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Statistical Model to DNA Melting

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ABSTRACT: We explore a DNA statistical model to obtain information about the behavior of the thermodynamics quantities. Special attention is given to the thermal denaturation of this macromolecule.

KEYWORDS: DNA, melting denaturation, statistical model for macromolecules.

Introduction

DNA macromolecule properties have been intensely studied in the last decades.

Experimental results and theoretical models has appeared and contributed both to a better understanding of this complex system (see, for example[8,13]).

A special attention has been given to the DNA transcription. This process has some similarities with thermal denaturation. There are evidences that both start from local opening in the double helix. Therefore, the study of thermal denaturation is a preliminary step towards the investigation of the transcription. The thermal denaturation or melting is the separation of the two complementary ribbons by heating the system.

A simple model describing the statistical mechanics of the melting and the non-linear motions of the bases was proposed in ref.[12]. Recently, modifications in this model were introduced[1,2] in order to construct a more detailed description of DNA macromolecule. In ref.[2], for instance, the discrete case is investigated and the results are compared with the continuum original model.

In this work the model before thermal denaturation proposed in ref.[12] is adopted and we suggest that after the melting each ribbon is treated in separate. This approach gives a different mathematical description for DNA in two cases: before and after the thermal denaturation. The model, with parameters fixed in previous works[1,2,4], gives the melting temperature consistently with experimental data[13]. The free energy and specific heat are analytically determined.

The model

The model adopted here for DNA macromolecule is based on Peyrard and Bishop work[12]. This model is planar and composed of two ribbons jointed by H-bond between adjacent nucleotides. Each ribbon is a spring-mass system where the nucleotides are represented by equal mass (m) and are connected by elastic springs of spring constant k. The H-bonds are simulated by non-harmonic potential, namely the Morse one[1,12], although other potentials have been used for this purpose[6,15].

The Hamiltonian for this model is

$$H_I=\sum_{n}\{(½)m(\dot{u}_n^{2}+\dot{v}_n^{2}) + (½)k[(u_n - u_{n-1})^2 + (v_n - v_{n-1})^2] + V(u_n - v_n)\} \qquad (1)$$

where u_n e v_n are the transverse displacement for each mass in the ribbons, the indices n represents the n-th nucleotide. V $(u_n - v_n)$ is the potential for H-bond interaction. The longitudinal displacement is not considered here because their amplitudes are typically smaller than the amplitude of the transverse one[2]. The equation[8] can be written in terms of the variables $x_n = (u_n + v_n)/\sqrt{2}$ and $y_n = (u_n - v_n)/\sqrt{2}$ as

$$H_I = \sum_{n} \{(½)p_n^2/m + (½)k(x_n - x_{n-1})^2 + (½)q_n^2/m + (½)k(y_n - y_{n-1})^2 + V(y_n)\} \qquad (2)$$

where $p_n = m\dot{x}_n$ and $q_n = m\,\dot{y}_n$

The partition function for N pair of bases is

$$Z_I = \prod_{n=1}^{N} \int dp_n dq_n dx_n dy_n e^{-\beta H} \qquad (3)$$

where b = $1/(k_B T)$, k_B is the Boltzmann§ constant and T is the absolute temperature.

This function may be factored as $Z_I = Z_p Z_q Z_x Z_y$, where the kinetic parts are the usual one dimension partition function $Z_p = Z_q = \{2pmk_B T\}^{N/2}$. The term Z_x after integration of gaussian-like function results in $Z_x = [2pk_B T/k]^{N/2}$.

The coupling between the two ribbons involves only the nearest neighbor interaction. Then, Z_y can be expressed as

$$Z_y = \int_{-\infty}^{\infty} \prod_{n=1}^{N} dy_n\, e^{-\beta f(y_n, y_{n-1})} \qquad (4)$$

where $f(y_n, y_{n-1})$ is the potential energy in y coordinates.

