

Mathematical Physiology

Neuron models

Toni Guillamon

Matemàtica Aplicada I - UPC

November 29th, 2013

Outline and references

This file is an outline of the first session of Theme II (models of neural activity), from ionic channels modelling (reversal potentials given by Nernst and Goldman-Hodgkin-Katz equations) to the different models of neurons. It is important to have the following files in the appropriate folders (the path given). Check if these links work:

- [Externs/JosicBook.pdf](#)
- [Externs/Izhikevich2006.pdf](#)
- [../articles/Llinas-Science1998.pdf](#)
- [../articles/Compte-JNP-2003a.pdf](#)
- [../articles/Izhikevich-IEE-2004.pdf](#)

Nernst equation

In Section 2.1 of [K. Josic's notes](#) this equation is deduced. We just sketch the main steps.

Next two slides are related to the the Nernst equation:

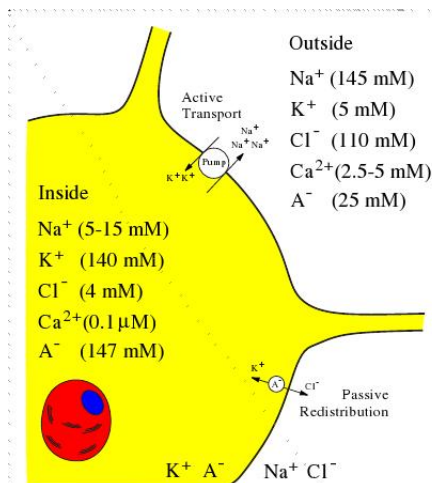
- Different examples of reversal potentials obtained from the Nernst equation.
- Illustrative graphic of different ionic concentrations in and out of the cell and the corresponding reversal potentials.

Examples of reversal potentials applying the Nernst equation.

Table 2.1. Typical ion concentrations in cells. (From Johnston and Wu).

Ion	Inside (mM)	Outside (mM)	Equilibrium Potential $E_i = \frac{RT}{zF} \ln \frac{[C]_{out}}{[C]_{in}}$
Frog Muscle			$T = 20^\circ C$
K^+	124	2.25	$58 \log \frac{2.25}{124} = -101 mV$
Na^+	10.4	109	$58 \log \frac{109}{10.4} = +59 mV$
Cl^-	1.5	77.5	$-58 \log \frac{77.5}{1.5} = -99 mV$
Ca^{2+}	10^{-4}	2.1	$29 \log \frac{2.1}{10^{-4}} = +125 mV$
Squid Axon			$T = 20^\circ C$
K^+	400	20	$58 \log \frac{20}{400} = -75 mV$
Na^+	50	440	$58 \log \frac{440}{50} = +55 mV$
Cl^-	40-150	560	$-58 \log \frac{560}{40-150} = -66 \text{ to } -33 mV$
Ca^{2+}	10^{-4}	10	$29 \log \frac{10}{10^{-4}} = +145 mV$
Mammalian cell			$T = 37^\circ C$
K^+	140	5	$62 \log \frac{5}{140} = -89.4 mV$

Illustration of different ionic concentrations and the corresponding reversal potentials.



Equilibrium Potentials

$$\text{Na}^+ \quad 62 \log \frac{145}{5} = 90 \text{ mV}$$

$$62 \log \frac{145}{15} = 61 \text{ mV}$$

$$\text{K}^+ \quad 62 \log \frac{5}{140} = -90 \text{ mV}$$

$$\text{Cl}^- \quad -62 \log \frac{110}{4} = -89 \text{ mV}$$

$$\text{Ca}^{2+} \quad 31 \log \frac{2.5}{10^{-4}} = 136 \text{ mV}$$

$$31 \log \frac{5}{10^{-4}} = 146 \text{ mV}$$

Goldman-Hodgkin-Katz equation: resting potential

It is a weighted mean of all possible ions present in the membrane. It is used to obtain the **resting potential** of a neuron.

$$V_M = \frac{RT}{F} \ln \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^+]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^+]_{out}}$$

Also deduced in Section 2.1 of K. Josic's notes

For instance, in the **squid axon**, at rest: $P_K : P_{Na} : P_{Cl} = 1 : 0.03 : 0.1$, $[K, Na, Cl]_{in} = 400, 50, 40$ mM, $[K, Na, Cl]_{out} = 10, 460, 540$ mM. At room temperature, thus, $V_M \approx -74$ mV.

Mechanistic interpretation of the Goldman-Hodgkin-Katz equation.

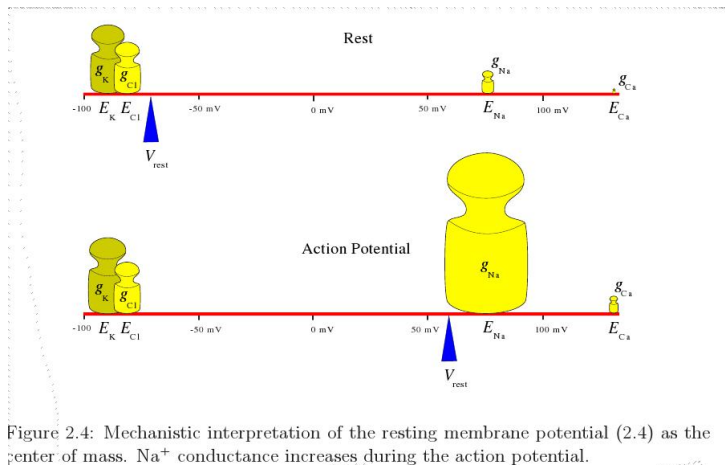


Figure 2.4: Mechanistic interpretation of the resting membrane potential (2.4) as the center of mass. Na^+ conductance increases during the action potential.

Equivalent electric circuit, representing the presence of many ionic channels.

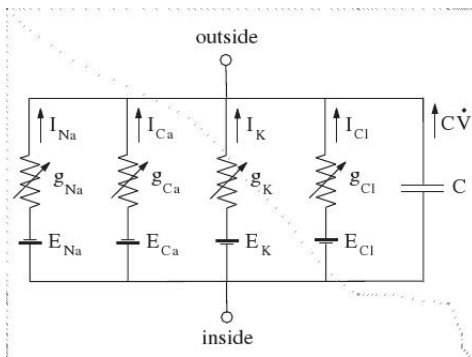


Figure 2.3: Equivalent circuit representation of a patch of cell membrane.

Basic equation of a circuit

From **Faraday's law**, $q = C V$; derivating, we obtain:

$$I(t) = C \frac{dV}{dt}.$$

Type of currents

The current $I(t)$ can come from different sources:

- Resting potential. A leak current, $g_L (V - E_L)$, is always considered. In absence of other currents, the membrane potential tends a V_L (by ionic pumpings...energy consuming).
- Ionic channels.
- Coupling among compartments of the same neuron (soma/dendrite for instance).
- Synapses.
- “External” current (electromagnetic stimuli, sensorial stimuli, noise, ...).

Type of currents

The current $I(t)$ can come from different sources:

Taking also into account diffusion (see **cable equation**):

$$C \frac{\partial V}{\partial t} = \frac{a}{2r_L} \frac{\partial^2 V}{\partial x^2} - I_{leak} - I_{ionic} - I_{synaptic} + I_{ext}$$

The biophysical model of a neuron is obtained by adding the appropriate components...dictated by the anatomical, physiological, pharmacological,...data.

Ionic channels: the experiments of Hodgkin and Huxley

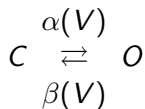
We explain how to extract information about the conductances with a technique that clamps the voltage and records the current needed to maintain it fixed. Then, from equation

$$I_{ion}(t) = g_{ion}(t) (V - E_{ion}),$$

one can know the dynamics of $g_{ion}(t)$.

To extend your knowledge, you can read Section 2.1.5 of [E.M. Izhikevich, “Dynamical systems in neuroscience”].

Voltage-gated ionic channels.

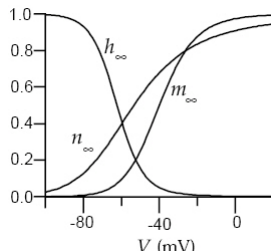


w = fraction of open gates. Law of mass action:

$$\frac{dw}{dt} = \phi (\alpha_w(v) (1 - w) - \beta_w(v) w) = \phi \frac{w_\infty(v) - w}{\tau_w(v)}, \quad (1)$$

$$w_\infty(v) = \frac{\alpha_w(v)}{\alpha_w(v) + \beta_w(v)},$$

$$\tau_w(v) = \frac{1}{\alpha_w(v) + \beta_w(v)},$$



Voltage-gated ionic channels: sketch of *voltage-clamp* technique.

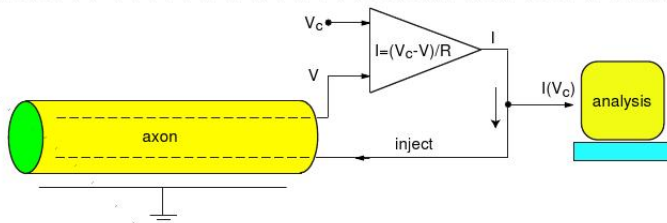


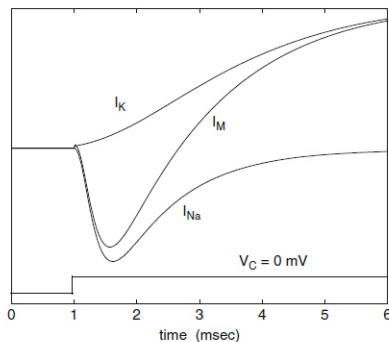
Figure 2.5: Two-wire voltage-clamp experiment on the axon. The top wire is used to monitor the membrane potential V . The bottom wire is used to inject the current proportional to the difference $V_c - V$, to keep the membrane potential at V_c .

Voltage clamp: determining the leakage conductance.

voltage clamp: allows the experimenter to hold the membrane potential at a constant or holding level V_C

space-clamp: $\frac{\partial^2 V}{\partial x^2} = 0$.

closing voltage-gated channels at rest: $I_M \approx g_L(V_C - E_L)$



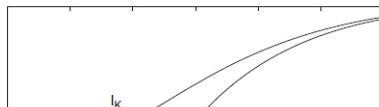
Voltage clamp: determining the ionic conductances.

Hodgkin and Huxley were able to isolate the K^+ current by replacing Na^+ ions in the external bathing solution with a larger, impermeant cation. This eliminated the inward Na^+ current. Now there are dozens of compounds that selectively block different currents, many derived from natural toxins. (For example, tetrodotoxin, which blocks Na^+ channels, comes from the Pacific puffer fish, a tasty, if slightly dangerous, Japanese delicacy called fugu.)

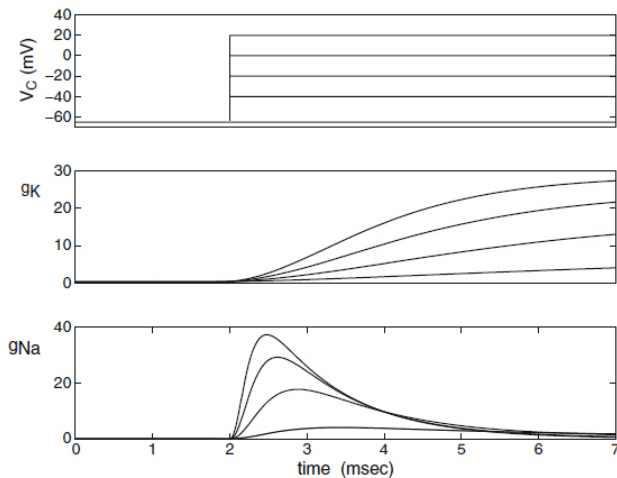
$$I_K = I_M - I_L$$

By Ohm's law:

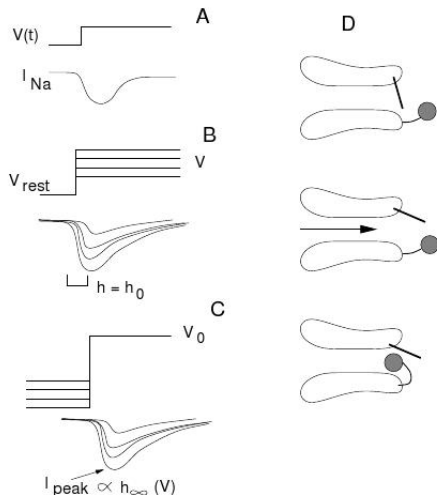
$$g_K(t) = \frac{I_K(t)}{(V - E_K)}.$$



Voltage clamp: determining the ionic conductances.



Voltage-clamp to determine the dynamics of a sodium channel.



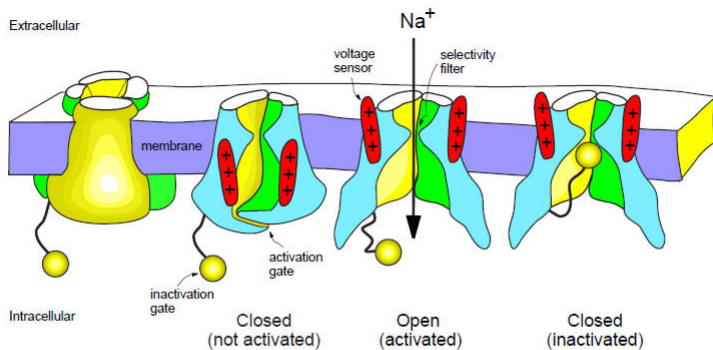


Figure 2.8: Structure of voltage-gated ion channels. Voltage sensors open an activation gate and allow selected ions to flow through the channel according to their electrochemical gradients. The inactivation gate blocks the channel. (Modified from Armstrong and Hille 1998.)

