THE MATHEMATICS OF DNA STRUCTURE, MECHANICS, AND DYNAMICS

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Abstract. A brief review is given of the main concepts, ideas, and results in the fields of DNA topology, elasticity, mechanics and statistical mechanics. Discussion includes the notions of the linking number, writhe, and twist of closed DNA, elastic rod models, sequence-dependent base-pair level models, statistical models such as helical worm-like chain and freely jointed chain, and dynamical simulation procedures. Experimental methods that lead to the development of the models and the implications of the models are also discussed. Emphasis is placed on illustrating the breadth of approaches and the latest developments in the field, rather than the depth and completeness of exposition.

Key words. DNA topology, elasticity, mechanics, statistical mechanics, stretching.

1. Introduction. The discovery of DNA structure 55 years ago marked the beginning of a process that has transformed the foundations of biology and medicine, and accelerated the development of new fields, such as molecular biology or genetic engineering. Today, we know much about DNA, its properties, and function. We can determine the structure of short DNA fragments with picometer precision, find majority of the genes encoded in DNA, and we can manipulate, stretch and twist individual DNA molecules. We can utilize our knowledge of gene regulatory apparatus encoded in DNA to produce new microorganisms with unexpected properties. Yet, there are aspects of DNA function that defy our understanding, mostly because the molecule is just one, albeit essential, component of a complex cellular machinery.

From the very beginning, abstraction and modeling played a significant role in research on DNA, since the molecule could not be visualized by any available experimental methods. These models gave rise to mathematical concepts and techniques for study of DNA configurations at the macroscopic and mesoscopic levels, which are the subject of this short review. The paper begins with a brief description of DNA atomic-level structure, followed by a discussion of topological properties of DNA such as knotting, catenation, and the definitions of linking number and supercoiling. It continues with an outline of continuum and discrete models of DNA elasticity, focusing on local energy contributions and analysis of equilibrium states. Modeling of long range electrostatic interactions is described next, followed by the treatment of thermal fluctuations and statistical mechanics. The paper concludes with an outline of dynamical models of DNA, and

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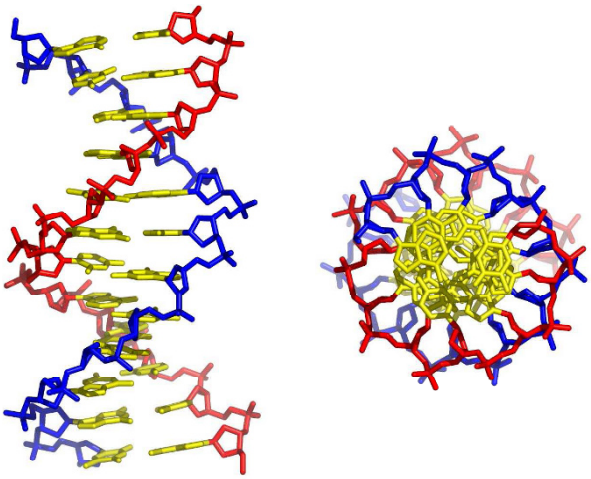

FIG. 1. *Side view (left) and a view along the axis (right) of DNA double helix in atomic level detail, showing the two DNA backbones (blue and red) and the base pairs (yellow).*

a discussion of future directions in DNA research. The analysis of DNA sequences, or modeling of the atomic-level structure and dynamics of DNA are not covered here.

2. Background. DNA is made up of two polymeric strands composed of monomers that include a nitrogenous base (A-adenine, C-cytosine, G-guanine, and T-thymine), deoxyribose sugar, and a phosphate group. The sugar and phosphate groups, which form the backbone of each strand, are located on the surface of DNA while the bases are on the inside of the structure (see Fig. 1). Weak hydrogen bonds between complementary bases of each strand (i.e., between A and T and between C and G) give rise to pairing of bases that holds the two strands together. The base pairs (bp) are flat and stack on top of each other like dominoes with centers separated by approximately 0.34 nm. In normal conditions each base pair is rotated relative to its predecessor by approximately 34°, giving rise to the familiar right-handed Watson-Crick double helix.

The chemical nature of the backbone gives each strand an orientation - one end is called the 5′-end and the other the 3′-end. In duplex DNA the two strands run antiparallel to each other. A closed DNA (also called a plasmid or ring) is formed when the ends of each strand are joined by a covalent bond. A prokaryotic organism, e.g., a bacterium, lacks nuclear structures and its entire genome is in the form of a single closed duplex DNA. Genomic DNA of a eukaryotic cell is contained within a nucleus and it is divided into a number of chromosomes.

The DNA of any organism must be folded and packed in a complicated fashion in order to fit inside a cell.[1] This is complicated by the fact that DNA resists bending and twisting deformations and also has a tendency to repel itself electrostatically. In addition to being compacted, portions of DNA must be accessible at various moments during the lifetime of the cell, so that the genes encoded in the DNA can be expressed and proteins produced when necessary. The effort to understand how DNA is packed and unpacked in cells, and how its mechanical properties influence the processes of transcription, replication and recombination, is one of the driving forces behind the development of mathematical models of DNA.

3. Topology. When Watson and Crick first proposed the double helical model for DNA [147], they remarked:

> "Since the two chains in our model are intertwined, it is essential for them to untwist if they are to separate. Although it is difficult at the moment to see how these processes occur without everything getting tangled, we do not feel that this objection would be insuperable."

The entanglement of DNA and Nature's ways of coping with it is the subject of DNA topology.

In the first approximation, a closed DNA molecule can be treated as a single closed curve in space. (The resistance of DNA to bending implies that this curve is rather smooth.) Because during regular deformation the bonds in DNA strands do not break, it is natural to consider the problems of DNA knotting and catenation.[2]

DNA plasmids can become catenated during DNA replication, a process in which the two strands of DNA are separated, each strand is complemented by one newly formed strand, and instead of a single plasmid one obtains two plasmids that are catenated in the same way the strands were linked in the original plasmid. Of course, it is crucial that during replication the catenation of the plasmids is removed so that they can be separated and placed one in each of the daughter cells. The enzymes that preform decatenation are called *type II topoisomerases* [146]. They operate by a *strand passage* mechanism in which two DNA segments are brought to a close contact, one of the segments is severed in such a way that both backbone chains of the molecule are broken, the second segment of DNA is passed through the gap in the first segment, and finally the severed segment is resealed.

[1] For example the DNA of *E. coli* is a closed DNA of circumference 1.58 mm that must fit inside a cell of diameter 1 μm. Human genome has more that 3 billion bp, i.e., a linear length of 1 m. Two copies of the genome must be packed inside every cell of human body, which range in size between 3 and 35 μm.

[2] As is customary in DNA research we here use the term *catenation* for linking of two DNA molecules and reserve the term *linking* for topological relation between two DNA strands.

