Modeling sequence and quasi-uniform assumption in computational neurostimulation

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Abstract

Computational neurostimulation aims to develop mathematical constructs that link the application of neuromodulation with changes in behavior and cognition. This process is critical but daunting for technical challenges and scientific unknowns. The overarching goal of this review is to address how this complex task can be made tractable. We describe a framework of sequential modeling steps to achieve this: (1) current flow models, (2) cell polarization models, (3) network and information processing models, and (4) models of the neuroscientific correlates of behavior. Each step is explained with a specific emphasis on the assumptions underpinning underlying sequential implementation. We explain the further implementation of the quasi-uniform assumption to overcome technical limitations and unknowns. We specifically focus on examples in electrical stimulation, such as transcranial direct current stimulation. Our approach and conclusions are broadly applied to immediate and ongoing efforts to deploy computational neurostimulation.

Keywords

Neuromodulation, Direct current, Computational models, Finite Element Model, Quasi-uniform, Electrical stimulation

1 A SEQUENTIAL MULTISTEP MODELING PROCESS

Computational neurostimulation (first formalized in Bestmann et al., 2015) argues that advancement of experimental and clinical interventions will be accelerated through development of quantitative models linking stimulation dose to behavioral and clinical outcomes. But doing so requires significant technical sophistication and

Progress in Brain Research, ISSN 0079-6123, http://dx.doi.org/10.1016/bs.pbr.2015.08.005

assumptions. To make the process tractable, we explain here how computational neurostimulation can be divided into distinct steps that are implemented sequentially. The steps are distinct when they are assumed sequential, such that later steps do not need to inform earlier ones. By conceptualizing computational neurostimulation into discrete steps, the technical challenges and assumptions at each stage can be properly addressed. This review focuses on electrical neuromodulation of the cortex (invasive and noninvasive, electrical and magnetic), though the sequence described here generally applies to other targets and forms of neuromodulation with any energy (e.g., light, ultrasound). Specifically for electrical stimulation, we review the "quasi-uniform" assumption, initially made explicit in 2013 (Bikson et al., 2013a).

The first step in electrical neuromodulation is the use of "forward models" to predict current flow patterns through the head or brain target region. The second step is to consider how current flow directly polarizes cell membranes and changes neuronal firing rate. Third, the consequences of cellular polarization on neuronal information processing are modeled. Fourth, these changes in neuronal processing are implicated in changes in behavior or higher order cognitive function. In aggregate, this process achieves the goal of computational neurostimulation: to quantitatively predict the cognitive or behavioral consequences of electrical stimulation for the purpose of understanding and refining interventions. In addition to considering these steps as sequential, the application of the quasi-uniform assumption (defined below) makes this complex process more tractable.

The first step of predicting brain current flow is assumed to be independent of brain activity state or the response of activity to electrical stimulation. Therefore, the first step of predicting current flow can be conducted ignoring brain neurophysiology. Indeed, this assumption is universal to brain stimulation modeling, (Warman et al., 1992) spanning applications as diverse as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS; Esser et al., 2005), and transcranial direct current stimulation (tDCS), and both analytical and numerical approaches. Whatever the limitations of this assumption in relation to the physics of current flow (Bossetti et al., 2008) or activity-dependent changes in tissue conductivity, they are considered relatively minor.

In the second step, the direct cellular polarization produced as a consequence of current flow (through a brain region of interest) is predicted, essentially independent of brain activity. This separation of the first and second steps dates back to the earliest examples of electrical stimulation modeling, where analytical solutions were used to predict current flow in homogenous media and the response of simple axons was derived analytically. This separation of steps persists even as more sophisticated numerical techniques for predicting current flow and neuronal responses have developed. Thus, state-of-the-art computational neurostimulation efforts adopt this two-stage process. Though the validity and limitations of this process has been questioned (Bossetti et al., 2008), it was generally concluded that any theoretical errors are minor compared to other, the unknowns within each step itself. Polarization can be used, for example, to predict resulting changes in firing rate either as a result of pacing by suprathreshold stimulation or changes in threshold by subthreshold

stimulation. It is understood that changes in activity secondary to polarization can feedback to further change polarization and firing (e.g., polarization changes oscillation activity which then changes firing; Rahman et al., 2013), but it is still possible to predict the initial direct polarization—which serves to establish mechanisms and causality.

In the third step, the polarization of a population of cells by electrical stimulation is used to predict change in neuronal information processing—this will change brain state as well as be entirely determined by baseline brain state. While brain state depends on cognition and behavior, approaching this question from a systems level allows analysis on a neuronal network scale. Finally, these changes in network function can be quantitatively linked to changes in performance or clinical symptoms.

