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Low-frequency vibrations of DNA molecules

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A model for calculating the low-frequency modes in DNA molecules is presented. The present model is associated with the 'breathing' of a DNA molecule as well as its complementary hydrogen bonds. The calculated results show excellent agreement with the observed low-frequency wavenumber ($30\,cm^{-1}$). Consequently, such an internal motion as reflected in the proposed model might be the origin of the observed low-frequency vibration in DNA molecules. This is helpful for investigating the relevant biological functions, which so far have been discussed by many scientists.

Since Brown *et al.* (1972) observed low-frequency vibrations in α-chymotrypsin and pepsin, more and more evidence (Genzel *et al.*, 1976; Painter *et al.*, 1981, 1982; Evans *et al.*, 1982) has confirmed that such low-frequency vibrations with wavenumbers of $10–40\,cm^{-1}$ do indeed exist in proteins and some other biomacromolecules. In parallel with this development, many speculations have been made about their biological functions (Green, 1974; Ji, 1974; Fröhlich, 1975; Careri *et al.*, 1975; Chou & Chen, 1977, 1978; Sobell *et al.*, 1979, 1983; Englander, 1980; Chou *et al.*, 1981; Zhou, 1981; Chou, 1983*a*, 1984), and this should no doubt stimulate investigation of the aspect of dynamics in the principles and mechanism of the action of biomacromolecules. However, for a serious approach to such a subject, a key prerequisite is the unequivocal identification of this kind of low-frequency modes in biomacromolecules (Chou, 1983*b*). Although in principle the normal mode calculation method developed by Wilson (1939), Itoh & Shimanouchi (1970) and Fanconi *et al.* (1971) could be used to calculate and analyse vibrational movements in any molecules, unfortunately this is in practice formidable, owing to the extreme complexity of biomacromolecules. To overcome this difficulty, some simplified and feasible models have been proposed (Suezaki & Gō, 1975; Chou, 1983*a*,*b*). The results calculated in terms of these models (Chou, 1983*a*,*b*) are quite close to the observed values. In addition, a common feature of these models is in that an intuitive picture is clearly presented for the low-frequency motion concerned, which should doubtless be helpful for other developments in this field, both theoretical and experimental. Nevertheless, all these models can be used to calculate and describe the low-frequency modes in protein molecules only, but not those in DNA molecules. However, as discussed by many scientists (Careri *et al.*, 1975; Sobell *et al.*, 1979, 1983; Englander, 1980; Zhou, 1981), the low-frequency vibrations in DNA molecules might possess very important biological functions. The present study was therefore initiated in an attempt to develop a model for calculating and describing the low-frequency modes in DNA molecules.

Continuity model for double-helix structure

For simplicity, let us approach the derivation first for a homo-DNA double-helix structure; the equation thus obtained can, however, be appropriately extended to treat a general DNA molecule as illustrated in the next section. According to the Watson–Crick base-pairing model, a DNA molecule can be considered as a structure of double helices, as illustrated in Fig. 1, where a view perpendicular to the helix axis is depicted. In that schematic illustration, the two polynucleotide chains are shown as two right-handed helical ribbons intertwining around the same axis, with the nitrogen bases shown as hatched rectangles. The broken lines between nitrogen bases of each pair are the hydrogen bonds, which hold the double helices together, and which consecutively rotate around the axis z by about 36°. The diameter of the helix is roughly 2.2nm (22Å), and the distance between neighbouring base-pair planes is about 0.35nm (3.5Å). Therefore, if viewed along the helix axis, these base-pair planes would appear as a spiral progression (Fig. 1) with a pitch of 0.35nm (3.5Å).

