Review: The cytoskeleton

Match the following scenarios with the affected component of the cytoskeleton:

The nuclear envelope demonstrates an odd morphology

A vesicle carrying a hormone destined for cell secretion is unable to traverse the endomembrane system

A migratory cell is unable to move in response to a chemical signal

The respiratory tract has a build-up of mucus

A physical stress leads to the separation of neighboring endothelial cells

Microtubules

Intermediate Filaments

Actin Filaments

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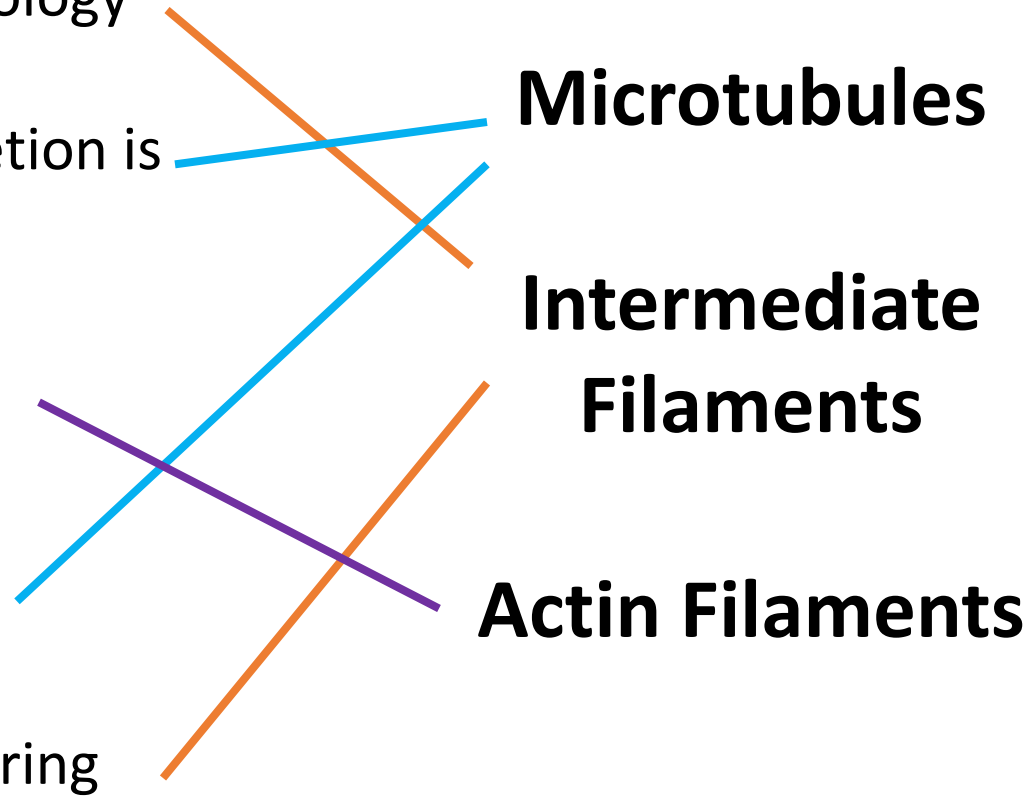

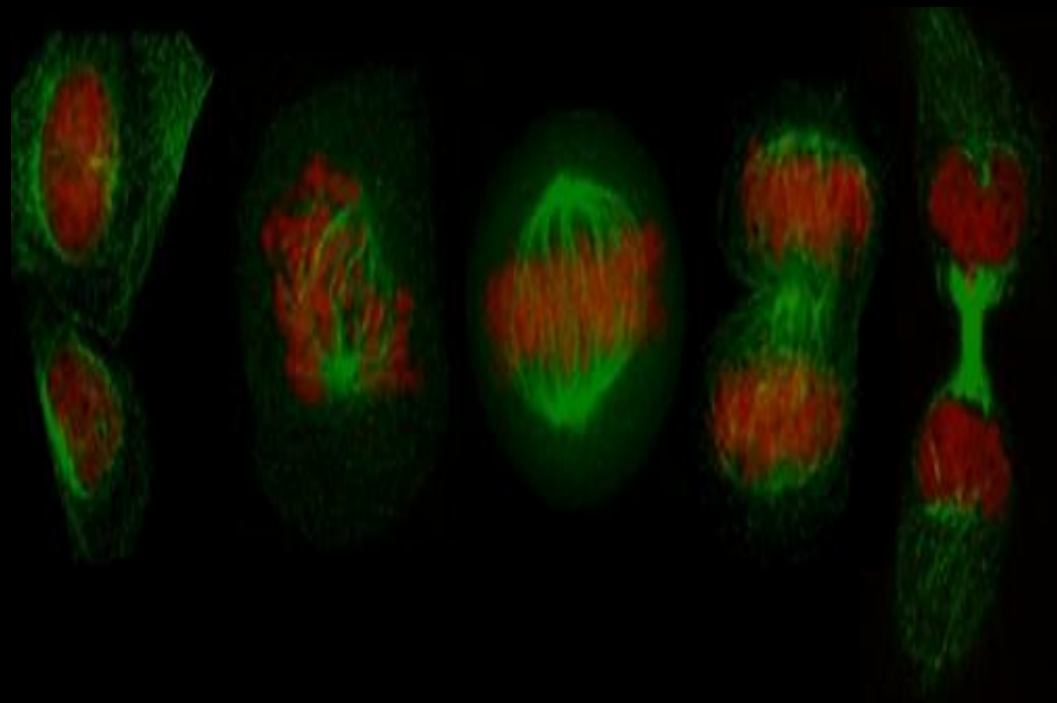

The Cell Cycle

April 24, 2025

Chapter 18

BIOL366

Matthew Ellis, PhD

Learning Objectives for Today's Lecture:

Upon completing this module, **you should be able to**:

- Identify the different phases of the **cell cycle**
- Explain the process and phases of **mitotic** cell division
- Describe how **cyclin dependent kinases** regulate cell cycle progression
- Apply knowledge of the cell cycle to understand case studies

Key Terms

- **Mitosis**: The process by which a single cell divides into two identical daughter cells
- **Homologous Chromosome:** Paired chromosomes that share the same genes at the same locations, with one inherited from each parent
- **Sister Chromatids:** Two identical copies of a chromosome produced during DNA replication, prior to cell division
- **Centrosome:** Microtubule organizing center (MTOC) near nucelus containing centrioles that forms spindle fibers in cell division
- **Mitotic Spindle:** Series of microtubules that ensures accurate chromosomal segregation during cell division
- **Kinetochore:** Protein structure linking chromosomes to the mitotic spindle
- **Apoptosis:** Programmed cell death for unneeded or abnormal cells
- **Cytokinesis**: The fission of the plasma membrane at the end of mitosis leading to two separate daughter cells
- **Cyclin-dependent Kinase:** A protein family involved in the tight regulation of cell cycle checkpoint progression

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What is your favorite season of the year and why?

To grow

To divide

Winter

Spring

Summer

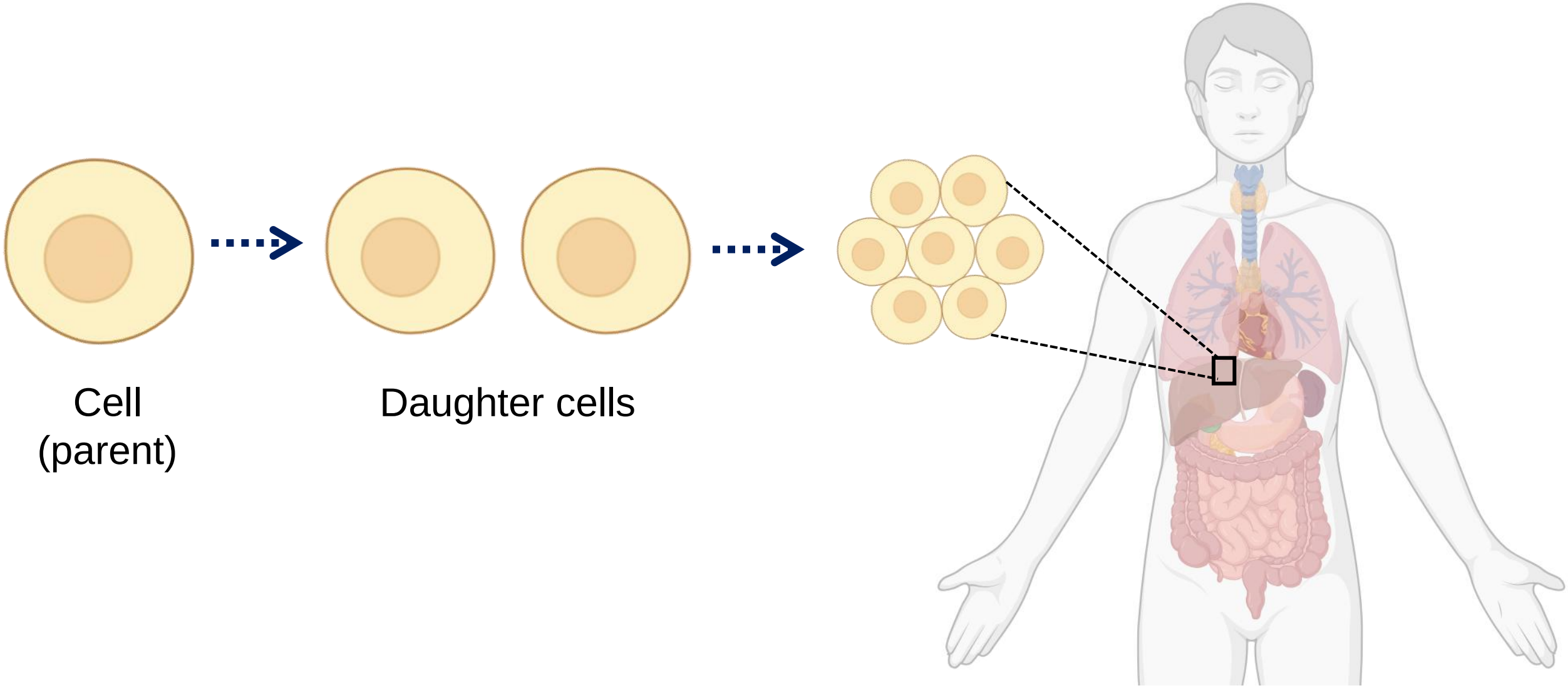
Fall

To rest and recover

To build

Our cells have “seasons” too!

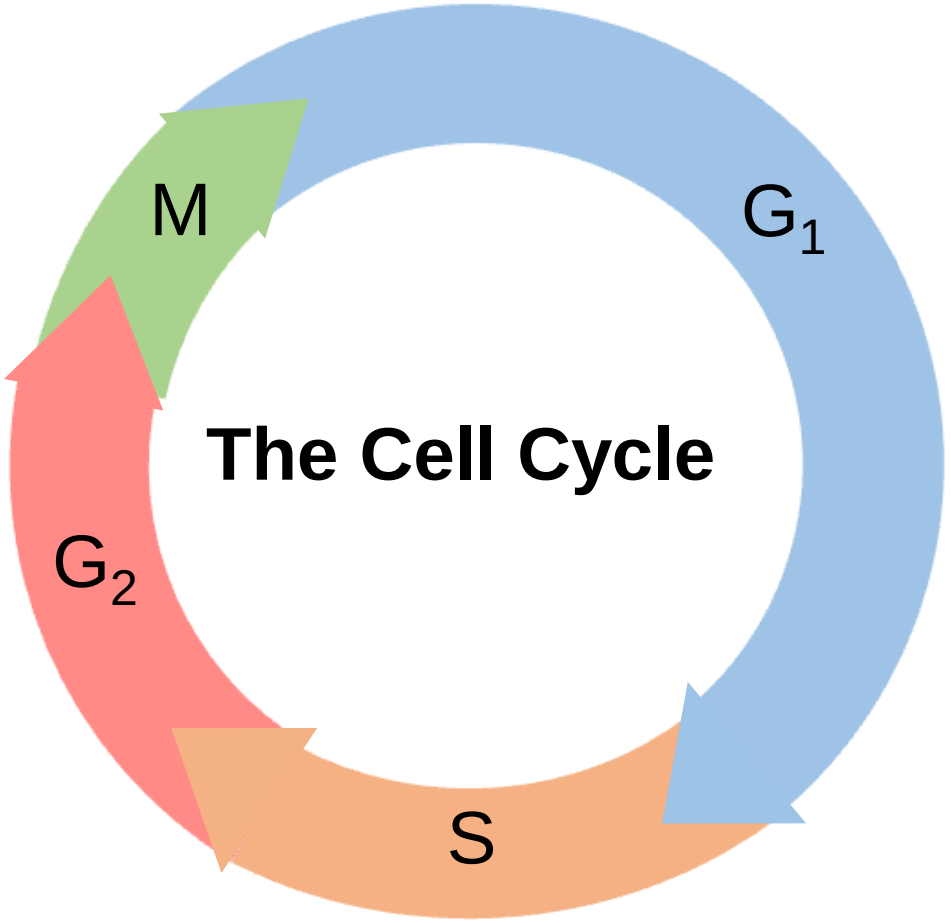
Cells are essential for tissues to function properly



The Cell Cycle describes the process of cell growth and division

Events of the Cell Cycle:

