Influence of external interactions on lipid interfaces

H. J. Risselada, Y. Smirnova, L. Endter, K. Stroh, J. Methorst, N. van Hilten, A. Soleimani, M. Müller, *Institute for Theoretical Physics, University of Göttingen*

In Short

- We implement state-of-the-art methods to model and understand biological processes on a molecular level.
- Close collaboration with experimental groups helps us to refine our models and in return we try to elucidate mechanisms not visible by experiment.
- Transformations of membrane topology are complex and often hard to grasp. Combining a variety of techniques we can tackle calculations of physical observables of large systems.

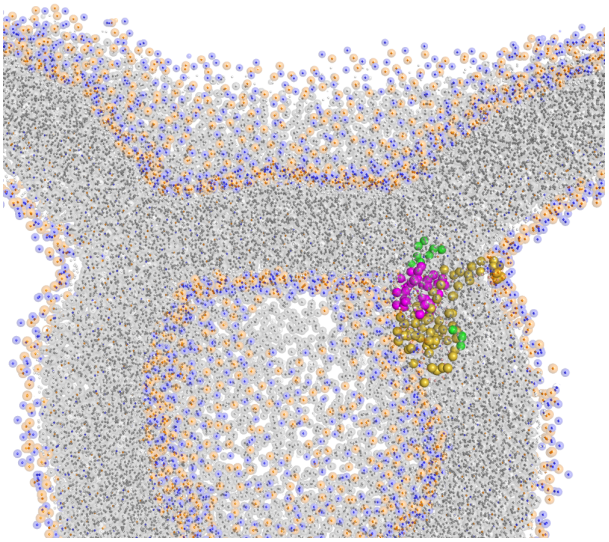

Figure 1: *Snapshot of a IFITM3 protein attracted to the virus-induced hemifusion diaphragm. Will changes to viral fusion peptides abolish the inhibitory effect of IFITM3?*

Research questions – Membrane remodeling (including membrane fusion, fission, etc.) plays a fundamental role in biological cells, involved in intracellular trafficking, viral infection, and biogenesis [1–4]. These cooperative processes are essential for the biological functions of membranes and are highly regulated by a complex protein machinery. Proteins can sense regions of action in the membranes through curvature, membrane tension, or changes of lipid composition and are thus attracted or expelled. Seemingly small changes at the molecular level can have a large impact on functionality of a whole mechanism. Changes in the protein sequence, for example, can lead to complete inactivation or enhancement of its function by changing their interaction with other molecules. Often there are pathological conditions linked to malfunctions or exploitation, for example by viruses, of membrane related biological mechanisms.

In our research we try to understand how interactions with biological inclusions such as proteins, peptides and viral RNA strains (re)model the shape and topology of lipid membranes using particle based simulations models. Computer simulations allow us to explore details on a length and time scale – micrometers and microseconds – that is difficult if not beyond the capabilities of experimental procedures. The model systems we use, though not capturing all details of a natural system, mimic the features thought to be of relevance to the mechanism under investigation. This omission of attributes is not a flaw in the method but rather helps to break down the mind-blowing complexity of nature in digestible pieces.

Models and methods – In our group, use models for lipid membranes and proteins with varying degrees of coarse-graining, which is a technique where we reduce the details in which the molecules are represented, *e.g.*, by bundling several atoms into one particle [5]. This allows us to simulate larger systems because of a lesser computational demand. We have developed and/or used models, ranging from a systematically coarse-grained model like the MARTINI force field to a highly coarse-grained, solvent-free model, as well as near-continuum models (ultra coarse-graining) such as elastic Helfrich-like models. We also use and develop advanced methods to calculate relative free energy differences between the start and the end state of a transformation [6,7]. Free energy stands for the overall energy that is set free by bringing a system into a energetically more favorable state or the energy that need to be put into a system to drive a transformation even if the end state is less stable. Knowledge about the energetics of transformations in conjunction with hypotheses about the role of proteins in mediating the process, *e.g.*, by stabilizing or destabilizing morphologies, is our key to mechanistic understanding.

