A linear model for characterization of synchronization frequencies of neural networks

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Abstract The synchronization frequency of neural networks and its dynamics have important roles in deciphering the working mechanisms of the brain. It has been widely recognized that the properties of functional network synchronization and its dynamics are jointly determined by network topology, network connection strength, i.e., the connection strength of different edges in the network, and external input signals, among other factors. However, mathematical and computational characterization of the relationships between network synchronization frequency and these three important factors are still lacking. This paper presents a novel computational simulation framework to quantitatively characterize the relationships between neural network synchronization frequency and network attributes and input signals. Specifically, we constructed a series of neural networks including simulated small-world networks, real functional working memory network derived from functional magnetic resonance imaging, and real large-scale structural brain networks derived from diffusion tensor imaging, and performed synchronization simulations on these networks via the Izhikevich neuron spiking model. Our experiments demonstrate that both of the network synchronization strength and synchronization frequency change according to the combination of input signal frequency and network self-synchronization frequency. In particular, our extensive

experiments show that the network synchronization frequency can be represented via a linear combination of the network self-synchronization frequency and the input signal frequency. This finding could be attributed to an intrinsically-preserved principle in different types of neural systems, offering novel insights into the working mechanism of neural systems.

Keywords Synchronization frequency · Neural networks · Neuroimaging · Izhikevich model

Introduction

Functional oscillation and synchronization are essential characteristics of neural systems at multiple scales (e.g., Gray et al. 1989; Ermentrout 1994; Fries 2001; Buzsaki and Draguhn 2004; Ishikane et al. 2005; Fox and Raichle 2007; Friston 2009; Koepsell et al. 2009; Du et al. 2012). It is widely recognized that functional network synchronization and its dynamics are jointly determined by network topology, network connection strength, i.e., the connection strength of different edges in the network, and external input signals, among other important factors (e.g., Honey et al. 2007; Perc and Gosak 2008; Ozer et al. 2009; Mandonnet et al. 2010). Recent neuroscience research suggests that the cognitive functions of the brain arise from the dynamic interactions of distributed brain areas operating in the functional brain networks (Friston 2009), and the network dynamics such as synchronization can provide important insights for our understanding of the brain's function (Pikovsky et al. 2001; Fox and Raichle 2007). Therefore, exploration of how network structure and external stimulus determine the functional synchronization of a complex brain network has received significant

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attention recently (Zhou et al. 2006; Fox and Raichle 2007; Bullmore and Sporns 2009; Friston 2009; Hagmann et al. 2010; Yu et al. 2013). Among a variety of important dynamics attributes of functional brain networks, the synchronization frequency and its dynamics have important roles in deciphering the working mechanisms of brain networks (Pikovsky et al. 2001; Buzsaki and Draguhn 2004). For instance, it has been reported that the gamma-band oscillatory synchrony plays a crucial role in grouping different brain areas into one task in human visual cognition (Tallon-Baudry 2009).

Despite increasing interests in network-based analysis of neural systems in the literature in recent years (Pikovsky et al. 2001; Honey et al. 2007; Sporns et al. 2007; Kaiser et al. 2007; Brette et al. 2007; Hagmann 2007; Bullmore and Sporns 2009; Hagmann et al. 2010; Mandonnet et al. 2010), quantitative characterizations of the relationships between network synchronization frequency and other important factors such as network topology, network connection strength, and external input signals are still lacking. Essentially, such quantitative modeling and simulation can offer novel insights into the working mechanisms of neural systems, and can potentially shed lights on how such working mechanisms are altered in neurological or psychiatric brain conditions. In this paper, we present a quantitative model of the synchronization frequency characteristics and their dynamics on functional brain networks. Specifically, we constructed three types of neural networks including simulated small-world networks, real functional working memory network derived from functional magnetic resonance imaging (fMRI) (Faraco et al. 2011), and real large-scale structural brain networks derived from diffusion tensor imaging (DTI) (Mori 2006), to model different layers of neural networks. Then, the coupled neuronal spiking of each node in these functional networks was simulated via the Izhikevich (2003) neuron spiking model. With the simulated coupled spiking, we studied the relationships among the frequencies of the network self-synchronization that is intrinsically determined by the network topology and connection strength, the strength and frequency of the external input signals, and the frequency and strength of network synchronization under external input signals. Our extensive experimental results have shown that: (1) when the strength of the input stimuli is moderate, the functional brain network operates like an acceptance filter. That is, it achieves better synchronization when the frequency of external stimuli is approximately 1.2 or 2 times the oscillation frequency of the network's self-synchronization; (2) When the input strength is strong, the network performs like a band-pass filter. That is, the functional network can achieve synchronization when the input signal possesses a wide frequency band around 1.2 times the self-synchronization frequency; (3) The

synchronization frequency under input signals could be represented by a linear combination of the network self-synchronization frequency and the input signal frequency.