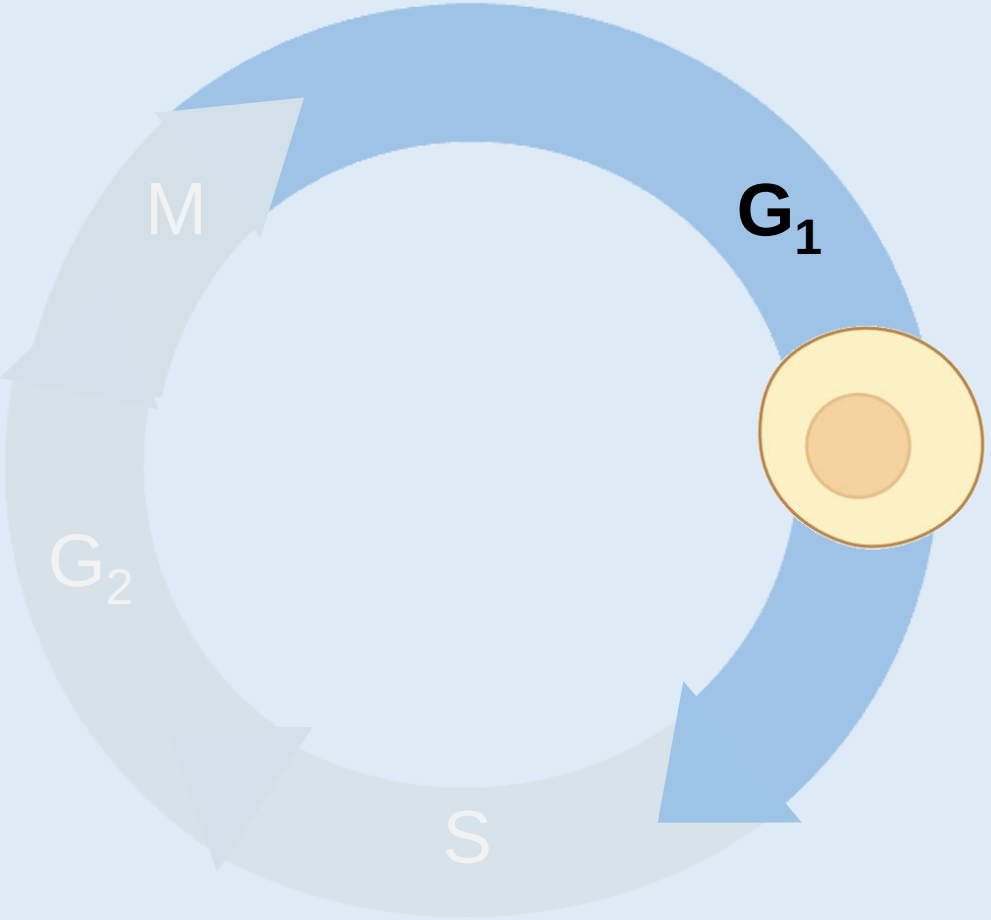
- DNA replication
- Preparation for division,
- Actual cell division



Goal of the cell cycle:
To produce two genetically identical daughter cells from one parent cell

Cell Cycle occurs in 4 main phases:
G_1

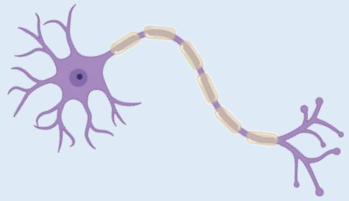
- **G_1: "growth" or "Gap 1" phase**
- Cells increase in size, synthesize proteins, and gathers necessary materials to prepare for DNA replication
- **Cells that divide more rapidly will spend less time in G_1**
- **Cells that divide infrequently will spend more time in G_1**



Cells that enter the G_0 phase do not undergo cell division

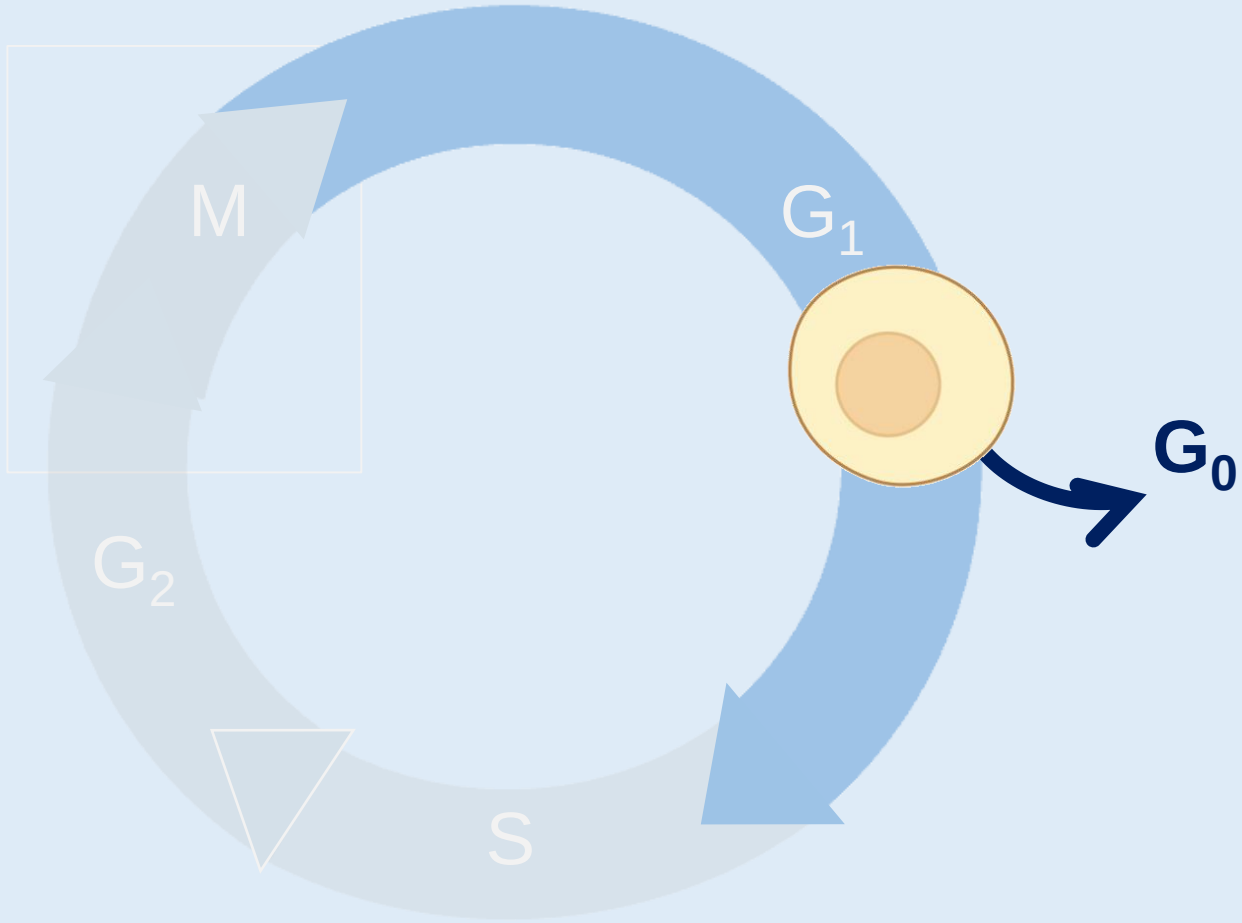
- **G_0: "resting" phase**
- Phase of the cell cycle where cells are **no longer dividing**

Mature Cardiomyocytes (heart cells)



Mature Neurons

- **Cells may also enter G_0 if there is DNA damage, lack of nutrients or growth factors**
- Length of time a cell spends in **G_0** can vary from a few hours to years



Cells that enter the G_0 phase do not undergo cell division…However…

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Mature Neurons

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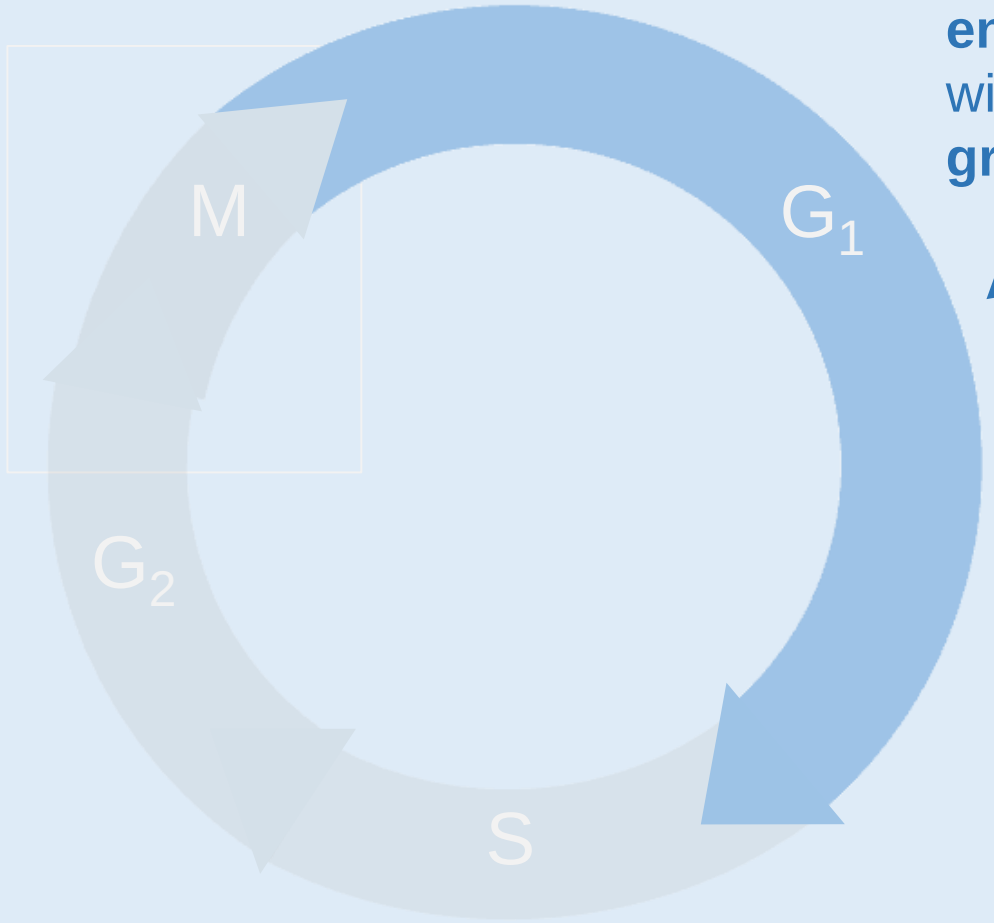
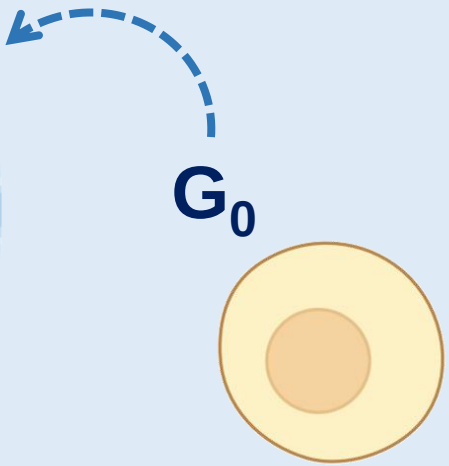


- Some cells can **re-enter the G_1 phase** with the help of **growth factors**



Cells that enter the G_0 phase do not undergo cell division…However…

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Mature Cardiomyocytes (heart cells)

Mature Neurons

- **Cells may also enter G_0 <u>if there is DNA damage</u>**, lack of nutrients or growth factors
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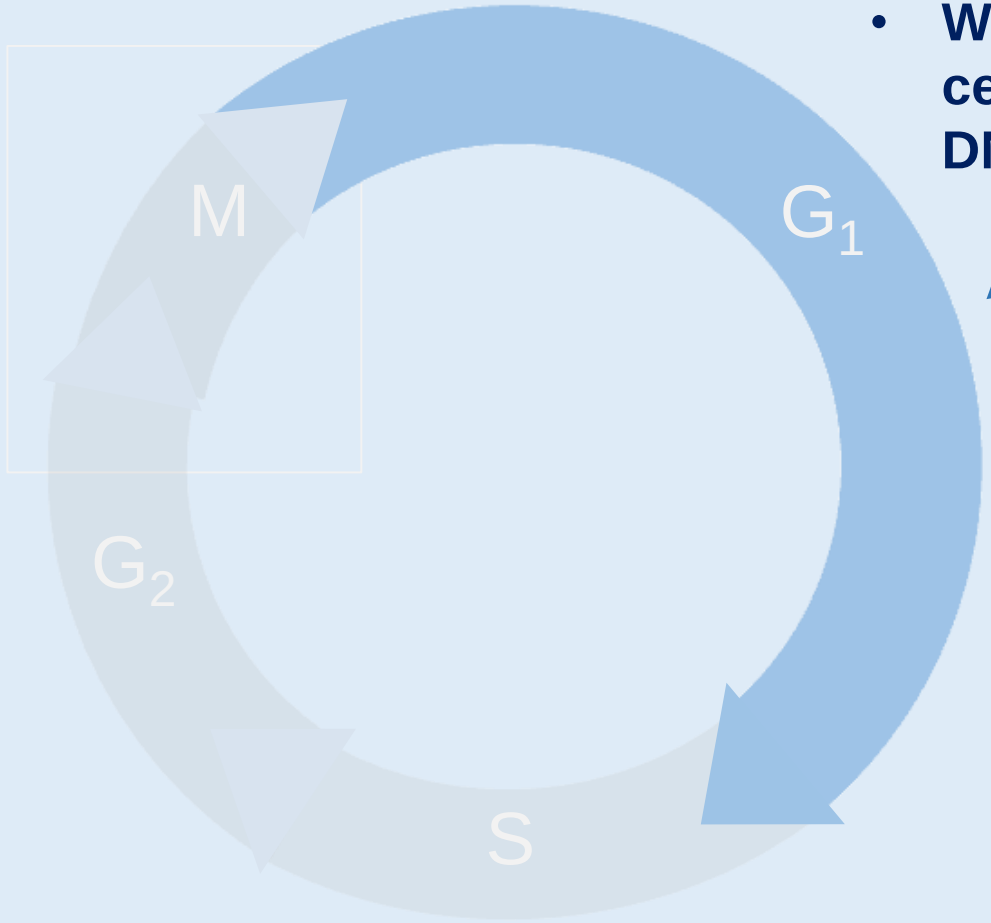
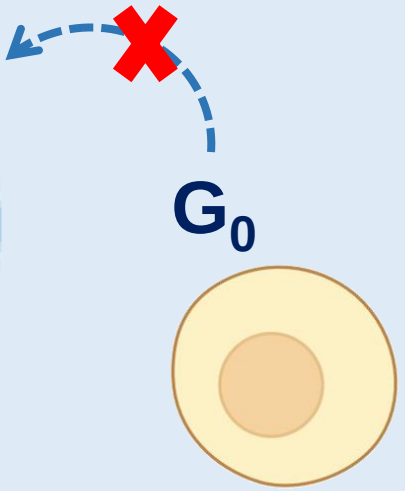
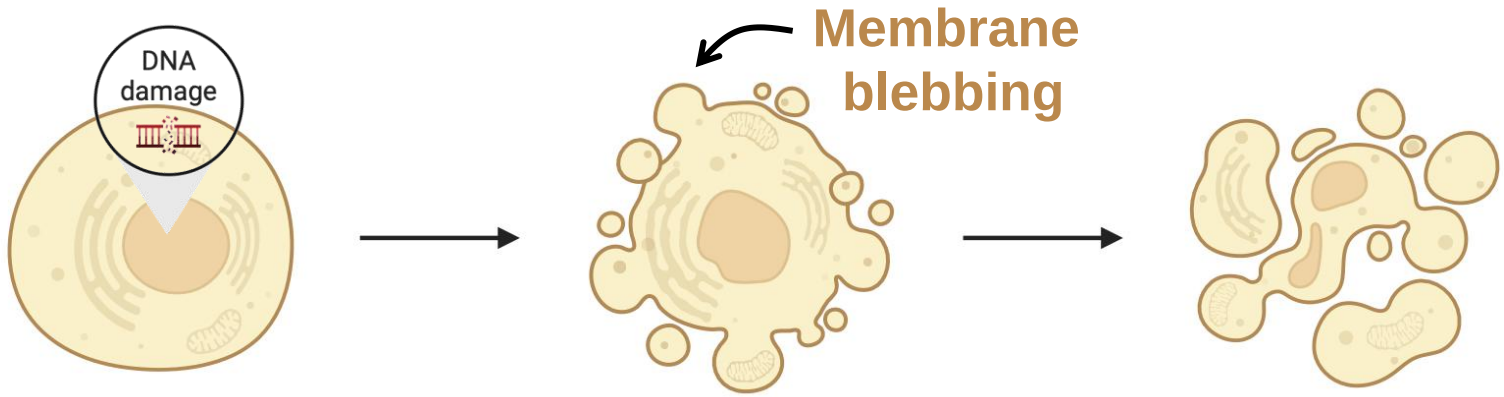


