Protein Search Processes on DNA

Sequence dependent sliding of a dimeric lac repressor protein along DNA; a molecular dynamic study

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Kurzgefasst

- How protein search its DNA target site via 1D sliding
- How protein-DNA interactions change during the sliding
- How different domains communicate with eachother to facilitate the sliding process
- What are the water and ions role in sliding motion

Transcription factors (TFs) are specific protein that regulate the gene expression in the cell. The DNA recognition process of these TFs depends on specific target sequences, which are engaged in specific Protein-DNA interaction. It has been established that TFs proteins reach their target sites faster than the maximal diffusion rate in solution, specified by the Debye-Smoluchowski theory **??**. This implies that the protein lowers its searching process to a 1D diffusion mode along the DNA sequence **??**. In the theoretical frame of study, the best established model is the facilitated diffusion model, where a protein binds non-specifically to a random DNA sequence and undergoes 1D diffusion; such as sliding, hopping, and intersegmental transfer **??**(Figure 1) until it reaches the cognate specific target or re-alters its search mode to 3D diffusion. One of the best studied system in this regard is the Lac operon, which acts as a gene regulator in bacteria. The Lac operon repressor structurally is a homotetramer, which is organized as dimer of dimers while each dimer is composed of two DNA binding head domains **??**.The long standing question is how dimeric LacI searches the target site among these non-specific sequnces along the DNA. Recently, Erik G. Marklund, et. al. studied the sliding of the Lac repressor via umbrella sampling method and characterized the free energy landscapes that underline the sliding dynamic and its dissociation kinetic **??**. Nevertheless, there are many details that are not understood; for instance, the water and ions role in dynamical fluctuation and diffusion of the Lac repressor, communication pattern status among different factors that controls sliding motion, and sequence dependent role in facilitating of this sliding.

In a very recent paper **??**, the sliding of the Lac repressor on non-specific sequences has been studied, verifying that the sliding motion velocity of the protein when its slide on DNA. Significantly, the measured sliding velocities on different non-specific sequences show that this velocity changes in the range of about 30-100 nm/ms, dependent on the DNA sequences that the protein interacts with. In other words, the sliding rate is on the order of 4-13 μs per base-pair, which is the time scale that interestingly is accessible in unbiased MD simulations. Therefore, via unbiased MD simulation we would be able to capture the dynamical features that are important in controlling the sliding process. For instance, we will learn how the flexibility in hydrogen bond interactions facilitates the sliding motion, how different sub domains of the protein and the DNA communicate with each other in order to the conformationally re-arrange . We will gain insight into the diffusion pattern and what is its rate during the sliding motion. Recently, another study has revealed the existence of an energetic funnel formed by up to about two hundred base pairs on both sides,right and left, of the target sites **??**. To this aim, we will use MD simulation of the specific Lac-DNA complex so as to calculate the net stiffness matrix in a dinucleotide model. Then, by combining this stiffness matrix with the parameters of the free DNA base pairs, we can calculate the deformation energy of each shifted sequence up to n base-pairs. This way, we will be able to estimate how the protein imported stress on individual base pairs will change from differently positioned nonspecific DNA sequences to the correctly bound specific DNA sequences.

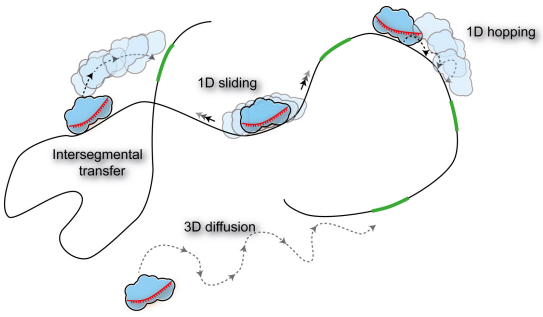

Abbildung 1: *Facilitated diffusion. Four different modes are distinguished in this model. 1) 3D diffusion 2) Sliding 3) Hopping 4) Intersegmental transfer. Figure is from* **??**

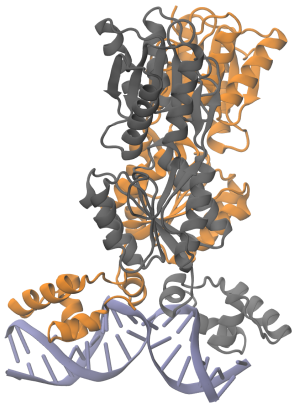

Abbildung 2: *The dimer structure of the Lac repressor in binding to its specific DNA sequence. The PDB ID is 1EFA.*

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http://www.physik.fu-berlin.de
http://www.physik.uni-potsdam.de

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