



Implementation of Intra and Extracellular Nonperiodic Scale-Free Stimulation *in silico* for the NEURON Simulator

Heitor de Carvalho Barros Terra¹ , Fernando da Silva Borges^{2,3} ,
Marcio Flávio Dutra Moraes⁴ , and Vinícius Rosa Cota¹

¹ Laboratory of Neuroengineering and Neuroscience (LINNce), Universidade Federal de São João Del-Rei, Pça. Frei Orlando, 170 – Centro, São João Del-Rei, MG 36302-600, Brazil
vrcota@uftsj.edu.br

² Department of Physiology and Pharmacology, State University of New York Downstate Medical Center, New York, NY 11203, USA

³ Centro de Matemática, Computação e Cognição, Universidade Federal do ABC, Av. dos Estados, 5001 -Bangú, Santo André, SP 09210-580, Brazil

⁴ Núcleo de Neurociências (NNC), Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Av. Pres. Antônio Carlos, 6627 - Pampulha, Belo Horizonte, MG 31270-901, Brazil

Abstract. Electrical stimulation of the brain is a largely used alternative for the treatment of myriad neurological disorders. Although recognizably efficacious and safe, many details of the underlying mechanisms remain obscure. Our group devised and successfully tested, in animal models of epilepsy, a novel nonstandard form of electrical stimulation in which the intervals between pulses are randomized. Termed Nonperiodic Stimulation (NPS), it has been specifically tailored to suppress hypersynchronism supporting seizure generation. For a better understanding of the underpinnings of NPS, we sought to carry out *in silico* investigation, but we found no easy way to implement its temporal pattern in the very successful NEURON simulator, given the unconventional nature of our stimulus. In this work, we report two approaches devised and tested to implement NPS applied both intra and extracellularly using the NEURON simulator. Neuronal responses reproduced the distinct temporal patterns of stimulation in a high-fidelity fashion, while being influenced by both stimulus polarity and distance from electrode tip. These results suggest our solutions successfully implemented intra and extracellular NPS (as well as other temporal patterns of interest) and represent an early but essential step in enabling *in silico* investigation of the mechanisms of such neuromodulation method.

Keywords: NEURON platform · Intracellular · Extracellular · Electrical stimulation · NPS · Temporal-pattern

1 Introduction

Epilepsy is a serious neurological disorder affecting circa 1 to 2% of the world population [1]. Although pharmacological and surgical treatments are considerably effective,

circa 15% of the patients are unable to properly control their seizures [2]. A promising alternative in this case is the electrical stimulation (ES) of the brain, a method termed Deep Brain Stimulation (DBS), which is usually delivered as square pulses of current or voltage fired at a fixed rate to myriad different neural substrates [3]. Although DBS is a very promising neurotechnology, a less empirical and a more engineered-oriented development of such methods is much needed [4].

The design of a neuromodulation technology, for the treatment of any disorder, should always aim at reducing the energy transferred from the pulse generator to the tissue, for safety reasons and to increase the duration of batteries and electrodes [5]. Yet, virtually all DBS methods need high frequencies of operation (100 Hz and above) to properly attain therapeutic effect [6]. In fact, low frequencies have yielded controversial results in both human and animal experimentation [7]. To work around this issue, our group devised and successfully tested a novel approach of ES with robust anticonvulsant power while delivering only four pulses per second, with conventional amplitude and duration, and thus with very low energy ($\sim 0.100 \mu\text{C/s}$) [5, 8]. Termed Nonperiod Stimulation (NPS), our method constitutes of randomizing the intervals between pulses (IPI – interpulse intervals) following a natural-like scale-free pattern in which the distribution curve of values approximates a power law of unitary exponent [9]. The rationale behind NPS is that such a temporal pattern would impair hypersynchronous processes occurring in neural circuitry known to support epileptic phenomena, while having minor effects on healthy neural function. NPS applied to the basolateral amygdala has shown robust anticonvulsant effects against seizures in both animal models of acute [8] and chronic seizures [10], and it is maxed out when applied bilaterally in an asynchronous fashion [11].

Mechanistic investigation has also been carried out to suggest that NPS is capable of disrupting aberrant synchronization within and between afferences of the basolateral amygdala, putatively by randomly (thus in an out-of-phase fashion) recruiting them and consequently impairing their coupling [12–14]. Some additional evidence corroborates this line of reasoning: 1) synchronization of brain areas is attained by means of a shared rhythmic oscillation (in contrast to non-periodic activity) [15] and; 2) scale-free stimuli mimics natural-like input that entrains single neurons and small networks in high fidelity activity [16–18]. By this token, we have recently hypothesized that the never-repeating temporal patterns in NPS easily recruits distinct microcircuits in the neighborhood of the amygdala, entraining them in healthy activity and impairing their abnormal coupling, while at the same time competing with aberrant synchronization that underlies epileptic phenomena [9].

