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Computational Neuromodulation: Future Challenges for Deep Brain Stimulation

Over the past two decades, deep brain stimulation (DBS) has been leading a renaissance of neurosurgical treatments for neurological and neuropsychiatric disorders. DBS has become an established adjunct therapy for movement and mood disorders that, despite maximal medical treatment, remain sufficiently debilitating to warrant the risks of brain surgery [1]. The procedure has been approved by the U.S. Food and Drug Administration (FDA) for essential tremor (ET), Parkinson's disease (PD), dystonia, and obsessive compulsive disorder, and the growing spectrum of treatable conditions is expanding to pain and major depression, among others. Interestingly, the large phenomenological variance of the treatable symptoms that span the motor and affective domains is addressed by the same therapeutic principle: similarly to how a cardiac pacemaker works, a medical device called a *neurostimulator* sends frequent (50–250 Hz) electrical pulses to electrodes implanted into a subcortical nucleus associated with the disorder. Despite its simplicity, the procedure, when applied accurately, may alleviate symptoms of complicated diseases.

After 20 years of clinical practice and a variety of hypotheses formulated at the local or the network scale, the physiological mechanisms of DBS remain unclear. Although the surgical implantation procedure offers a unique opportunity to record in vivo neural signals as close to their generators as possible, the recording conditions significantly vary depending on the intrinsic variability of the brain, the divergence in structural changes caused by the underlying neuropathophysiology, the compensation mechanisms that each brain has possibly developed, and the long-term administration of medication in the patients on whom were operated. Consequently, DBS improvement has been hampered by stagnation in discovering personalized and dynamic methodologies that can leverage the intranuclear neural signals to address the highly diverse clinical phenotype and the fluctuating symptom severity. This is about to change as recently introduced DBS systems create new frontiers for the neural signal processing community. In this article, we discuss the basic principles and challenges faced by the new technological advances in DBS and describe the race toward personalizing therapy to each patient's clinical state.

Over the past two decades, deep brain stimulation has been leading a renaissance of neurosurgical treatments for neurological and neuropsychiatric disorders.

Neural signals drive automatic detection of deep structures inside the human brain

The DBS implantation procedure is typically guided by microelectrode recordings (MERs) of the neural activity at different subcortical depths inside and outside the nucleus (Figure 1). The activity is mapped via one or more microelectrodes traveling along the putative implantation path, and the resultant pattern of neural spikes is transduced to audio. When a neurophysiologist acoustically verifies the pattern of multiunit spikes that corresponds to the entry/exit of the implantation target, the recording electrode is removed and a stimulation electrode is implanted along this trajectory. The process gives intraoperative access to two important neurophysiological signals from deep structures: 1) the local field potential (LFP), which is the low frequency content (up to 100 Hz) of the MERs representing the synchronized oscillatory activity mainly at the dendrites of neurons up to 3 mm away from the electrode, and 2) the multiunit activity (MUA), which is the high frequency content of the MERs representing the neural spiking patterns from neurons with a distance 100–300 μm. Although our study on the LFP-MUA relationship has revealed interesting nonlinear correlations between the two signals [2], their functional interconnection remains unclear, and they are typically treated as signals carrying different types of information. Nevertheless, incorporating LFP- and MUA-derived features into neural area classifiers has supported the

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laborious and subjective detection of DBS targets.

