**Thermomechanics of DNA: Theory of Thermal Stability under Load**

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A theory for thermomechanical behavior of homogeneous DNA at thermal equilibrium predicts critical temperatures for denaturation under torque and stretch, phase diagrams for stable B-DNA, supercoiling, optimally stable torque, and the overstretching transition as force-induced DNA melting. Agreement with available single molecule manipulation experiments is excellent.

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DNA is a sophisticated nanomechanical object. The interplay between strong covalent bonds of the backbone and weak hydrogen interactions between bases [1], the thermal bath in which it is immersed, and the proximity of physiological conditions to the denaturation temperature, make DNA highly and nonlinearly responsive to mechanical and thermal changes, and render any solely mechanical approach incomplete. This is critical for nanotechnology, where DNA is the basis for novel materials [2], but understanding double helix thermomechanics would also illuminate biology, where, e.g., enzymes involved in replication and repair are viewed as molecular motors.

In the past 20 years, direct single molecule manipulation [3] has revolutionized our understanding of key aspects of DNA, revealing new couplings and transitions between different structures, whose nature and forms, however, are still speculative. When a few micrometer long strand of DNA is stretched to a tension of the order of piconewtons (pN) to avoid formation of plectonemes, sharp transitions are activated at positive and negative torques, while an overstretching transition is observed for DNA under tension of ≈ 60–70 pN at zero torque [3–5]. Tentative tension-torque phase diagrams for the stability of B-DNA [4], and various phenomenological theories, some of which are highly parametrized, have been proposed to explain these effects [5–11]. The robustness of the Peyrard-Bishop-Dauxois (PBD) approach [12–14] has been corroborated by Cocco and co-workers [15,16]: they incorporated torque and successfully reproduced denaturation by unwinding. However, these recent studies do not include tension, do not explain denaturation at overwinding, and do not provide phase diagrams in the tension-torque plane. Also, although much simpler than the molecular structure they describe, their complexity cannot offer analytic equations to more easily guide experiments.

We address these issues by modeling the pitch dependence of the base bond and therefore the effect of tension and torque in a way suitable for elimination of the angular degrees of freedom via integration of the partition function, and obtain an effective energy for a PBD model which incorporates temperature and external loads. We compute the phase diagram for B-DNA and the dependence of supercoiling on torque, tension, and temperature at criticality. Finally, we propose simple algebraic formulas for the observables. Although here we neglect bending modes [17,18], we will show elsewhere [19] how to incorporate them into our framework.

In our model $i$ labels nucleotides separated by a distance $a$ along the DNA backbone (Fig. 1), $x_i$ is the length of the $i$th base’s bond, $\omega_j = (\theta_{i+1} - \theta_{i-1}) / 2 - \Omega$ is the angular shift between nucleotides along the backbone, and $\theta_i$ is their angular coordinate. As in the Cocco-Barbi models [15,16], the two strands of DNA are assumed symmetrical, with a fixed rigid center line, and infinitely long. $\Omega$ denotes the natural pitch of the helix, and $\omega_i$ describes deviations from equilibrium. The potential energy of the system is $E = a \sum_i E_i$, with

$$E_i = \frac{k}{2} \frac{\Delta x_i^2}{a^2} + \frac{\nu}{2} (\omega_i + \Omega)^2 + [\chi(x_i) - 1] V(\omega_i)$$

the sum of a stacking potential ($\Delta x_i = x_{i+1} - x_i$), in harmonic approximation for simplicity (see discussion later), an elastic term which restores the $\theta_{i+1} = \theta_i$ angular configuration for open strands, and a square well potential for the hydrogen bond between bases $[\chi(x)]$ is a step function which is 0 for $0 \leq x \leq x_c$ and 1 for $x_c < x$, where $x_c$ is a length associated with the hydrogen bond), whose depth $V$ depends on the angle $\omega_i$. Because of a complex

