SIMULATION OF FUNCTIONAL CONNECTIVITY AMONG BRAIN CORTICAL AREAS USING A NEURAL MASS MODEL

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Abstract: Analysis of functional connectivity between different brain areas has become a fundamental problem in neuroscience today. Aim of this work is to use a neural mass model, consisting of several populations arranged in parallel, in order to simulate power spectral density of EEG activity in a region of interest (ROI) and to study how this is modified by various connectivity patterns among ROIs. Results show that i) the proposed model is able to mimic the power spectral density of EEG activity in different ROIs quite well, acting on its external input, ii) the power spectral density is significantly modified by the kind of coupling hypothesized among the ROIs. The present study suggests that the model can be used as a simulation tool, able to produce reliable intracortical EEG signals. The possibility to simulate the effect of connectivity on EEG power spectral density might be exploited in future works, to design new methods for connectivity assessment from scalp EEG based on physiological models.

Introduction

Brain processing, even during simple cognitive tasks, is the result of the interaction among several cortical regions, which are reciprocally interconnected and functionally integrated. In this context, a crucial role in neurophysiology is played by the concept of brain connectivity. Knowledge of connectivity is considered essential today to understand how the brain works, and to assess the role of different regions in the achievement of specific cognitive functions.

Despite the large number of studies appeared in last years for assessment of connectivity from EEG/MEG data, there is no definite consensus today on the best method, nor on the significance of the results obtained, and on the possible causes of error.

An interesting new opportunity, still at the pioneering stage, consists in the use of neurophysiological models (i.e., models based on biology) to derive effective connectivity from real data. These models may be useful to establish causal relationships among remote cortical regions, to gain a deeper insight into the underlying neural processes, and to establish some basic mechanisms for signal generation (including non-linearities).

Two main classes of models are used in neurophysiological simulation: detailed models, which include a description of network dynamics at the level of a single neuron [1], and mascroscopic models. In the latter, the state variables represent the dynamics of entire neural populations instead of single neurons. This dynamics generally emerges from the interaction of excitatory and inhibitory sub-populations, arranged in feedback. Neural mass-models of cortical columns, particularly useful to simulate realistic EEG signals, were developed by Lopes da Silva et al.[2] and by Freeman [3] in the mid seventies, and subsequently improved and extended by Jansen and Rit [4] and Wendling et al. [5]. Although neural mass models have been used to simulate several aspects of EEG, only a few studies used these models to simulate the overall frequency content of electrical activity in a cortical region of interest (ROI), or to assess effective connectivity among several ROIs participating to the same task.

Recently, David et al. [6] used the Jansen model to simulate how the MEG/EEG spectrum can be modified by changing a few parameters which describe population kinetics, and investigated how these spectra can be altered by a connection between two coupled cortical areas, and including simple different hierarchical arrangements [7]. The authors reached the conclusion that both the coupling strength and propagation delay have a critical impact of MEG/EEG spectra. Then, the authors used signals generated by the same model to test the validity of different measures of functional connectivity [8].

Robinson, Rowe et al. proposed a model to generate EEG signals [9], and used this model to estimate neurophysiological parameters from EEG [10] in a broad range of frequency (0.25-50 Hz). These works represent a significant advancement in EEG modelling, and provide an understanding of EEG spectra in terms of cortical and thalamo-cortical mechanisms. However, they are not explicitly devoted to the problem of effective connectivity assessment among ROIs.

The present study continues on the same route, with the aim of using a neural mass model [5] to study connectivity among cortical regions. Two main objectives are pursued. First, we wish to investigate whether a model, based on several populations arranged in parallel, is able to mimic the frequency content of

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real EEG spectra, with a suitable choice of synaptic parameters, and acting on the input signals only. This step has the objective to choice a model for EEG generation in a single ROI, devoted to the problem of input/output assessment (hence connectivity), with a good compromise between accuracy and complexity. Second, we wish to investigate the effect of different patterns of connectivity among ROIs (each described via the previous model), by using a sensitivity analysis on the parameters specifying this connectivity. Here, the objective is to reach a deeper understanding of how connectivity influences spectra.

Although the present results are clearly preliminary, and still require further validation, they may open a promising route in the problem of estimation connectivity using neurophysiological models.

