MEDICAL UNIVERSITY - PLEVEN
FACULTY OF MEDICINE
DEVISION OF PHYSICS AND BIOPHYSICS

Lecture № 10

TRANSPORT OF MATTER ACROSS CELL MEMBRANES

Prof. M. Alexsandrova, DSc

1. Transport classification

Depending on the transport mechanism

Nonmediated and *Mediated* transport

- occurs through simple diffusion

- occurs through the action of specific carrier proteins.

The driving force for the nonmediated flow of a substance through a medium is its chemical potential gradient.

The substance diffuses in the direction that eliminates its concentration gradient, at a rate proportional to the magnitude of this gradient. The rate of diffusion of a substance also depends on its solubility in the membrane's nonpolar core.

Depending on the type of energy supply

Passive transport in which a specific molecule flows from high concentration to low concentration.

Three distinctive types of passive transport are recognised in biological systems:

- simple diffusion;
- osmosis and hydrostatic pressure driven flow;
- facilitated diffusion.

Active transport, in which a specific molecule is transported from low concentration to high concentration, i.e. against its concentration gradient. Such an endergonic process must be coupled to a sufficiently exergonic process to make it favourable (dG <0).

1. *Primary active transport* – directly powered by the chemical reaction (like ATP hydrolysis). Sodium-potassium pump is a known example of primary active transport.

2. *Secondary active transport* – coupled with primary active transport. Transport of glucose from the intestine lumen into the epithelial cells is an example of such a transport.

Depending on the number of transported species and direction of their translocation

Uniport – transport of one substance in one direction.

Joint transport – simultaneous transport of two or more substances by one transport system

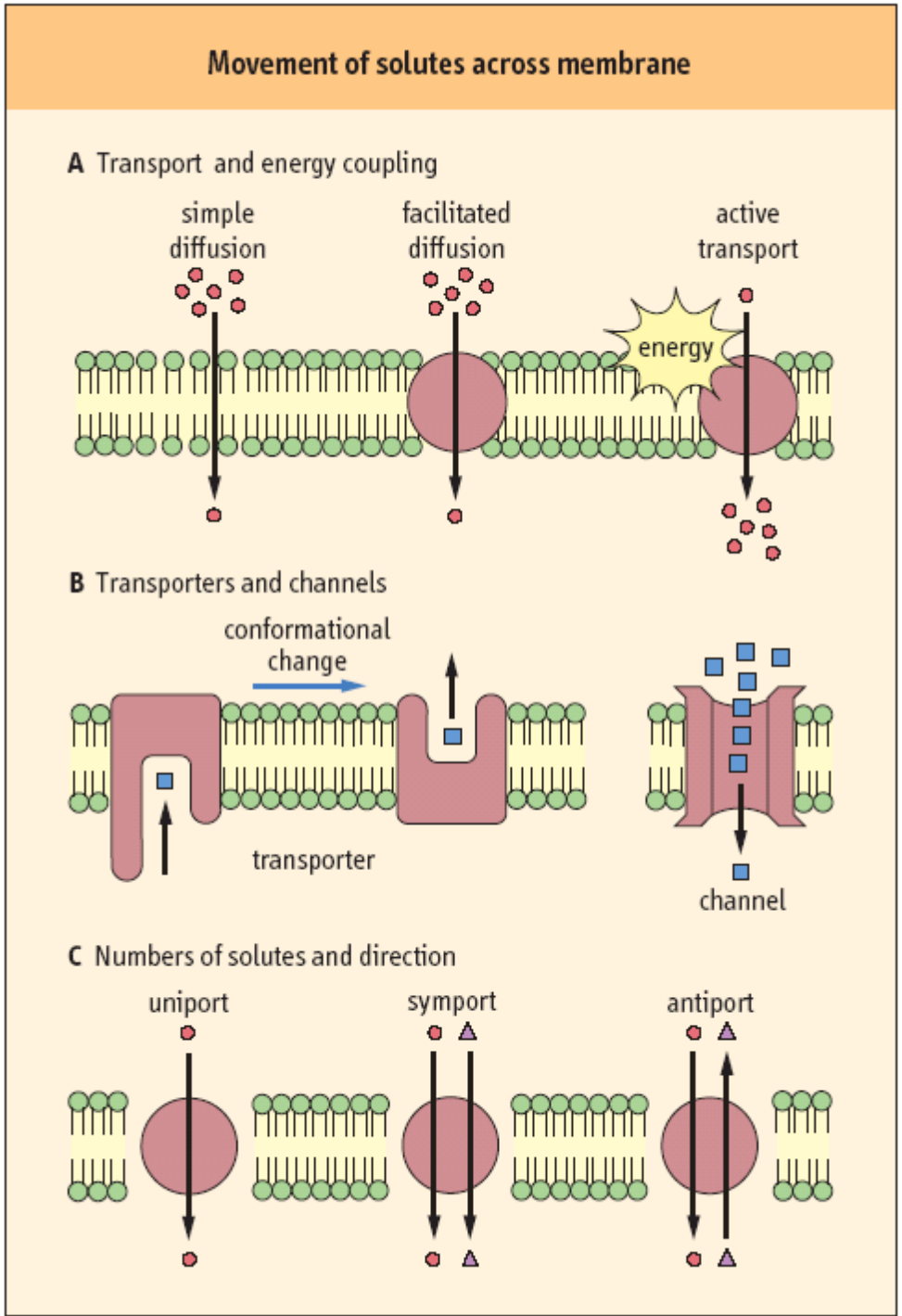
if in the same direction - symport

if in the opposite directions - antiport

The movement of one substrate uphill can be driven by the movement of another substrate (usually a cation such as Na^+ or H^+) down a gradient. Uniport of charged substrates may also be electrophoretically driven by the membrane potential of the cell. The proteins participating in these transport systems are termed uniporters, symporters, and antiporters, respectively.

