Bending and curvature calculations in B-DNA

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ABSTRACT

A simple program, BEND, has been written to calculate the magnitude of local bending and macroscopic curvature at each point along an arbitrary B-DNA sequence, using any desired bending model that specifies values of twist, roll and tilt as a function of sequence. The program has been used to evaluate six different DNA bending models in three categories. Two are bent non-A-tract models: (a) A new model based on the nucleosome positioning data of Satchwell *et al* 1986 (*J. Mol. Biol.* 191, 659–675), (b) The model of Calladine *et al* 1988 (*J. Mol. Biol.* 201, 127–137). Three are bent A-tract models: (c) The wedge model of Bolshoy *et al* 1991 (*Proc. Natl. Acad. Sci. USA* 88, 2312–2316), (d) The model of Cacchione *et al* 1989 (*Biochem.* 28, 8706–8713), (e) A reversed version of model (b). The last is a junction model: (f) The model of Koo & Crothers 1988 (*Proc. Natl. Acad. Sci. USA* 85, 1763–1767). Although they have widely different assumptions and values for twist, roll and tilt, all six models correctly predict experimental A-tract curvature as measured by gel retardation and cyclization kinetics, but only the new nucleosome positioning model is successful in predicting curvature in regions containing phased GGGCCC sequences. This model—showing local bending at mixed sequence DNA, strong bends at the sequence GGC, and straight, rigid A-tracts—is the only model consistent with both solution data from gel retardation and cyclization kinetics and structural data from x-ray crystallography.

INTRODUCTION

Sequence-dependent DNA bending, like sequence-dependent protein folding, is a problem that remains frustratingly elusive. The issue has obvious biological importance in such matters as the winding of DNA in nucleosomes (1), or the recognition of particular DNA loci by restriction enzymes, repressors and other control proteins. The binding of the catabolite gene activator protein (2) and of the TATA-box recognition protein (3,4) to a DNA double helix are only two spectacular examples in which major bends in the helix are induced at specific sequence loci. It is of interest to consider whether the particular recognition sequences are bent even in the absence of proteins: a preformed

bend in the DNA would form a custom site for protein binding, or an enhanced bendability of a given sequence would facilitate protein-induced bending.

Two possible models of sequence-dependent bending in free DNA have been proposed in the past. Nearest neighbor models propose that large-scale measurable curvature may arise by the accumulation of many small local deformations in helical twist, roll, tilt and slide (for definitions see reference 5) at individual steps between base pairs (6–11). Junction models, on the other hand, propose that bending occurs at the interfaces between two different structural variants of the B-DNA double helix (12,13). Note that in both of these models, sequences which are anisotropically bendable—for instance, sequences with steps that preferentially bend only to compress the major groove—will lead to an average structure which is similar to a sequence with a rigid, intrinsic bend. The work below will not distinguish between these two possibilities.

For any particular bending model, it is useful to be able to compute quickly and easily the curvature that would be predicted at all positions along a chosen base sequence (11,14). The larger problem of defining and following a helix axis in the most general case is not trivial. The coordinate transformation from one base pair to the next and calculation of curvature is a fairly intricate example of matrix algebra. Detailed calculation of local helix axis trajectories have been described by numerous authors (14–20).

But for the special case of B-DNA, and for purposes of obtaining a rapid evaluation of sequence-dependent curvature along an arbitrary base sequence, this mathematical sophistication is not necessary. B-DNA has the special property of having its base pairs very nearly perpendicular to the overall helix axis. Hence the normal vector to each base pair can be taken as representing the local helix axis at that point, and curvature and bending can be studied simply by observing the behavior of the normal vectors from one base pair to another along the helix. This is both easy to calculate and simple to interpret. A short FORTRAN program, BEND, has been written to study curvature of an arbitrary sequence, using any of the current bending models as desired, and is available to the reader upon request. The program displays the *magnitude* of bending and curvature at each point along the sequence. It is not intended as a substitute for more elaborate three-dimensional trajectory calculations, but only to express bending tendencies as a function of sequence. The

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Table 1. Roll, tilt and twist parameters used in various DNA-bending models**I. Trimer Models**

(a) Nucleosome Positioning Model: adapted from Satchwell, Drew & Travers (6).