The major contributions of this paper are summarized as follows. First, we have applied novel and effective methods to construct real-world macro-scale brain networks from in vivo human neuroimaging data including fMRI and DTI images, in addition to traditional simulated small-world neural networks. The integration of realistic neuroimaging data into the computational modeling and simulation of neural systems could potentially enhance the realisms of neural network modeling. In particular, the DTI tractography can reconstruct in vivo white matter fibers (Mori 2006) from the human brain and provides a realistic reconstruction of the structural substrates of large-scale brain networks. In addition, we applied both monolayer and bilayer models on the reconstructed neural networks to examine the quantitative relationships between network synchronization frequency and other important factors including network topology, network connection strength, and external input signals. This combination of neural networks and simulation models enhances the comprehensiveness of our computational simulations. Second, our extensive simulations using different combinations of neural networks (simulated networks and real human brain networks) and simulation models (monolayer and bilayer models) with different settings of parameters consistently demonstrate that the network synchronization frequency can be represented via a linear combination of the network self-synchronization frequency and the input signal frequency. This interesting finding could be attributed to an intrinsically-preserved principle in different types of neural systems, and offer novel insights into the working mechanism of neural systems.

The rest of the paper is organized as follows. Section “Methods” describes our experimental paradigm in details, including construction of different types of networks, simulation of the coupled neuronal spiking in the brain network, and measurement of synchrony strength and frequency. Third section presents the experimental results, and final section concludes the paper.

Methods

Figure 1 summarizes the framework of experiment designs and approaches in this work. First, we use both simulated small-world networks (Watts and Strogatz 1998) and real functional and structural brain networks constructed from fMRI and DTI datasets (Faraco et al. 2011; Zhu et al. 2011a, 2012) to represent the neural systems. Then, the coupled neuronal spiking of the nodes in the neural networks is simulated via the Izhikevich (2003) neuron

spiking model. Therefore, the self-synchronization (the network synchronization without input stimulus) and synchronization under external input signals can be modeled and simulated on these neural networks with different parameter settings. Afterwards, we studied the quantitative relationships among the frequencies of the self-synchronization that is intrinsically determined by the network topology and the strength of connection, the synchronization frequencies and strength of the network under external stimulus, and the strength and frequency of the external stimulus. Based on extensive experiments, our results demonstrate that in all of these above simulations, the network synchronization frequency can be represented via a linear combination of the network self-synchronization frequency and the input signal frequency. The following subsections will describe the details of network constructions, network simulation models and quantitative analyses, respectively.

Neural networks and simulation models

Recently, there have been several studies that investigated the structural and functional brain networks by using both simulated datasets and brain imaging datasets (e.g., Zhou et al. 2006; Kaiser et al. 2007; Brette et al. 2007; Schmidt et al. 2010). For example, Zhou et al. (2006) assessed the relationship between structural and functional brain

networks using multi-level neuronal spiking model. Kaiser et al. (2007) evaluated the robustness of brain networks against brain lesions by comparing the cortical inter-areal connectivity networks of the cat and the macaque brains with the simulate small-world, scale-free and random networks. There are also other approaches intending to reproduce the dynamics of cortex by simulated brain network with interconnected spiking neurons (Brette et al. 2007). Zhou et al. (2006) use the bilayer neuron model to simulate the cortical dynamics of cat brain and reported the similarity between anatomical community and dynamical clusters. Schmit et al. (2010) demonstrated that monolayer model could reproduce this phenomenon.

Meanwhile, in the neuroimaging field, fMRI (Fox and Raichle 2007; Friston 2009; Faraco et al. 2011; Zhu et al. 2011a) and DTI (Mori 2006; Zhu et al. 2012) techniques provide non-invasive approaches to studying the functional and structural brain networks, respectively. For example, Sporns et al. (2007) used diffusion spectrum imaging (DSI) datasets to construct structural brain networks and identified the hub regions on the cerebral cortex. Damoiseaux et al. (2006) identified consistent resting-state functional brain networks across healthy subject using resting-state fMRI (R-fMRI). Honey et al. (2007) investigated the relationship between structural and functional brain networks by a joint analysis of fMRI and DTI datasets.

Fig. 1 The framework of our experiment designs and approaches. Three steps are included in three dashed frames from the left to the right including network construction (step 1), network simulations (step 2), and quantitative relationship modeling (step 3). In Step 1, three types of neural networks were constructed including simulated small-world networks (top) (Watts and Strogatz 1998), working memory networks via fMRI data (middle) (Faraco et al. 2011; Zhu et al. 2011a), and structural brain networks via DTI data (bottom) (Zhu et al. 2012). In Step 2, self-synchronization and synchronization under external input signals are simulated on the neural networks. In Step 3, the quantitative relationships between network synchronization strength and frequency and self-synchronization frequency and input signal frequency are modeled

