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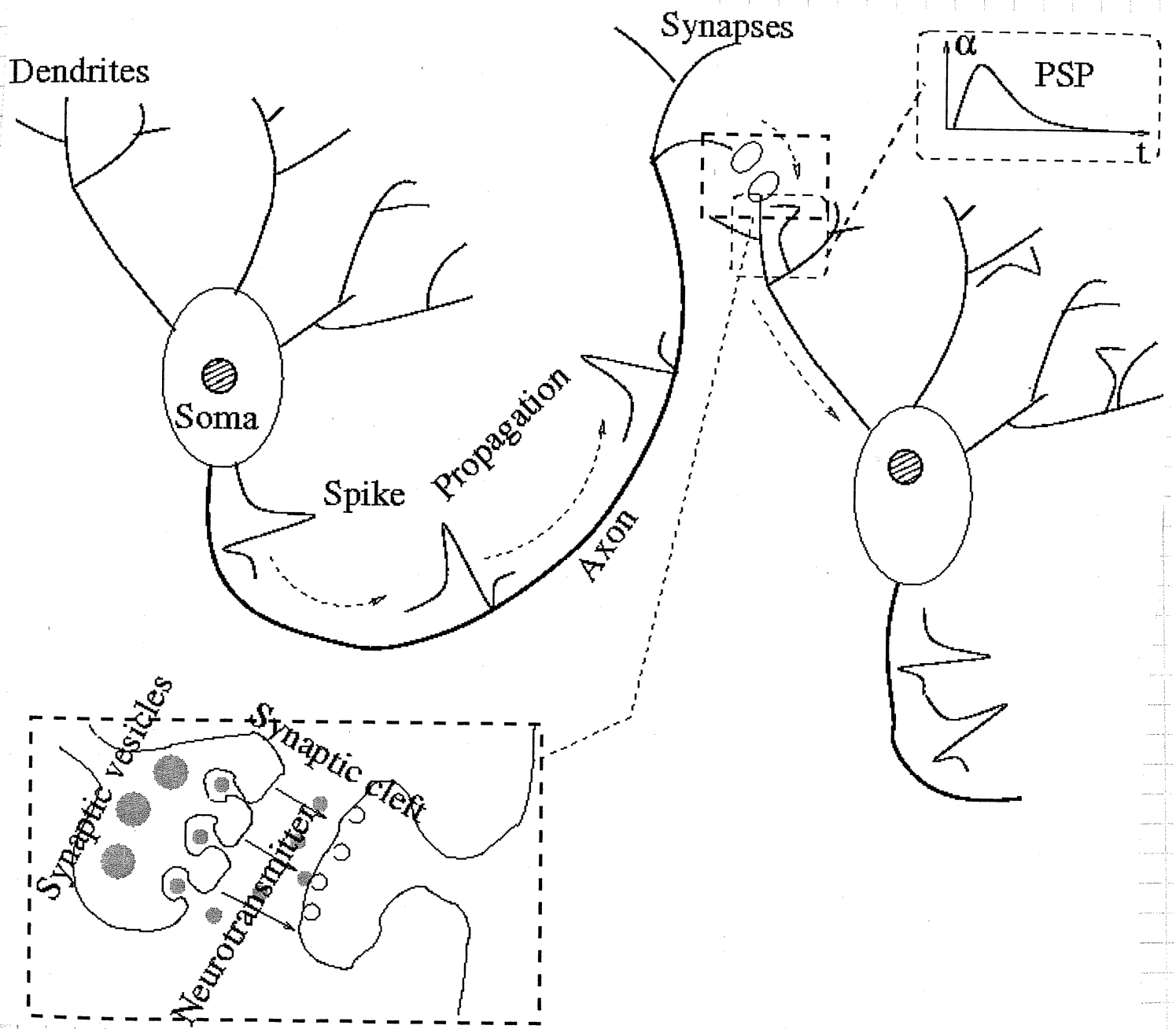
Neuronal modeling and neural dynamics.

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.

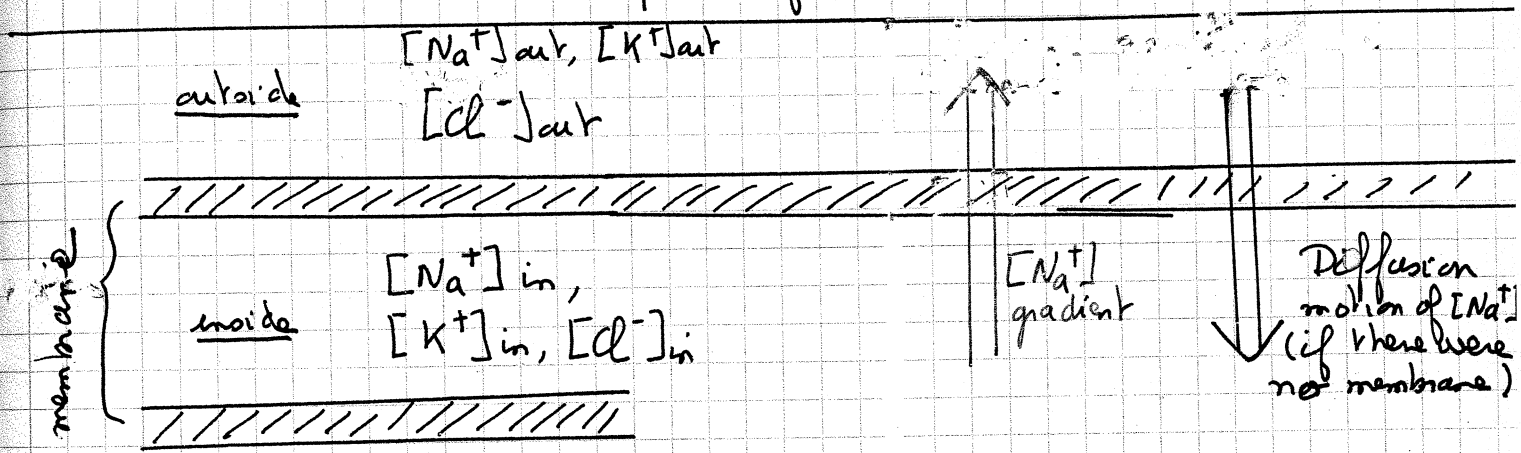
A.L. Hodgkin and A.F Huxley (1952) "Current carried by Sodium and Potassium ions through the membrane of the giant axon of Loligo", J. Physiol (Lond), 116, 449-472.

" " " " " " (1952) "A quantitative description of ion currents and its application to conduction and excitation in nerve membranes", J. Physiol. (Lond) 117, 500-544.

→ Nobel price in medicine, 1901.

Ionic concentrations

Let us consider a small piece of axon.



outside $[Na]^+_{out} = [Cl^-]_{out} \sim 140\,mM$ ⟹ Concentrations gradients ⟹ Electric potential

$[K^+]_{out} \sim 10\,[Na^+]_{in}$

$[K^+]_{in} \sim 5\,[K^+]_{out}$

Nernst 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 ⟹

$$[X]_{in} \sim \exp -\frac{q V_{in}}{kT}, \quad [X]_{out} \sim \exp -\frac{q V_{out}}{kT} \qquad (q = ne, |e| = 1.6 \cdot 10^{-19})$$

$$\Rightarrow \quad V_{in} - V_{out} = \frac{kT}{q} \log \frac{[X]_{out}}{[X]_{in}} = \frac{dV\,kT}{dV\,q} \log \frac{[X]_{out}}{[X]_{in}}$$

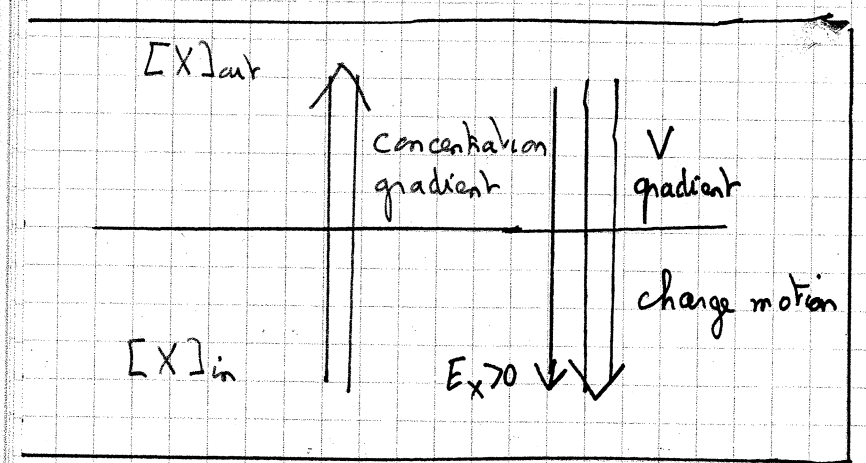
Set $F = \mathcal{N}e = 96500\ C/mol$ (Faraday's number) and $R = \mathcal{N}k$ the ideal gaz constant, we have

$$E_X = V_{in}(X) - V_{out}(X) = \frac{RT}{nF} \log \frac{[X]_{out}}{[X]_{in}} \quad (1.2.1\_1)$$

Nernst potential

Ex: For the giant axon of the squid, at $T = 6{,}3\ °C$,

$E_{Na} \sim 55\ mV$, $E_K \sim -75\ mV$

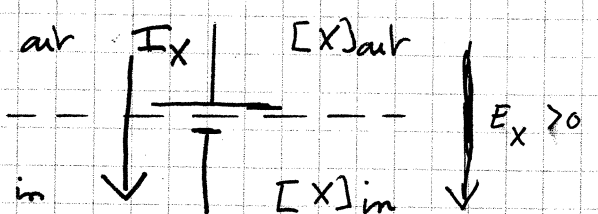


NB: If $[X]_{out} > [X]_{in}$

$\Leftrightarrow E_X > 0 \Leftrightarrow V_{in} > V_{out}$

From Fick's law, concentration gradient $\Rightarrow$ current.

$\vec{j}_X = -D \vec{\nabla} [X]$ (when membrane is removed)

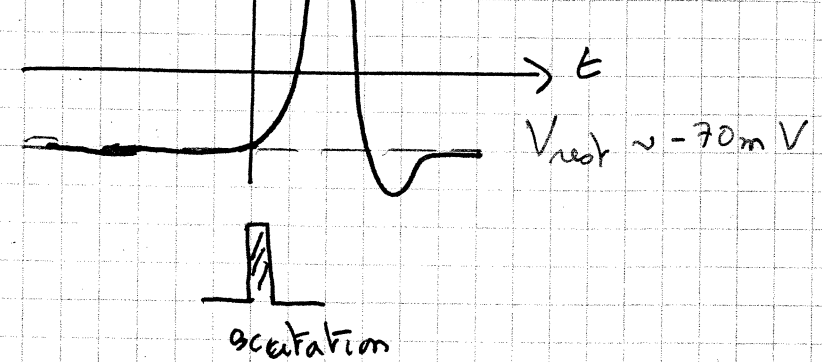


$\Rightarrow$ Current generator (with positive charges)

Related face: In the direction of $E_X = V_{in} - V_{out}$

A few facts:

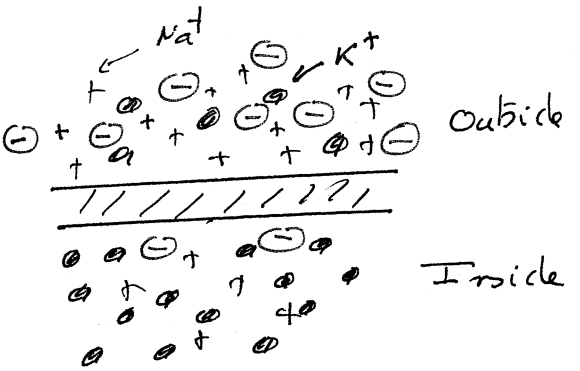
1) When submitted to excitation, a piece of membrane potential is subject to a strong and typical variation of its potential (spik



There is a charge transfert through the membrane

Ionic concentrations

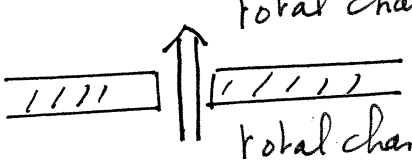
	Inside	Outside
K^+	140	5
Na^+	10	140
Cl^-	10	50
Ca^{2+}	0.0001	2
(Proteins PO_4^{3-} etc..		



Steady state

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

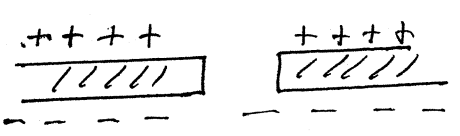
Open a K^+ channel $\Rightarrow$ Potassium diffusion



Diffusion does not continue until concentration gradient vanishes.

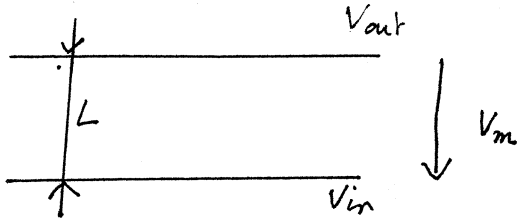
Indeed diffusion stops when the electric gradient equilibrates the concentration gradient.

$\Rightarrow$ In the steady state there are more positive charges outside than inside.



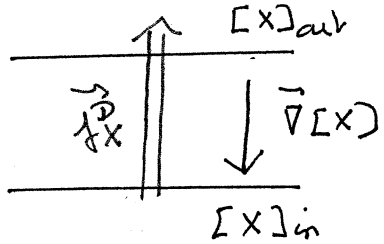
The membrane potential is determined by the Goldman - Hodgkin - Katz equations.

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 j_X the current flux (number of ions crossing per unit time and per unit area of the membrane. It is due to 2 contributions.

Ex for K^+

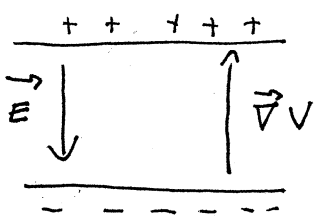


→ A diffusion current given by Fick's law.

$$\vec{j}^D_X = -D_X \vec{\nabla}[X] \quad \leftarrow \text{mol/m}^3$$

This gives rise to a charge current

$$(1) \quad \vec{j}^e_X = -q\rho D_X \vec{\nabla}[X]$$



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

→ The charge displacement generates a gradient of electric potential which induces an opposite electric current given by:

$$\vec{j}'^e_X = q^2 \rho_X \mu_{el} \vec{E} \qquad (2)$$

where μ_{el} is the electric mobility $\mu_{el} = \frac{v_d}{F} = \frac{v_d}{qE}$ and v_d being the terminal drift velocity. Moreover the mobility is related to the diffusion coefficient by:

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

ρ_X is the particle density $\rho_X = \mathcal{N}[X]$

Thus $j_x = q \frac{d\mathcal{P}_x [X] D_x}{RT} = -q \frac{D_x}{RT} \frac{n_x [X] E}{D_x L}$

Setting $F = d\mathcal{P}_e = 96500\,C$ being the Faraday constant.

