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A model for membrane potential and intracellular ion distribution

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ABSTRACT

Most cells carry a negative electric charge. It produces a potential difference across the membrane, which regulates voltage-sensitive ion transport and ATP synthesis in mitochondria. The negative charge comes partly from an excess of negative ions in the cell interior (Donnan potential) and partly from ionized groups on the membrane (surface potential). In this work we propose some important modifications to the existing theory of membrane potential. First, we calculate the concentration profile of intracellular positive ions and derive a simple equation to assess the submembrane depletion of positive ions that gives rise to the Donnan potential. The extent of depletion varies with potential, which may provide a regulatory mechanism for ion pumps and channels. Next we consider the surface component of the potential and note that the standard Gouy–Chapman theory has been developed for planar membranes, whereas real cell membranes have a closed geometry. In this case, charges on the membrane surface are not expected to generate fields extending into the cell interior. This fact calls for reinterpretation of some theoretical points as well as experimental data. In particular, the experimentally demonstrated electrostatic attraction between cationic proteins and the negative membrane must now be explained without invoking intracellular fields, and we suggest a new mechanism that can account for this interaction.

1. Introduction

Most healthy cells and mitochondria are characterized by a negative resting potential. The process mainly responsible for its generation is intracellular accumulation of K^+ (by the Na^+, K^+ pump) combined with high permeability for K^+; this allows some ions to exit the cell down the concentration gradient, leaving behind an unbalanced negative charge. This is the classic Donnan mechanism, which is considered in detail in physiology textbooks (Blaustein et al., 2004; Wright, 2004). Additionally, the stoichiometry of the Na^+, K^+ pump is such that bringing two K^+ ions into the cell is coupled with extrusion of three ions of Na^+. Direct electrogenic contribution of the pump to the membrane potential is usually small (Thomas, 1972; Sperelakis, 2012) but can be significant or even dominant in some cell types (Bashford and Pasternak, 1986; Glitsch, 2001; Ishida and Chused, 1993). The large (150–200 mV) negative potential of mitochondria is generated exclusively by pumping out protons by the respiratory chain (Nicholls and Ward, 2000).

Regardless of the exact mechanism of potential generation, a deficit of positive ions is created inside a cell or an organelle. In a typical animal cell, the total concentration of charges is on the order of 300 mM. Negative charges are mostly associated with proteins and nucleic acids; the contribution of Cl^- can range from 4 to 60 mM, depending on the cell origin (Bregestovski et al., 2009). Positive charges are mostly represented by freely diffusible K^+ and, sometimes, by Na^+; the ion composition of mitochondrial matrix is similar to that of the cytosol (Arrebola et al., 2006; Somlyo et al., 1979). It is estimated that an excess of negative charges by about 3 μM should be sufficient to create a 90 mV difference across the membrane (Blaustein et al., 2004).

The other contribution to the total potential comes from fixed charges on the membrane. These charges are associated with anionic phospholipids that are present both on the inner and outer sides of the membrane (Burry and Wood, 1979). Surface charges are efficiently screened by the ions present in the aqueous media but can produce local fields extending about a Debye distance (on the order of a nanometer) into the aqueous phase. Quantitatively, this field is described by the Gouy–Chapman theory (Glaser, 2012; McLaughlin, 1989); more detailed models include dipolar fields from zwitterionic lipids and explicit polarization of water molecules (Bohinc et al., 2014). Applications of the surface

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potential theory to biological membranes have been extensive (Honig et al., 1986; Loew, 1993; McLaughlin, 1989; Neumcke, 1981; Ohki, 1985; Sperelakis, 2012; Yeung and Grinstein, 2007); in particular, the field originating from surface charges has been implicated in binding of positively charged cytoplasmic proteins to the inner leaflet of the plasma membrane (Goldenberg and Steinberg, 2010; Olivotto et al., 1996).

In the present paper we propose some modifications to the existing theory of membrane potential. We note that whether the cell potential has a Donnan or a surface origin, the entire charge that generates the transmembrane potential difference is localized to a nanometer-deep strip under the membrane (in the case of Donnan potential, this layer has a reduced concentration of positive ions). This effect has been recognized before (Jäckle, 2007), but here we present a simple theoretical model to describe the concentration profile of intracellular charges. Next, we reexamine the origin of the surface potential. The standard treatment of surface charges is based on the assumption that the entire membrane is a plane sheet. In reality, biological membranes have a closed geometry, and we show that this fact is expected to have important consequences for electric phenomena: surface charges, on the average, are not supposed to generate internal fields. This calls for reassessment of a large body of experimental data; in particular, the new model must be reconciled with the evidence of electrostatic attraction between positively charged cytoplasmic proteins and the negative membrane. We thus suggest an alternative general mechanism of protein–membrane binding based on minimization of electric energy of the system.

