Coarse-Grained Molecular Modeling of DNA: From Nanotechnology to Chromatin

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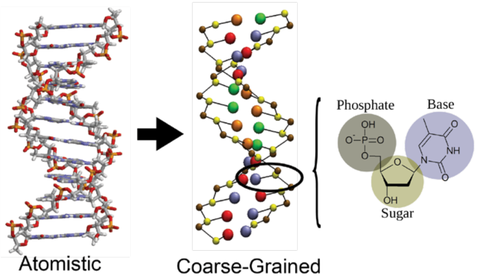
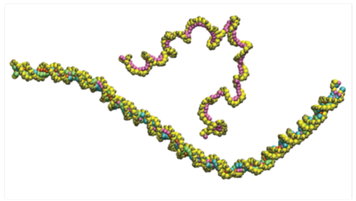
Mesoscale Coarse-Grained DNA Modeling

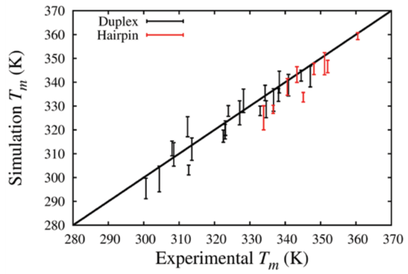
Molecular-level information of DNA at nanometer length scales is of fundamental interest to many aspects of nanotechnology and biology. At these length scales, precise dynamic information is frequently inaccessible to experiments and the details of these phenomena are often poorly understood. Molecular models provide a powerful tool to interrogate these systems. Towards this end, our group has developed a mesoscale coarse-grained model of DNA referred to as **3SPN**. By representing DNA by **3**-**S**ites-**P**er-**N**ucleotide (hence **3SPN**) we maintain many properties of DNA (e.g. minor and major groove widths, excluded volume, melting) while achieving a significant computational speed-up relative to atomistic simulations.



Knotts et al. J Chem Phys (2007), Sambriski et al. Biophys J (2009), Sambriski et al. PNAS (2009)

Single and Double-Stranded DNA Flexibility and Thermodynamics (3SPN.2)

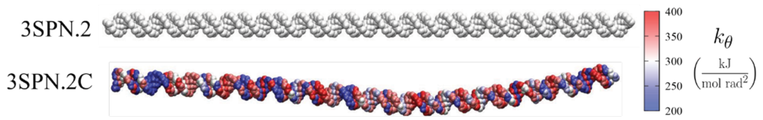




3SPN.2 is the most recent version in the 3SPN model family. In addition to correctly capturing structural properties (i.e. helix, width, major and minor groove widths, etc.), 3SPN.2 correctly recapitulates the persistence length of both single and double-stranded DNA. 3SPN.2 also reproduces the correct thermodynamics of both DNA duplexes and hairpins as a function of both sequence and salt.

Hinckley et al. J Chem Phys (2013)

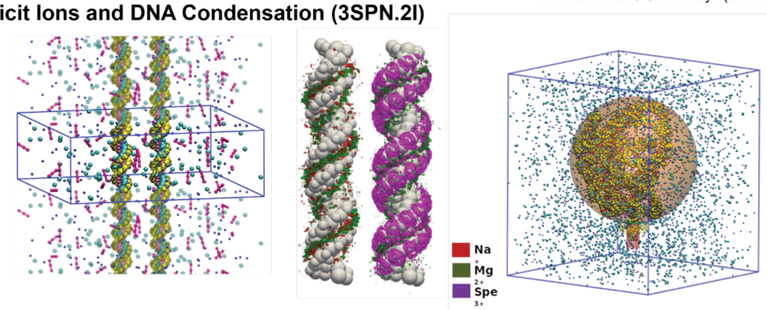
Sequence Dependent Stiffness and Intrinsic Curvature (3SPN.2C)



The interaction of DNA with proteins is mediated by both DNA's local sequence-dependent stiffness and its intrinsic shape (i.e. minor groove dimensions and net curvature). 3SPN.2C is an extension of 3SPN.2 that incorporates these phenomena into the 3SPN framework. 3SPN.2C allows the study of molecular recognition in DNA - Protein systems.

