

Molecular Simulations for Mechanistic Discovery and Allosteric Modulation in SARS-CoV-2

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The emergence of pandemic RNA viruses such as MERS-CoV, SARS-CoV, and SARS-CoV-2 emphasizes the importance of understanding the molecular mechanisms supporting viral genome replication. In SARS-CoV-2, a complex of two nonstructural proteins, nsp10 and nsp14, plays a central role in RNA proofreading and maintaining the integrity of the virus's large ~30 kb genome. Nsp14 contains a 3'-5' exoribonuclease (ExoN) domain responsible for removing misincorporated nucleotides, while the small cofactor nsp10 stabilizes the ExoN activity of nsp14. This complex and similar analogues contribute to the high fidelity of coronavirus genome replication found in these RNA viruses.

Understanding the mechanisms of this complex at the molecular level requires elucidation of its dynamic behavior, which cannot be captured by static experimental structures alone. In this work, molecular dynamics (MD) simulations are being used to investigate the structural dynamics of the nsp10/nsp14 complex as a whole and as two separate components. Nsp10 is a particularly small cofactor with no catalytic site of its own, yet contains two zinc-finger motifs that require careful parameterization to accurately represent the coordination environments. Additionally, experimentally determined structures of Nsp14 contain multiple unresolved regions and missing loops that must be reconstructed before the protein can be sufficiently represented in simulation.

The individual simulations of these two proteins provide a foundation for subsequent simulations of the complete nsp10/nsp14 complex. By progressively building from the individual proteins to the complex, this work aims to characterize how structural changes in the proteins are necessary for the formation of the complex. Ultimately, this research aims to examine the structural and dynamic aspects of the activation of nsp14 by nsp10 and for identifying molecular features that may contribute to SARS-CoV-2 RNA proofreading activity.