Clinically Localized Seizure Focus Maybe Not Exactly the Position of Abating Seizures: A Computational Evidence

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Clinically localized seizure focus maybe not exactly the position of abating seizures: a computational evidence

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Abstract Seizure focus localization is the key to control seizures. However, in this paper, we show that the clinically localized seizure focus may be not exactly the positions to abate seizures. Firstly, the reliability of a previously proposed methodology employed to estimate the synchronicity and directionality of information flows over time between EEG signals, is numerically assessed with a coupled mass neural model. Then 10 channels' EEG signals from a patient with focal epilepsy are used to reconstruct the dynamical complex network of pathological seizure. This may facilitate to identify the evolution paths of information flows and localize the potential seizure foci. What's more, based on the controllability and observability principles of complex systems, we can focus on the key nodes which is effective to control the network seizure behaviors and the key ones that can allow us to estimate the state of all other variables. Results show that to fully control the epileptic network may not just be related to the focus zone, it may also involves in other non-focus nodes. In addition, we use the spatiotemporal neural network model connected by our modeled dynamical adjacent matrix to successfully reproduce the original EEG signals which can be effectively abated by applying the normal dis-

tribution noise stimulation with cathodic phase pulses (cNDNs) on the identified key nodes or resecting them. Our results enrich the clinical results and provide new insights into the seizure resection and electronic stimulation therapies.

Keywords Focal seizures · neural field model · focus localization · directed synchronous information flow · controllability and observability · brain stimulation.

1 Introduction

Neocortical focal seizures are thought to be arised from the spatially localised pathological tissue of brain, i.e., epileptogenic zone (EZ)[1–3]. Surgical removal of EZ is often the final treatment option [4,5]. However, the most widely used techniques for localizing the EZ in patients with focal epilepsy is only the visual identification of raw data, lacking the spatio-temporal correlations of different seizure regions which might mask the true EZ and fail to prevent future seizures [6].

In principle, the aberrant brain activity of neurological diseases [7,8] can be restored through electrical stimulation. It is currently believed that electric stimuli can cause specific state-dependent transitions [9, 10], which has been considered as the potential supplemental approach to abate seizures [11–13]. Epilepsy is a chronic disorder which is considered a change in brain state (interictal, preictal, ictal and postictal) [14]. Epileptic seizures are generated by the collective activity of extended neuronal networks. They are often referred to as pathologically hypersynchronized states [15, 16]. Synchronization measures have also been applied to predict and localize the epileptic activity [17–19]. This means seizure control may be induced by modulating synchronization level. However, the synchronization

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between different brain areas, in particular, the synchronous coupling direction between signals, cannot be measured directly. To better understand seizure onset and propagation, as well as propose an effective seizure interfering strategy, it is needed to identify the coherent evolution and transferring process of the dynamic signal within the epileptogenic network by applying an appropriate analysis method.

Applications include localization[20], detection [21] and prediction [22] of epileptic activities have been broadly explored and viewed as the most challenging issues. At present, our aim is to employ a simple and fast methodology [23] to investigate the synchronicity and directionality (leading role) over time between signals from different brain areas. Then this method along with the controllability [24,25] and observability [26, 27] of complex systems are applied to investigate the focus localization and its synchronous evolution based on the intracranial human EEG recordings. Also, the macroscopic neural population model network dynamics [28] will be used to compare with the clinical EEG data. Finally, the effect of stimulation on seizure abatement will be computationally explored.

2 Materials and Methods

2.1 Clinical Data

In this paper, the SEEG data were recorded from 10 channels of a *patient who had been admitted to the hospital with refractory focal epilepsy at Sanbo Brain Hospital of Capital Medical University in Beijing*. This study protocol was approved by the *ethics committee of Sanbo Brain Hospital of Capital Medical University and the subject was written informed consent*. Due to the *hospitals regulations, the data cannot be made publicly available*. Part of the time series of the signals are shown in Fig. 4. Detailed description was exhibited previously in Yang et al. [29,30]. The 10 channels are denoted by F08, M09, C09, D03, D04, G05, H10, J07, K01, K02, where F: the middle frontal gyrus-medial frontal lobe, M: the middle frontal gyrus-outer side of frontal lobe, C: the front of the forehead back triangle area-frontal island cover-buckle belt back front lower part, D: the posterior central anterior sulcus, G: the back of the middle frontal gyrus-the inner side of the frontal lobe, H: the anterior central gyrus-cingulate gyrus, J: the front central back to upper middle, K: the central posterior middle-cingulate gyrus, respectively. The clinical EEG showed that two clinical seizures of epilepsy were recorded during the monitoring, which were mainly manifested as complex movements. At the beginning, the F08, M09 and C09 displayed low-amplitude

and high-frequency discharges. After 0.5-1s later, the discharges spread to D(03-04), then to G05, H10, J07 and finally to K(01-02), which successively showed the transition from the low amplitude and fast activity to spike-slow wave discharges.

2.2 Statistic method

2.2.1 Definition of event

For a time series $x(n)$ ($n = 1, 2, \dots, T$) with total T steps, the events can be defined as the local maxima by the following law [23,31]:

$$\begin{cases} x(t_k) > x(t_{k+m}), & m = -M + 1, \dots, 0, \dots, M - 1 \\ x(t_k) > x(t_{k \pm M}) + h \end{cases} \quad (1)$$

where the event times are denoted by t_k ($k = 1, \dots, n_e$) with n_e being the total event number; M and h are the parameters which have different values for the EEG data from epileptic animal model and epileptic patient.

