Part2

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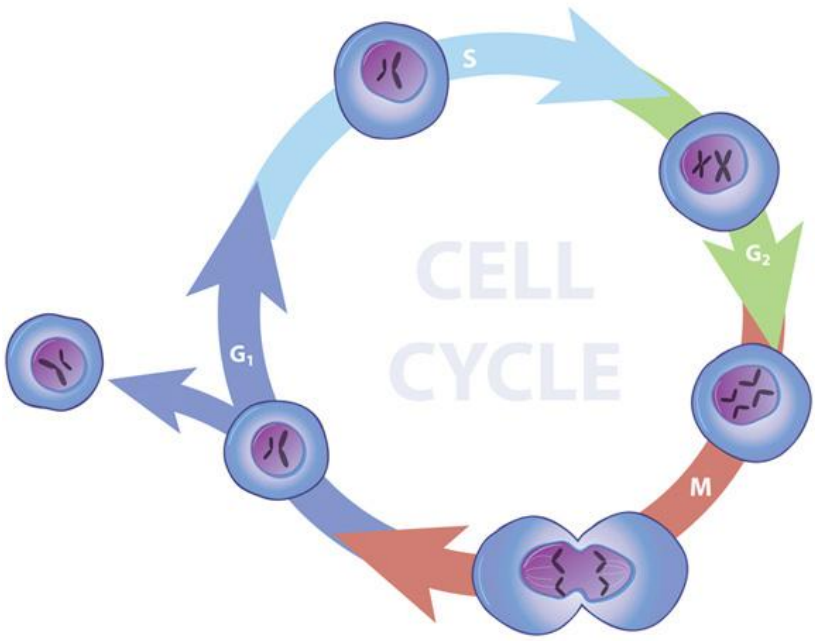
Cell Division or cell cycle

When cells reproduce, the genetic material is distributed between the newly-produced cells, called daughter cells, this is called the cell cycle. The cycle consists of four phases, ***G***1, ***S***, ***G***2 and ***M***. The first three phases (***G***1, ***S*** and ***G***2) comprise interphase while ***M*** constitutes cell division (mitosis or meiosis). The ***S*** phase lasts about 6–8 hours in mammalian cells, ***G***2 about 3–4 hours, while the length of ***G***1 is variable. Whereas ***DNA*** synthesis is restricted to the ***S*** (synthetic) phase, protein synthesis takes place throughout interphase. A cell entering mitosis or meiosis has double the quantity of ***DNA*** and chromosomal proteins. The cell organelles such as mitochondria and ribosomes are assembled throughout interphase in the cytoplasm and passed on to the two daughter cells. This topic looks at different types of cell reproduction.



Mitosis

Somatic cells and gametes reproduce differently. Somatic cells divide by mitosis. Mitosis is the process by which the parent cell divides into two identical daughter cells. These daughter cells are genetically identical to their parent cell. Mitosis is the type of cell division that leads to the growth and development of an organism. All cells, except gametes, divide by mitosis. The process of mitosis can be divided into the following stages. ***See figure.***

1. Interphase
Before actual cell division occurs, the cell grows in size. This growth stage can take a few hours or a few months. DNA molecules replicate but are still in the form of chromatin. The cell's nucleus is still intact.

2. Prophase
DNA molecules are more condensed and coiled. The nucleus is no longer a membrane-bound organelle. A spindle apparatus starts forming, which is also called a mitotic spindle. It is called that because all the microtubules attached to centrosomes at opposite poles of the cell, make it look like a spindle. The mitotic spindle helps chromosomes move in opposite directions. It is formed by the centrosome - the non-membrane bound organelle of the animal cell. Spindle micro-tubules 'drag' chromosomes apart to the newly-formed daughter cells.

3. Metaphase
Spindle microtubules attach themselves to the chromosome centromeres. Chromosomes get aligned along the cellular 'equator'.

4. Anaphase
The micro-tubules of the spindle shorten and separate and drag sister chromatids towards the opposite poles of the cell.

5. Telophase
At this stage, chromosomes reach the opposite poles of the parent cell and the nuclear envelope reforms. Chromosomes uncoil and turn into chromatin again. The spindle fibres disintegrate. The parent cell splits into two daughter cells in the process called cytokinesis. Each daughter cell is diploid and contains the same type of chromosomes as the parent cell.
The process of mitosis can happen in any part of the body.