The total electric current is:

$$\vec{j}_{el} = q \left[-d\mathcal{P} D_x \vec{\nabla}[X] + D_x \frac{F n_x}{RT} [X] \vec{E} \right]$$

$$= q d\mathcal{P} \left[-D_x \vec{\nabla}[X] + D_x \frac{F n_x}{RT} [X] \vec{E} \right]$$

Considering the current in the vertical direction z

$$j_{el} = q d\mathcal{P} \left[-D_x \frac{d[X]}{dz} + D_x \frac{F n_x}{RT} \frac{V_m}{L} [X] \right]$$

Set $j_x = \frac{j_{el}}{q d\mathcal{P}}$; $\mu = \frac{F V_m}{RT}$; $P_x = \frac{D_x}{L}$

(matter current) (dimensionless) (permeability)

$$\boxed{j_x = -D_x \frac{d[X]}{dz} + \mu n_x P_x [X]}$$

Hence $$\frac{d[X]}{-j_x + \mu n_x P_x [X]} = P_x^{-1} dz$$

We assume that j_x is constant through the membrane.

$$\int_0^L \frac{d[X]}{-j_x + \mu n_x P_x [X]} = \frac{1}{n_x \mu P_x} \left[\ln\left(-j_x + n_x \mu P_x [X]\right) \right]_{in}^{out} = \frac{L}{D_x}$$

$$\Rightarrow \frac{-j_x + n_x \mu P_x [X]_{out}}{-j_x + n_x \mu P_x [X]_{in}} = \exp\left(n_x \mu P_x D_x^{-1} L\right) = \exp(n_x \mu)$$

>

$$-j_X\left[1-e^{n_X\nu}\right] = n_X\nu\left[P_X[X]_{out} - e^{n_X\nu}P_X[X]_{in}\right]$$

$$\boxed{j_X = \nu n_X P_X\left(\frac{[X]_{out} - e^{n_X\nu}[X]_{in}}{\left(1-e^{n_X\nu}\right)}\right)}$$

To each species is associated such a current. In the steady state, $V = V_m$ and: $j_{tot} = \sum_X j_X = 0$.

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

Then:

$$\sum_{\text{cations } C} j_C + \sum_{\text{anions } A} j_A = 0 \qquad \text{avec} \quad j_C \text{ orienté de l'ext. opposé à } j_A$$

$$0 = \nu\left[\sum_C P_C\left(\frac{[C^+]_{out} - e^{\nu}[C^+]_{in}}{1-e^{\nu}}\right) + \sum_A P_A\left(\frac{[A^-]_{out} - e^{-\nu}[A^-]_{in}}{1-e^{-\nu}}\right)\right]$$

$$= (1-e^{-\nu})\sum_C P_C\left([C^+]_{out} - e^{\nu}[C^+]_{in}\right) + (1-e^{\nu})\sum_A P_A\left([A^-]_{out} - e^{-\nu}[A^-]_{in}\right)$$

$$= \sum_C P_C[C^+]_{out} - e^{\nu}\sum_C P_C[C^+]_{in} - e^{-\nu}\sum_C P_C[C^+]_{out} + \sum_C P_C[C^+]_{in}$$

$$+ \sum_A P_A[A^-]_{out} - e^{\nu}\sum_A P_A[A^-]_{out} - e^{-\nu}\sum_C P_C[A^-]_{in} + \sum_A P_A[A^-]_{in}$$

Set $w = \sum_C P_C[C^+]_{out} + \sum_A P_A[A^-]_{in}$

$$v = \sum_C P_C[C^+]_{in} + \sum_A P_A[A^-]_{out}$$

$$w - e^{\nu}v - e^{-\nu}w + v = 0 \Rightarrow w - e^{\nu}v = e^{-\nu}w - v = e^{-\nu}(w - e^{\nu}v)$$

$$\Rightarrow \quad w - e^{\nu}v = 0 \qquad (\text{since } e^{-\nu} > 0)$$

Therefore $\beta = \frac{v_m}{v} = \frac{v_m}{RT} \Rightarrow v_m = \frac{RT}{F} \ln \frac{w}{v}$

$$V_m = \frac{RT}{F} \ln \left(\frac{\sum_C P_C [C^+]_{out} + \sum_A P_A [A^-]_{in}}{\sum_C P_C [C^+]_{in} + \sum_A P_A [A^-]_{out}} \right)$$

These are the Goldman-Hodgkin-Katz equations.

As a particular case, if there is only one species, X

$$V_m = \frac{RT}{nF} \ln \frac{[X]_{out}}{[X]_{in}}$$

Nernst Potential

Membrane conductance

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

For each species X (eq. 2)

$$j_x = -D_x \frac{d[X]}{dz} + \frac{D_x n_x F}{RT} [X] \underbrace{\frac{dV}{dz}}_{E}$$

$$\Rightarrow j_x \frac{RT}{F D_x} \frac{dz}{[X]} = -\frac{RT}{F} \frac{d[X]}{[X]} + n_x dV$$

Assuming j_x = cte inside the membrane

$$j_x \underbrace{\frac{RT}{F D_x} \int_0^L \frac{dz}{[X]}}_{\Gamma_X(V)} = \underbrace{-\frac{RT}{F} \ln \frac{[X]_{out}}{[X]_{in}}}_{-n_x E_X} + n_x V$$

$$j_x \Gamma_X(V) = n_x (-E_X + V) = n_x (V - E_X)$$

$$j_{el} = -\sum_x \underbrace{n_x F}_{q_x dP} (j_x + j_p) = -\sum_x n_x F \left(j_p - \Gamma_x^{-1}(V)(V - E_x) \right)$$

j_p : ionic pump (→ out)

Set $g_x(V) \doteq n_x F \Gamma_x^{-1}(V)$ conductance

$$\boxed{j_{el} = -j_p + \sum_x g_x(V)(V - E_x)}$$

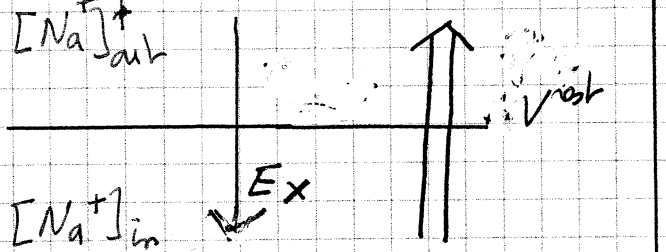
NB : Electrophysiologist use the opposite sign (opposite convention)

2) At rest ($V_2 = -70\,mV$) the concentration of $[Na^+]$, $[K^+]$, $[Cl^-]$, $[Ca^{2+}]$... is roughly constant $\Rightarrow$ membrane is not permeable to ions at rest.

NB: This is precisely the concentrations of species, inside and outside which fixes the difference of potential between inside and outside to:

$V^{rest} = V_{in}^{(rest)} - V_{out}^{(rest)} \sim -70\,mV$

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



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

$= qE_x - q\,V^{rest} = q(E_{Na} - V^{rest})$

$\Rightarrow$ At rest, the effective potential viewed by $[Na]^+$ is:

$E_{Na} - V^{rest} \sim 125\,mV$

In the same way:

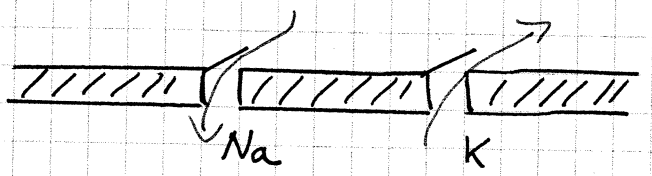
$E_K - V^{rest} \sim \pm 0.05\,mV$

$\Rightarrow$ At rest, the Na^+ ions view a strong electromotric force, $q(E_{Na} - V^{rest})$ which leads them to enter inside the membrane. But they can't since the membrane is not permeable at rest.

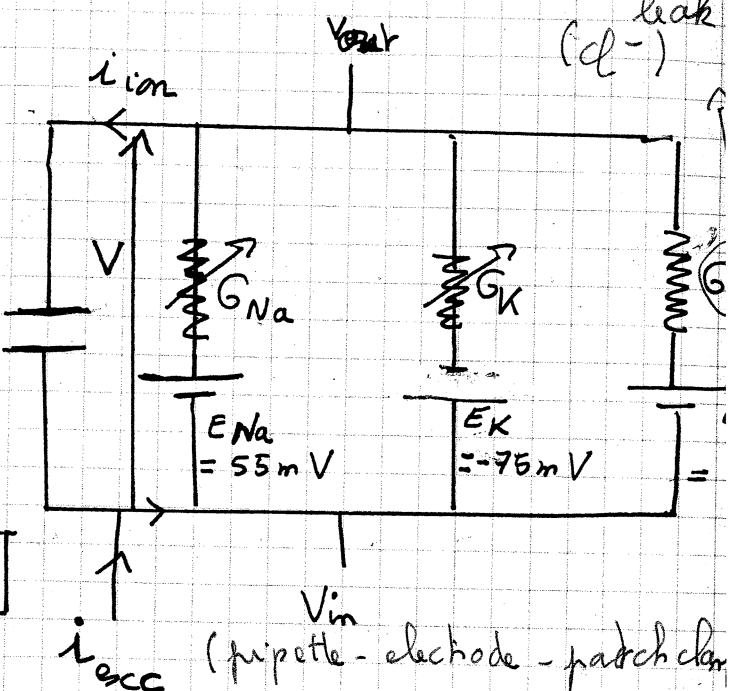
Hypothesis 1 The spike arises because the membrane becomes permeable to ions, due to the excitation.

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.

$\Rightarrow$ The conductance of the membrane potential, varies, due to these channels, and depends on V. $\Rightarrow$ to each species X associ... a conductance $G_X(V)$.



This provides an equivale... electric circuit.



Now, apply the laws of electricity

$$i_{ion} = i_{Na} + i_K + i_L \quad (1.2.1\_2)$$

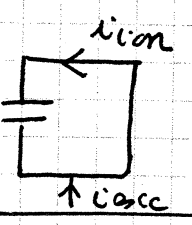
(the total current crossing the membrane is due, in HH model, to these 3 current)

Ohm's law

$$i_X = G_X(E_X - V) = -G_X(V - E_X) \quad (1.2.1\_3)$$

Kirchhoff's law

$$C\frac{dV}{dt} = i_{ion} + i_{ext} \quad (1.2.1\_4)$$



NB: if $V = E_K$ the corresponding current vanishes.

$\Rightarrow$

$$C\frac{dV}{dt} = -G_{Na}(V - E_{Na}) - G_K(V - E_K) - G_L(V - E_L) + i_{ext} \quad (1.2.1\_5)$$

First Hodgkin - Huxley equation

Conductances

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 $\rightarrow$ activation
h $\rightarrow$ inactivation

By a slight abuse of language m, h is also the probability that a gate m, h be open.

To K^+ channel is associated one type of gate : n

Now, experiments showed that: (the conductance is prop. to the product of probability that a gate is open)

$$G_{Na} = g_{Na}\, m^3 h \qquad (1.2.1-6)$$

and

$$G_K = g_K\, n^4 \qquad (1.2.1-7)$$

Master equations

At this stage we have made an explicit hypothesis. The piece of membrane is considered over a space and time scale large enough so that the conductances are defined via probabilities of open/closed ionic gates. Therefore, this amounts to assuming that there are sufficiently many gates in the piece of membrane, and there are sufficiently many events open/closed, so that the notion of probability of being open/closed is relevant in the present modelling.

These gates are specific molecules, and considering the membrane at the scale of these gates would require a different physics (quantum).

Let us now make another assumption. The probabilities are given by a master equation:

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

where $\alpha(V)$ = transition closed → open ; β : transition open/closed

$\alpha(V)$ → Depends on V

Define:

$$\tau(V) = \frac{1}{\alpha(V)+\beta(V)} \quad ; \quad p^\infty(V) = \frac{\alpha(V)}{\alpha(V)+\beta(V)}$$

$$\Rightarrow \boxed{\frac{dp}{dt} = \frac{p^\infty(V) - p}{\tau(V)}} \qquad (1.2.1-8)$$

with solution: (1.2.1-9)

$$\boxed{p(t) = p^\infty(V) - [p^\infty(V) - p_0(V)]\, e^{-t/\tau(V)}}$$

Hence, $\tau(V)$ is the characteristic time to equilibrate, while $p^\infty(V)$ is the equilibrium probability.

The Hodgkin-Huxley equations

Combining all these equations we end up with

$$C\frac{dV}{dt} = -g_{Na}m^3h(V-E_{Na}) - g_K n^4(V-E_K) - g_L(V-E_L) + I_{ext}$$

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

$$\frac{1}{\gamma(T)}\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m = \frac{m^\infty(V)-m}{\tau_m(V)} \qquad (1.2.1\text{-}10)$$

$$\frac{1}{\gamma(T)}\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h = \frac{h^\infty(V)-h}{\tau_h(V)}$$

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

$$\gamma(T) = 3^{(T-6.3)/T}, \quad T \text{ in } {}^\circ C,$$

thus, it is equal to 1 at 6.3 °C

Finally, the factors α, β have been obtained empirically by H. H. They are given by: (1.2.1-11)

$$\alpha_m(V) = \psi\left(-\frac{(V+45)}{10}\right) \quad ; \quad \beta_m(V) = 4e^{-\frac{(V+70)}{18}}$$

$$\alpha_n(V) = 0.1\,\psi\left(-\frac{(V+60)}{10}\right) \quad ; \quad \beta_n(V) = 0.125\,e^{-\frac{(V+70)}{80}}$$

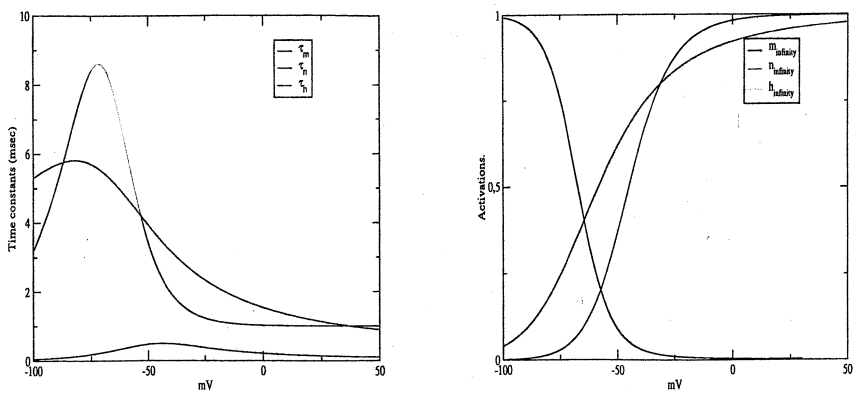
$$\alpha_h(V) = 0.07\,e^{-\frac{(V+70)}{20}} \quad ; \quad \beta_h(V) = \frac{1}{1+e^{-\frac{(V+40)}{10}}}$$

where

$$\psi(x) = \begin{cases} \dfrac{x}{e^x-1} & \text{if } x \neq 0 \\ 1 & \text{if } x = 0 \end{cases} \qquad (1.2.1\text{-}12)$$

The time constants

Let us now draw the time constants τ_m, τ_n, τ_h and the steady state values n^∞, m^∞, h^∞ as functions of V.



The main remarks are :

1) The time constant for the activation variable m of the Na is about one order of magnitude less than 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.

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

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

The spike generation

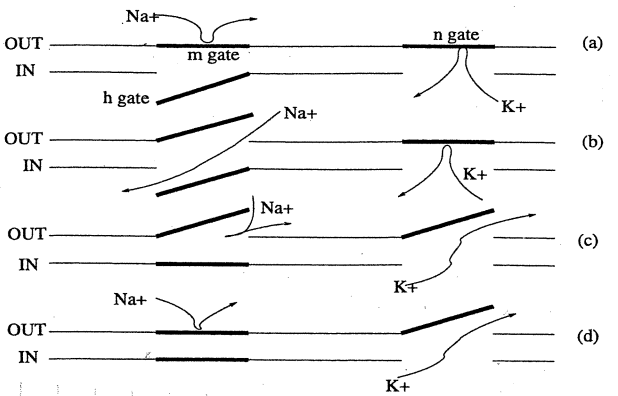
The next figure summarizes how a spike is produced, taking into account all informations we have collected.

