Neuronal modeling and neural dynamics.
Chapter I: Neurons and Synapses

1) The neuron.
   1.1) Biological structure of the neuron.
1.2) Neuron Modelling

1.2.1) The Hodgkin-Huxley model.


→ Nobel prize in medicine, 1961.

Ionic concentrations

Let us consider a small piece of axon.

\[ [\text{Na}^+]_{\text{out}}, [\text{K}^+]_{\text{out}} \]
\[ [\text{Cl}^-]_{\text{out}} \]

\[ [\text{Na}^+]_{\text{in}}, [\text{K}^+]_{\text{in}}, [\text{Cl}^-]_{\text{in}} \]

\[ [\text{Na}^+]_{\text{out}} \] gradient

Diffusion motion of \([\text{Na}^+]\)

(of there were not membrane)

\[ [\text{Na}^+]_{\text{out}} = [\text{Cl}^-]_{\text{out}} \approx 140 \text{mM} \]
\[ [\text{K}^+]_{\text{out}} = 10[\text{Na}^+]_{\text{in}} \]

\[ [\text{K}^+]_{\text{in}} \approx 5[\text{K}^+]_{\text{out}} \]

Neuro potential

Assume that there is only one species, \( X \). The difference of concentration between inside and outside is related to a difference potential \( V_{in} - V_{out} \).

Assuming local equilibrium at temperature \( T \) →

\[ [X]_{\text{in}} \approx \exp \left( \frac{-q V_{in}}{kT} \right), \quad [X]_{\text{out}} \approx \exp \left( \frac{-q V_{out}}{kT} \right) \]

\[ V_{in} - V_{out} \approx \frac{kT}{q} \log \frac{[X]_{\text{out}}}{[X]_{\text{in}}} \]

\[ \frac{-q V_{in}}{kT} = \frac{-q V_{out}}{kT} \log \frac{[X]_{\text{out}}}{[X]_{\text{in}}} \]

\[ V_{in} = V_{out} \]
For the giant axon of *V* *H* squid, at $T = 6.3$ °C, $E_{Na} \approx 55$ mV, $E_K \approx -75$ mV.

From Fick's law, the concentration gradient $\nabla [X]$ gives rise to a current $I$: $I = -D \nabla [X]$ (when $\nabla [X]$ is positive, $I$ is inward).

1. When subjected to a strong and rapid change of its potential (i.e., when the solution is transferred through the membrane).
ionic concentration

<table>
<thead>
<tr>
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<th>Inside</th>
<th>Outside</th>
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<tbody>
<tr>
<td>K⁺</td>
<td>140</td>
<td>5</td>
</tr>
<tr>
<td>Na⁺</td>
<td>10</td>
<td>140</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>10</td>
<td>50</td>
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<tr>
<td>Ca²⁺</td>
<td>0.0001</td>
<td>2</td>
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<tr>
<td>proteins</td>
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Steady state

For simplicity assume that we start from a situation where there are as much positive charges as negative charges inside and outside (ΔV=0).

Open a K⁺ channel \(\rightarrow\) Potassium diffusion

\[
\text{total charge becomes positive} \quad \uparrow \quad \text{total charge becomes negative}
\]

Diffusion does not continue until concentration gradient vanishes.

Indeed diffusion stops when the electric gradient equals the concentration gradient.

⇒ In the steady state there are more positive charges outside than inside.

The membrane potential is determined by the Goldman - Hodgkin - Katz equations.
Let $V_m$ be the membrane potential and $L$ the membrane thickness. Then the electric gradient is $\frac{V_m}{L}$ (gradient is supposed homogeneous through the membrane).

For a ionic species $X$, call $\mathbf{J}_X$ the current flux (number of concentrons per unit time and per unit area of the membrane). It is due to 2 contributions.

$$\mathbf{J}_X = \mathbf{J}_X^{\text{diff}} + \mathbf{J}_X^e$$

$\mathbf{J}_X^{\text{diff}}$ is a diffusion current given by Fick’s law.

$$\frac{\partial C_X}{\partial t} = -D_x \nabla [C_X] \text{ mol/m}^3$$

This gives rise to a change current

(2) $$\mathbf{J}_X^e = -q \mathbf{E}$$

where $q = n_X e$, $n_X$ is the valence of species $X$ and $e = 1.6 \times 10^{-19}$ is the charge of electron in absolute value.

$\rightarrow$ The change displacement generates a gradient of electric field, which induces an opposite current given by:

$\mathbf{J}_X^e = q^2 \mathbf{E} / \mu_{el}$

(2)

where $\mu_{el}$ is the electric mobility $\mu_{el} = \frac{\mathbf{v}_d}{E} = \frac{\mathbf{v}_d}{qE}$ and $\mathbf{v}_d$ being the terminal drift velocity. Moreover the mobility is related to the diffusion coefficient by:

$$\mu_{el} = \frac{D_x}{kT}$$

$C_X$ is the particle density $C_X = N[X]$
Thus \( \frac{\partial}{\partial x} = q \frac{\partial (xLx)}{RT} = q \frac{\partial}{\partial x} \left( \frac{xLx}{RT} \right) \).

Setting \( F = \epsilon \partial x = 96500 \)C being the Faraday constant.

The total electric current is:

\[
\vec{j}_{el} = q \left[ -c \frac{\partial}{\partial x} \nabla [x] + \frac{\partial}{\partial x} F_n x [x] \frac{E}{RT} \right]
\]

\[
= q \frac{c}{\partial x} \left[ -D_x \nabla [x] + \frac{\partial}{\partial x} F_n x [x] \frac{E}{RT} \right]
\]

Considering the current in the vertical direction \( \hat{z} \):

\[
\vec{j}_{el} = q \frac{c}{\partial x} \left[ -D_x \frac{d [x]}{d \hat{z}} + \frac{\partial}{\partial x} F_n x \frac{V_m}{RT} \frac{E}{RT} \right.
\]

Set \( \delta x = \frac{\vec{j}_{el}}{q \frac{c}{\partial x}}; \quad \mu = \frac{F V_m}{RT}; \quad \text{p}_x = \frac{D_x}{L \text{ (dimensionless)}}; \quad \text{perm.ability} \quad \mu = \frac{D_x}{L \text{ (dimensionless)}}
\]

\[
\delta x = -D_x \frac{d [x]}{d \hat{z}} + \mu n_x \frac{p_x [x]}{x}
\]

Hence

\[
\frac{d [x]}{-\delta x + \mu n_x p_x [x]} = \frac{1}{D_x^{-1}} d \hat{z}
\]

We assume that \( n_x = \text{constant} \) through the membrane.

\[
\int_{0}^{L} \frac{d [x]}{-\delta x + \mu n_x p_x [x]} = \frac{1}{n_x \mu p_x} \left[ \ln \left( -\delta x + n_x \mu p_x [x] \right) \right]_{0}^{L} = \frac{L}{D_x}
\]

\[
\therefore \frac{-\delta x + n_x \mu p_x [x]}{-\delta x + n_x \mu p_x [x]} = \exp \left( n_x \mu p_x D_x^{-1} L \right) = \exp(n_x \mu)
\]
To each species is annotated such a current. In the steady state, \( V = \mathbf{W}_m \) and: \( \delta x = \sum_x \delta x = 0 \).

Assume for simplicity that all ions are monovalent \((n = \pm 1 \rightarrow K^+, Cl^-, Na^+)\)

Then:

\[
\sum \delta c + \sum \delta A = 0 \quad \text{since} \quad \delta c \quad \text{and} \quad \delta A
\]

\[
0 = \mu \left[ \sum_c p_c \left( [C^+]_{\text{act}} - e^\mu [C^+]_{\text{in}} \right) + \sum_A p_A \left( [A^-]_{\text{act}} - e^\mu [A^-]_{\text{in}} \right) \right]
\]

\[
= (1 - e^\mu) \sum_c p_c \left[ [C^+]_{\text{act}} - e^\mu [C^+]_{\text{in}} \right] + (1 - e^\mu) \sum_A p_A \left[ [A^-]_{\text{act}} - e^\mu [A^-]_{\text{in}} \right]
\]

\[
= \sum_c p_c [C^+]_{\text{act}} - e^\mu \sum_c p_c [C^+]_{\text{in}} + \sum_c p_c [C^+]_{\text{in}}
\]

\[
+ \sum_A p_A [A^-]_{\text{act}} - e^\mu \sum_A p_A [A^-]_{\text{in}} + \sum_A p_A [A^-]_{\text{in}}
\]

Set \( W = \sum_c p_c [C^+]_{\text{act}} + \sum_A p_A [A^-]_{\text{in}} \)

\( V = \sum_c p_c [C^+]_{\text{in}} + \sum_A p_A [A^-]_{\text{act}} \)

\( W - e^\mu V - e^\mu W + V = 0 \Rightarrow W - e^\mu V = e^\mu (W - e^\mu V) \)

\( \Rightarrow W - e^\mu V = 0 \quad \text{(once} \quad e^\mu > 0) \)
Therefore \( \beta = \frac{\ln \omega}{V} = \frac{V_m}{R T} \Rightarrow V_m = \frac{R T \ln \omega}{F} \)

\[
V_m = \frac{R T}{n F} \ln \left( \frac{\sum_c p_c [c]_{out} + \sum_A p_A [A^-]_{out}}{\sum_c p_c [c]_{in} + \sum_A p_A [A^-]_{in}} \right)
\]

These are the Goldman–Hodgkin–Katz equations.