DNA knotting rarely occurs naturally, but it has been achieved in a laboratory using the aforementioned topoisomerases and also DNA recombinases, enzymes that cut two DNA molecules at specific recognition sites and then switch and reconnect the ends. Because a given recombinase only forms knots of certain types, knot theory, and in particular tangle analysis, has been applied to the problem of determining the structure and function of these enzymes [55, 47, 141]. The changes in knot type resulting from strand passages have been classified and the probabilities of such passages have been estimated [46, 70]. Knotting also occurs in DNA closure experiments in which open (linear) DNA segments spontaneously cyclize to form closed DNAs. Since DNA thermally fluctuates, the probability of forming a knot can be related to the probability that a random configuration of a phantom DNA (i.e., a DNA allowed to pass through itself) has the topology of a knot (see Section 6). It was shown that in the limit of length going to infinity a randomly cyclized polygon will be knotted with probability 1 [48].

A closed DNA molecule can also be viewed as a collection of two continuous curves - the DNA strands. This is because the biochemical nature of the strands guarantees that during closure ceach strand of the DNA can only bind to itself. The axial curve of a closed DNA, which can be thought of as the curve passing through the centroids of the base pairs, is also a closed curve.

For any two closed curves $\mathcal{C}_1$ and $\mathcal{C}_2$ one can define a quantity, called the *linking number* Lk, that characterizes how the curves are interwound with each other. The linking number can be found by examining a generic projection of the two curves on a plane (a projection in which every crossing of one curve with the other is transversal). First, orientation is assigned to each curve and a sign to each crossing of one curve over the other, in accord with the convention shown in Fig. 2A.

The linking number Lk is then taken to be one half the sum of all signed crossings (see Fig. 2B and C); it is a topological invariant of the two curves, i.e., a number independent of homotopic deformations of the curves that do not pass one curve through the another. In DNA research it is customary to take $\mathcal{C}_1$ to be the axial curve of the molecule and $\mathcal{C}_2$ one of the backbone chains.

For differentiable curves, a formula for linking number in terms of a double integral was found by Gauss [42]

$$Lk(\mathcal{C}_1,\mathcal{C}_2) = \frac{1}{4\pi}\oint_{\mathcal{C}_1}\oint_{\mathcal{C}_2} \frac{\mathbf{t}_1(s_1)\times\mathbf{t}_2(s_2)\cdot[\mathbf{x}_1(s_1)-\mathbf{x}_2(s_2)]}{|\mathbf{x}_1(s_1)-\mathbf{x}_2(s_2)|^3}\,ds_2 ds_1, \quad (3.1)$$

where $\mathcal{C}_i$ is defined by giving its position $\mathbf{x}_i(s)$ in space as a function of the arc-length s, and $\mathbf{t}_i(s) = \mathbf{x}_i'(s) = d\mathbf{x}_i(s)/ds$.

There are two geometric properties of curves that are intimately related to the linking number. The first property, called the *writhe* Wr,

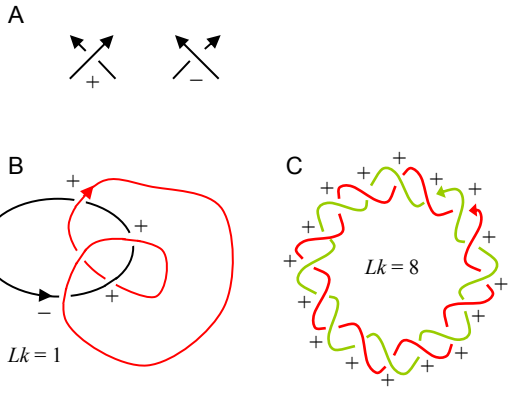

FIG. 2. *The linking number of two curves. A: A sign convention for crossings. B and C: Examples of calculation of Lk for two curves.*

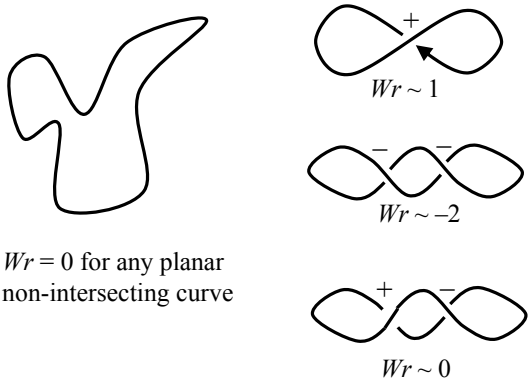

FIG. 3. *The writhe of a curve.*

characterizes the amount of chiral deformation of a single curve. To find Wr, one assigns orientation to the curve and computes the sum of signed crossings in a planar projection along every direction; Wr is equal to the average of such sums over all projections. Examples of curves with various values of Wr are shown in Fig. 3. For a closed differentiable curve $\mathcal{C}$ a formula for Wr analogous to (3.1) exists:

$$Wr(\mathcal{C}) = \frac{1}{4\pi} \oint_{\mathcal{C}} \oint_{\mathcal{C}} \frac{\mathbf{t}(s_1) \times \mathbf{t}(s_2) \cdot [\mathbf{x}(s_1) - \mathbf{x}(s_2)]}{|\mathbf{x}(s_1) - \mathbf{x}(s_2)|^3} \, ds_2 ds_1. \tag{3.2}$$

Alternative formulae relating Wr to the area swept by the vector $\mathbf{x}(s_1) - \mathbf{x}(s_2)$ on a unit sphere when traversing $\mathcal{C}$, or the difference in writhe of two closed curves can be found in [57, 1].

The second property, called the *twist* Tw, measures the winding of one curve about the other. The most familiar definition requires that the curves under consideration be differentiable; the twist of $\mathcal{C}_2$ about $\mathcal{C}_1$ is then

$$Tw(\mathcal{C}_2,\mathcal{C}_1)=\frac{1}{2\pi}\oint_{\mathcal{C}_1}[\mathbf{t}_1(s)\times\mathbf{d}(s)]\cdot\mathbf{d}'(s)ds \tag{3.3}$$

where $\mathbf{d}(s)=\mathbf{x}_2(\sigma(s))-\mathbf{x}_2(s)$ is taken to be perpendicular to $\mathbf{t}_1(s)$.

Neither the writhe nor the twist are topological invariants. However, it follows from the results of Calugareanu [29] and White [149] that the linking number of two closed curves is the sum of the writhe of one curve and the twist of the second curve about the first:

$$Lk(\mathcal{C}_1,\mathcal{C}_2)=Wr(\mathcal{C}_1)+Tw(\mathcal{C}_2,\mathcal{C}_1). \tag{3.4}$$

This relation has important implications for a closed DNA molecule. Since in a closed duplex DNA Lk is invariant, any change in Tw, which may come about as a result of binding of DNA to proteins (such as histones) or intercalating molecules, will induce a corresponding opposite change in Wr. Alternatively, DNA mechanics tells us that if Lk is changed by cutting and resealing of DNA strands, that change will be partitioned into a change in Tw and a change in Wr of equal signs. In DNA research an increase in the magnitude of writhe, accompanied by an increase in the number of crossings of the molecule, is called *supercoiling*, and a molecule with high $|Wr|$ is known as *supercoiled DNA*.

