Introduction and the Hodgkin-Huxley Model

Richard Bertram

Department of Mathematics and

Programs in Neuroscience and Molecular Biophysics

Florida State University

Tallahassee, Florida 32306

Reference: Chapters 2 and 3 of the Sterratt/Graham/Gillies/Willshaw text.

The **neuron** is the basic unit of the nervous system. It is a normal cell that has been adapted morphologically and in terms of protein expression for direct communication with other neurons, with various receptors (e.g., photoreceptors), and with muscle tissue.

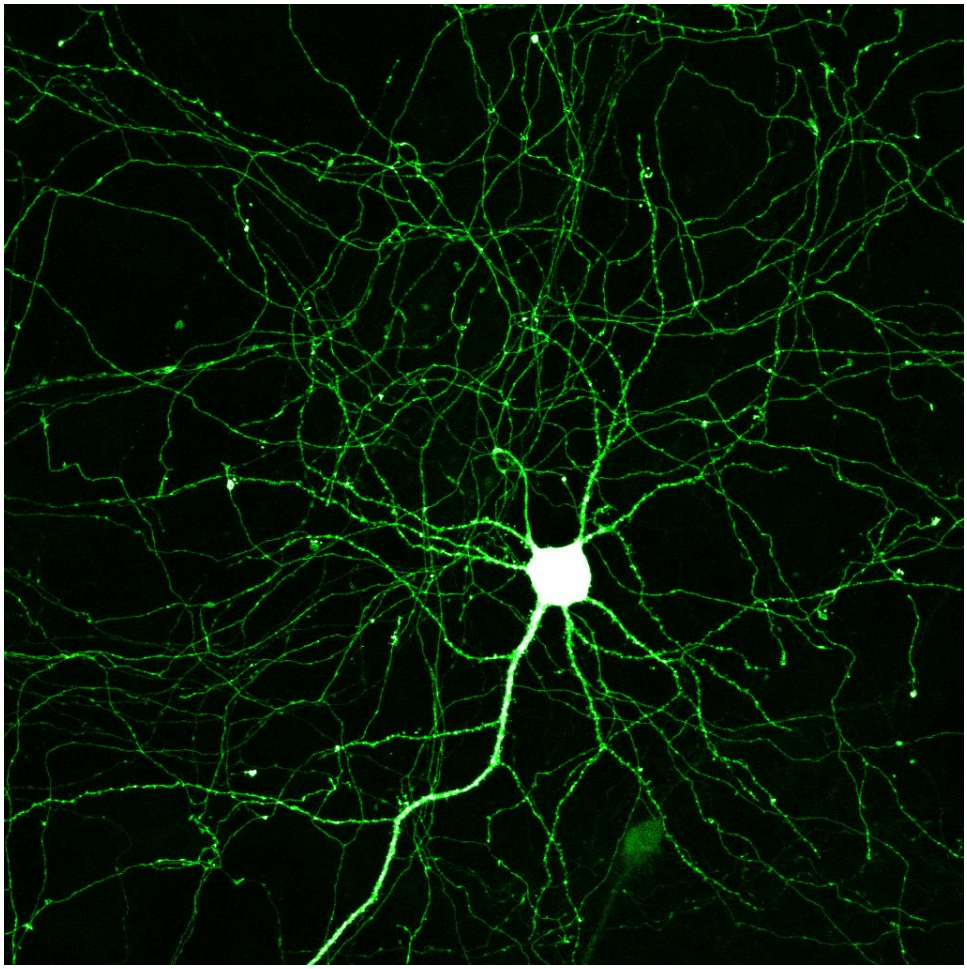


Figure 1: Stained single neuron

Dendrites: input pathways, from **afferent neurons**

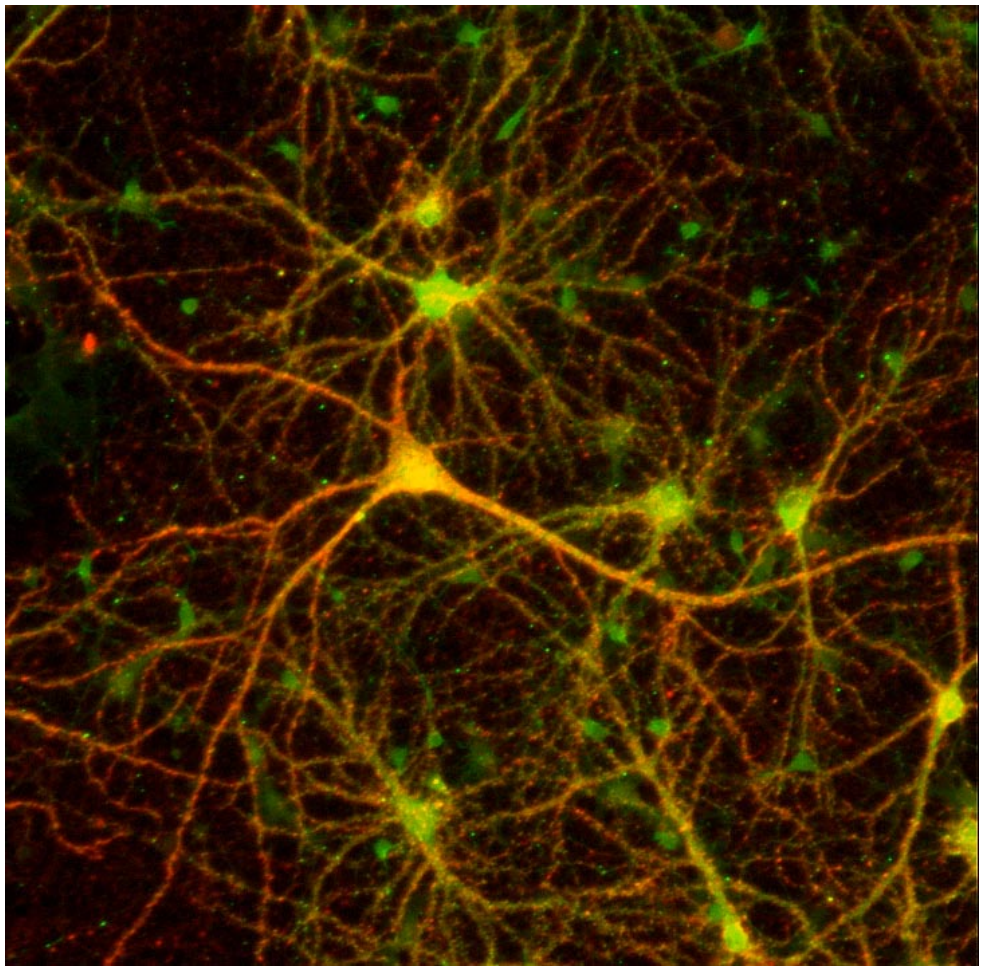


Figure 2: Population of interconnected stained neurons

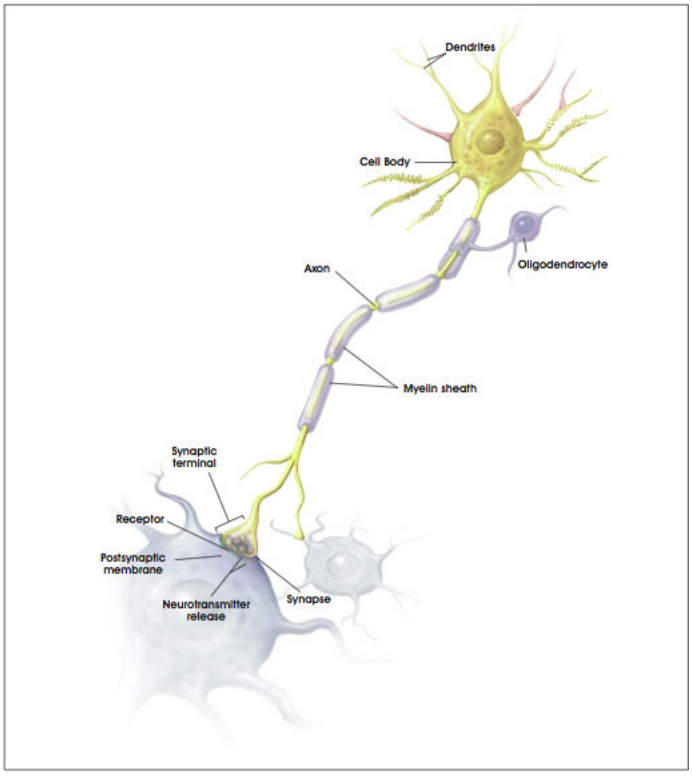


Figure 3: Structure of a neuron

Soma or cell body: integration center

