Topological Principles for deformatons of DNA

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Contents

The work

We started this work from 12 April 2012.

Motivation and Target

We have found the following relation between biological terms and knot theoretical terms.

Biology		Knot Theory
DNA replicon	$\Longrightarrow$	2-component link
Topoisomerases	$\Longrightarrow$	Unknotting Operation
Semi-conservative replication	$\Longrightarrow$	Splitting Link process
?	$\Longleftarrow$	Topological Scheme

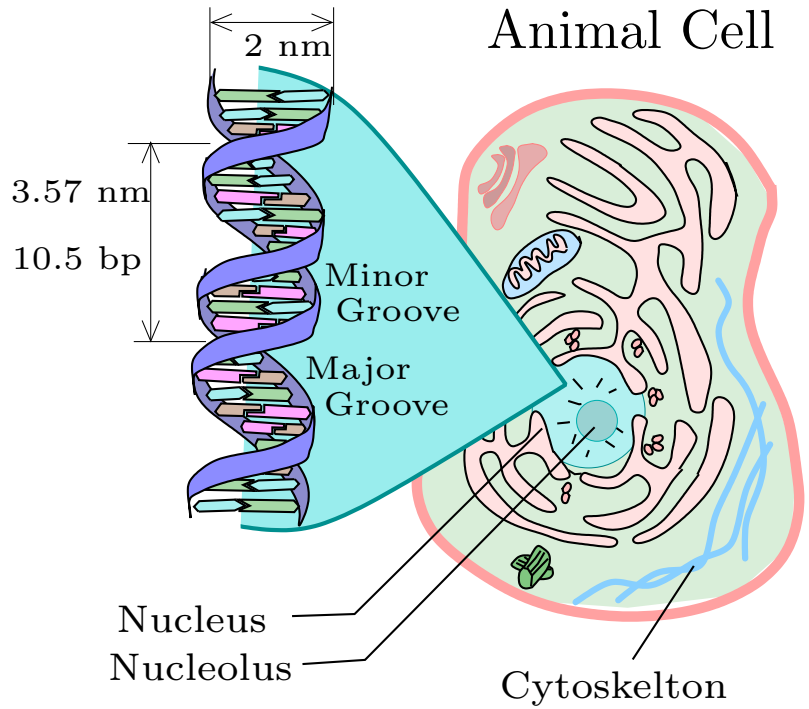
Target

To propose a topological scheme with knot theory to govern the replication process.

Structure of DNA

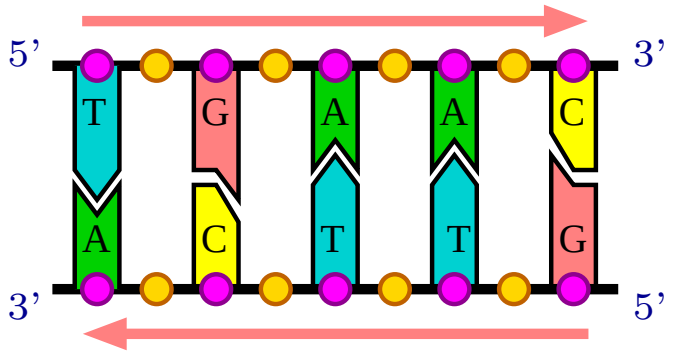
DNA (Deoxyribonucleic Acid) has the double helical backbones [WC53]:

- a right-handed double helical backbones on the outside and base pairs lined up on the inside, and
- antiparallel orientation.



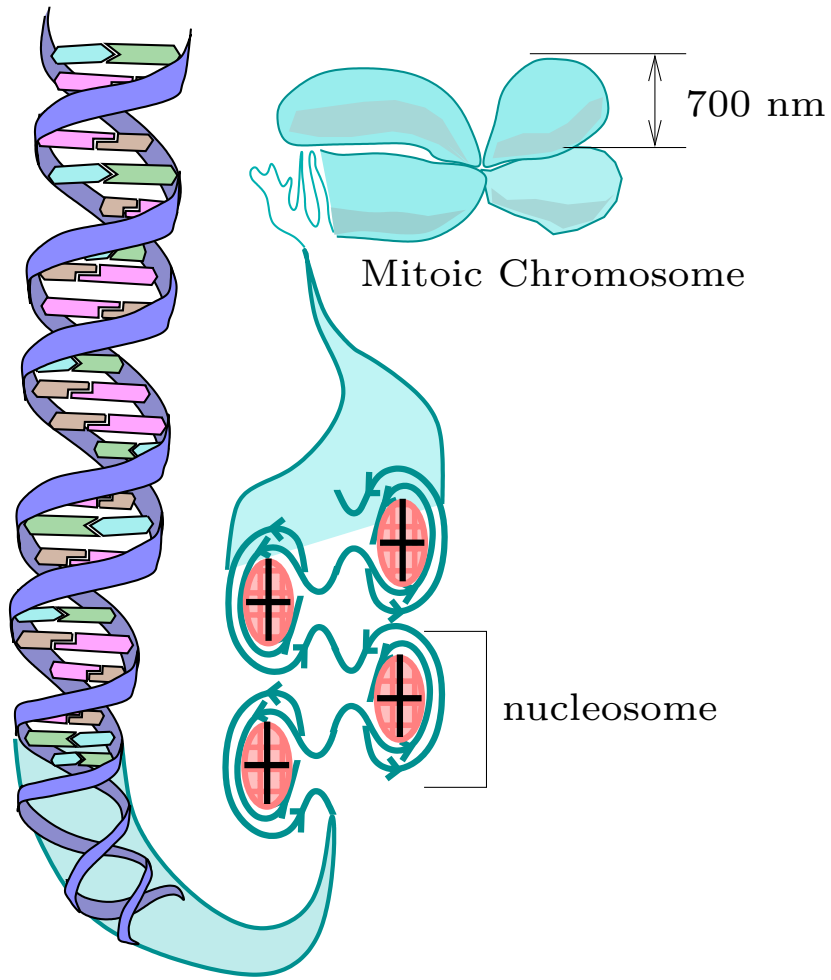
Base pairs

There are four bases with specific paring:
A =Adenine $\leftrightarrow$ T =Thymine, and
C = Cytosine $\leftrightarrow$ G =Guanine.



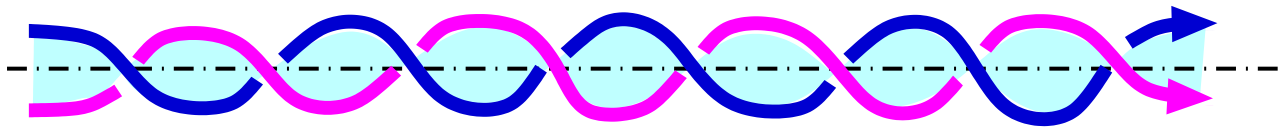
Chromosomes

The double strand DNA (ds-DNA) forms a winding structure around a histone core to make a bead structure called a **nucleosome**[BM+05][Sin94].



Topological Model of DNA

A possible model of the double-strand DNA is a lnog thin strip twisting around the core curve. The boundary curves correspond to the backbones of DNA.



Topological orientation

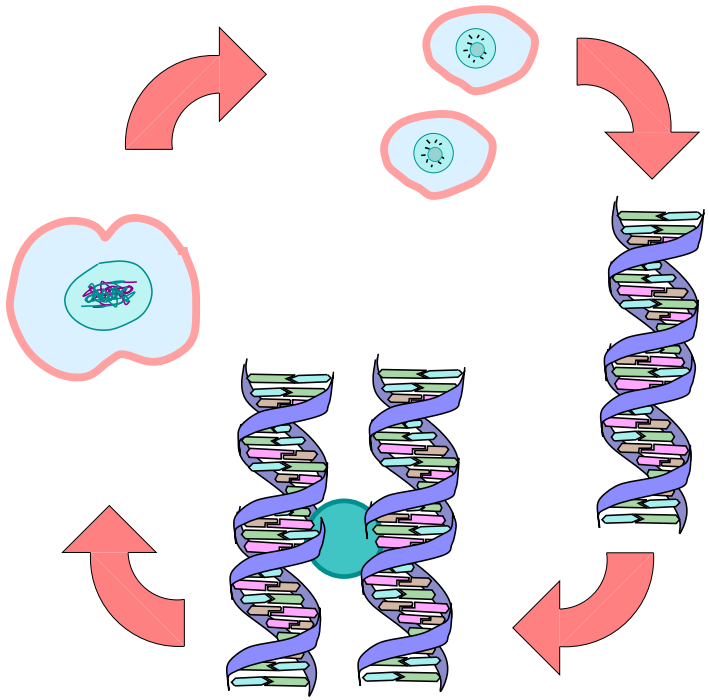
Topologically, we assume that DNA has a parallel orientation to be consistent with topological terminology.

Cell Cycle

The eukaryotic cell cycle has two phases,

- Mitoic phase and
- Interphase
  - G1 phase
  - S phase
  - G2 phase

During the S phase, DNA is replicated.



