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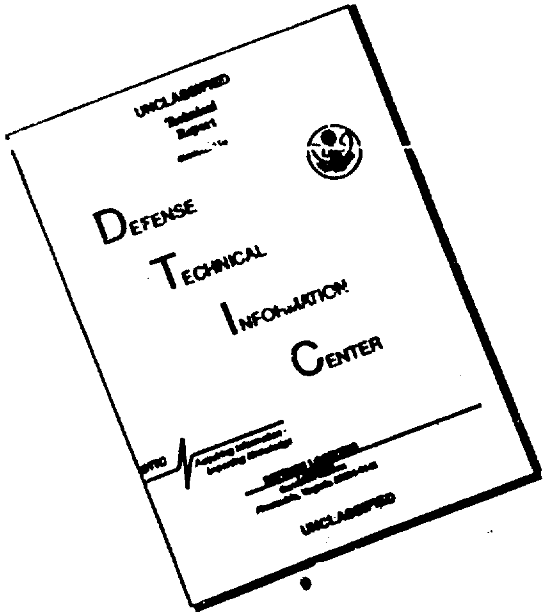

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CELL MEMBRANE PERMEABILITY TO WATER

(LONG-PORE EFFECT)

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In the literature we can find several citations [1-4] to the effect that measurements of water flow through natural membranes by two different methods, osmotic and isotope, give different values for the rate of water permeability. Permeability p_{isot} in isotope experiments is defined as

$$p_{isot} = \frac{f}{a} = \frac{f^x}{a^x} \tag{1}$$

where f and f^x are unidirectional flows of whole water and tagged water through a membrane and a and a^x are the activity of whole and tagged water on the one side of the membrane and the side where the tagging is applied.

In the osmotic experiments permeability p_{osm} is defined by the ratio

$$f_{osm} = p_{osm}(a_1 - a_2) \tag{2}$$

where a_1 and a_2 are water activity on both sides of the membrane and f_{osm} is the osmotic flow of water.

In the case of diluted solutions,

$$a_1 - a_2 \simeq c_2 - c_1$$

where c_1 and c_2 are the total concentrations of the dissolved substances in the water which do not pass through the membrane on both sides of the membrane.

In using this method for calculating permeability from experimental data on osmotic and isotopic flow we always find that $p_{osm} > p_{isot}$. In addition, erythrocyte experiments [1] showed that the isotopic flow depends on osmotic pressures on both sides of the membrane which does not follow from equation (1).

In order to explain these facts it is usually assumed [2 - 4] that the water passes through the membrane by long narrow pores having a diameter only slightly larger than that of the water molecule so that the molecules in the pore line up in a column. The following model can be considered: in a pore there are always n molecules some of which have entered from the left and some from the right. In some collisions of solution molecules against the edges of the pore the entire column shifts forward one position and the molecule which had the collision occupies the first place in the pore. At the same time one molecule passes from the pore into the solution on the other side of the membrane.

Setting up the problem in this fashion has led certain writers to the paradoxal conclusion that the frequency of passage to the right, let us say, of tagged molecules which were originally on the left depends in a nonlinear fashion on the concentration of these molecules on the left, in other words

$$\frac{\vec{f}^x}{\vec{f}} < \frac{a^x}{a}$$

where f^x and f are the flow of tagged water and whole water from left to right and a^x and a are the respective activities in the solution on the left.

The paradox in this conclusion can be readily seen from the following example. Let's divided all the water on the left into several equal parts and tag each part. Let's then measure the flow produced by each part. The total water flow is equal to the sum of these flows and must not depend on the tagging method. However we will obtain a smaller total flow, the greater the number of parts into which we divide the water.

Let us have a look at what constitutes the error in this approach. Let's take Harris' method [2]. We assume that a tagged molecule has taken over first place in the column. With the next collision at either end of the pore there is 1/2 probability that it will pass to second place (we assume that the total activity of the molecules entering from both ends is the same and the average frequency of collision on both ends of the pore is identical). The probability of passing from second to third position is also 1/2 and from from first to third $(1/2)^2$. The probability of passage of a tagged molecule from first place to (n+1)st is $(1/2)^n$. Hence the conclusion that the ratio of tagged flow to total flow from left to right equals $(a^x/a)\cdot(1/2)^n$. The first error in this judgment is obvious. The author considers the passage of tagged molecules as only one of the infinite number of possible methods, namely passage without return $(1\to2\to3\to\ldots n+1)$. However passages are possible with 1, 2, and more returns, for example $(1\to2\to3\to2\to3\to2\to1\to2\ \ldots)$. Lea [3] takes this possibility into account. For a starting ratio the author takes the obvious equation $W_i = uW_{i-1} + vW_{i+1}$ where W_i is the probability that the tagged molecule is in the i-st position from the left, u the probability of the movement of the entire column to the right in successive collision with the pore and v movement to the left. Unfortunately in this equation the positions of probabilities u and v were transposed.