This multistep process is evidently rife with simplifications, unknowns, and assumptions. The sequential methodology is largely determined by the mechanics of computer simulation (e.g., current flow models do not include active neuronal networks, neuronal networks models have membrane polarization as a parameter) and existing constructs in neuroscience (e.g., a given neuronal network model is linked to behavior). Making this modeling workflow rigorous and useful is precisely the goal of computational neurostimulation research. The quasi-uniform assumption is applied at the second step, with consequences throughout.

2 STEP 1: FORWARD MODELS OF CURRENT FLOW

Current flow prediction relies on relatively well-defined physical assumptions. To accurately predict brain current flow produced during stimulation, one needs to specify the (1) relevant aspects of the stimulation device, and (2) relevant tissue properties; below we consider the relevant features each case. In this review, we focus on electrical stimulation, but in any form of energy application where the physics are well defined, then defining device and tissue properties should lead to straightforward prediction of energy dissipation in the body (Cho et al., 2010; Deng et al., 2014; Ding et al., 2015; Jagdeo et al., 2012; Lee et al., 2015; Wu et al., 2012).

One of the most common and confounding mistakes in neuromodulation is to assume that placing an electrode "near" a nominal target guarantees current flow to that region. In the case of noninvasive electrical stimulation, such as tDCS, this has led to irrational assumptions such as that current is delivered to a brain region *smaller* than the primary electrode and that the second electrode can simply be ignored. Rather, when two large scalp electrodes are used current must flow *between* electrodes potentially influencing all intermediary regions, with a diffuse pattern determined by the underlying tissues (Datta et al., 2009), and the position of the second electrode even affects current under the first electrode (Bikson et al., 2010). With often unintuitive current flow patterns, models are required (Seibt et al., 2015).

Even in the case of implanted electrodes (e.g., DBS), where increased targeting is achieved by virtue of embedding an electrode near the target, oversimplistic assumptions about stimulation "near" targets should be avoided. As summarized by

Cameron McIntyre (Arle and Shils, 2011): "The electric field generated by an implanted electrode is a three-dimensionally complex phenomenon that is distributed throughout the brain. While the fundamental purpose of neurostimulation technology is to modulate neural activity with applied electric fields, historically, much of the device design work and clinical protocols were primarily based on anatomical considerations (i.e., stimulation of a specific brain nucleus). This approach was taken because logical hypotheses could be generated to relate the effects of selectively stimulating a given nucleus to a behavioral outcome. However, without considering the complete system of electrode placement in that nucleus, stimulation parameter settings, electrical characteristics of the electrode, and electrical properties of the surrounding tissue medium, it is impossible to determine if the stimulation effects will be contained in that nucleus or if they will extend to surrounding brain regions. Therefore, the first step in predicting the effects of neurostimulation is to characterize the voltage distribution generated in the brain."

Forward models are therefore needed, and the first element that needs to be reproduced in computer simulations is dose. The relevant aspects of stimulation that need to be reproduced is simply the "dose," which as defined in Peterchev and colleagues (2012) as those features of the stimulation device and electrodes or coils that influence the generation of current flow in the body. For electrical stimulation, this is the electrodes' shape and location, and the waveform applied to each electrode. For example, in DBS, dose is reflected in the location and configuration of the implanted electrodes and the high-frequency pulse train applied to them. While for tDCS, dose is the position of the electrodes on the head and the intensity of direct current applied. For TMS dose is coil geometry, current applied to the coil, and position relative to the head (Deng et al., 2014; Guadagnin et al., 2014). Given the well-defined stimulation dose, while there are some variations in how this is implemented (the simulation boundary conditions; Bikson et al., 2012; Saturnino et al., 2015), it is relatively straightforward to reproduce the dose of stimulation in a computational forward model.

Special care should be taken in voltage-controlled stimulation. Current-controlled stimulation provides the benefit that electrode impedance does not distort stimulation waveform (Merrill et al., 2005), and for this reason the complex electrode interface does not need to be incorporated in current flow models. The benefit provided by using current-controlled stimulation in physical devices is, in this sense, transferred to models. In contrast, simulating voltage control requires explicit consideration of the electrode interface (McIntyre et al., 2006). Current control is not without concerns in regard to nonideal performance (e.g., see ratcheting in Merrill et al., 2005) and voltage limits in Hahn et al. (2013), but such issues can generally be disregarded for current flow modeling. For both current- and voltage-controlled stimulation, there are issues regarding electrochemical reactions at the electrode that are important for safety and tolerability (Merrill et al., 2005), but can be considered separately from predictions of current flow.

