## Strong curvature effects in biological membranes

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### In Short

- Implement state-of-the-art methods to understand molecular mechanisms and role of high curvature in membrane fusion
- How does the vesicle-vesicle contact angle affect the free-energy landscape of membrane fusion?
- Optimize the analysis of small angle X-ray scattering data by quantitative comparison of experimental spectra of complex vesicle samples with simulated results

**Research questions** – Membrane remodeling (including membrane fusion, fission, etc.) plays a fundamental role in biological cells, involved in intracellular trafficking, viral infection, and biogenesis [1,2,3]. Importantly, these cooperative processes are often regulated by a protein machinery to perform the corresponding biological functions of membranes. Strong membrane curvatures, often provided by proteins, are involved in many steps along the remodeling path.

The aim of our new project is to understand – at different length scales ranging from molecular to continuum – the role of strong curvature on the structure and collective dynamics of biological membranes by studying vesicles as well as lipid droplets. Such a detailed understanding poses a challenge: the length and time scales involved in membrane remodeling – micron and microsecond – are too small and too short for a direct experimental observation, but too large and too long for atomistic molecular simulation. These difficulties can be overcome by computer simulation of coarse-grained models, which only incorporate the most relevant interactions for the processes under study.

**Models and methods** – In our group, different models for lipid membranes and proteins with varying degrees of coarse-graining have been developed and/or employed, ranging from the near-atomic coarse-grained models, capturing chemical specificity of lipids and proteins [4], to highly coarse-grained generic models [1,3], and continuum models. In our project we use these models to understand the role of high membrane curvature in membrane shape remodeling during the fusion process, involved in neuronal membrane fusion, and lipid droplet formation, as well as in vesicle-shape fluctuations and internal membrane structure that can be measured in X-ray scattering experiments.

Specifically, we will focus on four tasks: (i) obtain and compare different minimum free-energy paths (MFEPs) of vesicle fusion, (ii) investigate the role of docked vesicle-vesicle contact angle provided by tether-protein complexes in neuronal fusion pore formation, (iii) reveal the signature of strong curvature in small angle X-ray scattering data of an ensemble of vesicles, and (iv) study mechanisms of lipid droplet formation and stabilization.

To this end, for tasks (i) and (ii) we will use MD simulations of the MARTINI coarse-grained model. In the first subproject we will calculate the free-energy profiles of different thermodynamically reversible transformation paths of vesicle fusion, see Fig. 1. In the second task we will study the effect of the contact angle between docked vesicles imposed by tether-protein complexes [5] on the subsequent fusion pore expansion, see Fig. 2.

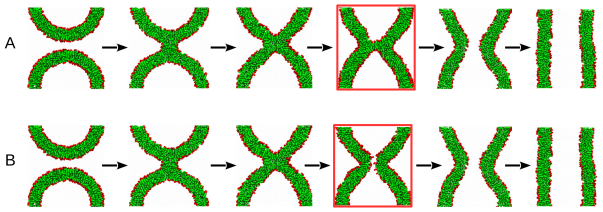


***Figure 1:*** *Two possible transformation paths for vesicle fusion: Path A goes over a hemifusion diaphragm, depicted by the red frame, whereas path B features the direct formation of the fusion pore after the stalk has only slightly expanded. MARTINI model snapshots with color code: lipid tails – green, lipid backbone – red, lipid heads and solvent beads are not shown.*

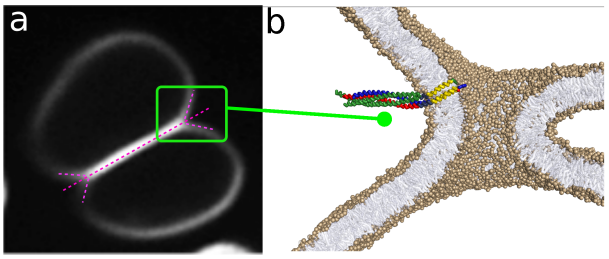


***Figure 2:*** *(a) Cryo-em imaging of two docked vacuoles. (b) Simulation of a fusion pore formed at the edge of the docking zone under a contact angle of 45 degrees.*

For task (iii) we will use MC simulations of an ensemble of vesicles with different shapes and sizes within an augmented Helfrich Hamiltonian to calculate the scattering function and guide the analysis of

small angle X-ray scattering spectra by quantitatively comparing experimental data with our simulated results. We will calculate the scattering intensity using a three-dimensional fast Fourier transform of the membrane electron density. In this way we will be able to extract information about the bilayer profile of non-trivial, fluctuating membrane geometries and to distinguish between curvature-induced asymmetry of the intrinsic profile, thermal undulations of the vesicle shape, and effects of size-polydispersity. Fig. 3 shows an illustration of such simulated vesicle.

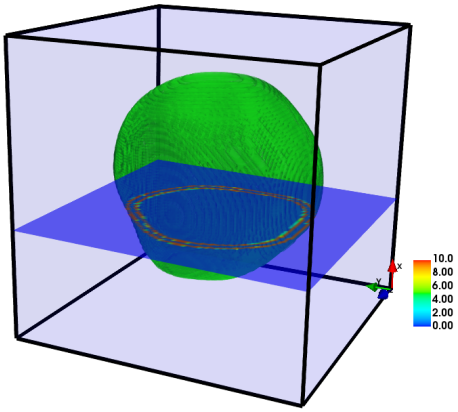


***Figure 3:*** *Simulated vesicle with shape fluctuations. On the horizontal blue plane we can see a cross section of the bilayer profile with the electron density obtained from a three-Gaussian model for the intrinsic membrane profile.*

In task (iv) the formation and stability of lipid droplets will be studied. Lipid droplets (LDs) serve as storage for neutral lipids and play an important role in regulatory processes regarding lipid metabolism and homeostasis. Thus they are linked to pathological conditions such as obesity, diabetes, lipodystrophy, and steatohepatitis. Emerging from the endoplasmatic reticulum, LDs interact with a large variety of organelles in the cell but, so far, only little is known about mechanisms and proteomics of the LD-organelle contact. Lipidic bridges, linking the phospholipid monolayer of these highly curved structures to the organelle bilayer, resemble topologically a hemifusion state and are thought to be a unique feature of LD interaction, see Fig. 4.

## WWW

http://www.theorie.physik.uni-goettingen.de/forschung/mm/

## More Information

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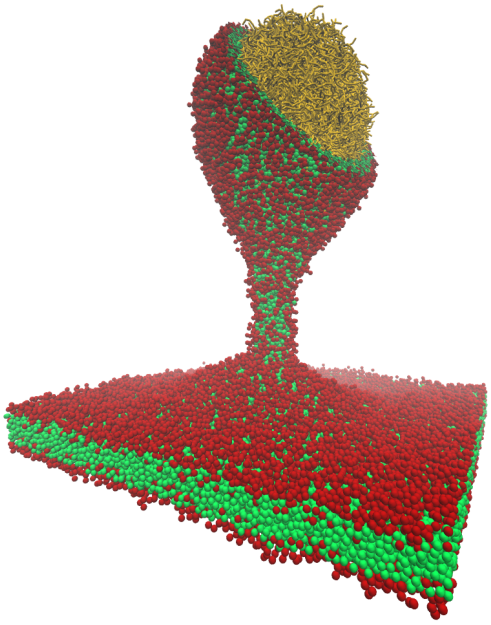

***Figure 4:*** *Coarse-grained molecular dynamics simulation of a modeled lipid droplet linked to a POPC bilayer, using MARTINI model. Solvent beads are not shown.*

## Project Partners

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