2.2.2 Coupling direction and synchronization measurement

Consider two time series $x^1(n)$ and $x^2(n)$ with equal T total steps, where the event times are t_r^1 and t_s^2 ($r = 1, \dots, n_1; s = 1, \dots, n_2$), respectively. Allowing a time delay τ (smaller than half the minimum inter-event distance of these two time series), we can define a quasi-simultaneous appearances of events, which can be described by Eq. (5). Then, $e^\tau(x^1|x^2)$ ($e^\tau(x^2|x^1)$) is used to denote the number of times an event appears in x^1 (x^2) shortly after it appears in x^2 (x^1). Their symmetrical and anti-symmetrical combinations expressed by Eqs. (2) and (3) can be used to describe the event total synchronization level and event delay pattern, respectively. Thus, Q^τ and q^τ are normalized to $[0,1]$ and $[-1,1]$, respectively. Here we suppose that the delay behavior suggests the directions of information flow between x^1 and x^2 signals, i.e., as a tool to identify the leading role between them. That is we can identify the driver-response relationship between them. If q^τ in Eq. (3) is larger than 0, x^1 can be considered as the reason which drive the propagations of pathological information to x^2 .

$$Q^\tau = \frac{e^\tau(x^2|x^1) + e^\tau(x^1|x^2)}{\sqrt{n_1 \cdot n_2}} \quad (2)$$

$$q^\tau = \frac{e^\tau(x^2|x^1) - e^\tau(x^1|x^2)}{\sqrt{n_1 \cdot n_2}} \quad (3)$$

where

$$e^\tau(x^1 | x^2) = \sum_{r=1}^{n_1} \sum_{s=1}^{n_2} E_{rs}^\tau \quad (4)$$

with

$$E_{rs}^\tau = \begin{cases} 1, & \text{if } 0 < t_r^1 - t_s^2 \leq \tau \\ \frac{1}{2}, & \text{if } t_r^1 = t_s^2 \\ 0, & \text{else} \end{cases} \quad (5)$$

To present the on-line changes in event synchronization and event delay pattern (leading role), we give the time resolved variants of $Q^\tau(n)$ and $q^\tau(n)$, which can be obtained by simply modifying the conditions of Eq.(4), i.e.,

$$e_n^\tau(x^1 | x^2) = \sum_{r=1}^{n_1} \sum_{s=1}^{n_2} E_{rs}^\tau(n) \quad (6)$$

with

$$E_{rs}^\tau(n) = \begin{cases} 1, & \text{if } t_s^2 < t_r^1 < t_s^2 + \tau; \\ & \& t_r^1 < T \\ \frac{1}{2}, & \text{if } t_r^1 = t_s^2 < T \\ 0, & \text{else} \end{cases} \quad (7)$$

Hence,

$$Q_{12}^\tau(n) = e_n^\tau(x^2 | x^1) + e_n^\tau(x^1 | x^2) \quad (8)$$

$$q_{12}^\tau(n) = e_n^\tau(x^2 | x^1) - e_n^\tau(x^1 | x^2) \quad (9)$$

where $Q_{12}^\tau(n)$ increases one step only if an event is found both in $x^1(n)$ and $x^2(n)$ within the window τ , $q_{12}^\tau(n)$ takes one step up (down) every time an event in $x^1(n)$ shortly (i.e., also within the window τ) precedes (after) one in $x^2(n)$.

To further observe the instantaneous changes in event synchronization and event delay pattern (directionality, i.e., the leading role of information flow between two signals) at time n , a window technique was applied to calculate them averaged over the slide window $\Delta n=5120$ time steps, expressed as follows:

$$dQ_{12}^\tau(n) = \frac{Q^\tau(n) - Q^\tau(n - \Delta n)}{\sqrt{\Delta n_1 \Delta n_2}} \quad (10)$$

$$dq_{12}^\tau(n) = \frac{q^\tau(n) - q^\tau(n - \Delta n)}{\sqrt{\Delta n_1 \Delta n_2}} \quad (11)$$

2.2.3 Network measurement

Epilepsy has been understood to be the network disorder, but how to capture the evolutions of pathological information over time and localize the focus remain a hard issue. Thus, we need to reconstruct the epileptic

network. To measure the network synchronization, the above equations can be modified as follows,

$$Q_{net}^\tau(n) = \sum_{i \neq j=1}^N [e^\tau(x^j | x^i) + e^\tau(x^i | x^j)] \quad (12)$$

$$dQ_{net}^\tau(n) = \frac{Q_{net}^\tau(n) - Q_{net}^\tau(n - \Delta n)}{\sum_{i \neq j=1}^N \sqrt{\Delta n_i \Delta n_j}} \quad (13)$$

where $i \neq j$ and $i, j \in \{1, 2, \dots, N\}$.

The directionality of synchronous information flow, i.e., drive-response relationship of any two signals within network can be represented by the directed connectivity matrix:

$$a_{ij}(n) = \gamma \cdot |(dq_{ij}^\tau(n) > 0) \cdot dq_{ij}^\tau(n)| \cdot dQ_{ij}^\tau(n) \quad (14)$$

where $\gamma=1000$ is the amplifying parameter. Here our analysis assumes a loop free graph, thus $a_{ii} = 0$, for $1 \leq i \leq N$.

2.3 Controllability and observability

Due to the ubiquity of complex networks, it is highly desirable to be able to apply proper control to guide the network dynamics toward states with the best performance. In fact, the brain system dynamics can be described by the generic state-space form:

$$\begin{cases} \frac{dx(t)}{dt} = f(t, x(t), u(t)) \\ y(t) = h(t, x(t), u(t)) \end{cases} \quad (15)$$

Even though most real systems are driven by nonlinear processes, the controllability of nonlinear systems is in many aspects structurally similar to that of linear systems[32]. Thus, the study of this nonlinear system can be reduced to a canonical linear time-invariant dynamic system:

$$\begin{cases} \frac{dx(t)}{dt} = Ax(t) + Bu(t) \\ y(t) = Cx(t) \end{cases} \quad (16)$$

$A_{N \times N}$ is the adjacency matrix and N is the number of nodes. M is the number of driver nodes, B is the $N \times M$ input matrix, and $u(t)$ is the time-dependent input. According to Kalman's controllability rank condition [33,34], the above system can be controlled from any initial state to any desired state in finite time, if the $N \times NM$ controllability matrix

$$J_1 = [B, AB, A^2B, \dots, A^{N-1}B] \quad (17)$$

has full rank, that is $rank(J_1) = N$.

Fig. 1 (Color online) Structure of two coupled populations model (i and j , upper panel) and the elementary model of single population i (lower panel). K^{ij} is the unidirectional coupling functions. cNDNS represents the normally distributed noise stimulation with cathodic phase pulses. Other signs and interpretations can be seen in Section 2.4.

