The Hodgkin-Huxley Model (1952)

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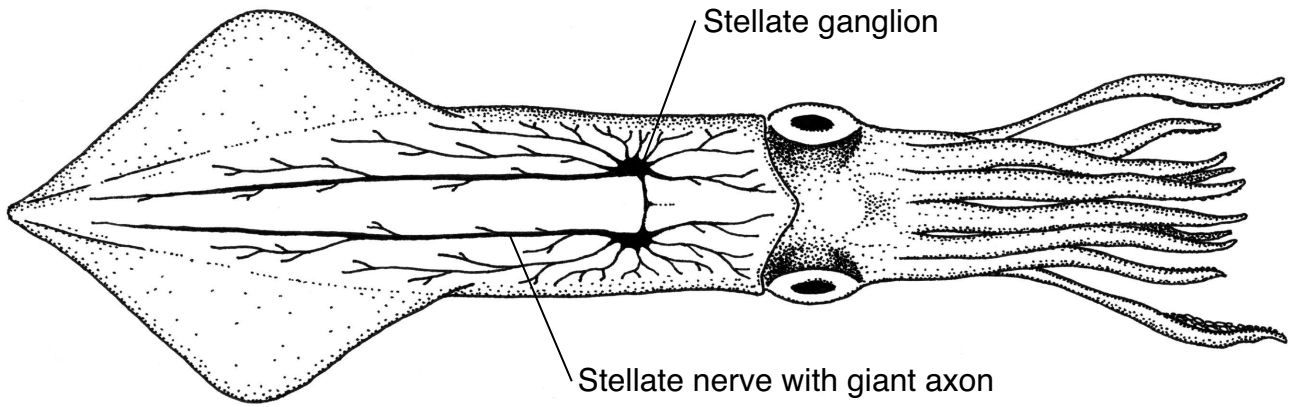
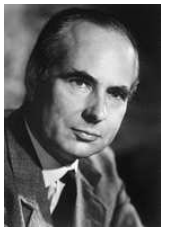


Introduction

Hodgkin

The HH model reproduces the dynamics of the membrane potential and of the ionic currents for the squid giant axon (1952).



Huxley

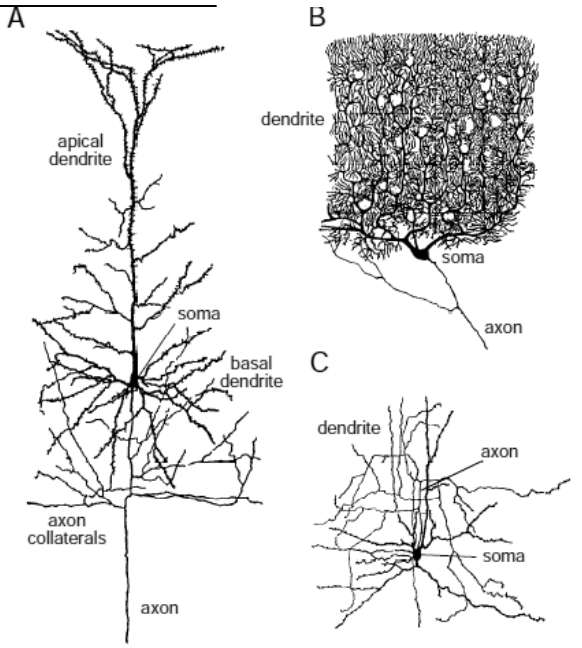
In 1952 Hodgking and Huxley (and Katz) published 5 fundamental papers which clarified how the action potentials are generated and developed a model which is considered the most successful in Neuroscience. In 1963 H & H have been awarded with the Nobel Prize for this research.

Plan

- The rest potential
- The Action Potentials
- Ionic Currents
- The Hodgkin-Huxley Model
- The Fitz-Hugh-Nagumo Model

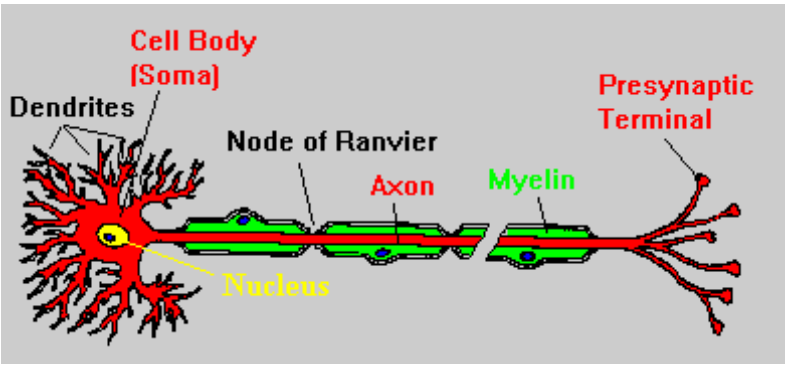
Neurons are different but. . .

- A) Cortical pyramidal neuron
- B) Purkinje cell of the cerebellum
- C) Stellate cell of the enthorinal cortex



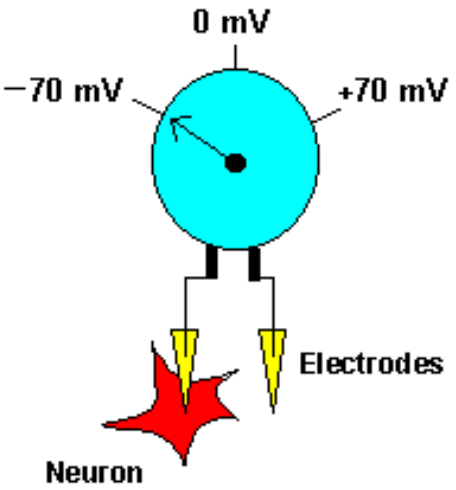
However, three parts (morphologically and functionally) distinct can be always identified:

- A) Soma or cell body (CPU)
- B) Dendrides (INPUT)
- C) Axon (OUTPUT)

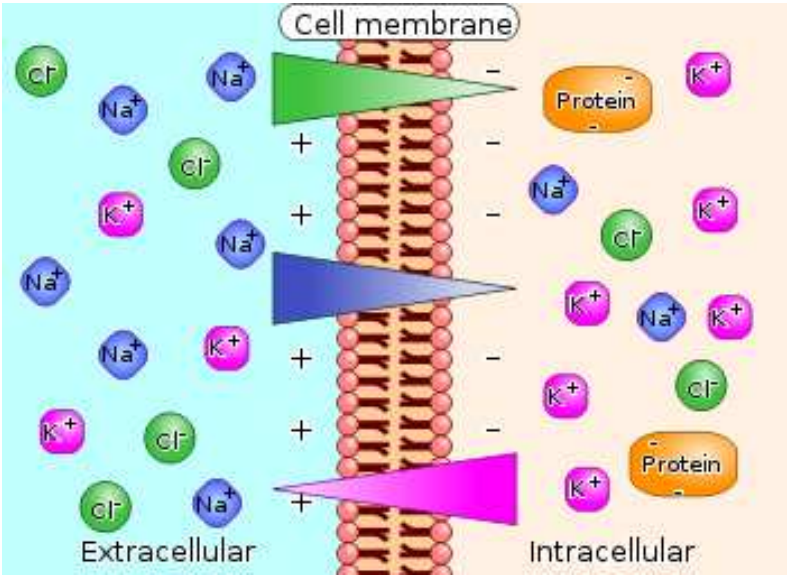


Which are the signals transporting information among neurons ?

Membrane Potential



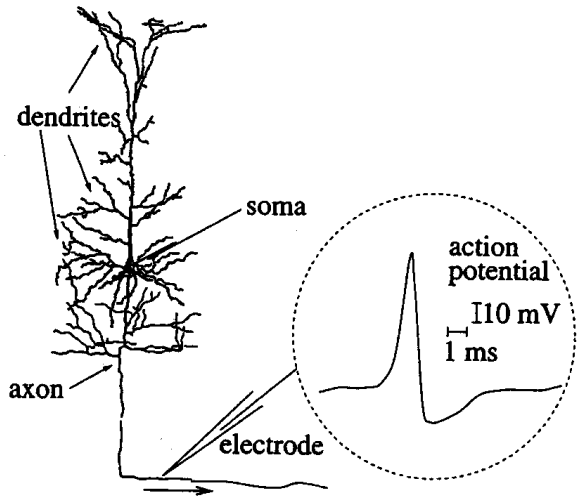
- The membrane potential V_m measures the electrical potential difference between interior and exterior of the neuron.
- The neuron at rest has $V_m \simeq$ -60mV / -75 mV



The neuron is an dynamical equilibrium state

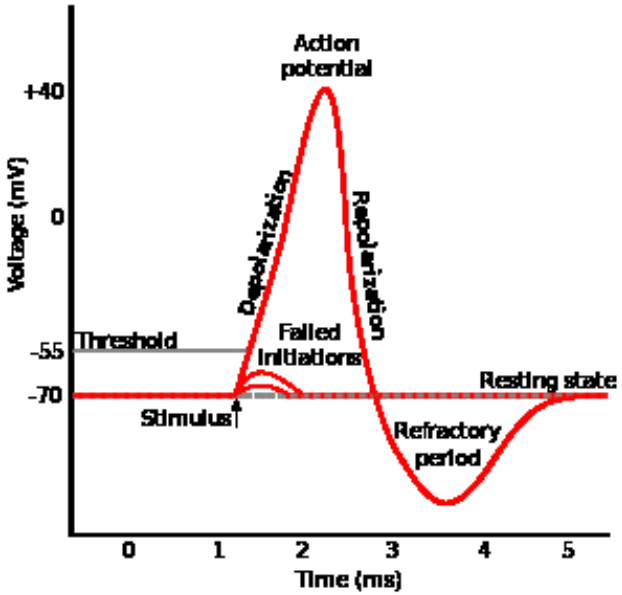
Action Potential

The elementary unit of information transmitted in neural circuits is the Action Potential (AP)