For a particular case, if there is only one species, \( X \)

\[
V_m = \frac{R T}{n F} \ln \frac{[X]_{out}}{[X]_{in}} \quad \text{Neurot Potential}
\]

Membrane conductance

Assume now that \( V \neq V_m \) (away from the steady state).

For each species \( X \) (eq. 2)

\[
\partial_x = -D_x \frac{d[X]}{d\theta} + D_x n_x \frac{F}{R T} [X] \frac{dV}{d\theta}
\]

\[
\Rightarrow \partial_x \frac{R T}{F D_x \frac{d[X]}{d\theta}} = -\frac{R T}{F} \frac{d[X]}{[X]} + n_x \frac{dV}{d\theta}
\]

Assuming \( \partial_x = \text{c.s.e. inside the membrane} \)

\[
\partial_x \frac{R T}{F D_x \int_0^1 \frac{d[\theta]}{[X]} = -\frac{R T}{F} \ln \frac{[X]_{out}}{[X]_{in}} + n_x V}
\]

\[
\int_0^{\theta_x} \frac{d[\theta]}{[X]} = -n_x \frac{F}{D_x}
\]

\[
\theta_x \Gamma_X(V) = n_x (-E_X + V) = n_x (V - E_X)
\]
\[ J_{el} = \sum_{x} \frac{n_{x} F (\delta_{x} + \delta_{p})}{q_{x}} \bigg|_{p_{\text{inj}}} - \sum_{x} n_{x} \int_{\mathbf{V}}^{\mathbf{V}_{C}} (V - \epsilon_{x}) \bigg) \]

Set \( g_{x}(V) = n_{x} F \Gamma_{x}^{-1}(V) \) conductance

\[ J_{el} = -\delta_{p} + \sum_{x} g_{x}(V) (V - \epsilon_{x}) \]

NB : Electrophysiologist use the opposite sign (opposite convention)
2) At rest ($V_\text{rest} = -70 \text{ mV}$) the concentration of $\left[\text{Na}^+\right]_\text{i}$, $\left[\text{K}^+\right]_\text{e}$, $\left[\text{Ca}^{2+}\right]_\text{i}$ is roughly constant $\implies$ membrane is not permeable to ions at rest.

NB: This precisely the concentration of species, inside and outside which forces the difference of potential between inside and outside to:

$$V_\text{rest} = V_{\text{in}}^{\text{rest}} - V_{\text{out}}^{\text{rest}} = -70 \text{ mV}$$

3) Each species is thus submitted to 2 forces. One due to the concentration gradient of this species, and the other is due to the global difference of potential generated by all species.

$$\begin{array}{c|c}
\left[\text{Na}^+\right]_\text{i} & \uparrow \\
\left[\text{Na}^+\right]_\text{e} & \downarrow \\
\end{array}$$

Here the two forces add up. $\vec{F} = -q \vec{V}$

$$= q E_\text{Na} - q (V_{\text{rest}} - V_{\text{rest}}) = q (E_{\text{Na}} - V_{\text{rest}})$$

$\implies$ At rest, the effective potential viewed by $\left[\text{Na}^+\right]_\text{i}$ to:

$$E_{\text{Na}} - V_{\text{rest}} \approx 125 \text{ mV}$$

In the same way:

$$E_K - V_{\text{rest}} \approx 10.05 \text{ mV}$$

$\implies$ At rest, the Na ions view a strong electromotive force $q (E_N - V_{\text{rest}})$ which lacks them to enter inside the membrane. But they can't since the membrane is not permeable at rest.

**Hypothesis 4** The spike arises because the membrane becomes permeable to ions, due to the oscillation.

**Hodgkin - Huxley's hypothesis:** The membrane has "holes", i.e. ionic channels, specific to species, with gates which open or close according to $V$. The membrane potential difference between inside and outside.
The conductance of the membrane potential, varies, due to the channel, and depends on $V$. To each species $X\in \{Na, K\}$, a conductance $G_X(V)$.

The provides an equivalent electric circuit.

Now, apply the laws of electricity:

$$i_{ion} = i_{Na} + i_{K} + i_L$$

(The total current crossing the membrane is due, in the HH model, to these 3 currents)

Ohm's law:

$$i_X = G_X(E_X - V) = -G_X(V - E_X)$$

Kochhoff's law:

$$\frac{CdV}{dt} = i_{ion} + i_{ext}$$

$$\Rightarrow \frac{CdV}{dt} = -G_{Na}(V - E_{Na}) - G_K(V - E_K) - G_L(V - E_L) + i_{ext}$$

First Hodgkin-Huxley equation

Let us now detail $G_X$. After many trials and experiments, Hodgkin and Huxley proposed the following hypothesis:

To Na$^+$ channels are associated to 2 types of gates:

- $m$ → activation
- $h$ → inactivation

By a slight abuse of language, $m$, $h$ is also the probability that a gate is open.
For K+ channel is associated an array of gates: n.

Now, experiments showed that: (the conductance is proportional to the product of)

\[ g_{Na} = gNa \cdot m^3 \cdot h \]  
(2.2.1-6)

and \[ g_K = gK \cdot n^4 \]  
(2.2.1-7)

Master equations

At this stage, we have made some implicit hypothesis. The piece

of membrane is considered to be a space and time scale large enough so

that the conductances are defined via probabilities of open/closed

ionic gate. Therefore, this amounts to assuming that there are

sufficiently many gates in the piece of membrane, and that the

gates are sufficiently spread out, open/closed, so that the notion of

probability of being open/closed is relevant in the present modeling.

The gates are specific molecules, and considering the membrane

at the scale of these gates would require a different physics (quantum)

Thus, we now make another assumption. The probabilities are

given by a master equation:

\[ \frac{dp}{dt} = \alpha(U) (1-p) - \beta(U) p = \alpha(U) - \frac{\alpha(U)}{\alpha(U) + \beta(U)} \quad p \]

where \( \alpha(U) \) : transition closed to open; \( \beta \) : transition open/closed

Define:

\[ \tau(U) = \frac{1}{\alpha(U) + \beta(U)} \]; \[ \rho(U) = \frac{\alpha(U)}{\alpha(U) + \beta(U)} \]

\[ \frac{dp}{dt} = \frac{\rho(U) - p}{\tau(U)} \]  
(2.2.1-8)

with solution:

\[ p(t) = \rho(U) - [\rho(U) - \rho_0(U)] e^{-\frac{t}{\tau(U)}} \]  
(2.2.1-9)

Hence, \( \tau(U) \) is the characteristic time to equilibrate, while \( \rho(U) \)

is the equilibrium probability.
The Hodgkin-Huxley equations

Combining all these equations, we end up with

\[ C \frac{dV}{dt} = -g_{Na} m^3 h (V - E_{Na}) - g_{K} n^4 (V - E_{K}) - g_{L} (V - E_{L}) + I_{in} \]

\[ \frac{1}{\gamma(T)} \frac{dm}{dt} = \alpha_m (V)(1-m) - \beta_m (V)m = \frac{m^* (V) - m}{\tau_m (V)} \]

\[ \frac{1}{\gamma(T)} \frac{dn}{dt} = \alpha_n (V)(1-n) - \beta_n (V)n = \frac{n^* (V) - n}{\tau_n (V)} \]

\[ \frac{1}{\gamma(T)} \frac{d\theta}{dt} = \alpha_h (V)(1-\theta) - \beta_h (V)\theta = \frac{\theta^* (V) - \theta}{\tau_h (V)} \]

There are the H.H. equations. The factor \( \gamma(T) \) is a rate factor depending on \( T \). It is equal to (empirical)

\[ \gamma(T) = 3 (T - 6.3) / T \]

Thus, it is equal to \( 1 \) at \( 6.3 \) °C.

