

Vibrational fluctuations of hydrogen bonds in a DNA double helix with nonuniform base pairs

Y. Feng and E. W. Prohofsky

Department of Physics, Purdue University, West Lafayette, Indiana 47907

ABSTRACT The Green's function technique is applied to a study of breathing modes in a DNA double helix which contains a region of different base pairs from the rest of the double helix. The calculation is performed on a G-C

helix in the B conformation with four consecutive base pairs replaced by A-T. The average stretch in hydrogen bonds is found amplified around the A-T base pair region compared with that of poly(dG)-poly(dC). This is likely

related to the A-T regions lower stability against hydrogen bond melting. The A-T region may be considered to be the initiation site for melting in such a helix.

INTRODUCTION

A Green's function technique (1) has been developed to study the vibrational properties of DNA polymers and has been applied to several examples of DNA double helix. These include the junction of AT/GC helices (2), the terminus of a DNA homopolymer (3), a junction of DNA double helix and single strands (4), and defect-mediated melting of DNA homopolymers (5). In these examples, the alterations in interactions between atoms from those of the perfect helix are treated as defects. The presence of such defects breaks the helical symmetry, thereby making the description of the normal modes much more difficult. However, for situations of interest, such defects usually exist in a finite region of the polymer and involve a relatively small number of atoms. The problem is then conveniently solved by the Green's function technique. A variety of realistic DNA molecules can be treated using this technique, including those with structural disorder, such as terminal regions, irregular base pair sequences, and various linking arrangements involving DNA double helices or single strands which occur during DNA replication, recombination, RNA transcription, and other biological processes. Those defects are believed to play an important role in the melting of the DNA double helix. It has been found that localized modes can exist around defects in DNA polymers, which enhance the vibrational fluctuations in the hydrogen bonds which link the two complementary strands of the DNA double helix. This can initiate melting of the DNA double helix around the defects (2-5). In natural DNA molecules, local A-T-rich regions are believed less stable and therefore melt at lower temperatures than G-C-rich regions (6-8), which leads

to initiation of melting from A-T-rich sites. Such open regions offer potential interaction sites. It is also found experimentally that the stability of a portion of DNA helix can be influenced by the nucleotide sequence of adjacent regions (9-11). Hence, alterations in the nucleotide sequence in regions adjacent to an actual DNA-protein interaction site could influence the recognition of that site, particularly if the frequency of breathing is important for protein binding.

In the present paper, we apply the Green's function technique to study vibrational properties of a DNA double helix which has a finite region containing base pairs different from the rest of the helix. Breathing modes of the hydrogen bonds are of particular interest. The Green's function method is used to study the thermal fluctuation in the average hydrogen bond stretch. The calculation is carried out for a DNA double helix in the B conformation, which has four consecutive A-T base pairs in the middle and G-C base pairs for the rest of the helix. This is equivalent to inserting a section of A-T helix into a long G-C double helix. It may also be viewed as a simplified model for a long DNA double helix which is A-T rich in a finite region and G-C rich elsewhere. Hydrogen bond thermal fluctuations around the A-T base pairs and in G-C base pairs far away from the A-T base pairs are examined and compared with those of poly(dA)-poly(dT) and poly(dG)-poly(dC) in the same conformation.

It is believed that DNA molecules bend at A-T-rich regions (12). The bending and curvature result in anomalous physical properties of poly(dA) tracks in DNA molecules. Due to the complexity of the problem, how-

ever, the effects to the hydrogen bond thermal fluctuations due to such variation in local structure are neglected here and will be investigated in further studies.

FORMALISM

We construct the helix system starting with a perfect double helix (B poly[dG]-poly[dC]) and a finite section (N base pairs) of double helix with the same conformation but different base pairs (A-T). Then we replace N consecutive cells of the perfect helix by the finite section. This is achieved by setting the force constants linking the atoms across cell boundary to zero at two junctions N cells apart in the infinite helix and adding corresponding forces to connect the finite section to the two semiinfinite strands as shown in Fig. 1. We choose to cut the O5-C5 bond so that the number of valence forces involved is a minimum.

The unperturbed helix system, consisting of an infinite double helix and a finite section of helix of different base pairs, is described by the eigen problem

$$(\mathbf{F} - \omega^2 \mathbf{I})\mathbf{q} = 0, \quad (1)$$

where \mathbf{F} is the force constant matrix, \mathbf{I} is a unitary matrix, ω and \mathbf{q} are eigen values and eigen vectors in the mass-weighted Cartesian (MWC) coordinates. Because there is no interaction between the infinite helix and the finite section, the force constant matrix \mathbf{F} has a block diagonal form, and Eq. 1 can be written as two separate equations, describing the infinite double helix and the finite helix section, respectively. Whereas the equation describing the perfect helix is solved in the usual way by utilizing the helical symmetry (13), the equation describing the finite section may be solved exactly if the number of cells, N , is small. To avoid the complexity added due to end effects that ultimately go away and to reduce the computing time for large N , we approximate the eigen frequencies and eigen vectors for the finite segment by those extracted

