

## REVIEW

## THE KNOT THEORY OF MOLECULES

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**Abstract**

Macromolecules (such as polymethylene and DNA) are large and flexible, and can present themselves in 3-space in topologically interesting ways. The branch of topology known as *knot theory* is the mathematical study of flexible graphs in 3-space. Knot theory can be used to quantify and compare the various configurations of large molecules, and to study the various spatial isomers of molecules which have complicated molecular graphs.

**1. Introduction**

Topology is a branch of mathematics which studies those properties of objects which do not change when the object is elastically deformed. Topology allows stretching, shrinking, twisting – any kind of continuous deformation short of breaking and reassembling the object. For example, to a topologist, a coffee cup and a doughnut are one and the same – each can be deformed into the other – never mind the difference in taste! The basic idea in topology is to relax the rigid Euclidean notion of equivalence (congruence) and replace it with the more flexible notions of equivalence (homeomorphism, diffeomorphism, etc.). One can think of topology as a mathematical attempt to quantify “shape”. A flexible molecule does not usually maintain a fixed three-dimensional configuration. Such a molecule can assume a variety of configurations, driven from one to the other by thermal motion, solvent effects, experimental manipulation, etc. From an initial configuration for a molecule, topology can help identify all of the possible attainable configurations of that molecule. For molecules which possess complicated molecular graphs, topology can also aid in the prediction and detection of various types of spatial isomers. As evidence for the utility of topology in chemistry and molecular biology, see the excellent survey articles by Walba [1], and Wasserman and Cozzarelli [2].

## 2. What is knot theory?

Knot theory is the branch of topology which studies the properties of flexible graphs in 3-space. Although at present there are few introductions to knot theory written for non-mathematicians (see Neuwirth [3]), there are a number of excellent mathematical expositions (Crowell and Fox [4], Fox [5], Rolfsen [6], Burde and Zieschang [7]). For a given flexible graph, the phenomenon of *knotting* is defined to be the existence of three-dimensional configurations of that graph which are not superimposable through elastic deformation of space. That is, the given graph must admit two configurations, such that to change from one configuration to the other, one must either break and then reassemble the graph, or allow an elastic spatial deformation to pass edges of the graph through each other. Knots are relatively difficult to detect – one has to develop a fair amount of algebraic and geometric machinery in order to prove that there is no deformation whatsoever which will make a given configuration coincide with another. What follows is a short and simple description of knot theory, which attempts to convey the flavor and intuition of the subject, while suppressing the details. Throughout this discussion, we disallow chemically irrelevant, extreme topological pathology such as tying an infinite sequence of smaller and smaller knots converging to a point, and pulling a knot infinitely tight so as to make it disappear.

Knot theory is the study and quantization of configurations of graphs (1-complexes) in Euclidean 3-space ( $R^3$ ). We first think of graphs as abstract objects. As an abstract object, a *graph* consists of a finite number of vertices (points) and edges (line segments). Two graphs  $\{G, H\}$  are *isomorphic* if there is a function

$$f: G \rightarrow H$$

such that  $f$  is a *homeomorphism* ( $f$  is 1-1, onto, and both  $f$  and  $f^{-1}$  are continuous) which takes vertices to vertices and edges to edges. Figure 1 shows the molecular graphs of three familiar compounds – ethane (a),  $n$ -butane (b), and isobutane (c). No

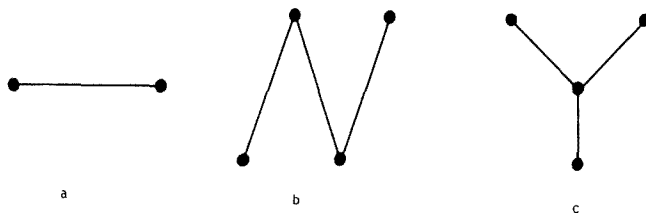


Fig. 1.

pair of these graphs is isomorphic, but the graphs of ethane and  $n$ -butane are homeomorphic. The homeomorphism, however, forgets the chemically important information that the interior vertices of  $n$ -butane code the positions of carbon atoms, and regards them as just points in a (bent) line segment connecting the endpoints.