Finally, the factors \( \alpha, \beta \) have been obtained empirical by H.H. They are given by:

\[
\begin{align*}
\alpha_m (V) &= \Psi \left( -\frac{(V+45)}{10} \right) \\
\beta_m (V) &= \Psi \left( -\frac{(V+70)}{18} \right) \\
\alpha_n (V) &= 0.1 \Psi \left( -\frac{(V+60)}{10} \right) \\
\beta_n (V) &= 0.125 \Psi \left( -\frac{(V+70)}{80} \right) \\
\alpha_h (V) &= 0.07 \exp \left( -\frac{(V+70)}{20} \right) \\
\beta_h (V) &= \frac{1}{1 + \exp \left( -\frac{(V+70)}{10} \right)}
\end{align*}
\]

where

\[
\Psi(x) = \begin{cases} 
\frac{e^x}{e^x - 1} & \text{if } x \neq 0 \\
1 & \text{if } x = 0
\end{cases}
\]
Let us now draw the time constants $T_m$, $T_n$, $T_h$ and the steady state values $m^\infty$, $n^\infty$, $h^\infty$ as functions of $V$.

The main remarks are:

1) The time constant for the activation variable $m$ is about one order of magnitude the same for the Na inactivation and the K activation through the entire range. This means that $m$ reaches the steady state quite a bit faster than the other variables.

2) When voltage is large and $m$ is large, it will take a while for $h$ to decrease and $n$ to increase (see fig on right).

3) At rest, $h$ gates are open, while $m, n$ are closed. This is the opposite when $V$ is large.

The spike generation

The next figure summarizes how a spike is produced, taking into account all information we have collected.

Phase a: Rest. The gates $m, n$ are closed while $h$ opens. Therefore, Sodium and Potassium are neither leaving nor entering the cell.

Phase b: Depolarization. If $V$ increases, due to a local depolarization, first the $m$ gates open fast, allowing Sodium to diffuse into the cell. Following the concentration gradient, while then gates are still closed.
c) Repolarization. Then, the gate n open slowly, generating an efflux \( K^+ \) current. In the same time \( h \) decreases and \( h \) gate close, preventing sodium from coming into the cell. In this phase, \( V \) decreases.

d) Refractory period. In this phase, the m gate close, \( h \) gate closed, and \( n \) close. Finally, \( h \) open and the initial configuration of gates is restored. The ionic balance is restored by ionic pump. During this phase it is not possible to excite the neuron.
The previous equations characterize the dynamics of a small piece of membrane. Let us now consider a spatially distributed membrane with a "tube" shape modeling either the axon or a dendrite. For simplicity we assume that the radius of the tube is constant.

\[ i_a(x) = \frac{d}{dx} \left( i_m(x) + i_{ext} \right) \]

We have

\[ \frac{d^2 i_a}{dx^2} = \frac{d}{dx} \left( \frac{d}{dx} i_m + i_{ext} \right) \]

Moreover, \[ i_a = \pi R^2 j_a \] where \( j_a \) is the density of longitudinal current. We have \[ j_a = \frac{\delta a}{\delta t} E_{int} \] and there is also an external current but negligible. The longitudinal current is mainly due to charge transport inside the membrane.

Also,

\[ E_{int} = -\frac{d}{dx} V_{int} \quad \text{and} \quad E_{ext} = -\frac{d}{dx} V_{ext} \]

\[ E_{int} - E_{ext} = -\frac{\partial}{\partial x} \left( V_{int} - V_{ext} \right) = -\frac{\partial V}{\partial x} = \frac{j_a}{\sigma a} - \frac{j_{ext}}{\sigma a} \]

\[ \Rightarrow -\frac{\partial V}{\partial x} = \frac{j_a}{\pi R^2 \sigma a} \]

Call \[ Ra = \frac{1}{\sigma a \pi R^2} \]

We have \[ -\frac{\partial V}{\partial x} = Ra i_a \]
Finally: \[
\frac{\partial^2 V}{\partial x^2} = R_a \frac{\partial}{\partial x} \frac{\partial V}{\partial x}
\] 

(1.2.2 - 1)

denotes the density of current crossing the membrane and given by HH equations.

\[
\frac{\partial m}{\partial t} = C \frac{\partial V}{\partial t} + \frac{\partial}{\partial t} \left[ g_N a m^3 h (V-E_{Na}) + g_k n^4 (V-E_K) + g_L (V-E_C) \right]
\]

(1.2.2 - 2)

We obtain in this way the cable equations:

\[
\frac{1}{R_a} \frac{\partial^2 V}{\partial x^2} = C \frac{\partial V}{\partial t} + \left[ g_N a m^3 h (V-E_{Na}) + g_k n^4 (V-E_K) + g_L (V-E_C) \right] + \Delta V_{int}
\]

\[
\frac{\partial m}{\partial t} = \alpha_m (V) (1-m) - \beta_m (V)m
\]

\[
\frac{\partial h}{\partial t} = \alpha_h (1-h) - \beta_h h
\]

\[
\frac{\partial n}{\partial t} = \alpha_n (1-n) - \beta_n n
\]
The spike propagates along the axone, consequent by propagation solutions of form:

\[ V(x, t) = U(x - ct) = U(s), \]

such, with \( c \), propagation speed, and \( s = x - ct \). Thus,

\[ \frac{\partial}{\partial x} = \frac{\partial}{\partial s} \quad \text{and} \quad \frac{\partial}{\partial t} = -c \frac{\partial}{\partial s}. \]

We assume, for simplicity, that axone is finite (i.e., its length is quite large than diameter) and that axone is almost at infinity, i.e., \( V(x) \rightarrow 0 \) as \( s \rightarrow \infty \).

We obtain a set of reduced equations:

\[
\begin{align*}
\frac{1}{R} \frac{d^2 V}{ds^2} & = -a c \frac{dV}{ds} + \left[ g_N a m^3 h \left( V - E_{Na} \right) + g_K n^4 \left( V - E_K \right) + g_L \left( V - E_L \right) \right] \\
\frac{dm}{ds} & = -\frac{1}{c} \left[ \alpha_m (1-m) - \beta_m m \right] \\
\frac{dh}{ds} & = -\frac{1}{c} \left[ \alpha_h (1-h) - \beta_h h \right] \\
\frac{dn}{ds} & = -\frac{1}{c} \left[ \alpha_n (1-n) - \beta_n n \right].
\end{align*}
\]

Here \( V_x = E_x + V_0 \) with \( V_0 = -70 \text{ mV} \) assuming that at rest \( V = 0 \) (change in the array of potentials).

It is possible to show that these equations have a solution corresponding to a propagating speed \( c = 18.8 \text{ m/s} \) very close to the speed found experimentally. \( c = 21.2 \text{ m/s} \). They also give with a good accuracy the characteristics.

Note also the role of refracting period which select a duration of propagation.
Dynamics of Hodgkin-Huxley's model

Though improved models for the membrane potential of the squid axon have been formulated (Klang, J Neurophysiol, 30 [1998] 903-913), the Hodgkin-Huxley model remains the paradigm for the so-called conductance-based models of neural systems.

This model exhibits an astonishing variety of dynamical regimes, which are observed in real neurons, and summarized in the next figure.

From a mathematical viewpoint, and though varied properties of the Hodgkin-Huxley vector field have been studied, we remain far from a comprehensive understanding of its dynamics.

In this section, we briefly summarize work, especially by Gutknecht and collaborators, illustrating the overwhelming richness of this model.


The Hodgkin-Huxley vector field has four dimensions, corresponding to the variables \( (V, m, h, n) \) and a lot of parameters:

- The Nernst potential: \( E_{Na}, E_K, E_L \)
- The conductance: \( g_{Na}, g_K, g_L \)
- The imposed current: \( I_{ext} \)
- The temperature: \( T \)

Some of these parameters can be controlled experimentally, while \( E_{Na}, E_K, E_L, g_{Na}, g_K, g_L \) cannot. Varying these parameters induces bifurcations, i.e., qualitative changes in dynamics. Some of these bifurcations have been mathematically studied.

Here is a short dictionary of bifurcations occurring in the Hodgkin-Huxley model (codimension 1, i.e., two parameters are varying simultaneously):

- **Saddle-node (on)**: 2 equilibrium points coalesce and disappear.

\[ \frac{dx}{dt} = \mu - x^2 \]

- **Hopf bifurcation**:\n
  Appearance (or disappearance) of a periodic orbit by destabilization of a stable fixed point.

The amplitude of the orbit grows like \( \sqrt{\mu - \mu_0} \).

