

Theory of action potentials

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Contents

5 Propagation of action potentials	1
5.1 Cable theory	1
5.1.1 The cable equation	1
5.1.2 The cable equation with constant diameter	2
5.1.3 The cable equation with variable diameter	3
5.1.4 The cable equation with a resistive extracellular medium	3
5.2 Passive propagation	4
5.2.1 The linear cable equation	4
5.2.2 Stationary response	4
5.2.3 Filtering properties	6
5.2.4 Impulse response	8
5.3 Action potential propagation in unmyelinated axons	9
5.3.1 Conduction velocity	9
5.3.2 Shape of the propagated action potential	11
5.4 Action potential propagation in myelinated axons	11
5.4.1 Myelin	11
5.4.2 Ranvier nodes	13
5.5 Extracellular potential and current circulation	14
5.5.1 The line source approximation	14
5.5.2 Extracellular signature of a propagated action potential	14
5.5.3 Current circulation	15

Chapter 5

Propagation of action potentials

In previous chapters, we have considered action potentials produced by an isopotential membrane. In this chapter, we look at how electrical signals, and in particular action potentials, propagate along neurites. This is modeled by *cable theory*. Linear cable theory is described in great detail in Rall (2011), and in two books: Tuckwell (1988) and Koch (1999).

5.1 Cable theory

5.1.1 The cable equation

Let us consider a neurite (axon or dendrite), which we model as a conductor with intracellular resistivity R_i (in $\Omega\cdot\text{m}$), separated from the extracellular medium by an insulating membrane. Let us consider a transversal slice at a point x along the neurite, of width dx . There is a current going through the membrane (capacitive and ionic), proportional to the width dx , which we denote $I_m(x)dx$. Note that I_m is in A/m and oriented inward ($I_m > 0$ means inward positive current). There is also a current in the axial direction, which we denote $I_a(x)$ (in A). The axial current enters the slice as $I_a(x)$ and exits as $I_a(x+dx)$, and by Kirchoff's law, the difference must equal the membrane current, which means:

$$I_m = \frac{\partial I_a}{\partial x}$$

Since we consider the intracellular medium as a conductor, the axial current is determined by Ohm's law: the axial current flowing between two nearby points x and $x+dx$ is

$$I_a(x) = \frac{V_i(x) - V_i(x+dx)}{r_a(x)dx} = -\frac{1}{r_a} \frac{\partial V_i}{\partial x}$$

where V_i is the intracellular potential and $r_a(x)$ is the axial resistance per unit length at point x . Thus we obtain the equation

$$I_m = -\frac{\partial}{\partial x} \left(\frac{1}{r_a} \frac{\partial V_i}{\partial x} \right)$$

Note that this relates the membrane current to the intracellular potential, and not to the membrane potential. In the following, we will assume that the extracellular potential is spatially constant along the neurite. This amounts to assuming that the extracellular medium is conductor, with negligible resistance (see section 5.1.4 for the case when the extracellular medium is resistive). In this case, we obtain:

$$I_m = -\frac{\partial}{\partial x} \left(\frac{1}{r_a} \frac{\partial V_m}{\partial x} \right)$$

This is called the *cable equation*.

5.1.2 The cable equation with constant diameter

We start by assuming that the neurite has a constant section, for example that it is a cylinder. In this case, the resistance per unit length r_a is independent of x . Therefore the cable equation simplifies as

$$r_a I_m = -\frac{\partial^2 V_m}{\partial x^2}$$

What is the value of the resistance per unit length r_a ? Resistance is inversely proportional to the section area S of the conductor, and therefore:

$$r_a = \frac{R_i}{S}$$

where R_i is a proportionality factor called *intracellular resistivity*, of order 100 $\Omega \cdot \text{cm}$. If we consider a cylindrical geometry with diameter d , then we obtain:

$$r_a = \frac{4R_i}{\pi d^2}$$

The membrane current per unit length I_m is related to the membrane current density \tilde{I}_m , per unit of membrane area, by the relation $I_m = P\tilde{I}_m$, where P is the perimeter of the section. For a cylindrical geometry, we obtain

$$I_m = \pi d \tilde{I}_m$$

Thus the cable equation with constant diameter is

$$\tilde{I}_m = -\frac{d}{4R_i} \frac{\partial^2 V_m}{\partial x^2}$$

The membrane current density \tilde{I}_m is composed of a capacitive current and a ionic current I_{ionic} :

$$\tilde{I}_m = I_{\text{ionic}} - c_m \frac{\partial V_m}{\partial t}$$

Therefore the cable equation can be expressed as follows:

$$\frac{d}{4R_i} \frac{\partial^2 V_m}{\partial x^2} = c_m \frac{\partial V_m}{\partial t} - I_{\text{ionic}}$$

We recover the membrane equation of an isopotential model by setting $\frac{\partial^2 V_m}{\partial x^2} = 0$.