- The neuronal signal is given by the temporal and spatial variation of V_m.
- The action potentials (APs) are electrical impulses delivered when a (depolarizing) stimulus leads V_m above a threshold $\Theta \sim -55$ mV

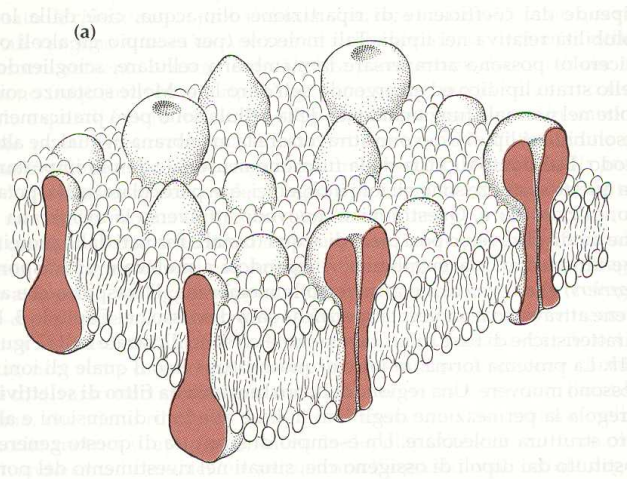
- The AP lasts 1-2 ms and it has an amplitude of 100-120 mV
- Refractory Period: it is a phase of 10 ms (corresponding to membrane hyperpolarization) occuring after the AP emission

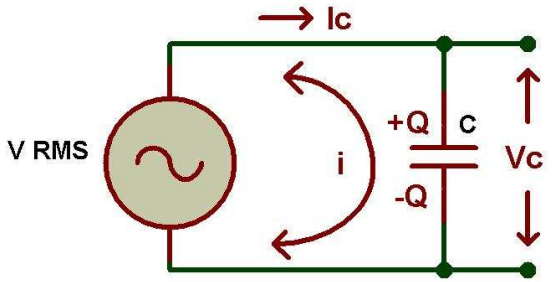


Cellular Membrane

The membrane is made by lipid molecules and proteins.
The membrane skeleton is composed by a double layer of fosfolipids with hydrophilic heads pointing towards the cell interior and exterior. This membrane is an insulating layer of 30-50 A dividing the charges inside and outside the cell.

The charge separation is at the origin of the potential difference between inside and outside of the cell.
Therefore the membrane acts as a capacitance , accumulating charges on its two sides





$$Q = CV_c$$

$$I_c = \frac{dQ}{dt} = C\frac{dV_c}{dt}$$

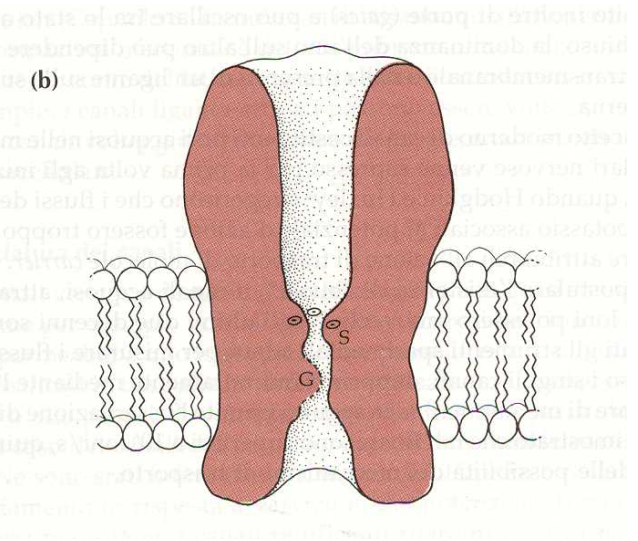
Ionic Channels

In the lipid matrix are inserted proteins that cross all the cellular membrane and they are in contact with both the interior and exterior of the cell. This are called protein channels
They ions (Na^+, K^+, Ca^{++} e Cl^-) can cross the membrane in two different ways

- active : by binding to specific molecules transport molecules (ionic pumps)
- passive : via the ionic channels or (pores) - this is the prevailing mechanism during the AP generation

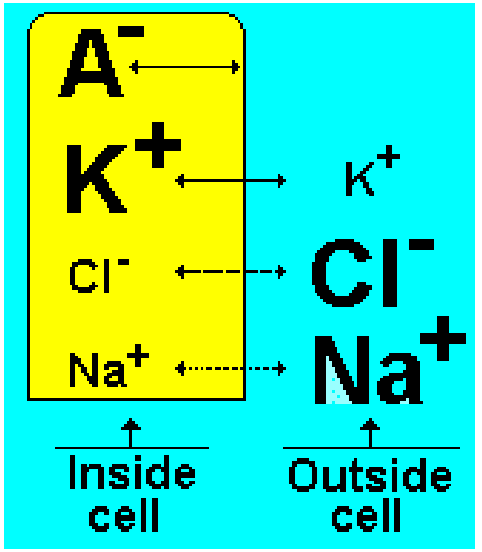
The ionic channels are made of :

- a central pore filled of water;
- a selective filter regulating the ions transit in terms of their dimension and chemical-physical characteristics;
- a system of gates which open or close in stochastic manner, however the closed state usually prevail when V_m is at his rest value.



Origin of the rest potential

A simplified model for the cell



- The cell contais ions to which the mebrane is permeable (Na^+, K^+, Ca^{++}, Cl^-)
- The ions have higher concentration outside the cell, apart for K^+
- Each ion use a specific ionic channel to cross the membrane

The ions tend to cross the membrane due to

- the concentration gradient which induces a movement from the more to the less dense areas;
- the electrical potential difference present across the membrane.

The equilibrium potential of a ion is the value of the membrane potential V_m for which there is no net flux of such ion across the membrane

K^+ tends to leave the cell following the concentration gradient, while the rest membrane potential tends to ostacolate this motion, the opposite is true for Cl^-

Origin of the rest potential

Equilibrium Potentials

The equilibrium potential of each species is related to the ionic concentrations intra- and extracellular ($[n]_e$ and $[n]_i$) via the Nerst Equation:

$$E_{ion} = \frac{kT}{q} \ln \frac{[n]_e}{[n]_i}$$

$k = 1.3810^{-23} J/K$ is the Boltzmann constant; T the temperature in Kelvin; q the charge of the ion n Coulomb

Derivation

- From the statistical mechanics the probability density $p(U)$ of have a system at thermal equilibrium T with total energy U is given by $\boxed{p(U) \propto \mathrm{e}^{-\frac{U}{kT}}}$ with $p(U)dU$ being the probability that the systems has an internal energy in the interval $[U; U + dU]$;
- The energy of a ion of positive charge $q > 0$ in a point x within an electric field is $U(x) = qV(x)$, where $V(x)$ is the electric potential in the point x;
- The probability density $p(U(x))$ will be clearly proportional to the ionic concentration (density) $[n(x)]$

Origin of the rest potential

Derivation

- Therefore

$$\frac{p(U(x_1))}{p(U(x_2))} = \frac{[n(x_1)]}{[n(x_2)]} = \mathrm{e}^{\frac{-q[V(x_1)-V(x_2)]}{kT}} = \mathrm{e}^{\frac{-q\Delta V}{kT}}$$

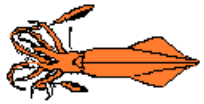
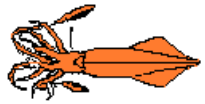
- Finally we get the Nernst equation $\boxed{\Delta V = \frac{kT}{q} \ln \frac{[n]_2}{[n]_1}}$

The Nerst Equation for the Equilibrium potential of a ionic species $\Delta V = E_{ion}$:

$$E_{ion} = \frac{kT}{q} \ln \frac{[n]_e}{[n]_i}$$

- $k = 1.3810^{-23} J/K$ is the Boltzmann constant
- T in Kelvin
- q in Coulom
- E_{ion} in mVolt
- $[n]$ in Mol (1 Mol contains $N_A = 6.02214076 \times 10^{23}$ ions)

Origin of the rest potential


Squid giant axon


His diameter is 1 mm, against 70 μm for mammals, therefore it is easier to insert an electrode to measure the potential differences (Huxley, 1964)

$$K^+ \quad [n]_i = 400mM \quad [n]_e = 20mM \quad E_{K+} = -75mV$$

$$Na^+ \quad [n]_i = 50mM \quad [n]_e = 440mM \quad E_{Na+} = +55mV$$

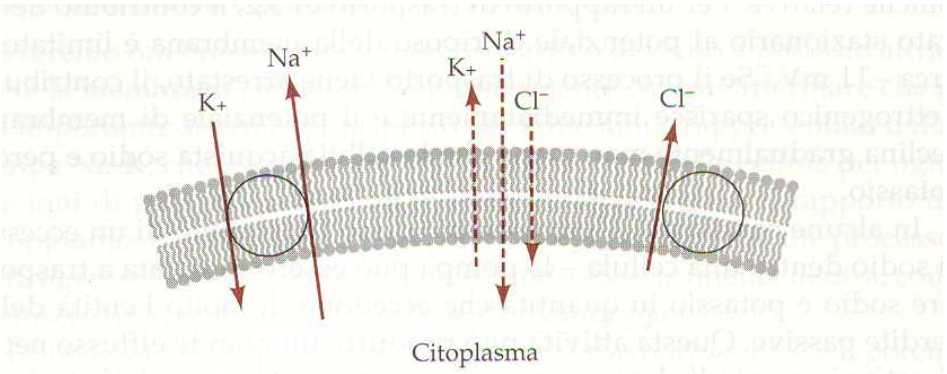
$$Cl^- \quad [n]_i = 40mM \quad [n]_e = 560mM \quad E_{Cl-} = -66mV$$

$$Ca^{++} \quad [n]_i = 10^{-4}mM \quad [n]_e = 10mM \quad E_{Ca++} = +145mV$$

Is all so simple ?