The period approaches a positive limit as \( \mu \rightarrow \mu_0 \).
Saddle loop or homoclinic bifurcation (sb)
The amplitude of a periodic orbit increases until it captures a saddle point and disappears. Its period tends to infinity as $\lambda \to \infty$

Saddle node of cycle: Two periodic orbits coalesce and disappear.

Period doubling: A periodic orbit changes its stability while a periodic orbit of twice its period coalesces with the bifurcating periodic orbit.

Bifurcation diagram:

Bogdanov-Takens

$$\begin{align*}
\dot{u} &= v \\
L \dot{v} &= a + bu + ku^2 + 5u^4v
\end{align*}$$

$$0 \leq 0$$
Chaos in HH model

(Selected work)

The Hodgkin-Huxley equations also exhibit a chaotic dynamic. This has been shown by several authors, Dai and Kupagai (*Non-linear dynamics of small-scale biophysical neural networks* Biochim Biophys Acta 1996; 1317:164-173) have shown the existence of chaotic attractors for values of parameters which are outside the physical range.

More recently, Guckenheimer and Pichon have shown, using numerical methods, the existence of chaos for realistic values of the parameters. They precisely have shown the existence of a homoclinic which is the paradigm of a chaotic system (see Appendix).

The biological significance of a chaotic dynamic is the following.

A chaotic dynamic has the characteristics to be highly dependent on initial conditions, thus to be highly unpredictable. In HH model, the chaotic invariant set is a highly unstable structure associated with the notion of "threshold" for action potentials.

Action potentials in neurons are large all-or-nothing voltage spikes. It is commonly believed that a spike is triggered when the amplitude of the membrane potential reaches a critical value, called a threshold. However, in this paradigm applied to the HH model, a function \( V(m, n, h) \) is a threshold function of initial states with \( V < V(m, n, h) \) do not generate a spike while initial states with \( V > V(m, n, h) \) yield action potentials.

Unfortunately, the work by Guckenheim and Pichon suggests that the boundary between initial states that lead to action potentials and those that do not is a fractal set. Therefore, initial states that lead to a rest state are those leading to being able to evolve into one of infinitely many.

There are also uncountable sheets in the phase space that lead neither to the stable state nor to budding from action potentials and given any initial conditions contain stable state and budding state.

Therefore, there is a degree of unpredictability in the response of HH model to stimulation. However, this structure is hardly observable due to its small scale and inherent noise in the membrane has a large scale.

But this result highlights the overwhelming complexity of neuron dynamics, and the risks of simplifying its dynamics description.
Bifurcation of HH model

Here is an example of bifurcation diagram occurring with $E_K$ and $I_{inj}$ (from Ermentrout-Stanley, 83).

**Student work**: Read the paper and summarize it. Represent numerically the various dynamical regimes in the phase space and in the space $\mathbb{R}^3$.

**Fig. 18** – Bifurcation diagram of the Hodgkin-Huxley equations when varying the parameters $I, \nu_K$. This figure has been drawn "by hand" from the Figure 1 in (79). Stable equilibrium points are shown as black dots, unstable focus as white dots, stable limit cycles are closed curves with solid lines and unstable periodic orbits are dashed lines. One dimensional unstable manifolds of equilibrium points are shown together with curves of the "weak stable manifolds" of equilibrium points with three dimensional stable manifolds (see e.g. in the "tsl" and "pd" regions).
The Hodgkin-Huxley equations are quite complex, and although they have been proposed more than fifty years ago, they still resist to a complete analytical solution. Moreover, their numerical simulation is heavy, especially at the network level. Consequently, many models have been proposed to capture the fundamental phenomenology of neuron dynamics and spike generation, while simplifying the equations, especially by reducing the dimensionality.

In this spirit, a major model has been independently proposed by FitzHugh (1961) and Nagumo and Amemiya (1962).


The main observation leading to neuron excitability is the separation of time scale, where the variable depends quite faster than $\tau_n$. Set:

$$T_H(V) = \frac{Z_m(V)}{\max Z_m(V)}$$  
$$T_P(V) = \frac{Z_P(V)}{\max Z_P(V)}$$  
$$T_n(V) = \frac{Z_n(V)}{\max Z_n(V)}$$

which provides a characteristic time between 0 and 1. For the previous analysis we know $\max Z_m(V)$ is about 10 times smaller than $\max Z_n(V)$ and $\max Z_P(V)$. Set:

$$\varepsilon_h = \frac{\max Z_m(V)}{\max Z_P(V)} \sim 0.1$$
$$\varepsilon_n = \frac{\max Z_m(V)}{\max Z_n(V)} \sim 0.1$$

Then Hodgkin-Huxley equations write, using these definitions:
\[
\frac{dv}{dt} = -\frac{1}{c} \left[ g_{Na} m^3 h_b (V-E_{Na}) + g_K n^4 (V-E_K) + g_L (V-E_L) + \text{Iext} \right] \\
\frac{dm}{dt} = \frac{m_{\text{eq}}(V) - m}{T_m(V) \max T_m(V)} \\
\frac{dn}{dt} = \frac{n_{\text{eq}}(V) - n}{T_n(V) \max T_n(V)}
\]

Small factors → small speed → slow variable

\[\text{Since } m \text{ is an extremely fast variable, FitzHugh proposes to assimilate } \dot{m} \text{ as a constant, and thus, he eliminates } \dot{m}. \]

Moreover, it is observed that \( v > 0.8 \) along the whole spike.

This gives a reduction to a two-dimensional system:

\[
\begin{align*}
\frac{dv}{dt} &= -\frac{1}{c} \left[ g_{Na} m^3 (0.8 - n) (V-E_{Na}) + g_K n^4 (V-E_K) + g_L (V-E_L) + \text{Iext} \right] \\
\frac{dn}{dt} &= \frac{1}{\max T_n(V)} \left[ n_{\text{eq}}(V) - n \right]
\end{align*}
\]

The characteristic values of parameters for the giant axon of the squid are:

\[c = 1 \mu F/cm^2, \quad g_K = 36 mS/cm^2, \quad g_{Na} = 120 mS/cm^2, \quad g_L = 0.3 mS/cm^2, \quad \max T_n(V) \approx 6 \times 10^{-3} \]

Therefore \( \frac{1}{c} \gg \frac{1}{\max T_n(V)} \) · Eq:

\[\varepsilon = \frac{c}{\max T_n(V)} \approx \frac{10^{-6}}{6 \times 10^{-3}} \approx 1.6 \times 10^{-4} \]

which is a small parameter. Defining a new time \( \tilde{t} = t / \max T_n(V) \)

leads to:
\[
\begin{align*}
\frac{dv}{dt} &= -g_k n^4 (v-E_K) - g_{Na} m^3 (0.8-n)(v-E_{Na}) - g_L (v-E_L) - i_{ext} \\
\frac{dn}{dt} &= \frac{n^{\infty}(v)-n}{\tau_n(v)}
\end{align*}
\]

Finally, setting \( \tau \rightarrow \tau'/\varepsilon \Rightarrow \)

\[
\begin{align*}
\frac{dv}{dt} &= \beta(v,n) = -g_k n^4 (v-E_K) - g_{Na} m^3 (0.8-n)(v-E_{Na}) - g_L (v-E_L) - i_{ext} \\
\frac{dn}{dt} &= \varepsilon \left( n^{\infty}(v)-n \right) = \varepsilon g(v,n) \quad (4.2.4-1)
\end{align*}
\]

The variable \( V \) is called fast and \( n \) is slow. Indeed, \( \frac{dv}{dt} \) is of order \( 1 \), while \( \frac{dn}{dt} \) is of \( \varepsilon \) order \( 1. \) Thus \( V \) changes quite faster than \( n \).