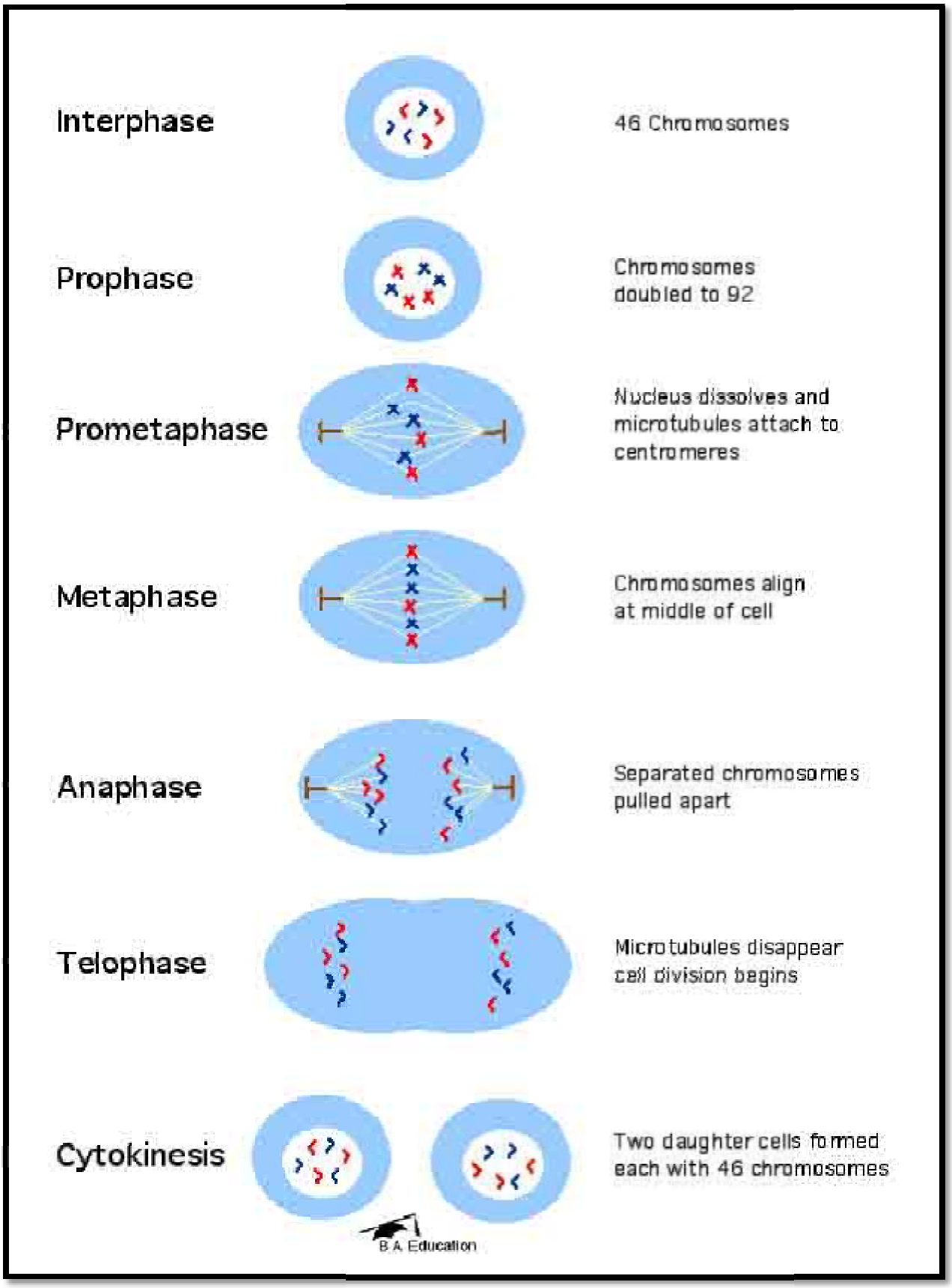


Figure: stage of mitosis in plant cell

Meiosis

A cell division, in which eggs and sperm are produced, is called meiosis. Meiosis takes place in all sexually reproducing organisms. In the process of meiosis, the number of chromosomes is reduced by half, so all gametes are haploid cells (1n). Sometimes meiosis is also called reductive cell division. During fertilization gametes fuse, forming a diploid zygote: 1n+1n=2n. Meiosis consists of two, consecutive nuclear divisions with only one round of DNA replication. At the end of meiosis, four non-identical haploid daughter cells are produced.
Meiosis consists of two stages: meiosis I and meiosis II. ***See figure.***

Meiosis I

1. Interphase 1

As in mitosis, at this stage the cell grows in size getting ready for division. Chromosomes are duplicated, but are still in the cell's nucleus in the form of chromatin.

2. Prophase 1

DNA molecules are more condensed and visible. The key, new events (compared to mitosis,) are the formation of tetrads and a crossover. Each tetrad is composed of four chromatids. Non-sister chromatids of the homologous chromosomes exchange pieces of DNA in the process of crossing over. Later, the envelope of the nucleus breaks down and tetrads migrate to the opposite cell poles.

3. Metaphase 1

Tetrads line up along the cell's equator with their centromeres facing the opposite cell poles.

4. Anaphase 1

Chromosomes move to the opposite cell poles with the help of centrosome micro-tubules. The homologous chromosomes move to the opposite cell poles, yet sister chromatids remain together.

5. Telophase 1

Meiotic spindles continue to move the homologous chromosomes to the poles. Once movement is complete, each pole has a haploid number of chromosomes. The chromosomes are double stranded. Two genetically non-identical daughter cells are formed in the process of cytokinesis.
The genetic material does not replicate again.

Meiosis II

There is no interphase stage in meiosis II. It starts with prophase.

1. Prophase 2

The nuclear envelope breaks and the spindle apparatus forms. Chromosomes begin to migrate towards the cell's equator.

2. Metaphase 2

Chromosomes line up at the cell's equator with their centromeres facing opposite poles of the cell.

3. Anaphase 2

Sister chromatids separate and move toward opposite cell poles.

4. Telophase 2

The cellular nucleus is formed and daughter cells are formed after cytokinesis is complete. At the end of meiosis II, there are four daughter cells, each with half the number of chromosomes of the original parent cell. Each daughter cell gets one of the four chromatids from the tetrads.

The process of meiosis can happen only in organs which produce sex cells. It is possible to see different stages of cell division through the microscope because condensed chromosomes stain well with biological dyes.

