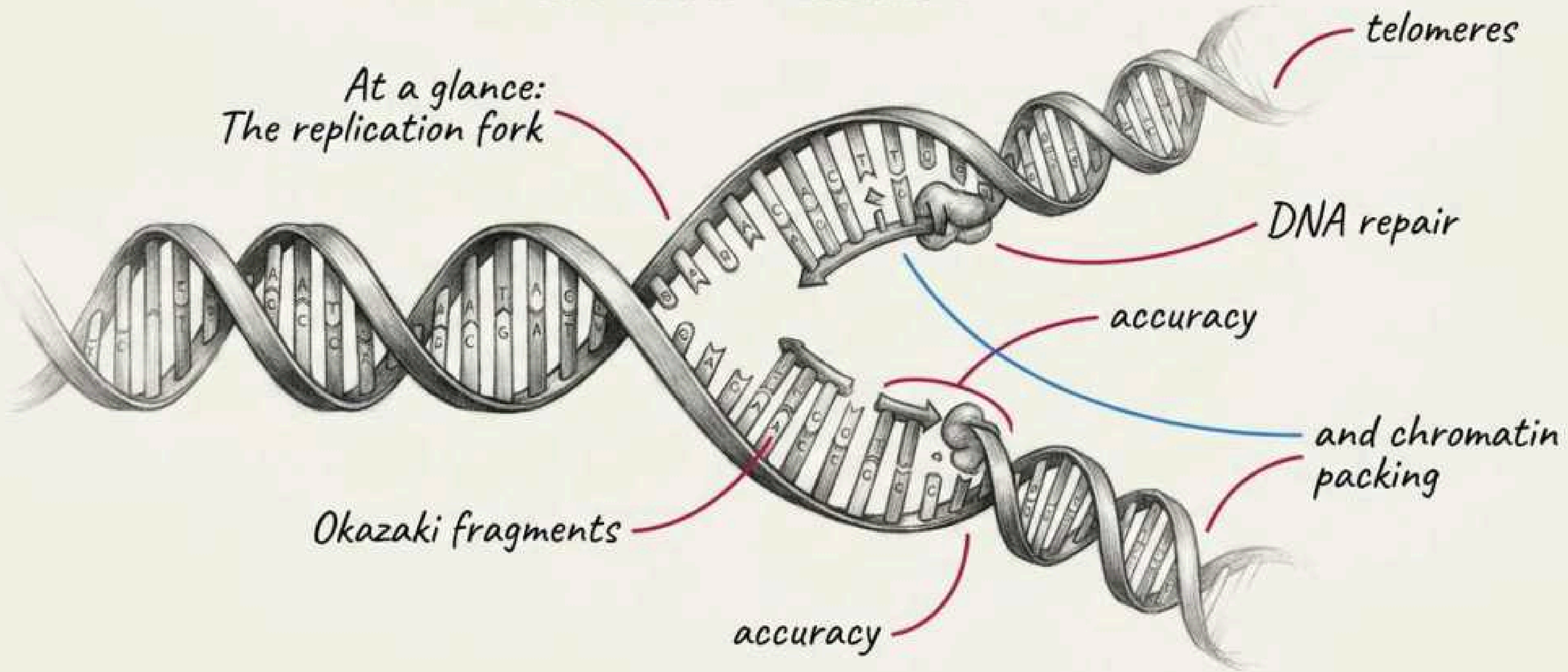
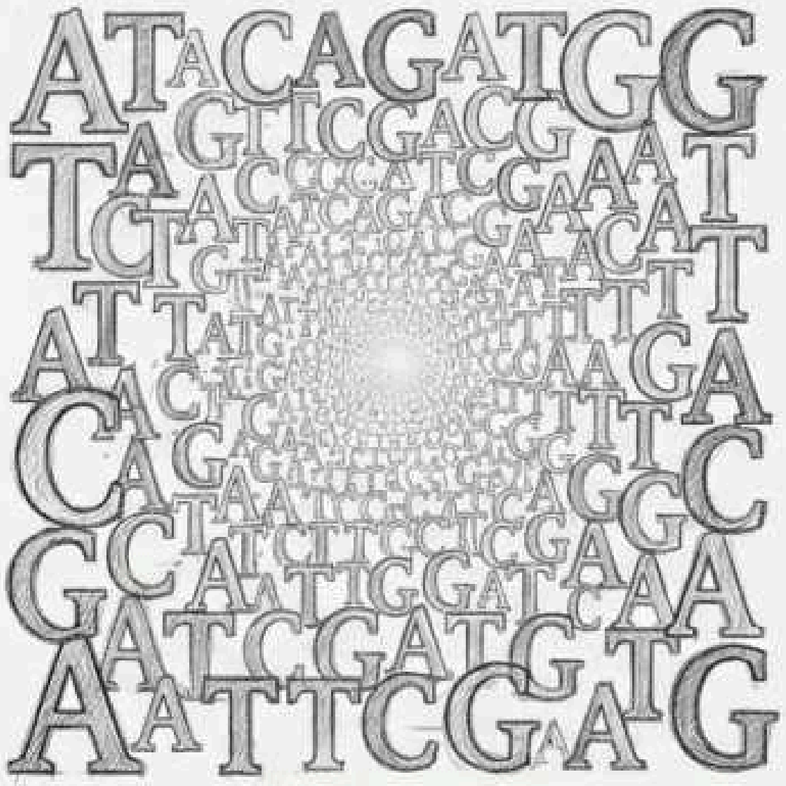
DNA Replication, Repair, and Chromosomes

BIO 120 B — Lecture 4

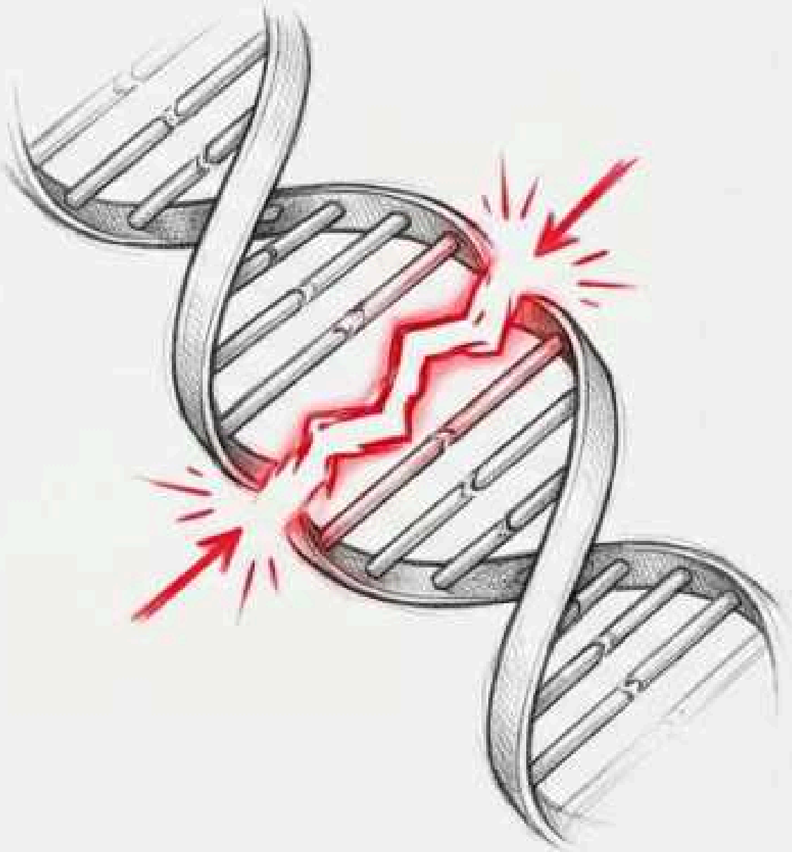


Understanding biology at the extremes of scale

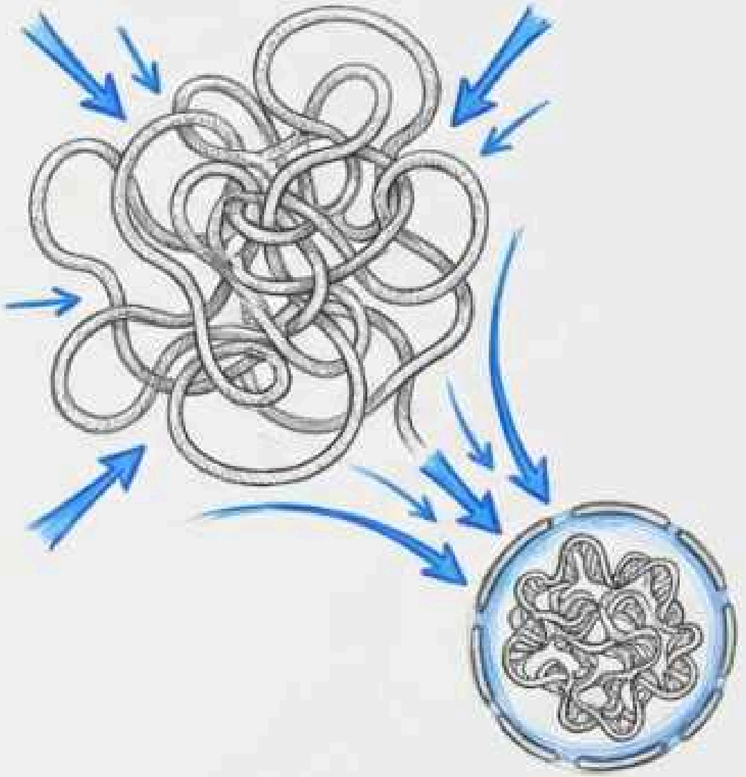
How is a molecule billions of letters long copied quickly and accurately?



What happens when it is damaged?