Supercoiling is a characteristic deformation of a closed DNA that can be observed and quantified experimentally. Supercoiling can be either detrimental or beneficial to a cell, depending on its magnitude and circumstances. Each cell contains enzymes topoisomerases that regulate DNA supercoiling by constantly adjusting the linking number. Since the linking number of a closed DNA molecule remains constant during any deformation of the molecule that preserves chemical bonding, it can therefore be changed only by mechanisms in which chemical bonds are disrupted. There are two such mechanisms: (i) a relaxation, in which a bond in one of the backbone chains is broken, one end of the broken backbone is rotated about the other backbone by 360° and the broken bond is repaired, or (ii) a strand passage, described earlier, in which one segment of DNA is passed through a gap created in the second segment. Type I DNA topoisomerases use the first mechanism and hence change Lk by by ±1, while type II topoisomerases use the second mechanism and change Lk by ±2.

Natural questions arise, such as what is the configuration of supercoiled DNA with prescribed Lk, what is the probability of occurence of topoisomers or knot types, or how much time does it take for a segment of DNA to form a closed molecule. These questions can be answered with the help of theories of DNA elasticity, statistical mechanics and dynamics, described in subsequent sections.

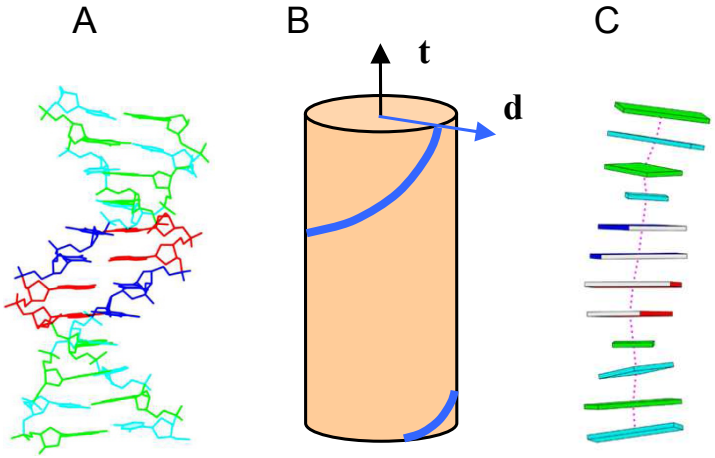

FIG. 4. *Schematic representations of DNA. A: a wireframe representation of the atomic level structure. B: continuum elastic rod. C: base-pair level description*

4. Elasticity. The elasticity of DNA is governed by interactions between the atoms of the molecule and by interactions of the molecule with the surrounding solvent. The primary interaction responsible for DNA bending stiffness is base stacking, a tendency of the flat hydrophobic nucleotides to aggregate in such a way as to minimize water accessible surface [115]. Such a stacking occurs even in the absence of backbone connections. The twisting rigidity of the molecule is due to the presence of two backbone polymeric chains. The elastic properties are signigficantly affected by electrostatic interaction between negatively charged phosphate groups in the backbone, which are strongly modulated by ionic properties of the surrounding solvent.

Continuum models. The simplest model of DNA deformability treats DNA as an *ideal elastic rod*, i.e., thin elastic body that is inextensible, intrinsically straight, transversely isotropic and homogeneous [12, 13]. The configuration of DNA is described by giving the position $\mathbf{x}(s)$ of its axial curve in space and its twist density $\Omega(s)$ as functions of the arc-length s, where $\Omega(s) = [\mathbf{t}_1(s) \times \mathbf{d}(s)] \cdot \mathbf{d}'(s)$ with $\mathbf{d}(s)$ a vector pointing from the axial curve to one of the backbones (see Figure 4A and Eq. (3.3)). The elastic energy of the rod is given by

$$\Psi = \frac{1}{2} \int_0^L A\kappa(s)^2 + C \left(\Omega(s) - \bar{\Omega}(s)\right)^2 ds \tag{4.1}$$

where $\kappa(s) = |\mathbf{t}'(s)|$ is the curvature of the axial curve and $\bar{\Omega}(s)$ is the twist density in a stress free state. The bending modulus A and the twisting mod-

ulus C characterize the elastic properties of DNA. The accepted "average" value of A for B-DNA under standard conditions is 50 kT·nm [66, 23] and C is between 25 kT·nm and 100 kT·nm [69, 121, 131], (here kT, an widely used unit of energy in molecular biology, is the product of Boltzmann constant k and absolute temperature T).

A rod with the energy (4.1) obeys the classical theory of Kirchhoff [75, 51], which implies that in equilibrium $\Delta\Omega = \Omega(s) - \bar{\Omega}(s)$ is constant and $\mathbf{t}(s)$ obeys a differential equation,

$$A(\mathbf{t} \times \mathbf{t}'') + C\Delta\Omega\mathbf{t}' = \mathbf{F} \times \mathbf{t} \tag{4.2}$$

with the constant F playing the role of a force. Solutions of (4.2) have been obtained in a closed form in terms of elliptic functions and integrals [82, 139].

Although each solution of (4.2) corresponds to an equilibrium configuration of the rod, from a practical point of view it is important to know which of these solutions are locally stable in the sense that any small perturbation of the configuration compatible with the boundary conditions leads to an increase in elastic energy. Stability theory for closed Kirchhoff elastic rods has been developed by a number of researchers using the framework of calculus of variations; necessary conditions (the slope of the graph of Lk versus Wr for a family of equilibrium configurations [88, 140, 41]), suficient conditions (the absence of conjugate points [96, 67]), or general observations about stability of rod configurations [84].

Bifurcation theory of straight rods subject to tension and twist is a classical subject [92, 3, 136, 105] and bifurcations of a closed rod with a given linking number have also been analyzed [155, 87, 49]. The general conclusion is that the straight or circular solution of (4.2) is stable for Lk smaller than a critical value, while other solutions of (4.2) can be stable only if $|Wr|$ is small and C/A is larger than a critical value that depends on the boundary conditions.[3] Experiments with steel wires, which have $C/A < 1$, confirm this result [137]. Consequently, the solutions of (4.2) cannot represent minimum energy configurations of supercoiled DNA with high $|Wr|$, because such configurations show self-contact, i.e., a contact between the surfaces of two distinct subsegments of the rod.