Origin of the rest potential

The sodium-potassium pump



Na^+ is much more concentrated outside the cell, furthermore since at rest V_m is negative, Na^+ can freely enter the cell

The inflow of Na^+ depolarizes slightly the membrane with respect to the equilibrium potential of K^+, which is no more equlibrated and now it can flow outside the neuron

To maintain the equilibrium are needed active mechanisms of the cell to renintegrate the lost ions: the ionic pumps

The most known is the pump Na-K which for every three ions of Na^+ pumped out, it pumps in two ions K^+.

Many other pumps exists, therefore the cell is always in a dynamical equilibrium

Origin of the rest potential

The membrane permeability

The complex mechanisms for the mobility of each species are encompassed empirically by introducing a membrane permeability p specific for each ion

$$J = -p\Delta[C]$$

where J is the molar flux and $\Delta[C]$ is the difference of the ionic concentration between the two side of the membrane.

The rest potential

The rest potential can be finally estimated by considering the permeability with some reasonable physical assumption as follows [D.E. Goldman (1943), A.L. Hodgkin e B. Katz (1949)]:

$$V_{rest} = \frac{kT}{q} \ln \frac{p_k[K^+]_e + p_{Na}[Na^+]_e + p_{Cl}[Cl^-]_i}{p_k[K^+]_i + p_{Na}[Na^+]_i + p_{Cl}[Cl^-]_e};$$

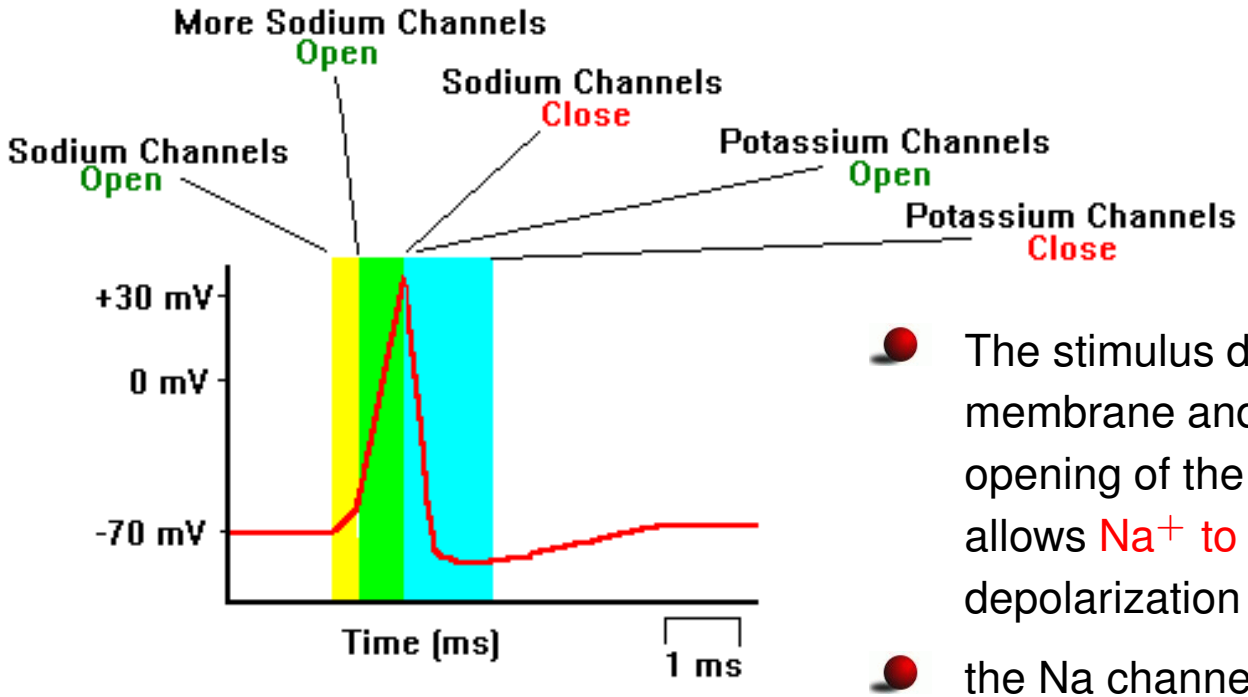
where q is the ion charge and p_k, p_{Na}, p_{Cl} are the ionic permeability for each species.

For the squid giant axon $p_k : p_{Na} : p_{Cl} = 1 : 0.03 : 0.1$ one finds $V_{rest} = -70$ mV in good agreement with the experiments and not far from $E_{K^+} = -75mV$.

Action Potential

Activation and Deactivation of the Channels

An excitatory stimulus DEPOLARIZES the membrane potential from rest $V_{rest} = -70$mV above the threshold $\Theta = -55$ mV $\rightarrow$ an AP or a SPIKE is emitted



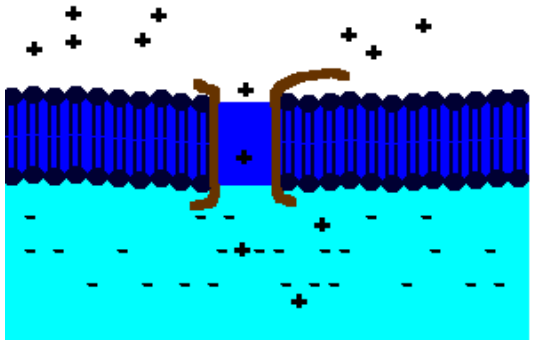
$[Na^+]_e >> [Na^+]_i$ $[K^+]_e << [K^+]_i$

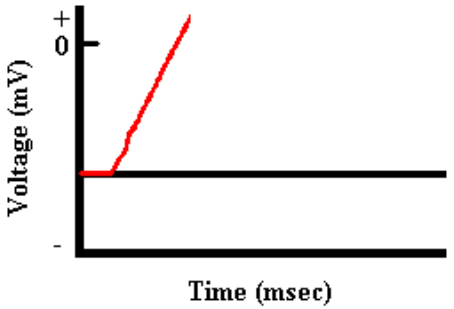
- The stimulus depolarizes the membrane and this leads to an opening of the Na channels, this allows Na^+ to enter the cell, the depolarization increases;
- the Na channels are then inactivated ;
- with a certain delay the K channels are activated this leads to the exit of K^+ and to the repolarization of the membrane