In this paper, we used both simulated small-world networks and real human brain networks reconstructed from neuroimaging data for network synchronization frequency modeling. Also, we presented hierarchical network models to represent the structural and functional architecture of the different brain layers (Fig. 2). Specifically, we first used a monolayer simulated small-world network, in which each node was represented as an excitable neuron. Then, we constructed the working memory (WM) brain network by joint modeling of task-based fMRI and DTI dataset. That is, the regions of interest (ROIs) in the WM network were identified via a modified operation span (OSPAN) task (Faraco et al. 2011) and the connectivity among the network nodes was quantified via stochastic fiber tracking performed on the DTI dataset. We used two different strategies to simulate the coupled neuronal spiking on the constructed WM network, namely, monolayer and bilayer model (Fig. 2). In the monolayer model, each node was represented as an excitable neuron, the same as that in the simulated small-world network. While in the bilayer model, each network node was represented as a small-world network. We demonstrated that similar conclusions were obtained from both the monolayer and bilayer WM networks. Finally, we used the structural brain network represented by the DICCOLs (Dense Individualized and Common Connectivity-based Cortical Landmarks) (Zhu et al. 2011b, 2012; Li et al. 2012c) as the network representation covering the entire cerebral cortex. It is preferred to use the bilayer model to study the dynamics on the DICCOL-based structural brain network, since the computational burden is much increased in the 358 nodes of the DICCOL network (Zhu et al. 2011b, 2012; Li et al. 2012c). Here, each node was represented by a single excitable neuron in our study. Figure 2 summarizes the three types of neural networks and two network simulation models used in this paper. Table 1 at the end of section “Neural networks and simulation models” summarizes the parameters in the three types of network.

Small-world network model

Small-worldness has been frequently reported as a distinctive characteristic of both the structural and functional human brain networks (Bassett and Bullmore 2006; Bullmore and Sporns 2009). It incorporates the basic features of neural networks in the local area of the cortex, i.e., neurons are mainly connected to their spatial neighbors, but also with additional distant counterparts (Zhou et al. 2006). In this paper, small-world networks were simulated according to the approach proposed by Watts and Strogatz (1998) to represent the architecture of the brain (Bullmore and Sporns 2009). In brief, a regular array of N nodes with the same degree k_a is firstly interconnected with their nearest

Fig. 2 The hierarchical neural network simulation models used in our paper. Our strategy is to expand the model covering while simplifying the network structure

neighbors, and then the connections are rewired with a probability p . Such manipulation decreases the average path length greatly while maintaining the original clustering coefficient (Watts and Strogatz 1998). Given the clustering coefficient C and minimum average path length L , the small-worldness (small world index) is calculated as $SW = (C/C_{rand})/(L/L_{rand})$ (Bassett and Bullmore 2006). C_{rand} , L_{rand} is the clustering coefficient and minimum average path length of the same network rewired with $p = 1$. In our experiment, there are 100 nodes in small world network, the degree k_a of each node is 14, and the small world index (small worldness) is varied as 1.86, 2.23, 2.75, 3.15 by changing the rewiring probability p as 0.3, 0.2, 0.15, 0.1, respectively. The clustering coefficients are 0.31, 0.39, 0.46 and 0.52, respectively.

Functional working memory network

The working memory (WM) brain network was constructed by a joint modeling of task-based fMRI and DTI dataset (Faraco et al. 2011; Zhu et al. 2011a). Specifically, the nodes in the WM network were first identified by activation detection in a modified version of the operation span (OSPAN) task-based fMRI (Faraco et al. 2011). In the block-based task, each run was preceded by visual instructions and it contained 15 epochs; The OSPAN, Arithmetic, and Baseline conditions were structured so that subjects received similar amounts of visual input and gave the same amount of motor output. FMRI scans were acquired for 25 healthy adults using a T2*-weighted single shot echo planar imaging (EPI) sequence and was aligned to the AC-PC line (Faraco et al. 2011). The imaging parameters are as follows: TE = 25 ms, TR = 1,500 ms, 90° RF pulse, 30 interleaved slices, acquisition matrix = 64 × 64, spacing = 0 mm,

Table 1 Parameters of different types of network

Parameter	Network			
	Small world network	OSPAN network		DICCCOL network
		Monolayer	Bilayer	
Number of nodes	100	16	1600	358
Average degree	14	11.88	15.19	53.86
Standard deviation of degree	Around 1.5	2.45	1.72	27.55
Whether weighted or not	No	Yes	Yes	No