To explore interactions of proteins beyond known sequences we combine our calculations with evolutionary algorithms, which are part of the Artificial

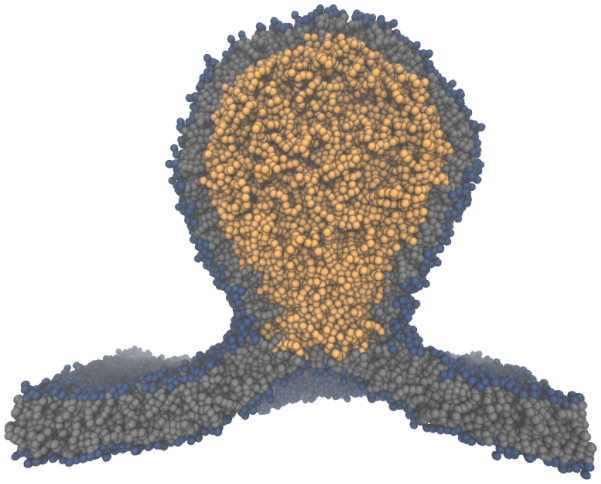

Figure 2: *Coarse-grained Lipid Droplet (LD) model, showing a neutral lipid lens budded from a membrane bilayer. Does seipin help to drive this process and stabilize the structure?*

Intelligence class, to search for global solutions, *i.e.* the most active form, in the chemical space of protein motifs.

By working on several distinct systems, each having its own peculiarities and challenges, we learn from difficulties in one system and benefit form the experience in another and thus are able to make our methods as generally applicable as possible. Specifically, we chose four also medically relevant systems:(i) mitochondrial oil bodies (lipid droplets) and their interaction with the seipin protein complex (ii) viral fusion pores and how RNA release influences them , (iii) the IFITM protein family and how they inhibit membrane remodeling, (iv) proteins that are able to sense local membrane features such as differences in membrane curvature, tension, and composition (e.g., the membranes of cancerous cells).

Subproject (i), (iii) and (iv) will use MD simulations of the MARTINI coarse-grained model. These simulations are set up to model processes actually taking place in real organisms. Lipid droplets, for example, serve as fat storage in cells in form of neutral lipids. If there are malfunctions of related proteins, such as seipin, the storage mechanism is disturbed and can lead to severe diseases. The molecular structure of seipin has only recently been elucidated by cryo-EM imaging. Through modelling we will now test our hypothesis on its function on a biophysical level.

Studying fusion inhibitors (task iv) on a molecular level will help us and the experimentalists to understand what factors determine a successful or failed viral infection. Ultimately, this knowledge may help to design highly effective drugs to prevent or cure viral infections.Finally, by using evolutionary algorithms to tune protein motifs to display an increased affinity for cancerous cell membranes we hope to elucidate ways to improve the detection of tumors and help design new selective drugs within the medical fields.

WWW

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

More Information

[1] J.-P. Mattila, A.V. Shnyrova , A.C. Sundborger, E. Rodriguez Hortelano, M. Fuhrmans, S. Neumann, M. Müller, J.E. Hinshaw, S.L. Schmid, and V.A. Frolov, "A hemi-fission intermediate links two mechanistically distinct stages of membrane fission", *Nature*, 524, 109 **2015**.

[2] M. Fuhrmans, G. Marelli, Y. G. Smirnova, and M. Müller, "Mechanics of membrane fusion/pore formation", *Chem. Phys. Lipids*, 185, 109 **2015**.

[3] M. Fuhrmans and M. Müller, "Coarse-grained simulation of dynamin-mediated fission", *Soft Matter*, 11, 1464 **2015**.

[4] M. D'Agostino, H. J. Risselada, A. Lürick, C. Ungermann, and A. Mayer, "A tethering complex drives the terminal stage of SNARE-dependent membrane fusion", *Nature* 551, 634 **2017**.

[5] S. Marrink, H. Risselada, S. Yefimov, D. Tieleman, and A. de Vries, "The MARTINI Force Field: Coarse Grained Model for Biomolecular Simulations", *J. Phys. Chem. B*, 111, 7812 **2007**.

[6] L. J. Endter, Y. G. Smirnova, and H. J. Risselada (in press), "Density Field Thermodynamic Integration (DFTI): A 'soft' approach to calculate the free energy of surfactant self-assemblies", *J. Phys. Chem. B* **2020**.

[7] N. van Hilten, K.S. Stroh, H.J. Risselada, "Membrane Thinning Induces Sorting of Lipids and the Amphipathic Lipid Packing Sensor (ALPS) Protein Motif", *Front. Physiol.*, 11, 250, **2020**.

Project Partners

Soft Matter/Biophysics, University of Göttingen

Funding

DFG-SFB 803: B3
DFG-SFB 1073: A3
DFG Einzelantrag: Mu 1674/15-2, Mu 1674/16-2, Mu 1674/17-1, RI 2791/2-1