

Biological Physics - Neurons

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Membrane potential and neurons: structures for information transfer and processing

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1.1 Membrane potential

The physical chemistry of electric fields in aqueous ionic solutions has been introduced in the Part II Soft Condensed Matter course. In the presence of an electric field (which could be an external field, or a field due to surface-bound charges) ions in a solution drift to an equilibrium concentration distribution which minimises the free energy, i.e. a distribution that balances the electrostatic field energy together with the entropy. The details of this are in general extremely complex, and simple solutions exist only for simple geometries and weak fields where it's possible to linearise the equations.

Biological membranes composed of lipid bilayers are impermeable to both ions and macromolecules. Transport across membranes only occurs through specific protein complexes, which can be passive stable pores (channels, sometimes specific for particular ionic species) or active pumps (consuming chemical energy to transport ions in a directed fashion). The hydrophobic core of the lipids is a very non-polar chemical species with very low dielectric constant. So the bilayer as well as preventing ionic flow is also a very good isolator. Strong electric fields can be generated by confining ions on opposite sides of a membrane, and these conditions are at the heart of many cellular processes. One example is the generation of ATP, the chemical ‘fuel’ for most cellular activity, from glucose in mitochondria. This ATP synthesis is powered by the proton gradient across the inner membrane of the mitochondria. Another example is the propagation of electrical signals along the axons of neural cells (see Figures 1.1 and 1.2).

The combination of lipid bilayer, channels and pumps in the membrane can be thought of as resistors (voltage dependent), batteries (dependent on ionic concentrations) and capacitors in parallel. By modulating the number or activity of the channel molecules, the cell can regulate the gradient of different ionic species, and thus tune the membrane electrical potential.

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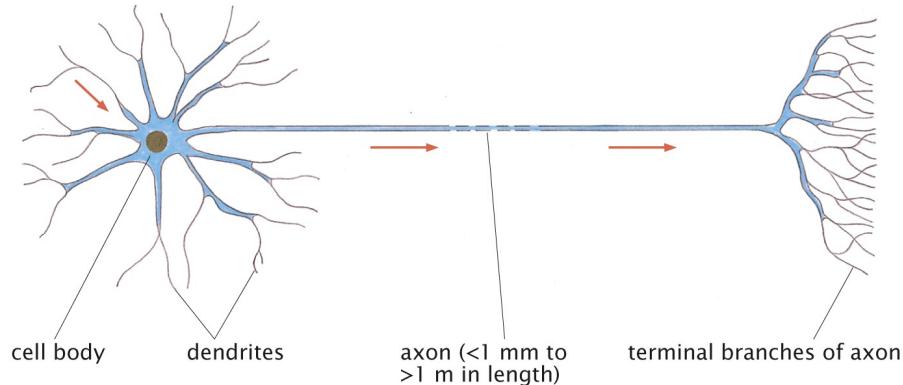


Figure 17.1 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Fig. 1.1 Illustration of a nerve cell. The action potential carries a signal along the axon.

The Nernst equation relates the voltages across a septum that allows only positive ions to cross:

$$V_2 - V_1 = \frac{k_B T}{ze} \ln \frac{c_1}{c_2}, \quad (1.1)$$

where c_1, c_2 are the concentrations at either side, ze is the charge on the ion. $k_B T/e \approx 25 \text{ mV}$. Voltages across membranes of neurons are in the range $10 - 100 \text{ mV}$, see Table 1.1, so thermal effects can be important.

Looking at the ions, there is an excess of positive charge inside the cell. This is partly balanced by the negative charges of the nucleic acids and of many proteins. In a typical neural cell, the potential difference is -90 mV . Other cells will typically have smaller gradients. In thermodynamic equilibrium, one would expect eq.1.1 to hold separately for each ionic species, with the same Nernst potential, but clearly this is not consistent with the data in Table 1.1. The cell is not in equilibrium. There are voltage dependent, ion-selective channels, and energy consuming ion pumps. The most important pumps in the cell membrane are of two types: to pump calcium ions out of the cell, and to exchange sodium with potassium ions. Several hundred distinct ion channels are coded for in the human genome.

By evolving the distribution and properties of channels, axons have emerged as structures where a voltage can propagate as a signal. These signals are typically pulses of around 50 mV in amplitude, and of width between 1 and 500 ms depending on the organism and cell type. This pulse travels down the axon without changing shape, at speeds between 10 and 100 m/s, see Figure 1.3. A threshold value of voltage is required to trigger the action potential.

