

Johns Hopkins Engineering

Molecular Biology

Mitosis and the Cell Cycle



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Outline

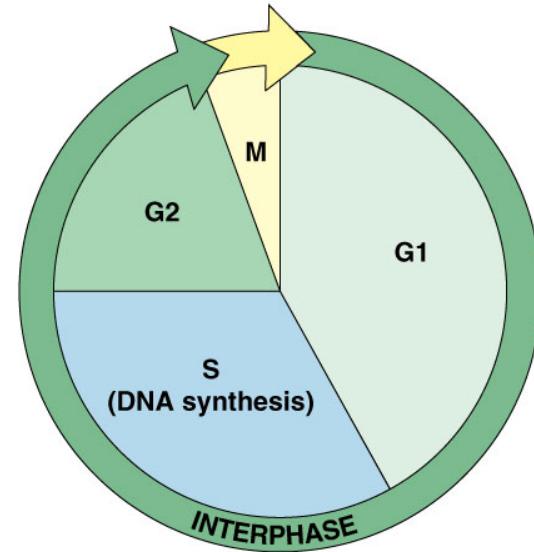
- Cell Cycle
- Mitosis
- Motor Proteins
- Cell Division

The Cell Cycle, DNA Replication, and Mitosis

- Cell growth is generally accompanied by **cell division**, whereby one cell gives rise to two new daughter cells
- All the genetic information in the nucleus must be accurately duplicated and carefully distributed to the daughter cells
- In doing this a cell passes through a series of stages known as the *cell cycle*

Overview of the Cell Cycle

- The **cell cycle** begins when two new cells are formed by division of a parent cell and ends when one of these cells divides again
- The two copies of each chromosome made during S phase are distributed into daughter cells during M phase
- M phase** is when the cells actually divide; the nucleus first, followed by the cytoplasm (**M = mitosis**)
- Nuclear division is **mitosis** and division of the cytoplasm is **cytokinesis**

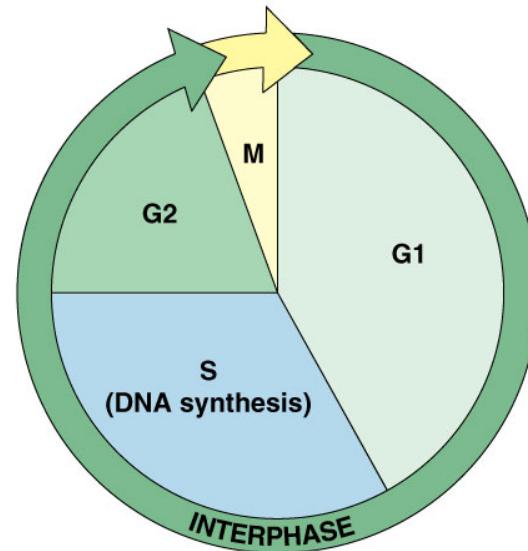


(b) The cell cycle

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Mitosis is a relatively short part of the cell cycle

- Cells spend very little time in M phase
- Most of the time is spent in interphase, which is composed of **G1 phase**, **S phase** (when DNA is replicated), and **G2 phase**
- The overall length of the cell cycle is called the *generation time*; in cultured mammalian cells this is about 18–24 hours

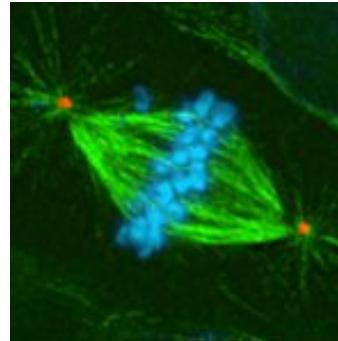
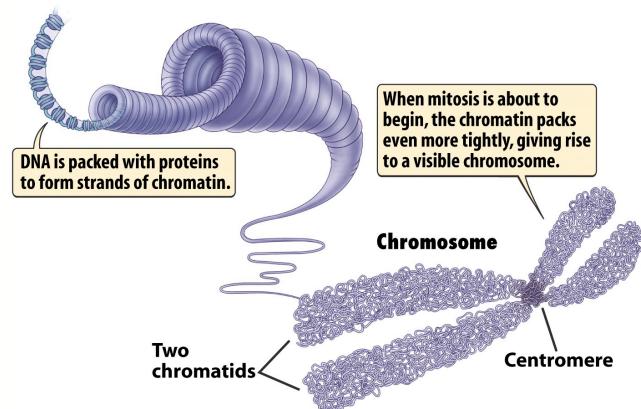


(b) The cell cycle

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Chromosomes in mitosis

- At the beginning of mitosis, chromatin folds and condenses to produce visible chromosomes
- At this part of the cycle, the DNA has replicated, so each chromosome is composed of two sister chromatids
- The *mitotic spindle* microtubules distribute the chromatids to opposite ends of the cell

