

Probing the Structural Dynamics of BET Protein-IDP Peptide Complexes: A Pep-GaMD Investigation

Yisel Martinez Noa, Arup Mondal, Alberto Perez

University of Florida, Department of Chemistry, Quantum Theory Project, Gainesville, FL

The extra-terminal (ET) domain of bromo and extra-terminal domain proteins (BET) is involved in disease pathology through two main pathways: misregulation, and its interaction with viruses. Therefore, BET proteins play an important role in the regulation of genes involved in immunogenic response and inflammation. Proteins bind through peptide epitopes that are intrinsically disordered, with different peptides adopting diverse bound conformations. Recent studies that combine MELD with limited NMR data predicted structures of complexes between the ET receptor and IDPs. Nonetheless, it is paramount to understand the kinetics of these dynamic systems, which remain an unexplored area. Conventional Molecular Dynamics (cMD) cannot access the long timescales required to study these events and even enhanced sampling tools that can capture kinetics are limited by the high computational cost. In this study, we employed Pep-GaMD to elucidate thermodynamic and kinetic parameters of the complexes involving the ET receptor and several IDP peptides. We applied a dual-boost potential on the peptides to accelerate their dissociations from the receptor, as well as their rebinding processes. This allowed us to sample unbinding events, from the strongest to the weakest peptide binders. However, association occurrences were more difficult to detect. We also report the results of an exhaustive hyperparameter search to determine the most effective framework for sampling unbinding/rebinding events. Ultimately, we are going to quantify the rate constants, as well as the free energy of binding for the studied systems. This will help establish a generalized protocol for binding affinity with broad applicability in high throughput peptide screening studies.