

# Seizure Inhibition in an *In-Silico* Model of Epilepsy Applying BELBIC

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**Abstract**—Electrical onset of an epileptic seizure is characterized by low frequency and high amplitude rapid discharges at hippocampus. An intelligent controller based on emotional learning algorithm of the brain has been developed to abate this bursting activity. The control input has been applied to the lumped parameter model of epilepsy with the purpose of steering the epileptic spikes to normal activity. The results reveal that rapid discharges occurring at seizure onset can be manipulated by applying bounded stimuli to the model.

**Index Terms**—Epilepsy, Electrical stimulation, Emotional based learning, Intelligent control, *In-Silico* model.

## I. INTRODUCTION

ALMOST 50 million people worldwide are afflicted by epilepsy [1] and approximately one third are pharmacoresistant and cannot be sufficiently cured by medications [2]. On the other hand despite prosperity of surgically removing the seizure focus in ceasing focal seizures, probable side effects on brain structures abandons this therapeutic alternative [1], [2]. Reports on the effect of electrical currents on neural behavior and their success in seizure abatement have motivated many scientists to consider electrical stimulation therapies as a less invasive alternative for manipulating the epileptic activity [3], [4]. Several electrical stimulating protocols have been developed recently [5] but only a few have resulted in effective therapies [2]. Complexity and variety of seizure manifestations in addition to ambiguous neuronal mechanisms underlying seizure activity have been considered the main drawbacks regarding this dissatisfaction.

Evolution of therapeutic methods has been largely due to the employment of novel experimental and computational models of epilepsy. These models have improved our understanding of underlying neurophysiological mechanisms associated with initiation and propagation of seizures in the neural tissue [6]. However, unlike experimental *in-vivo* and *in-vitro* models which have been used extensively in developing distinctive curative methods for suppressing seizures [1], [3], [5], [7], computational *In-*

*silico* models have not been exploited [6]. In fact these models provide mathematical representations of neural activity during epilepsy from which stimulation strategies can evolve [3], [5], [8]. Moreover compared to experimental models, they do not need any particular preparation of brain slices and can be simply simulated via computers.

Incorporating novel achievements from computational neuroscience and control engineering can result in developing curative stimulation treatments. Following this idea, in their first attempt, the authors employed backstepping algorithm as a nonlinear Lyapunov-based recursive procedure to restrain undesired epileptic spikes in the normal brain activity [9]. The results revealed the capability of the method in moderately stopping the bursts but the main drawback was the infeasible electrical stimulation needed to reach this goal. Furthermore four control inputs were applied to the system which could be difficult in practical implementation of the algorithm. In order to overcome the aforementioned restrictions, in this paper we have extended another control approach established upon emotional learning algorithm of the brain to control the epileptic bursting.

Brain emotional learning based intelligent controller (BELBIC) is a model free approach established by Lucas et al. [10] based on a physiologically relevant computational model of learning procedure in the brain [11]. In fact discovering the vigorous role of emotions in making satisfactory and fast decisions encouraged them to adapt computational model of emotional learning in limbic system for control implementations. Results obtained from applying the algorithm to various applications indicate the efficiency of the method in regulating short time procedures because of its fast learning capability [12]-[14]. On the other hand, the stability of the algorithm has also been endorsed by cell to cell mapping method [15]. These features as well as the method's conspicuous performance in systems with uncertainties and complex dynamics make this algorithm plausible for elaborating an electrical stimulation technique to counteract seizure activity.

In this work we have initially simulated the neural behavior during an epileptic seizure employing a nonlinear lumped parameter model [16]. The model is in fact a modification of the neural population model proposed by Wendling et al. [17] which was previously used in [9]. In the next step the BELBIC controller has been used to inhibit the bursting behavior caused by abnormal hypersynchronization of neurons at the onset of a seizure. The simulation results of the *In-silico* lumped parameter model along with the applied controller are provided.

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## II. METHODS

## A. Computational neuronal population model

The model simulates the activity of a neural population. Each population is considered to consist of four interacting subpopulations namely: pyramidal cells, excitatory interneurons, slow dendritic inhibitory interneurons and fast somatic inhibitory interneurons. Each of these subsets is described with a second order nonlinear differential equation as described in (1).

$$\begin{cases} \dot{z}_{11} = z_{12} \\ \dot{z}_{12} = EXC.a.S(z_{21} - z_{31} - z_{41}) - 2az_{12} - a^2z_{11} \\ \dot{z}_{21} = z_{22} \\ \dot{z}_{22} = EXC.a.(p(t) + C_2.S(C_1z_{11}) - 2az_{22} - a^2z_{21} \\ \dot{z}_{31} = z_{32} \\ \dot{z}_{32} = SDI.b.C_4.S(C_3z_{11}) - 2bz_{32} - b^2z_{31} \\ \dot{z}_{41} = z_{42} \\ \dot{z}_{42} = FSI.g.C_7.S(C_5z_{11} - C_6z_{31}) - 2gz_{42} - g^2z_{41} \end{cases} \quad (1)$$

