Introduction to Neural Computing

based on *MIT 9.40 Introduction to Neural Computation, Spring 2018, Dr. Michale Fee*

Ashish V

4 May 2022

Contents

1 Making of a biophysical model of Neuron

Bottom line- "wires" are intracellular(cytoplasm) and extracellular(outside of cell) salt solutions, and current flow results from the movement of the ions in aqueous solution. Current flows through the salt solution by diffusion and/or drift in an electric field.

1.1 Thermal energy

Every degree of freedom comes to the thermal equilibrium with an energy proportional to temperature(K). Average Kinetic energy of a particle at thermal equilibrium

$$KE = \langle 1/2 m V_x^2 \rangle = \frac{1}{2} kT$$

$$\langle V_x^2 \rangle = \frac{kT}{m}$$

Mass of Na ion = $3.8 \times 10^{-}26$ Kg

$$\langle V_x^2 \rangle = 10^5 m^2/s^2$$

$$V_x = 32 \times 10^2 m/s$$

1.2 Diffusion

A particle in solution undergoes collisions with water molecules very often and the particle constantly changes it's direction. Diffusion is fast at short length scales and slow at long length scales.

An ensemble of particles diffusing from a point acquires a Gaussian distribution. This arises from a Binomial distribution for large numbers of time-steps. The probability of the particle moving exactly k steps to the right in time step n will be

$$P\left(k;n,p\right) = \left(\begin{array}{c} n \\ k \end{array} \right) p^k \left(1-p\right)^{n-k}$$

$$\lim_{np\to\infty} \left(k;n,p\right) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}}$$

1.3 Random walk in 1D

Particle moves left or right randomly at fixed velocity V_x for a time τ before collision. Each collision randomly resets the direction. On every time-step, half the particles step right by a distance
$\delta = +V_x\tau$
and other half step to left by a distance
δ = -$V_x\tau$

Assume N particles, x=0, t=0
x_i(n)= position of the i^{th} particle on time-step n:

$$n = \frac{t}{\tau} \tag{1}$$

position of each particle at time-step n:

$$x_i(n) = x_i(n-1) \pm \delta$$

Average position of our ensemble :

$$\begin{aligned}\langle x_i(n)\rangle_i &= \frac{1}{N}\sum_i x_i(n) \\ &= \frac{1}{N}\sum_i [x_i(n-1) \pm \delta] \\ &= \frac{1}{N}\sum_i [x_i(n-1)] + \frac{1}{N}\sum_i [\pm\delta]\end{aligned}$$

$\frac{1}{N}\sum_i [\pm\delta] = 0$, because half of the particles will go to the right and rest to the left, so average distance will be zero. So,

$$\langle x_i(n)\rangle_i = \langle x_i(n-1)\rangle_i$$

thus average position of particles at n^{th} time step is equal to average position of particles of the previous time step $(n-1)^{th}$.

Average *absolute value* of distance from origin due to diffusion is the Root Mean Square Distance:

$$\langle |x(n)| \rangle = \sqrt{\langle x^2(n)\rangle}$$

RMSD is same as square root of the average of squares, which is variance.

$$\langle x^2(n) \rangle = \frac{1}{N} \sum x_i^2(n)$$

Square root of Variance of a distribution it is the standard deviation i.e. how wide it is, which is just how far on average the particles got from where they started.

Position of i^{th} particle at n^{th} time step:

$$\begin{aligned} x_i(n) &= x_i(n-1) \pm \delta \\ x_i^2(n) &= x_i^2(n-1) + \delta^2 \pm 2x_i(n-1)\delta \\ \langle x_i^2(n) \rangle &= \langle x_i^2(n-1) \rangle + \langle \delta^2 \rangle + \langle \pm 2\delta x_i(n-1) \rangle \end{aligned}$$

Since half of the particles will go to the right and rest to the left, so average distance will be zero.

$$\langle \pm 2\delta x_i(n-1) \rangle = 0$$

So,

$$\langle x_i^2(n) \rangle = \langle x_i^2(n-1) \rangle + \langle \delta^2 \rangle$$

Variance at n^{th} time step is equal to variance at previous time step + a constant δ

$\langle\ x_i^2(0)\ \rangle$, particles are at the origin, x = 0, δ=0

$$\langle x_i^2(1)\rangle = \langle x_i^2(0)\rangle + \delta^2 = 0 + \delta^2 = \delta^2$$
$$\langle x_i^2(2)\rangle = \langle x_i^2(1)\rangle + \delta^2 = \delta^2 + \delta^2 = 2\delta^2$$
$$\langle x_i^2(3)\rangle = \langle x_i^2(2)\rangle + \delta^2 = 2\delta^2 + \delta^2 = 3\delta^2$$
$$\langle x_i^2(n)\rangle = (n-1)\delta^2 + \delta^2 = n\delta^2$$

Variance of this distribution is growing linearly with the time steps.
Since, $n = \frac{t}{\tau}$

$$\langle x_i^2(t)\rangle = \frac{t}{\tau}\delta^2$$

Variance is growing linearly with time.
$\langle x_i^2\rangle$ = 2Dt, where D= $\frac{\delta^2}{2\tau}$, is the Diffusion constant.

The average distance from the starting point is the standard deviation, and it is growing as square root of the time

$$\sqrt{\langle x_i^2\rangle} = \sqrt{2Dt}$$

Typical diffusion constant (D) for small molecules and ions are $10^{-5} cm^2 s^{-1}$
Suppose if distance L = 10^{-3} cm

$$L^2 = 2Dt$$
$$t = \frac{L^2}{2D}$$

so we get t = 50 milliseconds. Likewise if L = 1 mm, we get t = 500 milliseconds. Diffusion is too slow for larger distances.

Fick's First law

Diffusion produces a net flow of particles from region of high concentration to the region of lower concentration.

$$J_x = -D\frac{d\phi}{dx}$$

$\frac{d\phi}{dx}$ is the concentration gradient

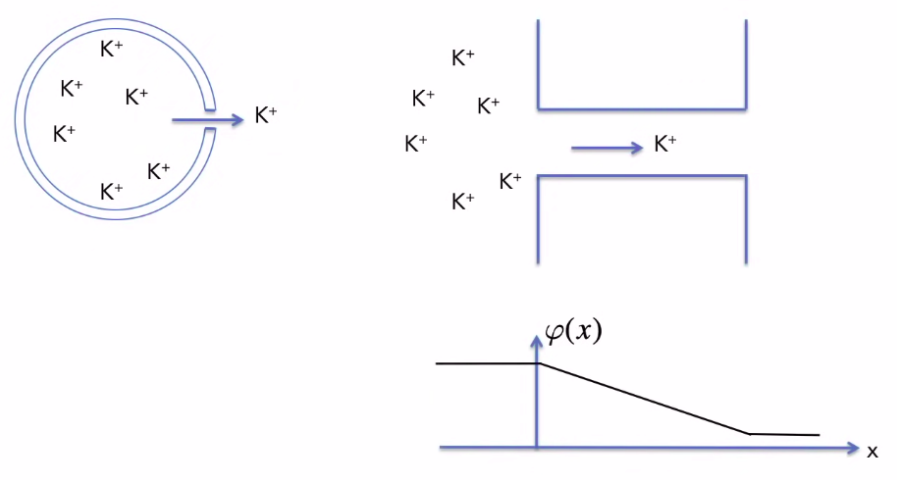


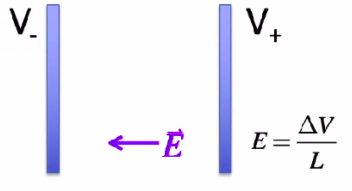
Figure 1: Fick's law

Each particle diffuses independently and randomly! And yet concentration gradients produce currents. Eventually all concentration gradients go away as concentration becomes equal at both sides.

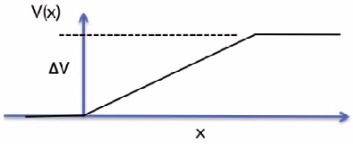
1.4 Electrical properties of neuron

Current flow in neurons obey Ohm's law. For ex. in the intracellular/extracellular solutions of the cell, the current flow through that resistive medium is proportional to the voltage difference.

$$I = \frac{\Delta V}{R}$$



(a) Electric field



(b) Electric field variation

$$Force, \vec{F} = q\vec{E}$$

Electric field produces a force which, in a solution, causes an ion to drift with a constant velocity - a current (against the viscous drag). The force acting on the ions produce a constant velocity, not acceleration.

$\vec{F} = \mathrm{f}\vec{V_d}$, where V_d is the drift velocity and f is the coefficent of friction.

f=$\frac{kT}{D}$ (Einstein-Smoluehovski relation)

Drift velocity, $\vec{V_d} = \frac{D}{kT}\vec{F} = \frac{D}{kT}(\mathrm{q}\vec{E})$

Amount of current, I α V_dA. Where A is cross-sectional area between the electrodes where there is the electric field.

$$I\ \alpha\ EA = \frac{\Delta V}{L}A$$
$$I = \frac{1}{\rho}\frac{\Delta V}{L}A$$

Comparing it with Ohm's law, I = $\frac{\Delta V}{R}$

$$I = \frac{A}{\rho L}\Delta V$$

thus, Resistance

$$R = \frac{\rho L}{A}$$

As the area of the plates increases the resistance decreases. And as space L, between the plates increases the potential difference ΔV remains constant, but electric field ($\vec{E}$=$\frac{\Delta V}{L}$) decreases, so V_d is small, so increased resistance.

Resistivity(ρ) for saline in the mammalian brain is 60 Ω cm. That means a 1 cm block of brain saline solution

has a resistance of 60 Ω. It is a huge resistance, so voltage just drops drastically thus you need huge voltage to send tiny currents.

2 Building models

2.1 A simple model

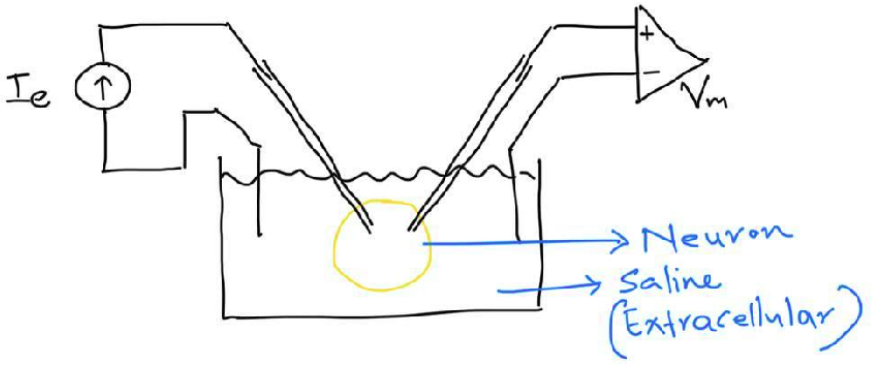


Figure 3: Injecting current to a neuron

Injecting current in to the neuron will change the state of voltage sensitive ion channels on the neuronal membrane and leads to change in membrane potential of the neuron (or locally). In in-vivo, the voltage changes because other cells are injecting currents to the neuron.

Neurons can perform analog numerical integration over time

$$voltage(t) = \int_0^t current(t) d\tau \tag{2}$$

In the experiment we control I_e (electrode current) which is injected to the cell. The differential amplifier measures the voltage difference (V_m) which is the potential difference between the interior and exterior of the cell, which is same as the membrane potential.

The extracellular and intracellular saline, which is the conductor or wire, are separated by the insulating lipid bilayer. So the system is similar to two condutors separated by an insulator, and is essentially equivalent to a capacitor.

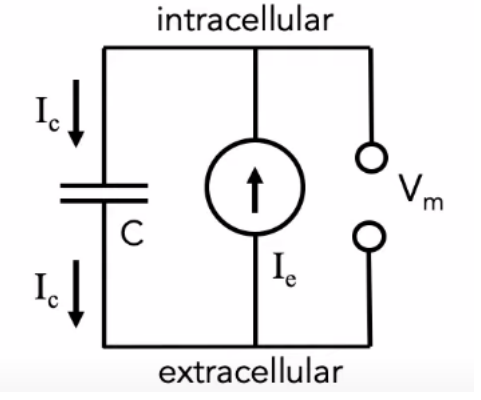


Figure 4: Equivalent circuit

When we turn ON the current source, it takes charges from extracellular saline and sticks them through the

electrode and pumps them into the cell.

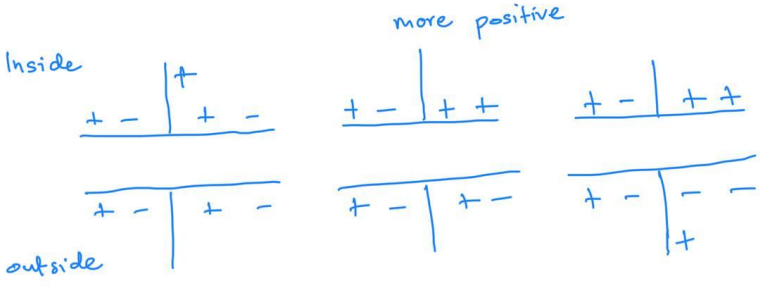


Figure 5: Change in charges inside and outside of the cell

Like charges repel pushing off one of the charges away from the other membrane. Charges coming in and charges leaving, which constitute a current. Thus we have a current flowing through an insulator, called capacitive current.

