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Nonlinear and stochastic models in Neuroscience

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Modèles nonlinéaires et stochastiques en neuroscience

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A Rose,
A ses histoires qui ont éveillé ma curiosité,
A sa modestie, sa morale, qu'elle a si admirablement transmises.

A mon grand-père Yvon
Au brillant mathématicien qu'il aurait été.
Au grand homme qu'il fut;

A mon grand copain.
A son infinie sagesse et à son humanité;
A sa main tendrement posée sur mon épaule;

A Mamie Nelly
A sa générosité sans limite,
A son amour sans borne.

Vous manquez à ma vie.

Abstract

The brain is a very complex system in the strong sense. It features a huge amount of individual cells, in particular the neurons presenting a highly nonlinear dynamics, interconnected in a very intricate fashion, and which receive noisy complex informations. The problem of understanding the function of the brain, the neurons' behavior in response to different kinds of stimuli and the global behavior of macroscopic or mesoscopic populations of neurons has received a lot of attention during the last decades, and a critical amount of biological and computational data is now available and makes the field of mathematical neurosciences very active and exciting.

In this manuscript we will be interested in bringing together advanced mathematical tools and biological problems arising in neuroscience. We will be particularly interested in understanding the role of nonlinearities and stochasticity in the brain, at the level of individual cells and of populations. The study of biological problems will bring into focus new and unsolved mathematical problems we will try to address, and mathematical studies will in turn shed a new light on biological processes in play.

After a quick and selective description of the basic principles of neural science and of the different models of neuronal activity, we will introduce and study a general class of nonlinear bidimensional neuron models described from a mathematical point of view by an hybrid dynamical system. In these systems the membrane potential of a neuron together with an additional variable called the adaptation, has free behavior governed by an ordinary differential equation, and this dynamics is coupled with a spike mechanism described by a discrete dynamical system. An extensive study of these models will be provided in the manuscript, which will lead us to define electrophysiological classes of neurons, i.e. sets of parameters for which the neuron has similar behaviors for different types of stimulations.

We will then deal with the statistics of spike trains for neurons driven by noisy currents. We will show that the problem of characterizing the probability distribution of spike timings can be reduced to the problem of first hitting times of certain stochastic process, and we shall review and develop methods in order to solve this problem.

We will eventually turn to popoulation modelling. The first level of modelization is the network level. At this level, we will propose an event-based description of the network activity for noisy neurons. The network-level description is in general not suitable in order to understand the function of cortical areas or cortical columns, and in general at the level of the cell, the properties of the neurons and of the connectivities are unknown. That is why we will then turn to more mesoscopic models. We first present the derivation of mesoscopic description from first principles, and prove that the equation obtained, called the mean-field equation, is well posed in the mathematical sense. We will then simplify this equation by neglecting the noise, and study the dynamics of periodic solutions for cortical columns models, which can be related

to electroencephalogram signals, with a special focus on the apparition of epileptic activity.

Résumé

Le cerveau est un système très complexe au sens fort. Il est composé d'un nombre immense de cellules, en particulier les neurones, qui présentent une dynamique fortement non-linéaire, interconnecté de façon très complexe, recevant des entrées bruitées et très complexes. Comprendre le fonctionnement du cerveau et le comporement des neurones en réponse à différents types de stimulations et le comportement global de populations macroscopiques ou mésoscopiques de neurones a été l'objet d'intenses recherches depuis les dernières décénies, et une quantité critique de données biologiques et computationnelles est maintenant disponible, faisant du domaine des neurosciences un champ de recherche actif et passionant.

Le but de ce manuscrit est d'utiliser des outils mathématiques avancés afin de résoudre des problèmes biologiques pertinents émergeant dans le domaine de la neuroscience. Nous nous intéresserons particulièrement au rôle des nonlinéarités et aux aspects stochastiques dans le cerveau, tant au niveau de cellules individuelles que de populations neuronales. L'étude théorique de récents problèmes biologiques pose de nouveaux problèmes matématiques non encore résolus que nous cherchons à traiter, et l'étude mathématique de problèmes biologiques nous permettra d'avoir un nouveau regard sur les processus biologiques en jeu.