Action Potential

Membrane depolarization and repolarization

Depolarization

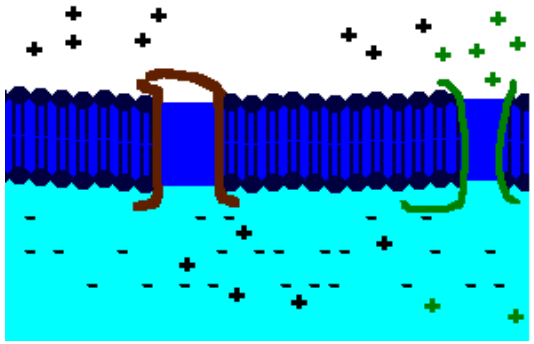


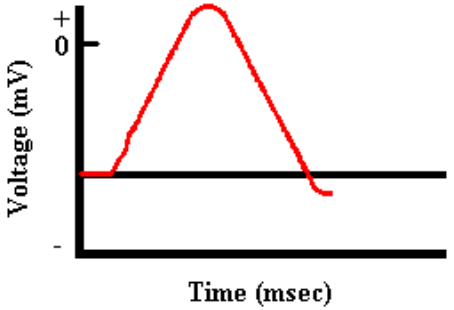


Na^+ enters in the neuron

$V_m \rightarrow E_{Na+} = +55$ **mV**

Repolarization

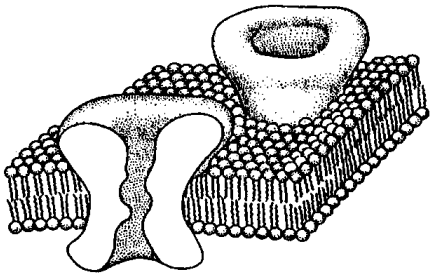


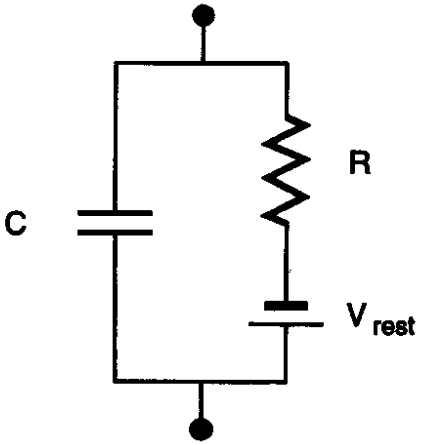


K^+ leaves the cell

$V_m \rightarrow E_{K+} = -75$ **mV**

Membrane as an Electric Circuit



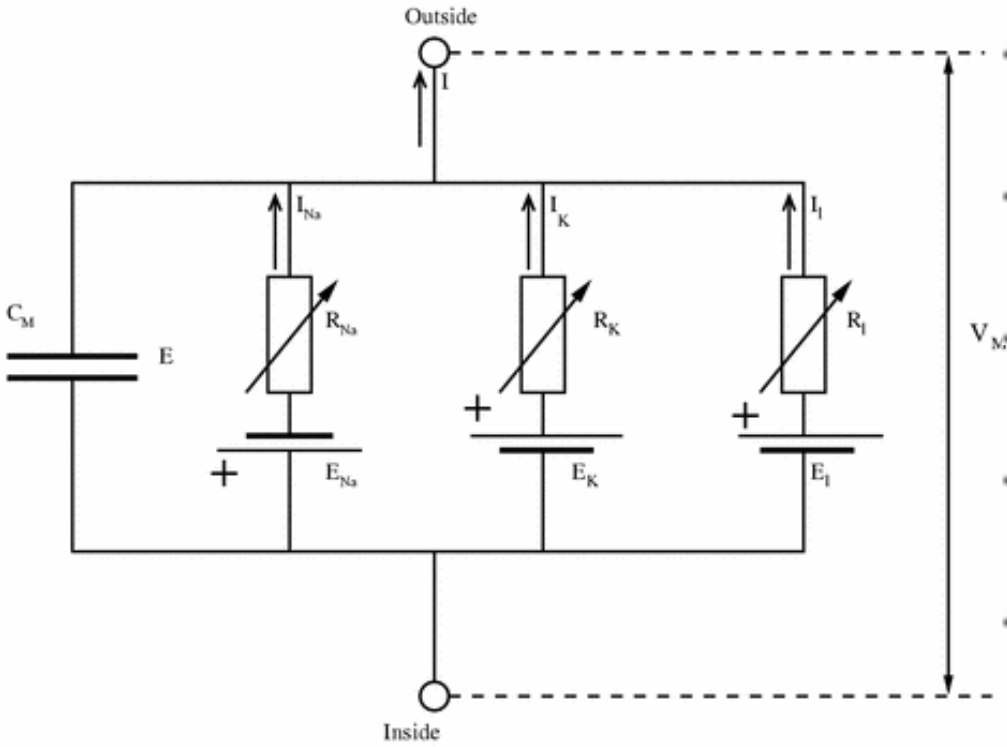


The membrane can be seen as an electric circuit with passive characteristics

- the membrane separates positive and negative charges, it acts as a capacitance
  $C_m \simeq 1\mu F/cm^2 \rightarrow 4x10^{11}$ monovalent ions/cm^2
- the ionic channels have specific membrane resistance/conductance :
  Leakage Resistance $R_m \simeq 10^3 \Omega \cdot cm^2$
  Leakage Conductance $G_m = 1/R_m \simeq mS/cm^2$
- V_{rest} can be seen as a voltage generator
- the membrane is also active , e.g. the ionic pumps , and highly nonlinear (some conductance depends on V_m)

Action Potential

Membrane as an electric circuit for AP generation



- Scheme for a piece of membrane
- Kirchhoff's Current Law
  $I(t) = I_C + I_{Na} + I_K + I_L$
- Capacitive current
  $I_C = dQ/dt = CdV/dt$
- Ionic currents I_{Na} e I_K (Nonlinear)
- Leakage Current (Linear)

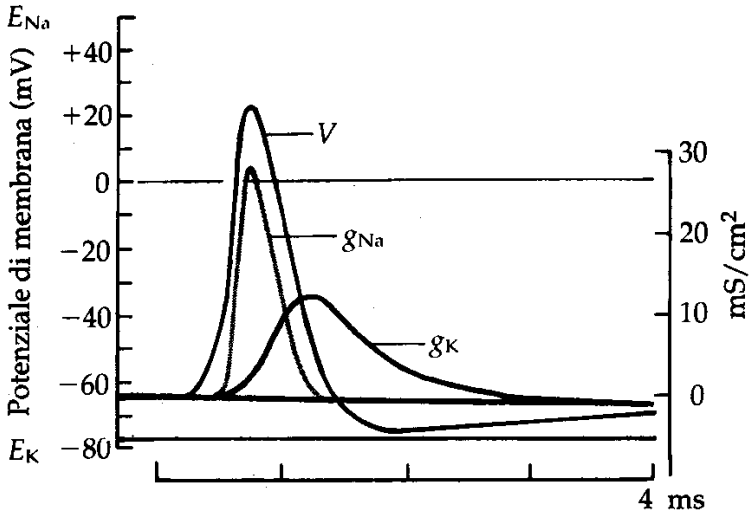
$$C\frac{dV_m}{dt} = -I_{Na} - I_K - I_L + I(t)$$

Action Potential

Currents and conductances

For the AP generation in the squid giant axon only 3 currents are relevant:

- sodium current $I_{Na} = g_{Na}(V_m - E_{Na})$ —- $g_{Na} = \frac{1}{R_{Na}} = g_{Na}(V_m)$
- potassium current $I_K = g_K(V_m - E_K)$ —- $g_K = \frac{1}{R_K} = g_K(V_m)$
- leakage current $I_L = g_L(V_m - E_L)$ this is mainly associated to the ion Cl^-, but it includes the effect of other minor ionic currents

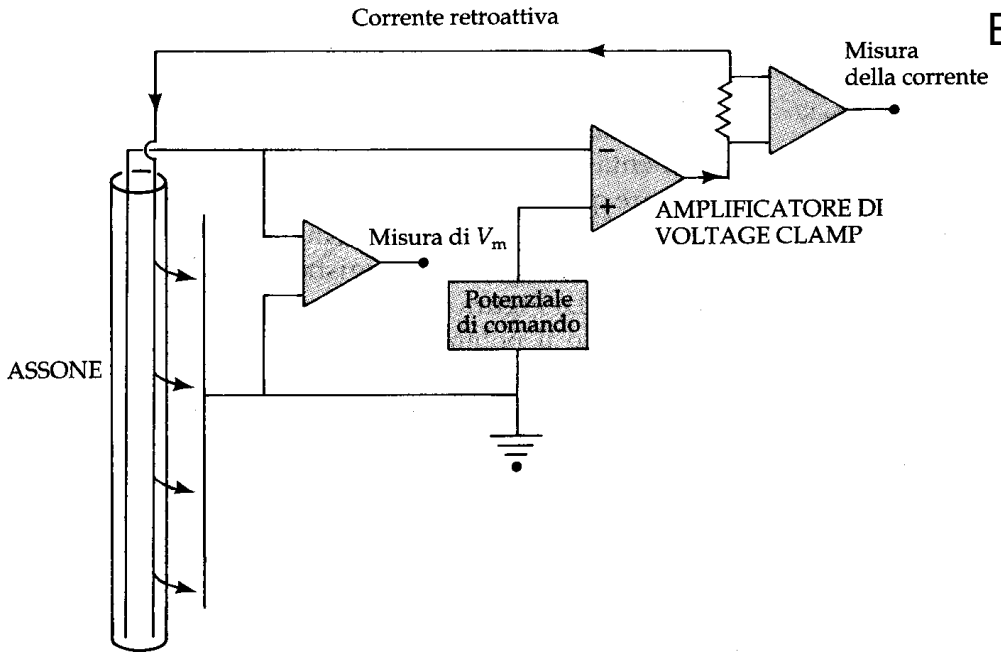


The opening (closure) of the Na and K channels depends on the value of V_m, therefore the conductance of Na and K vary with V_m and the Na and K currents are nonlinearly dependent on V_m

How to measure the conductances g_{Na} and g_K, which depends on V_m ?

