The critical role of spiny stellate cells in seizure onset based on dynamic analysis of a neural mass model

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Abstract

Increasing evidence has shown that excitatory neurons in the brain play a significant role in seizure generation. However, spiny stellate cells are cortical excitatory non-pyramidal neurons in the brain which their basic role in seizure occurrence is not well understood. In the present research, we study the critical role of spiny stellate cells or the excitatory interneurons (EI), for the first time, in epileptic seizure generation using an extended neural mass model introduced originally by Taylor and colleagues in 2014. Applying bifurcation analysis on this modified model, we investigated the rich dynamics corresponding to the epileptic seizure onset and transition between interictal and ictal states due to the EI. Our results indicate that the transition is described by a supercritical Hopf bifurcation which shapes the preictal activity in the model and suggests why before seizure onset, the amplitude and frequency of neural activities increase gradually. Moreover, we showed that 1) the altered function of GABAergic and glutamatergic receptors of EI can cause seizure, and 2) the pathway between the thalamic relay nucleus and EI facilitates the transition from interictal to the ictal activity by decreasing the preictal period. Thereafter, we considered both sensory and cortical periodic inputs to drive the model responses to various harmonic stimulations. Our results from the bifurcation analysis of the model suggest that the initial stage of the brain might be the main cause for the transition between interictal and ictal states as the stimulus frequency changes. The extended thalamocortical model shows also that the amplitude jump phenomenon and nonlinear resonance behavior result from the preictal stage of the brain. These results can be considered as a step forward to a deeper understanding of the mechanisms underlying the transition from brain normal activities to epileptic activities.

Keywords: Neural mass model, Bifurcation, Resonance, Excitatory interneurons, Preictal state

1. Introduction

Epilepsy is one of the most common disorders of the Central Nervous System (CNS) which causes sudden abnormal and synchronized brain activities, resulting in seizures. Interactions between excitatory and inhibitory neurons shape mainly brain activities and some transitory disparity in the inhibitory/excitatory balance can trigger epilepsy. One-third of people with epilepsy are likely to have pharmacoresistant epilepsy, and treatments such as surgery or stimulation-based treatments like deep brain stimulation (DBS) can be considered for these kinds of drug-resistant patients [1]. A seizure can be composed of four distinct states including: preictal, ictal, interictal and postictal. The preictal state appears before seizure begins and indicates that seizures do not simply start out of nothing. Experimental studies [2] and [3] in human and intracranial EEG signals have shown that preictal spikes are distinguishable from ictal and interictal signals, and can be used to predict the seizure occurrence. Understanding mechanism of generation of the preictal period opens the way for a more precise seizure prediction and thereby more reliable automatic interventions to prevent the seizure occurrence [4].

Studies have shown that interneurons are cell types which play a key role in the initiation and termination of epileptic seizures [5,6]. Interneurons in the cortex, not only control the activity of pyramidal neurons, but they also receive thalamic relay nucleus inputs. Therefore, they play a role in transferring and integrating the sensory information coming from the thalamus to the cortex [7]. Interneurons are traditionally regarded as inhibitory, and use the neurotransmitter gamma-aminobutyric acid (GABA) or glycine; but more precisely, there are two kinds of interneurons in the CNS: excitatory and inhibitory interneurons. Inhibitory interneurons use GABA as their neurotransmitters and excitatory interneurons are spiny stellate cells in the CNS which use glutamate as their neurotransmitters [8]. Genetic mutation study on mice has shown that in the spiny stellate cells (lamina IV) an alteration in the kinetic of N-methyl-D-aspartate receptors (NMDA) was sufficient enough to cause neuronal hyper excitability leading to epileptic activity in the brain [9]. An experimental study has also shown that synchronous discharges of excitatory interneurons could spread the epileptic activity in the brain, and EI could play an important role in the initiation and propagation of spike and wave discharges (SWD), in which the spike is due to the extracellularly synchronous and powerful depolarization of excitatory interneurons, and wave is due to the inhibitory interneurons. Therefore, spike and wave discharges can be generated as a result of the interactions between inhibitory and excitatory interneurons [10]. Nevertheless, from dynamical system point of view, it is not well understood how excitatory interneurons can cause seizure. This perspective deepens our knowledge about the role of excitatory interneurons along with other excitatory neurons in the cerebellar cortex in triggering the epileptic seizures.

On the other hand, computational modelling of epilepsy has provided dynamical insights into the mechanism underlying the transition from normal to epileptic activities. Different seizures can be categorized into focal and generalized seizures. Tonic, clonic, absence and tonic-clonic seizures are the generalized types of seizures and they occur when a widespread activity triggers in both hemispheres of the brain [11]. Recorded electroencephalogram (EEG) signals indicate that seizures can vary in their frequencies. A typical absence seizure can be considered as approximately synchronous SWD with a frequency of 2~4 Hz, but, atypical absence seizures show different frequency ranges (< 2 Hz and > 4 Hz) [12]. A tonic seizure is fast-spiking activity (> 14 Hz) with low amplitude, and clonic seizure is slow wave activity (approximately 3 Hz) with high amplitude. Generally, in tonic-clonic seizures, a clonic activity follows the tonic activity. Electrophysiological observations have shown the two-way transition between absence and tonic-clonic seizures [13] and dysfunction of the cortical and/or thalamic circuitries is believed to produce the absence, clonic and tonic epileptic activities, together with transitions between them. Fan et al. [14] used a modified computational field model of a cortical microzone and showed that the two-way transitions between absence and tonic-clonic epileptic seizures are induced by disinhibition between slow and fast inhibitory interneurons. Nevertheless, they ignored the role of thalamic circuitry and its interaction with the cerebral cortex in the proposed computational model; whereas, in [15, 16] it is shown that the mechanism of seizures can rely on a thalamocortical network. Experimental evidence suggests that interactions between thalamus and cerebral cortex influence the initiation and propagation of SWD [17]. For that reason, Taylor et al [18] developed a thalamocortical model investigating the generation of the SWD seizures, but then again, the model did not describe the generation of other important types of seizures and the preictal state.

Therefore, in the present study, we modified and extended a thalamocortical model, originally proposed by Taylor et al [18], to investigate the role of excitatory interneurons on seizure onset using dynamical analysis. For this purpose, we introduced an additional group of interneurons into the model which were excitatory and considered their interactions with pyramidal neurons, inhibitory interneurons and thalamic relay nucleus in brain. As will be shown, this model is not only capable of producing different types of epileptic seizures such as absence, clonic and tonic, but, it also generates other epileptic activities such as preictal period. This period is the appropriate time for predicting seizure occurrence.

The organization of the paper is as follows. in section 2, the modified epileptic dynamical model inspired by the model proposed in [18] is introduced. Then in section 3, using the modified model, the role of GABAergic and glutamatergic receptors of excitatory interneurons in seizure generation and transition between interictal and ictal states is dynamically analyzed. Through numerical simulations and bifurcation analysis, we show that dysfunction of excitatory and inhibitory receptors of excitatory interneurons and impairments in interactions between thalamic relay nucleus and excitatory pyramidal neurons give rise to interictal to preictal transition,

and that the same dysfunction also facilitates the occurrence of epileptic seizure. Finally, in section 4, we examine the frequency responses of our thalamocortical model subjected to various sensory and cortical periodic inputs to identify the effect of various stimulus on epileptic seizures. The obtained results show that brain starts its nonlinear resonator behavior when the shift from normal activity to preictal state takes place. Therefore, the amplitude jump phenomenon correspond to chaos behavior occurs prior to seizure onset.

