Normal Mode Analysis on Three Different Structures of a Duplex DNA d(CGCGAATTCGCG) *

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Normal mode analysis in dihedral angle space was carried out on two X-ray crystal structures and one model structure responded to the same sequence of duplex DNA: d(CGCGAATTCGCG). Comparing these results indicates that it is reliable and meaningful to carry out normal mode analysis on model structures. The reliability is greater except for the ends of helix.

Keywords Normal mode analysis, Duplex DNA, Atomic fluctuation, Molecular dynamics

Introduction

Computer simulation approaches have been proved to be powerful tools to determine and characterize dynamics of proteins and nucleic acids. Molecular dynamics calculation, normal mode analysis and Monte Carlo simulation are three main types of computational methods. Molecular dynamics calculation is free from the assumption of the harmonicity of motion made by normal mode analysis, however, its approach is limited to the study of conformational phenomena occurring in the time range of 10^{-10} s or faster[1]. In a majority of not-very-low-frequency modes the assumption of the harmonicity is valid[2], and normal mode analysis is useful for understanding dynamics of molecular conformations in these modes.

Recently, normal mode analysis in DAS(Dihedral Angle Space) has been employed to reveal the conformational dynamics of proteins[3~5] and nucleic acids[6]. In DAS, only rotatable dihedral angles are treated as independent variables and bond lengths and bond angles are fixed. The low-frequency modes from both analyses in DAS and CCS(Cartesian Coordinate Space) span the same subspace[7]. However, the choice of DAS leads to considerable reduction of the number of independent variables compared with that of CCS. Normal mode analysis starts usually from a X-ray crystal structure. However, for many duplex DNA molecules, it is difficult or unavailable to obtain experimental structures from Protein Data Bank(PDB) or other sources. In this work we carried out normal mode analysis in CAS on two X-ray structures from PDB and a model structure which responded to the same sequence of a duplex DNA, and compared these results to understand the reliability of using a model structure to carry out normal mode analysis.

Normal Mode Analysis

Based on the harmonic assumption, normal mode analysis can be used express the conformational energy around a minimum as a multidimensional parabola[1]:

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$$E = (1/2)\sum_{i,j} f_{ij}\Delta\theta_i\Delta\theta_j \quad (1)$$

where f_{ij} is the second derivative of the conformational energy function at the minimum. $\Delta\theta$ is the infinitesimal change of dihedral angle θ.

By separating the external motions of the molecule from internal motions with the method of Eckart[8], the kinetic energy Lagrangian of internal motions in a nucleic acid molecule is given by

$$T = (1/2)\sum_{i,j} h_{ij}\Delta\dot{\theta}_i\Delta\dot{\theta}_j \quad (2)$$

Newton equation is given by

$$\boldsymbol{H}\Delta\ddot{\theta} + \boldsymbol{F}\Delta\theta = 0 \quad (3)$$

where $\boldsymbol{F}$, $\boldsymbol{H}$ are matrices whose elements are f_{ij} and h_{ij} respectively. To solve equation (3), $\Delta\theta$ is expressed as linear combination of the motions of new variables $\Delta\sigma$ (named as normal mode variables) as follows:

$$\Delta\theta = \boldsymbol{V}\Delta\sigma \quad (4)$$

where matrix $\boldsymbol{V}$ transforms the positive definite symmetric matrices $\boldsymbol{F}$ and $\boldsymbol{H}$ into a positive definite diagonal matrix Ω and an identical matrix $\boldsymbol{I}$, respectively:

$$\boldsymbol{V}^t\boldsymbol{F}\boldsymbol{V} = \Omega \quad (5)$$

$$\boldsymbol{V}^t\boldsymbol{H}\boldsymbol{V} = \boldsymbol{I} \quad (6)$$

The main strategy of normal mode analysis is to solve simultaneously the two eigen-problems(*i.e.*, the generalized eigen-problem). In the new collective variables, the equation of motion is decomposed into

$$\Delta\ddot{\sigma} + (2\pi\nu)^2\Delta\sigma = 0 \quad (7)$$

where $(2\pi\nu)^2$ is an element of the diagonal elements of matrix Ω. Equation (7) describes a harmonic oscillator, *i.e.*, a normal mode with frequency ν.