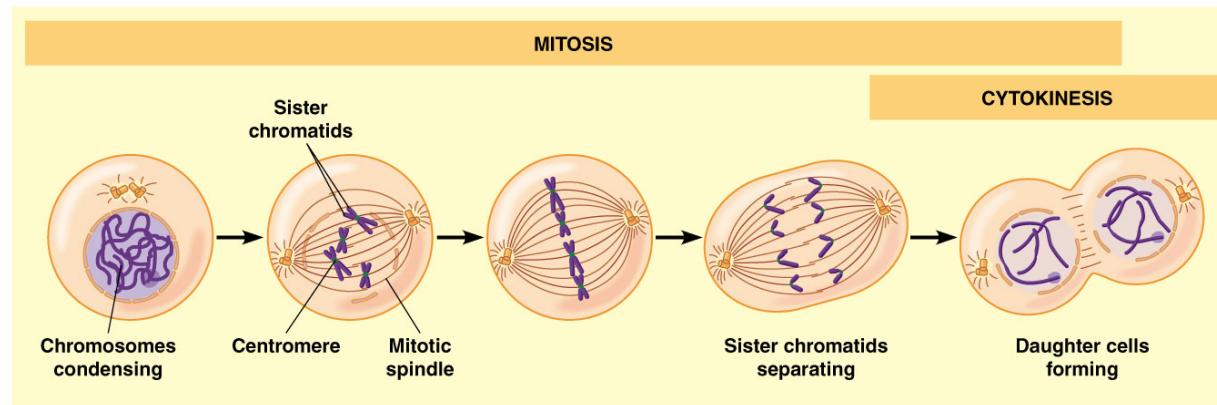


Metaphase spindle organization in a human cell. Microtubules are stained green, centrosomes are stained red and chromosomes are stained blue. See Levesque et al., 2003

<https://geiselmed.dartmouth.edu/compton/photos/photos/>

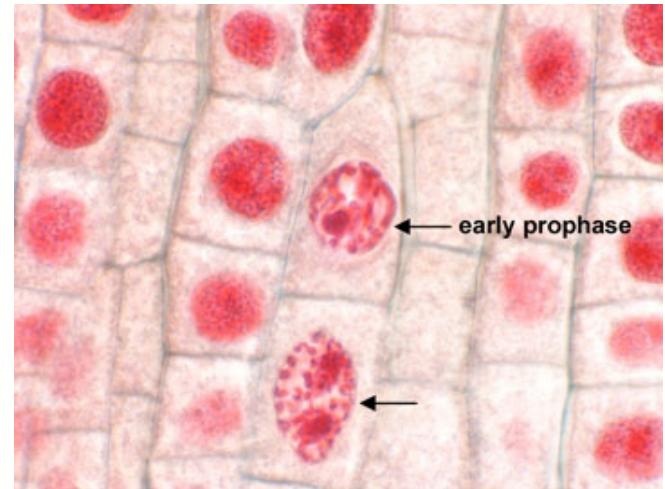
Mitosis Is Subdivided into Prophase, Prometaphase, Metaphase, Anaphase, & Telophase

- Mitosis is divided into five stages based on changing appearance and behavior of chromosomes
- Events during each stage are directed toward the correct distribution of one copy of each chromosome into daughter nuclei



Prophase

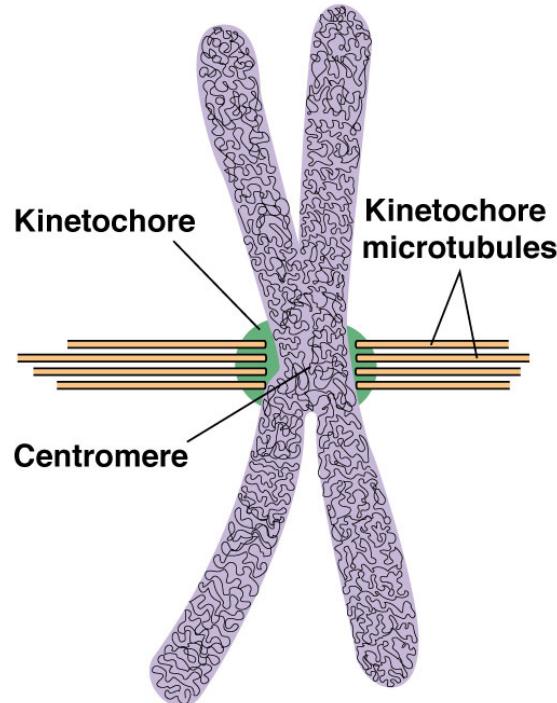
- After DNA replication, cells exit S phase and enter G2 phase, where final preparations are made for entry into mitosis
- Toward the end of G2, chromosomes begin to condense into more compact, folded structures
- The G2 → prophase transition is not sharply defined but cells are in **prophase** when individual chromosomes become visible
- Centrosomes complete their movement to opposite sides of the nucleus and the spindle MTs contact the condensed chromosomes
- MTs attach to chromosomes in the **centromere** region