In order to properly assess these ideas, our group set out to perform *in silico* investigations of the mechanisms underlying NPS in different levels of brain organization. Particularly, testing the response of single cells or of small networks of neurons to NPS is important considering the previously mentioned features of such temporal pattern of stimuli. A biophysically realistic model such as the Hodgkin Huxley applied to anatomically correct cells using simulation software such as NEURON (from Duke University) is an obvious choice for such investigation. Yet, considering the very unusual form of stimulation, there are no tools within the simulator to reproduce our ES methods. Thus, in this work, we sought to implement a programmable add-on to simulate nonperiodic ES

both intra and extracellularly. Two different solutions were developed: 1) a *.hoc* file routine that creates a point-process for single pulse stimulation for each of the NPS pulses, and; 2) a NetPyne routine that creates NPS delivered from an extracellular point source within a small network of neurons and then performs the field propagation calculation to affect individual cells.

2 Methodology

2.1 Intracellular Stimulation Using Point-Processes

The point process is the way that NEURON uses to represent signal sources, such as localized membrane shunts, synapses, and electrodes [19]. So, one way to create a stimulus could be by using point processes. With this option in mind, our strategy was to choose a point process included in the NEURON environment that, with a specific configuration, could mimic the NPS temporal pattern.

To do that, we first created a very simple cell that would receive the stimulus. The cell created had only two compartments, a soma and an axon, both modeled by Hodgkin & Huxley equations. It is, in fact, a simplified cell to use in a computational model of the cellular level, but since the goal of this work is to implement a new wave stimulus and not to study the cellular behavior, this simple model was sufficient.

After creating the neuron, we attached the point process that would represent the electrode and stimulate the cell. The mechanism chosen to create the NPS stimulus was the “IClamp”, which injects current with a constant amplitude, duration, and delay. Of particular importance here, the delay variable represents the latency period since the beginning of the stimulation in which the current will actually be injected to the cell. IClamp mechanism does not provide an option to change the interval between pulses, just delays, frequency or pre-determined distributions among which the scale-free nature of NPS is not included. Thus, instead of using one electrode that fires in the temporal pattern, our strategy was to create several electrodes in the same position and with the same duration and amplitude, but each one with a different delay. By their turn, delays corresponded to the temporal pattern of NPS according to the original algorithm of generation [8]. This strategy was implemented in a HOC language routine and we achieved it by creating a vector that saves the times that the pulses should be injected. Using a for loop with the number of iterations equals to the length of the vector, that creates one “IClamp” point process per iteration, each one receiving a delay corresponding to one element of the vector created.

Total simulation time for the intracellular ES was ten seconds (10000 ms) and the initial potential was set as -65 mV.

2.2 Extracellular Stimulation Using Field Propagation

The NEURON environment does not have an option for extracellular stimulation. The only alternative is the extracellular mechanism, which adds an additional layer to the equivalent circuit corresponding to the extracellular milieu. With this extra layer (which

can be adjusted to the interest of the research), the extracellular potential can be influenced by an electric current while without it, the potential would be considered to be zero for all its extension.

In order to implement the extracellular ES, we had to use the extracellular mechanism to model an extracellular field that would be responsible for propagating the potential across all the space outside the membrane. Furthermore, since the NEURON environment does not have an option for an extracellular electrode, we also created a function to simulate the behavior of having a current injected extracellularly. This was achieved by choosing a position for the hypothetic electrode, calculating the distance between it and each cell of the network, and creating an equation that represents the decay rate of the electrical potential.

To implement all these strategies, we used the NetPyNE package and Neuron library on a colab notebook [20]. With the NetParams block from the NetPyNE package, we created a network of 50 pyramidal cells, in which 40 of them are excitatory and 10 are inhibitory (Fig. 1). The position of cells was randomly set inside a $250 \times 400 \times 250$ μm space, while the electrode position (in blue) was set to be (250, 250, 250) for x, y, and z axes respectively.

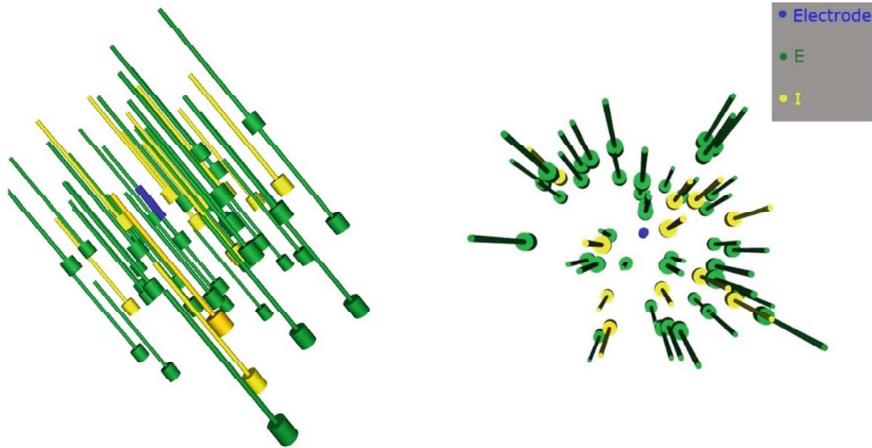


Fig. 1. Reconstruction of the network of simple neurons used for the simulation of extracellular stimulation using NetPyNE GUI. Green cells are excitatory and yellow cells are inhibitory, having their soma represented by a larger cylinder and the axon by a thinner cylinder. Electrode tip is shown at the center by a small blue cylinder. (Color figure online)