There is a charge imbalance across the membrane. Inner membrane has more positive charges than the outside. So an Electric field $\vec{E}$ is formed between the conductors. There is an energy stored in the Electric field. An electric field over some the distance between the conductors constitutes a voltage difference.

$$\Delta Q = C\Delta V \tag{3}$$

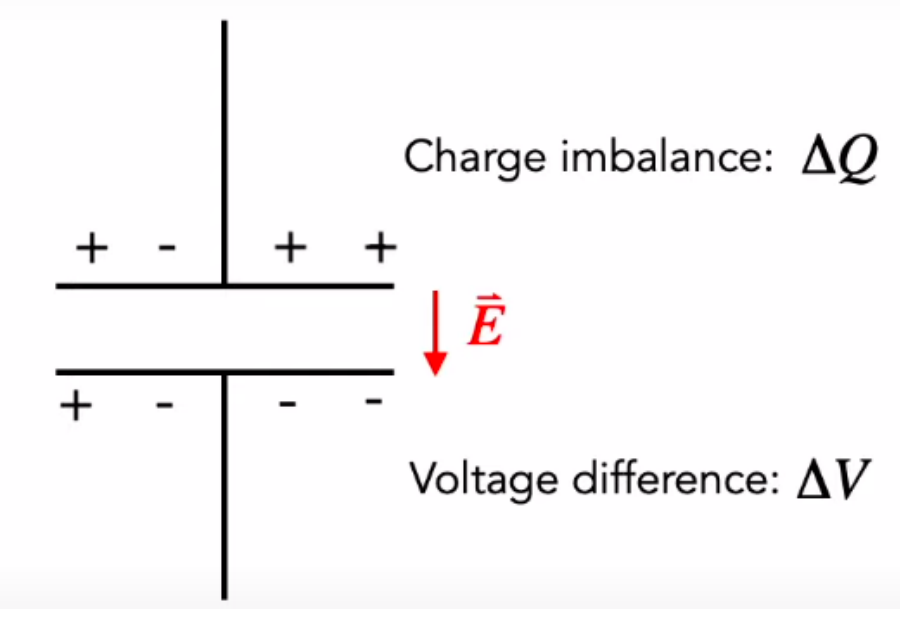


Figure 6: Electric field between the conductors

Capacitance C α A, C α $\frac{1}{L}$

The capacitive current is the rate of change of charge imbalance.

$$I_c(t) = \frac{dQ}{dt} = C\frac{dV_m}{dt} \tag{4}$$

Capacitive current thorugh a membrane is just capacitance times rate of change of membrane potential.

Kirchoff's law- sum of all currents into a node is zero. Current going into the wire has to be equal to the amount of current leaving that wire.

$$-I_c + I_e = 0$$

$$I_e(t) = C\frac{dV_m}{dt} \tag{5}$$

Membrane potential is equal to some initial membrane potential V_0 + membrane potential(from $t = 0$ to $t = t$) due to the injected current.

$$V_m(t) = V_0 + \frac{1}{C}I_e(\tau)d\tau \tag{6}$$

$$\int_0^t I_e(\tau)d\tau = \Delta Q$$

$$V_m(t) = V_0 + \frac{\Delta Q}{C} \tag{7}$$

$$V_m(t) = V_0 + \Delta V \tag{8}$$

$$V_m(t) = V_0 + \frac{I_0}{C}t \tag{9}$$

I_0 is the value of injected current I_e

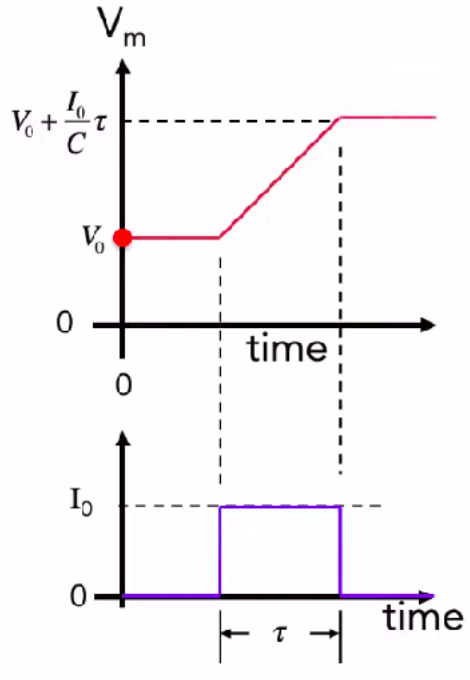


Figure 7: Response to current injection. V_m variation with a pulse of $I_e = I_0$

2.2 Introducing an ion channel

A neuron is a leaky capacitor. Neurons have ion channels that allow currents to flow through the membrane. We can think of it as a hole or leak in the cell in our model. Ion channel and leak conductance can be represented in our model by a resistor.

So now we have membrane capacitive current (I_c) and membrane ionic current (I_L) due to ions flowing

through ion channels.

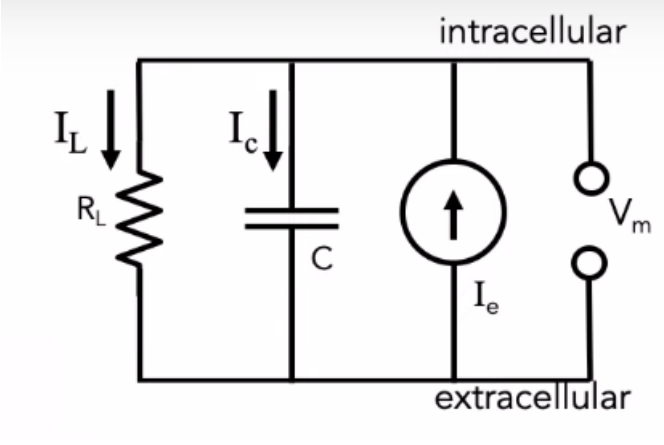


Figure 8: Introducing an ion channel which is represented as a resistor. R_L is the leak resistance

By Kirchoff's rule, $I_L + I_c = I_e$

$$I_L + C\frac{dV_m}{dt} = I_e \tag{10}$$

Sign convention in neuroscience: Membrane current (I_L) that are outward (inside of the cell to outside) are positive in sign. + charges leaving the cell are positive in sign. Inward current, + charges entering the cell are negative in sign.

2.3 Simple case - a leak

Consider a simple leak due to a hole in the membrane. Current through the ion channel/hole

$$I_L = \frac{V_m}{R_L} \tag{11}$$

$$\frac{V_m}{R_L} + C\frac{dV_m}{dt} = I_e \tag{12}$$

$$V_m + R_L C\frac{dV_m}{dt} = R_L I_e \tag{13}$$

The voltage V_m reaches a steady-state when we inject some current, we hold the current constant, the voltage will change and eventually becomes constant $\frac{dV_m}{dt} = 0$.

$$V_m = R_L I_e \tag{14}$$

Definition:At steady state, the membrane potential becomes V_∞. Its the voltage that systems reaches at $t = \infty$

$$V_m \to V_\infty = R_L I_e \tag{15}$$

So, by injecting current, we are changing the V_∞.

Rewriting equation 12.

$$\tau = R_L C$$

$$V_m + \tau \frac{dV_m}{dt} = V_\infty \tag{16}$$

τ has unit of time.

$$\frac{dV_m}{dt} = -\frac{1}{\tau}(V_m - V_\infty) \tag{17}$$

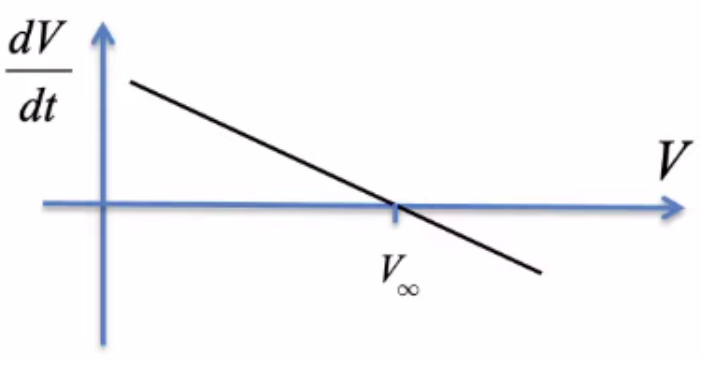


Figure 9: V_m approaching V_∞

The derivative $\frac{dV_m}{dt}$ is a function of voltage, and, at $V_m = V_\infty$ the derivative is zero. When $V_m < V_\infty$, the derivative is positive and it is approaching V_∞. When $V_m > V_\infty$, the derivative is negative and it is approaching V_∞. So no matter where V_m is, it always approaches V_∞.

The slope, rate at which V_m approaches V_∞ is proportional to the difference (V_m-V_∞). In other words, the rate at rate at which V_m approaches V_∞ is proportional to how far it is from V_∞. It is an exponential function. And it approaches with a time scale of τ.

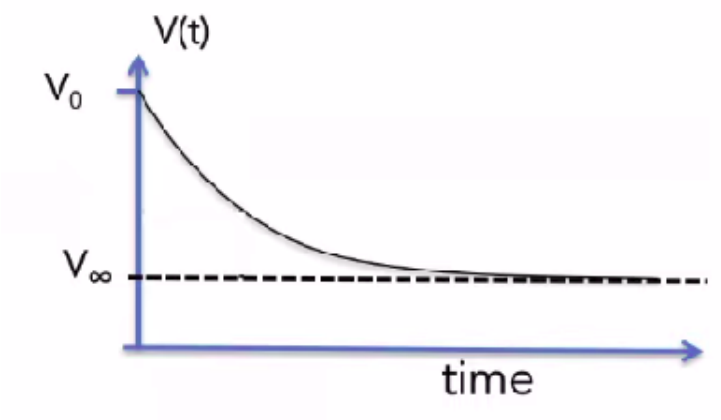


Figure 10: V_m approaching V_∞

The smaller the τ, bigger the derivative, that means V_m approaches V_∞ quickly. The larger the τ, smaller the derivative, means V_m approaches V_∞ slower.

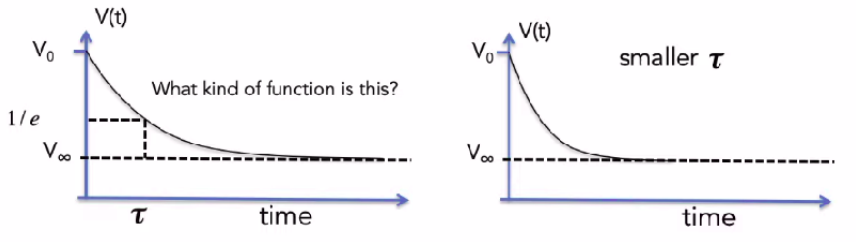


Figure 11: V_m approaching V_∞

At t=0, $V_m - V_\infty = V_0 - V_\infty$
At t=τ, $V_m - V_\infty = \frac{1}{e}(V_0 - V_\infty)$

That means in 1 τ the $V_m - V_\infty$ drops by a about a third ($\frac{1}{e}(V_0 - V_\infty)$, e=2.718) and in another τ, it drops by another third and keeps going.

A general solution, when the I_e is constant (so is the V_m)

$$V_m(t) - V_\infty = (V_0 - V_\infty)e^{\frac{t}{\tau}} \tag{18}$$

$$V_m(t) = V_\infty + (V_0 - V_\infty)e^{-\frac{t}{\tau}} \tag{19}$$

This solutions applies only in the case of constant V_∞. $V_m(t) - V_\infty$ is the voltage difference at time = t. $(V_0 - V_\infty)$ is the initial voltage difference.

if t = τ

$$V_m(\tau) - V_\infty = (V_0 - V_\infty)e^{-1} = \frac{1}{2.71}(V_0 - V_\infty)$$

Voltage difference is one-third the original voltage difference.

Current controls V_∞. As current is injected $V_\infty$is increased to $R_L I_0$ and when the injected current is zero V_∞ drops back to 0. V_∞ is the steady state voltage of the cell. Voltage of the cell V_m approaches V_∞ exponentially and when V_∞ is zero V_m relaxes to 0 exponentially at some time constant.

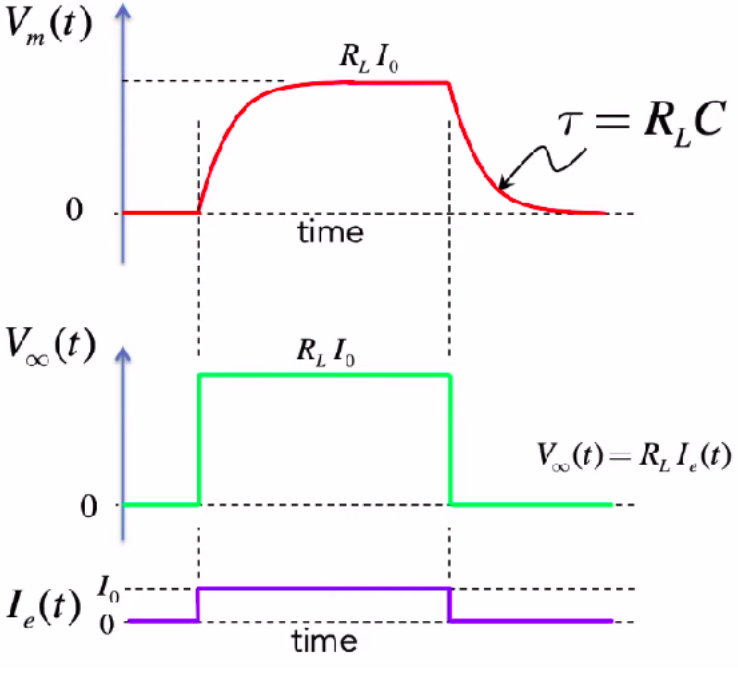


Figure 12: Response to injected current.

An RC system is a first order linear system that acts

like a filter. A neuron that just has a capacitor is an integrator, which integrates over time. When you add a resistor, its an integrator too, but its stops integrating and relaxes to some steady state V_∞.
RC system acts like a filter that responds well to inputs(injected current) slower (low frequency) than τ, but not to inputs faster than τ. So, its a low-pass filter, which means, for long pulses it responds well (relaxes to V_∞), but for short pulses, V_m starts relaxing towards the $V_\infty = 0$ before reaching the V_∞ for the same input pulse, but low frequency.
Low-pass filter responds well to slowly changing things but barely responds to rapidly changing things, so its' passing low frequencies, thus "low-pass".

For a neuron
$R \approx 10^8\Omega = 10M\Omega$
$C \approx 10^{-10}F = 100picoF$
$\tau = RC \approx 10ms$

If you inject current to a neuron it takes about 10-100 ms for it to fully respond to that step of current. Voltage will jump and relaxes to the new V_∞ in 10-100 ms.

