Generalized Poland-Scheraga model for supercoiled DNA

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The Poland-Scheraga (PS) model for the helix-coil transition of DNA considers the statistical mechanics of the thermally induced binding of two complementary strands of DNA. In this paper, we show how to modify the PS model when a torque is applied to the extremities of DNA: We propose a simple model for the energy of twisted DNA and compute the entropy of a loop, subject to angular constraints (supercoiling). The denaturation curves are shifted towards lower or higher temperatures depending on the sign of the torque, and the UV absorption peaks are softened. The properties of supercoiled DNA can be deduced through the use of a numerical Legendre transform. In the homogeneous case, we find that for weak supercoiling, the phenomenological quadratic law relating the torsional energy to the number of unpaired bases is recovered.

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Natural DNA exists as a double helix bound state. Upon heating, the two complementary strands may separate. This thermal unbinding transition is called DNA denaturation (see references therein). It has been modeled in various ways, the most prominent being the Poland-Scheraga (PS) model. Even though this model does not take into account spatial aspects of the denaturation transition, it correctly treats sequence effects, and has been numerically implemented in the program MELTSIM. It has also been shown that a mechanically induced denaturation transition is possible, by the combined application of a stretching force and an untwisting torque (see references therein). In a brief review of the standard PS model, we emphasize the role of the loop exponent $c$ on the existence and nature of the denaturation transition. We generalize the theory to include a torque which introduces a torsional enthalpy term, and results in a modified loop exponent $c' < c$. Numerical simulations on biological sequences show that the denaturation curves are shifted, while the peaks are smoother than their zero torque counterparts. Extension to supercoiled or undercoiled DNA, through the use of a numerical Legendre transform, yields denaturation isotherms for the same sequences.

We briefly review the Poland-Scheraga (PS) model for DNA melting, and consider a double stranded (ds) DNA fragment, made of $N$ complementary base pairs, assuming that bases $(1)$ and $(N)$ on both strands are paired. We denote by $Z(\alpha)$ the forward partition function of the two strands, starting at base $(1)$ and ending at base $(\alpha)$, with bases $(\alpha)$ being paired. This partition function satisfies the recursion relation (Figure 1)

$$Z(\alpha + 1) = e^{-\beta\varepsilon_{\alpha,\alpha+1}} Z(\alpha) + \sigma_S \sum_{\alpha'=1}^{\alpha-1} Z(\alpha') \mathcal{N}(\alpha';\alpha + 1)$$

(1)

where $\beta = 1/k_B T$ is the inverse temperature, $\varepsilon_{\alpha,\alpha+1}$ is the stacking energy of base pairs $(\alpha, \alpha + 1)$, and $\sigma_S$ is the bare loop formation (cooperativity) parameter (we assume that $\sigma_S$ is base independent).

FIG. 1: Recursion relation for $Z(\alpha + 1)$ (eq. (1)) in the PS model.

The factor $\mathcal{N}(\alpha';\alpha + 1)$ counts the number of conformations of a pair of chains starting at base pair $(\alpha')$ and ending at base pair $(\alpha + 1)$. It also represents the number of conformations of a closed polymer of $2(\alpha - \alpha')$ monomers, which is asymptotically given by $\mathcal{N}(\alpha';\alpha + 1)$ as $\beta \varepsilon_{\alpha,\alpha+1} < 1$. 

$$
\begin{align*}
\begin{array}{c}
1 \\
\alpha + 1
\end{array}
&=
\begin{array}{c}
1 \\
\alpha + 1
\end{array} + \begin{array}{c}
\sigma_S \\
\alpha + 1
\end{array}
\end{align*}
$$
\[ N(\alpha'; \alpha + 1) = \mu_0^{\alpha - \alpha'} g(\alpha - \alpha') = \frac{\mu_0^{\alpha - \alpha'}}{(\alpha - \alpha')^c} \]  

(2)

where \( k_B \log \mu_0 \) is the entropy per base pair (assumed to be independent of the chemical nature of the pair), and \( g(x) = \frac{1}{x^c} \) is the probability of return to the origin of a loop of length \( 2x \). The exponent \( c \) depends on the interaction of the loop with itself and with the rest of the chain: It has been extensively discussed in the context of homopolymeric DNA. If one neglects the interaction with the rest of the chain, we have \( c = 3\nu \) (yielding \( 3/2 \) for a Gaussian loop and \( \approx 1.8 \) for a self avoiding loop). Taking into account the interaction with the rest of the chain is a difficult problem: approximations and numerical calculations point toward a value \( \approx 2.15 \) for the full problem.

