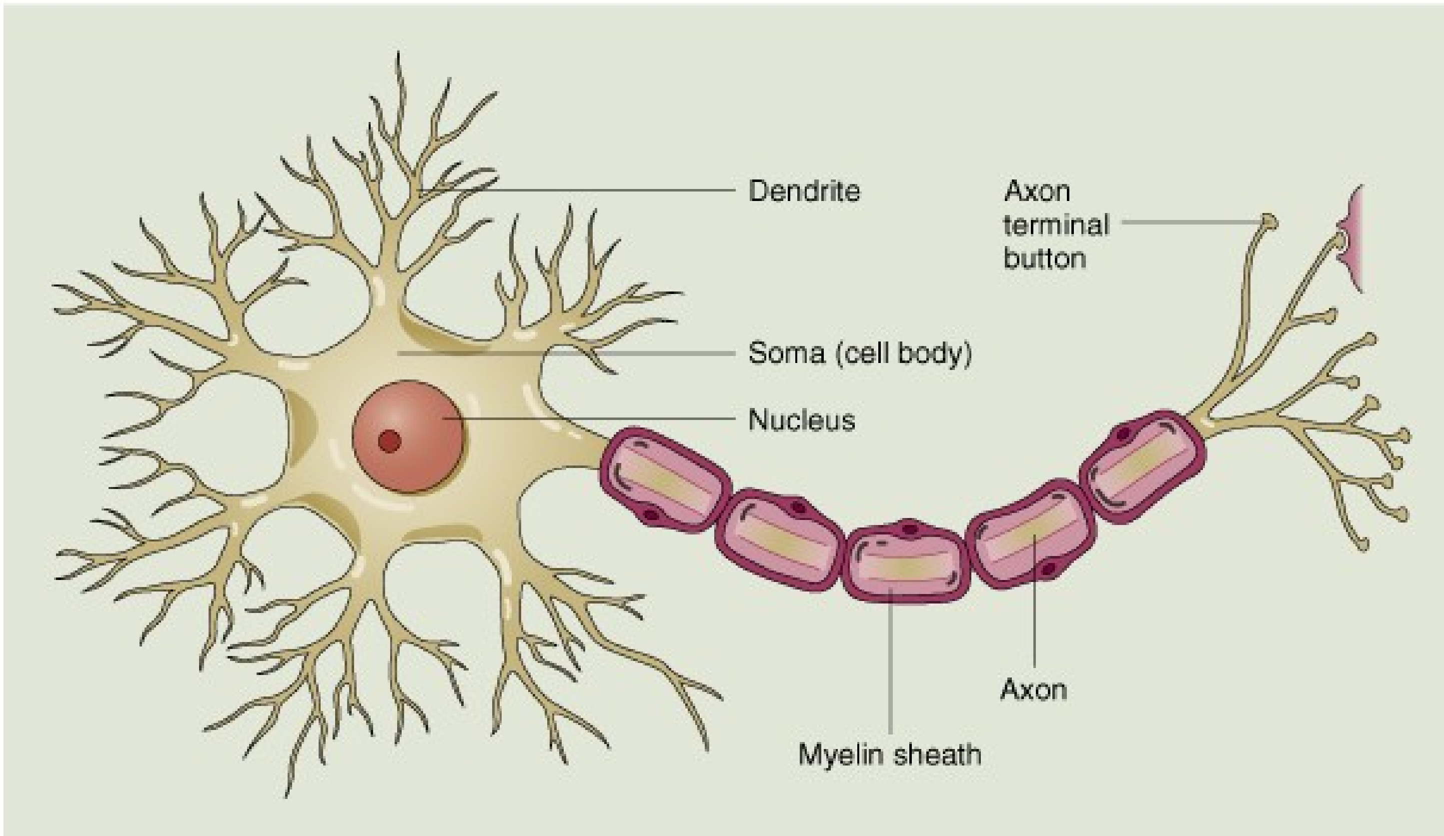


Mathematical model of Neuron conduction

Neurons Neurons are cells in the brain and other subsystems of nervous system. Neurons are typically composed of a soma(cell body), a dendritic tree and an axon.
Soma can vary in size from 4 to 100 micrometers (10^{-6}) in diameter. The soma is the central part of the neuron. It contains the nucleus of the cell, and therefore is where most protein synthesis occurs. The nucleus ranges from 3 to 18 micrometers in diameter.
Dendrites of a neuron are cellular extensions with many branches. The overall shape and structure of a neuron's dendrites is called its dendritic tree, and is where the majority of input to the neuron occurs.
Axon is a finer, cable-like projection which can extend tens, hundreds, or even tens of thousands of times the diameter of the soma in length. The axon carries nerve signals away from the soma (and also carry some types of information back to it).

The nerve axon of the giant squid is nearly a millimeter thick, significantly larger than any nerve cells in humans. This fact permits researchers, neuroscientists in particular, to study the various aspects of nerve cell form and function with greater ease.

Action potential: The propagation of a nerve signal is electrical in nature; after being initialized at axon hillock (the part of the axon where it emerges from the soma), propagates down the length of the axon to the terminal branches, which form loose connections with neighboring neurons. A propagated signal is called an action potential.

It is known that neuronal signals travel along the cell membrane of the axon in the form of a local voltage difference across the membrane.

Cell membrane In the rest state, cells have an ionic composition that differ from that of their environment. Active transport maintains a lower sodium Na^+ and a higher potassium K^+ concentration inside the cell, which makes the cell interior slightly negative in electric potential (-50) mV difference) with respect to the outside. Such a potential difference is maintained as a metabolic expense to the cell by active pumps on the membrane, which continually transport sodium ion Na^+ to the outside of cell and potassium ion K^+ inward.