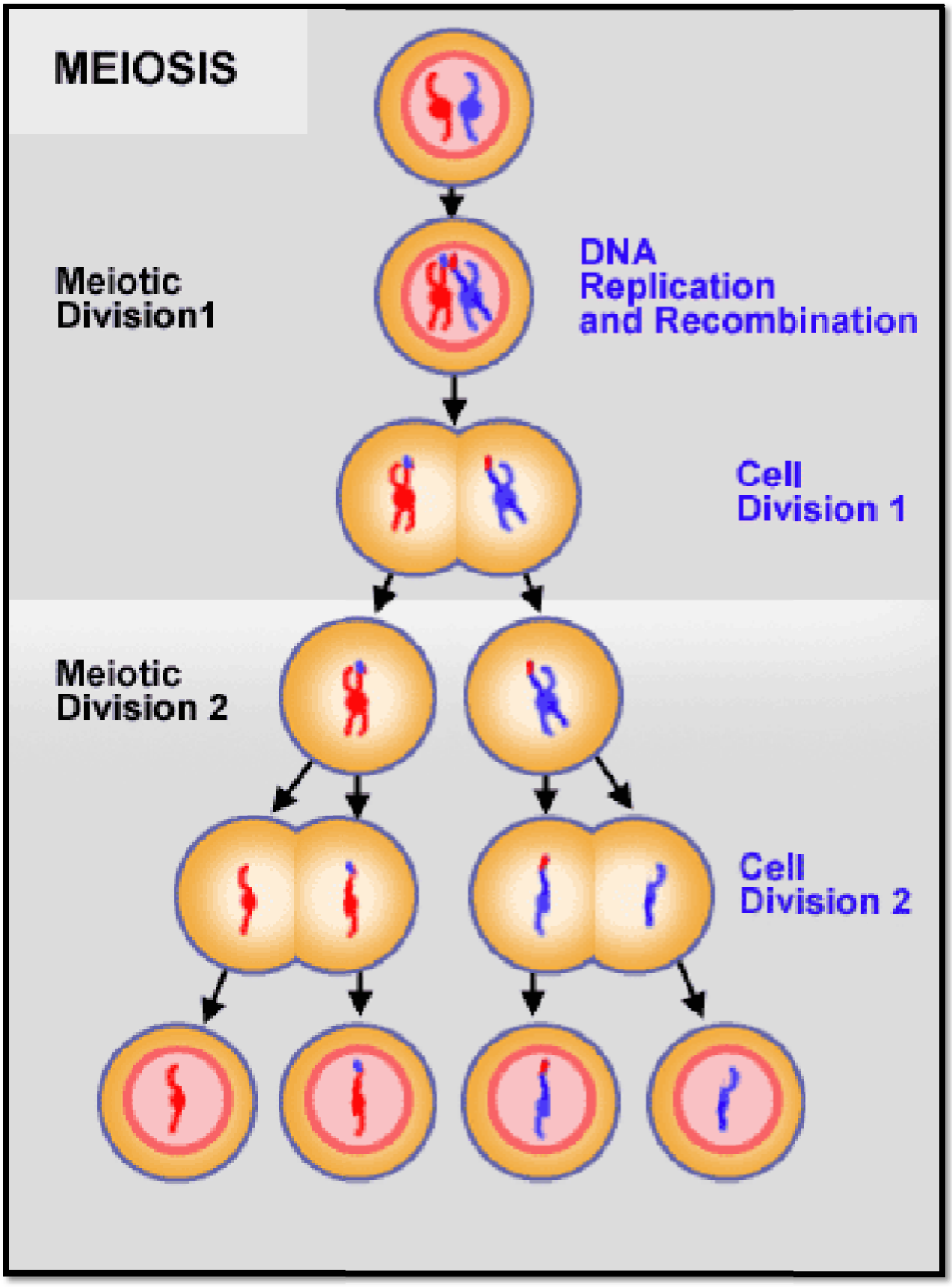
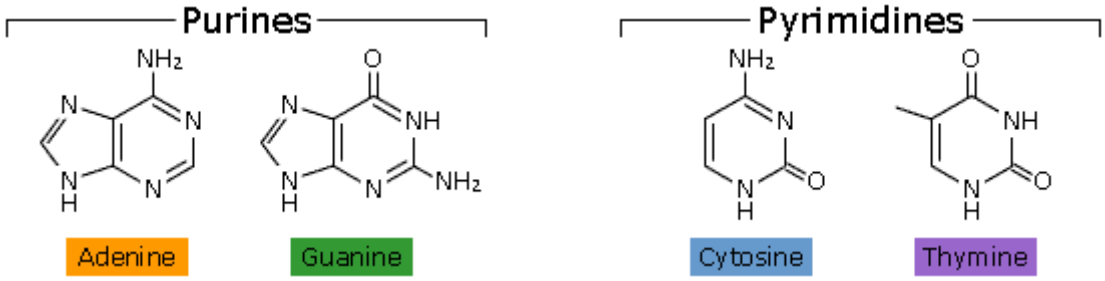


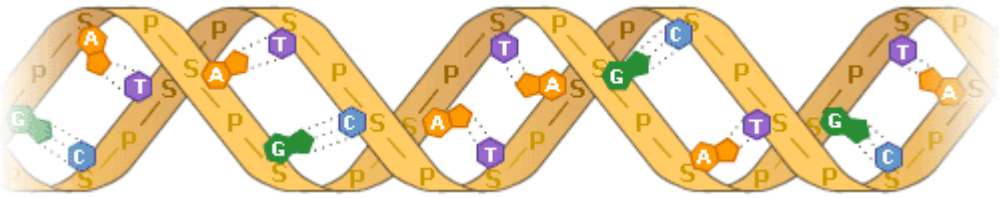
Figure: comparison of meiosis as it occurs in spermatogenesis and in oogenesis

DNA (Deoxyribonucleic Acid)

Deoxyribonucleic Acid (DNA) is the genetic material found in the cells of all living organisms. DNA is the fundamental building blocks for life. Nearly every cell (with a nucleus) in a person's body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but DNA can also be found in the mitochondria (where it is called mitochondrial DNA or mtDNA).
The information in DNA is made up of four bases which combine to form chains. These bases include two purines (Adenine and Guanine) and two pyrimidines (Cytosine and Thymine). These are commonly referred to as A, G, C and T respectively. Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people. It is the order, or sequence, of these bases which determines genetic characteristics.