2.4 Thinking the conductance way

The leak current through the ion channel

$$I_L = \frac{V_m}{R_L}$$
$$I_L = V_m R_L^{-1}$$
$$G_L = R_L^{-1} \tag{20}$$
$$I_L = G_L V_m \tag{21}$$

G_L is the conductance. It has unit of Ω^{-1} or *siemens*

Ion channels of a neuron are in parallel, current flows through them separately. So, by Kirchoff's law the total current is the sum of currents through the separate conductances (ion channels or resistors).

$$I_{total} = I_1 + I_2$$
$$I_{total} = G_1 V + G_2 V$$
$$I_{total} = (G_1 + G_2) V$$

$$G_{total} = G_1 + G_2 \tag{22}$$

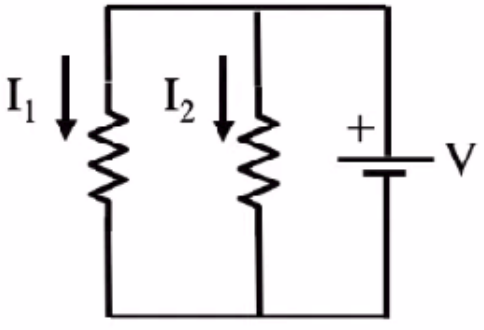


Figure 13: Two parallel conductances.

$$I_L = G_L V_m = A g_L V_m$$

g_L - specific leak conductance or specific membrane conductance, A- area

Capacitance in parallel

$$\begin{aligned} I_{Ctotal} &= I_{C1} + I_{C2} \\ &= \frac{dQ_{C1}}{dt} + \frac{dQ_{C2}}{dt} \\ &= C_1 \frac{dV}{dt} + C_2 \frac{dV}{dt} \\ &= (C_1 + C_2) \frac{dV}{dt} \end{aligned}$$

$$C_{total} = C_1 + C_2$$

Capacitance of a cell depends on linearly on surface area, $C = c_m A$, where c_m is specific capacitance

Neuron time constant or Membrane time constant

$$\begin{aligned} \tau_m &= R_L C \\ &= \frac{C}{G_L} \\ &= \frac{c_m A}{g_l A} \\ &= \frac{c_m}{g_L} \end{aligned}$$

$$\tau_m = \frac{c_m}{g_L} \tag{23}$$

Time constant is a property of the membrane and has nothing to do with the cell. Different parts of the same

cell can have different time constant, but it's a property of the membrane.

2.5 Batteries of a neuron

In the models we have discussed until now, when $I_e = 0$ and so, V_m=0. So, for a $V_m \neq 0$, one need to inject current continuously. Introducing a battery can do this. So, now, it can change it's own voltage.

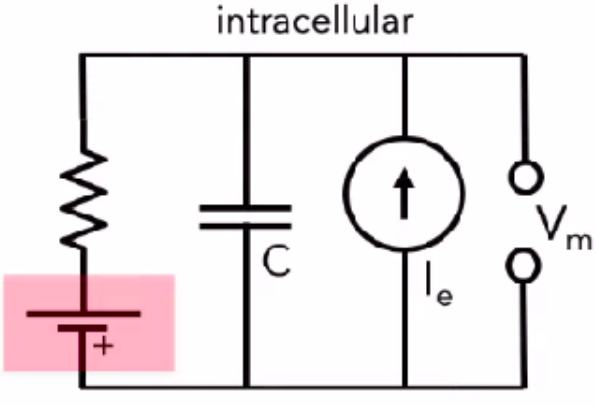


Figure 14: Introducing a battery.

Battery in neuron allows it to change it's own voltage. Neurons have ion channels (aka conductances) that are voltage dependent and they are connected to the inside wire(intracellular fluid) at different times in different ways.

Where do the batteries of a neuron come from?
1) Ion concentration gradient
2) Ion selective permeability of ion channels.

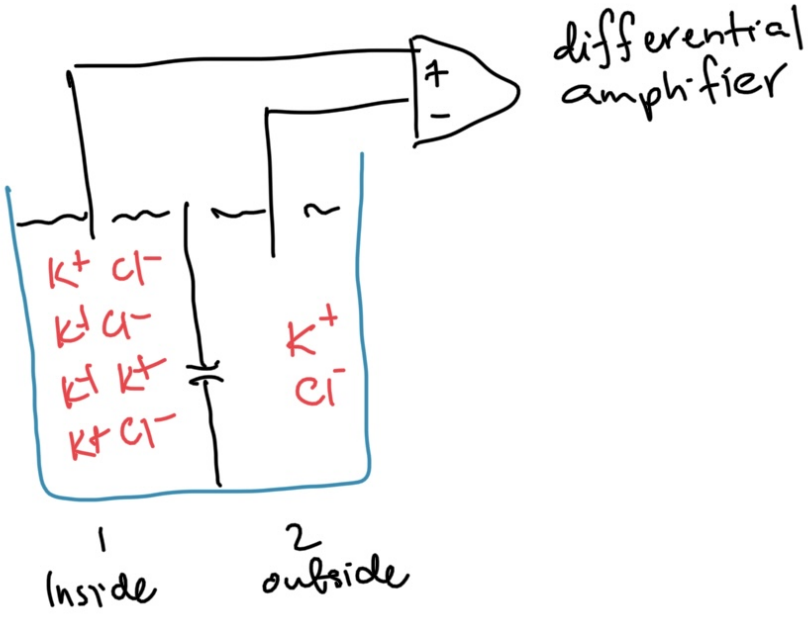


Figure 15: Potassium ions passing through a non selective pore.

It has a non selective pore which passes all ions. Ions diffuse from inside to outside. K concentration on outside (side 2) increases and decreases inside (outside). And eventually both the concentration become equal.

$[K]_{in}$ and $[K]_{out}$ will stop changing in a short time during the diffusion. And it will never become equilibrium. K current from inside to outside goes to zero very quickly, why?

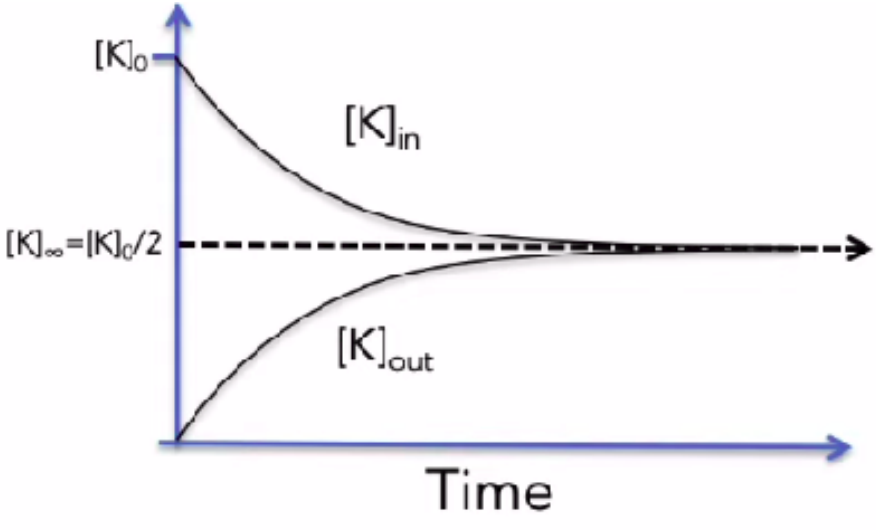


Figure 16: [K] over time.

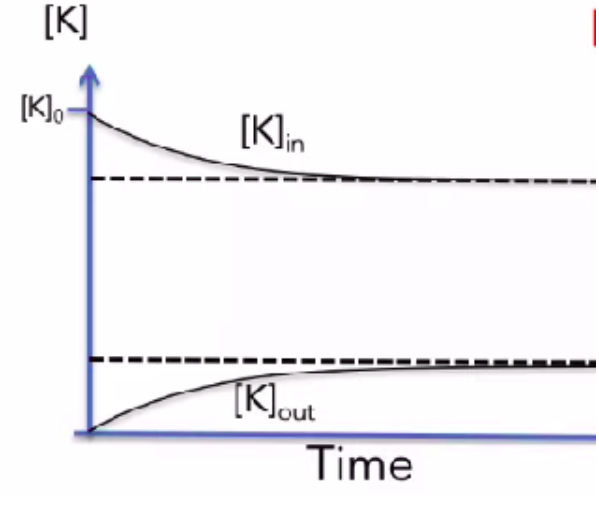


Figure 17: [K] over time.

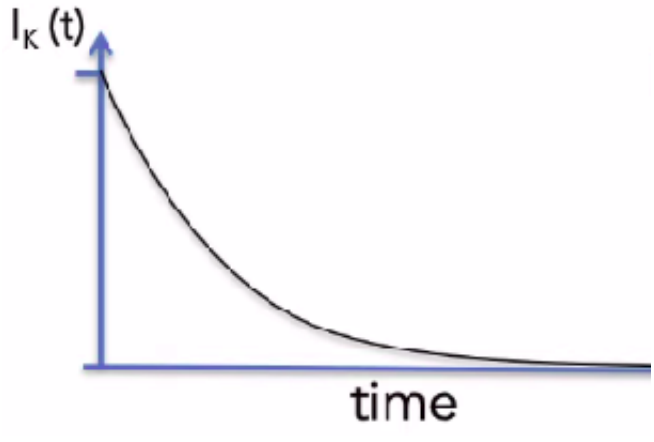


Figure 18: K current drops to zero

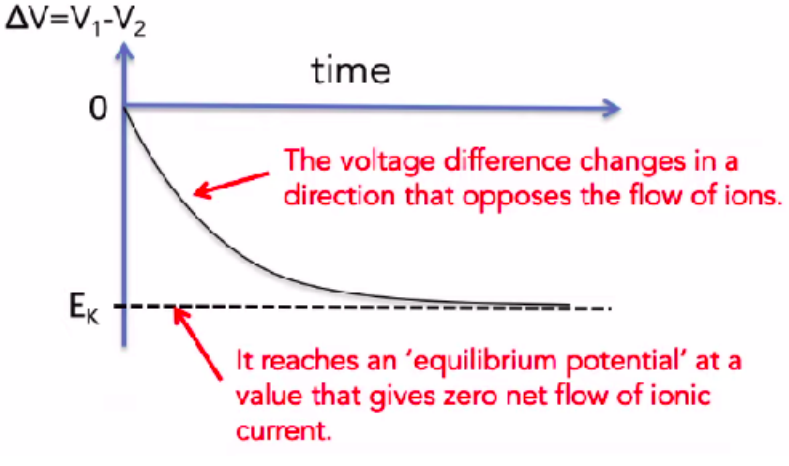


Figure 19: negative voltage difference

Positive charges diffused from 1 (inside)→ 2(outside). So, 2 is charged up and has positive voltage and more

positive change in 2 means, voltage in 2 goes up. Thus $(V_1 - V_2) < 0$. So, there is negative voltage in 1 and positive voltage in 2. The positive voltage in 2 repulses the positive charge flowing into it. Preventing more K^+ ions diffusing through the hole. It reaches an equilibrium potential $V_1 = V_2$, that gives zero net flow of ionic current. This voltage difference is a battery.

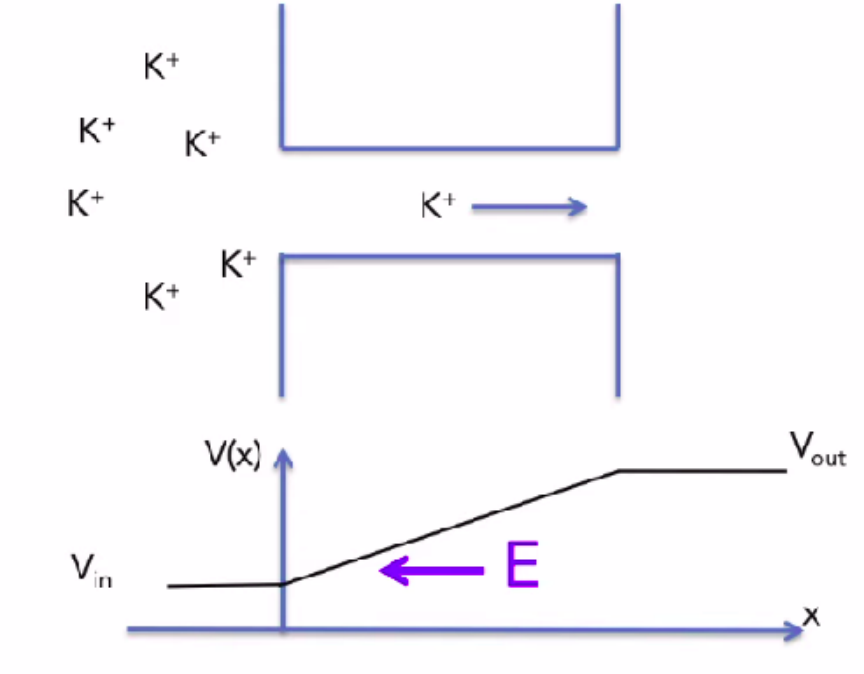


Figure 20: Diffusion is opposed by the drift due to $\vec{E}$

Here the diffusion of K ions from inside to outside is opposed by the drift due to the $\vec{E}$. So, at this voltage, I_{drift} in the electric field exactly balances $I_{diffusion}$ due

to concentration gradient.

$$I_{total} = I_{drift} + I_{diffusion} = 0 \tag{24}$$

(derivation is not shown. ϕ is the concentration.)

At equilibrium,

$$\Delta V = \frac{kT}{q} \ln \frac{\phi_{out}}{\phi_{in}} \tag{25}$$

Boltzmann equation says that the ratio of probabilities of a particle being in any two states at thermal equilibrium is a function of energy difference between those two states.

$$\frac{P_{state1}}{P_{state2}} = e^{-\frac{U_1 - U_2}{kT}} \tag{26}$$

k=Boltzmann constant, T=Temperature in K, KT= Thermal energy (J)

States here is particle being inside or outside of the membrane. Outside and inside has different energies.

When T = 0 there is no jostling and the particles sits at state 2. So, if kT=0, $e^{-bignumber} = 0$. Thus $\frac{P_{state1}}{P_{state2}}$ =0.