Hodgkin and Huxley worked between the 30s and the 50s measuring nerve signals, and managed to produce a model that was

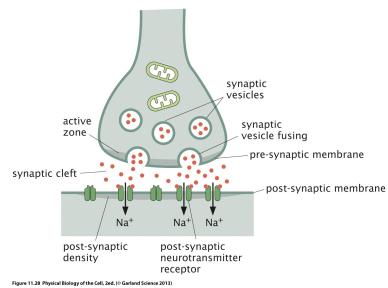


Fig. 1.2 Illustration of a synapse. When the action potential reaches the end of the axon, the electrical signal is converted to a chemical signal thanks to the presence of vesicles loaded with neurotransmitters, the “synaptic vesicles”. These vesicles release the cargo into the cleft, and the neurotransmitters are sensed at the membrane of another cell. These neurotransmitters have the effect of lowering the polarisation state of the receiving cell membrane, and thus a chemical signal is turned back into an electrical signal.

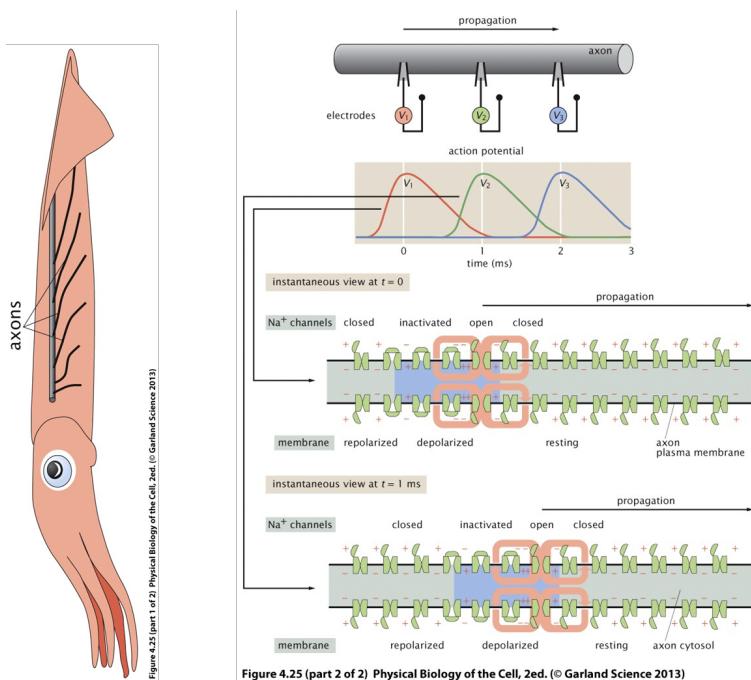


Figure 4.25 (part 1 of 2) Physical Biology of the Cell, 2ed. © Garland Science 2013

Fig. 1.3 The giant squid axon was the structure studied in original experiments on neural signals. These are for a mammalian skeletal muscle cell, for which the resting potential is around $V_{mem} = -90$ mV.

phenomenological (at the time a lot of the molecular structures were unknown) but yet had the correct mechanisms. They were awarded the 1962 Nobel prize in Physiology.

It is the transient (due to opening and closing of the channels) permeability to K⁺ and Na⁺ ions that lies at the heart of the action potential. The opening and closing are regulated by voltage (in other context, they can also be regulated by mechanical forces, membrane tension, ligand binding, phosphorylation). Membrane voltage keeps the channels closed, and their ‘preferred’ configuration (in absence of voltage) is open, see Figure 1.4.

Ion species	Intracellular concentration (mM)	Extracellular concentration (mM)	Nernst potential (mV)
K ⁺	155	4	-98
Na ⁺	12	145	67
Ca ²⁺	10 ⁻⁴	1.5	130
Cl ⁻	4	120	-90

Table 1.1 Physical Biology of the Cell, 2ed. © Garland Science 2013

Table 1.1 Typical concentrations and voltages. These are for a mammalian skeletal muscle cell, for which the resting potential is around $V_{mem} = -90$ mV (i.e., the inside of the cell is 90 mV lower than the exterior).

