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Abstract—The methods of information theory and of irreversible thermodynamics are applied to membranes. Equations are derived for the negentropy production of a membrane maintaining a concentration difference. The results are converted to bits. When applied to typical data for a nerve transporting Na^+ against a concentration gradient, the equation gives for the negentropy or information production,

$$\dot{H} = 7.3 \times 10^{13} \text{ bits/cm}^2 \text{ second.}$$

Enumeration based on $Na^+ : Cl^- : K^+ = 1 : 1 : 10$ gives a value of

$$4.3 \times 10^{13} \text{ bits/cm}^2 \text{ second.}$$

IN a classification of the significant problems of biophysics DANIELLI (1) listed four. Two of these relate intimately to membranes and their role in biological systems: cell permeability and cell electrophysiology. It is almost mandatory, then, to inquire into the behavior of membranes from the point of view of information theory. For if information theory is to have relevance to important biological problems, a coherent relation should be exhibited for membrane phenomena. This attitude was exhibited in the initial attempts to discuss biological problems within this discipline in QUASTLER's pioneering book (2).

The formidable complexity of biological membranes is a recurring theme in the immense amount of experimental data which are being accumulated. Phenomena encountered in biological membranes may range from those explainable by the assumption of simple pores of various sizes, to those requiring charged pores, and on to those necessitating a picture of the surface as possessing pores, binding sites, permeability barriers, enzymes, and transport mechanisms. It is possible, however, to ignore the details of structure and specific mechanism —as is usually the case in thermodynamics—and formulate a limited model of membrane activity satisfactory to our analysis. Thus membranes may be classified by the manner in which they react to or treat a given substance. If we schematize the membrane as separating two media in each of which the reference substance is soluble, calling one region the 'inside' and the other the 'outside', we may introduce the following notation:

Indifferent: A membrane is indifferent to a substance if the concentration of that substance is the same on both sides of the membrane at all times. Thus $C_i = C_0$, for all t.

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Responsive: A membrane is responsive to a substance if the concentrations of that substance differ on each side at the same time. But neither concentration is zero. Thus, $C_i \neq C_0$ for some t.

Exclusive: A membrane is exclusive with respect to a given substance if, for all time, the concentration on one side is finite but the concentration on the other is zero. Thus, $C_i = 0$ and $C_0 \neq 0$, or $C_i \neq 0$ and $C_0 = 0$, for all t.

The analysis of this paper will be limited to substances to which a given membrane is responsive. It must not be concluded, however, that indifferent and exclusive substances are of no biological significance. There are examples where seemingly the most important role of a membrane is its action to exclude a given substance from the internal medium or keep a component from diffusing out.

The preliminary work (2) on a responsive membrane attempted to derive by the methods of irreversible thermodynamics an expression for the negentropy production of a membrane maintaining a concentration difference. The approach rested upon the concept that the entropy is an absolute maximum at equilibrium. Hence any deviation from equilibrium would mean a decrease in the entropy. Expanding the change in entropy, ΔS, in a Taylor's series about the equilibrium point yields as the first approximation, since the first derivative terms vanish at equilibrium,

$$\Delta S = -1/2 \sum_{l,m} g_{l,m}\, a_l a_m \, \cdot \cdot \tag{1}$$

Equation (1) was combined with some descriptive equations for the membrane and the final result

$$\frac{dH}{dt} = k\alpha \tag{2}$$

was deduced. In equation (2), H is the negentropy or the information (3), α is the rate constant governing the rapidity with which the membrane would approach uniform concentration on each side if it were not actively maintaining the concentration difference and k is Boltzmann's constant (1.380×10^{-16} ergs per degree).

Equation (2) had to be examined to determine if it is applicable to a membrane maintaining a considerable concentration difference. Its significance with respect to the relation

$$\Delta S_{\mathrm{irr.}} = k \ln C_i/C_0 \tag{3}$$

had to be clarified (4). Equation (3) gives the irreversible production of entropy for the passage of a single particle from concentration C_i to the concentration C_0. If C_0 is greater than C_i, we have the situation postulated for the membrane, thereupon $\Delta S_{\mathrm{irr.}}$ is negative and may be equated to information, H.