2. Materials and Methods

2.1. Model Structure

Recent studies [19,20] have shown that during the generalized seizures, structural and functional disturbances have been identified in the thalamocortical network. According to these findings, a thalamocortical model is developed as shown in Fig. 1, which includes cortical excitatory pyramidal neuron population (PY), mutual fast and slow inhibitory interneuron populations (I1, I2) of inhibitory $GABA_A$ and $GABA_B$ receptors, and thalamic subsystem TC-RE circuit model. The thalamic subsystem includes a population of thalamic relay nucleus (TC) and the population of neurons located in the reticular nucleus (RE). To investigate the effect of spiny stellate cells on seizure onset, we considered the excitatory interneurons population, EI, in our thalamocortical model (see Fig 1). In this new model version, we will investigate the synaptic connectivity strength of excitatory interneurons to explore dynamics which lead to preictal state and dynamics during transitions between absence, tonic and clonic seizures.

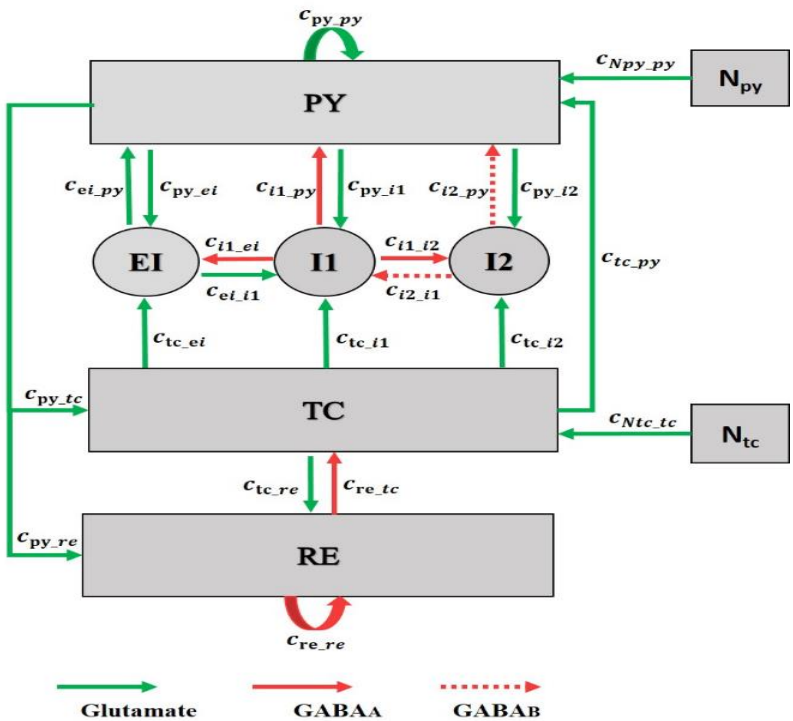

Fig. 1. **Scheme of the thalamocortical model which includes the excitatory interneuron population in cortex.** The model involves cortex and thalamus subnetworks. In the cortex subnetwork, PY is the pyramidal neural population, EI is the excitatory interneurons population, I_1 and I_2 are the fast and the slow inhibitory interneurons populations, respectively. In the thalamus subnetwork, TC is the thalamic relay nucleus population and RE is the thalamic reticular nucleus population. green arrows define the excitatory glutamatergic receptor. Red solid and dashed arrows define the $GAGA_A$ and $GABA_B$ inhibitory receptors, respectively. The value of parameters of this model are: $C_{py\_py} = 1.89$, $C_{py\_i1} = 4$, $C_{i1\_py} = 1.8$, $C_{re\_re} = 0.01$, $C_{tc\_re} = 10$, $C_{re\_tc} = 1.4$, $C_{py\_tc} = 3$, $C_{py\_re} = 1.4$, $C_{tc\_py} = 1$, $C_{py\_i2} = 1.5$, $C_{tc\_i1} = 0.05$, $C_{tc\_i2} = 0.05$, $C_{ei\_i1} = 0.05$, $C_{ei\_py} = 0.442$, $C_{i2\_py} = 0.05$, $C_{i2\_i1} = 0.1$, $C_{i1\_i2} = 0.5$, $C_{Npy\_py} = 1$, $C_{Ntc\_tc} = 1$, $\tau au_1 = 21.5$, $\tau au_2 =$ the 31.5, $\tau au_3 = 0.1$, $\tau au_4 = 4.5$, $\tau au_5 = 3.8$, $\tau au_6 = 3.9$, $h_{py} = -0.4$, $h_{i1} = -3.4$, $h_{i2} = -2$, $h_{ei} = -1$, $h_{tc} = -2.5$, $h_{re} = -3.2$, $\varepsilon = 250000$, $a_{tc}=0.02$, $a_{py}=0.02$, $B_{Npy}=0.7$ and $B_{Ntc}=0.1$.

strength of the synaptic connections. These synaptic connections are associated with the type of receptors. In the brain, receptors are either excitatory (glutamatergic) or inhibitory (GABAergic). In the cortex, the pyramidal population is an excitatory population and there is a mutual excitatory connection between pyramidal and excitatory interneurons by the glutamatergic receptors [21]. Excitatory and inhibitory interneurons are locally connected to each other [22], and based on this fact, we consider an excitatory and an inhibitory connection between excitatory interneurons and fast inhibitory interneurons. Thalamus is globally connected to the excitatory interneurons by the thalamic relay nucleus, and thalamic relay nucleus is regarded as an excitatory population [23]. Here, we consider an excitatory connection from the thalamic relay nucleus population to the excitatory interneurons.

The thalamic relay nucleus receives all the sensory information from different parts of the brain and then this information is sent to the appropriate area in the cortex for further processing [24,25]. Here, in order to investigate the dynamic of the model according to the effects of the input on the model' output, we consider an input (Ntc) to the thalamic relay nucleus by adding a periodic sensory input with frequency ftc, bias B_{Ntc} and amplitude a_{tc}. Moreover, we consider a cortical input (Npy) to the pyramidal neural population by adding a biased sinusoidal waveform with bias of B_{Npy} , frequency of fpy and amplitude of a_{py}.

We implement the model on the basis of the Amari neural field equations [26]. The differential equations of the model are given below.

$$\frac{\mathrm{dPY}}{\mathrm{dt}} = \mathrm{tau}_1\,(\mathrm{h_{py}} - \mathrm{PY} + \mathrm{C_{py_{py}}}\,\mathrm{f(PY)} - \mathrm{C_{i1_{py}}}\,\mathrm{f(I1)} + \mathrm{C_{tc_{py}}}\,\mathrm{f(TC)} - \mathrm{C_{i2_{py}}}\,\mathrm{f(I2)} + \mathrm{C_{ei_{py}}}\,\mathrm{f(EI)}) + \mathrm{N_{py}} \quad (1)$$

$$\frac{dI1}{dt} = tau_2\,(h_{i1} - I1 + C_{py\_i1}\,f(PY) - C_{i2\_i1}\,f(I2) + C_{tc\_i1}\,f(TC) + C_{ei\_i1}\,f(EI)) \quad (2)$$

$$\frac{dI2}{dt} = tau_3\,(h_{i2} - I2 + C_{py\_i2}\,f(PY) - C_{i1\_i2}\,f(I1) + C_{tc\_i2}\,f(TC)) \quad (3)$$

$$\frac{dEI}{dt} = tau_4\,(h_{ei} - EI + C_{py\_ei}\,f(PY) - C_{i1\_ei}\,f(I1) + C_{tc\_ei}\,f(TC)) \quad (4)$$

$$\frac{dTC}{dt} = tau_5\,(h_{tc} - TC + C_{py\_tc}\,f(PY) - C_{re\_tc}\,f(RE)) + N_{tc} \quad (5)$$

$$\frac{dRE}{dt} = tau_6\,(h_{re} - RE + C_{py\_re}\,f(PY) - C_{re\_re}\,f(RE) + C_{tc\_re}\,f(TC)) \quad (6)$$

$$N_{py} = B_{Npy} + a_{py} * sin(2\pi\,fpy\,t) \quad (7)$$

$$N_{tc} = B_{Ntc} + a_{tc} * sin(2\pi\,ftc\,t) \quad (8)$$

Where $c_{1,\ldots,16,iny,ei,in1,in2}$ are the connectivity parameters which determine the coupling strength between the populations, and $h_{py,i1,i2,ei,tc,re}$ are input parameters, $\tau au_{1,2,\ldots,6}$ are time scales parameters, $f(x) = {}^{1}/_{(1+\varepsilon^{-x})}$ is the transfer function, where ε determines steepness and x=PY,I1,I2,EI,TC and RE. The EEG is taken as the mean activity of the four cortical populations.

