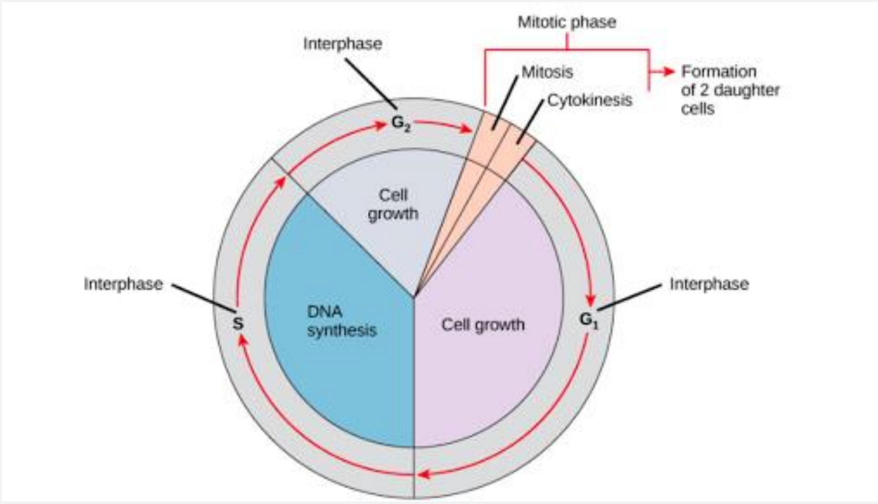
Phases of the Cell Cycle



The Cell Cycle is a 4-stage process consisting of Gap 1 (G1), Synthesis, Gap 2 (G2) and Mitosis. An active **eukaryotic** cell will undergo these steps as it grows and divides. After completing the cycle, the cell either starts the process again from G1 or exits the cycle through G0. From G0, the cell can undergo terminal differentiation.

G1 phase

- Cell increases in size
- Cellular contents duplicated

S phase

- DNA replication
- Each of the 46 chromosomes (23 pairs) is replicated by the cell

G2 phase

- Cell prepares for cell division

M phase

- Mitosis followed by Cytokinesis (cell separation)
- Formation of two identical daughter cells

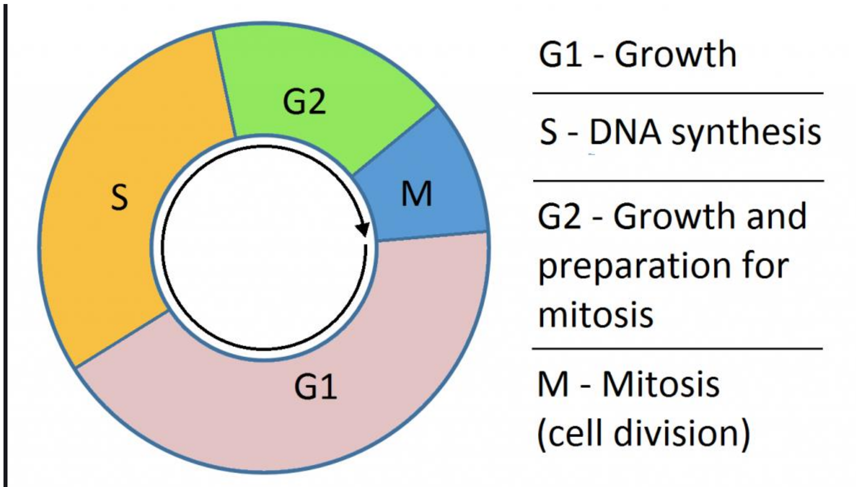


Fig 1.0 – Diagram showing the stages of the cell cycle.

