Mesoscopic Simulations of Complex Nanostructures and Processes

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The traditional boundaries between the scientific disciplines of Physics, Chemistry and Biology are being rapidly eroded at the nanoscale. This is a new development largely because at the macroscale it is clear that there is a vast difference between whole organisms, even ones as small as an amoeba, and the atoms and molecules of chemistry and physics. As one probes down to smaller length scales, however, these distinctions become increasingly artificial. Progress in electron microscopy, fluorescence techniques and micromanipulation have pushed the experimental resolution of investigations of the protein and lipid components of cells to smaller and smaller length scales while, simultaneously, novel computer simulation techniques are starting to reveal structure above the 50 nm and 100 ns marks. However, the intermediate region, between 100 nm and 1 micron, and 100 ns and 100 microseconds, is still partially obscure: the so-called twilight zone **[1]**.

In this project, we are using a mesoscopic simulation technique, Dissipative Particle Dynamics (DPD), to probe this twilight zone. We hope to predict the properties of "smart" self-assembled materials, such as amphiphilic membranes and actin filaments, from a knowledge of their constituents (see **Fig. 1**); and to reveal details of biophysical processes, such as vesicle fusion, unobtainable from continuum theoretical models and difficult to quantify from experiment. In collaboration with a group at University of Pennsylvania, we have also started to perform a systematic comparison of DPD simulations with more traditional Molecular Dynamics (MD) simulations using diblock copolymers as a target system of topical interest.

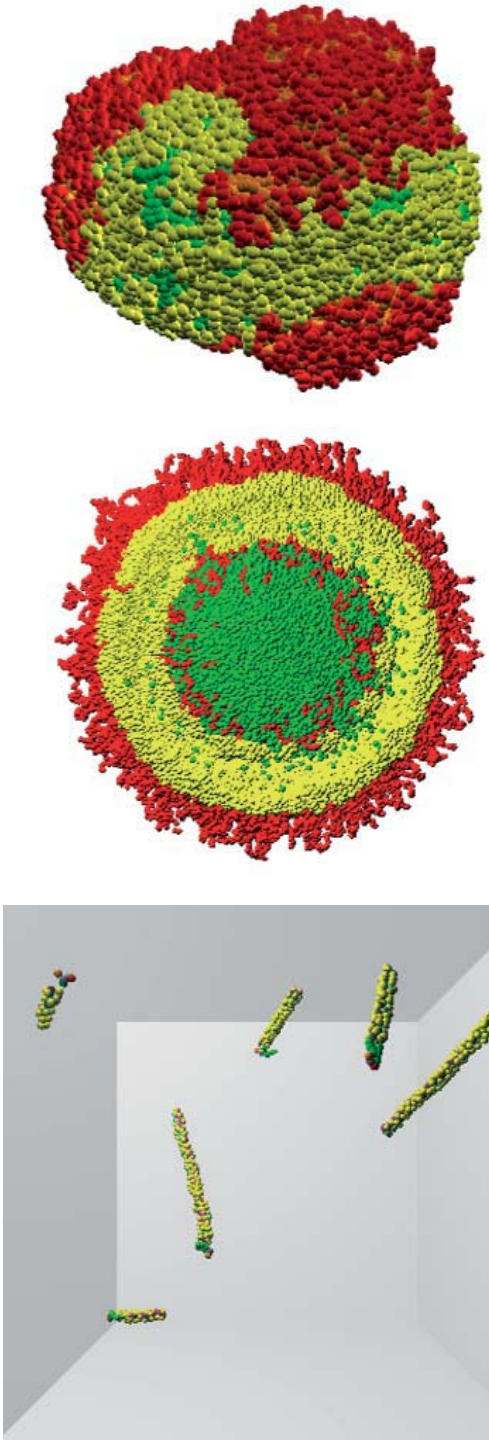

Fig. 1: Illustrations of a two-component vesicle (Illya, PhD Thesis, 2004), a 40 nm polymersome (Ortiz et al., 2005), and growing actin filaments (Shillcock and Lipowsky, in progress). Note that the images are not to the same scale.

Amphiphilic membranes are ubiquitous in nature, and have important technological applications as well. Ms Gregoria Illya, who graduated in December 2004, has used DPD simulations to map out the dependence of amphiphilic membrane structural properties (area per molecule, thickness, density profile) and material properties (lateral stress profile, area stretch modulus and bending modulus) for a homologous series of amphiphiles **[2]**. Mixed membranes containing two types of amphiphile with different tail lengths have also been investigated. For amphiphiles that mix ideally, the membrane area stretch modulus is a non-monotonic function of the composition, in agreement with mean field theories. Amphiphiles that tend to phase separate in the membrane form domains whose shape changes from small circular patches, through stripes, to inverted circular patches as the concentration of the close-packed amphiphile is increased.

Diblock copolymers form closed vesicles called Polymersomes. These systems are of great interest as drug delivery vehicles, amongst other applications, because they are more robust than lipid vesicles, and their material properties can be systematically varied depending on the molecular details of their constituents **[3]**. Together with the group of Prof. Dennis Discher at University of Pennsylvania, we have used DPD simulations to study the properties of polymersomes. We have calibrated the parameters of our DPD diblock model using the Penn group's all-atom and coarse-grained MD simulations. The results are currently being submitted **[4]**, and show that the common assumption in DPD simulations to date that all beads have a common density must be abandoned if the physical properties of the diblock model are to match those of the corresponding experimental system.

The second part of our work is the study of dynamic processes on a mesoscopic scale. As a model system, the fusion of a 28 nm vesicle to a 50 x 50 nm^2 patch has been simulated for up to 2 microseconds using two protocols. The first places the vesicle and membrane patch under initial tensions, and lets the system evolve without further interference. The second protocol places an initially relaxed vesicle next to a relaxed planar membrane patch, and uses a sequence of bending and stretching forces, mimicing the actions of the fusion proteins, to drive the fusion process. The tension-controlled fusion depends sensitively on the size of the membrane patch to which the vesicle fuses and, for the 50 nm patch used here, predicts a pore formation time (measured from the time of first contact between vesicle and planar membrane) of 200-300 ns. This is far below the current experimental resolution of fusion, showing that coarse-grained simulations can already explore regimes that are not yet experimentally characterised. These results have recently been accepted for publication **[5]**. The fusion of membranes with novel molecular architectures and material properties is being extended by a recently-arrived post-doctoral fellow, Dr Lianghui Gao, and a new PhD student, Ms Andrea Grafmüller. The second protocol is still being developed, and we aim to compare the forces required to drive fusion with experimentally-measured forces **[6]**) in order to make predictions about the minimal molecular machinery that can produce reliable vesicle fusion.

Finally, we are using DPD to simulate the self-assembly of actin filaments. Within the framework of a Human Frontier Science Project grant, we are exploring a model of Formin-mediated filament assembly. Formin is a protein that sequentially adds actin monomers to a growing filament while maintaining a constant "grip" on the filament. The monomers bind using non-covalent forces; the filaments are polar, with different growth/shrinkage rates at each end; and the filament stiffness is sensitive to the nature of the bonds holding monomers together. This system has been the subject of recent experimental work **[7]**, and we hope to measure the force exerted by a formin molecule bound to a small bead on a growing filament.

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