MATHEMATICAL METHODS IN DNA TOPOLOGY

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Abstract: In this paper we used DNA in mathematics. The main purpose of this paper is to study the topology and geometry of DNA under different special constraints and to solve the topological mechanism of enzymes sites specific recombinases and topoisomerases. In this paper we illustrate the use of mathematical and computational methods in variety of DNA topology problem. It is intended to introduce the reader to the exciting the application of topology to the study of DNA.

Index terms: DNA knots, Bacteriophage P$_4$, DNA packing, Random knots, specific recombination, Xer, Tangles.

1.Introduction: 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 34^0, 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 anti parallel 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. This is complicated by the fact that DNA resists bending and twisting deformations and also has a tendency to repel itself electro statically. 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.

2. How to use topology in DNA?

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.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. 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 It was shown that in the limit of length going to infinity a randomly cyclized polygon will be knotted with probability1 [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 each 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 C1 and C2 one can define a quantity, called the linking number Lk, that characterizes how the curves are inter wound 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 C1 to be the axial curve of the molecule and C2 one of the backbone chains.

 For differential curves, a formula for linking number interms 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   Ci is defined by giving its position xi(s) in space as a function of the arc-length s, and
ti(s) = xi(s) = dxi(s)/ds .
There are two geometric properties of curves that are intimately related to the linking number. The first property, called the writhe Wr,

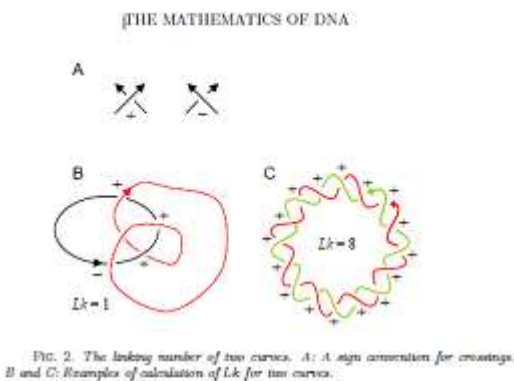

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Fic. 2. The linking number of two curves. A: A sign convention for crossings.
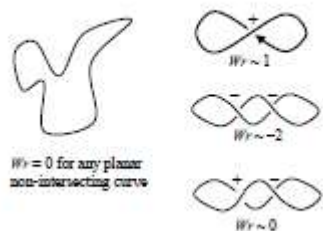B and C: Examples of calculation of Lk for two curves.

Fic. 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 C a formula for W r analogous to (3.1) exists:

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

Alternative formulae relating Wr to the area swept by the vector x(s1) − x(s2) on a unit sphere when traversing 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 C2 about C1 is

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

where d(s) = x2(σ(s)) − x2(s) is taken to be perpendicular to t1(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:

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

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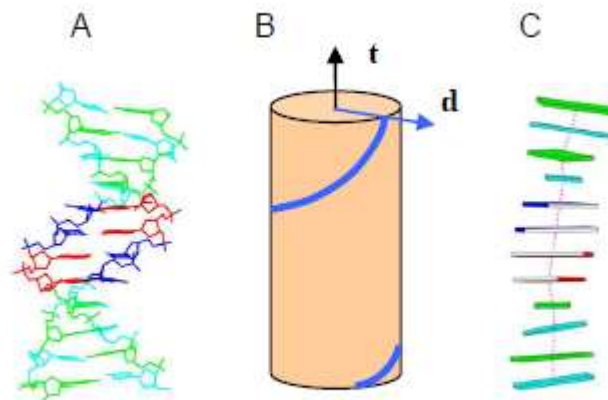
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FIG. 4. Schematic representations of DNA. A: a wireframe representation of the atomic level structure. B: continuum elastic rod. C: base-pair level description

3. APPLICATION OF TOPOLOGY TO DNA

3.1. Differential geometry and DNA: $Lk = Tw + Wr$, a well known formula in differential geometry, may be even better known in molecular biology. The meanings of twist and writhe are probably best demonstrated with a belt. While holding on to one end of the belt, twist the other end 180^0 for half a twist, 360^0 for 1 full twist, etc. Twist describes how two strands (in this case, the two edges of the belt) wind about each other in space. Now, without letting go of the twist, close up the belt. If you relax the belt, the twist is converted into writhe. If the belt is unknotted, writhe describes the amount of supercoiling. Writhe measures how the center line of the belt winds around in space. It is defined to be the sum of all signed self-crossings of the center line averaged over all projections in R3.


