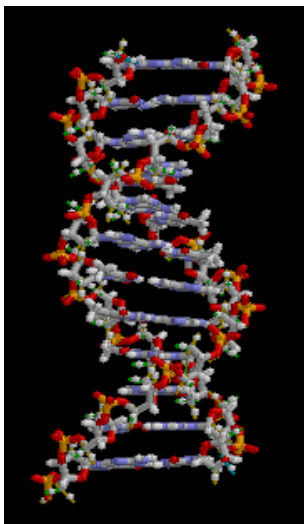


Molecular models of DNA



While this purified DNA precipitated in a water jug (left) appears to be a formless mass, nucleic acids actually possess several intricate structures at the nanoscale, such as the animated, DNA double helix structure shown at right.

Molecular models of DNA structures are representations of the molecular geometry and topology of Deoxyribonucleic acid (DNA) molecules using one of several means, with the aim of simplifying and presenting the essential, physical and chemical, properties of DNA molecular structures either *in vivo* or *in vitro*. These representations include closely packed spheres (CPK models) made of plastic, metal wires for 'skeletal models', graphic computations and animations by computers, artistic rendering. Computer molecular models also allow animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*.

The more advanced, computer-based molecular models of DNA involve molecular dynamics simulations as well as quantum mechanical computations of vibro-rotations, delocalized molecular orbitals (MOs), electric dipole moments, hydrogen-bonding, and so on. **DNA molecular dynamics modeling** involves simulations of DNA molecular geometry and topology changes with time as a result of both intra- and inter- molecular interactions of DNA. Whereas molecular models of Deoxyribonucleic acid (DNA) molecules such as closely packed spheres (CPK models) made of plastic or metal wires for 'skeletal models' are useful representations of static DNA structures, their usefulness is very limited for representing complex DNA dynamics. Computer molecular modeling allows both animations and molecular dynamics simulations that are very important for understanding how DNA functions *in*

vivo.

History



The A-DNA double-helix molecular model of Crick and Watson (consistent with their X-ray data) for which they received a Nobel prize together with M.H.F. Wilkins.

Double Helix Discovery



William Astbury
Oswald Avery
Francis Crick
Erwin Chargaff
Max Delbrück
Jerry Donohue
Rosalind Franklin
Raymond Gosling
Phoebus Levene
Linus Pauling
Sir John Randall
Erwin Schrödinger
Alex Stokes
James Watson
Maurice Wilkins

Herbert Wilson

From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were successfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953^[1]. The first calculations of the Fourier transform of an atomic helix were reported one year earlier by Cochran, Crick and Vand^[2], and were followed in 1953 by the computation of the Fourier transform of a coiled-coil by Crick^[3].

Structural information is generated from X-ray diffraction studies of oriented DNA fibers with the help of molecular models of DNA that are combined with crystallographic and mathematical analysis of the X-ray patterns.

The first reports of a double-helix molecular model of B-DNA structure were made by Watson and Crick in 1953^[4]^[5]. Last-but-not-least, Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads^[6]. The development of the first correct double-helix molecular model of DNA by Crick and Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules^{[7] [8] [9] [10] [11] [12]}. Although such initial studies of DNA structures with the help of molecular models were essentially static, their consequences for explaining the *in vivo* functions of DNA were significant in the areas of protein biosynthesis and the quasi-universality of the genetic code. Epigenetic transformation studies of DNA *in vivo* were however much slower to develop in spite of their importance for embryology, morphogenesis and cancer research. Such chemical dynamics and biochemical reactions of DNA are much more complex than the molecular dynamics of DNA physical interactions with water, ions and proteins/enzymes in living cells.