Uniport, symport, and antiport are alternative mechanisms of facilitated transport.

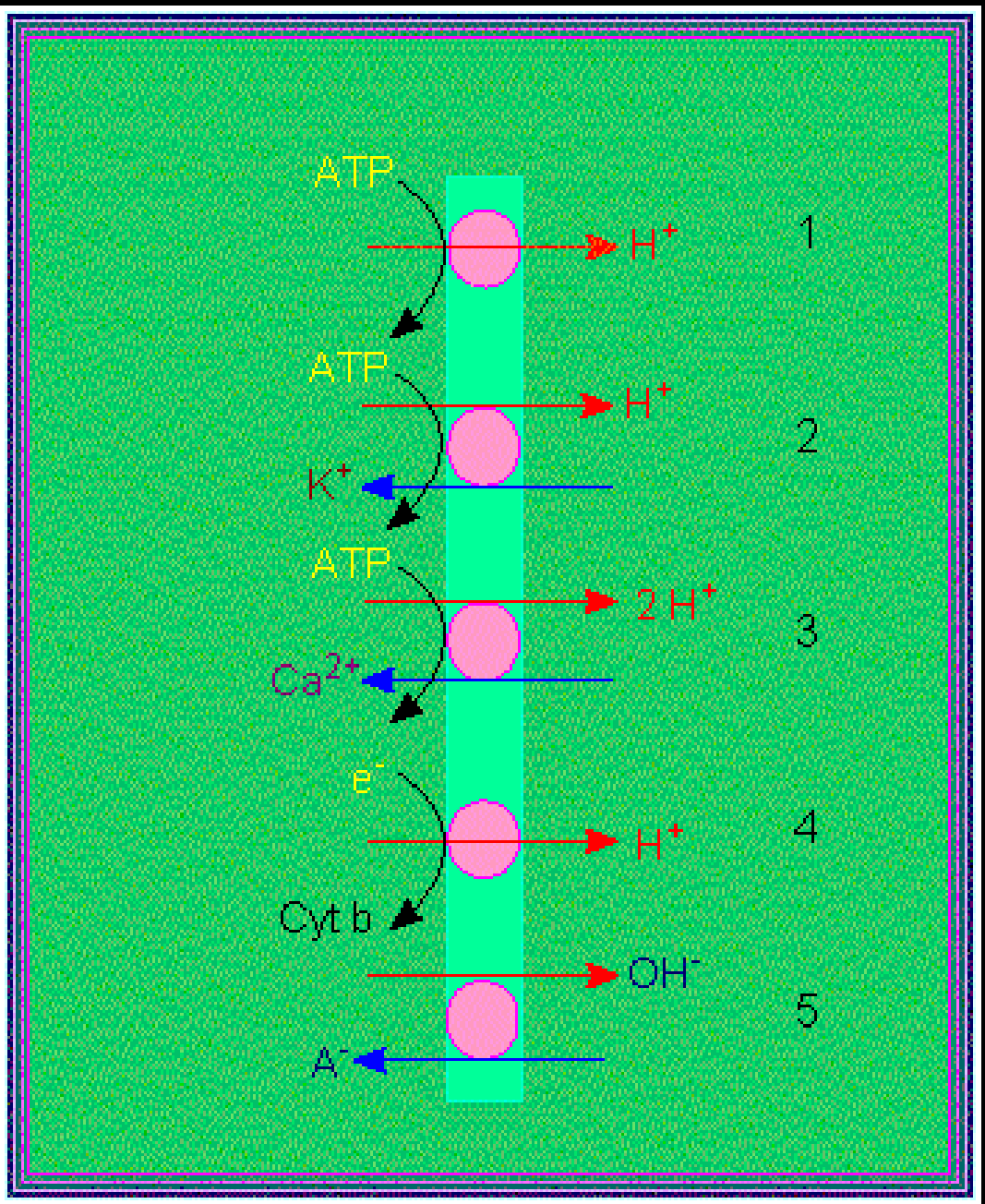
Movement of solutes across membrane



Depending on the changes produced in the transmembrane electric voltage

ELECTRONEUTRAL TRANSPORT – it does not change the value of the transmembrane potential ($1Na^+$ and $1Cl^-$ in one direction or $1Na^+$ and $1K^+$ in opposite directions).

ELECTROGENIC TRANSPORT – it changes the membrane potential. For example charged particles of the same magnitude and sign of the charge are transported in one direction or charged particles of the different magnitude and same sign of the charge are transported in opposite direction ($3Na^+$ against $2K^+$).