In addition, it is needed to estimate and reconstruct the system's internal state from its outputs, i.e., the observability of complex system. Of course, the simultaneous measurement of all internal variables can completely observe the system's state, but, in practice, the complete description of a complex system can only limited to a subset of variables (termed sensors in [26]). According to the previous method [26], here we will also adopt a graphical approach to determine the sensors that are necessary to reconstruct the full internal state of a complex system. The observability criteria can be formulated algebraically for linear dynamical systems, in particular, the system (16) is observable if the Jacobian matrix

$$J_2 = [C^T, (CA)^T, \dots, (CA^{N-1})^T]^T \quad (18)$$

has full rank, that is $\text{rank}(J_2) = N$

2.4 Neural field model

The model we used here is modified from Wendling et al. [28]. The single-compartment model includes two subsets of neurons, namely the main pyramidal cells and the inhibitory interneurons. The corresponding block diagram representation is shown in Fig. 1. h_e and h_i , viewed as the static gains of filters, describe the impulse response of linear transfer function changing the excitatory and inhibitory average presynaptic potentials into the excitatory and inhibitory post-synaptic potentials (EPSP, IPSP), respectively. x_1 denotes the output of interneuron EPSP transfer function h_e , x_2 denotes the output of Pyramidal EPSP transfer function h_e and x_3 denotes the output of Pyramidal IPSP transfer function h_i . $S(v)$ model the saturation effects

resulted from average pulse density of action potentials. $p(t)$ globally measures the influence of neighboring or distant populations, which is assumed to be Gaussian white noise. $(C_1, C_2) = (135, 108)$ and $(C_3, C_4) = (33.75, 33.75)$ are the average number of synaptic contacts in the excitatory and inhibitory feedback loop, representing the interactions between the main cells and interneurons. cNDNS indicates the population perturbations.

Note that, each linear transfer function h_e or h_i can introduce a second-order ordinary differential equation. Hence, according to the block diagram, the following set of 3 second-order differential equations that describe the state of every population can be established:

$$\begin{aligned} \frac{d^2 x_1}{dt^2} &= AaS(x_2 - x_3) - 2a\frac{dx_1}{dt} - a^2 x_1 \\ \frac{d^2 x_2}{dt^2} &= Aa[p(t) + \text{cNDNS}(t) + C_2 S(C_1 x_1)] \\ &\quad - 2a\frac{dx_2}{dt} - a^2 x_2 \end{aligned} \quad (19)$$

$$\frac{d^2 x_3}{dt^2} = Bb[C_4 S(C_3 x_1)] - 2b\frac{dx_3}{dt} - b^2 x_3$$

where $a = 100s^{-1}$ and $b = 50s^{-1}$ are the membrane average time constant and dendritic tree average time delays, respectively; A and $B = 35mV$ are the average excitatory and inhibitory synaptic gain, respectively. $S(v) = e_0 / (1 + e^{r(\nu_0 - v)})$, $e_0 = 5s^{-1}$ is the maximum firing rate, $\nu_0 = 6mV$ is the post-synaptic potential corresponding to the half of e_0 , $r = 0.56mV^{-1}$ is the steepness of the sigmoid. In the model, the noise current is modelled as $p(t) = \mu + \sigma \cdot \xi(t)$, where μ is the bias current, σ is the noise intensity and $\xi(t)$ is the Gaussian white noise with zero mean and unit variance.

K^{ij} is introduced to define the coupling gain constant from populations j to population i , where a impulse response h_d , viewed as a filter, is introduced to model the delay connection from population i . Hence, the two-compartment coupled model is governed by 4 second-order differential equations describing the inter-population behavior:

$$\begin{aligned} \frac{d^2 x_1^i}{dt^2} &= AaS(x_2^i - x_3^i) - 2a\frac{dx_1^i}{dt} - a^2 x_1^i \\ \frac{d^2 x_2^i}{dt^2} &= Aa[p^i(t) + \text{cNDNS}^i(t) + C_2 S(C_1 x_1^i) \\ &\quad + K^{ij} x_4^j] - 2a\frac{dx_2^i}{dt} - a^2 x_2^i \end{aligned} \quad (20)$$

$$\frac{d^2 x_3^i}{dt^2} = Bb[C_4 S(C_3 x_1^i)] - 2b\frac{dx_3^i}{dt} - b^2 x_3^i$$

$$\frac{d^2 x_4^i}{dt^2} = Aa_d S(x_2^i - x_3^i) - 2a_d\frac{dx_4^i}{dt} - a_d^2 x_4^i$$

where x_4 is the output of the EPSP transfer function h_d , $a_d = 33s^{-1}$ is the average time delay on efferent connection from a population.

Fig. 2 (a) Simulated background state signals using model (19) when $A=3.25mV$ with (upper panel) and without (lower panel) the coupling function ($K_{12}=200$) from the subsystem (middle panel) with $A=4.85mV$. (b) The dominant frequency of system (19) with A increasing. (c,d) The variants of delay pattern, q^τ (b), and event synchronization, Q^τ (c), with the coupling strength increasing from 0 to 300. The green lines correspond to the 50 averages $\pm\sigma$ of the surrogate obtained by disordering the subsystem 2's signals. In Eq.(1), $M=10$, $h=(\max(\text{signal})-\min(\text{signal}))/4$. Simulation duration is 20s, $dt=0.005s$.

2.5 Normal distribution noise stimulation with cathodic(c) phase pulses(cNDNS)

It is shown that external stimulus and electromagnetic induction as well as the noise can disturb the neuron population activity [35–37]. In particular, transcranial random noise stimulation (tRNS) [38–41] involving the application of random noise oscillations to the selected brain regions was shown to be a painless and unharmed neuromodulation method. It can increase the neuronal excitability via stochastic resonance and hence modulate the cortical plasticity. Due to the advantage of noise stimulation, in this paper, we employ the normally distributed noise stimulation with cathodic phase pulses (cNDNS) to computationally explore the seizure abatement effect. During the simulation, $\text{normrnd}(\mu, \sigma, 1, \text{time}/dt)$, i.e., a Matlab function with $\mu = 75$ and $\sigma = 25$ is used, where time is the simulation duration, dt is the integration step size.