2. Theory and discussion

2.1. Concentration profiles of intracellular charges

We assume for now that negative charges (e.g., anionic proteins) are fixed and uniformly distributed throughout the bulk of the cell. Monovalent positive charges, on the other hand, are mobile and are present at a slightly lower net concentration. As with any conductor, an unbalanced charge should be confined to a thin surface layer (which, in our case, is the space immediately under the membrane), so that the potential deep inside the cell would be constant. The concentration profile for positive ions can be found from the balance between the diffusion flux and the flux created by electric field (Fig. 1):

$$-D\left(\frac{dn}{dr}\right) + n\mu eE = 0 \tag{1}$$

Here D is the diffusion coefficient, n is the concentration of positive ions (number per m^3), r is the distance along a normal to the membrane, μ is the mobility, e is the electron charge, and E is the electric field created by nonuniform distribution of charges. If we assume that a cell has a spherical or a flat shape, the electric field E can be calculated by applying the Gauss theorem:

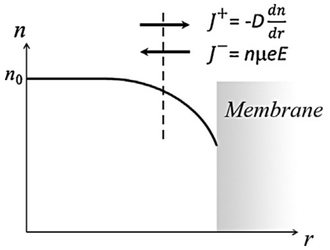

Fig. 1. The balance between diffusion and electromotive fluxes in a sub-membrane layer. Membrane is shown by the shaded area and the ion concentration profile by the solid line. Nonuniform distribution of ions creates two opposite fluxes, electrostatic and diffusional; the balance between these fluxes at any point (indicated by the dashed line) determines the equilibrium concentration profile.

$$E(r) = \frac{\sigma}{(\varepsilon\varepsilon_0)} = (\varepsilon\varepsilon_0)^{-1} e \int_{-\infty}^{r} (n - n_0)dr', \tag{2}$$

where σ(Cm^{-2}) is the charge density per membrane area, ε and ε_0 are the relative and absolute dielectric permittivity, and n_0 is the concentration of negative ions. Only the total charge on the left of the dashed line in Fig. 1 contributes to the electric field at the position of the line. By combining Eqs. (1) and (2) and the Einstein–Smoluchowski relation: $D = \mu kT$ (where k is the Boltzmann constant and T is the absolute temperature), one obtains the equation

$$\frac{dn}{dr} = \frac{e^2 n}{(\varepsilon\varepsilon_0 kT)} \int_{-\infty}^{r} (n - n_0)dr'. \tag{3}$$

By introducing the relative concentration $c = n/n_0$ and the characteristic Debye–Hückel length

$$\lambda = \left\{\frac{\varepsilon\varepsilon_0 kT}{e^2 n_0}\right\}^{1/2}, \tag{4}$$

Eq. (3) can be rewritten as

$$\frac{dc}{dr} = \lambda^{-2} c \int_{-\infty}^{r} (c - 1)dr'. \tag{5}$$

For $T = 300$ K, $\varepsilon = 60$, and n_0 corresponding to 0.1 M, the Debye–Hückel length is about 1 nm. Finally, in terms of the dimensionless coordinate $x = r/\lambda$, Eq. (5) assumes the form

$$\frac{dc}{dx} = c \int_{-\infty}^{x} (c - 1)dx'. \tag{6}$$

This integral-differential equation describes the concentration profile resulting from the balance between the diffusion flux and the flux created by electric field. Because direct numerical solution of Eq. (6) is computationally inefficient, it was solved by converting it to a second-order differential equation:

$$\frac{d^2(\ln c)}{dx^2} = c - 1. \tag{7}$$

The soliton-like solution describes a transition from $c = 1$ (at $x \to -\infty$) to $c = 0$ at large x (Fig. 2a). The solution can be shifted by an arbitrary constant along the x-axis; this shift represents one of the integration constants. In Fig. 2a, zero value of x was arbitrarily chosen at a point where $c = 0.5$. For practical calculations, the following empirical function was found to give an accurate approximation to the solution:

$$\begin{aligned} c(x) = 0.5\tanh(&0.0021236 - 0.632263x - 0.0642222x^2 \\ &-0.0108275x^3) + 0.5 \end{aligned} \tag{8}$$

To find the position of the membrane boundary x_0 we relate our solution to the cell potential $\Delta\phi$. In doing so we assume that most of the potential drop $\Delta\phi$ occurs within the membrane; the rationale for this will be given later in the text. In this case we can estimate $\Delta\phi$ as the product of $E(r_0)$ found from Eq. (2) and the membrane thickness l. Relative dielectric permittivity ε of the electrolyte should now be replaced by that of the membrane ε_m.