CHAPTER

Computational modeling of neurostimulation in brain diseases

9

Yujiang Wang*, Frances Hutchings*, Marcus Kaiser*,†,1

**Interdisciplinary Computing and Complex BioSystems, School of Computing Science, Newcastle University, Newcastle upon Tyne, UK*

†Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

[1]Corresponding author: Tel.: +44 (0)1912088161; Fax: +44 (0)1912088232, e-mail address: marcus.kaiser@newcastle.ac.uk

Abstract

Neurostimulation as a therapeutic tool has been developed and used for a range of different diseases such as Parkinson's disease, epilepsy, and migraine. However, it is not known why the efficacy of the stimulation varies dramatically across patients or why some patients suffer from severe side effects. This is largely due to the lack of mechanistic understanding of neurostimulation. Hence, theoretical computational approaches to address this issue are in demand.

This chapter provides a review of mechanistic computational modeling of brain stimulation. In particular, we will focus on brain diseases, where mechanistic models (e.g., neural population models or detailed neuronal models) have been used to bridge the gap between cellular-level processes of affected neural circuits and the symptomatic expression of disease dynamics. We show how such models have been, and can be, used to investigate the effects of neurostimulation in the diseased brain. We argue that these models are crucial for the mechanistic understanding of the effect of stimulation, allowing for a rational design of stimulation protocols. Based on mechanistic models, we argue that the development of closed-loop stimulation is essential in order to avoid inference with healthy ongoing brain activity. Furthermore, patient-specific data, such as neuroanatomic information and connectivity profiles obtainable from neuroimaging, can be readily incorporated to address the clinical issue of variability in efficacy between subjects.

We conclude that mechanistic computational models can and should play a key role in the rational design of effective, fully integrated, patient-specific therapeutic brain stimulation.

Keywords

Parkinson's disease, Epilepsy, Cortical spreading depression, Migraine, Neglect, Aphasia, Closed-loop, Patient-specific, Mechanistic modeling, Optogenetics

Progress in Brain Research, Volume 222, ISSN 0079-6123, http://dx.doi.org/10.1016/bs.pbr.2015.06.012

1 INTRODUCTION

Brain stimulation as a therapeutic tool to treat disorders of the brain has become widely accepted in diseases such as Parkinson's (using deep brain stimulation (DBS)), epilepsy (using vagus nerve stimulation), and depression (mainly using noninvasive brain stimulation devices). However, the mechanisms of action are not fully understood and the discovery of stimulation treatment is either incidental or based on explorative animal experiments (George et al., 2000; Miocinovic et al., 2013). Stimulation parameters are often set by the clinician in a trial and error approach on a subject-specific basis, and it is not understood why some subjects do not respond to the stimulation or show severe side effects. A systematic, rational design of brain stimulation adapted to each patient is lacking. Furthermore, the current invasive stimulation devices for both epilepsy and Parkinson's operate in an open-loop fashion, meaning that the stimulus is always delivered, regardless of the state the brain is in. Modolo et al. (2012) have compared this to the situation where the air conditioning in a car is set to continuously blow out cold air, irrespective of the inside temperature, weather, or season. Certainly, this is not only an issue for energy consumption but also it can be speculated that the open-loop approach might underlie large parts of the observed side effects, i.e., stimulating the brain at the wrong time can have negative consequences. Hence, it becomes clear that therapeutic brain stimulation should be designed rationally, consider subject-specific needs, deliver the stimulus only when necessary (close-loop approach), and only control abnormal activity. In short, highly targeted patient-specific closed-loop brain stimulation should be rationally designed based on mechanistic insight. This will enable brain stimulation to become a truly integrated and tolerated part of the brain.

Along with animal and clinical experiments, computational approaches have proven crucial to achieve the rational design of stimulation protocols. Computational models of brain activity incorporate knowledge regarding the relevant biological components (often neurons or neural populations) and how these components interact to then describe the complex activities and dynamics of the brain (Dayan, 2005; Sterratt et al., 2011). Such an approach is extremely useful as mechanistic insight can be achieved regarding how brain activity is generated based on basic assumptions. Furthermore, computational models can give a more holistic picture of what possible dynamics a system can generate under different conditions (e.g., using parameter and bifurcation analysis). This point becomes especially important when modeling certain brain disorders (e.g., epilepsy, migraine), where a mechanistic explanation is sought regarding why the same components as in a healthy brain start to generate abnormal dynamics (e.g., Breakspear et al., 2006; Wang et al., 2012; Wei et al., 2014). These models used in conjunction with animal and clinical experiments can lead to a fruitful iterative process, where experiments inform and validate computer models, and computer models provide further hypotheses and predictions to be tested in experiments. The insight gained from such a process can serve to inform the rational design of countermeasures in the diseased brain.

An additional point on the usefulness of computational models in the design of brain stimulation is the possibility to actually simulate the stimulation effect and to integrate methods from control engineering in such simulations. In other words, computer models can serve as a platform to design and test brain stimulation protocols. The advantage over animal models is the capacity to scan a wide range of protocols or to find optimal parameters (e.g., in terms of energy consumption or stimulation duration; Feng et al., 2007a,b; Taylor et al., 2015). The insight from such analyses can help to narrow down and focus further animal or clinical experiments.

Finally, following recent advocation of personalized medicine (Hamburg and Collins, 2010; Lu et al., 2014), there are moves to incorporate patient-specific data in computational models to develop specific stimulation protocols for the individual. In particular, in the case of brain stimulation, we know that subject-specific adjustments are necessary to achieve efficacy and to avoid side effects. Hence, it is a natural step to incorporate patient-specific data in computer models of brain stimulation in order to predict subject-specific protocols and parameters. So far, some improvements are demonstrated by the use of subject-specific head models, which predict the stimulated tissue based on the anatomical structures in individual patients (Frankemolle et al., 2010). However, this can clearly be taken a step further also to integrate subject-specific data and parameters in the mechanistic models of brain dynamics (e.g., model parameters inferred from EEG/ECoG (Freestone et al., 2011) or white matter connectivity (Kaiser, 2013; Taylor et al., 2014a)) to arrive at truly patient-specific stimulation.

In summary, we argue that computational models of brain stimulation are crucial for mechanistic insight and hence the rational design of neurostimulation. It also serves as a platform to integrate clinical subject-specific data with control engineering approaches to systematically find patient-specific stimulation protocols. This approach has the potential to produce more accurate and individualized predictions of the impact of stimulation on pathological brain dynamics.

With this introduction, we have motivated the use of computational modeling to rationally design and test closed-loop subject-specific brain stimulation. We shall now focus on brain stimulation for therapeutic usage. We review the literature for existing computational approaches to the rational design and development of stimulation protocols in brain disorders. We will specifically examine approaches for closed-loop patient-specific stimulation protocols. When such approaches are lacking in a particular field, we review and highlight how such an approach could be incorporated.

The review is structured as follows: we begin with a summary of the methods, i.e., the relevant computational models and how stimulation modalities can be incorporated in those models. This will enable us to review brain stimulation in disorders from the conceptual perspective, without having to explain the exact model and method in each case. We focus on a specific subset of brain disorders, beginning with Parkinson's disease (PD), where DBS is an active therapeutic tool that has received much attention and research. Of all brain disorders, Parkinson's is perhaps the most advanced field for computational brain stimulation. This is followed by a review of

epilepsy research, where computational brain stimulation is an actively developing field, with promising perspectives and opportunities. Lastly, we review computational brain stimulation in cortical spreading depression (CSD), where there is still much scope for future research. We choose CSD as an example of a field that has received much computational attention in terms of the mechanistic understanding, and review how this can be used for the rational design of brain stimulation. Finally, we shall discuss some general considerations and challenges for the rational design of patient-specific closed-loop brain stimulation *in silico*.

1.1 MODELING OF STIMULATION MODALITIES

We shall begin the review with a brief overview of how some widely used brain stimulation modalities are computationally simulated. This will form a point of reference and will enable us to focus on the conceptual level of brain stimulation for the remaining review. The simplest way to incorporate a generic stimulus in a model is to induce a change in one of its parameters, or change the values of certain variables that are thought to be affected by the stimulus. This approach is followed by modeling studies that investigate the effect of a generic stimulus (e.g., Goodfellow et al., 2012; Taylor et al., 2014b). Alternatively, the exact effect of specific stimulation modalities can be modeled to reflect experimental conditions better. This latter approach is often easier to relate to experiments and is what we shall summarize in the following. However, we would like to remark that the modeling of stimulation modalities is a developing field in itself, with some of the mechanistic underpinnings of the stimulation still being unknown. Hence, we shall only provide a brief overview here, in order to bridge the gap between abstract concepts of brain stimulation and the experimental stimulation modalities.

Before we begin the summary of the modeling of brain stimulation, we shall very briefly introduce some basic concepts of computational modeling of brain circuits. These models of brain circuits are essential to describe the effect of the stimulus on the brain. Different levels of detail can be described when modeling brain circuits. In this review, we shall broadly distinguish two levels that are relevant to the characterization of stimulus effects: (i) the neuronal description level, where the (firing and sometimes dendritic) activity of single neurons are modeled; and (ii) the population description level, where the activity of an entire neural population is described, often by population average variables. Figure 1 illustrates examples of these two approaches on simulating a cortical patch of tissue in two recently developed models (Tomsett et al., 2015; Wang et al., 2014). There are several books and reviews on either approach and on the relationship between the two (Coombes, 2006; Deco et al., 2008; Gerstner and Kistler, 2002). Both approaches are used in the modeling of brain stimulation, each with their advantages and disadvantages. For example, the neuronal description level is easier to relate to measurable biological entities, but the amount of detail (and hence parameters) can be overwhelming and difficult to understand and to analyze. The population description level is often easier to understand mechanistically, with a limited number of parameters. However, the

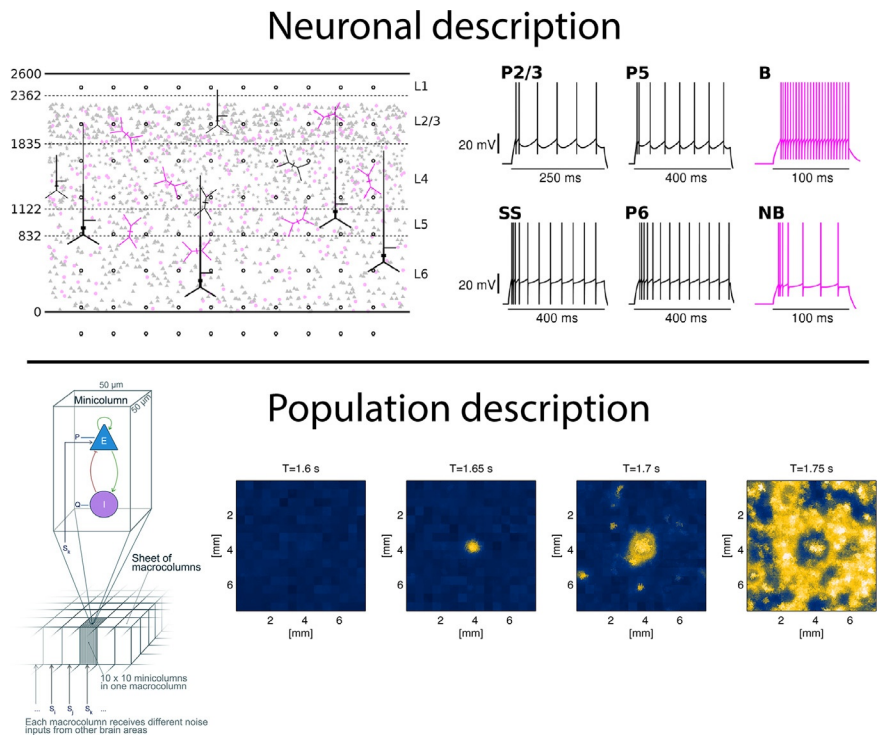

FIGURE 1

Top: Neuronal description level, where the neurons in the different cortical layers are simulated. The multicompartment dendritic tree structure is shown for some of the neurons. The structure of an example cortical patch of tissue is shown on the left. Some example time series of the firing dynamics of excitatory (black) and inhibitory (magenta; gray in the print version) neurons are shown on the right. Numbers on the right indicate cortical depth in micrometers. See Tomsett et al. (2015) and www.vertexsimulator.org for details. Bottom: Population-level description, where average excitatory and inhibitory population firing dynamics are simulated. The structure of the cortical slab consisting of multiple minicolumns is shown on the left. An example time series is shown of the dynamics at different time points. See Wang et al. (2014) for details.

Figures modified from Tomsett et al. (2015) and Wang et al. (2014).

parameters are often more difficult to interpret or measure, and cellular processes are often only included in an abstract fashion. The choice of the description level is often dependent on the specific research question, the data available to validate the model against, and the need for mechanistic understanding. Broadly speaking, detailed neuronal models are mostly used for investigating how molecular- and cellular-level processes influence local circuits. Based on the knowledge of local circuits,

population-level models allow for mesoscopic and whole-brain level investigations of brain dynamics. For the modeling of brain stimulation, both approaches have been shown to be very useful in different contexts.

1.2 NONINVASIVE ELECTRIC STIMULATION

Noninvasive electric stimulation has been used in varying forms for centuries, with reports from the ancient world of electric fish used to provide stimulation for headache treatment to the more recent and infamous usage of transcranial electrical stimulation (TES) in treatment of mental illness. The ability to apply currents to the brain without need for any lesion of the skin or skull has made noninvasive stimulation an attractive prospect for medical practitioners. Today, the use of noninvasive electrical stimulation is mainly focused on transcranial current stimulation (TCS), and it is used for treatment as well as research.

TCS involves placing electrodes over the scalp, and channeling a current flow from a positive "anode" electrode to the negative "cathode." The type of current can be varied, with the most studied being transcranial direct current stimulation (tDCS) where the current is ramped up to a steady level, which is then applied for the duration of the stimulation protocol. Other variants, which are growing in popularity, include transcranial random noise stimulation and transcranial alternating current stimulation, which has recently shown some ability to entrain cortical oscillations (Helfrich et al., 2014) leading to an increase in interest in this technique. Unlike TES, the currents used for TCS are small and the reported side effects are very minor. There is still no full agreement on the mechanism of action of TCS, and this might differ for the treatment of different conditions. The general consensus is that TCS is essentially modulating the excitability of the stimulated tissue (Nitsche et al., 2005). We refer the reader to some reviews on this topic for a summary (Bestmann et al., 2015; Brunoni et al., 2012; de Berker et al., 2013; Krause et al., 2013; Liebetanz et al., 2002; Medeiros et al., 2012; Nitsche et al., 2015; Pelletier and Cicchetti, 2014).