Each base is attached to a Sugar (S) molecule and a Phosphate (P) molecule. Together, a base, sugar, and phosphate are called a nucleotide. Nucleotides are arranged in two long strands that form a spiral called a double helix. The structure of the double helix is somewhat like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the vertical sidepieces of the ladder.



The number of purine bases in DNA is equal to the number of pyrimidines. This is due to the law of complimentary base pairing; which is Thymine (T) can only pair with Adenine (A), and Guanine (G) can only pair with Cytosine (C). Knowing this rule, we could predict the base

sequence of one DNA strand if we knew the sequence of bases in the complimentary strand.
Where is DNA Found in the Human Body?
DNA is contained in blood, skin cells, hair, semen, bones, teeth, saliva, perspiration, fingernails, tissue, muscles, brain cells, organs, mucus, urine, feces, vomit, etc...

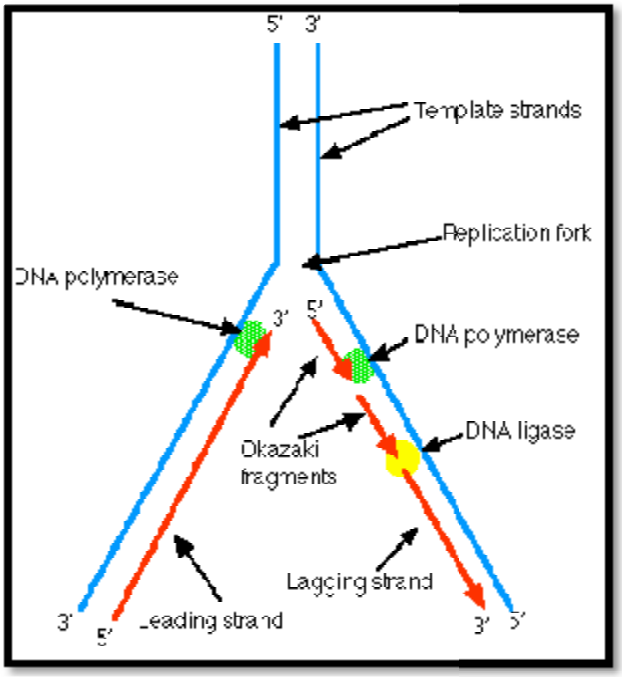
Mitochondrial DNA
Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA. This genetic material is known as mitochondrial DNA or mtDNA.
Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Each cell contains hundreds to thousands of mitochondria, which are located in the fluid that surrounds the nucleus (the cytoplasm).
Mitochondria produce energy through a process called oxidative phosphorylation. This process uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source. A set of enzyme complexes carry out oxidative phosphorylation within mitochondria.
In addition to energy production, mitochondria play a role in several other cellular activities. For example, mitochondria help regulate the self-destruction of cells (apoptosis). They are also necessary for the production of substances such as cholesterol and heme (a component of hemoglobin, the molecule that carries oxygen in the blood).
Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. 13 of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making molecules called transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs). These types of RNA help assemble protein building blocks (amino acids) into functioning proteins.

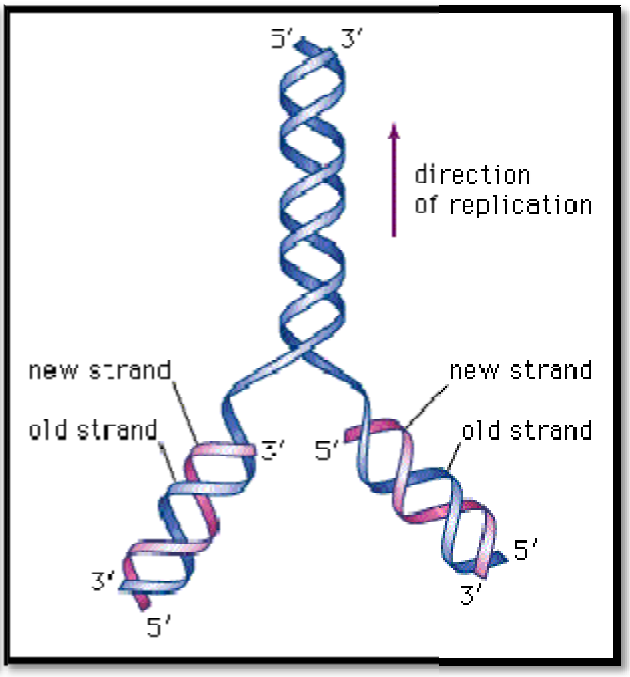
DNA Replication
Is the process of copying a double-stranded DNA strand, prior to cell division (in eukaryotes, during the S phase). The two resulting double strands are identical, and each of them consists of one original and one newly synthesized strand. The process of replication consists of three steps, ***initiation***, ***replication*** and ***termination***. Initiation In the initiation step, several key factors are recruited to an origin of replication. This is a sequence that is rich in adenine-thymine base pairs, which are more easily

separated than cytosine-guanine base pairs. Once the strands are initially unwound, several factors come into play. The partially unwound strands form a "replication bubble", with one "replication fork" on either end. Each group of enzymes at the replication fork proceeds away from the origin, unwinding and replicating the DNA strands as they move.
Replication
Termination

