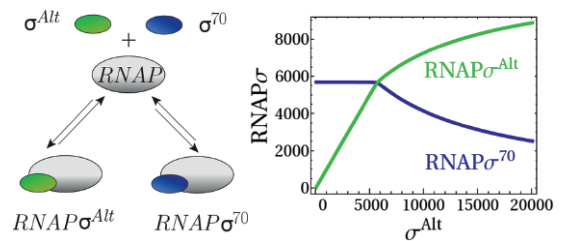


Fig. 2: Sigma factor competition: Two types of sigma factors (σ^{70} and σ^{Alt}) compete for binding to the RNA polymerase (RNAP) core enzyme and direct it to different sets of genes. Beyond a threshold concentration of σ^{Alt} , competition sets in and any further increase in the concentration of σ^{Alt} indirectly inhibits the formation of the $RNAP\text{-}\sigma^{70}$ complex and the expression of the associated genes.

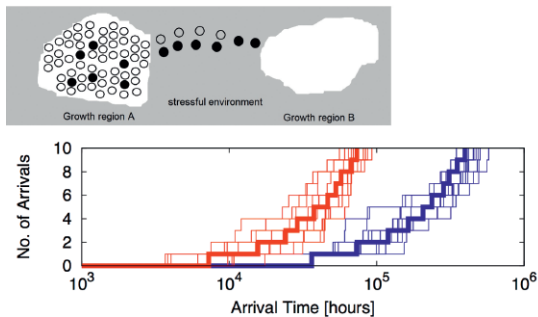


Fig. 3: Crossing of a stressful environment by a heterogeneous population: A population (red trajectories) with a small subpopulation of more tolerant cells (black cells in the sketch) spreads faster in space than a homogeneous population (blue) with only one cell type (white) [4].

In addition, we are interested in understanding the consequences of the coupling of gene expression and growth, in particular for cases where growth mediates (wanted or unwanted) feedback [1]. We have focused on cases where positive feedback leads to phenotypically heterogeneous populations with subpopulations growing with different growth rates. An important example is bacterial persistence, where a slow-growing subpopulation has increased tolerance towards antibiotics. These examples also allow us to study the population dynamics with phenotypic heterogeneity. Heterogeneity arises as a strategy to survive in varying environmental conditions. We proposed recently that it also provides an advantage for the spreading of a population in spatially structured environments (Fig. 3) [4].

Bacterial Motility

The second topic of the group is bacterial motility. Recently, we have studied two systems, both in collaboration with experimental groups: twitching motility and magnetotaxis (Fig. 4). In the case of twitching motility (in collaboration with the group of B. Maier, Köln), we have focused on the mechanical coordination of type IV pili that exert forces on each other. The pili are filamentous appendages of these cells that pull the cells forward through cycles of growth, adhesion to a surface and retraction. We have developed a stochastic tug-of-war model integrating the force-dependent dynamics of individual pili to predict the motility pattern (persistent random walks) of the bacteria [5]. Comparison with experimental bacterial trajectories indicated that a mechanism for directional memory is required to circumvent a limitation due to the two-dimensional geometry of the tug-of-war (pili pulling in random directions on a surface), which can be provided by sufficient stability of the pilus base complex. This idea was confirmed by analyzing the statistics of single pilus retraction experiments (bursts of retractions).

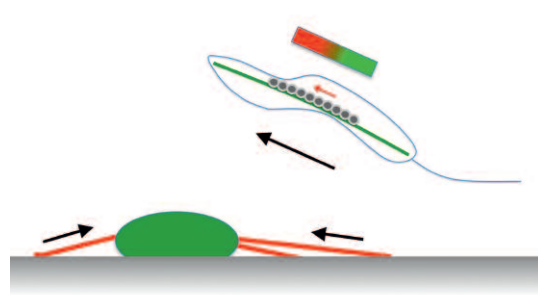


Fig. 4: Bacterial motility: (top) A magnetotactic bacterium swims in the direction defined by an external magnetic field, driven by the rotation of its flagellum. (bottom) The retraction of type IV pili drives the twitching motility of bacteria on surfaces.

Magnetotactic bacteria align along magnetic field lines with the help of magnetic organelles called magnetosomes. Magnetosomes contain magnetic nanoparticles and are aligned along a cytoskeletal filament to form a cellular “compass needle”, called the magnetosome chain. We study both mechanical aspects of the magnetosome chain and the navigation of the bacteria (in collaboration with the group of D. Faivre, Biomaterials department). Specifically, we have studied how magnetic alignment helps the cells to swim in an oxygen concentration gradient towards the preferred micro-oxic zone, a behavior known as magneto-aerotaxis. The magnetic field with a component parallel to the oxygen gradient can provide an axis and/or a direction for motility. A comparison of the magneto-aerotactic behavior of different strains of magnetotactic bacteria shows that many strains use the direction given by the magnetic field instead of sensing an oxygen concentration gradient and that such replacement can occur separately for low-oxygen and high-oxygen conditions [6]. Other questions we have addressed recently include mechanical properties of the magnetosome chain such as its bending stiffness, its response to magnetic fields as well as aspects of cell division.

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→ Mechano(Bio)Chemistry

MAX PLANCK RESEARCH GROUP

MECHANO(BIO)CHEMISTRY



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Thesis: Molecular Force Sensors –
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From a Materials Science perspective, biological systems are highly sophisticated smart materials. They are stimuli-responsive and possess impressive self-reporting and self-healing properties. One example of such a multifunctional biomaterial is the extracellular matrix (ECM) that forms the interface between cells as well as between cells and surfaces. The ECM combines structural, mechanical support with biochemical signalling. Both of these functions are often fulfilled by one and the same molecule that has evolved to translate a (bio)chemical into a mechanical signal and *vice versa*.

Biological materials in general, and the ECM in particular, are consequently an important source of inspiration for materials scientists who aim at integrating several different functions within synthetic materials. Towards this goal, we are currently focussing on four different topics: 1) Understanding the mechanical properties of the molecular building blocks of the ECM and the different strategies of converting (bio)chemical and mechanical information. 2) Design of artificial building blocks that mimic the function of ECM components, especially molecular force sensors. 3) Design of smart materials with force sensing properties. 4) Development of novel measurement techniques that allow for measuring molecular forces *in situ* both at the ensemble and at the single molecule level.

Characterization of Mechanical Building Blocks

Fibrillar proteins forming superhelical structures are important components of both the cytoskeleton and the ECM. Whereas the intracellular cytoskeletal components are mechanically well characterized, much less is known about their extracellular counterparts, *e.g.* collagen. Using synthetic superhelical peptide fragments, we aim to characterize the mechanical stability of these structural proteins at the molecular level (collaboration with Dr. L. Bertinetti and Dr. A. Masic, Biomaterials). Using single molecule force spectroscopy, we aim to investigate how length, sequence composition, assembly state and pulling direction affect the mechanical response of these important ECM components. In such a well-controlled experiment we are further able to systematically investigate the influence of molecular binding events on helix stability. We expect that these experiments will provide direct molecular insights into the interplay between the biochemical environment and structural stability.

Often ECM proteins do not only possess mechanical function. More importantly, they are equipped with specialized domains that are able to convert a mechanical into a biochemical signal. These so-called molecular force sensors (**Fig. 1**) undergo a conformational change that alters their function. In the ECM, force sensing often involves the exposure of cryptic binding sites or cryptic catalytic sites that become exposed following a mechanical stimulus. With the goal of understanding the force-sensing properties of these ECM proteins, we aim to develop novel techniques that allow

us to screen for cryptic sites in ECM proteins and to subsequently characterize their structure-function relationships (see below).

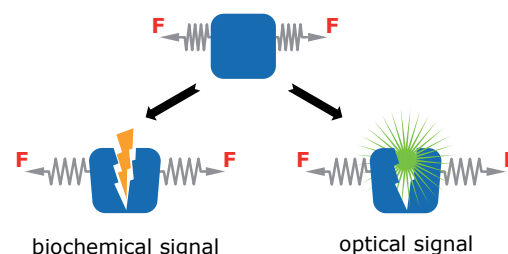


Fig. 1: Molecular force sensors convert mechanical signals into a different readout signal. *a)* Natural force sensors generate biochemical signals. *b)* Synthetic force sensors provide an 'optical signal' that can be detected with spectroscopic techniques.

Design of Synthetic Molecular Force Sensors

Inspired by the function of different ECM components, especially the molecular force sensors, we aim at developing synthetic molecules with force sensing properties. In contrast to natural force sensors, which convert the mechanical stimulus into a biochemical signal, we will equip these force sensors with an optical readout signal (**Fig. 1**). In this way, we will be able to detect the response of the sensor molecule with fluorescence microscopy techniques [1]. Depending on the desired application, different force sensor designs are possible (**Fig. 2**).

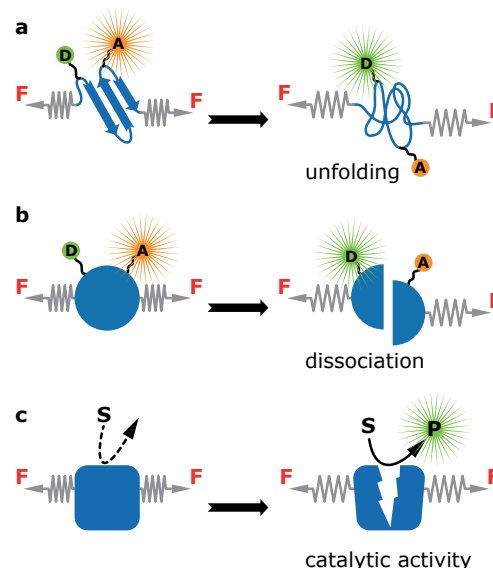


Fig. 2: Design principles of synthetic molecular force sensors. *a)* Monitoring the mechanical unfolding of a protein domain or a synthetic polymer using a FRET reporter system. *b)* FRET-based detection of the force-induced dissociation of a molecular interaction. *c)* Activation of a cryptic catalytic site.

In collaboration with Dr. John Dunlop (Biomaterials) we will, for example, use these sensors for measuring the forces that cells are able to exert on their environment. In this project we will immobilize integrin ligands to a solid surface via a range of dissociation-based force sensors (Fig. 2b) that are calibrated for different rupture forces. The sensor will remain intact if the cell-generated forces are lower than the rupture force of the sensor and the cells will be able to grow. If, on the other hand, the cell-generated forces will exceed the rupture force of the sensor, it will break, leading to a change in the FRET signal. In this way, we will be able to determine the critical force range that determines the interaction between integrins and their specific ligands at the molecular level directly in the cell culture system.

Design of Synthetic Stimuli-Responsive Materials

Utilizing the knowledge generated in the above projects, we will then combine the mechanically characterized structural ECM building blocks with synthetic molecular force sensors (Fig. 3). This will deliver a novel ECM mimic with unique force sensing properties. Depending on the location of the force sensors, we will be able to monitor the force distribution in the material itself (Fig. 3a, b). Alternatively, using a similar strategy as described above, a readout of the forces that act between cells and the matrix will become possible in a 3D cell culture environment (Fig. 3c).