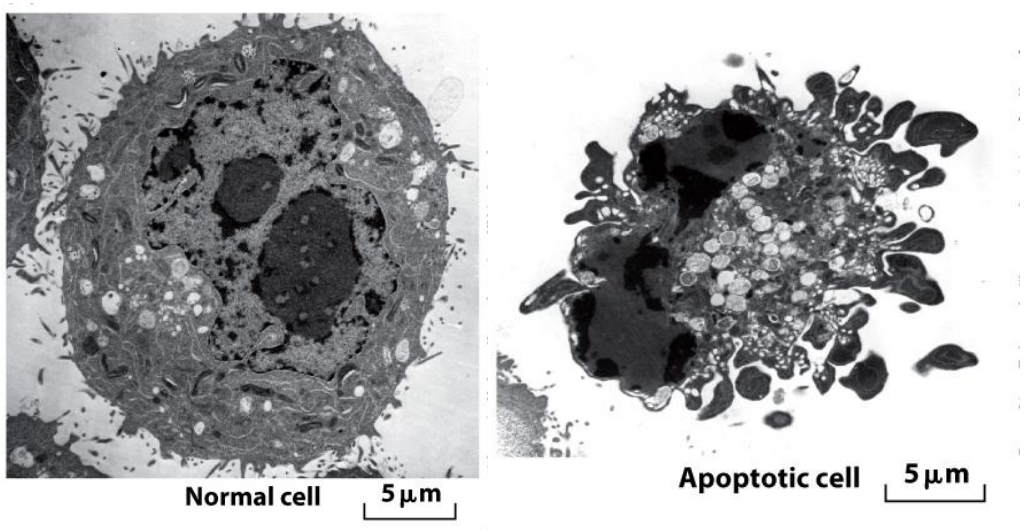
- **What happens if a cell has significant DNA damage?**



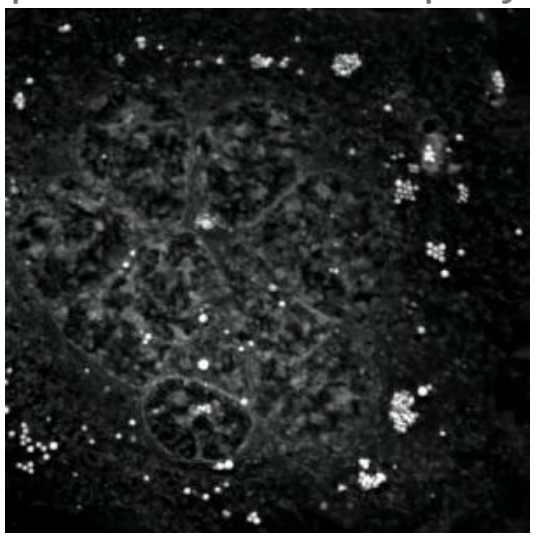
Apoptosis: programmed cell death



Macrophages engulf apoptotic bodies



Apoptosis of mouse adipocytes



Apoptosis is not always due to problems in the cell

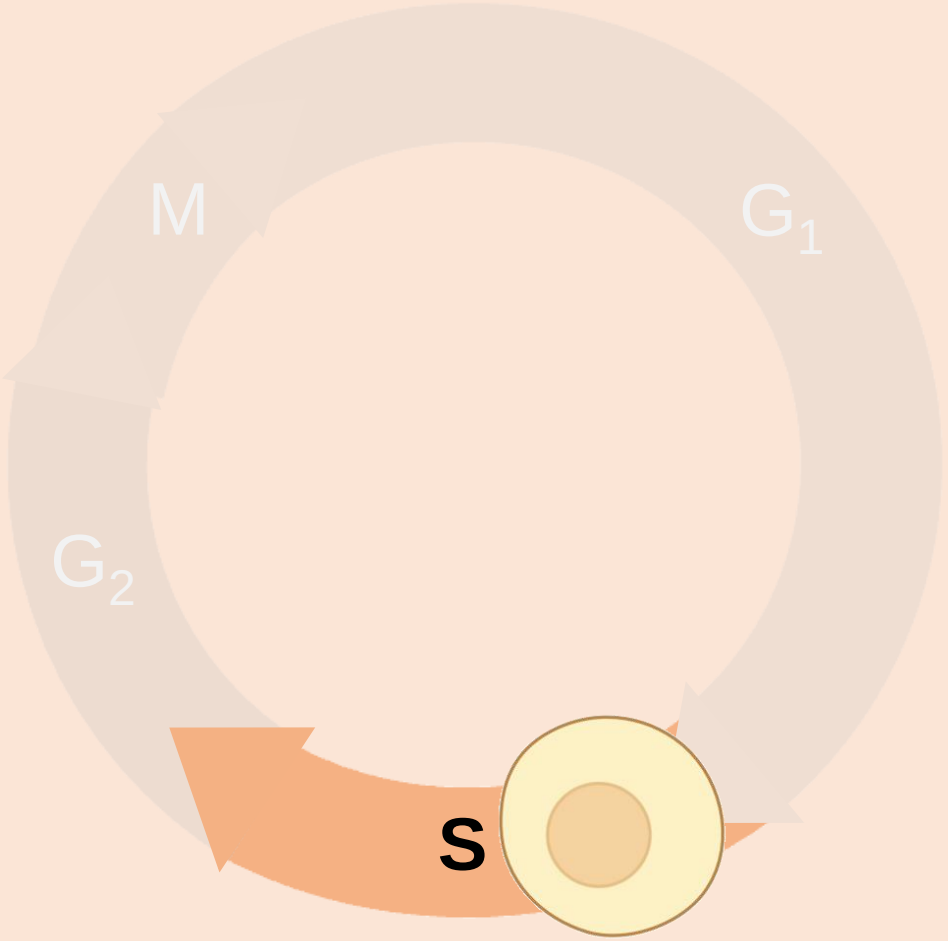
- Normal turnover of cells that are no longer necessary
  - Such as in the immune system after fighting off an infection

- Apoptosis is very important during development, in the correct formation of organs and tissues
  - Syndactyly – the webbing of fingers or toes is an example of when normal apoptosis does not occur

Syndactyly

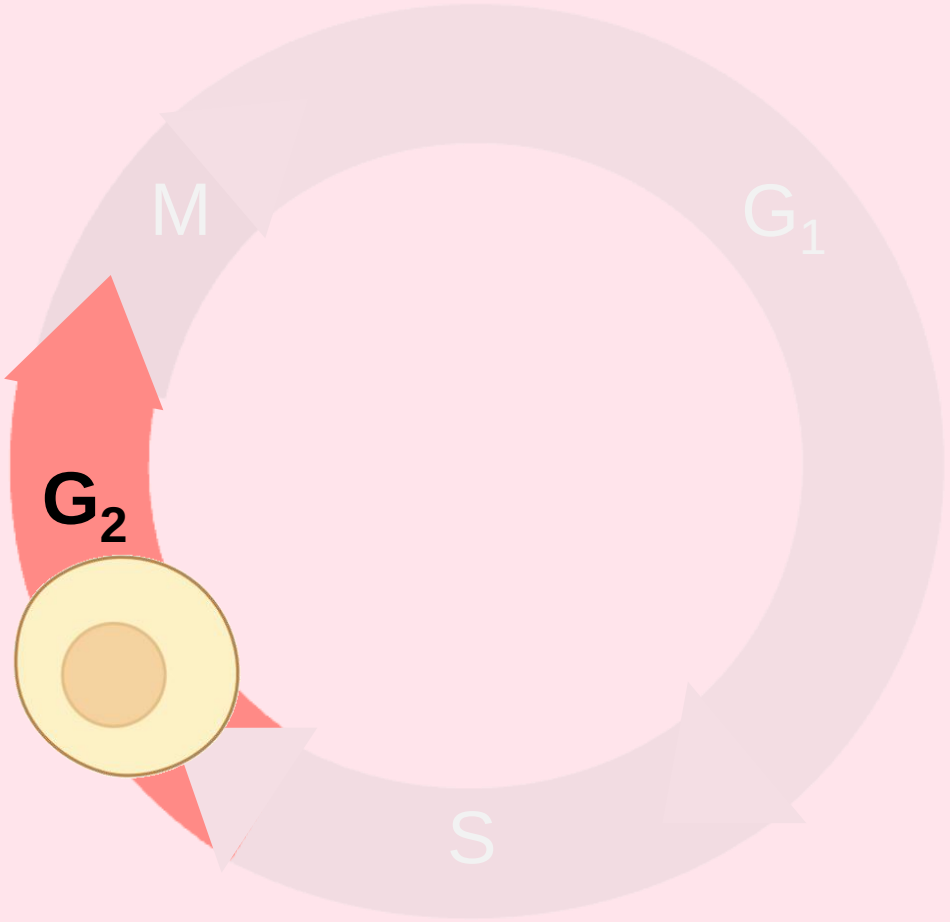
Cell Cycle occurs in 4 main phases: S phase

- **S: “synthesis” phase**
- DNA replication occurs which is crucial so that each cell has a complete set of DNA
- Chromosomes are duplicated to create two sister chromatids
- In adult humans, S phase occurs in ~10-12 hrs

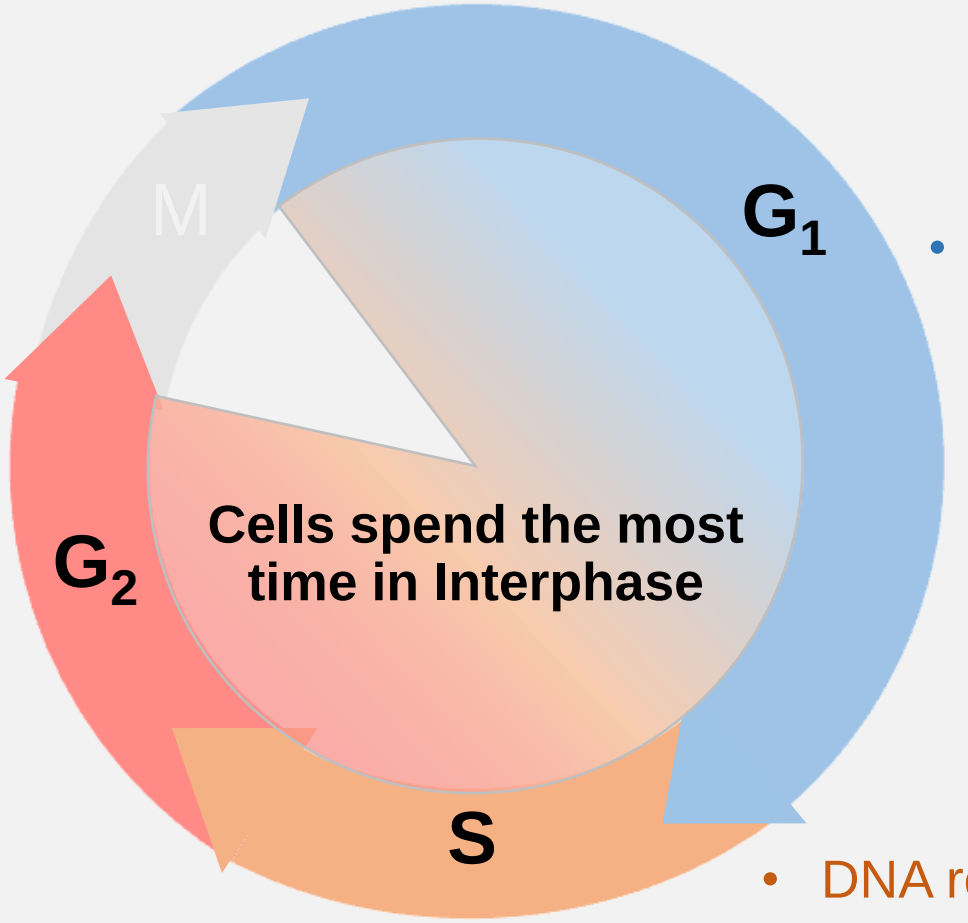


Cell Cycle occurs in 4 phases: G_2 phase

- **G_2: "Growth and preparation for mitosis" or "Gap 2" phase**
- Involves more preparation for cell division such as protein and organelle synthesis, and cell growth
- Cells generate **microtubules** to prepare for the M phase
- Genetic material is organized and condensed
- In adult humans, G_2 phase occurs in ~4-6 hrs



