

Abstract

Protein-protein and protein-peptide interactions constitute a fundamental component of biological processes, determining the functioning of signaling pathways, regulation of gene expression, enzymatic activity, and mechanisms of cellular response. The ability to model these interactions reliably is crucial both for structural biology and for the design of modern therapies, in particular peptide drugs and inhibitors of protein-protein interactions. The main goal of this dissertation was to develop and advance multiscale computational methods enabling realistic modeling of these interactions while accounting for conformational flexibility, topological constraints, environmental effects, and post-translational modifications.

This work combines coarse-grained approaches, molecular dynamics simulations, and modern artificial intelligence-based methods. A significant part of the research focused on the development of flexible docking methods, including extending the CABS-dock approach to protein-protein systems and devising procedures for docking cyclic peptides, in which closed topology introduces strong coupling of conformational motions and restricts the accessible conformational landscape. A hybrid strategy for docking model assessment was also proposed, using short molecular dynamics simulations as a selection stage to identify structures with the highest stability.

An important element of the dissertation is the integration of docking methods with structure predictions generated by protein language models, illustrated using ESMFold. It was shown that such models can provide useful starting structures in protein-peptide docking tasks, particularly in cases of limited availability of evolutionary information, thereby extending the practical applications of AI-based methods beyond single-chain structure prediction.

Another research area involved modeling protein structural flexibility using the CABS-flex method, including the development and release of CABS-flex 3.0 as a publicly available web server for rapid analysis of protein and peptide dynamics. The dissertation also presents the development of the Aggrescan4D tool, enabling the analysis and design of protein aggregation propensity while accounting for pH effects, structural information, and conformational variability. Complementing this work are all-atom molecular dynamics simulations used to analyze the effects of post-translational modifications - particularly phosphorylation - on the functioning of protein complexes.

The methods and tools presented in this dissertation form a coherent set of solutions enabling the analysis and design of molecular interactions in a realistic, dynamic biological context. The results are significant for structural biology, protein engineering, and next-generation drug design, representing a step toward integrating AI-based methods with classical and multiscale molecular modeling techniques.