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Entropy-driven DNA denaturation

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We present a nonlinear dynamical model for DNA denaturation which includes cooperativity effects through *anharmonic* nearest-neighbor stacking interactions. Transfer-integral calculations show that this one-dimensional model, without including long-range interactions, exhibits a sharp denaturation reminiscent of a first-order transition at a temperature lower than a similar model with harmonic coupling. Self-consistent phonon calculations point out the essential role of nonlinear effects in the mechanism.

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There is a growing appreciation that biomolecular structure is not sufficient to determine biological activity which is also governed by large-amplitude dynamics of a molecule [1]. DNA transcription is a typical example since the reading of the genetic code involves the propagation along the helix of a local opening which exposes the bases for chemical reaction. However, a microscopic theory of this basic process of life is still beyond our capabilities due to the complex role played by RNA polymerases in the mechanism. Since it involves a local denaturation of the double helix, a preliminary step for the understanding of the transcription is the study of DNA thermal denaturation. A semiquantitative understanding of DNA melting based on the Ising model of statistical physics has been available since the late 1960's [2] but a quantitative understanding of the transition remains elusive. Moreover, the Ising model, in which a base pair is considered as a two-state system being either closed or open, could not describe the dynamics of the precursor effects and, in particular, the large-amplitude fluctuational openings observed well below the denaturation temperature [3]. Adding to the statistical-mechanics analysis of the melting the ideas developed in the past few years that collective nonlinear excitations could play a large role in DNA dynamics [4], a simple model describing the nonlinear motions of the bases was proposed [5,6]. In the most reduced form of the model, each base pair is described by a single degree of freedom representing the stretching of the hydrogen bonds connecting the two bases. A transfer-integral (TI) approach showed that the model can exhibit a denaturation transition, and analytical investigations of its nonlinear dynamics suggested that intrinsic energy localization could initiate the denaturation. This was later confirmed in the model by molecular-dynamics simulations [7].

Although this nonlinear dynamical model exhibited a thermal behavior in qualitative agreement with the experiments, an essential feature was still missing. Namely, although DNA is essentially a one-dimensional (1D) system, the thermal denaturation of a homopolymer occurs in a remarkably narrow temperature range (a few K) [8], so that it seems to challenge the usual belief that phase transitions do not occur in 1D [9]. This peculiarity, which was not properly accounted for in our model, had been considered by Poland and Scheraga in 1965 (Ref. [10]) within the Ising description. They showed that an extremely sharp change in the population of closed states can occur in models in which certain types of many-body or long-range interactions exist. For DNA, the Ising model must include *cooperativity effects* which amount to saying that a closed base pair which is at the boundary of an open domain has a higher probability to open. Moreover, as shown in 1974 by Azbel [11], the winding entropy which is released when the two strands are separated contributes to the denaturation, which appears as an entropy driven phase transition [12]. However, these concepts appear in the Ising models through phenomenological parameters which have not been related to microscopic physical properties of the molecule such as the potential parameters linking its different components.

In this Rapid Communication, we show how the simple 1D model that we introduced previously for the nonlinear dynamics of DNA denaturation [5] can be modified to include the cooperativity effects in terms of a *nonlinear* contribution to the base-pair stacking interaction potential. This results in a dramatic change in the denaturation rate, i.e., the proportion of broken base pairs for a given temperature increase. Although we do not know analytically that this 1D model with nearest-neighbor interactions exhibits a true phase transition, numerically it shows a very sharp melting transition in good agreement with experimental observations. Moreover, while the previous model required unrealistically weak stacking interactions to avoid a too high denaturation temperature, the large entropy increase associated with melting in the presence of the nonlinear stacking interaction significantly lowers the denaturation temperature so that more realistic stacking potential parameters can be used.

Our model can be considered as a simple extension of the Ising models. Instead of a two-state variable, the status of each base pair n is described by the scalar variable y_n which represents the transverse stretching of the hydrogen bonds connecting the two bases. The Hamiltonian is

$$H=\sum_n\left[\tfrac{1}{2}m\dot{y}_n^2+V(y_n)+W(y_n,y_{n-1})\right] . \qquad (1)$$

The first term is the kinetic-energy term for bases of mass m. The on-site Morse potential $V(y_n)=D(e^{-ay_n}-1)^2$ represents not only the H bonds connecting two bases belonging to opposite strands, but also the repulsive interactions of the phosphates, and the surrounding solvent effects. The stacking energy between two neighboring base pairs is described by the anharmonic potential:

$$W(y_n,y_{n-1})=\frac{k}{2}(1+\rho e^{-\alpha(y_n+y_{n-1})})(y_n-y_{n-1})^2 . \qquad (2)$$