Materials and Methods

Model of one neural population - The model of a single population was obtained by modifying equations proposed by Wendling et al. [5]. In this model cortical activity derives from the interaction among four neural groups: pyramidal cells, excitatory interneurons, inhibitory interneurons with slow synaptic kinetics, and inhibitory interneurons with faster synaptic kinetics (see Figure 1).

Each neural group receives an average postsynaptic membrane potential from the other groups, and converts the average membrane potential into an average density of spikes fired by the neurons. This conversion is simulated via a static sigmoidal relationship. The effect of the synapses is described via second order linear transfer functions, which convert the presynaptic spike density into the postsynaptic membrane potentials. Three different kinds of synapses, with impulse response h_e, h_i and h_g, (see Figure 1), are used to describe the synaptic effect of excitatory neurons (both pyramidal cells and excitatory interneurons), of slow inhibitory interneurons and of fast inhibitory interneurons, respectively.

According to Figure 1, model equations can be written as follows:

Pyramidal neurons

$$\begin{aligned}
&\frac{dy_0(t)}{dt} = y_5(t)\\
&\frac{dy_5(t)}{dt} = A\cdot a_1\cdot z_0(t) - 2\cdot a_1\cdot y_5(t) - a_1^{\,2}\cdot y_0(t)\\
&z_0(t) = \frac{(2\cdot e_0)}{1+e^{r\cdot(s_0-v_0)}}\\
&v_0(t) = \mathrm{C}_2\cdot \mathrm{y}_1(\mathrm{t}) - \mathrm{C}_4\cdot \mathrm{y}_2(\mathrm{t}) - \mathrm{C}_7\cdot \mathrm{y}_3(t)
\end{aligned} \tag{1}$$

Excitatory interneurons

$$\begin{aligned}
&\frac{dy_1(t)}{dt} = y_6(t)\\
&\frac{dy_6(t)}{dt} = A\cdot a_1\cdot (z_1(t) + \frac{p(t)}{C_2}) - 2\cdot a_1\cdot y_6(t) - a_1^{\,2}\cdot y_1(t)\\
&z_1(t) = \frac{(2\cdot e_0)}{1+e^{r\cdot(s_0-v_1)}}\\
&v_1(t) = \mathrm{C}_1\cdot \mathrm{y}_0(\mathrm{t})
\end{aligned} \tag{2}$$

Slow inhibitory interneurons

$$\begin{aligned}
&\frac{dy_2(t)}{dt} = y_7(t)\\
&\frac{dy_7(t)}{dt} = B\cdot b_1\cdot z_2(t) - 2\cdot b_1\cdot y_7(t) - b_1^{\,2}\cdot y_2(t)\\
&z_2(t) = \frac{(2\cdot e_0)}{1+e^{r\cdot(s_0-v_2)}}\\
&v_2(t) = \mathrm{C}_3\cdot \mathrm{y}_0(\mathrm{t})
\end{aligned} \tag{3}$$

Fast inhibitory interneurons

$$\begin{aligned}
&\frac{dy_3(t)}{dt} = y_8(t)\\
&\frac{dy_8(t)}{dt} = G\cdot g_1\cdot z_3(t) - 2\cdot g_1\cdot y_8(t) - g_1^{\,2}\cdot y_3(t)\\
&z_3(t) = \frac{(2\cdot e_0)}{1+e^{r\cdot(s_0-v_3)}}\\
&v_3(t) = \mathrm{C}_5\cdot \mathrm{y}_0(\mathrm{t}) - \mathrm{C}_6\cdot y_2(t)
\end{aligned} \tag{4}$$

In these equations, the symbols v_i represent the average membrane potential (i = 0, 1, 2, 3 for the four groups). These are the input for the sigmoid function which converts it into the spikes (z_i, i = 0, 1, 2, 3) fired by the neurons. Then, this output enters into the synapses (excitatory, slow inhibitory or fast inhibitory), represented via the second order linear functions. Each synapse is described by a synaptic gain (A, B, G for the excitatory, slow inhibitory and fast inhibitory synapses, respectively) and a time constant (the reciprocal of a_1, b_1 and g_1, respectively). The outputs of these equations, which can be excitatory, slow inhibitory or fast inhibitory, represent the postsynaptic membrane potential (y_i, i = 0, 1, 2, 3). Interactions among neurons are represented via seven connectivity constants (C_i). Finally, $p(t)$ represents a Gaussian white noise with assigned mean value and variance, which describes the overall density of action potentials coming from other regions. This term will be modified to simulate connectivity among different ROIs.

