A rigid-base model for DNA structure prediction

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Introduction

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Background. 30 years of history; lack of data hindered progress; recent construction of large MD dataset is making it accessible.
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MD dataset. (consortium+local)

• over 50 different DNA oligomers (12-18 bp each)
• all 136 unique tetramer sub-sequences represented
• all 10 unique dimer end-sequences represented
• standard simulation protocol w/AMBER program
• all simulations w/explicit water and counterions
• 50-200 ns simulation time for each oligomer
Basic problem

Under fixed solvent conditions, we seek a model to predict the ground-state structure and flexibility of any given DNA oligomer.

$$\rho(w) = \frac{1}{Z} e^{-\beta U(w)}$$

- $w$: configuration coordinates
- $\rho(w)$: probability density function
- $U(w)$: free energy
- $Z, \beta$: constants

Ground-state fluctuations (measure of flexibility)

DNA config space $w \in \mathbb{R}^N$
Rigid-base representation

We consider a model in which each base is modeled as a separate rigid body; side-chains are not considered explicitly.

\[ X = \{ T, A, C, G \}, \quad a = 1 \ldots n \]

\[ \overline{X}_1 \overline{X}_2 \overline{X}_3 \ldots \overline{X}_n \]

\[ \overline{X}_1 \overline{X}_2 \overline{X}_3 \overline{X}_n \]

\[ \overline{A} = T, \quad \overline{T} = A, \quad \overline{C} = G, \quad \overline{G} = C \]
Configuration coordinates

An oligomer with \( n \) basepairs has \( 6n \) intra-basepair and \( 6(n - 1) \) inter-basepair degrees of freedom; a total of \( N = 12n - 6 \).

The oligomer coord vector is

\[
\begin{align*}
\mathbf{y}_a &\in \mathbb{R}^6 \text{ intra} \\
\mathbf{z}_a &\in \mathbb{R}^6 \text{ inter}
\end{align*}
\]

\[
\mathbf{w} = (y_1, z_1, \ldots, z_{n-1}, y_n) \in \mathbb{R}^N.
\]
Motivated by observed data, we consider a model in which the free energy is quadratic.

\[ \rho(w) = \frac{1}{Z} e^{-\beta U(w)}, \quad U(w) = \frac{1}{2} (w - \mu) \cdot K(w - \mu) \]

\[ \mu = \mu(S) \in \mathbb{R}^N \quad \text{ground-state configuration} \]

\[ K = K(S) \in \mathbb{R}^{N \times N} \quad \text{ground-state stiffness} \]

We seek explicit approximations to the functions \( \mu(S) \) and \( K(S) \).
Sample data: coordinate marginals

\[ S = \text{GCTATATATATATATATAGC} \]
Sample data: ground-state configuration

$$S = \text{GCTATATAATATAGC}$$
Sample data: ground-state configuration

\[ S = \text{GCTATTTATATATATAGC} \]
Sample data: ground-state stiffness

\[ S = \text{GCGATCGATCGATCGAGC} \]
A monomer/dimer based model

We consider a model based on two types of interaction energies.

monomer interaction energy

\[ U_m = \frac{1}{2} (w_m - \mu_m^X) \cdot K_m^X (w_m - \mu_m^X) \]
\[ \mu_m^X \in \mathbb{R}^6, \quad K_m^X \geq 0 \in \mathbb{R}^{6 \times 6} \]
\[ X \in \{ T, A, C, G \} \]

\[ w_m = y \in \mathbb{R}^6 \]

dimer interaction energy

\[ U_d = \frac{1}{2} (w_d - \mu_d^{XY}) \cdot K_d^{XY} (w_d - \mu_d^{XY}) \]
\[ \mu_d^{XY} \in \mathbb{R}^{18}, \quad K_d^{XY} \geq 0 \in \mathbb{R}^{18 \times 18} \]
\[ X, Y \in \{ T, A, C, G \} \]

\[ w_d = (y_-, z, y_+) \in \mathbb{R}^{18} \]
A monomer/dimer based model

By summing the monomer/dimer contributions along an oligomer, we obtain the energy

\[ U(w) = \frac{1}{2} (w - \mu) \cdot K(w - \mu) + C \]

\[ \mu = \mu(S, \mathcal{P}), \quad K = K(S, \mathcal{P}), \quad C = C(S, \mathcal{P}), \]

where \( S \) is the oligomer sequence and \( \mathcal{P} \) is the model parameter set

\[
\mathcal{P} = \begin{cases}
K^X_m, & \sigma^X_m := K^X_m \mu^X_m, \quad X \in \{ T, A, C, G \} \\
K^XY_d, & \sigma^XY_d := K^XY_d \mu^XY_d, \quad X, Y \in \{ T, A, C, G \}.
\end{cases}
\]
A monomer/dimer based model