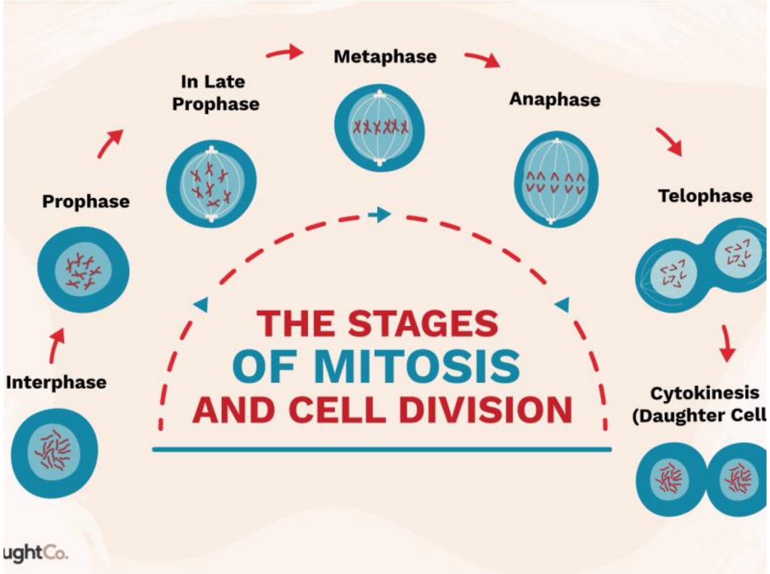
Regulation

The progression of cells through the cell cycle is controlled by checkpoints at different stages. These detect if a cell contains damaged DNA and ensure those cells do not replicate. The **Restriction point (R)** is located at G1 and is a key checkpoint. The vast majority of cells that pass through the R point will end up completing the entire cell cycle. Other checkpoints are located at the transitions between G1 and S, and G2 and M.

If damaged DNA is detected at any checkpoint, activation of the checkpoint results in increased **protein p53** production. p53 is a tumour suppressor gene that stops the progression of the cell cycle and starts repair mechanisms for the damaged DNA. If this DNA cannot be repaired, then it ensures the cell undergoes apoptosis and can no longer replicate.

This cell cycle is also closely regulated by **cyclins** which control cell progression by activating cyclin-dependent kinase (CDK) enzymes.

Mitosis



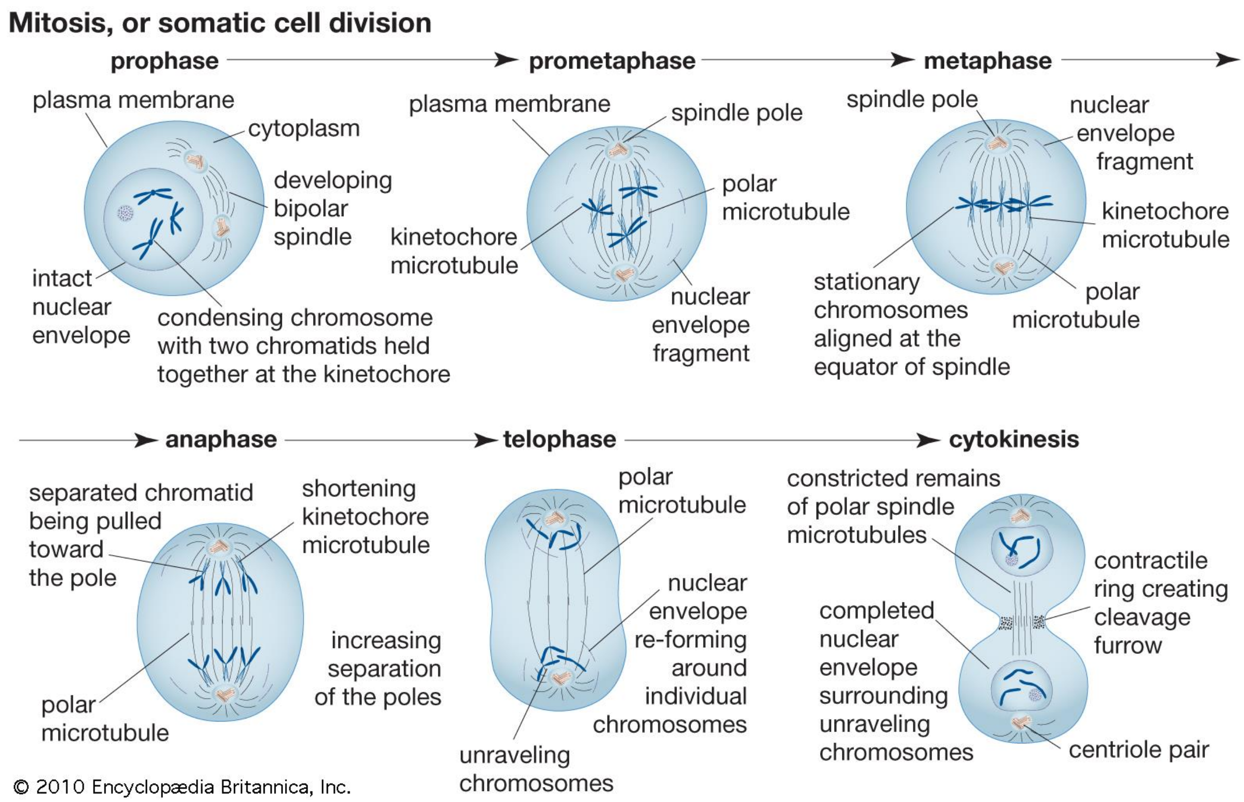
Definition: Mitosis is the type of cell division that results in two daughter cells each having the same number and kind of chromosomes as the parent nucleus, typical of ordinary tissue growth.

