NeuroImage 90 (2014) 335–347

Contents lists available at ScienceDirect

NeuroImage

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

# Network diffusion accurately models the relationship between structural and functional brain connectivity networks

Farras Abdelnour *, Henning U. Voss, Ashish Raj

*Department of Radiology, Weill Cornell Medical College, New York, NY, USA*

ARTICLE INFO

*Article history:*
Accepted 16 December 2013
Available online 30 December 2013

*Keywords:*
Networks
Brain connectivity
Functional connectivity
Structural connectivity

ABSTRACT

The relationship between anatomic connectivity of large-scale brain networks and their functional connectivity is of immense importance and an area of active research. Previous attempts have required complex simulations which model the dynamics of each cortical region, and explore the coupling between regions as derived by anatomic connections. While much insight is gained from these non-linear simulations, they can be computationally taxing tools for predicting functional from anatomic connectivities. Little attention has been paid to linear models. Here we show that a properly designed linear model appears to be superior to previous non-linear approaches in capturing the brain's long-range second order correlation structure that governs the relationship between anatomic and functional connectivities. We derive a linear network of brain dynamics based on graph diffusion, whereby the diffusing quantity undergoes a random walk on a graph. We test our model using subjects who underwent diffusion MRI and resting state fMRI. The network diffusion model applied to the structural networks largely predicts the correlation structures derived from their fMRI data, to a greater extent than other approaches. The utility of the proposed approach is that it can routinely be used to infer functional correlation from anatomic connectivity. And since it is linear, anatomic connectivity can also be inferred from functional data. The success of our model confirms the linearity of ensemble average signals in the brain, and implies that their long-range correlation structure may percolate within the brain via purely mechanistic processes enacted on its structural connectivity pathways.



## Introduction

Whole brain connectivity networks or "connectomes" come in two flavors: structural networks extracted from tractography algorithms applied to diffusion MRI (dMRI) (Gong et al., 2009; Iturria-Medina et al., 2007); and (resting-state) functional networks, inferred from the strength of long-range second order temporal correlation structure of activation signals in various brain regions (Cabeza and Kingstone, 2006). Subsequent analysis using ICA (Calhoun et al., 2009) or graph clustering techniques (Shi and Malik, 2000), indicates the presence of distinct sub-networks, prominently the default mode and salience networks (Greicius et al., 2009). Diffusion tensor imaging (DTI) has been extensively used as an estimate of structural connectivity (Bullmore and Sporns, 2009; Bullmore and Bassett, 2011; van den Heuvel and Pol, 2010). Probabilistic tractography methods for estimating structural connectivity from DTI have been adopted in the literature, e.g. (Iturria-Medina et al., 2007, 2008). Both forms of connectivity have experienced great interest from the neuroscience community, as shown in Achard and Ed (2007); Bassett et al. (2010); Honey et al. (2007, 2009) and Joyce et al. (2013).

A major goal of connectome research is to discover whether, and how, the structural and functional networks of the brain are related — an active area with tremendous interest and wide ramifications in neuroscience and computational biology (Cabral et al., 2011; Deco et al., 2009, 2012; Ghosh et al., 2008a; Honey et al., 2007, 2009, 2010; Mars et al., 2011). Previous investigations have relied on non-linear models of cortical activity which were extended to model whole-brain behavior via coupling between regions based on structural connectivity (Honey et al., 2009). Other studies place non-linear oscillators at each cortical location and likewise couple them using anatomic connectivity strength (Cabral et al., 2011; Deco et al., 2009, 2012; Ghosh et al., 2008a). Since these powerful *generative simulation models* are only revealed through large scale, fine-grained finite difference stochastic simulations over thousands of time samples, they present a practical challenge for the task of inferring functional connectivity from anatomic. The field has not actively considered linear graph-theoretic dynamic models for this purpose, with a few exceptions described below. Although complex brain dynamics preclude completely linear responses, *ensemble-averaged* behavior of large connected but individually non-linear neural populations can be quite linear (Stephan et al., 2008).

