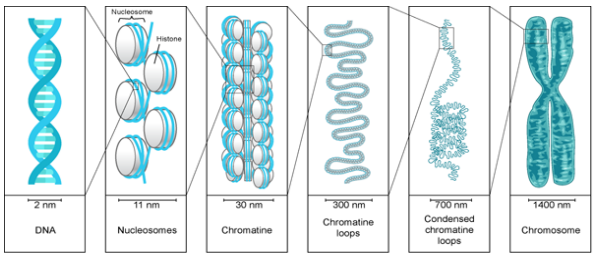
# *CELL DIVISION*

A) **Cell Division** = **Nuclear Division** (nucleus division – mitosis/meiosis) + **Cytokinesis** (cytoplasm division)

B) **Chromosome** – found in dividing cells during mitosis = **condensed chromatin** + tightly coiled + shorter (**euchromatin = not dividing cell)**
1 DNA Molecule wound around **histone octamer** = nucleosome -> coiled further – chromosome
- After **replication,** chromosome = 2 genetically identical sister chromatids (held tgt. at centromere)




C) **Ploidy:** No. of single sets of chromosomes (**diploid = 2 idential sets** w/ homologous chromosome pairs – e.g. somatic cells) VS. (**haploid = 1 complete set** – e.g. gametes)

D) **Homologous Chromosomes**: pair of chromosomes w/ same **length** (1), **centromere position** (2) + **genes** for same characteristics (3) at same **loci** (4)
- may have different **allele** (alternative form of gene w/ different phenotype)

E) **Cell Div. Factors** – surface area to volume ratio (1), nucleo-cytoplasmic ratio (2), growth factors (e.g. auxin)

F) **Cell Cycle** – Interphase (longest phase – 90%), nuclear division, cytokinesis
- **Interphase**: DNA Replication (1), Growth + Synthesis (2), Organelle Prod. (3)
- **G1:** Centriole replication, synthesis of organelles, proteins, ATP
- **S** (synthesis): DNA replication -> **DNA content** of entire cell **doubles**
- **G2:** Cellular synthesis w/ spindle protein synthesis (tubulin)

G) **Mitosis**: nuclear division to produce **2 genetically identical daughter nuclei** with identical no. and type of chromosomes

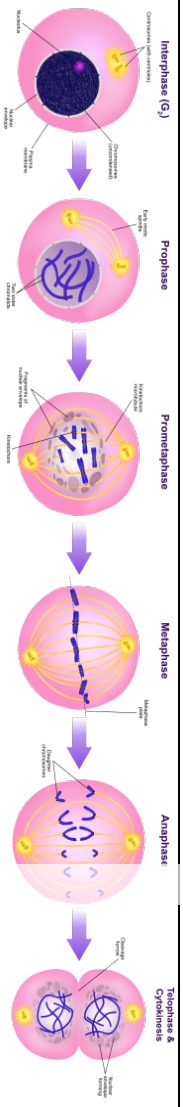
**1) Interphase (**not part of mitosis**):** longest part of cell division (90% of cell cycle) w/ G1, S and G2 Phases
- **X2 DNA** (chromatin)**, X2 Centrosomes,** stained nucleolus + **nuclear envelope** – present

**2) Prophase:**
(1) **Centrioles** move to opposite poles
(2) **Nuclear envelope + nucleus** disintegrates
(3) **Chromatin condensation** into chromosomes
(4) Formation of **mitotic spindle + spindle fibres**

**3): Metaphase:** (longest stage)
(1) **Spindle fibres** fully formed & attached to kinetochores on chromosome centromere
(2) **Chromosomes** aligned at the **metaphase plate** in a **single file** – equidistant from spindle poles)

**4) Anaphase:** (shortest stage)
(1) **Elongation** of non-kinetochore microtubules – cell elongation + spindle poles move apart
(2) **Centromeres** divide and separate
(3) **Chromatids** -> daughter chromosomes move to opposite poles in 'V' formation – pulled to opposite poles by **shortening** kinetochore microtubules

**5) Telophase + Cytokinesis**
(1) **Cleavage furrow/cell plate** formation + spindle fibres disintegration
(2) Daughter chromosomes decondense into **chromatin**
(3) Nuclear envelope reforms and **nucleolus** reappears – spindle fibres disintegrate