Where  $z_{11}$ ,  $z_{12}$  represent the dynamics of pyramidal cells,  $z_{21}$ ,  $z_{22}$  represent excitatory interneurons,  $z_{31}$ ,  $z_{32}$  simulate dendritic slow inhibitory interneurons and  $z_{41}$ ,  $z_{42}$  are characterizing somatic fast inhibitory interneurons. Average trans-membrane potential ( $v$ ) is related to the average pulse density of spikes at each neuron's output by an asymmetric sigmoid function ( $S(v)$ ) defined as  $S(v) = 2e^v / (1 + e^{v-\theta})$ . This average presynaptic signal is then transformed to postsynaptic action potential by a second order linear transfer function which stands for the synaptic effect of each neural subpopulation.

[*EXC*, *SDI*, *FSI*] and [ $a$ ,  $b$ ,  $g$ ] represent the synaptic gains and time constants for each neuronal group respectively.  $P(t)$  is a Gaussian white noise representing the effect of the neighbor neurons which enters the excitatory interneurons. Interneuron interactions are presented by means of seven connectivity constant  $C_1$  to  $C_7$ . The neural population activity is defined as the postsynaptic potential of the pyramidal cells and presented as in (2).

$$PA = z_{21} - z_{31} - z_{41} \quad (2)$$

The model is capable of reproducing a wide range of brain rhythms. This can be done by adjusting the population gains: *EXC* (excitation), *SDI* (slow dendritic inhibition) and *FSI* (fast somatic inhibition) [17]. In this work the parameters were chosen to reconstruct the data obtained from electrophysiological recordings of hippocampal neurons during an induced epileptic seizure. Each seizure period was divided into four distinct stages of transition from normal behavior to seizure activity namely: interictal, preonset, onset and ictal which differ in the density and frequency content of the rhythms observed [16].

"Interictal" segment is defined as the stage during which no high amplitude epileptic spikes is observed and is chosen about 1 minute before seizure starts. This period is preceded by "preonset" period when high amplitude bursts commence. The electrical "onset" of the seizure with beta

and low gamma frequency (15-40 Hz) bursting activity occurs 10-50 seconds after preonset segment and moves on to the "ictal" stage during which the seizure develops and rhythmic activity in theta and alpha band (4-10 Hz) is recorded.

## B. Brain emotional learning based intelligent controller (BELBIC)

Inspired by the fast decision making property of the mammalian brain, an intelligent controller was introduced by [10] based on the brain emotional learning algorithm. They exploited a computational model of limbic system [11] composed of the thalamus, sensory cortex, amygdala and orbitofrontal cortex. These parts have been historically considered to play a crucial role in processing emotions.

The first inputs to the structure are the afferent fibers bringing sensory information from different body structures. They enter BELBIC via thalamus and continue on to sensory cortex. In fact thalamus provides a coarse coding of the present sensory condition. This code enters both sensory cortex and amygdala. Sensory cortex provides more detailed analysis of the crude sensory information of thalamus and distributes the differentiated data to both amygdala and orbitofrontal cortex. The thalamus output is also projected to amygdala in order to help it produce a primary fast emotional reaction to the upcoming stimuli. Amygdala associates analyzed stimulus received from sensory cortex with an emotional value through classical emotional conditioning [15]. This emotional value is assigned, based on the reinforcing signal (*stress*) that enters the structure from environment and its biological origin is not known [11]. Since amygdala is incapable of forgetting the experienced emotional reaction once learned, orbitofrontal cortex takes the responsibility for correcting the unsatisfactory responses and inhibiting amygdala's reactions. It controls extinguishment of learning in amygdala by responding to elimination of expected reward or punishment.

As stated above the main learning process occurs within amygdala and orbitofrontal cortex. In fact the difference between the corresponding excitatory and inhibitory outputs of amygdala and orbitofrontal cortex assigned by  $A_i$  and  $OC_i$  form the control signal (*MO*) as shown in (3).

$$MO = \sum_i A_i - \sum_i OC_i \quad (3)$$

Respective outputs of amygdala and orbitofrontal cortex are estimated by multiplication of the sensory input (*SI*) with an adaptive plastic connection weight ( $V_i$  for amygdala and  $W_i$  for orbitofrontal cortex) as formulated in (4) and (5).

$$A_i = SI_i V_i \quad (4)$$

$$O_i = SI_i W_i \quad (5)$$

Thus the associative learning routine in amygdala and orbitofrontal cortex is performed by modifying these gains via rules given in (6) and (7).