DNA synthesis

Size of DNA

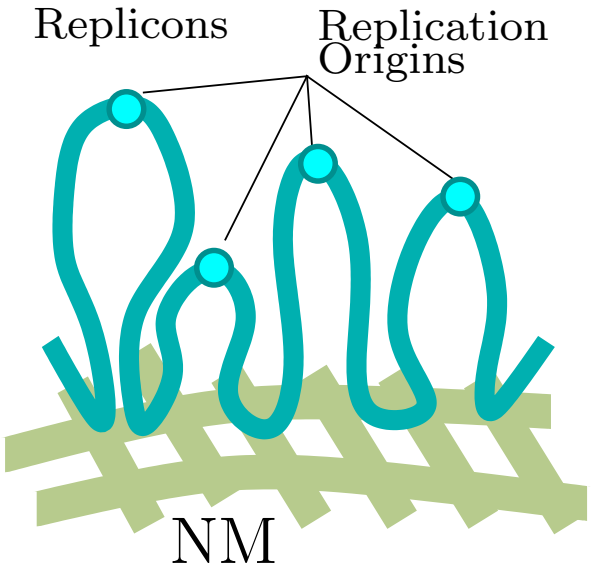
DNA is a long molecule with diameter 2 nm ($1\,\text{nm} = 1 \times 10^{-9}\text{m}$). The total length of human DNA is about 2 m

Replicons

The replication is done on each looped segment called a **replicon**. It is believed that the ends of replicon are anchored at the **nuclear matrix (NM)**[RGII13][RMHMMAA11][WC13].

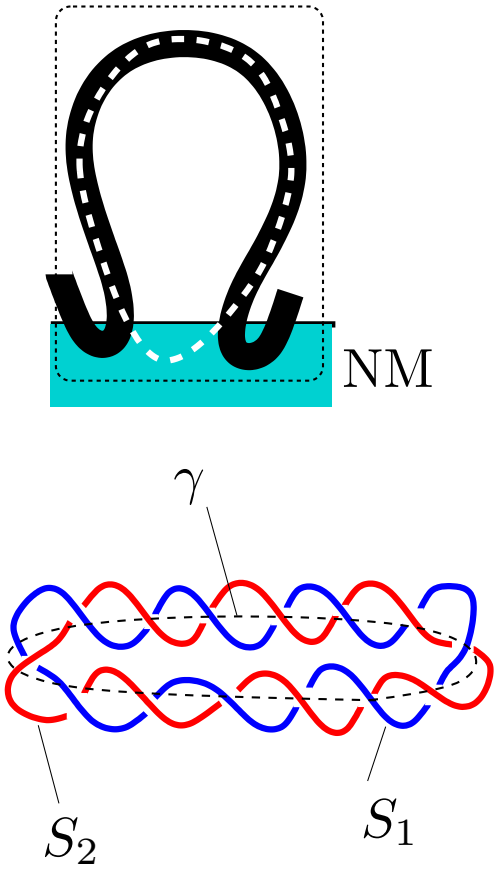
Size of Replicon

The length of a replicon is about 100,000 bp. The number of full-twists along the replicon is about 10,000.



Topological Model of DNA

Topologically, the replicon is viewed as a special 2-component link $L(S_1, S_2; \gamma)$, where S_1 and S_2 form a double helix structure along γ. We call this link a **DNA-link**.

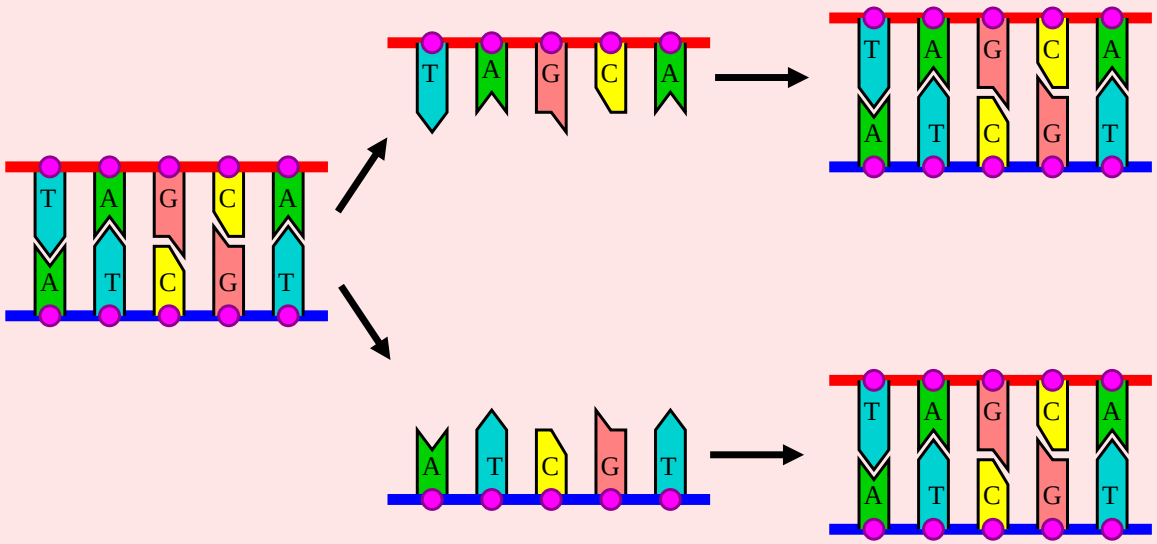


Semi-Conservative Replication

In 1958 Meselson and Stahl [MS58] did an experiment to show that DNA is replicated by **semi-conservative** replication.

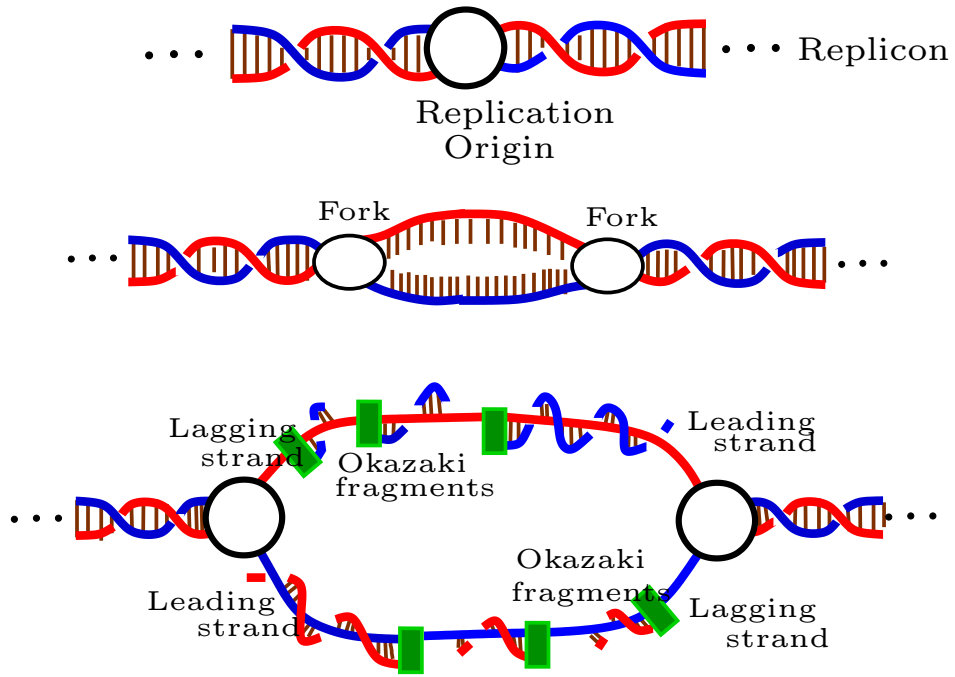
Semi-Conservative Scheme

The sequence of bases along each backbone is preserved in copied DNA.



