

DNA: the Double Helix or the Ribbon Helix?

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ABSTRACT

The well-known difficulty of the Watson-Crick model gives the right to assume its incorrectness. An alternative model of the structure of the DNA molecule called a ribbon helix is proposed. Unlike the double helix, in it two chains are not intertwined, but go in parallel; unlike another earlier proposed structure, the so-called side-by-side model, it differs in that it has a homogeneous, dextrorotatory character. The advantages of the proposed structure are shown.

From the author. This is a slightly modified and supplemented translation of my article «Двойная спираль или лента-спираль?» (The Double Helix or the Ribbon Helix) published in the Russian popular science journal "Chemistry and Life" (1999, No. 9) – there is on my site: <http://lev-verkhovsky.ru/>

Almost two-thirds of the century has passed since the publication by J. Watson and F. Crick (Nature, April 1953) of the proposed DNA molecule structure, which soon became the symbol of a new science -- molecular biology. All the vicissitudes associated with this achievement are described by Watson in his famous book "The Double Helix" (1968). But is there full confidence that this model is correct?

There is an intertwining -- there is a problem

In the 19 century, V. Flemming discovered the phenomenon of the longitudinal splitting of chromosomes in dividing cells. The model of the carrier of hereditary information in the form of two complementary chains gave a remarkably simple and beautiful explanation to the processes of doubling and transferring genetic information; the proposed structure became a concrete chemical embodiment of N. Koltsov's "matrix" idea expressed by him in 1927. It was in the

discovery of the principle of complementarity of nucleic acids the revolutionarity of Watson and Crick model consisted of.

But the double helix immediately led to a contradiction that its authors could not fail to notice: in it, the sugar-phosphate strands are twisted on each other, and when cells are dividing (with DNA replication), the two chains must be separated. However, in one chromosome the DNA molecule can be a centimeter long and, therefore, contain millions of turns; moreover, it is extremely densely packed in the microscopic volume of the cell nucleus. How can one imagine that chains will be unwinded under these conditions?

Why did Watson and Creek come to the conclusion that the two strands coil plectonemically round one another and form a homogeneous double helix? From general considerations, more precisely, from a desire for maximum symmetry. Here is what is said about this in the Watson's «Double Helix»: «... We decided to suppose -- until we reach a dead end, -- that the structure of the sugar-phosphate backbone is very regular one».

And they actually built such a regular helix -- in the form of a spiral staircase in which all steps are equal (and the two chains are intertwined). M. Delbrück, one of the first to learn about their discovery, immediately wrote to Watson that he is confident in the correctness of the principle of complementarity, but the intertwining of the threads see as erroneous. In the 1950s and 1960s, the problem of threads separation was quite acute, but the authors of the model and most other scientists hoped that in the future it would somehow be resolved.

Light at the beginning of the tunnel

Indeed, in the 70s it seemed as if there was a way out: in the cells, proteins (topoisomerases) have been found that can cleave and link single strands of DNA. This means that similar enzymes can in principle cut up chains at once in many places, where they will unwind, and then the enzymes are able to link the ends of the individual pieces. This idea, although was not supported by concrete evidence (the participation of such proteins in replication was not experimentally confirmed), calmed many of researchers.

Many, but not all of them, because in this case the process of separating of the two chains, all the same, rest be very, fantastically difficult. And this fact became the basis for the search for other -- alternative -- DNA models in which the chains are not intertwined at all.

And what, the reader will ask, the long-term studies of DNA by all possible methods in hundreds of laboratories in the world have not yet uniquely determined its structure? Surprisingly, the answer will be negative.

It would be good to have seen the structure of native (biologically complete) DNA with atomic resolution but this not yet possible. As for X-ray structural analysis, single crystals are required, and they are only able to be obtained from short stretches of DNA. It is clear that the conformation of such "stumps" will be affected by their free ends, because of which the natural

form of DNA molecules can be distorted (by the way, the first structure completely deciphered by this method suddenly looked like a broken left spiral, which was called the Z-shape).

