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An introduction to the mechanics of DNA

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This article gives an overview of recent research on the mechanical properties and spatial deformations of the DNA molecule. Globally the molecule behaves like a uniform elastic rod, and its twisting and writhing govern its compaction and packaging within a cell. Meanwhile high mechanical stresses can induce structural transitions of DNA giving, for example, a phase diagram in the space of the applied tension and torque. Locally, the mechanical properties vary according to the local sequence organization. These variations play a vital role in the biological functioning of the molecule.

Keywords: DNA stiffness; DNA structure; DNA mechanics; protein-induced DNA bending

1. Introduction

The discovery of the double-helical structure of DNA (Watson & Crick 1953) emphasized the role of the polymer as a carrier of genetic information encoded by a precise sequence of base pairs (bp). However, the regulation of the expression of this biological information depends strongly on the physico-chemical properties of the DNA molecule. Of these the mechanics of bending and twisting are especially important.

2. DNA as a bendable rod

The classic early images of DNA represented the molecule as a straight rigid rod (figure 1), yet in its natural state inside a cell this polymer is characteristically tightly bent. In aqueous solution a DNA molecule does indeed behave like a relatively stiff rod but both in bacteria and in organisms with nucleated cells (eukaryotes) DNA is necessarily packaged in a small volume with the result that its length can be compacted by a factor of up to 10^4. For example, in the common gut bacterium *Escherichia coli* a single DNA molecule measuring *ca.* 1.4 mm has to fit inside an organism at least 1000 times shorter in its longest dimension. Other notable examples of such large-scale packaging include many kilobases of viral DNA inside a particle considerably smaller than most bacteria (discussed by Odijk 2004) and many megabases in the highly condensed state of eukaryotic chromosomes associated with

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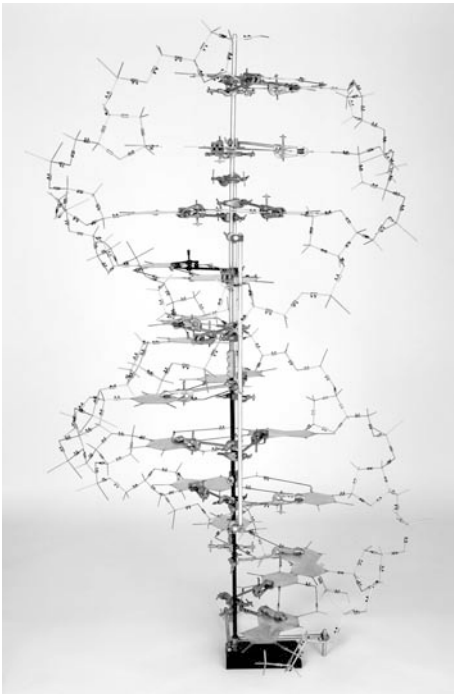

Figure 1. Replica of the original model of DNA constructed by Watson and Crick. (Courtesy of the Medical Research Council Laboratory of Molecular Biology.)

cell division. At an entirely different level of molecular organization, 145 bp of DNA are packaged into a nucleosome core particle, the fundamental structural unit of eukaryotic chromatin, in which this length of DNA is compacted 8–9 fold. However, DNA bending is not only a concomitant of packaging. In addition, looping between sequences that are linearly distant from each other often promotes genetic recombination and the regulation of gene expression by bringing the sites into close spatial proximity. A particular example of this phenomenon is analysed by Balaeff *et al.* (2004).

In the cell, DNA frequently exists in a circular rather than a linear form. In addition protein binding may delimit segments of DNA into closed domains whose ends are prevented from rotating with respect to each other. Both these topological constraints may force the DNA double helix to adopt a higher-order trajectory or supercoil (figure 2). Such forms have a higher energy than the corresponding relaxed DNA, and indeed in certain Enterobacteria it seems likely that the conversion of nutritional energy into the free energy of supercoiling acts as a major mechanism of growth control. A further consequence of the supercoiling of a closed domain is the facilitation of the close approach of distant sequences and the consequent stabilization of DNA loops. Finally, the higher-energy deformations can have a profound influence on the torsional properties of the double helix either promoting or antagonizing the untwisting of biologically important sequences depending on the topological sense of the supercoils.

