ICAM2009

11th International Conference
on Advanced Materials

Rio de Janeiro Brazil
September 20 - 25

# Optimizing the Search for Target Sites within DNA: Inspiration from Gene Regulatory Proteins

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**Abstract** – We develop a reaction-diffusion theory of the search process of a gene regulatory protein along DNA in order to predict the optimal strategy for target site localization. Our model incorporates non-specific binding and DNA conformation into a formalism that is capable of modeling the search along genome length DNA at biologically relevant time scales. Using our model, we explore the complex trajectory of gene regulatory proteins and discuss the role of non-specific binding in gene expression. These concepts are then extended to nanoparticle transport within the nucleus for therapeutic and imaging applications.

In a variety of therapeutic and imaging applications, it is critical for proteins and nanoparticles to find specific DNA target sites within the genome. The search process within the crowded environment of the cell's nucleus has already been optimized for biological gene expression; thus, a great deal can be gleaned from Nature on how to successfully search the DNA strand. Gene expression is orchestrated by a host of regulatory proteins that coordinate the transcription of DNA to RNA. Regulatory proteins function by locating specific binding sequences of DNA and binding to these sequences to form the transcription initiation complex. In many instances, these regulatory proteins only have several hundred copies that must efficiently locate target sequences on the genome-length DNA strand. The non-specific binding of regulatory proteins to random sequences of DNA is believed to permit the protein to slide along the DNA in a stochastic manner. Periodically, a thermal kick or an interaction with another bound protein will disengage the regulatory protein from the DNA surface, leading to three-dimensional diffusion. Eventually, the protein will reattach to the DNA at some new location that is dictated by both the diffusivity of the protein and the DNA configuration. Cycling through these random events constitutes a search strategy for the target site (see Fig. 1).

Our theoretical model for the target-site search of gene regulatory proteins provides insight into the role of binding and unbinding rates on the translocation rate. The search rate is optimized by balancing the on and off times, as demonstrated in Fig. 2 from dynamic Monte Carlo simulation. We construct optimization curves for both speed and efficiency using our analytical theory (see Fig. 3). Using our theoretical model, we explore the impact of DNA configuration [1], protein interactions [2], and local occlusion on target site localization in order to predict how the search will vary under different experimental conditions.

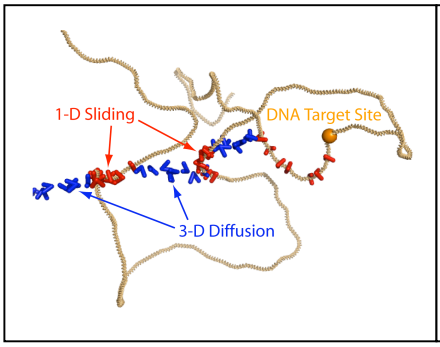


**Figure 1:** Schematic of the target-site search of a gene regulatory protein.

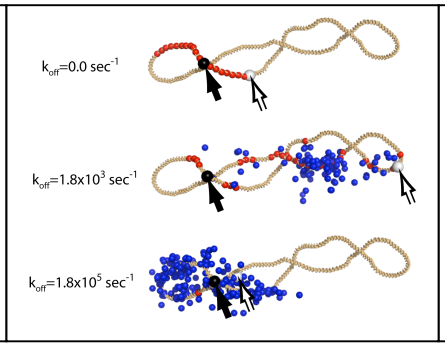


**Figure 2:** Simulations showing how balanced on-off processes optimize the search process along supercoiled DNA

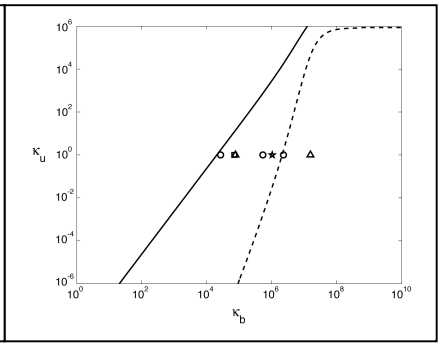


**Figure 3:** Theoretical prediction of optimized parameters for speed (solid curve) and efficiency (dashed curve), along with data for various proteins.

## References

[1] S. Mehraeen, B. Sudhanshu, E. F. Koslover, A. J. Spakowitz. End-to-end distribution for a wormlike chain in arbitrary dimensions. Phys. Rev. E, **77**, 061803 (2008).
[2] E. F. Koslover, A. J. Spakowitz. Twist and tension-mediated elastic coupling between DNA-binding proteins. Phys. Rev. Lett., **102**, 178102 (2009).