CECÍLIA ROMARO

ESTUDOS EM MODELOS DE REDES CORTICAIS
STUDIES IN CORTICAL NETWORK MODELS

Ribeirão Preto
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Tese apresentada à Faculdade de Filosofica Ciências e Letras de Ribeirão Preto da Universidade de São Paulo para obtenção do Título de Doutor em Ciências.

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Área de Concentração:

Física Aplicada à Medicina e Biologia

Orientador:

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Co-orientador:

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2020

I dedicate this work to all people who, in some way, act for a better world.

ACKNOWLEDGMENTS

"I'm late! I'm late! For a very important date! No time to say hello, goodbye! I'm late! I'm late! I'm late!"

--White Rabbit (Alice in Wonderland)

RESUMO

Esta tese apresenta-se em cinco capítulos-artigos resolvendo de forma simples problemas e perguntas não triviais na neurosciencia computacional.

O primeiro capítulo apresenta uma reimplementação do modelo de Potjans-Diesmann (PD) para a microcircuitaria cortical local e uma técnica de redimensionamento do número de neurônios do modelo capaz de manter as probabilidades de conexões e o comportamento da atividade da rede mesmo quando redimensionada para 1% do tamanho original.

O segundo capítulo, baseado no potencial de campo médio, explica formalmente o método de redimensionamento e apresenta um novo método de corrigir e compensar a atividade dos neuronios da borda em redes com extensão espacial sem introduzir conexões toroidais e/ou oscilaçôes.

O terceiro capítulo introduz extensão espacial ao modelo PD, soluciona o problema de borda e estuda a resolução espacial (topográfica) da atividade da rede como um reflexo da resolução estrutural.

O quarto capítulo, baseado em transição de fase e metaestabilidade, inovadoramente estuda o falso estado estacionário e o tempo de duração da atividade em redes que não recebem entrada externa forçada capaz de mantê-las ativas.

O quinto capítulo contém a caracterização da rede de neurônios do córtex somatossensorial primário do rato em termos do levantamento estatístico dos parâmetros. Em seguida, um modelo do córtex somatossensorial utilizando o neurônio estocástico de Galves-Löcherbach (GL) é construido com base nos parâmetros levantados. No fim do capítulo, apresenta-se um método para substituição de neurônios determinísticos do tipo integra-e-dispara com vazamento por neurônios GL em modelos de redes de neurônios.

Palavras-Chave – modelagem do córtex somatossensorial, potencial de campo médio, metaestabilidade, redimensionamento de rede neuronal, transição de fase.

ABSTRACT

This thesis consists of five chapter-articles, each proposing simple solutions to nontrivial questions and problems in computational neuroscience.

The first chapter presents a reimplementation of the Potjans-Diesmann (PD) model of the local cortical microcircuitry, and a rescaling method for the number of neurons in the model that is capable of maintaining both the connection probabilities and the behavior of the network activity even when rescaled to 1 % of original size.

The second chapter, based on mean field potential, formally explains the scaling method and presents a new method to correct and compensate for the activity of boundary neurons in networks with spatial extension without introducing toroidal connections and/or oscillations.

The third chapter introduces spatial extension to the PD model, solves the boundary problem, and studies the spatial (topographic) resolution of the network activity as a consequence of the structural resolution.

The fourth chapter, based on phase transition and meta-stability, innovatively studies the false steady state and activity lifetime in networks that do not receive forced external input to keep them active.

The fifth chapter contains a characterization of the primary somatosensory cortex network of the rat in terms of a statistical survey of the parameters. It also presents a model of the somatosensory cortex using the stochastic Galves-Löcherbach (GL) neuron, which was constructed based on the somatotopic parameters raised. At the end of the chapter, a method for replacing deterministic leaky integrate-and-fire neurons by GL neurons in neural network models is presented.

Keywords – somatosensory cortex model, mean-field potential, metastability behavior, rescaling neuron network, phase transition.

INTRODUCTION

Understanding the brain is challenging, given both its complex mechanisms and inaccessibility. Every year new pathways, channels, proteins, and other mechanisms are discovered, but how these components interact at the system level remains a mystery (Markram et al., 2015; Yin and Wang, 2016; Lisman and Raghavachari, 2006; Diekman et al., 2013; Antunes et al., 2016). A strong mathematical research line appeared in the early XX century to explain the neuron behavior. The Hodgkin-Huxley (HH) (Hodgkin et al., 1952) and leaky integrate-and-fire (LIF) (Lapicque, 1907) models are some of the most classic and oldest mathematical models of neurons, and pools of these neurons were put together in attempts to study their collective behavior. However, it was only with the advancement of computational resources that the study of neuron networks was able to develop further (De Schutter, 2008). *In silico* simulation studies started to provide a quantitative framework for integrating disparate pieces of evidence from *in vivo* and *in vitro* experiments into coherent predictive models that can be used to investigate brain function.

