The Cell Cycle Lecture-2

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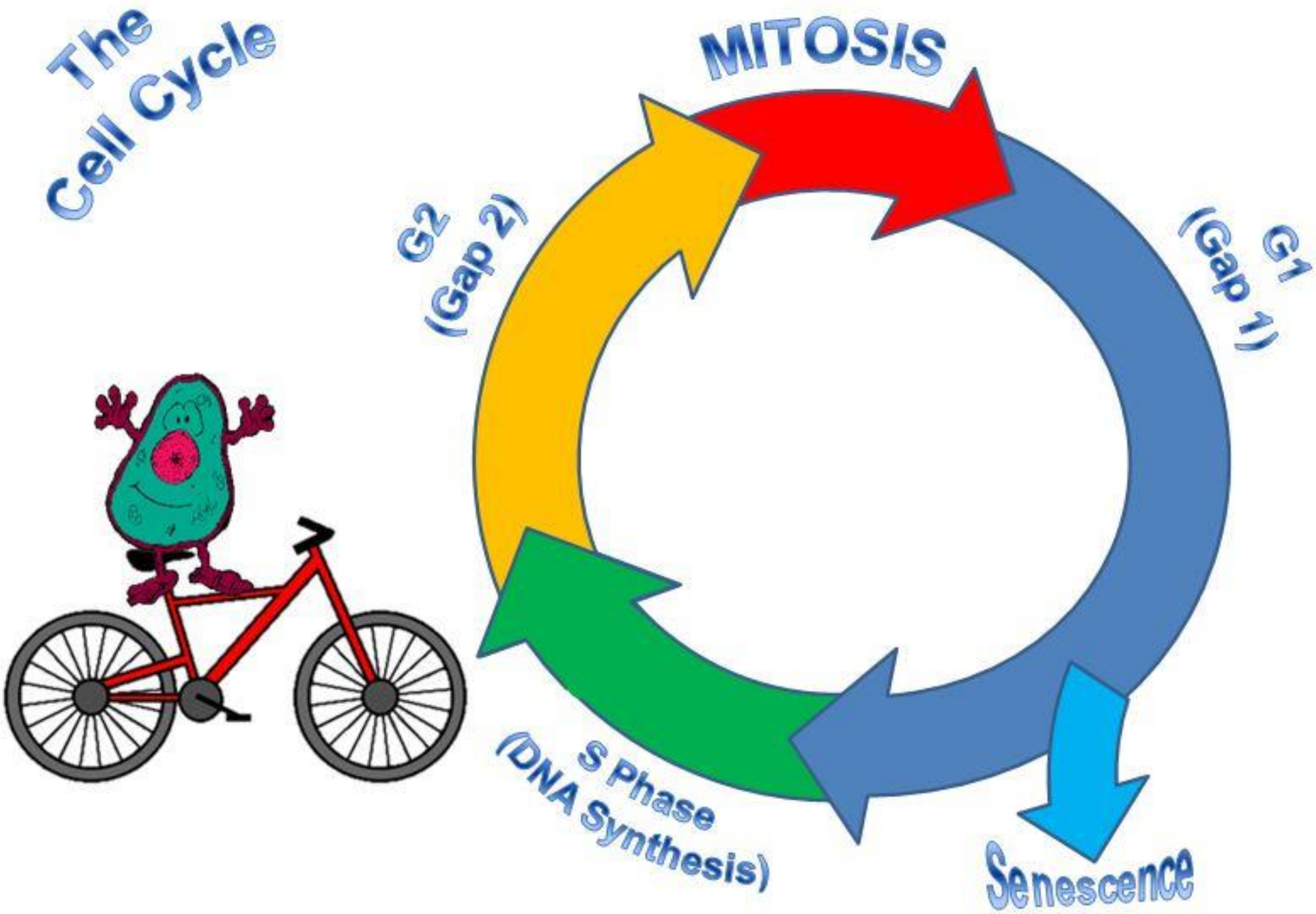

The Cell Cycle
MITOSIS
G1 (Gap 1)
G2 (Gap 2)
S Phase (DNA Synthesis)
Senescence

- **Prophase:** Events that take place during prophase are discussed below-
  - **Formation of mitotic chromosomes:**