Because DNA is a double helix, superhelicity can change both the twist between adjacent base pairs and also the trajectory of the double-helical axis. The distribution

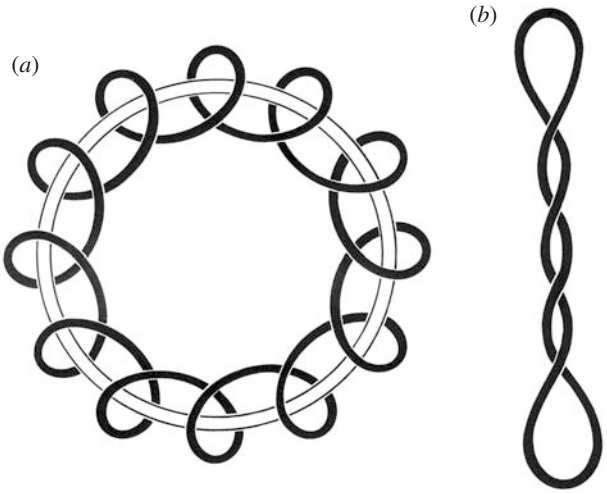

Figure 2. The two general varieties of DNA supercoil. (*a*) The DNA coils in a series of spirals about an imaginary toroid or ring (shown here by the open lines); this type of wrapping is known as 'toroidal'. (*b*) The DNA crosses over and under itself repeatedly and so this type of wrapping is known as 'interwound' or 'plectonemic'. In both examples the DNA is negatively supercoiled. (Reproduced with permission from Calladine *et al*. (2004).)

between changes in twist and trajectory differ in the alternative forms—plectonemic and toroidal (figure 2)—of supercoiled DNA (Boles *et al*. 1990). Although the toroidal form is unstable with respect to the plectonemic (Benham 1979; LeBret 1979; Calladine 1980; Schlick & Olson 1992) it is capable of compacting DNA to a greater extent and is the preferred mode of packaging *in vivo*, although less constrained DNA may still adopt the plectonemic form. In toroidally wrapped DNA, as in other modes of packaging, the DNA is bent to a much greater extent than is normally observed for DNA free in solution. DNA bending of the magnitude observed in tight packaging requires substantial changes in both the external and internal geometry of the polymer. For example, since the width of the polymer (20 Å) is often significant in relation to the average radius of curvature (42 Å in the nucleosome core particle), the DNA surface on both the outside and the inside of the bend must be considerably stressed and distorted. Thus in the nucleosome core particle the external circumference of the wrapped DNA is nearly 25% longer than the internal circumference. This difference is accommodated by altering the width of the DNA grooves—both the major and minor—widening them on the outside and narrowing them on the inside. In turn these alterations in groove width require corresponding adjustments in the interactions between adjacent base pairs (figure 3).

Some of the above-mentioned supercoiling features can be observed experimentally in a stretched and twisted rubber rod, as examined theoretically and experimentally by Thompson & Champneys (1996) and Thompson *et al*. (2002). A typical loading sequence of a silicone rubber rod of *ca*. 3 mm diameter and total length 18 cm is shown in figure 4. The rod is first put under tension, and its ends then fixed against any further axial movement. The rod is then incrementally loaded by slowly increasing the twisting rotation of one end relative to the other. The initially straight rod first buckles into the localized mode of spatial deformation shown in part (*a*). The

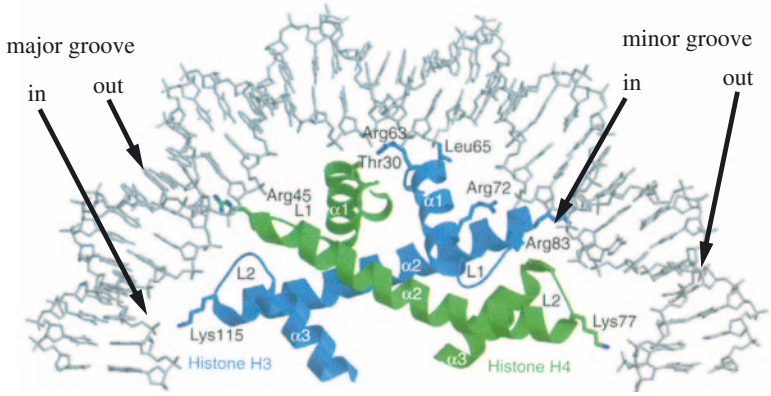

Figure 3. DNA bending on the surface of histone octamer has an average radius of 4.3 nm. The width of the double helix is 2 nm and consequently this widens grooves on the outside of the bend and narrows grooves on the inside. (Adapted with permission from Murphy & Churchill (2000).)

