

# An Approach to the Heartbeat from Basic Physical Laws

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## Abstract

This text gives a short introduction to the biology of membranes and transmembrane proteins especially ion channels and ion pumps. Based on basic laws of chemical physics describing membrane potentials, ion channel switching, and osmotic pressure, it will be possible to develop a model for the electrical activity of cells of the sinoatrial node. The equations are studied with numerical methods. The results are found to be in good agreement with experimental results.

## 1 Introduction

Life is the most complex process known. Biological processes have been developed by evolution, they are not straightforward. Since there is not always an “extra-cost” involved in developing variations of the same solution, these variations exist. Evolution also means that there is no masterplan for life, nature develops solutions step by step. But nevertheless we can try to model complex processes on the basis of simple physical laws. No one should expect that they will explain life completely like the movement of a single mass point, but simple equations may allow a deeper understanding than the more complex ones. Models with many parameters tend to tell nothing at all.

The subject of this text is an introduction to the description of electrical phenomena occurring at membranes in living cells. Based on rate equations, concepts of stochastic processes, electro diffusion and numerical simulations we will approach a model for the electrical behavior of cells in the pacemaker region of the heart.

See [5] for a textbook on biological membranes. [6] is an introduction to the physics of nerve cells. [7] covers the whole range of chemical biophysics within a textbook.

## 2 Biology of Membranes and Their Proteins

Before we start with the mathematical description, let us have a closer look on the processes we want to

model.

Cells have an outer membrane defining their boundary. Some cells also have membranes inside, dividing the plasma into compartments. In these compartments specific biochemical reactions are performed or they are used to carry or store substances. Therefore the cell needs some material, that can be deformed, heals and has a controllable permeability. This is achieved by membranes made from lipids (see Fig. 1). The permeability is controlled by special membrane proteins, which extend from one side to the other. They act like a selective valve. The status of these valves can be controlled for example by voltages or the presence of certain substances.

This section follows the textbook of Alberts et al. [1] on cell biology, which is recommended to the reader for further information on the biological aspects of this text.

### 2.1 Lipids form Membranes

Lipids are defined as the water-insoluble molecules in cells that are soluble in inorganic solvents. Fatty acids are an important examples of lipids, because they are the basis for all kinds of membranes found in cells. These about 50 atoms thick sheets are largely composed from molecules with a hydrophilic head, which can also be charged and a hydrophobic tail (see Fig. 2). If immersed in sufficiently high concentration in water, these lipids will form a bilayer or a micelle to minimize the exposure of hydrophobic tails to water.

Since the lipids are free to move in the membrane, it is a two dimensional fluid. Spontaneous flipping from



Figure 1: Two views of a cell membrane. (A) An electron micrograph of a plasma membrane. (B) Schematic drawing. Fig. taken from [1].

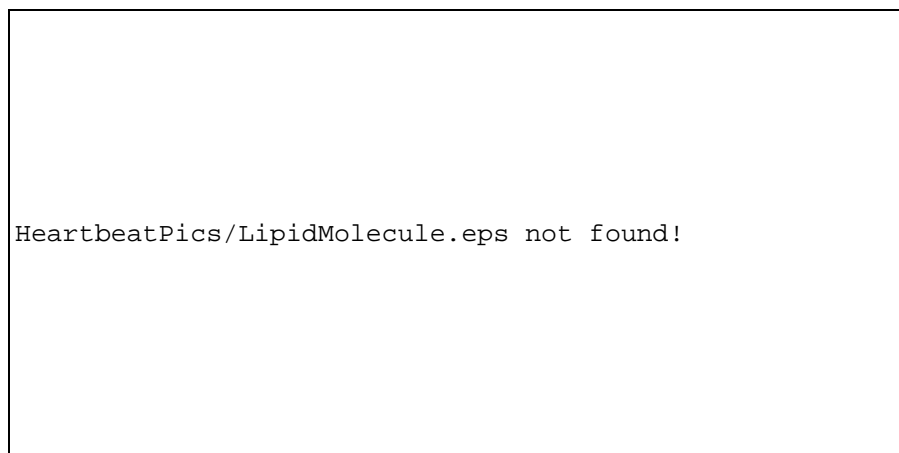


Figure 2: A phosphatidyl choline molecule. It is represented (A) schematically, (B) in formula, (C) as space-filling model and (D) as a symbol. This phosphide is built from five parts. It is common in most cell membranes. Fig. taken from [1].

one layer to the other is a very rare process. The fluidity is determined by the temperature and the shape of the tail. Shorter tails and a high number of double bonds in the hydrophobic part decrease the interaction between the fatty acids and therefore increases the fluidity of the membrane. Due to their structure including a hydrophobic layer in the middle, pure lipid bilayers are almost impermeable to solutes and ions. Only very small hydrophobic molecules like oxygen, carbon dioxide, nitrogen and benzene and small uncharged polar molecules like water, glycerol and ethanol can diffuse across it, while larger uncharged polar molecules like amino acids and ions are essentially blocked. The diffusion rate depends on temperature and strongly on size and charge of the molecule. Since ions are prevented by the solvation energy to enter the hydrocarbon phase of the bilayer, their permeability can be as much as a billion times less than that for water even for small ions like sodium.

## 2.2 A Class of Membrane Proteins: Ion Channels and Pumps

The cell needs to take up molecules from the outside and release other to its surrounding. But since this process needs to be selective and the lipid bilayer itself is impermeable to these molecules, special proteins have to be used for this function. For our purpose it is sufficient to focus on the subclass of ion channels and pumps. One can divide the types of transport into two classes:

1. **Passive Transport:** The ions follow the electrochemical gradient through the appropriate ion channel. This happens for example to transmit an electrical impulse in an axon of a nerve cell (see Fig. 3). Ion channels are not only selective, they are also controlled by parameters like membrane potential, mechanical stress and density of certain signaling molecules.
2. **Active Transport:** Ion pumps use an energy source (for example ATP or light) to pump ions against their electrochemical gradient. Animal cells use a coupled sodium potassium pump driven by ATP to lower the sodium concentration and raise the potassium concentration on the inside within the same process (see Fig. 4).