Tilt = 0°; Twist = 34.3° (10.5 base pairs per turn)

Roll:

2nd base:

3rd base:

		G	G	C	T	A	G	C	T
		A				A			
1st base:	A	3.3°	5.4°	7.5°	5.8°	0.0°	5.2°	3.7°	0.7°
	G	3.8°	6.0°	10.0°	5.4°	3.0°	5.4°	5.4°	5.3°
	C	8.3°	4.7°	7.5°	5.4°	3.3°	4.2°	6.5°	6.7°
	T	5.4°	5.4°	6.0°	5.2°	2.0°	2.2°	3.7°	2.8°

II. Dimer Models

Base Step Type:

Base Step:

Purine–Purine

AA

GA

AG

GG

Purine–Pyrimidine

AT

AC

GC

Pyrimidine–Purine

TA

CA

CG

(b) Calladine, Drew & McCall Model (7):

Roll:	0°	3.3°	3.3°	3.3°	3.3°	3.3°	3.3°	6.6°	3.3°	3.3°
Tilt:	0°	0°	0°	0°	0°	0°	0°	0°	0°	0°
Twist:	35°	34°	34°	34°	34°	34°	34°	34°	34°	34°

(c) Bolshoi, McNamara, Harrington & Trifonov Model (8):

Roll:	−6.5°	−2.7°	8.4°	1.2°	2.6°	−0.9°	−5.0°	0.9°	1.6°	6.7°
Tilt:	3.2°	−4.6°	−0.3°	−1.8°	0°	−0.7°	0°	0°	3.1°	0°
Twist:	35.62°	36.90°	27.70°	33.67°	31.50°	34.40°	40.00°	36.00°	34.50°	29.80°

(d) Cacchione, De Santis, Foti, Palleschi & Savino Model(10):

Roll:	−5.4°	2.0°	+1.0°	1.3°	−7.3°	−2.4°	−3.7°	8.0°	6.7°	4.6°
Tilt:	−0.5°	−1.7°	−1.6°	−0.6°	0°	−2.7°	0°	0°	0.4°	0°
Twist:	35.9°	35.8°	35.6°	33.0°	35.0°	34.6°	33.3°	34.6°	34.5°	33.7°

(e) Reversed Calladine, Drew & McCall Model

Roll:	3.3°	0°	0°	0°	0°	0°	0°	−3.3°	0°	0°
Tilt:	0°	0°	0°	0°	0°	0°	0°	0°	0°	0°
Twist:	35°	34°	34°	34°	34°	34°	34°	34°	34°	34°

(f) Koo & Crothers Model (12)

		***	***			***		***	***	
Roll:	0°	5.8°	0°	0°	0°	0°	0°	11.6°	5.8°	0°
Tilt:	0°	−9.6°	12.0°	0°	0°	12.0°	0°	0°	−9.6°	0°
Twist ⁺ :	34.3°	34.3°	34.3°	34.3°	34.3°	34.3°	34.3°	34.3°	34.3°	34.3°

In models *b–f*, Roll and Twist are the same for complementary pairs (i.e.—CT and AG). Tilt reverses sign for such pairs.

*** = Only when associated with 3 or more successive A's. Roll and Tilt are zero otherwise.

⁺Not explicitly specified in paper. Chosen here to correspond to 10.5 base pairs per turn.

power of this simple approach is in its ease in screening for regions of a given DNA sequence where phased local bends add constructively to form an overall curve.

For purposes of clarity, the terms *bending* and *curvature* will be used in a restricted sense in this paper. *Bending* of DNA describes the tendency for successive base pairs to be non-parallel in an additive manner over several base pair steps. Bending most commonly is produced by a rolling of adjacent base pairs over one another about their long axes, although in principle, tilting of base pairs about their short axes could make a contribution. In contrast, *curvature* of DNA represents the tendency of the helix axis to follow a non-linear pathway over an appreciable length, in a manner that contributes to macroscopic behavior such as gel retardation or ease of cyclization into DNA minicircles. The distinction between local bending and macroscopic curvature is illustrated in Figure 1.

An x-ray crystal structure analysis cannot show curvature, but can and often does show local bending (21–24). On the other hand gel electrophoresis and cyclization kinetics can detect macroscopic curvature, but not local bending. A complete knowledge of local bending would permit the precise calculation of curvature, but a knowledge of macroscopic curvature alone does not allow one to specify precisely the local bending elements that produce it (13, 25–27). This is one of the scale paradoxes

that have plagued the DNA conformation field for a decade or more. There is more than a passing resemblance to a familiar problem of classical statistical mechanics: A complete knowledge of instantaneous positions and velocities of all molecules of a gas allows one to calculate bulk properties such as temperature, pressure and volume. But the most detailed knowledge of bulk properties cannot lead one to precise molecular positions. Many molecular arrangements can produce identical bulk properties, and in the present case, many bending combinations can produce identical macroscopic curvature. A choice of bending model must be made on other grounds.