2.2. Simulations

Simulations are performed by the standard fourth-order Runge-Kutta integration using MATLAB 9.4 and in the XPPAUT environments, with a step size of 0.0039 s. We set the time window at 60 s, and use the last two seconds of the time series to analyse the stable state of the time domain. We use the frequency domain and time domain analysis to explore the transitions from interictal to ictal and between seizures. We extract dominant frequency (the energy which carries the maximum energy) from the power spectral density using the fast Fourier transform, and for the bifurcation analysis, we extract extrema (local maximum and minimum) of the mean of four cortical populations from the time series. By doing so, we

can observe seven different epileptic activities such as interictal state (normal background activity), preictal state which occurs before the seizure onset and is less chaotic and more synchronized than the interictal signal, slow rhythmic activity that can be observed at seizure onset or during the seizures, typical absence seizures, atypical absence seizures, tonic and clonic seizures. For hybrid bifurcation analysis when both of the parameters of c_{py_ei} and c_{i1_ei} are changed, we compute the extrema and frequency of last two seconds of the model output, and then we sort the local maximums and minimums from large to small, and we categorized the signals according to the Table 1.

Table 1. The specific characteristics of seven simulated signals. Dominant frequency, largest minima, largest maxima, largest minima and largest maxima are characteristics used to separate seven different activities of mean of cortical populations.

Type of the signal	Dominant frequency range	largest minima (Pmin1) and smallest minima (Pmin2)	largest maxima (Pmax1) and smallest maxima (Pmax2)
Normal background activity	DF = 0 Hz	-	-
Preictal spikes	DF < 3.5 Hz	Pmin1-Pmin2<0.2	0.01< Pmax1-Pmax2<0.12
Slow rhythmic activity	DF =0 Hz	-	-0.8<Pmax1 <-0.1
Typical absence seizure	DF ϵ [2,4] Hz	0.004<Pmin1-Pmin2	-
Atypical absence seizure	DF > 4 Hz and DF < 2 Hz	0.01 <Pmin1-Pmin2	-
Clonic seizure	DF ≤ 7 Hz	Pmin1-Pmin2<0.15	0.01<Pmax1-Pmax2
Tonic seizure	DF ≥ 14 Hz	Pmin1-Pmin2<0.01	0.01<Pmax1-Pmax2

3. Results

In this section, the role of excitatory interneurons in transition from interictal to ictal, and the frequency response the thalamocortical model, when it receives sensory and cortical inputs, are examined using various bifurcation analysis and dynamical simulations. In section 3.1, in order to explore the transition dynamics of the model we assume that the inputs of model are constant; *i.e.*, $N_{py} = B_{Npy}$ and $N_{tc} = B_{Ntc}$. In section 3.2, for investigating the frequency response of the model, a sinusoidal waveform signal is added to both sensory and cortical inputs, that is, $N_{py} = B_{Npy} + a_{py} * \sin(2\pi\, fpy\, t)$ and $N_{tc} = B_{Ntc} + a_{tc} * \sin(2\pi\, ftc\, t)$.

3.1. Transition dynamics

Excitatory interneurons are connected to the pyramidal neurons and fast inhibitory interneurons by glutamatergic and GABAergic receptors, respectively. Experimental evidences have shown that, changes in the function of GABAergic and glutamatergic receptors in the cortex of rats can be seen in genetic absence, tonic and clonic seizures onset [27,28,29]. However, the transition dynamics from interictal to ictal, and transitions between absence, tonic and clonic seizures contributed to the abnormalities in glutamatergic and GABAergic receptors of EI are still unclear. In this section, by using bifurcation analysis, we explore the effect of impairment in the function of GABAergic and glutamatergic receptors of EI population on the epileptic dynamics of model as the synaptic strengths $c_{i1\text{-}ei}$ and $c_{py\text{-}ei}$ change, respectively.

3.1.1. Transition dynamics produced by GABAergic receptor-mediated inhibition in EI

Increasing the inhibitory function of GABAergic receptors of excitatory interneurons suppresses the EI excitation, therefore EI population could less excite the fast inhibitory interneurons in the cortex, and decrease the GABA neurotransmitters release from I1 neuronal population and consequently cause a seizure. Furthermore, the synaptic strength from fast inhibitory interneurons to spiny stellate neurons is ten times more powerful than the synaptic strength between pyramidal and spiny stellate cells. Thus, the interaction between EI and fast inhibitory interneurons in the cortex is crucial. It is also observed that abnormality in the kinetics of synaptic strength of GABAergic receptors in the EI layer can increase the synchrony between neural circuitry, and generate epileptic activities [30]. Based on the study on a murine model, GABAergic receptor dysfunction could lead to absence, tonic and clonic seizures [31]. According to the experimental study on rats, impaired function of $GABA_A$ receptors enhances the excitability of neurons in the brain and causes the absence activity evolves into tonic-clonic seizure [32]. Here, we investigate the dynamics of model to explore the epileptiform activity induced by the dysfunction of GABAergic receptor of the excitatory interneuron population as the synaptic strength $c_{i1\text{-}ei}$ changes. Results of Fig. 2 show that model displays rich dynamic as the parameter $c_{i1\text{-}ei}$ varies.

