A topological model of splitting double strand DNA

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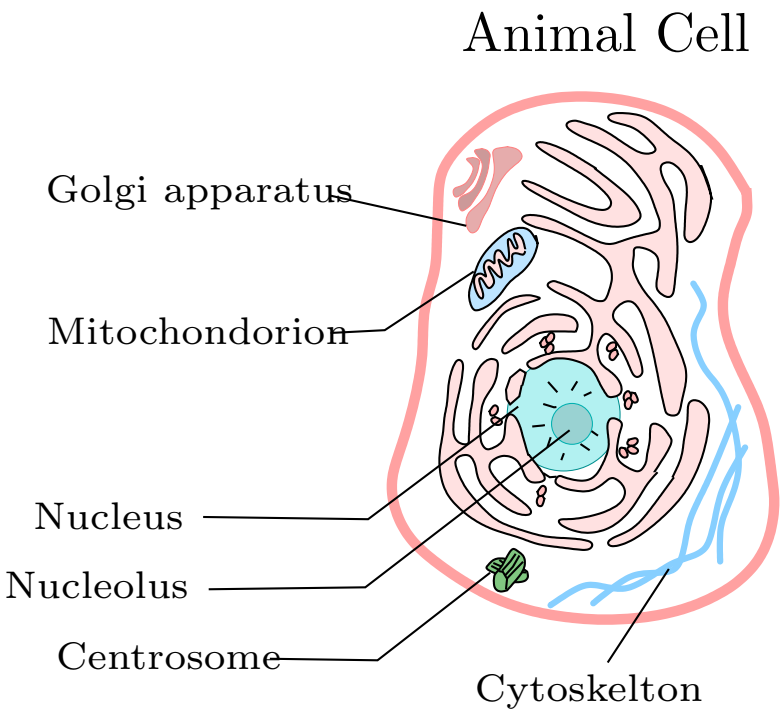
25 January 2021

Contents

Animal Cells

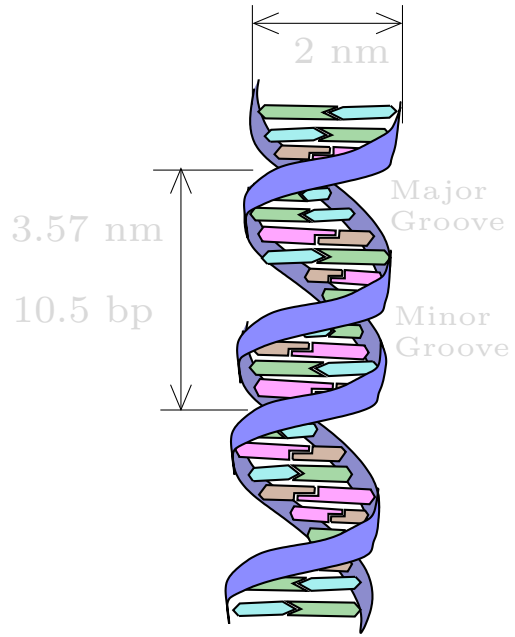


Animal cells are shown as the left figure. The nucleus contains most of genetic information stored in DNA (deoxyribonucleic acid).

Basic structure of DNA

DNA has:

- a right-handed double helix,
- sugar-phosphoate backbones on the outside and base pairs lined up on the inside.
- antiparallel orientation, and
- major/minor grooves.



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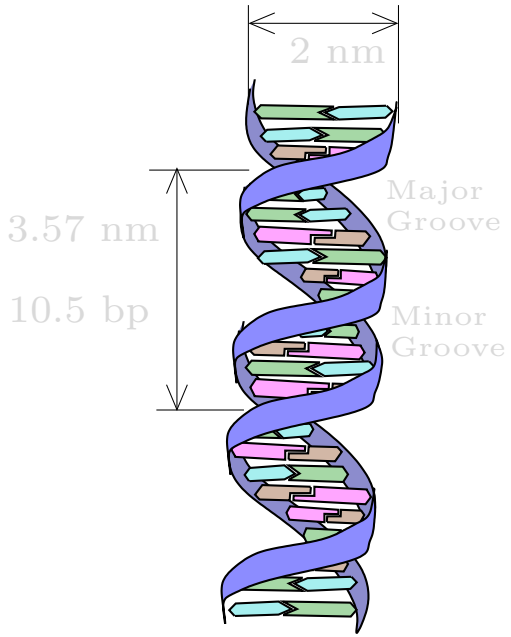

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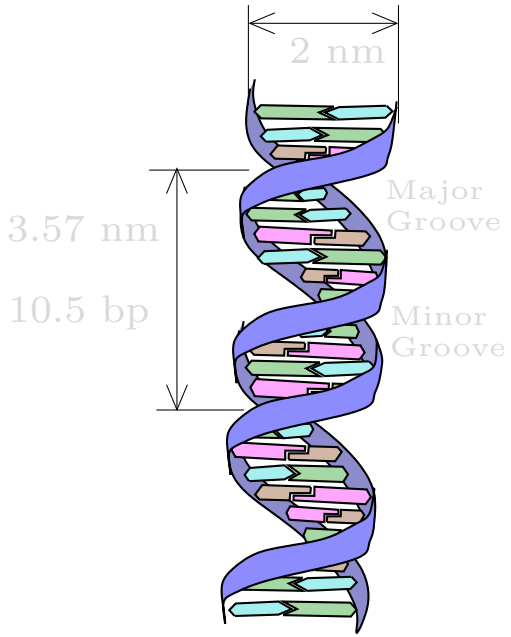

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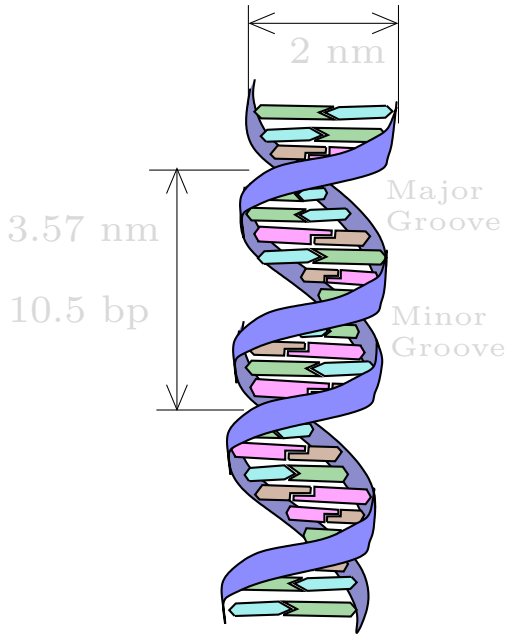

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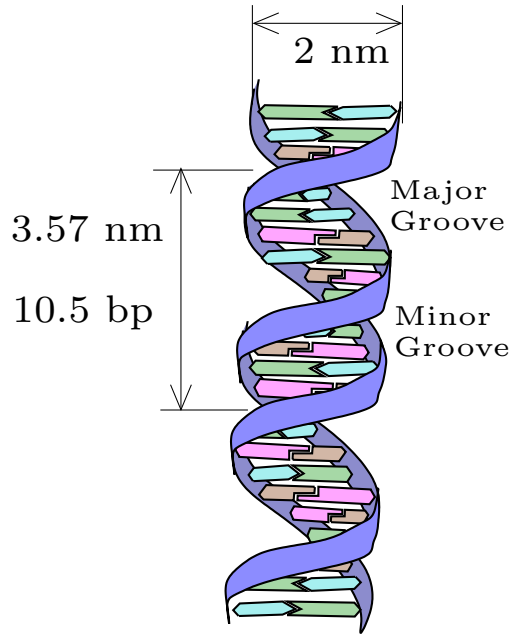

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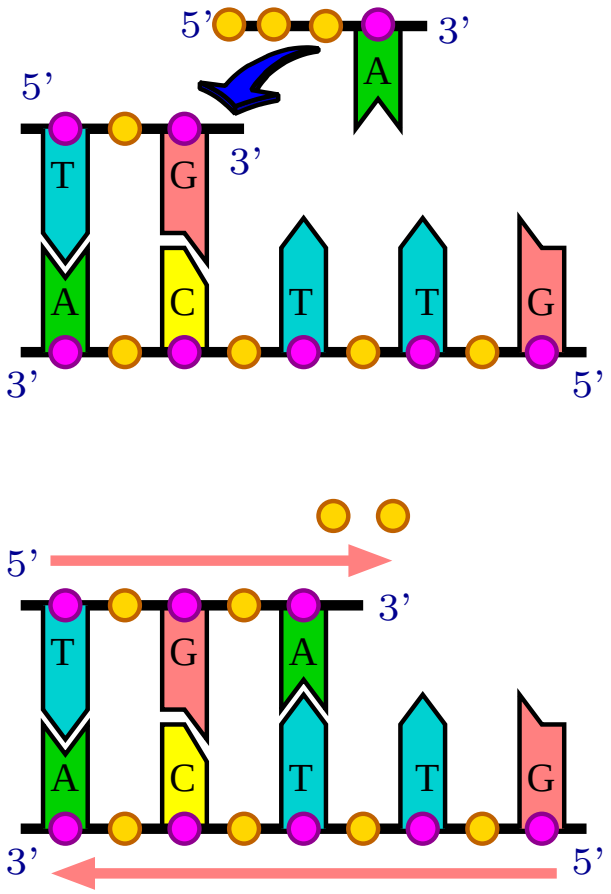
Base Pairs of DNA

DNA has two linear backbones alternating sugar and phosphorus.

