# THE DOUBLE FIXED CHARGE MEMBRANE

## SOLUTION-MEMBRANE ION PARTITION EFFECTS AND MEMBRANE POTENTIALS

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ABSTRACT An analysis is made of the effect of solution-membrane partition of ions on the electrostatic potential and ion concentration profiles in fixed charge membranes. It is shown that the inclusion of partition effects gives rise to large solution-membrane "Donnan" potentials even when the concentration of fixed charges is of the same order as the concentration of the external solution. This effect renders the system and the simplified analysis of the double fixed charge membrane (FCM) previously given more applicable to biological membranes. An analysis is also given of the voltage dependence of the fluxes of individual ion species in the double FCM when it separates different ionic solutions and an expression is deduced for the membrane resting potential. Although the latter is similar in form to the Goldman-Hodgkin-Katz (GHK) equation the corresponding value of the permeability ratio $P_{Cl}/P_K$ is under certain specified conditions both concentration and potential dependent.

## INTRODUCTION

The membrane potential developed across a membrane consisting of a single lattice of fixed charges has been investigated in some detail (see Meyers and Sievers, 1936; Teorell, 1953). The effects of ion selectivity in such FCM's have also been the subject of detailed studies (Eisenman, 1962; Karreman and Eisenman, 1962; Conti and Eisenman, 1965, *a*, *b*).

The electrical characteristics of a membrane consisting of the juxtaposition of two fixed charge lattices of opposite sign display many of the features observed in biological membranes. These include both the DC and AC characteristics, the punch-through effect, the effect of pH on these characteristics (e.g., Coster, 1965, 1969, 1973) and other ramifications of the model (e.g., Adam, 1970; Candia, 1970; Coster, 1972).

In view of the possible relevance of the double fixed charge model to biological systems an analysis has now been made to determine: (*a*) the effect of solution-membrane ion partition on the potential and ion concentration profiles, (*b*) the fluxes of individual ion species when the membrane separates different ionic solutions, and, (*c*) the resting potential developed across the membrane under these conditions.

## THE DOUBLE FCM MODEL

The system to be considered consists of a lattice of fixed positive charges imbedded n an inert matrix which is in contact with a similar lattice of fixed negative charges. The membrane separates two different ionic solutions (see also Fig. 2). Details of this model have been discussed previously (e.g., see Coster, 1965). In the present analysis the ion partition effect, which arises from differences in the values of the dielectric constant of the membrane and the aqueous solutions, will also be investigated and taken into account.

## THE EFFECT OF SOLUTION-MEMBRANE ION PARTITION IN FCM's

The value of the dielectric constant of the various regions of the plasma membrane are not known. It would appear from various electrical measurements and permeation studies, however, that the value is less than the value of 78.5 for the external solution.

For two media of different dielectric constant differences in the ion concentrations occur as a result of the differences in the electrostatic self-energies of the ions (Born, 1920). The partition of ions between the two media can be obtained from the energy difference with the aid of the Boltzmann equation. Thus if the energy difference is $\Delta W$ the concentrations $C_1$ and $C_2$ of the ions are related by,

$$\frac{C_2}{C_1} = \exp - \Delta W/kT = \gamma, \tag{1}$$

where $\gamma$ is the partition coefficient.

The complete profiles of the energy difference $\Delta W$ (and hence the ion concentrations) near the interface of the two media can be obtained by application of the method of electrostatic images (Neumcke and Läuger, 1969). The results of Neumcke and Läuger show that the profiles settle down over a distance of about 5 Å from the interface. In the following analysis it will be assumed that the energy profiles settle down in distances small compared with the widths of the fixed charge regions.

Consider the system shown in Fig. 1. It consists of a lattice of fixed charge concentration $N^+$ and dielectric constant $\epsilon_2$, immersed in an ionic solution of dielectric constant $\epsilon_1$. The concentration of cations in the external solutions is $P_0$, equal to the concentration $N_0$ of anions.