Building upon neurophysiological hypotheses on disease- and symptom-specific network activities, a variety of neural signal features have recently been employed to inform the DBS implantation procedure and its clinical outcome. For example, the most prominent feature in STN-DBS, the neural activity in the beta band (~13–35 Hz) stems from strong evidence that an elevated beta power in motor regions of the cerebral cortex and basal ganglia is associated with reinforcement of the current motor state [3], a process that is pathophysiologically disturbed in the presence of rigidity and bradykinesia, two of the cardinal symptoms for PD. We, along with others, have speculated about the existence of beta-band islands, local functional neuronal organizations found in STN areas other than the dorsolateral area where one expects to find sensorimotor activity [4]. This could support the idea that spatially distributed synchronizations may be a key feature of the STN pathophysiology in PD and a possible future target for DBS. The DBS implantation procedure can also be informed by using the second major component of MERs, the intranuclear MUA. For example, we have extracted quantitative temporal trends (feature activity versus time) from MERs to generate spatial profiles (feature activity versus MER depth) of the nearby brain structures. By employing kernel depth-time interpolation (KDT) for the spatial profiles, we performed local-weighted averaging of multiple features, both spike dependent and spike independent, and integrated them into a fuzzy classifier [Figure 2(a) and (b)] [5]. The resultant distances to each cluster's centroid are visualized either offline or in an updated, pseudo-real-time approach [Figure 2(c) and (d)].

Subsequent identification of the STN via visualization of MER activity became a far easier and highly accurate task. Without stopping the procedure for careful recording and being susceptible to frequent spike overlaps among

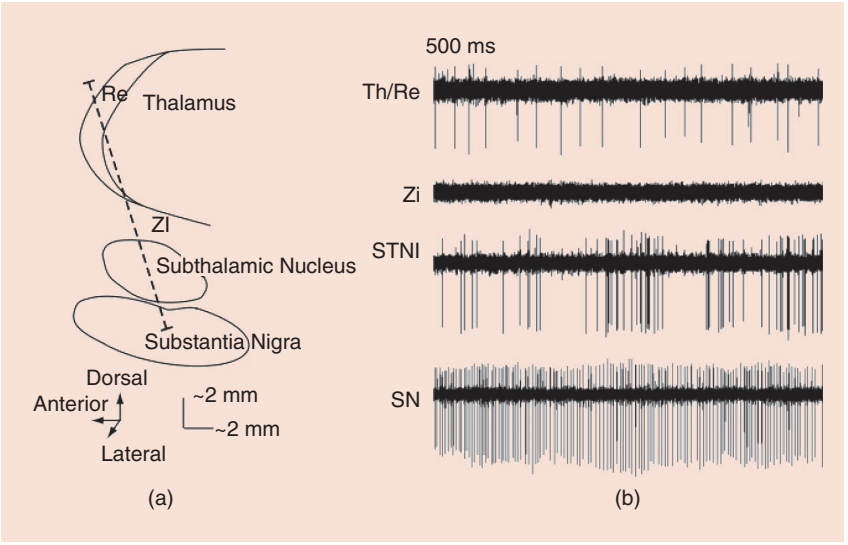

FIGURE 1. The functional targeting of the subthalamic nucleus with microelectrode recordings during DBS implantation for PD. (a) A schematic sagittal view of the typical microelectrode trajectory showing midbrain structures approximately ~12 mm lateral to the midline, beginning ~2 cm above the presumptive target. The subcortical structures along the trajectory typically include the thalamus (Th), zona incerta (ZI), subthalamic nucleus (STN), and substantia nigra (SN). (b) Distinct neurophysiological spiking and spike background patterns, corresponding to the different structures, are encountered as the electrode advances. In the example shown, the fast firing rate within SN is consistent with a typical pars reticulata (SNr) neuron.

neurons, our method paved the way for more powerful supervised learning tools and feature proliferation via, e.g., genetic methods, to further enhance the accuracy of STN detection.