$$\Delta V_i = \alpha [SI_i \max(0, stress - \sum_j A_j)] \quad (6)$$

$$\Delta W_i = \beta [SI_i \sum_j (MO - stress)].$$

Where  $\alpha$  and  $\beta$  are the respective learning rates of amygdale and orbitofrontal cortex. *Stress* represents the emotional value assigned, based on the reinforcing signal that enters each structure. As revealed in (6) a negative feedback loop reduces the learning signal once output reaches the stress signal. Furthermore monotony of weight assignment is illustrated in (6) which supports the idea of aforementioned disability of amygdale to forget a learned process. In order to implement this strategy to our neuronal model we constructed the closed loop control system as illustrated in Fig. 1.

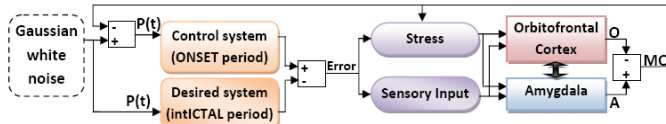


Fig. 1. Control system configuration using BELBIC.

The BELBIC control signal (*MO*) enters the excitatory interneurons. The purpose for choosing this site for applying the stimulus is that the electrical stimuli to a brain structure is in fact an excitatory arousal of the neural tissue and thus should be added to the excitatory effect of neighboring populations which is considered in the model via white noise. The sensory and stress signals have been defined as follows:

$$stress = |MO|(-W_1 \cdot e \cdot \dot{e} + W_2 \cdot |e|). \quad (8)$$

$$SI = W_3 \cdot e. \quad (9)$$

Where  $e$  stands for error signal defined as the difference between the simulated epileptic activity at seizure onset ( $PA_{ONSET}$ ) and the simulated desired interictal behavior ( $PA_{intICTAL}$ ) as shown in (10).

$$e = PA_{ONSET} - PA_{intICTAL}. \quad (10)$$

$W_1$ ,  $W_2$  and  $W_3$  are positive constants. In fact sensory input which will be reinforced or punished due to the stress signal is simply chosen as a proportional function of error. The stress signal has also been defined as suggested in [13]. This definition guarantees an increase in the stress signal in correspondence to decrease in error which results in enhancement of amygdale gains. On the other hand increase in error level will cause decrease in stress and thus intensification of orbitofrontal inhibitory gains. The error derivative is also included to eliminate the offset error.

### III. RESULTS

#### A. Simulation of epileptic activity

As briefly discussed in section II, the neuronal behavior during transition from normal neuronal background behavior (interictal period) to fast epileptic discharges (ictal period) have been reconstructed via a modified version of the lumped parameter computational model of epilepsy proposed by wendling [17]. Model equations (1) have been solved by numerical integration methods with fixed time

(7) step, equal to 5 milliseconds. Model parameters are set according to Table 1.

TABLE I  
MODEL PARAMETERS

Parameter	Value
a	100 s <sup>-1</sup>
b	30 s <sup>-1</sup>
g	350 s <sup>-1</sup>
C <sub>1</sub> , C <sub>7</sub>	135
C <sub>2</sub>	108
C <sub>3</sub> , C <sub>4</sub>	33.75
C <sub>5</sub>	40.5
C <sub>6</sub>	0.4
V <sub>0</sub>	6 mv
e <sub>0</sub>	2.5 s <sup>-1</sup>
r	0.56 mv <sup>-1</sup>
p(t)	Mean=90 pulses. s <sup>-1</sup> , SD=900 pulses. s <sup>-1</sup>

Synaptic population gains (*EXC*, *SDI* and *FSI*) for each segment have been set according to those identified by Wendling [17]. Fig. 2 depicts the simulated EEG activity at interictal and onset states as well as the power spectral density (PSD) of each segment.

