Introduction

Function of the brain is the consequence of the interaction among several cortical regions, which are reciprocally interconnected. Knowledge of connectivity facilitates our understanding of how the brain works, and helps us to assess the role of different areas in the success of specific cognitive functions. Connectivity can be defined in the following three ways: structural, functional, and effective connectivity (Lee et al., 2003a,b; Wendling et al., 2002). The anatomical layout of axons and synaptic connections can be considered as the structural connectivity that shows the direct interaction among neural units (Zeki and Shipp, 1988). The functional connectivity in the analysis of neuroimaging time-series is defined as the temporal correlations between spatially remote neurophysiological events (Friston, 1994). The influence that one neural system exerts on another one has been defined as effective connectivity which requires a causal model connecting several brain regions (Friston, 1994; Friston et al., 1993, 2003).

Two main classes of models have been proposed for the effective connectivity: detailed models, which are at the level of a single neuron (Makarov et al., 2005), and macroscopic models in which the state variables represent the dynamics of entire neural populations. In detailed models, due to the very large number of parameters involved and the strong dependencies between them, it is usually impossible to fit them to empirical data. However, they can be used for simulations (Deco et al., 2004; Husain et al., 2004). The macroscopic models such as the neural mass model (NMM) and the mean-field model were originally developed to simulate activity in the olfactory cortex (Freeman, 1987) and the spontaneous alpha rhythms (Lopes da Silva et al., 1974). These models have subsequently been improved and extended (Jansen and Rit, 1995; Wendling et al., 2002; Wendling et al., 2000). They use a few state variables to represent the mean activity of a large neuronal population. In recent years, the NMM has been used in neuroimaging applications to generate spontaneous rhythms in various frequency bands (Babiloni et al., 2003; David and Friston, 2003), to study generation of the epileptic activities (Wendling et al., 2002, 2000), to analyze the connectivity and coherence on electroencephalography (EEG) rhythms (Zavaglia et al., 2008), and to generate the event related responses (David et al., 2005; Rennie et al., 2002). The NMM
has also been used to simulate positron emission tomography (PET) imaging (Horwitz et al., 1999; Tagamets and Horwitz, 1998, 2000) as well as for integrated modeling of EEG, magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI) (Babajani and Soltanian-Zadeh, 2006; Daunizeau et al., 2007; Riera et al., 2005, 2007, 2006; Sotero and Trujillo-Barreto, 2008).

Friston et al. (2003) and Stephan et al. (2007a) developed Dynamic Causal Modeling (DCM), a general framework for the effective connectivity that makes inferences about processes at the neural level given measured imaging data. DCM is represented by state-space equations whose state equation is deterministic (noise-free) and thus the noise model is limited to the measurement noise. Parameters of the DCM are estimated from measured data using variational Bayesian inversion. DCM has been used separately for fMRI (Allen et al., 2008; Booth et al., 2008; Booth et al., 2007; Brazdil et al., 2007; Cao et al., 2008; Etheofer et al., 2006; Grefkes et al., 2008; Kasess et al., 2008; Kiebel et al., 2007b; Kim et al., 2007; Marreiros et al., 2008; Mechelli et al., 2003; Schlosser et al., 2008; Sonty et al., 2007; Stephan et al., 2006a, 2007b) and EEG/MEG (Chen et al., 2008; David et al., 2005, 2006, 2008; Fastenrath et al., 2009; Garrido et al., 2007; Kiebel et al., 2006, 2007a; Lee et al., 2006). For EEG/MEG data, DCM is based on Jansen’s NMM (Jansen and Rit, 1995) where long-range cortico-cortical connections are embodied by considering forward, backward, and lateral connections among remote areas (David et al., 2006). DCM is used for investigating a wide range of functional neuroimaging applications at different temporal and spatial scales (David and Friston, 2003; Moran et al., 2007, 2008; Stephan et al., 2008b). There are alternative approaches for characterizing effective connectivity, e.g., proposed methods in Riera et al. (2006) and Valdes-Sosa et al. (2005), however, DCM is used in a variety of studies for broad neuroimaging purposes.

We proposed two integrated E/MEG and fMRI models for the effective connectivity Babajani et al. (2005). In the first model, we introduced a stochastic model based on the conditions of the postsynaptic potentials (PSPs) that generate MEG and fMRI signals. Here, directions and strengths of PSPs are modeled using several physiological parameters which are treated as random variables. The expected values of the direction and strength of the current flow of PSPs in active voxels are calculated and used to generate the corresponding MEG and fMRI signals. We estimated the parameters of the model in a real condition using MEG and fMRI datasets from seven normal subjects gathered using a simple auditory stimulus (Babajani-Feremi et al., 2008). For the auditory tone stimulus, we illustrated the capability of the proposed integrated analysis method to generate high-resolution spatiotemporal activation map.

In the second integrated E/MEG and fMRI model which is the base of this paper, we proposed an extended neural mass model (ENMM) in a single cortical area (Babajani and Soltanian-Zadeh, 2006). In the ENMM, the area contains several minicolumns where the intra-minicolumn dynamics are modeled by the Jansen’s NMM using the intra-minicolumn parameters (Jansen and Rit, 1995). Using the physiological principles of the cortical minicolumns and their connections according to previous studies (Buxhoeveden and Casanova, 2002; Mountcastle, 1997), we considered short-range inter-column connections and extended the Jansen’s model to the ENMM. In the model, the EEG and MEG signals are generated by synaptic activations of the pyramidal cells in the minicolumns. We extracted the fMRI signal from the proposed ENMM by calculating the relationship between the stimulus and the overall neural activity and using it as the input of the extended Balloon model (Friston et al., 2000). We validated the proposed model by comparing the simulations with the experimental results.

In this paper, we further extend our proposed ENMM from a single-area model to the entire brain containing all active cortical areas related to a specific external stimulus. For multi-area modeling, two connection types are considered: short-range connections (SRCs) and long-range connections (LRCs). The SRCs among intra-area minicolumns were previously modeled in the ENMM (Babajani and Soltanian-Zadeh, 2006). The LRCs characterize configuration of the multi-area model with describing the connections among the cortical areas. To define LRCs among the cortical areas, we consider that the three cell populations (stellate cells, pyramidal cells, inhibitory interneurons) of all minicolumns in the destination area are affected by the excitatory afferent of the pyramidal cells of all minicolumns in the source area. The state-space representation of the multi-area model is derived considering the SRCs’ and LRCs’ parameters. Here, we focus on the EEG and the MEG signals in the model to verify the effects of the parameters of the model on its dynamics and find valid ranges for the parameters. In future, we will extend the proposed model to a multi-area integrated E/MEG and fMRI model.

DCM uses the variational Bayesian approach to estimate the parameters of the model based on the assumption that the state equation is noise-free and the system noise is limited to the measurement noise. Therefore, DCM is a deterministic state-space model (SSM) stated in terms of ordinary differential equations. Stochastic extension of the DCM is recently proposed where both of the state noise and the observation noise are considered in the model (Daunizeau et al., 2009). Similar to stochastic DCM, both of the state noise and the observation noise are considered in our proposed multi-area model. In future, we will introduce a variational Bayesian expectation maximization (VBEM) method to estimate the sufficient statistics of the parameters and the hidden state variables as well as the precisions (inverse variances) of the state and observation noises of the proposed multi-area model. The VBEM method will be based on the proposed method in Beal and Ghahramani (2001a), Beal (2003), Ghahramani and Beal (2000, 2001), and Ghahramani and Hinton (1996) for the linear SSM. The performance and excellent capability of the VBEM method for linear SSM are illustrated in Beal (2003). We will extend the proposed method in Beal and Ghahramani (2001a), Beal (2003), Ghahramani and Beal (2000, 2001), and Ghahramani and Hinton (1996) from a linear SSM to our multi-area ENMM which is a nonlinear SSM. The VBEM algorithm leads to analytically tractable forms and has the capability to outperform the Laplace approximation method which is used in the deterministic or stochastic versions of the DCM (see Discussions). It should be noted that a combination of the proposed multi-area ENMM and an inversion method to estimate its parameters, e.g., VBEM method, is expected to improve solution of the inverse problem of E/MEG. This is because the multi-area ENMM can realistically model the interactions among the active cortical areas.

Our proposed approach will generate several improvements compared to the DCM which has been widely used for the effective connectivity. First advantage of our proposed multi-area NMM is to use more realistic model compared to the DCM. Each cortical area in the DCM is modeled by the Jansen’s NMM which is a simplified model and is unable to generate complicated dynamics of the cortical area. However, our proposed model uses the ENMM in each area which has superior performance compared to the Jansen’s model, as we illustrated in Babajani and Soltanian-Zadeh (2006). Therefore, our model more realistically and comprehensively models the dynamics of the cortical areas. The DCM can separately analyze E/MEG and fMRI signals but our proposed multi-area model has the capability of integrated E/MEG and fMRI modeling and analysis that enables us to exploit complementary spatio-temporal aspects of these techniques.

The organization of the paper is as follows. In the next section, the multi-are model is presented considering the SRCs as well as LRCs in the model and the state-space representation of the model is derived. In the Simulation results section, effects of the parameters of the model on its dynamics are explored to find valid ranges of variations of the parameters based on a stability analysis. Discussions and Conclusions are presented at the end of the paper.
Multi-area EEG/MEG modeling

Single-area model

We proposed an integrated E/MEG and fMRI model in Babajani and Soltanian-Zadeh (2006) based on the physiological principles of the cortical minicolumns and their connections in one cortical area. The minicolumn is the basic unit of the mature neocortex which is a narrow chain of neurons extending vertically across the cellular layers II–VI. Each minicolumn in primates contains ~80–100 neurons (Mountcastle, 1997). The width of minicolumn is 50 μm and the mean value for inter-columnar distance is 80 μm (Buxhoeveden and Casanova, 2002). There are three basic cell types in minicolumns: stellate cells, local interneurons, and pyramidal cells; the axon of the two former ones spread vertically in their minicolumn without considerable outputs to the neighboring minicolumns. The layer IV stellate cells receive afferent thalamic input and also input from neighboring minicolumns. The local interneurons are inhibitory input of the pyramidal cells. Pyramidal cells in layers III and IV send inputs to the minicolumns within the area.

