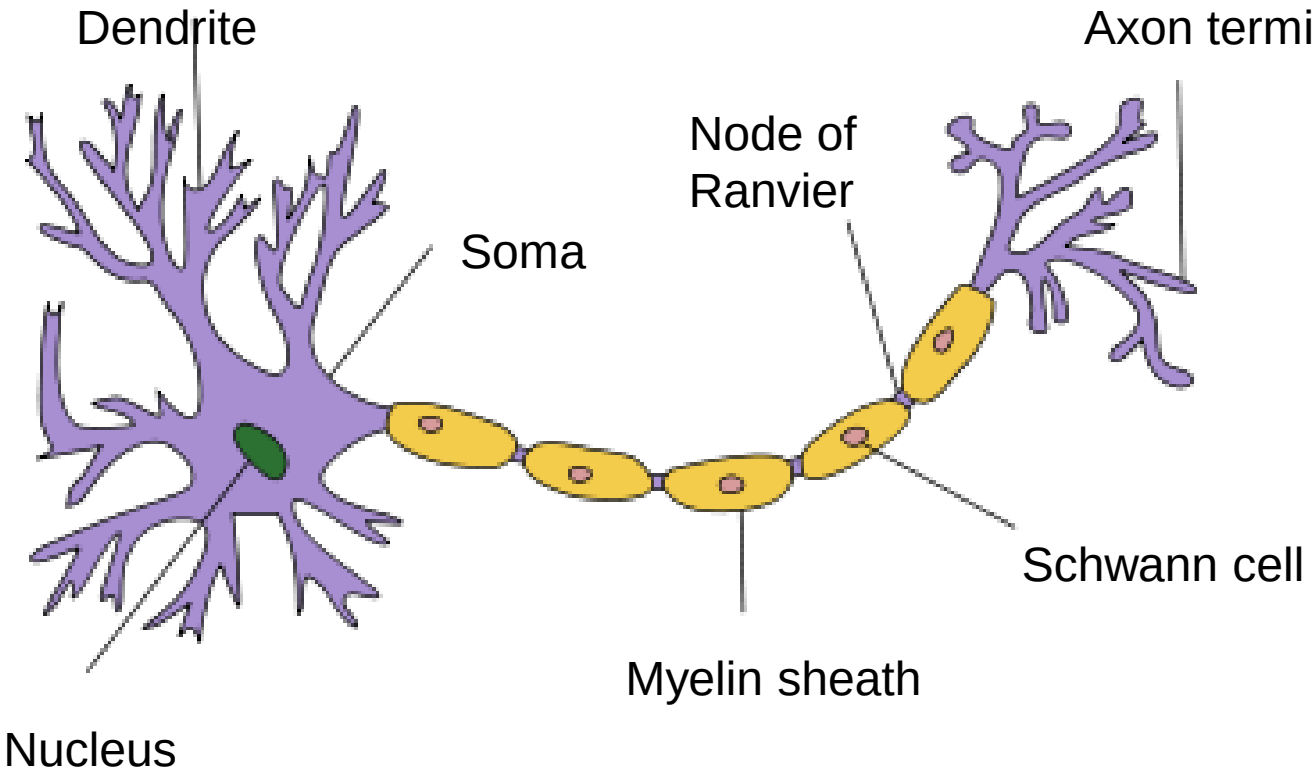
Neurons



Wikipedia

Ion Channels

