Mathematical modeling in biology.

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03-07 september 2018

From the microscopic to macroscopic scale ?

Macroscopic scale via mean field assumptions leading to PDE's :

- Infinitely many neurons
- Homogeneous interconnexions
- Each neuron receive the mean activity of the network

Many PDE models obtain via this paradigm

- time-elapsed model
- Leaky-integrate and fire type models (Fokker-Planck model)
- oscillators (Kuramoto equation)
- ...

Introduction and position of the problem

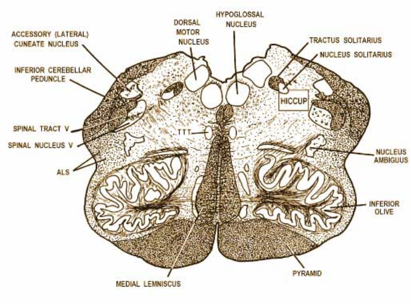
Aim : Test the different assumptions made on

- the unit neuron
- the coupling
- memorization effect

to understand the impact on the patterns generated by the network.

Biological motivation and setting

Biological motivation and setting : From Pham, Pakdaman, Champagnat, Vibert



http://www.neuroanatomy.wisc.edu/virtualbrain/BrainStem/11Solitarius.html

- Networks at the Nucleus Tractus Solitarius (NTS) responsible of basic rhythms.
- NTS contains neural circuits with only excitatory connections displaying a spontaneous activity.
- No pacemaker neurons responsible for the spontaneous activity.
- Simple partial differential equation model to explore the possible mechanisms of spontaneous activity generation ?

First studies

First studies :

- Simulation of several computational models adjusted to the experiments revealed that the network could sustain regular rhythmic activity in some parameter ranges
- Phenomenon of spontaneous activity persists in networks with diverse connectivity.

Conclusion

- That the phenomenon can be observed in many models suggests that the fine details of the model may not be at the core of the mechanism, and that to get the gist of the phenomena, one may focus on a few features of neural dynamics.
- We have proposed a simple mathematical model where neurons are describe via the time elapsed since the last discharge to obtain theoretically this phenomenon of spontaneous activity observed.

Elapsed time model

Main assumptions on the model.

Dynamic on each neuron :

- The neurons are excitatory
- Even without stimulations, the neurons have an activity
- Neurons describe via the time elapsed since the last discharge
- When a neuron discharge, it's new intrinsic dynamic may depends on it's past activity

Interconnexions :
The amplitude of stimulation $X(t)$ is homogeneous with

$$X(t) = \int_0^t \alpha(s) N(t-s) ds$$

where $N(t)$ is the flux of neurons which discharge at time t. To simplify, we take here $X(t) = N(t)$.

Time elapsed model

$$\underbrace{\frac{\partial n(t,s)}{\partial t} + \frac{\partial n(t,s)}{\partial s}}_{\text{aging neurons}} + \underbrace{p(s,N(t))n(t,s)}_{\text{discharge of the neurons}} = 0,$$

$$N(t) := \int_0^{+\infty} p(s,N(t))\; n(s,t)ds, \quad n(t,s=0) = N(t), \quad n(t=0,s) \text{ given.}$$

- $n(t,s)$: density of neurons at time t such that the time elapsed since the last discharge is s.
- $N(t)$: flux of neurons which discharge at time t
- $p(s,u) \geq 0$: firing rate of the neurons of age s which discharge when they are submitted to an amplitude of stimulation $u \geq 0$.

We can remark that we have mass conservation, that is

$$\int_0^{+\infty} n(t,s)ds = \int_0^{+\infty} n(s,0)ds.$$

Time elapsed model : case where $p = 0$

Case where $p \equiv 0$: we simply have the transport equation

$$\frac{\partial n(t,s)}{\partial t} + \frac{\partial n(t,s)}{\partial s} = 0, \quad n(t=0,s) \text{ given}$$

$$n(t, s=0) = 0.$$

- Construction of explicit solution via a method called the method of characteristics.