The mean-square amplitude of thermal fluctuations of the normal mode variables is given by

$$\langle\Delta\sigma^2\rangle = kT/(2\pi\nu)^2 \quad (8)$$

The mean-square fluctuation of atomic coordinates is given by

$$\langle\Delta\boldsymbol{r}_a^2\rangle = \sum_i \boldsymbol{D}_{ai}^2 \quad (9)$$

$$\boldsymbol{D}_{ai} = (kT)^{1/2}/(2\pi\nu)\sum_j k_{aj}V_{ji} \quad (10)$$

where $\boldsymbol{D}_{ai}$ is the displacement vector of the ath atom in the ith normal mode, k_{aj} is an element of matrix $\boldsymbol{K}$, *i.e.*,

$$k_{aj} = \partial r_a/\partial\theta_j \quad (11)$$

Results and Discussion

1 Minimum Structures

We chose the double-stranded dodecamer d(CGCGAATTCGCG) for our study because of the extensive crystal structural data and analysis on this sequence[9—12]. The structural perturbation attributable to crystal packing is a smooth 19 °bend in the overall helix axis. The crystal atomic coordinates were taken from 9bna[12] and 7bna[11] in PDB with the same resolutions of 0.19 nm respectively. The third structure is a model structure built by a molecule modeling software Insight Ⅱ. The total number of atoms is 758. Therefore, the number of independent variables in CCS is 2 274. In DAS the number of independent vari-

ables is 194 including 24 pseudo-rotation variables and 6 external variables between two strands.

From the three conformations we minimized the conformational energy. The AMBER potential[13] was employed as an empirical conformational energy function. The program FEDER/2N[14] was used for the minimization. The distance-dependent dielectric constant was taken equal to $4r$, *i. e.* four times interatomic distance. The minimization was performed in vacuum with Newton's method. During the minimization, the weight parameters of PDB data constraints from the X-ray conformation were decreased gradually as increasing the steps.

Fig. 1 shows that the stereo drawings of the three superimposed structures before minimizing and after minimizing. Table 1 gives the root-mean-square deviations (rms D) of Cartesian coordinates of all the atoms and the backbone atoms between the minimum structures and the original structures (those before minimizing). After minimizing, the model structure changes largely than the X-ray structures do. Table 2 gives rms D of Cartesian coordinates of the heavy atoms among the three structures, which indicates that the differences among the model structure and the X-ray structures become smaller with respect to those among the original structures. Therefore, it may be expected that the differences between the result of normal mode analysis on the model structure and those on the X-ray structures are smaller.

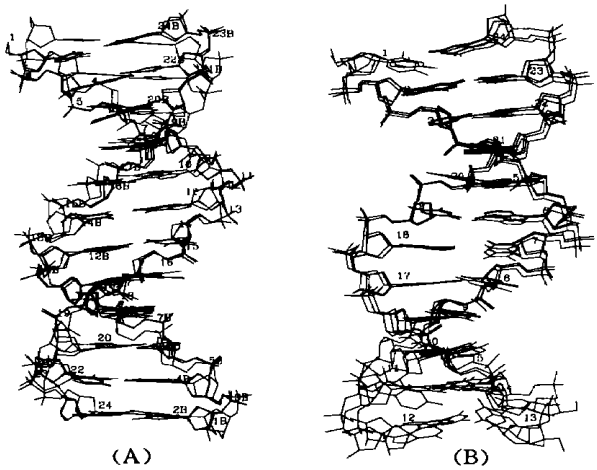

Fig. 1 Stereo drawings of the three superimposed structures.
(A) before minimizing; (B) after minimizing.

Table 1 rms D of Cartesian coordinates of the atoms between the minimized structures and the original structure (in nm)

Structure	All atoms	Backbone atoms
9bna	0.174 2	0.179 2
7bna	0.174 6	0.181 3
Model	0.226 0	0.226 1

Table 2 rms D of Cartesian coordinates of the heavy atoms among the three structures (in nm)

Structure	Before minimizing		After minimizing	
	7bna	model	7bna	model
9bna	0.030 9	0.153 9	0.069 3	0.087 6
7bna		0.151 6		0.120 8

2 Frequency Histogram

For each structure, 194 normal modes were obtained, which is the number of independent variables in DAS. The distributions of the calculated frequencies are illustrated in Fig. 2. The frequencies are shown by corresponding light wave numbers. The number of normal modes in each interval of 5 cm^{-1} is shown. The number of normal modes with fre-

quencies 200～450 cm^{-1}, is 6 for 9bna structure, 4 for 7bna structure and the model structure, respectively. Fig. 2 shows that the low-frequency modes are very similar to high-frequency modes, the significant difference occurs in a few modes with frequencies 200～450 cm^{-1}. It has been shown[7] that the atomic fluctuations of the duplex DNA are mainly determined by a small number of low-frequency normal modes, the normal modes with frequencies below 30 cm^{-1} make major contributions to the site-dependence of atomic fluctuations, those with frequencies above 30 cm^{-1} contribute mainly to site-independent "background" motions. Therefore the differences among the modes with frequencies 200～450 cm^{-1} are trivial.