Technical advances in DBS systems

There are a handful of DBS systems manufactured by Medtronic (Activa; Medtronic, Minneapolis, Minnesota), Boston Scientific (Vercise; Boston Scientific, Valencia, California), St. Jude (Infinity; St. Jude Medical, St. Paul, Minnesota), and Aleva (directStim; Aleva Neurotherapeutics, Lausane, Switzerland). The systems comprise stimulating brain leads that target a variety of neural substrates, depending on the disorder. The implanted stimulating tip is of a quadripolar configuration with the four annular stimulating contacts clustered closely at the end. Medtronic provides the greatest detail, with each contact being 1.5 mm in height, 1.27 mm in diameter, and the spacing between contacts being either 0.5 mm or 1.5 mm, dependent upon the model. The contact materials consist of an 80/20 platinum/iridium alloy, with the connecting wires constructed from an identical mix, coiled around a removable tungsten stylet to assist with rigidity for placement and all embedded within polyurethane for insulation, biostability, and elasticity. The insulated, nontargeted end of the stimulating lead is connected to subcutaneous extension cables running beneath the scalp and neck leading to a neurostimulator typically located subclavically on the torso. The entire system is enclosed within the body and communicated with via radio telemetry or Bluetooth (St. Jude and Boston Scientific).

We and others have speculated about the existence of beta-band islands.

The materials and details of the DBS systems provided by Boston Scientific and Aleva Therapeutics are similar, with St. Jude being the exception utilizing stimulating contacts composed of the same platinum/iridium alloy, while connecting wires and extension contacts are composed of MP35N-LT, a nickel cobalt alloy, all embedded in ethylene tetrafluoroethylene and covered with Bionate hypo tubes (polycarbonate

