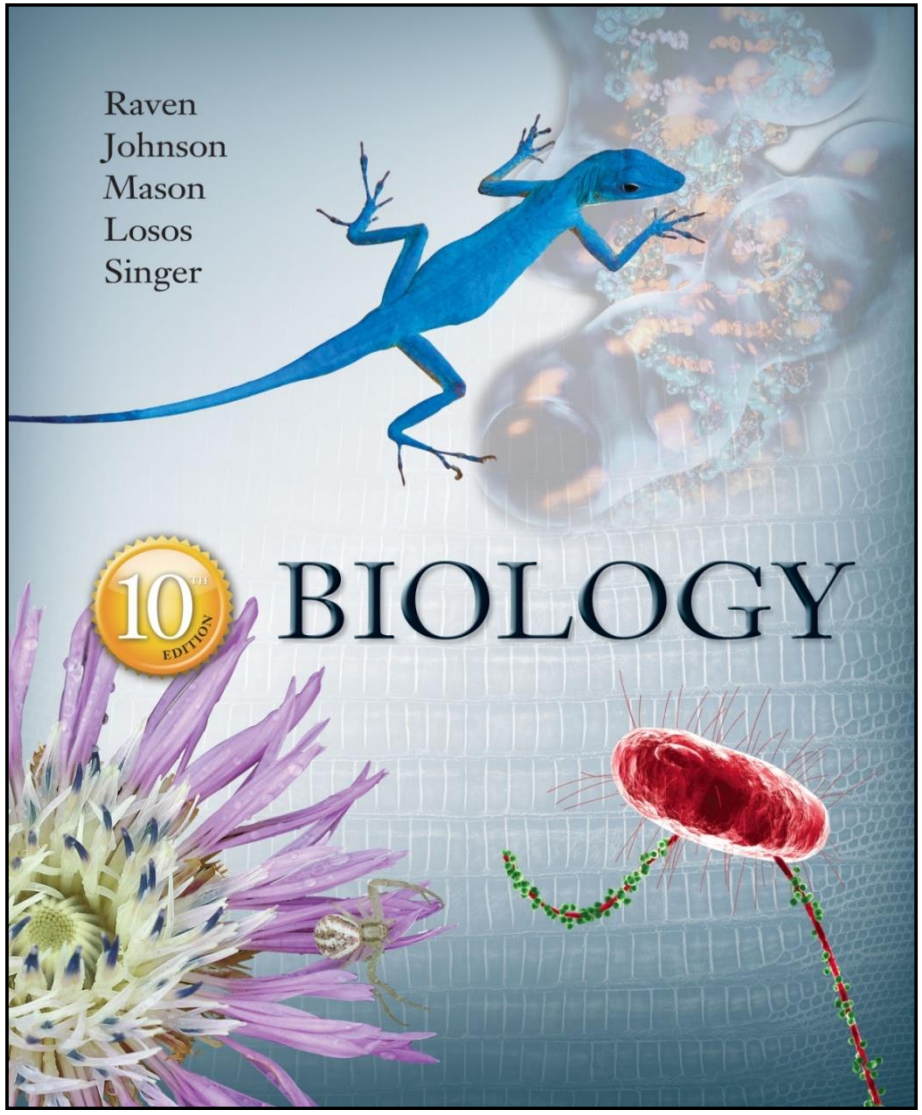
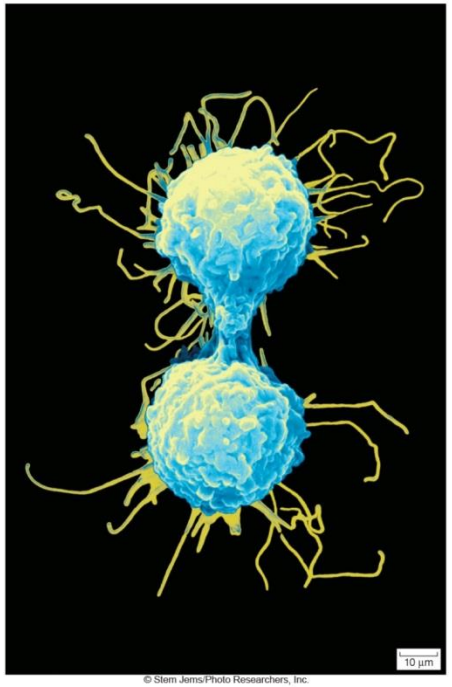
Chapter 10

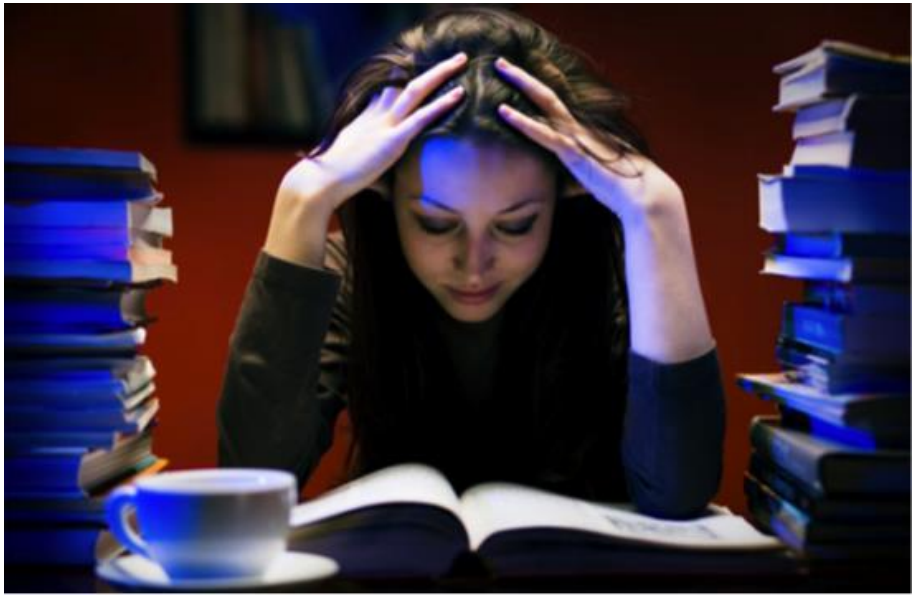
How Cell Divide





Important study hints

- You get the idea by now!!



http://www.hercampus.com/school/wisconsin/it-s-finals-time-5-ways-prepare-week-we-re-all-dreading

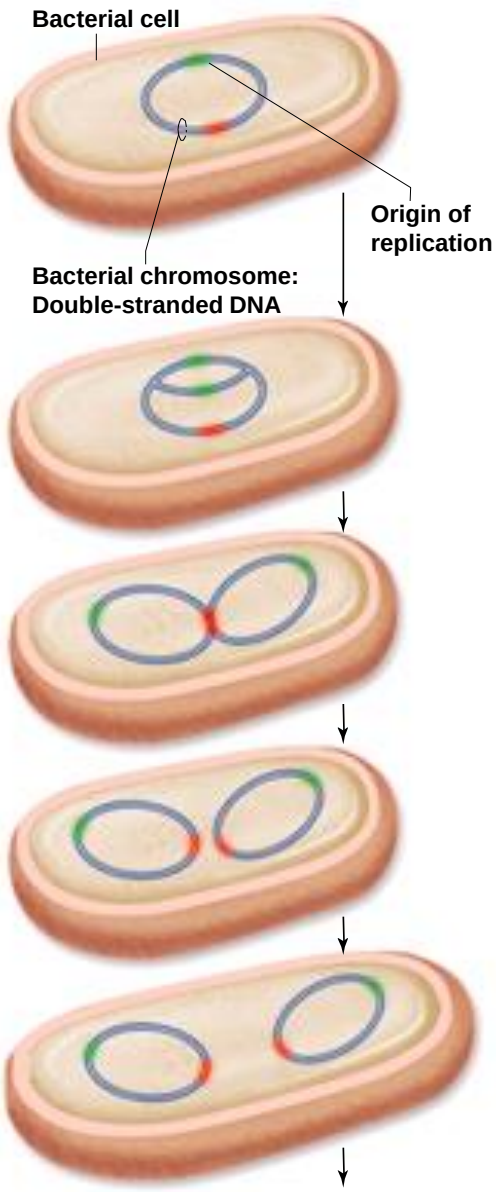
Chapters Contents

- Bacteria Cell Division
- Eukaryotic Chromosomes
- Overview of the Eukaryotic Cell Cycle
- Interphase: Preparation for Mitosis
- M Phase: Chromosome Segregation and the Division of Cytoplasmic Contents
- Control of the Cell Cycle

10.1 Bacterial Cell Division

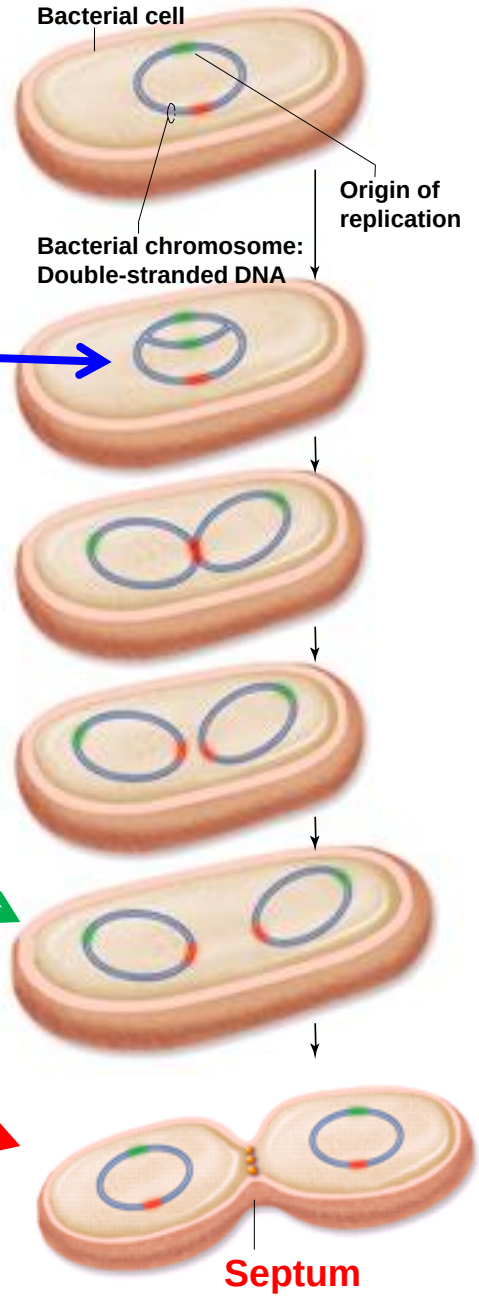
- Bacteria divide by **binary fission**
  - No sexual life cycle
  - Reproduction is clonal

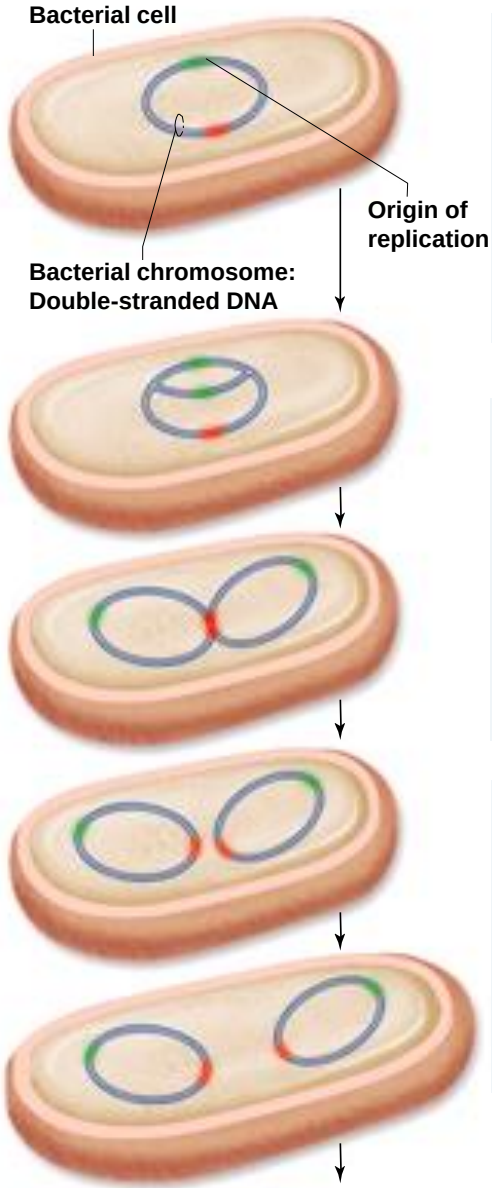
- Bacterial genome
  - Single, circular chromosome
  - Tightly packed in the cell at the **nucleoid region**



10.1 Bacterial Cell Division

- Replication begins at the origin of replication and proceeds in two directions to site of termination
- New chromosomes are partitioned to opposite ends of the cell
- Septum forms to divide the cell into 2 cells

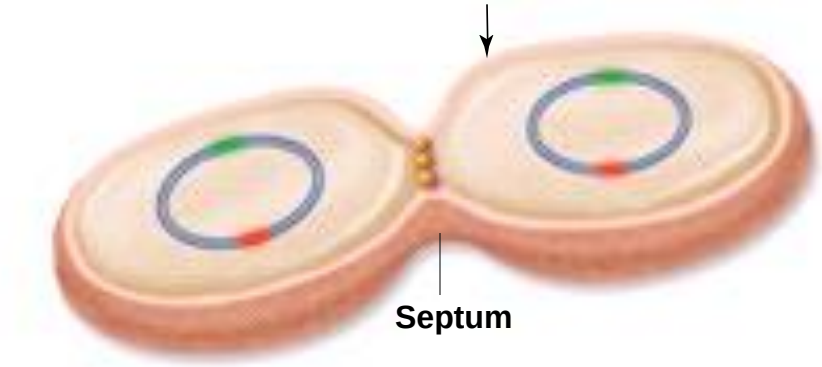




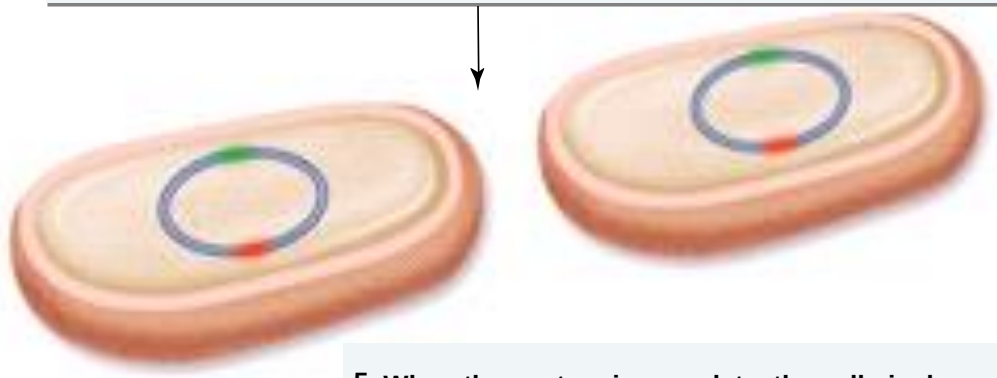
1. Prior to cell division, the bacterial DNA molecule replicates. The replication of the double-stranded, Circular DNA molecule that constitutes the genome of a bacterium begins at a specific site, called the origin of replication (green area).

2. The replication enzymes move out in both directions from that site and make copies of each strand in the DNA duplex. The enzymes continue until they meet at another specific site, the terminus of replication (red area).

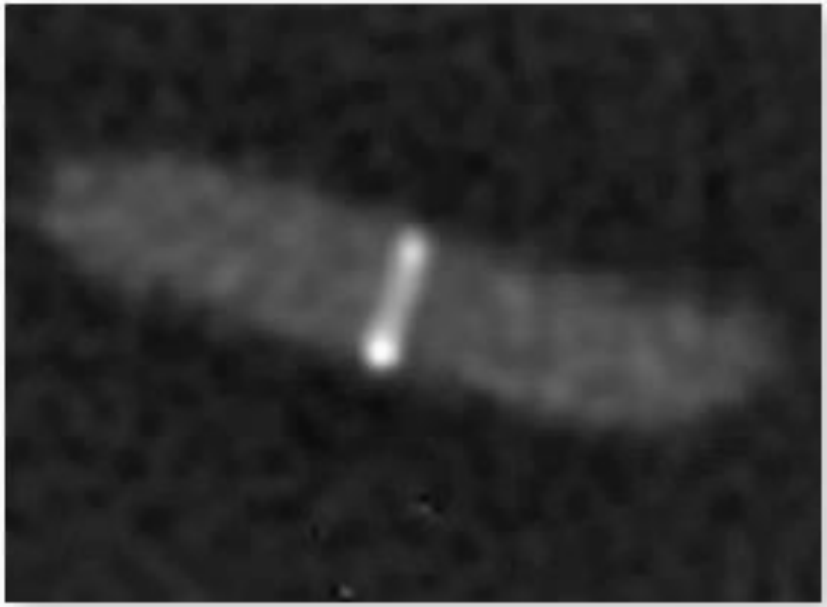
3. As the DNA is replicated, the cell elongates, and the DNA is partitioned in the cell such that the origins are at the ¼ and ¾ positions in the cell and the termini are oriented toward the middle of the cell.

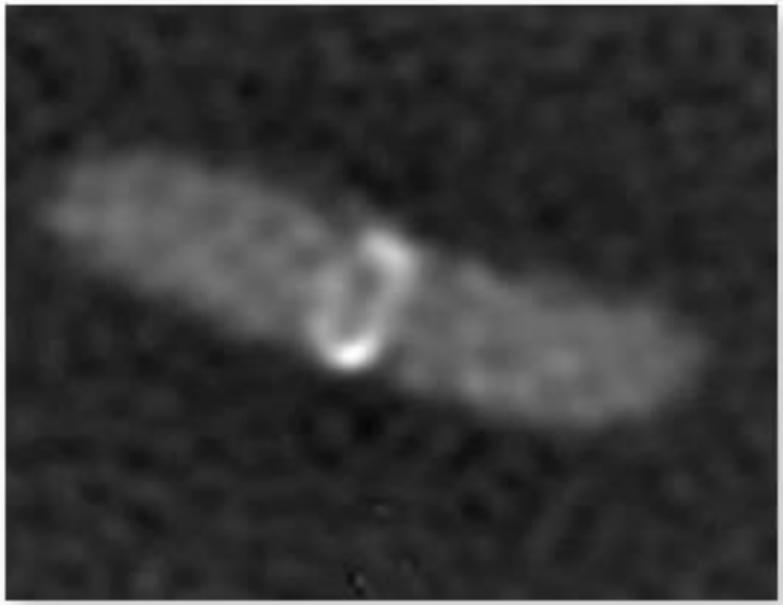


4. Septation then begins, in which new membrane and cell wall material begin to grow and form a septum at approximately the midpoint of the cell. A protein molecule called FtsZ (orange dots) facilitates this process.