slice thickness = 4 mm, FOV = $240 \times 240 \text{ mm}^2$, and ASSET factor = 2. Those most consistent activation peaks that appear in all of the participants were selected as the functional ROIs (Li et al. 2010, 2012a; Faraco et al. 2011). 16 ROIs are identified as the nodes in the network. The connections among the ROIs, that is, the edges of the network, were quantified as the DTI-derived structural connectivities between any pair of ROIs. Specifically, the stochastic DTI tractography algorithm (Behrens et al. 2003) implemented in FSL (Smith et al. 2004; Woolrich et al. 2009) was adopted to derive the structural connectivity from the DTI data for each subject individually. By specifying a seed ROI and a terminate ROI, the stochastic fiber tracking resulted in a volume image, in which the intensity of the voxel indicates the probability of the fibers penetrating the corresponding voxel. Figure 3a shows an exemplar joint visualization of the cortical surface and the volume rendering of the resulted probability map. The above procedure was repeated for all possible ROI pairs in the identified 16 brain regions via task-based fMRI. Denote the probability volume for ROI pair R_i and R_j as I_{ij} , and the structural connectivity matrix of the identified functional brain network as C . Denote $x_{i,j,k}$ as one voxel in a DTI volume image of I_{ij} , where i, j, k corresponds to the three dimensional coordinates of a voxel, denote $p(x_{i,j,k})$ as the connectivity probability of the voxel obtained from stochastic fiber tracking (Behrens et al. 2003). For a given probability threshold T , we set $x_{i,j,k} = 0$ if $p(x_{i,j,k}) < T$, and $x_{i,j,k} = 1$ if $p(x_{i,j,k}) \geq T$. Based on the obtained binary volume image x , we detect whether there are connected positive voxel masses joining any given pair of ROIs by using the bwlabel MATLAB toolbox (Shapiro 1992). Denote $C(i,j) = 1$ when ROI R_i and R_j were connected, otherwise $C(i,j) = 0$. We varied T from 0.01 to 1 with the step length of 0.01, and summed up $C(i,j)$ in each step to obtain the connectivity strength $z_{ij} = \sum_{T=0.01}^1 C(i,j)$, which indicates the strength of the direct structural connection between the corresponding ROI pairs (Sun et al. 2012). The element with higher value of $Z_{i,j}$ indicates the stronger direct structural connection between the corresponding ROI pair. Figure 3b shows the working memory network.

DICCCOL-based structural brain network

Recently, we developed and validated an effective data-driven strategy that discovered 358 consistent and corresponding Regions of Interests (ROIs) in 240 brains (Zhu et al. 2011a, 2012), in which each identified ROI was optimized to possess maximal group-wise consistency of DTI-derived fiber shape patterns (Li et al. 2010, 2012a; Zhu et al. 2011a). The neuroscience basis is that each brain's cytoarchitectonic area has a unique set of extrinsic inputs and outputs, called the "connectional fingerprint" (Passingham et al. 2002), which largely determine the functions that each brain area performs. This close relationship between structural connection pattern and brain function has been replicated in a series of our recent works (Li et al. 2010, 2012a, b, c; Zhang et al. 2011, Zhu et al. 2011a, 2012). These 358 ROIs are named Dense Individualized and Common Connectivity-based Cortical Landmarks (DICCCOL) (Zhu et al. 2011a; 2012). This set of 358 DICCCOL ROIs has been replicated in over 240 brains and its predictions in five different datasets (over 240 brains) have been released online at: <http://dicccol.cs.uga.edu>. In particular, large-scale fMRI datasets have been used to validate the functional correspondences of 95 out of the 358 DICCCOLs (Zhu et al. 2012) across individuals and populations. Given the intrinsically-established structural and functional correspondences across individuals, the 358 common DICCCOLs provide natural structural substrates for the construction of structural and functional networks (Zhu et al. 2012). In this work, the connectivities among the DICCCOL nodes were quantified by deterministic fiber tracking, instead of stochastic fiber tracking used previously, to alleviate the computational burden. The number of fiber tracks penetrating each DICCCOL-pair was recorded and the connectivity between the paired nodes (Zhu et al. 2012) was measured according to the number of fiber tracks averaged over 30 healthy subjects. To the best of our knowledge, there has not been quantitative model to characterize the relationship between fiber numbers and inter-areal dynamic interaction strength. Thus we binarize the connectivity

Fig. 3 Stochastic fiber tracking and working memory network. **a** Joint visualization of the cortical surface and the probability map resulted from stochastic fiber tracking for two ROIs (represented by two blue spheres). **b** Visualization of the working memory network, the colorbar illustrated the connectivity strength z_{ij} between ROI i and j . (Color figure online)

matrix C by setting $C(i,j) = 1$ if there is more than 1 fiber linking DICCCOL node i and j on average over the 30 subjects, and setting $C(i,j) = 0$ otherwise.

