Editorial Annual Reviews in Control 2022 – special section on "Analysis and control design for neurodynamics"

Sérgio Pequito, Erfan Nozari, and Fabio Pasqualetti

September 2022

Neurotechnologies bring the potential to unlock new treatments for neurological diseases and disorders. They have inspired, and continue to do so, many companies and start-ups to engineer new devices that enable interaction with the neural substrate with precision and coverage previously unattainable. Furthermore, algorithmic advances in machine learning and artificial intelligence have provided a groundbreaking opportunity for efficient classification and inference from data. Yet, in contrast to several other by-now classical applications (e.g., image and natural language processing), such tools' success is limited in neurotechnology. The main reasons are threefold: (i) low amount of data available to train the models and the tight limits imposed by on computational power available for training the models at wearable devices (ii) large subject intra- and inter-variability leading to lack of transferable models between subjects aggravated by artifacts; and (iii) lack of interpretability and explainability of the algorithmic models in the neuroscience and medical domain.

To mitigate neurological diseases and disorders, we must be able to interact with the neural substrate by, for instance, performing neurostimulation. Nowadays, neurotechnologies capable of neurostimulation entail one or multiple modalities: electrical, optogenetics, magnetic, or ultrasound. In clinical applications, electrical neurostimulation is the principal methodology and is often used in open-loop, i.e., a stimulation scheme is (a priori) selected without taking into consideration the present state of the neural activity in the hope of mitigating a specific neurological condition. The success of this strategy is thin, and different communities have already agreed that the solution must be closed-loop. Simply speaking, by closed-loop, we mean that based on a particular state of the neural system, a stimulus is selected to be deployed into the neural substrate to change it to another state. That said, and unfortunately, almost all current closed-loop neurotechnologies rely on the so-called responsive closed-loop stimulation, where "if-then" rules are considered for the stimulus selection and, therefore, cannot infer how exactly the current state is going to change. Instead, we need a paradigm shift that uses predictive closed-loop control to be deployed in an iterated fashion and aims at crafting the ongoing state of the neural system towards a desirable state through a sequence of timely crafted stimuli used to interact with the neural substrate. Notice that a desirable state may not be attainable, but at least one should strive to guarantee that a given set of states are avoidable. In this special section, we provide a collection of five papers that state and overview some of the main challenges and developments toward effective predictive closed-loop control.

Despite the promise of new neurostimulation devices, currently approved devices for medical treatment are still limited. Deep brain stimulation (DBS) is used by over 100000 patients worldwide [17] to mitigate the effects of Parkinson's disease (PD) [2, 12] and other neurological disorders including depression [20], Alzheimer's disease [14], Tourette syndrome [25], epilepsy [16], and obsessive-compulsive disorder [10]. From a purely biophysical perspective, the action of DBS is relatively well-understood, with DBS pulses inducing some combination of activation or inhibition in the neurons adjacent to the probe [1, 21]. By contrast, the dynamical mechanisms that influence the aggregate behavior of large populations of neurons are not well understood, leading to many open questions and control problems associated with DBS as a therapeutic treatment. In [5], the authors provide a compelling review on how to control aggregate oscillations that emerge in large populations of coupled neurons which are often modeled using conductance-based ordinary differential equations (ODEs) to describe the flow of current across a cell membrane [8]. Evidence suggests that pathological synchronization among neurons in the basal ganglia contributes to the motor control symptoms of PD, and that DBS helps to restore normal function by disrupting this synchronization [13, 15, 3]. Therefore, the authors focus mainly on the desynchronization of a pathologically synchronized population of neural oscillators. In pursuit of this control objective, a variety of model order reduction, analysis, and control techniques were developed in recent years that can be applied to large populations of coupled, periodically firing neurons. Nonetheless, objectives including entrainment, phase randomization, synchronization, and clustering, are also reviewed due to their relevance in neural control applications.

Motivated by ideas from impedance control in robotics [11], where the idea is to design a controller that shapes the mechanical impedance of the closed-loop system to comply with the environment, the authors in [23] shows how the same philosophy can be useful to control a neurological system. In particular, they leverage the well-established framework of conductance-based modeling both for the controller and for the system to be controlled in the context of conductance-based neural networks in which each neural node is a one-port circuit composed of one leaky capacitor in parallel with a bank of linear and nonlinear ohmic sources of variable conductance. The controller is itself an additional set of ohmic current sources connected in parallel to those of the neuron. Most of the involved conductances are voltage- and/or time-dependent, gating the current flow in a specific temporal and amplitude window. As such, the goal is to use adaptive control to attain maximal conductances of a conductance-based model that is aligned with the concept of neuromodulation, which is of crucial importance in the biological control of neuronal systems [18, 26, 6].

