

# Advanced Biology Course in Computational Neuroscience

## Introductory Class

1. **Brain function and clinical issues, examples** (October 4) Nathalie Kubis (Hôpital Lariboisière)

Consciousness relies on a highly interconnected network of neurons. Predicting coma outcome is a challenge in the intensive care unit and achieved through combined evaluation of clinical examination, blood biomarkers, brain MRI, and neurophysiological tools namely electroencephalography and evoked potentials. Unfortunately, a grey zone persists for many patients with inconclusive results. After an introduction of basic nervous system anatomy and organization, I will describe coma and different subtypes, what factors contribute to bad and good prognosis and finally how computational neurosciences may help solving that issue.

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## Sensory transduction

2. **Modelling hair cells as sensory receptors and mechanical amplifiers for hearing** (October 11) Pascal Martin (Institut Curie)

Hearing relies on mechanosensitivity of specialized epithelial cells called “hair cells”. Hair cells serve as the cellular microphones of the inner ear: they transduce mechanical vibrations evoked by sound into electrical signals that are relayed to the brain. Hearing achieves astonishing sensitivity and frequency selectivity to sound stimuli. The ear is also capable to operate over sound-pressure levels that vary by one millionfold. Hearing starts with the deflection of the hair bundle, a cohesive tuft of extended microvilli—the “hairs” of the hair cell. I will describe in this lecture how a dynamical interplay between mechanosensitive ion channels, molecular motors that actively pull on the channels via proteinaceous links, and calcium feedback on the ion channels’ open probability can lead to spontaneous mechanical oscillations of the hair bundle. I will then assess the consequences of these active oscillatory movements for hearing and discuss limits on hair-cell function. I will finally argue that the remarkable properties of hearing emerge from a general physical principle: operation of the hair cells near an oscillatory instability, specifically, a Hopf bifurcation.

### *Bibliography:*

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2. Martin, P. Physical principles of hearing. Chapter 7 in Physics and biology: from molecules to life (eds. Allemand, J. & Desbiolles, P.) 127–147 (World Scientific Publishing Co, 2014).

*Another general review, but with more focus on active motility of the hair-cell bundle. This is nearly a write-up of my lecture (without any detail about mathematical modeling).*

3. Martin, P. & Hudspeth, A. J. Mechanical Frequency Tuning by Sensory Hair Cells, the Receptors and Amplifiers of the Inner Ear. *Annu. Rev. Condens. Matter Phys.* 12, 29– 49 (2021). *A review article describing models of mechano-electrical transduction by the hair cell as well as of active hair-bundle motility, including spontaneous oscillations.*
4. Tinevez, J. Y., Julicher, F. & Martin, P. Unifying the various incarnations of active hair-bundle motility by the vertebrate hair cell. *Biophys. J.* 93, 4053–67 (2007). *A paper reporting different forms of active hair-bundle motility as well as a detailed description of a model that can account for them.*
5. Mehta, A. D., Martin, P. & Hudspeth, A. J. Negative stiffness betrays a mechanism for mechanical amplification by the hair cell. *Biophys. J.* 80, 346A-346A (2001). *Experimental demonstration of negative stiffness by the hair bundle.*
6. Martin, P. & Hudspeth, A. J. Active hair-bundle movements can amplify a hair cell's response to oscillatory mechanical stimuli. *Proc. Natl. Acad. Sci. USA* 96, 14306–11 (1999). *Experimental demonstration of mechanical amplification by the hair cell under conditions for which its mechanosensory hair bundle oscillates spontaneously.*

### 3. **Modelling the transduction of light into an electrical signal by rod and cone photoreceptors in the retina** (October 18) Jürgen Reingruber (ENS)

The eyes of humans and most vertebrates contain two kinds of photoreceptors: rods for monochrome night vision, and cones for colored daylight vision. Rods and cones are the fundamental sensory neurons underlying vision. Rods are highly sensitive to light and respond to single photon absorptions. Cones signal only in brighter light, but contrary to rods they adapt and remain functional even in brightest light conditions. Rods and cones combine polarized cell structures and complex signal transduction pathways to convert light into electrical responses. In this class we will introduce phototransduction models together with analysis to show how the photoreceptor geometry and the transduction pathway interplay to generate the electrical responses. We will discuss the remarkable properties of rods to reliably amplify a single photon absorption, why cones are much less sensitive to light than rods, and the regulatory function of the calcium dynamics.