5.1.3 The cable equation with variable diameter

We now consider the more general case when geometry varies with x . Let us assume that the neurite has circular sections of varying diameter $d(x)$. First, we need to calculate the resistance per unit length $r_a(x)$.

In this case, the cable equation is:

$$\begin{aligned} I_m &= -\frac{\partial}{\partial x} \left(\frac{\pi d^2}{4R_i} \frac{\partial V_m}{\partial x} \right) \\ &= \frac{\pi d^2}{4R_i} \left(\frac{\partial^2 V_m}{\partial x^2} + 2 \frac{d'}{d} \frac{\partial V_m}{\partial x} \right) \end{aligned}$$

We now calculate the area of a slice of membrane of width dx . If we cut the neurite through two transversal sections, then we obtain a geometrical shape called a frustum. We consider that it is a conical frustum, that is, a truncated cone, with circular end sections of diameter $d_1 = d(x)$ and $d_2 = d(x + dx)$. The surface area of a conical frustum, not including the two circular sections, is

$$\begin{aligned} A &= \frac{\pi}{2} (d_1 + d_2) s \\ &= \frac{\pi}{2} (d_1 + d_2) \sqrt{\frac{1}{4} (d_2 - d_1)^2 + dx^2} \end{aligned}$$

where s is the slant height of the frustum (length of a minimal segment connecting the two circular sections). With a small dx , we obtain:

$$A \approx \pi d \cdot dx \sqrt{\frac{d'^2}{4} + 1}$$

Finally, we obtain the cable equation with variable diameter:

$$\frac{1}{4R_i \sqrt{\frac{d'^2}{4} + 1}} \left(d \frac{\partial^2 V_m}{\partial x^2} + 2d' \frac{\partial V_m}{\partial x} \right) = c_m \frac{\partial V_m}{\partial t} - I_{\text{ionic}}$$

We can see that we recover the previous cable equation if $d(x)$ varies slowly (small d').

5.1.4 The cable equation with a resistive extracellular medium

In reality, the extracellular medium has non-zero resistivity, of about $300 \Omega \cdot \text{cm}$ in grey matter¹ (conductivity $\sigma \approx 0.3 - 0.4 \text{ S/m}$ (Einevoll et al., 2013)).

Let us consider a neurite with constant section (for example a cylinder), surrounded by a resistive extracellular medium with geometry that is invariant along the longitudinal axis of the neurite. Then applying Kirchoff's law, we obtain:

$$I_m = \frac{1}{r_a^e} \frac{\partial^2 V_e}{\partial x^2}$$

where r_a^e is the extracellular resistance per unit length. This quantity depends both on extracellular resistivity and on the geometry of the extracellular space.

¹Note that this corresponds to measurements taken with two distant electrodes in tissue, which therefore take into account the presence of the tissue. A lower value would be expected from just the liquid content of the extracellular medium.

For example, extracellular resistance could be large if cells are tightly packed or if the axon is immersed in oil, so that only a thin layer of extracellular medium surrounds the axon.

Combining this equation with the equation relating membrane current and intracellular potential, we obtain:

$$(r_a^i + r_a^e)I_m = -\frac{\partial^2 V_m}{\partial x^2}$$

This means that the effect of the resistance of the extracellular medium is simply to increase the axial resistance. Note that this could be more complicated if the geometry of the extracellular space varied along the axon.

5.2 Passive propagation

5.2.1 The linear cable equation

In this section we only consider passive properties with a linear current-voltage model, and cylindrical neurites. This makes the cable equation linear:

$$\frac{d}{4R_i} \frac{\partial^2 V_m}{\partial x^2} = c_m \frac{\partial V_m}{\partial t} - g_L(E_L - V_m)$$

where g_L is leak conductance density and E_L is leak reversal potential. To simplify the notations, we will take E_L as the reference potential by defining $V = V_m - E_L$. We then define $r_m = 1/g_L$ the *specific membrane resistance*. We can then rewrite the membrane equation as follows:

$$\lambda^2 \frac{\partial^2 V}{\partial x^2} = \tau \frac{\partial V}{\partial t} + V$$

where $\tau = r_m c_m$ is the membrane time constant and

$$\lambda = \sqrt{\frac{dr_m}{4R_i}}$$

has the dimensions of a length and is thus called the *characteristic length* or *space constant* or *electrotonic length*.

