

Thermodynamics of a nonlinear model for DNA denaturation

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We study a model for the dynamical stretching of DNA which uses the stretching of the hydrogen bonds in a base-pair as its main variable. We present a statistical mechanical analysis of the denaturation and specific heat curves, obtained with the transfer integral method; discreteness effects are treated exactly by a numerical solution of the transfer integral operator. Second order self-consistent phonon theory agrees with the exact transfer integral results in the low and intermediate temperature range and explains the phonon softening observed in the molecular dynamics simulations. When the temperature approaches the denaturation temperature, the second order self-consistent phonon results deviate significantly from the exact ones, pointing to the fundamental role of nonlinear processes in DNA denaturation.

1. Introduction

The discovery of DNA structure has highlighted the fundamental relationship between structure and function in molecular biology. Molecular dynamics has perhaps been at the origin of this new attitude [1] because it has shown that chemical reactions that seem to be impossible according to the molecular structure might indeed take place due to temporary large molecular distortions.

DNA transcription is a typical example in which the dynamics of the molecule is essential to a biological function since the double helix has to be locally opened in order to expose the coding bases to chemical reactions. This process, however, is very complex because it is activated by an enzyme and it is probably still beyond a detailed analysis. Thermal denaturation has some similarities with the transcription because it starts locally by the formation of a so-called “denaturation bubble” similar to

the local opening occurring in the transcription. Therefore investigating thermal denaturation is a valid preliminary step toward the understanding of the transcription. At temperatures well below the denaturation temperature, DNA shows also large amplitude motions known as “fluctuational openings” in which base pairs open for a very short time and then close again. These motions are important because, when the base pairs reclose they can trap some external molecules causing a defect in the sequence. These large amplitude motions can be considered as intrinsic precursors to the denaturation.

The denaturation or “melting” transition is the separation of the two complementary strands. It can be induced by heating or by changing the ionicity of the solvent. It has been extensively investigated experimentally and models have been proposed to explain the complicated denaturation curves found in the experiments [2]. However these models are essentially Ising-like, where a base pair is considered as a two-state system which is either closed or open. Such an approach cannot reproduce the full dynamics of the denaturation and it relies on phenomenolog-

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ical parameters for the probability of opening or cooperative character of this opening, which are not easily derivable from first principle calculations.

On the other hand, many investigations of DNA dynamics have been based on the idea that vibrational energy might be trapped into solitary wave excitations. This idea, originally suggested by Englander et al. [3] to explain the open states of the DNA molecule, has given rise to numerous investigations using soliton-like solutions to describe open states, transition between the *A* and *B* forms, or energy transport along the molecule [4–6]. Most of these investigations have focused on the *propagation* of solitons along the double helix. However, the biological function of DNA does not necessarily involve transport along the molecule. Consequently, although it is clear that a realistic model will exhibit nonlinear excitations owing to the very large amplitude motions known to exist, their ability to propagate along the helix is not a requirement of the model. Rather, for denaturation (and transcription) we are concerned by the *formation and growth* of these excitations. It is this question that we want to investigate in this paper. This is an extension to nonlinear dynamics of the Ising models mentioned above. As in the Ising models, however our approach uses a very simple description of the molecule restricted to the most relevant degrees of freedom.

The model was introduced in previous work [7] in which we investigated its statistical mechanics and determined its denaturation temperature in a continuum limit. Numerical simulations have shown that when parameters which are expected to be representative of DNA are used, discreteness effects are very important. For this reason, we have extended the statistical mechanics investigations to take into account the intrinsic discreteness of the molecule. Section 2 introduces the model. Exact numerical results for its thermodynamics, obtained with the transfer integral approach are presented in section 3 to determine the statistical mechanics of

the model. Finally, in section 4 a self-consistent phonon theory is used to discuss some of these results, provide an analysis of the melting process, and present useful analytical expressions for some thermodynamical functions in the low and high temperature regimes.