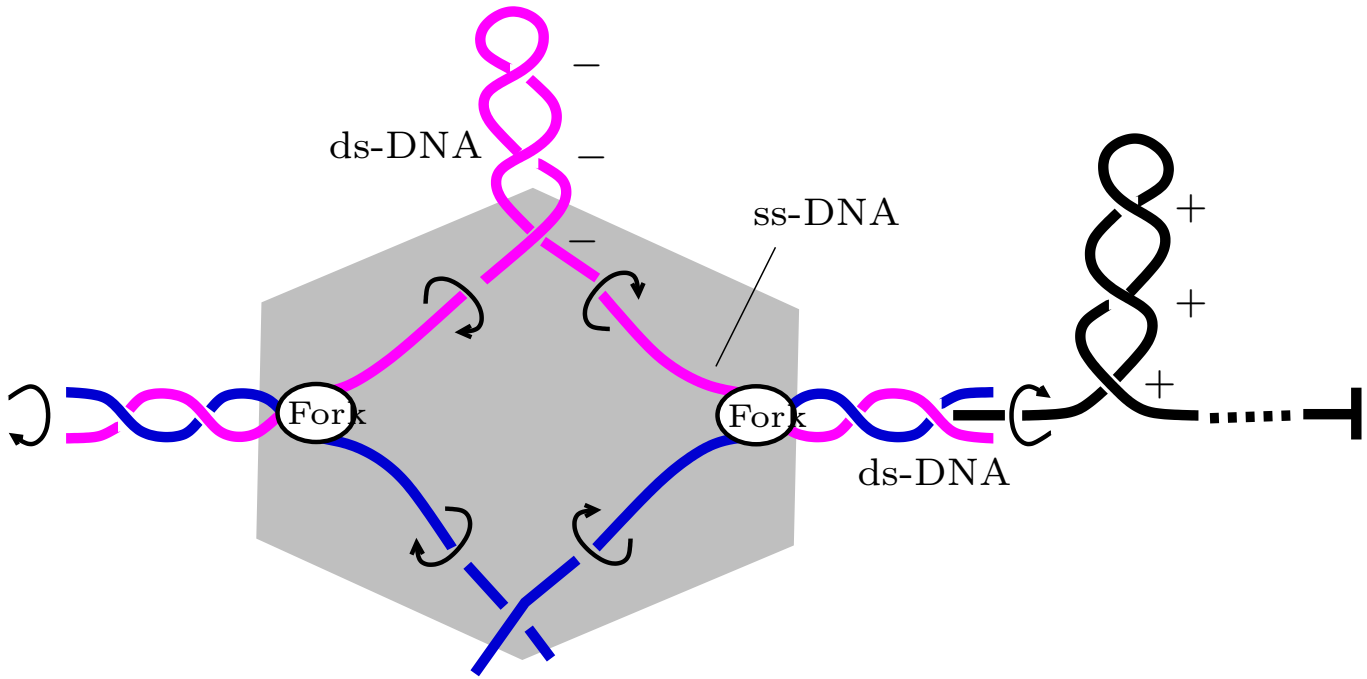
At the replication origin,

1. The ds-DNA is unwound at a specific site (the replication origin),
2. the base pairs are split to form templates along a ss-DNA, and
3. new nucleotides and double helix are constructed.



Unwinding and Supercoil

As the forks move away from the replication origin, both single strand DNA (ss-DNA) and ds-DNA are rotated. Some positive and negative **supercoils** are introduced ahead of and behind the fork respectively.

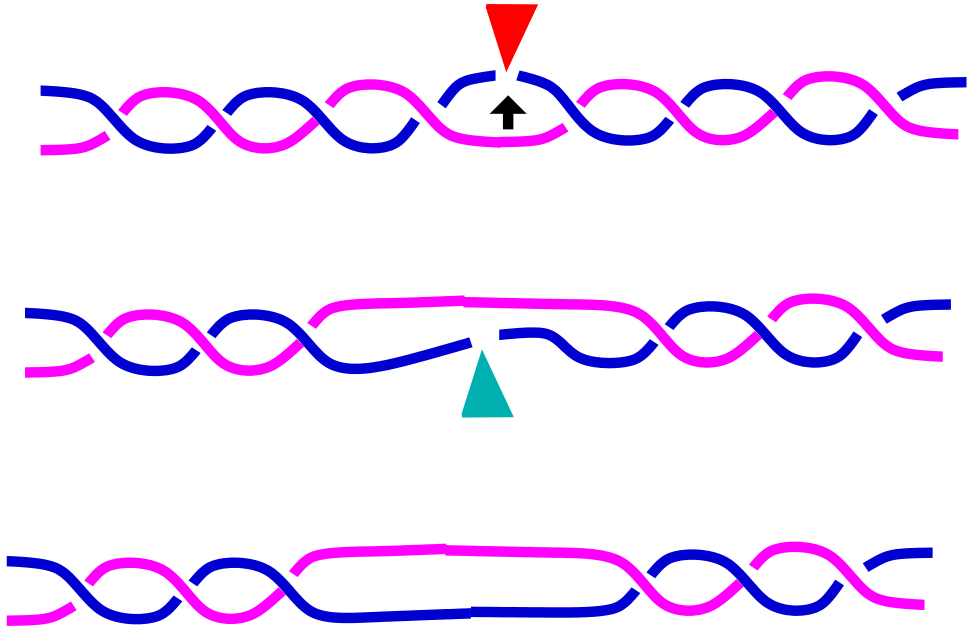


The supercoil becomes an obstruction against the replication process.

Biological Unknotting Operations

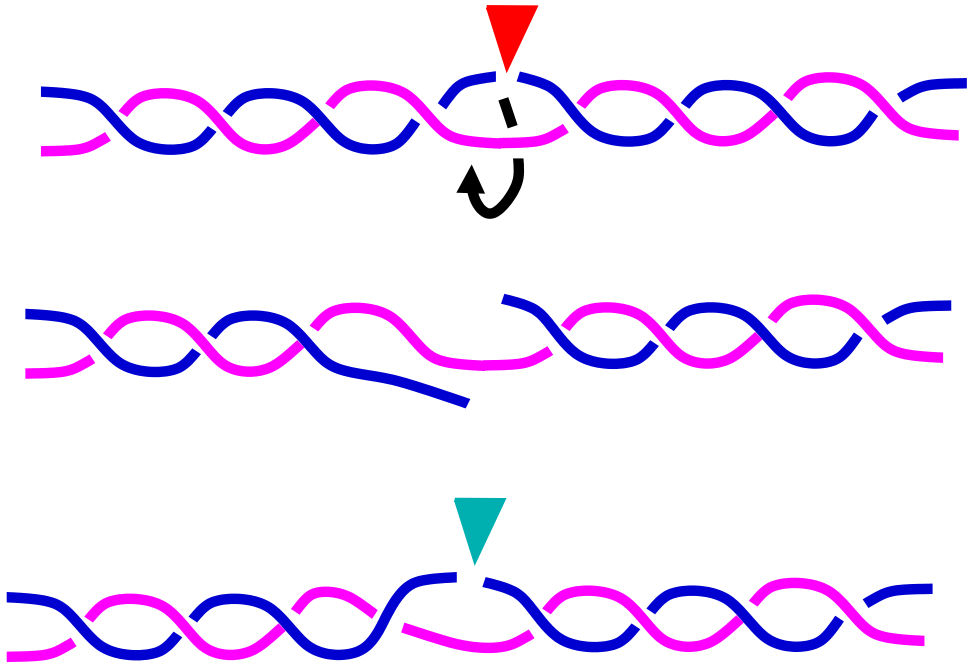
Type-I topoisomerase decreases the twisting number of ss-DNA.

The type-IA topoisomerase nicks one single strand to make a gap to let another single strand pass through the gap, and reseal the gap.



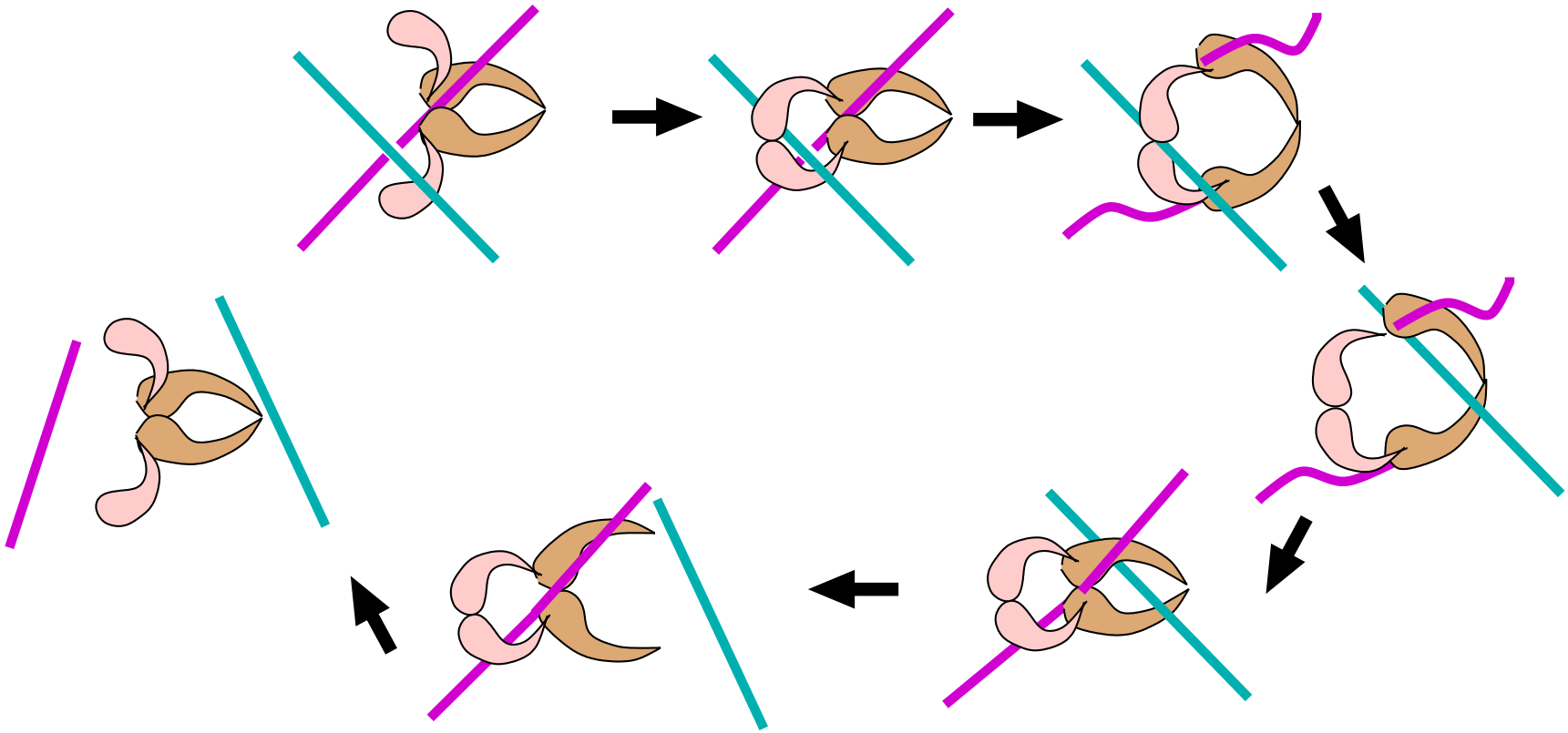
Biological Unknotting Operations

The type-IB topoisomerase nicks one single strand to make a pair of free ends and let one of the free ends rotate around the complete single strand.