The transfer integral operator is used to evaluate exactly the integral (4) in the thermodynamic limit of a large system (N ® ¥) [3,12]. The transfer integral operator is written as

$$\int_{-\infty}^{\infty} dy_{n-1}\, e^{-\beta f(y_n, y_{n-1})}\, \phi_i(y_{n-1}) = e^{-\beta\varepsilon_i}\, \phi(y_n) \qquad (5)$$

and the calculations for large system yields

$$Z_y = e^{-N\beta\varepsilon_0} \qquad (6)$$

where e_o is the lowest eingenvalue of the operator. In the continuum limit approximation, the method reduced the problem to solve a Schrödinger –like equation;

$$[-1/(2\beta^2 k)]\partial^2\phi_i/\partial y^2 + V(y)\,\phi_i(y) = (\varepsilon - s_o)\,\phi_i(y) \qquad (7)$$

with s_o = (1/2b)ln(bk/2p). This equation is formally identical to the Schrödinger equation and the potencial V(y) represents the H-bond interaction.

As usual[11,12] we adopt the Morse potential to simulate H-bond interaction in our analysis. Then, the equation (7) can be rewritten as

$$[-1/(2\beta^2 k)]\partial^2\phi_i/\partial y^2 + D(e^{2ay} - 2e^{-ay})\,\phi_i(y) = (\varepsilon - s_o - D)\,\phi_i(y) \qquad (8)$$

where $V(y) = D(e^{-ay} - 1)^2$ is the Morse potential. The determination of the parameters D and a for this potential and the spring constant k to stacking interaction is not a trivial matter[7,14]. We adopt here the parameters indicated in ref.[1,2,4], which have been used to study several dynamics and statistical proprieties of DNA macromolecule.

The mean stretching áyñ gives a measure of the extent of denaturation of the DNA macromolecule. Using the transfer integral method[3,12] áyñ can be calculated as:

$$\langle y\rangle = \langle \phi_o(y)\,|\,y\,|\,\phi_o(y)\rangle = \int y\,\phi^2_o(y)\,dy \qquad (9)$$

remembering that, for large systems, the result is again dominated by the lowest energy eigenvalue with the eigenfunction $f_o(y)$.

The equation (8) is similar to Schrödinger equation for a particle in one-dimensional Morse potential. This equation has exactly analytical solution[5,10] and we get a discrete or a continuum spectrum. In this case, different from the usual Schrödinger equation, the solutions are temperature dependent ones.

There is a specific temperature T_d that can be used to classify the spectrum. For temperatures below T_d the spectrum is discrete and corresponds to bond states. On the other hand, for T ñ T_d, the spectrum is continuum and corresponds to delocalized states. Then, it is natural to consider T_d as the denaturation temperature[2,4]. The melting temperature can also be determined by analyzing a plot of áyñ vs temperatures. The divergence in the curve indicates the denaturation.

The normalized ground state eingenfunction of Schrödinger-like equation (8) is known[12] and can be written as

$$\phi_o(y) = (\sqrt{2a})^{1/2}[(2d)^{d-1/2}/\Gamma(2d-1)]\{\exp[-d\exp(\sqrt{2}\,ay)]\}\{\exp[-(d-1/2)(\sqrt{2}\,ay)]\} \quad (10)$$

where G(2d-1) is a usual gamma function and $d = (ba)(2kD)^{1/2}$ must be greater than ½ in order to obtain a " bound" state. Using this condition we obtain the value of T_d:

$$2\sqrt{2kD}/(ak_B) = T_d \quad (11)$$

Then, for $T < T_d$ the energies have discrete values and the two ribbons are jointed by the H-bonds. The ground state energy in this case is

$$\varepsilon_o = (1/2\beta)\ln(\beta k/2\pi) + (a/\beta)\,(D/2k)^{1/2} - a^2/(8\beta^2 k) \quad (12)$$