Voltage-Clamp

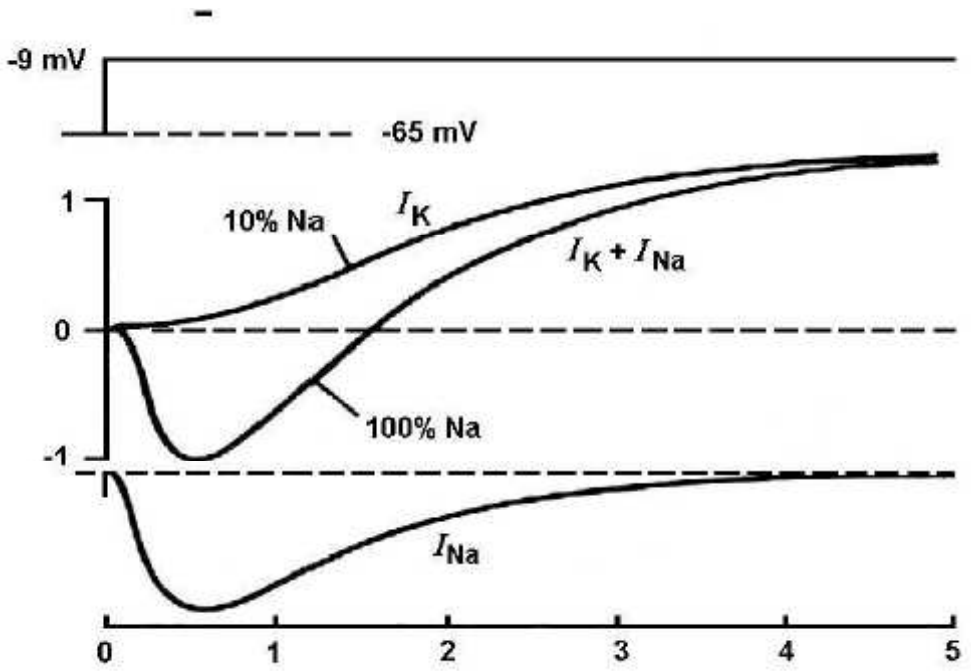
During the voltage clamp experiment two electrodes (silver wires) are inserted along the whole squid giant axon, one electrode measures V_m and the other transmits a feedback current adjusted to maintain V_m to a desired constant value.



Effects of the voltage clamp:

- the capacitive current is eliminated $I_C \equiv 0$;
- the temporal evolution of the ionic currents/conductances can be measured at constant V_m;
- the insertion of the electrodes along the whole axon allow for the space-clamp of V_m

Ionic currents



Measurements of K and NA currents via voltage clamp:

- a low concentration of Na in the bath reduces the I_{Na} current;
- this allows to measures directly I_K;
- I_{Na} is measured by subtracting I_K from the normal response.

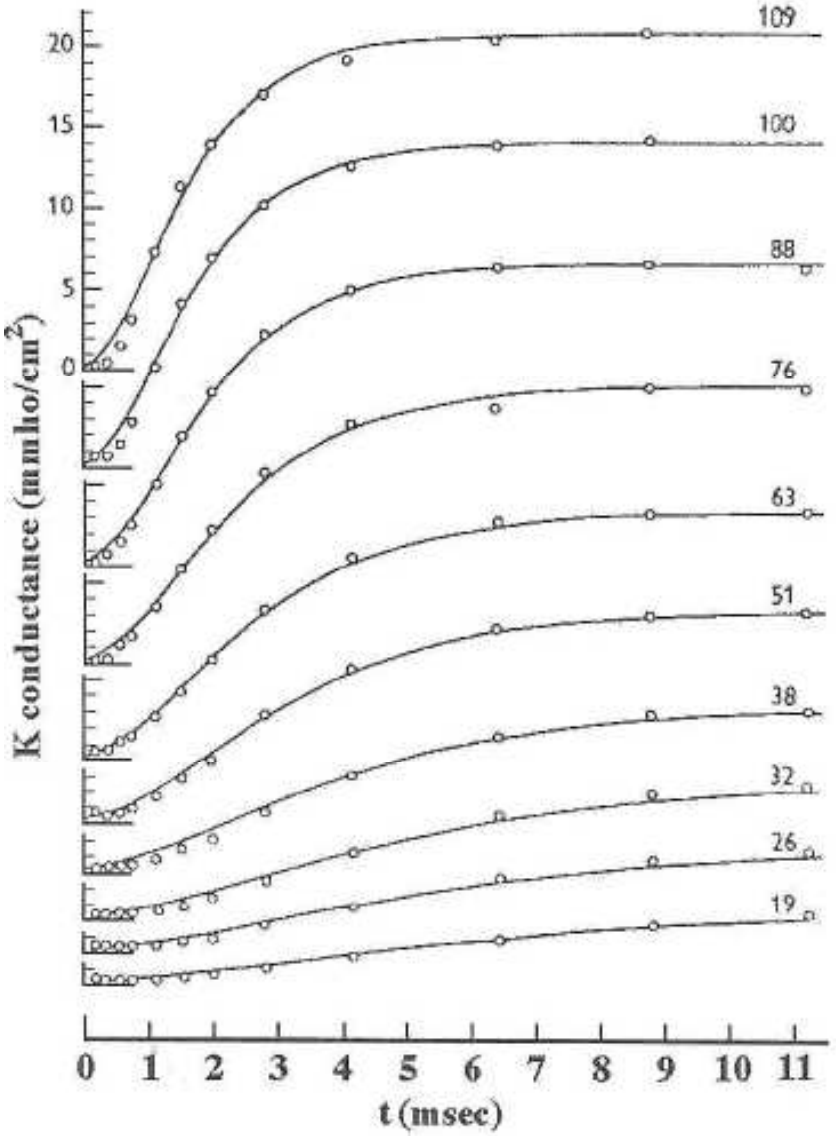
(Hodgkin & Huxley, 1952)

Ionic currents

HH model the ionic currents as follows

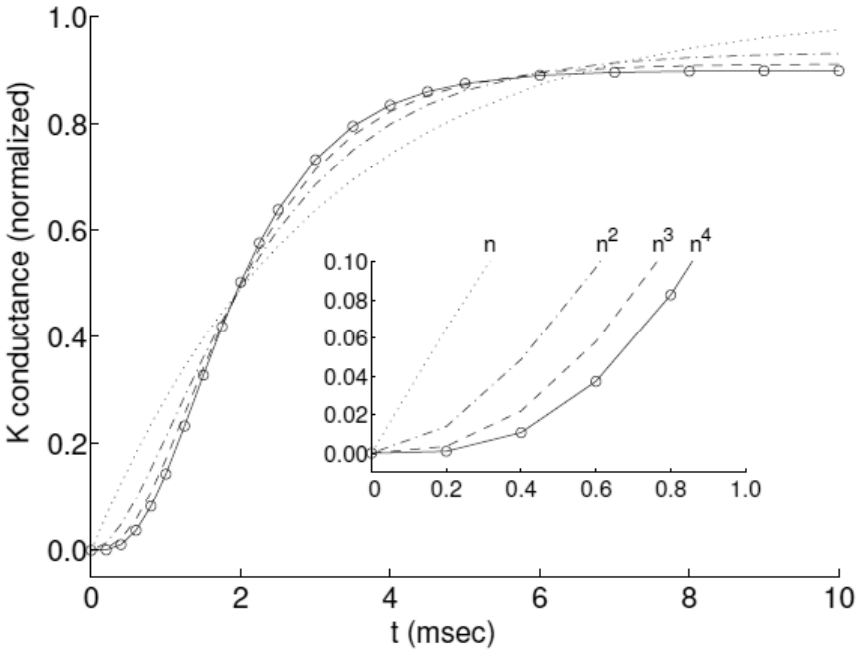
- each current follows the Ohm Law $I_i = g_i(V(t), T)(V(t) - E_i)$
- The inversion (equilibrium) potential E_i is given by the Nernst equation
- The conductances $g_i(V(t), T)$ depends on fictious gating variables that are related to the activation and de-activation of the channels
- $g_K = G_K n^4(V, t)$where $n(V, T)$ is the gating variable for the activation of K
- $g_{Na} = G_{Na} m^3(V, t) h(V, T)$ where $m(V, T)$ and $h(V, T)$ are the gating variables for the activation and deactivation of Na

Potassium Conductance



- $g_K = G_K n^4(V,t)$
- Evolution of $g_K(t)$ for a fixed membrane potential $V_m = V$
- The circles are experimental data , the curve the theoretical results

Potassium Conductance



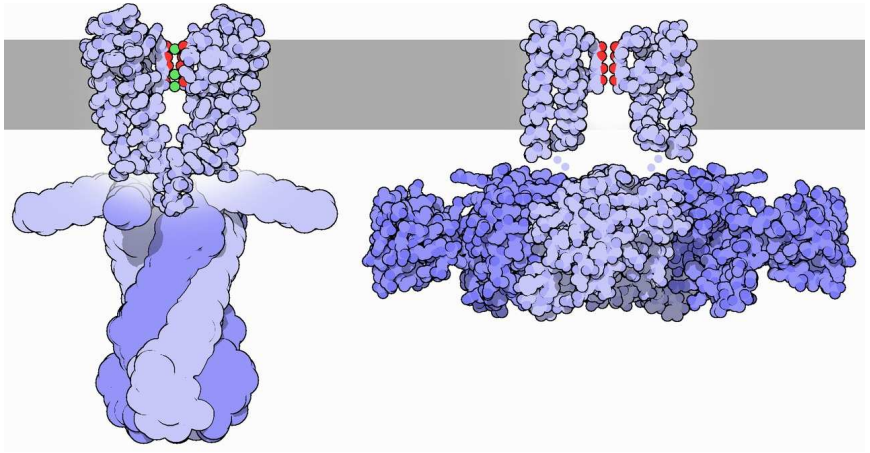
- many channels allow the passage of K^+;
- the opening of each channel is regulated by 4 gates;
- each gate may assume 2 states open (with probability n) or closed (with probability $1-n$);
- the channel is open when all the 4 gates are in the open state ($g_k \propto n^4$)

