NeuroImage 272 (2023) 120042

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Moving from phenomenological to predictive modelling: Progress and pitfalls of modelling brain stimulation in-silico

Danielle L. Kurtin[a,b,*], Valentina Giunchiglia[b], Jakub Vohryzek[c,d], Joana Cabral[e], Anne C. Skeldon[f], Ines R. Violante[a]

[a] Neuromodulation Laboratory, School of Psychology, University of Surrey, Guildford, GU2 7XH, United Kingdom
[b] Department of Brain Sciences, Imperial College London, London, United Kingdom
[c] Centre for Brain and Cognition, Computational Neuroscience Group, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, Spain
[d] Centre for Eudaimonia and Human Flourishing, Linacre College, University of Oxford, UK
[e] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal
[f] Department of Mathematics, Centre for Mathematical and Computational Biology, University of Surrey, Guildford, United Kingdom

ARTICLE INFO

Keywords:
phenomenological models
biophysical models
oscillatory models
brain stimulation
model construction
parameter optimisation

ABSTRACT

Brain stimulation is an increasingly popular neuromodulatory tool used in both clinical and research settings; however, the effects of brain stimulation, particularly those of non-invasive stimulation, are variable. This variability can be partially explained by an incomplete mechanistic understanding, coupled with a combinatorial explosion of possible stimulation parameters. Computational models constitute a useful tool to explore the vast sea of stimulation parameters and characterise their effects on brain activity. Yet the utility of modelling stimulation in-silico relies on its biophysical relevance, which needs to account for the dynamics of large and diverse neural populations and how underlying networks shape those collective dynamics. The large number of parameters to consider when constructing a model is no less than those needed to consider when planning empirical studies. This piece is centred on the application of phenomenological and biophysical models in non-invasive brain stimulation. We first introduce common forms of brain stimulation and computational models, and provide typical construction choices made when building phenomenological and biophysical models. Through the lens of four case studies, we provide an account of the questions these models can address, commonalities, and limitations across studies. We conclude by proposing future directions to fully realise the potential of computational models of brain stimulation for the design of personalized, efficient, and effective stimulation strategies.

Introduction

"All models are wrong, but some are useful" - George E P Box. A fundamental question in neuroscience is how the brain's structure and function may be manipulated to counteract injury or disease. One effective way to establish the relationship between brain and behaviour is to employ targeted electrical brain stimulation and study the subsequent effects. While direct manipulations applied at different neural scales (from cells to circuits) enrich our knowledge, the translation to clinical applications is by no means trivial. This is because many of the mechanisms by which electrical brain stimulation influence brain function and behaviour remain elusive. A better understanding of the relationship between stimulation parameters and their behavioural and physiological effects is necessary for the effective deployment of this promising clinical and research tool. Computational modelling can help us understand the mechanisms underlying the effects of stimulation and how to optimise stimulation parameters to increase the efficacy of treatments.

Here we discuss the current state-of-the art in computational models of the effects of electrical brain stimulation. We first introduce the most common methods of electrical brain stimulation and computational model design. We then consider how recent work uses phenomenological and biophysical computational models to gain insight on the effects of stimulation using a "case study approach" Finally, we critically assess the current state of the field and suggest possible future directions.

Electrical brain stimulation

The purpose of electrical brain stimulation is to extraneously manipulate neural activity through the generation of local electric fields. The

* Corresponding author.
E-mail address: d.kurtin@surrey.ac.uk (D.L. Kurtin).

https://doi.org/10.1016/j.neuroimage.2023.120042.
Received 29 September 2022; Received in revised form 6 February 2023; Accepted 16 March 2023
Available online 23 March 2023.
1053-8119/© 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

generated electric fields can result in both local neurochemical changes and network-level changes (Little and Brown, 2012; Bekar et al., 2008; Warren et al., 2019; Li et al., 2019a; Kurtin et al., 2021). Electrical brain stimulation can be broadly separated into invasive and non-invasive brain stimulation.

Invasive brain stimulation is commonly applied in the form of deep brain stimulation (DBS). DBS uses surgically implanted electrodes, which typically target subcortical structures (Herrington et al., 2016). The stereotactically guided implantation of the electrodes to the stimulation target results in highly precise spatial localisation.

DBS has a long history of trial-and-error underpinning its current use. Animal studies conducted as early as the late 18th century investigated responses to cortical stimulation, and in the 1950's, thalamic ablations were shown to reduce tremor (Pycroft et al., 2018). In the late twentieth century DBS had become established as a treatment for Parkinsonian tremors (Bronstein et al., 2011), and now is an FDA-approved treatment for movement and psychiatric disorders, such as dystonia (Ostrem et al., 2014) and obsessive-compulsive disorder (Kohl et al., 2014), respectively. Yet, over a century of trial and error has not resulted in a complete mechanistic understanding of how DBS operates. Recent work has posited several theories (Dostrovsky and Lozano, 2002), but none have been conclusively embraced. Extending the application of DBS to processes that rely on distributed functions, such as cognition, requires a stronger mechanistic understanding of an expanding suite of stimulation parameters and their effects on brain function.

Non-invasive brain stimulation (NIBS) has been lauded as a well-tolerated, safe, and cheap neuromodulatory tool (Hallett, 2000; Coffman et al., 2014). NIBS encompasses an umbrella of techniques developed to manipulate brain function by applying current through the scalp. The most widely used methods include transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). TMS employs transcranial electromagnetic induction to generate an electric field (Terao and Ugawa, 2002; Miniussi et al., 2010), whereas tES produces neuromodulatory effects via weak currents applied to the scalp (Reed and Kadosh, 2018). Two popular methods of tES include transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS) (Woods et al., 2016; Polania et al., 2018; Nitsche and Paulus, 2000). Temporal Interference (TI) is a novel NIBS approach for sculpting electrical fields to enable non-invasive neural stimulation at depth (Grossman et al., 2017; Lee et al., 2020). While NIBS eliminates the risk associated with surgical implantation of electrodes, it is inherently associated with lower spatial resolution. One way to address this limitation is via the usage of multiple electrodes to enable more focal stimulation (commonly referred to as high-definition (HD)-tES) (Villamar et al., 2013). Another development in the delivery of NIBS is the more widespread availability of devices with several independent channels for current delivery to allow for multi-site stimulation. This move is supported by evidence that the effects of NIBS can be enhanced when stimulation is delivered to multiple regions in the same functional network (Fischer et al., 2017); Dagan et al., 2018; Hill et al., 2018).

Despite brain stimulation's utility as a clinical and research tool, an undeveloped mechanistic understanding of the parameters underpinning its function limit its effective deployment (Bergmann and Hartwigsen, 2020; Horvath et al., 2015). Some parameters are outside of experimental or clinical control, including individual anatomy, the organization of local inhibitory and excitatory circuits, neurochemistry, and genetics (Li et al., 2015; Wagner et al., 2007). However, many parameters can be controlled, including the type of stimulation applied, the duration/intensity of stimulation, and the targeted region(s) and/or brain state (Li et al., 2015; Wagner et al., 2007).

One way to both cultivate a mechanistic understanding and optimise delivery of brain stimulation is to utilise computational models of stimulation. Before discussing some specific examples, we first set the broader context of the types of models that have been used in neuroscience.

Introducing models of the effects of stimulation on brain function

Brain stimulation manipulates neural activity at different topological levels (micro, meso and macroscale) and over different timescales (seconds to days or weeks). Across these levels, the effects of stimulation can be thought to follow a casual pathway, as framed by Bergman and Hartwigsen Bergmann and Hartwigsen (2020): Stimulation is delivered → inducing changes in neural function → that can manifest in physiological changes that impact behavioural outcomes [Fig 1]. Computational models are able to simulate some or all stages of the causal path of stimulation.

Models that consider the first stage in the causal path, the **delivery of stimulation**, often concern the effects of applying current directly (via DBS) or indirectly (via NIBS) to the brain. Models of this nature often focus on how current spreads through skin, skull, and brain tissues, and estimate electric field distributions in the brain. Comprehensive reviews on these computational forward modeling studies using finite elements can be found in Saturnino et al. (2019); Johansson et al. (2019); Petrov et al. (2017).

Models of the second and third steps dealing with **changes in neural function** and **behaviour** can be built at the micro, meso, and macrocale. Models focusing on the microscale level investigate neurochemical and cellular-level mechanisms (Gubellini et al., 2009). At the mesoscale, models focus on brain structures in between the cellular and whole-brain resolution, including white matter tracts, small circuits, and cortical tissues (Khodashenas et al., 2019). Models that explore macroscale levels investigate the effects of brain stimulation on multiple brain regions, often in the form of neural networks, and/or their consequences on behaviour (Weerasinghe et al.; 2019; Muldoon et al., 2016; Giannakakis et al.; 2020; Deco et al., 2019). These models will be explored in greater detail in here.

Macroscale models often employ phenomenological or biophysical models, which group populations of neurons into functional units and consider how they interact. Macroscale models often capture oscillatory behaviour, and come in two popular versions: the neural mass model and the neural field model. Neural mass models characterise activity over time only, whereas neural field models describe how properties of neural units (such as average depolarization of a neural population) evolve over both space and time. Three models that have played a seminal role in mathematical neuroscience and have been used to model the effects of electrical brain stimulation on (different) aspects of neural function are Wilson Cowan Models (WCM) [Box 1], Kuramoto Oscillators (KO) [Box 2], and Stuart-Landau Oscillators (SLO) [Box 3] (Wilson and Cowan, 1972; Strogatz, 2000; Landau, 1944).

Box 1. Wilson Cowan Models

The original Wilson Cowan Model (WCM) was defined in Wilson and Cowan's seminal 1972 paper (Wilson and Cowan, 1972). It is a mean-field biophysical model that represents the properties of a spatially localised population of neurons, rather than individual neurons. The original WCM is composed of two coupled nonlinear equations that model the firing rate of excitatory neurons, $E(t)$, and the firing rate of inhibitory neurons, $I(t)$, within a brain region as a function of time t respectively.

A sigmoidal transfer function, also known as an "input-output" function, δ, determines how the input current to the subpopulations is transformed into neural firing rates. Connectivity or coupling coefficients, c_i, where i=1 to 4, represent the average number of excitatory (i=1,3) and inhibitory (i=2,4) synapses per population. There are different external inputs to the excitatory and inhibitory subpopulations – P and Q, respectively – to account for cell type-specific afferents to the population. The equations describing the time evolution of $E(t)$ and $I(t)$ are then

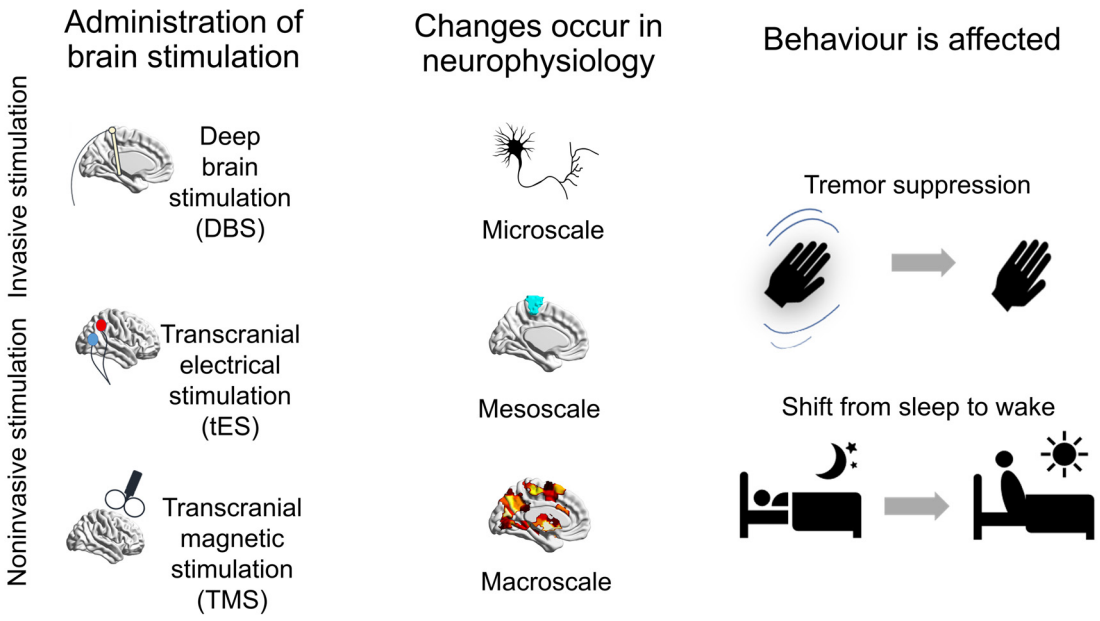
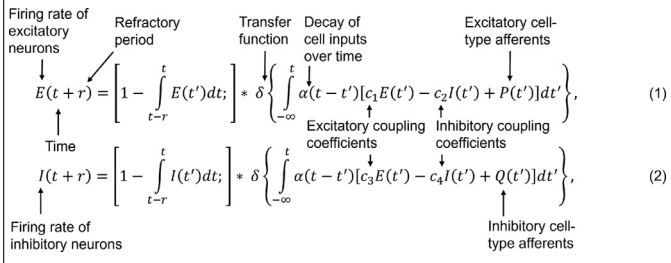