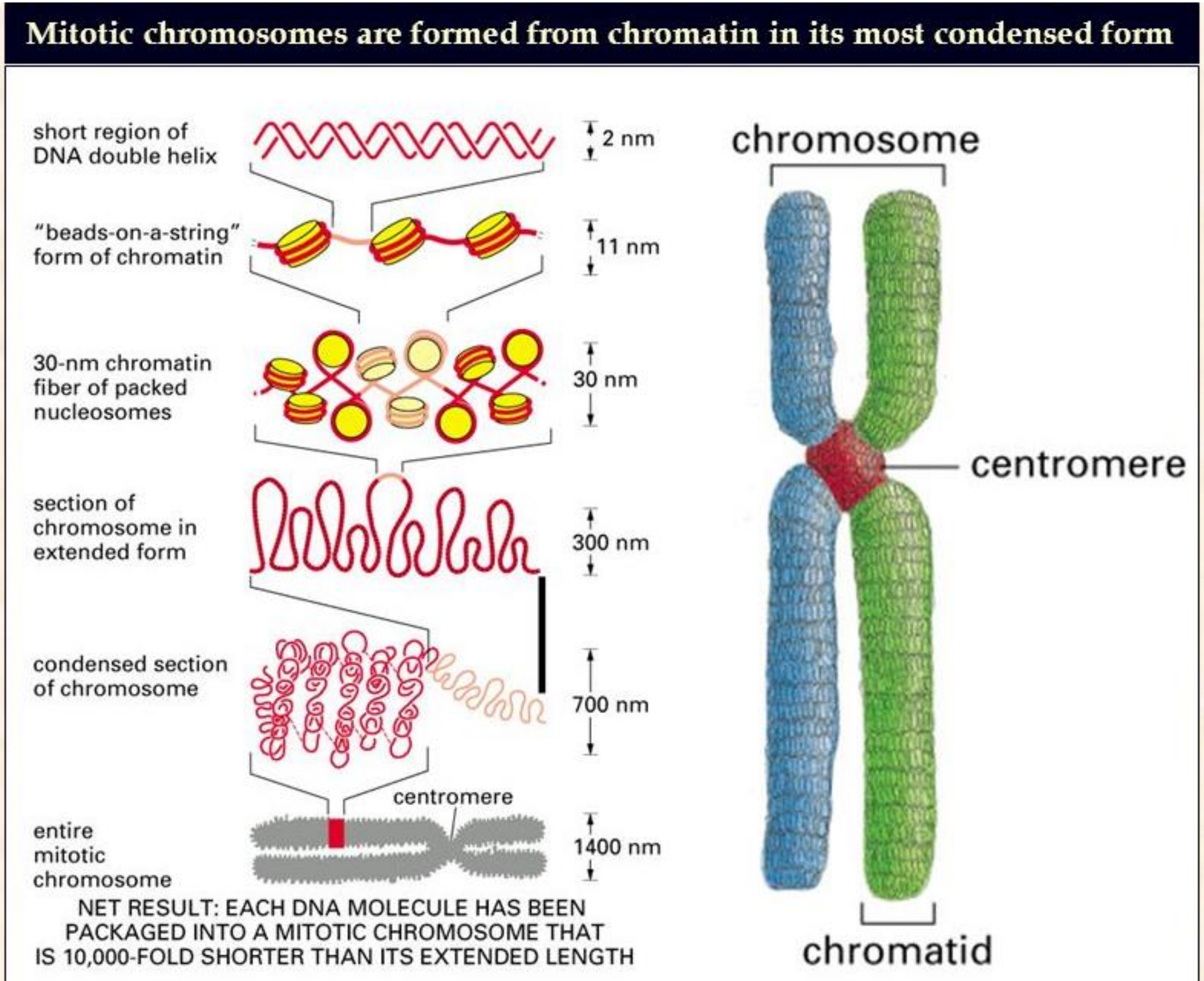
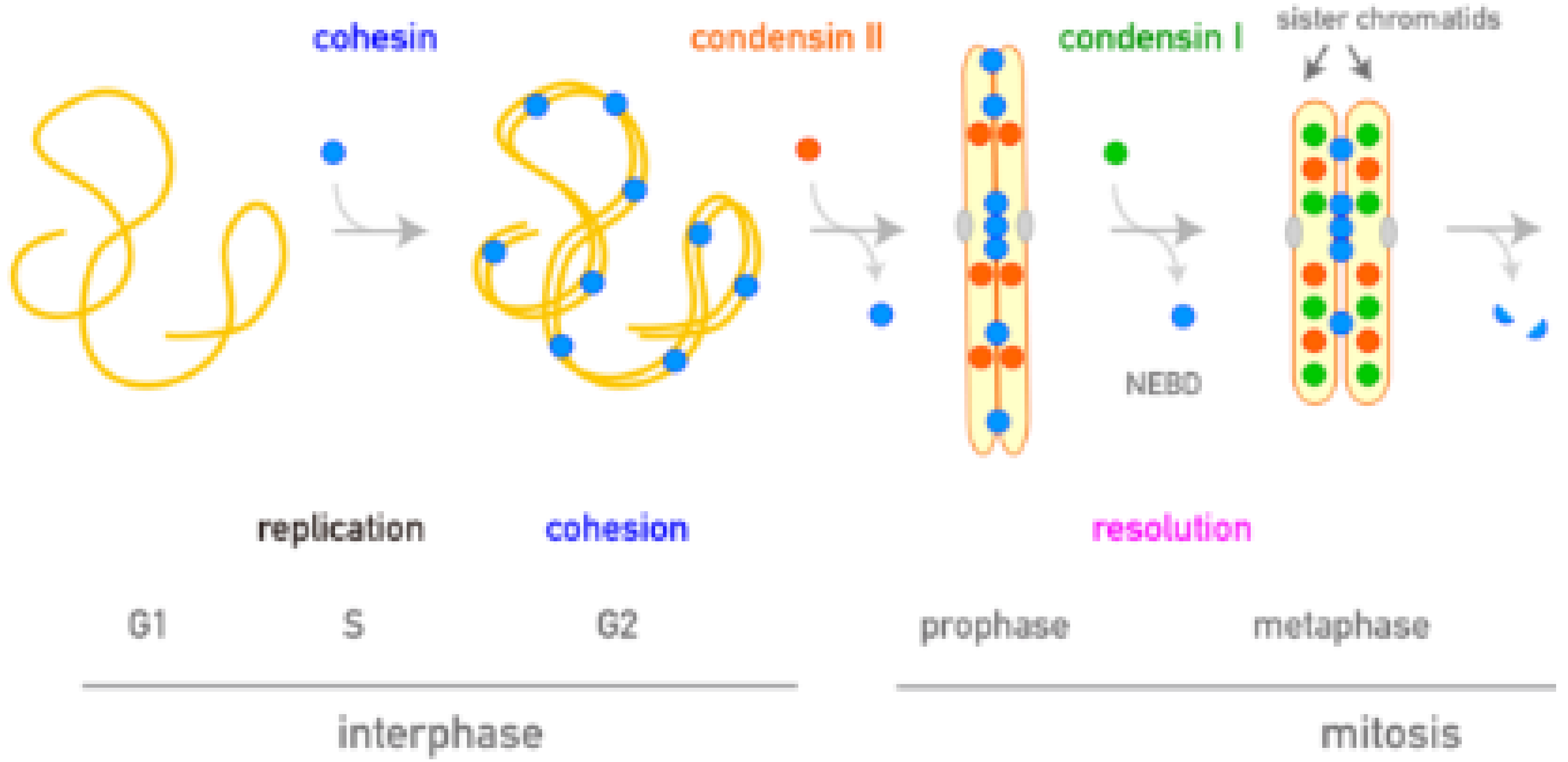
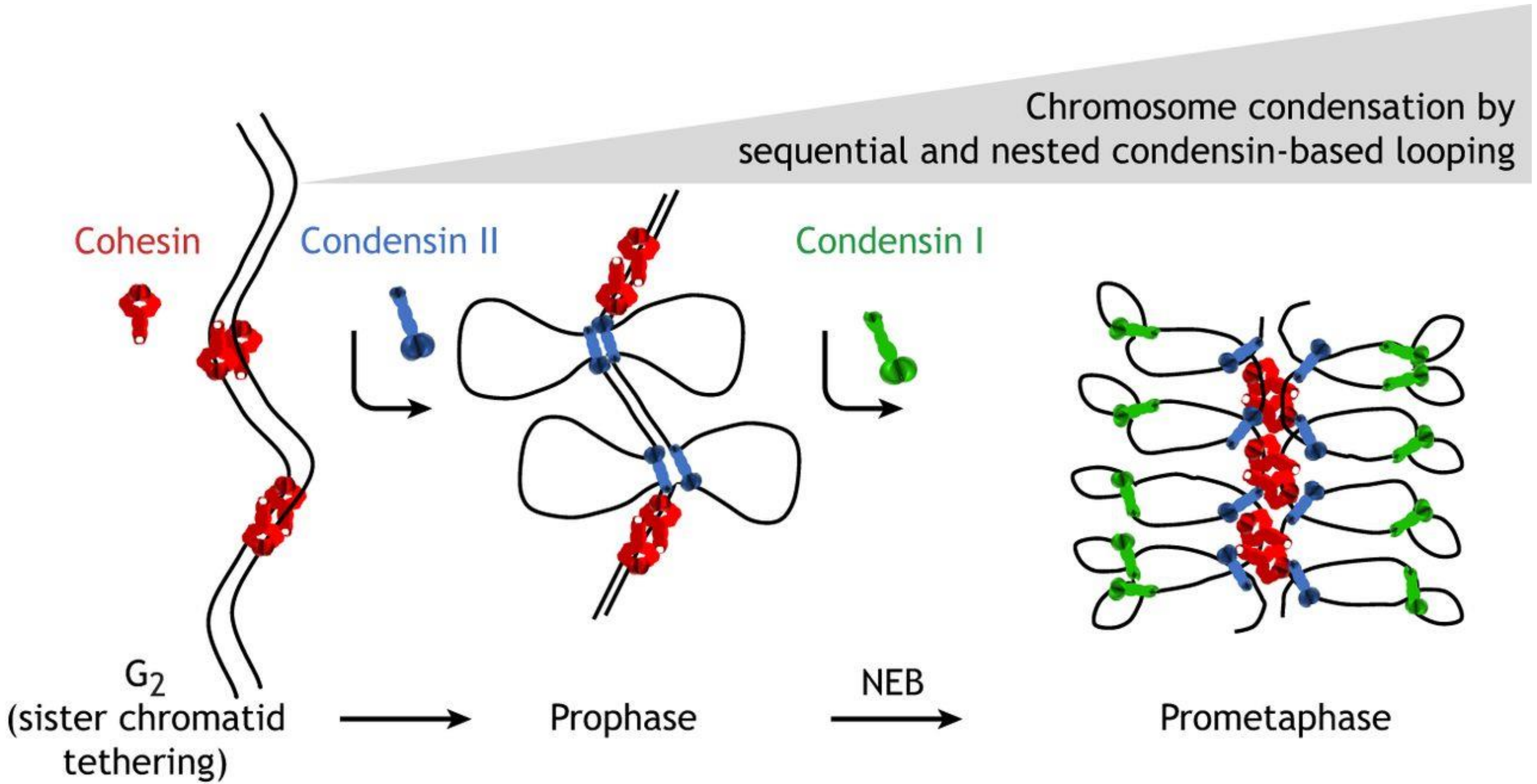


Figure 4–55. Molecular Biology of the Cell, 4th Edition.

- **<u>Role of condensin and cohesin in formation of mitotic chromosomes:</u>**
- **<u>Cohesin:</u>** It functions to keep the two sister chromatids tied to each other.
- **<u>Condensin:</u>** It functions to loop the DNA thread in each chromatid on the scaffold protein.
- They both are considered as SMC proteins. SMC= Structural Maintenance of Chromosome.
- They both are not a single protein but complex of many proteins.




Chromosome condensation by
sequential and nested condensin-based looping
Cohesin
Condensin II
Condensin I
G2
(sister chromatid
tethering)
Prophase
NEB
Prometaphase

- Most of the cohesin dissociates from the arms of the chromosomes as they become compacted during prophase.