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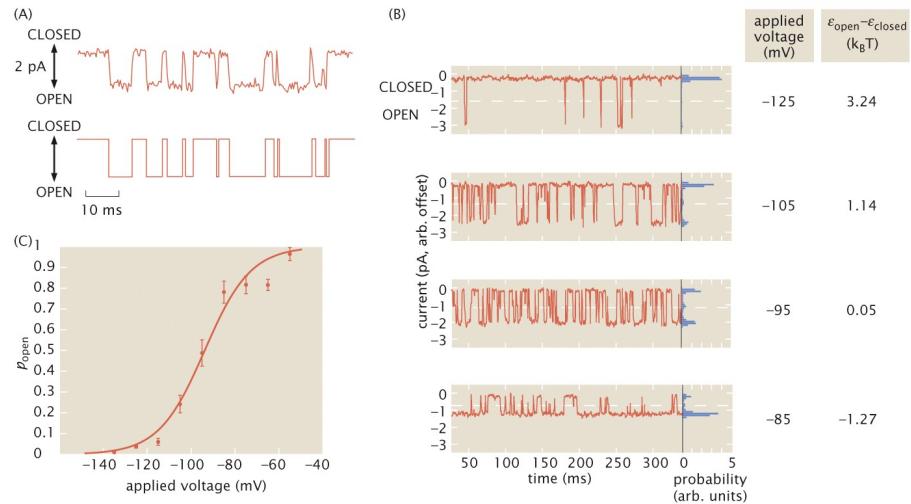


Figure 7.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Fig. 1.4 Patch clamp experiments can measure the current through membranes. These data are for sodium channels. A two state approximation for the channel is appropriate. In (B), single channel data.

In the approximation of a two state model with energy differences $\Delta\epsilon$, the probability of the channel being open is:

$$p_{open} = \frac{e^{-\beta\Delta\epsilon}}{1 + e^{-\beta\Delta\epsilon}}. \quad (1.2)$$

The energy depends on the membrane potential:

$$\Delta\epsilon = \Delta\epsilon_{conf} - QfV_{mem}, \quad (1.3)$$

where $\Delta\epsilon_{conf}$ is the energy difference in the protein channel conformational states, and the second term accounts for the motion of charges Q in the potential. The quantity f is a fraction. If we have the field across the thickness d as $E = V_{mem}/d$, then $fV_{mem} = f d E$ is the drop in potential experienced by the 'gating charge' when it switches from the open to the closed position.

One has $p_{open} = 1/2$ at $\Delta\epsilon = 0$, which defines:

$$V^* = \frac{\Delta\epsilon_{conf}}{Qf}. \quad (1.4)$$

So we can rewrite the channel being open probability as:

$$p_{open} = \frac{1}{1 + e^{\beta q(V^* - V_{mem})}}, \quad (1.5)$$

with $q = Qf$. This sigmoidal shape is a key ingredient in the action potential.

1.2 Biological electricity and the Hodgkin-Huxley model

Two channel proteins are important in explaining propagating pulses:

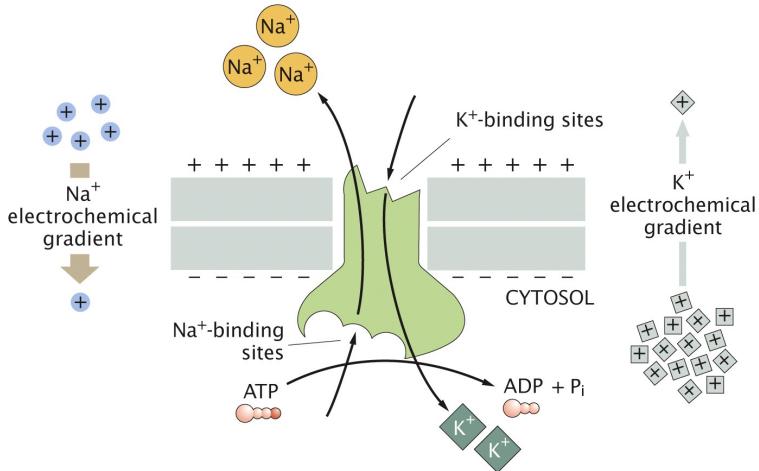


Figure 17.8 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Fig. 1.5 The sodium-potassium pump.