In any theory of rod configurations with self-contact, the forces exerted on the surface of DNA can be accounted for as external forces in the balance equations. The existence of a globally minimizing configuration for general nonlinearly elastic rods with self-contact has been demonstrated [62, 120]. In the case of an ideal elastic rod, segments of the rod between points of contact can be treated using Kirchhoff's theory, and by putting together explicit expressions for contact-free segments and balance equations for forces at the contact points one obtains a system of algebraic equations

[3]This critical value is 11/8 for closed rods subject to twisting.

that can be solved to obtain a configuration of DNA plasmid with self-contact [88, 74, 49, 39]. The ideal rod model with self-contact has been applied to the study of DNA supercoiling [41, 39], configurations of straight DNA subject to stretching and twisting [132], and configurations of DNA loops in mononucleosomes [133].

The ability to account for self-contact is critical if one intends to study equilibrium configurations of knotted DNA, for it has been shown that knotted contact-free equilibrium configurations of closed DNA have the topology of torus knots and are all unstable [84]; examples of such configurations can be found in [88, 49, 129]. Thus any stable configuration of a DNA knot shows self-contact; minimum energy configuration of a DNA plasmid with the topology of a trefoil knot as a function of Lk has been found [40].

Departures from ideality, such as intrinsic curvature, bending anisotropy, shearing, or coupling between modes of deformation can be treated using *special Cosserat theory of rods* (see, e.g., [2]). In that theory the configuration of the rod is described by giving, as functions of the arc-length s, its axial curve $\mathbf{x}(s)$ and an orthonormal triad $(\mathbf{d}_1(s), \mathbf{d}_2(s), \mathbf{d}_3(s))$, which is embedded in the cross-section of the rod in such a way that $\mathbf{d}_3$ is normal to the cross-section. The vector $\mathbf{d}_3(s)$ need not be parallel to $\mathbf{x}'(s)$ and hence the theory can describe rods with shear. The elastic energy is expressed in terms of the variables $(\kappa_1, \kappa_2, \kappa_3, \nu_1, \nu_2, \nu_3)$ describing local deformation of the rod, i.e.,

$$\Psi = \int_0^L W(\boldsymbol{\kappa} - \bar{\boldsymbol{\kappa}}, \boldsymbol{\nu} - \bar{\boldsymbol{\nu}}) ds \tag{4.3}$$

where

$$\mathbf{d}_i'(s) = \boldsymbol{\kappa}(s) \times \mathbf{d}_i(s) \tag{4.4}$$

$$\nu_i(s) = \mathbf{x}_i'(s) \cdot \mathbf{d}_i(s). \tag{4.5}$$

When this theory is applied to DNA research [93, 6, 58], it is usually assumed that DNA is inextensible and unshearable (i.e., $\mathbf{d}_3(s) = \mathbf{x}'(s)$), and shows no coupling; consequently the energy density is given by

$$2W(\boldsymbol{\kappa} - \bar{\boldsymbol{\kappa}}) = K_1(\kappa_1 - \bar{\kappa}_1)^2 + K_2(\kappa_2 - \bar{\kappa}_2)^2 + K_3(\kappa_3 - \bar{\kappa}_3)^2. \tag{4.6}$$

Variational equations in the Cosserat theory are identical to the balance equations in the Kirchhoff theory:

$$\mathbf{F}' + \mathbf{f} = 0 \tag{4.7}$$

$$\mathbf{M}' + \mathbf{x}' \times \mathbf{F} + \mathbf{m} = 0. \tag{4.8}$$

These equations cannot be solved explicitly and therefore are usually integrated numerically. Accurate numerical schemes employ a parametrization

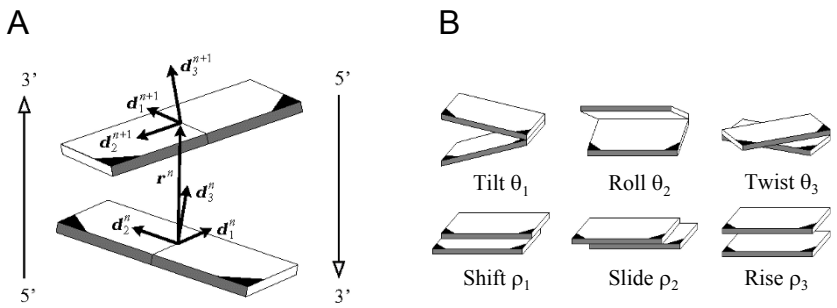

FIG. 5. *Parameters characterizing the base-pair step.*

for $(\mathbf{d}_1, \mathbf{d}_2, \mathbf{d}_3)$ using Euler angles or Euler parameters and reformulate the problem as a set of differential equations for these parameters [49]. The practical problem of computing DNA configurations using the Cosserat model requires one to determine the unstressed values $\bar{\boldsymbol{\kappa}}$ and elastic moduli K_1, K_2, K_3 for a given DNA sequence, which can be done, for example, by comparing computed equilibria with the results of a cyclization experiment [95]. Cosserat theory has been employed to show that intrinsically curved DNA circles and DNA segments with fixed ends can have multiple stable contact-free equilibrium configurations [58, 142, 68], and was also used to compute the structure of protein-induced DNA loops [7, 65].

Discrete models. Discrete models have been developed to model sequence-dependent elasticity of DNA in a way that closely resembles detailed DNA structure. The most common discrete models treat DNA as a collection of rigid subunits representing the base-pairs (see Figure 4C). This description has long been used by chemists to characterize DNA crystal structures [28, 107]. The DNA configuration is specified by giving, for each base pair, numbered by index n, its location $\mathbf{x}^n$ in space and its orientation described by an embedded orthonormal frame $(\mathbf{d}_1^n, \mathbf{d}_2^n, \mathbf{d}_3^n)$. The relative orientation and position of the base pair and its predecessor are specified by six kinematical variables $(\theta_1^n, \theta_2^n, \theta_3^n, \rho_1^n, \rho_2^n, \rho_3^n)$, termed, respectively, tilt, roll, twist, shift, slide, and rise (see Fig. 5). In the simplest, so-called *dinucleotide models*, the elastic energy Ψ is taken to be the sum of the base-pair step energies ψ^n , each of which is a function of the kinematical variables, i.e.,

$$\Psi = \sum_{n=1}^{N-1} \psi^n(\theta_1^n, \theta_2^n, \theta_3^n, \rho_1^n, \rho_2^n, \rho_3^n) \tag{4.9}$$

TABLE 1
Sequence-dependent variability of DNA elastic properties.