The responses of the excitatory and the inhibitory synapses are represented by overall post-synaptic potentials of different cell populations. The four constants represent the strength of the connections of different cell populations between the th minicolumn as well as the interactions with other minicolumns within the area.

\[
\begin{align*}
\tilde{z}_1^{(i)} &= -\frac{1}{\tau_e} z_1^{(i)} - \frac{2}{\tau_e} z_1^{(i)} + \frac{H_z}{\tau_e} \left[ u(t) + \gamma_1 S(y^{(i)}) + \sum_{j=1}^{L} \sum_{j \neq i} \gamma_2^{ij} S(y^{(j)}) \right] \\
\tilde{z}_2^{(i)} &= -\frac{1}{\tau_e} z_2^{(i)} - \frac{2}{\tau_e} z_2^{(i)} + \frac{H_z}{\tau_e} \left[ \gamma_2 S(z_1^{(i)}) + \sum_{j=1}^{L} \sum_{j \neq i} \gamma_3^{ij} S(y^{(j)}) \right] \\
\tilde{z}_3^{(i)} &= -\frac{1}{\tau_e} z_3^{(i)} - \frac{2}{\tau_e} z_3^{(i)} + \frac{H_z}{\tau_e} \gamma_4 S(z_2^{(i)}) \\
\tilde{z}_4^{(i)} &= -\frac{1}{\tau_e} z_4^{(i)} - \frac{2}{\tau_e} z_4^{(i)} + \frac{H_z}{\tau_e} \gamma_5 S(y^{(i)}) + \sum_{j=1}^{L} \sum_{j \neq i} \gamma_6^{ij} S(y^{(j)}) \\
y^{(i)} &= z_2^{(i)} - z_3^{(i)}
\end{align*}
\]

where \(z_1^{(i)}, z_2^{(i)}, z_3^{(i)},\) and \(z_4^{(i)}\) are the overall post-synaptic potentials of different cell populations, \(y^{(i)}\) is the synaptic activities of the pyramidal cells of ith minicolumn which generates the EEG and MEG signals, \(u(t)\) represents the stimulus related afferent input to the cortical area which is assumed to have the same effect on all minicolumns within the area, and \(L\) is the number of minicolumns within the area.

In the ENMM, minicolumns inside an area are assumed to be approximately parallel to each other and perpendicular to the cortical surface, and have a regular rectangular lattice form as shown in Fig. 2. Eq. (1) shows the state-space representation of the dynamics of the ith minicolumn which generates the EEG and MEG signals, \(\Omega\) is the sigmoid function in Eq. (3). \(z_1^{(i)}, z_2^{(i)}, z_3^{(i)},\) and \(z_4^{(i)}\) are the overall post-synaptic potentials of different cell populations. The four constants \(\gamma_1, \gamma_2, \gamma_3,\) and \(\gamma_4\) represent the total number of synapses in the corresponding subpopulations. Three gain parameters \(g_s, g_r,\) and \(g_t\) represent the influence of the neighboring minicolumns on the stellate cells, pyramidal cells, and interneurons, respectively. The \(C_{S}, C_{R},\) and \(C_{I}\) represent the strength of the connections of different cell populations between the ith and the jth minicolumns according to Eq. (A.4). The \(e\) represents the strength of the afferent input to the minicolumns within the area.

Fig. 1. Interactions among different cell populations within the ith minicolumn as well as the interactions with other minicolumns in the proposed extended neural mass model (ENMM) (Babajani and Soltanian-Zadeh, 2006). The solid box shows the classical Jansen’s model within the ith minicolumn. The left dash-dot box illustrates contributions of the neighboring minicolumns to the ith minicolumn. The EEG and MEG signals are generated by the post-synaptic potentials of the pyramidal cells, i.e., \(y^{(i)}\), in this figure. The impulse responses of the excitatory and the inhibitory synapses are represented by \(h_s\) and \(h_i\), respectively. The operator “\(\Omega\)” is the sigmoid function in Eq. (3). \(z_1^{(i)}, z_2^{(i)}, z_3^{(i)},\) and \(z_4^{(i)}\) are the overall post-synaptic potentials of different cell populations. The four constants \(\gamma_1, \gamma_2, \gamma_3,\) and \(\gamma_4\) represent the total number of synapses in the corresponding subpopulations. Three gain parameters \(g_s, g_r,\) and \(g_t\) represent the influence of the neighboring minicolumns on the stellate cells, pyramidal cells, and interneurons, respectively. The \(C_{S}, C_{R},\) and \(C_{I}\) represent the strength of the connections of different cell populations between the ith and the jth minicolumns according to Eq. (A.4). The \(e\) represents the strength of the afferent input to the minicolumns within the area.
average values of the physiological parameters $H_a$, $H_i$, $\tau_e$, $\tau_i$, $\gamma_1$, $\gamma_2$, $\gamma_3$, and $\gamma_3$ are given in Table 1. Here, the propagation delay between minicolumns within the area is neglected because of its small value.

$I_{Sij}^S$, $I_{Pij}^P$, and $I_{Iij}^I$ in Eq. (1) represent the intra-area short range connections (SRCs) from the $j$th minicolumn to the $i$th minicolumn. The stellate cells, pyramidal cells, and inhibitory interneurons of the $i$th minicolumn receive afferent inputs from the pyramidal cells of the $j$th minicolumn whose strengths are represented by $I_{Sij}^S$, $I_{Pij}^P$, and $I_{Iij}^I$, respectively. We proposed the following Gaussian kernel for modeling the strength of the

![Fig. 2](image)

**Table 1**

<table>
<thead>
<tr>
<th>Cortical Level</th>
<th>Parameter</th>
<th>Description</th>
<th>Unit</th>
<th>Mean value</th>
<th>Variation range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-minicolumn</td>
<td>$H_a$</td>
<td>Maximum amplitude of the excitatory post synaptic potential</td>
<td>mV</td>
<td>3.25</td>
<td>[0, 5.15]</td>
</tr>
<tr>
<td>Intra-minicolumn</td>
<td>$H_i$</td>
<td>Maximum amplitude of the inhibitory post synaptic potential</td>
<td>mV</td>
<td>29.3</td>
<td>[1.02, 141.70]</td>
</tr>
<tr>
<td>Intra-minicolumn</td>
<td>$\tau_e$</td>
<td>Average synaptic time constants for excitatory populations</td>
<td>ms</td>
<td>10</td>
<td>[0, 15.84]</td>
</tr>
<tr>
<td>Intra-minicolumn</td>
<td>$\tau_i$</td>
<td>Average synaptic time constants for inhibitory populations</td>
<td>ms</td>
<td>15</td>
<td>[0.52, 37.23]</td>
</tr>
<tr>
<td>Intra-minicolumn</td>
<td>$\gamma_1$</td>
<td>Average number of synaptic contacts to the stellate cell</td>
<td>$-$</td>
<td>50</td>
<td>[0, 0.97]</td>
</tr>
<tr>
<td>Intra-minicolumn</td>
<td>$\gamma_2$</td>
<td>Average number of synaptic contacts to the excitatory pyramidal cells</td>
<td>$-$</td>
<td>40</td>
<td>[0, 7.76]</td>
</tr>
<tr>
<td>Intra-minicolumn</td>
<td>$\gamma_3$</td>
<td>Average number of synaptic contacts to the inhibitory interneurons</td>
<td>$-$</td>
<td>12</td>
<td>[0.42, 15.23]</td>
</tr>
<tr>
<td>Intra-minicolumn</td>
<td>$\gamma_4$</td>
<td>Average number of synaptic contacts to the inhibitory pyramidal cells</td>
<td>$-$</td>
<td>12</td>
<td>[0.42, 15.23]</td>
</tr>
<tr>
<td>Intra-minicolumn</td>
<td>$\epsilon_0$</td>
<td>Parameters of the nonlinear sigmoid function in Eq. (3)</td>
<td>$s^{-1}$</td>
<td>2.5</td>
<td>[0, 5.29]</td>
</tr>
<tr>
<td>Intra-minicolumn</td>
<td>$r$</td>
<td>Parameters of the nonlinear sigmoid function in Eq. (3)</td>
<td>$V^{-1}$</td>
<td>560</td>
<td>[0, 1185]</td>
</tr>
<tr>
<td>Intra-area</td>
<td>$i$</td>
<td>Number of minicolumns in the cortical area (see Eq. (4) and Fig. 2)</td>
<td>$-$</td>
<td>81</td>
<td>$\geq 1$</td>
</tr>
<tr>
<td>Intra-area</td>
<td>$D$</td>
<td>The unit inter-minicolumn distance in the cortical area (see Fig. 2)</td>
<td>$\mu m$</td>
<td>80</td>
<td>$-$</td>
</tr>
<tr>
<td>Intra-area</td>
<td>$\sigma_s$</td>
<td>Standard deviations of the Gaussian kernel in Eq. (2) related to the exponential decays of the strengths of connections among minicolumns within an area</td>
<td>$\mu m$</td>
<td>160</td>
<td>$-$</td>
</tr>
<tr>
<td>Intra-area</td>
<td>$g_{Sij}^{1}$</td>
<td>Three parameters in Eq. (4) describe the SRCs among minicolumns within the $n$th area (S: stellate cells; P: pyramidal cells; I: inhibitory interneurons)</td>
<td>$-$</td>
<td>2.50</td>
<td>[0, 5.70]</td>
</tr>
<tr>
<td>Intra-area</td>
<td>$g_{Pij}^{1}$</td>
<td>$-$</td>
<td>1.08</td>
<td>[0, 2.15]</td>
<td></td>
</tr>
<tr>
<td>Intra-area</td>
<td>$g_{Iij}^{1}$</td>
<td>$-$</td>
<td>1.00</td>
<td>[0, 2.00]</td>
<td></td>
</tr>
<tr>
<td>Intra-area</td>
<td>$g_{Sij}^{2}$</td>
<td>$-$</td>
<td>0.450</td>
<td>[0, 0.900]</td>
<td></td>
</tr>
<tr>
<td>Intra-area</td>
<td>$g_{Pij}^{2}$</td>
<td>$-$</td>
<td>0.078</td>
<td>[0, 0.155]</td>
<td></td>
</tr>
<tr>
<td>Intra-area</td>
<td>$g_{Iij}^{2}$</td>
<td>$-$</td>
<td>0.073</td>
<td>[0, 0.145]</td>
<td></td>
</tr>
</tbody>
</table>