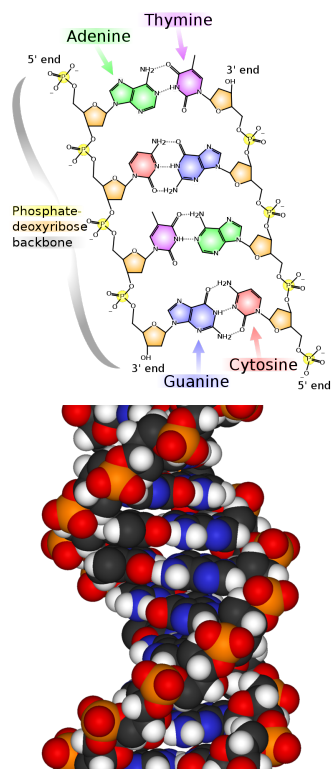
Importance

An old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Although DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains (that are made of repeating nucleotide units of four basic types, attached to deoxyribose and phosphate groups), its molecular structure *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules and ions. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA into an especially challenging problem for both molecular biologists and biotechnologists. Like other large molecules and biopolymers, DNA often exists in multiple stable geometries (that is, it exhibits conformational isomerism) and configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule.

Such varying molecular geometries can also be computed, at least in principle, by employing *ab initio* quantum chemistry methods that can attain high accuracy for small molecules, although claims that acceptable accuracy can be also achieved for polynucleotides, as well as DNA conformations, were recently made on the basis of VCD spectral data. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started especially in connection with results obtained by VCD in solutions. More detailed comparisons with such *ab initio* quantum computations are in principle obtainable through 2D-FT NMR spectroscopy and relaxation studies of polynucleotide solutions or specifically labeled DNA, as for example with deuterium labels.

In an interesting twist of roles, the DNA molecule itself was proposed to be utilized for quantum computing. Both DNA nanostructures as well as DNA 'computing' biochips have been built.

Fundamental concepts



At left, the chemical structure of DNA showing the base-pairing. This depiction of a DNA duplex lacks information about the molecule's three-dimensional structure, at right.

The chemical structure of DNA is insufficient to understand the complexity of the 3D structures of DNA. On the other hand, animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The DNA model shown (far right) is a space-filling, or CPK, model of the DNA double-helix. Animated molecular models, such as the wire, or skeletal, type shown at the top of this article, allow one to visually explore the three-dimensional (3D) structure of DNA. One visualization of DNA model is a space-filling, or CPK, model.

The hydrogen bonding dynamics and proton exchange is very different by many orders of magnitude between the two systems of fully hydrated DNA and water molecules in ice. Thus, the DNA dynamics is complex, involving nanosecond and several tens of picosecond time scales, whereas that of liquid ice is on the picosecond time scale, and that of proton exchange in ice is on the millisecond time scale. The proton exchange rates in DNA and attached proteins may vary from picosecond to nanosecond, minutes or years, depending on the exact locations of the exchanged protons in the large biopolymers.

A simple harmonic oscillator 'vibration' is only an oversimplified dynamic representation of the longitudinal vibrations of the DNA intertwined helices which were found to be anharmonic rather than harmonic as often assumed in quantum dynamic simulations of DNA.

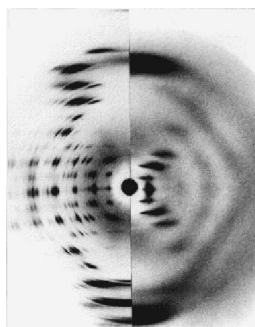
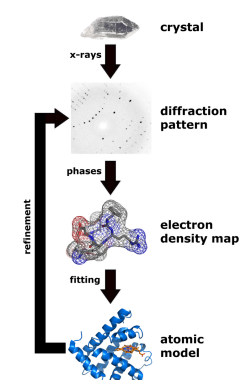
DNA structure

The structure of DNA shows a variety of forms, both double-stranded and single-stranded. The mechanical properties of DNA, which are directly related to its structure, are a significant problem for cells. Every process which binds or reads DNA is able to use or modify the mechanical properties of DNA for purposes of recognition, packaging and modification. The extreme length (a chromosome may contain a 10 cm long DNA strand), relative rigidity and helical structure of DNA has led to the evolution of histones and of enzymes such as topoisomerases and helicases to manage a cell's DNA. The properties of DNA are closely related to its molecular structure and sequence, particularly the weakness of the hydrogen bonds and electronic interactions that hold strands of DNA together compared to the strength of the bonds within each strand.

