Mathematical modeling in biology.

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03-07 september 2018

Introduction and position of the problem

Aim and setting of the course :

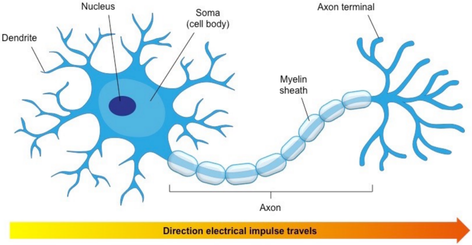
- Introduce some typical deterministic mathematical tools in analysis widely used to study phenomena from biology.
- This course is based on neural models.
- The methods presented in this course are not at all exhaustive in neuroscience, but are useful in many settings.

Plan of the course

Plan of the course :

- Ordinary differential equations : some classical models for single neuron
- Partial Differential Equations as the time elapsed PDE model : models used for homogenous neural networks

Neural cell.



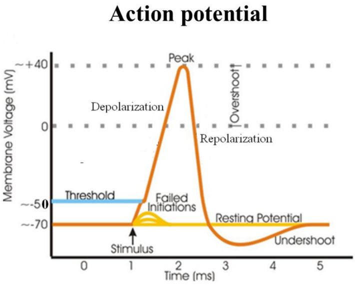
Neuron: specialized cell that

- is electrically excitable
- receive, analyse and transmit signal to other neurons

Neural cell.

Description of a unit neural activity :

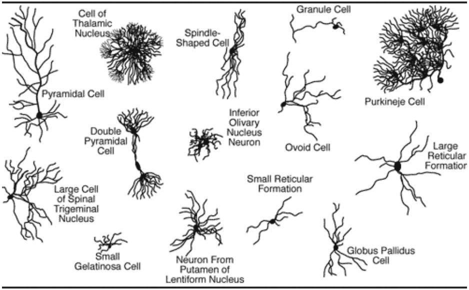
To communicate neurons emit action potential that is also calling ”spike”.



This phenomenon involves several complex processes including: opening and closing of various ion channels.

Neural cell

Vast spectrum of different types of neurons that can be classified according to their shape, their intrinsic dynamics ...



Model of neural cell

Two aspects of modelling :

- Description via intrinsic mechanisms involved on a unit neuron
- Description via the frequency of ”spikes” of the neuron, omitting the explicit modelling of the intrinsic mechanisms involved on the neuron.

Principal mathematical tools :

- deterministic dynamical systems
- stochastic models.

Description via intrinsic mechanisms on a unit neuron

Intrinsic mechanisms on a unit neuron :

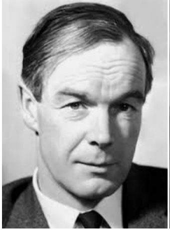
- In the simplest models, the cell is assimilated to an electrical circuit
- In more precise models, for example, propagation of signal along the axon or the impact of dendrites may be included

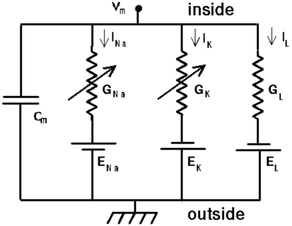
Main electrical circuit model type :

- Hodgkin-Huxley model
- FitzHugh Nagumo model
- Integrate and fire model
- Morris-Lecar model
- ...

Hodgkin-Huxley model

Hodgkin-Huxley model (1952) :





$$C\frac{dV(t)}{dt} = \underbrace{m^3 h g_{Na}(E_{Na} - V(t))}_{\text{Sodium current}} + \underbrace{n^4 g_K(E_K - V(t))}_{\text{Potassium current}} + \underbrace{g_L(E_L - V(t))}_{\text{leak current}} + \underbrace{I(t)}_{\text{Input}}$$

$$\tau_n(V)\frac{dn}{dt} = (n_\infty(V) - n), \quad n\text{: probability of potassium channel to be open}$$

$$\tau_m(V)\frac{dm}{dt} = (m_\infty(V) - m) \quad m\text{: probability of Sodium channel to be actif}$$

$$\tau_h(V)\frac{dh}{dt} = (h_\infty(V) - h) \quad h\text{: probability of Sodium channel to be open.}$$

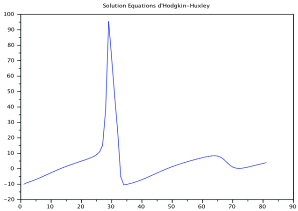
Hodgkin-Huxley model

Hodgkin-Huxley model (1952) :

- 4 coupled equations (one on membrane potential and three on ion channels)
- Allow to reproduce several typical patterns
- Difficult to study mathematically and numerically expensive

Simplified models allowing to well capture several patterns of neurons ?