Fig. 3 (Color online) (a) The upper two panels correspond to the original EEG data from channels D03 and D04. The lower panel corresponds to the surrogate obtained by shifting channel D03 signal 2000 data points ($\sim 7.8s$). (b,d) Time resolved event synchronization (b) and delay asymmetry (d). (c,e) The instantaneous time-resolved event synchronization (c) and delay asymmetries (e). The cyan lines correspond to the surrogate. The vertical red dashed lines indicate the seizure onsets. (sampling rate is 256Hz). $M=10$, $h=30$ in Eq.(1).

The standard fourth-order Runge-Kutta integration scheme under the MATLAB (MathWorks, USA) simulating environment was used with Eqns. (19–20). Initial conditions were set to zero in all simulations, and an integration step size of $\sim 4ms$ (corresponding to the clinic sampling frequency: 256 Hz) was used. Simulation duration is 100s for Fig. 2(a), 20s for Figs. 2(c) and 2(d), 136.25s for Fig. 10.

3 Results and Discussion

3.1 Synchronization and leading role between two coupled EEG signals

The above mentioned statistical analysis for estimating synchronization and delay pattern [23] was directly applied into the analysis for EEG data without the verification of effectiveness. However, this is more or less

Fig. 4 Original EEG data recorded from 10 channels, i.e., F08, M09, C09, D03, D04, G05, H10, J07, K01, K02. The red bar indicates the seizure onset.

a shortcoming. Hence, in this paper we first verify the effectiveness of this method using a coupled neural system, as shown in Fig. 1.

Fig. 2(b) shows that the firing of the system typically depends on the average excitatory synaptic gain A . It is seen that when A is larger than $A \approx 4.5mV$ the system can generate spikes from background state, the dominant frequency of which can successively increase with A progressively increasing. As illustrations, in the middle and upper panels of Fig. 2(a), the system shows the spiking state and background state with $A=4.85mV$ and $3.25mV$, denoted by system 1 and 2, respectively. However, as shown in the lower panel of Fig. 2(a), the coupling function ($K_{12}=200$) from system 1 makes the system 2 generate spikes from the background state. Further, we explore the synchronization level and the leading role between the two unidirectional coupling systems using the above statistic method for measuring synchronization (Q^τ) and time delay pattern (q^τ). It is clearly observed that when $K_{12}=200$ the two coupled systems have high level of synchronization (Fig. 2(d), $Q^\tau \approx 0.9$) and the system 1's leading role obviously dominates (Fig. 2(c), $q^\tau \approx 0.9$). In particular, this method can consistently, steadily and subtly capture the increasing evolutions of time delay pattern (i.e., the leading role of system 1) and synchronization by gradually increasing the K_{12} from 0 to 300. However, for the surrogate data which is obtained by disordering the discrete time series of system 2 (lower panel in Fig. 2(a)), it is seen from the green lines in Figs. 2(c) and 2(d) that as expected the drive-response relationship with system 1 disappears and desynchronizes (a background 'zero' level) between them. Therefore, these results verifies the reliability of the above mentioned statistical analysis [23] in determining the real synchronous level and drive-response relationship of two signals.

Then two original signals from channels D03 and D04 (Fig. 3(a)) are used to analyze their synchronous level and delay patterns (i.e., leading role). In particular, we aim to observe their evolutions over time, i.e.,

Fig. 5 (Color online) Time-resolved event synchronization (c,d) and delay asymmetries (a,b) between an contact G05 and the remaining channels. $M=10$, $h=30$ in Eq.(1). The horizontal dashed lines in (a) indicate the zero event delay $q^\tau(n) = 0$ and significant event delay threshold $q^\tau(n) = 10$. Vertical dashed line (a) and red bars in (b), (c) and (d) indicate the seizure onset. The meanings for the color of lines in (b), (c), (d) is same to (a). The black lines in (c,d) indicate the situations of whole network.

time-resolved event synchronization ($Q^\tau(n)$) and delay pattern ($q^\tau(n)$), where n denotes datapoint (total 40000 datapoints with sampling rate 256Hz used in this paper, the seizure onset is labeled at $n=27880$ denoted by vertical dashed lines). It is seen from Fig. 3(b) that with time going the synchronization between the signals of channels D03 and D04 gradually increases. Along with that, as shown in Fig. 3(d), the leading role (event delay patterns) of D04 for D3 also increasingly dominates. Remarkably, after the seizure starts, their synchronization level and the leading role of D04 are transiently, quickly and significantly increased. This suggests the quick synchronous information flow from D04 to D03, which is consistent with the previous clinical results that pointed out that increasing synchronization may promote seizure termination. The corresponding instantaneous time-resolved event synchronization ($dQ^\tau(n)$) and delay pattern ($dq^\tau(n)$) can be observed in Figs. 3(c) and 3(e), where there are evident humps at the beginning of seizures. Then, the synchronization increasing become weak. And the leading role of D04 also weakens a little, i.e., the slight decreasing in $q^\tau(n)$ which corresponds to the $dq^\tau(n) < 0$.

These results are credible when compared to the pairs of D04 signal and the surrogate signal of D03, where the surrogate data (The usefulness of such surrogates was discussed in more detail in [23]) are obtained by shifting the signals 2000 data points (~ 7.8 sec) to

the left without changing the individual properties of each signal. The result of surrogate pairs corresponds to the cyan lines which reach to lower level and even the background 'zero' level for the synchronization level and delay patterns.

3.2 Network analysis based on the clinical EEG signals

Next, we aim to explore the network evolutions of event synchronization and delay patterns by reconstructing the directional network based on the analysis of clinical EEG signals. Fig. 4 displays the original EEG data with 40000 datapoints from 10 channels, i.e., F08, M09, C09, D03, D04, G05, H10, J07, K01, K02, respectively. These ten channels are mainly divided into four groups (see Fig. 7) according to the clinical observations, i.e., group I: F08, M09, C09; group II: D03 and D04; group III: G05, H10, J07; group IV: K01 and K02. Epileptiform discharges are observed to spread from group I to group IV.

