CHAPTER

# 7 Dynamic brain network models: How interactions in the structural connectome shape brain dynamics

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## Introduction to dynamic brain network models

Dynamic brain network models come in many different forms, ranging from highly abstract mathematical models to moderately detailed and biologically realistic simulations of interacting neuronal populations. They can be used to explore a wide range of questions, from the basic principles of macroscale organization such as collective brain rhythms, to the prediction of therapeutic outcomes following clinical interventions such as (invasive or noninvasive) neurostimulation, surgery, and drugs.

The main theoretical context for brain network models consists in the fact that brain areas do not work in isolation but are embedded in a network, and the activity in a given brain area is affected by the activity of the brain regions to which it is coupled. These in turn are also coupled to other brain regions, and so it is crucial to consider the entire brain even when investigating the function of a specific brain region (Sporns and Tononi, 2001). In other words, neuroscientists face a version of the so-called "N-body problem," which lies at the foundations of complexity science and chaos theory, for which exact mathematical solutions cannot be adequately obtained, and henceforth, computer simulations are a powerful tool to investigate the complex behavior of interacting units. Indeed, the simulated dynamics resulting from brain network models link directly with studies describing interesting dynamic phenomena occurring in complex networks, irrespective of their scale and nature (Boccaletti et al., 2006; Newman et al., 2006; Arenas et al., 2006; Yeung and Strogatz, 1999).



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Generally, a brain network model is a system of interacting dynamical units, each representing a distinct brain subsystem, coupled together according to a specific wiring diagram representing the axonal tracts that physically connect brain subsystems together. Brain network models were introduced in the first decade of the 21st century, first using the wiring diagram obtained from ex vivo tracing studies of one hemisphere of the macaque brain (Kötter, 2004), and rapidly extended to humans following the development of in vivo human tractography studies using diffusion MRI, providing the so-called structural connectome (Hagmann et al., 2008), see (Griffiths et al., 2022).

Over the years, brain network models have evolved in two primary and divergent directions. On the one hand, mechanistic models aim to identify essential properties and fundamental mechanisms that give rise to observed patterns. This is usually achieved by replicating with a minimal number of variables certain qualitative features of brain activity such as long-range correlations, plasticity mechanisms, collective brain rhythms, nonstationary dynamics, or transitions between different brain states. On the other hand, predictive models focus on enhancing the fit with recorded data by refining parameters and increasing biophysical realism, opening the door for personalized planning of therapeutic interventions.

Although brain network models can vary substantially in terms of biological realism, spatial scale, and assumptions, they are generally built by specifying the following three ingredients:

I. The *local dynamics* at the network nodes, which can exhibit fixed point, oscillatory, or chaotic equilibria with varying degrees of biochemical and biophysical realism and heterogeneity.
II. The *coupling function*, which defines how each node responds to the activity of the nodes coupled to it, considers for instance, excitatory or diffusive coupling, and includes or neglects the time delays between nodes.
III. The *connectivity matrix*, which defines the wiring diagram of the network, weighs each link as a function of the structural neuroanatomical connections detected between each pair of brain areas.

In the following sections, we provide an overview of the main distinct models that have been proposed in the field, highlighting the insights they have brought to neuroscience. In addition to exploring the nontrivial link between structural and functional connectivity, these models have been used to better understand the self-organizing principles of brain activity at the macroscale, the differentiating factors across brain states, and ultimately their value for personalized planning of surgical or pharmacological interventions (Vohryzek et al., 2022; Kurtin et al., 2023; Lang et al., 2023) (Fig. 1).