The recursion relation (1) is supplemented by the boundary conditions \( Z(1) = 1; \ Z(2) = e^{-\beta \varepsilon_1} Z(1) \). This recursion relation can easily be solved analytically if one assumes that all stacking energies are equal. One may for instance introduce a grand canonical partition function \( Z(z) = \sum_{\alpha=1}^{\infty} z^\alpha Z(\alpha) \). We summarize the results of this homopolymeric study: i) If \( 2 < c \), there is a first order (discontinuous) unbinding transition. ii) If \( 1 < c < 2 \), there is a second order (continuous) unbinding transition, with a specific heat exponent \( \alpha = \frac{2c-3}{c-1} \). iii) If \( c < 1 \), the two strands are always bound and loops open in a continuous way.

For non homogeneous sequences, the calculation cannot be done analytically. However, the results pertaining to the existence of an unbinding transition are expected to hold. In addition, in order to calculate the probability of opening of a base pair, it is necessary to introduce forward and backward partition functions. The forward partition function \( Z_f(\alpha) \) is nothing but \( Z(\alpha) \) whereas the backward partition function \( Z_b(\alpha) \) is the partition function of the two strands, starting at base \( (N) \) and ending at base \( (\alpha) \), with base \( (\alpha) \) being paired. These points will be discussed in detail in the following sections.

We now generalize the Poland-Scheraga model to the case where a torque is applied to the DNA fragment.

We assume that base pairs \( (1) \) and \( (N) \) of the DNA fragment are kept fixed and apply a weak torque \( \Gamma \) on base pair \( (\alpha) \). By “weak”, we mean that there are no plectonemes on the chain: Experimentally, applying a force \( F > 0.5 \) pN on a DNA fragment of a few persistence lengths \( l_p \) (\( l_p \approx 150 \) bp in (ds) DNA) is enough to prevent the formation of plectonemes.

If the force \( F \) is applied along the \( z \)-axis, the DNA fragment will be aligned (on the average) along this direction. One may then assign, in the \( xy \) plane, an angle \( \theta_\alpha \) to a paired base pair \( (\alpha) \), representing the angle of this pair with the \( x \)-axis (fig. 2). We denote by \( \theta_0 \) the natural twist angle of the DNA helix per base pair (\( \theta_0 = \frac{2\pi}{10.4} \) in radians), and model the torsional energy between neighboring base pairs by

\[ \varepsilon_0(\alpha, \alpha + 1) = \frac{1}{2} \kappa_0(\theta_{\alpha+1} - \theta_\alpha - \theta_0)^2 \]  

(3)

where \( \kappa_0 \) is the elastic torsion constant of (ds) DNA.
Generalizing the PS model, one may define a partition function \( Z(\alpha, \theta_\alpha) \) of the two strands, starting at base pair \((1)\) with orientation \(\theta_1\), and ending at base pair \((\alpha)\), with orientation \(\theta_\alpha\). This partition function satisfies

\[
Z(\alpha + 1, \theta_{\alpha+1}) = e^{-\beta \varepsilon_{\alpha, \alpha+1}} \int_{-\infty}^{+\infty} \frac{d\theta_\alpha}{M_0} e^{-\frac{\beta}{2}(\theta_{\alpha+1} - \theta_\alpha)^2} Z(\alpha, \theta_\alpha)
\]

\[
+ \sigma_s \sum_{\alpha' = 1}^{\alpha - 1} \int_{-\infty}^{+\infty} \frac{d\theta_{\alpha'}}{M_1} e^{-\beta E_1(\alpha', \theta_{\alpha'}; \alpha + 1, \theta_{\alpha+1})} N(\alpha', \theta_{\alpha'}; \alpha + 1, \theta_{\alpha+1}) Z(\alpha', \theta_{\alpha'})
\]

where \(\varepsilon_{\alpha, \alpha+1}\) again denotes the stacking energy of base pairs \((\alpha, \alpha + 1)\) and \((M_0, M_1)\) are normalization factors (see below).