After thermal desnaturation, $T > T_{d,}$ the two ribbons are not interacting. Then, the H-bond potential becomes zero. Thus, we can rewrite equation (1) considering $V(u_n - v_v)$ equal to zero:

$$H_{II} = \sum_n \{ (P^2_n/2m + Q^2_n/2m) + (1/2)K[(u_n - u_{n-1})^2 + (v_n - v_{n-1})^2]\} \quad (13)$$

where $P_n = m\dot{u}^2_n$ and $Q_n = m\dot{v}^2_n$. This Hamiltonian corresponds to two independents spring-mass systems. The partition function is

$$Z_{II} = \prod_{n=1}^{N} \int du_n dv_n dP_n dQ_n \exp(-\beta H_{II}) = Z_P Z_Q Z_u Z_v \quad (14)$$

The integration on the variables reduces to gaussian-like ones and they can be analytically evaluated. For the momenta integrations we get

$$Z_P = Z_Q = (2\pi m k_B T)^{N/2} \quad (15)$$

And, for the coordinates, we obtain

$$Z_u = Z_v = (2\pi k_B T/k)^{N/2}\ . \quad (16)$$

It is important to note that we have obtained analytical expressions for the partitions functions. This approach permits to determine, in a simple way, the melting temperature and to describe the thermodynamics properties of the system before and after the thermal denaturation.

Results

The parameters used here are D = 0.04eV, that corresponds to dissociation energy; $a = 4.45\text{Å}^{-1}$, that is the spatial scale of the Morse potential, and the coupling constant is $k = 0.06\text{eVÅ}^{-1}$ [1,2,4].

The denaturation temperature, using these parameters and the relation (11), is $T_d = 361K$. This value can be confirmed plotting the mean stretching value á y ñ against temperature, as in figure (1). The curve obtained shows a clear divergence near 360K.

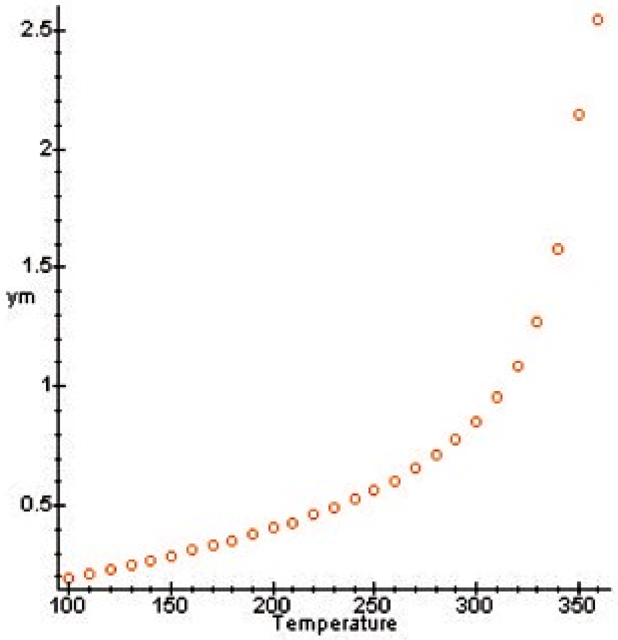

Figure 1 – Mean stretching value <y> versus temperature . The curve is obtained from the relation (9) with the eingenfunction $\phi_o(y)$ given by equation (11).

The free energy and the specific heat can be determined before and after the melting from partition functions (3) and (14), respectively. For $T < T_d$, Z_I is computed from (3) as

$$Z_I = (\, 2\pi m k_B T)^N (2\pi k_B T / k)^{N/2} e^{-N\beta\varepsilon_o} \qquad (17)$$

where e_o is given in (12). The free energy ($Á_I = -k_B T \ln Z_I$) in this condition is

$$\Im_I = -(\, N\, k_B\, T/2\,)\, \ln(2\pi\, m\, k_B\, T) - (\, N\, k_B\, T\, /\, 2)\, \ln(2\pi k_B T/k) + N\varepsilon_o \qquad (18)$$

and the specific heat ($C_V = ¶^2 Á_I / ¶T^2$) using e_o given in equation (12) is

$$C_{v,I} = (3/2) N\, k_B + [a^2 k^2{}_B N / 4k] T \qquad (19)$$

For $T > T_d$, Z_{II} is evaluated from (14), using (15) and (16). We get

$$Z_{II} = (2\pi\, m\, k_B\, T)^N (2\pi k_B T\, /\, k)^N \qquad (20)$$

In this case, the free energy is

$$\Im_{II} = -k_B T \ln Z_{II} = -N k_B T \;\; \ln(m/k) - 2 N k_B T \ln(2\pi k_B T) \qquad (21)$$

and the specific heat has the simple form

$$C_{v,II} = 2k_B N \qquad (22)$$

In figure 2 it is shown the specific heat as function of the temperature. We observe that C_v increases up to the melting temperature and, as a consequence of the approach adopted; it drastically decreases and became constant. The curve presented in fig.2 is similar to that one obtained in ref.[2,4] by numerical integration.