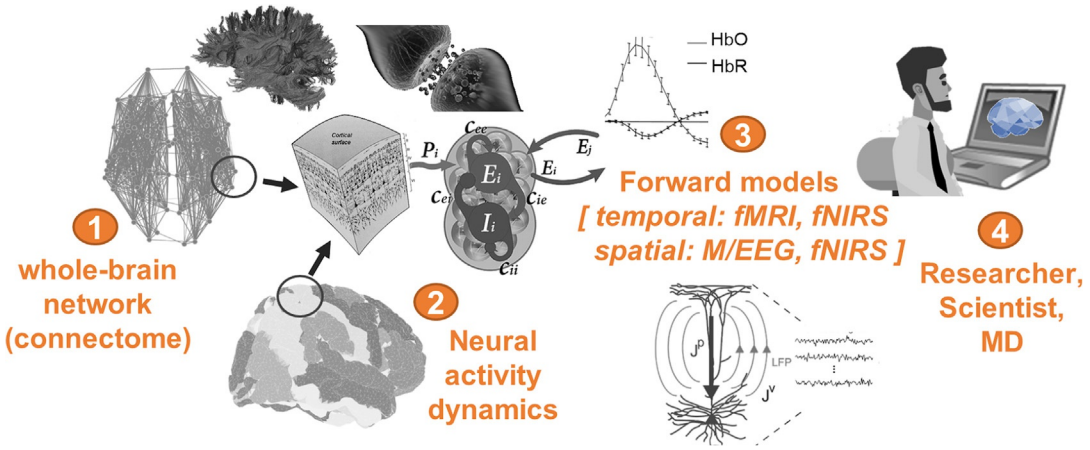



**FIG. 1**

Brain network modeling schematic. (1) Whole-brain activity is modeled with a large-scale brain network (anatomical connectome), with nodes representing brain regions and edges representing long-range white matter fiber tracts. (2) Neural activity dynamics at each network node is described by a mesoscopic neural model, summarizing local cortical microcircuitry in terms of, for example, interacting excitatory and inhibitory neural populations. (3) Hemodynamic and electromagnetic signals generated by local neural activity are mapped on to channel-level measurements via spatial (M/EEG $\geq$ Maxwell equations + electromagnetic sensitivity matrix), temporal (fMRI $\geq$ Balloon-Windkessel model), or spatiotemporal (fNIRS fDOT $\geq$ balloon + optical sensitivity matrix) measurement models. (4) Modeler/research scientist/clinician end-user uses the above process (technically or nontechnically presented, as needed) to generate personalized brain simulations and to estimate brain state and physiological parameters from neuroimaging and neurophysiology measurements.

## Examples of dynamic brain network models

### Emergence of correlated brain activity patterns in the resting state

In the advent of brain Connectomics research, one crucial question concerned whether the long-range correlations detected in fMRI signals between brain areas (Biswal et al., 1995)—generally referred to as functional connectivity—could be directly related to neuroanatomical connectivity. Christopher Honey, Olaf Sporns, Patrick Hagmann, and colleagues (Honey et al., 2009) used the by-then recently-available whole-brain structural connectome obtained from applying advanced tractography algorithms to in vivo diffusion-weighted MRI from humans. Honey et al. (2009) demonstrated that, despite the differences between structural and functional connectivity maps, human resting-state functional connectivity could be predicted from structural connectivity using a dynamic brain network model. Interestingly, comparable performance in reconstructing fMRI functional connectivity was observed in models with rich (nonlinear chaotic) local dynamics and models with simpler (linear) local dynamics—an unexpected result that has been repeatedly confirmed in subsequent studies over the past decade (Cabral et al., 2011; Hansen et al., 2015; Deco et al., 2017).

Until then, previous dynamic brain network models had used a connectome obtained from a collection of ex vivo tracing studies on the macaque brain, termed CoCoMac (Stephan et al., 2001; Kötter, 2004), which had served to demonstrate how the specific network topology of the mammalian brain could shape brain activity in space and time, as previously hypothesized and mimicked using synthetic network topologies ( Jirsa, 2004). Although not directly comparing with fMRI functional connectivity, the simulations on the CoCoMac network were relevant to put forward the key role of the connectivity structure and the time delays between brain regions in shaping slow and macroscale spatiotemporal patterns in brain dynamics (Honey et al., 2007; Ghosh et al., 2008a,b; Deco et al., 2009).

Dynamic brain network models have served to demonstrate how the transient correlations observed in resting-state fMRI—usually referred to as dynamic functional connectivity—can be linked to metastable synchronization between brain regions, a phenomenon observed in systems of coupled oscillators in nature. Adapting the Kuramoto model of coupled oscillators (Kuramoto, 1984; Acebrón et al., 2005) to incorporate realistic coupling weights and time delays between brain areas, simulations revealed a critical range of coupling and delays, where the system is positioned between incoherence and synchrony, with subsets of nodes transiently synchronizing and desynchronizing even in the absence of noise (Cabral et al., 2011). During periods of transient synchrony, a collective slowdown in the frequency of oscillations generates correlated amplitude fluctuations, which could explain the slow and spatiotemporally organized fluctuations detected in EEG/MEG (Cabral et al., 2014). This mechanism was later demonstrated to be

robust in more realistic settings, i.e., by replacing phase oscillators with damped oscillators or even Wilson-Cowan units (Cabral et al., 2022; Castaldo et al., 2023). The switching behavior of functional connectivity over time has also been reproduced using a brain network model without time delays, by placing in each node a variant of the "dynamic mean field" model (Wong and Wang, 2006; Deco et al., 2013), minimally modified to introduce bi-stability between high and low firing rate states (Hansen et al., 2015). This approach enhanced the dynamic repertoire of the whole-brain model, leading to spontaneous switching between functional connectivity states, which shared qualitative features with known resting state networks.