	Squid giant axon	frog sartorius muscle	human red blood cell
Intracellular			
Na^+	50	13	19
K^+	397	138	136
Extracellular			
Na^+	437	110	155
K^+	20	2.5	5

Mechanism of action potential

0. A potential difference is raised to about -30 to -20 mV at the axon hillock in response to an integrated appraisal of excitatory input impinging on the soma.

1. Sodium channels open, Na^+ ions enter the cell interior. This causes the membrane potential to depolarize (inside becomes positive w.r.t. outside, the reverse of resting-state polarization.)

2. After a slight delay, the potassium channels open, K^+ ions leave the cell. This restores the original polarization, but further causes an overshoot of the negative rest potential.

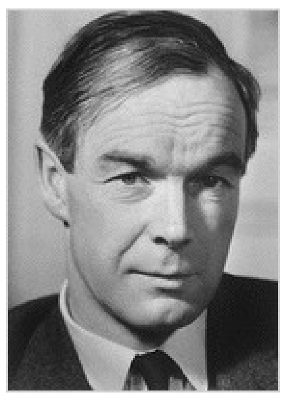
3. The sodium channels then close in response to a decrease in the potential difference.

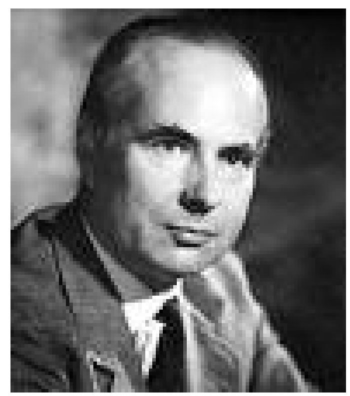
4. Adjacent to a site that has experienced these events the potential difference exceeds the threshold level necessary to set in motion step 1. The process repeats, leading to a spatial conduction of the spike-like signal.

`http://www.biology.eku.edu/RITCHISO/301notes2.htm`

Hodgkin, A., and Huxley, A. (1952): A quantitative description of membrane current and its application to conduction and excitation in nerve. Journal of Physiology 117:500544.

Alan Lloyd Hodgkin(1914-1998), and Andrew Fielding Huxley (1917-) won the 1963 Nobel Prize in Physiology or Medicine for their work on the basis of nerve action potentials, the electrical impulses that enable the activity of an organism to be coordinated by a central nervous system. Hodgkin and Huxley shared the prize that year with John Carew Eccles, who was cited for research on synapses. Hodgkin and Huxley's findings led the pair to hypothesize the existence of ion channels, which were isolated only decades later. Confirmation of ion channels came with the development of the patch clamp, which led to a Nobel prize in 1991 to Erwin Neher and Bert Sakmann.