Axon: output pathway

Synapses: structures where electrical signals are converted to chemical signals and transmitted to **efferent neurons**

Myelin: insulating cells on vertebrate axons

Neurons often encode information in the frequency of spiking, or electrical impulse **firing rate**. How are electricity and the neuron related? Answer: ion channels.

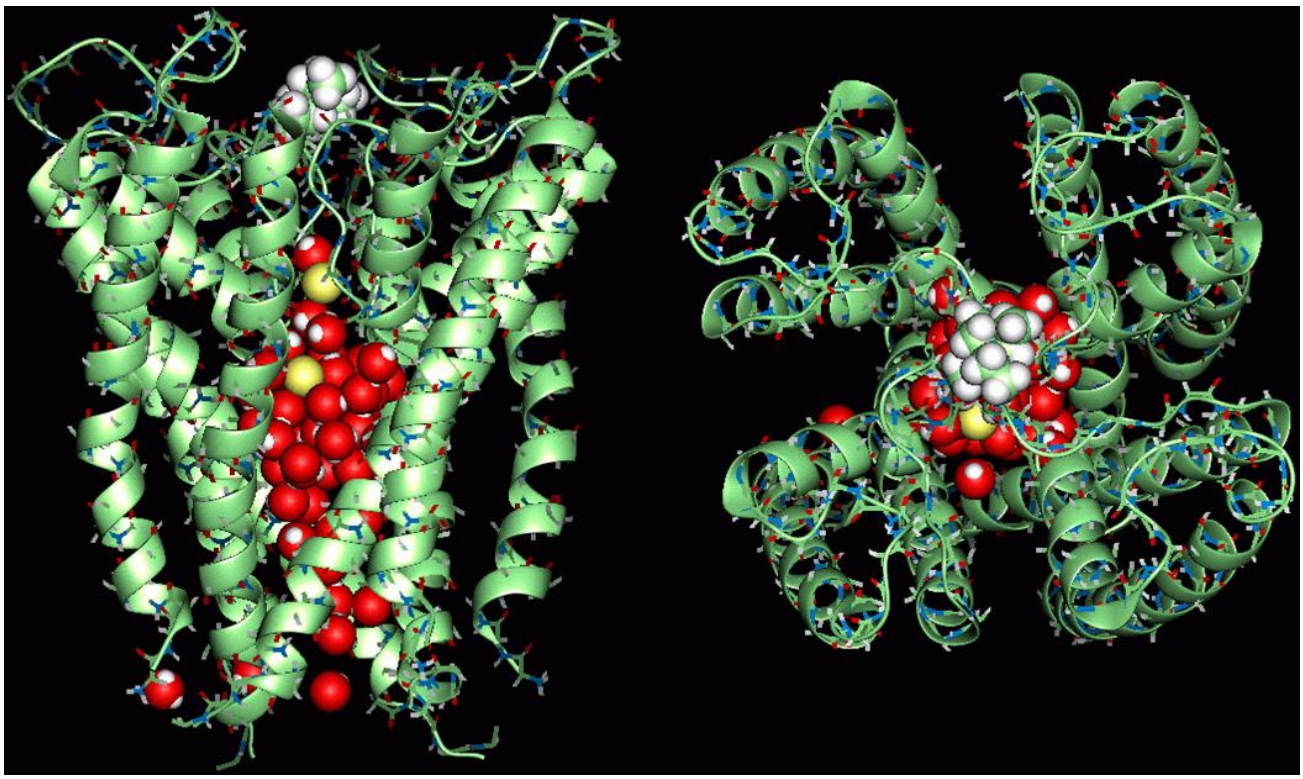


Figure 4: Atomic model of the bacterial KcsA K^+ channel

A concentration gradient is maintained across the plasma membrane by **ion pumps**, which hydrolyze ATP to provide the energy to pump ions upstream. An ion channel is a portal that allows ions of a specific type (e.g., potassium ions, K^+) to move through the membrane. The channel is like a gate; when it is open the ions move through it in a downstream fashion, powered by the concentration gradient.