By moving the belt you are continuously converting writhe to twist and vice versa. Thus, these values are neither integers nor topological invariants. However, their sum, Lk, is both an integer and a topological invariant. The linking number is one-half the sum of all the signed crossings between the two curves. DNA prefers a certain helical twist base pairs/turn in the test tube). Therefore changes in linking number are converted to writhe, i.e., the DNA becomes supercoiled. The more supercoiled the DNA is, the more compact it is, and the faster it travels through a gel. Thus the integer differences in linking number can be detected by gel electrophoresis.


For example, biologists used differences in linking number to determine that a mutant of Gin recombinase was capable of relaxing supercoiled DNA and performing recombination using more than one DNA configuration, whereas wild-type Gin can only perform recombination when the DNA is in one specific configuration. This information gave insight into the enzyme mechanism as well. Linking differences have also been used to determine topoisomerase activity.

3.2. Graph theory and DNA: Trypanosome is parasite that infects the Tse-tse fly, which in turn infects humans and cows with sleeping sickness. The kinetoplast DNA of trypanosome consists of about 5000 mini circles (small circles of DNA consisting of about 2500 base pairs) and 25 maxi circles (37,000 base pairs) linked together. Biologists wanted to determine how the mini circles were linked together. Electron micrographs of the kinetoplast DNA suggested that the huge kinetoplast link admits a diagram in which each individual minicircle has no self-crossings, and that pairs of minicircles are linked (if at all) like the Hopf link to adjacent minicircles. Ignoring the maxicircles, this assumption allows the complex of minicircles to be translated into graph theory. Each mini circle became a vertex; two vertices were connected by an edge if and only if their respective minicircles were linked, giving rise to a planar graph. For biological reasons, it is believed that the circles are uniformly linked and monolayered. Thus the researchers investigated the seven different ways to tile the plane where all vertices have the same valence and either the tiles have the same shape or there exist two different tile shapes each of which is equally well represented:
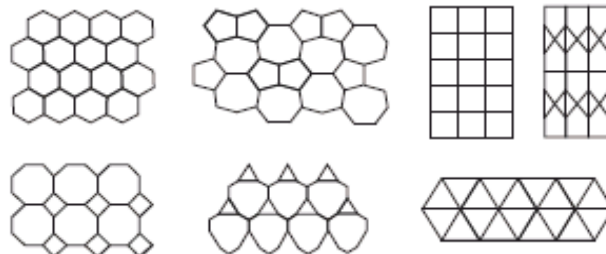

They then looked at the probability that if some circles were randomly broken from the graph that a monomer (single circle not linked to any other circle) or a dimer (two linked circles) or some other configuration would result. For example, if p is the probability that a

circle is broken, then for a 4-valent graph, the monomer probability is p4(1 − p) since the 4 circles that the monomer is linked to would have to be broken(probability = p4), but the monomer itself would have to remain unbroken (probability= 1 − p). For a 3-valent graph the monomer probability is p3(1 − p).Biologists determined the above probabilities applied to the trypanosome k DNA by adding endonucleases, enzymes that break the backbone of DNA, in order to randomly break the minicircles. The results were then subjected to gel electrophoresis in order