The transitions between open and closed states are regulated by a first order kinetics with different rates $n \overset{\beta_n}{\to} (1-n)$ e $(1-n) \overset{\alpha_n}{\to} n$

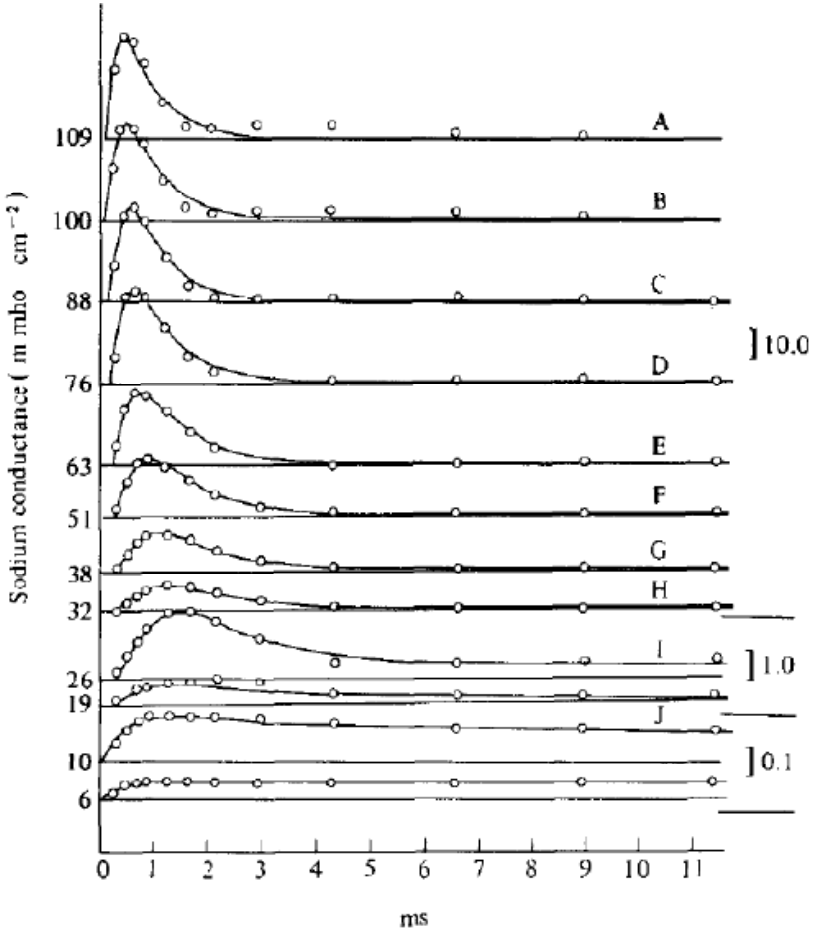
$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n = \frac{n_\infty(V) - n}{\tau_n(V)}$$

Potassium Channel

- The experimental data could have been reproduced with many other choices of the function, no physical basis for this in 1952.
- However in recent years (Hille, 2001) it has been revealed that potassium channels have a tetrameric structure in which 4 identical protein subunits associate to form a fourfold symmetric complex arranged around a central ion conducting pore.
- The concomitant activation of the 4 voltage sensing domains (VSDs) opens a central cavity through which the K^+ ions flow driven by the electrochemical potential gradient across the membrane.
- n ca be interpreted as the proportion of VSDs in the active state, $1 - n$ as the proportion of inactive VSDs.



Sodium Conductance



- $g_{Na} = G_{Na} m^3(V,t) h(V,T)$
- Evolution of $g_{Na}(t)$ for a fixed membrane potential $V_m = V$
- The circles are experimental data , the curve the theoretical results
- No possible physiological relationship between Na channel structure and the law chosen by H&H for their fitting

Gating Variables

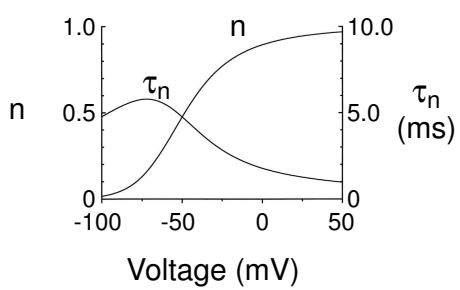
$$g_K = G_K n^4(V,t) \qquad g_{Na} = G_{Na} m^3(V,t) h(V,T)$$

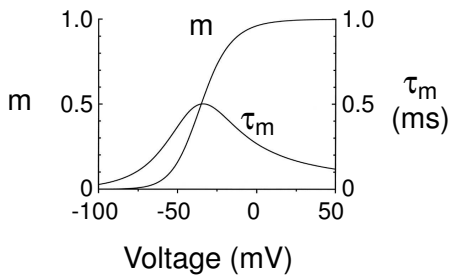
The dynamics of the gating variable $n(t)$ can be written as

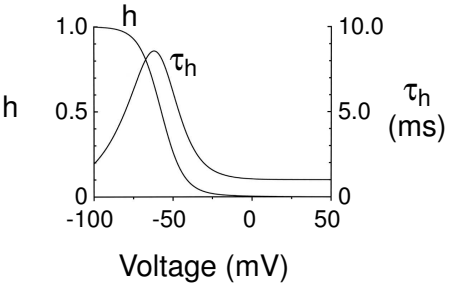
$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n = \frac{n_\infty(V) - n}{\tau_n(V)}$$

- the parameter $\tau_n(V) = 1/(\alpha_n + \beta_n)$ is the decay constant of n(t)
- $n_\infty(V) = \alpha_n/(\alpha_n + \beta_n)$the equilibrium value of n(t)

These values have been measured experimentally by H & H for n , h , m .

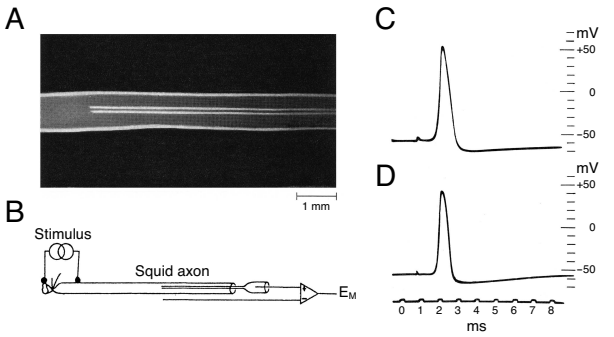






At $V \sim V_{rest}$ $\tau_m \sim 0.4ms << \tau_n, \tau_h$, the sodium activation is much faster

The complete HH model



$C = 1\mu F/cm^2$ - Membrane Capacitance

V - Membrane Potential (mV)

I_j - Ionic Currents ($\mu A/cm^2$)

g_x - Maximal Ionic Conductances (mS/cm^2)

$$C\frac{dV}{dt} = \sum_j I_j + I_{syn} = -g_{Na}m^3h(V - V_{Na}) - g_K n^4(V - V_K) - g_L(V - V_L) + I_{syn}$$

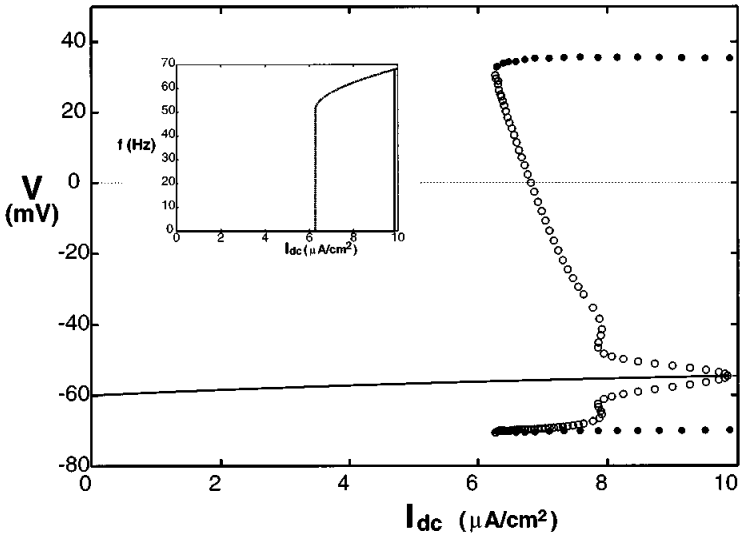
$$\frac{dx}{dt} = \alpha_x - x(\alpha_x + \beta_x) \qquad x = n, m, h \qquad \text{gating variables}$$