Fig. 1. Illustration of the causal path of stimulation. Brain stimulation can be administered invasively or non-invasively, both of which effect neurophysiology at the micro, meso, and macroscale. Then, the stimulation-induced changes in the brain exert downstream effects on behaviour. The brain images were made using BrainNet (Xia et al., 2013)



$$E(t+r) = \left[1 - \int_{t-r}^{t} E(t')dt;\right] * \delta\left\{\int_{-\infty}^{t} \alpha(t-t')[c_1 E(t') - c_2 I(t') + P(t')]dt'\right\}, \quad (1)$$

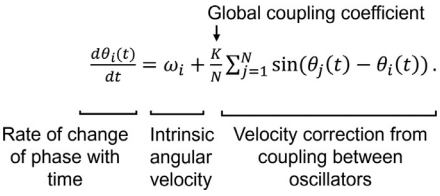
$$I(t+r) = \left[1 - \int_{t-r}^{t} I(t')dt;\right] * \delta\left\{\int_{-\infty}^{t} \alpha(t-t')[c_3 E(t') - c_4 I(t') + Q(t')]dt'\right\}, \quad (2)$$

where r is a constant that defines the refractory period, and $\alpha(t-t')$ models the decay of cell inputs with time. The parameters of a WCM are often selected so that the system has three potential states: a low fixed point, a high fixed point, or a limit cycle. Fixed points, also known as steady-states, are largely uneventful (Wilson and Cowan, 1972). At the low fixed point the firing rates of the subpopulations are stable and at a low level, creating a baseline state. At the high fixed point, the firing rates of the subpopulations are stable at a high level. Limit cycles represent oscillatory activity emerging from a balanced excitation and inhibition (Wilson and Cowan, 1972), and have been used as models for the gamma-frequency oscillations (≈40 Hz) detected from neuronal populations at the level of local field potentials. Additionally, these limit cycles have been extended to address pathological oscillations, reflecting excess synchrony that arises during epilepsy and essential tremor (Kim and Robinson, 2008; Deuschl and Bergman, 2002).

In network models of the brain, the dynamics of each node may be represented as a WCM operating in the limit-cycle regime, resulting in a system of coupled oscillators (Deco et al., 2009).

Box 2. Kuramoto Oscillators

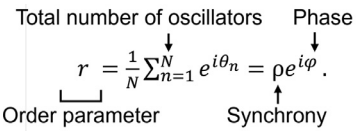
The dynamics of a brain region exhibiting oscillations in local field potentials can be further reduced from the WCM to a simple phase oscillator (Cabral et al., 2011). Each phase oscillator in isolation has very simple dynamics, being described by its phase rotating at its natural frequency. However, when phase oscillators are coupled together, their interactions are described by the Kuramoto model of coupled oscillators:



$$\frac{d\theta_i(t)}{dt} = \omega_i + \frac{K}{N}\sum_{j=1}^{N} \sin(\theta_j(t) - \theta_i(t)). \quad (3)$$

In the Kuramoto model of coupled oscillators, $\theta_i(t)$ represents the phase at time t for node i, N is the total number oscillators, ω_i is the intrinsic frequency of oscillator i, and K is the global coupling coefficient.

As K increases the solutions of the model tend towards phase synchronisation, where "synchronisation" refers to the stability of phase relationships. If all nodes have the same phase so that $\theta_i(t) - \theta_j(t) = 0$ for all i and j then the oscillators are synchronised in-phase. If the phases of different nodes differ, but the phase differences do not vary with time, then the oscillators are synchronised out-of-phase, or "phase locked". In general, the phase coherence of a population of oscillators can be captured by the Kuramoto order parameter. The order parameter r defines the relationship between synchrony (ρ) and the average phase (ψ) for N nodes



$$r = \frac{1}{N}\sum_{n=1}^{N} e^{i\theta_n} = \rho e^{i\varphi}. \quad (4)$$

The order parameter ranges from 0 to 1. When r=1, nodes are considered in-phase, and when r=0, nodes are perfectly out of phase. For further reading, see the review written by Bick et al. (2020). The review covers Ott-Antonson and Wantanabe-Strogaz reductions, which allow researchers to analytically solve solutions for simple systems of Kuramoto oscilla-

tors (rather than rely on computer simulations) (Bick et al., 2020). While these reductions are helpful to bridge the microscale to the macroscale, they do not extend to systems with added complexity, such as in the presence of heterogeneous couplings and time delays, which have been shown to modulate network activity not only in space and time, but also in the frequency domain, which is a crucial feature of brain activity (Cabral et al., 2014).

Box 3. Stuart-Landau Oscillators

The Stuart-Landau oscillator is a reductionist approach to model population-level oscillations in neural activity considering both the phase and the amplitude dynamics.

The original equation was proposed in 1944 by Landau Landau (1944) to describe a system exhibiting a Hopf bifurcation, i.e., a system that transitions from a stable fixed point to a limit-cycle upon a change in parameters (Uddin and Dorning, 1986). The canonical form defined by Stuart and colleagues in 1960 Palm (1960); Watson (1960); Stuart (1960) is defined as:

Amplitude, Growth rate, Landau constant

$$\frac{dA}{dt} = \sigma A - \frac{l}{2} A|A|^2. \quad (5)$$

Rate of change of amplitude with time

Here A is a complex number expressing the evolution of the amplitude $|A|$ and the phase ϕ over time as $A = |A|e^{i\phi}$. The parameter σ expresses the growth rate (or decay rate if σ is negative) and the real part of l is known as the Landau constant (Landau, 1944). Similar to the WCM, for some values of σ and l the SLO exhibits either a fixed point equilibrium or a stable limit cycle. Importantly, if the system is in a fixed-point regime but sufficiently close to the bifurcation point (sub-critical), it exhibits a damped oscillation with decaying amplitude in response to input. As such, sub-critical SLOs perturbed with noise can be used to approximate the transient and short-lived oscillations detected in neural activity.

Four common construction choices for computational models

So far, we have introduced different types of brain stimulation and the causal path of stimulation's effects on the brain and behaviour. We described the different topological scales at which the brain is commonly modelled, and introduced three common macroscale models of brain function – WCM, KO, and SLO. Direct comparison of different modelling studies is difficult, as each step in constructing a model, from defining nodes and edges to parameter choices for the oscillatory equations, requires choosing from a number of options (see Fig. 2 for definition of nodes and edges). Nevertheless, there are commonalities, and here we list and briefly discuss four common construction choices used when building phenomenological or biophysical models of the effects of brain stimulation [Fig 2].

1. Network nodes describe brain regions

Most studies to date opted for atlas-based parcellations of the brain to relate brain regions to nodes in a network. Studies have proposed that including cerebellar and subcortical structures may increase the biophysical relevance of models (Murray et al., 2018; Giannakakis et al., 2020), as well as accounting for differences in tissue excitability. For example, in Giannakakis et al. (2020) differences between healthy and epileptic brains were distinguished by modifying the internal weight values in the WC oscillators. Another consideration when defining model nodes is that atlas parcellations based on cytoarchitectural characteristics may define regions with non-uniform functional characteristics. Models that group independent functional subunits into a region do not capture the individual contributions of each subunit, but rather a net misrepresentation of both. An alternative approach involves parcellating the brain into functional regions (Soreq et al., 2019), which can be done on a group or individual level (Shen et al., 2013). Functionally derived parcellations can reduce confounds of overlapping representations of regional activity that arise when independent functional subunits are grouped within the same structural/anatomical regions (Shen et al., 2013).

Another consideration when researchers decide whether to use a structurally or functionally defined atlas for dynamical models is provided by the work of Domhof *et al*, who used Kuramoto and Wilson Cowan models to systematically investigate how several parameters, including atlas parcellation, influenced the specificity and reliability of simulated data to participants' empirical data (Domhof et al., 2022). The authors showed there was a substantial, significant effect of atlas type (structurally or functionally defined), particularly on how well the simulated structural-functional relationships captured empirical ones. The simulated data generated using a structurally defined atlas more reliably related model outputs to the empirical data, whereas the functionally defined atlas showed improved specificity of simulated data to participants' empirical data (Domhof et al., 2022). Thus, the systematic influences of atlas parcellation technique observed by Domhof *et al* should be considered when designing and implementing modelling studies.

2. Network edges and their weights

Connections between nodes are often derived from diffusion weighted imaging (DWI) to create models that capture connectivity among functional units and how stimulation propagates through the brain. DWI measures white matter density as a function of water anisotropy across imaging voxels, and is well-suited for detecting long, continuous projections of axonal bundles, such as the corpus callosum (Basser et al., 2000), corticospinal, and frontal aslant tracts (Kierońska and Słoniewski, 2020). Work by Nowak and Bullier (1998) showed that postsynaptic responses to grey matter stimulation are due to axonal, but not cell body, activation. Recent work confirms and expands these results, showing that DBS near white matter (WM) tracts are more likely to deliver excitatory effects (Mohan et al., 2020) and the efficacy of non-invasive brain stimulation depends on WM structure (Li et al., 2015; Kurtin et al., 2021; Lin et al., 2017). Moreover, modelling studies found that stimulation of WM tracts with coherent fibre orientation result in more focused electric fields (Metwally et al., 2012; Shahid et al., 2013). Therefore, modelling weighted connections between regions should better simulate how stimulation will propagate through the brain. In some studies, the signal propagation time between brain areas is included by considering a time delay associated with each edge. Time delays can be approximated by considering the distance between brain areas (Deco et al., 2009) or the average length of the fibres (Cabral et al., 2022) and assuming a conduction velocity. While accounting for the effect of time delays in conduction velocity and interregional communication increases the biological relevance of the work, there are a wide range of conduction speeds that generate simulated brain function that reproduce features of empirical brain function (Triebkorn et al., 2020).

Models that use participant's structural or functional connectivity to inform edges and their weights are referred to as personalised Brain Network Models (BNM) (Bansal et al., 2018b). Simulations of brain stimulation on BNM thus reveal individual responses to stimulation, and provide insights as to how individual connectivity influences the effects of brain stimulation (Bansal et al., 2018b). This enables the identification of key nodes that, when targeted by stimulation, innervate whole-brain networks. One such study was conducted by Muldoon *et al* and is explored later in this work (Muldoon et al., 2016).

3. Local brain activity is described by dynamical models

The dynamics of each node are then described by a mathematical model such as WCM, KO, or SLO, all of which are capa-

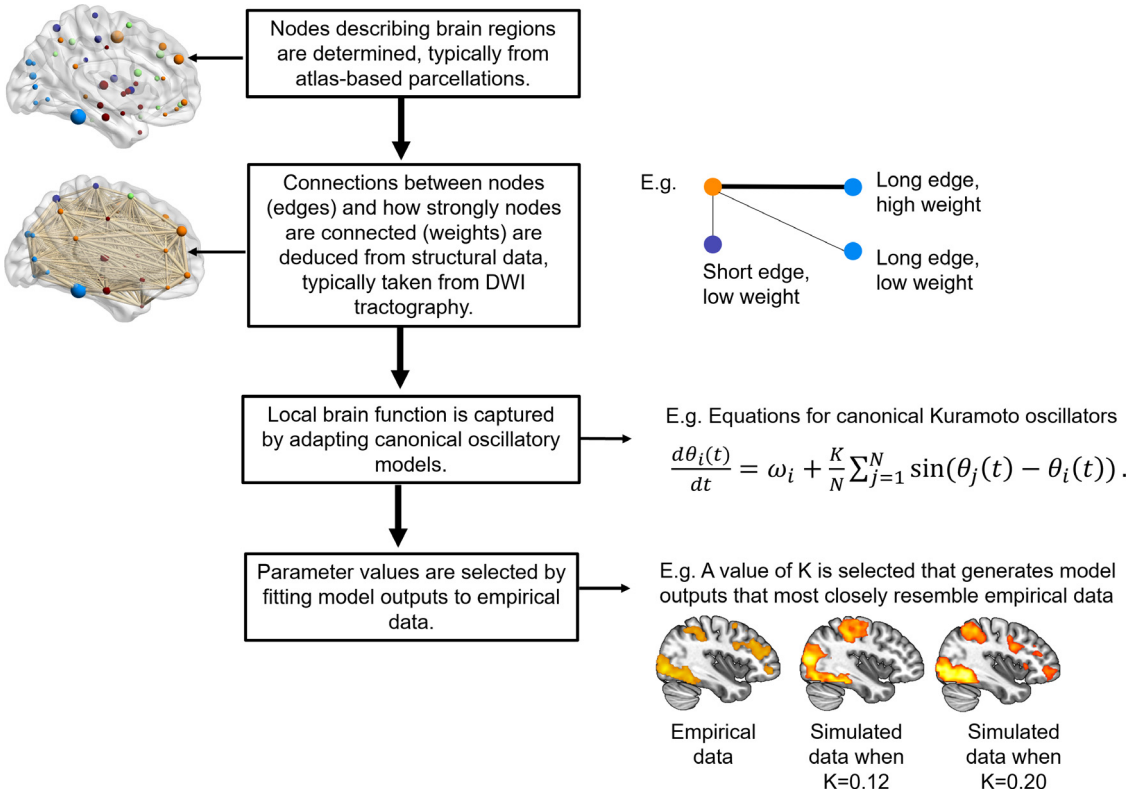


Fig. 2. Illustration of the four common construction choices made when developing computational oscillatory brain models. DWI = diffusion weighted imaging. Brain images were made using BrainNet Xia et al. (2013) and MRIcroGL

ble of reflecting the stochastic, complex variability in brain activity (Murray et al., 2018). For example, WCM and SLO can both model state transitions through a bifurcation point known as a Hopf bifurcation. On one side of the bifurcation (the "subcritical" side) there are low amplitude noise-driven oscillations. On the other side of the bifurcation, there are self-sustained oscillations.