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

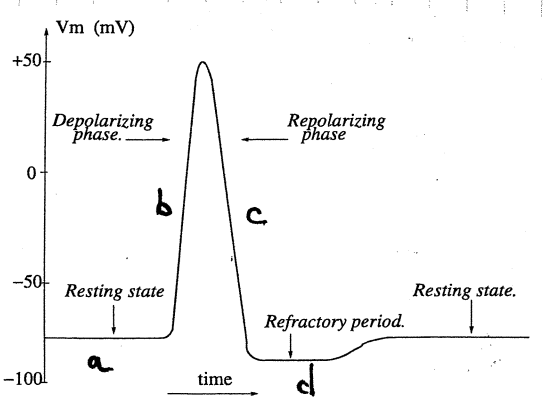
Phase b : Depolarization. If V increases, due to a local excitation then, first the m gates open fast allowing Sodium to diffuse inside the cell, following the concentration gradient, while the n gates are still closed.

This increases the membrane potential. +

c) Repolarization. Then, the gate n open slowly, generating an outpu
K^+ current. In the same time h decreases and h gates close, preventing
Sodium from coming into the cell. In this phase, V decreases



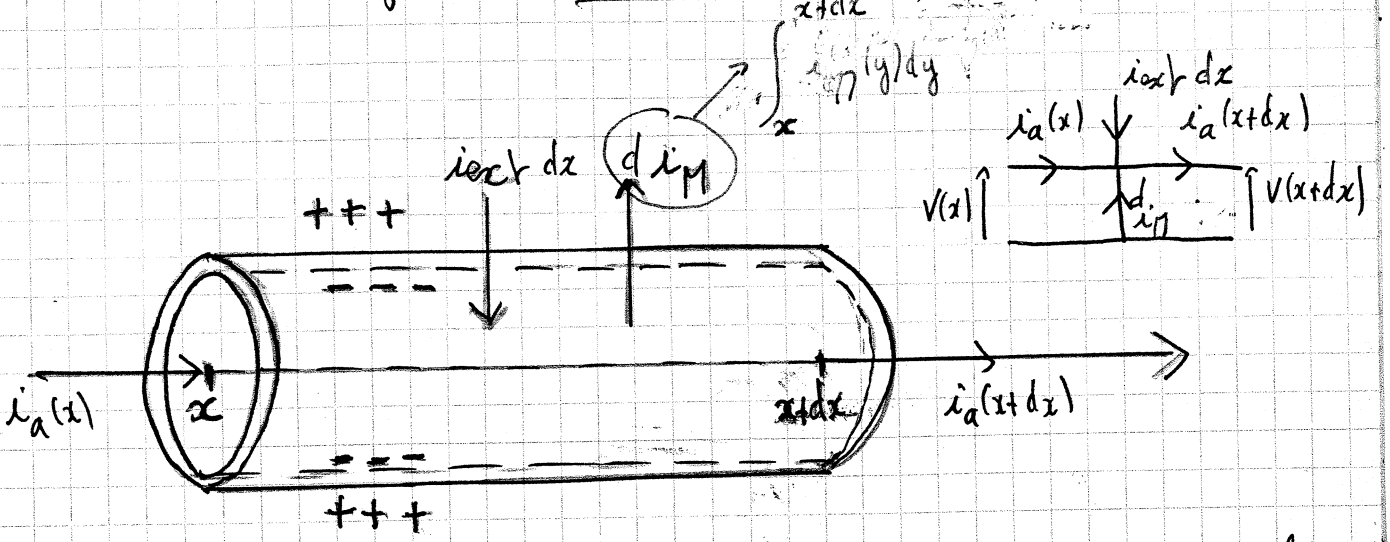
Successive phases in a spike generation



d) Refractory period. In this phase, the m gate close, the h gate
are closed, and n is open. Finally h open and the initial configuratio
of gates is restored. The ionic balance is restored by ionic pump.
During this phase it is not possible to excite the neuron.

1.2.2) Propagation of spikes

The previous equations characterize the dynamics of a small piece of membrane. Let us now consider a spatially extended membrane, with a "tube" shape modelling either the axon or a dendrite. For simplicity we assume that the radius a of the tube is a constant, a.



NB: we use here the electrophysiologists convention: A current is positive when it goes out of the cell.

We have $i_a(x) + i_{ext}\,dx = di_m(x) + i_a(x+dx) \Rightarrow$

$$\frac{\partial i_a}{\partial x} = -\frac{di_m}{dx} + i_{ext}$$

Moreover: $i_a = \pi a^2 j_a$ where j_a is the density of longitudinal current. We have $j_a = \sigma_{int} E_{int}$. There is also an external current, but negligible. The longitudinal current is mainly due to charge transport inside the membrane.

Also, $E_{int} = -\frac{\partial V_{int}}{\partial x}$; $E_{ext} = -\frac{\partial V_{ext}}{\partial x} \Rightarrow$

$$E_{int} - E_{ext} = -\frac{\partial}{\partial x}(V_{int} - V_{ext}) = -\frac{\partial V}{\partial x} = \frac{j_a}{\sigma_{int}} - \frac{j_{ext}}{\sigma_{ext}}$$

$$\Rightarrow -\frac{\partial V}{\partial x} = \frac{i_a}{\pi a^2 \sigma_{int}}.$$

call $R_a = \frac{1}{\sigma_{int}\pi a^2}$ the longitudinal cytoplasm resistance

We have $-\frac{\partial V}{\partial x} = R_a i_a$.

Finally. $\boxed{\frac{\partial^2 V}{\partial x^2} = R_a \frac{di_m}{dx} + i_{ext}}$ (1.2.2-1)

$\frac{di_m}{dx}$ is the density of current crossing the membrane and given by HH equations.

$$\frac{di_m}{dx} = C\frac{\partial V}{\partial t} + i_{ion} = C\frac{\partial V}{\partial t} + \underbrace{2\pi r(x)}_{S(x)=2\pi r(x)dx} \left[g_{Na} m^3 h (V-E_{Na}) + g_K n^4 (V-E_K) + g_L (V-E_L \right.$$

We obtain in this way the cable equations:

$$\frac{1}{R_a}\frac{\partial^2 V}{\partial x^2} = C\frac{\partial V}{\partial t} + \left[g_{Na} m^3 h (V-E_{Na}) + g_K n^4 (V-E_K) + g_L (V-E_L) \right] 2\pi r + i_{ext}$$

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

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

$$\frac{\partial n}{\partial t} = \alpha_n(1-n) - \beta_n n$$

(1.2.2-2)

Spike propagation

The spike propagates along the axon, consequently propagation solutions of form:

$$V(x,t) = \mathcal{U}(x-ct) = \mathcal{U}(\xi),$$

exist, with c, propagation speed, and $\xi = x - ct$. Thus,

$\frac{\partial}{\partial x} = \frac{\partial}{\partial \xi}$ and $\frac{\partial}{\partial t} = -c\frac{\partial}{\partial \xi}$. We assume, here, for simplicity that axon is infinite (i.e. its length is quite large than dendrites) and that axon is at rest at infinity i.e $V(x) \to 0 \Leftrightarrow \mathcal{U}(\xi) \to 0$ $x \to +\infty$ $\xi \to \infty$.

change in ref. of potentials

We obtain a set of reduced equations.

$$\frac{1}{R}\frac{d^2V}{d\xi^2} = -c\,C\frac{dV}{d\xi} + \underbrace{\left[g_{Na}m^3h(V-V_{Na}) + g_K n^4(V-V_K) + g_L(V-V_L)\right]}_{\times 2\pi\Omega}$$

$$\frac{dm}{d\xi} = -\frac{1}{c}\left[\alpha_m(1-m) - \beta_m m\right] \qquad (1.2.2\text{-}3)$$

$$\frac{dh}{d\xi} = -\frac{1}{c}\left[\alpha_h(1-h) - \beta_h h\right]$$

$$\frac{dn}{d\xi} = -\frac{1}{c}\left[\alpha_n(1-n) - \beta_n n\right].$$

Here $V_X = E_X + V_0$ with $V_0 = -70\,mV$ assuming that at rest $V = 0$ (change in the average reference of potentials)

It is possible to show that these equations have a solution corresponding to a propagating speed $c = 18.8\,m/s$ very close to Hodgkin found experimentally $c = 21.2\,m/s$. They also give with a good accuracy the evolution of m, h, n.

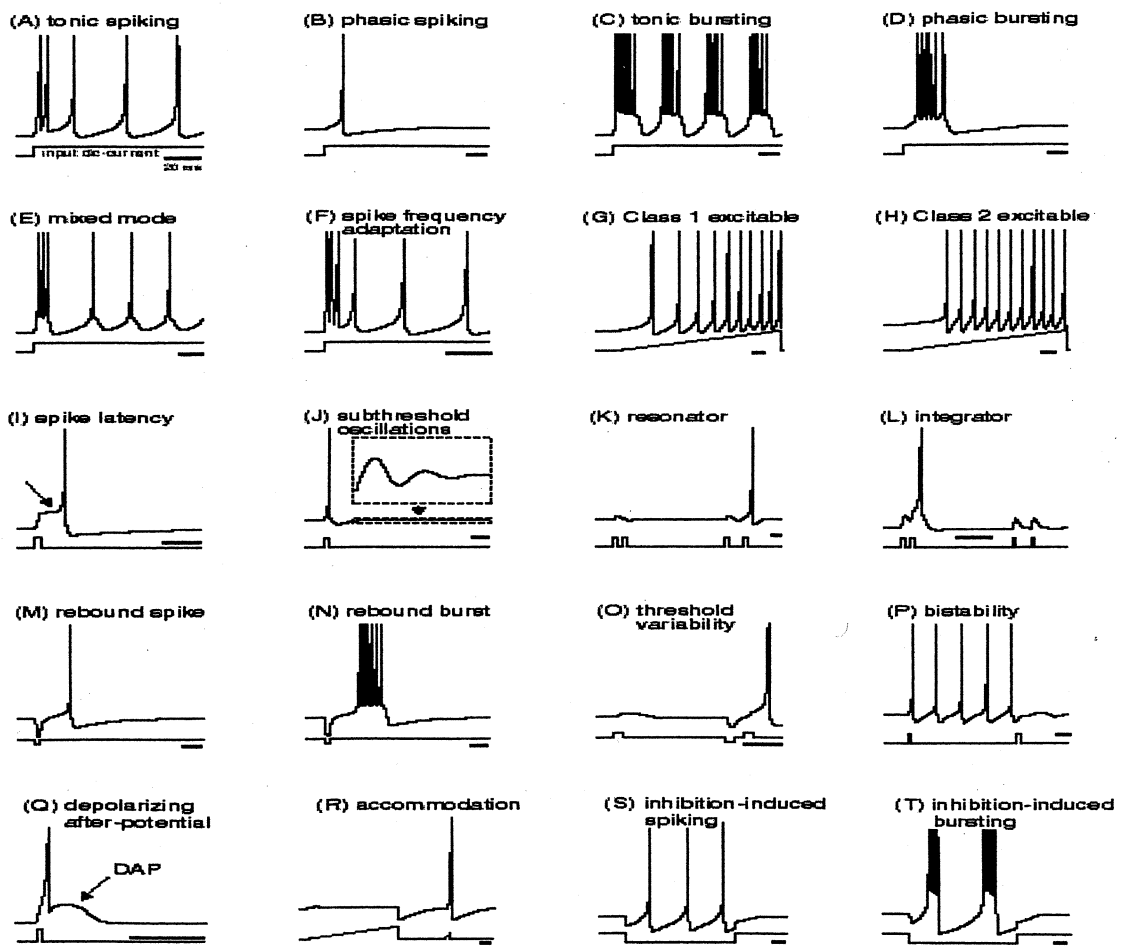
Note also the role of refactory period which select a direction of propagation.

1.2.3) Dynamics of Hodgkin-Huxley's model

Though improved models for the membrane potential of the squid axon have been formulated (Clay, J Neurophysiol, 80 (1998) 903-913) the Hodgkin-Huxley model remains "the paradigm" for the so-called conductance based models of neural systems.

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

Izhikevich, E. (2004, September). Which model to use for cortical spiking neurons? IEEE Trans Neural Netw, 15 (5), 1063–1070.



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 works, especially by Guckenheimer and collaborators, illustrating the overwhelming richness of this model.

Refs: J. Rinzel and R. Miller "Numerical calculation of stable and unstable periodic solutions to the Hodgkin-Huxley equations"; Math. Biosci, 49 (1980) 27-59.

J. Guckenheimer, I.S. Labouriau "Bifurcations of the Hodgkin-Huxley equations: A new twist", Bull. Math. Biol, 55, (1993), 937-952

J. Guckenheimer, R.A. Oliva "Chaos in the Hodgkin-Huxley model", Siam J. Applied dynamical systems, Vol 1, No 1, (2002), 105-114

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

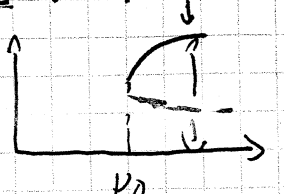
- the Nernst potential : E_{Na}, E_K, E_L
- the conductances : g_{Na}, g_K, g_L
- the imposed current : I_{ext}
- the temperature : T

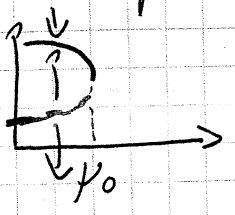
Some of these parameters can be controlled experimentally like E_{Na}, E_K or I_{ext}. Varying these parameters induces bifurcations, i.e. qualitative changes in dynamics. Some of these bifurcations have been mathematically studied.

Here is a short dictionnary of bifurcations occuring in the Hodgkin-Huxley model (codimension 1, 2, i.e. 1, 2 parameters are varying simultaneously).

Codimension 1 bifurcations

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

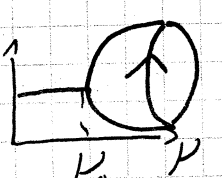




$$\dot{x} = \mu - x^2$$

Hopf bifurcation

Apparition (or disparition) of a periodic orbit by destabilization of a stable fixed point.

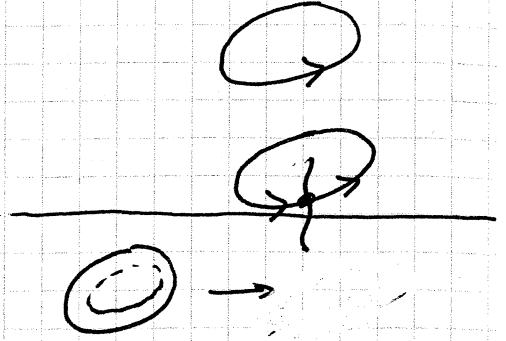


The amplitude of the orbit growths like $\sqrt{\mu - \mu_0}$.

The period approaches a positive limit as $\mu \to \mu_0$

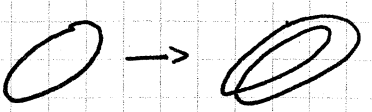
Saddle loop or homoclinic bifurcation (sl)

The amplitude of a periodic orbit increases until it captures a saddle point and disappears. Its period tends to infinity as $\mu \to \mu_0$



Saddle node of cycles : Two periodic orbit coalesce and disappear.