## 2.3 Energy Scales in Biochemistry

For a better understanding of the phenomena in biological systems, we should have a look at the energies involved. A suitable scale is the thermal energy of a particle at room temperature. The strongest connection between atoms is the covalent bond, which is due to its energy of  $100k_B T$  essentially never broken by thermal fluctuations. The universal energy source to drive endothermic processes in living organisms is the hydrolysis of ATP to ADP. This frees about  $10k_B T$ . The binding energy of an hydrogen bond is about  $3k_B T$ , while the interaction energy of two elementary charges or typical Van-der-Waals interaction energy in water and hydrophobic interactions are in the order of  $k_B T$ . Essentially all these forces can be tracked down to electrostatic or electrodynamic interactions.

Structural integrity of proteins is kept by the strong interaction of covalent bonds. The weak interactions dominate folding, connection of subunits, signaling and information transfer. The strength of the binding can be scaled by simply adjusting the number of bonds. This allows nature to set the kinetics of protein interaction and their arrangement, because it can be set sufficiently high to not allow thermal fluctuations to break it and keep it still low enough to disrupt it easily if required for signaling.

## 3 Modeling Ion Channels

Ion channels can respond to many parameters like membrane voltage, presence of certain chemicals and mechanical stress by adjusting their ion flow. This allows nature to use them for regulation, signal transmission and as a sensor. The adjustment of the flow is achieved by conformational changes. As we have just seen in subsection 2.3 thermal energy is sufficient to drive such changes, but leaves the protein intact. The thermally driven changes are moderated by the external parameter, to which the ion channel is sensitive.

### 3.1 Experimental Procedures

Within the last decades it became possible to measure the electrical current flowing through a single ion channel. The procedure is known as patch-clamp recording (see Fig. 5). It provides direct information about how individual ion channels work.

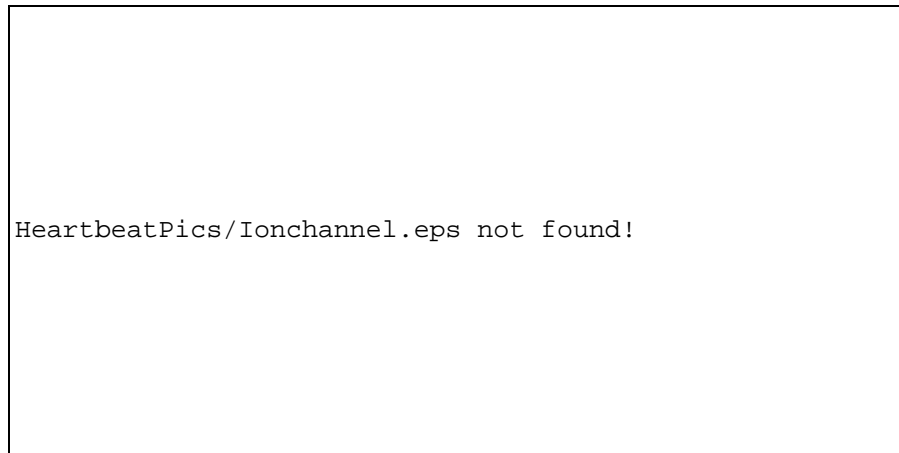


Figure 3: The structure of an ion channel. The ion channel shown is present in the plasma of muscle cells and opens to let  $\text{Na}^+$  and  $\text{K}^+$  pass when acetylcholine binds to it. Even with the acetylcholine it flickers randomly between open and closed states, without acetylcholine bound, it rarely opens. Fig. taken from [1].

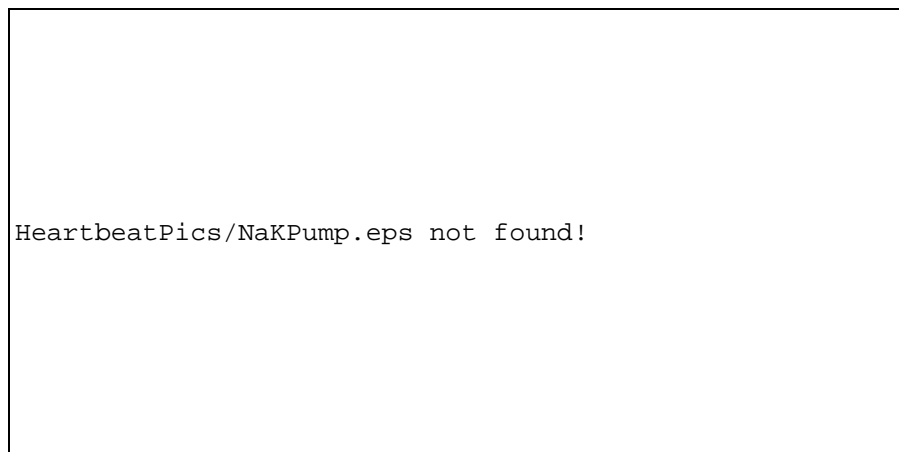


Figure 4: The  $\text{Na}^+$  -  $\text{K}^+$  pump. This carrier protein uses the energy of ATP hydrolysis to pump sodium out of the cell and potassium in, both against their electrochemical gradients. Fig. taken from [1].