Biological Unknotting Operations

Type-II topoisomerase decreases the rotational stress of ds-DNA.
The type-II topoisomerase makes a gap on the double strand DNA and let other piece of double strand pass through the gap, and reseal the gap.



Biological Explanation

The obstruction introduced by supercoils seem to be resolved by those enzymes, type-I and type-II topiomerases.

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During the process of the DNA replication, if the ds-DNA is supercoiled or knotted, then topoisomerases make it simple.

Many research work have been done to investigate how the enzymes work to resolve the entanglement of DNA. However, there still exist topological problems to be solved.

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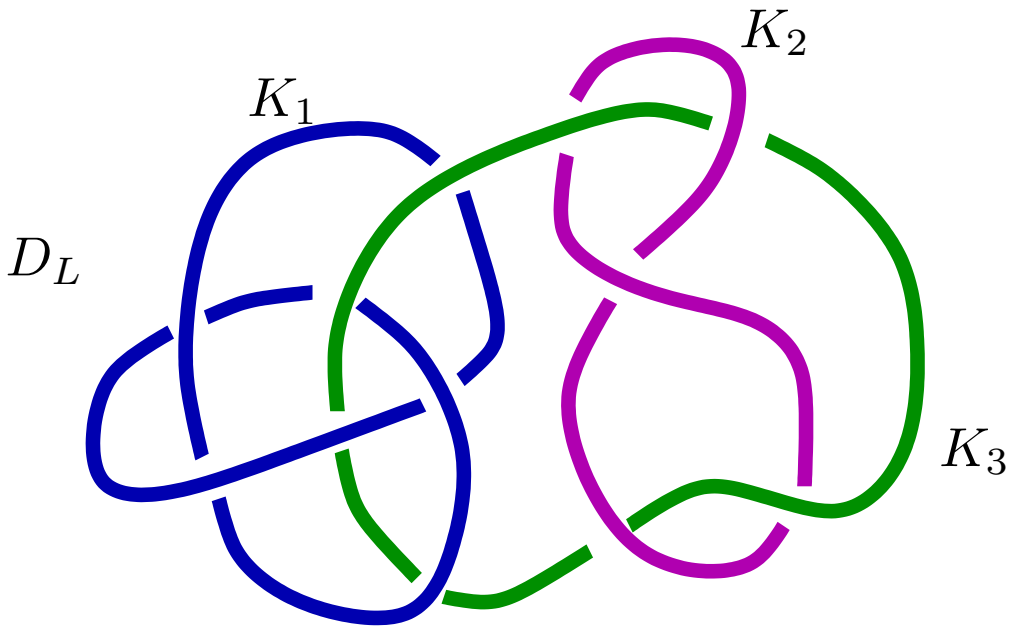
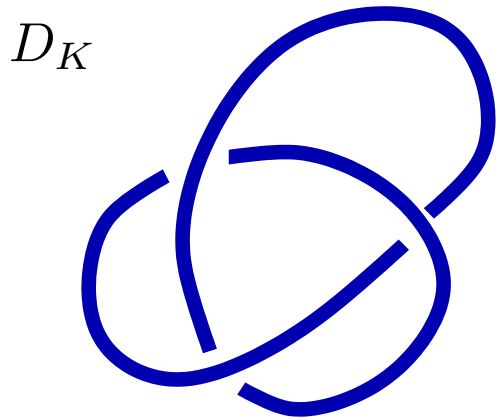
Topological Scheme

Knots and Links

A link L is a union of a finite number of disjoint circles embedded in 3-space. If a link L consists of n embedded circles, then it is called an n component link. A knot is one component link. A link(knot) diagram of link L (knot K) is the orthogonally projected image of L (K) in the plane with crossing information denoted by D_L (D_K)



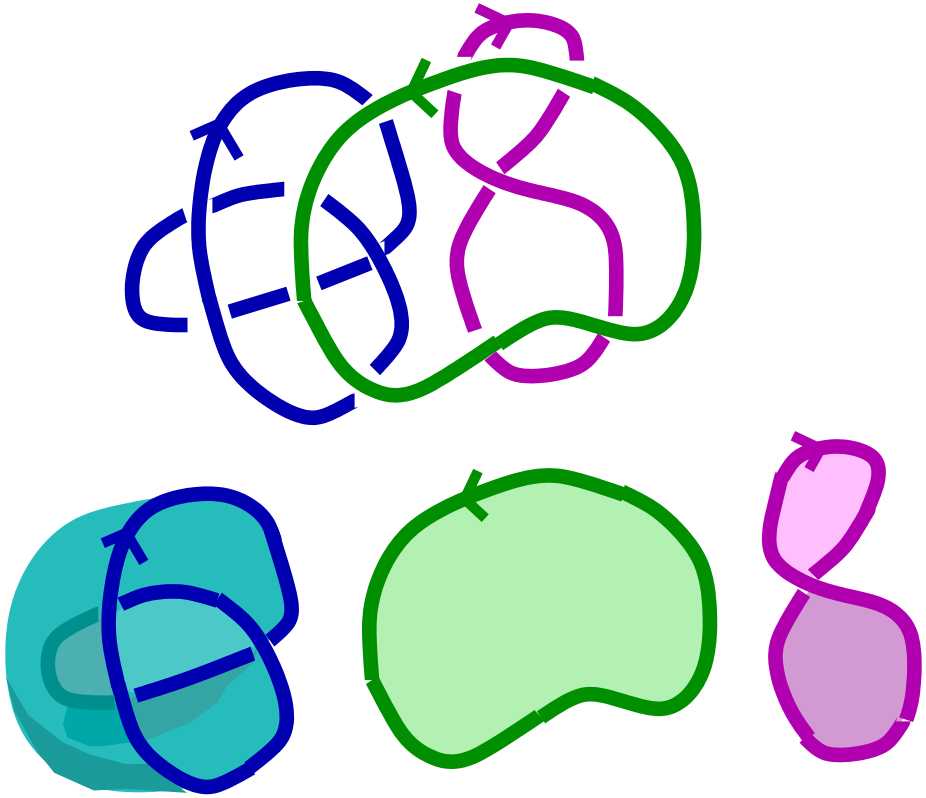
$L = \{K_1, K_2, K_3\}$



K

Trivial Link

A link is **trivial** if each component of L bounds a disc and the discs are mutually disjoint. A knot is **trivial** if the knot bounds an embedded disk.



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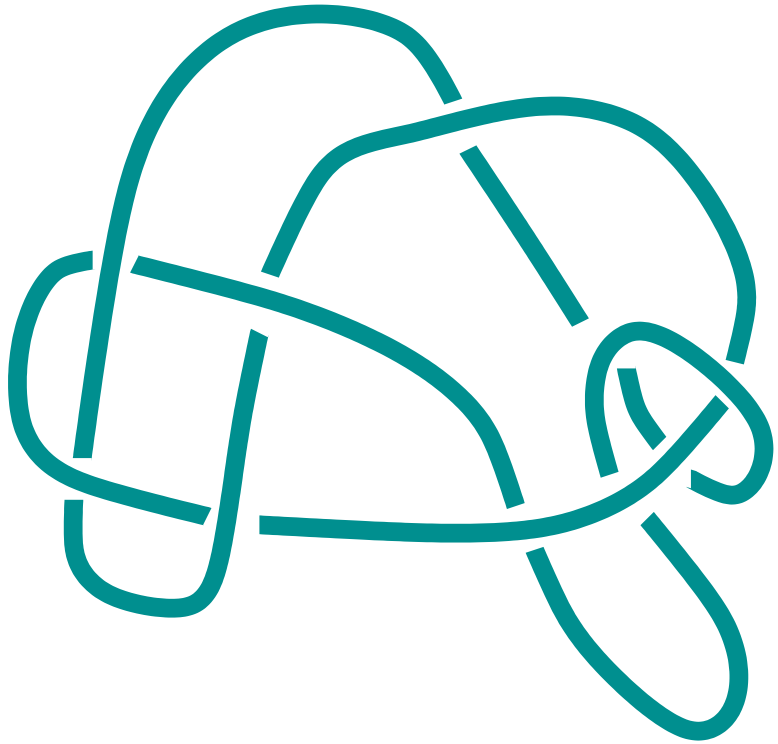