In the light of the results previously discussed (Mauro, 1962; Coster, 1965) for a system with equal dielectric constants, it is most convenient to approach the present problem from considerations of the conditions required for electrochemical equilib-

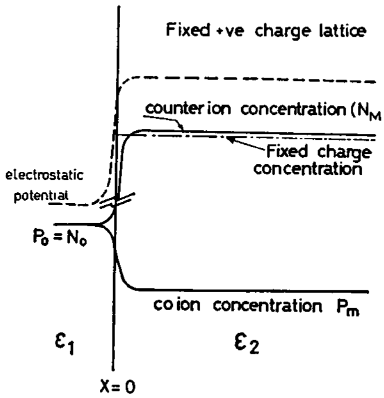

FIGURE 1 Qualitative profiles of the electrostatic potential and mobile ion concentrations for a positive (+ve) fixed charge lattice of dielectric constant $\epsilon_2$ immersed in an aqueous solution of dielectric constant $\epsilon_1$. The fixed charge lattice extends from $x = 0$ to the right. At large negative distances from the lattice the concentration $P_0$ of cations equals the concentration $N_0$ of anions.

rium. To this end the (dielectric) self-energies of the ions are specifically included in the standard chemical potentials of the ions in the two media.

At equilibrium the following condition prevails for the cations $P$

$$\mu_P^0(x = -\infty) + kT \ln P_0 + z_P e\psi(-\infty) = \mu_P^0(x) + kT \ln P(x) + z_P e\psi(x). \quad (2)$$

A similar expression holds for the anions. Here $\mu_P^0(x)$ refers to the standard chemical potential of the cations $P$ ($\mu_N^0$ for the anions) $-\mu_P^0$ and $\mu_N^0$ are the functions of the dielectric constants $\epsilon_1$ and $\epsilon_2$ ; $P(x)$ is the concentration of the cations [$N(x)$ for the anions], here expressed in ions per unit volume; $\psi(x)$ is the electrostatic potential; $z_P$ is the valency of the cations; and $e$ is the absolute value of the electronic charge.

From the equilibrium condition 2 the concentration of, for instance, the cations in the fixed charge lattice is given by,

$$P(x) = P_0 \gamma_P \exp -\left(\frac{z_P e[\psi(x) - \psi(-\infty)]}{kT}\right), \quad (3)$$

where

$$\gamma_P = \exp -\left(\frac{[\mu_P^0(x) - \mu_P^0(-\infty)]}{kT}\right).$$

Similar expressions hold for the anions.

If at $x = -\infty$, where the ion concentration $P_0 = N_0$, the potential $\psi(-\infty)$ is taken as zero, then using the expression 3, the space charge density $\rho$ inside the lattice is given by

$$\rho(x) = q\left(\gamma_P P_0 \exp -\frac{q\psi(x)}{kT} - \gamma_N N_0 \exp +\frac{q\psi(x)}{kT}\right) + qN^+, \quad (4)$$

where $q = | ze |$ is the absolute value of the charge on the ions, here assumed to be of equal valency. The partition coefficients $\gamma_P$ and $\gamma_N$, as defined, are functions of $x$.

The profile of potential can now be calculated using the Poisson equation,

$$\frac{d^2\psi}{dx^2} = -\frac{\rho(x)}{\epsilon}.$$

The detailed form of this profile near the lattice boundary can be evaluated using the method described by Mauro (1962). Since it is not required for the remaining analysis this detail of the profile near the boundary will not be investigated here.

At large distances from the boundary both $d\psi/dx$ and $d^2\psi/dx^2 \rightarrow 0$. As in previous analysis of this fixed charge system (Mauro, 1962; Coster, 1965) it then follows that at large distances the first term in Eq. 4 is small compared with the second and the electrostatic potential is given by,

$$\psi = \frac{kT}{q}\ln\left(\frac{N^+}{\gamma_N N_0}\right), \tag{5}$$

*provided* that

$$N^+ \gg \gamma_P P_0. \tag{6}$$

By way of example, for a dielectric constant of 20 for the fixed charge lattice, the calculated[1] partition coefficient for a singly charged ion of radius 2 Å is about $5 \times 10^{-8}$. The criterion 6 for the validity of the analysis in such a system, with $N^+ = 0.1\ N$ as used previously (e.g., Coster, 1965, 1973), can therefore be easily met in most physiological situations. The inclusion of the partition effect thus improves the applicability of the model system to biological membranes.

