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A bio-inspired stimulator to desynchronize epileptic cortical population models: A digital implementation framework

Mohsen Piri [a,b], Masoud Amiri [c], Mahmood Amiri [c,*]

[a] Department of Electronic, College of Engineering, Kermanshah Science and Research Branch, Islamic Azad University, Kermanshah, Iran

[b] Department of Electronic, College of Engineering, Kermanshah Branch, Islamic Azad University, Kermanshah, Iran

[c] Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

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ABSTRACT

Pathophysiologic neural synchronization is a hallmark of several neurological disorders such as epilepsy. In addition, based on established neurophysiologic findings, astrocytes dynamically regulate the synaptic transmission and have key roles in stabilizing neural synchronization. Therefore, in the present study, based on the dynamic model of astrocyte, a digital bio-inspired stimulator is proposed to avoid the hyper-synchronous seizure-like activities in a cortical population model. The complete digital circuit of the close loop system that is the bio-inspired stimulator and the cortical population model are implemented in hardware on the ZedBoard development kit. Based on the results of MATLAB simulations, hardware synthesis and FPGA implementation, it is demonstrated that the digital bio-inspired stimulator can effectively prevent the occurrence of spontaneous paroxysmal episodes with a demand-controlled characteristic. In this way, the designed digital stimulator successfully maintains the normal ongoing activity.

1. Introduction

The brain is a complex network of interacting subsystems and synchronization plays an important role in its normal and abnormal functioning. Epilepsy is a well-known example for pathophysiologic neuronal synchronization, which is one of the most prevalent serious neurological disorders that affect more than 65 million people worldwide (Tejada, Costa, Bertti, & Garcia-Cairasco, 2013). It is characterized by a sudden occurrence of synchronous neural activity which is termed seizure or *ictal* event that impairs the normal function of the brain Amiri, Bahrami, & Janahmadi, 2011a; Amiri, Davoodi-Bojd, Bahrami, & Raza, 2011c; Lehnertz et al., 2009.

Deep brain stimulation (DBS) is a successful clinical therapy for patients with medically intractable neurological diseases (Bronstein et al., 2011; Kringelbach, Jenkinson, Owen, & Aziz, 2007). Recently, a feedback-based DBS has been tested in primate model of Parkinson disease (Rosin et al., 2011) and a rodent model of epilepsy (Berényi, Belluscio, Mao, & Buzsáki, 2012; Fisher et al., 2010; Sun, Morrell, & Wharen, 2008). In addition to DBS, other methods for suppression of synchrony have been proposed in the literature (Hauptmann, Popovych, & Tass, 2007; Luo, Wu, & Peng, 2009; Popovych & Tass, 2010). Rosenblum, Tukhlina, Pikovsky, and Cimponeriu (2006) proposed two control methods: direct control and differential control, based on the time-delayed feedback via the mean field, to suppress synchrony in a network of globally coupled oscillators. A linear feedback loop with a built-in, second-order filter to desynchronize an ensemble of all-to-all interacting units has been proposed by Tukhlina and Rosenblum (2008). Hauptmann and colleagues in (2005; 2007) and Omel'chenko, Hauptmann, Maistrenko, and Tass (2008) introduced the demand-controlled desynchronization technique using a multisite delayed feedback stimulation. In line of this research, impacts of the mixed nonlinear delayed feedback control on desynchronization were studied by Popovych and Tass (2010). On the other hand, feedback-based stimulator can be categorized into static and dynamic ones. In dynamic stimulators, the stimulation signal is the output of a system consisting of a set of ordinary differential equations. Although these stimulators are difficult to construct, their dynamics can compensate the undesired synchrony in dynamics of oscillators more effectively (Montaseri, Yazdanpanah, Pikovsky, & Rosenblum, 2013).

