Preface

Early on, the mechanical properties of DNA (deoxyribonucleic acid) attracted the interest of both physicists and biologists, because of their importance to numerous biological processes, such as DNA transcription, gene expression and regulation, and DNA replication. DNA is a very complicated biological object, with complex structure and functions that contain and translate genetic information to the RNA (ribonucleic acid) and proteins. The DNA molecule is a long polymer made from repeating units called nucleotides.

Despite the fact that DNA was discovered in the late 1860s by Friedrich Miescher, its helical structure in the form of three-dimensional right double helix B-DNA or dsDNA with two strands was elucidated only in 1953 by American biologist James Watson and English physicist Francis Crick. Other forms of DNA molecules are the short A-DNA, Z-DNA with left helix, stretched S-DNA, overtwisted P-DNA, and a single stranded ssDNA. The dsDNA structure of all species comprises the double helical chains, each coiled around the same axis, and each with a helical pitch of 3.3–3.4 nm and radius of 1–1.1 nm. The backbone of the DNA strand is made from alternating phosphate and sugar residues. The sugar in DNA is 2-deoxyribose. The discovery of the structure of DNA was the beginning of a process that has transformed the foundations of biology and accelerated the developments of the genetic engineering.

The sugars joined by phosphate groups form phosphodiester bonds between the third and fifth carbon atoms of adjacent sugar rings. These asymmetric bonds mean that a strand has a direction. The nucleotides in a double helix have one strand, with the direction of the bonds opposite to their direction in the other strand (strands are antiparallel). The asymmetric ends of DNA strands are called 5′ and 3′, with the 5′ end having a terminal phosphate group, and the 3′ end having a terminal hydroxyl group. One major difference between DNA and RNA is the sugar, with the 2-deoxiribose in DNA being replaced by the pentose sugar ribose in the RNA.

The genetic information is held within genes, and the complete set of this information in an organism is called the genotype. A gene is a unit of heredity, and is a region of DNA. Genes contain an open reading frame. Within a gene, the sequence of bases along a DNA strand defines a messenger RNA sequence that then defines one or more protein sequences. The genetic code consists of three letter words, called codons (the nucleoside triphosphates) that form a sequence of three nucleotides (e.g., ACT, CAG, TTT, where (A) is adenine, (G) is guanine, (T) is thymine, and (C) is cytosine).

Twin helical strands form the dsDNA backbone. Another double helix may be found tracing the spaces, or grooves, between the strands. As the strands are not symmetrically located with respect to each other, the grooves are unequally sized. The major grove is 2.2 nm wide, and the minor groove is 1.2 nm wide. As a result, proteins, such as transcription factors, usually have contacts to the sides of the bases exposed in the major groove.

DNA nanotechnology uses the unique molecular recognition properties of DNA and other nucleic acids to create self-assembling branched DNA complexes with the useful properties. DNA is thus used as a structural material, rather than as carrier of biological information. Recently, the first living organism has been created with artificial DNA.

The elastic properties of DNA are essential for its biological functions. They control its stretching, bending, and twisting, as well as the induction of structural modification in the molecule. These can affect its interaction with the cell machinery. The mechanical flexibility of DNA plays a key role in all of its cellular functions, including folding, packaging, regulation, recombination, replication, and transcription. The connections between DNA's molecular interactions and its mechanical properties are, therefore, of considerable interest to biologists and biophysicists.

From the very beginning, abstraction and modeling has played a significant role in the research on DNA. These models gave rise to mathematical concepts and techniques for the study of DNA configurations at microscopic and mesoscopic levels. Today, we can determine the structure of short DNA fragments, their stretching, bending, and twisting with nanometer and picoNewton resolution, with the application of atomic force microscopy (AFM) and with even higher measurement accuracy, up to femtometer and zeptogram, by AFM with higher oscillation modes. The number of DNA research publications is huge because their results have a large impact on the development of molecular biology and medicine.

This book is dedicated to the analysis of existing DNA molecule mechanical models, and the development of more comprehensive advanced mechanical models of DNA elasticity.