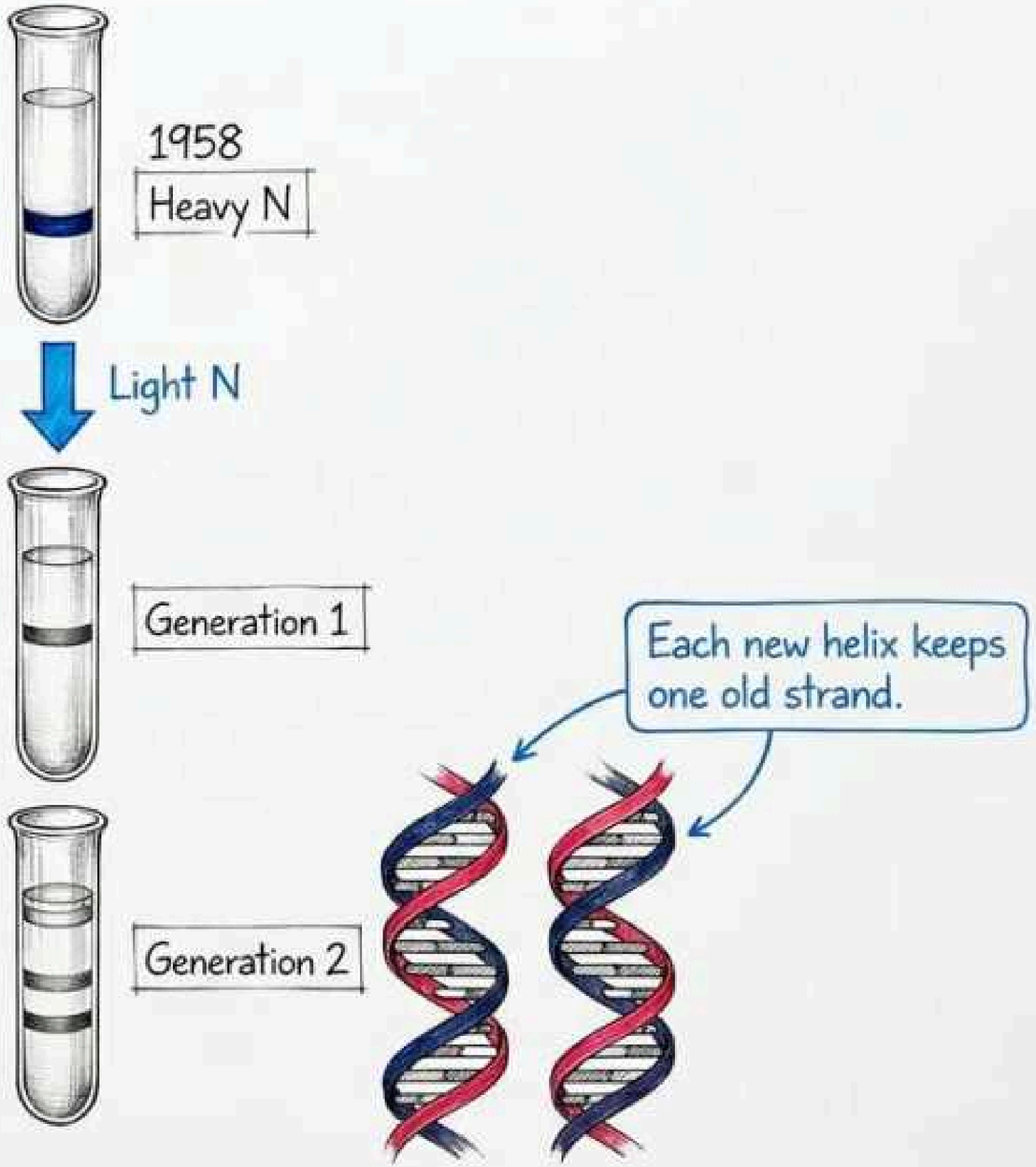
How is a molecule billions of letters long packed into a tiny nucleus?



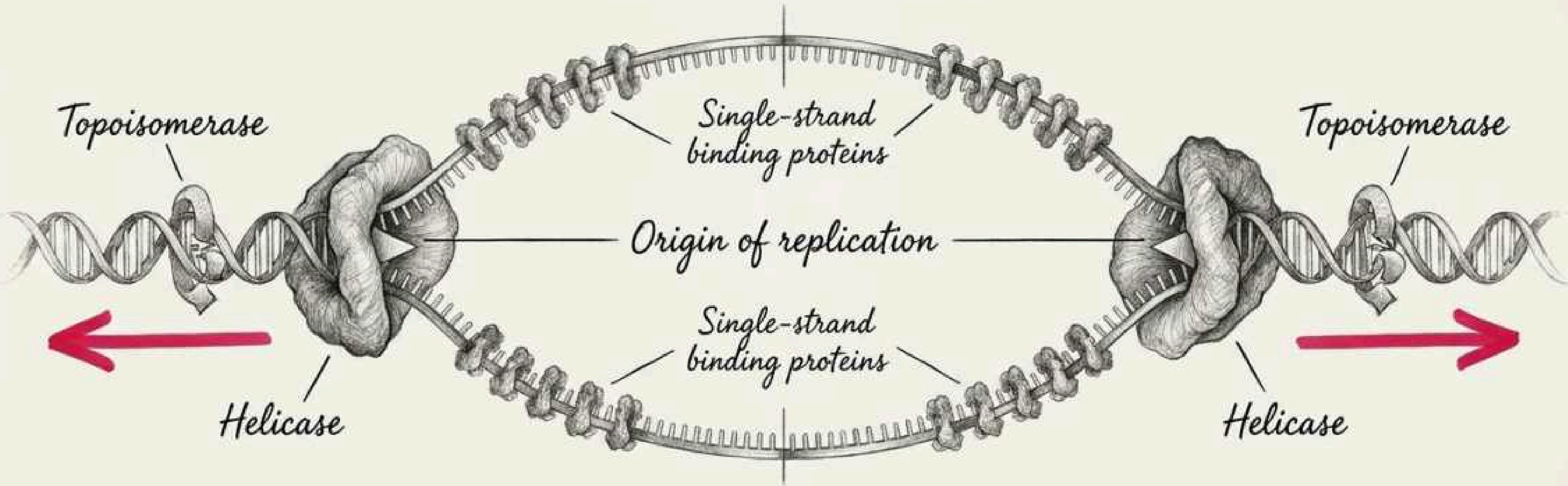
Answered with molecules, speeds, and numbers.

Meselson and Stahl proved semiconservative replication through isotopic density

¶ 4.3

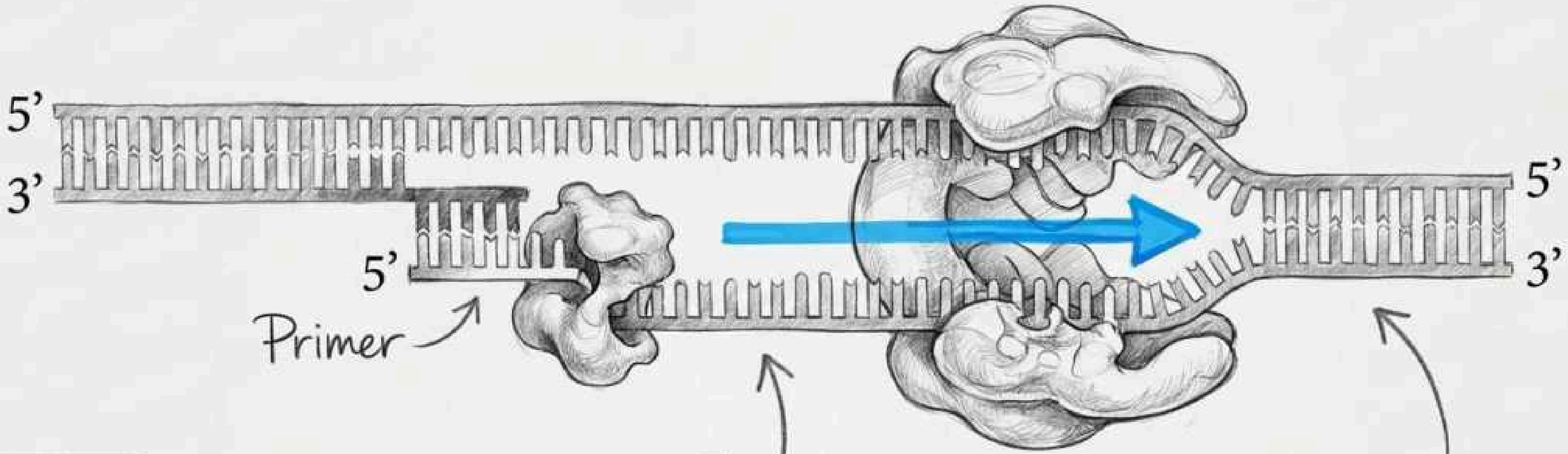


The replication machinery opens the helix to form bidirectional Y-forks



Each origin makes two forks moving in opposite directions.

DNA polymerase builds under two strict biochemical rules



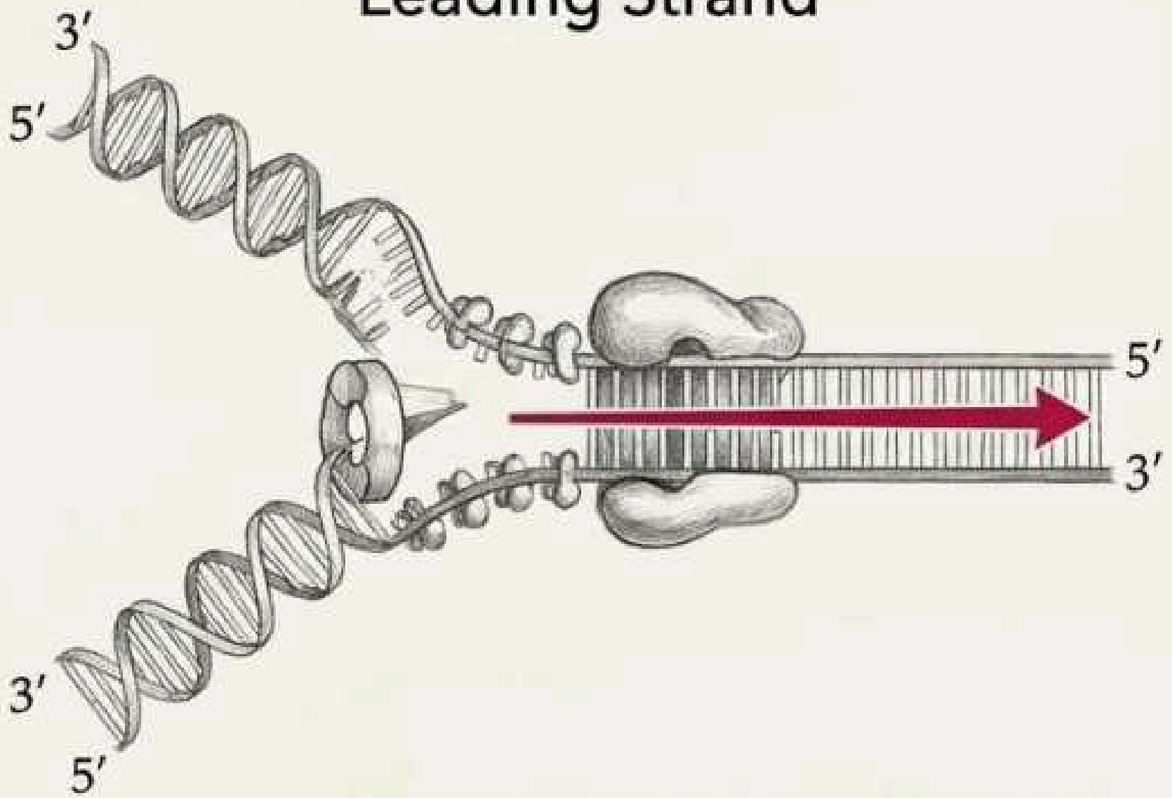
1. Requires a short primer (supplied by primase) to add nucleotides to an existing end.

