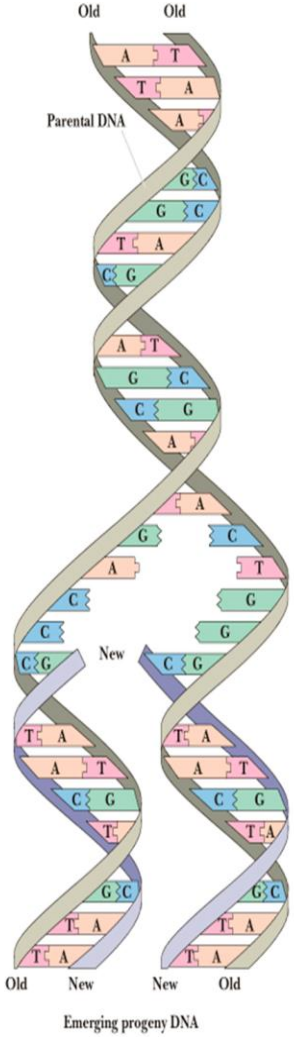
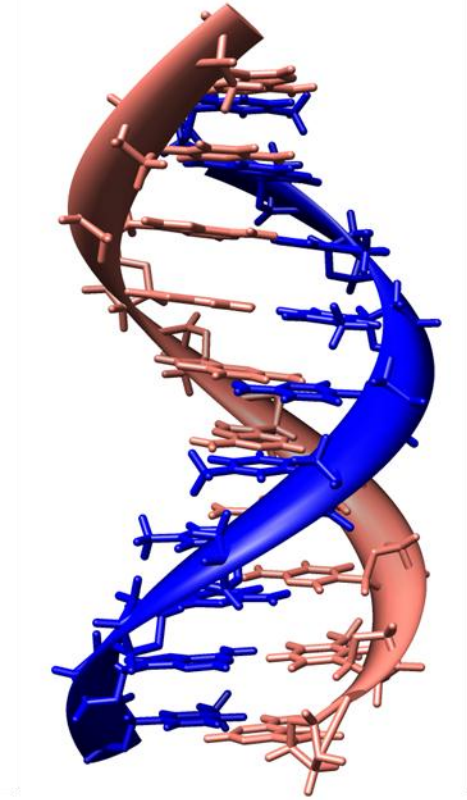
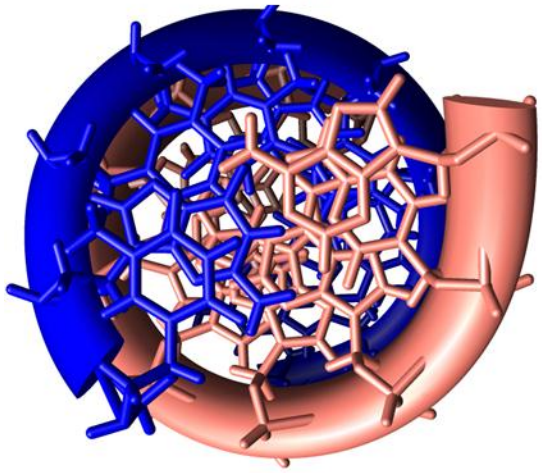


Nucleic acid





DNA Replication

- Semiconservative Replication
- Bidirectional Replication
- Semidiscontinuous replication

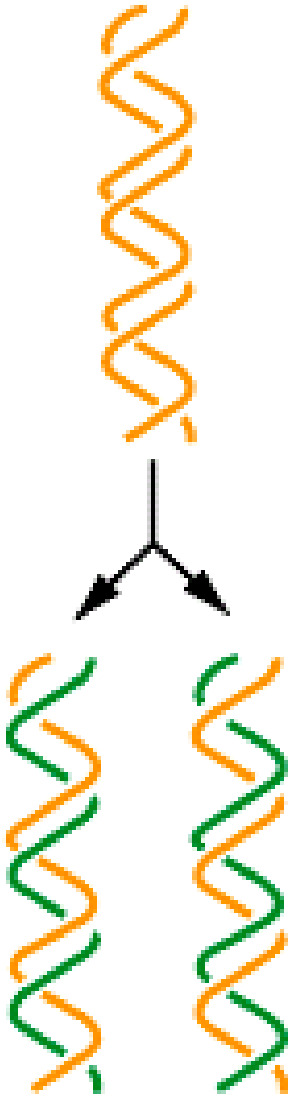
- When a eukaryotic cell divides, the process is called **mitosis**
  - the cell splits into two identical daughter cells
  - the DNA must be replicated so that each daughter cell has a copy
- **DNA replication** involves several processes:
  - first, the DNA must be unwound, separating the two strands
  - the single strands then act as templates for synthesis of the new strands, which are complimentary in sequence
  - bases are added one at a time until two new DNA strands that exactly duplicate the original DNA are produced

Semiconservative Replication

Parent molecule

Replication

Daughter molecules



- The process is called **semi-conservative replication** because one strand of each daughter DNA comes from the parent DNA and one strand is new
- DNA replication is semi-conservative: Each new strand of DNA contains one parental (old, template) strand and one daughter (newly synthesized) strand
- The energy for the synthesis comes from hydrolysis of phosphate groups as the phosphodiester bonds form between the bases

DNA is replicated by the coordinated efforts of a number of proteins and enzymes.