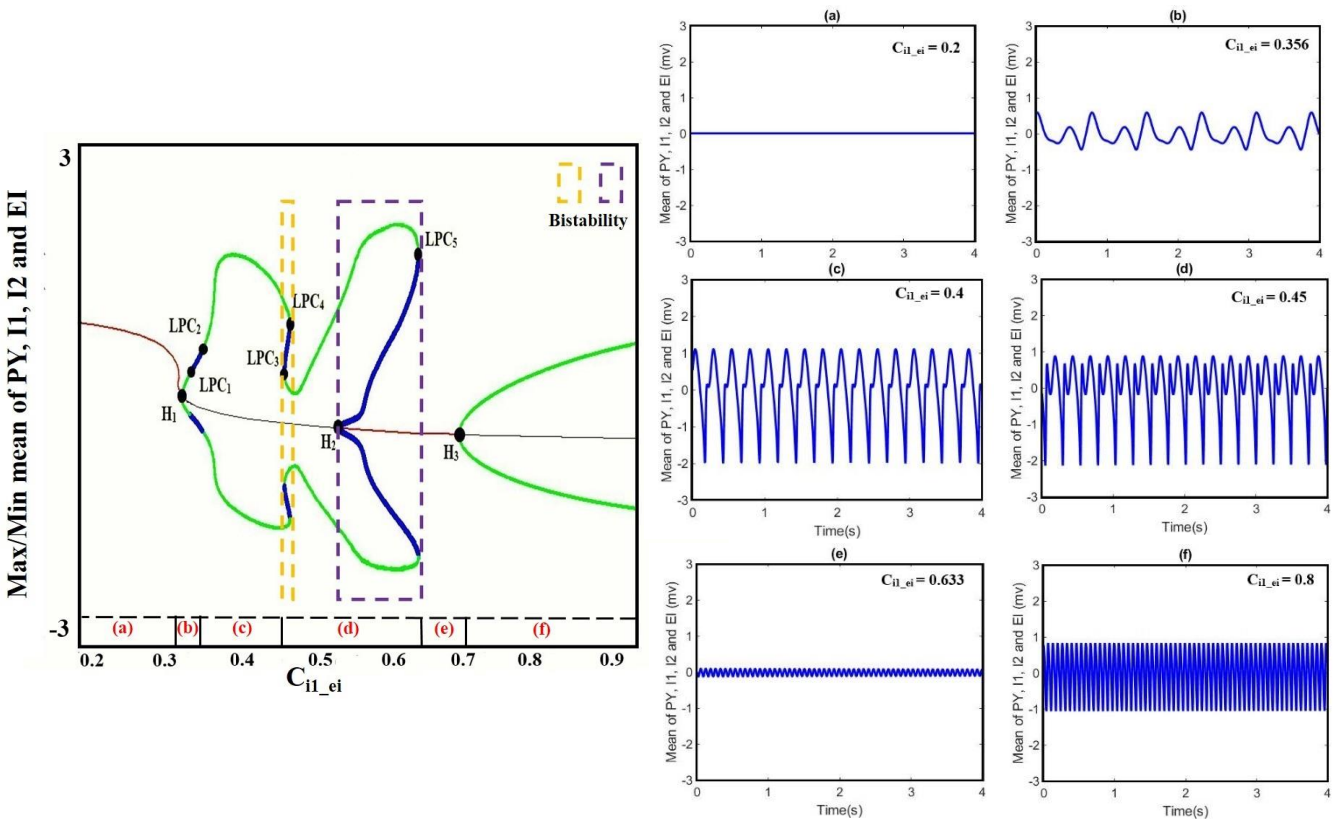

Fig. 2. **Bifurcation diagrams and their corresponding time series as the c_{i1_ei} changes.** The bifurcation diagram of model as the c_{i1_ei} changes with c_{py_ei} =0.8, c_{tc_ei} =4.5, a_{tc}=0 and a_{py}=0 . According to the diagram as the parameter c_{i1_ei} changes, the model produces (a) normal background firing, (b) pre-ictal spikes, (c) clonic discharges, (d) spike and wave discharges, (e) slow rhythmic activity and (f) tonic discharges. In the plot, blue and green cycles, represent the unstable and stable limit cycles, respectively, and red and black dots, represent the stable and unstable points, respectively.

According to Fig. 2, the overall bifurcation in detail with changes of $c_{i1\text{-}ei}$ is shown. In the bifurcation diagram from left to right, the red line corresponds to the stable fixed points which are related to the normal background activity (Fig. 2a), and upon increasing the $c_{i1\text{-}ei}$ to ~ 0.35 a stable fixed point coalesces with a stable limit cycle

and a supercritical Hopf bifurcation point (H_1) happens and forms the preictal spikes patterns (transition from normal background activity to ictal activity, Fig. 2b), with increasing the $c_{i1\text{-}ei}$ to ~ 0.358 a fold limit cycle bifurcation (LPC_1) occurs which generates coexistence of stable limit cycles and unstable ones. With a further increase of $c_{i1\text{-}ei}$ parameter to ~ 0.365, another fold limit cycle bifurcation (LPC_2) happens and shapes the clonic seizure patterns (Fig. 2c). In addition, as $c_{i1\text{-}ei}$ parameter is increased until ~ 0.412, the third fold limit cycle bifurcation (LPC_3) occurs, and another fold limit cycle (LPC_4) takes place with further increase of $c_{i1\text{-}ei}$ parameter. With the coexistence of two stable limit cycles in the range of $c_{i1\text{-}ei}$ bounded by two-fold limit cycles bifurcations (LPC_3 and LPC_4) a bistable region appears and creates coexistence of the two different amplitude spike and wave discharge (SWD) patterns (Fig. 2d). Moreover, stable points appear again at $c_{i1\text{-}ei}$ ~ 0.479, where the first subcritical Hopf bifurcation (H_2) takes place, and another bistable region happens with the coexistence of stable fixed points and a stable limit cycle until the fifth fold limit cycle bifurcation (LPC_5) at $c_{i1\text{-}ei}$ ~ 0.582. Upon increasing the $c_{i1\text{-}ei}$ parameter, the stable focus points which are corresponded to slow rhythmic activity take place (Fig. 2e), and then at $c_{i1\text{-}ei}$ ~ 0.627 another supercritical Hopf bifurcation (H_3) arises from the steady-state and shapes the tonic seizure patterns (Fig. 2f).

The inhibition of intra-EI weakens the glutamatergic receptors of EI, and according to the experimental and genetic mutation studies on mice, the altered function of glutamatergic receptors in the cortex could cause the epileptic seizures [33,34]. Based on a vivo study on mice model of tuberous sclerosis complex (TSC), the mutation in either TSC1 or TSC2 can disturb the function of NMDA receptors in the excitatory interneurons which in turn can cause a shift from normal activity to ictal activity [35]. Hence, insights into the effect of intra-EI glutamatergic receptors mechanisms on epileptiform activities are dynamically provided in the next section.

3.1.2. Transition dynamics produced by glutamatergic receptor-mediated excitation in EI

Experimental study on mice has shown that the disturbance in glutamatergic transmission and signalling, could be associated with the epileptic seizure occurrence [36]. Decreasing the function of glutamatergic receptors in excitatory interneurons attenuates the EI excitation, and reduces the glutamate neurotransmitters release from EI population in the cortex. In vitro studies on rats suggest that reducing the function of glutamatergic receptors in the hippocampus might participate in the excitability of the brain during the epileptic seizures [37,38]. Based on the in vitro study on mice, impairment in glutamate release which is either due to the decreased function of glutamate receptors or loss of glutamate receptors causes the generalized absence and tonic-clonic epileptic seizures [39]. Abnormality in the function of glutamatergic receptors may cause the transition from interictal signal to preictal signal [40], and the transition between absence and tonic-clonic seizures [41,42]. However, the mechanisms underlying the transition from interictal to ictal activities associated with glutamatergic receptors on EI remained unclear. Here, we take $c_{py\text{-}ei}$ as the growing bifurcation parameter to investigate the dynamics of model to explore the epileptiform activity induced by the glutamatergic receptor function of EI. According to Fig. 4, by gradually decreasing the EI excitability in the cortex, we can observe rich epileptiform transition dynamics.