METHODS

The BEND program reads a base sequence list and a matrix of standard twist, roll and tilt angles for each type of base pair step. This matrix is entirely at the disposal of the user, and can be altered, for example, to represent any of the DNA-bending models listed in Table 1. The program creates a postscript file displaying a profile of the bending and the curvature at each base step.

The program begins by applying the indicated twist, roll and tilt at each step along the sequence, and calculating the resulting base pair normal vector. The first base pair is aligned normal

Table 2. Fractional variation of occurrence of trinucleotides on the outside or inside of DNA wound around nucleosomes or in closed minicircles

Triplet		% out	Triplet	Triplet	% out
GGC/GCC	+45	TGG/CCA	+8	TAC/GTA	−6
TCG/CGA	+31	CGT/ACG	+8	AAC/GTT	−6
AGC/GCT	+25	AGG/CCT	+8	AGA/TCT	−9
CGC/GCG	+25	GAC/GTC	+8	CAA/TTG	−9
CAT/ATG	+18	TGA/TCA	+8	GAA/TTT	−12
CAC/GTG	+17	GAT/ATC	+7	TAT/ATA	−13
GGG/CCC	+13	TGT/ACA	+6	TAG/CTA	−18
TGC/GCA	+13	AAG/CTT	+6	TAA/TTA	−20
AGT/ACT	+11	CGG/CCG	+2	AAT/ATT	−30
GAG/CTC	+8	CAG/CTG	−2	AAA/TTT	−36
GGT/ACC	+8	GGA/TCC	−5		

Fractional variation $\times 100$ or expressed as percent. + = outside; - = inside. From (6).

to the z axis, with a twist value of 0.0 degrees. The specified twist is applied to the second base pair, and roll and tilt values are used to calculate its normal vector relative to the first. If either roll or tilt is nonzero, the new normal vector will be angled away from the z axis, producing the first 'bend'. This process is continued along the sequence, applying the appropriate twist, roll and tilt to each new base pair relative to its predecessor. The result is a list of normal vectors for all base pairs in the sequence.

Local bends then are calculated from the normal vectors. The user defines a bracket, n_b , across which the bend is calculated. For instance, with $n_b = 2$, the program calculates the angle between the normal vectors of base pairs $N-2$ and $N+2$, and assigns this as the 'bend' at base pair N . The bracket parameter n_b should be small, 1 or 2. Larger values will measure too large a fraction of a full turn of helix, smoothing away sites of local bending.

Curvature is calculated in two steps. Base pair normals are first averaged over a 10-base-pair window to filter out the local writhing of the helix. The normals of the nine base pairs from $N-4$ to $N+4$, and the two base pairs $N-5$ and $N+5$ at half weight, are averaged and assigned to base pair N . Curvature then is calculated from these averaged normal vector values, using a bracket value, n_c , of the order of 15. That is, the curvature at base pair N is the angle between averaged normal vectors at base pairs $N-n_c$ and $N+n_c$.

BEND is available as a short FORTRAN program upon request by electronic mail to: goodsell@scripps.edu, or to: red@uclaue.mbi.ucla.edu.

APPLICATIONS

Bending models

Any bending model that assigns a value of twist, roll and tilt to each type of base step may be used with this program. Six examples are listed in Table 1 and are tested in Figure 2. All but the first model were deliberately crafted to reproduce the curvature that results when short A-tracts are interspersed with general-sequence B-DNA in phase with the natural turn of the helix, as measured by electrophoretic gel migration and cyclization kinetics. Models *a* and *b* can be described as 'bent non-A-tract' models, since the resulting curvature is ascribed to local bends within the general sequence, not the A-tracts. Models *c*, *d*, and *e*, on the other hand, are 'bent-A-tract' models, since they predict that curvature in phased A-tracts arises mainly from

Figure 1. Bending and curvature in DNA. Local *bending* is defined as the deviation from a straight helix over a fraction of a helical repeat: two or three base pairs, and *curvature* is measured over several helical repeats: twenty or more base pairs. This diagram shows two pieces of DNA, the upper one uncurved, the lower curved. Each segment represents five base pairs or half a turn of B-DNA helix. (a) An equivalent local bend at each base step in general-sequence DNA, produced, for example, by base pair roll, yields an uncurved but gently writhed overall helix. (b) Substitution of every other five-base-pair segment by an unbent segment induces macroscopic curvature.

bending within the short A_n segments themselves. Finally, model *f* is a 'junction model' which ascribes the observed curvature to a change of helix axis orientation at junctions between A-tract and general-sequence DNA.