Fig. 5(a) shows the time-resolved event delay pattern evolutions between G05 and the other 9 channels. The leading roles of G05 to other 9 channels can be determined if $q^\tau(n) > 0$. Note that, to avoid the hidden wrong outcomes induced by the noise disturbance, we set a event delay threshold $q^\tau(n) = 10$ that can define the significant leading role of G05 when $q^\tau(n) > 10$ (the same hereinafter). In particular, after seizures starts (denoted by the vertical dashed lines), we can observe the evident driving roles of G05 to M09, C09, D04, K01 and K02, respectively, in seizure spreading. Fig. 5(b) give the corresponding instantaneous changing rate of $q^\tau(n)$, i.e., $dq^\tau(n)$. Fig. 5(c) shows the corresponding time-resolved event synchronization evolutions of each pair of signals consisting of G05 and each other channel, as well as the whole network. As a whole, the network presents the higher synchronization level while seizure occurs. As shown in Fig. 5(d), the instantaneous rate is also high, meaning the very active synchronous activity.

The other similar scenarios can be found in Fig. (6), where we provide rich drive-response relationships between each channel and every other channels. The significant leading roles are in bold. We can observe the larger delay patterns in Figs. 6(b), 6(d), 6(e), 6(g) and 6(h), especially in Fig. 6(e) where $q^\tau(n) > 50$. Based on the analysis of event delay patterns of the whole network, as shown in Fig. 7, we can particularly identify the intra-group drive-response links, such as the $F08 \rightarrow M09 \rightarrow C09$ in group I, $D04 \rightarrow D03$ in group II, $J07 \rightarrow G05$ and $J07 \rightarrow H10$ in group III, and $K01 \rightarrow K02$ in group IV, which may be difficult to detect in clinic but facilitates to determine the leading role node in each group. However, the inter-group

drive-response relationships or leading roles conforming to the clinical observation has not clearly captured. In fact, inter-group interactions is progressed in a scattered and staggered manner. For example, G05 (see Fig. 5(a)) or J07 (Fig. 6(g)) have the significant leading roles (event delay) for about 5 or 6 other channels in other groups, respectively. They thus may be the potential common hidden driving source. However, observations in detail on the timing reaching to the threshold $q^\tau(n) = 10$ show that there exit evident relative biases in the five event delay patterns. As shown in Figs. 7(b) and 7(c), this may suggest the presence of different spatiotemporal propagating delays from G05 or J07 to these five channels, respectively. In contrast, the other channels only display the sporadic leading roles. We should remark that Figs. 7(b) and 7(c) clearly shows the presence of a time delay of one signal with respect to the other, but does not necessarily prove a spatial and temporal disparities of signal propagations, although it might suggest it. These results may assist us to design the effective network control strategy.

3.3 Directed network reconstruction and the analysis of controllability and observability of seizures

3.3.1 Seizure focus of directed network

In this section, we aim to reconstruct the directed seizure network based on the above analysis of the time-resolved event delay patterns. Then, based on this constructed directed network we try to seek the potential seizure focus nodes using the in-degree and out-degree distributions of networks. The channels with the maximum out-degree are regarded as the theoretical epileptogenic focus. Figs. 8(b) and 8(c) give the reconstructed directed network before (Fig. 8(b)) and after (Fig. 8(c)) seizures. Clinical stereo-EEG report shows that in the inter-ictal period and ictal period F08/D03 and D03 are the possible epileptogenic focuses, corresponding to the node 1 and node 4. However, our results, shown in left panels of Figs. 8(b) and 8(c), suggest that node 8, i.e., J07, with largest out-degree and no in-degree before seizures, may be the primary focus. Detailed observation shows that before seizure node 8 has the leading role for node 1 and ignites it. After seizure, the leading role of node 8 to node 1 turns to node 6 (i.e., G05) and the leading roles of node 6 to others (i.e., nodes 2, 3, 4, 5, 9 and 10) are doubled than that before seizure. In sum, nodes 6 and 8 traverse almost all of the network nodes. Therefore, they potentially play the vital role to the epileptic network seizures. Due to the complexity of epileptic network, these results may broaden

Fig. 6 (Color online) Time-resolved delay asymmetries between a channel and the other remaining 9 channels. The horizontal dashed lines $q^\tau(n)=0$ and $q^\tau(n)=10$ (threshold) correspond to no and dominant delay asymmetries. The vertical dashed line denotes the seizure onsets. $M=10$, $h=30$ in Eq.(1).

the understanding of seizure origins from the network view.

Our another desire is to identify the key nodes in directed network by utilizing the theory of complex network that can effectively control the network seizures and can also sense the full internal state of complex system. That is, we will explore the controllability and observability of directed network, respectively.

3.3.2 Controllability

Note that, due to the similarity of exploration for the network before and after seizures, we only focus on the post-seizure case. The post-seizure intra-network connectivity can be denoted by the following adjacent ma-

trix,

$$A = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ a_{21} & 0 & 0 & 0 & a_{25} & a_{26} & 0 & 0 & 0 & 0 \\ 0 & a_{32} & 0 & 0 & 0 & a_{36} & 0 & a_{38} & 0 & 0 \\ 0 & 0 & 0 & 0 & a_{45} & a_{46} & 0 & 0 & 0 & 0 \\ a_{51} & 0 & 0 & 0 & 0 & a_{56} & 0 & a_{58} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{68} & 0 & 0 \\ a_{71} & 0 & 0 & 0 & 0 & 0 & 0 & a_{78} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & a_{96} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_{10,4} & a_{10,5} & a_{10,6} & 0 & a_{10,8} & a_{10,9} & 0 \end{pmatrix} \quad (21)$$

where a_{ij} , $i, j = 1, 2, \dots, 10$, calculated by Eq. (14), indicates the leading role of channel j relative to i .

As shown in the schematic diagram of Fig. 8(a), we wish to know whether it would be possible to apply a certain number of control signals to typical nodes which can drive the network system toward some desirable state, i.e., the network controllability. Of course, the whole network would be controlled with high likelihood if each node receives one control signal. But this will cost high. Thus, in the premise of bringing system under control, the minimum number of nodes, N_d , prerequisite for controlling seizures are thus a natural aim of interest.