Quantity	Range	Units
Intrinsic bending	$0.4 < \bar{\theta}_2 < 5.1$	deg
Bending anisotropy	$1.3 < F_{11}/F_{22} < 3.0$	
Twisting/bending ratio	$0.7 < F_{33}/F_{22} < 2.7$	
Twist-roll coupling	$0.1 < F_{23}/F_{22} < 0.6$	
Twist-stretch coupling	$-0.8 < G_{33} < -0.25$	$kT/(deg \cdot \text{Å})$
Shearing anisotropy	$0.7 < H_{22}/H_{11} < 2.8$	

where the function ψ^n depends on the base-pair composition of the nth step, and is commonly assumed to be a quadratic function

$$\psi^n = \frac{1}{2}\sum_{i=1}^{3}\sum_{j=1}^{3} F_{ij}^{\mathrm{XY}}\Delta\theta_i^n\Delta\theta_j^n + G_{ij}^{\mathrm{XY}}\Delta\theta_i^n\Delta\rho_j^n + H_{ij}^{\mathrm{XY}}\Delta\rho_i^n\Delta\rho_j^n. \quad (4.10)$$

Here XY is the nucleotide sequence (in the direction of the coding strand) of the nth base pair step, $\Delta\theta_i^n = \theta_i^n - \bar{\theta}_i^{\mathrm{XY}}$, $\Delta\rho_i^n = \rho_i^n - \bar{\rho}_i^{\mathrm{XY}}$ are the deviations of variables from their intrinsic values $\bar{\theta}_i^{\mathrm{XY}}$, $\bar{\rho}_i^{\mathrm{XY}}$, and F_{ij}^{XY}, G_{ij}^{XY}, H_{ij}^{XY} are the elastic moduli. A discrete version of the ideal elastic model can be obtained by taking

$$\bar{\theta}^{\mathrm{XY}} = \begin{pmatrix} 0 \\ 0 \\ 34^\circ \end{pmatrix}, \bar{\rho}^{\mathrm{XY}} = \begin{pmatrix} 0 \\ 0 \\ 0.34 \end{pmatrix} \text{nm}, F^{\mathrm{XY}} = \begin{pmatrix} A & 0 & 0 \\ 0 & A & 0 \\ 0 & 0 & C \end{pmatrix}, \quad (4.11)$$

$$G^{\mathrm{XY}} = 0, \qquad H^{\mathrm{XY}} \to \infty. \quad (4.12)$$

Empirical estimates of intrinsic values and elastic moduli have been deduced from the averages and fluctuations of base-pair step parameters in high-resolution DNA protein complexes [108] after normalization so that the persistence length of mixed-sequence DNA matches observed values (circa 500Å). Departures from ideal behavior found by Olson and collaborators [108] and listed in Table 1 include intrinsic bending (in the roll variable), bending anisotropy, inhomogeneity in twisting to bending stiffness ratio, twist-roll coupling, twist-stretch coupling, and shearing anisotropy. Analysis of X-ray crystal structures and NMR experiments yields the most detailed information to date about DNA structure and flexibility. Other experimental methods, such as cyclization [43, 8], fluorescence resonance energy transfer (FRET) [111], gel mobility [20], or single-molecule stretching [27, 23] and twisting [24, 130], have been used to examine elastic behavior of longer segments in which the effects of individual base-pair steps are

averaged over. The sequence-dependent nature of DNA deformability has been independently confirmed by research aimed to deduce DNA elastic properties from molecular dynamics simulations [17, 52].

For the dinucleotide model with energy (4.9) variational equations have been derived [38] and equilibrium configurations for plasmids of various compositions and end conditions have been found [38, 109], including (i) multiple equilibria of ligand-free DNA o-rings (plasmids that are circular when stress-free), (ii) minimum configuration of DNA o-rings with bound intercalating agents (iii) optimal distribution of intercalating agents that minimizes elastic energy of DNA o-rings, (iv) collapsed configurations of DNA o-rings subject to local overtwisting, (v) minimum energy configurations of intrinsically straight DNA plasmids with various distributions of twist-roll coupling, (vi) minimum energy of S-shaped DNA subject to local overtwisting. The theory has been extended to account for electrostatic repulsion and thermal fluctuations and applied to the study of minimum energy configurations and looping free energies of LacR-mediated DNA loops [134], and minimum energy configurations of free segments of promoter DNA bound to Class I and Class II CAP dependent transcription-activation complexes [86].

There have been suggestions that the local energy of DNA deformations may depend on the composition, or even the deformation, of more than just the immediate base-pair neighbors, for example

$$\Psi = \sum_{n=1}^{N-1} \psi^n(\theta^n, \rho^n, \dots, \theta^{n+k}, \rho^{n+k}). \tag{4.13}$$

Trinucleotide and tetranucleotide models have been proposed to account for some DNA structural features [110], and they also seem to better represent averaged DNA properties extracted from molecular dynamics simulations [17, 52]; the mechanical theory of such models has not yet been constructed.

5. Electrostatics. DNA has a net negative charge that resides primarily at the phosphate groups on the DNA backbone (see Figure 6). Electrostatic interaction is an integral component of DNA response to deformations but its role in DNA is not completely understood, mainly because it is difficult to decouple such an effect from purely elastic local contributions. The effect of electrostatics is modulated by the ionic conditions of the solvent, such as its dielectric properties and the valence of counterions. The two most important effects of electrostatic repulsion appear to be the increase in DNA effective diameter [144, 118] and increase in DNA bending stiffness [10].

In accord with the classical theory of electrostatics, in the absence of counterions (charged particles in the solution) the electrostatic energy of DNA with M charged sites would be given by

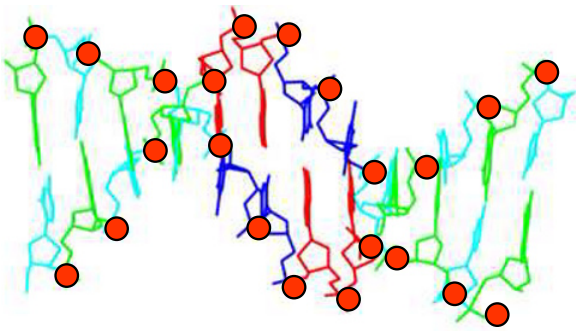

FIG. 6. *Negative charge on DNA is located at the phosphate groups (red).*

$$\Phi = \frac{(2\delta)^2}{4\pi\epsilon} \sum_{m=1}^{M-1} \sum_{n=m+1}^{M} \frac{1}{|\mathbf{r}^{mn}|} \tag{5.1}$$

where $\mathbf{r}^{mn} = \mathbf{x}^m - \mathbf{x}^n$ is the position vector connecting the charges m and n, δ is the elementary charge, and ϵ is the permittivity of water at 300K.

