Growth and activity of neuronal cultures: emergence of organized behaviors

In this thesis, I provide models and numerical tools to better understand and predict the behavior and development of neuronal cultures and devices. I decided to focus on these systems because the are of prime interest to study the development and activity of neurons, thus improving our understanding of the brain. To me, this approach was more appealing than a direct investigation of the brain because these systems possess many interesting properties which make them more accessible, alterable, and thus more versatile as objects of study.

Neuronal cultures are two-dimensional networks of neurons which are obtained by seeding and growing neurons in a Petri-dish filled with nutritive medium. They have proven invaluable in improving our understanding of how the brain processes information, enabling researchers to investigate neuronal and network response functions to various drugs, perturbations, and stimuli. Recently, progress in microfluidics have also opened the gate to more elaborated neuronal devices, bringing us one step closer to complex signal processing with living *in vitro* neurons. These devices are obtained through "lab-on-a-chip" technologies: multiple chambers and micrometric channels are etched into a polymer chip and form a complex environment which will guide the development of neurons into a precise shape.

In order to take advantage of such complex structures for signal processing studies or medical applications, it is necessary to understand the intrinsic behavior of the small random networks which are the main building blocks in these systems. My PhD thus aimed at understanding the emerging structure and dynamical patterns of these neuronal ensembles, providing a coherent explanation for their dynamics based on properties of the networks as well as biological mechanisms at the cellular scale.

First, I proposed a mechanism to explain the epileptiform bursts of activity present in cultures, mechanism which I formulated as a concise theoretical model. I subsequently tested the predictions of this model on cultures and showed that they were indeed compatible with the behavior observed *in vitro*. In addition, I discussed how this dynamical mechanism could also be associated to percolation phenomena when addressed from the standpoint of statistical physics. This relation to a very universal framework notably explained the robustness of the bursting behavior. Furthermore, I described how the statistical properties of the bursting dynamics can provide information on the properties of the neurons involved, especially in the context of a very interesting phase transition which was observed in experiments. This transition between an asynchronous behavior and the usual bursting pattern can be explained mechanistically by the theoretical description underlying the previous theoretical model. The framework, based on the existence of pacemaker neurons and the importance of adaptation currents on the neuronal dynamics, was thus able to provide a coherent and comprehensive picture of the various phenomena observed in neuronal cultures.

Because of the importance of space and structure in neuronal devices, I devoted the second part of the thesis to the interactions between spatial and temporal dynamics. I further developed the initial description to analyze the spatiotemporal properties of the activity, and especially the fact that bursts nucleate in specific areas in the network. Though correlations were found between the structure of these complex networks and the dynamical properties, and in spite of the fact that they provided some predictive power, these correlations were strongly dependent on the precise properties of the neurons and on the relative importance of the mechanisms driving the activity. Furthermore, the nucleation centers also varied significantly depending on the precise network topology, hinting at an intrinsic limitation of this modeling endeavor given the absence of precise connectivity data for neuronal cultures and devices.

Since prediction and analysis of these nucleation centers strongly depend on the network structure, and because precise spatial descriptions are necessary to study neuronal devices, a new perspective

was necessary. A significant part of my PhD was therefore dedicated to the development of a simulation platform to enable efficient modeling of the network development. This software, `DeNSE`, takes into account the interactions between neurons and their environment and is the first platform to provide versatile and complete models to simulate the entire growth process of neurons. To attain a description of the growth mechanisms as exhaustive and coherent as possible, I designed a systematic framework which I used to revise existing models. This enables me to provide more generic algorithms which are able to interact with various additional mechanisms, as well as to make the models' parameters relate more closely to biological mechanisms. Furthermore, I also presented new models to account for competition between the growing extremities of neurons, as well as branching mechanisms to describe the development of complex neuronal arbors. These realistic morphologies, through their interactions, could then be used for the generation of more plausible connectivity structures to describe neuronal networks. I demonstrated that this simulator was able to generate valid neuronal morphologies and that, through their interactions, new connectivity structures could be generated. I asserted the plausibility of these structures, using them to provide more accurate descriptions of neuronal cultures and efficiently reproduce neuronal devices *in silico*. I finally showed that the activities sustained by the networks were compatible with experimental recordings.

Eventually, I discussed future directions for which neuronal devices would enable us to circumvent current limitations of neuronal cultures, such as their resilient bursting behavior. I concluded that these new structures would provide better tools to investigate neuronal signal processing. As a new source of information, they could also provide critical insights on the mechanisms which underlie brain development and plasticity, as well as leads for medical applications in the field of neuroprosthetics.