Traveling waves and spiral waves have also been shown to emerge spontaneously from a brain network model of coupled neural masses, demonstrating that metastability and waves are compatible dynamical regimes that can be explained with a unified mechanism (Roberts et al., 2019). For a critical value of coupling weight between brain areas, a rich array of three-dimensional wave patterns could be observed even in the absence of noise, with nonlinear instabilities driving constant reconfigurations of underlying phase flows.

It is also important to note that some features of the signals simulated using brain network models can be solved analytically from the model equations without the need to numerically simulate the network behavior in a computer. Resting-state networks observed in fMRI signals have been shown to be predicted from the brain network structure using established algebraic expressions for the steady-state correlation structure of a discrete- or continuous-time linear system given its connectivity matrix (e.g., Honey et al., 2009; Robinson, 2012; Deco et al., 2013) or its connectivity Laplacian (Atasoy et al., 2016; Abdelnour et al., 2018). Additionally, incorporating time delays in these linear equations improves the detection of canonical functional networks (Xie et al., 2021). These studies provide supporting evidence that the brain network structure plays a key role in shaping the emergence of functional networks observed with fMRI, and furthermore that "slow" features of resting-state dynamics such as static long-term correlation patterns are not as dependent as faster time-varying features on the dynamical richness introduced by nonlinearity, time delays, and metastability.

## Perturbation with electrical/magnetic/acoustic/optical stimulation

In both experimental and clinical contexts, electromagnetic stimulation techniques such as transcranial magnetic stimulation (TMS), transcranial electrical stimulation (TES), and deep brain stimulation (DBS) are commonly employed in an attempt to characterize and modulate neural activity.

Therapeutically, neurostimulation paradigms are highly successful in some conditions (e.g., DBS for tremor in Parkinson's disease) but only moderately effective in

others (e.g., TMS and DBS for major depressive disorder). Part of the reason limiting the success of brain stimulation therapies can be attributed to a lack of comprehensive mechanistic understanding, compounded by a multitude of potential combinations of stimulation parameters, such as location, frequency, duration, and voltage, that cannot be iteratively tested in vivo due to ethical constraints. Brain network models offer the opportunity to test this extensive array of stimulation parameters and predict its impact on brain signals. However, the effectiveness of planning stimulation in a model depends on its alignment with the biophysical reality, on an adequate description of heterogeneous neural processes, and on how the neuroanatomy and other physiological processes configure the collective dynamics (Kurtin et al., 2023; Vohryzek et al., 2023).

Brain stimulation paradigms, across all invasive and noninvasive modalities, can be broadly classified into two general types: immediate effects and persistent effects. Immediate effects are brain activity changes observed either during a block of sustained repetitive stimulation (steady-state response) or as a transient following a single stimulation pulse (evoked response). Persistent effects are responses that are visible minutes, hours, or days after cessation of the input stimuli and are thus, by definition, instances of stimulation-induced neural plasticity, which at the level of synaptic weights may be positive (long-term potentiation; LTP) or negative (long-term depression; LTD). The majority of brain network modeling work in this area has focused on immediate stimulation effects, leaving the investigation of enduring LTP/LTD effects relatively underexplored.

A notable line of work exploring immediate stimulation effects has been led by Spiegler and colleagues (Fig. 2C), who investigated this using brain network models in the human (Spiegler et al., 2016) and mouse brain (Spiegler et al., 2020). The latter of these is particularly notable due to its use of extremely high-quality and rarely-used experimental data, high-resolution and "ground-truth" anatomical connectivity data (Allen Mouse Brain Atlas) and whole-cortex wide-field calcium imaging of neural activity, both of which allow superior spatial and temporal resolution than the noninvasive methods used in humans. Two key questions of interest in this work were: (a) the balance between local (cortical neural field) vs long-range (white matter) connectivity and (b) whether canonical ("dynamically responsive") resting-state networks could be evoked by stimulation at multiple cortical locations. To study these relationships, brain network models with Fitzhugh-Nagumo equations for local dynamics were developed, and tens of thousands of in silico stimulation experiments were performed, an exercise that would be completely infeasible to undertake experimentally. The conclusions are broadly similar in the human and mouse studies, that a set of "dynamically responsive networks," closely resembling resting state networks seen in resting-state functional connectivity, are observable in stimulation-evoked responses for a wide variety of stimulus locations.