![FIG. 1 (color online). (a) Schematics of our DNA model. $i$ labels nucleotides separated by a distance $a$ along the DNA backbone. $\theta_i$ is their angular coordinate, $x_i$ is the length of the $i$th base’s bond. (b) A closed portion of the double helix. (c) We assume that in region where base pairs are open, the two backbones twist with bases pointing outwards.](image-url)
combination of hydrophobic, $\pi-\pi$, and dipolar interactions, the bonding of opposite bases is responsible for DNA's pitch. Therefore, $V(\omega)$ is not symmetric but rather $V'(0) = \nu \Omega$, since DNA is in equilibrium at $\omega_i = 0$. Also, $\mu = -V''(0)$ must be positive: indeed, $\nu + \mu$ being the torsional rigidities of the joined double helix and $\nu$ of the (much softer) open strands, we have $\mu \gg \nu > 0$ (we shall see that $\mu/\nu \sim 10^2$). We can now expand $V$ as

$$V(\omega) \approx V_0 + \nu \Omega \omega - \frac{1}{2} \mu \omega^2. \quad (2)$$

Our choice of a square well potential and separation of variables $x_i$, $\omega_i$ in (1) keeps the model analytically soluble: no substantial changes in the thermodynamics arise from surrendering it in favor of, e.g., the Morse potential [14]. We show elsewhere how to introduce a smooth potential, desirable for dynamics and other studies [19].

Now consider the external loads. The torque $\Gamma$ is incorporated in (1) via a term $-\sum \omega \alpha_i$ (for dimensional convenience $\Gamma = \tau \alpha$). Tension is more subtle: the total stretch $h_i = \sum \chi(x_i)h_i^0 + \sum \chi(x_i - 1\ h_i^0$ from both closed ($h_i^0$) and open ($h_i^0$) DNA sections can only arise from winding or unwinding, since the backbone is effectively inextensible. While elongation due to a change in pitch for the joined double helix is trivially $(h_i^0)^2 = h_0^2 - R^2(\omega_i^2 + 2\omega_i \Omega)$ ($R$ is the radius of the DNA helix, $h_0$ < $a$ the vertical distance between nucleotides), assumptions are necessary to explain the coupling between stretch and twist when the strands are open. We assume that the two backbones twist with bases pointing outwards as in P-DNA (Fig. 1), and therefore the length of openings responds to winding: $h_i^0 = a^2 - r^2(\omega_i + \Omega)^2$, where $r < R$ is an effective diameter for the backbone. Below, we will expand these expressions to second order around their stable configurations ($\omega_i = 0$ for closed, $\omega_i = -\Omega$ for open sections). All the quantities $E_i, k, \nu, \mu, V_0, \tau, f$ and $\pi$ have the dimension of a force.

Equilibrium thermodynamics is implemented by integration of $\exp[-\beta(E - \sum \omega \alpha_i - \sum f h_i)]$ over $\{\chi_i\}$ and $\{\omega_i\}$. Since everything is quadratic in $\omega_i$, we can express the product of the Gaussian integrals in the angular variables $\omega_i$ and obtain the partition function

$$Z = e^{-\beta L \delta} \int \prod_i dx_i e^{-\beta a(k/2)(\Delta \xi_i^2/\alpha^2 + \bar{V}(x_i))} \quad (3)$$

for an equivalent PBD model, whose effective potential

$$\bar{V}(x_i) = [\chi(x_i) - 1][\bar{V}_0 + \Omega \bar{\tau} - \frac{1}{2} \frac{\bar{\mu}}{(\bar{\nu} + \bar{\mu})} \bar{\nu}^2] \quad (4)$$