If temperature is increased and kT > 0, so it becomes approximately equal to the energy difference between

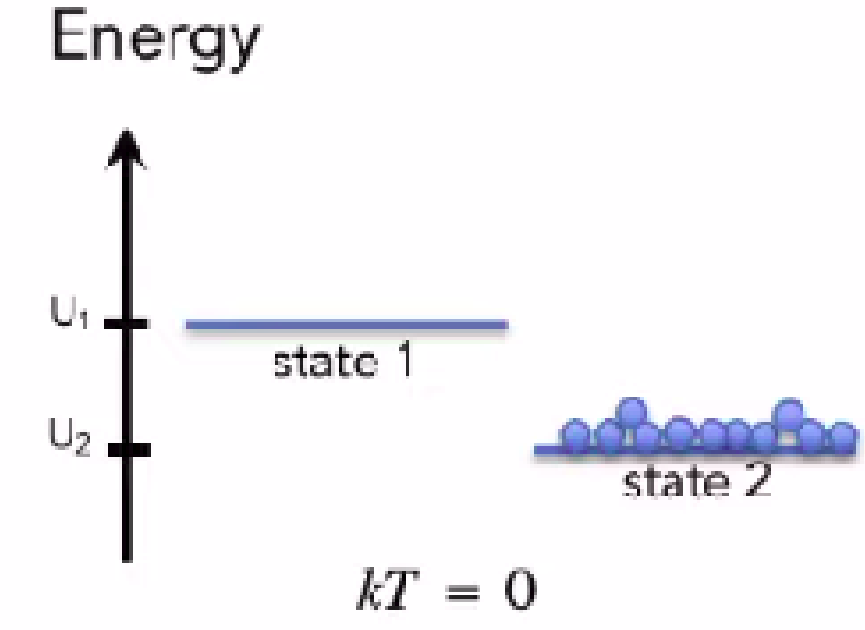


Figure 21: Particles in the two energy states

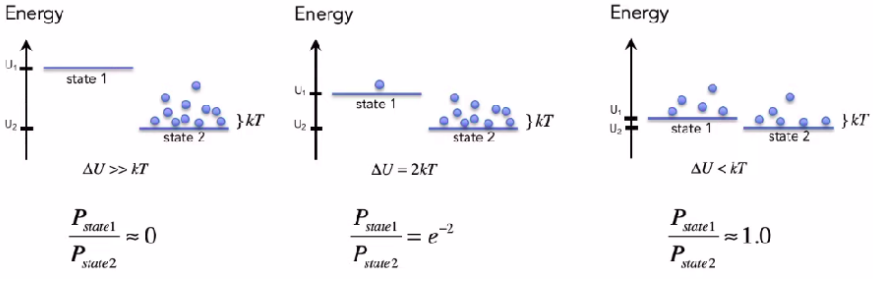


Figure 22: Energy difference and probability of particles in states 1 and 2

state 1 and state 2. So that some of the particles can get jostled over to state 1. $\frac{P_{state1}}{P_{state2}} > 0$.
Suppose $\Delta U = 2\text{kT}$, then $\frac{P_{state1}}{P_{state2}} = e^{-2}$.

If the energy difference is bigger $\Delta U >> \text{kT}$, then $\frac{P_{state1}}{P_{state2}} \approx 0$. If the energy difference $\Delta U < \text{kT}$, then $\frac{P_{state1}}{P_{state2}} \approx 1$.

Applying it in our case of neuron, where state 1 is inside and state 2 is outside of the cell. K ion diffuses from state 1 to state 2.

$$\begin{aligned} \frac{P_{in}}{P_{out}} &= e^{-\frac{U_{in}-U_{out}}{kT}} \\ &= e^{-\frac{q(V_{in}-V_{out})}{kT}} \end{aligned}$$

Taking log on both sides

$$V_{in} - V_{out} = -\frac{kT}{q} \ln \frac{P_{in}}{P_{out}} \tag{27}$$

Ion	Cytoplasm (mM)	Extracellular(mM)
K^+	400	20
Na^+	50	440
Cl^-	52	560
Ca^{2+}	10^{-4}	2

Table 1: Ion concentrations of squid axon.

For K^+, $\frac{kT}{q} = 25$ mV, at 300 K for monovalent ion.

$$\begin{aligned}\Delta V &= 25mV \ln \frac{P_{out}}{P_{in}} \\ &= 25mV \ln \frac{[K_{out}]}{[K_{in}]} = E_K\end{aligned}$$

E_K is the equilibrium potential for the K^+ ion.

$$\begin{aligned}E_K &= \frac{kT}{q} \ln \frac{20}{400} \\ &= 25mV \times (-3.0) \\ &= -75mV\end{aligned}$$

Which means, opening up the K^+ ion selective channels leads to diffusion of K^+ ions out of the cell and lead to 75 mV drop in the voltage or equilibrium potential.Positively charged ions going out of the cell decreases the potential.

For Na^+

$$\begin{aligned} E_{Na^+} &= 25mV \ln \frac{[Na_{out}]}{[Na_{in}]} \\ &= 25mV \ln \frac{440}{50} \\ &= 25mV \times (2.17) \\ &= 54.3mV \end{aligned}$$

So, when Na^+ diffuses in, the equilibrium potential increases by 54.3 mV. Positively charged ion going inside the cell increases the potential.

For Cl^-

$$\begin{aligned} E_{Cl^-} &= 25mV \ln \frac{[Cl_{out}]}{[Cl_{in}]} \\ &= 25mV \ln \frac{52}{560} \\ &= -59.4mV \end{aligned}$$

Negatively charged ions going inside decreases the potential.

For Ca^{2+}

$$
\begin{aligned}
E_C a^{2+} &= \frac{kT}{q} \ln \frac{[Ca_{out}]}{[Ca_{in}]} \\
&= 12.5mV \ln \frac{2}{10^{-4}} \\
&= 124mV
\end{aligned}
$$

2.6 I-V relation

Consider the same neuron in the dish set up. We have K^+ diffusing out and a K conductance G_{K^+}. We measure the steady state voltage in the cell as a function of amount of current injected or the current passing through the membrane.
Let's inject current until the voltage(V_m) get to zero. If we inject no current, the steady state voltage will be -75 mV (Nernst potential or equilibrium potential of K^+). Then to make V_m =0, we inject a positive current I_K, because inside has negative potential and positive charges will raise it to 0.

If you hold the voltage above the equilibrium potential E_K, Potassium current I_K will flow out through the membrane. If you hold the voltage below E_K, then the current will flow into the cell. Note that the current reverses at the equilibrium potential and the direction ionic current will be such that it will bring the cell's potential to the the equilibrium potential of the ion.

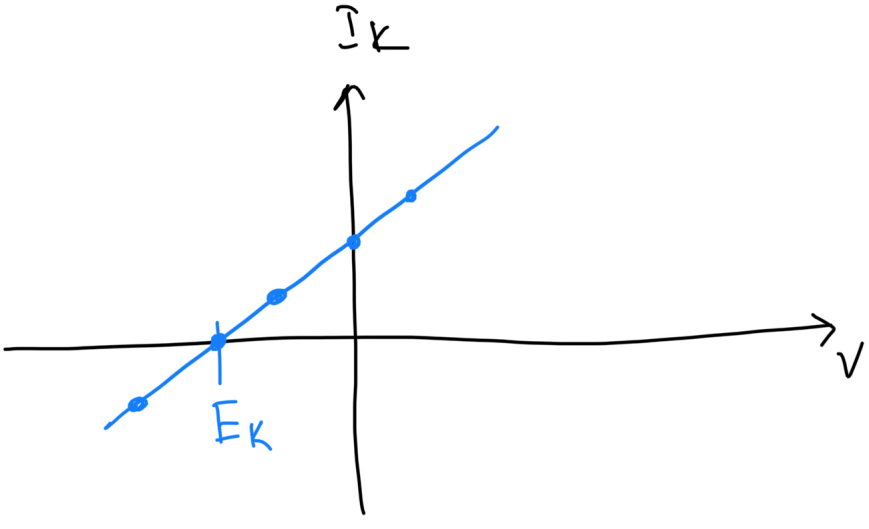


Figure 23: Current reverses at equilibrium potential

$$I_K = G_K(V_m - E_K) \tag{28}$$

We can model this as a battery in series with a resistor. And this equivalent circuit include the effect of the ion-specific conductance in presence of a concentration gradient. Where we take our conductance (resistance here) and put it in series with the battery (concentration gradient).

V_m is the potential difference between inside and outside of the cell. And is equal to the sum of the voltage drops across the two components.

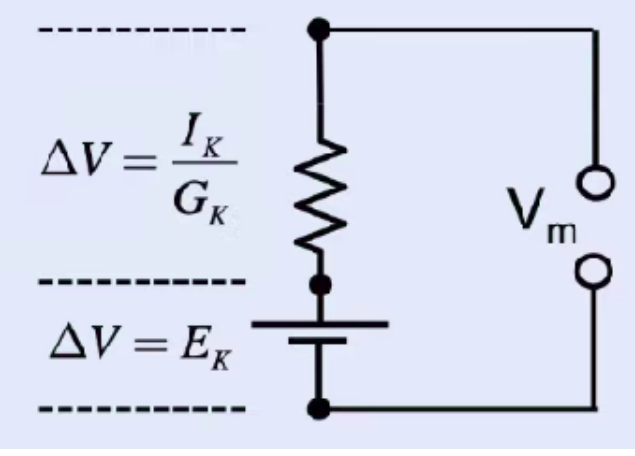


Figure 24: Equivalent circuit

$$V_m = \frac{I_K}{G_K} + E_K$$
$$I_K = G_K(V_m - E_K)$$

$(V_m - E_K)$ is the driving potential, if it is 0, then no current. Current through the channel is proportional to driving potential.

So, now our cell which is a cap whose membrane has leaks in it where there is ion specific permeability of the pore and the ion concentration gradient to produce the battery.

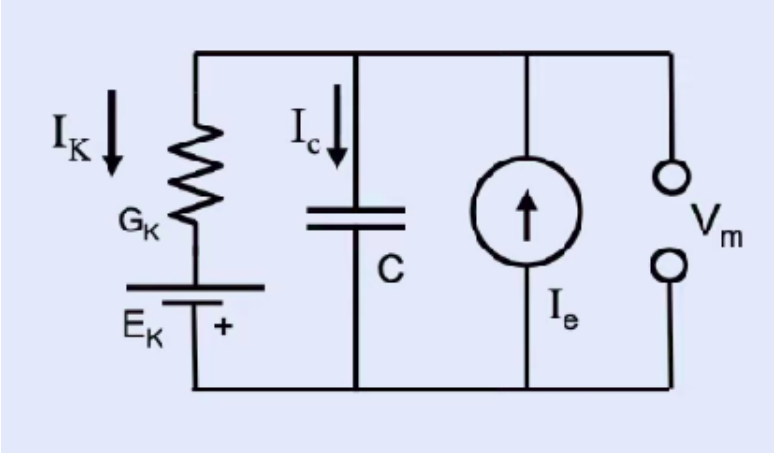


Figure 25: Equivalent circuit of our current model

$$I_K + C\frac{dV_m}{dt} = I_e$$
$$G_K(V_m - E_K) + C\frac{dV_m}{dt} = I_e$$
$$V_m + \tau\frac{dV_m}{dt} = E_K + I_e R_K$$

If you set $\frac{dV_m}{dt}$ =0,

$$V_m = E_K + R_K I_e$$

If you inject a constant current at steady state $\frac{dV_m}{dt} = 0$, the injected current is just equal to the K^+ current leaking out through the membrane.

$$V_m + \tau\frac{dV_m}{dt} = V_\infty \tag{29}$$

Every moment V_m is relaxing towards V_∞.

$$V_\infty = E_K + R_K I_e \tag{30}$$

So, now E_K and potential due to injected current contributes to V_∞.

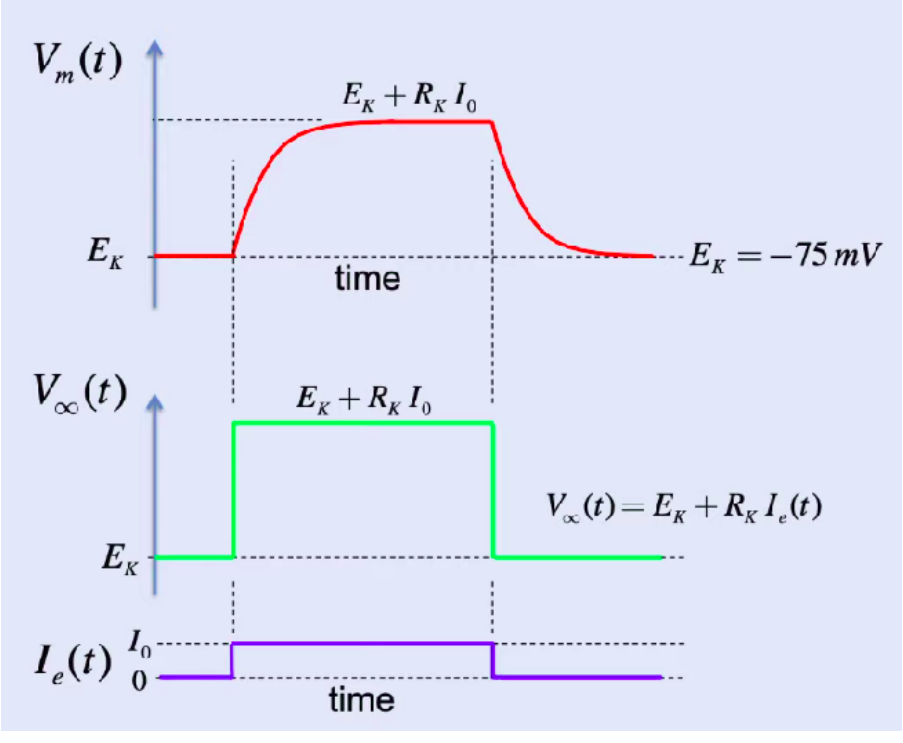


Figure 26: Response to current injection

2.7 Integrate and fire model

Before going to the Hodgkin-Huxley model we are discussing a simplified version of the HH same.

