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The model-based study of stimulation parameter effects in controlling epileptic seizures

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Abstract: *In this paper, based on the coupled 2-compartment thalamocortical network model, we applied pulse stimulation in PY and IN of the first compartment to investigate how the brain stimulation parameters, including the period, duration of positive input and amplitude, suppress epileptic seizure under certain conditions. The results indicate that epileptic seizures can be effectively controlled when stimulation parameters are set in a proper range. In particular, the increasing amplitude of stimulus can make the epileptic seizures easily terminate at shorter period and lower duration of positive input. To sum up, we highlight the effect of two coupling strengths between two coupled compartments and the stimulating efficacy of various stimulation parameters on controlling epileptic seizures.*

Keywords: *Epileptic seizures; State transition; Pulse stimulation; Coupled thalamocortical network; Bifurcation*

1. Introduction

As we know, the clinical treatment of epileptic seizure is more and more popular to employ the method of brain stimulation, but the specific value of stimulation parameters are still uncertain. Brain stimulation is more popular in recent years since it has successful to suppress epilepsy seizures [1], [2], [3],[4],[5]. Previous studies [6],[7],[8],[9],[10], [11] have explored the impact of direct neuronal stimulation in thalamocortical system with pathological oscillations. For example, Suffczynski et al. (2004)[6] showed that ictal state can be abate by single-pulse perturbations in a bistable model. Taylor et al. (2014)[7] predicted that single pulse stimulation could terminate SWD seizures. Taylor et al. (2015)[8] demonstrated that pseudospectral method with time-varying stimuli offered an effective approach to simulate seizure abatement which has modeled as an optimal control problem. Fan et al. (2017a)[9] showed that single-pulse stimulation which acted on thalamic reticular nucleus could induce the onset and self-terminate of SWDs on the cortical subsystem of single-compartment thalamocortical neural field model.

In addition, most studies [12],[13],[14],[15] have demonstrated that the proper range of stimulation parameters including frequency, amplitude and positive input duration are critical to initiate and abate epileptic seizure. In particular, the stimulation frequency is a key factor to control epileptic seizure [16]. For instance, Hu (2015, 2017)[12],[13] and Wang (2017a, b)[17],[14] explored how the deep brain stimulation parameters suppress the absence seizure in the mean-filed model. Haghighi (2017) [15]suggested that the transition between ictal and interictal states is triggered by changing stimulation parameters. Most previous works of the antiepileptic effect of stimulation parameters mainly focus on mean-filed models of the thalamocortical loop, however, the eliminating efficacy of stimulation parameters on controlling epileptic seizure based on the thalamocortical neural field model is still elusive.

In brief, underlying the 2-compartment unidirectionally coupled thalamocortical network model, we directly apply brain stimulation in PY_1 and IN_1 of the first compartment to explore how stimulation parameters including the frequency, amplitude and the positive input duration control epileptic seizures.

2. Method and Model

The model utilizing in this paper is the coupled 2-compartment unidirectionally thalamocortical network model, which mainly consists of two single-compartment thalamocortical neural field models. Neural field models play an important role in analyzing the dynamic mechanism of the spatial structure of macroscopic neuronal populations. For example, the dynamical mechanism of 2-4 Hz SWDs which represent absence seizures in clinic can be explored by thalamocortical neural field model[18],[7],[8],[9],[19]. The connective schematic of network in this paper is described in Fig. 1, and it contains four neuronal

ISSN 2616-5805 Vol. 6, Issue 1: 51-57, DOI: 10.25236/AJMS.2025.060106

populations: cortical excitatory pyramidal (PY) population, cortical inhibitory interneural (IN) population, specific relay nucleus (SRN) in thalamus and thalamus reticular nucleus (TRN). Meanwhile, it also includes the corresponding connective strength between different populations. All the connectivities of 2-coupled thalamo-cortical network fellows the works by Fan et al.[9],[20].

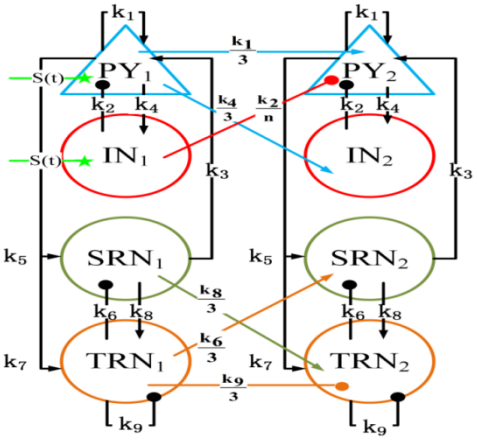

Fig. 1 Schematic diagram of the coupled 2-compartment thalamocortical network model. The lines with arrows represent excitatory connections, and the lines with closed cycles represent inhibitory connections. The green stars indicate stimulation targets.