With the aid of Eqs. 3 and 5 the counterion concentration at large values of $x$ is then given by

$$N_M \approx \gamma_N N_0 \exp\left(q\psi/kT\right) = N^+, \tag{7}$$

and the minority coion concentration by

$$\begin{aligned} P_m &= \gamma_P P_0 \exp - (q\psi/kT), \\ &= \frac{\gamma_P \gamma_N P_0 N_0}{N^+}. \end{aligned} \tag{8}$$

With the condition 6 the counterion concentration is thus equal to the concentration of fixed charge, as it was for the case when the dielectric constants were equal. The

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[1] The partition coefficients can be calculated using Eq. 1 and the Born (1920) expression for the electrostatic self-energy differences of the ion in the two media, $\Delta W = q^2/8\pi R(1/\epsilon_2 - 1/\epsilon_1)$, where $R$ is the ionic radius and $\epsilon = \epsilon_R\epsilon_0$ ($\epsilon_R$ is the relative permittivity [dielectric constant] and $\epsilon_0$ the permittivity of free space).

coion concentration, however, is lower, being depressed both by the electrostatic potential and the partition effect.

## ION FLUXES IN DOUBLE FCM's SEPARATING DIFFERENT IONIC SOLUTIONS

In the first instance the situation will be considered in which the membrane separates two solutions of different concentrations of the same uni-univalent salt. The concentration of ions in the solution in contact with the $N^-$ lattice of the membrane, (denoted the "internal" solution) are $P_i = N_i$ and in the external solution $P_0 = N_0$, as before.

For biological systems the negative fixed charge lattice must be located on the cytoplasmic side of the membrane (i.e., in contact with the internal solution) in order to give the correct electrical characteristics (e.g., the direction of rectification and the sign of the punch-through potential). The profiles of electrostatic potential and ion concentrations for the system are shown qualitatively in Fig. 2 B. For comparison the profiles for the case of equal concentrations are shown in Fig. 2 A.

As discussed in previous considerations[2] of this system, deviations from the equilibrium profiles of the ion concentrations are largely reflected in changes in the (minority) coion concentrations. The concentrations of coions near the solution-membrane interface (subscript $m$), however, are not perturbed and are still given by:

$$P_m = \gamma_P \gamma_N P_0 N_0 / N^+, \quad \text{and} \quad N_m = \gamma_N \gamma_P N_i P_i / N^-.$$

Following the analysis given earlier (Coster, 1965), the values of the coion concentrations $P_j$ and $N_j$ at the depletion layer boundaries can be determined from the corresponding counterion concentrations $P_M$ and $N_M$ in the opposite fixed charge lattices using the Boltzmann relation. Thus

$$P_j = P_M \exp - q\psi_j'/kT.$$

Here $\psi_j'$ is the total potential across the depletion layer. $\psi_j'$ is the algebraic difference of the two solution-lattice potentials $(\psi_0 - \psi_i)$ and the potential difference $V$ between the solutions (for the algebraic signs[3] refer to Fig. 2).

Thus

$$P_j = P_M \exp - [q(\psi_0 - \psi_i - V)/kT], \tag{9}$$

and

$$N_j = N_M \exp - [q(\psi_0 - \psi_i - V)/kT].$$

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[2] Computer solutions of the field equations for a double FCM separating identical solutions (Coster et al., 1969) have shown that the simplified analytical methods used previously and now to be used here are substantially correct for a wide range of membrane potentials.

[3] Here $\psi_0$, $\psi_i$, and $V$ are measured relative to the external solution where $\psi(-\infty)$ is taken as zero. In a previous communication (Coster, 1965) $\psi_0$ and $\psi_i$ were both taken as positive.

