

# Theoretical Effects of Transmembrane Electroneutral Exchange on Membrane Potential

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**ABSTRACT** Transmembrane electroneutral transport mechanisms [e.g., Na/H exchange, Cl/HCO<sub>3</sub> exchange, (K + Cl) cotransport] have recently been identified in a wide variety of cell types. If these exchanges sum to give a net electroneutral Na/K exchange, they may hyperpolarize the membrane potential beyond the value calculated from the Mullins-Noda equation, provided the cell maintains steady state intracellular ionic concentrations. In extreme circumstances, the membrane potential could hyperpolarize beyond the potassium reversal potential. This effect is mediated by the electrogenic Na/K pump. If either Na or K exchanges electroneutrally against a third ion (e.g., Na/Ca exchange), then the exchange may depolarize the membrane potential.

## INTRODUCTION

Electroneutral transport is usually assumed not to contribute to the membrane potential ( $E_m$ ), although  $E_m$  can be affected by direct interaction within the membrane between an electroneutral process and an electrodiffusive pathway (Schwartz, 1971). We will show that, for a cell in steady state and in the absence of any such interaction within the membrane, the magnitude of an electroneutral exchange can affect  $E_m$  even to the extent, in extreme circumstances, of driving  $E_m$  beyond the most negative ionic equilibrium potential (usually  $E_K$ ).

Of the various equations for  $E_m$ , the most widely used, the Goldman, Hodgkin, Katz (GHK) equation (Goldman, 1943; Hodgkin and Katz, 1949), was originally derived by assuming a constant electric field across the membrane and equating the sum of the passive ionic currents to zero. The derivation only requires constant fluxes (flux steady state) so that, when applied to a membrane enclosing a cell, the intracellular concentrations may be changing. Indeed, because no allowance is made for active transport, there must be a net flux of each permeant ion across the membrane. Thus, the equation does not strictly apply to living cells, which have constant intracellular concentrations (concentration steady state).

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## MODIFICATIONS OF THE GHK EQUATION

*Active Na/K Transport*

The constant field requirement has been relaxed in a variety of ways (Schultz, 1980) to make the GHK equation more generally applicable to membranes with no active transport. To accommodate active transport, the GHK equation has been modified in two different ways. Moreton (1969) included the absolute fluxes caused by the pump using the same zero net current constraint as used in deriving the GHK equation. Mullins and Noda (1963), on the other hand, derived a steady state equation, which included the Na/K coupling ratio (stoichiometry) of the pump and not the magnitude of the pump fluxes.

*Mullins-Noda Equation*

To derive the Mullins-Noda (MN) equation, the sum of the fluxes across the membrane is equated to zero for each ionic species so that passive diffusion is balanced by active transport and there is no net transmembrane movement of ions. The equation describes a concentration steady state and the constraints necessarily imply that the net transmembrane current is zero. Considering a simple case where the membrane is permeable only to K and Na (as is often assumed, for example, in nerve [Hille, 1977] and resting cardiac muscle [Spere-lakis, 1979]) and the gradients for these ions are maintained by an active Na/K pump, the MN equation reads

$$E_m = \frac{RT}{F} \ln \left[ \frac{r \cdot P_K \cdot K_o + P_{Na} \cdot Na_o}{r \cdot P_K \cdot K_i + P_{Na} \cdot Na_i} \right],$$

where  $K_o$  and  $K_i$  are extra- and intracellular potassium concentrations,  $Na_o$  and  $Na_i$  are extra- and intracellular sodium concentrations,  $P_K$  and  $P_{Na}$  are potassium and sodium permeabilities,  $r$  is the Na/K pump stoichiometry,<sup>1</sup> and  $R$ ,  $F$ , and  $T$  have their usual meaning. Assuming reasonable values for the concentrations and calculating  $E_m$  for varying  $P_{Na}/P_K$  shows that the difference in membrane potential between a cell with an electroneutral and an electrogenic Na/K pump (with  $r = 3/2$ ) will not be much greater than 10 mV: this pump contribution is maximum when  $P_{Na} \approx P_K$  and cannot hyperpolarize the membrane beyond  $E_K$  in the steady state (see also Ascher, as referred to in Thomas, 1972).