5.2.2 Stationary response

In this section, we look at the stationary response, that is, when the potential does not change anymore. The cable equation, which is a partial differential equation, then becomes an ordinary differential equation that depends only on x :

$$\lambda^2 \frac{d^2 V}{dx^2} = V$$

The solutions of this second-order equation can be expressed as a linear combination of two independent solutions, for example:

$$V(x) = Ae^{x/\lambda} + Be^{-x/\lambda}$$

or

$$V(x) = A \cosh(x/\lambda) + B \sinh(x/\lambda)$$

The choice of the basis of solutions will depend on which one is more convenient for the specific problem to be solved.

Injecting current in the middle of a cylinder

Let us consider an infinite cylinder with diameter d . We inject some current I at a point $x = 0$. This will depolarize the membrane, with an effect that attenuates with distance. On each half cylinder ($x > 0$ and $x < 0$), the stationary cable equation has a solution of the form

$$V(x) = Ae^{x/\lambda} + Be^{-x/\lambda}$$

Since the potential must be bounded at infinity, it follows that:

$$\begin{aligned} V(x) &= Ae^{-x/\lambda} & x > 0 \\ &= Be^{x/\lambda} & x < 0 \end{aligned}$$

We then use continuity at $x = 0$ to deduce:

$$V(x) = Ae^{-|x|/\lambda}$$

Thus the membrane potential decreases exponentially with distance, with characteristic length λ , which explains the name that we have given to λ .

What is the value of A ? First, the linearity of the problem implies that A should be proportional to the current I , i.e.:

$$V(x) = RIe^{-|x|/\lambda}$$

where $R = V(0)/I$ is called the *input resistance*. To determine this resistance, we will use Kirchoff's law. The injected current I must equal the difference between the axial currents just after $x = 0$ and just before $x = 0$, that is:

$$\begin{aligned} I &= I_a(0^+) - I_a(0^-) \\ &= \frac{1}{r_a} (V'(0^-) - V'(0^+)) \\ &= \frac{2RI}{r_a\lambda} \end{aligned}$$

We conclude that the input resistance is:

$$R = \frac{r_a\lambda}{2} = \frac{1}{\pi} \sqrt{r_m R_i} d^{-3/2}$$

This formula is somewhat intuitive: the input resistance is half the resistance of a characteristic length of cylinder. The half comes from the fact that the current flows towards both directions (negative and positive x).

Injecting current through one end of a cylinder

Let us consider now a semi-infinite cylinder, with current injected at $x = 0$. This current must equal the axial current at $x = 0$, and it is easy to see that the potential must again follow:

$$V(x) = RIe^{-x/\lambda}$$

with input resistance $R = r_a\lambda$.

Finite cylinders

Let us now consider a finite cylinder of length L , with a current I injected at the end $x = 0$. We will consider that no current flows through the other end; this is called a *sealed end* condition². These two conditions mean:

$$\begin{aligned} V'(0) &= -r_a I \\ V'(L) &= 0 \end{aligned}$$

For this problem, it will prove more convenient to use the hyperbolic basis of solutions:

$$\begin{aligned} V(x) &= A \cosh(x/\lambda) + B \sinh(x/\lambda) \\ V'(x) &= \frac{B}{\lambda} \cosh(x/\lambda) + \frac{A}{\lambda} \sinh(x/\lambda) \end{aligned}$$

We now use the two boundary conditions to find the two unknowns A and B :

$$\begin{aligned} B &= -r_a \lambda I \\ A &= -\frac{B}{\tanh(L/\lambda)} \end{aligned}$$

Thus the solution is:

$$V(x) = r_a \lambda I \left(\frac{\cosh(x/\lambda)}{\tanh(L/\lambda)} - \sinh(x/\lambda) \right)$$

We recover the solution for an infinite half-cylinder when $L \rightarrow \infty$. The input resistance is:

$$R = V(0)/I = \frac{r_a \lambda}{\tanh(L/\lambda)}$$

5.2.3 Filtering properties

We again consider an infinite cylinder of diameter d , but we now inject a sinusoidal current at $x = 0$. A general approach for this type of problem is to apply the Fourier or Laplace transform to the cable equation (see for example Tuckwell (1988)). Equivalently, we can start from the fact that the response of a linear system to a sinusoidal input is also sinusoidal, possibly with a phase shift. It is more convenient to look at the problem in the complex domain. That is, we consider an oscillating input defined by a complex exponential:

$$I(t) = I_0 e^{i\omega t}$$

with $\omega = 2\pi f$, where f is the input frequency. The membrane potential at any point along the cable must take the same form, that is:

$$V(x, t) = v(x) e^{i\omega t}$$

²the condition $V(L) = 0$ is called a *killed end* condition. Note that neither a sealed nor a killed end is realistic, since capacitive and leak currents should flow through the piece of membrane at the end.