<http://faculty.ccbcmd.edu/~gkaiser/biotutorials/dna/mitosis/pcprophaseA.html>

Centromeres

- DNA in centromeres consists of simple, tandemly repeated *CEN* sequences, with considerable variation among species
- CENP-A recruits additional proteins to the centromere to form the **kinetochore**, to which MTs attach



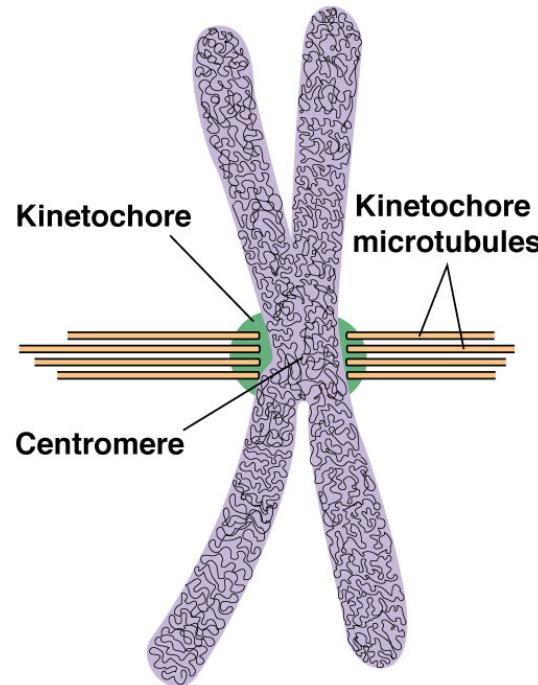
(a)

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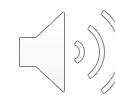
Kinetochores

- Kinetochore proteins begin to assemble on centromeres shortly after S phase
- During prometaphase spindle MTs bind the kinetochores associated with each chromatid
- Forces exerted by these **kinetochore microtubules** gradually move chromosomes toward the center of the cell



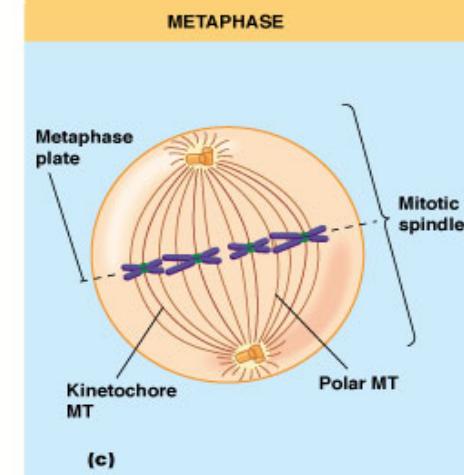
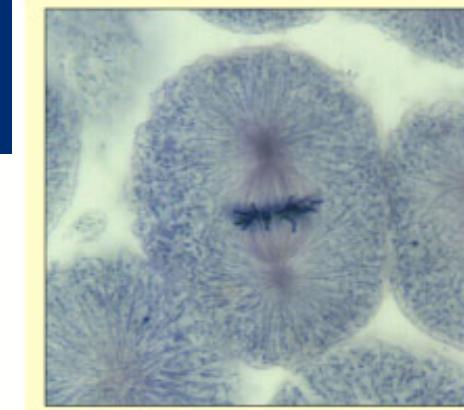
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Metaphase

