Title: Challenges and Opportunities For Physiologically Controlled Therapy in Neural Systems

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Abstract:
Targeted electrical stimulation of the brain is an effective therapy for a wide range of neurological disorders. A new generation of brain stimulation devices offers the opportunity to measure ongoing brain activity and automatically adjust therapy in response. Implementing such physiologic closed-loop controller (PCLC) systems for brain stimulation has the potential to improve therapy and reduce side effects, but this comes with an important set of additional challenges and risks to consider. In this work, we will describe key aspects of closed-loop systems for brain stimulation and outline some of the important additional considerations for their implementation. The obstacles highlighted here are equally relevant for the engineers designing these devices as they are for the physicians implanting and programming them.

Introduction:
Brain stimulation technology for the treatment of neurological disorders is rapidly evolving. With the advent of “bidirectional” systems, such as the Medtronic Percept, which are able to sense from and stimulate the brain simultaneously, there is opportunity to modify stimulation based on changes in brain activity. The utility of such a bidirectional application is exemplified by the success of the NeuroPace Responsive NeuroStimulation (RNS) device in the reduction of seizures[1] and pivotal trials of spinal cord stimulation for chronic leg pain using evoked compound action potentials to facilitate a homeostatic feedback system[2].

The potential for automating bioelectronic therapies using feedback represents a step change for the field. The current standard of clinical practice is open-loop control where a clinician sets therapy parameters to run continuously. Feedback occurs via a “clinician-in-the-loop” that adjusts parameters based on patient reports at follow-up. Each visit becomes a balancing act between symptom control and side-effects. The hypothetical, state-of-the-art practice is a closed-loop therapy that responds to changes biomarkers of neural activity to tailor the level of therapy that is needed with minimal side effects. However, such closed-loop devices come with important additional challenges and risks. For instance, closed-loop systems have the potential to become unstable while trying to limit deviations from a setpoint[3]. Additionally, closed-loop systems rely on the accurate measurement of a physiological variable, but sensor measurements can be affected by a range of artifacts. The main obstacles to closed-loop stimulation therapy for any brain disorder are rooted in physiological and engineering considerations.

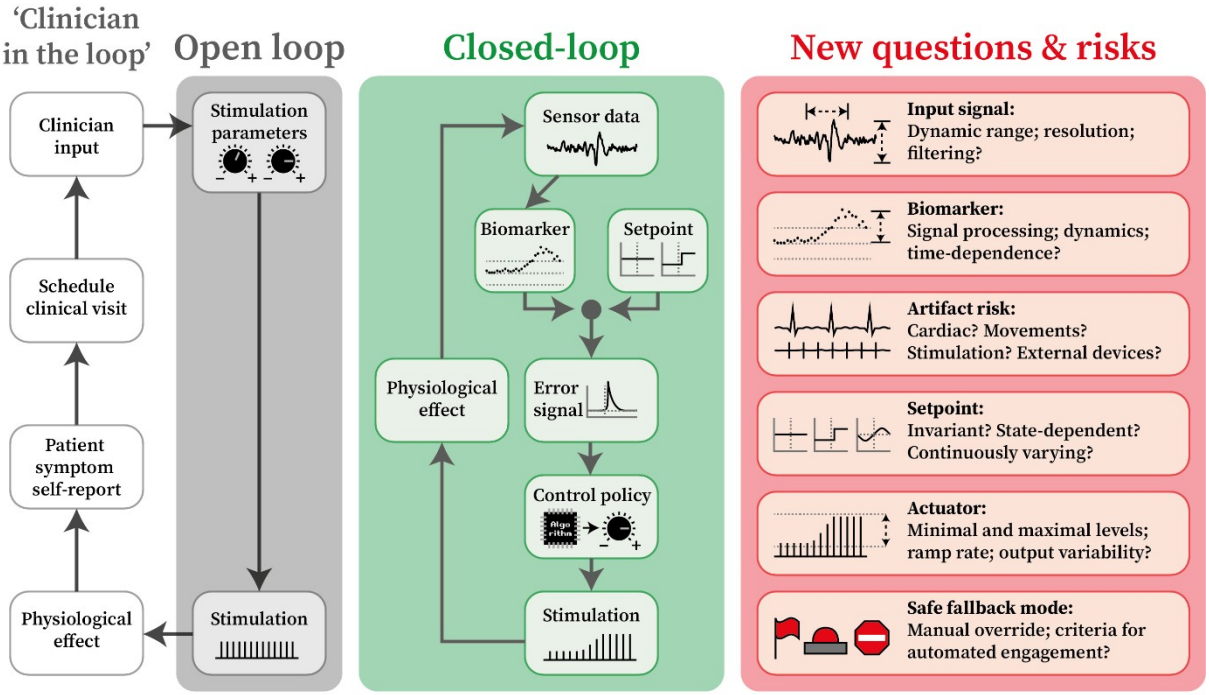

Figure 1. Progression from open-loop to closed-loop systems generates many new questions and risks. Some systems may be significantly more complex, with multiple fallback modes and inputs, but core principles should remain the same. The grey boxes display current open-loop (or "clinician-in-the-loop) controlled systems. The green box outlines the main components of a physiologic closed-loop control system. The red box summarizes some of the main challenges to implementing effective closed-loop control systems (moving from the grey box to the green box).

