EPILEPSY CURRENTS

Current Literature
in Basic Science

Epilepsy Currents
2024, Vol. 24(4) 283-285

DOI: 10.1177/15357597241254274
journals.sagepub.com/home/epi
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Forgotten Tides: A Novel Strategy for Bayesian Optimization of Neurostimulation

From Dawn Till Dusk: Time-Adaptive Bayesian Optimization for Neurostimulation

Fleming JE, Pont Sanchis I, Lemmens O, Denison-Smith A, West TO, Denison T, Cagnan H. *PLoS Comput Biol.* 2023;19(12): e1011674. doi:10.1371/journal.pcbi.1011674. PMID: 38091368

Stimulation optimization has garnered considerable interest in recent years in order to efficiently parametrize neuromodulation-based therapies. To date, efforts focused on automatically identifying settings from parameter spaces that do not change over time. A limitation of these approaches, however, is that they lack consideration for time dependent factors that may influence therapy outcomes. Disease progression and biological rhythmicity are two sources of variation that may influence optimal stimulation settings over time. To account for this, we present a novel time-varying Bayesian optimization (TV-BayesOpt) for tracking the optimum parameter set for neuromodulation therapy. We evaluate the performance of TV-BayesOpt for tracking gradual and periodic slow variations over time. The algorithm was investigated within the context of a computational model of phase-locked deep brain stimulation for treating oscillopathies representative of common movement disorders such as Parkinson's disease and Essential Tremor. When the optimal stimulation settings changed due to gradual and periodic sources, TV-BayesOpt outperformed standard time-invariant techniques and was able to identify the appropriate stimulation setting. Through incorporation of both a gradual "forgetting" and periodic covariance functions, the algorithm maintained robust performance when a priori knowledge differed from observed variations. This algorithm presents a broad framework that can be leveraged for the treatment of a range of neurological and psychiatric conditions and can be used to track variations in optimal stimulation settings such as amplitude, pulse-width, frequency and phase for invasive and non-invasive neuromodulation strategies.

Commentary

Electrical neurostimulation is increasingly used worldwide for treating medication-refractory epilepsy. While medications are primarily adjusted through timing and dosage, neurostimulation involves a broader range of adjustable parameters, including amplitude, frequency, duty cycle, and charge density. Responsive neurostimulation and vagus nerve stimulation have additional settings to detect brain or heart activity. Neurostimulation devices provide an extensive range of adjustable parameters, which may allow for individualized therapy optimization but carry a cost of significant complexity and effort.

The process of optimizing neurostimulation takes time. During each patient visit, interval history and device logs are reviewed. An empiric trial-and-error approach is typically employed, where new settings are selected based on prior responses to therapy. Initially, the road map is relatively straightforward: providers usually choose electrode contacts thought to be closest to the target region, select stimulation settings that match prior reports of therapeutic ranges, and gradually increase stimulation amplitude over several weeks until seizures are well-controlled. If the patient develops side effects, the stimulation amplitude is typically reduced. However, if seizures persist, the road map becomes less clear. Should the clinician make minor adjustments to avoid side effects, or large jumps to explore the parameter space? The multidimensional nature of treatment can sometimes overwhelm clinicians, leading to early abandonment of the optimization process and acceptance of sub-optimal results.

While deep brain stimulation (DBS) for treating movement disorders can have near-immediate results, therapeutic and adverse effects on epilepsy typically emerge over a more extended period, sometimes several months or longer. Long-term follow-up studies of DBS in refractory epilepsy have noted a sustained downward trend in median seizure frequency lasting up to 6 years postimplantation,[1] suggesting a cumulative seizure-suppressive effect. This extended timeline underscores the importance of identifying early indicators predictive of long-term success. Furthermore, the variable nature of epileptic activity, with its potential for gradual, random, or semi-periodic fluctuations,[2] further complicates the optimization process, necessitating a dynamic and responsive approach.