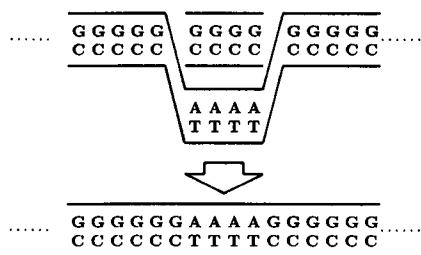


FIGURE 1 The double helix is constructed by cutting the perfect helix, poly(dG)-poly(dC), and joining the finite section of A-T helix to the semiinfinite strands.

from the eigen values and eigen vectors of the corresponding infinite double helix for only the following θ values.

$$\theta = -\pi + \frac{2\pi n}{N}, \quad n = 1, 2, 3, \dots, N.$$

For a finite A-T section four base pairs long, the eigen values and eigen vectors corresponding to $\theta = 0, \pm \pi/2$ and π from those of B poly(dA)-poly(dT) are used. These four θ values for each band of the periodic helix give the correct number of states associated with a four-unit cell section.

The perturbed helix system is described by a similar eigen equation,

$$(\mathbf{F} - \omega^2 \mathbf{I} + \mathbf{C})\mathbf{q} = 0, \quad (2)$$

where \mathbf{F} is the force constant matrix for the unperturbed system. ω and \mathbf{q} are the new eigen values and eigenvectors. The perturbation matrix, \mathbf{C} , is the change in \mathbf{F} necessary to bring about the severing of the infinite helix and the joining of the two semiinfinite helices created, to the finite section. The perturbation breaks the helical symmetry. A normal mode description would be much more difficult. However, because \mathbf{C} is a matrix of relatively low dimensionality, Eq. 2 can be solved in terms of Green's function of the unperturbed system. Following the procedure outlined previously (2, 3), we may obtain the thermal mean-square displacement amplitude for the melting coordinate (2) in cell m by

$$D(m) = \frac{\hbar}{\pi} \int d\omega \operatorname{Im}[G_{mm}^{mm}(\omega^2)] \coth\left(\frac{\hbar\omega}{2kT}\right) + \frac{\hbar}{2} \sum_{\kappa} \frac{|s_{\kappa}^m|^2}{\omega_{\kappa}} \coth\left(\frac{\hbar\omega_{\kappa}}{2kT}\right), \quad (3)$$

where T is the temperature, room temperature is used in this calculation, G is the Green's function of the final system and could be written in terms of the perturbation matrix \mathbf{C} and the Green's function for the unperturbed system, g (14). The normalized average hydrogen bond stretch in cell m associated with the κ th localized mode, s_{κ}^m is given by

$$s_{\kappa}^m = g_{si}^{mn} C_{ij} s_{j\kappa}^n, \quad (4)$$

where $s_{j\kappa}^n$ is the j th internal coordinate which is directly effected by a perturbation between cell n and cell $n + 1$. In Eq. 3, the first term represents the contribution to the hydrogen bond fluctuation from an in-band mode of frequency ω ; the second term represents that from a localized mode of frequency ω_{κ} . Eqs. 3 and 4 are written in the internal coordinates where the dimension of the perturbation matrix \mathbf{C} is the total number of forces involved by the cutting and joining, which is usually smaller than the total number of Cartesian coordinates

involved. In the internal coordinates, \mathbf{C} is a diagonal matrix and its elements are the same in magnitude as the force constants involved in constructing the helix. The negative of the force constant is used to cut a particular bond, and a positive force constant, not previously there, is added to create a new join between particular atoms. Geometrical factors are involved in the actual magnitude of the added and subtracted force constants.

The Green's function for the unperturbed system can be written in terms of the solution of the eigen value equation (14). In the internal coordinates,

$$g_{ij}^{mn}(\omega^2) = \frac{1}{\pi} \sum_{\lambda} \int_0^{\pi} d\theta \frac{\text{Re}[s_i^{\lambda}(\theta) s_j^{\lambda*}(\theta) e^{i(m-n)\theta}]}{\omega^2 - \omega_{\lambda}^2(\theta)} + \frac{1}{N} \sum_{\lambda', \theta'} \frac{s_i^{\lambda'}(\theta') s_j^{\lambda'*}(\theta') e^{i(m-n)\theta'}}{\omega^2 - \omega_{\lambda'}^2(\theta')}, \quad (5)$$

