Protein Sliding Processes on DNA

Sequence dependent sliding of a methyl cytosine binding protein along DNA; a molecular dynamic study

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In Short

- 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 1. This implies that the protein lowers its searching process to a 1D diffusion mode along the DNA sequence 2. 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 2(2) until it reaches the cognate specific target or re-alters its search mode to 3D diffusion. An 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. This is the distance a protein is likely to slide on the DNA to reach its specific site.

In a very recent paper [4], the sliding of the Lac repressor on non-specific sequences has been studied, verifying that the sliding motion velocity of the protein when it slides on DNA. Interestingly, they have shown that the sliding of the Lac repressor along DNA and hence its velocity is quite sequence dependent. 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 micro second 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.

An important target site on DNA are methylated cytosines, epigenetically modified DNA bases, in particular in the context of CpG (cytosine, guanine) dinucleotides. Areas with an increased number of CpGs are important for gene promotion and, when methylated, result in down regulation of the respective gene 6. In this project, using MD simulations we plan to investigate the sequence-dependent sliding of the protein MDB2 (methyl cytosine binding domain) on the DNA up to two base-pairs at each side of the target sequence. 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.

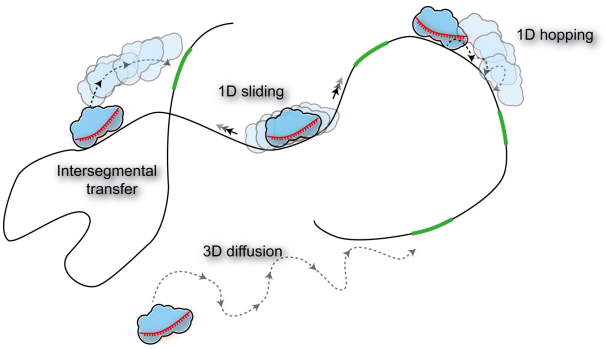

Figure 1: *Facilitated diffusion. Four different modes are distinguished in this model. 1) 3D diffusion 2) Sliding 3) Hopping 4) Intersegmental transfer. Figure is from. Figure is from [klein2017argonaute].*

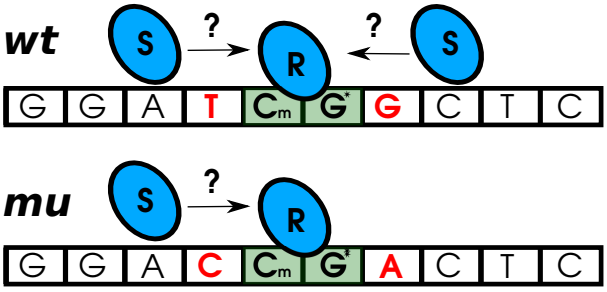

Figure 2: *Facilitated diffusion. Four different modes are distinguished in this model. 1) 3D diffusion 2) Sliding 3) Hopping 4) Intersegmental transfer. Figure is from. Figure is from [klein2017argonaute].*

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More Information

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