Activation and time functions

Hodgkin and Huxley studied the dynamics of the gating variables and gave next modelization (w can be h , m or n ,...or others not seen yet):

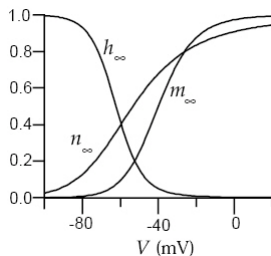
$$\frac{dw}{dt} = \phi (\alpha_w(\mathbf{v}) (1 - w) - \beta_w(\mathbf{v}) w) = \phi \frac{w_\infty(\mathbf{v}) - w}{\tau_w(\mathbf{v})}, \quad (2)$$

$$w_\infty(\mathbf{v}) = \frac{\alpha_w(\mathbf{v})}{\alpha_w(\mathbf{v}) + \beta_w(\mathbf{v})},$$

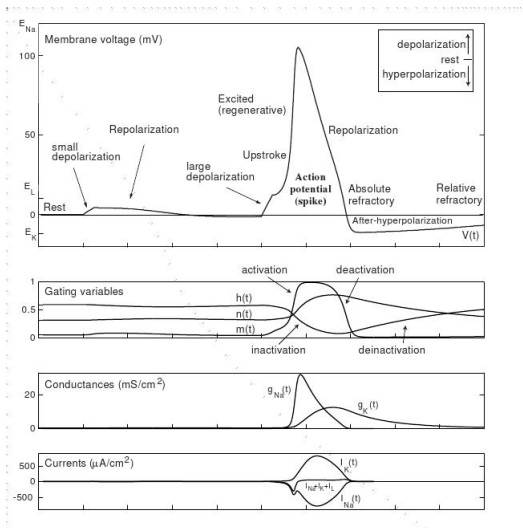
$$\tau_w(\mathbf{v}) = \frac{1}{\alpha_w(\mathbf{v}) + \beta_w(\mathbf{v})},$$

$$\alpha_w(\mathbf{v}) = 0.07 \exp(-(\mathbf{v} + 50)/10),$$

$$\beta_w(\mathbf{v}) = \frac{1}{1 + \exp(-0.1(\mathbf{v} + 20))}.$$



Different phases of an action potential (main features of the neurons and the Hodgkin-Huxley model)



Voltage-gated channels

Types:

- 1 activating/opening channels (m - Na^+ , n - K^+);
- 2 inactivating/closing channels (h).

The proportion of open channels in a large population is

$$p = m^a h^b$$

where a is the number of activation gates and b is the number of inactivation gates per channel. The channels can be partially ($0 < m < 1$) or completely activated ($m = 1$); not activated or deactivated ($m = 0$); inactivated ($h = 0$); released from inactivation or deinactivated ($h = 1$).

- $b = 0 \rightarrow$ persistent currents.
- $b \neq 0 \rightarrow$ transient currents.

Activation of Persistent Currents

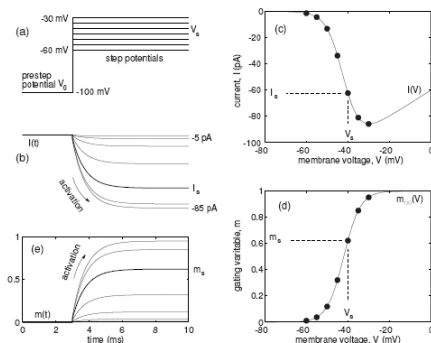


Figure 2.10: An experiment to determine $m_\infty(V)$. Shown are simulations of the persistent Na⁺ current in Purkinje cells (see section 2.3.5).

Figure: Initially, hold $V = V_0$ so that all activation gates are closed and $I \approx 0$. Then, step-increase V to $V_s > V$ until its asymptotic value, which is I_s . Repeating the experiment for various V_s , one obtains the entire steady-state $I - V$ relation.

Activation of Persistent Currents

The dynamics of the activation variable m is described by the first-order differential equation

$$m' = (m_{\infty}(V) - m)/\tau_m(V),$$

where the voltage-sensitive steady-state activation function $m_{\infty}(V)$ and the time constant $\tau_m(V)$ can be **measured experimentally** (voltage-clamp).

Activation and time functions

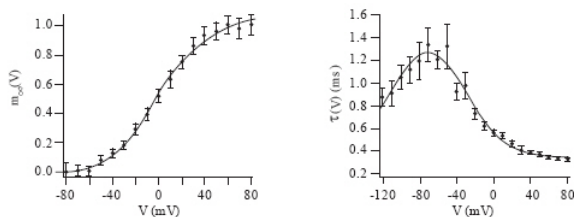


Figure 2.9: The activation function $m_{\infty}(V)$ and the time constant $\tau(V)$ of the fast transient K^+ current in layer 5 neocortical pyramidal neurons. (Modified from Korngreen and Sakmann 2000.)

$$w_{\infty}(v) = \frac{1}{1 + \exp((V_{1/2} - V)/k)},$$
$$\tau_w(v) = C_{base} + C_{amp} \exp\left(\frac{-(V_{max} - V)^2}{\sigma^2}\right).$$

Activation and time functions

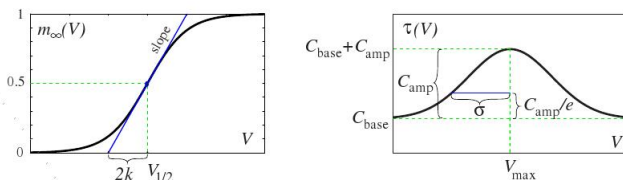


Figure 2.20: Boltzmann (2.11) and Gaussian (2.12) functions and geometrical interpretations of their parameters.

$$w_{\infty}(v) = \frac{1}{1 + \exp((V_{1/2} - V)/k)},$$

$$\tau_w(v) = C_{\text{base}} + C_{\text{amp}} \exp\left(\frac{-(V_{\max} - V)^2}{\sigma^2}\right).$$

Activation of Persistent Currents

- Smaller values of $\tau_m(V)$ result in faster dynamics of m .
- Observe that $I(V) = \bar{g}m_\infty(V)(V - E)$; i.e.,
 $m_\infty(V) = I(V)/(V - E)$ and normalized so that $\max m_\infty(V) = 1$.
- To determine the time constant $\tau_m(V)$ one needs to analyze the convergence rates.

Inactivation of Transient Currents

$$h' = (h_{\infty}(V) - h)/\tau_h(V).$$

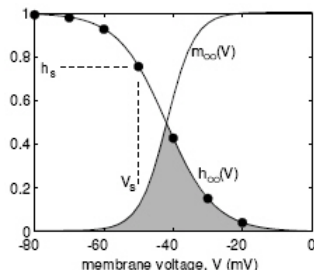


Figure 2.11: Steady-state activation function $m_{\infty}(V)$ from Fig.2.10, and inactivation function $h_{\infty}(V)$ and values h_s from Fig.2.12. Their overlap (shaded region) produces a noticeable, persistent “window” current.

Hyperpolarization-Activated Channels

- Channels that are open by hyperpolarization and turn on currents.
- For biologists, it is “exceptional” or “weird”: I_Q (queer), I_f (funny), I_h (hyperpolarization-activated), or I_{Kir} (K^+ inward rectifier).
- Mathematically, they are “normal” transient currents with the understanding that they are always activated (either $a = 0$ or $m = 1$), but can be inactivated by depolarization.

Membrane potential in the *Hodgkin-Huxley* model

$v = v(t)$ **membrane potential**:

$$C_m \frac{dv}{dt} = -I_L - I_{Na} - I_K - I_{syn} + I_{app}. \quad (3)$$

I_{syn} **synaptic current**; I_{app} **applied current**.

$$\begin{cases} I_L &= g_L (v - V_L), & \text{leakage current} \\ I_{Na} &= g_{Na} m^3 h (v - V_{Na}), & \text{sodium current} \\ I_K &= g_K n^4 (v - V_K) & \text{potassium current,} \end{cases}$$

h , m , n are the gating variables.

Beyond the classical Hodgkin-Huxley model...

The HH model is based on experiments performed on the giant axon of a squid, but there is a huge variety of neurons and animals. This paper is a good reference to see many of them:

[R. Llinás, “Intrinsic Electrophysiological Properties Of Mammalian Neurons: Insights into The Central Nervous System Function”]

In general,

$$w_{\infty}(v) = \frac{1}{1 + \exp((V_{1/2} - V)/k)},$$

$$\tau_w(v) = C_{base} + C_{amp} \exp\left(\frac{-(V_{max} - V)^2}{\sigma^2}\right).$$

Parameter values of several types of ionic channels (I)

Na ⁺ currents	Parameters (Fig.2.20)					
	Eq. (2.11)		Eq. (2.12)			
	$V_{1/2}$	k	$V_{\max}$	σ	C_{amp}	C_{base}
Fast transient ¹	$I_{\text{Na,t}} = \bar{g} m^3 h (V - E_{\text{Na}})$					
activation	-40	15	-38	30	0.46	0.04
inactivation	-62	-7	-67	20	7.4	1.2
Fast transient ²	$I_{\text{Na,t}} = \bar{g} m_{\infty}(V) h (V - E_{\text{Na}})$					
activation	-30	5.5	-	-	-	-
inactivation	-70	-5.8	$\tau_h(V) = 3 \exp((-40 - V)/33)$			
Fast transient ³	$I_{\text{Na,t}} = \bar{g} m_{\infty}(V) h (V - E_{\text{Na}})$					
activation	-28	6.7	-	-	-	-
inactivation	-66	-6	$\tau_h(V) = 4 \exp((-30 - V)/29)$			
Fast persistent ^{4,a}	$I_{\text{Na,p}} = \bar{g} m_{\infty}(V) h (V - E_{\text{Na}})$					
activation	-50	4	-	-	-	-
inactivation	-49	-10	-66	35	4.5 sec	2 sec
Fast persistent ^{5,a}	$I_{\text{Na,p}} = \bar{g} m_{\infty}(V) (0.14 + 0.86h) (V - E_{\text{Na}})$					
activation	-50	6	-	-	-	-
inactivation	-56	-7	$\tau_h(V) = 63.2 + 25 \exp(-V/25.5)$			
Fast persistent ²	$I_{\text{Na,p}} = \bar{g} m (V - E_{\text{Na}})$					
activation	-54	9	-	-	-	0.8
Fast persistent ⁶	$I_{\text{Na,p}} = \bar{g} m (V - E_{\text{Na}})$					
activation	-42	4	-	-	-	0.8

Parameter values of several types of ionic channels (II)

K ⁺ currents	Parameters (Fig.2.20)					
	Eq. (2.11)	Eq. (2.12)				
	$V_{1/2}$	k	V_{max}	σ	C_{amp}	C_{base}
Delayed rectifier ¹	$I_K = \bar{g} n^4 (V - E_K)$					
activation	-53	15	-79	50	4.7	1.1
Delayed rectifier ^{2,4}	$I_K = \bar{g} m h (V - E_K)$					
activation	-3	10	-50	30	47	5
inactivation	-51	-12	-50	50	1000	300
M current ³	$I_{K(M)} = \bar{g} m (V - E_K)$					
activation	-44	8	-50	25	320	20
Transient ⁴	$I_A = \bar{g} m h (V - E_K)$					
activation	-3	20	-71	60	0.92	0.34
inactivation	-66	-10	-73	23	50	8
Transient ⁵	$I_A = \bar{g} m h (V - E_K)$					
activation	-26	20	-	-	-	-
inactivation	-72	-9.6	-	-	-	15.5
Transient ⁶	$I_A = \bar{g} m^4 h (V - E_K)$					
Fast component (60% of total conductance)						
activation	-60	8.5	-58	25	2	0.37
inactivation	-78	-6	-78	25	45	19
Slow component (40% of total conductance)						
activation	-36	20	-58	25	2	0.37
inactivation	-78	-6	-78	25	45	19

$\tau_h(V) = 60$ when $V > -73$

Parameter values of several types of ionic channels (III)

Cation currents	Parameters (Fig.2.20)					
	$V_{1/2}$	Eq. (2.11) k	V_{max}	Eq. (2.12) σ	C_{amp}	C_{base}
I_h current ¹ (opened by hyperpolarisation)		$I_h = \bar{g} h (V - E_h)$	$E_h = -43$ mV			
inactivation	-75	-5.5	-75	15	1000	100
I_h current ²		$I_h = \bar{g} h (V - E_h)$	$E_h = -1$ mV			
inact. (soma)	-82	-9	-75	20	50	10
inact. (dendrite)	-90	-8.5	-75	20	40	10
I_h current ³		$I_h = \bar{g} h (V - E_h)$	$E_h = -21$ mV			
fast inact. (65%)	-67	-12	-75	30	50	20
slow inact. (35%)	-58	-9	-65	30	300	100

1. Thalamic relay neurons (McCormick and Pape 1990; Huguenard and McCormick 1992).
2. Hippocampal pyramidal neurons in CA1 (Magee 1998).
3. Entorhinal cortex layer II neurons (Dickson et al. 2000).

Hodgkin-Huxley variations: types of ionic channels

Summary types of currents:

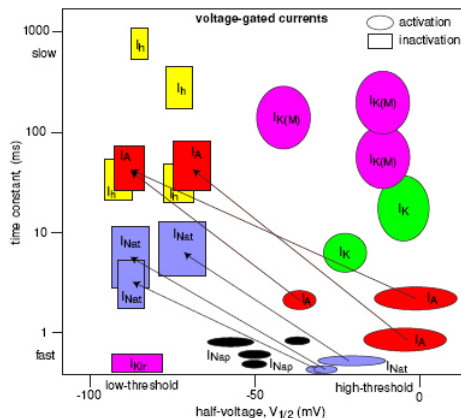
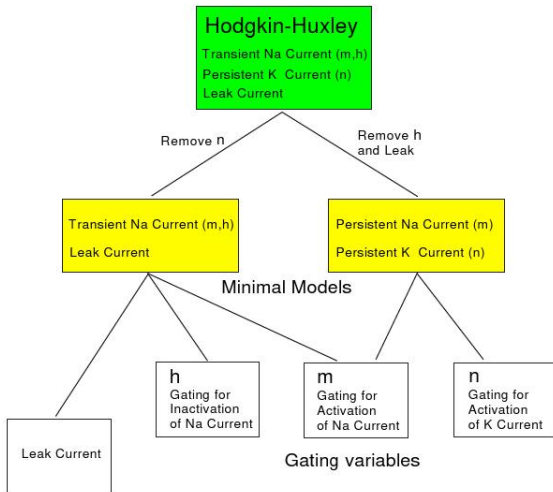


Figure 2.21: Summary of current kinetics. Each oval (rectangle) denotes the voltage and temporal scale of activation (inactivation) of a current. Transient currents are represented by arrows connecting ovals and rectangles.