(a) *Nucleosome positioning model, Table 1a.* The roll-tilt-twist parameters of this model are derived purely from experimental observations of sequence location preferences of base trimers in small circles of DNA, without reference to

Figure 2. Profiles of bending and curvature in several test sequences, using six different local bending models. Bending at each step is shown as a solid line, and curvature as a dashed line. The upper 50 base sequence contains phased A-tracts, the second contains A-tracts exactly out-of-phase, and the third contains phased GGGCCC hexamers. The lower five lines contain a sequence from kinetoplast minicircles, with the experimentally determined center of curvature marked by an arrow. Bent-non-A models: (a) Nucleosome positioning model, Table 1a. (b) Calladine *et al* model, Table 1b. Bent-A-tract models: (c) Bolshoy *et al* model, Table 1c. (d) Cacchione *et al* model, Table 1d. (e) Reversed Calladine *et al* model, Table 1e. Junction-bend model: (f) Koo & Crothers model, Table 1f (adenine and thymine bases which are not in A-tracts are written in lower case and are treated as general sequence). Note that all six models predict the same curvature behavior in phased A-tracts and no curvature in the out-of-phase A-tracts, even though the pattern of local bending is quite different. Note also that only the nucleosome positioning model *a* successfully predicts curvature in the phased-GGGCCC sequence.

c. Bolshoy *et al* Model

Phased A-tracts

Out-of-phase A-tracts

Phased GGGCCC

Kinetoplast DNA

d. Cacchione *et al* Model

Phased A-tracts

Out-of-phase A-tracts

Phased GGGCCC

Kinetoplast DNA

e. Reversed Calladine *et al* Model

Phased A-tracts

Out-of-phase A-tracts

Phased GGGCCC

Kinetoplast DNA

f. Koo & Crothers Model

Phased A-tracts

Out-of-phase A-tracts

Phased GGGCCC

Kinetoplast DNA

and oligonucleotide circularization data from 54 different synthetic oligonucleotides (8,9). This model has the largest tilt values, and greater excursions from 36° twist (28° to 40°) than any of the alternates.

(d) *Cacchione et al model*, Table 1d. This model uses local twist, roll and tilt values for all two-base-pair steps, as obtained originally from conformational energy calculations (10,11). The results are said to be not incompatible with single crystal analyses of oligonucleotides. They also are successful in accounting for experimental electrophoretic gel mobilities of 62 different sequences.

(e) *Reversed Calladine et al model*, Table 1e. An interesting feature of the Fourier series expressions used by Calladine, Drew and McCall (7) is that mathematically identical curvature results are obtained if all roll and twist values are added to, or subtracted from, any arbitrary constant. Hence the published straight-A-tract model with roll values of 0°, +3.3° and +6.6° for AA, general sequence and TA steps, respectively, will predict exactly the same curvature and gel migration behavior as a reversed or bent-A-tract model with roll values of +3.3°, 0° and -3.3°, respectively. The Calladine *et al* 'bent-non-A-tract' model can be turned into a reversed Calladine *et al* 'bent-A-tract' model by simply subtracting the three standard roll angles from a constant 3.3°.

(f) *Koo and Crothers model*, Table 1f. This junction model was proposed originally by Koo and Crothers (12) specifically to explain anomalous electrophoretic migration through gels. Appreciable roll and tilt values are assigned to steps at either end of a run of three or more successive adenines ('A-tracts'), with zero roll and tilt elsewhere. TA steps in the middle of an A-tract are considered disruptive, but not AT steps. A uniform twist angle is assumed corresponding to 10.5 base pairs per turn.

Base sequences

Four sequences were used as test cases. The phased A-tract sequence contains A₆-tracts phased with the ten base pair helix periodicity. This sequence shows strong curvature in gel migration and cyclization kinetics experiments (29–34). The out-of-phase A-tract sequence contains A₆-tracts placed exactly out of phase via a periodicity of 15 base pairs or 1.5 helix turns. This sequence shows no appreciable curvature in solution experiments (29–34). The phased GGGCCC sequence contains the hexamer GGGCCC in phase with the helix periodicity. In the presence of magnesium, this sequence shows a curve of similar magnitude to phased A-tract sequences (35–37). The kinetoplast DNA sequence contains the first example of an intrinsically bent sequence to be characterized. The sequence is from *Leishmania tarentolae* kinetoplasts (29, corrected by 38). The center of bending was located experimentally at the center of four phased A-tracts (31), as indicated by the arrow in Figure 2.