Main Principles and Terms:

New FDA guidance[4] defines a physiological closed-loop controlled device as any medical device that "adjusts or maintains a physiological variable through automatic adjustments to delivery or removal of energy or article … using feedback from a physiologic-measuring sensor." Figure 1 depicts the key components of open-loop and closed-loop control systems. The "controller" is where the algorithm lives. It is what determines how therapy is adjusted, and it is where feedback, feedforward, and adaptive factors are integrated. This makes the selection of "sensor," inputs of relevant signals and biomarker selection critical to the functionality of the device. The "actuator" affects the change on the system and enacts the "control policy," or changes to stimulation. Where open-loop systems make adjustments based on patient symptom self-reports, closed-loop systems rely on feedback loops that feed the difference between the biomarker and its expected setpoint back into the actuator as an "error signal." Also critical are the safety features implemented to collectively limit risks, including but not limited to the entrance and exit criteria (i.e., the conditions that must be met for a specific control policy to become active or inactive) for the adaptive loop, battery checks, sensor integrity monitors, and alerts. Ideally, the user interface for monitoring and interacting with this system should be intuitive but flexible. Lastly, there must be a testing plan for system verification and validation. Verification is the process of making sure the system behaves in the expected way. Validation is the process of making sure the system is the solution to the unmet need. For PCLCs, verification is likely to involve test bench setups with real or simulated data representing the expected evolution of the control signal over

time, while validation will usually take the form of clinical trials to confirm the closed-loop therapy is safe and effective. Most of the examples in this work will refer to deep brain stimulation (DBS) systems, as there are already regulatory body (e.g., FDA) approved DBS devices that have the capacity to run closed-loop therapies. The key components of a closed-loop DBS system are displayed in Figure 2. Deep brain electrodes in the target brain area sense electrophysiological changes in the brain and are connected to an implantable pulse generator (IPG).