In the context of brain diseases, TCS has been used to experimentally modulate cortical excitability, and hence change properties of CSD waves (Liebetanz et al., 2006). Similarly, in epilepsy, TCS has been used to experimentally modulate cortical excitability and terminate seizures early (Berényi et al., 2012; Nitsche and Paulus, 2009). Even in PDs, for patients suffering from severe side effects of DBS, or where DBS is not an option, the possibility of applying tDCS to the motor cortex is investigated (Benninger et al., 2010; Fregni et al., 2006).

The majority of computational modeling work that has been accomplished for TCS has been in finite element models (FEM). These models can take the morphology of the cortex and the conductivities of various tissues into account in order to predict the spread of electrical currents spatially and temporally on the head from anode to cathode. This enables practitioners and researchers to find the best electrode positions for targeting desired brain areas. There is no direct indication from these models of what effect the current may be having, only *where* effects are likely to

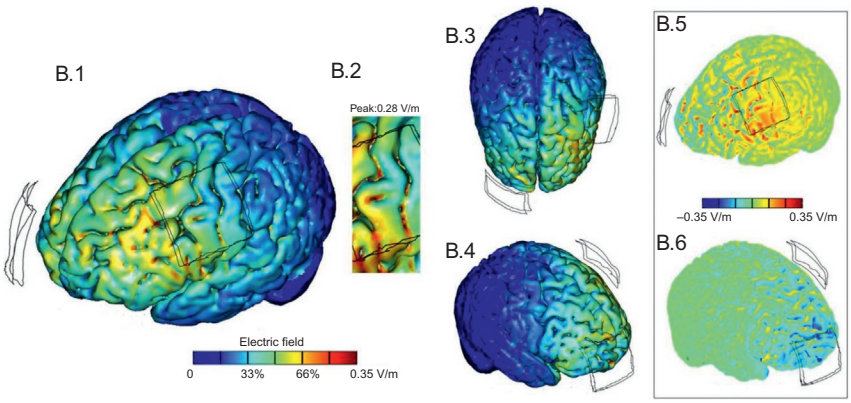

FIGURE 2

An example of FEM visualization, with current intensity shown through the color maps and the electrode positions overlaid. Several different angles of view are displayed, including a close up (B.2) look at the central area under the anode.

Figure adapted from Datta et al. (2012).

occur, so FEMs need to be used in combination with prior knowledge or further mechanistic modeling to form predictions about behavioral outcomes. These FEMs vary in complexity; however, they consistently include calculations of different tissue resistances to predict the amount of current that will actually reach the brain (Bikson et al., 2012), see Fig. 2 for an example. Many of these models approximate the head to several spherical layers with different conductivities and thicknesses (Datta et al., 2008; Miranda et al., 2006). This simplistic approach is widespread and has been used in many studies for planning electrode positions. Recent modeling studies have taken this approach a step further by including cortical folding (Parazzini et al., 2011) and varying skull thickness. Subject-specific anatomy has also been incorporated from magnetic resonance imaging (MRI) (Windhoff et al., 2013), with results indicating that this is an important addition to the models as it can make a crucial difference to current flow. Finally, in addition to considering tissue conductivity differences based on MRI, tissue anisotropy in the white matter has also been shown to influence the electric field (Rampersad et al., 2014; Suh et al., 2012). There has been some experimental validation of FEM predictions of current flows (Datta et al., 2013) on the skull; however, no direct validation exists for the currents on the cortex.

There have been a small number of studies incorporating TCS stimulation mechanistically in computational models. An intuitive approach is to model the TCS stimulus as an extracellular field polarizing the neurons in the field. The degree of polarization can be simulated in reconstructed neurons that include some morphological detail (Arlotti et al., 2012; Rahman et al., 2013). Extrapolating from the detailed models in network models point neurons have been used, where only

pyramidal neurons are affected by the stimulation due to their geometry (Reato et al., 2010). On the neural population level, a similar extrapolation has been used, where the stimulus was modeled as a perturbation on the mean membrane potential of populations (Ali et al., 2013; Dutta and Nitsche, 2013; Molaee-Ardekani et al., 2013). It was assumed that the perturbation is linearly related to the stimulus amplitude and direction dependent (relative to the stimulus field). Interestingly, Molaee-Ardekani et al. (2013) found that only when including an effect of the stimulation field on interneuron populations, the model produced a better prediction of experimental measurements. Finally, at the population level, the modeling of the TCS stimulation can be combined with the FEM approach, where MRI-derived head models inform the positioning of neural populations, and a realistic electric field is simulated (Merlet et al., 2013).

These models of TCS have aided the understanding of the mechanism of action, and some degree of validation with experimental results has been achieved. Nevertheless, the modeling of the effect of TCS is still an active field that will continue to progress together with experimental insight and validation.

1.3 NONINVASIVE MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) involves inducing electric currents in the brain by applying pulsed magnetic field changes. It is noninvasive, focal, and thought to have minimal negative side effects (Rossi et al., 2009). While the effect on the brain is still the induction of an electrical current, the magnetic mechanism of induction means that the skull does not act as a barrier to the stimulation as magnetic fields are not restricted by it (Post and Keck, 2001). The fields are created by passing electrical current through coils held over the head above the targeted areas. TMS pulses produce a large enough electric current to elicit action potentials in the underlying tissue and have been used to create "virtual lesions" for short durations in experiments which try to discern the function of different cortical areas (Hallett, 2000; Siebner et al., 2009). The pulses induced can be either monophasic or biphasic, named after the waveform the pulses produce, with each likely activating different neuronal populations (Arai et al., 2005). As with TCS, there exist a number of TMS variants. Two that have proved popular in recent years are theta burst stimulation which involves using TMS to deliver short fast trains of stimulation (Huang et al., 2005), and repetitive TMS (rTMS) which applies either monophasic of biphasic pulses many times at regular intervals (Post and Keck, 2001). These TMS variants have been tested in various clinical settings where stimulation is employed therapeutically with encouraging results (Kindler et al., 2012; Koch et al., 2012; Lefaucheur et al., 2014; Talelli et al., 2012).

Similar to TCS, TMS has been suggested as an effective therapeutic tool in PD, possibly as an alternative to invasive treatment in some patient groups (Kimura et al., 2011). In epilepsy, experimental and clinical studies were conducted using TMS as a tool for diagnosis and treatment (Kimiskidis et al., 2014). In migraine,

the first clinical study demonstrates the beneficial effect of early TMS stimulation in order to reduce pain (Lipton et al., 2010).

In terms of computational modeling of TMS, numerous finite element head models exist for the practical purpose of providing clinicians or experimentalists with a prediction of the stimulated tissue. As in the case of TCS, these head models account for the electric properties and geometries of different tissues (Deng et al., 2013; Salinas et al., 2009; Wagner et al., 2004) but do not model the current effects on neurons or neuronal populations (as opposed to more "mechanistic" models), only estimating the location of effect. In the case of TMS, the induced electric field is dependent on the coil position, shape, orientation, and pulse strength (Roth et al., 1991). Again similar to TCS, there is a movement toward using subject-specific models, taking personal cortical anatomy into account for greater accuracy (Bijsterbosch et al., 2012). One model took an interesting approach, combining a FEM with a mechanistic focus, predicting, based on neuron morphology, which neuron types would be stimulated by different protocols in an area of folded cortex (Silva et al., 2008). These head models are helpful for experimental design and accuracy in tissue targeting but do not make predictions about what behavioral effects or underlying mechanisms stimulation may have.

The mechanistic modeling of the effect of TMS stimuli is similar to the modeling of TCS, as the electric field induced by TMS is ultimately thought to be driving the polarization of the neurons. At the level of individual neurons, TMS stimulation is generally modeled by modifying compartmental membrane potentials of neurons according to their position in relation to the TMS-induced electric field (Kamitani et al., 2001; Nagarajan et al., 1993; Pashut et al., 2011). Interestingly, when Rusu et al. (2015) introduced a current input with a monophasic waveform shape to neurons, they found that current shape does not have a great impact on results. At the mesoscopic scale, most models approximate TMS stimulation as an additional input to the membrane potential of some or all neurons (Miyawaki and Okada, 2005; Miyawaki et al., 2012; Yu et al., 2013). The proportion of the population stimulated varies to represent different pulse strengths (Esser et al., 2005). A number of these models have successfully replicated experimental findings, in some cases capturing EEG changes following stimulation (Cona et al., 2011; Esser et al., 2009). A different approach was taken by Husain et al. (2002), attempting to predict TMS effects on task performance with a connectionist network model of visual attention. By simulating TMS as a change in incoming connection weights to a stimulated area, the model could replicate a number of experimental findings.

Computational models have increased understanding of how TMS influences the brain at different levels of complexity. However, while changes in membrane potential have proved to be a successful analogue for TMS in many studies, there is still a great deal that is not fully understood, such as which neuronal populations are stimulated by which protocols, and why responses to TMS can vary so greatly between protocols and individuals. As with TCS, modeling in this field is still active and progressing rapidly.

1.4 INVASIVE ELECTRICAL STIMULATION

Invasive electric stimulation is used in a range of therapeutic and experimental settings. The stimulation electrodes are surgically placed within the brain and the stimulation is delivered to the tissue directly. Depending on the clinical need, the device, the electrode size, and stimulation setup may vary. Common invasive electric stimulation devices include DBS devices for PD and electric mapping of eloquent cortex during resective brain surgeries. The range of applications for invasive electric stimulation is vast; hence, we shall focus on how the stimulation is modeled here and show their specific application later in the context of different brain diseases.

There are many parallels in the modeling of invasive electrical stimulation and TCS. Invasive electric stimuli are also modeled as electric fields which influence the activity of neurons and neural networks in the peri-electrode space. Computational models of different levels of detail exist, starting with simple FEM head models simulating the fields from the stimulation electrode relative to the head, for example, for DBS (Grant and Lowery, 2009). More in-depth considerations further include MRI-derived positions of different types of brain tissue, their anisotropy, and their bioelectric properties (Åström et al., 2011; Schmidt and van Rienen, 2012; Yousif and Liu, 2009). The effect of multiple electrodes and the possible fields that can be created is also analyzed (Buhlmann et al., 2011; McIntyre and Grill, 2001). This is not only for realistic recreation of experimental conditions, but also for designing (patient-specific), electric fields that only stimulate specific desired targets. Furthermore, models and experiments have shown that brain tissue can have a stimulation frequency-dependent effect, which further complicates modeling of the stimulation (Wagner et al., 2014). Finally, the effect of the stimulation field on the neural circuit can be modeled using the same approaches mentioned in the TCS section (see section 1.2). It is again the case that some detailed models exist investigating the polarizing effect of the stimulation field on neurons with detailed morphologies (Rattay, 1999; Yousif et al., 2010), but approximations exist, for example, when the electric field induces action potentials in point neurons (Warman et al., 1992). Joucla and Yvert (2012) summarize different approximations and approaches in their review.

1.5 OPTOGENETICS

Optogenetic stimulation is a fairly recent development, which uses light-sensitive ion channels to manipulate the membrane potential and activity of a target cell (Deisseroth et al., 2015). The advantage is that selective cell types can be targeted (using cell-specific promoters) to express these ion channels. This leads to a great level of fine-grained control of the stimulus, which is not achievable by any conventional brain stimulation devices. Additionally, the effect of a light stimulus is relatively straightforward to understand on the cellular level, which again is not the case for conventional brain stimulation devices. Due to these advantages, optogenetics has become a vital tool for studying and controlling neural circuits, at least in research. Optogenetics as a therapeutic tool is still in its infancy, but promising studies

are paving the way for optogenetics to become a clinically accepted tool. For more details, we refer the reader to the summaries and reviews in the field (Fenno et al., 2011; Kim et al., 2011; LaLumiere, 2011; Rein and Deussing, 2012; Tye and Deisseroth, 2012; Williams and Denison, 2013).

Computational models of optogenetic stimulation have been developed following two approaches. In the first approach, the dynamics of the opsin are simply modeled as an input with an exponential rise and decay (Vierling-Claassen et al., 2010). Following such inputs, the effect of the stimulus is observed on the network level. In the second approach, the intrinsic channel dynamics of the opsin are specifically modeled to address questions regarding the detailed light-stimulation parameters required to achieve the desired change in membrane potential (Grossman et al., 2011). In terms of modeling, the detailed dynamics of the opsin, the main focus of attention has been the well-known channelrhodopsin (Foutz et al., 2012; Grossman et al., 2011; Nikolic et al., 2013; Stefanescu et al., 2013; Williams et al., 2013). However, detailed models of other opsins (such as halorhodopsin, see Stefanescu et al., 2013) are in development.

The natural choice of models for the incorporation of optogenetic stimulation is neuronal models, where the opsin channels can be represented as conductances. However, when dealing with large network dynamics, it is often desirable to switch to a mean-field population-based modeling approach. Hence, population-level descriptions of the effect of optogenetic stimulation have also been suggested (Selvaraj et al., 2014).

Given this collection of pioneering work in modeling optogenetic stimulation, we are provided with a library of modeling tools to address a range of questions on the different temporal and spatial scales. Questions regarding optimal protocols of the light input, as well as network-level effects of the stimulation can now be answered in a computational framework. We shall later highlight the use of optogenetic stimulation models specifically in the context of epilepsy stimulation.

2 COMPUTATIONAL MODELING OF STIMULATION IN BRAIN DISORDERS

2.1 PARKINSON'S DISEASE

In this section, we shall review the development and design of stimulation protocols for PD *in silico*. To this end, we begin with an overview of the disease itself before addressing some of the existing therapeutic stimulation methods. The primary observation in PD is the degeneration of dopaminergic neurons in the substantia nigra, located in the basal ganglia. It is believed that this loss of dopaminergic innervation in the basal ganglia is the primary cause of the symptoms associated with PD. Classical symptoms include tremor, rigidity, reduced movement amplitude, and slow movements. A range of psychological, autonomic, and sensory symptoms can also be present. Currently, no cure exists, but some options (e.g., medication compensating

for the lack of dopamine or DBS) are available to treat the symptoms (Dauer and Przedborski, 2003; Davie, 2008; Dexter and Jenner, 2013).

Computational models of the basal ganglia and PD have been developed alongside clinical and animal experiments for over two decades. We refer the reader to a series of excellent reviews on the topic (Cutsuridis, 2014; Moustafa et al., 2014; Rubchinsky et al., 2007; Rubin et al., 2012). Most computational models in PD focus on the motor symptoms, which are thought to be related to the abnormal output of the basal ganglia following the loss of the dopaminergic innervation. Some models additionally address the cognitive deficits sometimes observed in PD (e.g., Hélie et al., 2012).