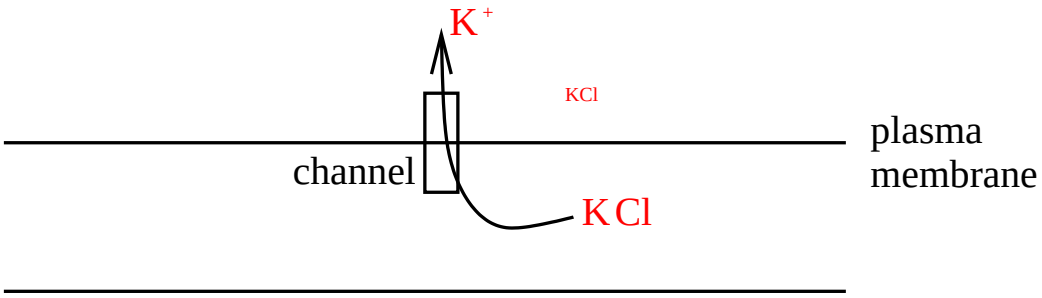


Figure 5: An ion channel allows specific types of ions to flow through

As ions move through the channels an electrical potential develops, which opposes the concentration gradient. There is diffusion of atoms due to the concentration gradient, countered by electrical drift due to the potential gradient that builds up as ion diffuse. The combination is called electrodiffusion. The total ion flux across the membrane, the total electrodiffusion, is described by the Nernst-Planck equation:

$$J = -D\left(\frac{dC}{dx} + \frac{zCF}{RT}\frac{d\Phi}{dx}\right) \tag{1}$$

where C is ion concentration and Φ is the electrical potential. (D is the diffusion coefficient, R is the gas constant, T is temperature, and F is the Faraday constant.) The first term describes the concentration gradient, while the second describes the electrical potential gradient. Eventually an equlibrium is reached ($J = 0$). The equilibrium potential is called the Nernst potential:

$$\boxed{V_{Nernst} = \frac{RT}{zF}\ln\frac{C_{\text{out}}}{C_{\text{in}}}} \tag{2}$$

where $V_{Nernst} = \Phi_{in} - \Phi_{out}$ and z is the ion valence. Typically,

$$[K^+]_{in} > [K^+]_{out} \tag{3}$$

so $V_K < 0$,

$$[Na^+]_{in} < [Na^+]_{out} \tag{4}$$

and

$$[Ca^{2+}]_{in} < [Ca^{2+}]_{out} \tag{5}$$

so V_{Na}, $V_{Ca} > 0$. In fact, typical values are:

$$V_K \approx -70 \text{ mV} \tag{6}$$

$$V_{Na} \approx 50 \text{ mV} \tag{7}$$

$$V_{Ca} \approx 100 \text{ mV} \tag{8}$$

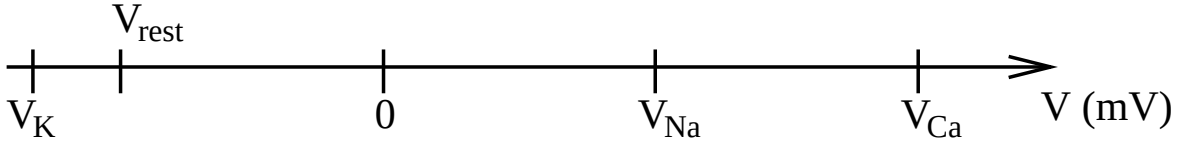


Figure 6: Relative locations of Nernst and resting potentials

The **resting potential** is the weighted average of the Nernst potentials, with the weights being the macroscopic conductance (g) of the channels in the membrane:

$$\boxed{V_{rest} = \frac{g_{Na}V_{Na} + g_{Ca}V_{Ca} + g_K V_K}{g_{Na} + g_{Ca} + g_K}} \tag{9}$$

Here, macroscopic conductance reflects the permeability of an ion type through all open channels permeable to that ion type. For example, g_{Ca} is the total permeability of Ca^{2+} through all open Ca^{2+} channels.

An Equivalent Circuit Description

The plasma membrane of a cell consists of phospholipids with proteins like ion channels and ion pumps inserted.