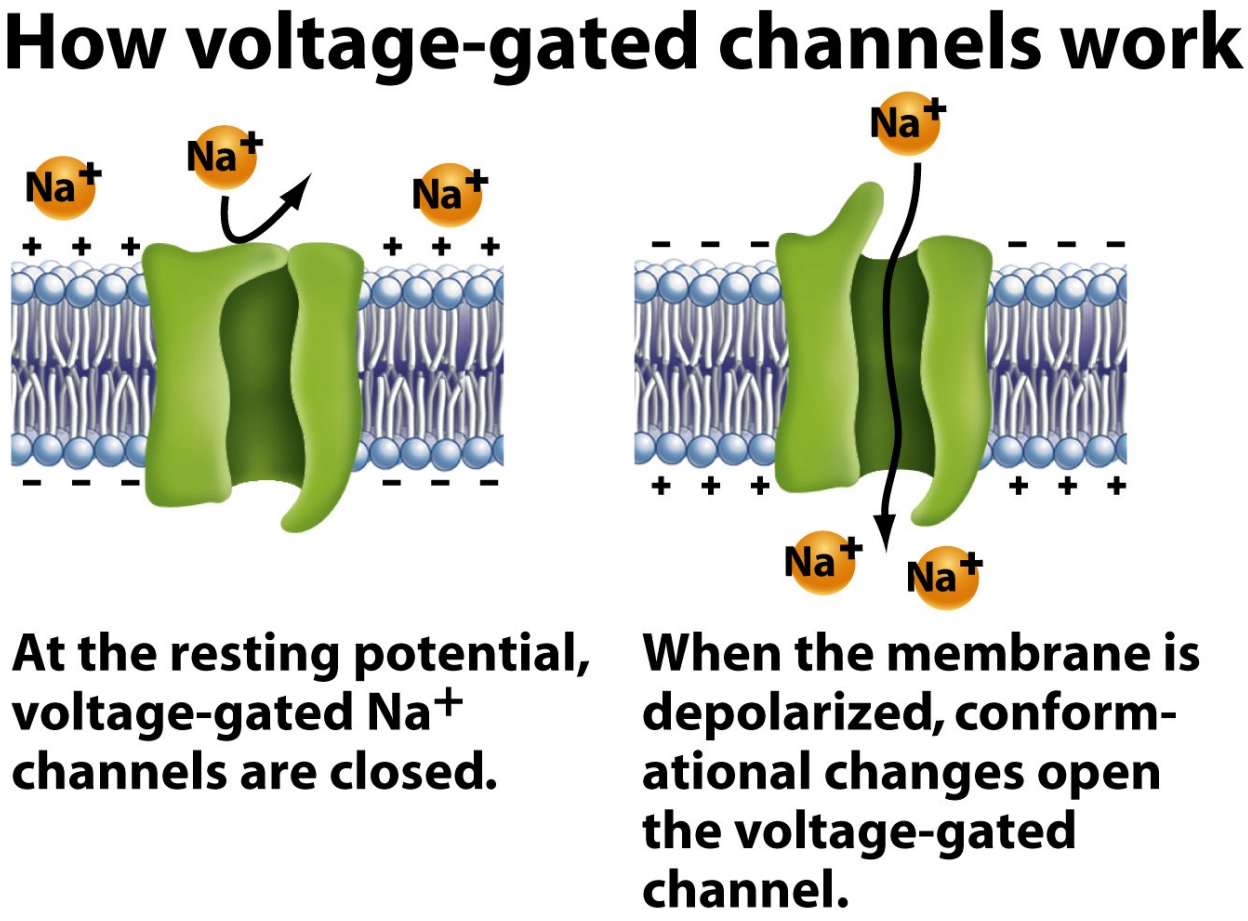
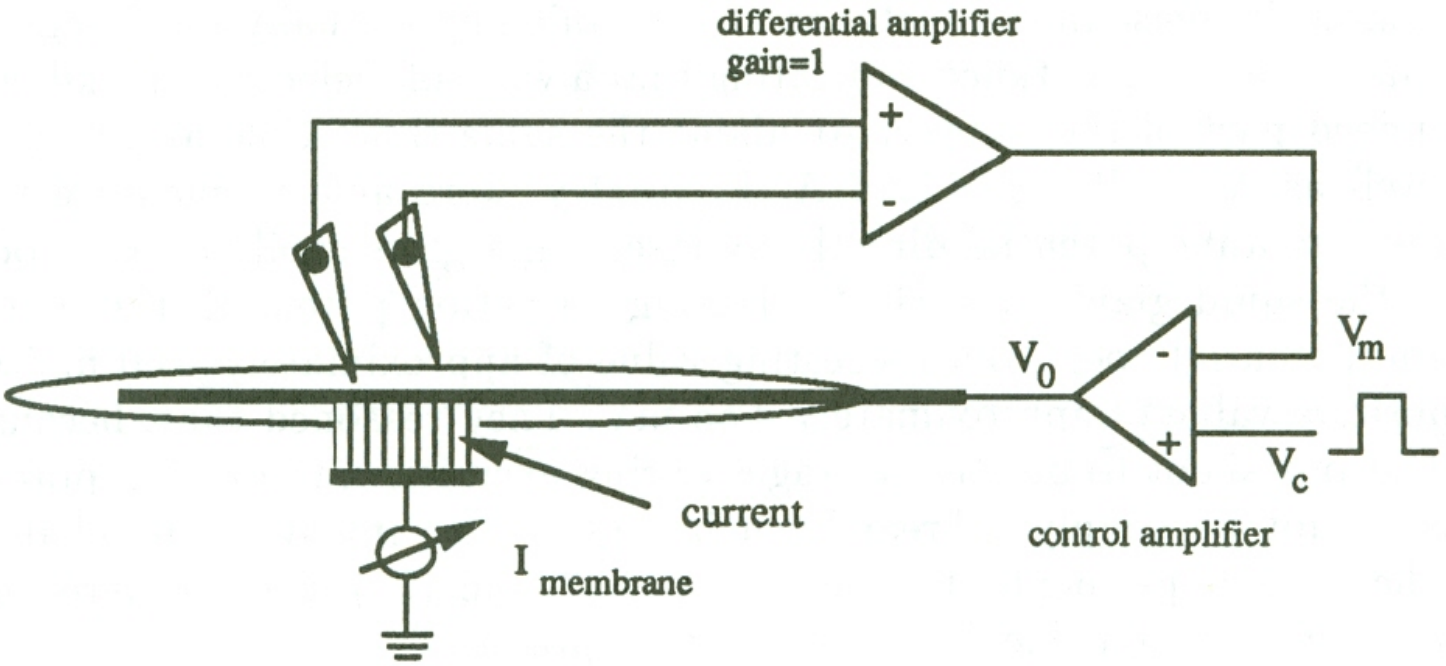