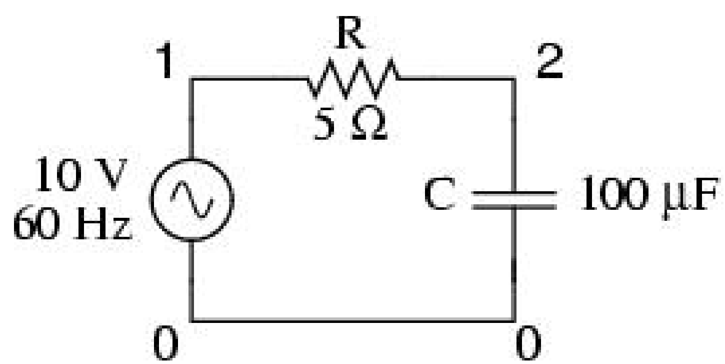
The experimental measurements on which the pair based their action potential theory represent one of the earliest applications of a technique of electrophysiology known as the voltage clamp. The second critical element of their research was the so-called giant axon of the Atlantic squid (*Loligo pealei*), which enabled them to record ionic currents as they would not have been able to do in almost any other neuron, such cells being too small to study by the techniques of the time. The experiments took place at the University of Cambridge beginning in the 1930s and continuing into the 1940s, after interruption by World War II. The pair published their theory in 1952. In the paper, they describe one of the earliest computational models in biochemistry, that is the basis of most of the models used in Neurobiology during the following four decades.

`http://en.wikipedia.org/wiki/Hodgkin-huxley_model`

Electric-circuit and axonal membrane

ionic conductivity $\leftrightarrow$ electric circuit resistor

voltage across the membrane $\leftrightarrow$ voltage across resistors

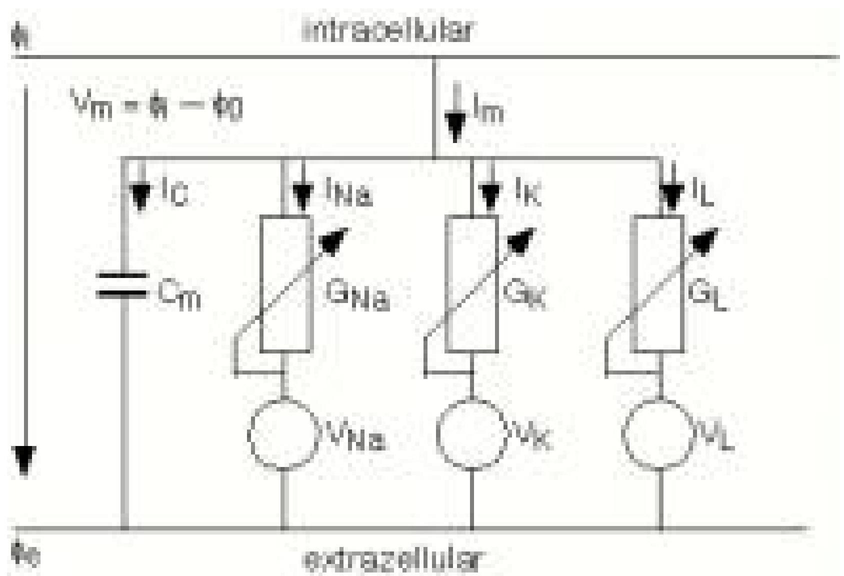


RC (Resistor-Capacitor) circuit

RC circuit (Math 302 or Physics ?)
$q(t)$: total charge; $I(t) = q'(t)$: current; $V(t)$: voltage
R: resistance (property of a material that tends to impede the flow of charged particles)
$g = 1/R$: conductance
C: capacitance (property that tends to separate physically one group of charged particles from another)

Ohm's law: the voltage drop across a resistor is proportional to the current through the resistor $V_R(t) = RI(t) = Rq'(t)$
Faraday's law: the voltage drop across a capacitor is proportional to the electric charge $V_C(t) = q(t)/C$
Kirchhoff law: the voltage supplied is equal to the total voltage drops in the circuit. $V(t) = V_R(t) + V_C(t)$.

