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Creating the feedback loop: Closed Loop Neurostimulation

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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 proven to be effective for treatment of essential tremor[2], Parkinson’s disease[3,4], and dystonia[5,6]. As we expand our understanding of the neurophysiological mechanisms of both DBS and movement disorders, the shortcomings of open loop therapy DBS are evident and will be discussed in this review. The design of a “closed-loop” implantable pulse generator (IPG) to sense and respond to physiological signals (“closed-loop” meaning bidirectional signals moving in both sensing and responding directions, allowing for the use of 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.

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 due to the complexity of brain signals. Whereas cardiac pacemakers detect the P-wave signal of the atrial pacemaker, brain-generated signals are statistically complex. Perhaps

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more importantly, the clinical meaningfulness of recordable brain signals is not immediately obvious.

Strategy development for interpreting neuronal signals in closed-loop neurostimulation application 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 utilization of the signal as a surrogate marker for clinical states. Clinical states are disease specific but collectively can be categorized by pathological expressions of the disease (e.g. the magnitude of tremor) and behavioral intentions (i.e. 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 neurophysiological 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 article will present current developments in closed loop neurostimulation and strategies for manipulation of recordable signals in order to relate this information to a patient's clinical state (Figure 1). Specifically, this review will cover 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's Disease will be a primary focus; however, principles can be applied to other movement disorders, as well as epilepsy, mood disorders, and other neuropsychiatric diseases. This review article is intended as an introduction of engineering issues for clinicians and of clinical issues for engineers.

Rationale for closed loop stimulation: Parkinson's Disease

Open-loop DBS is effective for treating the motor signs of Parkinson's disease, but side effects of this therapy and its inefficiencies may be diminished within a closed loop system. Side effects of open-loop DBS experienced by some patients include impaired cognition, speech, gait and balance[15]. Open loop DBS could potentially disrupt decision making, learning, and cognitive association through its effect on LFP oscillations of the brain. Open-

loop DBS therapy was developed prior to an understanding of how LFP oscillations influence the precise timing of neuronal action potentials (integral to the mechanism of Hebbian learning[16,17]), and influence communication between distant neuronal ensembles (the basis of cognitive association[18,19]). Studies have demonstrated that open-loop DBS impairs learning and object-naming during stimulation of the pulvinar[20], and impairs verbal fluency and reactive inhibition during stimulation of the subthalamic nucleus. These impairments may be due to disruption of cortico-cortical or cortico-subcortical oscillatory synchronization between LFPs of connected brain regions[20].

As a result of dopaminergic depletion in Parkinson's disease, the basal ganglia are characterized by radical changes at the level of a single neuron and above. Neuronal firing patterns change significantly in animal models and in humans with Parkinson's disease. In the pathological state, neuronal pairs within and across boundaries of basal ganglia nuclei fire together with increased synchrony[21]. This phenomenon is reflected in the abnormal oscillatory activity revealed by LFPs within and between those structures.

The method by which high frequency stimulation influences cortico-basal ganglia circuits and leads to a therapeutic outcome is under debate[22,23]. DBS effects are likely a combination of a local inhibitory effect and an excitatory effect on distal connected nuclei. The local inhibitory effect of DBS may be evident by the fact that both stimulation and lesioning of the globus pallidus lead to similar therapeutic effects in the clinical treatment of Parkinson's disease. For the treatment of essential tremor, clinical effects of stimulation and lesioning of the thalamus are roughly equivalent. The distal excitatory effect of subthalamic nucleus DBS is evident by its observed effect of increasing the firing rate of neurons in the globus pallidus, a distal connected nucleus[24].

Though the mechanism of DBS therapeutic benefit is poorly understood, an end-result of open-loop DBS may be a neuronal network that is able to retain partial functionality despite insufficient dopaminergic innervation. If this is true, the present therapeutic methods may not be restoring basal ganglia functionality to the fullest extent possible, due to limitations of the static approach of open-loop DBS in an inherently dynamic system. It is therefore compelling to seek a treatment that could enhance "surviving" functionality in the basal ganglia. Dynamic restoration of neuronal rhythms by the integration of responsive signal processing might be an advantage of a closed-loop system. Conversely, damage to the basal ganglia may be the result of irreversible loss of neuronal circuitry involved in highly specialized information processing[25]. In this case, dynamic and responsive signal processing may not present an advantage compared to current open-loop DBS, especially if a damaged neuronal network generates faulty signal outputs.

Restoring the desired state: A role for closed-loop stimulation

A central challenge for closed loop therapy is the definition of a therapeutic or optimal state that neurostimulation attempts to maintain or restore. Therefore, closed-loop systems incorporate a single or multiple set points, that is, reference values corresponding to the desired state. Returning to the example of optimizing behavioral goals, each of these set

points could correspond to a different behavioral intention, such as walking, talking, or writing.

The goal of closed-loop DBS in Parkinson's disease is to restore lost functionality by stimulating the target nucleus. Stimulation of the basal ganglia is based on a "state-space model" of the basal ganglia dynamics. Stimulation is intended to force a certain feature that leads to some desired LFP reference value associated with the desired therapeutic state (Figure 1). The compensator attempts to bring the controlled variable closer to the desired reference value. The "state-space model" relies on the assumption that a disease symptom is attributable to one or more features (often just one) that is constant at some reference value level in a non-diseased physiological state. A second assumption is that restoring the value of the LFP output feature to the desired value is sufficient to restore basal ganglia functionality. These assumptions may be implausible if the pathological etiology of Parkinson's disease is characterized more by loss of neuronal organization (precluding signal processing of normal neuronal signals) than by a disturbance of LFP oscillations.