However, under thermal equilibrium, not all the

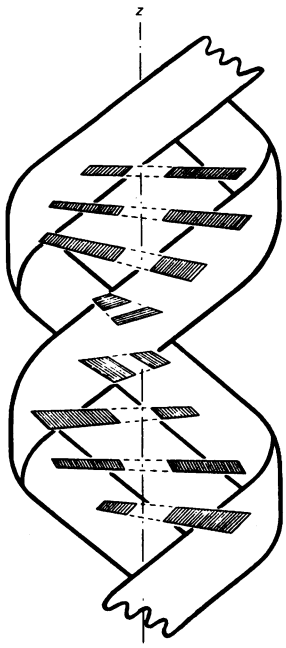

Fig. 1. *View perpendicular to the DNA double-helix axis z* The two polynucleotide chains are shown as two right-handed helical ribbons intertwining around the same axis, and the nitrogen bases are denoted by hatched rectangles. The interchain hydrogen bonds between complementary bases are represented by broken lines, rotating consecutively around the *z*-axis by about 36°.

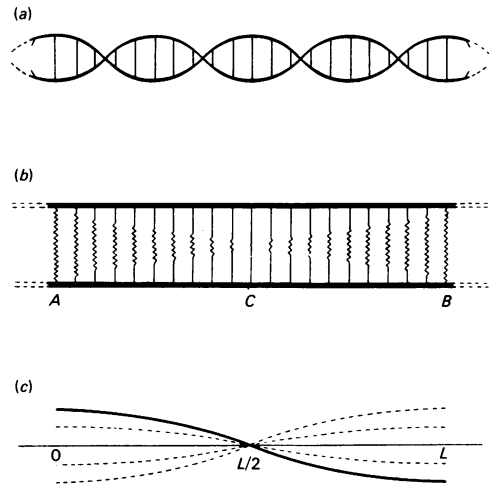

Fig. 2. *Illustrations to show (a) the closed–open motion between complementary bases, the so-called 'breathing' of a DNA molecule, (b) how the amplitude of a complementary base-pair depends on its location, and (c) the features of a standing wave for the vibration described in (b)* In (*b*), the amplitude at *A* and *B* is the largest because they are closest to an open base-pair, and the amplitude at the remotest point *C* is the smallest. In (*c*), the node is at $z = L/2$, corresponding to *C* of (*b*), and the antinodes are at $z = 0$ and *L*, corresponding to *A* and *B* of (*b*) respectively. The continuous curve represents the picture of the standing wave at one instant, and the broken curves represent it at other instants.

base-pairs are closed so as to form the intact Watson–Crick hydrogen bonds, and they are actually governed by the following thermodynamic relation (Manning, 1983):

$$\text{Closed base-pair} \underset{}{\overset{K_{\text{open}}}{\rightleftharpoons}} \text{open base-pair} \quad (1)$$

for which it may be considered that for every *n* closed base-pairs, where

$$n = 1/K_{\text{open}} \quad (2)$$

there is one open base-pair at equilibrium. The closed–open motion is familiarly known as the 'breathing' of a DNA molecule. In this case, the forces that hold the double helices are of course no longer uniform along the axis (Fig. 2*a*). Consequently, when a pair of bases are vibrating with respect to each other along their hydrogen bonds, the amplitude will depend on the location of this base-pair in a 'breathing' DNA molecule: the closer the base-pair to an open base-pair, the larger its amplitude should be, and vice versa (Fig. 2*b*). Besides, if *n*, the number of the adjacent closed base-pairs, is not very small (such a condition can always be satisfied, as shown in the next section), the smallest amplitude (corresponding to *C* of Fig. 2*b*) can virtually be neglected. Obviously, this kind of vibration has the feature of a standing wave, as illustrated in Fig. 2(*c*), where $z = L/2$ (corresponding to *C* of Fig. 2*b*) is the node, and the antinodes are at $z = 0$ and *L* (corresponding to *A* and *B* in Fig. 2*b* respectively). The continuous curve represents the picture of the standing wave at one instant, and the broken curves represent it at other instants. Therefore the vibrational displacements for such a standing wave can be formulated as:

$$u(z,t) = \sigma \cdot \cos(\pi z/L) \cdot \sin \omega \cdot t \quad (3)$$

where *z* is the axis of the DNA double-helix axis, *L* is the distance between two antinodes, i.e. the half-wavelength of the standing wave, ω is the round frequency and σ is the maximum amplitude.