2. Model

In our model we consider a simplified geometry for the DNA chain, in which we neglect the asymmetry of the molecule and we represent each strand by a set of point masses which correspond to the nucleotides. The main characteristics of the model are as follows:

(i) We only take into account transverse motions. The displacements from equilibrium of the *n*th nucleotide is denoted by u_n for one chain and v_n for the other. The longitudinal displacements are not considered because their typical amplitudes are significantly smaller than the amplitudes of the smaller ones [8].

(ii) Two neighboring nucleotides belonging to the same strands are connected by an harmonic potential. The bonds connecting two bases belonging to different strands are extremely stretched when the double helix opens locally: their nonlinearity must not be ignored. We use a Morse potential which represents not only the hydrogen bonds but the repulsive interactions of the phosphate ions, partly screened by the surrounding solvent as well.

The Hamiltonian for the model is then the following:

$$H = \sum_n \left\{ \frac{1}{2} m (\dot{u}_n^2 + \dot{v}_n^2) + \frac{1}{2} K [(u_n - u_{n-1})^2 + (v_n - v_{n-1})^2] + D (e^{-a\sqrt{2}(u_n - v_n)} - 1)^2 \right\}. \quad (1)$$

When it is expressed in terms of the variables $x_n = (u_n + v_n)/\sqrt{2}$ and $y_n = (u_n - v_n)/\sqrt{2}$, it decouples into two parts:

$$\begin{aligned}
H = \sum_n & \left[\frac{1}{2} m \dot{x}_n^2 + \frac{1}{2} K (x_n - x_{n-1})^2 \right] \\
& + \left[\frac{1}{2} m \dot{y}_n^2 + \frac{1}{2} K (y_n - y_{n-1})^2 \right] \\
& + D (e^{-ay_n} - 1)^2. \tag{2}
\end{aligned}$$

The component of the Hamiltonian depending on the variable x_n corresponds to a harmonic chain without substrate potential: it is well behaved, and it is not coupled to the other one. We can ignore this term. The part of (2) dependent on the y_n we are interested in, has a much more interesting behavior as attested by molecular dynamics simulation at constrained temperature [9].

The choice of appropriate model parameters is a very controversial topic, currently debated in the literature [10]. There are well established force fields for molecular dynamics of biological molecules, but they have been designed to provide a good description of the *small* amplitude motions of the molecule and are not reliable for the very *large* amplitude motions involved in the denaturation. In our model, the Morse potential is an effective potential which links the two strands. It results from a combination of an attractive part due to the hydrogen bonds between two bases in a pair and the repulsive interaction between the charged phosphate groups on the two strands. The potential for the hydrogen bonds can be rather well estimated [11], but the other part is not well known. We have chosen a parameter set which gives realistic properties for the model when it is investigated by molecular dynamics, however, future work has to be done to confirm this choice. We do not expect, however, that a better choice would change *qualitatively* the results discussed here. The parameters that we have chosen are: a dissociation energy $D = 0.04$ eV, $a = 4.45 \text{ \AA}^{-1}$, a coupling constant $K = 0.06$ eV/\AA, and a mass $m = 300$ atomic mass units.

3. Transfer operator method

In this section we use the transfer operator method as it applies to the calculation of the classical canonical partition function, because it provides exact results, including the full nonlinearities. For a chain containing N units, the classical partition function, given in terms of the Hamiltonian (2), may be factored as

$$\mathcal{Z} = \int_{-\infty}^{+\infty} \prod_{n=1}^N dy_n dp_n e^{-\beta H} = \mathcal{Z}_p \mathcal{Z}_y. \tag{3}$$

The momentum part is readily integrated to give the familiar kinetic factor for N particles $\mathcal{Z}_p = (2\pi m k_B T)^{N/2}$. Since the coupling involves only nearest neighbor interactions, \mathcal{Z}_y can be expressed in the form

$$\mathcal{Z}_y = \int_{-\infty}^{+\infty} \prod_{n=1}^N dy_n e^{-\beta f(y_n, y_{n-1})}, \tag{4}$$

where f denotes the potential energy in y_n of the Hamiltonian (2). This integral (4) can be evaluated exactly in the thermodynamic limit of a large system ($N \rightarrow \infty$) using the eigenfunctions and eigenvalues of the transfer integral operator [12–14]

$$\begin{aligned}
& \int dy_{n-1} e^{-\beta f(y_n, y_{n-1})} \phi_i(y_{n-1}) \\
& = e^{-\beta \epsilon_i} \phi_i(y_n). \tag{5}
\end{aligned}$$