Although the Kuramoto model focuses solely on the interaction between the phases of oscillatory regions, it has the advantage of being analytically tractable. We note that spiking (integrate and fire) models, traditionally used for micro or mesoscale investigation, can also be used in macroscale models to generate dynamic asynchronous and/or oscillatory behaviour comparable to the phenomenological models covered in this work, but the additional degrees of complexity make the numerical and analytic solutions less tractable (Cakan and Obermayer, 2020).

4. Parameter values are selected by fitting model outputs to empirical data

Parameter values are selected that align model outputs with empirical neural phenomena. Parameter values are often informed by literature (as in Muldoon et al. (2016)) or searching through a range of parameter values (as in Deco et al. (2019) or Weerasinghe et al. (2019)). The choice of parameter values greatly impacts model outputs (Cabral et al., 2022; Triebkorn et al.; 2020), and thus the validity of conclusions drawn from modelling studies. We end this work by introducing how machine learning approaches may improve parameter selection.

In the next two sections we provide case studies of work using computational models to answer either mechanistic or predictive questions of the effects of brain stimulation on brain function and/or behaviour. We have focused on a few particular exemplars which are representative of the use of WC, Kuramoto, or Stuart-Landau models, and highlight how the four common construction choices are implemented in current research.

Mechanistic modelling of stimulation effects

In this section, we consider two models that aim to develop a mechanistic understanding of the effects of stimulation. Specifically, the system-wide impact of regional stimulation (Muldoon et al., 2016) and the long-term effects of stimulation (Giannakakis et al., 2020).

"How to maximise the system-wide impacts of regional stimulation?"

Different psychiatric (Baker et al., 2019) and neurological (Watanabe et al., 2021) conditions are characterised by pathological brain function, the mitigation of which is the goal of neuromodulatory interventions. Indeed, a large body of empirical evidence shows that focal brain stimulation influences whole-brain network dynamics (Battleday et al., 2014; Fertonani and Miniussi, 2017) which attenuate the effects of neuropathology (Bronstein et al., 2011; Ostrem et al., 2014; Kohl et al., 2014). Therefore, the extent to which stimulation affects local and global brain dynamics is of important clinical utility. Further characterisation of how underlying structural connectivity influences the effects of regional brain stimulation on local and whole-brain function is an important step in identifying targets suitable for stimulation to attenuate pathological brain function.

Recent, state-of-the-art modelling (West et al., 2020; Farokhniaee and Lowery, 2021) and empirical (Muthuraman et al., 2020) work shows focal deep brain stimulation influences cortical and subcortical network communication. For example, work by Bansal *et al* constructed personalised BNM to investigate the role of interregional connectivity on the whole-brain effects of stimulation, and showed that interindividual variability in structural connectivity explain local and global effects of brain stimulation (Bansal et al., 2018a). Moreover, measures of the local and global effects of simulated stimulation explained differences in

participant's performance of less and more complex tasks, respectively (Bansal et al., 2018a). Collectively, the work by Bansal *et al* provides a compelling case that individual structural connectivity provides a scaffold upon which stimulation exerts its influence.

An example of research addressing the relationship between the functional and structural properties of stimulation targets and their local to global impacts is found in the first case study presented in this work, which features work by Muldoon *et al*. The authors modelled the effects of regional stimulation on whole-brain networks (Muldoon et al., 2016). Their framework is based on Network Control Theory (NCT) (Tang and Bassett, 2018) which identifies regions that are influential in shifting neural network dynamics; that is, a region's controllability (Tang and Bassett, 2018; Muldoon et al., 2016). Controllability originated from engineering and physics research, and evaluates the potential that an external input to a part of a system can drive the whole system's dynamics to a target state (Kalman et al., 1963). In a neurological context, a target state refers to the desired pattern of activity or connectivity which the stimulation is intended to induce. For example, if stimulation is delivered in hopes of shifting aberrant dynamics to emulate those of healthy controls, then the pattern of activity or connectivity in healthy controls is considered to be the target state.

The authors first focused on the system-wide impacts of regional stimulation. They subsequently applied their results to the neural networks that underpin cognitive function. Here, we will focus on the first part of their study to provide an example of how computational models were constructed and employed to run a systematic assessment of how individual connectivity influences the controllability of stimulation targets.

The authors constructed their model by parcellating the brain into discrete regions using anatomical scans obtained with MRI [Fig 2Ai]. These regions formed the nodes of the network. The network's edges were defined through the number of streamlines between regions estimated using DWI [Fig 2Aii]. This resulted in a weighted, undirected, structural connectivity matrix for each study participant, in line with previous literature (Caumo et al., 2012). This was used to inform a personalised BNM, where individual connectivity is used as a scaffold for the dynamical components of the model.

The dynamics of each brain region was described by a WCM Box 1 [Fig 2Aii]. We note that the authors only included excitatory inputs to the excitatory subpopulation, assuming that most long-range connections are excitatory. The time delay in communication between regions was set to be proportional to their physical distance to ensure activity propagated through the system in a biologically relevant manner.

Having defined nodes and edges, the authors then selected their model's parameters. They kept all region-specific parameters and the sigmoidal transfer function the same as in the canonical WCM (Muldoon et al., 2016; Wilson and Cowan, 1972). The authors selected the global coupling coefficient so that the dynamics of the system were close to the transition from steady, baseline activity, to a state where the firing rate at most nodes oscillated at around 20Hz. The transition point was dependent on structural connectivity and Muldoon *et al* found that the transition value of global coupling coefficient had low within-subject variability and high between-subject variability, which highlights the importance of personalised BNM (Bansal et al., 2018b).

Though Muldoon *et al* do not specify which modality of brain stimulation they are modelling, we infer that they are investigating the general effects of brain stimulation. Muldoon *et al* modelled the effects of brain stimulation by changing the current input to the system via the excitatory subpopulation, P, for a target region. The "stimulation" was delivered as a single pulse for 1 second, which caused the target region to transition from a baseline non-oscillatory state to an oscillatory state operating near 20 Hz Box 1.

In Wilson and Cowan's paper introducing the model, they related increased population firing due to an increase in the input current P to primate studies that show increased firing due to constant motor stimulation (Wilson and Cowan, 1972).

The local changes in the target region then resulted in changes in the dynamics of other regions. A functional connectivity matrix one second before and during the stimulation was constructed by considering the cross-correlation in firing rates between all pairs of regions.

The authors measured the effects of stimulation by defining the "functional effect" and the "structural effect". The functional effect measured the difference between the functional connectivity matrix before and during stimulation. The structural effect measured the change in the difference between the structural *and* functional connectivity matrices before and during stimulation. The "functional effect" of a region is a measure of its ability to shift whole-brain activity and connectivity. The "structural effect" is a measure of the extent to which a region's structural connectivity accounts for its influence on neural network dynamics.

Key results from their study were that first, individual variation in structural connectivity lead to variations in the neural/physiological response to stimulation, further supporting the use of BNM as a method to understand how structural constraints influence the functional effects of brain stimulation (Bansal et al., 2018b). Second, NCT identified nodes with high controllability. Regions of low structural effect (regions with high structural connectivity) induced global changes in the brain state, whereas regions of high structural effect (which were more constrained due to sparse structural connectivity) induced more focal effects (Muldoon et al., 2016).

The work by Muldoon *et al* provides a useful example of how personalised BNM may be constructed to investigate how subject-specific controllability influences the effects of stimulation. Findings by Muldoon *et al* were corroborated and expanded by recent work from Menardi *et al*, who constructed personalised BNM and showed that in their models, choosing stimulation targets based on their controllability more effectively modulated the target network of interest, further encouraging the use of NCT (Menardi et al., 2022). Thus, NCT accompanies structural and functional connectivity as measures that can, and arguably should, be considered when evaluating neural features contributing to individual responses to brain stimulation (Bansal et al., 2018b; Domhof et al., 2022).

"What are the long-term effects of stimulation?"

As evidence accumulates that tDCS (Gangemi et al., 2021; Bystad et al., 2016) and other brain stimulation modalities (Janicak et al., 2010; Limousin and Foltynie, 2019) have clinically relevant benefits when delivered over more than a single session, insights characterising and understanding the source of the differential effects of brain stimulation in patients and healthy controls are increasingly important. For example, it is thought that the long-term effects of tDCS increase neural plasticity by shifting the balance of excitatory and inhibitory neurotransmitters (Yamada and Sumiyoshi, 2021; Hurley and Machado, 2017), though it is unclear how stimulation in clinical populations (who may already exhibit dysregulated excitatory/inhibitory dynamics) affects this balance. Yet, there are many practical limitations to characterising the effects of brain stimulation over 24 hours, let alone over week- or month-long interventions. Models of the long-term effects of brain stimulation in clinical populations are increasingly needed, as they mitigate many of the difficulties inherent to long-term studies and can inform how stimulation differentially influences clinical populations.

In our second case study answering a mechanistic question, Giannakakis *et al* modelled the effects of stimulation on structural connectivity and neural network dynamics over different time periods, throughout 30 minutes of stimulation ("short-term"), and 24 hours after ("long-term") (Giannakakis et al., 2020). Using structural data from healthy controls and people with epilepsy, they considered how differences in connectivity and inherent regional excitability influence the effects of stimulation (Giannakakis et al., 2020).

The authors parcellated the brain into discrete cortical and subcortical regions as defined by the Desikan atlas

(Desikan et al., 2006) [Fig 2Ai]. As in Muldoon *et al*, personalised BNM were created by using streamline tractography data to inform the coupling between regions [Fig 2Aii]. However, a key difference from Muldoon et al. (2016) is that the structural connectivity was updated during and after the simulation via a Hebbian learning rule where the connection strength is increased between two nodes if increases in firing in one node precede increased firing in the post-synaptic node; otherwise, pairwise connectivity decreased.

The dynamics of the nodes of the network were modelled as modified WCM based on their previous study (Papasavvas et al., 2015) [Fig 2Aiii]. The author's version of the WCM deviates from the canonical by including two inhibitory subpopulations as opposed to one, to model the effects of both subtractive and divisive inhibition. They cite two main reasons for including two inhibitory subpopulations. First, by including two inhibitory subpopulations, the model exhibits complex dynamics without abrupt transitions to chaos (Feigenbaum, 1978). Papasavvas *et al* argue that this increased complexity better reflects the brain's ability to balance long-range synchronous activity (Klimesch, 1999; Papasavvas et al., 2015). Secondly, this increased complexity also better models selective attention (Hillyard et al., 1998), sensory Schwartz and Simoncelli (2001), and motor processing (Peuskens, 2004). The study by Giannakakis *et al* was selected as a case study in this work because the inclusion of the second inhibitory population exemplifies how canonical models can be improved and adapted.

Next, the internal weight values between the excitatory and inhibitory subpopulations were chosen to model the differences between healthy and epileptic regions of the brain. The internal weights for the healthy regions were selected to give high amplitude oscillations for both the excitatory and inhibitory subpopulations, with the oscillatory amplitude tapering off after a few hours (Giannakakis et al., 2020). Epileptic regions were modelled as having a greater excitatory and lesser inhibitory weights than healthy regions, in line with the nature of the pathology (Giannakakis et al., 2020).

Other differences from the canonical WCM were the use of a logistic instead of a sigmoid input-output function. Within the input-output function, the inputs to both inhibitory populations are the same, but the inputs from the inhibitory populations to the excitatory reflects their differing physiological targets. Divisive inhibition occurs through targeting the soma, while subtractive inhibition occurs at dendrites (Wilson et al., 2012; Pouille et al., 2013).

Similar to the study conducted by Muldoon et al. (2016), the authors modelled stimulation by changing the value of P, which represents excitatory afferents to the region. During stimulation, the authors decreased the value of P (i.e., excitatory input) by 50% for 3 target regions, simulating the possible inhibitory effects of cathodal tDCS (Giannakakis et al., 2020) Box 1. The target regions were the amygdala, hippocampus, and parahippocampal gyrus and were selected because of their known role in inciting seizures. While cathodal tDCS would not be a feasible method of stimulating subcortical regions, TI stimulation can non-invasively target stimulation to subcortical regions (Grossman et al., 2017). Recent work has shown TI stimulation of the anterior hippocampus modulates task-related hippocampal activity and connectivity (Violante et al., 2022). Thus, inferences gained from Giannakakis *et al's* effects on subcortical regions may inform empirical work employing TI.

Three scenarios were considered. In this first scenario, the network structure was based on healthy controls and all regions were modelled as healthy regions. In the second scenario, the network structure was based on epilepsy patients and the target regions for stimulation were modelled as epileptic, more excitable, regions. For the third scenario, the network structure was based on epilepsy patients and all regions were modelled as healthy regions.