The soma compartment of each cell, inhibitory and excitatory, had the Hodgkin & Huxley and the extracellular mechanism inserted. The dendrites were modeled by the passive mechanism. The connectivity rules were set to each cell to have 0.1 probability of being connected to any other cell. Figure 2 shows the connectivity of the network. The creation of the external field was made using the “numpy.vectorize” function to insert all the calculated potential values of each cell into a vector. To insert the NPS extracellularly, we created a numpy array with the wave time stamps and multiplied it

to the extracellular field. By doing this, we got a vector with different weights for each cell, multiplied by another vector with a fix amplitude for each time stamp of the NPS stimulus. A total of 5 s (5000 ms) was simulated.

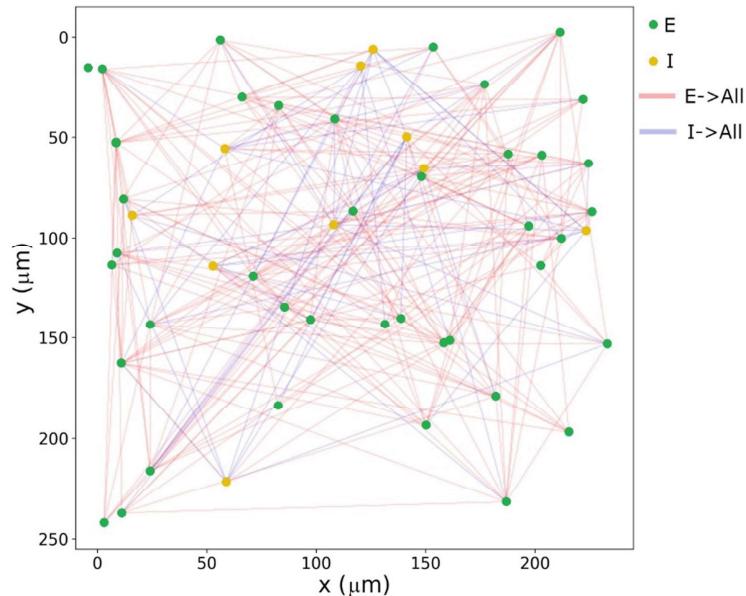


Fig. 2. Connectivity of the network created. Excitatory cells (green circles) send excitatory afferences (pink lines) to several other neurons, while inhibitory cells (yellow circles) project inhibitory afferences (blue lines), both with a 10% probability. (Color figure online)

2.3 Temporal-Patterned Stimuli

To test and compare the cellular responses to stimuli, we created three more ES temporal patterns, aside from the NPS described earlier: burst, periodic, and another form of nonperiodic stimulus, called NPSLH. The burst pattern consisted of a wave with four pulses per second and IPI of 20 ms. The periodic stimulus also had four pulses per second, but with a constant IPI of 250 ms. The NPSLH, differently from the NPS, did not have a distribution of IPI values that approximates a power law of unitary exponent, but that of a linear decay. In original animal studies, NPSLH was not effective in suppressing seizures. Histograms of IPI distributions for each of the tested temporal pattern is showed in Fig. 3.

Also, as a way to help the validation of the model created, we tested both types of current, anodic and cathodic. The cathodic intracellular stimulations should depolarize the cell and the anodic, hyperpolarize it. For the extracellular stimulations, the opposite should happen, even though both polarities can induce the firing of action potentials by different mechanisms. Moreover, as the stimulus intensity decays with distance from the tip, it is expected that neurons closer to the electrode will have a greater tendency to fire.

Intracellular current pulses had 3 nA and 100 μ s of width. Extracellular pulses were 25 μ s in width, but with variable amplitude (supra- and subthreshold). On both cases, there was no background noise.

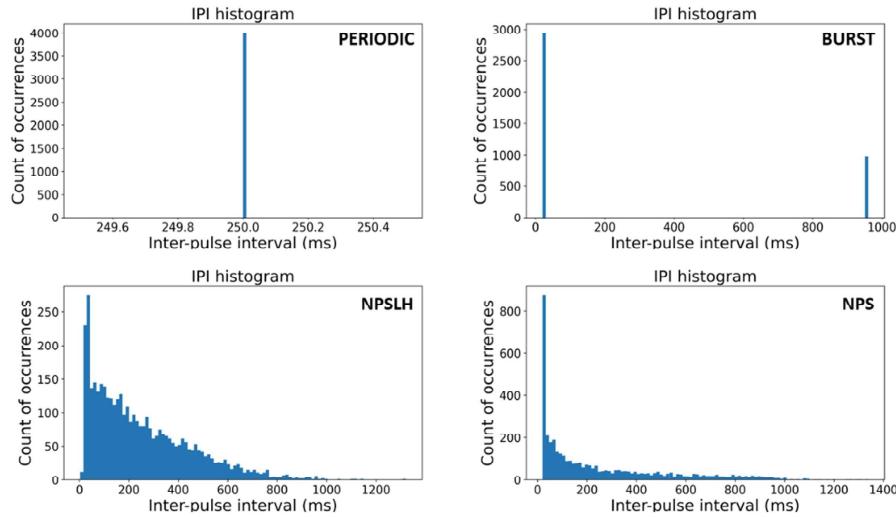


Fig. 3. Histograms of IPI distributions for each of the temporal pattern generated for both the intra and the extracellular stimulations: periodic (top left), burst (top right), NPSLH (bottom left), and NPS (bottom right).

