

A Topological Model for Deformations of DNA

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The work

We started this work from 12 April 2012.



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- 1 Motivation and Target
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Motivation and Target

DNA ([Deoxyribonucleic acid](#)) has double helical backbones [WC53] with a sequence of base pairs lined up inside. In a eukaryotic cell cycle, DNA is replicated and each copy will be distributed to the nucleus of each of new cells. When DNA is synthesized, the backbones are separated and each string with bases acts as a template to produce the counterpart of bases.

Motivation

We topologists are interested in that the backbones are initially [linked](#), and during the separation process, the link is [split](#).

How can it be topologically done?

Knot Theory (topology) describes knotted or linked strings. Thus we would like to describe the biological process in terms of knot theory.

Motivation and Target

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

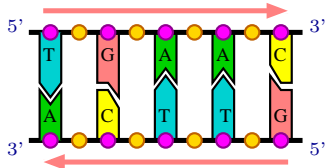
Biology		Knot Theory
DNA replicon	\longleftrightarrow	2-component link
Topoisomerases	\longleftrightarrow	Unknotting Operation
Semi-conservative replication	\longleftrightarrow	Splitting Link process
?	\longleftarrow	Topological Scheme

Target

To propose a topological scheme that governs the replication process in biology.

Structure of DNA

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



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

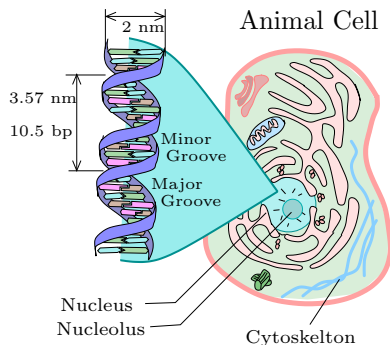


Figure 1: Animal cell

Size of DNA

DNA is a long molecule with diameter of 2 nm ($= 2 \times 10^{-9}\text{m}$). The total length of human DNA is about 2m. This thin and very long string is packed into the spherical cell nucleus whose diameter is about $6 \mu\text{m} = 6 \times 10^{-6}\text{m}$. The volume ratio of DNA and the nucleus is about 5.6%.

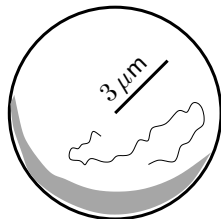
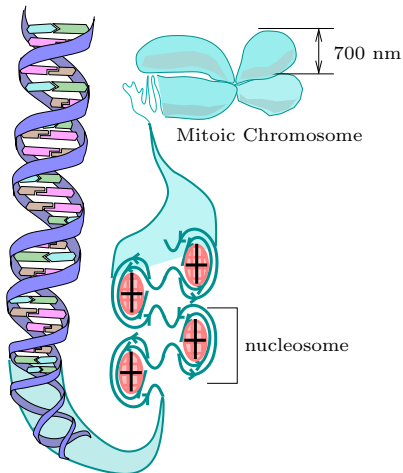


Figure 2: The nucleus and DNA

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].

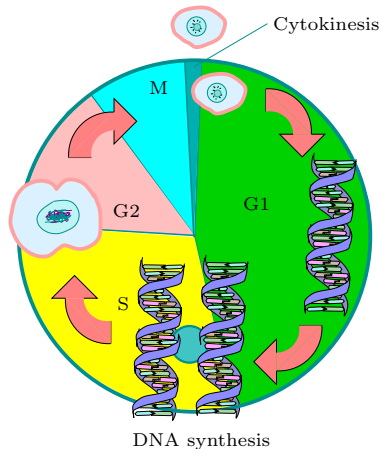


Cell Cycle

The eukaryotic cell cycle has two phases,

- Mitotic phase and
- Interphase
 - ▶ G1 phase
 - ▶ S phase
 - ▶ G2 phase

During the S phase, DNA is replicated.

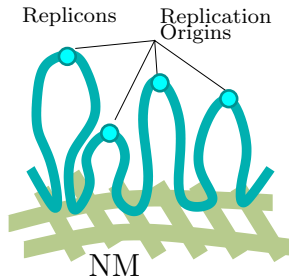


Replicons

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.