Biologically detailed computational modeling became an excellent research tool to explain brain mechanisms and to propose supporting experiments *in vivo* (Markram et al., 2015; Mazza et al., 2004; Bower and Beeman, 2012). At the same time, simplified neurons became a study subject to understand the dynamics of neuron networks (Galves and Löcherbach, 2013; Potjans and Diesmann, 2014a; Brunel, 2000). These techniques are being largely adopted by research groups worldwide such as the Allen Institute for Brain Science (AIBS) (Jones et al., 2009) (`https://alleninstitute.org/what-we-do/brain-science/`), the Human Brain Project (HBP) (Markram, 2012) (`https://www.humanbrainproject.eu/en/`), the NEST initiative (Gewaltig and Diesmann, 2007) (`https://nest-initiative.org/`), and the Research, Innovation and Dissemination Center for Neuromathematics (NeuroMat) (`https://neuromat.numec.prp.usp.br/`). In this scenario, three neural simulators stand out today:

The NEURON simulator (Carnevale and Hines, 2006) (`https://neuron.yale.edu/neuron/`) allows modeling of networks of neurons with detailed neuronal morphologies, and different ion channels and neurotransmitter receptors. Developed at Yale University, NEURON is the most widely used simulator of its type, both in university labs and large research groups, including AIBS and HBP. It is an excellent software for the construction and simulation of biologically-detailed neuron networks, although it requires a large amount of machine

processing time.

The NEST simulator (Morrison et al., 2005; Gewaltig and Diesmann, 2007) (`https://nest-simulator.org/`) allows modeling of large networks of simplified neurons. It does not allow the direct introduction of morphology, ion channels and neurotransmitter receptors, but allows parallel and distributed simulation inboard build up in order to save machine time.

The Brian simulator (Goodman and Brette, 2009) (`https://briansimulator.org/`) has inboard differential equation solvers and other facilities to simulate spiking neural networks. Brian is an easy install simulator, given it is a Python package. It is not as fast as NEST, but it is more plastic. Neither Brian nor NEST allow the direct introduction of morphology or physical characteristics of neurons.

Although great advancement has been achieved, it seems that computational resources still pose a limiting factor to simulate, process, and understand detailed models of large networks (Markram et al., 2015; Towns et al., 2014). This limit is being pushed further and further away as computational resources become more powerful and cheaper, and this both supports and inspires the work done in this thesis.

This thesis starts by presenting a re-implementation of the Potjans-Diesmann (PD) model (Potjans and Diesmann, 2014a) in NetPyNE/NEURON (Dura-Bernal et al., 2019b; Carnevale and Hines, 2006) (`http://www.netpyne.org/`), a high-level Python interface to the NEU-RON simulator. The PD model, originally implemented in NEST (Gewaltig and Diesmann, 2007), is an eight-cell population model which reproduces the neuronal connectivity under a 1 mm^2 area of cortical surface in full scale (the model has 77,169 neurons). The PD model generates spontaneous activity with population-specific firing rates similar to those observed experimentally (de Kock and Sakmann, 2009; Sakata and Harris, 2009; Swadlow, 1989). The re-implementation of the PD model in NetPyNE/NEURON allows the use of more detailed neuron models with multicompartmental morphologies and multiple realistic biophysical ion channels. Additionally, some analyses can be provided automatically.

Due to the required memory and processing power to re-implement the PD model in NEU-RON (Carnevale and Hines, 2006), a rescaling method was developed to scale down the model to variable levels, down to the lowest level of 1%. The method allows to decrease the number of connections to 10^{-4} of the original number still maintaining characteristics of network activity behavior compatible with experimental data: mean population firing rate, synchrony and irregularity (Romaro et al., 2018, 2020a).

The re-scaling method introduced here can be applied not only to the PD model but to random neuron network models in general, e.g. the Brunel model (Brunel, 2000). This method

is further explored in chapter 2, and both a detailed mathematical explanation based on mean field potential and a list of the method limitations are presented there. Based on the re-scaling method, networks with spatial extension are considered in chapter 2 and a boundary solution method is introduced. The boundary solution method is able to correct and compensate the lack (or excess) of connections at the boundary in order to reestablish the correct activity of boundary-neurons and core-neurons.

The boundary solution method was developed because it was needed in the construction of a model of the primary somatossensory cortex exhibiting somatotopy, the main subject of Chapter 3.

Somatotopy is the topographic organization of somatic sensory pathways – touch and proprioception – in the primary somatosensory cortex (S1, located in the post-central gyrus) (Bear et al., 2020). That is, the mapping of neighboring areas of the skin to neighboring areas in the cortex, e.g. two sensors in the skin close together activate in the cortex two groups of neurons that are close together. Many models have been proposed to reproduce and explain the mechanisms and effects of the topographic organization in S1, including the re-organization properties following some lesion (Ramachandran, 1998; Bear et al., 2020). A property of the somatotopic maps is the direct proportionality between the cortical area allocated to represent a body surface and the sensitivity of this surface. In other words, the higher the sensitivity of a body area, the higher the cortical area allocated to process it (Bear et al., 2020). However, none of these models explored the influence of the connectome on the resolution of the topographic map in S1.