Focusing more specifically on established immediate stimulation effects in humans, Bensaid et al. (2019) used brain network modeling to demonstrate how the modulation of thalamo-cortical connectivity could explain differences in the TMS-evoked potential (TEP) EEG response during wakefulness vs sleep or vs patients with disorders of consciousness. In related work, Momi et al. (2023) studied the role of recurrent feedback in shaping specific aspects of the TEP waveform (Fig. 2A). Using a brain network model with tractography-based anatomical connectivity and Jansen-Rit cortical units, these authors demonstrated that the N100 component within the TEP is heavily dependent on recurrent activity reverberating across the connectome network away from, and then re-converging on, the stimulated region. The magnitude of this canonical brain stimulation response was also found to be strongly influenced by the level of inhibitory feedback within the cortical circuit. This study is also notable as it demonstrated the feasibility of fitting whole-brain network models to subject-specific TEP waveforms, employing a novel machine learning-based parameter estimation approach. Earlier work from the same authors (Griffiths and Lefebvre, 2019; Griffiths et al., 2020) examined immediate steady-state stimulation responses to periodic drive. Using a model of resting-state EEG activity able to reproduce frequency band-specific functional connectivity as well as an alternation between "idling" alpha and "active" gamma states, these studies observed that the alpha state exhibits greater stability and is less susceptible to periodic stimulation effects than the gamma state, consistent with the notion of alpha as an active neurocognitive suppression mechanism.

Work on brain network models of plasticity effects in computational brain stimulation modeling has tended to focus on the mechanisms and dynamics of plasticity processes at the level of meso-scale local dynamics (Shouval et al., 2002; Fung and Robinson, 2013; Wilson et al., 2018, 2021). Notably, Wilson et al. (2018, 2021), extending the calcium-dependent synaptic plasticity formulations of previous authors (Fung and Robinson, 2013; Shouval et al., 2002), developed a model of how multiple minutes of repetitive TMS (rTMS) lead to LTP or LTD depending on waveform characteristics including stimulation frequency, (for theta-burst rTMS specifically) carrier frequency, and number of pulses per burst. A key component of these models is the "'omega function" (Fig. 2A), which implements the experimental observation that lowered intracellular calcium levels lead to synaptic depression, raised levels lead to synaptic enhancement, and baseline levels have no effect. Brain network models have also been extended to integrate Hebbian learning mechanisms at the level of long-range excitatory connections between brain regions, with a view to explain experimental findings of frequency-dependent plasticity in neuroimaging data. These model results support the hypothesis that the intrinsic resonant properties of the brain network may play a role in plasticity processes at the whole-brain level (Lea-Carnall et al., 2017).