Most of the time, a neuron is 'integrating' it's inputs which are separated by time scales. All the spikes are the same, there are no information carried in the details of action potential waveforms. Here we describe spike or action potential (AP) as δ function which are discrete events at single time when the voltage in a neuron reaches a particular membrane potential, called the spike threshold. This is a reasonable approximation for most of the neurons.

In integrate and fire model we replace the Na and K conductances by a spike generator.

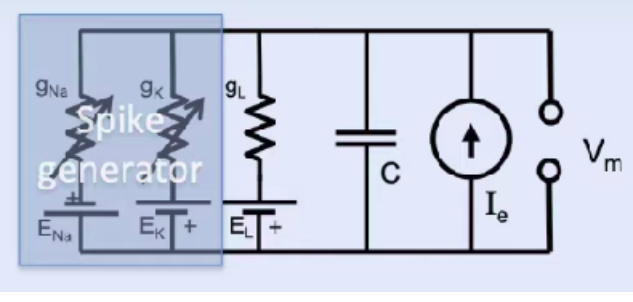


Figure 27: Integrate and fire model.

The cell gets input from an electrode or a synaptic

input. And it integrates the input till it reaches the threshold voltage V_{th}. When the voltage (V_m) reaches the V_{th}, it resets the neuron to a hyperpolarized voltage V_{res} or V_{reset}.

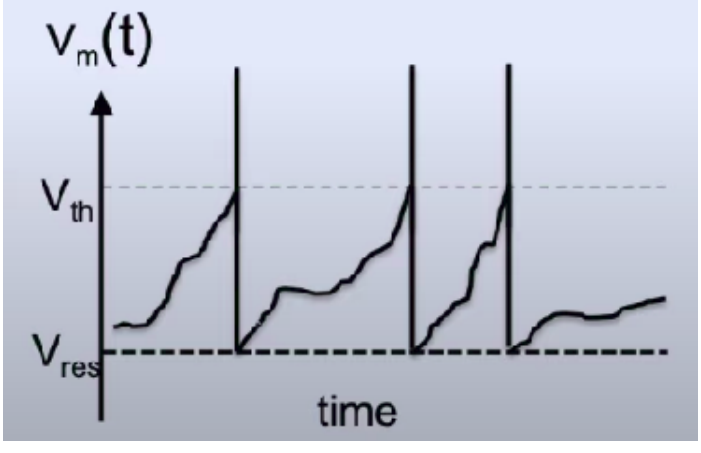


Figure 28: If we draw a line at the time when V_m becomes V_{res}, that's the spike.

Firing rate

- Case 1 - No leak/conductances
  We inject a constant current to our cell, the cell generates spikes (AP) at regular intervals, and the interval between those spikes is going to be controlled by how long it takes for capacitor to charge up from the V_{res} to V_{th}.

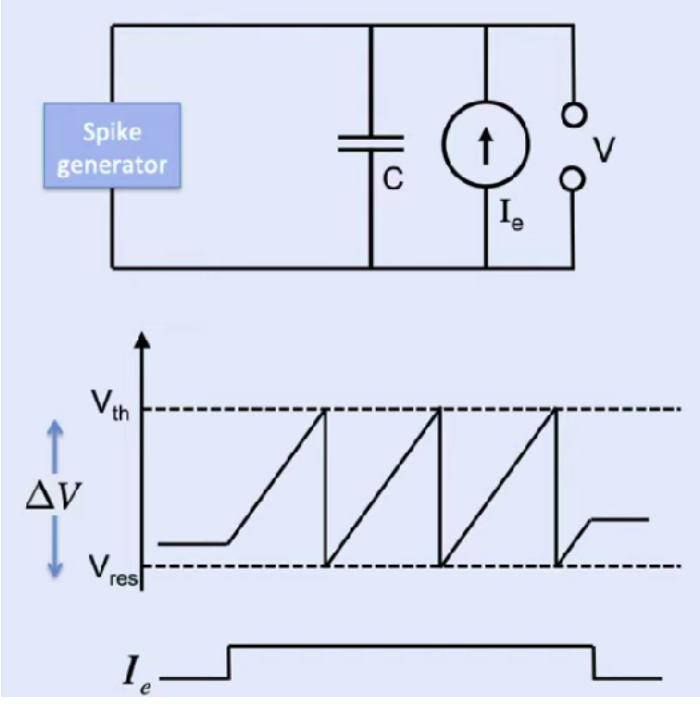


Figure 29: Response when there's no leak.

$$firingrate = \frac{1}{\Delta t}$$

$$slope = \frac{\Delta V}{\Delta T}$$

$$C\frac{\Delta V}{\Delta t} = I_e$$

$$f = \frac{1}{\Delta t} = \frac{1}{C\Delta V} I_e \tag{31}$$

Firing rate, f α I_e (injected current)

- Case 2: Putting the leak conductance back in.

  Refer figure 27. Think of G_L like a small potassium conductance that is constantly ON. It has no voltage dependence and time dependence. E_L= -75mV. When we have a leak, $V_\infty > V_{th}$ for a spike to happen, thus there is a threshold current below which the neuron wont spike. That is, when $V_\infty < V_{th}$ the neuron wont spike. When $I_e = 0$, $E_L = V_\infty$, so V_m will relax to E_L.

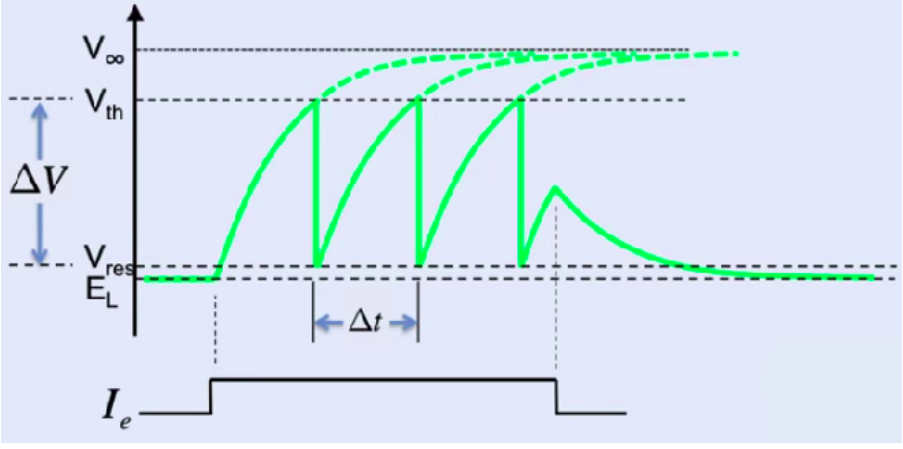


Figure 30: Response when potassium conductance is present.

Rheobase- The current at which the neuron begins to spike.

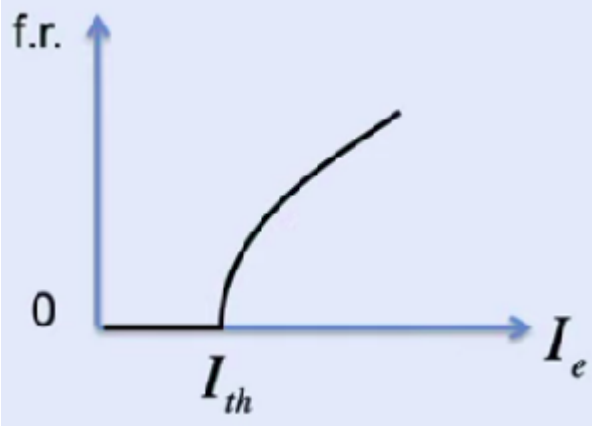


Figure 31: Firing rate at I_{th}

Suppose V_∞ is right at threshold, then time to reach

the threshold is very low. If V_∞=V_{th}, it will never actually reach it, and the firing rate=0. If we inject a tiny bit more current, it will begin to spike.

Injected current required to reach the threshold, set V_∞=V_{th}. From equation 30,

$$E_L + R_L I_e = V_{th}$$

$$I_{th} = I_e = G_L(V_{th} - E_L) \tag{32}$$

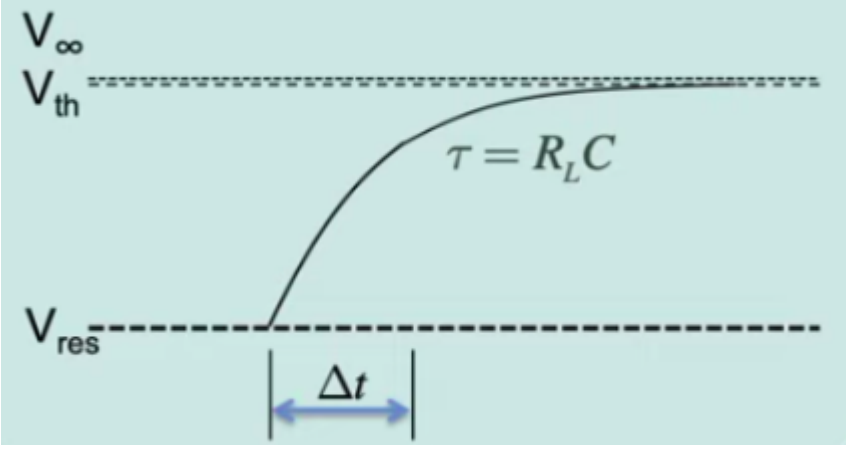


Figure 32: Rheobase

Firing rate as a function of injected current- We calculate the amount of time (Δt) before the cell spike again. At some $I_e > I_{th}$ the cell relaxes exponentially to V_∞.

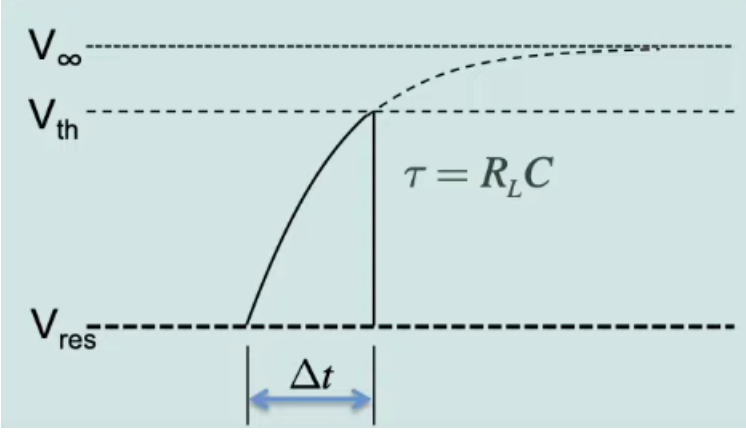


Figure 33: Spike after Δt

$$V_m(t) - V_\infty = (V_0 - V_\infty)e^{-}\frac{t}{\tau}$$

The difference from V_m to V_∞ decreases exponentially. At t = Δt, initial voltage $V_o = V_{res}$, $V_m(t)$ at Δt is V_{th}. (Refer figure 33)

$$\begin{aligned} V_{th} - V_\infty &= (V_{res} - V_\infty)e^{-}\frac{\Delta t}{\tau} \\ e^{-}\frac{\Delta t}{\tau} &= \frac{V_\infty - V_{th}}{V_\infty - V_{res}} \\ \Delta t &= -\tau \ln \frac{V_\infty - V_{th}}{V_\infty - V_{res}} \end{aligned}$$

$$f = \frac{1}{\Delta t} = \left[\tau \ln \left[\frac{V_\infty - V_{res}}{V_\infty - V_{th}}\right]\right]^{-1} \tag{33}$$

When the injected current is large, V_∞ is large.

$$V_\infty >> V_{th}, V_{res}$$
$$\frac{V_\infty - V_{res}}{V_\infty - V_{th}} = 1$$

$$f = \left[\tau \ln \left[\frac{V_\infty - V_{res}}{V_\infty - V_{th}}\right]\right]^{-1}$$
$$f = \tau^{-1}$$

on further solving (how?)

$$f = \frac{1}{C\Delta V}(I_e - I_{th}) \tag{34}$$

ΔV is the difference from V_{res} to V_{th}. This equation is true only when $I_e > I_{th}$. So, firing rate is zero until I_e hits I_{th}, then it increases linearly.

2.8 Hodgkin-Huxley Model

A mathematical model of a neuron by Alan Hodgkin and Andrew Huxley, 1952.

There are three conductances in this model, leak conductance G_L, the time and voltage dependent G_{Na} and

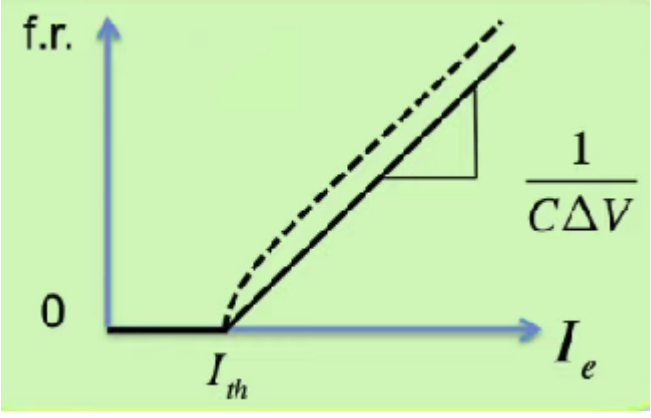


Figure 34: Firing rate when I_e is large. Solid line is linear approximation. Dashed line- actual solution

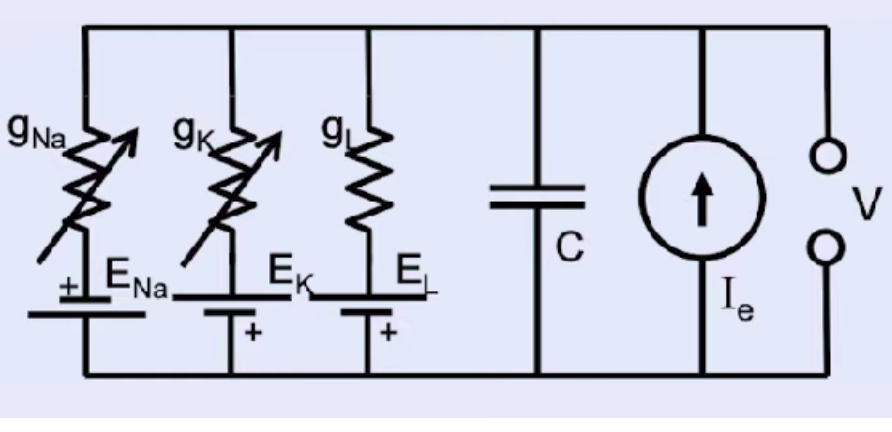


Figure 35: Hodgkin-Huxley model. $E_{Na} = +55mV$, $E_K = -75mV$, $E_L = -50mV$

G_K. Total ionic membrane current:

$$I_m = I_{Na} + I_K + I_L \tag{35}$$

By Kirchoff's law, total membrane ionic current + capacitive current = injected current

$$I_m(t) + C\frac{dV_m(t)}{dt} = I_e(t) \tag{36}$$

$$I_{Na} = G_{Na}(V,t)(V_m - E_{Na}) \tag{37}$$

$$I_K = G_K(V,t)(V_m - E_K) \tag{38}$$

$$I_L = G_L(V_m - E_L) \tag{39}$$

I_X=$G_X(V-E_X)$, (V_m-E_X) is the voltage drop across the particular conductance and is called the driving potential of that conductance.

