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Solid State Mechanisms of Ion Transport in Biological Systems†

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Abstract—Leakage of Na^+ across the surface of muscle cells has been observed to obey the Elovich equation, which previously was found to describe various electron transport processes at surfaces of inorganic semiconductors. Analogies between solid state electron transport and liquid or gel state ion transport permit the derivation of the Elovich equation for Na^+ transport across the surface of the muscle cell, but only if it is assumed that muscle Na^+ exists mostly in a complexed form. Direct experimental verification of this theoretical prediction was obtained by n.m.r. analysis of muscle Na^+. The similarities between the behavior of ions in cells and electrons in semiconductors suggest the presence of some degree of order or crystallinity in cells, which suggests the applicability to biology of concepts derived from the study of liquid crystals.

Kinetic and n.m.r. evidence indicates that Na^+ ions in the cell occupy discrete binding sites or energy levels like electrons in a semiconductor. This suggests the existence of some sort of order or crystallinity in the living cell, which suggests the applicability of concepts involving liquid crystals.

The kinetic evidence for ion binding is derived from an analysis of the following experimental observation.[1,2] When a piece of muscle is incubated in 0.3 M sucrose solution and the outflow of Na^+ from muscle is measured, one finds a curve like Fig. 1 (plotted on semilog paper). This can be approximated by two straight lines (see Fig. 1) or by two first order processes, but the curve also fits well an equation of the form.

$$-\frac{dx}{dt} = me^{nx}$$

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where x is Na^+ concentration in the muscle, t is time and m and n are constants.

Is this an arbitrary curve fit? Has this equation been seen before?

It was seen 30 years ago in solid state physics. Beginning in Russia about 1934, this equation was observed to describe the kinetics of various processes at the surfaces of inorganic semiconductors.[3,4] The equation is generally named after the Russian Elovich who was one of the first to use it. Various derivations of the Elovich equation were given by solid state physicists, but none seemed too satisfactory.[5]

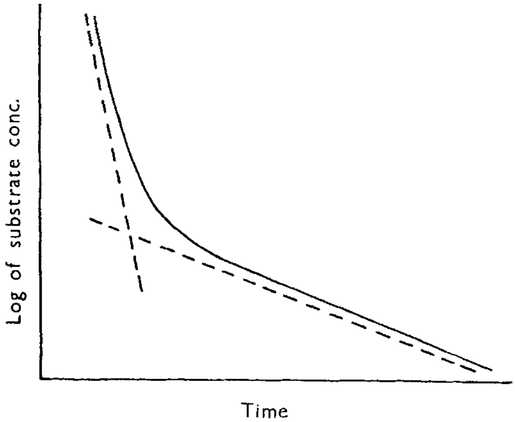

Figure 1. Approximate shape of curve observed during washout of Na^+ from muscle incubated in 0.3 M sucrose solution. Logarithm of concentration of Na^+ within the muscle is plotted against time of incubation of the muscle in 0.3 M sucrose solution.

Recently it was found that the Elovich equation could be derived in a simple way from a theory of biological electron transport across liquid–solid interfaces of subcellular particles[5,6] and that the Elovich equation described experimental data from two such biological systems.[5,7] A similar derivation was then shown probably to be valid for ion transport across the cell surface,[2] suggesting that the cell in some ways resembled a semiconductor.

The derivation of the Elovich equation for biological electron transport goes as follows:

Let us assume that electron conduction occurs across a liquid–solid interface, driven by the potential difference across the interface. For the simplest case, the potential in the liquid is assumed to be determined by the redox potential of a reducible ion dissolved in it. Let there be a compound (x) dissolved in the liquid which can undergo a reversible redox reaction as follows:

$$x_{\mathrm{ox}} + e^- \rightleftharpoons x_{\mathrm{r}}$$

and hence has a redox potential[8] given by

$$E_x = E_x^0 - \frac{kT}{F} \log_e \left[\frac{x_{\mathrm{r}}}{x_{\mathrm{ox}}}\right] \tag{1}$$

where x_{ox} and x_{r} refer to concentrations of the oxidized and reduced species respectively, e^- refers to the electron, T is absolute temperature, F is the Faraday, k is the gas constant and E_x^0 is a constant. It is also evident that

$$x_{\mathrm{ox}} + x_{\mathrm{r}} = C_x \tag{2}$$

where C_x is the total concentration of the oxidized plus reduced species. Hence, Eq. (1) may be written

$$E_x = E_x^0 - \frac{kT}{F} \log_e \left[\frac{x_{\mathrm{r}}}{C_x - x_{\mathrm{r}}}\right] \tag{3}$$