This new intersite coupling, replacing the simple harmonic coupling of our previous approach [5], is the essential feature of the model and is responsible for its qualitatively different properties. The choice of this potential has been motivated by the observation that the stacking energy is not a property of *individual* bases, but a character of the base *pairs* themselves [13]. When the hydrogen bonds connecting the bases break, the electronic distribution on bases is modified, causing the stacking interaction with adjacent bases to decrease. In Eq. (2), this effect is enforced by the prefactor of the usual quadratic term $(y_n-y_{n-1})^2$. This prefactor depends on the *sum* of the stretchings of the two interacting base pairs and decreases from $\frac{1}{2}k(1+\rho)$ to $\frac{1}{2}k$ when either one (or both) base pair is stretched. The qualitative features of potential (2) are in agreement with the properties of chemical bonds in DNA. They also provide the cooperativity effects that were introduced phenomenologically in the Ising models. A base pair which is in the vicinity of an open site has lower vibrational frequencies, which reduces its contribution to the free energy [14]. Simultaneously a lower coupling along the strands gives the bases more freedom to move independently from each other, causing an entropy increase which drives a sharp transition. Our approach can be compared to recent views on structural phase transition in elastic media which stress that intrinsic nonlinear features characterize the physics of these transformations, and extend the standard soft mode picture [15]. It is important to note that, although cooperativity is introduced through purely *nearest-neighbor* coupling terms, it has a remarkable effect on the 1D transition.

In order to make the above qualitative discussion precise, we have investigated the statistical mechanics of Hamiltonian (1) with the TI method. This provides exact results, including the full nonlinearities. The classical partition function may be factored as $\mathcal{Z}=\mathcal{Z}_p\mathcal{Z}_y$, where the kinetic part is the usual 1D partition function $\mathcal{Z}_p=(2\pi m k_B T)^{N/2}$. The potential part $\mathcal{Z}_y$ is expressed as $\mathcal{Z}_y=\sum_i e^{-\beta N\varepsilon_i}$ in terms of the eigenvalues of the symmetric TI operator [16]:

$$\int dy_{n-1}\exp(-\beta\{W(y_n,y_{n-1})+\tfrac{1}{2}[V(y_{n-1})$$

$$+V(y_n)]\})\phi_i(y_{n-1})=e^{-\beta\varepsilon_i}\phi_i(y_n) , \qquad (3)$$

ϕ_i being the eigenfunction associated with the eigenvalue ε_i. In the thermodynamic limit, $\mathcal{Z}_y$ reduces to $\mathcal{Z}_y=e^{-\beta N\varepsilon_0}$ (Ref. [17]) and the potential part of the free energy per particle is then given by $\mathcal{F}_y=-(k_BT/N)\ln\mathcal{Z}_y=\varepsilon_0$, where ε_0 is the lowest eigenvalue of the TI operator [18]. Owing to the presence of the nonlinear coupling and to avoid any continuum approximation (because realistic DNA parameter corresponds to rather large discreteness effects [3]), we numerically determined the spectrum of the TI operator [16] rather than relying on a pseudo-Schrödinger approximation [17]. Due to the Morse shape of the one-site potential, the spectrum of the TI operator contains both a discrete part and a continuum. As in the harmonic case, the melting is associated with the disappearance of bound states [5], and to a qualitative change of the eigenfunction associated with the lowest eigenvalue.

The mean stretching $\langle y\rangle$ of the hydrogen bonds is given by [5] $\langle y\rangle=\langle\phi_p(y)|y|\phi_0(y)\rangle=\int\phi_0^2(y)y\,dy$. This is shown versus temperature in Fig. 1 for two cases of harmonic stacking interactions with coupling constants k and $k(1+\rho)$ and for the anharmonic stacking potential (2). The denaturation is much sharper for the anharmonic case than for any harmonic stacking interaction, and furthermore the denaturation temperature is significantly

