Diffusion as a result of «random walk» of particles

Ion movement in the membrane substance

Chaotic heat motion of molecules results in that substances are transferred from a regions of higher concentration of particles to that of lower concentration.

Diffusion process is usually regarded as the result of chaotic wandering of particles (molecules or ions) under action of heat collisions with environmental molecules. In this circumstances a particle (e.g. an ion) performs chaotic jumps in any direction; hence, each particle transition during a jump is a vector that can be epressed, as any vector, as a sum of constituents of three directions. Choose one of them and designate it as the X-axis direction.

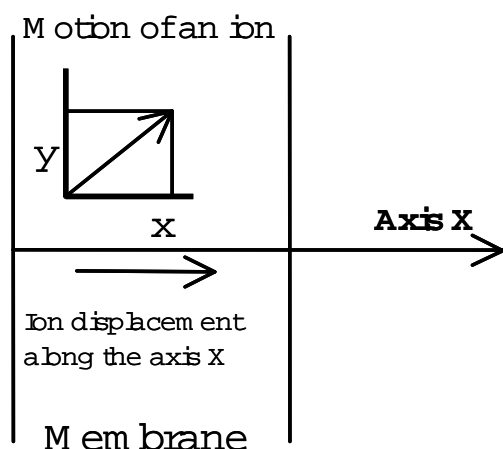Only the constituent along the X-axis is considered.

Fig. 1. Choice of flow direction in transmembrane ion transfer.

In the case of ion transfer through biomembranes, an axis normal to membrane and directed from inside the vesicle (cell, for instance) outwards can be taken for X-axis (see Fig. 1).

In what way does ion transfer across the width of the membrane lipid layer?

It was mentioned in Section 1 that such a transfer can be possible due to configuration rearrangements of fatty-acid chains and formation of a new «kink». Ion moves as if jumping from kink to kink, as it is presented in Fig. 2.
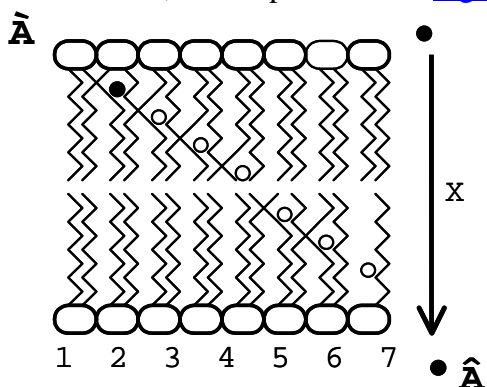

Fig.2. Ion motion across membrane by way of jumping from one kink to another.

The ion moves along X-direction. The figure shows *no different phospholipid molecules* in bilayer but different stages of the process of ion transfer across the membrane. 2–8 - changes in time of ion location in the membrane.

The cause of formation of new kinks and ion jumps are heat impacts of surrounding molecules.

It is clear that no every interaction with surrounding molecules causes a change of this particle's coordinate. In order to move (push) apart fatty-acid chains and leap up (jump) to a new loop, a molecule must have (possess) sufficient kinetic energy. In a homogeneous medium (such as membrane's lipid layer) the ion is located as if in a potential well. It is possible to get out of it only if the ion overcomes a definite energetic barrier (see Fig. 3). Nevertheless, due to the chaotic heat motion of the surrounding molecules and the ion itself, the particle can sometimes jump from one

well to another, next well. The possibility of such a jump depends on the well depth and temperature (for details see Section 4).
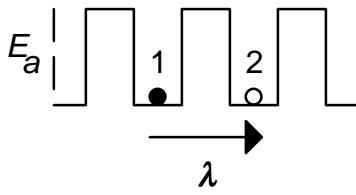

Fig.3. Scheme of ion transfer in membrane as the result of accidental ion jumps between energetic wells.

Designations: **n** - frequency of particle jumps to a next stable position, c. Every particle will jump, on the average (mean), **n/2** times every second from left to right; and the same quantity from right to left. **1** - distance between two neighbouring energetic wells, i.e. the length of the particle's path during every jump.

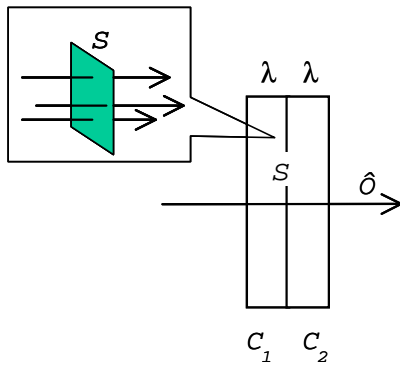Imagine that a plane (S) normal to the X-axis is drawn through membrane (see).