- First, the sodium-potassium pump, see Figure 1.5. This pump consumes the energy of an ATP molecule ($20 k_B T$ for hydrolysis of ATP) and uses that to pump 3 Na⁺ ions out of the cell, and 2 K⁺ ions inside.
- Second, potassium (and sodium) ‘leak’ channel, which selectively allows potassium (or sodium) to transport.

If a potassium ‘leak channel’ is open, K⁺ escape the cell following their concentration gradient. However, this change reduces the magnitude of the membrane potential. Potassium will reach a balance close to its Nernst potential. Now if a sodium channel opens, sodium will move both in response to its own concentration gradient, and also to re-equilibrate the charge lost by the potassium. Sodium will reach a balance close to its Nernst potential. The sodium channels are normally closed. They open transiently and locally, if a neighboring patch of membrane has been depolarised. These ideas can be made into a quantitative model.

The capacitance of a patch of the membrane is defined as

$$C_{patch} = \frac{Q_{patch}}{V_{mem}}, \quad (1.6)$$

where Q_{patch} is the excess charge on either side of the membrane patch. In terms of charge density σ , and patch area, we have $Q_{patch} = \sigma A_{patch}$. In a parallel plate capacitor the field is uniform and given by $\sigma/\epsilon_0\epsilon_r$, so with membrane thickness d we have

$$V_{mem} = \frac{\sigma d}{\epsilon_0\epsilon_r}, \quad (1.7)$$

hence with eq. 1.6

$$C_{patch} = \frac{\epsilon_0\epsilon_r A_{patch}}{d}. \quad (1.8)$$

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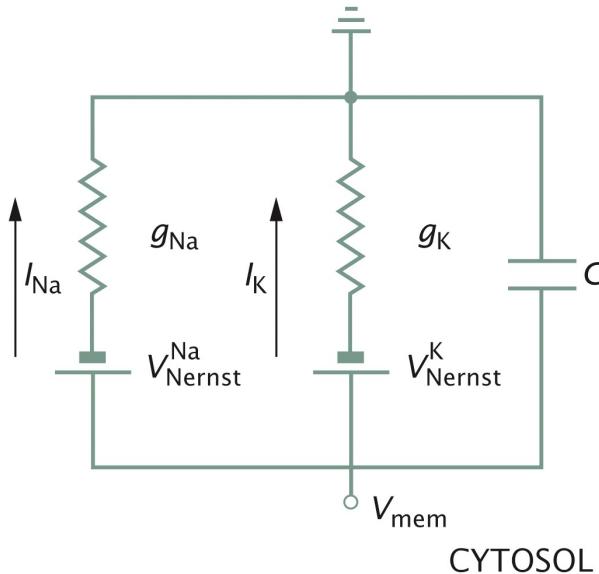


Figure 1.6 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Fig. 1.6 Mapping of an excitable membrane into an electric circuit. The g are conductances.

With $\epsilon_r \simeq 2$ and $d \simeq 5 \text{ nm}$, the capacitance per unit area is expected as $0.4 \mu\text{F}/\text{cm}^2$. Cell membranes have $1 \mu\text{F}/\text{cm}^2$.

It is possible to verify building on eq. 1.8 that a significant $\Delta V_{mem} \simeq 100 \text{ mV}$ depolarisation can be carried out by moving a vanishingly small fraction (of order 10^{-5} of the ions in a cell) across the membrane.

The ionic current across the membrane is:

$$I = g \left(\frac{k_B T}{z e} \ln \frac{c_{in}}{c_{out}} + V_{in} - V_{out} \right), \quad (1.9)$$

where g is the conductance per unit area. Here positive current is a flow of positive ions out of the cell.

With eq. 1.1, we can write $I = g(V_{mem} - V_{Nernst})$, the form of an Ohm law.

If G_1 is the conductance of a single ionic channel, then $g_{patch} = N_{patch} p_{open} G_1$. Recall that p_{open} is not linear in the voltages, see eq. 1.5.

If p_{open} were *always* =1, i.e. the channel always open, then we'd expect Ohm conduction, and a linear $I - V$ dependence from eq. 1.9. This is what happens for the potassium ions in Figure 1.7. If p_{open} were a step change, opening at voltage V^* , and allowing g to jump to a higher value, then current I would drop suddenly as the voltage increases across V^* . The voltage would grow linearly both below and above V^* , but with a discontinuous jump.