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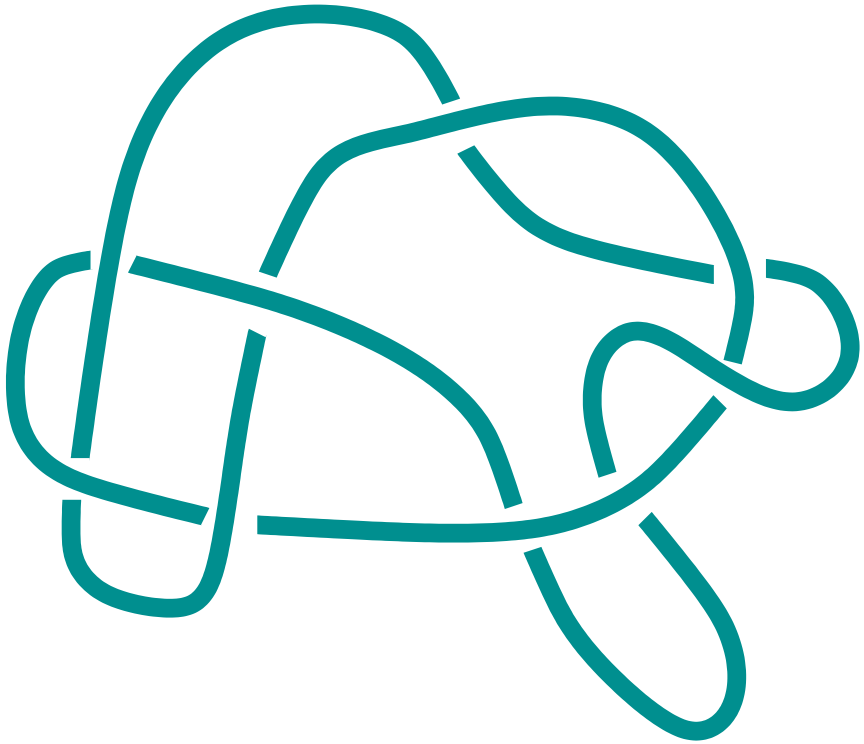

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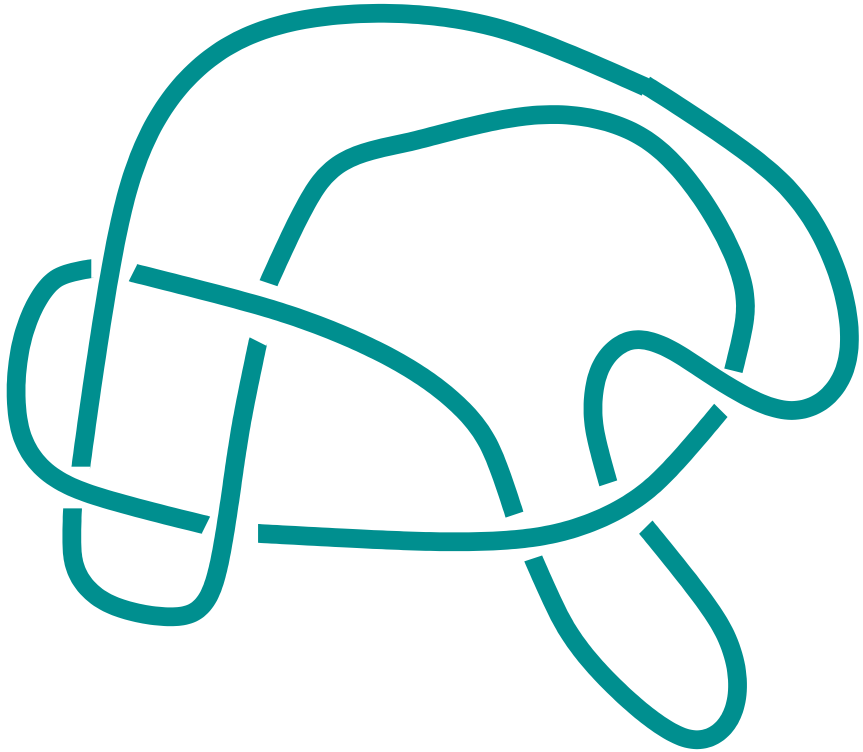

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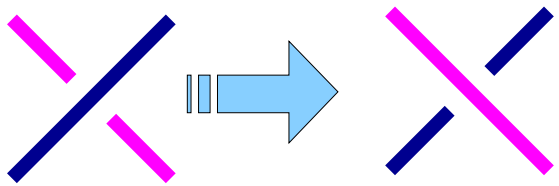
Topological Unknotting Operation

Topoisomerases

To resolve the supercoils and linking of the DNA strands, we need type-I and type-II topoisomerases.

Unknotting Operation

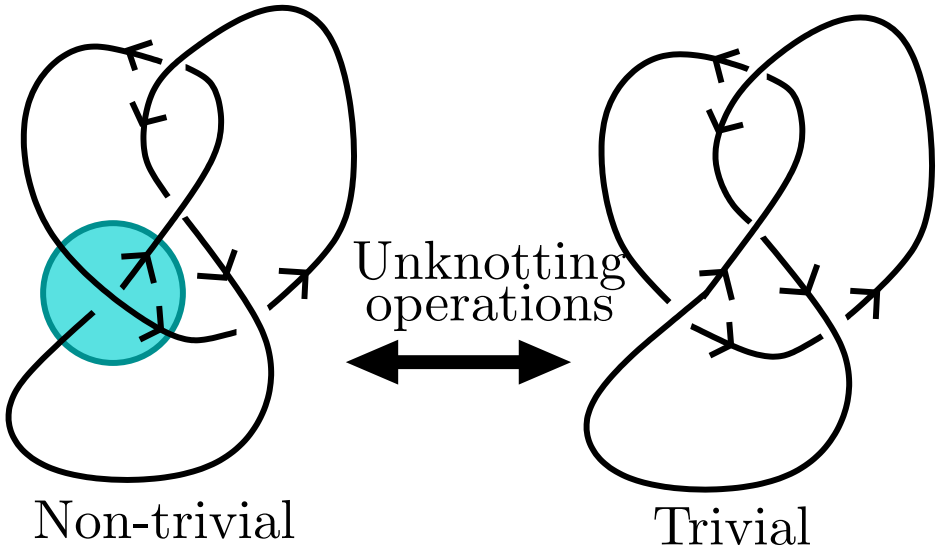
In topology, there is a corresponding operation called **unknotting operation** which exchanges the upper and lower arcs at a crossing.



Unknotting Theorem

Theorem 3.1

For a link L, every link diagram D_L, it can be deformed into a trivial link by applying a finite number of unknotting operations.



Note:

Randomly applying unknotting operations to a non-trivial knot does not work.

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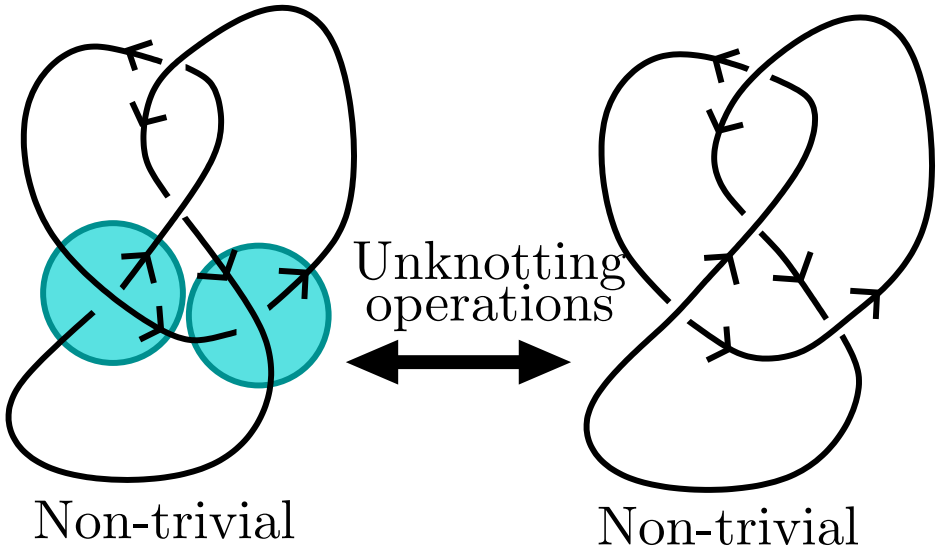

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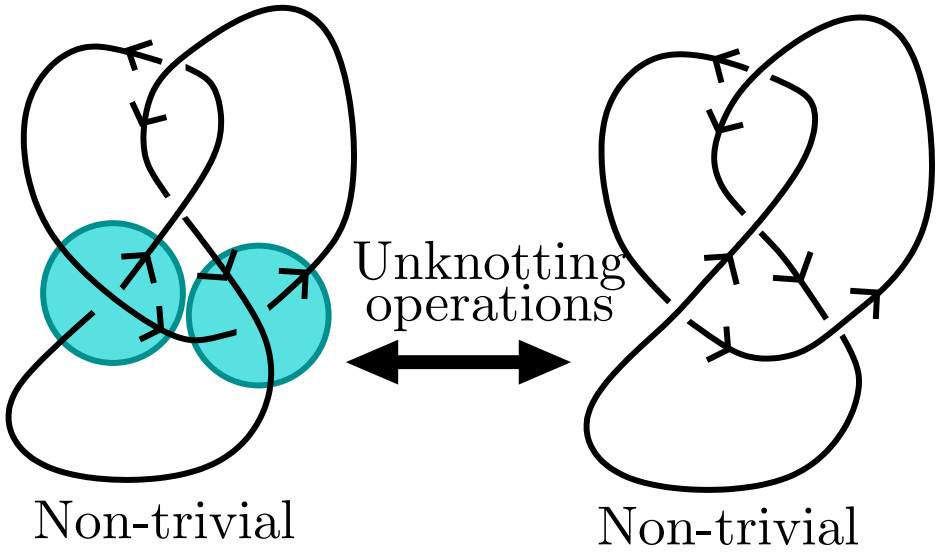