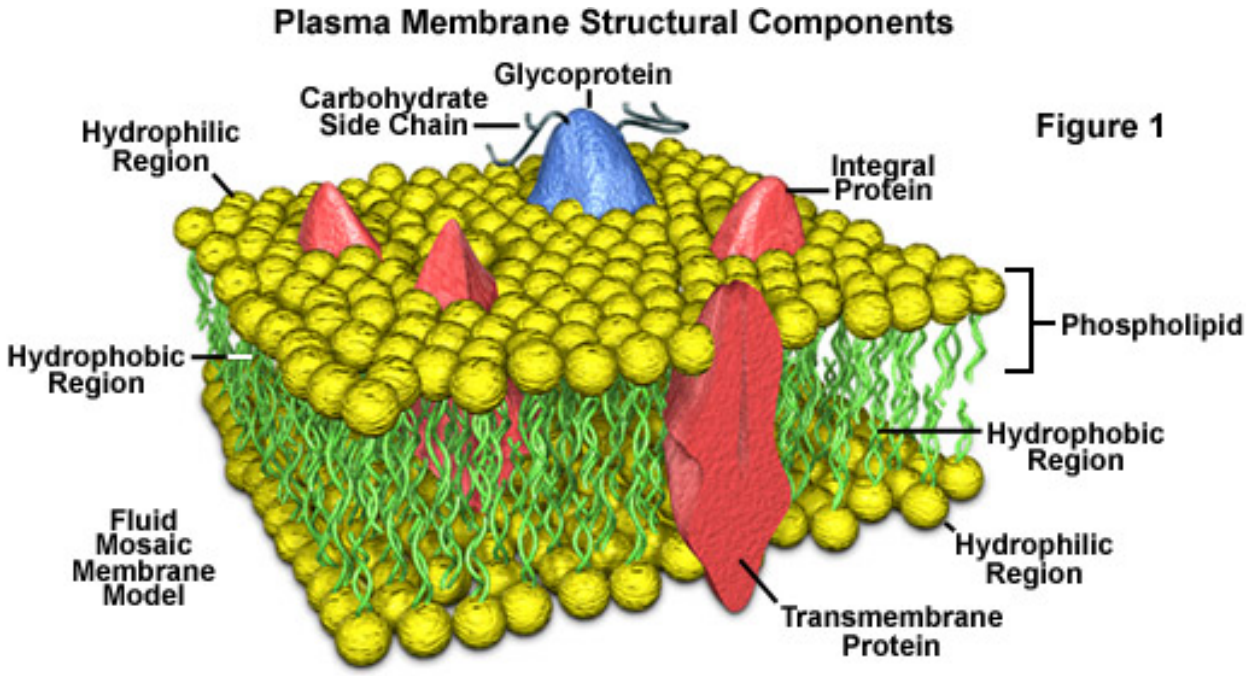
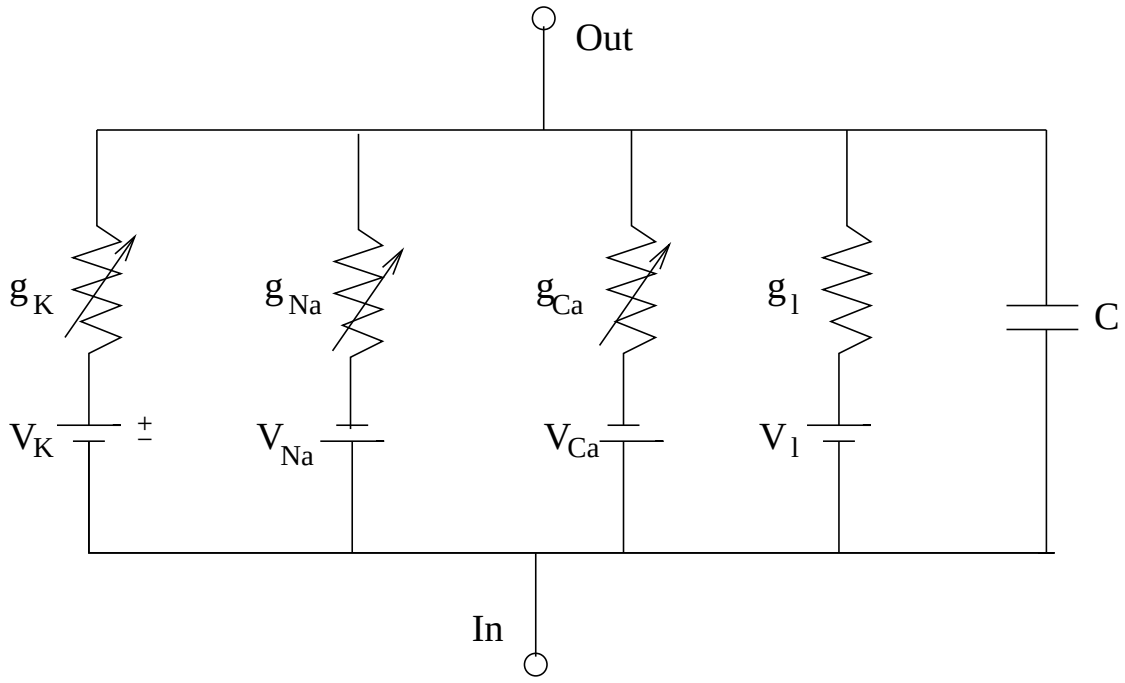


Figure 7: Illustration of the plasma membrane of a cell

The phospholipid bilayer acts as a parallel-plate capacitor, separating charges (inside and outside of cell). The dialectric of the capacitor is low, since it is hard for charged particles to get through the electrically neutral lipids. The ion channels that span the bilayer act as electrical conductors, allowing ions to pass through the membrane without crossing through the

electrically neutral lipids. According to Thévenin's theorem, the effects of all the ion channels of each type can be added together and treated as a single conductor, as can the voltage sources (the ions separated by the membrane). Thus, one can describe the current through each type of channel by Ohm's law: the conductance times the voltage source. This observation led K. S. Cole to suggest, in 1968, that the electrical properties of a patch of neural membrane are similar to a parallel electrical circuit. This equivalent circuit description allows one to immediately derive equations, based on circuit theory.



The capacitance is $C = 1\ \mu\mathrm{F/cm}^2$, and is the same for all neural membranes since it reflects the properties of the lipid bilayer. Each type of channel acts as a conductor (conductance=g), while the Nernst potentials

provide ionic driving forces. Each conductor, with the exception of the leak, changes with the membrane potential. That is, each is rectifying.

The leak conductance is largely due to Cl^- leaking through the various channels. (Most neurons don't have Cl^- channels, although some do.) Typically, the Cl^- concentration is highest on the outside, and since the valence is -1, $V_l < 0$.

We now use several laws from physics to derive the voltage equation. First, by **Ohm's law**,

$$V = IR \tag{10}$$

where V is the voltage (membrane potential in the case of neurons), I is the current, and R is resistance. But conductance $= 1/$resistance, so

$$I = gV \quad . \tag{11}$$

We modify this by noting that the current through, say, a K^+ channel is 0 when $V = V_K$, not when $V = 0$. Hence, in general,

$$I = g(V - V_{\text{Nernst}}) \quad . \tag{12}$$

Thus,

$$I_K = g_K(V - V_K) \tag{13}$$

$$I_{Na} = g_{Na}(V - V_{Na}) \tag{14}$$

$$I_{Ca} = g_{Ca}(V - V_{Ca}) \tag{15}$$

$$I_l = g_l(V - V_l) \quad . \tag{16}$$

In almost all cases, the membrane potential will be greater than V_K and less than V_{Na} or V_{Ca} (the only exception would be under pathological conditions or in in vitro brain slice experiments where one could move the membrane potential to almost any value by injection current into the neuron). Thus, in all physiological cases,

$$I_K > 0 \tag{17}$$

$$I_{Na} < 0 \tag{18}$$

$$I_{Ca} < 0 \tag{19}$$

and I_l could be positive or negative. A positive current makes the voltage more negative, and is called hyperpolarizing. A negative makes the voltage less negative and is called depolarizing. These terms stem from the fact that a circuit with a non-zero voltage is said to be polarized. So a resting neuron, with $V \approx -70$ mV is polarized, and making voltage any lower is hyperpolarizing, making it closer to 0 is depolarizing.

These describe the currents through the ion channels. All current passing through the membrane either charges or discharges the membrane capacitance. So the rate of change of charge on the membrane dq/dt is the same as the net current flowing through the membrane:

$$I = \frac{dq}{dt} \quad . \tag{20}$$

But for a capacitor

$$q = CV \tag{21}$$

so

$$\frac{dq}{dt} = C\frac{dV}{dt} \tag{22}$$

and thus

$$I_c = C\frac{dV}{dt} \tag{23}$$

is the capacitive current.