where $s^{\lambda}(\theta)$, normalized within a unit cell, is the eigen vector belong to the eigen value $\omega_{\lambda}(\theta)$ for a phase angle θ in the internal coordinates. The first term in Eq. 5 represents the contributions from all of the vibrational modes of the long G-C helix section, whereas the second term represents those from the finite section of A-T double helix. To estimate the thermal mean-square displacement amplitude for the melting coordinate, one has to calculate the Green's function for any frequency in the entire spectrum. If ω lies within one or more phonon dispersion branches of the perfect helix, then the perfect helix Green's function involves an integration over one or more singularities which can be removed by performing the integration over the Brillouin zone if the singularity is of first order. Close to the zone center or zone edge, a singularity could be second order which cannot be removed by performing the integration over the Brillouin zone. The Green's function is also singular if the frequency at which the Green's function is evaluated is close to that of an AT mode. This difficulty may be circumvented by giving ω a small imaginary part i/τ . Physically, this corresponds to an exponential decay of the normal modes caused by, for example anharmonic interactions causing loss of energy to nearby modes or by dissipative forces such that the molecule would feel in a solution environment. Therefore we replace ω^2 by $\omega^2 + i\gamma$, where $\gamma = 2\omega/\tau$, for small $1/\tau$. Then the evaluation of the second term in Eq. 5 is straight forward. Assuming that ω^2 has an intersection with branch λ at θ_0 , the integration in the first term (denoted by $g_{ij}^{mn}[\lambda, \omega^2]$) in Eq. 5 can be written as

$$\frac{1}{\pi} \int_0^{\pi} d\theta \left\{ \frac{\text{Re}[s_i^{\lambda}(\theta) s_j^{\lambda*}(\theta) e^{ik\theta}]}{\omega^2 - \omega_{\lambda}^2(\theta) + i\gamma} + \frac{\text{Re}[s_i^{\lambda}(\theta_0) s_j^{\lambda*}(\theta_0) e^{ik\theta}]}{b(\theta - \theta_0) - i\gamma} \right\} - \frac{1}{2\pi b} \left[s_i^{\lambda}(\theta_0) s_j^{\lambda*}(\theta_0) I\left(k, \theta_0 + \frac{i\gamma}{b}\right) + [s_i^{\lambda}(\theta_0) s_j^{\lambda*}(\theta_0)]^* I\left(-k, \theta_0 + \frac{i\gamma}{b}\right) \right] \quad (6)$$

for a first order pole, and

$$\frac{1}{\pi} \int_0^{\pi} d\theta \left\{ \frac{\text{Re}[s_i^{\lambda}(\theta) s_j^{\lambda*}(\theta) e^{ik\theta}]}{\omega^2 - \omega_{\lambda}^2(\theta) + i\gamma} + \frac{\text{Re}[s_i^{\lambda}(\theta_0) s_j^{\lambda*}(\theta_0) e^{ik\theta}]}{b(\theta - \theta_0) + a(\theta - \theta_0)^2 - i\gamma} \right\} - \frac{1}{2\pi \sqrt{b^2 + i4a\gamma}} \left[s_i^{\lambda}(\theta_0) s_j^{\lambda*}(\theta_0) [I(k, z_+) - I(k, z_-)] + s_i^{\lambda*}(\theta_0) s_j^{\lambda}(\theta_0) [I(-k, z_+) - I(-k, z_-)] \right] \quad (7)$$

for a second order pole, where

$$k = m - n$$

$$a = \frac{1}{2} \frac{d^2 \omega_{\lambda}^2(\theta_0)}{d\theta^2}$$

$$b = \frac{d\omega_{\lambda}^2(\theta_0)}{d\theta}$$

$$z_{\pm} = \theta_0 + \frac{-b \pm \sqrt{b^2 + i4a\gamma}}{2a}$$

The function $I(k, z)$ is defined as

$$I(k, z) = \int_0^{\pi} \frac{e^{ik\theta} d\theta}{\theta - z}, \quad (8)$$

and is given by

$$\begin{aligned} \ln(1 - \pi/z) & \quad (k = 0) \\ -f_1(ikz) - (-1)^k & \cdot f_1(ikz - ik\pi) \pm \pi i e^{ikz} \quad (\text{Re}(z) = 0, k\text{Im}(z) > 0) \\ f_1(ikz) - (-1)^k & \cdot f_1(ikz - ik\pi) \pm 2\pi i e^{ikz} \quad (0 < \text{Re}(z) < \pi, k\text{Im}(z) > 0) \\ f_1(ikz) + (-1)^k & \cdot f_1(ikz + ik\pi) \pm \pi i e^{ikz} \quad (\text{Re}(z) = \pi, k\text{Im}(z) > 0) \\ f_1(ikz) - (-1)^k & \cdot f_1(ikz - ik\pi) \quad (\text{otherwise}), \end{aligned} \quad (9)$$

where $f_1(z)$ and $f_i(z)$ are the products of the exponential function and the exponential integrals, $E_1(z)$ and $E_i(z)$,

$$f_1(z) = e^z E_1(z)$$

$$f_i(z) = e^z E_i(z).$$

The upper signs are taken if $k > 0$ and the lower signs are used when $k < 0$ in Eq. 9. In obtaining the above results (Eqs. 6, 7) for the integral in the perfect helix Green's function, a term which approximates the original integrand in the neighborhood of the singularity is added and then subtracted from the integrand so that the integration is easily done numerically. In case of more than one singularity, the above expression must be summed over all of the singularities. Whereas γ may be allowed to approach zero for a first order pole, a small but finite relaxation time is necessary to remove a second order singularity near a maximum or a minimum in the phonon dispersion curves for the perfect helix. We choose a

relaxation time such that a vibration will continue for 1,000 oscillations before dying to e^{-1} of its original amplitude. A different choice has been shown to have little effect on the hydrogen bond stretch, particularly when it is close to the defects (2). The lifetime does have effects far from the defect site. The same relaxation time is assumed in the second term of Eq. 5.

