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Network connectivity modulates power spectrum scale invariance

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ABSTRACT

Measures of complexity are sensitive in detecting disease, which has made them attractive candidates for diagnostic biomarkers; one complexity measure that has shown promise in fMRI is power spectrum scale invariance (PSSI). Even if scale-free features of neuroimaging turn out to be diagnostically useful, however, their underlying neurobiological basis is poorly understood. Using modeling and simulations of a schematic prefrontal-limbic meso-circuit, with excitatory and inhibitory networks of nodes, we present here a framework for how network density within a control system can affect the complexity of signal outputs. Our model demonstrates that scale-free behavior, similar to that observed in fMRI PSSI data, can be obtained for sufficiently large networks in a context as simple as a linear stochastic system of differential equations, although the scale-free range improves when introducing more realistic, nonlinear behavior in the system. PSSI values (reflective of complexity) vary as a function of both input type (excitatory, inhibitory) and input density (mean number of long-range connections, or strength), independent of their node-specific geometric distribution. Signals show pink noise ($1/f$) behavior when excitatory and inhibitory influences are balanced. As excitatory inputs are increased and decreased, signals shift towards white and brown noise, respectively. As inhibitory inputs are increased and decreased, signals shift towards brown and white noise, respectively. The results hold qualitatively at the hemodynamic scale, which we modeled by introducing a neurovascular component. Comparing hemodynamic simulation results to fMRI PSSI results from 96 individuals across a wide spectrum of anxiety-levels, we show how our model can generate concrete and testable hypotheses for understanding how connectivity affects regulation of meso-circuits in the brain.

Introduction

Measures of complexity are sensitive in detecting disease, which has made them attractive candidates for diagnostic biomarkers. One straightforward way of characterizing complexity is the use of power spectrum scale invariance (PSSI), which measures the relative frequency content of signals whose spectra show power law behavior: $S(f) \propto f^{\beta}$. In this context, the scaling exponent β is 0 (white-noise) at maximum entropy, with $\beta = -1, -2$ representing the increasing regularity of pink and brown noise respectively. To date, several studies have applied complexity analyses to fMRI, and have shown that for healthy neurobiological states, the entropy of neural time-series is characterized by roughly $\beta = -1$ ($S(f) \propto 1/f$), while neural time series in schizophrenia (Rădulescu et al., 2012), anxiety (Tolkunov et al., 2010), and autism (Lai et al., 2010), show a significant shift towards $\beta = 0$. In contrast, EEG signals from patients with epilepsy also deviate from the pink noise range, but in this case towards greater regularity (Bhattacharya et al., 2000; Bruzzo et al., 2008; Molteni et al., 2008; Protzner et al., 2010). The fact that complexity should be able to identify disease states is not unique to the brain: the diagnostic use of fractals and complexity as applied to ECG has a long-standing history in physiology, most particularly in its application of heart-rate variability (HRV) to detect risk for myocardial infarction and heart disease (Cerutti et al., 2009; Ho et al., 1997; Kaplan et al., 1991; Li et al., 2007; Mäkikallio et al., 1998; Mujica-Parodi et al., 2005; Peng et al., 1994; Pincus and Goldberger, 1994; Stanley et al., 1992; Valencia et al., 2009; Voss et al., 1995).

Even if spectral power law features of neuroimaging turn out to be diagnostically useful, however, their underlying neurobiological basis is poorly understood. In the case of HRV, complexity in the healthy heart-rate is assumed to be a consequence of autonomic control. A healthy autonomic nervous system has excitatory (primarily sympathetic) and inhibitory (primarily parasympathetic) components that work in tandem, ensuring a system that is supple enough to easily respond to even small stimuli, yet constrained enough to efficiently return to baseline. Thus, the fact that healthy heart rates fall in the pink noise range (Peng et al., 1993, 1995), balanced between chaos and order, seems intuitive not only from a physical and dynamical systems perspective, in which pink noise is associated with the metastable point at which phase transitions occur (Gisiger, 2001), but also as a physiologically-plausible consequence of negative feedback.

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Unlike the autonomic nervous system, however, the brain's networks (at multiple scales) are still very much in the early stages of being defined, and thus present a much greater challenge in terms of identifying their relationship to the complexity of measured electrophysiological or hemodynamic signals. Nevertheless, and in spite of numerous parallel pathways within the system, there do appear to be meso-circuits that have predominant excitatory and inhibitory components, and that function at scales measurable in the awake animal and human. One such meso-circuit is the prefrontal-limbic system, for which the amygdala and prefrontal (orbitofrontal, ventromedial, dorsolateral) regions provide up and down-regulation of the emotional arousal response, respectively (Baxter et al., 2000; Davis et al., 2001; Izquierdo and Murray, 2005; LeDoux, 2000; Mujica-Parodi et al., 2009; Phelps et al., 2004; Rosenkranz et al., 2003; Sotres-Bayon et al., 2006).

Recent studies have used random network approaches to investigate the organizational principles of brain networks (Bullmore and Sporns, 2009), with nodes and edges defined according to modality appropriate scales (Sporns, 2010). Since the temporal evolution of a network is expected to depend on a combination of its hardwired circuitry and its dynamic coupling, much work has been directed towards understanding the effect of the neural architecture on neural function (Boccaletti et al., 2006). The stability and synchronization patterns of brain networks with coupled randomly distributed excitatory and inhibitory neural populations have been investigated, both analytically and numerically, in a variety of contexts: from biophysical models (Gray and Robinson, 2008), to simplified systems (Siri et al., 2007). These analyses reveal a rich range of potential dynamic regimes and transitions (Brunel, 2000), shown to depend as much on the coupling parameters of the network as on the arrangement of the excitatory and inhibitory connections (Gray and Robinson, 2009). In fact, from a graph theoretical perspective, studies support certain generic topological properties of the human brain architecture, such as modularity, small-worldness, the existence of hubs and other connectivity density patterns (He and Evans, 2010).