We combine the currents through the different branches of the parallel circuit using **Kirchoff's current law**. This states that the total charge through a circuit must be conserved, and in the case of a parallel circuit the sum of the currents through the different branches must equal 0. Thus,

$$I_c + I_K + I_{Na} + I_{Ca} + I_l = 0 \quad . \tag{24}$$

Rewriting,

$$I_c = -(I_K + I_{Na} + I_{Ca} + I_l) \tag{25}$$

or

$$\boxed{\frac{dV}{dt} = -(I_K + I_{Na} + I_{Ca} + I_l)/C} \tag{26}$$

This is the Voltage Equation.

Since each ionic current is linear in V when the conductances are constant, this is a *linear* ODE. In this case,

$$\frac{dV}{dt} = (-aV + b)/C \tag{27}$$

where a is the sum of the ionic conductances and b is the sum of the Nernst potentials weighted by the conductances. (If we set $\frac{dV}{dt} = 0$ to get the equilibrium voltage this comes out to be the resting potential, Eq. 9.) This can be rewritten as

$$\frac{dV}{dt} = (V_\infty - V)/\tau_v \tag{28}$$

where $V_\infty = \frac{b}{a}$ is the equilibrium potential or resting potential V_{rest} and $\tau_v = \frac{C}{a}$ is the membrane time constant. The solution to a linear ODE of this form is:

$$V(t) = V_\infty + (V_0 - V_\infty)\mathrm{e}^{-t/\tau_v}. \tag{29}$$

where V_0 is the initial voltage. Thus, if V is perturbed from rest to some value V_0 then it will return to rest exponentially. If the time constant τ_v is large then the return to rest is slow, if small then the return to rest is rapid.

What happens if some external current is applied? Then while that current is on the equilibrium voltage will change from V_{rest} to some new equilibrium V_∞. The **input resistance** is then defined as

$$\boxed{R_{in} = \frac{V_\infty - V_{rest}}{I_{ap}}} \tag{30}$$

where I_{ap} is the applied current. In practice, the input resistance is determined by injecting a small applied current and measuring the new equilibrium potential. Small injected currents are used since for small deviations

from rest the conductances are approximately constant (as we shall see, for larger depolarizing deviations the conductances change).

There is a reciprocal relationship between resistance and conductance, so

$$g_{in} = \frac{1}{R_{in}} \tag{31}$$

and if the conductances are constant, then

$$g_{in} = g_K + g_{Na} + g_{Ca} + g_L = a \quad . \tag{32}$$

Thus,

$$\tau_v = \frac{C}{g_{in}} \tag{33}$$

and so

$$\boxed{\tau_v = R_{in}C} \quad . \tag{34}$$

In practice, this formula is used to calculate the membrane time constant, after first measuring R_{in} and the capacitance C.

The membrane time canstant tells us how fast the membrane potential responds to an applied current. It is roughly the time required to reach two thirds of the way from the original voltage to the new equilibrium voltage.

ELECTRICAL EXCITABILITY

If the conductances were constant, then the neuron would act like a passive resister in parallel with a capacitor. However, the conductances

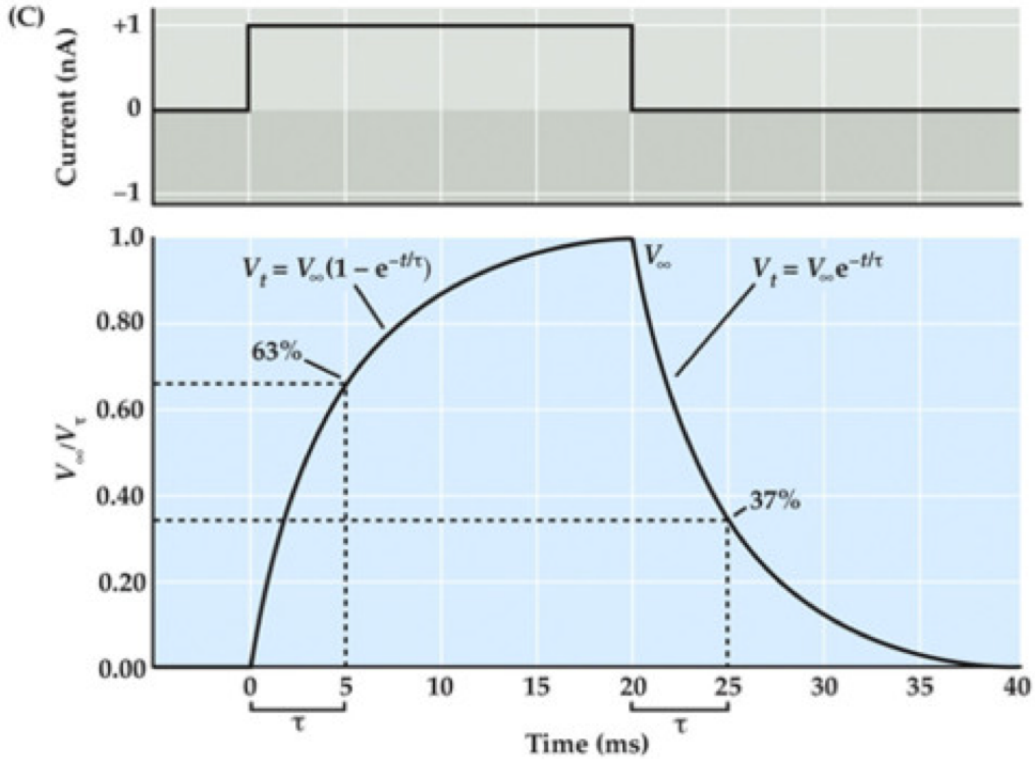


Figure 8: Time constant τ (or τ_v) describes response rate to application or removal of an applied current.

are voltage-dependent; they all increase with voltage, but at different rates and with different time constants. The **depolarizing currents** $I_{Na} = g_{Na}(V - V_{Na})$ and $I_{Ca} = g_{Ca}(V - V_{Ca})$ raise the voltage V and activate first. The **hyperpolarizing current** $I_K = g_K(V - V_K)$ returns the voltage to rest and activates later. This combination of positive feedback and delayed negative feedback produces an electrical impulse or action potential.