Other than defining dose, models of current flow must reproduce the relevant tissue properties. Here, the framework is well agreed-upon, if not the specific tissue

parameters that should be used in any given case (Datta et al., 2013a; Opitz et al., 2011; Schmidt et al., 2015; Wagner et al., 2014). The tissue properties are generated in forward models by first dividing the anatomy into individual masks, such as gray and white matter. Then, electrical properties are assigned to each mask. The importance of separating masks derives from the need to assign each mask its own electrical properties. While in principle this approach is well established, there are significant unknowns and debate about which masks should be segmented and what electrical properties (e.g., frequency-specific tissue conductivities) should be assigned. Masks may be synthetic (i.e., generic in a rendering software with simplified shapes; Wagner et al., 2007) or based on imaging from individuals (e.g., MRI, CT; Datta et al., 2009; Lu and Ueno, 2013). Specific imaging sequences may provide further insight into tissue properties, such as use of DTI to predict anisotropy (Schmidt and van Rienen, 2012; Sweet et al., 2014)—though implementation is not without debate (Diczfalusy et al., 2015; Shahid et al., 2014).

While there is a general trend toward increased model complexity (e.g., the number and detail of tissue masks), it is important to note that increased precision does not necessarily translate to increased accuracy (Bikson and Datta, 2012). In some cases, synthetic (abstracted) incorporation of preexisting information not evident in the scans is needed (e.g., not resolved by scan contrast or not resolved full by scan resolution), for example, ensuring CSF continuity in transcranial stimulation models (Datta et al., 2009) or an encapsulation layer in DBS (Butson et al., 2006). Relevant tissue details will depend on the dose, for example, gyri-precise cortical representation is critical for tDCS (Datta et al., 2009) but not DBS. Similarly, spinal anatomy details may be critical for stimulation of the spine (Song et al., 2015), but not for cortical microstimulation (Song et al., 2013). Ultimately, the validity of forward models in informing clinical trial design relates to the specific questions being asked of them.

If and how to individualize models, to account for variations in anatomy, remain an open area of investigations (Dougherty et al., 2014; Edwards et al., 2013; Lee et al., 2013; Opitz et al., 2015; Russell et al., 2013; Truong et al., 2013; Viskochil et al., 1990). In some cases, interventions such as TMS, DBS, and ECT inherently use individual dose titration, but the process is empirical. In other cases, no individual dose titration is attempted, such as tDCS. Models can inform both extremes. While naturally model accuracy will increase with consideration of individual anatomy, the open question is what benefits are provided for computational neurostimulation (Pourfar et al., 2015). Will individualized models explain data from human trials in a way explicitly not possible with nonindividualized models (Douglas et al., 2015; Kim et al., 2013)? Or will individualized models result in a different dose being applied in a human trial in a way that impacts outcomes (Edwards et al., 2013)? If the answer to both questions is “no” then it is not evident the value of individual models, especially given the cost. One alternative is to rely on a preexisting head library to select a comparable anatomy or to warp preexisting models—but these steps still require (potentially costly and complex) subject-specific measurement and analysis. Dealing with susceptible populations, such as

children (Gillick et al., 2014) or cases of brain injury (Datta et al., 2011), may magnify the need for individual models.

Various tools have been developed for computational modeling; spanning workflows with varied engineering simulation packages (Huang and Parra, 2015), to stand-alone workflows (e.g., Matlab; SCIRun; Dannhauer et al., 2012; Windhoff et al., 2013), to GUI-based simulation (Truong et al., 2014). In principle, the process involves exploring various montages (dose) with the goal of identifying a current flow pattern that best supports the presumed mechanism of action or experimental hypothesis (Wongsarnpigoon and Grill, 2012). However, how to select a "best" target and consider collateral brain current flow (side effects) is an open question (Cheung et al., 2014; Fytagoridis et al., 2013) because the relationship between brain current flow patterns and cognition is complex. One solution, which is implicitly adopted in many reports though not made explicit, is the quasi-uniform assumption. Under the quasi-uniform assumption the electric field (or current density) in each brain region is assumed to predict the degree of polarization and neuromodulation (Bikson et al., 2013a). The quasi-uniform assumption is addressed in detail in the next section.

3 STEP 2: CELLULAR RESPONSE MODELS OF POLARIZATION AND THE QUASI-UNIFORM ASSUMPTION

Significantly more complicated than the prediction of current flow patterns in the head during stimulation is predicting the resulting neurophysiological and then cognitive/behavioral outcomes. The second step in the sequential computational neurostimulation process is calculating the cellular polarization produced by the brain current flow patterns predicted in Step 1. While the theory for this is well established, the details of complete implementation can be a (intractable) burden in CNS stimulation. The process of complete implementation is described, setting up the discussion of the utility of the quasi-uniform assumption alternative.