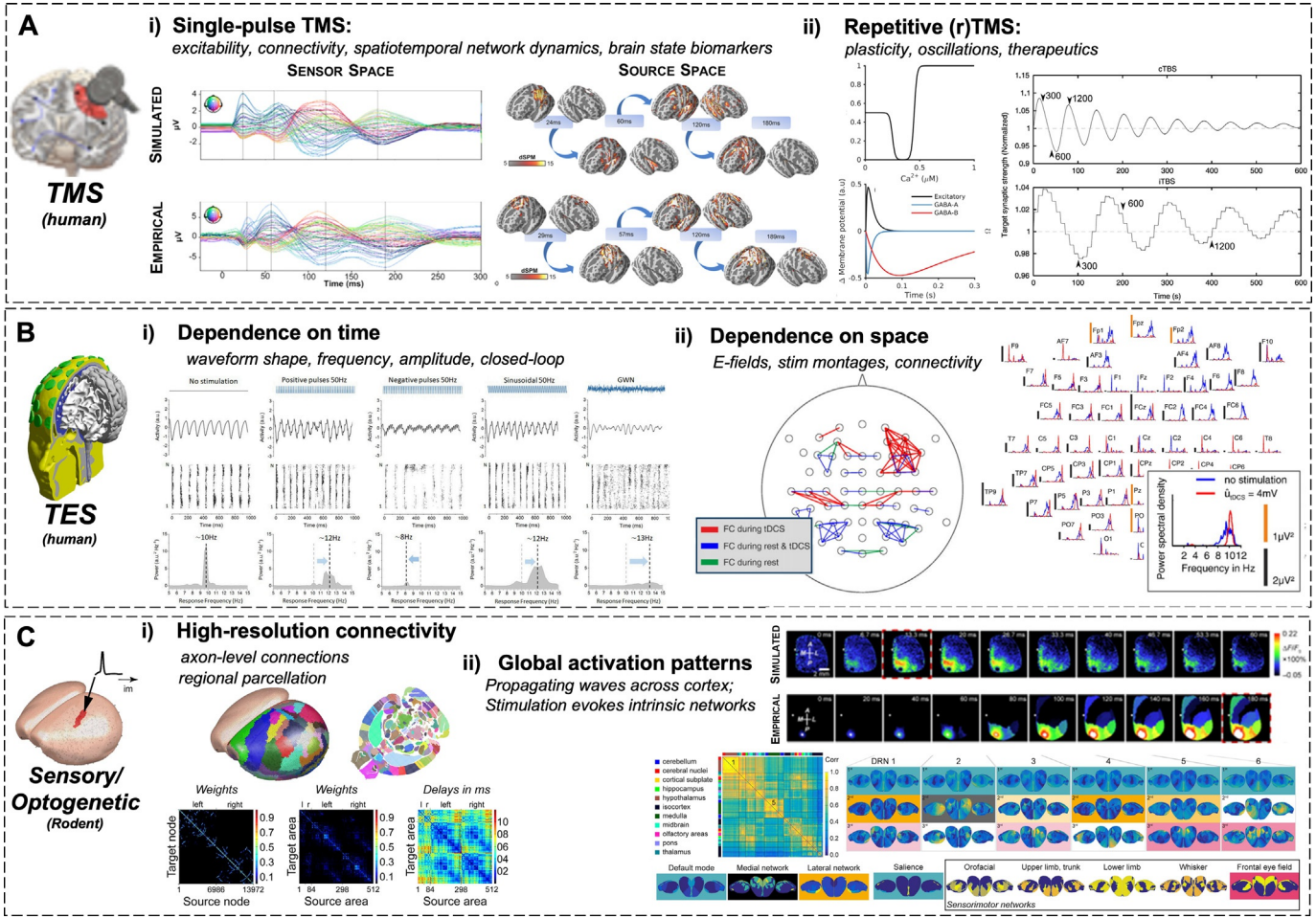



**FIG. 2**

Examples of brain stimulation modeling studies. (A) Models of transcranial magnetic stimulation (TMS) stimulation; (i) example of recorded TMS evoked potentials in EEG sensors (top) and simulated signals (bottom) (Momi et al., 2023), (ii) same for brain signals reconstructed in source space. (B) Models of transcranial electric stimulation (TES) serving to study the impact of stimulation on either (i) the signal responses over time (Hutt et al., 2018) or (ii) alterations in the spatial configuration of the signals (Kunze et al., 2016). (C) Models of sensory/optogenetic stimulation; (i) high spatial resolution (Spiegler et al., 2020) and (ii) map of empirical vs simulated activity and activation of dynamically responsive networks following optogenetic stimulation in mice (Spiegler et al., 2020).

### Psychopharmacological perturbation and the role of the neuromodulatory systems

Brain network models have also been used to explain large-scale effects of molecular neuromodulation observed in neuroimaging data (Kringelbach et al., 2020; Shine et al., 2021). Considering how a given neurotransmitter affects neuronal activity at the node level, it is possible to incorporate those effects in the model equations, simulate the resulting outcome at the network level and evaluate its predictive value by comparing it with neuroimaging data (Fig. 3). For instance, using the receptor density maps of serotonin obtained using PET imaging, Deco and colleagues demonstrated how the alterations observed at the level of dynamic functional connectivity following the infusion of LSD (which binds to specific serotonin receptors) could be predicted by selectively tuning the slope of the sigmoid function converting excitatory currents into neuronal firing rates in each node of the network as a function of receptor density (Deco et al., 2018).

## Assumptions of brain network models

Brain network models are based on several key assumptions, including:

- *The brain is a complex network:* Brain network models assume that the brain is a complex network made up of interconnected regions or nodes. These nodes can represent individual neurons, groups of neurons, or larger brain regions.
- *Nodes interact through connections:* Brain network models assume that nodes in the brain are connected through some form of communication or interaction such as the synaptic transmission of electrical or chemical signals via long-range axonal projections.
- *Network structure affects function*: Brain network models assume that the structure of the network, including the pattern of connections between nodes, has a direct impact on brain function. For example, some models suggest that certain network structures are more efficient for processing information, while others may be better suited for generating complex patterns of activity.

Overall, brain network models provide a framework for understanding how different regions of the brain work together to produce complex behaviors and cognitive processes. By simulating the behavior of these networks, researchers can gain insights into how the brain functions under different conditions and develop new strategies for treating neurological and psychiatric disorders.

