Elucidating the thermodynamic and kinetic parameters of IDP peptides towards the ET receptor using Peptide Gaussian accelerated Molecular Dynamics (Pep-GaMD)

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The extra-terminal (ET) domain of bromo and extra-terminal domain proteins (BET) are involved in disease through two main pathways: misregulation, leading to multiple types of cancer, and 2) virus interacting with the ET domain. Therefore, BET plays an important role in the regulation of genes involved in immunogenic response and inflammation. It has been demonstrated that proteins bind through peptide epitopes that are intrinsically disordered and, that different peptides adopt diverse bound conformations. Recently, methods that combine MELD with limited NMR data, yielded outstanding predictions of structure and the relative binding affinities of different peptides towards the ET receptor. Nonetheless, it's paramount to understand the kinetics of these dynamic systems, that remains as an unexplored area. Despite the countless efforts to reproduce the binding/unbinding events of peptide-protein complexes through conventional Molecular Dynamics (cMD), the long timescale and high computational cost have endured as its major limitations. Nowadays, the diversity and power of enhanced sampling methodologies to improve the study of protein-peptide interaction is increasing. A recent method peptide Gaussian accelerated molecular dynamics (Pep-GaMD) has emerged as an efficient and accurate technique that allows to reduce the energy barriers as the simulations are accelerated by orders of magnitude. In our present study, we proposed to employ Pep-GaMD to elucidate thermodynamics and kinetics parameters of the complex involving the ET receptor and the murine leukemia virus integrase tail peptide (TP). We show that the time evolution of the peptide TP backbone RMSDs suggest repetitive binding and unbinding events. We are currently expanding the analysis of our system by calculating the energetic reweighting of our data which is critical to extract different metastable states and quantify the binding and dissociation rate constants, as well as the free energy of binding. Finally, we aim to develop a generalized protocol for binding affinity which will be useful in a high throughout peptide screening study.