Time elapsed model : case where $p \neq 0$

Case where $p = p(s)$: we add a ”death” term

$$\frac{\partial n(t,s)}{\partial t} + \frac{\partial n(t,s)}{\partial s} + p(s)n(t,s) = 0, \quad n(t=0,s) \text{ given}$$

$$n(t, s=0) = \int_0^{+\infty} p(s)n(t,s)ds = N(t).$$

- Also construction of explicit solution via a method called the method of characteristics.

Assumptions on p. in our setting

Assumptions on the function $p(s,u)$:

- The probability for a neuron to survive up to the age t :

$$P(s \geq t) = e^{-\int_0^t p(s,u)ds}.$$

- The account of refractory period

$$\partial_s p \geq 0 \text{ and } p \equiv 0 \text{ for } s \text{ small enough.}$$

- Excitatory neurons :

$$\partial_u p \geq 0.$$

- Interconnexions between the neurons :

$$\text{modeled via } \partial_u p, \quad \text{if no interconnexions } \partial_u p = 0.$$

Assumptions on p. in our setting

Typical example:

$$p(s,u) = \mathbb{I}_{s \geq \sigma(u)}, \qquad \text{where } \sigma' \leq 0.$$

- Here, the coupling between the neurons is only taking into account via the length of the refractory period, length given by $\sigma(u)$.
- The function p is singular, however, this example will allow us to well understand the problem and to construct explicit periodic solutions later.

Main questions

Main questions : What is the impact of the strength of interconnections on the dynamic of the neural network ?

- 1. When the interconnections are low or inexistant, intuitively, we expect that the solution converges to a stationary state.
- 2. For hight interconnections, we expect the apparition of more complex patterns as periodic solutions.

Methods to tackle the problem

Case 1: dynamic ”almost linear” :

- Spectral methods (Mischler, Weng)
- With entropy generalized methods, inspired by Laurençot and Perthame where we search decreasing functional by multiply the Equation by judicious test functions.
- With the Doeblin Theory (Canizo, Holdas)

Case 2 : Situation more complex :

- Many different patterns and periodic solutions numerically observed.
- By well choosing p, we can construct explicitly infinitely many periodic solutions.

Plan of study without interconnexions.

Plan of study without interconnexions

- Existence and uniqueness of stationary state.
- Proof of convergence to a stationary state

Doeblin type Theorem (from Canizo Holdas).

We say that a function $f : \mathbb{R}^+ \to \mathbb{R}$ is in $L^1(\mathbb{R}^+)$ if

$$\int_{s=0}^{+\infty} |f(s)| ds < +\infty.$$

Theorem (from Canizo Holdas)

Assume that there exists $s_0 \geq 0$ such that for all $s \geq s_0$,

$$0 < p_{min} \leq p(s) \leq p_{max}.$$

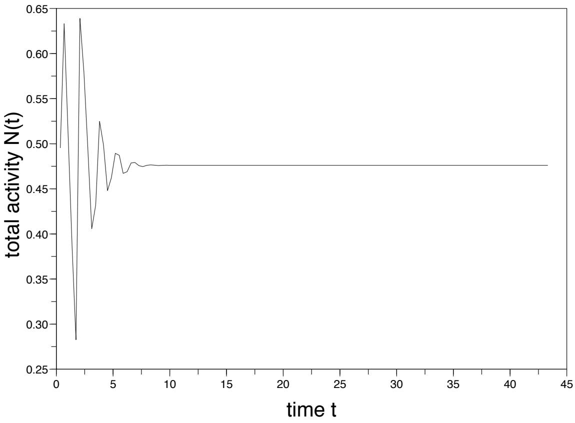
Assume that there exists $t_0 > 0$, $1 > \alpha > 0$ and a nonnegative function $\nu \in L^1(\mathbb{R}^+)$ of total mass 1 such that for all nonnegative initial data $n(t = 0, s) \in L^1(\mathbb{R}^+)$ of total mass 1

$$n(t_0, s) \geq \alpha\nu.$$

Then, there exists $\mu > 0$ such that for all initial data $n(t = 0, s) \in L^1(\mathbb{R}^+)$ of total mass 1 and for all $t \geq 0$, the following estimate holds