-Topoisomerase: Enzyme uncoils DNA

-Helicase: Protein that unwinds the DNA double helix.

-DNA polymerase: Enzyme that replicates DNA using each strand as a template for the newly synthesized strand.

-DNA ligase: enzyme that catalyzes the formation of the phosphodiester bond between pieces of DNA.

Bidirectional Replication

- Replication forks move in opposite directions.
- During replication in bacteria (E.coli) a bubble is initiated the origin and circular DNA molecule.
- Replication is bidirectional both strands of DNA are replicated .

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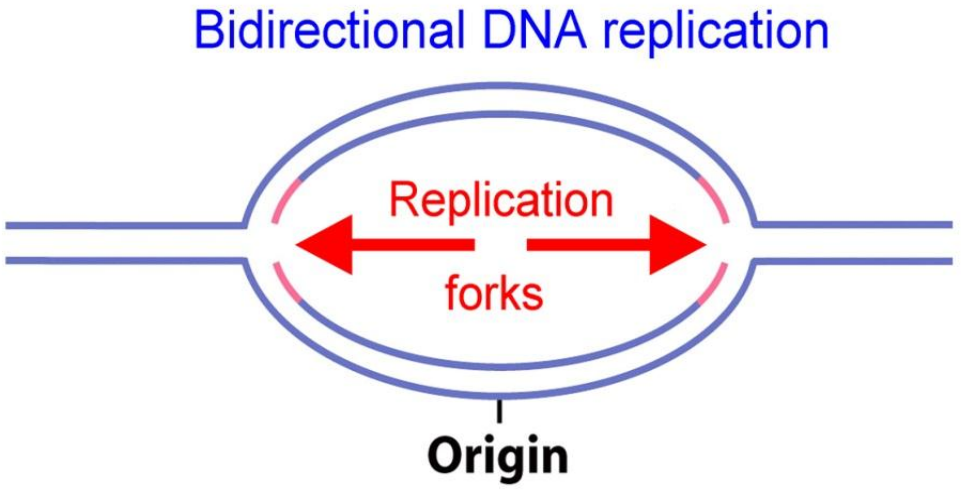