Reductions of Hodgkin-Huxley: scheme

- Simplifications $m = m_{\infty}(V)$.
 - Wang's model:
"Calcium Coding and Adaptive Temporal Computation in Cortical Pyramidal Neurons", X.J.Wang, JNP 1998, used for the study of the estimation of conductances.
- Direct 2D models from Hodgkin-Huxley or similar. See Izhikevich, Ch. 5, *minimal models*], or Chow-Kopell, NC 1999, p.34.
- Morris-Lecar. See Section 3 of Toni G. "Una introducció a les matemàtiques de l'activitat neuronal". If you like it, you can read all the paper, which is intended to faithfully reflect its title...!
- "Geometrical" reductions: **Fitzhugh-Nagumo** model. Used, for instance, in [to study synchronization of oscillating neuron networks](#). Very useful to study analytical properties.
- *Integrate & fire* models (I&F, Lapicque 1907) and variants: QIF, EIF, I&F with adaptation, EIF with adaptation, Izhikevich model,...

Examples of possible reductions of the Hodgkin-Huxley model



We go through (very cautiously!) Fig. 2, p. 1066, of
[E.M.Izhikevich, “Which Model to Use for Cortical Spiking Neurons?”]

An exemple of a “sophisticated” model

Observe the nuances of the models appearing in pages 2708–2709 of [Compte *et al.*, “Cellular and Network Mechanisms of Slow Oscillatory Activity (1 Hz) and Wave Propagations in a Cortical Network Model”]; in particular, the high dimensionality of a single neuron model when one seeks a realistic representation.

It is also important to note that we take into account two compartments for the excitatory neurons (pyramidal): soma and dendrite.

FitzHugh-Nagumo equations

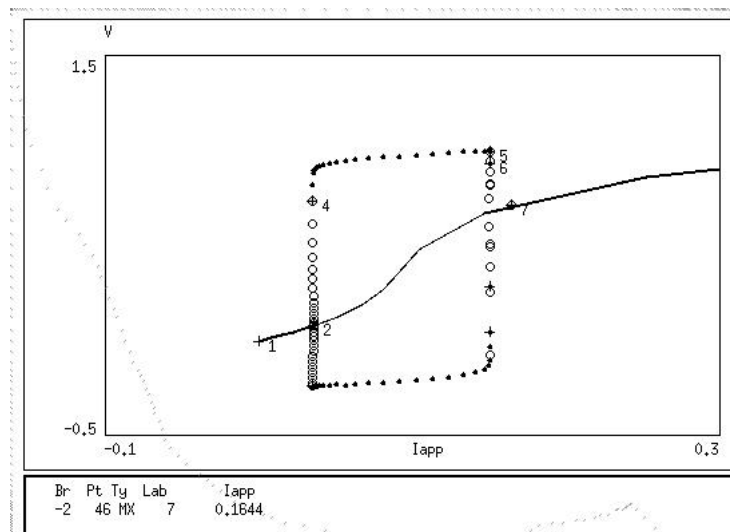
The Fitzhugh and Nagumo reduction isolates slow variables (gathered on w and considered *gating variables*) and the fast variables (represented by the *membrane potential* V).

The equations are the simplest ones giving rise to nullclines geometrically equivalent to those of the classical Hodgkin-Huxley model.

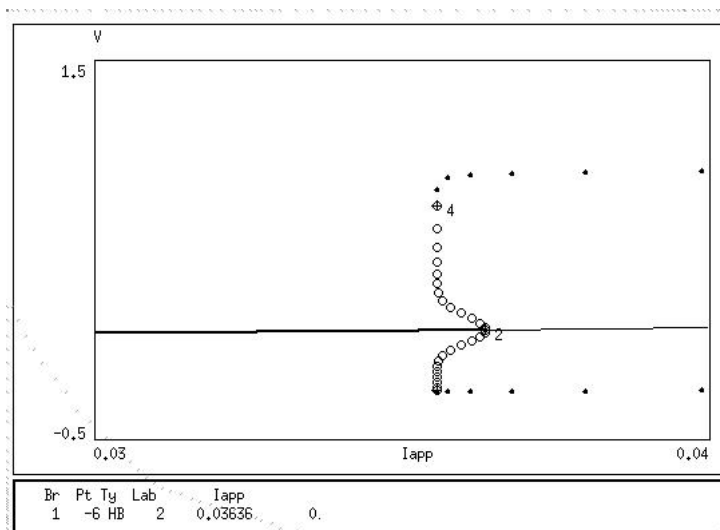
$$\begin{cases} dv/dt &= -V(V-1)(V-a) - w + I_{app} \\ dw/dt &= \epsilon(V - \gamma w). \end{cases}$$

For our simulations, we take $a = 0.14$, $\epsilon = 0.01$, $\gamma = 2.54$ and vary I_{app} .

FitzHugh-Nagumo: bifurcation diagrams

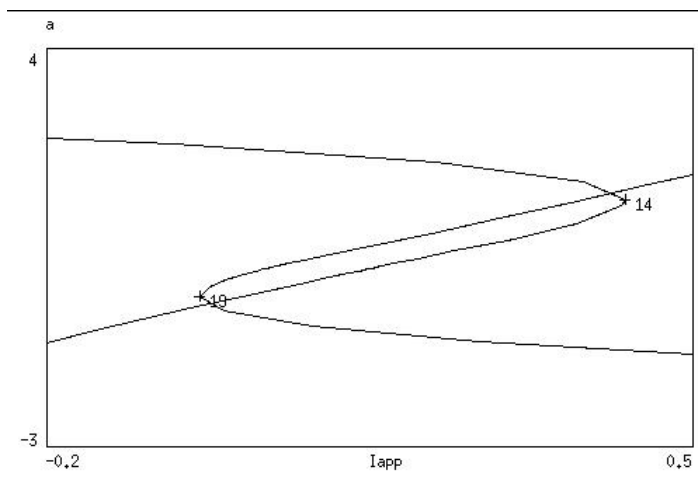


FitzHugh-Nagumo: bifurcation diagrams



FitzHugh-Nagumo: bifurcation diagrams

Biparametric:



Mathematical Models in Biology Neuroscience

Stochastic models

Toni Guillamon

Matemàtica Aplicada I - UPC

November 7th, 2013

Foreword

- Neurons live in a **noisy environment**, subjected to many **sources of noise**.
 - opening and closing of channels is a probabilistic event
 - spontaneous release of neurotransmitter which leads to random bombardment of small depolarizations and hyperpolarizations
 - In vivo, cortical neurons live in a high-conductance state due to the asynchronous firing of the presynaptic cells.

We mostly concentrate on scalar models for the firing of action potentials, such as the LIF, mostly to see the effects of noise on the subthreshold properties of neurons.

Informal treatment, not into the Itô integral.

Stochastic Differential Equations

$$dX = A(X, t) dt + B(X, t) dW_t.$$

with $X \in \mathbb{R}^n$, $A : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R}^n$, B is an $n \times n$ matrix of functions, $B_{jk} : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R}$, and W_t is a vector of independent **Wiener processes**. In general, the equations that we get are not easily solved either numerically or analytically, but the **scalar equation** is **treatable**:

$$x(t) = x(t_0) + \int_{t_0}^t a(x(s), s) ds + \int_{t_0}^t b(x(s), s) dW_s,$$

an extension of the Picard formula with a second integral which is a **stochastic integral**.

Wiener process

W_t is a continuous-time **stochastic or random process** (also called **Brownian motion**) characterized by three properties:

- $W_0 = 0$.
- The function $t \rightarrow W_t$ is *almost surely* everywhere continuous.
- The probability distribution W_t is **Gaussian**; in other words, its density function satisfies

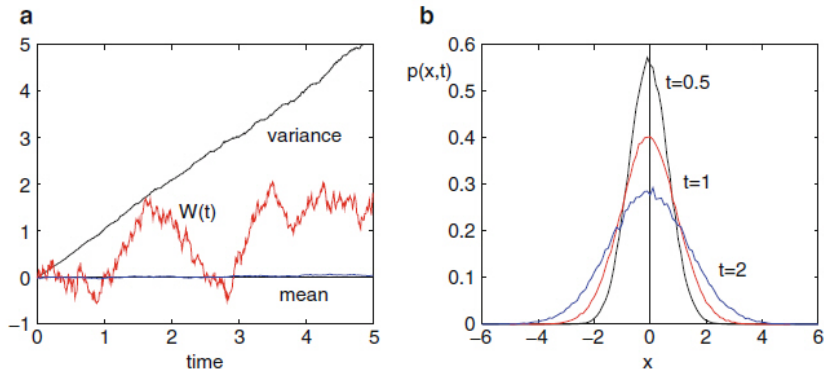
$$\frac{\partial p(x, t)}{\partial t} = \frac{\sigma^2}{2} \frac{\partial^2 p(x, t)}{\partial x^2}, \quad p(x, 0) = \delta(x).$$

- W_t has independent increments with $W_t - W_s \sim N(0, t - s)$ (for $0 \leq s < t$); equivalently,
 - for any finite collection times $t_1 < t_2 < \dots < t_n$, the random variables $W_{t_j} - W_{t_{j-1}}$ are **independent**.
 - $E[W_t] = 0$ and $E[(W_t - W_s)^2] = \sigma^2(t - s)$ for all $0 \leq s \leq t$.

The Wiener process can be simulated by

$$W_{t+h} = W_t + \sqrt{h} N(0, 1).$$

The Wiener Process (simulations)



Simulated Wiener process, $h = 0 : 01$. (a) Sample path and mean and variance of 1000 sample paths. (b) Probability histogram for 100 000 sample paths starting at $W_0 = 0$;
 $p(x, t) = 1/(\sqrt{2\pi t}) \exp(-x^2/(2t))$.

Langevin equation and discretization

Consider

$$dX = A(X, t) dt + B(X, t) dW_t,$$

that can be solved numerically by

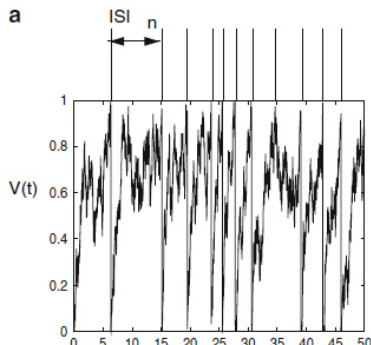
$$X(n+1) = X(n) + h A(X(n), t_n) + B(X(n), t_n) \sqrt{h} \hat{N}(0, 1),$$

where h is the discretization time step and $\hat{N}(0, 1)$ is a vector of **normally distributed** independent random numbers with unit variance.

What does noise do to neurons?

It allows them to **fire in the presence of subthreshold inputs** (the addition of zero mean noise can induce a “silent” neuron to fire). We consider a **leaky integrate&fire model with constant noise**:

$$dV = (I - V) dt + \sigma dW_t.$$



Simulation of the integrate-and-fire model with additive noise. $I = 0.95$, $\sigma = 0.1$, $h = 0.01$ with Euler method,
 $V_{n+1} = V_n + h(I - V_n) + \sigma \sqrt{h} \hat{N}(0, 1)$. See also Langevin.ode

In a Morris-Lecar model close to a HB

$$\frac{dv}{dt} = -g_L (v - E_L) - g_K w (v - E_K) - g_{Ca} m_\infty(v) (v - E_{Ca}) + I_{app},$$

$$\frac{dw}{dt} = \phi \frac{w_\infty(v) - w}{\tau_w(v)},$$

where

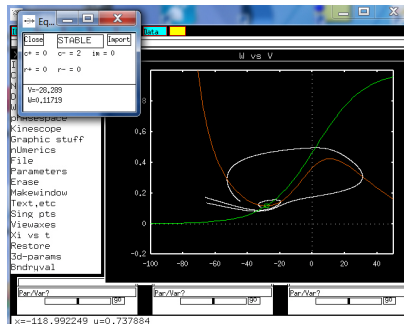
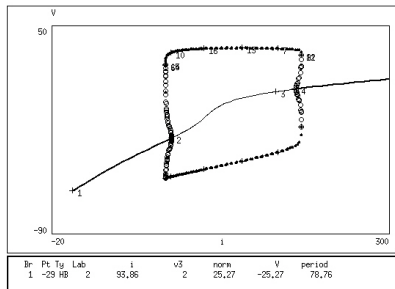
$$\begin{aligned} m_\infty(v) &= (1 + \tanh((v - V_1)/V_2))/2 \\ w_\infty(v) &= (1 + \tanh((v - V_3)/V_4))/2 \\ \tau_w(v) &= (\cosh((v - V_3)/(2 V_4)))^{-1}. \end{aligned}$$

$$\begin{array}{llll} V_L = -60, & V_K = -84, & V_{Ca} = 120 & \text{en mV} \\ V_1 = -1.2, & V_2 = 18, & V_3 = 2, & V_4 = 30 \\ g_L = 2, & g_K = 8.0, & g_{Ca} = 4.4 & \text{en mS/cm}^2 \\ C = 20 \mu\text{F/cm}^2 & \phi = 0.04 & I_{app} = 85 \mu\text{A/cm}^2. & \end{array}$$

