Computational Predictions of Optimal Inter-Operator A-tract Phasing for DNA Looping

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Abstract

It is well established that sequence-dependent mechanical properties of DNA affect the assembly of nucleoprotein complexes. However, it has been challenging to design experiments that test the validity of sequence-dependent mechanical models of DNA. To bridge the gap, we present rod mechanics simulations that suggest future experiments to test specific predictions. Our simulations are motivated by experiments on lac-repressor mediated looping for inter-operator DNA with a designed A-tract bend. Results from these simulations agree well with experiments in showing that the helical phasings between the A-tract bend and operators strongly influence the energetics and topology of the lac-mediated loops. In fact, our simulations predict that proper choice of phase angles can reduce the mean energy of 180 bp looping sequences to under 8kT. By conducting a parametric study of the effect of the two phase angles, we deduce the phase-energy relationship and predict the probability distributions of various loop topologies. By comparing our theoretical predictions with published experimental results we expect to gain a better metric for comparing existing models of DNA curvature and to improve our understanding of the role of protein flexibility in DNA looping.

Method

- Rod model [2] describes DNA mechanics
  - Supercoiling
  - DNA-protein interaction
  - DNA looping (described here)
- Sequence-dependent intrinsic curvature influences loop energetics
  - A-tract sequences are intrinsically helical and influence loop energetics
- One representation describes many A-tract sequences
- A-tract sequences (as in [3]) are represented as a rod with straight and helical segments
- We alter the number of base-pairs in straight domains to change operator phasing
- Changes in the number of base-pairs are denoted by Δhp,1 and Δhp,2
- Objective: identify loop with minimum deformation energy
- Potential binding topologies for optimal loop

Questions

- Why study DNA looping?
  - DNA looping is a known gene regulatory mechanism
  - LacR is a well studied example with abundant experimental data
- Gene repression level is a periodic function of inter-operator DNA length (phasing)
  - Period ~ 1 helical turn
  - Periodicity is a result of bp twist (~36 deg/bp)
  - See [1] for example
- Can we develop a computational rod model to explore DNA looping?
- Can this model predict optimal A-tract sequences (lowest energy configuration)?
- What experimental insights can these predictions offer?

Results

- Energy and topology contours for varying Δhp,1 and Δhp,2
- Minimum energy loops
- Optimal binding topologies for optimal loop

Experimental Insights

- Experimental sequences can be located on energy contour maps
- Results suggest experimental sequences that form loops having:
  - Preferred binding topology
  - Minimum energy
  - Preferred loop topology (Tw, Wt, Lk)
  - Equal energies suggest equi-probable topologies
- Results suggest probability distribution of stable and meta-stable states

Conclusions

- Computational model predicts deformation energy and topology of LacR-DNA complex
- Energy minima identify most likely binding topologies and loop topology over wide range of designed A-tract sequences
- Results reveal experimentally testable hypothesis and offer experimental insights on looping mechanics

Ongoing Work

- Sensitivity to variation in A-tract curvature and twist
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