* Parameters $\sigma_s$, $\sigma_p$, and $\sigma_i$ are assumed fixed at their mean physiological values in the model to reduce the redundancy in the model.
intra-area SRCs based on the physiological principle that the greater the distance between the two minicolumns, the weaker their influence on each other:

\[
\begin{align*}
I_S^{ij} &= g_S \sigma_i \sigma_j = g_S \exp \left( -\frac{\text{dist}(i,j)^2}{2\sigma^2} \right) \\
I_P^{ij} &= g_P \sigma_i \sigma_j = g_P \exp \left( -\frac{\text{dist}(i,j)^2}{2\sigma^2} \right) \\
I_I^{ij} &= g_I \sigma_i \sigma_j = g_I \exp \left( -\frac{\text{dist}(i,j)^2}{2\sigma^2} \right)
\end{align*}
\]

where dist(.,.) is the Euclidean distance between two minicolumns (see Fig. 2), \(\sigma\) is the standard deviation of the Gaussian kernel, gain coefficients \(g_S, g_P,\) and \(g_I\) represent strengths of the SRCs, and subscripts \(S, P,\) and \(I\) represent the stellate cells, pyramidal cells, and interneurons, respectively. Although \(\sigma_S, \sigma_P,\) and \(\sigma_I\) may have different values in different areas, their average values based on experimental data in Mountcastle (1997) are \(\sigma_S = \sigma_P = \sigma_I = 2D = 160 \, \mu m\) where \(D\) is the unit inter-minicolumn distance (see Fig. 2). Sigmoid function “\(S\)” in Eq. (1) transforms the average membrane potential into an average rate of fired action potentials as described by

\[
S(v) = \frac{2e_0}{1 + \exp(-rv)} - e_0
\]

where \(e_0\) and \(r\) are physiological parameters of the sigmoid function and their mean values are given in Table 1.

The variable \(y^{(i)}\) in Eq. (1) shows the synaptic currents of the pyramidal cells of \(i\)th minicolumn which generates the EEG and MEG signals. The apical dendrites of the pyramidal cells within the minicolumns are approximately parallel and perpendicular to the cortical surface. In addition, minicolumns are small compared to their distances to the EEG and MEG sensors. Therefore, minicolumns within the cortical area and their pyramidal cells can be assumed parallel and the algebraic sum of the synaptic currents of all minicolumns, i.e.,

\[
y(t) = \sum_{i=1}^{\text{num}} y^{(i)}(t),
\]

can be assumed as the equivalent current dipole (ECD) of the area that generates the EEG and MEG signal. The generated signals on E/MEG sensors can be calculated using the generated ECD and the lead field matrix, i.e., forward electromagnetic model (Mosher et al., 1999).

**Multi-area model**

In this section, we further extend our ENMM model from the single-area model to the entire brain containing all active cortical areas activated by a specific external stimulus. To this end, we define the inter-area long-range connections (LRCs) in the multi-area ENMM and derive the state-space representation of the model. The multi-area model contains two types of connections: intra-area SRCs and inter-area LRCs. The SRCs are made by cortical neurons whose local branches can reach a maximum of about 10 mm (Jirsa and Haken, 1997). In the ENMM, the SRCs represent the intra-area connections among minicolumns inside an area which are made by afferent pyramidal cells within the source minicolumn to the three cell populations of the destination minicolumns (see Fig. 1). The SRCs between minicolumns within an area in the ENMM are characterized based on Eqs. (1) and (2) which are represented by parameters \(c_S, c_P, c_I, g_S, g_P,\) and \(g_I\). Large values of \(c_S, c_P,\) and \(c_I\) model an area with strong connections among its minicolumns that not only close minicolumns have strong connections but also distant minicolumns have significant effects on each others. The intra-area minicolumns will tend to be independent and disconnected if \(c_S, c_P,\) and \(c_I\) have small values. In addition, variation of the three gain parameters \(g_S, g_P,\) and \(g_I\) changes strength of the SRCs among the minicolumns within a cortical area.

![Fig. 3. Illustration of the SRCs and LRCs in the two representative areas of the proposed multi-area model. Area1 and Area2 receive inputs from the thalamus and Area1, respectively. Within each area, pyramidal cells (PC) of all minicolumns affect the three cell populations (SC, PC, and II) of other minicolumns as SRCs (brown arrows) where \(g_S^{1,2}, g_P^{1,2},\) and \(g_I^{1,2}\) represent the SRCs within the area. Pyramidal cells of minicolumns in Area1 affect the three cell populations of all minicolumns in Area2 as LRCs (blue arrows). The \(g_S^{1,2}, g_P^{1,2},\) and \(g_I^{1,2}\) represent the LRCs from all pairs of minicolumns within Area1 to Area2. To prevent complexity, the LRCs from one minicolumn in Area1 to one minicolumn in Area2 is illustrated. SC: Stellate Cells; PC: Pyramidal Cells; II: Inhibitory Interneurons; MC: Minicolumn.](image-url)
Both of the standard deviation "c" and gain parameter "g" can represent strength of the intra-area connections that may generate redundancy in the model. Therefore, we assumed that the parameters $c_l$, $c_s$, and $c_f$ are fixed at their physiological average values given in Table 1 and the SRCs parameters of the model are limited to the three gain parameters $g_S$, $g_p$, and $g_b$. We will use notations $g_{S}^{lm}$, $g_{P}^{lm}$, and $g_{B}^{lm}$ for the SRCs gain parameters hereafter in this paper where the superscript $m$ shows the source number, the superscript $s$ represents the SRCs, and subscripts $S$, $P$, and $I$ stand for the stellate cells, pyramidal cells, and inhibitory interneurons, respectively.

LRCs characterize configuration of the multi-area model by describing the connections among the cortical areas. LRCs are mainly created by axons of pyramidal cells that pass through the white matter to connect the cortical areas and their length may be more than 100 mm (Jirsa and Haken, 1997). While the effective strength of the SRCs between two minicolumns within an area diminishes exponentially with their distance, LRCs do not show such a regular and smooth pattern (Sotero et al., 2007). To define LRCs between two cortical areas, we consider that the three cell populations of all minicolumns in the destination area are affected by the excitatory afferent of the pyramidal cells of all minicolumns in the source area as illustrated in Fig. 3. Based on the uniform structure of the minicolumns within the cortical areas, strengths of the LRCs do not show such a regular and smooth pattern (Sotero et al., 2007). To define LRCs between two cortical areas, we consider the fact that the three cell populations of all minicolumns in the destination area are affected by the excitatory afferent of the pyramidal cells of all minicolumns in the source area as illustrated in Fig. 3. Based on the uniform structure of the minicolumns within the cortical areas, strengths of the LRCs do not show such a regular and smooth pattern (Sotero et al., 2007). To define LRCs between two cortical areas, we consider the fact that the three cell populations of all minicolumns in the destination area are affected by the excitatory afferent of the pyramidal cells of all minicolumns in the source area as illustrated in Fig. 3. Based on the uniform structure of the minicolumns within the cortical areas, strengths of the LRCs do not show such a regular and smooth pattern (Sotero et al., 2007). To define LRCs between two cortical areas, we consider the fact that the three cell populations of all minicolumns in the destination area are affected by the excitatory afferent of the pyramidal cells of all minicolumns in the source area as illustrated in Fig. 3. Based on the uniform structure of the minicolumns within the cortical areas, strengths of the LRCs do not show such a regular and smooth pattern (Sotero et al., 2007). To define LRCs between two cortical areas, we consider the fact that the three cell populations of all minicolumns in the destination area are affected by the excitatory afferent of the pyramidal cells of all minicolumns in the source area as illustrated in Fig. 3. Based on the uniform structure of the minicolumns within the cortical areas, strengths of the LRCs do not show such a regular and smooth pattern (Sotero et al., 2007). To define LRCs between two cortical areas, we consider the fact that the three cell populations of all minicolumns in the destination area are affected by the excitatory afferent of the pyramidal cells of all minicolumns in the source area as illustrated in Fig. 3. Based on the uniform structure of the minicolumns within the cortical areas, strengths of the LRCs do not show such a regular and smooth pattern (Sotero et al., 2007).

Consider a multi-area model which contains $N$ cortical areas where the intra-area and the inter-area connections are specified by the SRCs and the LRCs, respectively. Each area contains $L$ uniform minicolumns which are assumed to be perpendicular to the cortical surface. In Appendix A, we derive the state-space representation of a single-area model which contains $L$ minicolumns. Based on the definitions of the SRCs and LRCs in the previous section and similar to Appendix A, the following equation can be derived. It shows the dynamics of the $i$th minicolumn within the $n$th area in the multi-area model.

\[
\dot{x}_{i,n} = a_{0i} x_{i,n} + a_{1i} S_{i,n} x_{i,n} + \sum_{j=1, j \neq i}^{L} \left[ g_{S}^{ij} r_{s} + g_{P}^{ij} r_{p} + g_{B}^{ij} r_{b} \right] S_{j} x_{j,n} + \sum_{m=1, m \neq n}^{N} \sum_{j=1}^{L} \left[ g_{S}^{m,n} r_{s} + g_{P}^{m,n} r_{p} + g_{B}^{m,n} r_{b} \right] S_{j} x_{j,m} + b_n u(t); \quad i = 1, 2, ..., L; \quad n = 1, 2, ..., N
\]  

(4)

Here, $x_{i,n}$ is the $8$-by-$1$ state vector of the $i$th minicolumn within the $n$th area, and $a_{0i}$, $a_{1i}$, $r_{s}$, $r_{p}$, $r_{b}$, and $b_n$ are defined in Appendix A. Parameters $\Omega_{S}$, $\Omega_{P}$, and $\Omega_{B}$ show the patterns of connections among the intra-area minicolumns which are defined in Eq. (A.4), and their values can be calculated using the average values of the related parameters in Table 1. Scalar $b_n$ represents the strength of the afferent input from the external stimulus to the $n$th area. Parameters $g_{S}^{ij}$, $g_{P}^{ij}$, and $g_{B}^{ij}$ are related to the SRCs where the superscripts $i$ and $j$ are the area number. $g_{S}^{mn}$, $g_{P}^{mn}$, and $g_{B}^{mn}$ are parameters related to the LRCs from the $m$th area to the $n$th area.