Therefore, the potential difference (V) across the liquid–solid interface is given by (if the potential in the solid is a constant $= A$)

$$V = E_x - A \tag{4}$$

Let us now ask, what would be the current across such an interface? Both experimental and theoretical evidence suggest the use of a logarithmic voltage–current law, of the following form

$$V = b - \frac{kT}{Fa} \log_e \left[-\frac{i}{A'}\right] \tag{5}$$

where V is the voltage difference across the interface, i is the current across the interface, A' is surface area of the interface, and a and b are constants. This equation may be derived theoretically from the general concept of conduction across an activation energy barrier at an interface by charge carriers having a Boltzmann distribution of energies and constant total charge carrier concentration. The diode equation, which is approximately equivalent to this equation, has been derived in a more complex way by Shockley[9] for the solid–solid interface.

One may avoid theoretical considerations by regarding the logarithmic law as an empirical relationship, whose use is justified by the fact that it describes much experimental data on various types of interfaces. The logarithmic law was first observed for *liquid–solid* interfaces by Tafel[10] in 1905. Many more recent observations on liquid–solid interfaces are summarized by Kortüm and Bockris.[11] The logarithmic voltage–current law for *solid–solid* interfaces of diodes has been justified by experimental experience.[12] In addition, the logarithmic law sometimes describes Na^+ and K^+ currents across the *liquid–gel* interface of the cell surface.[2]

One must also mention the relationship between total current across the interface and the concentration of reduced substrate, which is

$$i = \frac{dq}{dt} = F\frac{dx_r}{dt} \tag{6}$$

because transport of 1 mole of electrons across the interface must oxidize or reduce 1 mole of substrate ($q = \text{charge}$).

The *trans*-interface driving potential (given by Eq. (4)) may then be set equal to the voltage drop across the interface given by the logarithmic law (Eq. (5)), so that if one also makes use of Eqs. (3) and (6), one may derive

$$-\frac{kT}{F}\log\left[\frac{x_r}{C_x - x_r}\right] = -\frac{kT}{Fa}\log\left[-\frac{F}{A'}\frac{dx_r}{dt}\right] + (b - E_x^0 + A) \tag{7}$$

which easily may be converted to

$$-\frac{dx_r}{dt} = \frac{A'}{Fg}\left[\frac{x_r}{C_x - x_r}\right]^a \tag{8}$$

where g is a new constant.

Equation (8) is the exact differential equation of activated electron conduction across an interface driven by a redox potential. It will now be shown that the Elovich equation is a close approximation to Eq. (8). The approximation is accurate to about 1–2% over the middle 80% of the reaction.

Let us define a new variable λ as the fractional reduction of substrate, as follows:

$$\lambda = \frac{x_r}{C_x} \tag{9}$$

Combining Eqs. (8) and (9), we obtain

$$-\frac{dx_r}{dt} = \frac{A'}{Fg}\left[\frac{\lambda}{1-\lambda}\right]^a \tag{10}$$

If the expression $\log_{10}[\lambda/(1-\lambda)]$ is expanded in a Taylor series about the point $\lambda = 0.5$, the first two terms are $(-1+2\lambda)$. Therefore, one may write the approximate equation

$$\log_{10}\left[\frac{\lambda}{1-\lambda}\right] \cong 2\lambda - 1 \tag{11}$$

In the range of $0.1 \leqslant \lambda \leqslant 0.9$, Eq. (11) happens to be quite accurate,[6] as can be seen from Fig. 2, which is simply a plot of λ *vs* the log