PD is one of the few diseases where brain stimulation is an established, and highly effective, treatment. DBS in PD is one of the most common treatment options when patients develop disabling motor symptoms, with the subthalamic nucleus (STN) and globus pallidus interna (GPi) being the primary stimulation targets (Miocinovic et al., 2013). However, following its incidental discovery in 1987 (Benabid et al., 1987), the mechanism of action of the DBS therapy is still debated (Da Cunha et al., 2015; DeLong and Wichmann, 2012; Dostrovsky and Lozano, 2002; Lobb, 2014; McIntyre and Hahn, 2010) and its effects are not consistent for all patients. Proposals range from DBS introducing antidromic action potentials stimulating the motor cortex (Li et al., 2012) to DBS changing the large-scale structural connectivity of the brain (van Hartevelt et al., 2014). Computational models have proven to be crucial for the emerging mechanistic understanding of DBS in PD (Modolo and Beuter, 2009; Modolo et al., 2011; Rubin et al., 2012). Using such computational models, it is for the first time possible to link molecular and cellular observations to the behavioral-level expression of disease symptoms in a mechanistic, systematic way.

Alternative stimulation modalities such as noninvasive TCS and TMS stimulation are also in development (Benninger et al., 2010; Fregni et al., 2006; Kimura et al., 2011). In this context, it is also worth mentioning the development of optogenetic DBS (Rossi et al., 2015; Tierney et al., 2011), where the cellular mechanism of action is more straightforward and accessible. In such scenarios, where the effect of the stimulation on the components of the targeted neural circuit is more clear, predictions can be made regarding how the affected components will behave and give rise to systems level output following stimulation. Again, computational models will play a crucial role in such a prediction process.

DBS of the STN and GPi is currently routinely performed in an open-loop protocol, where a high-frequency stimulus is permanently stimulating the deep brain structures. This does not only come with technical drawbacks, such as battery-recharging issues, but also some potential negative side effects (e.g., confusion, delirium, weight-gain, cognitive impairment) have been noted as a result of the permanent stimulation (Da Cunha et al., 2015). Hence, some effort has been invested in the development of closed-loop on-demand protocols (see Carron et al., 2013; Modolo et al., 2015, for motivation and review). An intuitive way to close the loop is to attenuate the beta-band power measured in the STN on demand using

high-frequency stimulation, since an increased beta power has been associated with the motor symptoms in PD. Indeed, such a closed-loop device has been recently demonstrated to be effective in a proof-of-principle study (Little et al., 2014). Excitingly, this closed-loop protocol has demonstrated not only reduced power requirements but also improved clinical scores of the subjects. It is also interesting to note that the exact beta-band frequency selected for attenuation is subject-specific based on their peak power in the beta band. Hence, this study not only demonstrates that closed-loop protocols are superior to open-loop protocols but also emphasizes the need for patient-specific closed-loop protocols.

To support this point, we highlight the results of several modeling studies concerned with the rational development of improved stimulation designs. Very similar to the principles used in Little et al. (2014), Santaniello et al. (2011), and Modolo et al. (2010) suggest control of the LFP power spectrum (measured by electrodes in the cortex or thalamus) and demonstrate possible implementations of such a controller. Interestingly, the LFP power spectrum control has been approached from both the detailed cellular level (Santaniello et al., 2011) and the population level (Modolo et al., 2010). On the cellular level, the tremor condition is simulated by a range of different model neurons, each with their intrinsic activity matched to recordings from patients. The control is achieved by an adaptive minimum variance controller, which uses information from a recursive algorithm that identifies the relationship between stimulation and corresponding change in LFP power. The advantage of this approach is that the desired changes in firing patterns of single cells can be studied. Santaniello et al. (2011) also shows that in the model the closed-loop regime achieves a better control than the open-loop regime. On the mesoscopic level, Modolo et al. (2010) model the tremor condition as a peak in the beta band of motor-cortex activity. The motor cortex is represented by a cortical sheet modeled by a neural field. A simulated multielectrode array is used to monitor the activity in time and space. A stimulus is delivered when the beta-band power in an electrode crosses a threshold. The stimulus signal is a function of the measured ongoing activity. Figure 3 illustrates the simulated effect of such a closed-loop control. This mesoscopic approach has the advantage of allowing control to be investigated spatially as well as temporally. This is not trivial, as the spatial locations (different areas of the cortex) are interconnected and stimulating one region has a knock-on effect on other regions too. In this case, tissue of the size of 135 cm^2 is to be modeled, and a population-level abstract approach is computationally and conceptually tractable while still being interpretable from a biological perspective.

Moving away from power spectrum control, coordinated reset (see Popovych and Tass, 2014 for a review) has been proposed as a stimulation protocol, where the goal is essentially to desynchronize the output of the basal ganglia (which is linked to the increase in beta power and the appearance of tremor). The authors suggest that a spatially distributed and heterogeneous stimulus might achieve such a resynchronization. Interesting again in this idea is the role of closed-loop feedback, which can stabilize the desynchronized state (Hauptmann et al., 2005; Popovych et al., 2005) restoring dynamics to match those found in healthy subjects and therefore potentially alleviating the pathological tremor.

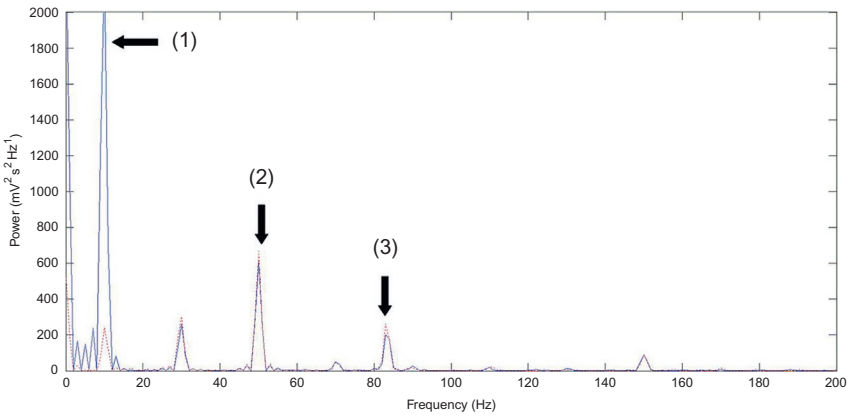

FIGURE 3

Power spectrum of simulated neural activity before (blue; dark gray in the print version) and during (red; light gray in the print version) closed-loop stimulation. The stimulation algorithm targets the "pathological" 10 Hz rhythm (labeled 1) and attenuates it while leaving other rhythms (labeled 2 and 3) intact.

Figure reused from Modolo et al. (2011).

From the control engineering perspective, closed-loop protocols that are optimized toward power consumption and minimal stimulation strength have been developed based on computational models of the basal ganglia (Feng et al., 2007a,b). The method developed by the authors is essentially a global search algorithm for the best stimulation parameters—in this case optimized to find the minimal strength needed to successfully suppress PD abnormalities. Importantly, it can be applied in a model-free environment and the parameters can be optimized to fit individual patients. Alternatively, Schiff (2010) suggests using online model parameter estimation techniques to inform closed-loop stimulation and demonstrated that such a closed-loop protocol is superior in efficacy compared to an open-loop system.

Finally, computational models have not only contributed to the design of stimulation protocols but have also given indications regarding the best stimulation locations. Detailed models of the spatial reach of the DBS electrode (Frankemolle et al., 2010; Yousif et al., 2007) can give us subject-specific guidance regarding implantation site and improve side effects (Frankemolle et al., 2010). On the mechanistic level, computational models have suggested alternative stimulation sites (Modolo et al., 2010, 2011; Pirini et al., 2008; Zwartjes et al., 2012), such as the motor cortex, which could be targeted by noninvasive stimulation and may improve clinical treatment in certain groups of patients where DBS is not an option.

We conclude that the development of closed-loop protocols, where the stimulation location and parameters are derived patient specifically (online or offline) is crucial for the improvement of brain stimulation in PD. This is not only a consideration of battery life, but as we have highlighted, also a question of reducing side effects and

increasing efficacy. Computational models could not only help to find optimal stimulation protocols and parameters but can also guide the search for best stimulation location in a patient-specific manner. Finally, we remark that although we have focused the review on PD, some of the concepts discussed here could be applied to the stimulation of other movement disorders, such as tremor (Rehan and Hong, 2013).

2.2 EPILEPSY

Epilepsy is a family of neurological disorders characterized by recurrent unprovoked seizures. Seizures are generally transient periods of interrupted or abnormal brain function. Ever since the term "dynamical diseases" was coined (Glass and Mackey, 1979; Mackey and Milton, 1987), epilepsy has been used as a classic example (Lopes da Silva et al., 2003; Milton and Jung, 2002). The number of theoretical approaches and computational studies in the field of epilepsy is vast, and we point the reader to a range of excellent reviews in the field (Baier et al., 2012; Case and Soltesz, 2011; Lytton, 2008; Stefanescu et al., 2012; Suffczynski et al., 2008; Ullah and Schiff, 2009; Wendling, 2008; Wendling et al., 2015). In agreement with the overall trend in computational neuroscience, computational models of epileptic activity are built based on knowledge regarding the relevant underlying neural components. The models often explain the network-level observation of epileptic seizures as an emergent hypersynchronous/high amplitude rhythmic state of a network of neurons or neural populations (e.g., Taylor et al., 2013). Using these models, the link between the behavioral level of the disease symptoms (often seizures in this case) and how such behavior is generated from basic neural components (e.g., neurons) can be investigated. These models are then used to address particular questions regarding the disease, such as how particular types of seizures start (e.g., Wang et al., 2014); how seizure evolve (Nevado-Holgado et al., 2012); or how seizures terminate (e.g., Kramer et al., 2012). Often a mechanistic insight is sought in order to better understand the disease. Some models additionally provide testable hypotheses for further experiments, or even propose improved strategies for clinical treatment.

The clinical treatment of epilepsy is focused on seizure control using antiepileptic drugs, which are highly successful in certain types of seizures, but fail in about one-third of patients (Engel et al., 2008). In the search for alternative treatments, brain stimulation has recently demonstrated some degree of success (Fisher and Velasco, 2014) in controlling seizures. In addition to established vagus nerve stimulation, recently anterior thalamic DBS and stimulation of the seizure focus in focal seizures have been demonstrated to be good approaches. Noninvasive methods are also being investigated from the perspective of modulating excitability, and hence it is argued that they may reduce seizure likelihood (Nitsche and Paulus, 2009). However, the stimulation protocols are only loosely based on experimental and theoretical insight, and the mechanistic underpinnings of why the stimulation is (in) effective are largely lacking (see Stacey and Litt, 2008 for review). The need for theoretical studies becomes immediately clear at this point, as they enable us to

use the existing mechanistic knowledge in the development of stimulation protocols. The existing theoretical studies can be broadly classified into two categories.

The first category focuses on developing stimulation protocols based on conceptual insight. For example, Lopes da Silva et al. (2003) proposed the idea of a coexisting seizure state, which can be reached from the healthy background state by perturbations. In patients, the seizure state and the background state are not well separated, such that spontaneous transitions to the seizure state can occur due to noise perturbation (illustrated in Fig. 4). This conceptual idea of seizure occurrence can be demonstrated in many models of neural activity (Kalitzin et al., 2010; Kim et al., 2009; Marten et al., 2009; Wang et al., 2012). Following such an idea, single-pulse stimulation, which could perturb the brain back to the coexisting background state, has been proposed as a tool to terminate seizures early (Kim and Robinson, 2008; Suffczynski et al., 2008; Taylor et al., 2014b; Wang et al., 2014). Taylor et al. (2014b) specifically demonstrate in spike-wave seizures that the timing and amplitude of the single-pulse stimulus nontrivially determines stimulation success, explaining the previously reported mixed results in the experimental literature. The authors show that this effect is due to a complex basin of attraction of the background state. As a solution, the authors suggest using online state space reconstruction combined with a learning algorithm to design an effective closed-loop single-pulse stimulation protocol (see Fig. 5).

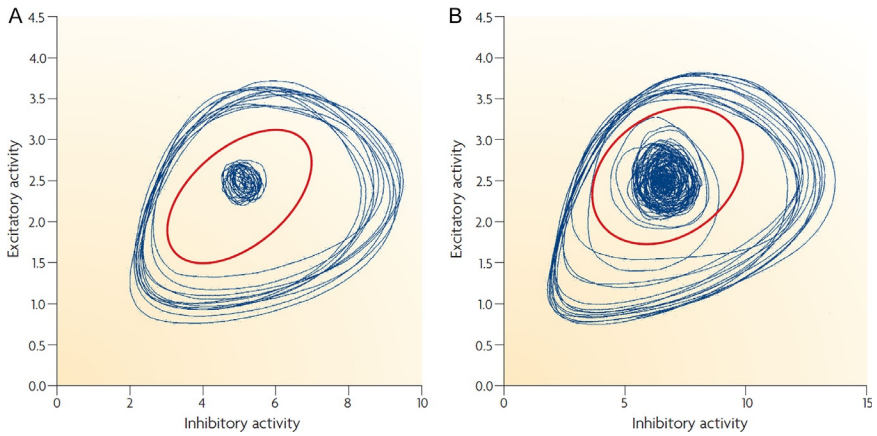

FIGURE 4

Illustration of example trajectories of a healthy brain (A) and an epileptic brain (B). The red line (black in the print version) illustrates the separation of the seizure state (outer trajectories) from the background state (inner trajectories). In an epileptic brain, the two states are much closer together enabling transitions between them. In the healthy brain, such transitions are unlikely without big perturbation or provocation.

Figure from Lytton (2008).

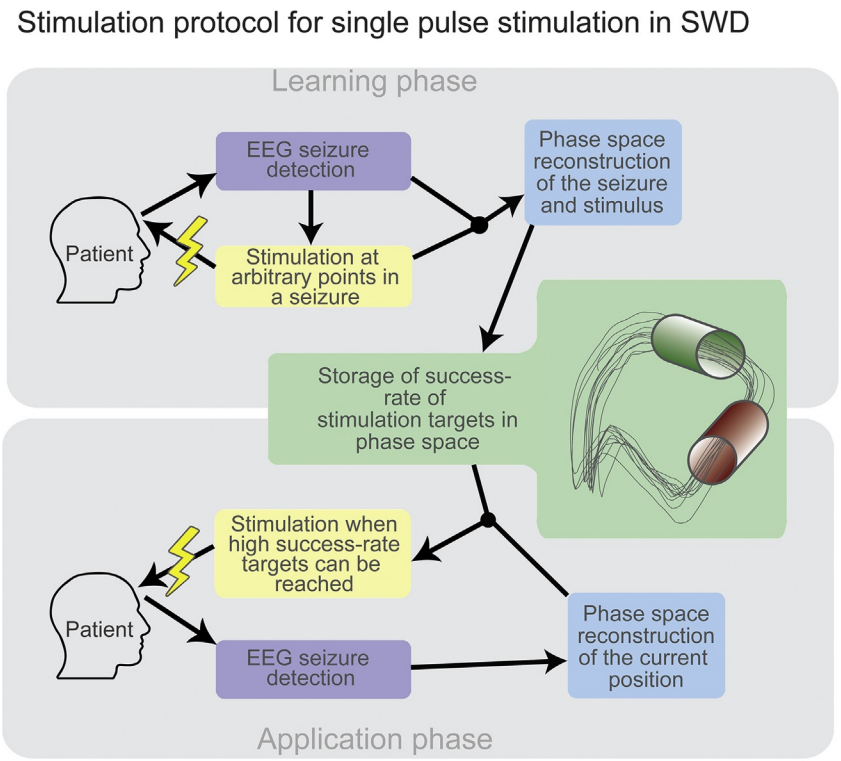

FIGURE 5

In the learning phase, (top) success rate of state space targets are stored based on arbitrary stimulations during seizures. Once the state space is charted, the application phase (bottom) can use the information of the success rate of state space targets to deliver high success rate stimuli to abate SWD seizures.

