The influence of environment on biomolecular function, structure and interactions – project overview.

Tremendous advances in structural biology methods allow insights into increasingly complex biological macromolecules and their assemblies. Looking at their idealised three-dimensional representation at computer screen we easily forget that all those structures function in a dense environment, composed predominantly of aqueous and lipid compartments. Since the particles comprising the surrounding media exert physical forces no weaker than those arising from direct macromolecular interactions, our reasoning about the stability, function, and interactions of biomolecules is rather incomplete without considering environmental contributions. Unfortunately, due to inherent difficulty of separating specific solute-solvent interactions from bulk effects in experiment, and unavoidable complexity of their theoretical description, our knowledge concerning the actual role of environment is still limited, and a number of methodological problems call for solution. In this project we will combine work on theoretical advances in description of the role of water in biomolecular recognition, with computer simulations targeted at the analysis of environment-related effects for protein folding and stability as well as protein function within lipid membranes.

Our first task will be devoted to quantifying the role of hydration in interactions between protein receptors and their drug-like molecular ligands. Binding of a drug into protein receptor pocket on the one hand involves their partial dehydration but, on the other hand, leads to the formation of specific interactions bridged by solitary water molecules that remain trapped at the binding interface. Both those effects have significant contribution to the overall binding free energy, but at the same time are difficult to assess, posing a major obstacle in computer aided drug design. In order to tackle this problem, we will develop a computationally efficient method of assessing hydration contributions based on our previously introduced hydration model, which combines mean-field description of bulk solvent interactions with atomistic treatment of individual water molecules. We will combine its predictions with scoring functions that represent direct protein-ligand interactions, in order to optimise ranking of true receptor-ligand geometries among false solutions obtained in docking experiments.

Within the second subproject, we will develop a predictor of protein-protein interaction sites on protein surface. Most proteins interact with other macromolecular binding partners, forming larger functional assemblies or participating in cellular signalling networks. Given vast array of such interactions, their often transient character, and the fact that most protein structures are obtained in isolation, computational prediction of protein-protein binding is of high practical value for cellular biology. One of important characteristics of surface interaction sites is their relatively small desolvation penalty. Accordingly, we will leverage one of unique features provided by our hydration model, that is fast estimation of surface hydration propensity based on combined contributions of electrostatic, hydrophobic and topography related effects, in order to establish a method allowing classification of protein surface into interface and non-interface areas.

The third task will be dedicated to the analysis of stability and interaction patterns within basic protein building blocks, so called supersecondary structure elements. Current theory concerning the origin of complex protein structures assumes that they were initially formed by merger of simpler peptides. Indeed, a trace of such ancient units, in the form of sequentially and structurally similar polypeptide fragments present in modern, unrelated protein domains, has been identified. Given the idea that they survived during evolution likely acting as folding seeds for protein domains, we will perform their extensive molecular dynamics simulations to verify if they possess any extra stability in comparison to structurally analog but sequentially unrelated protein fragments, and if yes, than what are the determinants of this stability. Answering those questions will shed light on a) the mechanism by which proteins fold overcoming unfavourable hydration contributions, b) the emergence of hydrophobic protein cores, c) the principles allowing the design of new protein structures.

In the final task we will investigate the mechanism by which trans-membrane protein helices are able to sense membrane curvature. Unlike wedge-like, multipass integral membrane proteins, whose shape naturally fits to a curved rather than flat bilayer, single cylindrical helices need to specifically recognise lipid packing defects at the convex leaflet or increased surface polarity at the concave one. In order to uncover the underlying principles we will conduct multi-scale simulations of model trans-membrane peptides during which we will attempt to modify their residues located at lipid-water interface to achieve desired curvature specificity. Several most interesting such peptides will be tested experimentally, opening door for future design of curvature-specific peptide probes.