5. When the septum is complete, the cell pinches in two, and two daughter cells are formed, each containing a bacterial DNA molecule.





Courtesy of William Margolin

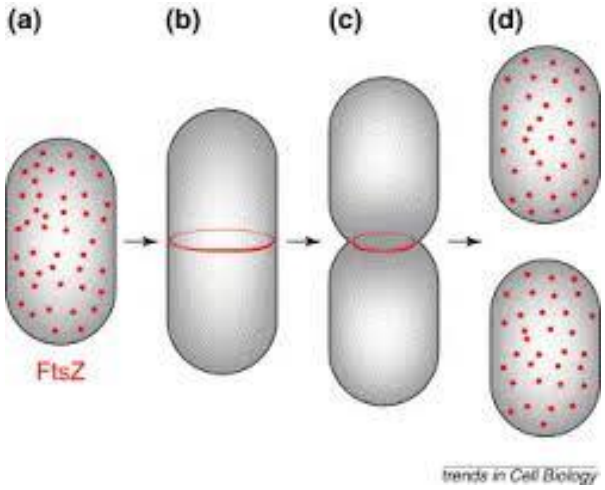
Septation

- Production of septum separates cell's other components
- Begins with formation of ring of **FtsZ proteins at midpoint of the cell**
- Accumulation of other proteins follow
- Structure contracts radially to pinch cell into two new cells
- FtsZ protein found in most prokaryotes

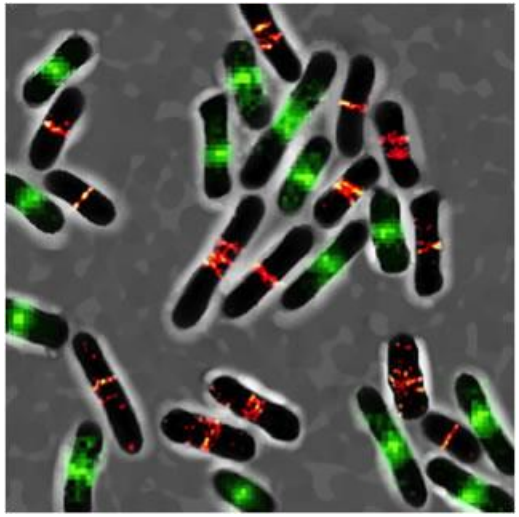
http://www.sciencedirect.com/science/article/pii/S0962892400018407

FtsZ protein

- FtsZ protein found in most prokaryotes
- High degree of similarity to eukaryotic tubulin
- However, its role in bacteria division is quite different from the role of tubulin in mitosis in eukaryotes
- Tubulin are used to construct the microtubules of the spindle apparatus that is used to separate chromosomes during eukaryotic cell division



Binary fission with stained FtsZ protein

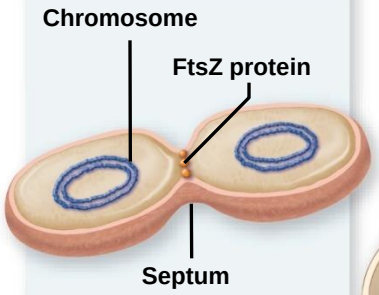


http://www.hopkinsmedicine.org/dmontell/gallery/

Look over, but don't memorize

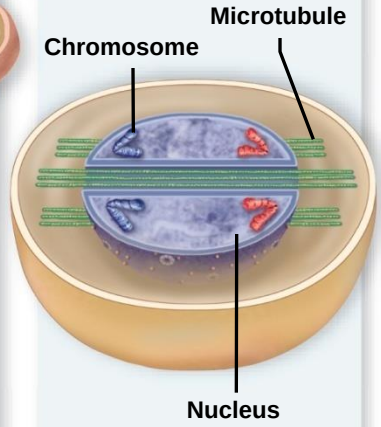
Prokaryotes

No nucleus, usually have single circular chromosome. After DNA is replicated, it is partitioned in the cell. After cell elongation, FtsZ protein assembles into a ring and facilitates septation and cell division.



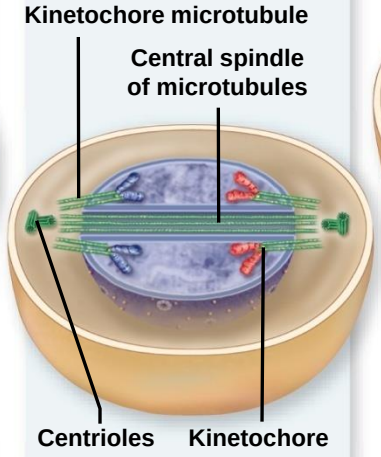
Some Protists

Nucleus present and nuclear envelope remains intact during cell division. Chromosomes line up. Microtubule fibers pass through tunnels in the nuclear membrane and set up an axis for separation of replicated chromosomes, and cell division.



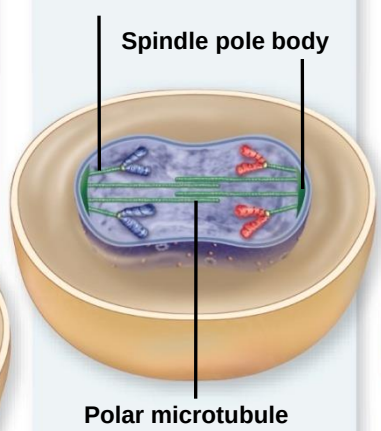
Other Protists

A spindle of microtubules forms between two pairs of centrioles at opposite ends of the cell. The spindle passes through one tunnel in the intact nuclear envelope. Kinetochore microtubules form between kinetochores on the chromosomes and the spindle poles and pull the chromosomes to each pole.



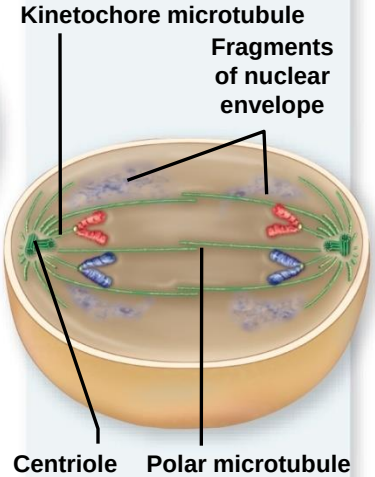
Yeasts

Nuclear envelope remains intact; spindle microtubules form inside the nucleus between spindle pole bodies. A single kinetochore microtubule attaches to each chromosome and pulls each to a pole.



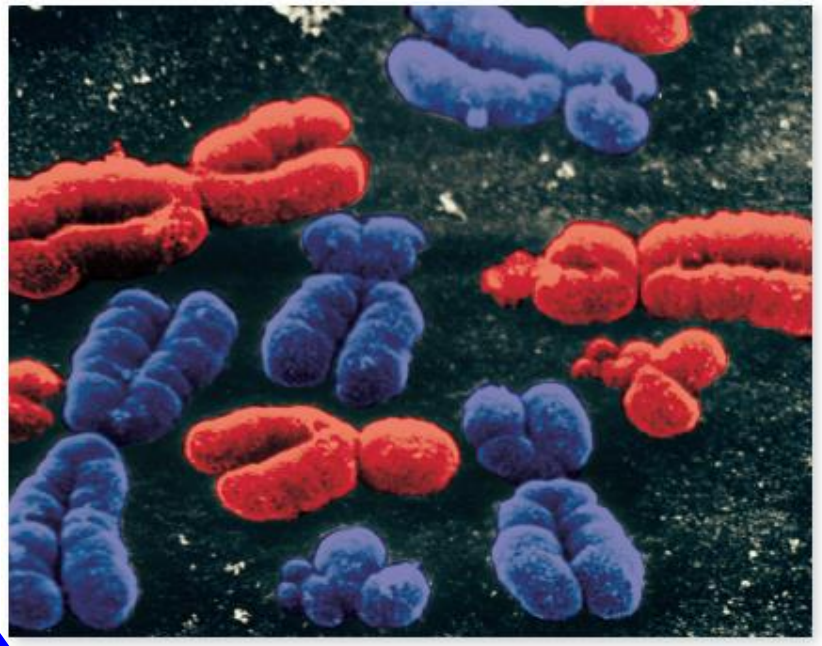
Animals

Spindle microtubules begin to form between centrioles outside of nucleus. Centrioles move to the poles and the nuclear envelope breaks down. Kinetochore microtubules attach kinetochores of chromosomes to spindle poles. Polar microtubules extend toward the center of the cell and overlap.



Eukaryotic Chromosomes

- Every species has a different number of chromosomes
- Humans have 46 chromosomes in 23 nearly identical pairs
  - Additional/missing chromosomes usually fatal with some exceptions (Chapter 13)

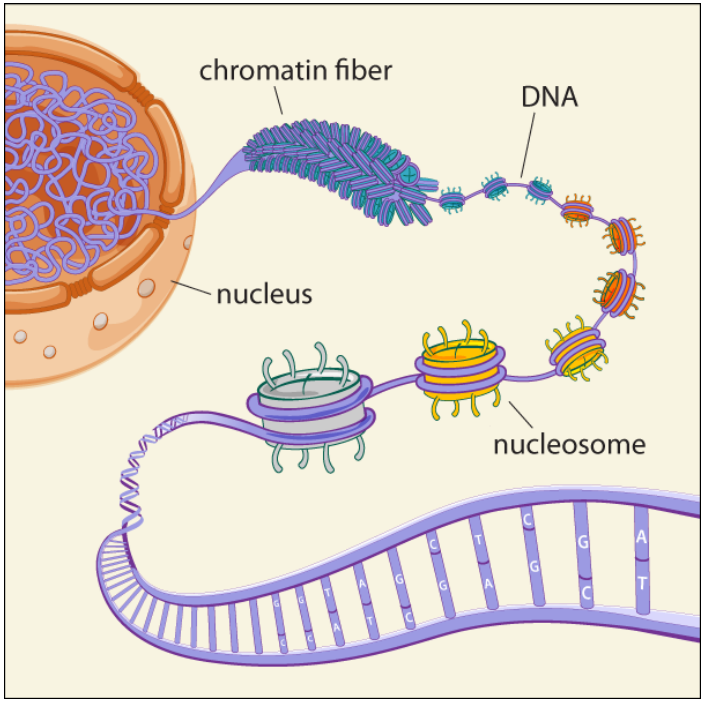


950x

Know this!!

Chromosomes Composition

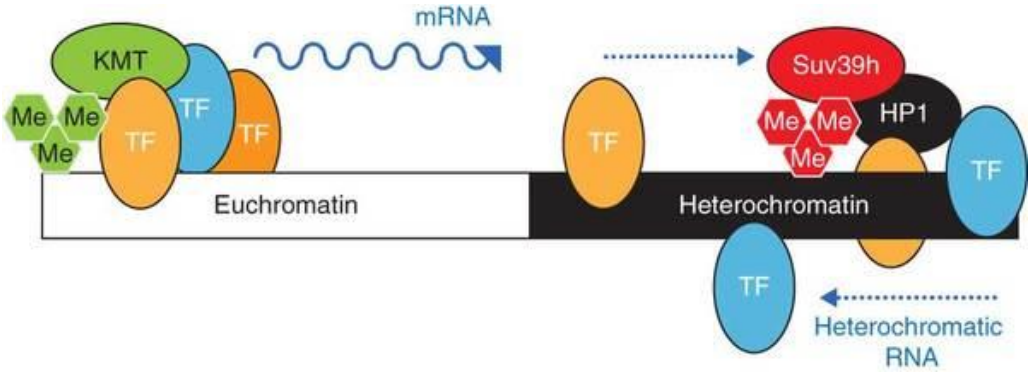
- Chromosomes are composed of **chromatin** – complex of DNA and protein
- DNA of a single chromosome is one long continuous double-stranded polynucleotides
- RNA is also associated with chromosomes during RNA synthesis



http://www.broadinstitute.org/news/1504

Chromosomes Composition

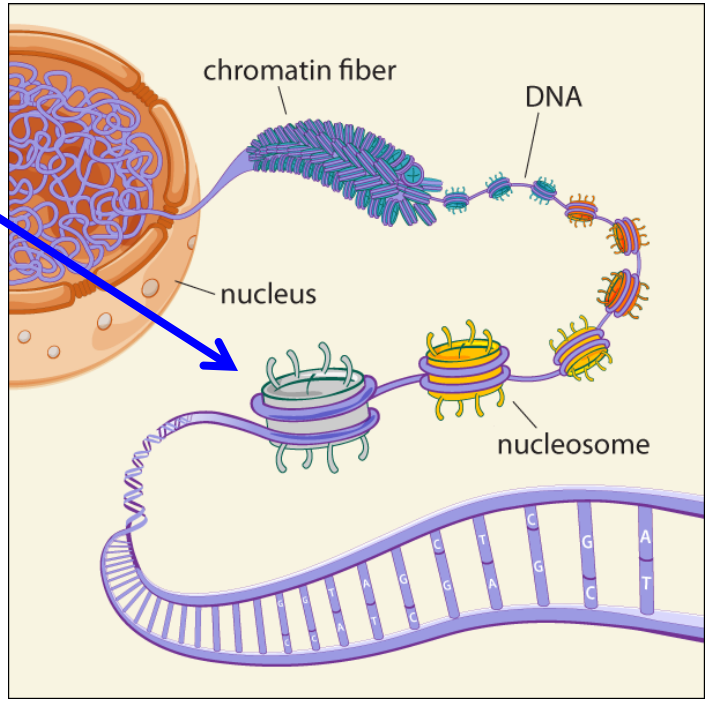
- Typical human chromosome 140 million nucleotides long
- In the non-dividing nucleus
  - **Heterochromatin** – not expressed (“blocked”)
  - **Euchromatin** – expressed



http://www.nature.com/nsmb/journal/v19/n10/full/nsmb.2382.html?WT.ec_id=NSMB-201210

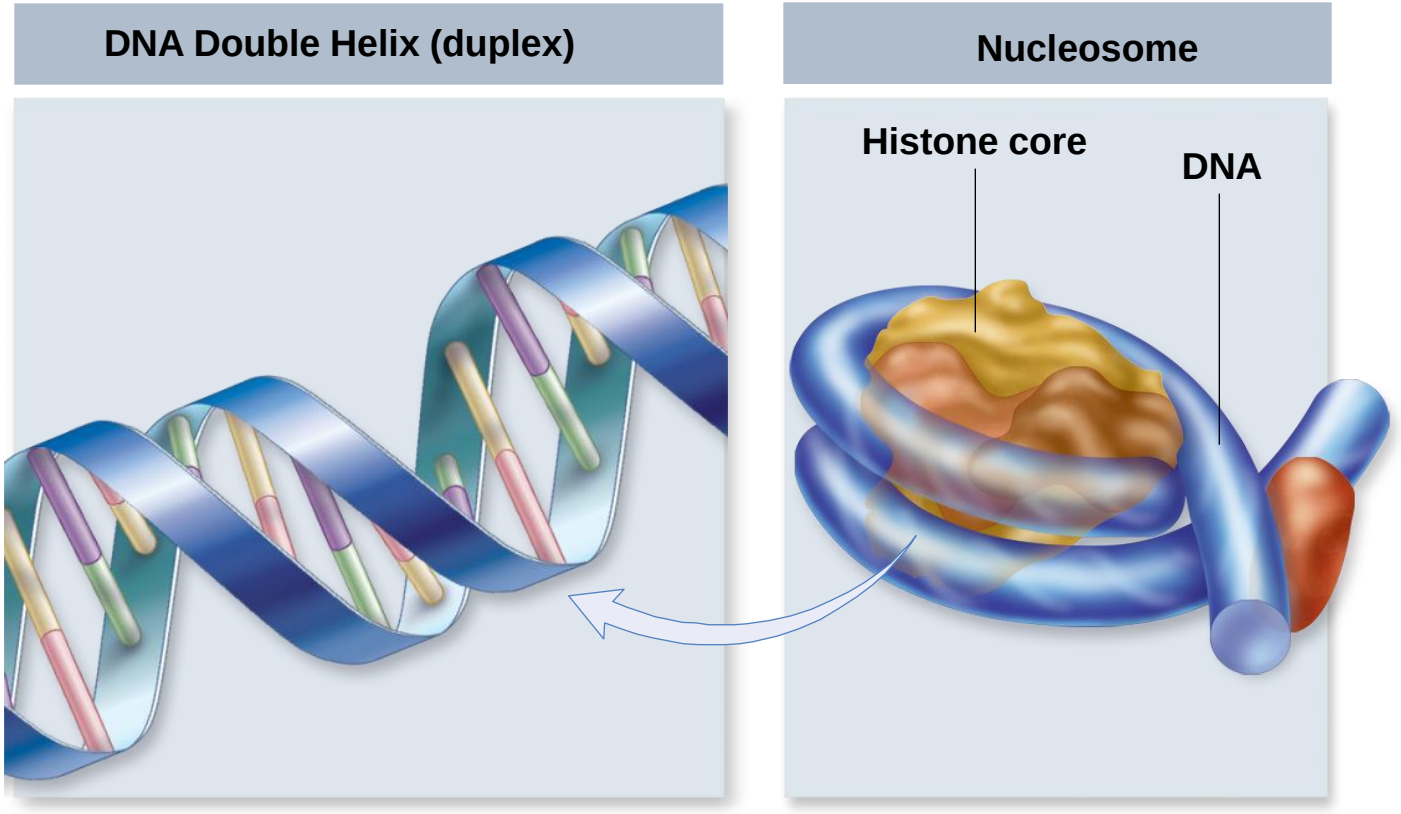
Chromosome Structure

- **Nucleosome**
  - Complex of DNA & **histone proteins**
  - Promotes and guides coiling of DNA
  - DNA duplex coiled around 8 histone proteins every 200 nucleotides
  - **Histones** are positively charged and strongly attracted to negatively charged phosphate groups of DNA



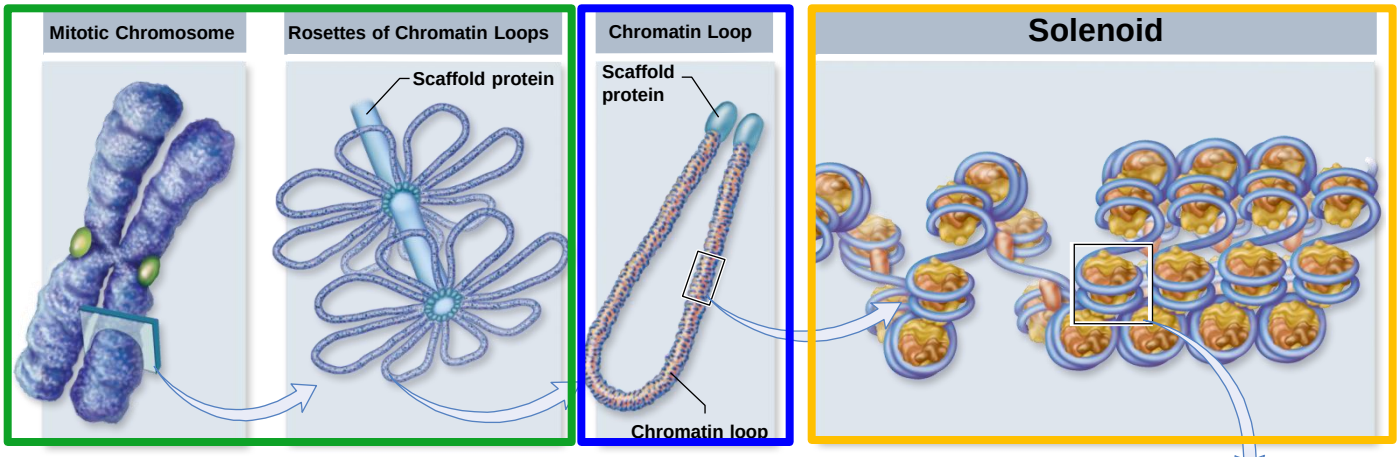
http://www.broadinstitute.org/news/1504

- The double stranded DNA is coiled around a core of eight histones proteins, the complex is termed a **nucleosome**