Derivation of the Rate of Production of Information

The methods of irreversible thermodynamics as presented by DeGroot (5) are applicable to effect the derivation. Following DeGroot's nomenclature, we have

$$\Delta \dot{S} = J_u X_u + J_m X_m + J_\mu X_\mu \tag{4}$$

where $\Delta \dot{S}$ is the rate of entropy production. The J's are 'fluxes' and the X's are 'forces', u is energy, m matter, and μ chemical potential. The J's are related to the X's through

$$J_u = L_{11} X_u + L_{12} X_m + L_{13} X_u.$$

Assuming an isothermal system, the X's and J's are

$$X_u = \Delta (1/T) = 0 \qquad J_u = 0$$

$$X_m = -\Delta \mu / T \qquad J_m = \frac{dm}{dt}$$

$$X_\mu = -\Delta m / T \qquad J_\mu = \frac{d\mu}{dt}$$

Whereupon, equation (4) becomes

$$\Delta \dot{S} = -J_m \Delta \mu / T - J_\mu \Delta m / T. \tag{5}$$

Substituting into equation (5),

$$\mu = \mu_0 + RT \ln a$$

where a is the activity, we get

$$\Delta \dot{S} = (R \ln a_i / a_0) \frac{dm}{dt} + R \Delta m \, d/dt \, (\ln a_i / a_0). \tag{6}$$

The a's refer to the activities in the two different regions.

Equation (6) is the basic relation replacing both equations (2) and (3). If we assume that the activities may be replaced by the concentrations and that we are concerned with the passage of N particles from a lower to a higher concentration, $C_0 > C_i$, then equation (6) becomes

$$\frac{dH}{dt} = \dot{H} = k \frac{dN}{dt} \ln C_0 / C_i + Nk \, d/dt \, (\ln C_0 / C_i).$$

If the outside is taken to be very large with no change in concentration by the addition of the particles from within,

$$\dot{H} = k \frac{dN}{dt} \ln C_0 / C_i - \frac{Nk}{C_i} \frac{dC_i}{dt} . \tag{7}$$

Equation (7) gives the rate of decrease of entropy or the rate of production of negentropy or information by a membrane which is transferring material from a lower to a higher concentration where the particles leave at the rate dN/dt and the concentration within changes at the rate dC_i/dt. Thus one may look upon equation (7) as the dynamic equation describing real transport. On the other hand equation (2) describes a situation where there is no macroscopically discernible change in concentration within or without. But inasmuch as the membrane maintains a concentration difference, it is producing information at the rate given to continue the imbalance.

If the concentration within is stabilized in such a manner that for a slight change the system returns to the resting value following the equation

$$(1/C_i)\, dC_i/dt = -\alpha \tag{8}$$

where α is analogous to the rate constant appearing in equation (2), equation (7) may be written

$$\dot{H} = k\frac{dN}{dt}\ln C_0/C_i + kN\alpha. \tag{9}$$

Equations (8) and (9) seem harmonious with equation (2) interpreted as being applicable to the resting case when there is no net transport or to actual transport with the condition that $C_0 = C_i$.

The application of equation (9) to a fluctuation should follow this sequence. Initially $C_0 = C_i$, and ΔN particles jump from one solution to the other. The rate of negentropy production or the rate of production of information is $\dot{H} = \Delta H/\Delta t = k\Delta N\alpha$. At the end of this fluctuation equation (9) becomes for the *next* fluctuation $k\Delta N\alpha$

$$\dot{H} = k(\Delta N/\Delta t)\ln\left(\frac{C + \Delta C}{C - \Delta C}\right) + k\Delta N\alpha. \tag{10}$$

Suppose that the next fluctuation is the movement of ΔN particles in the direction opposite to the first fluctuation in the same interval of time, Δt. We should expect $\dot{H}$ to be the negative of its original value. Expressing the logarithm in equation (10) as $\ln\dfrac{1 + \Delta C/C}{1 - \Delta C/C}$ and making use of the relation

$$\ln\frac{1 + X}{1 - X} = 2(X + X^3/3 + \cdots), \quad \text{for} \quad X^2 < 1,$$

the equation becomes

$$\dot{H} = 2k\,\Delta N/\Delta t\,\Delta C/C + k\Delta N\alpha$$

but

$$\Delta N/\Delta t\,\Delta C/C = \Delta N/C\,\Delta C/\Delta t = -\Delta N\alpha$$

from equation (8), and since ΔC is negative in the second fluctuation.