Experimental techniques which can directly measure the mechanical properties of DNA are relatively new, and high-resolution visualization in solution is often difficult. Nevertheless, scientists have uncovered large amount of data on the mechanical properties of this polymer, and the implications of DNA's mechanical properties on cellular processes is a topic of active current research.

The DNA found in many cells can be macroscopic in length - a few centimetres long for each human chromosome. Consequently, cells must compact or "package" DNA to carry it within them. In eukaryotes this is carried by spool-like proteins known as histones, around which DNA winds. It is the further compaction of this DNA-protein complex which produces the well known mitotic eukaryotic chromosomes.

DNA structure determination using molecular modeling and DNA X-ray patterns

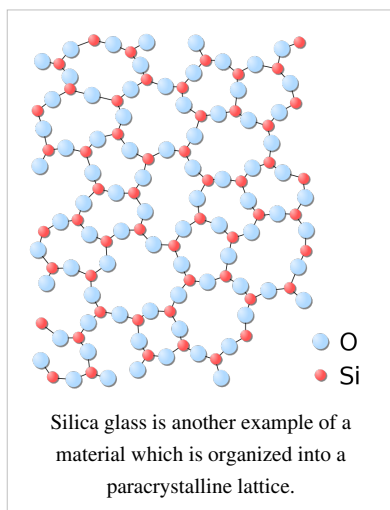


A-DNA B-DNA

Left, the major steps involved in DNA structure determination by X-ray crystallography showing the important role played by molecular models of DNA structure in this iterative process. Right, an image of actual A- and B- DNA X-ray patterns obtained from oriented and hydrated DNA fibers (courtesy of Dr. Herbert R. Wilson, FRS- see refs. list).

After DNA has been separated and purified by standard biochemical techniques one has a sample in a jar much like in the figure at the top of this article. Below are the main steps involved in generating structural information from X-ray diffraction studies of oriented DNA fibers that are drawn from the hydrated DNA sample with the help of molecular models of DNA that are combined with crystallographic and mathematical analysis of the X-ray patterns.

Paracrystalline lattice models of B-DNA structures



A paracrystalline lattice, or paracrystal, is a molecular or atomic lattice with significant amounts (e.g., larger than a few percent) of partial disordering of molecular arrangements. Limiting cases of the paracrystal model are nanostructures, such as glasses, liquids, etc., that may possess only local ordering and no global order. A simple example of a paracrystalline lattice is shown in the following figure for a silica glass:

Liquid crystals also have paracrystalline rather than crystalline structures.

Highly hydrated B-DNA occurs naturally in living cells in such a paracrystalline state, which is a dynamic one in spite of the relatively rigid DNA double-helix stabilized by parallel hydrogen bonds between the nucleotide base-pairs in the two complementary, helical DNA chains (see figures). For simplicity most DNA molecular models omit both water and ions dynamically bound to B-DNA, and are thus less useful for understanding

the dynamic behaviors of B-DNA *in vivo*. The physical and mathematical analysis of X-ray^[13] ^[14] and spectroscopic data for paracrystalline B-DNA is therefore much more complicated than that of crystalline, A-DNA X-ray diffraction patterns. The paracrystal model is also important for DNA technological applications such as DNA nanotechnology. Novel techniques that combine X-ray diffraction of DNA with X-ray microscopy in hydrated living cells are now also being developed (see, for example, "Application of X-ray microscopy in the analysis of living hydrated cells" ^[15]).