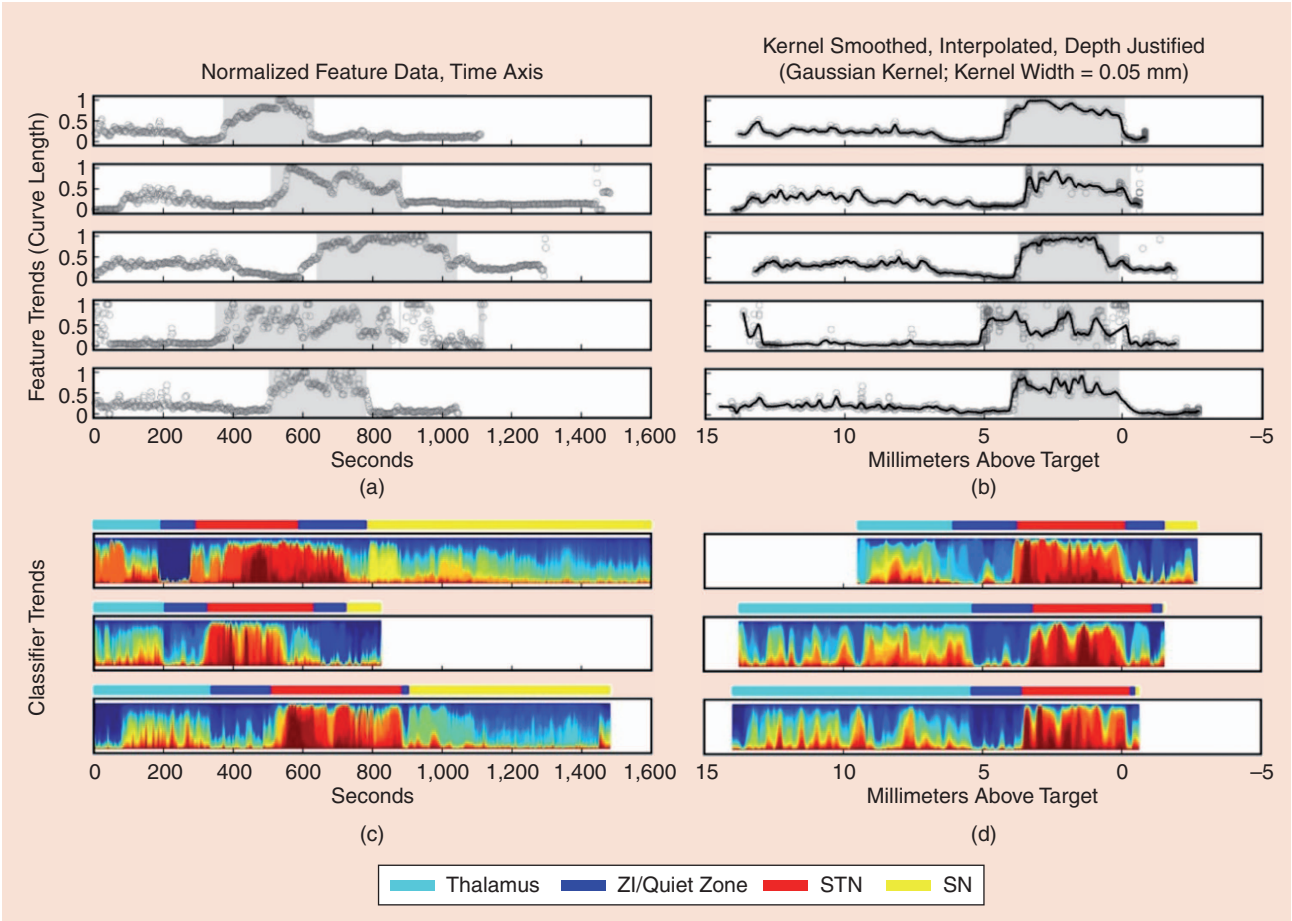

FIGURE 2. MER activity via a fuzzy clustering of multiple features for STN detection. The STN is recognizable as a red portion flanked by blue or aqua portions that represent distinct physiology obtained from white matter tracts or other neuronal structures surrounding the STN. (a) and (b) Feature trends from a single feature calculation (curve length). Open circles represent feature activity normalized to the data window length. STN boundaries are marked by gray boxes. (c) and (d) Activity maps generated via fuzzy clustering of multiple features [8]. Different subcortical structures are marked by colored bars (see legend), with the target STN in red and ventral edge located at 0 mm above target. (a) and (c) Feature trends/activity maps presented on the time-axis. (b) and (d) KDT interpolation with a Gaussian kernel (width = 0.05 mm). In (b) and (d), the thick black lines indicate the result of KDT and interpolation (with 1,000 points). For (c) and (d), the interpolation of normalized feature trends is used.

polyurethane). Medtronic systems were FDA approved in 1997 (ET) and 2002/2003 (PD), while St. Jude's Infinity system was FDA approved for both in September 2016. Boston Scientific won the approval of Conformité Européene in September 2015, and the Aleva stimulating lead system is still undergoing clinical trials.

When active, DBS systems deliver a continuous train of asymmetric biphasic square waves, either current or voltage based, whose setting of multiple contact configurations and programmable parameters of amplitude, pulse width, and frequency can be adjusted to maximize an individual's symptom control, while minimizing adverse simulation effects (thereby maximizing the therapeutic window).

Much of the split ring annular electrodes may salvage the benefit of DBS for nonoptimally placed leads.

Steering the neurostimulation

Directional current steering is offered by the Boston Scientific (Vercise) and St. Jude's (Infinity) DBS systems, with only the Infinity currently being available in the United States. Horizontal steering of the stimulation fields emitted by the two middle annular contacts of the quadripolar electrode is achieved by segmenting the annular ring into three 120° partitions that can be individually activated or deactivated. Thus, if the stimulating electrode is placed more medially than it should, the more lateral facing segments of the split ring can be activated selectively, preventing medial spillage of the stimulation field outside the desirable target region to reduce side effects. Aleva Neurotherapeutics has also engineered a similar three-way split ring stimulating electrode, except utilizing the lower two annular contacts of the quadripolar stimulation lead. These electrodes were recently trialed intraoperatively, exhibiting greater benefit for directional over omnidirectional stimulation in 13 movement disorder DBS candidates [6].

Much of the split ring annular electrodes may salvage the benefit of DBS

for nonoptimally placed leads. Yet, the split ring does not provide the resolution and shaping capabilities of the 32 contact stimulating lead trialed intraoperatively by Contarino et al [7]. The 32 tessellating contact resolution allows the annular shape to slide up and down the stimulating lead in a near continuous fashion, in contrast to jumping between nonoverlapping dorsal-ventral segments. As such, the sculpting possibilities are endless, fulfilling the real potential of stimulation field shaping. Not surprisingly, the results from the intraoperative pilot indicated that directional stimulation could be increased much greater before evoking adverse events than could the annular mimicking stimulation.