Introduction

The term "mitosis", coined by Walther Flemming in 1882, is derived from the Greek word (*mitos*, "warp thread").There are some alternative names for the process, e.g., "karyokinesis" (nuclear division), a term introduced by Schleicher in 1878, or "equational division", proposed by August Weismann in 1887.

Today, mitosis is understood to involve **five** phases, based on the physical state of the chromosomes and spindle. These phases are prophase, prometaphase, metaphase, anaphase, and telophase. Cytokinesis is the final physical cell division that follows telophase, and is therefore sometimes considered a sixth phase of mitosis. All phases of mitosis, as well as the flanking periods of interphase and cytokinesis before and after, are shown in Figure. Researchers' biochemical understanding of mitotic phases has greatly increased in recent years, revealing that this highly orchestrated process involves hundreds, if not thousands, of cellular proteins.

- Mitosis is a crucial process that happens in the body continually to replace damaged or dead cells. For example, the skin will entirely replace itself every 28 days. The dead and damaged cells will be lost from the skin, and replaced by cells created from mitosis.



Stages of Mitosis

Prophase

This is the first stage of mitosis. Firstly during prophase there is a process known as **chromosome condensation**. During DNA replication the genetic material is loosely packed as chromatin. For mitosis however, the DNA needs to be more tightly packed to allow for easier separation in anaphase. At the start of prophase, chromatin begins condensing into chromosomes. Each chromosome being made of two genetically identical chromatids, joined by a centromere.

In addition, mitotic spindles begin to form. Mitotic spindles are structures made from **microtubules** that aid in the organisation and arrangement of chromosomes. The spindles originate from an organelle known as the **centrosome**. Each cell in mitosis has two centrosomes. During prophase the centrosomes begin to move apart in opposite directions.

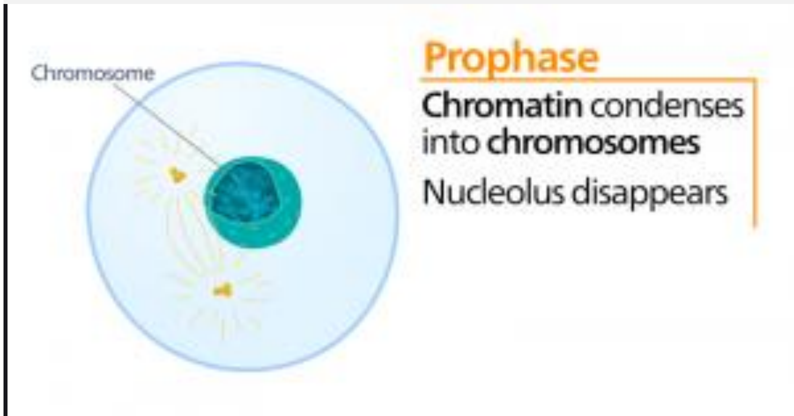


Fig 2 – Prophase

Prometaphase

In this stage the chromosomes finish condensing into their compact state. The nuclear envelope begins to breakdown, allowing the mitotic spindles to attach to the chromosomes. The breakdown of the nuclear membrane is an essential step for spindle assembly. Because the centrosomes are located outside the nucleus in animal cells, the microtubules of the developing spindle do not have access to the chromosomes until the nuclear membrane breaks apart.

Prometaphase is an extremely dynamic part of the cell cycle. Microtubules rapidly assemble and disassemble as they grow out of the centrosomes, seeking out attachment sites at chromosome kinetochores, which are complex platelike structures that assemble during prometaphase on one face of each sister chromatid at its centromere. The mitotic spindles attach at a site called the **kinetochore**. The kinetochore is an area of the centromere on each sister chromatid. The sister chromatids are attached to spindles that originate from the opposite centrosome