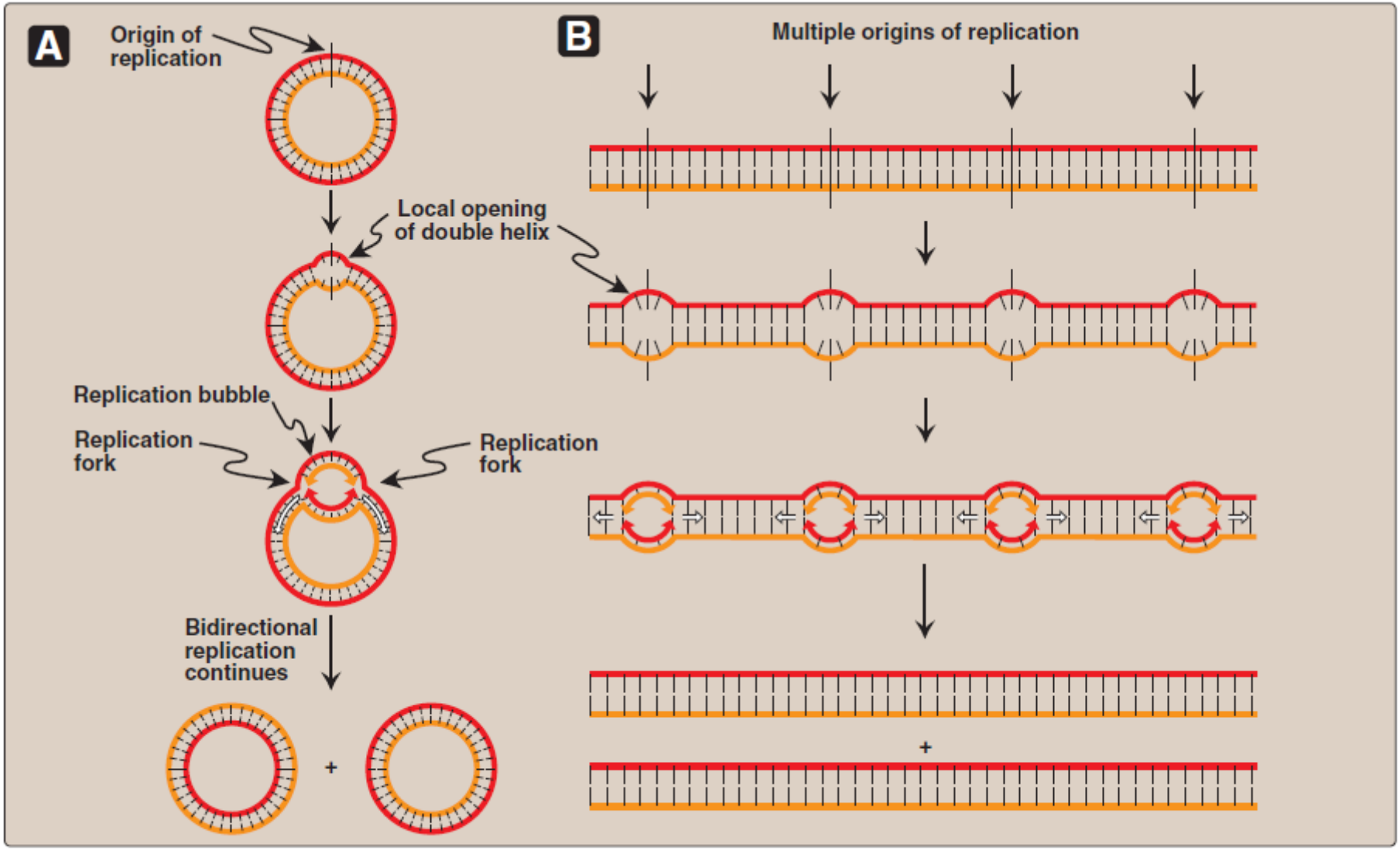
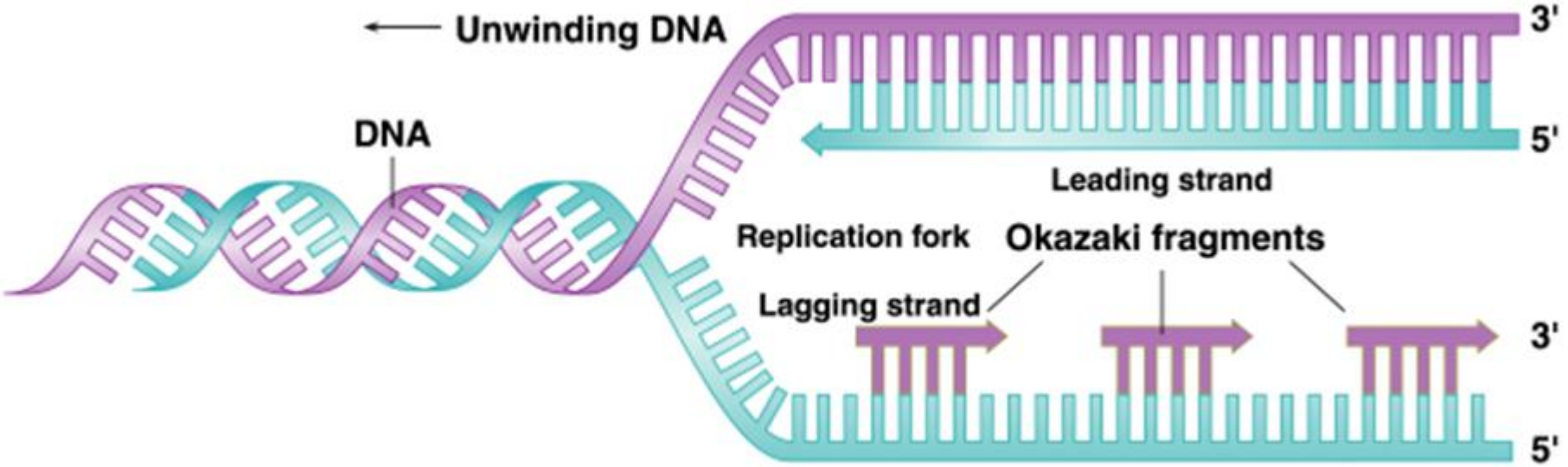