In the case of long DNA, only fibers are obtained in which the molecules lie in parallel but can rotate about their longitudinal axes, that is, they are not ordered azimuthally. Their roentgenograms were studied by Rosalind Franklin; she was a good crystallographer, and whoever read Watson's book remembers her "anti-spiral" views. As A. Klug wrote after her death, in her working diary (winter 1952--53) there are considerations that "**the x-ray patterns of the fibers indicate not a regular helix, but rather a strip or pseudo-helix with nonequivalent phosphates, which in the projection looks as a figure of eight**".

The DNA contour is already seen in the electron microscope (although not so clearly as to draw decisive conclusions), and it can be noticed that it is not the same as in the double helix. But the probe microscopists made an important and demonstrative trial of this molecule and are already close to making a final verdict to double helix: they began to mechanically stretch ends of the two chains in different directions -- break hydrogen bonds between complementary bases (in other words, denature DNA) and have seen that the two strands of long molecule behave as if they were free to separate (see Appendix).

Fashion on the models

In 1976, two groups of researchers -- from India and New Zealand -- independently proposed a so-called **Side by Side** (SBS) model, in which the direction of twist of both chains varies through each half-turn, so in general, they remain unconnected. Published in good scientific journals, this structure caused a small stir at the time: it turned out that, despite its apparent illogicality (for what reason does the spiral change its spin all the time?), it is not so easy to refute it.

To this aim, special, and rather sophisticated, experiments were conducted (they were based on the effect of supercoiling of DNAs closed in a ring). The bottom line is that such a DNA behaves like an elastic telephone cord, which, as we know, when is overtwisted relieves stress, forming supercoils. So, the SBS model, because of its right-left twists, should behave somewhat differently from the double helix with respect to supercoiling, and as a result, it was possible to show its inconsistency with the data obtained.

Another model, called **Ribbon** (strip, tape) **Helix**, was proposed in 1979 by the author of these lines. In it two sugar-phosphate chains form oppositely directed parallel spirals shifted relative to each other by the length of the bridge of the base pair; the size of the turn and the distance between adjacent pairs are the same as in the double helix. From SBS structure it is distinguished by a homogeneous dextrorotatory nature of chains -- there are no "wags".

Together with R.-H. Mikelsaar of Tartu University one turn of the new structure was built, using Tartu space-filling atomic-molecular models, that is, its steric (spatial) opportunity was shown. This work is reflected in the theses of the "First Republican Conference on Biophysics",

Academy of Sciences of the Moldavia, Chisinau, 1984; a year earlier, a brief oral report about it was made at the All-Union (USSR) School on Nucleic Acid Biophysics in Kharkov (Ukraine).

(Incidentally, in the 1990s, the editor-in-chief of Nature, J.Maddox, said that now the original article by Watson and Crick probably would not have been accepted for publication: the reviewers would say that this is only the construction of models, some speculation; in addition X-ray data was obtained not by them, but by R. Franklin.)

Three models

Schematically, all three structures -- the double helix, the SBS model, and the ribbon helix are shown on the "triptych" (Fig. 1). It is clear that those properties of the Watson and Crick model, which determined its significance for genetics, -- the presence of two chains connected by pairs of complementary bases, -- suggested alternative models do not reject. They only suppose other spatial forms of chains and their mutual arrangement.

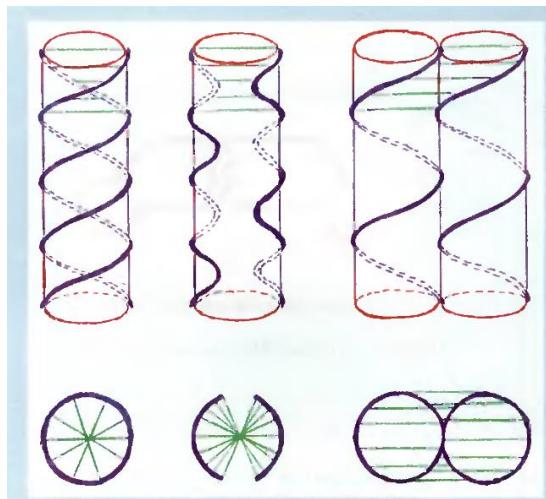


Figure 1. Schematic representation of a double helix, side by side model and ribbon helix. Side view and top view

Often in textbooks and articles, DNA is simply drawn in the form of two parallel straight lines connected by perpendicular bridges, that is, in the form of a ladder, which reflects the most essential in its structure (another, more realistic scheme, called the "cis-ladder", is shown in Fig. 2).