A = Adenine, – T = Thymine,
C = Cytosine, – G = Guanine.

A sequence of bases along one backbone becomes a **template** to construct the DNA.



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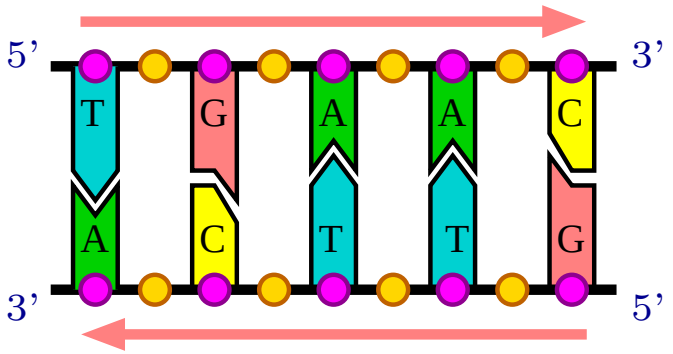
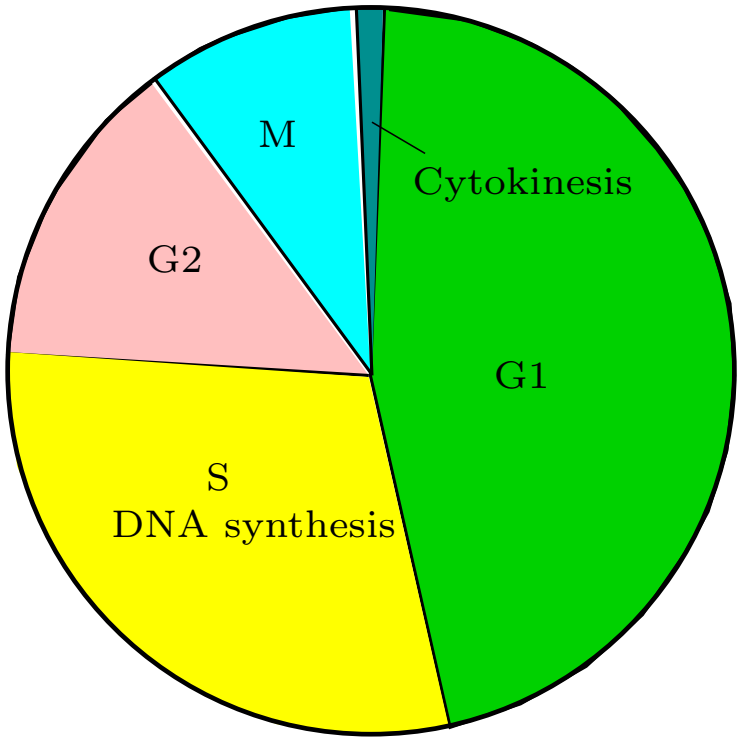


Topological Orientation

We assume that the DNA has a parallel orientation.

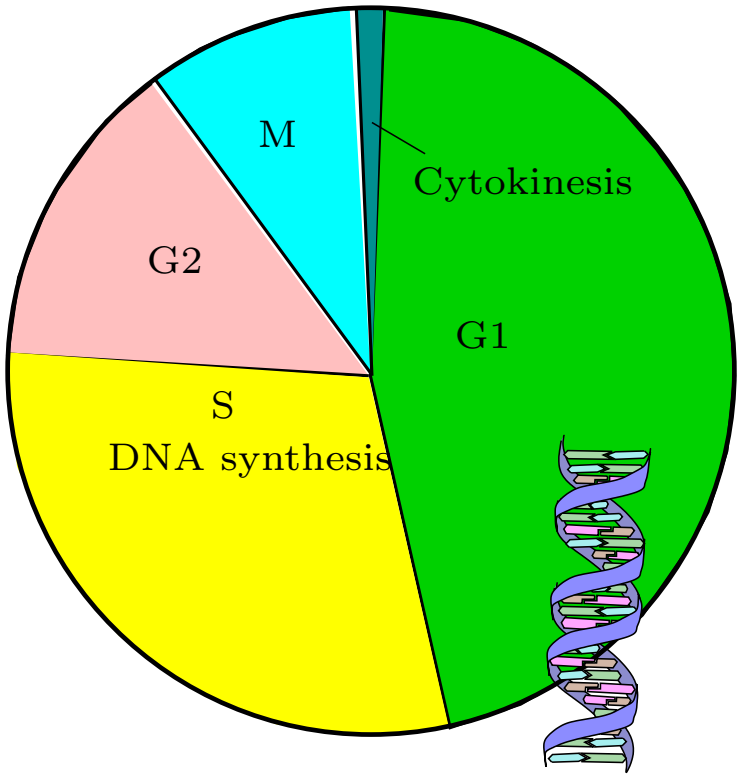
Cell Cycle



The eukaryotic cell cycle has two phases,

- Mitosis/cytokinesis and interphase, and also,
- During the interphase, DNA is replicated.

Cell Cycle



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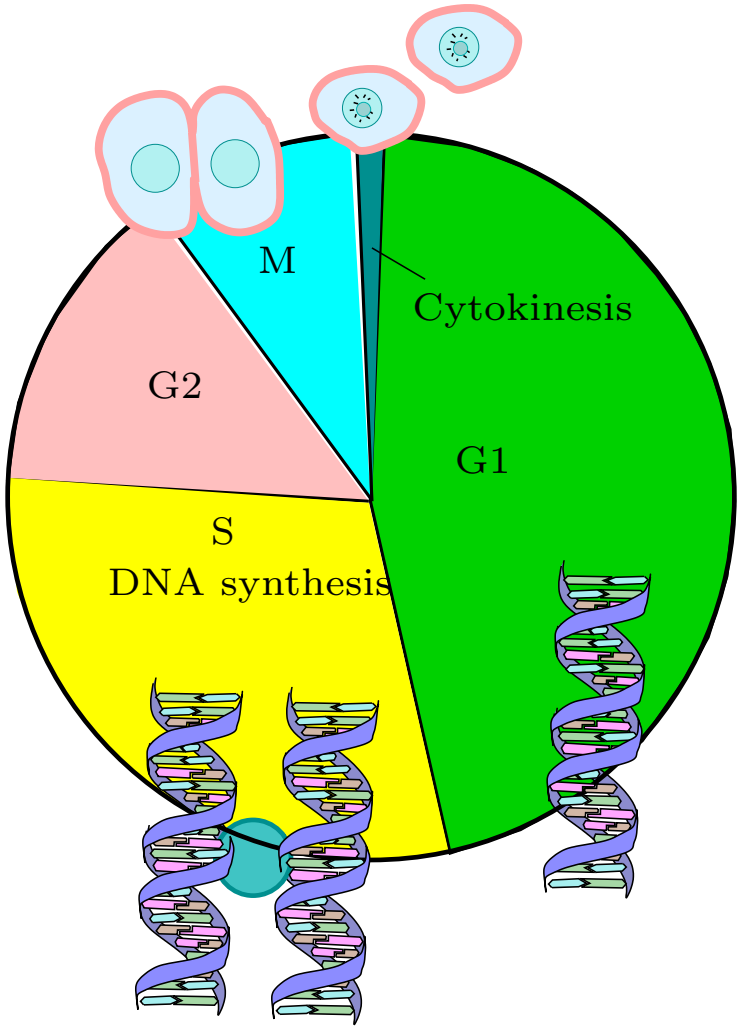