3 Results

3.1 Single Neuron Response to Intracellular Stimulation

Responses to the intracellular stimulation are shown in Fig. 4 and in Fig. 5, which show the cellular responses for the cathodic and anodic stimulations, respectively. As Fig. 4 shows, the neuron responded in a high-fidelity one cathodic pulse (red diamonds) to one action potential fashion and, thus, faithfully reproduced the temporal-pattern being applied. Analogously, anodically-stimulated cells (Fig. 5) also responded in a one-to-one fashion. This was of course expected, given we purposefully chose a suprathreshold current applied to a simple cell without any other kind of background noise. All panels of both figures contain insets with isolated representative action potentials generated after stimulus. They are all stereotypical in morphology, with depolarization, repolarization, and hyperpolarization phases. On the other hand, only when anodic pulses are applied, action potential are preceded by a hyperpolarizing electronic potential. This suggest action potentials are fired by different mechanisms.

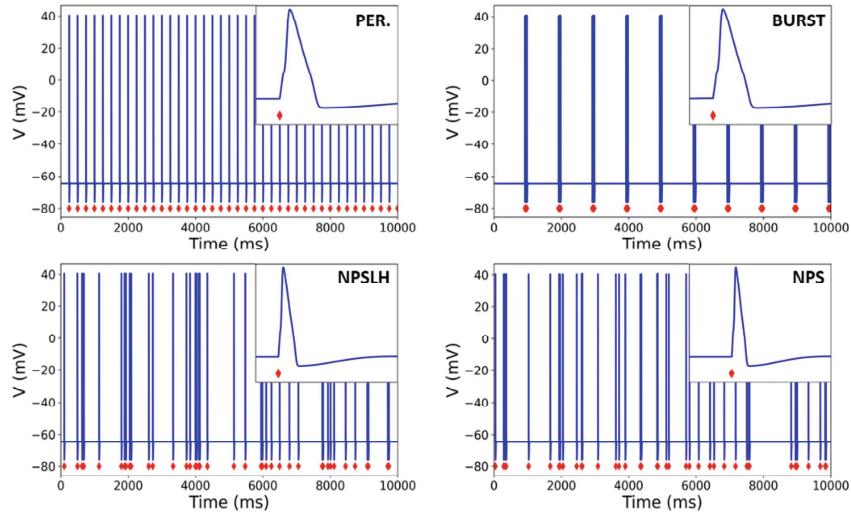


Fig. 4. Cellular response of the neuron to the four intracellular cathodic stimulation patterns. Red diamonds depict time points when stimulation pulses were applied. Insets display stereotypical action potentials generated in each case. Stimulation was periodic (top left), burst (top right), NPSLH (bottom left), and NPS (bottom right). (Color figure online)

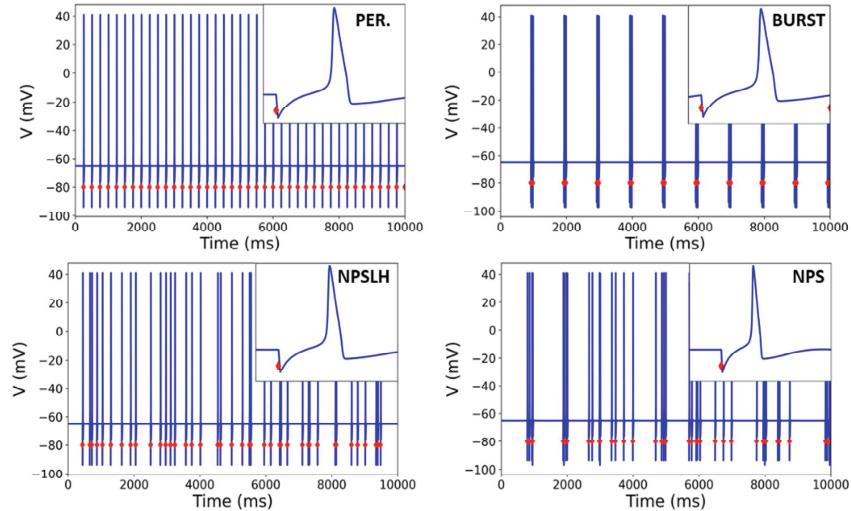


Fig. 5. Cellular response of the neuron to the four intracellular anodic stimulation patterns. Red diamonds depict time points when stimulation pulses were applied. Insets display stereotypical action potentials generated in each case. They were preceded by hyperpolarizing electrotonic potentials. Stimulation was periodic (top left), burst (top right), NPSLH (bottom left), and NPS (bottom right). (Color figure online)