Figure from Taylor et al. (2014b).

In the second category, specific models of seizure activity are first developed, and subsequently control parameters (such as inputs) are used to inform stimulation protocols to suppress the seizure activity. Parameters such as stimulation frequency can be explored in the model (Mina et al., 2013). Often, tools from control theory (the branch of engineering which investigates the effects of inputs and feedback on dynamical systems) are used, such as linear and nonlinear feedback controllers (Kramer et al., 2006). The authors demonstrate that the controller effectively changes the bifurcation structure of the original model and prevents the bifurcation to the seizure state. Additionally considering the optimal stimulation in terms of energy, Ruths et al. (2014) use a pseudospectral approach to find an optimal control for a model of spike-wave seizure. Similarly, Wilson and Moehlis (2014) use their Hamilton–Jacobi–Bellman method to find the optimal control in terms of energy and time.

These studies not only provide possible stimulation profiles and protocols but also show that in principle, we should be able to treat neural circuits as dynamical systems to which we can apply methods from control theory (Schiff, 2009). This notion is also supported by some degree of success in the experimental literature (Gluckman et al., 2001).

Despite the presented existing work, the computational modeling of brain stimulation in epilepsy is only in its infancy. Fundamental questions about where, what, how, and when to stimulate remain unanswered, and urgently require theoretical insight. The question of where to stimulate is particularly interesting, as the presented approaches so far largely discard spatial information. This question is also dependent on the type of epilepsy. For example, in generalized seizures (involving bilateral brain networks) such as absence seizures, computational studies have proposed subcortical structures linked to the thalamus as suitable targets (Hu et al., 2014). In partial seizures, the seizure onset zone can be targeted by stimulation (Wang et al., 2014). However, when taking into consideration that the circuits generating seizure activity are not isolated, but rather embedded in a complex brain network, Ching et al. (2012) highlights certain issues associated with stimulation and control of seizure activity. These complex networks might not be controllable by a focal stimulation, but might require a more distributed, "nuanced" approach. In this context, it is also important to mention that the connectivity of brain networks will play a crucial role in the specific design of the control. Taylor et al. (2015) have made a first step toward designing controls for models of seizures including data on brain connectivity. The authors show that the power required to control a generalized seizure is very different in different brain areas due to the underlying connectivity. This suggests the possibility of using a few control points in the network to achieve seizure control. Furthermore, animal experiments of DBS show that a patient-specific approach is required, as stimulation success depends very sensitively on the exact stimulus position and protocol (Zhang and Bertram, 2015). Hence, we argue that in order to design successful stimulation protocols, patient-specific data (e.g., connectivity) and experimental knowledge of the dynamics in the neural circuits have to be combined.

The question of what to stimulate is somewhat limited by the choice of stimulation device. Electric stimulation is the main modality in use today. However, it is known to broadly activate/modulate the activity of the entire tissue around the stimulation site. Computational models can take these effects into account. However, we want to highlight the promising possibility of optogenetic stimulation, whereby specific neuronal populations can be targeted locally (Bentley et al., 2013). So far, this is still only an experimental stimulation modality, but its specificity has led to some projects aiming at developing it for clinical usage in epilepsy (see, for example, www.CANDO.ac.uk). The advantage of computational modeling of optogenetic stimulation is that the cellular effects of the stimulus are much more specific and better characterizable than for instance electric stimulation (see Section 1.5 above). In the context of epilepsy, this has led to the first experimental (Krook-Magnuson et al., 2013; Paz et al., 2013; Wykes et al., 2012) and modeling (Selvaraj et al.,

2014) studies, investigating the possibility of optogenetic seizure control. For the immediate future, we predict the most accurate and specific computational models combined with experimental data arising in this field will aid the understanding and control of seizures.

The question of how to stimulate is so far approached by either modeling single-pulse stimulation or bifurcation control, as discussed above. However, given the discussion on the necessity of spatial-temporal control, we want to point to another perspective. Increased synchronization has been suggested to support seizure generation in the experimental (Paz and Huguenard, 2015) and clinical (Frauscher et al., 2015; Jiruska et al., 2013) literature. Borrowing from the field of PD (see Section 2.1), where desynchronizing oscillations is successfully inhibiting the tremor, we suggest a similar approach for epilepsy. Particularly in DBS of epilepsy, a feasible avenue to be explored is the possibility of desynchronization (Popovych and Tass, 2014) of the thalamus, where abnormal synchronization has been identified as a possible mechanism of seizure generation (Paz and Huguenard, 2015). This is furthermore also applicable to neocortical epilepsies, where abnormal synchronization could also underlie seizure initiation or termination (Jiruska et al., 2013). How such desynchronization stimuli would be implemented can be explored in computational models. Whether these stimuli would serve to stop seizures early, or prevent seizures in the first place, remains to be answered by future computational and experimental studies.

Finally, we discuss the question of when to stimulate. The approach so far in experimental literature is to deliver a constant stimulus in an open-loop system (Halpern et al., 2008). Although some attempts have been made in experimental (Berényi et al., 2012; Paz et al., 2013; Pineau et al., 2009; Smith et al., 2010) as well as theoretical literature (Ehrens et al., 2015; Taylor et al., 2014b) to develop closed-loop stimulation protocols. Such closed-loop systems often rely on the detection of a seizure, which triggers the delivery of the stimulation protocol. The goal of such a system is to abate the seizures early. However, an interesting debate has arisen over whether seizures could be predicted (Alvarado-Rojas et al., 2014; Cook et al., 2013; Mormann et al., 2007). In other words, the existence of a pre-ictal (before seizure) state has been discussed, at least in some types of seizures. Here, we speculate about the possibility of stimulation following the detection of a pre-ictal state. There are numerous advantages to such a pre-ictal state control: (i) the seizure will never occur as opposed to just being stopped early, which might help to reduce the likelihood for further seizures (Balish et al., 1991). (ii) The energy required to control a pre-ictal state might be much lower than that required to control a seizure, due to the high amplitude of activity in the seizure state compared to the background state. (iii) The pre-ictal state might be closely related to the mechanisms of ictogenesis. This could target the mechanism of the epilepsy itself, rather than targeting only the seizure.

Despite this promising prospective, the biggest challenge remains the detection of such pre-ictal states. We suggest that relaxing the pre-ictal state detection problem to a pro-ictal (high seizure susceptibility) state detection problem might prove crucial, followed by a biological and theoretical characterization of such pro-ictal states. Some

experimental (Badawy et al., 2009; Kimiskidis et al., 2015) and theoretical (Wang et al., 2014) evidence already exists, on which future work can build. Furthermore methods of deriving model parameters from data have been developed (Freestone et al., 2011; Ullah and Schiff, 2009), enabling the possibility of model-based design of patient-specific closed-loop stimulation protocols for the pro-ictal state.

2.3 CORTICAL SPREADING DEPRESSION

CSD is described as a slow propagating wave of metabolic and ionic disturbance on the cortex that effectively results in the loss of transmembrane potentials. This phenomenon is closely associated with migraine attacks (reviewed in Charles and Baca, 2013; Costa et al., 2013), but can also be observed around areas of brain injury, subarachnoid hemorrhage, and ischemic stroke (Dreier, 2011). In migraine, CSD is thought to underlie the aura preceding the pain attack, and it is proposed as one of the processes by which the pain is generated (Charles and Baca, 2013; Costa et al., 2013). In peri-infarct tissue (e.g., after stroke), CSD is suggested to contribute to further tissue damage, but could also play a neuro-protective role (Fabricius et al., 2006; Lauritzen et al., 2011). A recent review by Dreier and Reiffurth (2015) also discusses the overlaps in the CSD phenomena between migraine and stroke.

Similar to epilepsy, computational models of CSD also have a long-standing history. We refer the reader to excellent reviews on computational models of CSD and their role in different brain disorders (Dahlem, 2013a; Miura et al., 2013; Seidenstein et al., 2015; Zandt et al., 2015). The success of computational models of CSD is especially highlighted in their application to understand disease pathology and mechanisms. For example, Dahlem (2013b) and Dahlem (2016) demonstrate that complex propagation patterns of CSD can arise on the folded cortex, which was confirmed recently by experiments (Santos et al., 2014). The strength of predicting such patterns is that these could be related to the different types of migraine: migraines with aura only; migraine with aura and headache; and migraines without aura but with headaches (see Fig. 6). Another example is the work by Yao et al. (2011), which simulates the effect of NMDA-blockade on the CSD. Interestingly, only NMDA-blockade at the initiation site could prevent the CSD, further away, NMDA-blockade did not stop the CSD, but could only modulate the level of transmembrane depolarization. Such modeling predictions are significant, as they highlight potential issues in the spatial localization when designing intervention methods to prevent CSDs or terminate CSDs early. There are numerous other computational models of CSD, all of which provide some degree of mechanistic insight regarding the conditions triggering and supporting the CSD. In the following, we shall discuss how these models could be useful in the design of brain stimulation protocols to control CSD.

Although brain stimulation in diseases associated with CSD is not an established treatment option so far, some preliminary studies exist in migraine (DaSilva et al., 2012; Lipton et al., 2010; Magis and Schoenen, 2012) and are proposed in traumatic brain injury (Kumaria and Tolias, 2012; Strong et al., 2007). Computational models

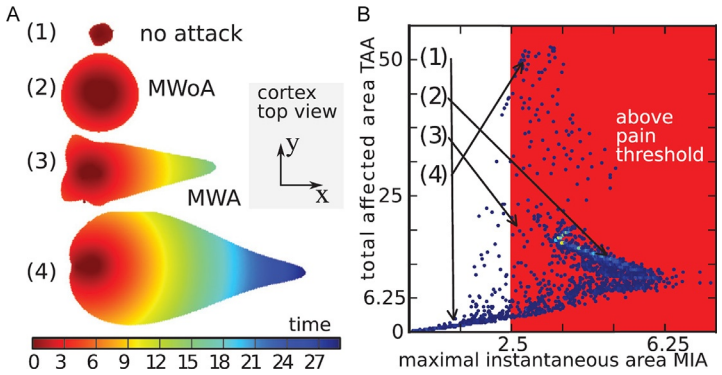

FIGURE 6

(A) Simulated spatiotemporal extent of CSD wave on the human cortex can explain different phenomena in migraine. MWoA refers to a migraine attack without aura, but followed by pain. MWA refers to migraine attacks with aura, followed by pain. (B) Illustration of the corresponding affected cortical surface area of the four cases in (A), where the maximal instantaneous area is thought to determine the pain threshold.

Figure from Dahlem (2013b).

of CSD in migraine and in stroke suggest clear benefits from controlling the CSD (Chapuisat et al., 2008; Dahlem, 2013a; Revett et al., 1998). However, so far in the fields of ischemic stroke and brain injury, brain stimulation is mainly focused on improving mental and cognitive performance. Similarly, computational modeling of stimulation is also mainly focused on the effect of stimulation in rehabilitation. As the exact nature and role of CSD is still unclear in ischemic stroke and brain injury, we shall restrict our review of modeling stimulation in spreading depression to the case of migraine. Some of the concepts and proposals might apply similarly to controlling CSD in peri-infarct tissue.

In migraine, based on the computational results in Dahlem (2013b), it is suggested that targeted stimulation altering or stopping the spreading depression might interrupt the migraine attack and prevent the pain response (Dahlem et al., 2015). Indeed, some clinical evidence using TMS stimulation supports such a theory (Lipton et al., 2010). The particular prediction in Dahlem et al. (2015) is that such stimulation must be patient-specific due to the individual gyrification patterns of each patient. Furthermore, Dahlem et al. (2013) also suggests the possibility of detecting impending CSDs early and respond with a control accordingly. Control points in such a scenario could be the CSD initiation site (if detectable); or subcortical structures involved in pain modulation and perception (Dahlem et al., 2015). The latter point has been demonstrated by DaSilva et al. (2012), who show in a tDCS study that anodal tDCS of the primary motor cortex might decrease pain intensity and migraine duration. Using FEM simulations of the current flow, the authors could show the stimulation of several cortical and subcortical regions involved in the pain circuit. These initial studies demonstrate that

computational models are not only useful for the design and testing of stimulation protocols in migraine, but are essential due to the requirement of patient-specific stimulation protocols. We hypothesize that the patient-specificity might not only arise in the context of stimulation location but also in the question of the exact stimulation protocol. A range of conditions can lead to the onset of CSD as demonstrated in experimental and computational models. Hence, computational models including some details regarding the neuronal, glial, and metabolism activity levels of the tissue (e.g., Hübel and Dahlem, 2014; Wei et al., 2014; Yao et al., 2011) could be used to simulate the effect of various stimulation protocols. More abstract models of CSD have also proven to be useful in suggesting stimulation protocols based on conceptual insight. For example, Dahlem et al. (2015) suggest that a noise stimulus might be more efficient to terminate CSD events than the currently applied two single-pulse stimulus (Lipton et al., 2010). Similar to the computational literature in epilepsy, a control-theoretic perspective could also be adopted to examine how CSD waves can be optimally redirected, altered, or abated. In this context, we highlight again the possibility of simulating optogenetic stimulation, where cell type-specific (including glial) stimulation can be investigated.

An alternative to interacting with the CSD directly in migraine, which might prove difficult to control due to its extreme deviation from physiological conditions and the loss of transmembrane potentials, is to stimulate the tissue between the attacks. The (noninvasive) stimulation could modulate the likelihood of the next attack, or reduce the pain intensity, or shorten the duration of the next attack (DaSilva et al., 2012). Altered excitability of the occipital cortex of migraine patients even between attacks has been shown by various studies (Badawy and Jackson, 2012; Siniatchkin et al., 2012). Increased excitability has also been associated with increased CSD speed (Liebetanz et al., 2006). The possibility of neurostimulation to modulate neuro-excitability in migraine is also supported by some experimental evidence using TMS and TCS (Brighina et al., 2002; Fregni et al., 2007). However, the link between the change in cortical excitability and the CSD or the migraine attack is experimentally shown to be nontrivial (Rocha et al., 2015) and demands computational investigation. Hence, we conclude that especially in this stimulation-between-the-attacks paradigm, it is still largely unclear what is to be stimulated using which modality/protocol and to what end. This is directly linked with the lack of full mechanistic understanding of the CSD event itself, how it is initiated on the human cortex, and how it relates to the debilitating symptoms of migraine. We suggest that in order to rationally design successful stimulation protocols in migraine, mechanistic insight is crucial, which still requires multiple iterations of experimental and computational efforts.