The dominant constraint in deriving the MN equation is the Na/K pump stoichiometry ( $r$ ): the membrane must seek a potential, defined by the equation, where the passive sodium and potassium fluxes ( $j_{Na}$  and  $j_K$ ) flow in the same ratio as the active fluxes ( $m_{Na}$  and  $m_K$ ) so that the passive fluxes can be balanced by the Na/K pump. With one-to-one pump stoichiometry ( $r = 1$ ), the MN equation formally reduces to the GHK equation because  $j_{Na}/j_K = -1$  (or  $j_{Na} + j_K = 0$ ), which is the constraint used to derive the GHK equation. However, the GHK equation is not a special case of the MN equation because the GHK equation applies only to a flux steady state, whereas the MN equation with  $r = 1$  applies to a concentration steady state.

<sup>1</sup> We assume that the Na/K pump has a fixed stoichiometry and is unable to respond to changing conditions by varying its stoichiometry ("slippage").

*Electroneutral Na/K Exchange*

Evidence from several cell systems suggests the existence of various exchangers and cotransporters that appear to be electroneutral. These include Na/H exchange (Roos and Boron, 1981; Piwnica-Worms and Lieberman, 1983), Cl/HCO<sub>3</sub> exchange (for review, see Lowe and Lambert, 1983), and (K + Cl) cotransport (for review, see Hoffman, 1982) (Fig. 1a), which may act in unison in a variety of physiological phenomena including pH<sub>i</sub> regulation (Roos and Boron, 1981; Nuccitelli and Deamer, 1982) and changes in cell volume (Lowe and Lambert, 1983; Cala, 1980). In the steady state, the net effect of these exchange mechanisms could be an electroneutral Na/K exchange (Fig. 1b): for

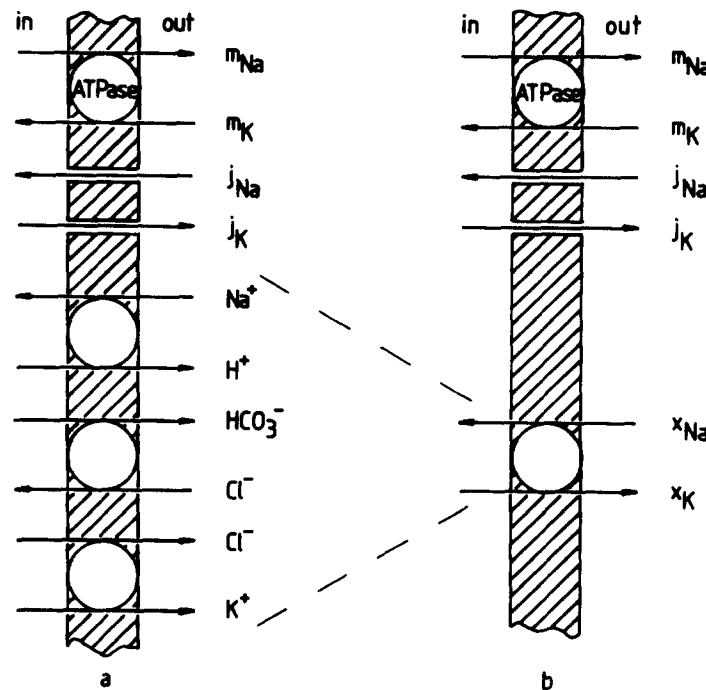


FIGURE 1. (a) Schematic for a membrane containing an Na/K pump, electrodiffusive pathways for Na and K, and various electroneutral exchangers. (b) Equivalent schematic with an electroneutral Na/K exchange. The outward movement of an HCO<sub>3</sub><sup>-</sup> is equivalent to the inward movement of an H<sup>+</sup> so that the movements of HCO<sub>3</sub><sup>-</sup> and H<sup>+</sup> cancel out.

this system, the following equations define the constraints.