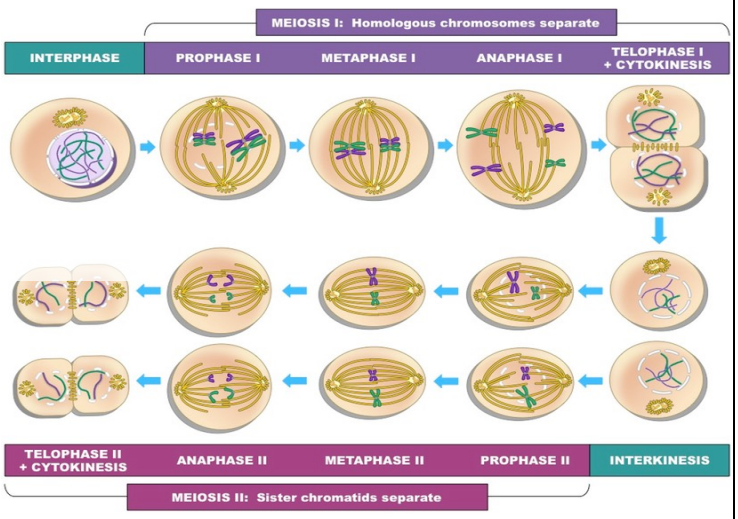

K) **Meiosis**: nuclear division to produce **4 daughter nuclei** with **half the no. of chromosomes** (haploid gametes = ploidy level **n**)
- **Meiosis I: Pairing of homologous chromosomes** – separation into 2 daughter cells (which reduces **chromosome number by half**)
- **Meiosis II**: Separation of the 2 sister chromatids
- Interphase, PMAT(I) + PMAT (II)

**1) Prophase I:**
(1) Homologues pair up via **synapsis** to form **bivalents**
(2) **Crossing over** between **non-sister chromatids** of homologous chromosomes + chiasmata formation

**2) Metaphase I:**
(1) Independent arrangement of bivalents – regardless of orientation **(Independent assortment and segregation)**

**3)** Anaphase I: homologues separate (not chromatids)

Meiosis II = Mitosis (**but w/ haploid cells + nonidentical sister chromatids)**




**J) Mitosis –** maintains genetic stability (semi-conservative replication + even chromosome distribution = 0 genetic variation)
- allows for asexual reproduction, growth and cell replacement

**L) Genetic Variation:**
(1) **Crossing Over – Prophase I** = new combination of alleles on chromosomes
(2) **Independent assortment & arrangement** – **Metaphase/Anaphase I &II** = **I:** arrangement & separation of homologous chromosomes of bivalent vs. **II:** arrangement & separation of non-identical sister chromatids
(3) **Random fusion of gametes during fertilization**

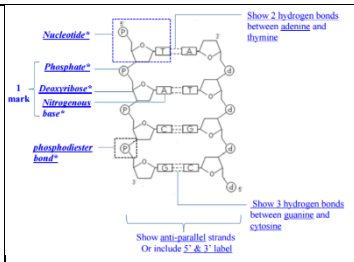
# *DNA & GENOMICS I*

**A) DNA & RNA** – nucleic acid polymers carrying genetic material **(monomer = nucleotides)**

**B) Nucleotide** = 5C sugar, nitrogenous base + PO4- group(s)
- No. of PO4- groups = 1-3 (variable)
- Nucleoside (5-carbon sugar, nitrogenous base)

**(1) Sugar** – pentose (5C) sugar: DNA = **oxyribose** sugar (-H at C2) vs. RNA = **ribose** sugar (-OH group at C2)
**(2) Phosphate** – attached to **C5** of sugar (gives nucleic acids their **-ve charge** and **acidic** character)
**(3) Nitrogenous base** – attached to carbon 1:
**Purine (3-ringed):** adenine (A), guanine (G)
**Pyrimidine(2-ringed):** cytosine (C), thymine (T) and uracil (U)

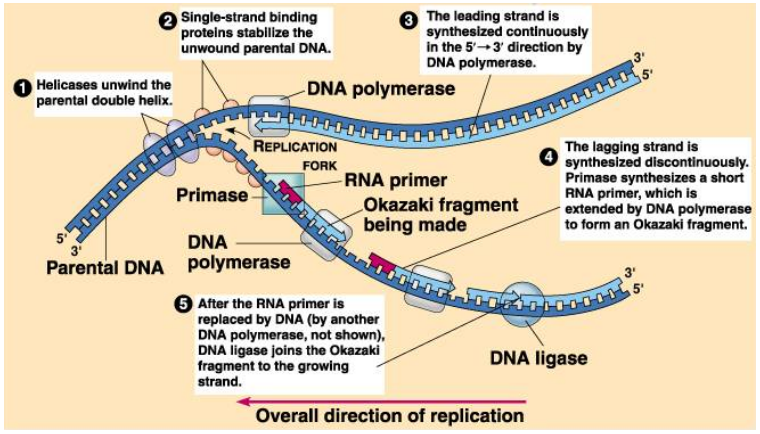
**C)** Nucleic Acids – **polymer of free nucleotides**
**-** **covalent** bond between two adjacent **nucleotides** is called a **phosphodiester bond**
**-** polynucleotide: sugar-phosphate backbone + nitrogenous base
- **5' end** = C5 end w/ free PO4- group vs **3'end** = C3 end w/ OH group