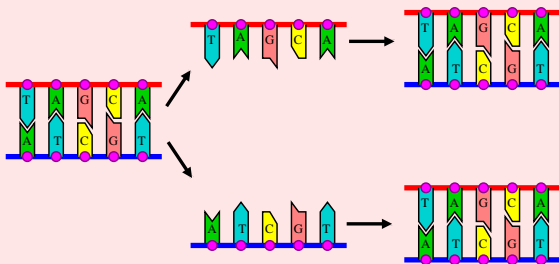


Semi-Conservative Replication

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

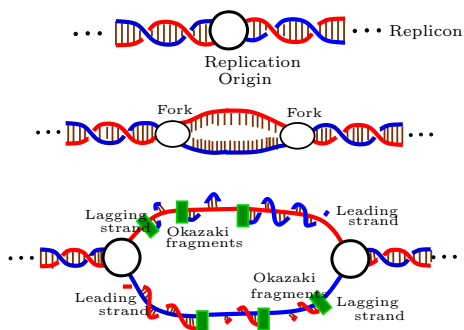
Semi-Conservative Scheme

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



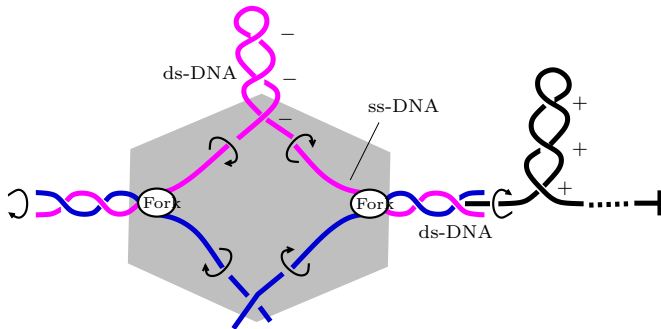
Replication Process

- 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 to produce some positive and negative **supercoils** ahead of and behind the fork respectively.

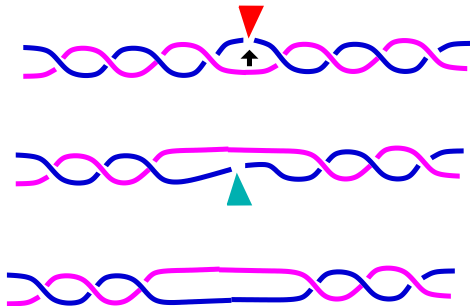


The supercoil becomes an obstruction against the replication process.

Type-IA topoisomerase

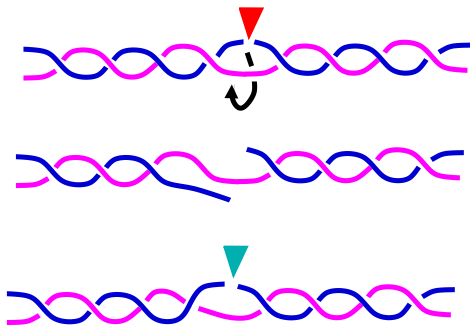
Type-I topoisomerase decreases the twisting number of ss-DNA.

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.



Type-IB Topoisomerase

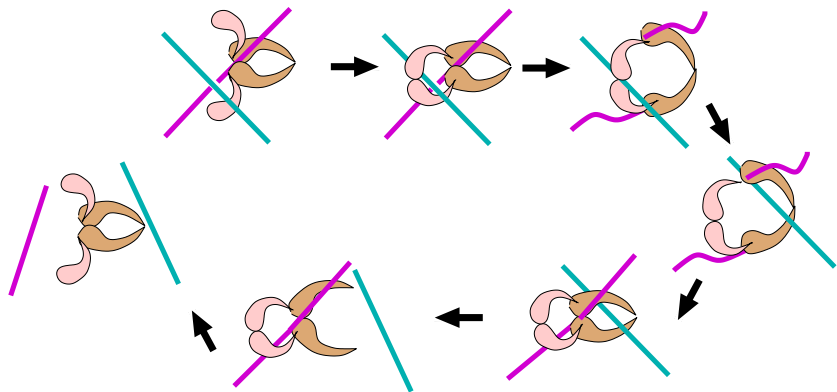
The type-IB topoisomerase nicks one single strand to make a pair of free ends and let one of the free ends rotate around the complete single strand.



