Data-driven model-based control of neural dynamics to restore function in human neurological conditions.

Abstract:
The human brain maintains structured neural activation in motor and somatosensory areas even in the absence of motor output, caused by injury [*Shelchkova et al. 2023, Bashford et al 2021*]. Rehabilitation of such injuries requires creating neural interfaces that can read out this structured activity of the brain and transform this activity into commands controlling external devices. Mastering the control of such neural interfaces requires practice and can be facilitated by providing proprioceptive feedback via neurostimulation akin to the harmonised feedback between movement and proprioceptive sensations in healthy individuals [*Flesher et al. 2021*]. Both decoding movement intentions from the brain and returning proprioceptive sensations via neurostimulation critically rely on identifying neural dynamics based on the electrophysiological recordings of neural population activity [*Yang et al. 2021*]. However, the ability to precisely control transitions from one dynamical state to another is an unmet challenge. This research project aims to uncover strategies for identifying and controlling neural dynamics in motor and somatosensory areas of human cortex. The approach aims to learn input-output properties of neuronal populations intracranial recording and stimulation in human clinical studies to enable data-driven model-based control of the neural dynamics, using deep learning and optimal control theory. By developing novel dynamical system identification methods, integrating deep generative networks with Kalman filters (DeepKalman filters), and employing optimal control strategies, the project seeks to advance our understanding of neural codes for closed-loop control of neural activity. This is an interdisciplinary project, spanning basic neuroscience and computer science, with implications for enhancing Brain-Computer Interfaces (BCIs) and progressing first-in-human clinical translation.

Introduction:
The human brain coordinates complex movements through intricate neural dynamics which are coupled to the external environment via an action-perception loop. In this loop, the movement intentions in motor cortical areas are transformed to commands controlling muscles, this generates feedback through sensory systems with returns back to somatosensory cortical areas, which further communicate with motor areas towards generating precise and robust closed-loop motor control. Understanding these closed-loop dynamics is crucial for decoding movement intentions as well as providing sensory feedback to improve performance and embodiment of BCIs [*Armenta Salas et al. 2018*].

Research Challenge:
Both decoding movement intentions from the brain and feeding back proprioceptive sensations via neurostimulation critically relies on identifying the neural dynamics. This remains an unsolved problem and an area of active research [*Durstewitz et al. 2023*].
This project aims to identify and predict neural population dynamics during neurostimulation in somatosensory areas using tools from **deep learning**, and then apply **optimal control theory** for finding the most controllable dimensions that can be utilized to develop a next generation of neuromodulation protocol.
This research will advance current approaches to mapping motor and somatosensory areas in the human brain, which at present relies on verbally reported sensations and trial-and-error random

exploration for finding effective neuromodulation parameters that elicit sensations [*Armenta Salas et al. 2018*].

Furthermore, the project will explore the potential for using universal dynamics shared across individuals to make the findings broadly generalizable, crucial for clinical translation. Recent evidence from animal models suggests that motor cortex has universal dynamics patterns across individuals within a species [*Safaie et al. 2023, Azabou et al. 2023*]. This result has not been confirmed in humans. In humans, however, shared hand motor neuron dynamics was recently utilized for building non-invasive human-machine interfaces [*CTRL-labs at Reality Labs et al. 2024*].

If the hypothesis of shared neural dynamics extends to human sensorimotor cortex, this would further facilitate identifying the embedding of this universal dynamics in a particular neural population of a particular patient and further improve clinical protocols.

Data & Methodology:

Human neural signals (single- and multi-unit activity, and local field potentials) from primary sensory cortex have been recorded in clinical trial participants at rest. During this period randomly selected parameters, within an approved range, of intracortical microstimulation (ICMS) were delivered to map the changes in resting neural activity evoked by the ICMS. This data is available from the ongoing clinical trial run by an external partner/supervisor (Dr. Luke Bashford, Newcastle University, UK).

In this project we will analyse the dynamic responses to these randomly performed stimulations of the neural population in order to: 1) learn the intrinsic dynamics of the biological neural population, similar to system identification; and 2) identify the most controllable dynamic modes and corresponding optimal neurostimulation parameters to causally control the population. Such an approach to data-based modelling and control has previously been applied to brain-wide neuromodulation in animal models [*Yang et al. 2021*], yet has not been developed for the human sensorimotor circuit and at a single-neuron resolution.