The calculation is similar to the one performed by Krumhansl and Schrieffer [13] for the statistical mechanics of the ϕ^4 field. It yields $\mathcal{Z}_y = \exp(-N\beta\epsilon_0)$, where ϵ_0 is the lowest eigenvalue of the operator. We can then compute the free energy of our model as the sum of the different contributions in \mathcal{Z}

$$\begin{aligned}
\mathcal{F} & = -k_B T \ln \mathcal{Z} \\
& = -\frac{N k_B T}{2} \ln(2\pi m k_B T) + N\epsilon_0. \tag{6}
\end{aligned}$$

From this result we can derive the specific heat $C_v = -T \partial^2 \mathcal{F} / \partial T^2$, the quantity which is characteristic of the thermal denaturation is the mean stretching $\langle y_m \rangle$ of the hydrogen bonds, which is given by

$$\begin{aligned} \langle y_m \rangle &= \frac{1}{Z} \int \prod_{n=1}^N y_m e^{-\beta H} dy_n dp_n \\ &= \frac{1}{Z_y} \int \prod_{i=1}^N y_m e^{-\beta f(y_n, y_{n-1})} dy_n. \end{aligned} \quad (7)$$

As the model is assumed to be homogeneous, the result does not depend on the particular site m considered. The integral can again be calculated with the transfer integral method [12] and yields

$$\begin{aligned} \langle y \rangle &= \langle y_m \rangle \\ &= \frac{\sum_{i=1}^N \langle \phi_i(y) | y | \phi_i(y) \rangle e^{-N\beta\epsilon_i}}{\sum_{i=1}^N \langle \phi_i(y) | \phi_i(y) \rangle e^{-N\beta\epsilon_i}} \\ &= \langle \phi_0(y) | y | \phi_0(y) \rangle \\ &= \int \phi_0^2(y) y dy, \end{aligned} \quad (8)$$

since in the limit of large N , the result is again dominated by the lowest eigenvalue ϵ_0 associated with the normalized eigenfunction $\phi_0(y)$.

In the continuum limit approximation, the transfer integral eigenvalue problem can be reduced to a Schrödinger-like equation [7]. When temperature is lower than $T_d = 2\sqrt{2KD}/ak_B$, the equation has a discrete spectrum which corresponds to localized eigenfunctions; for T exceeding T_d , they correspond to delocalized states and $\langle y \rangle = \langle y_m \rangle$ diverges so that T_d appears as the melting temperature. However the results are not in good agreement with the numerical results because the discreteness is too important. We must take into account the intrinsic discreteness of the Hamiltonian. Small discreteness effects have been treated by a perturbative approach [15], but here we consider a physical system in which the discreteness effects can be extremely large. Therefore we have solved numerically the eigenvalue equation for

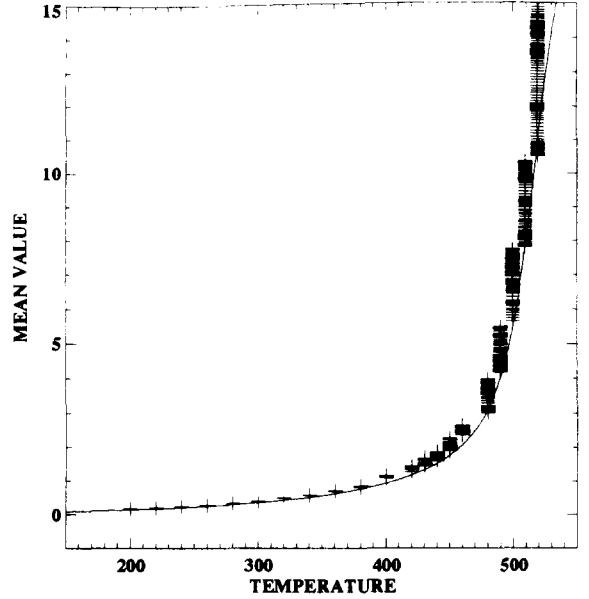


Fig. 1. Variation of $\langle y \rangle$ versus temperature: the solid line corresponds to the transfer integral results and the plus signs correspond to molecular dynamics simulations.