In Chapter 1, we discuss the mechanical properties of DNA molecules, and more than twenty effective mechanical models of DNA elasticity, based on discrete statistical mechanics, atomistic, continuum, and approximation methods. Among them, there are such models as freely jointed chain (FJC), wormlike chain (WLC), helical wormlike chain (HW or HWLC), and discrete persistent chain (DPC) models that played an important role in the development of the scientific approach to the study of DNA elasticity. We also discuss dynamic models of DNA, its persistence length features and structural phases, such as ds-DNA (B-form), S-DNA (stretched one), ssDNA (single stranded), and P- DNA (overwind). Most of these models were introduced at the end of 1990s and the beginning of this century. The important Kratky-Porod model was introduced

as early as 1949. These models play a significant role in the understanding and evaluation of DNA elasticity properties. But our analysis of these models shows that they have some limitations, specifically for the applicable force ranges with difference for small (less than 10 pN) and comparatively large forces (but less than 65 pN), and even some unfeasible results in calculations. Therefore, we concluded that the development of a more comprehensive explicit functional helicoidal model (EFHM or, briefly, EHM) that covers all stretch ranges from the beginning to the transition of dsDNA to S-DNA, overwinding options, nonlinear elasticity and nonlinear thermomechanical fluctuations is very important. Modeling of ssDNA was done by A.V. Tkachenko with zigzag (ZZM), and by C. Storm and P.C. Nelson with DPC models, and may require application of the coiled ribbons (EHMR) model. In this chapter, we also discuss DNA dynamics with different pulling speeds, traveling waves, models of molecular length fluctuations, polymer dynamics and hydrodynamics, the persistence length definition, polymer material properties used for DNA modeling, limitations of micro object measurement accuracy, size and mass DNA conversion, and the DNA technical applications.

Chapter 2 focuses on the discussion and development of the experimental research methods for determining the mechanical properties of DNA, including force application by solutions flow, stretching micropipette, glass needles, optical and magnetic tweezers, the measurement of force and displacements by atomic force microscopy (AFM), and small-angle X-ray scattering interference measurements of the DNA molecular length fluctuations. Special attention in this chapter is paid to more sensitive atomic force microscopy with micro-nanocantilevers. In addition, the micromanipulation technique is also considered, including different types of cantilevers, and effective flexure hinges with cylindrical, elliptical, parabolic, hyperbolic, segmented, and any computer approximated concave profiles by an application of the reliable reverse conformal mapping.

Chapter 3 focuses on atomic force microscopy with higher vibration modes and sensitivity, up to zeptogram and femtometers. AFM calibration, effective increase of cantilever spring constants ratio, quality factor influence, sensitivity to additional mass, specifics of the V-shaped cantilever (with end extended mass) features at higher mode oscillations are considered. The contact dynamics at AFM tapping mode and an influence of measurand object profile surface roughness is also under consideration. The sensitivity of AFM with higher mode oscillations allows us to get increased resolution in mass, force, and dimensions measurements. Bimodal AFM is especially effective in measurement of biological objects and small dimensions in nanometer range, where interaction forces depend on the Hamaker and Lifshitz constants. However, the contact deformation can be larger at higher cantilever modes of vibration, as a result of large spring constants. Internal and external damping, ambient influence (temperature, vibration, acoustic noise, electromagnetic field, etc.) on the measurement and calibration accuracy (including information criterion of

expanded uncertainty negligibility), and methods of measuring system protection are also discussed.

The kinematics of an elastic helicoidal beam and its physical realization in the thin pretwisted (helicoidal) micro-nanostrips – an important part of a new explicit functional helicoidal model of DNA, are considered in Chapter 4. This chapter shows the mathematical dependencies of the elastic helicoids parameters on their specific rigidities, stress, and fatigue conditions. We found, on this basis, the nonlinear relations in the pretwisted (helicoidal) strip's motion transformation, and its effective cross-section configurations. The parameters of the quasi-helicoids with shells (particular coiled ribbon) are also analyzed. We developed these relations using the principles and methods of continuum mechanics, because the connection between the motion and corresponding stress tensors, elastic, shear moduli, and Poisson's ratio plays a very important role in our helicoidal model of the DNA. The mathematical apparatus of this chapter is necessary in order to develop the functional relations of new DNA explicit helicoidal models presented in Chapter 6 and Chapter 7. Developed displacement-loading relations of helicoidal sensors are even wider for further DNA modeling in different environments and applications.