The long-standing approach to model polarization response to electrical stimulation is to consider "which elements are activated" (Ranck, 1975)—where elements refer not only to which cells but which specific compartments of cells such as a branch of the dendrite, the soma, or a segment of the axon. It is essential to appreciate that separate compartment of a single neuron will respond different to electrical stimulation, even as the compartments interact. Which elements respond will be highly dose (electrode position and stimulation waveform) dependent. Regardless of downstream actions, the primary response of the nervous system to current flow is typically considered (foremost) polarization of neuronal membranes. Understanding which neurons are polarizing, and which compartments within those neurons, is thus considered a critical substrate for a quantitative model of electrical stimulation. The answer will evidently depend on the modality (dose) of stimulation, which regions of the nervous system receive significant current flow as a result, and the types of cells in those regions.

For computational neurostimulation, it is important to situate this second step in the context of the series. The first step generates current flow predictions that methodologically do not consider neuronal morphology, except globally when it affects gross resistivity such as gray versus white matter or white matter anisotropy. In the second step, this current flow pattern is "overlaid" on neurons (or other cells of interest), explicitly considering their morphology and membrane biophysics—taking current flow patterns and cell morphology/biophysics together provides the information needed, in principle, to predict resulting membrane polarization in each compartment of each cell. These polarizations are a quantity that can be used as an input to the neuronal networks models in the third step, as membrane potential (or a cell parameter of excitability) is often factored in network models. Alternatively, for suprathreshold approach, the second step can be used to predict which neural elements are driven to fire action potentials (and with what periodicity/rate) and this action potential rate information can be provided in the third step to a network model where firing is a parameter. A separate variation for subthreshold stimulation is to predict the change in synaptic efficacy produced at a given synapse by stimulation (Rahman et al., 2013), and provide this as a coupling parameter in to a network model that considers synaptic coupling strength. There may be still other "cell level" parameters that can be transferred to a network model. The decision of what parameter(s) to carry forward from the second to third state depends on hypothesis for mechanisms (what parameters considered relevant) and ultimately the mechanics of the models (what parameters are applicable).

In those applications where suprathreshold pulses are used (such as DBS, TMS) identification of cellular targets has focused on axons (Nowak and Bullier, 1998). In the case of stimulation targeting the peripheral nervous system, axons evidently are a unique target. But also in the central nervous system they may represent the structures more sensitive to stimulation, in the sense they have the lowest threshold to be driven to fire action potentials—specifically axon terminals. For subthreshold stimulation, such as produced by tDCS, attention has traditionally focused on compartments other than axons. Specifically, weak current produces a biphasic polarization profile along the neuronal axis producing polarization of the soma and dendrites (Bikson et al., 2004). However, ongoing research on subthreshold as refocused attention on axon terminals (Arlotti et al., 2012; Rahman et al., 2013) brings cellular targets more in line with suprathreshold.

How does one predict the polarization produced in each compartment of every cell, and in turn which specific neurons fire or how synaptic efficacy changes at each connection? The theory for modeling neuronal polarization, and so action potential generation, by electrical stimulation is well established but requires considering of each neurons and its distributed segmented morphology and membrane biophysics at each segment. Specifically, the activating function (derivative of electric field) along each neuronal compartment must be calculated and then the polarization of the entire neuron solved, one unique neuron at a time. In contrast to the PNS where relatively uniform axonal bundles make this tractable, in the CNS the number and diversity of cell types make this complex (McIntyre et al., 2007). The complexity is then

amplified when considered how stimulation of axons that are part of a complex and active brain network results in an aggregate change of activity in the third step The traditional way to make this second-step process tractable in the CNS is some combination of reductionism (considering only a few type of homogeneous neurons in a few brain regions) and increasing complexity and speculation (since parameters are largely unknown).

This approach can be daunting. For example, in discussing cortical stimulation, Sergio Canavero concludes (Arle and Shils, 2011) "In the end, this discussion highlights the extreme aspecificity of current cortical stimulation paradigms, since stimulation tends to affect the cortex across the board. A first step would be complexity analysis with closed-loop stimulation devices (e.g., the NeuroPace device for epilepsy control), but it is moot that this alone may circumvent the amazing intricacy of cellular architecture. Does cortical stimulation affect differentially positioned cells in the same way? Does a homogeneous wave of excitation create intracortical conflicts (e.g., two self effacing inhibitions)? Should dendrites, soma, axon hillocks, nodes, internodes and unmyelinated terminals, all having different electrical properties, be stimulated differentially? This is way beyond current technology. When it comes to details, the only currently feasible approach is to consider the cortex a sort of black box, from which a net effect is sought through trial and error."

