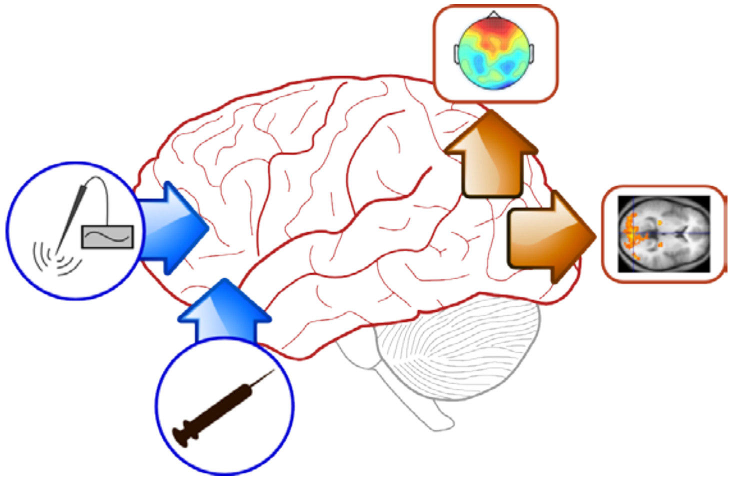
Control-Theoretic Approaches in Neuroscience and Brain Medicine

Emerging technologies in neuroscience and brain medicine are providing ever more sophisticated ways of both measuring and manipulating neuronal circuits *in vivo*. As evidenced by therapies such as deep brain stimulation, such technologies hold immense medical promise. The full realization of this promise will require the recognition of these technologies—and conventional treatments involving pharmacologic agents—as inputs and outputs of a dynamical system. Appropriately and tractably modeling brain dynamics will open new avenues for the exploration of control-theoretic approaches to elucidating brain function and optimizing new therapeutic strategies.



Emerging technologies for brain stimulation, coupled with pharmacologic manipulation, are providing an ever-increasing ability to "actuate" brain dynamics. Paired with modalities for measuring these dynamics, new opportunities in neuronal control theory will emerge.

Current Paradigms in Pharmacologic and Stimulation-Based Neural Control

Closed-Loop Control of Anesthesia: General anesthesia is the most prevalent "actuator" of human brain dynamics in current clinical practice. Despite efforts to develop closed-loop anesthetic delivery solutions, several challenges remain related to ensuring robustness in the presence of significant patient variability and unreliable feedback signal quality. By developing a new class of nonlinear biophysical models that more accurately reflect drug action, new and improved control designs will be possible.

Deep Brain Stimulation (DBS) for Treatment of Parkinson's Disease: In DBS, specialized electrodes are implanted in certain brain structures and electric current is delivered to disrupt pathological neural activity. At present, this stimulation consists of periodic pulse trains whose frequency is set empirically. Biophysical modeling and principled application of control theory will enable the design and optimization of closed-loop controllers for delivering this therapy in the next generation of DBS technology.

Applications in Basic Neuroscience: Optogenetics

Optogenetics is a powerful and popular technique in experimental neuroscience that uses genetic manipulation to make specific classes of neurons sensitive to light. These neurons can then be activated, that is, caused to spike, through illumination (e.g., via fiber optics) *in vivo*. The power of this technique lies in the ability to probe how certain populations of neurons are involved in behavior and function. Currently, this technique is used in open loop, and illumination takes the form of constant pulses. Large populations of neurons are turned on or off en masse. Control theory is certain to play an important role as neuroscientists seek to induce more sophisticated patterns of activation and to manipulate neural activity in real time.

How Can Control Theory Contribute?

Many control theoretic notions—dynamics, stability, feedback, identification—are of direct importance to neuroscience and brain medicine. Particular areas of interest include:

- Robust methods for designing feedback controllers in the presence of patient uncertainty
- Dimensionality reduction for developing tractable biophysical models of neuronal activity in response to exogenous stimulation
- System identification of neuronal dynamics at multiple scales
- Constrained design of persistent excitation for estimating neuronal circuits
- Analysis and characterization of dynamics in neuronal networks toward uncovering basic brain function
- Optimization of therapeutic strategies using multiple types of drugs or stimulation modalities