3.2 Network Response to Extracellular Stimulation

Figures 6 and 7 depict the time course of the membrane potential of responsive (blue) and non-responsive (orange) cells, in terms of firing action potentials, when submitted to anodic and cathodic pulses, respectively. Notice the high-fidelity firing of action potentials to the different temporal patterns of stimulation for both cells. When undergoing anodic stimulation, while the responsive cell fires an action potential for each stimulus pulse, non-responsive cell responds only with a depolarizing subthreshold potential (Fig. 6). Insets in all of the panels show action potential waveforms in which both cells display initial depolarizing potentials, but of different magnitudes. Curiously, the burst temporal pattern has both kinds of response in the same cell, firing an action potential after the first pulse and only depolarizing electrotonic potentials for the other three pulses. One possibility is that this may be due to a polysynaptic effect in the network that causes the cancelling of potentials to a subthreshold threshold sum.

Similar results were obtained when the network was submitted to cathodic stimuli (Fig. 7). On the other hand, as insets show, both cells are preceded by a hyperpolarizing electrotonic potential. Again, burst stimulus was followed by the firing of an action potential only after the first pulse in the train. Integration of post-synaptic potentials in the network may also be in place here.

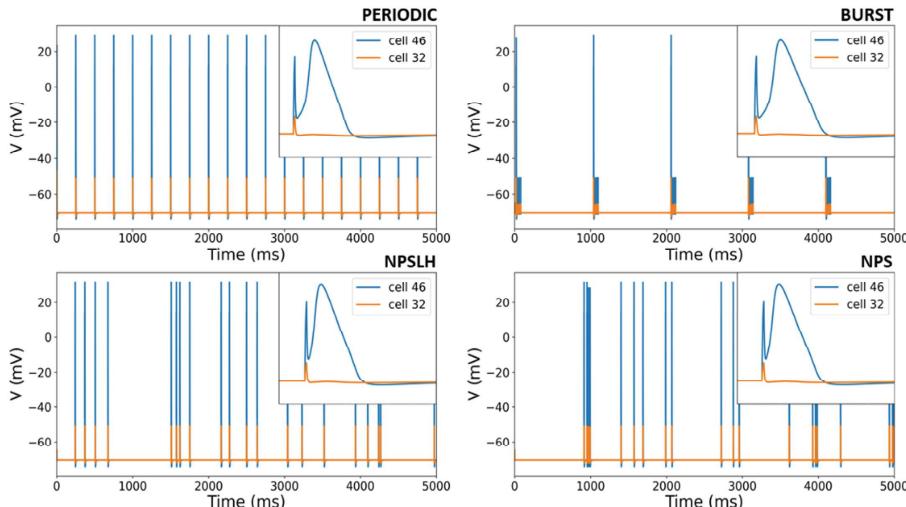


Fig. 6. Membrane potential of a responsive (blue) and a non-responsive (orange) neuron to the extracellular anodic stimulation. Notice in the insets the presence of an initial depolarizing electrotonic potential. (Color figure online)

Stimulus amplitude was chosen carefully in order to evoke action potentials in some cells and not in the other ones. In this way, we were able to show the two types of responses, sub and suprathreshold. A major determinant for this difference is the distance from the electrode tip. In order to verify this factor, we performed an additional simulation with a smaller network composed of 25 cells randomly located also inside a $250 \times 400 \times$

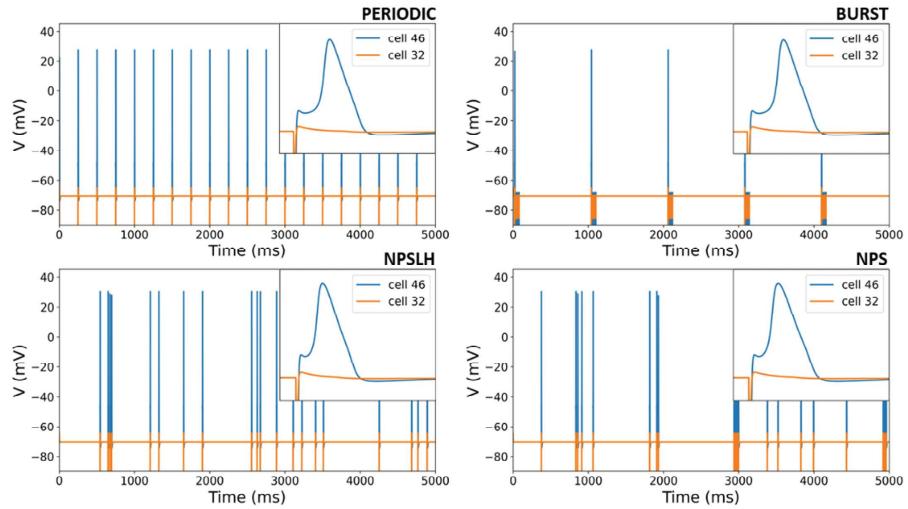


Fig. 7. Membrane potential of a responsive (blue) and a non-responsive (orange) neuron to the extracellular cathodic stimulation. Notice in the insets the presence of an initial hyperpolarizing electrotonic potential. (Color figure online)

250 μm space with an electrode positioned at (0, 0, 125) for x, y, and z axes, respectively (Fig. 8, left). Responsive (firing) cells, highlighted in thick blue, tend to be closer to the electrode tip when compared to silent cells in magenta (Fig. 8, right). Position of cells on the other axes and polysynaptic effects are additional factors here.