Type-II topoisomerase

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 topoisomerases.

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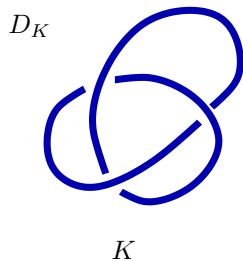
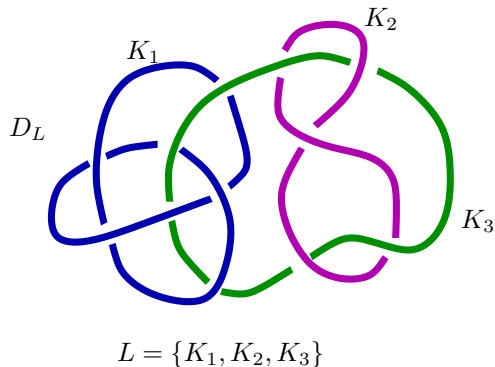
During the process of the DNA replication, if the ds-DNA is supercoiled or knotted, then topoisomerases make it simple.

Much work has been done to investigate how the enzymes solve the entanglement of DNA. **However, there still exist topological problems to be solved.**

Topological Viewpoint

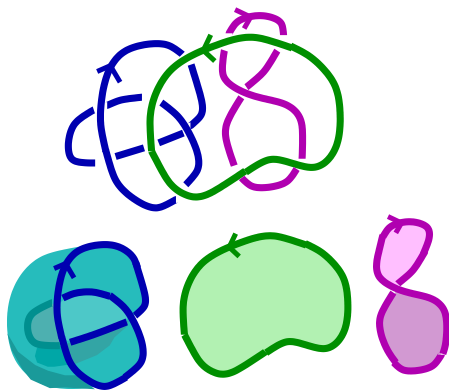
Knots and Links

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)



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.



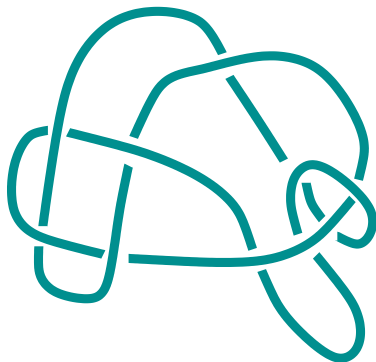
Trivial Knot is not always Simple



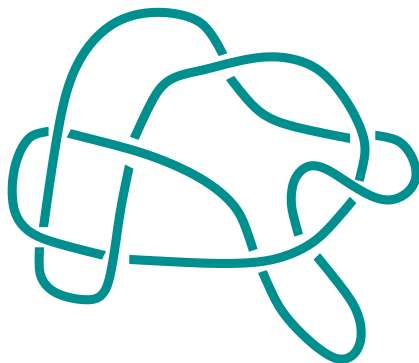
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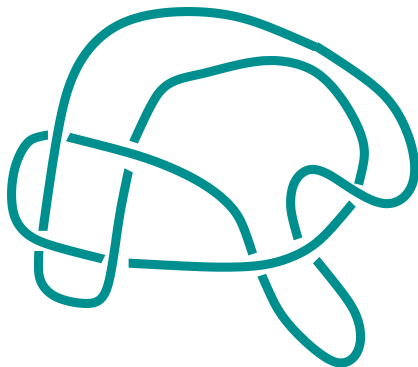
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Topological Model of DNA

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

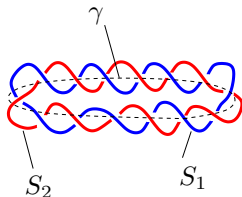
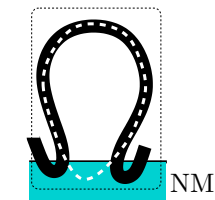


Topological orientation

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

Topological Model of Replicon

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**.