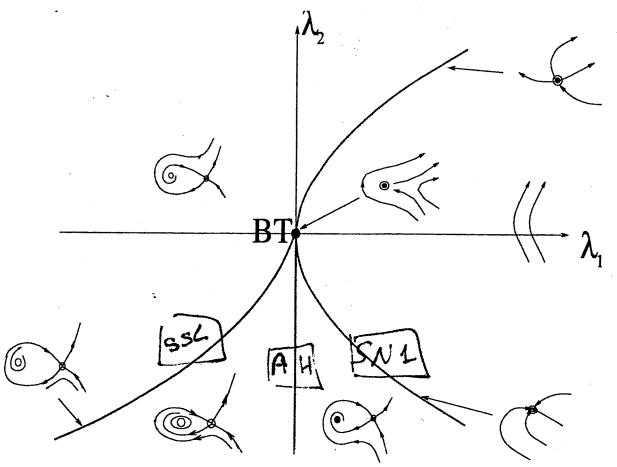
Period doubling : A periodic orbit changes its stability while a periodic orbit of twice its period coalesces with the bifurcating periodic orbit.



Codimension 2 bifurcations

Cusp (c) 3 eq points coalesce into one

Bogdanov - Takens



$\sigma < 0$

$$\begin{cases} \dot{u} = v \\ \dot{v} = a + bu + u^2 \\ \qquad + \sigma u v \end{cases}$$

Chaos in HH model. (Student work)

The Hodgkin-Huxley equations also exhibit a chaotic dynamic. This has been shown by several authors. Dai and Kumagai ("Nonlinear dynamics of small-scale biophysical neural networks", Biophy Neural Networks, R.R. Poznanski, ed. Mary Ann Liebert, Inc, Larchmont, NY, 2001, pp 261-301) have shown the existence of chaotic attra but for values of the parameters which are outside the physical range.

More recently, Guckenheimer and Oliva, have shown, using numerical methods the existence of chaos for realistic values of the parameters. More precisely they have shown the existence of a horseshoe which is the paradigm of a chaotic system (see appendix)

The biological significance of a chaotic dynamics is the following. A chaotic dynamics has the characteristics to be highly dependent on initial conditions, this to be highly unpredictible. In HH model the chaotic invariant set is a highly unstable structure associated with the notion of "threshold" for action potentials.

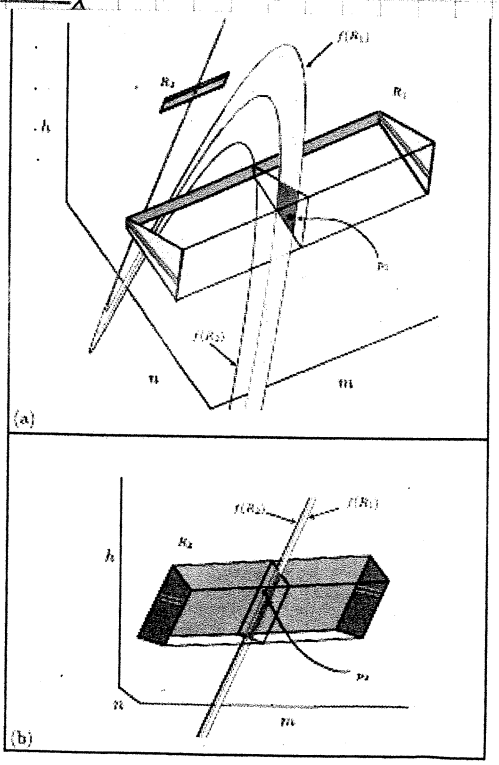
Action potentials for neurons are large all-or-nothing voltage spikes. It is commonly believed that a spike is triggered when the amplitude of the membrane potential reaches a critical value, called a threshold. Hence, in this paradigm, applied to the HH model, a function $v_T(m,n,h)$ is a threshold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

Unfortunately, the work by Guckenheimer and Oliva suggests that the boundary between initial states that lead to action potential and those that do not is a fractal set. Therefore, initial states that lead to a rest state and those leading to firing are interleaved, and, instead of a single function v_T, there are infinitely many.

There are also uncountable sheets in the phase space that lead neither to the stable state nor to firing and action potentials, and every neighborhood contains stable state and firing state.

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

But this result highlight the overwhelming complexity of neuron dynamics, and the risks of simplifying its dynamics description



Bifurcations of HH model

Here is an example of bifurcations diagram occuring when E_K and I varies (from Guckenheimer-Labouriau, 93).

Student work: Read the paper and summarize it - Represent numerically the various dynamical regimes in the phase space and in the space E_K, I.

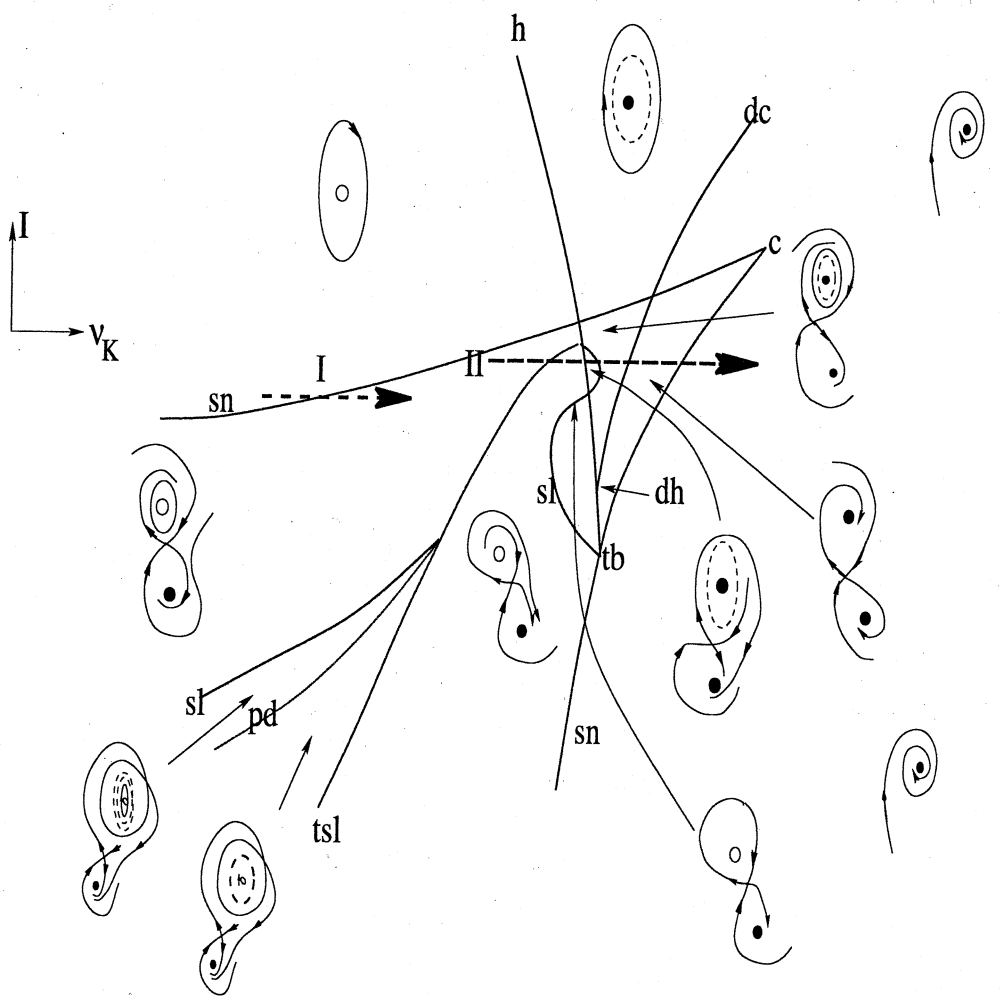


FIG. 18 – *Bifurcation diagram of the Hodgkin-Huxley equations when varying the parameters I,ν_K. This figure has been drawn "by hand" from the Figure 1 in (79). Stable equilibrium points are shown as black dots, unstable focus as white dots, stable limit cycles are closed curves with solid lines and 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).*

1.2.4) The FitzHugh-Nagumo model (Student work)

The model

The Hodgkin-Huxley equations are quite complex and although they have been proposed more than fifty years ago, they still resist to a complete analysis. 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 & Arimoto & Yoshizawa (1962).

Refs :

FitzHugh R. (1961), "Impulses and physiological states in models of nerve membrane", Biophys. J., 1: 445-466.

Nagumo J. S., Arimoto S, Yoshizawa (1962), "An active pulse transmission line simulating nerve axon", Proc. IRE, 50: 2061-2070.

The main observation leading to neuron excitability is the separation of time scale, where the variable n respond quite faster than h, n. Set:

$$T_M(V) = \frac{\tau_m(V)}{\max_V \tau_m(V)} \quad ; \quad T_H(V) = \frac{\tau_h(V)}{\max_V \tau_h(V)} \quad ; \quad T_N(V) = \frac{\tau_n(V)}{\max_V \tau_n(V)}$$

which provides characteristic times between 0 and 1. From the previous analysis we know that $\max_V \tau_m(V)$ is about 10 times smaller than $\max_V \tau_n(V)$, and $\max_V \tau_h(V)$. Set:

$$\varepsilon_h = \max_V \tau_m(V) \Big/ \max_V \tau_h(V) \sim 0.1$$

$$\varepsilon_m = \max_V \tau_m(V) \Big/ \max_V \tau_n(V) \sim 0.1$$

Then Hodgkin-Huxley equations write, using these definitions:

$$\frac{dV}{dt} = -\frac{1}{C}\left[g_{Na} m^3 h (V-E_{Na}) + g_K n^4 (V-E_K) + g_L (V-E_L) + i_{ext}\right]$$

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{T_M(V) \max_V \tau_m(V)}$$

$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{T_H(V) \max_V \tau_h(V)} = \varepsilon_h \left(\frac{h_\infty(V) - h}{T_H(V)}\right) \frac{1}{\max_V \tau_m(V)}$$

$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{T_N(V) \max_V \tau_n(V)} = \varepsilon_n \left(\frac{n_\infty(V) - n}{T_N(V)}\right) \frac{1}{\max_V \tau_n(V)}$$

small factor $\Rightarrow$ small speed $\Rightarrow$ slow variable

Since m is an exchanely fast variable Fitz Hugh proposes to assimilate it as a constant, and, thus, to eliminate it. Moreover, it is observed that $h + n \approx 0.8$ along the whole spike.

This gives a reduction to a two dimensional system:

$$\begin{cases} \frac{dV}{dt} = -\frac{1}{C}\left[g_{Na} m^3 (0.8-n)(V-E_{Na}) + g_K n^4 (V-E_K) + g_L (V-E_L) + i_{ext}\right] \\ \frac{dn}{dt} = \frac{1}{\max_V \tau_n(V)} \left[\frac{n_\infty(V) - n}{T_N(V)}\right] \end{cases}$$

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

$C = 1 \mu F/cm^2$, $g_K = 36 m S/cm^2$, $g_{Na} = 120 m S/cm^2$, $g_L = 0.3 m S/cm^2$, $\max_V \tau_n(V) \sim 6 \times 10^{-3} s$.

Therefore $\frac{1}{C} >> \frac{1}{\max_V \tau_n(V)}$. Set:

$$\varepsilon = \frac{C}{\max_V \tau_n(V)} \sim \frac{10^{-6}}{6 \times 10^{-3}} \sim 1.6 \times 10^{-4}$$

which is a small parameter. Defining a new time $t' = t / \max_V \tau_n$ leads to:

$$\begin{cases} \varepsilon \dfrac{dV}{dt'} = -g_K n^4 (V-E_K) - g_{Na} m^3 (0.8-n)(V-E_{Na}) - g_L (V-E_L) - i_{stim} \\ \dfrac{dn}{dt'} = \dfrac{n^\infty(V)-n}{\tau_n(V)} \end{cases}$$

Finaly, setting, $t = t'/\varepsilon \Rightarrow$

$$\begin{cases} \dfrac{dV}{dt} = f(V,n) = -g_K n^4 (V-E_K) - g_{Na} m^3 (0.8-m)(V-E_{Na}) - g_L (V-E_L) - i_{stim} \\ \dfrac{dn}{dt} = \varepsilon \left(\dfrac{n_\infty(V)-n}{\tau_n(V)} \right) = \varepsilon\, g(V,n) \end{cases} \qquad (1.2.4\_1)$$

The variable V is called fast, and n is slow. Indeed, if f, g are of order 1, then $\frac{dV}{dt}$ is of order 1 while $\frac{dn}{dt}$ is of order ε. Thus V changes quite faster than n.

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

$$\begin{cases} \dfrac{dv}{dt} = v - v^3 - w + I = f(v,w) \quad (F.N). \\ \dfrac{dw}{dt} = \varepsilon (v - a - bw) = \varepsilon\, g(v,w) \end{cases} \qquad (1.2.4\_2)$$

Typically $\varepsilon \simeq 0.08$, $a \simeq 0.7$, $b \simeq 0.8$

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

$$\begin{cases} \dfrac{dv}{dt} = f_\lambda(v,w) \\ \dfrac{dw}{dt} = \varepsilon\, g_\lambda(v,w) \end{cases} \qquad (1.2.4\_3)$$

where λ are control parameters (e.g. $\lambda = (a,b)$ in F.N model)

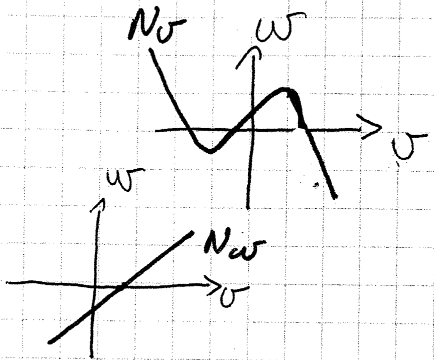
Analysis of FitzHugh-Nagumo equations

The analysis uses the method of singular perturbations developped by Mischenko and Rozov (1980) "Differential equations with small parameters and relaxation oscillations", New York, plenum.

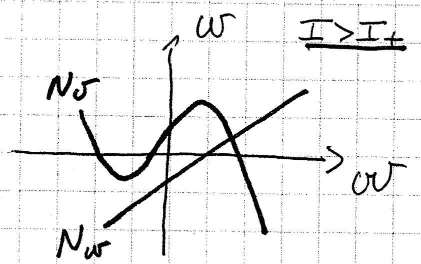
Let us first define the isoclines. $N_v = \{(v,w);\ f(v,w)=0\}$ and $N_w = \{(v,w),\ g(v,w)=0\}$. Thus:

$$N_v = \{(v,w);\ w = -v + v^3 + I\}$$

$$N_w = \{(v,w);\ w = \frac{v-a}{b}\}$$



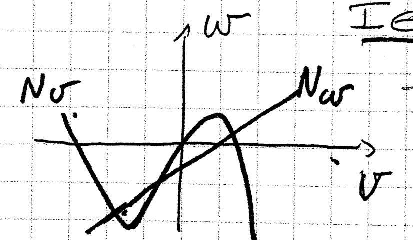
At the intersection of nullclines we have fixed points. It is easy to see that there are either one or 3 fixed points, depending on I.