Figure 45-8c Biological Science, 2/e

Number densities of ion channels vary enormously, from $\sim 1 - 10^4\ \mu^{-2}$. A typical number might be about $10 - 100\ \mu\mathrm{m}^{-2}$, or $10^9 - 10^{10}\ \mathrm{cm}^{-2}$.

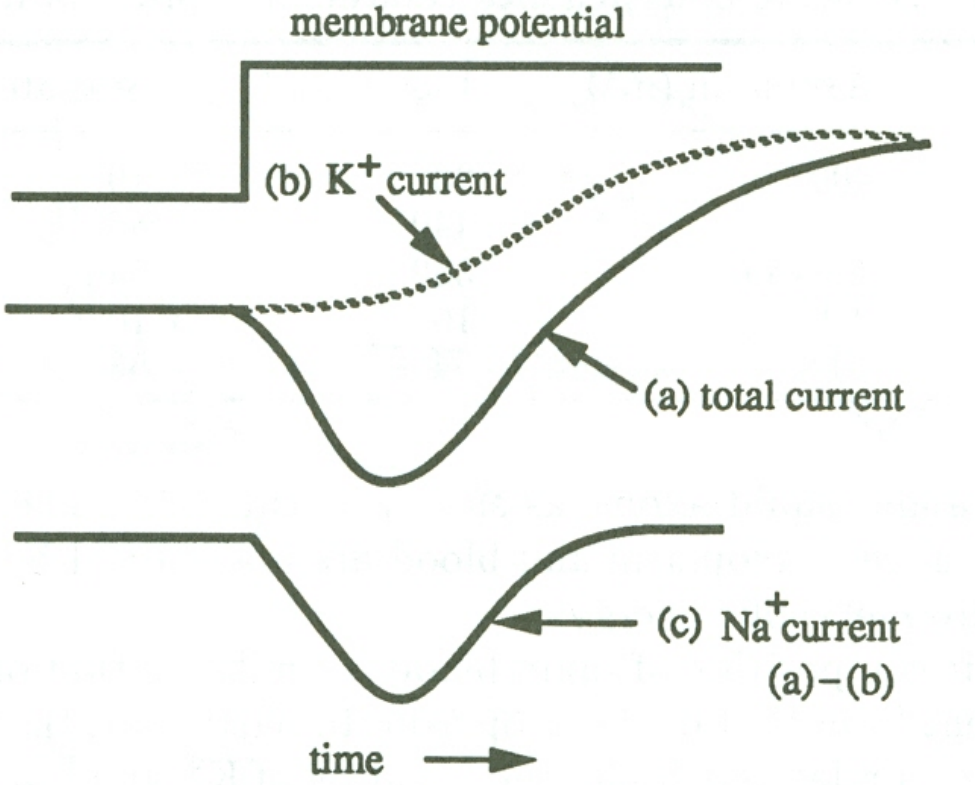
The Voltage Clamp (K.S. Cole)