- Replace some variables by their stationary states (fast variables)
- Do not explicitly model ion channels



FitzHugh-Nagumo model

FitzHugh Nagumo model : Involves two variables

- The membrane voltage v
- The recovery variable w

Equations :

$$v'(t) = v - \frac{v^3}{3} - w + I(t), \quad I(t): \text{ external current input}$$

$$w'(t) = (v + a - bw).$$

FitzHugh-Nagumo model

Typical patterns that may capture FitzHugh Nagumo model : Depending of the choice of the parameters (even in the simplest case $I = 0$, $b = 0$)

- Fast convergence to a stationary state
- Excitable case : the neuron emit a spike before coming back to its resting state
- Oscillations and convergence to a periodic solution (limit cycle)

FitzHugh-Nagumo model

How study the FitzHugh Nagumo model ?

- Does the solution exists globally in time ? (Cauchy-Lipschitz theorem)
- How obtain qualitative properties on the solution ?

1. We search the simplest possible solutions : the stationary states (independent of time)
2. We study the behavior of the solution for initial data closed to the stationary states
3. We give the general aspect of the solution by splitting the space in judicious different aera.

Cauchy-Lipschitz Theorem

Theorem (Cauchy-Lipschitz Theorem)

Let the system

$$x'(t) = f(t, x(t)), \quad x(0) = x_0, \quad x(t) \in \mathbb{R}^d, \quad t \in \mathbb{R}.$$

Assume that for all $T > 0$ and all $R > 0$, there exists $M > 0$ such that

$$|f(t,x) - f(t,y)| \leq M|x - y|, \quad \forall t \in [-T, T], \quad \forall |x| \leq R, \quad |y| \leq R.$$

Then,

- there exists $T_0 > 0$ which depends on f and the initial data such that there exists a unique solution of the differential equation.
- Moreover there exists a maximal time $T > 0$ such that there exists a unique solution on $[0, T)$ and

$$\text{either } T = +\infty, \text{ either } \lim_{t \to T} |x(t)| = +\infty.$$

Remarks

- The main idea of the proof is to use a fixed point argument
- Even if $f \in \mathcal{C}^\infty$, the solution is not necessary global in time

$$u'(t) = u^2(t), \quad u(0) = u_0 > 0, \text{ then } u(t) = \frac{u_0}{1 - tu_0}.$$

Study of stationary states (autonomous systems)

Definition

Let the system, for $f \in \mathcal{C}^2$, $f : \mathbb{R}^d \to \mathbb{R}^d$

$$x'(t) = f(x(t)) \quad x(t) \in \mathbb{R}^d, \quad t \in \mathbb{R}.$$

The set of the stationary states of this system is given by

$$S = \{x^* \in \mathbb{R}^d \quad \text{such that} \quad f(x^*) = 0\}.$$

Study of stationary states (autonomous systems)

Definition

Let x^* a stationary state.

- The stationary state x^* is stable, if, for all $\epsilon > 0$, there exists $\eta > 0$ such that

$$|x(0) - x^*| < \eta \Rightarrow |x(t) - x^*| \leq \varepsilon, \quad \forall t \geq 0.$$

- If moreover, there exists $\varepsilon > 0$ such that

$$|x(0) - x^*| < \varepsilon \Rightarrow \lim_{t \to +\infty} x(t) = x^*,$$

  the stationary state x^* is said asymptotically stable.
- A stationary state x^* which is not stable is said unstable.

Criteria for stability

Theorem

Let the system, for $f \in \mathcal{C}^2(\mathbb{R}^d)$

$$x'(t) = f(x(t)) \quad x(t) \in \mathbb{R}^d, \quad t \in \mathbb{R}$$

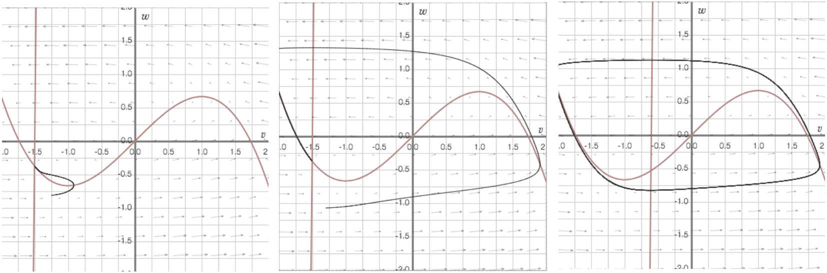
and x^* a stationary state. Let us note J_{x^*} the Jacobian matrix of f at the point x^*. Then,

- If all the eigenvalues of J_{x^*} has strictly negative real part, then x^* is asymptotically stable.
- If there exists an eigenvalue of J_{x^*} which has strictly positive real part, then x^* is unstable.

