

Knot Theory and DNA

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1 Introduction

1.1 Mathematical Knots

Knot Theory is a section of topology which focuses on the study of mathematical knots. Similar to knots we see around us, like the knots in shoelaces, for example, mathematical knots are 3 dimensional and are made of crossing strands of a string. However, a mathematical knot, unlike the knots we see in day-to-day life, **is composed of a theoretical string, with its two ends attached to one another permanently.** The most basic knot in knot theory is known as the "unknot". In its simplest form, the unknot is simply a ring. Two knots are considered **equivalent** if one can be made into a perfect replica of the other through a series of deformations known as **ambient isotopies.** These are deformations that do not alter the knot by cutting, gluing, or passing the string through itself.

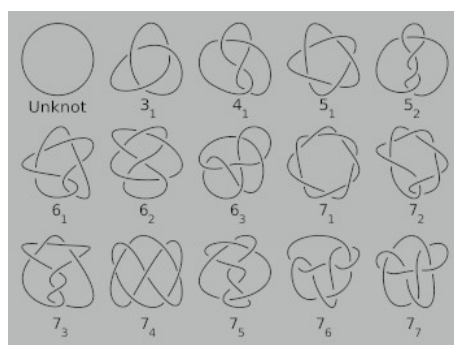


Figure 1: A few simple knots

1.2 Main Ideas of Knot Theory

Projections are representations of 3 dimensional knots on a 2 dimensional surface, such as a piece of paper. Because they are shown from a certain point of view, two knots that are actually equivalent may look different. **One of the main goals in Knot Theory is to be able to distinguish various knots from one another.** One method to do so is to actually try to deform one knot into another through a series of actions known as the **Reidemeister moves** (Figure 2).

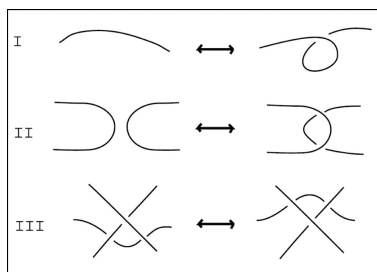


Figure 2: An diagram of the 3 **Reidemeister moves**

These actions change the appearance of the projection of a **knot by twisting, pulling, and stretching the string**. The Reidemeister moves do not change the type of knot it is, however, they change what the projection looks like. For example, twisting the string in an unknot will not change it into some other knot, but the appearance of the unknot will change. With enough Reidemeister moves, you can prove that two knots are equivalent. This can be done by making them resemble each other exactly. Unfortunately, it is almost impossible to prove that knots are **nonequivalent** solely through the Reidemeister moves. This is because, while n Reidemeister moves may show two projections that look different, $n + 1$ moves, meaning one more Reidemeister move, may show that the two knots are, in fact, identical. A solution to this problem is to calculate and compare **knot "invariants"**. An invariant is, as the name suggests, a value that does not vary as long as the type of knot is not changed. Throughout equivalent knots, invariants will stay constant, meaning an invariant found in one figure-eight knot will be the same in another figure-eight knot. In other words, an invariant calculated from one knot will be calculated to be the same for equivalent knots. If two knots have two distinct invariant values, those two knots must be nonequivalent. **Unfortunately, knots that are nonequivalent sometimes have the same invariant values, so invariants alone cannot prove two knots as being identical.**

1.3 Writhe and unknotting number

A mathematical **link** is a group of knots that, while separate, are intertwined, like a **chain link fence**. Links cannot be separated from one another without cutting at least one of the knots in the link. A knot is simply a link with one element. Strands are lengths, or snippets, of the theoretical string that knots are made of. It is important to note that, like the knots that are seen in day-to-day life, mathematical knots are formed when strands of a string cross each other. An **over crossing** ($K+$) occurs when a given strand crosses over another. An **under crossing** ($K-$) is when a given strand is crossed over by another strand. Such crossings in a knot diagram can be counted by picking a starting point on the string and tracing the knot in a direction. Each time the strand goes under another, forming an under crossing, count it as -1 . Each time it goes over a strand, creating an over crossing, count it as $+1$. The **writhe** of a link is the difference between the total number of positive and negative crossings.

