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A theory for the membrane potential of living cells

Abstract We give an explicit formula for the membrane potential of cells in terms of the intracellular and extracellular ionic concentrations, and derive equations for the ionic currents that flow through channels, exchangers and electrogenic pumps. We demonstrate that the work done by the pumps equals the change in potential energy of the cell, plus the energy lost in downhill ionic fluxes through the channels and exchangers. The theory is illustrated in a simple model of spontaneously active cells in the cardiac pacemaker. The model predicts the experimentally observed intracellular ionic concentration of potassium, calcium and sodium. Likewise, the shapes of the simulated action potential and five membrane currents are in good agreement with experiment. We do not see any drift in the values of the concentrations in a long time simulation, and we obtain the same asymptotic values when starting from the full equilibrium situation with equal intracellular and extracellular ionic concentrations.

Key words Membrane potential · Cells · Cardiac pacemaker · Osmotic pressure

Introduction

The purpose of the work we present here is to obtain a model for the membrane potential of a single cell which is reasonably realistic, and yet so simple that it can be used in practice to simulate numerically single cells or several coupled cells. For simplicity, experimentally observed currents (Boyett et al. 1996) are omitted if they seem too small to have a significant influence on the intracellular ion concentration, or at least too small to change the dynamics of the cell. On the other hand, we try to make the theory realistic by using equations that are compatible with, or can be derived from, basic physical principles.

It is a basic assumption of most models (Wilders 1993) for the electrical activity of cells that only the motion of positive ions, and specifically those of potassium, calcium and sodium, influence the membrane potential. This assumption is usually expressed as a differential equation for the time dependence of the potential. We observe that this differential equation can be integrated exactly, and argue that the integration constant is given by the requirement that the potential is zero when the ion concentrations on both sides of the membrane are equal, as the density of negative charge happens to be the same on both sides. Then it follows that the potential is directly proportional to the excess number of positive ions inside the cell, a formula which is nothing but the one for an electric capacitance that follows from Gauss’s law in electrostatics.

We derive equations for ionic currents flowing through channels, exchangers and electrogenic pumps. These are based on the Boltzmann distribution law (Boltzmann 1868), which states that a particle in thermal equilibrium spends less time in states of higher energy than in states of lower energy, the Markov assumption (Markov 1906) which says that the transition probabilities of a stochastic system (of Markov type) is only dependent on its present state, and the principle of detailed balance (Onsager 1931) which says that the microscopic laws of physics are invariant with respect to the reversal of time. Our equations were inspired by Ehrenstein and Lecar’s model of channel gating (1977), Nonner and Eisenberg’s model for channel current (1998), Mullins’ model of the Na⁺,Ca²⁺ exchanger (1979), and Chapman’s model of the Na⁺,K⁺ pump (1978). In particular the book by Mullins (1981) “Ion transport in heart” has been a major source of inspiration for us.
The theory is illustrated with a simple model of spontaneously active cells in the rabbit sinoatrial node. The observable parameters in the model are based on the experiments of Shibasaki (1987), Hagiwara et al. (1988), Muramatsu et al. (1996) and Sakai et al. (1996). The non-observable parameters in the model are determined numerically, in the same way as in an earlier study (Endresen 1997a), by comparing the action potentials generated by the model with the shape of the action potentials recorded by Baruscotti et al. (1996).

By using an algebraic equation for the potential in place of the standard differential equation, as mentioned above, we obtain a model which is stable against a slow drift of the intracellular ion concentrations, sometimes seen in other models. Furthermore, by fixing the integration constant for the voltage we obtain from the model a prediction of the steady state ion concentrations. It is even possible to predict these steady state concentrations by starting with an initial state having equal concentrations inside and outside the cell. The energy dissipated by the potential energy that depends upon the ionic concentrations in the cell, while the rest is dissipated by the electrical potential. The fact that the mobility in Fick’s law must be identical to the mobility in Ohm’s law was first noticed by Einstein (1905). If we combine Eqs. (1) and (2), we obtain the Nernst–Planck equation for the total flux of ions due to diffusion and electric forces.

\[
\bar{\phi} = -zeu[S] \nabla U
\]

where \( z \) is the valence, \( e \) the elementary charge and \( U \) the electrical potential. \( \bar{\phi} \) is the ionic flux, \( [S] \) the concentration of ions and \( u \) is the mobility, \( T \) is the absolute temperature and \( k \) is Boltzmann’s constant. The empirical law of Ohm (1827) describes the net motion of charged particles in an electric field:

\[
\bar{\phi} = -uT \exp \left( -\frac{zeU}{kT} \right) \nabla \left[ S \exp \left( \frac{zeU}{kT} \right) \right]
\]

The Nernst (1888) equilibrium potential for which the flux is zero

\[
v_S = U_i - U_e = \frac{kT}{ze} \ln \frac{[S]_i}{[S]_e}
\]

It can be found by setting \( \bar{\phi} = 0 \) in Eq. (3) and integrating from the extracellular (e) to the intracellular (i) side of the membrane. Here \( U_i \), \( U_e \), \( [S]_i \) and \( [S]_e \) are the intracellular and extracellular potentials and concentrations. The same formula can be derived in a more general way using the Boltzmann factor (Boltzmann 1868). The relative probability at equilibrium that an ion is at the intracellular or extracellular side of a cell membrane is

\[
\frac{p_i}{p_e} = \frac{[S]_i}{[S]_e} = \exp \left( -\frac{ze(U_i - U_e)}{kT} \right)
\]

where \( ze(U_i - U_e) \) is the energy difference between the two positions of the ion. Solving Eq. (5) for \( U_i - U_e \) gives Eq. (4). The equilibrium potentials for the predominant cellular cations are then:

\[
v_K = \frac{kT}{e} \ln \frac{[K]_i}{[K]_e}
\]

\[
v_{Ca} = \frac{kT}{2e} \ln \frac{[Ca]_i}{[Ca]_e}
\]

\[
v_{Na} = \frac{kT}{e} \ln \frac{[Na]_i}{[Na]_e}
\]

Ionic channels

**Ionic channels gating**

Imagine that ionic channels are either completely open or completely closed and randomly fluctuate between these states in a simple Markov process (Markov 1906), described by the first-order kinetics (Ehrenstein and Lecar 1977):

\[
C = O \quad \frac{z}{\beta}
\]

where the rate constants \( z \) and \( \beta \) are functions of transmembrane voltage and control the transitions between the closed (C) and the open (O) states of the gate. The rate for a closed channel to open is \( z \), and \( \beta \) is the