$$x_{Na} = -x_K \tag{1}$$

$$r = -m_{Na}/m_K \tag{2}$$

$$\beta = x_{Na}/j_{Na} \tag{3}$$

$$j_{Na} + m_{Na} + x_{Na} = 0 \tag{4}$$

$$j_K + m_K + x_K = 0 \tag{5}$$

where  $x_{\text{Na}}$  and  $x_{\text{K}}$  are the electroneutral Na and K fluxes, and efflux is defined as positive. Eq. 1 constrains the exchange to be electroneutral; Eq. 2 defines the pump stoichiometry; Eq. 3 defines  $\beta$  as a dimensionless measure of the magnitude of the electroneutral exchange flux; and Eqs. 4 and 5 are for mass conservation of Na and K.

The passive fluxes are functions of the ionic concentrations and the membrane potential:

$$j_{\text{Na}} = P_{\text{Na}} \cdot f(E_m) \cdot (\text{Na}_o - \text{Na}_i e^\xi) \quad (6)$$

$$j_{\text{K}} = P_{\text{K}} \cdot f(E_m) \cdot (\text{K}_o - \text{K}_i e^\xi), \quad (7)$$

where  $\xi = E_m F / RT$  is a dimensionless measure of the membrane potential. The function  $f(E_m)$  depends on the particular model for the electric field profile across the membrane and for a constant field,  $f(E_m) = \xi / (1 - e^\xi)$ . However,  $f(E_m)$  cancels out in the following derivation.

Using Eqs. 1–5,

$$r = \frac{-m_{\text{Na}}}{m_{\text{K}}} = \frac{-(j_{\text{Na}} + x_{\text{Na}})}{(j_{\text{K}} + x_{\text{K}})} = \frac{-(j_{\text{Na}} + \beta j_{\text{Na}})}{(j_{\text{K}} - \beta j_{\text{Na}})}$$

Therefore,

$$\frac{j_{\text{Na}}}{j_{\text{K}}} = \frac{-r}{1 + \beta(1 - r)} = -\gamma, \quad (8)$$

where  $\gamma = -j_{\text{Na}}/j_{\text{K}}$  is the ratio of the passive fluxes. Given a fixed electroneutral exchange flux<sup>2</sup> ( $\beta$ ) and a fixed Na/K pump stoichiometry ( $r$ ), Eq. 8 is the constraint placed on the ratio of the passive fluxes so that they can be balanced by the sum of the exchange and the pump fluxes. Thus,  $\gamma$  fulfills the same function as does  $r$  in the derivation of the MN equation in which the passive fluxes are constrained to flow in the ratio  $-j_{\text{Na}}/j_{\text{K}} = r$ , so that they can be balanced by the pump fluxes. Substituting Eqs. 6 and 7 into Eq. 8:

$$E_m = \frac{RT}{F} \ln \left[ \frac{\gamma \cdot P_{\text{K}} \cdot \text{K}_o + P_{\text{Na}} \cdot \text{Na}_o}{\gamma \cdot P_{\text{K}} \cdot \text{K}_i + P_{\text{Na}} \cdot \text{Na}_i} \right], \quad (9)$$

which, as expected, has the same form as the MN equation but with  $r$  replaced by  $\gamma$ . If  $\beta = 0$  (no electroneutral exchange), then  $\gamma = r$ , and Eq. 9 reduces to the MN equation. Similarly, if  $r = 1$  (electroneutral Na/K pump), then  $\gamma = 1$ , and Eq. 9 reduces to the MN equation with  $r = 1$ , regardless of the value of  $\beta$ . Therefore, electroneutral Na/K exchange only affects  $E_m$  in the presence of an electrogenic Na/K pump. This reflects the fact that the greater the passive Na influx, the greater the pump rate required to maintain a constant  $\text{Na}_i$ , and, therefore, the greater the electrogenic component of  $E_m$ . In other words, changes

<sup>2</sup> Strictly speaking, since  $\beta = x_{\text{Na}}/j_{\text{Na}}$  and  $j_{\text{Na}}$  is a function of  $E_m$ ,  $\beta$  will vary with  $E_m$  even when  $x_{\text{Na}}$  is fixed. The assumption of  $\beta$  being set independently of  $E_m$  does not invalidate the argument; the problem is treated more fully below.

in membrane potential are generated by the Na/K pump response as the system endeavors to maintain a concentration steady state.