Après une description rapide et sélective des connaissances en neuroscience et de différents modèles d'activité neuronale, nous introduirons et étudierons une classe générale de modèles de neurones bidimensionnels décrits mathématiquement par un système dynamique hybride. Dans ces sytèmes, le potentiel de membrane d'un neurone est couplé avec une variable additionnelle, dite d'adaptation. La dynamique libre est gouvernée par une équation différentielle ordinaire, et cette dynamique est couplée avec un système dynamique discret modélisant l'émission de potentiels d'action. Une étude extensive de ces modèles est développée dans cette dissertation, et les résultats obtenus nous permettent de définir des classes électrophysiologiques de neurones, c'est-à-dire des jeux de paramètres pour lesquels le système a des comportements similaires en réponse à différents types de stimuli.

Nous nous intéressons ensuite aux statistiques de trains de potentiels d'actions émis par un neurone recevant des entrées bruitées. Nous montrons que caractériser les distributions des temps de spikes peut se ramener à un problème de temps d'atteinte d'une courbe par un processus stochastique. Nous présentons différentes techniques existantes et développons de nouvelles méthodes afin de résoudre ces problèmes.

Enfin, nous nous intéresserons au problème de la modélisation de populations de neurones. Le premier niveau de modélisation est le réseau. A ce niveau de description, nous proposons un modèle événementiel de l'activité du réseau décrite en termes de temps d'impulsions de potentiels d'actions. Ce niveau de description ne permet pas en général de comprendre le fonctionnement d'aires ou de colonnes corticales. De plus, les connectivités et le fonctionnement d'une cellule unique dans un réseau

sont assez mal connues, alors qu'elles forment des structures identifiables à l'échelle d'une population. Pour cette raison nous nous intéressons ensuite aux modélisations mésoscopiques de populations de neurones. Tout d'abord nous présentons la façon de passer d'une description microscopique à une description macroscopique, et démontrons que l'équation ainsi obtenue, appelée équation de champ-moyen, est mathématiquement bien posée. Enfin, nous simplifions ces modèles en négligeant le bruit, et étudions la dynamique des solutions périodiques dans certains modèles de colonnes corticales, qui peut être mis en relation avec les signaux d'électroencéphalogrammes, et nous intéressons particulièrement à l'apparition d'une activité épileptiforme.

I am interested in bringing together advanced mathematical tools and biological problems of interest arising in biological science, and particularly in neuroscience. I am particularly interested in stochastic and nonlinear models. I have been so far working on hybrid dynamical systems defined by both a continuous and a discrete dynamical system, modeling the dynamics of a single nerve cell. I studied it mathematical properties and related these features with biological notions. I am also interested in the problem of describing first hitting times of stochastic processes, and developped a new method to compute the probability distribution of the first hitting times of Double Integral Processes to curved boundaries. These studies were motivated by the problem of characterizing the statistics of spike trains. I am also interested in population modeling: I proposed an event-based description of the network activity for stochastic neurons, studied the mean-field equation of large neuronal networks, and the dynamics of periodic solutions for some cortical column models and related it to electroencephalogram signals and epilepsy.

Acknowledgments

Questions of science, Science and progress,
Do not speak as loud as my heart.
– Coldplay

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I would eventually like to dedicate this thesis to Claude Brunschwig (X1943 "bis"), a bright student who successfully passed the entrance examination at the École Polytechnique in 1943 though the numerus clausus applied to Jewish people. His mathematical creativity was recognized, and with the support of his classes préparatoires professors he registered new mathematical findings as a Soleau envelope, which unfortunately is now destroyed. He was never able to join the school in Paris. After the examination, he had to hide in the Vercors, was denounced by farmers, arrested, deported in Drancy, and in April 1944 to Auschwitz where he was exterminated. One name, one picture, among six million.

Claude Brunschwig

Without memory, our existence would be barren and opaque,
like a prison cell into which no light penetrates;
like a tomb which rejects the living.
If anything can, it is memory that will save humanity.
For me, hope without memory is like memory without hope...
– Elie Wiesel

Jonathan Touboul.