The ground-state configuration $\mu(S, P)$ and stiffness $K(S, P)$ are determined by $S = X_1 X_2 \cdots X_n$ and $P = \{K_m^X, \sigma_m^X, K_d^{XY}, \sigma_d^{XY}\}$.

$$K: \begin{array}{c}
\begin{array}{c}
1
2
3
4
\ldots
n
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
1
2
3
4
\ldots
n
\end{array}
\end{array} + \begin{array}{c}
\begin{array}{c}
1
2
3
4
\ldots
n
\end{array}
\end{array} = \begin{array}{c}
\begin{array}{c}
1
2
3
4
\ldots
n
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
1
2
3
4
\ldots
n
\end{array}
\end{array}$$

$$\sigma: \begin{array}{c}
\begin{array}{c}
1
2
3
4
\ldots
n
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
1
2
3
4
\ldots
n
\end{array}
\end{array} + \begin{array}{c}
\begin{array}{c}
1
2
3
4
\ldots
n
\end{array}
\end{array} = \begin{array}{c}
\begin{array}{c}
1
2
3
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\ldots
n
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
1
2
3
4
\ldots
n
\end{array}
\end{array}$$

$$\mu: \mu(S, P) = K(S, P)^{-1} \sigma(S, P)$$
Data for parameter estimation

To estimate the parameter set $\mathcal{P}$, we used a database of MD-observed probability densities $\rho_o^{(j)}(w)$ for sequences $S^{(j)}$, $j = 1, \ldots, J$.

$$\rho_o^{(j)}(w) = \frac{1}{Z^{(j)}} e^{-\beta U_o^{(j)}(w)}$$

$$U_o^{(j)}(w) = \frac{1}{2} (w - \mu_o^{(j)}) \cdot K_o^{(j)}(w - \mu_o^{(j)})$$
Functional for parameter estimation

A best-fit parameter set $\mathcal{P}$ can be obtained by minimizing the objective functional

$$\mathcal{F}(\mathcal{P}) = \sum_{j=1}^{J} D(\rho(S^{(j)}, \mathcal{P}), \rho^{(j)}_o),$$

where $D$ is the Kullback-Leibler divergence (pre-distance)

$$D(\rho_*, \rho_o) = \int \rho_* (w) \ln \left[ \frac{\rho_*(w)}{\rho_o(w)} \right] dw.$$

For Gaussians,

$$D(\rho_*, \rho_o) = \frac{1}{2} \left[ K_*^{-1} : K_o + (\mu_* - \mu_o) \cdot K_o (\mu_* - \mu_o) - \ln \left( \frac{\det K_o}{\det K_*} \right) - I : I \right].$$
Results

A best-fit parameter set $\mathcal{P}$ was obtained from the MD dataset via numerical minimization of the Kullback-Leibler functional.

The parameter set $\mathcal{P}$ allows us to predict the ground-state configuration $\mu(S, \mathcal{P})$ and stiffness $K(S, \mathcal{P})$ for any sequence $S$. 
MD vs Model: ground-state configuration

$S = \text{GCTATA}\text{TATATATATAGC}$
MD vs Model: ground-state configuration

\[ S = \text{GCTATTATATATATAGC} \]
MD vs Model: ground-state stiffness

$S = \text{GCGATCGATCGATCGAGC}$
Summary

• A model to predict the ground-state configuration and flexibility of B-form DNA from its sequence has been developed.

• The model can resolve sequence-effects both within and between oligomers.

• The model was parametrized using MD and its predictive capabilities have been tested against MD.

• The model provides a way to quantify the intrinsic pre-stress or frustration in DNA.

• The model suggests non-local dependence of ground-state on sequence is due to pre-stress.
Thank You