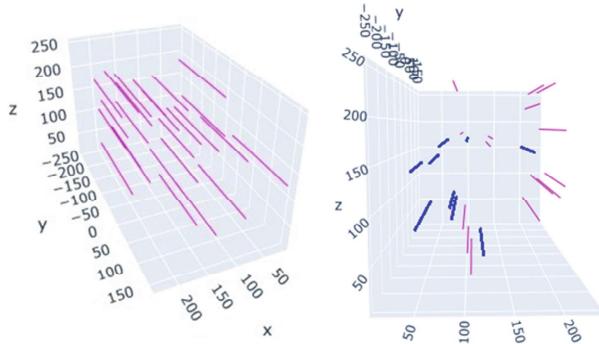


Fig. 8. A network of 25 randomly positioned neurons submitted to extracellular stimulation from a point source located in the middle of the y-z plane. Cells responding with an action potential are highlighted in blue, while non-responsive cells are depicted in magenta (right panel). Activated neurons tend to be closer to the electrode tip. (Color figure online)

4 Discussion and Conclusions

The primary objective of this work was to implement a solution to perform both intracellular and extracellular electrical stimulation with nonconventional temporal patterns of firing of pulses inside the NEURON simulator. The driving goal was to be able to simulate NPS and compare it to other temporal patterns used in previous *in vivo* studies and, thus, to get better insight of the mechanisms underlying the therapeutic efficacy of our neuromodulation method, given the obvious advantages of *in silico* experimentation. Considering that the time stamps of pulses in NPS (and also NPSLH) stimuli cannot be easily determined by simple mathematical formulation, there was no easy nor straightforward way to implement such computational experiment.

To the extent of our knowledge, the vast majority of therapeutic electrical neuromodulation approaches employ fixed high-frequency pulsatile methods. Only a few have tried modifying the temporal structure of stimuli to treat experimental epilepsy [5, 8, 9, 21–24] or motor disorders in pre-clinical and clinical trials [25–28]. Among these studies, at least one group has developed solid supporting theoretical work with computational neuroscience methods. A pioneering *in silico* investigation using network of oscillators has shown that stimulation, in which its temporal structure is tailored to specifically disrupt hypersynchronization, has the potential to be highly beneficial in disorders characterized by this hallmark (mainly Parkinson’s disease and epilepsy) [29]. Several *in silico* studies of the same group using an approach inspired on these ideas (termed Coordinate Reset or CR) were carried out to understand the nuts and bolts of its desynchronizing effects, recently showing the relative irrelevance of the number of stimulation sites and the benefits of introducing jitter noise in inducing neural plasticity for the stabilization of synchronism levels [30–37]. Recently, they simulated networks of leaky integrate-and-fire (LIF) neurons submitted to ES with randomized temporal patterns and also locations, in a variant technique termed L/M-Random Reset [38]. They found out that such an approach induced plasticity and long-lasting effects (i.e., after stimuli terminated), while high-frequency stimuli did not. Although representing a remarkable advance in the theoretical investigation of the neurophysics of temporal structure of pulsatile neurostimulation, these studies do not provide a set of tools that can be transferred to the research on NPS. Not only temporal patterns are different, but also, they were not implemented in the NEURON simulator, which is of major importance, given the possibility of running biophysically realistic simulations.

In this work, we report initial results showing the solutions found for each type of stimulation, which were tested intracellularly on isolated neurons or extracellularly on small networks, using both cathodic and anodic pulses (known to have differential effects on neuronal activation). As expected, neurons responded according to what have been initially postulated, in a high-fidelity mode such as could be predicted by the well-established neurophysics of stimulation in a very well-controlled condition, such as this. In fact, the dependency of the nature of responses (presence of action potentials and directions of membrane voltage deflections) on the different polarities applied (cathodic and anodic) and also on the distance from electrode tip within the network of neurons were strong indicators that the implemented code is properly working. Moreover, neurons fired action potentials (or electrotonic potentials) in a high-fidelity mode reproducing the

temporal pattern used for stimulation, adding further evidence that the solutions found are efficacious.

One important limitation of solutions presented here is the fact that the intracellular implementation of NPS does not scale well for longer periods of stimulation, once four new IClamp point processes have to be added for each neuron and each second. Although this is not a major concern to our own research, in which we pursue the replication of short-time *in vivo* experiments (few minutes), this may be a real issue if one is aiming at simulating many hours of stimulation and neuronal activity. In any case, we are pursuing an optimal solution for this issue, which may be attained by completely rewriting the point process using *.mod* routines. Furthermore, additional experiments could certainly help in establishing the quality of present solutions. These includes obtaining intensity versus duration curves for the determination of rheobase current and chronaxie, delineation of activation threshold curves for anodic versus cathodic pulses, and investigation of the effects of the electrode position in relation to the cell (closer to soma or axon). On the other hand, given such experimentation is highly constrained to a sophistication of the current models of the cell and the network, it was postponed to a later phase in our studies.