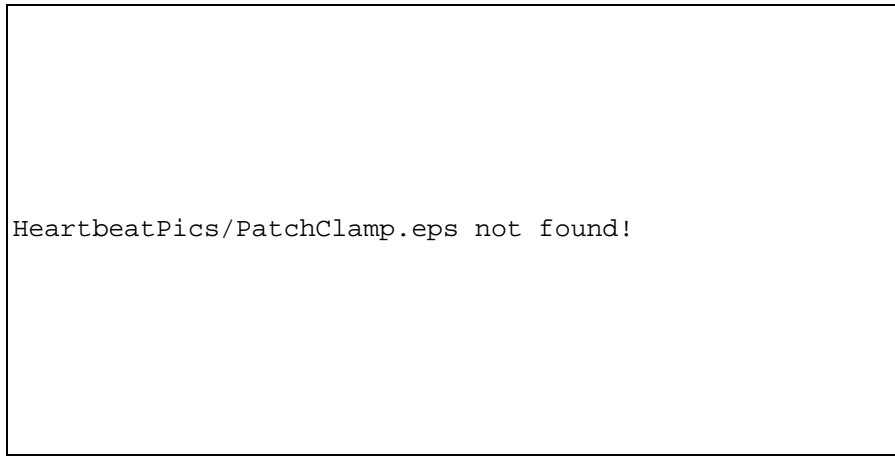


Figure 5: The technique of patch-clamp recording. Because of the very tight seal between microelectrode and membrane, current can only flow via ion channels in the membrane patch covering the tip of the microelectrode. Measurements can be made with the cell (A), or detached from the cell (B). (C) shows a nerve cell, held by a suction pipet from the left side. (D) The circuitry for patch-clamp recording. Fig. taken from [1].

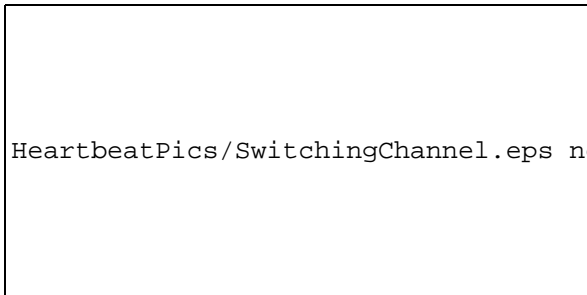


Figure 6: The current through a single ion channel as seen in Fig. 3, recorded by the patch-clamp technique. Fig. taken from [1].

For this technique a fine glass tube is used as a microelectrode to contact a small area of a cell membrane. With gentle suction a few square micrometers of the cell surface are attached to the pipet and removed from the cell. Now the current can be measured via contacts in the bath where the experiment is taking place and the interior of the microelectrode. Currents measured are in the order of pico Ampere.

Surprisingly one measures jumps in the current between two distinct states, even when the conditions are held constant (see Fig. 6). Thermal fluctuations are switching the channel on and off. It switches only be-

tween fully open and totally closed. But parameters can control the ration between the averaged duration of open and closed states. This allows for the adjustment of currents. For our model of the heartbeat generation, we need to model these channels using statistics.

### 3.2 Ionic Channels Gating

The data obtained by patch-clamp experiments (see Fig. 2) shows that ion channels switches between distinct states with a certain probability. This can be described with a Markov model [2]. In such a model the current state is independent of the previous state. Brownian motion falls for example into this subclass of stochastic processes.

Imagine that ionic channels are either completely open or closed and randomly toggling between these two states [3]. This can be described in a simple Markov process



where the rate constants  $\alpha$  and  $\beta$  are functions of the transmembrane voltage (see Fig. 7). They control the transition between the closed (C) and open (O) state of the gate. Let  $x$  be the probability that a given channel is open. If we have an ensemble of channels,  $x$  is the

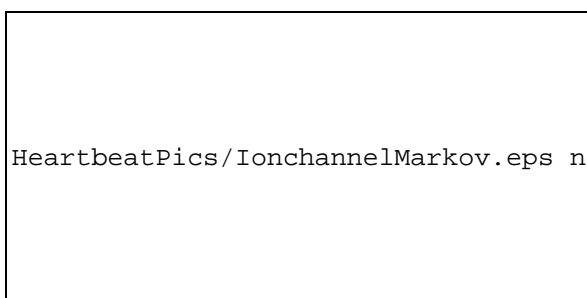


Figure 7: Diagram of a Markov process for a controlled ion channel

fraction of open channels. This yields

$$\frac{dx}{dt} = \alpha(1-x) - \beta x \quad (2)$$

$$\equiv \frac{x_\infty - x}{\tau} \quad (3)$$

where

$$x_\infty = \frac{\alpha}{\alpha + \beta} \quad (4)$$

$$\tau = \frac{1}{\alpha + \beta} \quad (5)$$

Here  $x_\infty$  denotes the steady state fraction of open channels and  $\tau$  the relaxation time.

In equilibrium  $dx/dt = 0$  holds. Then Eq. (2) turns into

$$\frac{x_\infty}{1-x_\infty} = \frac{\alpha}{\beta} \quad (6)$$

This is known as the principle of detailed balance.

Since this ratio must be in agreement with the Boltzmann distribution, we set

$$\frac{x_\infty}{1-x_\infty} = \exp\left(-\frac{\Delta G}{k_B T}\right) \quad (7)$$

Now we solve this equation for the steady state fraction of open channels.

$$x_\infty = \left[1 + \exp\left(\frac{\Delta G}{k_B T}\right)\right]^{-1} \quad (8)$$

This calculation has to be in agreement with the result of the Markov model (6). Therefore it becomes possible to determine the dependency of the rate constants:

$$\alpha \sim \exp\left(-\frac{\Delta G}{2k_B T}\right) \quad (9)$$

$$\beta \sim \exp\left(+\frac{\Delta G}{2k_B T}\right) \quad (10)$$

It can be assumed that the energy difference between open and closed states is

$$\Delta G = G_O - G_C \quad (11)$$

$$\equiv q(v_x - v) \quad (12)$$

where  $q$  is the gating charge, which is moved during the transition of the ion channel, usually  $q \approx \pm 4e^-$ . Then  $qv$  represents the change in electrical potential energy and  $qv_x$  in mechanical energy due to deformation during the transition.