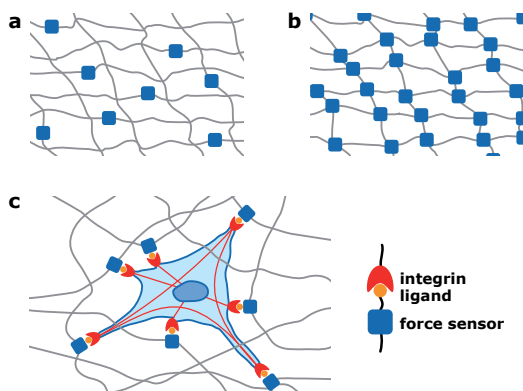


Fig. 3: Strategies for the assembly of synthetic materials with mechanosensing properties. a) Intrachain force sensors. b) Mechanosensitive crosslinkers. c) Force sensors for measuring cell-material interactions.

Development of Characterization Techniques

The identification and characterization of natural and synthetic force sensors requires a set of integrated measurement techniques that combine an activity readout with a possibility for mechanical manipulation [1]. Synthetic force sensors need to be calibrated to directly relate the force applied on the sensor molecule to the optical signal. This calibration requires a single molecule approach to provide a defined stoichiometry and to ensure that exactly one molecular force sensor is measured. We will achieve this with the integration

of atomic force microscopy with a total internal reflection fluorescence (TIRF) detection scheme. This allows us to perform single molecule force spectroscopy while following the response of the force sensor optically (Fig. 4a).

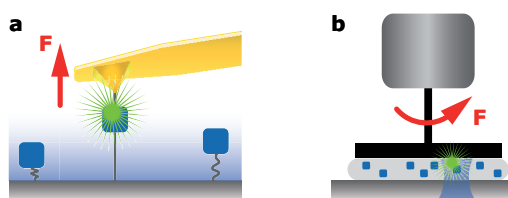


Fig. 4: Combining mechanical characterization techniques with fluorescence microscopy. a) Integrated AFM-TIRF setup. b) Confocal rheology.

Once the molecular force sensors are integrated into the material, again methods need to be developed that allow a defined mechanical manipulation of the material while following the response of the force sensors with a fluorescence measurement. A commonly applied technique for the characterization of (protein-based) polymeric materials is rheology, which applies a defined shear stress to the material. Combining a rheology setup with confocal microscopy will allow us to follow the behaviour of the force sensors as a function of the applied stress (Fig. 4b). Such a measurement can be performed with a high concentration of force sensors providing information about the global material response. Reducing the sensor concentration will eventually allow the localization and observation of individual sensor molecules providing unique information about the local force distribution in the material.

Lastly, we will apply these techniques not only to our synthetic systems, but also to the 'natural' ECM and its components. We will develop confocal rheology as a new screening method for identifying cryptic binding sites or catalytic sites in the ECM. Once a new cryptic site has been found, the single molecule approach will allow for a detailed characterization of its molecular mechanism. In summary, using an integrated, interdisciplinary approach, we aim to understand the interplay between mechanics and biochemistry in the ECM and to utilize these principles for designing novel stimuli-responsive materials that report on their mechanical state down to the level of their molecular building blocks.

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→ Nanostructured Interfaces

EMERITUS GROUP

Nanostructured Interfaces



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1974-1975: Postdoc (IBM San Jose)

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1978-1981: Scientific Coworker

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Since 1993: Director and Scientific

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Since 1995: Professor, Physics and Physical Chemistry (University Potsdam)

Since 2001: Honorary Professor (Zhejiang University, Hangzhou)

Since 2004: Honorary Professor (Fudan University, Shanghai)

Since 2006: Honorary Professor (Institute of Chemistry at the Chinese Academy of Sciences, Beijing)

Since 2014: Director (em.) and

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Since 2014: Consultant (CEA Marcoule)

Since 2014: Honorary Professor

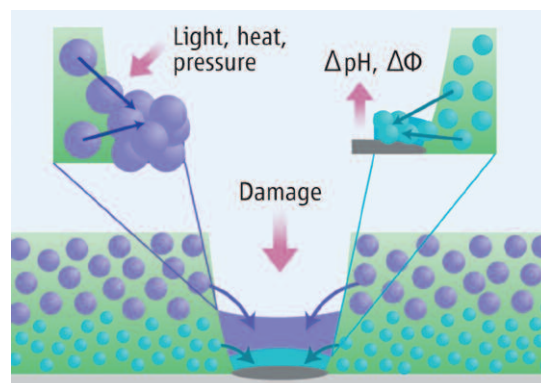
(Institute of Process Engineering at the Chinese Academy of Sciences, Beijing)

The department Interfaces has been terminated with my retirement on 31 January 2014, and the group leaders on permanent positions, G. Brezesinski, R. Miller and H. Riegler were transferred to the departments Colloid Chemistry, Biomaterials and Theory & Bio-Systems, respectively. Their report is thus integrated into that of their department. Also E.V. Skorb has moved to the department Biomaterials, and she is reporting there as independent postdoc. Therefore this report focusses on work, where I as emeritus have been involved. This concerned continuation of work of the previous groups of A. G. Skirtach and D. G. Shchukin, who have left on professor positions, but where some scientists were completing their work in collaboration with these former group leaders before they found the next position. In addition there were independent postdocs who were directly supervised by me, and I also continued cooperation with former co-workers, where the experiments were performed at their new positions.

As the topics are rather diverse, resulting in about 60 publications in the reporting period, this report concentrates on only few highlights intended to show the breadth:

Feedback Active Coatings

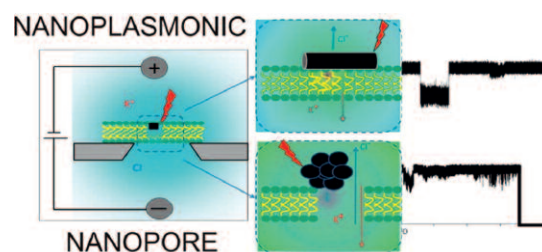
This subject concerns a long development predominantly to achieve corrosion protection. There corrosion inhibitors are incorporated into nano- or microcapsules that release their cargo upon an environmental stimulus. This may result from a defect in the material to be protected, e.g. a change in pH or redox potential (**Fig. 1**). The process has been shown to work in many cases, and the research concerns the development of different types of containers [**1**]. The types of containers, that have been studied, varied from polyelectrolyte multilayer capsules to hollow silica nanotubes (halloysites) to mesoporous inorganic containers. As a recent achievement it could be shown for porous silica containers that with the same amount of inhibitor loaded smaller capsules (80nm diameter) provide a much better corrosion protection than large ones (diameter 700 nm). This is demonstrated not only by macroscopic scratch tests, but also by impedance spectroscopy and by the scanning vibration electrode technique allowing a local resolution [**2**]. Work under this topic develops more and more into very concrete applications and for this funding has been achieved from the federal ministry of economy with the aim to found a start-up company. The main problems in commercialization are not the corrosion protection or missing economic benefits, but side reactions with the container material, leading to smell. In any case the ecologic benefits are obvious, as the cancerogeneous Cr (VI) can be avoided as protective agent.



*Fig. 1: Nanocontainer-based smart coatings. A fine dispersion of nanocapsules lends active functionality to the coating matrix. Capsules (spheres) can be loaded with various active materials depending on the functionalities required. The sensitivity of the capsule shell can be adjusted to different stimuli (e.g. pH changes or changes in the electrochemical potential) for opening and release of the encapsulated active material by nanoengineering of the shell components and structure. [**1**]*

Manipulation and Study of Membranes and Cells by Nanoplasmonics

In cooperation with University Gent and Jacobs University Bremen cells were manipulated by optically exciting metallic nanoparticles and nanorods. If these are attached to a membrane, the membrane can be reversibly opened to transient currents. These single channel currents can be studied by means of supported bilayer membranes (**Fig. 2**) [**3**].



*Fig. 2: Left: Schematics of a set-up to measure the conductance of a single channel in a membrane. Middle: Sketch of a nanorod or a nanoparticle aggregate with strong IR absorption to create local heating by light. Right: Single channel conductance/time traces. [**3**]*

Huge efforts have been devoted to arrive at an ultrasensitive detection of Raman signals from the interior of different cells. These efforts basically involve the design of so-called hot spots, i.e. local spaces with extremely high intensity of the electromagnetic field. These exist at sharp tips of metallic nanostructures, most intensely at the junction of two or more tips. At these junctions the tips should be as close as possible, but at sufficient distance to leave space for the analyte. The main challenge is to establish these structures with high precision and reproducibly to arrive at a quantitative signal enhancement. An example of such a structure is given in **Fig. 3**.

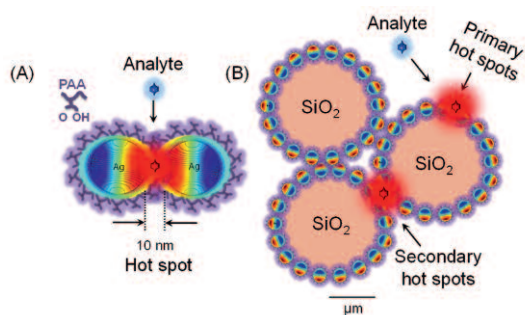


Fig. 3: Schematic illustration of primary and secondary SERS hot spot formation by Ag-PAA (polyacrylic acid) nanofilms on colloidal silica. (A) Pre-formed silver nanoparticles are embedded in the matrix of PAA (Ag-PAA nanofilms) with fixed gaps (~10 nm) that can serve as primary SERS hot spots. (B) Ag-PAA nanofilms are deposited on silica microparticles (~1.5 μm) that can form secondary SERS hot spots at the interparticle junctions during self-assembly. [4]

Ag nanoparticles are coated by a thin polymer film that enables penetration of low molecular weight compounds, but keeps the nanoparticles apart. These nanoparticles are adsorbed on the surface of SiO_2 microparticles, and at the junction of 2 such microparticles a hot spot with reproducible dimension can be established. This hierarchical structure is still smaller than a cellular dimension and thus can be brought into a cell for imaging or sensitive local analysis of cellular compartments. An example on this is given in **Fig. 4 [4]**. Obviously one can create images using the most pronounced lines in the spectra that correspond to nucleus, cytoplasm, etc., but above all the information content is so rich that it has not yet been analyzed in more detail. At this stage these studies concern first principles laying the ground by additional calculations of local field strength. Theory and experiments agree that enhancement factors around 10^9 can be achieved, and this suffices also for single molecule detection.