Differential equation: $RC\dfrac{dq(t)}{dt} + q(t) = CV(t)$



g_K, g_{Na} and g_L: resistance to ionic flow across the membrane
C: capacitance of membrane

Variables in the model:

x: the length of axon, assume $-\infty < x < \infty$; t: time

$q(x,t)$=charge density inside the axon at location x and t

$I_i(x,t)$=net rate of exit of positive ions from the exterior to the interior of the axon per unit membrane area at (x,t)

$v(x,t)$=departure from the resting voltage of the membrane at (x,t)

Now fix x at one point, we only record the change with respect to the time at this point, so functions are not dependent on x.

$$\frac{dq}{dt} = -2\pi a(I_{Na} + I_K + I_L), \quad q(t) = 2\pi a C v(t)$$

$$\frac{dv}{dt} = -\frac{1}{C}(I_{Na} + I_K + I_L)$$

$$= -\frac{1}{C}[g_{Na}(v)(v - v_{Na}) + g_K(v)(v - v_K) + g_L(v)(v - v_L)]$$

Mathematical work: data fitting

Hodgkin and Huxley assume g_L is a constant, but g_{Na} and g_K are not. They define three hypothetical quantities n, m and h (they suggested that n, m and h are voltage-sensitive gate proteins). Then $g_{Na} = \bar{g}_{Na} m^3 h$, and $g_K = \bar{g}_K n^4$,
and n, m and h satisfy some differential equations (!):

$n'(t) = \alpha_n(v)(1-n) - \beta_n(v)n$,

$m'(t) = \alpha_m(v)(1-m) - \beta_m(v)m$,

$h'(t) = \alpha_h(v)(1-h) - \beta_h(v)h$,

$\alpha_n(v) = 0.01(v+10)(e^{(v+10)/10} - 1)^{-1}$, $\beta_n(v) = 0.125e^{v/80}$

$\alpha_m(v) = 0.01(v+25)(e^{(v+25)/10} - 1)^{-1}$, $\beta_m(v) = 4e^{v/18}$

$\alpha_h(v) = 0.07e^{v/20}$, $\beta_h(v) = (e^{(v+30)/10} + 1)^{-1}$

Hodgkin-Huxley model:

$$v'(t) = -\frac{1}{C}[\overline{g}_{Na}m^3h(v - v_{Na}) + \overline{g}_K n^4(v - v_K) + g_L(v - v_L)]$$
$$n'(t) = \alpha_n(v)(1 - n) - \beta_n(v)n,$$
$$m'(t) = \alpha_m(v)(1 - m) - \beta_m(v)m,$$
$$h'(t) = \alpha_h(v)(1 - h) - \beta_h(v)h,$$

where

$\alpha_n(v) = 0.01(v + 10)(e^{(v+10)/10} - 1)^{-1}$, $\beta_n(v) = 0.125e^{v/80}$
$\alpha_m(v) = 0.01(v + 25)(e^{(v+25)/10} - 1)^{-1}$, $\beta_m(v) = 4e^{v/18}$
$\alpha_h(v) = 0.07e^{v/20}$, $\beta_h(v) = (e^{(v+30)/10} + 1)^{-1}$
and $\overline{g}_{Na} = 120$, $\overline{g}_K = 36$, $g_L = 0.3$, $v_{Na} = -115$, $v_K = 12$, and $v_L = -10.5989$

Numerical simulation of HH-model was a great success!