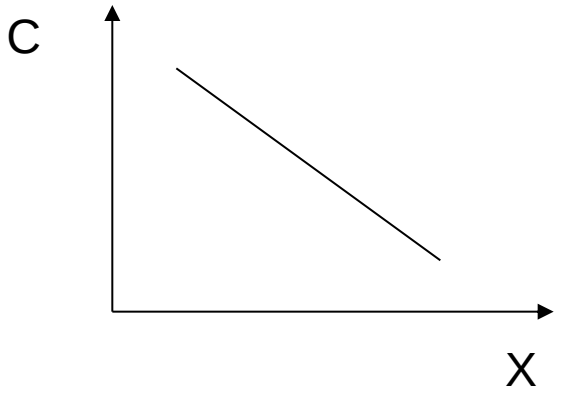


Proton pumps:

1. electrogenic pump
2. electroneutral pump
3. **3.** electroneutral pump with calcium as its counterion
4. **4.** electrogenic proton transport
5. **5.** electroneutral anion / OH antiport

Free diffusion of non-charged particles

$$J = -D\frac{dc}{dx}$$



Uniform medium

Einstein in 1905 showed that diffusion coefficient (D) and mobility (u) can be related by:

D = uRT, where T is absolute temperature and u is particle mobility.

V=u F (u is a coefficient of proportionality which can be defined as the velocity of molecule per unit force). Thus Fick's law can be rewritten in the following way:

$$J = -uRT\frac{dc}{dx}$$

Free diffusion of charged particles (Drift)

It is also called electrophoresis. It is the movement of electrically charged particles in electric fields.

$$J = -cuFz\frac{d\varphi}{dx}$$

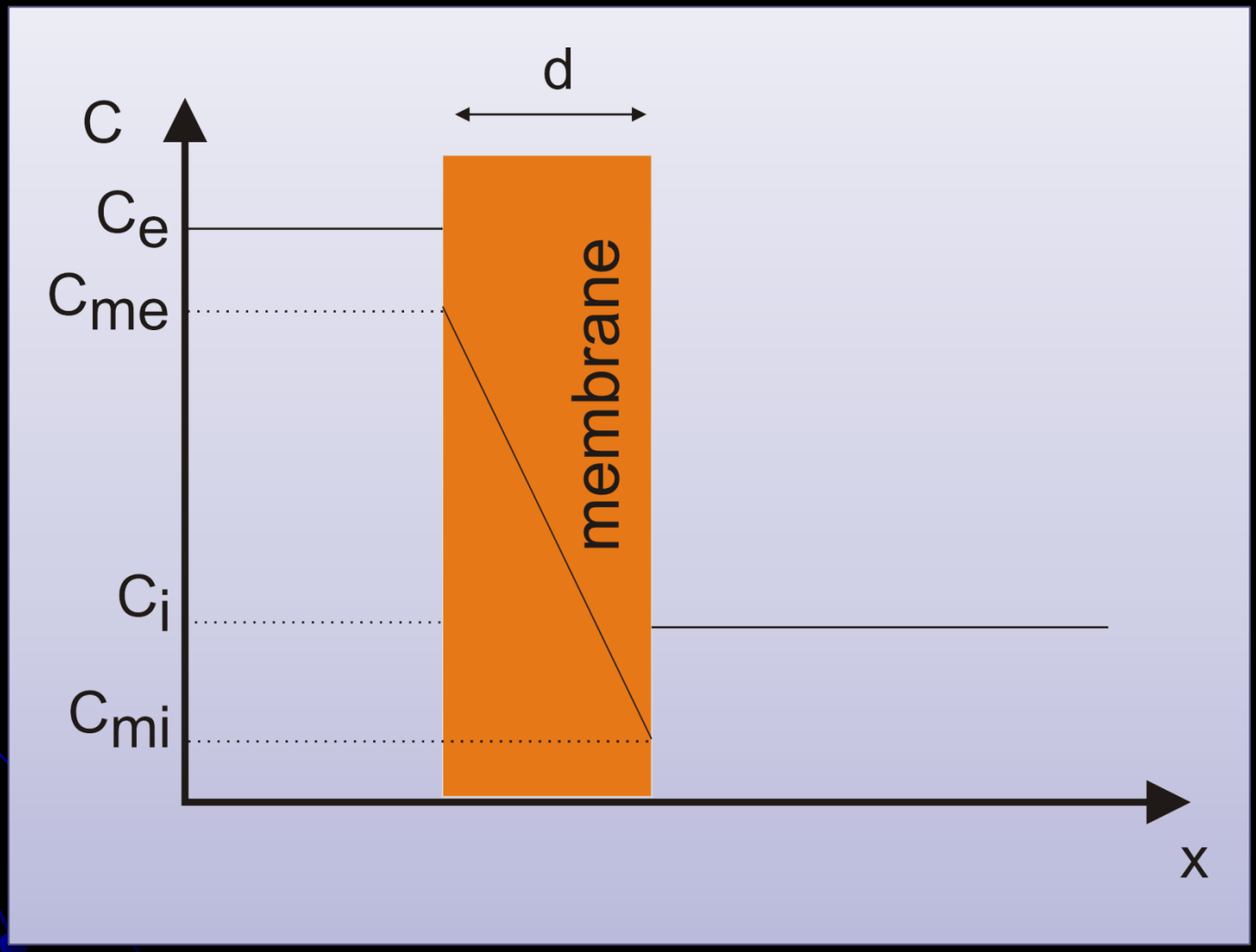
$$J = -uRT\frac{dc}{dx} - cuFz\frac{d\varphi}{dx}$$

Nernst-Planck molar flux equation

Permeability

$$P = \frac{Dk}{d}$$

is called the membrane permeability.



