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Landscape model of protein-DNA search: coupling of folding and sliding. MICHAEL SLUTSKY, MEHRAN KARDAR, LEONID MIRNY, MIT — In search for its specific site on genomic DNA, a DNA-binding protein needs to sample 10^6-10^9 other sites. Classical model of this process suggests that sliding along DNA provides an efficient mechanism for sampling sites. This model however disregards the sequence-specific energy of binding and flexibility of the protein. Recent NMR studies suggest that a protein searching for its site is partially unfolded, while folding on the cognate site. Can conformational flexibility of the protein-DNA complex help it to sample sites fast and then strongly bind its cognate site? Here we study how a protein finds its site on DNA by modeling protein sliding as diffusion in the sequence-specific free energy landscape. The landscape has two dimensions: one corresponds to motion along DNA, the other is a reaction coordinate of protein's conformational transition. Our simulations demonstrate that low-energy sites can trigger folding transition in the protein, making it fold preferentially on cognate-like sites. This mechanism provides kinetic pre-selection of sites, allowing a protein to search fast and strongly bind its cognate site. Importantly our study connects microscopic time of the conformational transition (10^{-5}-10^{-3}s) to the macroscopic time of promoter binding (10^1-10^3s). Comparison with recent experimental studies of LacI conformational dynamics suggests that coupling between protein flexibility and sequence-specific binding is necessary for rapid regulation of gene expression.

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