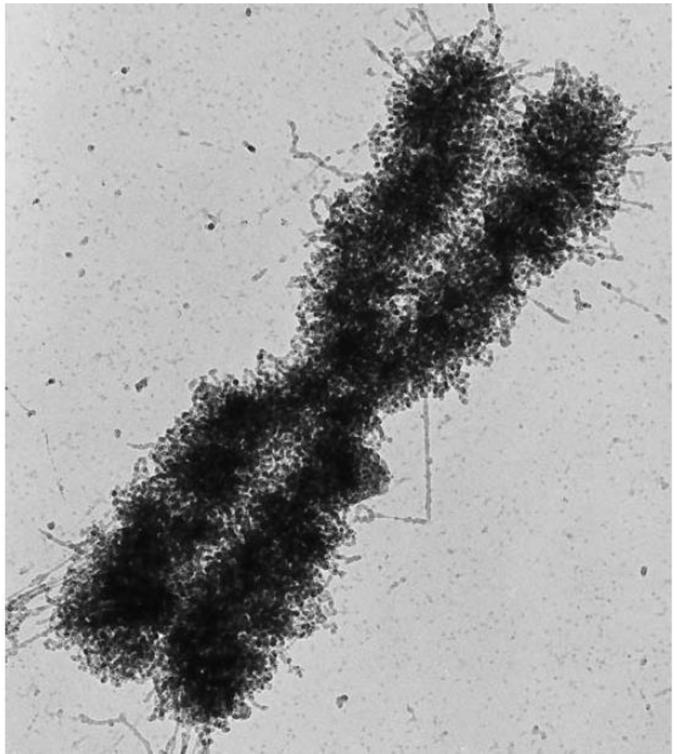
- Dissociation is induced by phosphorylation of cohesin subunits by two important mitotic enzymes called Polo-like kinase and Aurora B kinase.

- Due to activity of these enzymes, the chromatids of each mitotic chromosome are held relatively loosely along their extended arms, but much more tightly at their centromeres.

- Cohesin remains at the centromeres because of the presence there of a phosphatase that removes any phosphate groups added to the protein by the kinases.

- Release of cohesin from the centromeres occurs at anaphase.
- **<u>Centromeres and kinetochores:</u>**

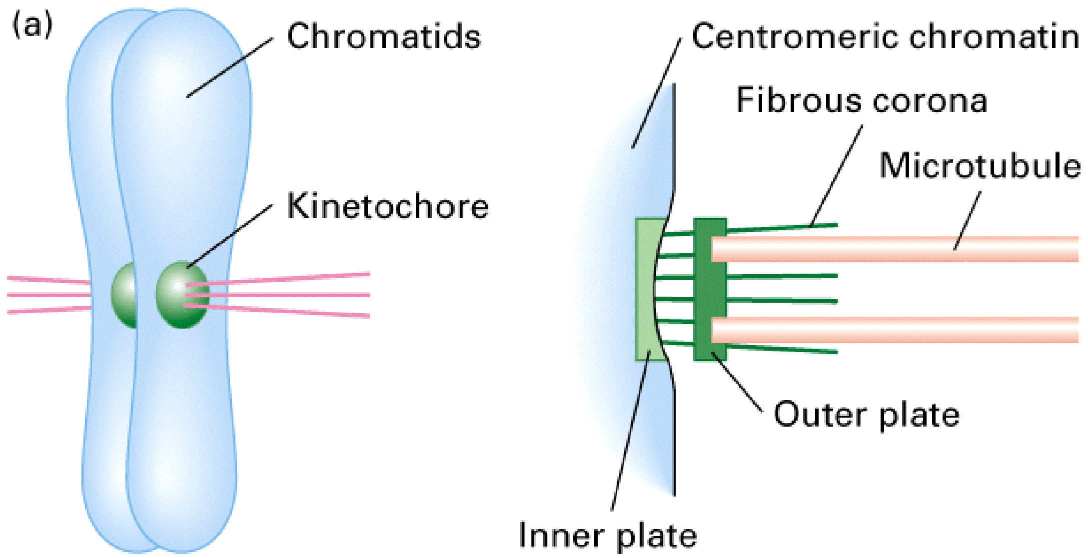
- The most notable landmark on a mitotic chromosome is an indentation or *primary constriction*, which marks the position of the centromere.

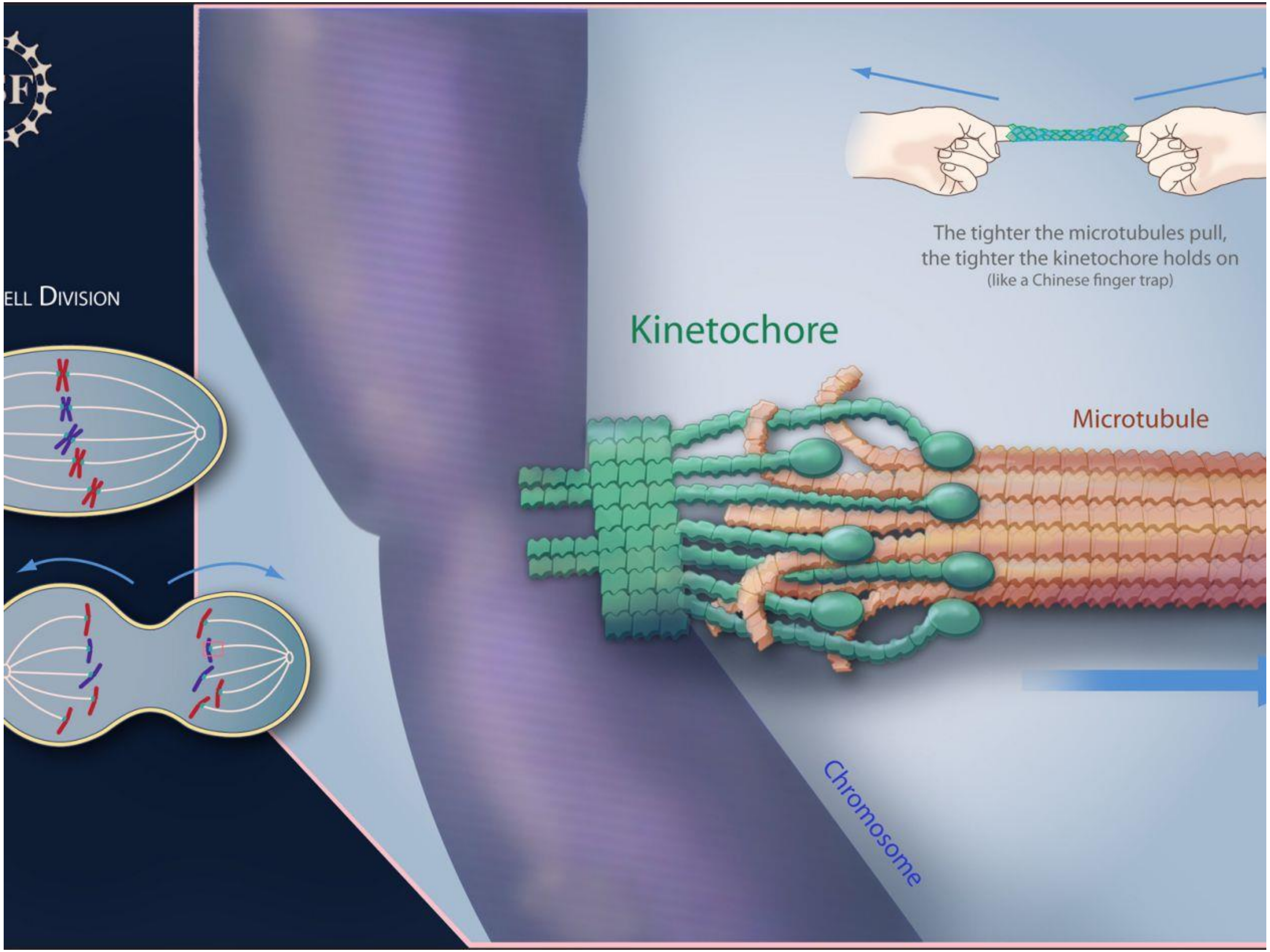


- The centromere is made of highly repeated DNA sequences that serve as the binding sites for specific proteins.
- It is these assembled proteins on the centromere that give it a button like appearance and are called as kinetochore.
- It assembles at the outer surface of the centromere on each chromatid.
- The kinetochore assembles at the centromere during prophase.
- The kinetochore functions as