Similar considerations hold for a pump which quickly reaches saturation. This allows to consider the sum of forward and backward movement as constant  $\lambda$

$$\alpha + \beta = \lambda \quad (13)$$

At equilibrium the reaction pathway frequency is given by the Boltzmann distribution

$$\frac{\alpha}{\beta} = \exp\left(-\frac{\Delta G}{k_B T}\right) \quad (14)$$

After solving for the transition probabilities their difference is given by

$$\alpha - \beta = \lambda \tanh\left(-\frac{\Delta G}{2k_B T}\right) \quad (15)$$

## 4 Concepts From Physical Chemistry

Before we can proceed to the description of the electrical activity of cells, we need to derive some relations between chemical potentials, fluxes and electrostatic interaction. The description can be made much easier, if the following assumptions are made:

- Currents flow through the membrane only perpendicular to the surface.
- Electrical potentials and ion concentrations change only in the direction perpendicular to the surface.

Then we only need an one dimensional description. The assumptions are justified by the symmetry of the problem.

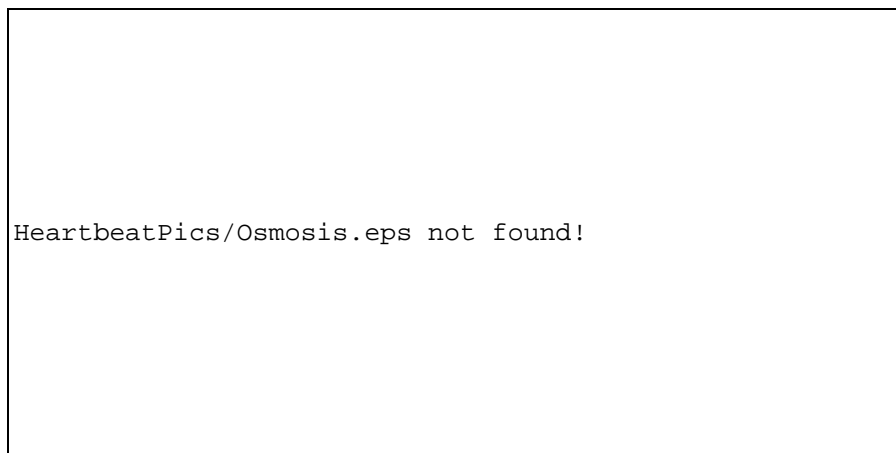


Figure 8: Osmosis. If the concentration of solutes inside the cell is higher than outside, water will move in by osmosis. If the difference in solute concentration is great enough, the cell will swell until it bursts (lysis). Fig. taken from [1].

#### 4.1 Osmosis

Membranes are not impermeable to water, but impermeable to ions. So in equilibrium, water would tend to diffuse into the regions of high ion concentration. Since animal cells do not have a rigid cell wall like plant cells to resist the pressure of incoming water they would swell until they burst (see Fig. 8). Animal cells prevent themselves from lysis by adjusting the ion concentrations. They actively pump sodium and calcium out of the cell and potassium into the cell against the electrochemical potential (see subsection 5.1). Active pumping is necessary since other membrane proteins are using the electrochemical gradient as a energy source and are therefore releasing ions to go down the gradient.

Let us describe the phenomenon of osmosis using thermodynamics: We assume an ideal solution. This means that the forces between solvent and solute molecules are equal to those between the solvent molecules themselves. A semipermeable membrane divides the system into the parts  $A$  and  $B$ . Only to part  $B$  a solute was added. Furthermore the system should be in thermal equilibrium.

The chemical potential of the solvent is equal on both sides:

$$\mu_s^A = \mu_s^B \quad (16)$$

The chemical potential of the solvent can be written as:

$$\mu_s^B = \mu_s^0(T, p^B) + N_A k_B T \ln X_s \quad (17)$$

$$\mu_s^A = \mu_s^0(T, p^A) \quad (18)$$

where  $X_s$  the mole fraction of the solvent and  $N_A$  denotes the Avogadro constant. The pressures must satisfy the equilibrium condition (16) for a given  $X_s$ :

$$\mu_s^0(T, p^A) = \mu_s^0(T, p^B) + N_A k_B T \ln X_s. \quad (19)$$

$$\mu_s^0(T, p^A) - \mu_s^0(T, p^B) = N_A k_B T \ln X_s \quad (20)$$

Since we have taken the temperature as equal in both parts of the system, formally the term on the right side can be rewritten as:

$$N_A k_B T \ln X_s = \int_{p^B}^{p^A} \left( \frac{d\mu_s^0}{dp} \right) dp \quad (21)$$

The Gibbs function is given by:

$$dG = -SdT + Vdp + \sum_k \mu_k dN_k \quad (22)$$

In our case it reduces to

$$dG = Vdp \quad (23)$$

If now use the inner energy  $U = TS - pV + \sum_k \mu_k N_k$  of a homogenous system in the definition of the Gibbs

free energy  $G = U + pV - TS$ , we obtain  $G = \sum_k \mu_k N_k$  and the corresponding differential:

$$dG = \sum_k N_k d\mu_k + \mu_k dN_k \quad (24)$$

It follows that for a pure substance at a constant temperature the chemical potential is the molar free energy of the substance:

$$d\mu_s^0 = \bar{V}_s dp \quad (25)$$

where  $\bar{V}_s = V_s/N$  is the molar volume of the solvent. Now the integration of Eq. (21) becomes simple:

$$N_A k_B T \ln X_s \approx \langle \bar{V}_s \rangle (p^A - p^B) \quad (26)$$

$$\equiv -\langle \bar{V}_s \rangle \Pi \quad (27)$$

Where  $\langle \bar{V}_s \rangle$  is the mean value of the molar volume in the pressure range between  $p^A$  and  $p^B$  and  $\Pi$  is the osmotic pressure. This can be rewritten as:

$$\Pi = -\frac{N_A k_B T}{\langle \bar{V}_s \rangle} \ln X_s \quad (28)$$

$$= -\frac{N_A k_B T}{\langle \bar{V}_s \rangle} \ln(1 - X_S) \quad (29)$$

With  $X_S$  being the molar fraction of the solute.