A model for a closed-loop system that contains multiple modes of compensation could be useful in an attempt to replicate the non-linear characteristics of the basal-ganglia system and subcortical motor network facilitating a wide range of motor and cognitive tasks[26]. Such a model would address the need to generate a variety of concurrent signal patterns corresponding to multiple desired reference values. For example, prior to movement initiation, a desired reference value could constitute high suppression of the beta (13–30Hz) oscillatory power of the LFP signal, while continuous execution of movement might call for concurrent beta suppression with an increase in high frequency gamma (>30Hz) oscillatory power. The advantage of multiple modes of compensation compared to a single set-point closed-loop compensation system is that therapy could be tailored to an individual patient's goals. First, desired reference values for normal cortico-basal ganglia activity must be defined in order to later dynamically adjust the controlled variables. Those values could be obtainable by recording from motor-planning cortical areas[10] or sites in the basal ganglia, including those at the stimulation site[27].

Available signals

The availability of reliably detectable bio-signals capable of driving feedback is essential to a closed-loop neuromodulation system. In current open-loop systems, the patient's clinical status and the provider's assessment of the clinical status via physical examination provides the feedback to regulate neuromodulation. While effective and the basis for newer neuromodulation models, this approach may be overly subjective/observer-dependent, time-intensive, overly consumptive of battery power, and most importantly, may not provide patients with optimal clinical benefit. Ideally, bio-signals for closed-loop neuromodulation would be easily detectable in a biocompatible manner, reliably recorded with limited noise and error, over an extended time (i.e. years), rich in content, and dynamically and accurately related to clinical states. For example, while functional magnetic resonance imaging (fMRI) is used extensively to study brain function, brain organization, and neural connectivity, fMRI is an impractical resource for measurable neuronal activity on an ongoing basis. On the other hand, invasive and implantable electrophysiological sensors that can detect

neuronal signals on an ongoing basis would improve signal detection and feedback within closed-loop systems. Current research is focused primarily on neuroelectrophysiological signal processing; however, biochemical, optical, electromyographic, and mechanical signals are other potentially useful resources.

Depending on the location of neuroelectrophysiological signal recording, signals may represent the activity of one neuron or an aggregate of cortical or subcortical neurons[28]. In general, the further away parenchymal recordings are from the brain, the poorer the temporal and spatial resolution and the higher the noise content in the measurements, but the better the perceived safety of each signal source.

Single-unit recordings, performed with invasive high-impedance (0.4–1.0 MΩ) penetrating microelectrodes such as those used for microelectrode recording in DBS surgery or those used with the Utah microelectrode array, detect action potentials from neighboring neurons (single or multiple). The action potential is considered the core unit of communication between neurons and therefore is extremely appealing as a potential data source for driving closed-loop systems. Recordings of single- and multi-unit neuronal activity have provided insight into patterned activity within the subthalamic nucleus and globus pallidus[29], and for cognitive processing and memory[30]. Despite the potential appeal of microelectrode recording, the practicality of recording action potentials for long-term use are hindered by requirement for repeated re-calibration and difficulty in maintaining the fidelity of recordings over extended periods[31,32]. Moreover, because the measurement of unit activity requires penetrating microelectrodes, spatial sampling is inherently limited (although spatial resolution is outstanding), and necessitates precision when selecting a cortical or subcortical region for recording. Nevertheless, an ongoing trial, the BrainGate trial, is making use of Utah arrays as a signal source for prosthetic control, underscoring the potential of single neuron recordings[33,34].

Unlike measurement of individual action potentials, LFP provide a measure of integrated population level activity, which is thought to be a combination of action potential activity, sub-threshold membrane voltage changes, and changes in glial potentials. LFP can be measured with an array of electrodes, including the same microelectrodes that are used for detection of unit activity as well as standard DBS leads and subcortical electrocorticographic strips and grids[35–37]. LFPs are less susceptible to drift over time and therefore provide higher fidelity and more reliable long-term recordings, which is a desirable characteristic for a control signal. Moreover, because LFPs measure population level oscillatory activity, the data is very rich in content, both in the temporal as well as the frequency domain, providing several potential bands of interest (e.g., alpha, theta, beta, gamma, high-gamma). Because signals are recorded using invasive probes, spectral content includes very high frequencies. These high frequency bands may be critical to the control of closed-loop systems[38,39]. For example, within subthalamic nuclei and globus pallidus, very high frequency bands in the 200–300 Hz range and greater than 300 Hz range have been described and correlate with degree of Parkinson’s disease motor states[38,39]. Investigations of LFP measured via electrocorticographic arrays in patients with Parkinson’s disease have noted increased beta band activity and synchronization within the motor cortex in patients with Parkinson’s disease compared to other patients[35]. These studies have also shown that therapeutic

stimulation in patients with Parkinson's diseases specifically modulates aberrant beta band activity[40]. Adaptations of DBS devices already in clinical use for invasive recording or stimulation, have simplified development of biocompatible probes for a closed-loop system[8]. The only closed-loop neuromodulation trial to date (NeuroPace) utilized recordings made by penetrating macroelectrodes and subdural electrocorticographic arrays[41]. Though there have been concerns regarding potential limitations of spatial resolution, studies using LFPs have so far concluded LFP recording allows for sufficient specificity and functional localization, suggesting LFP recording is usable in closed-loop systems[13,27].

Although measurement of unit activity and LFPs involves invasive recording approaches, non-invasive measurement of neuroelectrophysiological activity using electroencephalography (EEG) is also a consideration. A model of the brain-computer interface, the P300 speller, utilizes EEG detection of evoked cerebral electrophysiological activity to restore communication to locked-in patients[42]. In patients with Parkinson's disease, EEG has detected aberrant patterns of cortical activity that are potential biomarkers of the disease state[43]. EEG essentially measures the same neuronal signals measured by electrocorticography. However, because EEG signals are measured noninvasively, the recording electrode is further away from the electrical source and much of the higher frequency spectra (i.e., >70–100Hz) is filtered by the scalp and skull. Both of these factors contribute to a significant loss of spatial resolution. Additionally, because EEG sensors are not implanted, EEG sensors must be affixed to the scalp or skull and this may or may not be acceptable to the patient. Care must be taken in the sampling and recording process to avoid inadvertent creation of artifacts (such as aliasing)[44].