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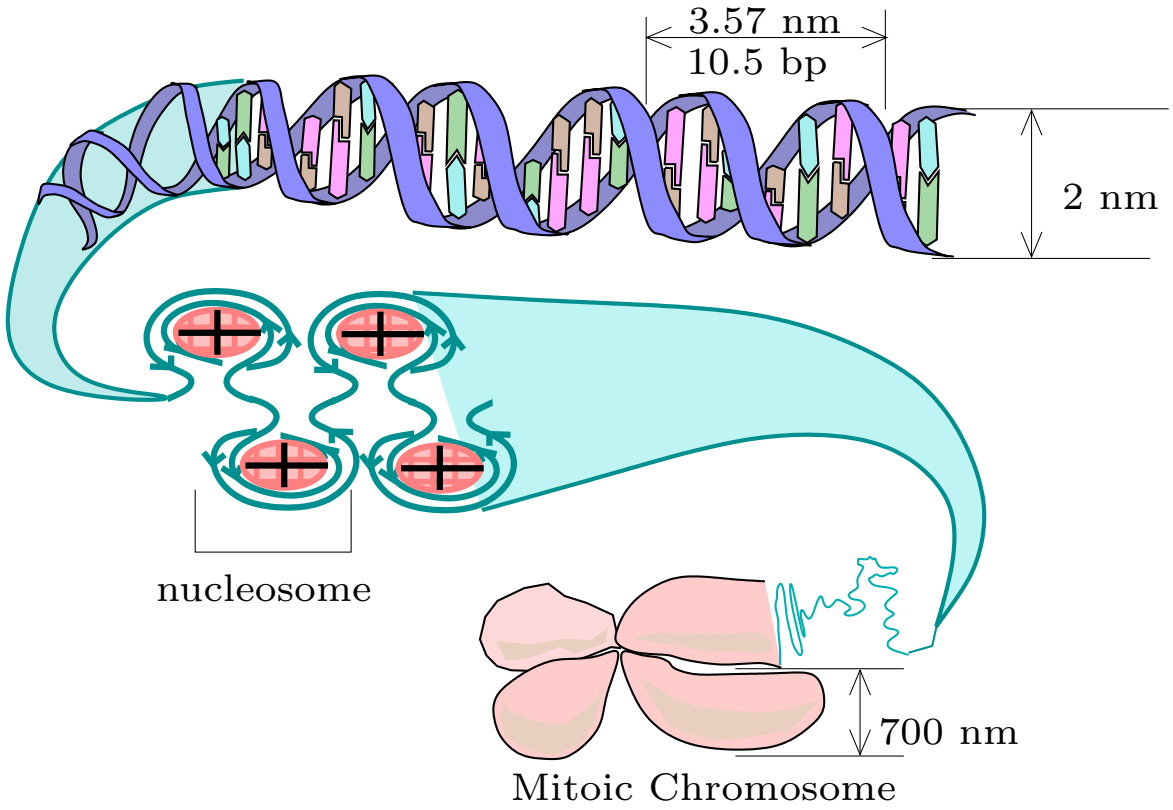
Chromosomes

The ds-DNA forms a winding structure around histones to make a beads structure.

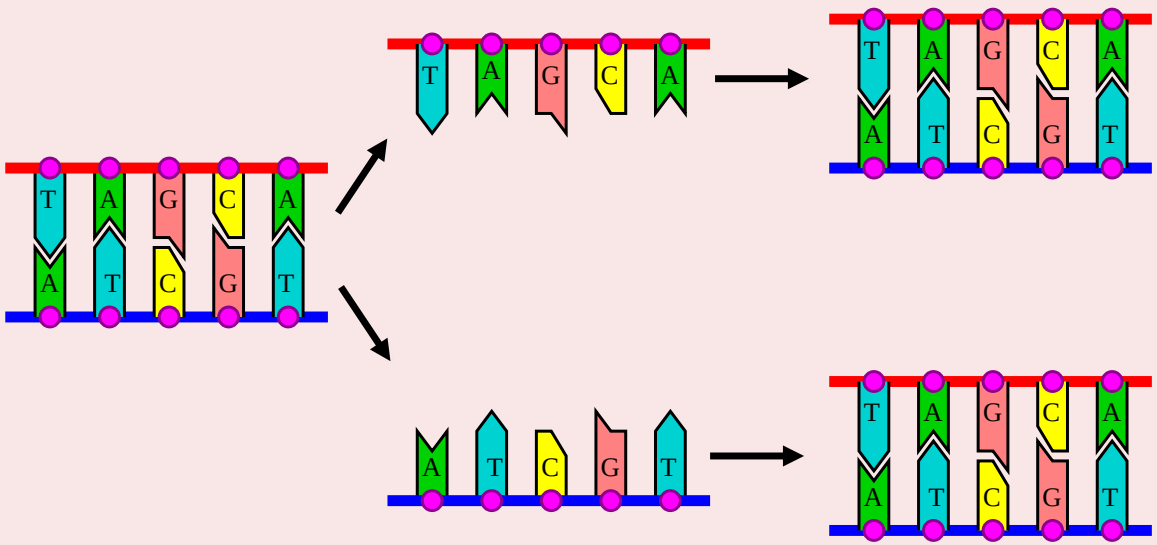


Semi-Conservative Scheme

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

Semi-Conservative Scheme

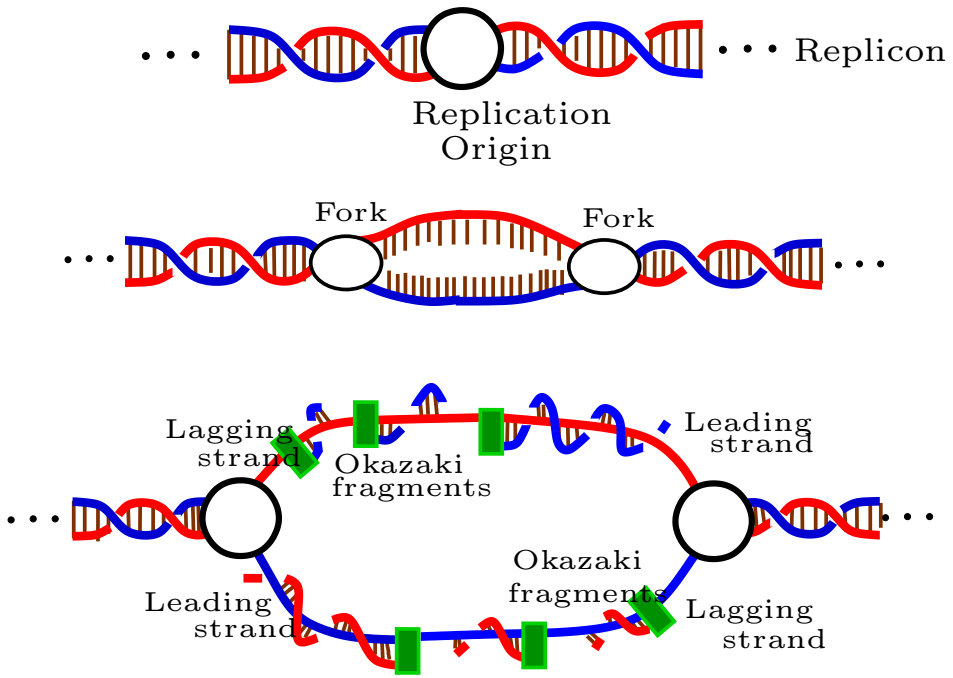
The sequence of bases along each backbone is preserved in copied DNA.



Replicons

The replication is done on each looped segment called a **replicon**.

1. The ds-DNA is relaxed and split into two ss-DNAs at the origin.
2. New nucleotids and double helix are created.

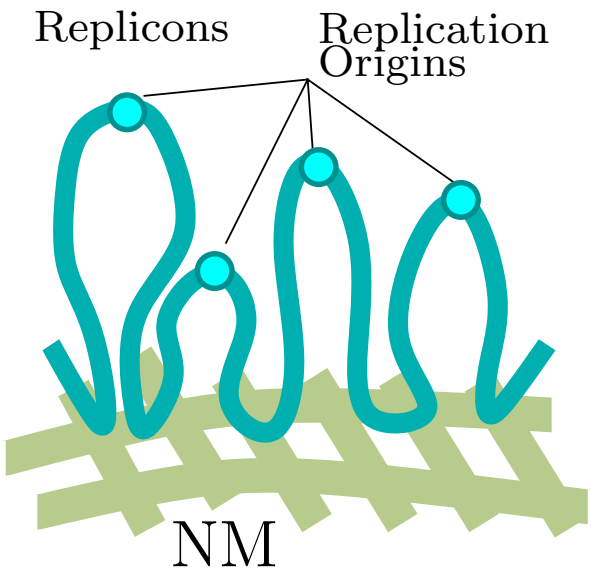


Replicons

It is believed that the ends of segments of DNA are anchored at the **nuclear matrix (NM)** to form loops, called **replicon**.