The deterministic coupled 2-compartment thalamocortical network model is described as fellow:

$$\frac{dPY_1}{dt} = (\varepsilon_{py} - PY_1 + k_1F[PY_1] - k_2F[IN_1] + k_3F[SRN_1])\tau_1 + S(t),$$
$$\frac{dIN_1}{dt} = (\varepsilon_{in} - IN_1 + k_4F[PY_1])\tau_2 + S(t),$$
$$\frac{dSRN_1}{dt} = (\varepsilon_{srn} - SRN_1 + k_5F[PY_1] - k_6G[TRN_1])\tau_3,$$
$$\frac{dTRN_1}{dt} = (\varepsilon_{trn} - TRN_1 + k_7F[PY_1] + k_8G[SRN_1] - k_9G[TRN_1])\tau_4,$$
$$\frac{dPY_2}{dt} = (\varepsilon_{py} - PY_2 + k_1F[PY_2] - k_2F[IN_2] + k_3F[SRN_2])\tau_1 + \frac{k_1}{3}F[PY_1] - \frac{k_2}{3}F[IN_1],$$
$$\frac{dIN_2}{dt} = (\varepsilon_{in} - IN_2 + k_4F[PY_2])\tau_2 + \frac{k_4}{3}F[PY_1],$$
$$\frac{dSRN_2}{dt} = (\varepsilon_{srn} - SRN_2 + k_5F[PY_2] - k_6G[TRN_2])\tau_3 + \frac{k_6}{3}G[TRN_1],$$
$$\frac{dTRN_2}{dt} = (\varepsilon_{trn} - TRN_2 + k_7F[PY_2] + k_8G[SRN_2] - k_9G[TRN_2])\tau_4 + \frac{k_8}{3}G[SRN_1] - \frac{k_9}{3}G[TRN_1],$$

where $\varepsilon_{py,in,srn,trn}$ are input parameters, parameters $\tau_{1,\ldots,4}$ signify time scale and $k_{1,\ldots,9}$ represent connectivity strengths which interconnect various populations, and their corresponding linking rules are in agreement with experimentally known. $F(x)=1/(1+v^{-x})$ is the sigmoid transition function with x=PY$_i$, IN$_i$, SRN$_i$, TRN$_i$, where the subscript $i\in\{1,2\}$, and the parameter v determines the sigmoid steepness. $G(x)=\alpha x+\beta$ is the linear activation function which is used to describe the thalamic subsystem.

$S(t)$ in this model represents the brain stimulus applied in the cortex, which is a period step function with the following expression (Wang et al. 2017):

$$S(t) = A \times (H(sin(\frac{2\pi t}{P}))) \times (1 - H(sin(\frac{2\pi(t+D)}{P})))$$

where A means the amplitude, P means the period and D means the duration of positive input which signifies duty circle of positive pulse. H is the Heaviside bi-value step function, such that $H(x)=0$ if $x<0$ and $H(x)=1$ if $x>0$. Fig. 2 shows an example of a square stimulation voltage.

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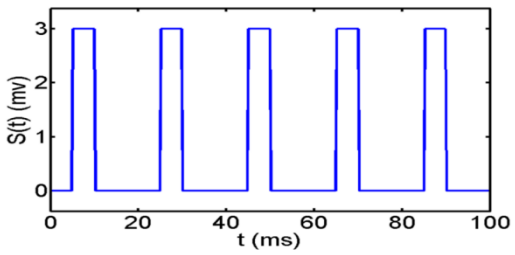

Fig. 2 An illustrative example of square stimulus voltage pulses that according to the proposed model. We choose the parameters of pulse with A=3 mv, P=20 ms and D=5 ms, respectively.

Most model parameter values are obtained from the previous literatures[18],[7],[9],[20], and their specific values are list in Table.1. The values of brain stimulation parameters are estimated in a physiologically reasonable range to explore the effect on controlling epileptic seizures. The solution of differential equations is utilized four-order Runge-Kutta method, and its temporal step is fixed at 1 ms. The MATLAB (Mathworks, USA) is used to perform the simulation environment. The fast Fourier transform (FFT) for the time series of PY_2 is applied to evaluate the dominant frequency of firing series.