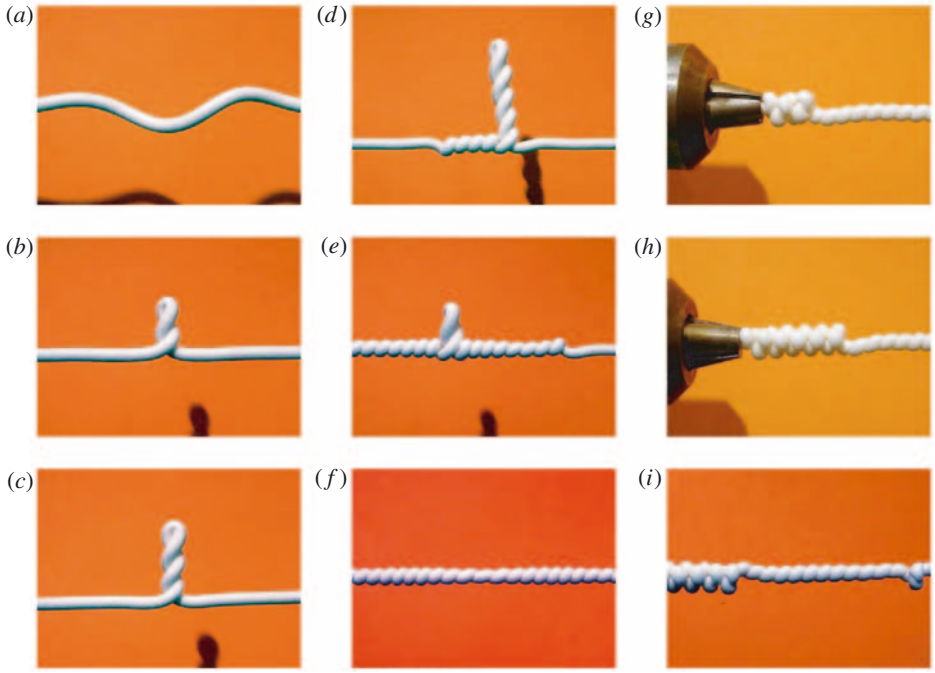

Figure 4. Examples of toroidal and interwound forms encountered during the stretching and twisting of a circular silicone rubber rod.

deformation becomes increasingly localized, and then jumps into a self-contacting loop. As more end rotation is imposed, a helical ply grows at right angles to the original rod axis, as seen in parts (*b*) and (*c*). This is the plectonemic form of DNA supercoiling. Since the ends are axially constrained, the (passive) tension in the rod will increase rapidly during this phase of loading. Eventually the ply gives birth to a close-packed toroidal form growing away from the ply along the original axis, as

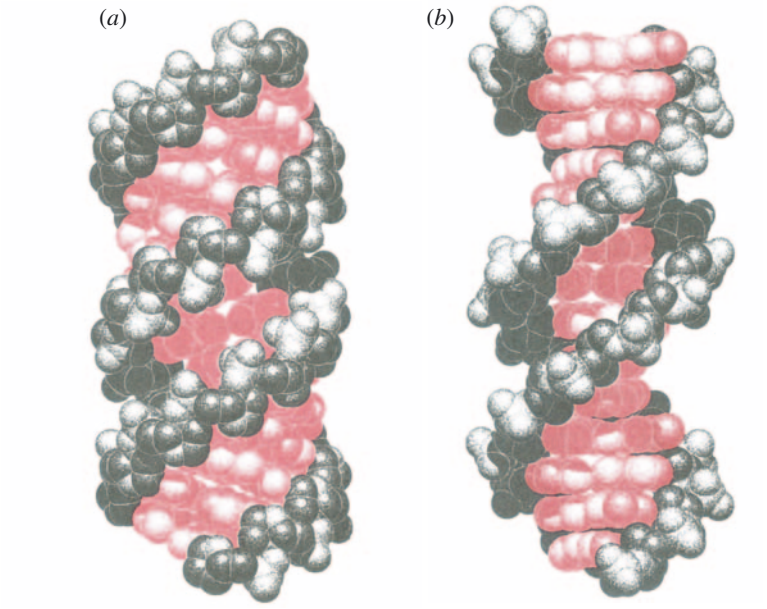

Figure 5. Polymorphism of DNA structure. The A-DNA (*a*) and B-DNA (*b*) forms of DNA fibres differ in both intrinsic helical repeat (11 and 10 bp per turn, respectively) and in the inclination of the base pairs to the helical axis (−20° and *ca.* 0°, respectively). A-DNA is stable at lower humidities than B-DNA. (Adapted with permission from IMB Jena Image Library.)