We now simply insert this expression into the cable equation, and we obtain:

$$\lambda^2 v'' = (1 + i\omega\tau)v$$

This is an ordinary differential equation, whose solution is a linear combination of two exponential functions $e^{\pm ax}$. We find

$$\begin{aligned} a &= \pm \frac{1}{\lambda} \sqrt{1 + i\omega\tau} \\ &= \pm \frac{1}{\sqrt{2}\lambda} \left(\sqrt{\sqrt{1 + \omega^2\tau^2} + 1} + i\sqrt{\sqrt{1 + \omega^2\tau^2} - 1} \right) \end{aligned}$$

Since the potential must be finite at infinity, we must choose the solution with a positive real part. If we focus on the amplitude of the response, we then obtain:

$$|v(x)| = |v(0)|e^{-x/\lambda(f)}$$

where

$$\begin{aligned} \lambda(f) &= \sqrt{\frac{2}{\sqrt{1 + \omega^2\tau^2} + 1}} \lambda \\ &= \sqrt{\frac{2}{\sqrt{1 + 4\pi^2 f^2\tau^2} + 1}} \lambda \end{aligned}$$

is the characteristic length of voltage attenuation at frequency f . Note that, to derive this result, we have in fact not used the boundary conditions, but only the fact that the membrane is stimulated at frequency f . This means that same result would be obtained if current were injected at one end of a semi-infinite cylinder, or if one end of a semi-infinite cylinder were voltage-clamped at frequency f . In all these cases, the voltage attenuates over a distance that is shorter than the space constant λ .

The input resistance is related to the space constant in the same way as with a constant current injection:

$$R = \frac{r_a \lambda(f)}{2}$$

Thus, there is a smaller input resistance at higher frequency.

High-frequency response

At high frequency, the space constant is

$$\lambda(f) \approx \frac{\lambda}{\sqrt{\pi f\tau}} = \sqrt{\frac{d}{4\pi R_i f c_m}}$$

and the input resistance is:

$$R = \sqrt{\frac{R_i}{f c_m}} (\pi d)^{-3/2}$$

Thus at high frequency, the response of the cable does not depend on membrane resistance anymore, only on membrane capacitance.

5.2.4 Impulse response

What happens when we deliver an instantaneous shock at $x = 0$ on a cylindrical membrane, carrying a charge Q_0 ? We are now looking for a time-dependent solution $V(x, t)$ to the cable equation, which is a linear partial differential equation. This problem is not trivial but can be solved using a linear transform, for example the spatial Fourier transform or the Laplace transform. Details can be found for example in (Tuckwell, 1988). Here we will use a different approach that is physically more intuitive.

Total charge

Let us consider the total charge $Q(t)$ stored in the membrane capacitance, relative to the charge at rest. This charge is initially 0, then becomes Q_0 at the time $t = 0$ of the shock. How does it change over time? This charge changes because of the transmembrane ionic current, which in the case we consider is simply the leak current. Thus:

$$\frac{dQ}{dt} = - \int \frac{V}{\bar{r}_m}$$

where the integral is over x and \bar{r}_m is the membrane resistance per unit length. The charge per unit length is $q = \bar{c}_m V$, where \bar{c}_m is capacitance per unit length. Therefore:

$$\frac{dQ}{dt} = - \int \frac{q}{\bar{r}_m \bar{c}_m} = - \frac{Q}{\tau_m}$$

This result is independent of the geometry of the neurite, and in particular is the same as in an isopotential membrane. This gives a new interpretation of the membrane time constant: τ is the characteristic time of decay of the total charge over the membrane. The solution of this equation is:

$$Q(t) = Q_0 e^{-t/\tau}$$

General solution

Or: local charge V times $\pi d c_m$

Now we look at how this total charge is distributed over the cylinder. The local charge is $q(x, t) = \bar{c}_m V(x, t)$ and therefore satisfies the same cable equation as the potential. We look for a solution of the form $q(x, t) = Q(t)U(x, t)$, where $\int U(x, t) dx = 1$. Substituting this expression in the cable equation gives:

$$\lambda^2 Q \frac{\partial^2 U}{\partial x^2} = \tau \frac{dQ}{dt} U + \tau \frac{\partial U}{\partial t} Q + QU$$