If there are *n* adjacent base-pairs that are closed along the DNA axis, then the *i*th base-pair can be assigned on the *z* axis as:

$$z_i = (i-1)L/(n-1) \quad (4)$$
$$(i = 1, 2, \ldots n)$$

Let the force constant for each base-pair be k_{base}; the maximum vibrational potential is thus:

$$\text{Max. } U = (k_{base}/2)\cdot\sum_{i=1}^{n}[\sigma\cdot\cos(\pi z_i/L)]^2$$
$$= (k_{base}\cdot\sigma^2/2)\cdot\sum_{i=1}^{n}\cos^2[(i-1)\pi/(n-1)]$$
$$= (k_{base}\cdot\sigma^2/2)\cdot\sum_{j=0}^{n-1}\cos^2[j\pi/(n-1)] \quad (5)$$

On the other hand, the maximum kinetic energy of the standing wave in this segment is (Chou, 1983*a*):

$$\text{Max. } T = \Sigma(\rho\Delta z/2)\cdot\text{Max.}(du/dt)^2$$
$$= \int_0^L(\rho\sigma^2\omega^2/2)\cdot\cos^2(\pi z/L)\cdot dz$$
$$= \rho L\sigma^2\omega^2/4 \quad (6)$$

where ρ is the mass per unit length of DNA segment along the z-axis. Note that the kinetic energy corresponding to the open-base-pair portion is relatively much smaller when $n \gg 1$, and hence can be neglected here. According to energy conservation, i.e. Max. T = Max. U, it follows that:

$$\omega = \sqrt{(2k_{base}/\rho L)\cdot\sum_{j=0}^{n-1}\cos^2[j\pi/(n-1)]} \quad (7)$$

and hence

$$\tilde{\nu} = \frac{\omega}{2\pi c} = \frac{1}{2\pi c}\cdot\sqrt{(2k_{base}/\rho L)\cdot\sum_{j=0}^{n-1}\cos^2[j\pi/(n-1)]} \quad (8)$$

where $\tilde{\nu}$ is the wavenumber and c is the speed of light in a vacuum. In terms of the mathematical formula

$$\sum_{j=0}^{n-1}\cos^2 j\phi = \frac{n+1}{2} + \frac{1}{2}\cos(n\phi)\cdot\sin[(n-1)\phi]\cdot\cos\phi \quad (9)$$

eqn. (8) can be further reduced to:

$$\tilde{\nu} = \frac{1}{2\pi c}\cdot\sqrt{(n+1)K_{base}/\rho L}$$
$$= \frac{1}{2\pi c}\cdot\sqrt{(n+1)k_{base}(n\langle m\rangle} \quad (10)$$

where

$$\langle m\rangle = \frac{\text{total mass of a DNA molecule}}{\text{total number of its base pairs}} \quad (11)$$

Results and discussion

Now let us use the equations derived in the above section to calculate the low-frequency modes in DNA molecules. Before going on, some points should be justified in order to make the actual calculation feasible. First, the only force constants to be counted below are those of the hydrogen bonds. The reason why the higher force constants, such as those of bond length and bond angle of the phosphodiester backbone, are not involved is as follows. If we wish to calculate the whole frequency spectrum of a DNA molecule, the discrete model must be adopted and the force constants of all those stronger bonds should be taken into account as well. This, however, is computationally impossible at the present stage owing to lack of molecular symmetry and limitations on computer size and speed. Nevertheless, if we are only interested in calculating the dominant lowest frequency (Chou, 1984) that possesses relatively much more significance in biological function (Careri *et al.*, 1975; Chou & Chen, 1977, 1978; Englander, 1980; Chou *et al.*, 1981; Zhou, 1981; Sobell *et al.*, 1983), it will be both mathematically more convenient and physically quite reasonable to apply the continuity model and take the weak bonds such as hydrogen bonds into account, as already fully demonstrated in previous papers (Chou, 1983*a*,*b*, 1984). Secondly, although the low-frequency vibration described in the preceding section is associated with, or even more has a considerable influence upon, the DNA 'breathing' via, e.g., energy transmission (Zhou, 1981) and lowering the 'threshold' value (Chou & Chen, 1977, 1978) of the barrier for 'breathing', the low-frequency vibration is by no means itself the 'breathing' motion. The latter involves the rupture of hydrogen bonds, and hence no longer belongs to elastic vibration. Furthermore, as shown below (eqn. 14), the number of hydrogen bonds thus ruptured is much smaller than that of the non-ruptured ones, and especially the period of the 'breathing' (Careri *et al.*, 1975) is much longer than that of the low-frequency vibration. Consequently, when calculating the low-frequency mode of a DNA molecule, the effect of torsional deformation of phosphodiester backbone stemming from the rupture of such a minor number of hydrogen bonds can safely be ignored. In other words, the low-frequency vibrational mode of interest is presented as involving hydrogen-bond fluctuations within a particular conformation of a 'breathing' DNA molecule, which means that, within a certain interval of time that is much larger than the period of the low-frequency vibration but smaller than the 'breathing' period, only the coupled effect of the low-frequency vibration with a particular 'breathing state', but not with the 'breathing motion',

