

# Compartmentalization of Metabolic Pathways (FBLT)

## Under construction / Forgotten

This article was marked by its author as *Under construction*, but the last edit is older than 30 days. If you want to edit this page, please try to contact its author first (you will find him in the history ([https://www.wikilectures.eu/index.php?title=Compartmentalization\\_of\\_Metabolic\\_Pathways\\_\(FBLT\)&action=history](https://www.wikilectures.eu/index.php?title=Compartmentalization_of_Metabolic_Pathways_(FBLT)&action=history))). Watch the page as well. If the author will not continue in work, remove the template `{{Under construction}}` and the page.

Last update: Wednesday, 30 Nov 2022 at 4.22 pm.

This article has been translated from WikiSkripta; ready for the **editor's review**.

## Subchapter content

1. Meaning of compartmentation for the cell
2. Biological membranes
3. Selective transport
4. Intracellular transport
5. Compartmentation of tracks

## Significance of compartmentation for the cell

All reactions taking place in cells take place in a certain space - a compartment, which is separated from other compartments by semipermeable membranes. In this way, even chemically diverse environments are separated, which helps to optimize the course of chemical reactions in them. Enzymes catalyzing individual reactions often have different temperature and pH optima, and if there is only one space in the cell, some of the enzymes would probably not be functional or the catalysis mediated by them would not be efficient enough. By dividing the space, optimal conditions can be created for the course of individual enzymatically catalyzed reactions. At the same time, the cell itself is also protected from the activity of lytic enzymes. For example, by confining cellular digestion to lysosomes, unwanted self-digestion of cellular structures becomes impossible. A frequent phenomenon related to the disruption of cell compartmentation (e.g. spilling out of the contents of lysosomes or mitochondria) is necrosis or activation of apoptosis - programmed cell death. The separation of the environment also affects the regulation of metabolic pathways. The latter can be more precise and targeted and does not interfere with the operation of pathways running in other compartments. Sometimes the course of reactions can be regulated already at the point of entry of individual substrates into the compartment (transfer through the membrane, often mediated by transport mechanisms). However, compartmentalization also places increased demands on the energy consumption of the cell. It is necessary to use ATP-dependent transporters transporting substances through membranes against the concentration gradient and thus creating different environments in separate spaces.

## Biological Membranes

### Architecture

The basic architecture of the approximately 6-10 nm thick cytoplasmic membrane is a phospholipid bilayer permeated by proteins and cholesterol. Carbohydrates can be attached to both proteins and phospholipids, which form glycolipids and glycoproteins. This basic structure, altered to varying degrees in the membranes of individual organelles, affects the physico-chemical properties of the membranes (especially their permeability) closely related to the function and course of biochemical processes in the relevant organelle.

An example can be the myelin sheath of neurons, in which the ratio of proteins to lipids is 19%: 81% (which causes their excellent insulating properties) or the inner membrane of mitochondria, in which the ratio turns in favor of proteins 76%: 24% (and is related to its considerable impermeability even for substances that normally pass through membranes).

Phospholipid molecules form two physically distinct parts:

#### 1. Polar (hydrophilic) part

The polar part is made up of a phosphate group, or groups attached to it - this part faces the aqueous environment (or another polar solvent).

## 2. Non-polar (hydrophobic) part

The non-polar part is formed by MK chains facing each other, thus forming the hydrophobic core of the membrane. It is precisely on the basis of hydrophobic interactions that phospholipids tend to aggregate and form membranes.

The phospholipid molecule therefore contains both polar and non-polar parts, it is a so-called amphipathic molecule.

### Historical correlation

A currently used model describing the structure of biological membranes was created in 1972 by SJ Singer and GL Nicolson. According to this fluid mosaic model, membranes can be considered as a form of 2-dimensional liquid in which phospholipid and protein molecules diffuse to varying degrees.

The mobility of phospholipids is much higher than the mobility of other membrane components. Therefore, the places in which proteins or cholesterol are embedded in the membrane show lower lateral mobility and thus stabilize the membrane (this applies especially to cholesterol). Parts of the membrane made up mainly of lipids can sometimes flip to the opposite side by a so-called *flip-flop mechanism*.

### The fluidity of the membrane depends mainly on:

1. **Temperature** - at higher temperatures, the membrane is more mobile, the so-called *gel phase*, at lower temperatures it is stiffer, the so-called *sol phase*
2. **The proportion of unsaturated MK - the higher their content, the more mobile the membrane (gel phase).**

Proteins form the basic component of cell membranes. According to their storage in the membrane, we divide them into peripheral and integral.

- **Peripheral proteins** do not penetrate into the hydrophobic core of the membrane, they only bind to its surface (from the extra- or intracellular side), and therefore can be separated from the membrane without damaging it. The interactions involved in bonds are primarily electrostatic forces and hydrogen bonds.
- **Integral proteins** penetrate the membrane, either through its entire thickness – so-called transmembrane proteins – or to varying depths. Separation of these proteins from the membrane is associated with disruption of its integrity

### Proteins fulfill the function of biological membranes:

- receptor.
- transportation.
- enzymatic.