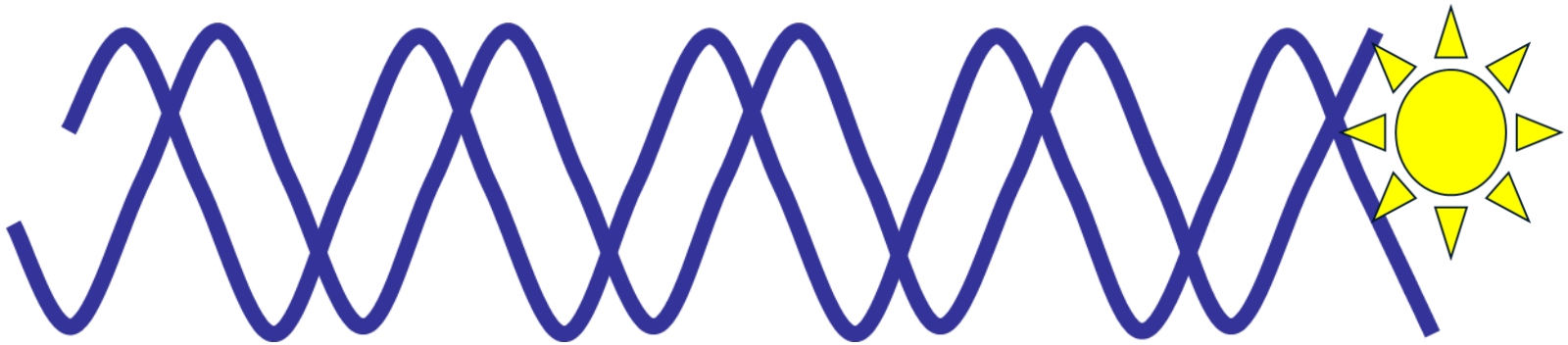
Figure 29.9
Replication of DNA: origins and replication forks. A. Small prokaryotic circular DNA. B. Very long eukaryotic DNA.

Semidiscontinuous Replication

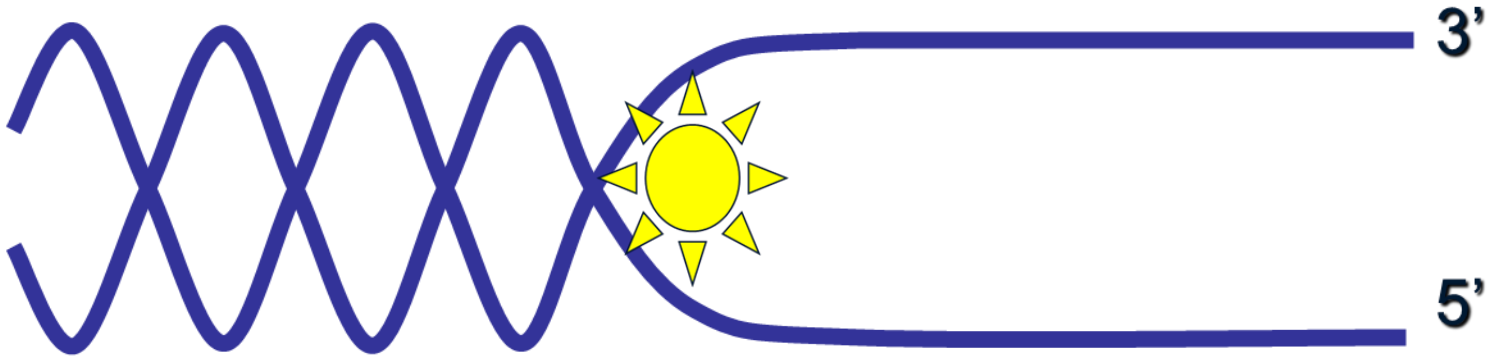
- The enzyme *helicase* unwinds several sections of parent DNA
- At each open DNA section, called a **replication fork**, DNA *polymerase* catalyzes the formation of 5'-3'ester bonds of the **leading strand**
- The **lagging strand**, which grows in the 3'-5' direction, is synthesized in short sections called **Okazaki fragments**
- The Okazaki fragments are joined by DNA *ligase* to give a single 3'-5' DNA strand



New DNA Strands



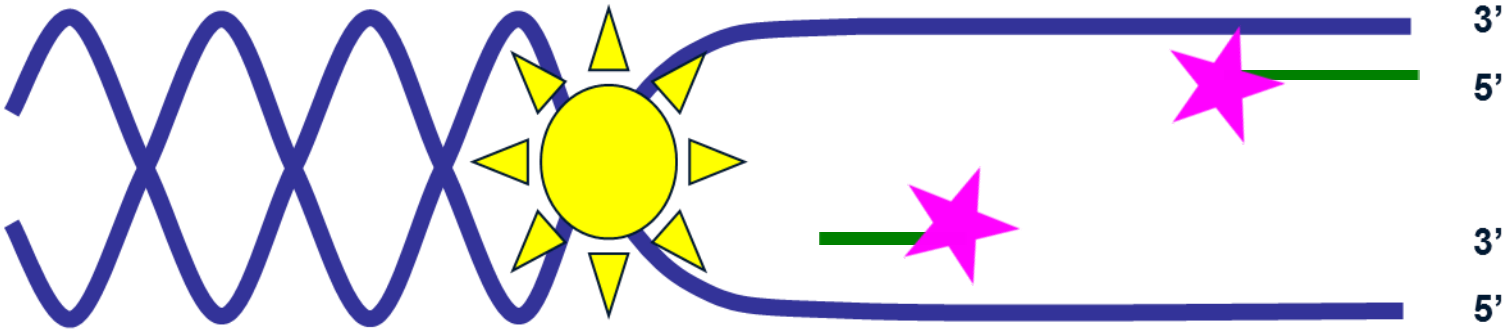
Helicase enzyme splits and unwinds the two stranded DNA.