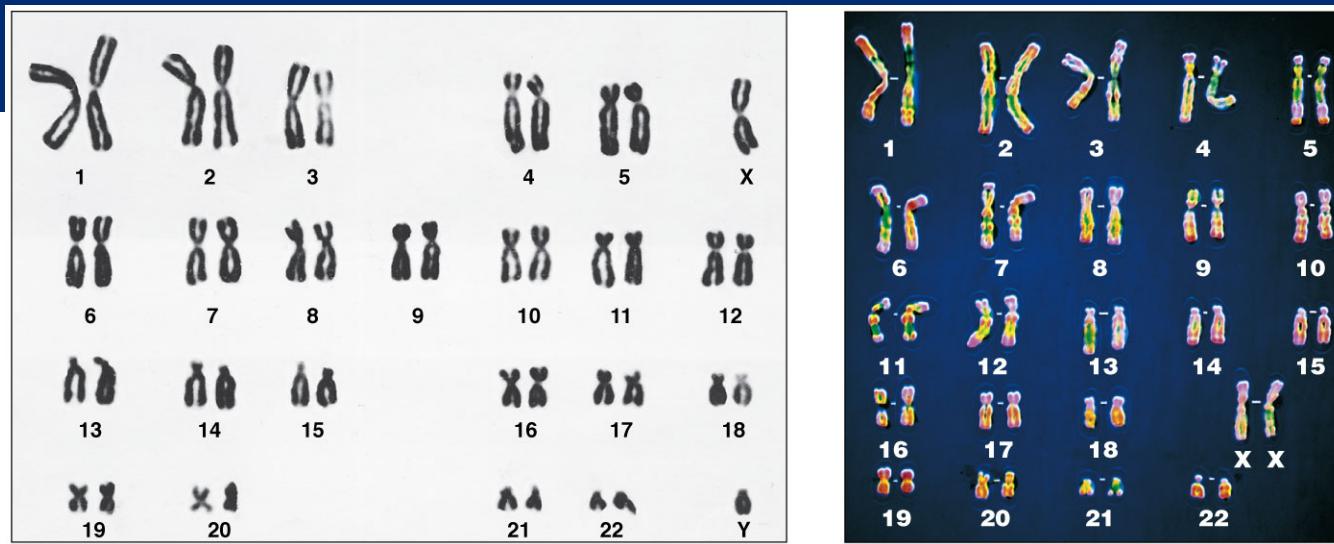
- A cell is in **metaphase** when the fully condensed chromosomes are all aligned at the *metaphase plate* (a plane equidistant between the two poles of the spindle)
- Agents that interfere with spindle function (e.g., *colchicine*) are used to arrest cells at metaphase
- Examining metaphase cells allows chromosomes to be identified, generating a **karyotype**



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Figure 19-23



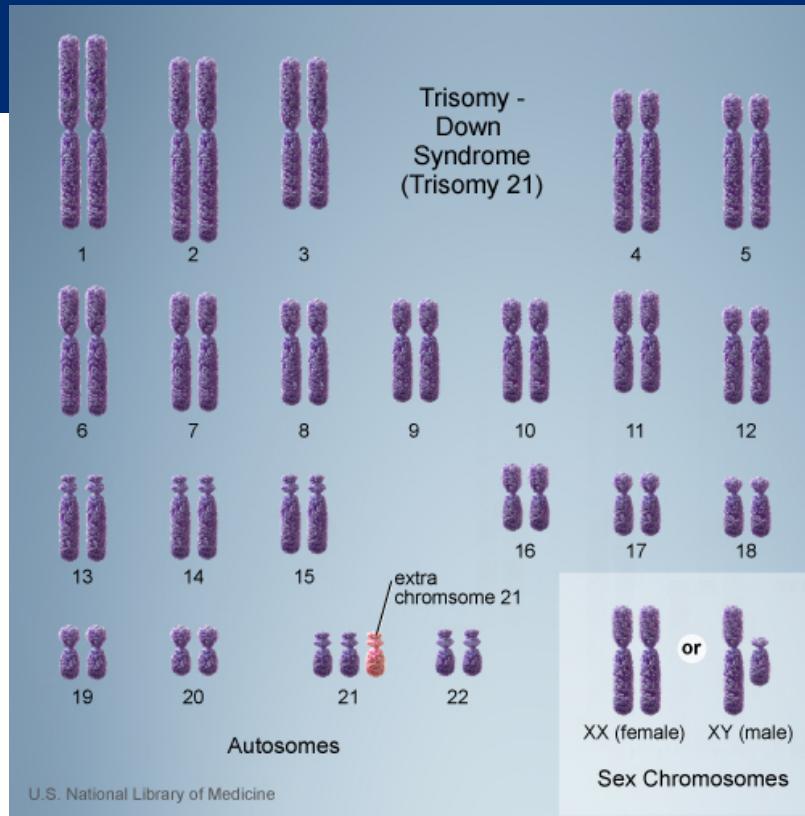
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Karyotyping is the process of pairing and ordering all the chromosomes of an organism, thus providing a genome-wide snapshot of an individual's chromosomes. Karyotypes are prepared using standardized staining procedures that reveal characteristic structural features for each chromosome. Clinical cytogeneticists analyze human karyotypes to detect gross genetic changes—anomalies involving several megabases or more of DNA. Karyotypes can reveal changes in chromosome number associated with aneuploid conditions, such as trisomy 21 (Down syndrome). Careful analysis of karyotypes can also reveal more subtle structural changes, such as chromosomal deletions, duplications, translocations, or inversions. In fact, as medical genetics becomes increasingly integrated with clinical medicine, karyotypes are becoming a source of diagnostic information for specific birth defects, genetic disorders, and even cancers.

