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Inference of direct and multistep effective connectivities from functional connectivity of the brain and of relationships to cortical geometry

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HIGHLIGHTS

- Neural field theory (NFT) can yield effective connectivity from functional connectivity.
- Effective and functional connectivity are related to cortical geometry.
- Norm-minimization is a useful method to infer effective connectivity.

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ABSTRACT

Background: The problem of inferring effective brain connectivity from functional connectivity is under active investigation, and connectivity via multistep paths is poorly understood.
New method: A method is presented to calculate the direct effective connection matrix (deCM), which embodies direct connection strengths between brain regions, from functional CMs (fCMs) by minimizing the difference between an experimental fCM and one calculated via neural field theory from an ansatz deCM based on an experimental anatomical CM.
Results: The best match between fCMs occurs close to a critical point, consistent with independent published stability estimates. Residual mismatch between fCMs is identified to be largely due to interhemispheric connections that are poorly estimated in an initial ansatz deCM due to experimental limitations; improved ansatzes substantially reduce the mismatch and enable interhemispheric connections to be estimated. Various levels of significant multistep connections are then imaged via the neural field theory (NFT) result that these correspond to powers of the deCM; these are shown to be predictable from geometric distances between regions.
Comparison with existing methods: This method gives insight into direct and multistep effective connectivity from fCMs and relating to physiology and brain geometry. This contrasts with other methods, which progressively adjust connections without an overarching physiologically based framework to deal with multistep or poorly estimated connections.
Conclusions: deCMs can be usefully estimated using this method and the results enable multistep connections to be investigated systematically.

1. Introduction

The need to understand how the brain perform tasks rapidly, processes inputs, develops, responds to damage, and changes its connectivity as a result of lesions, has led to enormous interest in identifying the interrelationships between function and anatomy

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of the brain (Friston, 2011; Bullmore and Sporns, 2009; Rubinov et al., 2009, 2011; Sporns et al., 2004, 2000, 2005; Kaiser et al., 2010; Honey et al., 2007, 2010, 2009; Robinson et al., 2009; Henderson and Robinson, 2011; Sporns, 2010; Bassett et al., 2006; Gray and Robinson, 2009; Gray et al., 2009; Kitzbichler et al., 2009; Beggs and Plenz, 2003; Stam and de Bruin, 2004; Linkenkaer-Hansen et al., 2001; Albert and Barabási, 2002; Barthélemy, 2011; Galán, 2008). Experiments and analysis on the "resting" (i.e., free of conscious processing and experimental tasks) human brain show that the functional connectivity is supported by anatomical connectivity (Hagmann et al., 2008; Honey et al., 2009; Deco et al., 2014; Damoiseaux et al., 2006).

Connectivity between brain regions is often expressed via connection matrices (CMs), where rows and columns of the matrix represent brain regions (Friston, 2011; Bullmore and Sporns, 2009; Sporns, 2010) and entries represent the connections between them. Anatomical connection matrices (aCMs, sometimes termed structural connection matrices in the literature) summarize the known anatomical connectivity between pairs of regions of interest (RoIs) in the brain, regardless of whether they are active; sometimes published aCMs are binary and sometimes weighted by an approximate estimate of relative fiber density. In matrix notation RoIs are represented as nodes and the corresponding weights that connect these RoIs are represented as matrix entries. A symmetric aCM can be obtained using diffusion spectrum imaging or diffusion tensor imaging (DSI or DTI) that estimates weighted strengths of direct fiber links between brain regions, but does not record the direction of these links or whether they are active in any particular brain state. Symmetric functional connection matrices (fCMs) are most often determined from the covariance of activity in RoIs of the brain using functional magnetic resonance imaging (fMRI) (Friston, 2011; Bullmore and Sporns, 2009; Sporns, 2010; Aquino et al., 2012).