In equation (4), the existence of the stretching force \(F\) is implicit. The functions \(E_1(\alpha', \theta_{\alpha'}; \alpha + 1, \theta_{\alpha+1})\) and \(N(\alpha', \theta_{\alpha'}; \alpha + 1, \theta_{\alpha+1})\) represent respectively the torsional energy and the number of conformations of a pair of chains starting at base pair \((\alpha')\) with orientation \((\theta_{\alpha'})\) and ending at base pair \((\alpha + 1)\) with orientation \((\theta_{\alpha+1})\).

We first discuss \(N(\alpha', \theta_{\alpha'}; \alpha + 1, \theta_{\alpha+1})\). With unconstrained orientations, equation (2) emphasizes the importance of the loop exponent \(c\), representing the interaction of the loop with itself and with the rest of the chain. In a forthcoming paper [13], we show that \(c\) can also be modeled through the introduction of a specific repulsive potential in an otherwise Gaussian loop. In a nutshell, the two strands partition function can be factorized as a product of a center of mass partition function \(Z_{cm}(F)\) and a relative coordinate partition function

\[
Z_\rho = \int D\tilde{\rho}(s) e^{-\beta H_\rho}
\]

with \(\beta H_\rho = \frac{3}{2\pi^2} \int ds \tilde{\rho}^2(s) + D \int ds \frac{1}{|\rho(s)|} \), where \(a \approx 50\ \text{Å}\) is the single strand (ss) DNA Kuhn length. The effective chain described by \(\tilde{\rho}(s)\) has length \(2(\alpha - \alpha')\), and the probability of return to the origin is given by

\[
g_D(\alpha - \alpha') = \frac{<0|e^{-2(\alpha - \alpha')(\beta\rho_D)|0>}{\int <r|e^{-2(\alpha - \alpha')(\beta\rho_D)|0>}
\]

with \(\beta h_D = -\frac{a^2}{3} \tilde{\rho}^2 + \frac{D}{\rho^\alpha}\).

This model will mimic the original problem, if one has \(g_D(\alpha - \alpha') \sim \frac{1}{(\alpha - \alpha')^\lambda}\). A scaling argument then implies \(\lambda = 2\). The precise relation between the strength \(D\) of the repulsive potential and the loop exponent \(c_D\) depends on the behaviour of the density of states of the Hamiltonian \(\beta h_D\) at low energy. It can be obtained numerically; in particular \(D\) can be chosen so that one has \(c_D = c\) (e.g. \(c = 1.8\) is recovered with \(\frac{D}{\rho^\alpha} \approx \frac{1}{A}\)).

On the other hand, the orientation constraint can be written as

\[
\Delta \theta = \theta_{\alpha+1} - \theta_{\alpha'} = \int_{\alpha'}^{\alpha+1} \frac{x\dot{y} - y\dot{x}}{x^2 + y^2} \ ds
\]

where \((x, y)\) are the coordinates \(\tilde{\rho}\) perpendicular to the stretching force \(F\). This type of constraint arises in entangled polymers [14].

Following a calculation of Wiegel [13], the use of a directed approximation for the stretched strands enables us to write the number of conformations \(N(\alpha', \theta_{\alpha'}; \alpha + 1, \theta_{\alpha+1})\) as (compare with eq. (2))

\[
N(\alpha', \theta_{\alpha'}; \alpha + 1, \theta_{\alpha+1}) = \frac{\mu(F)}{(\alpha - \alpha')^c} h(\theta_{\alpha+1} - \theta_{\alpha'})
\]

where \(\mu(F) = \mu_0 e^{\frac{\beta^2 y_{\beta}^2}{4a^2}}\) and \(h(\theta_{\alpha+1} - \theta_{\alpha'})\) is a (normalized) measure of the torsional entropy reduction given by