the transfer integral operator. The operator is symmetrized and the integrand is expressed as a discrete sum by a standard numerical integration formula [16] (we have tested different orders). The problem is then equivalent to finding the eigenvalues and eigenvectors of a symmetric matrix. The results obtained in this process are in good agreement with the numerical simulations as shown in fig. 1.

In fig. 2 we show the specific heat versus the temperature which also shows a good agreement with the MD results.

4. Self-consistent phonon (SCP) method

Because the Schrödinger equation approximation to find the eigenvalues of the transfer operator breaks down, we are not able to find an analytical expression for the thermodynamical functions, and particularly for the free energy. Therefore we applied the self-consistent phonon (SCP) method [17], which can give us not only

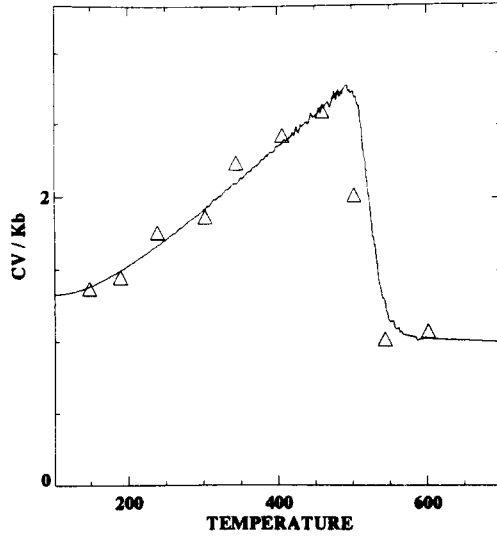


Fig. 2. Variation of the specific heat versus temperature: the solid line corresponds to the transfer integral results and the signs correspond to molecular dynamics simulations.

approximate thermodynamic expressions, but also the dependence of the phonon frequencies on the temperature. The explicit evaluation of the second order correction gives successful results away from the actual transition region.

In the low temperature regime, introducing $u_n = y_n - \langle y \rangle = y_n - \eta$ and two parameters Ω^2 and ϕ , we apply the SCP method [18], by considering the trial harmonic Hamiltonian

$$H_0 = \sum_n \left(\frac{1}{2} m \dot{u}_n^2 + \frac{1}{2} \phi (u_n - u_{n+1})^2 + \frac{1}{2} \Omega^2 u_n^2 \right). \quad (9)$$

The canonical partition function \mathcal{Z} can be expressed as the product of the unperturbed partition function \mathcal{Z}_0 and the perturbation factor \mathcal{Z}_1 :

$$\begin{aligned} \mathcal{Z} &= \int \prod_i du_i e^{-\beta V} \\ &= \left(\int \prod_i du_i e^{-\beta H_0} \right) \langle e^{-\beta(H-H_0)} \rangle_0 \\ &= \mathcal{Z}_0 \mathcal{Z}_1. \end{aligned}$$

The perturbation series for \mathcal{Z}_1 is obtained by expanding the exponential, and the logarithmic function; the coefficient of $(-\beta)^n/n!$ in the expansion of $\ln \mathcal{Z}_1$ is termed the n th cumulant and is written [19] $\langle (H - H_0)^n \rangle_{0,c}$. Thus

$$\begin{aligned} \mathcal{F} &= -k_B T \ln \mathcal{Z} \\ &= -k_B T \ln \mathcal{Z}_0 - k_B T \ln \langle e^{-\beta(H-H_0)} \rangle_0 \\ &= N \mathcal{F}_0 - k_B T \sum_{n=1}^{\infty} \frac{(-\beta)^n}{n!} \langle (H - H_0)^n \rangle_{0,c} \\ &= N (\mathcal{F}_0 + \mathcal{F}_1 + \mathcal{F}_2 + \dots). \end{aligned}$$

