Creating the Feedback Loop
Closed-Loop Neurostimulation

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KEYWORDS

• Deep brain stimulation • Closed-loop • Local field potentials • Oscillations • Subthalamic nucleus • Control systems • Machine learning

KEY POINTS

- Closed-loop stimulation may be superior to open loop therapy by reducing the impact of DBS on cognitive processes that depend on coordinated neuronal oscillations.
- Understanding the relationship between the gross patient behavior (or severity of disease) and a neuronal signal that is under the influence of external stimulation is fundamental to using the signal in a control system.
- A closed loop system extracts a particular feature of a biological signal that has a desired reference value associated with a desired therapeutic state. The system attempts to bring the feature closer to the desired reference value to induce the desired therapeutic state.
- Reference values for biosignal features are expected to vary over time in the same patient, and vary over behavioral goals of the patient. Thus, systems must be designed to update with time and cover a range of behavioral situations, such as walking, talking, or writing.

INTRODUCTION

Implantable devices for electrical stimulation of the brain have been in routine clinical use since 1997, when the first commercial deep brain stimulation (DBS) system was approved for the treatment of tremor.[1] These DBS devices provide an invariant train of stimulatory pulses at a fixed frequency. This open-loop mode (meaning unidirectional signal generated from the device and delivered to the brain) of DBS therapy has proved to be effective for treatment of essential tremor,[2] Parkinson disease,[3,4] and dystonia.[5,6] As understanding of the neurophysiologic mechanisms of both DBS and movement disorders expands, the shortcomings of open-loop therapy DBS are evident and are discussed in this review. The design of a closed-loop implantable pulse generator (IPG) to sense and respond to physiologic signals (closed-loop meaning bidirectional signals moving in both sensing and responding directions, allowing sensor signals to provide feedback modulation of stimulation) within or outside the brain is considered the next frontier in brain stimulation research and will likely broaden the field to include new applications for neuromodulation.

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Neurosurg Clin N Am 25 (2014) 187–204
http://dx.doi.org/10.1016/j.nec.2013.08.006
1042-3680/14/$ – see front matter

Implantable closed-loop stimulation systems are well established in the treatment of cardiac arrhythmias. Cardiac pacemaker devices capable of sensing and responding to atrial activity are closed-loop mode cardiac stimulation devices and have been in clinical use since 1963.[7] Despite the precedent for an IPG with dual sensing and stimulating functionality set 50 years ago, efforts to bring similar concepts to DBS devices[8,9] have been delayed 50 years in part because of the complexity of brain signals. Whereas cardiac pacemakers detect the P-wave signal of the atrial pacemaker, brain-generated signals are statistically complex. Perhaps more importantly, the clinical meaningfulness of recordable brain signals is not immediately obvious.

Strategy development for interpreting neuronal signals in closed-loop neurostimulation applications is underway. In broadest terms, an understanding of the relationship between a patient's clinical state and a neuronal signal under the influence of external stimulation is fundamental to any future use of the signal as a surrogate marker for clinical states. Clinical states are disease specific but collectively can be categorized by pathologic expressions of the disease (eg, the magnitude of tremor) and behavioral intentions (ie, attempting a task at hand such as walking, talking, or writing). Therefore, closed-loop neurostimulation relates available neuronal recording to meaningful clinical states and uses the surrogate measurements to update neurostimulation as the device is operating.

Recordable neurophysiologic signals are available from multiple levels of the brain, including a single neuron, multiple individual neurons, a localized population of neurons, or a large-scale population of neurons. Single-neuron recordings have been shown to be related to certain specific aspects of movement[10] and cognition.[11] Technical challenges of chronic recording from single neurons exist, such as increased sampling rate requirements, difficulty maintaining recordings from the same neuron for extended periods of time, and degradation at the neuron-electrode interface. These challenges contribute to the overall difficulty in maintaining sustained recordings from a single neuron. Recording from large populations of neurons, or local field potential (LFP) recordings, are much more stable over time. Oscillatory components of LFP recordings from highly specialized cortex, such as motor cortex or visual cortex, have been successfully related to clinical states such as movement and visual percepts.[12–14] However, recordings from these specialized cortical regions of the brain are limited because these regions are not typically accessed during routine surgery for neurostimulation.

This review presents current developments in closed-loop neurostimulation and strategies for manipulation of recordable signals to relate this information to a patient's clinical state (**Figs. 1** and **2**). Specifically, this review covers the rationale for closed-loop stimulation, meaningful categories of clinical patient states, brain signals available for recording, signal processing for prediction of patient states, and interventional DBS patterns aimed at restoring a desired state, or facilitating a desired state. Parkinson disease is a primary focus; however, principles can be applied to other movement disorders, as well as epilepsy, mood disorders, and other neuropsychiatric diseases. This review is intended as an introduction to engineering issues for clinicians and clinical issues for engineers.

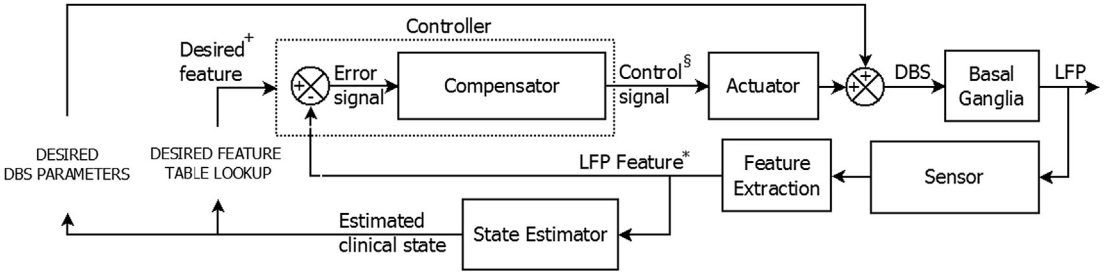

Fig. 1. General control system diagram representing a conceptualized closed-loop neurostimulation system for DBS. In this diagram, the reference signal (LFP Feature*) is the feature extracted from the basal ganglia local field potential. This reference signal* is used to predict a meaningful clinical state of the patient (estimated or predicted clinical state) and these states subsequently direct the selection of desired DBS parameters and appropriate reference values (Desired^{+} feature). The controller compares (and calculates an error signal) the reference signal* and value^{+}, and calculates the controlled variable (Control§ signal). The control signal§ and actuator, together with the selection of desired DBS parameters, influence the DBS feedback to the basal ganglia, ultimately affecting the LFP and extracted features*. This impact on the LFP serves as a surrogate marker for the beneficial effect of DBS on the patient, bringing the reference signal* and value^{+} closer together.