Similar to Appendix A, the matrix form of Eq. (4) can be derived as follows.

\[
X_{nL \times 1} = A_{A_{d}} X + \left( A_{B} + (G_{S} \otimes A_{S}) + (G_{P} \otimes A_{P}) + (G_{B} \otimes A_{B}) \right) S(X) + (B_{i} \otimes B_{0}) u
\]  

(5)

where

\[
A_{A_{d}} = I_{N \times N} \otimes a_{i_s,k_s} ; \quad A_{B} = I_{N \times N} \otimes a_{i_s,k_s} ; \quad B_{i} = [b_{1} b_{2} ... b_{N}]^{T} \]

\[
A_{d} = I_{L \times 1} \otimes \omega_{k_s} ; \quad A_{B} = I_{L \times 1} \otimes \omega_{k_s} ; \quad B_{i} = I_{L \times 1} \otimes \omega_{k_s} ;
\]

\[
G_{S,k_s} = \text{diag} \left( \begin{bmatrix} g_{S1}^{1} & \cdots & g_{SN}^{1} \end{bmatrix} \right) ; \quad G_{P,k_s} = \text{diag} \left( \begin{bmatrix} g_{P1}^{1} & \cdots & g_{PN}^{1} \end{bmatrix} \right) ; \quad G_{B,k_s} = \text{diag} \left( \begin{bmatrix} g_{B1}^{1} & \cdots & g_{BN}^{1} \end{bmatrix} \right)
\]

\[
G_{S} = \begin{bmatrix} 0 & g_{S1}^{12} & \cdots & g_{SN}^{1N} \\ g_{S1}^{12} & 0 & \cdots & g_{SN}^{2N} \\ \vdots & \vdots & \ddots & \vdots \\ g_{S1}^{N1} & g_{S2}^{N2} & \cdots & 0 \end{bmatrix} N \times N \quad ; \quad G_{P} = \begin{bmatrix} 0 & g_{P1}^{12} & \cdots & g_{PN}^{1N} \\ g_{P1}^{12} & 0 & \cdots & g_{PN}^{2N} \\ \vdots & \vdots & \ddots & \vdots \\ g_{P1}^{N1} & g_{P2}^{N2} & \cdots & 0 \end{bmatrix} N \times N \quad ; \quad G_{B} = \begin{bmatrix} 0 & g_{B1}^{12} & \cdots & g_{BN}^{1N} \\ g_{B1}^{12} & 0 & \cdots & g_{BN}^{2N} \\ \vdots & \vdots & \ddots & \vdots \\ g_{B1}^{N1} & g_{B2}^{N2} & \cdots & 0 \end{bmatrix} N \times N
\]

$A_{d}$, $A_{B}$, and $A_{B}$ in Eq. (5) are three $8L$-by-$8L$ matrices which are defined in Eq. (A.5), and $I_{L \times L}$ is $L$-by-$L$ matrix with 1 in all its entries. Superscripts "s" and "p" in Eq. (5) stand for the SRCs and LRCs, respectively. The compact matrix form of Eq. (5) is:

\[
X_{nL \times 1} = A_{A_{d}} X + \left( A_{B} + (G_{S} \otimes I_{8L \times 8L}) A_{S} + (G_{P} \otimes I_{8L \times 8L}) A_{P} \right) S(X) + B_{i} u
\]  

(6)
The local linearization (LL) approach is an accurate and stable technique to discretize SDE (Ozaki, 1992a). It has been widely used in several applications (Jimenez and Ozaki, 2006b; Riera et al., 2007; Valdes-Sosa et al., 2008; Valdes et al., 1999). The stochastic Ito-Taylor expansion of function $f$ is used in LL method to discretize the SDE in Eq. (11) (Jimenez et al., 1999).

Discretizing stochastic state-space model

After considering the state noise and the observation noise in Eq. (7), we have:

$$\begin{align*}
\dot{X}(t) &= \{A_2 X(t) + [A_3 + (G^\top \otimes I_{N \times L}) A_4 + (G^\top \otimes I_{N \times L}) A_5] S(x(t)) + B u(t)\} dt + \Sigma d w(t) \\
Y(t) &= H C_1 x(t) + v(t)
\end{align*}$$

(10)

where $w(t)$ is an 8NL-dimensional Wiener process, $\Sigma$ is the square root of a covariance matrix, $x_0$ is the initial value of the state vector, and $v(t)$ is the measurement Gaussian noise. The state equation (10) is a stochastic differential equation (SDE) that we consider its following from for the sake of simplicity.

$$\begin{align*}
\dot{X}(t) &= f(X(t), t) dt + \Sigma d w(t)
\end{align*}$$

(11)

The local linearization (LL) approach is an accurate and stable technique to discretize SDE (Ozaki, 1992a). It has been widely used in several applications (Jimenez and Ozaki, 2006b; Riera et al., 2007; Valdes-Sosa et al., 2008; Valdes et al., 1999).
The LL approximation of the solution of the SDE (11) is derived by the iterative computation of the following expression (Jimenez et al., 1999):

\[ X_{t_{k+1}} = X_{t_k} + \Psi(t_k, X_{t_k}) + \zeta(t_k) : t_{k} = t_0 + k\Delta t, k = 0, 1, 2, \ldots \]  

(12)

where \( \Delta t \) is the sampling time and the function \( \Psi(...) \) is defined as

\[ \Psi(t, X(t)) = J_f^{-1}(e^{\Delta t f} - I)f(X(t), t) + J_f^{-2}(e^{2\Delta t f} - I - J_f \Delta t) \frac{\partial f(X(t), t)}{\partial t} , \]

(13)

and \( \zeta \) is a stochastic process with zero mean and covariance matrix

\[ \Sigma_\zeta = \int_1^{t + \Delta t} e^{(t + \Delta t - w)J_f} \Sigma J_f^T(t + \Delta t - w)dw. \]  

(14)

The \( J_f \) in Eqs. (13) and (14) is the Jacobian matrix of the function \( f \). The discretized form of the state-space model in Eq. (10) is derived as

\[
\begin{align*}
X_{t_{k+1}} &= X_{t_k} + J_f^{-1}(e^{\Delta t f} - I)\left(A_2 X_{t_k} + \left\{ A_3 + (G^G \oplus I)A_4 + \left(G^G \oplus I\right)A_3 \right\} S(X_{t_k}) + Bu(t_k) \right) \\
& \quad + J_f^{-2}(e^{2\Delta t f} - I - J_f \Delta t) Bu(t_k) + \zeta(t_k) \\
Y_{t_k} &= HC_i X_{t_k} + v_{t_k}
\end{align*}
\]

(15)

where \( u^{(i)} \) is the derivative of the input \( u(t) \) in the time \( t_k \) and the Jacobian matrix \( J_f \) depends on the derivative of the sigmoid function in Eq. (3) as follows.

\[
J_f = A_2 + \left\{ A_3 + (G^G \oplus I)A_4 + \left(G^G \oplus I\right)A_3 \right\} S(X_{t_k}) + Bu(t_k) \]

(16)

The calculation of the matrix exponential \( e^{\Delta t f} \) generates a computational burden that can be substantially reduced using Krylov subspace methods (Jimenez, 2002; Jimenez and Carbonell, 2005).

If the sampling time \( \Delta t \) is small, the matrix exponential \( e^{\Delta t f} \) can be approximated as

\[ e^{\Delta t f} \approx I + J_f \Delta t. \]

(17)

Consequently, the following discrete state-space model is derived by substituting the approximation shown in Eq. (17) in Eq. (15).

\[
\begin{align*}
X_{t_{k+1}} &= X_{t_k} + \Delta t \left\{ A_2 X_{t_k} + \left\{ A_3 + (G^G \oplus I)A_4 + \left(G^G \oplus I\right)A_3 \right\} S(X_{t_k}) + Bu(t_k) \right\} + \zeta(t_k) \\
Y_{t_k} &= HC_i X_{t_k} + v_{t_k}
\end{align*}
\]

(18)

In addition, the covariance matrix of \( \zeta \) in Eq. (14) is approximated as

\[ \Sigma_\zeta = \Sigma \Sigma^T \Delta t + \frac{1}{2} J_f \Sigma \Sigma^T + \Sigma \Sigma^T J_f^T \Delta t^2 + \frac{1}{3} \left( 0.5 J_f \Sigma \Sigma^T + J_f \Sigma \Sigma^T J_f^T + 0.5 \Sigma \Sigma^T J_f^T \right) \Delta t^3 + \ldots \approx \Sigma \Sigma^T \Delta t. \]

(19)

It should be noted that if the state-space representation of the multi-area model in Eq. (7) is approximated using the Euler–Maruyama method (Kloeden and Platen, 1999), the discrete state-space model in Eq. (18) will be generated.

## Parameters of the multi-area model

Based on Eqs. (5) and (7), the multi-area model contains the following groups of parameters.

### Intra-minicolumn parameters

Referring to Fig. 1 and Eq. (A.2), parameters of the neural mass model at the level of a minicolumn are: \( H, H_a, \tau_c, \tau_r, \gamma_1, \gamma_2, \gamma_3, \gamma_4, e_0 \), and \( r \). We will show that these parameters can be fixed at their physiological average values, as given in David et al. (2005) and Table 1, to reduce the redundancy in the model. Once the intra-minicolumn parameters of the model are assumed to be fixed, matrix \( B_0 \) in Eq. (5) as well as matrices \( A_2, A_3 \), and \( C_1 \) in Eq. (7) will be fixed matrices.