The size of replicon

If the diameter of DNA is $2\ \mathrm{cm}$, then the length of a replicon is about $17\ \mathrm{m}$

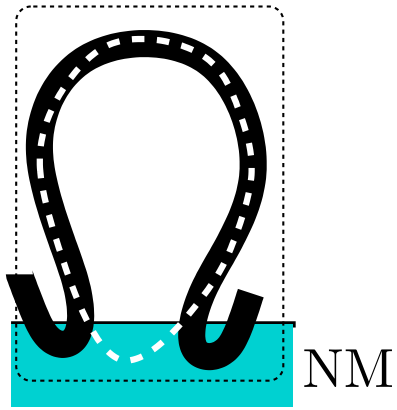


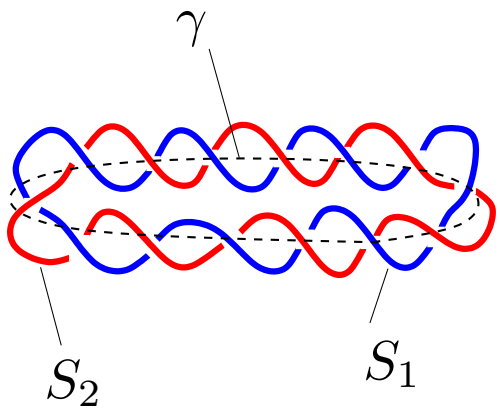
DNA-link

Topologically, it is viewed as a special 2-component link. Its components S_1 and S_2 correspond to backbones of DNA and the centre curve is denoted by γ.

$$L(S_1, S_2; \gamma)$$

We call this link a **DNA-link**.

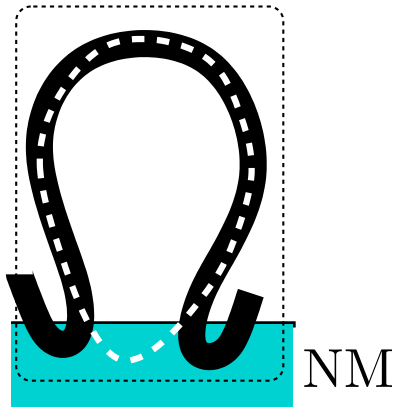


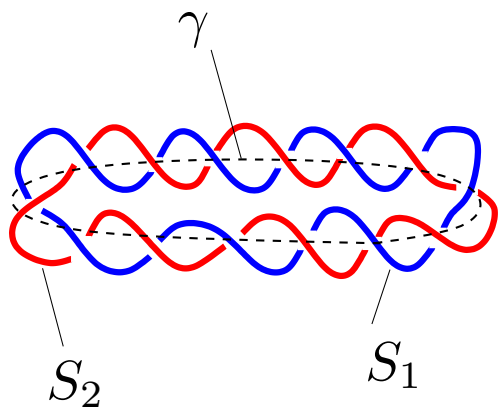


DNA-link

The DNA-link $L(S_1, S_2; \gamma)$ has the following properties.

1. L is a 2-component link.
2. γ is a trivial knot.
3. S_1 and S_2 form a double helix along γ.





Linking Number Formula for DNA

It is known that the following formula holds:

Proposition 3.1 (White)

[1] *For a DNA-link* $L(S_1, S_2; \gamma)$,

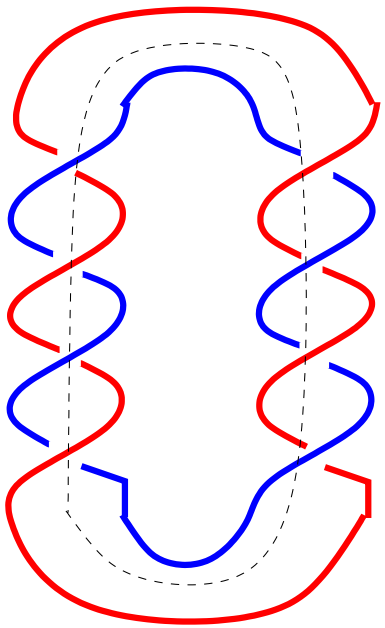
$$Lk(L) = Lk(S_1, S_2) = Tw(S_1, S_2) + Wr(\gamma)$$

Corollary 3.1

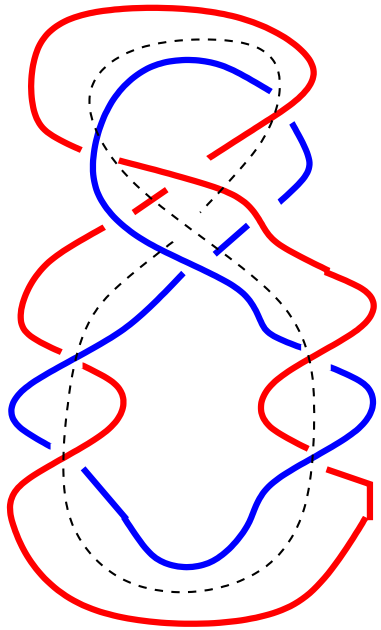
For $L(S_1, S_2; \gamma)$, $Lk(L) = 0$ *if and only if* L *is split.*

[1] J. H. White,Self-linking and Gauss integral in higher dimensions, Amer. J. of Math.,(1969), 693-728

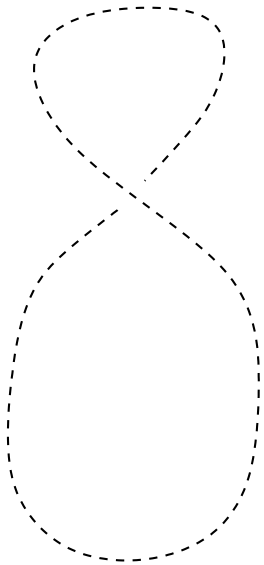
Linking Number Formula for DNA



$\mathrm{Lk} = 4$
$\mathrm{Tw} = 4, \ \mathrm{Wr} = 0$



$\mathrm{Tw} = 3$



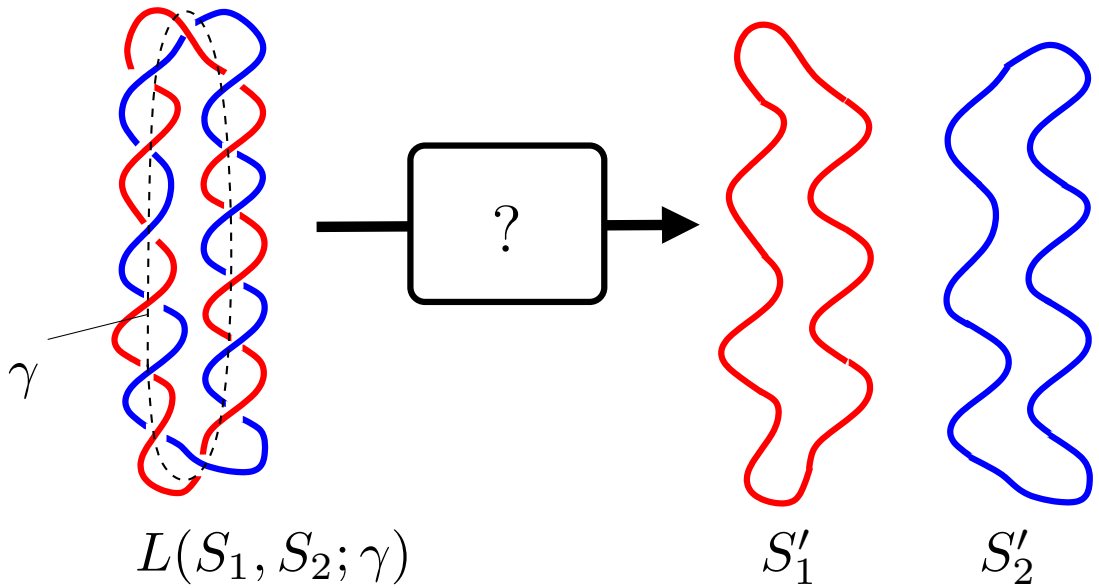
$\mathrm{Wr} = 1$

Actual linking number for a replicon is about $10,000$.