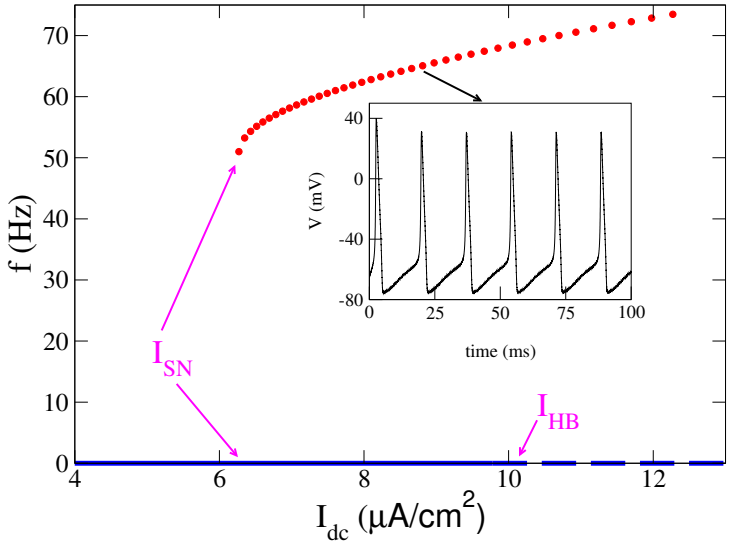
$\alpha_x = \alpha_x(V)$ and $\beta_x = \beta_x(V)$ are highly nonlinear functions

X	$\alpha_X(V)\ (s^{-1})$	$\beta_X(V)\ (s^{-1})$
m	0.1(V+40)/(1-exp(-(V+40)/10))	4exp(-(V+65)/18)
n	0.01(V+55)/(1-exp(-(V+55)/10))	0.125exp(-(V+65)/80)
h	0.07exp(-(V+65)/20)	1/(exp(-(V+35)/10)+1)

Phase diagram

Constant Synaptic Current $I_{syn} = I_{dc}$



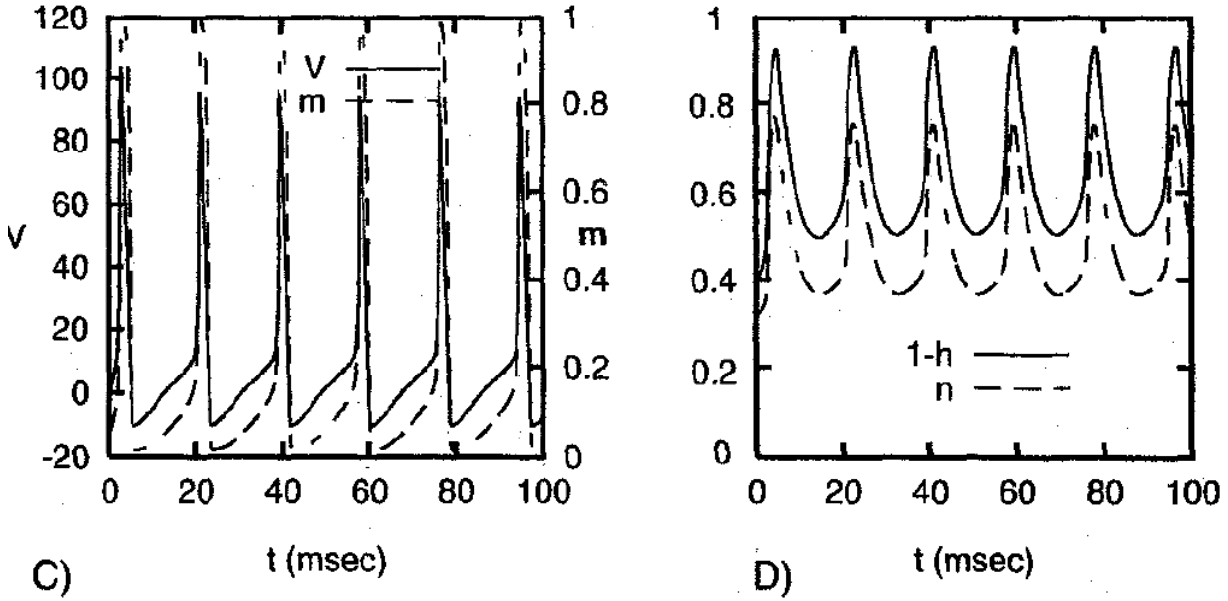


- $I < I_{SN}$ silent neuron
- $I_{HB} < I < I_{SN}$ Bistability
- $I > I_{HB}$ Tonic Firing

- Subcritical Hopf bifurcation at $I_{HB} \simeq 9.78 \mu A/cm^2$
- Saddle-node bifurcation of limit cycles at $I_{SN} \simeq 6.27 \mu A/cm^2$

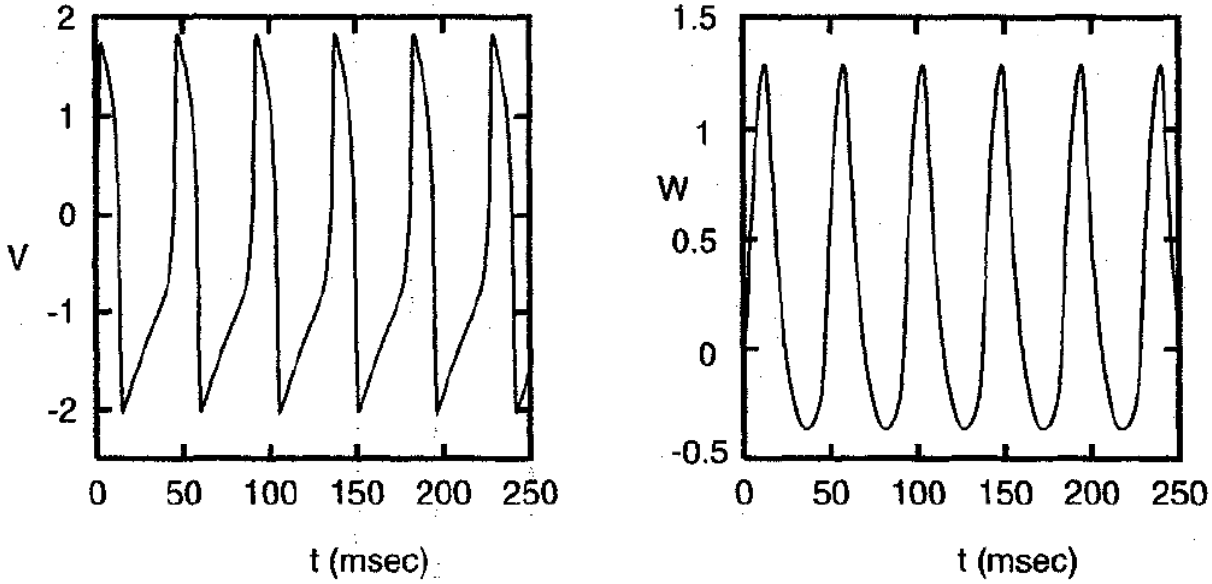
A simplified model

The HH model is too complex may we simplify it ?



- the variables V and m evolve similarly on a time scale $\tau_m \simeq 0.4$ ms;
- n and $1-h$ are also evolving similarly on a slower time scale $\tau_n \simeq 5$ ms.

FHN model



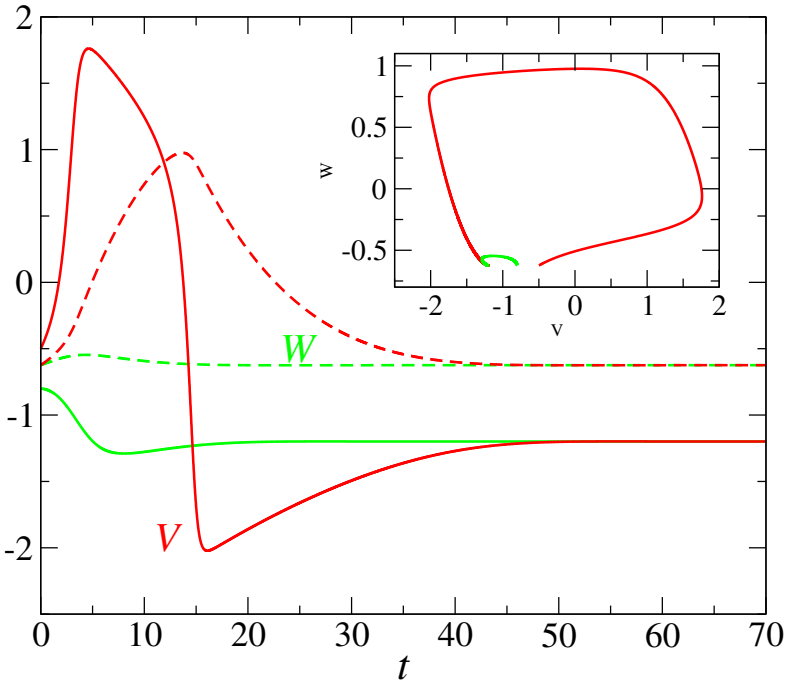
FitHugh (1961) and Nagumo, Arimoto, Yoshizawa (1962) introduced a model for an excitable neuron with only two variables