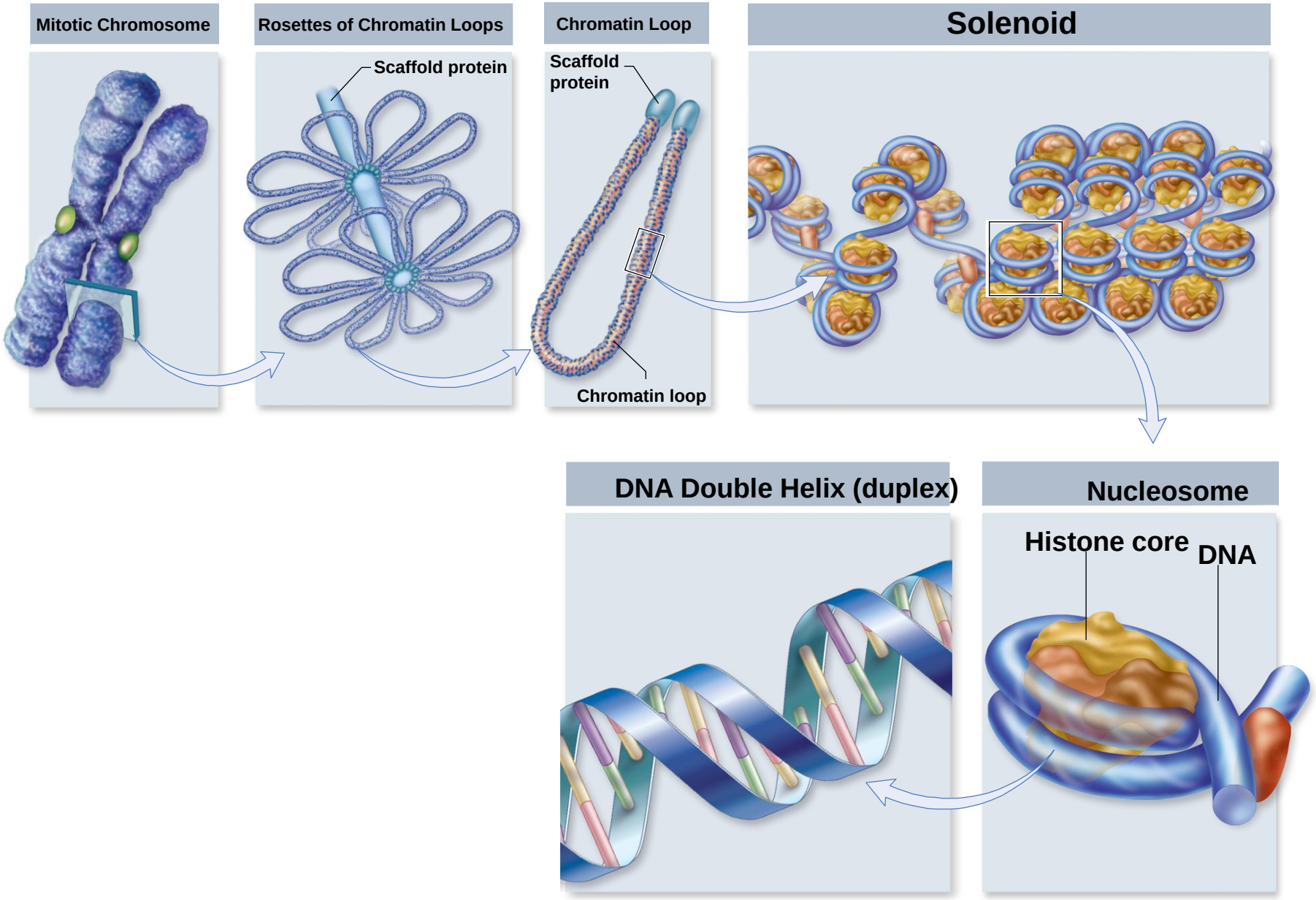


- Nucleosomes wrapped into higher order coils called **solenoids**
  - Leads to a fiber (chromatin loop) 30 nm in diameter
  - This 30-nm fiber is the usual state of nondividing (interphase) chromatin

- During mitosis, chromatin in solenoid arranged around scaffold of protein *to achieve maximum compaction*
  - Radial looping aided by **condensin proteins**

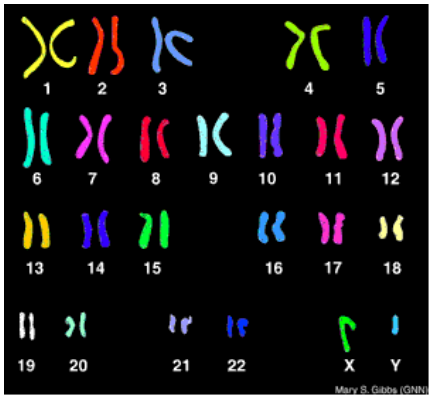


Levels of Eukaryotic Chromosomal Organization



Chromosome Karyotypes

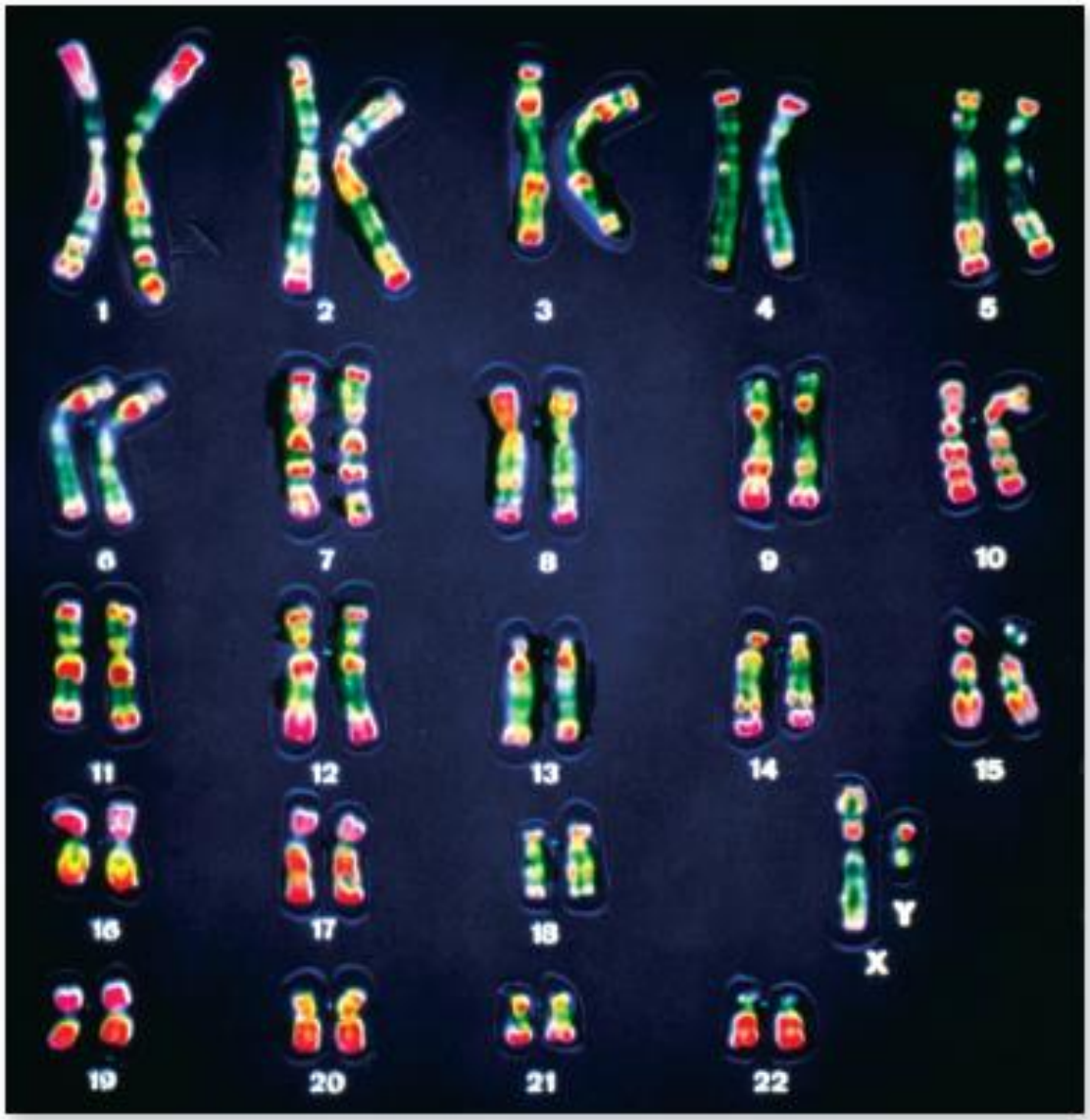
- Particular array of chromosomes in an individual organism is called **karyotype**
  - Arranged according to size, staining properties, location of centromere, etc.
- Humans are diploid (*2n*)
  - 2 complete sets of chromosomes
  - 46 total chromosomes
  - Pair of chromosomes are **homologous**
    - Each chromosome of the pair is a **homologue**
- Haploid (*n*) = 1 set of chromosomes
  - 23 in humans



http://www.odec.ca/projects/2005/anna5m0/public_html/background.htm

A Human Karyotype

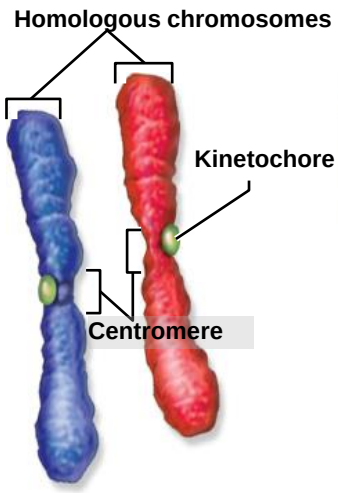
Is this a individual haploid or diploid?

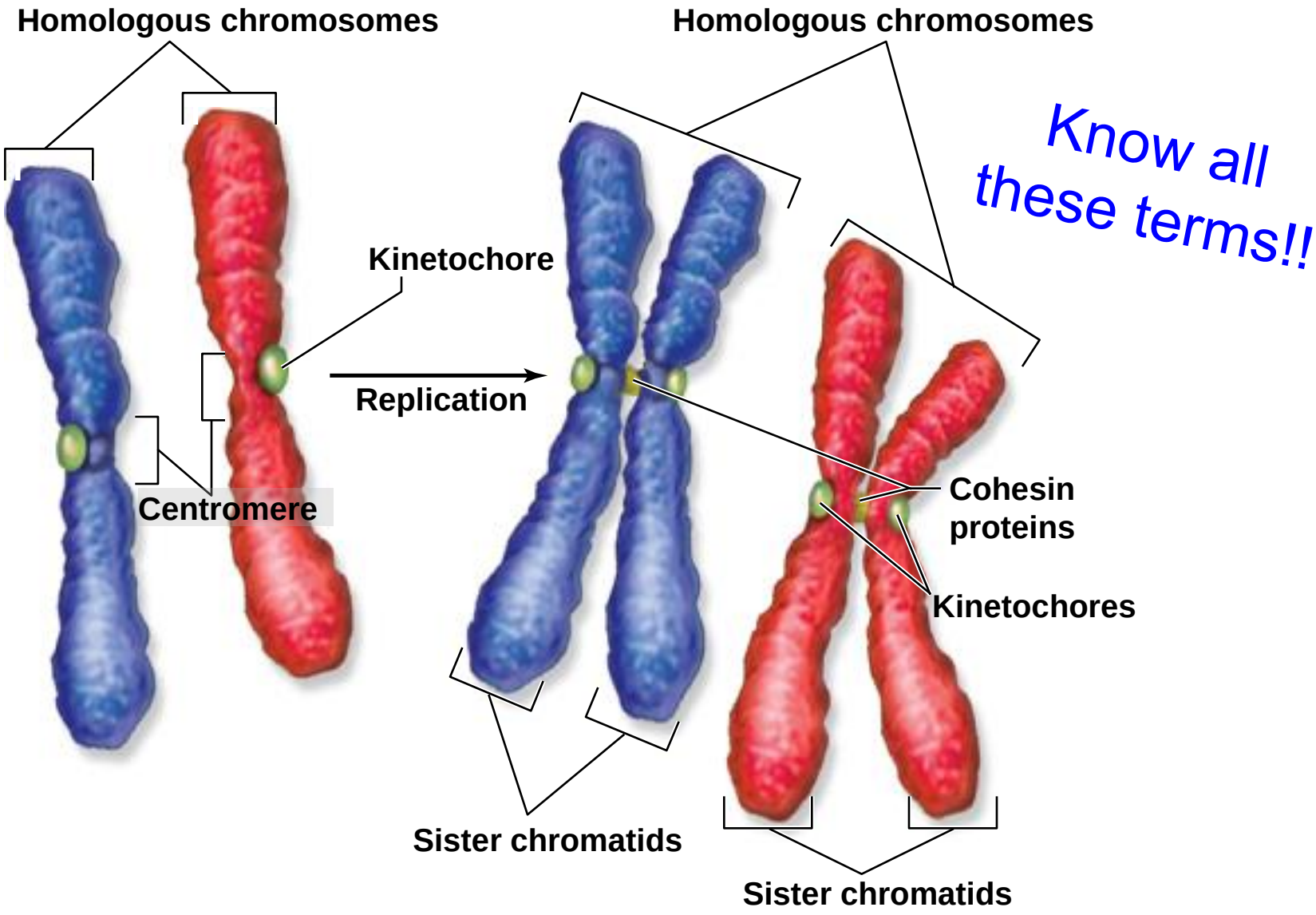


500x

Chromosome Replication

- Prior to replication, each chromosome is composed of a single DNA molecule
- After replication, each chromosome composed of 2 identical DNA molecules
  - Held together by **cohesin proteins**
- Visible as 2 strands held together as chromosome becomes more condensed
  - One chromosome composed of 2 **sister chromatids**

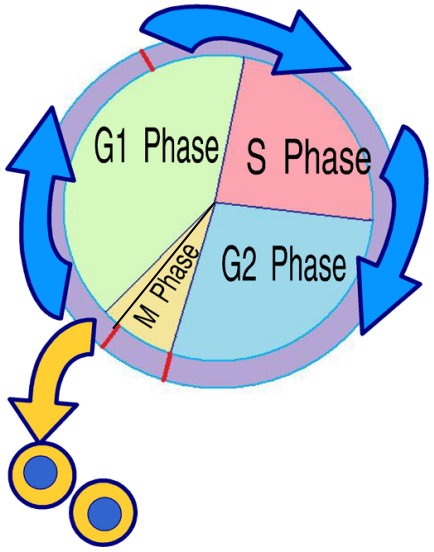




Eukaryotic Cell Cycle

1. **G_1 (gap phase 1)**
   - Primary growth phase, longest phase
2. **S (synthesis)**
   - Replication (**s**ynthesis) of DNA
3. **G_2 (gap phase 2)**
   - Organelles replicate, microtubules organize
4. **M (mitosis)**
   - Subdivided into 5 phases
5. **C (cytokinesis)**
   - Separation of 2 new cells

Interphase

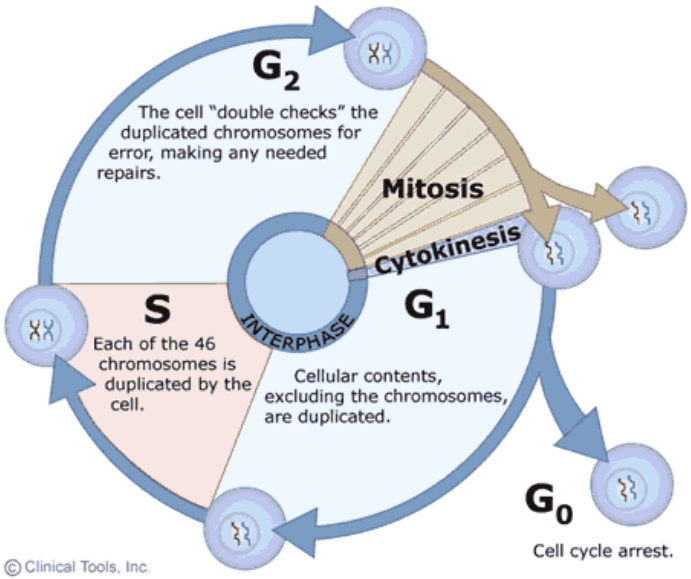


http://www.the-simple-homeschool.com/cell-cycle-control.html

Duration of Cell Cycle

Time it takes to complete a cell cycle varies greatly

- Shortest known animal cell cycles occur in fruit fly embryos = 8 minutes
- Mature cells take longer than those in embryonic tissue
  - Typical mammalian cell takes 24 hours
  - Liver cell takes more than a year



- Growth occurs during G_1, G_2, and S phases
  - M phase takes only about an hour
- Most variation in length of G_1
  - **Resting phase (G_0)** – cells spend more or less time here

http://scientopia.org/blogs/scicurious/2010/05/31/cell-cycle-p21-depression-and-neurogenesis-and-in-the-hippocampus/