Fig. 7 (Color online) (a) Clinical observed evolution process of epileptic discharges from Group I (F08, M09, C09) to Group II (D03, D04), Group III (G05, H10, J07) and to Group IV (K01, K02). (b) Polar coordinate is used to reflect the pathological information flow evolutions over time (i.e., time disparity, TD) and space (spatial disparity, SD) originated from G05 (b) and J07 (c), inferred by Fig. 5(a) and 6(g), respectively.

Liu et al. [24] proposed the maximum-matching set of network nodes (i.e., the nodes with incoming links but not sharing the starting or ending links) which can be used to assess structural controllability of the built network. In other word, we can also identify the minimum number of unmatched nodes (viewed as driver nodes), N_d , (the number of maximum-matching set is $N_M = N - N_d$) using the structural controllability theorem and the minimum inputs theorem. That is, N_d nodes are required to be controlled for the system to satisfy the full-rank condition (17).

In our constructed network, according to the minimum inputs theorem, N_d can be calculated as $N_d = 4$. And as an example the nodes 1, 4, 6 and 8 are identified as a driving nodal (unmatched nodal) set. Thus, in Eq. (17) $M = N_d = 4$ and the input matrix B is given as follow:

$$B^T = \begin{pmatrix} u_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & u_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & u_6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & u_8 & 0 & 0 & 0 \end{pmatrix} \quad (22)$$

It is easy to be calculated that $\text{rank}(J_1) = N = 10$ is full rank and the network is structurally controllable. Note that, the driving nodes are not unique, but their minimum number is. This suggests that the controllability of epileptic network depends not only on the clinical or computational seizure focus but also on the method of network analysis. In particular, the control channels may be not unique. In fact, following the above structural controllability theorem, the unmatched nodal sets $\{1, 5, 7, 8\}$, $\{1, 2, 6, 8\}$, $\{1, 2, 7, 8\}$ can also satisfy the full-rank condition of controllability. Similar to [25], corresponding to matching nodes, we can determine the maximum-matching links (i.e., the green arrows in Figs. 8(b) and 8(c) that do not share the starting or ending nodes. The number of maximum-matching links

Fig. 8 (a) The seizure dynamics can be approximated as a directed network consisting of 10 variables $x_1, x_2, \dots, x_{10}$ (n-nodes) corresponding to 10 channels (left in Figs. (b)(c)). (b)(c) corresponding to 10 channels (left in Figs. (b)(c)). The network states before (b) and after (c) seizures can be controlled (rightward arrow, controllability) to reach to some desired final state from initial state by inputs stimulation perturbations, $u = (u_1(t), u_2(t), u_3(t), u_4(t))$, applied on unmatched nodes (e.g., nodes 1, 4, 6 and 8). In turn, the initial state can also be inferred from the current state (leftward arrow, observability, see also Fig. 9). The networks in the left of (b) and (c) also show the heterogeneous degree distribution. The node size denotes the out-degree of the network. The yellow nodes have only the in-degree. The width of the arrows represent the significance of leading role ($q^+(n) > 10$). The right of (b) and (c) show all the four matching paths (green arrows) orderly connected by pink arrows. Other links are marked by light gray.

is equal to the number of maximum-matching nodes, i.e., N_M . We can next give the matching paths that is the subset of the maximum-matching links. As shown in the right panels of Figs. 8(b) and 8(c), before and after seizures the network can be divided into four independent matching paths, respectively. Each matching path is either (i) an "isolated" node (node 8) or (ii) starts from an unmatched node and ending at a matched node without outgoing link belonging to the maximum-matching set. Before seizure, these matching paths shown in Fig. 8(b) are $1 \rightarrow 7$, 8 , $6 \rightarrow 5 \rightarrow 2 \rightarrow 3$,

Fig. 9 (Color online) Graphical approach of structural observability of epileptic network before (a) and after (b) seizure, corresponding to Fig. 8 but having the opposite directions. The inferred balance equations of seizure network is shown in Eq.(23). Inference diagram is constructed by drawing a directed link ($x_i \rightarrow x_j$) if x_j appears in the right-hand side of x_i 's balance equation. The red nodes having no incoming links is termed as root sensor nodes (observation group) whose measurements allow us to reconstruct the state of all other variables or to ensure observability of the whole system.

Fig. 10 Time series for the simulated ten channels corresponding to Fig. 4(a). Simulated EEG (a) without stimulation perturbation; (b) with stimulation perturbations applied on channels F08, D03, G05, J07; (c) with stimulation perturbations applied on channels C09, K01; (d) by resecting channels F08, D03, G05, J07. The integration step size of $4ms$ (sampling frequency: 256 Hz) is used. A in Eq. (20) is equal to $\text{linspace}(4.35mV, 4.75mV)$ for first two channels and $3mV$ for other channels.

$4 \rightarrow 10 \rightarrow 9$, respectively. After seizure, these matching paths shown in Fig. 8(c) are $1 \rightarrow 5 \rightarrow 2 \rightarrow 3$, $4 \rightarrow 10$, $6 \rightarrow 9$, $8 \rightarrow 7$, respectively.

Another issue of significant practical interest in network control is to reduce the N_d so that the network can be harnessed by less control signals. In particular, when $N_d=1$, only one node is unmatched and the network can be optimally controlled by mere one input control signal, i.e., which can make the network meet the full-rank condition [24,25]. However, the matching

paths determined above are abjunct. A way to reduce N_d is to make unmatched nodes to be matched. This can be implemented by enhancing beforehand the controllability of the network via adding links between two independent matching paths because the topological changes can alter the network controllability according to [24]. In addition, to make the network fully controllable under only one external controller, i.e., $N_d=1$, we need to identify a minimum number $N - N_M - 1$ of additional links. In particular, we first randomly order the found four matching paths and then link the ending nodes of each matching path next to it in order, as illustrated in right panels of Figs. 8(b) and 8(c). Then, the network can be fully and structurally controlled with a single controller applied on the starting node of the first matching path (here, the driver can be the node 1), i.e., satisfying the full-rank condition with a single input (see Supplemental Material [25]). Note that, the obtained network in our paper doesn't include close matching paths where any one node can be viewed as the driver. These results may be instructive to the epileptic network reconstruction and modification.

3.3.3 Observability

A complex system can be quantitatively described and observable by estimating and reconstructing the system's internal state, respectively. However, this description is constrained by our estimating ability from experimentally accessible outputs. This is mainly because in practice experimental access is limited to only a subset of variables, or sensors, even though the simultaneous measurement of all internal variables can offer a complete description of a system's state.