An *embedding of the graph  $G$*  is a particular configuration (or placement) of  $G$  in  $R^3$ ; that is, an embedding is a 1-1 continuous function

$$g : G \rightarrow R^3 .$$

The function  $g$  is a homeomorphism (not necessarily an isomorphism) between the abstract graph  $G$  and the subset  $g(G)$  of  $R^3$ . We note that the edges of  $g(G)$  do not have to be straight. It may also happen that  $g(G)$  has fewer vertices and edges than does  $G$ . One of the reasons for allowing this is that we may wish to think of a chain of edges of the graph as a single edge, as in figs. 1(a) and 1(b). By doing this, we purposefully forget some of the fine structure, all the while retaining the essential topological elements of configuration and symmetry which we wish to study. It is possible to fine-tune the theory in order to distinguish and remember certain vertices and edges, and our topological methods are adaptable to such restricted settings.

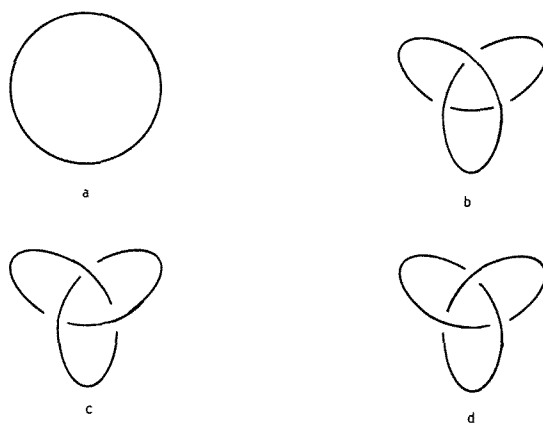


Fig. 2.

Figure 2 depicts four embeddings of the circle. Figure 2(a) is the standard unit circle in the plane, called the "unknot". Among all of the many configurations of the circle in  $R^3$ , fig. 2(a) is the simplest, the one of minimum complexity. Figure 2(b) is also called the unknot, because the configuration it depicts can be deformed to that of fig. 2(a). Figure 2(c) is the "+" (or right-hand) trefoil knot, and fig. 2(d) is the "-" (or left-hand) trefoil knot. Neither 2(c) nor 2(d) can be deformed to 2(a), nor can they be deformed into each other. What is depicted in fig. 2 are representations of three-dimensional configurations. These pictures are *projections* of the embedded circles onto planes, with breaks in the lower segment at the crossover points of the projection. Think for the moment of an embedded circle as a rigid, immovable object in  $R^3$ , and a projection as a photograph of this object. Depending on where the photographer stands, each configuration clearly admits many different projections. If, in addition,

we allow the configuration to be deformed, we obtain many more projections of the "same" object, as in figs. 2(a) and 2(b).

We say that the embeddings  $\{g_1(G), g_2(G)\}$  are *equivalent* if there is a 1-parameter family of homeomorphisms

$$F_t : R^3 \rightarrow R^3 \quad 0 \leq t \leq 1$$

such that  $F_0 = \text{identity}$  and  $F_1(g_1(G)) = g_2(G)$ . One thinks of the parameter  $t$  as time, and the family of homeomorphisms as an elastic motion of 3-space which starts at time  $t = 0$ , and at time  $t = 1$ , the configuration  $g_1(G)$  has been moved so that it coincides with (is superimposed on) the configuration  $g_2(G)$ . With this mathematical notion of equivalence, it is possible to show that the configurations of figs. 2(a), 2(c), and 2(d) represent three inequivalent embeddings of the circle. An equivalence class of embeddings is called a *knot type* (or just "knot") of the graph, and a particular embedding is a representative of its equivalence class. Some abstract graphs do not exhibit knotting – every pair of embeddings is equivalent. Figure 3 shows two equivalent embeddings of a line segment. The apparently "knotted" line segment of

