The Hodgkin-Huxley Model (1952)

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Introduction

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

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) Dendrites (INPUT)
C) Axon (OUTPUT)

Which are the signals transporting information among neurons?
The membrane potential $V_m$ measures the electrical potential difference between interior and exterior of the neuron.

The neuron at rest has $V_m \simeq -60 \text{mV} / -75 \text{mV}$

The neuron is an *dynamical equilibrium* state
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 $\Theta \sim -55 \text{ mV}$

- 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) occurring after the AP emission
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.
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 contains ions to which the membrane is permeable (Na⁺, K⁺, Ca²⁺, Cl⁻).
- The ions have higher concentration outside the cell, apart for K⁺.
- Each ion uses 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 oppose this motion, the opposite is true for Cl⁻.
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:

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

$k$ is the Boltzmann constant; $T$ the temperature and $q$ the charge of the ion.

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 ?
$Na^+$ 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 equilibrated 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 neurons 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)]:

\[
V_{\text{rest}} = \frac{kT}{q} \ln \frac{p_k[K^+]q + p_{Na}[Na^+]e + p_{Cl}[Cl^-]i}{p_k[K^+]i + p_{Na}[Na^+]i + p_{Cl}[Cl^-]e};
\]

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 \( V_{\text{rest}} = -70 \) mV in good agreement with the experiments and not far from \( E_{K^+} = -75mV \).
Activation and Deactivation of the Channels

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

The stimulus depolarizes the membrane and this leads to an opening of the Na channels, this allows $\text{Na}^+$ 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 $\text{K}^+$ and to the repolarization of the membrane

\[ [\text{Na}^+]_e \gg [\text{Na}^+]_i \quad [\text{K}^+]_e \ll [\text{K}^+]_i \]
Membrane depolarization and repolarization

**Depolarization**

\[ V_m \rightarrow E_{Na^+} = +55 \text{ mV} \]

**Repolarization**

\[ V_m \rightarrow E_{K^+} = -75 \text{ mV} \]
The membrane can be seen as an electric circuit with **passive** characteristics

- the membrane separates positive and negative charges, it acts as a capacitance
  \[ C_m \simeq 1 \mu F/cm^2 \rightarrow 4 \times 10^{11} \text{ monovalent ions/cm}^2 \]

- the ionic channels have specific **membrane resistance/conductance**:
  \[
  \text{Leakage Resistance} \quad R_m \simeq 10^3 \Omega \cdot cm^2 \\
  \text{Leakage Conductance} \quad G_m = 1/R_m
  \]

- \( V_{rest} \) can be seen as a voltage generator

However the membrane is also **active**, e.g. the ionic pumps, and highly **nonlinear** (some conductance depends on \( V_m \))
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
\[ I_C = \frac{dQ}{dt} = CdV/dt \]

Ionic currents \( I_{Na} \) and \( I_K \) (Nonlinear)

Leakage Current (Linear)

\[ C' \frac{dV_m}{dt} = -I_{Na} - I_K - I_L + I(t) \]
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 nonlinearily dependent on \( V_m \)

How to measure the conductances \( g_{Na} \) and \( g_K \), which depends on \( V_m \) ?
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 $V_m$
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)
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 fictitious 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
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 $n \xrightarrow{\beta_n} (1 - n) \ e \ (1 - n) \xrightarrow{\alpha_n} n$

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

$n$ can 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

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

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 (\( mS/cm^2 \))

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

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

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

<table>
<thead>
<tr>
<th>X</th>
<th>( \alpha_X(V) ) (s(^{-1}))</th>
<th>( \beta_X(V) ) (s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>m</td>
<td>( 0.1(V+40)/(1-\exp(-(V+40)/10)) )</td>
<td>( 4\exp(-(V+65)/18) )</td>
</tr>
<tr>
<td>n</td>
<td>( 0.01(V+55)/(1-\exp(-(V+55)/10)) )</td>
<td>( 0.125\exp(-(V+65)/80) )</td>
</tr>
<tr>
<td>h</td>
<td>( 0.07\exp(-(V+65)/20) )</td>
<td>( 1/(\exp(-(V+35)/10)+1) )</td>
</tr>
</tbody>
</table>
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
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.
FitHugh (1961) and Nagumo, Arimoto, Yoshizawa (1962) introduced a model for an excitable neuron with only two variables

\[
\begin{align*}
\frac{dV}{dt} &= V - \frac{V^3}{3} - W + I \\
\frac{dW}{dt} &= \frac{1}{\tau}(V + a - bW)
\end{align*}
\]

\(\tau = 12 \rightarrow V\) is fast – \(W\) is slow
Response of the FHN model to a step of current
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)
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.