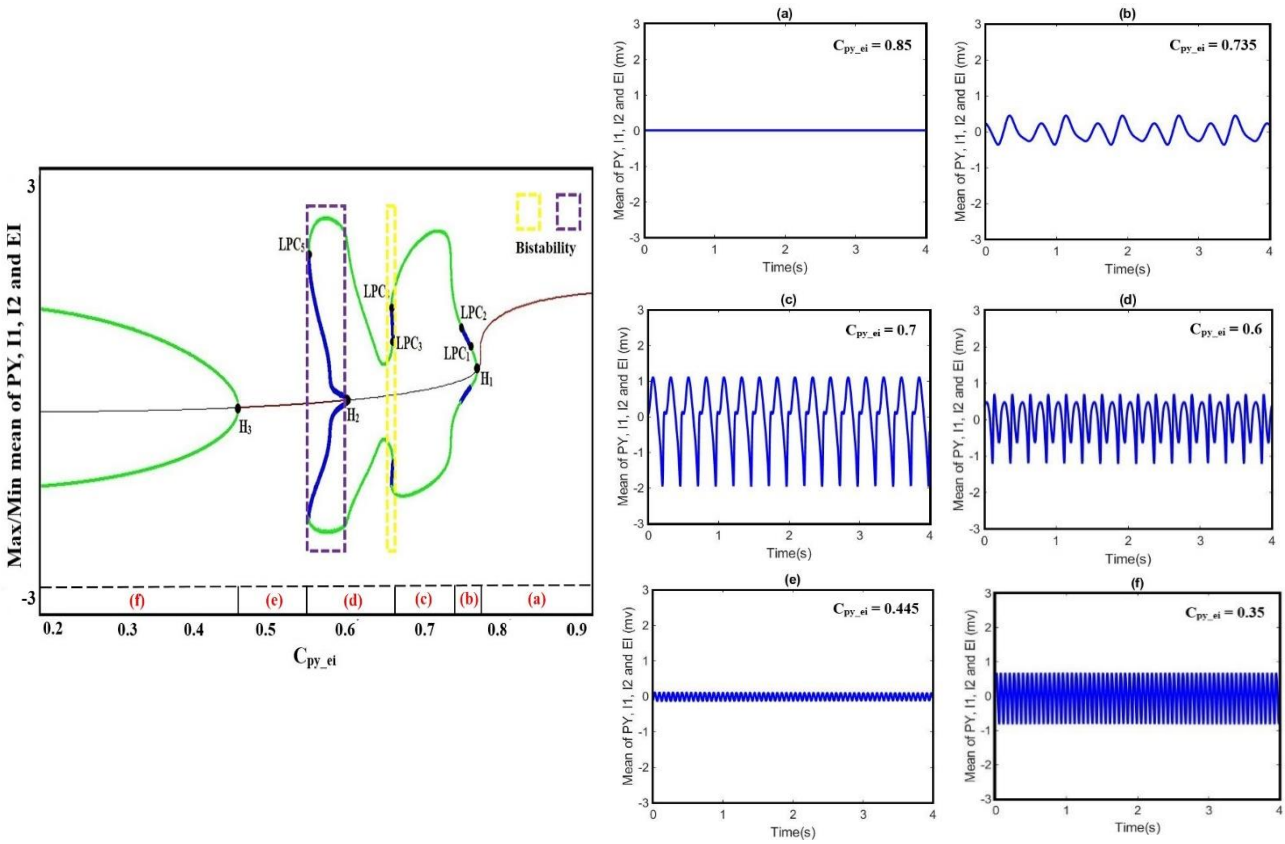

Fig. 3. **The bifurcation diagrams and their related time series as the parameter of $c_{py\text{-}ei}$ changes**. The bifurcation diagrams of model as the parameter of $c_{py\text{-}ei}$ changes as the parameters of $c_{i1\text{-}ei}$ =0.3 and $c_{tc\text{-}ei}$ = 4.5 are fixed**.** We also set a_{tc}=0 and a_{py}=0. It can be found from the bifurcation diagram that as the parameter $c_{py\text{-}ei}$ decreases, (a) normal background firing (interictal), (b) pre-ictal spikes, (c) clonic discharges, (d) spike and wave discharges, (e) slow rhythmic activity and tonic discharges can appear. In the bifurcation plot, blue and green cycles, represent the unstable and stable limit cycles, respectively, and red and black dots, represent the stable and unstable points, respectively.

According to the bifurcation diagram in the Fig. 3, from right to left, we can observe the normal background activity, preictal spikes, clonic seizures, absence seizures, slow rhythmic activity and tonic seizures, respectively, combined with corresponding time series, as the parameter $c_{py\text{-}ei}$ decreases. Hence, suppression of glutamatergic receptor on EI can actually lead to transition from interictal to preictal signals, and also transition between epileptic seizures. With decreasing the synaptic strength $c_{py\text{-}ei}$, the system encounters with normal background activity (Fig. 3a) for the normal value of $c_{py\text{-}ei}$. As the $c_{py\text{-}ei}$ becomes smaller, a supercritical Hopf bifurcation point (H_1) happens and the stable fixed points become unstable at $c_{py\text{-}ei}$ ~0.74, and forming the preictal spikes pattern (Fig. 3b). Upon $c_{py\text{-}ei}$ is approaching to ~0.73, a fold limit cycle bifurcation (LPC_1) takes place, and generating one stable and one unstable limit cycles. Further decrease of $c_{py\text{-}ei}$ parameter to ~ 0.72, another fold limit cycle bifurcation (LPC_2) happens and shapes the clonic seizure patterns (Fig. 3c). In addition, with further decreasing the $c_{py\text{-}ei}$ parameter to ~ 0.678, a bistable region including two stable limit cycles takes place between the third- and fourth-fold limit cycle bifurcations (LPC_3 and LPC_4), and shapes the spike and wave discharge (SWD) patterns (Fig. 3d). As the $c_{py\text{-}ei}$ parameter decreases to ~ 0.591, the first subcritical Hopf bifurcation (H_2) occurs and the stable points appear again. The second bistable region consists of stable focus points and a stable limit cycle happens between the subcritical Hopf bifurcation (H_2) and the fifth fold limit cycle (LPC_5) until $c_{py\text{-}ei}$ is approaching to ~0.532. Upon decreasing the $c_{py\text{-}ei}$ parameter, slow rhythmic activity

(Fig. 3e) happens, and then at $c_{py\text{-}ei}$ ~0.451 the second supercritical Hopf bifurcation (H_3) arises from the steady-state and shapes the tonic seizure patterns (Fig. 3f).

Altogether, this model showed that impairment of GABAergic or glutamatergic receptors in the EI population causes the transition from normal background activity to seizures (preictal signal) and the transition between absence, tonic and clonic seizures. This model shows the possible existence of supercritical Hopf bifurcation with growing amplitude oscillations when the transition from interictal to ictal state occurs. In order to have a deeper understanding of the interictal to ictal transition dynamics, we investigate the bifurcation of the cortical and sensory input frequencies in our model.

According to the electrophysiological evidence [43], altered function of glutamatergic and GABAergic receptors can be seen in the striatum, hippocampus and frontal cortex of rat after pilocarpine-induced seizure. Therefore, we investigate the dual interaction between GABAergic and glutamatergic receptors in the initiation and termination of epileptic seizures in the next section.

3.1.3. Hybrid cooperation of GABAergic and glutamatergic receptors of EI in epileptic transition dynamics

Experimental study on genetic animal model of a mouse has shown that abnormal joint action of GABAergic and glutamatergic receptors can lead to generalized seizure activities, and these excitatory and inhibitory receptors are important targets for seizure controls [44]. The genesis of generalized seizures requires interdependencies in different thalamocortical connections. Studies on genetic rat models have shown that the abnormal coupling strength of thalamus to cortex may facilitate the maintenance and propagation of absence seizure [45,46]. Here, we investigate the effect of a dual collaboration of intra-EI GABAergic and glutamatergic synaptic strength in the cortex on the transition between different kinds of activity, either from interictal to ictal signal or from absence seizure to tonic and clonic seizures, and we also explore the influence of TC to EI pathway dominated by glutamatergic receptors on the initiation and propagation of epileptic activities based on the altered ratio of dual cooperation of intra-EI GABAergic and glutamatergic receptors in the cortex. According to the Fig. 4, the pattern evolutions for different values of $c_{tc\text{-}ei}$ are obtained to investigate the state transition produced by this model and their corresponding dominant frequency distributions as the parameters of $c_{py\text{-}ei}$ and $c_{i1\text{-}ei}$ varies in region $[0.1,0.9] \times [0.2,0.9]$.

