Native, non-native and nonspecific and interactions in the kinetics of DNA sequence recognition

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We describe the formation of protein-DNA contacts in two parallel kinetic routes for DNA sequence recognition by a transcriptional regulator. In the two-state route, direct sequence readout establishes in the transition state and constitutes the bottleneck of complex formation. In the multistate route with populated intermediates, the two molecules first associate through a diffuse transition state with some non-native interactions. These non-native interactions have disappeared by the last transition state of the pathway, which is stabilized by native-like nonspecific interactions with the DNA backbone. In contrast with the fast two-state binding route, sequence-specific interactions play only a small role in the slow multistate route. A quantitative analysis of free energy correlations along the two kinetic routes shows that the "direct" two-state route has a smooth energy landscape for binding that speeds up DNA recognition. The multistate route has a frustrated energy landscape that bears little similarity to the smooth landscape of the two-state route and can slow down target sequence search by the protein bound to a short DNA fragment.

Keywords: protein-DNA interactions, kinetics, energy landscape

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