Neuronal spiking models

Single neuron spiking model

The Izhikevich's simple spiking model (Izhikevich 2003) is used to simulate the single and coupled neuronal spiking of network nodes. The Izhikevich's model is as biological plausible as the Hodgkin-Huxley model, and it can reproduce spiking and bursting behavior of known types of cortical neurons. Meanwhile, this model is computational efficient and suitable for large-scale simulation. In our experiment, the neurons are set as regular spiking type, which is the most typical in the cortex (Izhikevich 2003, 2004). For a node denoted by v_i in a network with the set of nodes $V = \{v_i, i = 1, 2, \dots, N\}$, and the set of edges $E = \{e_{u,v}, u, v \in V\}$, its oscillation follows the following equations (Izhikevich 2003):

$$p'_i = 0.04p_i^2 + 5p_i + 140 - q_i + I_i \quad (1)$$

$$q'_i = a_i(b_i p_i - q_i) \quad (2)$$

$$I_i = I_0 \left(1 + \alpha \sum_{\forall p_j \geq 30} S(i,j) \right) + \beta_i + \xi_i \quad (3)$$

$$\text{If } p_i \geq 30 \text{ mV then } p_i \leftarrow c_i, q_i \leftarrow q_i + d_i \quad (4)$$

The part $p'_i = 0.04p_i^2 + 5p_i + 140$ was obtained by fitting the spike initiation dynamics of a cortical neuron (other choices are also feasible) so that the membrane potential p has *mV* scale and the time t has *ms* scale where p_i denotes the membrane potential of node v_i . When p_i is over 30 mV, v_i fires (Izhikevich 2003). q_i is the membrane recovery variable. a_i represents the time scale of q_i . Smaller value results in slower recovery. b_i is the sensitivity of q_i to the sub-threshold fluctuations of p_i . Greater values couple p_i and q_i more strongly, resulting in possible sub-threshold

oscillations and low-threshold spiking dynamics. A typical value is $b = 0.2$. c and d are the after spiking reset variable for p and q , taking -65 and 8 for regular spiking type, respectively. I_i is the synaptic currents or injected dc-currents (Izhikevich 2003), and it describes the pulse coupling between neurons and the impacts of input stimuli. α is the coupling strength between nodes, and taken a value around 0.75 . β_i denotes the inputs on v_i . S is a square matrix describing the connectivities among the nodes in the network, which is calculated as:

$$S(i,j) = \begin{cases} w_{ij} & \text{if } e_{ij} \in E \\ 0 & \text{otherwise} \end{cases} \quad (5)$$

w_{ij} is the weight of edge e_{ij} , which is determined by the connectivity matrix described in “Neural networks and simulation models” section. $\xi_i = \Xi_{0,1}(t)$ stands for the normal distributed white noise, with average of 0 and standard deviation of 1. Equations (1) and (3) describe how the membrane potential of a node changes. It is notable that it is determined by both node v_i and all the firing nodes that connected to v_i . Equation (2) describes the change of membrane recovery variable q_i , and it is only determined by v_i . Equation (4) resets p_i and q_i after spiking.

The input signal

The input signal has different meanings depending on different networks simulated. For instance, in the local cortical network represented by single small-world network, the input could represent the neural coding of certain firing rate coming from the sensory systems (Kandel et al. 1991). For the working memory functional network, the input could represent the binding rhythm from the central executive in the Baddeley's working memory model that coordinates the subsystems (Baddeley et al. 1996). For the whole cortex DICCCOL network, it could represent the input from the thalamus or brain stem, which has massive input to the cortex, and acts as a powerful pacemaker in brain rhythm (Bear et al. 2006). To represent the most general cases,

Table 2 Parameters used in the simulation

Parameters	Values
a	0.0025 to 0.01
b_i	0.2
c_i	−65 to −64
d_i	7.4–8
I_0	4

we speculate that the input stimulus is applied averagely to the networks. Hence, the external input signal is added in following way:

$$\beta_i(t) = \begin{cases} \omega(t) & \text{mod}(i, m) = 1 \\ 0 & \text{otherwise} \end{cases} \quad (6)$$

where $\omega(t)$ is a square wave, with period $T_1 = 1/f_1$, and the input is switched on 15 ms per period, while input strength is denoted by g . As there is only a small portion of neurons that receive external input signal, and to make sure that the input has enough influence on the network at the same time, we set 1 out of every 5 neurons to receive input signal by denoting $m = 5$, in all the three different types of networks. Input stimulus was turned on from $t = 8000$ to 20000 ms in the simulation period. The recovery coefficient a is changed from 0.0025 to 0.01 to simulate f_0 from 1.624 to 5.374 Hz. Value of parameters taken in the simulation are summarized in Table 2.

Interactions among network nodes

In the small-world network, one node was represented by an Izhikevich spiking neuron, and we used the small-world model (Bassett and Bullmore 2006) to represent a local cortical area as stated in “small-world network model” section. Interactions in the working memory network were