Despite the success and development of the brain network modeling paradigm over the past decade, it remains unclear whether network models per se are the best representation of brain activity in order to understand its function. An alternative and reemerging scenario is aligned with wave/field theory (Jirsa and Haken, 1996),

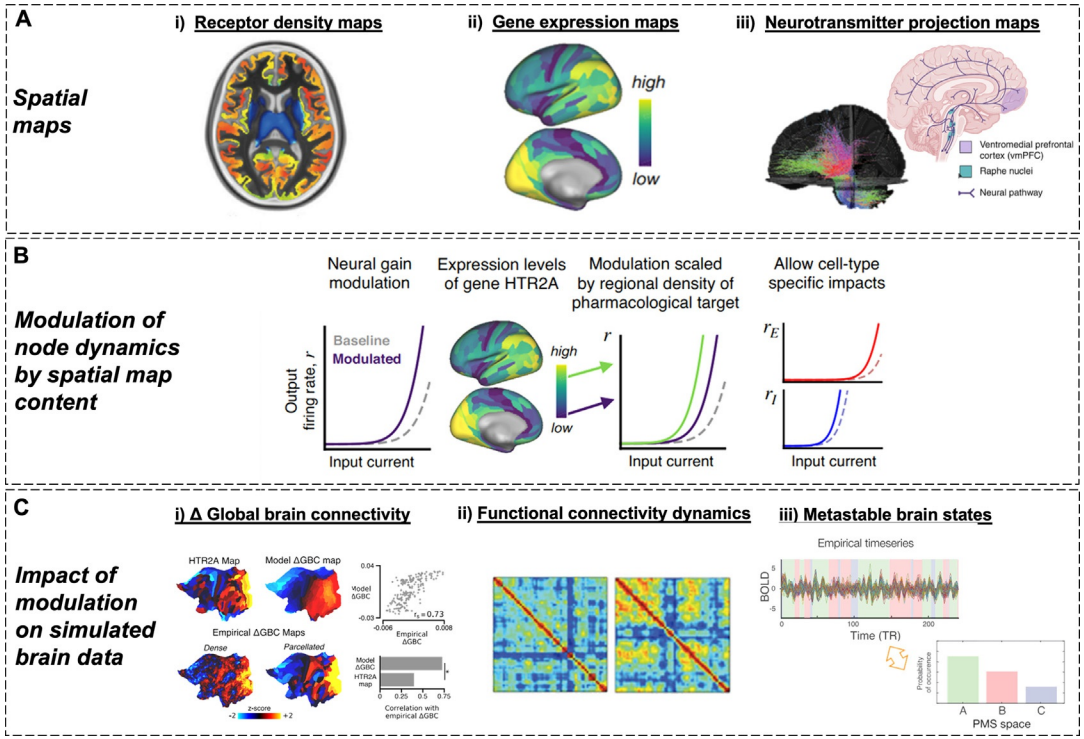



**FIG. 3**

Modeling brain neuropharmacological interventions. (A) The effect of pharmacological neuromodulation can be heterogeneously modulated by altering the local dynamics in each brain region as a function of a given spatial map, i.e., taking into account; (i) the density of neurotransmitter receptors as captured with PET imaging (Deco et al., 2018), (ii) the expression of specific genes (Burt et al., 2021), or (iii) the projection maps of neurotransmitters (Shine et al., 2021). (B) The impact of neuromodulation on the local node dynamics can be modeled by changing how the firing rate depends on the input current. For instance, a higher concentration of a given gene can be modeled by increasing the slope of the gain function (Burt et al., 2021). (C) The impact of neuromodulation in neuroimaging data can be assessed by comparing the simulation results with empirical data, either in terms of (i) the global brain connectivity (GBC) (Burt et al., 2021), (ii) the functional connectivity dynamics (Deco et al., 2017), or (iii) the relative occupancy of different states of functional connectivity, also known as probabilistic metastable substates (PMS) (Kringelbach et al., 2020).

where the brain is treated as a continuum system and its activity is described by a macroscale wave function reflecting the superposition of fundamental wave patterns extending across the whole brain evolving in time (Pang et al., 2023; Cabral et al., 2023). Although the network and the wave/field approaches are not necessarily mutually exclusive and may reflect different perspectives of a common process, it is important to embrace the insights that field theories may provide in order to improve our models of macroscale brain activity.