The realistic sigmoidal form of p_{open} is quite similar to a jump, just smoothed out. Voltage drops, as in Figure 1.7 for the sodium ions.

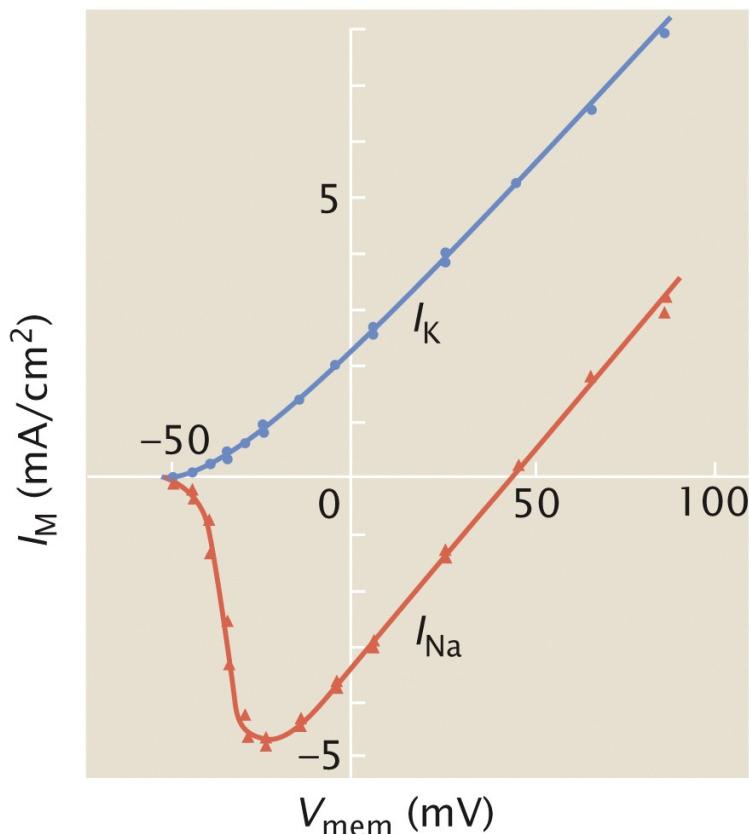


Figure 17.13 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Fig. 1.7 Data of current through a membrane patch, as a function of membrane voltage. Note the linear I_V characteristics of the potassium ion current, and the extremely non-linear response of the sodium ions.

1.2.1 Bistable behaviour of membrane voltage

The charge across the membrane can be written as $\Delta Q = -(I_K + I_{\text{Na}})\Delta t$ and also as $\Delta Q = C\Delta V_{\text{mem}}$, so putting the two together we obtain the differential equation valid in each small patch of membrane:

$$C \frac{dV_{\text{mem}}}{dt} = g_K(V_{\text{Nernst}}^K - V_{\text{mem}}) + g_{\text{Na}}(V_{\text{Nernst}}^{Na} - V_{\text{mem}}). \quad (1.10)$$

An interesting property of this is that it is bi-stable. Setting the time derivative =0,

$$V_{\text{mem}} = \frac{g_K V_{\text{Nernst}}^K + g_{\text{Na}} V_{\text{Nernst}}^{Na}}{g_K + g_{\text{Na}}}. \quad (1.11)$$

If $g_K \gg g_{\text{Na}}$ then $V_{\text{mem}} \simeq V_{\text{Nernst}}^K$. If instead $g_{\text{Na}} \gg g_K$ then $V_{\text{mem}} \simeq V_{\text{Nernst}}^{Na}$. The ion species with the highest conductance through the membrane sets the membrane potential to its Nernst potential. The conductances are of course related to the open/closed balance of the channels, and we have seen that this is Voltage regulated.