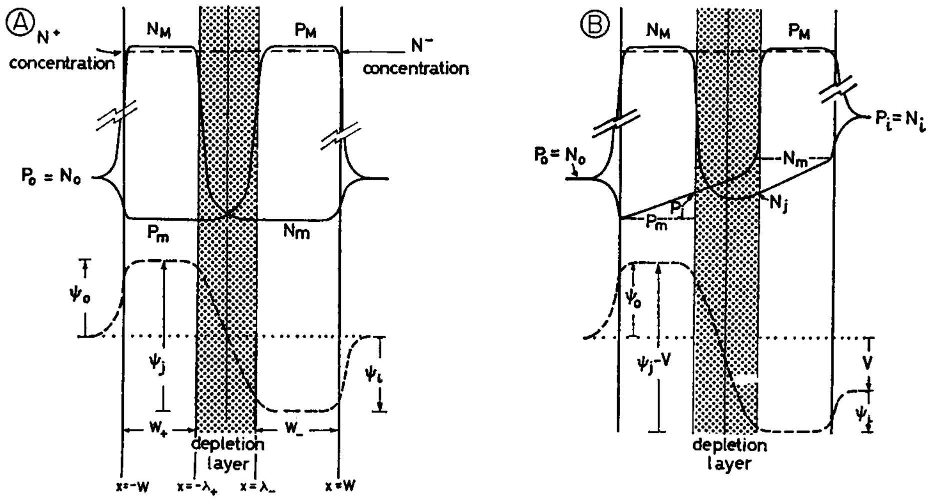

FIGURE 2 The qualitative profiles of ion concentrations and electrostatic potential in the double FCM. A) The double FCM separates two identical solutions and the gradient of the coion concentrations at zero current vanishes. B) The membrane separates solutions of different concentrations of the same uni-univalent salt. In this case the coion concentrations $P_j$ and $N_j$ at the depletion layer boundaries are not in equilibrium with the values $P_m$ and $N_m$ at the solution-membrane boundaries. At zero current a potential $V_R$ is developed across the membrane.

These values for the coion concentrations at the depletion layer boundaries are not in equilibrium with the coions in the remainder of the lattices outside the depletion layers. A diffusion of the ions therefore takes place, the flux being given by

$$\phi_P = D_P \frac{P_j - P_m}{W_+}, \tag{10}$$

where $D_P$ is diffusion coefficient of the positive mobile ions and $W_+$ is the width of the region outside the depletion layer in the $N^+$ lattice (i.e., $W_+ = W - \lambda_+$ see also Fig. 2). Thus

$$\phi_P = -\frac{D_P}{W_+} [P_M \exp - (q\{\psi_0 - \psi_i - V\}/kT) - P_m], \tag{11}$$

and a similar expression holds for the anions.

When the membrane potential $V$ is equal to the Nernst equilibrium potential $E_P$ for the positive ions, the flux $\phi_P$ vanishes. The (minority) cation concentration gradient is then zero (i.e., $P_j = P_m$) and hence from Eq. 11.

$$P_m = P_M \exp - [q(\psi_0 - \psi_i - E_P)/kT]. \tag{12}$$

Using Eq. 12 in the expression 9, at any other membrane potential, $P_j$ is given by:

$$P_j = P_m \exp + [q(V - E_P)/kT].$$

Using Eq. 10 the flux of cations is then given by

$$\phi_P = \frac{D_P}{W_+} P_m \left(\exp\left[q(V - E_P)/kT\right] - 1\right), \qquad (13)$$

and the flux of anions by,

$$\phi_N = \frac{-D_N}{W_-} N_m \left(\exp\left[q(V - E_N)/kT\right] - 1\right).$$

An analogous expression was obtained, in a similar manner, by Adam (1970) in his treatment of the ionic psn membrane model.

## THE RESTING POTENTIAL

At the resting potential $V = V_R$, the total electric current $q\phi_P - q\phi_N = 0$. Using this condition,

$$V_R = \frac{kT}{q} \ln \left[\frac{(A_P + A_N) \exp q(E_P + E_N)/kT}{A_P \exp qE_N/kT + A_N \exp qE_P/kT}\right], \qquad (14)$$

where

$$A_P = D_P P_m / W_+ \quad \text{and} \quad A_N = D_N N_m / W_- .$$

Using the expressions 8 for the coion concentrations $P_m$ and $N_m$, the Eq. 14 can also be written in the form

$$V_R = \frac{kT}{q} \ln \left[\frac{B_P P_0 + B_N (P_i/N_0) N_i}{B_P P_i + B_N (P_i/N_0) N_0}\right], \qquad (15)$$

where

$$B_P = \frac{D_P \gamma_P \gamma_N}{N^+ W_+} \quad \text{and} \quad B_N = \frac{D_N \gamma_N \gamma_P}{N^- W_-} .$$