G1, S, and G2 are collectively known as Interphase



- Cells increase in size, synthesize proteins, and gathers necessary materials to prepare for DNA replication

- Involves more preparation for cell division such as protein and organelle synthesis, and cell growth

- DNA replication occurs

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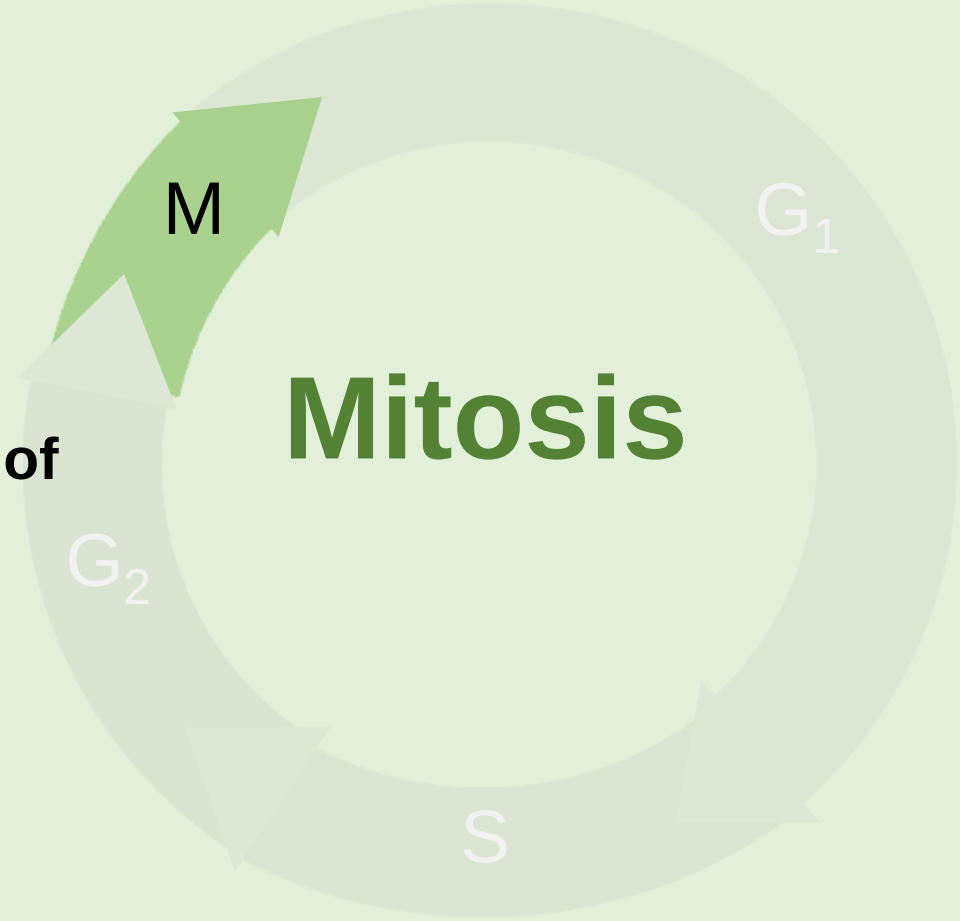
Cells that are ready to divide enter the M phase of the Cell Cycle

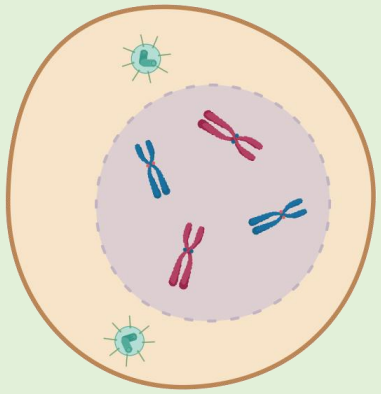
- **M: “Mitosis” phase**

- Cells spend very little time in M phase (for mammals, ~30 min-1 hr)

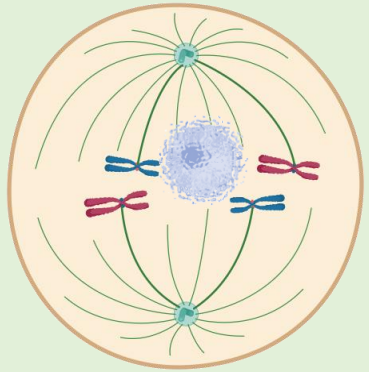
- **M phase is comprised of a series of highly regulated stages**



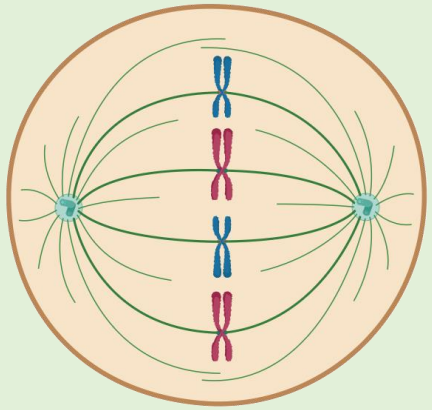
Mitosis (M phase) occurs in 5 stages



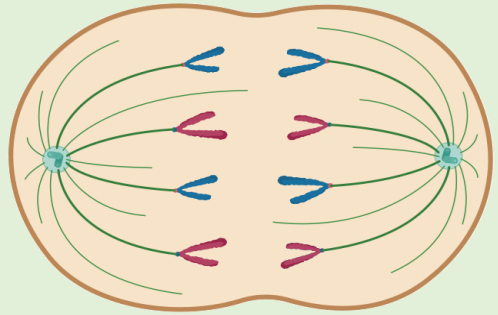
Prophase



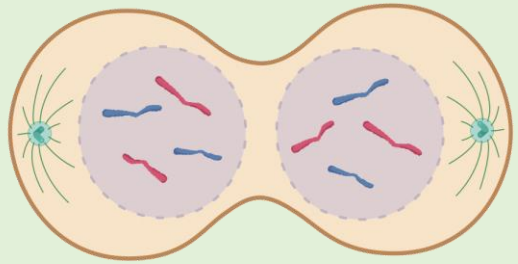
Prometaphase



Metaphase



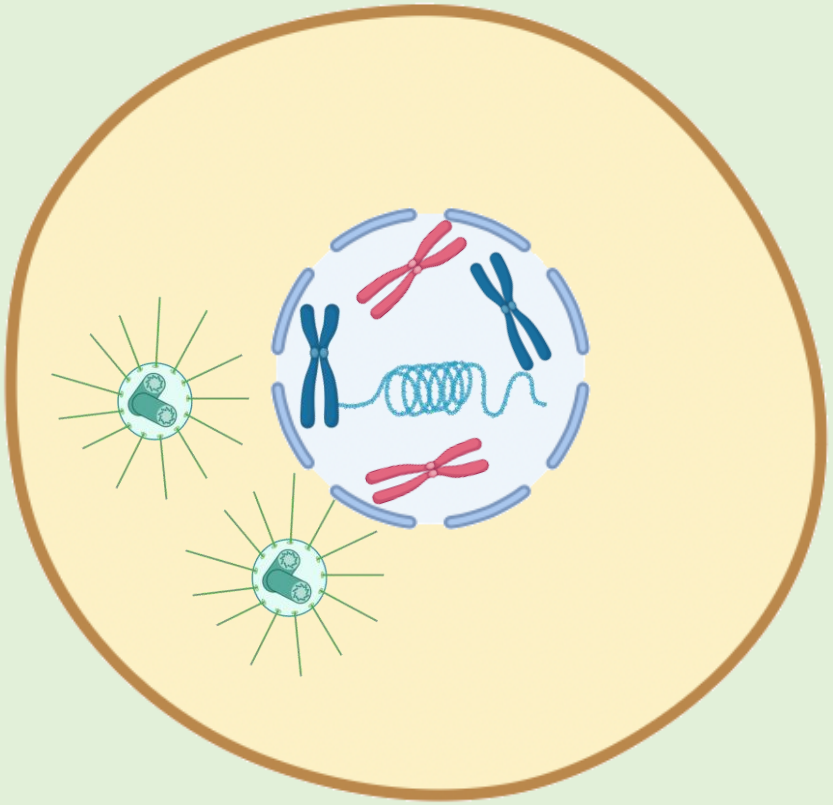
Anaphase



Telophase

Mitosis (M phase) occurs in 5 steps:

Prophase



Prophase

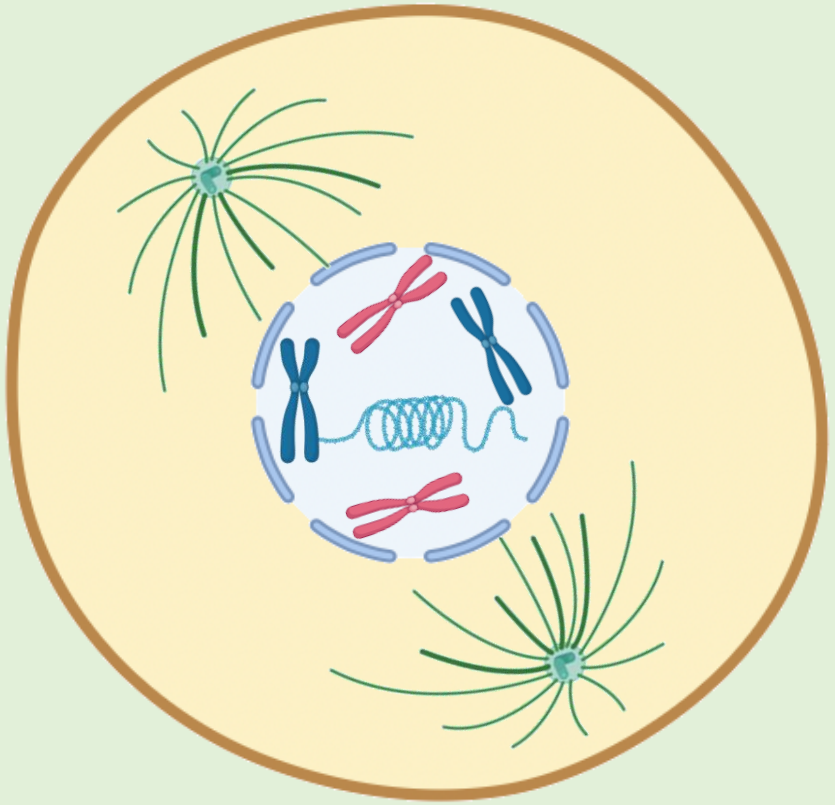
- Humans have 23 pairs of chromosomes (one set from each parent), and each chromosome is made of two “sister chromatids” following DNA replication

- Individual chromosomes are condensed (G_2 → prophase) and become visible as discrete objects (sister chromatids)

- **Centrosomes** (MTOCs) and a network of **microtubules** migrate away from each other

Mitosis (M phase) occurs in 5 steps:

Prophase



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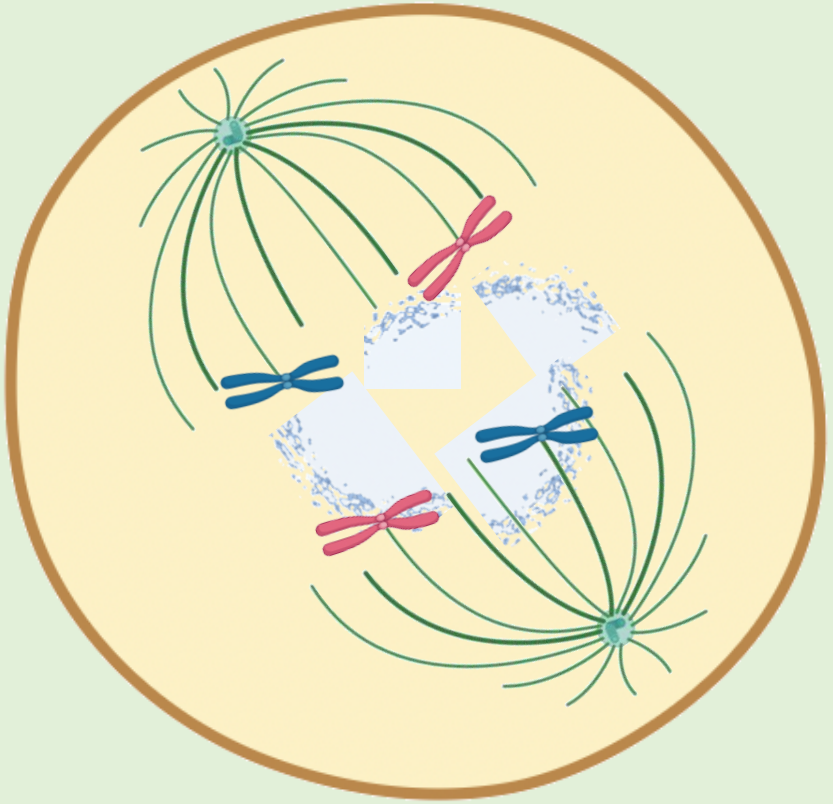
- Individual chromosomes are condensed (G_2 → prophase) and become visible as discrete objects

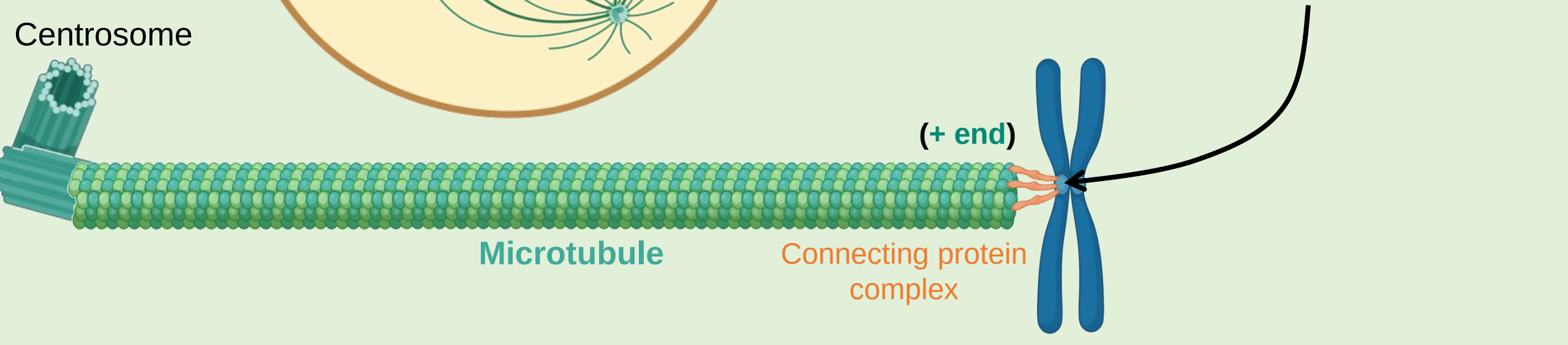
- **Centrosomes** (MTOCs) and a network of **microtubules** migrate away from each other to form the mitotic spindle