Aside from recording neuronal electrophysiological signals, a closed-loop system might also utilize non-neuronal biological signals. For example, the biochemical state of various deep brain regions may be detected in real time using cyclic voltometry[45]. Given the dopaminergic-related origins of Parkinson's disease and biochemical basis of other neuropsychiatric diseases, the concept of integrating real-time biochemical assessments may be useful for managing dynamic fluctuations in medication effects. The groundwork for such models has begun with efforts to develop a wireless non-neuronal feedback system[46]. This approach would have potential limitations related to sampling error and would require additional implantation of penetrating electrodes, which might impart greater risk than other approaches. Other non-neuronal biosignals given serious consideration are recording of peripheral signals by EMG and non-invasive accelerometers, because such signals indicate patient movement and clinical status in real-time. Hilliard and colleagues have reported the use of accelerometers attached to patients' wrists for determining effective stimulation sites within the subthalamic nucleus for treatment of tremor, bradykinesia, and gait disturbance[47]. Such kinesthetically-rich information derived from noninvasive peripheral measurement of clinical states might soon drive a successful closed loop system.

The various biosignals available for incorporation within a closed-loop system each have distinct advantages and disadvantages with respect to invasiveness, resolution, signal content and clinical relevance (Table 1). It is unlikely that any single signal source will be appropriate for all closed-loop neuromodulation approaches. The selection of appropriate

source will ultimately depend on the design of the entire system and is intimately related to the feature extraction and signal classification, as described in the subsequent sections.

Prediction Methods

Feature Extraction

The purpose of feature extraction is to transform this time series data for successive processing and/or improved computational efficiency. For example, time series data could be transformed from the time domain into the frequency domain, thus changing the meaning of the data stream from “when an event occurs” to “how frequently an event occurs.” Neuronal ensembles may use frequency coding to communicate, and therefore transformation of data into the frequency domain can be considered translation of data into the language of neuronal networks.

To improve computational efficiency and increase processing speed, data is compressed, transformed or otherwise reduced in dimension to remove redundancy and condense overall data size. After signal features are extracted, an additional processing component or feature selection/dimensionality reduction may be required to further reduce the number of features and/or dimensions, or remove noise/outlier features. As a result, the features that are meaningful in the learning and classification stage are identified and chosen, while outliers and artifacts are excluded from the data.

Time domain—Time domain features of EEG or LFP signals such as event related potentials (ERP) may be extracted by splicing long (e.g. 10 minutes) time series data recordings into shorter time segments/epochs (e.g. 500 milliseconds), before and after an event. By averaging many event-aligned epochs, features of the data related to the event are emphasized and those features unrelated to the event cancel out through averaging. This technique is used to identify visual evoked potentials (VEP), somatosensory evoked potentials (SSEPs), and the cognitive oddball response, the P300.

Quantified temporal information derived from action potentials includes neuronal firing rates, peri-stimulus time histograms (PSTH), and interspike time intervals (ISI). These measures are useful for interpreting neural information from cerebral neurons that are responding to external influences such as visuospatial memory[59], visual presentation of faces[60], or passive joint movements[61]. Firing rates are modulated by neurons responding to these external influences and also encode motor plans. An example of this is evidenced in the motor cortex by the cosine tuning of neuronal firing rates in a manner corresponding to the direction of arm reach[62]. The timing of an electrophysiological spike relative to the previous spike provides other specific information useful for decoding neural information[63]. The timing of the neuronal spikes is further influenced by the phase of low frequency LFPs, as demonstrated by spike clustering at the trough of beta frequency LFP oscillations in the subthalamic nucleus[64].

Time-Frequency Domain—Several power spectral estimation methods are used to transform recorded time domain data into time-frequency domain data and allow quantification of neuronal electrical oscillations. Common techniques to estimate spectral

power include variations of short time Fourier transform, wavelet transformation, and autoregressive models[65–67]. Frequency bands of interest within neuronal signals have historically been defined by their visual appearance and spatial distribution on EEG tracings. These include delta (<4Hz), theta (4–8Hz), alpha (8–13Hz), mu (7–11Hz), beta (13–30Hz), and gamma rhythms (>30Hz)[68]. These definition terms are also applied to equivalent frequency signal ranges recorded invasively by electrocorticography (ECoG) and LFP. Unlike synchronous processes which are band frequency limited, asynchronous processes have been shown to produce broad band spectral power, whereby power exponentially decreases at increasing frequencies[69]. Such changes in relative power within frequency bands have been correlated to movement and speech in both cortical and subcortical recordings[13,27], and thus show promise for use in neural decoding within closed loop neurostimulation paradigms.

Phase Domain—Features of amplitude, frequency, and phase can describe a sinusoidal function infinite in time. Phase can be interpreted as a shift or offset in time of that wave from some arbitrary reference time point. Valid phase values vary from $-\pi$ to $+\pi$, or $-\lambda/2$ to $\lambda/2$, where λ is the wavelength ($\lambda = 1/\text{frequency}$). Simple signal processing techniques such as filtering can change the phase of a signal in a frequency dependent fashion. Phase analysis is inherently more difficult than simple signal processing due to the absence of a clear zero-phase reference point and the presence of artifacts resulting from signal processing techniques. Neural oscillations are finite in time and statistically non-stationary signals. For these reasons, no definitive method has been demonstrated to measure the phase of neural oscillations[70–72]. Furthermore, there is no clear interpretation for the instantaneous phase of a neural signal[72]. Despite these limitations, phases of neural oscillations have been shown to influence spike timing[64], and are particularly relevant to mechanisms of cognitive processes like memory[18].