For the case in which more than one cation is present, say $P'$ and $P''$, such as in biological systems, Eq. 55 can be readily extended to include the additional cations by noting that the expressions 3, 4, and 5 then yield the relations:

$$P'_m = (\gamma'_P \gamma_N P'_0 N_0)/N^+, \qquad P''_m = (\gamma''_P \gamma_N P''_0 N_0)/N^+,$$

and

$$N_m = [(\gamma'_P P'_i + \gamma''_P P''_i) \gamma_N N_i]/N^- .$$

Taking the case in which $K^+$, $Na^+$, and $Cl^-$ are present, the membrane potential is then given by,

$$V_R = \frac{kT}{q} \ln \left[\frac{K_0 + \alpha\, Na_0 + \beta \left(\dfrac{K_i + (\gamma_{Na}/\gamma_K)\, Na_i}{Cl_0}\right) Cl_i}{K_i + \alpha\, Na_i + \beta \left(\dfrac{K_i + (\gamma_{Na}/\gamma_K)\, Na_i}{Cl_0}\right) Cl_0}\right], \qquad (16)$$

where

$$\alpha = D_{\mathrm{Na}}\gamma_{\mathrm{Na}}/D_{\mathrm{K}}\gamma_{\mathrm{K}} \quad \text{and} \quad \beta = \frac{D_{\mathrm{Cl}}}{N^{-}W_{-}} \bigg/ \frac{D_{\mathrm{K}}}{N^{+}W_{+}}.$$

$\alpha$ and $\beta$ therefore correspond to the permeability ratios in the usual GHK equation (Goldman, 1943; Hodgkin and Katz, 1949).

It should be pointed out that $W_+$ and $W_-$ are weakly dependent on the membrane potential; both $W_+$ and $W_-$ decrease with increasing hyperpolarization (Coster, 1965). For a symmetric system, however, this does not lead to any potential dependency in $\beta$. For asymmetric systems the possibility arises that $\beta$ is potential dependent. The value of $\beta$ which is proportional to $W_+/W_-$ will in any case be only a weak function of the potential provided that $W_-$ or $W_+$ does not approach zero. The latter condition is associated with the punch-through effect which occurs at membrane potentials $\sim -300$ mV (Coster, 1965, 1969).

## DISCUSSION

It was seen that the inclusion of ion partitioning reduces the coion concentration while the requirement of electrostatic neutrality maintains the counterion concentration at a high value, independent of the value of the partition coefficient. This gives rise to a high membrane-solution Donnan potential even when the concentration of ions in the external solution is of the same order of magnitude as the concentration of fixed charges in the membrane. The latter situation is often the case under physiological conditions.

The foregoing is also related to the validity of the analysis of the system here presented (cf. Eqs. 5 and 6). In the absence of the ion partition effect many of the biologically relevant properties of the model membrane and the validity of the analysis previously given are only established when the concentration of fixed charge is much greater than that of the external solution. The presence of ion partitioning therefore renders the theoretical model more applicable to cellular membranes.

The expressions 15 and 16 for the potential developed across the membrane when it separates different ionic solutions are very similar in form to the GHK equation. There are some notable differences, however.

Thus the ratio $\beta = P_{\mathrm{Cl}}/P_{\mathrm{K}}$ in the GHK equation is replaced by a term incorporating $P_{\mathrm{Cl}}/P_{\mathrm{K}}$ multiplied by the factor $[\mathrm{K}_i + (\gamma_{\mathrm{Na}}/\gamma_{\mathrm{K}})\mathrm{Na}_i]/\mathrm{Cl}_0$. For situations in which the total ionic strength of the external solution is kept constant this modification is of no consequence and the Eqs. 15 and 16 yield results identical in the GHK expression. When the total ionic strength is varied the value of the equivalent GHK ratio $P_{\mathrm{Cl}}/P_{\mathrm{K}}$ decreases with increasing concentration of the external solution.