The first contribution \mathcal{F}_0 gives the contribution of N harmonic oscillators of frequency

$$\omega^2(p) = \Omega^2 + 4\phi \sin^2 \left(\frac{\pi p}{N} \right),$$

and its contribution to the free energy is

$$\mathcal{F}_0 = \frac{-k_B T}{2} \sum_{q=0}^{N-1} \ln \frac{2\pi k_B T}{\omega^2(p)}. \quad (10)$$

Introducing the parameters η , $\langle u^2 \rangle = \langle u_n^2 \rangle$ and $\langle v^2 \rangle = \langle u_n u_{n+1} \rangle$, the only difficulty in evaluating \mathcal{F}_v is the self-consistent substrate potential. Expanding the exponent in a series as

$$\begin{aligned} \langle e^{-a u_k} \rangle &= \left\langle \sum_p \frac{(-a)^p}{p!} u_k^p \right\rangle \\ &= \sum_p \frac{(-a)^{2p}}{(2p)!} \langle u_k^{2p} \rangle + \sum_p \frac{(-a)^{2p+1}}{(2p+1)!} \langle u_k^{2p+1} \rangle \\ &= \sum_p \frac{(-a)^{2p}}{(2p)!} \frac{(2p)!}{2^p p!} \langle u_k^2 \rangle^p + 0 \\ &= e^{a^2 \langle u^2 \rangle / 2}. \end{aligned} \quad (11)$$

we obtain an “effective” potential, which keeps the shape of the Morse one, but with a temperature dependent minimum, as shown in fig. 3a. The expression for the first order correction for the free energy is then

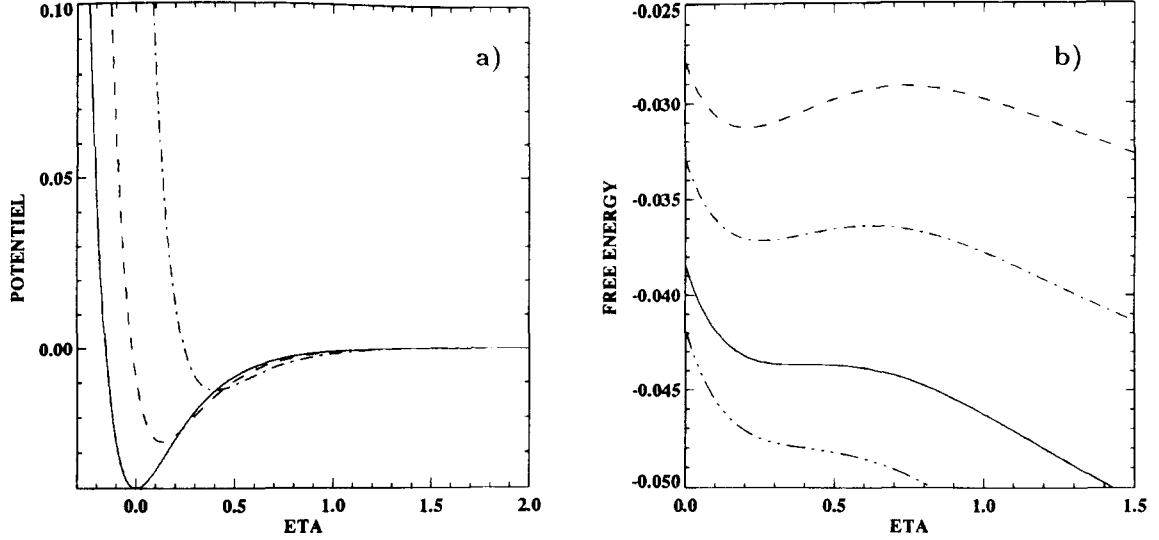


Fig. 3. (a) Substrate potential in the SCP approximation for a 1D chain of Morse oscillators coupled by harmonic springs. The potential is plotted for the 3 following values of $\langle u^2 \rangle = 0$ (solid curve), 0.02 (dashed), 0.06 (dash-dot) \AA^2 (which corresponds to the 3 temperatures $T = 0, 275, 411$ K). (b) Free energy \mathcal{F}_v versus η at different temperatures: $T = 350$ (dashed), 380 (dash-dot), 411 (solid), 430 (dash-dot-dot-dot) K.