<http://www.nature.com/scitable/topicpage/karyotyping-for-chromosomal-abnormalities-298>



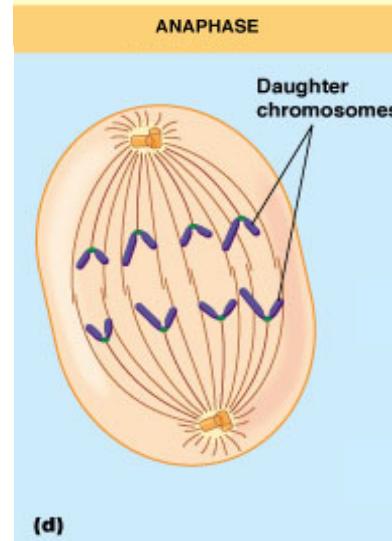
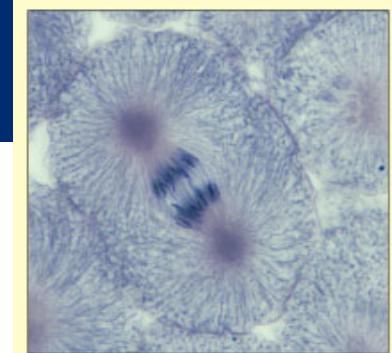
Karyotype example: Down's Syndrome



https://embryology.med.unsw.edu.au/embryology/images/2/2a/Chromosome-_trisomy.jpg

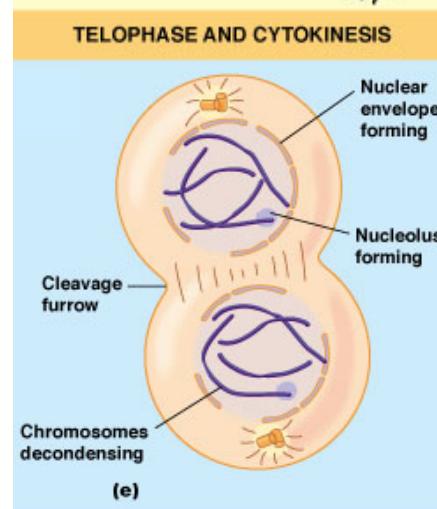
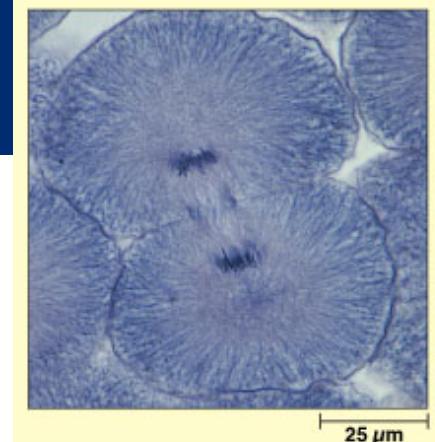
Anaphase

- Anaphase is the shortest phase of mitosis
- The two sister chromatids of each chromosome abruptly separate and move toward opposite poles
- In **anaphase A**, the chromosomes are pulled toward spindle poles as kinetochore MTs get shorter
- In **anaphase B** the spindle poles themselves move away from each other as polar MTs lengthen



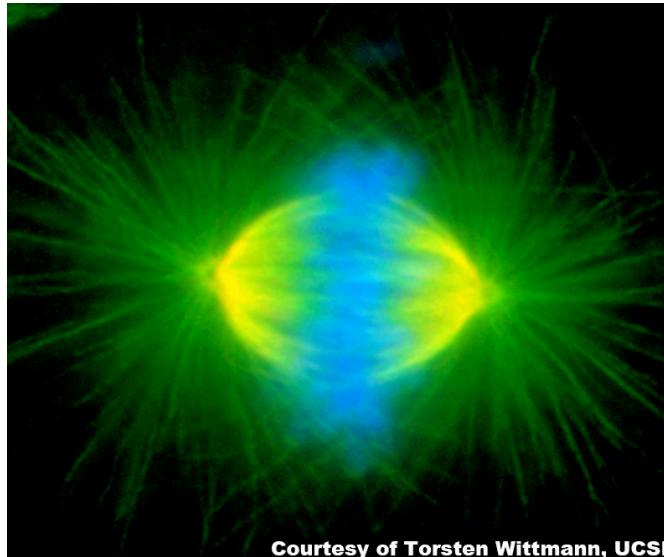
Telophase

- At the beginning of **telophase** the daughter chromosomes arrive at the poles of the spindle
- Chromosomes uncoil into interphase chromatin
- Nucleoli reappear and nuclear envelopes reform
- During this period, cytokinesis also takes place