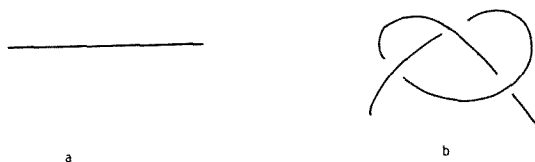


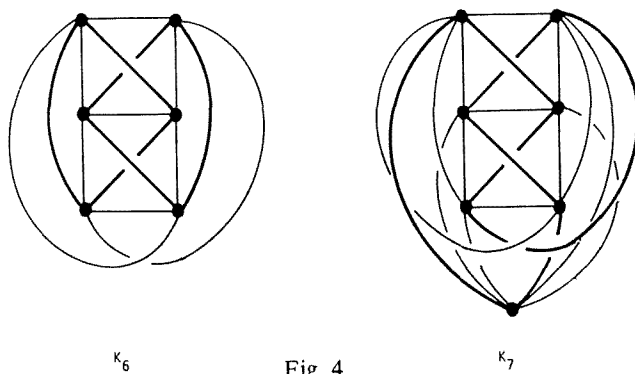
Fig. 3.

fig. 3(b) is in fact equivalent to the straight line segment of fig. 3(a) – all entanglements can be eliminated because one has two free ends to work with. Similarly, one can show that any two embeddings of the same tree graph are equivalent – trees do not knot! A graph must contain a cycle in order to admit inequivalent embeddings. The simplest graph which contains a cycle is the circle. A majority of the work in knot theory has been concentrated on the case of  $G = \text{a family of circles}$ . An embedding of one circle is usually called a *knot* in mathematics, and an embedding of two or more circles is called a *link* in mathematics, and a *catenane* in chemistry. The reason mathematicians have concentrated on circles is that this case is the simplest one, and it is not yet completely understood! Recent interest in chemical applications of knot theory (Walba [1]) has encouraged mathematicians to renew the attack on the general case (Simon [8], Jonish and Millett [9], Kauffman [10]).

Figure 2 shows three "knots" of the circle: the unknot, to which all other embeddings are compared, and two nontrivial embeddings, the "+" and "-" trefoil (three leaf) knots. The "+" and "-" trefoils bear a special relationship to each other

– figs. 2(c) and 2(d) are mirror images of each other. Reflecting space in a mirror switches right-handed (“+”) and left-handed (“–”) objects. It can be shown that the homeomorphism on  $R^3$  obtained by reflection in a plane (the mirror) can not be the result of a motion of 3-space (in the sense of the above definition of equivalence). Any embedding of a graph which is inequivalent to its mirror image is said to represent a *chiral* knot. Figures 2(c) and 2(d) exhibit a pair of chiral knots of the circle.

In the case of the circle, it was clear which embedding was to be distinguished as the benchmark embedding – the “unknot” is chosen to be the knot type of the unit circle in the plane. For an arbitrary graph, it is a nontrivial question as to which (if any!) equivalence class of embeddings should be called the “unknot”. Presumably, this class of embeddings will contain an embedding of “minimal” complexity in the world of all embeddings of a given graph, an embedding by which all other embeddings will be measured. An abstract graph is called *planar* if it can be embedded in the plane. For any planar graph (such as the circle), the question of distinguishing an unknot is easy – any one of the planar embeddings will do, since all planar embeddings are equivalent (Mason [11]). Therefore, for a planar graph, an embedding represents a nontrivial knot if and only if the embedding is not deformable into a plane. Some abstract graphs, however, admit no planar embeddings at all. For graphs such as this, distinguishing an unknot involves choosing a specific non-planar embedding. Perhaps one should select that embedding which is most nearly planar – one which admits a projection which minimizes the number of crossovers. The problem here is that such an embedding is almost certainly not unique – different knot types will be “minimal”. In fact, it is known that if a graph is complex enough, every embedding will exhibit pathology! For example, let  $K_n$  denote the abstract complete graph on  $n$  vertices; this graph has  $n$  vertices and an edge connecting every pair of vertices. Conway–Gordon [12] show that every embedding of any graph that contains  $K_6$  will have at least one pair of disjoint linked cycles, and every embedding of any graph that contains  $K_7$  will have at least one knotted cycle! This means that “unknotted” embeddings of  $K_6$  and  $K_7$  will be difficult to come by. Figure 4 shows possible candidates for “unknotted” embeddings of  $K_6$  and  $K_7$ , with the pathological parts highlighted.