**Cholesterol** makes up about one quarter of all the lipids in the membrane. The cholesterol molecule, like the phospholipid molecule, has an amphipathic character due to the OH- group attached to the third carbon. The basic function of cholesterol in the membranes of animal cells is their **stabilization** and **reduction of fluidity**.

## Properties of biological membranes

The permeability of the membrane (which expresses the rate of passive diffusion of particles through the membrane), is based on the Fick's law of diffusion and depends on several factors:

1. **Size and polarity of the permeating molecule** – small and non-polar molecules cross the membrane easily, while larger and polar molecules usually need transporters or channels.
2. **Concentration gradient** – the higher the concentration of a substance on one side of the membrane, the greater the **tendency for it to penetrate** to the opposite side. This rule also applies to other gradients – such as electrochemical (given by the difference in charges on both sides of the membrane) or osmotic (given by the difference in osmotically active particles on both sides of the membrane).
3. **Membrane thickness** – the thicker the membrane, the slower substances pass through it.
4. **Membrane area** – a larger amount of substance can pass through a larger area of the membrane per unit of time.

Other properties of membranes include the degree of thermal and electrical insulation, electrical charge. The overall charge of the cytoplasmic membrane is **negative** – it is primarily due to negative sialic acid residues in glycolipids and glycoproteins. Membranes have the ability of **selective transport**.

## Selective Transport

Selective transport can be divided into:

1. Passive transport
2. Active transport
3. Permeation of macromolecules

This diagram shows the transport of substances across the blood-brain barrier (blood-brain barrier - the barrier between blood and nervous tissue) as an example:

## Passive transport

It takes place **without energy consumption**, based on the physical principle of diffusion, only using the concentration gradient of the substance between both sides of the membrane. Without the existence of a gradient, passive transport stops. We distinguish two basic types of passive transport – simple and facilitated diffusion..

### simple diffusion

It is the transfer of substances through the membrane without the help of transport proteins. Substances must pass through the hydrophobic center of the membrane, and therefore this type of transport is particularly typical for:

- small non-polar molecules – gases ( $\text{CO}_2$ ,  $\text{O}_2$ , ...);
- small polar molecules – water, Urea;
- larger non-polar molecules – MK, cholesterol, Fat-soluble vitamins .

Hydrophilic and larger molecules (especially with  $M_r > 200$ ) undergo simple diffusion only very slowly, or almost not at all. The transport of ions, whose molecules are relatively small, is mainly prevented by the bulky **hydration shell** formed by water molecules.

### Facilitated (facilitated) diffusion

This is passive transport with the help of **transport proteins**, to which the transferred molecule is non-covalently bound and through which it is transferred to the other side of the membrane. Facilitated diffusion takes place faster than simple diffusion and can be associated with the transport of another substance in the opposite direction – the so-called. **antiport**, e.g. ATP for ADP,  $\text{Cl}^-$  for  $\text{HCO}_3^-$ ). There is also the possibility of transport through a **tunnel protein** passing through the entire thickness of the membrane. During transfer, its conformation changes. Some channels can be controlled based on changes in membrane potential (voltage-gated channels).

### Diffusion kinetics

The kinetics of simple and facilitated diffusion are different. In simple diffusion, there is a linear increase in the rate of diffusion as the concentration of the transported substance increases. Carrier proteins of facilitated diffusion have a limited capacity (it is determined by their total number in the membrane) and at high concentrations of the substance, the rate of diffusion slows down until it stabilizes at the maximum speed at which the carrier proteins are fully saturated.

náhled|GLUT 2 (<https://www.wikiskripta.eu/index.php?curid=59490#/media/Soubor:Kapitola-09-03-07.jpg>)

### GLUT transporter

The most important examples of facilitated diffusion include glucose transport via **GLUT** transporters (Glucose transporters). The continuous existence of a concentration gradient for glucose is ensured by its intracellular conversion to **glucose-6-phosphate** and its subsequent use in metabolic pathways. In total, there are up to seven types of GLUT transporters. We will mention only some of them in more detail:

1. **GLUT 1 and 3** serve to maintain basal glucose uptake by tissues whose metabolism is **dependent on glucose**, e.g. brain, erythrocytes, but also kidneys and placenta.
2. **GLUT 2** located on the membrane of  **$\beta$ -cells of the pancreas** and **hepatocytes** also enables the transfer of glucose from the absorptive epithelia (proximal tubule of the kidney, enterocytes of the intestine) into the blood.
3. **GLUT 4** is a glucose transporter in so-called **insulin-dependent tissues** (skeletal muscle, myocardium and adipose tissue). Its exposure on the membrane is conditioned by the presence of higher levels of insulin in the blood. This happens especially after a meal, when the mentioned tissues are responsible for the metabolism of up to 80% of glucose from the blood. In the period between meals, on the contrary, they do not absorb it and save it for tissues dependent on it.

