Folding on membranes

Hydrogen-bond dynamics at protein interfaces

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In Short

- Protein folding
- Lipid-protein interactions
- Hydrogen-bond networks
- Protein binding
- Protein conformational dynamics

The fold of the proteins is governed by the sequence of the protein, intra-protein interactions, and interactions with the environment. A proper fold of the protein is essential for the biological function of the protein. The research planned here aims to decipher how the interplay between intra-protein, protein-water, and protein-lipid interactions shape the fold and dynamics of Mistic (Fig. 1). Mistic is an intriguing system to study protein folding because, although it contains numerous charged and polar groups (Fig. 2), it is thought to associate with the lipid membrane.

To derive a molecular picture of how Mistic binds at the lipid membrane interface, and to characterize its conformational dynamics, we will utilize atomistic molecular dynamics simulation approaches. These approaches are suitable here, because they allow us to probe the role of hydrogen bonding in protein binding at membrane interfaces. Moreover, the computer simulation approach allows us to study the dynamics of the protein in the presence of membranes composed of different lipids, and in lipid nanodiscs.

Molecular dynamics simulations generate trajectories that describe how the atoms of the simulation system (for example, the protein at the interface of a hydrated lipid bilayer) move in time. This trajectory can then be used to vizualize the motions of the system, and to compute various parameters to characterize the system. A particularly powerful approach is to combine molecular dynamics simulations with data derived from experiments.

An important example here is to use the simulation trajectories to identify protein groups of interest for further study with site-directed mutagenesis experiments, or to model a mutant protein to interpret results from experiments. Likewise, data from site-directed mutagenesis experiments can be used to validate observations from simulations.

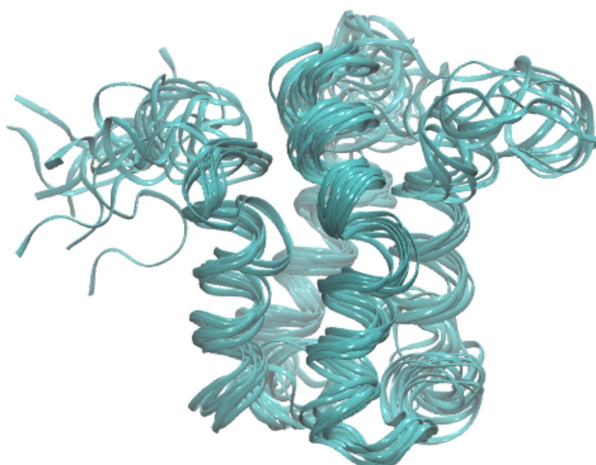

Figure 1: *Ribbon representation of the protein. The image is based on the coordinates solved with Nuclear Magnetic Resonance (NMR) in ref. [2]. All molecular graphics were prepared with Visual Molecular Dynamics, VMD.[1] Note that the protein has flexible termini.*

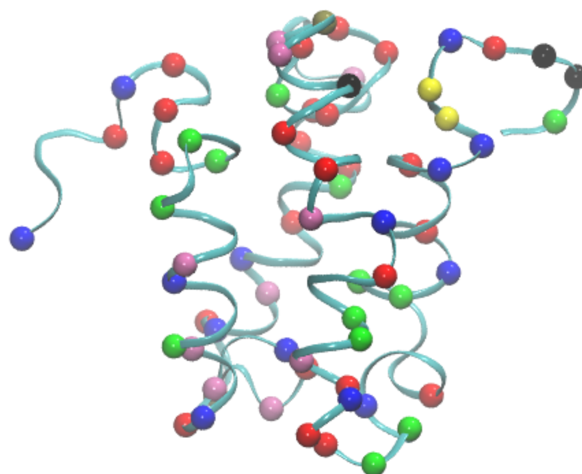

Figure 2: *Distribution of the charged and polar amino acid residues of the protein. Except for the black spheres, which indicate two selected hydrophobic groups, all other colored spheres indicate CA atoms of charged and polar amino acid residues of the protein.*

We will probe the binding of the protein at membranes composed of lipids with different headgroups and different alkyl chains. This will allow us to understand how physical-chemical properties of the membrane impact protein binding.