This is still a highly non-linear system, but FitzHugh show that it can be approximated by:

\[
\begin{align*}
\frac{dv}{dt} &= v - v^3 - w + I = \beta(v,w) \quad (F.N). \\
\frac{dw}{dt} &= \varepsilon (v-a-bw) = \varepsilon g(v,w) \quad (4.2.4-2)
\end{align*}
\]

This is the so-called FitzHugh-Nagumo model. Now generally, extensions of F-N have the form:

\[
\begin{align*}
\frac{dv}{dt} &= \beta(v,w) \\
\frac{dw}{dt} &= \varepsilon \gamma g(v,w) \quad (4.2.4-3)
\end{align*}
\]

where \( \gamma \) are control parameters (e.g. \( \gamma = (a,b) \) in F-N model)

Let us first define the solutions. \( N_\circ = \{ (u, w) \}; f(u, w) = 0 \) and \( N_\circ w = \{ (v, w) \}; g(v, w) = 0 \). Thus:

\[
N_\circ = \begin{cases} (u, w) ; w = -u + u^3 + I \end{cases} \\
N_\circ w = \begin{cases} (v, w) ; w = \frac{v^2 + 1}{2} \end{cases}
\]

At the intersection of nullclines, we have fixed points. It is easy to see that there are either one or three fixed points, depending on I:

Since \( I \) is small, away from the nullclines, the vector field is essentially dominated by the linear term, i.e., the vector field is quasi-horizontal. In other words, we can replace the FN equations by:

\[
\begin{align*}
\frac{du}{dt} &= u - u^3 - w - I \\
\frac{dw}{dt} &= 0
\end{align*}
\]

Vector field away from \( N_\circ \).
Near the \( N^0 \) nullcline, setting \( \varepsilon = \varepsilon^+ \) gives:

\[
\begin{align*}
\frac{d\sigma}{dt} &= f(\sigma, w) \\
\frac{dw}{dt} &= g(\sigma, w)
\end{align*}
\]

Then, setting \( \varepsilon = 0 \) gives \( f(\sigma, w) = 0 \) and \( \frac{dw}{dt} = g(\sigma, w) \). This means that, whenever it is possible, \(\sigma\) is just rapidly to maintain a pseudo-equilibrium corresponding to \( f(\sigma, w) = 0 \) and then the nullcline \( \sigma = \sigma(\varepsilon) \) moves along the stable manifold of the \( \sigma \) nullcline. These branches compose the so-called slow manifold. It is only on (or very close to) this curve that the motion of the solution curve is not very fast in a nearly horizontal direction.

The key claim of the real paper is that the composed of pieces coming from these two approximations. These are the so-called slow-manifold trajectories, for sufficiently small \(\varepsilon\).

---

**Spikes generation**

Consider the unstable case and considering the following figure:

A is the stable fixed point. There is a curve, called the separatrix, defined by

\[
S = \{ (\sigma, w) \mid f(\sigma, w) = 0, g(\sigma, w) < 0 \}
\]

whose equation is given by.

\[
w = 1 + \varepsilon \sigma + \sigma(1 - \varepsilon) - \varepsilon^3
\]

(Exercise)
The curve has the following property. Consider a small perturbation \( \Delta V \) about \( A \) (case I). If the trajectory \((V, W)\) make the escape from \( I \) in the phase space, corresponding to a small line fluctuation of the minimum potential \( V \).

Now, a slightly larger perturbation (case II) generate a big excursion in the phase space, corresponding to a spike emission.

The difference between the 2 cases is that in case I, perturbation is "before" the separatrix, while in case II, it is after.

This leads to the notion of threshold. The threshold is the horizontal distance between \( A \) and \( S \). In the present case, it is given by:

\[
\Theta = \Delta V - \Delta A, \quad \frac{W^2}{\Delta A} = \frac{I + E^2 \Delta A + \Delta^2 (1 - E) - \Delta^3}{1 - E^2}. 
\]  

Consider now the 3 following regions:

1. **Absolute refractory**: In this region, it is impossible to excite the neuron so that it generates a spike.

2. **Relative refractory**: In this region, a sufficiently large \( \Delta V \) generates a spike.

3. **Enhanced**: Here a \( \Delta V \) increase, smaller than the threshold, generates a spike.

**Periodic spike emission**

Here, \( A \) was a stable fixed point. Consider now the case where \( A \) is unstable.

Here a small perturbation of \( A \) generates a periodic spike.
The transition from case I to case II corresponds to a Hopf bifurcation. In the framework of neurobiology, this is called type II excitability. The spike train is generated with a frequency obeying a specific domain.

\[ \mu (\text{parameter}) \]

\[ \mu_c \]

\[ x (t, p) \]

**Anodal break excitation.** Assume that an action potential is generated and, during this, an external potential (anodal shock) is applied at the instant where the system is the point \( P \) in Fig. 11, with the effect to move \( P \) to \( P' \). If the shock is large enough such that \( P'' \) is on the left of the threshold separatrix, the action potential is abolished by the anodal shock. This phenomenon has been observed experimentally (see (48) and references therein).

**FIG. 11** - Anodal break excitation in the FitzHugh-Nagumo model.

**Spike emission by Hyperpolarization**
**Type I excitability**

This type of effect does not occur in the classical FitzHugh-Nagumo model, but in some variant, where the activation variable $u$ obeys a quadratic equation (i.e., it is a parabola). This occurs, for example, in the Morris-Lecar model.

\[
\begin{align*}
\frac{du}{dt} &= -g_{Ca} m_p(V)(V-E_{Ca}) - g_{K} w_p(V-E_K) - g_L(V-E_L) + I \\
\frac{dw}{dt} &= \varepsilon \left[ \frac{w_p(V) - w}{\tau_p(V)} \right]
\end{align*}
\]

\[
\begin{align*}
m_p(V) &= \frac{1}{2} \left[ 1 + \tanh \left( \frac{V-U_2}{U_2} \right) \right] \\
w_p(V) &= \frac{1}{2} \left[ 1 + \tanh \left( \frac{V-U_3}{V_3} \right) \right] \\
\tau_m(V) &= \frac{1}{\cosh \left( \frac{V-U_3}{V_3} \right)}
\end{align*}
\]
Spike propagation in the FitzHugh-Nagumo model.

Let us return to the spike propagation equations, rewritten in the context of the FitzHugh-Nagumo model. They write \( \text{(2.2.4-7)} \)

\[
\begin{align*}
\varepsilon \dot{w} + E \dot{v} + f(v, w) &= 0 \\
\dot{v} + g(v, w) &= 0
\end{align*}
\]

where \( \dot{v} = \frac{dv}{dt} \), \( \dot{w} \) being the variable \( x - ct \) (see section 1.2.2).

We describe the spike propagation using singular perturbation theory. If we set \( \varepsilon = 0 \), we obtain the so-called "inner equations"

\[
\begin{align*}
f(v, w) &= 0 \\
g(v, w) &= 0
\end{align*}
\]

\( \rightarrow \) No nullclines depending parametrically on \( w \).

The trajectory moves slowly on the stable branches \( N^+ \), \( N^- \) and this motion corresponds to the excited phase (resp. recovery phase) of the pulse. The pulse appears then as a hysteresis connecting the 2 branches.

Schematic sketch of spike propagation in the spatially extended Fitzhugh-Nagumo model.

It is convenient to rescale \( \varepsilon \) as \( \tilde{\varepsilon} / \varepsilon \), and to write \( \text{(2.2.8)} \) in the form

\[
\begin{align*}
\dot{v} &= -c \dot{v} - \frac{dv}{dt} \\
\dot{w} &= \varepsilon \left( v - a - bw(t) \right)
\end{align*}
\]

\( v \) is the formal analog of a potential, depending parametrically on the slow variable \( \tilde{w} \).
\[ \frac{1}{R_a} \frac{\partial^2 V}{\partial x^2} = C \frac{\partial V}{\partial t} + \left[ g_{Na} m^3 h (V-E_{Na}) + g_L n^4 (V-E_L) + g_L (V-E_L) \right] \]

\[ \frac{\partial m}{\partial t} = \alpha_m(V)(1-m) - \beta_m(V)m \]
\[ \frac{\partial h}{\partial t} = \alpha_h(V)(1-h) - \beta_h(V)h \]
\[ \frac{\partial n}{\partial t} = \alpha_n(V)(1-n) - \beta_n(V)n \]

**FitzHugh-Nagumo reduction**

\[ m v + n + n v = \text{etc...} \Rightarrow \]

\[ \frac{1}{R_a} \frac{\partial^2 \omega}{\partial x^2} = C \frac{\partial \omega}{\partial t} - f(\omega, \omega) = C \frac{\partial \omega}{\partial t} - (\omega - \omega^3 - \omega - I) \]

\[ \frac{\partial \omega}{\partial t} = \epsilon (\omega - a - b \omega) = \epsilon g(\omega, \omega) \]

**Propagation equation**

\[ u(x,t) = \omega(x-ct) = \omega(\xi) \quad ; \quad \frac{\partial}{\partial x} = \frac{\partial}{\partial \xi} \quad ; \quad \frac{\partial}{\partial t} = -c \frac{\partial}{\partial \xi} \]

\[ \frac{1}{R_a} \frac{\partial^2 \omega}{\partial \xi^2} = -c \frac{\partial \omega}{\partial \xi} - f(\omega, \omega) \]

\[ -c \frac{\partial \omega}{\partial \xi} = \epsilon g(\omega, \omega) \]

\[ \text{Set} \ R_a = 1, \ c = \frac{\partial \omega}{\partial \xi} \Rightarrow \]

\[ \dot{\xi} = -c \omega - f(\omega, \omega) \]
\[ \dot{\omega} = -\frac{\epsilon}{c} g(\omega, \omega) \]
First equations

\[ \frac{\varepsilon}{\varepsilon} \rightarrow \frac{\partial}{\partial \varepsilon} \rightarrow \varepsilon \frac{\partial}{\partial \varepsilon} \]  

\[ \Rightarrow \begin{cases} \varepsilon^2 \dddot{\nu} + \varepsilon c \ddot{\nu} + f(\nu, w) = 0 \\ c \dot{\nu} + g(\nu, w) = 0 \end{cases} \]
1.2.5) Integrate and Fire models (lapique 1907)

In this model, one fixes a threshold $\Theta > 0$ such that:

1) If $V < \Theta$ then $V$ obeys:

$$ T_m \frac{dV}{dt} = -V(t) + RI(t) \tag{1.2.5-1} $$

with $T_m = RC$ is the characteristic constant of the membrane.