One alternative to this complexity is the "quasi-uniform" assumption that presumes that regional polarization (as a global quantity) and even neuromodulation is predicted simply by local electric field (Bikson et al., 2013a). Under the quasi-uniform assumption, current flow models are used to predict regional electric fields, and these values in the brain are presented a representative of the aggregate likelihood a brain region will be polarized and so modulated. Other postprocessing methods to simplify visualizing of predicted activation maps have been proposed (Hartmann et al., 2015; Madler and Coenen, 2012).

The quasi-uniform assumption is not trivial because membrane polarization has long been linked to the *change* in electric field along a cell, via the so-called activating function (see above), but it is precisely because of this dependence that traditional approach depends on exhaustive cell-specific data. Rather, the quasi-uniform approach considers that in a "soup" of noncompact, bending, and terminating processes (axons, dendrites), the electric field may indicate maximal polarization (Arlotti et al., 2012; Rattay, 1986), while compact neuron polarization will also track electric field (Joucla and Yvert, 2009; Radman et al., 2009a). Straight axonal will be sensitive to electric field when crossing resistive boundaries (Miranda et al., 2006; Salvador et al., 2011), and local terminations and bends will polarize with electric field (Arlotti et al., 2012).

The possibility that nonneuronal cells, such as glia or endothelial cells, may be targets for stimulation remains an highly open but critical debate (Lopez-Quintero et al., 2010; Pelletier and Cicchetti, 2014) and would require separate classes of models. Interestingly, the polarization of spheres (or spheroids; Kotnik and Miklavcic, 2000) is directly linked to electric field, making the quasi-uniform

assumption relevant to these cases. Predicting clinical and behavioral outcomes would still require coupling action on nonneural cells types to neurons.

Finally, the quasi-uniform assumption helps support the concept of coupling constant (also called polarization length) which can be defined as the amount of cell membrane compartment polarization (in mV) per unit uniform electric field (in mV/mm). The coupling constant (Bikson et al., 2004) is a powerful concept because it can be readily quantified in experimental or neuron models (assuming a linear sensitivity to low-intensity electric fields) and can be generalized to many types of computational neurostimulation (Frohlich and McCormick, 2010). The coupling constant may be waveform specific (e.g., AC fields; Deans et al., 2007).

4 STEP 3: INFORMATION PROCESSING AND NETWORK CHANGES

The third step in computational neurostimulation is modeling active network responses to electric stimulation. Warren Grill summarizes (Arle and Shils, 2011): "Electrical activation of the nervous system has traditionally been thought of and analyzed as a two-part problem. The first part is determining, through measurement or calculation, the electrical potentials (voltages) generated in the tissue by the application of stimulation pulses [or other waveforms]. The second part is determining, again through measurement or calculation, and now, through imaging, the response of neurons to the stimulation pulses (i.e., to the voltages imposed in the tissue). However, recent progress highlights the need to add a third part to this problem—the network effects of stimulation. That is, given the changes in the pattern of activity in the neurons directly affected by stimulation, what changes occur either downstream from the point of stimulation or even further distant within interconnected networks of neurons."

It is increasingly recognized that functional outcomes of electrical stimulation on the nervous system can often *only* be understood in the context of network architecture (e.g., the connectivity of the brain) and ongoing activity (e.g., the state of the brain; Kwon et al., 2011). This is manifest on several scales. On the global scale, electrical neuromodulation will travel along the brains existing connections. For these reasons, even presumably focal stimulation will produce brain-wide changes. Modern analysis of interventions such as TMS (Bestmann, 2008) and DBS (Kahan et al., 2014; Kent et al., 2015; Min et al., 2012) leverages characterization of these connections. On a local network scale, the ongoing activity of a network will fundamentally influence what actions electrical stimulation has; with highly organized processes such as oscillations, the effects of stimulation are almost entirely explained by how these processes are altered (Frohlich and McCormick, 2010; Kang and Lowery, 2013; Reato et al., 2010, 2013b). At the cellular level, the background activity of neurons may influence their responsiveness to stimulation, more simply that an active neurons will be closer to threshold (Radman et al., 2009b) but also through

amplifying synaptic activity onto neurons (Bikson et al., 2004; Rahman et al., 2013) and other processes (Rosenbaum et al., 2014).