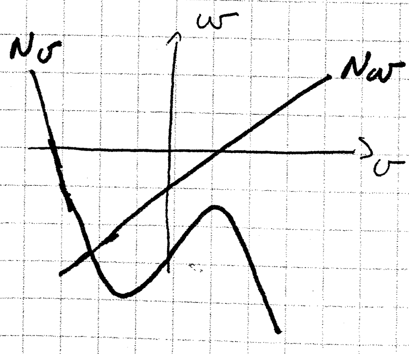
$I > I_+$ One fixed p

Since ε is small, away from the N_v nullcline the vector field is essentially dominated by the first component, i.e. the vector field is quasi horizontal. In other words we can replace the FN equations by:

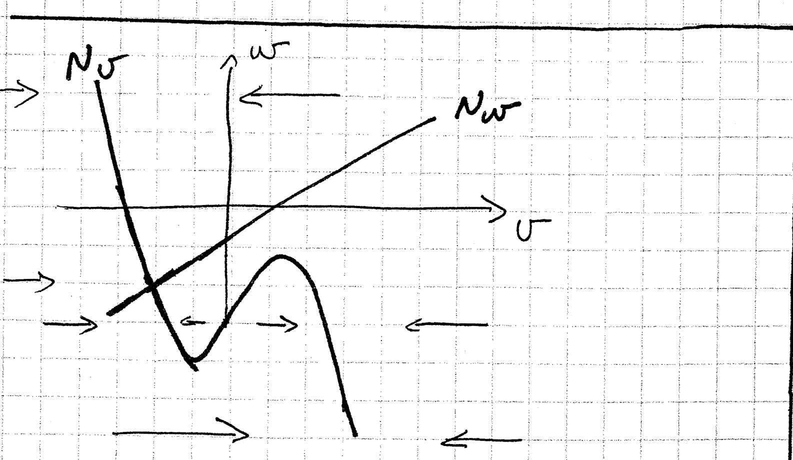
$$\begin{cases} \dfrac{dv}{dt} = v - w^3 - w - I \\ \dfrac{dw}{dt} = 0 \end{cases}$$



$I \in [I_-, I_+]$ Three fixed points.



$I < I_-$ One fixed point.

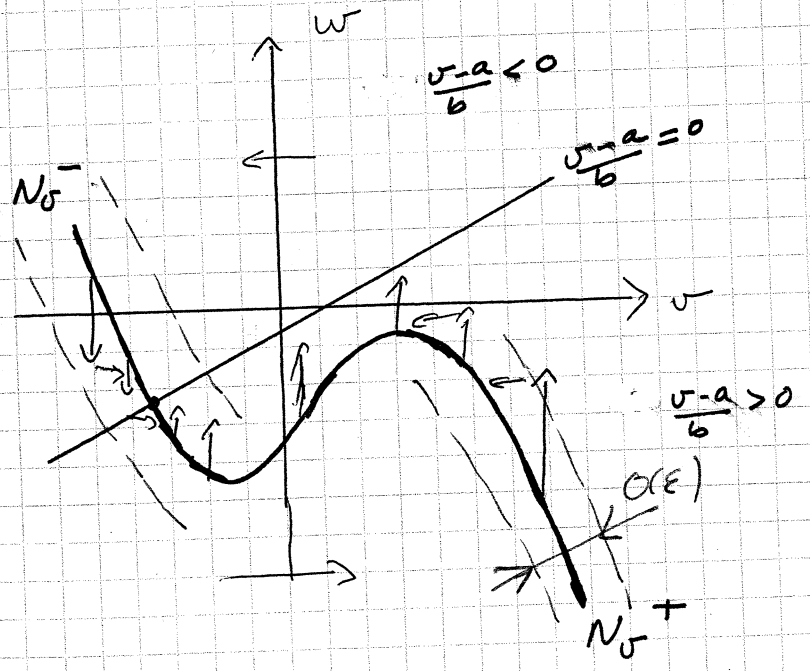


Vector field away from N

On the opposite, on the N_v nullcline, the vector field is vertical
Near the N_v nullcline, setting $\varepsilon' = \varepsilon t$ gives:

$$\begin{cases} \varepsilon \dfrac{dv}{dt} = f(v,w) \\ \dfrac{dw}{dt} = g(v,w) \end{cases}$$

Then, setting $\varepsilon = 0$ gives $f(v,w)=0$ and $\dfrac{dw}{dt} = g(v,w)$. This means that, wherever it is possible, v adjust rapidly to maintain a pseudo equilibrium corresponding to $f(v,w)=0$ and plays the role of an implicit parameter in the evolution of w. In other words, the point (v,w) moves slowly along the stable branche of the v nullcline. These branches compose the so-called slow manifold. It is only on (a very close) this curve that the motion of the solution curves is not very fast in a nearly horizontal direction.



The trajectories of the real system are composed of pieces coming from these two approximations. There are theorems controlling how close the real trajectories are to the piecewise trajectories, for sufficiently small ε.

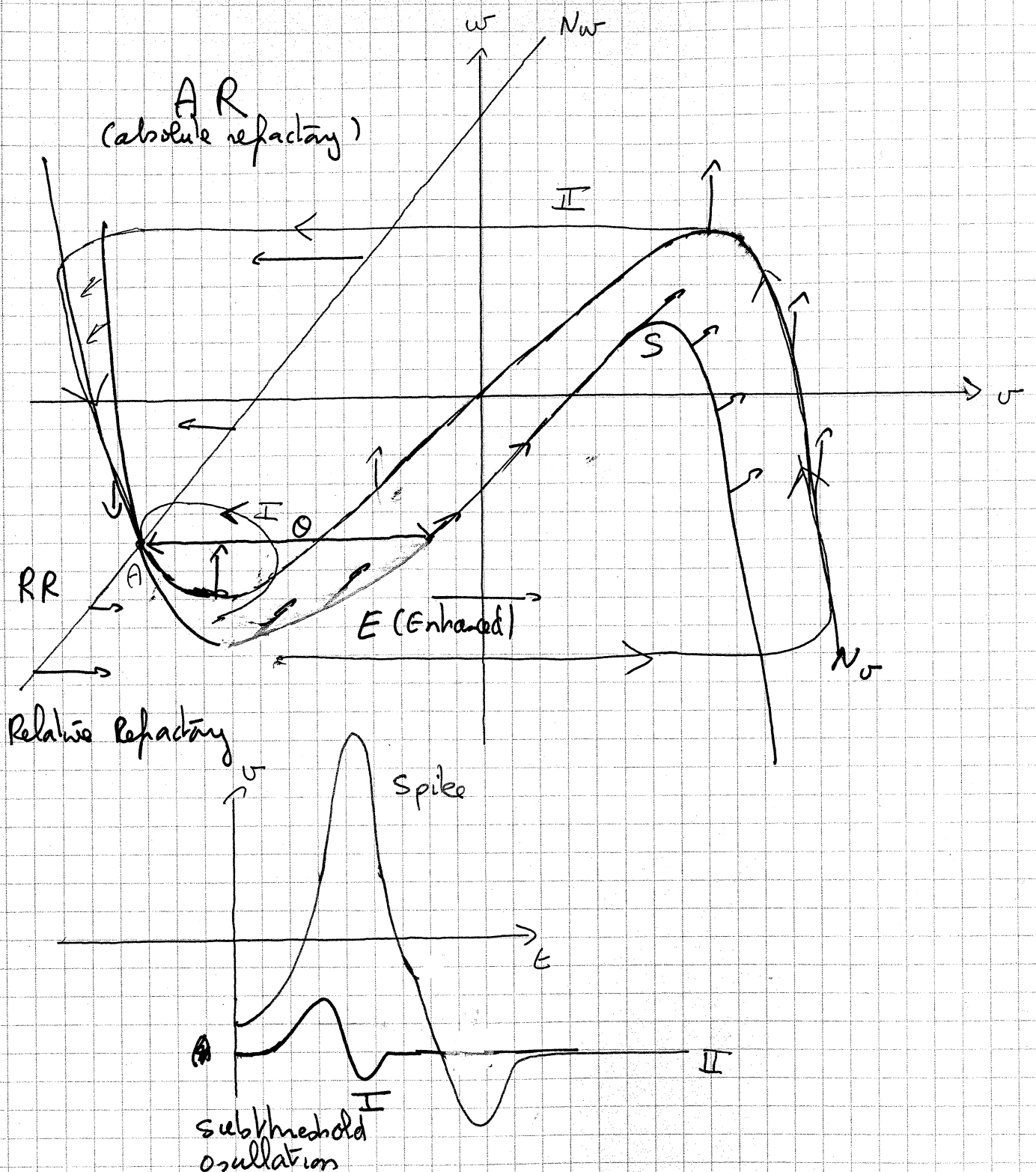
Spike generation

Consider the monostable case and considering the following figure. A is the stable fixed point. There is a curve, called the separatrix defined by

$$S = \{(v,w) \,;\, f_v(v,w) = f_w(v,w)\}$$ ("45° inclination of the vector field")

whose equation is given by, in the present case:

$$w = \frac{I + \varepsilon a + v(1-\varepsilon) - v^3}{1 - \varepsilon b}$$ (Exercise)


w
Nw
AR
(absolute refractory)
II
S
v
I
O
A
RR
E (Enhanced)
Nv
Relative Refractory

v
Spike
t
II
I
subthreshold
oscillations

The curve has the following property. Consider a ... about A (case I). The variable (v, w) make the excursion I in the phase space, corresponding to a small the fluctuation of the membrane 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 separatrice, 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:

$$\theta = v_S - v_A \; ; \quad v_A = \frac{I + \varepsilon a + v_S(1-\varepsilon) - v_S^3}{1 - \varepsilon b} \qquad (1.2.4\text{-}5)$$

Consider now the 3 following regions:

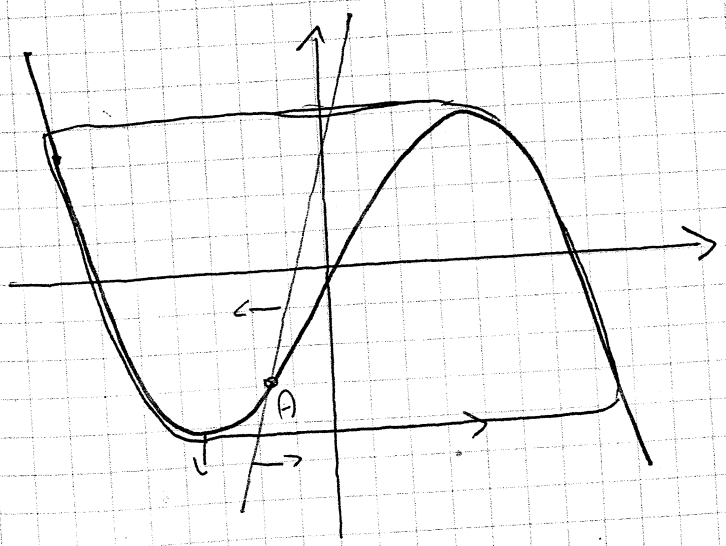
Absolut Refractory. In this region it is impossible to excite the neuron so that it generates a spike.

Relative refractory. In this region a sufficiently large v generate a spike

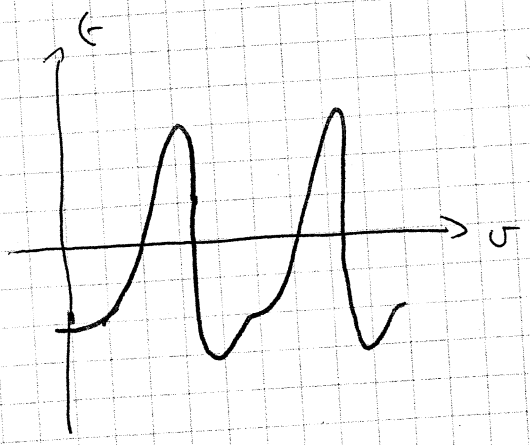
Enhanced. Here a v increase, smaller than the threshold generate a spike

Periodic spike emission

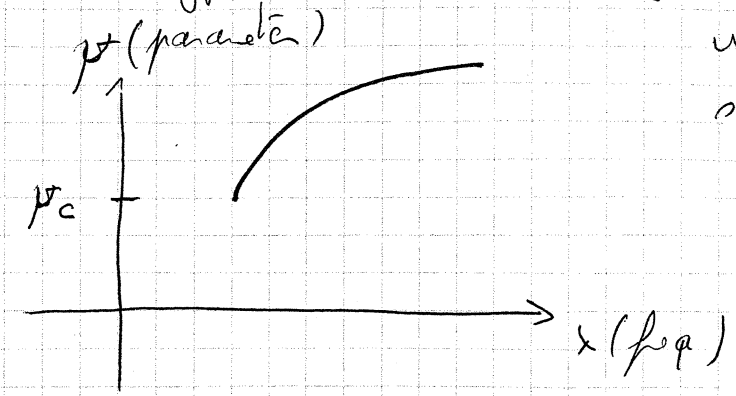
Here A was a stable fixed point. Consider now the case when it is unstable.

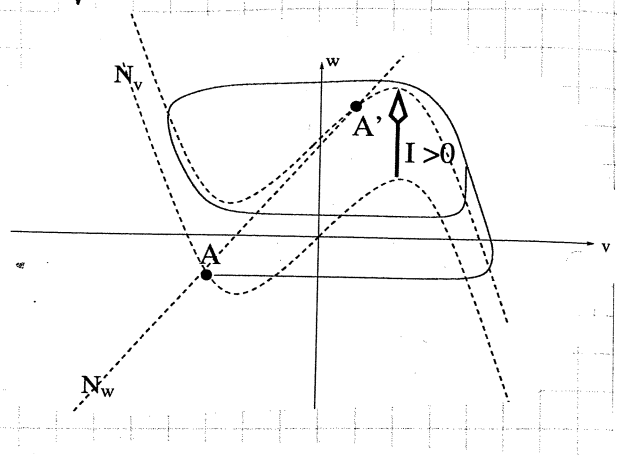


Here a small perturbation of A generate a periodic spike train.



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 changing in a specific domain





Anodal break excitation

– *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).