It may reasonably be asked, "How does one decide if two embeddings of a given graph are inequivalent?" The mathematical answer follows. A *knot invariant* is some mathematical object (a number, a group, a polynomial, a topological space, etc.) which can be unambiguously assigned to a knot type. Although it may be that knots of differing type have an invariant in common (in which case that particular invariant fails to distinguish them), we nevertheless can correctly conclude that knots which have different invariants are in fact different knot types.

The most common knot invariants are derived from the knot complement  $X = (R^3 - g(G))$ . If two knots are of the same type, then the homeomorphism which superimposes one representative embedding onto the other also takes the complement of one embedding homeomorphically to the complement of the other. So, the knot complement itself is a knot invariant. A popular invariant derived from the knot complement is the fundamental group  $\pi_1(X)$ . The elements of this group are loops in  $X$  which can not be shrunk to a point. If two knots are of the same type, then the fundamental groups of their complements are isomorphic. Although a prototypical invariant and computable from any knot projection, the problem with the fundamental group is that it is infinite and (in general) non-Abelian. It can be a very difficult question to decide whether or not two such groups are isomorphic. See Thistlethwaite [13] for an interesting survey of this problem for circle knots.

A new family of polynomial invariants has recently arisen (Brandt et al. [14], Freyd et al. [15]) inspired by the Jones Polynomial [16]. These invariants are defined for embeddings of a family of circles (knots and links). These polynomial invariants are combinatorial in nature, and are computed inductively for knot and link projections by relating a given projection to simpler projections via changing and removing cross-overs in certain specified ways. On the face of it, the polynomials appear to be projection-dependent, but in fact are topological invariants. For example, if  $\alpha$  denotes a knot or link type, let  $P_\alpha(x, y, z)$  denote the polynomial invariant defined in [15]. If  $\alpha$  denotes the "+" trefoil of fig. 2(c), and  $\beta$  denotes the "-" trefoil of fig. 2(d), we have the following result [15]:

$$P_\alpha(x, y, z) = x^{-2} z^2 - 2x^{-1} y - x^{-2} y^2$$

$$P_\beta(x, y, z) = y^{-2} z^2 - 2xy^{-1} - x^2 y^{-2}.$$

Versions of the above polynomial invariant have been developed for embeddings of graphs other than families of circles (Jonish and Millett [9], Kauffman [10]).

Another question of interest in both knot theory and chemistry is chirality. Let  $g(G)$  represent the knot type  $K$ . Take the standard  $(XYZ)$  coordinate system for  $R^3$ . Suppose that  $g(G)$  lies above the  $z = 0$  hyperplane. Reflect  $g(G)$  in the plane  $z = 0$  to obtain the mirror image embedding  $g'(G)$ , which represents the knot type  $K^*$ . In terms of knot projections, one obtains a projection of the mirror image by changing

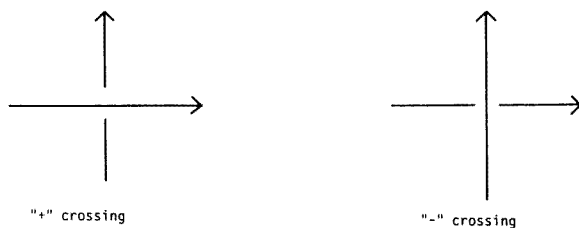


Fig. 5.

the sense of every crossover – over becomes under and vice versa, as in figs. 2(c) and 2(d). We say that the knot  $K$  is *chiral* if  $K \neq K^*$ . Detecting this chirality is not easy. For example, the calculation of the polynomial invariants for the “+” and “-” trefoils in the above paragraph proves that these form a chiral pair. Chemists have utilized the “skew lines convention” [1] for chirality purposes: for a pair of oriented skew lines in space, fig. 5 shows a “+” or right-hand crossing, and a “-” or left-hand crossing. In order to apply the skew lines convention for a circle knot  $K$ , first assign an orientation (put an arrow on it), and then select a minimum (minimum number of crossovers) projection for  $K$ , and then add up the signed crossovers in that projection. One hopes that if a minimum projection has an excess of “+” or “-” crossings ( $C(K) \neq 0$ ), then this will be an indication of chirality for that circle knot. Unfortunately, this may not always be the case. The computation of  $C(K)$  for a circle knot involves two choices – choice of orientation and choice of minimum projection. The first choice is no problem, because switching the orientation on the circle switches the arrows on both lines at a crossover, so the sign of the crossing is unchanged. The choice of minimum projection is another matter. In the world of circle knots, one is forced to take a minimum projection because if a projection has extraneous (removable) crossings, such as those in fig. 6, these crossings can be of either sign, and