In a Morris-Lecar model close to a HB

$$\frac{dv}{dt} = -g_L(v - E_L) - g_K w(v - E_K) - g_{Ca} m_\infty(v)(v - E_{Ca}) + I_{app},$$

$$\frac{dw}{dt} = \phi \frac{w_\infty(v) - w}{\tau_w(v)},$$



Bifurcation diagram and simulation of the Morris-Lecar model without noise. Right panel,

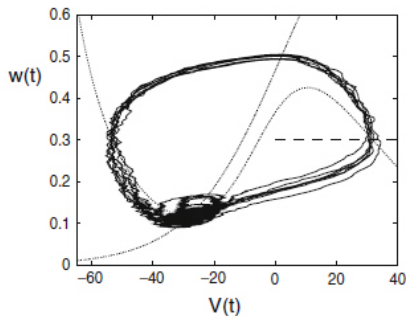
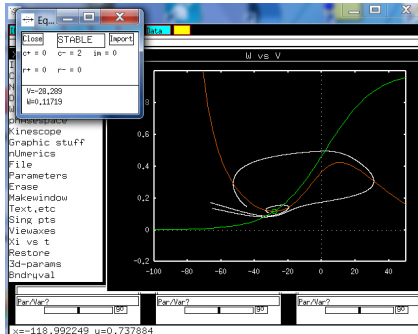
I — 85

In a Morris-Lecar model close to a HB

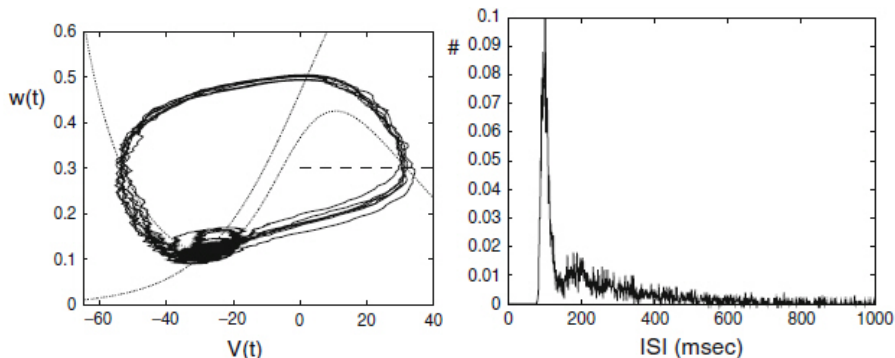
$$\frac{dv}{dt} = -g_L(v - E_L) - g_K w(v - E_K) - g_{Ca} m_\infty(v)(v - E_{Ca}) + I_{app},$$

$$\frac{dw}{dt} = \phi \frac{w_\infty(v) - w}{\tau_w(v)},$$

(1)



How does one detect a spike in a stochastically driven model?



Distribution of crossings of $w=0.3$. Right: Histogram of **ISIs, interspike intervals**.

Remark: The trajectory will **not** be **differentiable**, so it could cross a fixed value arbitrarily many times in a given time interval. This is not an issue with the I&F model because of reset conditions. In the ML model, a crossing level of $w = 0.3$ is a very reliable indicator of a spike.

From SDEs to the ODE rate equations through the Fokker-Planck PDE I

The Fokker-Planck equation is a **fundamental method** to study SDEs. We concentrate in the scalar case.

- $P(x, t)$ is the probability that a random variable $X = x$ at time t .
- We assume that the new state only depends on the current state.
- Let $M(x', x, t) dt$ be the rate at which the process whose state is $X = x'$ at time t jumps to $X = x$ at time $t + dt$.

The **master equation** is defined as

$$\frac{\partial P}{\partial t}(x, t) = \int [M(x', x, t)P(x', t) - M(x, x', t)P(x, t)] dx'.$$

Equivalently ($Q(y, x, t) = M(x, x + y, t)$):

$$\frac{\partial P}{\partial t}(x, t) = \int [Q(y, x - y, t)P(x - y, t) - Q(y, x, t)P(x, t)] dy.$$

From SDEs to the ODE rate equations through the Fokker-Planck PDE II

Assuming y small (realistic in synaptic events) and Taylor-expanding we get the **Kramers-Moyal expansion**:

$$\frac{\partial P}{\partial t}(x, t) = \int dy \left[(-y) \frac{\partial Q(y, x, t) P(x, t)}{\partial x} + \frac{y^2}{2} \frac{\partial^2 Q(y, x, t) P(x, t)}{\partial x^2} + \dots \right]$$

Defining

$$\alpha_j(x, t) = \int dy y^j Q(y, x, t),$$

$$\frac{\partial P}{\partial t}(x, t) = -\frac{\partial \alpha_1(x, t) P(x, t)}{\partial x} + \frac{1}{2} \frac{\partial^2 \alpha_2(x, t) P(x, t)}{\partial x^2} + \dots$$

Observe that α_1 is the **mean jump size** and α_2 the **variance**.

From SDEs to the ODE rate equations through the Fokker-Planck PDE III

In the case of Gaussian processes, all the moments of Q higher than two vanish (m -cumulants of a Gaussian random variable are zero for $m > 2$). Thus, we get the **Fokker-Planck equation**:

$$\frac{\partial P}{\partial t}(x, t) = -\frac{\partial \alpha_1(x, t)P(x, t)}{\partial x} + \frac{1}{2} \frac{\partial^2 \alpha_2(x, t)P(x, t)}{\partial x^2}$$

The Fokker-Planck equation for the Langevin equation

$$dx = a(x, t) dt + b(x, t) dW_t$$

In the discretized SDE $x(t+h) = x(t) + h a(x, t) + \sqrt{h} b(x, t) N(0, 1)$, we can think of $h a(x, t)$ being the **mean jump size** and $h b(x, t)^2$ being the **variance**.

Since the mean and the variance in the master equation are defined in terms of the rate per unit time, we divide by h , and obtain the corresponding FP equation:

$$\frac{\partial P}{\partial t}(x, t) = -\frac{\partial a(x, t) P(x, t)}{\partial x} + \frac{1}{2} \frac{\partial^2 b(x, t)^2 P(x, t)}{\partial x^2}.$$

The Fokker-Planck equation for the scalar with constant noise SDE: $dX = a(x, t) dt + \sigma dW_t$

$$\frac{\partial P}{\partial t}(x, t) = -\frac{\partial a(x, t) P(x, t)}{\partial x} + \frac{\sigma^2}{2} \frac{\partial^2 P(x, t)}{\partial x^2},$$

which can be written as this **conservation law**:

$$\frac{\partial P}{\partial t}(x, t) + \frac{\partial J}{\partial x}(x, t) = 0,$$

for $J(x, t) = a(x, t) P(x, t) - \frac{\sigma^2}{2} \frac{\partial P(x, t)}{\partial x}$, which is a current with a **drift** or **transport** term and a **diffusive** part.

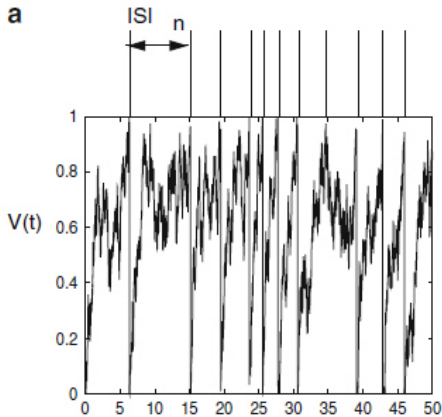
To solve the Fokker-Planck differential equation we need boundary and initial conditions. We are going to explore them in a **LIF neuron model**.

The Fokker-Planck equation for integrate&fire models

Consider

$$dV = \mathbf{f}(\mathbf{V}, \mathbf{t}) dt + \sigma dW_t$$

with a **reset condition**: when V reaches V_{spike} , then $V = V_{reset}$.



The Fokker-Planck equation for integrate&fire models

Consider

$$dV = \mathbf{f}(\mathbf{V}, \mathbf{t}) dt + \sigma dW_t, \quad \mathbf{V}(\mathbf{t}^-) = \mathbf{V}_{\text{spike}} \Rightarrow \mathbf{V}(\mathbf{t}^+) = \mathbf{V}_{\text{reset}}.$$

Different $\mathbf{f}(\mathbf{V}, \mathbf{t})$ give the different types of I&F neuron models (LIF, QIF, EIF, ...)

$$\frac{\partial P}{\partial t}(V, t) = -\frac{\partial J}{\partial V}(V, t) + \delta(\mathbf{V} - \mathbf{V}_{\text{reset}}) \mathbf{J}(\mathbf{V}_{\text{spike}}, \mathbf{t}),$$

where $J(V, t) = f(V, t) P(V, t) - \frac{\sigma^2}{2} \frac{\partial P(V, t)}{\partial V}$,

- defined for $V \in (-\infty, V_{\text{spike}})$, and
- with boundary conditions $P(-\infty, t) = 0 = P(V_{\text{spike}}, t)$.

Remark: $J(V_{\text{spike}}, t) =: \nu$ is the firing rate of the neuron.

The Fokker-Planck equation for integrate&fire models I

Stationary solutions:

$$0 = -\frac{dJ(V)}{dV} + \delta(V - V_{reset}) J(V_{spike})$$

Thus,

$$J_0 = -J(V) + J(V_{spike}) H(V - V_{reset}), \quad H = \text{Heaviside.}$$

In fact, we can obtain $J_0 = 0$ evaluating J at $-\infty$ since by definition $J(-\infty) = f(-\infty) P(-\infty, t) - \frac{\sigma^2}{2} \frac{\partial P(-\infty, t)}{\partial V} = 0$ and $J_0 = -J(-\infty)$. Moreover, from $P(V_{spike}) = 0$, using again the definition at steady state:

$$J(V_{spike}) = -\frac{\sigma^2}{2} \frac{dP(V_{spike})}{dV} \equiv \nu.$$

The Fokker-Planck equation for integrate&fire models II

Thus, we finally get a first order ODE:

$$f(V) P(V) - \frac{\sigma^2}{2} \frac{dP(V)}{dV} = \nu H(V - V_{reset}).$$

We have (using normalization):

$$\begin{aligned} f(V) P_-(V) - \sigma^2/2 P'_-(V) &= 0, & -\infty < V < V_{reset}, \\ f(V) P_+(V) - \sigma^2/2 P'_+(V) &= \nu, & V_{reset} < V < V_{spike}, \\ P_-(-\infty) &= 0, \\ P_-(V_{reset}) &= P_+(V_{reset}), \\ P_+(V_{spike}) &= 0, \\ \int_{-\infty}^{V_{reset}} P_-(V) dV + \int_{V_{reset}}^{V_{spike}} P_+(V) dV &= 1. \end{aligned}$$

The Fokker-Planck equation for integrate&fire models III

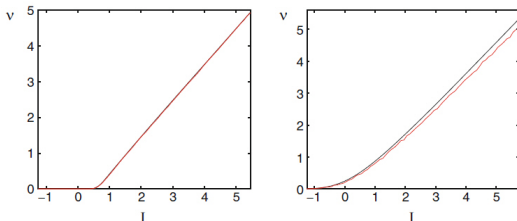
Defining $F(x)$ as $F'(x) = f(x)$, we can obtain that:

$$\begin{aligned}\nu^{-1} &= \frac{2}{\sigma^2} \int_{-\infty}^{V_{\text{reset}}} \exp(2 F(x)/\sigma^2) dx \int_{V_{\text{reset}}}^{V_{\text{spike}}} \exp(-2 F(y)/\sigma^2) dy \\ &+ \frac{2}{\sigma^2} \int_{V_{\text{reset}}}^{V_{\text{spike}}} \exp(2 F(x)/\sigma^2) \int_x^{V_{\text{reset}}} \exp(-2 F(y)/\sigma^2) dy dx \\ &= \frac{2}{\sigma^2} \int_{-\infty}^{V_{\text{spike}}} \exp(2 F(x)/\sigma^2) \int_{\max(x, V_{\text{reset}})}^{V_{\text{spike}}} \exp(-2 F(y)/\sigma^2) dy dx\end{aligned}$$

The rate function for the LIF model, $f(V) = I - V$

The firing rate for the leaky integrate-and-fire model, see [Fourcaud, Brunel], is:

$$\nu^{-1} = \sqrt{\pi} \int_{\frac{V_{\text{spike}} - I}{\sigma}}^{\frac{V_{\text{reset}} - I}{\sigma}} e^{s^2} (1 + \text{erf}(s)) \, ds, \text{ with } \text{erf}(s) = \frac{1}{\sqrt{\pi}} \int_{-x}^x e^{-s^2} \, ds.$$



F-I curves for the LIF model ($V_{\text{spike}} = 1$, $V_{\text{reset}} = 0$). **Solutions to the boundary value problem** and **solutions to the Monte-Carlo simulations**: $\sigma = 0.25$ (left), $\sigma = 1.0$ (right).

Mathematical Models in Biology Neuroscience

Building networks of neurons

Toni Guillamon

Matemàtica Aplicada I - UPC

October 23th, 2014

Neuronal networks: outline (ELEMENTS)

- We have seen that **single neurons** can have quite **complex dynamics**.
- Now, we have to consider their connections (**synapses**).
- Which kind of structures do the **neuronal networks** have?

Neuronal networks: outline (CHALLENGES) I

- How will the new dynamics be? This will depend on the type of neuron, the strength of the synapses, the timing among the pre- and post-synaptic neurons,... So, **synchrony** becomes an important question to explore.
- Does the structure of the network influence the dynamics? How? This involves both **statistical methods** to extract information about **connectivity**, but also **graph theory** to characterize each type of network. This approach mainly leads to highly computational tasks.

