instytut biologii doświadczalnej
im. Marcelego Nenckiego PAN

Prof. dr hab. Daniel Krzysztof Wójcik
Laboratory of Neuroinformatics
Nencki Institute of Experimental Biology
of the Polish Academy of Sciences
02-093 Warsaw, Pasteur St. 3, Poland

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Review of the doctoral thesis by Mr. Damiano Gentiletti entitled "Computational modeling of epileptic seizures in the brain"

Epilepsy is among the top three brain disorders in terms of incidence. Despite years of studies its treatment remains elusive and the mechanisms leading to seizure initiation are still contested. In his thesis. Mr. Damiano Gentiletti, considers a computational model of epileptic seizure generation, development and termination, supported by recent experimental and clinical evidence, but going against the grain of dominating views in the field. I think the topic is important, the treatment is a good step towards explaining observed seizure dynamics, and **my general judgment of this research and the thesis is positive**.

The thesis consists of about 90 pages of text with some 50 illustrations supported by references to about 100 research works. The literature overview is adequate for the purposes of the thesis. The introduction is very brief mentioning shortly the nervous system and computational neuroscience but largely focusing on traditional and nontraditional aetiology of epilepsy using the known experimental results as the departure point for setting author's goals in this thesis. In particular, the author indicates that the traditional view where the seizure is a consequence of excitation/inhibition imbalance due to growing excitation with insufficient inhibition at the network level has recently been challenged. His goal is to study a recently proposed mechanism where the seizure is generated by imbalance of extra- and intracellular concentrations of the major ions, arising in consequence of increased activity of the interneurons. The study is computational but strongly informed by published experimental material and performed in collaboration with clinical and experimental team from Istituto Neurologico Carlo Basta in Milan, Italy. The experimental data which form the reference for the author are presented in some detail in the second chapter, where he introduces a specific experimental scenario which he attempts to reproduce within his computational work. He also presents the data which are his modeling target that is intracellular recordings within a pyramidal cell and an interneuron and extracellular potassium trace during a seizure. This chapter ends with biophysical explanation of the critical role of extracellular concentration of potassium for neuronal activity in general and for seizure generation in particular.

Author's results are presented in chapters 3 and 4 entitled "The minimal model" and "The extended model". The minimal model consists of two coupled two-compartment cells, one excitatory and one inhibitory, interacting with a glial buffer which is engaged in potassium uptake, in simulations where diffusion of potassium, sodium and chloride, through extracellular millieu, is tracked. Chapter 3 goes into detail describing cell biophysics and the reasons for the choosing the primitive morphologies, as well as synaptic and non-synaptic mechanisms affecting the system activity. The second half of Chapter 3 discusses the simulation results in the simple model comparing them with the experimental evidence. In particular, the author studies the dynamics of different ions within both cells as well as the effects of different K^+ clearing mechanisms on the dynamics and he shows that all four of them (glial buffer, diffusion, Na/K pump and differing ion concentrations) are needed to reproduce observed experimental behavior.

Chapter 4 is the pinnacle of the thesis. The author extends his basic model to four pyramidal cells, adds the possibility of cell swelling, increases the number of ion species that he tracks, and considers more complex models of ion exchanges between extracellular shells and calcium dynamics. More cells in the model gives an opportunity to consider more connections and indeed, all are used. After specifying the extensions introduced in the new model the author presents simulation results for the default model and shows that the model captures multiple qualitative features observed experimentally in the studied seizures. Several properties of the system are studied, such as the bursting mechanism, the mechanism of seizure termination, which was absent from the basic model, and the role of the newly introduced mechanisms in reproducing experimentally viable dynamics. The author observes that the model predicts exponential growth of inter-burst intervals which is consistent with experimental data from the studied preparation as well as for an epileptic patient. Finally, the author proposes a novel epilepsy therapy using nanoparticles for uptake of overaccumulated extracellular potassium.

In the final chapter called Conclusions the author briefly discusses the context of his work and his main results, trying to provide a synthetic overview of the mechanics of the studied seizure scenario. He also briefly considers some limitations of his work and possible future developments.

Overall I found this work interesting and reasonably convincing that the author has captured some main mechanisms of the studied seizure scenario. The model defined here is very interesting, going significantly beyond the bread and butter approaches of neuron simulations, including keeping track of multiple ionic species in different regions of space as well as allowing for volume changes of the cellular compartments while simulating voltage changes. I found the introduction and simulation of non-synaptic mechanisms in the system the strongest part of the thesis. There are relatively few typos in the work and editorial level is adequate. Figures are generally readable. Nevertheless, I was not completely happy with the developments and the presentations. Even if most my critical comments below are minor, I present them for completeness.