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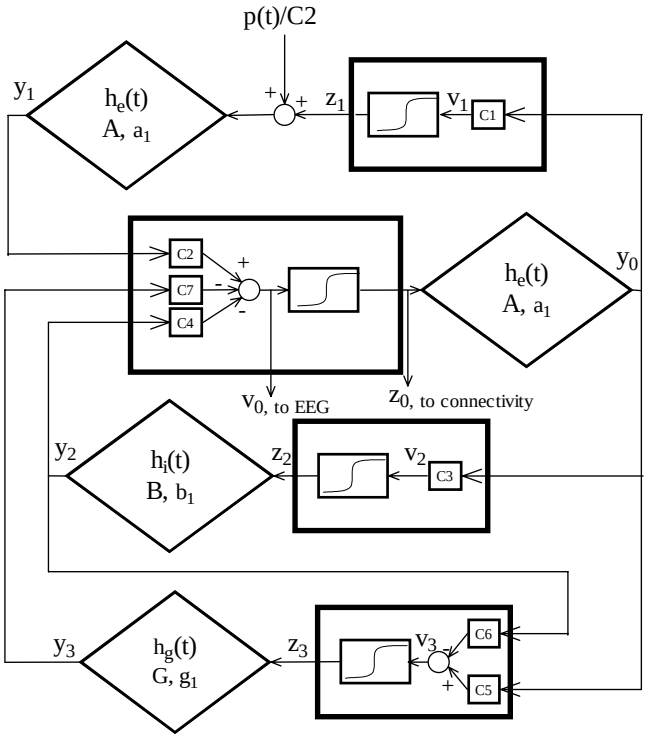

Figure 1: Layout of a single population model

Model of a region of interest (ROI) - The previous model was used to simulate a single population, the dynamic of which ensues from the interactions of the four neural subgroups. As shown in David et al. [6], however, a single population can produces just a single rhythm, i.e., it is unable to simulate the entire frequency content of a real EEG. For this reason, the model of an overall ROI has been constructed by using three populations arranged in parallel. Each population is characterized by different values of time constants (i.e., of parameters a_1, b_1, g_1) and so can produce a different rhythm. In the following, these three populations will be denoted with the superscript L, M and H, to represent rhythms at low, medium and high frequency. The cortical EEG of a ROI (say $v_{out}(t)$) is obtained as the mean value of the membrane potentials of pyramidal neurons in the three populations (i.e., averaging quantity v_0). We have

$$v_{out(t)} = \frac{1}{3}\sum_k v_0^k(t) \qquad \text{k} = \text{L, M, H} \tag{5}$$

Finally, in order to simulate connectivity among different ROIs (see below), we also computed the average spike density of all pyramidal cells in the three populations (say $z_{out}(t)$). We have:

$$z_{out}(t) = \frac{1}{3}\sum_{k=1}^{3} z_0^k(t) \qquad \text{k} = \text{L, M, H} \tag{6}$$

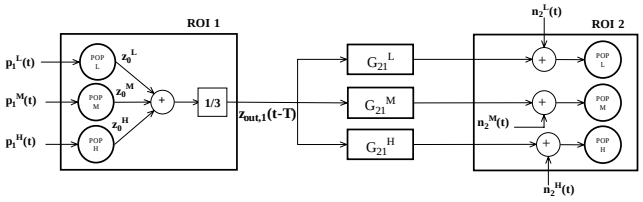

Figure 2: Example of connectivity between two ROIs

Model of connectivity - A critical problem in this study concerns the choice of the model for connectivity among different ROIs. In fact effective connectivity is model-dependent, and different choices may lead to different results. David et al., in a recent paper [7], simulated various types of connectivity among two cortical areas: "bottom-up", top-down" and "lateral". In all these patterns the output is the spike density of pyramidal cells, but the targets depend on the type of connection.

In the present work we assumed that all connections among ROIs are "bottom-up" in type. This choice is justified by the fact that we wish to apply our model to a generic cognitive task, without entering into a hierarchical organization of the different zones involved.