As a result of their simulations, Giannakakis *et al* predicted that the more excitable, epileptic group had a larger change in whole-brain and local connectivity than healthy controls at the end of the 30 minute stimulation session. Over the next 24 hours, although the trajectory of effects of stimulation on whole-brain and local connectivity differed, ultimately, the changes in connectivity were similar between the healthy control and epileptic groups. They conclude that the temporal dynamics between the two groups must also be different, considering the effects of stimulation decay at varying rates for each model (due to the different stimulation-induced behaviors) for them all to approach equilibrium within 24 hours.

Modelling to optimise the delivery of stimulation

In this section we discuss two studies that address predictive questions on how to optimise closed-loop stimulation (Weerasinghe et al., 2019) and how to force a transition between brain states (Deco et al., 2019).

"How can we optimise closed-loop stimulation?"

Closed-loop stimulation systems use biomarkers to inform the timing of delivery of stimulation, and have the potential to increase the efficacy of brain stimulation by delivering stimulation protocols when markers of pathology are present, which offers both greater precision and efficiency compared to continuous DBS approaches by mimicking endogenous circuits more closely (Rosin et al., 2011).

There are a number of studies investigating computational models of closed-loop stimulation (Daneshzand et al., 2017; Daneshzand et al., 2018; Weerasinghe et al., 2019). Here we focus on the study by Weerasinghe et al. (2019) who sought to devise a closed-loop DBS strategy that most effectively reduces pathological neural oscillations. To do this, they investigated whether phase, amplitude, or phase and amplitude of neural oscillations provided the best biomarker to inform delivery of closed-loop DBS. In the first part of the study, the authors used a theoretical model to predict changes as a result of stimulation. Then, the authors applied these predictions to empirical data from essential tremor patients, and introduced a novel stimulation strategy.

The model consisted of a system of N Kuramoto oscillators Box 2 where each oscillator was connected to every other oscillator. This model is phenomenological (i.e., descriptive), meaning that each oscillator included in the model does not explicitly represent a particular brain region, and the authors stated that each oscillator represented either a neuron or microcircuit (Weerasinghe et al., 2019). The parameter k determined the coupling strength in the following equation:

$$\frac{d\theta_i}{dt} = \omega_i + \frac{k}{N}\sum_{j=1}^{N}\sin(\theta_j - \theta_i) + I\,X(t)Z(\theta_i). \tag{5}$$

The third term on the right-hand side describes stimulation. The stimulation of intensity I acts on all oscillators but its effect depends on the phase of each oscillator as through the phase response function $Z(\theta_i)$. The stimulation is turned "on or off" with $X(t)$. When $X(t) = 1$, stimulation is on, and $X(t) = 0$ means stimulation is off.

In DBS, the response to stimulation can be described by amplitude and/or phase response curves (ARC and PRC, respectively). In the study, ARC and PRC described how amplitude and phase of pathological oscillations (such as tremor, which has been shown to operate within 3 to 8 Hz (Cagnan et al., 2013)) varied as a function of the phase at which stimulation was delivered. To capture the relationship between the ARC or PRC and stimulation the authors used the reduction method of Ott and Antonsen (2008); Bick et al. (2020), which in the limit of large N for an instantaneous pulse and a sinusoidal phase response function, gives analytical expressions that describe how the ARC or PRC change over time.

Weerasinghe *et al* then simulated a population of $N = 3000$ oscillators using pulsatile stimulation at $\omega = 30$ Hz and a range of phases. They found that stimulating at phase π resulted in the largest change to the ARC, a result of the strong correlation between the ARC and the negative gradient of the PRC.

Then, the authors also explored how harmonics in the phase response function, $Z(\theta)$, influenced the effects of stimulation. They found if $Z(\theta)$ contains a dominant first harmonic, and stimulation is applied when the amplitude of oscillation ρ is low, then the effects of stimulation are magnified.

These results provide two predictions which they tested by examining responses to phase-locked DBS in experimental data collected from patients. In this experiment, DBS was applied at a range of phases and the effect of DBS was measured using hand accelerometer data, since the hand tremors of essential tremor patients parallel the neural oscillations that underpin the movement itself (both occurring around 5 Hz) (Cagnan et al., 2016). Though only one out of nine subjects fit their predicted response to theoretically-driven, closed-loop stimulation, it is highly commendable that Weerasinghe *et al* empirically tested their model-driven predictions.

Research building upon the work of Weerasinghe *et al* may employ models developed with more consideration for the role of brain regions and circuits underpinning motor disorders, which are often characterised by well-known pathology in the basal ganglia (Graybiel, 2000). For example, Meier et al. (2022) developed a personalised BNM that incorporates a spiking network model of the basal ganglia with a whole-brain model created using The Virtual Brain (Sanz Leon et al., 2013), an online platform that enables researchers to input subject-specific MRI data to inform mean-field oscillatory models of brain function. The authors showed simulated DBS to either the subthalamic nucleus or globus pallidus internus (GPi) restored normative thalamic and cortical activity, providing a proof-of-concept that a multiscale model can be used to develop and test new stimulation paradigms.

"Can stimulation force a transition between brain states?"

Brain states refer to the transient patterns that underpin brain function, and identifying parameters that drive state transitions is an important step in advancing the ability to alter the dynamics of large-scale networks. Modulating pathologically dysregulated brain network activity would have translational impact for treatments ranging from disorders of consciousness, traumatic brain injury (Stephens et al., 2018; Woytowicz et al., 2018; Li et al., 2020), schizophrenia (Jia et al., 2020; Saris et al., 2021), sleep disorders (Witt et al., 2018; Yu et al., 2018), autism (Padmanabhan et al., 2017; Smith et al., 2018; Hong et al., 2019), and more (Liu et al., 2018, Dai et al., 2021).

Recent modelling work has made advances in developing a mechanistic understanding of how oscillatory synchronisation results in metastable, brain state-like behaviour (Vohryzek et al., 2022), and how brain states dynamics change when moving from wakefulness to sleep (Jobst et al., 2017; Deco et al., 2019) or the response to psychedelics (Deco et al., 2018). For example, work by Bansal *et al* used WCO to develop personalised BNM with the aim of characterising the states that emerge in response to simulated brain stimulation of each node (Bansal et al., 2019). The authors showed that there is a large variety of states that emerge in response to stimulation, which can be grouped into three categories - coherent states (which exhibit global synchrony), metastable states (which exhibit low levels of synchrony and little network structure), and chimera states (which are dominated by groups of synchronised regions) (Bansal et al., 2019). Regional stimulation was most likely to evoke chimera states, inviting future work to explore whether prioritising target states exhibiting chimera-like properties provide better stimulation targets than metastable or coherent states.

Here we focus on a study by Deco *et al* in which a modified SLO system was employed to model the activity of two different brain states (sleep and wakeful resting state) (Deco et al., 2019). The authors used their model to predict what stimulation parameters could force a transition between these two states.

First, Deco *et al* characterised each of the two discrete brain states – sleep and wakefulness – into three metastable substates (patterns of brain network activity that characterise a state) (Deco et al., 2019). This was done using the Leading Eigenvector Dynamic Analysis (LEiDA) developed by Cabral et al. (2017). LEiDA characterised the temporal evolution of dynamic functional connectivity through calculating the leading eigenvector of a phase coherence matrix. This simultaneously reduces dimensionality, improves signal to noise ratios, and allows for the smooth characterization of recurring patterns over time. Moreover, the metastable substates identified by LEiDA have been shown to capture functional organisation spanning the coherent, metastable, and chimera categorisations of states observed by Bansal et al. (2019).

Second, whole-brain models were generated and fitted to the probability distributions of all the substates [Fig 2Aiv]. Similar to Muldoon et al. (2016), the authors parcellated the brain using the AAL atlas, this time into 90 regions, each of which became a node in their network [Fig 2Ai]. Connections between nodes were set by a structural connectivity matrix created via tractography techniques [Fig 2Aii]. The dynamics of each node was described using a modified LSO [Fig 2Aiii], written in Cartesian form as

$$\frac{dx_n}{dt} = [a_n - x_n^2 - y_n^2]x_n - \omega_n y_n + G\sum_{p=1}^{N} C_{np}(x_p - x_n) + \beta\eta_n(t) \quad (6)$$

$$\frac{dy_n}{dt} = [a_n - x_n^2 - y_n^2]y_n + \omega_n x_n + G\sum_{p=1}^{N} C_{np}(y_p - y_n) + \beta\eta_n(t). \quad (7)$$

Here, x_n modelled the BOLD activity for each node. The intrinsic frequencies ω_n were 0.04 to 0.07 Hz, in line with the average peak frequency of the BOLD signal in each node. The coupling parameter C_{np} measures the strength of the coupling node p to node n. For $a_n \leq 0$ the baseline state is a stable fixed point dominated by noise, which the authors describe as "a low-activity noisy state" Deco et al. (2019). At $a_n = 0$ this baseline state loses stability and transitions to a self-sustained oscillatory state. Note this type of transition is a supercritical Hopf bifurcation, as discussed in the Section "Four common construction choices for computational models".

Fitting the model to the empirical data was done in two stages. First, the authors updated the effective connectivity coefficients C_{np} to optimise the fit between the modelled and empirical time-averaged phase coherence matrix of the sleep and wake conditions. Second, the global coupling parameter, G, was tuned to fit the SLO activity to the empirically derived probability of occurrence of the three substates. Previous work by Deco *et al* showed that the global coupling parameter played a critical role in shaping simulated brain network function to fit empirically derived measures of brain function (Deco et al., 2017), and recent work by Triebkorn et al. (2020) evaluated the importance of conduction velocity, global coupling, or graph theoretic properties in shaping modelling dynamics that resemble empirical dynamics. Assessment of the first two free parameters was conducted using a systematic, exhaustive search of all combinations of parameter values, and showed that individuals typically exhibit a narrow range of values for global coupling parameters that generated simulated dynamics close to empirically derived ones, in line with previous work (Deco et al., 2017). Thus, by tuning the global coupling parameter, G, Deco *et al* ensured the simulated data closely emulated properties of the empirical data.

In the final step they demonstrated that they could force a transition between the two states of wake and sleep through stimulation. Stimulation was administered bilaterally to pairs of nodes, so if a node on the left was stimulated, then so was the corresponding node on the right. Stimulation was modelled by changing the bifurcation parameter a_n for target nodes. Increasing values of the bifurcation parameter resulted in stimulation-induced oscillations; conversely, decreasing values of the bifurcation parameter modelled noise. This provided a contrast between stimulation parameters that serve to either reinforce or disrupt brain activity.

Furthermore, the authors investigated whether stimulating multiple regions with weaker stimulation more effectively forced a transition be-

tween brain states. Their best fit for multi-site stimulation resulted from stimulating two pairs of regions.

Though the modelling study by Deco et al. (2019) was not empirically validated, a study by Chen et al. (2019) directly compared whether stimulation of the primary motor cortex or multi-site stimulation of the primary motor cortex, premotor cortex, and supplementary motor area increased a measure of the synchrony between cortical and muscular activity. The authors showed that multi-site stimulation resulted in significantly higher and longer-lasting measures of cortico-muscular synchrony, thus corroborating the simulated results from Deco *et al* that multisite stimulation can more effectively drive a neural system towards a desired state (Chen et al., 2019; Deco et al., 2019).

Steps to move from phenomenological to predictive modelling

This work began by introducing different types of brain stimulation, how brain stimulation affects brain function, and how macroscale computational models can represent such relationships. We then described studies that use phenomenological or biophysical models to simulate brain stimulation and its effect on neural function with the aim of answering either a mechanistic or predictive question concerning the effects of brain stimulation. The results from the Muldoon *et al* study not only suggested that differences in structural connectivity could explain some of the interindividual variability that hounds NIBS studies (Horvath et al., 2015; Li et al., 2019b), but also provided a framework for deciding which regions to stimulate based on their controllability (Muldoon et al., 2016). In the study by Giannakakis *et al* the authors suggested variations in excitability and connectivity may underpin the differences in the brain's immediate response to stimulation (Giannakakis et al., 2020). Weerasinghe *et al* suggested a novel form of closed-loop DBS called "Hybrid DBS". This would deliver high frequency stimulation when endogenous oscillations surpass a threshold amplitude (Weerasinghe et al., 2019). Finally, results from Deco *et al* suggest popular one-site or single-channel stimulation setups may not be as effective as those using multi-channel setups concomitantly targeting multiple regions (Deco et al., 2019).