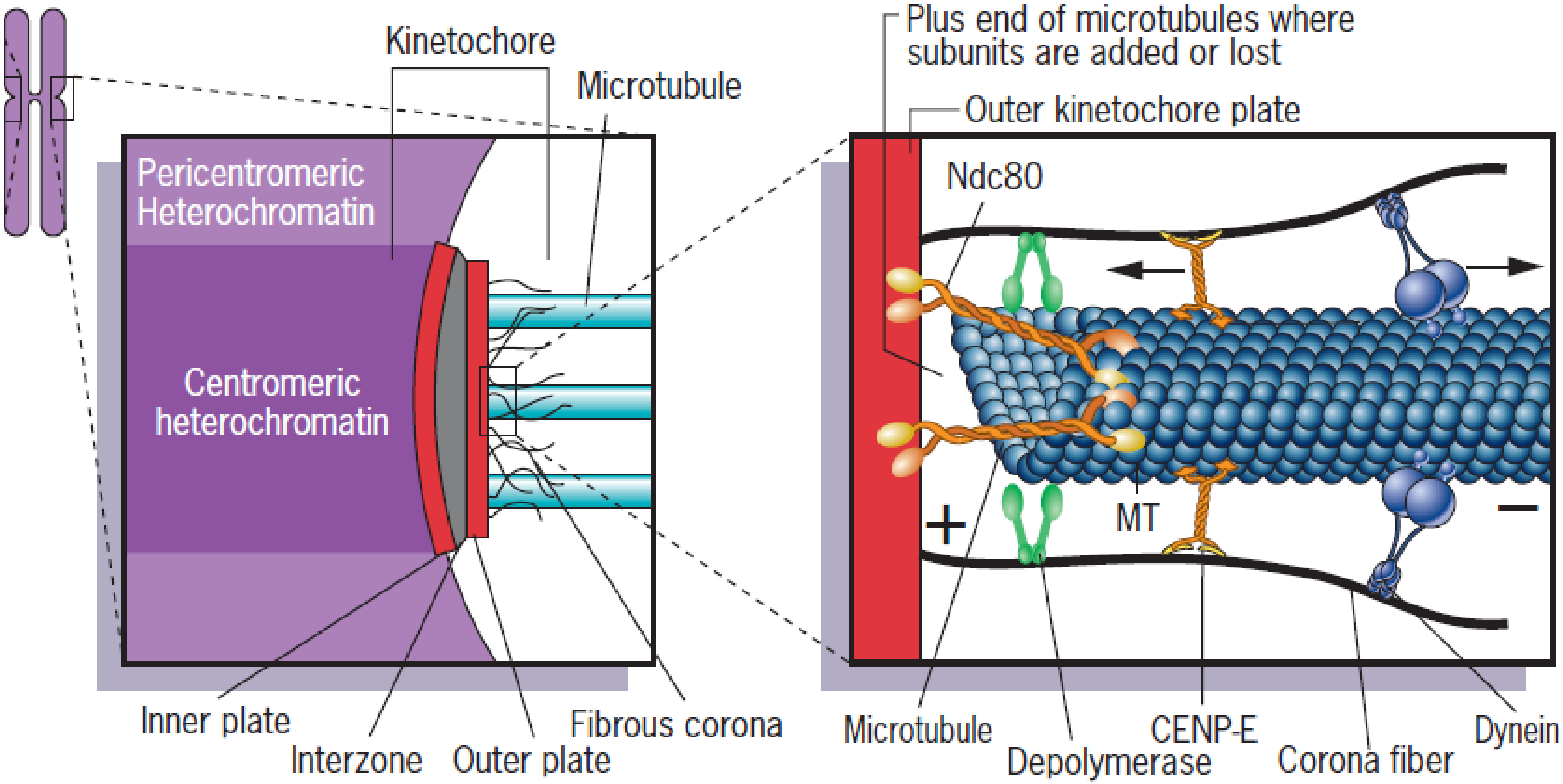
(1) the site of attachment of the chromosome to microtubules of the mitotic spindle

(2) the residence of several motor proteins involved in chromosome motility.





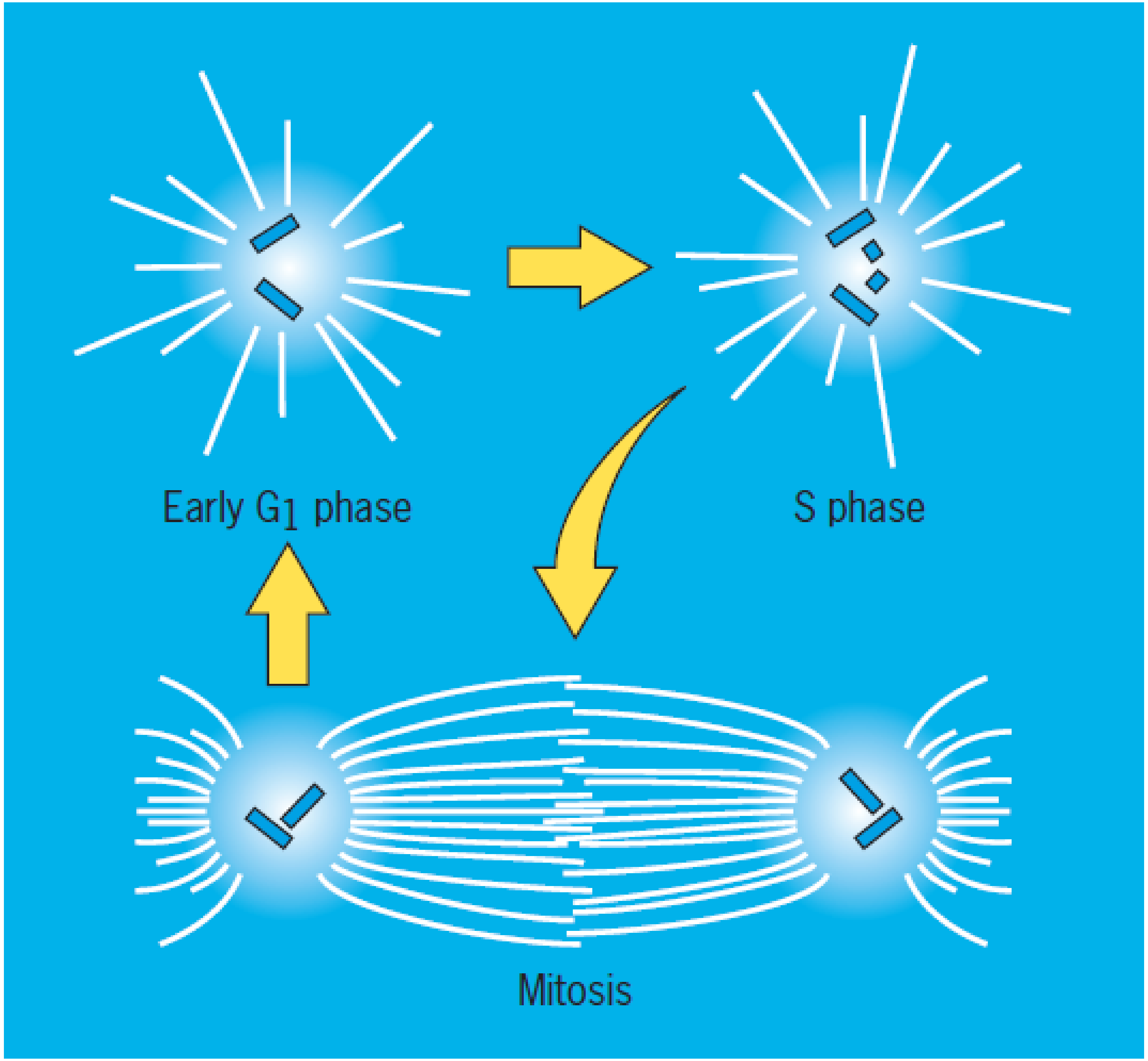
ELL DIVISION
The tighter the microtubules pull,
the tighter the kinetochore holds on
(like a Chinese finger trap)
Kinetochore
Microtubule
Chromosome