Using the differential equation for Q , we then obtain:

$$\lambda^2 \frac{\partial^2 U}{\partial x^2} = \tau \frac{\partial U}{\partial t}$$

This is the heat equation or diffusion equation, with a diffusion coefficient $D = \lambda^2/\tau$. The solution is a Gaussian function of x with standard deviation $\sigma = \sqrt{2Dt} = \sqrt{2t/\tau\lambda}$. In summary, the solution for $t > 0$ is:

$$q(x, t) = Q e^{-t/\tau} \times G\left(\frac{x}{\sqrt{2t/\tau\lambda}}\right)$$

5.3. ACTION POTENTIAL PROPAGATION IN UNMYELINATED AXONS 9

where G is the Gaussian function with unit standard deviation:

$$G\left(\frac{x}{\sqrt{2t/\tau\lambda}}\right) = \frac{1}{\sqrt{4\pi t/\tau\lambda}} e^{-\frac{\tau x^2}{4t\lambda^2}}$$

and therefore the potential is:

$$V(x, t) = \frac{Q}{\pi d c_m} e^{-t/\tau} \times G\left(\frac{x}{\sqrt{2t/\tau\lambda}}\right)$$

where we have used $\bar{c}_m = \pi d c_m$.

Some plots of it

Propagation speed

Let us now look at the potential at some distance x of the point of current injection. The potential first increases then decays. The peak of $V(x, t)$ is reached at some time t that we shall call the latency $L(x)$. Clearly, latency increases with $|x|$. We may then define a speed of passive propagation as the distance divided by the latency. Let us calculate this speed.

Instead of calculating the peak of $V(x, t)$, we calculate the peak of $\log V$, which is simpler and reached at the same time. We have:

$$\log V = -\frac{t}{\tau} - 2\pi \frac{t}{\tau} - \lambda - \frac{\tau x^2}{4t\lambda^2} + \text{constant}$$

We set $d(\log V)/dt = 0$ and find:

$$t = \frac{\tau}{4} (\sqrt{1 + 4(x/\lambda)^2} - 1)$$

For large x , this is

$$t \approx \frac{\tau x}{2\lambda}$$

and thus the speed is

$$v = \frac{2\lambda}{\tau}$$

Note that this is not the speed at which electricity travels. As we have previously mentioned, speed of electrical conduction through a ionic solution has the same order of magnitude as the speed of light. This is merely distance over peak latency, which has the dimension of velocity.

5.3 Action potential propagation in unmyelinated axons

5.3.1 Conduction velocity

We consider an infinite cylinder of diameter d . As we have shown in section 5.1.2, the cable equation is:

$$\frac{d}{4R_i} \frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} - I_{\text{ionic}}$$

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where I_{ionic} is a current density, expressed per unit of membrane area. We have previously considered the case when the ionic current is a linear leak current. Here we assume that it is a voltage-dependent current, as in the Hodgkin-Huxley model. Thus there are additional state variables that depend on V_m (m , h and n in the Hodgkin-Huxley model), and are functions of x and t .

We are looking for a wave that propagates at velocity v . This means that the potential V is a function of $x - vt$: $V(x, t) = U(x - vt)$. Here $U(\cdot)$ is the spatial profile of the propagated action potential. Thus we have:

$$\begin{aligned}\frac{\partial^2 V}{\partial x^2} &= U'' \\ \frac{\partial^2 V}{\partial t^2} &= v^2 U'' = v^2 \frac{\partial^2 V}{\partial x^2}\end{aligned}$$

Thus the cable equation now reads:

$$\frac{d}{4R_i v^2} \frac{\partial^2 V}{\partial t^2} = c_m \frac{\partial V}{\partial t} - I_{\text{ionic}}$$

This is not a partial differential equation anymore, but an ordinary differential equation, since all derivatives (including in equations for the state variables) are with respect to time. We can thus fix a particular value for x and solve this equation. The same solution will be found at a different x , except with a delay (x/v). There are two difficulties here: the equations are nonlinear (because of the equations for m , h and n) and v is unknown. Hodgkin and Huxley used the following procedure (Hodgkin and Huxley, 1952). First, a guess value for v is inserted in the equation, which is numerically integrated starting from the resting potential. This typically gives a solution that diverges to $+\infty$ when v is too small, or $-\infty$ when v is too large. The value of v is then adjusted and the procedure is repeated until v converges to some value. By this method, Hodgkin and Huxley (1952) found a predicted conduction velocity of 18.8 m/s, close to the empirically measured value of 21.2 m/s.