3 DISCUSSION

We have reviewed the current literature in the computational modeling of stimulation in brain disorders. Throughout the review, we have motivated and demonstrated the need for the rational development of closed-loop patient-specific stimulation protocols. Some fields, such as PD and epilepsy, show progress in this direction already.

In other disorders computational modeling of brain stimulation is yet to become established. However, we suggest that there is a universal need for the closed-loop patient-specific approach in therapeutic brain stimulation. For specific diseases, we have highlighted what the closed-loop patient-specific approach involves.

For the rational design of therapeutic brain stimulation *in silico*, we suggest to use a patient-specific model and a closed-loop control of the model. In order to develop the patient-specific model, at least one of three components can be used: (i) a subject-specific head model, (ii) a model of the effect of the stimulation modality, and (iii) a mechanistic model simulating brain dynamics based on biological units. Ideally, all three components are incorporated to be able to address questions regarding the stimulation location, modality, protocol, parameter, and mechanism. It is worth noting that in order to develop certain components (e.g., the mechanistic model) the data to inform the model is not necessarily patient-specific. Rather the patient-specificity arises when the exact stimulation protocol is to be developed. Using a computational model consisting of the three components, the stimulation can be rationally developed. In the most explorative investigation, different protocols can be tested *in silico* for efficacy. Alternatively, in cases where the protocol is fixed, effective stimulation parameters can be predicted. In more systematic approaches, optimization algorithms can explore high-dimensional stimulation parameter spaces finding the most optimal parameters in terms of an objective function (e.g., energy consumption). Knowledge and methods from control theory can also be applied at this stage. Figure 7 shows an illustration of our suggested approach. Finally, such an approach allows for the seamless interaction of engineers, experimentalists, clinicians, and modelers, which is paramount in the development of therapeutic brain stimulation.

Our suggestion for a closed-loop protocol is intuitive for invasive stimulation modalities, as the stimulator is permanently located at the stimulation site. However, we argue that this could also be expanded to noninvasive stimulation modalities that are removable, and which are only used for short intervals. For example, in the treatment of epilepsy, TCS has been suggested to reduce cortical excitability (see San-Juan et al., 2015 for review). In a traditional scenario, a clinical treatment protocol could be: apply TCS every day for 30 min continuously in order to reduce cortical excitability and hence reduce seizure likelihood. In a closed-loop regime, several options can be considered. A continuous EEG monitor can be used (e.g., single electrode over the seizure focus) to monitor the cortical excitability and advise the patient when a TCS treatment would be beneficial. Alternatively, a head-worn TCS device is possible, for example, for patients with seizures occurring in sleep. In those patients, a continuous monitoring and closed-loop stimulation is possible during the night. Our suggestions are only few examples to demonstrate that closed-loop protocols are not limited in their application to invasive devices.

In this review, we used the term control theory, or control engineering fairly loosely, referring to the field concerned with how input/feedback modifies dynamical behavior of systems. However, in control theory, "control" is often understood as an input/feedback signal that can modify behavior of a given system to reach a desired state (reference state). This concept can become problematic in therapeutic brain stimulation, as such a reference state is not well defined or understood. In

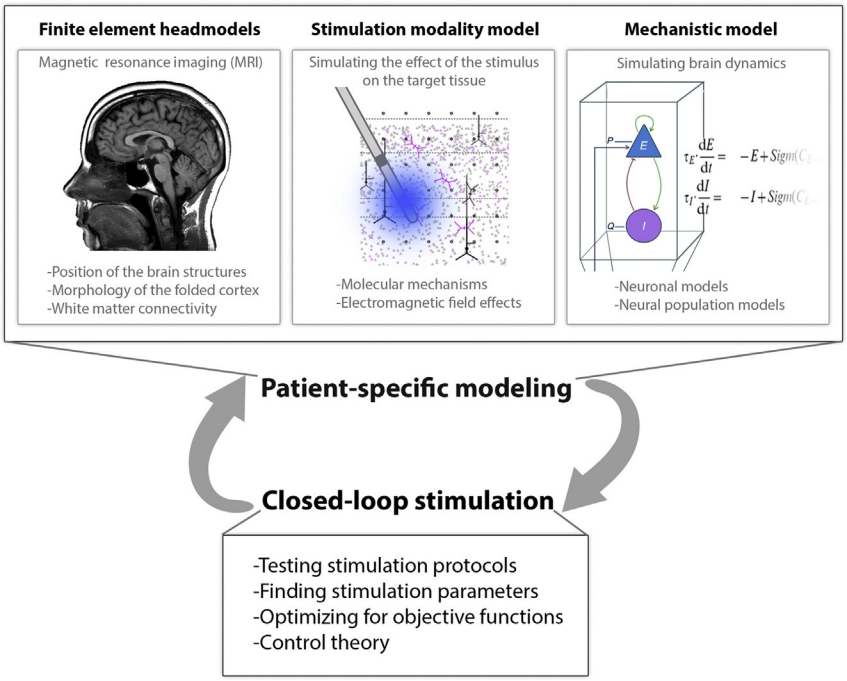

FIGURE 7

Rational development of patient-specific closed-loop stimulation protocols *in silico*. FEM models predicting *where* the stimulation interacts with the brain, models of the stimulation modality simulating *how* the stimulation interacts with the brain, and mechanistic model simulating the *relevant brain circuits* together enable patient-specific modeling of neurostimulation. In such a patient-specific approach, a closed-loop control paradigm can be validated, developed, and tested.

the broadest terms, it is the "healthy state," but it cannot be understood as a single state in the control engineering sense. Hence, we suggest that certain control theory concepts might have to be relaxed in the application to brain stimulation. For example, some advances have been made recently on the controllability of complex networks, identifying driver nodes that essentially determine the dynamics of the entire network (Liu et al., 2011). However, the controllability concept might be too strong in the context of therapeutic brain stimulation. Instead, a more useful approach might be to investigate the level of influence certain nodes exert on a network (Chen et al., 2012a). In the context of therapeutic brain stimulation, this could be used in identifying suitable stimulation targets.

Cognitive models which predict disease effect on task performances or specific behaviors may in the future be useful for determining which stimulation protocols promote an improved state in an individual. Adapting models which already produce behavioral predictions seems a logical step forward for testing stimulation effects on

behavior. This is particularly plausible where models simulate neuronal population activity, (e.g., Deco and Rolls, 2002, 2004; Deco and Zihl, 2004), as stimulation modalities have already been successfully modeled in this context.

The role of synchronization in brain networks has been mentioned in the context of Parkinson's and epilepsy. Here, we highlight some literature that further conceptualizes network synchrony in the broader context of brain function and brain disease. One such concept is termed dynamic network biomarkers, where synchronization between network components can be used as an biomarker indicating an impending change (bifurcation) to a disease state (Chen et al., 2012b; Liu et al., 2013). This concept has been adopted by Dahlem (2013b) and Dahlem et al. (2014) to suggest the possibility of detecting migraine attacks early by observing synchrony in brain network dynamics. Similarly, in epilepsy, we discussed that changes in synchrony as measured in electrographic recordings could serve as a marker of the pre-ictal state. In PD, the overly synchronized output from the basal ganglia is thought to underlie the observed motor symptoms. Voytek and Knight (2015) propose in a complementary thesis that communication between brain areas is established by transient phases of synchronization between the regions. Disruptions to the communication by means of either over or under synchronizing brain regions would then give rise to brain deficits and diseases. Hence, we suggest that synchronization levels in brain networks might prove to be an overarching conceptual framework for designing stimulation in brain diseases. Changing synchrony level by means of stimulation has been suggested in the previously described approach of coordinated reset (Popovych and Tass, 2014) in PD. Other similar approaches are conceivable, where a multilocation stimulation device essentially modulates local activity differently to influence synchronization between the targeted areas. We suggest that computational models incorporating information about the underlying connectivity (e.g., derived from diffusion imaging) between the targeted regions are ideal to design such (de)synchronizing stimulation devices.

So far, we have discussed brain stimulation effects in fairly short-term time scales. However, it is known that the brain is constantly adapting and learning. Hence, in order to assess the long-term effects and efficacy of stimulation protocols, clearly plasticity effects need to be accounted for. There are numerous ways to incorporate plasticity into computational models (see Shouval, 2007 for a review). Appropriate approaches have to be selected based on the disease, relevant brain areas, and mechanistic model. An interesting perspective in the context of therapeutic brain stimulation is that plasticity may actually be considered as an active mechanism working in conjunction with brain stimulation (as in the case of coordinated reset; Popovych and Tass, 2014). In other words, brain stimulation together with plasticity may act together to coerce the brain to "unlearn" the disease state. This is so far only a theoretical proposal, and to date the coordinated reset approach has only shown some efficacy in tinnitus (Tass et al., 2012). Also, only indirect evidence is provided that plasticity played a role in the efficacy of the stimulation. In summary, this appealing idea still requires further computational and experimental investigation to become a consideration for therapeutic interventions.

We conclude our review with the perspective that computational modeling is an essential tool in the rational development of stimulation in brain diseases. We foresee fascinating and promising opportunities in the future, where therapeutic brain stimulation truly integrates with each patient's individual ongoing brain activity to become a specific, targeted, and effective treatment of brain disorders.

ACKNOWLEDGMENTS

Y.W. thanks Gerold Baier, Markus Dahlem, and Peter Neal Taylor for discussion. F.H. thanks Michael Nitsche for discussion. Y.W. and M.K. are supported by the CANDO project (http://www.cando.ac.uk/) funded through the Wellcome Trust (102037) and EPSRC (NS/A000026/1). F.H. is funded by the School of Computing Science, Newcastle University. M.K. is supported by the Human Green Brain project (http://www.greenbrainproject.org) funded through EPSRC (EP/K026992/1).

REFERENCES

Ali, M.M., Sellers, K.K., Fröhlich, F., 2013. Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. J. Neurosci. 33 (27), 11262–11275.

Alvarado-Rojas, C., Valderrama, M., Fouad-Ahmed, A., Feldwisch-Drentrup, H., Ihle, M., Teixeira, A., Sales, F., Schulze-Bonhage, A., Adam, C., Dourado, A., Charpier, S., Navarro, V., Le Van Quyen, M., 2014. Slow modulations of high-frequency activity (40-140Hz) discriminate preictal changes in human focal epilepsy. Sci. Rep. 4, 4545.

Arai, N., Okabe, S., Furubayashi, T., Terao, Y., Yuasa, K., Ugawa, Y., 2005. Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. Clin. Neurophysiol. 116 (3), 605–613.

Arlotti, M., Rahman, A., Minhas, P., Bikson, M., 2012. Axon terminal polarization induced by weak uniform dc electric fields: a modeling study. In: Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp. 4575–4578.

Åström, M., Lemaire, J.-J., Wårdell, K., 2011. Influence of heterogeneous and anisotropic tissue conductivity on electric field distribution in deep brain stimulation. Med. Biol. Eng. Comput. 50 (1), 23–32.

Badawy, R.A.B., Jackson, G.D., 2012. Cortical excitability in migraine and epilepsy: a common feature? J. Clin. Neurophysiol. 29 (3), 244–249.

Badawy, R., Macdonell, R., Jackson, G., Berkovic, S., 2009. The peri-ictal state: cortical excitability changes within 24 h of a seizure. Brain 132, 1013–1021.

Baier, G., Goodfellow, M., Taylor, P.N., Wang, Y., Garry, D.J., 2012. The importance of modeling epileptic seizure dynamics as spatio-temporal patterns. Front. Physiol. 3, 281.

Balish, M., Albert, P.S., Theodore, W.H., 1991. Seizure frequency in intractable partial epilepsy: a statistical analysis. Epilepsia 32 (5), 642–649.

Benabid, A.L., Pollak, P., Louveau, A., Henry, S., De Rougemont, J., 1987. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Stereotact. Funct. Neurosurg. 50 (1–6), 344–346.

Benninger, D.H., Lomarev, M., Lopez, G., Wassermann, E.M., Li, X., Considine, E., Hallett, M., 2010. Transcranial direct current stimulation for the treatment of Parkinson's disease. J. Neurol. Neurosurg. Psychiatr. 81, 1105–1111.
Bentley, J.N., Chestek, C., Stacey, W.C., Patil, P.G., 2013. Optogenetics in epilepsy. Neurosurg. Focus 34 (6)E4.
Berényi, A., Belluscio, M., Mao, D., Buzśaki, G., 2012. Closed-loop control of epilepsy by transcranial electrical stimulation. Science 337 (6095), 735–737.
Bestmann, S., de Berker, A.O., Bonaiuto, J., 2015. Understanding the behavioural consequences of noninvasive brain stimulation. Trends Cogn. Sci. 19 (1), 13–20.
Bijsterbosch, J.D., Barker, A.T., Lee, K.-H., Woodruff, P.W., 2012. Where does transcranial magnetic stimulation (tms) stimulate? Modelling of induced field maps for some common cortical and cerebellar targets. Med. Biol. Eng. Comput. 50 (7), 671–681.
Bikson, M., Rahman, A., Datta, A., 2012. Computational models of transcranial direct current stimulation. Clin. EEG Neurosci. 43 (3), 176–183.
Breakspear, M., Roberts, J.A., Terry, J.R., Rodrigues, S., Mahant, N., Robinson, P.A., 2006. A unifying explanation of primary generalized seizures through nonlinear brain modeling and bifurcation analysis. Cereb. Cortex 16 (9), 1296–1313.
Brighina, F., Piazza, A., Daniele, O., Fierro, B., 2002. Modulation of visual cortical excitability in migraine with aura: effects of 1 Hz repetitive transcranial magnetic stimulation. Exp. Brain Res. 145 (2), 177–181.
Brunoni, A.R., Nitsche, M.A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, J., Valero-Cabre, A., Rotenberg, A., Pascual-Leone, A., Ferrucci, R., Priori, A., Boggio, P.S., Fregni, F., 2012. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 5 (3), 175–195.
Buhlmann, J., Hofmann, L., Tass, P.A., Hauptmann, C., 2011. Modeling of a segmented electrode for desynchronizing deep brain stimulation. Front. Neuroeng. 4, 15.
Carron, R., Chaillet, A., Filipchuk, A., Pasillas-Lépine, W., Hammond, C., 2013. Closing the loop of deep brain stimulation. Front. Syst. Neurosci. 7, 112.
Case, M., Soltesz, I., 2011. Computational modeling of epilepsy. Epilepsia 52, 12–15.
Chapuisat, G., Dronne, M.A., Grenier, E., Hommel, M., Gilquin, H., Boissel, J.P., 2008. A global phenomenological model of ischemic stroke with stress on spreading depressions. Prog. Biophys. Mol. Biol. 97 (1), 4–27.
Charles, A.C., Baca, S.M., 2013. Cortical spreading depression and migraine. Nat. Rev. Neurol. 9 (11), 637–644.
Chen, D., Lu, L., Shang, M.-S., Zhang, Y.-C., Zhou, T., 2012a. Identifying influential nodes in complex networks. Phys. A 391, 1777–1787.
Chen, L., Liu, R., Liu, Z.-P., Li, M., Aihara, K., 2012b. Detecting early-warning signals for sudden deterioration of complex diseases by dynamical network biomarkers. Sci. Rep. 2, .
Ching, S., Brown, E.N., Kramer, M.A., 2012. Distributed control in a mean-field cortical network model: implications for seizure suppression. Phys. Rev. E 86 (2), 021920.
Cona, F., Zavaglia, M., Massimini, M., Rosanova, M., Ursino, M., 2011. A neural mass model of interconnected regions simulates rhythm propagation observed via tms-eeg. Neuroimage 57 (3), 1045–1058.
Cook, M.J., OBrien, T.J., Berkovic, S.F., Murphy, M., Morokoff, A., Fabinyi, G., DSouza, W., Yerra, R., Archer, J., Litewka, L., Hosking, S., Lightfoot, P., Ruedebusch, V., Sheffield, W.D., Snyder, D., Leyde, K., Himes, D., 2013. Prediction of seizure likelihood