Topological Semi-conservative scheme

The semi-conservative scheme (Topological version)

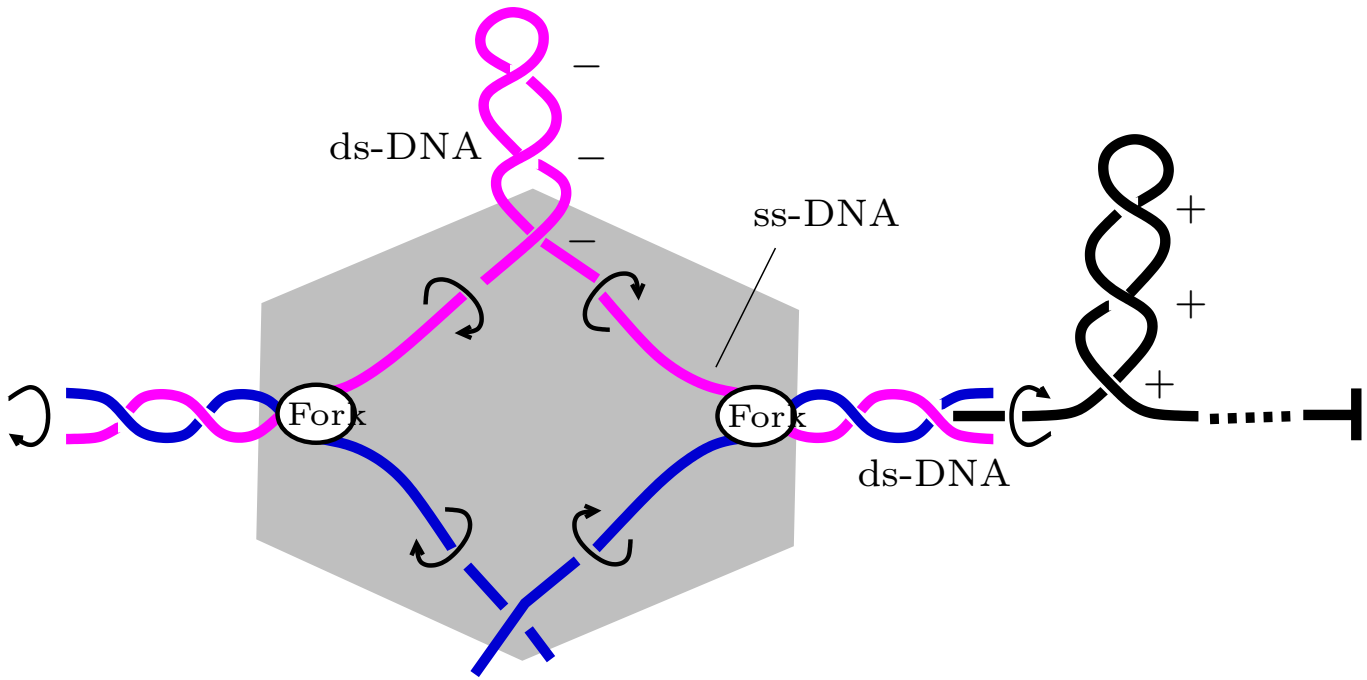
During the DNA replication process, the DNA-link $L(S_1, S_2; \gamma)$ is deformed into a split link $\{S_1', S_2'\}$.



There must be some unknotting operations between the original DNA and the synthesised DNAs.

Problem?

As the forks move away from the replication origin, both single strand DNA (ss-DNA) and ds-DNA are rotated and some supercoils are introduced.

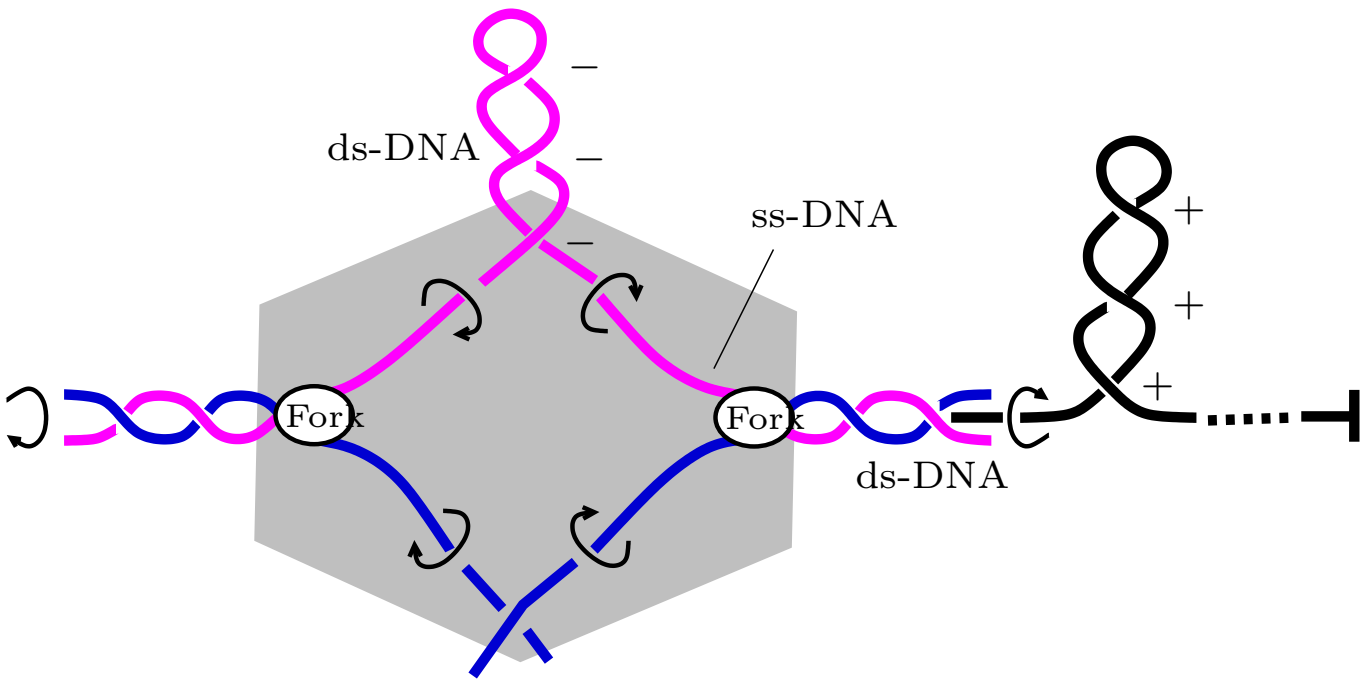


The supercoil becomes an obstruction.

Problem?

At the fork, n full-twist are unwound, then the supercoil ahead of the fork introduces $+n$ writhe.

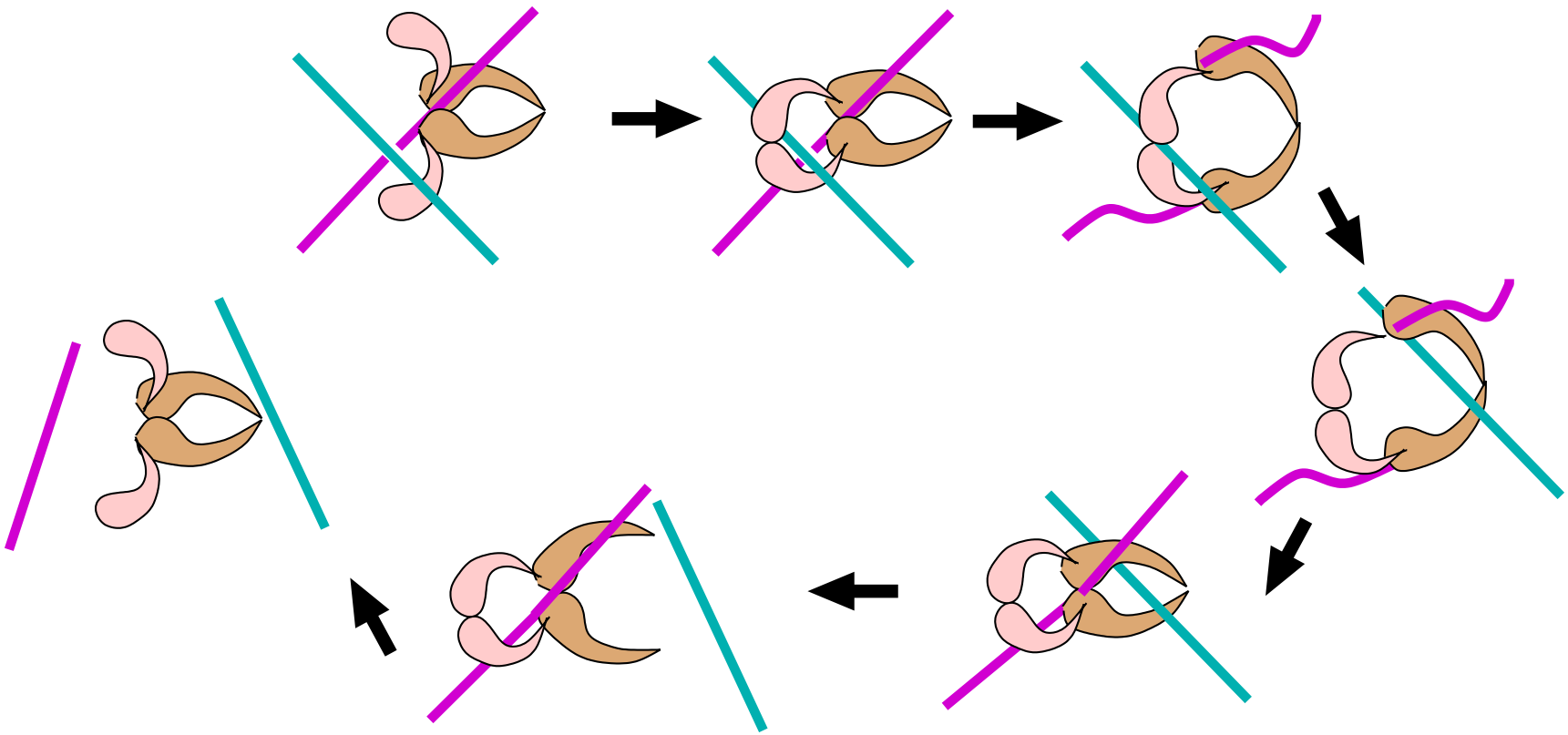
$$\Delta \mathrm{Tw} = -n, \qquad \Delta \mathrm{Wr} = +n$$



The supercoil becomes an obstruction.