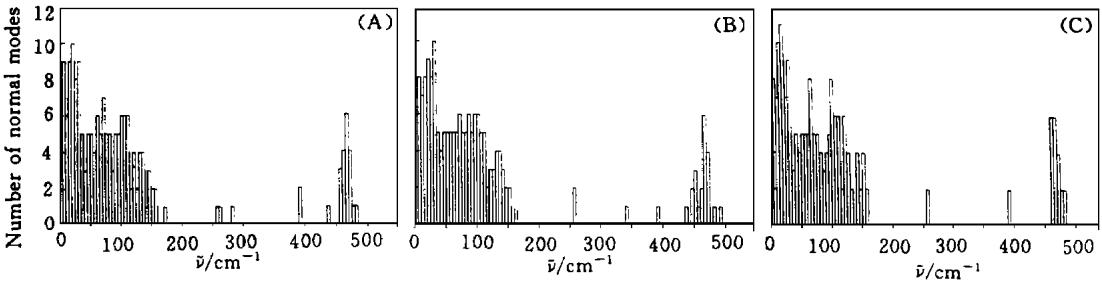

Fig. 2 Histograms of calculated vibration frequencies of normal modes in this dodecamer for 9bna structure (A), 7bna structure (B) and the model structure (C).

Table 3 gives the frequencies of four very-low-frequency modes LFM 1, LFM 2, LFM 3, LFM 4 and the highest frequencies HFM for the three structures. Table 3 together with Fig. 2 indicates that the frequency distributions of the three structures are very similar.

Table 3 The four very-low-frequency modes and the highest frequencies for the three structures($\tilde{\nu}$/ cm^{-1})

Structure	LFM 1	LFM 2	LFM 3	LFM 4	HFM
9bna	2.13	2.36	3.58	4.35	485.93
7bna	2.10	2.29	3.74	5.05	496.84
model	2.19	2.41	3.81	4.96	486.14

3 Fluctuations of Positions of Atoms

Fig. 3 shows the site-dependencies of rms fluctuations of positions of all the atoms for

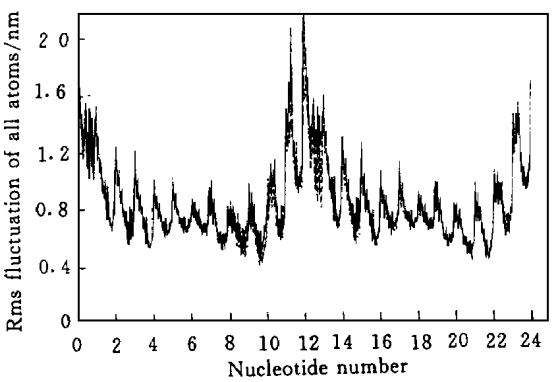

Fig. 3 Site-dependencies of rms fluctuations of positions of all atoms for 9bna structures(Solid line), 7bna structure(broken line) and the model structure(dotted line).

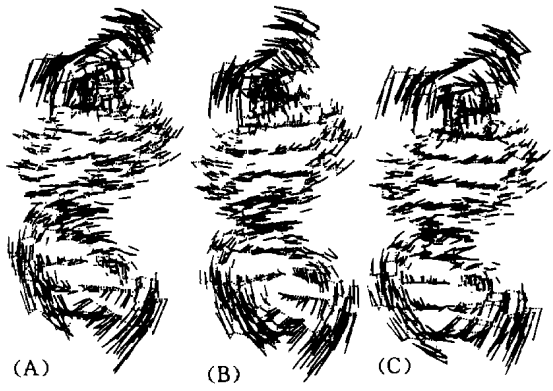

Fig. 4 Stereo drawings of atomic displacement vectors in the second lowest frequency mode LFM 2 of 9bna structure(A), 7bna structure(B) and the model structure(C).

the three structures. Solid line is for 9bna structure, broken line for 7bna structure, dotted line for the model structure. Except for the terminal nucleotide G12, the differences among rms atomic fluctuations of the three structures are much small. By examining the three structures, we observed a larger base-pair bucking between G12-C13 in these minimum structure. Fig. 3 illustrates the similarity between the atomic fluctuations of strand A and those of strand B, which suggests the presence of a two-fold pseudo-symmetry axis with its origin located at the center of the molecule. The ideal two-fold symmetry is destroyed by the 19 °bend in the helix axis. Fig. 3 also exhibits that the atoms at the ends of helix move more than in the center, possibly due to the incompleteness of base-stacking at the ends of helix. Fig. 4 shows the stereo drawings of atomic displacement vectors in the second lowest frequency mode LFM2 of the three structures. These plots are similar to each other on the whole.

4 Conclusions

The similarities among the results of normal mode analysis on two X-ray crystal structures(9bna and 7bna) and a model structure suggest that we can carry out normal mode analysis on a model structure of duplex DNA if the experimentally obtained structure is unavailable. The reliability is greater except for the ends of helix. This is excepted to be meaningful for some bigger DNA molecules, in which the influences of terminal nucleotides are trivial.

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