Table. 1 Main parameters in our model.

Parameter	Interpretation	Value
k_1	PY→PY connectivity strength	1.8
k_2	IN→PY connectivity strength	1.5
k_3	SRN→PY connectivity strength	1
k_4	PY→IN connectivity strength	4
k_5	PY→SRN connectivity strength	3
k_6	TRN→SRN connectivity strength	0.6
k_7	PY→TRN connectivity strength	3
k_8	SRN→TRN connectivity strength	10.5
k_9	TRN→TRN connectivity strength	0.2
τ_1	PY timescale	26
τ_2	IN timescale	32.6
τ_3	SRN timescale	2.6
τ_4	TRN timescale	2.6
ε_{py}	Input PY	-0.35
ε_{in}	Input IN	-3.4
ε_{srn}	Input SRN	-2
ε_{trn}	Input TRN	-5
v	Sigmoid steepness	250000
α	Linear intersection steepness	2.8
β	Linear intersection offset	0.5

3. Eliminating epileptic seizures through brain stimulation in the excitatory pyramidal neuronal population and the inhibitory interneuronal population in first compartment

In this section, we investigate the beneficial stimulation effect of stimulation parameters on inhibiting the epileptic seizures which choose cortical excitatory pyramidal population and inhibitory interneural population in the first compartment as stimulation targets. In particular, we devote to find the proper range of stimulation parameters on controlling the epileptic seizures.

The effect of the stimulation by single pulse in controlling the epileptic seizures has been considered in the thalamocortical neural field model, however, it is few to investigate the stimulating efficacy of pulse stimulation. Thus, in this part, we firstly verify that pulse stimulation can terminate epileptic seizures in the coupled thalamocortical model. Fig. 3 shows the results of the stimulus effect which applied stimulation in PY_1 and IN_1 on abatement of pathological rhythmic discharges with proper k_1, and stimulation parameters severally set at P=80 ms, D=7 ms and A=0.5 mv. For the case of k_1=1.3, 2 (like Fig. 3(a,b)), respectively, PY_2 initially shows low and high saturated firings when t <10 s , the pulse stimulation be added between 10 s $\leq t \leq$50 s can induce small perturbation in few time and quickly return to a new background state. Thus, in this condition, the results show that the sustained pulse stimulation with proper parameters can make PY_2 keep in resting state. In addition, it can be seen from Fig. 3(c) that

ISSN 2616-5805 Vol. 6, Issue 1: 51-57, DOI: 10.25236/AJMS.2025.060106

the manifestation of PY_2 is the 2-4 Hz SWD oscillation with k_1=1.87 (in accord with Fig. 3) in the first 10 seconds, and after stimulus added, its behavior transits into resting state. Similarly, Fig. 3(e,g) also indicate the case of k_1=1.85, 1.6 which respectively transits from the 7.5-12.5 Hz alpha wave oscillation and more than 13 Hz rapid spike oscillation to resting state after applying stimulation. In sum, Fig. 3(a,b,c,e,g) manifest that stimulating in PY_1 and IN_1 can terminate epileptic seizures including absence seizure and tonic seizure.

