You only fuse once (or do you?)

Reversibility and Inhibition of Biological Membrane Fusion

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In Short

- We investigate collective changes in the topology of biological membranes in the context of fusion and fission
- We employ particle-based and continuum models on various levels of coarse-graining, complemented by free-energy calculation methods and genetic algorithms
- The developed techniques facilitate the identification of transition states and free-energy barriers
- We utilize our methods to understand the molecular mechanisms of synaptic transmission and viral infection

Topological transitions in lipid membranes – pore formation, fusion, and fission – are a key factor in the understanding of multifarious phenomena in biological cells. Two highly relevant topics in this respect are synaptic signal transmission and viral infection. In our previous project *nic00072*, we have developed molecular models and simulation techniques to address topological changes in the form of membrane fusion and fission. The goal of our new project is to further shed light on the role of lipid properties, membrane behaviour and protein machinery on the underlying molecular mechanisms. We ultimately intend to assess under which conditions membrane fusion can be arrested and even be reversed from a hemi-fusion state [1].

One process where such considerations are particularly relevant is the *kiss-and-run* (K&R) mechanism [2]. K&R is a mode of synaptic exo- and endocytosis where neurotransmitter-carrying vesicles do presumably not collapse into the fusing plasma membrane. Such a mechanism would explain the fast release of neurotransmitters and high-fidelity recycling of synaptic vesicles observed in experiments. Similar questions play an important role in the fusion of virus capsules with host cells. Understanding the arresting and reversal of fusion in this context provides a way towards the prevention of viral infections [3]. During recent years, major public interest in this respect has been on the corona virus, whose proliferation continues to impede economic development as well as public life in general.

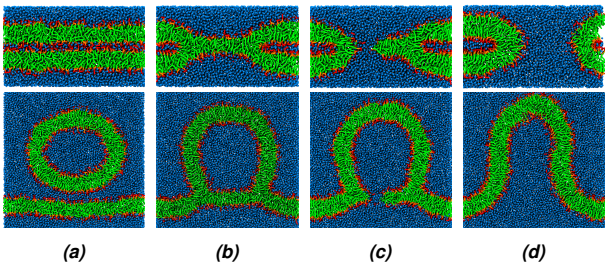

Figure 1: *Snapshots of the fusion of two lipid bilayers obtained from coarse-grained molecular dynamics simulations. The four states show the transition from opposed bilayers (a) towards a hemifusion diaphragm (b), the nucleation of a rim pore (c) and the fully formed fusion pore (d). We consider the scenarios of two planar membranes (top) and a vesicle interacting with a flat membrane (bottom).*

In our new project, we aim to further investigate influencing factors of the K&R mechanism employing coarse-grained molecular dynamics (CGMD) simulations. These simulations will be carried out with the GROMACS simulation engine [4] and the MARTINI coarse-grained force field [5]. We combine these simulations with a state-of-the art string method to determine the minimum-free-energy-path (MFEP) of the fusion/fission process. Our string method relies on a particle-mesh technique in the form of field-theoretic umbrella sampling [6,7]. In extension of the previous project period, we now consider vesicular systems in addition to flat bilayers, to account for the effects of membrane curvature (c.f. figure [1]).

To expand the accessible parameter space of our investigations, we newly employ self-consistent field theory (SCFT) calculations [8]. SCFT provides a continuum modelling approach which, in combination with the string method [9], allows for the screening of a large number of parameter sets. The most promising candidates can subsequently be investigated in more detail using particle-based methods.

In order to mechanistically understand the occurring phenomena and analyze our simulation data, we develop a phenomenological model for the (transient) behaviour of pores in a hemi-fusion state. We plan to further refine this model and to determine line tensions from a Fourier analysis of the contour-shape fluctuations of fusion intermediates, informed by simulations.

Ultimately, our investigations will allow us to determine free energy barriers and reaction coordinates of the fusion and fission process in K&R. This, in turn, will enable an assessment of the physiological viability of the process under different conditions.

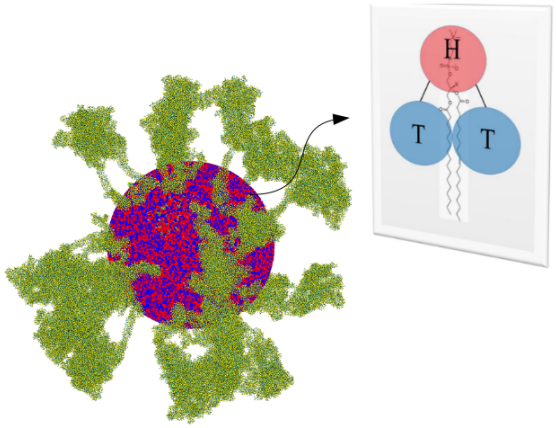

Figure 2: *Coronal virus: Multiple copies of proteins inserted into the equilibrated vesicle are shown in green colors while the red and blue colors represent the highly CG lipid model consisting of three beads.*

For the (considerably larger) corona virus capsule, we introduce an additional level of coarse-graining, modelling a lipid by three beads. We further parameterize this model with a Many-Objective Optimization based Genetic Algorithm developed in our group. This evolutionary algorithm determines the ”fitness” of a parameter set - the genome - to optimize the thermodynamic and structural properties of the membrane model. The target values for the optimization will be obtained from CGMD simulations using GROMACS and MARTINI. The corresponding model setup is depicted in figure [2]

Combining the highly coarse-grained model with free-energy calculation techniques, we intend to study the influence of transmembrane proteins on the inhibition of viral fusion. These insights will lead to a further understanding for the potential of tailor-made antiviral peptide drugs.

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

More Information

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Project Partners

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