Designing a deep brain stimulator to suppress pathological neuronal synchrony

Ghazal Montaseri\textsuperscript{a,b}, Mohammad Javad Yazdanpanah\textsuperscript{c,*}, Fariba Bahrami\textsuperscript{d}

\textsuperscript{a}Advanced Control Systems Laboratory, School of Electrical and Computer Engineering, College of Engineering, University of Tehran, Tehran, Iran.
\textsuperscript{b}Department of Systems Immunology, Helmholtz Centre for Infection Research, Braunschweig, Germany.
\textsuperscript{c}Advanced Control Systems Laboratory, Control and Intelligent Processing Center of Excellence, School of Electrical and Computer Engineering, College of Engineering, University of Tehran, Tehran, Iran.
\textsuperscript{d}Human Motor Control and Computational Neuroscience Laboratory, Control and Intelligent Processing Center of Excellence, School of Electrical and Computer Engineering, College of Engineering, University of Tehran, Tehran, Iran.

Abstract

Some of neuropathologies are believed to be related to abnormal synchronization of neurons. In the line of therapy, designing effective deep brain stimulators to suppress the pathological synchrony among neuronal ensembles is a challenge of high clinical relevance. The stimulation should be able to disrupt the synchrony in the presence of latencies due to imperfect knowledge about parameters of a neuronal ensemble and stimulation impacts on the ensemble. We propose an adaptive desynchronizing deep brain stimulator capable of dealing with these uncertainties. We analyze the collective behavior of the stimulated neuronal ensemble and show that, using the designed stimulator, the resulting asynchronous state is stable. Simulation results reveal the efficiency of the proposed technique.

Keywords: Adaptive structure, Desynchronizing stimulation, Hindmarsh-Rose neural networks.

\quad *Corresponding author. Tel.: +982182084925

Email addresses: montaseri@theoretical-biology.de (Ghazal Montaseri), yazdan@ut.ac.ir (Mohammad Javad Yazdanpanah), fbahrami@ut.ac.ir (Fariba Bahrami)
1. Introduction

When self-sustained oscillators couple to each other, they adjust their individual rhythms such that they all oscillate with a common frequency. This phenomenon is called synchronization which is observed in physical, social phenomena and many biological systems like neuronal ensembles which are of special interest in this paper. Although synchronization of neurons plays an important role in movement control (Cassidy, Mazzone, Oliviero, Insola, Tonali, Lazzaro & Brown, 2002), memory (Klimesch, 1996) and vision (Sompolinsky, Golomb & Kleinfeld, 1991), diseases such as Parkinson’s diseases (PD) (Alberts, Wright & Feinstein, 1969; Paré, Curro’Dossi & Steriade, 1990; Lenz, Kwan, Martin, Tasker, Dostrovsky & Lenz, 1994; Tass, 1999), essential tremor (Kane, Hutchison, Hodaei, Lozano & Dostrovsky, 2009) and epileptic seizures (Milton & Jung, 2003) are believed to be related to pathological synchronization of neurons. In the line of therapy, the main objective is to suppress the collective synchrony.

Deep Brain Stimulation (DBS) is a successful clinical therapy for patients suffering from the mentioned diseases that their symptoms cannot be controlled only by using conventional pharmaceutical treatments. Applying DBS, selected areas of the brain (depending on the type of the disease, e.g., the globus pallidus of the basal ganglia in PD) are stimulated by a train of pulses (with a frequency of, e.g., 120Hz in PD) applied via implanted microelectrodes (Benabid, Pollak, Gervason, Hoffmann, Gao, Hommel, Perret & de Rougemont, 1991; Chkhenkeli, 2003; Kringelbach, Jenkinson, Owen & Aziz, 2007; Bronstein, Tagliati, Alterman, Lozano, Volkman, Stefani, Horak, Okun, Foote, Krack, Pahwa, Henderson, Hariz, Bakay, Rezai, Marks, Jr, Moro, Vitek, Weaver, Gross & DeLong, 2011). Despite clinical success of DBS, its exact mechanism is not fully understood (Hammond, Ammari, Boulac & Garcia, 2008), and its parameters are tuned empirically. In addition, constant stimulation of the brain tissue results in fast discharge of batteries of the stimulator. In general, DBS has limitations and side effects, like speech problems and involuntary muscle contractions. All these facts have encouraged experimentalists to search for more efficient stimulation mechanism.