(D) **Chargaff's Rule** – ratio of A: T = ratio of G:C = 1;1
- complementary base pairing between A, T and G, C (large purine + small pyrimidine = constant width of **2.0 nm)**
**- one complete turn** of the DS-helix = 10 base pairs (3.4nm)
- double helix (2 polynucleotide chains)
- **antiparallel strands** w/ weak H-bonds between nitrogenous bases (H-bonds stabilize structure of DNA)

**G) Semi-conservative DNA Replication:**
- Both parental strands separate through **breakage of H-bonds** and each strand -> template for new strand synthesis through **complementary base pairing**
- New DNA molecule = 1 **original** + 1 newly synthesized strand

**H) DNA Replication:**
- Occurs during **S-phase** of interphase + in **G1 –** free deoxyNTPs are synthesized + transported to nucleoplasm

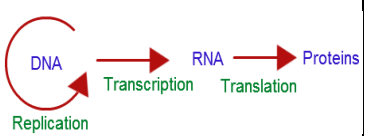



**Start:**
1) Replication begins at origin of replication – **"Ori"**
2) **Helicase** – binds and unzips DNA molecule (by **breaking H-bonds** between complementary base pairs)
3) **SSBP –** bind to and prevent reannealing of strands -> **Topoisomerase** relieves overwinding strain ahead of replication forks – breaking and rejoining strands
4) **Primase** catalyses RNA primer synthesis
5) Complementary base pairing occurs between **template strand** and free incoming **dNTPs** -> A + T (2 bonds), C + G (3 bonds)
6) **DNA polymerase** catalyses formation of phosphodiester bond linking DNA nucleotides -> synthesizing **new DNA strand** from the 5' to 3'direction
7) RNA primers -> replaced by **DNA nucleotides** by another DNA polymerase
8) **Leading strand** – synthesized continuously towards replication fork (vs.) **Lagging strand** – synthesized discontinuously = Okazaki fragments (phosphodiester bond to seal the nicks between fragments – **DNA ligase)**

**L) Telomeres**
**-** regions found at ends of chromosomes – **non-coding** regions of DNA made up of **tandem repeat sequences**
- **buffer DNA** – prevents loss of vital genetic information w/ each replication cycle
- telomerase **– extends telomere length**

**M) Genetic Code**
(1) **triplet code** (codon = complementary triplets in mRNA)
(2) **degenerate** (more than one codon code for same amino acid)
(3) **regulated** (start & stop codons necessary for any process)
(4) **universal** across all organisms
(5) **non-overlapping** - each nucleotide in a triplet code is only used once.
(6) **continuous** - code is read as a continuous sequence of nucleotide bases

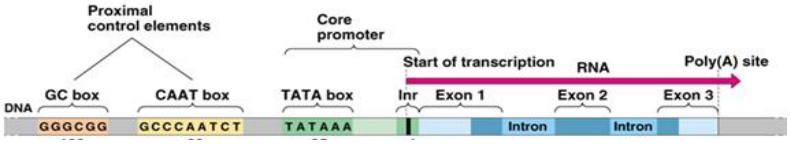
**N) Central Dogma**
Flow of genetic information from **DNA** to **RNA** to **protein**
**(1) Replication**: DNA-directed DNA synthesis
**(2) Gene Expression/ Protein synthesis**:
(a) **transcription** – information in DNA is transcribed from DNA to RNA
(b) **translation**: nucleotide sequences on **RNA** is translated into **amino acid sequence** of a polypeptide