Although Eq. 9 appears to be formally equivalent to the MN equation, it is actually quite different. As can be seen from Eqs. 3 and 6,  $\beta$  (and hence  $\gamma$ ) is a function of  $E_m$  even for a constant  $x_{Na}$ , whereas in the MN equation,  $r$  is fixed. Moreover, Eq. 9 is transcendental in  $E_m$  as can be shown by substituting Eq. 6 in its constant field form into Eq. 9. Another difference is that  $r$  in the MN equation must be positive, whereas  $\gamma$  ( $= -j_{Na}/j_K$ ) in Eq. 9 can be negative (Fig. 2). At first sight, the singularity occurring in Fig. 2 at  $\beta = 2$  may appear unphysiological, but this represents the point at which  $x_K = m_K$  ( $j_K = 0$ ) and this occurs when  $E_m = E_K$ .

The existence of a region of negative  $\gamma$  is an interesting consequence of a large electroneutral flux. As  $x_{Na}$  increases, the bulk of the increase must be offset by  $m_{Na}$  because variations in  $E_m$  affect  $j_{Na}$  less than  $j_K$ : this can be deduced from Eqs. 6 and 7 since  $P_{Na} \ll P_K$  and  $Na_o/Na_i \gg K_o/K_i$ . Linked to these increases in

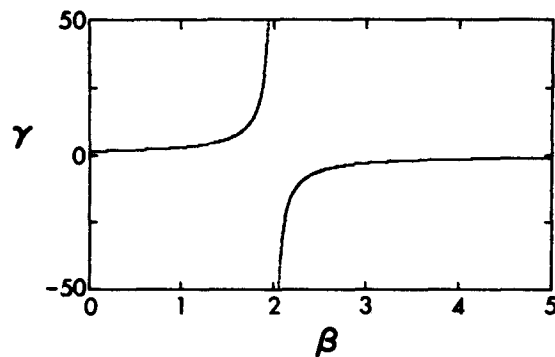


FIGURE 2. Relation between  $\beta = x_{Na}/j_{Na}$  and  $\gamma = j_{Na}/j_K$  calculated for  $r = 3/2$ . Both variables are dimensionless.

$x_{Na}$  and  $m_{Na}$  are increases in  $x_K$  (equal to the increase in  $x_{Na}$ ) and  $m_K$ . Because  $r > 1$ ,  $m_K$  increases less than  $m_{Na}$  (and hence less than  $x_{Na}$ ) and the discrepancy between  $m_K$  and  $x_K$  has to be balanced by  $j_K$ . Inevitably, a point is reached when  $x_K$  becomes so large that the only way Eq. 5 can be satisfied is for  $j_K$  to become negative (i.e., *inward* passive K flux). This, implies that  $E_m$  must become negative to  $E_K$ . The theoretical limit to this type of behavior is when  $E_m \rightarrow -\infty$  as the membrane tries to compensate the increasing electroneutral exchange flux with an increasing inward potassium flux. In practice, the Na/K pump rate will saturate and this will limit the degree to which the pump can drive  $E_m$  below  $E_K$ .

The incorporation of an electroneutral exchange into the system has altered the balance between the ratio of the active fluxes ( $r = -m_{Na}/m_K$ ) and the ratio of the passive fluxes ( $\gamma = -j_{Na}/j_K$ ). In the MN equation,  $\gamma$  must equal  $r$  for the maintenance of a concentration steady state; otherwise the Na/K pump, no matter what its rate, will be unable to balance  $j_{Na}$  and  $j_K$  simultaneously. On the other hand, in Eq. 9, to enable the system to maintain a concentration steady

state,  $\gamma$  must now differ from  $r$  in a manner determined by the magnitude of the electroneutral exchange.