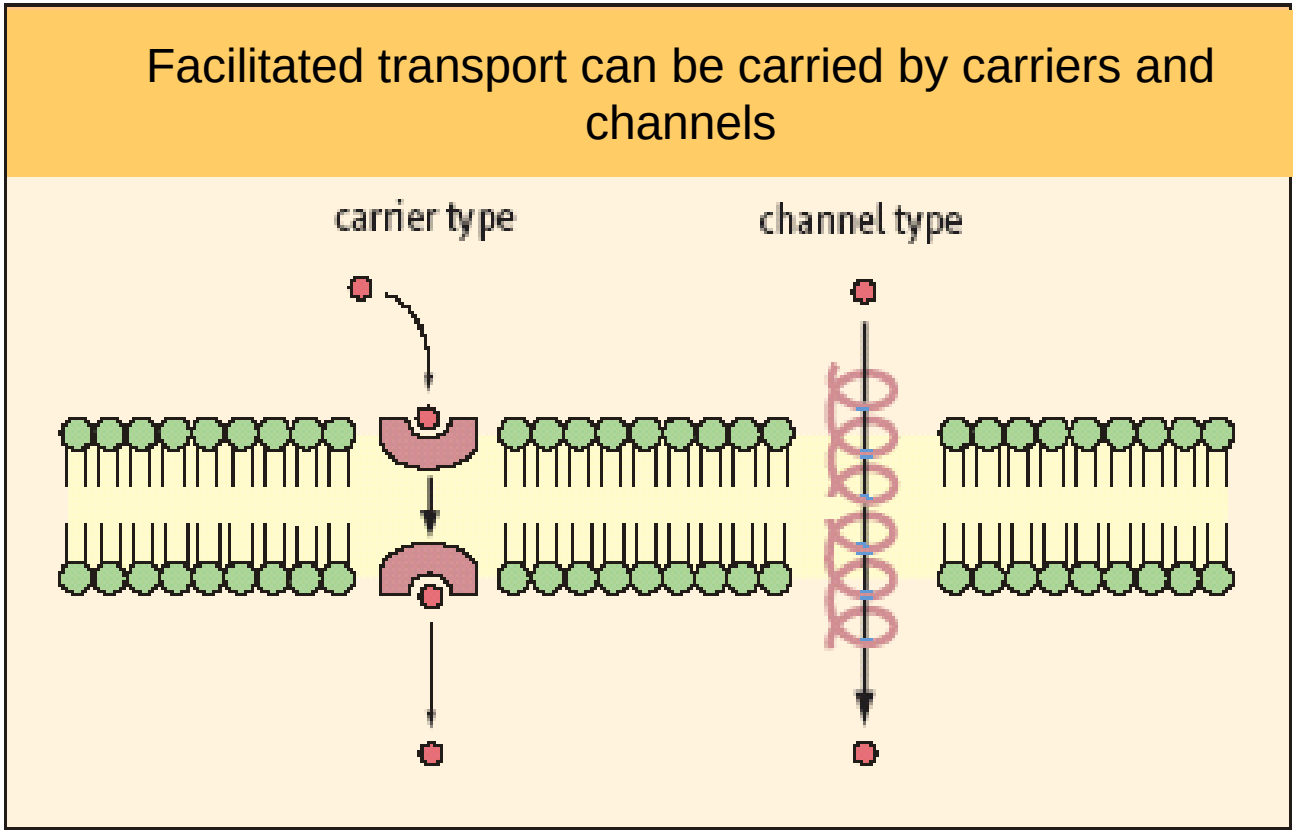
Facilitated Diffusion

1. Transport by carrier proteins

Transport of larger, polar molecules into a cell requires the involvement of membrane proteins known as transporters or carrier proteins.

The term ‘carrier’ is also applied to ionophores, which move passively across the membrane together with the bound ion. Transporters are as specific for their substrates as the enzymes and work by one of two mechanisms: facilitated diffusion or active transport.

Facilitated diffusion catalyzes the movement of a substrate through a membrane down a concentration gradient and does not require external energy.



Mobile carriers and channel-forming transporters

They permit net movement of molecules only down their electrochemical gradients.

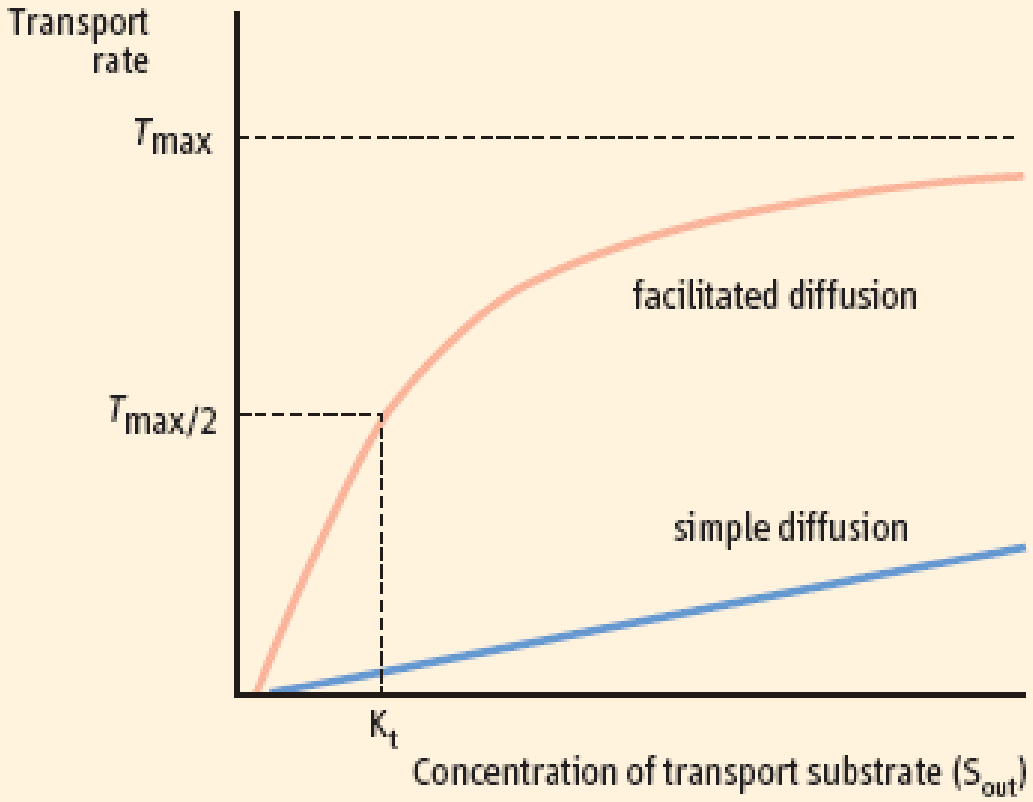
Saturability and specificity are important characteristics of the membrane transport systems.