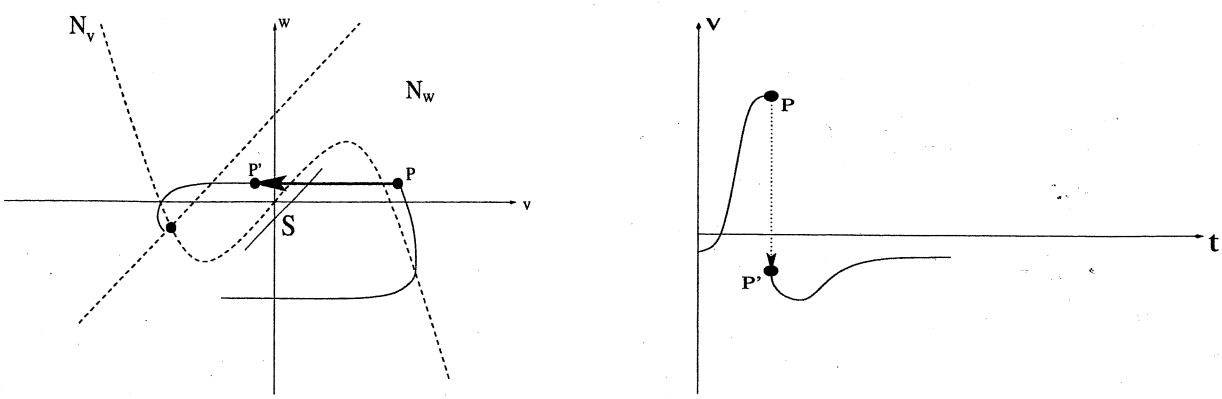


FIG. 11 – *Anodal break excitation in the FitzHugh-Nagumo model.*

Spike emission by Hyperpolarization

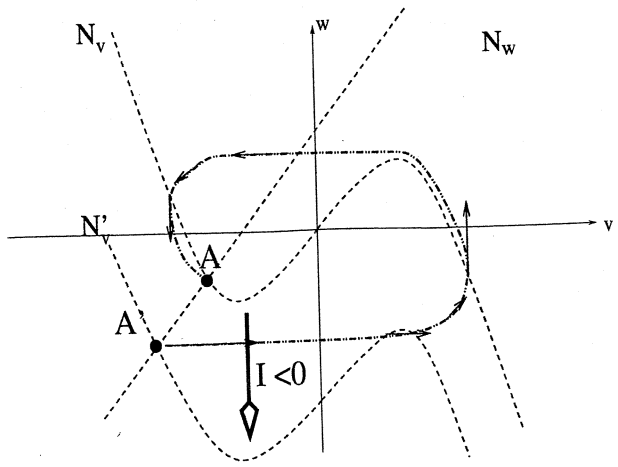
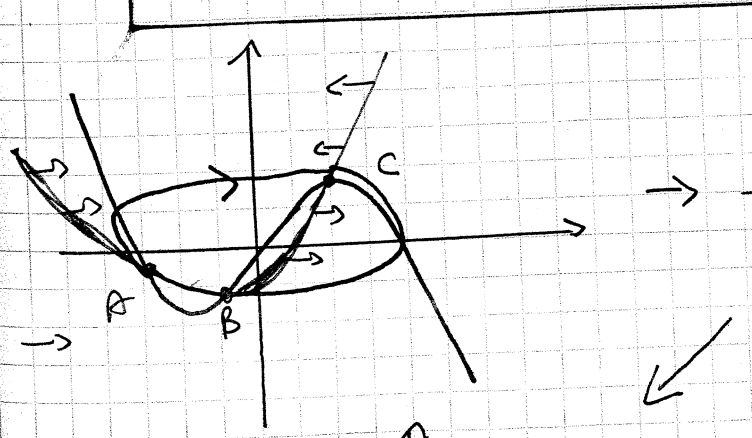


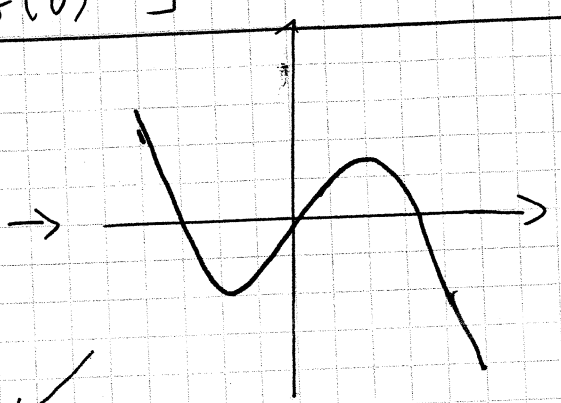
FIG. 12 – *Spike emission by hyperpolarization in the FitzHugh-Nagumo model.*

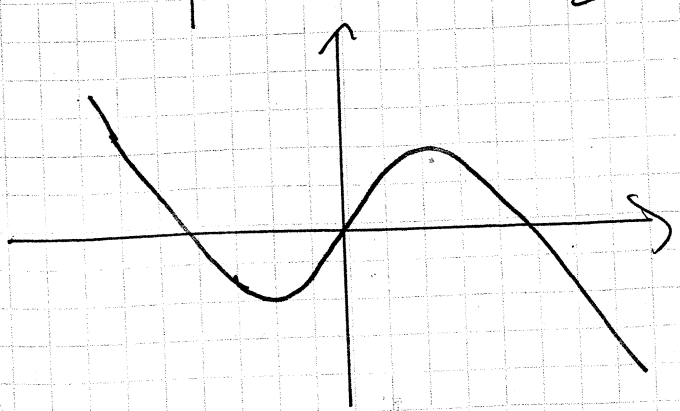
Type II excitability

This type of effect does not occur in the classical Fitz Hugh - Nagumo model, but in some variant, where the inactivation variable w obeys a quadratic equation (ie it is a parabola). This occurs for example in the Morris-Lecar model.

$$(1.2.4\text{-}6)\quad \begin{cases} \dfrac{dv}{dt} = -g_{Ca}\, m_\infty(V)(V-E_{Ca}) - g_K w (V-E_K) - g_L(V-E_L) + I \\ \dfrac{dw}{dt} = \varepsilon \left[\dfrac{w_\infty(V) - w}{\tau_w(V)} \right] \end{cases}$$







$$m_\infty(V) = \frac{1}{2}\left[1 + \tanh\left(\frac{V-V_1}{V_2}\right)\right]$$

$$w_\infty(V) = \frac{1}{2}\left[1 + \tanh\left(\frac{V-V_3}{V_4}\right)\right]$$

$$\tau_w(V) = \frac{1}{\operatorname{ch}\left(\frac{V-V_3}{V_4}\right)}$$

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: (see appendix C)

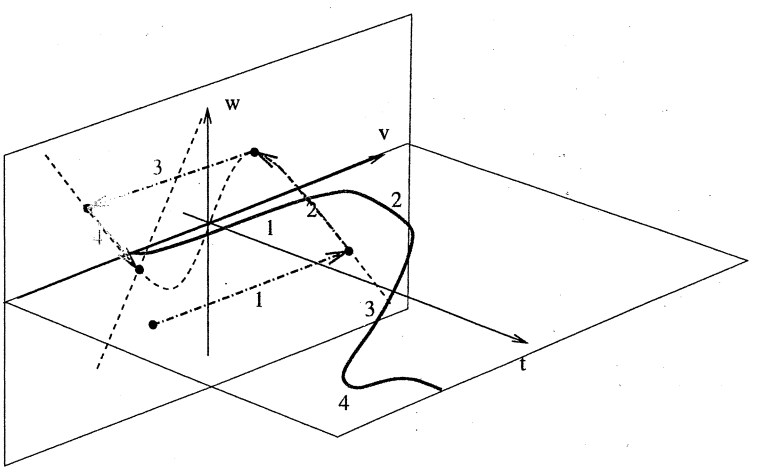
$$\begin{cases} \varepsilon^2 \ddot{v} + \varepsilon c \dot{v} + f(v,w) = 0 \\ c\dot{w} + g(v,w) = 0 \end{cases} \qquad (1.2.4\_7)$$

where $\dot{v} = \frac{dv}{d\xi}$, ξ 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 "outer equations":

$$(1.4\_8) \quad \begin{cases} f(v,w) = 0 \\ c\dot{w} + g(v,w) = 0 \end{cases} \longrightarrow N_v \text{ nullcline depending parametrically on } w.$$

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



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

It is convenient to rescale ξ as εs and to write (1.2.4_8) in the form:

$$\begin{aligned} \ddot{v} &= -c\dot{v} - \frac{\partial \mathcal{V}}{\partial v} \quad ; \quad \mathcal{V}(v,w) = \frac{v^2}{2} - \frac{v^4}{4} - wv \\ \dot{w} &= -\frac{\varepsilon}{c}(v - a - bw) \end{aligned} \qquad (1.2.4\_9)$$

$\mathcal{V}$ is the formal analogon of a potential, depending parametrically on the slow variable w.

Propagation equations for FitzHugh-Nagumo

Remainder: Propagation equation for Hodgkin-Huxley

$$\frac{1}{R_a}\frac{\partial^2 V}{\partial x^2} = C\frac{\partial V}{\partial t} + \left[g_{Na} m^3 h (V-E_{Na}) + g_K n^4 (V-E_K) + g_L (V-E_L)\right] 2\pi a + \text{elect}$$

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

$$\frac{\partial h}{\partial t} = \alpha_h(V)(1-h) - \beta_h(V) h$$

$$\frac{\partial n}{\partial t} = \alpha_n(V)(1-n) - \beta_n(V) n$$

FitzHugh-Nagumo reduction

m v ste, $h+n \sim$ ste etc... $\Rightarrow$

$$\frac{1}{R_a}\frac{\partial^2 V}{\partial x^2} = C\frac{\partial V}{\partial t} - f(v,w) = C\frac{\partial v}{\partial t} - (v - v^3 - w - I)$$

$$\frac{dw}{dt} = \varepsilon(v - a - bw) = \varepsilon g(v,w)$$

Propagation equation

$v(x,t) = w(x-ct) = w(\xi)$; $\frac{\partial}{\partial x} = \frac{\partial}{\partial \xi}$; $\frac{\partial}{\partial t} = -c\frac{\partial}{\partial \xi}$

$$\frac{1}{R_a}\frac{\partial^2 w}{\partial \xi^2} = -c\frac{\partial w}{\partial \xi} - f(w,w)$$

$$-c\frac{\partial w}{\partial \xi} = \varepsilon g(v,w)$$

Set $R_a = 1$, $\dot{v} = \frac{\partial v}{\partial \xi}$ $\Rightarrow$

$$\boxed{\begin{aligned} \ddot{v} &= -c\dot{v} - f(v,w) \\ \dot{w} &= -\frac{\varepsilon}{c} g(v,w) \end{aligned}}$$

Inner equations

$$\xi \Rightarrow \xi/\varepsilon \quad \Rightarrow \quad \frac{\partial}{\partial \xi} \rightarrow \varepsilon \frac{\partial}{\partial \xi} \quad -$$

$$\Rightarrow \boxed{\begin{cases} \varepsilon^2 \ddot{v} + \varepsilon c \dot{v} + f(v, w) = 0 \\ c \dot{w} + g(v, w) = 0 \end{cases}}$$

1.2.5) Integrate and Fire models (Lapicque 1907)

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

i) If $V < \theta$ then V obeys:

$$\tau_m \frac{dV}{dt} = -V(t) + RI(t) \qquad (1.2.5\text{-}1)$$

with $\tau_m = RC$ is the characteristic constant of the membrane. This is the equation of load for a RC circuit. $-\frac{1}{\tau_m}$ is called the leak rate.

ii) If V reaches the threshold, at some time t_f then V is instantaneously reset to a rest value $V_R < \theta$, i.e.

$$V(t_f^-) = \theta \implies V(t_f^+) = V_R.$$

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 arising at time t_1 and before the next spike at time t_2 is given by:

$$V(t) = V_R\, e^{-\lambda\left(\frac{t-t_1}{\tau_m}\right)} + \frac{1}{C}\int_0^{t-t_1} e^{-\frac{\lambda s}{\tau_m}} I(t-s)\, ds \qquad (1.2.5\text{-}2)$$

This model is also easy to use for networks dynamics.

However, its dynamics is rather poor, compared to the HH model. Moreover the notion of instantaneous reset introduces spurious mathematical properties, as we shall see.

Nevertheless, this is an extremely fruitfull model to provide analytical results at the level of networks. It allows one to figure out dynamical complexity generated by non linear collective neurons dynamics, before extrapolating to more complex neurons models.

However, some properties can be spurious and generated by model-definition.

...ducing ϑ ... uses to interpret eq. (1.84.9): the formal equivalent of a particle moving in a potential $\mathcal{V}$ with a shape ... with a friction coefficient c and where ξ plays the role of time.

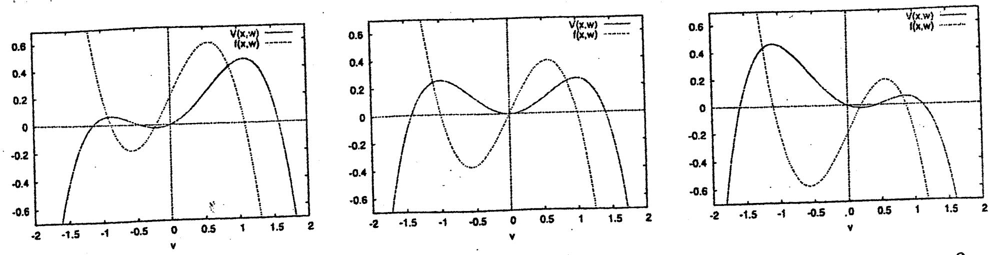


Fig. 21. Potential $\mathcal{V}$ of eq. (50) for : Fig. 21a : $w < 0$; Fig. 21b : $w = 0$; Fig. 21c : $w > 0$.

It is then easy to draw the phase portrait of v for a fixed value of w.

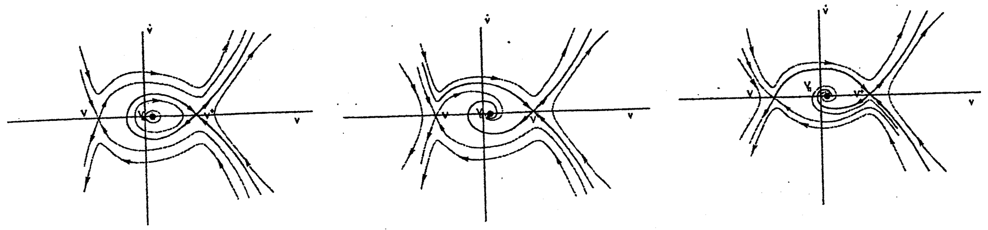
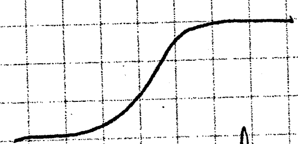
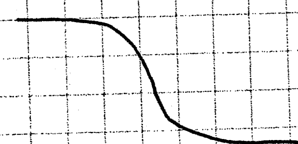


Fig. 22. Phase portrait of eq. (54) for : Fig. 22a : $c = 0$; Fig. 22b : $c > 0$; Fig. 22c : $c = c_0$. The situation corresponds to $w > 0$.

For $c=0$, there is no effective dissipation and there is an homoclinic trajectory connecting the unstable point v^+ to itself. When c is large enough, the phase portrait has the shape depicted in Fig 22b. By continuity there is an intermediate value of c, $c_0(w)$, where there is an heteroclinic orbit connecting v^- and v^+. 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^+ and v^-. The global curve is a pulse or a spike propagating at speed c_0, selected by the medium.



Ascending front



Descending front

$d = 2$

The limits of FitzHugh-Nagumo equations

→ 2 dimensional system instead of a 4 dimensional HH model.

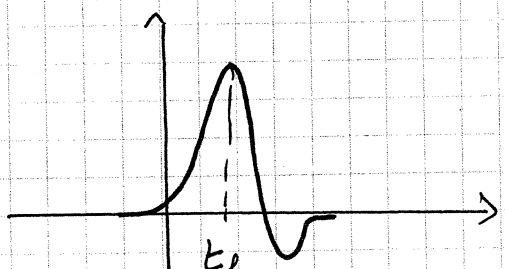
→ less dynamical regimes than observed in HH and in live neurons.

1.2.7) Measuring neuron activity

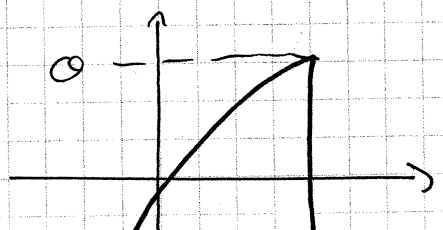
1.2.7.1) Spike trains

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

The spike time has not a unique definition in real neurons. One can take either the time when the membrane potential reaches its maximal value, or the time when membrane potential reaches some threshold value. This means that, on practical/empirical grounds this time is defined with some uncertainty. On the opposite, in models such as Integrate and Fire models, spike time is defined as the time w membrane potential reach the threshold (which is here precisely defi and uniquely defined, contrarily to real spikes). Hence, spike time is known with an infinite precision in IF models. This is a spuri and non realistic property which leads to severe misinterpretati and wrong extrapolations to real neural networks.



Spike time for a real spike



Spike time for an IF model

The refractory period τ_r fo that a spike immediately fo another spike.

