Some of the human cells have to be able to react to the changing environment in order to function correctly. To accomplish this task, they are equipped with specialized proteins that serve as receptors and are localized on the surface of the cell – in its plasma membrane. The membrane receptors perform a number of functions, which include transmitting extracellular signals – such as those mediated by hormones. In consequence, they play a key role in function regulation of many elements of human organism, for example: the nervous, endocrine, immune or vascular systems. The peptides naturally synthesized in our bodies are an example of the signaling molecules that interact with the membrane receptors.

Because of the fundamental role the membrane receptor-peptide complexes play, they are intensely researched with both experimental and theoretical methods. One of the theoretical approaches to predict the structure of protein-peptide complexes is the molecular docking. It involves computer-based prediction of the optimal position of the peptide at the binding site of the receptor. Our newely developed CABS-dock server (http://biocomp.chem.uw.edu.pl/CABSdock/) is one of such methods.

The CABS-dock approach is unique due to the fact it allows for modeling large-scale conformational changes of the receptor upon docking. The idea behind it is to create a simple model of the system in which each amino-acid residue is represented by up to four pseudo-atoms. Thank to this coarse-graining it is possible to perform the calculations more efficiently and to analyze a vast number of generated models in search for the best ones.

Unfortunately, in the current version of the CABS-dock it is not possible to properly model the interactions of membrane proteins with peptides. The aim of this project is to extend the CABS-dock method to include elements required for efficient prediction of the structures of membrane protein-peptide complexes. In order to do so, in this project we will develop and optimize a plasma membrane model, compatible with the CABS model. The membrane is a unique medium, that significantly influences the structures that are embedded in it, so it will be necessary to account for it at each stage of the simulation procedure. This will require, for example, developing a procedure allowing for an automatic placement of the input structure of the receptor properly aligned and oriented in the membrane as well as a procedure for random generation of the initial peptide poses on the proper site (“extra-” or “intracellular”) of the membrane.

The project will eventually investigate chosen interesting cases from cellular physiology and medicine. Additionally, we will also analyze the cases that interesting from the point of view of drug design – potential target-receptors for peptide drugs and candidates for their ligands.

The main result of the project will be the software suited for molecular docking of peptides to membrane receptors, which will allow for efficient modeling of their complexes. Taking into the account uniquely high efficiency of the planned method for accounting for significant structural changes during the docking and large potential of peptides as potential drug candidates that interact with the membrane proteins, we expect the results of this project to be of great significance for the biomedical basic research and for the drug design.