first modeled by a bilayer model, and then by a monolayer model. In this paper, a small-world network consisting of 100 neurons was used to represent a cortical area in the working memory network. The brain networks are characterized by dense local clustering and a few long-range connections (Bassett and Bullmore 2006), which indicates that the inter-areal connection should be far more sparse than the inner-areal connection. For each connection between two nodes, we randomly select 10 neurons from each node to form 10 interacting pairs to represent the interaction between the nodes. As a result, one neuron interacts with 14 neurons within the same area, and 1.19 neurons outside the area on average. Then, we reduced the bilayer model to single layer model by representing each cortical area with a single neuron. Notably, although the single neuron model is greatly simplified and could be unrealistic in terms of simulating neuronal activity of a cortical region, it is still very informative to explore the dynamical characteristics of brain networks (Schmidt et al. 2010). Also, we aimed to examine whether the single neuron model could reproduce the dynamics observed in bilayer model. As to the structural brain network represented by the DICCOLs, due to its large scale, we used one neuron to represent each node in the network in order to alleviate the computation burden. Computationally, we use the parameter $S(i, j)$ and w_{ij} introduced in “The input signal” section to represent the interaction, where $S(i, j) = w_{ij}$ if the connection between node i and node j exists, otherwise $S(i, j) = 0$. Specially, for small world network, and DICCOL network, $w_{ij} = 1$ for existed connection between node i and node j ; for monolayer OSPAN network, $w_{ij} = z_{ij}/100$ by normalizing the structural connectivity strength z_{ij} introduced in “Functional working memory network” section; for bilayer OSPAN

Fig. 4 Illustration of the calculation of synchronization frequency. **a** A visualization of synchronization process in a neural network of 100 nodes. The average time interval between two spiking is 569.12 ms with standard deviation of 14.20 ms. **b** Number of neurons firing in a time interval ($\delta(t)$) obtained from **a**. **c** $\delta(t)$ in **b** thresholded by $\lambda = 0.6$. **d** The radical frequency calculated from the Fourier transformation is 1.8 Hz. The radical frequency could represent the synchronization frequency truthfully

network, as to the inner-areal neuronal interaction, the representation is the same as small world network, i.e., $w_{ij} = 1$ for existed connection between node i and j , and for the inter-areal interaction between neurons in area I and area J , $w_{IJ} = z_{ij}/100$.

Measurement of synchrony

The parameter χ^2 coefficient is used to measure the synchrony in a network over a time period (Golomb et al. 2006). Denote $p_i(t)$ as the neuronal spiking of the i -th node in the network with N nodes. χ^2 is calculated as:

$$\chi^2 = \frac{\sigma_P^2}{\frac{1}{N} \sum_{i=1}^N \sigma_{P_i}^2} \quad (7)$$

$\sigma_P^2 = \langle [P(t)]^2 \rangle_t - [\langle P(t) \rangle_t]^2$ is the variance of the fluctuation of $P(t)$ over time where $P(t) = \frac{1}{N} \sum_{i=1}^N p_i(t)$. $\sigma_{P_i}^2 = \langle [p_i(t)]^2 \rangle_t - [\langle p_i(t) \rangle_t]^2$ is the variance of the fluctuation of $p_i(t)$ over time. Here, $\langle \dots \rangle_t = (1/T_m) \int_0^{T_m} dt \dots$ denotes the average over a long time. χ^2 is between 0 and 1, where 1 indicates that all nodes in the network fire in strict synchrony, and 0 indicates that neurons fire asynchronously. In our experiment, the synchrony was measured at interval from 12000 ms to 16000 ms when the synchronization has entered a stable state.

Measurement of synchronization frequency

The frequency of the self-synchronization of the neural network is obtained by the Fourier analysis. Let $\delta_i(t)$ denote whether v_i is fired at time t , that is

$$\delta_i(t) = \begin{cases} 1 & v_i \text{ is firing} \\ 0 & \text{otherwise} \end{cases} \quad (8)$$

Then, we deal with $\delta_i(t)$ by using a sliding time window of width T (T was chosen to be 40 ms according to observation to the temporal spiking margin of the synchronized neurons), by means of

Fig. 5 Synchrony pattern of the small-world network with the input strength of 10. The colorbar on the top shows the value of g . We can see an obvious zonal pattern. **a** Original synchrony pattern. **b** Synchrony pattern after thresholded by 0.5. **c** Linear regression results of the zonal zones in **b**

Fig. 6 Synchrony pattern of the small-world network with the input strength of 30. The colorbar on the top shows the value of χ^2 . **a** Original synchrony pattern. **b** Synchrony pattern after being thresholded by 0.5

$$\delta(t) = \sum_i \sum_{t-T/2}^{t+T/2} \delta_i(t) \quad (9)$$

$\delta(t)$ represents the number of neurons fired within the sliding time window. Then $\delta(t)$ is thresholded by a given parameter λ :

$$\delta'(t) = \begin{cases} 1 & \delta(t) > \lambda N \\ 0 & \text{otherwise} \end{cases} \quad (10)$$

In our experiment, λ was set to be 0.6, so that this measurement is sensitive to the network synchrony and robust to the noise in the oscillation. The synchronization frequency of

the neural network, that is, the radical frequency of $\delta'(t)$ is identified by a Fourier transformation. Figure 4 illustrates the above method of measuring synchronization frequency.