In its present form, a DBS system is an open-loop pulse generator. However, recently, researchers have tested feedback-based DBS in a primate model of PD (Rosin, Slovik, Mitelman, Rivlin-Etzion, Haber, Israel, Váadia & Bergman, 2011) and feedback transcranial electrical stimulation in a rodent model of epilepsy (Berényi, Belluscio, Mao & Buzsáki, 2012).
Besides these empirical results, there are some theoretical (mathematical)
approaches which can be divided into two groups: the first group are non-
feedback methods which are based on the idea of phase resetting (Tass, 1999,
2001, 2002a,b, 2003; Lysyansky, Popovych & Tass, 2011). The second group
takes advantages of the feedback theory and is pioneered by Rosenblum and
Pikovsky (Rosenblum & Pikovsky, 2004a). The feedback-based techniques
also consist of two subdivisions: 1) delayed feedback techniques (Rosenblum
& Pikovsky, 2004a,b) and their variants (Hauptmann, Popovych & Tass,
2005, 2007; Popovych, Hauptmann & Tass, 2005, 2006, 2008; Omel’chenko,
Hauptmann, Maistrenko & Tass, 2008; Popovych & Tass, 2010; Guo & Rubin,
2011); and 2) non-delayed feedback methods (Tukhлина, Rosenblum,
Pikovsky & Kurths, 2007; Tukhлина & Rosenblum, 2008; Tukhлина, Rosen-
blum & Pikovsky, 2008; Luo, Wu & Peng, 2009; Luo & Xu, 2011; Franci,
Chaillot, Panteley & Lamnabhi-Lagarrigue, 2012; Montaseri, Yazdanpanah,
Pikovsky & Rosenblum, 2013b; Montaseri, Adhami-mirhosseini & Yazdan-
panah, 2013a, 2014).

In (Montaseri, Adhami-mirhosseini & Yazdanpanah, 2013a, 2014), we
solved the desynchronization problem assuming the known effect of stimu-
lator on the Stuart-Landau oscillators. However, in many stimulated popu-
lations, the “exact” mechanism of interaction between the desynchronizing
stimulator and the population is not “completely” known. In (Montaseri,
Yazdanpanah, Pikovsky & Rosenblum, 2013b), to tackle unknown impacts
of stimulation, we introduced the idea of using adaptive desynchronizing
scheme. In neuronal populations, this uncertainty seems more crucial; e.g.,
when an electrode is implanted deeply into a nuclei it is not clear whether
the stimulation affects only the membrane voltage of neurons or it influences
the gating variables. In addition, it is not exactly known how the effect of
stimulation decreases with the distance from the electrode. McIntyre and his
group have been working on disentangling the ambiguity on the stimulation
impact (see (McIntyre, Grill, Sherman & Thakor, 2004)). However, in this
study, we describe mathematically the ambiguity (uncertainty) in the whole
system as an uncertain parameter of the system model.

The stimulator we want to design not only should work based on general
models of emergent collective activity, but also should handle system un-
certainties. Furthermore, some neurological considerations, imposed in the
design procedure, motivated us to develop a new adaptive structure compared
to what was proposed in (Montaseri, Yazdanpanah, Pikovsky & Rosenblum,
2013b). The structure of the stimulator is based on a model originally pro-
posed in (Montaseri & Yazdanpanah, 2014). In this study, using the idea of adaptive scheme proposed in (Montaseri, Yazdanpanah, Pikovsky & Rosenblum, 2013b), we modify the model and introduce an adaptive parameter. Finally, the resulting model with the adaptive parameter constructs the main core of the proposed stimulator. Compared to (Montaseri, Yazdanpanah, Pikovsky & Rosenblum, 2013b), although both simulators take advantages of adaptive property, the basis of designing their structures are different. In addition, satisfying some neurological considerations is one of the outstanding features of the stimulator designed in this work.

The paper is organized as follows. In Section 2, incidence of synchronous and asynchronous oscillations in a neuronal ensemble is investigated. In Section 3, first, we propose the adaptive desynchronizing stimulator and, then, we apply the stimulation to a neuronal ensemble. We analyze the stability of the asynchronous state in the stimulated population in Section 4. Finally, Section 5 concludes the paper.