Chapter 5 is dedicated to the dynamics and vibration of elastic helicoids, their periodic and transient functions. We study the influence of large and small impedance, elastic longitudinal links, and internal friction (damping) asymmetry in the helicoidal multivibrators. State of stress and sensitivity to additional mass are also considered. This study shows that the relaxation of helicoids with different speed follows with less uncertainty than at a dynamic stretching. Limits of the transmission entropic fluctuations, flexural wave propagation, and break speed are also considered.

Mathematical relations, developed in Chapter 4 and Chapter 5, are essential to the structuring of the new explicit helicoidal models of the DNA molecule.

The main linear and nonlinear features of the DNA molecule elasticity are defined in Chapter 6, with the application of the explicit functional helicoidal model (EHM), where its Young's and shear moduli, conditional Poisson's ratio, persistence length, twist-stretch coupling, and overwinding options are evaluated. Calculation results are in good agreement with the experimental data for the certain DNA parameters. Problems of linear and nonlinear thermomechanical molecular length fluctuations of the DNA are carefully discussed, on the basis of EHM application. The dynamics of force application influence on the DNA stretching features, including the pulling speed factor, are also considered in this chapter.

Models for the transition of dsDNA to S-DNA and ssDNA at stretching are evaluated and developed in Chapter 7. We show that practical application of the discrete persistence chain (DPC) model is not a simple solution to the transition of B-DNA to S-DNA evaluation, as a result of the significant number of parameters used, the complexity of their estimation, and their

complex mathematical relations. The theoretical approach of the quasi-reverse WLC transition B-DNA to S-DNA model does not take into account important aspects of the problem, such as the possible dependence of the parameters on the base pair (bp) sequence, the possibility of denaturation, and the effect of ionic strength of the medium. It also ignores the coupling of the chain elongation with torsion energy, that is, it assumes that the chain is free to rotate. Representation of B to S forms of DNA transition by a sequence of linear springs is useful for an approximation of the average experimental data at dsDNA and ssDNA stretching, but does not reveal a real mechanism of the dsDNA and ssDNA molecules' elasticity and overstretching behavior. It uses an imaginary combination of "multiple soft and hard linear springs" that does not exist in a real DNA molecule structure. Besides, the number of required constants depends on the accuracy of experimental data, and may not all be known *a priori*.

Calculation results with explicit functional helicoidal (EHM) model correspond well to the experimental data for all provided estimations and increase of the middle plateau by transformation with the unit singular function. This comprehensive model is simpler than other known models that reflect the transition from dsDNA to S-DNA or ssDNA. The widely known freely jointed chain (FJC), wormlike chain (WLC), and helical worm like chain (HW or HWLC) models do not represent this option directly at all. The EHM model works in a large range of stretching forces, and applied torques and, in the case of flexural waves, transition. Possible coiled ribbon applications for the single stranded ssDNA modeling (EHMR) at strong stretching and corresponding stress evaluation are also studied, in comparison with the ZZM and DPC chains. The EHM model can be included in eWLC and eFJC DNA extensible chain models, as well. The latter option is represented in detail. We also study in this chapter the buckling of a DNA molecule, and DNA mechanical stability. As a result, we have found that EHM, the explicit helicoidal model, is more comprehensive in comparison with other known mechanical models of the DNA, not only in the mathematical representation of main static and dynamical features of its elasticity and transitions, but also in the adequate presentation of this molecule's helical structure and geometric parameters.

This book reflects the author's experience, and represents his ideas and opinions. Results of many other researchers in this field are also discussed in the book.

Of course, all these assumptions and the explicit helicoidal model's application to DNA mechanics may be experimentally more thoroughly verified, and theoretically developed in more detail. However, the closeness of biomechanics and precision nanoelastic mechanics is evident.

Although every effort has been made to eliminate errors, experience dictates their inevitable presence in such comprehensive work. When detected, the author would be grateful for guidance on errors or omissions. Extensive references

are included to enable the reader to verify discussed problems and solutions. We should also note that, in the preparation of this book, reasonable efforts have been made to publish reliable data and information, but the author cannot assume responsibility for the validity of all referenced materials, or for the consequences of their inappropriate use.

The author hopes that this book will help to develop new and more advanced mechanical models of DNA elasticity, and provide effective means for the better understanding of DNA mechanical features and functions.