Conductances are like knobs that allow the cell to control it's voltage. Turning the G_{Na} high (same as lowering the resistance of Na channel), the V_m jumps towards E_{Na} because you are connecting the inside of the cell to that battery. Turning G_{Na} OFF and turning G_K ON, now the inside of the cell is connected to E_K and the V_m lowers towards the E_K. When both G_{Na} and G_K are turned off, then the V_m relaxes to E_L=-50mV.If both channels are open at same time, the voltage V_m will be near the middle. Each conductance is

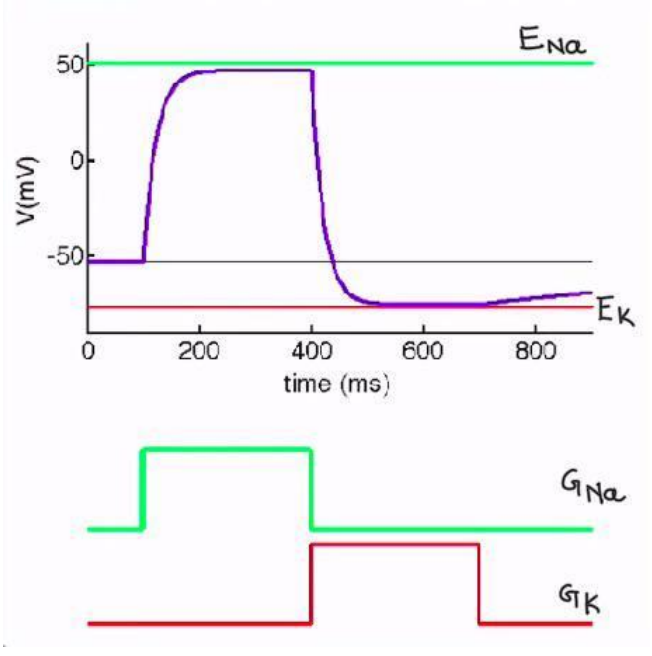


Figure 36: Varying V_m with varying Na and K conductance

causing the cell to be dragged towards it reversal potential. Na channels push membrane potential positive. K channels push membrane potential negative. Together these channels generate an action potential. The leak conductance G_L has E_L=-50mV and tends to keep the cell hyperpolarized. Membrane potential depends on current, which depends on the conductances, which depend on the membrane potential.

2.8.1 Hodgkin-Huxley Experiment

Objectives:

- set voltage at different values
- measure the current required to hold that voltage
- plot I-V
- find G(conductance), which is the slope of I-V curve.

It is not easy to do this, because as soon as you depolarize the axon, the axon begins to spike. Hodgkin-Huxley made a device called the Voltage clamp that holds the membrane potential of the cell to any desired 'command' voltage V_c, and measure the current required to hold that voltage.

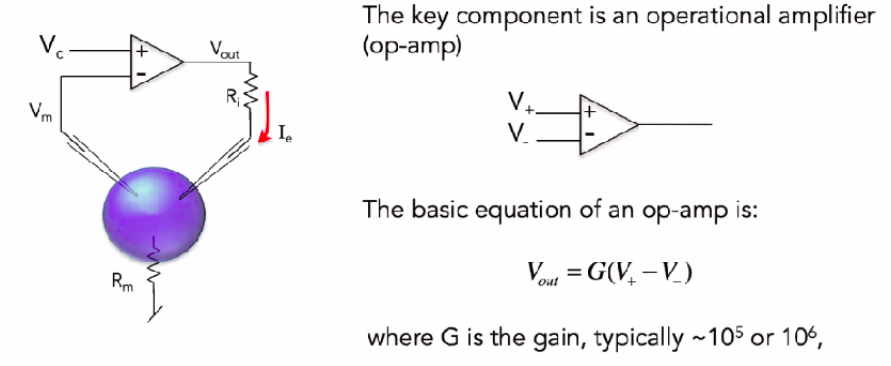


Figure 37: Voltage clamp set up. G is Gain, not conductance.

It tries to make V_m equal to the V_c by feeding current

back into the cell.

$$V_{out} = G(V_c - V_m)$$

If $V_m < V_c$, then $V_{out} >> 0$ and it drives current into the cell and increases the membrane potential V_m and make it approach V_c.

If $V_m > V_c$, then $V_{out} << 0$ and it pulls current of the neuron, decreasing the membrane potential i.e, membrane potential is pulled towards the command potential V_c.
In both cases V_m is pulled towards the command voltage V_c. Thus the voltage clamp circuit drives whatever current (I_e) is necessary to "clamp" the voltage of the neuron to the command voltage. During a voltage clamp experiment, we step the V_c around with in the voltage range of interest and measure I_e.

When voltage is stepped up from -65mV to 0mV , there is an initial pulse of current which is negative. Negative current means there are positive ions going into the cell, it's charging the cell up (depolarisation, increased V_m). The negative current remains for few milliseconds and the the current reverses the sign becomes positive stays on. What causes this trend? How do we figure out the contribution of Na and contribution of K to this?

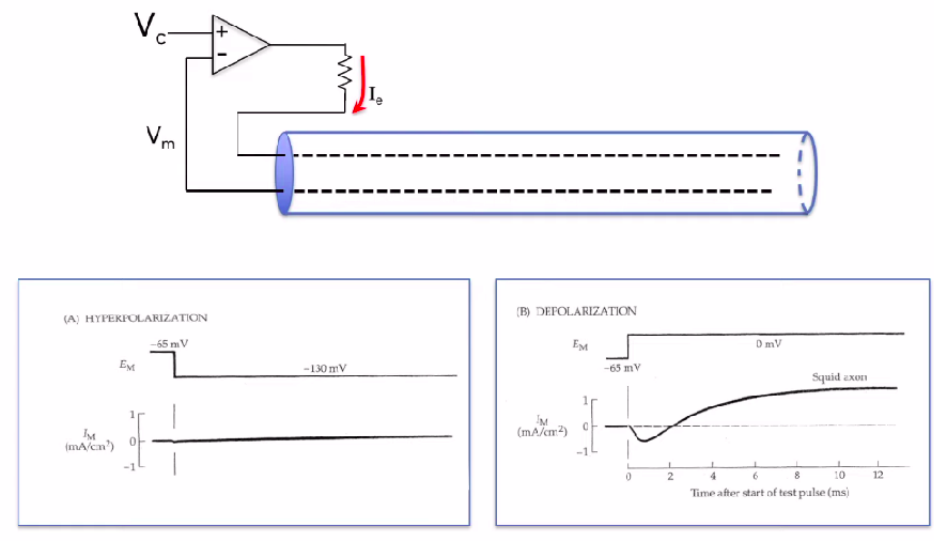
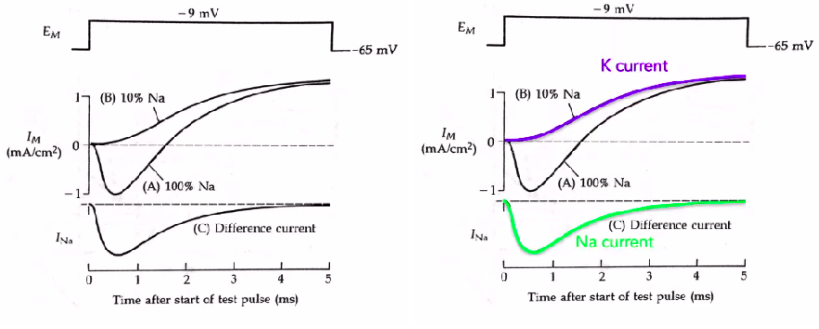


Figure 38: Experimental set up and variation of current with different voltages.

In the same experiment they replaced Na outside the cell/axon. Ionic substitution eg- replace NaCl with Choline chloride.



(a) current when NaCl was replaced

(b) Na and K currents

Without the Na, they got almost the same thing (cur-

rent profile) except the initial negative pulse. They hypothesized that, the initial negative pulse part is due to Na. And if you subtract I_M at 10% Na and I_M at 100% Na and it gives the sodium current I_{Na}. In another experiment they showed that the current when Na was removed(10% Na) is actually due to K.

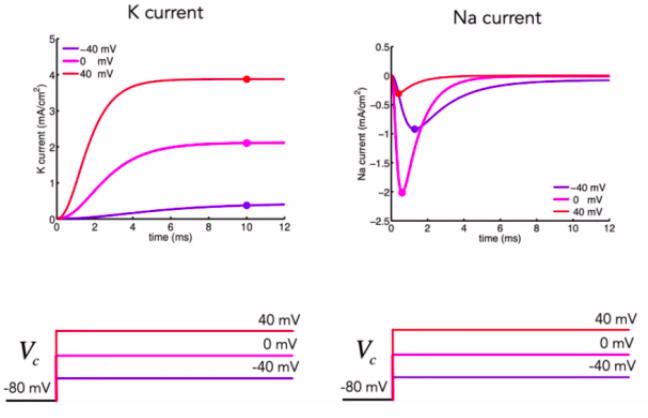


Figure 40: Sodium and Potassium current as a function of time at different voltages

Small Na current at +40mV is because it is close the equilibrium potential or Reversal potential (+50mV) of of Na conductance.

K current is zero for the voltages closer to E_K and it stays zero for voltages lower than E_K and grows as the voltage become more positive. Na current is linear for voltages above zero, at E_{Na} its zero.Since $I_{Na} = G_{Na}(V)(V - E_{Na})$, current depends on the driving potential and conductance, which in turn depends

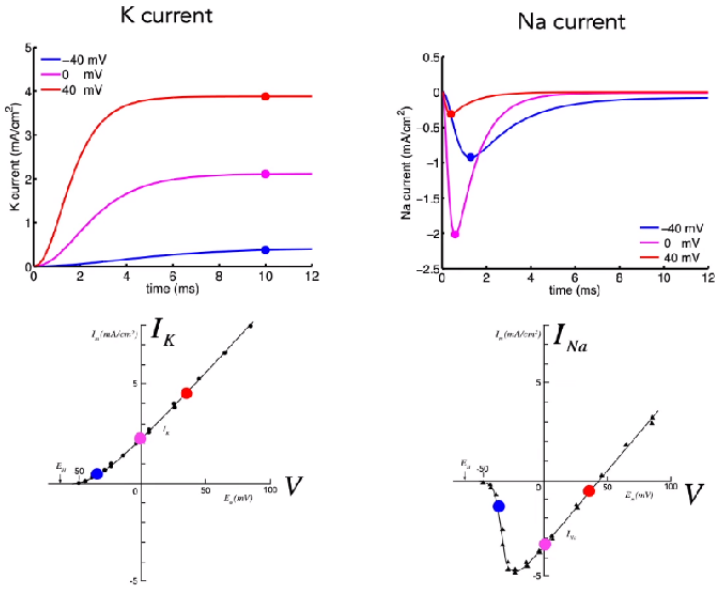


Figure 41: Peak current as a function of voltage

on the voltage.

You can get a zero current even with a negative driving potential is when the conductance = 0. In case of K, I doesn't go negative because G_K reached zero(i.e voltage dependence of conductance turns it off) before the driving potential can go negative. But in case of Na, the driving potential goes negative (V-E_{Na}) much before the G_{Na} is turned off due its voltage dependence.

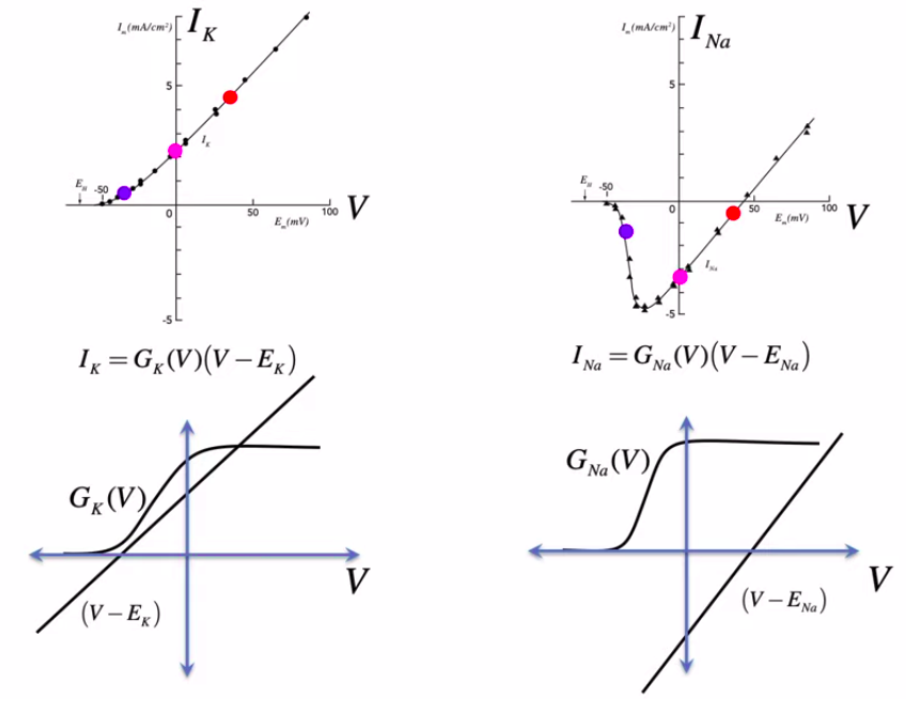


Figure 42: I-V curve, G-V curve

2.8.2 Voltage and time dependence of conductance

Voltage dependence

I_K is approximately linear above -50mV. $I_K > 0$ when (V-E_K) >0 and $I_K < 0$ when V < E_K. $I_N a$ is approximately linear for positive voltages and crashes to zero at negative voltages . $I_v > 0$ when (V-E_v) > 0 and I_{Na} <0 when V < E_{Na}. First quadrant of the I_K-V plot, I_K is linear, same is the V-E_K. S0, G_K must be constant. For large negative driving potential (V-E_K),

I_K=0, that means G_K=0. Conductance turns off at negative voltage and turns on at positive voltages and stays on. Why isn't I_K negative? Because G_K turns off due to it's voltage dependence. Had G_K been turned off at more negative voltage, then I_K would be negative.