In the presence of counterions this long-range electrostatic interaction will be screened. Two main theories have been proposed to describe the effect of screening by monovalent counterions. The *Poisson-Boltzmann theory* replaces counterions by a continuous charge density and assumes that the this density is proportional to the Boltzmann factor of the electrostatic potential ϕ, which, after substituting in the classical equation of electrostatics, obeys the equation

$$\nabla(\epsilon(\mathbf{x})\nabla\phi(\mathbf{x})) = -4\pi\left(\rho(\mathbf{x}) + qe^{-\frac{q\phi(\mathbf{x})}{kT}}\right) \tag{5.2}$$

where ϵ is the dielectric, ρ is the charge density of DNA, q is the charge of counterions, and kT is Boltzmann constant times temperature. The electrostatic energy of DNA is then

$$\Phi = \frac{\delta}{2} \sum_{m=1}^{M} \phi(\mathbf{x}^m). \tag{5.3}$$

It was shown by Kirkwood [76] that the PB equation ignores the distinction between two different types of averages of the potential, which causes serious errors in the theory of strong electrolytes. Nonetheless, PB theory remains popular in studies of DNA at the atomic scale level [59, 19, 21, 138].

Alternative theory, proposed by Manning [94] and called the *counterion condensation theory*, separates the counterion distribution around

DNA into two parts: some counterions condense on the DNA and becomes immobile in all but one direction (along the DNA), the rest of the counterions remain mobile. The condensed portion of counterions neutralizes DNA charge to 24% of the original value, independent of the ionic strength. The weakened DNA charge can now be treated using Debye-Huckel theory (a linearized version of Poisson-Boltzmann theory) and yields, in place of (5.1) or (5.3), the following expression for DNA electrostatic energy:

$$\Phi = \frac{(2\delta)^2}{4\pi\epsilon} \sum_{m=1}^{M-1} \sum_{n=m+1}^{M} \frac{e^{-\kappa|\mathbf{r}^{mn}|}}{|\mathbf{r}^{mn}|} \tag{5.4}$$

where δ is now the net effective charge of $0.24e^-$ and κ is the Debye screening parameter, which, for monovalent salt such as NaCl, depends on the molar salt concentration c as $\kappa = 0.329\sqrt{c}\text{Å}^{-1}$.

The counterion condensation theory has been included in some calculations of minimum energy configurations of DNA using continuum and discrete elastic models. The electrostatic energy gives rise to an additional term in the balance equation for forces, accounting for the force of repulsion between a DNA base pair and the rest of the molecule. For simplicity, the charges are usually assumed to be located in the centers of base-pairs, as opposed to the phosphate groups. The singularity in (5.4) makes it difficult to account for electostatics by a continuous charge density and hence, even in continuum models, the charges are generally assumed to be discrete and the resulting equations are solved numerically. The cases studied to date include superoiled configrations of DNA plasmids [148], the effect of electrostatics on LacR-induced DNA loops [6, 7], and the straghtening effect of electrostatics on intrinsically curved DNA segments [18].

Vologodskii and Cozzarelli have employed an alternative method to account for electrostatic repulsion of DNA, the so called *hard-core repulsion model* in which no energy is added to the elastic energy of DNA but configurations with intersegmental distance smaller than some effective DNA radius R are inadmissible [144]. They found that such a model yields accurate results in Monte Carlo simulations of the dependence of knotting probability on on ionic strength, in the sense that R can be calibrated for each ionic strength and with this calbibrated value their statistical model of DNA was able to predict correctly knotting probability for various types of experiments.

The effects of multivalent counterions are much more difficult to treat because such ions have the ability to interact with more than one charged phosphate group. They have been hypothesized to bridge DNA segments in DNA condensation or to participate in charge-neutralization induced DNA bending [72, 80].

6. Statistical mechanics. A long molecule of DNA in solution is subject to thermal fluctuations that perturb its shape away from the minimum energy configuration. Statistical mechanical theories of DNA account

for fluctuations by assuming that each attainable configuration has a probability of occurence proportional to the Boltzmann factor of its total energy. Depending on the length and level of detail one seeks to describe, a fluctuating DNA can be treated using one of several polymer chain models: a freely-jointed chain, a worm-like chain, or a helical worm-like chain. In each of these models a DNA molecule is represented by a chain with vertices $\mathbf{x}^n{}_{n=1}^N$. The models are characterized by the dependence on N of the mean square end-to-end distance $< R^2 >=< |\mathbf{x}^N - \mathbf{x}^1|^2 >$, end-to-end (or radial) probability distribution function $\rho(R)$, or the closure (looping) probability $P(R = 0, \mathbf{t}^1 = \mathbf{t}^N)$.

The *freely-jointed chain* represents DNA as a chain of N rigid segments of length l, referred to as the Kuhn length, with uncorrelated orientations, i.e., $|\mathbf{x}^{n+1} - \mathbf{x}^n| = l$, $< (\mathbf{x}^{n+1} - \mathbf{x}^n) \cdot (\mathbf{x}^n - \mathbf{x}^{n-1}) >= 0$. (It corresponds to an unbiased random walk of equidistant steps in 3-space.) In the limit as $N \to \infty$, one finds that [53]:

$$< R^2 > \to Nl^2, \qquad \rho(R) \to \left(\frac{3}{2\pi N l^2}\right)^{3/2} \exp\left(-\frac{3R^2}{2Nl^2}\right) \tag{6.1}$$

provided that the orientation of the first segment is random, which implies that the root mean squared end-to-end distance scales with the square root of the length of the chain.

The *worm-like chain* accounts for bending rigidity of DNA. It can be derived in two ways - as a Kratky-Porod limit of a freely rotating chain with fixed angles between neighboring segments [81], or using Landau and Lifshitz method of averaging of configurations of an elastic rod with bending energy but no twisting energy (i.e., with C = 0 in (4.1)) [83]. In both cases one obtains the following expression:

$$< R^2 >= 2P\left(L - P(1 - e^{-L/P})\right) \cong \begin{cases} L^2(1 - L/3P) & \text{for } L << P \\ 2P(L - P) & \text{for } L >> P \end{cases} \tag{6.2}$$

where the persistence length P is a constant characterizing the stiffness of DNA; it is related to the bending rigidity A as $A = PkT$. The two limits of $< R^2 >$ in expression (6.2) tell us that a DNA that is much shorter than P behaves essentially as a stiff rod, while a DNA that is much larger than P behaves as a freely jointed chain with segments of length $l = 2P$.