to determine the percentage of monomers versus dimers, etc., that were formed. The experimental results were then compared to the mathematical results to determine that the following is the most likely configuration:
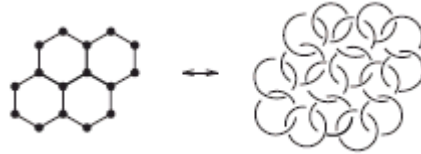
3.3. Knot theory and DNA: tangles. Some enzymes require DNA to be in a certain configuration in order for the enzyme to act. Electron micrographs of the enzyme-DNA complex show the enzyme as a blob with DNA looping out of it. The configuration of the DNA within the blob cannot be determined from the EM. Thus, the mathematics of tangles has been used in many cases to determine the configuration of the DNA within the enzyme blob.
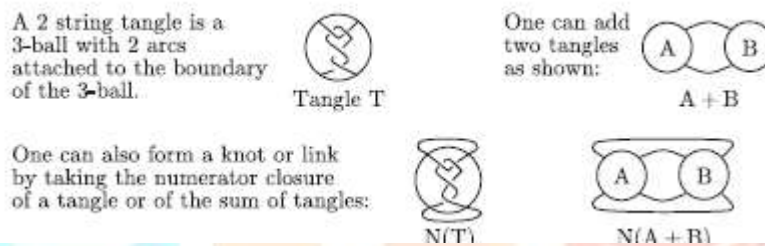
The enzyme action is modeled by replacing tangle P with tangle R. Many recombinaseact processively (i.e. it acts more than once in the same place before releasing the DNA). This is modeled by adding on multiple R tangles. Since the substrate and products of the experiment are known, this gives several equations which can then be solved for some of the unknown tangles:

N (Of + Ob + P) = Substrate

N (Of + Ob + R) = Product 1

...

N (Of + Ob + R + ... + R) = Product n

unknotting numbers and topoisomerases. Topoisomerases are enzymes that (1.) break the backbone of DNA, (2.) allow passage of another segment of DNA through the transient enzyme-bridged break, and (3.) reseal the break. They are responsible for unknotting, unlinking, and maintaining the proper supercoiling of DNA during the processes of replication, transcription, and recombination. Topoisomerases are also the targets of many antibacterial and anti-cancer drug [Rc][Wa]. There are two main types of topoisomerases. Type 2 topoisomerases break both backbone strands of double-stranded DNA and thus can change the topology of double-stranded DNA knots and links. Type 1 topoisomerases can only break a single backbone strand of DNA and thus can only change the topology of single-stranded DNA knots and links or double-stranded DNA knots and links if the double-stranded DNA contains a nick (a nick is a broken phosphodiester bond between the sugars of two consecutive bases in one of the strands of DNA). Type I topoisomerases can then break the phosphodiester bond between the sugars of the complementary bases, thereby breaking the duplex DNA segment. Since topoisomerase substrate can be either double-stranded or single-stranded, the line drawings in this paper can represent either double-stranded or single-stranded DNA, depending on context.

Crossing change = DNA strand passage.
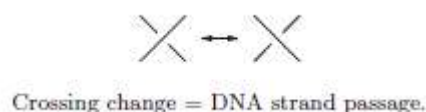
In the test tube, at high concentrations, topoisomerases may produce knots by performing strand passages [Hs][DSKC][WC][RBW][Rd]. Hence, the unknotting number from knot theory can be used to study topoisomerase action.

3.4. Definition. The unknotting number of a knot is the minimum number of crossing changes needed to convert the knot into the unknot where the minimum is taken over all possible diagrams for the knot.

This is equivalent to determining the minimum number of times needed for topoisomerase to mediate strand passage on a DNA knot to convert it to the unknot, because this temporal sequence of spatial events (strand passages mediated by the enzyme topoisomerase) can be simultaneously visualized in a single knot diagram. To see this, for each strand passage event tie an imaginary string between the segments of string that pass through each other. Simultaneously shorten all the strings until all such pairs are almost touching; now project. Each of the n short strings give rise to a crossing in the resulting diagram; changing all these crossings converts the diagram to a diagram of the unknot. Thus if the unknotting number is n, then biologically, the enzyme must act n times to convert the knot to the unknot, and mathematically, there exists a diagram of the knot in which one can see n crossings which if changed convert the knot to an unknot.