Although there is no closed form for the conduction velocity as a function of biophysical parameters, it is possible to obtain a scaling relation with axon diameter d . Let us assume that the following differential equation:

$$\alpha \frac{d^2 V}{dt^2} = c_m \frac{dV}{dt} - I_{\text{ionic}}$$

has a bounded solution, obtained with the aforementioned procedure, for a unique value of α . Then we have the following relationship:

$$v = \sqrt{\frac{d}{4R_i \alpha}}$$

or in other words:

$$v \propto \sqrt{\frac{d}{R_i}}$$

In particular, $v \propto \sqrt{d}$. Note that to obtain this result, we have implicitly assumed that surfacic conductance densities are constant. This scaling relation also implies two other facts: 1) the time course $t \mapsto V(x, t)$ is invariant with

velocity and thus with diameter; 2) the spatial profile $x \mapsto V(x, t)$ expands with velocity and thus with \sqrt{d} (broader profile for thicker axons).

Also consistent with this result is the observed decrease in conduction velocity when the squid axon is immersed in oil, increasing R_i (Hodgkin, 1939)³.

measurements of Rushton and others

5.3.2 Shape of the propagated action potential

In an isopotential model, the initial rising phase of the action potential is determined by the opening of Na^+ channels. In the propagated action potential, it is the axial current that is responsible for the initial rising phase. It is then possible to calculate this initial shape by neglecting voltage-dependent currents (Taylor, 1963):

$$\frac{d}{4R_i v^2} \frac{d^2 V}{dt^2} = c_m \frac{dV}{dt} + g_L V$$

where g_L is leak conductance density, and we have set the resting potential at 0. This is a linear differential equation, and thus it can be solved. We first rewrite it as

$$a \frac{d^2 V}{dt^2} = \tau \frac{dV}{dt} + V$$

where

$$a = \frac{dR_m}{4R_i v^2}$$

and $R_m = 1/g_L$. We find two exponential solutions of the form $e^{\gamma t}$, with

$$\gamma = \frac{\tau \pm \sqrt{4a + \tau^2}}{2a}$$

With the empirical values in the squid axon used in the Hodgkin-Huxley model, we find $4a \approx 1.5 \text{ ms}^2$ and $\tau \approx 11 \text{ ms}^2$. Therefore, one of the two values is close to 0 and the other is

$$\gamma \approx \frac{\tau}{a} = \frac{4R_i c_m v^2}{d}$$

With the same values, we find $\gamma \approx 8.7 \text{ ms}^{-1}$. In fact, we have seen that v depends on the other parameters, so that

$$\gamma \approx \frac{c_m}{\alpha}$$

where α depends on conductance densities and channel properties. Thus the initial shape of the propagated action potential does not depend on geometry or intracellular resistivity, only on channel properties and densities.

5.4 Action potential propagation in myelinated axons

5.4.1 Myelin

Show voltage imaging data

³More precisely, it increases the extracellular resistance per unit length because of the thinner layer of water around the membrane, and this resistance plays the same role as intracellular resistance, see section 5.1.4.

Myelin is a substance surrounding the axon of certain nerve cells, in general large axons of vertebrate neurons, which provides electrical insulation. It is produced by Schwann cells in the peripheral nervous system, and oligodendrocytes in the central nervous system.

Let us start by analyzing the effect of myelin on passive electrical properties. We denote c_m and r_m the specific capacitance and specific resistance of myelin. For a cylindrical axon, the capacitance per unit length of one layer of myelin of diameter d_i is $C_i = \pi d_i c_m$. When arranged in series, inverse of capacitances add. Therefore, the total capacitance of n layers of myelin satisfies:

$$\frac{1}{C} = \frac{1}{\pi c_m} \sum_{i=0}^{n-1} \frac{1}{d_i}$$

If the myelin layers are equally spaced by Δ , then

$$d_i = d_{\text{in}} + \Delta i$$

where $d_{\text{in}} = d_0$ is the inner diameter and $d_{\text{out}} = d_{n-1}$ is the outer diameter of the axon. It follows that

$$\begin{aligned} \frac{1}{C} &\approx \frac{1}{\pi \Delta c_m} \int_{d_{\text{in}}}^{d_{\text{out}}} \frac{1}{d} \\ &= \frac{1}{\pi \Delta c_m} \log \left(\frac{d_{\text{out}}}{d_{\text{in}}} \right) \end{aligned}$$