Eq. 9 is useful conceptually but is inconvenient for calculation because of its transcendental nature. An alternative form can be derived from Eqs. 1-7 in conjunction with the constant field expression for  $f(E_m)$ :

$$E_m = \frac{RT}{F} \ln \left[ \frac{rP_K \cdot K_o + P_{Na} \cdot Na_o - \frac{x_{Na} \cdot (r-1)}{\xi}}{rP_K \cdot K_i + P_{Na} \cdot Na_i - \frac{x_{Na} \cdot (r-1)}{\xi}} \right] \quad (10)$$

Eq. 10 is still transcendental in  $E_m$ , but for calculation purposes it can be inverted to give an analytical function for  $x_{Na}$  as a function of the other variables. This has been used to calculate the family of curves in Fig. 3, which show how  $E_m$

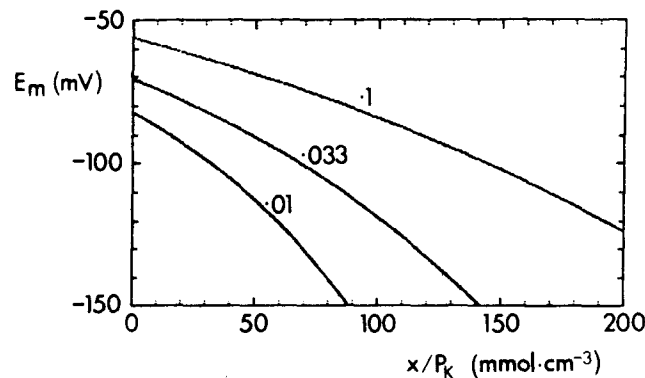


FIGURE 3. Dependence of  $E_m$  on  $x_K$  where  $x_K$  is expressed relative to  $P_K$ . Calculated for (mM)  $Na_i = 12$ ,  $K_i = 130$ ,  $Na_o = 144$ , and  $K_o = 5.4$ . The numbers adjacent to the curves are the values of  $P_{Na}/P_K$ .

depends on the electroneutral exchange flux for various values of  $P_{Na}/P_K$ : small values of  $P_{Na}/P_K$  make  $E_m$  more sensitive to the exchange flux magnitude.

El-Sharkaway and Daniel (1975) considered the contribution of an electrogenic pump (with no electroneutral exchanges) to the membrane potential in the non-steady state and obtained (neglecting their  $P_{Cl}$  terms):

$$E_m = \frac{RT}{F} \ln \left[ \frac{P_K \cdot K_o + \left(1 - \alpha + \frac{\alpha}{r}\right) \cdot P_{Na} \cdot Na_o}{P_K \cdot K_i + \left(1 - \alpha + \frac{\alpha}{r}\right) \cdot P_{Na} \cdot Na_i} \right], \quad (11)$$

where  $\alpha = -m_{Na}/j_{Na}$ . Eq. 11 is the same as Eq. 9 except that  $\beta$  is replaced by  $\alpha - 1$ , leading to  $1/\gamma = 1 - \alpha + \alpha/r$ . The reason for this similarity is that both equations result from the relaxation of the constraint,  $j_{Na}/j_K = m_{Na}/m_K$  (i.e.,  $\gamma =$

$r$ ), in one case because of the introduction of an electroneutral exchange (Eq. 9), and in the other by allowing a non-steady state (Eq. 11).

#### *Na/H Exchange*

In most cell systems, metabolically produced protons have to be extruded, and in many cases the Na/H exchanger has been identified as the mechanism by which this is done.

In cell systems that have a low free  $\text{Cl}^-$  permeability (e.g., cardiac muscle [Piwnica-Worms et al., 1983], nerve [Junge, 1981]) the  $\text{Cl}/\text{HCO}_3$  exchange and the (K + Cl) cotransport would have to run at almost the same rate to maintain the steady state Cl concentration, whereas the Na/H exchange is free to run at a different rate. Indeed, if the Na/H exchange runs at the same rate as the other exchangers, then no acid equivalents will be pumped out of the cell.