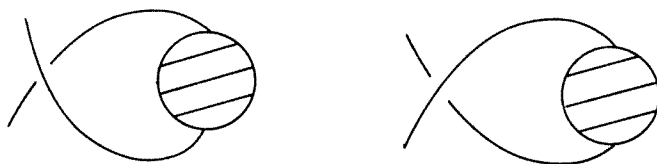
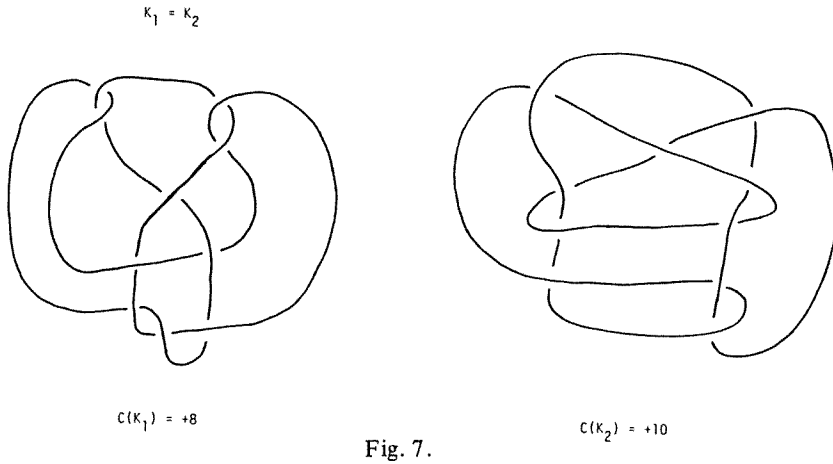


Fig. 6.

$C(K)$  will have no chance of being a knot invariant. Sadly, it turns out that restricting the calculation to minimum projections is not enough to guarantee invariance. For example, fig. 7 shows the infamous “Perko” pair, a pair of minimum (10-crossing) projections of the same knot. The signed crossover numbers for these projections are +8 and +10, respectively! In terms of invariance, the situation for pairs of oriented circles is much better. In this case, take any projection and let  $C(K)$  denote the sum



of the signed crossovers between circular components (forget the self-crossings of each component). We define the *linking number* of the two circles as  $C(K)/2$  (see sect. 4). The linking number is a knot invariant for pairs of oriented circles.

Recently, Kauffman [17] has shown the signed crossover number to be a chirality detector. A circle knot is *composite* (or *factorable*) if it can be obtained by tying first one knot in a string, then further along the string, another knot, and then closing the ends up to produce a circle. Figure 8 shows the "granny" knot, a

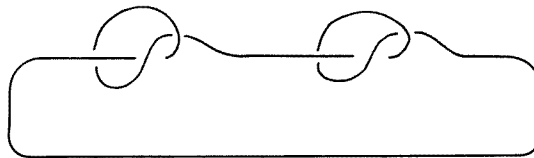


Fig. 8.

composite of the "–" trefoil with itself. A knot which can not be factored into other knots is called *prime*. A projection of a circle knot is *alternating* if, when traversed, one encounters the crossings alternately above and below. For example, the granny knot of fig. 8 is alternating. A circle knot projection is *reduced* if no crossings of the form shown in fig. 6 are present. In fig. 6, the hatched circle denotes a region of the diagram into which a single string enters and later leaves. If a circle knot admits an alternating projection, then it admits a reduced alternating projection, by removing crossovers such as those in fig. 6 until no more removals of this type are possible.

**THEOREM [17]**

Suppose that  $K$  is a prime circle knot, and that  $K$  admits a reduced alternating projection with  $N$  crossings. Let  $C(K)$  be the signed crossover number of this projection. If  $|C(K)| \geq N/3 \geq 1$ , then  $K$  is chiral.



