COGRIMEN - coarse-grained method
for modeling of large biological systems in implicit environments

The most important completed tasks

The aim of the project was to construct a coarse-grained method of molecular modeling in the water-membrane implicit environment for molecular dynamics of large biomolecular systems, in particular to study the interaction of peptide ligand-membrane protein, membrane protein with extramembrane protein, interaction of proteins in membrane oligomers, and to study the crowding effects in the membranes.

In the constructed COGRIMEN method, the MARTINI force field was implemented for the coarse-grained representation of proteins, and the membrane potential used in the IMM1 method. The solvation parameters were introduced and calibrated in COGRIMEN using genetic algorithms, and the obtained sets of parameters were tested for a system of several dozen membrane and extramembrane proteins with known structures. The longer simulations of the order of tens of microseconds were performed for bacteriorhodopsin oligomers and opioid receptors, as well as for the membrane protein-extramembrane protein systems (GPCR receptor complexes with G protein trimer and arrestin). The obtained results indicate the stability of all these complexes in the modeled water-membrane environment (Fig. 1).

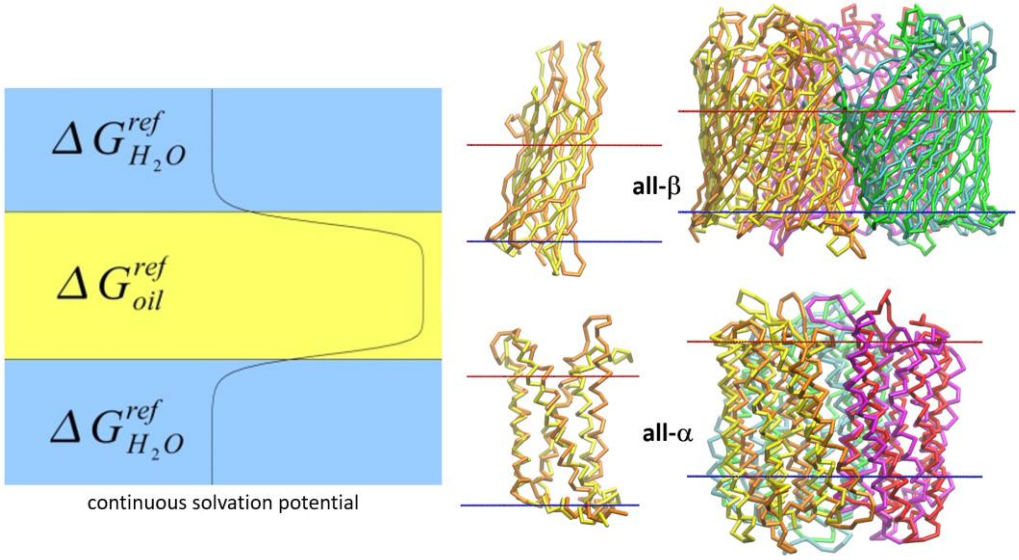

Fig. 1. Visualization of the continuous change of the solvation potential in the water-membrane environment (**on left**). Comparison of all-α (bundle of helix) and all-β (β-barrel) membrane proteins before and after 10 μs simulation in the COGRIMEN method. For oligomeric proteins, trimers of bacteriorhodopsin (all-α) and maltoporin (all-β) were tested (**on right**).

Significance of the project

Usage of a coarse-grained representation of proteins in implicit solvents allows for extending the simulation times of the molecular dynamics of membrane systems by several orders of magnitude compared to all-atom simulations in explicit water-membrane environments. It also allows the number of proteins in the system to be increased by several orders of magnitude, instead of one or two, to hundreds or thousands depending on size of proteins. This also applies to spherical systems such as liposomes or endosomes, since the spherical implicit environments have also been implemented. The COGRIMEN method can be used to study the formation of protein oligomers and their dynamics in cell membranes. This method facilitates usage of large number of proteins in a single simulation, which makes it possible to estimate the kinetic parameters of processes related to protein-protein interactions in cell membrane, as well as the binding of peptide ligands by these proteins, so it can also be used to study the cell signaling processes.