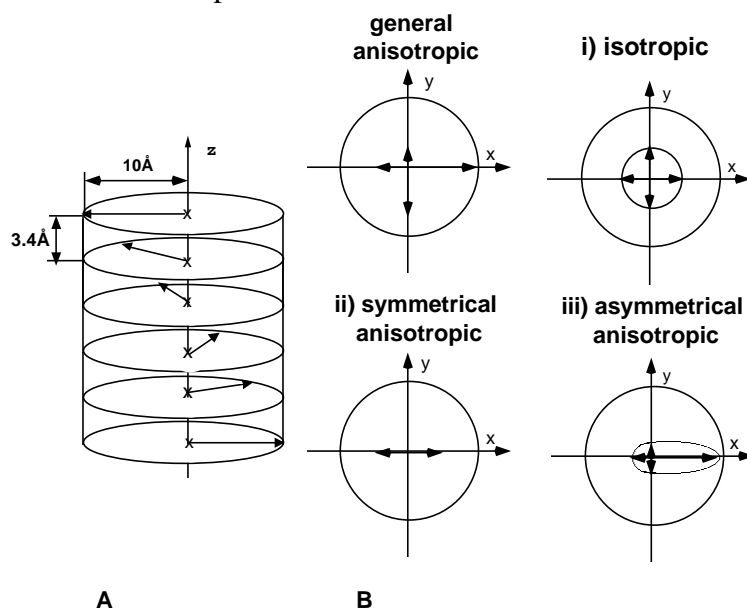


## NON-LINEAR BEHAVIOUR OF ANISOTROPIC ELASTIC BENDING MODELS OF DNA

Mircea Gh. Munteanu, M. Michael Gromiha and Sándor Pongor  
International Centre for Genetic Engineering and Biotechnology  
Area Science Park, Padriciano 99, 34012 Trieste, Italy

The possibility that the DNA molecule may contain local bends and kinks has profoundly influenced the current thinking of biologists. DNA is no longer considered to be a straight double helix, but rather like a series of structural and functional domains differing in shape and flexibility. In fact, inherent or induced bending of DNA seems to occur at precise sequence locations and now have been shown to play important roles in virtually all processes affecting DNA. Flexibility of DNA was known to be non-uniform, i.e. *sequence dependent* [Brukner et al, 1995], and seems to be a carrier of conformational signals [Gabrielian et al, 1996, Gabrielian and Pongor, 1996].

The structure of DNA has been studied with several models of varying complexity. The simplest of these is the elastic rod model which describes DNA as a long, isotropically elastic rod under tension-compression, torsional and bending stress. Sequence-dependent bending of DNA is not incorporated in these models. Instead, most authors use the average Young's modulus value of DNA,  $3.4 \times 10^8 \text{ N/m}^2$ , which is known from experiments.



**Figure 1** Schematic outline of the sequence-dependent bending models

**A** DNA as a segmented elastic rod model. Each element corresponds to one basepair. The arrows in each basepair schematically indicate the direction pointing towards the major groove of the double helix..

**B** Schematic outline of the flexibility anisotropy within an element. The length of the arrows are proportional to the flexibility ( $\sim$ the inverse of stiffness) in a given direction (+x, -x, +y, -y). In the general case, all of these are different. In the isotropic case (i) all of them are equal. In the symmetrical anisotropic case (ii) two of them are equal and bending is disallowed in the two other directions. In the asymmetrical anisotropic case (iii) one direction (that of the major groove) is more flexible, the other three are more rigid.

A *sequence dependent* elastic DNA model is a segmented elastic rod with circular cross-section of radius  $10 \text{ \AA}$  consisting of  $3.4 \text{ \AA}$  thick discs corresponding to each basepair (Figure 1a). Each of these

will have a different Young's modulus value. Anisotropic flexibility of DNA within a disk (basepair) is meant to express the experimental finding that DNA can bend primarily in one direction and much less in the three other directions. This can be best pictured by considering the top view of a disc as shown in Figure 1b. The distinguished direction is the +x direction, and stiffness in all the other directions is  $a$ -times greater. We name this factor the *anisotropy ratio*. In biology a sequence of basepairs is indicated by a letter string, for instance: (aaaatttgc)<sub>n</sub>, subscript n indicates that the sequence is repeated n times.