Nonetheless, the use of neurotechnology brings fundamental problems on how to model neural dynamics (and its networks) using state space representations, and what control objective one should consider to attain a desirable clinical outcome. Thus, a challenge and opportunity exists to extend the synergy between control engineering and clinical neuroscience to develop principled and interpretable strategies for brain stimulation that can enhance cognitive function in patients and, perhaps eventually, in healthy individuals. In [19], the authors explore the challenges and potentials of a control-systems framework for designing controllers to enhance human cognitive function, with a focus on the development of conceptual and mathematical objective functions. The intent of this paper is to identify current technical and theoretical challenges in human neural control across spatial scales and suggest promising pathways forward. In particular, they authors focus on the formulation of objectives and system identification paradigms as a precursor to the eventual synthesis of control strategies for brain stimulation. In particular, they review some of the current methods used in the context of non-invasive neurotechnologies known as transcranial electrical stimulation (tES) [9, 22], which involves applying weak currents to the brain using two or more electrodes positioned on the scalp.

The authors of [4] bring us their vision toward the future of therapeutic peripheral nerve stimulation for chronic pain. Current computational models of chronic pain often fail to explain the dynamics of certain firing patterns and the relationships between these patterns and pain conditions. These models can reproduce some of the observed neuronal responses, but they assume a fixed circuit topology, are high-dimensional, and are nonlinear. They are not amenable to analysis because analytically characterizing a set of sensory stimuli, model parameters, and treatment parameters that produce the observed firing patterns is intractable. Additionally, designing optimal controllers for such complex nonlinear models can be a complicated process. Therefore, the authors advocate for a tractable linear mathematical model of pain transmission that can be used to inform the development of closed-loop neuromodulation treatments. In particular, they leverage $\mathcal{H}_\infty$ model-matching control to show in a proof-of-concept simulation that the closed-loop can maintain all vital acute (short-lasting) pain responses while eliminating the hyperactive chronic (long-lasting) pain responses. Furthermore, they advocate for the idea that the application of $\mathcal{H}_\infty$ model-matching control to neurotechnology can be expanded and applied across neuromodulation applications regardless of disease type or target location in the body. For instance, it could also be used in PD, depression, and essential tremor, to name a few. For PD, there are several known biomarkers, such as excessive beta-band oscillations in basal ganglia structures, and previously proposed DBS strategies aim to suppress these pathological oscillations [24]. Additionally, other observable and measurable symptoms, such as resting-state tremors in the limbs, could be used as feedback measurements to tune DBS patterns and have indeed been proposed for used within a closed-loop approach.

Lastly, the authors of [7] propose to use fractional-order systems for the phenomenological behavior of the neural activity captured by neurotechnology sensing capabilities. They overview the formalism behind creating such models with an account for their bio-plausability and physically explainable parameters. In this setting, they overview recent advances in learning such models with uncertainty guarantees, resilient state estimation suitable to perform artifact removal from collected neural data (e.g., electroencephalographic data), and predictive closed-loop control under possible state and input constraints. In particular, they provide evidence of the efficiency of terminating seizures when considering various computational models of epilepsy from the neuroscience and medical community. Notwithstanding, the proposed neurostimulation schemes can be extended to mitigate other neurological diseases and disorders, possibly using different stimulation modalities, as long as sufficient sensing and actuation capabilities are available.

The works presented in this special section highlight the promises and challenges of further research at the intersection of control systems engineering and neuroscience with potentially transformative applications in the clinical treatments of neurological disorders. Furthermore, these works clearly demonstrate that the success of an enterprise as ambitious as crafting brain activity and subsequent behavior is a highly interdisciplinary endeavor that requires multidisciplinary collaboration. As such, the current Special Section is not only targeted to inform researchers of recent and ongoing efforts in the field, but is also aimed at challenging them to criticize and improve the current methodologies using unconventional and out-of-the-box approaches. Only when the fundamental scholarly work is done will we then be able to move forward with the assessment in animal models and human clinical trials. Ultimately, all the works in this Special Section strive towards a future where neurotechnologies can have meaningful, accessible, and robust impacts on improving the quality of life of the millions of people suffering from neurological diseases and disorders worldwide.

References

[1] Ross W Anderson, AmirAli Farokhniaee, Kabilar Gunalan, Bryan Howell, and Cameron C McIntyre. Action potential initiation, propagation, and cortical invasion in the hyperdirect pathway during subthalamic deep brain stimulation. *Brain stimulation*, 11(5):1140–1150, 2018.

[2] Alim-Louis Benabid, Pierre Pollak, Alain Louveau, S Henry, and J De Rougemont. Combined (thalamotomy and stimulation) stereotactic surgery of the vim thalamic nucleus for bilateral parkinson disease. *Stereotactic and functional neurosurgery*, 50(1-6):344–346, 1987.

[3] Chiung Chu Chen, Vladimir Litvak, Thomas Gilbertson, Andrea KŘhn, Chin Song Lu, Shih Tseng Lee, Chon Haw Tsai, Stephen Tisch, Patricia Limousin, Marwan Hariz, et al. Excessive synchronization of basal ganglia neurons at 20áhz slows movement in parkinson's disease. *Experimental neurology*, 205(1):214–221, 2007.

[4] Wanru Duan Yun Guan Sridevi V. Sarma Christine Beauchene, Claire A. Zurn. The future of therapeutic peripheral nerve stimulation for chronic pain. *Annual reviews in control*, 2022.