Oscillations in the motor network are related to each other through non-linear interactions. In particular, the phase of slower oscillations in the theta, alpha, and beta bands modulates the amplitude of faster rhythms in the beta, gamma and very high gamma ranges[38,73,74], a phenomenon referred to as phase-to-amplitude cross-frequency coupling (PA-CFC). PA-CFC indicates the extent to which the phase of one oscillation extracted from a LFP determines the amplitude of another oscillation. Hierarchical relationships between oscillations might play a significant role in a variety of cognitive and motor tasks[73,74] and could be applied as parameters in the design of a closed-loop DBS system. Despite accumulating evidence for PA-CFC's ubiquity and functional importance in the nervous system, PA-CFC has not received much attention as a potential closed-loop system parameter for indicating motor task selection and planning.

Studies have shown that PA-CFC is correlated with the pathological state of the basal ganglia in movement disorders. For example, PA-CFC in the motor cortex (beta-gamma) is exaggerated in Parkinson's disease patients compared to patients with epilepsy who do not have a movement disorder[35]. Therapeutic stimulation of the STN and dopaminergic therapy reduce the magnitude of coupling between beta-phase and gamma-amplitude[35,38], highlighting the potential of PA-CFC as a biomarker of disease.

A current goal in the development of closed-loop DBS systems is to discover reference points to which a controlled variable converges and thereby leads to enhancement of motor capacity. Feature extraction is truly limitless in its potential for abstract manipulation of raw data. Table 2 highlights techniques and approaches for a subset of major approaches.

Pattern Classification

The objective of pattern classification is to learn a mathematical model (a classifier) that can recognize and segregate novel patterns. Pattern classification algorithms are powerful in that they can be applied naively to data. These "machine learning" algorithms may be applied to recordings of the human voice for speech recognition,[116] images of handwriting for association with personality,[117] functional MRI to decode emotion evoked by facial expressions[118] and scalp EEG to allow communication[119]. For instance, in the case of brain computer interfaces, a classifier given a segment of recorded brain signal is able to associate the neural signal with a given state, such as emotion, thought, behavior, or intention (a "class label"). During the training phase, subjects perform activities for which the corresponding class label is known (e.g., "motor activities" class label) and the algorithm "learns" the corresponding pattern. Table 3 summarizes several classification methods used for brain signal classification, including Support Vector Machines (SVMs), Artificial Neural Networks (ANNs), K-Nearest Neighbor (KNN), Bayesian Classification, and Hidden Markov Model (HMM). We will describe two well-known techniques for pattern classification, KNN (a non-linear classifier), and SVM (a linear classifier), also presented in Figure 3.

KNN[120] is a simple but effective non-linear classification technique. After a training phase using samples with known corresponding class labels in the feature space, KNN predicts the class label of a novel sample based on the label of its K closest ("neighbor") samples. For example, if K is set to 3, KNN first finds the 3 neighbor samples closest to the test sample and then chooses the label of the novel sample based on the majority label of those 3 neighbor samples (Figure 3A). Techniques for finding the nearest neighbors include calculations for Euclidean distance and Manhattan distance. The parameter K is usually selected empirically and can affect the sample recognition rate. In this KNN algorithm, the training data sets do not need to be linearly separable, as illustrated in Figure 3.

Support Vector Machine (SVM) is another common method for pattern classification and regression[121] introduced by Cortes and Vapnik[122]. SVMs are used in many applications including isolated handwritten digit recognition[122,123], brain signal classification[124,125], face recognition in images[126], and text categorization[127]. A linear binary SVM classifier technique uses two parallel hyper-planes to separate the margin between two different classes of data in the feature space (Figure 3B). The SVM selects directions for the hyper-planes via an optimization problem algorithm where the objective is to maximize the margin between the separating hyper-planes. SVM solves the optimization problem using training samples, called support vectors, that lie on the margin. Two classes of data are often not able to be separated by a plane in the original space (Figure 3C) and require mapping into a higher dimensional space to become linearly separable (Figure 3D). SVM uses kernel functions to project feature vectors onto a more discriminative space by representing data

with a higher dimensionality, allowing the separation of data groups using non-linear functions (e.g., separating curves). The use of several different types of kernel mappings, such as radial basis function (RBF)[128] and the polynomial function[129], is reported in the literature.

Classification techniques such KNN and SVM are directly applicable to closed loop neurostimulation, and DBS devices with these algorithms embedded within the system hardware is in the near future[130]. With the appropriate choice of neural signals and feature extraction techniques, machine learning algorithms have the potential to classify behavior and would allow the DBS system to adapt to dynamic patient requirements.

Closing the Loop: DBS Parameter Interventions

Current DBS system neurostimulation consists of a delivering a train of biphasic pulses with adjustable parameters (amplitude, pulse width, and frequency). This train is spatially applied across a cathode and an anode that are adjusted according to the size of the stimulation electrode array. The charge is deposited at the cathode, the negative pole, and the current flows from the cathode to the anode[132]. Safety of the DBS is ensured because of a net-zero current application across the biphasic waveform of each pulse of the train of stimulation[133–135], use of platinum-iridium electrode material[136], and limiting the charge density and charge per phase to 26μC/cm^2/phase and 0.018μC/phase respectively[136]. The exact threshold for neural injury is unknown, however neural injury has been noted at charge density of 50μC/cm^2/phase and charge per phase of 1.0μC/phase with platinum electrodes[137], and at considerably lower values for stainless steel electrodes[136]. Although the spatial and pulse parameters of stimulation may be variably controlled in a closed loop system, early closed loop systems have used only an on/off control[49] for these parameters, or have used variable control of amplitude only[138].

There are a limited number of published studies demonstrating mature closed loop stimulation systems for essential tremor, Parkinson's disease, and epilepsy. Therefore, individual reports of human and animal closed loop neurostimulation systems will be reviewed.