# *DNA & GENOMICS II*

**Transcription:** synthesis of mRNA using DNA as template (sense strand)

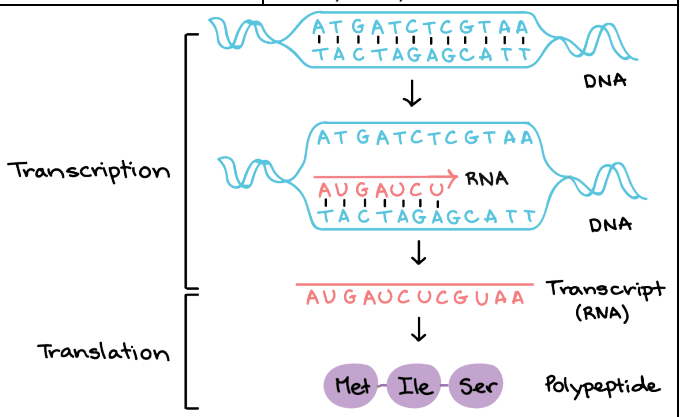
**Gene** – specific sequence of nucleotides in a DNA molecule => codes for specific aa sequence
(1) **Promoter**: recognition site for **RNA polymerase + general transcription factors binding** -> initiates transcription
- determines which strand = template strand
(2) **Transcription Unit:** region of DNA that is transcribed into an RNA molecule – template (non-coding/antisense strand): **complementary to mRNA** vs non-template (coding/sense strand): **identical to mRNA**
(3) **Terminator:** DNA sequence w/ stop codons



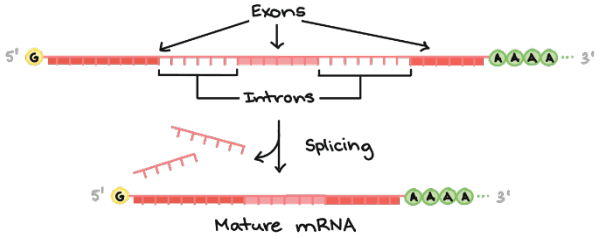

**B) Key Features of Transcription**
(1) Formation of **single-stranded RNA** – unlike replication, **1 DNA strand transcribed** = 1 **ssRNA** synthesized
(2) **5' to 3'** synthesis -> template strand read from 3' to 5' (**synthesis of strand starts from its 5' end)**
(3) **RNA Polymerase** – catalyses **phosphodiester** bond between ribonucleotides
(4) **Complementary base pairing** -> T & A, A&U, C&G

**Transcription: Complete Process**
(1) **Initiation - RNA polymerase + transcription factors** bind to promoter region of gene (TATA box)
(2) **Initiation -** RNA polymerase unzips DNA double helix by breaking H-bonds between complementary base pairs

(3) **Elongation -** 3‟ to 5‟ DNA strand = **template strand** for complementary mRNA strand synthesis
(4) **Elongation -** Free ribonucleotides bind by complementary base pairing to existing nucleotides on template strand
(5) **Elongation -** A = 2 H-bonds w/ U, T = 2 H-bonds w/ A, C = 3 H-bonds w/ G
(6) **Elongation -** RNA polymerase forms **phosphodiester bonds** between free ribonucleotides to form **sugar phosphate backbone =** formation of **new mRNA strand (5' to 3' synthesis)**
(7) **Termination -** RNA polymerase will **dissociate from template DNA strand** when it reaches **termination sequence**



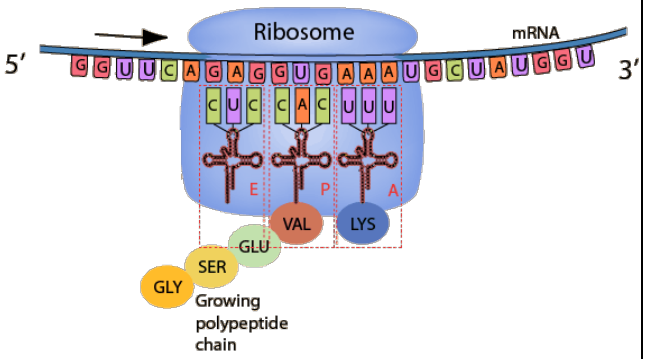

**Primary Transcript + Post-transcriptional modification**
-> 5' untranslated region (UTR): facilitates **binding of mRNA onto subunit** = increased translational efficiency
-> 3' untranslated region (UTR): maintains stability of mRNA
**Post-transcriptional modification:**
(1) **RNA splicing -** introns out, exons in (**intron excision** + **remaining** exons spliced)
(2) addition of **poly (A) tail to 3' end** – polyadenylation + **GTP cap to 5' end**