Steps of DNA Replication

1. An enzyme called DNA gyrase makes a nick in the double helix and each side separates
2. An enzyme called helicase unwinds the double-stranded DNA
3. Several small proteins called single strand binding proteins (SSB) temporarily bind to each side and keep them separated
4. An enzyme complex called DNA polymerase "walks" down the DNA strands and adds new nucleotides to each strand. The nucleotides pair with the complementary nucleotides on the existing stand (A with T, G with C).
5. A subunit of the DNA polymerase proofreads the new DNA
6. An enzyme called DNA ligase seals up the fragments into one long continuous strand
7. The new copies automatically wind up again





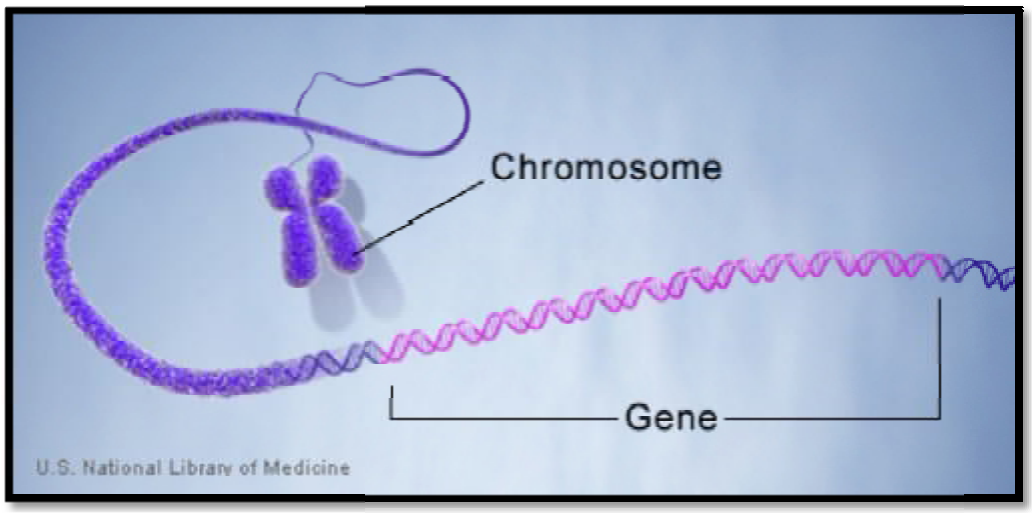
Mistakes in DNA replication

DNA replication is not perfect. Errors occur in DNA replication, when the incorrect base is incorporated into the growing DNA strand. This leads to ***mismatched*** base pairs, or ***mispairs***. DNA polymerases have proofreading activity, and a DNA repair enzymes have evolved to correct these mistakes. Occasionally, mispairs survive and are incorporated into the genome in the next round of replication. These mutations may have no consequence, they may result in the death of the organism, they may result in a genetic disease or cancer; or they may give the organism a competitive advantage over its neighbors, which leads to evolution by natural selection.

What is a gene

A gene is the basic physical and functional unit of heredity. Genes, which are made up of DNA, act as instructions to make molecules called proteins. In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases. The Human Genome Project has estimated that humans have between 20,000 and 25,000 genes.

Every person has two copies of each gene, one inherited from each parent. Most genes are the same in all people, but a small number of genes (less than 1 percent of the total) are slightly different between people. Alleles are forms of the same gene with small differences in their sequence of DNA bases. These small differences contribute to each person's unique physical features.



Genes are made up of DNA. Each chromosome contains many genes.

Gene on the X Chromosome: X-Linkage

The X and Y chromosomes don't just determine sex, but also contain many other genes that have nothing to do with sex determination. The Y chromosome is very small and seems to contain very few genes, but the X chromosome is large and contains thousands of genes for important products such as rhodopsin (a protein in the membrane of a photoreceptor cell in the retina of the eye, basically a light absorbing pigment), blood clotting proteins and muscle proteins. Females have two copies of each gene on the X chromosome (i.e. they're diploid), but males only have one copy of each gene on the X chromosome (i.e. they're haploid). This means that the inheritance of these genes is different for males and females, so they are called sex linked characteristics.

X-Linkage: An Examples

1- Hemophilia is a blood clotting disorder caused by a mutant gene encoding either