For higher values of synaptic strength like $c_{tc\text{-}ei}$ =4.5 (Fig. 4a, b), this model demonstrates seven different types of activities, when ci1-ei varies from 0.2 to 0.9. We denoted these seven activities as follows: type1, normal background activity (DF = 0 Hz in Fig. 4b); type2, preictal activity (DF < 3.5 Hz in Fig. 4b); type6, clonic seizure (DF ≤ 7 Hz in Fig. 4b); type5, atypical absence seizure (DF > 4 Hz and DF < 2 Hz in Fig. 4b); type4, typical absence seizure (2 Hz < DF < 4 Hz in Fig. 4b); type3, slow rhythmic activity (DF = 0 Hz in Fig. 4b); type7, tonic seizure (DF ≥ 14 Hz in Fig. 4b). Upon decreasing the synaptic strength $c_{tc\text{-}ei}$ from 4.5 to 4 (Fig. 4c, d), one can see that the surface of the yellow region (atypical absence seizure; Type5) and red region (tonic seizure; Type7) increase with the reduction level of excitation of intra-EI. Accordingly, the regions correspond to normal background activity (Type1), preictal activity (Type2), clonic seizure (Type6), typical absence seizure (Type4) and slow rhythmic activity (Type3) decreases. Biologically, decreasing the excitatory coupling strength from TC to EI reduces the information flow input from the thalamus to the cortex and interrupts the normal activity of the thalamic relay nucleus in the thalamocortical network. This interruption facilitates the transition from interictal to ictal and the transition between seizures, i.e., with the increasing of $c_{py\text{-}ei}$ and $c_{i1\text{-}ei}$ from their normal state, the transition from normal background activity to ictal activity and also the transition between clonic, absence and tonic seizures can occur faster. Upon further decreasing of the $c_{tc\text{-}ei}$ to 3.5 (Fig. 4e, f), the yellow and red regions correspond to atypical absence seizure (Type5) and tonic seizure (Type7) extend, respectively, However, the whole other regions decrease which shows that the transition from normal background activity to epileptic seizure activities in this model can be influenced by the intra-EI GABAergic and glutamatergic receptors in the cortex under the impact of the thalamus to the cortex synaptic strength.

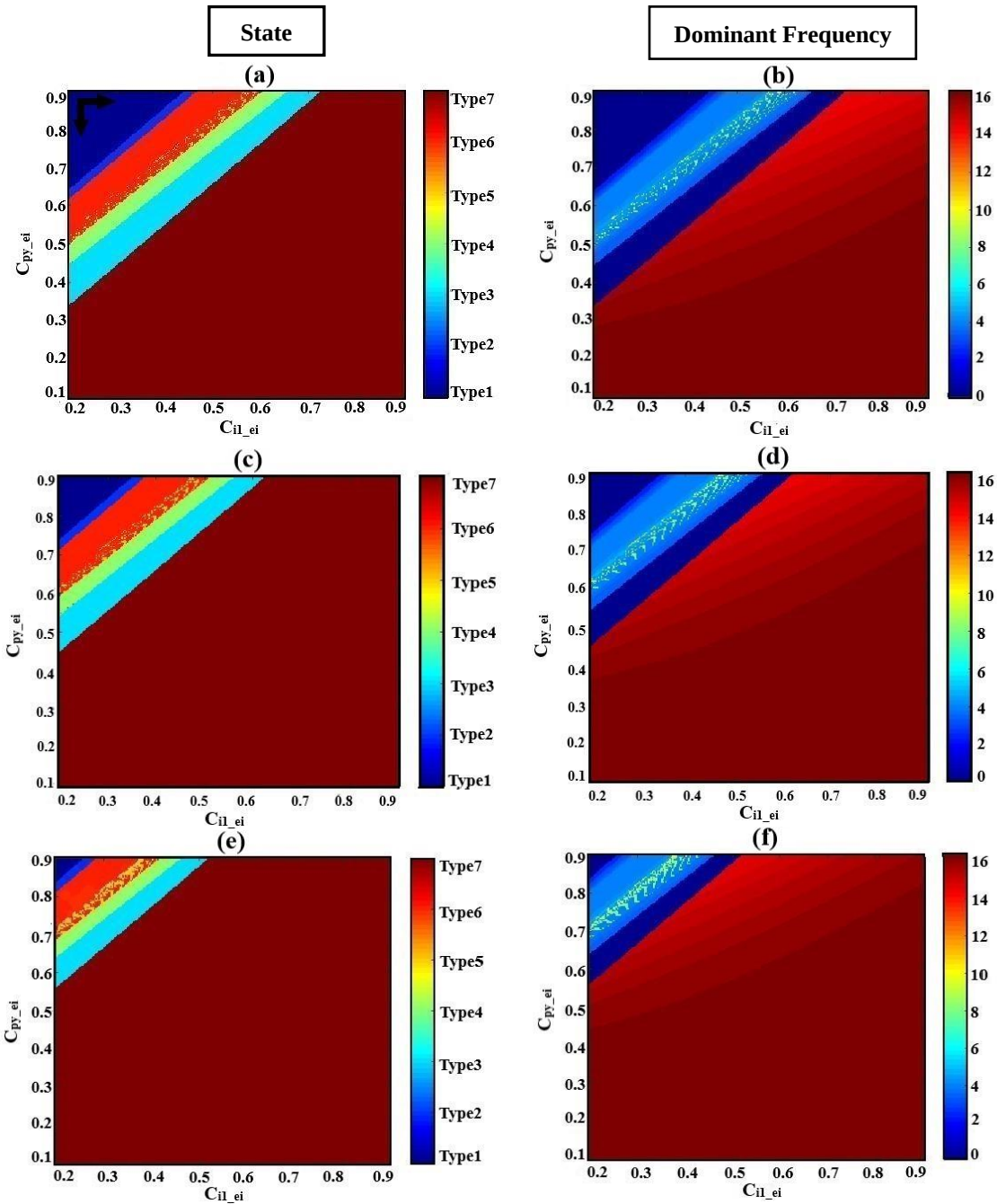

Fig. 4. The hybrid modulation of model. The pattern evolutions of model of intra-EI GABAergic and glutamatergic receptors ($c_{py\text{-}ei}$, $c_{i1\text{-}ei}$) in the cortex forced by the changes of TC to EI excitatory synaptic strength ($c_{tc\text{-}ei}$). We set the a_{tc}=0 and a_{py}=0. The various activities **(a), (c)** and **(e)** and their corresponding dominant frequencies **(b), (d)** and **(f)** with decreasing the excitatory synaptic strength $c_{tc\text{-}ei}$ from top to bottom, set as 4.5, 4 and 3.5, respectively, are shown. Model with variation of $c_{py\text{-}ei}$, $c_{i1\text{-}ei}$ can produce different firing sates such as normal background firing (Type1; DF = 0 Hz), preictal activity (Type2; DF < 3.5 Hz), slow rhythmic activity (Type3; DF = 0 Hz), typical absence seizure (Type4; 2 Hz < DF < 4 Hz), atypical absence seizure (Type5; DF > 4 Hz and DF < 2 Hz), clonic seizure (Type6; DF ≤ 7 Hz) and tonic seizure (Type7; DF ≥ 14 Hz). The black horizontal and vertical arrows represent the transition routes from the normal state to the pathological states.

In summary, the intra-EI GABAergic and glutamatergic receptors in the cortex can elicit seven different kinds of activity in this model under the effect of excitatory synaptic strength from TC to EI. The lower excitatory synaptic strength of $c_{tc\text{-}ei,}$ in the model, causes a faster transition from interictal to ictal and between seizures due to the more interruption of information flow from the thalamus to the cortex. This implies the important role of thalamus to cortex synaptic strength in the initiation and maintenance of generalized epileptic seizures.

According to the clinical observations, the sensory [47] and cortical [48] stimulations can provoke an epileptic seizure. Therefore, in the next section examine the effect of sensory and cortical input in the interictal to ictal transition in this thalamocortical model.

