Multi-Electrode Stimulation enabling Next-Generation Artificial Retinas

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Project Aims

Next-generation artificial retinas rely on electrical neuro-stimulation to evoke the activation pattern of different neurons by timely releasing current in the neural tissue at multiple electrodes to form complex patterns. Due to the complex tissue-electrodes interface, a stimulation artifact corrupts the recorded neural activity at different electrodes. Thus, it precludes the assessment of neural activity needed for calibration and crafting complex patterns. We seek to develop the mathematical control systems foundation of discrete fractional dynamics to enable new mechanisms to regulate neural activity while mitigating artifacts using spatiotemporal properties of the neural tissue and electrodes' interface. Towards this goal, we seek to leverage recent results in the cybersecurity of dynamical systems by considering the artifacts as prototype attacks that aim to preclude the measurement of the underlying neural activity. We will validate the proposed mechanism *in silico* and *in vivo* through our international collaborators.

Background

Electrical neuro-stimulation (ENS) enables the crafting of neural activity (i.e., neuromodulation) by timely releasing electrical charges in the neural tissue to evoke the activation of neurons with a desirable activation pattern. ENS is a promising therapeutics for many mental diseases and disorders resulting from neural dysfunctions [1] that cost more than €798 billion annually to European countries [2]. Our application domain is the retinal prosthesis for treating vision disorders such as retinitis pigmentosa and age-related macular degeneration [3].

For the first time, we aim to reproduce the complex neural patterns of activation of neurons in the retina. To do so, we need neural interfaces with bidirectional multi-electrode arrays that

- *sense* the underlying neural activity and learn the location and type of neurons near the array; and
- *actuate* by deploying a sequence of calibrated stimuli (i.e., electrical charges) at multiple locations to evoke the activation of neurons with single-cell and cell-type resolution.

Yet, due to the difference in the electrochemical properties of the neural tissue and the materials of the electrodes – the *electrode-tissue interface*, when an external electrical stimulus is applied, it propagates through the neural tissue without necessarily leading to neural activity. Hence, it may lead to stimulation artifacts at different electrodes, i.e., a measured activity that is not originated from the neural activity. These artifacts can obscure any useful neural activity precluding us from determining the neuronal activity. Thus, artifacts limit our ability to modulate neural dynamics as we cannot assess the effect of a specific electrical stimulus, and subsequently, it limits the applicability and efficiency of ENS [4,5]**.** Here, we will develop artifact mitigation techniques of artifacts by relying on state-of-the-art cybersecurity techniques used in the context of dynamical systems [6] for fractional-order dynamical systems suitable to model neurophysiological models. Such methodology will solve a key problem that needs to be addressed to enable efficient and reliable ENS devices. In particular, this project will enable future schemes where sequences of stimuli at different electrodes can generate complex neural activation patterns in the retina to be interpreted as a dynamic sequence of images by the brain; thus, instrumenting the next generation of artificial retinas.

Project description

Our approach seeks to develop a novel methodology to simultaneously infer the *overall* neural activity at *all* electrodes (even the ones with stimulation artifact) by exploiting the spatiotemporal dynamical model describing the electrodes' activity, and the measured activity in targeted electrodes which stimulation waveform is crafted to reduce the artifacts and their duration by exploiting the electrode-tissue interface.

Toward this goal, we consider discrete-time fractional-order systems suitable for modeling neurophysiological processes [7,8]. Specifically, given the Grünwald-Letnikov fractional derivative (a finite-difference operator) defined as follows for the i^{th}-state:

$$\Delta^{\alpha_i} x_i[k] = \sum_{j=0}^{k} \phi(\alpha_i, j) x_i[k-j], \qquad \phi(\alpha_i, j) = \frac{\Gamma(j-\alpha_i)}{\Gamma(-\alpha_i)\Gamma(j+1)},$$

where α_i is the fractional-order exponent, we obtain the state-space representation of the linear fractional-order system considered next, and referred to simply as *fractional-order dynamical systems (FODS)*, is given by

$$\Delta^{\alpha} x[k] = Ax[k] + Bu[k],$$

where $\alpha = (\alpha_1, \cdots, \alpha_n)$, $x[k]$ is the n-dimensional state at time k, and the last term Bu[k] represents the stimuli injected into the neural substrate perceived by the dynamics at the electrodes. Additionally, disturbance and sensor noises can be considered *(i)* stochastic or *(ii)* deterministic, unknown, and bounded, suitable for later approaches.

We first propose to treat the electrode-tissue interface as a linear fractional-order dynamical channel modeled using electrochemical impedance spectroscopy. We will leverage this model to apply pre-distortion to the stimulation waveform to minimize the artifact duration, such that we can increase the number of target electrodes to be used as targeted electrodes in the following step. With these models and the measurements collected at the target electrodes, it will be possible to estimate the neural activity at all the electrodes and the perceived inputs using an input-state estimator [9]. Nonetheless, such estimators are still in their infancy in the context of fractional-order dynamical models, and their properties still need to be asserted. The overall methodology will lead to an *electrode-artifact estimator* that can infer the most likely electrodes' measured data and the artifacts present in such electrodes. Subsequently, an assessment (e.g., hypothesis tests or change-point detection methods) will be considered to determine if the prototype attack is likely to be present and, subsequently, mitigated.