2. Can only build from the 5’ end to the 3’ end.

Directionality rules force continuous and discontinuous building strategies

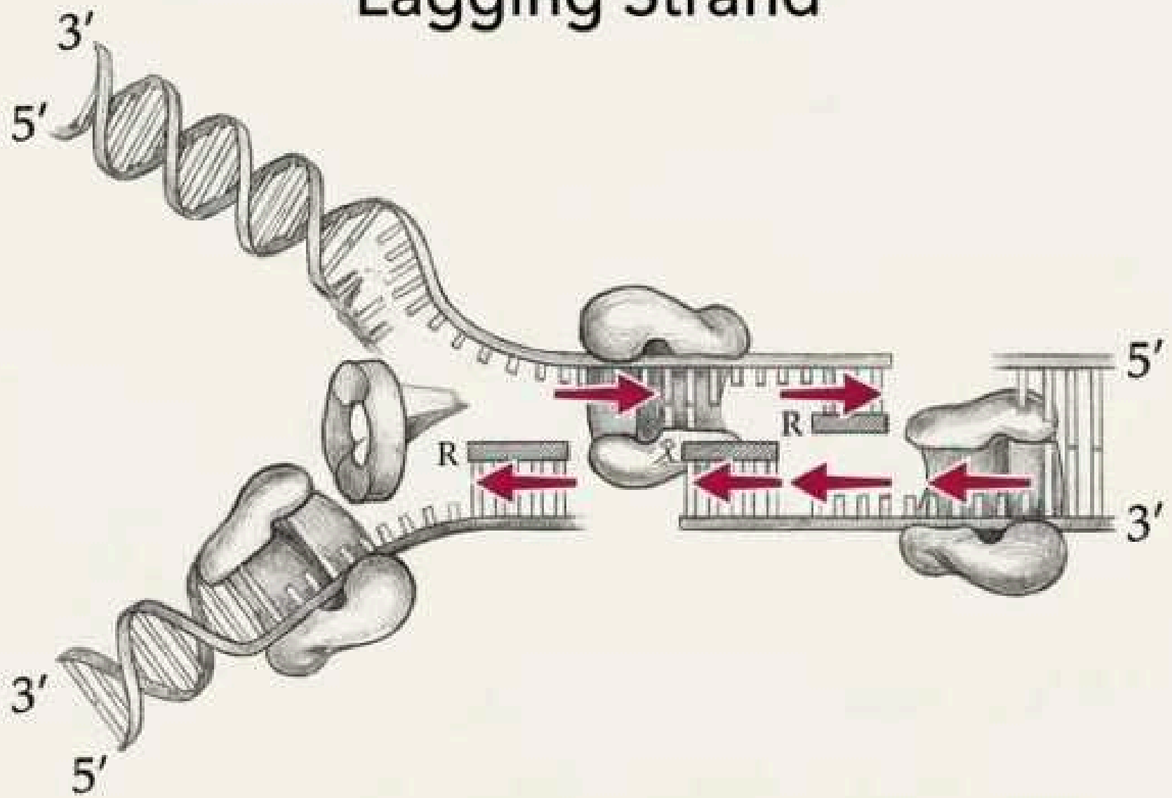
¶ 4.6

Leading Strand



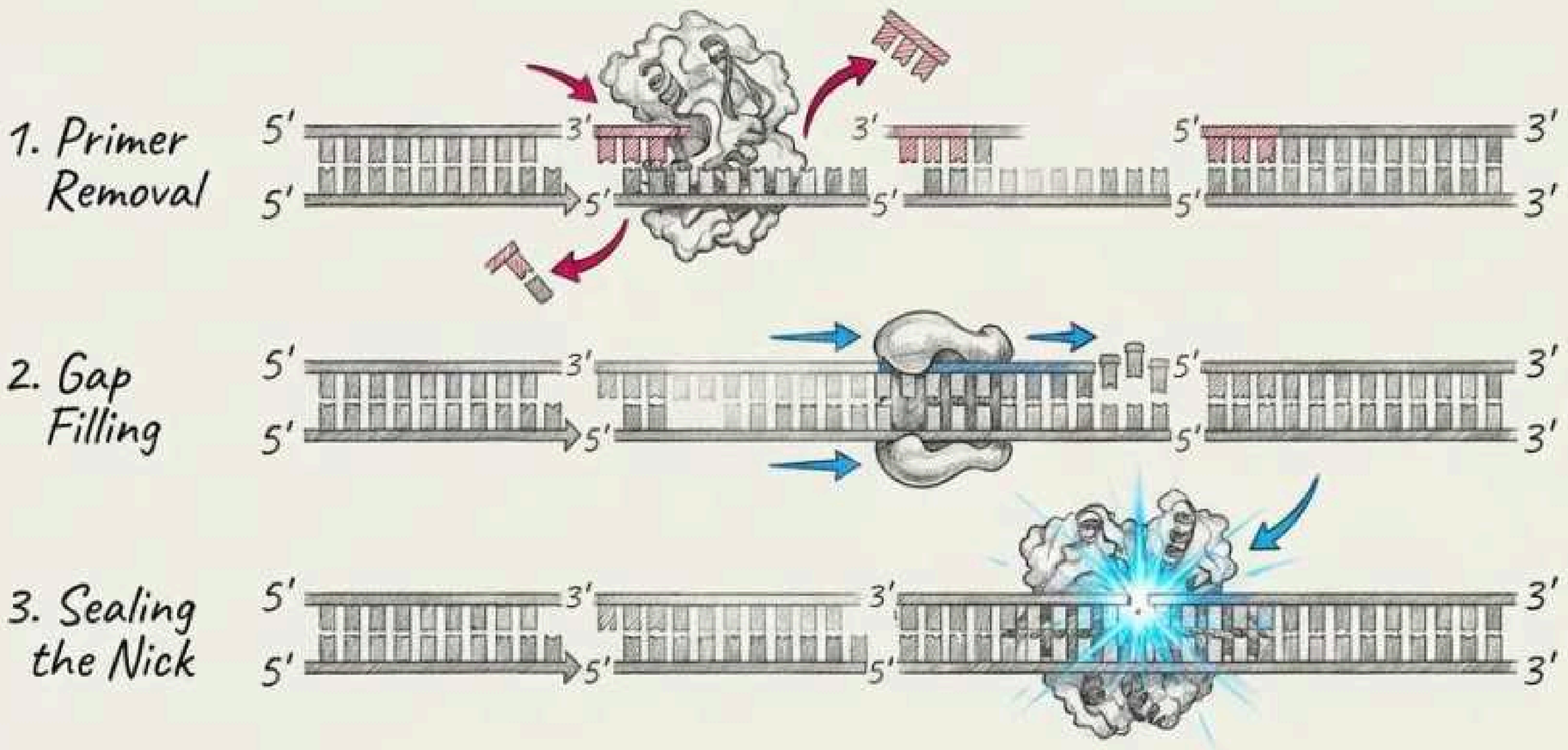
Builds continuously, following the fork.

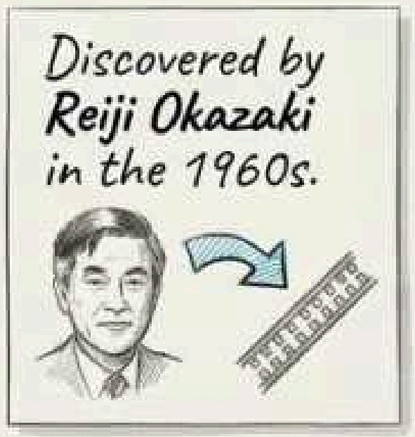
Lagging Strand



Builds discontinuously, moving away from the fork. Creates Okazaki fragments.

Okazaki fragments require enzymatic cleanup to become a seamless strand





DNA ligase seals the nick to create one seamless strand.