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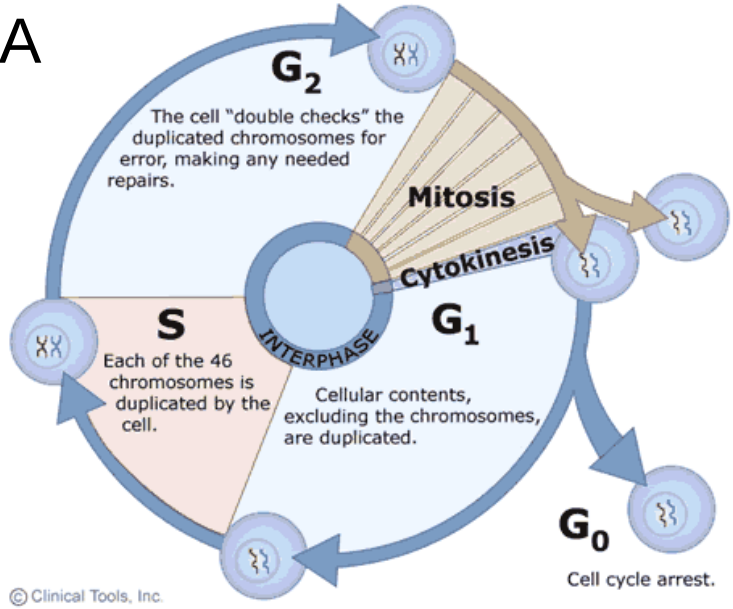
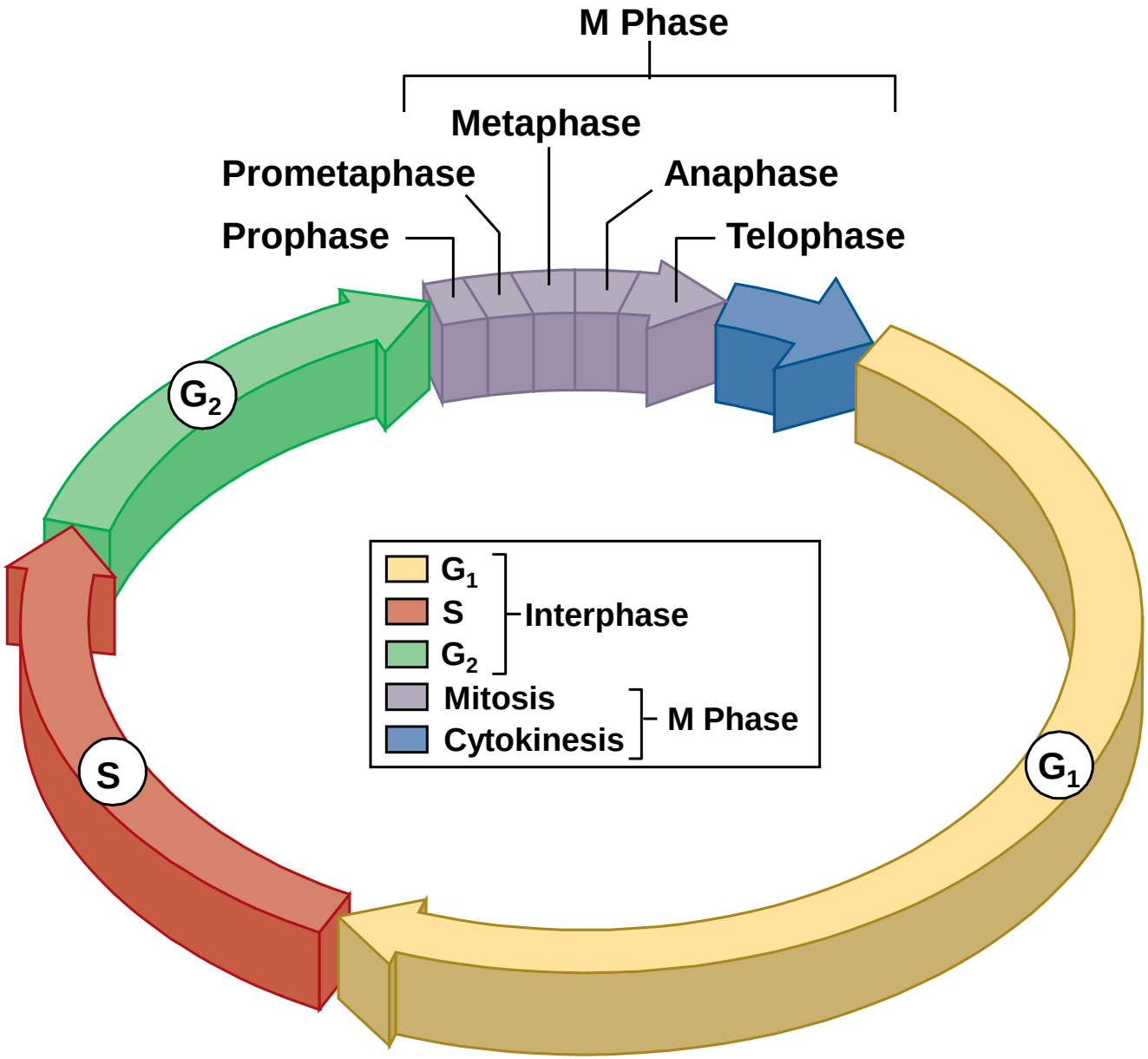
Duration of Cell Cycle

- Most variation in the length of the cell cycle between organisms or cell types occurs in G_1
  - Cells often pause in G_1 before DNA replication → enter resting phase
  - **Resting phase (G_0)** – cells spend more or less time here before resuming cell division
  - Most cells in animal's body are in G_0 phase
  - Muscle and nerve cells remain there permanently
  - Liver cells can resume G_1 phase in response to factors released during injury



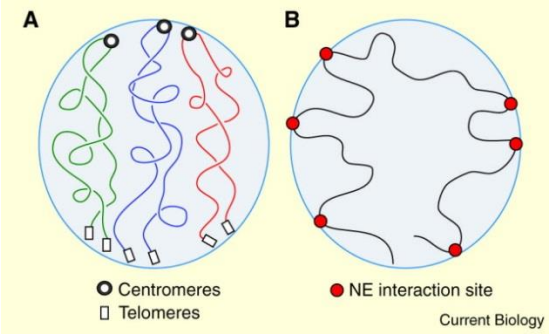
The Cell Cycle

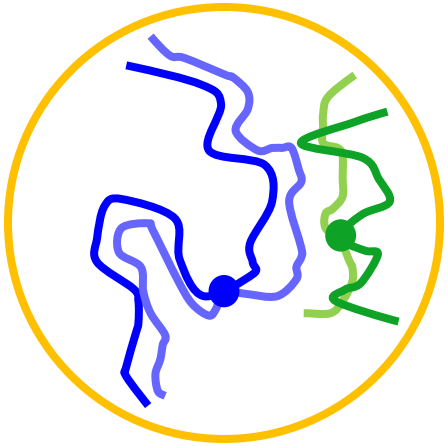


Interphase: Preparation for Mitosis

- **Interphase**
  - **G_1** phase
    - cells undergo major portion of growth
  - **S** phase
    - replicate DNA produce **two sister chromatids** attached at the **centromere**
    - Chromosomes still in *unwound chromatin form* (unlike pictures in textbook)
  - **G_2** phase
    - Preparing for mitosis
    - Chromosomes coil more tightly using motor proteins
    - Centrioles replicate & tubulin synthesis

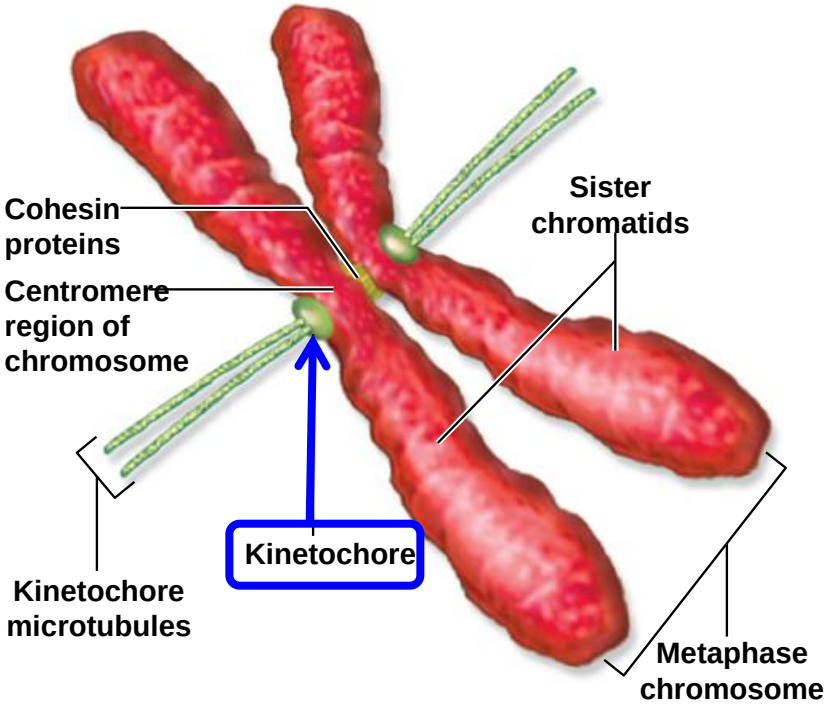
Interphase chromosomes are not just randomly arranged, but partially constrained in position





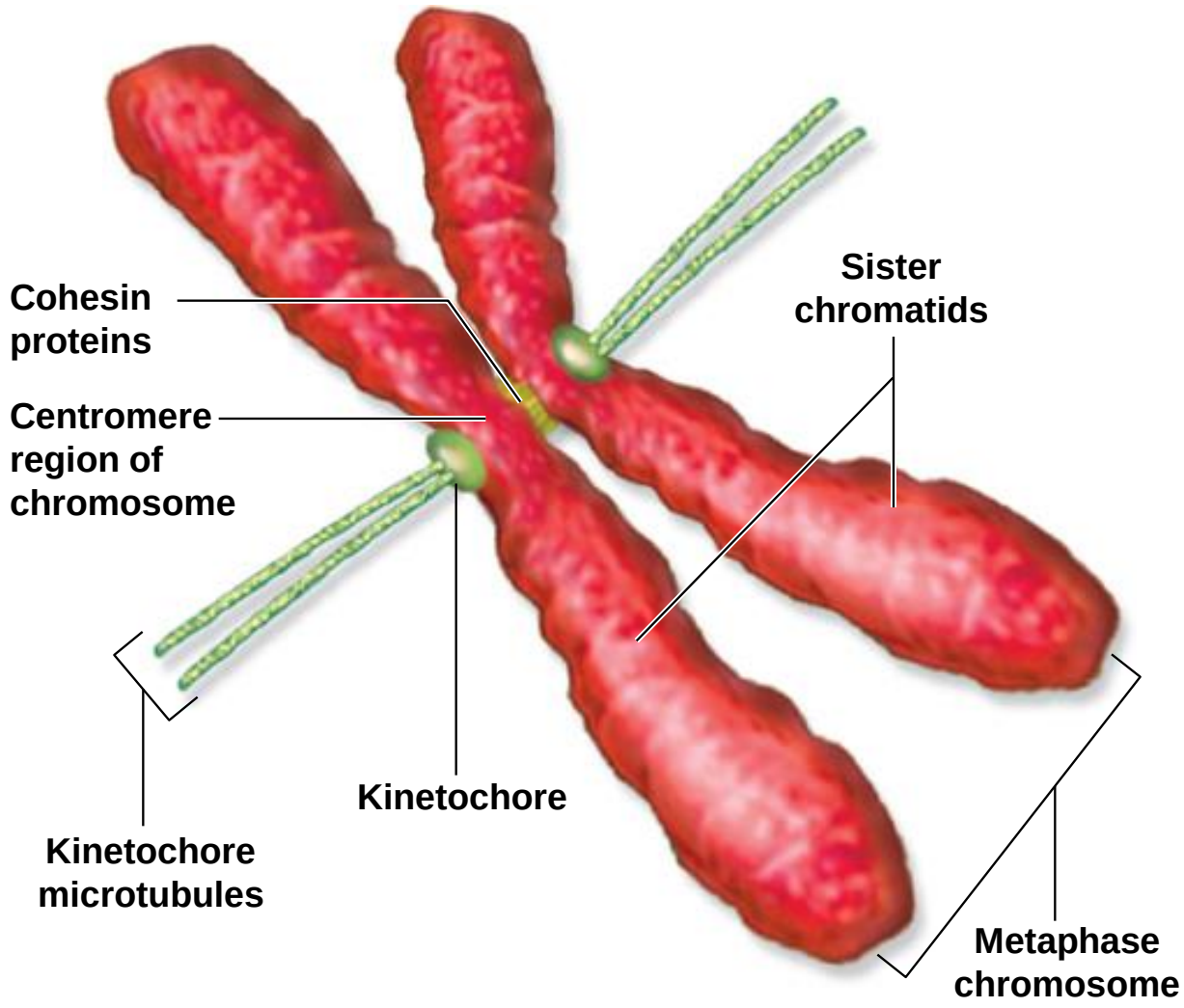
http://www.sciencedirect.com/science/article/pii/S0960982202007248

Interphase: Preparation for Mitosis



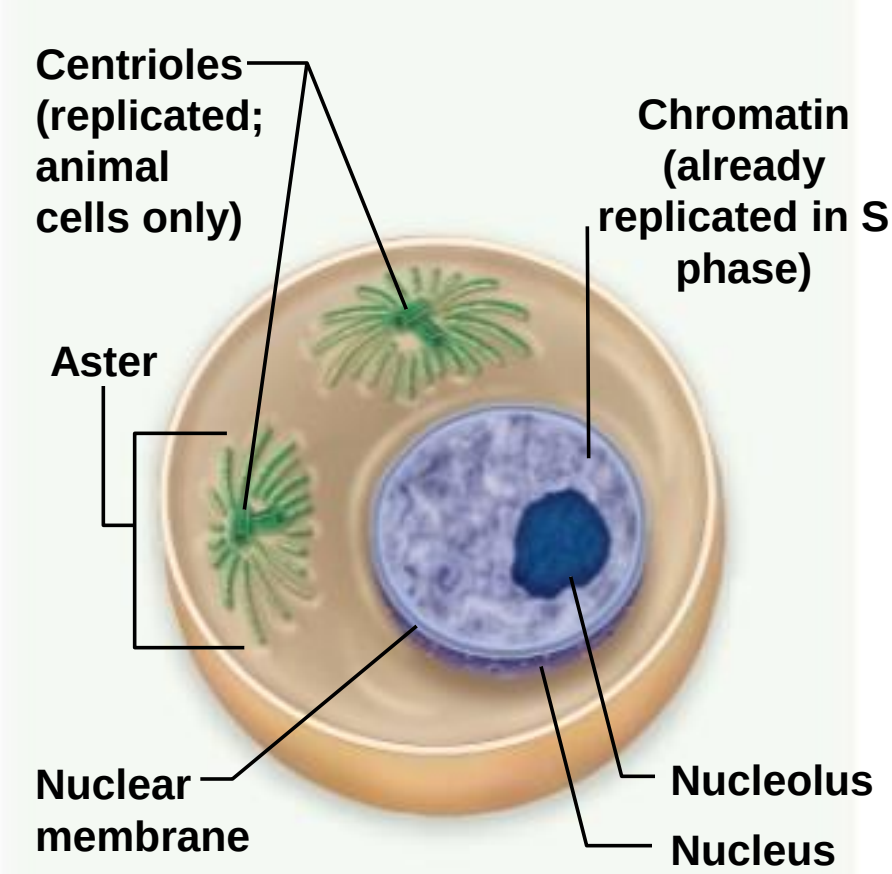
- **Centromere**
  - Point of constriction
  - **Kinetochore** – attachment site for microtubules
  - Each sister chromatid has its own **centromere** with its own kinetichore
  - Chromatids stay attached at centromere by **cohesin**

Kinetochores



Interphase G_2

(Ready for mitosis to begin)



- DNA has been replicated
- Centrioles replicate (animal cells)
- Cell prepares for division

M phase: Chromosome Segregation and the Division of Cytoplasmic Contents

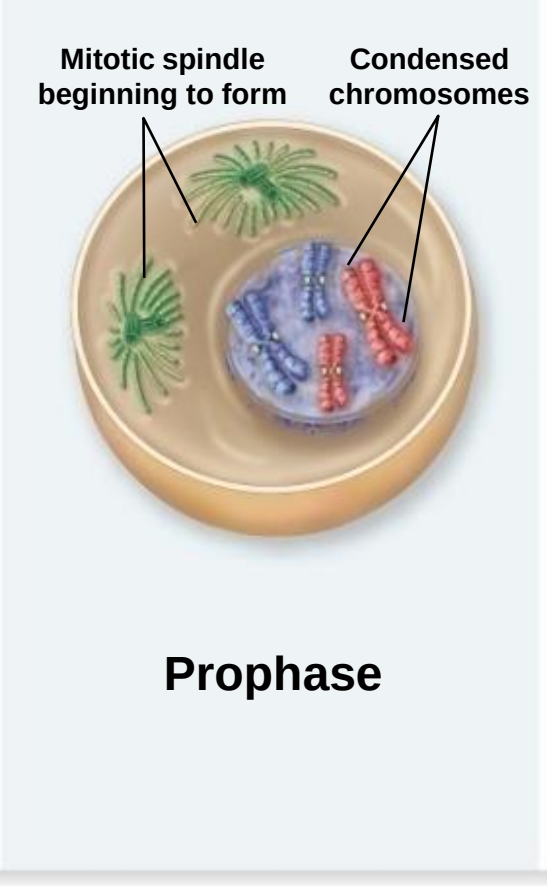
Mitosis is divided into five phases:

1. Prophase
2. Prometaphase
3. Metaphase
4. Anaphase
5. Telophase

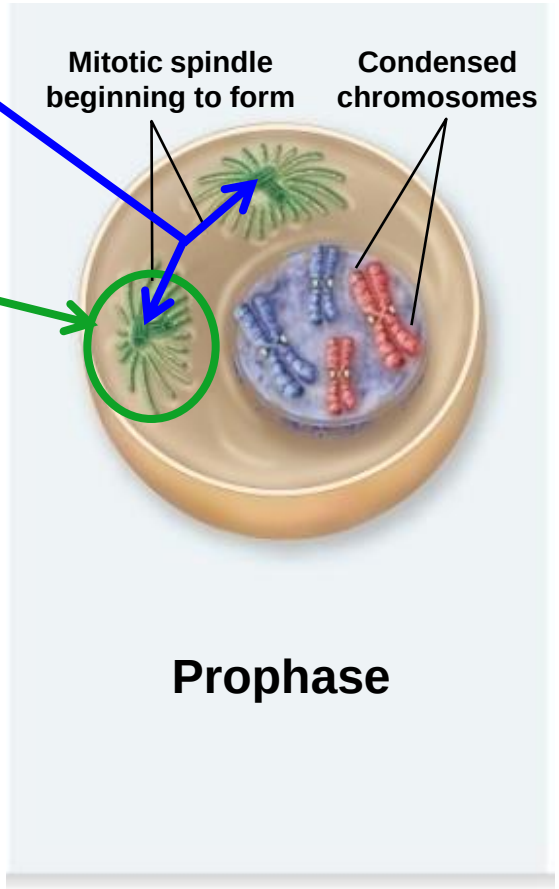
Know these different phases, and the processes that go on in each!!