- **Mitotic spindle** starts to form
  - Self-organizing center composed of **microtubules**

Mitosis (M phase) occurs in 5 stages:
Prometaphase

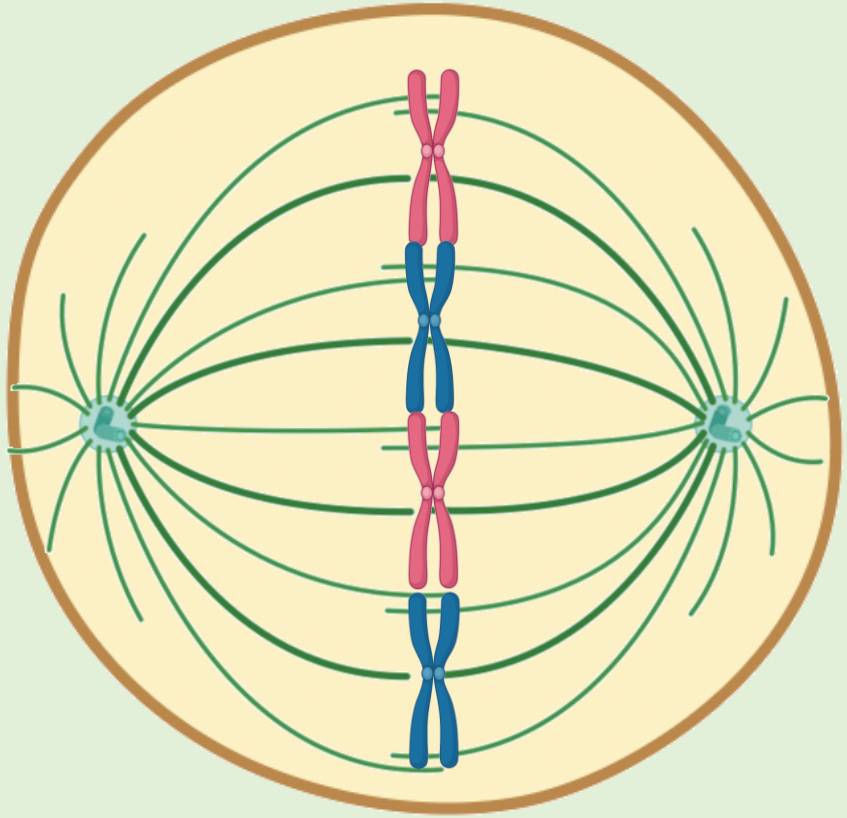


- The onset of **prometaphase** is marked by the **fragmentation of the nuclear envelope**
- Centrosomes complete their movement to opposite sides of the nucleus forming poles of the **mitotic spindle**
- Spindle microtubules attach to the sister chromatid via the **kinetochores**



Mitosis (M phase) occurs in 5 stages:
Metaphase

- Sister chromatids align at the metaphase plate (a plane usually equidistant between the two poles of the spindle)



- Sister chromatids are actively tugged toward opposite poles (continual growth and shrinkage of microtubules)

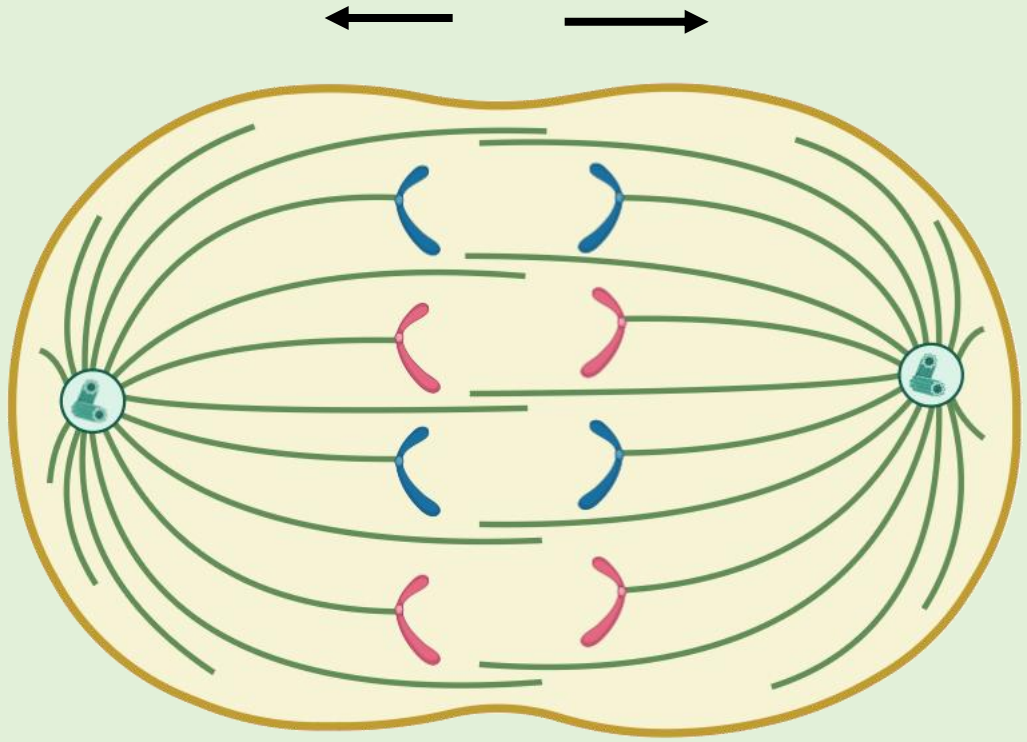
Mitosis (M phase) occurs in 5 stages:

Anaphase

- The mitotic spindle drives *movement of chromosomes* at anaphase

- The sister chromatids separate and move toward opposite poles in 2 steps:

- **Anaphase A:** the chromosomes are pulled toward the spindle poles as microtubules attached to kinetochore shorten “reeling in” toward the pole



Anaphase

Mitosis (M phase) occurs in 5 stages:
Anaphase

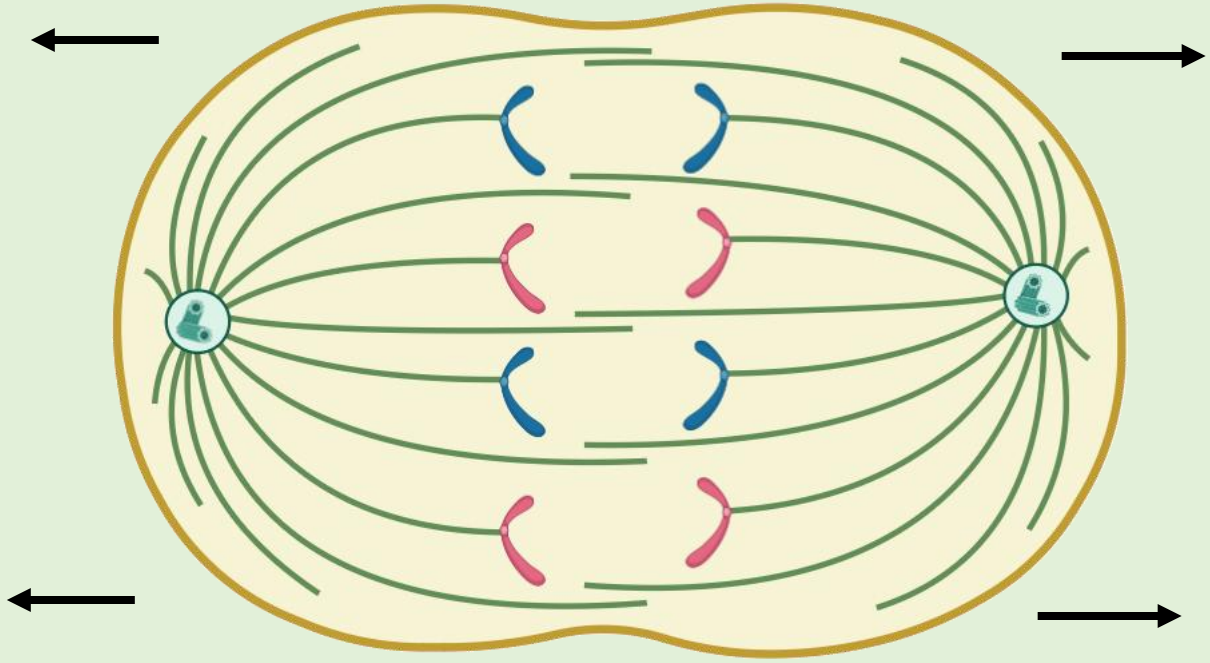
- The mitotic spindle drives *movement of chromosomes* at anaphase

- The sister chromatids separate and move toward opposite poles in 2 steps:

- **Anaphase B:** the spindle poles themselves move away from each other as microtubules lengthen

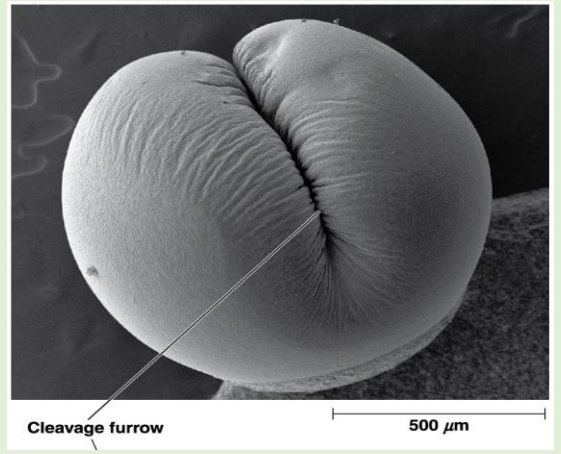
    - Elongation (polymerization) and sliding of non-kinetochore microtubules past each other push poles apart

    - Pulling force at each spindle (connected to the actin cortex) further push poles apart

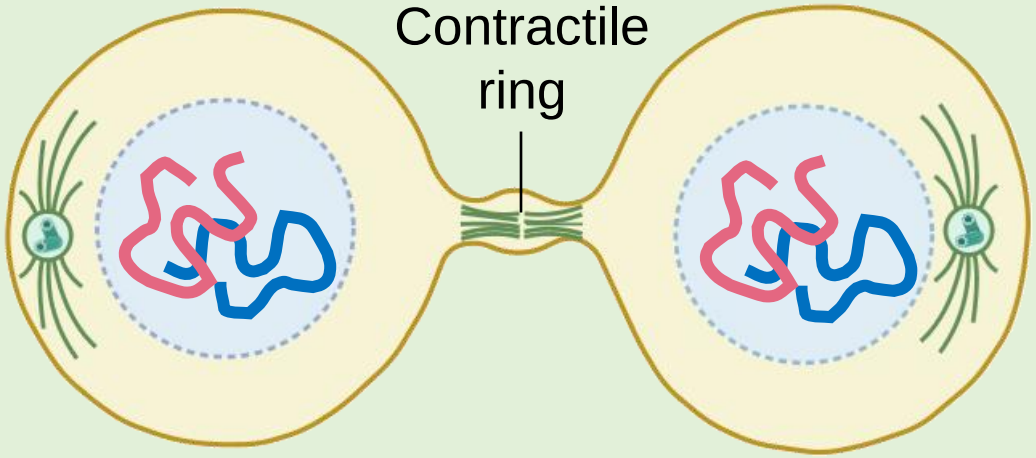


Anaphase

Mitosis (M phase) occurs in 5 stages:
Telophase



- At the beginning of **telophase,** the daughter chromosomes arrive at the poles of the spindle
- Nuclear envelopes re-form, creating two nuclei
- Kinetochore breaks down and chromosomes begin to decondense
- Contractile ring forms and positions itself at the cell equator



Telophase

Cytokinesis occurs after the 5 stages of Mitosis (M phase)

- **The cell is split into 2 separate daughter cells**

- Primarily driven by a contractile ring made of **Actin** and **Myosin** filaments

As cleavage progresses, the ring tightens around the cytoplasm eventually cleaving membrane into two