For I_{Na} the (V-E_{Na}) is linear. Reversal potential E_{Na}=55mV. When I_{Na} and (V-E_{Na}) are linear so that means G_{Na} is constant. For large negative driving potential (V-E_{Na}), I_{Na}=0, that means G_{Na}=0. G_K and G_{Na} is off at negative potentials and they turn on at positive voltage and remain constant. Any non linearity in the current is accounted for by changes in the voltage dependence of the conductances.

For both Na and K conductances, they have a characteristic exponential turn on followed by a saturation, i.e. constant conductance at higher voltages.

Time dependence

In our voltage clamp experiment, voltage is constant, so (V-E_K) is constant. Thus any dependence of the current due to the time dependence of the conductance.

$$I_K(t) = G_K(t)(V - E_K)$$
$$I_{Na}(t) = G_{Na}(t)(V - E_{Na})$$

The process of turning on is called activation.

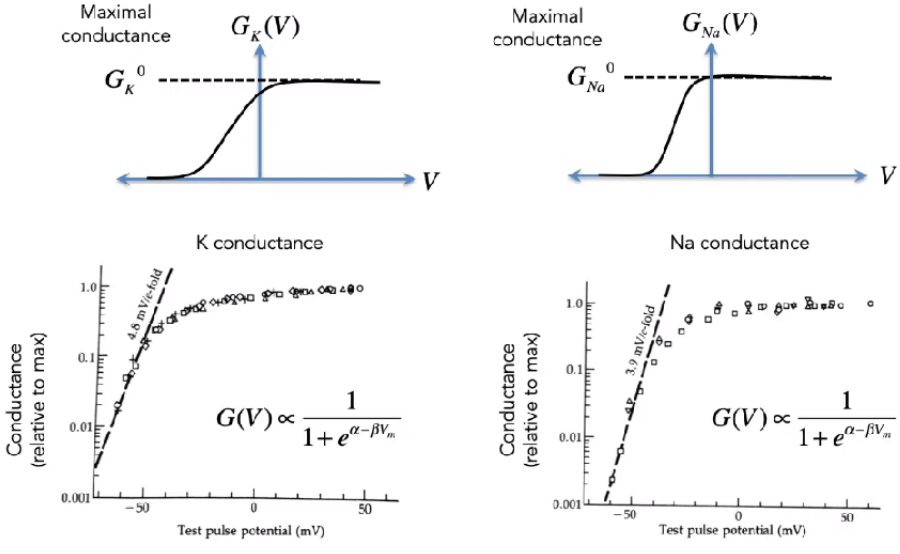


Figure 43: Voltage dependence of the two conductances on log scale.

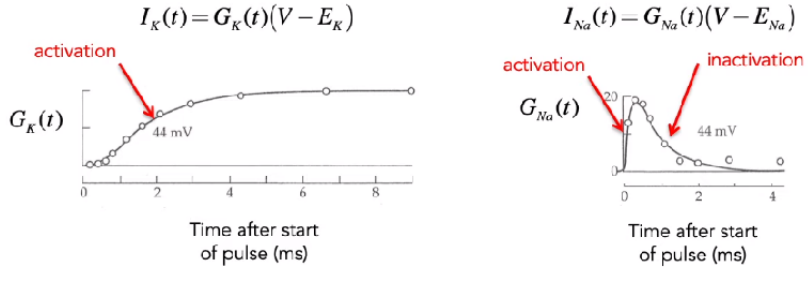


Figure 44: Time dependence of the conductances.

2.8.3 Biophysics of voltage and time dependence of conductance

It is possible to record from a single ion channel using patch clamp. Ensemble average of multiple experimental trials measuring the current through single channel

is similar to the current measured on the whole axon by H,H. The channels have two states and they flicker back and forth between those states, conducting and non-conducting.

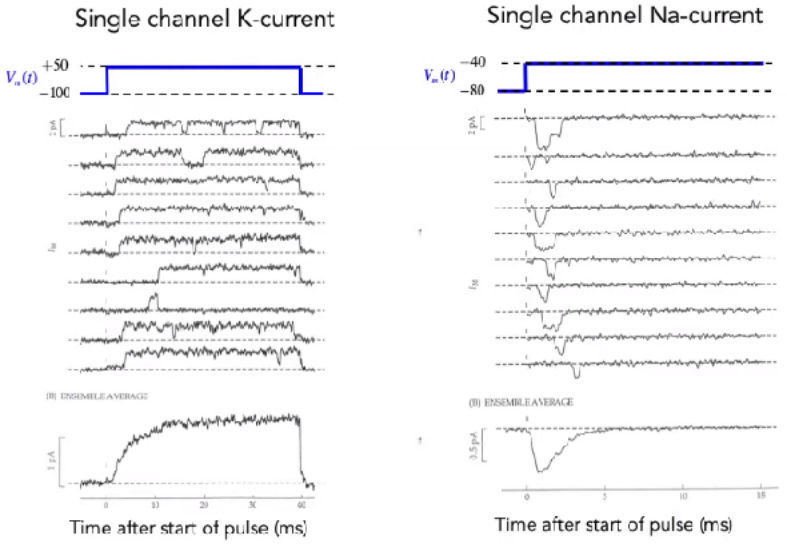


Figure 45: Ensemble average of multiple trials of measuring current through K and Na channel.

Ionic conductance in terms of single channels
Individual ion channels are either open or close. Total conductance of a membrane is given by the total number of open channels times the conductance of one ion channel.

Potassium channel
P_K = probability of Potassium channel being open
N_K = total number of ion channels
$P_K N_K$ = number of open channels
$\hat{g_k}$ = unitary conductance, conductance of one open channel

Total potassium conductance

$$G_K = P_K(V,t)N_K\hat{g_k} \tag{40}$$

$$I_K = G_K(V,t)(V - E_K) \tag{41}$$

Potassium channel is a tetramer, it has 4 identical subunits. Each subunit has a voltage sensor and gate to turn the channel on and off. Each subunit has two states, open and closed. n (gating variable) is the probability that any one subunit is open.
$P_K = n^4$, probability that the whole channel is open, that is all 4 subunit are in open state and assuming they are independent events.

$$\begin{aligned} G_K &= \overline{G_K}n^4 \\ I_K &= G_K(V - E_K) \end{aligned}$$

$\overline{G_k}$ is the maximal open conductance

$$I_K = \overline{G_K}n^4(V - E_K) \tag{42}$$

2.8.4 Voltage dependence of K channel using Boltzmann equation

Boltzmann equation says, the probability of being in any of the two states (open or closed) depends up on the energy difference between the two states.

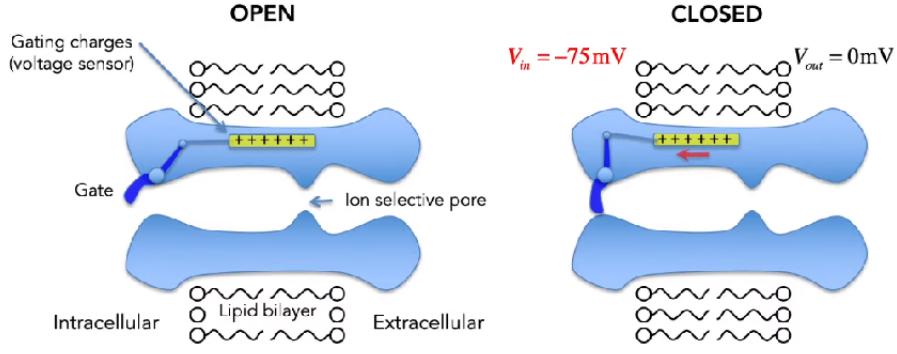


Figure 46: Cross-section of the tetramer. Opening and closing of gate. Every subunit of the tetramer has the gate.

Each subunit of a potassium channel tetramer has a voltage sensor. The voltage is sensed with charges, when there is voltage gradient or voltage difference, there exists an electric field and it exerts force on the charges.

Probability of one subunit being open:

$$P_o(V) = \frac{1}{1 + e^{w - q_g \frac{V_m}{kT}}} \tag{43}$$

V_m = membrane potential, q_g = gating charge, w = energy difference between the open and closed state

when the voltage difference is 0. It estimates how energy difference between open and closed state depends on the voltage of the cell.(*for detailed derivation refer lecture 4 of Neural Computing playlist MIT OCW*)

2.8.5 Time dependence of K channel

K channel subunits are in closed state (low energy state) when the cell is hyperpolarized and when the cell is depolarized it transitions to a open state (higher energy state). This transition from closed to open takes time, since it is caused by the thermal fluctuation and conformational change in the protein.

Modelling the transition with a simple rate equation:

$$\underset{\text{1-n}}{\text{closed}} \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} \underset{\text{n}}{\text{open}}$$

n = probability of a channel being open
α_n and β_n are transition rates, the probability per unit time of going from closed state to open state and vice-versa. They have units of s^{-1}. α_n and β_n are voltage dependent and in turn dependent on the energy difference between closed and open state.

Change in the number of open subunits = the # of closed subunits that open − the # of open subunits that

close

Change in the number of open subunits per unit time = the # of closed subunits, $(1-n)$, times the probability that closed subunit opens per unit time, α_n – the # of open subunits, n, times the probability that open subunit closes per unit time, β_n

$$\frac{dn}{dt} = (1-n)\alpha_n - n\beta_n \tag{44}$$

n = probability of a channel being open

$$\frac{dn}{dt} = \alpha_n - n(\alpha_n + \beta_n)$$

At steady state:

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}$$

$$\frac{dn}{dt} = \alpha_n - n(\alpha_n + \beta_n)$$

divide both sides by $(\alpha_n + \beta_n)$

$$\frac{1}{(\alpha_n + \beta_n)}\frac{dn}{dt} = \frac{\alpha_n}{(\alpha_n + \beta_n)} - n$$

α_n,β_n has units of $time^{-1}$. $(\alpha_n+\beta_n)$ has units of time.

$$\frac{1}{(\alpha_n + \beta_n)} = \tau_n$$

is a time constant.

$$\tau_n \frac{dn}{dt} = n_\infty - n \tag{45}$$

If we change n_∞, n relaxes exponentially to n_∞ with the time constant τ. n_∞ and τ_n are voltage dependent as they come from the α_n and β_n. n_∞ goes from zero for negative voltages, sigmoidal upto 1 (probability) and stays there for higher voltages.

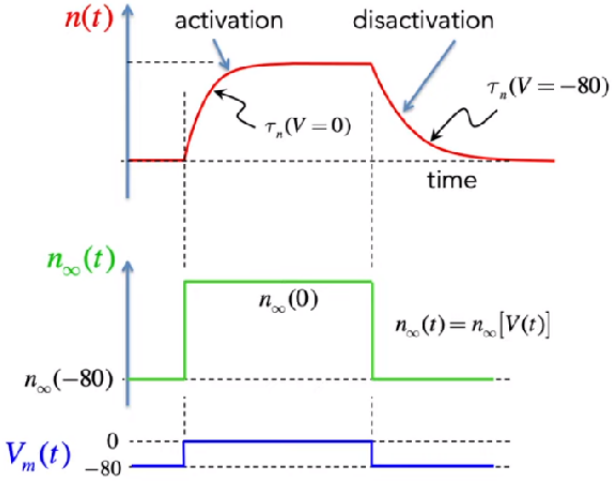


Figure 47: variation of gating variable with membrane potential

how does gating variable 'n' change as we step up the membrane potential. n_∞ will start from zero goes to 1. And falls to zero when voltage falls to zero. n starts at zero when voltage is stepped up, n will relax

exponentially to n = 1, as $n_\infty = 1$. When voltage is turned off, $n_\infty = 0$, and n relaxes exponentially back to zero.