Results

Synchrony

The parameters in Eq. (1) are adjusted so that the frequency of the self-synchronization of the simulated small-world

Fig. 7 The synchronization pattern of different network models at weak input strength ($g = 10$). **a–d** Small-world network model (small-worldness of 3.15, 2.75, 2.23, and 1.85 respectively); **e** Bilayer working memory network model; **f** Monolayer working memory network model;

g The DICCOL brain network model. **h, i** Fitting parameters of synchrony patterns with weak input strength ($g = 10$). The number in parentheses is the small-worldness value. **h** Fitting parameters of synchrony area II; **i** fitting parameters of synchrony area I

networks varies from 1.5 to 5.5 Hz. For each simulated network, a block-shaped stimulus with the frequency varying from 0.4 to 20 Hz with the step of 0.2 Hz is set as the input signal. The synchrony of the network is calculated according to Eq. (7). In general, when the strength of the input stimulus is weak, e.g., 10, the synchrony demonstrates a zonary pattern, indicating that the network synchronized selectively to the stimuli with specific frequencies. After applying a threshold, those observed zonary areas are fitted by using linear functions. Figure 5a, b show the synchrony pattern of the small-world network with small-worldness of 3.15 and input strength of 10. Figure 5c shows the linear regression results, and the zones can be regressed by three straight lines as indicated in the figure. When the input strength is larger, e.g., 30, this network demonstrates the characteristics of a band-pass filter, as shown in Fig. 6.

We performed the simulation in all networks depicted in “Methods” section with both weak and strong input strengths. When added with weak input strength, we found

that the zonary areas in all simulations can be fitted by two linear functions: $f_1 = 1.2 \times f_0 + b$ (we refer it as synchrony area I) and $f_1 = 2.0 \times f_0 + b$ (synchrony area II). When added with strong input strength, the synchrony pattern can be fitted by one linear function close to $f_1 = 1.2 \times f_0 + b$. And the network can synchronize in a wide band when input frequency is between one and two times of the self-synchronization frequency. Here, f_0 indicates the self-synchronization frequency of the network, and f_1 indicates the frequency of input signal. We summarized these results in the form of $f_1 = af_0 + b$. Values of a and b in different simulations are shown in Fig. 7 (weak input strength) and Fig. 8 (Strong input strength), respectively.

Intuitively, the results observed above can be explained based on the numerical interpretation of the Izhikevich neuronal spiking model as follows. The model combines the biological plausibility of Hodgkin–Huxley-type dynamics and the computational efficiency of integrate-and-fire neurons. The neurons are fired and reset when their

Fig. 8 Synchronization pattern of different network models at strong input strength ($g = 30$). **a–d** Small world network model (small-worldness of 3.15, 2.75, 2.23, and 1.85 respectively); **e** Bilayer working memory network model; **f** The DICCOL network model. **g** Fitting parameters of synchrony patterns with strong input strength ($g = 30$)

membrane potentials accumulate and exceed a threshold, and followed by another round of integrate-and-fire. When the external stimulus is moderate or weak, the accumulation of the membrane potential is dominated by both the intrinsic behavior of the neurons and the potential evoked by the external stimulus. All the neurons fired and reset simultaneously when the external stimulus frequency is around one or two times of self-synchronization frequency and thus the network achieved better synchronization (Fig. 9a). When the frequency of the external stimulus is not around the integral times of frequency of the self-synchronization, the potential evoked by the external stimulus disturbs the integrate-and-fire, and consequently disturbs the synchronization of the network (Fig. 9b). When the external stimulus is strong, the accumulation of the membrane potential is dominated by the potential evoked by the external stimulus. Hence, when the input signal frequency is in a certain band, the neurons fire synchronously following the external stimulus and the network can achieve synchronization (Fig. 9c).

Fig. 9 Synchronization under different input schemes. The *upper panel* in each subplot is the input signal, *dark dots* indicate spiking of nodes without input signal, and *red dots* indicate spikings of nodes with input signal. **a** Weak input and matched frequency pair ($f_1 = 4$ Hz, $f_0 = 1.87$ Hz, $f_1 \approx 2f_0$) lead to good synchronization ($\chi^2 = 0.52$). **b** Weak input ($g = 10$) and unmatched frequency pair ($f_1 = 2.86$ Hz, $f_0 = 1.87$ Hz, $f_1 = 1.53f_0$) lead to poor synchronization ($\chi^2 = 0.35$). **c** Strong input ($g = 30$) and unmatched frequency pair ($f_1 = 2.86$ Hz, $f_0 = 1.87$ Hz, $f_1 = 1.53f_0$) can also lead to good synchronization ($\chi^2 = 0.52$)