with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. Lancet Neurol. 12 (6), 563–571.
Coombes, S., 2006. Neural fields. Scholarpedia 1 (6), 1373.
Costa, C., Tozzi, A., Rainero, I., Cupini, L.M., Calabresi, P., Ayata, C., Sarchielli, P., 2013. Cortical spreading depression as a target for anti-migraine agents. J. Headache Pain 14 (1), 62.
Cutsuridis, V., 2014. Bradykinesia models. In: Jaeger, D., Jung, R. (Eds.), Encyclopedia of Computational Neuroscience. Springer, New York, pp. 1–7.
Da Cunha, C., Boschen, S.L., Gómez-A, A., Ross, E.K., Gibson, W.S., Min, H.K., Lee, K.H., Blaha, C.D., 2015. Toward sophisticated basal ganglia neuromodulation: Review on basal ganglia deep brain stimulation. Neurosci. Biobehav. Rev. http://dx.doi.org/10.1016/j.neubiorev.2015.02.003.
Dahlem, M., 2013a. Migraines and cortical spreading depression. In: Jaeger, D., Jung, R. (Eds.), Encyclopedia of Computational Neuroscience. Springer, New York, pp. 1–10.
Dahlem, M.A., 2013b. Migraine generator network and spreading depression dynamics as neuromodulation targets in episodic migraine. Chaos 23 (4), 046101.
Dahlem, M.A., Rode, S., May, A., Fujiwara, N., Hirata, Y., Aihara, K., Kurths, J., 2013. Towards dynamical network biomarkers in neuromodulation of episodic migraine. Translat. Neurosci. 4 (3), 282–294.
Dahlem, M.A., Kurths, J., Ferrari, M.D., Aihara, K., Scheffer, M., May, A., 2014. Understanding migraine using dynamic network biomarkers. Cephalalgia 35 (7), 627–630.
Dahlem, M.A., Schmidt, B., Bojak, I., Boie, S., Kneer, F., Hadjikhani, N., Kurths, J., 2015. Cortical hot spots and labyrinths: why cortical neuromodulation for episodic migraine with aura should be personalized. Front. Comput. Neurosci. 9, 29.
Dahlem, M.A., 2016. Mathematical modeling of human cortical spreading depression, In: Neurobiological Basis of Migraine, first ed. John Wiley Sons Inc. New York, USA. In press.
DaSilva, A.F., Mendonca, M.E., Zaghi, S., Lopes, M., DosSantos, M.F., Spierings, E.L., Bajwa, Z., Datta, A., Bikson, M., Fregni, F., 2012. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. Headache 52 (8), 1283–1295.
Datta, A., Elwassif, M., Battaglia, F., Bikson, M., 2008. Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. J. Neural Eng. 5 (2), 163.
Datta, A., Truong, D., Minhas, P., Parra, L.C., Bikson, M., 2012. Inter-individual variation during transcranial direct current stimulation and normalization of dose using mri-derived computational models. Front. Psychiatry 3, 91.
Datta, A., Zhou, X., Su, Y., Parra, L.C., Bikson, M., 2013. Validation of finite element model of transcranial electrical stimulation using scalp potentials: implications for clinical dose. J. Neural Eng. 10 (3), 036018.
Dauer, W., Przedborski, S., 2003. Parkinson's disease: mechanisms and models. Neuron 39 (6), 889–909.
Davie, C.A., 2008. A review of Parkinson's disease. Br. Med. Bull. 86 (1), 109–127.
Dayan, P., 2005. Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems, new ed. MIT Press, Cambridge, Massachusetts.
de Berker, A.O., Bikson, M., Bestmann, S., 2013. Predicting the behavioral impact of transcranial direct current stimulation: issues and limitations. Front. Hum. Neurosci. 7, 613.
Deco, G., Rolls, E.T., 2002. Object-based visual neglect: a computational hypothesis. Eur. J. Neurosci. 16 (10), 1994–2000.

Deco, G., Rolls, E.T., 2004. A neurodynamical cortical model of visual attention and invariant object recognition. Vis. Res. 44 (6), 621–642.
Deco, G., Zihl, J., 2004. A biased competition based neurodynamical model of visual neglect. Med. Eng. Phys. 26 (9), 733–743.
Deco, G., Jirsa, V.K., Robinson, P.A., Breakspear, M., Friston, K., 2008. The dynamic brain: from spiking neurons to neural masses and cortical fields. PLoS Comput. Biol. 4 (8), e1000092.
Deisseroth, K., Etkin, A., Malenka, R.C., 2015. Optogenetics and the circuit dynamics of psychiatric disease. JAMA 313 (20), 2019–2020.
DeLong, M., Wichmann, T., 2012. Deep brain stimulation for movement and other neurologic disorders. Ann. N.Y. Acad. Sci. 1265 (1), 1–8.
Deng, Z.-D., Lisanby, S.H., Peterchev, A.V., 2013. Electric field depth–focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. Brain Stimul. 6 (1), 1–13.
Dexter, D.T., Jenner, P., 2013. Parkinson disease: from pathology to molecular disease mechanisms. Free Radic. Biol. Med. 62, 132–144.
Dostrovsky, J.O., Lozano, A.M., 2002. Mechanisms of deep brain stimulation. Mov. Disord. 17 (S3), S63–S68.
Dreier, J.P., 2011. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat. Med. 17 (4), 439–447.
Dreier, J.P., Reiffurth, C., 2015. The stroke-migraine depolarization continuum. Neuron 86 (4), 902–922.
Dutta, A., Nitsche, M.A., 2013. Neural mass model analysis of online modulation of electroencephalogram with transcranial direct current stimulation. In: Neural Engineering (NER) 6th International IEEE/EMBS Conference on IEEE, pp. 206–210.
Ehrens, D., Sritharan, D., Sarma, S.V., 2015. Closed-loop control of a fragile network: application to seizure-like dynamics of an epilepsy model. Front. Neurosci. 9, 58.
Engel, J., Pedley, T., Aicardi, J., 2008. Epilepsy: A Comprehensive Textbook. Lippincott Williams & Wilkins, Philadelphia, USA.
Esser, S.K., Hill, S.L., Tononi, G., 2005. Modeling the effects of transcranial magnetic stimulation on cortical circuits. J. Neurophysiol. 94 (1), 622–639.
Esser, S.K., Hill, S., Tononi, G., 2009. Breakdown of effective connectivity during slow wave sleep: investigating the mechanism underlying a cortical gate using large-scale modeling. J. Neurophysiol. 102 (4), 2096–2111.
Fabricius, M., Fuhr, S., Bhatia, R., Boutelle, M., Hashemi, P., Strong, A.J., Lauritzen, M., 2006. Cortical spreading depression and peri-infarct depolarization in acutely injured human cerebral cortex. Brain 129 (3), 778–790.
Feng, X.-J., Greenwald, B., Rabitz, H., Shea-Brown, E., Kosut, R., 2007a. Toward closed-loop optimization of deep brain stimulation for Parkinson's disease: concepts and lessons from a computational model. J. Neural Eng. 4 (2), L14.
Feng, X.-J., Shea-Brown, E., Greenwald, B., Kosut, R., Rabitz, H., 2007b. Optimal deep brain stimulation of the subthalamic nucleus—a computational study. J. Comput. Neurosci. 23 (3), 265–282.
Fenno, L., Yizhar, O., Deisseroth, K., 2011. The development and application of optogenetics. Annu. Rev. Neurosci. 34 (1), 389–412.
Fisher, R.S., Velasco, A.L., 2014. Electrical brain stimulation for epilepsy. Nat. Rev. Neurol. 10 (5), 261–270.

Foutz, T.J., Arlow, R.L., McIntyre, C.C., 2012. Theoretical principles underlying optical stimulation of a channelrhodopsin-2 positive pyramidal neuron. J. Neurophysiol. 107 (12), 3235–3245.

Frankemolle, A.M.M., Wu, J., Noecker, A.M., Voelcker-Rehage, C., Ho, J.C., Vitek, J.L., McIntyre, C.C., Alberts, J.L., 2010. Reversing cognitive–motor impairments in Parkinson's disease patients using a computational modelling approach to deep brain stimulation programming. Brain 133 (3), 746–761.

Frauscher, B., Ellenrieder, N.v., Ferrari-Marinho, T., Avoli, M., Dubeau, F., Gotman, J., 2015. Facilitation of epileptic activity during sleep is mediated by high amplitude slow waves. Brain 138, 1629–1641.

Freestone, D.R., Aram, P., Dewar, M., Scerri, K., Grayden, D.B., Kadirkamanathan, V., 2011. A data-driven framework for neural field modeling. Neuroimage 56 (3), 1043–1058.

Fregni, F., Boggio, P.S., Santos, M.C., Lima, M., Vieira, A.L., Rigonatti, S.P., Silva, M.T.A., Barbosa, E.R., Nitsche, M.A., Pascual-Leone, A., 2006. Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. Mov. Disord. 21, 1693–1702.

Fregni, F., Liebetanz, D., Monte-Silva, K.K., Oliveira, M.B., Santos, A.A., Nitsche, M.A., PascualLeone, A., Guedes, R.C.A., 2007. Effects of transcranial direct current stimulation coupled with repetitive electrical stimulation on cortical spreading depression. Exp. Neurol. 204 (1), 462–466.

George, M.S., Sackeim, H.A., Rush, A.J., Marangell, L.B., Nahas, Z., Husain, M.M., Lisanby, S., Burt, T., Goldman, J., Ballenger, J.C., 2000. Vagus nerve stimulation: a new tool for brain research and therapy. Biol. Psychiatry 47 (4), 287–295.

Gerstner, W., Kistler, W.M., 2002. Spiking Neuron Models: Single Neurons, Populations, Plasticity. Cambridge University Press, Cambridge, UK.

Glass, L., Mackey, M.C., 1979. Pathological conditions resulting from instabilities in physiological control systems*. Ann. N.Y. Acad. Sci. 316 (1), 214–235.

Gluckman, B.J., Nguyen, H., Weinstein, S.L., Schiff, S.J., 2001. Adaptive electric field control of epileptic seizures. J. Neurosci. 21 (2), 590–600.

Goodfellow, M., Schindler, K., Baier, G., 2012. Self-organised transients in a neural mass model of epileptogenic tissue dynamics. Neuroimage 59, 2644–2660.

Grant, P.F., Lowery, M.M., 2009. Electric field distribution in a finite-volume head model of deep brain stimulation. Med. Eng. Phys. 31 (9), 1095–1103.

Grossman, N., Nikolic, K., Toumazou, C., Degenaar, P., 2011. Modeling study of the light stimulation of a neuron cell with channelrhodopsin-2 mutants. IEEE Trans. Biomed. Eng. 58 (6), 1742–1751.

Hallett, M., 2000. Transcranial magnetic stimulation and the human brain. Nature 406 (6792), 147–150.

Halpern, C.H., Samadani, U., Litt, B., Jaggi, J.L., Baltuch, G.H., 2008. Deep brain stimulation for epilepsy. Neurotherapeutics 5 (1), 59–67.

Hamburg, M.A., Collins, F.S., 2010. The path to personalized medicine. N. Engl. J. Med. 363 (4), 301–304.

Hauptmann, C., Popovych, O., Tass, P.A., 2005. Effectively desynchronizing deep brain stimulation based on a coordinated delayed feedback stimulation via several sites: a computational study. Biol. Cybern. 93 (6), 463–470.

Helfrich, R.F., Schneider, T.R., Rach, S., Trautmann-Lengsfeld, S.A., Engel, A.K., Herrmann, C.S., 2014. Entrainment of brain oscillations by transcranial alternating current stimulation. Current Biol. 24 (3), 333–339.