Neuromorphic VLSI is an important tool for investigating and implementing neural algorithms. The analog VLSI implementation

* Correspondence to: Parastar Ave., Kermanshah University of Medical Sciences, Kermanshah, Iran. Tel.: +98 83338237033.
E-mail address: ma.amiri@ece.ut.ac.ir (M. Amiri).

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of neural network in silicon (Indiveri & Horiuchi, 2011) offers high computational power at the expense of flexibility and design iteration times. Although VLSI implementation can provide high processing speed and compact structures, it is more time consuming and cannot be reconfigured easily (Wijekoon & Dudek, 2012). Therefore, it is necessary to have a rapid prototyping platform for neural models with similar flexibility to general purpose microprocessors. Field-programmable gate arrays (FPGA) hardware is an ideal technology to achieve these requirements (Rice, Bhuiyan, Taha, Vutsinas, & Smith, 2009). Its stability, reliability, and flexibility are interesting features to use FPGAs for designing neuromorphic systems (Li, Cheung, Chan, Song, & Berger, 2013). Recently, some researchers have made full use of parallelism characteristics of FPGA to process neural signal and dramatically improved the computation speed (Graas, Brown, & Lee, 2004). Recent experimental findings confirm the functional contribution of *astrocytes* in neural synchronization (Amiri, Bahrami, & Janahmadi, 2012a, 2012c; Amiri, Hosseinmardi, Bahrami, & Janahmadi, 2013a) and their abilities to regulate and stabilize the neural activities by providing appropriate feedback (Fellin, 2009). Astrocytes are the most abundant type of *glial* cells and perform a variety of tasks. Not only they control the content of extracellular fluid and regulate neurotransmitter release (Halassa, Fellin, & Haydon, 2009) but also they "*listen and respond*" to the synapse and act as a third active element of the synapse (Kanski, van Strien, van Tijn, & Hol, 2014). Motivated by this, in the current research a digital hardware platform of bio-inspired stimulator to desynchronize a cortical population model (CPM) is presented. The CPM consists of excitatory pyramidal neuron and inhibitory interneuron subpopulations and is constructed at an intermediate level (Suffczynski, Kalitzin, & Lopes Da Silva, 2004). It should be pointed out that there is strong experimental evidence that the cortex has a critical role in seizure generation (Destexhe, 2008; Steriade & Contreras, 1998). A purely cortical hypersynchronized oscillation was observed in the experiments with isolated cortex or athalamic preparations in cats where a complete thalamectomy was performed (Steriade & Contreras, 1998).

Similar to Luo et al. (2009), Montaseri et al. (2013) and Tukhlina and Rosenblum (2008) the bio-inspired stimulator is a dynamic stimulator. We use the astrocyte mathematical model proposed by Montaseri, Yazdanpanah, and Amiri (2011) which is a simplified version of the astrocyte biophysical model developed by Postnov, Koreshkov, Brazhe, Brazhe, and Sosnovtseva (2009). We have implemented a functional approach for the closed loop system and develop not only a digital circuit for the bio-inspired stimulator but also for the CPM as well. The open loop (CPM) and the closed loop system (bio-inspired stimulator with the CPM) are first simulated in MATLAB. Next, the designed digital circuits for the open and close loop systems are synthesized and finally they are implemented in hardware using ZedBoard development kit. The results of the FPGA implementation are in agreement with those of ModelSim and MATLAB simulations and verify that the bio-inspired stimulator could be a candidate as a new DBS technique.

The outline of this paper is organized as follows: the cortical population model and the proposed bio-inspired stimulator are explained in Sections 2 and 3 respectively. The designed digital circuits for the open loop and closed loop system are described in Section 4. The MATLAB, Verilog simulations and FPGA implementations are presented in Section 5. Finally, Section 7 concludes the paper.