Synchronization frequency

The prerequisite of measuring the synchronization frequency of a neural network is that the network should be synchronized. We regard the synchrony measurement (Eq. 7) of above 0.5 as the criterion of synchronization, which is chosen according to the Otsu method (Otsu 1979). Here, the time window T is 40 ms and λ is 0.6. For each simulation result shown in “Synchronization frequency” section, we measured the synchronization frequency (f_2) when synchrony measure is above 0.5. Then f_0 , f_1 and f_2 are fitted using a linear function. The fitting results have shown that f_2 could be well represented by a linear combination of f_0 and f_1 . We summarized the results in the form of $f_2 = a \times f_0 + b \times f_1 + c$. The values of a and b are shown in Fig. 10 (weak input strength) and Fig. 11 (strong input strength), respectively. These results indicate that when added with input signal, the synchronization frequency of the neural network will be changed by the input signal frequency, but still stay close to their self-synchronization frequency, as indicated by the analysis in “Synchronization frequency” section. Based on the results in Figs. 8, 9, 10 and 11, we conclude that the network synchronization frequency can be represented via a linear combination of the network self-synchronization frequency and the input signal frequency. It is interesting that this linear relationship is well replicated in all of the neural networks and simulation models with different parameter settings simulated in this paper, which suggest that this linear relationship might be attributed to a general principle in neural networks.

Discussion and conclusion

In this paper, we investigated the synchronization of three types of neural networks including simulated small-world neural networks and real structural/functional human brain networks reconstructed from in vivo neuroimaging data. In addition to the self-synchronization, synchronizations under external input signals applied to the network nodes were modeled and simulated. These input signals are encoded with external stimuli in their frequencies and amplitudes (Koepsell et al. 2009). Therefore, the neural network synchronizations with input signals could be viewed as their decoding processes. Different input frequencies and amplitudes can cause different synchrony strengths and synchronization frequencies in neural networks. Our extensive simulations demonstrate that these neural networks show selectivity to frequencies: when input strength is weak, the network synchronizes better at 1.2 or 2 times input frequency comparing to their self-synchronization frequency; when input strength is strong,

Fig. 10 The relationship between self-synchronization frequency (f_0), the input signal frequency (f_1) and synchronization frequency (f_2), with strong input strength ($g = 10$). **a–d** Small-world network model (small-worldness of 3.15, 2.75, 2.23, and 1.85 respectively); **e** Bilayer working memory network model; **f** Monolayer working memory network model; **g** DICCCOL brain network model. **h, i** Fitting parameters of synchrony frequencies with weak input strength ($g = 10$). Note that parameter a is near zero in most networks. **h** fitting parameters of synchrony area II; **i** fitting parameters of synchrony area I

Fig. 11 The relationship between self-synchronization frequency (f_0), the input signal frequency (f_1) and synchronization frequency (f_2), with strong input strength ($g = 30$). **a–d** Small-world network model (small-worldness of 3.15, 2.75, 2.23, and 1.85 respectively); **e** Bilayer working memory network model; **f** DICCCOL network model. **g** Fitting parameters of synchrony frequencies with strong input strength $g = 30$. Note that parameter a is near zero in most networks

the network synchronizes better at a wide frequency band around one time frequency. Our extensive experiments have shown that the network synchronization frequency can be well represented by a linear combination of the input signal frequency and self-synchronization frequency of the network. This suggests a compromise of maintaining self-synchronization frequency and following the input frequency in neural networks. Further analysis toward the oscillation neuron model shows that neurons with spike coupling (induced by weak input strength) could be phase-locked to input signals at integer times of input frequencies, and neurons with bursting coupling (induced by strong input strength) could be phase-locked to input signal at much wider frequency band (Izhikevich 2000). This could be attributed to the underlying physical reason for the phenomenon observed in our simulations.

In the current stage, we performed synchronization simulations in three types of neural networks with two

simulation models (monolayer and bilayer). In the future, we plan to construct other functional and structural brain networks such as the emotion, attention, language, visual and default mode networks via multimodal fMRI and DTI datasets (Zhu et al. 2012) and perform larger scale synchronization simulations on these networks, in order to examine the reproducibilities of the findings in this paper. Also, we will perform synchronization simulation studies by using other alternative neuron spiking models (e.g., Izhikevich 2004; Perc and Gosak 2008), in addition to the Izhikevich neuron spiking model, that have been well studied in the computational neuroscience literature, in order to examine the reproducibility of our findings. Once our findings are replicated and confirmed by these extensive simulations, we can premise that the linear relationship between network synchronization frequency, self-synchronization frequency, and input signal frequency could be attributed to a general principle in neural systems.

In the human neural system, the synchronization of different frequency, i.e., neural rhythm, also plays important role on brain functions, such as the neural coding by firing rate, the binding of different cortical area into a unity perception task with certain rhythm, and the coordination for more behaviors such as sleep and circadian by neural rhythm (Kandel et al. 1991; Baddeley et al. 1996; Bear et al. 2006). Given the above neuroscience knowledge, this linear relationship could offer novel insights into the working mechanisms of the brain and open new research directions of neural systems, particularly human brain networks constructed via in vivo neuroimaging data, in the future.

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