### SRCs parameters

According to Eqs. (2) and (4), strengths of the SRCs among minicolumns within an area are related to the parameters \( \sigma_B, \sigma_R, \sigma_0, \sigma_3, g^n_{BR}, g^n_{BB} \), and \( g^n \). As mentioned previously, the parameters \( \sigma_B, \sigma_R, \) and \( \sigma_3 \) can be fixed at their mean physiological values to reduce redundancy of the model. Consequently, \( A_4 \) in Eq. (6) will be a fixed matrix because its entries depend on the parameters \( \sigma_B, \sigma_R, \) and \( \sigma_3 \) according to Eqs. (A.5)
and (6). The remaining three gain parameters $g_{S,n}^i$, $g_{I,n}^i$, and $g_{P,n}^i$ which are included in matrix $G$ according to Eq. (5) represent the SRCs parameters of the $n$th area. The number of minicolumns within the area, $L$, is another parameter of the model.

**LRCs parameters**

Parameters $g_{S,n}^{l,nm}$, $g_{I,n}^{l,nm}$, and $g_{P,n}^{l,nm}$ which are included in matrix $G$ according to Eq. (5) represent the LRCs from the $n$th area to the $m$th area of the model.

For a multi-area model containing $N$ areas and $K$ inter-area connections, $G$ and $G'$ contain $3 \times N$ and $3 \times K$ parameters, respectively. However, if it is assumed that the effect of one or more cell populations can be neglected or approximated by the effects of the other cell populations, then the number of SROs or LRCs parameters can be reduced. For example, if the effect of the efferent input to the inhibitory interneurons in the LRCs is neglected, the number of LRCs parameters will be reduced to $2 \times K$ parameters.

**Comparison of proposed model with other models**

Several neural mass models have been proposed in the literature. Valdes et al. (1999) propose a neural mass model (NMM) based on the model introduced in Zetterberg et al. (1978). They extract the stochastic state-space representation of the proposed NMM. Using the LL inversion method, they estimate the parameters of the model to fit the spontaneous EEG data. Both of the model proposed in Valdes et al. (1999) and our multi-area NMM are represented by the stochastic state-space model in Eq. (10). The proposed NMM in Valdes et al. (1999) is equivalent to the Jansen’s NMM which we use to model the dynamics of the single minicolumn. Our multi-area model contains several minicolumns within the cortical areas which are connected according to the defined SRCs and LRCs. Based on the simulation results illustrated in this paper, our proposed multi–area NMM outperforms the NMM proposed in Valdes et al. (1999) which is equivalent to a single-column NMM.

An integrated EEG/fMRI NMM is proposed in Riera et al. (2006) where a canonical neural mass model of three subpopulations of neurons is proposed to model the generation of the membrane potentials in the somas of these neurons and the electric currents flowing in the neuropil. The electrovascular coupling is modeled by another component. The dynamics of the vascular states is modeled by the extended balloon model (Friston et al., 2000). The parameters of the proposed integrated EEG/fMRI model are estimated using the LL-innovation method (Riera et al., 2007). Although an interesting and comprehensive approach is proposed in Riera et al. (2006) to model the fMRI signal but the proposed NMM is limited to a single cortical area while we propose a multi-area model. In addition, the EEG part of the NMM proposed in Riera et al. (2006) is very simple and comparable to the NMM of a single-column in our model.

A general large scale NMM is proposed in Valdes-Sosa et al. (2008) which couples a neural mass EEG/fMRI model with a metabolic hemodynamic model. The proposed NMM is based on the Jansen’s model (Jansen and Rit, 1995). The connectivity matrix among the neural masses and the conduction delays among them are defined according to the ACP matrix calculated using the DWMRI techniques (Iturria-Medina et al., 2007). The LL method is proposed for the discretization of the stochastic state-space model. The LL-innovation and Dynamic Expectation Maximization (DEM) methods are proposed for the model inversion. The model proposed in Valdes-Sosa et al. (2008) seems suitable for simulation studies. However, it contains a large number of parameters, related to the connectivity and delay matrices, whose estimation in real applications may be challenging because of over-fitting problems. As noted by one of our reviewers, large scale models can be estimated, even in the presence of many parameters, by means of Bayesian constraints, which is in effect a non-parametric estimation method. Our proposed multi-area ENMM model has a limited number of parameters, reducing the chance of over-fitting. In addition, we have illustrated in the simulation studies that our model, with a small number of parameters, is capable of generating appropriate dynamics for the modeling of various types of EEG and MEG signals.

**Simulation results**

In the following simulations, we will investigate changing the dynamics of the model by variations of its parameters to find their valid ranges that generate a stable model. In addition, we will verify reducing the number of the parameters of the model and limiting them to the LRCs and the SRCs parameters by fixing other parameters at their mean physiological values. To achieve these goals, we will start from a simple model that contains only one minicolumn and step-by-step increase the complexity of the model towards the complete multi-area model.

A biological system, which models physiological phenomena, must be a stable system. This means that output of the biological system must be finite for a finite stimulus as its input. A linear system will be stable if all poles of the transfer function between the input and the output have negative real parts. Valid ranges for the parameters of our multi–area model can be calculated by stability analysis of the model. The nonlinear sigmoid function $S(X)$ in Eq. (7) generates nonlinearity in the model and the transfer function cannot be defined for the nonlinear model. Therefore, the stability analysis based on locations of the poles of the system cannot be employed for our model. However, the state Eq. (7) can be approximated by the linear terms of the Taylor series expansion of the sigmoid function around zero. We will derive the transfer function of the approximated linear model in order to perform the stability analysis of the model.

As shown in Fig. 4, linear approximation of the sigmoid function provides an appropriate result for a small input. The linear terms of the Taylor series expansion of the sigmoid function do not provide suitable approximation when the input is large. While the saturation characteristics of the sigmoid function limits the amplitude of the output for large inputs, the output of the linear approximation of the sigmoid function provides appropriate outputs for small inputs. Graphs #7 and #8 illustrate output of the sigmoid function and output of the linear function corresponding to a large input, i.e., graph #4, respectively. While the saturation characteristic of the sigmoid function causes to limit the amplitude of the output for large inputs, the output of the linear approximation of the sigmoid function has larger amplitudes because there is no saturation effect in the linear function.

![Fig. 4. Comparison of the sigmoid function with its linear approximation. Graphs #1 and #2 are the sigmoid function, according to Eq. (3), and the linear approximation of the sigmoid function using the Taylor series expansion around zero, respectively. Graphs #3 and #4 illustrate small and large amplitude sinusoid inputs, respectively. Graphs #5 and #6 illustrate output of the sigmoid function and output of the linear function corresponding to the small input, i.e., graph #3, respectively. Graphs #5 and #6 show that the linear approximation of the sigmoid function provides appropriate outputs for small inputs. Graphs #7 and #8 illustrate output of the sigmoid function and output of the linear function corresponding to a large input, i.e., graph #4, respectively. While the saturation characteristic of the sigmoid function causes to limit the amplitude of the output for large inputs, the output of the linear approximation of the sigmoid function has larger amplitudes because there is no saturation effect in the linear function.](image)
output for large inputs, the output of the linear approximation of the sigmoid function has larger amplitude because there is no saturation effect in the linear model (see Fig. 4). Therefore, the linear approximation of the sigmoid function in our model generates more unstable outputs compared to the real nonlinear model. Thus, finding valid ranges of the parameters of the model based on the stability analysis of the linear approximation of the model provides a conservative estimate and ensures that the model will be stable in the resulting ranges of the parameters.

The linear approximation of Eq. (7) generates

$$
\begin{align*}
\dot{X} &= AX + Bu, \\
Y &= CX, \\
A &\approx A_2 + 0.5e_0r A_3 + \left(G + I_{BL \times BL}\right)A_4 + \left(G + I_{BL \times BL}\right)A_5
\end{align*}
$$

where $e_0$ and $r$ are parameters of the sigmoid function whose mean values are given in Table 1. Taking the Laplace transform of Eq. (20), the system’s transfer function can be calculated as $C(sI - A)^{-1}B$. The stability of the state-space model can easily be determined by looking at the system’s transfer function whose poles are the eigenvalues of the matrix $A$. The system is asymptotically stable if and only if it has poles (or eigenvalues) only with strictly negative real parts. The system may still be input–output stable even though it is not internally stable. This may be the case if unstable poles are canceled out by zeros. In the proposed multi-area model as a stable biological system that generates the event related EEG and MEG signals, stability of the entire model rather than stability of its some parts is required. Therefore, we will consider all of the poles of matrix $A$ in the stability analysis rather than just the poles that appear in the system’s transfer function $C(sI - A)^{-1}B$.

**Single-column model**

The building block of the proposed model is the neural mass model of one cortical minicolumn. In the ENMM, the interaction among different cell populations within a minicolumn is modeled by the Jansen’s neural mass model (Jansen and Rit, 1995). The solid box in Fig. 1 shows the neural mass model at the level of a minicolumn. The state-space representation of the single-column model is

$$
\begin{align*}
\dot{x}_{8 \times 1} &= a_0 x_{8 \times 1} + a_1 S(x) + b_0 u \\
y &= 10000000 \frac{x}{C_{138} C_{26}}
\end{align*}
$$

Fig. 5. Simulation results of the neural mass model in a single minicolumn showing variation of its poles locations due to the variation of its parameters. Eigenvalues of the state matrix in Eq. (22) are calculated and shown in the real-imaginary plots. For each subplot, only the parameter displayed in the title of the subplot vary and the other nine intra-minicolumn parameters stay at the mean values given in Table 1. The variation range of each parameter is specified in the title of the corresponding subplot. The minimum value is assigned as a quarter of the mean value of the parameter given in Table 1. The maximum value is the threshold value of the parameter for stability of the system. Circles show the locations of the poles of the model when all intra-minicolumn parameters stay at their mean values given in Table 1. Stars show locations of the poles of the model when the corresponding parameter is set at its minimum value specified in the title of the corresponding subplot. It should be noted that the system has eight poles but only six of the poles are plotted in this figure. The remaining two poles are double poles located at $1/\tau_e$ which depend on only $\tau_e$ and thus are not shown in this figure.
where $a_0$, $a_1$, and $b_0$ are defined in Appendix A. The state matrix $a = a_0 + 0.5re_0a_1$ contain the intra-minicolumn parameters $H_e$, $H_i$, $\tau_e$, $\tau_i$, $\gamma_1$, $\gamma_2$, $\gamma_3$, $\gamma_4$, $e_0$, and $r$. To find valid ranges for these parameters, the stability analysis is performed based on the eigenvalues of the state matrix $a$. By looking at the solid box in Fig. 1 as well as calculating the state matrix $a$, it can be inferred that six parameters $H_e$, $H_i$, $\tau_e$, $\gamma_1$, and $e_0$ can be assumed independent and the four remaining parameters, i.e., $\gamma_2$, $\gamma_3$, $\gamma_4$, and $r$ depend on the six parameters. Actually, multiplication of the parameters in the forms of $\gamma_1\gamma_2$, $\gamma_3\gamma_4H_i$, and $e_0r$ appear in the system’s transfer function.