The *helical worm-like chain* (HWLC) generalizes the worm-like chain model by accounting for the twisting deformation of DNA [123]. The partition function for HWLC is given by the path integral

$$Z(\mathbf{d}(L), \mathbf{t}(L), \mathbf{x}(L) | \mathbf{d}(0), \mathbf{t}(0), \mathbf{x}(0)) = \int_S \exp(-\Psi/kT) D\mathbf{x}(.) D\mathbf{d}(.) \tag{6.3}$$

with Ψ as in equation (4.1) and integration taken over the set S of all configurations $(\mathbf{x}(.), \mathbf{d}(.))$ with the specified end-conditions. For closed DNA plasmids these end-conditions are:

$$\mathbf{d}(L) = \mathbf{d}(0), \quad \mathbf{t}(L) = \mathbf{t}(0), \quad \mathbf{x}(L) = \mathbf{x}(0) \tag{6.4}$$

and an additional constraint of prescibed Lk is imposed on the contigurations in S which yields $Z = Z(Lk)$. This path integral cannot be evaluated explicitly but in various cases of interest approximate solutions have been obtained by asymptotic expansion [123, 99], Metropolis Monte-Carlo sampling [56, 90, 60], saddle-point expansion about the minimum energy configuration [156], or numerical integration on Euler motion group [34]. The integral (6.3) can also be evaluated using techniques developed for solving the Schrödinger equation [103, 22].

The HWLC theory has been employed in the study of DNA supercoiling and topoisomer distribution. Experimental results indicate that when DNA plasmids are reacted with type I topoisomerase [69], or are randomly formed by cyclization [125], one obtains a distribution of plasmid topoisomers that are identical apart from a difference in Lk. The resulting distribution of Lk is approximately Gaussian

$$P(Lk) \cong \exp(-G(Lk)/kT), \qquad G(Lk) = K(N)(Lk - N/h)^2, \tag{6.5}$$

where N is the plasmid size (in bp) and h is the helical repeat length (10.5 bp/turn). Theoretical predictions of this distribution [89] and the dependence of K on N by HWLC theory [79] were found to be in excellent agreement with experimental results. The shape of supercoiled configurations corresponding to high values of excess link $\Delta Lk = |Lk - N/h|$ was found to be of plectonemic nature with multiple terminal loops [119, 98].

The DNA cyclization experiment is one of the most sensitive methods for measuring DNA structural and elastic properties in solution [126, 43]. In the experiment identical linear DNA molecules with complementary free ends are reacted with an enzyme ligase that connects the free ends. The molecules can connect in two ways: (i) the two ends of a single molecule can join to form a cyclized molecule, or (ii) the ends of two molecules can dimerize to form a linear DNA segment of twice the length. The rates of cyclization and dimerization can be measured and their ratio, called the Jacobson-Stockmayer factor (or the J factor), can be plotted as a function of N to obtain the characteristic J curve [126, 124, 43, 8]. The J factor has been shown to be proportional to the probability of cyclization, which is an equilibrium quantity that can be computed using a HWLC model. Thus, material properties of DNA can be estimated by fitting the measured data with a computed J curve [123, 156, 90].

During a closure experiment DNA molecules may become knotted [122]. The probability of DNA knotting can be estimated using HWLC model [113], and the results are sensitive to DNA electrostatic repulsion, both in the magnitude of the screening and the treatment of electrostatic interaction [144]. DNA knotting is also produced by the action of topoisomerases of type II and type I (on nicked DNA), which has been used to elucidate the function of those enzymes. An important issue related to type II

topoisomerases is that they are very efficient in removing knots, catenations, and supercoils well below the thermodynamic equilibrium [114], which is made possible by the fact that they utilize ATP, a source of energy, during their action. A definite mechanism of how a small enzyme manages to recognize a global property of DNA as a knot type has not yet been found although several hypotheses have been proposed [145, 152, 25]. DNA knotting probability within the confined volume of bacteriophage head has also been studied using FJC model [5, 101].

Another area of DNA research that has greatly benefitted from and stimulated the development of statistical modeling is the area of single-molecule DNA manipulation experiments. Single-molecule DNA stretching and twisting experiments represent breakthroughs in the study of DNA properties because they allow researchers to track time-dependent behavior of individual molecules as opposed to ensemble averaged quantities. In these experiments one end of DNA is attached to a fixed object, for example the microscope slide or a bead that is held by a pipette, while the other end is attached to a bead that is captured and manipulated by an optical or magnetic trap. By varying the distance between the beads experimenters can stretch the captured molecule, and by rotating the magnetic bead they can twist the molecule.

Results of DNA stretching experiments [128, 26] are in excellent accord with theoretical predictions using WLC and HWLC models in ranges of loading that preserve the duplex DNA structure. The dependence of force on extension for a torsionally relaxed molecule of length L is fitted very accurately by the formula [99]

$$\frac{FP}{kT} = \frac{1}{4}\left(1 - \frac{x}{L}\right)^{-2} - \frac{1}{4} + \frac{x}{L} \tag{6.6}$$

where P is the persistence length. DNA twisting experiments [131, 30] have also been found in close agreement with HWLC predictions [103, 102, 22]. When large forces and/or twist is imposed on DNA, the molecule changes its secondary structure into alternative structures - overstretched DNA [127, 97], melted duplex with separated strands [131], or Pauli structure with backbone on the inside and bases on the outside [130] - none of which are governed by the HWLC theory.

The HWLC theory is built on the simplest, ideal model of DNA elasticity. An equivalent statistical mechanical theory has been developed also for sequence-dependent base-pair level DNA model [61]. Various cases of interest for DNA with sequence dependent properties have been analyzed, such the statistics of polymer chains with intrinsic bends or elastic inhomogeneity [112], the looping free energy of LacR-mediated DNA loops [134, 6], the free energy of LacR loops in the presence of CAP [135], the effect of intrinsic curvature, anisotropy, or twist-roll coupling on ring closure probability [44].

7. Dynamics. Dynamical models of DNA have been constructed to help us uncover time-dependent features of DNA behavior, such as perturbation relaxation times, rates of transition between configurational states, rates of closure and loop formation, etc. The primary interactions controling DNA dynamics are hydrodynamic resistance and thermal fluctuations.

Dynamical models of DNA can be divided into two groups - those based on theories of elastic rods and those based on theories of polymer dynamics. Dynamical theories of rods can be formulated within both Kirchhoff and special Cosserrat theories (see, e.g., [2]). Suppose that the rod is described by giving, as functions of the arc-length s and time t, its axial curve $\mathbf{x}(s,t)$ and an orthonormal triad $(\mathbf{d}_1(s,t), \mathbf{d}_2(s,t), \mathbf{d}_3(s,t))$ embedded in the cross-section. The equations of motion are given by

$$\dot{\mathbf{P}} = \mathbf{F}' + \mathbf{f} \tag{7.1}$$

$$\dot{\mathbf{R}} = \mathbf{M}' + \mathbf{x}' \times \mathbf{F} + \mathbf{m} \tag{7.2}$$

where dot stands for the time derivative, $\mathbf{P}$ and $\mathbf{R}$ are the linear and angular momentum of the cross-section, $\mathbf{F}$ and $\mathbf{M}$ are the contact forces and moments applied on the cross-section at s by material with arc-length greater than s, and $\mathbf{f}$ and $\mathbf{m}$ are the external forces and moments. The precise form of $\mathbf{P}$ and $\mathbf{R}$ and the constitutive equations for $\mathbf{F}$ and $\mathbf{M}$ depend on the type of rod under consideration and the approximations taken. The terms $\mathbf{f}$ and $\mathbf{m}$ account for hydrodynamic resistance.