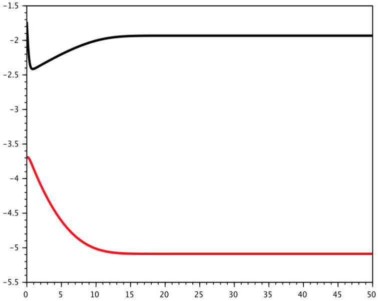
FitzHugh-Nagumo model

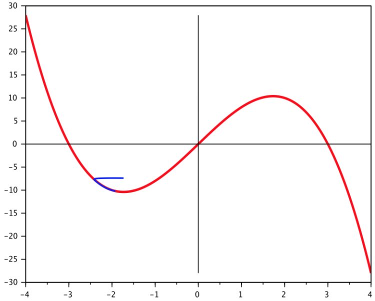
Case $I = cste$, $b = 0$

- Unique stationary state
- Stable if $f' < 0$ and unstable if $f' > 0$.

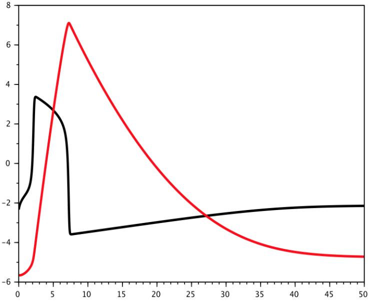


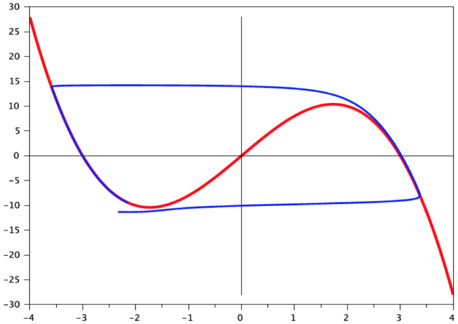
FitzHugh-Nagumo model



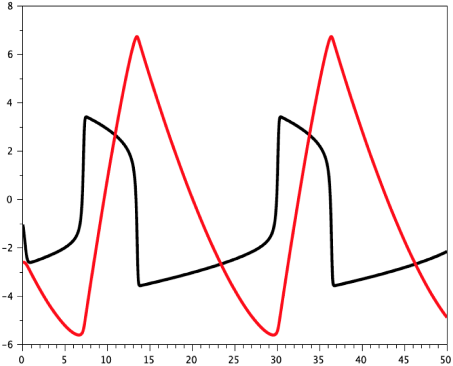


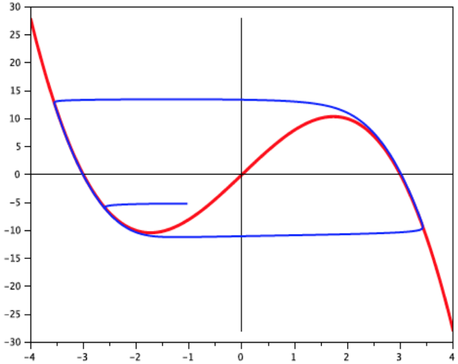
FitzHugh-Nagumo model





FitzHugh-Nagumo model

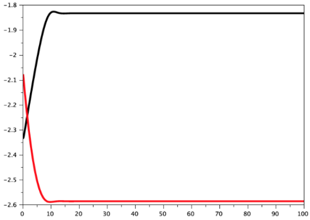


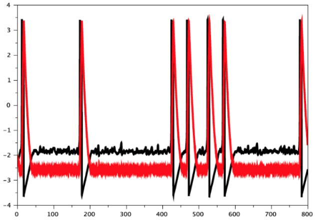


FitzHugh-Nagumo model, role of noise

$$v'(t) = v - \frac{v^3}{3} - w + I(t), \quad I(t): \text{ external current input}$$

$$w'(t) = (v + a - bw) + \frac{dB(t)}{dt}.$$





Leaky Integrate and Fire Model (from Lapicque,1907).