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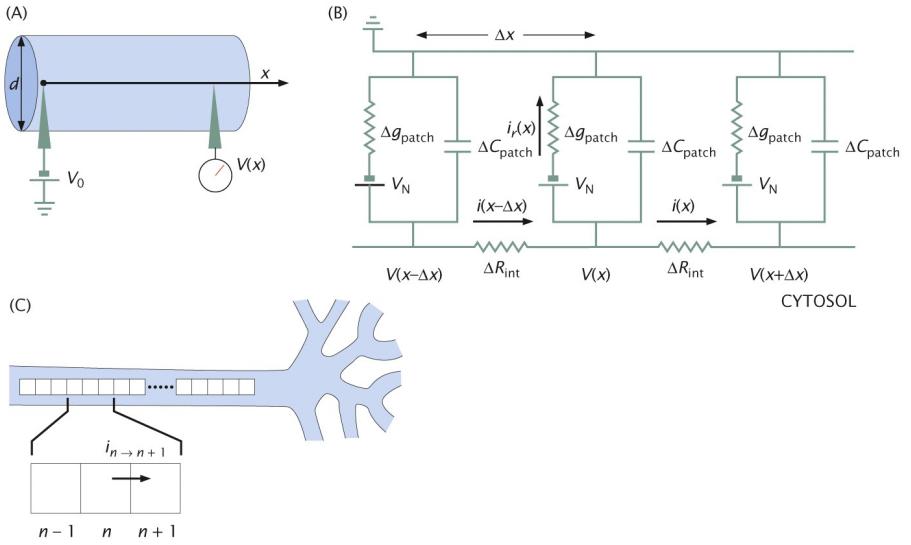


Figure 1.8 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Fig. 1.8 We model the axon as a series of elements. Each element is a cylinder of diameter d and length Δx .

An approximation is to consider the potassium conductance as fixed; this is justified because its dynamics is slower than the dynamics of the sodium channel. Then, we have that the sodium conductance is proportional to its own p_{open} from eq. 1.5. For $V_{mem} < V^*$ this gives a low conductance, and therefore the membrane will take the Nernst potential of potassium. If $V_{mem} > V^*$ the sodium channels open, sodium conductance dominates. The membrane potential goes to the Nernst voltage of potassium, a positive value.

1.2.2 Cable equation

We can model the spatial transmission of signal by considering a series of circuits as in Figure 1.8. The change of voltage along the axon is connected to the longitudinal current: $V(x+\Delta x) - V(x) = -i(x)\Delta R_{int}$. The current $i(x)$ can change along the axon due to currents in the radial direction $i_r(x)$. In each module there is also conservation of current, which gives $i(x-\Delta x) - i(x) = i_r(x) = \Delta g_{patch}(V(x) - V_{Nernst})$. Since $\Delta R_{int} = \rho\Delta x/(\pi d^2/4)$ and $\Delta g_{patch} = g\pi d\Delta x$, where d is the axon diameter, ρ the resistivity of the intracellular medium, and g the conductance per unit area, we can combine these to give:

$$\frac{d^2V(x)}{dx^2} = \frac{1}{\lambda^2}(V(x) - V_{Nernst}), \quad (1.12)$$

with

$$\lambda = \sqrt{\frac{d}{4\rho g}}. \quad (1.13)$$

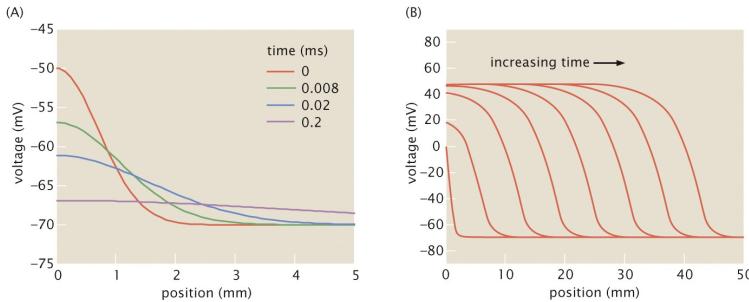


Figure 1.9 Physical Biology of the Cell, 2nd. (© Garland Science 2013)

Fig. 1.9 Propagation for an input that overcomes the threshold.

The quantity λ gives the exponential decay of the voltage perturbation, along the axon. It is $\simeq 9$ mm in the squid axon, where $d \simeq 0.5$ mm, $\rho \simeq 0.3 \Omega \text{m}$ and $g \simeq 5 \Omega^{-1} \text{m}^{-2}$.

1.2.3 Depolarisation Waves

To describe waves on the axon we have to combine the voltage bistability property with the cable equation.