For this reason in the final expression for unidirectional flow obtained for solving this equation it is essential to exchange positions u and v.

However the principal reason for the paradoxal conclusions of Harris and Lea ties up with an incorrect interpretation of the final result. Both authors assume that untagged molecules located originally on the left pass out into the solution on the right at a rate of 1 emergence per collision and equate the small numerical probability of passage of a tagged molecule with the ratio of tagged to total flow from one side of the membrane to the other.

Derivation of an equation for unidirectional flow

Let a membrane with identical pores separate two aqueous solutions of substances which cannot penetrate a membrane. Let the activity of the water on the left and right be represented as a_1 and a_2. It is natural to assume that the column can be moved forward only by the impact of molecules with a speed component along the pore axis greater than a certain value v_0. Let α represent the ratio of the number of water molecules whose impact advance the column to the total number of molecules. Then the number of molecules moving the column to the right will be αa_1 and to the left αa_2. Let us use as a unit of time the average time between column movements

$$\overline{\Delta t} = \frac{1}{\alpha a_1 + \alpha a_2}$$

The probability of advancement of the column one place to the right in a unit of time will be

$$u = \frac{\alpha a_1}{\alpha a_1 + \alpha a_2} = \frac{a_1}{a_1 + a_2}$$

and one place to the left

$$v = \frac{a_2}{a_1 + a_2}$$

In a pore with n places it is possible to have n+1 combinations of molecules from each side (diagram). When the column moves to the right a molecule of the left solution will be carried to the right solution only with the first combination and only with the (n+1)st combination will a molecule of the right solution pass to the left.

Hodgkins and Keynes [5] considered a similar problem and obtained an equation for the ratio of unidirectional flows by the following method: with stationary flow an accurate relationship is $up_{i+1} = vp_i$, where p_i is the probability of the i-st combination. Then

$$p_i = \frac{u}{v} p_{i+1} = \left(\frac{u}{v}\right)^2 p_{i+2} = \ldots = \left(\frac{u}{v}\right)^n p_{i+n}$$

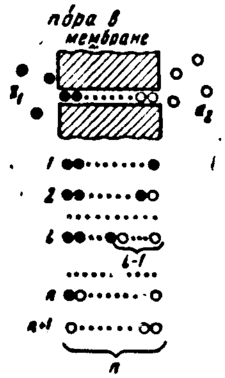
With

$$i = 1;\ \frac{p_1}{p_{n+1}} = \left(\frac{u}{v}\right)^n = \left(\frac{a_1}{a_2}\right)^n$$

Since the rate of entry of a molecule from the left solution into first place on the left is proportional to a_1 and the molecules on the right to a_2 then

$$\frac{\vec{f}}{\overleftarrow{f}} = \frac{a_1}{a_2}\,\frac{p_1}{p_{n+1}} = \left(\frac{a_1}{a_2}\right)^{n+1} \qquad (3)$$

Diagram: pore in membrane



We will try to obtain an equation for unidirectional flow and use it in determining the water permeability of the membrane.

The process described is a very simple Markov chain and the rate of emergence of molecules of the left-hand solution on the right may be defined as the product of the probability that the system is in the first state at a given moment times the rate of progress of the column toward the right.

In a stationary state the probabilities of the states can be determined through the probabilities of transition between states. From the numeration of the combinations we can see that the probability of a transition from the i-st to the (i+1)-st state is equal to the probability of a collision on the right, i.e. v and the probability of a trasition from the (i+1) to the i state -- u.

The probabilities of the states in a stationary system are equal to the absolute possible probabilities, a column of which (p_i) is the proper vector of matrix P' for a characteristic number $= 1$:

$$P' \cdot (p_k) = (p_i) \qquad (4)$$

Here the matrix PI is the transitional matrix for the matrix of probabilities of transitions P.