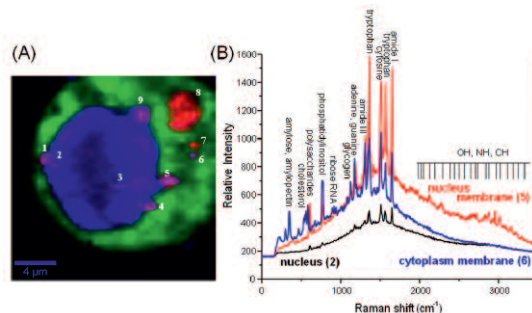


Fig. 4: (A) Raman spectroscopic imaging of a live NIH/3T3 fibroblast with embedded $\text{SiO}_2\text{:@Ag-PAA}$ particles in a colored spectral map (scale bar is $4\text{ }\mu\text{m}$). The map reflects the differences found in the Raman data and SERS active Ag-PAA nanofilms. This map is a linear combination of the averaged single spectra and characteristic for cell compartments (green cytoplasm and blue – nucleus). Intense green and blue colors of spots separated by a darker background contrast indicate the presence of SERS effective $\text{SiO}_2\text{:@Ag-PAA}$ particles inside the cellular medium. Spots with violet and red colors show $\text{SiO}_2\text{:@Ag-PAA}$ particles that are located at the membrane interface or at its surface (highlighted with numbers). A confocal Raman image is generated by integration of the intensity of the strongest bands in the three spectral ranges: (i) $<1000\text{ cm}^{-1}$, (ii) $1000\text{--}2000\text{ cm}^{-1}$ and (iii) $2500\text{--}3500\text{ cm}^{-1}$ after local baseline subtraction using the hypercluster analysis (HCA) as one of the efficient label-free methods for the visualization of intracellular components and processes. (B) Selected SERS spectra that are collected from nucleus (2 in A) and periphery membranes of the nucleus (5 in A) or cytoplasm (6 in A). The laser excitation wavelength was 532 nm and the grating was 600 g mm^{-1} (BLZ = 500 nm) and spectral resolution of 3 cm^{-1} . [4]

A similar approach decorating SiO_2 microparticles with carbon nanotubes and Au nanoparticles also led to well resolved cellular Raman images, but in this case theory and the approach are not yet as well developed [5].

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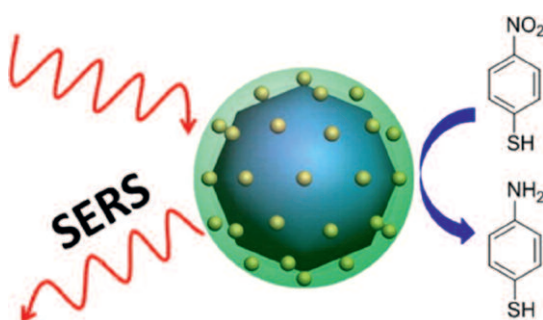
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Surface Enhanced Raman Spectroscopy and Catalysis

Au nanostructures are well established catalysts. Therefore these nanostructures can be used not only for catalysis, but at the same time the high sensitivity can also be used for studying reaction intermediates (Fig. 5). This has been achieved using a model reaction in cooperation with Univ. Potsdam and Beijing Univ. of Science and Technology [6].

Fig. 5: A Au „nanoflower” (blue core) with high specific surface is coated with a gelatin film in which catalytically active Au nanoparticles were synthesized in situ. A catalytic model reaction can then be followed by surface enhanced Raman spectroscopy (SERS). [6]



Nanoplasmonic Surfaces

The development of colloidal lithography was extended and cultivated at Jilin University to obtain films with unusual optical as well as wetting properties. With this technique one first prepares an organized layer of latex spheres, that then are etched into a cone by reactive ion etching (Fig.6).

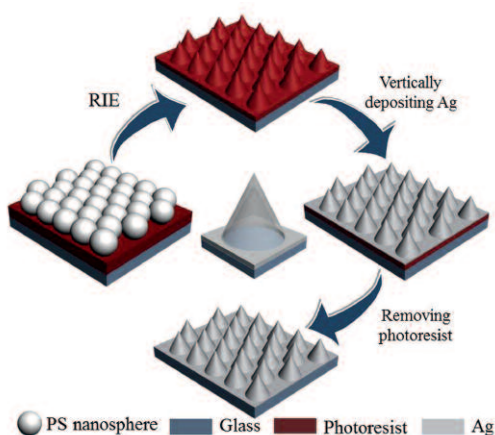


Fig. 6: Outline of the process for fabricating hollow nanocone array films. The central schematic shows a transparent hollow nanocone to stress the relevance of the central structural element. [7]

Coating the structure with Ag and removing the organic part then leads to arrays of Ag cones. Varying the etching angle one may also produce asymmetric cones or cones with the tip truncated (volcanos). This then results in structures with unusual properties. As example Fig. 7 shows that a Ag film with a thickness of about 100 nm is intransparent, but a film of cones with the same Ag thickness is reasonably transparent. By means of field simulations one can understand this as an interaction of a surface plasmon at the base and at the tip of the cone [7].

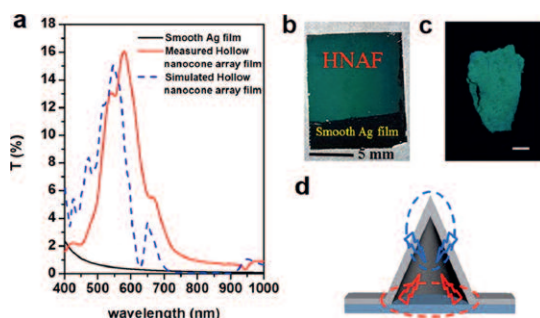


Fig. 7: (a) Measured (red curve) and simulated (blue dash curve) transmission spectra of a hollow nanocone array film (HNAF) and a 100 nm Ag film with the same thickness (black curve). (b) Optical image of an HNAF sample with a small part of a smooth Ag film at the bottom. (c) Optical image of a HNAF island surrounded by a 100 nm smooth Ag film. The scale bar corresponds to 10 μ m. (d) Description of one single unit of the hollow nanocone array and the predicted mechanism generating the greatly enhanced optical transmission. [7]

Self-Propelling Janus Particles

A method has been developed to prepare Janus particles, i.e. particles with 2 different sides. One side is coated with catalytically active Ag nanoparticles, where a gas is created (Fig. 8). This bubble preferably grows on hydrophobic areas and its formation causes directed motion. Near a surface the nanoparticle/bubble couple may be attracted or repelled from the surface, and therefore via changing the hydrophilicity of the surface one can switch between surface and bulk motion [8].

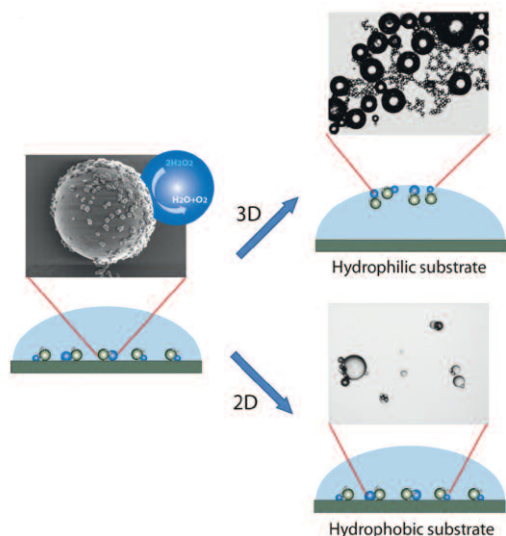


Fig. 8: Janus particles propelled by the formation of an oxygen bubble due to the splitting of H_2O_2 . Increased hydrophobicity of the glass substrate changes the particle motion from three- to two-dimensional. [8]

Functionalized Fullerenes as Amphiphiles

Previous work in the joint laboratory with the National Institute of Materials Science in Tsukuba was based on the notion that aromatic and aliphatic systems are incompatible. Hence fullerenes with aliphatic chains attached can behave like amphiphiles, but not in water. Thus they form organized structures in organic solvents like traditional amphiphiles in water (bilayers, micelles) [9]. Technologically this is interesting, as one phase contains a high concentration of pi-electrons, which are responsible for high charge carrier mobility and special optical properties. This work has meanwhile been extended to demonstrate the existence of even worm-like micelles (Fig. 9) [10].

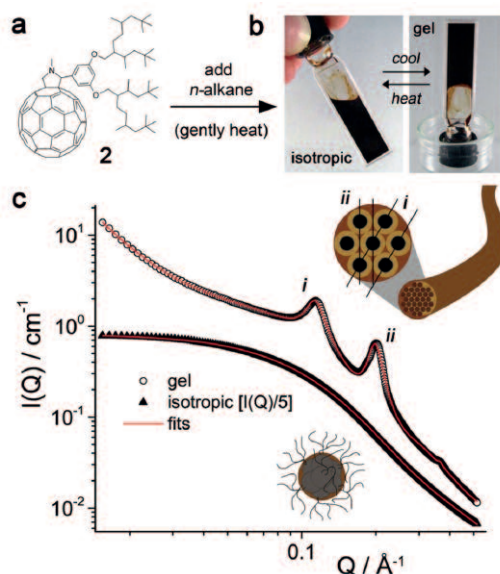


Fig. 9: Gel formation by **2**, driven by addition of *n*-alkane solvents. a) Chemical structure of **2**. b) Photographs showing the gelled and isotropic states that arise on dissolving **2** in *n*-decane. c) Fitted synchrotron SAXS data for **2** with *n*-hexane, **2** at 19.8 wt%, taken at 5°C (gel state) and 55°C (isotropic state), respectively. Red lines indicate fits to the data. For clarity, the SAXS data and fit for the isotropic state have been divided by a factor of 5. Inset: schematic depictions of the structures (micelles and gel fibres) present in the system in both states. The peaks in the SAXS data taken at 5°C marked i and ii arise from a hexagonal arrangement of the C_{60} -rich columns within the fibres, with *d*-spacings corresponding to the distances indicated on the schematic of the gel fibre. The steep increase in $I(Q)$ at low Q suggests a fractal-like network structure, indicating that individual fibres are bundled and substantially interwoven. [10]

Self-assembly of Peptidic Structures

There exist known peptide libraries that endow these systems self-assembly. This could be used to form tubes that possess wave guiding properties as well as capsules with responsive properties. These systems are further continued in cooperation with the Chinese Academy of Science Institutes of Chemistry and Process Engineering [11]. They exhibit the special property that the structure depends sensitively on environment.

Final Remark

The work of the emeritus group has been experimentally terminated in Golm, with the exception of the work on self-repairing coatings, but is continued at various external institutions, to a large part in cooperation with our institute. I received recently as awards from the ACS the Langmuir lectureship and the Elhuyar-Goldschmidt award from the Royal Spanish Society of Chemistry. I am grateful for this, but especially for the many co-workers, who contributed much to our success and who now can continue their career in our institute or at other institutions in the world.

