Abstract of doctoral dissertation

Enzymes are among nature's most efficient and powerful biological catalysts, with approximately 50-60% featuring buried active sites where their functional mechanisms are intricately regulated by transport tunnels. These tunnels play an essential role in the movement of biomolecules, driving critical processes like catalysis and signal transduction. Due to the dynamic and often transient nature of these tunnels, molecular dynamics (MD) simulations—commonly known as computational microscopy—are the primary method for examining their behavior and function. However, classical MD (cMD) simulations struggle with capturing rare events, such as transient tunnel openings, limiting the depth at which these pathways can be explored and understood.

In my Ph.D. research, I have focused on advancing methods to overcome these limitations, enabling more detailed exploration of both stable and transient tunnels in enzymes. By implementing Gaussian accelerated MD (GaMD), I was able to examine dynamic tunnel openings in model enzymes, capturing rare tunnel events that are often inaccessible through conventional cMD. GaMD achieves this by applying a boost potential to lower the energy barriers between enzyme metastable states, thus allowing enzymes to explore an extensive conformational space. This led to the discovery of previously unknown, rare tunnels that proved effective in facilitating the transport of both water and ligands, opening up new perspectives on the mechanisms underlying enzyme activity and ligand transport.

Additionally, I conducted a detailed evaluation of coarse-grained (CG) simulation methods to benchmark their effectiveness in studying tunnel networks over longer timescales. These CG approaches, which include Martini and SIRAH models, offer a balance between computational efficiency and a level of detail sufficient to capture critical aspects of tunnel dynamics, including the ability to distinguish between transient and permanent tunnels. These methods demonstrated strong potential for accurately representing tunnel behavior in diverse enzyme systems, allowing for efficient and comprehensive analysis.

Overall, my research contributes to the advancement of simulation techniques for investigating rare tunnel events in proteins. By enabling a deeper understanding of enzyme mechanisms and ligand transport, these approaches present exciting opportunities for applications in fields such as drug discovery and protein engineering. By addressing the inherent limitations of classical MD simulations, these advanced methods pave the way for future exploration of complex protein dynamics and their functional implications in biological systems.

Keywords : Tunnels, enhanced MD simulations, coarse grained simulations, gates, enzymes