$$\|n(t, s) - A(s)\|_{L^1} \leq Ce^{-\mu t}\|n(0, s) - A(s)\|_{L^1}.$$

Numerical simulation



Time elapsed model : generalization with a kernel

$$\underbrace{\frac{\partial n(s,t)}{\partial t} + \frac{\partial n(s,t)}{\partial s}}_{\text{aging neurons}} + \underbrace{p(s, N(t))n(s,t)}_{\text{death of the neurons}} = \underbrace{\int_0^{+\infty} K(s,u)p(u, N(t))n(u,t)du}_{\text{Redistribution in age of the death neurons}},$$

$$N(t) := \int_0^{+\infty} p(s, N(t))\, n(s,t)ds, \quad n(s=0,t) = 0.$$

- $n(s,t)$: density of neurons at time t such that the time elapsed since the last discharge is s.
- $N(t)$: flux of neurons which discharge at time t
- $p(s,u)$: firing rate of the neurons of age s which discharge when they are submitted to an amplitude of stimulation $u \geq 0$.
- $K(s,u)$: Positive measure allowing to give the repartition of neurons which discharge at the state u and which reset at the state s.

Assumptions on p and K.

The kernel fragmentation $K(s,u)$:

- For each $u \geq 0$, $K(s,u)$ models the measure of probability for a neuron which has discharge at the age u to reset in the new state s.
- $K(s,u) = 0$ for $s > u$: all the neurons which discharge at an age u, reset at an age s smaller than u
- $\int_0^u K(s,u)ds = 1$, and so $\int_0^{+\infty} n(s,t)ds = 1, \quad \forall t \geq 0$.

Assumptions on p and K

The kernel fragmentation $K(s, u)$:

We also introduce the two following quantities :

- $0 \leq f(s, u) := \int_0^s K(s, u)ds \leq 1$ which is the probability for a neuron which discharge at the state u reset to an age smaller than s.
- $-\partial_u f := \Phi(s, u) \geq 0$ which implies that the bigger u is, the smaller the probability that a neuron which has discharge at the age u reset to a state smaller than s is small.

We assume that

$$\int_0^{+\infty} \Phi(s, u)ds = \theta < 1;$$

and

$$\int_0^u sK(s, u)ds \leq \theta u$$

i.e. the expected value of the new state of a neuron which has discharge at age u is smaller or equal to θu.

Case of strong interconnections.

The study of periodic solution is complex. Numerically, we observe many periodic solutions when the strength of interconnections is strong enough.

Aim of this part : Explicitly construct many different periodic solutions in a particular case where the solution of the equation can be reduced to a time delay Equation on the flux of neurons $N(t)$.

Assumptions : We assume that $p(s,u) = \mathbb{I}_{s \geq \sigma(u)}$, where σ is a decreasing function, and $K(s,u) = \delta_{s=0}$.

Case of strong interconnections.

Reduction to a delay equation on N. Assume that we have a solution of our transport Equation and that

$$\frac{d}{dt}(\sigma(N(t)) \leq 1$$

Then, by using the mass conservation law, we have for all $t \geq \sigma^+$,

$$N(t) + \int_{t-\sigma(N(t))}^{t} N(s)ds = 1.$$

Proof

With the mass conservation, for all $t \geq \sigma^+$ we have

$$\int_0^{+\infty} n(s,t)ds = \int_0^{\sigma(N(t))} n(s,t)ds + \int_{\sigma(N(t))}^{+\infty} n(s,t)ds = \int_0^{\sigma(N(t))} n(s,t)ds + N(t).$$

Now, as $\frac{d}{dt}(\sigma(N(t)) \leq 1$, for $s \leq \sigma(N(t))$, we deduce that

$$n(s,t) = N(t-s).$$

Case of strong interconnections.