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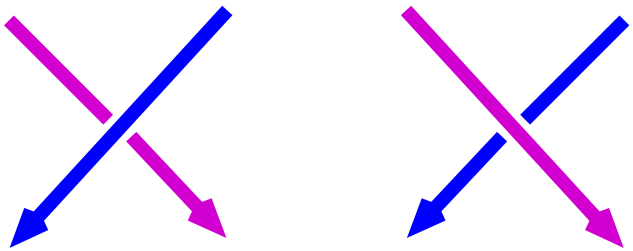
Linking number

Let L be an oriented link and let D_L be its link diagram. Then the linking number is defined by the formula:

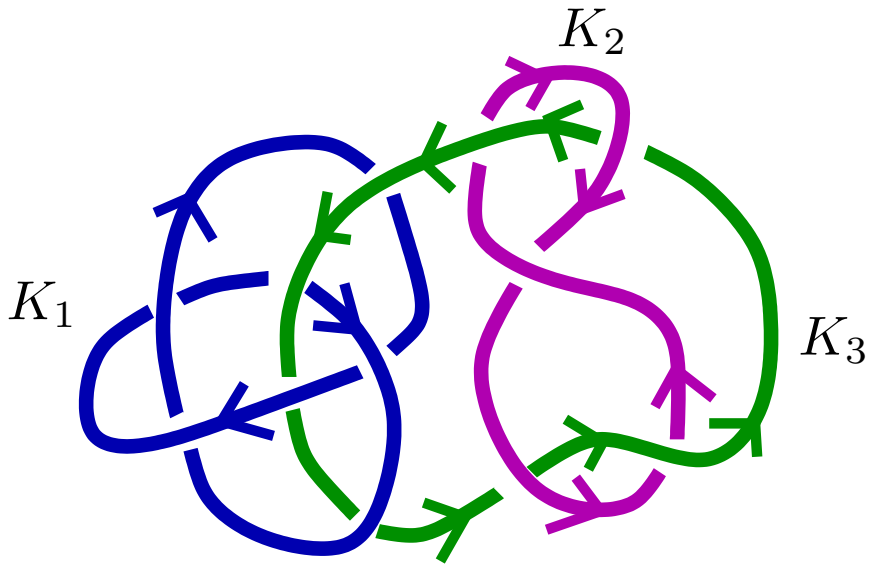
$$\mathrm{Lk}(K_i, K_j) = \frac{1}{2} \sum_{c \in \mathcal{C}(D_L)} \varepsilon(c) d(c),$$

where c is a crossing of D_L, $\varepsilon(c)$ is the sign ± 1 according to the diagrams shown below, also $d(x) = 1$ if the crossing c involving distinct components, otherwise 0.



$+1$ $\quad$ -1

Example of Linking number



$$L = \{K_1, K_2, K_3\}$$

The linking numbers

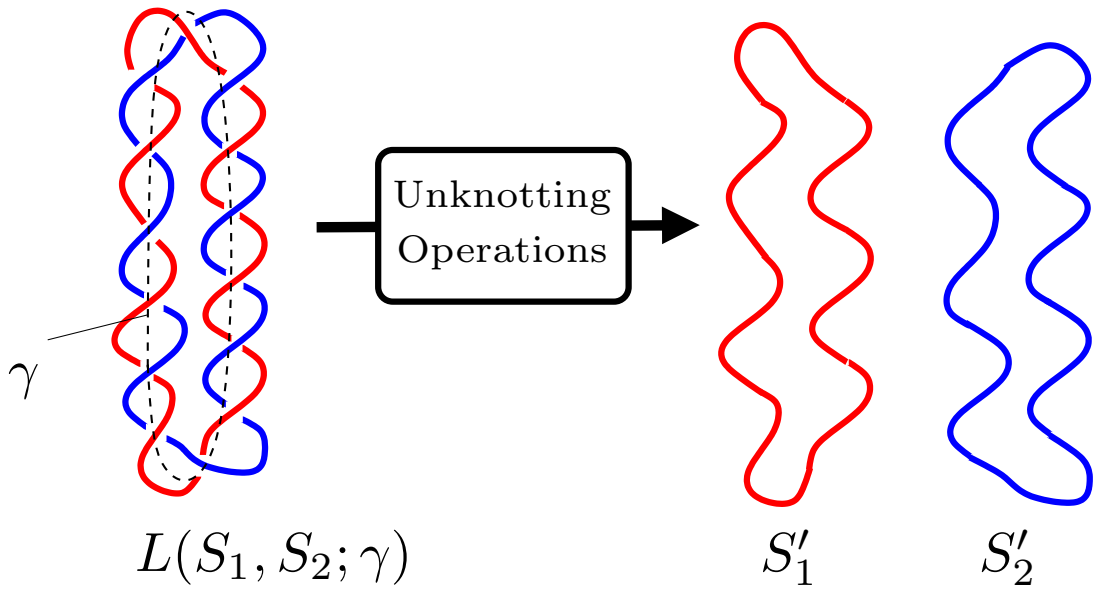
$$\mathrm{Lk}(K_1, K_3) = 2,$$
$$\mathrm{Lk}(K_2, K_3) = 0.$$

Topological Semi-conservative Scheme

The semi-conservative scheme (Topological version)

The semi-conservative scheme is interpreted as such: the DNA-link $L(S_1, S_2; \gamma)$ is deformed into a split link $\{S_1', S_2'\}$; that is,

$$\mathrm{Lk}(S_1', S_2') = 0$$



Possible Procedure

The authors proposed the following procedure to obtain zero linking number [MY22].

- S1 Unwind n full twists at a specified point of the DNA-link.
- S2 Crearte positive n crossings (supercoil) in front of each fork.
- S3 Apply the unknotting operations on the n crossings of the supercoil to obtain $-n$ crossings.
- S4 If the linkning number is not zero, then go back to S1.

We estimate the number of repetitions that is about 11.5 times if only type-II topoisomerases are used [MY22]. With applying type-I topoisomerase, it will be reduced to 1.3 times [MY20].

Theoretical conclusion 1

A combination of type-I and type-II topisomerases efficiently reduce the linknig number.

Similar results are confirmed
in [BDC$^+$07] [SFR06b][MHS$^+$18][SJKG11][HZL21]

Topological Problems

Topologists might have the following questions.

Topologists' Questions

1. Do enzymes know if the ds-DNA is knotted?
   Not likely. Knot Theory suggests that it is not easy to detect if a given entangled string is knotted or trivial.
2. Do enzymes know which crossings should be changed?
   Not likely. Knot Theory suggests that it is not known how a knotted circle is deformed into a trivial circle with only local information. Thus it is difficult to specify which crossing should be changed to make it trivial.

Theoretical Conclusion 2

It seems not possible to resolve the entangled DNA if the entangled DNA is non-trivially knotted or linked.

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Topological Principles

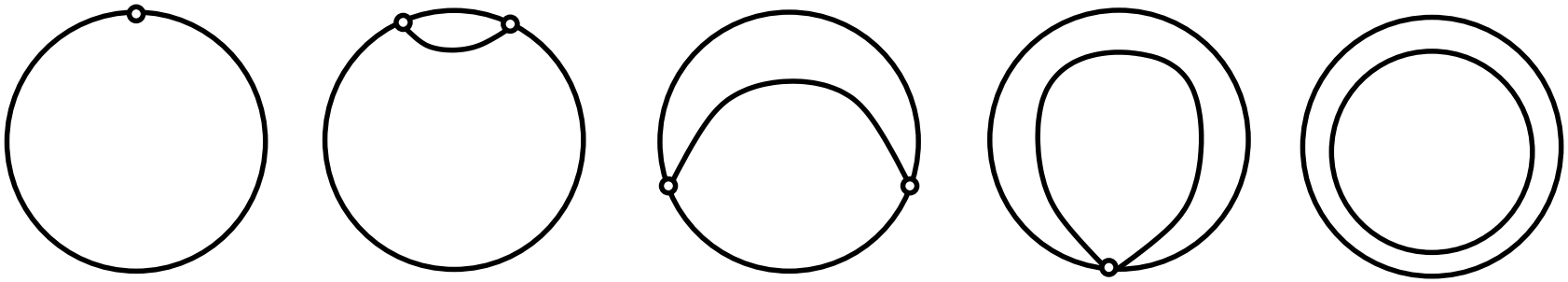
From the observation above, we would like to propose the following topological principles.

Topological Principles

- X1 Initially, the double strand DNA segments are not knotted (trivial), and not mutually linked to each other.
- X2 Any deformation on DNA preserves its triviality.
- X3 Any physical obstruction against the process will be removed.

Topological DNA replication

We model the replication process to fit the three principles. The the core curve γ is deformed into a θ-curve and then a pair of trivial circles.