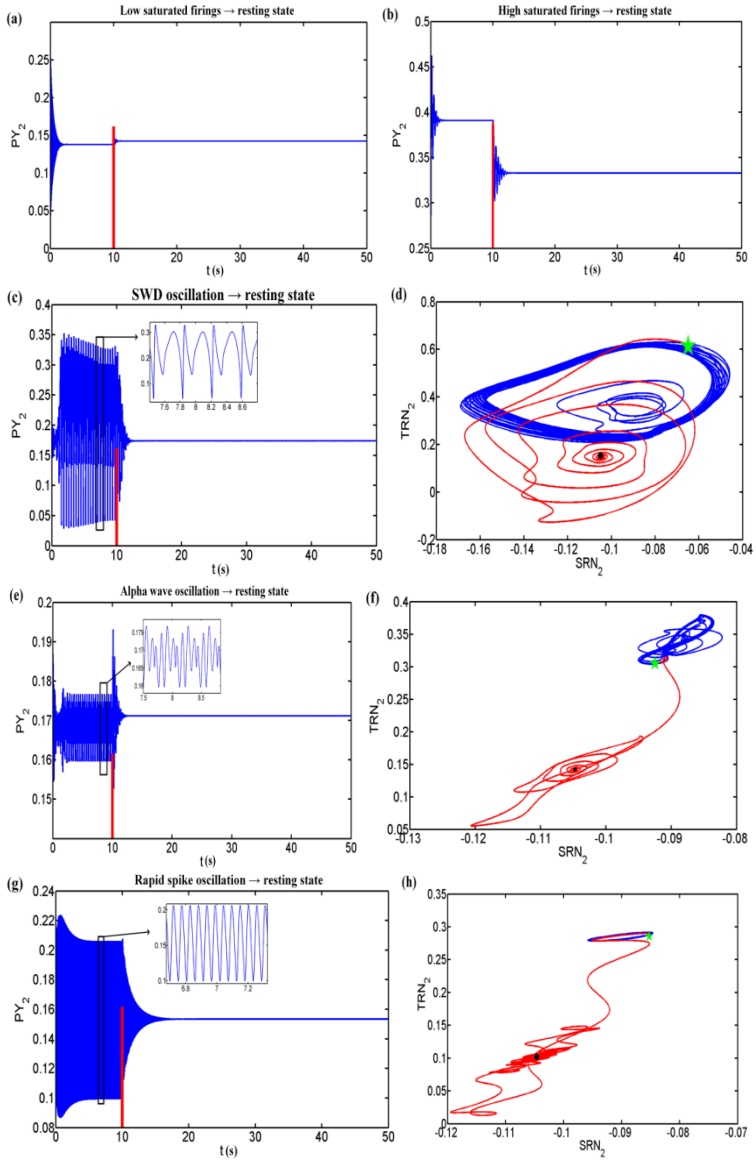

Fig. 3 Pulse stimulation which applies in the excitatory pyramidal neuronal population PY_1 and inhibitory interneural population IN_1 can terminate epileptic seizures, as sets stimulation parameters period P=80 ms, duration of positive input D=7 ms and amplitude A=0.5 mv. (a) The time series of PY_2 with k_1=1.3. (b) The time series of PY_2 with k_1=2. (c,e,g) The time series of PY_2, and (d,f,h) two-dimensional phase diagram of SRN_2 and TRN_2 with k_1=1.87,1.85,1.6, respectively. Red vertical bars mean the time point to add stimulus, and green stars represent the location to add stimulus. Red lines indicate phase trajectory with stimulation. Black dots describe focus.

In addition, to elucidate the mechanisms of epileptic seizure termination, the corresponding two-dimensional phase diagram has been shown in Fig. 3 (d,f,h). It can been clearly observed that the transition between abnormal rhythmic oscillation and resting state can be attributed to the bistable mechanism consisting of stable limit cycle and stable focus, in which blue limit cycles describe pathological oscillations and black dots represent background state.

Many studies showed that the choice of stimulation parameters is critical to obtain the stimulating efficacy on eliminating the epileptic seizure. Hence, we try to explore how stimulation parameters

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influence the control effect of epileptic seizures based on applying stimulation in PY_1 and IN_1.

Firstly, we consider the stimulating efficacy with varying a single stimulation parameter in proper range. In Fig.4, we respectively display the transition process of different states and corresponding dominant frequency of PY_2 with varying stimulation parameters when k_1 changes in [0, 2]. As shown in Fig.4(a) which fixed D=5 ms and A=0.5 mv, it can be clearly seen that when k_1 is in the range of [0.54, 1.86] the system has four rich dynamical behaviors including (I) saturated state, (II) SWD oscillation, (III) alpha wave oscillation and (IV) rapid spike oscillation with P increasing from 30 ms to 150 ms. As k_1 changes into [1.98, 2.5], the system mainly alternately displays saturated state and SWD oscillation with P changes from 30 ms to 150 ms. All of them demonstrate that smaller period of stimulation has a beneficial effect on controlling epileptic seizures when k_1 in the proper range. In Fig. 4(c) that fixed P=60 ms and A=0.5 mv, it exhibits that the state of PY_2 is alpha wave oscillation in the rarely smallest region of (D, k_1) panel. When D is bigger than 2.4 ms, the system appears saturated state as k_1 in the ranges of [0.54, 1.87] and [1.98, 2.5]. And when D is smaller than 2.4 ms and k_1 is also in the same ranges, the model shows four dynamical state as above mentioned. The results indicate that bigger positive duration of input is more efficient to abate epileptic seizures. Similarly, fixed P=60 ms and D=5 ms, Fig. 4(e) shows PY_2 transits into saturated state when $A \geq 0.25$ mv and $0.54 \leq k_1 \leq 1.88$ or $1.89 \leq k_1 \leq 2.5$. k_1 is in the ranges as same as the foregoing, the system transits between four states, as A changes from 0 mv to 0.24 mv. Interestingly, in Fig. 4, it is obviously observed that no matter which stimulation parameter has been considered, the system always shows SWD oscillation when k_1 is less than 0.53 or in the range of [1.87 1.97]. To sum up, the single stimulation parameters in proper range can have a better stimulating efficacy in the treatment of epileptic seizures.