3.2. Frequency analysis of the different initial states of model

Studies on thalamocortical models [49, 50], have shown that changes in the frequency of a cortical and sensory periodic input can cause a transition from chaotic to periodic activities in the output of the model. Therefore, here we examine not only the effect of frequency of the cortical and sensory inputs on the chaotic-periodic transition behaviour of our model, but most importantly, we investigate the effect of the initial stage of model on this transition. Fig. 5, shows the bifurcation diagrams for different initial stages of model such as normal background activity (interictal), preictal activity and ictal activity as the parameter c_{py_ei} changes with a frequency step increment of 0.01 Hz for each sensory and cortical input. In Fig. 5a, b, we set the c_{py_ei} at its normal value ($c_{py\_ei} = 0.76$) in order to explore the behaviour of the output of model versus the frequency of the cortical and the sensory inputs when the model is in its interictal initial stage, respectively. For the interictal initial stage, model shows a linear resonant behaviour with a resonant frequency of fpy ≈ 0.2 and ftc ≈ 4.7 as the cortical and sensory input frequencies increase, respectively. This model behaves like a bandpass filter for sensory input and a low pass filter for cortical input. As it is shown in Fig. 5c, d, by decreasing the parameter c_{py_ei} to 0.748, the initial stage of model changes to preictal activity. With increasing the cortical input frequencies, we can observe a chaotic behaviour. In the Fig. 5c, by further increasing the bifurcation parameters of fpy, we can notice a jump near the frequencies of fpy ≈ 1.7. Moreover, by increasing the sensory input frequency, it is shown in the Fig. 5d that two jumps take place near the frequencies of ftc ≈ 1.8 and ftc ≈ 4. Then, upon increasing the fpy and ftc, model returns to its periodicity behaviour. Therefore, when model's initial stage changes from normal background activity to preictal activity, the behaviour of model changes from a linear resonator to a nonlinear resonator. In the Figs. 5e, f, we change the initial stage of model to its ictal stage by decreasing the c_{py_ei} parameter to 0.72. By increasing the fpy and ftc frequencies, it is shown that model displays a drastic chaotic behaviour and then comes back to the periodicity.

Fig. 6 illustrates the effect of initial stage of the brain on the transition between small amplitude oscillation and large amplitude seizure activity. In Fig. 6a, model receives a cortical input with fixed frequency, fpy=1 Hz in the absence of sensory input to the model. However, in Fig. 6b, we just consider the sensory input on the output of our model and we set its frequency, ftc, at 1 Hz. In Figs. 6a, b, it is shown that by changing the c_{py_ei} parameter from 0.76 to 0.748, the state transition from normal activity to typical absence seizure activity occurs and then it returns to normal activity as the c_{py_ei} returns to its initial value.

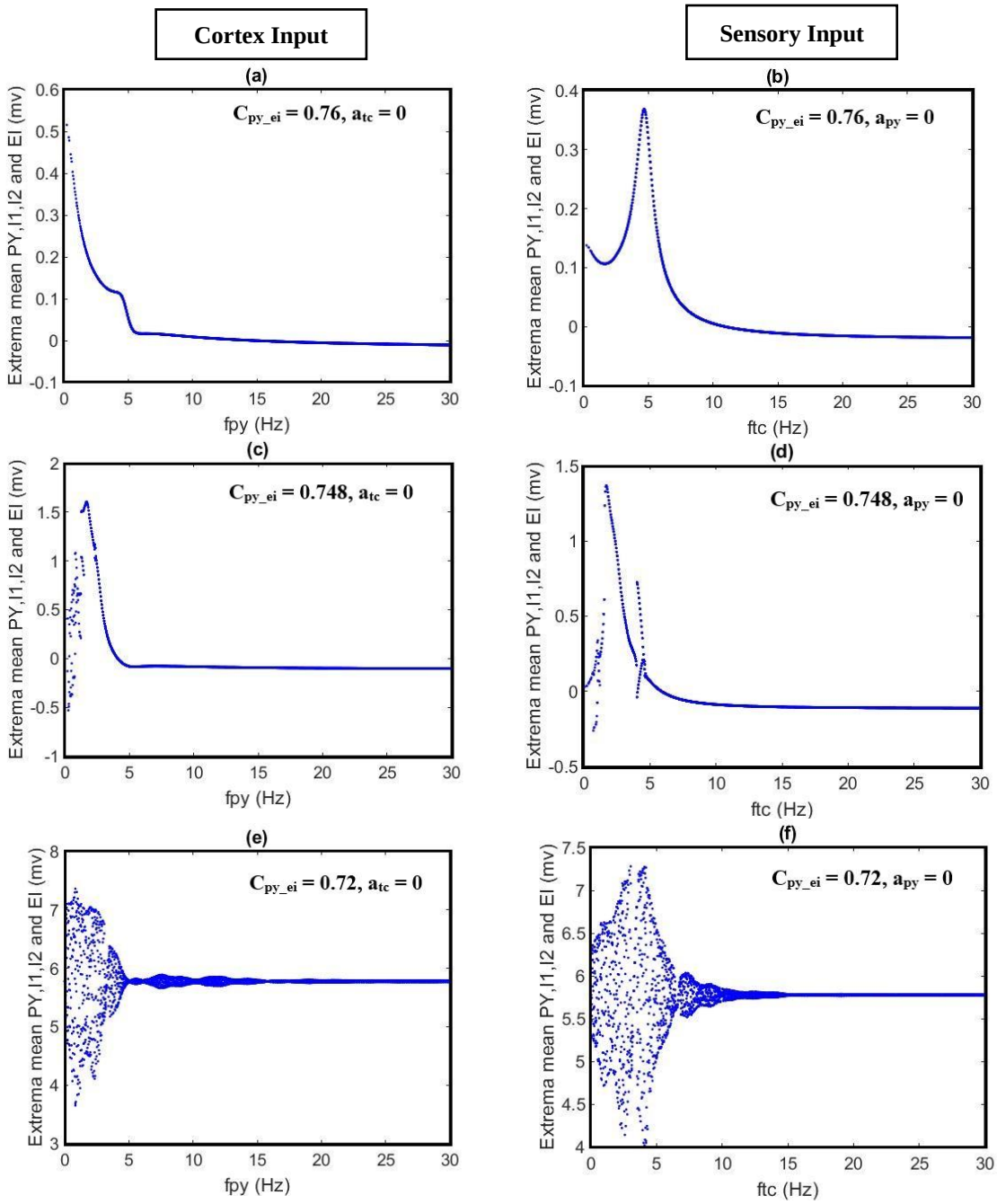

Fig. 5. **The bifurcation diagrams as each parameter of fpy and ftc changes**. The bifurcation diagrams model as the input cortical frequency (fpy) and sensory frequency (ftc) change by fixing the parameters of the $c_{i1\text{-}ei}$ =0.3 and $c_{tc\text{-}ei}$ = 4.5**.** In the left- hand side diagrams, the fpy changes and we set the ftc = 0, and in the right-hand side diagrams the ftc changes and the fpy is set to zero.