The Mitotic Spindle Is Responsible for Chromosome Movements During Mitosis

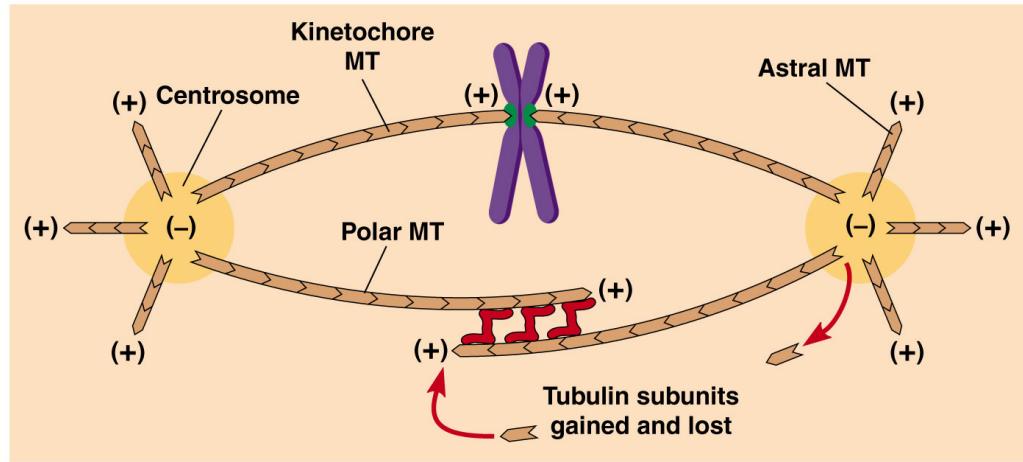
- The microtubule-containing apparatus responsible for separation of chromatids into daughter cells is the **mitotic spindle**



Courtesy of Torsten Wittmann, UCSF

Spindle Assembly and Chromosome Attachment

- Microtubules have an inherent polarity (the two ends have different chemical properties)
- The end where MT assembly is initiated (the centrosome in the case of the spindle) is the minus end
- The end where most growth occurs is the plus end

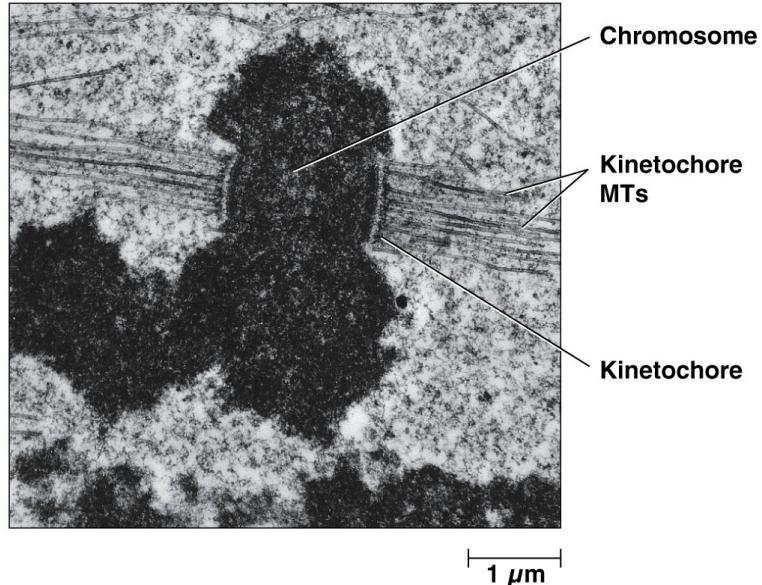


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- The minus end is at the initiating centrosome
- The plus end points away from the centrosome
- Tubulin subunits are added and removed during mitosis

Spindle Assembly

- During late prophase, MT growth speeds up dramatically and initiation of new MTs at centrosomes increases
- When the nuclear envelope disintegrates, kinetochores and MTs can come into contact
- When the plus end of MTs and the kinetochore bind, the MT becomes a kinetochore MT