The *Voltage Clamp* is an electronic device which uses an applied current to maintain a chosen voltage across an excitable membrane while the conductance of the membrane goes throughh transient changes. This is done via feedback loop. A metallic electrode is inserted longitudinally down the centre of the axon. This short-circuits the inner axoplasmic core so that the interior is longitudinally isopotential and curren flow across the membrane is radial. This is called "space clamping".

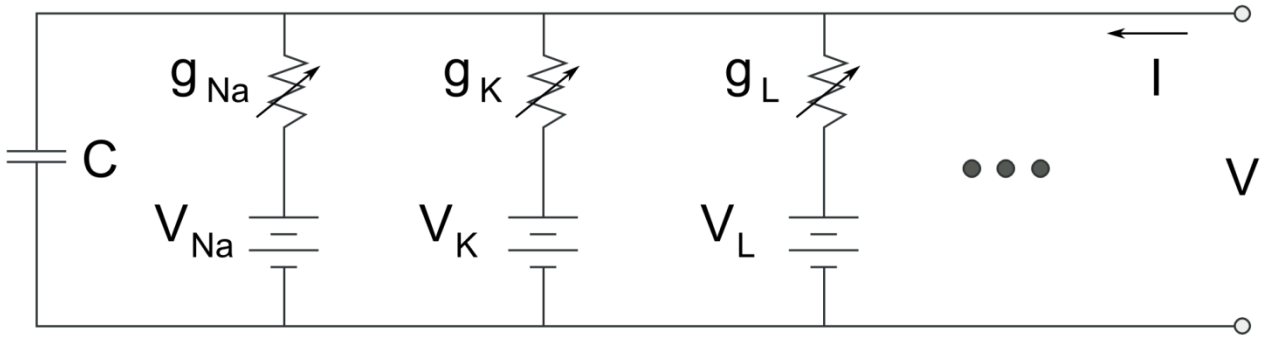
See R. Nossal and H. Lecar, *Molecular & Cell Biophysics* (Addison-Wesley, 1991)

The Essential Results from Voltage Clamp Expts



A change of the membrane potential from its resting value of ~ -60 mV to a "depolarized" value of 0 mV leads to an inward transient current followed by an outward current that reaches a steady state (a). When the outer bathing fluid's Na^+ is replaced by an impermeable ion, only the outward current remains (b), taken to be K^+. Sodium is fast, potassium is slow, and both appear with delays.

Equivalent Circuit



In this model,

$$I = C\frac{\partial V}{\partial t} + I_{\text{ionic}} \ ,$$

where

$$I_{\text{ionic}} = I_{\text{ext}} + g_K\,(V - V_K) + g_{Na}\,(V - V_{Na}) + \cdots + g_{leak}\,(V - V_{leak}) \ ,$$

where $V_K = -72$ mV, $V_{Na} = +55$ mV, $V_{leak} = -50$ mV.
Here, the $g(V)$s are *voltage-dependent conductances* of the ion channels (recall, conductance=1/resistance). Hodgkin and Huxley made semi-phenomenological models of these in terms of putative multiple internal states with V-dependent relaxation kinetics.

