Inverse design of motifs that sense membrane specificity

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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.
- Optimizing the physicochemical properties of peptides to specifically target characteristic membrane compositions of certain diseases, e.g. cancer, might lead to the development novel therapeutic opportunities.

Research questions – Cells and most organelles inside cells are bounded by membranes typically composed of lipid bilayers. Local differences in membrane curvature, tension or composition result in altered membrane properties and concomitant interactions with membrane proteins that are either embedded within the membrane or are bound the surface of the membrane. Such a spatial change in membrane properties can give rise to a thermodynamic sorting force that drives the self-organization and recruitment of functional proteins – a phenomenon called 'sensing'. Developing suitable theoretical and computational models, such as coarse-graining, advanced simulation techniques for free-energy calculations, and evolutionary algorithms to efficiently sample chemical space, are crucial steps to study the membrane sensing of protein motifs.

The overall purpose of our project is to understand how proteins/peptides are able to sense characteristic membrane signatures and, in particular, which specific chemical features determine these abilities (conservation). A central question is how sensing can be exploited to selectively target cancerous cells based on their altered membrane composition. In addition, we will study whether the up-regulation of certain transmembrane proteins in cancerous cells can be explained by an increased affinity for the altered cell membrane. Knowledge of these 'cancerous motifs' may enable the prediction of proteins that are over-expressed in cancerous cells, and which could guide the development of novel therapeutic strategies.

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, we 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 [1]. 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 [2,3]. 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 Intelligence class, to search for global solutions, *i.e.* the most active form, in the chemical space of protein motifs. We have developed a highly parallel software package coined EVOMD that integrates the GROMACS MD simulation package into a custom–Python based and MPI compatible–genetic algorithm (GA) code (Methorst et al., [4]). Genetic algorithms seek to optimize a specified problem through application of a simplified version of evolution.

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.

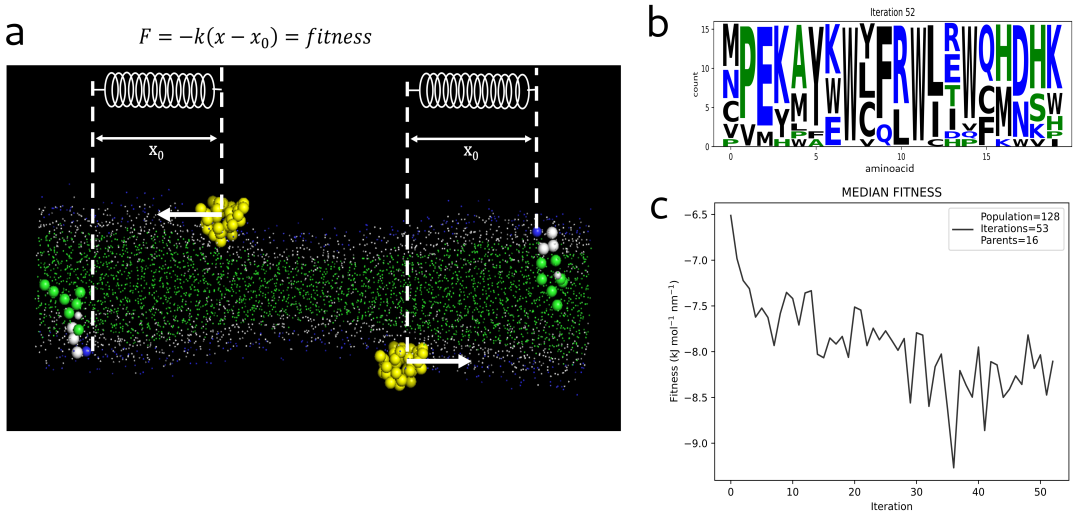

Figure 1: *Evaluating the membrane sensing ability of peptide motifs using a gradient approach [3]. (a) Setup used to extract the sensing force using the gradient approach in a pure POPC membrane. Note the central thinned membrane region that holds increased lipid packing defects. A similar lateral dependency will be implemented for membrane composition (a composition gradient). The thermodynamic sorting force can be calculated from a single simulation by measuring the average net force on the peptide while being constrained to the intermediate buffer zone. (b) Sequence of a resolved defect sensor after 52 iterations. Large letters depict conserved residues (minima) in the chemical space of amino acids. (c) Example of the convergence of evolution after 52 iterations based on the highly parallel Gromacs MD engine. The sorting force increases in the course of evolution.*

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

More Information

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Project Partners

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