This is the equation of load for a RC circuit, $\frac{1}{T_m}$ is called the leak rate.

2) If $V$ reaches the threshold, at some time $t^*$ then $V$ instantaneously resets to a new value $V_0 < \Theta$, i.e.

$$ V(t^*) = \Theta \Rightarrow V(t^*) = V_0 $$

This approach has the advantage to provide an exactly solvable model of neurons, which mimics the spike. For example, the membrane potential after a spike arriving at time $t_+$ and before $t_2$, i.e., at time $t_2$, is given by:

$$ V(t) = V_0 e^{-\frac{t-t_2}{T_m}} + \frac{1}{C} \int_{t_2}^{t} e^{-\frac{t-t_0}{T_m}} I(t_0) dt $$ \tag{1.2.5-2}$$

This model is also easy to use for network dynamics. However, its dynamics is rather slow, compared to the HH model. Moreover, the notion of instantaneous reset introduces spurious mathematical properties, as we shall see.

Nevertheless, this is an extremely fruitful model to provide analytical results at the level of networks. It allows one to figure out the dynamical complexity generated by non-linear collective neuron dynamics, before embarking on more complex neuron model.

However, these properties can be spurious and generated by model definition.
Fig. 21. Potential $V$ of eq. (50) for: Fig. 21a: $w < 0$; Fig. 21b: $w = 0$; Fig. 21c: $w > 0$.

Fig. 22. Phase portrait of eq. (54) for: Fig. 22a: $c = 0$; Fig. 22b: $c > 0$; Fig. 22c: $c = c_0$. The situation corresponds to $w > 0$.

For $c = 0$, there is no effective dissipation and there is an homoclinic trajectory connecting the unstable limit $V_r$ to itself. When $c$ is large enough, the phase portrait has a shape depicted in Fig. 22b. By continuity, there is an intermediate value of $c$ ($c_w$) for which there is an heteroclinic orbit connecting $V_r$ and $V_r^+$. This orbit corresponds to an ascending front moving at a speed $c_0$, selected by the medium. In the same way, there is a descending front for $w < 0$, connecting $V_r$ and $V_r^-$. The global curve is a pulse of a spiky propagating at speed $c_0$, selected by the medium.

The limit of FitzHugh–Nagumo equations:

- 2-dimensional system instead of a 4-dimensional HH model.
- Less dynamical regimes than observed in HH and in the nervous system.
1.2.7.1) Measuring neuron activity

The activity of a neuron is manifested by emission of spikes. A sequence of spikes is called a spike train. A spike train is a complex shape with a depolarizing phase, a repolarizing phase, and a refractory period. However, it is possible to simplify this notion by introducing the notion of spike time and refractory time.

The spike time has not a unique definition in real neurons. One can define either the time when the membrane potential reaches a maximum value, or the time when the neuron potential reaches a threshold value. The latter, in a practical sense, is a practical upper limit to the time window of interest. In the opposite case, the spike time is defined as the time when the membrane potential reaches the threshold (which is here practically, and uniquely defined, consistently to real spikes). Hence, spike time is defined with an infinite precision in IF models. This is a quasi and non-realistic property which leads to stochastic meaning in real neural networks.

The refractory period is what a spike immediately follows another spike.

Formally, a spike train can be defined as a list of spike times:

$\{t_1, \ldots, t_n\}$

where $t_i$ is the $i$-th spike emitted by neuron $i$.

The above constraints impose that $t_i$ and $t_{i+1}$ are at least separated by $\tau$, and that $t_i$ is not defined with an infinite precision.

A spike train can also be viewed as a rate signal of the form:

$$S(t) = \sum_{n=1}^{\infty} \lambda(t - t_n)$$

where $\lambda$ is a constant probability of the spike occurring between time $0$ and time $t$.

In the simplest case, $\lambda$ is a step function. Note that the sum is discrete (i.e., there are finitely many spikes in a finite time interval). This property does not hold anywhere else. No assumptions made above.
For simplicity, we assume that $\tau_0$ is small but positive. We use it as a time step for the discretization of a grid. In this setting, the frequency rate is given by:

$$
\nu_i(\tau_0, \Delta) = \frac{\text{Prob} \left[ V_i(t + \Delta) > 0 \right]}{\text{Prob} \left[ V_i(t + \Delta) < 0 \right]}
$$

where for simplicity we identify the spike occurrence, and the crossing of a fixed threshold $\tau_0$.

During the time interval $[t, t + \Delta t]$, the local piece of membrane associated with $V_i$ receives signals; and evolves like:

$$
V_i(t + 1) = V_i(t) + \Delta (V_i(t), t, \cdot)
$$

where $\Delta$ integrates all effects leading to a change in $V_i$. Then:

$$
\nu_i(\tau_0) = \text{Prob} \left[ \Delta (V_i(\tau_0), t) : \geq \tau_0 - V_i(t) \right]
$$

$$
= 1 - F_{\tau_0} (\tau_0 - V_i(t))
$$

$F_{\tau_0} (\tau_0 - V_i(t))$ is a repetition function. Hence it is sigmoidal (monotonically increasing, with $F(-\infty) = 0$, $F(+\infty) = 1$).

Consequently $1 - F_{\tau_0} (\tau_0 - V_i(t))$ is also sigmoidal.
This is the frequency with which a neuron emits a spike, or the probability that a spike is emitted over a small time interval. These are different ways of defining it.

Mathematically, the firing rate of neuron \( i \), \( \lambda_i(t) \), is the probability density that a spike occurs between \( t \) and \( t + \delta t \):

\[
P(i \text{ fires in } [t, t + \delta t]) = \lambda_i(t) \delta t
\]

Empirically, it can be estimated by repeating a large number of trials (assuming that the system has not evolved meanwhile).

In the case of idealized spikes, modeled by a $S$ function, let us introduce

\[
P_i(t) = \sum_j S(t - \tau_j^i)
\]

(corresponding to eq. (12.7.14) with $\theta = 8$). We may write

\[
\lambda_i(t) \delta t = \int_t^{t + \delta t} \langle p_i(z) \rangle \, dz
\]

where \( \langle \cdot \rangle \) denotes the trial average. In this case, for any suitable

\[
\langle f \times p_i \rangle = \int f(z \langle p_i(z) \rangle \, dz = \int f(z) \lambda_i(t - z) \, dz = \langle f \rangle \lambda_i
\]

If $f$ is related to a linear response when the average response (over trials) to a spike train is given by the firing rate.

Another way of defining the firing rate (not equivalent) is to perform a time average:

\[
\lambda = \frac{1}{T} \int_0^T \langle p_i(z) \rangle \, dz
\]

called the spike count rate (over a time window of length $T$).

Finally, one can average $\lambda_i$ over trials giving

\[
\langle \lambda_i \rangle = \frac{1}{T} \int_0^T \langle p_i(z) \rangle \, dz = \frac{1}{T} \int_0^T \lambda_i(z) \, dz
\]

In the literature, these three are called firing rates even if they are not always equivalent. They are under ergodic hypothesis.
1.3) Modelling the synapse

Neurons interact together via synapses (and gap junctions). Spikes get along the axon, until they reach a synaptic terminal. A local variation of the membrane potential triggers the release of a neurotransmitter into the synaptic cleft.

The neurotransmitter reaches the postsynaptic receptor localized at the dendritic spine. It generates an postsynaptic potential (PSP).

Depending on the pre-cytosynaptic neuron and on the neurotransmitter used by the neuron, the PSP can be either positive or negative. In the first case, the postsynaptic neuron and the synaptic connections are called excitatory. Spikes coming from the pre-synaptic neuron increase the membrane potential of the postsynaptic neuron, which is more likely to generate a spike train. If PSP is negative, corresponding to an inhibitory pre-synaptic neuron.