Criticism

The author is using LFP or local field potential without going into details of the definition. When he computes it, it is clear he means extracellular potential. LFP is usually defined as the low pass filtered extracellular potential, typically under 300 Hz. It is considered to largely carry synaptic information. The high part of the potential spectrum is called multi-unit activity and believed to carry information on spiking within the probed structure. In the present context it is rather fuzzy what is practical and what is and what should be used. Experimentally LFP is a population measure. In the model studied here, given maximum synchrony between the primary cells, the population signal is practically equal to extracellular signature of a single cell. Perhaps looking at the full spectral content makes sense. I think these semantic worries only matter really in Figure 4.25 where comparison between model and experimental data is provided. I have doubts how compatible are the data being compared here.

The results provided in the thesis are largely anecdotal. The author mentions that the experiments have been carried out multiple times resulting in multiple recordings. Only single recordings are shown here, however, and are typically matched with single simulation runs. This raises doubts regarding stability of the model and generality of the observations. The model could have been tuned so as to reproduce the unique recordings presented. There are no parameter scans, no stability checks, etc.

This anecdotal aspect of the thesis manifests in several ways. For example, on p. 59 the author writes "simulation results match in many regards the experimental data". Yes, but how do you quantify that? How can you show that the expanded model is better than the basic model (or the opposite)? Would it be better with more cells? with more complex morphology? Should we be satisfied with this model? How good agreement with experiment have we achieved? I miss any measures comparing the experimental and simulated results more directly in a way which would allow further improvement. I agree that the visual agreement is very good but how similar is similar?

Looking at Figure 4.8 I can see all pyramidal cells have very similar dynamics but I cannot say how similar or different they are. I cannot even say what is the difference between activities in the somatic and dendritic compartments within the same cell. They look the same. Are they?

The decision to leave some definitions, parameter values, and results in a recent preprint and not including them in the thesis is rather surprising to me. I have always believed that the papers should be succinct but the thesis gives an opportunity to expand on the results which could not have been presented in full in the paper. I found it rather strange that the author decided to do the opposite. Why not put them in an appendix?

Given that five years have passed from publication of the first paper containing the results on the basic model there was ample time to study scaling, larger network, parameter ranges, etc. For example, I miss a study of the model which has all the mechanisms as the extended model but with a single pyramidal cell with the two models studied here. What are the benefits of having four cells in the extended model rather than one? This is not clear to me given that they are all the same and strongly coupled. **I would find it interesting to see such a comparison at the defense.**

It is mentioned that the simulations are challenging but no mention of the architectures used for simulation and simulation times have been given so it is hard to estimate the actual computational demands. My feeling is that a simple scaling study investigating dynamics of the system with large, heterogeneous, not fully connected populations of pyramidal cells and interneurons should have been within reach of the candidate.

Figure 4.6 shows concentration of sodium, potassium and chloride within soma and dendrite and they are significantly different. Do you assume constant concentration within the full compartment and so discontinuous / step-wise distribution of ions? What about the extracellular potassium concentration, how can it be different for the soma and dendrite (Fig. 4.6 D)? Should I understand stratification of the extracellular space along the cellular morphology?

Despite this minor criticism, **I judge the doctoral thesis by Mr Damiano Gentiletti positively**. I believe the study of mechanisms of epileptic seizures is very important. The specific study selected here is interesting and the results are very promising. The amount of consistency does convince me of the viability of the obtained insight despite my complaints on the lack of broader evidence. **In my opinion this thesis satisfies all the usual and formal demands set out for** doctoral theses and I strongly support awarding doctoral degree to Mr Damiano Gentiletti. [Uważam, że rozprawa doktorska mgr. Damiano Gentilettiego spełnia warunki określone w art. 187 Ustawy z dnia 20 lipca 2018 r. o szkolnictwie wyższym i nauce (Dz. U. 2018 poz. 1668), dlatego zwracam się do Wysokiej Rady Dyscypliny Naki Fizyczne Uniwersytetu Warszawskiego o dopuszczenie mgr. Damiano Gentilettiego do dalszych etapów przewodu doktorskiego.]

Prof. Daniel K. Wójcik

Instytut Biologii Doświadczalnej im. Marcelego Nenckiego, Polska Akademia Nauk
ul. Ludwika Pasteura 3, 02-093 Warszawa, telefon: (48 22) 58 92 200
www.necki.gov.pl