Hydrogen bonds between protein groups and lipid headgroups can impact the orientation of the protein relative to the membrane normal [3]. In the case of a protein that is highly charged, the key question is how it associates with the membrane. To address this question, we will perform extensive computa-

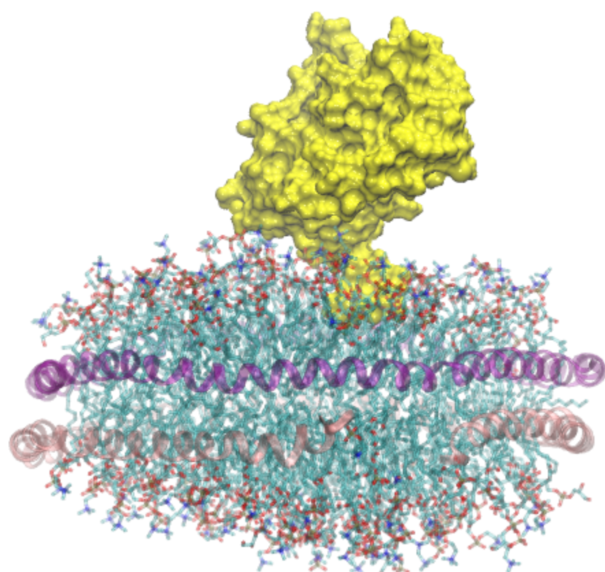

Figure 3: Illustration of the protein bound at a nanodisc lipid membrane interface. Mistic is shown as a yellow surface, protein chains of the nanodisc are shown as magenta and pink ribbons, and lipids are shown as bonds. For clariry, water molecules are not shown.

tions of the protein in the presence of different lipid environments, and study mutant proteins for whom we predict defective binding.

To predict mutations for furter investigation, we will inspect the simulations to identify proteingroups that can directly hydrogen bond to lipids. An illustration of how the protein might bind at a lipid interface is presented in Fig. 3.

A challenge when studying hydrogen-bond systems is that hydrogen bonds can be rather dynamic, i.e., they can break and reform rapidly at room temperature. This issue could be particularly important for Mistic, as it contains numerous charged and polar groups, and for the question addressed here of the role of hydrogen bonding in membrane protein function.

To analyze of the hydrogen bonds of the system we will use Bridge, a graph-based algorithm that enables highly efficient data analyses [4]. Fig. 4 illustrates a preliminary analysis with Bridge of a short trajectory fragment of Mistic in a box of water molecules. In this graph of hydrogen bonds, the nodes (green filled circles) indicate amono acid residue sidechains of Mistic that hydrogen bond, and lines between two nodes indicate hydrogen bonding whose occupancy, in percentage of the simulation fragment used for analyses, is indicated by the numbers. Even though Mistic is a rather small protein (Fig. 1), numerous hydrogen bonds can be sampled, albeit most have rather low occupancy, i.e., they are sampled only transiently.

The research planned here will provide a compre-

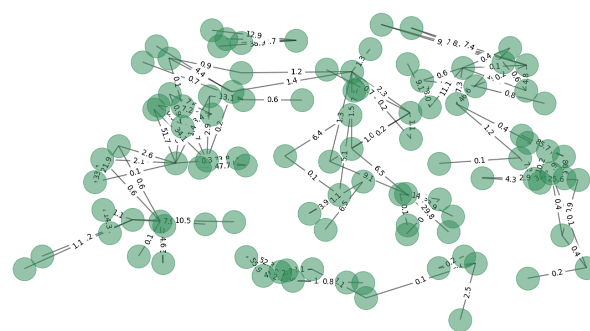

Figure 4: Illustration of a preliminary computation of the graph of hydrogen bonds of the protein. Note that most of the hydrogen bonds have low occupancies, i.e., they are dynamic.

hensive description of how a protein associates with membranes that have different physical-chemical properties. Advanced graph-based analyses of the protein hydrogen bonds will provide insight into the conformational dynamics of the protein in different lipid environments.

Research planned here will be performed in collaboration with the laboratory of Prof. Bernd Reif from the Technische Universität München, where NMR spectroscopy is being used to decipher the structure and dynamics of Mistic [5].

WWW

http://www.physik.fu-berlin.de/en/einrichtungen/ag/ag-bondar/

More Information

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Project Partners

Prof. Bernd Reif, Technische Universität München

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