#### *Bibliography:*

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- Reingruber, J, Holcman, D. and Fain, G.L., 2015. How rods respond to single photons: Key adaptations of a G-protein cascade that enable vision at the physical limit of perception. *Bioessays*, 37(11), pp.1243-1252.
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- Reingruber, J., Ingram, N.T., Griffis, K.G. and Fain, G.L., 2020. A kinetic analysis of mouse rod and cone photoreceptor responses. *The Journal of physiology*, 598(17), pp.3747-3763.
- G. Fain, H. Matthews, M. Cornwall, and Y. Koutalos, Adaptation in vertebrate photoreceptors, *Physiol. Reviews*, vol. 81, no. 1, pp. 117–151, 2001.

#### 4. **Neural coding in the retina and vision restoration** (October 25)

Olivier Marre (Institut de la Vision)

I will first present the retina, focusing on why the retina performs non-linear processing on the visual stimulus. I will then explain how we and others have tried to model and understand retinal non-linear computations. The lessons learned here also apply to other sensory systems. Finally, I will finish by connecting these computational studies to clinically relevant research topics by talking about vision restoration strategies that are currently tested on blind patients.

### **Fundamental brain constituents**

#### 5. **Electrodiffusion model for synapses and dendritic spines** (November 2) Thibault Lagache (Institut Pasteur)

The biophysical properties of dendritic spines play a critical role in neuronal integration but are still poorly understood, due to experimental difficulties in accessing them. Spine biophysics has been traditionally explored using theoretical models based on cable theory. However, cable theory generally assumes that concentration changes associated with ionic currents are negligible and, therefore, ignores electrodiffusion, i.e. the interaction between electric fields and ionic diffusion. This assumption, while true for large neuronal compartments, could be incorrect when applied to femto-liter size structures such as dendritic spines.

To extend cable theory and explore electrodiffusion effects, we will introduce in this course the Poisson (P) and Nernst-Planck (NP) equations, which relate electric field to charge and Fick's law of diffusion, to model ion concentration dynamics in spines receiving excitatory synaptic potentials (EPSPs).

We will present recent experiments that measure voltage transients from spines with nanoelectrodes, and we will use PNP modeling to understand measured dynamics and extract biophysical parameters. We will show how (i) passive diffusion and electrodiffusion jointly affect the dynamics of spine EPSPs; (ii) spine geometry plays a key role in shaping EPSPs; and, (iii) the spine-neck resistance dynamically decreases during EPSPs, leading to short-term synaptic facilitation.

Finally, we will give few examples to illustrate how PNP formalism can be easily adapted to model ionic biophysics in other nanoscale bio-compartments.

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- Stuart, G. J., & Spruston, N. (2015). Dendritic integration: 60 years of progress. *Nature Neuroscience*, 18(12), 1713–1721.

#### 6. **Modelling Neuron-Glial interactions and synaptic plasticity** (November 8) David Holcman (ENS)

This class will present  
1-tripartite synapses

- 2-Diffusion model of neurotransmitters
- 3-Compartment model of neuron-glia interaction
- 4-Electrophysiology analysis of nanopipette.
- 5-Analysis of spontaneous calcium responses in astrocytic networks.

## Neural Networks

### 7. **Modelling and analysis of neural circuit dynamics: emergent rhythms and their interplay.** (November 15) Boris Gutkin (ENS)

Large scale brain rhythms and neural oscillations emerge from synaptic interactions within neuronal circuits. Over the past years, such rhythms have been suggested to play a crucial role in a multitude of functions, from navigation and working memory to routing the flow of information across cortical regions, resulting in a functional connectome.