2. Cortical population model

Computational models of cortical and corticothalamic circuits have been increasingly employed to explain a variety of healthy and dysfunctional states. In this study, we consider cortical neural

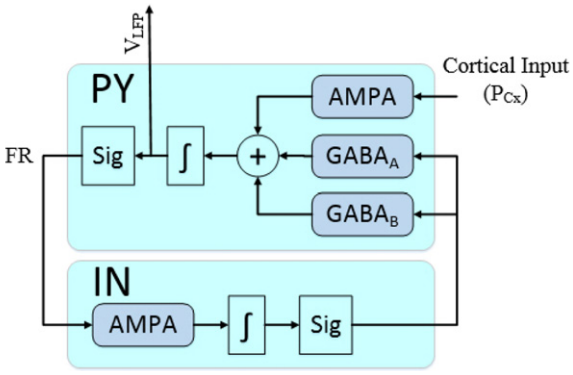

Fig. 1. The block diagram of cortical population model which consists of excitatory pyramidal (PY) and inhibitory interneuron (IN) subpopulations. Cortical input $P_{Cx}(t)$ is modeled by white Gaussian noise with nonzero mean and is the output of other cortical pyramidal neurons not considered in the population. The output of the CPM is the mean membrane potential of the pyramidal cells which simulates experimental recordings of the local field potentials (LFP). FR represents the firing rate.

population model based on the thalamocortical model proposed by Suffczynski et al. (2004); Suffczynski, Kalitzin, and Lopes da Silva (2008).

Recent experimental studies established the cortical origin of epileptic seizures. For example, injection of high doses of $GABA_A$ (γ-aminobutric acid) antagonists such as bicuculline to the cortex, without any change in thalamus, resulted in seizure activities (Steriade & Contreras, 1998). Furthermore, the threshold for epileptogenesis was much lower in the cortex compared to the thalamus. For a comprehensive review, in the involvement of cortical circuits in seizure generation, interested readers can refer to Destexhe (2008) and Frohlich, Timofeev, Sejnowski, and Bazhenov (2008). These experiments confirm the importance of the cortex in generating seizure, although both cortex and thalamus are required for generating the typical spike-and-wave patterns of generalized seizures (Frohlich et al., 2008).

A cortical population model (CPM) consists of excitatory pyramidal (PY) and inhibitory interneurons (IN) subpopulations. The interaction between these subpopulations is facilitated via AMPA (α-amino-3-hydroxy-5-methyl-4isoxazolepropionic acid) mediated excitatory synapses and $GABA_A$ and $GABA_B$-mediated inhibitory synapses. The schematic diagram of the CPM is shown in Fig. 1 (Suffczynski et al., 2004, 2008). Each neural subpopulation is described by two variables: membrane potential and firing rate (FR). Cortical input $P_{Cx}(t)$ is modeled by non-zero mean white Gaussian noise and is the output of other cortical pyramidal neurons not considered in the population. The output of the CPM ($V_{LFP}(t)$) is the mean membrane potential of the pyramidal cells which simulates experimental recordings of the local field potentials (LFP). It should be pointed out that the aim of this type of modeling is not to reproduce the exact brain output. Instead, the goal is to capture the essential functional parts of its operation. Selecting suitable value of $\langle P_{Cx} \rangle$, the mean value of signal, the CPM demonstrates normal activity. For further details, the reader can refer to Suffczynski et al. (2004); Suffczynski, Wendling, Bellanger, and Lopes Da Silva (2006).

The membrane potentials of the pyramidal and interneuron subpopulation are described as follows:

$$C_m \frac{dV^{(i)}}{dt} = -\sum I_{syn}^{(i)} - g_{leak}\left(V^{(i)} - V_{leak}^{(i)}\right) \quad (1)$$

$$I_{syn}^{(i)} = g_{syn}\left(V^{(i)} - V_{syn}\right) \quad i = \{PY, IN\}$$

$$syn = \{AMPA, GABA_A, GABA_B\} \quad (2)$$

where V is the membrane potential, C_m denotes the membrane capacitance, g_{leak} is the leak current conductance, g_{sym} is the synaptic