These challenges have motivated the development of "adaptive" DBS, wherein stimulation parameters are automatically adjusted. One approach would be to use neurophysiological biomarkers, like frequency band activity, to algorithmically adjust stimulation in an automated fashion.[3] A semi-automated approach would involve a clinician who iteratively sets parameters and observes effects.[4] This shift toward adaptive DBS promises to improve the response to therapy and reduce the burden of frequent programming visits.

One promising approach toward adaptive DBS is to leverage historical parameter data through Bayesian techniques, which is a statistical method that uses past events to predict the likelihood of future events. This method can be used to identify the most efficacious or informative settings. A recent study in animal models of epilepsy used Bayesian techniques to detect and treat epileptiform activity.[5] Gaussian process based algorithms, which define a space of functions that fit a given set of data points, have been used to select parameters to drive specific movements,[6,7] treat resting tremor,[8] and reduce muscle rigidity[4] in Parkinson's disease. Gaussian process algorithms have the potential to provide advanced autonomous parameter optimization; however, they traditionally rely on stable inputs, and their performance can deteriorate over time. Moreover, fluctuations in epileptic activity due to disease progression, medication adjustments, state changes, and circadian rhythms would further reduce their performance.

To address some of these limitations, a new study by Fleming et al[9] presents a novel time-varying Bayesian optimization method to account for processes that change over time. They use a computational population-based model of neural activity with oscillatory states that fluctuate from a random arrhythmic activity ("baseline") into highly synchronous and rhythmic activity ("symptomatic"). This model has several important features, including gradual changes over time and the fact that the oscillatory activity can be perturbed between states. They tuned the population of oscillators to have a characteristic frequency that roughly corresponds to essential tremor, where the tremor is observed to occur between 4 and 12 Hz. They evaluated how high-frequency stimulation, typically used to treat tremors, would induce a shift in the population activity by advancing or delaying spike firing.

They found that conventional, time-invariant forms of Bayesian optimization initially work well, showing that stimulation could break the population from synchrony. However, stimulation showed gradually diminishing performance. In contrast, by adjusting for repeating variations in activity (periodic covariance) and for gradual changes ("forgetting" covariance), they found that stimulation can maintain consistent optimization over time, regardless of changes in the underlying system dynamics.

One limitation of the current study is that it is tuned to a single oscillatory frequency (8 Hz), which may be relevant to movement disorders like essential tremors but is not directly applicable to epilepsy. In epilepsy, there is no single interictal frequency that corresponds to seizure risk. Similar analyses of the technique in model systems with more complex frequency patterns and discrete activity that corresponds to seizures would be of great interest.

This study is not the first effort to design a time-variant adaptation to optimize stimulation settings for electrophysiologic signal control. A dual-control algorithm[10] can also account for short- (inner parameterized feedback) and long-term changes (outer parameter adjustment loop). Their approach provides a structured method to adapt to newly encountered changes, which may be more adaptable to real-world clinical applications where the periods of underlying dynamics are unknown.

Neural networks based on radial basis functions have also been used to optimize stimulation parameters for Parkinson's disease[11] in response to dynamic changes. Radial basis functions give greater influence on data points close to centers of interest, helping to find key parameter settings with noisy data. However, Bayesian approaches have several advantages over neural network models; they are inherently more robust and allow for more adaptive decision-making under uncertainty. Making rationally based adjustments to neural network parameters, such as modifying the algorithm to adapt to time-varying changes, is also intrinsically more challenging with neural networks than with Bayesian approaches.

There is a pressing need to improve the process of optimizing neurostimulation parameters for epilepsy. Bayesian approaches that are robust to fluctuating neurologic states are promising; however, autonomous programming for epilepsy will require a reliable assessment of seizure risk, something that remains to be discovered. Seizure counts are sporadic and, when rare, are an ineffective feedback signal. Further advances in electrophysiologic signal analysis are likely needed to improve real-time assessment. It is becoming increasingly clear that epilepsy also has periodic rhythms that need to be accounted for when assessing seizure risk. Methods that address the evolution and periodicity of epilepsy and other neurologic diseases are an essential next step toward improving outcomes with neurostimulation therapy.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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