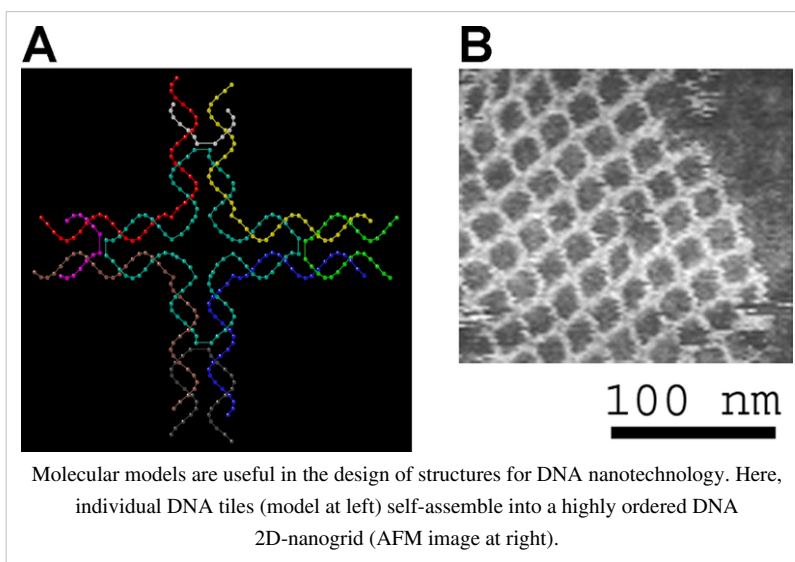
Genomic and biotechnology applications of DNA molecular modeling

There are various uses of DNA molecular modeling in Genomics and Biotechnology research applications, from DNA repair to PCR and DNA nanostructures. Two-dimensional DNA junction arrays have been visualized by Atomic force microscopy.^[16]

DNA molecular modeling has various uses in genomics and biotechnology, with research applications ranging from DNA repair to PCR and DNA nanostructures. These include computer molecular models of molecules as varied as RNA polymerase, an E. coli, bacterial DNA

primase template suggesting very complex dynamics at the interfaces between the enzymes and the DNA template, and molecular models of the mutagenic, chemical interaction of potent carcinogen molecules with DNA. These are all represented in the gallery below.

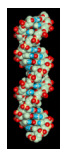
Technological applications include a DNA biochip and DNA nanostructures designed for DNA computing and other dynamic applications of DNA nanotechnology. The image at right is of self-assembled DNA nanostructures. The DNA "tile" structure in this image consists of four branched junctions oriented at 90° angles. Each tile consists of nine DNA oligonucleotides as shown; such tiles serve as the primary "building block" for the assembly of the DNA



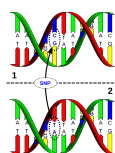
nanogrids shown in the AFM micrograph.

Quadruplex DNA ^[17] may be involved in certain cancers^{[18] [19]} . Images of quadruplex DNA are in the gallery below.

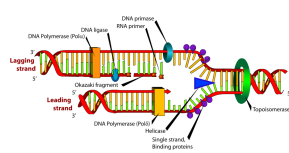
Gallery of DNA models



Spinning
DNA
generic
model.



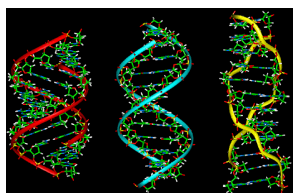
An
oversimplified
sketch of the
double-helix
structure of
A-DNA.



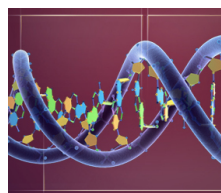
A model of DNA replication
based on the double-helix
concept.



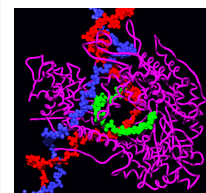
A large-scale
Crick-Watson
DNA Model
shown in the
Museum of
Príncipe Felipe.



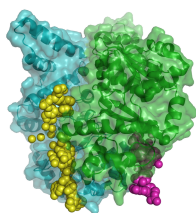
Side view of molecular models of
A- , B-, Z- DNA.



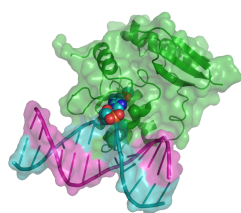
Oversimplified model of
the A-DNA double-helix.



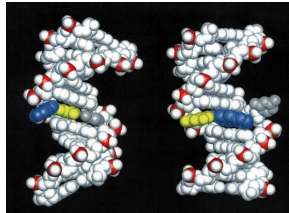
Molecular modeling of
RNA Polymerase.



Molecular modeling of
a bacterial DNA
Primase Template.



Molecular modeling of DNA
interactions with the
carcinogen molecule MGMT.



3D Molecular model of DNA
damaged by carcinogenic
2-aminofluorene(AF).