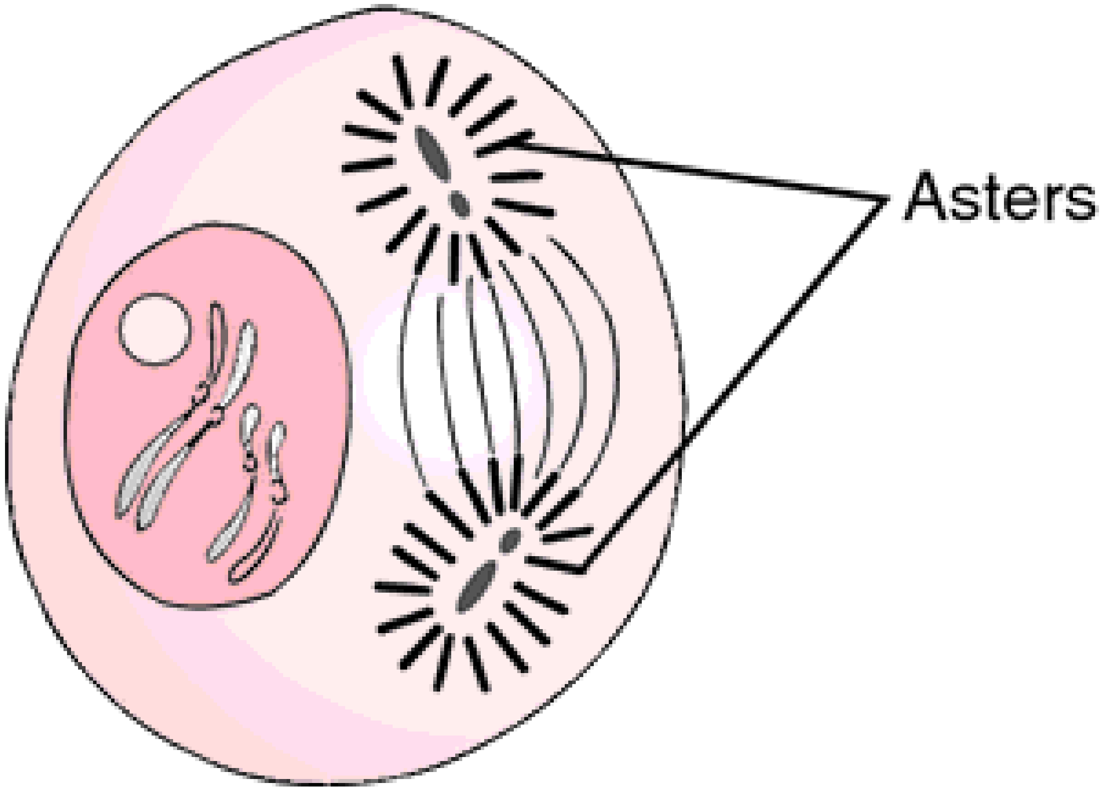
Kinetochore
Microtubule
Pericentromeric Heterochromatin
Centromeric heterochromatin
Inner plate
Interzone
Outer plate
Fibrous corona
Plus end of microtubules where subunits are added or lost
Outer kinetochore plate
Ndc80
+
MT
−
Microtubule
Depolymerase
CENP-E
Corona fiber
Dynein

- **<u>Formation of mitotic spindles:</u>** It refers to the development of microtubule arrays and their attachment on the kinetochores.
- Microtubule assembly in animal cells is initiated by a special microtubule-organizing structure, the **centrosome.**
- As a cell progresses from G_2 into mitosis, the microtubules of the cytoskeleton undergo rapid disassembly because they have to reassemble as components of the **mitotic spindle**.
- ***<u>Centrosome cycle:</u>***
- It progresses in concert with the cell cycle.
- When an animal cell exits mitosis, the cytoplasm contains a single centrosome containing two centrioles situated at right angles to one another.
- As DNA replication begins in the nucleus at the onset of S phase, each centriole of the centrosome initiates its “replication” in the cytoplasm.
- At the beginning of mitosis, the centrosome splits into two adjacent centrosomes, each containing a pair of mother–daughter centrioles.

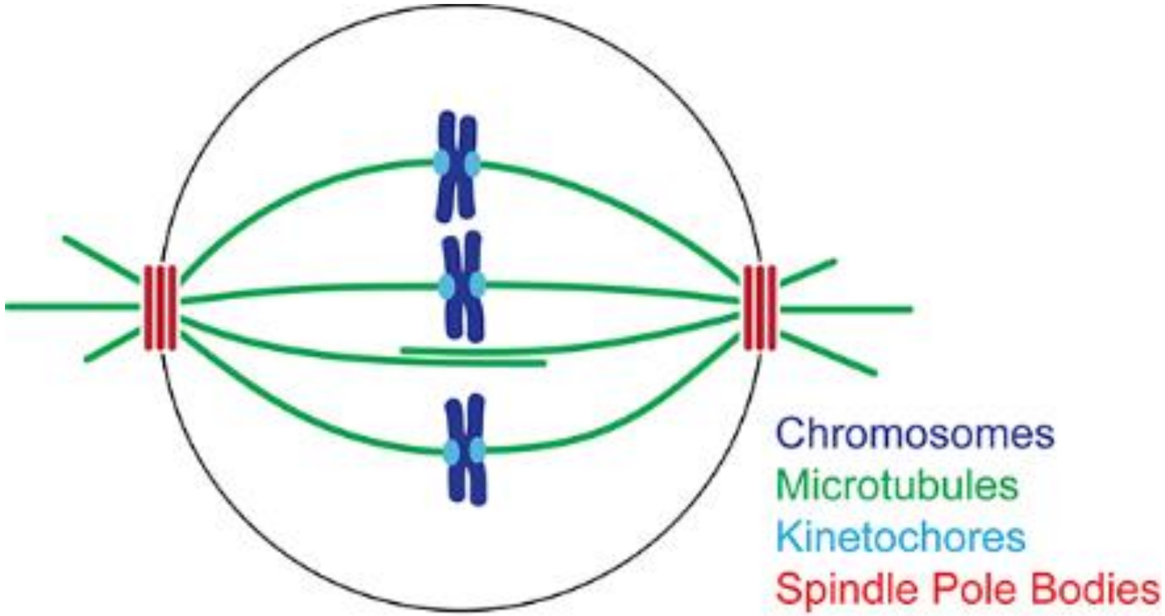
Figure: Centrosome cycle



- The first stage in the formation of the mitotic spindle in a typical animal cell is the appearance of microtubules in a “sunburst” arrangement, or **aster**, around each centrosome during early prophase.
- The process of aster formation is followed by separation of the centrosomes from one another and their subsequent movement around the nucleus toward opposite ends of the cell.



- Eventually, the two centrosomes reach points opposite one another, thus establishing the two poles of a *bipolar* mitotic spindle.
- Following mitosis, one centrosome will be distributed to each daughter cell.



- This type of mitotic spindle formation is called as **centrosome-dependent.**

- A number of different types of animal cells (including those of the early mouse embryo) lack centrosomes, as do the cells of higher plants.

- Yet all of these cells construct a bipolar mitotic spindle and undergo a relatively typical mitosis.

- Functional mitotic spindles can even form in mutant *Drosophila* cells that lack centrosomes or in mammalian cells in which the centrosome has been experimentally removed.

- It is possible because of the presence of **centrosome-independent pathway** for the formation of mitotic spindle.