There is no dispute that the human brain is complex, with trillions of neural synapses packed into 1.41 dmm^3 (Lüders et al., 2002). Initiatives such as the Virtual Brain (Sanz Leon, et al. 2013) and NiMARE (Salo et al., 2022) aim to capture this complexity *in-silico* by developing detailed computational models. But such models are limited by computational power and current knowledge of neurological structure and function. Instead, macroscale approximations take a coarse-grain approach, supposing that clusters of billions of neurons act as a single oscillatory unit. These oscillatory models are grounded in physiological truths that have not changed substantially since Wilson and Cowan's seminal paper (Wilson and Cowan, 1972). Such models are complex enough to exhibit some of the brain's macroscale dynamical patterns, yet simple enough to offer a mechanistic insight into brain dynamics, and to suggest ways to optimise stimulation delivery. Computational models hold real promise as ways to understand both how the brain works and how brain stimulation can be employed with maximal clinical benefit. Though all the models described in this work have been informed by and compared to empirical data, only one (Weerasinghe et al., 2019) empirically tested their model-generated predictions. In our view, a critical next step is for more widespread laboratory, and ultimately clinical, confirmation of model insights, and the integration of models in closed-loop, personalised, neuromodulation interventions. Moving from phenomenological to predictive modelling is not a clear-cut process; nevertheless, here we propose three modelling phases researchers may follow to generate testable stimulation parameters [Fig 3]**Phase 1: Identifying the question**

In this phase what neural correlates best predict a clinical or behavioural outcome are identified. First, the behavioural or clinical outcome to be modulated with stimulation is chosen, and their functional, neural correlates (EEG/MEG/functional Magnetic Resonance Imaging (fMRI)) are acquired. Then, researchers select the neural correlate that best predicts the behavioural or clinical outcome measure. This is considered the target feature, which can be used to define the relationship between the neural correlate and outcome response. There are inherent complexities when choosing which neural correlate best captures the experimental spatio-temporal dynamics of the brain, and how it relates to behavioural or clinical outcomes. For example, models simulating brain activity captured with fMRI often aim to fit the functional connectivity between brain areas averaged over time (Muldoon et al., 2016). However, recent work has focused on the temporal nature of brain dynamics by quantifying recurrent, metastable brain states rather than a static representation of network connectivity (Deco et al., 2019; Cabral et al., 2017). Another method to select a neural correlate of clinical or behavioural outcomes is to use a feature extraction method, such as Highly Comparative TimeSeries Analysis (HCTSA) (Fulcher et al., 2013; Fulcher and Jones, 2017). HCTSA identifies neural features and ranks their ability to predict behavioural or clinical outcome measures. Deciding which neural correlate serves as an optimal target feature and determining how it relates to the behavioural or clinical outcome measure is not straightforward, yet it is a crucial step when developing model-driven targets for brain stimulation.

Phase 2: Constructing the model

A computational model is created that can generate the target feature identified in Phase 1. Phase 2 starts by constructing a computational model in line with the four common construction choices – first, identifying an atlas to define nodes, and second, informing edges between the nodes using participant's structural or functional connectivity data. Though DWI is often used to inform connectivity between edges, there are several well-characterised limitations in DWI, including both the usual confounds in MR imaging (motion artefacts, eddy currents, etc) as well as difficulties harmonising nonuniform tract distribution, or whether fibre trajectories cross or 'kiss' (Basser et al., 2000). Efforts to reconcile differences between individuals (Zhang et al., 2018), inform structural connectivity with functional connectivity (Deco et al., 2011; Arbabyazd et al., 2021), or create new scanning/analysis sequences (Ressel et al., 2018; Caan, 2016) will improve applicability of DWI not only for clinical (Kierońska and Słoniewski, 2020) and research use (Basser et al., 2000), but also for informing model edges and their weights. Then, in line with the third common construction choice, researchers choose a phenomenological or biophysical model to represent each node, and fourth, select the free parameters to be tuned. A non-exhaustive list of suggestions include a global coupling coefficient, interregional transmission delays, or the natural frequency of each node, all of which have been shown to influence the presence of empirically relevant metastable oscillatory modes (Cabral et al., 2022). Parameter tuning works to identify the configuration of free parameters that, once implemented in the model, generates outputs most similar to the target feature. Different parameter tuning methods are covered in more detail in the following section.

Phase 3: Testing and evaluating the model

Parameters that represent the delivery of stimulation are added to the model constructed in Phase 2. Suggested parameters include the shape of the stimulation waveform, the region(s) that are stimulated, and the duration, intensity, and the frequency or frequencies of stimulation. As in Phase 2, free parameters would be optimised using a parameter tuning method. Phase 2 sought to identify which parameter configuration gave the closest relationship to the target feature; in Phase 3, we wish to see which parameter configuration pushes the target feature along the target-response relationship to achieve an improved outcome measure. For example, if Phase 1 identified metastability as a target feature and a positive target-outcome response relationship, then the optimal parameter configuration in Phase 3 would generate increased metastability. The final step is to conduct an empirical study testing whether the parameter configuration identified by the model effectively modulates the clinical or behavioural outcome measure. This final important step remains as an Achilles' heel for most cur-

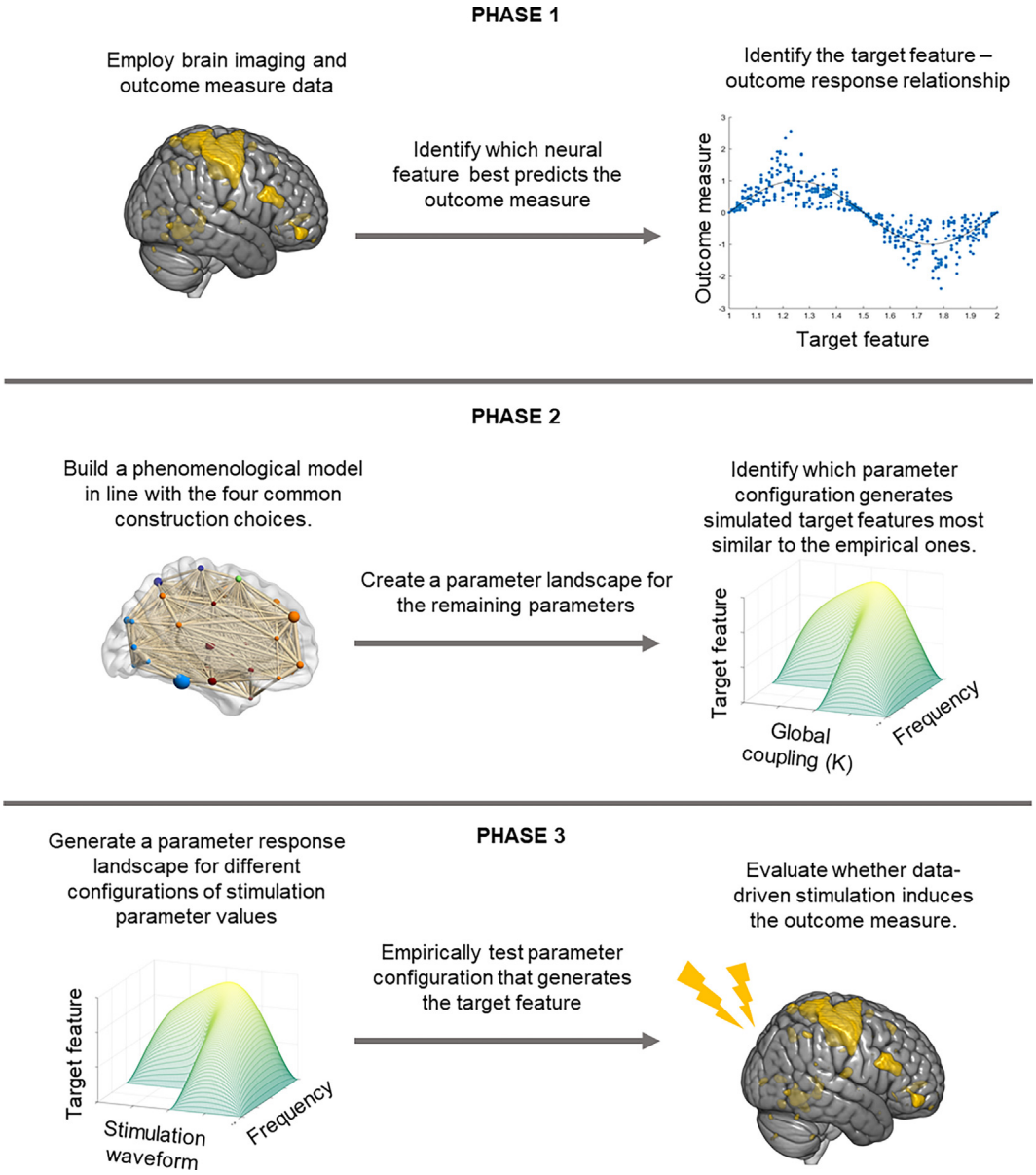


Fig. 3. Illustration of the three suggested phases to move models from phenomenological to predictive. Brain images were made using BrainNet and MRIcoGL Xia et al. (2013)

rent modelling studies. While considerable advances have been made in establishing computational models, empirical validation is more limited.

Finding the optimal parameters for computational models

In comparison to manual fitting or choosing parameter values based on literature, machine learning approaches may provide systematic, computationally tractable methods to evaluate and select parameter configurations, defined as parameter optimisation, or tuning, approaches. There are many different automated algorithms for parameter tuning (Liashchynskyi and Liashchynskyi, 2019; Mollee et al., 2017; Ruder, 2016; Kangasrääsiö et al., 2019; Bergstra and Bengio, 2012), and in Box 4 we describe four of the most common examples. The four examples provided can be grouped into two sets, where each set has a different approach to identify the optimal parameters. The first set of parameter tuning methods (Fig 4i-ii) identifies the optimal parameter values by running the computational models using different parameter configurations, and then determines the combination of parameter values that generated simulated data that most closely resemble the experimental values. The second set identifies the optimal parameter values by searching the parameters space in the training phase of the model, during which the parameter values are updated at each iteration of the training according to specific criteria set by the optimisation approach selected (Fig 4iii-iv].

There are several factors that may influence which parameter tuning method is most appropriate, including the size of the parameter space (i.e., the set of values that parameters can acquire), the available computational resources, whether the functions in the models are differentiable, whether the set of potential solutions is continuous or discrete, and whether there are constraints in the values that the parameters can acquire. All these requirements and criteria can make the selection of the appropriate approach difficult. A further complexity in using parameter tuning approaches is that their implementation for the optimisation of computational models of brain function might not be trivial, considering that they are commonly developed and integrated within

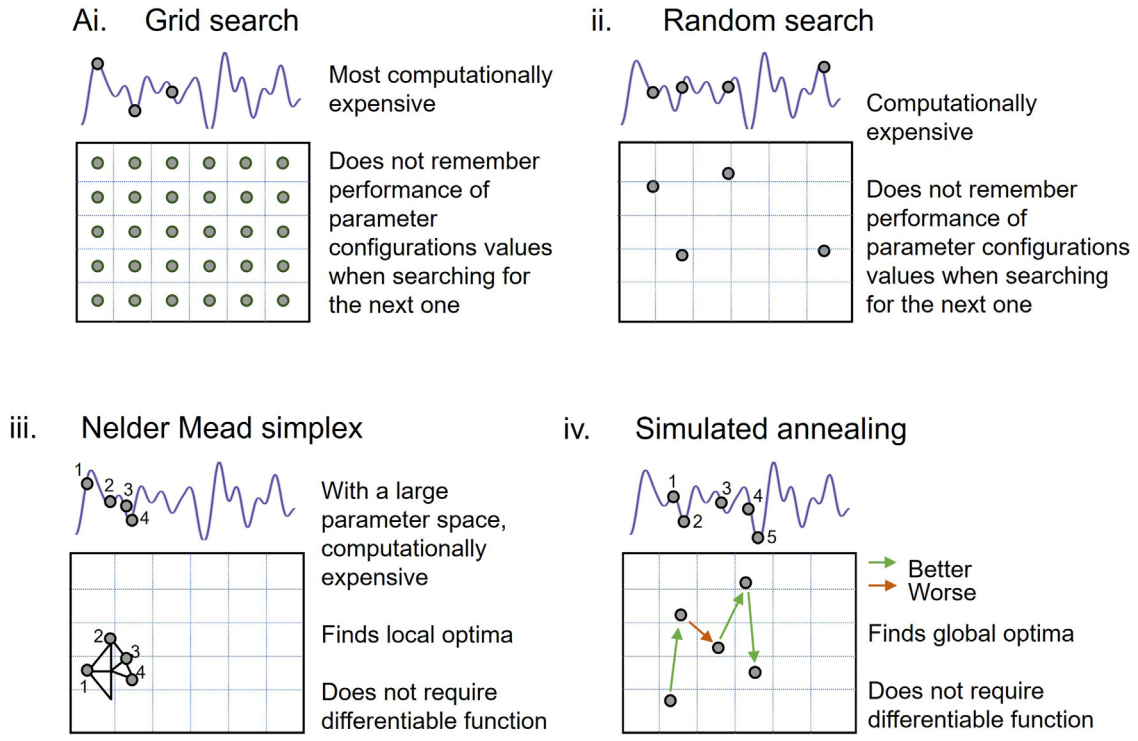


Fig. 4. Illustration of parameter tuning methods, including (Ai.) Grid search, (ii.) random search, (iii.) Nelder Mead simplex (as an example of local search) and (iv.) simulated annealing (an example of global search). We selected Nelder Mead simplex algorithms to represent local search as it does not require the model to be differentiable. Given the fact that some biophyical models, including the WC model, utilise partially differential equations, the Nelder Mead simplex algorithm may be a better local search method than GD.

machine learning pipelines (Liashchynskyi and Liashchynskyi, 2019). Therefore, adapting parameter tuning methods for these type of generative models may not be straightforward. Finally, and most importantly, some machine learning methods (especially those in the second category) are not necessarily expected to identify parameter values within biologically feasible ranges. This is a common concern in NCT studies (Muldoon et al., 2016; Gu et al., 2015), which have been shown to better capture theoretical controllability, rather than practical controllability (Suweis et al., 2019). Constraining stimulation parameters within ranges suitable for brain stimulation would ensure that model-generated stimulation hypotheses are practical. Yet even this suggestion is not readily implemented, as the relationship between modelled and empirical stimulation parameters is not known. To constrain the simulated stimulation parameters to biologically relevant ranges, we suggest researchers implement an approach such as that described in Phase 1 to identify the response relationship between simulated and empirical brain stimulation.