A neuron receives a lot of spikes from other neurons. A typical dendritic tree receives about ten thousand synaptic entries, distributed in the dendritic tree space. As a matter of fact, dendrites are the most important part in surface and volume of the brain. According to their morphological properties, one classifies the neurons: pyramidal, amacrine, stellate, etc...

Dendrites constitute in fact the basic element of information handling in the brain since most of the messages exchanged by neurons travel via synapses - dendrites.

The local modification of membrane potential of the postsynaptic neuron (PSP) propagates along the dendritic tree, according to the same equations/mechanisms as we saw for the axon, up to the soma. Here all PSP are summed up generating a response of the postsynaptic neuron.
Modelling of synaptic

The shape of a PSP is represented in the following figure.

Mathematically, it is expressed by a function \( a_i \) called the response.

This response is typically represented by a Green's function of type

\[
\sum_{\ell=0}^{\infty} a_{i\ell} \frac{d}{dt} e^{-t/\tau_i} \alpha_i(t) = S(t)
\]

where \( S(t) \) is the Dirac delta, \( \alpha_i(t) \) is the response of neuron \( i \), and \( a_{i\ell} \) are characteristic coefficients.

Typical examples of synaptic responses are

\[
\alpha_i(t) = \frac{\alpha_i}{\tau_i} e^{-t/\tau_i} H(t)
\]

where \( H(t) \) is the Heaviside function (causality) corresponding to the Green equation:

\[
\frac{1}{\tau_i} \frac{d\alpha_i}{dt} + \frac{\Delta}{\tau_i^2} \alpha_i = 8(t)
\]

Another example, corresponding to the previous figure, is:

\[
\alpha_i(t) = \frac{\alpha_i}{\tau_i} e^{-t/\tau_i} H(t)
\]

where Green equation is:

\[
\frac{1}{\tau_i} \frac{d^2\alpha_i}{dt^2} + \frac{2}{\tau_i} \frac{d\alpha_i}{dt} + \frac{1}{2\tau_i^2} \alpha_i = 8(t)
\]

Now, there are two alternatives. In the first case, corresponding to so-called voltage-based models, one assumes that not synaptic potentials have the same shape no matter which pre-synaptic population causes (but the sign and amplitude may vary though). Therefore, the input of neuron \( i \) to a stimulus from neuron \( j \) is:

\[
\alpha_{ij}(t) = W_{ij} \alpha_i(t)
\]
where $W_{ij}$ is called synaptic efficiency or synaptic weight.

On the opposite, activity-based models, the shape of the PSP depends on the presynaptic cell:

$$\dot{x}_{ij}(t) = W_{ij} x_{ij}(t)$$  \hspace{1cm} (1.3.2-7)

In this realm, the response of neuron $i$ to a signal $s_j(t)$ (e.g., spike train) coming from neuron $j$ is given by

$$r_{ij}(t) = (d_{ij} * s_j(t))(t)$$  \hspace{1cm} (1.3.2-8)

i.e., for a voltage-based model:

$$\sum_{e=0}^{e=k} a_e(t) \frac{d}{dt} r_{ij}(t) = \sum_{e=0}^{e=k} a_e(t) s_j(t) = W_{ij} s_j(t) = W s_j(t)$$

In the same way, for an activity-based model:

$$\sum_{e=0}^{e=k} a_{ij}(e) \frac{d}{dt} r_{ij}(t) = W_{ij} s_j(t)$$  \hspace{1cm} (1.3.2-9)

1.3.3 Neuron response

The response $r_{ij}$ of each synapse to excitation copying from neuron $j$, propagates along the dendritic tree, up to the soma where it is summed up. As a consequence, the membrane potential at the soma of neuron $i$ is ruled by the equation:

$$\sum_{e=0}^{e=k} a_{ij}(e) \frac{d}{dt} V_i = \sum_{j=1}^{N} W_{ij} s_j(t - \tau_j)$$  \hspace{1cm} (1.3.2-10)

where $N$ is the number of neurons (with the convention that $W_{ii} = 0$ if there is no synaptic connection from $i$ to $i$), and $\tau_j$ is the propagation delay from the dendrite to the soma.

In most examples, $s_j(t)$ is the sequence of spikes ($0$'s) arriving from presynaptic neuron $j$. In the simplified modelling, the
\[ S(\delta(t)) = \sum_{n=0}^{\infty} S(t - \delta^n) \]

where \( \delta \) is a time of occurrence of the \( n \)-th spike emitted by neuron \( j \), from a fixed time origin. Note that this modelling introduces a spurious notion: the spike time is instantaneous.

A more precise modelling would write \( \delta(t) \) as a function fitting the spike shape. For example, to avoid the notion of instantaneous spike line one may replace \( S \) by \( S_e \), where \( S_e \) is the function:

\[
S_e(x) = \begin{cases} 
1, & x \in [-\epsilon, \epsilon], \\
0, & \text{otherwise},
\end{cases}
\]

Here \( \epsilon \) takes into account the fact that a spike has a duration and that the notion of instantaneous spike has no biological foundation. More detailed spike shape can be introduced as well.

### 1.3.4 Frequency rate

In the next example we shall adopt the simplest modelling of spike within a Dirac function, keeping in mind the warning raised in the previous discussion.

We consider first a situation where the characteristic time constant of the membrane potential (e.g. the time \( \tau \) in the synaptic integration) is quite a bit longer than the characteristic spike time \( \tau_s \). In this setting the variation of \( V \) on the time constant \( \tau \) corresponds to the arrival of many spikes, and therefore an integration over all spike fluxes. The firing rate, as we saw in the probabilistic emission of a spike between \( \tau_s \) and \( \tau \), is given by:

\[
\nu_j(t) dt = \int \frac{\left( \sum_{n=0}^{\infty} S(t - \delta^n) \right) dt}{\tau_s} = \frac{1}{\tau_s} \text{urge}(t) \]

Assume here that \( \nu_j(t) \) is replaced by \( \nu_j(t) \), in eq. (1.3.2.12)

In this case, the \( S_j(t) \) is replaced by \( \nu_j(t) \), in eq. (1.3.2.12)

The frequency rate is a function of the membrane potential of \( V_j \), of sigmoidal type, i.e.
13.5 Generalized Integrate and Fire models

There are Integrate and Fire models where the synaptic conductance depends on spikes received from pre-synaptic neurons. Then, the membrane potential change, below the threshold $\theta$, is:

$$\frac{dV_k}{dt} = \frac{-1}{C_m} \left( V_k - E_I \right) - \sum_{j \in I} g_{kj} (V_k - E_j) - \sum_{j \in E} g_{kj} (V_k - E_j) + I_{ext}(t). \quad (13.5-1)$$

Here, $g_{kj}$ is the synaptic conductance of the synapse connecting neuron $j$ to neuron $k$, $I$ is the set of inhibitory neurons and $E$ is the set of excitatory neurons. $E_j$ are the corresponding reversal potentials. Note that $g_{kj} \geq 0$. Typically, for inhibitory neurons $E_j = E^- = -75$ mV and for excitatory neurons $E_j = E^+ = 0$

Therefore, a negative $V_k - E_I$ the inhibitory term is negative, which decreases $V_k$, while the excitatory term is positive, thus increasing $V_k$

Note that here, there is no spatial sub-division for the neuron, it is punctal. Indeed, we combine local excitation for the total of synapses to somata which normally occurs at soma.

In conductance based gIF models, $g_{kj}$ does not depend on as it should, but on past spikes received by neuron $k$, from neuron $j$. More precisely, $g_{kj}$ reads:

$$g_{kj} = \sum_{n=1}^{M_j(t,\tau_j)} \alpha \left( t - \tau_j^{(n)} \right)$$

where $\tau_j^{(n)}$ is the "time" of occurrence of the $n$-th spike emitted by pre-synaptic neuron $j$, counting from a starting time $\alpha(x)$ is the synaptic response. According to modelling, it can be on $k$ or on $j$.

$\tau_j^{(n)}$ is the list of spikes time $\tau_j^{(n)}$. Finally $M_j(t,\tau_j)$ is the number of spikes occurring from some initial time origin. The dot is important. Indeed, spikes emitted by pre-synaptic neurons
\[ V_j(t) = S_j(V_j(t)) \] (1.3.4.1)

where \( S_j \in [0,1] \) is a sigmoid, with slope \( q_j \).

This is what is experimentally observed. On theoretical grounds it has been justified in the previous chapter 1.2.7

In this case, eq. (1.3.2.11) becomes

\[ \sum_{e=0}^{K} \alpha_i^{(e)} \frac{d}{dt} V_i = \sum_{j=1}^{N} W_{ij} S_j(V_j(t)) + I_i(t) + B_i(t) \] (1.3.4.2)

for a voltage-based model.