- **<u>Prometaphase:</u>**

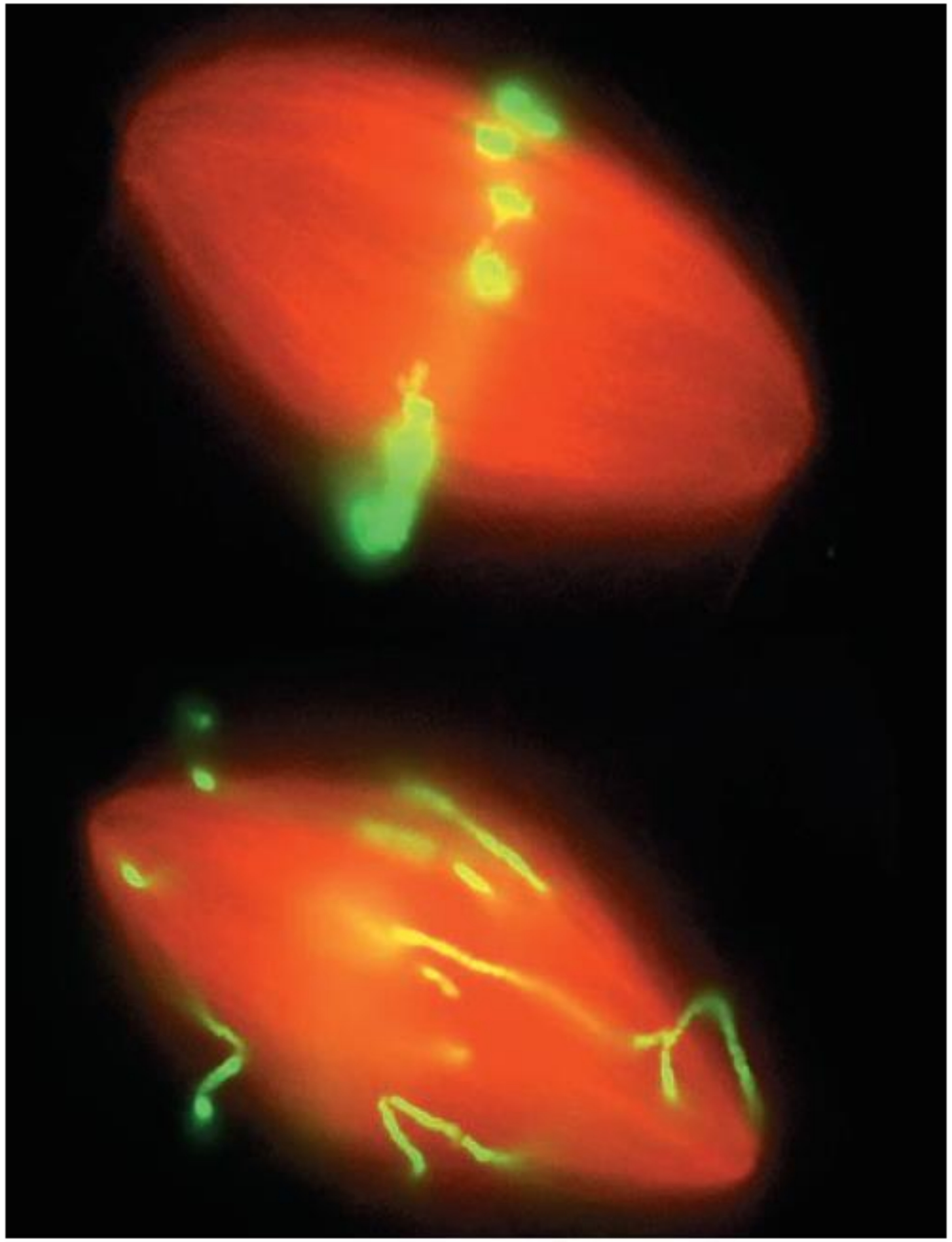
- The dissolution of the nuclear envelope marks the start of the second phase of mitosis, **prometaphase**.

- During this phase mitotic spindle assembly is completed and the chromosomes are moved into position at the center of the cell.

- The chromosomes of a prometaphase cell are moved by a process called **congression,** toward the center of the mitotic spindle, midway between the poles.

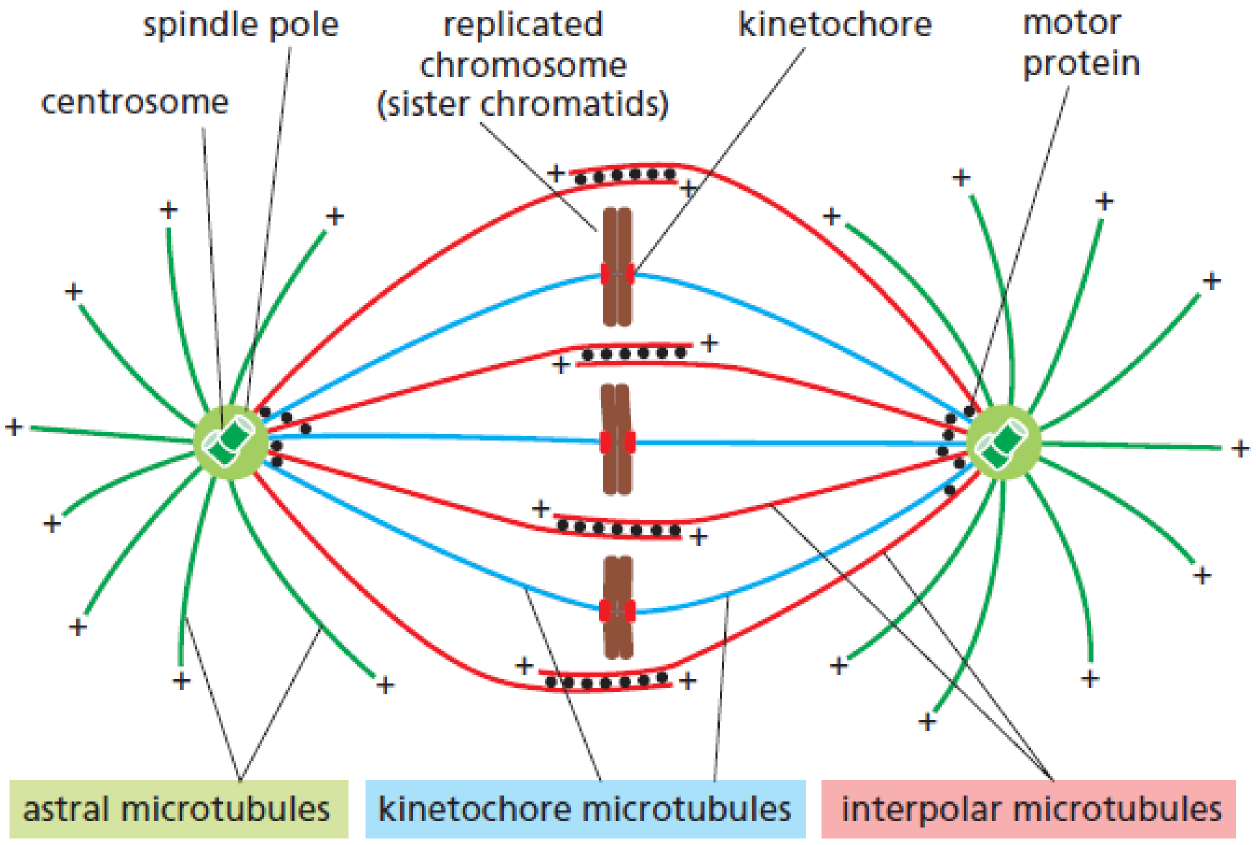
- The forces required for chromosome movements during prometaphase are generated by motor proteins associated with both the kinetochores and arms of the chromosomes.

Movement of chromosomes when all the required proteins are present.



Movement of chromosomes when one of the motor proteins is absent.

- **Metaphase:**
- Once all of the chromosomes have become aligned at the spindle equator—with one chromatid of each chromosome connected by its kinetochore to microtubules from one pole and its sister chromatid connected by its kinetochore to microtubules from the opposite pole—the cell is said to be in the stage of **metaphase.**



- ***Astral microtubules*** that radiate outward from the centrosome into the region outside the body of the spindle.

- They help position the spindle apparatus in the cell.

- ***Chromosomal*** **(or** ***kinetochore*****)** ***microtubules*** that extend between the centrosome and the kinetochores of the chromosomes.

- During metaphase, the chromosomal microtubules exert a pulling force on the kinetochores.

- As a result, the chromosomes are maintained in the equatorial plane by a “tug-of-war” between balanced pulling forces exerted by chromosomal spindle fibers from opposite poles.