Fig. 5 illustrates the real-imaginary plots of the calculated poles of the state equation (22) when each of the six parameters changes in a specific range. For each subplot, only one parameter changes and the other nine parameters are fixed at their mean values given in Table 1. The variation range of each parameter is specified in the title of the corresponding subplot. The minimum value is a quarter of the mean value of the parameter given in Table 1 and the maximum value is the threshold value of the parameter for stability of the system. The state-space system in Eq. (22) contains eight poles but it can be approximated by a second order system containing two dominant poles, as shown in Fig. 5. Therefore, there should be an equivalent representation of Eq. (22) which needs a smaller number of parameters than the ten intra-minicolumn parameters. This means that there is redundancy in the parameters of Eq. (22), as we mentioned before.

Time courses of the simulated event related signals in a single minicolumn using different values of two intra-minicolumn parameters, i.e., $H_e$ and $\tau_e$, are illustrated in Fig. 6 where an impulse is considered as the “Stimulus” input in Fig. 1. To investigate the effect of the nonlinear sigmoid function as well as its linear approximation, stimuli with small and large amplitudes are utilized for the subplots in the top and bottom rows, respectively. For the case of the small input shown in the top row of Fig. 6, the calculated outputs using the exact representation and the linear approximation of the nonlinear sigmoid function are compared. The subplots in the bottom row show the output of the model when the exact representation of the sigmoid function and a large input are used. Values of the parameters in the two subplots of each column are the same to compare the characteristics of the model for small and large inputs.
large input, the threshold values of the parameters are larger than those calculated based on the linear approximation. Therefore, the calculated threshold values of the parameters based on the linear approximation represents the lower bounds of the maximum values of the parameters.

### Single-area model

**Number of minicolumns within areas**

A cortical area contains several minicolumns where the strengths of their connections are diminished exponentially with their distances according to Eq. (2). How many minicolumns should be considered within an area to represent a suitable approximation of the dynamics of the area? The exponential term in Eq. (2) diminishes to about 1% of its maximum value for two minicolumns with a distance more than $3\sigma$. Therefore, minicolumns with distances more than $3\sigma$ have negligible effects on each other. Thus, all minicolumns within a square shape macrocolumn block with a diagonal dimension of $6\sigma$ have considerable effects on the central minicolumn. The cortical area shown in Fig. 2 can be divided in to a number of square shape macrocolumns whose diagonal dimensions are equal to $6\sigma$. The distance between central minicolumns of the two adjacent macrocolumns is equal to $3\sqrt{2}\sigma$ and the exponential term in Eq. (2) showing the strength of their connection diminishes to about 0.01% of its maximum value. Thus, it can be assumed that macrocolumns have small influences on each other and they can be approximately considered independent. In addition, the afferent outputs from as well as the efferent inputs to all macrocolumns within the area have similar configurations. Therefore, the dynamics of a cortical area can be approximated by the dynamics of one macrocolumn.

Consider a square shape macrocolumn (similar to the structure shown in Fig. 2) which contains $m_1 \times m_2 = L$ minicolumns where the unit inter-minicolumn distance is $D$. Based on the data in Mountcastle (1997), we estimated the mean value of the standard deviation of the spatial Gaussian kernel in Eq. (2) as $\sigma = 2D$ (Babaji and Soltanian-Zadeh, 2006). The maximum distance of the central minicolumn from other minicolumns within a macrocolumn is $(m_1 - 1)D\sqrt{2}/2$. This distance needs to be greater than or equal to $3\sigma = 6D$. Consequently, the number of the minicolumns within a macrocolumn is $L \geq 81$ ($m_1 \geq 9$). Therefore, the minimum number of minicolumns within the areas of the multi-area model is assumed to be 81.

The simulation results of a single-area model using different numbers of minicolumns are illustrated in Fig. 7. As illustrated in Fig. 7A, the locations of the poles of model using 81 and 225 minicolumns are very close (compare especially the locations of the dominant poles). As shown in Fig. 7B, the real part of the dominant pole of the model has no significant change when the number of minicolumns increases from 81 to 225. The event related signals generated using different numbers of minicolumns are illustrated in Fig. 7C. It can be inferred based on Figs. 7B and C that 81 minicolumns within the area gives a good approximation of the model. Whereas using a large number of the minicolumns (e.g., 225) in the model does not generate a significant improvement, it will add a huge computational load. Actually, number of states in the state vector for a single area with 225 minicolumns is $8 \times 225 = 1800$. On the other hand, considering a small number of minicolumns (e.g., one minicolumn) cannot suitably represent the dynamics of the states within the areas.

### Valid ranges of SRCs parameters

The valid ranges for the SRCs parameters can be derived based on the stability analysis of the single-area model. The state-space representation of the single-area model containing $L$ minicolumns is represented in Eq. (A.5). Variation of the SRCs parameters, i.e., $g_5$, $g_6$, and $g_I$, changes the eigenvalues of the state matrix and consequently changes the dynamics of the model. In the simulation results shown in Fig. 8, the state matrix of Eq. (A.5) is derived based on the linear approximation of the sigmoid function. The single-area model contains 81 minicolumns. The locations of the poles of the model change when the SRCs parameters vary. In each subplot, one SRCs parameter changes while the other SRCs parameters stay at their mean values given in Table 1. The variation range of each parameter is specified in the title of the corresponding figure. One half of the calculated threshold value is assigned as the mean value of the corresponding SRCs parameter in Table 1 which is the mean of the minimum value of the parameter, i.e., zero, and the maximum value of the parameter, i.e., the calculated threshold value.

### Multi-area model

#### Valid ranges of LRCs parameters

To verify the effects of LRCs on the dynamics of the multi-area model, we consider a simple two-area model where each area contains 81 minicolumns. The SRCs related matrix $G$ in Eq. (20) is assumed to be fixed and is calculated using the mean values of the SRCs parameters in Table 1. There are three LRCs parameters related to the three cell populations which represent the forward connections form one area to another area. Considering the backward connections,
there are totally six LRCs parameters in the two-area model. We assume the same strengths for the forward and backward connections and thus the model contains three LRCs parameters. The eigenvalues of the state matrix in Eq. (20) is calculated and plotted in Fig. 9 where the LRCs change in the ranges specified in the titles of the subplots. In each subplot, one parameter changes while others are fixed at their mean values given in Table 1. Based on the stability analysis, each parameter can change in a range from zero to the threshold value specified in the title of the corresponding subplot. Circles show the locations of the poles of the single-column model when all intra-minicolumn parameters stay at their mean values given in Table 1.

Reducing model parameters

The intra-minicolumn, SRCs, and LRCs parameters in the multi-area model contain several parameters that may cause redundancy in estimating their values. An approach to reduce the number of parameters is to fix some parameters at their physiological mean values. In the following simulation, we investigate the validity of fixing the intra-minicolumn parameters. A two-area model as described in the previous section is used. Eq. (20) represents the state-space equations of the model where matrices $A_2$, $A_3$, and $A_4$ depend on the intra-minicolumn parameters. Matrices $G_2$ and $G_1$ in Eq. (20) are related to the SRCs and LRCs parameters of the model, respectively. Matrix $A_4$ in Eq. (20) is a fixed matrix and its entries depend on the mean values of parameters $\sigma_S$, $\sigma_P$, and $\sigma_I$ given in Table 1.

The aim of this simulation is to verify our hypothesis that varying all parameters of the model in small ranges can be approximated by larger ranges of variations for a few of the parameters and fixing the remaining parameters at their mean values. The effects of variation of a parameter on the dynamics of a model can be verified by looking at its poles' variations. Therefore, we compare variations of the poles of the model in two conditions where all or a few of the parameters vary. In the real-imaginary plots shown in Figs. 10A and B, the blue dots show the locations of the poles when all parameters of the model (including the intra-minicolumn, SRCs, and LRCs) randomly change 10% around their mean values. The red star plots in Figs. 10A and B show the locations of the poles when the intra-minicolumn parameters stay at their mean values and the parameters related to SRCs and LRCs vary 34% or 100%. As illustrated in Fig. 10B, the change in the dynamics of the model generated by the variations of the intra-minicolumn parameters can be represented by the variations of the SRCs and LRCs parameters.

Fig. 9. Simulation results of the two-area model showing variation of its poles locations with variation of the LRCs parameters. Each area contains 81 minicolumns. The state-space representation in Eq. (20) considering the linear approximation of the sigmoid function is used. The SRCs related matrix $G_1$ in Eq. (20) is assumed to be fixed. It is calculated based on the mean values of the SRCs parameters given in Table 1. For the LRCs, the same strengths for the forward and the backward connections between the two areas are assumed and thus the model contains three LRCs parameters. The eigenvalues of the state matrix in Eq. (20) is calculated and plotted in this figure where the LRCs change in the ranges specified in the titles of the subplots. In each subplot, one parameter changes while the others stay at their mean values given in Table 1. Based on the stability analysis, each parameter can change in a range from zero to the threshold value specified in the title of the corresponding subplot. Circles show the locations of the poles of the single-column model when all intra-minicolumn parameters are fixed at their mean values given in Table 1.