In this lecture we will discuss some of the classical dynamical routes by which neural oscillations arise and their properties. We will introduce salient aspects of weakly coupled oscillator theory and the concepts of phase response functions. I will then focus on the more recent work on using exact reduced network models to analyze gamma rhythms in spiking networks and the emergence of phase-locked states.

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### 8. **Modelling spatial memory and navigation** (November 22) Denis Sheynikhovich (Institut de la Vision, Paris)

The sense of place and the ability to navigate are fundamental to our existence. How do we know where we are? How can we find the way from one place to another? The discovery of place cells and grid cells in the rat brain, which was awarded the Nobel Prize in Physiology and Medicine in 2014, marked the first step in characterizing the neural network responsible for creating and storing a mental representation of the space that surrounds us. In this lecture, I will describe the primary components of the brain's spatial navigation network and explore theoretical models that connect neural activity within this network to spatial memory and behavior.

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9. **Mesocopic models: from neural circuits to large-scale activity, in normal and pathological states** (November 29) Alain Destexhe (University Paris-Saclay)

To model large-scale phenomena, such as traveling waves, or the propagation of evoked activity across brain areas, it is difficult to use cellular-level models. Instead, one can derive mean-field models from the spiking networks, and create networks of mean-field units to model large scale phenomena. The course will illustrate this approach by considering models at different scales, from neural circuits, mesoscale (millimeters) and whole-brain scale. This approach can be used to link scales, for example to predict the emerging brain-wide consequences of changes at the molecular level, such as drugs or anesthetics.

10. **Big data analysis applied to behavioral neuroscience** (December 6) Gisella Vetere (ESPCI)

In this course I will present how to investigate the formation and consolidation of memories in mice by analyzing neuronal data collected at different levels:

1. I will explore the study of network of brain regions to understand how neuronal circuits in the brain communicate to each other to allow the recall of a long-lasting memory;
2. I will present new approaches, based on optogenetics, used to identify the nature of memory neurons, called engram, by “tagging” and “reactivating” cells and correlating it to behavioral effects;
3. I will give an overview of the type of analyses that can be applied to study big data sets in evaluating neuronal response in freely moving animals over time. These data can be collected with a miniaturized microscope, that allow visualization in real time of calcium changes in single cells.

## **EEG analysis and Brain-Computer Interfaces**

11. **Analyse des signaux électrophysiologiques: : des cycles lents aux oscillations rapides** (December 13) Michel Le Van Quyen (Sorbonne University)

12. **Signal processing and machine learning for Brain-Computer Interfaces** (December 20) Theodore Papadopoulos (INRIA Nice)

From the discovery of biofeedback (the ability for a subject to voluntarily modulate his/her brain signals) in years 1960-1970, it was quickly realized that this phenomenon can be used to

control a computer [1,2] and consequently any machine. A Brain-Computer Interface is typically a system that records the brain signals of a subject and identifies the performed type of activity among a small set of predefined ones. Each of these predefined activities (or some of their characteristics) can be associated to a specific computer task, which effectively allows the subject to control a computer interface. Since 50 years, while great progress has been achieved in the field: acquisition devices have improved and are sometimes more affordable, computer power has increased allowing for more and more sophisticated real time signal analysis, software tools have emerged that allow a more widespread use of BCI techniques... Yet, there are still big challenges that still need to be overcome [3]: efficiency of the interfaces (in most cases, they are much less effective than standard “through muscles” computer interaction, limiting BCIs to niche cases), ease-of-use of BCIs (setting up an acquisition device can take time, variability of the measured signals often requires the adaptation of the signal modeling to each subject and each session, ...), ...

The course will explore this time of interfaces, describe their principles and main characteristics, and will present some of the signal analysis/learning techniques used in BCIs through some examples like the P300 speller [4] or motion imagination [5]....

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