$$\begin{aligned} \mathcal{F}_1 = & (K - \phi)(\langle u^2 \rangle - \langle v^2 \rangle) - \frac{1}{2}\Omega^2 \langle u^2 \rangle \\ & + D(1 + e^{-2a\eta + 2a^2 \langle u^2 \rangle}) \\ & - 2e^{-a\eta + a^2/2 \langle u^2 \rangle}. \end{aligned} \quad (12)$$

The variational free energy gives an upper bound of the actual free energy [20]:

$$\mathcal{F} \leq \mathcal{F}_0 + \mathcal{F}_1 = \mathcal{F}_v. \quad (13)$$

Considering η , $\langle u^2 \rangle$ and $\langle v^2 \rangle$ as *variational* parameters, \mathcal{F}_v is minimized. The stationarity equations of \mathcal{F}_v are then equivalent to the system

$$\begin{aligned} \eta &= \frac{3}{2}a\langle u^2 \rangle \\ \phi &= K, \\ \Omega^2 &= 2a^2D e^{-2a\eta/3}. \end{aligned} \quad (14)$$

We can note that Ω^2 is temperature-dependent while K is not, which means that the coupling constant is not renormalized because of the anharmonicities of the substrate potential. The phonon dispersion curve is just translated parallel to the frequency axis as the temperature

is varied. As η is an increasing function of the temperature, Ω^2 is a decreasing function of T and the phonons will soften as T is raised, in agreement with molecular dynamics and experiments.

Using the system (14), we can simplify the expression for the first order correction of the free energy to obtain

$$\mathcal{F}_1 = D[1 - (1 + \frac{2}{3}a\eta) e^{-2a\eta/3}]. \quad (15)$$

Since $\langle u^2 \rangle$ and η are related, we have only to solve self-consistently the equation

$$\begin{aligned} \eta &= \frac{3ak_B T}{2N} \\ &\times \sum_p \frac{1}{2a^2D e^{-2a\eta/3} + 4K \sin^2(\pi p/N)}. \end{aligned} \quad (16)$$

In practice, eq. (16) is solved by a simple bisection method and fig. 3b shows the free energy \mathcal{F}_v versus η at different temperatures. We see clearly that the self-consistent solution which

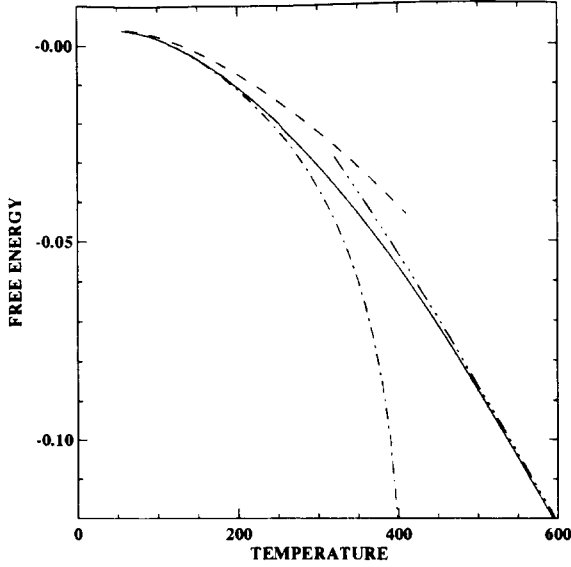


Fig. 4. Variation of the free energy versus temperature. The solid line corresponds to the exact free energy calculated with the transfer integral method, the dashed line to the first order SCP result, the dash-dotted line to the second order SCP, and the dash-dot-dot-dot line to the high-temperature harmonic approximation. Note that while the first order SCP method is necessarily an upper bound to the exact free energy this is not a constraint for the second order approximation.

corresponds to the metastable minimum of the dashed and dash-dotted curves, disappears at $T_c = 411$ K to give a strictly decreasing function of η . Over T_c , the minimum is only obtained for an infinite value of η , which does not correspond to a self-consistent solution of the problem. Consequently, T_c can be identified as the denaturation temperature given by SCP. We can note that at this temperature there is still a small well in the substrate potential of fig. 3a, but not deep enough to support a bound state, i.e., a localized state.