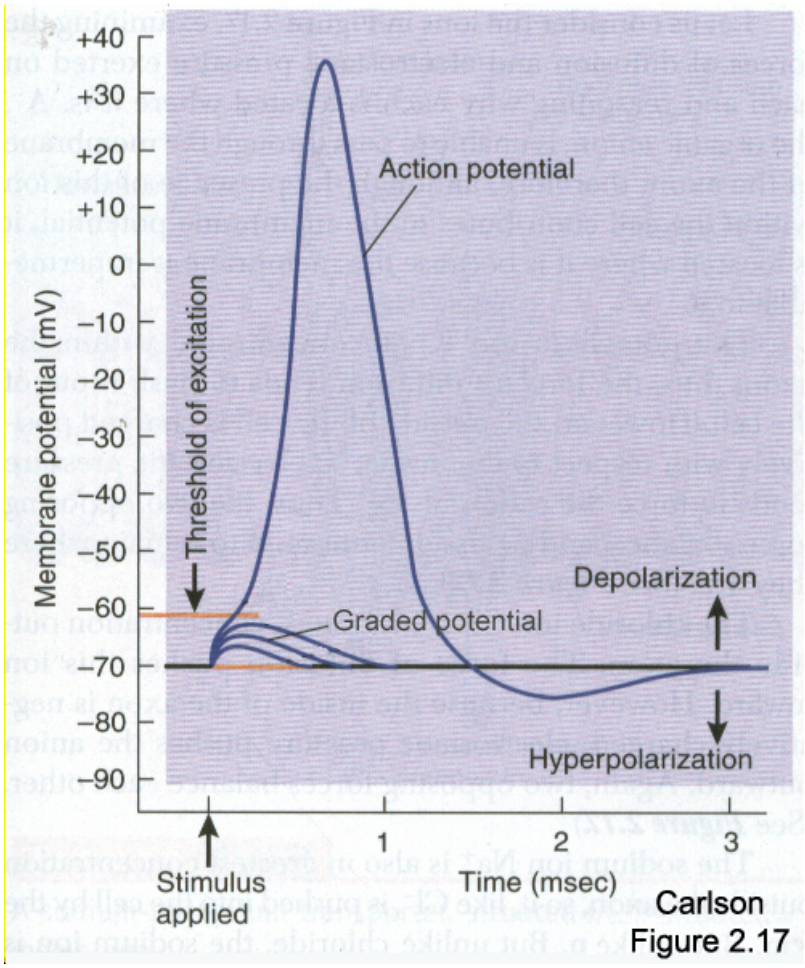


Figure 9: An action potential along with some subthreshold responses

A key property of the neuron's electrical dynamics is the presence of a

threshold. Voltage perturbations above this threshold evoke an impulse.

The conductance of an ionic current is the product of the single-channel conductance and the number of open channels. The single-channel conductance is roughly constant, while the number of open channels depends on the membrane potential. Let $\bar{g}$ denote the **maximum conductance**, i.e., the single-channel conductance times the total number of channels of a single type. Then

$$g = \bar{g}\,\text{Prob[channel open]} \quad . \tag{35}$$

To determine this probability function (which depends on V), **Alan Hodgkin** and **Andrew Huxley** used the squid giant axon as a model system. This is a large axon (up to 1 mm in diameter) that controls part of the squid's water jet propulsion system. Because it is large, it is fairly easy to work with.

The technique that Hodgkin-Huxley used to determine Prob[channel open] is the **voltage clamp**. This acts like a thermostat, injecting the right amount of current to hold the potential at any value of V desired. The injected current is the negative of the current generated by the axon at this voltage. If all currents other than, say, K^+ current, are blocked pharmacologically, then

$$I_{cmp} = -g(V_{cmp})(V_{cmp} - V_K) \tag{36}$$

so that

$$g(V_{cmp}) = \frac{-I_{cmp}}{V_{cmp} - V_K} \quad . \tag{37}$$

This can be done for a range of clamping voltages to obtain the $g(V)$ function.The $\bar{g}$ parameter is just $g(V)$ at a high (saturating) voltage. Then

$$\text{Prob[channel open]} = g(V)/\bar{g} \quad . \tag{38}$$

Using this approach, H-H found that the best fit is

$$\text{Prob[channel open]} = n_\infty^4(V) \tag{39}$$

where $n_\infty(V)$ is a *sigmoid function*:

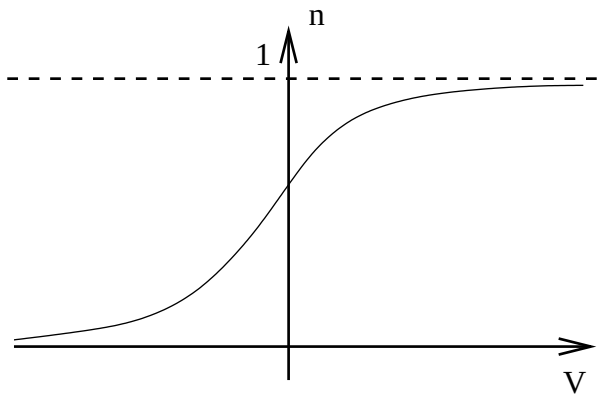


Figure 10: Sigmoidal n_∞ function.

The equation for this is

$$n_\infty(V) = 0.5 \left[1 + \tanh \left(\frac{V - V_1}{s_1} \right) \right] \tag{40}$$

which can be re-written as

$$n_\infty(V) = \frac{\mathrm{e}^u}{\mathrm{e}^u + \mathrm{e}^{-u}} \tag{41}$$

where $u = \frac{V-V_1}{s_1}$ with parameters V_1 and $s_1 > 0$ that modify the shape of the function (I call them shape parameters). By raising n_∞ to the fourth power, the curve is sharpened:

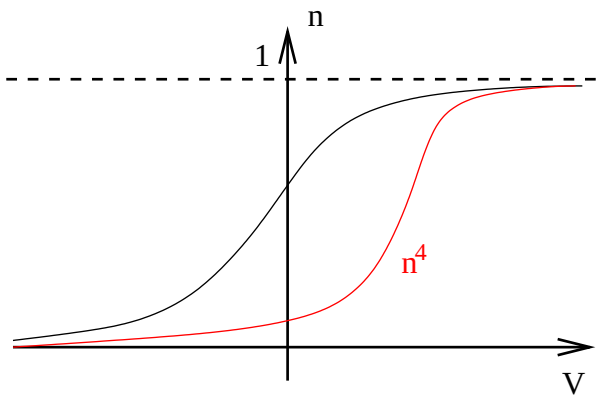


Figure 11: Curve is sharpened by raising n_∞ to an integer power.