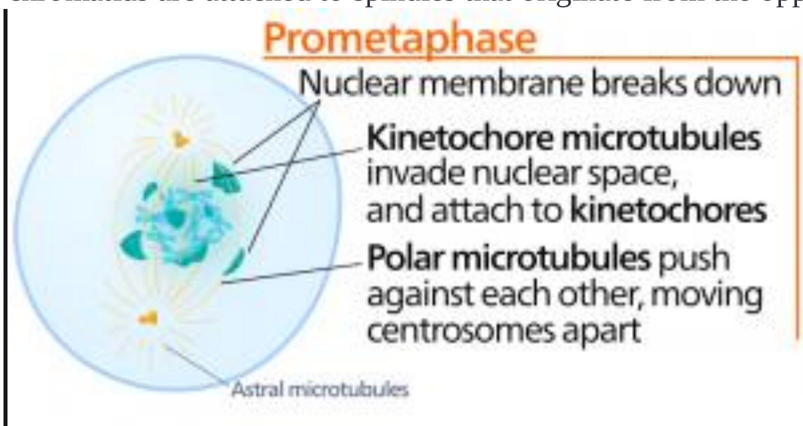


Fig 3 – Prometaphase

Metaphase

At this stage, the chromosomes align upon a theoretical line known as the **metaphase plate**. Furthermore the centrosomes have both now orientated themselves to opposite ends of the cell. Importantly at this stage the cell will check that all the chromosomes are aligned along the metaphase plate, with their kinetochores correctly attached. This helps to ensure sister chromatids are split evenly between the two daughter cells. An error in alignment or in a spindle attachment will result in the cell halting further progress until the problem is fixed.

Metaphase is particularly useful in cytogenetics, because chromosomes can be most easily visualized at this stage. Furthermore, cells can be experimentally arrested at metaphase with mitotic poisons such as colchicine. Video microscopy shows that chromosomes temporarily stop moving during metaphase. A complex checkpoint mechanism determines whether the spindle is properly assembled, and for the most part, only cells with correctly assembled spindles enter anaphase.

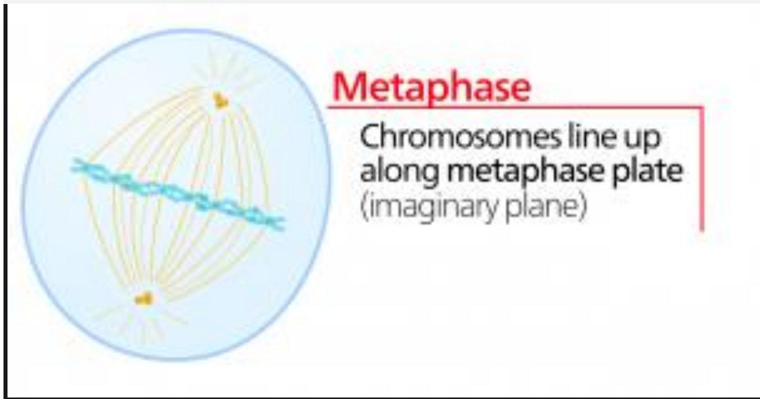


Fig 4 – Metaphase

Anaphase

Anaphase is the critical phase of mitosis. During this stage the **sister chromatids** are pulled to opposite ends of the cell. The spindle fibres decrease in length, breaking the chromatids at the centromere. To add to this spindle fibres not attached to chromatids will elongate the cell to prepare the cell for division. Two separate classes of movements occur during anaphase. During the first part of anaphase, the kinetochore microtubules shorten, and the chromosomes move toward the spindle poles. During the second part of anaphase, the spindle poles separate as the non-kinetochore microtubules move past each other. These latter movements are currently thought to be catalyzed by motor proteins that connect microtubules with opposite polarity and then "walk" toward the end of the microtubules.

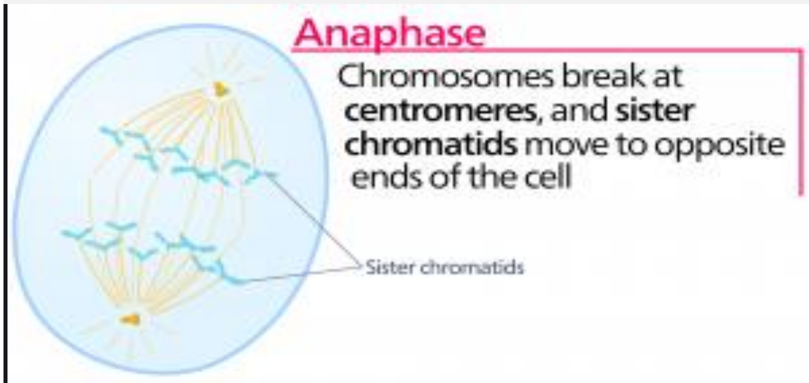


Fig 5 – Anaphase

Telophase

In this phase the cell has elongated and is nearly finished dividing. Cell-like features begin to reappear such as **reformation o**f two nuclei (one for each cell). The chromosomes decondense and the mitotic spindles fibres are broken down.