To reduce the size of the matrix **C** and thus the computing time, the long range Coulomb and Van de Waals interactions are replaced by a set of effective forces (2,15) which produces equivalent potential energies and a similar spectrum for each DNA homopolymer as those obtained using the exact long range forces. To emphasize the effects on the breathing modes due to the different base pairs, we used the same set of effective forces for the unperturbed system (Eq. 1) so that any effect introduced by replacing the Coulomb and Van de Waals forces with effective forces are excluded. In a previous investigation (2), tilting and torsion forces were found to be unimportant in such calculations, and they are neglected in the **C** matrix to further reduce the computing time.

RESULTS AND DISCUSSION

We carried out the calculation for an infinite DNA double helix in the B conformation, which has four A-T base pairs in the middle and G-C base pairs for the rest of it. We have found that breathing modes exist around 85 wave numbers in both homopolymers (16). We scanned through the entire spectra of both poly(dA)-poly(dT) and poly(dG)-poly(dC) and found that the average hydrogen bond stretch amplitude is significant only for a few branches of the perfect helix dispersion curves between 60 and 140 cm^{-1} . Therefore only this frequency range is considered in studying the breathing modes of the perturbed helix. The dispersion curves for the frequency range of interest are shown in Fig. 2, where solid lines are phonon dispersion curves of poly(dG)-poly(dC), dashed lines are those of poly(dA)-poly(dT). Only those corresponding to $\theta = 0, \pm \pi/2$ and π of the normal modes of poly(dA)-poly(dT) are selected as approximations to the normal modes of the finite section of A-T helix. The dispersion curves are different from those given in reference 2 because torsions for backbone atoms and tiltings between bases in adjacent cells are neglected in the present calculation.

First, the thermal mean-square amplitude of the average stretch in hydrogen bonds is estimated from Eq. 3 for the four A-T base pairs and 11 G-C base pairs closest to the A-T section on each side of it. The results are shown in Fig. 3. Here the solid circle represents total thermal fluctuation, the open circle represents that without the contribution from localized modes, the solid straight lines

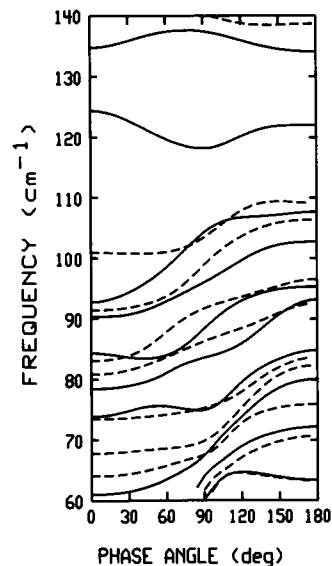


FIGURE 2 Phonon dispersion curves of poly(dA)-poly(dT) (dashed lines) and poly(dG)-poly(dC) (solid lines).

are the corresponding values for poly(dA)-poly(dT) and poly(dG)-poly(dC). Significant change in the hydrogen bond fluctuation from that of the perfect helices is observed in the A-T base pairs and in a few G-C base pairs closest to the A-T section. The hydrogen bond fluctuation is increased by a factor of 2 or 3 around the A-T base pairs compared to that of poly(dG)-poly(dC). Considering the nonlinear effects in the hydrogen bond stretch at large vibrational amplitude (17, 18), this indicates that the existence of A-T base pairs in a long G-C double helix should reduce the stability of the G-C helix at the region of the insert. The hydrogen bonds in the A-T base pairs or the G-C base pairs closest to the

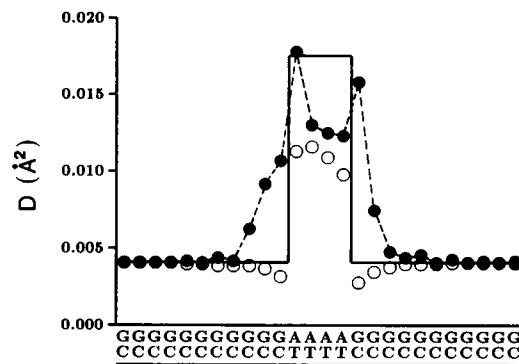


FIGURE 3 Thermal mean-square displacement amplitude D for the melting coordinate is shown with (\bullet) and without (\circ) local mode contribution. The solid lines are corresponding values for poly(dG)-poly(dC) and poly(dA)-poly(dT).

A-T section may break first as temperature increases and thus initiate melting of the double helix.