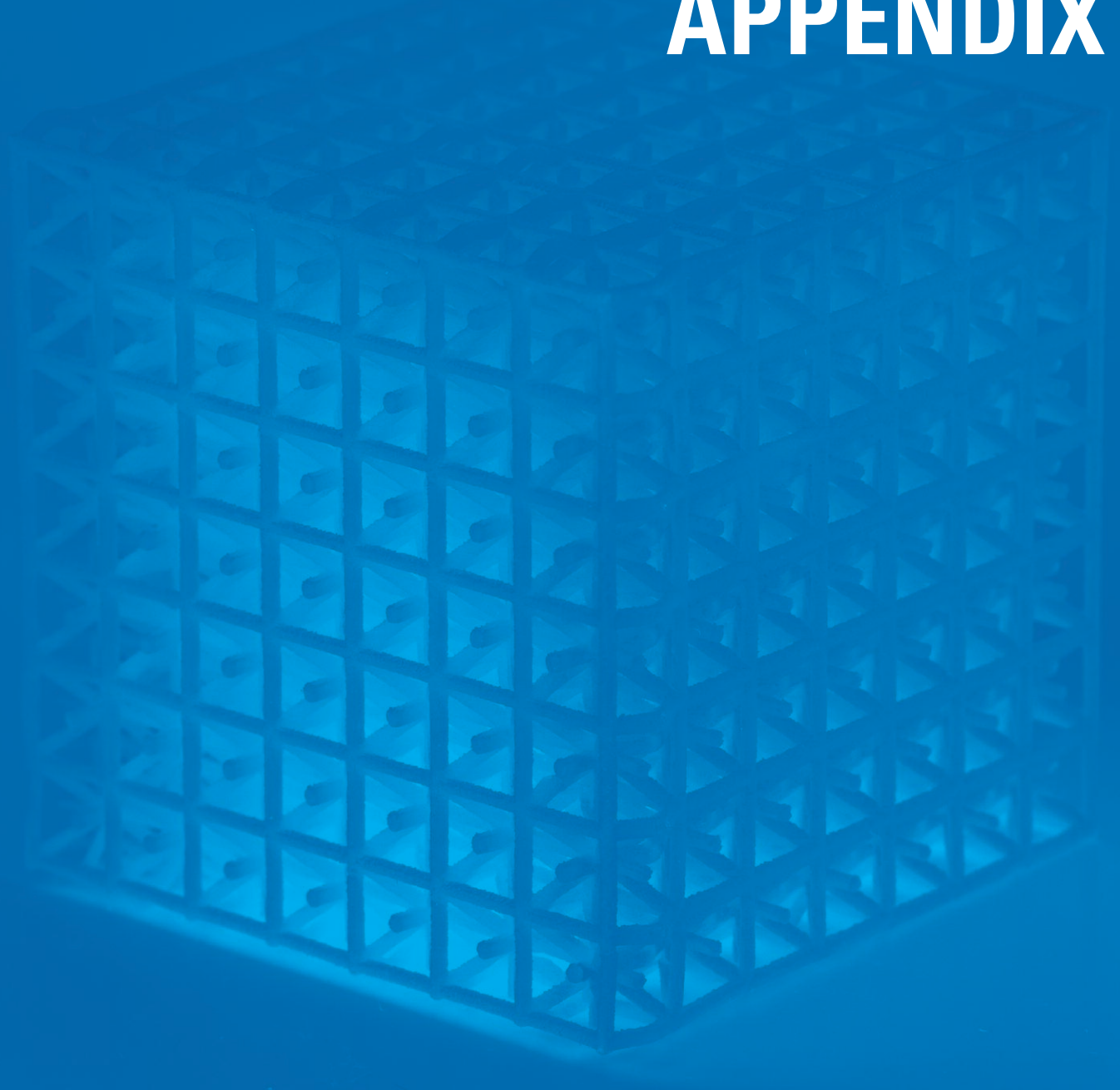
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[11] Zou, Q., Zhang, L., Yan, X., Wang, A., Ma, G., Li, J., Möhwald, H., Mann, S.: Multifunctional Porous Microspheres Based on Peptide-Porphyrin Hierarchical Co-Assembly. *Angew. Chemie Int. Ed.* **53**, 2366-2370 (2014).

- Organization Chart
- Scientific Advisory Board and Board of Trustees
- Third Party Funds
- Selected Events
- Scientific Degrees
- Appointments and Honors
- Publications

APPENDIX



Organigramm

Organization Chart

Biomaterials Prof. Dr. Dr.h.c. Peter Fratzl · Personal Assistant: Kerstin Gabbe

- Biomimetic Actuation and Tissue Growth/Dr. John Dunlop
- Plant Material Adaptation/Dr. Michaela Eder
- Molecular Biomimetics and Magnets Biomineralization/Dr. Damien Faivre
- Biochemical Strategies in Load-Bearing Natural Materials/Dr. Matthew Harrington
- Thermodynamics, Kinetics and Rheology of Interfacial Layers/Dr. Reinhard Miller
- Biological Chitin-Based Tools and Sensors/Dr. Yael Politi
- Physics of Biomolecular Interfaces/Dr. Emanuel Schneck
- Hierarchical Structure of Biological and Biomimetic Materials/Dr. Wolfgang Wagermaier
- Mechanobiology/Dr. Richard Weinkamer

Independent Researchers

- Water Interactions in Complex Biological Materials/Dr. Luca Bertinetti
- Evolutionary Perspectives on Vertebrate Hard Tissues/Dr. Mason Dean
- Synthesis and Thermodynamic Stability of Amorphous Minerals/Dr. Wouter Habraken
- Advanced Raman Spectroscopic Imaging of Biological Tissues/Dr. Admir Masic
- Methodologies for Formation of Encapsulation System Scaffolds/Dr. Katja Skorb
- In-Situ Mechanical Characterization of Internal Interfaces in Biomaterials/Dr. Igor Zlotnikov

Biomolecular Systems Director: Prof. Dr. Peter H. Seeberger · Personal Assistant: Dorothee Böhme

- GPI and Glycoproteins/Dr. Daniel Varón Silva
- Chemical Glycobiology of Infectious Diseases/Prof. Peter Seeberger
- Glycobiology of Microbe/Host Interaction/Dr. Chakkumkal Anish
(Since September 2014 Senior Scientist Johnson & Johnson, Janssen Vaccines Division)
- Glycoimmunology/Dr. Bernd Lepenies
(Since July 2015 Associate Professor (W2) for Infection Immunology at the University of Veterinary Medicine Hannover)
- Continuous Chemical Systems/Dr. Kerry Gilmore
- Polymeric Biomimetics (Emmy Noether Nachwuchsgruppe)/Dr. Laura Hartmann
(Since June 2014 Full Professor (W3) for Preparative Polymer Chemistry at the University of Düsseldorf)
- Synthetic Plant Carbohydrates/Dr. Fabian Pfengle
- Automated Carbohydrate Synthesis/Prof. Peter Seeberger
- Glycoproteomics/Dr. Daniel Kolarich
- Immunomics/Dr. Zoltan Konthur
- Structural Glycobiology/Dr. Christoph Rademacher

Colloid Chemistry Director: Prof. Dr. Dr. h.c. Markus Antonietti · Personal Assistant: Carolin Nuglisch

- Biorefinery/Dr. Davide Esposito
- Poly(ionic liquid)s: Synthesis and Materials Application/Dr. Jiayin Yuan
- Artificial Photosynthesis/Dr. Dariya Dontsova
- Electrochemical Energy Materials/Dr. Tim-Patrick Fellingner
- Heterophase Polymerizations/Dr. Klaus Tauer

Modern Techniques of Colloid Analysis

- Electron Microscopic Studies of Colloidal Systems and Biomaterials/Dr. Jürgen Hartmann
- Supramolecular Porous Materials/Dr. Nina Fechner
- Nanofunction Design for Uphill Photosynthesis/Dr. Menny Shalom

Self-Organizing Polymers

- Bioinspired Polymers und Block Copolymers/Dr. Helmut Schlaad
(Since June 2014 Full Professor (W2) for Polymer Chemistry at the University Potsdam)

Mesoporous Materials and Nanoparticles

- De Novo Nanoparticles: Novel synthetic routes for nanoparticle production/Dr. Christina Giordano
(Since March 2014 Independent Researcher in the Research Group Physical Chemistry/Molecular Material Sciences at the TU Berlin)
- Organic Energy Polymers/Dr. Filipe Vilela
(Since September 2013 Lecturer in Chemistry at Heriot-Watt University in Edinburgh)
- Interactions in Complex Monolayers/Prof. Gerald Brezesinski

Managing Director (2013-2014)

Prof. Dr. Dr.h.c. Peter Fratzl

Theory & Bio-Systems Director: Prof. Dr. Reinhard Lipowsky · Personal Assistant: Susann Weber

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- Multiscale Modelling/[Dr. Andrea Grafmüller](#)
- Proteins and Membranes/[Dr. Thomas Weikl](#)
- Carbohydrates and Polysaccharides/[Dr. Mark Santer](#)
- Polymers and Polyelectrolytes/[Dr. Christian Seidel](#)
(Since September 2014 retired)
- Stochastic Processes in Complex and Biological Systems/[Dr. Angelo Valleriani](#)
- Regulation of Bio-Processes/[Dr. Stephan Klumpp](#)
- Soft Matter Simulations/[Dr. Ana Vila Verde](#)
- Phase Transitions and Transport Phenomena in Thin Films at Solid/Air Interfaces/[Dr. Hans Riegler](#)

Max Planck Research Group Mechano(bio)chemistry Head: Dr. Kerstin Blank · Personal Assistant: Stefanie Riedel

The research group started to work on July 1st 2014 and is currently being set up.

Emeritus Group (Interfaces) Prof. Dr. Dr. h.c. Helmuth Möhwald, Director (em.)

The Department of Interfaces was closed on February 1st, 2014 with the retirement of Helmuth Möhwald. Since then he serves as emeritus at the institute. With termination of the Department Interfaces the remaining groups were transferred to

- The Department of Colloid Chemistry · Interactions in Complex Monolayers/[Prof. Dr. Gerald Brezesinski](#)
- The Department of Biomaterials · Thermodynamics, Kinetics and Rheology of Interfacial Layers/[Dr. Reinhard Müller](#)
- The Department of Theory & Bio-Systems · Phase Transitions and Transport Phenomena in Thin Films at Solid/Air Interfaces/[Dr. Hans Riegler](#)

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Jan von Szada-Borrryskowski

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Michael Born, Klaus Bienert, Henryk Pitas

Glass Blowing Workshop

Cliff Janiszewski

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Head: [Heiko Jung](#)

Guido Behrendt, Olaf Gaida, Hagen Hannemann,

Jannick Krüger, Dirk Nast, Marco Stetzmann,

Thomas Vogt

Caretaker

Head: [Olaf Gaida](#)

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Prof. Dr. Annette Zippelius	Universität Göttingen, Institut für Theoretische Physik

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Prof. Dr. Robert Seckler	Vizepräsident für Forschung und Wissenschaftlichen Nachwuchs an der Universität Potsdam