Bacteria: 1,000 - 2,000 nucleotides



Humans: 100 - 200 nucleotides

Bacterial replication solves for speed by overlapping replication cycles

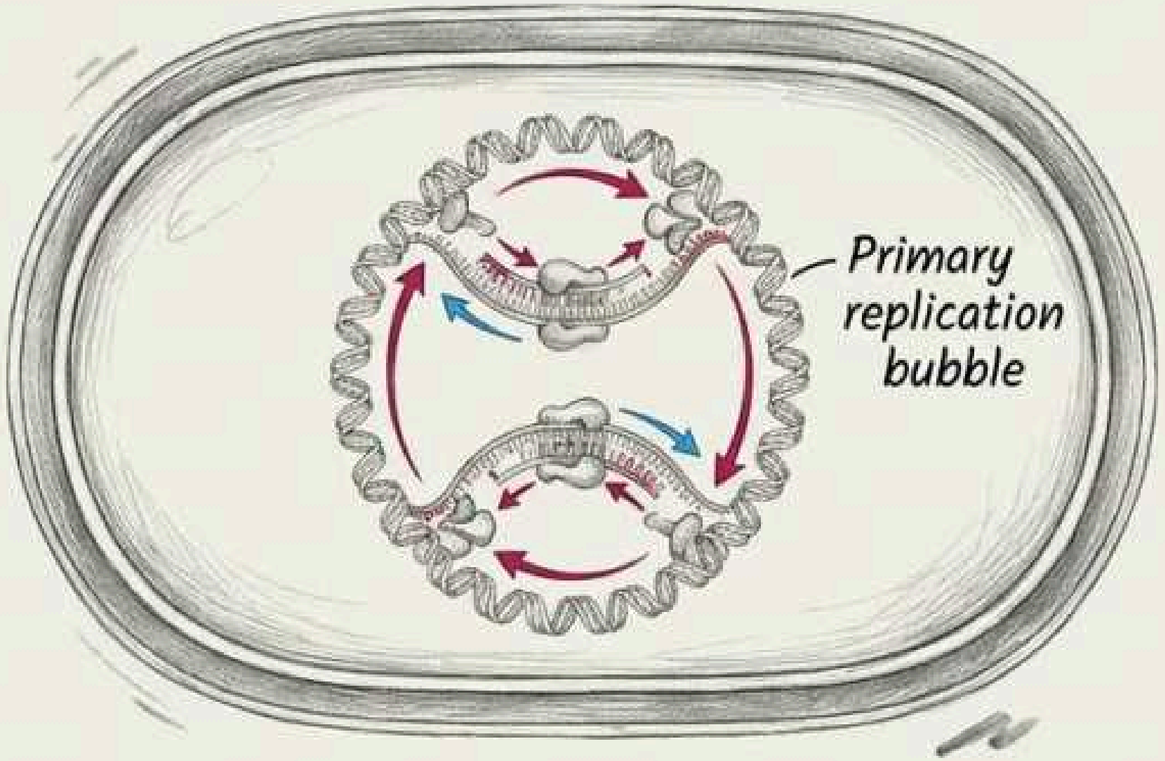
4.6×10^6 base pairs.

1 origin → 2 forks.

2.3×10^6 base pairs per fork at 1,000 nucleotides/second.

Result: 2,300 seconds

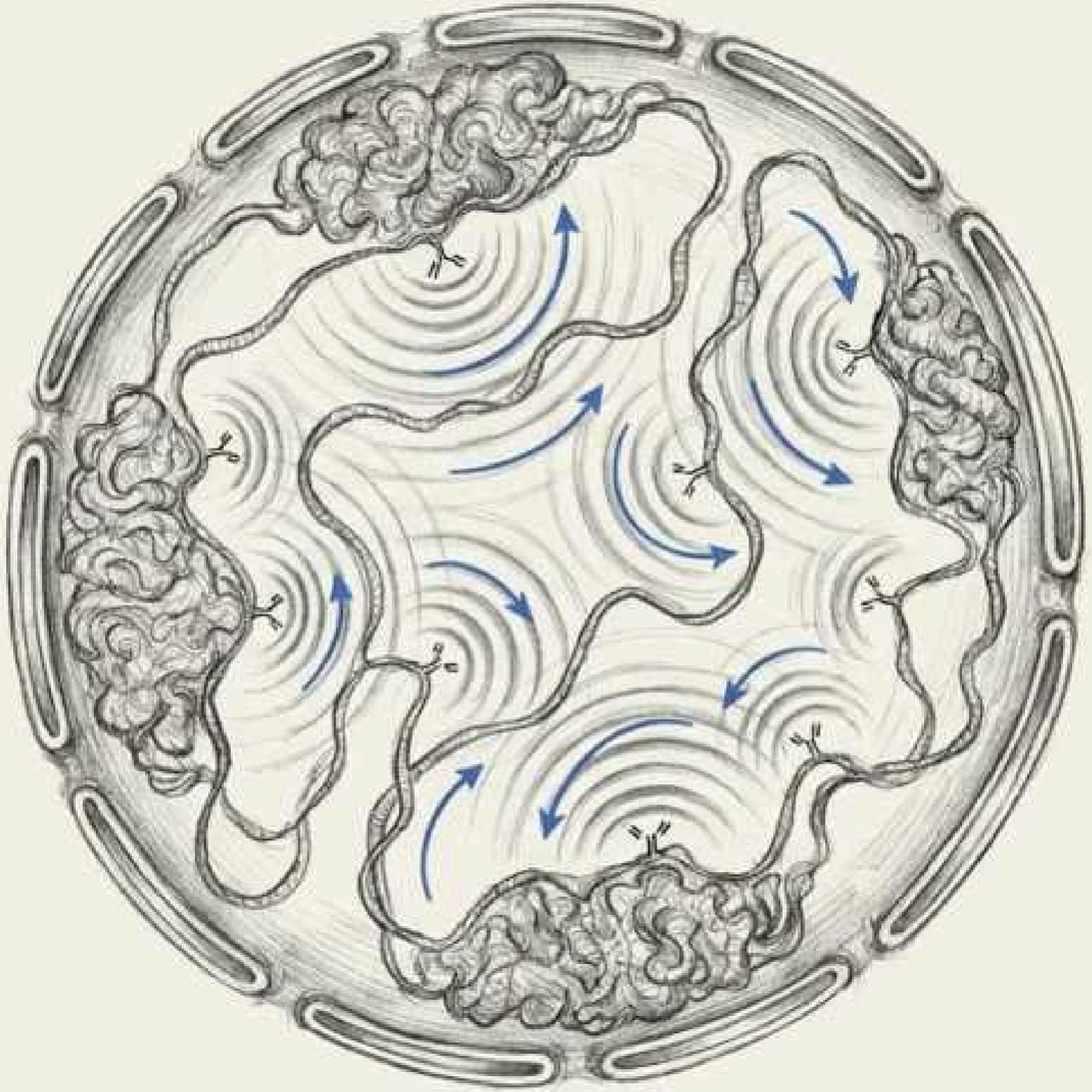
~38 minutes (~38 minutes).



Speed matters: Fork moves at 1,000 nucleotides per second.

Division occurs in 20 minutes because new rounds start before the old finishes.

Human cells overcome slower speeds through massive parallel processing



6.2×10^9 base pairs.

Fork speed is only 50 nucleotides/sec.

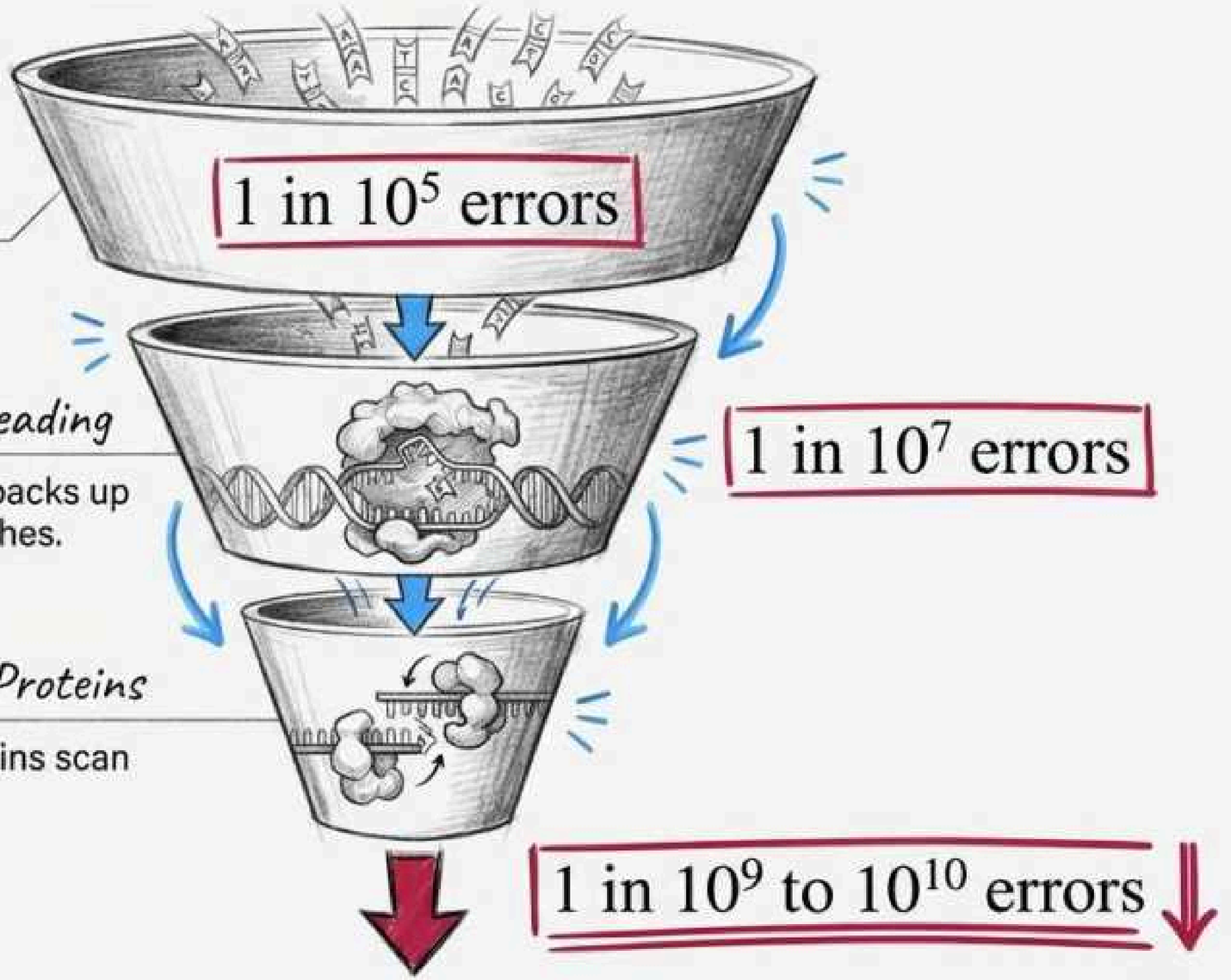
1 fork = 4 years.