In our understanding, although representing a very early stage, these initial results are of considerable importance to biophysically realistic *in silico* investigation of NPS and other nonstandard forms of electrical stimulation applied to epilepsy phenotypes, once it benefits from a very well-developed simulator in computational neuroscience. With these novel tools, we expect to be able of reproducing all the previous *in vivo* experiments, now, computationally. All code is freely available and links will be shared upon request to authors. As for the improvements and perspectives, we are already pursuing to implementing more realistic models of neuronal cells from areas of interest (e.g., basolateral amygdala, subthalamic nuclei, and hippocampal CA1) to investigate, with appropriate measures of synchronization, the application of temporally coded ES on them isolatedly or embedded in cytoarchitectonic-realistic microcircuits. We are positive that such endeavor will provide great insights into the therapeutic mechanisms underlying NPS in particular and ES in general.

Acknowledgment. We are grateful to Héctor Julian Tejada for all discussions that helped us develop this work, to Monica Bell Vila for sharing part of her code and help implementing it, and to FAPEMIG (Fundação de Amparo à Pesquisa do Estado de Minas Gerais) for the financial support.

References

1. Thurman, D.J., et al.: Standards for epidemiologic studies and surveillance of epilepsy. *Epilepsia* **52**, 2–26 (2011)
2. French, J.A.: Refractory epilepsy: clinical overview. *Epilepsia* **48**, 3–7 (2007)
3. Montgomery, E.B., Jr.: Deep Brain Stimulation Programming. Birmingham, Oxford (2010)
4. Sunderam, S., Gluckman, B., Reato, D., Bikson, M.: Toward rational design of electrical stimulation strategies for epilepsy control. *Epilepsy Behav.* **17**, 6–22 (2010)

5. Cota, V.R., Drabowski, B.M.B., Oliveira, J.C., Moraes, M.F.D.: The epileptic amygdala: toward the development of a neural prosthesis by temporally coded electrical stimulation. *J. Neurosci. Res.* **94**(6), 463–485 (2016)
6. Viswas, D., Limousin, P., Foltyne, T.: Subthalamic nucleus deep brain stimulation in Parkinson's disease: the effect of varying stimulation parameters. *J. Parkinson's Dis.* **7**(2), 235–245 (2017)
7. Klinger, N.V., Mittal, S.: Clinical efficacy of deep brain stimulation for the treatment of medically refractory epilepsy. *Clin. Neurol. Neurosurg.* **140**, 11–25 (2016)
8. Cota, V.R., Mesquita, M.B.S., Medeiros, D.C., Richardson, M.P., Williams, S., Moraes, M.F.D.: Distinct patterns of electrical stimulation of the basolateral amygdala influence pentylenetetrazole seizure outcome. *Epilepsy Behav.* **14**(1) (2009)
9. Cota, V.R., Oliveira, J.C., Damázio, L.C.M., Moraes, M.F.D.: Nonperiodic stimulation for the treatment of refractory epilepsy: applications, mechanisms, and novel insights. *Epilepsy Behav.* **121**, 106609 (2019)
10. Oliveira, J.C., Medeiros, D.C., Rezende, G.H.S., Moraes, M.F.D., Cota, V.R.: Temporally unstructured electrical stimulation to the amygdala suppresses behavioral chronic seizures of the pilocarpine animal model. *Epilepsy Behav.* **36**, 159–164 (2014)
11. Oliveira, J.C., Maciel, R.M., Moraes, M.F.D., Cota, V.R.: Asynchronous, bilateral, and biphasic temporally unstructured electrical stimulation of amygdala enhances the suppression of pentylenetetrazole-induced seizures in rats. *Epilepsy Res.* **146**, 1–8 (2018)
12. Mesquita, M.B.S., Medeiros, D.C., Cota, V.R., Richardson, M.P., Williams, S., Moraes, M.F.D.: Distinct temporal patterns of electrical stimulation influence neural recruitment during PTZ infusion: an fMRI study. *Prog. Biophys. Mol. Biol.* **105**(1–2), 109–118 (2011)
13. Medeiros, D.C., Cota, V.R., Vilela, M.R.S.P., Mourão, F.A.G., Massensini, A.R., Moraes, M.F.D.: Anatomically dependent anticonvulsant properties of temporally-coded electrical stimulation. *Epilepsy Behav.* **23**(3), 294–297 (2012)
14. Oliveira, J.C., Drabowski, B.M.B., Rodrigues, S.M.A.F., Maciel, R.M., Moraes, M.F.D., Cota, V.R.: Seizure suppression by asynchronous non-periodic electrical stimulation of the amygdala is partially mediated by indirect desynchronization from nucleus accumbens. *Epilepsy Res.* **154**, 107–115 (2019)
15. Donoghue, T., Schawronkow, N.: Methodological considerations for studying neural oscillations. *Eur. J. Neurosci.*, 1–26 (2021)
16. Mainen, Z.F., Sejnowsky, T.J.: Reliability of spike timing in neocortical neurons. *Science* **268**, 1503–1507 (1995)
17. Gal, A., Marom, S.: Entrainment of the intrinsic dynamics of single isolated neurons by natural-like input. *J. Neurosci.* **33**(18), 7912–7918 (2013)
18. Scarsi, F., Tessadri J., Chiappalone M., Pasquale V.: Investigating the impact of electrical stimulation temporal distribution on cortical network responses. *BMC Neurosci.* **18**, 49 (2017)
19. Carnevale, N.T., Hines, M.L.: The Neuron Book. New Haven, Cambridge (2004)
20. Dura-Bernal, S., et al.: NetPyNE, a tool for data-driven multiscale modeling of brain circuits. *Elife* **8**, e44494 (2019)
21. Wyckhuys, T., Boon, P., Raedt, R., Van Nieuwenhuyse, B., Vonck, K., Wadman, W.: Suppression of hippocampal epileptic seizures in the kainate rat by Poisson distributed stimulation. *Epilepsia* **51**, 2297–2304 (2010)
22. Nelson, T.S., et al.: Exploring the tolerability of spatiotemporally complex electrical stimulation paradigms. *Epilepsy Res.* **96**, 267–275 (2011)
23. Buffel, I., et al.: The effect of high and low frequency cortical stimulation with a fixed or a Poisson distributed interpulse interval on cortical excitability in rats. *Int. J. Neurol. Syst.* **24**, 1430005 (2013)

