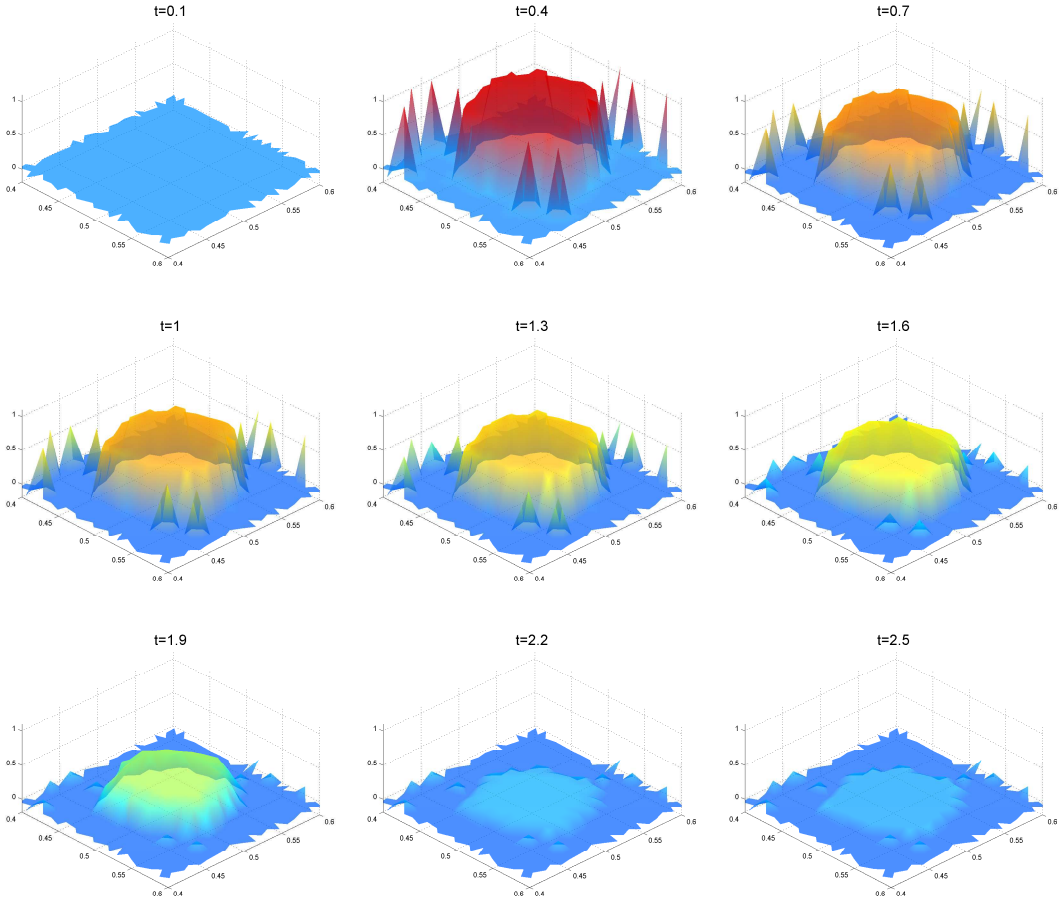

Figure 5.9: Snapshots describing center surround phenomenon. GrCs centered in a circle of radius 1/10 receive constant external current from MFs. GoCs (not depicted here) receive excitation from GrCs. Each GoC inhibits, in turn, all GrCs in a small rectangle having itself as the center, the smaller edge is set to 1/4 while the bigger one has length as the whole domain. Lateral inhibition by GoCs limited in space GrC excitation. An external current to GrCs in the circle, located in the center of the domain, and to the 5% of others is injected for $t > 0$, and it continues until the simulation ends