Hélie, S., Paul, E.J., Ashby, F.G., 2012. A neurocomputational account of cognitive deficits in Parkinson's disease. Neuropsychologia 50 (9), 2290–2302.
Hu, B., Guo, D., Wang, Q., 2014. Control of absence seizures induced by the pathways connected to SRN in corticothalamic system. Cogn. Neurodyn. 9, 279–289.
Huang, Y.-Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta burst stimulation of the human motor cortex. Neuron 45 (2), 201–206.
Hübel, N., Dahlem, M.A., 2014. Dynamics from seconds to hours in Hodgkin-Huxley model with time-dependent ion concentrations and buffer reservoirs. PLoS Comput. Biol. 10 (12), e1003941.
Husain, F., Nandipati, G., Braun, A., Cohen, L., Tagamets, M., Horwitz, B., 2002. Simulating transcranial magnetic stimulation during pet with a large-scale neural network model of the prefrontal cortex and the visual system. Neuroimage 15 (1), 58–73.
Jiruska, P., Curtis, M.D., Jefferys, J.G.R., Schevon, C.A., Schiff, S.J., Schindler, K., 2013. Synchronization and desynchronization in epilepsy: controversies and hypotheses. J. Physiol. 591, 787–797.
Joucla, S., Yvert, B., 2012. Modeling extracellular electrical neural stimulation: from basic understanding to MEA-based applications. J. Physiol. 106 (3–4), 146–158.
Kaiser, M., 2013. The potential of the human connectome as a biomarker of brain disease. Front. Hum. Neurosci. 7, 484.
Kalitzin, S.N., Velis, D.N., Lopes da Silva, F.H., 2010. Stimulation-based anticipation and control of state transitions in the epileptic brain. Epilepsy Behav. 17 (3), 310–323.
Kamitani, Y., Bhalodia, V.M., Kubota, Y., Shimojo, S., 2001. A model of magnetic stimulation of neocortical neurons. Neurocomputing 38, 697–703.
Kim, J.W., Robinson, P.A., 2008. Controlling limit-cycle behaviors of brain activity. Phys. Rev. E 77 (5), 051914.
Kim, J.W., Roberts, J.A., Robinson, P.A., 2009. Dynamics of epileptic seizures: evolution, spreading, and suppression. J. Theor. Biol. 257 (4), 527–532.
Kim, G.U., Kim, H.-I., Chung, E., 2011. Towards human clinical application of emerging optogenetics technology. Biomed. Eng. Lett. 1 (4), 207–212.
Kimiskidis, V.K., Valentin, A., Kälviäinen, R., 2014. Transcranial magnetic stimulation for the diagnosis and treatment of epilepsy. Curr. Opin. Neurol. 27, 236–241.
Kimiskidis, V.K., Koutlis, C., Tsimpiris, A., Kälviäinen, R., Ryvlin, P., Kugiumtzis, D., 2015. Transcranial magnetic stimulation combined with EEG reveals covert states of elevated excitability in the human epileptic brain. Int. J. Neur. Syst 25 (5), 1550018.
Kimura, H., Kurimura, M., Kurokawa, K., Nagaoka, U., Arawaka, S., Wada, M., Kawanami, T., Kurita, K., Kato, T., 2011. A comprehensive study of repetitive transcranial magnetic stimulation in Parkinson's disease. ISRN Neurol. 2011, 845453.
Kindler, J., Schumacher, R., Cazzoli, D., Gutbrod, K., Koenig, M., Nyffeler, T., Dierks, T., Müri, R.M., 2012. Theta burst stimulation over the right brocas homologue induces improvement of naming in aphasic patients. Stroke 43 (8), 2175–2179.
Koch, G., Bonni, S., Giacobbe, V., Bucchi, G., Basile, B., Lupo, F., Versace, V., Bozzali, M., Caltagirone, C., 2012. Theta-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect. Neurology 78 (1), 24–30.
Kramer, M.A., Lopour, B.A., Kirsch, H.E., Szeri, A.J., 2006. Bifurcation control of a seizing human cortex. Phys. Rev. E 73 (4), 041928.
Kramer, M.A., Truccolo, W., Eden, U.T., Lepage, K.Q., Hochberg, L.R., Eskandar, E.N., Madsen, J.R., Lee, J.W., Maheshwari, A., Halgren, E., Chu, C.J., Cash, S.S., 2012. Human

seizures self-terminate across spatial scales via a critical transition. Proc. Natl. Acad. Sci. USA 109 (51), 21116–21121.
Krause, B., Márquez-Ruiz, J., Kadosh, R.C., 2013. The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? Front. Hum. Neurosci. 7, 602.
Krook-Magnuson, E., Armstrong, C., Oijala, M., Soltesz, I., 2013. On-demand optogenetic control of spontaneous seizures in temporal lobe epilepsy. Nat. Commun. 4, 1376.
Kumaria, A., Tolias, C.M., 2012. Is there a role for vagus nerve stimulation therapy as a treatment of traumatic brain injury? Br. J. Neurosurg. 26 (3), 316–320.
LaLumiere, R.T., 2011. A new technique for controlling the brain: optogenetics and its potential for use in research and the clinic. Brain Stimul. 4 (1), 1–6.
Lauritzen, M., Dreier, J.P., Fabricius, M., Hartings, J.A., Graf, R., Strong, A.J., 2011. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. J. Cereb. Blood Flow Metab. 31 (1), 17–35.
Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D., et al., 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125 (11), 2150–2206.
Li, Q., Ke, Y., Chan, D.C.W., Qian, Z.-M., Yung, K.K.L., Ko, H., Arbuthnott, G.W., Yung, W.-H., 2012. Therapeutic deep brain stimulation in Parkinsonian rats directly influences motor cortex. Neuron 76 (5), 1030–1041.
Liebetanz, D., Nitsche, M.A., Tergau, F., Paulus, W., 2002. Pharmacological approach to the mechanisms of transcranial DC stimulation induced aftereffects of human motor cortex excitability. Brain 125 (10), 2238–2247.
Liebetanz, D., Fregni, F., Monte-Silva, K.K., Oliveira, M.B., Amâncio-dos-Santos, A., Nitsche, M.A., Guedes, R.C.A., 2006. After-effects of transcranial direct current stimulation (tDCS) on cortical spreading depression. Neurosci. Lett. 398 (1–2), 85–90.
Lipton, R.B., Dodick, D.W., Silberstein, S.D., Saper, J.R., Aurora, S.K., Pearlman, S.H., Fischell, R.E., Ruppel, P.L., Goadsby, P.J., 2010. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, shamcontrolled trial. Lancet Neurol. 9 (4), 373–380.
Little, S., Pogosyan, A., Neal, S., Zrinzo, L., Hariz, M., Foltynie, T., Limousin, P., Brown, P., 2014. Controlling Parkinson's disease with adaptive deep brain stimulation. J. Vis. Exp. (89).
Liu, Y.-Y., Slotine, J.-J., Barabási, A.-L., 2011. Controllability of complex networks. Nature 473 (7346), 167–173.
Liu, R., Aihara, K., Chen, L., 2013. Dynamical network biomarkers for identifying critical transitions and their driving networks of biologic processes. Quant. Biol. 1 (2), 105–114.
Lobb, C.J., 2014. Abnormal bursting as a pathophysiological mechanism in Parkinson's disease. Basal Ganglia 3 (4), 187–195.
Lopes da Silva, F., Blanes, W., Kalitzin, S., Parra, J., Suffczynski, P., Velis, D., 2003. Dynamical diseases of brain systems: different routes to epileptic seizures. IEEE Trans. Biomed. Eng. 50 (5), 540–548.
Lu, Y.-F., Goldstein, D.B., Angrist, M., Cavalleri, G., 2014. Personalized medicine and human genetic diversity. Cold Spring Harb. Perspect. Med. 4 (9), a008581.
Lytton, W., 2008. Computer modelling of epilepsy. Nat. Rev. Neurosci. 9, 626–637.
Mackey, M.C., Milton, J.G., 1987. Dynamical diseases. Ann. N.Y. Acad. Sci. 504 (1), 16–32.

Magis, D., Schoenen, J., 2012. Advances and challenges in neurostimulation for headaches. Lancet Neurol. 11 (8), 708–719.
Marten, F., Rodrigues, S., Suffczynski, P., Richardson, M., Terry, J., 2009. Derivation and analysis of an ordinary differential equation mean-field model for studying clinically recorded epilepsy dynamics. Phys. Rev. E 79 (2), 021911.
McIntyre, C.C., Grill, W.M., 2001. Finite element analysis of the current-density and electric field generated by metal microelectrodes. Ann. Biomed. Eng. 29 (3), 227–235.
McIntyre, C.C., Hahn, P.J., 2010. Network perspectives on the mechanisms of deep brain stimulation. Neurobiol. Dis. 38 (3), 329–337.
Medeiros, L.F., de Souza, I.C.C., Vidor, L.P., de Souza, A., Deitos, A., Volz, M.S., Fregni, F., Caumo, W., Torres, I.L.S., 2012. Neurobiological effects of transcranial direct current stimulation: a review. Front. Psychiatry 3, 110.
Merlet, I., Birot, G., Salvador, R., Molaee-Ardekani, B., Mekonnen, A., Soria-Frish, A., Ruffini, G., Miranda, P.C., Wendling, F., 2013. From oscillatory transcranial current stimulation to scalp eeg changes: a biophysical and physiological modeling study. PLoS One 8 (2)e57330.
Milton, J., Jung, P., 2002. Epilepsy as a Dynamic Disease. Springer Science, Business Media, Berlin, Heidelberg, New York.
Mina, F., Benquet, P., Biraben, A., Wendling, F., 2013. Modulation of epileptic activity by deep brain stimulation: a model-based study of frequency-dependent effects. Front. Comput. Neurosci. 7, 94.
Miocinovic, S., Somayajula, S., Chitnis, S., Vitek, J.L., 2013. History, applications, and mechanisms of deep brain stimulation. JAMA Neurol. 70 (2), 163–171.
Miranda, P.C., Lomarev, M., Hallett, M., 2006. Modeling the current distribution during transcranial direct current stimulation. Clin. Neurophysiol. 117 (7), 1623–1629.
Miura, R.M., Huang, H., Wylie, J.J., 2013. Mathematical approaches to modeling of cortical spreading depression. Chaos 23 (4), 046103.
Miyawaki, Y., Okada, M., 2005. Mechanisms of spike inhibition in a cortical network induced by transcranial magnetic stimulation. Neurocomput. 65, 463–468.
Miyawaki, Y., Shinozaki, T., Okada, M., 2012. Spike suppression in a local cortical circuit induced by transcranial magnetic stimulation. J. Comput. Neurosci. 33 (2), 405–419.
Modolo, J., Beuter, A., 2009. Linking brain dynamics, neural mechanisms, and deep brain stimulation in Parkinson's disease: an integrated perspective. Med. Eng. Phys. 31 (6), 615–623.
Modolo, J., Bhattacharya, B., Edwards, R., Campagnaud, J., Legros, A., Beuter, A., 2010. Using a virtual cortical module implementing a neural field model to modulate brain rhythms in Parkinson's disease. Front. Neurosci. 4, 45.
Modolo, J., Legros, A., Thomas, A.W., Beuter, A., 2011. Model-driven therapeutic treatment of neurological disorders: reshaping brain rhythms with neuromodulation. Interface Focus 1 (1), 61–74.
Modolo, J., Beuter, A., Thomas, A.W., Legros, A., 2012. Using "smart stimulators" to treat Parkinson's disease: re-engineering neurostimulation devices. Front. Comput. Neurosci. 6, 69.
Modolo, J., Legros, A., Beuter, A., 2015. The next move in neuromodulation therapy: a question of timing. Front. Comput. Neurosci. 8, 162.
Molaee-Ardekani, B., Márquez-Ruiz, J., Merlet, I., Leal-Campanario, R., Gruart, A., SánchezCampusano, R., Birot, G., Ruffini, G., Delgado-García, J.-M., Wendling, F.,

2013. Effects of transcranial direct current stimulation (tdcs) on cortical activity: a computational modeling study. Brain Stimul. 6 (1), 25–39.
Mormann, F., Andrzejak, R.G., Elger, C.E., Lehnertz, K., 2007. Seizure prediction: the long and winding road. Brain 130 (2), 314–333.
Moustafa, A.A., Bar-Gad, I., Korngreen, A., Bergman, H., 2014. Basal ganglia: physiological, behavioral, and computational studies. Front. Syst. Neurosci. 8, 150.
Nagarajan, S.S., Durand, D.M., Warman, E.N., 1993. Effects of induced electric fields on finite neuronal structures: a simulation study. IEEE Trans. Biomed. Eng. 40 (11), 1175–1188.
Nevado-Holgado, A.J., Marten, F., Richardson, M.P., Terry, J.R., 2012. Characterising the dynamics of EEG waveforms as the path through parameter space of a neural mass model: application to epilepsy seizure evolution. Neuroimage 59 (3), 2374–2392.
Nikolic, K., Jarvis, S., Grossman, N., Schultz, S., 2013. Computational models of optogenetic tools for controlling neural circuits with light. In: 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp. 5934–5937.
Nitsche, M.A., Paulus, W., 2009. Noninvasive brain stimulation protocols in the treatment of epilepsy: current state and perspectives. Neurotherapeutics 6, 244–250.
Nitsche, M.A., Seeber, A., Frommann, K., Klein, C.C., Rochford, C., Nitsche, M.S., Fricke, K., Liebetanz, D., Lang, N., Antal, A., et al., 2005. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J. Physiol. 568 (1), 291–303.
Nitsche, M.A., Kuo, M.-F., Paulus, W., Antal, A., 2015. Transcranial direct current stimulation: protocols and physiological mechanisms of action. In: Rasche, D., Knotkova, H. (Eds.), Textbook of Neuromodulation. Springer, New York, pp. 101–111.
Parazzini, M., Fiocchi, S., Rossi, E., Paglialonga, A., Ravazzani, P., 2011. Transcranial direct current stimulation: estimation of the electric field and of the current density in an anatomical human head model. IEEE Trans. Biomed. Eng. 58 (6), 1773–1780.
Pashut, T., Wolfus, S., Friedman, A., Lavidor, M., Bar-Gad, I., Yeshurun, Y., Korngreen, A., 2011. Mechanisms of magnetic stimulation of central nervous system neurons. PLoS Comput. Biol. 7 (3), e1002022.
Paz, J.T., Huguenard, J.R., 2015. Microcircuits and their interactions in epilepsy: is the focus out of focus? Nat. Neurosci. 18 (3), 351–359.
Paz, J.T., Davidson, T.J., Frechette, E.S., Delord, B., Parada, I., Peng, K., Deisseroth, K., Huguenard, J.R., 2013. Closed-loop optogenetic control of thalamus as a tool for interrupting seizures after cortical injury. Nat. Neurosci. 16 (1), 64–70.
Pelletier, S.J., Cicchetti, F., 2014. Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models. Int. J. Neuropsychopharmacol. 18 (2).
Pineau, J., Guez, A., Vincent, R., Panuccio, G., Avoli, M., 2009. Treating epilepsy via adaptive neurostimulation: a reinforcement learning approach. Int. J. Neural. Syst. 19 (04), 227–240.
Pirini, M., Rocchi, L., Sensi, M., Chiari, L., 2008. A computational modelling approach to investigate different targets in deep brain stimulation for Parkinson's disease. J. Comput. Neurosci. 26 (1), 91–107.
Popovych, O.V., Tass, P.A., 2014. Control of abnormal synchronization in neurological disorders. Front. Neurol. 5, 268.
Popovych, O.V., Hauptmann, C., Tass, P.A., 2005. Effective desynchronization by nonlinear delayed feedback. Phys. Rev. Lett. 94 (16), 164102.

Post, A., Keck, M.E., 2001. Transcranial magnetic stimulation as a therapeutic tool in psychiatry: what do we know about the neurobiological mechanisms? J. Psychiatr. Res. 35 (4), 193–215.

Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L.C., Bikson, M., 2013. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. J. Physiol. 591 (10), 2563–2578.

Rampersad, S., Janssen, A., Lucka, F., Aydin, U., Lanfer, B., Lew, S., Wolters, C., Stegeman, D., Oostendorp, T., 2014. Simulating transcranial direct current stimulation with a detailed anisotropic human head model. IEEE Trans. Neural Syst. Rehab. Eng. 22 (3), 441–452.

Rattay, F., 1999. The basic mechanism for the electrical stimulation of the nervous system. Neuroscience 89 (2), 335–346.

Reato, D., Rahman, A., Bikson, M., Parra, L.C., 2010. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J. Neurosci. 30 (45), 15067–15079.