24. Santos-Valencia, F., Almazán-Alvarado, S., Rubio-Luviano, A., Valdés-Cruz, A., Magdaleno-Madrigal, V.M., Martínez-Vargas, D.: Temporally irregular electrical stimulation to the epileptogenic focus delays epileptogenesis in rats. *Brain Stimul.* **12**, 1429–1438 (2019)
25. Dorval, A.D., Kuncel, A.M., Birdno, M.J., Turner, D.A., Grill, W.M.: Deep brain stimulation alleviates parkinsonian bradykinesia by regularizing pallidal activity. *J. Neurophysiol.* **104**, 911–921 (2010)
26. Birdno, M.J., Kuncel, A.M., Dorval, A.D., Turner, D.A., Gross, R.E., Grill, W.M.: Stimulus features underlying reduced tremor suppression with temporally patterned deep brain stimulation. *J. Neurophysiol.* **107**, 364–383 (2012)
27. Grill, W.M.: Temporal pattern of electrical stimulation is a new dimension of therapeutic innovation. *Curr. Opin. Biomed. Eng.* **8**, 1–6 (2018)
28. Tass, P.A., et al.: Coordinated reset has sustained aftereffects in Parkinsonian monkeys. *Ann. Neurol.* **72**, 816–820 (2012)
29. Tass, P.A.: A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopulations. *Biol. Cybern.* **89**, 81–88 (2003)
30. Hauptmann, C., Popovych, O., Tass, P.A.: Multisite coordinated delayed feedback for an effective desynchronization of neuronal networks. *Stoch. Dyn.* **5**, 307–319 (2005)
31. Hauptmann, C., Popovych, O., Tass, P.A.: Effectively desynchronizing deep brain stimulation based on a coordinated delayed feedback stimulation via several sites: a computational study. *Biol. Cybern.* **93**, 463–470 (2005)
32. Hauptmann, C., Tass, P.A.: Cumulative and after-effects of short and weak coordinated reset stimulation: a modeling study. *J. Neural Eng.* **6**, 016004 (2009)
33. Buhlmann, J., Hofmann, L., Tass, P.A., Hauptmann, C.: Modeling of a segmented electrode for desynchronizing deep brain stimulation. *Front. Neuroeng.* **4**, 15 (2011)
34. Ebert, M., Hauptmann, C., Tass, P.A.: Coordinated reset stimulation in a large-scale model of the STN-GPe circuit. *Front. Comput. Neurosci.* **8**, 154 (2014)
35. Manos, T., Zeitler, M., Tass, P.A.: How stimulation frequency and intensity impact on the long-lasting effects of coordinated reset stimulation. *PLoS Comput. Biol.* **14**, e1006113 (2018)
36. Kromer, J.A., Khaledi-Nasab, A., Tass, P.A.: Impact of number of stimulation sites on long-lasting desynchronization effects of coordinated reset stimulation. *Chaos* **30**, 083134 (2020)
37. Khaledi-Nasab, A., Kromer, J.A., Tass, P.A.: Long-lasting desynchronization effects of coordinated reset stimulation improved by random jitters. *Front Physiol.* **10**, 1446 (2021)
38. Khaledi-Nasab, A., Kromer, J.A., Tass, P.A.: Long-lasting desynchronization of plastic neural networks by random reset stimulation. *Front Physiol.* **11**, 1843 (2020)