Drittmittelprojekte

Third Party Funds

Bund

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
BMBF	Nachwuchsgruppe Glykobiotechnologie: Malaria-Untersuchung der Erythrozyteninvasion und der schweren Pathologie	Dr. Anish BS	01.04.2009-31.03.2014	
BMBF	Nachwuchsgruppe Glykobiotechnologie: Funktion der C-Typ Lektinrezeptoren (CLRs) bei der Modulation der Immunantwort	Dr. Lepenies BS	01.02.2009-31.12.2013	Bernhard-Nocht-Institut für Tropenmedizin, Hamburg Universität Regensburg Technische Universität München Universität Würzburg
BMBF	Verbundprojekt: Spitzenforschung und Innovation in den neuen Ländern-Das Taschentuchlabor: Impulszentrum für Integrierte Bioanalyse (IZIB)	Prof. Seeberger BS	01.10.2009-30.09.2014	Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V. (FhG), München Universität Potsdam Charité-Universitätsmedizin Berlin Helmholtz-Zentrum für Infektionsforschung GmbH, Braunschweig Ruhr-Universität Bochum IDM Institut für Dünnschichttechnologie und Mikrosensorik e.V., Teltow Technische Fachhochschule Wildau MicroDiscovery GmbH, Berlin BST Bio Sensor Technologie GmbH, Berlin Congen Biotechnologie GmbH, Berlin Scienion AG, Dortmund Poly-An Gesellschaft zur Herstellung von Polymeren für spezielle Anwendungen und Analytik mbH, Berlin
BMBF	Verbundprojekt: Spitzenforschung und Innovationen in den neuen Ländern-Light2Hydrogen - Energie für die Zukunft-Photokatalytische Spaltung von Wasser zu Wasserstoff -TP2	Prof. Antonietti KC	01.11.2009-31.10.2014	Leibniz-Institut für Katalyse e.V. an der Universität Rostock Leibniz-Institut für Plasmaforschung und Technologie e.V. (INP), Greifswald Technische Universität Berlin Helmholtz-Zentrum Berlin für Materialien und Energie GmbH (HZB), Berlin Fachhochschule Stralsund Universität Rostock

BM – Abteilung Biomaterialien/Department of Biomaterials
 BS – Abteilung Biomolekulare Systeme/Department of Biomolecular Systems
 GF – Abteilung Grenzflächen/Department of Interfaces
 KC – Abteilung Kolloidchemie/Department of Colloid Chemistry
 TH – Abteilung Theorie & Bio-Systeme/Department of Theory & Bio-Systems

Bund

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
A.v.H.	Max-Planck-Forschungspreis 2008: Biological and Biomimetic Materials	Prof. Fratzl BM	01.09.2008-31.08.2013	Ludwig Boltzmann Institute of Osteology, Vienna, Austria Harvard University, Department of Chemistry and Chemical Biology, USA University of California at Santa Barbara, USA Weizmann Institute of Science, Rehovot, Israel Montanuniversität Leoben, Austria Institut National Polytechnique de Grenoble, France Department of Materials Science, Technion, Haifa, Israel
BMBF	Verbundprojekt: Molekulare Pathologie der Osteoporose (OsteoPath)	Prof. Fratzl Dr. Wagermaier BM	01.06.2010-31.05.2013	Ludwig Boltzmann Gesellschaft, Ludwig Boltzmann Institut für Osteologie, Wien
BMBF-DLR	Fortführung der experimentellen und theoretischen Untersuchungen zur Bildung und Deformation von Einzeltropfen als Modell für Schäume und Emulsionen sowie Begleitung der FASES-Experimente auf der ISS	Dr. Miller GF Since 31.01.2014 BM	01.07.2011-30.06.2014	
BMBF-PTJ	WoodWisdom-Net: WOP-Wood Supply TP Mechanische und nanostrukturelle Charakterisierung von Pappeln	Dr. Eder BM	01.02.2012-31.01.2015	University Helsinki, Helsinki Swedish University of Agricultural Sciences, Umea
BMBF-PTJ	EXIST-Forschungstransfer: Smart Pigments für nachhaltige umweltfreundliche Antikorrosionsbeschichtungen „Sigma“	Dr. Grigoriev GF	01.06.2014-30.11.2015	
BMBF	KMU - innovative-8: ProgRate Prognostische Marker in der Rheumatoiden Arthritis zur Verwendung als Therapieentscheider	Dr. Konthur BS	01.03.2013-31.12.2014	in.vent Diagnostica GmbH, Henningsdorf Charité Universitätsmedizin Berlin
BMBF - AiF	Entwicklung und Herstellung der Nanopartikel und Nanocontainer zur Einbindung in elektrolytische und mechanische Zink-Schichten im Labormaßstab	Prof. Möhwald Dr. Grigoriev GF		

EU

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
EU/ ERC Adv. Grant	Hydrothermal and Ionothermal Chemistry for Sustainable Materials	Prof. Antonietti KC	01.11.2008-31.10.2013	
EU/ ERC Adv. Grant	Automated Synthesis of Heparin and Chondroitin Libraries for the Preparation of Diverse Carbohydrate Arrays	Prof. Seeberger BS	01.01.2009-31.12.2013	
EU/ ERC Adv. Grant	Molecular Biomimetics and Magnets Biomaterialization: Towards Swimming Nanorobots	Dr. Faivre BM	01.01.2011 - 31.12.2015	
EU	Biomimetic and Biomaterialized Magnetic Nanoparticles for Magnetic Resonance Imaging	Prof. Fratzl Dr. Faivre BM	01.09.2011 - 31.08.2014	Pannon Egyetem, Veszprem, Hungary Latvijas Universitate, Riga, Latvia nanoPET Pharma GmbH, Berlin Ludwig-Maximilians Universität, München Ludwig Boltzmann Gesellschaft Österreichische Vereinigung zur Förderung der Wissenschaftlichen Forschung, Wien Eidgenössische Technische Hochschule Zürich, Switzerland
EU	Biomimetic Membrane Systems	Prof. Brezesinski GF Since 31.01.2014 KC	01.03.2011-29.02.2014	Universite Claude Bernard Lyon, Villeurbanne, France Institute of Chemistry, Chinese Academy of Sciences, Beijing, China Harbin Institute of Technology, Harbin, China
EU	Quantitative Glycomics and Glycoproteomics for Biomarker Discovery	Dr. Kolarich BS	01.08.2011-31.07.2015	
EU	Diagnostic and Prognostic Biomarkers for Inflammatory Bowel Disease	Dr. Kolarich BS	01.10.2012 - 30.09.2016	The University of Edinburgh, UK Genos Doo Za Vjestacenje I Analiz, Osijek, Croatia Ludger Ltd, Abingdon, UK IP research Consulting Sasu, Noisy le Grand, France Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy Academisch Ziekenhuis Leiden - Leids Universitair Medisch Centrum, Leiden, Netherlands Faculty of Science University of Zagreb, Zagreb, Croatia Cedars-Sinai Medical Center, Los Angeles, US

EU

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
EU	Advanced European Lithium Sulphur Cells for Automotive Applications	Prof. Antonietti KC	01.10.2012-30.09.2016	Kemijski Institut, Ljubljana, Slovenia Centre National de la Recherche Scientifique, Paris, France Chalmers University of Technology, Goeteborg, Sweden Sincrotrone Trieste S.C.p.A., Basovizza Trieste Italy Centre of Excellence for Low-Carbon Technologies, Ljubljana, Slovenia Renault SAS, Boulogne Billancourt, France Solvionic SA, Toulouse, France Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V., Münschen Saft SAS, Bagnolet, France Volvo Technology AB, Göteborg, Sweden
EU	Nanomar - Nanocontainer-Based Active Coatings for Maritime Applications	Prof. Möhwald Dr. Shchukin GF	01.05.2012-30.04.2014	IPT Brazil ICRAS Russia UAVR Portugal
EU	Training Network in Innovative Polyelectrolytes for Energy and Environment	Prof. Antonietti KC	01.05.2012-30.04.2016	University of the Basque Country, Leioa, Spain Centre National de la Recherche Scientifique, Paris, France Linköpings Universitet, Linköping, Sweden Universite de Liege, Liege, Belgium Fundacion IMDEA Energia, Mostoles, Spain Kitozyme SA, Herstal, Belgium Procter&Gamble Italia SPA, Santa Palomba-Pomezia, Italy

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	<p>Institut National de la Sante et de la Recherche Medicale, Paris, France</p> <p>Assistance Publique - Hopitaux de Paris, Paris, France</p> <p>Inserm-Transfert SA, Paris, France</p> <p>Academic Medical Center, Amsterdam, The Netherlands</p> <p>Medical University of Graz, Clinical Institute for Medical and Chemical Laboratory Diagnosis, Graz, Austria</p> <p>Syddansk Universitet, Odense, Denmark</p> <p>Universitätsklinikum Erlangen, Erlangen</p> <p>University of Twente, Enschede, Netherlands</p> <p>CEA-LETI, Commissariat à l'Energie Atomiques et aux Energies Alternatives, Paris, France</p> <p>CLINAM - European Foundation for Clinical Nanomedicine, Basel, Switzerland</p> <p>WizSoft, Tel Aviv, Israel</p> <p>nanoPET Pharma GmbH, Berlin</p> <p>Semmelweis University, Budapest, Hungary</p> <p>Bracco Imaging S.p.A., Milan, Italy</p> <p>Edinethics Ltd., Edinburgh, UK</p>
EU	Systems Glycobiology of Gastric Cancer	Dr. Kolarich BS	01.05.2013-30.04.2017	<p>University of Gothenburg, Göteborg, Sweden</p> <p>National Institute for Bioprocessing Research & Training, Dublin, Ireland</p> <p>Institute of Molecular Pathology and Immunology of the University of Porto, Porto, Portugal</p> <p>Swiss Institute of Bioinformatics, Geneva, Switzerland</p> <p>Umeå University, Umeå, Sweden</p> <p>University of Copenhagen, Copenhagen, Denmark</p> <p>OLINK AB, Uppsala, Sweden</p> <p>University of Siena, Siena, Italy</p> <p>Uppsala University, Uppsala, Sweden</p> <p>Syddansk Universitet, Odense, Denmark</p> <p>Ariana Pharma SA, Paris, France</p>

EU

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
EU	Complex Wetting Phenomena	Dr. Miller GF Since 31.01.2014 BM	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-Sklodowska University, Lublin, Poland University of Twente, Enschede, Netherlands Evonik AG, Essen Unilever UK Central Resources Limited, London, UK
EU	1D Magnetic Nanostructures Using Mineralizing Peptidess	Prof. Fratzl BM	01.03.2014-29.02.2015	
EU	Network for Integrated Cellular Homeostasis	Prof. Lipowsky Dr. Valleriani TH	01.01.2012-31.12.2015	University of Groningen, Groningen, Netherlands University of Potsdam University of Aberdeen, UK Consejo Superior de Investigaciones Científicas, Madrid, Spain University of Oxford, UK DSM Biotechnology Center, Delft, Netherlands AstraZeneca, London, UK RiNA GmbH, Berlin