- This plane of alignment of the chromosomes at metaphase is referred to as the *metaphase plate*.

- ***Polar (or interpolar) microtubules*** that extend from the centrosome past the chromosomes.

- Polar microtubules from one centrosome overlap with their counterparts from the opposite centrosome.

- The polar microtubules form a structural basket that maintains the mechanical integrity of the spindle.

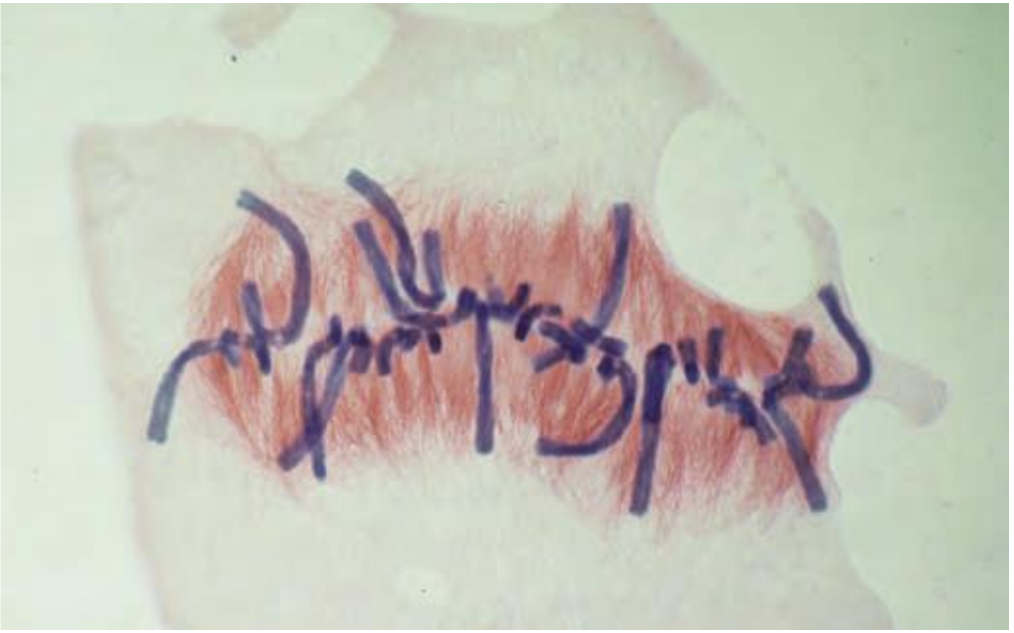
- Because chromosomes are perfectly aligned and highly condensed at this stage, this is the best stage for the counting of number of chromosomes under the microscope.

- **<u>Anaphase:</u>**

- This phase begins when the sister chromatids of each chromosome split apart and start their movement toward opposite poles.

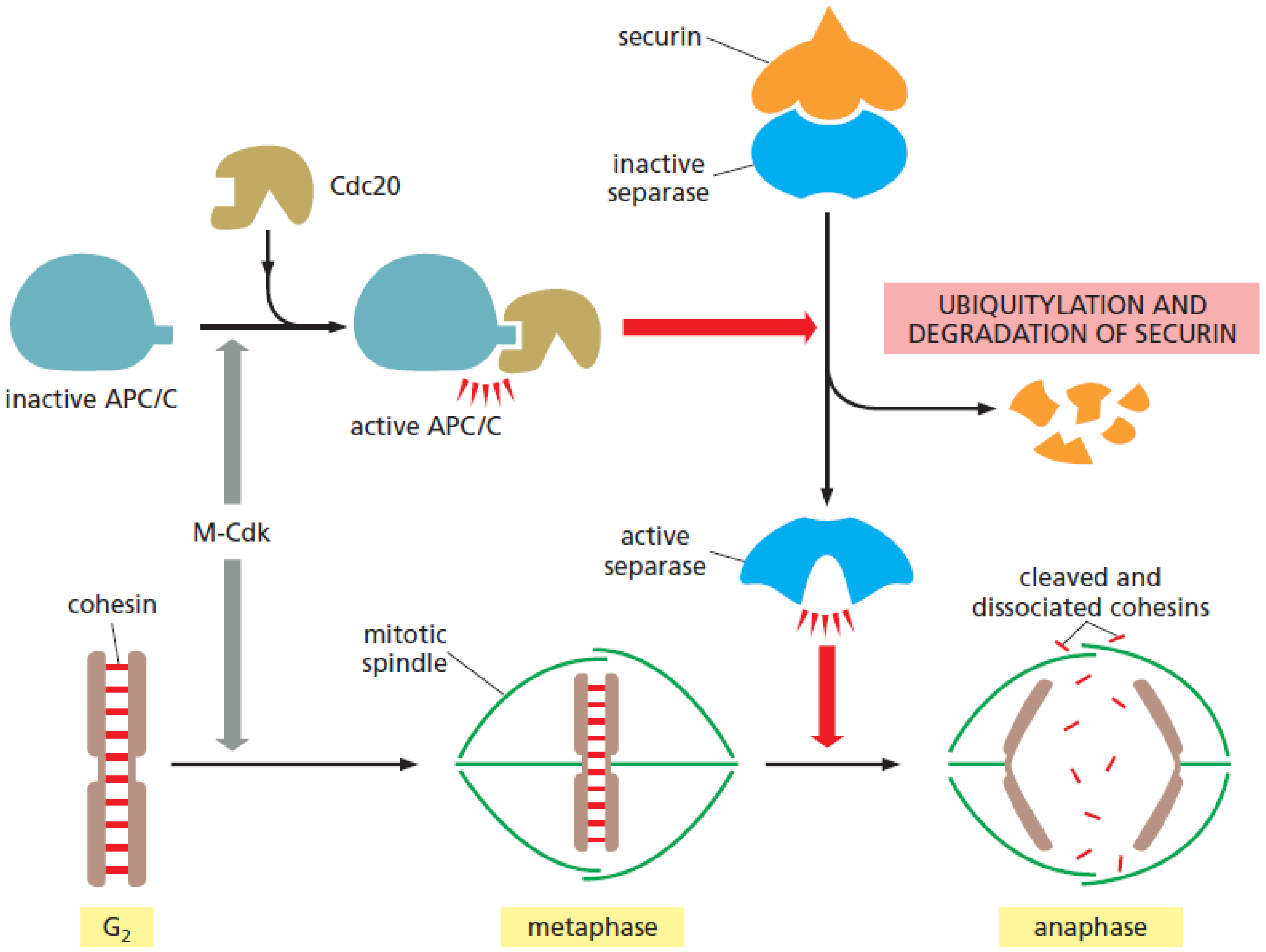
- All the chromosomes of the metaphase plate are split in synchrony at the onset of anaphase, and the chromatids (now referred to as chromosomes, because they are no longer attached to their sisters) begin their poleward migration.

<u>Metaphase</u>



<u>Anaphase</u>

- **Why chromatids are separated during anaphase and not before??**
- It is because anaphase promoting complex also called as APC/C becomes active just before metaphase and initiates events that lead to anaphase.



- The activation of APC/C by Cdc20 leads to the ubiquitylation and destruction of securin, which holds separase in an inactive state.
- The destruction of securin allows separase to cleave the cohesin complex holding the sister chromatids together.
- The pulling forces of the mitotic spindle then pull the sister chromatidsapart.