**Transcription:** synthesis of polypeptides using mRNA template

**AA Activation**
(1) **Aminoacyl-tRNA synthetase** catalyses covalent attachment of **specific** AA to 3'CCA* stem of tRNA w/ **specific anticodon** to form aminocyl-tRNA

**Initiation**
(2) **Translation initiation factors** facilitate binding of small ribosomal subunit + **initiator tRNA to mRNA strand**
(3) The **anticodon (UAC) of the initiator tRNA** will complementary base pair with the **start codon (AUG)** of the mRNA.
(4) Binding of the large ribosomal subunit will complete the ribosome forming the translational initiation complex




**Elongation (P-site** = peptidyl transferase site, A-site: aminoacyl-tRNA binding site)
(5) Initiator tRNA at P site leaving A site vacant for new A-tRNA
(6) New A-tRNA binds to the specific mRNA codon at A site via complementary base-pairing
(7) Peptidyl transferase catalyses formation of peptide bond between adjacent amino acids
(8) Ribosome translocates in 5' to 3'* direction, shifting first tRNA to E-site -> exits ribosome for reactivation = process repeats

**Termination:**
(9) Stop codon reaches A site, release factor binds to stop codon
(10) Hydrolysis of bond between polypeptide chain and tRNA -> polypeptide released from ribosome for further folding
(11) **Several ribosomes translating a single mRNA strand is known as a polyribosome. It allows for a faster rate of protein synthesis especially when there is a greater demand for the protein.**

- The ability of organisms to reproduce their kind is the one characteristic that best distinguishes living things from nonliving matter.
- The continuity of life is based on the reproduction of cells, or cell division.
  **Cell division functions in reproduction, growth, and repair.**

- The division of a unicellular organism reproduces an entire organism, increasing the population.
- Cell division on a larger scale can produce progeny for some multicellular organisms.
- This includes organisms that can grow by cuttings.
- Cell division enables a multicellular organism to develop from a single fertilized egg or zygote.
- In a multicellular organism, cell division functions to repair and renew cells that die from normal wear and tear or accidents.
- Cell division is part of the cell cycle, the life of a cell from its origin in the division of a parent cell until its own division into two.

**Concept 12.1 Cell division results in genetically identical daughter cells**

- Cell division requires the distribution of identical genetic material—DNA—to two daughter cells.
- What is remarkable is the fidelity with which DNA is passed along, without dilution, from one generation to the next.
- A dividing cell duplicates its DNA, allocates the two copies to opposite ends of the cell, and then splits into two daughter cells.
- A cell's genetic information, packaged as DNA, is called its genome.
- In prokaryotes, the genome is often a single long DNA molecule.
- In eukaryotes, the genome consists of several DNA molecules.
- A human cell must duplicate about 2 m of DNA and separate the two copies such that each daughter cell ends up with a complete genome.
- DNA molecules are packaged into chromosomes.
- Every eukaryotic species has a characteristic number of chromosomes in each cell nucleus.
- Human somatic cells (body cells) have 46 chromosomes, made up of two sets of 23 (one from each parent).
- Human gametes (sperm or eggs) have one set of 23 chromosomes, half the number in a somatic cell.
- Eukaryotic chromosomes are made of chromatin, a complex of DNA and associated protein.
- Each single chromosome contains one long, linear DNA molecule carrying hundreds or thousands of genes, the units that specify an organism's inherited traits.
- The associated proteins maintain the structure of the chromosome and help control gene activity.
- When a cell is not dividing, each chromosome is in the form of a long, thin chromatin fiber.
- Before cell division, chromatin condenses, coiling and folding to make a smaller package.
- Each duplicated chromosome consists of two sister chromatids, which contain identical copies of the chromosome's DNA.
- The chromatids are initially attached by adhesive proteins along their lengths.
- As the chromosomes condense, the region where the chromatids connect shrinks to a narrow area, the centromere.
- Later in cell division, the sister chromatids are pulled apart and repackaged into two new nuclei at opposite ends of the parent cell.
- Once the sister chromatids separate, they are considered individual chromosomes.
- Mitosis, the formation of the two daughter nuclei, is usually followed by division of the cytoplasm, cytokinesis.
- These processes start with one cell and produce two cells that are genetically identical to the original parent cell.
- Each of us inherited 23 chromosomes from each parent: one set in an egg and one set in sperm.
- The fertilized egg, or zygote, underwent cycles of mitosis and cytokinesis to produce a fully developed multicellular human made up of 200 trillion somatic cells.
- These processes continue every day to replace dead and damaged cells.
- Essentially, these processes produce clones—cells with identical genetic information.
- In contrast, gametes (eggs or sperm) are produced only in gonads (ovaries or testes) by a variation of cell division called meiosis.
- Meiosis yields four nonidentical daughter cells, each with half the chromosomes of the parent.
- In humans, meiosis reduces the number of chromosomes from 46 to 23.
- Fertilization fuses two gametes together and doubles the number of chromosomes to 46 again.