The resistance per unit length of one myelin layer of diameter d is $r_m/(\pi d)$. Resistances in series add, therefore we find that the total resistance per unit length is

$$R = \frac{r_m}{\pi \Delta} \log \left(\frac{d_{\text{out}}}{d_{\text{in}}} \right)$$

It follows that the membrane time constant is unchanged by myelination: $\tau = RC = r_m c_m$. Does the space constant λ depend on myelination? To calculate the space constant, we first note that the resistance per unit length R corresponds to an effective resistance per axonal membrane area of $r_m^* = R \times \pi d_{\text{in}}$. Then we use the formula for λ :

$$\lambda = \sqrt{\frac{dr_m^*}{4R_i}} = \frac{d_{\text{in}}}{2} \sqrt{\frac{r_m}{R_i \Delta} \log \left(\frac{d_{\text{out}}}{d_{\text{in}}} \right)}$$

Optimal myelination

How many myelin layers should there be? The formula for the space constant shows that adding layers, i.e., increasing the outer diameter of the axon, increases the space constant, which means better conduction. On the other hand, it also increases the volume occupied by the axon. We may then ask: for a given volume occupied by the axon, i.e., for a given value of d_{out} , what is the optimal number of layers, or equivalently, what is the value of d_{in} that maximizes the space constant?

If d_{out} is constant, then the optimization is equivalently with respect to the ratio $x = d_{\text{in}}/d_{\text{out}}$. Maximizing λ is the same as maximizing λ^2 , and therefore when d_{out} is constant this is equivalent to maximizing the following function:

$$f(x) \equiv -x^2 \log x$$

This function reaches its maximum at:

$$x = \frac{1}{\sqrt{e}}$$

and therefore the optimal ratio between inner and outer diameter of the axon is $d_{\text{in}}/d_{\text{out}} = 1/\sqrt{e} \approx 0.6$. It turns out that this value is close to experimental measurements.

Put this

With this optimal ratio, the expression for the space constant simplifies as follows:

$$\begin{aligned} \lambda &= \frac{d_{\text{in}}}{2} \sqrt{\frac{r_m}{2R_i\Delta}} \\ &= \frac{d_{\text{out}}}{2} \sqrt{\frac{r_m}{2eR_i\Delta}} \end{aligned}$$

We find in particular that the space constant is proportional to diameter, instead of the square root of diameter as with unmyelinated axons.

5.4.2 Ranvier nodes

In myelinated axons, voltage-gated channels are placed at discrete locations called *nodes of Ranvier*. These are short unmyelinated segments of axon. Thus the internode segments are passive, and the nodes of Ranvier are active. This leads to a particular mode of conduction called *saltatory conduction*, where the action potential attenuates in the internodes, and is regenerated at the nodes.

As we have seen in section 5.4.1, the space length λ in the internodes is proportional to axon diameter, assuming optimal myelination. This suggests that internode length should be proportional to axon diameter. Let us examine the currents at a node. We assume that a node is isopotential. The transmembrane current I_n at the node must equal the difference between the two axial currents coming from the neighboring internodes. How do these axial currents scale with axon diameter? The axial current is

empirical measurements

$$I_a = \frac{1}{r_a} \frac{\partial V}{\partial x}$$

where r_a is axial resistance per unit length. In units of the space length, this is:

$$I_a = \frac{1}{\lambda r_a} \frac{\partial V}{\partial \bar{x}}$$

where $x = \lambda \bar{x}$. Since $\lambda \propto d$ and $r_a \propto d^{-2}$, we find that the axial current is proportional to d . Therefore, the transmembrane current at the node should be proportional to d . If channel densities are constant, this means that the length of a node must be constant, independent of axon diameter⁴.

With these scaling relations, we obtain equations that are invariant with axon diameter when expressed in units of the internode space length λ . It follows that conduction velocity is proportional to d . Since conduction velocity in unmyelinated axons is proportional to \sqrt{d} , it follows that there is a diameter above which myelination increases conduction velocity.

⁴Here d implicitly refers to d_{in} , but since we only consider proportionality relations, we might equivalently refer to d_{out} .

5.5 Extracellular potential and current circulation

5.5.1 The line source approximation

Electrostatic theory stipulates that a point source of current $I(t)$ in a resistive medium generates an electrostatic potential V equal to:

$$V = \frac{1}{4\pi\sigma} \frac{I}{r}$$

where σ is the conductivity of the medium in S/m (inverse of resistivity) and r is the distance to the source.

