Development of a new protein-protein docking method based on the flexible docking of short peptide fragments.

Physiological processes in living cells are rigorously controlled by highly-specific, context-dependent physical interactions of cell's components, which strongly depend on the communication between interacting partners and their surroundings. Proteins among all other cell members developed the highest adaptation to cooperate in groups, as they can detect, integrate or mediate interaction with molecules of virtually any type (nucleic acids, lipids, sugars, etc.). The method for reliable characterization of protein complexes with other biomolecules is one of the most awaited scientific breakthroughs. The successful method will have impact both directly and inexplicitly on multiple branches of science, business, healthcare, agriculture and more. Most predominantly, the pharmaceutical industry may utilize the method for the design of highly specific drugs, where knowledge of the target protein structure is often crucial.

The protein docking problem was first formulated to ask how to predict the structure of the protein complex given the structures of its isolated components [1]. Despite immense progress made in the protein docking field in the last four decades, the original question remains unanswered. Benchmark tests show that even the best-performing protein-protein docking methods achieve barely ~ 10% success rate [2], when only one top-scored model is considered. The reason for that may be the fact that many of the popular docking protocols consider protein molecules as rigid bodies enriched with very modest level of flexibility, usually limited only to the amino acids' sidechains.

The main goal of this project is to develop a novel method for protein-protein docking, which addresses the problem of protein flexibility on unprecedented level. The method will allow for arbitrary large conformational changes between the unbound and bound forms both of the side chains and the protein backbone, including motions of the whole sub-domains. The method aims to qualitatively surpass popular docking protocols, especially for target complexes that undergo large conformational changes upon binding. Computer simulation of massive conformational changes can only be possible by significant reduction of the degrees of freedom of the system. Therefore, the new method will be based on the CABS [3] – highly efficient coarse-grained model of proteins and their dynamics.

The novel approach to protein-protein docking will be based on the assumption that protein-protein docking can be accomplished via protein-peptide docking of carefully selected fragments, extracted from the protein surface. To prove this thesis, a new protocol will be developed and implemented. It will employ the CABSdock[4] method to facilitate protein-peptide docking. Final objective of the project includes design and development of a freely-available web service, reinforced with the computing power of the cluster supercomputer.

References:

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