\[
h(\theta_{\alpha+1} - \theta_{\alpha'}) = \frac{1}{\sqrt{2\pi A}} \exp \left( -\frac{(\theta_{\alpha+1} - \theta_{\alpha'})^2}{2A} \right)
\]

with \(A = \sqrt{\frac{a^2}{2\pi^2}} \log(\frac{1}{a^2}(\alpha - \alpha'))\). In the previous equation, \(d\) denotes the diameter of the double helix \((d \approx 20\ \text{Å})\) and as seen above, \(a\) denotes the Kuhn length of (ss) DNA \((a \approx 50\ \text{Å})\). The experimental value of \(\log \mu_0\) is taken as
For forces $F$ of order 1 pN, the difference between $\log \mu$ and $\log \mu_0$ is of order 0.1 and will thus be neglected in the following. The validity of the directed approximation for this calculation will be discussed thoroughly in a forthcoming paper \cite{ref13}.

In equation (4), the torsional energy $E_1(\alpha', \theta_\alpha'; \alpha+1, \theta_{\alpha+1})$ of a bubble $(\alpha', \alpha+1)$ is assumed to be of the form

$$E_1(\alpha', \theta_\alpha'; \alpha+1, \theta_{\alpha+1}) = \frac{\kappa_l}{2} \frac{(\theta_{\alpha+1} - \theta_{\alpha'})^2}{(\alpha - \alpha')/2}$$

where $\kappa_l$ is the torsional constant of a DNA bubble.

For long enough loops $(\alpha - \alpha' > \log(\alpha - \alpha'))$, this energy is small compared to the entropy reduction of eq. (8). Furthermore, due to the softness of unbound fragments, one expects that $\kappa_l << \kappa_0$. In the following, we will thus set this torsional energy to zero.

The recursion relation for the partition function therefore reads

$$Z(\alpha, \theta_\alpha) = \int_{-\infty}^{\infty} d\theta_\alpha e^{-\beta \varepsilon_{\alpha,\alpha} \theta_\alpha} Z(\alpha, \theta_\alpha)$$

where $N(\alpha', \theta_\alpha'; \alpha+1, \theta_{\alpha+1})$ is given in eqs. \cite{ref7} \cite{ref8}.

Since the integration over the angular variables $\theta_\alpha$ should yield back equation (11), the normalization factors are $M_0 = \sqrt{\frac{2a}{3\kappa_0}}$ and $M_1 = 1$.

Setting $\theta_1 = 0$, the boundary conditions pertaining to equation (10) are $Z(1, \theta_1) = \delta(\theta_1)$ and $Z(2, \theta_2) = \frac{1}{M_0} e^{-\beta \varepsilon_{1,2} \theta_0 - \frac{\kappa_0}{2}(\theta_2 - \theta_0)^2}$

Equation (10) can be brought to the form of a standard PS recursion relation by going to the torque representation. We define the Laplace transform

$$Z(\alpha, \Gamma) = \int_{-\infty}^{\infty} d\theta_\alpha e^{\beta \Gamma \theta_\alpha} Z(\alpha, \theta_\alpha)$$

The quantity $Z(\alpha, \Gamma)$ represents the partition function of a DNA chain of length $\alpha$ fixed at the origin, and subject to a torque $\Gamma$. Taking the Laplace transform of (10), we obtain

$$Z(\alpha + 1, \Gamma) = e^{-\beta \varepsilon_{\alpha,\alpha+1} \Gamma} Z(\alpha, \Gamma) + \sigma_S' \sum_{\alpha' = 1}^{\alpha-1} \frac{\mu_0 \alpha - \alpha'}{(\alpha - \alpha')^2} Z(\alpha', \Gamma)$$

with

$$\varepsilon_{\alpha,\alpha+1} = \varepsilon_{\alpha,\alpha+1} - \Gamma \theta_0 - \frac{\Gamma^2}{2\kappa_0}$$

$$\varepsilon' = c - \frac{\beta^2 \Gamma^2}{2} \frac{a^2}{3D}$$

$$\sigma_S' = \sigma_S \left( \frac{4a^2}{3d^2} \right) \frac{\varepsilon'^2}{\varepsilon'^2 + \frac{c^2}{D}}$$
The boundary conditions translate into $Z(1, \Gamma) = 1$ and $Z(2, \Gamma) = e^{-\beta\epsilon_{1,2}}$

In the form (12), we recognize a standard PS recursion equation, with stacking energies given by (13), loop exponent given by (14) and loop formation (cooperativity) parameter given by (15). These new effective parameters have the following properties: i) the loop exponent is decreased by the torque, so that the probability of return to the origin is increased (see eq.(2)), ii) the loop formation parameter is increased by the torque. With realistic values of the parameters (see below), this effect is very weak.