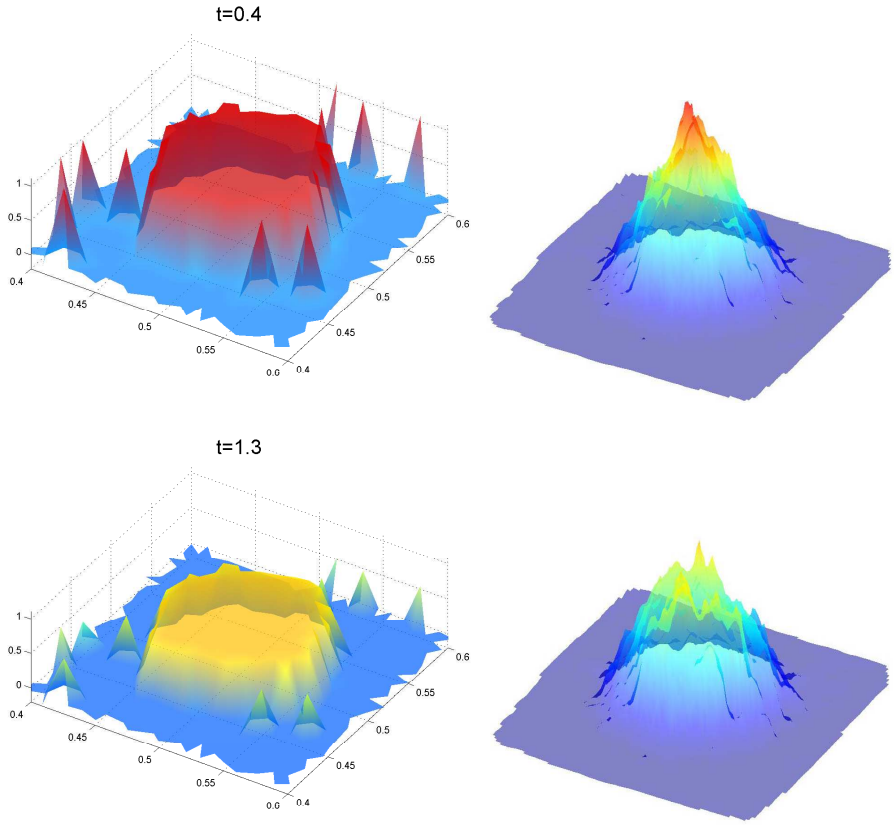

Figure 5.10: Frames at $t = 0.4$ and $t = 1.3$ taken from Figure 5.9 are compared to snapshots shown in [50], Figure 5. It is remarkable that a bounded GrC excitation in space, typical to the center-surround phenomenon, is depicted in frames on the left, and that it is qualitative similar to the benchmark dynamics on the right

to conclude that this delay equals to 0.1. The fixed delay in simulation involving dimensional variables, e.g. in [50], is 1 ms. This leads to observe that, in all the dynamics presented in this chapter, each time interval of about 0.1 translates into 1 ms in a realistic framework. This estimation is consistent with the duration of about 15 ms of the time-window of activity observed in the granular layer. This time-window is similar to the time of firing of granule cells (13 ms) in the realistic network [50] in Fig. 5B. Since we have determined a transformation law in time scales between our case and that one in [50], we are able to compare the computational costs between them. On the one hand, in [50, 47] the full model simulation of 25 ms of activity required about 108 sec on a Intel computational cluster 72 cores (Intel Xeon CPU X5650 @ 2.67GHz) for a network of 24336 granule cells and 504 Golgi cells. Since the NEURON simulator is able to keep a linear scaling of simulation time with network size ([47]), 25 ms of activity of 338 granule cells and 7 Golgi cells are computed in 108 sec on a single core CPU. Therefore, we should expect at simulation time of about 2500 sec for a network composed by about 8000 granule cells. On the other hand, our network consists in 7933 Granule and 94 Golgi cells. Considering an equivalent of 25 ms of activity, our simulation required about 1000 sec. Therefore, our network simulator is 2.5 times faster than the NEURON simulator. This analysis quantitatively confirms the reduced computational cost in considering our simplified model instead of a detailed one, without losing information about fundamental activity in time and space as the center-surround and the time windowing. Let us stress that improvements of our codes will lead to further time simulation saving. The most significant one will consist in translating our routines into a programming language that could be compiled rather than interpreted, i.e. C rather than Matlab, and in restructuring our code in order to take advantage of the multithreading or parallelization programming feature of the C programming language.

Conclusions

Based on the observation that neural populations present in brain areas have a specific density, we described large networks involving different populations by taking advantage of their density difference, often by several orders of magnitude. Thanks to this feature, we were able to formalize what we call the *multispecies model*. Such a model is very promising for the description of large neuronal networks, since it allows a significant computation cost reduction. In particular, this saving is guaranteed by the fact that the higher populations are described by only one PDEs system, while the sparse ones necessitate an ODEs system for each cell. The principal conclusions and accomplishments are:

- Starting from an idealized neuronal network with electrical-type coupling between neurons, we carefully investigated the "passage to the limit" as the number of neurons tends to infinity, while they remain confined in a fixed and bounded spatial region. We identified two different methods of increasing the population of the network so that a non-trivial continuum limit was obtained. The first assumes a fixed topology of the network (nearest-neighbour connections) but makes the proportionality in the diffusion coefficient depend upon the total number of neurons according to a specific law; conversely, the second method keeps this coefficient fixed but increases the number of connections per neuron. Both methods lead to equivalent continuous models in which the action potential is the solution of a reaction-diffusion partial differential equation (or a reaction-convection-diffusion equation if connections are not symmetric, i.e., if rectifying electrical synapses are allowed).

