MESOSCALE SIMULATION OF HOLLIDAY FOUR WAY JUNCTION

Quantitative Analysis Center Summer '13 Apprenticeship Program

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Introduction

As the chemical basis of genetics, DNA has been the focus of intense research. Computational molecular modeling of DNA has focused primarily on all-atom representations, which pose a challenge to study large length and time scales relevant for biological processes. Recently, a coarse grain representation, the 3 site-per-nucleotide (3SPN) model, has been introduced and is able to quantitatively capture the properties of the DNA double helix. However, its adaptability has never been tested in more complex structures, such as the Holliday four-way junction. I have been doing research to examine to ability of the model to simulate the Holliday junction in both STX and OPN conformations. We compare our results against existing experimental and all-atom computations to verify our findings. The model offers a speed-up of more than a factor 100, as compared to the all-atom simulations for the same structures. Our initial findings indicate that improvements to the model are necessary to make it appropriate for studying these more complex structures.

3SPN.2 Model

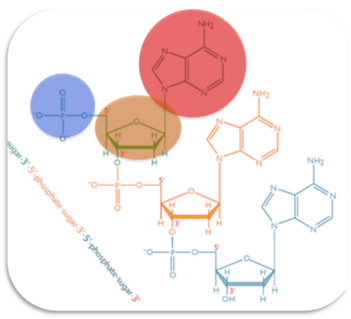
Different from the atomistic model, 3spn simplifies each nucleotides to three sites: bases, phosphates and ribose. It has some advantages in preserving persistence length and B-DNA geometry especially the minor and major grooves. The force fields have the following form:

Ub = Ubond + Ubend + Udihedral

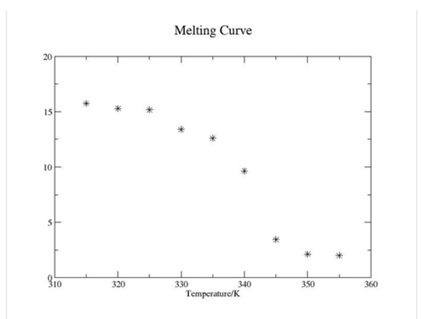
potentials for non-bonded interactions:

Unb = Uexe + Ubstk + Ucstk + Ubp + Uelec

This model can be verified by testing its melting temperature taken under 20.0μM concentration(see graph below),which is consistent with experiment result of 340K

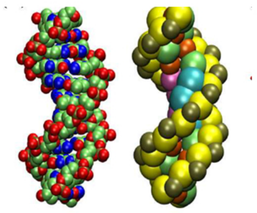


(a)



(b)

(a). DNA atomistic formula with coarse grain representation
(b). The melting curve for DNA sequence. The horizontal axis represent the number of base-pairs. This is consistent with the experimental result which



Representation of (right) coarse grain 3spn model (left) atomistic model [1]

The Effect of Salt Concentration

Intuitively, increasing the ions will shield the repulsive potential between phosphate groups with negative charges.

This also can be theoretically viewed using Debye Screening approximation.

The form of electrostatic potential has the following form:

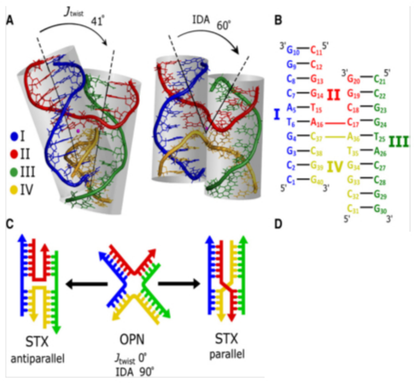
$$U_{elec} = \sum_{i<j}^{n_{elec}} \frac{q_i q_j e^{-r_{ij}/\lambda_D}}{4\pi\epsilon_o\epsilon(T,C)r_{ij}}$$

where the Debye length approximates the radius where there will be negligible shielding. This provides the theoretical background for transition between STK and OPN.

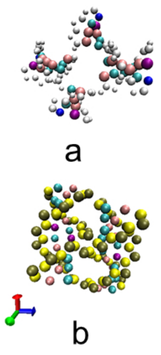
Holliday Four Way Junction

Holliday junction exits in all organisms and play an important role hereditary modification. The structure I look at is pdb1dcw(CCGGTACCGG)(ApC). It has two major forms : planar open-X forms (OPN) and immobile stacked-X forms(STK).

Some interesting phenomenon such as branch migration and the conformational change between STK and OPN are interesting to capture.



Graphic representation of Holliday Four-Way junction [2]

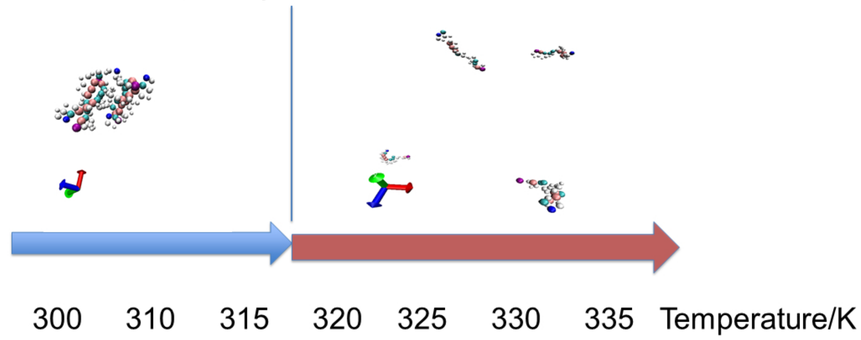


Initial configuration: OPN((a), and STK(b) pictures generated by VMD

Results

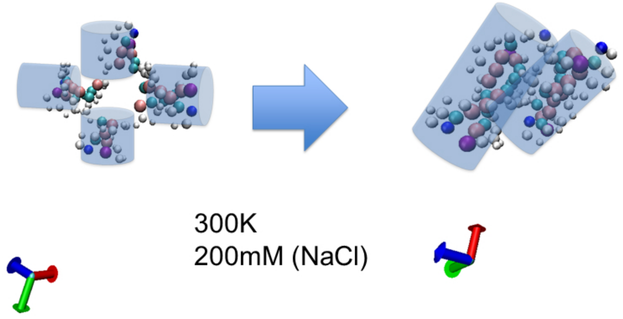
We run simulations of both STX and OPN structure under conditions that match those of previous all-atom simulations [3]; specifically, we simulate at T=300 K, and 200mM NaCl concentration, which results in relatively strong electrostatic screening.

The Melting of ApC from 300K to 335K



Transformation from OPN to STK

Simulations are done under conditions of 300K and 200mM salt concentration



Future plan

1. Further modify the force field to improve its adaptability of other structures.
2. Explore more about the conformational change between STK and OPN
3. Try to capture the branch migration

Reference

1.D. M. Hinckley, G. S. Freeman, J. J. Whitmer and J. J. de Pablo, Journal of Chemical Physics, submitted (2013)

2,3. E. G. Wheatley, S. N. Pieniazek, I. Murkerji and D.L. Beveridge, Biophysical Journal 102 (2012)