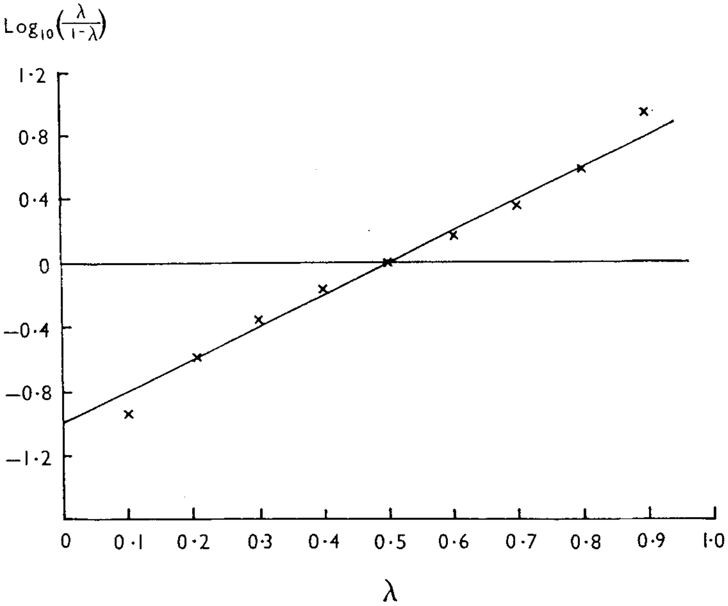

Figure 2. Plot of λ *vs* $\log_{10}[\lambda/(1-\lambda)]$.

function. Equation (11) may also be written in the form

$$\left[\frac{\lambda}{1-\lambda}\right] = \exp[2.3(2\lambda-1)] \tag{12}$$

Combining Eqs. (9), (10), and (11) we obtain

$$-\frac{dx_r}{dt} = \frac{A'}{Fg}\exp\left[2.3a\left(\frac{2x_r}{C_x}-1\right)\right] \tag{13}$$

If we define new constants m and n by

$$m = \frac{A'}{Fg}\exp(-2.3a) \tag{14}$$

$$n = \frac{4.6a}{C_x} \tag{15}$$

then Eq. (13) may be written

$$-\frac{dx_r}{dt} = m\,e^{nx_r} \tag{16}$$

which is a form of the Elovich equation.

To relate this derivation to our muscle Na$^+$ transport experiment, we must consider the analogies between the electron and ion current and potential equations.

First, experimental justification was sought for the postulate of a logarithmic voltage–current law for *ion* conduction across the cell surface. From data of Hodgkin and Huxley[13] for ion transport across the surface of the isolated squid axon at peak membrane current during nervous activity, Na$^+$ and K$^+$ currents were computed as the products of voltage x conductance.[2] The curve of voltage *vs* K$^+$ current for the squid axon is plotted on semilog paper in Fig. 3, and the curve for Na$^+$ current has a similar shape. The data is fairly well approximated by two straight lines, showing that the logarithmic law does indeed apply over reasonably large ranges of current. Two different values of the constant a must be used for different parts of the curve. Such graphs for liquid—solid interfaces of electrodes also sometimes change slope at low values of current.[14] Since the surface of axon membrane is described by the logarithmic conduction law under at least one set of conditions, it seems reasonable to expect that the same might also be true for some other cell surfaces.

Second, it was necessary to justify experimentally the description of ion potential within the cell by Eq. (3), since this is required to derive the Elovich equation. Conventional ion transport theory assumes that the ion potential in the cell equals the chemical potential for ions in *free solution* in the cell, which is given by an equation of the form

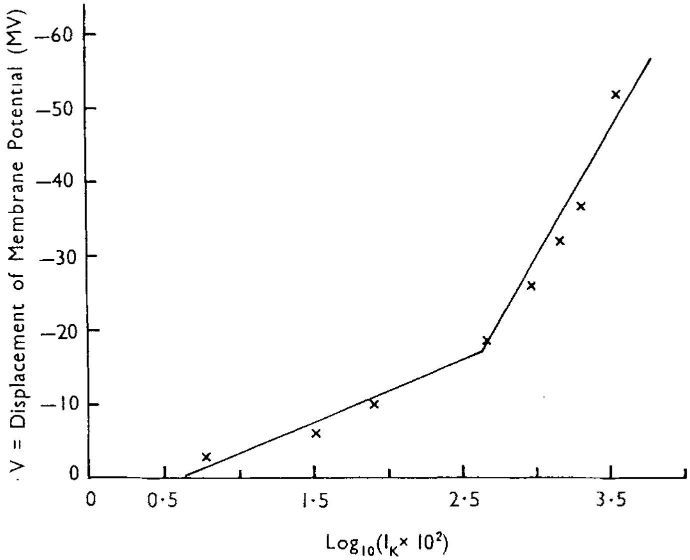

Figure 3. Voltage–current curve of K^+ current across the surface of a single squid axon calculated from data of Hodgkin and Huxley.[13]

$$E_w = E_w^0 - \frac{kT}{F}\log(w) \tag{17}$$

where E_w is the chemical potential for ion w within the cell, w is ion concentration (or activity) within the cell, and E_w^0 is a constant. However, an equation of this form can *not* be used to derive the Elovich equation, and hence can not explain the experimental data which fits the Elovich equation.