## 4.2 Nernst-Planck Equation

Let us now see the effect of an electrical field applied to an electrolyte.

The electrical current caused by diffusion due to a concentration gradient is given by Fick's law:

$$j_{diff} = -Dq \frac{dc(x)}{dx} \quad (30)$$

where  $D$  is the temperature dependent diffusion coefficient,  $q$  the charge per particle and  $c$  the concentration. The law can be derived from a random-walk model, where the transition probability depends on the direction of the step. See [4, 5] for details on random-walk models.

In a fluid with the viscosity  $\eta$  the Einstein relation gives for the diffusion coefficient

$$D = \frac{k_B T}{6\pi r \eta}. \quad (31)$$

Here  $r$  is the hydrodynamic radius of the diffusing particle. Instead of  $6\pi r \eta$  a more general constant could have

been introduced.  $6\pi r \eta$  was chosen since it shows the explicit dependency of friction on  $r$  and  $\eta$  for a spherical particle, like an ion.

With the electrical field  $E$  and the conductivity  $\sigma$  Ohm's law can be written as:

$$j_{ohm} = \sigma E.$$

Since the total current is given by the sum of diffusive and ohmic contribution, we obtain the Nernst-Planck equation

$$j = -Dq \frac{dc}{dx} + \sigma E. \quad (32)$$

This can be rewritten. To obtain the conductivity  $\sigma$  we consider a stationary state of a charged sphere in a viscous medium under the influence of an electrical field:

$$6\pi r \eta v = qE \quad (33)$$

Solving for  $v$  and using  $j = qvc = \sigma E$  we obtain:

$$\sigma = \frac{q^2}{6\pi r \eta} c \quad (34)$$

The electrical field can be expressed as a gradient of a potential  $E = -dU/dx$  and the Nernst-Planck Equation becomes

$$j = -Dq \frac{dc}{dx} - c \frac{q^2}{6\pi r \eta} \frac{dU}{dx}. \quad (35)$$

## 4.3 Nernst Equation

In equilibrium diffusion and ohmic current cancel each other. With this condition  $j = 0$  we obtain from the Nernst-Planck equation (35)

$$\frac{dU}{dx} = -\frac{6\pi r \eta D}{q} \frac{1}{c} \frac{dc}{dx}. \quad (36)$$

Integration over the membrane from side  $A$  to side  $B$  leads to

$$U = \frac{6\pi r \eta D}{q} \ln \frac{c(x_A)}{c(x_B)} \quad (37)$$

where  $c(x_A)$  denotes the concentration on side  $A$  of the membrane and  $c(x_B)$  of side  $B$ . Using the Einstein relation (31) this equation can be rewritten as

$$U = \frac{k_B T}{q} \ln \frac{c(x_A)}{c(x_B)} \quad (38)$$

This equation holds if the membrane is permeable to only one ion species. It follows also directly from the Boltzmann distribution.

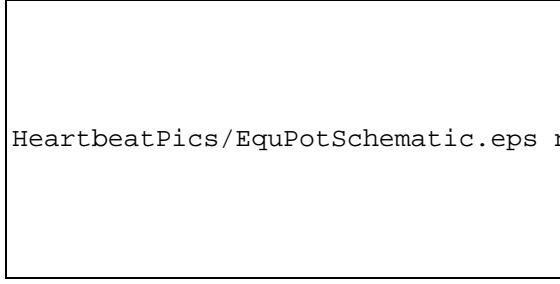


Figure 9: The Donnan equilibrium describes the case of two phases separated by a semipermeable membrane. Fig. taken from [7].

#### 4.4 Donnan Equilibrium

Let us now discuss the equilibrium of two different solutions in contact via a semipermeable membrane. This membrane is permeable to simple electrolytes like for example  $\text{Na}^+$  and  $\text{Cl}^-$  but impermeable to colloidal electrolytes (see Fig. 9).

Consider first an aqueous solution of  $\text{Na}^+$  and  $\text{Cl}^-$ . Because the membrane is permeable to all components, in equilibrium the chemical potentials will be equal in part  $A$  and  $B$  of the system:

$$\mu_i^A = \mu_i^B. \quad (39)$$

The system should fulfill electro-neutrality:

$$\sum_{i \in A} q_i c_i^A = \sum_{i \in B} q_i c_i^B \quad (40)$$

Now we add some proteins to side  $B$ . Proteins are large and normally positively charged. All proteins in a cell have to carry charges of the same sign to prevent them from sticking together. Nature has for unknown reasons chosen to make them all positively charged. Proteins without a charge would simply lead to a higher osmotic pressure on side  $B$ . Ultimately there will be a movement of water,  $\text{Na}^+$  and  $\text{Cl}^-$  to side  $B$ .

In the next step we switch on the charge of the protein. This violates the electro-neutrality and side  $B$  become positively charged. Equilibrium will be reestablished, as a compromise between the demand for electro-neutrality and the expense of establishing a chemical gradient. Thus we will have:

$$\begin{aligned} c_{\text{Na}^+}^A &> c_{\text{Na}^+}^B \\ c_{\text{Cl}^-}^A &< c_{\text{Cl}^-}^B \end{aligned}$$

with a offsetting electrical and chemical potentials. Although  $\Delta G = 0$ , there will be a electrochemical gradient. It is called Gibbs-Donnan or just Donnan potential.