To simulate connectivity, we assumed that the average spike density of pyramidal neurons (i.e., the quantity $z_{out}(t)$ in Eq. 6) affects excitatory interneurons in the target region via a gain factor, G, and a time delay, T. This is achieved by modifying the quantity $p(t)$ in Eq. 2. In the following, in order to deal with several ROIs simultaneously, we will use the subscripts i (or j) to denote a quantity which belongs to the ith (or jth) ROI, while the superscript k will be used to denote the kth population in the same ROI. Hence, the input $p_i^k(t)$ to the kth population in the ith ROI can be computed as follows

$$p_i^k(t) = n_i^k(t) + \sum_j G_{ij}^k z_{out,j}(t-T) \tag{7}$$

where G_{ij}^k is the gain of the synaptic link from the jth (pre-synaptic) ROI to the kth population of the ith (post-synaptic) ROI, T is the time delay (assumed equal for all synapses), $n_i^k(t)$ represents a gaussain white noise with mean value m_i^k and standard deviation σ_i^k, and the sum in the right hand member of Eq. 7 is extended to all ROIs, j, which target into the ROI i.

An example of connectivity among 2 ROIs is illustrated in Figure 2. In the present study, all time delays among ROIs have been taken equal to 10 ms. The gain factors have been assigned different values, in order to simulate various patterns of connectivity and analyze their influence on the EEG of the downstream region.

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Results

The first group of simulations has been performed to analyze how the EEG power spectral density of a single ROI depends on the input noise (i.e., on the quantities $n_i^k(t)$ in Eq. 7) in the absence of connectivity. This preliminary analysis is important to understand whether the model is able to mimic reliable spectral patterns, characterized by different rhythms, by acting on its input only. Simulations, not shown here for brevity, show that different patterns of EEG, characterized by power in different frequency ranges, can be easily obtained by modifying the mean value of the input noise to the individual populations (see an example in Figure 3). This result confirms that the proposed model for a ROI is general enough to embrace the complexity of EEG spectral content, with a suitable choice of its endogenous input.

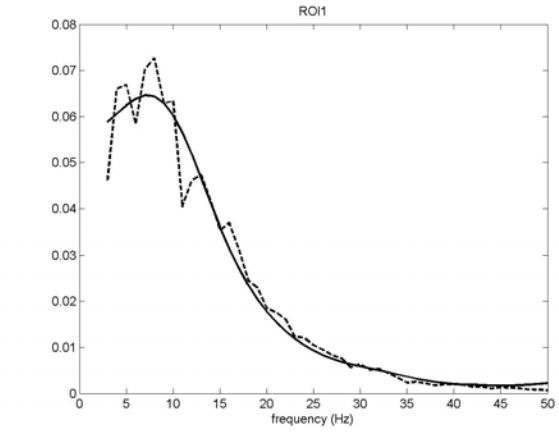

Figure 3: Example of manual fitting of an experimental ROI (continuous line). The power spectral density of the model output (dashed line) is obtained using these values for the mean and variance of the three populations: m_1^L =10, m_1^M =200, m_1^H =-50 and $(\sigma_1^L)^2 = (\sigma_1^M)^2 = (\sigma_1^H)^2$ =20.

In the reality, the input (Eq. 7) reflects not only external stimuli, but above all activity coming from other regions participating to the same task and functionally integrated. Hence, in the subsequent simulations we will consider a network of three ROIs, and we will study how their power spectral densities can be modified by the pattern of connectivity among them. The use of just three ROIs is justified by the wish to maintain a moderate level of complexity in this initial study. In particular, we will assume that the first ROI (subscript i = 1) receives significant input noise but does not receive connections from the other regions. Parameters of the input noise (mean values and variances) have been chosen to mimic the power spectral density of cortical activity in an exemplary brain region evaluated from scalp EEG using the inverse propagation method described in [11], during a finger motor task.