Widening the neurostimulation parameter space

As attractive as physical shaping of the stimulation field may appear, real advances may alternately be available through a better understanding of programmable stimulation parameters of pulse frequency, width, and amplitude. The parameter values that are used today have been dictated by the technical limitations of the available neurostimulation devices and tuned within these limits by clinical experience. Recent studies have proposed various ways for widening the parameter space with the goal of selectively stimulating therapeutic target neurons at the lowest energy possible.

Varying temporal patterns through interleaving is unique to Medtronic's Activa family of neurostimulators and was first introduced in 2009. Here, alternating pulses are emitted from different contacts of the same stimulating lead, each with independently programmable amplitude and pulse width, but with the same interdigitated frequency. This was originally intended to allow dual regions of a target substrate along the dorsal/ventral axis of the stimulating lead to be activated, while leaving the region in between unperturbed. Thus, it was thought that multiple symptoms could be captured by multiple sites.

However, if the stimulation fields are brought in close proximity to each other, either by using adjacent contacts or by increasing the amplitude and pulse width, then the two stimulation fields may overlap creating a region of stimulation that will receive twice the programmed frequency, in addition to nonoverlapped regions receiving the programmed frequency. As such, two-tiered frequency stimulation fields can be sculpted, allowing multiple symptoms to be captured or alternately adverse effects released by engaging multiple temporal frequencies.

While the St. Jude (Infinity) system can drive the stimulation of different leads at independent frequencies, the Boston Scientific (Vercise) DBS system is capable of programming independent frequencies on the same lead, for two active "areas," defined as any aggregate of contacts and/or contact segments. Thus, the Vercise system can create temporal "patterned" stimulation in the overlapped regions of the generated fields. The two areas would be driven at different frequencies, with the initial stagger interval between them being determined by the lagging anodal phase of the initial area pulse, ultimately resulting in doublets or triplets instead of continuous stimulation trains. Medtronic's interleaving and Boston Scientific's staggered independent frequencies are two ways to implement multiple frequency fields or patterned stimulation. However, the clinical significance of these new technical capabilities remains to be seen. If the utility of these simple temporal stimulation patterns can be clinically demonstrated then more complicated bursting capabilities could be intentionally engineered. Neurons in the brain lend themselves to bursting, why not DBS?

Many open questions on the neural underpinnings of neuromodulation are expected to be addressed by recent scientific and technical achievements in DBS systems.

Future perspectives: Toward adaptive and precise neuromodulation

Many open questions on the neural underpinnings of neuromodulation are expected to be addressed by recent scientific and technical achievements in DBS systems. Notwithstanding the dramatic improvement that DBS already brings to the quality of life for many patients, we are far from securing, if not defining, its maximum clinical outcome. For DBS implantation, two straightforward objectives are to provide 1) pre- and intra-operative support in localizing the DBS target area and 2) neuromarkers that depict the neurophysiological variability and, therefore, are predictive of the DBS outcome. Especially for psychiatric diseases that are typically believed to be due to brain network imbalances, DBS localization is expected to benefit from approaches that link DBS with other, noninvasive, stimulation techniques applied on the same functional networks [8]. For DBS programming, one possible objective is to step away from the stereotyped stimulation patterns that current open-loop DBS systems provide and move toward neuromodulation that adapts at the millisecond scale, where neurons communicate.