#### 4.5 Goldman Equation

The Nernst equation (38) holds if the membrane is permeable to only one ion species. In case the membrane is permeable to several ion species, a different approach has to be taken. We start again with  $dj/dx = 0$  and the Nernst-Planck equation (35). Furthermore we assume, that the electrical field in the membrane is homogeneous, therefore  $dE/dx = 0$  must hold.

With

$$\frac{dc}{dx} + bc \frac{dU}{dx} = e^{-U(x)b} \frac{d}{dx} \left( ce^{U(x)b} \right) \quad (41)$$

and the Einstein relation (31) the Nernst-Planck equation (35) turns into

$$-\frac{j}{Dq} = e^{-U(x)\frac{q}{k_B T}} \frac{d}{dx} \left( ce^{U(x)\frac{q}{k_B T}} \right) \quad (42)$$

This gives integrated from one side of the membrane to the other using  $dj/dx = 0$

$$\begin{aligned} -\frac{1}{Dq} \int_{x_A}^{x_B} j e^{U(x)\frac{q}{k_B T}} dx \\ = \int_{U(x_A), c(x_A)}^{U(x_B), c(x_B)} d \left( ce^{U(x)\frac{q}{k_B T}} \right). \end{aligned} \quad (43)$$

$$-\frac{j}{Dq} = \frac{c(x_A) e^{U(x_A)\frac{q}{k_B T}} - c(x_B) e^{U(x_B)\frac{q}{k_B T}}}{\int_{x_A}^{x_B} e^{U(x)\frac{q}{k_B T}} dx} \quad (44)$$

Since  $dE/dx = 0$  holds, we have

$$\frac{dU}{dx} = -E = -\frac{U}{x_A - x_B} \quad (45)$$

Now the last integral can be calculated

$$\begin{aligned} \int_{x_A}^{x_B} e^{U(x)\frac{q}{k_B T}} dx = -k_B T \frac{x_A - x_B}{qU} \\ \cdot \left( e^{U(x_A)\frac{q}{k_B T}} - e^{U(x_B)\frac{q}{k_B T}} \right) \end{aligned} \quad (46)$$

Using this result in Eq. (44) leads to:

$$-\frac{j}{Dq} = \frac{c(x_A) e^{U(x_A)\frac{q}{k_B T}} - c(x_B) e^{U(x_B)\frac{q}{k_B T}}}{-k_B T \frac{x_A - x_B}{qU} \left( e^{U(x_A)\frac{q}{k_B T}} - e^{U(x_B)\frac{q}{k_B T}} \right)} \quad (47)$$

Setting  $U(x_A)$  to zero yields:

$$j = \frac{Dq^2U}{k_B T(x_A - x_B)} \frac{c(x_A) - c(x_B)e^{\frac{q}{k_B T}U}}{1 - e^{\frac{q}{k_B T}U}}. \quad (48)$$

This equation is known as the Goldman-Hodkin-Katz equation. It gives the current for one ion species.

If we want to know the potential  $U$  for a membrane under the condition  $\sum_i j_i = 0$  and  $q = e^-$ , we can simplify (48) to:

$$0 = \sum_i \frac{D_i(e^-)^2U}{k_B T(x_A - x_B)} \frac{c_i(x_A) - c_i(x_B)e^{\frac{e^-}{k_B T}U}}{1 - e^{\frac{e^-}{k_B T}U}} \quad (49)$$

Note that since the potential is equal for all ion species, it has no index. With Eq. (31) we can define the permeability  $P_i \equiv r_0/r_i$ . Now we obtain from the last equation:

$$\sum_i P_i c_i(x_A) = e^{\frac{e^-}{k_B T}U} \sum_i P_i c_i(x_B) \quad (50)$$

Taking the logarithm and solving for  $U$  leads to the Goldman equation:

$$U = \frac{k_B T}{e^-} \ln \frac{\sum_i P_i c_i(x_A)}{\sum_i P_i c_i(x_B)}. \quad (51)$$

This equation was determined by Goldman in 1943 [8]. He measured the conductivity of membranes with an AC bridge. The membranes used were plastics, powder from blood and cooked (!) cuticles from plants all with a thickness in the micrometer range. Therefore these experiments have no relevance at least for this text. However, his name was established in the literature for the derivation of the equation, since this is one of the rare cases that a solution to the problem of membrane currents in the presence of several ion species can be written explicitly.

## 5 Heartbeat

Now we are provided with the tools to set up a simple model of a pacemaker cell. (This section follows [3]. Therefore no additional references are given within the section.) The model should be reasonable realistic and yet so simple that it can be used in practice to simulate numerically single or several coupled cells. Therefore the only significant currents considered are that of potassium, sodium and calcium.

### 5.1 Specific Equations

The equations for the ionic currents flowing through channels, exchangers and electrogenic pumps are derived. The general formulas from section 3 and 4 are applied to the specific problem where only the significant currents of potassium, sodium and calcium are considered.

**Equilibrium Potentials** The equilibrium potentials of the predominant ions are given by the Nernst equation (38)

$$v_K = \frac{k_B T}{e} \ln \frac{c_K^A}{c_K^B} \quad (52)$$

$$v_{Ca} = \frac{k_B T}{2e} \ln \frac{c_{Ca}^A}{c_{Ca}^B} \quad (53)$$

$$v_{Na} = \frac{k_B T}{e} \ln \frac{c_{Na}^A}{c_{Na}^B} \quad (54)$$

**Ion Channels** Let us first calculate the ion current through a pore of the length  $d$  and the cross section  $A$ . With  $i = qjA$  and the Nernst-Planck equation (35), we can get the current by an integration from one end to the other through the membrane. To fully compute the integral, it is necessary to make more assumptions. Like Goldman we assume that the field inside the membrane is constant. Additionally we assume, that the channel is a cylinder with a short constriction with the area  $A_p$  much smaller than  $A$  and the length  $\epsilon d$ . The calculation (see [3] for details) lead to:

$$i = k_S \sinh \left( \frac{q(v - v_S)}{2k_B T} \right) \quad (55)$$

$$k_S = 2qu k_B T \sqrt{c_A c_B} \frac{A_p}{\epsilon d} \quad (56)$$

Here is  $u$  the mobility of the ions. In contrast to the Goldman equation, this equation shows inward rectification, which is also seen in many excitable cells.