Finally: $$\Delta H = -k\Delta N\alpha\,\Delta t.$$

Thus the system returns to the equilibrium position on the entropy surface with an increase in entropy exactly equal to the decrease of entropy experienced in the first fluctuation.

Analysis for Charged Particles

In the derivation of the basic equations (6) and (7), the chemical potential was employed, which limits the applicability of the analysis to uncharged particles. To derive the corresponding equations for an ion, the electrochemical potential μ' replaces μ,

$$\mu' = \mu_0' + RT\ln a + ZF\phi$$

where Z is the valence, F is the Faraday, and ϕ is the potential. Substituting

and carrying through an identical analysis as followed in deriving equation (7), $\dot{H}$ becomes

$$\dot{H} = k[(dN/dt) \ln C_0/C_i + N\alpha] + (Zq/T)[dN/dt(\phi_0 - \phi_i) \\ + N(d/dt)(\phi_0 - \phi_i)] \tag{11}$$

where q is the numerical value of the charge on the electron, when the membrane transports ions from the lower concentration to the higher concentration, $C_i \rightarrow C_0$.

Application to a Nerve

Data on the movement of ions across the nerve membrane may be substituted into equation (11) to obtain numerical values for $\dot{H}$. The knowledge of the transport of ions across the nerve membrane although quite extensive is still not complete enough to permit unequivocal choice of a model. There are two possibilities which suggest themselves for consideration. In the first, following the transport of an impulse, the nerve returns to its resting condition with respect to the concentration of Na$^+$ or K$^+$ before it can pass another impulse. The resting potential is reached at the beginning of this period. Calling this example model one, we have these data for a squid axon (6):

[K$^+$]	$C_0 = 10$	$C_i = 410$
[Na$^+$]	$C_0 = 460$	$C_i = 49$
[Cl$^-$]	$C_0 = 540$	$C_i = 40$

in units of millimoles/kg. At 300°K, $\phi_0 - \phi_i = 50$ mV with the outside positive. If the length of the recovery period is taken as 1 millisecond, the equation (11) becomes*

$$\dot{H} = k(dN/dt) [\ln C_0/C_i + (Zq/kT)(\phi_0 - \phi_i)]. \tag{12}$$

The first term on the right yields for the concentration gradient above

for K$^+$,	$\dot{H} = 5.3$ bits/ion-unit time,
for Na$^+$,	$\dot{H} = 3.3$ bits/ion-unit time,
for Cl$^-$,	$\dot{H} = 3.7$ bits/ion-unit time.

* In applying equation (11) the second and fourth terms contribute negligibly. Examining the two terms with the data that 3.7 $\mu\mu$ moles of Na$^+$ enter per impulse per cm², a cylindrical nerve of 100 μ radius with unit surface area would have,

$$\text{Area} = 2\pi rl = 1 \text{ cm}^2$$

$$\text{Vol} = \pi r^2 l = 5 \times 10^{-3} \text{ cm}^3;$$

and assuming that the nerve has the density of water, the section would weigh 5×10^{-3} gm. So 49 m mole/kg would correspond to 2.5×10^5 $\mu\mu$ mole/cm², whereupon for sodium

$$\dot{H} = 2.25 k(dN/dt) + 1.5 \times 10^{-5} kN \text{ per millisecond}$$

$$= 2.25 k(dN/dt),$$

since

$$\Delta N = N \quad \text{and} \quad \Delta t \text{ is taken as 1 millisecond.}$$

The term $\qquad\qquad \dfrac{Zq}{kT}(\phi_0 - \phi_i) = 1.94$

at 300°K. Using this value, the combined rates for both the concentration and electrical terms are

$$K^+: \qquad \dot{H} = 2.5 \text{ bits/ion-unit time,}$$
$$Na^+: \qquad \dot{H} = 6.1 \text{ bits/ion-unit time,} \qquad\qquad (13)$$
$$Cl^-: \qquad \dot{H} = 0.9 \text{ bits/ion-unit time.}$$

These values have been arrived at by multiplying equation (11) by $\dfrac{\log_2 e}{k}$ to convert from k units to entropy units.