Tens of thousands of origins fire in waves across the nucleus.

The entire diploid genome is copied in ~8 hours instead of 4 years.

↳ Massive parallel processing!

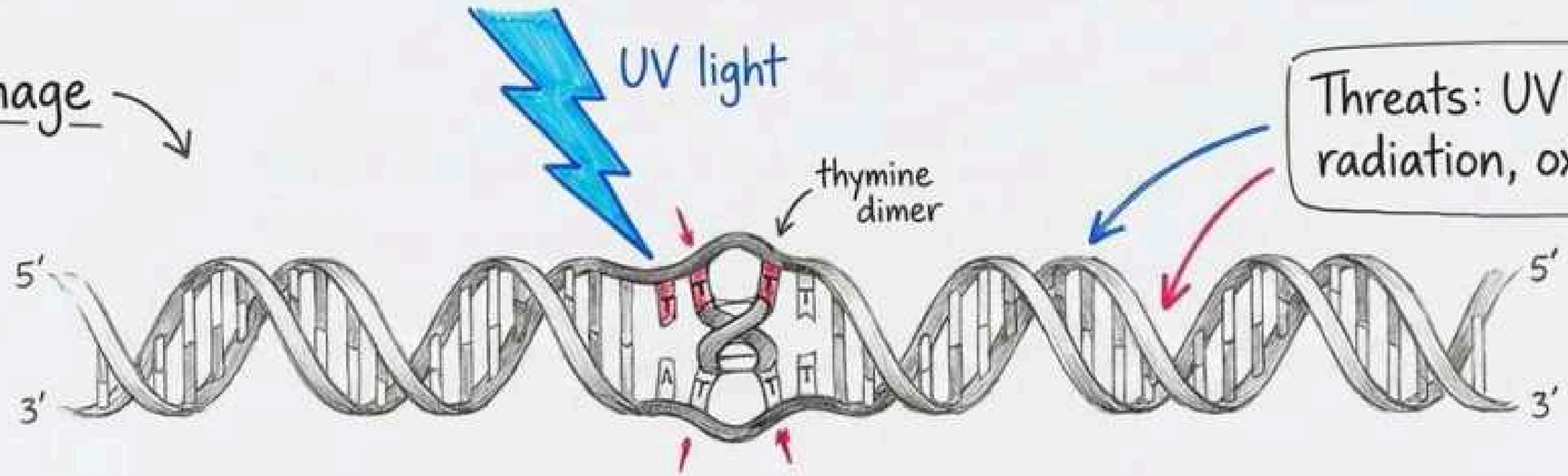
Multi-layered proofreading drives the error rate to near zero



Tens of thousands of lesions occur daily from environmental damage

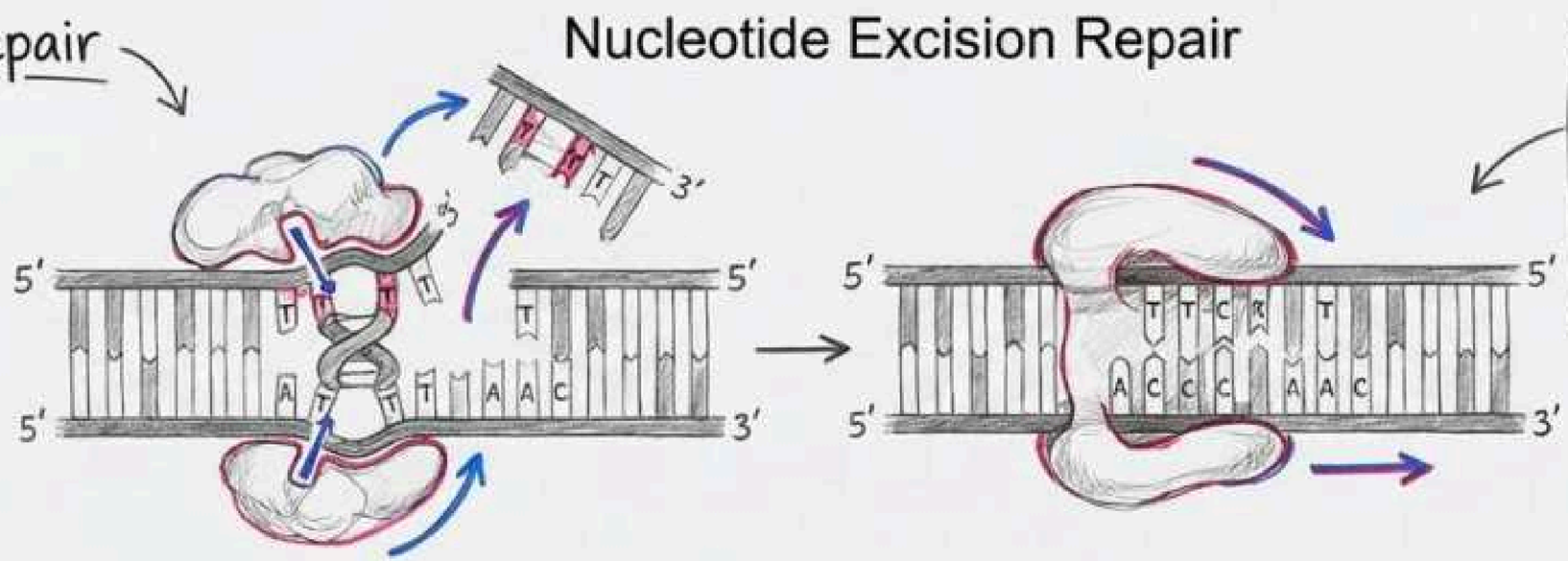
¶ 4.11

The Damage



Threats: UV light, chemicals, radiation, oxygen radicals.

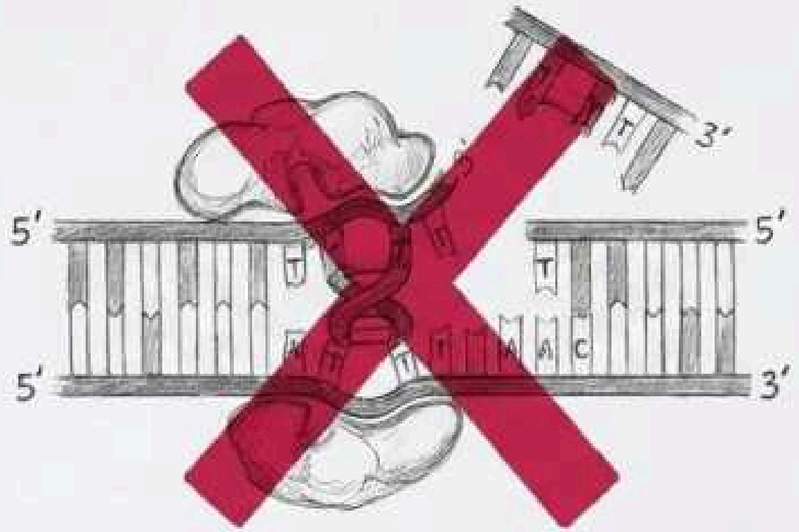
The Repair



Nucleotide excision repair cuts out the patch and refills from the intact strand.

The cost of failed nucleotide excision repair is paid in disease

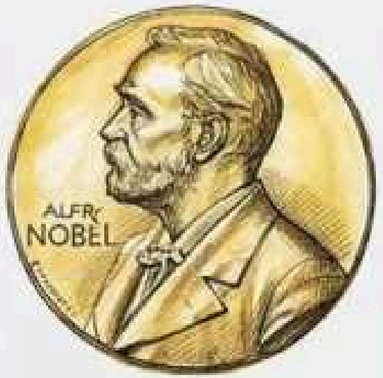
¶ 4.12



Xeroderma pigmentosum

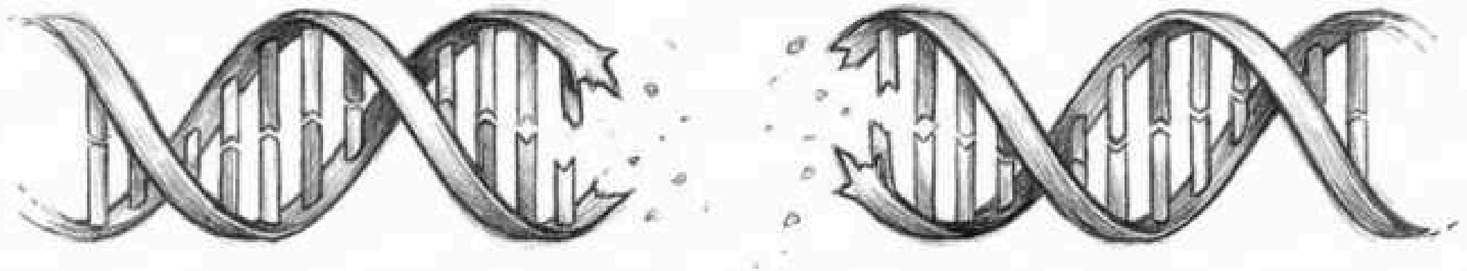
- Inherited fault in nucleotide excision repair.
- Skin cannot repair sunlight damage, leading to early skin cancers.