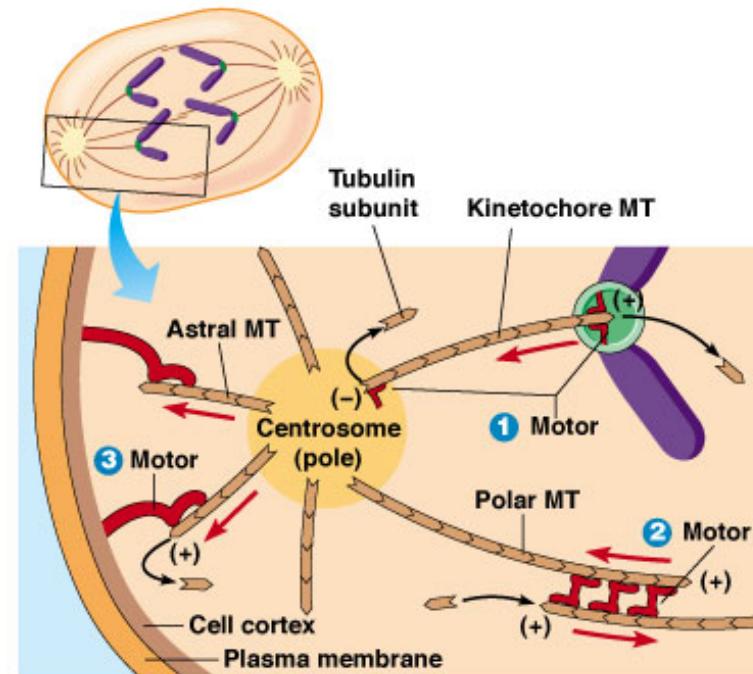
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Mitosis Summary:

<https://www.youtube.com/watch?v=C6hn3sA0ip0>

So What Drives Chromosome Movement?

- Several **motor proteins** play active roles in mitosis
 - Kinesins
 - Dynein
 - Myosin
- They use energy from ATP to change shape and exert force that causes movement of attached structures
- Motor proteins play at least three distinct roles in movement of anaphase chromosomes



(a) Three roles played by motor proteins

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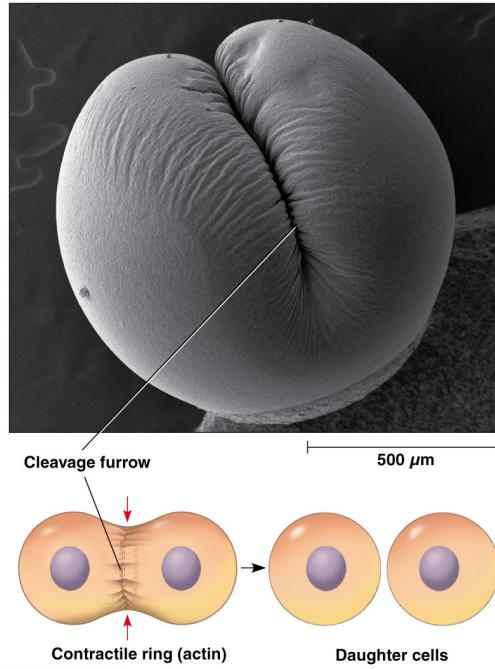
Dynein:

<https://www.youtube.com/watch?v=gpjcw-ltOfo>



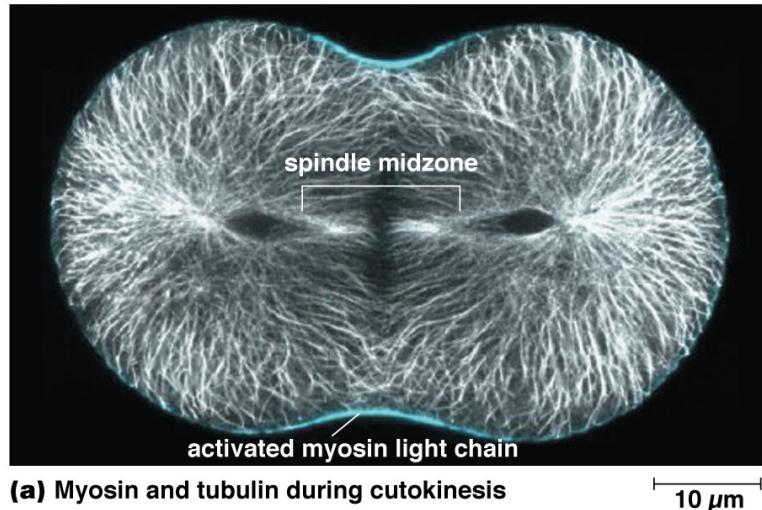
Cytokinesis Divides the Cytoplasm

- After the chromosomes have separated, cytokinesis divides the cytoplasm in two
- This usually starts in late anaphase or early telophase