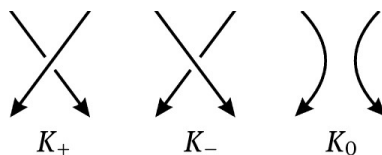


Figure 3: A positive crossing, a negative crossing, and a neutral crossing

While the writhe is not an invariant, and cannot distinguish two knots from one another, it is useful for determining how intertwined links, or knots, are. This becomes helpful when estimating how hard it will be to undo a knot or link. Another useful value is the **unknotting number**. The unknotting number, on the other hand, **is an invariant that serves a similar purpose**. The unknotting number of a knot **shows how difficult it will be to change a given knot into the unknot**. By turning at least one positive crossing into a negative crossing,

or vice versa, it is possible to change any knot, no matter how complex, into the unknot. Reversing a crossing like this is possible by cutting a strand, switching its position with the strand it crosses, and reconnecting the severed ends. The unknotting number of a knot is the **minimum** number of crossings that must be changed like this before it is possible to use the **Reidemeister moves** to make the knot resemble a ring.

2 DNA

2.1 Introduction to DNA

In 1869, Swiss physician and biologist, **Friedrich Miescher**, discovered DNA, also known as **Deoxyribonucleic acid**. DNA strands are comprised of long chains of alternating sugars and phosphates. These chains are joined together by at least one of the following nitrogen bases: Adenine, Cytosine, Thymine, or Guanine, to create a ladder-like, double-helix structure (Figure 4). These strings of genetic code contain millions upon millions of atoms and are tightly packed into the **nucleus** of a cell.

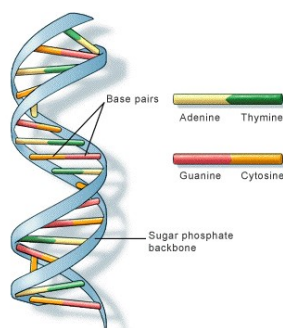


Figure 4: A simple diagram of DNA's double helix shape.

In 1953, James Watson, Rosalind Franklin, Maurice Wilkins, and Francis Crick discovered that, within its structure, DNA holds instructions for the reproduction, behavior, and growth of every known lifeforms. All but a few unique cells in any creature have a nucleus and, therefore, their own copy of the organism's DNA, which act as the instructions for that cell's behavior. In order for an organism to grow, it is necessary for its cells to reproduce. Most cells do this through cell division, a process which involves creating a copy of the original cell's DNA before splitting into two, hopefully identical cells.

2.2 Enzymes

Enzymes are proteins created by living organisms that bring about specific chemical reactions or chemical changes. Different enzymes can act as catalysts for different chemical changes within an organism. By speeding up chemical reactions, enzymes are vital supports to all life. They aid in almost every process that occurs in an organism, from digestion, to the metabolic system, to DNA replication.

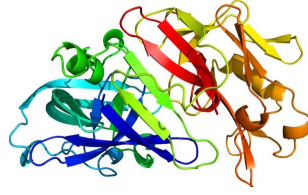
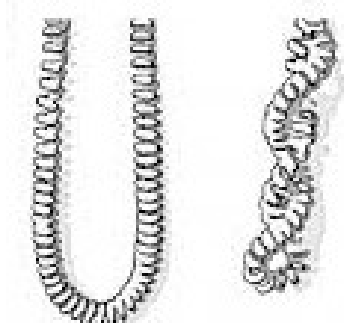


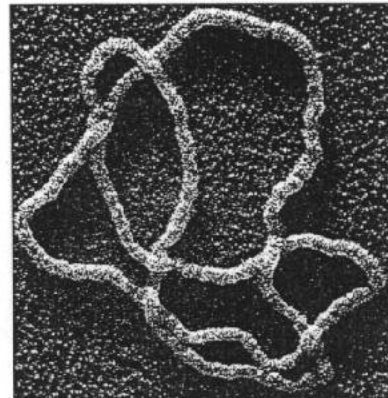
Figure 5: Visual representation of Pepsin, an enzyme that aids in digestion.