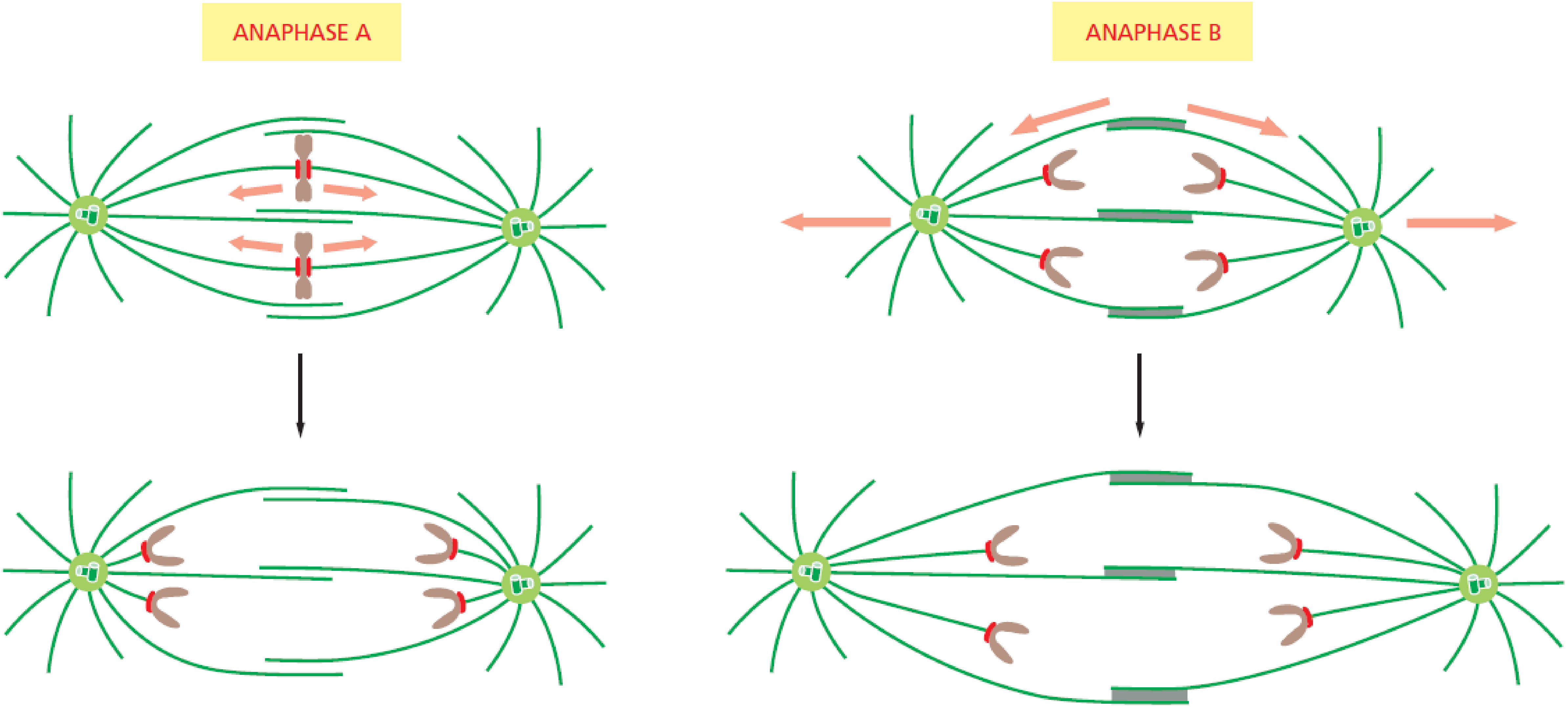
- **<u>Chromosomes Segregate in Anaphase A and B</u>**

- The sudden loss of sister-chromatid cohesion at the onset of anaphase leads to sister- chromatid separation, which allows the forces of the mitotic spindle to pull the sisters to opposite poles of the cell—called *chromosome segregation*.

- The chromosomes move by two independent and overlapping processes.

- The first, **<u>anaphase A</u>**, is the initial poleward movement of the chromosomes, which is accompanied by shortening of the kinetochore microtubules.

- The second, **<u>anaphase B</u>**, is the separation of the spindle poles themselves, which begins after the sister chromatids have separated and the daughter chromosomes have moved some distance apart.


ANAPHASE A
ANAPHASE B

- **Telophase:**
- During telophase, daughter cells return to the interphase condition:
  - ✓ the mitotic spindle disassembles,
  - ✓ the nuclear envelope reforms,
  - ✓ the chromosomes become more and more dispersed until they disappear from view under the microscope.

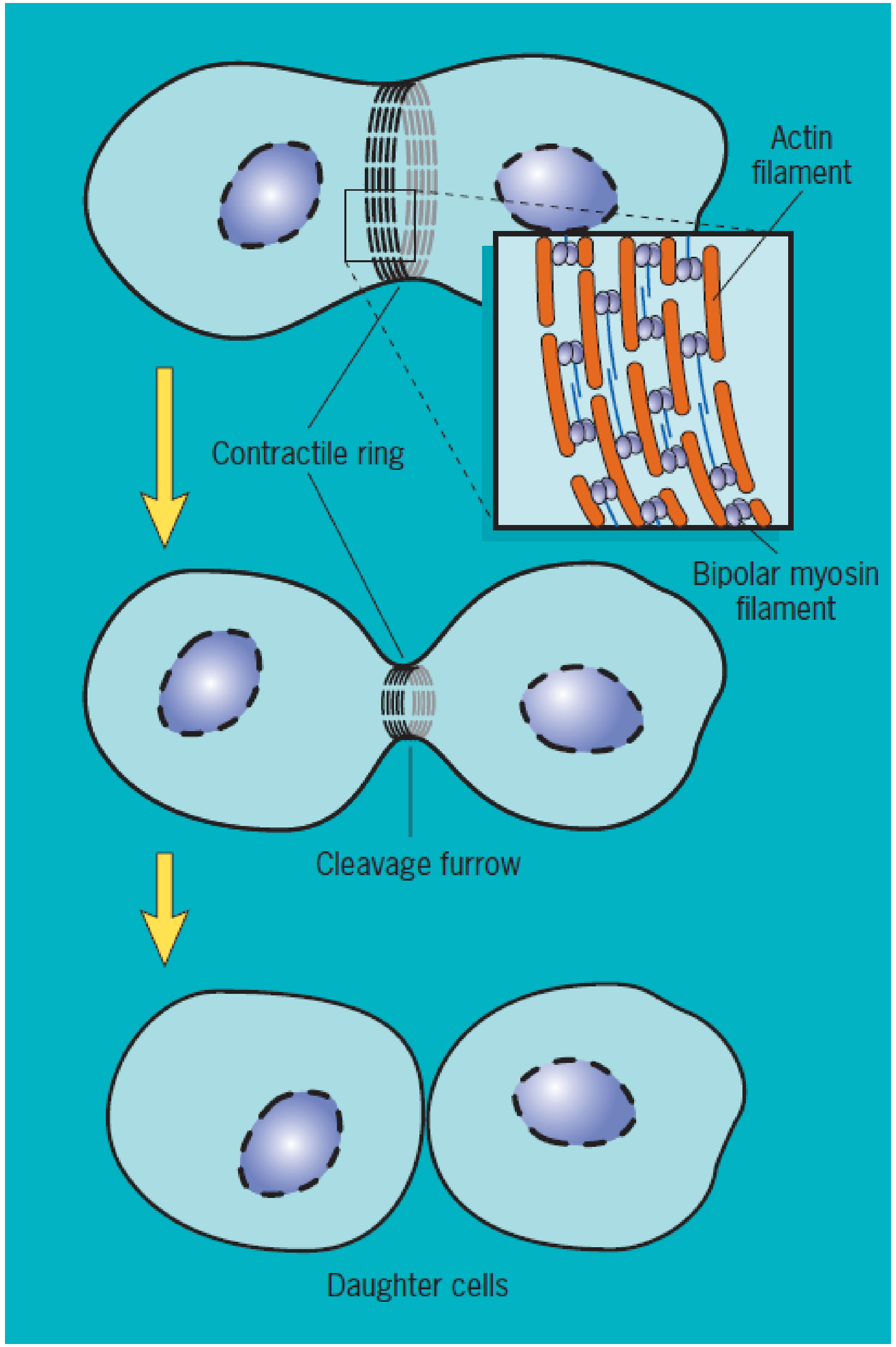
- **Cytokinesis:**
- Karyokinesis finishes the segregation of duplicated chromosomes into daughter nuclei, but the cell is divided into two daughter cells by a separate process called **cytokinesis**.

- In animal cells, this process occurs by cell pinching. In this, an indentation is seen in the membrane at the anaphase and is in the same plane as the metaphase plate.

- This indentation deepens as telophase is over and this process is helped by a contractile collar of actin and myosin.

- The opposite ends of the indentation move in centripetal manner and finally meet. This pinches the cell into 2 and completes the mitosis.

Process of cell pinching



Thank you