Example:

Unknotting number of $3_1 = u(3_1) = 1$
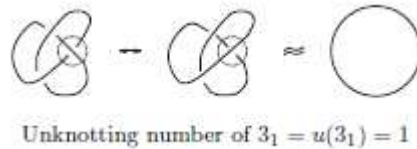
Note that the minimum is taken over all diagrams of the knot .For example, the minimal diagram of the knot 108 requires three crossing changes to change it to the unknot.

Minimal diagram of the knot 10_8

But Nakanishi in 1983 and Bleiler in 1984 found a more complicated non minimal diagram of 14 crossings of the same knot which required only 2 crossing changes to convert it to the unknot.

A non-minimal diagram of the knot 10_8 with 14 crossings

Perhaps there exists a diagram of this knot (with possibly a huge number of crossings) which only requires one crossing change to convert it to the unknot. This is the difficult question. Fortunately, there exist bounds on unknotting number ([Ms], [N1])

$$u(K) \leq \tfrac{1}{2}|\text{number of crossings} - 1|$$

$$u(K) \geq \underset{\underset{4-genus}{\uparrow}}{g^*(K)} \geq \underset{\underset{signature}{\uparrow}}{\tfrac{1}{2}|\sigma(K)|}$$

$$u(K) \geq sd(K) = \text{surgery description number of } K$$

For example, $\sigma(108) = 4$ and

$$u(10_8) \geq \frac{1}{2}|\sigma(10_8)| \geq \frac{1}{2}(4) = 2.$$

Thus u(108) = 2. No diagram of this knot can be changed to the unknot with only one crossing change. The unknotting number can be generalized to a metric on knot types where the distance between any two knots is defined as follows:
 Definition (Strand passage metric on knot types): u(K1,K2) = minimum number of strand passages needed to convert K1 to K2 where the minimum is taken over all diagrams.
This satisfies all the properties of a metric:
1) u (k$_1$,k$_2$) = 0 if and only if k$_1$ = k$_2$.
2) u (k$_1$,k$_2$) = u(k$_2$,k$_1$).

3)$u(k_1,k_2) \leq u(k_1,k)+u(k,k_2)$,for any knot k.

Example: $u(k_1,k_2) \leq u(k_1, 01) + u(01,k_2)$, where 01 is the unknot.

I.e., $u(k_1,k_2) \leq u(k_1) + u(k_2)$.

That is, the distance between two knots is less than or equal to the sum of theirun knotting numbers. However, there may be a shorter path that does not go through the unknot. By doing the crossing changes on a particular diagram, either by hand or by computer, one can easily determine upper bounds for the distance between two given knots. The difficult question is then knowing whether or not there exists a shorter path. For this lower bounds are needed. Murakami [Mk] generalized Murasugi's signature lower bound for the unknotting number to obtain the following lower bound for the strand passage metric:

$$u(K_1, K_2) \geq \frac{1}{2}|\sigma(K_1) - \sigma(K_2)|$$

This lower bound also holds for semi-oriented links. Example:

torus knot: $K(7,2)$ $K(5,2)$ $K(3,2)$ 0_1 $K(-3,2)$
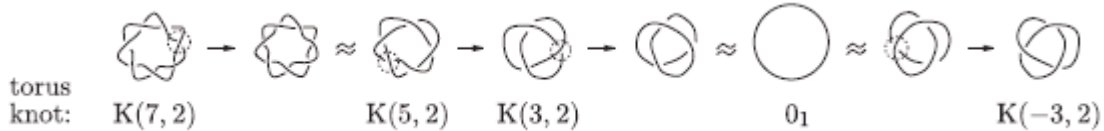
$$4 \geq u(K(7,2), K(-3,2)) \geq \frac{1}{2}|\sigma(K(7,2)) - \sigma(K(-3,2))| = \frac{1}{2}|6 - (-2)| = 4$$

Thus, $u(K(7,2), K(-3,2)) = 4$.