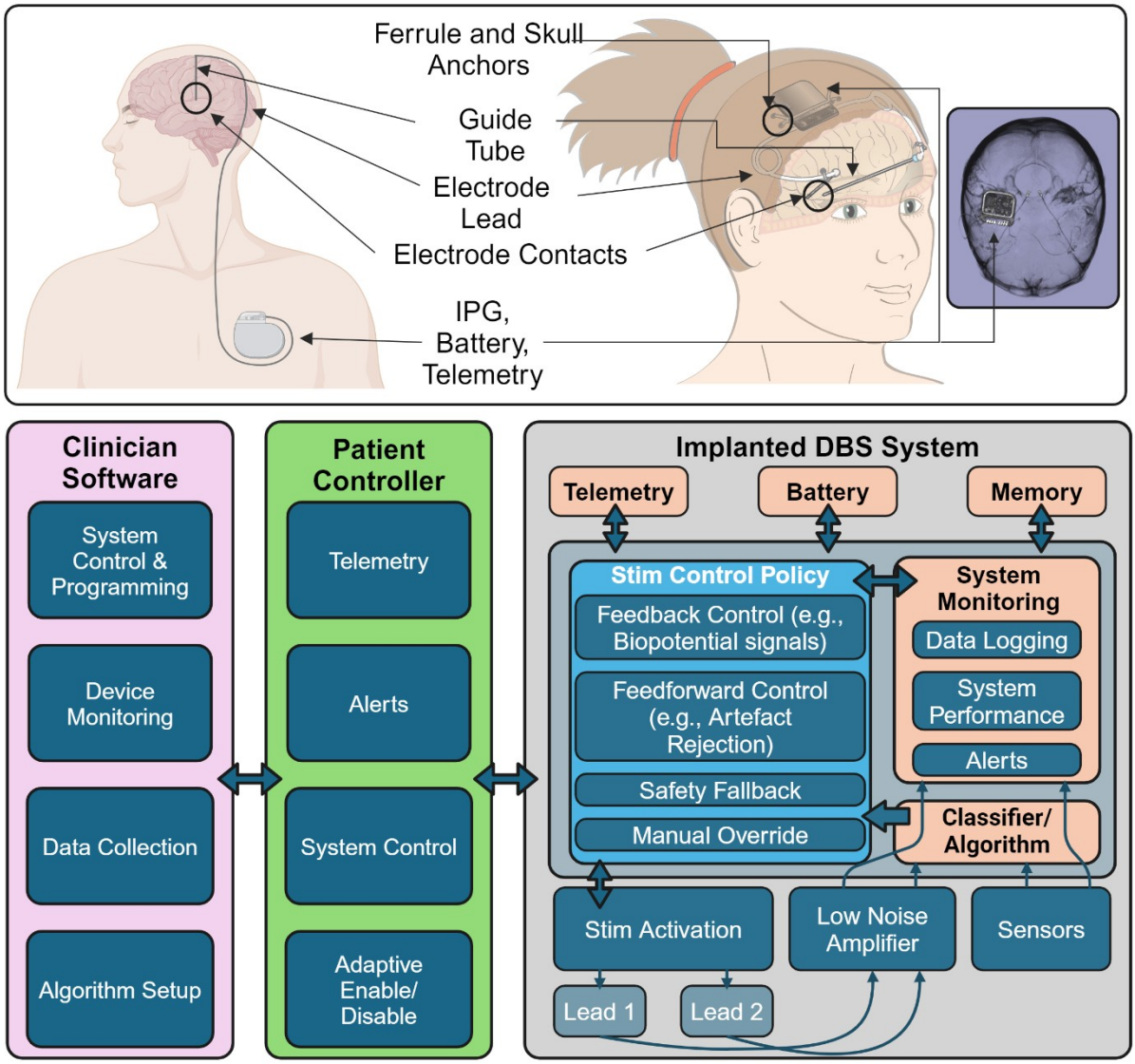

Figure 2. Example of a system for deep brain stimulation. The top panel shows the key implantable components of a DBS system. The IPG case may be implanted either in the chest (left) or cranially (right, with x-ray with investigational Picostim device inset). The implanted system contains all the components within the grey box, and communicates with the patient controller (green box) and the clinician software (purple box). IPG: Implantable Pulse Generator. (Created with Biorender)

Physiological Limitations:
A common pitfall of physiological controllers is to assume a relatively stable system, when, in reality, human physiology is hugely dynamic. There are many natural rhythms present in normal human physiology, from circadian to even longer, multi-

day (“multidien”), weekly, or monthly rhythms, which may affect not just the symptomatology but also the normal range of brain signal amplitudes, body temperature, or impedance of the brain tissue[5]. Identification, acknowledgement and incorporation of predictable factors could inform dynamic selection of optimal stimulation parameters. For a therapy to be deemed “optimal,” it must treat the primary symptoms (e.g., seizures) with minimal side effects (e.g., worsened sleep or cognition). The main limitation to neurostimulation is that the “optimal therapy” parameters are currently not well characterized and likely disease-specific, but adaptive therapies have the potential to move therapies in the right direction.

Many normal physiological events, such as movements or heartbeats, can cause artifacts in the sensor signal that must be accounted for in system design. Movement should be taken into consideration not just from a signal processing point of view, but also from how physiological systems could be impacted. Postural changes could prelude autonomic changes, such as when a patient with orthostatic hypotension stands-up, blood rushes to their legs, and there is a dramatic decrease in blood pressure. Likewise, attempting to move a limb may trigger essential tremor. Thus, adaptive therapies sensitive to changing conditions and states (e.g. movement, awake or asleep, etc.) are a preferrable direction for future closed-loop systems. Many obstacles to closed-loop systems posed by physiology, to an extent, can be solved with engineering solutions.

Engineering Limitations:
It is important to consider that novel neural implant devices are limited in scope by a number of engineering and technical challenges. When selecting feedforward, feedback, or adaptive variables, consider the signals that provide the most information on the disease state of the patient. These biomarkers may be autonomic signals (e.g., heart rate) or brain signals (e.g., from intracranial electrodes). It is important to note brain signals are nonstationary, with low frequency and DC drift overtime, so a high-pass filter is critical for combating such drifts. But whichever signal is chosen, the sensor must be able to capture the dynamic range of amplitudes and have a sampling frequency high enough to capture the biomarker of interest (e.g., the beta band in Parkinson’s). Also note that brain signals are very small, in the order of microvolts for Parkinson’s. Such a small biomarker is easily overcome by artifact. There also must be enough channels to capture all critical signals. For example, there may need to be one sensing channel in each hemisphere for bilateral, focal epilepsy.