More on Hodgkin-Huxley Model

The HH model describes the sodium and potassium conductances as

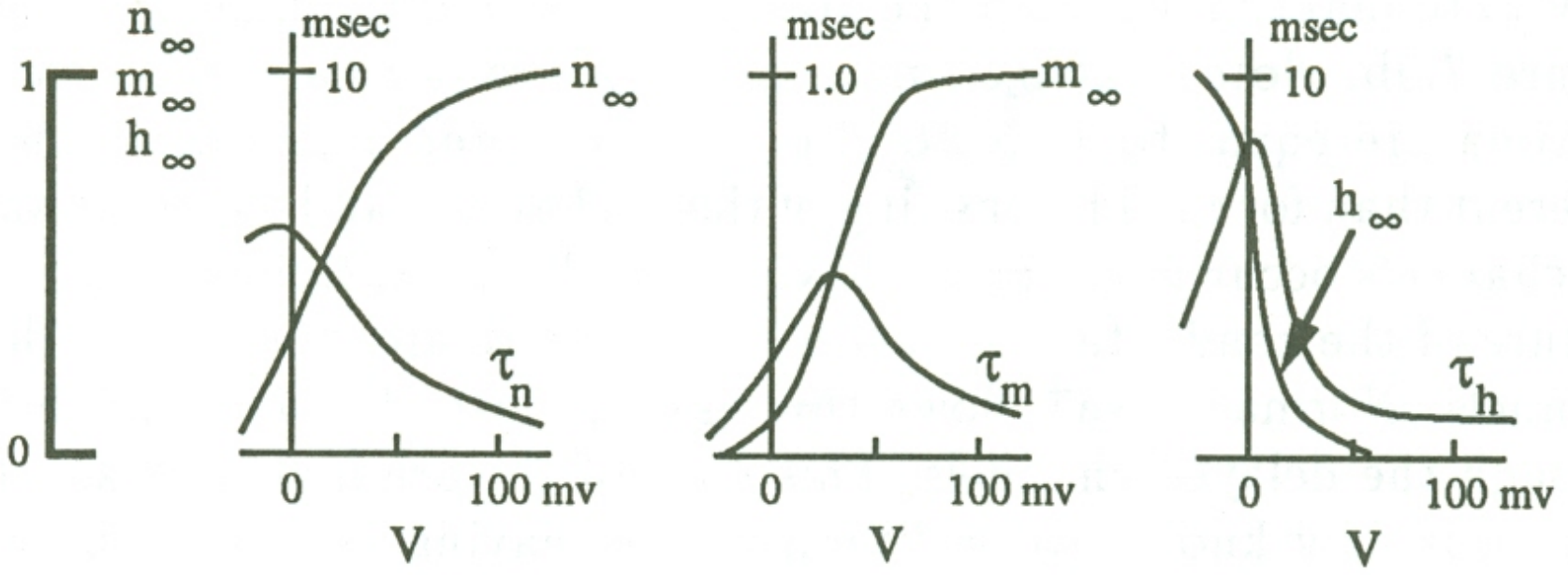
$$g_K = G_K n^4(t) \ , \qquad g_{Na} = G_{Na} m^3(t) h(t) \ ,$$

where $G_K = 36\,\mathrm{mmho/cm^2}$, $G_{Na} = 120\,\mathrm{mmho/cm^2}$ and $g_{leak} = 0.3\,\mathrm{mmho/cm^2}$. The gating kinetics are described by the functions n, m, h that satisfy the dynamics

$$\begin{aligned} \frac{dn}{dt} &= \frac{(n_\infty(V) - n)}{\tau_n(V)} \ , \\ \frac{dm}{dt} &= \frac{(m_\infty(V) - m)}{\tau_m(V)} \ , \\ \frac{dh}{dt} &= \frac{(h_\infty(V) - h)}{\tau_h(V)} \ , \end{aligned}$$

where the various functions are plotted below.