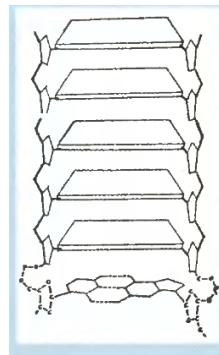


Figure 2. The scheme of the structure of DNA in the form of cis-ladder

The ribbon helix is similar to this cis-ladder, but only both of its handrails form independent spirals (more precisely, screw lines); while the flat pairs of bases approach one to another forming a stack. The view from the top gives namely figure eight (i.e. 8) -- remember the thought of Rosalind Franklin.

The nonequivalence of phosphates, about which she wrote, also exists (in DNA it is detected by NMR). The fact is that the ribbon helix, in contrast to the double helix, does not represent a regular spiral, since the mutual locations of adjacent base pairs (not the rotations in a certain angle, as in Watson and Crick model, but parallel shifts) are unequal inside the helix. This means that the dihedral angles in the sugar-phosphate chains in each step inside one turn of a spiral are also different -- that's where the divergence from the symmetry that Watson and Creek have required lies. (However, there is a symmetry axis of the second order in the center of the turn of the helix tape, so the smallest recurring motif in its structure will be the half-turn.)

Of course, the main advantage of the proposed model is that the two chains are not intertwined, so they can easily diverge during replication or denaturation (no intertwining -- no problem). But, as we will see, it is also good in other respects -- many molecular-genetic processes are greatly simplified. The important thing is that this model combines, as reflected in its name, properties of tape and helix.

Advantages of the ribbon structure

In fact, the ribbon helix looks like a punched tape, which can be read freely, holding the ends (for a double helix it is impossible because of its twisting). Therefore nucleic-nucleic and nucleic-protein recognition will easily occur. In addition, because of its ribbon-like nature, such a molecule can easily bend to wrap around the protein particles (nucleosomes) in chromatin or to fit inside the protein envelope of the virus (to bend a rigid double helix without its fracture in many points impossible). It is clear that a tape can be packed more densely (in chromatin and viruses) than a structure which is a cylinder-like one.

On the other hand, thanks to the homogeneous screw twist of both of its chains, the spiral ribbon will behave like an elastic spring. Therefore, it will not contradict experiments with a supercoiled DNA, on the basis of which the SBS model was rejected (some experts decided that

experiments that disproved the SBS structure simultaneously allow to discard any other models in which two chains go non-intertwined, but this is incorrect.)

Further, the same spiral ribbon may have different conformations, since any fixed pair of bases inside the helix is capable of occupying in principle sterically unequal positions -- on the crest, in the cavity or somewhere in the middle (let's call this degree of freedom the phase of the ribbon helix). Now let's imagine that a protein or other molecule interacts with DNA in some place. Because of this, a local phase shift can occur, and a wave of its change will propagate along the polymer. It is clear that in this way the signals could be transmitted over long distances, and similar effects in DNA are now well known.

The other fact. The location of nucleosomes relative to DNA may be different but differ by an integer number of spiral periods. In the Watson-Crick model, because of its helical symmetry, there are no any preferred positions. On the contrary, the structure of the tape-spiral is repeated only through a turn (after ten base pairs), thereby setting the natural discreteness.

Nucleic bobbins

It is known that when the properties of a solution change in some specific way or DNA interacts with certain molecules, a long polymer of DNA is twisted, forming compact toroidal particles that are visible in an electron microscope (the so-called psi-form of DNA). In the case of a double helix, in order to explain this effect, it was necessary to develop a complex thermodynamic theory.

In a case of a ribbon helix, everything will be easier. The fact is that its two broad sides of the molecule are stereochemically unequal: one of them corresponds to a small groove of a double helix (where the phosphate groups are located), and the other to a large one. Therefore, such a molecule behaves like a bimetallic plate, that is, when the conditions change, it will curl.

As the result, a tori will emerge which are optically active, indicating a long-range order in the location of the nitrogenous bases (the sign of the band in the spectrum may be different). Unusual optical properties of such DNA particles as a rule explained by the formation of cholesteric liquid crystals.