The above theorem by Kauffman detects that the trefoil is chiral. Kauffman's theorem also applies to prime alternating links.

### 3. Why is knot theory useful?

Macromolecules are molecules of large molecular weight, such as synthetic polymers (e.g. polymethylene), and biopolymers (e.g. DNA). We can model all molecules (macromolecules included) as molecular graphs in  $R^3$  – the vertices correspond to atoms and the edges correspond to covalent bonds. While one can think of small bits (the monomers) of these molecules as being rigid, when one concatenates long strings of these bits, the resulting molecules are very flexible indeed. Some molecules exist in closed circular form, both in synthetic chemistry (Schill [18], Roovers [19], Walba [20]), and in biochemistry (Sumners [21]), Wasserman and Cozzarelli [2]). If a molecule has a molecular graph which contains a cycle, then knot theory can be used to model it. It is clear that the definition of topological equivalence of molecular graphs involving highly elastic spatial motion is physically unrealistic. If an edge denotes a covalent bond, it can not be stretched or shrunk or bent at will! Atoms (vertices) can not be considered to be just another point in an edge. Since bond angles must be preserved, molecules are not infinitely flexible. Nevertheless, the topological point of view is, on the one hand, broad and robust enough to generate a useful body of mathematical knowledge and, on the other hand, precise enough to place useful and computable limits on the physically possible motions and configurations of molecules. As evidence, we will consider three applications of knot theory. These are just a few of a number of recent applications of knot theory in chemistry and molecular biology.

### 4. Chirality of synthetic molecules

In his effort to synthesize a hydrophilic molecule, Walba utilized a cyclization reaction on a molecular ladder, with double bonds forming the rungs [1,20]. The results of his synthesis are schematically depicted in fig. 9. Figure 9(a) shows a

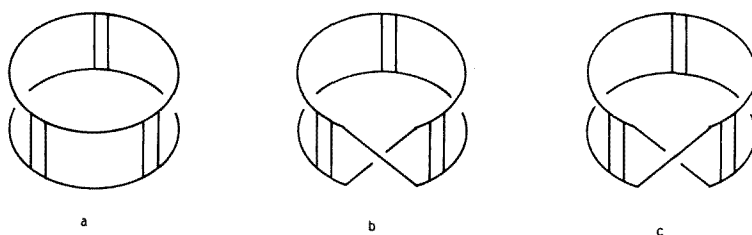


Fig. 9.

cylindrical molecule, and 9(b) and 9(c) show molecular Möbius bands, each the mirror image of the other. The cylindrical molecule formed a solid, and an apparent

racemic mixture of right-handed (b) and left-handed (c) Möbius molecules formed an oil. In order to bolster the chemical evidence of the existence of the two Möbius enantiomers, a mathematical proof was needed to demonstrate that the right-handed and left-handed versions of this molecule were different – that these two configurations were not interconvertible. Simon [8] was able to answer this chirality question by using linking numbers. Linking numbers are computed using the skew lines convention, as explained in sect. 2. Figure 10 shows a projection of two oriented linking

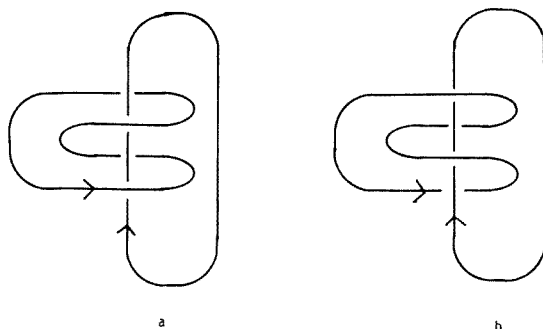


Fig. 10.

circles in  $R^3$ . In fig. 10(a), the linking number is  $+2$ ; in fig. 10(b) [the mirror image of 10(a)], the linking number is  $-2$ . If one pair of oriented circles is equivalent to another pair of oriented circles, then their linking numbers are equal.

Simon's idea was to use the molecular configurations in figs. 9(b) and 9(c) to construct invariant derived topological spaces, called the twofold branched cyclic coverings. Certain equivalent pieces of each diagram lifted to pairs of circles in these covering spaces – but their linking numbers were different, so the two molecular graphs represent different knot types. This means that the two Möbius molecules represent different compounds, because they are topologically constrained from being superimposable.