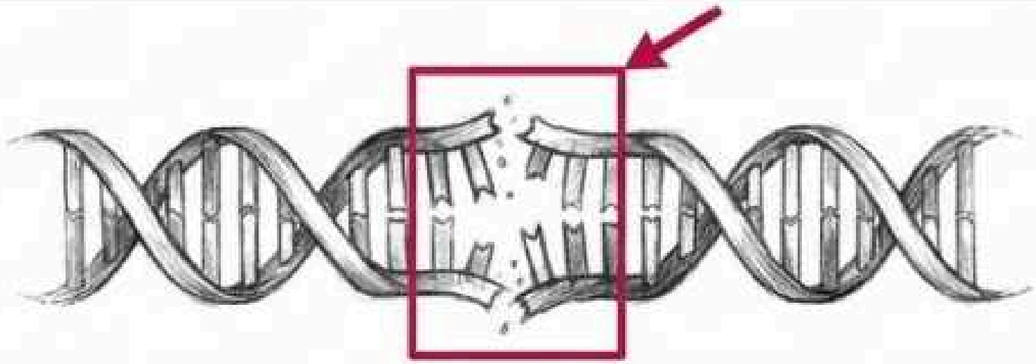
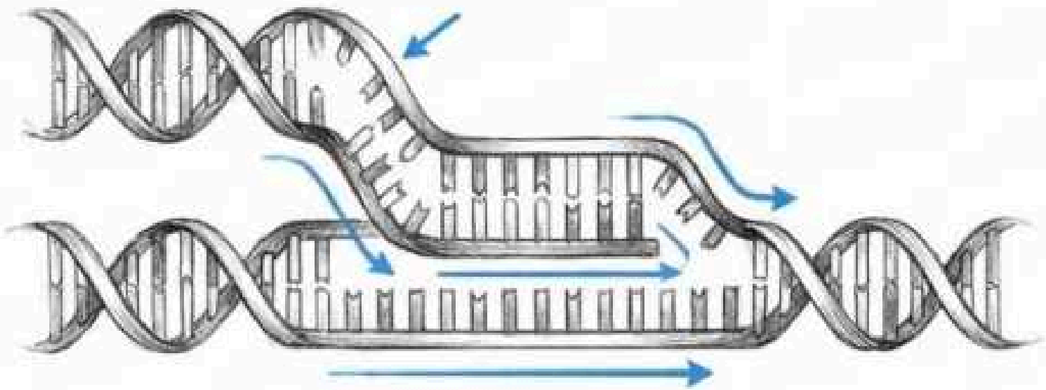
"Repair is not optional."



2015 Nobel Prize in Chemistry:
Tomas Lindahl, Paul Modrich, Aziz Sancar

Cells deploy two primary pathways to survive double-strand breaks



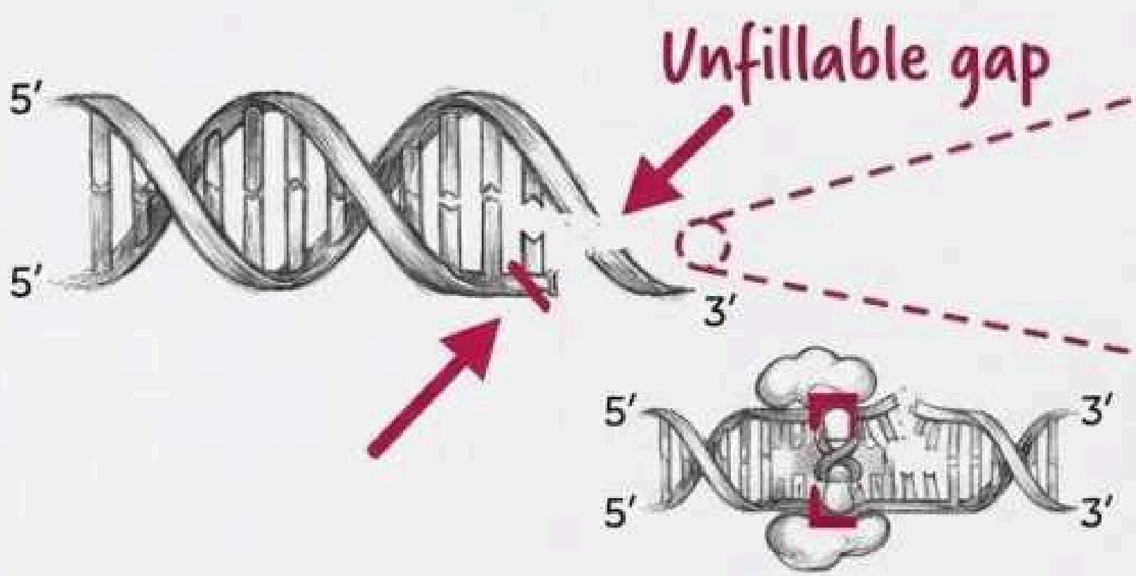
Non-homologous End Joining (NHEJ)	Homologous Recombination (HR)
	
Quick, Lossy (loses bases)	Accurate, Template-driven

Mutations in *BRCA1* and *BRCA2* weaken the accurate HR route, raising cancer risk.

The end replication problem requires disposable protective caps

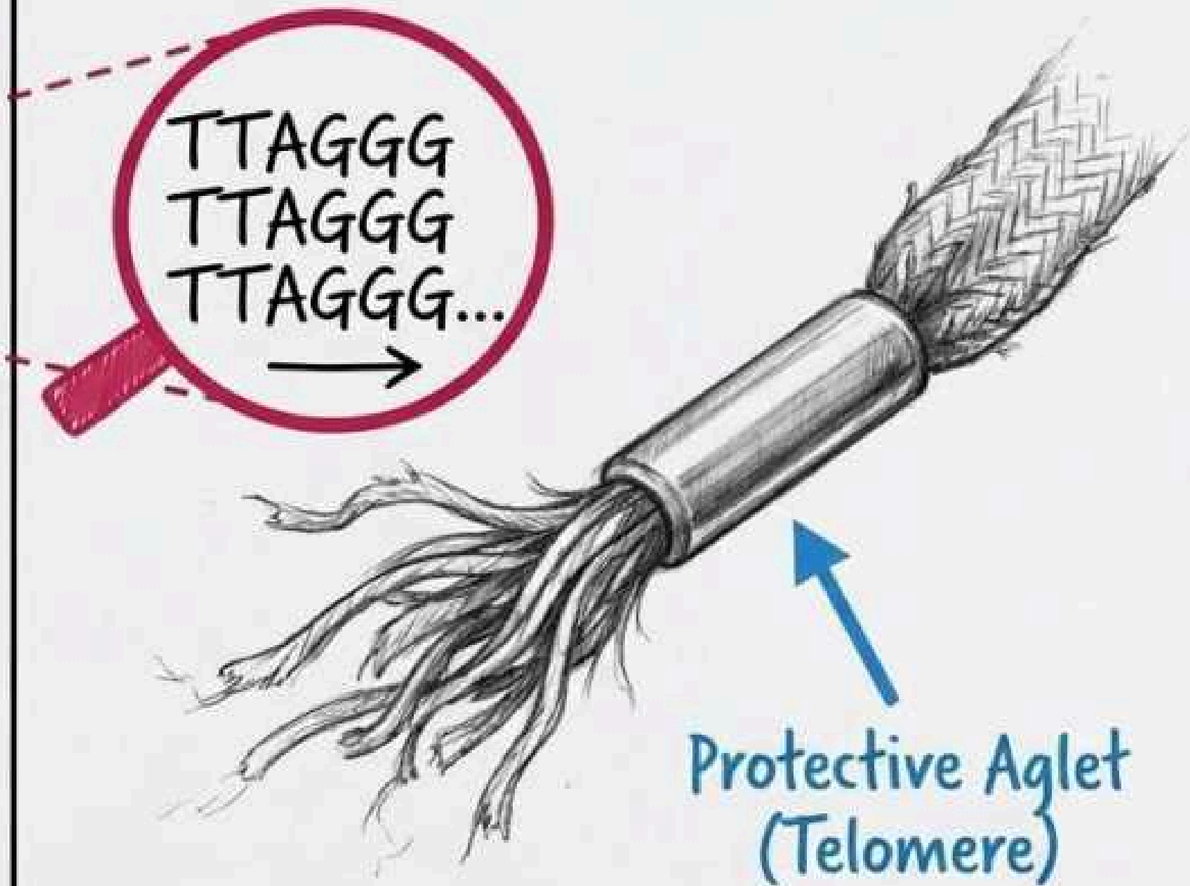
¶ 4.14

The Biology



Polymerase cannot fully copy the last stretch of the lagging strand. Chromosomes shorten with each round of copying.

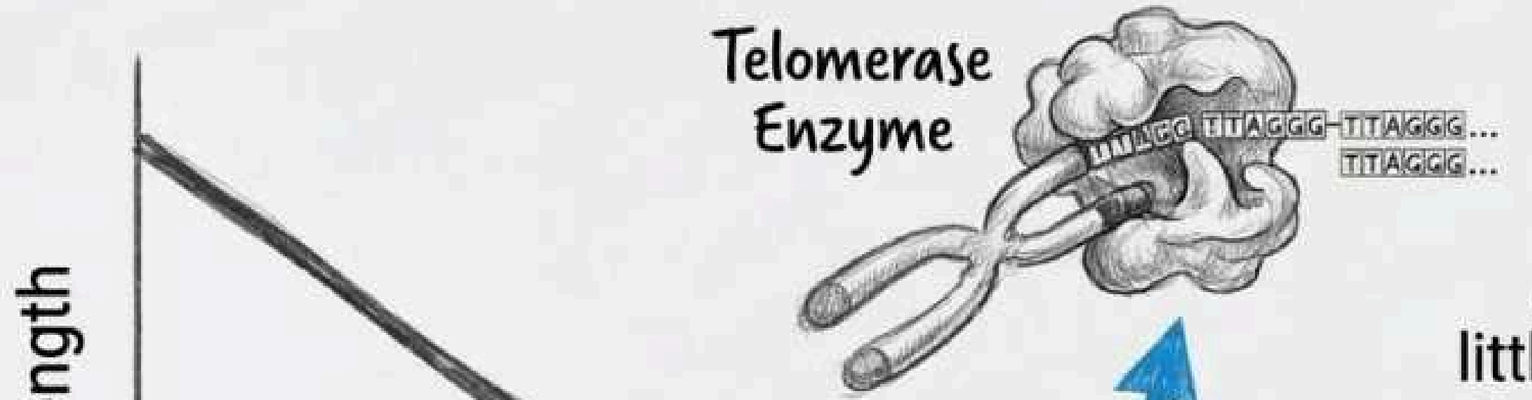
The Metaphor



Telomeres act as disposable buffers protecting real genes.

The Hayflick limit acts as a biological division countdown

¶ 4.15



Adult body cells have little telomerase; telomeres shorten until division stops.