Generalising the current equation to include two types of channels, and the capacitance current, gives:

$$\begin{aligned} i(x - \Delta x, t) - i(x, t) &= \Delta g_{patch}^{Na} (V(x, t) - V_{Nernst}^{Na}) + \\ &+ \Delta g_{patch}^K (V(x, t) - V_{Nernst}^K) + \Delta C_{patch} \frac{\partial V(x, t)}{\partial t}. \end{aligned} \quad (1.14)$$

We are again making the simplification that potassium conductance is a constant with voltage and low. The sodium conductance has the form described earlier, and values that switch from below the potassium to very high, increasing voltage.

The resulting equation, generalising the Cable equation to give time dependence, is:

$$\lambda^2 \frac{\partial^2 V(x, t)}{\partial x^2} - \tau \frac{\partial V(x, t)}{\partial t} = (V(x, t) - V_{Nernst}^K) + \frac{g_{Na}(V(x, t))}{g_K} (V(x, t) - V_{Nernst}^{Na}), \quad (1.15)$$

with λ as above, and $\tau = C/g$ with the conductances set by potassium (dynamics of the RC circuit).

The l.h.s. of Eq. 1.15 is the diffusion equation. If we imagine a localised current injected at $x = 0$ in a small region, then there can be two cases. (a) If the membrane voltage remains below the threshold to open the sodium channels. Then the r.h.s. of Eq. 1.15 remains small (negligible) and we simply have a diffusive relaxation of the voltage, see Figure 1.9(A). (b) If the voltage rises above the threshold to open the sodium channels, then the membrane potential near $x = 0$ changes to the Nernst potential of sodium. This then leads to a propagating front, see Figure 1.9(B).

The speed is λ/τ , and we had $\lambda \sim \sqrt{d}$, so large axons propagate signals faster.

1.3 A Hodgkin-Huxley model for spike propagation

A typical signal traveling in an axon has a conserved and local envelope - this is called a spike. To describe a spike, the missing concept from point (b) above is the inactivation of the sodium channels. In the membrane, sodium channels remain open for about 2 ms. After closing, they remain ‘inactive’ for few tens of ms. The voltage gated potassium channels are slower to open (several ms) but remain open as long as depolarisation is maintained. This time-asymmetry in the sodium response leads to uni-directional motion of the signal down the axon.

Information is coded as a frequency of spikes. i.e. a more intense input current is turned into a more rapid train of spikes compared to a low input current, with the shapes of the spikes being quite comparable. This process turns an analog input into a digital signal.

We now add inactivation of the sodium channels, with the concept of the inactive state, to complete the model of Eq. 1.15. There are three states for the sodium channel, and the transitions between them can be described by:

$$\begin{aligned}\frac{dp_C}{dt} &= -k_{open}p_C \\ \frac{dp_O}{dt} &= k_{open}p_C - k_{inactive}p_O \\ \frac{dp_I}{dt} &= k_{inactive}p_O.\end{aligned}\quad (1.16)$$

Note that we have not allowed in Eqs. 1.16 inactive→closed nor open→closed, so this simplification can only describe a single spike.

We take the rate of opening to be proportional to the probability of an open channel (same logic as elsewhere in the course, in regulating gene expression):

$$k_{open} = k_{open}^{max} \frac{1}{1 + e^{\beta q(V^* - V(x,t))}}, \quad (1.17)$$

and the inactivation rate as a constant.

The sodium conductance now depends on the state of the channels, and has the form:

$$g_{Na} = g_{Na}^{open} p_O + g_{Na}^{closed} p_C. \quad (1.18)$$

Crucially for the system to work, the parameters have evolved such that the open state conductivity of sodium channels is about

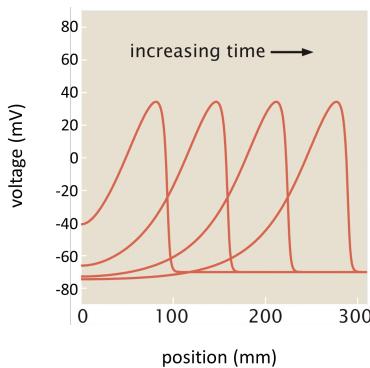


Fig. 1.10 Numerical solutions of the time dependent cable equation, with inactivation of the sodium channels.

20 times larger than g_K (potassium), and the closed state is about 20 times lower than potassium. This more complex sodium conductivity, function of the voltage, and hence space and time, needs to be considered in Eq. 1.15. The equation is readily solved numerically and the solutions are traveling spikes as in Figure 1.10.

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