The rate of facilitated diffusion is generally much greater than that of simple diffusion: transport proteins catalyze the transport process.

In contrast to simple diffusion, in which the rate of transport is directly proportional to the substrate concentration, facilitated diffusion is a saturable process, characterized by a maximum transport rate, T_{max} .

When the concentration of transport substrates becomes very high, T_{max} is achieved by saturation of the transporter proteins with substrate. The kinetics of facilitated diffusion for substrates can be described by the same equations that are used for enzyme catalysis.

Transport kinetics of facilitated diffusion and simple diffusion



The transport process is usually highly specific: each transporter transports only a single species of molecules or structurally related compounds.

The red blood cell GLUT-1 transporter has a high affinity for D-glucose, but 10–20 times lower affinity for the related sugars, D-mannose and D-galactose. L-glucose is not transported; its affinity is more than 1000 times less than that of the D-form.

Transport by channels and pores

The speed of facilitated transport is limited by the number of protein channels available, whereas the speed of diffusion depends only on the concentration gradient.

Channels are often pictured as tunnels across the membrane, in which binding sites for ions are accessible from either side of the membrane at the same time. Conformational changes are not required for the translocation of substrates.

However, voltage changes and ligand binding induce conformational changes in channel structure that have the effect of opening or closing the channels – processes known as voltage or ligand 'gating'.

Movement of molecules through channels is fast (10^7–10^8/s) in comparison with the rates achieved by transporters.

The terms ‘channel’ and ‘pore’ are sometimes used interchangeably.

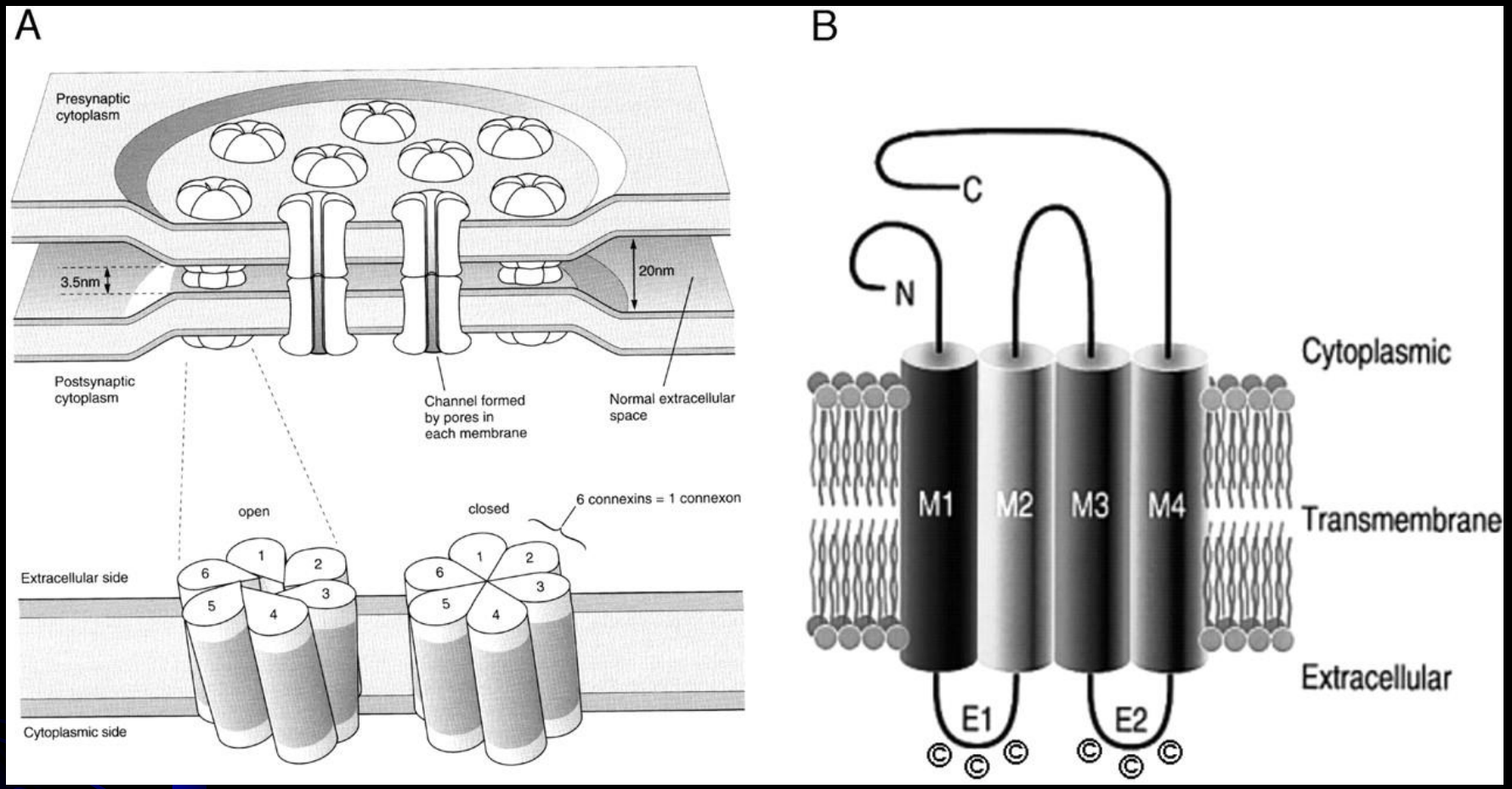
‘Pore’ describes more open, somewhat non-selective structures that discriminate between substrates, e.g. peptides or proteins on the basis of size.