In fig. 4 we compare \mathcal{F}_v and the exact transfer integral result \mathcal{F} as function of T . The approximation is good at low temperatures. As the temperature rises, the approximation becomes poor. Because of the even parity of the trial Hamiltonian H_0 , the infinity of odd powers in the potential do not contribute to \mathcal{F}_1 . In order to obtain

a more accurate expression, we must therefore calculate the second order correction \mathcal{F}_2 to the free energy. It can be expressed as

$$\begin{aligned} \mathcal{F}_2 &= \frac{\langle (H - H_0)^2 \rangle - \langle H - H_0 \rangle^2}{-2Nk_B T} \\ &= \frac{D^2}{2k_B T} e^{-4a\eta/3} \sum_{\ell} (2 e^{a^2 \langle u_1 u_{\ell} \rangle} - 1)^2 \\ &\quad - e^{4a^2 \langle u_1 u_{\ell} \rangle} + 2a^4 \langle u_1 u_{\ell} \rangle^2, \end{aligned}$$

where

$$\langle u_1 u_{\ell} \rangle = \frac{1}{N\beta} \sum_p \frac{\cos(2\pi p(l-1)/N)}{\Omega^2 + 4K \sin^2(\pi p/N)}.$$

Fig. 4 shows that \mathcal{F}_2 significantly improves the agreement with the exact results up to about 300 K. However the SCP calculation still fails for higher temperatures, emphasizing the fundamental role of the non-perturbative nonlinear effects in the denaturation process.

The very high temperature regime is again simple because the whole chain is on the plateau of the Morse potential, with an effective harmonic coupling constant K . Therefore, the system is equivalent to an harmonic chain, without substrate potential and its free energy is simply

$$\mathcal{F}_{HT} = -\frac{k_B T}{2} \sum_{p=1}^{N-1} \ln \frac{\pi k_B T}{2K \sin^2(\pi p/N)} \quad (17)$$

and the specific heat per particle, in units of k_B , is equal to 1. Figs. 2 and 4 show that, above the transition, this picture is indeed correct.

5. Conclusion

The model that we have discussed can be considered as an extension of the Ising-like models for DNA melting which includes a degree of freedom that describes the dynamics of the nucleotide motion. Therefore it can represent not only denaturation, but also precursor effects like fluctuational openings, which are a

potential guide to the mechanism of denaturation. Two complementary methods were used to study the statistical mechanics of this model. The transfer integral method has confirmed that the lattice discreteness effects are large enough to change significantly the results, whereas the SCP method has emphasized the dominant effects of the nonlinearity in a precursor regime near the transition. The use of the second order correction to the free energy gives us a useful approach to obtaining analytical expressions for thermodynamic functions. But this simple model is still not complete: the transition occurs at a quite high temperature and over a too large temperature range. This suggests that the model lacks a sufficiently efficient mechanism for an energy localization. As a step to address this problem, we have recently implemented anharmonic nearest neighbor interactions [21]; with this interaction the system shows a very sharp melting transition at a substantially reduced temperature, in good agreement with experimental observations.

Acknowledgement

The authors wish to acknowledge helpful and instructive discussions with S. Aubry, C. Reiss and C.R. Willis. Two of us (T.D. and M.P.) are grateful for the hospitality of the Theoretical Division and the Center for Nonlinear Studies of Los Alamos National Laboratory. This work was performed with computing resources of the Advanced Computing Laboratory of Los Alamos National Laboratory. Part of the work has been supported by the CEC under contract SC1-CT91-0705. Work at Los Alamos is under the auspices of the US DOE.

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