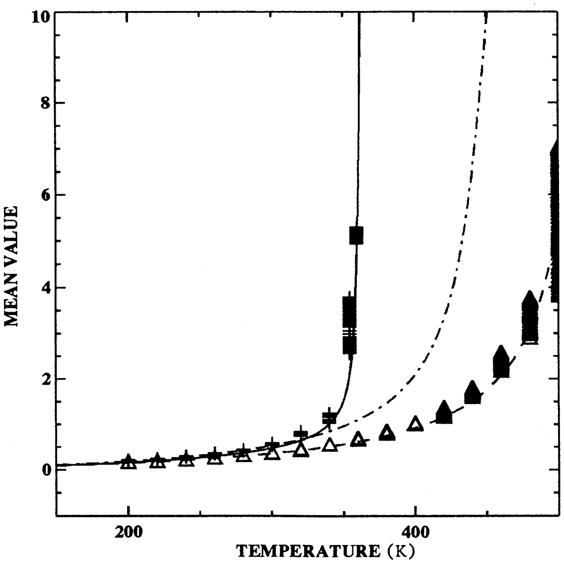

FIG. 1. Variation of the mean value $\langle y\rangle$ vs temperature for $k=0.04$ eV/Å, $D=0.04$ eV, $a=4.45$ Å^{-1}, $\alpha=0.35$ Å^{-1}, $m=300$ a.m.u., and $\rho=0.5$. The solid line corresponds to the anharmonic stacking interaction and the dashed and dash-dotted lines correspond to two cases of harmonic stacking interactions with coupling constant $k'=1.5k$ (which would correspond to $\alpha=0$, $\rho=0.5$) and $k''=k$ (which would correspond to $\alpha=0,\rho=0.0$), respectively. The plus signs correspond to molecular-dynamics simulations with the anharmonic stacking interactions and the triangles correspond to simulations for the harmonic coupling $k'=1.5k$.

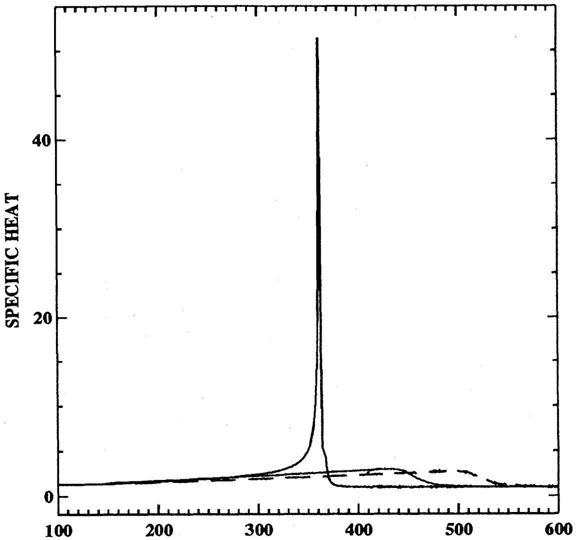

FIG. 2. Variation of the specific heat vs temperature. The very narrow peak corresponds to the anharmonic case ($\alpha=0.35, \rho=0.5$) and the dotted curve and the solid broad peak corresponds to harmonic coupling ($k'=1.5k$ and $k''=k$, respectively).

lowered in the anharmonic case. The difference between the behavior of the model with harmonic and anharmonic stacking interactions is even more striking in the specific heat shown in Fig. 2. While the curves present broad peaks, due to the 1D Schottky anomaly for harmonic coupling ($\alpha=0$), the anharmonic case exhibits an extremely sharp peak at $T=361.5$ K, which is very reminiscent of the behavior of a system undergoing a first-order transition. Whether or not the transition is truly first order (this can be destroyed by disorder anyway, especially in 1D), the TI results show that the thermal denaturation is extremely sudden in our model using a physically reasonable anharmonic nearest-neighbor interaction. It must be stressed that the qualitative change of behavior introduced by the anharmonic coupling is not due to special values of the parameters—the two harmonic coupling cases have been calculated for coupling constants corresponding to the maximum and minimum value possible in the anharmonic case. The thermal behavior of the model with anharmonic stacking interaction is in much better agreement with DNA denaturation curves than in the harmonic case.

The results of the TI calculation have been checked by molecular-dynamics simulations at temperatures constrained by the Nosé scheme [19]. The values of $\langle y \rangle$ deduced from the simulations are shown in Fig. 1. They are numerically in perfect agreement with the TI results. Besides this check, the molecular-dynamics simulations show that, while the coupling term (2) has a dramatic effect on the sharpness of the transition, it does not qualitatively affect the dynamics of the system in the vicinity of the transition. The results exhibit the same localization of energy leading to denaturation "bubbles" as with a harmonic coupling [7]. Details of nucleative events in the presence of the anharmonic springs will be discussed elsewhere.

Since the TI calculation indicates a spectacular influence from the anharmonicity, it is interesting to go beyond this numerical approach in order to obtain analytical results in the low- and high-temperature regimes and to better understand the denaturation mechanism. First, in the high-temperature regime the whole system is on the plateau of the Morse potential, with an effective harmonic coupling constant k. Therefore, the system being equivalent to a harmonic chain, without substrate potential we expect that its free energy will simply be

$$\mathcal{F}_y = -\frac{k_B T}{2} \sum_{p=1}^{N-1} \ln \frac{\pi k_B T}{2k \sin^2(\pi p/N)} \tag{4}$$

and the specific heat per particle in units of k_B will be equal to 1. Figures 1 and 2 show that, above the transition, this picture is correct.