Consider, for the sake of discussion, a cell with low proton permeability and the Na/H exchange as the only electroneutral exchanger. Defining the Na/H exchange flux as  $x_{\text{Na}} = \epsilon \cdot j_{\text{Na}}$  and combining this with Eqs. 2, 4, and 5 (but omitting the  $x_{\text{K}}$  term in Eq. 5) gives  $\gamma = r/(1 + \epsilon)$ , which implies that  $\gamma < r$  and hence that the membrane potential is less negative than predicted by the MN equation. As with the previous case of an electroneutral Na/K flux, the presence of an electroneutral Na flux has upset the balance between the passive electrodiffusive fluxes for Na and K: in this case, however, the effect is a depolarization. This is contrary to what may be predicted intuitively by linking an increased Na influx to stimulation of the electrogenic Na/K pump: although in the short term (i.e., non-steady state) an increased Na/H exchange may stimulate the Na/K pump to hyperpolarize the membrane, in the long term the ratio of passive Na and K fluxes ( $\gamma$ ), and not the pump rate, will determine  $E_m$ .

Returning to a membrane that possesses all three exchangers and for which the Na/H exchanger is running faster than the other two, the Na/H exchange can be divided into a part that matches the Cl exchange flux ( $x'_{\text{Na}}$ ) and a part that is in excess ( $x''_{\text{Na}}$ ). The matching part ( $x'_{\text{Na}} = \beta \cdot j_{\text{Na}}$ ) sums with the other electroneutral fluxes to give a net electrogenic Na/K exchange while the remainder ( $x''_{\text{Na}} = \epsilon \cdot j_{\text{Na}}$ ) pumps protons out of the cell. We have discussed these two cases in isolation and it is a trivial matter to show that, when combined,  $\gamma$  is given by:

$$\gamma = r/[1 + \beta(1 - r) + \epsilon].$$

This shows that, depending on the relative magnitudes of  $\beta$  and  $\epsilon$  (i.e.,  $x'_{\text{Na}}$  and  $x''_{\text{Na}}$ ), the membrane potential may be more or less negative than that predicted by the MN equation.

#### *Electroneutral Na/Ca Exchange*

Other electroneutral exchangers may also affect membrane potential. Consider, for the sake of discussion, the different effects on  $E_m$  of maintaining low  $\text{Ca}_i$  either by an electroneutral Na/Ca exchange or by an electrogenic Ca-ATPase pump (Fig. 4). In the case of a Ca-ATPase, the Ca pump flux,  $m_{\text{Ca}}$ , is regulated to exactly balance the diffusive flux,  $j_{\text{Ca}}$ , and Eq. 9 still applies, so that neither term will directly affect the membrane potential. In the case of a Na/Ca exchange,

we have

$$m_{\text{Na}} + j_{\text{Na}} + x_{\text{Na}} = 0 \quad (4)$$

$$m_{\text{K}} + j_{\text{K}} = 0 \quad (12)$$

$$j_{\text{Ca}} + x_{\text{Ca}} = 0 \quad (13)$$

$$x_{\text{Na}} = -2x_{\text{Ca}} \quad (14)$$

and the constant field expression for  $j_{\text{Ca}}$  (Sjodin, 1980):

$$j_{\text{Ca}} = \frac{P_{\text{Ca}} \cdot 2\xi}{1 - e^{2\xi}} (\text{Ca}_o - \text{Ca}_i e^{2\xi}). \quad (15)$$

From Eqs. 2, 4, and 12–14,

$$r = \frac{-m_{\text{Na}}}{m_{\text{K}}} = \frac{-(j_{\text{Na}} + x_{\text{Na}})}{j_{\text{K}}} = \frac{-(j_{\text{Na}} + 2j_{\text{Ca}})}{j_{\text{K}}}$$