shown in part (*d*). Often this is followed by a second, symmetrically disposed toroidal form growing in the opposite direction, as in part (*e*). Eventually, the ply is pulled out, allowing the two toroidal regimes to join up as in part (*f*): notice the thinning of the toroidal pattern at the centre where the ply has just vanished. Under increased loading the toroidal deformation extends to cover the full length of the rod, and a new mode of deformation sets in, usually from one end. In this new mode the toroidal form becomes itself toroidally wound as in parts (*g*) and (*h*). Finally, we notice that in part (*i*) a second regime of double-toroidal winding has just been initiated at the centre of the rod. Shortly after this last photograph was taken the highly stressed rod snapped into two pieces.

The toroidal form observed in this experiment is known in the textile industry as cylindrical snarling (Hearle & Yegin 1972). Theoretically, these authors made a rough energy analysis to predict the critical twist at which the ply mode is replaced by the toroidal form. This was shown to be in good agreement with their experiments on rubber filaments. The exact geometry for the toroidal solution is given by Neukirch & van der Heijden (2002), who study uniform n-plies formed from n strands of material. The toroidal form illustrated in figure 4*f* is their simplest example, the 1-ply.

3. Global properties of DNA

The physical properties of the DNA double helix are unique among known polymeric structures. The combination of base-stacking and chiral braided architecture confers unusual stiffness (Sarkar *et al.* 2001; Bryant *et al.* 2003; Bustamante *et al.* 2003). Other critically important characteristics include the hydration of the outer surface

and the high negative surface charge imparted by the phosphates in the backbones of two strands. Variation in hydration, particularly in the grooves, accounts for the originally described polymorphism of the DNA polymer, especially the transition from B-form to A-form DNA (figure 5). However, most experimental and theoretical studies of DNA mechanics are directed towards understanding the properties of the biologically important B-DNA double helix. Nevertheless, single-molecule manipulation experiments show that when subject to extensive and torsional forces greater than those normally encountered in the cell, DNA can assume structures that are very different in form to the classical B-type double helix (Smith *et al*. 1992; Strick *et al*. 1996). Such forms include the underwound S-DNA with an estimated 33 bp per turn and the overwound P-DNA with 2.7 bp per turn, the latter possibly corresponding to the 'inside-out' structure originally proposed by Pauling & Corey (1953) (figure 6). The formation of S-DNA requires an extensive force of at least 60 pN, while P-DNA is only stable at a positive torque in excess of 30 pN nm. Yet in the cell powerful molecular motors such as RNA polymerase exert forces of up to only *ca.* 20 pN (Yin *et al*. 1995; Wang *et al*. 1998), although in the possibly unique example of the motor packaging phage DNA forces as high as 50 pN may be generated (Smith *et al*. 2001; Marenduzzo & Micheletti 2003). As discussed by Odijk (2004) this force reflects the tight packing of DNA in the phage head. In addition the range of torque available in the cell is relatively small. Thus the DNA structures available to biology occupy only a comparatively small region of the phase diagram of DNA transitions (figure 6).

A long B-DNA molecule may be simply described as a moderately stiff (or moderately flexible, depending on the point of view) rod. The flexibility of the chain is described by the persistence length P, which is variously defined as the distance over which two segments of the chain remain directionally correlated or the length at which the time-averaged angle made between the two ends of a DNA molecule is equal to 1 rad (Bloomfield *et al*. 1974; Schellman 1980). For a random DNA sequence the value determined by most experimental methods is *ca.* 500 nm or 150 bp for B-DNA. The elastic behaviour of DNA can be described by various models. One way of classifying the contributions to the mechanics of DNA is by how the molecule is mathematically modelled.

Atomic modelling considers each atom as a point mass, interacting with its neighbours via interatomic potentials or imagined springs and linkages. Simulations at this level of modelling need massive computational facilities, and here Grindon *et al*. (2004) discuss the algorithms and techniques that can be used to harness the power of massive parallel computers in large-scale dynamic and thermodynamic molecular simulations.