A spiral ribbon removes the problem. After all, if it twists (like a belt on a hand), then in a section of the torus by a plane there will be a pile of equally azimuthally oriented molecules (Fig. 3) -- as if a crystal from parallel laid pairs of bases, which will give optical activity. With other parameters of the environment (or, again, the interaction of DNA with some molecules), the belt will twist to the other side, that is, the entire source will be turned inside out, like a glove.

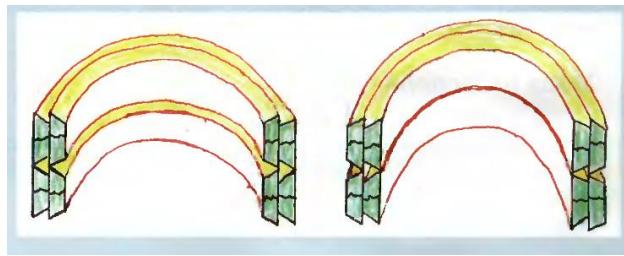


Figure 3. Two possible coiling of the ribbon helix during the formation of torus-like particles. Schematically shown the sections of tori by a plane

The result of such a reversal is analogous to the transition from one enantiomer to another -
- the spectrum transforms into its mirror image (the sign of the band in it will change).

Netlike chromosome

Now let's look at the process of mutual recognition of two DNA molecules having regions with identical base sequences. It occurs, for example, in meiosis, when two homologous parental chromosomes approach each other, aligned in parallel, and then there is an exchange of sections between them (crossing-over).

Unlike the double helixes, two ribbon helices (schematically shown as blue and red "ladders" in Fig. 4a) can be arranged so that the hydrogen bonds connecting the bases inside each molecule are ruptured, the bases turn 90° and form new pairs bases, but already intermolecular (Fig. 4b). Such heteroduplex would serve as a key step in crossing-over.

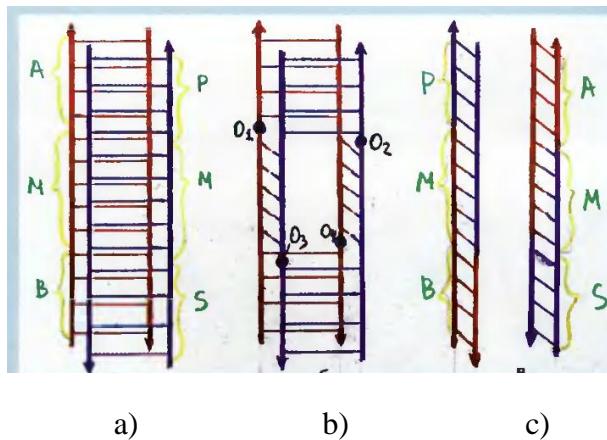


Figure 4. Stages of the crossing-over

Then the chains break at points O_1 , O_2 , O_3 , and O_4 , and after turning their ends by 90° they are sewn up in a new way (Fig. 4c). As a result, there is an exchange of sites (recombination) -- in the initial molecules there were sequences of blocks A-M-B and P-M-S, and as a result, A-M-S and P-M-B were obtained.

The ribbon-spiral opens interesting possibilities from the point of view of the organization of DNA in chromosomes. It is known that in the genome there are many repetitive sequences of nucleotides (they are called repetitions). These repetitions located on the same chromosome can also approach each other, therefore intra-chromosome heteroduplexes will be formed (Fig. 5b). If now there are no breaks in the chains (as in crossing-over), and parallel tapes will disperse, then loops will arise, from which (on the whole on the chromosome) a complex, branched network can be formed.

In general, the network device of chromosomes is known for a long time, but here the principle of their structure becomes clear. The resulting loops could reflect the associative links between the remote parts of the genome, and the network structure -- preserved when doubling the chromosomes, that is, to carry additional (epigenetic) hereditary information.

Energy and kinetics

But still, why did not we see the ribbon-helix in the X-ray diffraction analysis of short DNA segments? Apparently, the double helix is energetically more advantageous, and its parameters strongly depend on the base sequence (in particular, the Z form can be obtained). A conformation in the form of a ribbon-helix is a metastable state of double-stranded DNA. After all, as we know, with the folding of protein chains, the energy minimum can be unattainable kinetically.