Leaky Integrate and Fire Model :

$$\tau V'(t) = -V(t) + RI(t), \quad V(t) < V_F, \qquad I\text{: external input}$$

$$V(t_-) = V_F \Rightarrow V(t_+) = V_R, \quad V_R < V_F.$$

- V_F is the value of the action potential
- V_R is the reset potential
- We may add some noise : $\tau d_t V = (-V(t) + RI(t))dt + \sigma dW(t), \; V(t) < V_F.$

Very simple structure :

- Linear differential equation on the potential V (if $V < V_F$)
- Spiking modelled via a threshold V_F and jump of V to a given value V_R.

Leaky Integrate and Fire Model (from Lapicque,1907).

FIGURE 4 | Fitting spiking models to electrophysiological recordings. (A) The response of a cortical pyramidal cell to a fluctuating current (from the INCF competition) is fitted to various models: MAT (Kobayashi et al., 2009), adaptive integrate-and-fire, and Izhikevich (2003). Performance on the training data is indicated on the right as the gamma factor (close to the proportion of predicted spikes), relative to the intrinsic gamma factor of the neuron (i.e., proportion of common spikes between two trials). Note that the voltage units for the models are irrelevant (only spike trains are fitted). **(B)** The response of an anteroventral cochlear nucleus neuron (brain slice made from a P12 mouse, see Methods in Magnusson et al., 2008) to the same fluctuating current is fitted to an adaptive exponential integrate-and-fire [Brette and Gerstner, 2005; note that the responses do not correspond to the same portion of the current as in **(A)**]. The cell was electrophysiologically characterized as a stellate cell (Fujino and Oertel, 2001). The performance was $\Gamma = 0.39$ in this case (trial-to-trial variability was not available for this recording).

From C. Rossant et al, Frontiers in Neuroscience (2011)

Wilson-Cowan model.

Wilson-Cowan model : models probability of a neuron to spike at time t, typically

$$u'(t) = -u(t) + S(u(t)), \text{ where } S \text{ is a sigmoidal function.}$$

Several useful extention/application

- Including inhibitory/excitatory neurons
- Extension to spatial models leading to neural fields equations

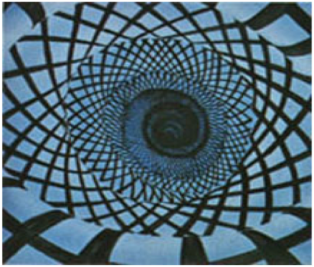
$$u'(t,x) = -u(t,x) + S(\int w(x,y)u(t,y)dy) + I(t,x).$$

- Application in epilepsy in visual cortex

Wilson-Cowan model.

Feature

- multiple steady states and bifurcation theory (S. Amari, Bressloff-Golubitsky, Chossat-Faugeras-Faye)
- Interpretation of visual illusions and visual hallucinations (Klüver, Oster, Siegel...)



Stochastic processes

Ponctual processes/counting processes :

- homogeneous Poisson processes
- inhomogeneous Poisson processes
- Renewal processes
- Hawkes processes
- ...

Homogeneous Poisson processes

Homogeneous Poisson processes : Given a parameter $\lambda > 0$ and a time interval I of size T,

$$P(\text{Neuron discharge } n \text{ times on } I) = \frac{(\lambda T)^n}{n!} e^{-\lambda T}.$$

Main properties

- Time independent
- No dependance with respect to the past
- Probability of a neuron that has not yet discharge at time t : $e^{-\lambda t}$

Inhomogeneous Poisson processes

Inhomogeneous Poisson processes : Given a function $\lambda > 0$ and a time interval $I = [a, b]$,

$$P(\text{Neuron discharge } n \text{ times on } I) = \frac{(\int_a^b \lambda(s)ds)^n}{n!} e^{-(\int_a^b \lambda(s)ds)}.$$

Main properties

- Time dependent
- No dependance with respect to the past
- Probability of a neuron that has not yet discharge at time t : $e^{-\int_0^t \lambda(s)ds}$.

Renewal processes/Hawkes processes

Renewal processes : include models with memory of the preceding spike and therefore useful to integrate the refractory period.

Main properties

- The delay between two consecutive spikes are independent
- The delay between two consecutive spikes are identically distributed

Hawkes processes : More complex processes that allows to model synaptic integration (see Caceres, Chevallier, Doumic, Reynaud-Bouret)