For network changes in the third step, we mean quantifiable metrics/features of the network activity such as oscillation power, frequency, or coherence (Frohlich and McCormick, 2010; Lee et al., 2011; Parra and Bikson, 2004; Reato et al., 2010). Precisely because many network behaviors are emergent properties of a coupled and active system, so to are the effects of stimulation a result of network dynamics (Berzhanskaya et al., 2013; Francis et al., 2003; Reato et al., 2013b). The network response to stimulation may therefore not be obvious from action at the level of isolated cell, even if stimulation acts by polarizing cells (Step 2). Similarly for information processing in the third step the tools are computational models with precise aggregate metrics, finally in the fourth step are these neuroscience quantities related to more abstract representations of cognitive function. Though evidently, with predicting behavioral changes the net outcome of computational neurostimulation, the selection of system in Step 3 is entirely based on making the bridge to higher function as well as hypothesis for cellular targets based on Step 2.

The third step of analysis of network function (and its bridging to behavior in the fourth step) is fundamental to understanding the specificity of stimulation. The purpose of any neuromodulation intervention is to generate a desired behavioral or clinical outcome (i.e., improvement in symptoms) without stimulation-generated side effects. Specificity can be enhanced by guiding current to specific brain regions (Step 1) but since no brain region is involved in one brain function and most brain functions involve multiple regions, anatomical targeting of current flow can enhance but does not in itself explain specificity. Similarly, the dose, and especially the waveform, of stimulation can shape which neuronal elements are activated (Step 2) but the ability to capture neurons specific to just one task is unrealistic. Therefore, we suggest only through nuance in understanding network and information processing changes, can we rationally consider the origins, and limits, of neuromodulation specificity.

Notions of activity dependence of stimulation support the concept of "functional targeting." We propose functional targeting, in contrast to anatomical targeting. Functional targeting supposes that an endogenously active brain process (e.g., a brain process activated by concurrent training) is preferentially sensitive to electrical stimulation—various forms of selectivity then can arise (Bikson et al., 2013b).

In some applications, especially for peripheral stimulation, simple changes in neuronal firing can be linked to the operative behavioral (functional) changes, for example, when the intended outcome of stimulation is a motor response. But in cases where actions are central, and where there is a higher order cognitive or behavioral target, a final step is needed to bridge from cellular and network changes.

As discussed in Step 2, electric field produced during electrical stimulation is coupled to the network via cellular polarization—meaning the cell that make up the computational model of Step 3 is polarized based on principles set in Step 2. Though the quasi-uniform assumption is applied in Step 2, it has important implications for the feasibility of Step 3. The quasi-uniform assumptions assumed a network

is exposed to one electric field or that discrete nodes in a network are each exposed to one electric field. This single electric field thus represents the input from electrical stimulation to that network. If one makes general assumptions about a homogeneous cellular structure in the network, one can apply the quasi-uniform assumption without needing to solve for the polarization of every element in a network. For example, one can assume stimulation primarily couples through soma polarization of the primary output excitatory neuron in a brain region, such as the CA1 pyramidal neuron soma, and then based on a single or distributed average coupling constant provide a polarization input to all excitatory neurons somas in the network. One can consider other neuronal elements such as various excitatory cell types, interneurons, or axon terminals, and apply a cell- or process-specific average polarization. The principle remains that under the quasi-uniform assumption, a regional electric field is applied to one or more "characteristic" neuronal elements that are replicated across the network. In this way, modeling stimulation of a network is tractable albeit with assumptions about average and net effects.

There are some situations where the effects on network activity are directly linked to desired behavioral outcomes. For example, for approaches such as ECT where therapy is based on the hypothesis that behavioral benefits derive from the generating seizures, modeling predictions may attempt to converge on regional seizure thresholds (Bai et al., 2010). These are often collapsed to functions of regional electric field, following the quasi-uniform assumption, where an (waveform specific) electric field seizure threshold is set any given brain region. Even so, refined approach for brain targeting, hypothesis that efficacy may be mediated by electrical stimulation independent of seizures, and approaches to reduce side effects (Sackeim et al., 2008), may adopt more sophisticated computational neurostimulation approaches (Bai et al., 2012).

Conversely, in the case of seizure control, reduction on network epileptiform activity is considered a direct aim of treatment or at least directly correlated with desired clinical outcomes. There is significant data on success in controlling epileptiform activity in animal models where often the goal is simply to stop or reduce neuronal firing (Ghai et al., 2000), but mixed success in the clinic (Sugiyama et al., 2015). The lack of correlation of epileptiform activity with behavior may therefore be a crutch holding back advancement, including recognizing that brain regions perform multiple complex functions (Sunderam et al., 2010).