Several authors have tried to predict functional connectivity from anatomical connectivity and vice versa (Hagmann et al., 2008; Honey et al., 2009; Pernice et al., 2011; Goñi et al., 2014; Hutchison et al., 2011), but these early methods were mostly statistical, without an overarching physiologically based framework to deal with indirect, missing, and/or inactive connections. More recent estimates of the deCM used dynamic neural field and neural mass models to fit the fCM of a specific dynamic model to experiment (Gilson et al., 2016; Deco et al., 2014). In their method, connectivity strengths were progressively adjusted until the best match with the resulting numerically calculated fCM was achieved; this work confirmed that near-criticality is required for a good match and that interhemispheric connections are underestimated, which is in accord with our earlier results that showed the brain functions in a near-critical state (Robinson et al., 1997, 2002, 2014; Robinson, 2012). The CM that embodies the strengths of direct connections between points in a given brain state is termed a direct effective CM to unambiguously distinguish it from other types of effective CM (deCM, which has also previously been termed an effective CM or a gain matrix in the literature). Our recent work (Robinson et al., 2014) demonstrated how to identify the correctly normalized deCM from an experimental fCM via neural field theory (NFT) and eigenfunction analysis in the symmetric case. This was based on the method of Robinson (2012) to interrelate total effective CMs (teCMs, which measure all effects via both direct and indirect paths), deCMs, and fCMs. Meier et al. (2016) used the resulting power series expansion in further image analysis; however, this expansion has yet to be used to systematically investigate multistep (indirect) connections and their relative importance.

Here we address issues of estimating effective connectivity from the functional connectivity, including both direct and multistep connections, via the NFT propagator approach (Robinson, 2012). A *bare* neural field (NF) propagator represents only effects via direct connections with other regions of the network, and hence is identified with the deCM. A *dressed* propagator represents effects that travel via both direct and indirect connections and is thus identified with the teCM (Robinson, 2012; Robinson et al., 2014). Firstly, we present a method to estimate the deCM by minimizing the norm of the difference between an experimental fCM and the analytically calculated fCM for the aCM. Secondly, we use these results to investigate underestimated connections in experimentally recorded aCMs. Thirdly, we explore the fact that the experimental fCM has fuller connectivity than the experimental aCM. Since DSI records direct connections only, we explore how various orders of multistep connections contribute to the observed activity (and hence the teCM and fCM) over and above the direct connectivity. This enables us to estimate the strengths of indirect connections via different numbers of intermediate RoIs and compare our result with experiment. Lastly, we present a method to analytically estimate the effective strengths of multistep connections vs. the number of steps.

2. Theory

Our work is based on NFT results that relate structure and functional connectivity (Robinson, 2012). In this section we briefly summarize the relevant aspects of NFT in propagator form, including how it interrelates effective and functional CMs.

2.1. Neural field theory and propagator approach to connection matrices

Our physiologically based NFT of brain dynamics incorporates arbitrary numbers of structures and neural populations (Robinson, 2005, 2012). These distinct neural populations are spatially distributed in the brain and their activity is influenced by neural inputs from various afferent populations.

The quantity $Q_a(\mathbf{r}, t)$ represents the spiking rate of a neural population a at position $\mathbf{r}$ at time t in the brain. An important point here is that Q_a can be used to represent either a mean firing rate or a perturbation from that mean. In the context of fMRI, experimental fCMs are constructed by calculating correlations or covariances of small differences from baseline activity (Friston, 2011; Bullmore and Sporns, 2009; Sporns, 2010; Honey et al., 2010). As discussed in detail elsewhere (Robinson, 2012; Robinson et al., 2014), we thus concentrate on perturbations from baseline activity and restrict attention to the linear regime, noting that BOLD signal fluctuations are driven by local neural activity, primarily that of excitatory pyramidal cells (Attwell and Laughlin, 2001; Aquino et al., 2012).

Since spikes in population a are elicited by inputs from various afferent populations, which we label $b = 1, \ldots, p$, we can write

$$Q_a(\mathbf{r}, t) = \sum_b \int\int \tilde{\Lambda}_{ab}(\mathbf{r}, t, \mathbf{r}', t') Q_b(\mathbf{r}', t') d\mathbf{r}' dt' + N_a(\mathbf{r}, t), \tag{1}$$

where the causal propagator $\tilde{\Lambda}_{ab}$ in Eq. (1) quantifies the effect of afferent activity in population b on population a, integrates over all sources locations $(\mathbf{r}', t')$, and $N_a(\mathbf{r}, t)$ is the external input (Robinson, 2012).

Eq. (1) allows for temporal dynamics. To obtain the most commonly measured purely spatial deCM that measures influences of one point on another without regard to timing, one must integrate $\tilde{\Lambda}_{ab}$ over all possible values of t and t' to account for all influences that travel directly to $(\mathbf{r}, t)$ from $(\mathbf{r}', t')$, regardless of timing (Robinson et al., 1997; Knock et al., 2009). This yields the purely spatial propagator,

$$\tilde{\Lambda}(\mathbf{r}, \mathrm{r}') = \int\int \tilde{\Lambda}(\mathbf{r}, t, \mathbf{r}', t') dt dt', \tag{2}$$