In this paper we (re)introduce a class of linear models capturing the correlation structure of whole brain dynamics at low frequency BOLD levels (Galán, 2008; Honey et al., 2007, 2010). We argue that while local brain dynamics are not linear or stationary (Bassett et al., 2010;

* Corresponding author at: Department of Radiology, Weill Cornell Medical College, 515 E. 71st St., S-125, New York, NY 10065, USA.
*E-mail address:* faa2016@med.cornell.edu (F. Abdelnour).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.12.039

Jones et al., 2012; Hutchison et al., 2013), the emergent behavior of *long-range steady state 2nd order correlations* should be insensitive to detailed local dynamics, and dependent only on the topology of structural networks. Thus, our hypothesis is that linear macroscopic models are sufficient to infer the long-range correlation structure of brain activity, without requiring detailed non-linear simulation models. Specifically, we present a simple, low-dimensional *network diffusion model* producing an accurate description of the structure–function relationship. Network diffusion models random walks on a graph, covering phenomena from image noise removal (Zhang and Hancock, 2008) to Markov random fields (Smolka and Wojciechowski, 2001). Interestingly, network diffusion successfully captured the progression of misfolded proteins within brain networks, and recapitulated patterns of dementias like Alzheimer's disease (Raj et al., 2012). We hypothesize that resting-state functional relationships between brain regions can be captured by a similar diffusion process applied to the structural network. While the proposed model is linear, similar to Galán (2008), we impose constraints modeled after the interaction of the various cortical regions by taking the Laplacian of the connectivity matrix. We test the proposed model using dMRI and fMRI brain scans of healthy subjects, and demonstrate higher structure–function correspondence than other competing methods including neural mass models (Breakspear et al., 2003; Deco et al., 2008; Moran et al., 2007). Our work could provide impetus for similar parsimonious approaches in modeling other complex biophysical phenomena.

Our key idea is that functional signals at the spatial and temporal resolutions of BOLD signals in brain regions are an ensemble average of millions of neurons, and are therefore governed mainly by the number of neurons firing at any time rather than by the complex behavior of individual neuronal activity. The non-linearities associated in neurons' individual firing patterns are largely obliterated in the ensemble signal. Thus, the signal correlation between two large connected regions ought to be governed dominantly by linear processes. We show that the simplest linear and purely mechanistic process enacted on the network can reproduce the functional relationship between brain regions. Since functional relationships appear to be enacted on a physical substrate the brain structural connectivity our work implies that the former is a derivative property of brain structure rather than an independent property.

## Theory

### *Network notation*

In a brain network each node represents a gray matter region located on either the neocortex or in deep brain subcortical areas. We define a network $\mathcal{G} = (\mathcal{V}, \mathscr{E})$ with a set of $N$ nodes $\mathcal{V} = \{v_i | i \in 1, \ldots, N\}$ and a set of edges given by an ordered node pair $\mathscr{E} = \{(i, j) | i \in \mathcal{V}, j \in \mathcal{V}\}$ (Agaskar and Lu, 2011). Between any two nodes $i$ and $j$ there is a fiber pathway whose connectivity weight $c_{i,j} \in [0, \infty)$ can be measured from dMRI tractography. The structural connectivity matrix $\mathbf{C} = \{c_{i,j} | (i,j) \in \mathscr{E}\}$ is obtained via anatomical connection probability (ACP), where the matrix elements are obtained as a function of weighted fiber densities between nodes (Iturria-Medina et al., 2008). Although some individual neurons are known to be directional, dMRI does not allow measurement of directionality. Major fiber bundles resolvable by dMRI, especially cortico-cortical pathways are generally bidirectional, having roughly equal number of connections in either direction (Albright, 1984). We define the *connectivity strength* or the *weighted degree* of a node $i$ in this graph as the sum of all connection weights: $\delta_i = \sum_{j|(i,j) \in \mathscr{E}} c_{i,j}$.