**Concept 12.2 The mitotic phase alternates with interphase in the cell cycle**

- The mitotic (M) phase of the cell cycle alternates with the much longer interphase.
- The M phase includes mitosis and cytokinesis.
- Interphase accounts for 90% of the cell cycle.
- During interphase, the cell grows by producing proteins and cytoplasmic organelles, copies its chromosomes, and prepares for cell division.
- Interphase has three subphases: the G1 phase ("first gap"), the S phase ("synthesis"), and the G2 phase ("second gap").
- During all three subphases, the cell grows by producing proteins and cytoplasmic organelles such as mitochondria and endoplasmic reticulum.
- However, chromosomes are duplicated only during the S phase.
- The daughter cells may then repeat the cycle.
- A typical human cell might divide once every 24 hours.
- Of this time, the M phase would last less than an hour, while the S phase might take 10–12 hours, or half the cycle.
- The rest of the time would be divided between the G1 and G2 phases.
- The G1 phase varies most in length from cell to cell.
- Mitosis is a continuum of changes.
- For convenience, mitosis is usually broken into five subphases: prophase, prometaphase, metaphase, anaphase, and telophase.
- In late interphase, the chromosomes have been duplicated but are not condensed.
- A nuclear membrane bounds the nucleus, which contains one or more nucleoli.
- The centrosome has replicated to form two centrosomes.
- In animal cells, each centrosome features two centrioles.
- In prophase, the chromosomes are tightly coiled, with sister chromatids joined together.
- The nucleoli disappear.

- The mitotic spindle begins to form.
- It is composed of centrosomes and the microtubules that extend from them.
- The radial arrays of shorter microtubules that extend from the centrosomes are called asters.
- The centrosomes move away from each other, apparently propelled by lengthening microtubules.
- During prometaphase, the nuclear envelope fragments, and microtubules from the spindle interact with the condensed chromosomes.
- Each of the two chromatids of a chromosome has a kinetochore, a specialized protein structure located at the centromere.
- Kinetochore microtubules from each pole attach to one of two kinetochores.
- Nonkinetochore microtubules interact with those from opposite ends of the spindle.
- The spindle fibers push the sister chromatids until they are all arranged at the metaphase plate, an imaginary plane equidistant from the poles, defining metaphase.
- At anaphase, the centromeres divide, separating the sister chromatids.
- Each is now pulled toward the pole to which it is attached by spindle fibers.
- By the end, the two poles have equivalent collections of chromosomes.
- At telophase, daughter nuclei begin to form at the two poles.
- Nuclear envelopes arise from the fragments of the parent cell's nuclear envelope and other portions of the endomembrane system.
- The chromosomes become less tightly coiled.
- Cytokinesis, division of the cytoplasm, is usually well underway by late telophase.
- In animal cells, cytokinesis involves the formation of a cleavage furrow, which pinches the cell in two.
- In plant cells, vesicles derived from the Golgi apparatus produce a cell plate at the middle of the cell.

