Title

In silico Studies of Protein-DNA Interaction & Aggregation of Disease-related Proteins

Abstract

In contrast to the naïve expectation based on stoichiometry, recent single-molecule studies on the dynamics of DNA-binding proteins have challenged the standard thermodynamic model of gene regulation. The standard model of protein dissociation from DNA, based on first-order unimolecular reaction scheme, fails under many *in vitro* and *in vivo* contexts. Specifically, the dissociation process is accelerated by increasing the concentration of the protein. However, the community has been puzzled by the molecular mechanism underlying this facilitated dissociation. In this study, I use the state-of-the-art coarse-grained protein-DNA force field to explore the binding landscapes of Fis protein (one nucleoid-associated protein in *E. coli.*) dissociating from DNA. The result provides a unique structural insight into the formation of Fis intermediate on DNA. When two Fis molecules are present, simulations uncover a ternary complex, where the originally bound Fis protein is partially dissociated from DNA. The simulations support a three-state sequential kinetic model for facilitated dissociation, thus explaining concentration-dependent dissociation.

Although aggregation of Amyloid β (Aβ) has received much attention among protein scientists, the question regarding why Aβ42 aggregates faster than Aβ40 is still one major puzzle in the community. Due to the transient nature of Aβ oligomers and small aggregates, the key to the question apparently lies in the nucleation at the early stages of Aβ aggregation. We solve this puzzle by exploring and comparing the aggregation free energy landscapes of Aβ40 and Aβ42 which allow us to accurately capture the key molecular event, backtracking, that governs the prefibrillar-to-fibrillar conformational conversion of Aβ40. The backtracking is responsible for slowing the aggregation process. This computational aggregation protocol along with the taxonomy of oligomer clusters that I develop offer a theoretical framework that forms the basis for a library of fully atomistic oligomer structures which may offer specific targets for drug design.