## 5. Synthetic polymer configuration

Some synthetic polymers (e.g. polymethylene) are very long linear chains of monomers, and have molecular graphs which are homeomorphic to a line segment. In a polymer melt, each molecule is topologically unconstrained (unknotted), so, given enough time and energy, each could be moved to a planar position. Given energetic and/or time constraints, these molecules may very well exhibit knotting. There is, however, a very interesting natural polymer configuration – namely semicrystalline polymers – in which topological constraints unavoidably arise. A semicrystalline

polymer is a mixture of anisotropic crystalline regions (*lamellae*) and isotropic (*amorphous*) regions. Intuitively speaking, the polymer has crystallized as much as it can, and is prevented from becoming totally crystalline by various entanglements of the long strands of the polymer. One can model the spatial configuration of a macromolecule as a random walk in  $R^3$ , where the vertices represent the positions of carbon atoms, and adjacent vertices are connected by straight line segments representing covalent bonds. In studying the statistical mechanics of such configurations, one often groups a few (not necessarily an integral number) monomers together, and represents the group as a straight line segment in the random walk model. The number of monomers grouped together is called the *statistical step size*. For example, for polymethylene, the statistical step size is about 3.5 monomers, and for closed circular double stranded DNA, about 500 base pairs. For a semicrystalline polymer, one models the amorphous region as a collection of random walks on a cubical lattice

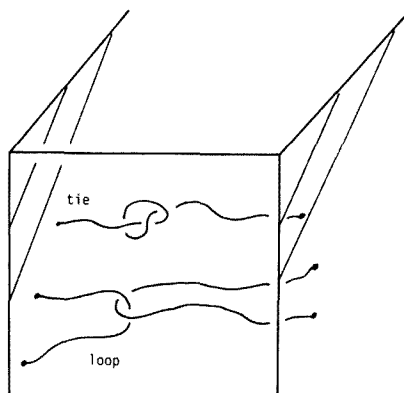


Fig. 11.

between two parallel absorbing walls (the sides of adjacent lamellae). The lattice unit is the statistical step size for the polymer under consideration. In this model, a polymer strand exits a crystalline wall and performs a random walk in the amorphous region until it either returns to the wall from which it exited (it is then a *loop*), or hits the opposite wall (it is then a *tie*). Figure 11 shows ties and loops. Lacher et al. [22] show through computer simulation that a strong form of topological entanglement (*linking*) occurs between loops based on opposite faces. It was found that the percentage of loops based on one face of a lamella which link at least one loop based on the opposite face remains constant as the thickness of the amorphous region is increased, and exceeds the percentage of ties for thicknesses greater than 20 units. Other linking invariants appear to increase with interlamellar distance. Thus, it may not be the case that the ultimate strength of a semicrystalline polymer depends on the percentage of ties, which decreases with interlamellar distance. On the contrary, it may be the topological entanglement (*linking*) of loops that is making a major contri-

bution to the physical characteristics of the polymer. Much work remains to be done in this area, including further computations of the statistics for the families of knots and links which occur in this model of the amorphous region, and in the development of simplified analytical models (Lacher et al. [23]) which explain the numerical results of computer simulation.

## 6. Topoisomerase mechanism

The DNA molecule is a biopolymer which is long and threadlike, and often naturally occurs in closed circular form. Knot theory has been brought to bear on the study of the geometric action of various naturally occurring enzymes (called topoisomerases) which alter the way in which the DNA is embedded in  $R^3$  (Wang [24], Wasserman and Cozzarelli [2]). In the cell, topoisomerases are believed to facilitate the central genetic events of replication, transcription and recombination via geometric manipulation of the DNA. This manipulation includes promoting the writhing (coiling up) of the molecule, passing one strand of the molecule through another via a transient enzyme-bridged break in the molecule, and breaking strands and rejoining to different ends (a move performed by recombinant enzymes). The strategy is to use knot theory to deduce enzymatic mechanism and substrate structure from changes in DNA topology effected by an enzyme reaction. Although these enzymes react with linear as well as circular DNA, experiments are done using circular DNA. This is because the changes in topology (the creation of knots) due to enzymatic action can be captured in circular DNA, but would be lost in linear DNA during work-up of the reaction products for analysis by gel electrophoresis and electron microscopy.