The above equation affords extensions where one adds an external current \( I_i \) and noise \( B_i \):

\[ \sum_{e=0}^{K} \alpha_i^{(e)} \frac{d}{dt} V_i = \sum_{j=1}^{N} W_{ij} S_j(V_j(t)) + I_i(t) + B_i(t) \] (1.3.4.3)

Note that, according to Green equation (1.3.2.1) the equivalent to

\[ V_i(t) = \alpha_i^* \left[ \sum_{j=1}^{N} W_{ij} S_j(V_j(t)) + I_i(t) + B_i(t) \right] \] (1.3.4.4)

The activity of a neuron is (see section 1.3.2):

\[ A_j(t) = [\alpha_j^* \times C_j(t)] = [\alpha_j^* \times S_j(V_j(t))] \]

Hence, in an activity-based model, the response depends on the postsynaptic cell

\[ A_j(t) = \alpha_j^* S_j \left[ \alpha_j^* \left( \sum_{j=1}^{N} W_{ij} S_j(V_j(t)) + I_i(t) + B_i(t) \right) \right] \]

\[ A_i(t) = \alpha_i^* S_i \left[ \sum_{j=1}^{N} W_{ij} A_j + I_i(t) + B_i(t) \right] \] (1.3.4.5)

This corresponds to the differential equation:

\[ \sum_{e=0}^{K} \alpha_i^{(e)} \frac{d}{dt} A_i = S_i \left[ \sum_{j=1}^{N} W_{ij} A_j + I_i(t) + B_i(t) \right] \] (1.3.4.6)
1.3.6) Synaptic plasticity

The synapses have the capacity of evolving and adapting according to the activity of the pre- and post-synaptic neuron. This property is one of the key elements explaining why neural networks have the ability of adapting, learning, recognizing, and generalizing.

There are several mechanisms of adaptation identified.

**Long Term Potentiation (LTP)**

Long Term Potentiation is a long-lasting enhancement of synaptic plasticity. Specifically, it is the long-lasting improvement in communication between two neurons that results from stimulating them repeatedly. LTP is due to several mechanisms that have not been fully identified. Basic LTP improves the probabilistic cells' sensitivity to synapse transmitter input by increasing the activity of receptors and their number.

![Diagram showing LTP mechanism](Image)

**Figure:** Increase in the PSP amplitude resulting from stimulating.

**Long Term Depression (LTD)**

Long Term Depression is the reduction of synaptic strength that lasts from hours to days. It results from either the synaptic stimulation or persistent postsynaptic depolarization. It results in changes in postsynaptic receptors, whereas changes in presynaptic release may also play a role.

![Diagram showing LTD mechanism](Image)

**Figure:** Decay in the PSP amplitude.

**Spike Time Dependent Plasticity (STDP)**

Spike Time Dependent Plasticity (STDP) is a mechanism for changes in synapses that are determined by the timing of pre- and post-synaptic spikes. If the pre-synaptic spikes precede the post-synaptic spikes, this leads to LTP. Conversely, if the pre-synaptic spikes follow the post-synaptic spikes, this leads to LTD.

The time scale varies, but it is typically in the order of milliseconds.
It is possible to write eq. (1.3.5.1) in a more compact form. Introducing the global conductance of neuron $k$,

$$g_k(t, t') = \sum_{j \in I} g_{kj}(t, t') + \sum_{j \in E} g_{kj}(t, t') + \frac{1}{\tau_{k}}$$

where $t'$ is the list of spike times received by neuron $k$, we shall introduce a more explicit and compact notation in a few sections and the "current"

$$i_k(t, t', s_k) = \frac{E}{\tau_k} + \sum_{j \in I} E_j g_{kj}(t, t') + \sum_{j \in E} E_j g_{kj}(t, t') + \Delta_i(t, t')$$

we may rewrite (1.3.5.1) in the form:

$$(1.3.5.5) \quad \frac{dV_k}{dt} + g_k(t, t', s_k) V_k = -i_k(t, t', s_k), \quad G = \pm$$

Note that this is a very complex (non-autonomous) dynamical system since evolution of neuron $k$ depend on the whole past of the network via firing times $t_i^{(m)}$. 
Examples

In this setting, STDP shows several possible implementations. Define the STDP function

\[ f(x) = \begin{cases} 
A - \exp \frac{x}{\tau_+} & x < 0; \\
A - \exp \frac{x}{\tau_-} & x > 0; \\
0 & x = 0 
\end{cases} \]

Then a basic implementation is:

\[ g(W_{ij}, [\omega_i]^T, [\omega_j]^T) = \frac{t}{t_0} \sum_{\Delta t = t - T_0} f(t_0 - \Delta t) \omega_i(t) \omega_j(t) \]

where \( T_0 \) is a characteristic time scale (e.g., max(\( \tau_-, \tau_+ \))). Usually, people add a small parameter \( \tau \) to keep the value of \( f(x) \) bounded in the definition of \( g \). Ensuring that \( \Delta t \) stays within bounds. In this case, \( \Delta t \) depends also on \( W_{ij} \).

Another implementation, called “nearest neighbors,” reads:

\[ g(W_{ij}, [\omega_i]^T, [\omega_j]^T) = \frac{t}{t_0} \sum_{\Delta t = t - T_0} f(t_0 - \Delta t) \omega_i(t) \omega_j(t) \]

where \( t_0 = \min(t, 0) \).

As a last example, Gerstner & Kohn (2002) propose:

\[ g(W_{ij}, [\omega_i]^T, [\omega_j]^T) = \frac{t}{t_0} \sum_{\Delta t = t - T_0} f(t_0 - \Delta t) \omega_i(t) \omega_j(t) \]
From these observations researchers try to extract some "rules" characterizing synaptic evolution. The most known is the Hebb rule.

D. Hebb (1949)

When an action of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

Note that Hebb's rule is somewhat misleading in LTP or LTD (the synapses change more quickly, respectively). The rule has been discovered before.

**Modelling plasticity**

On a mathematical ground, synaptic plasticity may be viewed as a modification of the synaptic weight, $w_{ij}$, depending on the past spike activity of neurons $i$ and $j$. Since neuron activity is measured in spikes per time interval, denoted by $E_i$, the sequence of spikes of neuron $i$, emitted during the time interval $[t-T,t]$, the change in the weight $w_{ij}$ is given by:

$$\frac{d w_{ij}}{dt} = g \left( w_{ij}, \sum_{t-T}^{t} E_i, \sum_{t-T}^{t} E_j \right).$$

Typically, people consider a time discretization so that spikes arrive on a time grid. In this case, the list of spike times emitted by neurons can be represented by a raster plot:

$$[\omega_{i}]_{t-T} = \{ \omega_i(t), i = 1-N, t = t-T, T \}
\omega_i(t) = \begin{cases} 1 & \text{if a spike at } t \\ 0 & \text{otherwise} \end{cases}$$

Then, the synapse update reads:

$$[\omega_{i}]_{t-T} = \{ \omega_i(t), i = 1-N, t = t-T, T \}
\omega_i(t) = \begin{cases} 1 & \text{if a spike at } t \\ 0 & \text{otherwise} \end{cases}$$

(1.3.6-2)
There are many implementations of Hebb's rule. They usually rely on frequency rates. Here are several examples:

\[ g(w_{ij}, [w_i], [w_j]) = \frac{1}{T} \sum_{t=T-D}^{T} \chi_{i}(t) \chi_{j}(t) \] (4.3.6-6)

with \( \chi_{i}(t) = \frac{1}{T} \sum_{t=T-D}^{T} \omega_{i}(t) \). This is a shrinkage version of Hebb's recipe. One can also add thresholding on the definition of activity:

\[ g(w_{ij}, [w_i], [w_j]) = H(\chi_{i}(t) - d_i) H(\chi_{j}(t) - d_j) \] (4.3.6-7)

where \( d_i \in [0, 1] \) is an activity threshold.

These rules have the effect of only increasing \( w_{ij} \). One can also add an opposite effect (decreases of the synapses with no correlated activity of pre and post synaptic neurons):

\[ g(w_{ij}, [w_i], [w_j]) = (\chi_{i}(t) - d_i)(\chi_{j}(t) - d_j) \] (4.3.6-8)

\[ g(w_{ij}, [w_i], [w_j]) = \frac{1}{T} \sum_{t=T-D}^{T} \frac{[\chi_{i}(t) - \chi_{i}(t)] [\chi_{j}(t) - \chi_{j}(t)]}{T} \] (4.3.6-9)