As a surgical treatment for movement disorders, DBS has been historically delivered in an open-loop fashion where a preprogrammed, chronic and continuous stimulation pattern could not avert suboptimal clinical outcomes. Leveraging the technical advances in new DBS devices, clinical studies show that a closed-loop DBS (CL-DBS) system is realizable. What still seems elusive is the driving signals for such systems, i.e., the neural signals and their features, that are informative enough to control the online real-time adaptation of the neuromodulator. One might argue that, for the current technology, the best control signal is the LFP, or some component of it. The reason is that LFP represents the neural information integrated over a larger area compared to the multiunit activity and, therefore, presumably carries more information about the cardinal symptoms of the disease and can account for intersubject

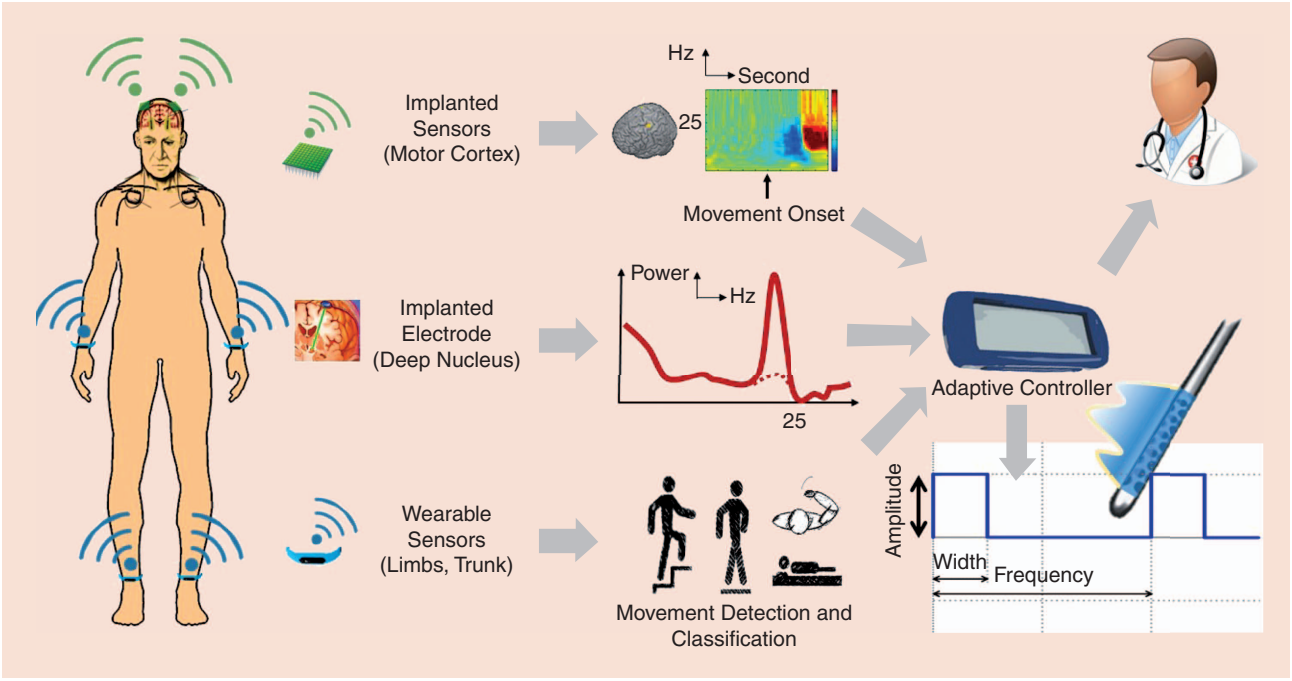

FIGURE 3. Closed-loop DBS controlled by neural signals acquired from multiple modalities across the spatial and temporal scales of brain function. A DBS controller adapts in real-time the therapeutic parameters (current distribution, frequency, amplitude, width) based on an algorithm that is driven by combining features extracted from 1) wireless, batteryless sensors implanted on cortical areas (e.g., motor cortex), 2) single and multineuron recordings (through the DBS implanted electrodes), and 3) wearable sensors identifying patters of movement.