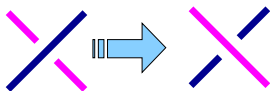
Topological Unknotting Operation

Topoisomerases

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

Unknotting Operation

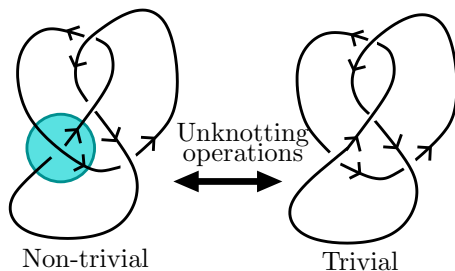
In topology, there is a corresponding operation called **unknotting operation** which exchanges the upper and lower arcs at a crossing.



Unknotting Theorem

Theorem 3.1

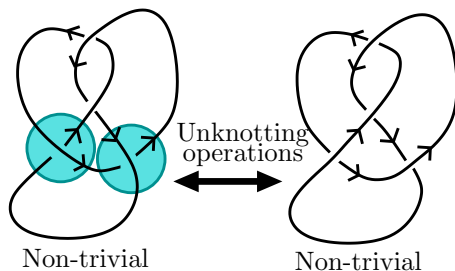
For a link L , every link diagram D_L , it can be deformed into a trivial link by applying a finite number of unknotting operations.



Unknotting Theorem

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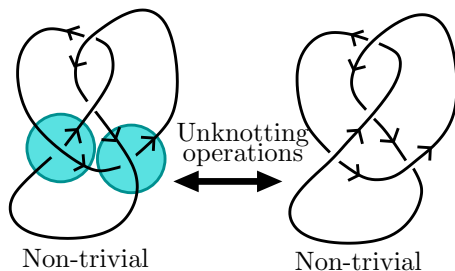
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Note:

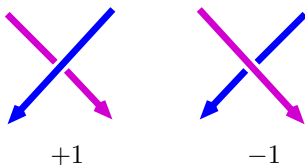
Randomly applying unknotting operations to a non-trivial knot does not work. We have to specify appropriate places where the unknotting operations are applied so that the non-trivial knot can be deformed into a trivial knot.

Linking number

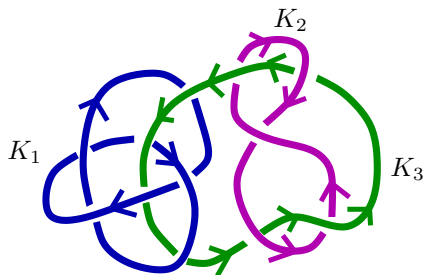
Let L be an oriented link and let D_L be its link diagram. Then the linking number is defined by the formula:

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

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



Example of Linking number



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

The linking numbers

$$\text{Lk}(K_1, K_3) = 2,$$

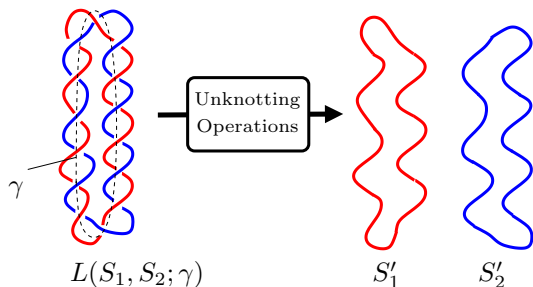
$$\text{Lk}(K_2, K_3) = 0.$$

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,

$$\text{Lk}(S'_1, S'_2) = 0$$



Linking Number Reduction Procedure

Topologically, to make the linked circles split, the linking number of ss-DNA is needed to be zero. To do so, we need to apply **unknotting operations**.

The authors proposed in [MY22] the **Linking Number Reduction Procedure** to obtain the linking number **zero**.

Linking Number Reduction Procedure

LNR Procedure

- S1 Unwind n full twists at a specified point of the DNA-link.
- S2 Create 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 linking number is not zero, then go back to S1.