5 STEP 4: FROM NETWORK TO BEHAVIOR

An ambitious step in computational neurostimulation is relating network changes produced by electrical stimulation to behavior. This process is challenging for issues generic to neuroscience, the link between cellular function and cognition is complex and unknown. Indeed, one of the attractions of experimental design informed by computational neurostimulation is to use interventional brain stimulation and observation on behavior to bridge this divide.

A key consideration in developing models that bridge to behavior is if to limit consideration to a brain "node" (a limited anatomical region) of interest or to explicitly model distributed brain processing (spanning multiple distant but connected brain regions). Evidently any higher brain function (behavior, cognition, therapeutic action) reflects distributed brain processes, but for the purposes of computational neurostimulation, this relevant question is what scale (node or distributed network) of models provides meaningful predictions of behavior changes produced by neuromodulation. Some stimulation modalities, like the conventional tDCS approach, inevitably influence regions across the brain—and interpretation of behavioral changes based on any single node is an assumption (Seibt et al., 2015). Alternatively, direct action on multiple nodes in a network can be embraced as inherent to the net actions of stimulation (Brunoni et al., 2014; Dasilva et al., 2012; Douglas et al., 2015; Senco et al., 2015) where connectivity parameters can be informed by functional imaging or tractography (Sweet et al., 2014). This analysis has been particularly advance for DBS (McIntyre and Hahn, 2010). Perhaps, the most obvious criticism of the single node notion is that when suprathreshold stimulation is applied, inevitably not only is the target activated but all antidromic orthodromic, and axons of passage—thus at the most basic level stimulation effects a network. This does not mean that one cannot link local (node specific) changes to behavior, but some sophistication in considering the function of the node is required.

One type of bridge to behavior is based on the modulation of network oscillations, either acutely or leading to lasting changes (Reato et al., 2015). For example, Schiff and colleagues demonstrated an empirical link between electrical stimulation frequency, oscillations, and behaviors in rat (La Corte et al., 2014). Reato and colleagues used computational neurostimulation constrained by human EEG recording to link entrainment of slow-wave oscillations by transcranial electrical stimulation which changes in plasticity that could in turn explain learning changes observed experimentally (Reato et al., 2013a). Merlet and colleagues proposed methods to link tACS with EEG changes (Merlet et al., 2013). Similarly, Ali and colleagues (Ali et al., 2013) developed a model for tACS based on large-scale cortical oscillations. There is a reasonable well-established experimental and theoretical pathways linking stimulation with changes in network oscillations (Park et al., 2005; Reato et al., 2013b). Network oscillations have in turn been linked to specific cognitive states and behavior (Cheron et al., 2015; Colgin, 2015).

A simplistic bridge from cellular/network activity to behavior is to adopt either a "sliding scale" concept of brain function (notably for tDCS and post-rTMS), paradigms of "virtual lesions" (including in acute TMS, DBS), or theories based on "pacing/over-riding" (for example in SCS). These concepts are node based in that they explain the actions of neuromodulation by local effects, though they are not exclusive of considering the stimulated node as part of distributed network. For example, DBS is hypothesized to create a virtual lesion of a node, thereby removing its influence on the broader network, or to pace the node, thereby increasing drive in upstream/downstream regions (McIntyre et al., 2004). Or, for example, tDCS may be hypothesized to shift the excitability of one node involved in task. In SCS, the

gating theory suggests driving (pacing) a set of neurons generates downstream effects related to gain control. These approaches are attractive (and ubiquitous) because they typically do not require any numerical simulation, but rather a block diagram approach to understanding brain function and disease. They do not require sophistication in understanding information processing with a node or the possibility that some functions may be enhanced while other disrupted in the same network. And these approaches lend themselves to simple integration with Step 2; for example, tDCS that depolarizes the soma slides excitability and so brain function "up." Neuroscientists, biomedical engineers, and clinicians naturally gravitate to trivial explanations, when faced with unknowns and complexity. But these approaches rarely withstand rigorous conceptual consideration or experimental validation. Computational neurostimulation is the alternative.

Changes in synaptic plasticity can be linked conceptually to any lasting changes and learning. Understanding how stimulation affects synaptic plasticity is therefore a generic substrate to link cellular/network and behavioral phenomena—in the sense that any evidence for some synaptic plasticity is used as a mechanistic substrate for some learning. But to avoid reverting to a "sliding scale" explanation (e.g., "more" synaptic plasticity is "more learning" and "more therapy"), it is necessary to develop computational neurostimulation models that are capable of different forms and pathway of synaptic plasticity. In this way, one can link a specific change in plasticity with a targeted change in learning or behavior.