DFG

DFG	Multivalenz als chemisches Organisations- und Wirkprinzip: Neue Architekturen, Funktionen und Anwendungen	Prof. Seeberger BS	01.01.2012-31.12.2015	Humboldt-Universität, Berlin Technische Universität Berlin Freie Universität Berlin Charité - Universitätsmedizin Berlin Leibniz-Institut für Molekulare Pharmakologie (FMP) Konrad-Zuse-Zentrum für Informationstechnik Berlin (ZIB)
DFG	Experimental and Computational Analysis of Fluidic Interfaces Influenced by Soluble Surfactant	Dr. Miller GF	01.05.2010-30.04.2013	Technische Universität Darmstadt
DFG	Experimental and Computational Analysis of Fluidic Interfaces Influenced by Soluble Surfactant	Dr. Miller GF Since 31.01.2014 BM	01.08.2013-31.07.2017	Technische Universität Darmstadt

DFG

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
DFG	Synthesis and Properties of Glycopolypeptide Biohybrid Materials Thema: Novel Polymer Synthesis and New Supramolecular Polymer Assemblies	Dr. Schlaad KC	01.01.2011-31.10.2013	
DFG	Einfluss von Proteinen auf die Schaumbildung und Schaumstabilität	Dr. Miller GF Since 31.01.2014 BM	01.08.2011-31.07.2014	
DFG	Protein Metal Complexes as Reversible Sacrificial Bonds in Self-Healing Biopolymers	Dr. Harrington BM	01.08.2011-31.07.2014	
DFG	Multifunctional Layered Magnetite Composites	Dr. Faivre BM	01.12.2012-31.11.2014	
DFG DIP Grant	Grundlegende Untersuchungen zu strukturellen Ordnungsübergängen in Materialien im Kontext der Biomineralisation	Prof. Fratzl BM	01.01.2012-31.12.2016	
DFG	Hygroskopische Eigenschaften von natürlichen Oligosacchariden Modellentwicklung und Test für die Wechselwirkungen mit Wasser	Dr. Grafmüller TH	01.11.2012-30.10.2015	Weizmann Institute of Science, Israel
DFG	Stochastic Processing of mRNA and tRNA by Ribosomes during Translational Elongation	Prof. Lipowsky TH	01.07.2012-30.06.2015	
DFG	Materials World Network: Structural Design and Micromechanical Properties of mechanotransducing Biological Materials	Dr. Yael Politi BM	01.12.2012-31.11.2015	
DFG	European Young Investigator Award	Dr. Degtyar BM	01.12.2013-31.05.2014	
DFG	Mechanische Anpassung von Biomaterialien durch Protein-Metall-Komplexe	Dr. Harrington BM	01.01.2014-31.12.2016	
DFG	Structural and Morphological Characterization of Ceramide-1-Phosphate Model Membranes	Prof. Brezesinski GF	01.04.2010-31.03.2013	
DFG	Generation of Nanoparticles with Tunable Surface Wettability and Surface Functionality to Cross Hydrophilic/Hydrophobic Interfaces of Biological Barriers	Prof. Möhwald Dr. Dayang Wang GF	15.04.2009-31.03.2014	
DFG	Thermodynamisch stabile Pickering-Emulsion	Dr. Miller GF	01.09.2011-31.08.2013	
DFG Emmy-Noether- Programm	Synthese monodisperser, multifunktionaler Neoglycopolymere und Neoglycopolymer-Hybride und ihre Anwendung in der Medizin	Dr. Hartmann BS	04.08.2009-01.07.2014	

DFG

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
DFG Emmy-Noether- Programm	Targeting C-type Lectins on Dendritic Cells Using Carbohydrate-Analogs for the Specific Delivery of Tumor Vaccines	Dr. Rademacher BS	01.06.2012-31.05.2015	
DFG	Multiscale Smart Coatings wiht Sustained Anticorrosive Action	Dr. Shchukin Prof. Möhwald GF	01.09.2012-31.08.2015	NIMS Louisiana Tech University Kazan Federal Universitiy
DFG	New Methods for the Synthesis of glycosylphosphatidylinositol Anchored Proteins with Therapeutic Applications	Dr. Varón Silva BS	01.11.2012-30.10.2015	
DFG	Untersuchung des Einflusses und der Funktion unterschiedlicher Ceramidspezies auf die Nanostruktur und die Dynamik von Stratum corneum Lipidmodellsystemen	Prof. Brezesinski GF Since 31.01.2014 KC	01.03.2013-28.02.2016	Martin-Luther-Universität Halle-Wittenberg Universität Leipzig Institut für Angewandte Dermatopharmazie an der Martin-Luther-Universität Halle-Wittenberg e.V.
DFG	Nanoporöse Polymere für die Wasseraufbereitung	Dr. Weber KC	15.04.2013-28.02.2014	
DFG	Graduiertenkolleg "1524"	Jaime Agudo TH	01.03.2013-29.02.2016	
DFG Transregios	Funktionelle Biomaterialien zur Steuerung von Heilungsprozessen in Knochen- und Hautgewebe - vom Material zur Klinik	Prof. Seeberger BS	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	Leibniz-Zentrum für Biodiversität der Tiere (ZFMK) Museum für Naturkunde Leibniz-Institut für Evolutions- und Biodiversitätsforschung Universität Rostock Rheinische Friedrich-Wilhelms-Universität Bonn
DFG	Multifunktionelle geschichtete Magnetit Komposite	Dr. Faivre BM	01.07.2014-31.12.2014	Universität Konstanz Forschungszentrum Jülich GmbH Friedrich-Alexander-Universität Erlangen-Nürnberg

DFG

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
DFG	Magneto-Aerotaxis bei magnetotaktischen Bakterien	Dr. Faivre BM	01.10.2014-30.09.2017	
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	01.07.2014-30.06.2017	Max-Planck-Institut für molekulare Pflanzenphysiologie, Potsdam
DFG Transregios	Verbesserte Anti-Kohlenhydrat-basierte Impfstoffe durch gezielte Aktivierung des angeborenen Immunsystems	Prof. Seeberger BS	01.07.2014-30.06.2018	Charité - Universitätsmedizin Berlin
DFG	Skalenskaskaden in komplexen Systemen	Dr. Weigl TH	01.10.2014-30.06.2018	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	01.11.2014-31.10.2017	
DFG	"Greigit oder Magnetit: Umwelt und genetische Faktoren, die die Biomineralisation in magnetotaktische Bakterien kontrollieren"	Dr. Faivre BM	01.04.2015-31.03.2018	
DFG	Biometric Materials Research: Functionality by Hierarchical Structuring of Materials	Prof. Fratzl Dr. Aichmayer Dr. Zaslansky Dr. Faivre Dr. Burgert Dr. Schlaad Dr. Cölfen BM	01.05.2010-	Institut National Polytechnique E.N.S.E.E.G./ L.T.P.C.M. Grenoble Foundry Institute of RWTH Aachen Department of Materials Engineering, Technical University Berlin Evolutionary Biomaterials Group, MPI für Metallforschung, Stuttgart Department of Materials Science and Engineering, University Erlangen-Nürnberg Dept. Of Microstructure Physics and Metal Forming, MPI Eisenforschung Düsseldorf Plant Biomechanics Group, Botanic Garden, University of Freiburg
DFG	Gottfried Wilhelm Leibniz-Programm	Prof. Fratzl Dr. Dunlop Dr. Wagermaier Dr. Dean BM	01.09.2010-31.08.2017	

DFG

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
DFG	Exzellenzcluster UniCat: Unifying Concepts in Catalysis	Prof. Möhwald GF Prof. Antonietti KC	01.01.2008-31.12.2010 01.11.2012-31.12.2015	Technische Universität Berlin Humboldt-Universität Berlin Freie Universität Berlin Universität Potsdam Fritz-Haber-Institut der Max-Planck-Gesellschaft Berlin

Supranationale Einrichtungen

ESA/ESTEC	Fundamental and Applied Studies of Emulsion Stability	Dr. Miller GF Since 31.01.2014 BM	01.10.2003-30.06.2014	IENI, Genua, Italien Université Aix-Marseille Université Compiègne, France Universität Complutense Madrid Universität Florenz, Italien IPF, Dresden CNR - Consiglio Nazionale delle Ricerche, Italien Eni S.p.A., Italien Aristotele Universität Thessaloniki
ESA/ESTEC	Topical Team: Foam and Emulsion Technologies-Concerted Action Team (FETCAT)	Dr. Miller GF Since 31.01.2014 BM	01.01.2013-31.12.2015	CNR, Genua, Italien Universität Florence, Italien Universität Marseille, Frankreich Universität Compiègne, Frankreich Murmansk State Technical University, Russland Aristotele Universität Thessaloniki, Griechenland Universität Stockholm, Schweden EniTecnologie, Milano, Italien University College Dublin, Irland Nestlé Research Center, Lausanne, Schweiz Wageningen University, Niederlande University of Manchester Institute of Science and Technology, Großbritannien Institute of Food Research, Norwich, Großbritannien Norwegian University of Science and Technology, Trondheim, Norwegen St. Petersburg State University, Russland Université d'Orsay et CNRS, Frankreich Université de Marne La Vallée, Frankreich Unilever, Großbritannien Norsk Hydro ASA, Norwegen IPF, Dresden
HFSP Research Grant		Dr. Dean BM	01.09.2013-31.08.2015	Wyss Institut - Harvard University, USA Konrad-Zuse-Zentrum für Informationstechnik Berlin (ZIB)

Stiftungen

Zuwendungs- geber	Thema	Projektleiter	Bewilligungszeitraum	Zusammenarbeit mit
Körber-Stiftung	Körber-Preis 2007	Prof. Seeberger BS	01.01.09.2007-	
VW-Stiftung	Synthetic Woven Bone Development by an Unconventional Biochemical Process	Prof. Omelon BM	01.02.2014-31.07.2015	
GIF-German Israeli Foundation	Emulsion-templated Porous Carbons: Hierarchical Porosities and Surface Functionalities	Prof. Antonietti KC	01.01.2013-31.12.2015	Technion, Haifa, Israel
GIF-German Israeli Foundation	Targeting Antibiotic Resistance of Bacteria with Self-Immolative Dendritic Prodrugs	Prof. Seeberger BS	01.01.2015-31.12.2017	Tel Aviv University

Sonstige deutsche Forschungsfinanzierer

DAAD	Projektbezogener Personenaustausch mit der China	Prof. Brezesinski GF Since 31.01.2014 KC Prof. Seeberger BS	2014-2015 2014	Shanghai Institute of Applied Physics, China Jiangnan University, Wuxi, China
DAAD	Projektbezogener Personenaustausch mit Frankreich	Dr. Wagermaier BM	2013-2014	Laboratoire d'Archéologie, Ivry-sur-Seine, France
DAAD	Projektbezogener Personenaustausch mit Polen	Prof. Brezesinski GF Since 31.01.2014 KC	2014-2015	Warsaw University of Technology, Poland
DAAD	Projektbezogener Personenaustausch mit Hong Kong	Dr. Jiayin Yuan KC	2014-2015	The Hong Kong Polytechnic University

Ausgewählte Veranstaltungen

Selected Events

2013

- **20.-22. March** The 7th Glycan Forum in Berlin
nhow Hotel, Berlin
- **24. April** Girls' Day
Max Planck Campus, Potsdam Golm Science Park
- **31. May** Alumni Meeting
MPI of Colloids and Interfaces
- **5.-6. June** Annual General Meeting of the Max Planck Society
Dorint Sanssouci, Potsdam
- **10.-13. June** 14th European Student Colloid Conference
MPI of Colloids and Interfaces
- **10. September** Open Day
MPI of Colloids and Interfaces
- **23.-25. September** Multiscale Motility of Molecular Motors
MPI of Colloids and Interfaces
- **25. October** Biomolecular Systems Day
MPI of Colloids and Interfaces

2014

- **17.-18. March** SPP1420 Winter School
- **27. March** Girls' Day
Max Planck Campus, Potsdam Golm Science Park
- **13.-16. April** Food Colloids
Karlsruhe Institute of Technology (KIT)
- **20. June** Alumni Meeting
Max Planck Institute of Colloids and Interfaces
- **1.-3. September** Biomembrane Days II
Max Planck Institute of Colloids and Interfaces
- **6. September** Open Day
Potsdam-Golm Science Park
- **10. October** Biomolecular Systems Day
Max Planck Institute of Colloids and Interfaces

Wissenschaftliche Abschlüsse

Scientific Degrees

Bachelor Theses

Department of Biomaterials

- Gjardy, A.: Untersuchung von Truthahnsehnen auf ihre Eignung als Matriz für die Infiltration von Nanopartikeln, Humboldt-Universität zu Berlin (2014).