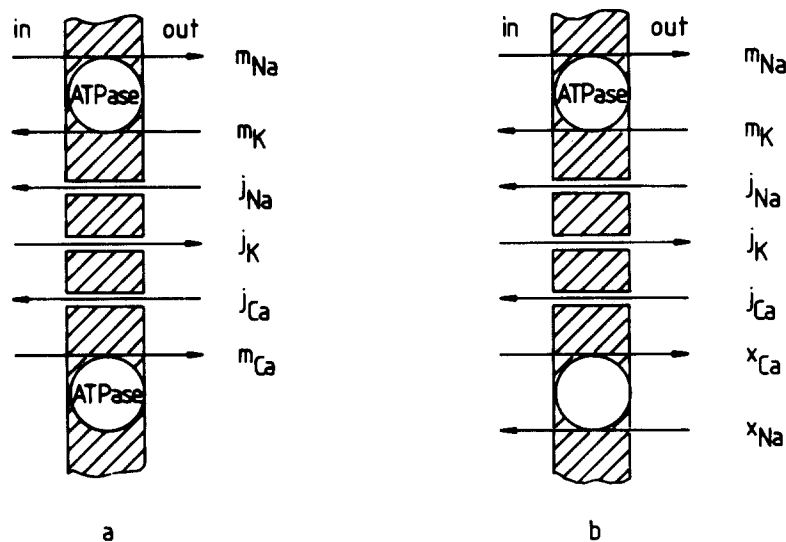


FIGURE 4. (a) Schematic for the maintenance of low  $\text{Ca}_i$  by a Ca-ATPase. (b) Schematic for the maintenance of low  $\text{Ca}_i$  by Na/Ca exchange.

or  $rj_{\text{K}} + j_{\text{Na}} + 2j_{\text{Ca}} = 0$ . Using Eqs. 6, 7, and 15, this gives an extension of the MN equation that includes  $P_{\text{Ca}}$ :

$$E_m = \frac{RT}{F} \ln \left[ \frac{4P'_{\text{Ca}} \cdot \text{Ca}_o + rP_{\text{K}} \cdot \text{K}_o + P_{\text{Na}} \cdot \text{Na}_o}{4P''_{\text{Ca}} \cdot \text{Ca}_i + rP_{\text{K}} \cdot \text{K}_i + P_{\text{Na}} \cdot \text{Na}_i} \right], \quad (16)$$

where  $P'_{\text{Ca}} = P_{\text{Ca}}/(1 + e^{\xi})$  and  $P''_{\text{Ca}} = P_{\text{Ca}}/(1 + e^{-\xi})$ .

Eq. 16 has been derived by Sjodin (1980), and when compared with Eq. 9, it suggests that a membrane with an electroneutral Na/Ca exchange may have a different membrane potential from that of a membrane with a Ca-ATPase: the Na/Ca exchange will shift  $E_m$  toward  $E_{\text{Ca}}$  (i.e., will depolarize the membrane) by an amount dependent on  $P_{\text{Ca}}$ .



Sjodin interprets Eq. 16 as showing that an electroneutral Na/Ca exchange does not affect membrane potential. However, his statement relates to a comparison between the case where an electrodiffusive Ca flux is balanced by an electroneutral Na/Ca exchange and the case where the electrodiffusive Ca flux is not balanced by any exchange or pump.

#### DISCUSSION

We have considered simple systems with fixed Na/K pump stoichiometry and negligible free chloride ion permeability. When these systems are in a concentration steady state, an electroneutral exchange can affect the membrane potential provided the exchange involves either Na or K. A net electroneutral exchange of Na for K operating in parallel with an electrogenic Na/K pump will hyperpolarize the membrane and could lead to a steady state in which  $E_m$  is negative to  $E_K$ . The hyperpolarization is generated by the electrogenic pump current as the pump rate increases to maintain the concentration steady state. On the other hand, a net electroneutral exchange involving either Na or K against a third cation (e.g., Na/Ca exchange) will shift  $E_m$  toward the Nernst potential for the third cation. Any ionic exchange can also indirectly affect membrane potential by altering the ionic distributions. In contrast, for a system in which the only constraint is that the net current is zero (i.e., flux steady state), the exchange cannot enter into the membrane potential equation because an electroneutral exchange cannot contribute to the net current.