variability, thus enabling sufficient personalization. It is not a coincidence that a specific feature of the LFP, the beta-band activity of STN neurons, is currently under intense testing on whether it can become an effective programming biomarker for CL-DBS for PD [4], [9]. The increased beta band within the STN may also represent a greater coherence and phase locking of this oscillation across multiple basal ganglia structures as part of the underlying pathophysiology of the system [10]. Incorporating other LFP oscillations such as theta frequency afferent from the medial prefrontal cortex to the STN [11] or gamma frequencies, found to correlate with PD symptoms, seem to be a natural next step. Moving beyond the MERs, one should consider the use of other neural as well as behavioral signals transmitted wirelessly to a wearable information processing platform. A potential helpful expansion of a DBS system could employ the fusion of neural and other signals acquired via multiple modalities, including wearable and implantable sensors (Figure 3). Implanting wireless sensors on the motor cortex and coupling the neural information with behavioral signals acquired through wearable devices that classify movement patterns could provide new information pathways (e.g., movement-triggered cortical oscillations such as beta-band rebound or mu-alpha suppression) toward controlling a CL-DBS system by integrating features from multiple modalities. We have shown earlier that employing a small number of neurophysiologically interpretable features inside the STN can predict, separately for each patient, the behavioral outcome of STN-DBS. The neurophysiological basis of using implanted wireless sensors of brain activity in the motor cortex stems from the fact that stimulating STN neurons can cause antidromic activation of the hyperdirect pathway, which consists of axon collaterals of pyramidal neurons in the motor cortex. Stimulating these axons within the STN is associated with changes in motor cortical activity, possibly masking or desynchronizing pathologically enhanced beta-band oscillations within the basal ganglia–thalamocortical network. Therefore, the goal for a CL-DBS system should be to maximize the stimulation of these target neurons while minimizing unintended activation of nontarget neurons such as corticospinal or corticobulbar fibers within the internal capsule, which may cause speech, walking, or fine motor skill impairments. Overall, a CL-DBS system will not only secure the clinical effectiveness but also minimize the potential for serious complications and side effects.

A potential helpful expansion of a DBS system could employ the fusion of neural and other signals acquired via multiple modalities.

Nevertheless, even if these objectives are met, the currently available DBS systems are presumed to modulate more cells than those affected by the disease, which could sometimes lead to side effects. Thanks to recent advances in neurosciences and signal processing, we are getting close to the development of electroceuticals, systems aiming to modulate the spike activity of individual and functional

groups of neurons in adaptive ways that are fully compatible with the biological function [12]. To this end, we will need a better mapping of the neural circuits associated with the treated pathophysiology; at the signal level, we will need better decoders of the neural language associated with the pathophysiological states and more precise therapeutic patterns of electrical impulses targeting the rate, even the timing of spikes. Generating such adaptive and precise neuromodulators will require a multidisciplinary effort: the development of neuromorphic circuits for real-time spike processing will translate the biological understanding of what is happening at the neural level in health and disease. That said, we shouldn't underestimate the complexity of such an endeavor that could result in another big data mining problem, this time at the neural level. Such problems can only be approached synergistically; to achieve this, we need initiatives that bring together scientists and engineers, the most prominent of which is the yearly workshop on neuromodulation organized by the Institute of Engineering in Medicine at the University of Minnesota.

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Conclusions

Recent advances in basic and clinical neuroscience have helped us understand which should be the target neurons for a particular DBS indication and which neural elements within the stimulation volume rather contribute to adverse effects of stimulation. Progress in medical technology has allowed the development of new DBS devices with unprecedented technical abilities that now offer a more refined, in time and space, neuromodulation. Ongoing computational analyses are proposing neurophysiologically optimized solutions for DBS while removing a significant burden for advanced clinical experience and repeated intra- and postoperative testing of the patient response. A tight interweaving of the multidisciplinary advances will allow the validation of neurophysiological concepts of neurostimulation in clinical practice and translate DBS, from a complex and poorly standardized therapy where treatment failures are not uncommon, to a flexible intervention, tailored to each patient's symptoms and neuropathophysiology. This direction merits further research.

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