2. Synchronous and asynchronous oscillations in a neuronal ensemble

Consider an ensemble of \( N \) all-to-all synaptically coupled neurons. We describe each neuron of the ensemble by the Hindmarsh-Rose model (Hindmarsh & Rose, 1984):

\[
\begin{align*}
\dot{x}_i &= 3x_i^2 - x_i^3 + y_i - z_i + I_i - \frac{C}{N-1}(x_i + V_e) \sum_{j \neq i}^N \left[ 1 + e^{\left( \frac{x_j - x_0}{\eta} \right)} \right]^{-1}, \\
\dot{y}_i &= -5x_i^2 - y_i + 1, \\
\dot{z}_i &= r[\nu(x_i - \chi) - z_i],
\end{align*}
\]

\( i = 1, 2, \ldots, N \). Where \( x_i \) is the membrane potential. Variables \( y_i \) and \( z_i \) model the fast and slow ion channel conductances, respectively. \( y_i \) is called spiking variable and \( z_i \) is the bursting variable. All variables in (1) are dimensionless. \( I_i \) stands for the background current entering the neuron. It has a Gaussian distribution with the mean value \( \bar{I} \) and the root mean square (rms) value \( \sigma \). The background current affects the oscillation frequency. The parameters \( r, \nu \) and \( \chi \) in the \( z_i \) dynamic determine which oscillatory behavior, spiking or bursting, the Hindmarsh-Rose model exhibits. In this paper, we set \( r = 0.006, \nu = 1 \) and \( \chi = -1.56 \) for spiking and \( r = 0.006, \nu = 4 \) and \( \chi = -1.6 \) for bursting.
We assume that spatially distinct neurons in the large network are synaptically linked to each other by long axons. In (1), inhibitory synaptic coupling is modeled by the term 

\[-C N^{-1} (x_i + V_c) \sum_{j \neq i} \left[ 1 + e^{\left(\frac{x_j - x_0}{\eta}\right)}\right]^{-1}\]

Where \(C\) is the coupling strength and \(V_c\) is the reverse potential. Note that, the considered all-to-all (globally) coupled network is a simplification of a more realistic case with a certain degree of local connectivity which is observed e.g., in the basal ganglia. The nominal values of synapse parameters are taken as: \(V_c = 1.4\), \(\eta = 0.01\) and \(x_0 = 0.85\).

For zero coupling (i.e., \(C = 0\)), each neuron shows its regular spiking or bursting activity. So, each neuron fires with the frequency depending on \(I_i\).

We define \(X = N^{-1} \sum_{i=1}^{N} x_i\) as a measure of the ensemble collective behavior. Incoherent collective activity of neurons leads to small fluctuation of \(X\) with the rms value proportional to \(\sqrt{N}^{-1}\). However, when \(C\) increases, neurons adjust their oscillations with each other such that asynchronous oscillations will be synchronized. Synchronous oscillations of neurons result in nonzero oscillation of \(X\). Therefore, by increasing \(C\) small fluctuation of \(X\) transits to oscillation with frequency equal to mean value of neurons frequencies. This phenomenon is called “Kuramoto transition” (Kuramoto, 1984; Pikovsky, Rosenblum & Kurths, 2001; Acebron, Bonilla, Vicente, Ritort & Spigler, 2005).

Synchronous and asynchronous oscillations of the neurons are shown in Fig. 1. For simulation, we consider \(N = 200\) Hindmarsh-Rose neurons (1). In the left panels, spiking activities are considered. We set \(\bar{I} = 6\) and \(\sigma = 0.1\). As it can be seen, for \(C = 0\) two arbitrary chosen neurons in the population oscillate asynchronously. Small fluctuation of \(X\) around 0.4 verifies presence of incoherent oscillations. For \(C = 0.6\) strongly coupled oscillators become synchronized and \(X\) displays oscillation with frequency \(\omega_0 = 2\pi/3.2\).

The neuron model (1) with \(I_i = 3.2\) and the previously introduced bursting parameters exhibits chaotic bursting, i.e., generation of action potentials (spikes) alternates with the epochs of quiescence, so that the oscillation can be characterized by two time scales.

In a population of bursting neurons, two types of synchronization may occur: burst synchronization which refers to coincidence between active (oscillation) phase onset and offset times of neurons, and spike synchronization which describes coincidence of spikes generated by bursting neurons during
their active phases. In this study, burst synchronization is of more relevance since it is observed in the basal ganglia of PD patients (Bergman, Feingold, Nini, Raz, Slovin, Abeles & Vaadia, 1998).

The asynchronous and synchronous bursting oscillations are figured in the right panels, respectively. When $C = 0.2$, $X$ shows a low frequency modulation with the average frequency of $\omega_0 = 2\pi/176$. However, some high frequency jitter is observed in $X$ (see $X$ in panel (d)). As explained in (Tukhlina, Rosenblum, Pikovsky & Kurths, 2007), the reason is that the synchronized chaotic bursting neurons burst nearly at the same time (burst synchronization), whereas the spiking within bursts is not synchronous (but not spike synchronization). Via the averaging in calculating $X$, the spiking within bursts is mostly average out. However, correlations in spiking lead to some high frequency jitter.