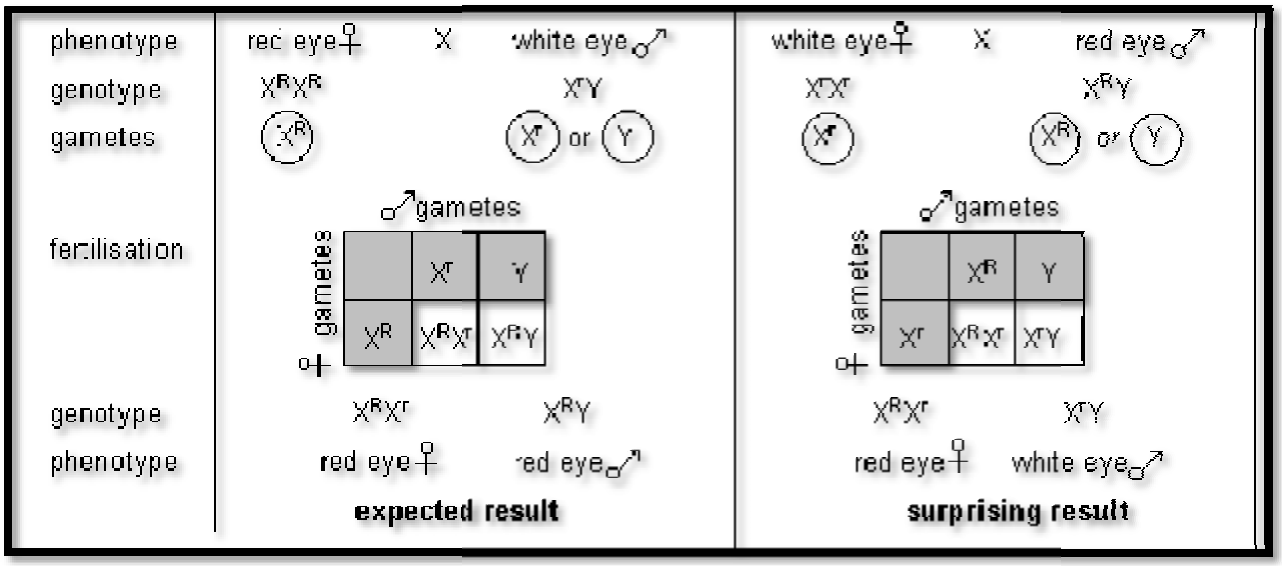
- clotting factor VIII, causing hemophilia A or
- clotting factor IX, causing hemophilia B.

Both genes are located on the X chromosome (X^h). With only a single X chromosome, males who inherit the defective gene (always from their mother) will be unable to produce the clotting factor and suffer from difficult-to-control episodes of bleeding. In heterozygous females, the unmutated copy of the gene will provide all the clotting factor they need. Heterozygous females are called "carriers" because although they show no symptoms, they pass the gene on to approximately half their sons, who develop the disease, and half their daughters, who also become carriers.

	X	Y
X	XX	XY
X^h	X^hX	X^hY

Women rarely suffer from hemophilia because to do so they would have to inherit a defective gene from their father as well as their mother. Until recently, few hemophiliacs ever became fathers.

2- Eye color in Drosophila, Red eyes (R) are dominant to white eyes (r) and when a red-eyed female is crossed with a white-eyed male, the offspring all have red eyes, as expected for a dominant characteristic (left cross below). However, when the opposite cross was done (a white-eye female with a red-eyed male) all the male offspring had white eyes (right cross below). This surprising result was not expected for a simple dominant characteristic, but it could be explained if the gene for eye color was located on the X chromosome. Note that in these crosses the alleles are written in the form X^R (red eyes) and X^r (white eyes) to show that they are on the X chromosome.



Males always inherit their X chromosome from their mothers, and always pass on their X chromosome to their daughters.

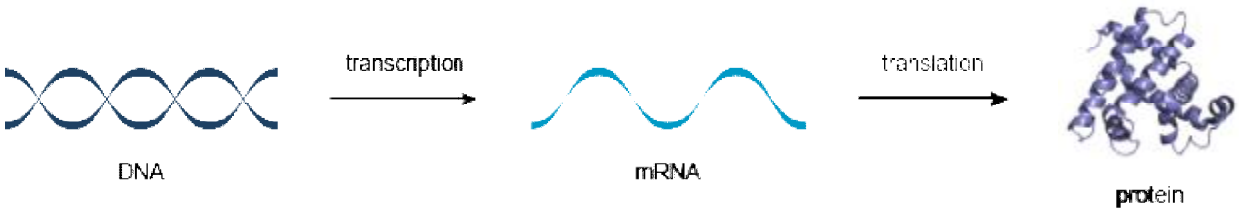
Gene transcription and translation to protein

DNA, RNA and protein synthesis

The genetic material is stored in the form of DNA in most organisms. In humans, the nucleus of each cell contains 3×10^9 base pairs of DNA distributed over 23 pairs of chromosomes, and each cell has two copies of the genetic material. This is known collectively as the human genome. The human genome contains around 30 000 genes, each of which codes for one protein.

Large stretches of DNA in the human genome are transcribed but do not code for proteins. These regions are called ***introns*** and make up around 95% of the genome. The nucleotide sequence of the human genome is now

known to a reasonable degree of accuracy but we do not yet understand why so much of it is non-coding. Some of this non-coding DNA controls gene expression but the purpose of much of it is not yet understood.
The ***Central Dogma of Molecular Biology*** states that DNA makes RNA makes proteins (Figure).



The process by which DNA is copied to RNA is called transcription, and that by which RNA is used to produce proteins is called translation.

Transcription

Transcription is the process by which DNA is copied (***transcribed***) to mRNA, which carries the information needed for protein synthesis. Transcription takes place in two broad steps. First, pre-messenger RNA is formed, with the involvement of RNA polymerase enzymes. The process relies on Watson-Crick base pairing, and the resultant single strand of RNA is the reverse-complement of the original DNA sequence. The pre-messenger RNA is then "edited" to produce the desired mRNA molecule in a process called ***RNA splicing***.

Formation of pre-messenger RNA

The mechanism of transcription has parallels in that of DNA replication. As with DNA replication, partial unwinding of the double helix must occur before transcription can take place, and it is the RNA polymerase enzymes that catalyze this process.
Unlike DNA replication, in which both strands are copied, only one strand is transcribed. The strand that contains the gene is called the ***sense*** strand, while the complementary strand is the ***antisense*** strand. The mRNA produced in transcription is a copy of the sense strand, but it is the antisense strand that is transcribed.
Ribonucleotide triphosphates (NTPs) align along the antisense DNA strand, with Watson-Crick base pairing (A pairs with U). RNA polymerase joins the ribonucleotides together to form a pre-messenger RNA molecule that is complementary to a region of the antisense DNA strand. Transcription ends when the RNA polymerase enzyme reaches a triplet of bases that is read as a "stop" signal. The DNA molecule re-winds to re-form the double helix.