Construction of periodic solutions : We take the "inverse" problem : Given a periodic function $N(t)$ of period T, we consider the following Equation

$$\begin{cases} \frac{\partial n(s,t)}{\partial t} + \frac{\partial n(s,t)}{\partial s} + p(s, N(t))\ n(s,t) = 0, & t \in \mathbb{R},\ s \geq 0, \\ n(s=0,t) = N(t). \end{cases}$$

As we look forward periodic solution n in time, we do not need initial data and the method of characteristics gives the solution

$$n(t,s) = N(t-s)e^{-\int_0^s p(u,N(u+t-s))du} \text{ if } t-s \geq 0.$$

By periodicity of n, we obtain that for all $s \leq kT$, $k \in \mathbb{N}$, we must have

$$n(t=0,s) = N(kT-s)e^{-\int_0^s p(u,N(u+kT-s))du}.$$

Hence finding periodic flux $N(t)$ of our Equation can reduced to find conditions on N such that the solution of the above Equation is also solution of the initial transport Equation; that is we must have

$$N(t) = \int_{\sigma(N(t))}^{+\infty} n(s,t)ds \text{ and } \int_0^{+\infty} n(s,t)ds = 1.$$

Case of strong interconnections.

Proposition (Criteria linking σ and N)

Let $\sigma(\cdot)$ be a decreasing function and let N be a T periodic function such that

$$\frac{d}{dt}\sigma(N(t)) \leq 1, \qquad 1 = N(t) + \int_0^{\sigma(N(t))} N(t-s)ds.$$

Assume that

$$p(s,N) = \mathbb{I}_{s>\sigma(N)}.$$

Then the solution of our Equation with N given is also solution of the non linear transport Equation.

Proof. We observe that, as $\frac{d}{dt}\sigma(N(t)) \leq 1$, then, for $s \in (0, \sigma(N(t)))$, we have $n(s,t) = N(t-s)$. We deduce, by setting $M(t) = \int_0^{+\infty} n(s,t)ds$, that

$$\frac{d}{dt}M(t) + M(t) = 1$$

and as M is periodic, we have $M = 1$, which proves the Proposition.

Case of strong interconnections.

Explicit construction of periodic solutions : We can construct infinitely many periodic solutions. The simplest example is the following

Let $\alpha > 0$, we set

$$0 < Nm(\alpha) := \frac{1}{2e^{\alpha} - 1} < Np(\alpha) := \frac{e^{\alpha}}{2e^{\alpha} - 1} < 1, \tag{1}$$

and we assume that

$$\sigma(x) = \begin{cases} 2\alpha & \text{on } [0, Nm(\alpha)], \\ \alpha - \ln(x) + \ln(Np(\alpha)) & \text{on } [Nm(\alpha), Np(\alpha)], \\ \alpha & \text{on } [Np(\alpha), \infty). \end{cases} \tag{2}$$

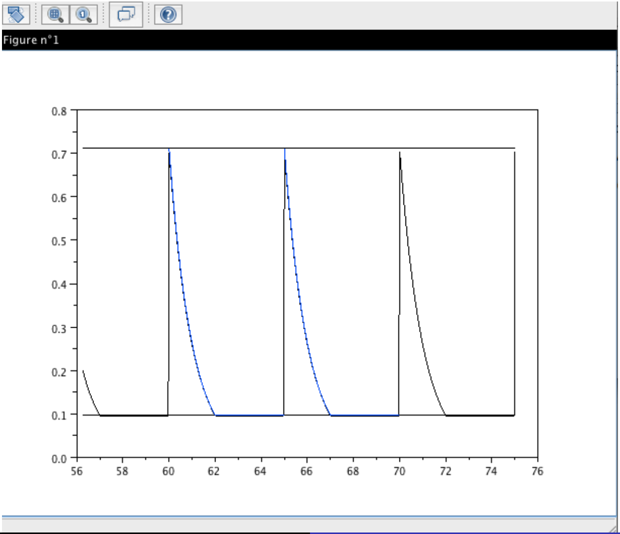
We can remark that, in this system, there exists a unique stationary state.

Then, the function N, α periodic defined by

$$N(t) = Np(\alpha)e^{-t}, \quad t \in (0, \alpha)$$

satisfies the assumptions of the Proposition.