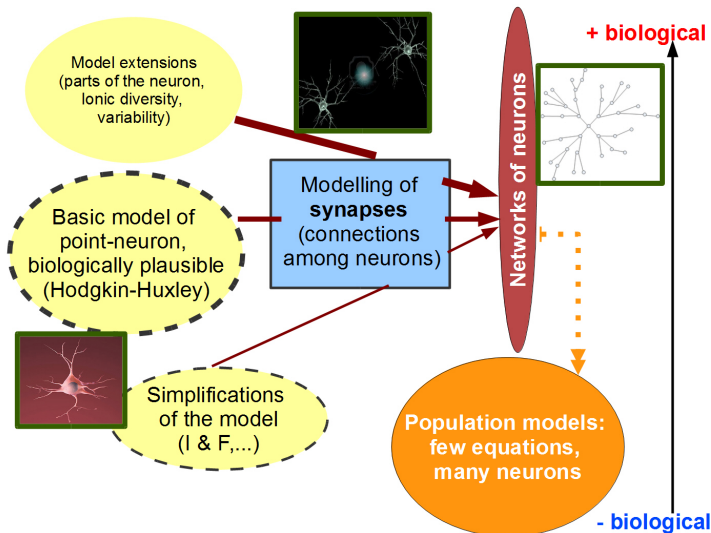
Neuronal networks: outline (CHALLENGES) II

- These complex networks, can be studied in a simple way? Is there a way to capture the essence of the network dynamics to be able to give rigorous results or, at least, make sure about the **mechanisms leading the overall dynamics**? This question leads to reduced models, mainly **rate models**, which are, in general, **systems of differential equations** that can be derived in several ways (Wilson-Cowan approach, Fokker-Planck approach, ...).

Overview on basic ELEMENTS when building up a network

- I. Choice of neuron models.
- II. Synaptic couplings.
- III. Structure of the network (space and topology).
- IV. Input current.

Models' paradigm



I. Choice of neuron models

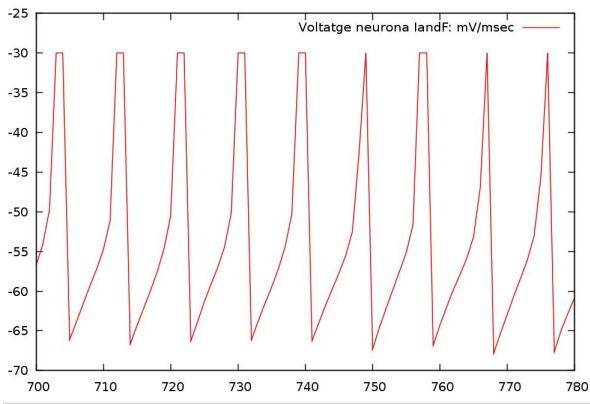
I. Choice of neuron features

Elements to take into account:

- Both excitatory and inhibitory neurons?
- Proportion exc/inh (≈ 4).
- Type of models according to the desired biological plausibility (ionic channels, compartments, adaptation, only spiking, ...)

Integrate and fire neurons (leaky)

$$\left\{ \begin{array}{l} C \frac{dv}{dt} = -g_L (v - V_L) + \mathbf{l_{app}(t)}, \\ v(t + T_{ref}) = v_{reset}, \text{ if } v(t) > v_{thresh} \end{array} \right.$$



Integrate and fire neurons (quadratic)

$$\left\{ \begin{array}{l} C \frac{dv}{dt} = -g_L (v - V_L) + \psi(v) + I_{app}(t), \\ v(t + T_{ref}) = v_{reset}, \text{ if } v(t) > v_{thresh} \end{array} \right.$$

$$\psi(v) = \frac{g_L}{2\Delta T} (v - V_T)^2 + g_L (v - V_L) - I_T$$

(Ermentrout-Kopell 1986)

Does not capture either spike generation dynamics at ms time scale (too slow)

Integrate and fire neurons (exponential)

$$\left\{ \begin{array}{l} C \frac{dv}{dt} = -g_L (v - V_L) + \psi(v) + I_{app}(t), \\ v(t + T_{ref}) = v_{reset}, \text{ if } v(t) > v_{thresh} \end{array} \right.$$

$$\psi(v) = g_L \Delta T \exp\left(\frac{v - V_T}{\Delta T}\right)$$

(Fourcaud-Trocme et al 2003)

Captures quantitatively very well the dynamics of more realistic neurons, because the activation curve of sodium currents can be well fitted by an exponential close to firing threshold.

II. Synaptic couplings

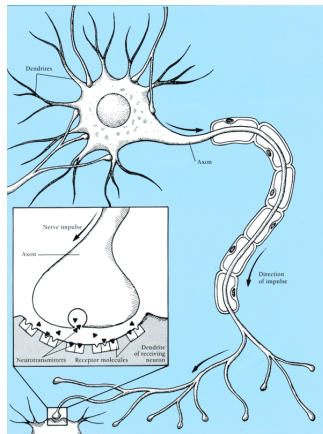
Networks: how many neurons and synapses?

Species	Neurons	Synapses
C Elegans	302	5 000
Fruit fly	10^5	10^7
Honey bee	10^6	10^9
Mouse	10^8	10^{11}
Cat	10^9	10^{12-13}
Human	10^{11}	10^{15}

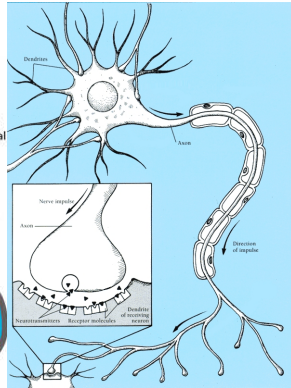
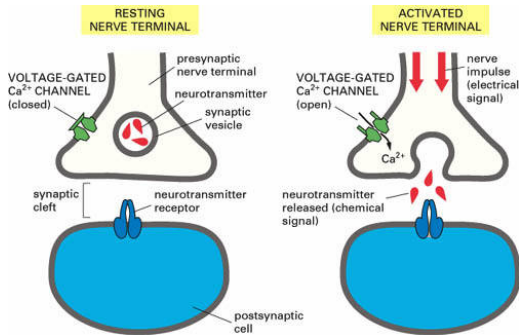


Structure of a neuron and synapses

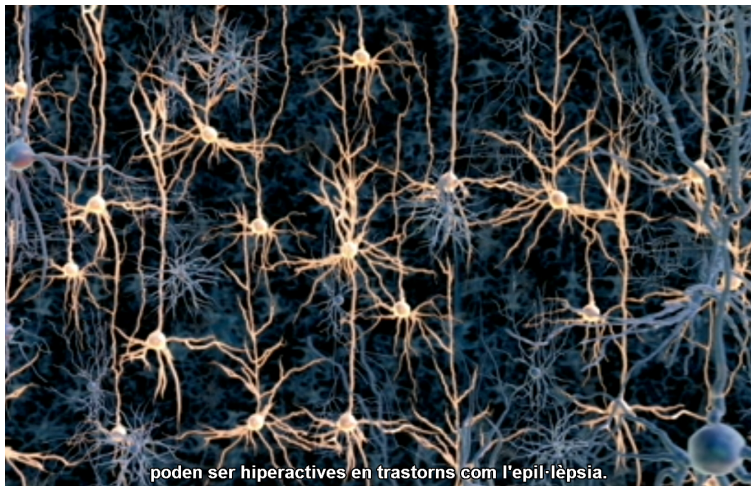
We have around 10^{11} neurons and 10^{15} connections (synapses) among them.



Structure of a neuron and synapses



Inhibition and excitation



Neurons and how they work, http://www.ted.com/talks/ed_boyden.html (Ed Boyden: A light switch for the neurons)

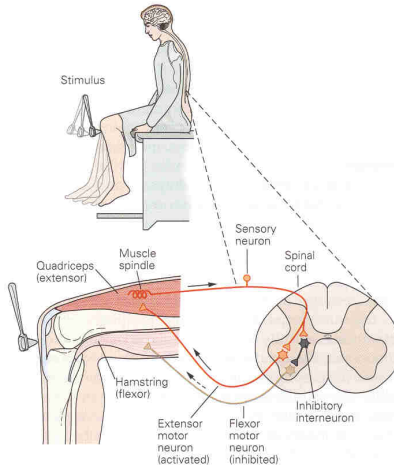
Inhibition and excitation



Neurons and how they work, http://www.ted.com/talks/ed_boyden.html (Ed Boyden: A light switch for the neurons)

How far synapsis can go? Monosynaptic reflexes

A kick on the knee makes the quadriceps to stretch. This triggers a process leading to the contraction of the quadriceps and the simultaneous relaxation of the biceps. Then, there is an extension of the leg.



Neurotransmitters and receptors

Neurotransmitters:

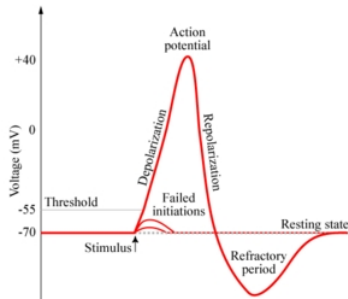
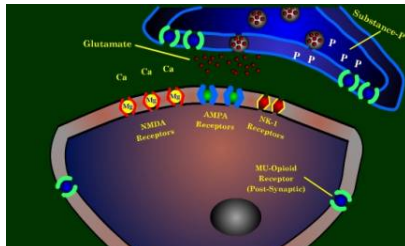
- **Excitatory:** Glutamate. It activates two kinds of receptors:
 - AMPA. Fast synapsis (rise time is less than 1ms)
 - NMDA. Slower than AMPA. Involved in short-term memory.

Both AMPA and NMDA receptors produce mixed-cation conductances with reversal potential around 0mV.

- **Inhibitory:** GABA (γ -aminobutyric acid). It activates two kinds of receptors:
 - GABA_A. Fast. Produce a fast Cl^- conductance.
 - GABA_B. Slower than GABA_A. Activates the conductance indirectly through an intracellular pathway (G-protein that activates a K channel). It produces a slower and long-lasting K conductance.

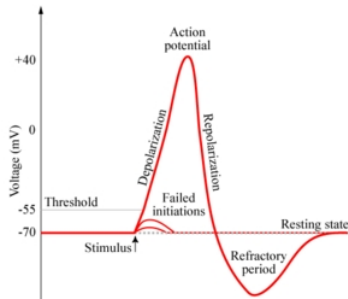
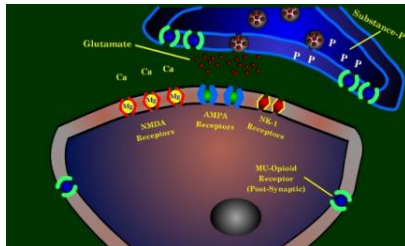
Neurotransmission, first issue: **excitation** or **inhibition**?

- Glutamate activates two kinds of receptors: AMPA (fast) and NMDA (slow).
- GABA (γ -aminobutyric acid) activates two kinds of receptors: GABA_A (fast) and GABA_B (slow).
- $I_{syn} = I_{syn,exc} + I_{syn,inh}$



Neurotransmission, first issue: **excitation** or **inhibition**?

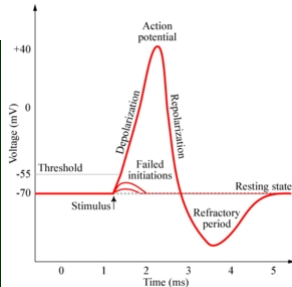
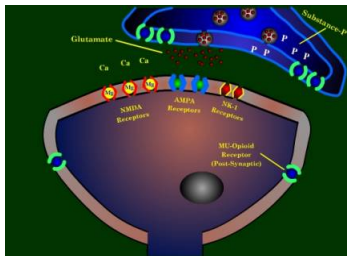
- Glutamate activates two kinds of receptors: AMPA (fast) and NMDA (slow).
- GABA (γ -aminobutyric acid) activates two kinds of receptors: GABA_A (fast) and GABA_B (slow).
- $I_{syn} = I_{syn,exc} + I_{syn,inh}$
- Excitation:** $I_{syn,exc} = g_E(t)(v - V_E)$, $V_E \approx 0 \text{ mV}$
- Inhibition:** $I_{syn,inh} = g_I(t)(v - V_I)$, $V_I \approx -80 \text{ mV}$



First step in neurotransmission modelling: the $g_{E,I}(t)$

- $I_{syn} = I_{syn,exc} + I_{syn,inh}$
- **Excitation:** $I_{syn,exc} = g_E(t)(v - V_E), \quad V_E \approx 0 \text{ mV}$
- **Inhibition:** $I_{syn,inh} = g_I(t)(v - V_I), \quad V_I \approx -80 \text{ mV}$

The conductances $g_{E,I}(t)$ depend on presynaptic neurons.



Simple modelling of conductances

The conductances depend only on the **spiking times** of the presynaptic neurons.

$$g(t) = \bar{g}_{max} \sum_{k \in \text{presyn}, j} \alpha(t - t_j^k),$$

t_j^k = time of the j th spike of the k th presynaptic neuron.

$$\alpha(t) = \frac{a_d a_r}{a_r - a_d} (e^{-a_d t} - e^{-a_r t}),$$

a_r =rise rate; a_r =rise rate;

Assuming $a_r = a_d$ (usual),

$$\alpha(t) = a_d^2 t e^{-a_d t},$$

with constants chosen under some normalization criterion (e.g.,

$$\int_{\mathbb{R}} \alpha(t) dt = 1)$$

Simple modelling of conductances

$$\begin{cases} g(t) &= \bar{g}_{max} \sum_{k \in presyn, j} \alpha(t - t_j^k), \\ \alpha(t) &= a_d^2 t e^{-a_d t} \end{cases}$$

- Very **useful for networks** (specially of I&F neurons). Indeed, $\alpha(t)$ is a solution of $z'' + (a_r + a_d)z' + a_r a_d z = a_r a_d \nu(t)$, $\nu(t)$ population spiking rate.

Simple modelling of conductances

$$\begin{cases} g(t) &= \bar{g}_{max} \sum_{k \in \text{presyn}, j} \alpha(t - t_j^k), \\ \alpha(t) &= a_d^2 t e^{-a_d t} \end{cases}$$

- Very **useful for networks** (specially of I&F neurons). Indeed, $\alpha(t)$ is a solution of $z'' + (a_r + a_d)z' + a_r a_d z = a_r a_d \nu(t)$, $\nu(t)$ population spiking rate.
- Difficulty in estimating **spiking times**.
- Out of the spirit of **voltage-gated-like modelling**.