Forming a New Strand

A topoisomerase enzyme cuts the DNA strand allowing it to twist and relieve pressure.

An enzyme DNA polymerase is used to add a short section of DNA to start the process.

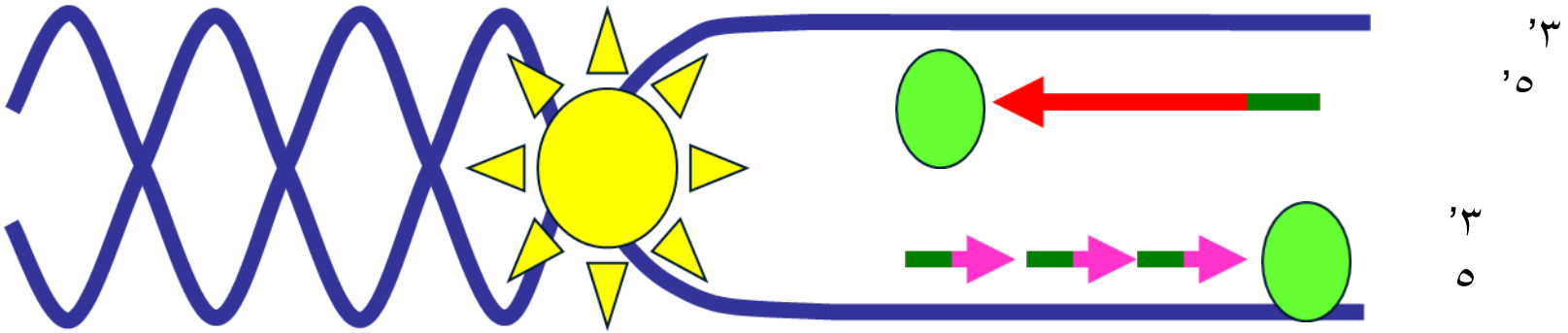


Addition of nucleotides

An enzyme DNA polymerase III is used to catalyse the addition of DNA nucleotides

When nucleotides are added to a new strand they can only do so in a 5’ (5 prime) to 3’ direction.

Nucleotides are added. A joins to T, C joins to G

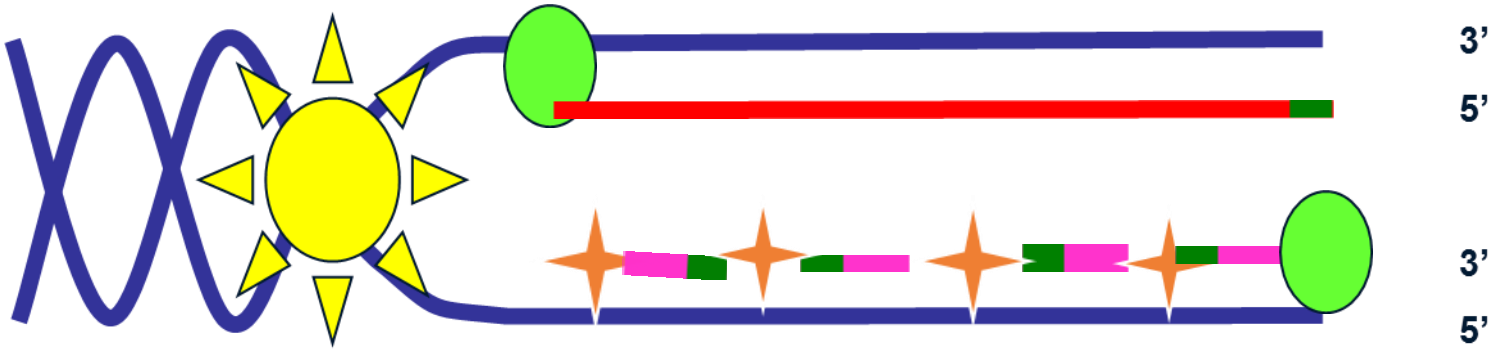


New DNA Strands

The leading strand (red) is synthesized continuously.