Telomerase

The Hayflick Limit

Telomere length

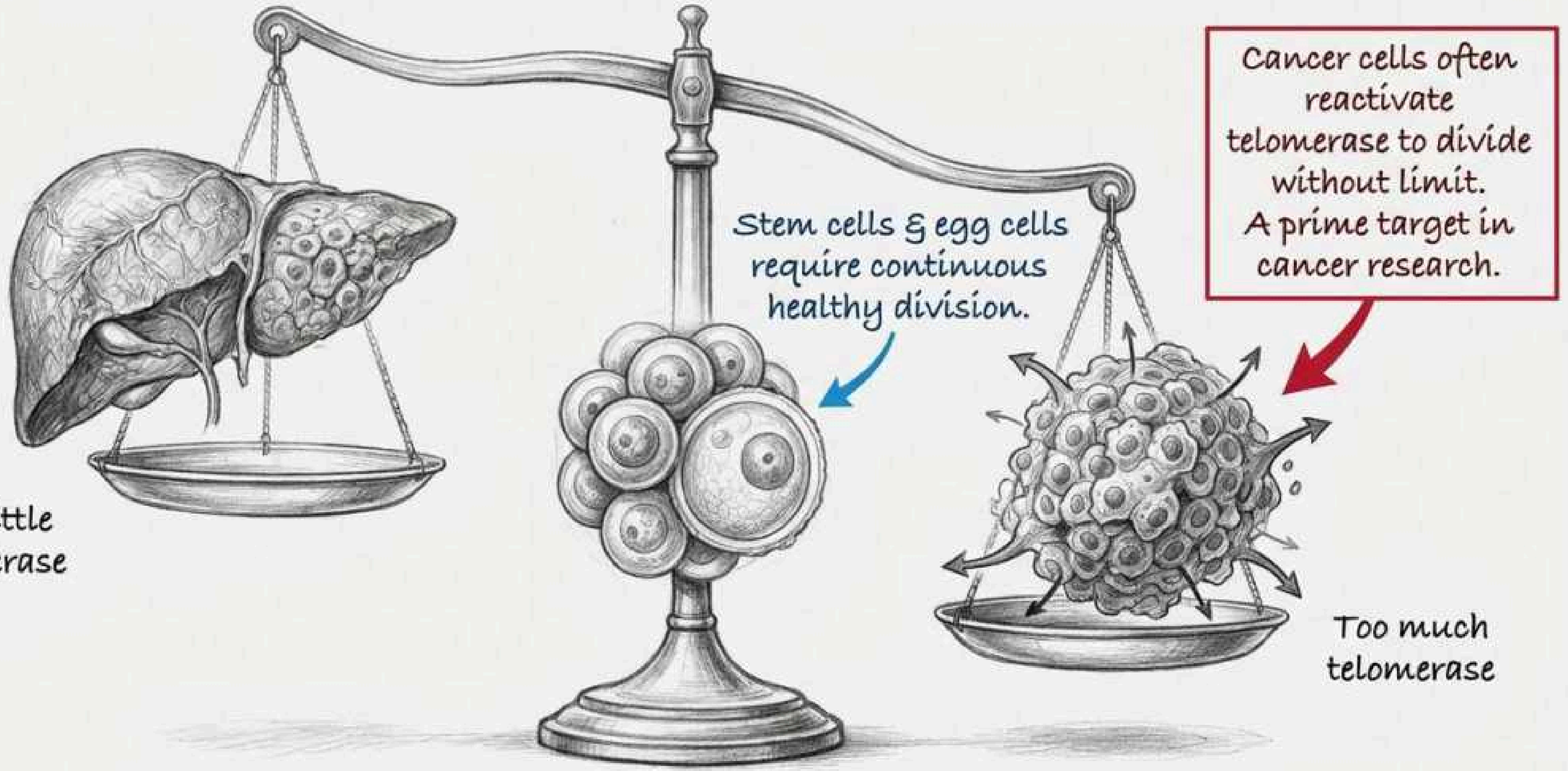
50 divisions

Number of cell divisions



2009 Nobel Prize:
Elizabeth Blackburn,
Carol Greider, Jack Szostak

Telomerase operates on a delicate tissue balance



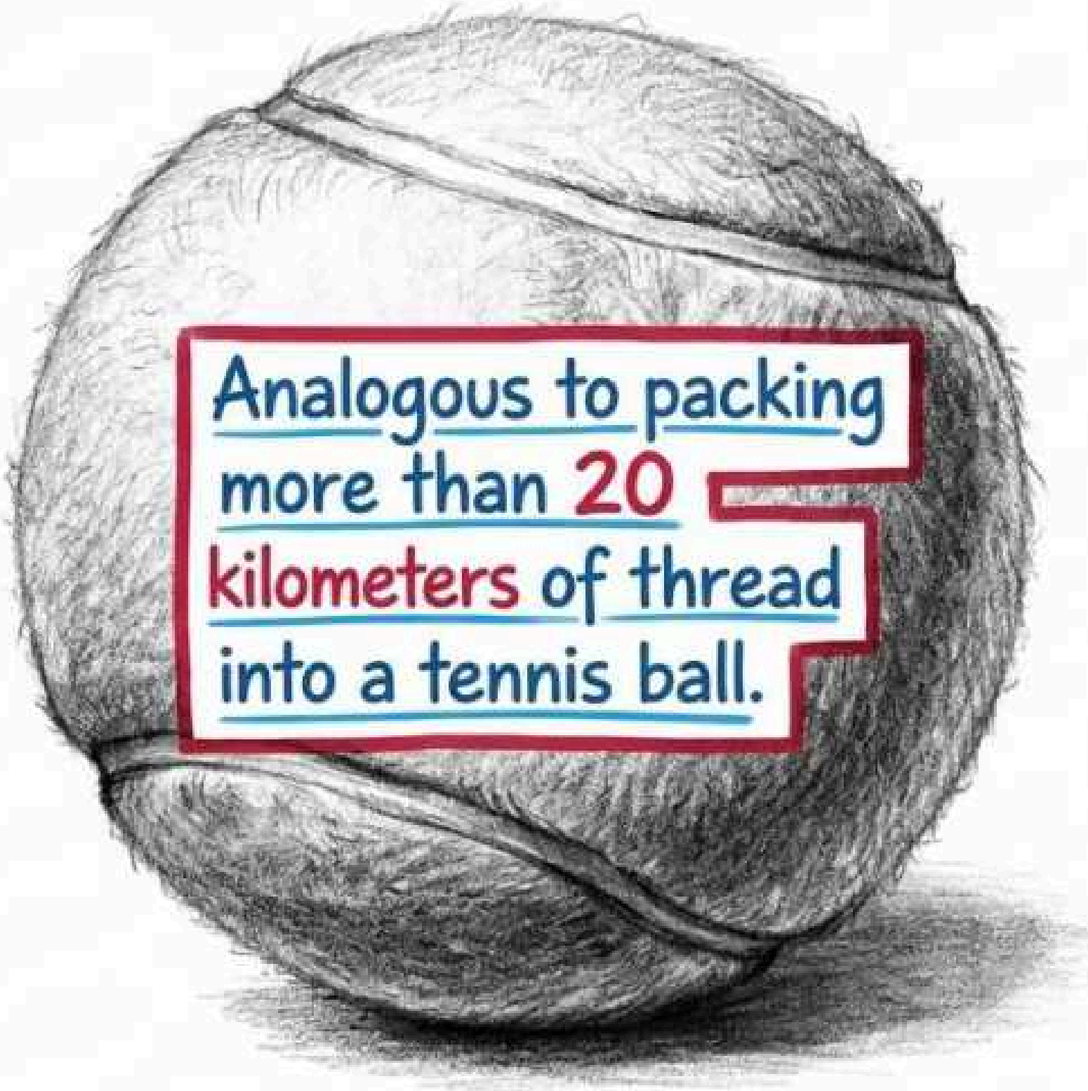
The mathematics of genomic compression

$0.34\,\text{nm per base pair} \times 6.2 \times 10^9 \text{ pairs}$
$= 2.1 \text{ meters of DNA.}$

6 micrometers wide

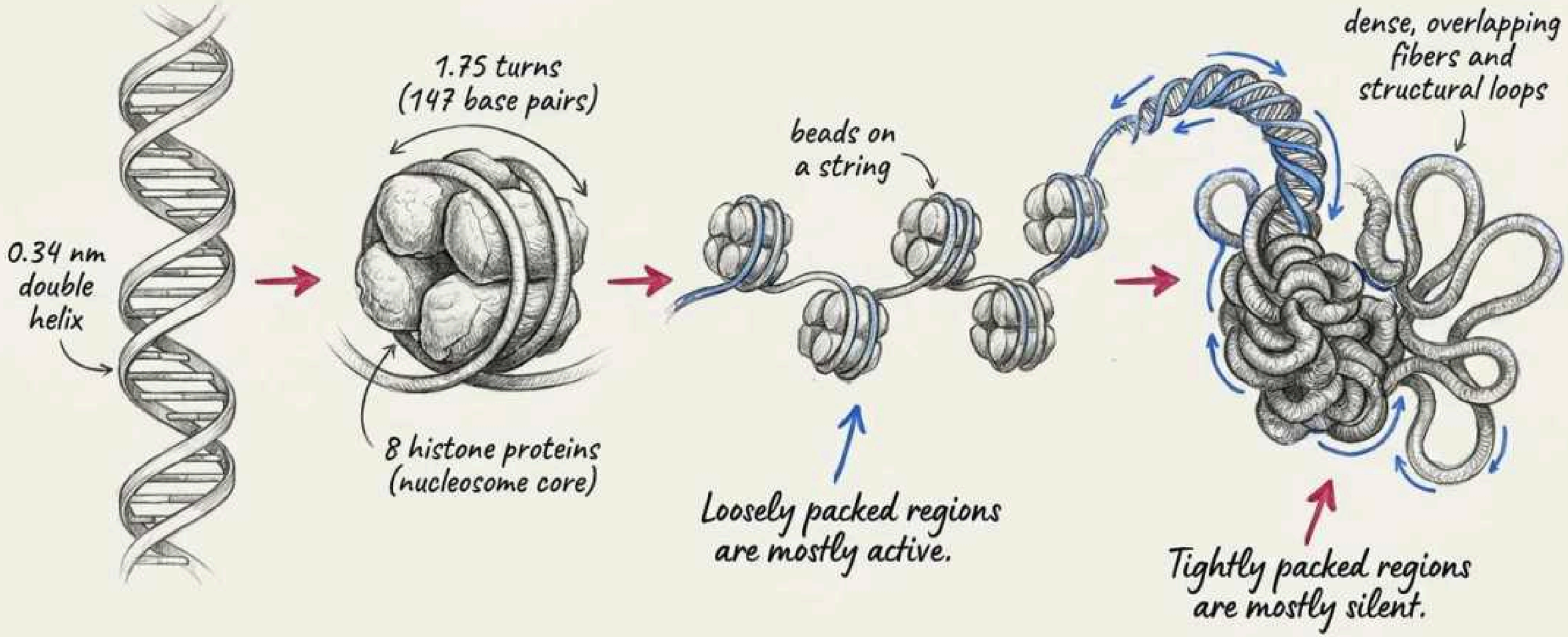


>350,000x compression



Analogous to packing more than 20 kilometers of thread into a tennis ball.