Prophase

- Individual chromosomes condense
  - First become visible under light microscope
  - Condensation continues throughout prophase
  - Chromosomes appear as two sister chromatids held together at the centromere

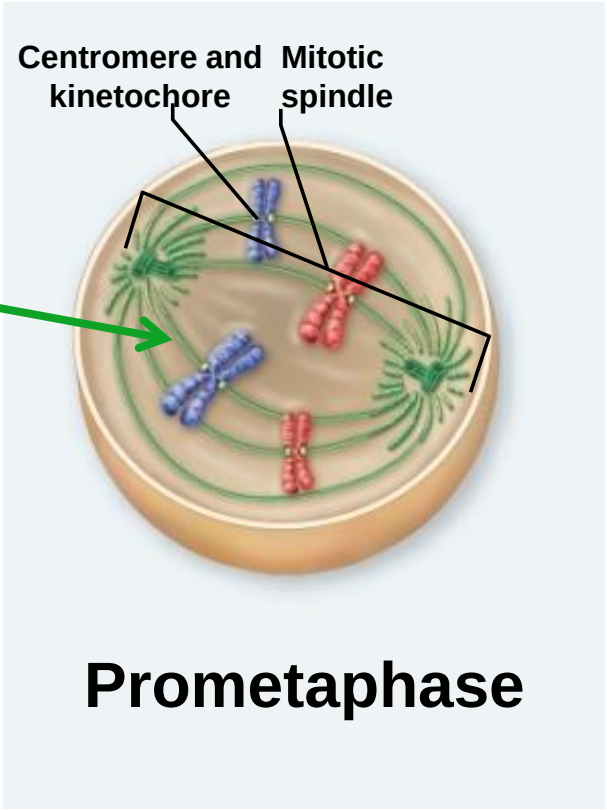


- **Spindle apparatus** assembles
  - 2 **centrioles** move to opposite **poles** forming **spindle apparatus** of microtubules (no centrioles in plants)
  - **Asters** are radial array of microtubules in animals (not in plants)
- Cytoskeleton is disassembled: spindle begins to form
- Golgi and ER are dispersed
- Nuclear envelope breaks down

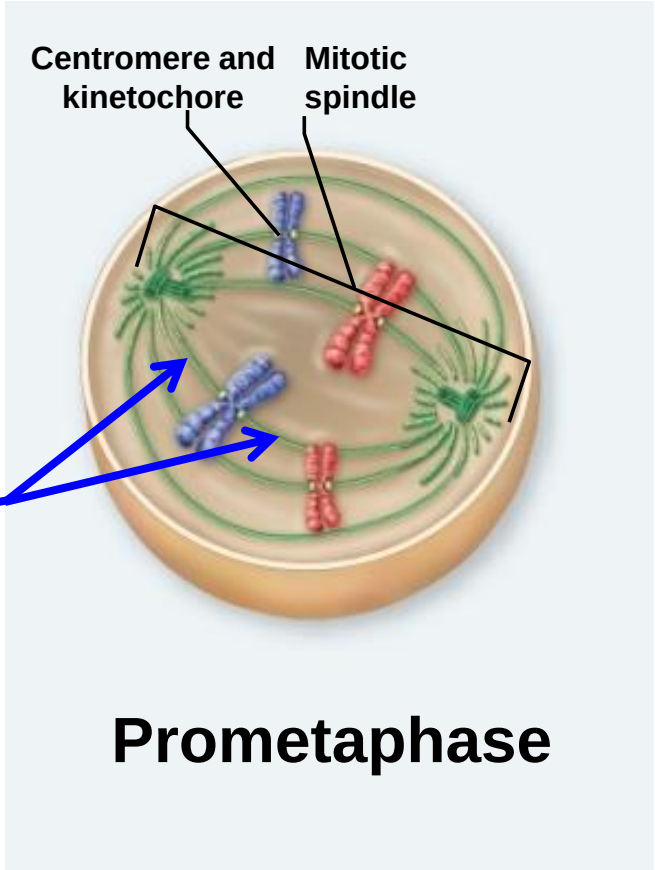


Prometaphase

- Transition occurs *after disassembly of nuclear envelope*
- Microtubule attachment between poles
  - 2nd group grows from poles and attaches to kinetochores
  - Each sister chromatid connected to opposite poles

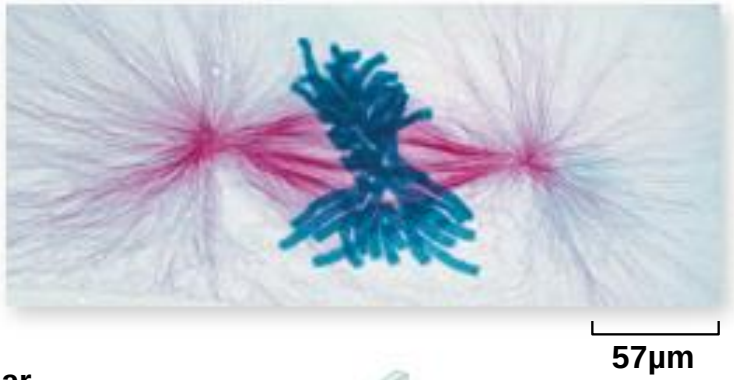


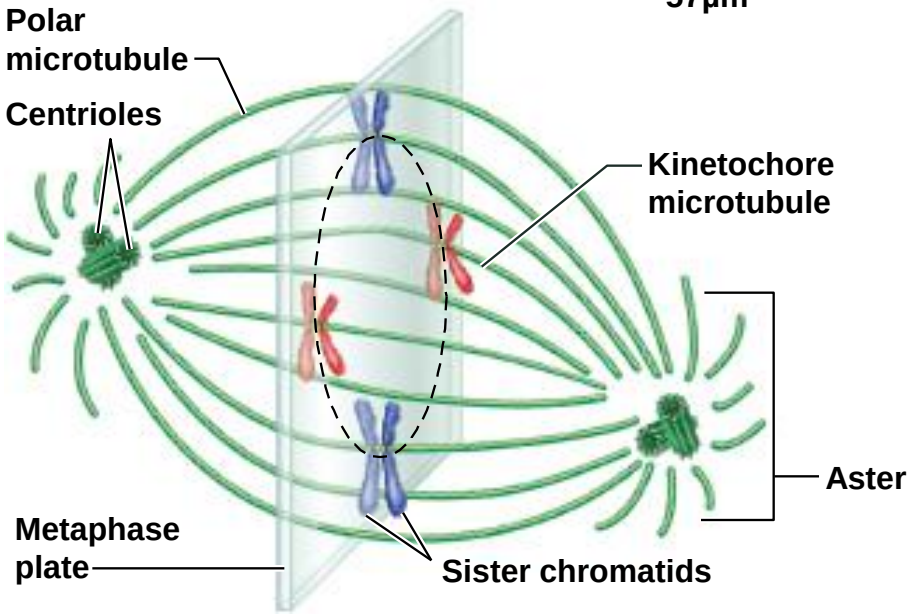
- Each chromosome is oriented such that the kinetochores of sister chromatids are attached to microtubules from *opposite poles*
- Chromosomes begin to move to center of cell – congression
  - **Motor proteins** at kinetochores
  - Partially by assembly & disassembly of microtubules
- Chromosomes move to equator of the cell



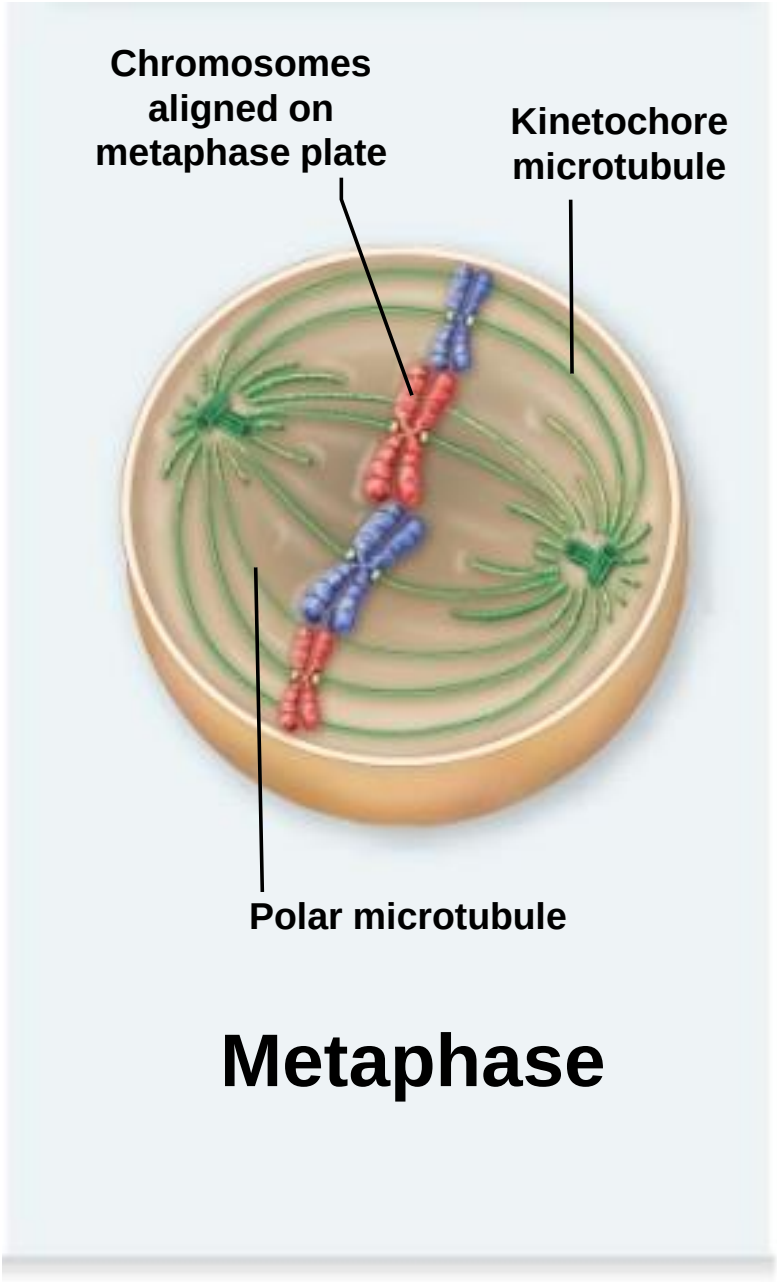
Metaphase

- Alignment of chromosomes along **metaphase plate** (**equator**)
  - Not an actual structure
  - Future axis of cell division





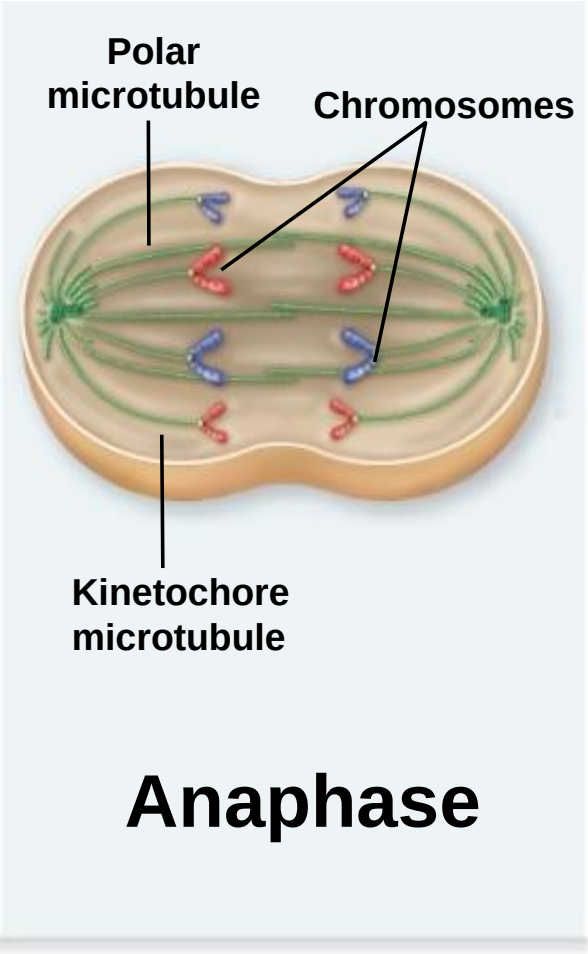
- Chromosomes are attached to opposite poles and are under tension



Anaphase

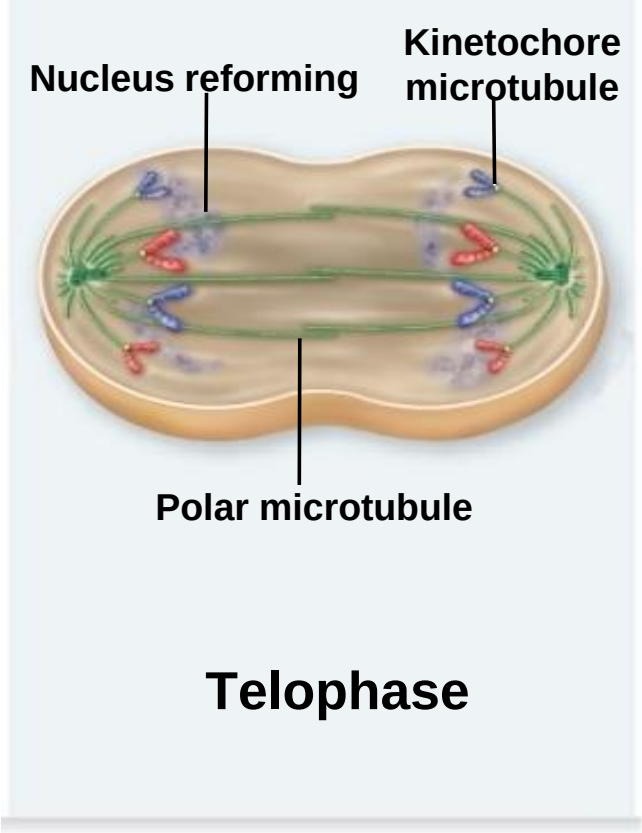
- Begins when centromeres split
- Key event is *removal of cohesin proteins* from all chromosomes, freeing individual chromosomes

- Sister chromatids pulled to opposite poles
  - 2 forms of movements
    - Anaphase A – kinetochores pulled toward poles
    - Anaphase B – poles move apart



Telophase

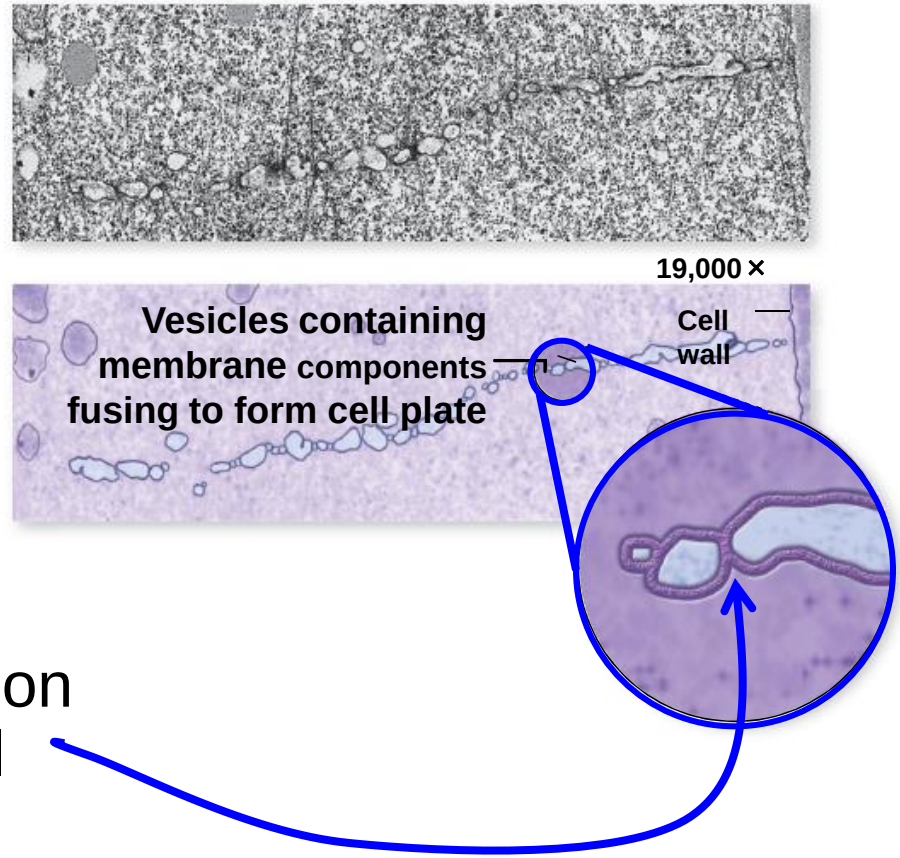
- Spindle apparatus disassembles
- Nuclear envelope reassembles around each set of sister chromatids
  - Now called chromosomes
- Chromosomes begin to uncoil
- Nucleolus reappears in each new nucleus
- Golgi complex & ER re-form



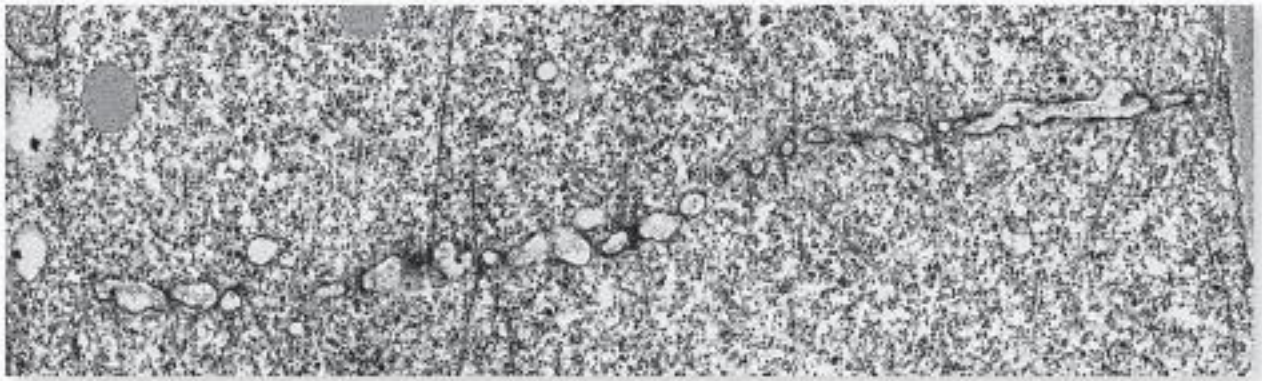
Cytokinesis

- Cleavage of the cell into equal halves
- Often occurs during telophase, but is separate event