Freeman et al. J Chem Phys (In Press)

Explicit Ions and DNA Condensation (3SPN.2I)

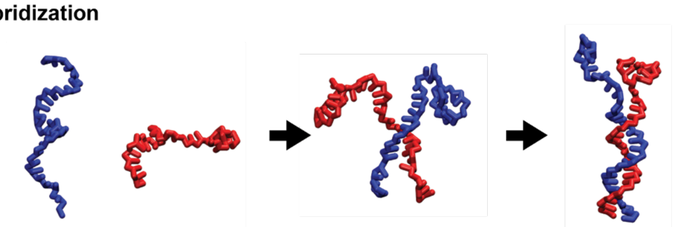


3SPN.2 treats electrostatics implicitly using Debye-Huckel theory. In many instances however, an explicit treatment of the electrostatics is necessary (e.g. Spermidine induced DNA-condensation or DNA packaging in a viral capsid). Towards understanding these phenomena, 3SPN.2I incorporates explicit ions into 3SPN.2.

Hinckley et al. In Preparation

DNA Nanotechnology

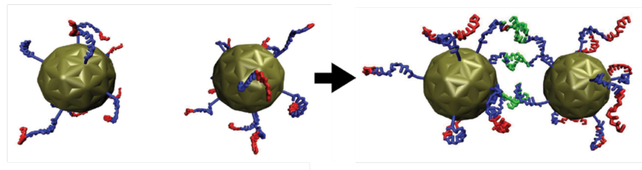
Hybridization

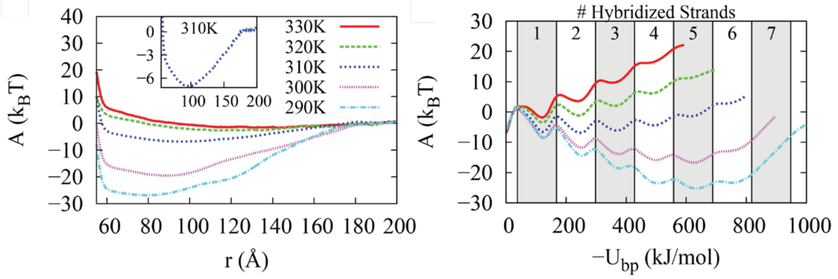


Despite its central role in biology, the mechanism of DNA hybridization is not well understood. In particular, the role of DNA sequence and its effect on the mechanism and rate of hybridization have only recently been studied. Using 3SPN.2, we demonstrate that out-of-register (i.e. non-native) base pairs are critical for duplex formation. In addition to enhancing the rate of hybridization, these out-of-register contacts can explain the various hybridization pathways for different DNA sequences.

Hinckley et al. J Chem Phys (2014)

DNA-Nanoparticle Association

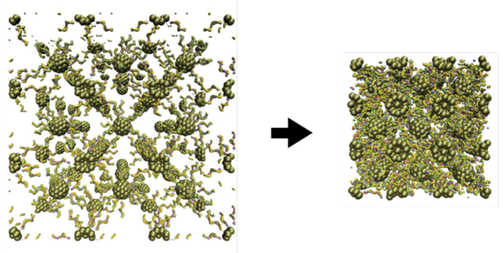




Short sequences of DNA conjugated to gold-nanoparticles represents a promising platform towards programmable self-assembly. By customizing the DNA sequence, the inter-particle can be precisely tuned. Using 3SPN.2, we have studied the details of the pair-wise association between two DNA-nanoparticles. We demonstrate that the association of these particles is a delicate balance between entropy and enthalpy and that small variations in the DNA sequence can have significant effects on the length and energy scale of interaction.