needs to be considered for the present calculation, at least as a first-order approximation. Thirdly, although the 'stacking interaction' is also important in DNA molecules, it should be realized that the stacking energy is largely from the interaction between neighbouring bases in the same single polynucleotide chain (Poland & Scheraga, 1970) rather than between two chains. The present model, however, describes the standing-wave motions, which are essentially governed by a series of the complementary hydrogen bonds between two polynucleotide chains (Figs. 1 and 2), and hence the effect of 'stacking interaction' can be neglected in a sense of approximation.

As is well known, in a DNA molecule, there generally are purine bases such as adenine (A) and guanine (G), and pyrimidine bases such as cytosine (C) and thymine (T). The novel feature of double-helix conformation is the interchain hydrogen-bonding between nitrogen bases on different chains directly opposite each other, with a purine always bonded to a pyrimidine. More specifically, base A is always bounded to base T with two hydrogen bonds (Fig. 3*a*), and base G is always bounded to base C with three hydrogen bonds (Fig. 3*b*). In fact A:::T and G⋮⋮C pairings are termed complementary base-pairs. Accordingly, the sum of A and C residues is balanced by the sum of G and T residues, i.e. (A+C) = (G+T). Owing to these constraints, a homo-DNA double-helix structure must be either poly(A:::T) or poly(G⋮⋮C). Therefore we have:

$$k_{\text{base}} = \begin{cases} 2k_{\text{H}} & \text{for poly(A:::T) DNA} \\ 3k_{\text{H}} & \text{for poly(G⋮⋮C) DNA} \end{cases} \quad (12)$$

where $k_{\text{H}} = 13\,\text{nN/nm}$ (0.13 mdyn/Å) is the stretching force constant of a hydrogen bond (Itoh & Shimanouchi, 1970; Chou, 1983*a*,*b*). Note that it has been tacitly assumed in eqn. (12) that the force constant for the hydrogen bond N–H···N be the same as that of N–H···O (see Fig. 3). It is necessary to take such an approximate treatment because the accurate force constant for N–H···N is not yet available. However, according to a classic analysis and comparison between the hydrogen bonds N–H···O and N–H···N (Pauling, 1960), the difference between their force constants would certainly not be large, and hence it would correct the calculated low-frequency wavenumber only very trivially if a precise force constant for the hydrogen bond N–H···N were available and employed in the calculation. And:

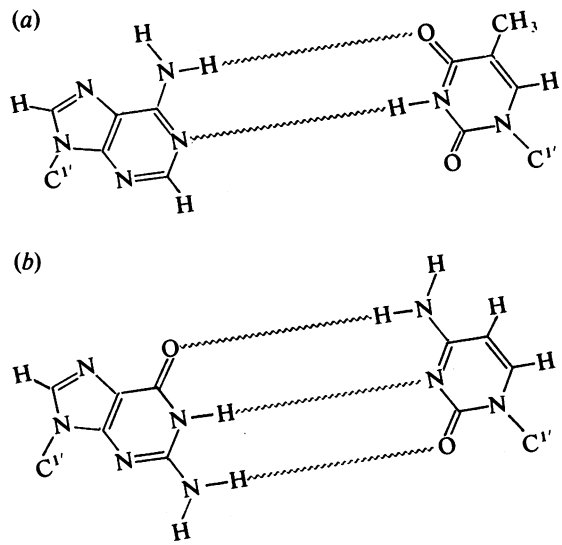

Fig. 3. *Illustrations to show that there are (a) two hydrogen bonds between the complementary nitrogen bases adenine (A) and thymine (T) and (b) that there are three hydrogen bonds between the complementary nitrogen bases guanine (G) and cytosine (C)*