The term ‘channel’ is usually applied to describe more specific ion channels.

Three examples of pores important for cellular physiology

1. The gap junction between endothelial, muscle, and neuronal cells is a cluster of small pores, in which two cylinders of six connexin subunits in plasma membranes join each other to form a pore about 1.2–2.0 nm in diameter. Molecules < 1 kDa can pass between cells through gap junctions.

Such cell–cell communication is important for physiologic coupling, e.g. in the concerted contraction of uterine muscle during labor and delivery. These pores are usually maintained in an open state, but will close when cell membranes are damaged or the metabolic rate is depressed. Mutations of the genes encoding connexin 26 and 32 cause deafness and Charcot–Marie–Tooth disease, respectively.



(A) Schematic drawing of gap junction channels. Each hemi-channel is formed by six protein subunits, called connexins. Six connexin subunits of the hemi-channel may coordinately change configuration to open and close the hemi-channel. Closure is achieved by connexin subunits sliding against each other and tilting at one end, thus rotating at the base in a clockwise direction. The darker shading indicates the portion of the connexon embedded in the membrane (adapted from Ref. [32]).

(B) Topological model of a connexin. The cylinders represent transmembrane domains (M1–M4).

Three examples of pores important for cellular physiology

2. Nuclear pores have a functional radius of about 9 nm (90 Å) through which proteins and nucleic acids enter and leave the nucleus.

3. A third class of pores is important for protein sorting. Mitochondrial proteins encoded by nuclear genes are transported to this organelle through pores in the outer mitochondrial membrane.

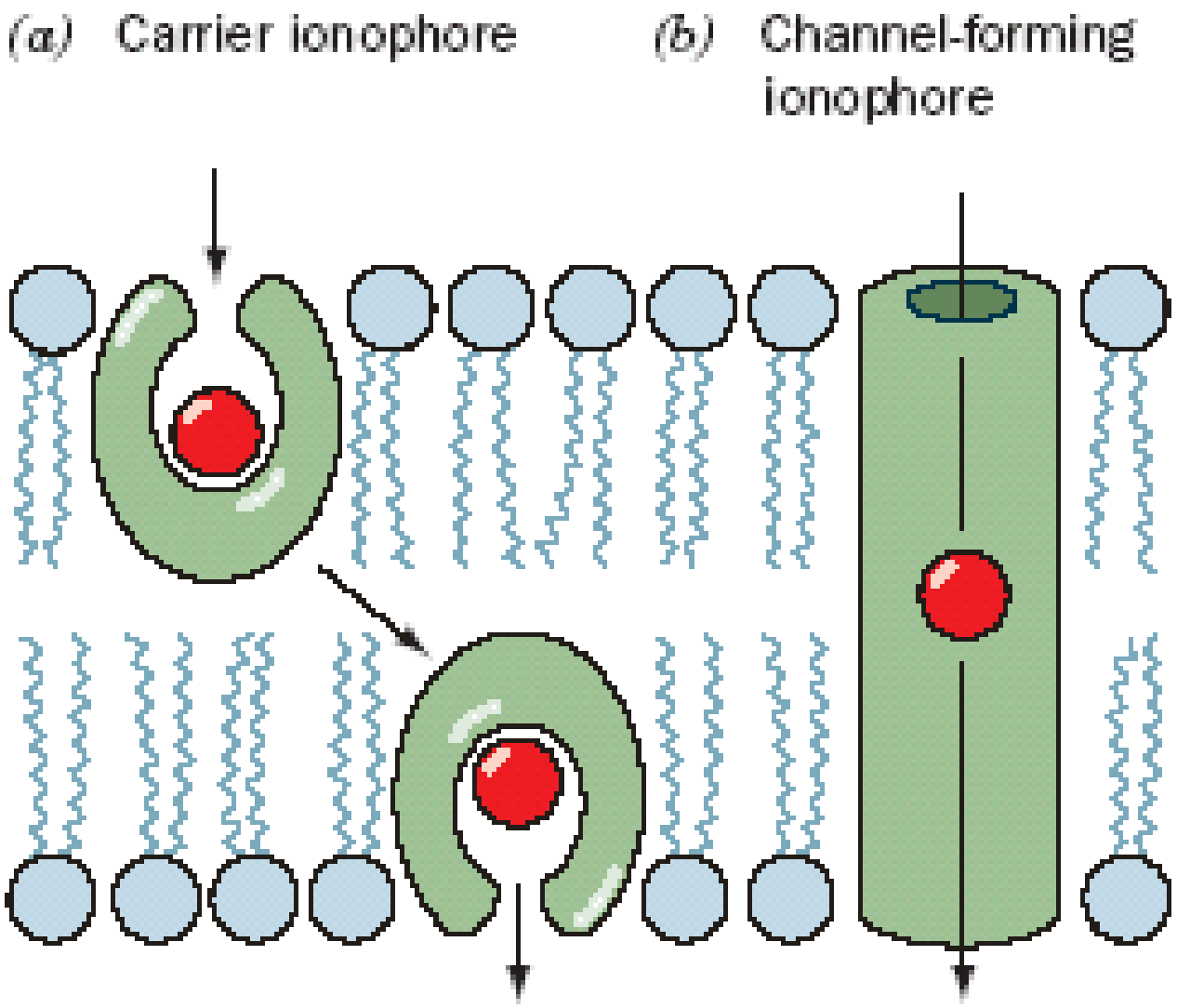
   Nascent polypeptide chains of secretory proteins and plasma membrane proteins also pass through pores in the endoplasmic reticulum membrane.