Biological Unknotting Operations

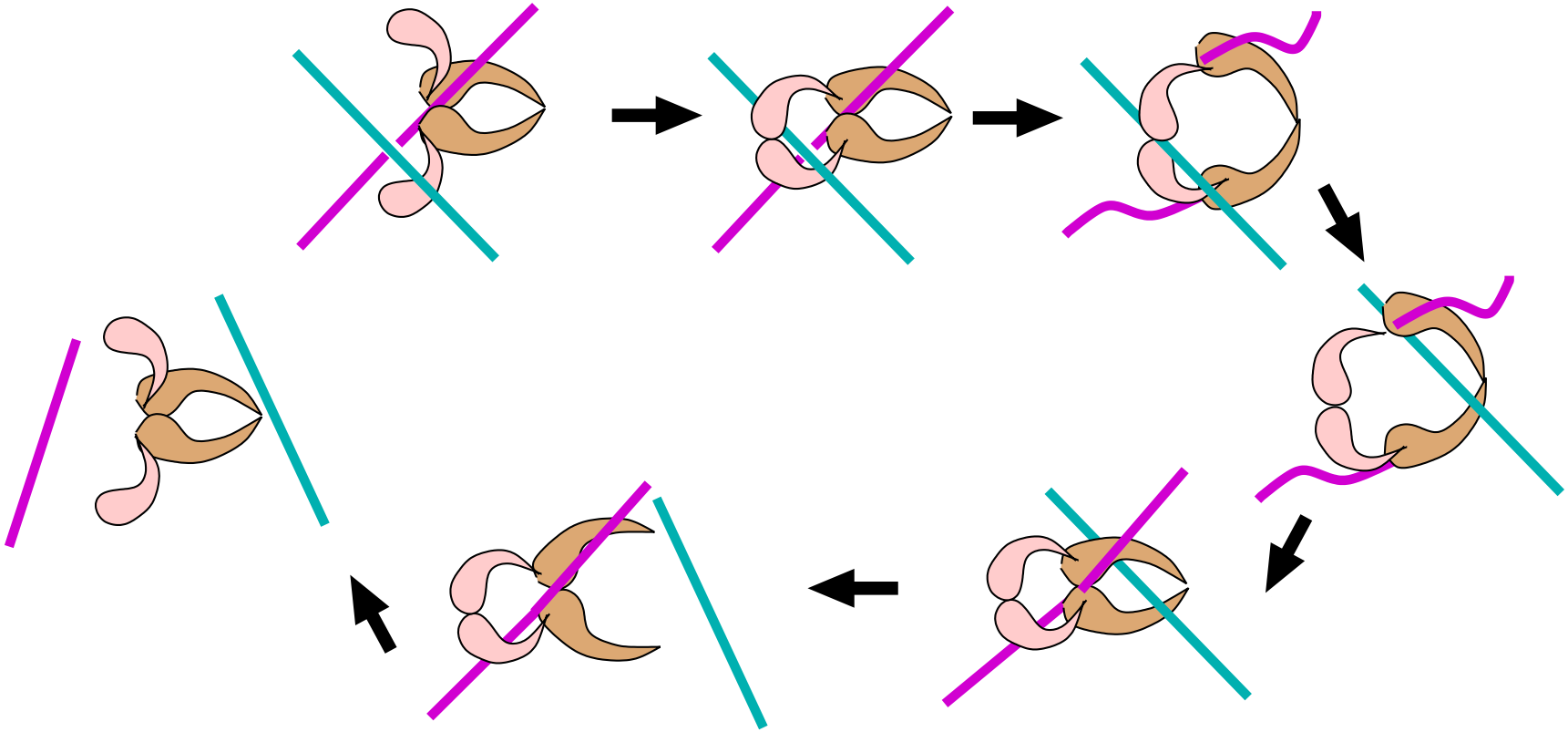
It is known that **Topoisomerase IA** and **II** change the crossings.



The red and bule strings must be very close to each other.

Biological Unknotting Operations

This operation is called an **unknotting operation**. We call it U-operation.



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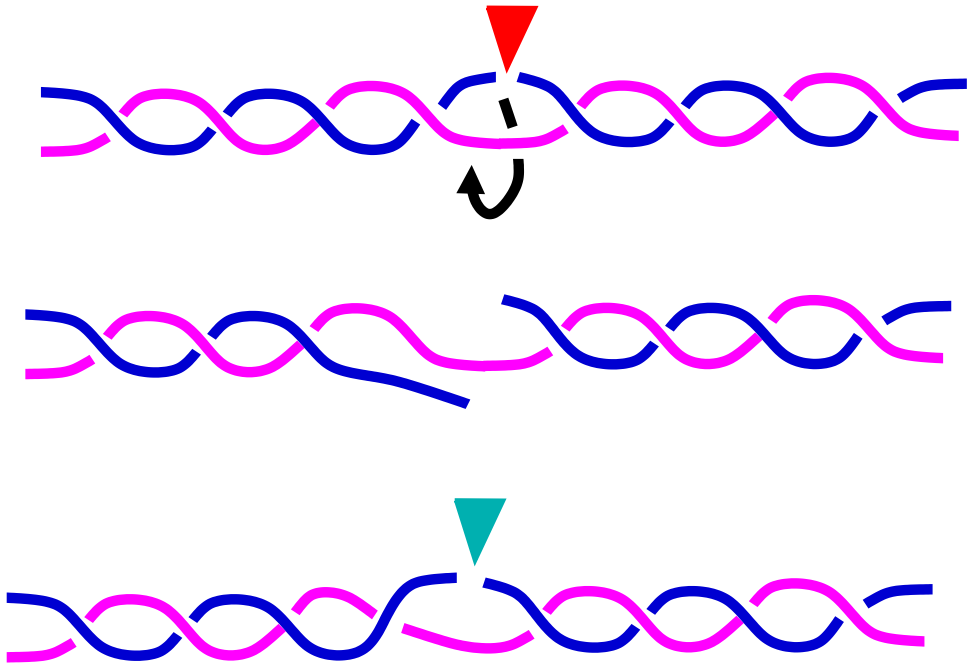
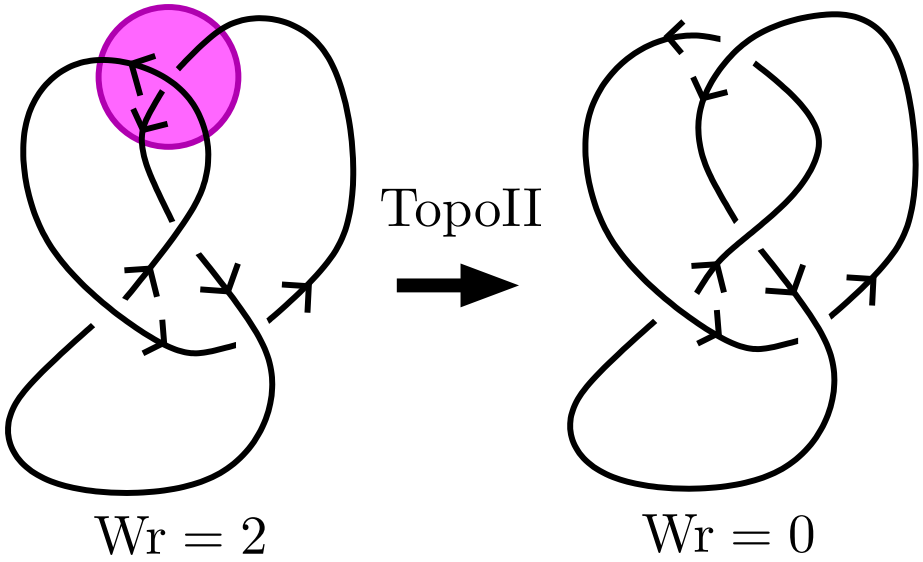
Biological Unknotting Operations