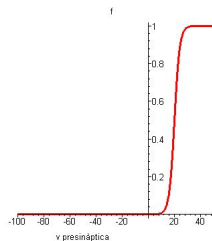
Ionic-channel-like conductance modelling

$$I_{syn} = g_{syn} \mathbf{s}(\mathbf{t}) (V - V_{syn})$$

Specific neurotransmission:

- **Fast excitation:** Neuroreceptors AMPA: $\tau = 2$ ms, $V_{syn} = 0$ mV
- **Inhibition:** Neuroreceptors GABA: $\tau = 10$ ms, $V_{syn} = -70$ mV

$$\frac{d\mathbf{s}}{dt} = \alpha_s f(V_{pre})(1 - \mathbf{s}) - \frac{\mathbf{s}}{\tau_s},$$



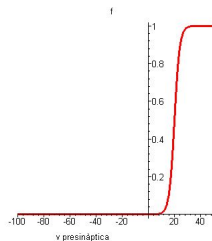
Ionic-channel-like conductance modelling

$$I_{syn} = g_{syn} \mathbf{s}(\mathbf{t}) (V - V_{syn})$$

Specific neurotransmission:

- **Fast excitation:** Neuroreceptors AMPA: $\tau = 2$ ms, $V_{syn} = 0$ mV
- **Inhibition:** Neuroreceptors GABA: $\tau = 10$ ms, $V_{syn} = -70$ mV

$$\frac{d\mathbf{s}}{dt} = \alpha_s f(V_{pre})(1 - \mathbf{s}) - \frac{\mathbf{s}}{\tau_s},$$



- **Slow excitation:** Neuroreceptors NMDA (memory processes)

$$\frac{d\mathbf{s}}{dt} = \alpha_s x (1 - \mathbf{s}) - \frac{\mathbf{s}}{\tau_s}, \quad \frac{dx}{dt} = \alpha_x f(V_{pre}) - \frac{x}{\tau_x},$$

Rate of neurotransmitters release: $f(V_{pre})$

$$I_{syn} = g_{syn} \mathbf{s(t)} (V - V_{syn}), \quad \frac{d\mathbf{s}}{dt} = \alpha_s f(V_{pre})(1 - \mathbf{s}) - \frac{\mathbf{s}}{\tau_s},$$

It is obtained from

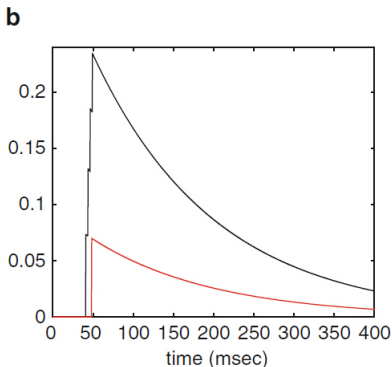
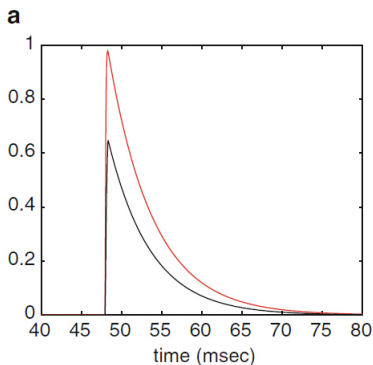
$$\frac{d\mathbf{s}}{dt} = a_r [T] (1 - \mathbf{s}) - a_d \mathbf{s},$$

where $[T]$ = concentration of released neurotransmitters and $s(t)$ is now the fraction of open channels; we assume $[T] \equiv T_{max}$ after a *spike*.

An usual model is

$$[T] =: f(V_{pre}) = \frac{T_{max}}{1 + \exp(-(V_{pre} - \theta)/k_p)}.$$

$s(t)$ dynamics after a spike



- (a) **AMPA** and **GABAA** conductance due to a single presynaptic spike.
- (b) NMDA conductance due to a **single spike** and a **burst of four spikes**.

Simplifications

$$I_{syn} = g_{syn} \mathbf{s}(\mathbf{t}) (V - V_{syn}),$$

- Factor elimination ($1 - s$):

$$\frac{d\mathbf{s}}{dt} = \alpha_s f(V_{pre}) - \frac{\mathbf{s}}{\tau_s},$$

Simplifications

$$I_{syn} = g_{syn} \mathbf{s}(\mathbf{t}) (V - V_{syn}),$$

- Factor elimination ($1 - s$):

$$\frac{d\mathbf{s}}{dt} = \alpha_s f(V_{pre}) - \frac{\mathbf{s}}{\tau_s},$$

- Substitution by a δ function:

$$\frac{d\mathbf{s}}{dt} = \alpha_s \delta(t - t_{spk}) - \frac{\mathbf{s}}{\tau_s},$$

Simplifications

$$I_{syn} = g_{syn} \mathbf{s}(\mathbf{t}) (V - V_{syn}),$$

- Factor elimination ($1 - s$):

$$\frac{d\mathbf{s}}{dt} = \alpha_s f(V_{pre}) - \frac{\mathbf{s}}{\tau_s},$$

- Substitution by a δ function:

$$\frac{d\mathbf{s}}{dt} = \alpha_s \delta(t - t_{spk}) - \frac{\mathbf{s}}{\tau_s},$$

- Direct effect in the synaptic current of the j -th neuron (e.g. [Rubin-Terman, SIADS2002]):

$$I_{syn}^{(j)} = \bar{g}_{syn} \frac{1}{N} \sum_{k \in presyn} s_{\infty}(v_k) (v_j - E_{syn}),$$

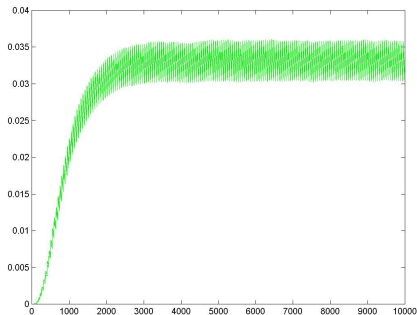
s_{∞} sigmoidal, Heaviside,...

Synaptic depression/facilitation (plasticity)

$$I_{syn} = g_{syn} s P_{rel} (V - V_{syn}),$$

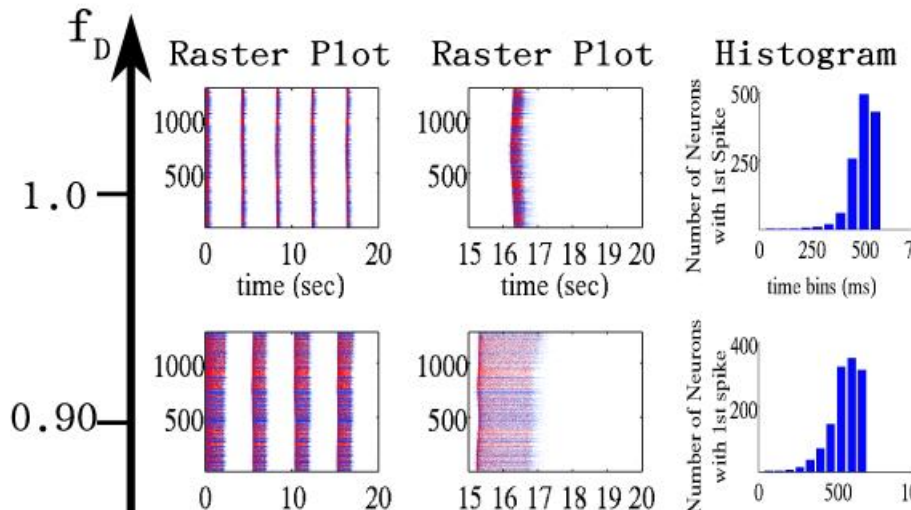
where P_{rel} , the release probability, can have its own dynamics:

$$\left\{ \begin{array}{l} \frac{dP_{rel}}{dt} = \frac{P_0 - P_{rel}}{\tau_{rel}}, \quad \tau_{rel} \approx 0.5 - 1s, \\ P_{rel}(t_{spk}^+) = f_D P_{rel}(t_{spk}^-) \end{array} \right.$$

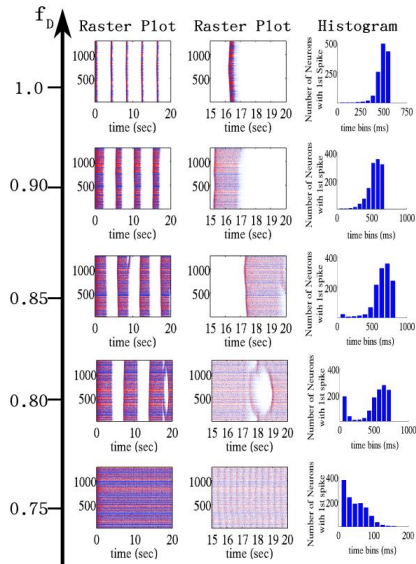
P_{rel} dynamics

Dynamics of the **release probability** variable during a **bombardment of presynaptic spikes**.

Effects of the depression in a network



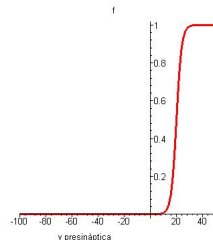
Effects of the depression in a network



Synaptic couplings

- **Dynamic** coupling (s_{ij} , $s_j, \dots$, or **static**).

$$\frac{d\mathbf{s}}{dt} = \alpha_s f(V_{pre})(1 - \mathbf{s}) - \frac{\mathbf{s}}{\tau_s},$$



- **Adjacency** matrix or **weighted** matrix.

Example: a routine to establish a Gaussian connectivity matrix in a ring of neurons I

- **ExcInh**: index that stores the excitatory or inhibitory character of a cell.
- **sigmaExc2**: the rang of excitation squared, σ_{exc}^2 .
- **sigmaInh2**: the rang of inhibition squared, σ_{inh}^2 .
- **h**: distance between adjacent neurons.
- **nDist**: number of neurons apart from neuron npre to neuron npost.
- **npre**, **npost**: index of the presynaptic and the postsynaptic neuron, respectively.
- **NCon[npre]**: counts the number of “projections” of neuron npre.
- **xi**: a random number.

Example: a routine to establish a Gaussian connectivity matrix in a ring of neurons II

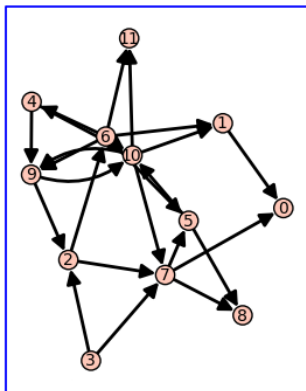
```

for(npre=1;j<=nNeurons;npre++){ //1
NCon[npre]=0;
for(npost=1;npost<=nNeurons;npost++){ //2
if(npost!=npre){ //3
nDist=fabs(npost-npre);
if(nDist>nNeurons/2){nDist=nNeurons-nDist;}
xDist=xDist*h;
if(ExcInh[npre]==0){sigma2=sigmaExc2}else{sigma2=sigmaExc2}
eDist=exp(-xDist*xDist/sigma2/2);
xi=rnd01();
if(xi<eDist)
{NCon[npre]++; P[npre][NCon[npre]] = npost; NCon[npre]++;}
}}//321

```

Example: a routine to establish a Gaussian connectivity matrix in a ring of neurons III

The **adjacency matrix** can be derived from P .



$$\begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 \end{pmatrix}$$

III. Structure of the network

Structure of the network (space and topology)

Depends on **physiological data** that can be obtained through several methods: electrophysiological recordings (MUA¹), EEG², MEG³, (f)MRI⁴, DTI⁵, optogenetics,...

¹MultiUnit Arrays

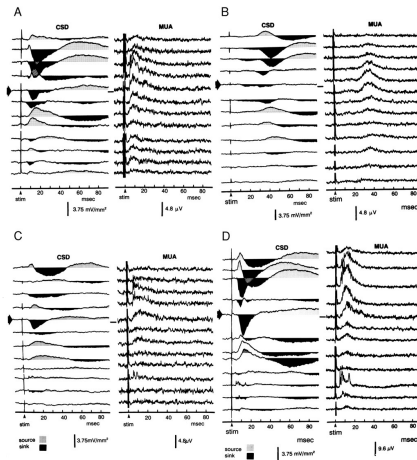
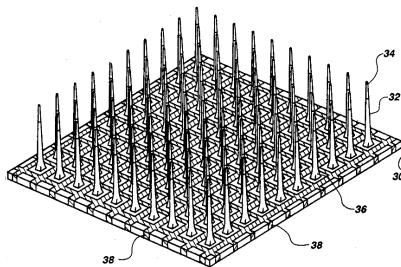
²ElectroEncephaloGram

³MagnetoEncephaloGram

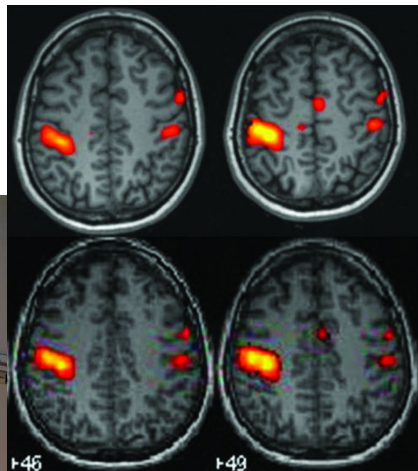
⁴(functional)Magnetic Resonance Imaging

⁵Diffusion Tensor Imaging

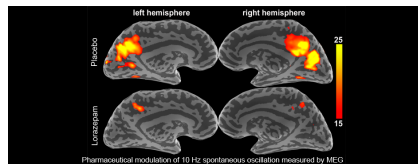
Data acquisition methods: MUA



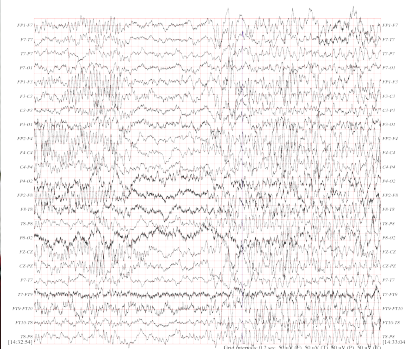
Data acquisition methods: fMRI



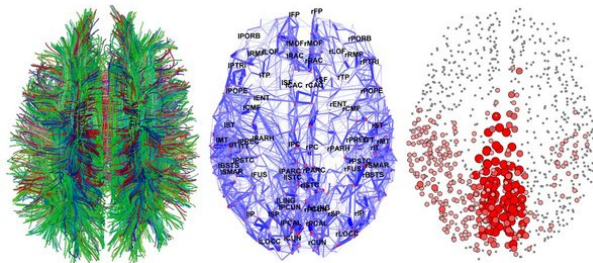
Data acquisition methods: MEG



Data acquisition methods: EEG



Data acquisition methods: DTI



Imaging techniques to obtain large scale structures. In this case, DTI (diffusion tensor imaging), a method for characterizing microstructural changes or differences with neuropathology and treatment obtained from measurements of the signal attenuation from water diffusion.