The lagging strand (pink) is formed in segments called okazaki fragments

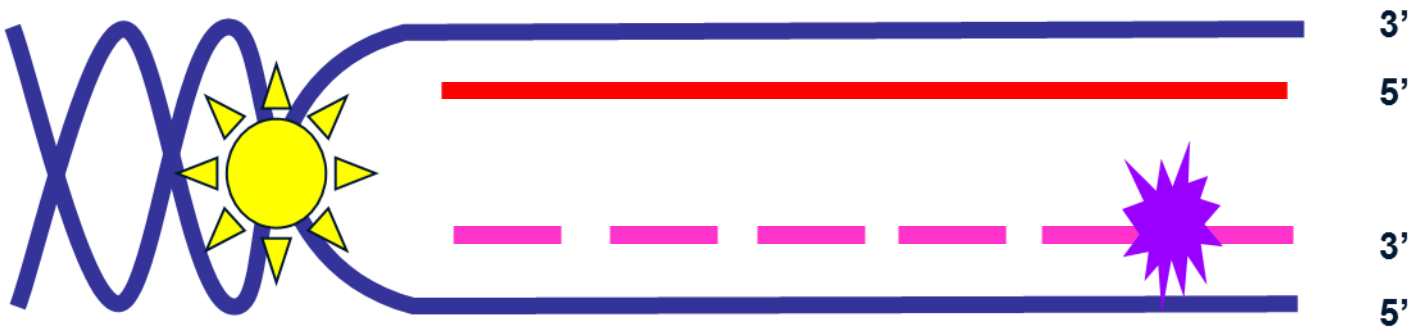
An enzyme DNA polymerase I replaces the RNA primers with DNA



Filling the Gaps

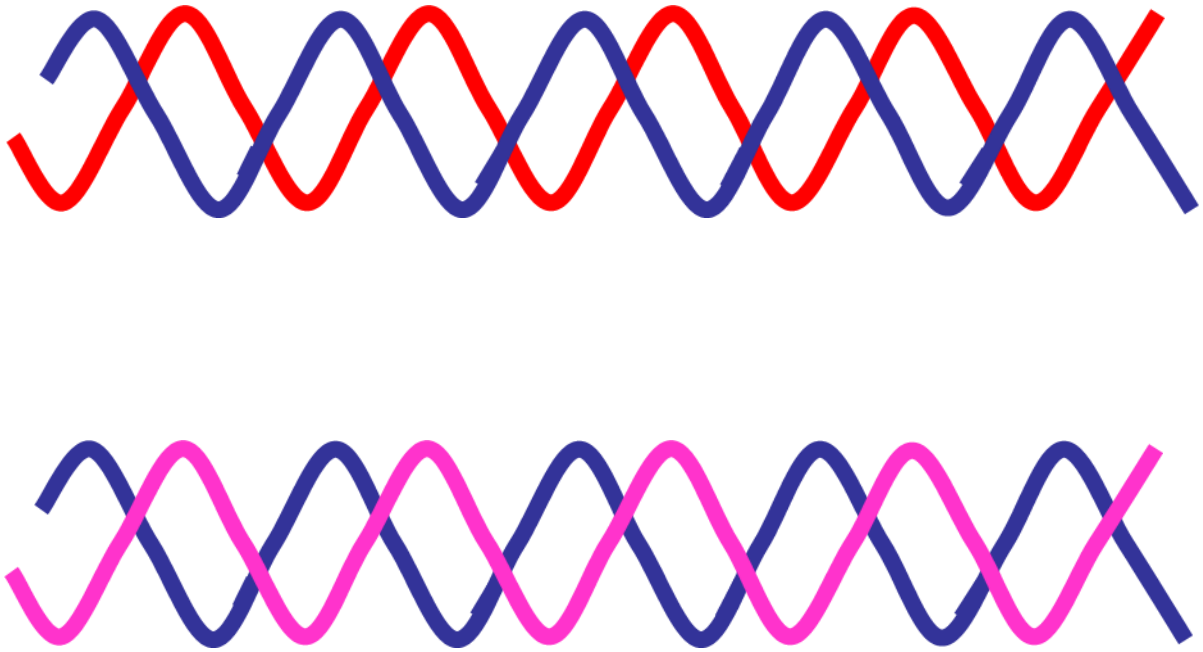
The DNA strands continue to form in a 5’ to 3’ direction.

An enzyme DNA Ligase is used to fill in the gaps in the okazaki fragments with nucleotides



When DNA replication is complete two molecules are formed.

Because half of each strand is new and half original it is called semi conservative replication.



Mutations

a mutation is a permanent change of the nucleotide sequence of the genome of an organism. Mutations result from unrepaired damage to DNA or to RNA genomes (typically caused by radiation or chemical mutagens), errors in the process of replication, or from the insertion or deletion of segments of DNA by mobile genetic elements

Mutations play a part in both normal and abnormal biological processes including: evolution, cancer, and the development of the immune system

Mutations can be caused by external (exogenous) or endogenous (native) factors, or they may be caused by errors in the cellular machinery. Physical or chemical agents that induce mutations in DNA are called mutagens and are said to be mutagenic.