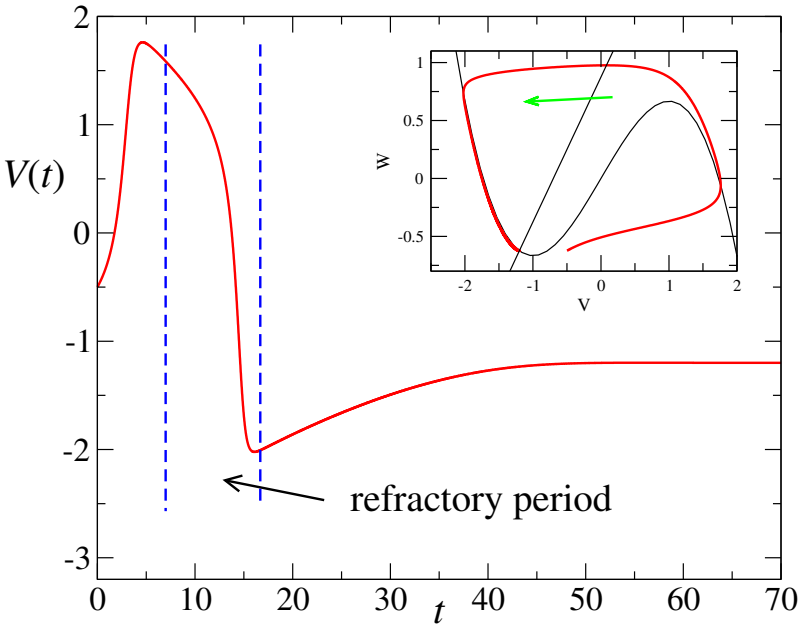
(1) $$\frac{dV}{dt} = V - \frac{V^3}{3} - W + I$$

(2) $$\frac{dW}{dt} = \frac{1}{\tau}(V + a - bW)$$

$\tau = 12 \rightarrow V$ is fast – W is slow

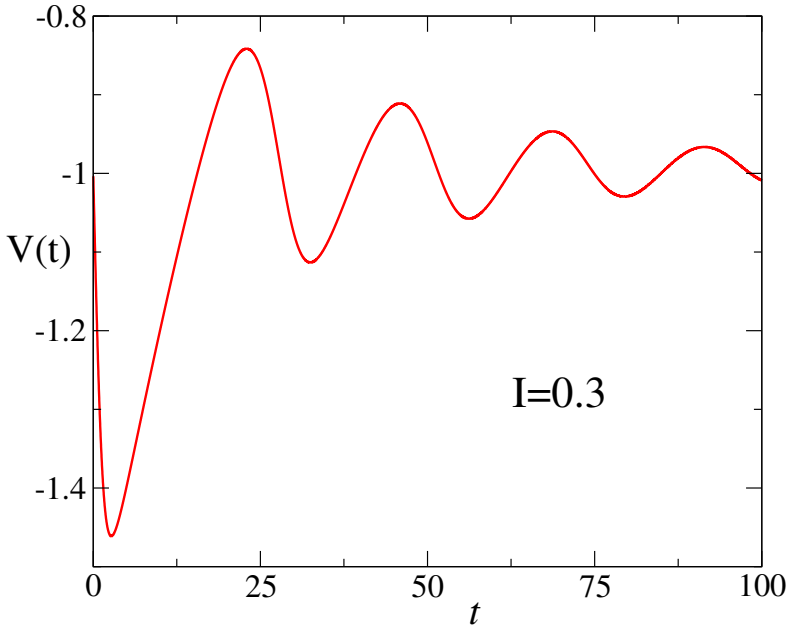
FHN model

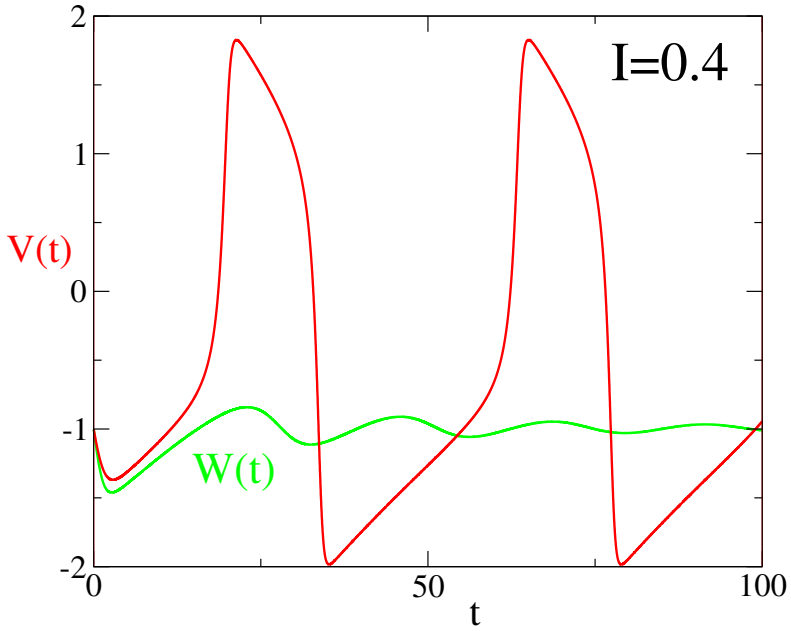




Response of the FHN model to a step of current

FHN model



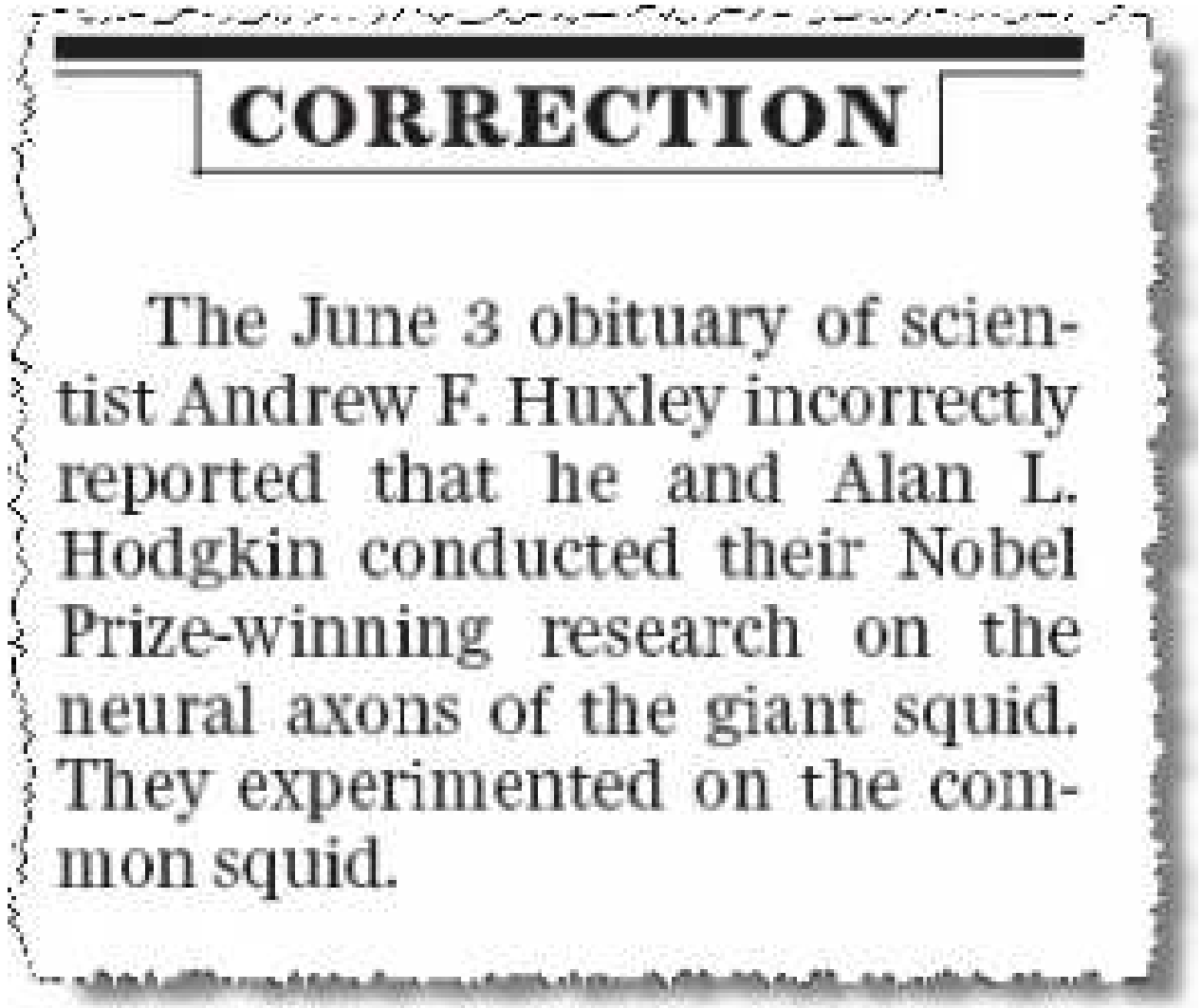


Response of the FHN model to a constant current I below and above the Hopf Bifurcation

Books

- Introduction to theoretical neurobiology H. C. Tuckwell (Cambridge University Press, New York, 1988)
- Biophysics of computation C. Koch, (Oxford University Press, New York, 1999)
- Spiking Neuron Models W. Gerstner and W. Kistler, (Cambridge University Press, Cambridge, 2002)
- Foundation of Cellular Neurophysiology D. Johnston and S. Miao-Sin Wu (The MIT Press, Cambridge, 1995)
- The 60th anniversary of the Hodgkin-Huxley model F. Faraci, M Sc Thesis, Leiden University (2013)

Squid giant axon



CORRECTION

The June 3 obituary of scientist Andrew F. Huxley incorrectly reported that he and Alan L. Hodgkin conducted their Nobel Prize-winning research on the neural axons of the giant squid. They experimented on the common squid.