2.3 Enzymes and DNA Replication

In order for DNA to be replicated, enzymes are needed to unwind the DNA found in the nucleus and make a copy. This is difficult, however, due to the fact that DNA is not organized in the nucleus in any way. Through **supercoiling**, the DNA coils itself in a manner similar to a telephone cord. By doing so, the length of the molecule shortens, allowing for more efficient storage in the nucleus. **By compressing the strand like this, none of the necessary information within is lost.** Supercoiling can lead to a strand of DNA ending up in a knotted tangle. **Knotted, it is impossible for it to interact with the enzymes responsible for its replication.**



(a) DNA coils like a telephone cord, making complex knots.



(b) Actual picture of supercoiled DNA.

2.4 Topoisomerases

Topoisomerases are a type of enzyme known for altering the supercoiling of DNA strands. They solve the problems encountered when trying to untangle a knotted strand of DNA. While in knot theory, mathematicians cannot break the knot or have the strands pass through one another, these enzymes do not have to follow these rules when untangling DNA. The topoisomerases act by quickly severing a given number of DNA strands and recombining them in a new fashion. **The number of strands severed and recombined relates closely to the unknotting number of that knot.** **In fact, if a strand of DNA is not equivalent to the unknot, there is no possible way to make it into a simple loop without passing the strands through one another by cutting them.** These enzymes can also perform operations on DNA strands, similar to the three Reidemeister moves, in order to unwind the tangle of DNA.

3 Knot Theory applications to medicine

3.1 Knot Theory and DNA

Biologists and mathematicians can picture knotted strands of DNA as links and use knot theory to gain insight into how topoisomerases interact with the double helix. The **writhe is the number of times the molecule crosses over, or under, itself due to the effects of supercoiling.** By calculating the writhe of a strand of DNA, biologists can use knot theory to estimate how difficult it will be for enzymes to unpack, unwind, and replicate DNA molecules. For example, after calculating the unknotting number of a coil of DNA, biologists can make accurate guesses on the minimum number of actions a topoisomerase must take in order to untangle the double helix. For example, to undo a figure-eight knot (Figure 7a) into the unknot, an enzyme would have to change only one over-crossing into an under-crossing. It would then have to use the Reidemeister moves to make the unknot resemble a loop (Figure 7b). By placing a controlled amount of topoisomerases into a certain amount of DNA, it is possible to measure the **rate** at which the enzymes work to unpack the DNA. By watching topoisomerases work, humans can observe the effects of these proteins on knotted DNA.