The aim of this work is to design simple elastic DNA models that reflect the experimentally known anisotropic bending behaviour of DNA. In the general case, one disk (one basepair) can have different stiffness values in the 4 perpendicular directions (+x, -x, +y, -y). The anisotropy can be described by 4 *anisotropy ratios* ( $a_{+x}$ ,  $a_{-x}$ ,  $a_{+y}$ ,  $a_{-y}$ ). We will consider three models:

i) In the *isotropic model* each disk is equally flexible in all four directions which amounts to saying that  $a_{+x} = a_{-x} = a_{+y} = a_{-y} = 1$ .

ii) In the *anisotropic symmetrical model*, bending is allowed in the +x and -x directions, but not in the other two directions. This is equivalent to saying that  $a_{+x}=a_{-x}=1$ , and stiffness is very large in the two remaining directions, e.g.  $a_{+y}=a_{-y} \gg 1$ .

iii) Finally, the *anisotropic asymmetrical model* allows bending only in the direction +x and is uniformly stiffer if bent in all other three directions. This can be expressed as  $a_{+x}=1$ , and  $a_{-x} = a_{+y} = a_{-y} \gg 1$ .

In fact,  $a$  is an arbitrary parameter whose value was taken as being in the range of 1 and 100. It has to be noted that the "distinguished direction" is not the same for the different disks (basepairs), it follows rather the helical symmetry. This means that this direction rotates around the z axis of DNA by the value of the twist angle,  $\omega$ , between two successive basepairs. In ideal B-DNA, the value of  $\omega$  is  $36^\circ$  which corresponds to 10 basepairs per helical turn. In "realistic B-DNA" this value is closer to  $10.5$  basepairs per turn which corresponds to  $34.3^\circ$ .

The goal of the simulation is to establish the response of the DNA models to bending distortion. This is best done by exposing the models to a concentrated bending moment, so that each basepair unit is subjected to an identical moment. Such pure bending can be modelled by representing a DNA molecule as an initially straight rod, of length  $L$ , clamped at one end and loaded with a concentrated bending moment at the other end. The bending moment may have any direction. Due to the anisotropic behaviour of the rod, although the moment has the same value in all directions, the resultant displacements are not the same, so that these displacements form an ellipsoid. It is possible to determine the average  $E$ , or the equivalent  $E$  modulus of the whole rod using the relation:

$$E = \frac{ML^2}{2\Delta I} \quad (1)$$

where  $I$  is the inertia moment of the cross-section. The value of the bending moment is  $M = 2 \times 10^{-11}$  NÅ. In order to eliminate the influence of the moment and of the length of the rod on the result, instead of displacement  $\Delta$ , the *reduced displacement* was computed as follows:

$$\delta = \frac{\Delta}{Mn^2} \quad (2)$$

where  $n$  is the number of the disks in the model. Each basepair was represented as one 3D beam element with two nodes. Both the isotropic and symmetrical anisotropic models are linear. On the contrary, *the asymmetrical anisotropic model is non-linear*. This was carried out by replacing the original structure by an alternative model using non-linear facilities of the COSMOS computer code. For example, the asymmetrical anisotropic model used for the sequence  $(tctctaaaaatatataaaaa)_n$  contained 210 basepairs, and was described by 1470 elements and 6300 equations.

It was demonstrated previously [Gromiha et al, 1996] that the average Young's modulus can be calculated from the isotropic moduli of the  $i^{\text{th}}$  element,  $E_{\text{iso},i}$ , and the anisotropy constants as follows:

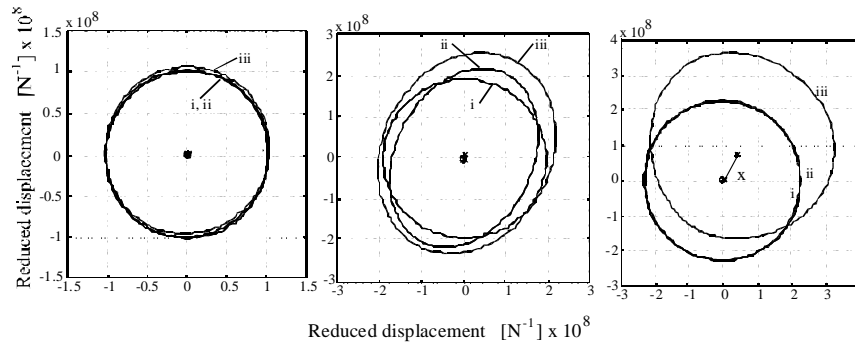
$$\frac{1}{E} = \frac{1}{4N} \sum_i \left[ \left( \frac{1}{a_{+x} \cdot E_{\text{iso},i}} + \frac{1}{a_{-x} \cdot E_{\text{iso},i}} + \frac{1}{a_{+y} \cdot E_{\text{iso},i}} + \frac{1}{a_{-y} \cdot E_{\text{iso},i}} \right) \right] \quad (3)$$