Master Theses

Department of Biomaterials

2013

- Młynarczyk, B.: The mechanical role of His-metal complexes in biological elastomers. Universität Potsdam.

2014

- Arngold, X.: Chemical and mechanical characterization of mussel derived metal binding domain. Universität Potsdam.

Department of Biomolecular Systems

2013

- Knaack, J.: Synthesis of Glycopeptides for Evaluating the Influence of N-Glycan Core-Fucosylation on Protease Activity, Freie Universität Berlin.
- Poremski, S.: Towards the De Novo Synthesis of Pseudaminic Acid. Freie Universität Berlin.
- Wang, H.: Functionalization of Soft Colloidal Probes for Biosensing. Freie Universität Berlin.
- Zhukova, Y.: Synthesis of porous PEG-protein particles by hard templating with CaCO_3 . Humboldt-Universität Berlin.
- Zimmermann, S.: The murine C-type lectin receptor Mincle: Functional characterization, ligand specificity, and its role in inflammation. Universität Potsdam.

2014

- Bartetzko, M.: Automated solid-phase synthesis of plant arabinogalactan fragments. Freie Universität Berlin.
- Czarnecki, M.: Solid Phase Synthesis and Characterization of Zwitterionic Precision Polymers for Biomedical Applications. Universität Potsdam.
- Größel, J.: Synthesis of glycosylated Dolichol Derivatives. Freie Universität Berlin.
- Schmidt, D.: Automated solid-phase synthesis of plant arabinoxylan fragments. Freie Universität Berlin.
- Wagner, T.: Generation of C-type lectin receptor-Fc fusion proteins and their functional characterization: SIGN-R1-hFc and Dectin-2-hFc. Universität Potsdam.
- Zelmer, Ch.: Precision Glycomacromolecules and their Multivalent Presentation at Soft Surfaces. Freie Universität Berlin.

Department of Colloid Chemistry

2013

- Blaszkiewicz, Joanna: The Potential of Hydroxylated Poly(N-alkyl glycine)s as Antifreeze Additives. Universität Potsdam.
- Castaño Romera Fernandez, M.: Sustainable building blocks for polymers. Humboldt-Universität Berlin.
- Doriti, A.: Synthesis of functionalized polypeptides. Humboldt-Universität Berlin.
- Metzke, S.: Synthesis and Characterization of Transition Metal Nitrides and Carbides for Catalysis and Electrochemistry Application. Universität Potsdam.

PhD Theses

Department of Biomaterials

2013

- Bidan, C.: Geometric Control of Tissue Growth and Organisation. Universität Potsdam
- Körnig, A.: Assembled biogenic magnetic nanoparticles: Properties of magnetosome chains and their stability against external magnetic fields. Universität Potsdam.
- Saxe, F.: Significance of cell-wall ultrastructure for growth and mechanical properties of *Arabidopsis thaliana*. Universität Potsdam.

2014

- Carillo, M. A.: Chains of nanomagnets: How biological macromolecules stabilize their assembly. Universität Potsdam.
- Ermeydan, M. A.: Wood Cell Wall Modification with Hydrophobic Molecules. Universität Potsdam.
- Guiducci, L.: Passive biomimetic actuators: the role of material architecture. Universität Potsdam.
- Hörth, R.: Structural and Mechanical Changes of Bone Tissue during Healing and Implant Integration at the Micrometer and Nanometer Scale. Dissertation. Technische Universität Berlin.
- Razghandi, K.: Passive Hydro-actuated Unfolding of Ice Plant Seed Capsules as a Concept Generator for Autonomously Deforming Devices. Technische Universität Berlin.
- Vach, P.: Solution Synthesis and Actuation of Magnetic Nanostructures. Humboldt-Universität Berlin.

Department of Biomolecular Systems

2013

- Behra, M.: Synthesis of Functional Porous Poly(ethylene glycol) Microgels for Biotechnological Applications. Freie Universität Berlin.
- Calin, O.: Assembly of Oligosaccharides: from the De novo Synthesis of Building Blocks to the Automated Solid Phase Synthesis. Freie Universität Berlin.
- Eriksson, M.: C-type Lectin Receptors: from Immunomodulatory Carbohydrate Ligands to a Role in Murine Colitis. Freie Universität Berlin.
- Grünstein, D.: Carbohydrate Systems for Biosensing, Imaging and Medial Applications. Freie Universität Berlin.
- Maglinao, M.: C-type lectin receptors in cell-specific targeting and malaria infection. Freie Universität Berlin.
- Mosca, S.: 3R3-Peptides -Peptidomimetic Foldamers for Biomedical Applications: Design, Structure and Activity. Freie Universität Berlin.

2014

- Götze, S.: Synthesis of Parasite Related Carbohydrates and their Use as Probes for Glycobiology. Freie Universität Berlin.
- Kurucz, R.: Generation and Characterization of monoclonal Antibodies directed against synthetic *P. falciparum* Glycosylphosphatidylinositol glycans. Freie Universität Berlin.
- Ponader, D.: Synthesis of Sequence defined Glycooligomers for Studying Multivalent Interactions. Freie Universität Berlin.
- Pussak, D.: Synthesis and Functionalization of Soft Colloidal Probes based on Poly(ethylene glycol) as Carbohydrate Biosensors. Freie Universität Berlin.
- Wojcik, F.: Sequence-Defined Oligo(amidoamines): Synthesis, Carbohydrate Functionalization and Biomedical Applications. Freie Universität Berlin.

Department of Colloid Chemistry

2013

- Glatzel, S.: Cellulose Based Transition Metal Nano-Composites: Structure and Development. Universität Potsdam.
- Robinson, J. W.: Novel poly(N-substituted glycine)s: synthesis, post-modification, and physical properties. Universität Potsdam.
- Yu, L.: Hydrothermal Synthesis of Carbon and Carbon Nanocomposite Materials for Environmental and Energy Applications. Universität Potsdam.
- Fechler, N.: Salts as Highly Diverse Porogens: Functional Ionic Liquid-Derived Carbons and Carbon-Based Composites for Energy-Related Applications. Universität Potsdam.
- Soll, S.: Structural Properties and Functional Materials of Vinylimidazolium-type Poly(ionic Liquid)s. Universität Potsdam.
- Krannig, K.-S.: Smart, Biohybrid Polymers: Synthesis and Structures of Novel Glycopolypeptides. Universität Potsdam.
- Haro Dominguez, P.: Nanostructured Poly(benzimidazole)s by Chemical Modification. Universität Potsdam.

2014

- Chung, K. K.: Heteroatom-containing carbons for high energy density supercapacitor. Universität Potsdam.
- Höhne, P.: Bioinspirierte Untersuchungen zu polymeren Hydrogelen. Universität Potsdam.
- Krüger, K.: Zur hydrophob initiierten Photoemulsionspolymerisation. Universität Potsdam.
- Men, Y.: Poly(ionic Liquid)-based Thermo-responsive Polymers and Porous Carbon Materials. Universität Potsdam.
- Prescher, S.: Poly(Ionic Liquid)s: Synthesis and Function as Nanoparticles and Liquid Bulk Materials. Universität Potsdam.
- Ran, Y.: Via Redox Heterophase Polymerisation. Universität Potsdam.
- Ressnig, D.: The Preparative Decomposition of Semi-Organic Crystals: Metal Carbodiimides become Functional. Universität Potsdam.
- Schipper, F.: Biomass Derived Carbon for New Energy Storage Technologies. Universität Potsdam.

Department of Interfaces

2013

- Dannehl, C.: Fragments of the Human Antimicrobial LL-37 and their Interaction with Model Membranes. Universität Potsdam.

Department of Theory & Bio-Systems

2013

- Bahrami, A.: Vesicles interacting with nanoparticles. Technische Universität Berlin.
- Fricke, N.: Eine Riesenvesikel-Studie zum Einfluss des Glycolipids GM1 auf Phospholipid-Membranen. Universität Potsdam.
- Pobandt, T.: Modeling Peptides at Interfaces in Atomic Detail. Technische Universität Berlin.
- Patra, P.: Population Dynamics of Bacterial Persistence. Universität Potsdam.

2014

- Raatz, M.: Modeling the wrapping of nanoparticles by membrane. Universität Potsdam.
- Jin, C.: Theoretical and Experimental Study of Capillary Effects on Melting. Universität Potsdam.
- Mauri, M.: A model for sigma factor competition in bacterial cells. Universität Potsdam.

Habilitations

Department of Biomaterials

[Damien, F.:](#) Biological and Biomimetic Formation and Organization of Magnetic Nanoparticles. Uni Potsdam (2014).

Department of Biomolecular Systems

[Hartmann, L.:](#) Precision Glycomacromolecules and Glycohydrogels: Synthesis and Applications in Biotechnology and Biomedicine. FU Berlin (2014).

[Lepenies, B.:](#) C-Typ Lektinrezeptoren – Ligandenidentifikation, zellspezifisches Targeting und ihre Funktion in Infektion und Inflammation. Freie Universität Berlin (2014).

Department of Colloid Chemistry

[Titirici, M. M.:](#) Sustainable Carbon Materials from Hydrothermal Processes. Universität Potsdam (2013).

[Giordano, Cristina:](#) A neglected World: Transition Metal Nitride and Metal Carbide Based Nanostructures. Novel Synthesis and Future Prospectives. Universität Potsdam (2014).