## Building, testing and interpreting dynamic brain network models

Building brain network models is a complex and interdisciplinary endeavor that requires expertise in neuroscience, mathematics, computational modeling, and often machine learning. Collaboration between researchers with different skill sets is crucial for successful model development. The process involves several steps, which we have enumerated briefly in the following:

1. Define scope and goals of the project

   This consists in determining the specific aspects of brain function one wants to model and the hypothetical mechanistic scenarios. This could range from oscillatory activity, functional connectivity, neurotransmitter modulation, stimulation outcome, and lesion impact, among others.
2. Choose an appropriate modeling approach

   A suitable modeling approach should have an adequate level of biophysical realism to address the specific goals of the project, balancing the right level of complexity to capture the desired emergent behaviors with sufficiently simplicity to allow interpretability. This involves defining the scale of brain parcellation, the node model, the coupling function and the variable parameters that will be used to regulate the dynamics of the system.
3. Consider nodal behavior

   Regarding the node model, the equations used to describe the activity of neural populations at each individual node can vary widely between studies, ranging from more realistic biophysical models considering the properties of active and passive membrane conductance as well as neurotransmitter concentrations and decay times (Honey et al., 2009; Naskar et al., 2021), to reduced models of neural populations such as the Wilson-Cowan model (Wilson and Cowan, 1972; Deco et al., 2009; Castaldo et al., 2023), through to linearized, algebraic model forms for phenomena such as power spectra (Lopes da Silva et al., 1974; Robinson et al., 2003; Abeysuriya et al., 2015) and functional connectivity (Robinson, 2012; Abdelnour et al., 2018; Verma et al., 2022).

4. Consider coupling functions

   The coupling function may consider the excitatory nature of long-range axonal connections, such that the response function of a node has a sigmoidal shape or instead assume a diffusive coupling, where the response of a node is a function of the difference with respect to coupled nodes. In the case of excitatory coupling, the general form is to consider a threshold input current above which the firing rate of a node will increase with increasing input current, up to a point where the firing rate reaches a plateau of high firing rate. However, given that long-range connections are usually assumed to be purely excitatory, this approach tends to lead to a globally excited state, and therefore, to reach an adequate fit with spontaneous brain activity, a local feedback inhibition is added to keep the global network in a low-firing state.
5. Data gathering

   Collect data from various sources such as electrophysiological recordings, functional MRI (fMRI) data, neuroanatomical data, and other experimental observations. This data will serve as the foundation for your model.
6. Model Development

   Based on your chosen approach, develop the model's architecture and equations. This involves defining the properties of neurons, synapses, connectivity patterns, and other relevant components. This step may require adjusting parameters to match the available experimental data.
7. Structural connectivity, equations describing local node dynamics, and coupling term

   Since the connection topology changes when anatomical scales are traversed, so will the corresponding network dynamics. As a consequence, different types of networks are encountered at different levels of neural organization.
8. Simulation and Validation

   Implement the model in a computational framework and run simulations. Compare the model's behavior and output with experimental data to validate its accuracy and performance. This may involve tweaking parameters and model structure to improve the fit.
9. Parameter Tuning and Optimization

   Fine-tune the model's parameters to better match experimental data and produce desired behaviors. This process might involve using optimization algorithms to find the parameter values that minimize the difference between model predictions and empirical observations.
10. Analysis and Interpretation

    Analyze the model's behavior and output to gain insights into the neural mechanisms and processes being simulated. This could involve examining firing rates, network dynamics, information flow, and other relevant measures.

11. Hypothesis Testing and Predictions
    Use the validated model to test hypotheses about the brain's functioning or make predictions about how the brain might respond under different conditions. This step helps refine our understanding of neural processes and guides further experimental research.
12. Model Refinement and Iteration
    Models are rarely perfect on the first attempt. Refine your model based on new data, feedback from the neuroscience community, and improved computational methods. Iterative refinement helps create more accurate and meaningful models over time.

Dynamic network models consist of sets of coupled differential equations that can be solved in any simulation environment, including, among others, C++, Matlab, Python, Julia, etc. The Virtual Brain (www.thevirtualbrain.org) is a software developed with the aim to "*Simulate a human brain, right on your PC!*," facilitating the access of nonexperts to the endeavors of brain network modeling, including several options for brain parcellations and node models (Sanz-Leon et al., 2015). For researchers with programming skills, it is recommended to develop their own scripts, making use of some toolboxes, such as the Brain Dynamics Toolbox (https://bdtoolbox.org) (Heitmann and Breakspear, 2022), which offers examples for solving coupled differential equations.

## Pitfalls of brain network modeling

Brain network modeling has emerged as a powerful tool for understanding the intricate workings of the human brain. However, it is essential to acknowledge that this approach comes with its own set of challenges and pitfalls that must be carefully navigated to ensure accurate and meaningful insights. Here we list some of the key pitfalls associated with brain network modeling.

1. Oversimplification of Complexity
   One of the primary pitfalls in brain network modeling is the risk of oversimplifying the complexity of the brain's intricate neural connections. While simplification is often necessary to depict the most primitive mechanisms and to make models computationally manageable, overly simplistic representations can lead to inaccurate conclusions. Failing to account for the rich diversity of neuron types, synaptic strengths, and dynamic interactions between regions can result in unrealistic predictions.
2. Lack of Ground Truth
   Brain network models heavily rely on empirical data, but the availability of accurate ground-truth data is often limited. This lack of ground truth can lead to models that are not adequately validated or calibrated. Without proper validation, it becomes challenging to ascertain whether the model's predictions truly reflect the underlying biological reality.

