Integrative methods for modeling protein-protein complexes and multimolecular assemblies

Proteins form different kinds of complexes. They range from protein pairs to multimolecular assemblies involving many proteins and other biomolecules. Detailed structural knowledge of such complexes at the atomic level is always helpful and often necessary for understanding biological processes and drug discovery. Many protein complexes form different transient structures making their structure determination a challenge for experimental methods such as NMR spectroscopy or X-ray crystallography. Structural data at atomic resolution is only available for a tiny fraction of expected protein–protein interactions. This gap can not be filled using solely experimental methods. An alternative and complementary approach is to apply computational protein docking. The protein docking field presently moves towards integrative computational approaches using experimental data and bioinformatics analyses from various sources. Integrating and using all available, even sparse, data can substantially improve the docking accuracy. Another critical challenge is the modeling of protein flexibility. Current docking approaches are limited to relatively rigid proteins, and effective modeling of large conformational changes in protein-protein docking remains an unsolved problem.

This project aims to address the challenges mentioned above by combining Polish and Chinese Partners' modeling approaches. We will also develop additional methods to create automated workflows for integrative modeling of protein-protein complexes and multimolecular assemblies. The research methodology will involve a multiscale modeling approach (coarse-grained combined with all-atom), which will be adapted to use data from various experiments or bioinformatic analyses. The coarse-graining modeling application will allow for accelerating computations and modeling large conformational changes and large protein assemblies. Both partners of this project have significant experience in the docking field and already developed well-established methodologies for protein-peptide and protein-protein docking based on different approaches. Merging our docking techniques offers an added value and is a promising way for modeling challenging protein complexes and potential breakthroughs in the field. Our goal is to outperform existing protein-protein docking protocols, especially for complexes in which proteins undergo large conformational changes upon binding.

The new tools will be made available to the scientific community as freely-available web services and standalone applications dedicated to regular computers or supercomputers for massive computations. Moreover, we will apply the developed tools to structure prediction of protein assemblies of biomedical importance, especially those targeting unmet medical needs. Therefore, the project is expected to deliver new, uniquely efficient tools and data for designing new drugs and a deeper understanding of life's machinery. In the broader perspective, we expect this project to significantly impact life sciences research and provide innovation opportunities in medicine, biology, and biotechnology.