These results can easily be understood for undercoiling ($\Gamma < 0$). However, in the case of strong positive supercoiling ($\Gamma > 0$), the spatial arrangements of the bases are important, a feature which is absent of the PS approach. This can lead to the appearance of new phases such as P-DNA [5]. We thus can trust our approach for negative and weakly positive torques.

If one takes all stacking energies equal to $-\epsilon_0$, equation (12) can be solved analytically by using the appropriate grand canonical partition function $Q(z, \Gamma) = \sum_{\alpha=1}^{\infty} z^{\alpha} Z(\alpha, \Gamma)$ with the results $Q(z, \Gamma) = \frac{z}{1 - ze^{\beta\epsilon_0 - \sigma_0 z} P_c'(z\mu_0)}$ where $P_c'(z) = \sum_{l=1}^{\infty} \frac{1}{l^c}$. As in the original PS model, the critical point is obtained when $z$ is a pole of the denominator and $z\mu_0 = 1$. As previously mentioned, the specific heat exponent (in the thermodynamic limit) reads $\alpha(\Gamma) = \frac{2c' - 3}{c' - 1}$.

A theoretical outcome of our model is that the denaturation transition disappears at large enough torque. Indeed, as we previously saw, the PS model displays a phase transition only if the loop exponent $c$ is larger than 1. Equation (14) shows that even though the bare exponent $c$ is larger than 1, it becomes smaller than 1 when the torque is increased. Therefore, the transition gets smoothed out as the torque is increased: The denaturation peaks broaden and are shifted to lower or higher temperatures, depending on the sign of the applied torque.

For non homogeneous stacking energies, the properties of $Q(z, \Gamma)$ are not amenable to analytic calculations and one has to resort to numerical calculations. The parameters we use are $c = 1.8$ (corresponding to $D/a^2 \approx 0.33$), $\sigma_S = 1.26 \times 10^{-5}$, and the MELTSIM stacking energies [4].

In Figure 3, we plot the derivative with respect to the temperature of the fraction of bound pairs $c = -\frac{d\theta}{dT}$ (related to the experimental UV absorption of DNA) for a biological sequence of 2000 base pairs as a function of temperature, for various values of the torque $\Gamma$. As $\Gamma$ increases, the peaks get smoothed out.

Up to here, we have considered the problem of a DNA fragment subject to a weak torque. We now come back to the case where the DNA fragment is supercoiled or undercoiled (as is the case of circular DNA in plasmids): the winding angle $\theta_N - \theta_1$ is not equal to the total natural twist angle $(N-1)\theta_0$. The supercoiling index $s$ is defined by

$$\theta_N - \theta_1 = (N-1) \theta_0 (1 + s)$$  (16)
It can be positive (supercoiling, $\Gamma > 0$) or negative (undercoiling, $\Gamma < 0$).

The partition function $Z(N, \theta_N)$ is related to the torque representation through an inverse Laplace transform

$$Z(N, \theta_N) = \beta \int_{C_0}^{C_0+i\infty} \frac{d\Gamma}{2i\pi} e^{-\beta \Gamma(N-1)\theta_0(1+s)} Z(N, \Gamma)$$

where $C_0$ is a constant which leaves all the singularities of $Z(N, \Gamma)$ to its right. For large $N$, one may perform a saddle point calculation, with $\Gamma_s$ defined by

$$\frac{1}{N} \left( \frac{\partial \log Z(N, \Gamma)}{\partial \Gamma} \right)_{\Gamma=\Gamma_s} = \beta \theta_0(1+s)$$

For homogeneous sequences (all stacking energies equal to $-\varepsilon_0$), one may go one step further since

$$Z(N, \theta_N) = \beta \int \frac{dz}{2i\pi z} e^{-zN} e^{-\beta \Gamma(N-1)\theta_0(1+s)} Q(z, \Gamma)$$

where the $z$ integral is to be performed on a circle containing the point 0.