Formally a spike train can be defined as a list of spi times

$$\{t_i^{(1)}, \dots t_i^{(n)}\}$$

where $t_i^{(k)}$ the k-th spike emitted by neuron i.

The above constraints impose th $t_i^{(k)}$, $t_i^{(k+1)}$ are at least separa by τ_r, and that $t_i^{(k)}$ is not def mined with an infinite precision

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

$$S(t) = \sum_{n=1}^{N_j(t)} h(t - t_j^n) \qquad (1.2.7.1\text{-}1)$$

where h is a function mimicing the spike, and such that $h(t)$ so e.g. the measurement of the spikes. $N_j(t)$ is the number of spik occuring between time 0 and time t.

In the simplest case h is a δ function. Note that the sum is discrete (i.e. there are finitely many spike in a finite time i val). This property does not hold anymore if one relaxes the assumptions made above.

Frequency rate versus ~~membrane~~ potential

For simplicity we assume that δt is small but positive. We use it as a time step for time discretization on a grid! In this setting, the frequency rate is given by:

$$\nu_i(t)\,\underset{1}{\cancel{\delta t}} = \text{Prob}\,[\underbrace{i \text{ fires at } t+\overset{1}{\cancel{\delta t}}}_{\text{instead of between } t,\ t+\delta t}] = \text{Prob}\,[V_i(t+\overset{1}{\cancel{\delta t}}) \geq \theta]$$

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

During the time interval $[t, t+\delta t]$ the local piece of membrane associated with V_i receives signals, and evolve in time. We can w

$$V_i(t+1) = V_i(t) + \mathcal{E}(V_i(t), t, \cdot)$$

where $\mathcal{E}$ integrate all effects leading to a change in V_i. Then:

$$\nu_i(t) = \text{Prob}\,[\,\mathcal{E}(V_i(t), t) \geq \theta - V_i(t)\,]$$

$$= 1 - F_{\mathcal{E}}\,(\theta - V_i(t)\,]$$

$F_{\mathcal{E}}(\cdot \mid V_i(t) < \theta)$ is a repartition function. Hence it is sigmoidal (monotonously increasing, with $F(-\infty) = 0$, $F(+\infty) = 1$).

Consequently $1 - F_{\mathcal{E}}(\theta - V_i(t))$ is a sigmoid

Agate
correlation
ISI
Reverse correlation

1.2.7.2 Firing rate

This is the frequency with which a neuron emits a spike, or the probability that a spike is emitted over a small time interval. There are different ways of defining it.

Mathematically the firing rate of neuron i, $\nu_i(t)$, is the probability density that i fires between t, and $t+\delta t$:

$$\boxed{P(i \text{ fires in } [t, t+\delta t]) = \nu_i(t)\,\delta t} \qquad (1.2.7.2-1)$$

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, modelled by a δ function, let us introduce

$$\rho_i(t) = \sum_n \delta(t - t_i^n) \qquad (1.2.7.2-2)$$

(sequence of spikes emitted by i)

(corresponding to eq. (1.2.7.1-1) with $h = \delta$). We may write

$$\nu_i(t)\,\delta t = \int_t^{t+\delta t} \langle \rho_i(\tau) \rangle\, d\tau, \qquad (1.2.7.2-3)$$

δt small but large enough to see spikes

where $\langle\ \rangle$ denotes the trial average. In this case, for any suitable function f

$$\langle f * \rho_i \rangle = \int f(\tau) \langle \rho_i(t-\tau) \rangle\, d\tau = \int f(\tau)\, \nu_i(t-\tau)\, d\tau = f * \nu_i \qquad (1.2.7.2-4)$$

If f is related to a linear response then 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.

$$r_i = \frac{1}{T} \int_0^T \rho_i(\tau)\, d\tau, \qquad (1.2.7.2-5)$$

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

Finally one can average r_i over trials giving

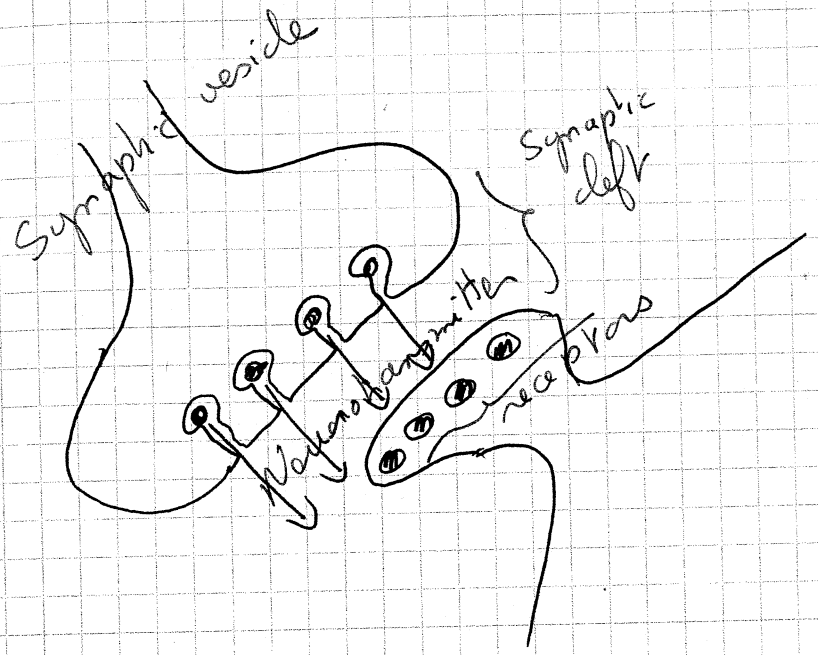
$$\langle r_i \rangle = \frac{1}{T} \int_0^T \langle \rho_i(\tau) \rangle\, d\tau = \frac{1}{T} \int_0^T \nu_i(\tau)\, d\tau.$$

In the literature this 3 terms are called firing rate, even if they are not always equivalent. They are under ergodic hypothesis.

1.3) Modelling the synapse

1.3.1 Short Summary of biology

Neurons interact together via synapses (and gap junctions). Spikes emitted by the soma go along the axon, until they reach synaptic terminations or synaptic vesicles. A local variation of the membrane potential triggers the release of a neurotransmitter into the synaptic cleft.



The neurotransmitter reaches by diffusion the post-synaptic receptors located at the dendritic spines. This generates a post-synaptic potential (PSP)

Contrarily to spikes, PSP have an amplitude which depends on the excitation and on the synaptic efficacy

Synaptic efficacy evolves according to various mechanisms (known under the generic name of synaptic plasticity), which depend on the activity of the pre and post synaptic neuron

Depending on the pre-synaptic neuron and on the neurotransmitter used by this neuron, the PSP can be either positive or negative. In the first case the pre-synaptic neuron and its synaptic connections are called excitatory. Spikes coming from pre-synaptic neuron increase the membrane potential of the post-synaptic neuron, which is more keen on generating spike trains. If PSP is negative, corresponding to an inhibitory pre-synaptic neuron.

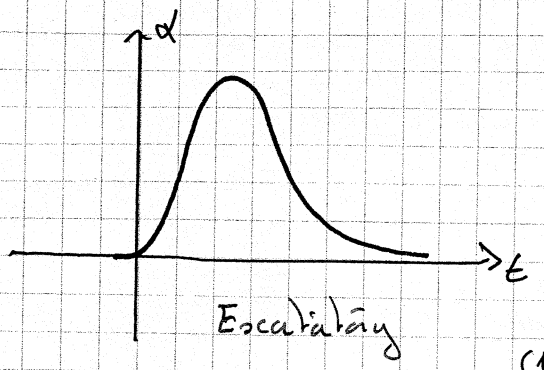
A neuron receives a lot of spikes from other neurons. A typical dendritic tree receives about ten thousand synaptic entries, distributed on the dendritic surface. As a matter of fact, dendrites are the most important part, in surface and volume, of the brain. According to their morphological properties,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

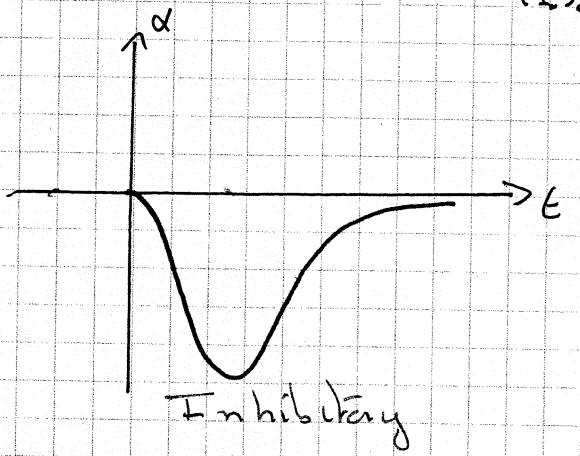
Dendrites constitute in fact the basic element of information treatment in the brain since most of the messages exchanged by neurons transit via synapses - dendrites.

The local modification of membrane potential of the post-synaptic neuron (PSP) propagates along the dendritic tree, according to the same equations / mechanisms as we saw for the axon up to the soma. There all PSP are summed up, generating a response of the post-synaptic neuron in form of a spike train.

13.2 Modelling of synapse

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





Mathematically, it is represented by a function α, called the synaptic response.

This response is typically modelled by a Green function of type

$$\sum_{l=0}^{k} a_i^{(l)} \frac{d^l}{dt^l} \alpha_i(t) = \delta_0(t) \qquad (1.3.2\_1)$$

where $\delta_0(t)$ is the Dirac distribution, α_i is the response of neuron i, and $a_i^{(l)}$ are characteristic coefficients.

Typical examples of synaptic responses are

$$\alpha_i(t) = e^{-t/\tau_i} H(t), \qquad (1.3.2\_2)$$

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

$$\frac{1}{K_i} \frac{d\alpha_i}{dt} + \frac{\alpha_i}{K_i \tau_i} = \delta_0(t) \qquad (1.3.2\_3)$$

(i.e. $\left\langle \frac{d\alpha_i}{dt}, g \right\rangle + \left\langle \frac{\alpha_i}{\tau_i}, g \right\rangle = -\left\langle \frac{\alpha_i}{\tau_i}, g \right\rangle + \left\langle e^{-t/\tau_i} \delta_0, g \right\rangle + \left\langle \frac{\alpha_i}{\tau_i}, g \right\rangle = \langle \delta_0, g \rangle$)

Another example, corresponding to the previous figure, is:

$$\alpha_i(t) = t e^{-t/\tau_i} H(t), \qquad (1.3.2\_4)$$

whose Green equation is:

$$\frac{1}{K_i} \frac{d^2\alpha_i}{dt^2} + \frac{2}{\tau_i} \frac{d\alpha_i}{dt} + \frac{1}{\tau_i^2} \alpha_i = \delta_0(t) \qquad (1.3.2\_5)$$

Now, there are two alternatives. In the first case, corresponding to the so called voltage based models, one assumes that post synaptic potentials has the same shape no matter which pre synaptic population caused it (but the sign and amplitude may vary though). Therefore, the response of neuron i to a stimulus from neuron j is:

$$\alpha_{ij}(t) = W_{ij} \alpha_i(t), \qquad (1.3.2\_6)$$

where W_{ij} is called "synaptic efficacy" or "synaptic weight".

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

$$\boxed{\alpha_{ij}(t) = W_{ij}\,\alpha_j(t)} \qquad (1.3.2\text{-}7)$$

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:

$$\boxed{r_{ij}(t) = (\alpha_{ij} * s_j)(t)} \qquad (1.3.2\text{-}8)$$

i.e., for a voltage based model:

$$\sum_{e=0}^{k} a_i^{(e)} \frac{d^e}{dt^e} r_{ij}(t) = \sum_{e=0}^{k} a_i^{(e)} \frac{d^e}{dt^e} \alpha_{ij} * s_j = W_{ij} \sum_{e=0}^{k} a_i^{(e)} \frac{d^e}{dt^e} \alpha_i * s_j = W_{ij}\, s * s_j$$

$$\Rightarrow \boxed{\sum_{e=0}^{k} a_i^{(e)} \frac{d^e}{dt^e} r_{ij} = W_{ij}\, s_j(t)} \qquad (1.3.2\text{-}9)$$

In the same way, for an activity based model:

$$\boxed{\sum_{e=0}^{k} a_i^{(e)} \frac{d^e}{dt^e} r_{ij} = W_{ij}\, s_j(t)} \qquad (1.3.2\text{-}10)$$

1.3.3

Neuron response

The response r_{ij} of each synapse to excitation coming 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:

$$\boxed{\sum_{e=0}^{k} a_i^{(e)} \frac{d^e}{dt^e} V_i = \sum_{j=1}^{N} W_{ij}\, s_j(t - \tau_j)} \qquad \begin{matrix}\text{Propagation without deformation} \\ \text{(voltage based)} \\ (1.3.2\text{-}11)\end{matrix}$$

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

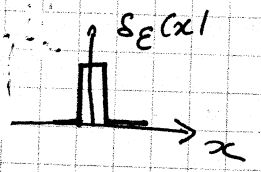
In most examples, s_j is the sequence of spike trains coming from the pre-synaptic neuron j. In the simplest modelling, the

$$S_j(t) = \sum_{n=0}^{M_j(t)} \delta(t - t_j^n), \qquad (1.3.2\text{-}12)$$

$M_j(t)$ → number of spikes that arrive between 0 and t.

where t_j^n is the time of occurence 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 s_j as a function fitting the spike shape. For example, to avoid the notion of instantaneous spike time one may replace δ by δ_ε, where δ_ε is the function

$$\delta_\varepsilon(x) = 1 \quad x \in [-\varepsilon, \varepsilon],$$
$$= 0 \quad \text{otherwise},$$



Here ε takes into account the fact that a spike has a duration and that the notion of instantaneous spike has no biological nor physical fundation. More detailed spike shape can be introduced as well.

1.3.4 Frequency rate

In the next examples we shall adopt the simplest modelling of spike with 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 evolution (e.g. the time τ in the synaptic integration) is quite a bit longer than the characteristic time of a spike. In this setting the variation of V_i on a time duration τ corresponds to the arrival of many spikes, and is therefore an integration over the spike flux. The firing rate, as we saw, is the probability of emission of a spike between t and $t+dt$, where dt is here of order τ. It is given by

$$V_j(t)\,dt = \left\langle \int_t^{t+dt} \sum_{n=0}^{N_j(\theta)} \delta(\theta - t_j^n)\, d\theta \right\rangle$$

($\langle\cdot\rangle$ = average over trials ⇒ phenomenological equation)

(Assume here that dt is so small that at most one spike can arrive between t, $t+dt$) ⇒ $\rho \in \{0, 1\}$

In this case, thus, $s_j(t)$ is replaced by $\rho_j(t)$, in eq. (1.3.2-11).

The frequency rate is a function of the membrane potential V_i, of sigmoïdal type, i.e.

1.3.5 Generalised Integrate and Fire models

These are Integrate and Fire models where the synaptic conductance depends on spikes received from pre synaptic neurons. Then, the membrane potential obeys, below the threshold θ:

$$C\frac{dV_k}{dt} = -\frac{1}{\tau_L}(V_k - E_L) = \sum_{j\in I} g_{kj}(V_k - E_j) - \sum_{j\in E} g_{kj}(V_k - E_j) + i_{ext}(t). \quad (1.3.5\_1)$$

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 the set of excitatory neurons. E_j are the corresponding Nernst/reversal potentials. Note that $g_{kj} \geq 0$. Typically, for inhibitory neurons $E_j = E^- \approx -75$ mV and for excitatory neurons $E_j = E^+ \approx 0$. Therefore, at rest $V \approx -70$ mV the inhibitory term is negative, thus decreases V_k, while the excitatory term is positive, thus increasing it.