incorporates explicitly the effect of the external torque $\Gamma = \tau \alpha$, and also of $f$, through the tension-increased torsional rigidities $\bar{\mu} = \mu + mf$, $\bar{\nu} = \nu + nf$, and the pitch under tension $\bar{\Omega} = \Omega - \frac{\alpha f}{\mu}$. Also, the depth of the effective potential in the absence of external torque, $V_0 = V_0 - \frac{f}{2a} \ln \frac{\bar{\nu} + \bar{\mu}}{\bar{\nu} - \frac{\mu}{2}} (\Delta \xi_i^2/\alpha^2 + \bar{V}(x_i))$, is weakened by tension $f$ and entropically by temperature $T$ (as also found via a different approach by Manghi et al. [10]. The term $\Delta = -\frac{\nu}{\alpha f} \ln \frac{\bar{\nu} + \bar{\mu}}{\bar{\nu} - \frac{\mu}{2}} - \frac{\bar{\nu} \Omega^2}{\bar{\nu} - \frac{\mu}{2}} (\Delta \xi_i^2/\alpha^2 + \bar{V}(x_i))$ from (3), while irrelevant for the phase diagram, must be kept when computing supercoiling. $L = Na$ is the length of the DNA. There are then purely geometrical parameters: $m = \frac{\bar{\mu}}{\alpha f}, \nu = \frac{\nu}{\alpha f}$, $\Omega = \frac{\alpha f}{\mu}$, $\nu = 1 - \frac{h_0}{a}$, where $R (= 10 \text{ Å})$ is the radius of the DNA molecule, $h_0 (= 3.4 \text{ Å})$ the elevation between consecutive nucleotides, $a (= 7 \text{ Å})$ their distance along the backbone, and $\Omega = 2\pi/10$ the pitch of DNA: these are established geometrical values for B-DNA, but our formalism works for A and Z forms.

The expression for $Z$ in (3) is exact within our model, and the resulting PB problem (or PBD if anharmonicity is included) is amenable to numerical transfer matrix treatment. Here we will proceed analytically. In the continuum limit, neglecting an irrelevant equipartition factor, and taking $L$ large, $Z$ in (3) can be written as

$$Z \sim e^{-\beta L \delta} \text{Tr} e^{-L \hat{H}}, \quad (5)$$

proportional to the trace of the operator

$$\hat{H} = -\frac{1}{2\kappa \beta} \hat{\Omega}^2 + \beta \hat{V}(x_i). \quad (6)$$

Torque, tension, and temperature enter the potential (4), and the critical surface corresponds [12] to the disappearance of the bound state for $\hat{H}$, or

$$\hat{\Omega}^2 - \frac{1}{2} \frac{\mu}{(\bar{\nu} + \bar{\mu})} \bar{\nu}^2 - \nu f + \frac{\alpha^2 f^2}{\bar{\nu} + \bar{\mu}} + \frac{T_D^2 - T^2}{\epsilon x_c} \quad (7)$$

where $\epsilon = 8kx_c/\pi^2$ has the dimension of an energy, $l = \ln[(\nu + \mu)/\nu]$, and $\hat{\Omega} = (\bar{\nu} + \bar{\mu})/(\nu + \bar{\mu})$ are pure numbers, and $T_D^2 = \epsilon x_c (V_0 - \frac{\nu}{\alpha f} + \frac{1}{2} \pi \Omega^2)$ is the denaturation temperature in the absence of torque or tension. There are only a few parameters to fit: a typical value for the denaturation temperature used in theoretical treatments [15,16] is $T_D \approx 350 \text{ K}$ [20]; we show below from data on torque-winding experiments that $\mu = 10^3 \text{ pN}$. Choosing the remaining three parameters as $\epsilon x_c = 45 \text{ pN \ Å}$, $\nu = 24 \text{ pN}$, and $n = 0.3$ provides a remarkably good fit for 10 experimental data points (20 numbers) [4] in the $f$ vs $\Gamma$ phase diagram of Fig. 2. The skewness of the critical lines can be quantified: from (7) one finds for $\Gamma_m = (\Gamma_c + \Gamma_r)/2$, the middle point between critical torques at given tension,

$$\Gamma_m = a \frac{\bar{\nu} + \bar{\mu}}{\mu} \bar{\nu} \Omega \approx a \nu \Omega + f \left( n \Omega - \frac{\alpha \nu}{\mu} \right) \quad (8)$$

independent of temperature. As (8) reveals, skewness results from backbones twisting under torque: it would be erroneously negative for $r = 0$. With our parameters,

$$\Gamma_m/(\text{pN nm}) = 11 + 92 \times 10^{-3} f/(\text{pN}) \quad (9)$$
As expected, negative torque destabilizes DNA, a property exploited in biology for DNA opening and replication. Solid (dotted) straight line indicates $\Gamma_m = a r \Omega$ (its approximation $\Gamma_m = 11 + 0.092 f$), the middle point between critical torques, which also corresponds to the highest critical temperature at given tension.