Numerical simulations



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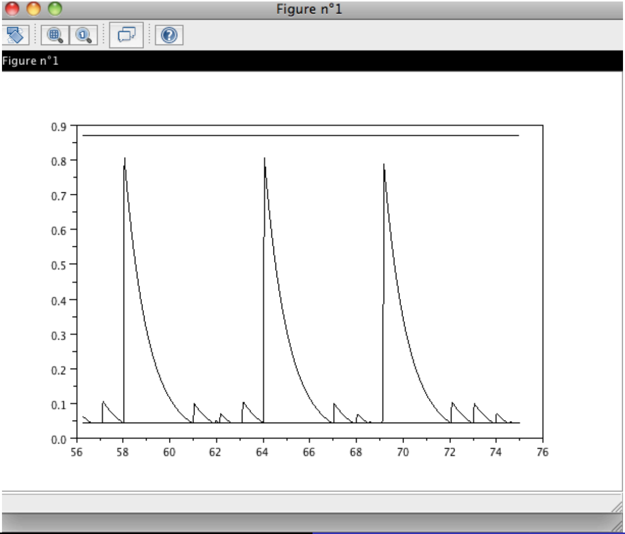

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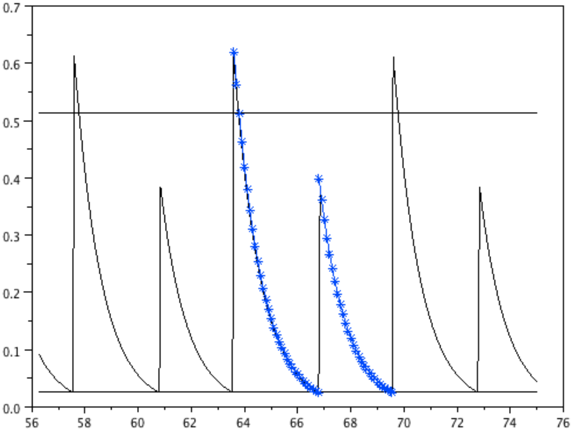
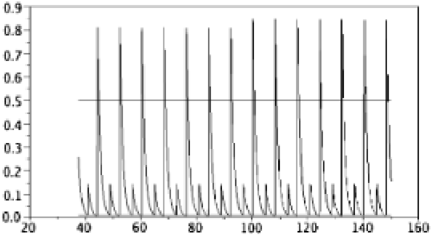
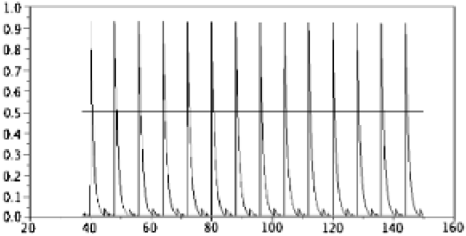
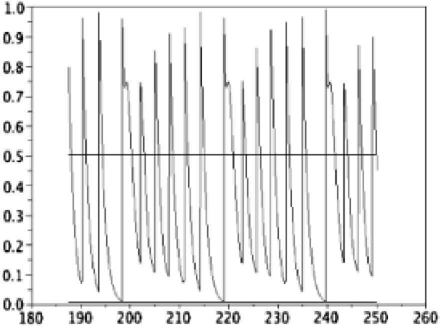


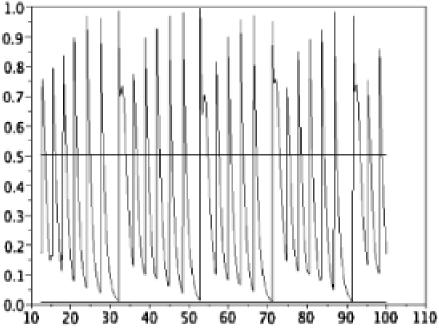
Comparaison with the case with kernel fragmentation.





Comparaison with the case with adaptative memory.





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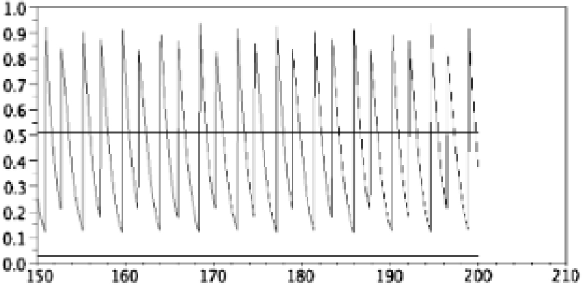
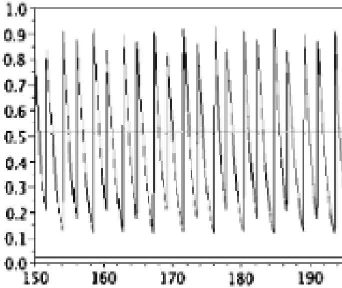




Finite size model.