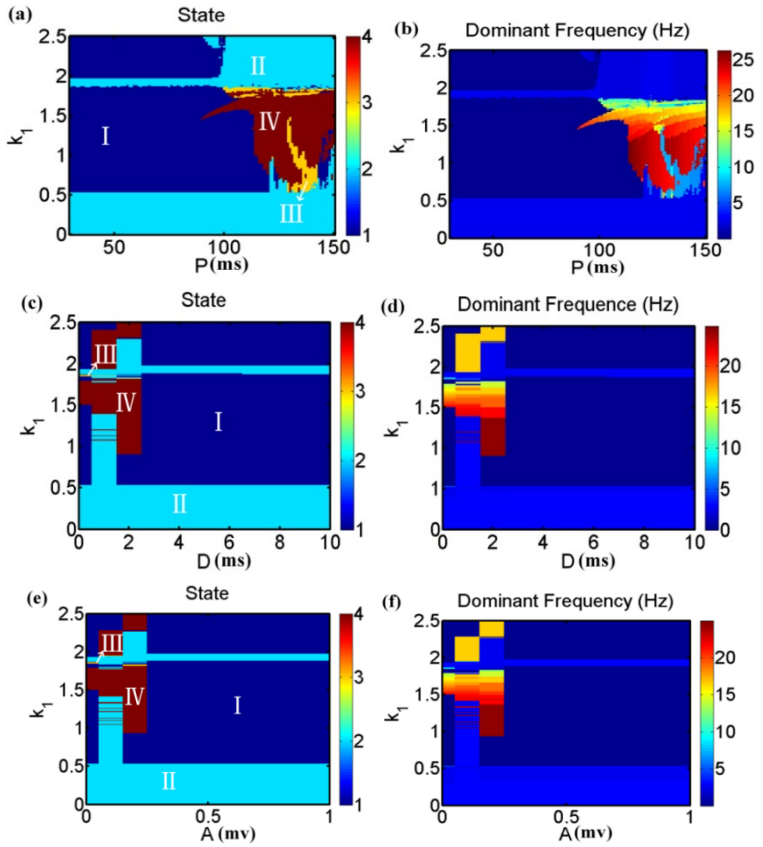

Fig. 4 Two-dimensional state analysis (a) and corresponding dominant frequency (b) in the (P, k_1) panel, as the period P changes from 30 ms to 150 ms with fixing the duration of positive input D=5 ms and the amplitude A=0.5 mv; The state analysis (c) and corresponding dominant frequency (d) in the (D, k_1) panel, as D changes from 0 ms to 10 ms with P=60 ms and A = 0.5 mv; The state analysis (e) and corresponding dominant frequency (f) in the (A, k_1) panel, as A changes from 0 mv to 1 mv with P=60 ms and D=5 ms. k_1 changes from 0 to 2 in all three conditions. In (a,c,e) numbers represent different dynamics states: the saturation state (I), the SWD oscillation state (II), the alpha wave state (III) and the rapid spike oscillation state (IV).

The stimulating efficacy of single stimulus parameters has been explored clearly in the front, but it is

ISSN 2616-5805 Vol. 6, Issue 1: 51-57, DOI: 10.25236/AJMS.2025.060106

too unitary to reveal how stimulation parameters influence the effect on controlling epileptic seizures. Thus, in this part we select the period P and duration of positive input D as bifurcation parameters to seek the beneficial ranges on inhibitory epileptiform oscillations. As shown in Fig. 5, we can survey that the system undergoes four states, (I) saturated state, (II) SWD oscillation, (III) alpha wave oscillation and (IV) rapid spike oscillation, in (P, D) panel. When A is fixed at 0.3 mv, the Fig. 5(a) demonstrates that the region in saturated state mainly in the upper left corner of figure, which likes a irregular terraced pattern with increasing P and D. For a relative weaker D, the parameter region in saturated state is a little rectangle no matter how to change P. And in the rest region of Fig.5(a), the manifestation of PY_2 mostly is rapid spike oscillation and fewly are SWD oscillation and alpha wave oscillation. It turned out that the brain stimulus is noneffective in controlling epileptic seizures when $P \geq 122$ ms.