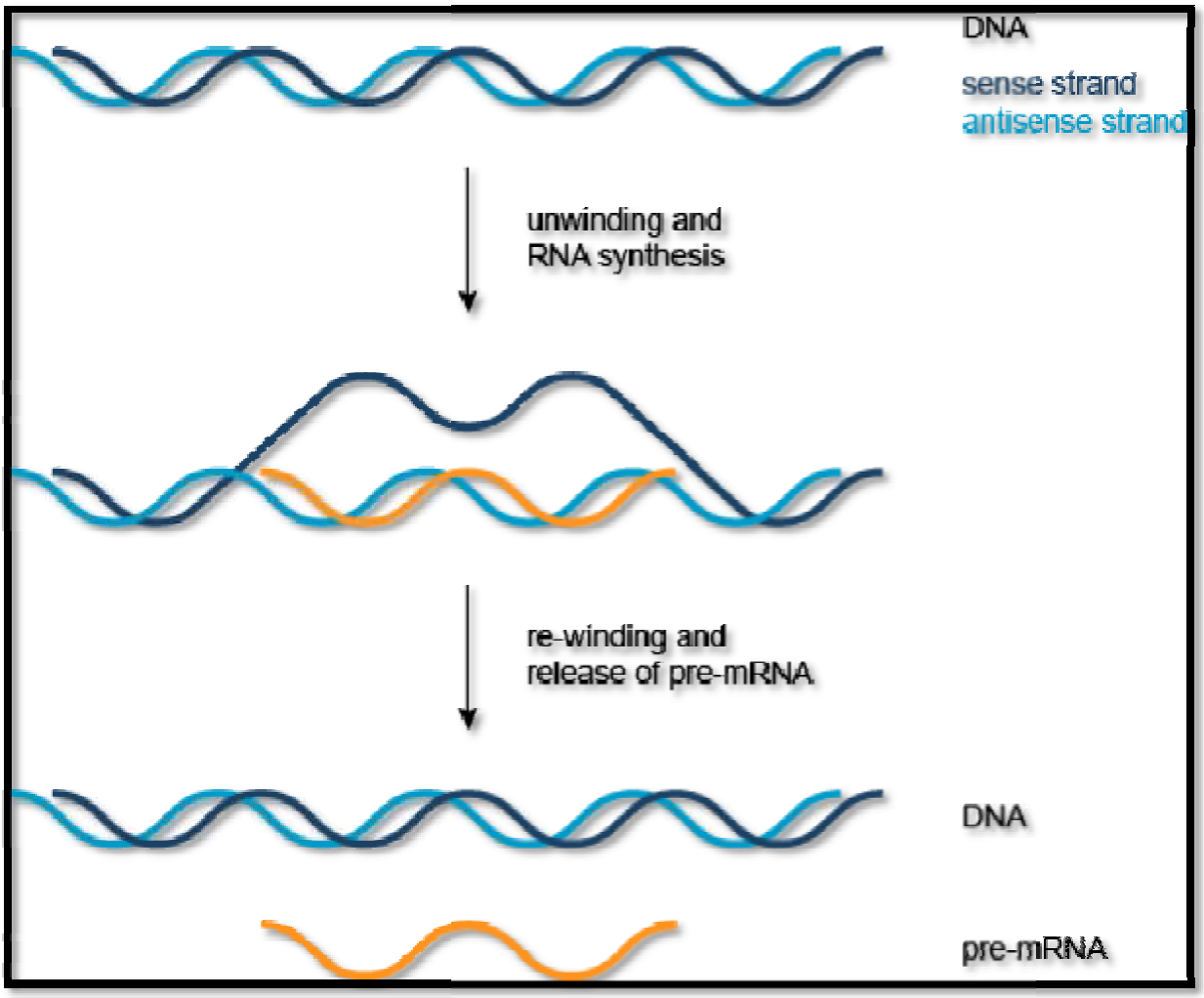


Figure | Transcription Simplified representation of the formation of pre-messenger RNA (orange) from double-stranded DNA (blue) in transcription.

RNA splicing

The pre-messenger RNA thus formed contains introns which are not required for protein synthesis. The pre-messenger RNA is chopped up to remove the introns and create messenger RNA (mRNA) in a process called RNA splicing (Figure).

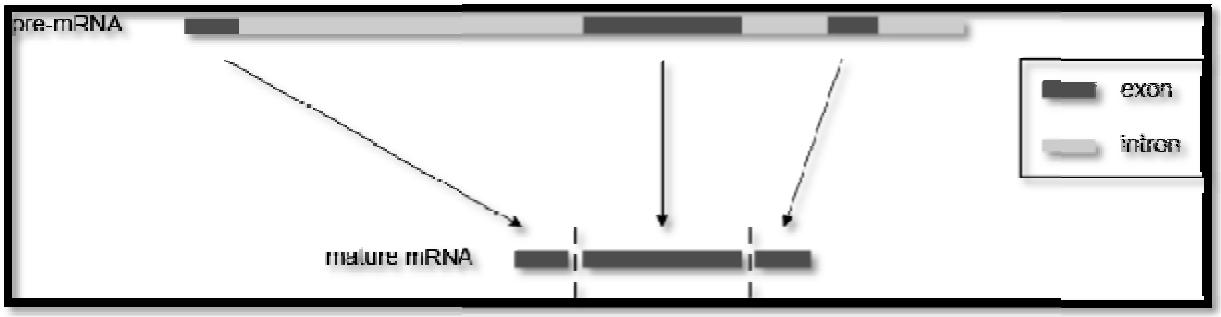


Figure | RNA splicing Introns are spliced from the pre-messenger RNA to give messenger RNA mRNA).