For the PDE model, we now chose the following amplitude of stimulation X such that

$$X(t) = \frac{1}{a}e^{-a\cdot} \star N(t)$$

$$\frac{1}{a}X'(t) = -X(t) + N(t).$$

Let us see what happens in the case where there is a finite number K of neurons.

Description of the dynamic.

- We have a neuron which receive an input signal X.
- If the time elapsed since the last discharge s is such that

$$s \leq \sigma(X) \text{ then } p(s,X) = 0, \text{ else } p(s,X) = 1.$$

- If $\sigma(X) > s$, the probability of discharge of a neuron is equal to 0, else it is given by an exponential law of parameter 1.

Finite size model.

Description of the dynamic.

- while there is no discharge X satisfies the Equation

$$X(v) = X(0)e^{-av}.$$

- When there is a discharge, at a time t_1, we have

$$X(t_1) = X(0)e^{-at_1} + a/K$$

To find the time t_1

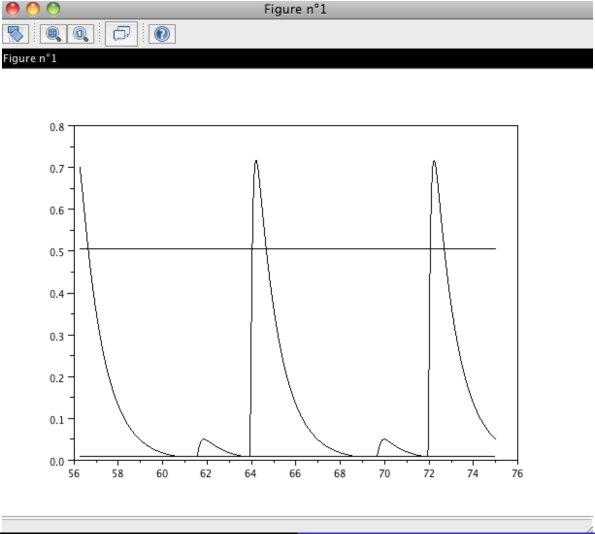
- We chose randomly a Δ which satisfies an exponential low of parameter 1.
- We define μ by

$$\mu(u) = \int_0^u \mathbb{I}_{[s(0)+v>\sigma(X(v))]} dv.$$

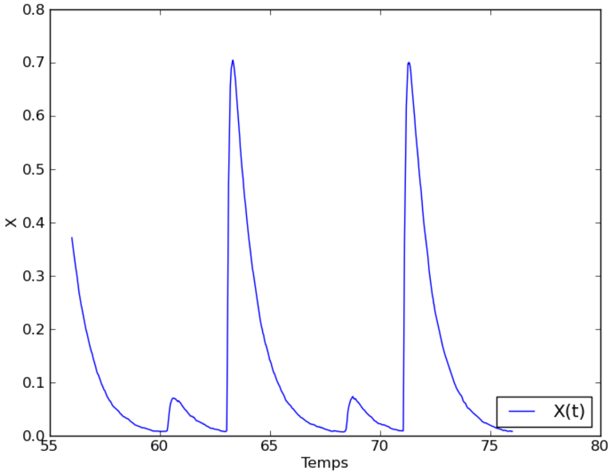
- The time of discharge of the neuron is then given by the time t such that

$$\mu(t) = \Delta.$$

Finite size model.



Finite size model.



Conclusion of the time elapsed model

Conclusion of the time elapsed model

- Simple model based on the time elapsed since the last discharge
- However, very rich dynamics with several patterns.
- Several possible extentions
- Link between the micro/macroscopic scale by Caceres, Chevallier, Doumic, Reynaud-Bouret
- Add of heterogeneity or spatial variable (with Kang, Perthame, Torres).