[5] Jeff Moehlis Dan Wilson. Recent advances in the analysis and control of large populations of neural oscillators. *Annual reviews in control*, 2022.

[6] Guillaume Drion, Timothy O'Leary, and Eve Marder. Ion channel degeneracy enables robust and tunable neuronal firing rates. *Proceedings of the National Academy of Sciences*, 112(38):E5361–E5370, 2015.

[7] Guilherme Ramos Paul Bogdan Sergio Pequito Emily Reed, Sarthak Chatterjee. Fractional cyber-neural systems – a brief survey. *Annual reviews in control*, 2022.

[8] Bard Ermentrout and David H Terman. *Mathematical foundations of neuroscience*, volume 35. Springer, 2010.

[9] Anna Fertonani and Carlo Miniussi. Transcranial electrical stimulation: what we know and do not know about mechanisms. *The Neuroscientist*, 23(2):109–123, 2017.

[10] Benjamin D Greenberg, Donald A Malone, Gerhard M Friehs, Ali R Rezai, Cynthia S Kubu, Paul F Malloy, Stephen P Salloway, Michael S Okun, Wayne K Goodman, and Steven A Rasmussen. Three-year outcomes in deep brain stimulation for highly resistant obsessive–compulsive disorder. *Neuropsychopharmacology*, 31(11):2384–2393, 2006.

[11] Neville Hogan. Impedance control: An approach to manipulation. In *1984 American control conference*, pages 304–313. IEEE, 1984.

[12] William Koller, Rajesh Pahwa, Karen Busenbark, Jean Hubble, Steve Wilkinson, Anthony Lang, Paul Tuite, Elspeth Sime, Andres Lazano, Robert Hauser, et al. High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, 42(3):292–299, 1997.

[13] Andrea A Kühn, Florian Kempf, Christof Brücke, Louise Gaynor Doyle, Irene Martinez-Torres, Alek Pogosyan, Thomas Trottenberg, Andreas Kupsch, Gerd-Helge Schneider, Marwan I Hariz, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory β activity in patients with parkinson's disease in parallel with improvement in motor performance. *Journal of Neuroscience*, 28(24):6165–6173, 2008.

[14] Adrian W Laxton, David F Tang-Wai, Mary Pat McAndrews, Dominik Zumsteg, Richard Wennberg, Ron Keren, John Wherrett, Gary Naglie, Clement Hamani, Gwenn S Smith, et al. A phase i trial of deep brain stimulation of memory circuits in alzheimer's disease. *Annals of neurology*, 68(4):521–534, 2010.

[15] Ron Levy, William D Hutchison, Andres M Lozano, and Jonathan O Dostrovsky. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *Journal of Neuroscience*, 20(20):7766–7775, 2000.

[16] Michael CH Li and Mark J Cook. Deep brain stimulation for drug-resistant epilepsy. *Epilepsia*, 59(2):273–290, 2018.

[17] Andres M Lozano and Nir Lipsman. Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron*, 77(3):406–424, 2013.

[18] Eve Marder, Timothy O'Leary, and Sonal Shruti. Neuromodulation of circuits with variable parameters: single neurons and small circuits reveal principles of state-dependent and robust neuromodulation. *Annual review of neuroscience*, pages 329–346, 2014.

[19] Michael W. Cole ShiNung Ching Matthew F. Singh, Todd S. Braver. Developing control-theoretic objectives for large-scale brain dynamics and cognitive enhancement. *Annual reviews in control*, 2022.

[20] Helen S Mayberg, Andres M Lozano, Valerie Voon, Heather E McNeely, David Seminowicz, Clement Hamani, Jason M Schwalb, and Sidney H Kennedy. Deep brain stimulation for treatment-resistant depression. *Neuron*, 45(5):651–660, 2005.

[21] Cameron C McIntyre, Susumu Mori, David L Sherman, Nitish V Thakor, and Jerrold L Vitek. Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. *Clinical neurophysiology*, 115(3):589–595, 2004.

[22] Walter Paulus. Transcranial electrical stimulation (tES–tDCS; tRNS, tACS) methods. *Neuropsychological rehabilitation*, 21(5):602–617, 2011.

[23] Rodolphe Sepulchre Raphael Schmetterling, Thiago Burghi. Adaptive conductance control. *Annual reviews in control*, 2022.

[24] Sabato Santaniello, John T Gale, and Sridevi V Sarma. Systems approaches to optimizing deep brain stimulation therapies in parkinson's disease. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, 10(5):e1421, 2018.

[25] Lauren E Schrock, Jonathan W Mink, Douglas W Woods, Mauro Porta, Dominico Servello, Veerle Visser-Vandewalle, Peter A Silburn, Thomas Foltynie, Harrison C Walker, Joohi Shahed-Jimenez, et al. Tourette syndrome deep brain stimulation: a review and updated recommendations. *Movement disorders*, 30(4):448–471, 2015.

[26] Rodolphe Sepulchre, Timothy O'Leary, Guillaume Drion, and Alessio Franci. Control by neuromodulation: A tutorial. In *2019 18th European Control Conference (ECC)*, pages 483–497. IEEE, 2019.