- Referring to a network whose neurons are linked through chemical synapses instead of electrical ones, the "passage to the limit" was investigated. A continuous

model was then formalized and the membrane potential became the solution of an integro-differential system.

- The results collected in the previous steps led to the formalization of a continuum model in which both kinds of synapses, the electrical and chemical ones, exist among neurons. Referring to the complete model, the fundamental synchronization phenomenon was displayed and studied by both qualitative and quantitative perspectives.

- Finally, all the previous steps merged into presenting the *multispecies model* through an interesting example involving the Golgi-Granular cell loop in the Cerebellum. The key aspect of such a model is that discrete and continuous systems interact with each other, leading to noteworthy phenomena, such as synchronization, travelling waves and center-surround which are present in the Cerebellum.

Throughout our work, the behaviour of each model is thoroughly investigated by means of carefully designed numerical experiments; in particular, we aim at tracking the influence of the various parameters of the model on the membrane potential dynamics. Specifically, our arguments apply in any spatial dimension, although we focused on them essentially in 2D. Much of the work presented in this thesis is explorative and further studies will be needed in order to highlight its novel insights and to fill in its gaps. Indeed, despite our results provide compelling evidence for describing some behaviour in a large neuronal network, a few limitations are worth noting. One of them concerns the single cell modelling. As described in Chapter 1, the FitzHugh-Nagumo model extracts from the Hodgkin-Huxley one some fundamental features which allow to replicate typical neural behavior. Throughout the whole work we exploited such a single cell model and it unveiled suitable for our purposes. Even more, in Chapter 5 we were able to exhibit the interesting center-surround and time-windowing phenomena. Although the FitzHugh-Nagumo model is able to reproduce interesting network behaviour as the center-surround and the time-windowing dynamics, i.e. activity control in space and time, it prevents the reconstruction of firing rate modulation. Moreover, the ability to modulate with continuity the generation of spikes would also allow the model to replicate more complex dynamics typical of neurons in the Cerebellum. Among those, the most interesting one is its ability to resonate to repeated stimuli showing a preference to fire with higher precision and intensity when its input is represented with a frequency within the Theta range ($4 - 8$ Hz), see [20]. A possible step forward in the single cell model would be to afford its reconstruction based on Adaptive Exponential Integrate and Fire models displayed in [10]. In principle also the Golgi cell model [48, 49] could

be approximated using the same dynamics described in [9] and proved to replicate also the resonant properties. This would allow our model to reproduce the entire set of properties described as the key features of the cerebellar granular layer reconstructed in computational models [20]: beyond the center surround and time-windowing modelling, also resonance to repeated stimuli modelling can be achieved. Among the wide variety of simplified models in literature, also the Izhikevich model presented in [30] could improve our treatments by allowing a differentiation between cells belonging to different populations. Moreover, future work should therefore include the plasticity in communication strength among neurons, as well as the delay in synaptic transmissions by means of delayed ordinary differential equations. A final remark should be made on the computational structure of our model. The modularity of our approach is well suited to translate our integration engine into a parallel code to run on computer clusters or Graphics Processor Units (GPU). Therefore, one of the main targets of our future work is to design a simulation engine capable of real-time performance.

Bibliography

[1] M. Abele. *Corticonics: Neural Circuits of the Cerebral Cortex*. Cambridge University Press, 1991.

[2] J. S. Albus. A theory of cerebellar function. *Mathematical Biosciences*, 10(1-2):25–61, 1971.

[3] C. A. Anastassiou, R. Perin, H. Markram, and C. Koch. Ephaptic coupling of cortical neurons. *Nature Neuroscience*, 14(2):217–223, 2011.

[4] J. Baladron, D. Fasoli, O. Faugeras, and J. Touboul. Mean-field description and propagation of chaos in networks of Hodgkin-Huxley and FitzHugh-Nagumo neurons. *The Journal of Mathematical Neuroscience*, 2(1), May 2012.

[5] R. B. Bapat, D. Kalita, and S. Pati. On weighted directed graphs. *Linear Algebra Appl.*, 436(1):99–111, 2012.

[6] A. Barbera and S. Berrone. Bbtr: an unstructured triangular mesh generator. *Quaderni del Dipartimento di Matematica, Politecnico di Torino*, 2008.