Rehan, M., Hong, K.S., 2013. Modeling and Automatic Feedback Control of Tremor: Adaptive Estimation of Deep Brain Stimulation. PLoS ONE 8 (4), e62888. http://dx.doi.org/10.1371/journal.pone.0062888.

Rein, M.L., Deussing, J.M., 2012. The optogenetic (r)evolution. Mol. Genet. Genomics 287 (2), 95–109.

Revett, K., Ruppin, E., Goodall, S., Reggia, J.A., 1998. Spreading depression in focal ischemia: a computational study. J. Cereb. Blood Flow Metab. 18 (9), 998–1007.

Rocha, S., Melo, L., Boudoux, C., Foerster, A., Araújo, D., Monte-Silva, K., 2015. Transcranial direct current stimulation in the prophylactic treatment of migraine based on interictal visual cortex excitability abnormalities: a pilot randomized controlled trial. J. Neurol. Sci. 349 (1–2), 33–39.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., Safety of TMS Consensus Group, 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin. Neurophysiol. 120 (12), 2008–2039.

Rossi, M.A., Go, V., Murphy, T., Fu, Q., Morizio, J., Yin, H.H., 2015. A wirelessly controlled implantable LED system for deep brain optogenetic stimulation. Front. Integr. Neurosci. 9, 8.

Roth, B.J., Saypol, J.M., Hallett, M., Cohen, L.G., 1991. A theoretical calculation of the electric field induced in the cortex during magnetic stimulation. Electroencephalogr. Clin. Neurophysiol. 81 (1), 47–56.

Rubchinsky, L., Kuznetsov, A., Wheelock MD, V., Sigvardt, K., 2007. Tremor. Scholarpedia 2 (10), 1379.

Rubin, J.E., McIntyre, C.C., Turner, R.S., Wichmann, T., 2012. Basal ganglia activity patterns in Parkinsonism and computational modeling of their downstream effects. Eur. J. Neurosci. 36 (2), 2213–2228.

Rusu, C., Murakami, M., Ziemann, U., Triesch, J., 2015. A model of TMS-induced I-waves in motor cortex. Brain Stimul. 8 (2), 407–408.

Ruths, J., Taylor, P.N., Dauwels, J., 2014. Optimal control of an epileptic neural population model. In: Proceedings IFAC.

Salinas, F.S., Lancaster, J.L., Fox, P.T., 2009. 3D modeling of the total electric field induced by transcranial magnetic stimulation using the boundary element method. Phys. Med. Biol. 54 (12), 3631.

San-juan, D., Morales-Quezada, L., Orozco Garduño, A.J., Alonso-Vanegas, M., González-Aragón, M.F., Espinoza López, D.A., Vázquez Gregorio, R., Anschel, D.J., Fregni, F., 2015. Transcranial direct current stimulation in epilepsy. Brain Stimul. 8, 455–464.

Santaniello, S., Fiengo, G., Glielmo, L., Grill, W.M., 2011. Closed-loop control of deep brain stimulation: a simulation study. IEEE Trans. Neural Syst. Rehab. Eng. 19 (1), 15–24.

Santos, E., Schöll, M., Sánchez-Porras, R., Dahlem, M.A., Silos, H., Unterberg, A., Dickhaus, H., Sakowitz, O.W., 2014. Radial, spiral and reverberating waves of spreading depolarization occur in the gyrencephalic brain. Neuroimage 99, 244–255.

Schiff, S.J., 2009. Kalman meets neuron: the emerging intersection of control theory with neuroscience. In: Engineering in Medicine and Biology Society, EMBC 2009. Annual International Conference of the IEEE, pp. 3318–3321.

Schiff, S.J., 2010. Towards model-based control of Parkinson's disease. Philos. Trans. Soc. A 368 (1918), 2269–2308.

Schmidt, C., van Rienen, U., 2012. Modeling the field distribution in deep brain stimulation: the influence of anisotropy of brain tissue. IEEE Trans. Biomed. Eng. 59 (6), 1583–1592.

Seidenstein, A., Barone, F., Lytton, W., 2015. Computer modeling of ischemic stroke. Scholarpedia 10 (3), 32015.

Selvaraj, P., Sleigh, J.W., Freeman, W.J., Kirsch, H.E., Szeri, A.J., 2014. Open loop optogenetic control of simulated cortical epileptiform activity. J. Comput. Neurosci. 36 (3), 515–525.

Shouval, H., 2007. Models of synaptic plasticity. Scholarpedia 2 (7), 1605.

Siebner, H.R., Hartwigsen, G., Kassuba, T., Rothwell, J.C., 2009. How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. Cortex 45 (9), 1035–1042.

Silva, S., Basser, P., Miranda, P., 2008. Elucidating the mechanisms and loci of neuronal excitation by transcranial magnetic stimulation using a finite element model of a cortical sulcus. Clin. Neurophysiol. 119 (10), 2405–2413.

Siniatchkin, M., Sendacki, M., Moeller, F., Wolff, S., Jansen, O., Siebner, H., Stephani, U., 2012. Abnormal changes of synaptic excitability in migraine with aura. Cereb. Cortex 22 (10), 2207–2216.

Smith, J.R., Fountas, K.N., Murro, A.M., Park, Y.D., Jenkins, P.D., Morrell, M., Esteller, R., Greene, D., 2010. Closed-loop stimulation in the control of focal epilepsy of insular origin. Stereotact. Funct. Neurosurg. 88 (5), 281–287.

Stacey, W.C., Litt, B., 2008. Technology insight: neuroengineering and epilepsy—designing devices for seizure control. Nat. Clin. Pract. Neurol. 4 (4), 190–201.

Stefanescu, R.A., Shivakeshavan, R.G., Talathi, S.S., 2012. Computational models of epilepsy. Seizure 21 (10), 748–759.

Stefanescu, R.A., Shivakeshavan, R.G., Khargonekar, P.P., Talathi, S.S., 2013. Computational modeling of channelrhodopsin-2 photocurrent characteristics in relation to neural signaling. Bull. Math. Biol. 75 (11), 2208–2240.

Sterratt, D., Graham, B., Gillies, D.A., Willshaw, D., 2011. Principles of Computational Modelling in Neuroscience, first ed. Cambridge University Press, Cambridge, New York.

Strong, A.J., Hartings, J.A., Dreier, J.P., 2007. Cortical spreading depression: an adverse but treatable factor in intensive care? Curr. Opin. Crit. Care 13 (2), 126–133.

Suffczynski, P., Kalitzin, S., da Silva, F.L., Parra, J., Velis, D., Wendling, F., 2008. Active paradigms of seizure anticipation: computer model evidence for necessity of stimulation. Phys. Rev. E 78 (5), 051917.

Suh, H.S., Lee, W.H., Kim, T.-S., 2012. Influence of anisotropic conductivity in the skull and white matter on transcranial direct current stimulation via an anatomically realistic finite element head model. Phys. Med. Biol. 57 (21), 6961.

Talelli, P., Wallace, A., Dileone, M., Hoad, D., Cheeran, B., Oliver, R., VandenBos, M., Hammerbeck, U., Barratt, K., Gillini, C., et al., 2012. Theta burst stimulation in the rehabilitation of the upper limb a semirandomized, placebo-controlled trial in chronic stroke patients. Neurorehab. Neural Repair. 26 (8), 976–987.

Tass, P.A., Adamchic, I., Freund, H.-J., von Stackelberg, T., Hauptmann, C., 2012. Counteracting tinnitus by acoustic coordinated reset neuromodulation. Restor. Neurol. Neurosci. 30 (2), 137–159.

Taylor, P.N., Goodfellow, M., Wang, Y., Baier, G., 2013. Towards a large-scale model of patient specific epileptic spike-wave discharges. Biol. Cybern. 107 (1), 83–94.

Taylor, P.N., Kaiser, M., Dauwels, J., 2014a. Structural connectivity based whole brain modelling in epilepsy. J. Neurosci. Methods 236, 51–57.

Taylor, P.N., Wang, Y., Goodfellow, M., Dauwels, J., Moeller, F., Stephani, U., Baier, G., 2014b. A computational study of stimulus driven epileptic seizure abatement. PLoS One 9 (12)e114316.

Taylor, P.N., Thomas, J., Sinha, N., Dauwels, J., Kaiser, M., Thesen, T., Ruths, J., 2015. Optimal control based seizure abatement using patient derived connectivity. Front. Neurosci. 9, 202.

Tierney, T.S., Sankar, T., Lozano, A.M., 2011. Deep brain stimulation: emerging indications. In: Garwicz, M., Danielsen, N., Schouenborg, J. (Eds.), Progress in Brain Research, vol. 194. Elsevier, Oxford, UK, pp. 83–95 Chapter 6.

Tomsett, R.J., Ainsworth, M., Thiele, A., Sanayei, M., Chen, X., Gieselmann, M.A., Whittington, M.A., Cunningham, M.O., Kaiser, M., 2015. Virtual Electrode Recording Tool for EXtracellular potentials (VERTEX): comparing multi-electrode recordings from simulated and biological mammalian cortical tissue. Brain Struct. Funct. 220, 2333–2353.

Tye, K.M., Deisseroth, K., 2012. Optogenetic investigation of neural circuits underlying brain disease in animal models. Nat. Rev. Neurosci. 13 (4), 251–266.

Ullah, G., Schiff, S., 2009. Models of epilepsy. Scholarpedia 4 (7), 1409.

van Hartevelt, T.J., Cabral, J., Deco, G., Møller, A., Green, A.L., Aziz, T.Z., Kringelbach, M.L., 2014. Neural plasticity in human brain connectivity: the effects of long term deep brain stimulation of the subthalamic nucleus in Parkinson's disease. PLoS One 9 (1)e86496.

Vierling-Claassen, D., Cardin, J.A., Moore, C.I., Jones, S.R., 2010. Computational modeling of distinct neocortical oscillations driven by cell-type selective optogenetic drive: separable resonant circuits controlled by low-threshold spiking and fast-spiking interneurons. Front. Hum. Neurosci. 4, 198.

Voytek, B., Knight, R.T., 2015. Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. Biol. Psychiatry 77 (12), 1089–1097.

Wagner, T.A., Zahn, M., Grodzinsky, A.J., Pascual-Leone, A., 2004. Three-dimensional head model simulation of transcranial magnetic stimulation. IEEE Trans. Biomed. Eng. 51 (9), 1586–1598.

Wagner, T., Eden, U., Rushmore, J., Russo, C.J., Dipietro, L., Fregni, F., Simon, S., Rotman, S., Pitskel, N.B., Ramos-Estebanez, C., Pascual-Leone, A., Grodzinsky, A.J., Zahn, M., ValeroCabr´e, A., 2014. Impact of brain tissue filtering on neurostimulation fields: a modeling study. NeuroImage 85 (Pt. 3), 1048–1057.

Wang, Y., Goodfellow, M., Taylor, P.N., Baier, G., 2012. Phase space approach for modeling of epileptic dynamics. Phys. Rev. E 85 (6), 061918.

Wang, Y., Goodfellow, M., Taylor, P.N., Baier, G., 2014. Dynamic mechanisms of neocortical focal seizure onset. PLoS Comput. Biol. 10 (8), e1003787.
Warman, E., Grill, W., Durand, D., 1992. Modeling the effects of electric fields on nerve fibers: determination of excitation threshold. IEEE Trans. Biomed. Eng. 39 (12), 1244–1254.
Wei, Y., Ullah, G., Schiff, S.J., 2014. Unification of neuronal spikes, seizures, and spreading depression. J. Neurosci. 34 (35), 11733–11743.
Wendling, F., 2008. Computational models of epileptic activity: a bridge between observation and pathophysiological interpretation. Expert. Rev. Neurother. 8 (6), 889–896.
Wendling, F., Benquet, P., Bartolomei, F., Jirsa, V., 2015. Computational models of epileptiform activity. J. Neurosci. Methods. http://dx.doi.org/10.1016/j.jneumeth.2015.03.027.
Williams, J.C., Denison, T., 2013. From optogenetic technologies to neuromodulation therapies. Sci. Transl. Med. 5 (177), 177ps6.
Williams, J.C., Xu, J., Lu, Z., Klimas, A., Chen, X., Ambrosi, C.M., Cohen, I.S., Entcheva, E., 2013. Computational optogenetics: empirically-derived voltage and light sensitive channelrhodopsin-2 model. PLoS Comput. Biol. 9 (9), e1003220.
Wilson, D., Moehlis, J., 2014. A Hamilton-Jacobi-Bellman approach for termination of seizure like bursting. J. Comput. Neurosci. 37 (2), 345–355.
Windhoff, M., Opitz, A., Thielscher, A., 2013. Electric field calculations in brain stimulation based on finite elements: an optimized processing pipeline for the generation and usage of accurate individual head models. Hum. Brain Mapp. 34 (4), 923–935.
Wykes, R.C., Heeroma, J.H., Mantoan, L., Zheng, K., MacDonald, D.C., Deisseroth, K., Hashemi, K.S., Walker, M.C., Schorge, S., Kullmann, D.M., 2012. Optogenetic and potassium channel gene therapy in a rodent model of focal neocortical epilepsy. Sci. Transl. Med. 4 (161), 161ra152.
Yao, W., Huang, H., Miura, R.M., 2011. A continuum neuronal model for the instigation and propagation of cortical spreading depression. Bull. Math. Biol. 73 (11), 2773–2790.
Yousif, N., Liu, X., 2009. Investigating the depth electrode–brain interface in deep brain stimulation using finite element models with graded complexity in structure and solution. J. Neurosci. Methods 184 (1), 142–151.
Yousif, N., Bayford, R., Bain, P.G., Liu, X., 2007. The peri-electrode space is a significant element of the electrode–brain interface in deep brain stimulation: a computational study. Brain Res. Bull. 74 (5), 361–368.
Yousif, N., Purswani, N., Bayford, R., Nandi, D., Bain, P., Liu, X., 2010. Evaluating the impact of the deep brain stimulation induced electric field on subthalamic neurons: a computational modelling study. J. Neurosci. Methods 188 (1), 105–112.
Yu, K., Wang, J., Deng, B., Wei, X., 2013. Synchronization of neuron population subject to steady dc electric field induced by magnetic stimulation. Cogn. Neurodyn. 7 (3), 237–252.
Zandt, B.-J., Haken, B.t., van Putten, M.J.A.M., Dahlem, M.A., 2015. How does spreading depression spread? Physiology and modeling. Rev. Neurosci. 26 (2), 183–198.
Zhang, D.X., Bertram, E.H., 2015. Suppressing limbic seizures by stimulating medial dorsal thalamic nucleus: factors for efficacy. Epilepsia 56 (3), 479–488.
Zwartjes, D.G.M., Heida, T., Feirabend, H.K.P., Janssen, M.L.F., Visser-Vandewalle, V., Martens, H.C.F., Veltink, P.H., 2012. Motor cortex stimulation for Parkinson's disease: a modelling study. J. Neural Eng. 9 (5), 056005.