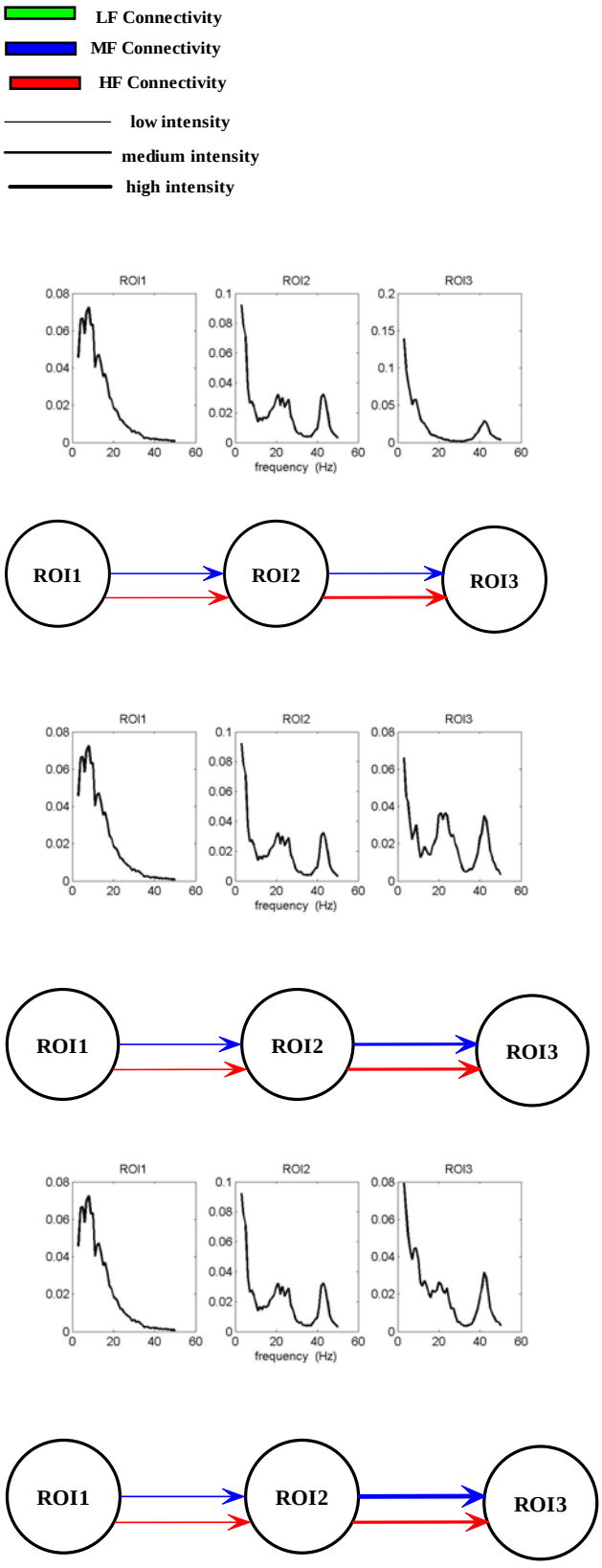

Figure 4: Examples of hypothetical connectivity among three regions, simulated by the model of a ROI described before.

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A comparison between model power spectral density of the first ROI and the experimental one is shown in Figure 3, where parameters used for the noise are also reported. By contrast, we assumed that the other two ROIs (i = 2, 3) receive negligible noise and are activated mainly as a consequence of connections from the other regions. The previous choice is the same as to assume that region 1 receives most of the external stimulus which triggers the motor task, and drives the other two regions.

Three simple examples of how feedforward connectivity can modify the EEG power spectral density in regions 2 and 3 are displayed in Figure 4. The effect of feedback connections among regions 2 and 3 will be analyzed in a subsequent work. This figure illustrates that the pattern of connectivity is reflected into evident and well-detectable changes in the EEG spectrum. In the first case the coupling moves from the first region (ROI1) to the second one (ROI2) with a MF connectivity strength of 10 (low intensity) and a HF connectivity strength of 10 (low intensity) and from the second region (ROI2) to the third one (ROI3) with a MF connectivity strength of 10 (low intensity) and a HF connectivity strength of 50 (medium intensity). Connectivity causes evident peaks in the ROIs. In the second case the coupling is the same as the previous example but with a MF connectivity strength of 50 (medium intensity) from ROI2 to ROI3. In this case the MF peak in ROI3 is more evident. Finally, in the third case the coupling is the same as in the previous example but with a MF connectivity strength of 120 (high intensity) from ROI2 to ROI3. In this case the peak is less evident because activity in the second population in ROI3 saturates, and this saturation reduces the power in the frequency band. This example illustrates the apparently paradoxical case in which an *increase* in connectivity strength (MF from ROI2 to ROI3) induces a *decrease* in power density, by causing neurons to enter into the saturation state. This is a direct consequence of the non-linear sigmoidal relationship used in these models to describe the spiking activity of neurons.