In the low-temperature regime, introducing $u_n = y_n - \langle y \rangle = y_n - \eta$ and two variational parameters, Ω^2 and ϕ, we apply the self-consistent phonon (SCP) method, by considering the trial harmonic Hamiltonian

$$H_0 = \sum_n \left[\frac{1}{2} m \dot{u}_n^2 + \frac{\phi}{2}(u_n - u_{n+1})^2 + \frac{\Omega^2}{2} u_n^2 \right] . \tag{5}$$

At first order, the free energy of the system is bounded from above by [20]

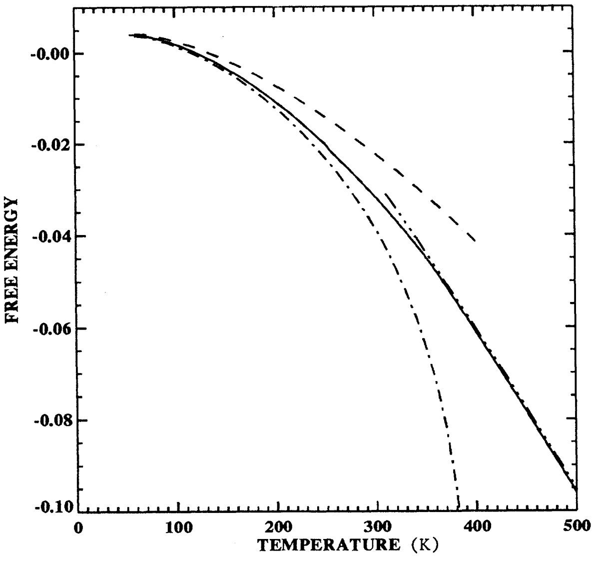

FIG. 3. Variation of the free energy vs temperature for the anharmonic coupling case ($\alpha=0.35, \rho=0.5$). The solid line corresponds to the exact free energy calculated with the TI method, the dashed line corresponds to the first-order SCP result, the dash-dotted line corresponds to the second-order SCP, and the dash-dot-dot-dot line corresponds to the high-temperature harmonic approximation. Note that while the first-order SCP method is necessarily an upper bound of the exact free energy, this is not required for the second-order approximation.

$$\mathcal{F} \leq -k_B T \ln Z_0 + \langle H - H_0 \rangle$$
$$= -\frac{k_B T}{2} \sum_{p=0}^{N-1} \ln \frac{2\pi k_b T}{\Omega^2 + 4\phi \sin^2(\pi p/N)} + \mathcal{F}_1 \ , \qquad (6)$$

where Z_0 is the partition function for the trial Hamiltonian and the mean value is calculated with this approximate Hamiltonian. Minimizing expression (6) with respect to η, $\langle u^2 \rangle = \langle u_n^2 \rangle$ and $\langle v^2 \rangle = \langle u_n u_{n-1} \rangle$, we obtain three equations which have to be solved self-consistently. This system has a solution for $T < 400.9$ K which appears as the transition temperature for the SCP calculation. The resulting first-order expression for the free energy is

$$\mathcal{F}_1 = D + De^{-a\eta + (a^2/2)\langle u^2 \rangle}[(a^2 + a\alpha)\langle u^2 \rangle - a\alpha \langle v^2 \rangle - 2]$$
$$+ De^{-2a\eta + 2a^2 \langle u^2 \rangle}[-(a\alpha + 2a^2)\langle u^2 \rangle + a\alpha \langle v^2 \rangle + 1]. \qquad (7)$$

As shown in Fig. 3, the agreement with the exact TI result is poor except at very low temperature because, given the even parity of H_0, the first-order expression of $\mathcal{F}$ averages out all the odd terms of the Morse potential. Although the calculation is tedious, the second-order correction for the free energy [20,21],

$$\mathcal{F}_2 = -[\langle (H - H_0)^2 \rangle - \langle H - H_0 \rangle^2]/2k_B T \ , \qquad (8)$$

can be calculated analytically exactly for our model. The result is too long to be given here but Fig. 3 shows that it significantly improves the agreement with the exact results up to about 250 K (with our parameter set). However, the SCP calculation still fails in the vicinity of the melting transition, emphasizing the fundamental role of the nonlinear effects in the denaturation: they cannot be described, even approximately, by a harmonic trial Hamiltonian with temperature-dependent coefficients.

In summary, the model that we have discussed here shows that the cooperative effects that had been introduced phenomenologically in the Ising models of DNA denaturation can be justified at a microscopic level by an appropriate anharmonic stacking interaction potential. This reflects the change in the electronic distribution on the bases when the hydrogen bonds are broken. With this interaction, the systems shows a very sharp melting transition at a substantially reduced temperature. The SCP calculation can be performed analytically up to second order and shows the essential role of the nonlinear effects in the vicinity of the transition. Besides its interest as a step toward the understanding of DNA transcription, this model shows that a simple 1D system with suitable nonlinear nearest-neighbor coupling can exhibit a very sharp transition. Although it does not contradict the well-known result that there are no phase transitions in 1D systems with short-range interactions, this example points out that, in some cases, such systems can support a very sharp transition as the analysis of Morris and Gooding [22] predicted.

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