Abstract

Computational rod theory predicts experimental characteristics of DNA looping by the L repressor

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Introduction

Why study DNA looping?

- DNA looping is a known gene regulatory mechanism
- LacI is a well studied example with abundant experimental data
- Gene repression is a periodic function of inter-operator DNA length (phasing)
  - Period ~ 1 helical turn (~36 deg./bp)
  - See [1] for example

- Intrinsically curved DNA forms hyperstable loops [2-4]
  - Changing the phase of an intrinsically curved domain yields distinct hyperstable loops
  - FRET and gel mobility assays measure loop topology [2-4]
  - Competition assays measure loop energetics (stability) [2]
  - Gel shift assays measure linking number distribution [2]

Potential binding topologies [7, 9]

Questions

- Do our computations agree with experiments?
- Can our results suggest new experiments?

Method

Rod model [5-7] describes DNA mechanics

- Supercoiling
- DNA-protein interaction
- DNA looping (described here)

Representing intrinsic curvature of three sequences (11C12, 9C14, 7C16) introduced in [2]

- Composed of straight domains and intrinsically curved A-tract domains

A-tract domain can be represented by a helical rod [8]

- Phasing of A-tract domain is parameterized by Atrp and Alt, to enable computation of all possible locations of A-tract within this sequence

Comparing Computational Theory and Experiment

Energetically preferred binding topology

- Two distinct looped states: Computations reveal A1 and P1 topologies as energetic minima

- Energies favor A1 state: Greater probability of achieving A1 state in designated sequences

Loop energetics

- Range of loop stabilities: Elastic deformation energy varies from min. ~5 kT to a max. ~12 kT
- Comparable minima for different states:
  - Both P1 and A1 loops yield comparable energies ~5 kT

Loop topology

- Range of linking numbers (\( L_k \)):
  - Minimum energy loops represent a range of possible \( L_k \)

Loops vary in size:

- Minimum energy A1 loops are generally larger than minimum energy P1 loops

Suggested Future Experiments

- Design most/least stable loops within the designed sequence space
- Design a DNA sequence that forms A1 and P1 topologies with equivalent energetics

References