Discussion

The study of brain connectivity represents a fundamental aspect of neurophysiology today. In fact, an integrate understanding of human brain function requires not only knowledge of the different areas involved in a given task, but also of their reciprocal connections and functional links. Various authors in past years suggested that neural mass models may represent a promising tool for the analysis of this problem, in association with data obtained with functional neuroimaging techniques (fMRI or PET) and/or high resolution EEG or MEG [12]. The present work aspires at analyzing the possible use of an updated neural mass model, for the study of brain connectivity. This study was divided in different phases. In the first, we simulated the main characteristics of cortical EEG power density in the range 3-50 Hz, by simply acting on its input. To this end, we adopted a model composed of three subpopulations arranged in parallel, each population being simulated with the model by Wendling et al [5], but with different values of its parameters (in particular, with different synaptic kinetics). This choice is justified by the observation that a single population can generate a power density spectrum with only one peak and quite a narrow frequency band. The choice to pack several populations in parallel within the same ROI, and adopt a linear combination of their activity (or of their membrane potential) as an output for the ROI, agrees with the choice adopted by David et al. recently [6].

The first purpose of our simulations was to verify whether the proposed model for a ROI is able to simulate different EEG PSD, by simply assuming a different input noise. This was a necessary requisite to use the model as an instrument to generate reliable signals and/or to infer connectivity from data. The subsequent step was to test how connectivity may modify EEG power density. Although in the present work we displayed just a few exemplary simulations these clearly show that connectivity induces evident changes in spectral content.

The example of feedforward connectivity among ROIs, depicted in Figure 4, resemble those shown in David et al. [6]. However, there are significant differences between our model of connectivity and that used by these authors. These differences may be reflected in different circuits for the interpretation of data. First, in David et al. connectivity from one ROI to another is described only by means of a constant gain factor and a time delay. By contrast, we used three gain factors, assuming that the connection strength may vary depending on the sub-population involved (i.e., with slow, medium or fast kinetics). The main consequence of this choice is that, in our model, a presynaptic ROI may induce a rhythm in a different frequency-band of the target ROI, i.e., it is not necessary that the pre-synaptic ROI contains the same rhythm that it induces downstream. This is evident, for instance, in Figure 4, where a rhythm at medium frequencies appears in the ROI 2, although this was not evident in ROI 1. We judge that this possibility is important to arrive at a proper understanding of brain connectivity. In our approach, connectivity may be described in the frequency domain: it is not a simple scalar number, but a more complex entity which depends on the particular rhythm (or frequency band) considered.

A second major difference between our model of connectivity and that by David et al. is that these authors maintained a constant average input to each ROI, i.e., they preserved mean value and standard deviation of presynaptic input independent of the connection strength (in their work coupling among two ROIs just modifies the ratio of the input attributable to the source area vs. the extrinsic noise). In other words, coupling does not modify the equilibrium activity of each population. By contrast, in our approach a strong connection may significantly modify the average

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activity. This has strong consequences, which are underlined in Figure 4. In certain cases, increasing connectivity may lead to a saturation of the post-synaptic population. This saturation may be reflected in a decreased variance of all quantities in the population and so in a reduced power density in the given frequency band. Hence, in our study non-linear effects become much more evident than in former ones.

Conclusions

The present study suggests that the model can be used as a simulation tool, able to produce reliable signals with different patterns of EEG power spectral density, and to mimic the effect of different imposed configurations of connectivity. The use of the model as a simulation tool can be useful in future studies, for instance to provide artificial signals to test methods actually adopted to infer connectivity from data [11]. The possibility to simulate the effect of connectivity on EEG power spectral density might be exploited to design new methods for connectivity assessment from high resolution scalp EEG, based on physiological underlying models, instead of on empirical or data-driven models.

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