Hodgkin-Huxley Model II



Hodgkin-Huxley Model III

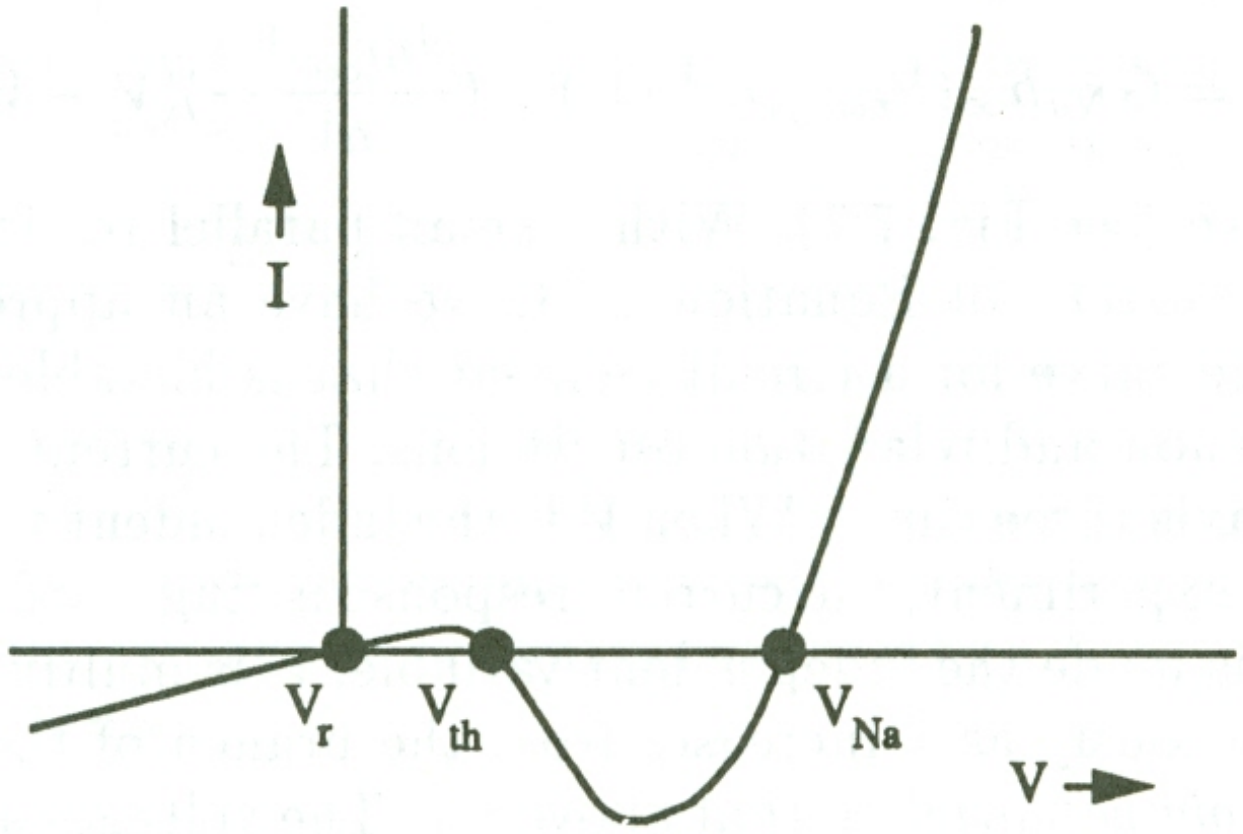
The key point is that the sodium dynamics are much faster than the potassium dynamics. With an inward current of Na^+ that depolarizes the membrane, the Na^+ conductance *increases*. This leads to an even larger inward current that depolarizes the membrane further. This is said to "regenerative". The process continues until the membrane potential approaches V_{Na}, at which point the driving potential $V - V_{Na}$ tends to zero. Now the K^+ pathway begins to open, forcing the membrane potential back to rest.

The feature of producing increasing inward current in response to depolarization is said to entail "negative resistance". This can be seen by exploiting the separation of time scales and setting h and n to their resting values $h_\infty(V_{rest})$ and $n_\infty(V_{rest})$. Then, the peak sodium current is

$$I_{Na}(V) = G_{Na} h_\infty(V_{rest}) m_\infty^3(V) \, (V - V_{Na}) \ ,$$

where $m_\infty(V)$ has the sigmoidal shape we saw earlier. Since $V - V_{Na}$ is negative when $V < V_{Na}$ and $m_\infty(V)$ is positive, I_{Na} has a region in which increasingly positive V causes a steeply increasingly negative current. If $m_\infty(V)$ is steep enough, negative conductance occurs.