In order to focus on the control effect of A, we fix A=0.5 mv, and portray the bifurcation diagram and corresponding dominant frequency (like Fig. 5(c,d)). Compared Fig. 55(a) to Fig. 5(c), we can explicitly know that the area of saturated state region becomes bigger in Fig. 5(c) than in Fig. 5(a). It demonstrates that in the same stimulation parameter ranges of P and D, increasing the amplitude A can make the termination of epileptic seizure easier.

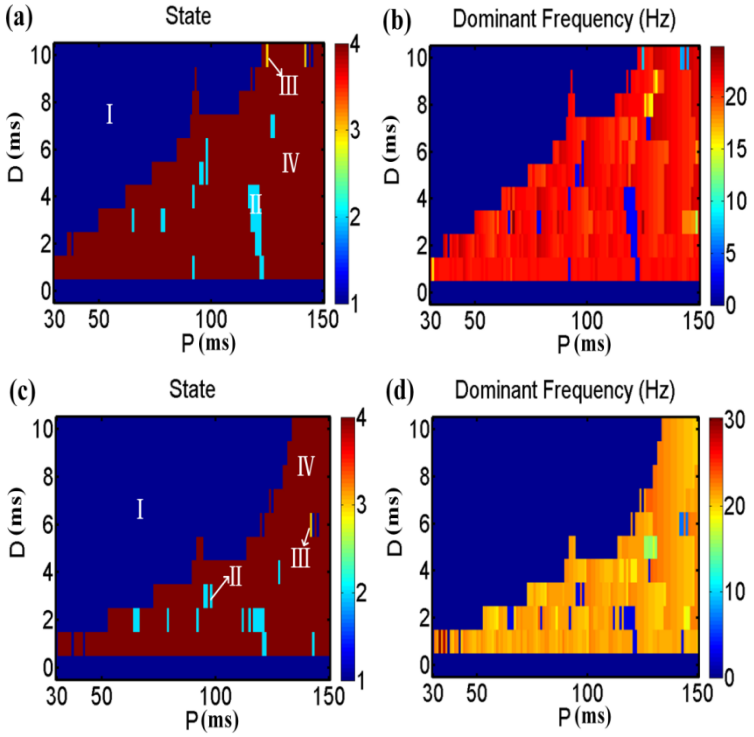

Fig. 5 Two-dimensional state analysis (a,c) and corresponding dominant frequency (b,d), as changes the period P from 30 ms to 150 ms and changes the duration of positive input D from 0ms to 10 ms. The amplitude A respectively fixes at A=0.3 mv and A=0.5 mv in (a,b) and (c,d), and the coupling strength k_1 fixed at k_1=1.5.

4. Conclusion

In this paper, utilizing the coupled 2-compartment thalamocortical model, we study the eliminating efficacy of stimulation parameters on controlling epileptic seizure with choosing the excitatory pyramidal neuronal population and inhibitory interneuronal population in first compartment as stimulus targets. The obtained results have demonstrated that the epileptic seizure, including absence and tonic seizure, can be effectively terminated by pulse stimulus with parameters in the proper range, and also have figured out the approximate stimulation parameter ranges which have beneficial control effect on epileptic seizure. In addition, compared the controlling effect of epileptic seizures with different stimulation parameters, it apparently discovers that the result of two-dimensional state analysis is similar in (D, k_1) and (A, k_1) panel, and different in (P, k_1) panel, so it manifests that the period of stimulation is the key factor on controlling epileptic seizures. Finally, it is interestingly founded that the stimulation can be easier to control pathological oscillation with increasing the amplitude, when the change of the period and duration of positive input remain in the same range. Although the coupled 2-compartment thalamocortical

ISSN 2616-5805 Vol. 6, Issue 1: 51-57, DOI: 10.25236/AJMS.2025.060106

network model is too simple to the human's brain, but it can help to well understand the effect on controlling epileptic seizure with stimulus in clinical treatment. We hope the obtained results can provide a theoretical guidance for the treatment of patients with epileptic seizures.

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