Delayed feedback for pulsatile electrical brain stimulation

Oleksandr V. Popovych[1], **Borys Lysyansky**[1], **Peter A. Tass**[2]

[1] *Institute of Neuroscience and Medicine - INM-7, Research Centre Jülich, Jülich, Germany (e-mail: o.popovych@fz-juelich.de, b.lysyansky@fz-juelich.de)*
[2] *Department of Neurosurgery, Stanford University, Stanford, CA, USA (e-mail: ptass@stanford.edu)*

Recent pre-clinical and clinical studies have shown that closed-loop adaptive deep brain stimulation (DBS) is a promising approach for the treatment of Parkinsons disease. The stimulation is administered to the extent and when necessary, for example, based on the ongoing neuronal activity as reflected by dynamics of the local field potential (LFP) measured via the implanted electrode. Under several test conditions, such a closed-loop stimulation setup can reduce the amount of the administered stimulation while maintaining or even improving the clinical effects. The closed-loop stimulation setup is naturally realized by delayed feedback methods designed for desynchronization of abnormal neuronal synchronization characteristic for Parkinsons disease, epilepsy, tinnitus and other neurological disorders. We computationally adapt and test delayed feedback methods for electrical brain stimulation. For this, the smooth feedback signals are used to modulate the amplitude of biphasic charge-balanced electrical pulses of the standard high-frequency (HF) DBS appropriate for electrical stimulation of the neuronal tissue. Single- and multi-site linear and nonlinear pulsatile delayed feedback techniques are tested and compared with each other and to the standard HF DBS on physiologically-motivated model network comprising neurons from subthalamic nucleus (STN) and external globus pallidus (GPe). We show that pulsatile delayed feedback methods can effectively desynchronize the STN-GPe network of model neurons, which is a robust effect with respect to parameter variation [1, 2]. We also show that an interphase time gap introduced between the recharging cathodic and anodic phases of the pulses can significantly improve the stimulation-induced desynchronization and reduce the amount of the administered stimulation [2, 3]. For the considered model, pulsatile nonlinear delayed feedback can require less stimulation current as compared to pulsatile linear delayed feedback, in particular, for the interphase gap of intermediate width [1, 2]. The efficacy of multi-site linear delayed feedback can be improved if a differential feedback signal is used such that its efficacy closely approaches that of single-site linear delayed feedback [3]. All considered delayed feedback methods are much more efficient in counteracting abnormal neuronal activity as compared to the standard HF DBS. In summary, the considered delayed feedback methods preserve their desynchronizing properties also in the case when the smooth feedback stimulation signal is replaced by a high-frequency pulse train of charge-balanced pulses with modulated amplitude. Our results can contribute to the development and optimization of the closed-loop brain stimulation methods, and pulsatile delayed feedback stimulation techniques can be suggested for pre-clinical and clinical tests for suppression of abnormal neuronal synchronization in the framework of closed-loop adaptive DBS.

[1] Popovych O. V., Lysyansky B., Rosenblum M., Pikovsky A., Tass P. A., Pulsatile desynchronizing delayed feedback for closed-loop deep brain stimulation, *Public Library of Science ONE* **12**(3):e0173363, 2017.

[2] Popovych O. V., Lysyansky B., Tass P. A., Closed-loop deep brain stimulation by pulsatile delayed feedback with increased gap between pulse phases, *Scientific Reports* **7**(1):1033, 2017.

[3] Popovych O. V., Tass P. A., Multisite delayed feedback for electrical brain stimulation, *Frontiers in Physiology* **9**:46, 2018.