**Bartłomiej Surpeta**

**Molecular modeling of structure-dynamics-function relationships in proteins**

Ongoing advances in science and computational methods and technology make it possible to study proteins better and better. Over the decades, it has become clear that proteins are dynamic entities, and to accurately study their function, it is not enough to look at the structure only, but also at the inherent dynamics component. As a result, the original structure-function paradigm is gradually being replaced by a focus on structure-dynamics-function relationships.

In my doctoral research, I contributed to addressing the global challenge of widespread bacterial resistance to antibiotics and focused on alternative solutions that will undoubtedly be needed in the future. Bacteria exhibit social behavior and use signaling molecules to communicate with each other and respond to environmental changes in a cell-density-dependent manner, a process called quorum sensing. Disruption of this communication is called quorum quenching and is considered a promising alternative to deal with bacterial colonies in various fields of life. It can be achieved enzymatically, by cleavage of signaling compounds, and thus such quorum quenching enzymes were the main interest of my thesis. In addition, these enzymes are useful models for studying the relationships between structure, dynamics and function in proteins.

The dissertation consists of four articles. In the first, I investigated details of the dynamic components that determine and limit the quorum quenching activity in N-terminal serine hydrolases. The second is a literature review that summarizes approaches in protein engineering that consider dynamics as crucial during the design process. The third part presents the TransportTools library, software developed in our laboratory to address the challenge of consistent analysis of interior spaces in protein ensemble data resulting from massive molecular dynamics simulations. Finally, the last part of the thesis combines the insights gained from the study of the wild-type quorum quenching enzymes, approaches for efficient design of protein dynamics, and advantages of the developed software to rationally design variants of *Escherichia coli* penicillin G acylase with improved activities and modulated specificities towards signaling molecules of different pathogenic bacterial species.

Keywords

*protein dynamics, structure-dynamics-function relationships, molecular dynamics, protein engineering, quorum quenching*