Exogenous factors: environmental factors such as sunlight, radiation, and smoking can cause mutations.

Endogenous factors: errors during DNA replication can lead to genetic changes as can toxic by-products of cellular metabolism.

Classification of mutation types

The sequence of a gene can be altered in a number of ways. Gene mutations have varying effects on health depending on where they occur and whether they alter the function of essential proteins. Mutations in the structure of genes can be classified as

A-By effect on structure

Small-scale mutations, such as those affecting a small gene in one or a few nucleotides, including:

1-Point mutations, often caused by chemicals or malfunction of DNA replication, exchange a single nucleotide for another. These changes are classified as transitions or transversions

Point mutations that occur within the protein coding region of a gene may be classified into three kinds, depending upon what the erroneous codon codes for:

Silent mutations, which code for the same (or a sufficiently similar) amino acid.

Missense mutations, which code for a different amino acid.

Nonsense mutations, which code for a stop and can truncate the protein.

2-Insertions add one or more extra nucleotides into the DNA. They are usually caused by transposable elements, or errors during replication of repeating elements

3-Deletions remove one or more nucleotides from the DNA.

2-Large-scale mutations in chromosomal structure, including:
Amplifications (or gene duplications) leading to multiple copies of all chromosomal regions, increasing the dosage of the genes located within them
a-Deletions of large chromosomal regions, leading to loss of the genes within those regions.
b-Mutations whose effect is to juxtapose previously separate pieces of DNA, potentially bringing together separate genes to form functionally distinct fusion genes. These include:
-Chromosomal translocations
-Loss of heterozygosity
-Chromosomal inversions
-Interstitial deletions

B- By effect on function
1-Loss-of-function mutations result in the gene product having less or no function.
2-Gain-of-function mutations change the gene product such that it gains a new and abnormal function.
3-Dominant negative mutations (also called antimorphic mutations) have an altered gene product that acts antagonistically.

4-Lethal mutations are mutations that lead to the death of the organisms that carry the mutations
5-A back mutation or reversion is a point mutation that restores the original sequence and hence the original phenotype.

C-By effect on fitness

In applied genetics, it is usual to speak of mutations as either harmful or beneficial.
1-A harmful, or deleterious, mutation decreases the fitness of the organism.
2-A beneficial, or advantageous mutation increases the fitness of the organism. .
3-A neutral mutation has no harmful or beneficial effect on the organism.
4-A nearly neutral mutation is a mutation that may be slightly deleterious or advantageous, although most nearly neutral mutations are slightly deleterious.

EXAMPLE:

Sickle-cell disease. The replacement of A by T at the 17th nucleotide of the gene for the beta chain of hemoglobin changes the codon GAG (for glutamic acid) to GTG (which encodes valine). Thus the 6th amino acid in the chain becomes valine instead of glutamic acid.

-Sickle-shaped cells don't move easily through blood. They're stiff and sticky and tend to form clumps and get stuck in blood vessels.

The clumps of sickle cell block blood flow in the blood vessels that lead to the limbs and organs. Blocked blood vessel can cause pain, serious infection, and organ damage.

Patient with cystic fibrosis

also known as mucoviscidosis, is an autosomal recessive genetic disorder that affects mostly the lungs but also the pancreas, liver, and intestine. Difficulty breathing is the most serious symptom and results from frequent lung infections.

Other symptoms including

sinus infections, poor growth, and infertility—affect other parts of the body.

CF is caused by one of many different mutations in the gene

The main signs and symptoms of cystic fibrosis are salty-tasting skin.

Protein Synthesis

The two main processes involved in protein synthesis are

- the formation of mRNA from DNA (transcription)

- the conversion by tRNA to protein at the ribosome (translation)

Transcription takes place in the nucleus, while translation takes place in the cytoplasm

Transcription: process by which the DNA genetic code is read and transferred to messenger RNA (mRNA). This is an intermediate step in protein expression.

Translation: The process by which the genetic code is converted to a protein, the end product of gene expression.

Genetic information is transcribed to form mRNA much the same way it is replicated during cell division

TRANSCRIPTION (Nucleus)