The *line source approximation* consists in approximating an axon (or dendrite) as a line of current sources, where each section of membrane is a source of current. Thus the extracellular potential V_e equals:

$$V_e = -\frac{1}{4\pi\sigma} \int \frac{I_m(x)}{r(x)} dx$$

where x is the linear coordinate along the axon and the integral runs over the entire axon. Here $I_m(x)$ is the total membrane current per unit length, including capacitive and ionic currents. With the convention that we have chosen ($I_m > 0$ means inward current), a section dx of membrane produces a current $-I_m(x)dx$ towards the extracellular space. As we have seen in section 5.1, the membrane current is related to the intracellular potential V_i by the cable equation. The extracellular potential can then be expressed as:

$$V_e = \frac{1}{4\pi\sigma} \int \frac{1}{r(x)} \frac{\partial}{\partial x} \left(\frac{1}{r_a} \frac{\partial V_i}{\partial x} \right) dx$$

We may replace V_i by the membrane potential V_m if the resistivity of the extracellular medium is low.

5.5.2 Extracellular signature of a propagated action potential

We now consider an action potential propagating along an unmyelinated cylindrical axon, and we measure the extracellular potential next to the axon, at some position $x = 0$. If $r(0) \approx 0$, then $1/r(x)$ diverges at $x = 0$ and therefore the extracellular potential essentially depends on the membrane current near $x = 0$. Therefore:

$$V_e \propto \frac{1}{4\pi\sigma r_a} \frac{\partial^2 V_m}{\partial x^2}$$

where we have assumed that the extracellular medium has low resistivity⁵. For a propagated action potential of speed v , we then have:

$$V_e \propto \frac{1}{4\pi\sigma r_a} \frac{1}{v^2} \frac{\partial^2 V_m}{\partial t^2}$$

⁵It can be shown that V_e is proportional to $\log h$, where h is the distance of the measuring extracellular electrode to the axon

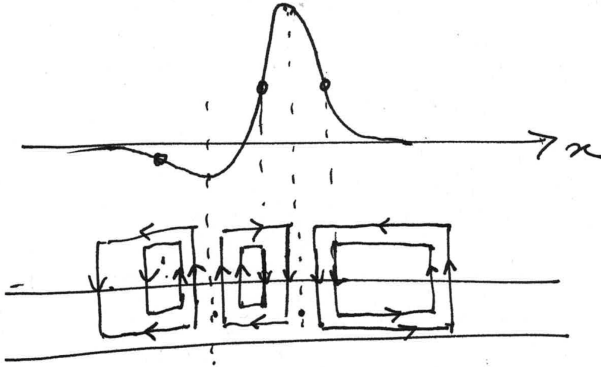


Figure 5.1: Circulation of current during a propagated action potential. Top, membrane potential as a function of distance x along the axon. Bottom, circulation of current around the axon.

We note that since $v \propto \sqrt{d}$ and $r_a \propto 1/d^2$, we have $V_e \propto d$: the extracellular potential is proportional to the axon diameter. The overall shape of the extracellular potential can be derived from the shape of the intracellular action potential. First, there is a steep rising phase where the potential accelerates: $\frac{\partial^2 V_m}{\partial t^2} > 0$; after the inflexion point, the potential decelerates, corresponding to $\frac{\partial^2 V_m}{\partial t^2} < 0$; then there is another inflexion point in the repolarization phase, after which $\frac{\partial^2 V_m}{\partial t^2} > 0$. Thus, the extracellular potential should consist of three phases: a positive peak, a negative peak and a (smaller) positive peak. This is indeed observed in extracellular recordings near axons.

There is an error in one of the arrows (bottom, first one to the left)

5.5.3 Current circulation

How does current circulate during an action potential? Figure 5.1 shows the membrane potential along an axon where an action potential propagates in the direction of increasing x . Axial current is proportional to $-\partial V/\partial x$, therefore it changes sign at the minimum and maximum of the action potential. This axial current must be matched by an opposite extracellular current. The transmembrane current is proportional to $-\partial^2 V/\partial x^2$, therefore it changes sign at inflexion points of the action potential. It is inward in the accelerating phases of the action potential, and outward in the decelerating phases. These remarks lead to the current loops displayed in Figure 5.1 (the major ones being the second and third sets of loops).

Show example, eg Tovar et al 2017

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List of Figures

5.1 Circulation of current	15
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Index

Cable equation, 2
Characteristic length, 4
Electrotonic length, 4
Input resistance, 5
Intracellular resistivity, 2
Line source approximation, 14
Ranvier nodes, 13
Sealed end, 6
Space constant, 4