Contrary effects are found for in-band modes and for localized modes. In-band modes tend to reduce the thermal fluctuation around the A-T bases. This is due to the fact that breathing modes of poly(dA)-poly(dT) and breathing modes of poly(dG)-poly(dC) usually exist in different frequency regions. For example, the average hydrogen bond stretch is largest for dispersion branches at 64.05, 100.94, 73.47, and 83.14 cm^{-1} for poly(dA)-poly(dT), whereas the modes with the same characteristics are branches at 90.35, 124.46, 134.78, and 84.37 cm^{-1} for poly(dG)-poly(dC). In a region where breathing modes of poly(dG)-poly(dC) exist, the average hydrogen bond stretch is enhanced for the A-T base pairs and reduced in a few G-C base pairs which are close to the A-T section. The enhancement in the A-T base pairs is usually unimportant because it is still much smaller than the contribution from the regions where breathing modes of poly(dA)-poly(dT) exist. However, the decrease in the G-C base pairs is appreciable because the average hydrogen bond stretch for G-C base pairs is essentially determined by such breathing mode branches. Similarly, in a region where breathing modes of poly(dA)-poly(dT) exist, the average hydrogen bond stretch is appreciably reduced in A-T base pairs while it is slightly increased in a few G-C base pairs near the A-T section. As a result, the A-T section is stabilized by the G-C helix and vice versa. Similar results have been observed in a junction of AT/GC double helix (2).

Localized modes tend to enhance the hydrogen bond fluctuation, which is most significant at the junctions of the A-T section and the G-C helix where defects exist. It is obvious that localized modes play a very important role in the thermal stability of such DNA double helices.

The average hydrogen bond stretch approaches that of poly(dG)-poly(dC) at about five base pairs from the A-T section, indicating that the A-T section would not effect hydrogen bond fluctuation in the G-C helix far away from the A-T base pairs. However, a number of experimental observations suggest long range effects. In studying cruciform structures in supercoiled DNA, Sullivan (19, 20) and co-worker have discovered a striking dependence of a structural transition in DNA on sequences that are distanced from those directly participating in the transformation. The remote DNA sequences are able to influence the entire nature of a structural transition. Patient et al. (21) also observed a destabilizing effect that was the result of an A-T-rich block over 100 base pairs away from the block itself. Here we give an estimate of average hydrogen bond stretch some distance away from the A-T section by taking the limit at $|m| \gg 1$ in Eq. 3. We number the A-T section as cells 1-4. From the relation $G = g + gTg$ where $T = C(I - gC)^{-1}$ and the expressions 3 and 4,

we see that $D(m)$ depends on m only through the Green's function for the unperturbed helices. Outside the A-T insert region, there are only G-C base pairs. The second term in Eq. 5 does not contribute if one of the internal coordinates involved is the average hydrogen bond stretch in a G-C base pair. The asymptotic behavior of the Green's function for a perfect helix is discussed in Appendices A and B for in-band modes and band gap modes, respectively. It is a decreasing function of distance for a localized mode and for an in-band mode which is close to a band maximum or minimum. In our calculation, only the removable singularities are of importance in determining the perfect helix Green's function for a large distance. Using the asymptotic Green's function given in Eq. A2,

$$[G(\omega^2) - g(\omega^2)]_{ii}^{mm} = g_{ij}^{m n_j}(\omega^2) T_{jk}(\omega^2) g_{ki}^{n_k m}(\omega^2) \xrightarrow{m \gg 1} - \sum_{\alpha\beta} A_{ii}^{\alpha\beta}(\omega^2) e^{im(\bar{\theta}_\alpha + \bar{\theta}_\beta)}, \quad (10)$$

where

$$A_{ii}^{\alpha\beta}(\omega^2) = \sum_{jk} \frac{\bar{S}_{ij}(\theta_\alpha) T_{jk}(\omega^2) \bar{S}_{ki}^*(\theta_\beta)}{|b_\alpha b_\beta|} e^{-i(n_j \bar{\theta}_\alpha + n_k \bar{\theta}_\beta)}.$$

$\bar{\theta}$ and \bar{S} are defined in Appendix A, n_j and n_k are given integers which indicate the unit cells where the j th and k th perturbed coordinate exists, respectively. They can take a value of 0 or 4 if the A-T base pairs are numbered as cells 1-4. Integration over ω of Eq. 10 weighted by the thermal distribution of phonons gives the change in the average hydrogen bond stretch from that of poly(dG)-poly(dC). Here θ_α and θ_β are functions of ω . For a cell far away from the defect, the Green's function for the perturbed helix oscillates rapidly as a function of θ_α and θ_β around that of the unperturbed helix and is also a rapid oscillatory function of frequency. When the integration over ω is performed to obtain the total hydrogen bond fluctuation, contribution by the term gTg is negligible. This indicates that the perturbation in a finite region does not produce any significant change in the average hydrogen bond stretch at a large distance. This calculation thus predicts no long-range effect by the A-T base pairs.

