Coarse-grained modelling of nucleic acids and DNA hybridization

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***Abstract*—We present a recently developed coarse-grained model of DNA. We use the model to study association of DNA single strands which is still not well understood despite its importance for biological and bio-inspired systems. We find that the process proceeds through a complex set of intermediate states and exhibits non-Arrhenius behavior. We identify new mechanisms by which two misaligned strands can rearrange to form a fully paired duplex and show that the association rate can be modulated by sequence content.**

I. Coarse-grained model

Our recently developed coarse-grained DNA model oxDNA [1] [2] quantitatively reproduces thermodynamical, structural and mechanical properties of DNA. It has been successfully applied to the study DNA overstretching [3], single-stranded DNA stretching [2], kissing hairpins [2] and DNA nanotechnology systems such as DNA motors [4] [5]. It has recently been used to explain the dependence of kinetic rates of toehold-mediated strand displacement on toehold length [6], a process which is crucial for many DNA nanodevices. Our coarse-graining techniques developed for DNA modelling have also recently been extended to a coarse-grained model of RNA.

II. DNA hybridization

While the thermodynamics of DNA hybridization is well understood, the kinetics of the process are less well studied and rationalized. However, knowledge of association kinetics is important for improving the function of DNA microarrays and DNA nanotechnology devices such as DNA motors, DNA tiles or DNA origami.

We study DNA association using a Langevin dynamics implementation of oxDNA [7]. We find that the strand hybridization proceeds through a complex set of intermediate states. Successful binding events start with the formation of a few metastable base-pairing interactions, followed by zippering of the remaining bonds. However, despite reasonably strong interstrand interactions, initial contacts frequently fail to lead to duplex formation because the typical configurations in which they form differ from typical states with the same number of base pairs in the double-stranded equilibrium ensemble.

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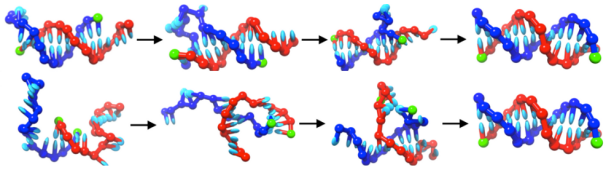

Fig. 1. Misaligned duplex can rearrange into a fully formed duplex via 'inchworm' (top) or 'pseudoknot' (bottom) internal displacement process.

Therefore, if the association process is analyzed on the base-pair (secondary structure) level, it shows non-Markovian behavior. Initial contacts must be stabilized by two or three base pairs before full zippering is likely. Non-Arrhenius behavior is observed because the number of base pairs in the effective transition states increases with temperature.

In addition, we find that alternative pathways involving misbonds can increase association rates. For repetitive sequences, we identify two processes by which misaligned duplexes can rearrange to form fully paired duplexes without having to detach. These are shown in Fig. 1. We show how the above described phenomena can explain why experimentally observed association rates of GC-rich oligomers are higher than rates of AT-rich equivalents. More generally, we argue that duplex association rates can be tuned by the choice of sequence, with possible applications in DNA nanotechnology.

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