Fig.4. Diffusional ion flow through the membrane.

S - square normal to the flow direction; λ - length of molecule path during each jump; C_1 and C_2 - molar ion concentrations to the left and right of the membrane in layers with λ thickness.

Every second all particles will be transferred from left to right in a volume of lS, which corresponds to $C_1 S_l (n/2)$ kilomoles of substance, where C_1 - substance concentration to the left of the plane S, kmoles/m^3; l - length of molecule path on every jump. This is a unidirectional ion flow through square S:

$$\Phi = C_1 S \lambda \frac{\nu}{2} \qquad (1)$$

The unidirectional flow of particles (K^+, for instance) from right to left can be found (determined) in a similar way:

$$\Phi = C_2 S \lambda \frac{\nu}{2} \qquad (2)$$

The difference between these flows gives a total value of ion flow in the X-axis direction:

$$\Phi = S \lambda \frac{\nu}{2}(C_1 - C_2); J = \lambda \frac{\nu}{2}(C_1 - C_2) \qquad (3)$$

Eq. 3 is worth being considered more thoroughly. The question arises how can each particle's accidental transfer lead to a directed summary flow of ions? The matter is in concentrations. It is because of a completely chaotic motion of every particle that ions leave the region of a higher concentration and transfer to the region with a lower concentration. Statistics becomes (appears to be) the motive force of the flow.

Unluckily, the exact values of mean concentrations in thin layers adjacent to the plane (S) are not known as well as their difference (C_1-C_2). To get out of this situation, the (C_1-C_2)/l ratio should be replaced by the function (dC/dx):

$$J = -\lambda^2 \frac{v}{2}(\frac{C_2 - C_1}{\lambda}) = -(\lambda^2 \frac{v}{2})\frac{dC}{dx} \tag{4}$$

This equation can be compared with a well-known from physics empirical Fick's first law of diffusion:

$$J = -D\frac{dc}{dx} \tag{5}$$

It is seen that the empirical proportionality constant D, called the **diffusion coefficient**, actually depends on the frequency v of molecule jumps and the distance λ, which the molecule jumps over during each jump.

$$D = \lambda^2 \frac{v}{2} \tag{6}$$

The diffusion and the solvent viscosity

There is a relationship between the diffusion coefficient and the solvent viscosity. I has been shown by Stokes that for spherical particles and nonturbulent flow the frictional coefficient $f = F / v$ (where F is the force applied and v is the particle velocity) is described by the equation:

$$f = 6\pi\eta r \tag{7}$$

On the other hand, Einstein has found that the diffusion coefficient is inversely proportional to the frictional coefficient.

$$D = \frac{RT}{N_A f} \tag{8}$$

So from equations (7) and (8) we found that the diffusion for a spherical particle is given by

$$D = \frac{RT}{N_A 6\pi\eta r} = kT / 6\pi\eta r \tag{9}$$

It is interesting that this relation can be used to determine the molar mass of a protein molecule that is nearly spherical.

Ion flow through the membrane. Permeability

The value (dC/dx) from Eq. 5 is beyond immediate experimental determination; how can one actually measure the *gradient of ion concentration* inside membrane lipid layer? To pass on to the values measured in the experiment, it is necessary to solve differential equation 5, i.e. to perform separation of variables and integration. This procedure can be realized under an important condition - the same flow density at different coordinates of plane S through which the flow passes.

Consider a physical sense of such a constancy of the flow. If a (some) new compound id added to a medium washing the cell, or the concentration of one of the compounds is changed, then in the first moment the concentration gradient (dC/dx) arises only at the external membrane surface and only there the ion flow «pours» into the membrane; but after that the flow stabilizes and reaches a steady-state value, the flow values in different membrane «sections (cuts)» being the same. A relationship between the value of such a stable-in-time flow and ion concentrations at the left (C_{m1}) and right (C_{m2}) membrane boundaries can be found. We integrate Eq. 5 having preliminarily separated the variables:

$$J = -D\frac{dc}{dx}; JDdx = -dc; JD(l-0) = -(C_{m2} - C_{m1}) \tag{10}$$

From Eq. 7:

$$J = \frac{D}{l}(C_{m1} - C_{m2}) \tag{11}$$

Alas, ion concentrations inside the membrane, although on the interface with water (C_{m1} and C_{m2}), are not known but they can be found if one knows ion concentrations in surrounding water medium (C_1 and C_2, see Fig. 5).
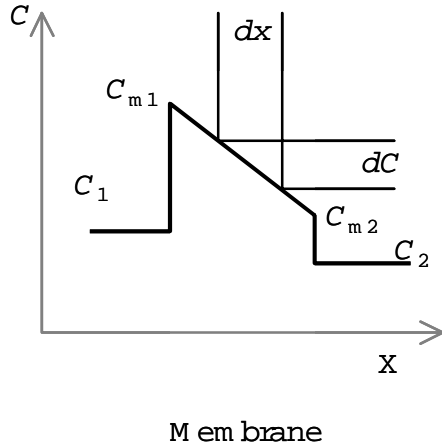

Fig. 5. Membrane's concentration profile, i.e. the dependence of ion concentration on a coordinate of the X-axis normal to the membrane plane.

The *ion concentration gradient* is the tangent of the slope of the concentration curve at a given membrane site (i.e. at a given X).

It can be considered that ions are distributed between phases according to the following law:

$$\frac{C_{m1}}{C_1} = \frac{C_{m2}}{C_2} = K \tag{12}$$

where K – the *coefficient of ion distribution* between membrane and water phases. It is obvious that this equation assumes that the membrane is symmetrical in the sense that ion distribution coefficients are the same on both membrane boundaries.

Placing values C_{m1} and C_{m2} from Eq. 9 to Eq. 8, the following final equation is obtained:

$$J = \frac{DK}{l}(C_1 - C_2) \tag{13}$$

where C_1 and C_2 are the ion concentrations in water phase; X - coordinate; l_1 and l_2 – the thickness of membrane-adjacent water layers.

This equation is analogous to an empirical observation that the flux is directly proportional to the concentration differetce between water solutions devided by the membrane:

$$J = P(C_1 - C_2) \tag{14}$$

where the empirical coefficient P is called the *permeability coefficient* or simply *permeability*.

Thus,

$$P = \frac{DK}{l} \tag{15}$$

The relation of the permeability coefficient with other values in the last equation is full of deep physical sense. Indeed, permeability is:

1. Directly proportional to the ion *diffusion coefficient* (D) in membrane substance. The latter value is associated with ion geometrical dimensions and membrane viscosity. For spherical

particles, the diffusion coefficient is related to medium viscosity (h) and ion radius r by the Stockes-Einstein equation:

$$D = kT \, / \, 6\pi\eta r \tag{16}$$

In a more viscous medium, diffusion is hampered and the permeability of a viscous membrane is lower than that of a membrane with a more «liquid», or better say more «fluid», lipid layer.

2. Directly proportional to the ion distribution coefficient (K) in the membrane/water system, i.e. to ion *hydrophobicity*. That is why fat-soluble drugs penetrate to cells better than water-soluble ones.

3. Inversely proportional to membrane thickness (l).

Role of membranous water layers

The permeability of membranes for many substances is limited not only by lipid bilayer or even the whole protein-lipid membrane but also by adjoining non-intermixing water layers.
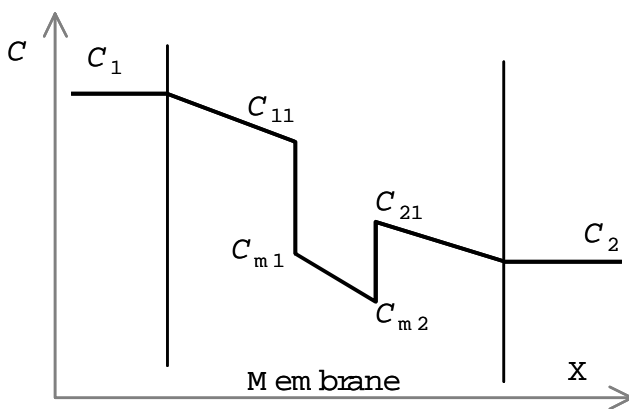

Fig. 6. Ion flow through the membrane with adjoining non-intermixing water layers.

This figure shows the dependence of ion concentration (C) on *ion coordinate* (X). Ion concentrations in different parts of the system are designated as follows:

C_1 - in intermixing *water solution* on the membrane's left, and in non-intermixing water layer at its left boundary;

C_{12} - in non-intermixing *water layer* on the membrane's left at its right boundary;

C_{m1} and C_{m2} - *within* the membrane at its left and right boundaries;

C_{21} - in non-intermixing *water layer* on the membrane's right at its left boundary;

C_2 - in intermixing *aqueous solution* on the membrane's right, and in non-intermixing aqueous layer at its right boundary;

l_1 and l_2 - *the thickness* of the left and right, respectively, non-intermixing water layers; and l_m - the thickness of the membrane.