More about **human connectome**:

Human Connectome Project

Article about **Connectoma** at *Scholarpedia*

Talk/performance by Sebastian Seung at TED

Structure of the network (space and topology)

Depends on **physiological data** that can be obtained through several methods: electrophysiological recordings (MUA⁶), EEG⁷, MEG⁸, (f)MRI⁹, DTI¹⁰, optogenetics,...

- Invasive versus non invasive.
- Anatomical data vs functional data.
- **Statistical methods** and **filtering techniques** are required to analyze the data and obtain the structure (topology) of the network.
- Once the topology is obtained, we can use indicators of the network (typically from **graph theory**).

⁶MultiUnit Arrays

⁷ElectroEncephaloGram

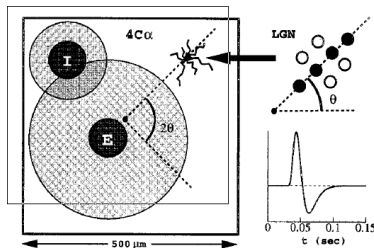
⁸MagnetoEncephaloGram

⁹(functional)Magnetic Resonance Imaging

¹⁰Diffusion Tensor Imaging

Structure of the network: general topologies I

- All to all.
- Random $P\%$ ($P = 10, 20, \dots$).
- Gaussian with ranges (eventually distinguishing excitation/inhibition), inspired by experimental data.



Different ranges in layer 4Cα of visual cortex, [MacLaughlin et al., PNAS 2000].

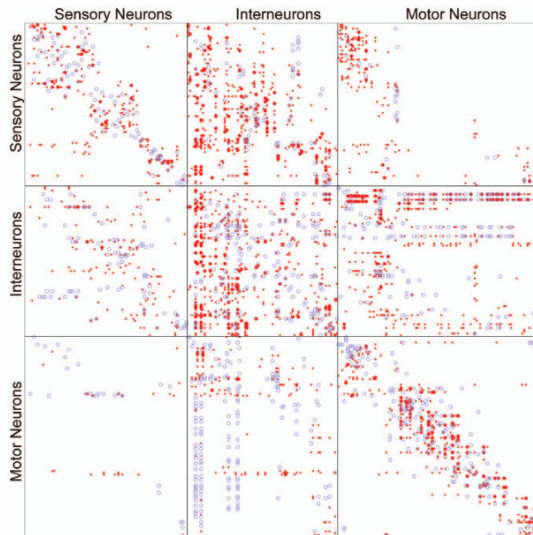
Structure of the network: general topologies II

- Fulfilling special statistics (the universe of **graph theory** and **complexity** explodes here): **Erdős-Renyi** networks, **power-law** degree distributions, ... See also the SAGE file `MathModBio_Networks.sws`, or the paper `BeggsPlenz-JNeuroscience2003.pdf` in the Scientific Articles section, or John. M. Beggs' webpage presentation (<http://www.indiana.edu/~iubphys/faculty/jmbeggs.shtml>), or ... to know more about.

Example 1: C Elegans (some numbers)

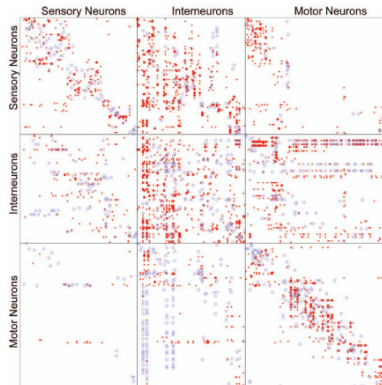
- 302 neurons
- 279 neurons in largest connected network
- 6393 chemical synapses, for 2194 directed connections (average 7.9/neuron, connection probability 0.03)
- 890 gap junctions, for 514 connected pairs (average 3.7/neuron, connection probability 0.01)
- 1410 neuromuscular junctions

C Elegans -connectivity matrix

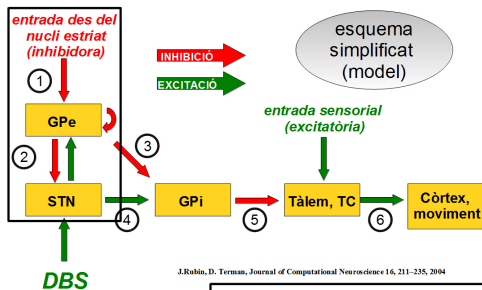


Feed-forward, recurrent, feed-back connections

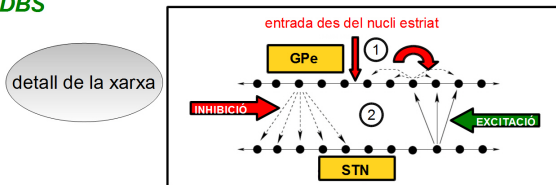
- Feed-forward connections: $S \rightarrow I, S \rightarrow M, I \rightarrow M$
- Recurrent connections: $S \rightarrow S, I \rightarrow I, M \rightarrow M$
- Feed-back connections: $I \rightarrow S, M \rightarrow S, M \rightarrow I$



Example 2: Medium scale (Parkinson's disease)

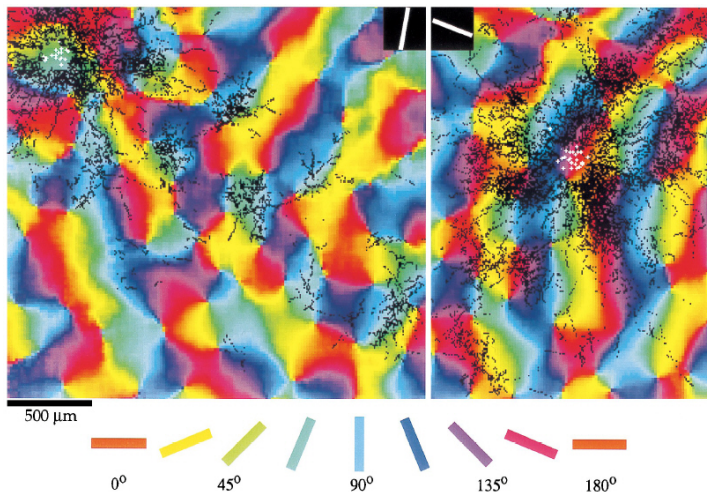


J. Rubin, D. Terman, *Journal of Computational Neuroscience* 16, 211–235, 2004



Computational model for the Parkinson's disease obtained from electrophysiological data, [Rubin & Terman, J. Comp. Neurosc. 16, 211–235, 2004].

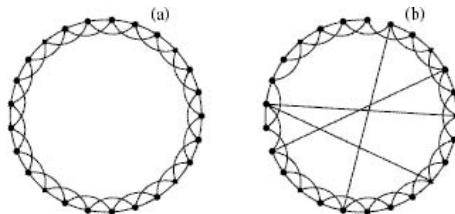
Example 3: primary visual cortex (medium-scale)



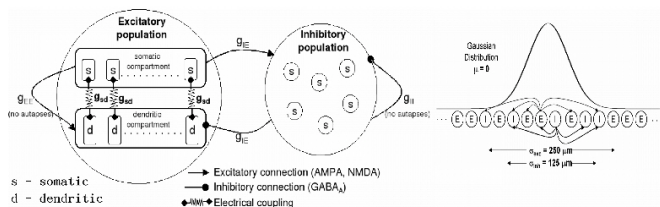
Local cortical circuits -some numbers

- Size $\sim$ cubic mm
- Total number of cells $\sim 100,000$
- Types of cells:
 - pyramidal cells -excitatory (80%)
 - interneurons -inhibitory (20%)
- Total number of synapses $\sim 1,000,000$ (10,000 per neuron)
- Cells connect potentially to all other cell types ($E \rightarrow E$, $E \rightarrow I$, $I \rightarrow E$, $I \rightarrow I$)
- Connection probability $\sim 10\%$

Local structure: dimensionality reduction



Rings of neurons.



Neuronal arrays, [Benita et al., Frontiers in Comp. Neuroscience, 2013].

IV. Input current

Types of input current

- Gaussian input, mostly for theory as in the Fokker-Planck approach.
- Localized stimuli as in the working memory example ([ww.crm.cat](http://www.crm.cat)).
- Poissonian current (more realistic).

Example: Poisson input train

The **input current** follows a first order dynamics

$$dI = -I/\tau_{noise} + S \sum \delta(t_{stimulus} - t),$$

- $\sum \delta(t_{stimulus} - t)$ follows a Poisson statistics at rate ν_0 KHz.
- S : single input strength.
- τ_{noise} : characteristic noise decaying time.

Example: Poisson train, programming routine I

- **S**: single input strength.
- **h**: integration step (in ms).
- **nu0**: Poisson rate (e.g., = 2.0KHz).
- **tauNoise**: characteristic noise decaying time.
- **I**: input current of a single neuron.
- **Irand**: a random number.

```
expNoise=exp(-h/tauNoise); //Decaying noise constant (aux)
I=I*expNoise; //Input current dynamics
Irand=rnd01(); //Random number in [0,1]
if(Irand<nu0*h){I+=S/tauNoise;}
```

Neuronal networks: outline (CHALLENGES) I

- How will the new dynamics be? This will depend on the type of neuron, the strength of the synapses, the timing among the pre- and post-synaptic neurons,... So, **synchrony** becomes an important question to explore.
- Does the structure of the network influence the dynamics? How? This involves both **statistical methods** to extract information about **connectivity**, but also **graph theory** to characterize each type of network. This approach mainly leads to highly computational tasks.

Neuronal networks: outline (CHALLENGES) II

- These complex networks, can be studied in a simple way? Is there a way to capture the essence of the network dynamics to be able to give rigorous results or, at least, make sure about the **mechanisms leading the overall dynamics**? This question leads to reduced models, mainly **rate models**, which are, in general, **systems of differential equations** that can be derived in several ways (Wilson-Cowan approach, Fokker-Planck approach, ...).

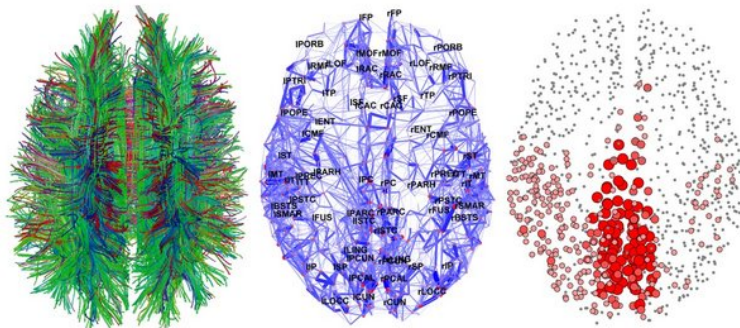
Challenges: graph theory, complex systems

Challenges: structure estimations, graph theory, complex systems

- Are there differences between patients and healthy subjects?
- Does the structure of the network influence the dynamics? How?

This involves both **statistical methods** to extract information about **connectivity**, but also **graph theory** to characterize each type of network. This approach mainly leads to highly computational tasks and largely overlaps with the theory of **complex systems**. See Hagmann *et al.*, Rubinov-Sporns and Iglesia *et al.* from the Scientific Articles folder.

Structural and functional connectivity: motivation



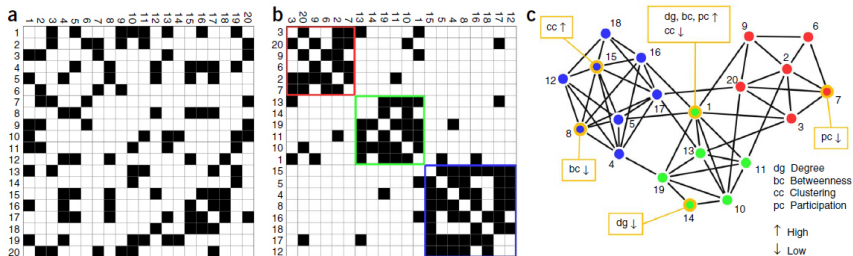
Structural (left and center) and functional connectivity map of human brain.

- The brain consumes approx. 20% of the body's energy consumption.
- A specific cognitive task may use 5% of the brain's total metabolic expenditure.
- What is the brain doing meanwhile? **Intrinsic activity!**
- It is currently understood that higher cognitive functions are not

Structural and functional connectivity: motivation

- Both methods tracking physical connections (**structural connectivity**) and methods recording time-correlated activations (**functional connectivity**) are used to study brain's connectivity.
- Consolidating the knowledge gleaned from various studies is a serious challenge that the neuro-scientific community faces today.
- Dysfunctions are no longer attributed to focal lesion or the alteration of a single brain area, but to complex disorders of connectivity between components of large-scale networks.