In general, for (p,2) torus knots (p odd):

$$u(K(p,2)) = \frac{1}{2}(|p| - 1)$$

and

$$u(K(p,2), K(q,2)) = \begin{cases} \frac{1}{2}|p-q|, & if \quad pq > 0 \\ \frac{1}{2}|p-q| - 1, & if \quad pq < 0 \end{cases}$$

$$since \quad \sigma(K(p,2)) = \begin{cases} p-1 & if \quad p > 0 \\ p+1 & if \quad p < 0 \end{cases}$$

Many of the unknotting number lower bounds such as signature were found by determining the effect a crossing change has on a particular invariant followed by an induction argument. The strand passage metric table on the next page lists the distance between two knots up to mirror images

(since $u(K1,K2) = u(K^*1, K^*2)$). Unfortunately, not all values are known. For example the distance between 41 and 51 is either 2 or 3. That is, 41 can be changed to 51 by only 3 strand passages. However, it is possible that there exists a projection of 41 in which only 2 strand passages are required to change 41 to 51, but there is no way to change 41 to 51 with only 1 strand passage. Also note that the knot designations refer to those given in Rolfsen's table of knots and not Burde and Zieschang's ([BZ]'s 52 = [R]'s 5^*2).

This metric was calculated for 4-plat knots and composites of 4-plat knots by computer (with 8 crossing non 4-plats put in by hand) using the following information:
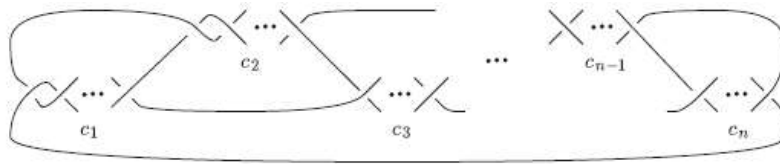
4-plat $\langle c_1, ..., c_n \rangle$

(1.) $d_2(\langle c_1, ..., c_i, ..., c_n \rangle, \langle c_1, ..., c_i - 2, ..., c_n \rangle) = 1$

(2.) [T][DS] Classification of distance one 4-plats.

(3.) Triangle Inequality.

(4.) [Mk]: $d_2(K_1, K_2) \geq \frac{1}{2}|\sigma(K_1) - \sigma(K_2)|$.

(5.) [Mk] Linking form requirements on $|H_1(M_K)|$.

(6.) [DS] Homology requirements on $H_1(M_K)$.

(7.) [Sc][Zh]: Unknotting number one knots are prime.

This metric gives the following information about topoisomerase experiments:

1.) The minimum number of times topoisomerase must perform strand passage to inter-convert knots.

2.) All possible reaction pathways in a topoisomerase experiment if all intermediates are known. For example, in an unpublished experiment of J. Wang, a topoisomerase acting on single-stranded circular DNA produced exclusively (+) (2n+1) torus knots which correspond to (2n+1)1 in the knot table. Suppose we are interested in the knot 51. The metric tells us that (1.) topoisomerase had to act to act at least two times on the unknotted DNA substrate in order to produce the knot 51. and (2.) since all products are of the form (2n+1)1, 51 can only be produced from topoisomerase action on the knot 31 or the knot 71

This kind of reasoning tells us that the only possible reaction pathway the experiment is

$0_1 \leftrightarrow 3_1 \leftrightarrow 5_1 \leftrightarrow 7_1 \leftrightarrow$.....