When $\mathbf{f} = \mathbf{m} = 0$, exact solutions of (7.1)–(7.2) can be obtained for special motions, called traveling waves, in which the shape of the axial curve remains invariant and its apex is moving with constant velocity along the rod [4, 37, 50]. Other results include perturbation analysis of looping and ring collapse transitions [63, 64]. Hydrodynamic resistance was accounted for in numerical analyses of the formation of supercoiled states of overtwisted rings plasmids [77, 91]. Some researchers have used the solution of dynamical equations as a method for finding stable equilibrium configurations of DNA [6, 65]. With the exception of [6], the studies of DNA dynamics using continuum models published to date ignore thermal fluctuations but, nonetheless, yield useful information about the transition from circular to supercoiled DNA configurations.

In *polymer dynamics* models, a DNA molecule is replaced by a collection of rigid spheres of radius R with centers at $\{\mathbf{x}^n\}_{n=1}^N$ that are connected by elastic linkages simulating the bending and twisting rigidity of DNA. The total energy E of the chain is composed of stretching, bending, twisting, and electrostatic energy components. Because of high hydrodynamics resistance of the solvent, the molecule is assumed to move by diffusion which results in a Brownian type dynamics. At each time step Δt the positions of the beads change in accord with the following formula

$$\mathbf{x}^n(t+\Delta t) = \mathbf{x}^n(t) - \frac{\Delta t}{kT} \sum_m \mathbf{D}^{mn}(t) \nabla_{\mathbf{x}^n} E + \mathbf{R}^n(t) \tag{7.3}$$

where the Rotne-Prager diffusion tensor $\mathbf{D}^{mn}$ accounts for hydrodynamic coupling between beads m and n, and the random displacements $\mathbf{R}^n(t)$ obey

$$< \mathbf{R}^n(t) >= 0, \qquad < \mathbf{R}^n(t)\mathbf{R}^n(t)^T >= 2\Delta t\mathbf{D}^{mn}(t). \tag{7.4}$$

Brownian dynamics has been employed in the study of DNA tumbling and twisting, where computed results were compared with data coming from fluorescence depolarization experiments [91]. It has also been used to study the dynamics of DNA supercoiling [31, 78], and the dependence of site juxtaposition in DNA on the distance between sites [73, 71] and supercoiling density [32]. It was found, for example, that at low salt juxtaposition times are accelerated by a factor of 10 or more due to supercoiling [73]. DNA supercoiling was found [32] to occur on the timescale of 3–6 μs starting from a planar closed molecule, with an initial phase of 1–2 μs during which toroidal supercoiling appeared, followed by a conversion into a plectonemic supercoiling. The effect of intrinsic curvature on DNA supercoiling [33] and looping [100] has also been studied

8. Conclusion. This survey outlines the main mathematical results and models used by researchers to discuss DNA deformability and structure at the macroscopic level, covering a whole range of topological, geometrical, mechanical, electrostatic, statistical and dynamical models. There are few important topics in DNA research that do not naturally fit under the headings above, and one of them is the connection between DNA denaturation and supercoiling. It is known that although DNA molecule is stable under the conditions mimicking the intracellular environment, the base-pairing interaction can be disrupted, in a process called denaturation, as a result of a high temperature or mechanical deformation such as large untwisting, stretching, or bending. The energy required for DNA denaturation depends on base-pair composition and have been determined very accurately in calorimetric experiments. Craig Benham has used this information to develop a theory of stress-induced duplex destabilization [14, 15], which he used to compute the sites in a genome that would be most prone to denaturation due to supercoiling, and found that such sites coincide with transcription initiation regions [16].

The response of DNA to large deformations is still not well understood. Extensive stretching or twisting can induce the transition of DNA to alternative conformations with disrupted base-pairing (see Section 6), but it is not known whether such conformations play any biological role. DNA kinking - a higher order response to bending associated with disruption of base-stacking - has been proposed [154, 151, 116, 85, 54] as an explanation for unusually large cyclization probabilities of certain special DNA sequences [35, 36]. Furthermore, in addition to the well known B-DNA form there are other, alternative forms of DNA - A-DNA, C-DNA, Z-DNA, - which are induced by special experimental conditions (ethanol,

high salt), and for which mechanical properties have not been explored, nor mechanical theories of transitions between these forms have been formulated.

A large area of DNA research is concerned with protein-DNA interactions. We are still far from complete understanding the principles of protein-DNA binding affinity and specificity, and the role of DNA deformations that many proteins impose on DNA. This problem requires the use of local atomic level description of DNA and proteins and is beyond the scope of this essay.

The modeling efforts described above have focused on the understanding of DNA physical properties. The ultimate goal of DNA modeling, however, is to address important biological problems such as the problem of DNA compaction, chromatin formation and remodeling, and the problem of the role of DNA deformability in replication, recombination, or regulation of transcription. The first steps in this direction are provided by methods that utilize current information about protein-DNA interaction (X-ray crystal data, binding affinity measurements, DNA footprinting, etc.) to compute the structures of complex multi-protein DNA assemblies [6, 142, 65, 134, 7, 86, 135, 45].

A new direction in simulation of DNA dynamics and mechanics is to move away from models tailored to the conditions *in vitro* (i.e., in the test tube) to models of DNA *in vivo* (i.e., inside of a living cell). One important difference here is that the DNA *in vivo* is subject to random interactions with a large number of DNA binding proteins, both sequence specific and non-specific, that bend and twist the molecule. The first examples of a reserch concerned with intracellular DNA modeling include the analysis of DNA stretching in the presence of randomly binding bending or stiffening agents [153], and the study of DNA cyclization in the presence of a nonspecifically binding bending protein HU [45].

Although this overview of various areas of DNA modeling is understandably sketchy and incomplete, it gives the reader an idea about the variety of areas of DNA research that benefit from the use of mathematics. Further information about specific areas can be found in numerous survey papers and books, e.g., DNA topology [9, 150], base-pair level DNA structure [28], detail DNA structure [104], DNA mechanics [11, 65], single-molecule DNA stretching [26] and twisting [130], DNA supercoiling [106, 117, 143], or DNA topoisomerase action [146]. Additional material is available online, and includes two lectures given by the author at the tutorial "Mathematics of Nucleic Acids" which has taken place at the IMA on September 15, 2007. The slides and videorecordings of these lectures can be found on the IMA website (www.ima.umn.edu).

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