Personalien

Appointments and Honors

Ehrungen/Mitgliedschaften/Honorarprofessuren Honors/Memberships/Honorary Professorships

2013

- Prof. Dr. Peter Fratzl: Director of the Department of Biomaterials has been elected as member of the German Academy of Science and Engineering (ACATECH).
- Prof. Dr. Peter Fratzl: Director of the Department of Biomaterials received the Jerome B. Cohen Distinguished Lecture Series of the Northwestern University, Evanston, USA.
- Prof. Dr. Peter H. Seeberger: Director of the Department of Biomolecular Systems has been elected to become a member of the Berlin Brandenburg Academy of Sciences and Humanities.
- Prof. Dr. Peter H. Seeberger: Director of the Department of Biomolecular Systems received the C. S. Hamilton Award for Organic Chemistry of the University of Nebraska.

2014

- Prof. Dr. Markus Antonietti: Director of the Department of Colloid Chemistry received the Friedrich Bergius Lecture award.
- Prof. Dr. Markus Antonietti: Director of the Department of Colloid Chemistry received the "Krister Holmberg Lecture", Göteborg.
- Dr. Rumiana Dimova: Group Leader in the Department of Theory & Bio-Systems received the Spring 2014 EPS Emmy Noether Distinction for Women in Physics.
- Prof. Dr. Helmuth Möhwald: Director (em.) has been named a 2014 Langmuir Lecturer.
- Dr. Jiayin Yuan: Group Leader in the Department of Colloid Chemistry received an ERC Starting Grant of the European Research Council.

Ruf an eine Universität Appointments

2013

- Dr. Filipe Vilela: Group Leader in the Department of Colloid Chemistry accepted a position as Lecturer in Chemistry at the Heriot-Watt University in Edinburgh.

2014

- Dr. Laura Hartmann: Group Leader in the Department of Biomolecular Systems, accepted a position as W3 professor for Preparative Polymer Chemistry at the Heinrich-Heine-University Düsseldorf.
- Dr. Helmut Schlaad: Group Leader in the Department of Colloid Chemistry accepted a position as W2 professor for Polymer Chemistry at the University Potsdam.

Biomaterialien 2013

Articles

Aizenberg, J.; Fratzl, P.; Addadi, L.: Preface for the special issue celebrating Stephen Weiner's 65th birthday. *J. Struct. Biol.* 183 105-106 (2013)

Aizenberg, J.; Fratzl, P.: New Materials through Bioinspiration and Nanoscience. *Adv. Funct. Mater.* 23 (36), 4398-4399 (2013)

Baumgartner, J.; Dey, A.; Bomans, P. H. H.; Le Coadou, C.; Fratzl, P.; Sommerdijk, N. A. J. M.; Faivre, D.: Nucleation and growth of magnetite from solution. *Nat. Mater.* 12 (4), 310-314 (2013)

Baumgartner, J.; Bertinetti, L.; Widdrat, M.; Hirt, A. M.; Faivre, D.: Formation of Magnetite Nanoparticles at Low Temperature: From Superparamagnetic to Stable Single Domain Particles. *PLoS One* 8 (3) (2013)

Baumgartner, J.; Morin, G.; Menguy, N.; Gonzalez, T. P.; Widdrat, M.; Cosmidis, J.; Faivre, D.: Magnetotactic bacteria form magnetite from a phosphate-rich ferric hydroxide via nanometric ferric (oxyhydr)oxide intermediates. *Proc. Natl. Acad. Sci. U. S. A.* 110 (37), 14883-14888 (2013)

Bennet, M.; Perez-Gonzalez, T.; Wood, D.; Faivre, D.: Magnetosomes. *Bionanotechnology: Biological Self-Assembly and its Applications* 241-271 (2013)

Bertinetti, L.; Fischer, F. D.; Fratzl, P.: Physicochemical Basis for Water-Actuated Movement and Stress Generation in Nonliving Plant Tissues. *PHYSICAL REVIEW LETTERS* 111 (23) (2013)

Bidan, C. M.; Wang, F. M.; Dunlop, J. W. C.: A three-dimensional model for tissue deposition on complex surfaces. *COMPUTER METHODS IN BIOMECHANICS AND BIOMEDICAL ENGINEERING* 16 (10), 1056-1070 (2013)

Bidan, C. M.; Kommareddy, K. P.; Rumpler, M.; Kollmannsberger, P.; Fratzl, P.; Dunlop, J. W. C.: Geometry as a Factor for Tissue Growth: Towards Shape Optimization of Tissue Engineering Scaffolds. *Adv. Healthc. Mater.* 2 (1 Sp. Iss. SI), 186-194 (2013)

Bikondoa, O.; Carbone, D.; Chamard, V.; Metzger, T. H.: Ageing dynamics of ion bombardment induced self-organization processes. *Sci Rep* 3 (2013)

Carillo, M. A.; Bennet, M.; Faivre, D.: Interaction of Proteins Associated with the Magnetosome Assembly in Magnetotactic Bacteria As Revealed by Two-Hybrid Two-Photon Excitation Fluorescence Lifetime Imaging Microscopy Förster Resonance Energy Transfer. *The Journal of Physical Chemistry B* 117 (47), 14642-14648 (2013)

Claes, J. M.; Dean, M. N.; Nilsson, D. E.; Hart, N. S.; Mallefet, J.: A deepwater fish with 'lightsabers' - dorsal spine-associated luminescence in a counterilluminating lanternshark. *Sci Rep* 3 (2013)

Dunlop, J. W. C.; Fratzl, P.: Multilevel architectures in natural materials. *Scr. Mater.* 68 (1), 8-12 (2013)

Eder, M.; Arnould, O.; Dunlop, J. W. C.; Hornatowska, J.; Salmen, L.: Experimental micro-mechanical characterisation of wood cell walls. *Wood Sci. Technol.* 47 (1), 163-182 (2013)

Erko, M.; Hartmann, M. A.; Zlotnikov, I.; Serrano, C. V.; Fratzl, P.; Politi, Y.: Structural and mechanical properties of the arthropod cuticle: Comparison between the fang of the spider *Cupiennius salei* and the carapace of American lobster *Homarus americanus*. *J. Struct. Biol.* 183 (2), 172-179 (2013)

Fischer, F. D.; Harrington, M. J.; Fratzl, P.: Thermodynamic modeling of a phase transformation in protein filaments with mechanical function. *New J. Phys.* 15 (2013)

Fritz-Popovski, G.; Van Opdenbosch, D.; Zollfrank, C.; Aichmayer, B.; Paris, O.: Development of the Fibrillar and Microfibrillar Structure During Biomimetic Mineralization of Wood. *Adv. Funct. Mater.* 23 (10), 1265-1272 (2013)

Gal, A.; Habraken, W.; Gur, D.; Fratzl, P.; Weiner, S.; Addadi, L.: Calcite Crystal Growth by a Solid-State Transformation of Stabilized Amorphous Calcium Carbonate Nanospheres in a Hydrogel. *Angew. Chem.-Int. Edit.* 52 (18), 4867-4870 (2013)

Galvis, L.; Dunlop, J. W. C.; Duda, G.; Fratzl, P.; Masic, A.: Polarized Raman Anisotropic Response of Collagen in Tendon: Towards 3D Orientation Mapping of Collagen in Tissues. *PLoS One* 8 (5) (2013)

Gamsjäger, E.; Bidan, C. M.; Fischer, F. D.; Fratzl, P.; Dunlop, J. W. C.: Modelling the role of surface stress on the kinetics of tissue growth in confined geometries. *Acta Biomater.* 9 (3), 5531-5543 (2013)

Guerette, P. A.; Hoon, S.; Seow, Y.; Raida, M.; Masic, A.; Wong, F. T.; Ho, V. H. B.; Kong, K. W.; Demirel, M. C.; Pena-Francesch, A.; Amini, S.; Tay, G. Z.; Ding, D.; Miserez, A.: Accelerating the design of biomimetic materials by integrating RNA-seq with proteomics and materials science. *NATURE BIOTECHNOLOGY* 31 (10), 908-915 (2013)

Gupta, H. S.; Krauss, S.; Kerschnitzki, M.; Karunaratne, A.; Dunlop, J. W. C.; Barber, A. H.; Boesecke, P.; Funari, S. S.; Fratzl, P.: Intrafibrillar plasticity through mineral/collagen sliding is the dominant mechanism for the extreme toughness of antler bone. *JOURNAL OF THE MECHANICAL BEHAVIOR OF BIOMEDICAL MATERIALS* 28 366-382 (2013)

Gur, D.; Politi, Y.; Sivan, B.; Fratzl, P.; Weiner, S.; Addadi, L.: Guanine-Based Photonic Crystals in Fish Scales Form from an Amorphous Precursor. *Angew. Chem.-Int. Edit.* 52 (1), 388-391 (2013)

Habraken, W. J. E. M.; Tao, J. H.; Brylka, L. J.; Friedrich, H.; Bertinetti, L.; Schenk, A. S.; ... [mehr] Ion-association complexes unite classical and non-classical theories for the biomimetic nucleation of calcium phosphate. *Nat. Commun.* 4 (2013)

Herzog, G.; Benecke, G.; Buffet, A.; Heidmann, B.; Perlich, J.; Risch, J. F. H.; Santoro, G.; Schwartzkopf, M.; Yu, S.; Wurth, W.; Roth, S. V.: In Situ Grazing Incidence Small-Angle X-ray Scattering Investigation of Polystyrene Nanoparticle Spray Deposition onto Silicon. *LANGMUIR* 29 (36), 11260-11266 (2013)

Huber, P.; Busch, M.; Calus, S.; Kityk, A. V.: Thermotropic nematic order upon nanocapillary filling. *Phys. Rev. E* 87 (4) (2013)

Hwang, D. S.; Masic, A.; Prajateljia, E.; Iordachescu, M.; Waite, J. H.: Marine hydroid perisarc: A chitin- and melanin-reinforced composite with DOPA-iron(III) complexes. *Acta Biomater.* 9 (9), 8110-8117 (2013)

Kerschnitzki, M.; Kollmannsberger, P.; Burghammer, M.; Duda, G. N.; Weinkamer, R.; Wagermaier, W.; Fratzl, P.: Architecture of the osteocyte network correlates with bone material quality. *J. Bone Miner. Res.* 28 (8), 1837-1845 (2013)

Krauss, S.; Metzger, T. H.; Fratzl, P.; Harrington, M. J.: Self-Repair of a Biological Fiber Guided by an Ordered Elastic Framework. *Biomacromolecules* 14 (5), 1520-1528 (2013)

Publikationen

- Kuttner, C.; Hanisch, A.; Schmalz, H.; Eder, M.; Schlaad, H.; Burgert, I.; Fery, A.: Influence of the Polymeric Interphase Design on the Interfacial Properties of (Fiber-Reinforced) Composites. *ACS Appl. Mater. Interfaces* 5 (7), 2469-2478 (2013)
- Lukas, C.; Ruffoni, D.; Lambers, F. M.; Schulte, F. A.; Kuhn, G.; Kollmannsberger, P.; Weinkamer, R.; Muller, R.: Mineralization kinetics in murine trabecular bone quantified by time-lapsed in vivo micro-computed tomography. *Bone* 56 (1), 55-60 (2013)
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