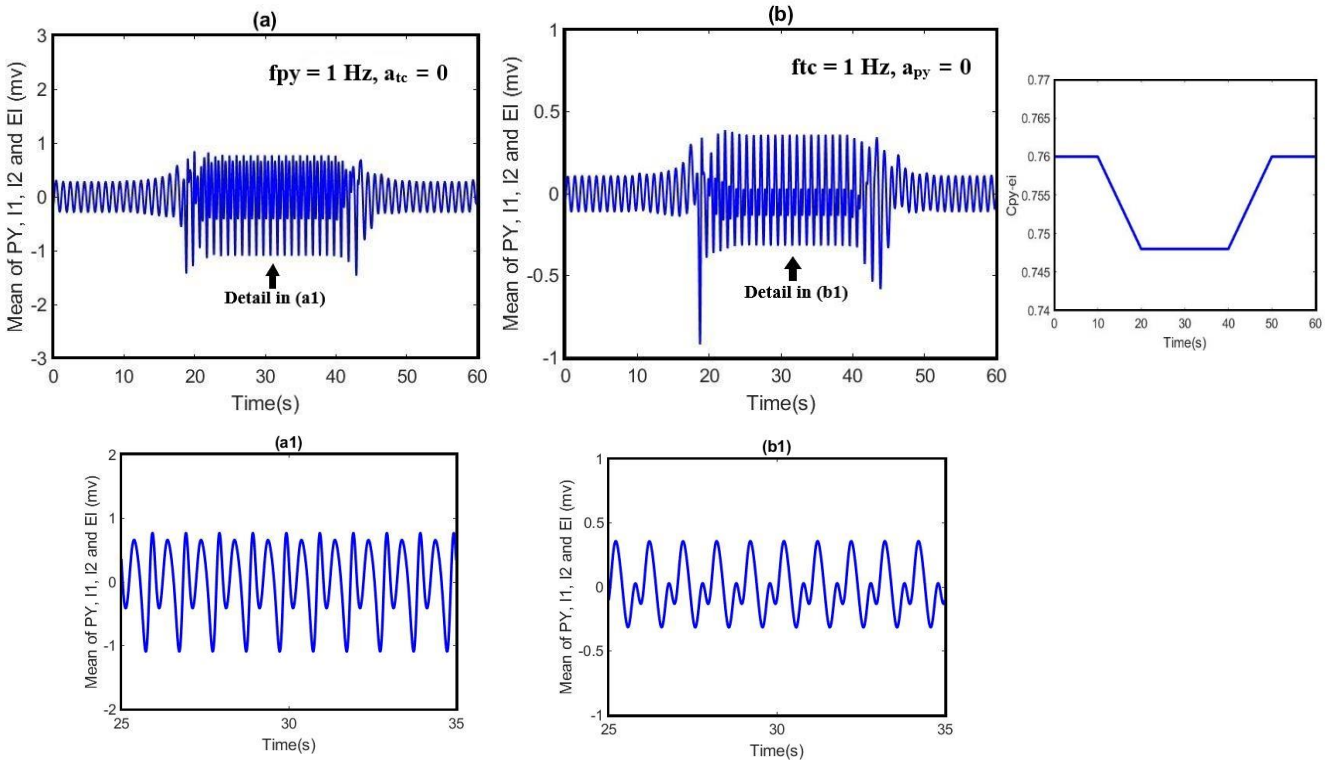

Fig. 6. **The state transition as the parameter of Cpy_ei changes**. The effect of initial stage of model on the transition between periodic signal and seizure when the cortical and sensory input frequencies are constant. At (a) we set the parameters of fpy to 1 Hz and atc to zero and at (b) we.set ftc=1 HZ and apy=0. The pattern of glutamatergic synaptic strength, Cpy_ei, is presented on the right-hand side diagram.

4. Discussion

The present study puts forward a new neural mass model which considers the role of the spiny stellate cell population connectivity with other cortical neural populations in different stages of seizure generation. The original thalamocortical model, which was developed by Taylor et al in 2014 [18], was modified and extended and then used to simulate the preictal activity that has a prevailing role in epileptic seizure prediction. Using this model, we investigated the interactions between excitatory interneurons and the glutamatergic pyramidal and inhibitory interneurons in the cortex, and how these interactions can lead to epileptic seizure activities. This model enabled us to generate preictal activities before the clonic seizure in addition to other types of epileptic activities. Our results show the richness of the dynamics that the proposed model can generate, including normal background activity, preictal spikes, slow rhythmic activity, clonic seizure, typical absence seizure and tonic seizure as the synaptic strength of glutamatergic and GABAergic receptors on the EI change. Furthermore, bifurcation diagrams of model were obtained by varying the coupling strength of GABAergic and glutamatergic receptors in EI. The diagrams in Fig.2 and Fig.3 show that pathologic transitions are consequences of supercritical as well as subcritical Hopf bifurcations and the fold limit cycle bifurcation. The onset of preictal discharges is characterized by a supercritical Hopf bifurcation. This, results in a preictal activity which is characterized by an escalation in amplitude and frequency of neural activities. Therefore, ictal discharges do not appear abruptly after a period of interictal activities. This increase in frequency and amplitude can be used effectively for seizure prediction and abatement. Some recent studies [51, 52] have explored in the

thalamocortical circuitry the effect of pyramidal neurons and inhibitory neurons in seizure generation and propagation but they didn't investigate the role that excitatory interneurons can play in epileptic seizures. However, according to the bifurcation analysis of our model, excitatory interneurons has an important role in the transition from interictal to generalized seizures. Using this fact, one will be able to control seizure development by keeping the GABAergic and glutamatergic synaptic strengths of the EI population at the appropriate level.

In order to have a deeper insight into the dynamics of this interictal to ictal transition, we also explored the effect of cortical and sensory periodic (sinusoidal) inputs on the output of the extended and modified model. Our simulation results reveal that the transition from normal activity to seizure activity can occur when a perturbation in the dynamic structure of the brain relocates the brain state from interictal to preictal state. Our results show that during the preictal stage, brain is more susceptible to sensory and cortical inputs, that in turn, causes typical absence seizures. Moreover, the frequency response of the model brings to light the fact that brain responses to the cortical and sensory input are dependent on the initial stage of the brain. According to the bifurcation analysis depicted in Fig. 5, when brain is in its normal stage, it behaves as a linear resonator. On the other hand, when an impairment occurs in the glutamatergic receptors in the excitatory interneurons which causes the brain to enter the preictal stage, then the same sensory and cortical stimulations can cause the brain to act like a nonlinear resonator and we can observe chaotic behaviours and jump phenomenon. This nonlinear behaviour increases when the initial stage of the brain changes to the ictal stage. Also, we investigated the effect of the initial stage of the brain in the generation of absence seizure. As it can be seen in Fig.6, when brain is in its normal state, we can observe the low amplitude activities which correspond to normal background activity of the brain. However, by changing the brain state from normal to preictal state, we can observe that the absence seizures take place. These observations (in our simulation studies) can explain why the typical absence seizure happens during light NREM sleep in which brain activities slow down and altered states of the consciousness happen [53]. These observations, consequently, suggest that during the sleep, the state of brain can change and this might result in transition from normal state into the preictal state and later on into the absence seizure. Therefore, we suggest that alteration in the initial states of the brain can be considered as one of the main causes of the absence and photosensitive seizures.

Finally, we examined the role of thalamus in epileptic seizure activities. We investigated the role of cooperation of glutamatergic and GABAergic receptors of EI under the effect of thalamic relay nucleus (TC) in seizure generation and propagation. As it can be observed in Fig.4, the results have shown the dependence of cortical function on the thalamic one in initiation, propagation and termination of epileptic seizures. It is demonstrated that the information flow from thalamus to cortex can affect the pathological transitions which are in accordance with previous results [54, 55]. Recent studies [56, 57] did not consider the thalamus and its synaptic connectivity with other neuronal populations such as excitatory interneurons in the cortical models they worked with. However, based on the bifurcation analysis obtained from hybrid modulation of intra-EI excitatory and inhibitory synaptic strength in the extended neural mass model, the pathway from thalamic relay nucleus to the excitatory interneurons facilitates the transitions between different types of epileptic activities, either from interictal to ictal or between clonic, absence and tonic seizures. We believe these results provide useful insights for understanding more thoroughly the function and dynamics of transitions between inter-ictal to preictal and ictal states and can be used in epileptic seizure prediction and abatement.

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