This is a steady state description of the channel open probability, but this probability (or channel open fraction) changes over time as it approaches its steady state. Thus,

$$\boxed{\text{Prob[potassium channel open}] = n^4} \quad . \tag{42}$$

where n is described by a *differential equation*. This variable, which satisfies $n \in [0, 1]$, is called an activation variable. It's time dynamics are described by

$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)} \tag{43}$$

which says that if n is smaller than its equilibrium value $n_\infty(V)$ then $\frac{dn}{dt} > 0$ so n will increase toward $n_\infty(V)$. The bigger the difference between the current value of n and its equilibrium value the faster n will move

towards n_∞. Also, the speed is regulated by the time constant τ_n; if τ_n is large then n will move slowly towards n_∞. Note that both the equilibrium function n_∞ and the time constant τ_n depend of the membrane potential V.

The K^+ conductance is then

$$g_K = \bar{g}_K \, n^4 \tag{44}$$

and the K^+ current is

$$\boxed{I_K = \bar{g}_K \, n^4 (V - V_K)} \quad . \tag{45}$$

What is n physically? Hodgkin and Huxley thought of the K^+ channel as composed of 4 independent gates, each of which must be open for the channel to be open. Then n represents the probability that one of the gates is open. This is not an accurate description (as we know today), but intuitively it is very helpful.

The Na^+ channel is more complicated, since now there is an inactivation gate as well as activation gates. This gate is the opposite of an activation gate, it closes when V is depolarized. Let

$$h = \text{Prob[inactivation gate open]} \quad . \tag{46}$$

There is also an activation gate, denoted by m, which is qualitatively similar to n:

$$m = \text{Prob[activation gate open]} \quad . \tag{47}$$

The differential equations for the time dynamics of the activation variable m and inactivation variable h are:

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \tag{48}$$

$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)} \tag{49}$$

According to the Hodgkin-Huxley data fitting,

$$g_{Na} = \bar{g}_{Na} m^3 h \tag{50}$$

which intuitively means that 3 activation gates and 1 inactivation gate must be open for the channel to be open. Then,

$$\boxed{I_{Na} = \bar{g}_{Na} m^3 h (V - V_{Na})} \tag{51}$$

is the Na^+ current.

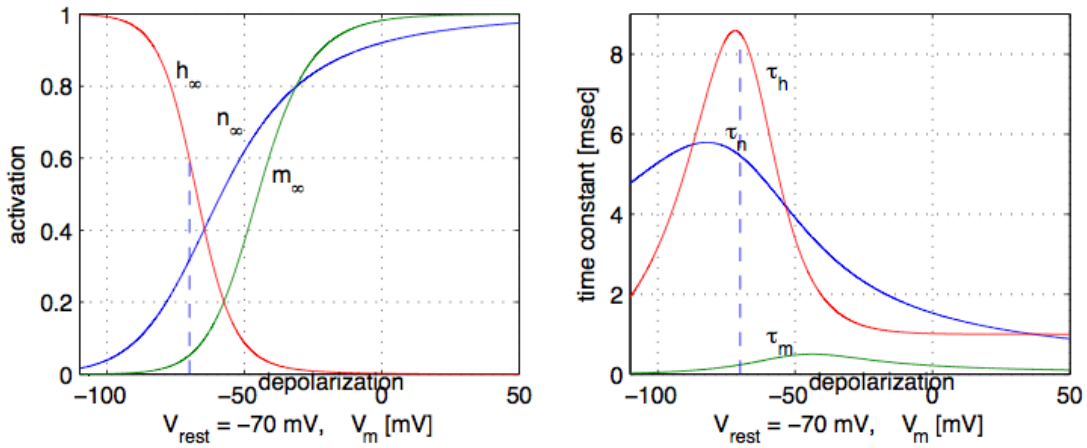


Figure 12: Infinity and time constant functions.

Figure 12 shows the V-dependent time constants and infinity functions. Notice that m_∞ and n_∞ are both increasing functions of V. That is, the

activation gates open when the membrane is depolarized. In contrast, h_∞ is a decreasing function of voltage. That is, the inactivation gate closes when the membrane is depolarized. The time constant functions are all bell-shaped; they are low at very hyperpolarized and depolarized voltages, and larger in between.

An important property of the two types of gate in the Na^+ current is that the activation time constant is smaller than the inactivation time constant (Fig. 12), so that when the membrane is depolarized the activation gates open first. This turns on the Na^+ current, causing voltage to rise further. It is only later that the inactivation gates close. So the current provides rapid positive feedback followed by a delayed negative feedback. The K^+ current provides only delayed negative feedback.

The last current in the Hodgkin-Huxley model is a constant-conductance **leak current**. This is due largely to non-specific flow of ions across the membrane through various channel types. The important feature here is that the conductance is not a function of V. The leak Nernst potential is usually about $V_L = -40$ mV, so the current is mildly depolarizing. Then

$$\boxed{I_L = g_L(V - V_L)} \tag{52}$$

Combining previous equations, we get the full Hodgkin-Huxley model:

$$\frac{dV}{dt} = -[\bar{g}_{Na}m^3h(V - V_{Na}) + \bar{g}_K n^4(V - V_K) + g_L(V - V_L)]/C \quad (53)$$

$$\frac{dn}{dt} = [n_\infty(V) - n]/\tau_n(V) \quad (54)$$

$$\frac{dm}{dt} = [m_\infty(V) - m]/\tau_m(V) \quad (55)$$

$$\frac{dh}{dt} = [h_\infty(V) - h]/\tau_h(V) \ . \quad (56)$$

The Hodgkin-Huxley model was developed to explain how action potentials are produced. The biophysical concept, implemented mathematically in the model, is described below.

Response to Input

Input to nerve cells comes primarily through synaptic connections that link neurons together. At these **synapses** the electrical signal (electrical impulses) is transduced to a chemical signal through the release or **exocytosis** of neurotransmitter molecules. The neurotransmitter diffuses across the space between presynaptic and postsynaptic neurons, called the synaptic cleft, and binds to receptors on the postsynaptic membrane. This induces the opening of ion channels, which could either be the postsynaptic receptor itself or other channels activated by the receptor, allowing ionic current to flow. Thus, the input is ultimately an ionic current.