3. Ionophores

Ionophores are organic molecules of diverse types, often of bacterial origin, that increase the permeability of membranes to ions. These molecules often exert an antibiotic effect by discharging the vital ion concentration gradients that cells actively maintain.

1. ***Carrier ionophores*** *increase the permeability of membranes to their selected ion by binding it, diffusing through the membrane and releasing the ion on the other side .*

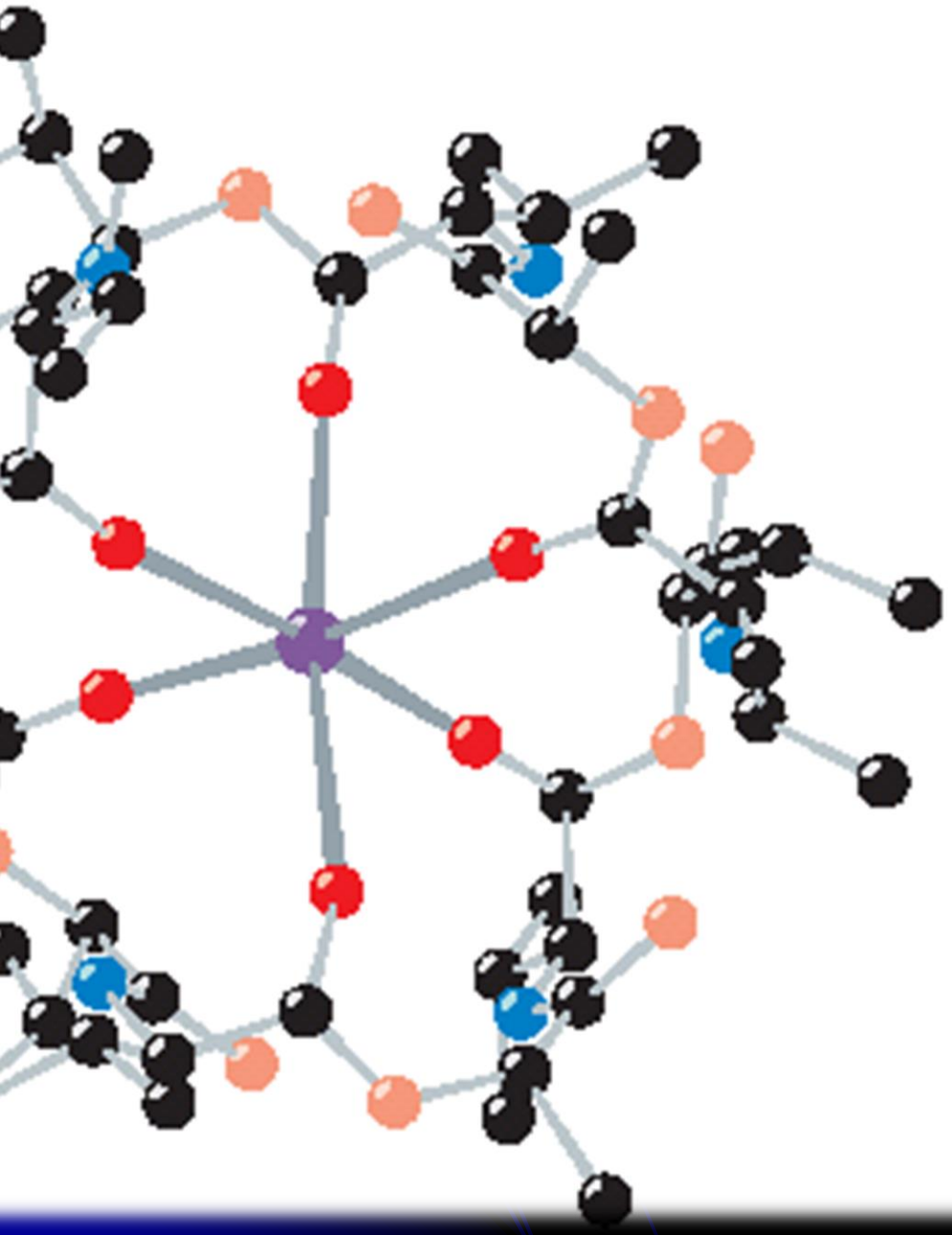
2. ***Channel forming ionophores*** *form transmembrane channels or pores through which their selected ions can diffuse.*