$$\langle m \rangle = \begin{cases} 614\,\text{a.m.u.} = 614\,\text{g}/N & \text{for poly(A:::T) DNA} \\ 615\,\text{a.m.u.} = 615\,\text{g}/N & \text{for poly(G⋮⋮C) DNA} \end{cases} \quad (13)$$

where a.m.u. are atomic mass units and N is the Avogadro constant. Further, substitution of $K_{\text{open}} = 0.026$ (Manning, 1983) into eqn. (2) will give:

$$n = 38 \quad (14)$$

Substituting eqns. (12)–(14) into eqn. (10), we have:

$$\tilde{\nu} = \begin{cases} 27.1\,\text{cm}^{-1} & \text{for poly(A:::T) DNA} \\ 33.2\,\text{cm}^{-1} & \text{for poly(G⋮⋮C) DNA} \end{cases} \quad (15)$$

However, for a general DNA molecule, the ratio of (A+T) to (G+C) is in the range 0.98–1.12:1 (Bohinski, 1976), i.e. very close to 1:1. Therefore for a DNA molecule, instead of eqns. (12) and (13), we generally, to a fair approximation, have:

$$k_{\text{base}} = 2.5\,k_{\text{H}} = 3.25\,\text{md/nm}\ (=0.325\,\text{md/Å}) \qquad \langle m \rangle = 614.5\,\text{g}/N \quad (16)$$

Substitution of eqns. (14) and (16) into eqn. (10) yields:

$$\tilde{\nu} = 30.3\,\text{cm}^{-1} \quad (17)$$

which is in precise agreement with the observed value of $30\,\text{cm}^{-1}$ by Painter *et al.* (1981).

Note that in eqn. (10) the factor n occurs in both numerator and denominator, although in the numerator it appears as $n+1$. Simple calculations show that when $n \geqslant 10$ the relative change of $\tilde{\nu}$ for different n will be always less than 0.05. This is very interesting, and actually gives a good explanation why the observed low-frequency peak is so sharp and stable (at $\sim 30\,cm^{-1}$) although along a DNA molecule the individual K_{open} values for different segments may be different and change with time as a consequence of the closed–open motion, the so-called 'breathing'. In other words, the number of the adjacent closed base-pairs is not necessarily the same throughout the length of a DNA molecule, but this does not influence the low-frequency wavenumber saliently if $n \geqslant 10$. For example, under general conditions, the value of K_{open} measured by Mandal *et al.* (1979) is 0.02–0.05, which gives (eqn. 2):

$$n = 50\text{–}20 \qquad (18)$$

Substituting eqn. (18) as well as eqn. (16) into eqn. (10), we obtain:

$$\tilde{\nu} = 30.2\text{–}30.6\,cm^{-1} \qquad (19)$$

which is also in very good agreement with the observed value.

Conclusion

The molecular dynamics of biomacromolecules, particularly low-frequency vibrations involving the relative displacements of subunits, are thought to play a key role in biological function. Sobell *et al.* (1979, 1983) and Zhou (1981) furthermore speculated that the low-frequency vibrations might play an important role in DNA 'breathing' and drug intercalation. In the present paper a model related to DNA 'breathing' and its interchain hydrogen bonds is presented, based on which the calculated low-frequency wavenumber is in very good agreement with the observed value. Therefore the observed low-frequency peak for DNA molecules might originate from the kind of intramolecular motion as described in the present model. Because of the uniqueness of this kind of motion as well as its internal connection with the 'breathing' of a DNA molecule and the complementary hydrogen bonds therein, such a finding may give us some new insights in understanding the biological function of low-frequency motions in DNA molecules.

This work was initiated in China, and was largely accomplished while I was a visiting professor in Sweden.

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