Several factors which could give rise to long-range effects have not been included in this calculation. We have not explored distortions of the basic structure. The junction regions may be displaced from B conformation positions. Another element not included is the synergistic interaction of two unique regions. A third effect not currently included is the synergistic interaction between sequence defects and self-consistent force constant softening. All of the above should be investigated for long-range effects.

APPENDIX A

Asymptotic behavior of the perfect helix Green's function for in-band modes

Due to the factor $e^{i(m-n)\theta}$, the integrand of the first term in Eqs. 6 and 7 oscillates rapidly for large $(m - n)$ while the amplitude of the oscillation is a slow varying function of θ . Throughout the Brillouin zone, contributions from different θ tend to cancel. Among the terms in $I(k, z)$, $f_1(ikz)$ and $f_2(ikz)$ decrease as $|k|$ increases. This can be seen from the asymptotic expansions of $f_1(z)$ and $f_2(z)$ (22):

$$e^z E_1(z) = \frac{1}{z} \left[\sum_0^N \frac{n!}{(-z)^n} + O\left(\frac{1}{|z|^{N+1}}\right) \right]$$

$$e^z E_2(z) = \frac{1}{z} \left[\sum_0^N \frac{n!}{(z)^n} + O\left(\frac{1}{|z|^{N+1}}\right) \right].$$

The term $\pm 2\pi i e^{ikz}$ or $\pm \pi i e^{ikz}$ for $k \text{Im}(z) > 0$ contains a decaying factor, $\exp[-k \text{Im}(z)]$. If $\text{Im}(z)$ is not sufficiently small, this term decreases rapidly as $|k|$ increases. This is the case when the singularity is a nonremovable singularity ($b \rightarrow 0$). For such a singularity, a small although finite relaxation time must be incorporated. This is necessary to remove the second order singularity. Because γ is a finite number and $b \rightarrow 0$, the quantity z_+ or z_- always has a finite imaginary part which is of the order $(\gamma/a)^{1/2}$. This finite imaginary part causes $2\pi i \exp(ikz)$ to decrease rapidly as $|k|$ increases for a second order pole.

If the singularity is a removable singularity ($|b/a| \gg 1$), then the quantity z is given by

$$z = \theta_0 = i \frac{\gamma}{b}.$$

Its imaginary part, γ/b , is usually very small. As a matter of fact, γ may be allowed to approach zero for a removable singularity. Only in this case, the decrease caused by $\exp[-k \text{Im}(z)]$ is not significant.

Therefore, second order poles (when $b \rightarrow 0$) are less important than first order poles, in the case where γ can be made small, in determining the perfect helix Green's function for large distance. For a first order pole, the only significant contribution comes from the term $\pm 2\pi i \exp(ikz)$ in $I(k, z)$ if it exists for large $|k|$. Because $\text{Re}(z) = \theta_0$, the condition $0 < \text{Re}(z) < \pi$ is always satisfied. Neglecting the terms which decrease as $|k|$ increases, we have

$$I(k, z) \xrightarrow{|k| \gg 1} \begin{cases} 2\pi i e^{ikz} & (k > 0, b > 0) \\ -2\pi i e^{ikz} & (k < 0, b < 0) \\ 0 & (\text{otherwise}) \end{cases}$$

or

$$I(k, z) \xrightarrow{|k| \gg 1} \begin{cases} 2\pi i e^{ik\theta_0} & (k > 0, b > 0) \\ -2\pi i e^{ik\theta_0} & (k < 0, b < 0) \\ 0 & (\text{otherwise}) \end{cases}$$

in the limit of $\gamma \rightarrow 0$.

Because the perfect helix Green's function is symmetric, i.e., $g_{ji}^{mn}(\omega^2) = g_{ij}^{mn}(\omega^2)$, it is sufficient to consider the case of $m > n$. Using the expression for $I(k, \theta_0)$ for large $(m - n)$ and $\gamma \rightarrow 0$ given above, we

have

$$g_{ij}^{mn}(\lambda, \omega^2) \xrightarrow{m \gg n} \begin{cases} -\frac{i}{b} s_i(\lambda, \theta_0) s_j^*(\lambda, \theta_0) e^{i(m-n)\theta_0} & (b > 0) \\ \frac{i}{b} s_i^*(\lambda, \theta_0) s_j(\lambda, \theta_0) e^{-i(m-n)\theta_0} & (b < 0). \end{cases} \quad (\text{A1})$$

If more than one singularity is involved for a given frequency, then Eq. A1 must be generalized to include the contribution from each singularity. Summation over all of the first order singularities gives the following asymptotic expression for the perfect helix Green's function for large $(m - n)$,

$$g_{ij}^{mn}(\omega^2) \xrightarrow{m \gg n} -i \sum_{\alpha} \frac{\bar{S}_{ij}(\theta_{\alpha})}{|b_{\alpha}|} e^{i(m-n)\theta_{\alpha}}, \quad (\text{A2})$$

where α labels the first order poles,

$$\bar{\theta}_{\alpha} = \begin{cases} \theta_{\alpha} & (b > 0) \\ -\theta_{\alpha} & (b < 0) \end{cases}$$

and

$$\bar{S}_{ij}(\theta_{\alpha}) = \begin{cases} s_i(\theta_{\alpha}) s_j^*(\theta_{\alpha}) & (b > 0) \\ s_i^*(\theta_{\alpha}) s_j(\theta_{\alpha}) & (b < 0). \end{cases}$$

The branch index λ is omitted because there always is a unique branch associated with each singularity.