0.4. Parameter tuning approaches

Grid Search: The parameter space is divided into different grids (Liashchynskyi and Liashchynskyi, 2019; Bergstra and Bengio, 2012). A model is trained for all the combinations of parameters within each grid, and the combination of parameters that leads to a model that generates the closest match between the simulated and empirical target features is identified as optimal. Two notable limitations of grid search are that it is computationally expensive, and it does not use information from past simulations in subsequent applications (e.g. if one parameter value was found to be suboptimal, it may still be used in following simulations if it is in another grid).

Random Search: Unlike the brute force approach of grid searching, in random search combinations of parameters are randomly selected as input to the model (Liashchynskyi and Liashchynskyi, 2019; Bergstra and Bengio, 2012). As in grid search, parameters generating a close match between the simulated and target feature are saved. Random search requires fewer computational resources than grid search, yet performance is equitable (Bergstra and Bengio, 2012).

Local Search: A loss function is defined as the difference between the experimental and simulated data obtained by the model. The aim of local search algorithms is to find the parameters that minimise this loss function; namely, to reduce to the minimum the difference between the simulated and experimental values. A commonly used local search algorithm is gradient descent (GD) (Ruder, 2016). GD is characterised by an iterative process in which the parameters p are updated gradually at each iteration. To find the minimum of the loss function $L(x)$, the algorithm calculates the gradient at each iteration, which corresponds to the partial derivative of the loss function with reference to each parameter's value $L(p)$. The gradient establishes the direction of the parameter's update, while its magnitude is commonly selected by the user through the learning rate and fine-tuned as hyper-parameter. Two limitations of GD are, however, that the function $L(p)$ needs to be differentiable and that GD tends to get stuck at local minimum. Furthermore, if multiple local minima are present, running the simulation with the same configuration might lead to different results, due to the random initialization of parameter values. An alternative to gradient descent is the Nelder-Mead simplex algorithm, which is a derivative-free local search algorithm (Nelder and Mead, 1965; Kangasrääsiö et al., 2019; Rios and Sahinidis, 2013). This algorithm represents the search area as a simplex with the number of points determined by the number of dimensions. At each iteration, the point of the simplex with the poorest performance is moved to a new position, resulting in a different simplex. This is repeated until a minimum is found. The algorithm, despite not requiring a derivable function, is computationally expensive at higher numbers of dimensions.

Global Search: Global search distinguishes itself from local search because it finds global minima across the entire parameter space. A commonly used global optimization approach is simulated annealing (SA) (Kirkpatrick et al., 1983; Bouleimen and Lecocq, 2003; Mollee et al., 2017). SA is a non-derivative approach that is capable of finding global minima in presence of multiple local minima. At each iteration, SA algorithms move in a random direction along the loss function, and then evaluate the results of the model. If the results improved from the previous iteration (i.e., the loss decreased), then the move is always approved. If not, the move is accepted with a certain probability lower than 1. The probability is regulated by both a parameter defined as Temperature *T*, which is kept high at the first iteration and then gradually reduced throughout iterations according to an annealing schedule, and the outcome after each move. At high temperatures, the probability of accepting a bad move is higher compared to lower temperatures. The advantages of this methodology are that it doesn't require the function to be derivable, it is capable to find global rather than local minima, and can be used both for discrete and continuous variables. It was successfully applied to fine tune parameters in other computational models (Mollee et al., 2017), and was shown to perform better than Nelder-Mead simplex algorithms (TÜRKŞEN and APAYDIN, 2013).

Conclusion

Creating computational models that are predictive, rather than descriptive, would enable a more efficient exploration of the effects of stimulation. In-silico stimulation studies would reduce the substantial time, human, and financial resources associated with a trial-and-error approach (Lozano et al., 2019), but until computational models of the effects of brain stimulation are effective at generating testable stimulation hypothesis, empirical research will remain the gold standard. This work began with the quote "All models are wrong, but some are useful" by George E. P. Box (1976). Yet without empirically testing the conclusions drawn from computational models of the effects of brain stimulation, we cannot answer Prof. Box's subsequent statement – "So the question you need to ask is not 'Is the model true?' (it never is) but 'Is the model good enough for this particular application?' " (Box et al., 2011).

Funding sources

D.K. was supported by the University of Surrey's Vice-Chancellor scholarship award, V.G. was supported by the NIHR Imperial Biomedical Research Centre (BRC) and I.R.V by the BBSRC (Ref: BB/S008314/1).

Author summary

Brain stimulation is an increasingly popular tool for both research and clinical use. However, its effects are not entirely known, and neither are the mechanisms by which brain stimulation changes brain activity. A tractable and efficient approach to investigate the effects of neuromodulation on brain function is to use computational models. These models allow researchers to run realistic simulations that show how the brain is influenced by neuromodulation or predict what effects stimulation will have on brain function and/or behavior. Here we introduce a general framework describing common model construction choices, and through a series of case studies show how models are used to investigate the effects of brain stimulation on brain function. We then suggest three steps future research can take to improve computational models' ability to generate testable predictions. We hope to make computational modelling more accessible by showing researchers the mathematics underpinning the models and how models are implemented in current research.

Data availability

No data was used for the research described in the article.

Credit authorship contribution statement

Danielle L. Kurtin: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Valentina Giunchiglia:** Writing – review & editing, Visualization. **Jakub Vohryzek:** Writing – review & editing. **Joana Cabral:** Writing – review & editing. **Anne C. Skeldon:** Supervision, Writing – original draft, Writing – review & editing. **Ines R. Violante:** Supervision, Writing – original draft, Writing – review & editing.

References

Arbabyazd, L., Shen, K., Wang, Z., Hofmann-Apitius, M., Ritter, P., McIntosh, A.R., Battaglia, D., Jirsa, V., Initiative, A.D.N., et al., 2021. Virtual connectomic datasets in alzheimer's disease and aging using whole-brain network dynamics modelling. bioRxiv. 2020–01

Baker, J.T., Dillon, D.G., Patrick, L.M., Roffman, J.L., Brady, R.O., Pizzagalli, D.A., Öngür, D., Holmes, A.J., 2019. Functional connectomics of affective and psychotic pathology. Proceedings of the National Academy of Sciences 116 (18), 9050–9059.

Bansal, K., Garcia, J.O., Tompson, S.H., Verstynen, T., Vettel, J.M., Muldoon, S.F., 2019. Cognitive chimera states in human brain networks. Science Advances 5 (4), eaau8535.

Bansal, K., Medaglia, J.D., Bassett, D.S., Vettel, J.M., Muldoon, S.F., 2018. Data-driven brain network models differentiate variability across language tasks. PLoS computational biology 14 (10), e1006487.

Bansal, K., Nakuci, J., Muldoon, S.F., 2018. Personalized brain network models for assessing structure–function relationships. Current Opinion in Neurobiology 52, 42–47.

Basser, P.J., Pajevic, S., Pierpaoli, C., Duda, J., Aldroubi, A., 2000. In vivo fiber tractography using dt-mri data. Magnetic Resonance in Medicine 44 (4), 625–632.

Battleday, R.M., Muller, T., Clayton, M.S., Cohen Kadosh, R., 2014. Mapping the mechanisms of transcranial alternating current stimulation: a pathway from network effects to cognition. Frontiers in psychiatry 162.

Bekar, L., Libionka, W., Tian, G.-F., Xu, Q., Torres, A., Wang, X., Lovatt, D., Williams, E., Takano, T., Schnermann, J., et al., 2008. Adenosine is crucial for deep brain stimulation–mediated attenuation of tremor. Nature Medicine 14 (1), 75–80.

Bergmann, T.O., Hartwigsen, G., 2020. Inferring causality from noninvasive brain stimulation in cognitive neuroscience. Journal of Cognitive Neuroscience 1–29.

Bergstra, J., Bengio, Y., 2012. Random search for hyper-parameter optimization. Journal of Machine Learning Research 13 (10), 281–305.

Bick, C., Goodfellow, M., Laing, C.R., Martens, E.A., 2020. Understanding the dynamics of biological and neural oscillator networks through exact mean-field reductions: a review. The Journal of Mathematical Neuroscience 10, 1–43.

Bouleimen, K., Lecocq, H., 2003. A new efficient simulated annealing algorithm for the resource-constrained project scheduling problem and its multiple mode version. European journal of operational research 149 (2), 268–281.

Box, G.E., 1976. Science and statistics. Journal of the American Statistical Association 71 (356), 791–799.

Box, G.E., Luceno, A., del Carmen Paniagua-Quinones, M., 2011. Statistical control by monitoring and adjustment, Vol. 700. John Wiley & Sons.

Bronstein, J.M., Tagliati, M., Alterman, R.L., Lozano, A.M., Volkmann, J., Stefani, A., Horak, F.B., Okun, M.S., Foote, K.D., Krack, P., et al., 2011. Deep brain stimulation for parkinson disease: an expert consensus and review of key issues. Archives of Neurology 68 (2). 165–165

Bystad, M., Grønli, O., Rasmussen, I.D., Gundersen, N., Nordvang, L., Wang-Iversen, H., Aslaksen, P.M., 2016. Transcranial direct current stimulation as a memory enhancer in patients with alzheimer's disease: a randomized, placebo-controlled trial. Alzheimer's research & therapy 8 (1), 1–7.

Caan, M.W., 2016. Dti analysis methods: fibre tracking and connectivity. In: Diffusion Tensor Imaging. Springer, pp. 205–228.

Cabral, J., Castaldo, F., Vohryzek, J., Litvak, V., Bick, C., Lambiotte, R., Friston, K., Kringelbach, M.L., Deco, G., 2022. Metastable oscillatory modes emerge from synchronization in the brain spacetime connectome. Communications Physics 5 (1), 1–13.

Cabral, J., Hugues, E., Sporns, O., Deco, G., 2011. Role of local network oscillations in resting-state functional connectivity. Neuroimage 57 (1), 130–139.

Cabral, J., Luckhoo, H., Woolrich, M., Joensson, M., Mohseni, H., Baker, A., Kringelbach, M.L., Deco, G., 2014. Exploring mechanisms of spontaneous functional connectivity in meg: how delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations. Neuroimage 90, 423–435.

Cabral, J., Vidaurre, D., Marques, P., Magalhães, R., Moreira, P.S., Soares, J.M., Deco, G., Sousa, N., Kringelbach, M.L., 2017. Cognitive performance in healthy older adults relates to spontaneous switching between states of functional connectivity during rest. Scientific Reports 7 (1), 1–13.

Cagnan, H., Brittain, J.-S., Little, S., Foltynie, T., Limousin, P., Zrinzo, L., Hariz, M., Joint, C., Fitzgerald, J., Green, A.L., et al., 2013. Phase dependent modulation of tremor amplitude in essential tremor through thalamic stimulation. Brain 136 (10), 3062–3075.

Cagnan, H., Pedrosa, D., Little, S., Pogosyan, A., Cheeran, B., Aziz, T., Green, A., Fitzgerald, J., Foltynie, T., Limousin, P., Zrinzo, L., Hariz, M., Friston, K.J., Denison, T., Brown, P., 2016. Stimulating at the right time: phase-specific deep brain stimulation. Brain 140 (1), 132–145. doi:10.1093/brain/aww286.

Cakan, C., Obermayer, K., 2020. Biophysically grounded mean-field models of neural populations under electrical stimulation. PLOS Computational Biology 16 (4), e1007822.

Caumo, W., Souza, I.C., Torres, I.L., Medeiros, L., Souza, A., Deitos, A., Vidor, L., Fregni, F., Volz, M.S., 2012. Neurobiological effects of transcranial direct current stimulation: a review. Frontiers in Psychiatry 3, 110.

Chen, C., Fang, Y., Wang, X., Bao, S.-C., Tang, Z., Tong, R.K.-y., 2019. Excitation comparison between multi-site stimulation using network-based tdcs and focal stimulation using high-definition tdcs. In: 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE, pp. 6884–6887.

Coffman, B.A., Clark, V.P., Parasuraman, R., 2014. Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. NeuroImage 85, 895–908.

Dagan, M., Herman, T., Harrison, R., Zhou, J., Giladi, N., Ruffini, G., Manor, B., Hausdorff, J.M., 2018. Multitarget transcranial direct current stimulation for freezing of gait in parkinson's disease. Movement Disorders 33 (4), 642–646.

Dai, X.-J., Liu, H., Yang, Y., Wang, Y., Wan, F., 2021. Brain network excitatory/inhibitory imbalance is a biomarker for drug-naive rolandic epilepsy: A radiomics strategy. Epilepsia.

Daneshzand, M., Faezipour, M., Barkana, B.D., 2017. Computational stimulation of the basal ganglia neurons with cost effective delayed gaussian waveforms. Frontiers in Computational Neuroscience 11, 73.