Substance flows through the left and right membraneous water layers are equal, according to Eq. 10:

$$J_1 = P_1 \, (C_1 - C_{11}); \quad J_2 = P_2 \, (C_{21} - C_2). \tag{17}$$

The flow through the membrane itself is

$$J_m = P_m \, (C_{11} - C_{21}). \tag{18}$$

Under stationary conditions (i.e. on a stable and constant in time flow)

$$J_1 = J_2 = J_m = J \qquad (19)$$

(the principle of the flow continuity), from where:

$$J = P_1(C_1 - C_{11}) \Rightarrow \frac{J}{P_1} = C_1 - C_{11}$$

$$J = P_2(C_{21} - C_2) \Rightarrow \frac{J}{P_2} = C_{21} - C_2 \qquad (20)$$

$$J = P_m(C_{11} - C_{21}) \Rightarrow \frac{J}{P_m} = C_{11} - C_{21}$$

By summarizing the equations (20) we obtain:

$$\frac{J}{P_1} + \frac{J}{P_2} + \frac{J}{P_m} = C_1 - C_2 \qquad (21)$$

On the other hand, if two membrane-associated water layers are considered as a single whole, the ion flow through this system J is dependent on the permeability of the whole system according to the above-mentioned equation $J = P(C_1 - C_2)$, from which follows that

$$\frac{J}{P} = C_1 - C_2 \qquad (22)$$

Comparing Eqs. 21 and 22,

$$\frac{1}{P} = \frac{1}{P_1} + \frac{1}{P_2} + \frac{1}{P_m} \qquad (23)$$

The value $1/P$ can be called the *resistance to flow*. Now the physical sense of Eq. 19 becomes clear:

> The resistance to flow in the system of sequent (consequent) elements is equal to the sum of the resistances of each of them.

In other words, the values $1/P$ act like (the same way as) a sequence of electric resistances.

Relative contribution of membrane lipid and adjacent water layers to the total resistance to the flow (“Flux resitance”?).

A ratio of the resistance to the flow for two membranous water layers to the resistance to the flow of the membrane itself can be designated as, say, α:

$$\alpha = \left(\frac{1}{P_1} + \frac{1}{P_2}\right) : \frac{1}{P_m} = \frac{P_m}{P_a} \qquad (24)$$

This value can serve as a quantitative characteristic of the contribution of membranous water to the resistance to the flow. What does it depend on?

To understand this, we shall substitute P in Eq. 20 for DK/l (see Eq. 11):

$$\alpha = \frac{D_m K}{D_a} \cdot \frac{l_a}{l_m} \qquad (25)$$

(K for water layers is, naturally, equal to 1). If the liquid inside the cell and in intracellular medium moves intensively, the thickness of membranous water layers ($l_a = l_1 + l_2$) has an order of magnitude of 0.3 to 1 mcm, i.e. it exceeds the thickness of the membrane itself more than 100 to 300-fold. On the other hand, membrane viscosity is 10 to 100 times as much than that of water viscosity; it means that ion diffusion coefficients in water and membrane relate to each other as 30–

100 to 1. By placing these though very approximate figures to Eq. 21, a very interesting formula is obtained:

$$\frac{K}{100} \cdot 100 \leq \alpha \leq \frac{K}{10} \cdot 300$$

$$\alpha \cong K(1 \div 30)$$

(26)

The matter appears to be in the coefficient of substance distribution in the membrane/water system, i.e. ion (molecule) *lipophilicity* plays a decisive role. In the case of such ions as K^+, Na^+, Ca^{2+}, K has values exceeding 10^{-14} and membranous liquid layers do not practically influence the total permeability - the basic barrier function belongs to the lipid bilayer. In the case of neutral molecules such as, say, oxygen K is close to (near) 1, thus the role of membranous layer becomes more significant.

The resistance to the flow of water layers becomes more significant if the liquid in the cell and intracellular medium do not intermix well. In this case l_a increases to 20–500 μm, and water layers become the main hinder on the path of diffusing gas. Since the motion of liquid inside and outside the cell depends on tissue metabolism, a not quite right impression can be formed that molecule transfer through membrane is an active process depending on cell energetic power. In fact, active is intermixing of liquids, and oxygen transfer through membrane and membranous water layers is a purely diffusion process requiring no energy expenditures.