

A New Look at an Old Twist

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Abstract

The more information that is discovered about genetics, the more complicated the field becomes. So, geneticists find themselves turning to topology to explain some of the processes that DNA undergoes. In this paper we will discuss some experiments with enzymes, how the enzymes effect DNA, and how knot theory can be applied in certain situations. We will explore some of the aspects of the fresh and exciting field of genetics through the application of century old knot theory.

1 Introduction

In the 1950s it was realized that our genetic code was contained in the double helix structure of DNA. When most of us think of DNA we think of something neat and tidy; something similar to a ladder grabbed at both ends and twisted as seen if Figure 1: DNA consists of two molecular strands, joined together by bonds, and twisted. Each strand of DNA is only a few molecules in width and several centimeters long, and all of this is coiled inside of every nucleus of every cell in our bodies. To put the measurement in perspective, we can size a nucleus to the size of a basketball, the width of DNA to that of a



Figure 1:

thin fishing line, and the length would end up being one hundred twenty miles long! Now, remember this is not coiled neatly and placed inside the basketball; this is a tangled mess! Because DNA molecules are long and flexible and can become knotted inside the nucleus, topological techniques are applicable to the study of DNA. It is because of the presence of knots in DNA that mathematics of knot theory is playing an ever increasing role in the study of DNA. The interest in knot theory first emerged in the 1880s, motivated by chemistry. However, the interest died down, and it wasn't until the 1980s, a century later, that knotting was discovered in DNA molecules. It was for this reason that scientists began using mathematical findings from knot theory to describe the occurrences in the nucleus of our cells.



Figure 2: Knotted DNA

Life proceeds with the reproduction of DNA. Replication, transcription, and recombination are the processes that a DNA molecule must undergo in order to reproduce. However, the knotting and tangling of the molecule makes these biological functions difficult. So, for DNA to complete these processes, special enzymes found in the nucleus topologically manipulate the DNA strand. Discovering the actions of specific enzymes can be translated into a problem of knot theory. It is the study of these enzymes that this paper will discuss.

2 Definitions

This section is going to present definitions of terms that will be used throughout the remainder of the paper. Note that these are not technical definitions, but simplified ones to aid with explanations. The enzymes discussed earlier are in the class **topoisomerase**. Although, the name seems complicated it describes exactly what the enzymes do: the enzymes erase the topology of the DNA molecule; they untangle it. These special enzymes actually cut the DNA strand and then reattach the loose ends when knotting occurs, so replication can continue. The enzyme does this using site-specific recombination. **Site-specific recombination** is the process whereby an enzyme attaches to two specific sites on two strands of DNA, called recombination sites, each of which corresponds to a particular sequence of base pairs that the enzyme recognizes.

We have been talking about deoxyribonucleic acid, DNA; a molecule that is formed by strands that are bonded together by ladder rungs and that spiral around each other. However, from this point on we will be discussing the application of the enzymes to circular DNA. The problem with applying the enzyme to the double helix form of DNA is if a knot is produced, it could slip off the free ends of the strands. So, to see the product of the enzyme on the DNA, scientists use circular DNA. **Circular DNA** is the double helix form with the two ends fused together to make a circle. Circular DNA can be found in nature in many bacteria, viruses, and in the mitochondria of human cells. More recently however, scientists have discovered how to artificially create cyclic DNA. Letting the enzymes act on these molecules, scientists are able to examine the results. Using this method, scientists can determine if the enzyme is causing knotting, because the knot will be captured on the circular DNA.

Figure 3 shows circular DNA and supercoiled circular DNA. To describe a supercoil, just think about a telephone cord that has been twisted up on itself. The initial form of the circular DNA is called the **substrate**, it is usually unknotted. After the enzyme acts on the strand, a new form of the DNA emerges, it is called the **product**. After multiple complicated techniques on the DNA, scientists are able to determine the knots and links contained in the product.