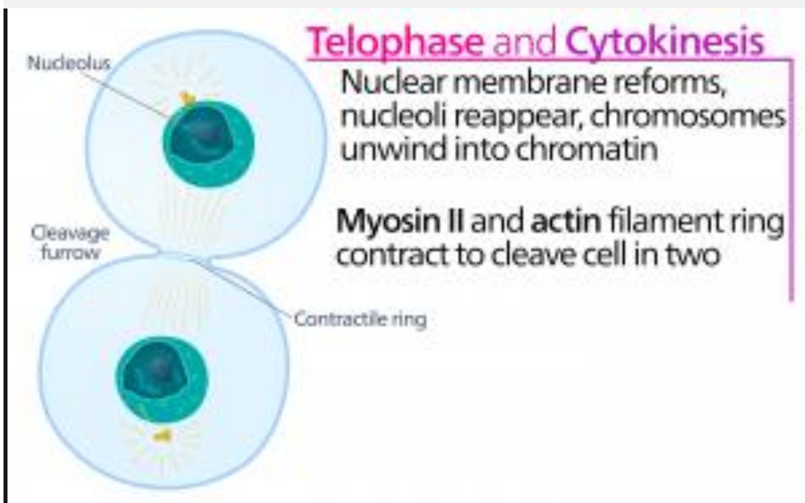


Fig 6 – Telophase & Cytokinesis

Cytokinesis

This is the division of the cytoplasm to form two new cells. This stage actually begins in either anaphase or telophase however it doesn't finish until after telophase. To separate the two cells, a ring of protein (actin ring) pinches the cytoplasm along a crease **(cleavage furrow)**. This splits the cytoplasm equally between the two cells.

Mitotic Apparatus

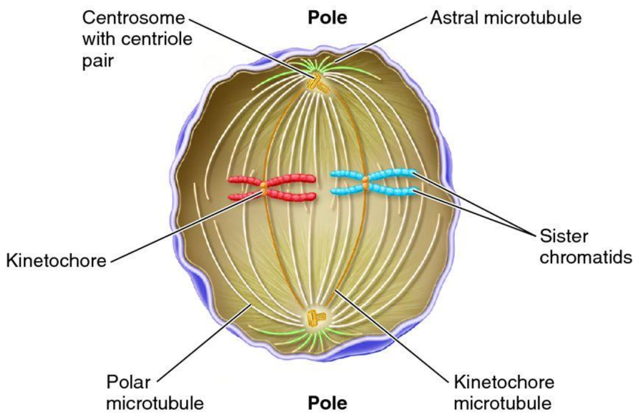
The mitotic apparatus is a structure that

- (a) **creates a framework forcing the separation of the genetic material** – thus separating the chromatids from a doublet form chromosome into the singlet form and
- (b) **helps elongate the cell** so that it is longer and larger for the purpose of giving each new cell a great deal of cytoplasm and organelles.
- The mitotic apparatus is composed of 4 sets microtubules –termed fibers. Each set of microtubules is performing different functions.
  - (1) **Centrioles**
  - (2) **Kinetochore Fibers** (old name chromosomal fibers
  - (3) **Polar Fibers**
  - (4) **Aster Fibers** (also termed Aster rays)

Spindle microtubules: There are two sets of microtubules from spindle. The two spindle microtubules are

1. **Kinetochore microtubule:** These microtubules attach to chromosomes at kinetochore.
2. **Polar microtubules:** They do not interact with the chromosomes. Polar microtubules are arranged from the opposite pole.

Function of mitotic apparatus: The spindles of the mitotic apparatus are larger than the nucleus. These microtubules are used to attach and capture chromosomes. So they align the chromosomes and finally separating them in such a way that equal distribution of chromosomes take place



Function of Mitosis

- Increase in number of cells leading to growth
- Repair of damaged tissues
- Asexual reproduction in some animals like amoeba.
- Vegetative reproduction in plants.
- Cell division also keeps cells small.
- In sexual reproduction, the first stages of gametogenesis (spermatogenesis and oogenesis) involve mitosis in order to increase the number of cells that will go into meiosis.
- A negative side to cell division is that uncontrollable mitosis results in cancer or tumors.