Note that here there is no spatial structure for the neuron (it is punctual). Indeed, we consider local equation for the conductance of synapses to somation which normally occurs at soma.

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

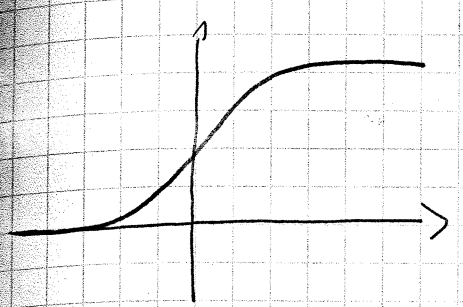
$$g_{kj} \equiv g_{kj}(t, \{t_j^{(n)}\}) = \bar{g}_{kj} \sum_{n=1}^{M_j(t,0)} \alpha(t - t_j^{(n)}), \quad (1.3.5\_2)$$

where $t_j^{(n)}$ is the "time" of occurence" 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 depend on k or on j.

$\{t_j^{(n)}\}$ is the list of spikes time $t_j^{(n)}$. Finally $M_j(t,0)$ is the number of spikes occuring from some critical time origin. The 0 is important. Indeed, spikes emitted by pre-synaptic neurons

$$\nu_j(t) = S_j(V_j(t)) \qquad (1.3.4\_1)$$

where $S_j \in [0,1]$ is a sigmoid, with slope g_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

$$\sum_{k=0}^{k} a_i^{(k)} \frac{d^k}{dt^k} V_i = \sum_{j=1}^{N} W_{ij} S_j(V_j(t)) \qquad (1.3.4\_2)$$

for a voltage based model.

This equation affords extensions where one adds an external current I_i and noise B_i:

$$\sum_{k=0}^{k} a_i^{(k)} \frac{d^k}{dt^k} V_i = \sum_{j=1}^{N} W_{ij} S_j(V_j(t)) + I_i(t) + B_i(t) \qquad (1.3.4\_3)$$

Note that, according to Green equation (1.3.2_1) this is equivalent to

$$V_i(t) = \alpha_i * \left[\sum_{j=1}^{N} W_{ij} S_j(V_j) + I_i + B_i \right](t) \qquad (1.3.4\_4)$$

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

$$A_j(t) = [\alpha_j * \rho_j](t) = [\alpha_j * S_j(V_j)](t),$$

hence in an activity based model

response depends on the presynaptic cell

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

$$A_i(t) = \alpha_i * S_i\left[\sum_{j=1}^{N} W_{ij} A_j + I_i + B_i \right]. \qquad (1.3.4\_5)$$

This corresponds to the differential equation:

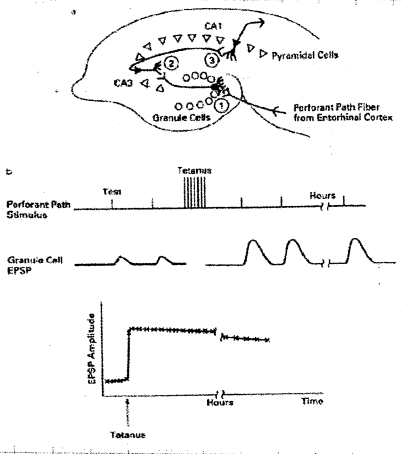
$$\sum_{k=0}^{k} a_i^{(k)} \frac{d^k}{dt^k} A_i = S_i\left[\sum_{j=1}^{N} W_{ij} A_j + I_i + B_i \right](t) \qquad (1.3.4\_6)$$

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 capacity is one of the key element explaining why neural networks have the ability of adapting, learning, recognizing, and generalizing.

There are several mechanism of adaptation identified.

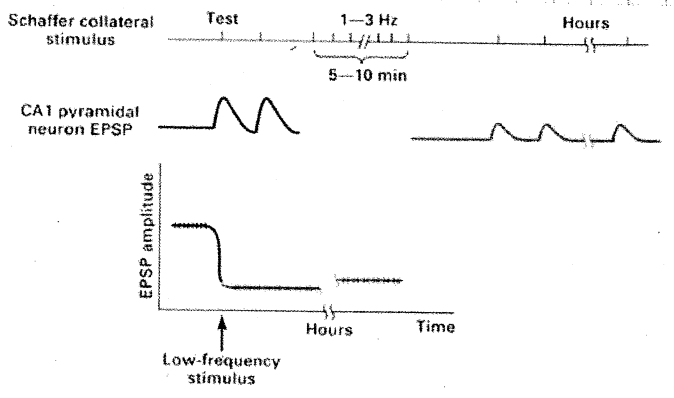
Long Term Potentiation (LTP)



Long Term potentiation is a long lasting form of synaptic plasticity. Specifically it is the long lasting improvement in communication between two neurons that results from simulating them rapidly. LTPs are due to several mechanisms that have not been fully identified. Basically LTP improves the postsynaptic cell's sensitivity to neurotransmitter in large part by increasing activity of receptors and their number.

Figure: Increase in the PSP amplitude resulting from when simulating

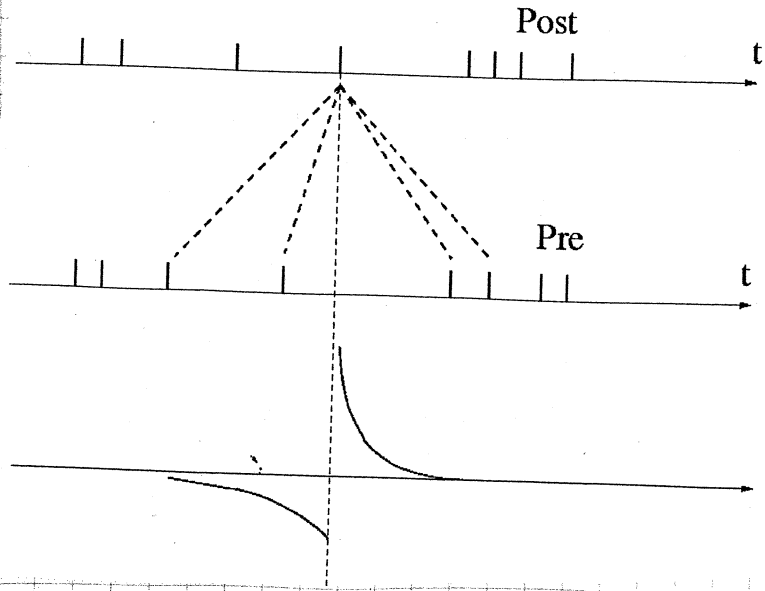
Long Term Depression (LTD)



Long Term Depression is the weakening of synapse that lasts from hours to days. It results from either short synaptic simulation or persistent weak synaptic simulation. It results from changes in postsynaptic receptors although changes in presynaptic neurons may also play a role.

Figure: Decay in the PSP amplitude

Spike Time dependent Plasticity (STDP)

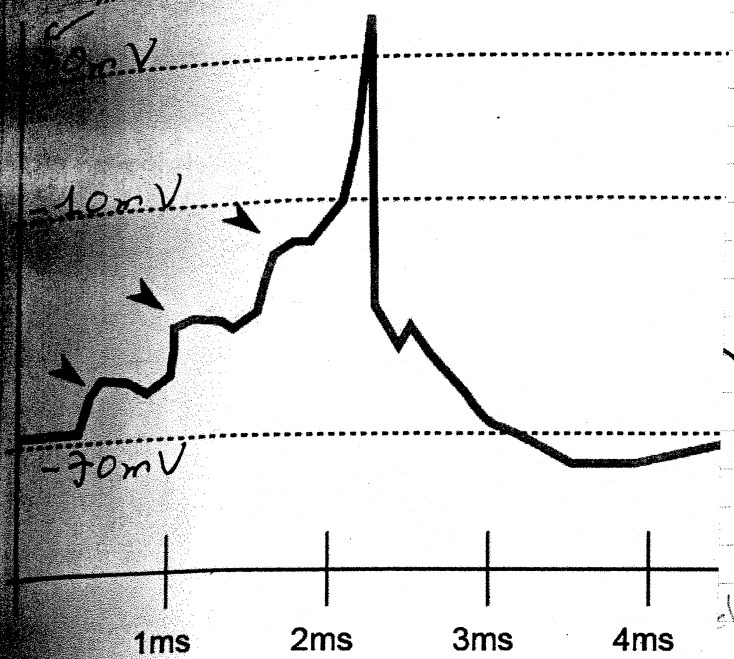


This is a general term for long changes at synapses that are sensitive to the timing of action potentials. It results from presynaptic spikes preceding post synaptic spikes leading to LTP or post synaptic spikes preceding presynaptic spikes leading to LTD.

The time sensitivities are in order of milliseconds.

depend on the spikes they themselves receive. Henceforth, $\gamma_j(t,\cdot)$ and $t_j^{(n)}$ depend in fact on the whole past neural network activity. In this sense, this form of conductance introduces a very complex memory dependence of the dynamics.

The physical interpretation of this conductance form is that each time synapse j receives a spike the corresponding conductance increases temporally of an amount $\alpha(t-t_j^{(n)})$



It is possible to write eq. (1.3.5_1) in a more compact form. Introducing the global conductance of neuron k,

$$g_k(t,\{t^{(n)}\}_k) = \underbrace{\sum_{j\in I} g_{kj}(t,\{t_j^{(n)}\})}_{\text{inhibitory}} + \underbrace{\sum_{j\in E} g_{kj}(t,\{t_j^{(n)}\})}_{\text{excitatory}} + \underbrace{\frac{1}{\varepsilon_L}}_{\text{leak}} \quad (1.3.5\_3)$$

where $\{t^{(n)}\}_k$ is the list of spike times received by neuron k up to time t (We shall introduce a more explicit and compact notation in a few sections) and the "current"

$$i_k(t,\{t^{(n)}\}_k) = \frac{E_L}{\varepsilon_L} + \sum_{j\in I} E_j\, g_{kj}(t,\{t^{(n)}\}_k) + \sum_{j\in E} E_j\, g_{kj}(t,\{t^{(n)}\}_k) + i_{ext}(t), \quad (1.3.5\_4)$$

we may rewrite (1.3.5_1) in the form:

$$\frac{C\,dV_k}{dt} + g_k(t,\{t\}_k)\,V_k = i_k(t,\{t^{(n)}\}_k), \quad k=1\dots N. \quad (1.3.5\_5)$$

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 $t_j^{(n)}$.

$$W_{ij}(t+1) = W_{ij}(t) + g\left(W_{ij}(t), [\omega_i]_{t-T}^{t}, [\omega_j]_{t-T}^{t}\right)$$

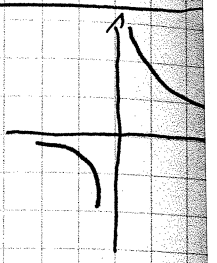
(1.3.6-3)

Examples

In this setting STDP has several possible implementations

Define the STDP function

$$f(x) = \begin{cases} A_- \exp x/\tau_- ; & x<0 ; \quad A_-<0; \\ A_+ \exp -x/\tau_+ ; & x>0 ; \quad A_+>0; \\ 0 \quad ; & x=0 \end{cases}$$



then a fast implementation is: (1.3.6-4)

$$g\left(W_{ij}, [\omega_i]_{t-T_0}^{t}, [\omega_j]_{t-T_0}^{t}\right) = \frac{\varepsilon}{T_0} \sum_{s_1, s_2 = t-T_0}^{t} f(s_1 - s_2)\, \omega_i(s_1)$$

where T_0 is a characteristic time scale (e.g. $\max(\tau_-, \tau_+)$), ε a small parameter. Usually people add "soft" "hard" bounds in the definition of g ensuring that, during synaptic plasticity dynamics, W_{ij} stays within bounds. In this case g depends also on W_{ij}.

Another implementation, called "nearest neighbors" reads:

$$g\left(W_{ij}, [\omega_i]_{t-T_0}^{t}, [\omega_j]_{t-T_0}^{t}\right) = \frac{\varepsilon}{T_0} \sum_{s=t-T_0}^{t} f(\tau_j(s) - s)\, \omega_i(\tau_j(s))\, \omega_j(s)$$

(1.3.6-4)

where $\tau_j(s) = \min_{t,\, \omega_j(t)=1} |t-s|$.

As a last example Gerstner & Kistler (2002) propose:

(1.3.6-5)

$$g\left(W_{ij}, [\omega_i]_{t-T_0}^{t}, [\omega_j]_{t-T_0}^{t}\right) =$$

$$\varepsilon \left[a_1^{pre} \sum_{s=t-T_0}^{t} \omega_j(s) + a_1^{post} \sum_{s=t-T_0}^{t} \omega_i(s) + \sum_{s_1, s_2 = t-T_0}^{t} f(s_1 - s_2)\, \omega_i(s_1)\omega_j(s_2) \right.$$

From these observations researchers try to extract some "rules" characterizing synapses evolution. The most known is the Hebb rule

D. Hebb (1949)

> When An axon 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 cell firing B is increased.

Note that Hebb's rule is somewhat including in LTP or STDP (but it has been discovered before). ~~Implementation aspects~~ usually differ.

Modelling plasticity

On mathematical grounds, synaptic plasticity may be viewed as a modification of the synaptic weight, W_{ij}, depending on the pre- and post synaptic neuron activity, and the current value of the synaptic weight. Since neuron activity is resumed in a spike train, denote by $\{t_i\}_{t-T}^{t}$ the sequence of spike times of neuron i, emitted during the time interval $[t-T, t]$. Then, in its most general form synaptic plasticity writes:

$$\frac{dW_{ij}}{dt} = g\left(W_{ij}, \{t_i\}_{t-T}^{t}, \{t_j\}_{t-T}^{t}\right) \quad (1.3.6\_1)$$

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

$$[\omega]_{t-T}^{t} = \{\omega_i(t),\ i = 1..N,\ t = t-T, T\}$$

$$\omega_i(t) = \begin{cases} 1 & \text{if } i \text{ fires at } t \\ 0 & \text{otherwise.} \end{cases}$$

(1.3.6_2)

Then, synapse update reads:

Hebb rule

There are many implementations of Hebb's rule. They usually rely on frequency rates. Here are several examples

$$g(w_{ij}, [\omega_i], [\omega_j]) = \nu_i(t)\,\nu_j(t) \qquad (1.3.6\text{-}6)$$

with $\nu_i(t) = \frac{1}{T}\sum_{t=T-t}^{t} \omega_i(\Delta)$. This is a straightforward implementation of Hebb's recipe. One can add thresholding on the definition of activity.

$$g(w_{ij}, [\omega_i], [\omega_j]) = H(\nu_i(t) - d_i)\,H(\nu_j - d_j) \qquad (1.3.6\text{-}7)$$

where $d_i \in [0, 1]$ is an "activity threshold".

These rules have the effect of only increasing w_{ij}. One can also add the opposite effect ("decay" of the synapse when no correlated activity of the endpost synaptic neuron).

$$g(w_{ij}, [\omega_i], [\omega_j]) = (\nu_i(t) - d_i)(\nu_j(t) - d_j) \qquad (1.3.6\text{-}8)$$

or

$$g(w_{ij}, [\omega_i], [\omega_j]) = \frac{1}{T_s}\sum_{s_1, s_2 = t - T_\Delta}^{T_\Delta} [\omega_i(s_1) - \nu_i(s_1)][\omega_j(s_2) - \nu_j(s_2)]$$

$$(1.3.6\text{-}9)$$