Case Study 1[48]: Pathological tremor prediction using surface electromyogram and acceleration

Population: Humans with Parkinson's disease (PD) and essential tremor (ET), open label feasibility trial

Objective: To develop a closed loop neurostimulation system to switch DBS on/off using a tremor prediction algorithm. Tremor was predicted using surface electromyogram (sEMG) and acceleration from tremor-affected extremities.

Approach: Signal features were extracted from recorded EMG and acceleration signals. These features included spectral parameters from Fourier and wavelet transforms, and nonlinear time series, such as sample entropy and recurrence quantification analysis (RQA).

Features are used to classify and predict PD and ET states using a simple thresholding classifier, to turn the DBS on and off.

Main results: The resulting algorithm predicted tremor onset for all 91 trials recorded in 4 Parkinson's disease patients and for all 91 trials recorded in 4 essential tremor patients. The predictor achieved a 100% sensitivity for all trials considered, with an overall accuracy of 80.2% for PD and 85.7% for ET.

Case Study 2[130]: Validation of a bi-directional pulse generator for neural state classification

Study design: Ovine model of acute epilepsy, feasibility trial

Objective: To determine the feasibility of the use of an implantable bidirectional sensing and recording pulse generator to create a closed loop neurostimulation system. Specific objectives were to measure disease related neural data to detect a desired neural state and to update neurostimulation parameters in real time based on the detection state of the embedded algorithm.

Approach: Hippocampal stimulation-induced seizures were induced with concurrent sensing and recording. SVM pattern classification was used to categorize the 30s stimulation train induced as a seizure, visible as after discharges on raw LFP tracing and visible in the frequency domain as increased low frequency power in the 5–20Hz band.

Main results: It is feasible to use LFPs recorded during ongoing stimulation to classify neural states such as an acute seizure. Attention must be given to the stimulation and recording electrode selection, as well as the stimulation frequency in order to minimize contamination of LFP with stimulation artifact.

Case Study 3[57]: Spike triggered closed-loop DBS for Parkinson's disease

Study design: Non-human primate MPTP Parkinsonian model, feasibility trial

Objective: To compare the effectiveness of open loop and closed loop neurostimulation paradigms for Globus Pallidus pars internus (GPi) DBS.

Approach: A single pulse or a short pulse train (7 pulses at 130 Hz, biphasic, 80 μA, 200 μsec) was delivered through a pair of GPi electrodes at a predetermined and fixed latency following action potential detection in either primary motor cortex or GPi. The open loop paradigm consisted of 130Hz continuous stimulation.

Main results. 7-pulse train after an M1 spike significantly reduced GPi firing rate and eliminated oscillatory firing patterns characteristic of PD and improved limb akinesia. Standard DBS had a lesser effect on GPi neuronal firing, with greater maintenance of oscillatory properties and less improvement in limb akinesia.

Case Study 4[41]: Prediction of seizure likelihood with an implanted seizure advisory system

Study design: Humans with medically refractory epilepsy, open label feasibility trial

Objective: To demonstrate feasibility of implanting devices to predict an oncoming seizure, and advise the patient using a handheld device.

Approach: Sixteen channels of electrocorticography recordings surrounding known seizure onset zones were transmitted wirelessly to a hand held device, which advised the patient of the likelihood of an upcoming seizure based on a proprietary algorithm based on patient-specific data. These algorithms were subsequently installed in the patient's hand held advisory device.

Main Results: 11 of 15 patients were able to train an algorithm for seizure prediction and advisory, and 8 of the 11 patients had a stable prediction algorithm over time. Five patients achieved a seizure prediction sensitivity of > 60%.

Case Study 5[139–141]: Responsive cortical stimulation for the treatment of epilepsy (NeuroPace Trial)

Study design: Humans with medically refractory epilepsy, randomized pivotal clinical trial with a 12 week blinded, randomized on- or off-stimulation period

Objective: To demonstrate effectiveness of a closed loop neurostimulation system to detect and react to seizures. The trial included 191 patients; 50% had mesial temporal lobe onset, and 73% had bilateral temporal lobe epilepsy.

Approach: The research group implanted a responsive neurostimulator with intracranial depth and surface electrodes at known seizure onset zones. The device was capable of three seizure detection algorithms: line length[142], half wave decomposition[143], and integrated area under the ECoG signal in a sliding time window. Responsive stimulation parameters included frequency (1–333Hz), current amplitude (0.5–12mA), pulse width per phase (40–1000 (μs), and burst duration (10 to 5000ms). Initial programming recommendations were provided. Maximum charge density was hardware limited at 25 $\mu C/cm^2$/phase[141]. Responders were defined as patients with 50% or greater reduction in seizure frequency.

Main Results: In the randomized pivotal study, there was a statistically significant difference in mean seizure count per month between sham and stimulation groups. During the blinded period, the reduction in seizures in stimulation arm was 38%, compared to a 17% reduction in sham group (p=0.012). The responder rate was 43% at one year.

Alternate Applications

While this chapter has focused on movement disorders, the principles involved in system design, signal sources, feature extraction, signal classification and effector control is applicable to virtually any neuropsychiatric disease neuromodulation system under development.

The most work in the closed loop neurostimulation field has been done in the area of epilepsy and signal classification algorithm design for prediction of seizure onset[144]. Such work has led to the first human implanted seizure prediction system for treatment of medically refractory epilepsy[41]. The challenges of developing closed-loop neuromodulation

systems for epilepsy, as it is with movement disorders, is identification of appropriate patient state variables to drive neuromodulatory therapy; development of informed models that accurately determine the optimal pattern of stimulation in response to patient states; and detection of reliable biomarkers indicating response to therapy. While the NeuroPace trial is seen as a success by some, the inability to precisely address all of these challenges of closed-loop systems may have, in part, contributed to sub-optimal results[140].