Although, the equivalent GHK permeabilities $P_{\mathrm{K}}$, $P_{\mathrm{Na}}$, and $P_{\mathrm{Cl}}$ for the FCM are potential dependent, the permeability ratio $\beta = (P_{\mathrm{Cl}}/P_{\mathrm{K}})$ is only potential dependent when asymmetries in the fixed charge lattice parameters exist, or when the total ionic strength of the solutions on the two sides of the membrane are significantly different. The latter occurs, for instance, in freshwater plant cells.

The potential dependence of $P_{Cl}/P_K$ when $N^+ > N^-$ and/or the width of the $N^+$ layer is greater than the $N^-$ layer, could, in principle, perhaps, account for the fact that in squid axons the GHK $P_{Cl}/P_K$ decreases as the membrane is depolarized by increasing $K_0$ (see the Hodgkin and Katz [1949] analysis of Curtis and Cole [1942]).

Since the fixed charges in the membrane could arise from the dissociation of free carboxyl and amino groups on the membrane proteins, a means of interpreting pH effects on membrane permeabilities also suggests itself.

In previous analysis of the double FCM the following expression for the current densities were derived and utilized (e.g., for cations),

$$J_P = \frac{D_P P_m}{W^+} (\exp qV/kT) - 1). \tag{17}$$

These expressions for the current densities of individual ion species are now replaced by (again for cations)

$$J_P = \frac{D_P P_m}{W_+} [\exp q(V - E_P)/kT - 1]. \tag{18}$$

Through the inclusion of the Nernst potentials $E_P$ the total current densities now no longer reduce to the neat form obtainable with Eq. 17. The widths $W_+$ and $W_-$, however, remain dependent only on the potential itself.

The results and conclusions reached in previous analysis regarding the punch-through effect (Coster, 1965, 1969, 1972), which occurs when $W_+$ and/or $W_- \rightarrow 0$, therefore remain unaltered. This is also true of many of the other considerations of the electrical characteristics of the system, such as, for instance, the low frequency dielectric dispersion which involves consideration of the effect of small AC perturbations of the membrane potential (Coster, 1973).

Indeed, qualitatively the description of the electrical characteristics remain unaltered. The present treatment, however, is more complete in that the contributions of individual ion species can be considered and this should allow a more detailed study to be made of the relevance of the double FCM model to biological membranes. Such a study should eventually also include an investigation into the effect of incorporating selective ion adsorption, such as described by Eisenman (1962) and Conti and Eisenman (1965 *a*, *b*) into the model.

## CONCLUSIONS

The analysis given of the double FCM shows that:

(*a*) The inclusion of ion partition effects leads to the presence of a large solution-lattice potential even when the fixed charge concentration in the lattice is of the same order as the concentration of ions in the external solution.

(*b*) Taking into account the partition coefficients $\gamma$, the new criterion for the application of the simplified analysis (Coster, 1965) of this system is:

$$N^+ \gg \gamma_P P_0 \quad \text{and} \quad N^- \gg \gamma_N N_i \,.$$

(*c*) The current densities of individual ion species are given by (e.g., for cations),

$$J_P = \frac{D_P \, P_m}{W_+} [\exp q(V - E_P)/kT - 1],$$

where $P_m$ is the concentration of $P$ in the $N^+$ lattice (where it is the coion); $E_P$ is the Nernst equilibrium potential of $P$; and $W_+$ is the width of the region outside the depletion layer in the $N^+$ lattice. $W_+$ is a function of the membrane potential $V$.

(*d*) The resting potential developed across the membrane is similar to that given by the GHK equation except that $\beta$ $(= P_{\text{Cl}}/P_{\text{K}})$ now contains a factor $[\text{K}_i + (\gamma_{\text{Na}}/\gamma_{\text{K}})\text{Na}_i]/\text{Cl}_0$ and for asymmetric membrane systems may have a weak potential dependence through an unequal dependence of $W_+$ and $W_-$ on the membrane potential.

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