Daneshzand, M., Faezipour, M., Barkana, B.D., 2018. Robust desynchronization of parkinson's disease pathological oscillations by frequency modulation of delayed feedback deep brain stimulation. PLOS One 13 (11), e0207761.

Deco, G., Cruzat, J., Cabral, J., Knudsen, G.M., Carhart-Harris, R.L., Whybrow, P.C., Logothetis, N.K., Kringelbach, M.L., 2018. Whole-brain multimodal neuroimaging model using serotonin receptor maps explains non-linear functional effects of lsd. Current Biology 28 (19), 3065–3074.e6. doi:10.1016/j.cub.2018.07.083.

Deco, G., Cruzat, J., Cabral, J., Tagliazucchi, E., Laufs, H., Logothetis, N.K., Kringelbach, M.L., 2019. Awakening: Predicting external stimulation to force transitions between different brain states. Proceedings of the National Academy of Sciences 116 (36), 18088–18097.

Deco, G., Jirsa, V., McIntosh, A.R., Sporns, O., Kötter, R., 2009. Key role of coupling, delay, and noise in resting brain fluctuations. Proceedings of the National Academy of Sciences 106 (25), 10302–10307.

Deco, G., Jirsa, V.K., McIntosh, A.R., 2011. Emerging concepts for the dynamical organization of resting-state activity in the brain. Nature Reviews Neuroscience 12 (1), 43–56.

Deco, G., Kringelbach, M.L., Jirsa, V.K., Ritter, P., 2017. The dynamics of resting fluctuations in the brain: metastability and its dynamical cortical core. Scientific reports 7 (1), 1–14.

Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., et al., 2006. An automated labeling system for subdividing the human cerebral cortex on mri scans into gyral based regions of interest. NeuroImage 31 (3), 968–980.

Deuschl, G., Bergman, H., 2002. Pathophysiology of nonparkinsonian tremors. Movement Disorders 17 (S3), S41–S48.

Domhof, J.W., Eickhoff, S.B., Popovych, O.V., 2022. Reliability and subject specificity of personalized whole-brain dynamical models. NeuroImage 119321.

Dostrovsky, J.O., Lozano, A.M., 2002. Mechanisms of deep brain stimulation. Movement Disorders 17 (S3), S63–S68. doi:10.1002/mds.10143.

Farokhniaee, A., Lowery, M.M., 2021. Cortical network effects of subthalamic deep brain stimulation in a thalamo-cortical microcircuit model. Journal of Neural Engineering 18 (5), 056006.

Feigenbaum, M.J., 1978. Quantitative universality for a class of nonlinear transformations. Journal of Statistical Physics 19 (1), 25–52.

Fertonani, A., Miniussi, C., 2017. Transcranial electrical stimulation: what we know and do not know about mechanisms. The Neuroscientist 23 (2), 109–123.

Fischer, D.B., Fried, P.J., Ruffini, G., Ripolles, O., Salvador, R., Banus, J., Ketchabaw, W., Santarnecchi, E., Pascual-Leone, A., Fox, M.D., 2017. Multifocal tdcs targeting the resting state motor network increases cortical excitability beyond traditional tdcs targeting unilateral motor cortex. NeuroImage 157, 34–44.

Fulcher, B.D., Jones, N.S., 2017. hctsa: A computational framework for automated time-series phenotyping using massive feature extraction. Cell systems 5 (5), 527–531.

Fulcher, B.D., Little, M.A., Jones, N.S., 2013. Highly comparative time-series analysis: the empirical structure of time series and their methods. Journal of the Royal Society Interface 10 (83), 20130048.

Gangemi, A., Colombo, B., Fabio, R.A., 2021. Effects of short-and long-term neurostimulation (tdcs) on alzheimer's disease patients: two randomized studies. Aging Clinical and Experimental Research 33 (2), 383–390.

Giannakakis, E., Hutchings, F., Papasavvas, C.A., Han, C.E., Weber, B., Zhang, C., Kaiser, M., 2020. Computational modelling of the long-term effects of brain stimulation on the local and global structural connectivity of epileptic patients. PLOS One 15 (2), e0221380.

Graybiel, A.M., 2000. The basal ganglia. Current biology 10 (14), R509–R511.

Grossman, N., Bono, D., Dedic, N., Kodandaramaiah, S.B., Rudenko, A., Suk, H.-J., Cassara, A.M., Neufeld, E., Kuster, N., Tsai, L.-H., et al., 2017. Noninvasive deep brain stimulation via temporally interfering electric fields. cell 169 (6), 1029–1041.

Gu, S., Pasqualetti, F., Cieslak, M., Telesford, Q.K., Alfred, B.Y., Kahn, A.E., Medaglia, J.D., Vettel, J.M., Miller, M.B., Grafton, S.T., et al., 2015. Controllability of structural brain networks. Nature Communications 6 (1), 1–10.

Gubellini, P., Salin, P., Kerkerian-Le Goff, L., Baunez, C., 2009. Deep brain stimulation in neurological diseases and experimental models: from molecule to complex behavior. Progress in Neurobiology 89 (1), 79–123.

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

Herrington, T.M., Cheng, J.J., Eskandar, E.N., 2016. Mechanisms of deep brain stimulation. Journal of Neurophysiology 115 (1), 19–38.

Hill, A.T., Rogasch, N.C., Fitzgerald, P.B., Hoy, K.E., 2018. Effects of single versus dual-site high-definition transcranial direct current stimulation (hd-tdcs) on cortical reactivity and working memory performance in healthy subjects. Brain Stimulation 11 (5), 1033–1043.

Hillyard, S.A., Vogel, E.K., Luck, S.J., 1998. Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 353 (1373), 1257–1270.

Hong, S.-J., De Wael, R.V., Bethlehem, R.A., Lariviere, S., Paquola, C., Valk, S.L., Milham, M.P., Di Martino, A., Margulies, D.S., Smallwood, J., et al., 2019. Atypical functional connectome hierarchy in autism. Nature Communications 10 (1), 1–13.

Horvath, J.C., Forte, J.D., Carter, O., 2015. Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tdcs). Brain Stimulation 8 (3), 535–550.

Hurley, R., Machado, L., 2017. Using tdcs priming to improve brain function: Can metaplasticity provide the key to boosting outcomes? Neuroscience & Biobehavioral Reviews 83, 155–159.

Janicak, P.G., Nahas, Z., Lisanby, S.H., Solvason, H.B., Sampson, S.M., McDonald, W.M., Marangell, L.B., Rosenquist, P., McCall, W.V., Kimball, J., et al., 2010. Durability of clinical benefit with transcranial magnetic stimulation (tms) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. Brain stimulation 3 (4), 187–199.

Jia, W., Zhu, H., Ni, Y., Su, J., Xu, R., Jia, H., Wan, X., 2020. Disruptions of frontoparietal control network and default mode network linking the metacognitive deficits with clinical symptoms in schizophrenia. Human Brain Mapping 41 (6), 1445–1458.

Jobst, B.M., Hindriks, R., Laufs, H., Tagliazucchi, E., Hahn, G., Ponce-Alvarez, A., Stevner, A.B.A., Kringelbach, M.L., Deco, G., 2017. Increased stability and breakdown of brain effective connectivity during slow-wave sleep: Mechanistic insights from whole-brain computational modelling. Scientific Reports 7 (11), 4634. doi:10.1038/s41598-017-04522-x.

Johansson, J.D., Alonso, F., Wårdell, K., 2019. Modelling details for electric field simulations of deep brain stimulation. In: World Congress on Medical Physics and Biomedical Engineering 2018. Springer, pp. 645–648.

Kalman, R., Ho, Y., Narendra, K., 1963. Controllability of linear dynamical systems.

Kangasrääsiö, A., Jokinen, J.P., Oulasvirta, A., Howes, A., Kaski, S., 2019. Parameter inference for computational cognitive models with approximate bayesian computation. Cognitive science 43 (6), e12738.

Khodashenas, M., Baghdadi, G., Towhidkhah, F., 2019. A modified hodgkin–huxley model to show the effect of motor cortex stimulation on the trigeminal neuralgia network. The Journal of Mathematical Neuroscience 9 (1), 1–23.

Kierońska, S., Słoniewski, P., 2020. The usefulness and limitations of diffusion tensor imaging–a review study. European Journal of Translational and Clinical Medicine 2 (2), 43–51.

Kim, J., Robinson, P., 2008. Controlling limit-cycle behaviors of brain activity. Physical Review E 77 (5), 051914.

Kirkpatrick, S., Gelatt Jr, C.D., Vecchi, M.P., 1983. Optimization by simulated annealing. science 220 (4598), 671–680.

Klimesch, W., 1999. Eeg alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Research Reviews 29 (2-3), 169–195.

Kohl, S., Schönherr, D.M., Luigjes, J., Denys, D., Mueller, U.J., Lenartz, D., Visser-Vandewalle, V., Kuhn, J., 2014. Deep brain stimulation for treatment-refractory obsessive compulsive disorder: a systematic review. BMC Psychiatry 14 (1), 214.

Kurtin, D.L., Violante, I.R., Zimmerman, K., Leech, R., Hampshire, A., Patel, M.C., Carmichael, D.W., Sharp, D.J., Li, L.M., 2021. Investigating the interaction between white matter and brain state on tdcs-induced changes in brain network activity. Brain Stimulation 14 (5), 1261–1270.

Landau, L.D., 1944. On the problem of turbulence. In: Dokl. Akad. Nauk USSR, Vol. 44, p. 311.

Lee, S., Lee, C., Park, J., Im, C.-H., 2020. Individually customized transcranial temporal interference stimulation for focused modulation of deep brain structures: a simulation study with different head models. Scientific reports 10 (1), 1–11.

Li, F., Lu, L., Shang, S., Hu, L., Chen, H., Wang, P., Zhang, H., Chen, Y.-C., Yin, X., 2020. Disrupted functional network connectivity predicts cognitive impairment after acute mild traumatic brain injury. CNS Neuroscience & Therapeutics 26 (10), 1083–1091.

Li, L.M., Uehara, K., Hanakawa, T., 2015. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Frontiers in Cellular Neuroscience 9, 181.

Li, L.M., Violante, I.R., Leech, R., Ross, E., Hampshire, A., Opitz, A., Rothwell, J.C., Carmichael, D.W., Sharp, D.J., 2019. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Human Brain Mapping 40 (3), 904–915.

Li, L.M., Violante, I.R., Zimmerman, K., Leech, R., Hampshire, A., Patel, M., Opitz, A., McArthur, D., Jolly, A., Carmichael, D.W., et al., 2019. Traumatic axonal injury influences the cognitive effect of non-invasive brain stimulation. Brain 142 (10), 3280–3293.

Liashchynskyi, P., Liashchynskyi, P., 2019. Grid search, random search, genetic algorithm: a big comparison for nas. arXiv preprint arXiv:1912.06059.

Limousin, P., Foltynie, T., 2019. Long-term outcomes of deep brain stimulation in parkinson disease. Nature Reviews Neurology 15 (4), 234–242.

Lin, R.L., Douaud, G., Filippini, N., Okell, T.W., Stagg, C.J., Tracey, I., 2017. Structural connectivity variances underlie functional and behavioral changes during pain relief induced by neuromodulation. Scientific Reports 7 (1), 1–14.

Little, S., Brown, P., 2012. What brain signals are suitable for feedback control of deep