- DNA ⟶ mRNA

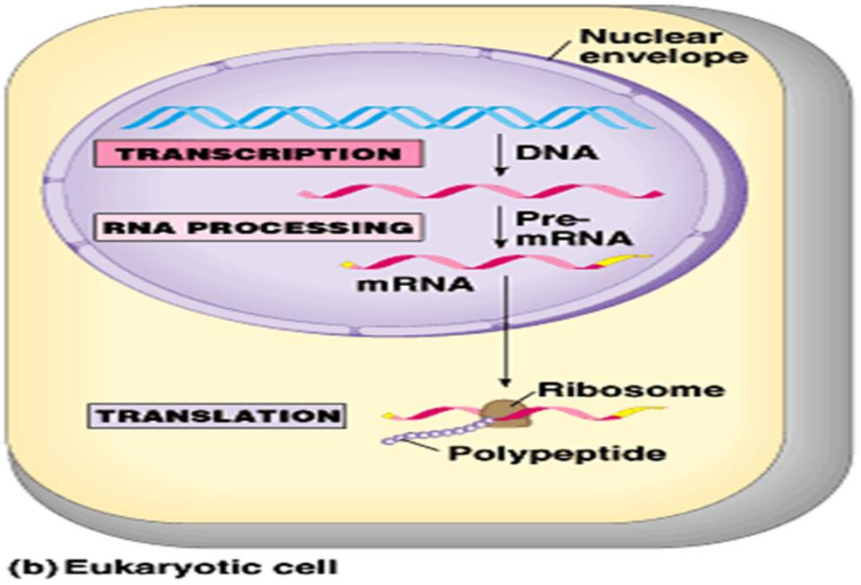
TRANSLATION (Cytoplasm)

-mRNA ⟶ protein

Importance of Protein Synthesis

-Production of hormones

-Production of enzymes



(b) Eukaryotic cell

Transcription :

only one of the DNA strands is copied (coding or antisense strand). An RNA polymerase replicates the DNA sequence into a complementary sequence of mRNA (template or sense strand).

mRNAs are transported from the nucleus to the cytoplasm,
where they acts as the template for protein biosynthesis (translation).

- The mRNA is positioned in the ribosome through complementary pairing of the 5'-untranslated region of mRNA.
- Transfer RNA (tRNA): t-RNAs carries an amino acid and catalyzes amide bond formation.

Transcription: The conversion of a DNA sequence to mRNA.

There are three distinct phases to transcription:

① Initiation: RNA polymerase recognizes a promoter site (specific sequence) of DNA upstream to the gene and locally unwinds the DNA to create a template.

② Elongation: The polymerase moves along the gene synthesizing a complementary copy of the DNA template, but using ribonucleoside triphosphates as precursors (serve as a source of energy for cellular reactions).

③ Termination: When the polymerase encounters a termination sequence it releases the RNA and dissociates from the DNA to end transcription.

The Genetic Code: a set of rules that determines how an mRNA is translated into an amino acid sequence, where the sequence is read as triplets called codons.

The genetic code is common for most organisms.

Each codon specifies an amino acid, except UAG, UGA and UAA (stop codons – where do I end?).

AUG, that codes for Methionine, also serves as an initiation codon (where do I start?)

First letter of codon (5′ end)	Second letter of codon: U		Second letter of codon: C		Second letter of codon: A		Second letter of codon: G	
U	UUU	Phe	UCU	Ser	UAU	Tyr	UGU	Cys
	UUC	Phe	UCC	Ser	UAC	Tyr	UGC	Cys
	UUA	Leu	UCA	Ser	UAA	Stop	UGA	Stop
	UUG	Leu	UCG	Ser	UAG	Stop	UGG	Trp
C	CUU	Leu	CCU	Pro	CAU	His	CGU	Arg
	CUC	Leu	CCC	Pro	CAC	His	CGC	Arg
	CUA	Leu	CCA	Pro	CAA	Gln	CGA	Arg
	CUG	Leu	CCG	Pro	CAG	Gln	CGG	Arg
A	AUU	Ile	ACU	Thr	AAU	Asn	AGU	Ser
	AUC	Ile	ACC	Thr	AAC	Asn	AGC	Ser
	AUA	Ile	ACA	Thr	AAA	Lys	AGA	Arg
	AUG	Met	ACG	Thr	AAG	Lys	AGG	Arg
G	GUU	Val	GCU	Ala	GAU	Asp	GGU	Gly
	GUC	Val	GCC	Ala	GAC	Asp	GGC	Gly
	GUA	Val	GCA	Ala	GAA	Glu	GGA	Gly
	GUG	Val	GCG	Ala	GAG	Glu	GGG	Gly

Translation:

the formation of proteins from the mRNA code (read in the 5' to 3'direction) by ribosomes:

① Activation of Amino Acids:
The amino acid is covalently bound to its corresponding tRNA.

② Initiation: The mRNA-ribosome complex is formed and the first aminoacyl-tRNA (initiator tRNA) binds to the first codon.

③ Elongation: The other codons are read sequentially by the ribosome that associates with the appropriate aminoacyl tRNA (amino acids covalently bound to tRNA) and the polypeptide sequence grows from N- to C-terminus.

④ Termination: When the ribosome encounters the stop codon, it releases the polypeptide and ceases protein synthesis

⑤ Folding and Posttranslational Processing:
The protein must fold properly to be active and may
or may not be modified by enzymes (portions cleaved off or substituents added).