### *Linear network models*

A previous implementation of a linear model for achieving the structure–function correspondence by Honey et al. (2009) is used in this paper as a comparison, following Galán (2008) where an *i.i.d.* Gaussian noise source $\xi(n)$ drives a discretized multivariate autoregressive linear system given as:

$$\mathbf{u}(n+1) = \mathbf{A}\mathbf{u}(n) + \xi(n). \tag{1}$$

Here vector $\mathbf{u}(n)$ is the activation signal at time point $n$ of all network nodes corresponding to the regions of the brain. The matrix $\mathbf{A}$ serves to relate the mixing between signals at different nodes, as per $\mathbf{A} = (1 - \alpha)\mathbf{I} + \mathbf{C}$, where $\alpha$ is some leak parameter from the activity of each node, and $\mathbf{C}$ is the anatomic connectivity matrix described earlier. Since a single "mixing" parameter $\alpha$ cannot access many interesting regimes in the space of linear models, here we modify $\mathbf{A}$ via two parameters:

$$\mathbf{A} = (1-\alpha)\mathbf{I} + \beta\mathbf{C}.$$

By allowing two degrees of freedom instead of one, we obtain a broader range of linear models than the one proposed by Galán. In order for the simulation to be stable, the matrix $\mathbf{A}$ is normalized to have unit norm, or $\| \mathbf{A} \| = 1$. Following Honey et al. (2009), resting state functional connectivity was obtained via stochastic discrete-time simulation over a range of $\alpha \in [-3, 3]$ and $\beta \in [0,6]$ in steps of 0.1 for both parameters. At each point $(\alpha, \beta)$, the $\ell_1$ error with respect to the true functional connectivity was computed. We chose the $(\alpha, \beta)$ pair that gives the smallest error for final computation of functional connectivity.

### *Non-linear neural mass models (NMMs)*

NMMs model neural activity in localized populations (minicolumns) in terms of second order state–space differential equations, where the post-synaptic potential (PSP) of neuronal populations is the hidden state, and the activation signal, whether measured via EEG, MEG or BOLD, is the output variables. The model gives rise to systems of coupled second order non-linear differential equations, whose coupling coefficients are determined by the amount of connectivity between them, which is not known a priori. Since no closed-form solution exists for these equations, the model is a *simulated generative model*, whose behavior is accessed via large-scale simulations over thousands of time points, starting from stochastic endogenous and exogenous signals representing mean firing rates.

An NMM defined in terms of voltages and conductances was utilized (Breakspear et al., 2003), and applied to networks ranging from 66 to 1000 nodes. In a more complex recent model, a set of coupled NMMs were instantiated at each node of a connected brain network, with inter-regional couplings determined by anatomic connectivity (Honey et al., 2009). In the proposed model, inter-regional coupling is modulated by a single coupling parameter $c$, whose chosen value greatly affects the behavior of this highly non-linear coupled system. Here we implement this approach using the original computer code used in Honey et al. (2009). Values of $c$ were varied over a range $c = \{0.02, 0.07, 0.12, 0.17, 0.22, 0.27, 0.32\}$ for each subject and the value yielding the highest match with empirical functional connectivity was chosen.

### *Proposed network diffusion model*

We now introduce from first principles a physically realistic linear dynamic network model of functional connectivity relying on its emergent linearity, and obtain a closed-form solution which obviates the need for generating simulated signals. Consider first an isolated cortical region *R1*. We assume that the average activation signal over all neurons in this region, denoted by $x_1(t)$, is proportional to the number of firing neurons per voxel (rather than to the actual action potentials thereof). Although the internal dynamics of this isolated neural population is complex and likely chaotic, in keeping with our emphasis on simple linear models, we allow the simplest possible dynamic behavior of a