While providing a valuable baseline, *Yang et al. 2021* approach assumes linear dynamics and linear separability between input-driven and intrinsic dynamics, which are unlikely to hold at a single neuron precision, where neural responses are known to add supralinearly. To accommodate higher demands for precision at the single-neuron level, this project will develop DeepKalman filters [*Krishnan et al. 2015*] for dynamical system identification, which is an extension of traditional Kalman filters (used in [*Yang et al. 2021*]) to nonlinear dynamics that leverages the universal approximator capabilities of deep neural networks. This is a timely approach as only recently have these principles been considered in computational systems neuroscience [*Dowling et al. 2024*], yet they have not been utilized for model-based control before. We will then utilize optimal control strategies to find controllable dimensions for efficient neuromodulation.

The first generation of models will be developed using existing data and computational approaches, including openly available non-human primate datasets and pre-recorded human data. Once the model is validated, we will be able to further the project to an experimental phase. This will be to assay these closed-loop control models in various neural tissues in-vitro, with our external partner.

RRI/Ethical Considerations:

This project relies on anonymised data that is already collected and used under the approvals of ongoing clinical trials. Any further experiments will be performed within the scope of ongoing studies with approvals in place. The computational analysis of the data does not require ethical approval. This research also seeks to re-use clinical data to investigate neural dynamics of sensorimotor coupling, which are traditionally studied in animals. Here, facilitating the transition to human closed-loop experiments will contribute to the reduction of the use of animals in neuroscience research (3R).

Expected Outcome & Impact:
The project expects to contribute to understanding the closed-loop control of human neural populations to further the potential of restoring function after neurological illness or injury that results in sensorimotor deficit. The impact of this would be that these algorithms are incorporated into software for clinical translation. Further, the project will provide a basic and computational neuroscience framework for probing the human sensorimotor system. The results of these unique datasets and analysis will be published in high quality neuroscience and bioengineering journals (e.g. ELife, Nature Biomedical Engineering) and computational proceedings (e.g. NeurIPS), accompanied with an open-source Python package.

References:

Armenta Salas, Michelle, et al. "Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation." Elife 7 (2018): e32904. https://doi.org/10.7554/elife.32904

Azabou, Mehdi, et al. "A unified, scalable framework for neural population decoding." Advances in Neural Information Processing Systems 36 (2024).

Bashford, Luke, et al. "The neurophysiological representation of imagined somatosensory percepts in human cortex." Journal of Neuroscience 41.10 (2021): 2177-2185. https://doi.org/10.1523/JNEUROSCI.2460-20.2021

CTRL-labs at Reality Labs, D. Sussillo, P. Kaifosh, and T. Reardon, “A generic noninvasive neuromotor interface for human-computer interaction,” Neuroscience, preprint, Feb. 2024. doi: 10.1101/2024.02.23.581779.

Dowling, Matthew, Yuan Zhao, and Il Memming Park. "Large-scale variational Gaussian state-space models." arXiv preprint arXiv:2403.01371 (2024). http://arxiv.org/abs/2403.01371

Durstewitz, Daniel, Georgia Koppe, and Max Ingo Thurm. "Reconstructing computational system dynamics from neural data with recurrent neural networks." Nature Reviews Neuroscience 24.11 (2023): 693-710. https://doi.org/10.1038/s41583-023-00740-7

Flesher SN, Downey JE, Weiss JM, Hughes CL, Herrera AJ, et al. 2021. A brain-computer interface that evokes tactile sensations improves robotic arm control. Science 372:831–36 https://www.science.org/doi/epdf/10.1126/science.abd0380

Krishnan, Rahul G., Uri Shalit, and David Sontag. "Deep kalman filters." arXiv preprint arXiv:1511.05121 (2015). http://arxiv.org/abs/1511.05121

Safaie M et al., “Preserved neural dynamics across animals performing similar behaviour,” Nature, vol. 623, no. 7988, pp. 765–771, Nov. 2023, doi: 10.1038/s41586-023-06714-0.

Shelchkova, Natalya D., et al. "Microstimulation of human somatosensory cortex evokes task-dependent, spatially patterned responses in motor cortex." Nature communications 14.1 (2023): 7270. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10638421/

Yang, Yuxiao, et al. "Modelling and prediction of the dynamic responses of large-scale brain networks during direct electrical stimulation." Nature biomedical engineering 5.4 (2021): 324-345. https://www.nature.com/articles/s41551-020-00666-w