Translation

The mRNA formed in transcription is transported out of the nucleus, into the cytoplasm, to the ribosome (the cell's protein synthesis factory). Here, it directs protein synthesis. Messenger RNA is not directly involved in protein synthesis − transfer RNA (tRNA) is required for this. The process by which mRNA directs protein synthesis with the assistance of tRNA is called ***translation***.

The ribosome is a very large complex of RNA and protein molecules. Each three-base stretch of mRNA (triplet) is known as a ***codon***, and one codon contains the information for a specific amino acid. As the mRNA passes through the ribosome, each codon interacts with the ***anticodon*** of a specific transfer RNA (tRNA) molecule by Watson-Crick base pairing. This tRNA molecule carries an amino acid at its 3′-terminus, which is incorporated into the growing protein chain. The tRNA is then expelled from the ribosome. Figure shows the steps involved in protein synthesis.

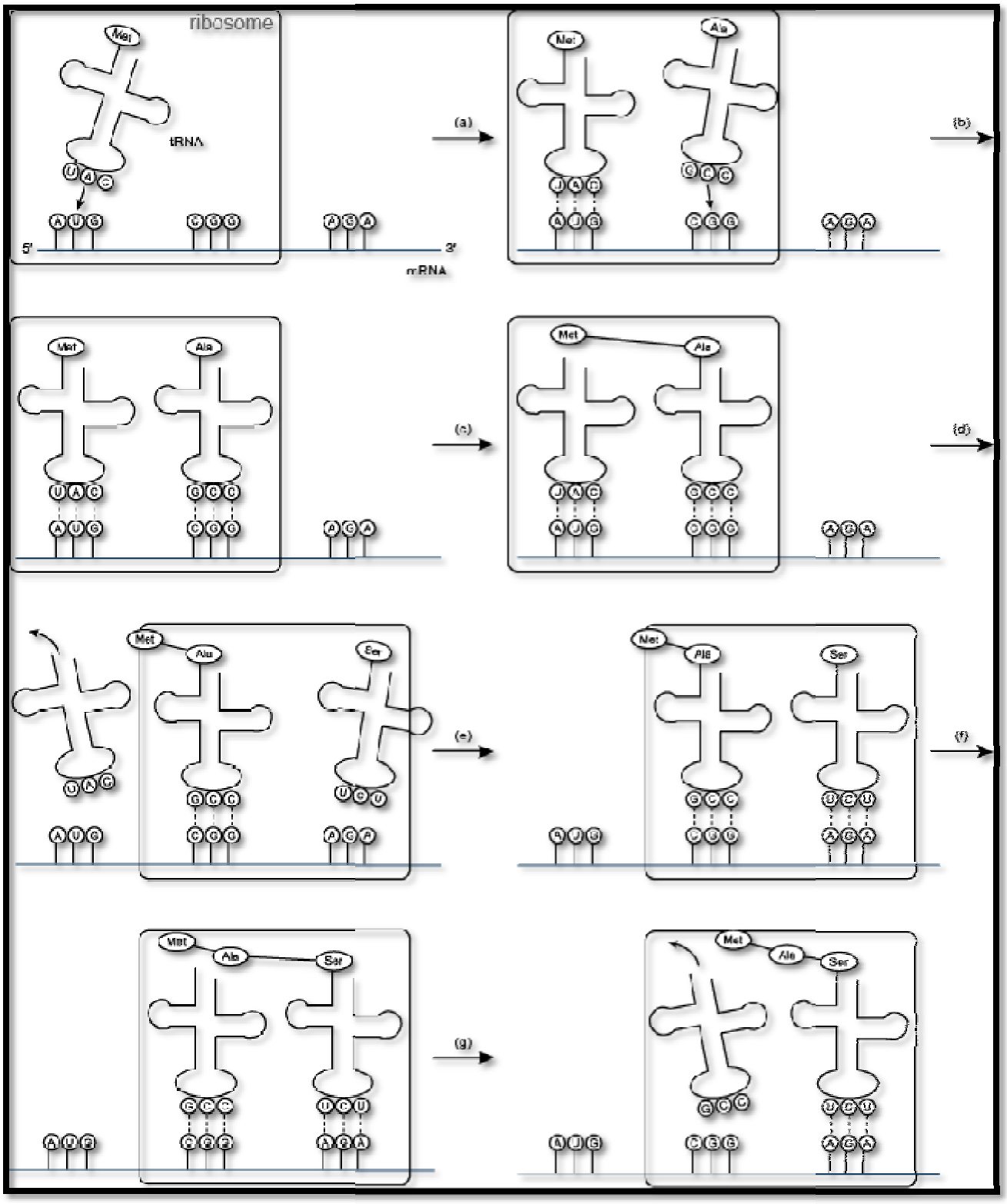


Figure | Translation(a) and (b) tRNA molecules bind to the two binding sites of the ribosome, and by hydrogen bonding to the mRNA; (c) a peptide bond forms between the two amino acids to make a dipeptide, while the tRNA molecule is left uncharged; (d) the uncharged tRNA molecule leaves the ribosome, while the ribosome moves one codon to the right (the dipeptide is translocated from one binding site to the other); (e) another tRNA molecule binds; (f) a peptide bond forms between the two amino acids to make a tripeptide; (g) the uncharged tRNA molecule leaves the ribosome.