One can foresee the application of closed loop systems to other neuropsychiatric diseases, particularly to diseases with cyclical symptom patterns, such as depression. Identification of neurophysiological biomarkers indicative of a diseased or pathological state could theoretically drive therapy parameters “on-demand.” Similarly, one could envision a system for closed-loop neuromodulation that delivers therapies coincident with memory acquisition states so as to reinforce learning.

Closing remarks

The field of closed loop neurostimulation is an interdisciplinary science incorporating disciplines of clinical neurosciences and electrical engineering. Given the importance of neuronal oscillations in the cooperative functioning of brain ensembles, the appeal for a neurostimulation system with a small electrical footprint is evident. Thus, closed loop stimulation is preferable over open loop stimulation for its less disruptive impact on cognitive processes that depend on coordinated neuronal oscillations.

Fundamentally, closed loop stimulation strategies must target certain desirable neural states that can be restored, such as an optimal state for walking, talking, or writing. Closed loop neurostimulation systems may use physiological signals available at the site of the stimulation (e.g. LFP data), or signals that are geographically removed from the site of stimulation (e.g. ECoG or EEG data). Non-central nervous system signals are also available for use in closed loop systems, such as EMG signals, or signals from internal and external sensors (e.g. accelerometers, timing devices, or audio devices). Once these signals are measured and digitized, they must be compressed or transformed into features suitably efficient for processing by pattern classification algorithms for accurate prediction of neural patient states. These algorithms may be pre-embedded in the device[130], or first explored within a high power computer cluster before downloading a lightweight patient-customized version into the device’s memory[41]. Finally, the algorithm must intelligently manipulate stimulation parameters in the domains of time, frequency, or space to optimize the patient’s neurological condition.

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Highlights

- 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.

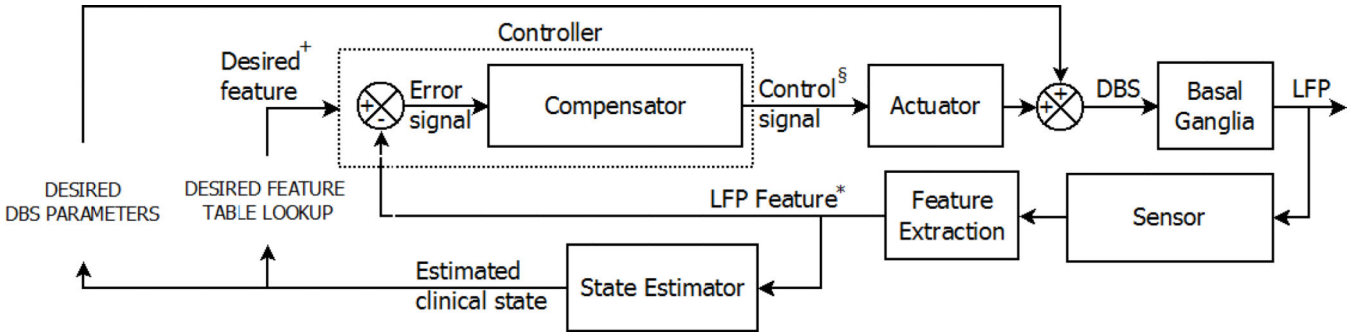

Figure 1.

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 impacting 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.

