At any moment, living systems contain several thousands of small organic molecules that need to arrive at sites of their action mostly represented by protein surfaces or internal cavities to exert their function. The transport of these small ligands is mainly facilitated by protein tunnels and channels. They secure the transport of ligands between different regions, connecting inner protein cavities with its surface, two or more different cavities, or even different cellular environments such as in the membrane proteins. In enzymes, the tunnels connect buried functional sites to the bulk solvent enabling access of substrates and release of products. The biological relevance of tunnels is further highlighted by the fact that many enzymes known to contain molecular tunnels have been linked to the development of various diseases, and that the inhibitors binding these tunnels can become viable drugs.

It is clear that the detailed understanding of mechanisms involved in the molecular transport is essential. However, despite notable advances in studies of factors that are critical to the function of enzymes with buried active sites, some considerations have not been addressed sufficiently. One of them is how the transport and binding of several molecules of substrate or products influence each other, either directly or indirectly by inducing changes in the tunnels of enzymes. Also, it is likely that both molecules will prefer to pass through same tunnels due to their similarities, which will result to mutual interferences. In this project, we will explore these vital factors by tightly combining adaptive molecular simulations with experimental methods. We will generate comprehensive kinetics models of ligand transport to reveal roles of direct interactions among ligands as well as allosteric effects on the tunnels induced by protein-ligand interactions. Such research will help us to identify structural features responsible for the substrate inhibition, cooperativity and ligands' interference. Ultimately the obtained knowledge could contribute to the engineering of better enzymes for application in various biotechnologies and development of novel inhibitors/drugs.