APPENDIX B

Asymptotic behavior of the perfect helix Green's function for band gap frequencies

For a defected DNA double helix, local vibrational modes could exist at frequencies outside the range of frequencies allowed by the modes of the unperturbed homopolymer. For such band gap frequencies, the integral in the perfect helix Green's function is never singular. For large $m - n$ the exponent factor $e^{i(m-n)\theta}$ in the integrand oscillates rapidly as a function of θ , and throughout most of the Brillouin zone contributions from different θ tend to cancel. The exception to this occurs in the neighborhood of those θ values for which the denominator is as small as possible, namely, the region about the maximum or minimum of the branch of $\omega_L^2(\theta)$ closest to ω^2 , assuming that there is only one maximum per branch in a zone. The extension of the present results to the more general case of a degenerate maximum frequency is trivial.

For simplicity let us assume that ω^2 is close to the maximum of λ th branch of the perfect helix dispersion curves, $\omega_L^2(\lambda)$, and consider the contribution to $g_{ij}^{mn}(\omega^2)$ from this branch. The results so obtained will have to be summed over all λ to yield the complete expression for $g_{ij}^{mn}(\omega^2)$. If we denote the θ value corresponding to the maximum frequency in the λ th branch by θ_0 , then about this point we have the expansion

$$\omega_{\lambda}^2(\theta) = \omega_L^2(\lambda) - a(\theta - \theta_0)^2 + \dots, \quad (\text{B1})$$

where

$$a = \frac{1}{2} \frac{d^2 \omega_\lambda^2(\theta_0)}{d\theta^2} > 0.$$

The linear term in this expansion vanishes because θ_0 is a maximum. Substitute Eq. B1 into the perfect helix Green's function, the first term in Eq. 5 and making the change of variable $t = \theta - \theta_0$, we can write the contribution to $g_{ij}^{mn}(\omega^2)$ from the λ th branch of $\omega_\lambda^2(\lambda, \theta)$ as

$$g_{ij}^{mn}(\omega^2, \lambda) = \frac{1}{2\pi} S_{ij}^{mn}(\lambda, \theta_0) \int_{-\pi-\theta_0}^{\pi-\theta_0} \frac{e^{i(m-n)t} dt}{\omega^2 - \omega_\lambda^2(\lambda) + at^2}, \quad (\text{B2})$$

where

$$S_{ij}^{mn}(\lambda, \theta_0) = s_i^m(\lambda, \theta_0) s_j^{n*}(\lambda, \theta_0) e^{i(m-n)\theta_0}.$$

We have replaced $s_i^m(\lambda, \theta)$ by its value at θ_0 in Eq. B2 because $s_i^m(\lambda, \theta)$ is a slow varying function of θ . Having made a small t expansion of $\omega_\lambda^2(\theta) - \omega_\lambda^2(\lambda)$ about θ_0 , we can extend the limits on the t integration to infinity with an error which is of higher order than concerns us here. Then the integral in Eq. B2 can be evaluated. We just give the result below.

$$g_{ij}^{mn}(\omega^2, \lambda) \approx \frac{S_{ij}^{mn}(\lambda, \theta_0)}{2\sqrt{a[\omega^2 - \omega_\lambda^2(\lambda)]}} e^{-\sqrt{[\omega^2 - \omega_\lambda^2(\lambda)]/a}(m-n)}. \quad (\text{B3})$$

The corresponding result for ω close to the bottom of a band is obtained from this by identifying $\omega_\lambda(\lambda)$ as the frequency of the minimum and changing the overall sign of expression B3 and replacing $\omega^2 - \omega_\lambda^2(\lambda)$ by $\omega_\lambda^2(\lambda) - \omega^2$.

It follows from the results given in Eqs. B3 and B4 that the displacement amplitudes for atoms vibrating in a perturbed mode whose frequency lies above the maximum frequency of the unperturbed helix decay exponentially with the distance from the perturbation region, $m - n$. The same results could be obtained for a gap mode. This decay for a perturbed DNA double helix mode is different from that for a bulk crystal where the displacement amplitudes for a local mode decay faster than exponentially with increasing distance from the perturbed atoms (23).

This work was supported by National Institutes of Health grant GM24443 and Office of Naval Research contract N00014-86-K-0252.

Received for publication 8 August 1989 and in final form 9 November 1989.