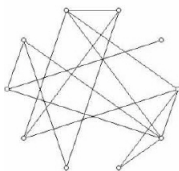
Link between brain connectivity and graph theory



O. Sporns, Nature Neuroscience Reviews, May 2014

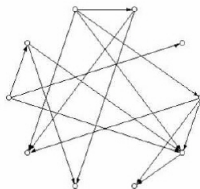
Graphs

Non-directed



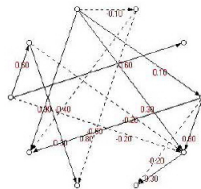
(a)

Directed



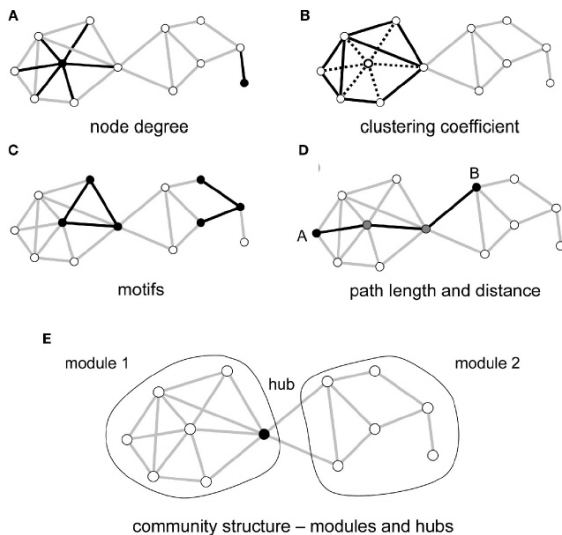
(b)

Weighted

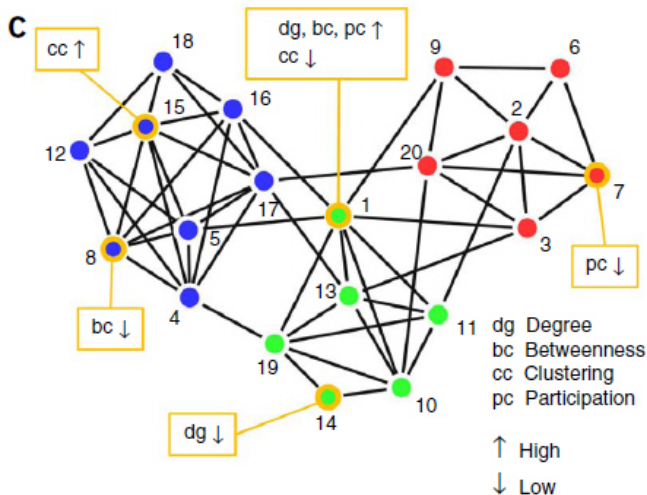


(c)

Quantifying network properties



Quantifying network properties



Erdős-Rényi network

- Network of N nodes, with connection probability p .
- In- and out- degree distributions:

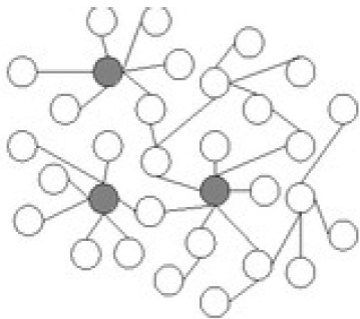
$$P(k) = C_{N-1}^k p^k (1-p)^{N-1-k}$$

- Clustering coefficient: $C = p$
- Shortest path length: $P(L=1) = p$;
 $P(L=2) = (1-p)(1-(1-p^2)^{N-2})$; ...
- Average shortest path length:

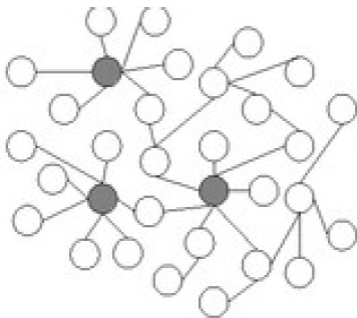
$$L \approx 2 - p, p \gg 1/\sqrt{N};$$

$$L \sim \frac{\ln N}{\ln pN}, p \leq 1/\sqrt{N}$$

Scale-free, small-world



Scale-free network

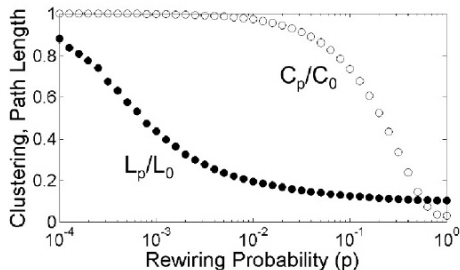
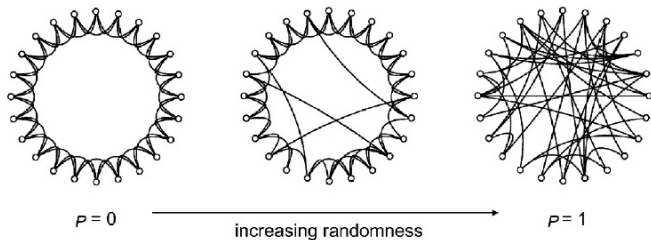


Small-world network^a

- Short mean path length
- High clustering coefficient

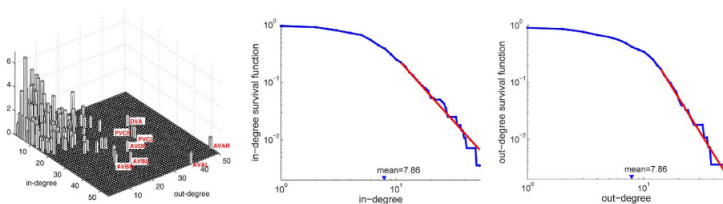
^aMost of the nodes are not neighbors of

Properties of small-world networks



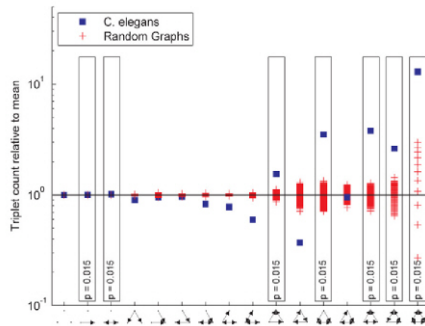
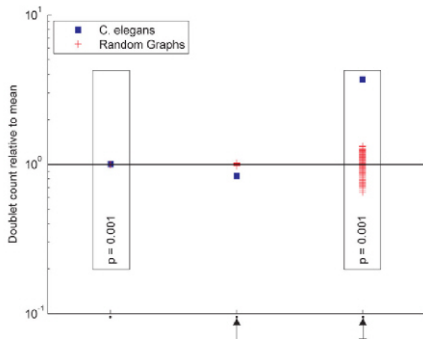
Analysis of C-Elegans network

- Degree distribution (in, out degree) with a power-law tail

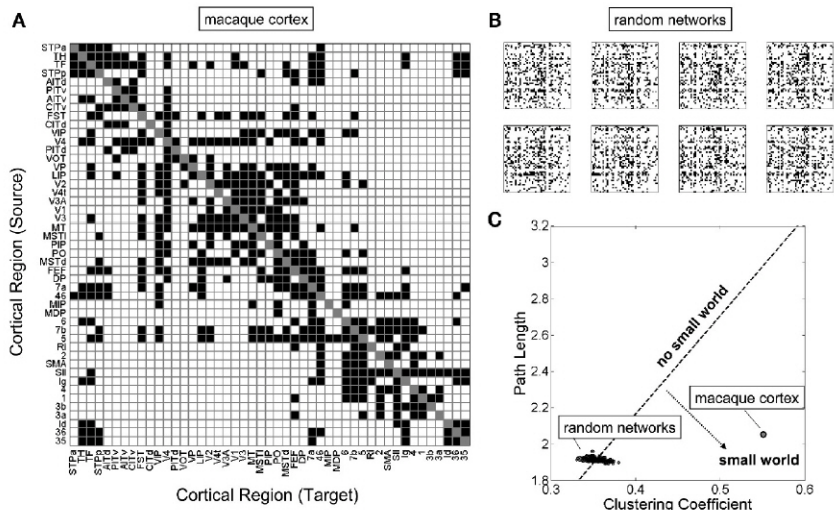


- Mean shortest path length 3.5 (for a random network: 2.9)
- Clustering coefficient 0.22 (for a random network: 0.08)

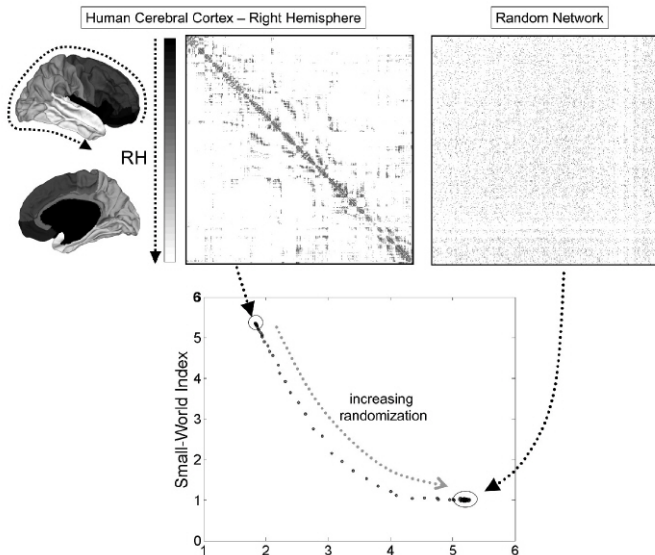
Motifs in C-Elegans network



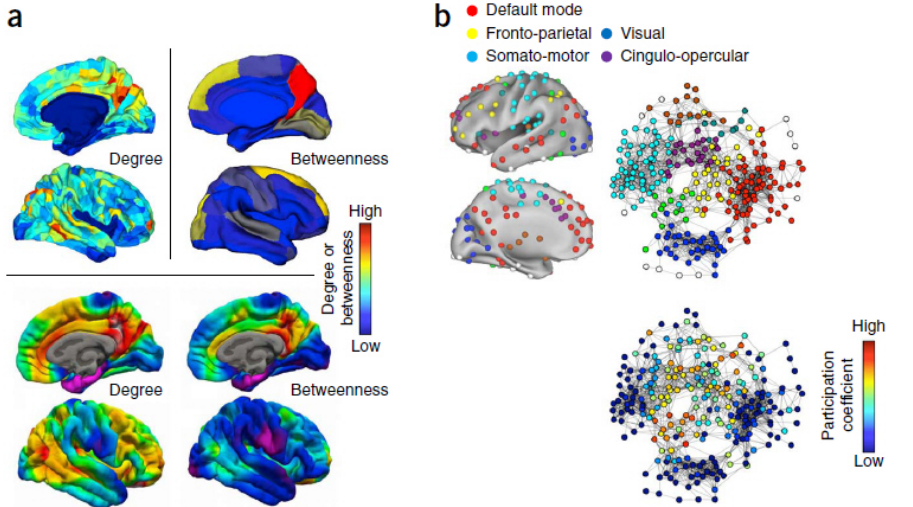
Macaque brain: large-scale connectivity



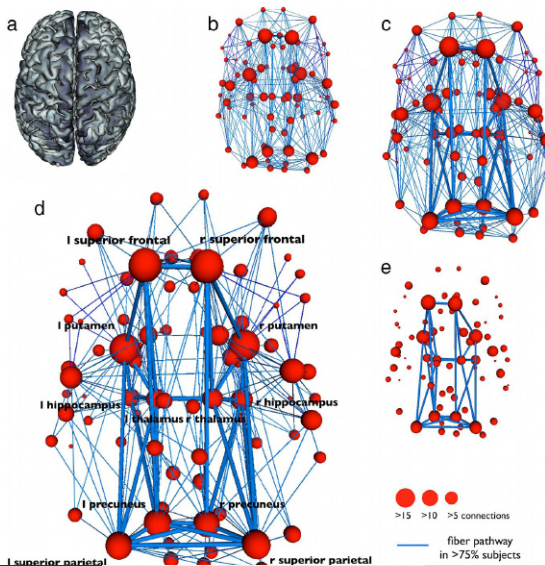
Human brain: large-scale connectivity



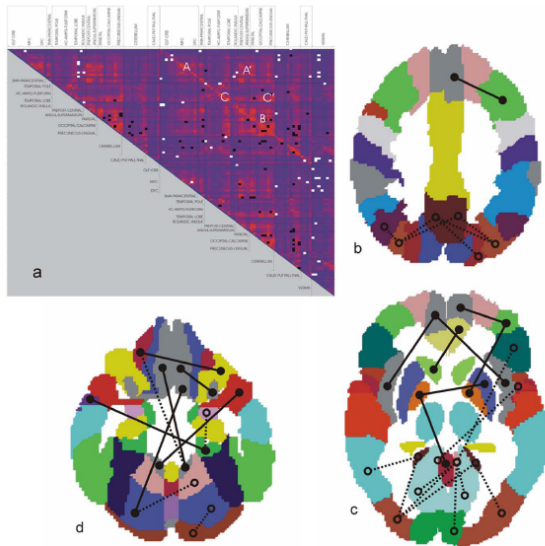
Resting state: identification of modules and *hubs*



“Rich-club” structure of large-scale connectivity



Differences in connectivity in Alzheimer Disease



Challenges: synchrony

Challenges: synchrony

How will the new dynamics be? This will depend on the type of neuron, the strength of the synapses, the timing among the pre- and post-synaptic neurons,... So, **synchrony** becomes an important question to explore.

Challenges: rate models

Big challenges: rate models

These complex networks, can be studied in a simple way? Is there a way to capture the essence of the network dynamics to be able to give rigorous results or, at least, make sure about the **mechanisms leading the overall dynamics**? This question leads to reduced models, mainly **rate models**, which are, in general, **systems of differential equations** that can be derived in several ways (Wilson-Cowan approach, Fokker-Planck approach, . . .).