Base-pair modelling takes the base pairs rather than the atoms as the fundamental units, and typically employs discrete, semi-empirical stiffnesses for the bending, torsional and extensional increments between adjacent pairs. These stiffnesses depend primarily on the physico-chemical properties of individual base steps and to a lesser extent on the DNA sequence context in which they are embedded. Since the physical characteristics of the 10 possible base pairs vary substantially, the flexibility of DNA is a sequence-dependent property and varies both locally, depending on the presence of a particular sequence, and globally, depending on the overall base composition of the molecule in question. Here, Olson *et al*. (2004) use a theory of sequence-dependent DNA elasticity. This is employed to calculate

the dependence of the equilibrium configurations of circular DNA on the binding of small intercalating agents and/or proteins that cause significant untwisting at a single base-pair step. Meanwhile Wattis (2004) studies *breather modes* in molecular dynamics simulations using a nonlinear Klein–Gordon lattice model of the DNA duplex. The model includes both nonlinear interactions between opposing bases, and a defect in the interaction at one lattice site: each of which can cause localization of energy.

Continuum modelling goes a step further, and imagines the DNA smeared out to form a continuous elastic rod. In the manner of classical elasticity theory, this rod is given torsional and bending stiffnesses. Very often the rod is assumed to be rigid against axial tension and lateral shearing stresses, but axial and shearing strains are easily incorporated if necessary. If the various described stiffnesses are assumed to be constant along the length of the rod, closed-form analytical solutions are sometimes available. Thus, Coleman & Swigon (2004) consider a continuum model of DNA and show how exact analytical solutions of Kirchhoff's equations of mechanical equilibrium can be obtained for the supercoiling of knotted and unknotted plasmids. They take into account the effects of impenetrability and self-contact forces, and derive criteria for determining whether an equilibrium configuration is stable in the sense that it gives a strict local minimum to the elastic energy. Likewise, Starostin (2004) examines symmetric multi-leafed closed equilibrium states with one multiple self-contact point, and examines their stability. In continuum modelling, the stiffnesses can easily be made to vary in a prescribed manner along the rod, and initial intrinsic curvature can be introduced: but then solutions naturally become harder to obtain. Here, Hoffman (2004) exploits the underlying variational structure of the elastic rod model to derive new methods that can identify the stable equilibrium configurations of inextensible and unshearable elastic rods. She then applies these to two intrinsically curved DNA molecules, a DNA filament with an A-tract bend and a DNA mini-circle with a CAP binding site. Tobias (2004) considers the statistical dynamics of small rings of DNA under thermal fluctuations. He shows that increasing the intrinsic curvature of the rods can broaden the writhe distribution, a result related to the stability properties of the circular equilibrium configuration of the elastic rings. Balaeff *et al*. (2004) extend the classical continuum model to account for sequence-dependent intrinsic twist and curvatures, anisotropic bending rigidities, electrostatic force interactions and overdamped Brownian motion in a solvent.

Finite-element analysis is a numerical technique developed by engineers in which a system that has been smeared out and modelled as a continuum is conceptually chopped up into finite elements. Here, White & Bauer (2004) use finite-element analysis to study the writhing of the DNA molecule under torsional stress as a loop deflects and folds in space. They show that the manner of this writhing depends critically on the distribution of the intrinsic curvature (see below) along the DNA axis and on the precise location at which the applied rotation is introduced.

The physical properties of the DNA rod are highly dependent on its chemistry. To a first approximation DNA may be regarded as an extended highly negatively charged polyanion. Accordingly, the physical properties of DNA, and in particular