(a) Carrier ionophore
(b) Channel-forming ionophore

Antibiotics that induce ion permeability

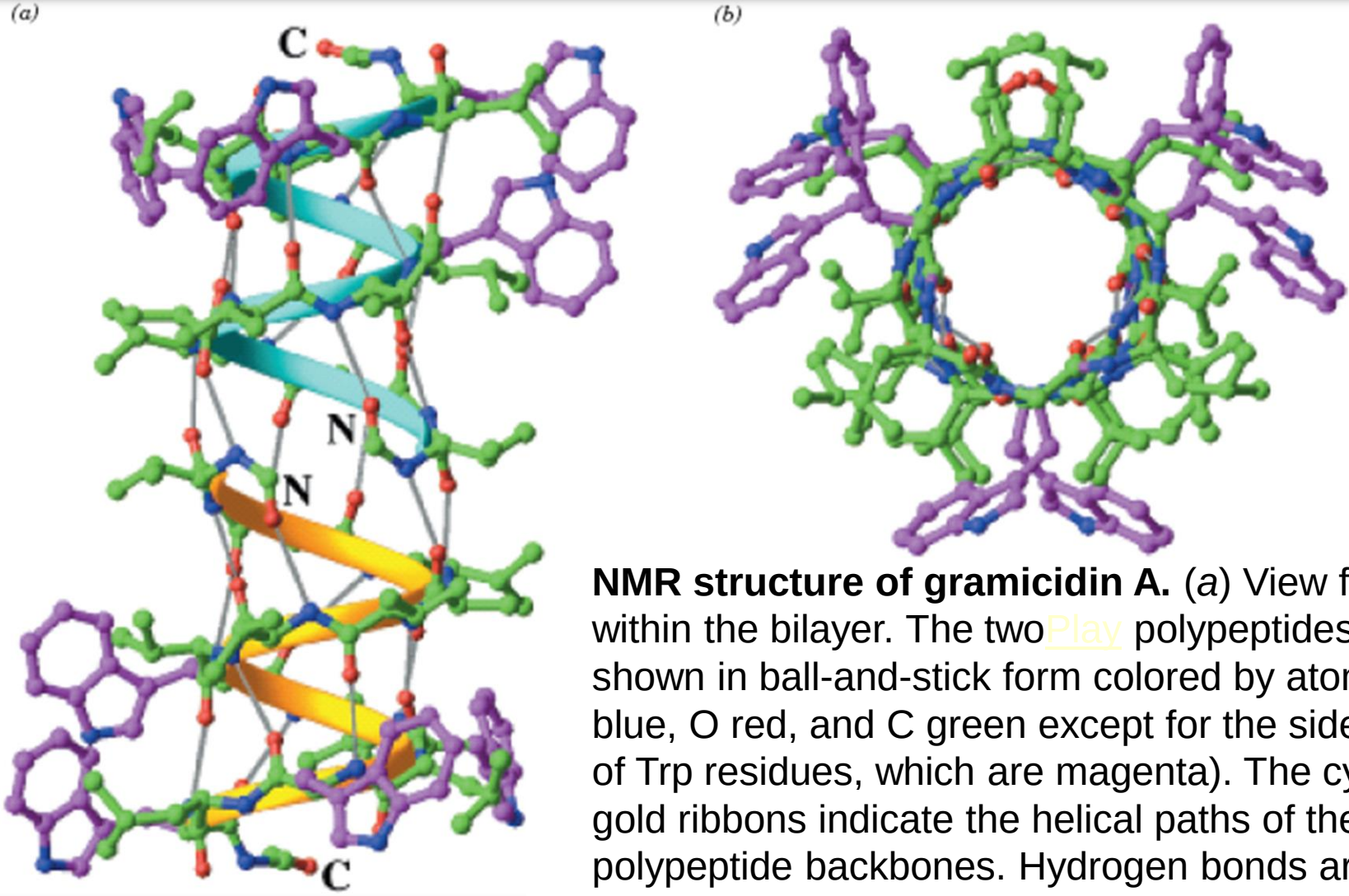
Valinomycin is a typical example of a mobile ion carrier. It is a cyclic peptide with a lipophilic exterior and ionic interior.

It dissolves in the membrane and diffuses between the inner and outer surfaces. K^+ binds to the central core of valinomycin, and the complex diffuses across the membrane, releasing the K^+ and gradually dissipating the K^+ gradient.



X-Ray structure of valinomycin in complex with K^+.

Six oxygen atoms (*dark red*) octahedrally coordinate the K^+ ion (*purple*).



NMR structure of gramicidin A. (*a*) View from within the bilayer. The two polypeptides are shown in ball-and-stick form colored by atom type (N blue, O red, and C green except for the side chains of Trp residues, which are magenta). The cyan and gold ribbons indicate the helical paths of the polypeptide backbones. Hydrogen bonds are represented by gray lines. H atoms are not shown. (*b*) View down the axis of the gramicidin A dimer. The 4-Å-diameter channel is lined by polar backbone groups and is wide enough to permit the passage of metal cations.