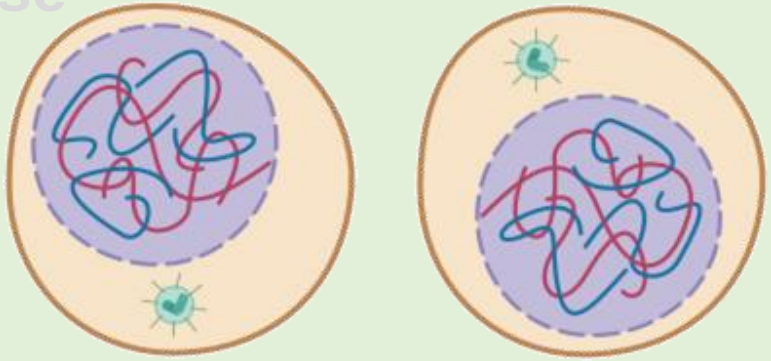
Prophase

Prometaphase

Metaphase

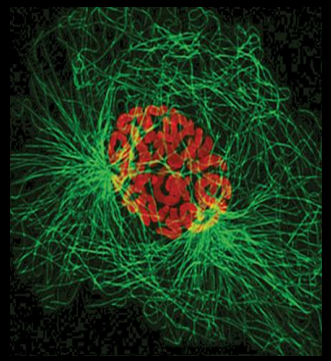
Anaphase

Telophase

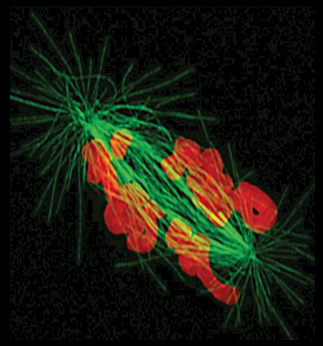


Cytokinesis

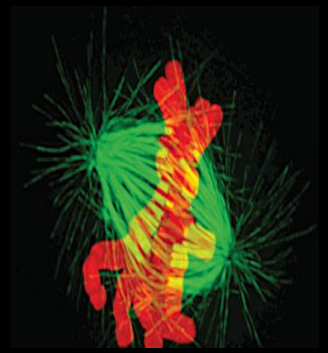
Mitosis (M phase) under the microscope



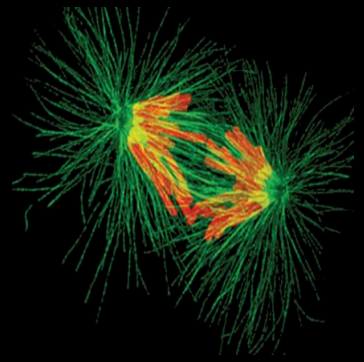
Prophase



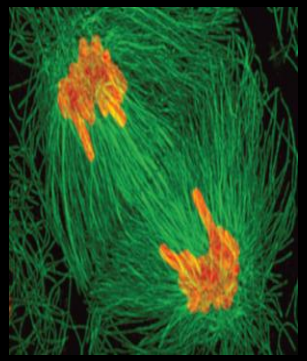
Prometaphase



Metaphase

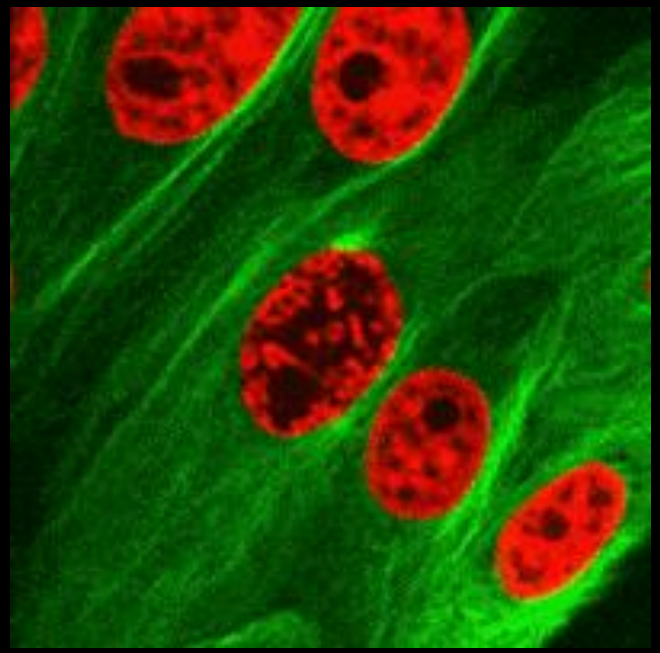


Anaphase



Telophase

Cytokinesis



Squarecap #1-2

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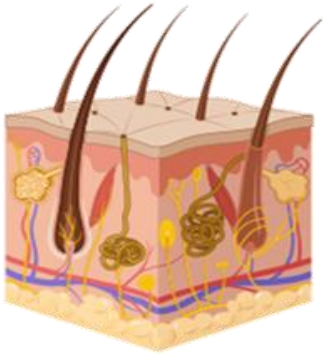
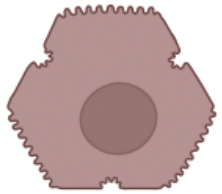
Cell division varies depending on the cell type

Some cells divide often



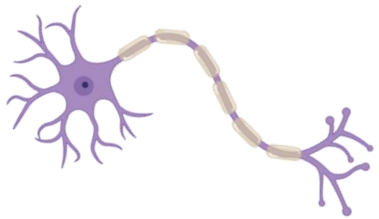
Skin

Some cells divide infrequently



Hepatocytes (liver cells)

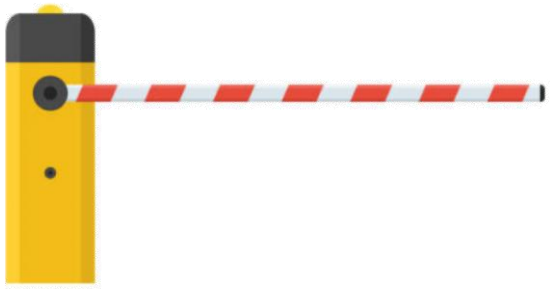
Some cells don’t divide at all once mature



Mature Neurons

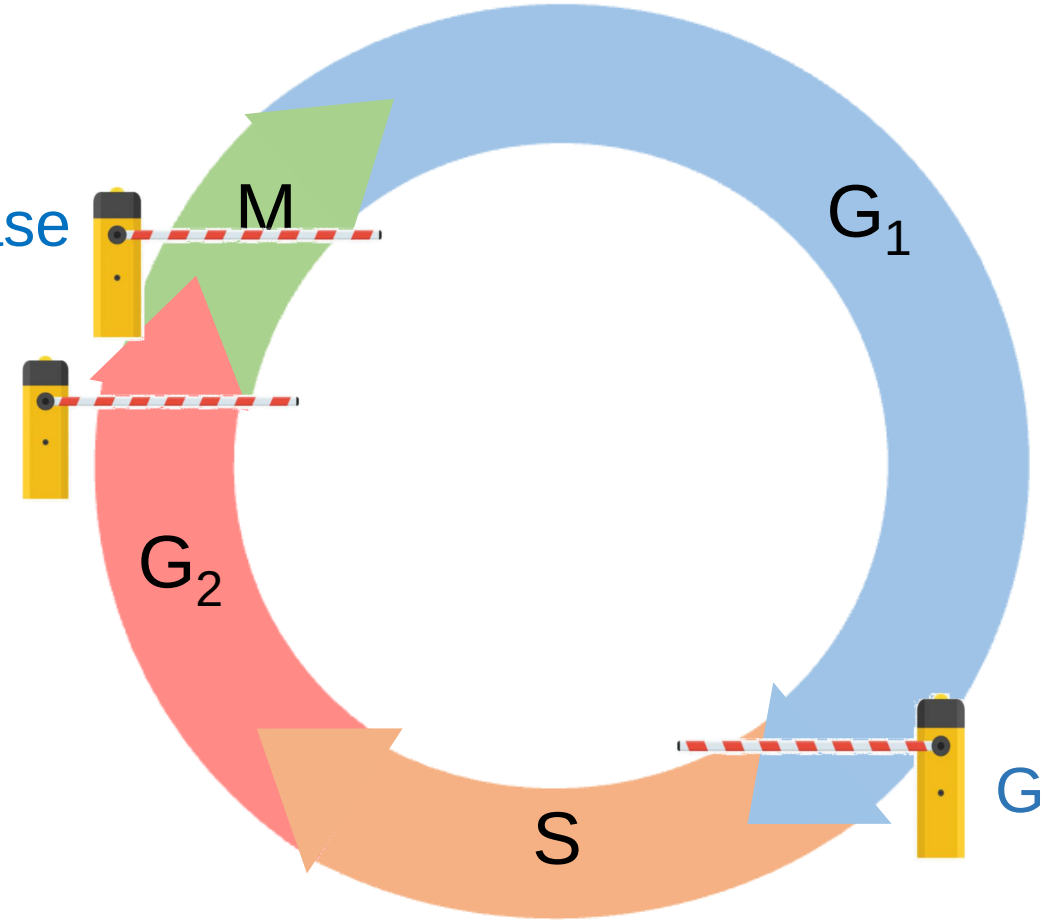
What controls the cell cycle?

The Cell Cycle Control System



(I) Regulatory checkpoints

There are 3 Regulatory Checkpoints in the Cell Cycle



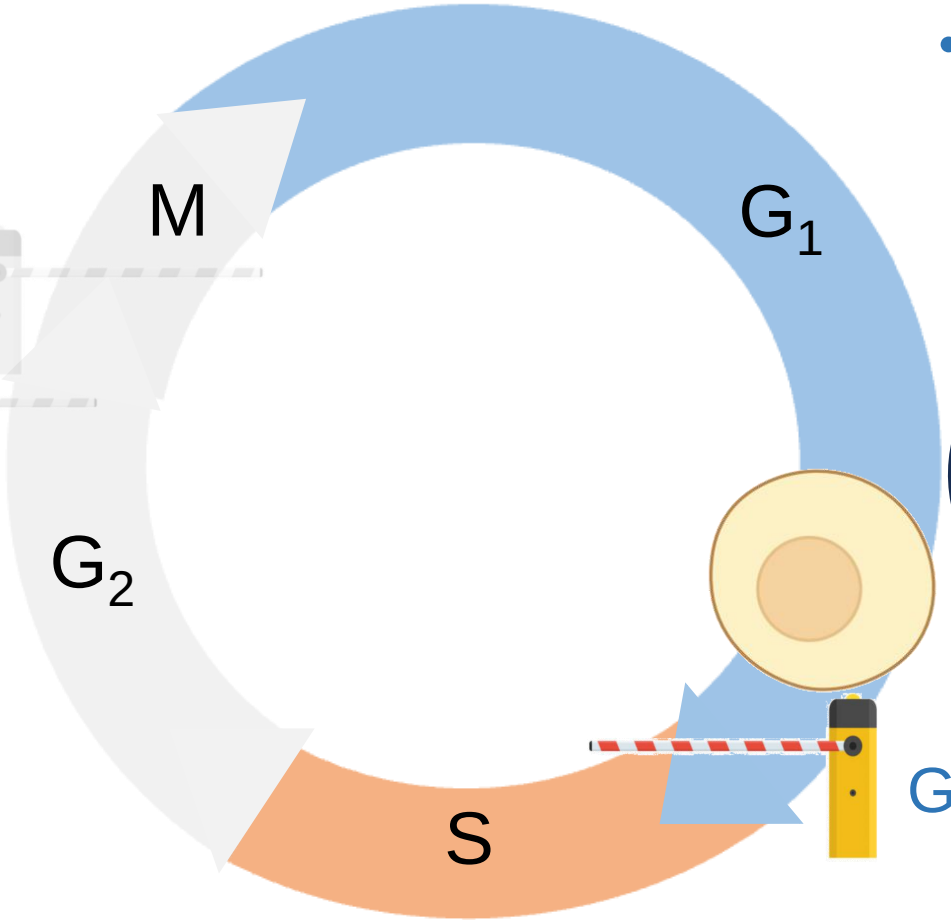
Metaphase/Anaphase transition

G_2/M transition

G_1/S transition

•Ensure that each phase is completed before the next one begins

The 3 Regulatory Checkpoints in the Cell Cycle



- G_1/S checkpoint occurs **before** cells enter the S phase

•Is the cell large enough?
•Are there enough nutrients?
•Is the DNA damaged?