Let's imagine, for example, that there are two long complementary strands. When they approach each other in some area, the bases there will turn towards each other and the "zipper" will immediately be fastened along the entire length of the site (renaturation will occur), but strands cannot twist on each other because of their "hanging" ends.

Probably, it is because of this that DNA replication requires an initial double-stranded site - a "primer", which special enzymes build. After the priming has been obtained, a formation of the helix tape can proceed further. A potential barrier separates the ribbon helix from the double helix so it cannot overcome it without violating the stacking interaction of neighboring base pairs, that is, without destruction of its native structure. As E. Bauer said, "life is a stable disequilibrium" -- it is possible that such a principle is also true of the structure of DNA, which also turns out to be non-equilibrium one.

Now we know about the wide variability of the shape of the DNA molecule, there are also unscrewed states, say, when two closed rings of single complementary chains associate (the so-called V-form). Probably, under certain conditions, individual sections of intracellular DNA may have the conformation of a double helix.

A new turn of a spiral

As already mentioned, there were no good reasons for choosing a model with interlocked chains as in the Watson and Crick model. Of course, the desire for simplicity is the most important heuristic principle, but it can also fail. Let's remember I. Kepler with his discovery of the ellipticity of planetary orbits -- it would seem, they should be circular. A. Einstein said that "we must try to make everything as simple as possible, but not easier".

The simplicity of the double helix turned out to be imaginary -- this model gave rise to a lot of difficulties in explaining the basic molecular-biological processes in which it participates. Why did she survive all these years? Probably, this is the normal conservatism of science, about which F. Bacon wrote in the "New Organon": "The human mind attracts everything to support and agree with what he once accepted ... Whatever the force of circumstances, the mind either does not notice them or neglects them..."

The ribbon helix has many advantages over the double helix. Of course, this structure needs to be investigated by methods of theoretical conformational analysis, and also to explore in other aspects. (Incidentally, it is possible that such a polymer will be promising in terms of searching for organic superconductors because it combines the stacking structure of flat bases with periodic changes in the electronic properties along the molecule.)

Development, as taught a philosopher Hegel, goes by a spiral. So, in the problem of DNA, apparently, it's time to go to its next turn.

APPENDIX

Torture for DNA ("Chemistry and Life", 1999, No. 5-6, p.8-9. The note in the rubric "Science News").

U.Bockelmann et al., «Phys.Rev.Lett.», 1997, v.79, p.4489; «Phys. Rev.», 1998, v.E58, p.2386

It seems that the most important molecule was already studied by all possible methods but it did not reveal some its secrets. Now the probe microscopes began to be applied to it, and, unable to withstand the "torture", DNA "spoke". These tools allow to manipulate individual molecules, and instead of indirect data that give chemical and spectroscopic methods which it is difficult to interpret, they are dealing with demonstrative mechanics.

Physicists from the Higher Normal School (Paris) placed in a solution (close to physiological) a single DNA molecule of phage lambda over 16 microns in length -- it contains 48,502 base pairs. From one end of the molecule, two strands were parted slightly, and the end of one of them was fixed (sewed to the wall), and the other end was attached to a microsphere mounted on the probe microscope needle, so it could be moved. And they began to stretch the ends in different directions. In doing so, they ruptured the hydrogen bonds between complementary bases, that is, they mechanically denatured molecule of DNA.

The most interesting thing is that the ends were able to reach a distance of tens of micrometers, that is, two sugar-phosphate strands became separated over the entire length of the original molecule. But in a double helix, they are twisted on each other! So, in order for these strands to diverge, all DNA must rotate around its long axis. We see that by stretching the ends,

it is necessary to cause the rotation of a huge polymeric molecule, which is also somehow coiled. How it may happen, it is impossible to imagine, because the diameter of the DNA is about 2 nm, and its length was 16 μm .

Authors of the work did not say a word -- for the sake of simplicity (!?) -- about the problem of unwinding, but it cannot be neglected. The very detection of this contradiction is the most important information extracted from the experiment. It can be recalled that in the 1970s and 1980s alternative DNA models, in which two strands were not twisted, were offered; probably, now it is necessary to return to their consideration.

But first of all, it is necessary to conduct an *experimentum crucis* -- to fix firmly the second end of a long molecule so that its rotation cannot occur in principle, and repeat the experiment. If the strands will be separated again, then the Watson-Crick model is really wrong.

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