[7] N. H. Barmack and V. Yakhnitsa. Functions of interneurons in mouse cerebellum. *J Neurosci*, 28(5):1140–52, 2008.

[8] N. Bellomo, L. Preziosi, and A. Romano. *Mechanics and Dynamical Systems with Mathematica*. Modeling and simulation in science, engineering & technology. U.S. Government Printing Office, 2000.

[9] M. Bezzi, T. Nieus, O. J. M. D. Coenen, and E. D'Angelo. An integrate-and-fire model of a cerebellar granule cell. *Neurocomputing*, 58-60:593–598, 2004.

[10] R. Brette and W. Gerstner. Adaptive Exponential Integrate-and-Fire Model as an Effective Description of Neuronal Activity. *J. Neurophysiol.*, 94:3637 – 3642, 2005.

[11] A. Citri and R. C. Malenka. Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 33(1):18–41, Jan. 2008.

[12] P. Colli Franzone and G. Savaré. Degenerate evolution systems modeling the cardiac electric field at micro- and macroscopic level. In *Evolution equations, semigroups and functional analysis (Milano, 2000)*, volume 50 of *Progr. Nonlinear Differential Equations Appl.*, pages 49–78. Birkhäuser, Basel, 2002.

[13] A. Destexhe, Z. F. Mainen, and T. J. Sejnowski. Synthesis of models for excitable membranes, synaptic transmission and neuromodulation using a common kinetic formalism. *Journal of Computational Neuroscience*, 1(3):195–230, 1994.

[14] S. Diwakar, P. Lombardo, S. Solinas, G. Naldi, and E. D'Angelo. Local field potential modeling predicts dense activation in cerebellar granule cells clusters under ltp and ltd control. *PLoS ONE*, 6(7):e21928, 07 2011.

[15] G. B. Ermentrout and D. H. Terman. *Mathematical Foundations of Neuroscience*. Springer, 1st edition, July 2010.

[16] A. Filippov. *Differential Equations with Discontinuous Righthand Sides*. Mathematics and its Applications. Kluwer Academic Publishers, 1988.

[17] R. FitzHugh. Impulses and physiological states in theoretical models of nerve membrane. *Biophysical Journal*, 1(6):445–466, 1961.

[18] R. FitzHugh. Motion picture of nerve impulse propagation using computer animation. *J Appl Physiol*, 25(5):628–30, 1968.

[19] M. Galarreta and S. Hestrin. Electrical synapses between gaba-releasing interneurons. *Nature Reviews Neuroscience*, 2(6):425–433, 2001.

[20] D. Gandolfi, P. Lombardo, J. Mapelli, S. Solinas, and E. D'Angelo. Theta-frequency resonance at the cerebellum input stage improves spike-timing on the millisecond time-scale. *Frontiers in Neural Circuits*, 7(64), 2013.

[21] W. Gerstner and W. Kistler. *Spiking Neuron Models: An Introduction*. Cambridge University Press, New York, NY, USA, 2002.

[22] D. Golomb and J. Rinzel. Dynamics of globally coupled inhibitory neurons with heterogeneity. *Phys. Rev. E*, 48:4810–4814, Dec 1993.

[23] A. Govindarajan, R. J. Kelleher, and S. Tonegawa. A clustered plasticity model of long-term memory engrams. *Nat Rev Neurosci*, 7(7):575–583, July 2006.

[24] J. Guckenheimer and P. Holmes. *Nonlinear oscillations, dynamical systems, and bifurcations of vector fields*. Applied mathematical sciences. Springer, New York, 2002.

[25] J. L. Hindmarsh and R. M. Rose. A model of neuronal bursting using three coupled first order differential equations. *Proceedings Of The Royal Society Of London. Series B, Containing Papers Of a Biological Character. Royal Society (Great Britain)*, 221(1222):87–102, 1984.

[26] A. Hodgkin and A. Huxley. A quantitative description of membrane current and its application in conduction and excitation in nerve. *J. Physiol.*, 117(4):500–544, 1952.

[27] A. L. Hodgkin. The local electric changes associated with repetitive action in a non-medullated axon. *The Journal of physiology*, 107(2):165–181, 1948.

[28] G. Ingram, I. Cameron, and K. Hangos. Classification and analysis of integrating frameworks in multiscale modelling. *Chemical Engineering Science*, 59(11):2171 – 2187, 2004.

[29] E. Izhikevich. *Dynamical Systems in Neuroscience*. Computational neuroscience. MIT Press, 2007.