## Active transport

It can also take place **against a concentration and electrochemical gradient**. In this case, the transport is coupled with the **hydrolysis of ATP**  $\rightarrow$  ADP and  $\text{P}_i$  and the released energy is **used for transport**. We distinguish between two basic types of active transport:

1. Primary active transport
2. Secondary active transport

náhled|vpravo|Na<sup>+</sup>/K<sup>+</sup>-ATPáza – animace (<https://www.wikiskripta.eu/index.php?curid=59490#/media/Soubor:AP.gif>)

## Primary active transport

ATP energy is used **directly to transfer the relevant substance** across the membrane. Examples include **Na<sup>+</sup>/K<sup>+</sup>-ATPáza**, **H<sup>+</sup>/K<sup>+</sup>-ATPáza** and **Ca<sup>2+</sup>-ATPáza**.

### Na<sup>+</sup>/K<sup>+</sup>-ATPáza

It is a tetramer composed of **two alfa** and **two beta subunits**. Alpha subunits penetrate the entire width of the membrane, intracellularly have **abinding site for Na<sup>+</sup>** and extracellularly for **K<sup>+</sup>**. Unlike them, beta subunits are glycosylated and are not transmembrane (they are turned by their oligosaccharide chains towards the extracellular space).

The enzyme can be present in two different conformations depending on whether it is phosphorylated or not. Na<sup>+</sup>/K<sup>+</sup>-ATPáza functions as an **antiport** and **when ATP is consumed, it transports 3 Na<sup>+</sup> cations out of the cell in and 2 cations K<sup>+</sup> into the cell**. In this way, it creates an uneven distribution of ions on the membrane, which is the basis of the **resting membrane potential**. Na<sup>+</sup>/K<sup>+</sup>-ATPáza je **ubiquitous** – it is most likely found on all cells of the human body.

### H<sup>+</sup>/K<sup>+</sup>-ATPáza

It is an antiport functioning similarly to Na<sup>+</sup>/K<sup>+</sup>-ATPáza, it is localized in the **parietal cells of the stomach**, where it participates in the formation of gastric juice, and in the **proximal tubules of the kidneys**. **transfers one H<sup>+</sup> ion out of the cytoplasm in exchange for one K<sup>+</sup> ion**.

### Ca<sup>2+</sup>-ATPáza

It is a calcium pump that occurs most in muscle and nerve cells. It actively pumps calcium ions out of the cytoplasm, either into the **sarcoplasmic reticulum** či **extracellularly**. In the muscles, it makes it possible to reduce the concentration of Ca<sup>2+</sup> to the level before contraction.

==== Secondary active transport (secondary active transport or cotransport)====

in case of ATP is used not directly during the transfer of the relevant substance (e.g. glucose), but to transfer another substance (e.g. sodium cation), for which a concentration or electrochemical **gradient** is created in the cell. This is the engine for the transfer of the relevant substance (glucose) using its transporters (Sodium Glucose Transporter - SGLT). A transporter carrying out secondary active transport (SGLT) therefore moves at least **two particles** – one that is to be transported (glucose), and one that drives this transport (Na<sup>+</sup>) – or for which there is a gradient in the cell.

In order to maintain this gradient, a **second transporter** (např. Na<sup>+</sup>/K<sup>+</sup>-ATPáza), is required, which can also be located on another part of the membrane. This second transporter is where **energy** (ATP) is consumed – hence active transport. In parentheses is an example of secondary active transport of glucose driven by a sodium cation gradient through the **Sodium Glucose Transporter**, the gradient for Na<sup>+</sup> is created by the Na<sup>+</sup>/K<sup>+</sup>-ATPáza. According to the direction of transport, we distinguish between **symport** (both particles are transported in the same direction – e.g. into the cell) and **antiport** (the particles are transferred in the opposite direction – one into the cell and one out of the cell). **SGLT performs the symport of glucose and Na<sup>+</sup>**.

**The existence of tertiary active transport** also works on a similar principle ..

## Permeation of macromolecules through the membrane

It can be by direction:

1. **Exocytosis**: the process by which macromolecules leave the cell. During exocytosis, the membrane of the transport vesicle and the cytoplasmic membrane fuse, and macromolecules can either be released into the intercellular space or remain part of the cell surface.
2. **Endocytosis**: the process by which macromolecules are taken up by a cell. The cytoplasmic membrane invaginates into the cell until a transport vesicle is formed. According to the chemical nature of the transferred molecules, these are:
  - **Pinocytosis**: transfer of macromolecules in the form of a solution. The process can be non-selective (the site of invagination on the cell surface is random) or selective (at the site of specific surface receptors).
  - **Phagocytosis**: ingestion of large particles, which the cell first wraps around protrusions of the cytoplasmic membrane (pseudopodie) and then forms a vacuole around them.

## Intracellular transport

Intracellular transport can occur through:

1. **Diffusion** – substances dissolved in the aqueous environment of the cytosol
2. **Transport by secretory vesicles** – typically, proteins formed by the rough ER are first moved to the GA , and secretory vesicles or lysosomes are then separated from it . Transport motor proteins (dynein and kinesin) participate in the transport of secretory vesicles, which move along the surface of microtubules (dynein towards – and kinesin towards + ends) when ATP is consumed.

</noinclude>

## Orbital Compartmentation

Orbital Compartmentation