Strand Passage Metric Table:

	0_1	3_1	4_1	5_1	5_2	6_1	6_2	6_3	$3_1 \# 3_1$	$3_1 \# 3_1^*$	7_1	7_2
3_1	1	0	2	1	1	2	1	1	1	1	2	2
3_1^*	1	2	2	3	2	2	2	1	3	1	4	2
4_1	1	2	0	2-3	2	1	1	2	2-3	2-3	3-4	2
5_1	2	1	2-3	0	1	2-3	2	2	2	2	1	2
5_1^*	2	3	2-3	4	3	2-3	3	2	4	2	5	3
5_2	1	1	2	1	0	2	2	2	2	2	2	1
5_2^*	1	2	2	3	2	2	2	2	3	2	4	2
6_1	1	2	1	2-3	2	0	1	2	2-3	1-3	3-4	2
6_1^*	1	2	1	2-3	2	1	2	2	2-3	1-3	3-4	2
6_2	1	1	1	2	2	1	0	2	2	2	2-3	2
6_2^*	1	2	1	3	2	2	2	2	3	2	4	2
6_3	1	1	2	2	2	2	2	0	2	2	3	2
$3_1 \# 3_1$	2	1	2-3	2	2	2-3	2	2	0	2	2-3	2-3
$3_1^* \# 3_1^*$	2	3	2-3	4	3	2-3	3	2	4	2	5	3
$3_1 \# 3_1^*$	2	1	2-3	2	2	1-3	2	2	2	0	3	2-3
7_1	3	2	3-4	1	2	3-4	2-3	3	2-3	3	0	2
7_1^*	3	4	3-4	5	4	3-4	4	3	5	3	6	4
7_2	1	2	2	2	1	2	2	2	2-3	2-3	2	0
7_2^*	1	2	2	3	2	2	2	2	3	2-3	4	2
7_3	2	3	2-3	4	3	2-3	3	2-3	4	2-3	5	3
7_3^*	2	2	2-3	1	1	2-3	2-3	2-3	2-3	2-3	1	1
7_4	2	2-3	2-3	3-4	2-3	2-3	2-3	2	3-4	2	4-5	2-3
7_4^*	2	1	2-3	2	1	2-3	2	2	2	2	2	2
7_5	2	1	2-3	1	1	2-3	2	2	2	2	1	1
7_5^*	2	3	2-3	4	3	2-3	3	2	4	2	5	3
7_6	1	1	1	2	1	2	2	2	2	2	2-3	1
7_6^*	1	2	1	3	2	2	2	2	3	2	4	2
7_7	1	2	1	2-3	2	2	2	2	2-3	1-2	3-4	2
7_7^*	1	1	1	2	2	2	2	2	2	1-2	3	2
$3_1 \# 4_1$	2	1	1	1-2	1-2	2	2	2	2	2	2-3	2-3
$3_1^* \# 4_1$	2	2-3	1	3-4	2-3	2	2	2	3-4	2	4-5	2-3
8_1	1	2	2	2-3	2	1	2	2	2-3	2-3	3-4	2
8_1^*	1	2	2	2-3	2	2	2	2	2-3	2-3	3-4	2
8_2	2	1	2	1	2	2	1	2	2	2	2	2-3
8_2^*	2	3	2	4	3	2-3	3	2	4	2	5	3
8_3	2	2-3	2	2-4	2-3	1	2	2-3	2-4	2-4	3-5	2-3
8_4	2	2	1	2-3	2-3	2	1	2-3	2-3	2-3	2-4	2-3
8_4^*	2	2-3	1	3-4	2-3	1	2	2-3	3-4	2-3	4-5	2-3
8_5	2	3	2	4	3	2-3	3	2-3	4	2-3	5	3
8_5^*	2	1-2	2	2-3	1-3	2	1	2-3	1	2-3	1-4	1-3
8_6	2	1	2	2	2	1	1	2	2	2	2-3	2-3
8_6^*	2	2-3	2	3-4	2-3	2	2-3	2	3-4	2	4-5	2-3
8_7	1	2	2	3	2	2	2	1	3	2	4	2

5. Conclusion: The paper presented the mathematical methods of topology DNA and its application. Besides
these topological DNA is very effective in mathematical tools and this technique can be useful in differential geometry in DNA, graph theory in DNA, knot theory in DNA. It becomes an integral part of modern science, being used in a vast number of different disciplines .they have quickly gained popularity among the intellectual community that deals with these subject on a day to day basis.

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