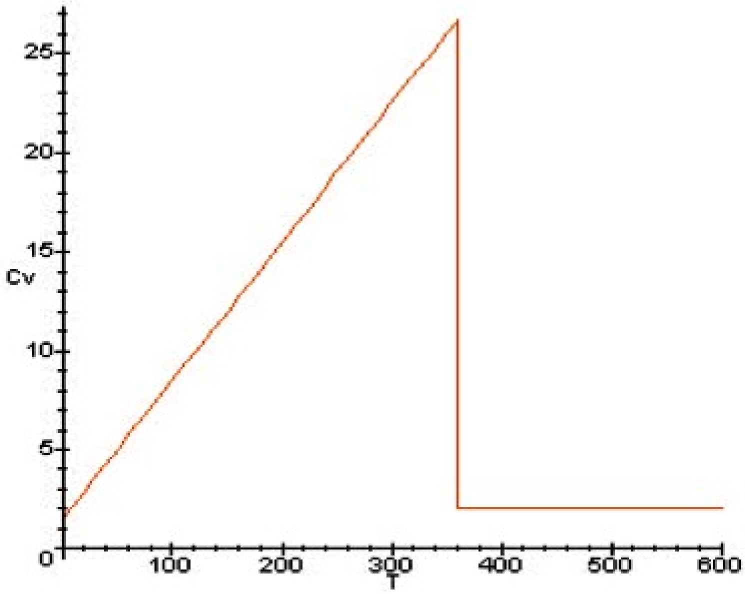

Figure 2 – Specific heat (C_V) as a function of absolute temperature (T). This plot is obtained using equation (19), for $T<T_d$, and equation (22), for $T>T_d$.

Conclusions

We explicitly divided the model in two temperature regions, $T < T_d$ and $T > T_d$. This approach gives a simplified mathematical approach to describe the statistical mechanics of thermal DNA denaturation.

Other works[2,4] get only the dependent part in y ($T<T_d$) that is the more important variable in the denaturation. However, we argue that it is necessary to get the same degree of freedom before and after the denaturation. The difference is the H-bond interaction and it does not affect the coordinate number.

Two important results in this kind of model are the melting temperature and the variation of specific heat versus temperature. In this way, our results are similar to other ones[2,4] including molecular dynamics simulations. The advantage is the simplicity and clearness of our approach. It is also important to note that our results are analyticals.

The experimental range of denaturation temperature[13] is from 318 K, for poly(dA-dT)·poly(dA-dT), to 372 K, for poly(dG-dC)·poly(dG-dC). Then, the result T_d = 361K is acceptable. Curiously, the introduction of discreteness in the model[2] results in a temperature over 500K, that is far from the experimental data. The introduction of non-harmonical potential for stacking interaction was proposed in order to improve this discrete description[3].

Finally, we would like to point out that the statistical mechanics analysis of DNA melting is as important as the study of the dynamics of this process. The dynamical aspects are not presented here but they are discussed, for instance, in ref.[1,11].

AUGUSTO, P.S.P. et al. Modelo estatístico para desnaturação térmica do DNA. *Ecl. Quím.* (São Paulo), v.26, p. , 2001.

RESUMO: Um modelo estatístico para o DNA é estudado a fim de se obter informações sobre o comportamento de variáveis termodinâmicas. Atenção especial é dada à desnaturação térmica desta macromolécula.

PALAVRAS-CHAVE: DNA, desnaturação térmica, modelo estatístico para macromoléculas.

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