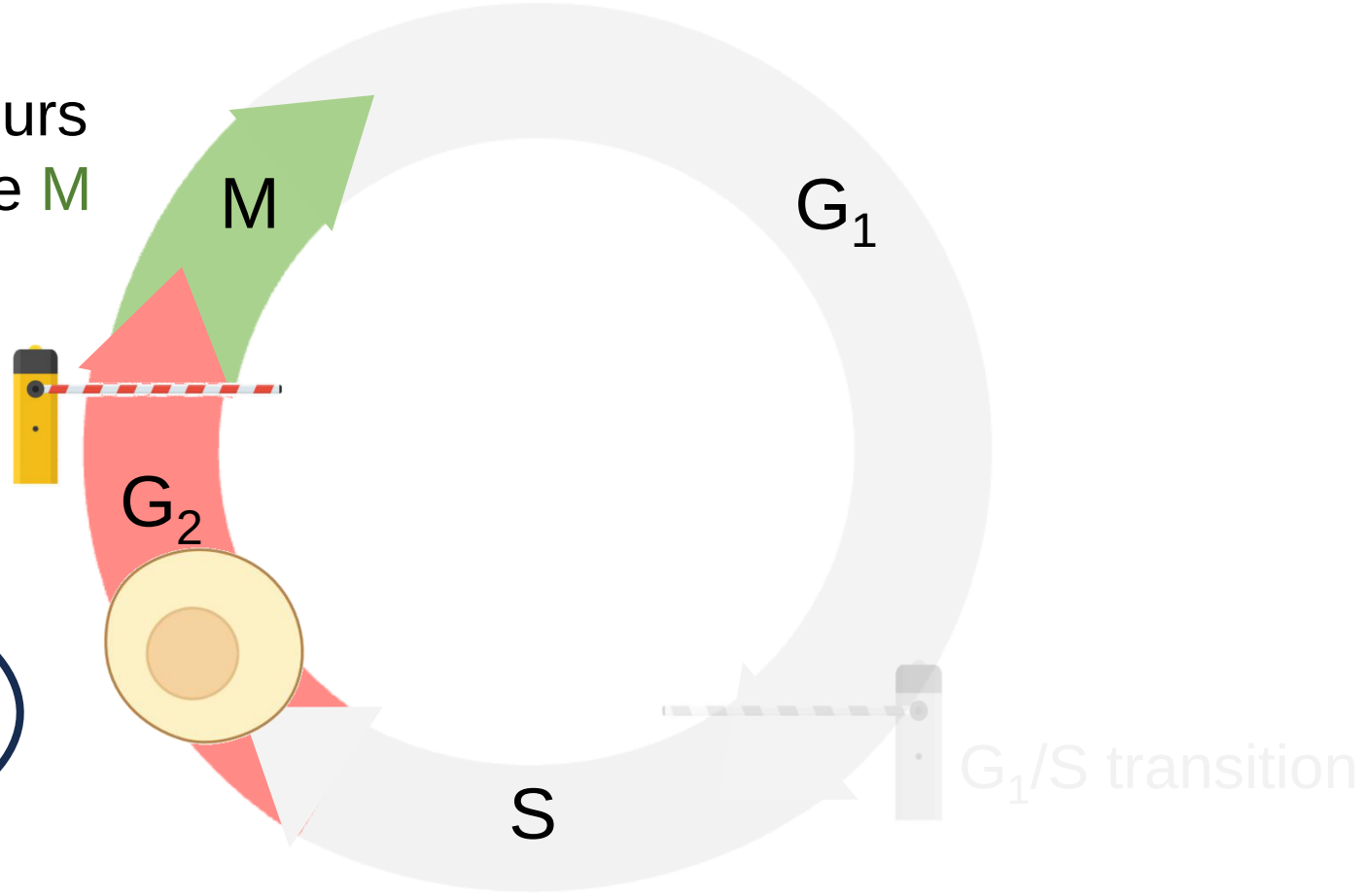
G_1/S transition

The 3 Regulatory Checkpoints in the Cell Cycle

- G_2/M checkpoint occurs **before** cells enter the M phase

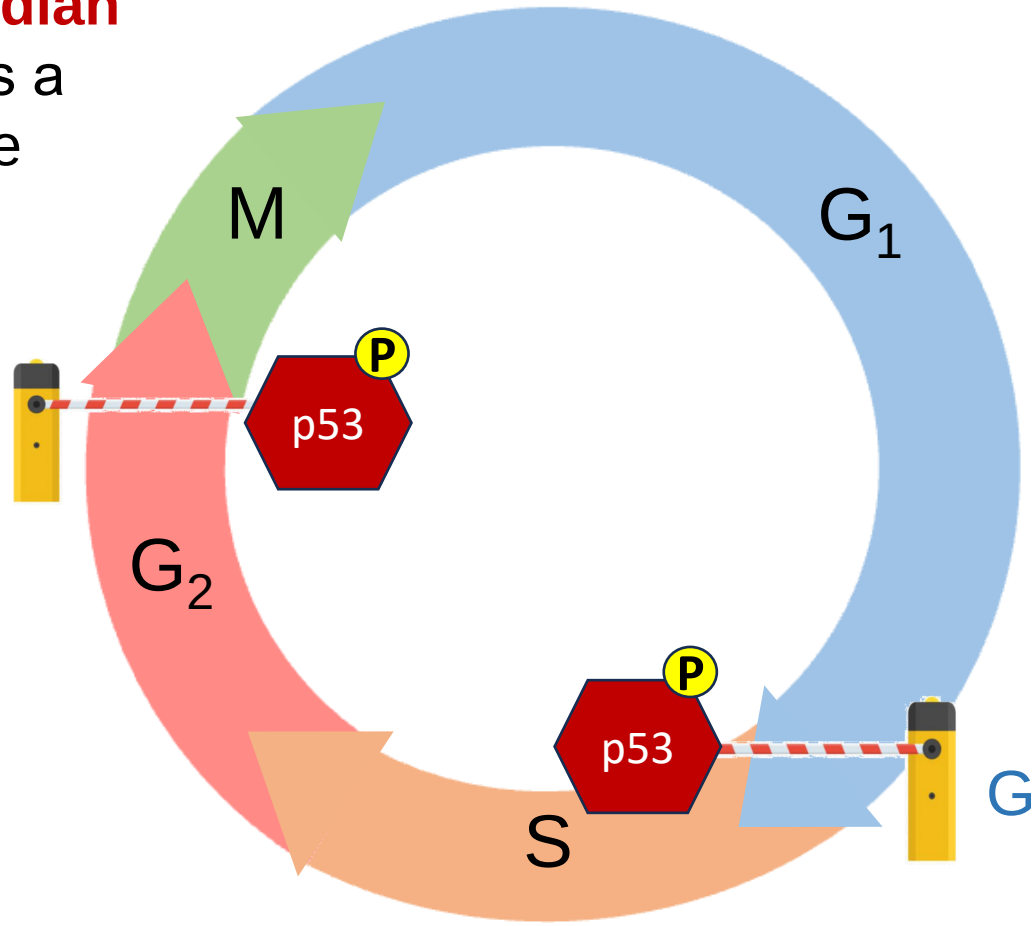
G_2/M transition

Is DNA replication completed correctly?
Is the DNA damaged?



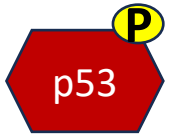
DNA Damage Checkpoints occur at G_1/S and G_2/M transitions of the Cell Cycle

- **p53** protein, the "**Guardian of the Genome**," plays a central role in cell cycle **checkpoints**



G_2/M transition

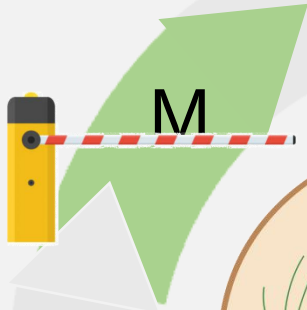
G_1/S transition

- DNA damage activates kinases that phosphorylate p53
- 

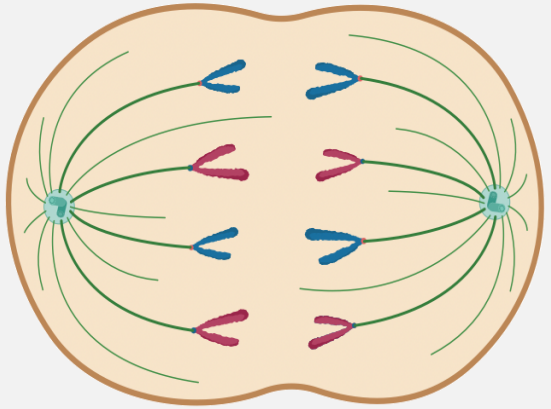
activates:
  1. **Cell cycle arrest (G_0)**
  2. **DNA repair**
  3. **Apoptosis**

The 3 Regulatory Checkpoints in the Cell Cycle

Metaphase/Anaphase transition (occurs during Mitosis)



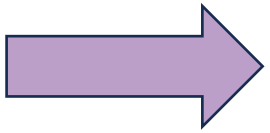
Metaphase

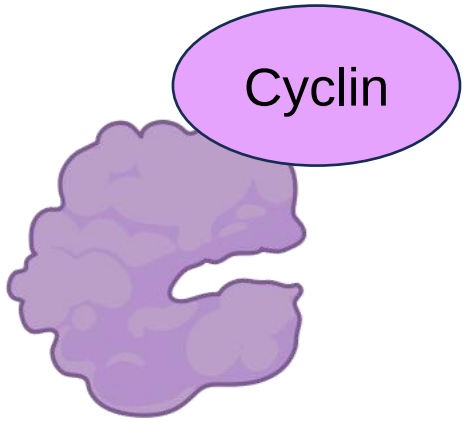


Anaphase

•Are the chromatids **properly attached** to the mitotic spindle before preceding to Anaphase?

The Cell Cycle Control System





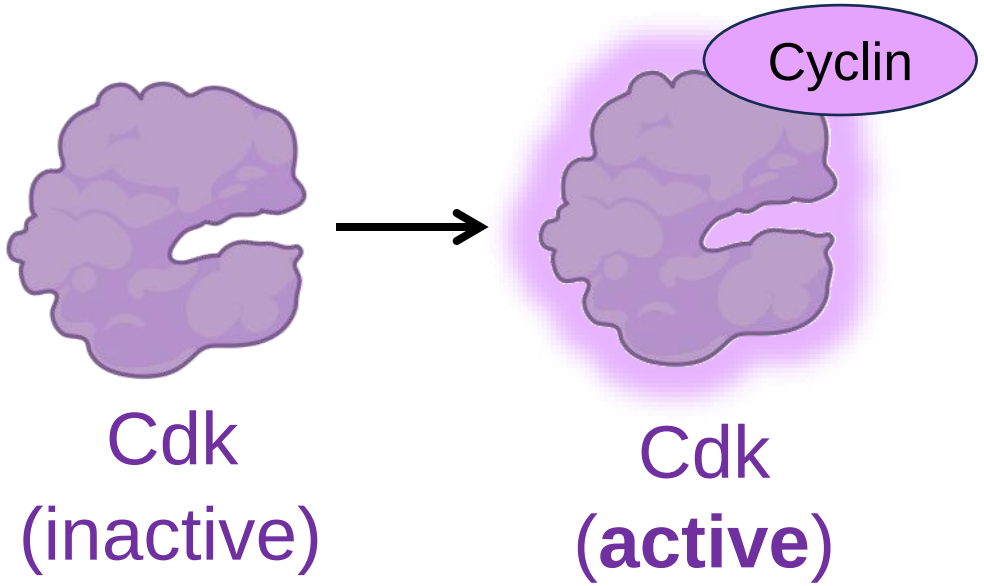
Regulatory check points

Cyclin-dependent kinases (Cdks)

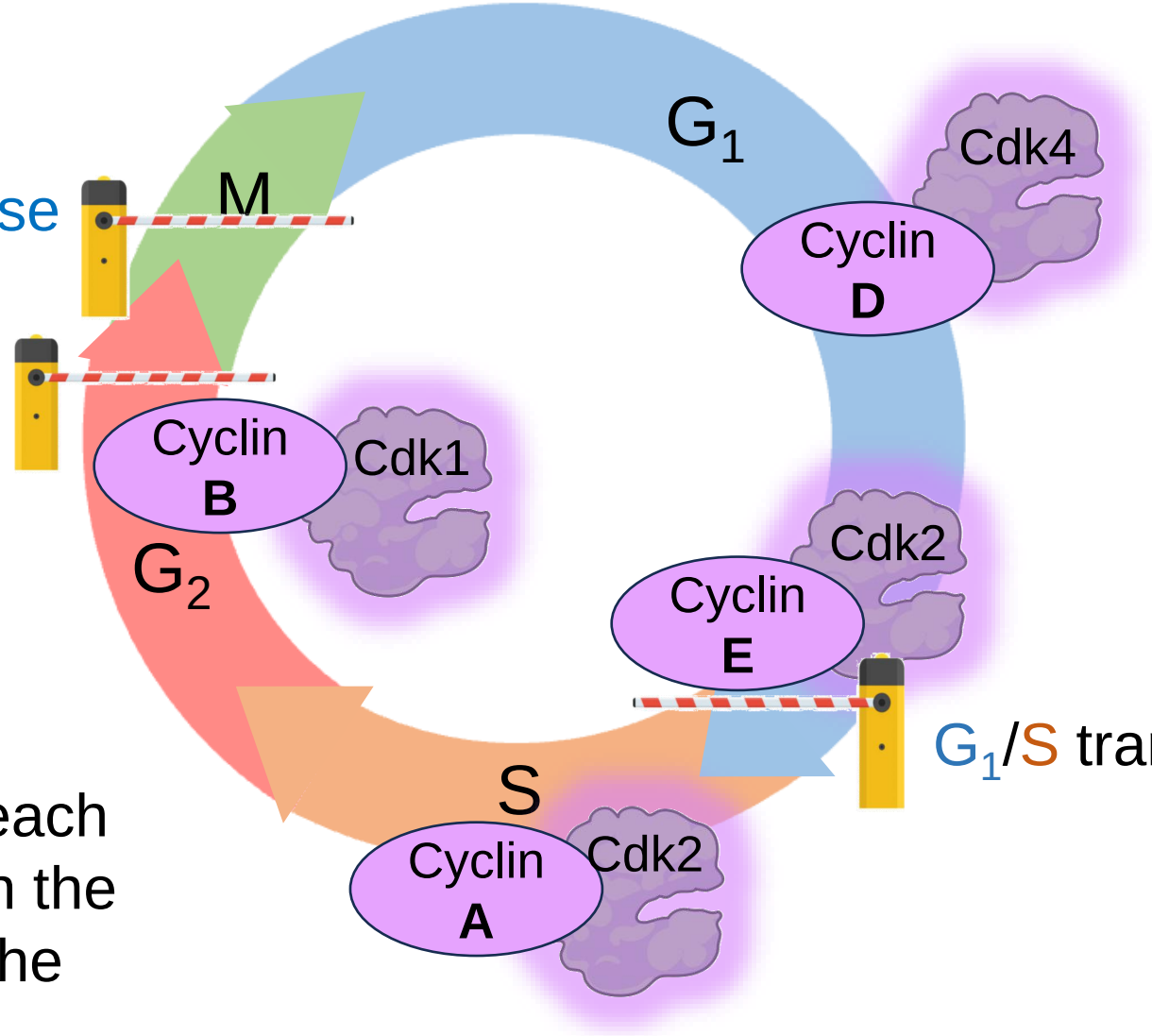
The cell cycle progression is driven by Cdks

- **Cyclin-dependent kinases (Cdks)** require **binding to Cyclin** proteins to become **active**

- **Cdks** and Cyclins play a crucial role in regulating the Cell Cycle

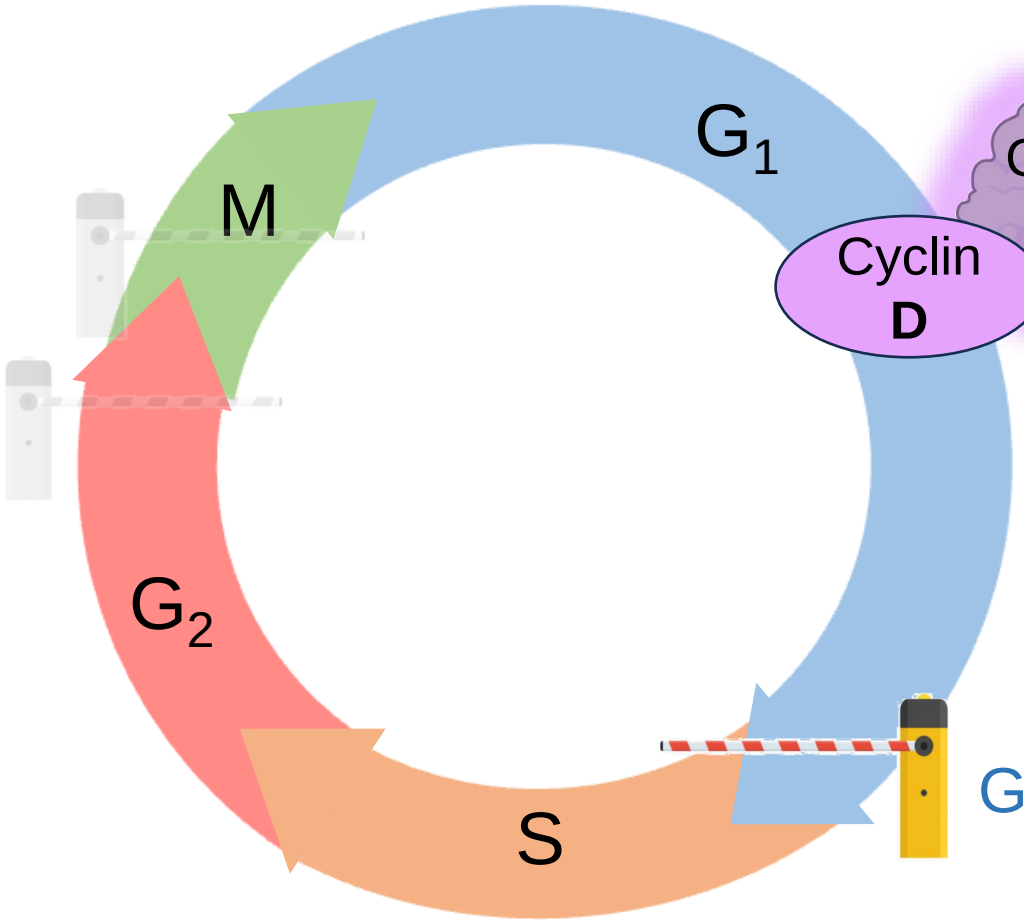


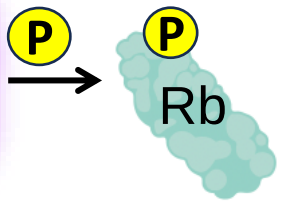
Specific Cyclin-Cdk complexes regulate activity at different phases of cell cycle