In the limit of large $N$, equation (19) can again be evaluated by the saddle point method on both $z$ and $\Gamma$. The saddle-point equation for $z$ is given by $N = z_s \frac{d}{dz} \log Q$. In the thermodynamic limit, $N \to \infty$, the saddle-point solution $z_s$ should approach the (\Gamma-dependent) pole $z^*$ of $Q(z, \Gamma)$, defined by

$$1 - z^* e^{\beta \varepsilon_0} - \sigma^* z^* = 0$$

The saddle point (18) then reads

$$\beta \theta_0(1+s) = \left( \frac{\partial \log z^*}{\partial \Gamma} \right)_{\Gamma=\Gamma_s}$$

and to leading order, the free energy per base pair $f(s)$ is given by

$$\beta f(s) = \log z^*(\Gamma_s) + \beta \Gamma_s \theta_0(1+s)$$

To make contact with previous work, we restrict ourselves to small supercoiling ($s \ll 1$) or equivalently small couple $\Gamma$. Using equation (20) we can expand $z^*$ to second order in $\Gamma$. The details of the calculations will be presented in [13] and we just quote the results:

$$\beta f(s) = \log z^*(\Gamma = 0) + \frac{\beta^2 \theta_0^2}{2 \Delta_2} \left( s + \frac{N\sigma}{N} \right)^2$$

where $\Delta_2$ is a constant, equal to the fluctuation of the end angle ($\Delta_2 = \langle \sigma^2 \rangle = \beta^2 \langle \langle \theta_N^2 \rangle - \langle \theta_N \rangle^2 \rangle_{T=0}$). The physical interpretation of equation (23) is fairly simple. It essentially states that for small supercoiling $s$, the free energy of a DNA strand is equal to the sum of the free energy of the non supercoiled fragment plus a free energy term which forces the fraction of unbound pairs to be close to the opposite of the supercoiling index. This form is very similar to the form which was devised phenomenologically by Benham [18]. In our case, this form is derived from the microscopic model, and the coefficients of the quadratic part are expressed in terms of the microscopic characteristics of the DNA.

For larger supercoiling, the relation between $s$ and the fraction of unbound pairs is not straightforward. Arguments that suggest that $-s \sim \frac{N\sigma}{N^2}$ for any $s$ are given in ref. [19].

Finally, we point out that the specific heats $C(T, \Gamma)$ and $C(T, s)$ are related through Fisher renormalization [20]. In particular, if $C(T, \Gamma)$ diverges, $C(T, s)$ will be finite at the transition.

For non homogeneous sequences, numerical calculations yield $Z(N, \Gamma)$, and through eq. (18), one obtains the isotherm curves $\Gamma(s)$. The application to the sequence used in Figure 3 is shown in Figure 4.
FIG. 4: Torque as a function of the supercoiling index for various temperatures, for the sequence of Figure 3.

The statistical mechanics of the torque induced DNA denaturation has been previously studied in different contexts [5, 21, 22, 23], and there is agreement with our results whenever they overlap. Ref [21] considers a transfer matrix formalism for homogeneous sequence with $c = \frac{3}{2}$. Ref [22] starts from the Benham phenomenological expression and obtains among other results - the critical curve $T_c(s)$ in the homogeneous case. Ref [23] studies the thermodynamic and dynamic properties of a random DNA fragment submitted to a torque. Finally Ref [5] discusses the experimental procedure in detail (ranges of force and torque); the comparison with our results is not straightforward as experiments rely on the extension curve, which is not included in PS type of models.

We have proposed a generalization of the PS model to include the effect of torsion on DNA denaturation. Torsion produces a very strong reduction of entropy in the loops, which eventually suppresses the denaturation transition. Application to cyclic DNA (plasmids) will be the subject of future work.

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