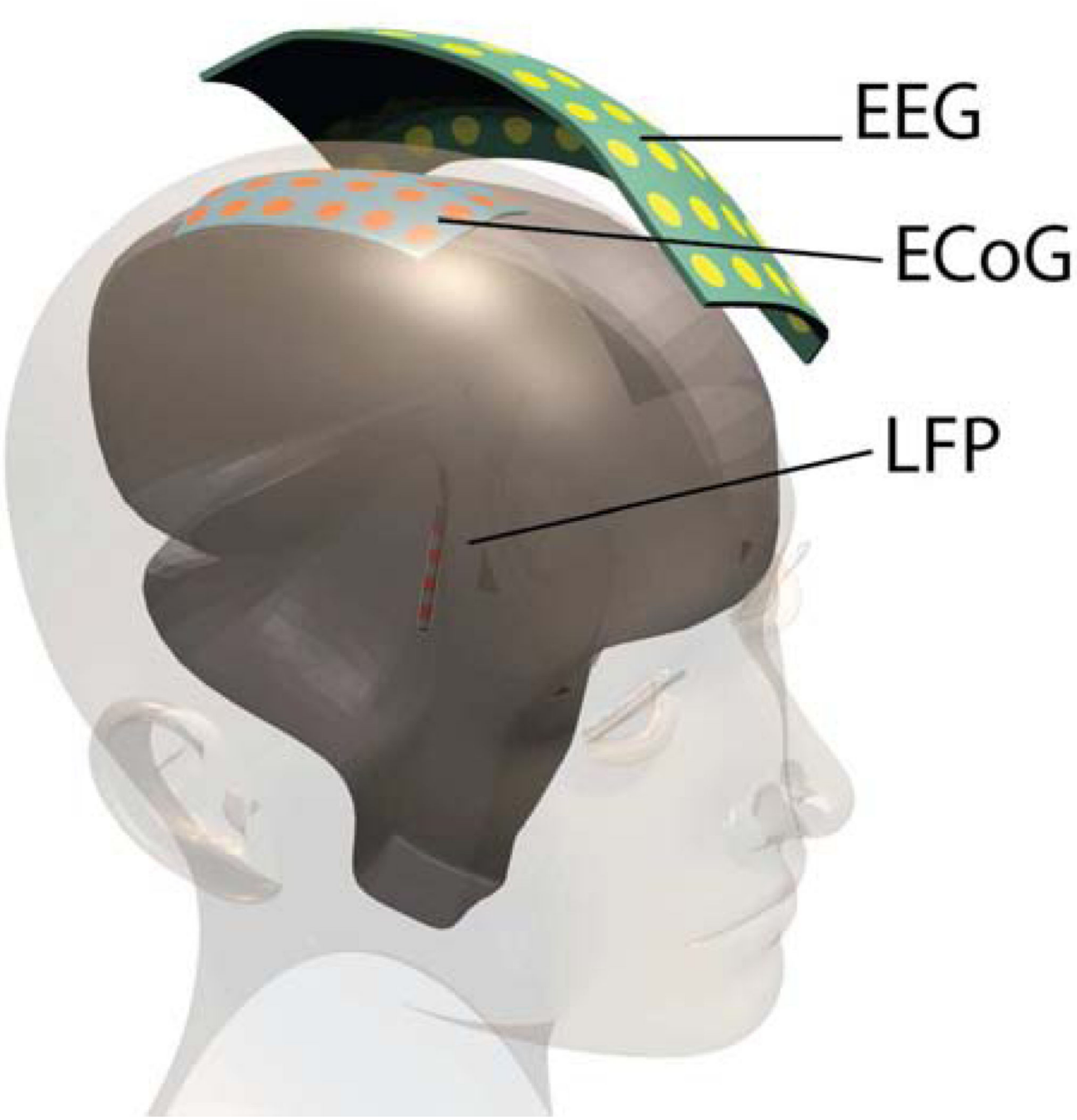

Figure 2.

Candidate neural signals for closed loop neurostimulation systems include non-invasive electroencephalography (EEG), or invasive electrocorticography (ECoG) or local field potentials (LFP). In addition to these brain signals, the system could use electromyography (EMG), or physicals sensors such as accelerometry (not shown).

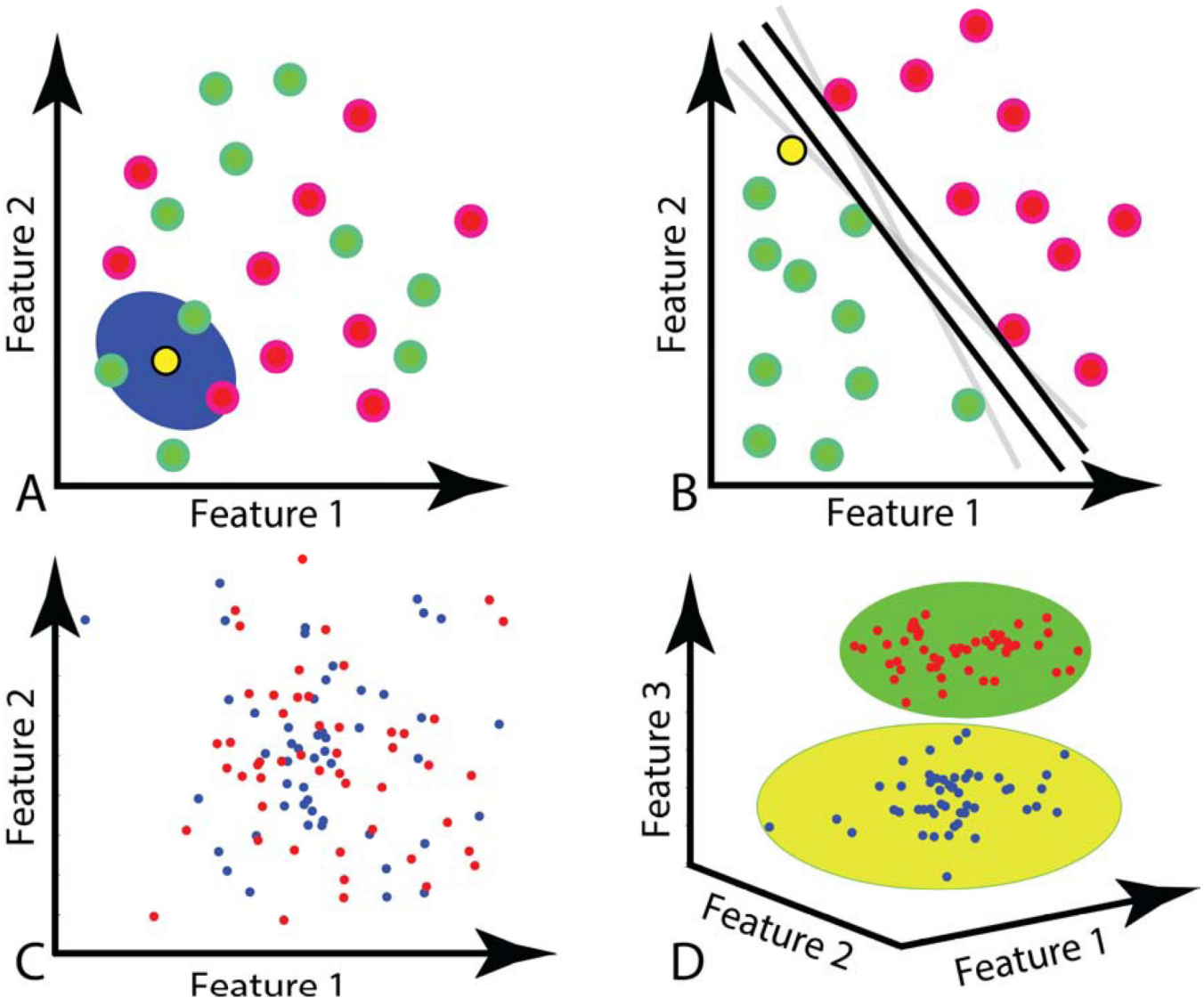

Figure 3.

Graphical representations of pattern classification algorithms. A: k-nearest neighbor (KNN). In this case, the yellow (unknown) sample will be classified by polling its 3 nearest neighbors, and will be classified as a member of the green group. B: Support Vector Machine (SVM). If two groups of data can be separated by a line or plane in feature space, SVM will provide the plane that defines the widest gap between the 2 data sets. The group members that lie on (support) the parallel planes are called support vectors. C: In this example, the two classes of data are not linearly separable in the depicted feature space. D: Here, kernel functions add additional dimensions, or features to data sets. By adding a third feature to the data set in C, the two groups are now separable and a SVM algorithm can classify new data.