Here, we take a similar random network based approach to investigate general constraints on how dynamic activity can emerge and be modulated by connectivity between excitatory and inhibitory nodes in a meso-circuit with feedback (e.g., the prefrontal-limbic system), viewed as a network of hemodynamic nodes relevant to fMRI studies. Using modeling and simulations, we present a framework for how network density within our control system can affect the complexity of signal outputs. We build upon our previous black-box models (Rădulescu, 2008, 2009), to include two interconnected brain networks, one excitatory and the other inhibitory. The model was designed within the constraints of three broad parameters. First, it needed to be simple enough to analyze mathematically as well as to simulate using reasonably-sized ($\sim 10^2$-node) networks. Second, it needed to be multi-layered, such that, at the hemodynamic scale, networks of nodes could be nested within the interaction of the two primary brain regions. Third, the model should schematically represent the prefrontal-limbic system in order to inform our neuroimaging results of that same system, but constraints should be sufficiently general to maintain relevance for other neural control circuits. With this last goal in mind, we chose to incorporate a neurovascular component and to characterize complexity using PSSI, to permit comparison with prior fMRI results (Lai et al., 2010; Rădulescu et al., 2012; Tolkunov et al., 2010).

The general aim was to provide a theoretical bridge between deviations in signal complexity measured at the hemodynamic scale, and the connectivity that might underlie it. Because many different models can produce the same behavior, it is not possible to use behavior to "test" whether a model is correct. Nevertheless, models can provide a way to determine whether certain types of parameters and their interactions are *capable* of leading to certain kinds of outcomes, generating well-defined hypotheses that can then be tested empirically. In this case, we wanted to identify a (neurobiologically-plausible, testable) mechanism that might explain how network properties in a control system affect the distribution of frequencies (complexity) of signal outputs. While the control structure is not unique to the prefrontal-limbic system, our reference to that meso-circuit was motivated by two considerations. First, animal and human experiments had already identified excitatory and inhibitory components, making it a reasonable candidate for control systems modeling. Second, we hoped that it might be able to inform our results from two fMRI studies of healthy individuals, one on stress vulnerability and the other on stress resilience, which together showed a consistent pattern between PSSI of the prefrontal-limbic system and susceptibility to anxiety.

Methods

Modeling methods

In our model, we construct two interacting networks of nodes, such that each node is self-damping, interacts locally with all others within its module (thus obtaining some degree of modular internal synchronization) and also has long-range connections with a variable fraction of the nodes in the opposite module (Fig. 1).

We represent these two interacting networks, module X and module Y, by two sets of variables: x_k, $k = 1,\ldots,N$ and y_k, $k = 1,\ldots,N$ respectively, obeying the constraints described by the following system of 2 N first order linear differential equations:

$$\begin{aligned}\frac{dx_k}{dt} &= -\gamma_x x_k + \sum_{p=1}^{N} g_{yx} A_{kp}\left(y_p - x_k\right) + \sum_{p=1}^{N} g_{xx}\left(x_p - x_k\right) + I_k(t)\\ \frac{dy_k}{dt} &= -\gamma_y y_k + \sum_{p=1}^{N} g_{xy} B_{kp}\left(x_p - y_k\right) + \sum_{p=1}^{N} g_{yy}\left(y_p - y_k\right),\end{aligned} \tag{1}$$

where the parameters represent the following: γ_x and γ_y are damping coefficients, g_{xx} and g_{yy} are local connection strengths, assumed to be the same within each module; g_{xy} and g_{yx} are long-range connection strengths (from nodes in X to nodes in Y, and conversely). The damping coefficients guarantee the decay to zero of solutions in absence of external forcing terms. These parameters can be drawn more generally from prescribed distributions of values (see the Modeling nonlinearity section); in this section, however, we use for each type of parameter a fixed (mean) value, in order to keep our formal calculation of the spectra more tractable. M_{xy} and M_{yx} represent densities of edges between X and Y. More precisely, one can define α to be the number of oriented edges from nodes in X to nodes in Y, and δ to be the number of oriented edges from nodes in Y to nodes in X, so that $0 \le \alpha, \delta \le N^2$. We consider the corresponding edge densities to be normalized as $M_{xy} = \alpha/N^2$ and $M_{yx} = \delta/N^2$, so that $0 \le M_{xy} \le M_{yx} \le 1$. Note that the densities M_{xy} and M_{yx} are fractions (or percentages) of N^2, which represent the maximum number of edges that could run from each module to the opposite one.

The equations were inspired by a system of coupled springs, in which the driving force imposed on each spring by another with

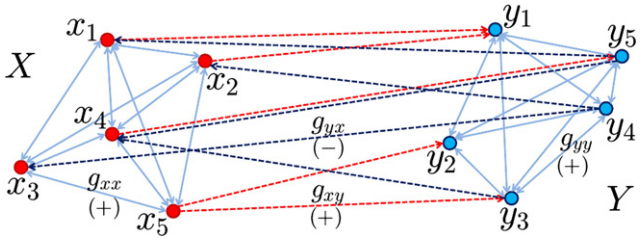

Fig. 1. Schematic representation of bimodular network for $N = 5$ nodes per module. The excitatory neural population X is shown on the left; the inhibitory population Y is shown on the right. They are both fully-connected, local sub-graphs of the full network. The dotted red arrows represent the long-range X–Y connections, and the dotted blue arrows represent the Y–X connections, all generated randomly for low feed-forward and feedback connectivity densities $M_{yx} = M_{yx} = 25\%$, to maintain clarity of the illustration.