RESULTS

Trials were run with the test sequences to determine the effect of different bracket sizes on bend and curvature calculations. Values of $n_b = 1$ for bending and $n_c = 15$ for curvature gave the best results. Larger values for the bend bracket made it difficult to locate the actual site of each bend; the profile smeared

into a uniform landscape. Values smaller than 15 for the curvature bracket, n_c , lost the discrimination of curved vs. non-curved regions, following instead the local bending behavior. Larger values of n_c , as with bending, smeared the curvature profiles excessively. However, the peak of curvature in the kinetoplast sequence changed by only a few base pairs as n_c was varied between 10 and 20, and remained centered on the experimental locus.

Bending and curvature profiles for the test sequences with all six trial models are shown in Figure 2. All models correctly predict curvature for phased A-tracts and no curvature for out-of-phase A-tracts. With appropriate adjustment of vertical scale the curvature plots would be almost exactly superimposable, even though the local bending patterns are totally different. For models *b–f* this is hardly surprising, as all were designed specifically to reproduce precisely these curvature results. Nucleosome positioning model *a*, however, was not formulated with A-tract bending in mind, so it is interesting that this model also predicts the correct curvature behavior. The difference in magnitude of curvature between the six plots of Figure 2 is not significant. Each curve profile may be scaled arbitrarily up or down to give the proper curvature by scaling uniformly each roll and tilt angle. The absolute magnitude of curvature in these sequences is still a subject of debate, so we made no attempt to normalize each curve.

The five models derived from A-tract studies, *b–f*, fail completely to anticipate appreciable curvature for the phased GGGCCC sequence. However, nucleosome positioning model *a* does predict a significant bend at the center of each GGGCCC sequence, constructively summing to yield a curvature for the entire segment. It does so, of course, because of the high positive 'percent-out' values of GGC triplets in Table 2, and the negative values for TAG and AGA triplets five base pairs away. This bending at GGC is no surprise: it has been inferred from cation-dependent electrophoretic gel migration studies (35–37), and directly observed in x-ray crystal structures of DNA decamers that show a 24° bend in the center of the sequence: CATGGCCATG (21), and across the interhelix junctions of stacked helices of sequence: CCAxxxxTGG CCAxxxxTGG (22).

Profiles for the kinetoplast sequence are shown in Figure 2. All six models accurately predict the experimental center of curvature (31), marked with an arrow, and a secondary center of curvature about 100 base pairs further down the sequence. Both curves are the result of A-tracts arranged approximately in phase with the helical repeat. Note that the kinetoplast sequence does not test the different bending models as rigorously as the previous sequence, because it has no phased repetitions of bend-favoring sequences such as GGCC.

DISCUSSION

The most striking observation from the preceding six comparisons is the fact that the same macroscopic curvature behavior for phased A-tracts can be reproduced by so many different models for local helix bending. This situation has been remarked upon by numerous authors in the past (13, 21–27, 39–42). As a consequence, the simple ability to account for experimental curvature cannot be used to imply the correctness of any one particular bending model. Explanation of experimental curvature is a necessary condition, but not a sufficient condition, for the correctness of a model. Other independent evidence must be examined to select from among the several theories that explain

the solution data. X-ray diffraction and nuclear magnetic resonance would seem to be the only sources of such evidence.

The second observation is that the local bending models that were designed specifically to fit gel retardation and cyclization data on phased A-tracts, models *b-f*, do so well, but fail completely when tested against other sequences that do not involve A-tracts. In contrast, nucleosome positioning model *a* was constructed in a totally objective manner, not involving retardation or cyclization experiments at all, but based solely upon observations as to which triplet sequences tend to favor locations on the concave or the convex surface of a bent double helix. This model can explain the A-tract bending data as well as the other five models; but it also can predict more general sequences such as the phased GGGCCC regions. Hence the nucleosome positioning model—showing local bending at mixed sequence DNA, strong bends at the sequence GGC, and straight, rigid A-tracts—must, provisionally at least, be adjudged the best model for predicting macroscopic curvature from local molecular bending.

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