Table 1

Available Signals for signal based neurostimulation: The following table summarizes recent studies, experiments and device development regarding brain signal based neurostimulation.

Feedback Signal	Stimulation Type	Feedback mechanism	Application	Subject	Reference
Arm and hand EMG and acceleration sensors	DBS (STN, VIM)	Features of EMG and acceleration signals are used to predict tremor onset, regulating DBS not implemented.	ET, PD	Human	48
EMG	DBS (VIM)	Features of EMG signals measure tremor and regulate DBS system via remote programmer.	Intention Tremor	Human	49
Cortical ECoG/LFP	Cortical stimulation via cortical depth electrodes or ECoG	Abnormal phase synchrony of cortical signals triggers stimulation.	Epilepsy, seizure detection	Animal model (on-line) and human (off-line)	50
Skull mounted EEG	Cortical stimulation via skull mounted EEG (F3)	Stimulation triggered by reduced EEG phase synchronization across multiple electrodes.	Epilepsy	Rats	51
ECoG	Pharmacological	Voltage window detectors and frequency analysis parameters matching patient's specific seizures trigger drug delivery system.	Epilepsy	Rat model and offline human ECoG	52,53
Single unit recording of spinal dorsal horn neurons	DBS Periaqueductal Grey	Stimulation triggered by user-defined clustering of inter spike intervals used to classify physical stimuli.	Pain	Rats	54
Neuronal firing rate	DBS	Adaptive algorithm adjusts DBS to maintain a stimulus to firing frequency ratio.	Epilepsy	Computational Model	55
Skull mounted EEG over frontal barrel cortex	DBS (Zona Incerta)	Linear least squares was utilized to classify seizures based on entropy and spectral power.	Epilepsy	Rats	56
Single unit recording of primary motor cortex	DBS (GPi)	DBS pulse train delivered at fixed latency following M1 spike detection.	PD	Primate model of PD	57
LFP recording (Hippocampus)	DBS (Hippocampus)	DBS and LFP recording via distinct contacts on macroelectrode. Seizures detected during stimulation with machine learning. Seizure modeled by afterdischarge potentials induced by hippocampa	Seizure	Sheep	58

Feedback Signal	Stimulation Type	Feedback mechanism	Application	Subject	Reference
		stimulation.			

EMG: Electromyography, DBS: Deep Brain Stimulation, STN: Subthalamic Nucleus, VIM: Ventral Intermedius Nucleus of the Thalamus, ET: Essential Tremor, PD: Parkinson's disease, ECoG: Electrocorticography, GPi: Globus Pallidus pars internus, LFP: Local Field Potential.

Table 2

Feature Extraction: Feature Extraction: This table summarizes the signal processing techniques for feature extraction which appear in a number of recent publications.

Domain	Method	Reference
Time-Domain	Linear filtering	75–78
	Linear combination and regression	76,77
	Blind source separation (BSS)	76,77
	Matched filter	76,79,80
	Autoregressive model parameters	76,80–84
	Independent component analysis (ICA)	76,80,83,85,86
	Karhunen-Loeve transform (KLT)	87,88
	Kalman filtering, Unscented Kalman Filter	76,80,89
	Correlation of temporal average of stimulus locked response with template	76,79,80,90
	Size of temporal average of stimulus locked response	76,80
	Covariate shift adaptation	91
	Neural time series prediction preprocessing	92
	Barlow- and Hjorth-based feature	76,92
	Neural firing rate	62,76,80,93,94
	Signal amplitude differences	76,80
	Event Related Potential P300, Steady-state visual evoked potential (SSVEP)	80,93–105
	Lateralized readiness potential (LRP)	99
	Slow cortical potentials (SCP)	94,96,99,100
	Cross-Correlation	90
Frequency Domain	Spectral parameters, frequency band power	27,75,76,80,83,87,88,93,96,97,106–110
	Event-related (de)synchronization (ERD, ERS)	27,75–77,80,81,95,98,99,102
	Sensorimotor activity PSD	94
	Motor imagery	84,93
	Neural time series prediction preprocessing	92
Time-Frequency Domain	Wavelet transform	76,80,83,111
	STFT	27,107
	Matching pursuit decomposition	112
Spatial Domain	Common spatial patterns (CSP)	76,83,106,113
	Beamforming	114
	Surface Laplacian derivation	75,81
	Linear minimum mean squared error (LMMSE) spatial filter	115
	Spatial filtering	75
Subspace Domain	Principle component analysis (PCA)	76,77

Domain	Method	Reference
Phase Domain	Coherence or phase calculation	76,80

Table 3

Prediction Methods: This table summarizes several feature processing techniques, including feature modeling, detection and classification reported in a number of recent publications.

Method	Reference
Support Vector Machines	76,80,82,86,95,102,105,111
K-Nearest Neighbors (KNN)	76,80,87,95
Thresholding	75,76,79,80,90
Bayesian Classification	76,80,104,106
Linear Discriminant Analysis (LDA), Fisher Linear Discriminant (FLD), Mahalanobis Linear Distance (MLD)	76,80,82,84,87,92,95,102–105,109,115
Quadratic Discriminant Analysis (QDA)	82,84
Hidden Markov Model (HMM)	76,80
Linear/Non-linear Continuous Transformation	76,80
Classifier Adaptation	91
Gaussian Process	110
Decision Tree	81,97
Gaussian Mixture Model	78,84
Genetic Algorithm	88,102
Logistic Regression Linear Classifier	114
Neural Network	82,92
Common Spatial Patterns (CSP), Multiple-class CSP	84,106,113
Filter Bank Common Spatial Patterns (FBCSP)	84
Iterative Spatio-Spectral Patterns Learning (ISSPL)	108
Fuzzy Inference	131