Thus, when cells are constrained to operate in a concentration steady state, the membrane potential may be affected by electroneutral exchanges so that  $E_m$  can either be positive or negative to the value predicted by the MN equation. When searching for such an effect, it is tempting to consider changes in metabolic rate that may well entail a change in the rate of proton production. However, interpretation of such experiments is complicated by changes in  $E_m$  caused by changes in the internal ionic concentrations, as well as effects of electrogenic cotransport mechanisms [e.g., (Na + glucose) and (Na + amino acid) cotransports (Gunn, 1980)].

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#### REFERENCES

- Cala, P. M. 1980. Volume regulation by *Amphiuma* red blood cells. The membrane potential and its implications regarding the nature of the ion-flux pathways. *J. Gen. Physiol.* 76:683-708.
- El-Sharkaway, T. Y., and E. E. Daniel. 1975. Electrogenic sodium pumping in rabbit small intestinal smooth muscle. *Am. J. Physiol.* 229:1277-1286.
- Goldman, D. E. 1943. Potential, impedance and rectification in membranes. *J. Gen. Physiol.* 27:37-60.

- Gunn, R. B. 1980. Co- and counter-transport mechanisms in cell membranes. *Annu. Rev. Physiol.* 42:249–259.
- Hille, B. 1977. Ionic basis of resting and action potentials. In *Handbook of Physiology, Section 1, Vol. 1: Cellular Biology of Neurons, part I*. J. Brookhart and V. Mountcastle, editors. American Physiological Society, Bethesda, MD. 99–136.
- Hodgkin, A. L., and B. L. Katz. 1949. The effect of sodium ions on the electrical activity of the giant axon of the squid. *J. Physiol. (Lond.)*. 108:37–77.
- Hoffmann, E. K. 1982. Anion exchange and anion-cation cotransport systems in mammalian cells. *Phil. Trans. R. Soc. Lond. B Biol. Sci.* 299:519–535.
- Junge, D. 1981. Ionic properties of resting and active membranes. In *Nerve and Muscle Excitation*. Second edition. Sinauer Associates, Inc., Sunderland, MA. 31–47.
- Lowe, A. G., and A. Lambert. 1983. Chloride-bicarbonate exchange and related transport processes. *Biochim. Biophys. Acta.* 694:353–374.
- Moreton, R. B. 1969. An investigation of electrogenic sodium pump in snail neurones using the constant field theory. *J. Exp. Biol.* 51:181–201.
- Mullins, L. J., and K. Noda. 1963. The influence of sodium-free solutions on the membrane potential of frog sartorius muscle. *J. Gen. Physiol.* 47:117–132.
- Nuccitelli, R., and D. W. Deamer, editors. 1982. *Intracellular pH: Its Measurement, Regulation, and Utilization in Cellular Functions*. Alan R. Liss, Inc., New York.
- Piwnica-Worms, D., R. Jacob, C. R. Horres, and M. Lieberman. 1983. Transmembrane chloride flux in tissue-cultured chick heart cells. *J. Gen. Physiol.* 81:731–748.
- Piwnica-Worms, D., and M. Lieberman. 1983. Microfluorometric monitoring of  $\text{pH}_i$  in cultured heart cells: Na-H exchange. *Am. J. Physiol.* 244:C422–C428.
- Roos, A., and W. F. Boron. 1981. Intracellular pH. *Physiol. Rev.* 61:296–434.
- Schultz, S. G. 1980. Diffusion potential. In *Basic Principles of Membrane Transport*. Cambridge University Press, Cambridge. 42–56.
- Schwartz, T. L. 1971. Direct effects on membrane potential due to “pumps” that transfer no net charge. *Biophys. J.* 11:944–960.
- Sjodin, R. A. 1980. Contribution of Na/Ca transport to the resting membrane potential. *J. Gen. Physiol.* 76:99–108.
- Sperelakis, N. 1979. Origin of the cardiac resting potential. In *Handbook of Physiology, Section 2, Vol. 1: The Cardiovascular System*. R. M. Berne, editor. American Physiological Society, Bethesda, MD. 187–267.
- Thomas, R. C. 1972. Electrogenic sodium pump in nerve and muscle cells. *Physiol. Rev.* 52:563–594.