6 DEALING WITH UNKNOWNS AND MULTISCALE APPROACHES

Cameron McIntyre summarized (ISBN: 978-0-12-381409-8): "Defining relationships between the anatomical placements of the electrode [Step 1], the stimulation parameter settings, the relative proportion of neurons directly stimulated [Step 2], the stimulation-induced network activity [Step 3], and the resulting behavioral outcomes [Step 4], represent the state-of-the-art process for deciphering the therapeutic mechanisms of neurostimulation therapies. However, integration of such systems is so complex that it typically requires computational models and numerous simplifying assumptions to analyze appropriately. In turn, numerous scientific questions remain unanswered on the stimulation-induced network activity generated by therapies like DBS. Nonetheless, as new experimental data become available, and modeling technology evolves, it will be possible to integrate synergistically the results of systems neurophysiology with large-scale neural network models to create a realistic representation of the brain circuits being modulated by neurostimulation. Such advances will enable the development of novel stimulation technology (electrodes, pulsing paradigms, pulse generators, etc.) that can be optimized to achieve specific clinical goals; thereby improving patient outcomes."

Computational neurostimulation is the framework by which to rationally organize empirical data, formulate quantitative hypothesis, and test new interventions.

Developing computational neurostimulation models requires the right balance of detailed multiscale model with appropriate reductionism (Douglas et al., 2015; Frohlich et al., 2015; Holt and Netoff, 2014; Karamintziou et al., 2014; Mina et al., 2013; Modolo et al., 2011; Shukla et al., 2014). This review attempts to present the modeling process as tractable, even when dealing with unknowns, including serializing modeling steps and applying the quasi-uniform assumption where relevant. The research and optimization process should be considered as iterative and so computational neurostimulation is a tool to continuously refine approaches. The alternative is a qualitative and *ad hoc* testing of protocols, where both isolated positive and negative clinical findings may do little to advance the science of treatment because they are not placed within a rational interventional framework.

A central motivation for computational neurostimulation is that the interventional parameter space (dose, timing, task, inclusion citation, etc.) is too wide, given the cost and risk of human trials, for "blind" empirical optimization. Computational neurostimulation is thus necessary for rational optimization of neuromodulation protocols (Beriault et al., 2012; de Aguiar et al., 2015). At early stages, such effort must be highly experimental data constrained (Douglas et al., 2015; Merlet et al., 2013; Shamir et al., 2015) and typically constrained to a limited range of dose settings. Computational neurostimulation is also the bridge by which data from animal studies can be rationally incorporated into models for interventions.

Approaches using closed-loop stimulation are inherently state dependent and require computational neurostimulation (Cheng and Anderson, 2015; Gluckman et al., 2001; Gorzelic et al., 2013; Grahn et al., 2014; Liu et al., 2013; Priori et al., 2013; Shamir et al., 2015). As relevant and practical for any given approach, feedback can be based on output at any of the four stages: (1) recording of current flow patterns for a given dose (Datta et al., 2013b), (2) monitoring of cellular responses such as unit firing rat, (3) changes in network activity such as local field potentials (Bergey et al., 2015; Gluckman et al., 2001; Merlet et al., 2013), and (4) behavior (Shamir et al., 2015). Even if based on assumptions (which can be tested) and simplifications (which may not necessarily reduce value in clinical optimization), a computational neurostimulation approach that spans across these stages is a rational substrate for closed-loop dose optimization.

In many instances, even if computational neurostimulation can be applied using conceptually sequential steps, a more holistic approach may be required. For example, ongoing neuronal activity (Step 3) may influence both polarization sensitivity (e.g., baseline oscillation level modulates polarization length; Reato et al., 2010) and resulting effects of stimulation on firing patterns (e.g., baseline firing pattern determines effects of stimulation). Thus network- and activity-dependent considerations can influence Step 2. The state of neuronal networks can be controlled through behavioral interventions (Step 4), such that engaging in a task will influence network activity (Step 3) and hence susceptibility to electrical stimulation.

It may be that only by integrating predictions at multiple scales can a valuable and coherent prediction arise (Ali et al., 2013; Douglas et al., 2015). For example, in a computational neurostimulation models of electrical modulation of sleep

homeostasis, it was necessary to consider both polarization polarity inversions across cortical folds (which at cellular level may seem to cancel a polarity-specific effects) with neuronal network binding across brain region products by slow-wave oscillations—whereby a net effect of stimulation was produced through rectification and modulation of oscillations and then plasticity (Reato et al., 2013a). This effort was both experimentally constrained by electrographic recordings from human, as well as animal data on polarization sensitivity (Reato et al., 2010), and used to predict behavioral (learning) changes. Such efforts, which use computational neurostimulation to bridge dose to behavior, however rudimentary, demonstrate the feasibility and application of computational neurostimulation, and so are encouraging for ongoing work.

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