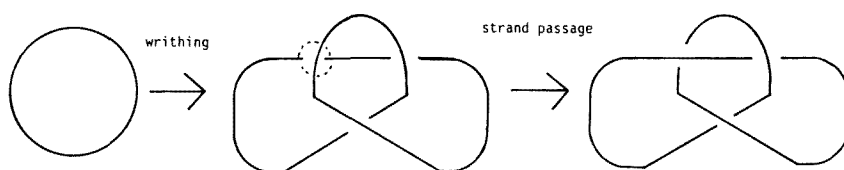


Fig. 12.

Figure 12 shows a hypothetical topoisomerase reaction in which an enzyme converts an unknotted circle to a "+" trefoil knot via mediating writhing, followed by strand passage. The experimental technique in these DNA experiments is to react unknotted circular DNA with an enzyme, and then to separate the reaction products via agarose gel electrophoresis. The surprising experimental result here is that the reaction products are circle knots and links, and that their gel electrophoretic mobility is determined by their crossover number – the minimum number of crossovers necessary in order to achieve a planar projection of the object (Dean et al. [25]). So the result of gel electrophoresis is a ladder of gel bands whose rungs correspond to knots

and links of the same crossover number! The DNA is then removed from the gel, and to greatly enhance resolution for electron microscopy, the molecules are coated with *recA* protein (Krasnow et al. [26]). This coating thickens the strands from about 10 Å to 100 Å, simultaneously affording unambiguous determination of the crossovers, and fewer extraneous crossovers. Figure 13 shows some DNA knots and links. Figure 13(a)

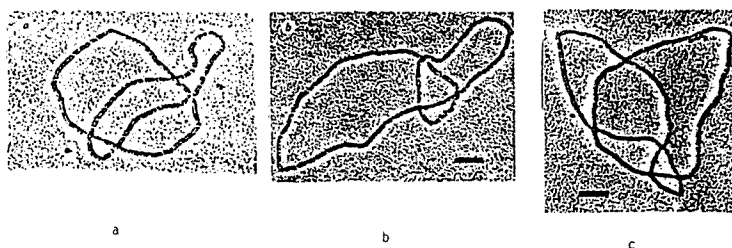


Fig. 13.

is a “+” trefoil knot, fig. 13(b) is a “-” trefoil knot, and fig. 13(c) is the “+” fig. 8 catenane (the crossover in the middle is a “+” crossover). When one is looking at experimental output such as that shown in fig. 13, the necessity for using knot theory becomes absolutely clear! Moreover, the resolution exhibited in these micrographs allows the precise determination of knot type for the reaction products.

Various enzymes can be characterized by the family of circle knots and catenanes which they produce when reacted with unknotted circular substrate. For example, the enzyme TOPO I (Dean et al. [25]) produces all possible circle knots (of low crossover number), and produces chiral knots racemically. The recombinant enzyme Phage  $\lambda$ , on the other hand, produces only “+” torus knots and torus catenanes of type  $(2, k)$  – all are chiral and of a very special type (Spengler et al. [27], Sumners et al. [28]).

One interesting problem here is to partition the enzyme mechanism between changes in the geometry (writhing) and changes in the topology (strand passage and strand exchange – both of which involve breaking strands) of the substrate. By changes in geometry, we mean enzyme manipulations of the substrate which do not change the knot type; by changes in topology, we mean enzyme manipulations which do change the knot type. Because work-up and analysis of reaction products necessarily introduces changes in geometry, it is difficult to detect changes due to enzyme action. However, enzymatic changes in the geometry can be trapped (as in fig. 12) by subsequent changes in the topology. Results of computer simulation of knot production via random crossover changes (Michels and Wiegel [29]) can be used to show that TOPO I produces changes in geometry as well as changes in topology (Dean et al. [25]). More work is needed here, both in terms of computer simulation of random knotting and linking, and in using “analytical” knot theory to deduce mechanism (Sumners et al. [28]).

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