**The mitotic spindle distributes chromosomes to daughter cells: a closer look.**

- The mitotic spindle, fibers composed of microtubules and associated proteins, is a major driving force in mitosis.
- As the spindle assembles during prophase, the elements come from partial disassembly of the cytoskeleton.
- The spindle fibers elongate by incorporating more subunits of the protein tubulin.
- Assembly of the spindle microtubules starts in the centrosome.
- The centrosome (microtubule-organizing center) is a nonmembranous organelle that organizes the cell's microtubules.
- In animal cells, the centrosome has a pair of centrioles at the center, but the centrioles are not essential for cell division.
- During interphase, the single centrosome replicates to form two centrosomes.
- As mitosis starts, the two centrosomes are located near the nucleus.
- As the spindle microtubules grow from them, the centrioles are pushed apart.
- By the end of prometaphase, they are at opposite ends of the cell.
- An aster, a radial array of short microtubules, extends from each centrosome.
- The spindle includes the centrosomes, the spindle microtubules, and the asters.
- Each sister chromatid has a kinetochore of proteins and chromosomal DNA at the centromere.
- The kinetochores of the joined sister chromatids face in opposite directions.
- During prometaphase, some spindle microtubules (called kinetochore microtubules) attach to the kinetochores.
- When a chromosome's kinetochore is "captured" by microtubules, the chromosome moves toward the pole from which those microtubules come.
- When microtubules attach to the other pole, this movement stops and a tug-of-war ensues.
- Eventually, the chromosome settles midway between the two poles of the cell, on the metaphase plate.
- Nonkinetochore microtubules from opposite poles overlap and interact with each other.
- By metaphase, the microtubules of the asters have grown and are in contact with the plasma membrane.
- The spindle is now complete.
- Anaphase commences when the proteins holding the sister chromatids together are inactivated.
- Once the chromosomes are separate, full-fledged chromosomes, they move toward opposite poles of the cell.
- How do the kinetochore microtubules function into the poleward movement of chromosomes?
- One hypothesis is that the chromosomes are "reeled in" by the shortening of microtubules at the spindle poles.
- Experimental evidence supports the hypothesis that motor proteins on the kinetochore "walk" the attached chromosome along the microtubule toward the nearest pole.
- Meanwhile, the excess microtubule sections depolymerize at their kinetochore ends.
- What is the function of the nonkinetochore microtubules?
- Nonkinetochore microtubules are responsible for lengthening the cell along the axis defined by the poles.
- These microtubules interdigitate and overlap across the metaphase plate.
- During anaphase, the area of overlap is reduced as motor proteins attached to the microtubules walk them away from one another, using energy from ATP.
- As microtubules push apart, the microtubules lengthen by the addition of new tubulin monomers to their overlapping ends, allowing continued overlap.

**Cytokinesis divides the cytoplasm: a closer look.**

- Cytokinesis, division of the cytoplasm, typically follows mitosis.
- In animal cells, cytokinesis occurs by a process called cleavage.
- The first sign of cleavage is the appearance of a cleavage furrow in the cell surface near the old metaphase plate.
- On the cytoplasmic side of the cleavage furrow is a contractile ring of actin microfilaments associated with molecules of the motor protein myosin.
- Contraction of the ring pinches the cell in two.

- Cytokinesis in plants, which have cell walls, involves a completely different mechanism.
- During telophase, vesicles from the Golgi coalesce at the metaphase plate, forming a cell plate.
- The plate enlarges until its membranes fuse with the plasma membrane at the perimeter.
- The contents of the vesicles form new cell wall material between the daughter cells.

**Mitosis in eukaryotes may have evolved from binary fission in bacteria.**

- Prokaryotes reproduce by binary fission, not mitosis.
- Most bacterial genes are located on a single bacterial chromosome that consists of a circular DNA molecule and associated proteins.
- While bacteria are smaller and simpler than eukaryotic cells, they still have large amounts of DNA that must be copied and distributed equally to two daughter cells.
- The circular bacterial chromosome is highly folded and coiled in the cell.
- In binary fission, chromosome replication begins at one point in the circular chromosome, the origin of replication site, producing two origins.
- As the chromosome continues to replicate, one origin moves toward each end of the cell.
- While the chromosome is replicating, the cell elongates.
- When replication is complete, its plasma membrane grows inward to divide the parent cell into two daughter cells, each with a complete genome.
- Researchers have developed methods to allow them to observe the movement of bacterial chromosomes.
- The movement is similar to the poleward movements of the centromere regions of eukaryotic chromosomes.
- However, bacterial chromosomes lack visible mitotic spindles or even microtubules.
- The mechanism behind the movement of the bacterial chromosome is becoming clearer but is still not fully understood.
- Several proteins have been identified and play important roles.
- How did mitosis evolve?
- There is evidence that mitosis had its origins in bacterial binary fission.
- Some of the proteins involved in binary fission are related to eukaryotic proteins.
- Two of these are related to eukaryotic tubulin and actin proteins.
- As eukaryotes evolved, the ancestral process of binary fission gave rise to mitosis.
- Possible intermediate evolutionary steps are seen in the division of two types of unicellular algae.
- In dinoflagellates, replicated chromosomes are attached to the nuclear envelope.
- In diatoms, the spindle develops within the nucleus.
- In most eukaryotic cells, the nuclear envelope breaks down and a spindle separates the chromosomes.