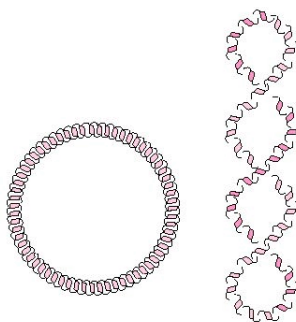


Figure 3: Circular DNA and supercoiled circular DNA

Now, to help later in the paper, we are going to cover some of the knot theory terms that we have been using, and will use. A knot can be described using a string: take a string, tie a knot in it. Now, glue the two ends of the string together to form a knotted loop, we can think of this as a **knot**. The specific knots that we are going to be discussing are the figure eight knot; which happens to be the only four crossing knot, seen in Figure 4:



Figure 4:

and the 6_2 knot, seen in Figure 5

We are also going to be discussing links found in DNA. A **link** is a set of knotted loops tangled together. Some of the links we will be discussing are the Hopf link, seen in Figure 6

and the Whitehead link, seen in Figure 7

Tangles will also be used to discuss the action of enzymes on DNA. A **tangle** in a knot or link projection, is a region in the projection plane surrounded by a circle such that the knot or link crosses the circle exactly four

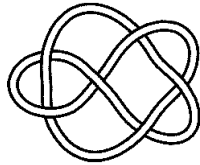


Figure 5:

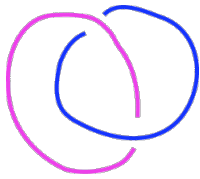


Figure 6:

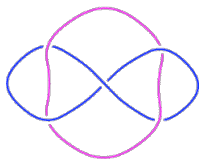


Figure 7:

times. An example of a rational tangle is provided in Figure 8. A rational tangle is represented by an integer, constructed by vertical and horizontal twists. It will be discussed in the next section.

3 Experiments and Theory

Scientists would like to understand the action of particular enzymes on DNA in the cell. Molecular biologists, Wasserman, Dungan, and Cozzarelli experimented with the topoisomerase RN3 Resolvase. They began with the substrate, an unknotted, supercoiled, closed circular duplex DNA. They were looking at the case that occurred five percent of the time; when the enzyme repeated the recombinations. During these experiments the scientists worked

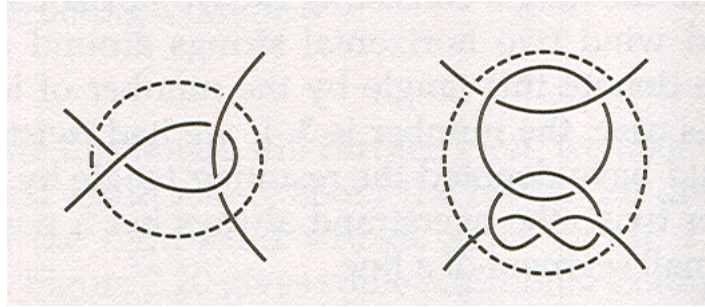


Figure 8:

under the assumption that the enzyme behaves the same way each time applied. After applying the enzyme and It is from these experiments that they formed the Wasserman et al. model based on the products. This model can be seen in Figure 9:

These experiments were done in 1985 and describe the action of the enzyme TN3 Resolvase after repeated recombinations. In 1990 Ernst and Summers used tangles to mathematically prove that the Wasserman et al. model correctly describes the action of TN3 Resolvase. They considered the circular DNA molecule as being made up of two tangles, the substrate tangle and the site tangle. The substrate tangle is denoted S and is the initial form of the tangle, consisting of three vertical right-handed twists. The site tangle