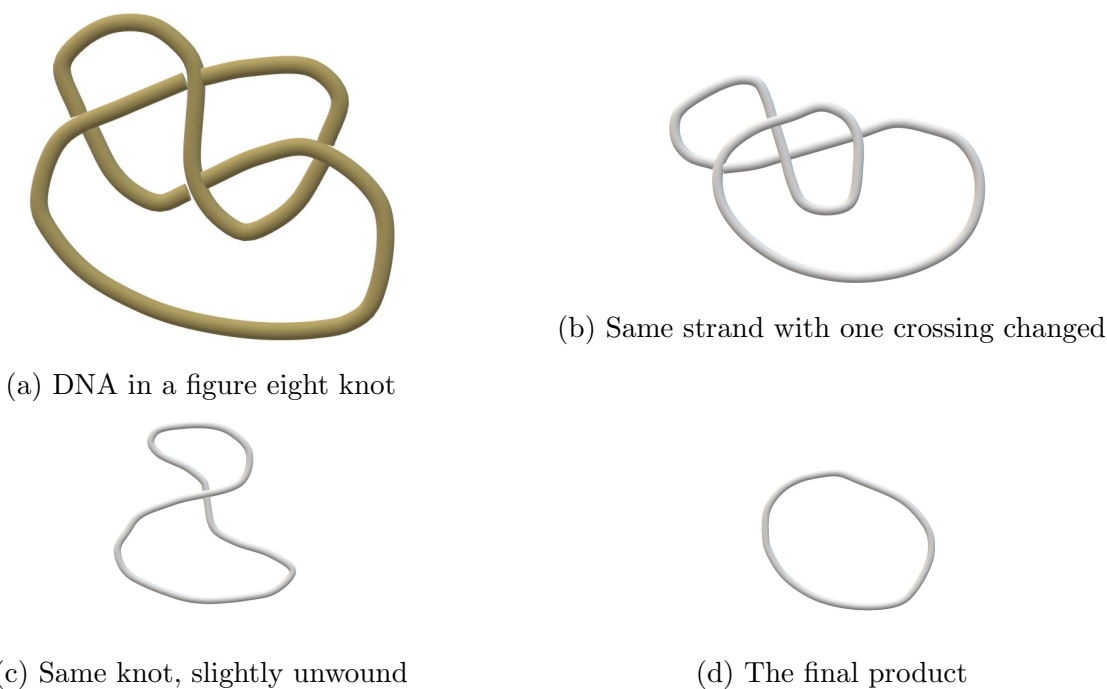


Figure 7: How a knot of DNA may look as it is unwound by enzymes

3.2 Studying enzymes

In 1979, Nicholas Cozzarelli and Patrick Brown studied the effects of **gyrase**. Gyrase is a topoisomerase found in *E. Coli* bacteria. Using ideas from knot theory, Borwn and Cozzarelli were able to discern how the gyrase operated. The researchers observed the shape

of the knotted DNA using an electron microscope. Calculating the writhe of the DNA from time to time, they found that its writhe would periodically decrease as the gyrase worked. Their conclusion was that the gyrase was slicing the double helix apart from time to time, and gluing the severed ends back together. The ends were glued together in another position, changing over-crossings into under-crossings, and vice versa. Through this process, the enzymes were able to change the strand of DNA into a shape resembling the unknot. By conducting studies such as this, humans may be able to gain insight into how various enzymes achieve their goals, and we may be able to replicate the effect for the future of medicine.

By observing the work of enzymes with knot theory, researchers may be able to gain insight into how these enzymes perform operations on DNA. As this is still a developing field of study, relatively little has been done to apply knot theory to study the work of enzymes. If, in the future, scientists learn to better manipulate topoisomerases and supercoiled DNA, it can take humans a step forward in the fight against cancer. Many of the drugs that fight cancer today try to limit the reproduction of cancerous cells.

3.3 Fighting cancer

Mariel Vazquez, is an American biologist from the University of California, Davis. During the 2018 SIAM Annual Meeting, Vasquez talked about how suppressing the actions of topoisomerases can work as a means to combat cancer. Cancer is a disease that is caused by abnormalities, or "glitches," in the DNA of a cell. Usually, a cancerous cell is instructed to reproduce and grow uncontrollably. This can result in severe damage to the surrounding tissue. One way in which a cell can grow uncontrollably is through the loss of its contact inhibition mechanism. Contact inhibition refers to how healthy cells will cease to grow and reproduce when they come into contact with more cells. This prevents the overgrowth of cells throughout an organism. Cells that have lost this mechanism will continue to grow even when they start to pile up onto other groups of cells. A tumor is formed when there is an accumulation of such abnormal cells in one area. Normal cells will detect when they are too old, or damaged, to function and will self destruct in a process known as apoptosis. New cells will be born to take the place of the newly deceased cell. Cells in a tumor, however, often lose this function. As a result, tumors can continue to proliferate long past the time when their cells should have died out. Growing with no end, tumors can continue to drain increasing amounts of nutrients from the body. If not fought against, this condition leaves the victim weak and is often fatal.

Some modern day chemotherapy drugs used to treat cancer work by damaging the DNA giving instructions to the cell. Abnormal DNA tells the cancerous cell to replicate itself in an abnormal fashion. Damaging the DNA will prevent it from telling the cell to divide and reproduce. If the cells are unable to divide, they will eventually die out and the tumor will shrink. Damaged cells may also go through apoptosis. While chemotherapy is sometimes effective against malignant cells, drugs such as these are also extremely harmful to healthy cells in the body. Just as they kill cancerous cells, cancer drugs will also destroy healthy tissue in the human body. Developing drugs that combat tumors while leaving minimal side effects has always been a goal of cancer treatment research.

Rather than using radiation and chemotherapy, knot theory can help us better manipulate DNA replication through enzymes. Stopping the replication of DNA through enzymes

will not allow such cells to multiply. This might prove to be a very effective addition to existing cancer treatments.

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