## Concept 12.3 The cell cycle is regulated by a molecular control system

- The timing and rates of cell division in different parts of an animal or plant are crucial for normal growth, development, and maintenance.
- The frequency of cell division varies with cell type.
- Some human cells divide frequently throughout life (skin cells).
- Others have the ability to divide, but keep it in reserve (liver cells).
- Mature nerve and muscle cells do not appear to divide at all after maturity.
- Investigation of the molecular mechanisms regulating these differences provide important insights into the operation of normal cells, and may also explain cancer cells escape controls.

**Cytoplasmic signals drive the cell cycle.**

- The cell cycle appears to be driven by specific chemical signals present in the cytoplasm.
- Some of the initial evidence for this hypothesis came from experiments in which cultured mammalian cells at different phases of the cell cycle were fused to form a single cell with two nuclei.
- Fusion of an S phase cell and a G1 phase cell induces the G1 nucleus to start S phase.
- This suggests that chemicals present in the S phase nucleus stimulated the fused cell.
- Fusion of a cell in mitosis (M phase) with one in interphase (even G1 phase) induces the second cell to enter mitosis.
- The sequential events of the cell cycle are directed by a distinct cell cycle control system.
- Cyclically operating molecules trigger and coordinate key events in the cell cycle.
- The control cycle has a built-in clock, but it is also regulated by external adjustments and internal controls.
- A checkpoint in the cell cycle is a critical control point where stop and go-ahead signals regulate the cycle.
- The signals are transmitted within the cell by signal transduction pathways.
- Animal cells generally have built-in stop signals that halt the cell cycle at checkpoints until overridden by go-ahead signals.
- Many signals registered at checkpoints come from cellular surveillance mechanisms.
- These indicate whether key cellular processes have been completed correctly.
- Checkpoints also register signals from outside the cell.
- Three major checkpoints are found in the G1, G2, and M phases.
- For many cells, the G1 checkpoint, the “restriction point” in mammalian cells, is the most important.
- If the cell receives a go-ahead signal at the G1 checkpoint, it usually completes the cell cycle and divides.
- If it does not receive a go-ahead signal, the cell exits the cycle and switches to a nondividing state, the G0 phase.
- Most cells in the human body are in this phase.
- Liver cells can be “called back” to the cell cycle by external cues, such as growth factors released during injury.
- Highly specialized nerve and muscle cells never divide.
- Rhythmic fluctuations in the abundance and activity of cell cycle control molecules pace the events of the cell cycle.

- These regulatory molecules include protein kinases that activate or deactivate other proteins by phosphorylating them.
- These kinases are present in constant amounts but require attachment of a second protein, a cyclin, to become activated.
- Levels of cyclin proteins fluctuate cyclically.
- Because of the requirement for binding of a cyclin, the kinases are called cyclin-dependent kinases, or Cdks.
- Cyclin levels rise sharply throughout interphase, and then fall abruptly during mitosis.
- Peaks in the activity of one cyclin-Cdk complex, MPF, correspond to peaks in cyclin concentration.
- MPF ("maturation-promoting factor" or "M-phase-promoting-factor") triggers the cell's passage past the G2 checkpoint to the M phase.
- MPF promotes mitosis by phosphorylating a variety of other protein kinases.
- MPF stimulates fragmentation of the nuclear envelope by phosphorylation of various proteins of the nuclear lamina.
- It also triggers the breakdown of cyclin, dropping cyclin and MPF levels during mitosis and inactivating MPF.
- The noncyclin part of MPF, the Cdk, persists in the cell in inactive form until it associates with new cyclin molecules synthesized during the S and G2 phases of the next round of the cycle.
- At least three Cdk proteins and several cyclins regulate the key G1 checkpoint.
- Similar mechanisms are also involved in driving the cell cycle past the M phase checkpoint.

**Internal and external cues help regulate the cell cycle.**

- While research scientists know that active Cdks function by phosphorylating proteins, the identity of all these proteins is still under investigation.
- Scientists do not yet know what Cdks actually do in most cases.
- Some steps in the signaling pathways that regulate the cell cycle are clear.
- Some signals originate inside the cell, others outside.
- The M phase checkpoint ensures that all the chromosomes are properly attached to the spindle at the metaphase plate before anaphase.
- This ensures that daughter cells do not end up with missing or extra chromosomes.
- A signal to delay anaphase originates at kinetochores that have not yet attached to spindle microtubules.
- This keeps the anaphase-promoting complex (APC) in an inactive state.
- When all kinetochores are attached, the APC activates, triggering breakdown of cyclin and inactivation of proteins holding sister chromatids together.