Here, based on the reconstructed network in Fig. 8, we try to search for the potential sensor nodes that are necessary to estimate the full internal state of the epileptic network system. Because the epileptic network can capture the pathological information flow in inferring the state of individual variables, we give the inference diagram in Fig. 9. Note that, the inferred directed diagram for observability analysis has the reverse direction (Fig. 9) in contrast to the network for controllability analysis (Fig. 8). We suppose the system is estimated

by the following equations:

$$\begin{cases} \dot{x}_1 = f_1(x_8; \circ) \\ \dot{x}_2 = f_2(x_4, x_5, x_6, x_8; x_1, x_5, x_6) \\ \dot{x}_3 = f_3(x_2, x_8; x_2, x_6, x_8) \\ \dot{x}_4 = f_4(x_5; x_5, x_6) \\ \dot{x}_5 = f_5(x_1, x_6; x_1, x_6, x_8) \\ \dot{x}_6 = f_6(\circ; x_8) \\ \dot{x}_7 = f_7(x_1; x_1, x_8) \\ \dot{x}_8 = f_8(\circ) \\ \dot{x}_9 = f_9(x_1, x_8, x_{10}; x_6) \\ \dot{x}_{10} = f_{10}(x_4, x_5, x_6, x_8; x_4, x_5, x_6, x_8, x_9) \end{cases} \quad (23)$$

where the variables before the semicolon in each equation correspond to the pre-ictal case while the variables after the semicolon correspond to the post-ictal case. The inferred directed link $x_i \rightarrow x_j$ in the inference diagram is determined if x_j appears in x_i 's differential equation. This means one can get the information on x_j by observe x_i . ($\circ$) in x_8 's differential equation means no information on any other variables can be captured by monitoring x_8 . Same to the ($\circ$) in other differential equations.

In the Fig. 9(a), all the nodes except for node 6 are sensors while in the Fig. 9(b) all the nodes except for nodes 1 and 8 are sensors. However, it is particularly interesting to identify the minimum set of sensors from whose observability one can infer the states of any other nodes. In particular, we define the sensor nodes having no incoming edges as the root sensor nodes shown in red and viewed as an observation group. Through these root sensor nodes we can directly and indirectly (e.g., nodes 4 and 6 in Fig. 9(a)) capture the information flows of the whole epileptic network. That is, we can monitor a subset of state variables, $y(t) = (x_3, x_7, x_9/x_{10})^T$, to estimate the whole network state variables, i.e., satisfying the full-rank condition of (18) where

$$C_b = \begin{pmatrix} 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \quad (24)$$

before seizure and after seizure

$$C_a = \begin{pmatrix} 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \quad (25)$$

In addition, it is found that even though these root sensor nodes are not identical before and after seizures, they belong to the same group I, III and IV, respectively, as shown in Fig. 7. But the information on nodes 4 and 5 in group II can be captured by monitoring the nodes in other groups. Here, node 4 is the clinically identified focus. These results suggest that in terms of the epileptic network observability the root sensor nodes may be not always the clinically localized focus node.

3.4 Reproduction of the clinical results using a spatially extended neural network model with the stimulation modulation of cNDNS

Computational model is a promising method to investigate the epileptic brain network dynamics [42, 43]. Finally, we try to reproduce the clinical results using the single-compartment neural field model of Eq. (19). To computationally reconstruct the clinical epileptic network, we need to extend the above model to model network (Eq. (20)) by coupling different populations, denoting the various cortical columns or brain structures. During the simulation, the $a_{ij}(t)$ depending on time in Eq. (14) obtained by the EEG analysis is used to describe the coupling connectivity of network with time going. Presently, we take $n = 10$ to reconstruct the epileptic network model representing the 10 spatial locations corresponding to the clinical 10 contacts' EEG recordings. That is, during the 10-compartment epileptic network, population i ($\in \{1, \dots, 10\}$) receive the outputs of EPSP transfer function h_d of the other 9 populations, i.e., $\sum_{j \in \{1, \dots, 10\}; j \neq i} K^{ij} x_4^j$.

The simulated results can be found in Fig. 10. Compared Fig. 10(a) with Fig. 4, we can see the qualitative agreement between original EEG signals and the simulations. Due to the advantage of painless and unharmed neuromodulation of cNDNS, i.e., normally distributed noise stimulation with cathodic phase pulses (here supposing the brain has the noise with anodic phase pulses), we then test the effect of cNDNS on the seizure abatement. In particular, we consider the effect of cNDNS applied on the typically selected contacts, e.g., the nodes 1, 4, 6 and 8 (i.e., F08, D03, G05 and J07), respectively, which are the driving nodes identified from the controllability analysis at last section. As shown in Fig. 10(b), the epileptic discharges are almost completely abated. Whereas, cNDNS is feeble in abating seizures when applied on the non-driving nodes, e.g., nodes 3 and 9, i.e., C09 and K01, as shown in Fig. 10(c). In addition, we also get rid of the nodes F08, D03, G05 and J07 from the network reconstruction to simulate the clinical resection of seizure focus, which shows the similar seizures abatement effect with cNDNS. This evidences the effectiveness of graph theory in identifying control nodes of seizures. These computational results also verify the dynamical network characteristics of epileptic seizures.

4 Conclusion and Discussion

In conclusion, the results obtained above evidence the effectiveness of graph theory in identifying control nodes of seizures and also verify the dynamical network

characteristics of epileptic seizures. In particular, we computationally found that the clinically localized seizure focus maybe not the real focus, or at least not the clinical surgical positions of abating seizures. That means to fully control the epileptic network may not just be related to the focus zone, it may also involves other non-focus nodes. This suggests that the clinically localized focus may be driven by a hidden source, which facilitates the search for the potential recessive, dominant or extended foci. These results largely enrich the clinical results and provide new insights into the seizure resection and electronic stimulation therapies.