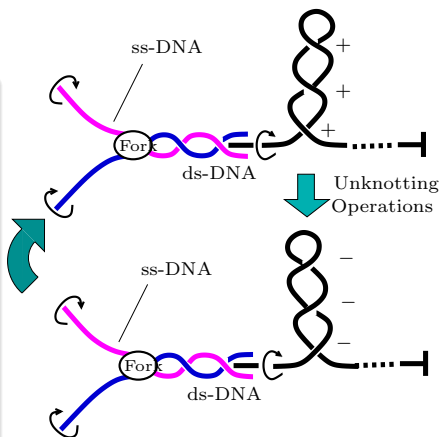


Figure 3: The Linking Number Reduction Procedure

Linking Number Reduction Procedure

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

Theoretical conclusion 1

A combination of type-I and type-II topoisomerases efficiently reduces the linking number.

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

Topological Problems

Topologists might have the following questions.

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Not likely. It is not easy to detect if a given entangled string is knotted or trivial.
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- ① Do enzymes detect if the ds-DNA is knotted?

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Not likely. It is not known how a knotted circle is deformed into a trivial circle from only local information. Thus it is difficult for enzymes to specify which crossing should be changed.

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Topologists' Questions

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Not likely. It is not easy to detect if a given entangled string is knotted or trivial.

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Theoretical Conclusion 2

It seems impossible to resolve the entangled DNA if it is a non-trivial knot or link.

Topological Principles

From the observation above, we can assume that the core curves of ds-DNA are trivial and not linked to each other.

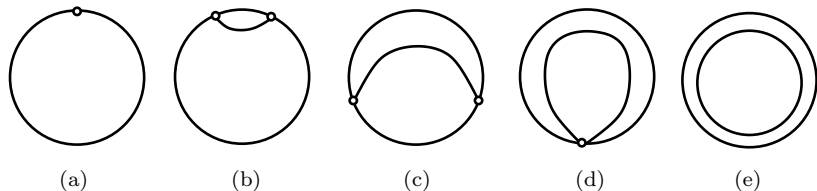
We propose the following principles.

Topological Principles

- X1 Each of the core curves of a set of DNA-links is trivial, and they are not mutually linked to each other.
- X2 Any deformation on a DNA-link preserves its triviality.
- X3 Any physical obstruction against the process will be removed.

Topological model for DNA replication

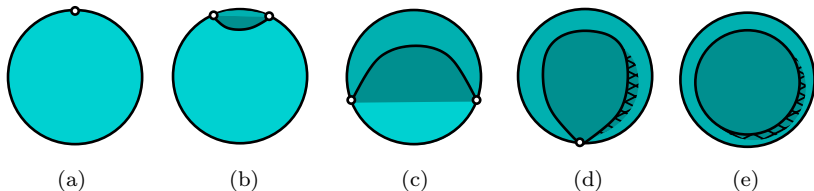
We model the replication process to fit the three principles. The the core curve γ is deformed into a θ -curve and then a pair of trivial circles.



During the defromation, the triviality is kept.

Tri-disc model

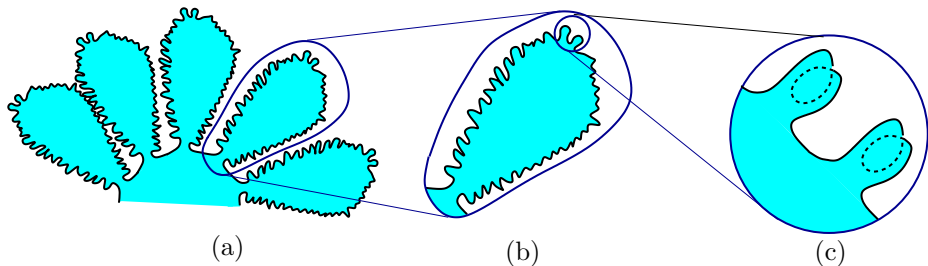
The θ -curve in each stage of the deformation bounds a tri-disc so that the arc segment of the θ -curve is not knotted.



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.