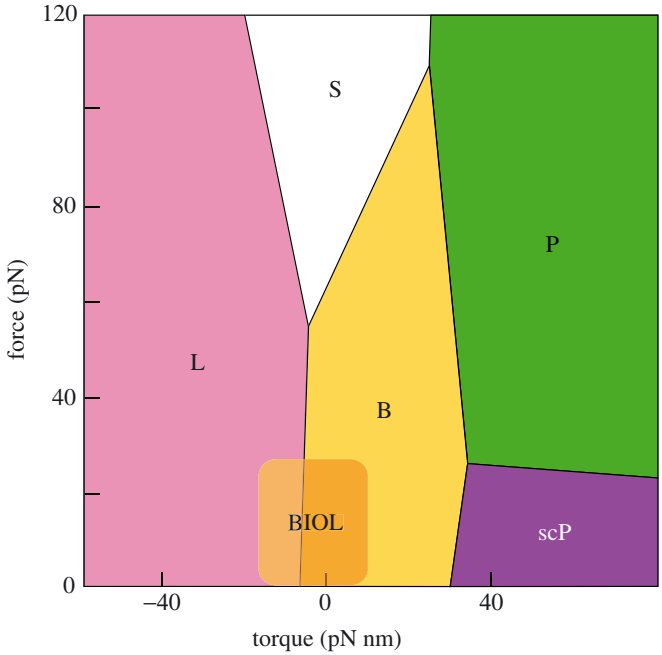

Figure 6. Phase diagram of structural transitions of DNA dependent on torque and tension. Coloured regions represent conditions under which pure DNA phases occur; lines indicate conditions for phase coexistence within a molecule (B, B-DNA; S, overstretched; P, Pauling structure; sc, supercoiled (shortened by forming plectonemes)). 'L' is a phase with an average left-handed twist. This form probably contains exposed bases, consistent with melted DNA, although a mixture of non-canonical forms may in fact be present. 'BIOL' indicates very approximately the range of forces and tension that might be encountered in a normal cell. (Adapted with permission from Bustamante *et al*. (2003).)

the bending, are strongly affected by its immediate ionic environment. At very low ionic strengths (e.g. less than 0.01 M NaCl) the repulsive forces between negative charges on the phosphates of the backbone act to oppose bending and thus impart rigidity (Odijk 1977). Neutralization of these charges by cations thus decreases the persistence length (Baumann *et al*. 1997). These effects depend on the nature of the cation. Monovalent cations or polyvalent cations, such as polyamines, in which the charges are linearly distributed are less effective than multivalent cations, such as Mg^{2+}, in which the charge is more centrally concentrated. The reduction in bending stiffness caused by multivalent cations will decrease the volume occupied by the DNA coil, enhancing the close packing of DNA. At its most extreme manifestation, charge neutralization by polyamines or hexa-ammonium cobaltic ion(s) results in the formation of DNA toroids (Klimenko *et al*. 1967; Richards *et al*. 1973; Gosule & Schellman 1976). Effects such as these are directly applicable to the biological packaging of DNA in a phage capsid or the nucleosome core particle. Indeed, anionic peptides found in the capsid of bacteriophage T4 induce the formation of a condensed DNA structure termed Ψ-DNA (Lerman 1971; Laemmli 1975). Ionic strength variations also affect the torsional properties of DNA such that low ionic strength can mimic negative superhelicity in promoting the local untwisting and