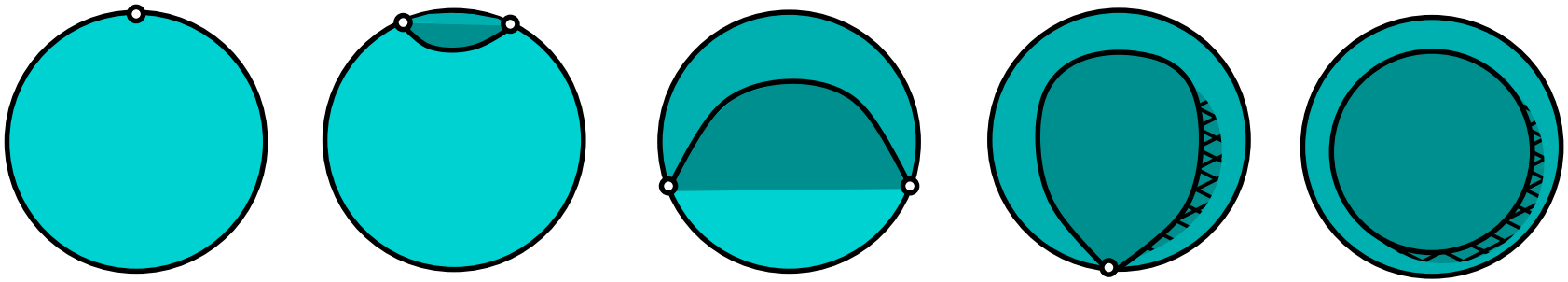


(a) (b) (c) (d) (e)

During the defromation, the triviality is kept.

Tri-disc model

The θ-curve in each stage of the deformation bounds a tri-disc so that the arc segment of the θ-curve is not knotted.

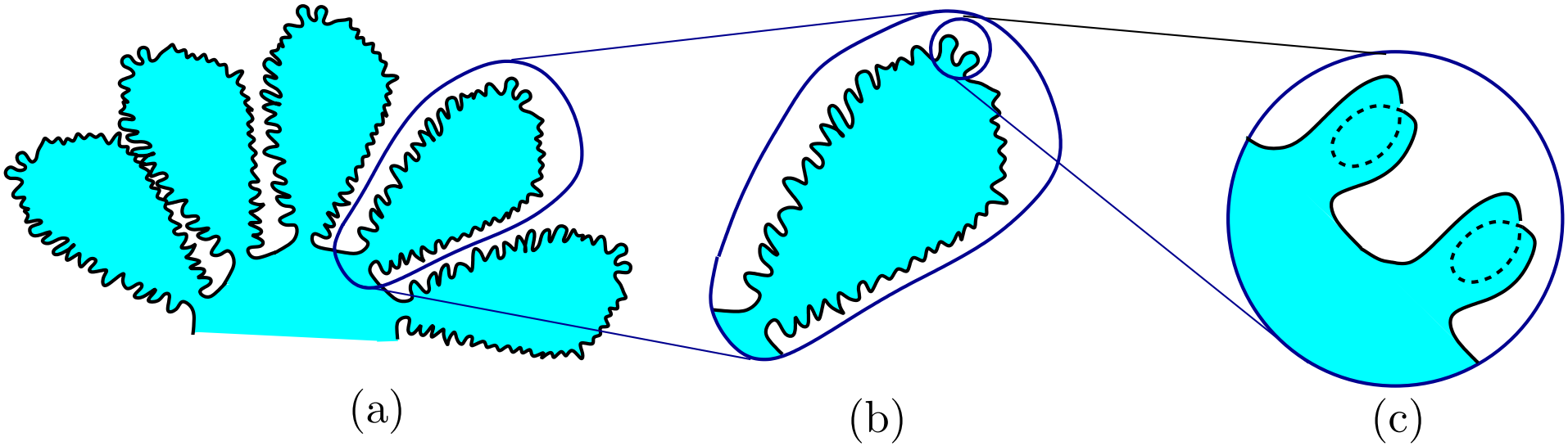


(a) (b) (c) (d) (e)

To keep the triviality, some structure support the DNA strings so that it keeps DNA trivial.

Topological scheme

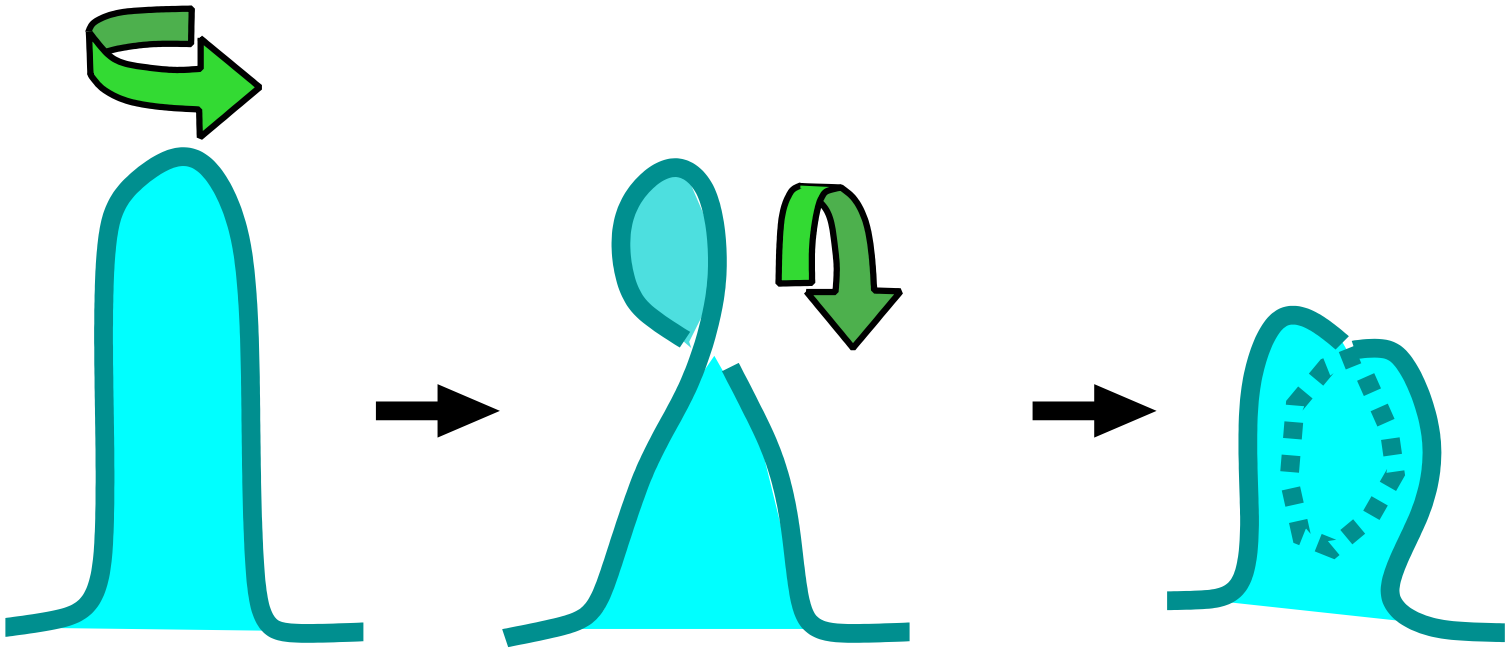
The DNA string forming a domain bounds a virtually embedded disc.



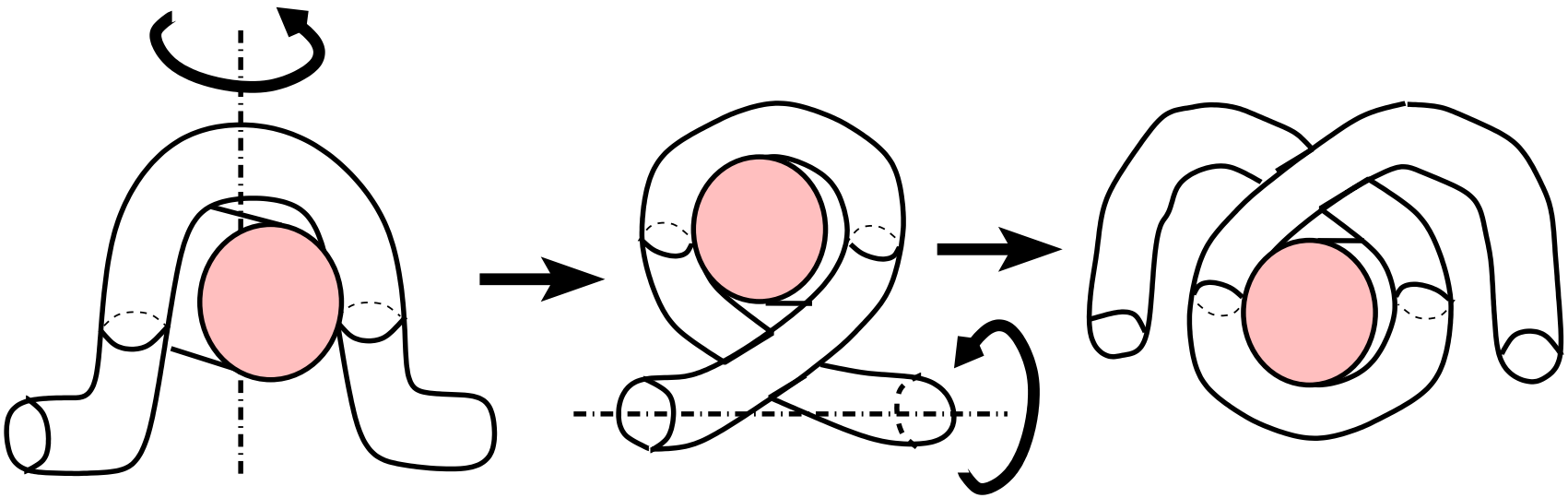
Extending the support to whole domain (groups of replicons).