REFERENCES

- Lifshitz, I. M., and S. I. Pekar. 1955. Tamm connected states of electrons on the surface of a crystal and the surface oscillations of the atoms of a lattice. *Usp. Fiziol. Nauk.* 56:531-568.
- Feng, Y., R. D. Beger, X. Hua, and E. W. Prohofsky. 1989. Breathing modes near a junction of DNA double helices. *Physiol. Rev. A.* 40:4612-4619.
- Putnam, B. F., L. L. Van Zandt, E. W. Prohofsky, and W. N. Mei. 1981. Resonant and localized breathing modes in terminal regions of the DNA double helix. *Biophys. J.* 35:271-287.
- Putnam, B. F., and E. W. Prohofsky. 1983. Localized vibrational modes at a double-helix-single-strand junction. *Biopolymers.* 22:1759-1767.
- Kim, Y., and E. W. Prohofsky. 1986. Defect-mediated hydrogen-bond instability of poly(dG)-poly(dC). *Physiol. Rev. B.* 33:5676-5681.
- Spatz, H. C., and D. M. Crothers. 1969. The rate of DNA unwinding. *J. Mol. Biol.* 42:191-219.
- Wada, A., and A. Suyama. 1985. Homogeneous double-helix stability in individual genes. In *Biomolecular Stereodynamics. IV. Proceedings of the Fourth Conversation in the Discipline Biomolecular Stereodynamics.* R. H. Sarma, editor. Adenine Press, Guilderland, NY. 21-46.
- Wada, A., and A. Suyama. 1986. Local stability of DNA and RNA secondary structure and its relation to biological functions. *Prog. Biophys. Mol. Biol.* 47:113-157.
- Wells, R. D., R. W. Blakesley, S. C. Hardies, G. T. Horn, J. E. Larson, E. Selsing, J. F. Burd, H. W. Chan, J. B. Dodgson, K. F. Jensen, I. F. Nes, and R. M. Wartell. 1977. The role of DNA structure in genetic regulation. *CRC Crit. Rev. Biochem.* 305-340.
- Burd, J. F., R. M. Wartell, J. B. Dodgson, and R. D. Wells. 1975. Transmission of stability (telestability) in deoxyribonucleic acid. *J. Biol. Chem.* 250:5109-5113.
- Burd, J. F., J. E. Larson, and R. D. Wells. 1975. Further studies on telestability in DNA. *J. Biol. Chem.* 250:6002-6007.
- Olson, W. K., M. H. Sarma, R. H. Sarma, and M. Sundaralingam. 1988. Structure and Expression. Vol. 3. DNA Bending and Curvature. Proceedings of the Fifth Conversation in the Discipline Biomolecular Stereodynamics. Adenine Press, Guilderland, NY.
- Higgs, P. W. 1953. The vibration spectra of helical molecules: infra-red and Raman selection rules, intensities and approximate frequencies. *Proc. R. Soc. Lond. A.* 220:472-485.
- Bottger, H. 1983. Principles of the Theory of Lattice Dynamics. Physik-Verlag, Weinheim, FRG. 87 pp.
- Putnam, B. F. 1981. Calculation of macromolecular force constants and vibrational properties of a semi-infinite strand of the DNA double helix. Ph.D. thesis. Purdue University, West Lafayette, IN. Ch. 4.
- Prohofsky, E. W. 1985. Motional dynamics of the DNA double helix. In *Biomolecular Stereodynamics. IV. Proceedings of the Fourth Conversation in the Discipline Biomolecular Stereodynamics.* R. H. Sarma, editor. Adenine Press, Guilderland, NY. 21-46.
- Peyrard, M., and A. R. Bishop. 1989. Statistical mechanics of a nonlinear model for DNA denaturation. *Physiol. Rev. Lett.* 62:2755-2758.
- Techera, M. 1990. Thermodynamics of a nonlinear model of the DNA double helix. *Physiol. Rev. A.* In press.
- Sullivan, K. M., and D. M. J. Lilley. 1986. A dominant influence of flanking sequences on a local structural transition in DNA. *Cell.* 47:817-827.
- Sullivan, K. M., A. I. H. Murchie, and D. M. J. Lilley. 1988. Long range structural communication between sequences in supercoiled DNA. *J. Biol. Chem.* 263:13074-13082.
- Patient, R. K., S. C. Hardies, J. E. Larson, R. B. Inman, L. E. Maquat, and R. D. Wells. 1979. Influence of A-T content on the fractionation of DNA restriction fragments by RPC-5 column chromatography. *J. Biol. Chem.* 254:5548-5554.
- Magnus, W., F. Oberhettinger, and R. P. Soni. 1966. Formulas and Theorems for the Special Functions of Mathematical Physics. 3rd ed. Springer-Verlag Inc., New York. 346 pp.
- Maradudin, A. A., E. W. Montroll, G. H. Weiss, and I. P. Ipatova. 1971. Theory of Lattice Dynamics in the Harmonic Approximation. 2nd ed. Academic Press, Inc., New York. 368 pp.