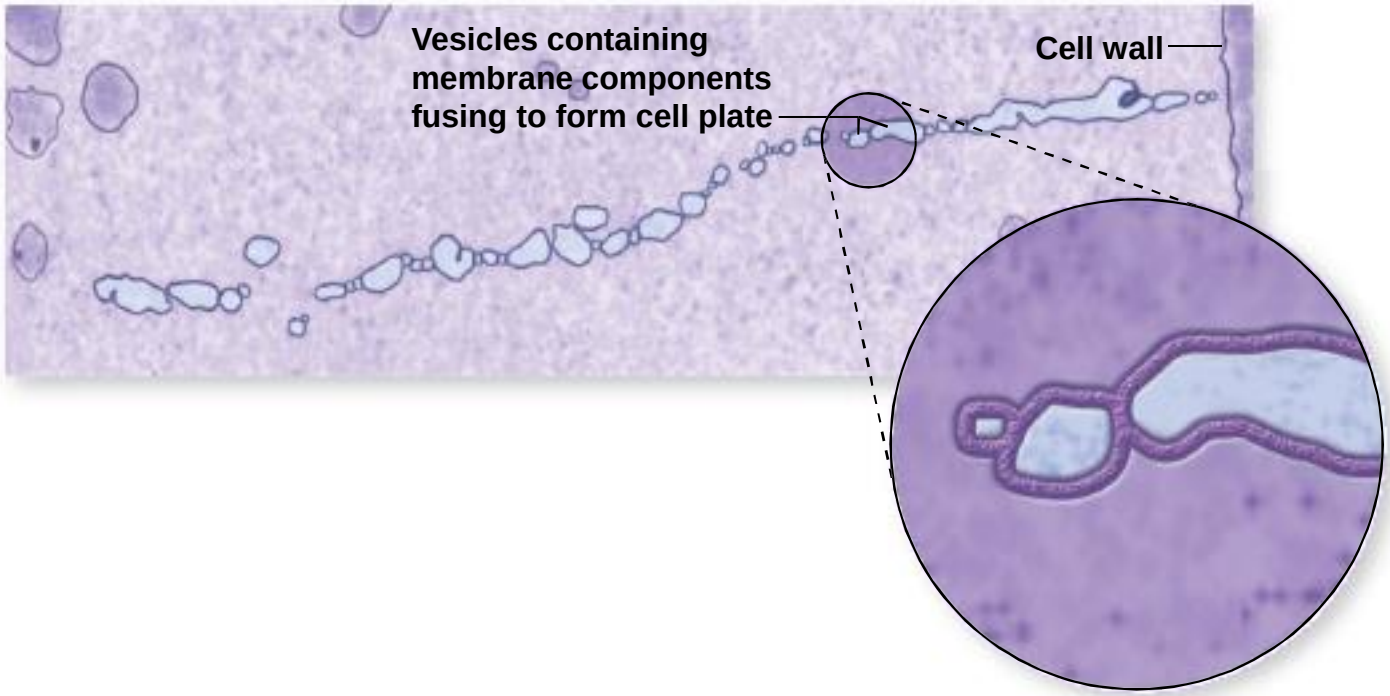
- Plant cells
  - **cell plate** forms between the two nuclei
  - Vesicles with cell wall material migrate and fuse on cell plate, forming cell wall



Cytokinesis in Plant Cell



19,000 ×

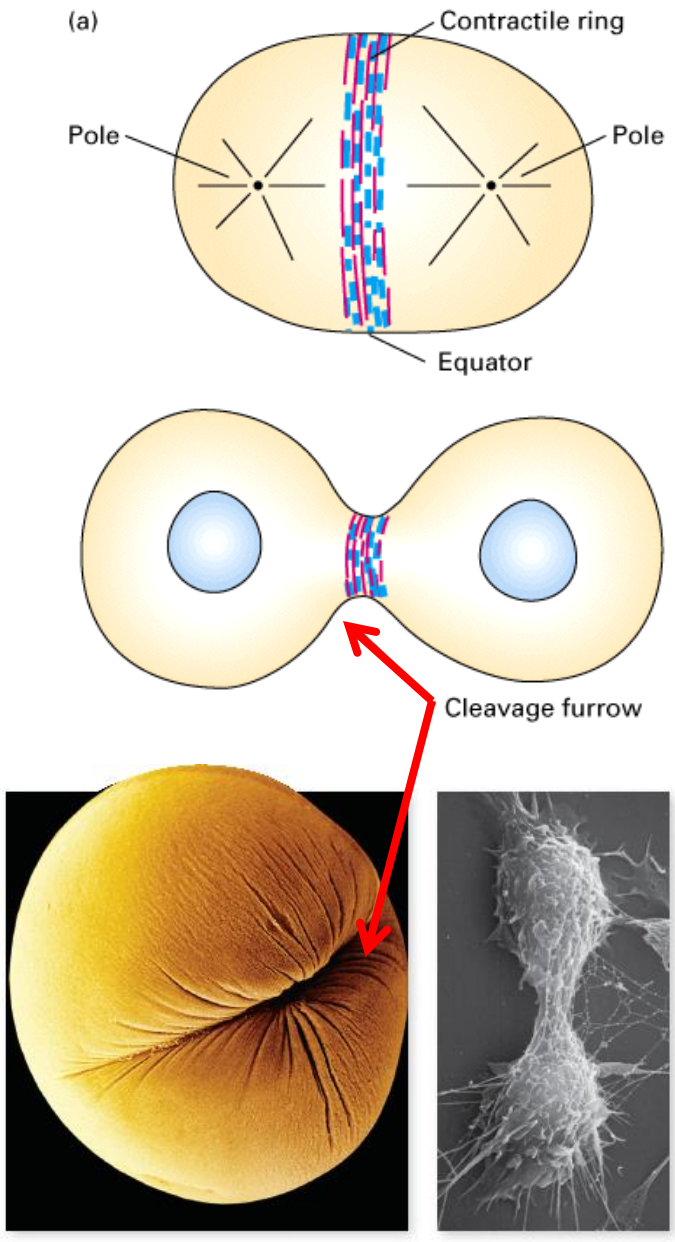


http://www.pha.jhu.edu/~ghzheng/old/webct/note7_6.htm

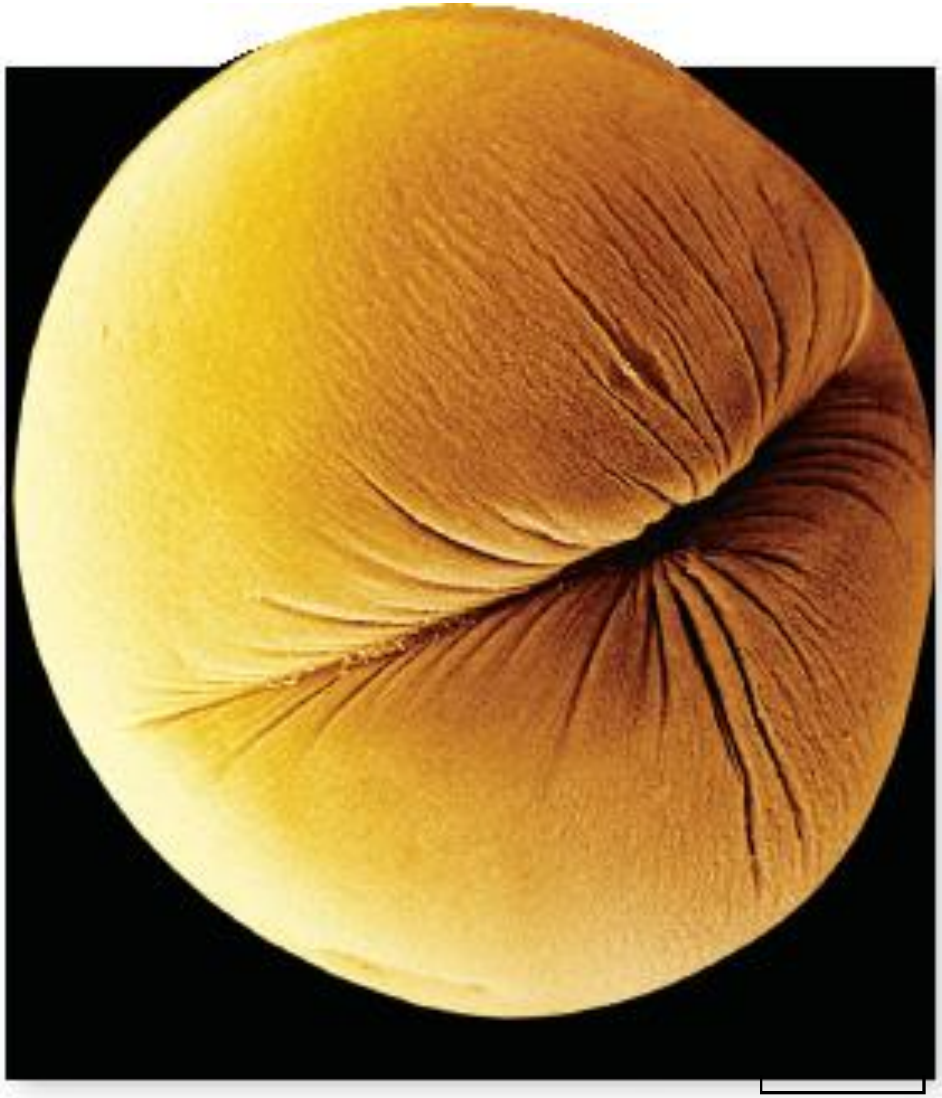
Cytokinesis

- Animal cells – constriction of **actin microfilaments** produces a **cleavage furrow**

- Fungi and some protists –
  - nuclear membrane does not dissolve
  - mitosis occurs within intact nucleus
  - division of nucleus occurs later with cytokinesis

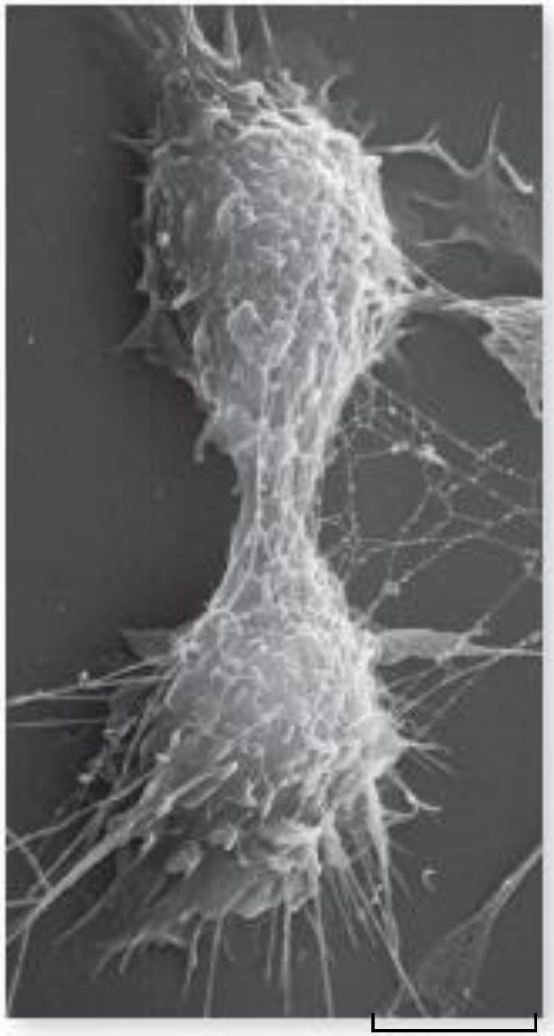


Cytokinesis in Animal Cell



a.

325 µm



b.

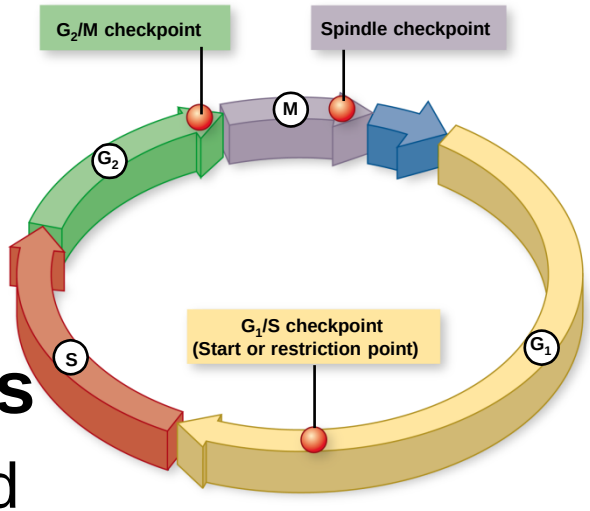
25 µm

Control of the Cell Cycle

Current view integrates 2 concepts

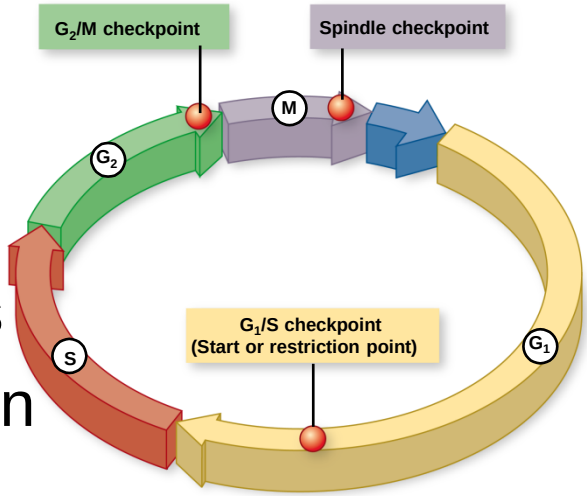
1. Cell cycle has two irreversible points
   - Replication of genetic material
   - Separation of the sister chromatids

2. Cell cycle can be put on hold at specific points called **checkpoints**
   - Process is checked for accuracy and can be halted if there are errors
   - Allows cell to respond to internal and external signals

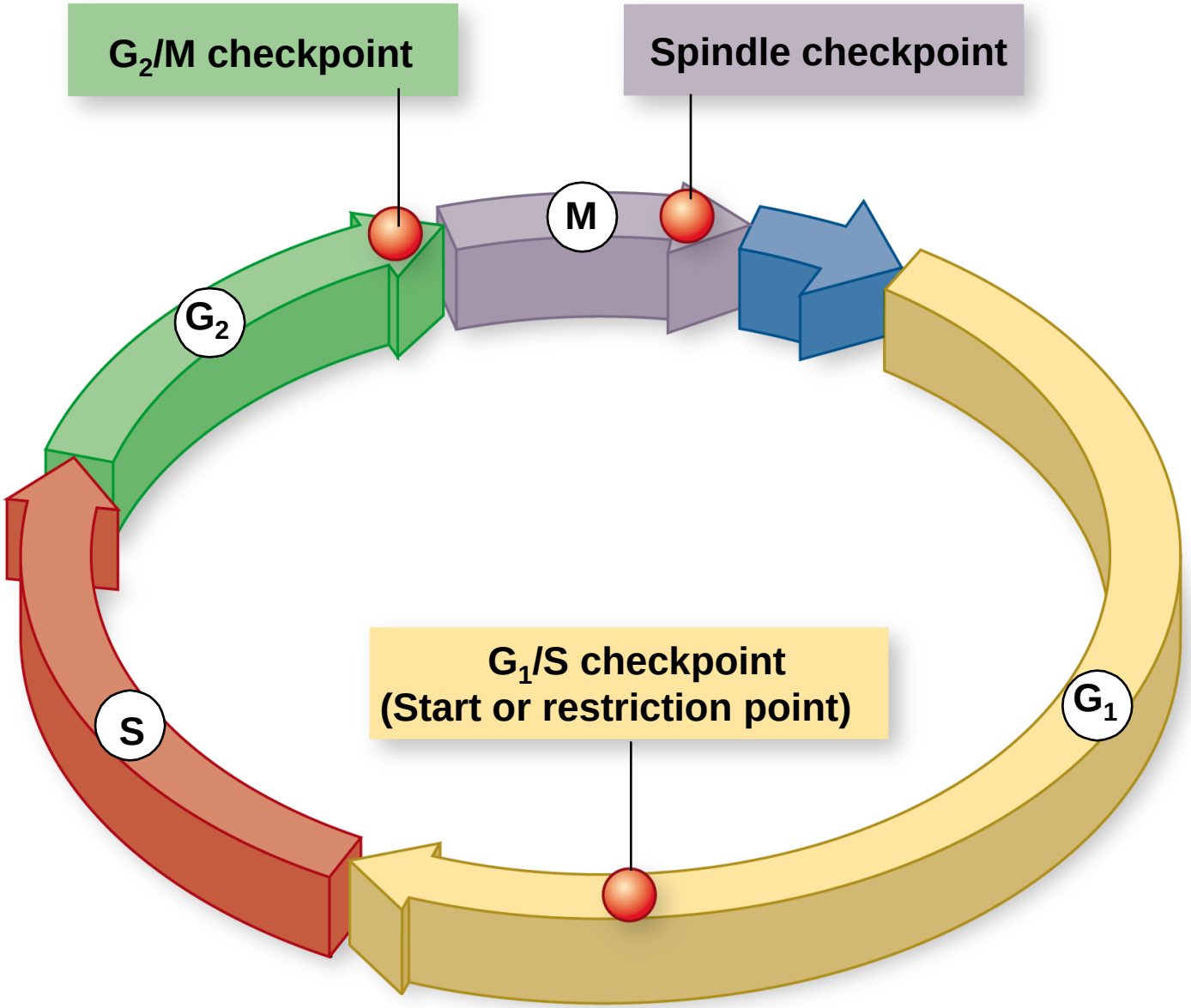


3 Checkpoints

1. **G_1/S checkpoint**
   - Cell "decides" whether or not to divide
   - Primary point for external signal influence
2. **G_2/M checkpoint**
   - Cell makes a commitment to mitosis
   - Assesses success of DNA replication
   - Can stall the cycle if DNA has not been accurately replicated.
3. **Late metaphase (spindle) checkpoint**
   - Cell ensures that all chromosomes are attached to the spindle

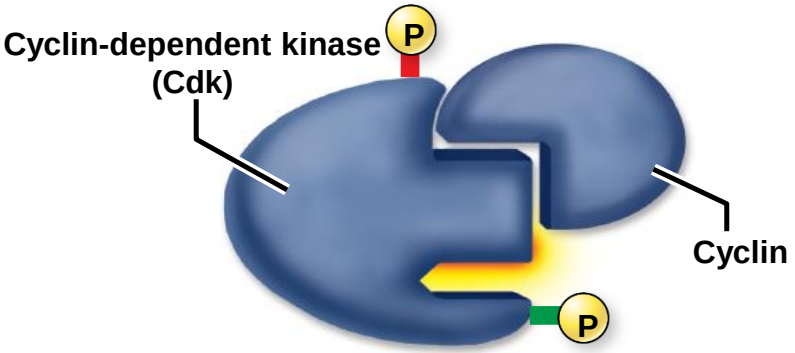


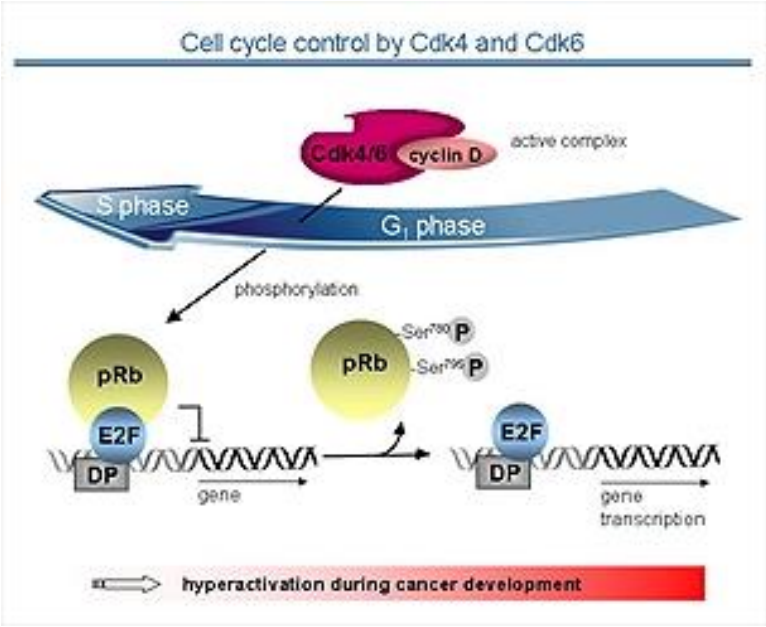
3 Checkpoints



Cyclin-dependent kinases (Cdks)