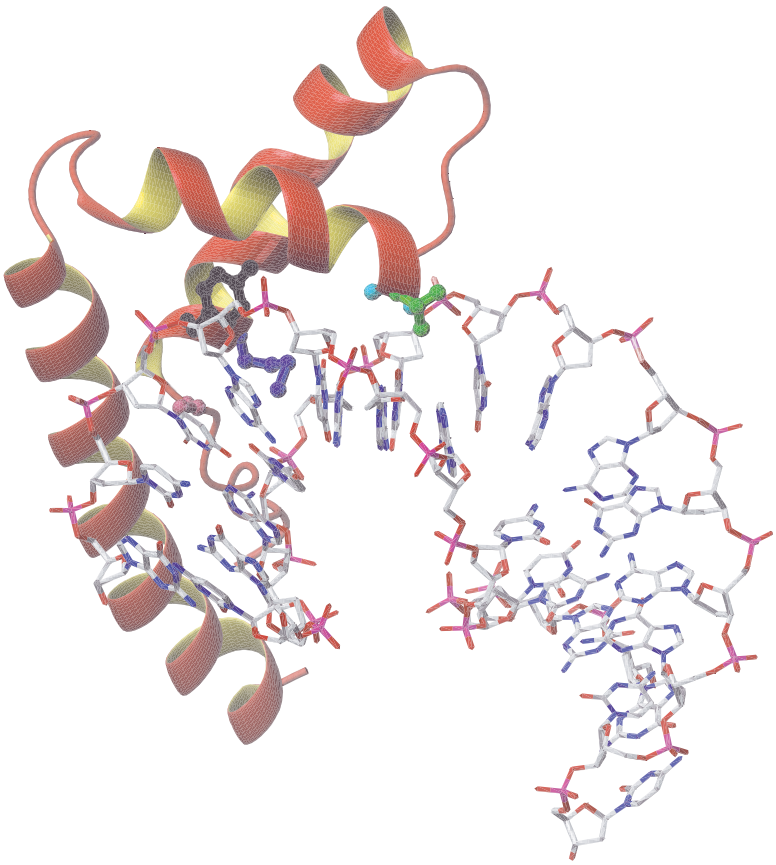

Figure 7. DNA bending by an HMG domain. The figure shows the DNA binding domain of the *Drosophila* High Mobility Group (HMG) protein HMG-D binding to a short DNA fragment. The protein binds in the minor groove widening the groove and concomitantly stabilizing a bend of *ca.* 100° in the DNA. This is achieved by inserting the side chains of hydrophobic amino acid residues (space-filling representation) between adjacent base pairs at two locations separated by one base-step. The α-helices of the protein are depicted in red and yellow. The DNA structure shown contains a 'bulge' in which two adjacent bases on one of the strands are unpaired. (Reproduced with permission from Cerdan *et al.* (2001).)

ultimately the breathing of DNA (Benham 1979; Drew *et al.* 1985; see also Wattis 2004).

4. Sequence-dependent properties of DNA

Although the behaviour of a long DNA molecule may be well approximated by treating it as an isotropically bendable rod, in actuality the magnitude and directionality of the local stiffness of a DNA molecule is strongly dependent on the precise DNA sequence. A striking consequence of this property is that whereas a histone octamer can bind with varying affinities to virtually all the sequences in a eukaryotic genome, if challenged with a defined sequence of suitable length it will often position itself rather precisely with respect to this sequence so that the midpoint of the binding site is well defined (Simpson & Stafford 1983; Ramsay *et al.* 1984; Rhodes 1985).

This positioning largely results from the ability of some DNA sequences to bend preferentially in a preferred direction, rather like a floppy bicycle chain (Calladine & Drew 1986; Satchwell *et al*. 1986; Travers & Klug 1987). An extreme example of sequence-dependent anisotropic bending is 'intrinsic curvature', a phenomenon where the DNA molecule naturally adopts a defined curved trajectory. Intrinsic curvature is most frequently observed when the DNA sequence contains short homopolymeric dA_n:dT_n tracts (where $n = 4$–6) in phase with the helical repeat (Marini *et al*. 1982; Wu & Crothers 1984). This sequence-imposed curvature results from the different structural properties of the homopolymeric tracts relative to the intervening sequences.

How can the properties of short (2–5 bp) DNA sequences affect the magnitude and isotropy of DNA flexibility? The concept that has been developed to describe these properties is that of 'conformational space', which postulates that the range and characteristics of the conformations available to individual types of base-step are highly variable (see Hunter (1993), El Hassan & Calladine (1997) and also the articles by Olson *et al*. (2004) and Travers (2004)). For example, certain base-steps, notably TpA, can adopt a wide range of available conformations and hence enhance both the bending and torsional flexibility. Conversely, other steps, in particular ApA which is characteristic of intrinsically bent DNA sequences, can only readily adopt a restricted range of conformations and are said to be conformationally rigid. In the case of ApA, or more properly the trimer ApApA, the preferred conformation is compatible with a narrow, but not with a wide, minor groove. Consequently, such sequences impose a significant energetic penalty for adopting a non-preferred conformation and both in solution and in protein binding sites are preferentially excluded from positions in bent DNA that require such conformations.

5. How proteins bend DNA

Although DNA in solution behaves largely as an extended rod, in many biological situations it is packaged in order to compact a substantial length of DNA into a small volume. Examples of such packaging include the ordered DNA in the head of a bacteriophage, the wrapping of DNA on the histone octamer, and ultimately the formation of the mitotic chromosomes where the end-to-end distance of a DNA molecule is reduced approximately 10 000 fold. In all these cases the compaction of the DNA molecules requires a directed bending that is often substantially greater than that observed in solution. This in turn implies that in the cell the range of conformational space available to individual base-steps be larger and consequently that the bending and torsional stiffness be effectively decreased. These changes are largely dependent on proteins which induce a particular trajectory to the axis of the double helix. Consequently, a fundamental difference between bending deflection in solution and that induced by proteins is that whereas the former, with important exceptions, is predominantly isotropic the latter is essentially anisotropic. The extent of this anisotropy depends on the size of the protein binding site, which can range typically between 6 and 170 bp.