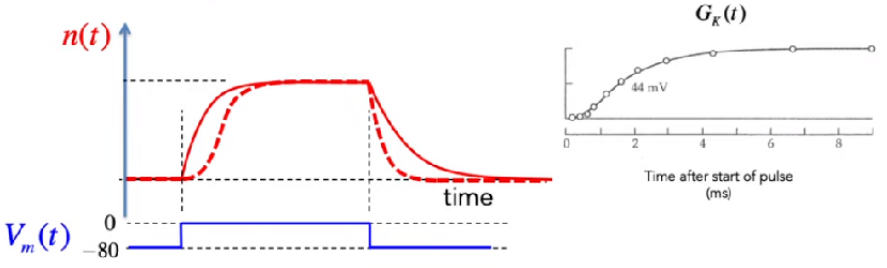


Figure 48: Fitting n^4 gives an exact fit of the variation of G_K with time

Fitting n^4 exactly fits the shape of the conductance curve. It's how H-H inferred G_K is a function of fourth power of gating variable, n. Fourth power means there are 4 independent first-order processes that turn on potassium conductance.

$$G_K(t) \propto n^4$$

Gating variable n relaxes exponentially but the conductance follows n^4

2.8.6 Time dependence of Na channel

Na channel time dependence can be modelled the same way we did for K channel,

Modelling the transition with a simple rate equation:

$$\underset{\text{1-m}}{\text{closed}} \underset{\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} \underset{\text{m}}{\text{open}}$$

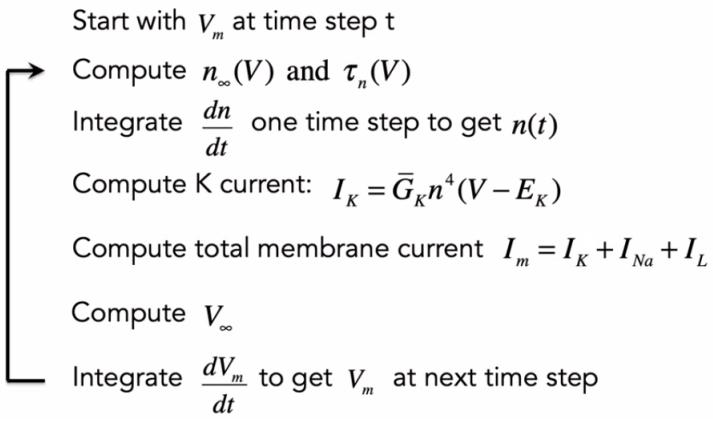


Figure 49: Algorithm for a spike w.r.t K current.

m = gating variable (probability of Na channel being open). α_m and β_m are transition rates, the probability per unit time of going from closed state to open state and vice-versa. They have units of s^{-1}. α_m and β_m are voltage dependent and in turn dependent on the energy difference between closed and open state.

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}$$

$$\tau_m \frac{dm}{dt} = m_\infty - m$$

Figure 50: Similar response of gating varible to volatage for both Na and K conductances

The Na and K conductaces look very similar (refer figure 43). They both have the same kind of the activation gating variable, the same simple model for how they turn on and off, same differential equation, same gating variable that has the sigmoidal dependece on the voltage.

At hyperpolarizing voltages, n_∞ is small, so is m_∞. Ion channels are closed at hyperpolarizing voltages, so the gating variables that represent the probabilities of being open, hence the gating variables are small when the voltage is very negative.

G_K, when cell depolarized, turns ON and stays ON. G_{Na} turns ON and then inactivates (turn OFF).

$$P_{Na} = m^3 h$$

is the probability of a channel being open. h = inacti-

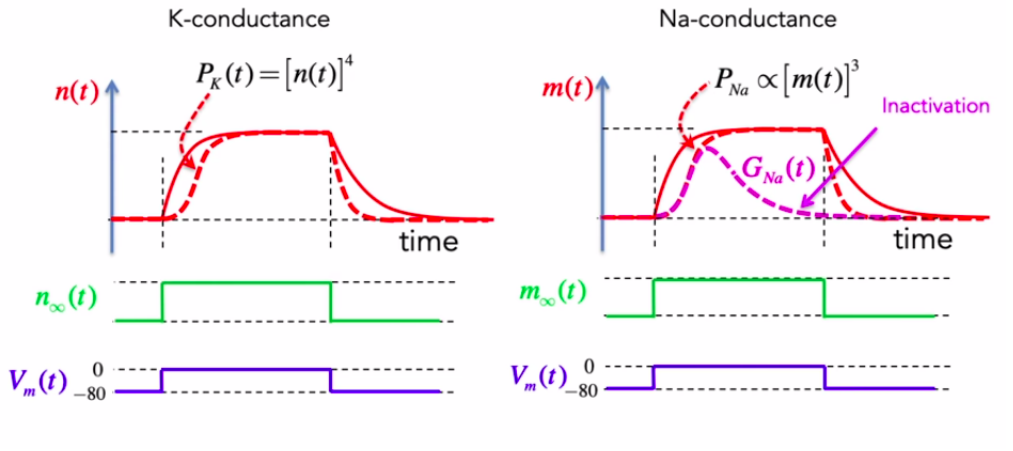


Figure 51

vation gating variable. m= activation gating variable. Fitting m^3 exactly fits the shape of the conductance curve. It's how H-H inferred G_{Na} is a function of third power of gating variable, n. Na channel is a big single protein unit unlike K channel which is tetramer.// h is high initially when the voltage is very negative as the voltage increases h decreases. h related to the dynamics of inactivation particle (see below).

Inactivation particle is a part of the Na channel. When cell is depolarised i.e. V_m becomes more positive, the positively charged inactivation particle falls in and block the pore, and prevents ions from flowing through the ion channel.

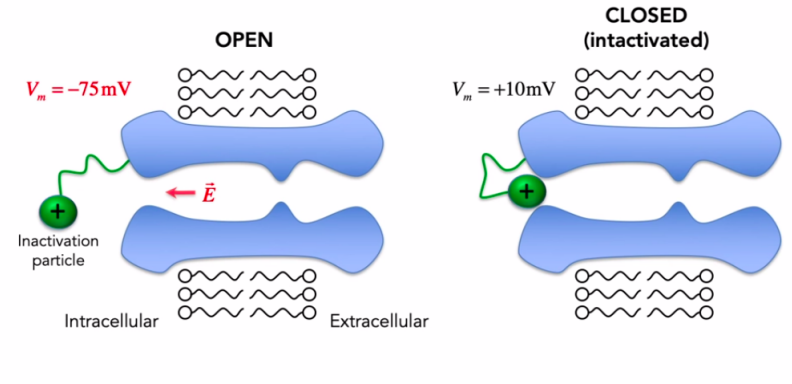


Figure 52

$$\underset{\text{1-h}}{\text{closed}} \underset{\beta_h}{\overset{\alpha_h}{\rightleftharpoons}} \underset{\text{h}}{\text{open}}$$

$$\tau_h \frac{dh}{dt} = h_\infty - h$$

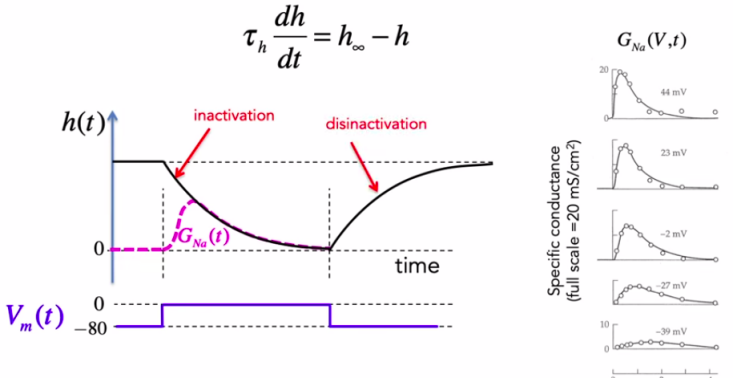


Figure 53

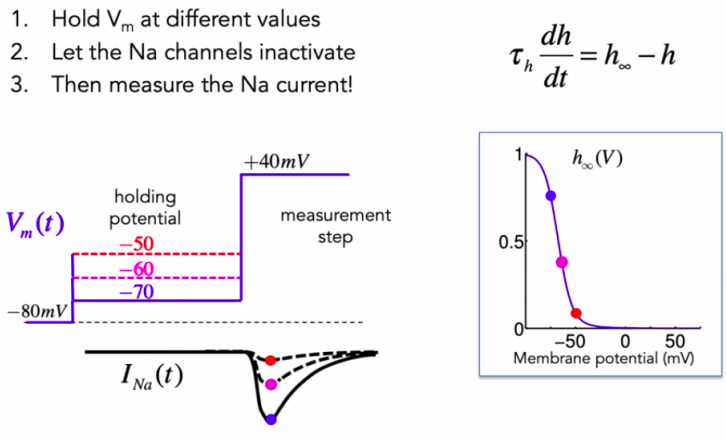


Figure 54

We hold the cell hyperpolarized and we can then step the cell to different membrane potentials, then we jump the membrane potential up, to turn on the activation gating variable, and we can see, depending on where you held the voltage before you did the big voltage step

you get Na current of different sizes. At lower V_m the inactivation particle doesn't block the channel, so stepping voltage from there gives bigger I_{Na}, but if when the potential is increased (-70mV, -60mV,-50 mV,) the inactivation particle blocks the channel, hence stepping voltage up from there gives smaller I_{Na}. We can see h is big fro low voltages and goes to zero fro high voltages. It means that, when the cell spikes the voltage goes up, h starts falling and many of Na channels on cell becomes inactivated.

$$P_{Na} = m^3 h$$

This equation assumes that mechanism for activation and mechanism for inactivation are independent, which is actually not the case.

Sodium conductance and sodium current respectively:

$$\begin{aligned} G_{Na} &= \overline{G_{Na}} m^3 h \\ I_{Na} &= \overline{G_{Na}} m^3 h (V - E_{Na}) \end{aligned}$$

$\overline{G_{Na}}$ is the maximal open conductance

We now have a full description of the K and Na conductances as a function of voltage and time. Let's put everything together:

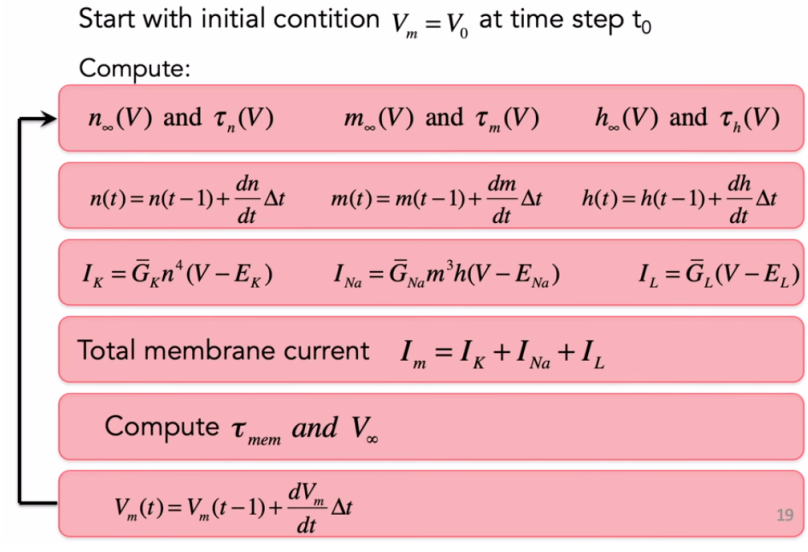

Start with initial contition $V_m = V_0$ at time step t_0
Compute:
$n_\infty(V)$ and $\tau_n(V)$
$m_\infty(V)$ and $\tau_m(V)$
$h_\infty(V)$ and $\tau_h(V)$
$n(t) = n(t-1) + \frac{dn}{dt}\Delta t$
$m(t) = m(t-1) + \frac{dm}{dt}\Delta t$
$h(t) = h(t-1) + \frac{dh}{dt}\Delta t$
$I_K = \bar{G}_K n^4 (V - E_K)$
$I_{Na} = \bar{G}_{Na} m^3 h (V - E_{Na})$
$I_L = \bar{G}_L (V - E_L)$
Total membrane current $I_m = I_K + I_{Na} + I_L$
Compute τ_{mem} and V_∞
$V_m(t) = V_m(t-1) + \frac{dV_m}{dt}\Delta t$
19

Figure 55

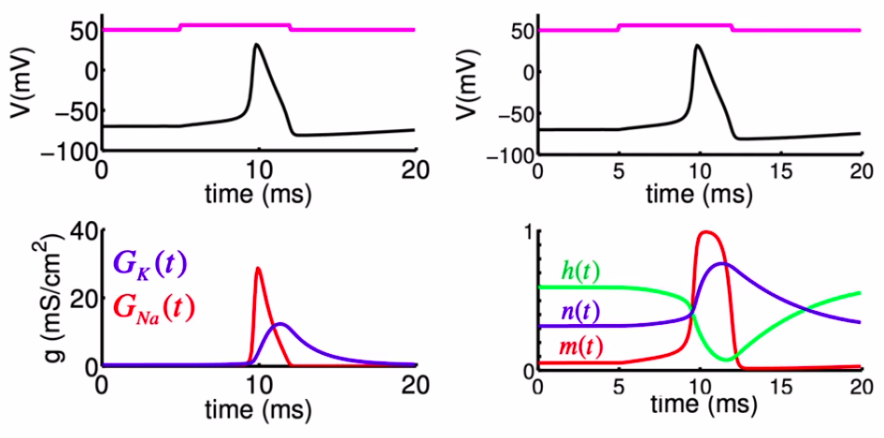


Figure 56

When you inject current, the cell starts to depolarize and m starts to grow. The Na conductance is starting to turn on. At the same time m gets big enough, it's turning on substantial amount of Na current into the cell, it depolarizes the cell more it causes m to grow faster which causes more current into the cell, cell depolarizes more, and m shoots up until the cell voltage reaches the equilibrium potential of Na. Na current stops even though the channel is open.
Meanwhile, n, during the hyperpolarized voltage, the K channel is starting to open, so n grows, K conductance turns on K current out of the cell and that starts hyperpolarizing the cells. During the whole time the inactivation gate -the cell is very depolarized and has very positive voltage- falls in blocking the Na channel.

h drops, shuts off the Na conductance, and K conductance finises bringing the cell back to hyperpolarized state.

Spike refractory period due to Na channel inactivation. Giving back to back current pulse to the cell doesn't give a spike. It is because the inactivation particle of Na channel is still blocking the channel and hasn't had time to fall out yet.

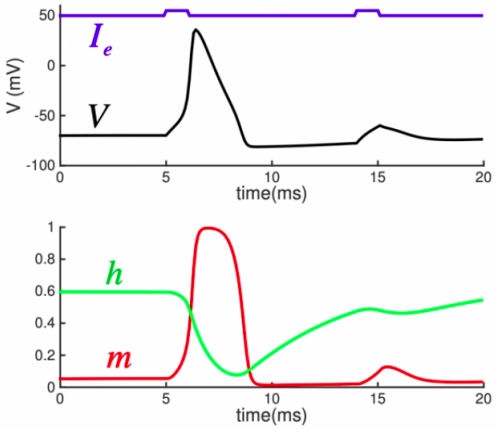


Figure 57