- Enzyme **kinases** that phosphorylate proteins (activate/inactivate)
- Primary mechanism of cell cycle control
- **Cdks** partner with different **cyclins** at different points in the cell cycle

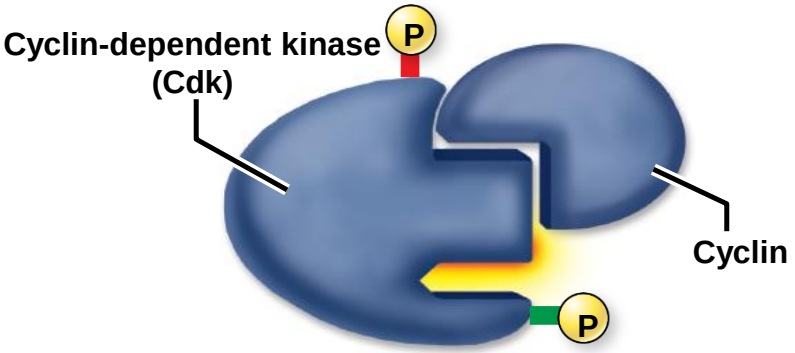


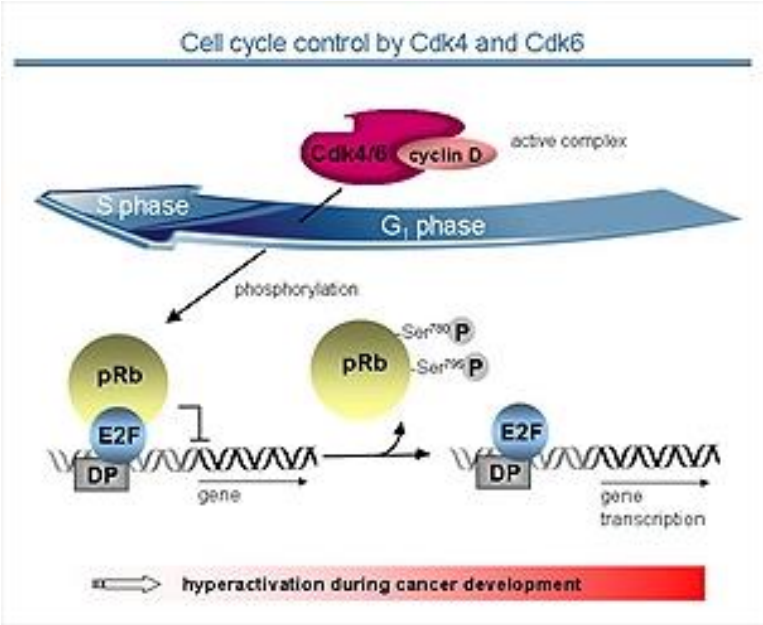


http://old.ecco-org.eu/Conferences-and-Events/Past-events/2009/ECCO-15-ESMO-34/Congress-Newspaper/Wednesday/Graf/page.aspx/1842

Cyclin-dependent kinases (Cdks)

- For many years, a common view was that cyclins drove the cell cycle – that is, the periodic synthesis and destruction of cyclins acted as a clock
- Now clear that Cdk itself is also controlled by phosphorylation





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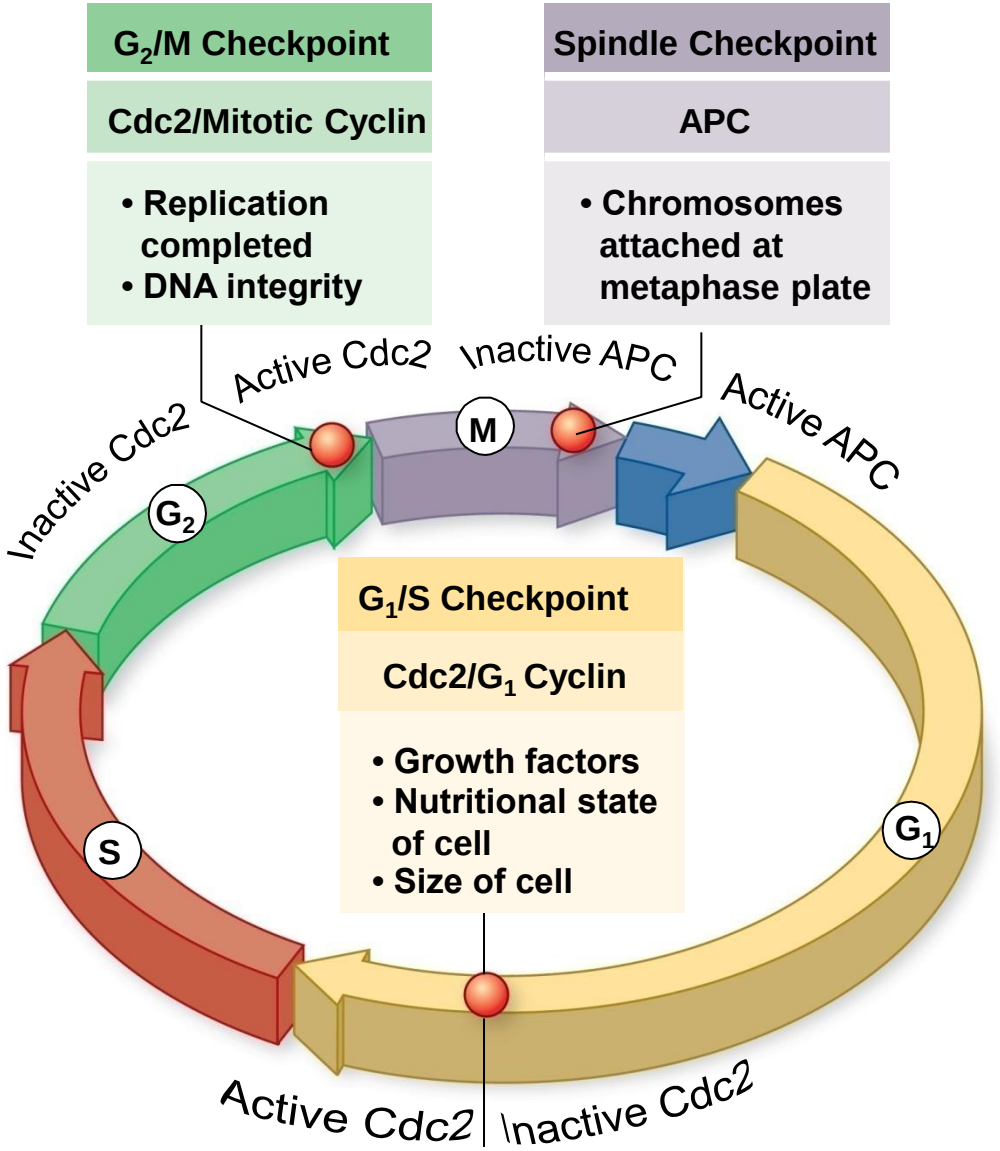
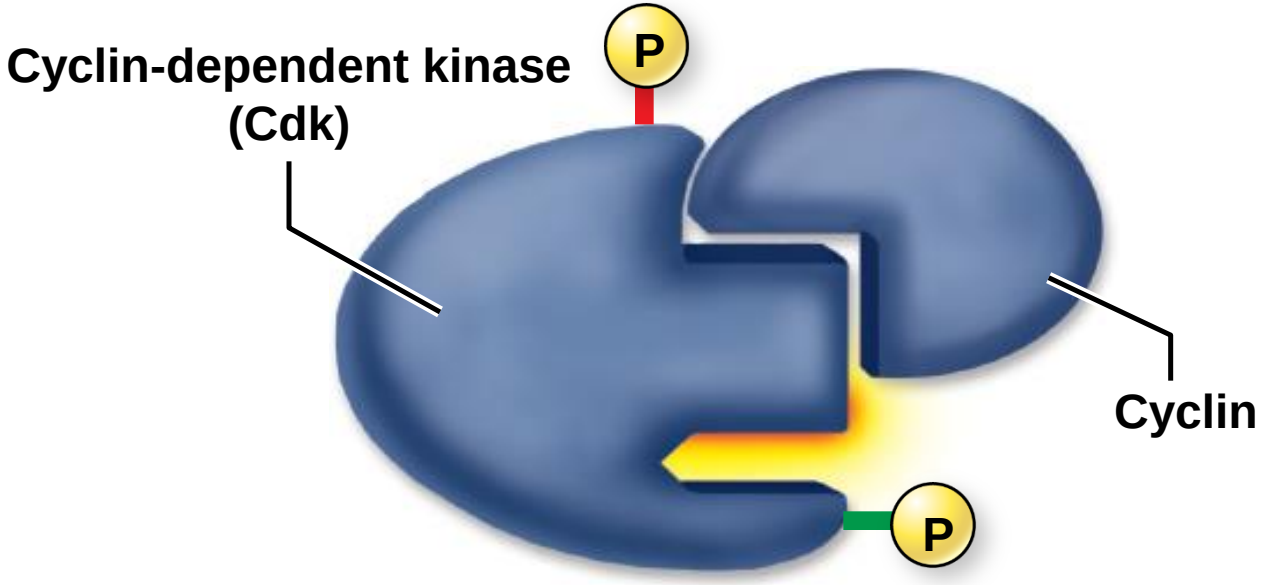
Checkpoints of the Yeast Cell Cycle

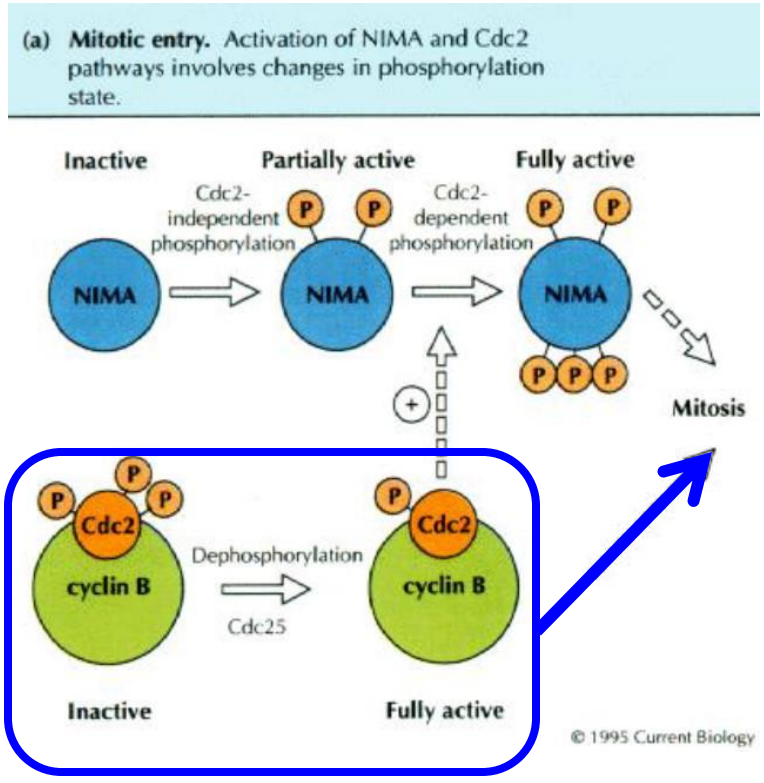




- **Cdk – cyclin complex**
  - Also called **mitosis-promoting factor (MPF)**
- *Activity of Cdk is also controlled by the pattern of phosphorylation*
  - Phosphorylation at one site (red) inactivates Cdk
  - Phosphorylation at another site (green) activates Cdk

Action of **Mitosis Promoting Factor** (MPF)

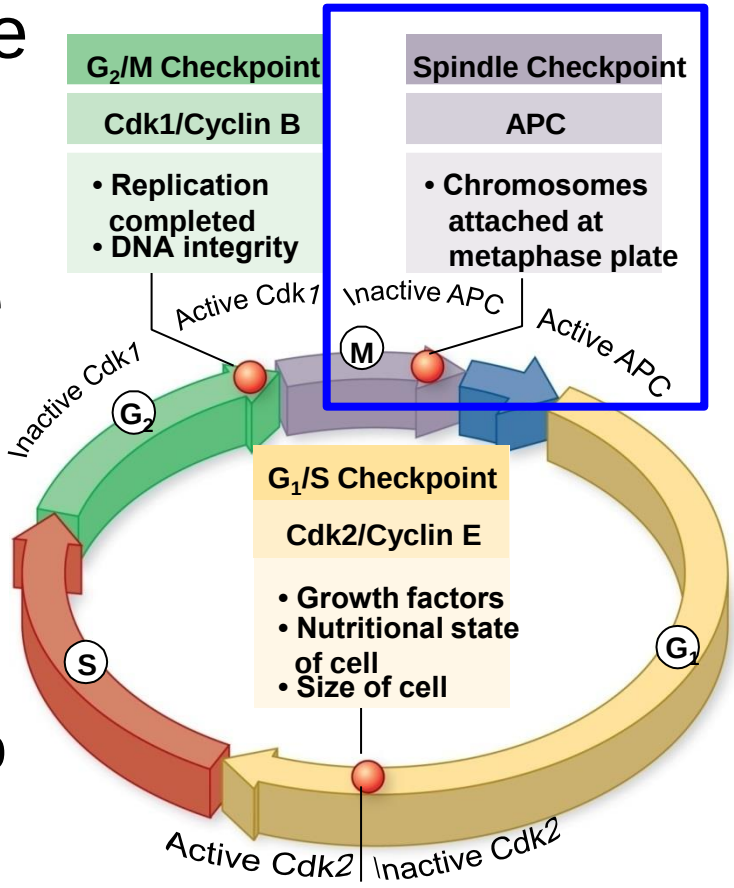
- Once thought that MPF (cyclin-cdk complex) was controlled solely by the level of the M phase-specific cyclins
- Although M phase cyclin is necessary for MPF function, *activity is controlled by inhibitory phosphorylation of the kinase component,* ***Cdc2***
- Damage to DNA acts through a complex pathway to tip the balance toward the inhibitory phosphorylation of MPF



http://www.sciencedirect.com/science/article/pii/S0960982295002272

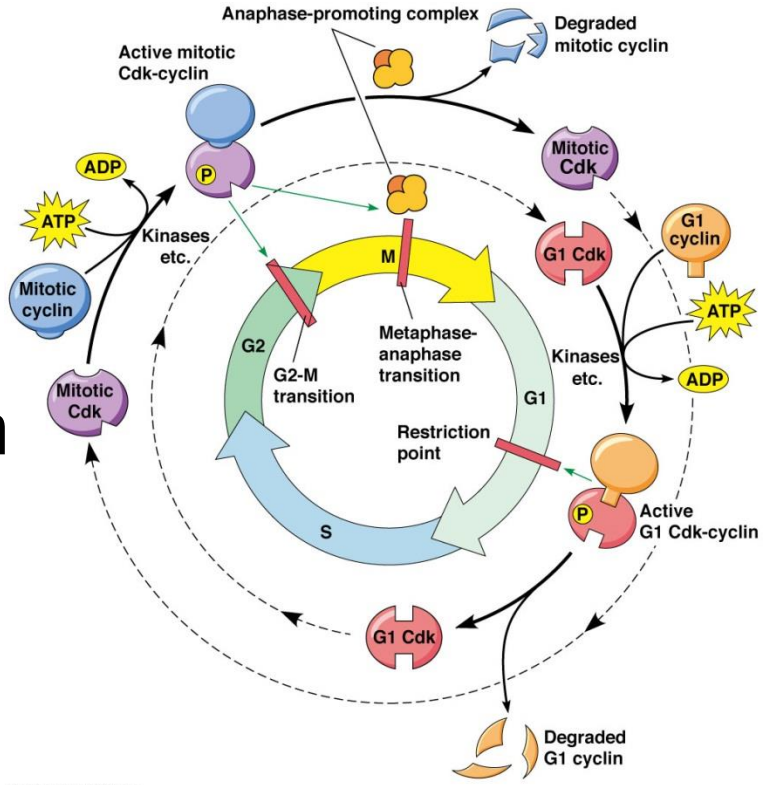
Anaphase-promoting complex (APC)

- Also called **cyclosome (APC/C)**
- At spindle checkpoint, presence of all chromosomes at metaphase plate & tension on microtubules between opposite poles are both important
- Function of the APC/C is to trigger anaphase itself →
  - Marks **securin** for destruction; no inhibition of **separase**; separase destroys **cohesin**