One of the 'purest' examples of protein-induced DNA bending is provided by the nucleosome core particle, the fundamental structural unit of eukaryotic chromatin, in which 145 bp of DNA are wrapped in 1.65 toroidal superhelical turns around a core of eight histone proteins (Richmond *et al*. 1984; Luger *et al*. 1997). This total

deflection of *ca.* 10 rad is in striking contrast to the average *ca.* 1 rad deflection due to thermal motion of a free random-sequence DNA molecule of the same length. This difference implies that on binding to the protein the intrinsic stiffness of the DNA is reduced by up to an order of magnitude. How might this be effected? The histone core provides a DNA binding surface in the form of a positively charged ramp. On binding to this ramp the negative charges on one side of the DNA are neutralized (Mirzabekov & Rich 1979; Manning 1989). This asymmetric neutralization, which can be mimicked in free DNA (Strauss & Maher 1994), creates an imbalance in charge distribution on opposite sides of the double helix so that repulsion between the opposing sugar-phosphate backbones on the unneutralized side facilitates bending by increasing the width of the grooves. Concomitantly, the reduction in this repulsion on the inside of the bend permits greater freedom in the motions of the base pairs, with a corresponding reduction in the width of the grooves.

The wrapping of DNA on the surface of the histone octamer also has consequences for DNA topology. The crystal structure of the nucleosome core particle shows that each particle contains −1.65 superhelical turns of DNA. Yet, early topological measurements indicated that in a nucleosome array each particle constrained only, on average, a reduction in linking number of −1, in contrast to the number of superhelical turns. This apparent discrepancy, the so-called 'linking number paradox', was at least partially explained by the discovery that the helical repeat of the bound DNA was *ca.* 10.2 bp instead of the solution value of *ca.* 10.5 bp (Satchwell *et al.* 1986; Klug & Travers 1989; White & Bauer 1989). Sivolob & Prunell (2004) re-evaluate this proposal in terms of thermal fluctuations of the path of the entering and exiting DNA.

An extension of the principle of asymmetric alteration of the ionic environment of DNA is provided by the High Mobility Group type B proteins, a class of abundant chromosomal proteins. They consist essentially of a small L-shaped protein domain with a cluster of hydrophobic residues on its inner surface and an extended unstructured basic region. When these proteins bind to DNA they produce a bend of 95–120° over about six base pairs and decrease both the bending and torsional stiffness (reviewed in Thomas & Travers (2001)) (figure 7). On the outer surface of the bend the hydrophobic 'wedge' towards the apex of the L binds in and widens the minor groove, concomitantly untwisting the DNA. This effect is believed to be facilitated by a local reduction in the dielectric constant, which increases the repulsion between opposing sugar-phosphate backbones on the approach of the protein to DNA (Travers 1995; Elcock & McCammon 1996). At the same time the basic region neutralizes the phosphates bounding the major groove on the inside of the bend thus decreasing the repulsive forces and permitting the narrowing of the groove. Additionally, the protein inserts, or intercalates, hydrophobic amino acids into two base-steps that are themselves separated by a single base-step. The extent to which this intercalation increases or simply stabilizes the induced bend is unclear.

Intercalation of hydrophobic residues in the minor groove is a common feature of other DNA-binding proteins that introduce bends of greater than 60° into DNA. Notable examples include the TATA binding protein and the 'Integration Host Factor' (IHF), which bend DNA by *ca.* 90° and 180°, respectively (Kim *et al.* 1993*a*, *b*; Rice *et al.* 1996). Whereas TBP binds as a monomer, IHF binds as a dimer, implying that local induced bending angle may be limited to *ca.* 90–120°. This limit is likely to be dependent on the stereochemistry of the inside of the bend. Zhang *et al.*

(2004) discuss how the covalent addition of benzopyrene to the TBP binding site can affect this stereochemistry with consequent effects on the stability of the TBP–DNA complex.

Proteins not only bend DNA but can also introduce other distortions. These include the simple untwisting of DNA required for the initiation of transcription and DNA replication and also for site-specific recombination. A more-complex structural transition discussed by Huang & MacKerell (2004) is the flipping of a base into an extra-helical configuration, a mechanism that is characteristic of enzymes, such as DNA methyltransferases and base excision repair endonucleases, which need access to DNA bases that undergo chemical reaction.

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