Lequieu et al. In Preparation

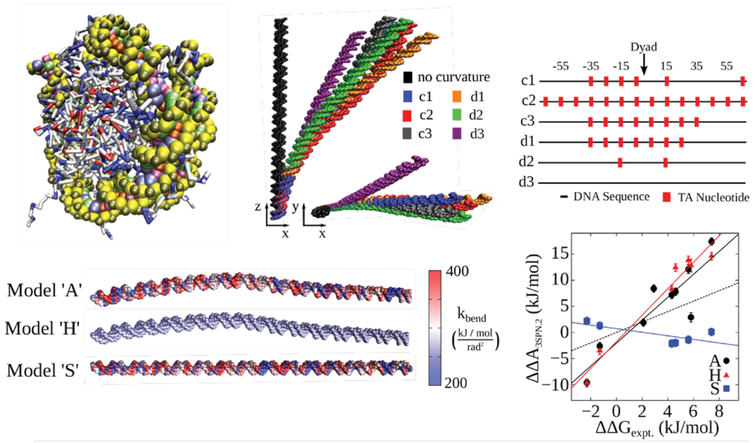
Mechanical Properties of DNA-Nanoparticle Crystals



Experimentally, it is well established that DNA-nanoparticles will spontaneously assemble into structures with long-range crystalline order. Unfortunately, the characterization of these crystals is limited to analysis of their structure with little attention on their mechanical response. Using 3SPN.2 we have calculated the mechanical response of DNA-nanoparticle crystals and show the response strongly dependent on DNA sequence properties and temperature.

Nucleosomes: The Building Block of Chromatin

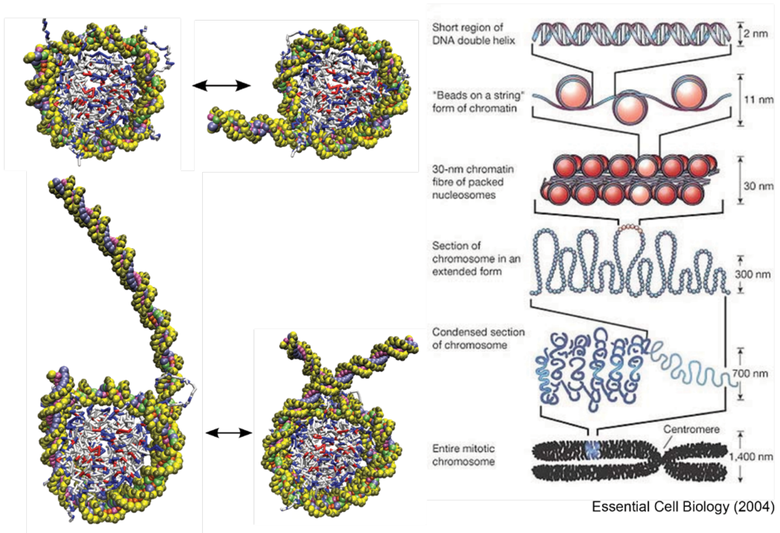
Nucleosome Formation



Nucleosomes provide the basic unit of compaction in eukaryotic genomes, and the mechanisms that dictate their position at specific locations along a DNA sequence are of central importance to genetics. In this work, we show how DNA's histone affinity is encoded in its sequence-dependent shape, including subtle deviations from the ideal straight B-DNA form and local variations of minor groove width. More generally, the results presented here explain how sequence, manifested as the shape of the DNA molecule, dominates molecular recognition in the problem of nucleosome positioning.

Freeman et al. Phys Rev Lett (In Press)

Nucleosome Positioning, Unwrapping and Higher-Order Structures



Essential Cell Biology (2004)

Chromatin is an extremely dynamic material that is simultaneously expanded and compacted as different genes are expressed. As the smallest unit of chromatin, understanding the mechanisms by which the nucleosomal DNA is rearranged is of fundamental importance. One phenomena of interest is the spontaneous unwrapping of DNA. By exposing regions of DNA previously bound to the histone, a region of DNA is accessible to binding factors and other transcriptional machinery. Further, the mechanism by which DNA "slides" to its optimal orientation is also not known. Understanding this rearrangement is critical for interpreting nucleosomal positioning maps and understanding the role of chromatin remodeling proteins.

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