Hodgkin-Huxley Model IV



FitzHugh-Nagumo (FHN) Model

The FHN model is a simplification of the Hodgkin-Huxley equations. There are two variables: u, which is related to the membrane potential, and v, which stands for everything else (ions) that tend to bring the system back to its resting state. First, we ignore spatial variations and consider the ODEs for the two variables. u, the *activator* is the fast variable, and v, the *inhibitor*, is slow. With $z(t)$ an applied voltage, the model equations are:

$$\dot{u} = c\left[v + u - \frac{u^3}{3} + z(t)\right] = f(u, v; z)$$
$$\dot{v} = -\frac{(u - a + bv)}{c} = g(u, v) \ ,$$

where $0 < b < 1$, $b < c^2$, and we take $c \gg 1$, and

$$1 - \frac{2b}{3} < a < 1 \ .$$

For $z = 0$, the nullclines are

$$\dot{u} = 0 \to v = \frac{u^3}{3} - u \quad \text{and} \quad \dot{v} = 0 \to v = \frac{a - u}{b} \ .$$

Exercise: verify that the quoted inequalities mean that there exists *one* fixed point $(\overline{u}, \overline{v})$ and it is to the right of the minimum of the $\dot{u} = 0$ nullcline.

FitzHugh-Nagumo (FHN) Model II

Let's look at the stability of the nontrivial fixed point:

$$J = \begin{pmatrix} c(1-\overline{u}^2) & c \\ -1/c & -b/c \end{pmatrix}.$$

Thus, $T = c(1-\overline{u}^2) - b/c$ and $D = -b(1-\overline{u}^2)+1$. We conclude that $D > 0, T < 0$ if $\overline{u} > 1$ (but not only if) and $T > 0$ if $\overline{u} < 1 - b/c^2$. In the former case, we have stability.

Now, suppose a negative voltage is applied as a step, $z = -V_0$. Then the $\dot{u} = 0$ nullcline will be shifted upwards. $[\dot{u} = c\{v + u - u^3/3 + z\}$ has the nullcline $v = -u + u^3/3 - z$. The fixed point will still be stable if $\overline{u} > 1 - b/c^2$. Thus, if V_0 is very small, nothing changes.

But suppose V_0 is big enough that the minimum of the cubic is *higher* than the $z = 0$ fixed point (i.e. $\overline{v} < V_0 - 2/3$), then, if c is large, the trajectory will miss the minimum and go on till it hits the opposite branche, where $\dot{u} = 0$, but $\dot{v}$ will be > 0.

There will be a big negative spike in u. Only one spike if the new equilibrium is stable, or if z is switched off by then, with slow recovery.

But, if z stays on and the equilibrium is unstable (V_0 large enough) you *must* get convergence to a limit cycle, by the P-B theorem. Repeated firing of the neuron while the stimulus is still applied - but not constant jamming because of the slow recovery ("refractory period") along the cubic.

FitzHugh-Nagumo (FHN) Model III

Let's estimate the period of the limit cycle - the time to return after one excursion. You can see from

$$\dot{u} = c\left[v + u - \frac{u^3}{3} + z(t)\right] = f(u, v; z)$$
$$\dot{v} = -\frac{(u - a + bv)}{c} = g(u, v)$$

that when $f(u, v; z) \neq 0$, $\dot{u}$ will be large (note c in front of the RHS), so the jump from the minimum at $u = 1$ across to the left hand branch for $u < 0$ will be quick. But once on that nullcline the rate of change of v will be slow - because $c \gg 1$. Therefore the period will be approximately twice the time it takes to go from P_1 to P_2.