Fig. 8. Simulation results of the single-area model showing variation of its poles locations with variation of the SRCs parameters, i.e., scalar parameters $g_S$, $g_P$, and $g_I$ in Eq. (A.5). The state-space representation of the single-area model in Eq. (A.5) is used considering $L = 81$ minicolumns, the linear approximation of the sigmoid function, and mean values of the parameters given in Table 1. Variation of the eigenvalues of the state matrix caused by variation of the SRCs parameters is shown. In each subplot, one SRCs parameter changes while the other SRCs parameters stay at their mean values given in Table 1. The variation range as well as the threshold value of each parameter is specified in the title of the corresponding subplot. Circles show the locations of the poles of the single-column model when all intra-minicolumn parameters stay at their mean values given in Table 1.
The accuracy of approximating the dominant poles of the model using limited number of parameters is illustrated in Figs. 10C and D. In the first step, all parameters of the model (including the intra-minicolumn, SRCs, and LRCs) randomly change from 5% to 50% around their mean values using 3000 runs and the dominant poles are calculated. In the second step, some parameters of the model stay at their mean values and the remaining parameters change 0%, 33%, 67%, and 100% around their mean values and the generated dominant poles are compared with the conditions in which only the LRCs and/or the SRCs change. In the subplot (C), the intra-minicolumn and the SRCs parameters are fixed and the x-axis shows the percentage of changes of the LRCs parameters. In subplot (D), the intra-minicolumn parameters are fixed and the x-axis shows the percentage of the changes of SRCs as well as the LRCs parameters.

The accuracy of approximating the dominant poles of the model using limited number of parameters is illustrated in Figs. 10C and D. In the first step, all parameters of the model (including the intra-minicolumn, SRCs, and LRCs) randomly change from 5% to 50% around their mean values using 3000 runs and the dominant poles are calculated. In the second step, some parameters of the model stay at their mean values and the remaining parameters change 0%, 33%, 67%, and 100% around their mean values and the generated dominant poles are calculated. Then, the dominant poles in the first and the second steps are compared and the mean square error between them is calculated and plotted in Figs. 10C and D. The first step is the same for both of Figs. 10C and D but the second step is different. For the second step in Fig. 10C, the intra-minicolumn and SRCs parameters are fixed and only the LRCs parameters vary. For the second step in Fig. 10D, the intra-minicolumn parameters are fixed and the SRCs and the LRCs parameters are varied. Referring to Fig. 10C, 100% variation of the LRCs parameters can approximate 5% to 50% variations of all parameters with 0.7% to 15.7% error, respectively. As shown in Fig. 10D, 100% variation of both SRCs and LRCs parameters can approximate 5% to 50% variations of all parameters with 0.06% to 2.3% error, respectively. Therefore, considering variations of both of the SRCs and the LRCs parameters and fixing the intra-minicolumn parameters at their mean values appropriately represents the dynamics of the model. Referring to Figs. 10C and D, when all parameters of the model change 50%,
approximation of the model using only the LRCs generates 15.7% error while using both of the LRCs and SRCs parameters generates 2.3% error. Therefore, the SRCs parameters are not redundant and represent some parts of the dynamics of the proposed model which cannot be modeled by the LRCs.

Evaluation of discretization

We compare two discretization methods, i.e., the LL and the Euler–Maruyama methods, using the simulation results based on Eqs. (15) and (18). The exact solution of the SDE in Eq. (10) is required to compare the performance of the LL and the Euler–Maruyama discretization methods. The nonlinear SDE in Eq. (10) seems to have no analytical solution. Therefore, we use a numerical method, i.e., the Runge–Kutta method, to calculate the solution of Eq. (10). The explicit Runge–Kutta formula is employed using the “ode45” function in Matlab (Dormand and Prince, 1980). The parameters “RelTol”, the relative error tolerance that applies to all components of the solution vector, and “AbsTol”, the absolute error tolerances determine the accuracy when the solution approaches zero, of the ode45 function are set at $10^{-12}$ to provide a solution with $10^{-10}$% accuracy.

We do not consider noise in the model to focus on the effect of discretization on the dynamics of the model. For the sake of simplicity, we use the state-space representation of the single-column model according to Eq. (21). As the derivative of the input appears in the LL formula (see Eq. (10)), we assign an analytical function to the input, i.e., $u(t) \propto e^{-t/10}; \tau = 5$ ms, to analytically calculate the derivative of the input. We calculate the mean squared error (MSE) between the solution of the Runge–Kutta, as an approximation of the exact solution, and the LL method as well as the Euler–Maruyama method and illustrate the results in Figs. 11 and 12. As expected, the LL method has a superior performance compared to the Euler–Maruyama method. However, the MSE of the Euler–Maruyama method is less than 0.25% for the sampling time smaller than 1 ms and therefore, the Euler–Maruyama method using the sampling time smaller than 1 ms is expected to be an appropriate discretization method for our multi-area model.

Discussions

In this paper, we propose a multi-area neural mass model to model the generated EEG and MEG signals from activations of the involved cortical areas related to a specific external stimulus. To this end, we further extend our previously proposed ENMM from a single-area model to the entire brain containing the interactions among all active cortical areas. Using the intra-area short-range connections (SRCs) and inter-area long-range connections (LRCs), the state space representation of the model is derived. The stochastic differential equations of the state space representation of the model are discretized using the local linearization (LL) and the Euler–Maruyama methods. We theoretically show that the LL discretization method can be approximated by the Euler–Maruyama discretization method when the sampling time is small. Parameters of the proposed model are categorized in three cortical levels: intra-minicolumn parameters, intra-area SRCs parameters, and inter-area LRCs parameters. In the Simulation results section, we find valid ranges of variations for the parameters of the model, verify reducing the number of the parameters of the model, and investigate the effect of discretization.

We use the stability analysis of the model to find valid ranges of the parameters (see Table 1). First, we derive a linear system based on the state space representation of the model using the linear approximation of the sigmoid function. Then, we find valid ranges for the parameters of the model using the analysis of the poles of the transfer function between the input and the output of the linear system. As shown in Figs. 4 and 6, finding valid ranges of the parameters based on the stability analysis of the linear approximation of the model provides a conservative estimation and ensures that the model will be stable in the resulting ranges of the parameters. For the stability analysis, we start from a simple model that contains only one minicolumn and step-by-step increase the complexity of the model towards the complete multi-area model. Figs. 5, 8, and 9 illustrate the variations of the locations of the poles of the model for the single-column, single-area, and multi-area models, respectively. For the numbers of minicolumns within the areas of the model, we infer that 81 minicolumns provides an appropriate approximation of the model (see Fig. 7).
The intra-minicolumn, SRCs, and LRCs parameters in the multi-area model contain several parameters that may cause redundancy in estimating their values. To reduce the number of the parameters, we investigate fixing the intra-minicolumn parameters at their physiological mean values and limiting the parameters of the model to the SRCs and LRCs parameters. Although the intra-minicolumn contains 10 parameters, the single-column model contains eight poles. Furthermore, it can be approximated by a second order system containing two dominant poles, as shown in Fig. 5. Therefore, there is redundancy in the intra-minicolumn parameters. The simulation results in Fig. 10 show that varying all parameters of the model in small ranges can be approximated by larger ranges of variations of the SRCs and the LRCs parameters while the intra-minicolumn parameters stay at their mean values. For example, if all parameters of the model change 50% around their mean values, approximation of the model using 100% changes of the LRCs and SRCs parameters generates 2.3% error (see Fig. 10D).

We evaluate the performances of the LL and the Euler–Maruyama discretization methods based on Eqs. (15) and (18). The mean squared errors (MSE) between the solution of the Runge–Kutta, as an approximation of the exact solution, and the LL method as well as the Euler–Maruyama method are illustrated in Figs. 11 and 12. The LL method has superior performance compared to the Euler–Maruyama method. However, the MSE of the Euler–Maruyama method will be less than 0.25% if the sampling time is smaller than 1 ms. Therefore, the Euler–Maruyama method using a sampling time smaller than 1 ms is expected to be an appropriate discretization method for the proposed model.

Future work: model inversion

Several approaches have been proposed for model inversion and estimation of the parameters of the SSM, e.g., the expectation maximization algorithm developed in Shumway and Stoffer (1982), a recursive optimization algorithm based on the local linearization (LL) filter (Jimenez and Ozaki, 2006a; Ozaki, 1992b, 1993; Riera et al., 2007), Monte Carlo based methods (Chen, 2003), methods derived from variational Bayesian techniques which reformulate the SSM by means of a path integral (Archambeau et al., 2008; Kappen, 2006; Wiegerinck and Kappen, 2006), the Ensemble Kalman Filter (EnKF) (Evensen, 2003; Evensen and van Leeuwen, 2000), DCM as well as Dynamic Expectation Maximization (DEM) proposed by Friston et al. (2003, 2008), and variational Bayesian expectation maximization (VBEM) method (Beal and Ghahramani, 2001a; Beal, 2003; Ghahramani and Beal, 2000, 2001; Ghahramani and Hinton, 1996).

There are currently three main approaches to estimate the parameters of the stochastic state-space model of EEG/MEG: (1) the recursive optimization algorithm based on the local linearization (LL) filter and an innovation method (LL-innovation) (Ozaki, 1992b); (2) the stochastic DCM (sDCM) method (Daunizeau et al., 2009); and (3) the Dynamic Expectation Maximization (DEM) method (Friston et al., 2008). The reader is referred to Valdes-Sosa et al. (2008) for a comprehensive review of the inversion methods. In the LL-innovation approach, first the same LL discretization scheme, described in Discretizing stochastic state-space model, is used to generate a linear SDE. Next, the locally linearized state equation together with the linearized observation equation and the measured data are fed into the Kalman Filter to provide an estimate of the state vector at all discretized time points. Then, the innovations or prediction error is estimated and used to calculate the likelihood of the model. Finally, the likelihood of the model given the data is maximized to calculate the maximum likelihood (ML) estimates of the parameters of the model.

In the sDCM, an approximate variational Bayesian inference scheme based on the VB-Laplace approximation method is presented to estimate the hidden-states, parameters, and hyperparameters of the stochastic dynamic nonlinear causal models (Daunizeau et al., 2009). DEM is another approach for inversion of the dynamic models (Friston et al., 2008). It provides time-dependent conditional densities on the path of a system’s states and the time-independent densities of its parameters which are obtained by maximizing a variational action with respect to conditional densities under the Laplace approximation. DEM is a variational learning scheme that optimizes the conditional density on model states (D-step), parameters (E-step), and hyperparameters (M-step).