brain stimulation in parkinson's disease? Annals of the New York Academy of Sciences 1265, 9–24.
Liu, X., Jiang, W., Yuan, Y., 2018. Aberrant default mode network underlying the cognitive deficits in the patients with late-onset depression. Frontiers in Aging Neuroscience 10, 310.
Lozano, A.M., Lipsman, N., Bergman, H., Brown, P., Chabardes, S., Chang, J.W., Matthews, K., McIntyre, C.C., Schlaepfer, T.E., Schulder, M., et al., 2019. Deep brain stimulation: current challenges and future directions. Nature Reviews Neurology 15 (3), 148–160.
Lüders, E., Steinmetz, H., Jäncke, L., 2002. Brain size and grey matter volume in the healthy human brain. Neuroreport 13 (17), 2371–2374.
Meier, J.M., Perdikis, D., Blickensdörfer, A., Stefanovski, L., Liu, Q., Maith, O., Dinkelbach, H.Ü., Baladron, J., Hamker, F.H., Ritter, P., 2022. Virtual deep brain stimulation: Multiscale co-simulation of a spiking basal ganglia model and a whole-brain mean-field model with the virtual brain. Experimental Neurology 114111.
Menardi, A., Momi, D., Vallesi, A., Barabási, A.-L., Towlson, E.K., Santarnecchi, E., 2022. Maximizing brain networks engagement via individualized connectome-wide target search. Brain Stimulation 15 (6), 1418–1431.
Metwally, M.K., Cho, Y.S., Park, H.-J., Kim, T.-S., 2012. Investigation of the electric field components of tdcs via anisotropically conductive gyri-specific finite element head models. In: 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE, pp. 5514–5517.
Miniussi, C., Ruzzoli, M., Walsh, V., 2010. The mechanism of transcranial magnetic stimulation in cognition. Cortex 46 (1), 128–130.
Mohan, U.R., Watrous, A.J., Miller, J.F., Lega, B.C., Sperling, M.R., Worrell, G.A., Gross, R.E., Zaghloul, K.A., Jobst, B.C., Davis, K.A., et al., 2020. The effects of direct brain stimulation in humans depend on frequency, amplitude, and white-matter proximity. Brain stimulation 13 (5), 1183–1195.
Mollee, J.S., Araújo, E.F., Klein, M.C., 2017. Exploring parameter tuning for analysis and optimization of a computational model. In: International Conference on Industrial, Engineering and Other Applications of Applied Intelligent Systems. Springer, pp. 341–352.
Muldoon, S.F., Pasqualetti, F., Gu, S., Cieslak, M., Grafton, S.T., Vettel, J.M., Bassett, D.S., 2016. Stimulation-based control of dynamic brain networks. PLOS Computational Biology 12 (9).
Murray, J.D., Demirtaş, M., Anticevic, A., 2018. Biophysical modeling of large-scale brain dynamics and applications for computational psychiatry. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 3 (9), 777–787.
Muthuraman, M., Bange, M., Koirala, N., Ciolac, D., Pintea, B., Glaser, M., Tinkhauser, G., Brown, P., Deuschl, G., Groppa, S., 2020. Cross-frequency coupling between gamma oscillations and deep brain stimulation frequency in parkinson's disease. Brain 143 (11), 3393–3407.
Nelder, J.A., Mead, R., 1965. A simplex method for function minimization. The computer journal 7 (4), 308–313.
Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of Physiology 527 (3), 633–639.
Nowak, L., Bullier, J., 1998. Axons, but not cell bodies, are activated by electrical stimulation in cortical gray matter i. evidence from chronaxie measurements. Experimental brain research 118 (4), 477–488.
Ostrem, J.L., Markun, L.C., Glass, G.A., Racine, C.A., Volz, M.M., Heath, S.L., de Hemptinne, C., Starr, P.A., 2014. Effect of frequency on subthalamic nucleus deep brain stimulation in primary dystonia. Parkinsonism & Related Disorders 20 (4), 432–438.
Ott, E., Antonsen, T.M., 2008. Low dimensional behavior of large systems of globally coupled oscillators. Chaos: An Interdisciplinary Journal of Nonlinear Science 18 (3), 037113.
Padmanabhan, A., Lynch, C.J., Schaer, M., Menon, V., 2017. The default mode network in autism. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2 (6), 476–486.
Palm, E., 1960. On the tendency towards hexagonal cells in steady convection. Journal of Fluid Mechanics 8 (2), 183–192.
Papasavvas, C.A., Wang, Y., Trevelyan, A.J., Kaiser, M., 2015. Gain control through divisive inhibition prevents abrupt transition to chaos in a neural mass model. Physical Review E 92 (3), 032723.
Petrov, P.I., Mandija, S., Sommer, I.E., Van Den Berg, C.A., Neggers, S.F., 2017. How much detail is needed in modeling a transcranial magnetic stimulation figure-8 coil: Measurements and brain simulations. PLOS One 12 (6), e0178952.
Peuskens, H., 2004. Complex Motion Processing in the Human Cerebral Cortex as Studied by Functional Imaging, Vol. 324. Leuven University Press.
Polania, R., Nitsche, M.A., Ruff, C.C., 2018. Studying and modifying brain function with non-invasive brain stimulation. Nature Neuroscience 21 (2), 174–187.
Pouille, F., Watkinson, O., Scanziani, M., Trevelyan, A.J., 2013. The contribution of synaptic location to inhibitory gain control in pyramidal cells. Physiological Reports 1 (5).
Pycroft, L., Stein, J., Aziz, T., 2018. Deep brain stimulation: An overview of history, methods, and future developments. Brain and Neuroscience Advances 2. doi:10.1177/2398212818816017. 2398212818816017
Reed, T., Kadosh, R.C., 2018. Transcranial electrical stimulation (tes) mechanisms and its effects on cortical excitability and connectivity. Journal of Inherited Metabolic Disease 41 (6), 1123–1130.
Ressel, V., Van Hedel, H.J., Scheer, I., Tuura, R.O., 2018. Comparison of dti analysis methods for clinical research: influence of pre-processing and tract selection methods. European radiology experimental 2 (1), 1–12.
Rios, L.M., Sahinidis, N.V., 2013. Derivative-free optimization: a review of algorithms and comparison of software implementations. Journal of Global Optimization 56 (3), 1247–1293.
Rosin, B., Slovik, M., Mitelman, R., Rivlin-Etzion, M., Haber, S.N., Israel, Z., Vaadia, E., Bergman, H., 2011. Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. Neuron 72 (2), 370–384.
Ruder, S., 2016. An overview of gradient descent optimization algorithms. arXiv preprint arXiv:1609.04747.
Salo, T., Yarkoni, T., Nichols, T.E., Poline, J.-B., Bilgel, M., Bottenhorn, K.L., Jarecka, D., Kent, J.D., Kimbler, A., Nielson, D.M., Oudyk, K.M., Peraza, J.A., Pérez, A., Reeders, P.C., Yanes, J.A., Laird, A.R., 2022. Nimare: Neuroimaging meta-analysis research environment. NeuroLibre 1 (1), 7. doi:10.55458/neurolibre.00007.
Sanz Leon, P., Knock, S.A., Woodman, M.M., Domide, L., Mersmann, J., McIntosh, A.R., Jirsa, V., 2013. The virtual brain: a simulator of primate brain network dynamics. Frontiers in Neuroinformatics 7, 10.
Saris, I.M., Aghajani, M., Reus, L.M., Visser, P.-J., Pijnenburg, Y., van der Wee, N.J., Bilderbeck, A.C., Raslescu, A., Malik, A., Mennes, M., et al., 2021. Social dysfunction is transdiagnostically associated with default mode network dysconnectivity in schizophrenia and alzheimer's disease. The World Journal of Biological Psychiatry 1–32.
Saturnino, G.B., Madsen, K.H., Thielscher, A., 2019. Efficient electric field simulations for transcranial brain stimulation. bioRxiv 541409.
Schwartz, O., Simoncelli, E.P., 2001. Natural signal statistics and sensory gain control. Nature Neuroscience 4 (8), 819–825.
Shahid, S., Wen, P., Ahfock, T., 2013. Numerical investigation of white matter anisotropic conductivity in defining current distribution under tdcs. Computer methods and programs in biomedicine 109 (1), 48–64.
Shen, X., Tokoglu, F., Papademetris, X., Constable, R.T., 2013. Groupwise whole-brain parcellation from resting-state fmri data for network node identification. NeuroImage 82, 403–415.
Smith, R.X., Jann, K., Dapretto, M., Wang, D.J., 2018. Imbalance of functional connectivity and temporal entropy in resting-state networks in autism spectrum disorder: a machine learning approach. Frontiers in Neuroscience 12, 869.
Soreq, E., Leech, R., Hampshire, A., 2019. Dynamic network coding of working-memory domains and working-memory processes. Nature Communications 10 (1), 1–14.
Stephens, J.A., Salorio, C.F., Barber, A.D., Risen, S.R., Mostofsky, S.H., Suskauer, S.J., 2018. Preliminary findings of altered functional connectivity of the default mode network linked to functional outcomes one year after pediatric traumatic brain injury. Developmental Neurorehabilitation 21 (7), 423–430.
Strogatz, S.H., 2000. From kuramoto to crawford: exploring the onset of synchronization in populations of coupled oscillators. Physica D: Nonlinear Phenomena 143 (1-4), 1–20.
Stuart, J., 1960. On the non-linear mechanics of wave disturbances in stable and unstable parallel flows part 1. the basic behaviour in plane poiseuille flow. Journal of Fluid Mechanics 9 (3), 353–370.
Suweis, S., Tu, C., Rocha, R.P., Zampieri, S., Zorzi, M., Corbetta, M., 2019. Brain controllability: Not a slam dunk yet. NeuroImage 200, 552–555.
Tang, E., Bassett, D.S., 2018. Colloquium: Control of dynamics in brain networks. Reviews of Modern Physics 90 (3), 031003.
Terao, Y., Ugawa, Y., 2002. Basic mechanisms of tms. Journal of Clinical Neurophysiology 19 (4), 322–343.
Triebkorn, P., Zimmermann, J., Stefanovski, L., Roy, D., Solodkin, A., Jirsa, V., Deco, G., Breakspear, M., McIntosh, A.R., Ritter, P., 2020. Identifying optimal working points of individual virtual brains: A large-scale brain network modelling study. BioRxiv.
TÜRKŞEN, Ö., APAYDIN, A., 2013. Estimating the earthquake source parameters: Simulated annealing versus nelder-mead simplex algorithm. Communications Faculty of Sciences University of Ankara Series A1 Mathematics and Statistics 62 (2), 53–66.
Uddin, R., Dorning, J., 1986. Some nonlinear dynamics of a heated channel. Nuclear Engineering and Design 93 (1), 1–14.
Villamar, M.F., Volz, M.S., Bikson, M., Datta, A., DaSilva, A.F., Fregni, F., 2013. Technique and considerations in the use of 4x1 ring high-definition transcranial direct current stimulation (hd-tdcs). JoVE (Journal of Visualized Experiments) (77) e50309.
Violante, I.R., Alania, K., Cassara, A.M., Neufeld, E., Acerbo, E., Carron, R., Williamson, A., Kurtin, D.L., Rhodes, E., Hampshire, A., et al., 2022. Non-invasive temporal interference electrical stimulation of the human hippocampus. bioRxiv.
Vohryzek, J., Cabral, J., Lord, L.-D., Fernandes, H.M., Roseman, L., Nutt, D.J., Carhart-Harris, R.L., Deco, G., Kringelbach, M.L., 2022. Brain dynamics predictive of response to psilocybin for treatment-resistant depression. biorxiv doi:10.1101/2022.06.30.497950. 2022.06.30.497950
Wagner, T., Valero-Cabre, A., Pascual-Leone, A., 2007. Noninvasive human brain stimulation. Annual Review Biomedical Engineering 9, 527–565.
Warren, K.N., Hermiller, M.S., Nilakantan, A.S., Voss, J.L., 2019. Stimulating the hippocampal posterior-medial network enhances task-dependent connectivity and memory. ELife 8, e49458.
Watanabe, H., Bagarinao, E., Maesawa, S., Hara, K., Kawabata, K., Ogura, A., Ohdake, R., Shima, S., Mizutani, Y., Ueda, A., et al., 2021. Characteristics of neural network changes in normal aging and early dementia. Frontiers in Aging Neuroscience 13, 747359.
Watson, J., 1960. On the nonlinear mechanics of wave disturbances in stable and unstable parallel flows. Journal of Fluid Mechanics 9 (371-389), 219.
Weerasinghe, G., Duchet, B., Cagnan, H., Brown, P., Bick, C., Bogacz, R., 2019. Predicting the effects of deep brain stimulation using a reduced coupled oscillator model. PLOS Computational Biology 15 (8), e1006575.
West, T.O., Farmer, S.F., Magill, P.J., Sharott, A., Litvak, V., Cagnan, H., 2020. State dependent beta oscillations in the cortico-basal ganglia circuit and their neuromodulation under phase-locked inputs. BioRxiv.
Wilson, H.R., Cowan, J.D., 1972. Excitatory and inhibitory interactions in localized populations of model neurons. Biophysical Journal 12 (1), 1–24.
Wilson, N.R., Runyan, C.A., Wang, F.L., Sur, M., 2012. Division and subtraction by distinct cortical inhibitory networks in vivo. Nature 488 (7411), 343–348.

Witt, S.T., Drissi, N.M., Tapper, S., Wretman, A., Szakács, A., Hallböök, T., Landtblom, A.-M., Karlsson, T., Lundberg, P., Engström, M., 2018. Evidence for cognitive resource imbalance in adolescents with narcolepsy. Brain Imaging and Behavior 12 (2), 411–424.

Woods, A.J., Antal, A., Bikson, M., Boggio, P.S., Brunoni, A.R., Celnik, P., Cohen, L.G., Fregni, F., Herrmann, C.S., Kappenman, E.S., et al., 2016. A technical guide to tdcs, and related non-invasive brain stimulation tools. Clinical Neurophysiology 127 (2), 1031–1048.

Woytowicz, E.J., Sours, C., Gullapalli, R.P., Rosenberg, J., Westlake, K.P., 2018. Modulation of working memory load distinguishes individuals with and without balance impairments following mild traumatic brain injury. Brain Injury 32 (2), 191–199.

Xia, M., Wang, J., He, Y., 2013. Brainnet viewer: a network visualization tool for human brain connectomics. PLOS One 8 (7), e68910.

Yamada, Y., Sumiyoshi, T., 2021. Neurobiological mechanisms of transcranial direct current stimulation for psychiatric disorders; neurophysiological, chemical, and anatomical considerations. Frontiers in Human Neuroscience 15, 631838.

Yu, S., Guo, B., Shen, Z., Wang, Z., Kui, Y., Hu, Y., Feng, F., 2018. The imbalanced anterior and posterior default mode network in the primary insomnia. Journal of Psychiatric Research 103, 97–103.

Zhang, F., Wu, W., Ning, L., McAnulty, G., Waber, D., Gagoski, B., Sarill, K., Hamoda, H.M., Song, Y., Cai, W., et al., 2018. Suprathreshold fiber cluster statistics: Leveraging white matter geometry to enhance tractography statistical analysis. NeuroImage 171, 341–354.