[The conversion factor was derived in a previous paper by the author in considering proteins (2). It is easily shown that $\log_y x \log_x y = 1$, which means that this conversion factor is the same as that derived by Linshitz (7) and others (8).]

On the basis of the first model the 3.7 $\mu\mu$ moles of Na^+ entering during the impulse would be extruded during the millisecond following the return to the resting potential. This time interval requires that the nerve produce information at the rate

$$\dot{H} = 9.3 \times 10^{15} \text{ ergs/°K cm}^2 \text{ sec,}$$

or $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (14)$

$$\dot{H} = 1.35 \times 10^{16} \text{ bits/cm}^2 \text{ sec.}$$

The alternative model is that the nerve does not extrude the Na^+ in so short a time. Rather the nerve passes it from within to the outside at a rate of 20 $\mu\mu$ mole/cm² second (9). However, the acceptance of this view does not alter equations (13). Inserting this value for Na^+ in equation (12) results in

$$\dot{H} = 7.3 \times 10^{13} \text{ bits/cm}^2 \text{ sec.} \qquad\qquad (15)$$

The experimental results seem to favor this model; thus equation (15) is the more reasonable result in comparison with equation (14).*

The alternative mode of viewing the nerve according to information theory makes use of the concept that the sodium ions are chosen from the pool of ions within the nerve by some mechanism. Within the nerve the ratios are $Na^+ : Cl^- : K^+ = 1 : 1 : 10$. The mechanism chooses the Na^+ from this group, requiring $\log_2 12$ bits of information for each Na^+ selected. This value, 3.57 bits/ion, leads to

$$\dot{H} = 4.3 \times 10^{13} \text{ bits/cm}^2 \text{ sec.,} \qquad\qquad (16)$$

for the nerve based on the second model which transports $20\mu\mu$ moles cm² sec. of Na^+ against the concentration and electrical gradient. Assuming that the

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* DR LEROY AUGENSTINE made the astute observation with respect to equation (14) in the discussion that it is consistent with a value of 10^3 Å² for the area of a protein and that on 1 cm² of nerve there could be 10^{13} proteins transporting one ion per millisecond. It may weaken the argument to assume that the nerve surface has that many protein molecules. The lower value 1.20×10^{13} ions/cm² second is consistent with any combination of rates and numbers of protein molecules responsible for transport such that the product equals this numerical value. Thus 1.20×10^{10} protein molecules transporting an ion per millisecond are suitable and require that only 0.001 of the nerve surface consists of such proteins, each of 10^3 Å² area.

information units, the bits, appearing in equations (15) and (16) are identical with those used in discussing the information content of the printed page, the interpretation is that a cm^2 of nerve has an enormous rate of production. The analogy of course is to a person who is called upon to separate red balls (Na^+) from white (K^+) and blue (Cl^-) balls in a box where he would reach in, pick up a ball, look at it, and if it is red it is taken out, and if not it is replaced. The nerve has some equivalent separating mechanism with the information rate of equation (15). In terms of a familiar example, taking the information content of a single printed page as 10^4 bits (9), equation (15) requires that the cm^2 of nerve surface produce information equivalent to that contained in a library of 7.3 million volumes of a thousand pages each second—this is over half the number of books in the Library of Congress! The value given by equation (15) is not inordinate, however, in comparison with the estimates of the information content of biological objects (9), where for man the value is of the order of 10^{25} bits.

The result in equation (16) may be viewed as the minimum information production necessary to effect the separation of sodium. The numerical value may be in error, for the choice could be from among more ions than the three employed. It is of interest to note that the nerve does not possess perfect coding inasmuch as it uses 1.7 times as much information to effect the separation as is required. Alternatively the information efficiency may be expressed as 59 per cent. These comparisons may be without substance because of the inadequacy of the data. The only relevant comparison may be that the physico-chemical determination of information production as summarized in equation (15) is of the same order of magnitude as the value determined by enumeration in equation (16).

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