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



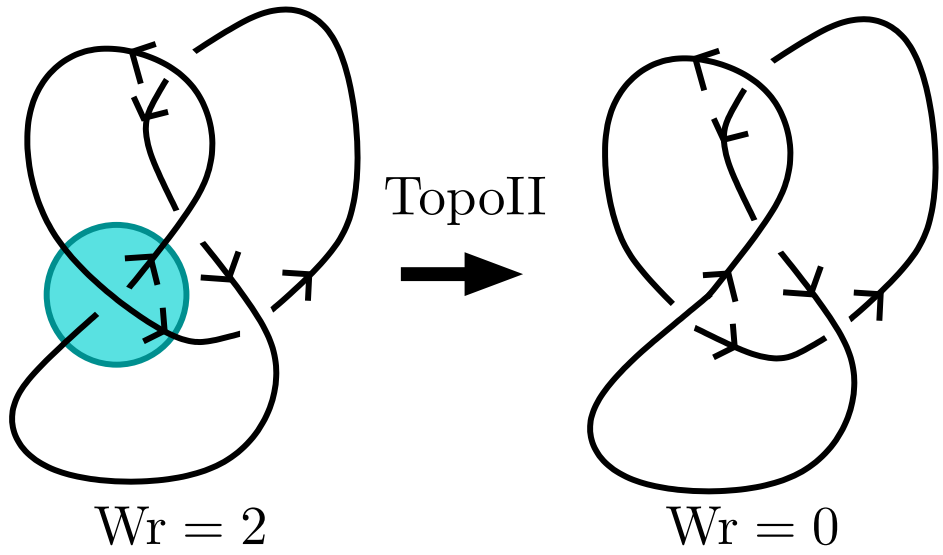
Still Problem?

We cannot activate TopoII at randomly chosen crossings. For example, one crossing change may give a non-trivial knot.



Still Problem?

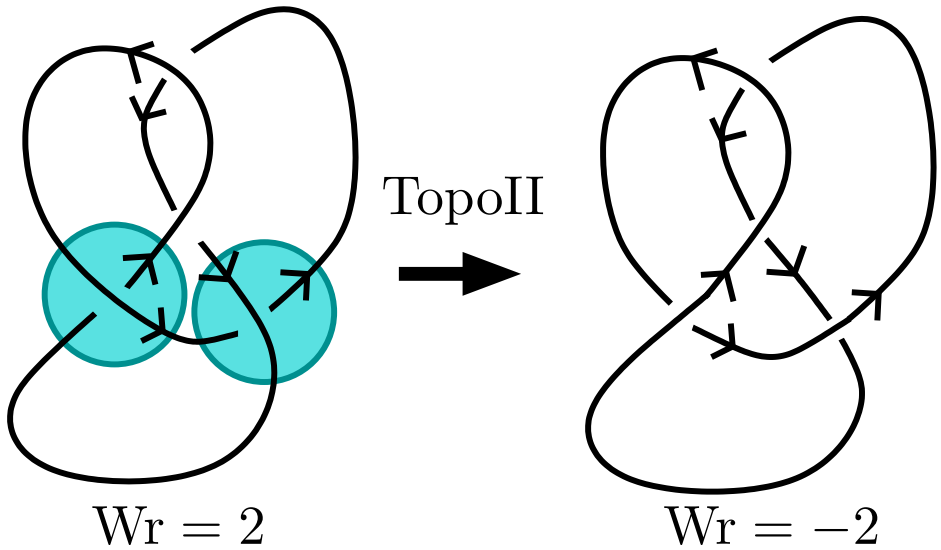
While changing another crossing reduces the writhe Wr and preserves the triviality of γ. Therefore, there must be a certain order of activations of enzymes to obtain relaxed DNA.



Still Problem?

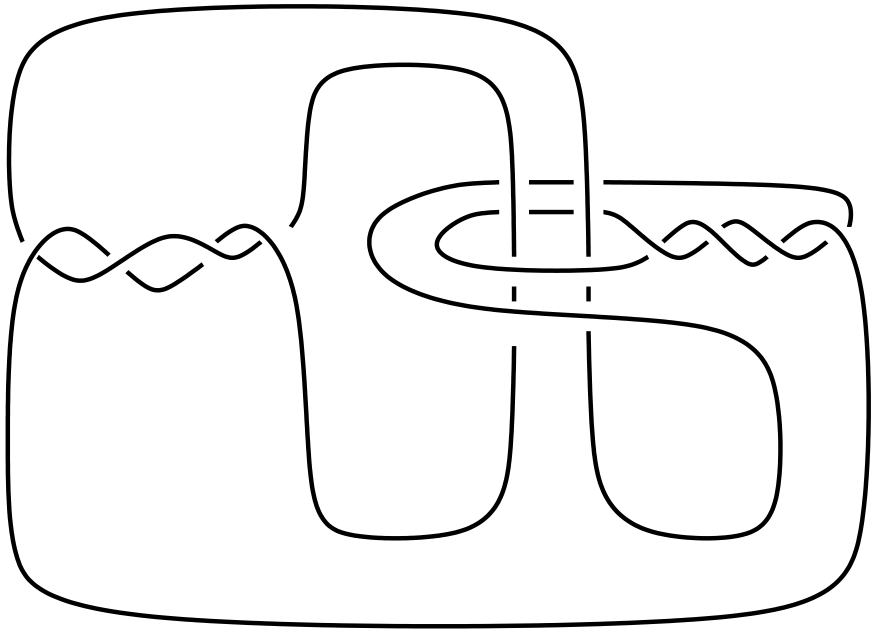
Question

How enzymes detect the right places on ds-DNA for activation?



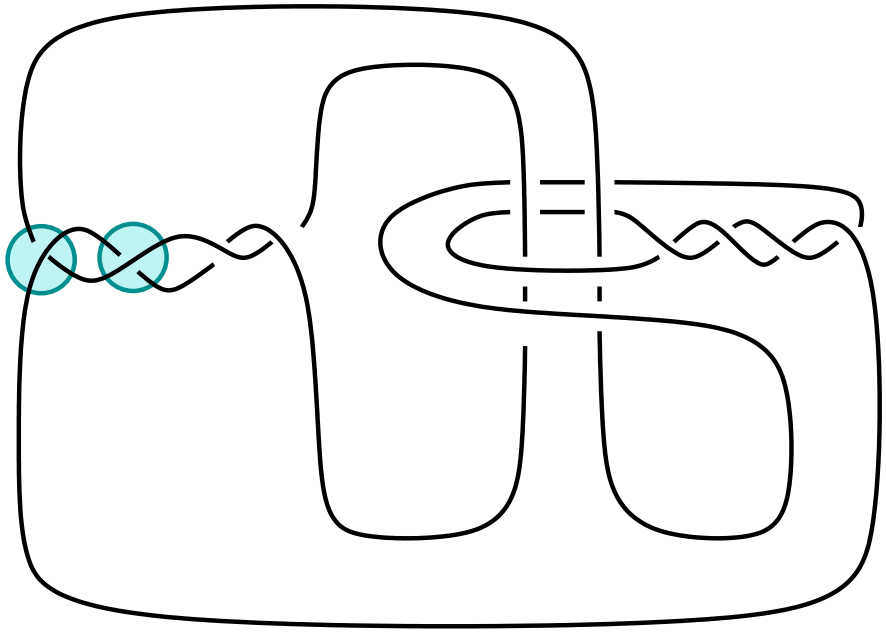
Still Problem?

This is a trivial knot.



Still Problem?

If the specified two crossings are changed, then it will be non-trivial.



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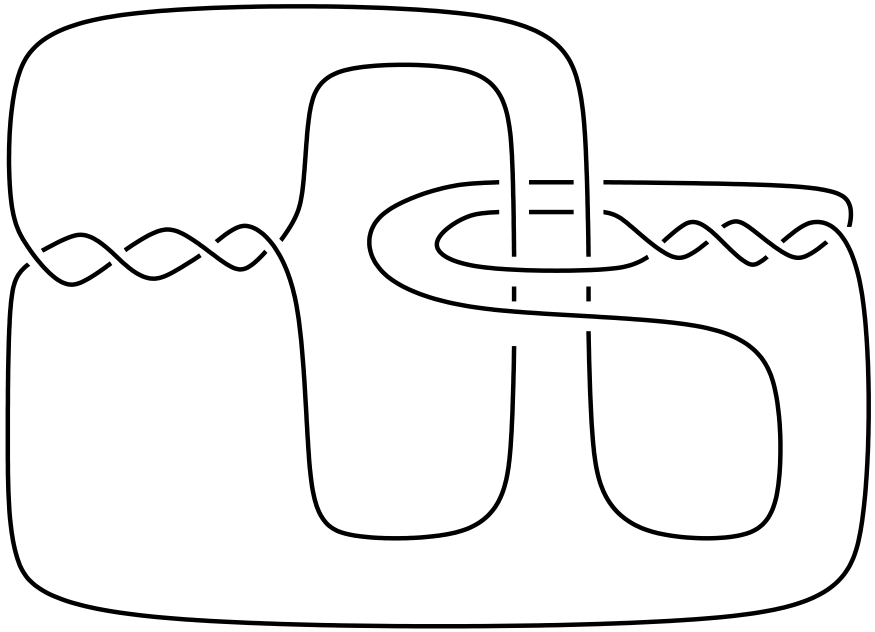