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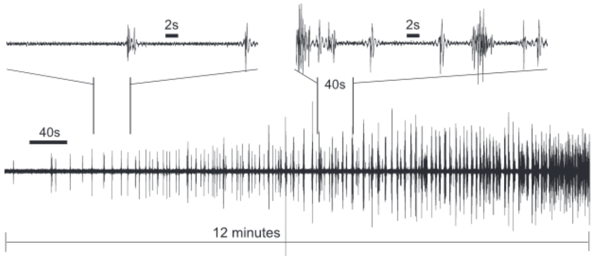
Toward New Therapies in Brain Medicine: The Dynamics of Neurological Disease

An emerging trend in clinical neurophysiology is to associate certain brain dynamics (e.g., oscillations, synchrony) with neuropathology, disease, or clinical state. Modeling these dynamics will open the door to new interventions motivated by control theory.

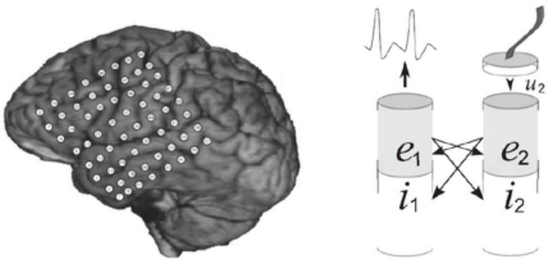
Control of Medically Induced Coma via Closed-Loop Anesthetic Delivery: A medically induced coma (a very deep level of general anesthesia) is characterized by bistable brain activity (see right). Recent nonlinear models have shed light on the underlying dynamics, opening the possibility of new nonlinear closed-loop designs.

Control of Seizure Activity Using Surface Stimulation: In an epileptic seizure, a focal region of pathological activity kindles an event that spreads through the brain in a network cascade. Grids of electrodes could be used in a distributed control scheme to induce stability (see right).

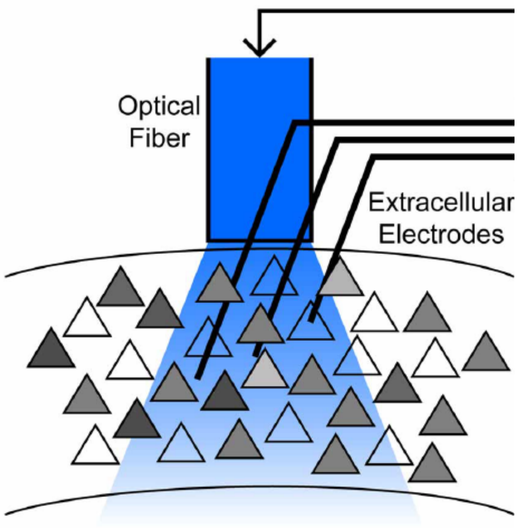
Control of Neuronal Spiking Patterns: Rather than simply activating/deactivating entire brain regions, an emerging challenge is that of true neuronal "control," in which specific patterns of brain activity are induced, potentially even at the scale of individual neurons (see below).



Twelve minutes of EEG activity showing emergence from a medically induced coma. Accounting for the nonlinear dynamics (note the bistability) is paramount in developing closed-loop methods to regulate such brain states.



Grids of stimulating electrodes could be used to control pathological activity. The spatial undersampling introduces challenges in distributed and decentralized control.



Optogenetics schematic. A single light source may affect hundreds of neurons. What is the appropriate notion of controllability in this setting?

The Challenge of Underactuation

Whether by pharmacology or stimulation, neuronal control is fundamentally underactuated: only a few inputs are used to affect a highly complicated system consisting of a vast number of interacting units (neurons, brain regions). The classical notions of controllability and observability are likely to be impractical and, arguably, not meaningful in this setting. Instead, new theoretical questions emerge:

- Rather than specifying complete state trajectories, what patterns (e.g., the order in which neurons are activated) can be achieved?
- How can desired activity be induced while satisfying strict constraints (e.g., stimulation power, drug quantity)?
- Can the intrinsic sparsity in neural activity be exploited for purposes of control?

For more information: S. Ching et al., Real-time closed-loop control in a rodent model of medically induced coma, Anesthesiology, 2013; S. Ching et al., Distributed control in a mesoscale cortical network model: Implications for seizure suppression, Physical Review E, 2013; S. Ching and J.T. Ritt, Control strategies for underactuated neural ensembles driven by optogenetic stimulation, Frontiers in Neural Circuits, 2013.