Sequence-dependent helical structure and global responses of DNA

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II. Implications of base sequence-dependent structural information on larger-scale genetic control
A. Quantitation of local, sequence-dependent properties of DNA
   1. Low resolution models, including knowledge-based potentials
DNA sequence-dependent features can be incorporated in a coarse-grained, dimeric (base-pair step) model.

The total energy $\Psi$ of a sequence of $N$ base pairs is the sum of the deformation scores of the $N-1$ base-pair steps:

$$\Psi = \sum_{n=1}^{N-1} V_n$$

$$V_n = \left(\frac{1}{2}\right) \sum_{i=1}^{6} \sum_{j=1}^{6} f_{ij} (\theta_i - \theta_i^0)(\theta_j - \theta_j^0)$$

Knowledge-based potentials

Dimeric “force constants” of individual steps are derived from the covariance of observed parameters in protein-bound DNA structures.

\[
F^{-1} = \begin{bmatrix}
\langle \Delta \theta_1 \Delta \theta_1 \rangle & \langle \Delta \theta_1 \Delta \theta_2 \rangle & \cdots & \langle \Delta \theta_1 \Delta \theta_6 \rangle \\
\langle \Delta \theta_1 \Delta \theta_2 \rangle & \langle \Delta \theta_2 \Delta \theta_2 \rangle & \cdots & \langle \Delta \theta_2 \Delta \theta_6 \rangle \\
\vdots & \vdots & \ddots & \vdots \\
\langle \Delta \theta_1 \Delta \theta_6 \rangle & \langle \Delta \theta_2 \Delta \theta_6 \rangle & \cdots & \langle \Delta \theta_6 \Delta \theta_6 \rangle 
\end{bmatrix}
\]

where

\[
\langle \Delta \theta_i \Delta \theta_j \rangle = \langle \theta_i^{\text{XZ}} \theta_j^{\text{XZ}} \rangle - \langle \theta_i^{\text{XZ}} \rangle \langle \theta_j^{\text{XZ}} \rangle
\]

Rest states are equated to the mean values of observed parameters.

DNA sequence carries a structural and deformational code.

Roll and Twist are anticorrelated at most steps.

The 10 unique base-pair steps exhibit characteristic sequence-dependent motions.

Non-equilibrium forms, corresponding to deformations along the longest principal axis, superimposed on the intrinsic (average) dimer structures.  

Olson et al. 2007
A. Quantitation of local, sequence-dependent properties of DNA
   2. Linear, sequence-dependent three-dimensional structures
Regular repetition of conformational “blocks” generates a naturally curved minicircle

DNA sequence can be “engineered” into a variety of intrinsic shapes.

<table>
<thead>
<tr>
<th>Step type</th>
<th>Shift (Å)</th>
<th>Slide (Å)</th>
<th>Rise (Å)</th>
<th>Tilt (deg)</th>
<th>Roll (deg)</th>
<th>Twist (deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideal</td>
<td>0</td>
<td>0</td>
<td>3.4</td>
<td>0</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>“Rolled”</td>
<td>0</td>
<td>0</td>
<td>3.4</td>
<td>0</td>
<td>7.4</td>
<td>35.6</td>
</tr>
</tbody>
</table>

Olson et al. (2004)
“Engineered” 150-bp DNA structures

**O-ring**
\[(X_5 Y_5)_{15}\]

**S-curve**
\[(Y_5 X_5)_7 Y_10 (X_5 Y_5)_7\]

**Ω-curve**
\[(Y_5 X_5)_3 Y_10 (X_5 Y_5)_7 Y_10 (X_5 Y_5)_3\]

*Olson et al. (2004)*
Sequence affects the response of DNA to imposed superhelical stress.

Ideal elastic rod (intrinsically straight, homogeneous)

Natural “o-ring” (5bp straight, 5bp rolled)

Imposed twisting $\alpha$ at a single base-pair step introduces very different changes in the equilibrium shape and uptake of twisting in DNA minicircles with different intrinsic shapes.

$\alpha = 0^\circ$    $120^\circ$    $240^\circ$    $300^\circ$

$\Delta$Twist (deg)

-3.5  0  +5

Olson et al. (2004)
B. Effects of sequence on ring closure properties of closed molecules

1. Sequence-dependent factors that enhance the formation of tight minicircles and loops
The presence of a protein like HU that sharply bends DNA enhances the likelihood of the chain ends coming into close contact.

The proportion of HU in this sample corresponds to the distribution of protein found in an ensemble of $10^{10}$ configurations of a 126-bp duplex simulated such that there is one HU per 100 bp.

L. Czapla
B. Effects of sequence on ring closure properties of closed molecules

2. Mechanics of superhelix formation: roles of bending, twisting, and base-pair displacement
Models that set one of the dimeric parameters to canonical values clarify the role of local deformations on the global folding of nucleosomal DNA.

The composite changes in Roll account for the curvature of nucleosomal DNA. The effects of Tilt are negligible.

Models that set one of the dimeric parameters to canonical values clarify the role of local deformations on the global folding of nucleosomal DNA.

The composite changes in Slide diminish the pitch of nucleosomal DNA from ~26 Å per superhelical turn (~80 bp) in the native structure to ~3 Å in the Slide-frozen model. The effects of Shift are negligible.

Tolstorukov et al. (2007)
B. Effects of sequence on ring closure properties of closed molecules

3. Nucleotide looping and global folding of RNA
RNA loops are single-stranded, contributing to molecular folding and function.


The anticodon loop of transfer RNA (tRNA) contains the three nucleotides that associate with the three bases of the codon on messenger RNA.
C. Effects of sequence on the equilibrium structures and normal modes of cyclized DNA
1. Constrains of bound proteins on global structure and motions
Some proteins bind DNA at distant sites, introducing a loop in the DNA.

The DNA recognition sequence in the LacR-DNA crystal complex is palindromic (madam I’m adam).

... 79 bp ...

5’-AATTGTGAGCGCTCACAAATT->3’
3’<-TTAACACTCGCGAGTGTTAA-5’

The directionality of DNA binding generates different types of looping.

Minimum-energy configurations of DNA fragments complexed with the crystalline V-shaped LacR tetramer assembly.

Deformation of protein structure and presence of other proteins alter the types and populations of looped structures.

Swigon et al. (2006)

\( P_1^E \)

L. Czapla, D. Swigon
The understanding of simple protein-bound loops offers hope for future understanding of higher levels of biomolecular organization.

Stereo views of global equilibrium structures of three minichromosome models, each binding 20 capstan-shaped, phantom histone octamers, illustrating the large configurational changes brought about by small deformations of protein shape. Linker DNA is set at 61 bp in all cases.

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