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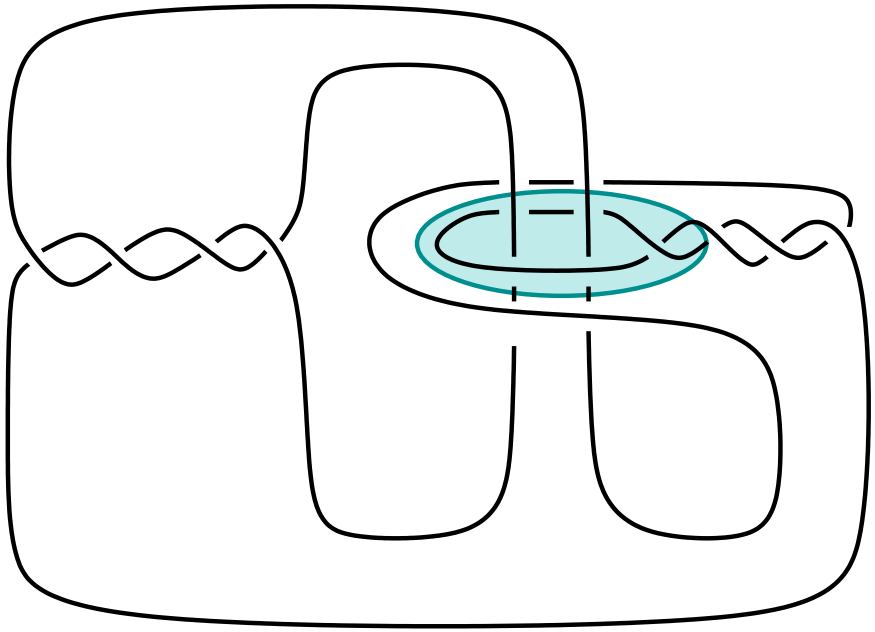

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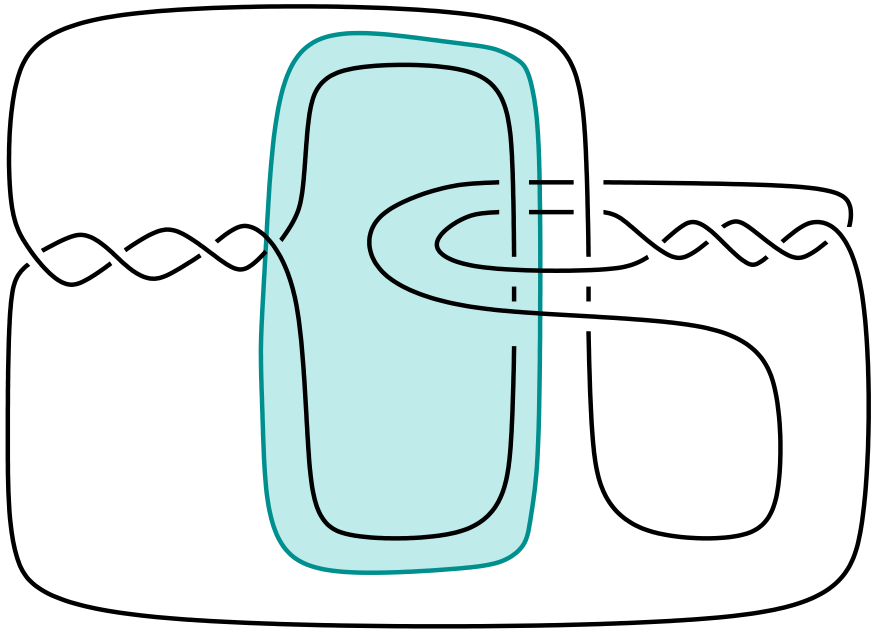
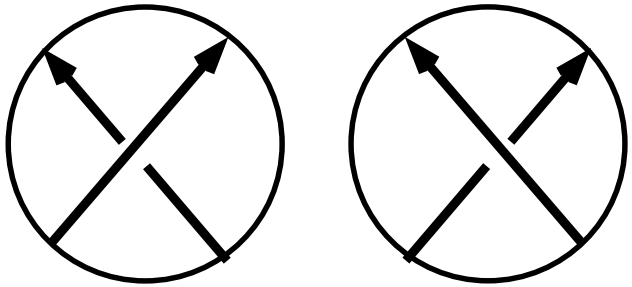


ε-crossings

Let γ be an oriented knot in $\mathbb{R}^3$. Suppose that there are a point $z \in \mathbb{R}^3 - \gamma$ and $\varepsilon > 0$ such that

- $B(z; \varepsilon/2) \cap \gamma$ is a pair of line segments e_1 and e_2.
- the pair $\{e_1, e_2\}$ has one of local diagrams below.

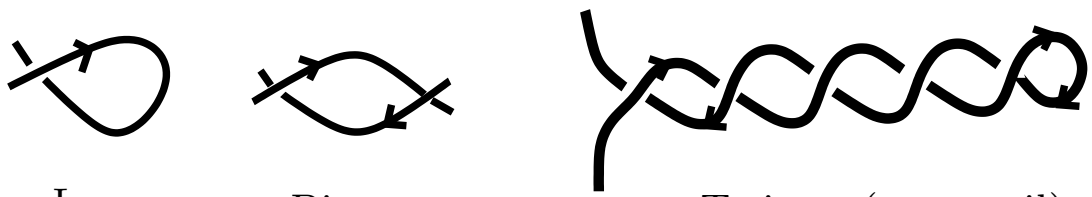


Then we call the crossing an ε-**crossing**.

ε is less than the size of the clamp of Topo II.

Loops and bigons

A **bigon** is a union of short segments bounded at the end ε-crossings of the segments. A **loop** is a simple closed curve starting and ending at the same ε-crossing. A **twister** is a union of a loop and some sonsecutive bigons.



Loop Bigon Twister (supercoil)

Loops and bigons

A **size** of a twister is the maximmum diameters of the loop and bigons of it.

Assertion 2.

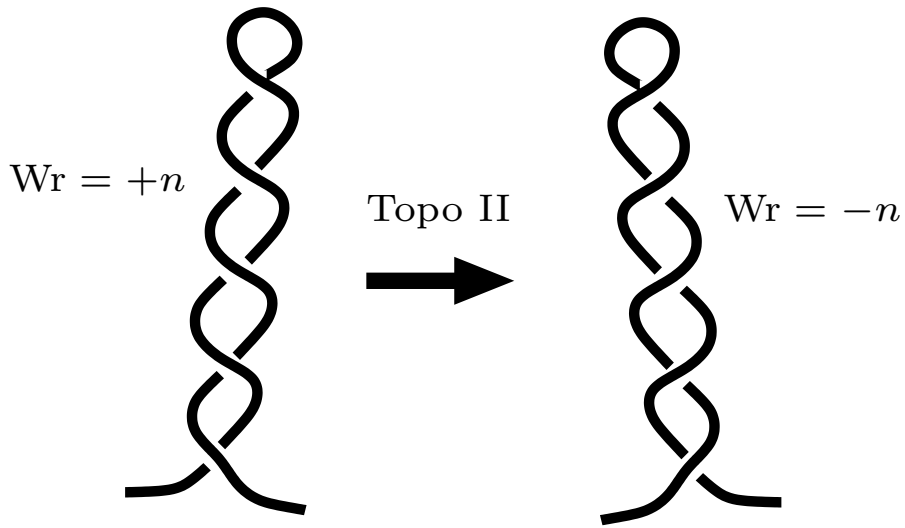
There is a number $\delta > 0$ such that if the diameter of a loop or bigon is less than δ, then the loop or bigon bounds a disc in 3-space.

Proposition 5.1

If the size of a twister is less than δ, then the acting the U-operations to the supercoil does not change the knot type of γ.

Loops and bigons

A positive twister (supercoil) can be modified into negative one by activating U-operations on the bigons. n of unwound full-twists introduces $+n$ writhe but the operation above changes it into $-n$. Thus $\Delta \mathrm{Lk} = -3n$. Therefore this modification is quite efficient.



Conclusion

If size of the supercoil is small enough, then the activation of topoisomerase II on the supercoil preserves the knot type of γ and reduce the writhe.
There are still many things to do:

- other topoisomerases.
- nucleosomes.
- experiments to check our model.

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Thank You!