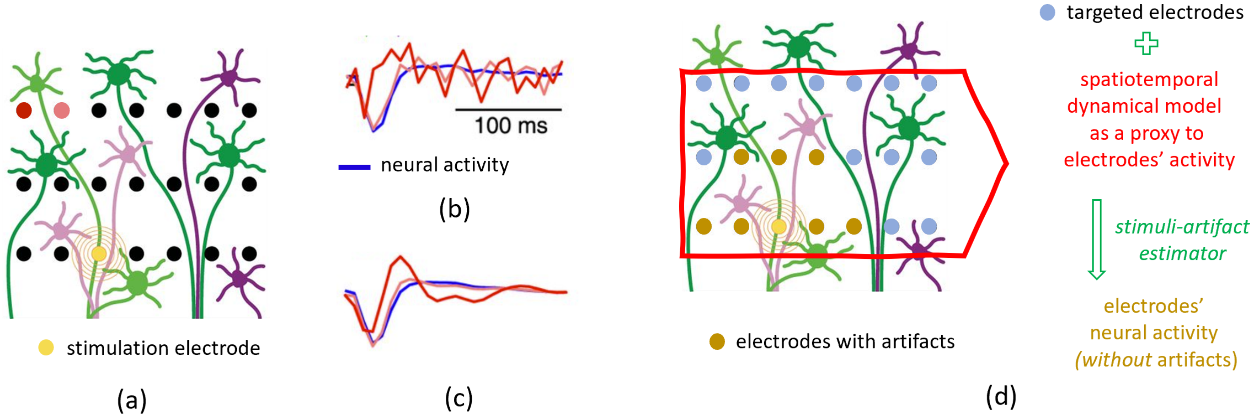

Figure 1 - The retina has a variety of neuron types depicted by the different colors, and colored circles depict the different electrodes in a bidirectional multi-array electrode. The yellow electrode functions as a stimulation electrode, whereas the remaining electrodes sense the neural activity and possible stimulation artifacts. In (a), the electrode in red and pink capture some stimulation artifacts illustrated in (b), which differ from the underlying neural activity in blue. Instead, if the stimulation waveform is chosen properly (i.e., using electrode-tissue interface properties), then it is possible to mitigate the artifacts as illustrated in (c). In (d), we provide an eye-bird view of the proposed approach to infer the neural activity (as well as the artifacts) at the electrodes depicted in brown by considering the spatiotemporal dynamical model of the electrodes' activity and the measurements collected at the targeted electrodes.

In summary, the proposed methods enable a systematic approach to determine the stimulation waveform required to maximize the number of electrodes minimally affected by artifacts. These provide us with more reliable data to infer the neural activity and possible artifacts at the remaining electrodes using our stimuli-artifact estimator. Furthermore, this estimator equips us with an algorithm to mitigate artifacts that can be deployed at the edge within the power and area constraints of implantable solutions.

Interdisciplinary research environment

This is a joint venture between science and engineering. On the one hand, the student will be mentored by local advisors Sérgio Pequito and André Teixeira, whose expertise entails control/estimation of fractional-order dynamics and cybersecurity, respectively. The Ph.D. student will develop a unified framework for assessing the state and artifacts in fractional-order dynamical systems by leveraging state-of-the-art tools in the cybersecurity of dynamical systems. On the other hand, the Ph.D. student will regularly interact with Professor Dante Muratore from Delft University of Technology, who is a bioelectronics expert in the domain of artificial retina circuitry, and Professor E.J.

Chichilnisky from Stanford and one of the world leaders in neurophysiology and computational neuroscience in the context of the artificial retina.

Professor Muratore's group will prototype a custom board to validate the waveform optimization method rapidly. Initial experiments with the board will inform the design of an application-specific integrated circuit (ASIC) that can interface at single-cell resolution within the constraints of a future implantable ENS. The ASIC will be validated with *ex-vivo* rat retina using standard techniques and procedures in our collaborator's laboratory.

Additionally, through Professor Chichilnisky's group, we have access to an extensive collection of recordings (>1000 recordings, >500k neurons, >50B spikes) from bidirectional multi-electrode arrays in the retina. These recordings are in the context of single-electrode stimulation with various stimulation waveforms and amplitudes. Additionally, we have access to the corresponding neurophysiological imaging and annotated data to determine neural activation. The goal is to use this data to validate the proposed methodology.

The successful candidate

The applicant should have a solid background in applied mathematics, control theory, optimization, artificial intelligence, machine learning, or a related field. The prospective candidate should have excellent analytical skills and possess curiosity and creativity. Excellent oral and written communication skills in English are required. The applicant should be highly scholarly and be able to work well in a team and independently.

Financial support

The Division of Systems and Control will host the student. A full-time sponsoring entails 80% research and 20% teaching. The research support is covered 50 % by CIM, and the Division of Systems and Control will provide 50 % of the funding. The division (through the department) will also cover teaching support.

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