Equations (8) and (9) along with experimental data for DNA that place melting at $f = 15$ pN, for $\Gamma^+ = 34$ pN nm, $\Gamma^- = -10$ pN nm, and at $f = 60$ pN, for $\Gamma^+ = 33$ pN nm [4], predict melting at zero torque and tension $f = 60$ pN (blue square in Fig. 2) in good agreement with the observed overstretching transition (if no effective torque is exerted by the experimental apparatus, otherwise higher critical force is reported, consistent with Fig. 2 [19,21]). Our analysis implies a force-induced melting [21] rather than a transition to a double helix with distortions [22]. A positive torque stabilizes DNA even at temperatures above denaturation (Fig. 2, inset), a property exploited by thermophile bacteria living at high temperatures [1]. As expected, negative torque destabilizes DNA, a mechanism exploited in biology for DNA opening and replication.

Under a given stretch, the critical temperature increases (decreases) under positive (negative) torque, as shown in Fig. 3. From (7) we see that $T^c$ is maximized at $\Gamma = \Gamma_m(f)$, which therefore induces the most stable configuration at any temperature, for a certain tension $f$. The highest temperature B-DNA can withstand is achieved under zero tension and positive torque $\Gamma_m = a r \Omega = 11$ pN nm, and corresponds to $T_m = 91 \, ^\circ C$.

DNA supercoils for packaging inside cells [1]. This corresponds to small positive or negative torques; in that biological regime, the critical temperature decreases monotonically with an applied tension, in fact linearly, with slope independent of the applied torque or degree of supercoiling. Yet, for torques larger than about 32 pN nm, a regime accessible to single molecule manipulation experiments and potentially useful in nanotechnology, the maximal critical temperature corresponds to a nonzero tension, suggesting that at low temperatures and large torques DNA can be stabilized by tension (Fig. 4).

The average change in pitch is given by $\langle \omega \rangle = \int L^{-1} \beta^{-1} \partial \tau \ln Z = \tau / \nu - \Omega - T \partial \tau \epsilon_B$ ($\epsilon_B$ is the bound eigenvalue of the Hamiltonian (6), whereas the remainder comes from $\Delta$). Near the critical point we find

$$\langle \omega \rangle = \omega_D - \frac{\omega_D \Gamma_c}{\Omega} \frac{\Gamma_c c}{\partial \nu} + \left(1 + \frac{\omega_D}{\Omega} \frac{\Gamma_c}{\beta + \nu} - \frac{\Gamma_c}{\beta + \nu} \right) = \frac{\Gamma_c}{\beta + \nu} \frac{\Gamma_c}{\beta + \nu} - \Omega,$$

where $\omega_D$ is the small negative unwinding (typically $\omega_D \approx -10^{-4} \, \text{rad}$) at denaturation ($T = T_D$, $\Gamma = 0$, $f = 0$). Equation (10) can be used to fit, from experimental data [4], $\mu = 10^3$ pN. When neglecting small nonlinear corrections, (10) is also a good approximation for the torque versus pitch curve away from criticality. While the derivation of (10) will be presented elsewhere [19], we note here that a well potential on an infinite half line in (6) would generate no contribution from the bound eigenvalue $\epsilon_B$ to criticality, and thus give $\langle \omega \rangle = \frac{\Gamma_c}{\beta + \nu} - \Omega$, the expected behavior for separated strands. The discontinuity at criticality in $\langle \omega \rangle$ seen in experiments
In summary, a range of predictions and phenomena for DNA thermomechanics (critical lines, phase diagrams, supercoiling under loads, optimally stable torque, tension-induced stability at high torque) that were inaccessible to previous models, or were covered partially and numerically, have been explained here within a unifying framework amenable to analytical treatment and further extensions and applications. It will be interesting to test experimentally our predictions at higher than room temperatures, and also at different ionic strength.

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