On the $f = 0$ nullcline we have

$$c\dot{v} = -u + a - bv \ ,$$

where $v = u^3/3 - u$ (letting $z = 0$). This gives $\dot{v} = (u^2 - 1)\dot{u}$, or

$$c(u^2 - 1)\dot{u} = -\frac{bu^3}{3} - (1 - b)u + a \ .$$

FitzHugh-Nagumo (FHN) Model III

Hence the time from P_1 to P_2 is

$$\int_{P_1}^{P_2} dt = c \int_{-2}^{-1} du \frac{(u^2-1)}{-bu^3/3-(1-b)u+a}$$

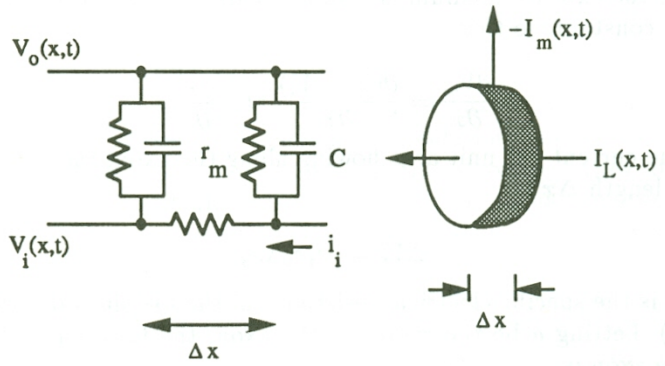
$= c\times$ an $\mathcal{O}(1)$ number if a and b are $\mathcal{O}(1)$

See Matlab file FHN.m

Action Potentials I

Let $V_{\rm in}(x,t)$ and $V_{\rm out}(x,t)$ be the interior and exterior voltages associated with a cylindrical neuron, and $V_m(x,t) = V_{\rm out} - V_{\rm in}$. As the exterior medium is (typically) a good conductor, we can take $V_{\rm out}$ to be constant. Thus,

$$\frac{\partial V_m}{\partial x} = -\frac{\partial V_i}{\partial x} \ .$$



Now let i be the current/area along the axon whose radius is a, and r be the electrical resistance (ohm-cm) of the axoplasmic core. In a small section of width Δx we have Ohm's law "$V = IR$", where $R = r\Delta x/\pi a^2$:

$$\Delta V_{\rm in} = -\frac{I}{\pi a^2} r \Delta x = -ir\Delta x \ .$$

Hence, $\partial V_{\rm in}/\partial x = -ir$. Now, the total (longitudinal) current flowing down the axon is $I_L = \pi a^2 i = -(\pi a^2/r)\partial V_{\rm in}/\partial x$, but by continuity the *inward* membrane current I_m satisfies $2\pi a I_m \Delta x = \Delta I_L$, or

$$I_m = \frac{1}{2\pi a}\frac{\partial I_L}{\partial x} = -\frac{a}{2r}\frac{\partial^2 V_{\rm in}}{\partial x^2} \ .$$

Action Potentials II

Now, suppose we have a passive cable, where the current density across the membrane would be V_m/r_m, with r_m the product of the membrane resistivity and thickness (thus having units of ohm-cm^2). Since I_m is defined as positive for an inward current we have

$$\frac{V_m}{r_m} = \frac{a}{2r}\frac{\partial^2 V_m}{\partial x^2} \quad \text{or} \quad \boxed{\frac{\partial^2 V_m}{\partial x^2} = \frac{1}{\lambda^2} V_m \ ,}$$

where $\lambda = (r_m a/2r)^{1/2}$ is a characteristic length. For a point-forcing,

$$\boxed{V_m(x) = V_m(0)\mathrm{e}^{-|x|/\lambda} \ .}$$

For the giant squid axon, $a \simeq 0.02$ cm, $r_m \simeq 2 \times 10^3$ Ω-cm^2, $r \simeq 50$ Ω-cm, so $\lambda \sim 5$ mm. Thus, a signal spreading *passively* would be degraded by cable losses before it could go an appreciable distance. Need some kind of regenerative mechanism.

Let us return to the relationship $I_m = (a/2r)\partial^2 V_m/\partial x^2$ and note that we can write $I_m = C\partial V_m/\partial t + I_{\rm ionic}$, where $I_{\rm ionic}$ represents all the other cross-membrane current contributions from ion channels. Then,

$$\boxed{\frac{a}{2r}\frac{\partial^2 V_m}{\partial x^2} = C\frac{\partial V_m}{\partial t} + I_{\rm ionic}(V_m, t) \ ,}$$

which is a nonlinear diffusion equation (!), also known as a cable equation. C is a capacitance per unit area, so $a/(2rC)$ is a diffusion constant (!).