Let us suppose then that Eq. (17) might be wrong, and suppose that ion potential in the cell is actually given by an equation of a form consistent with Elovich kinetics. For this we require an ion potential equation of the form

$$E_w = E_w^0 - \frac{kT}{F}\log\left[\frac{w}{C_w - w}\right] \tag{18}$$

where C_w is a constant. If Eq. (18) describes the ion potential in the cell, what does this imply regarding the physico-chemical state of the ions in the cell? How can Eq. (18) be derived for intracellular ions from basic physico-chemical principles?

The author has been able to conceive of only one situation where Eq. (18) would correctly describe the ion potential, which is that all of the ion in the cell is *complexed* by macromolecules. This idea is contrary to the general opinion, but is favored by evidence from several different laboratories.

Let us deal with a monovalent, positively-charged ion, such as Na^+, which we shall designate by w. Let us suppose that w is complexed by sites on the macromolecules of the cell, so that the following equilibrium exists

$$x + w \rightleftharpoons x_w \tag{19}$$

where x represents an unoccupied site, w represents the inorganic ion, and x_w represents the site-ion complex. If *all* of the ion w is complexed, so that the concentration of free w is zero, then this is analogous to the situation at an electrode surface in a solution containing an oxidant and reductant, which are interconvertible by the addition or subtraction of an electron, which might be described by the equation

$$x_{\mathrm{ox}} + e^- \rightleftharpoons x_{\mathrm{r}} \tag{20}$$

where x_{ox} is the oxidant, e^- is the electron, and x_{r} is the reductant.

If the redox pair represented by Reaction (20) were in contact with an electrode which conducted electrons, one might write an equation for the potential that would be experienced by that electrode (Eq. (1)). Analogously, if the ions x and x_w (as given in Reaction (19)) were in contact with a cell surface which conducted the ion w, one might expect the potential experienced by that surface to be describable by a similar equation, as follows

$$E_w = E_w^0 - \frac{kT}{F}\log_e\left[\frac{x_w}{x}\right] \tag{21}$$

where E_w is the potential experienced by the inner side of the cell surface and E_w^0 is a constant. Equation (21) for an *ionic* potential may be derived by the same thermodynamic method used to derived the *electronic* electrode potential, as given for example, by Clark.[8]

It is evident from Reaction (19) (when concentration of free w equals zero) that

$$x + x_w = C_w \tag{22}$$

where C_w = total concentration of sites. Since we have assumed that all ion in the cell is in the complexed form, then the concentration of site occupied by ion must equal the total concentration of ion in the cell, which we shall define as w. Therefore

$$x_w = w \tag{23}$$

Combining Eqs. (21), (22), and (23) we then derive Eq. (18). The Elovich equation for ion transport across a cell surface is then easily derived in a manner like that given for electron transport across a liquid–solid interface.

The above discussion shows that the experimental observation of the Elovich equation for Na^+ leakage from muscle may be considered as evidence in favor of the hypothesis that these ions are all or mostly in a complexed form within muscle cells. Although this hypothesis is not generally accepted at the present time, it is supported by experimental and theoretical studies from several different laboratories. The evidence for ion complexation includes the following: (a) the metabolism of the cell does not produce enough energy to maintain by pump mechanisms the observed intracellular ion concentrations;[15] (b) measurements of extracellular *vs* intracellular ion concentrations conform to the hypothesis that ions are bound by cells in conformity with the Langmuir adsorption isotherm,[16,17] which allows one to calculate that at physiological concentrations of ion, most ion in the cell is in the adsorbed state; and (c) n.m.r. spectra of Na^+ in fresh muscle compared with spectra of the same samples after ashing show that approximately 70% of total Na^+ of fresh muscle gives no detectable n.m.r. spectrum.[18] This is probably due to complexation of Na^+ with macromolecules which broadens the n.m.r. spectrum beyond detection. An analogous effect on the n.m.r. spectrum is observed when Na^+ interacts with ion exchange resin.

The findings that ions in cells occupy discrete binding sites (or energy levels) like electrons in a semiconductor, and that a logarithmic conduction law probably describes ion conduction across the cell surface as is true for electron conduction across a semiconductor surface, suggest that the cell, like a semiconductor, may possess a degree of crystallinity. It is then reasonable to expect that concepts derived from studies of liquid crystals may prove applicable to cellular phenomena.

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