Myosin and cleavage

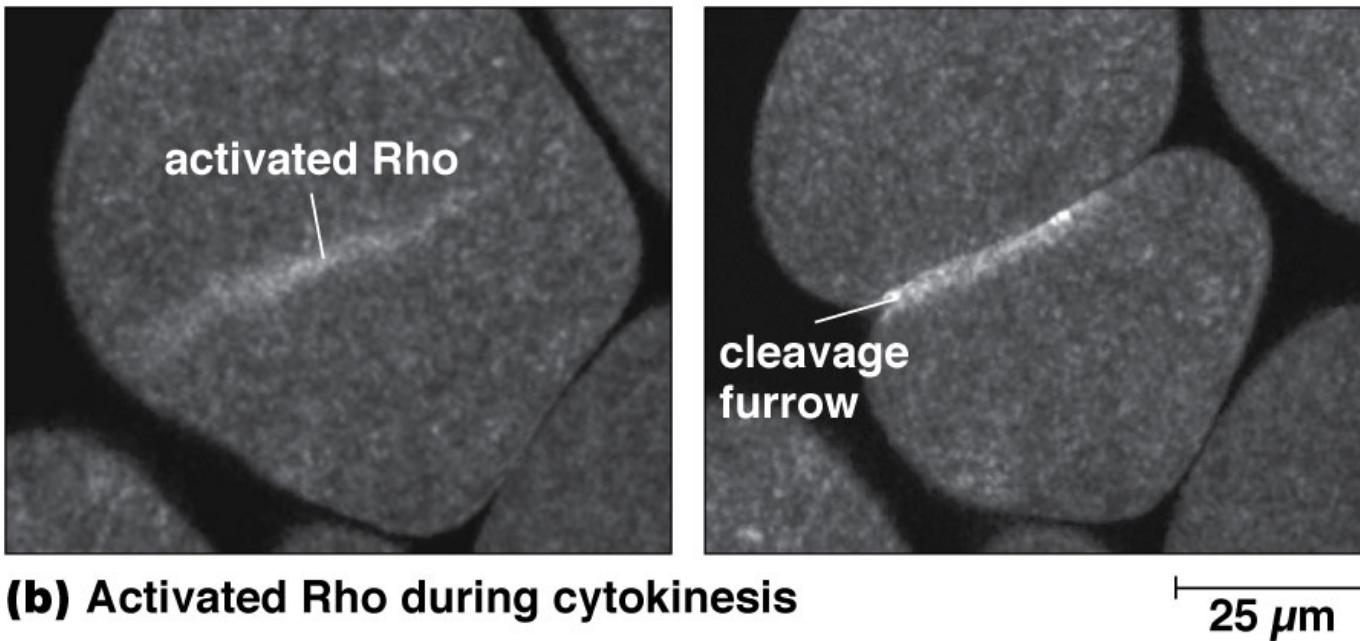
- Contraction of the ring is generated by interactions between actin and the motor protein, *myosin*
- Members of *Rho-GTP* binding proteins regulate assembly and activation of the contractile ring
- *RhoA* is recruited to the cleavage furrow to activate proteins needed for actin polymerization, and stimulate activation of myosin



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Figure 19-29B

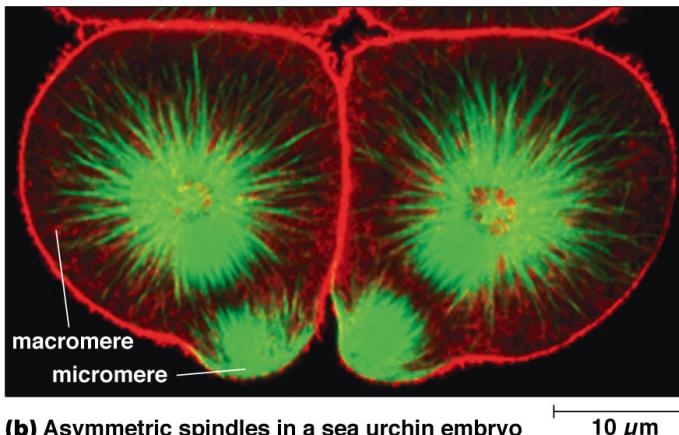
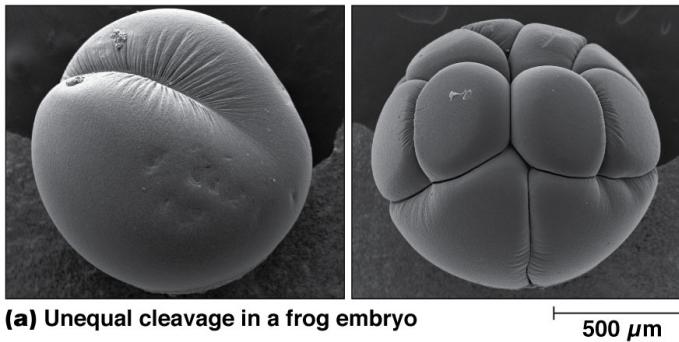


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Cell Division Is Sometimes Asymmetric

- Cytokinesis is not always symmetric; sometimes the spindle forms in asymmetric fashion
- This can result in one large and one small cell
- These occur frequently during embryonic development; sometimes cells formed in this way have differing developmental potentials



Summary

- Cell Cycle
- Mitosis
 - Prophase
 - Metaphase
 - Anaphase
 - Telophase
- Motor Proteins
- Cytokinesis



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