**Regulated Ion Channels** The current through a pore is given by (55) and regulated by the fraction of open channels  $x$ .

For a potassium channel ( $q = 1e$ ) we obtain therefore

$$i_K = k_K x_K \sinh \left( \frac{e(v - v_K)}{2k_B T} \right) \quad (57)$$

For calcium ( $q = 2e$ ) and sodium ( $q = 1e$ ) channels, the equation for potassium has to be modified, since

they have an additional inactivation process. These two mechanisms are independent Markov processes. Since the inactivation is very fast, we can use the steady state fraction of open channels  $x_\infty$  as a pre factor.

$$i_{Ca} = k_{Ca} x_{Ca} x_{Ca\infty} \sinh\left(\frac{e(v - v_{Ca})}{k_B T}\right) \quad (58)$$

$$i_{Na} = k_{Na} x_{Na} x_{Na\infty} \sinh\left(\frac{e(v - v_{Na})}{2k_B T}\right) \quad (59)$$

Because the gating charge is for the inactivation process is  $-4e$  instead of  $4e$  the differential  $dx/dt$  has to be adjusted as well.

**The Sodium-Potassium Pump** In almost all animals and plant the Na,K-ATPase is found. It pumps sodium out and potassium into the cytosol. For the breakdown of each ATP-molecule three sodium and two potassium ions are pumped. The change of the free energy is thus

$$\Delta G_{Na} = -3e(v - v_{Na}) \quad (60)$$

$$\Delta G_K = +2e(v - v_K). \quad (61)$$

The total change in the free energy is therefore

$$\Delta G = \Delta G_{ATP} + \Delta G_{Na} + \Delta G_K \quad (62)$$

$$= e(v_{ATP} + 3v_{Na} - 2v_K - v). \quad (63)$$

This result is applied to Eq. (15). Then the total current from  $M$  pumps is:

$$i_{NaK} = Me(\alpha - \beta). \quad (64)$$

**Sodium-Calcium Exchanger** The pump for calcium is not directly powered by ATP, but indirectly through the electrochemical sodium gradient. For each sodium ion that enters the cell one calcium ion is pumped out of the cell. The total change in free energy is given by

$$\Delta G = \Delta G_{Na} + \Delta G_{Ca} \quad (65)$$

$$= e(v - 3v_{Na} + 2v_{Ca}) \quad (66)$$

Since saturation is not expected and  $\Delta G$  will vary around zero, we set

$$\alpha = \lambda (c_{Na}^A)^3 c_{Ca}^B \exp\left(-\frac{ev}{2k_B T}\right) \quad (67)$$

$$\beta = \lambda (c_{Na}^B)^3 c_{Ca}^A \exp\left(\frac{ev}{2k_B T}\right) \quad (68)$$

$N$  exchangers will give a net current of

$$i_{NaCa} = -Ne(\alpha - \beta) \quad (69)$$

**Membrane Potential** To complete our model of the cell we will now turn to the membrane potential and its dependency on the five currents worked out above. The cell can be seen as a capacitor, if it is assumed, that no ion binding in the cell occur and the cell volume is fixed. The change in voltage is then given through

$$\frac{dv}{dt} = -\frac{i_{tot}}{C} \quad (70)$$

with

$$i_{tot} = i_K + i_{Ca} + i_{Na} + i_{NaCa} + i_{NaK} \quad (71)$$

Furthermore concentrations and currents are connected via the following relations

$$\frac{dc_K^B}{dt} = \frac{2i_{NaK} - i_K}{eN_A V} \quad (72)$$

$$\frac{dc_{Ca}^B}{dt} = \frac{2i_{NaCa} - i_{Ca}}{2eN_A V} \quad (73)$$

$$\frac{dc_{Na}^B}{dt} = \frac{-i_{Na} - 3i_{NaK} - 3i_{NaCa}}{eN_A V} \quad (74)$$

where  $V$  is the cell volume. Solving these three equations for their current yields

$$\frac{d}{dt} \left( v - \frac{N_A V}{C} (c_K^B + 2c_{Ca}^B + c_{Na}^B) \right) = 0 \quad (75)$$

This can be solved by integration. Since the voltage should be zero, when the concentrations are equal, the integration constant can be determined to

$$v_0 = -\frac{N_A V}{C} (c_K^B + 2c_{Ca}^B + c_{Na}^B) \quad (76)$$

which gives

$$v = \frac{N_A V}{C} (c_K^B - c_K^A + 2c_{Ca}^B - 2c_{Ca}^A + c_{Na}^B - c_{Na}^A) \quad (77)$$

In contrast to other models this is an algebraic equation and no differential equation. The use of a differential equation would lead to a superfluous extra dimension in phase space. The initial condition for this extra differential equation cannot be treated as independent of the initial intracellular ion concentrations or the membrane potential will be erroneous.