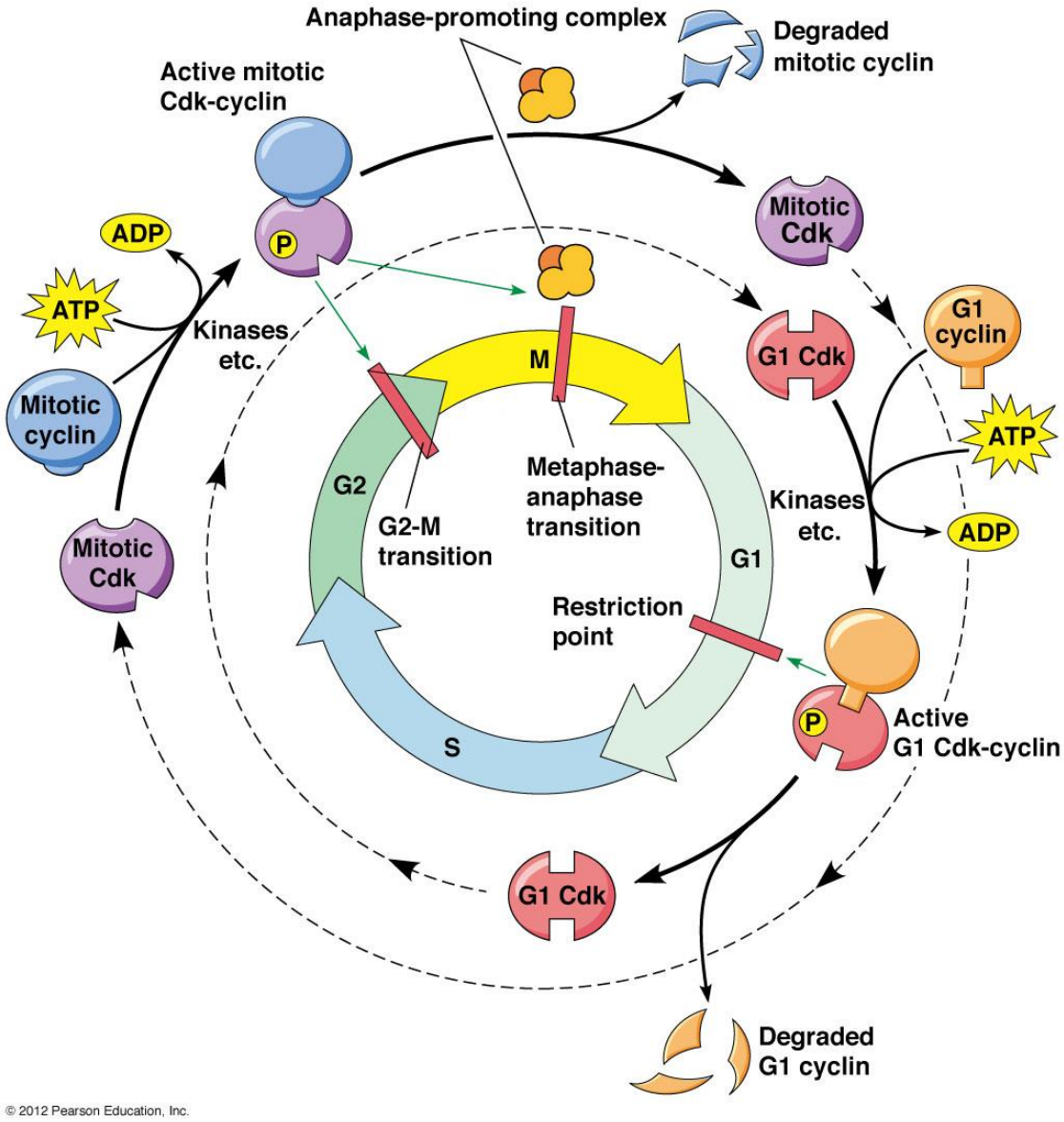
Control in Multicellular Eukaryotes

- Multiple Cdks control cell cycle as opposed to single Cdk in yeasts
- Animal cells respond to a greater variety of external signals than do yeasts, which primarily respond to signals necessary for mating
- More complex controls allow the integration of more input into control of cell cycle



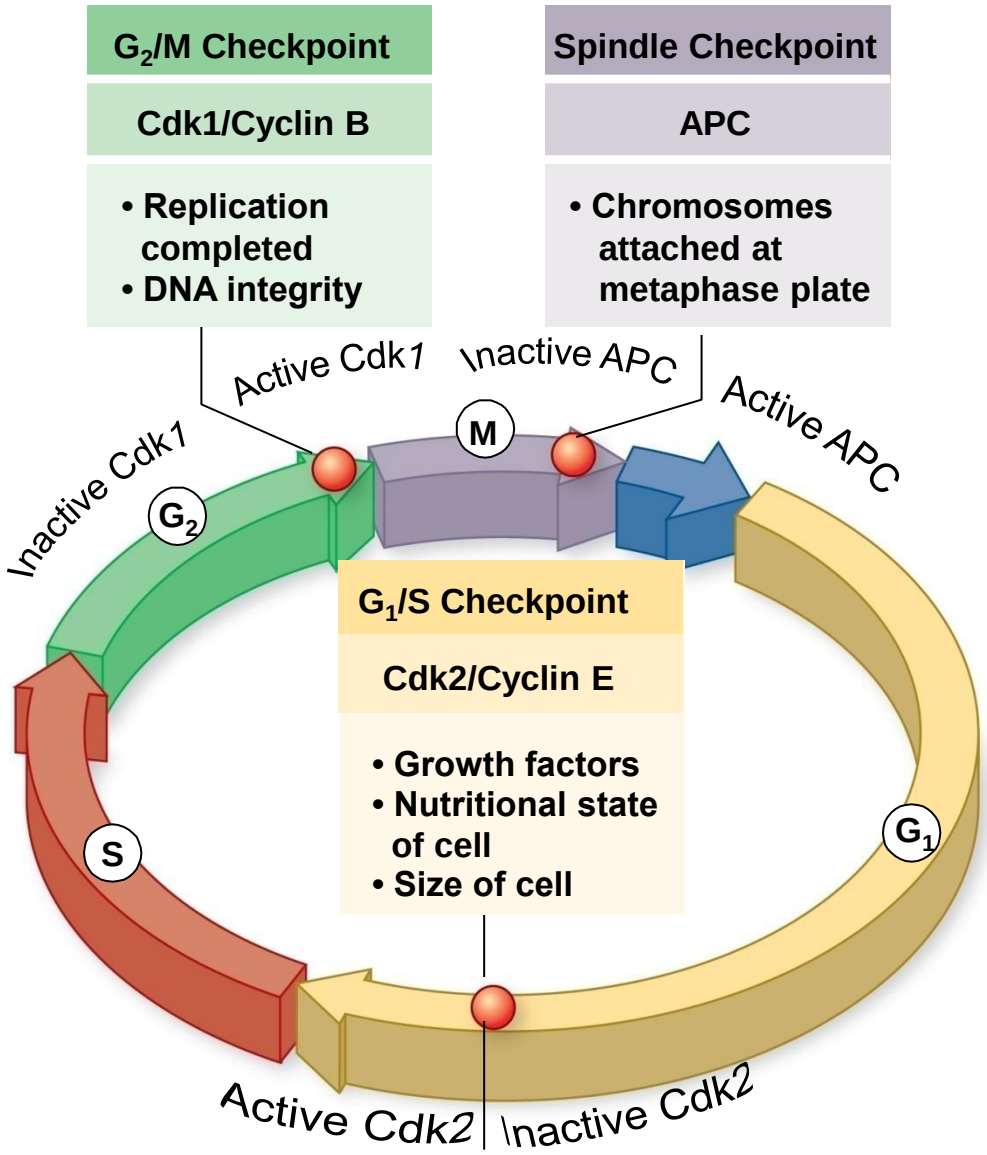
http://www.mun.ca/biology/desmid/brian/BIOL2060/BIOL2060-19/CB19.html

Control in Multicellular Eukaryotes



http://www.mun.ca/biology/desmid/brian/BIOL2060/BIOL2060-19/CB19.html

Checkpoints of the Mammalian Cell Cycle

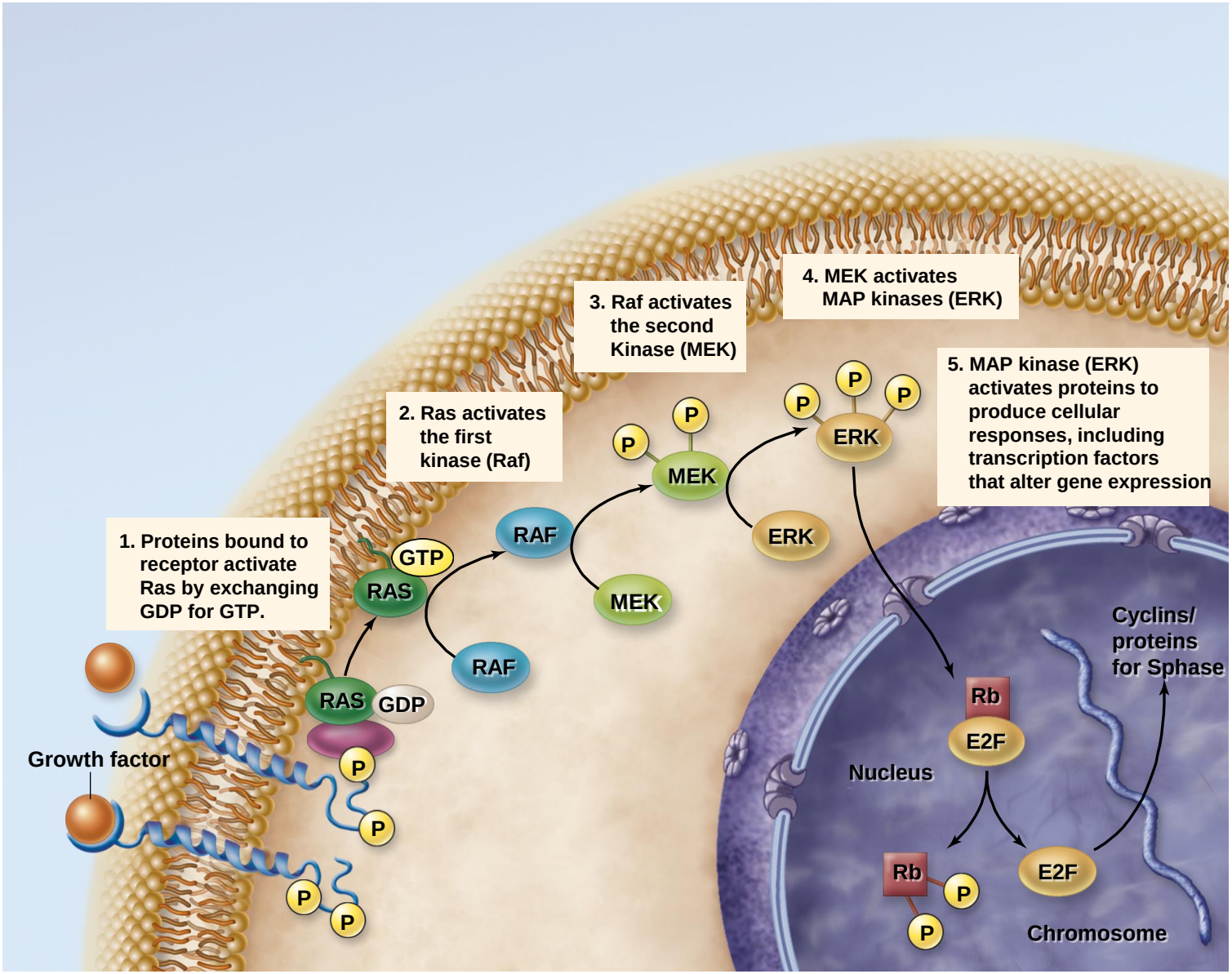


Same as yeast in textbook (see Figures 10.18 & 10.21)

Growth factors

- Act by triggering intracellular signaling systems
- Platelet-derived growth factor (PDGF) one of the first growth factors to be identified
- PDGF receptor is a receptor tyrosine kinase (RTK) that initiates a MAP kinase cascade to stimulate cell division
- Growth factors can override cellular controls that otherwise inhibit cell division

The Cell Proliferation-Signaling Pathway



Cancer

Unrestrained, uncontrolled growth of cells

- Failure of cell cycle control
- **Two kinds of genes can disturb the cell cycle when they are mutated**

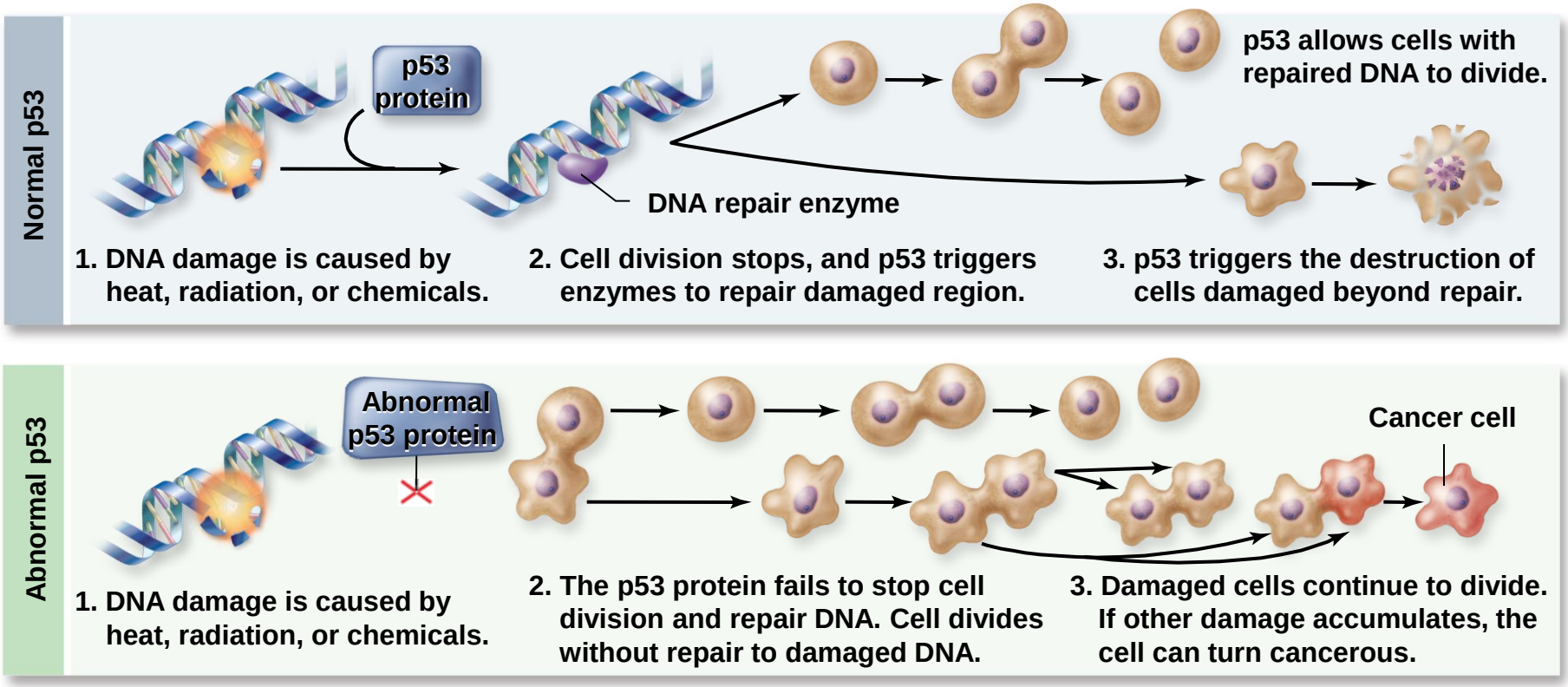
1. Tumor-suppressor genes

2. Proto-oncogenes

Tumor-suppressor genes

- *p53* plays a key role in G_1 checkpoint
- p53 protein monitors integrity of DNA
  - If DNA damaged, cell division halted and repair enzymes stimulated
  - If DNA damage is irreparable, p53 directs cell to kill itself
- Prevent the development of mutated cells containing mutations
- *p53* is absent or damaged in many cancerous cells

- Normal p53 protein destroys cells that have irreparable damage to their DNA
- Abnormal p53 protein fails to stop cell division, damaged cells divide, cancer develops



Proto-oncogenes

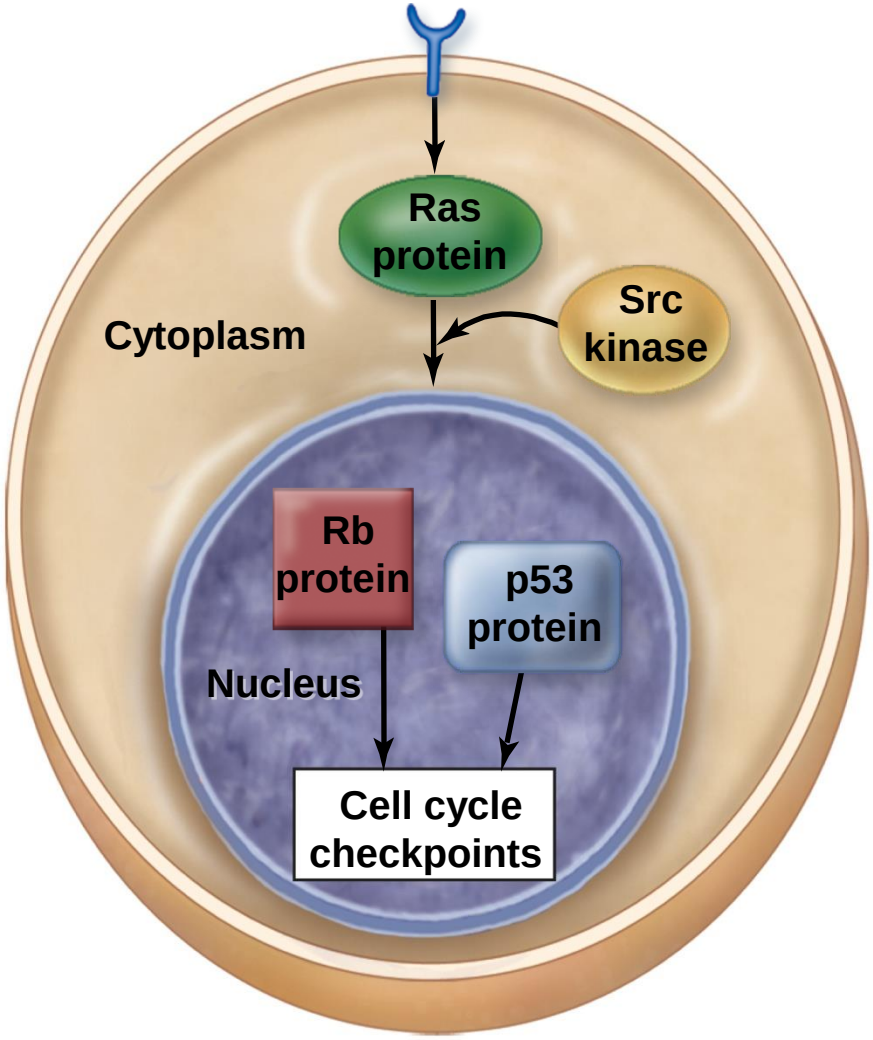
- **Proto-oncogenes** are normal cellular genes that become **oncogenes** when mutated
  - **Oncogenes can cause cancer**
- Some encode receptors for growth factors
  - If receptor is mutated in “on,” cell no longer depends on growth factors
- Some encode signal transduction proteins
- Only one copy of a proto-oncogene needs to undergo this mutation for uncontrolled division to take place

Tumor-suppressor genes

- *p53* gene and many others
- **Both copies of a tumor-suppressor gene must lose function for the cancerous phenotype to develop**
- First tumor-suppressor identified was the **retinoblastoma susceptibility gene *(Rb)***
  - Predisposes individuals for a rare form of cancer that affects the retina of the eye

- Inheriting a single mutant copy of *Rb* means the individual has only one “good” copy left
  - During the hundreds of thousands of divisions that occur to produce the retina, any error that damages the remaining good copy leads to a cancerous cell
  - Single cancerous cell in the retina then leads to the formation of a retinoblastoma tumor
- Rb protein integrates signals from growth factors
  - Role to bind important regulatory proteins and prevent stimulation of cyclin or Cdk production

Key Proteins Associated with Human Cancers



Mammalian cell

Proto-oncogenes

Growth factor receptor:
more per cell in many breast cancers.

Ras protein:
activated by mutations in 20–30% of all cancers.

Src kinase:
activated by mutations in 2–5% of all cancers.

Tumor-suppressor Genes

Rb protein:
mutated in 40% of all cancers.

p53 protein:
mutated in 50% of all cancers.