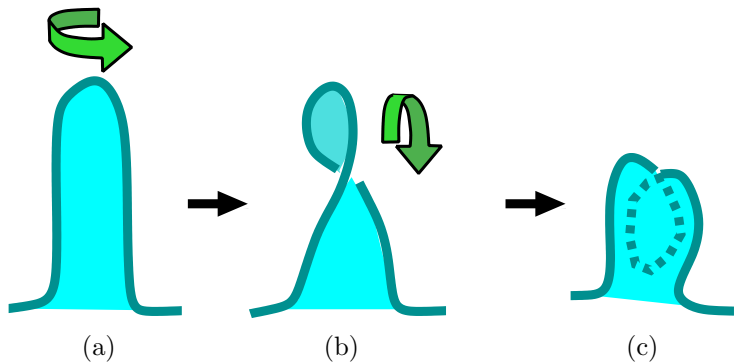
Extending the support to whole domain (groups of replicons).

Note:

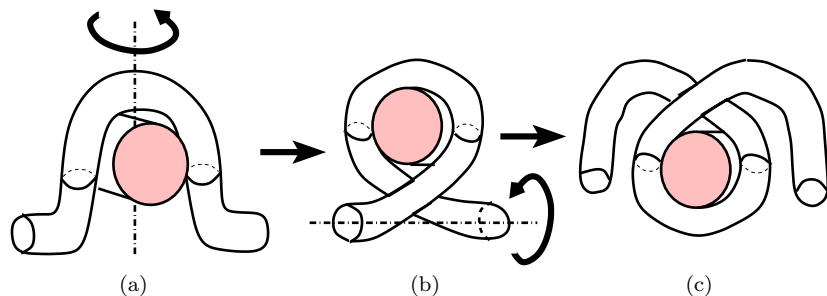
We do not claim that a real disc exists in the nucleus but some kind of supporting structure exists.

Twisting Disc and Nucleosomes

The twisting disc deformation will create the nucleosome.



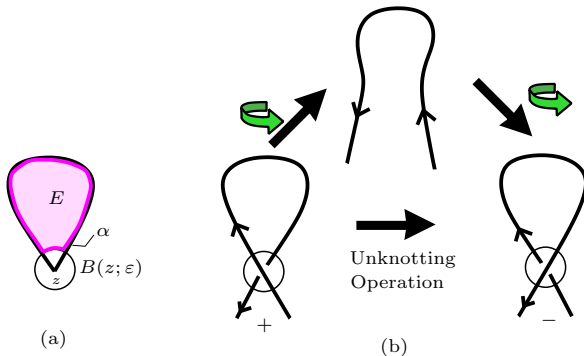
Twisting Disc and Nucleosomes



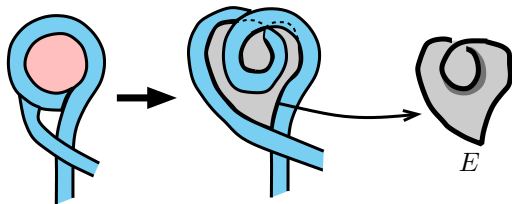
This construction gives the writhe -1.28 which is close to the writhe -1.26 obtained in [SJDJ⁺18].

Crossings of DNA

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



Similar model is considered 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.

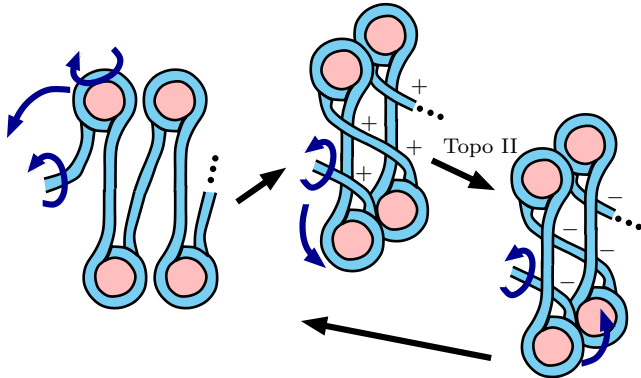


Figure 3: Unknotting operations near nucleosomes.

Conclusion and further study

Under the topological scheme

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

Further investigation needs to be done on

- 1 supercoils behind the forks and reconstruction of nucleosomes,
- 2 the existence of supporting structure of DNA in nucleus, and
- 3 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!