**Energy Balance and Osmotic Pressure** From the ion currents one can calculate the total change in free energy due to ion currents and break down of ATP over time.

$$i = q \frac{dn}{dt} \quad (78)$$

$$\Delta G = \int_0^t i(v - v_S) dt \quad (79)$$

The change in free energy due to ion movements  $\Delta G_{ion}$  in equilibrium can be expressed as a function depending only on the state of the cell.

$$\Delta G_{ion} = \frac{1}{2} C v^2 - ST - V\Pi \quad (80)$$

The more general description of the equilibrium according to the Donnan equation (see subsection 4.4) is omitted here and it is assumed that in equilibrium the potential across the membrane is zero ( $v = 0$ ). At the beginning of the integration extracellular and intracellular concentrations are equal  $c_i^A = c_i^B$ . Since  $\Delta G_{ion}$  is a state function, it represents a potential energy. Terms in Eq. (80) have a direct physical meaning.  $\frac{1}{2} C v^2$  is the contribution due to the charge on the capacitor formed by the cell membrane.  $TS$  is the entropy change due to changes in ion concentrations for ideal dilute solutions given by

$$S = N_A k_B V \sum_i c_i^B \ln \frac{c_i^A}{c_i^B} \quad (81)$$

The last term in Eq. (80) is the osmotic pressure across the membrane

$$\Pi = N_A k_B T \sum_i c_i^B - c_i^A \quad (82)$$

The osmotic pressure has not been included into the dynamics, since the volume was assumed to be constant. In a more refined model with variable volume it should be included.

The energy source of the process is the breakdown of ATP. But the energy pathways in nature are difficult to track. In this simple model it is possible to determine the potential energy of the membrane voltage and the energy dissipation due to ion currents through the exchanger and ionic channels. This allows to check the numerical results for computational errors.

## 5.2 Simulation of the Electrical Activity

In review the mathematical model of the membrane potential derived above contains the following equations:

- Equilibrium potentials (52, 53, 54)
- Ionic currents (57, 58, 59)
- Exchanger and pump currents (64, 69)
- Ionic concentration (72, 73, 74)
- Membrane potential (77)
- Osmotic pressure (82)

The model has six time dependent variables: The averaged fraction of open ion channels for potassium, sodium and calcium and the concentration of each of the ions inside the cell.

There are four classes of parameters which determine the behavior of the system:

- Fundamental physical constants:  $k_B, e^-$
- Experimentally observed constants: temperature  $T$ , extra cellular ion concentrations  $c_i^A$ , cell volume  $V$ , cell capacitance  $C$ , half activation potentials and for sodium and calcium as well as half inactivation potentials, the maximum relaxation time and the energy released from the breakdown of ATP.
- Adjustable parameters: density of pumps and ion channels. These constants were fitted to reproduce the dynamical behavior as seen in experiments.
- Initial conditions: the fraction of open channels and the intercellular concentrations. These are fitted numerically, too.

Simulations with many different combinations for the density of pumps and ion channels gave a good approximation of the experimentally obtained wave form. This supports the idea, that different cells produce the same wave forms although they have different mixtures of ion channels, exchangers and pumps.

The differential equations were solved numerically by fifth-order Runge-Kutta method with variable step size. In general this method progresses in one variable (here  $x$ ) in step sizes of  $h$  to determine the next value of the other variable.

$$x_1 = x_0 + h \quad (83)$$

$$y_1 = y_0 + \frac{1}{6} (k_1 + 2k_2 + 2k_3 + k_4) \quad (84)$$

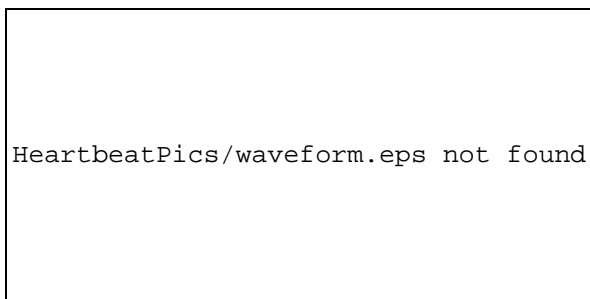


Figure 10: Action potential and currents. **a** Experimentally recorded and scaled (by a factor of 1.25) model-generated rabbit sinoatrial action potential waveform. **b** The outward delayed rectifying potassium current  $i_K$ , the inward calcium current  $i_{Ca}$ , the inward sodium current  $i_{Na}$ , the sodium calcium exchange current  $i_{NaCa}$  and the sodium potassium pump current  $i_{NaK}$ , Fig. taken from [3].

For a high number of steps it might become necessary to adjust the step size to minimize the computational error. The model can be checked for a significant contribution of computational errors. Therefore the law of energy conservation is used.

The calculations reproduce the shape but not the amplitude of the experimentally recorded wave (see Fig. 10). For comparison of the shape, the wave of the numerical computation has been multiplied by 1.25.

Long term simulations of the system show, that the model will lead to oscillations even from equilibrium (see Fig. 11). During several minutes the membrane potential is build up. After reaching a certain level, oscillations start. Observation over several minutes seems to indicate that the oscillations correspond to a stable limit cycle. This supports also the relative strong independence of the oscillations on the initial conditions.

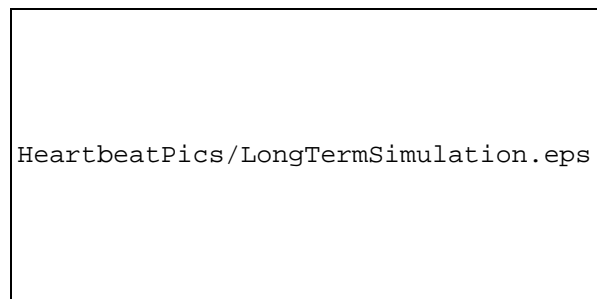


Figure 11: Long time simulation showing the membrane potential, Nernst potential and energies starting with intracellular and extracellular concentrations. **a** Nernst potential for calcium  $v_{Ca}$ , potassium  $v_K$ , sodium  $v_{Na}$  and membrane potential  $v$ , **b** work  $W$ , potential  $P$  and total energy balance  $W + P$ , Fig. taken from [3].

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