In chapter 3, adjustments are introduced in the PD model in order to adapt it to describe the somatosensory cortex and allow a study of the role of network structure and activity on the topographic organization and spatial resolution of inputs. These adjustments include the introduction of spatial locations for the neurons and consideration of distance-dependent connectivity to integrate anatomical and physiological data. This leads to a model that accounts for the topographic pattern of connections. The objective is to shed some light on the question of how the parameters of the topographic connections relate to the local activity patterns in specific cortical layers.

Work on cortical network models raised other questions that were studied during the period of this doctorate and resulted in chapters 4 and 5.

One of these questions is how to characterize the lifetime of active states in a network in the absence of external input. In the context of the Galves-Löcherbach (GL) model (Galves and Löcherbach, 2013), André has recently proved (André, 2019b) that for finite one-dimensional

lattices of continuous GL neurons with hard threshold rate function (Ferrari et al., 2018), in the sub-critical regime where the leak rate γ is smaller than a critical value γ_c the lifetime of the active state is finite but the exit time from this state is exponentially distributed. In chapter 4, a computational version of the finite lattice model considered by André is described together with extensions of the model to two- and three-dimensional square lattices and linear and sigmoidal rate functions. The simulation studies confirm the rigorous results obtained by André and provide evidence that they also hold in the extended settings considered (Romaro et al., 2019).

Another question is related to the common practice of using data from a mix of different cortical areas and animals in the construction of a model for a specific cortical area from a given animal. For example, the PD model uses data from the primary somatossensory, motor and visual cortices of rat and rabbit (Potjans and Diesmann, 2014a). To address this problem, in chapter 5 a statistical survey of parameters from the connectome of the primary somatosensory cortex of the rat is made. This allowed the construction of a model of the primary somatosensory cortex of the rat with GL neurons.

References are presented at the end of each chapter, except for introduction references, which are presented in the References section. Chapter 1 was developed in collaboration with Fernando Najman and Salvador Dura-Bernal. Chapter 4 was developed in collaboration with Fernando Najman and Morgan Andre.

CONCLUSION

This thesis focused on modeling neuronal networks and some mathematical tools and proprieties needed to do so.

The thesis proposed new approaches to known, yet limited, topics such as rescaling the network size while maintaining the first and second order statistics with the objective of decreasing machine time or increasing network details, and solving the boundary problem without loss of activity for spatially extended networks with topographic pattern of connections (Chapters 1 and 2).

A correlation between spatial resolution in activity and the standard deviation of the Gaussian distribution was utilized to propose a scheme for the construction of a network with topographic pattern of connections. This is the subject of Chapter 3.

The thesis also shows that the metastable phase transition depends on the spike-waste rate, and not on the network connectivity pattern (Chapter 4).

Lastly, the thesis presented a network model for the primary somatosensory cortex based on the GL stochastic neuron (Galves and Löcherbach, 2013). The network model was able to reproduce the biological average firing rate per layer, self-sustained activity without external input, and two activity states and the shift between them by a one-step interference in Layers L4e and L5e. This network also presented asynchronous activity and neurons with regular and irregular behaviour inside the same layer.

WORKS RESULTING FROM THIS THESIS

Articles submitted or placed in ArXiv

Romaro, C., Najman, F. A., Lytton, W. W., Roque, A. C., and Dura-Bernal, S. (2020). NetPyNE implementation and rescaling of the Potjans-Diesmann cortical microcircuit model. arXiv preprint arXiv:2005.03764. (Neural Computation)

Romaro, C., Najman, F. A., and André, M. (2019). A Numerical Study of the Time of Extinction in a Class of Systems of Spiking Neurons. arXiv preprint arXiv:1911.02609. (Journal of Statistical Physics)

Romaro, C., Roque, A. C., and Piqueira, J. R. C. (2020). Boundary solution based on rescalingmethod: recoup the first and second-order statistics of neuron network dynamics. arXivpreprint arXiv:2002.02381

Articles in preparation

Somatotopic organization in the cell-type specific cortical microcircuit and input spacial resolution. (Chapter 3)

Specific cortical microcircuit model based on somatossensory cortex connectome of juvenile rat. (Chapter 5)

Conference abstracts

Compensating method for the lack of connection on topographic neuron network edge (Submitted to CNS*2020)

Romaro, C., Najman, F. A., and André, M. (2019). Dynamical phase transitions study in simulations of finite neurons network. (In: Bojak, I. and Nowotny, T., eds. (2019) 28th Annual Computational Neuroscience Meeting: CNS*2019. BMC Neuroscience, pp190. doi: https://**doi.org/10.1186/s12868-019-0538-0** Available at http://centaur.reading .ac.uk/88633/)

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BMC Neuroscience, (64), sup-2. **This work won the Best Poster Award** (In: 27th Annual Computational Neuroscience Meeting (CNS*2018): Part One. BMC Neurosci 19, 64 (2018). https:**//doi.org/10.1186/s12868-018-0452-x**)

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