The stimulation parameters of the therapy delivered should be informed by physiology but also the technical capabilities of the device, including the ability to separate the stimulation artifact from the sensed signal. An established way to reduce stimulation artifact is through common-mode rejection, which leverages the relative orientations of sensing and stimulation dipoles to remove artifacts and noise. A caveat is this requires contacts having equal impedance, as any impedance mismatch may inadvertently amplify the unwanted component of the signal. It is usually prudent to implement a band-pass filter on sensing that excludes frequency bands where residual stimulation artifacts may be present. There are many other methods to reduce stimulation artifact, including not sampling the signal during stimulation pulses or synchronizing sensing and stimulation to be just offset of each other. Every method will have advantages and drawbacks.

Any calculations performed on the device to decide how therapy is changed over time must be computationally compact if they are to be embedded on the device (e.g., power-in-band thresholding, linear discriminant analysis). Alternatively, data can be streamed to another device to do more complex calculations (e.g., deep learning methods). Although, performing calculations on an additional device would reduce the speed at which the device responds to disturbances in the system and require the constant maintenance of a (wireless) connection. Unless dependent on external devices for computation, constant streaming of brain signals is not an absolute requirement for closed-loop systems. However, the ability to periodically review what is being sensed is useful for evaluating if the system is behaving as expected and avoiding complacency bias, loss of situational awareness, and skill degradation.

Streaming may provide the advantage of more information into how a system behaves, but it also drains device battery. Alternatively, increasing the data storage capacity of the device can reduce the necessary frequency of streaming. Closed-loop systems reduce the need for frequent downloads, but performing calculations on the device also consumes battery. Even stimulation parameters affect battery life, with lower frequencies and shorter pulse widths consuming less battery. Battery can be preserved during stimulation at higher frequencies and pulse widths by using "cycling," or short periods of "stimulation on" followed by short periods of "stimulation off." Making a device rechargeable can mitigate these issues.

Implant location impacts the performance of closed-loop systems, and the selection of the implant location is an important factor of the system design when moving from open-loop to closed-loop. Most devices currently use the subclavicular area (Figure 2, left), although cranially-mounted devices have the opportunity to further reduce cardiac artifacts[6] and totally remove the need to tunnel wires past the neck during surgery. The latter element saves time in surgery, may potentially reduce risk of infection, and reduces movement artifact. Cranial implants are also advantageous for paediatric applications as it removes the need for extra lengths of implanted wire for the device to accommodate the patient's still-growing body[7].

Safety:
The first measure to mitigate safety risks is to make sure the physician, researcher, or other operator understands the mental model under which the system is operating. This model should be flexible to signal latency, physiologic disturbances, and intra-/inter-patient variance. There should always be a fallback mode in case exit criteria from the control policy has been met. For instance, adaptive loops may only be active if above a specified battery charge level. Similarly, there should be entrance criteria for beginning a control policy loop. The state of the system should be logged whenever it changes, as should any unexpected or unsafe physiological changes.

Additional Considerations:
In addition to the physiologic and engineering concepts described above, human factors must also be taken into consideration when developing new neural therapies. Devices must be safe and easy to use for the duration of the implant's life cycle. All implanted materials should be biocompatible for the duration of implant, which in

most cases will be the lifetime of the patient. Predicate closed-loop systems like cardiac pacemakers are typically implanted late in a patient's life, but someone receiving a neural stimulator for obsessive compulsive disorder, chronic pain, or epilepsy may have their device implanted for many decades. The battery should have as long a lifetime as possible to match this timeline, and battery-replacement should be straightforward without requiring lead replacement too. It may be prudent to ensure newly developed devices are compatible with the leads from other companies in case 1) the device is no longer available when the battery is replaced or 2) if a patient or their provider prefers a different device in the future. When it comes to user interface, if the device is too complicated to program in clinic, physicians and researchers may avoid using it. If integration with other devices like activity monitors is necessary, then application program interfaces, or APIs, should be available and intuitive. The more often a user must interface with the device, the less likely they are to remain compliant. This is particularly true when it comes to charging a device. The process by which the device is charged should be infrequent, quick, easy and comfortable for the patient.

Conclusion:
Physiologic closed-loop control systems have the potential to revolutionize the neurotechnology space. This work used examples from multiple sensing-based domains to provide intuition for PCLC operation and the problems they help solve as a template for any system using adaptive technology. While simple feedback loops can be very effective in some applications, the incorporation of predictive feedforward and adaptive components would allow for devices to better mimic physiological systems. Device and algorithm design should balance technical trade-offs between sensing, stimulation, streaming, and battery life. The safety of the patient should be preserved through appropriate fallback modes, alerts, and performance monitoring. Most critically, as in all therapy development, the burden of the therapy should not be greater than the burden of the disease.

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