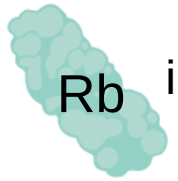


Ensure that events of each phase are carried out in the correct order and at the appropriate time

Cyclin D-Cdk4 complex regulates activity at the G_1 phase







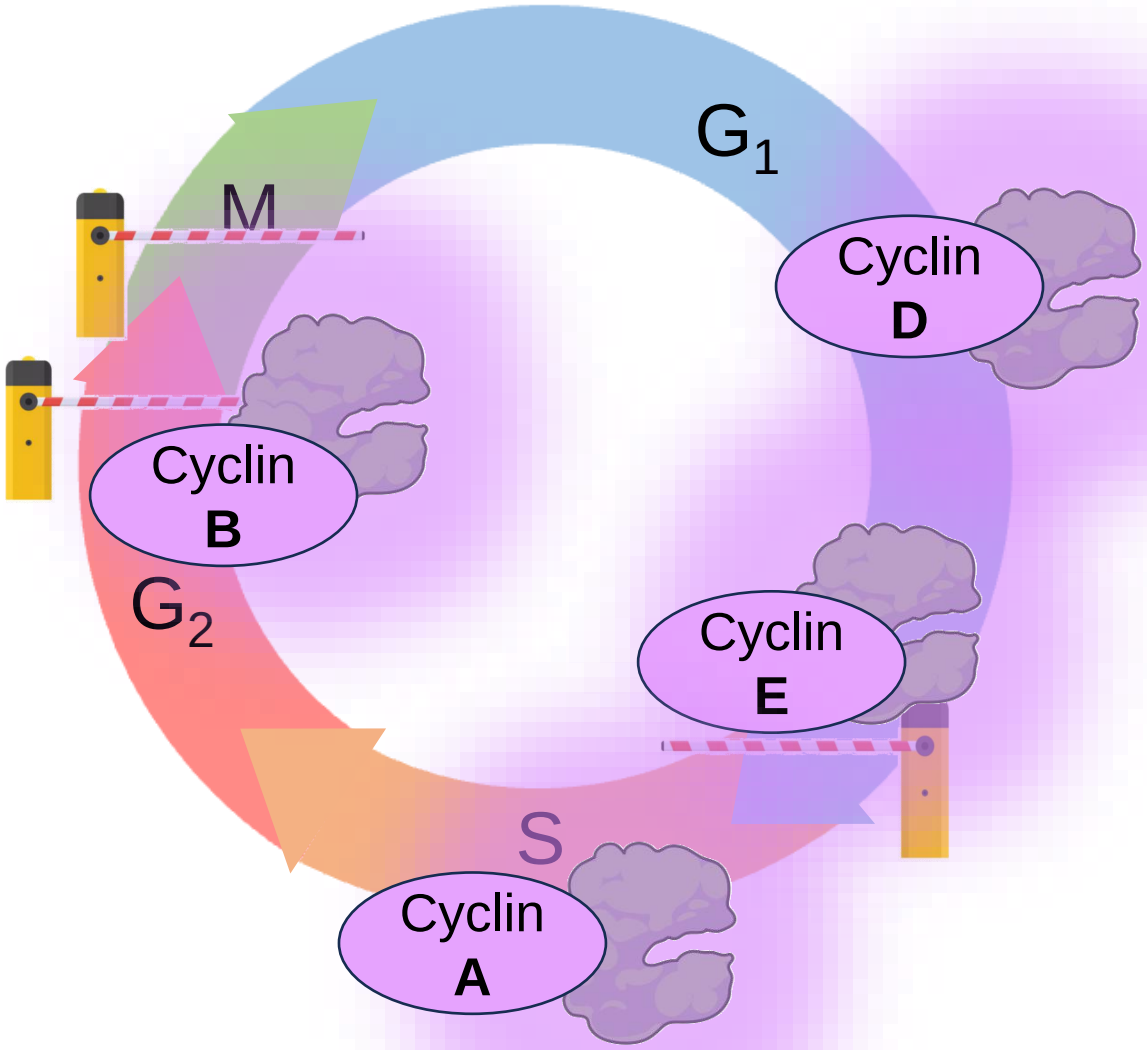
(active)
inhibits DNA replication

(inactive)

Genes turn on for DNA replication; cells can transition to S phase where DNA replication occurs

G_1/S transition

The cell cycle is dysregulated in Cancer cells



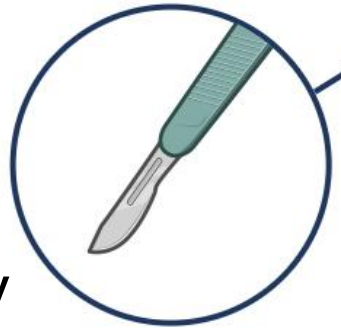
- Cancer cells ignore cell cycle checkpoints
- Cyclin-CDKs are often **overactivated** due to dysregulation in the cell cycle

Result: Uncontrolled cell proliferation and growth

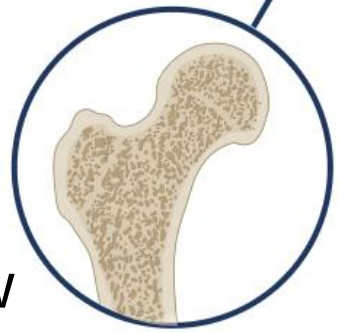
Types of Cancer Treatments

Hormonal therapy

Surgery



Bone marrow transplant

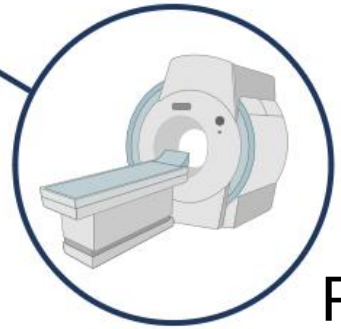


Chemotherapy

(targets rapidly dividing cells)

Personalized therapy

Immuno therapy



Radiotherapy

Learning Objectives for Today's Lecture:

Upon completing this module, **you should be able to**:

- Identify the different phases of the **cell cycle**
- Explain the process and phases of **mitotic** cell division
- Describe how **cyclin dependent kinases** regulate cell cycle progression
- Apply knowledge of the cell cycle to understand case studies

CASE STUDY

You are a researcher who is interested in the molecular pathways that underly cell division. You care culturing two different cell lines that are unable to divide.

You sequence Cell Line #1, and it appears to have a mutation in Cyclin-dependent kinase-1.

You fluorescently label the chromosomes in Cell Line #2 and find them stalled and aligned in the middle of the cell.

1. Which phase of the cell cycle would each cell line remain in?

2. Would p53 be active or inactive in each of these two cell lines?

3. What is a possible explanation for why Cell Line #2 is stalled?

CASE STUDY

You sequence Cell Line #1, and it appears to have a mutation in Cyclin-dependent kinase-1.
You fluorescently label the chromosomes in Cell Line #2 and find them stalled and aligned in the middle of the cell.

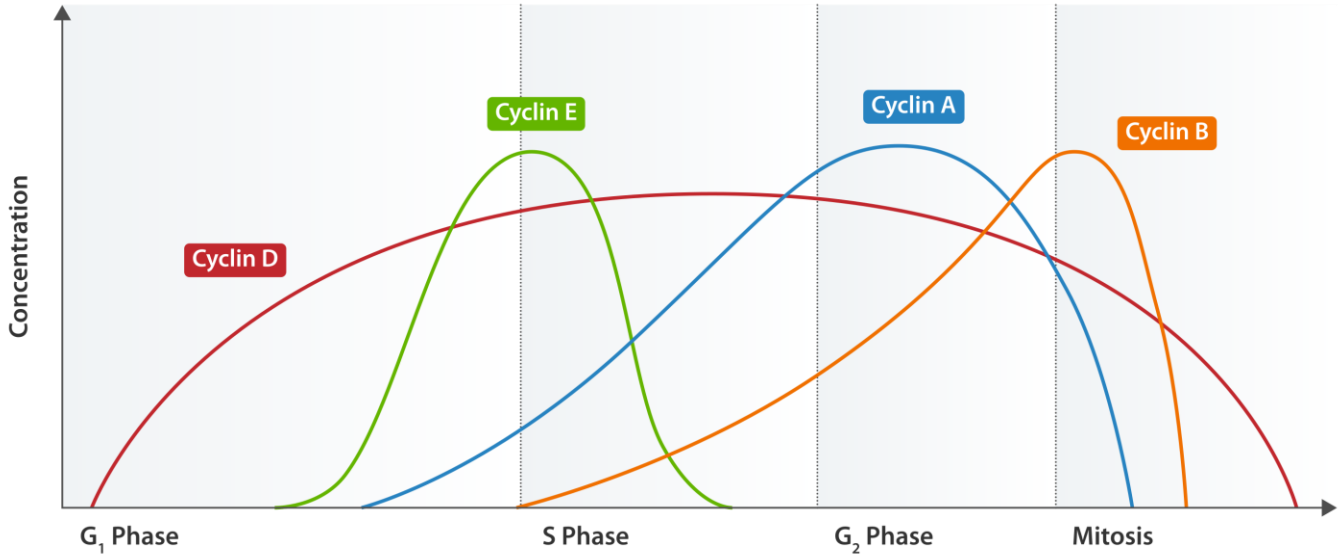
1. **Which phase of the cell cycle would each cell line remain in?**
   - #1 would be in G2 due to inability to pass the G2/M cell cycle checkpoint due to the mutation in Cdk1
   - #2 would be in metaphase of mitosis (M phase), unable to pass the metaphase/anaphase transition checkpoint

2. **Would p53 be active or inactive in each of these two cell lines?**
   - We would not expect p53 to be active, as p53 is generally activated in response to DNA damage, which does not appear to be the case with these lines

3. **What is a possible explanation for why Cell Line #2 is stalled?**
   - Cell line #2 is stalled because of an issue with the microtubules, either an inability to effectively attach to chromosome kinetochores or an issue with polymerization to pull the sister chromatids apart

Exercise: Cyclin concentration

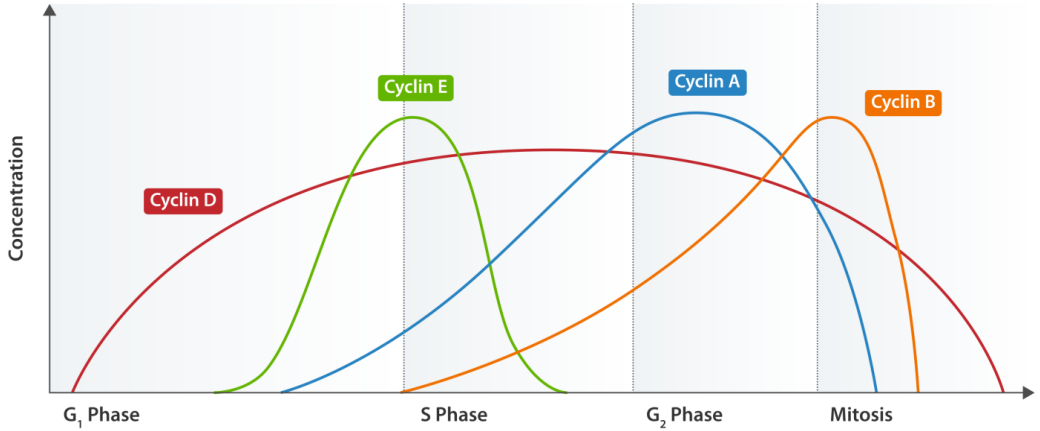
Below is a plot of cyclin concentrations during the cell cycle:



Why does cyclin concentration vary over time?

Why do the concentrations of Cyclins A, B, and E experience sharp decreases while Cyclin D does not?

Exercise: Cyclin concentration



Why does cyclin concentration vary over time?

When cyclin is present, it will activate cyclin-dependent kinase, which allows the cell to progress through the checkpoint. Our cells need mechanisms to control the concentration of cyclin produced to ensure the cells are sufficiently large, have correctly replicated DNA, etc., before proceeding

Why do the concentrations of Cyclins A, B, and E experience sharp decreases while Cyclin D does not?

Cyclin D is involved in G1, which is the longest portion of interphase, and Cyclin D levels in proliferating cells are sustained as long as the growth factors are present. This means that when the cell is growing (i.e., not in G0 or M phase) we would want Cyclin D to be present. Here Cdk levels are more tightly controlled to only proceed to S phase if intending to divide.

Cyclins A, B, and E are involved with very specific transitions in the cell cycle and can drop off in concentration after performing their task (as the decision to undergo cell division has passed)

Learning Objectives for Today's Lecture:

Upon completing this module, **you should be able to**:

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- Explain the process and phases of **mitotic** cell division
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Metacognitive Reflection Form