This paper describes an application of a graph theory and system identification for finding an epileptogenic nodes of epileptic seizure substrate to inform the epilepsy surgery or targeting the electric stimulation of the brain to suppress epilepsy seizures. The graph theory and controllability of complex system using graph models is a great vehicle and shown to be an effective tool in exploring of biologic complex systems as well as in controlling of such. Even in epilepsy, there has been multiple approaches using a graph theory to better describe epileptogenesis and target the therapies (either surgery or electrical brain stimulation). Based on latest research in epilepsy and graph theory applications, our results may provide a good way to go and explore to inform clinical decisions.

However, the focal cortical epilepsy is of very heterogeneous nature and in clinical practice sampling of the brain is usually very under sampled spatially and differ greatly patient by patient. Thus, it will be very important to test the method by application on multiple dataset consisting of several patients intracranial EEG data and present the results of the testing to prove the usefulness of the method in this field and its clinical applicability.

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Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving EEG data from patient who had been admitted to the hospital with refractory focal epilepsy at Sanbo Brain Hospital of Capital Medical University in Beijing. This study protocol was approved by the ethics committee of Sanbo Brain Hospital of Capital Medical University and the subject was written informed consent.

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Figures

Figure 1

(Color online) Structure of two coupled population- s model (i and j, upper panel) and the elementary model of single population i (lower panel). K_{ij} is the unidirectional coupling functions. cNDNS represents the normally distributed noise stimulation with cathodic phase pulses. Other signs and interpretations can be seen in Section 2.4.

Figure 2

(a) Simulated background state signals using model (19) when $A=3.25\text{mV}$ with (upper panel) and without (lower panel) the coupling function ($K_{12}=200$) from the subsystem (middle panel) with $A=4.85\text{mV}$. (b) The dominant frequency of system (19) with A increasing. (c,d) The variants of delay pattern, q^T (b), and event synchronization, Q^T (c), with the coupling strength increasing from 0 to 300. The green lines

correspond to the 50 averages $\pm \sigma$ of the surrogate obtained by disordering the subsystem 2's signals. In Eq.(1), $M=10$, $h=(\max(\text{signal})-\min(\text{signal}))/4$. Simulation duration is 20s; $dt=0.005s$.

Figure 3

(Color online) (a) The upper two panels correspond to the original EEG data from channels D03 and D04. The lower panel corresponds to the surrogate obtained by shifting channel D03 signal 2000 data points ($\sim 7.8s$). (b,d) Time resolved event synchronization (b) and delay asymmetry (d). (c,e) The instantaneous

time-resolved event synchronization (c) and delay asymmetries (e). The cyan lines correspond to the surrogate. The vertical red dashed lines indicate the seizure onsets. (sampling rate is 256Hz). $M=10$, $h=30$ in $E-q.(1)$.

Figure 4

Original EEG data recorded from 10 channels, i.e., F08, M09, C09, D03, D04, G05, H10, J07, K01, K02. The red bar indicates the seizure onset.

Figure 5

(Color online) Time-resolved event synchronization (c,d) and delay asymmetries (a,b) between an contact G05 and the remaining channels. $M=10$, $h=30$ in Eq.(1). The horizontal dashed lines in (a) indicate the zero event delay $qT(n) = 0$ and significant event delay threshold $qT(n) = 10$. Vertical dashed line (a) and red bars in (b), (c) and (d) indicate the seizure onset. The meanings for the color of lines in (b), (c), (d) is same to (a). The black lines in (c,d) indicate the situations of whole network.

Figure 6

(Color online) Time-resolved delay asymmetries between a channel and the other remaining 9 channels. The horizontal dashed lines $q_T(n)=0$ and $q_T(n)=10$ (threshold) correspond to no and dominant delay asymmetries. The vertical dashed line denotes the seizure onsets. $M=10$, $h=30$ in Eq.(1).

Figure 7

(Color online) (a) Clinical observed evolution process of epileptic discharges from Group I (F08,M09,C09) to Group II (D03,D04), Group III (G05,H10,J07) and to Group IV (K01,K02). (b) Polar coordinate is used to reflect the pathological information flow evolutions over time (i.e., time disparity, TD) and space (spatial disparity, SD) originated from G05 (b) and J07 (c), inferred by Fig. 5(a) and 6(g), respectively.

Figure 8

(a) The seizure dynamics can be approximated as a directed network consisting of 10 variables $x_1; x_2; \dots; x_{10}$ (n-odes) corresponding to 10 channels (left in Figs. (b)(c), 1-F08, 2-M09, 3-C09, 4-D03, 5-D04, 6-G05, 7-H10, 8-J07, 9-K01, 10- K02). The network states before (b) and after (c) seizures can be controlled (rightward arrow, controllability) to reach to some desired nal state from initial state by inputs stimulation perturbations, $u = (u_1(t); u_2(t); u_3(t); u_4(t))$, applied on unmatched nodes (e.g., nodes 1, 4, 6 and 8). In

turn, the initial state can also be inferred from the current state (leftward arrow, observability, see also Fig. 9). The networks in the left of (b) and (c) also show the heterogeneous degree distribution. The node size denotes the out-degree of the network. The yellow nodes have only the in-degree. The width of the arrows represent the significance of leading role ($qT(n) > 10$). The right of (b) and (c) show all the four matching paths (green arrows) orderly connected by pink arrows. Other links are marked by light gray.

Figure 9

(Color online) Graphical approach of structural observability of epileptic network before (a) and after (b) seizure, corresponding to Fig. 8 but having the opposite di- rections. The inferred balance equations of seizure network is shown in Eq.(23). Inference diagram is constructed by draw- ing a directed link ($x_i \rightarrow x_j$) if x_j appears in the right-hand side of x_i 's balance equation. The red nodes having no incoming links is termed as root sensor nodes (observation group) whose measurements allow us to reconstruct the state of all other variables or to ensure observability of the whole system.

Figure 10

Time series for the simulated ten channels corresponding to Fig. 4(a). Simulated EEG (a) without stimulation perturbation; (b) with stimulation perturbations applied on channels F08, D03, G05, J07; (c) with stimulation perturbations applied on channels C09, K01; (d) by resecting channels F08, D03, G05, J07. The integration step size of 4ms (sampling frequency: 256 Hz) is used. A in Eq. (20) is equal to $\text{linspace}(4.35\text{mV}, 4.75\text{mV})$ for rst two channels and 3mV for other channels.