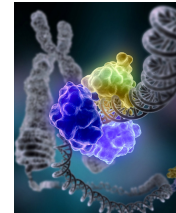
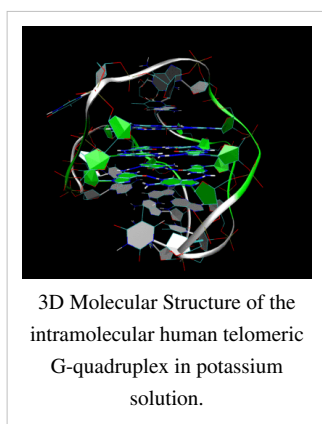
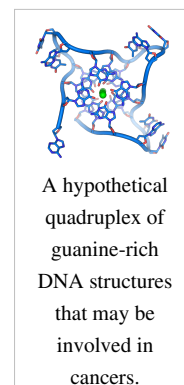
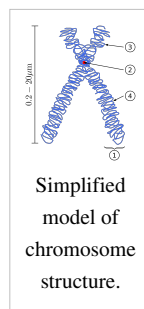
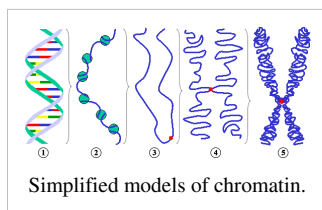
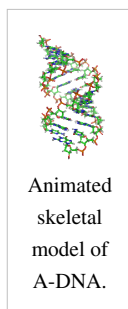


Fig.6. Molecular
modeling of DNA
repair



See also

- G-quadruplex
- Crystallography
- Crystal lattices
- X-ray scattering
- Sir Lawrence Bragg, FRS
- List of nucleic acid simulation software
- Neutron scattering
- X-ray microscopy
- Sirius visualization software
- QMC@Home
- 2D-FT NMRI and Spectroscopy
- FT-NMR^[20] ^[21]
- NMR microscopy^[22]
- Microwave spectroscopy
- Vibrational circular dichroism (VCD)
- FT-IR
- FT-NIR^[23] ^[24] ^[25]
- Spectral, Hyperspectral, and Chemical imaging^[26] ^[27] ^[28] ^[23] ^[24] ^[29] ^[30] .
- Raman spectroscopy/microscopy^[31] and CARS^[32] .
- Fluorescence correlation spectroscopy^[33] ^[34] ^[35] ^[24] ^[36] ^[37] ^[38] ^[23] ,
- Fluorescence cross-correlation spectroscopy and FRET^[39] ^[40] ^[41] .

- Confocal microscopy^[33]

Further reading

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External links

- DNA the Double Helix Game ^[44] From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA ^[45]
- Double Helix 1953–2003 ^[46] National Centre for Biotechnology Education
- DNALive: a web interface to compute DNA physical properties ^[47]. Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database ^[48]. The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data ^[49]
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. ^[50]
- Application of X-ray microscopy in analysis of living hydrated cells ^[15]
- overview of STM/AFM/SNOM principles with educative videos ^[51]

Databases for DNA molecular models and sequences

X-ray diffraction

- NDB ID: UD0017 Database ^[17]
- X-ray Atlas -database ^[52]
- PDB files of coordinates for nucleic acid structures from X-ray diffraction by NA (incl. DNA) crystals ^[53]
- Structure factors downloadable files in CIF format ^[54]

Neutron scattering

- ISIS neutron source: ISIS pulsed neutron source: A world centre for science with neutrons & muons at Harwell, near Oxford, UK. ^[55]

X-ray microscopy

- Application of X-ray microscopy in the analysis of living hydrated cells ^[15]

Electron microscopy

- DNA under electron microscope ^[56]

NMR databases

- NMR Atlas--database ^[57]
- mmCIF downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data ^[58]
- NMR constraints files for NAs in PDB format ^[59]

Genomic and structural databases

- CBS Genome Atlas Database ^[60] — contains examples of base skews.
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes ^[61].
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats ^[62]

Atomic force microscopy

- How SPM Works ^[63]
 - SPM Image Gallery - AFM STM SEM MFM NSOM and more. ^[64]
-

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