Multiple Binding Configurations of Fis Protein Pairs on DNA: Facilitated Dissociation versus Cooperative Dissociation

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As a master transcription regulator, Fis protein influences over two hundred genes of *E-coli*. Fis protein's non-specific binding to DNA is widely acknowledged, and its kinetics of dissociation from DNA is strongly influenced by its surroundings: the dissociation rate increases as the concentration of Fis protein in the solution-phase increases. In this study, we use computational methods to explore the global binding energy landscape of the Fis1:Fis2:DNA ternary complex. The complex contains a binary-Fis molecular dyad whose formation relies on complex structural rearrangements. The simulations allow us to distinguish several different pathways for the dissociation of the protein from DNA with different functional outcomes, and involving different protein stoichiometries: 1. Simple exchange of proteins and 2. Cooperative unbinding of two Fis proteins to yield bare DNA. In the case of exchange, the protein on the DNA is replaced by solution-phase protein through competition for DNA binding sites. This process seen in fluorescence imaging experiments has been called facilitated dissociation. In the latter case of cooperative unbinding of pairs, two neighboring Fis proteins on DNA form a unique binary-Fis configuration via protein-protein interactions, which in turn leads to the co-dissociation of both molecules simultaneously, a process akin to the "molecular stripping" seen in the NFκB/IκB genetic broadcasting system. This simulation shows that the existence of multiple binding configurations of transcription factors can have a significant impact on the kinetics and outcome of transcription factor dissociation from DNA, with important implications for the systems biology of gene regulation by Fis.

Reference

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