FitzHugh's simplification of HH-model (1960)

1. The change of n and h are very slow, but the change of v and m are fast, so assuming n and h are constants, then:

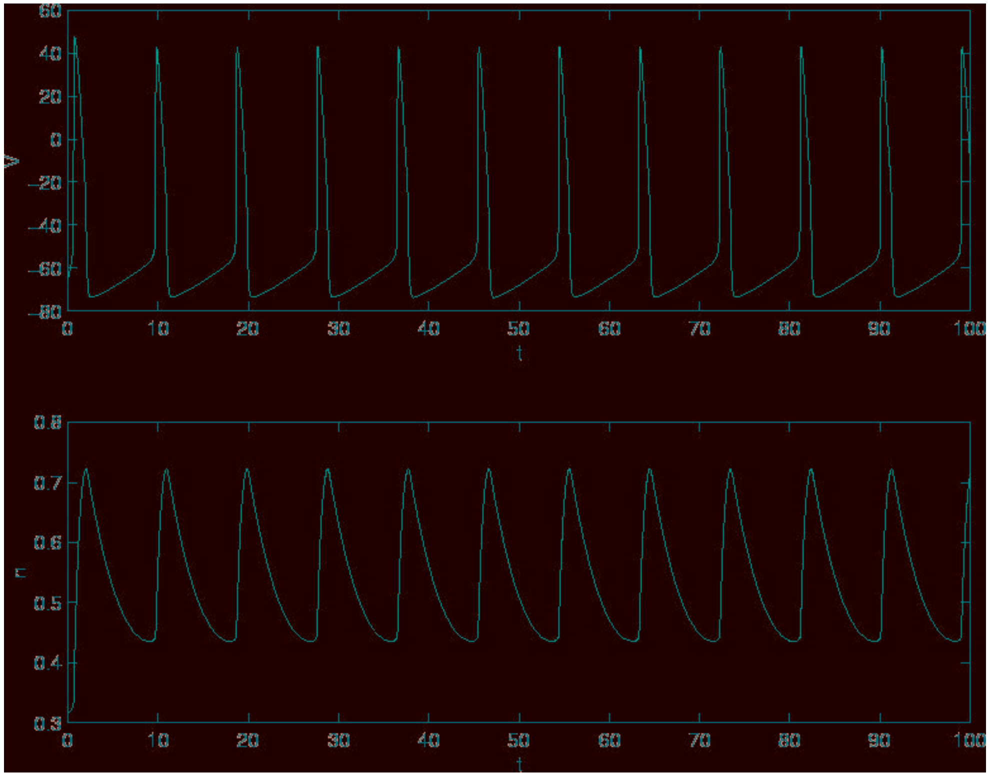
$$v'(t) = -\frac{1}{C}[\overline{g}_{Na}m^3h_0(v - v_{Na}) + \overline{g}_K n_0^4(v - v_K) + g_L(v - v_L)]$$
$$m'(t) = \alpha_m(v)(1 - m) - \beta_m(v)m.$$

Then $m(t) \to m_\infty = \dfrac{\alpha_m(v)}{\alpha_m(v) + \beta_m(v)}$

2. $h + n \approx 0.8$, and use $m(t) \approx m_\infty$, we get

$$v'(t) = -\frac{1}{C}[\overline{g}_{Na}m_\infty^3(0.8 - n)(v - v_{Na}) + \overline{g}_K n^4(v - v_K) + g_L(v - v_L)]$$
$$n'(t) = \alpha_n(v)(1 - n) - \beta_n(v)n,$$

FitzHugh's simplified 2-D equation



FitzHugh-Nagumo equation: a simpler system but retain many of qualitative features of Hodgkin-Huxley system (and the simplified 2-d system of FitzHugh) FitzHugh (1961), Nagumo et. al. (1962)

$$\epsilon \frac{dv}{dt} = v(v-a)(1-v) - w, \quad \frac{dw}{dt} = v - bw - c.$$

$v(t)$ is the excitability of the system (voltage),
$w(t)$ is recovery variable representing the force that tends to return the resting state

Excitability: small perturbation will return to resting state quickly, and a larger perturbation will cause a full circle going around before returning to the resting state.

Case 1: $\epsilon = 0.01$, $a = 0.1$, $b = 0.5$ and $c = 0$
Equilibrium $(0, 0)$ stable

Case 2: $\epsilon = 0.01$, $a = 0.1$, $b = 0.5$ and $c = 0.1$
Equilibrium $(0, 0)$ unstable, and a periodic solution

How about $v(x, t)$? we will see in the last week.......
traveling wave solution