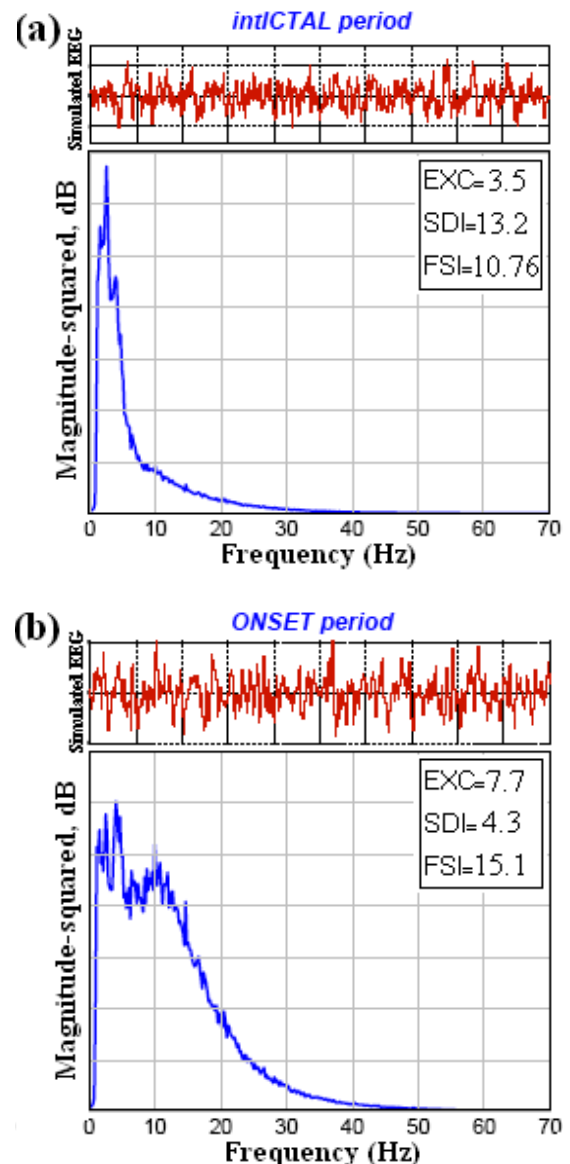


Fig. 2. Simulated EEG activity and power spectral density. (a) Interictal, (b) onset.

### B. Electrical stimulation

As mentioned in section II the BELBIC controller has been exploited to abate the epileptic bursting behavior due to its ability to defeat unidentified and complex dynamics as well as its fast learning rate. The inputs to this controller are stress and sensory signal which have been calculated from error between unwanted epileptic spikes at seizure onset and desired interictal behavior as presented in (8) and (9). Fig. 3 shows the results obtained from applying this algorithm to the neuronal model as shown in Fig.1.

Comparison between the closed loop PSD of the model output at onset period (Fig. 3a) with the one in the interictal period (Fig. 2a) shows that the applied control stimulus has successfully changed the behavior of the brain at onset period in a way that it resembles the normal brain rhythm in the interictal period.

Fig. 3b shows the control signal applied to the neural model. The total energy delivered to the brain structure is calculated as the root mean square of the control signal and is equal to 164 mV. The amplitude of the applied stimulus is approximately 100 mV which is tolerable for brain cells according to experiments performed on in-vitro brain slice preparations [5].

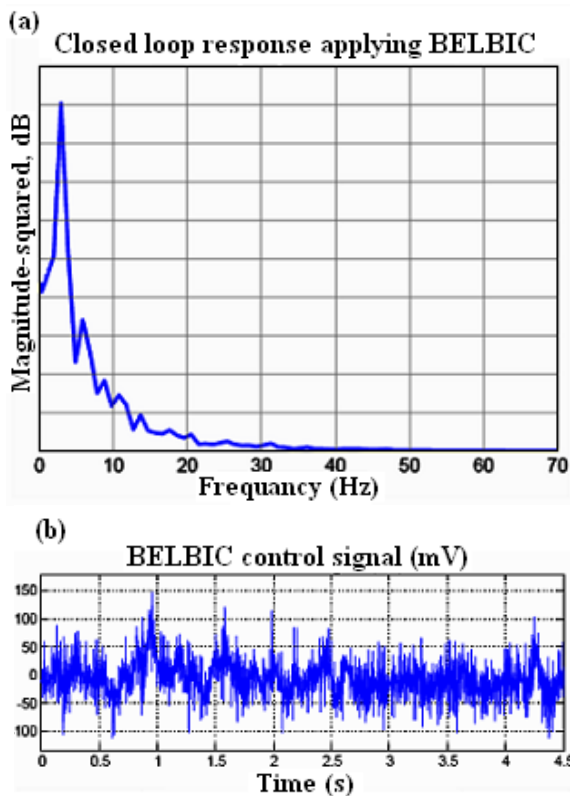


Fig. 3. BELBIC results. (a) closed loop power spectral density, (b) control signal.

### IV. CONCLUSION

The main purpose of this study was to investigate a control algorithm to restrain the epileptic seizures onset in the normal brain activity. The simulated EEG produced by the modified model described in (1), resembles that of real neural behavior recorded by intracerebral electrodes and then simulated by Wendling et al. [17].

Results show that applying the electrical stimuli derived from BELBIC algorithm to the neural population restores

the normal brain activity by redirecting the neural behavior from bursting activity at seizure onset to the normal low amplitude spikes at interictal state. BELBIC produces satisfactory results regarding both error and stimuli energy. Also despite the backstepping method reported at [9] only one stimulation site is needed which is desirable for practical implementations.

In this work we have used a single BELBIC cell. More investigations can be done on multi neuron BELBIC and also input sites for injecting the stimulus.

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