In our case matrix P is simple in appearance:

$$P = (p_{ik}) = \left.\begin{pmatrix} u & v & 0 & \cdot & \cdot & \cdot & \cdot & 0 \\ u & 0 & v & 0 & & & & \cdot \\ 0 & u & 0 & v & & & & \cdot \\ \cdot & & \cdot & \cdot & \cdot & & & \cdot \\ \cdot & & & \cdot & \cdot & \cdot & & \cdot \\ \cdot & & & & \cdot & \cdot & \cdot & 0 \\ \cdot & & & & & \cdot & \cdot & v \\ 0 & \cdot & \cdot & \cdot & \cdot & 0 & u & v \end{pmatrix}\right\} (n+1).$$

The solution of the system of equations in (4) looks thus

$$p_i = \left(\frac{v}{u}\right)^{i-1} \frac{1-\frac{v}{u}}{1-\left(\frac{v}{u}\right)^{n+1}}.$$

Consequently,

$$p_1 = \frac{1-\frac{v}{u}}{1-\left(\frac{v}{u}\right)^{n+1}} = \frac{1-\frac{a_2}{a_1}}{1-\left(\frac{a_2}{a_1}\right)^{n+1}} \qquad (5)$$

$$p_{n+1} = \left(\frac{v}{u}\right)^n \frac{1-\frac{v}{u}}{1-\left(\frac{v}{u}\right)^{n+1}} = \left(\frac{a_2}{a_1}\right)^n \frac{1-\frac{a_2}{a_1}}{1-\left(\frac{a_2}{a_1}\right)^{n+1}}. \qquad (5')$$

The probability of passage of molecules from the left solution into the right during the average time between collisions is

$$up_1 = \frac{\alpha a_1}{\alpha a_1 + \alpha a_2} \cdot \frac{1-\frac{a_2}{a_1}}{1-\left(\frac{a_2}{a_1}\right)^{n+1}}$$

and the frequency of emergence per unit of time, independent of the frequency of collisions is

$$\alpha a_1 \cdot \frac{1-\frac{a_2}{a_1}}{1-\left(\frac{a_2}{a_1}\right)^{n+1}}.$$

Total flow from left to right

$$\vec{j} = pa_1 \frac{1-\frac{a_2}{a_1}}{1-\left(\frac{a_2}{a_1}\right)^{n+1}}, \qquad (6)$$

where p is the water permeability of the membrane which depends on α and the ratio of the effective surface of the pores to the surface of the membrane.

$$\overleftarrow{f} = pa_2 \frac{1-\frac{a_1}{a_2}}{1-\left(\frac{a_1}{a_2}\right)^{n+1}} = pa_2 \frac{1-\frac{a_2}{a_1}}{1-\left(\frac{a_2}{a_1}\right)^{n+1}} \left(\frac{a_2}{a_1}\right)^n. \qquad (7)$$

If we divide (6) by (7) we obtain equation (3).

Flows $\overrightarrow{f}$ and $\overleftarrow{f}$ may be determined only by means of isotopes.

From (6) we can see that flow from left to right depends on water activity not only on the left but on the right.

Osmotic flow is computed like $\overrightarrow{f} - \overleftarrow{f}$ and equals

$$f_{osm} = \overrightarrow{f} - \overleftarrow{f} = pa_1 \frac{1-\frac{a_2}{a_1}}{1-\left(\frac{a_2}{a_1}\right)^{n+1}} - pa_2 \left(\frac{a_2}{a_1}\right)^n \frac{1-\frac{a_2}{a_1}}{1-\left(\frac{a_2}{a_1}\right)^{n+1}} = p(a_1 - a_2), \qquad (8)$$

i.e. looks the same as in an ordinary case of non-narrow pores.

Now we can readily see why we obtain different water permeability coefficients derived by using equations (1) and (2). The isotope coefficient must be computed in the case of different osmotic pressures on the two sides of the membrane by using (6). When the osmotic pressures are identical, i.e. when $a_2/a_1 = 1$, exposure of the inaccuracy in (5) by L'Hopital's rule gives

$$p_1 = \frac{1}{n+1}$$

and (6) is transformed into

$$\overrightarrow{f} = \frac{p}{n+1} a_1. \qquad (9)$$

Thus the use of equation (1) instead of (9) gives a value for the water permeability reduced n+1 fold.

Combined osmotic and isotope measurements of water flow through membranes makes it possible from ratios (6) and (8) to determine permeability p as well as the number of places in pore n.

Diamond [4], using equation (3) found n = 56 in measuring water flow through the gall bladder. The application of equation (9) to his data gives n = 54 - 56.

The case of a very wide pore signifies n = 0 and the absence of interaction of the flows. For a not too narrow pore (several molecule diameters) the interaction will be weaker than in the case of a narrow pore and the computed n will be less than the ratio of pore length to molecule diameter. We may assume that the computed ratios are applicable as well in a case where we consider n simply an indicator of the degree of interaction of the flows.

Conclusions

1. We have considered a mathematical model describing the passage of water through the long narrow pores of a membrane. In this case we have observed an interaction between the opposing unidirectional flows of molecules.

2. We have obtained equations for unidirectional flow of water through a membrane.

3. The ratios which we have obtained agree essentially with the experimental data provided by a number of writers on the passage of water through natural membranes and explain the difference in the values for water permeability of membranes obtained from osmotic and isotope experiments.

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