3. Parameter Sensitivity and Overfitting

   Brain network models often involve a multitude of parameters that control the strength of connections, time constants, and other dynamic properties. Fitting these parameters to experimental data can be prone to overfitting, where the model captures noise rather than meaningful patterns. Moreover, slight changes in parameter values can lead to dramatically different model outcomes, making the models sensitive to initial conditions and potentially less generalizable.
4. Ignoring Temporal Dynamics

   The brain's activity is highly dynamic, with neural processes occurring across various timescales. Neglecting temporal dynamics or oversimplifying them can lead to unrealistic network behaviors. For instance, ignoring delays in signal transmission can result in overly synchronous network activity that does not align with empirical observations.
5. Limited Incorporation of Individual Variability

   Individual differences in brain anatomy, connectivity, and function are significant factors that shape neural activity. However, many brain network models treat brains as homogeneous entities, ignoring these critical sources of variability. Neglecting individual variability can lead to models that fail to capture the full range of human brain functioning.
6. Interpretability and Validation

   Brain network models can produce intricate and complex results, making their interpretation and validation challenging. Ensuring that the model outcomes are biologically plausible and interpretable is crucial. Validating the model's predictions against multiple datasets and experimental designs can help establish the model's credibility.
7. Incorporating Realistic Stimulation and Intervention

   Interventions such as brain stimulation techniques are often explored using network models. However, accurately representing these interventions and their effects within the model can be intricate. Failure to capture the biophysics of interventions can lead to misleading conclusions about their potential efficacy.
8. Computational Complexity

   Developing and simulating brain network models often requires significant computational resources. As the complexity of models increases, so does the demand for computational power and memory. This can limit the accessibility and practicality of these models for researchers with limited resources.

In conclusion, while brain network modeling offers valuable insights into the brain's functional and structural organization, researchers must be aware of the potential pitfalls associated with this approach. Navigating these pitfalls requires a balanced consideration of model complexity, empirical validation, the incorporation of individual variability, and careful interpretation of results. Addressing these challenges will contribute to the development of more accurate and meaningful brain network models that advance our understanding of the brain's complexities.

## Open challenges and future directions

Whole-brain modeling and computational connectomics have raised great expectations for understanding brain disorders at a causal mechanistic level and provide novel, more effective therapeutic interventions, e.g., through drug discovery and new targets for deep brain stimulation (Deco and Kringelbach, 2014; Braun et al., 2018). However, although whole-brain network models have brought remarkable insights into brain organization and dynamics over the last decades, it is important to temper the notion of a "successful brain network model" in the sense that models have served mostly to test the validity of hypothetical mechanistic scenarios or to simulate the impact of perturbation, but their predictive value still needs to be improved and validated in preclinical models before they can serve to design successful interventions in clinical settings (Bassett and Sporns, 2017).

A central goal of the field is to build personalized replicas—or "digital twins"—of the human brain to test different types of interventions to define personalized therapeutic strategies for different brain disorders ( Jirsa et al., 2010; Kurtin et al., 2023; Vohryzek et al., 2023; Lang et al., 2023; Luppi et al., 2023). However, whether improvements in computer power or the use of machine-learning algorithms to optimize parameter search will be sufficient, or an entirely new paradigm shift is needed, remains an open question.

In terms of insight for cognitive neuroscience, brain network models have served to support the view of mental function as an emergent property resulting from interactions between distinct brain regions rather than a localized neuronal process (Deco et al., 2011). Describing the brain as a collective dynamical system, composed of multiple units capable of engaging in a multitude of collective activity patterns, links with theories of emergence, which may ultimately open up to a better understanding of mental function and coordinated behavior. Still, the link between models of brain activity and theories of consciousness remains correlational, and more efforts are needed to understand how brain network models can serve to solve still unanswered mechanistic questions regarding the emergence of consciousness and cognitive function (Cabral et al., 2017; Demertzi et al., 2019).

## Take-home points

- Brain network models serve to simulate the behavior of interacting brain areas.
- There are a variety of models for node dynamics and coupling functions, combined with choices on free and fixed parameter values.
- Models explain some features of neuroimaging data, but their predictive value remains insufficiently validated to translate into clinics.
- Personalized brain network models are poised to turn into digital twins to optimize pharmacological and/or electromagnetic interventions.

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