$N$  is the number of all different basepair types (there are 32 basepair types, that is  $N=32$ ). So, the  $E$  modulus for the all basepair are computed using two conditions: (a) the value of  $E$  given by eqn.(3) should remain equal to the experimental value,  $3.4 \times 10^8 \text{ N/m}^2$ . (b) The range of  $E$ -values will have to be specified. The ratio between the maximal and the minimal values of the Young moduli Assigned to the  $N$  basepair types is denoted by  $s$ . For  $s=1$  we obtain the sequence independent elastic model. In our models it was arbitrarily assumed that each nucleotide is 10 times more flexible in one direction than in the other directions ( $a = 10$ ) and the ratio of the maximum and minimum  $E$ -modulus is 5 ( $s=5$ ). The values of these parameters influence the bending behaviour of the models but the findings of the work do not crucially depend on them (for  $s>5$  and  $a>10$  the influence of these values is small). It has to be added that the measured quantities all depend on factors other than DNA rigidity. Thus a perfect agreement can not be expected.

For the calculations we selected two straight and two curved sequences whose behavior is well known from experiment. Poly(a) is known to be rigid and, as a homopolymer, it is devoid of macroscopic curvature. Also the repeat sequence  $(atctaataacacacacaca)_n$  was shown to be straight by electron microscopy. In contrast, the repeat sequences  $(tctctaaaaatatataaaaa)_n$  and  $(aaaattttgc)_n$  were both shown to be curved. As a rule we studied 200 or 210 nucleotide long DNA models built from the repeat sequences. The centre of the bendability ellipsoid corresponds approximately to the average displacement of the rod when exposed to the same bending moment from (equally distributed) random directions. For an isotropically elastic rod, this point is in the origin, i.e. the "average conformation" of the rod is straight.

The results are shown in Figure 2. Poly(A) behaves like an isotropically elastic rod, even though two of the models used are asymmetrical (Figure 2a). This is a consequence of the fact that poly(A) is a homopolymer, so each segment of the rod is equal. The curved sequences show quite different bendability ellipsoids (Figure 2c). First, the ellipsoids are more asymmetrical, especially in the case of the anisotropic asymmetric model. Second, the centre of the ellipsoids is substantially distant from the origin. One has to mention that the bending anisotropy (the distance between the centre of the bendability ellipsoid and the origin) depends also on the twist angle. For the sequence  $(aaaattttgc)_n$  the maximum asymmetry was obtained at  $\omega = 36^\circ$ , while for the sequence  $(tctctaaaaatatataaaaa)_n$  the maximum asymmetry was found at  $34.3^\circ$ .

## Non-linear Behaviour of Anisotropic Elastic Bending Models of DNA



**Figure 2** Bendability properties of DNA molecules as calculated according to the various bending models. The relative displacement (displacement/ moment/nucleotide) in the X and Y directions is plotted as a bendability ellipsoid fitted on 16 points calculated by using a constant moment in 16 equidistant directions 0, 22.5, 45, ... 135, 157.5 ... 315, 337.5 degrees with respect to the +x axis).  $x$  is the distance (relative displacement) of the centre of the bendability ellipsoid from the origin.

- Poly A
- (atctaataacacacaca)<sub>n</sub> and
- (tctctaaaaaatatataaaaa)<sub>n</sub>

From the biological point of view, the crucial finding of this simulation is that the sequence dependent anisotropic bendability of DNA, well known from experiment, can be simply reproduced by allowing one single property, i.e. the bending stiffness of DNA, be anisotropic and sequence dependent, as in model iii. This finding has the interesting consequence that some will be curved when exposed to randomly distributed bending distortions, which occurs when a DNA collides with water (solvent) molecules. This is in fact the case: these sequences behave as curved in solution.

Summarizing, we found that the sequence dependent anisotropic bending rigidity of DNA provides by itself a simple explanation for intrinsic DNA curvature. Asymmetric bending profiles were obtained for a number of sequence motifs that are known to be intrinsically bent, and, in contrast, symmetric bending profiles were obtained for straight sequence motifs. The models are simple so as to allow the study of longer sequences with finite element methods, not only statically, but also in the dynamic range.

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