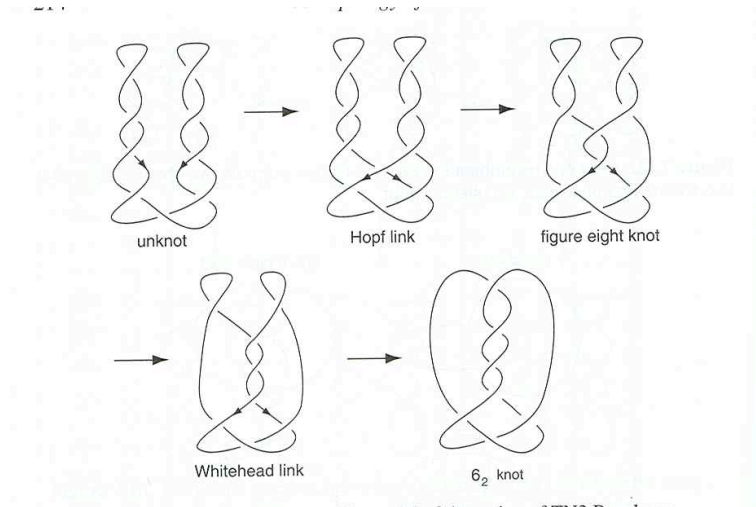


Figure 9:

(T) is where the enzyme attaches for recombination, and the recombination tangle (R) replaces the site tangle with one horizontal twist. Applying their knowledge of knot theory and working under the same assumptions that Wasserman, Dungan, and Cozzarelli used, Ernst and Sumners stated this theorem:

Theorem 1 *Suppose that S , T , and R are tangles satisfying the following*

equations: $N(S+T)$ = the unknot $N(S+R)$ = the Hopf link $N(S+R+R)$ = the Figure-eight knot $N(S+R+R+R)$ = the Whitehead link. Then S and R are both rational tangles. $S = (3,0)$, and $R=(1)$, and $N(S+R+R+R+R)$ is the 6_2 knot.

The theorem is stating that by beginning with the sum of two tangles, the unknot, after one recombination $N(S+R)$, the Hopf link is created; after the second recombination $N(S+R+R)$ the figure eight knot is created, and so on and so forth. The proof of the theorem uses classical techniques of knot theory, including the concepts of the fundamental group and Dehn surgery on a knot [3]. The main part of their proof is to show that both of the tangles S and R must be rational for the knots and links to be produced. Ernst and Sumners chose to use rational tangles in their proof because rational tangles are understood.

As you can see, the substrate tangle consists of three vertical twists, and remains the same. The recombination tangle replaces the site tangle with one horizontal twist for each application of the enzyme. If examined carefully, after the first recombination, the two tangles create the Hopf link, after the second recombination the Figure-eight knot is created, etc. So, Ernst and Sumners successfully proved that the Wasserman et al. model was correct. Here is a figure to help visualize the recombinations:

4 Conclusion

The ability to apply century old knot theory to a new field like genetics is very exciting! The applications of topological techniques for understanding molecular structures has become increasingly important over the last thirty years; these applications help simplify a complicated matter. Scientists are still searching for better techniques to unravel some of the mysteries of life. Turning to mathematics, chemists and biologists are finding simple and clear, but rigorous definitions of concepts they handle in their work [3]. "Mathematical content is not confined to mathematics [3]. The discovery of mathematical structures has answered questions in science and inspired new questions in pure mathematics.

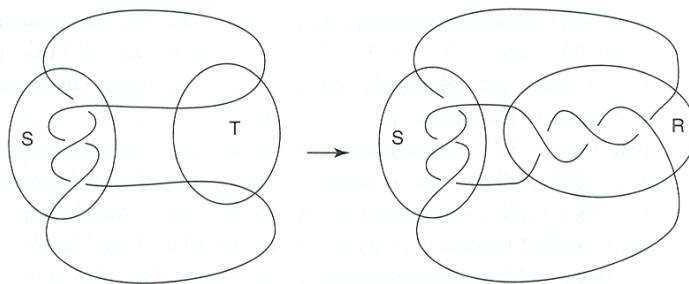
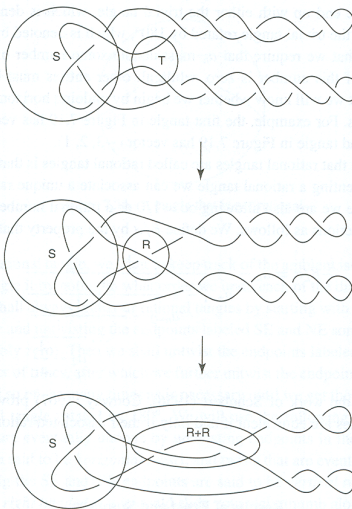


Figure 10:

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