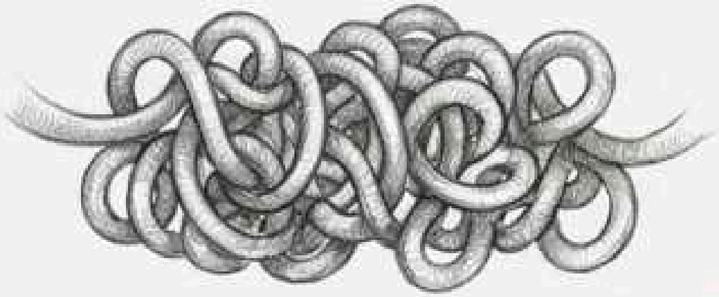
DNA is structurally compressed through a hierarchy of packing



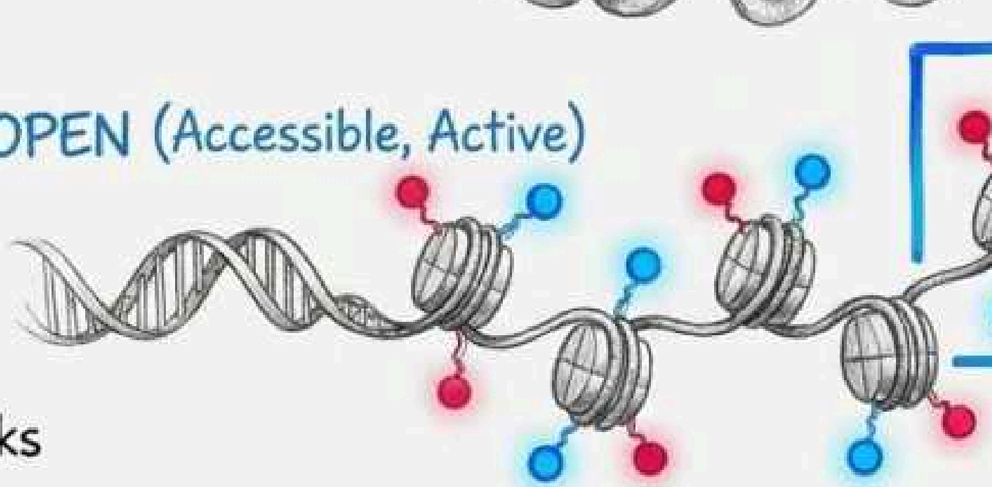
Packing is not just physical storage—it is epigenetic control

¶ 4.19

CLOSED
(Inaccessible)

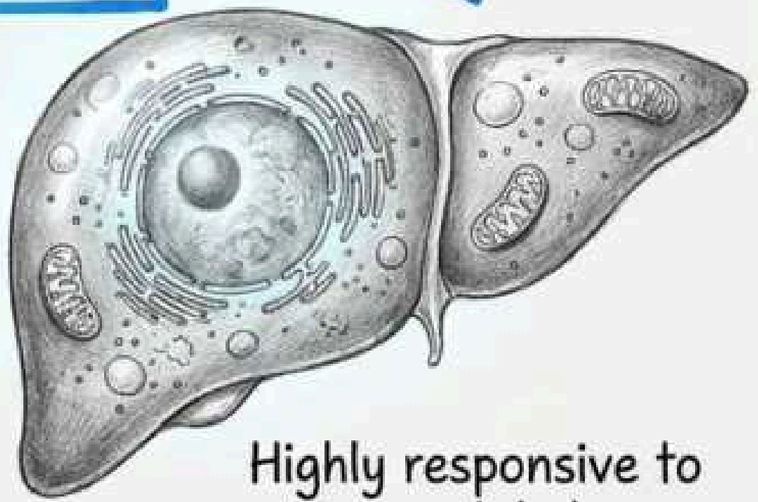


OPEN (Accessible, Active)



Epigenetic marks open or close genetic regions.

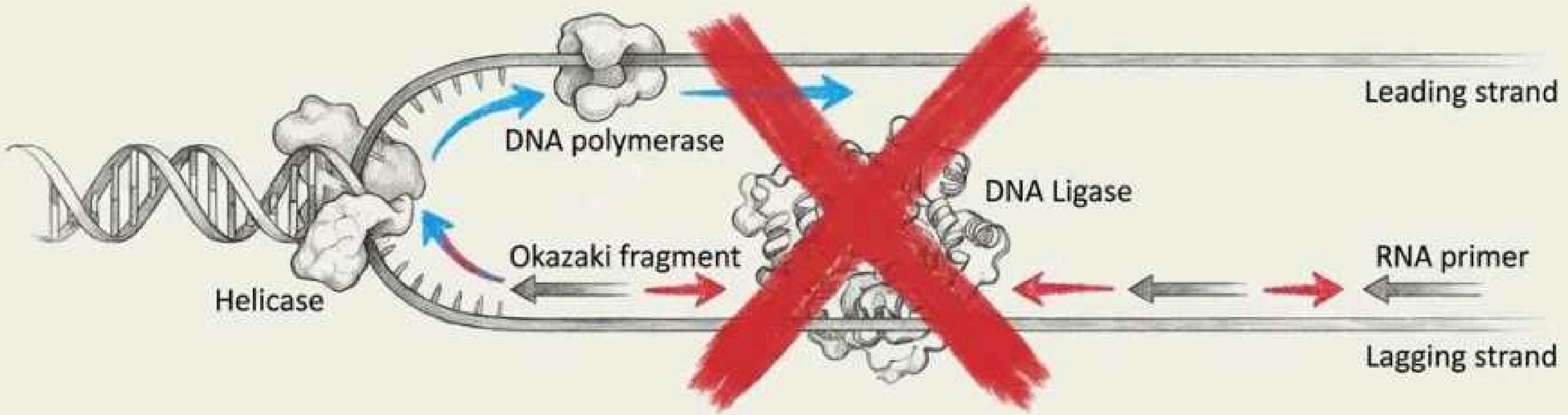
They copy during division, helping a liver cell stay a liver cell.



Highly responsive to environmental changes.

Synthesis Challenge: Predict the catastrophic failure

¶ 4.20



Suppose a drug blocks DNA ligase in human cells...

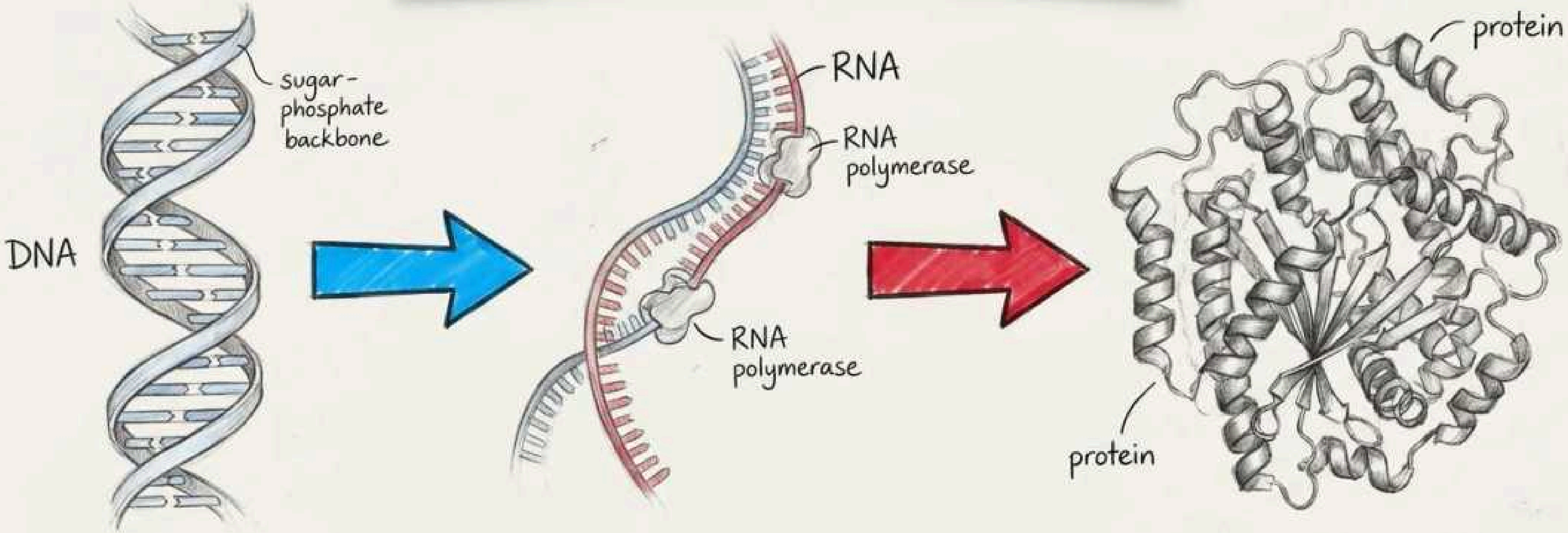
- ☐ Predict which strand is affected most.
- ☐ What would the cell look like under a microscope?
- ☐ How might the cell respond?

Explain your answer using leading and lagging strand mechanics.

Looking Ahead: From blueprint to biological machine

¶ 4.21

Lecture 5 Preview: The Central Dogma.



Following the information from DNA to RNA to protein, and discovering how cells decide which genes to use.