[30] E. M. Izhikevich. Which model to use for cortical spiking neurons? *IEEE Transactions on Neural Networks*, 15(5):1063–1070, 2004.

[31] J. G. Jefferys. Electrical field effects: their relevance in central neural networks. *Physiological reviews*, 69(3):821–863, July 1989.

[32] J. G. Jefferys. Nonsynaptic modulation of neuronal activity in the brain: electric currents and extracellular ions. *Physiological reviews*, 75(4):689–723, Oct. 1995.

[33] E. Kandel, J. Schwartz, and T. Jessell. *Principles of Neural Science, Fourth Edition*. McGraw-Hill Companies,Incorporated, 2000.

[34] J. Keener and J. Sneyd. *Mathematical physiology*, volume 8 of *Interdisciplinary Applied Mathematics*. Springer-Verlag, New York, 1998.

[35] Y. Kuramoto. *Chemical Oscillations, Waves, and Turbulence*. Dover Books on Chemistry Series. Dover Publications, 2003.

[36] L. F. Lago-Fernández, F. J. Corbacho, and R. Huerta. Connection topology dependence of synchronization of neural assemblies on class 1 and 2 excitability. *Neural Networks*, 14(6-7):687–696, 2001.

[37] L. Lapicque. Recherches quantitatives sur l'excitation electrique des nerfs traitée comme une polarization. *Journal de Physiologie et Pathologie General*, 9:620–635, 1907.

[38] E. Marder. Electrical synapses: rectification demystified. *Current Biology : CB*, 19(1):R34–5, 2009.

[39] D. Marr. A theory of cerebellar cortex. *The Journal of Physiology*, 202(2):437–470, June 1969.

[40] C. Morris and H. Lecar. Voltage oscillations in the barnacle giant muscle fiber. *Biophysical journal*, 35(1):193–213, 1981.

[41] J. D. Murray. *Mathematical biology. Vol.1. An introduction*, volume 17 of *Interdisciplinary Applied Mathematics*. Springer-Verlag, New York, third edition, 2002.

[42] W. Rall. Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input. *Journal of neurophysiology*, 30(5):1138–1168, Sept. 1967.

[43] S. Sanfelici. Convergence of the Galerkin approximation of a degenerate evolution problem in electrocardiology. *Numer. Methods Partial Differential Equations*, 18(2):218–240, 2002.

[44] A. Scott. The electrophysics of a nerve fiber. *Review of Modern Physics*, 47(2):487–533, 1975.

[45] F. Simoes de Souza and E. De Schutter. Robustness effect of gap junctions between golgi cells on cerebellar cortex oscillations. *Neural Systems and Circuits*, 1(1):7, 2011.

[46] J. Smoller. *Shock waves and reaction-diffusion equations*, volume 258 of *Grundlehren der Mathematischen Wissenschaften [Fundamental Principles of Mathematical Science]*. Springer-Verlag, New York, 1983.

[47] S. Solinas. personal communication.

[48] S. Solinas, L. Forti, E. Cesana, J. Mapelli, E. De Schutter, and E. D'Angelo. Fast-reset of pacemaking and theta-frequency resonance patterns in cerebellar golgi cells: simulations of their impact in vivo. *Front Cell Neurosci*, 1:4, 2007.

[49] S. Solinas, L. Forti, E. Cesana, J. Mapelli, E. D. Schutter, and E. D'Angelo. Computational reconstruction of pacemaking and intrinsic electroresponsiveness in cerebellar golgi cells. *Front Cell Neurosci*, 1:2, 2007.

[50] S. Solinas, T. Nieus, and E. D'Angelo. A realistic large-scale model of the cerebellum granular layer predicts circuit spatio-temporal filtering properties. *Front Cell Neurosci*, 4:12, 2010.

[51] H. C. Tuckwell. *Introduction to Theoretical Neurobiology: Volume 2, Nonlinear and Stochastic Theories*. Cambridge University Press, 1988.

[52] P. Wallisch, M. Lusignan, M. Benayoun, T. I. Baker, A. S. Dickey, and N. G. Hatsopoulos. *Matlab for Neuroscientists*. Academic Press (Elsevier Inc.), Burlington, USA, 2009. An introduction to Scientific Computing in Matlab.

[53] Y.-C. Yu, S. He, S. Chen, Y. Fu, K. N. Brown, X.-H. Yao, J. Ma, K. P. Gao, G. E. Sosinsky, K. Huang, and S.-H. Shi. Preferential electrical coupling regulates neocortical lineage-dependent microcircuit assembly. *Nature*, 486(7401):113–117, 2012.