Twisting Disc and Nucleosomes

The twisting disc deformation will create the nucleosome.



Twisting Disc and Nucleosomes

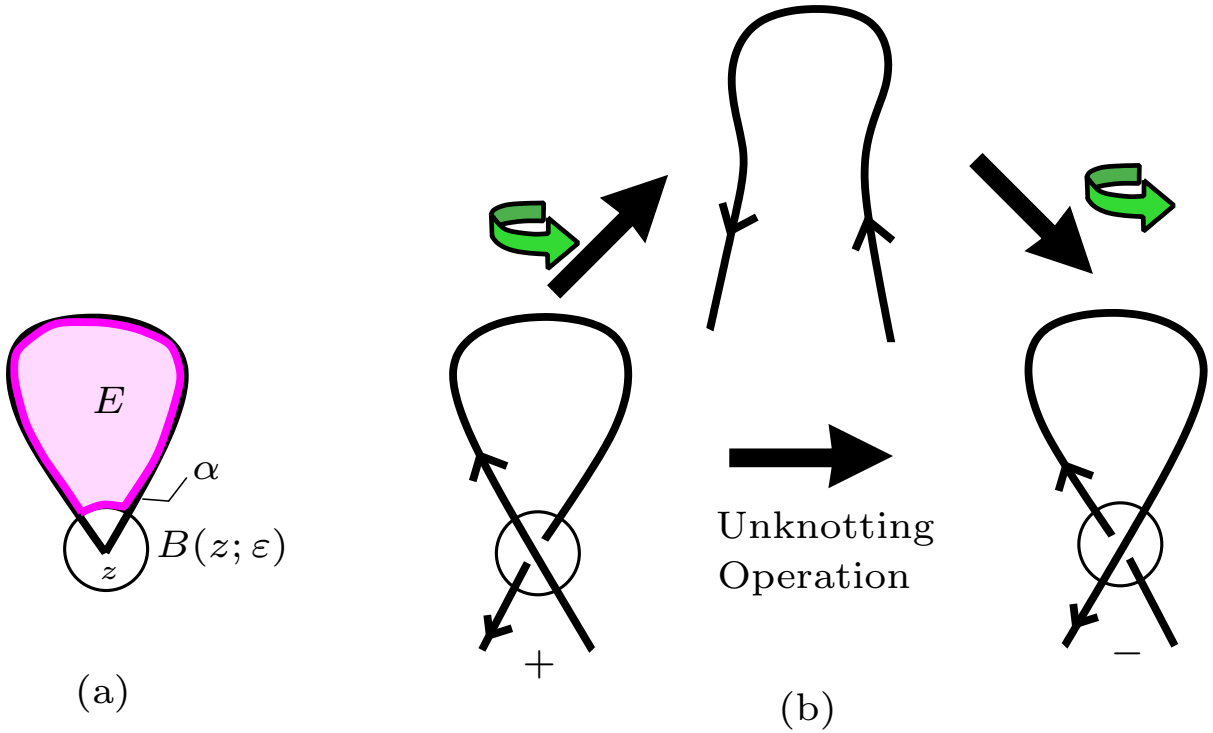


(a) (b) (c)

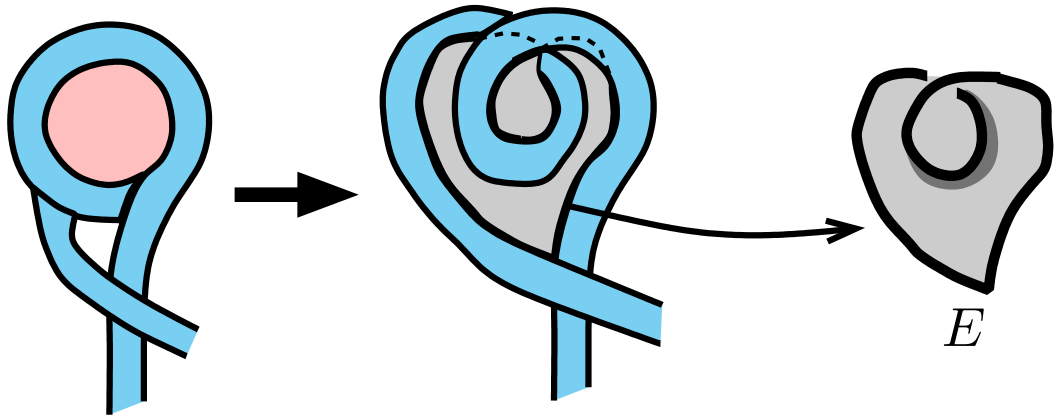
This construction gives the writhe -1.28 which is close to the writhe -1.26 obtained in [SJDI$^+$18].

Crossings of DNA

As far as the loop bounds an embedded disc, the unknotting operation does not affect the triviality of the loop.



This model is supported by the observation in [SFR06a].



The histone core plays a role of a virtually embedded disc bounded by the loop so that the unknotting operation does not change the link (knot) type of the DNA.

Topo II allocation

Under the topological scheme, as far as the crossing is created as a crossing of a simple loop bounding virtual disc, the unknotting operation keeps the core curve of DNA-link trivial. Unknotting operation near the nucleosome does keeps the triviality.

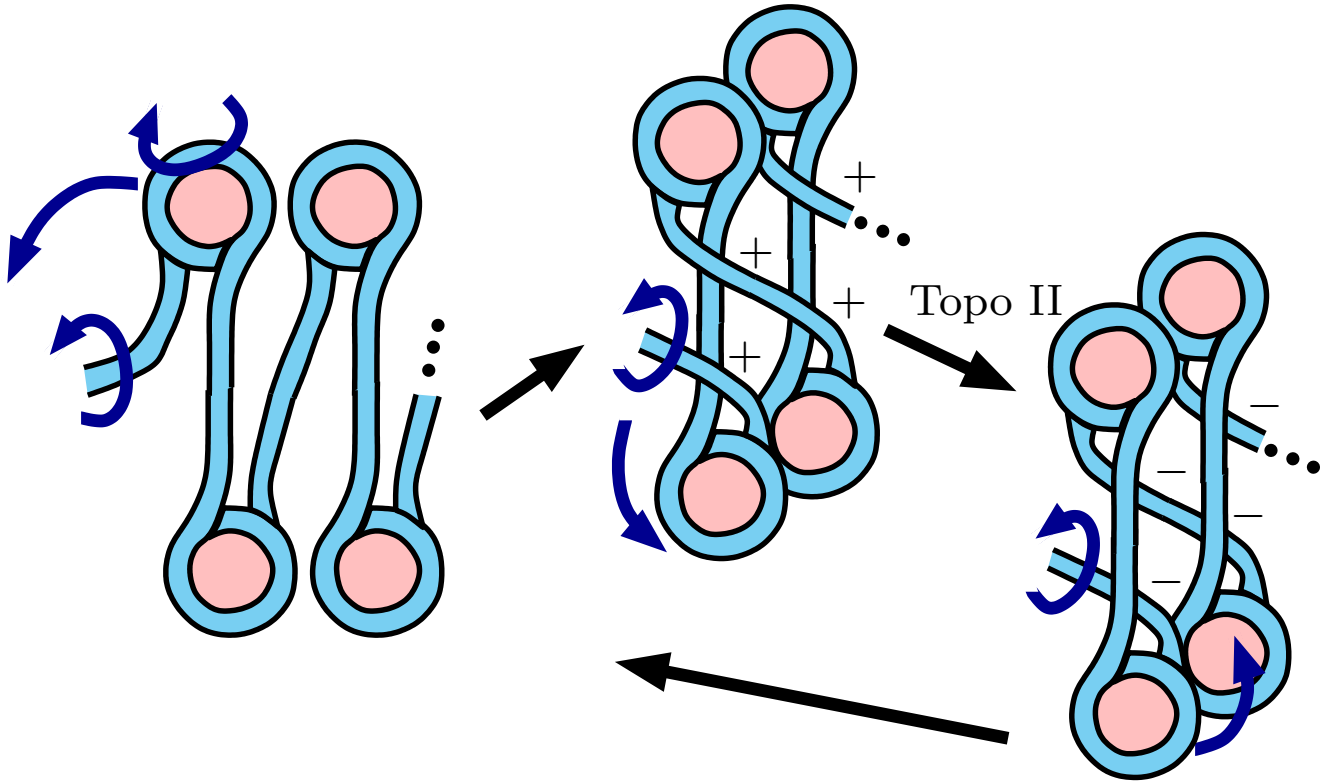


Figure 1: Unknotting operations near nucleosomes.

Conclusion and further study

We obtained the following conclusion.

Under the topological scheme

1. Enzymes do not have to detect the knottedness of DNA.
2. Enzymes can be allocated to right crossings.

The further investigation needs to be done on

1. supercoils behind the forks and reconstruction of nucleosomes,
2. time duration of the replication.

Possible application

For Anti-Cancer Medicines. Some anti-cancer medicines use prohibitor of type II topoisomerase.

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Thank You for listening!