We will propose a variational Bayesian learning method to estimate the posterior distributions of the parameters of our proposed multi-area E/MEG model. The proposed method will be based on the variational Bayesian approach introduced by Beal and Ghahramani for learning the posterior distributions of the parameters of the ordinary linear SSM (Beal, 2003; Beal and Ghahramani, 2001b, 2003). Based on their work, we will develop a variational Bayesian expectation maximization (VBEM) method for learning the posterior distributions of the parameters of our multi-area model which is a nonlinear SSM. We will introduce suitable prior distributions for the model parameters to benefit from the properties of the conjugate-exponential (CE) model in implementing the VBEM method. Consequently, the VBEM algorithm leads to analytically tractable forms.

The VBEM algorithm starts with initialization and consists of repeated iterations of the variational Bayesian expectation step (VB E-step) and the variational Bayesian maximization step (VB M-step). The posterior distributions of the model parameters are updated in the VB M-step. The distribution of the hidden state is updated in the VB E-step. We will introduce the variational extended Kalman smoother (VEKS) analogous to the Kalman filter and Rauch–Tung–Striebel smoothing algorithms (Rauch et al., 1963). To establish the VBEM method as an effective connectivity analysis tool for the E/MEG data, we will evaluate and validate the proposed VBEM method using simulations and real MEG studies.

The LL-innovation method is a ML estimation method that provides point estimates of the model parameters. In the VBEM method as a variational Bayesian approach, the model parameters are assumed to be random variables whose posterior distributions are estimated to infer their sufficient statistics (conditional mean and covariance in Gaussian distribution). While the LL-innovation method is limited to the estimation of the mean values of the parameters, the VBEM method not only estimates the mean values of the parameters but also the variances of the parameters to infer the precision of the estimates. In addition, the prior information about the model parameters can be more efficiently considered in the VBEM method compared to the LL-innovation method. While the mean values of the priors correspond to the expected values of the parameters, the amount of the prior knowledge about a parameter is shown by the variance of its prior distribution. A small variance represents a tight distribution and corresponds to precise prior knowledge. Using the VBEM method, we assign a small value to the prior variance of a parameter of the multi-area model if we are confident about its assigned mean value and vice versa.

The VBEM method assumes uncorrelated random components (e.g., a Wiener process for system noise) but the DEM deals with more realistic noise model where noise can be a correlated process to model smooth random fluctuations over time. This is accommodated in DEM using the generalized coordinates of high-order motion and a parametric form for the temporal correlations. The VBEM has an advantage compared to the DEM and the sDCM to estimate posterior distribution of the parameters of the multi-area model. The VBEM algorithm leads to analytically tractable forms because of using the properties of the CE model in its implementation while the Laplace approximation is employed in the DEM and sDCM. The Laplace approximation makes a local Gaussian approximation around a maximum a posteriori (MAP) parameter estimate. The Laplace approximation has several shortcomings which may affect the result
of the DEM and sDCM. The reader is referred to page 35 of Beal (2003) for details.

It should be noted that the proposed multi-area model can be extended to a multi-area integrated E/MEG and fMRI model. We proposed a single-area integrated E/MEG and fMRI model, shown in Fig. 1, based on the proposed ENMM (Babajani and Soltanian-Zadeh, 2006). In the ENMM, EEG and MEG signals originate from the overall synaptic activities of the pyramidal cells of all minicolumns (y(t) in Eq. 1) which can be calculated using the lead field matrix (i.e., forward electromagnetic model) (Mosher et al., 1999). We extracted the fMRI signal from the proposed ENMM by calculating the overall synaptic activities in the area and using it as the input of the extended balloon model (Friston et al., 2000). Using the physiological principles proposed in our work (Babajani and Soltanian-Zadeh, 2006) and others’ work (Riera et al., 2006; Sotero and Trujillo-Barreto, 2008), the multi-area integrated E/MEG and fMRI model can be developed.

Conclusions

In this paper, we have further extended our previously proposed extended neural mass model (ENMM) form a single-area model to a multi-area model and derived the state-space representation of the model to calculate the generated EEG and MEG signals. Effects of the intra-minicolumn, intra-area short-range connections (SRCs), and inter-area long-range connections (LRCs) parameters on the dynamics of the model have been verified using various simulation studies and led to the finding of valid ranges of variation for the model parameters as given in Table 1. To reduce the redundancy in the model, the simulation results have shown that changes in the dynamics of the model generated by the variation of the intra-minicolumn parameters can be represented by the variation of the SRCs and LRCs parameters. Thus, the parameters of the model can be limited to the LRCs and SRCs while the intra-minicolumn parameters stay at their physiological mean values. The proposed multi-area model can be extended to a multi-area integrated E/MEG and fMRI model. In addition, we have briefly introduced a Bayesian framework, i.e., variational Bayesian expectation maximization (VBEM) method, to estimate the posterior distribution of the parameters of the proposed multi-area model. The proposed multi-area model as well as the VBEM method will provide an efficient neuroimaging technique for the effective connectivity analysis. This will be a useful technique in neuroscience towards understanding of functions of the brain. It will provide great potentials for activation detection and connectivity analysis in healthy subjects as well as neurological and psychiatric patients.

Appendix A. State-space representation of the single-area model

Eq. (1) represents the dynamics of the ith minicolumn within a single-area model which contains L minicolumns. We define the following state vector for the ith minicolumn based on Eq. (1).

\[
\mathbf{x}_i(t) = \begin{bmatrix}
\mathbf{x}_i^1(t) \\
\mathbf{x}_i^2(t) \\
\mathbf{x}_i^3(t) \\
\mathbf{x}_i^4(t) \\
\mathbf{x}_i^5(t) \\
\mathbf{x}_i^6(t) \\
\mathbf{x}_i^7(t) \\
\mathbf{x}_i^8(t)
\end{bmatrix}
\]

Considering the above definition, Eq. (1) can be written as

\[
\begin{align*}
\mathbf{x}_i(t) &= \begin{bmatrix}
\mathbf{x}_i^1(t) \\
\mathbf{x}_i^2(t) \\
\mathbf{x}_i^3(t) \\
\mathbf{x}_i^4(t) \\
\mathbf{x}_i^5(t) \\
\mathbf{x}_i^6(t) \\
\mathbf{x}_i^7(t) \\
\mathbf{x}_i^8(t)
\end{bmatrix}
\end{align*}
\]

The above equation can be represented in the following matrix form:

\[
\mathbf{x}_i(t) = \mathbf{a}_i \mathbf{x}_i(t) + \mathbf{a}_i S(\mathbf{x}_i(t)) + \sum_{j=1, j \neq i}^{L} \left( g_{ij} \mathbf{x}_j(\tau) + g_{ij} \mathbf{x}_j(\tau) + g_{ij} \mathbf{x}_j(\tau) \right) S(\mathbf{x}_j(t))
\]

where \( g_{ij}, g_{ij}, \) and \( g_{ij} \) are three gain parameters which represent the SRCs and LRCs and \( L \) are based on Eq. (2) and defined as

\[
\begin{align*}
L_{ij} &= \exp \left( -\frac{\text{dist}(i,j)^2}{2\sigma_p^2} \right),
L_{ij} &= \exp \left( -\frac{\text{dist}(i,j)^2}{2\sigma_p^2} \right),
L_{ij} &= \exp \left( -\frac{\text{dist}(i,j)^2}{2\sigma_p^2} \right)
\end{align*}
\]

and

\[
\begin{bmatrix}
0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\
1/\tau_i & -2/\tau_i & 0 & 0 & -1/\tau_i & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & -1/\tau_i & -2/\tau_i & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & -1/\tau_i & -2/\tau_i & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -1/\tau_i & -2/\tau_i
\end{bmatrix}
\]

By looking at Eq. (A.2), we find that all eight intra-minicolumn state variables can affect each other but only the first state variable of the minicolumn, i.e., \( x_i^1(t) \), can affect the other minicolumns as represented by \( S(x_i^1(t)) \). However, the interaction among the minicolumns in Eq. (A.3) is
represented by the entire state variable $x(t)$ as $S(x(t))$ with considering unit vector $[1 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0]$ in the definitions of $\alpha_b$, $\alpha_d$, and $\alpha_g$.

To find the state space representation of the area and to calculate the generated EEG and MEG signals, the state vectors of $L$ minicolumns within the area are concatenated in one vector $x_{\text{local}} = [x_1(t), x_2(t), \ldots, x_L(t)]^T$. The strength of the generated ECD in the area can be calculated using the overall synaptic currents of the pyramidal cells of the minicolumns, i.e., $y_{\text{ECD}} = \sum_{i=1}^{L} y_i(t) = \sum_{i=1}^{L} x_i(t)$, which generates the EEG and the MEG signals. The following state-space representation can be derived from Eq. (A.3).

$$
\begin{align*}
\begin{bmatrix}
X_{n+1} \\
Y_{n+1}
\end{bmatrix}
&= \begin{bmatrix}
A & + & B & 0 & G & 0 & 0 & 0 & 0 \\
0 & & & & & & & & \\
C & & & & & & & & \\
D & & & & & & & & \\
\end{bmatrix}
\begin{bmatrix}
X_n \\
Y_n
\end{bmatrix}
+ \begin{bmatrix}
B_0 u \\
0 \\
0 \\
0
\end{bmatrix}

\begin{equation}
A_{\text{local}} = I_x \otimes \Omega, \\
A_{\text{local}}^T = I_x \otimes \Omega^{\text{T}}, \\
A_{\text{local}}^{\text{f}} = \Omega_{I_x} \otimes \Omega, \\
A_{\text{local}}^{\text{g}} = \Omega_{I_x} \otimes \Omega, \\
B_{\text{local}} = I_x \otimes \Omega_{I_x}, \\
C_{\text{local}} = I_x \otimes \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}_x
\end{equation}
\end{align*}
\]

$X_n$ is the EEG and MEG signals on the sensors. The $L$-by-$8$ $\Omega$, $\Delta$, and $\Omega$ are $L$-by-$L$ matrices whose entries are defined in Eq. (A.4), $A_{\text{local}}$ is $L$-by-$1$ vector with $1$ in all its entries, $H$ is the lead field matrix, $Y$ is the EEG and MEG signals on the sensors. The superscript "s" in $A_{\text{local}}$, $A_{\text{local}}^T$, and $A_{\text{local}}^{\text{f}}$ stands for the SRCs.

References