In the lab one can mimic this by applying current to the cell directly with an electrode. In terms of the equations, one simply modifies the voltage equation by adding a term for the applied current, I_{ap}:

$$\frac{dV}{dt} = -(I_{Na} + I_K + I_L - I_{ap})/C \tag{57}$$

where the minus sign is used for I_{ap} so that a positive applied current results in depolarization.

Threshold effect: The H-H model exhibits a threshold response to applied current. If a square pulse of current is applied and the magnitude and duration of the pulse is too small, then the system will have a passive or subthreshold response. If the input pulse is sufficiently large, then the

system will produce an impulse. So the output is all-or-none (Fig. 13).

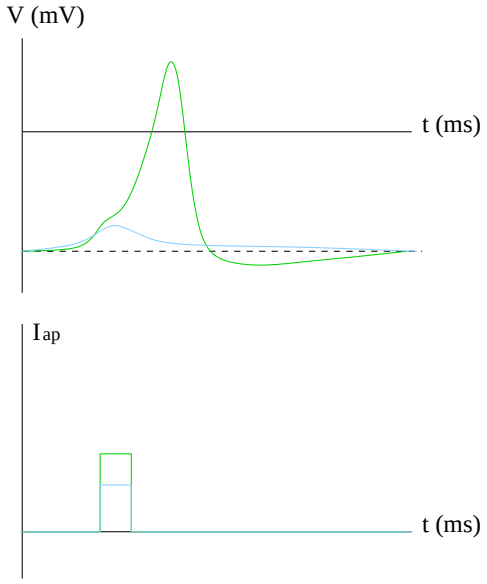


Figure 13: The H-H model produces a passive or subthreshold response if the current pulse is small, or an impulse if the pulse is large enough.

Firing rate and gain function: If applied current is maintained continuously, then the system may either produce a single impulse and then come to rest at a more depolarized voltage, or it may spike continuously if I_{ap} is sufficiently large (in this case, $I_{ap} > 6\ \mu\text{A/cm}^2$). In the H-H model this spike train will be periodic, with some period T. The firing rate is then $\nu = \frac{1}{T}$. The gain function is ν as a function of I_{ap}. For the H-H model, the spike frequency increases as the applied current increases (Fig. 14). This is not the case in all neurons, or all neuron models.

Notice that there is a discontinuity at $I_{ap} = 6\ \mu\text{A/cm}^2$, where the system goes from a rest state to a continuous spiking state with frequency near 50 Hz. This is an example of a **type II oscillator** since the fre-

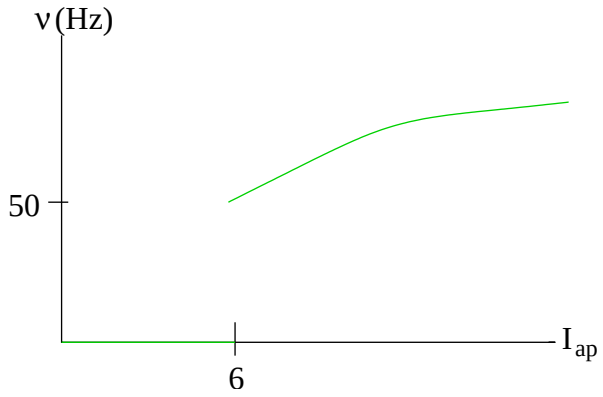


Figure 14: Gain function for the H-H model.

quency did not approach 0. We return to this later.

Refractoriness: If a short superthreshold current pulse is applied to the system, how quickly can a second pulse be applied and still produce an impulse? The H-H model exhibits a refractory period during which it is harder for a current pulse to evoke an impulse. That is, during this period the magnitude or duration of the current pulse must be greater for the system to reach spike threshold (Fig. 15). This limits the frequency at which the system can fire action potentials. It is due to the time required for the n and h variables to return to their resting values.

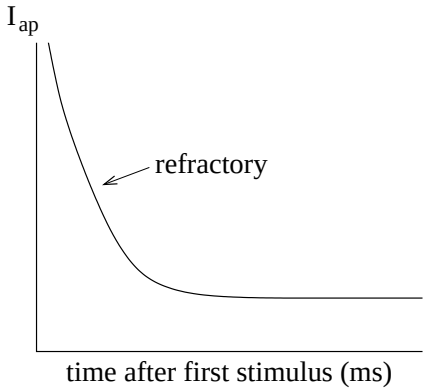


Figure 15: Magnitude of the I_{ap} pulse required to bring the system to threshold following an initial suprathreshold stimulus.

Traveling Pulse

The H-H model describes the electrical activity of a **space clamped** axon, where a wire is run through the center of the axon to maintain uniform potential. Physiologically, an impulse is typically generated in the soma or the **axon hillock** (initial portion of the axon) and travels down the axon by exciting adjacent portions of membrane. It travels down the axon without dissipation, unlike water waves that attenuate as they travel. This is called a traveling pulse or a soliton and is described mathematically by the Hodgkin-Huxley cable equation:

$$\boxed{C\frac{\partial V}{\partial t} = \frac{a}{2R}\frac{\partial^2 V}{\partial x^2} - [I_{Na} + I_K + I_L - I_{ap}]} \tag{58}$$

where a is the axon radius and R is the lateral resistivity. There are also the usual ODEs for the activation and inactivation variables. This system of partial and ordinary DEs could be solved numerically using a

finite difference method. Hodgkin and Huxley solved the equations using a shooting method and found that the pulse travels at the same speed as an actual impulse travels in the squid axon, providing more evidence that the mechanism for impulse generation is correct.

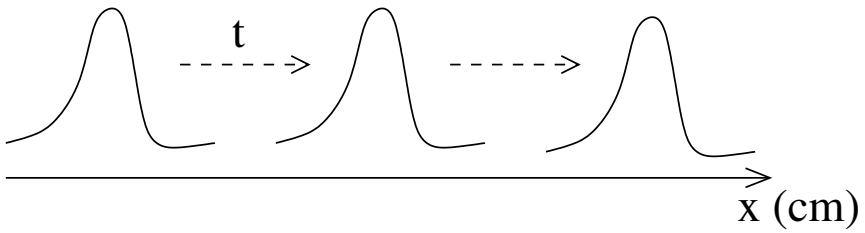


Figure 16: Traveling pulse from the H-H cable equation.