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Personalized brain network models for assessing structure–function relationships

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Many recent efforts in computational modeling of macro-scale brain dynamics have begun to take a data-driven approach by incorporating structural and/or functional information derived from subject data. Here, we discuss recent work using personalized brain network models to study structure–function relationships in human brains. We describe the steps necessary to build such models and show how this computational approach can provide previously unobtainable information through the ability to perform virtual experiments. Finally, we present examples of how personalized brain network models can be used to gain insight into the effects of local stimulation and improve surgical outcomes in epilepsy.

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Introduction

The brain is an inherently dynamical system, driven by an underlying complex network of connections, and much work has focused on the ability to relate brain activity and function to the underlying structure [1]. Understanding this important link is a key goal of Network Neuroscience — a rapidly evolving field that relies on complex network theory to model and study the brain across multiple scales and modalities of interactions [2••]. In this framework, network nodes are chosen depending upon the scale of interest and scientific question, and could range from neurons to brain regions. Network edges can represent structural connections (anatomical links; structural connectivity) or functional relationships (statistical relationships; functional connectivity) [3,4]. When using network theory to model the brain, many important questions can be asked. What is the relationship between structural and functional connectivity? Do structure–function relationships change over task, time, or disease state? How sensitive are the observed patterns of brain activity to small differences in the underlying structural connectivity?

Studies have shown that while certain features of brain network structure are conserved across individuals, differences in network structure can be observed across people [5,6,7•]. Individual differences in human task performance [8•,9] and differences between healthy and diseased individuals [10,11] have also been linked to differences in the underlying structural connectivity of the brain. These findings have motivated the formulation of data-driven computational models of brain activity (see Box 1). These personalized brain network models (BNM) combine an individual's structural connectivity with mathematical equations of neuronal activity in order to produce a subject-specific simulation of spatiotemporal brain activity. Due to recent advances in non-invasive imaging techniques to measure macro-scale structural connectivity of human brains [12,13], such models have gained popularity to study large-scale brain dynamics.

These computational models are sensitive to the underlying network structure [14•], and offer many advantages when investigating structure–function relationships. For example, one can perform *in silico* experiments that perturb the underlying brain structure such as lesioning (removing edges [15,16]) or resection (removing nodes [17,18]) and investigate the effects of such perturbations on simulated brain activity. Alternatively, one can impact local brain dynamics through modifications to the mathematical equations such as applying stimulation or modifying brain excitability and study the effects of these local perturbations on global brain function [14•,19••]. Importantly, due to the specificity of the model to a given individual, one can study the differential impact of similar perturbations across a cohort of individuals. Thus, this approach has the potential to lead to the development of personalized treatment strategies to combat disease or enhance human performance [20].

In this review, we summarize the basic steps involved in creating personalized BNM and provide examples from recent studies within the last 2–3 years that have used this

Box 1 Personalized brain network models (BNM)

'Everything should be made as simple as possible, but not simpler' — Albert Einstein.

Network neuroscience seeks to understand the organization of the brain using tools from complex network theory, applied across multiple scales and modalities. Given the ongoing experimental advances in non-invasive recording techniques, it is now possible to combine high quality structural brain data with neurophysiological information to create data-driven computational models of brain activity. These personalized BNM simulate brain dynamics using biologically inspired mathematical equations that model regional activity and are coupled through the observed brain structure. Incorporating personal data into the structure and dynamics of the model involves making multiple assumptions and choices that are driven by the question at hand. The flexibility associated with the model design makes it useful for performing *in silico* experiments across a diverse range of applications, but also implies that one must be cautious when interpreting model predictions and/or making generalizations.

Applications:

Personalized BNM can
- be tuned to produce dynamics that mimic the resting state activity patterns.
- predict the effect of targeted stimulation.
- be perturbed to study the impact of brain lesions.
- provide seizure onset probabilities and inform surgical outcomes.

Limitations:

When using macro-scale computational models, one must also keep in mind the underlying assumptions and limitations. These models
- are often optimized based on the scientific question at hand and are not always generalizable.
- do not necessarily produce waveforms that depict realistic brain activity.
- can provide predictive outcomes but might lack many neurophysiological details and/or mechanistic explanations.

methodology to gain insight in to brain structure–function relationships. We particularly highlight applications of this approach that study the effects of regional brain stimulation on global brain dynamics or use computational brain models to predict surgical outcomes in epilepsy.

Building data-driven brain network models

Building personalized BNM involves making decisions regarding the scale of the network, the type of underlying connectivity, and the level of neurophysiological complexity of the mathematical equations that constitute the model (see Figure 1). Generally, human brain modeling involves working at the macroscopic level where network nodes are either sensors (e.g., EEG data) or brain regions (e.g., imaging data) [21]. Brain regions are defined using a parcellation scheme that is based on one of many different available atlases [22]. Each atlas divides the brain into multiple spatial regions, but the location and total number of regions varies widely between atlases. Due to this variability, some work has investigated the impact of the choice or scale of atlas used for the parcellation. While the proper choice of scale depends on many factors, under certain sets of assumptions, it has been shown that an atlas with approximately 140 brain regions produces good agreement with experimental data [23].

Next, one needs to determine how network edges are defined. The modeling framework is based on the assumption that subject-specific structural connectivity data is available. The first modeling studies used a connectome derived from tract tracing studies in primates [24], but in order to model human brain dynamics, estimates of white matter tracts between brain regions obtained from diffusion weighted imaging data are instead used [25]. While some studies have used structural networks that represent data averaged across a cohort of individuals [26,27], using subject-specific connectomes increases the specificity of the model [19••,25,28] and is preferable if available.

In certain cases where subject-specific structural network data is not available, researchers have instead substituted functional for structural connectivity. However, it is important to remember that the mathematical assumption of the model is that the connections represent structural (not functional) coupling. While it has been shown that structural and functional networks are correlated [25,29], these two types of connectivity remain fundamentally different [30]. Nevertheless, assessing brain network model connectivity from functional data can still be shown to produce predictive results [31•] and can therefore be a useful tool, but one must be careful in the interpretation of the findings.

Finally, one must choose the set of mathematical equations that represent regional brain activity. In the simplest case, Kuramoto phase oscillators (simplistic oscillators commonly used in dynamical systems theory [32]) have been used to model neural activity. However, more sophisticated approaches instead choose some biologically informed neural mass model. See the excellent review by Breakspear [33••] for a detailed discussion on the choices of dynamical equations. If one's goal is to be able to accentuate the effect of the underlying structural connectivity, each brain region is generally governed by the same set of equations and same parameters. However, to more accurately model brain activity, one can modify parameters of the equations governing regional brain dynamics. This approach is particularly suitable to model changes related to brain states such as sleep *vs.* wake [26,27], or disease states such as epilepsy [19••], and is becoming increasingly used to create models that capture subject specific differences in both structure and dynamics.