3. Suppression of neuronal synchronous oscillations via adaptive deep brain stimulator

In this paper, we focus on the most potential application of the desynchronization problem, i.e., in neuropathologies. The special application needs a specific model which is the ensemble of coupled neurons (introduced in Section 2). In addition, in the design procedure, some special considerations arise which satisfying them is added to the specificity of the design. In the line of designing an efficient desynchronizing stimulator, first, in Subsection 3.1, the structure of the stimulator is designed and then, in Subsection 3.2, we apply the proposed stimulation to the Hindmarsh-Rose neural network.

3.1. Adaptive stimulator design

Consider again Hindmarsh-Rose neuron model (1). It requires some modifications to model an stimulated neuron. Generally, the mechanism that how brain stimulations affect neurons is not fully understood. This leads to ambiguities about the incorporation of the stimulation $u$ into model (1). In what follows, we try to define an appropriate framework to overcome this latency. The first concern is whether all neurons receive the same stimulation signal. In this regard, we assume that the designed stimulator is administered to the stimulated neurons via a single depth electrode implanted in the brain. So, as stated in (Popovych, Hauptmann & Tass, 2008), in a first approximation, all stimulated neurons sense the same signal from the single implanted electrode.
The next concern is whether the stimulation only affects the membrane voltage of a neuron or it has some direct influences on the dynamics of ion channel conductances. In (Hauptmann, Popovych & Tass, 2005; Popovych, Hauptmann & Tass, 2006, 2005; Tukhlina, Rosenblum, Pikovsky & Kurths, 2007; Hauptmann, Popovych & Tass, 2007; Luo, Wu & Peng, 2009; Luo & Xu, 2011), the effect of $u$ is considered only on the dynamics of the membrane voltage. Here, we hypothesize that in addition to the dominant impact of the stimulation is on the dynamics of the membrane voltage ($x$), the fast ion channel conductance ($y$) is also affected by the stimulation.

Considering the mentioned assumptions, we propose model of the stimulated neuron as:

\[
\begin{align*}
\dot{x}_i &= 3x_i^2 - x_i^3 + y_i - z_i + I_i - \frac{C}{N-1}(x_i + V_c)\sum_{j \neq i}^{N} \left[ 1 + e^{(x_j - x_0) / \eta} \right]^{-1} + u \cos \theta, \\
\dot{y}_i &= -5x_i^2 - y_i + 1 + u \sin \theta, \\
\dot{z}_i &= r[\nu(x_i - \chi) - z_i],
\end{align*}
\]

where $\theta$ is an unknown possibly time-variant parameter which shows the uncertainty in the impact of $u$ on neurons. The sinusoidal functions of $\theta$ are used as unknown multipliers of the stimulation signal $u$. In the $x$-dynamics, $u$ -as an external current- is added to the background current $I$. We assume that $u$ is incorporated in the $y$-dynamics additively as well. We consider $\theta \in (-\pi/4, \pi/4)$ to emphasize that the main impact of the stimulation is on the voltage variable.

The stimulation signal $u$ is distributed in the $x$ and $y$ dynamics of (2) by the sinusoidal multipliers. Since $(u \cos \theta)^2 + (u \sin \theta)^2 = u^2$, it is concluded that: 1) the total impact of $u$ is fixed for all $\theta$; and 2) the stimulation contributes in the both dynamics in a complementary manner with respect to $u^2$. Note that, stimulation coefficients are not unique. However, they must be continuous and bounded functions of $\theta$ and also satisfy the complementary condition.

To construct a stimulation, we need a signal that reflects the collective activity of the population. we assumed that using an extracellular electrode, the Local Field Potential (LFP) -which contains the neuronal activities- is measured. As mentioned in (Tukhlina, Rosenblum, Pikovsky & Kurths, 2007), the measured signal, in a first approximation, can be considered as the total membrane currents including the current due to the stimulation. According
to (2), the total current is \( \sim \sum_{i=1}^{N} \dot{x}_i \). So, we define \( m = N^{-1} \sum_{i=1}^{N} \dot{x}_i \) as the measured signal from the population.

Figure 2 illustrates the schematic representation of the neuronal population under the proposed stimulator. First, \( m \) is band-pass filtered through the second order filter
\[
\begin{align*}
\dot{\nu}_1 &= \nu_2, \\
\dot{\nu}_2 &= m - \omega_0^2 \nu_1 - \delta \nu_2,
\end{align*}
\]
where the damping factor \( \delta \) determines the width of the band pass and \( \omega_0 \) is chosen to be close to the mean frequency of the coupled neuronal population which can be easily measured in the experiment. Then, the filtered signal \( m_f \triangleq \delta \nu_2 \) feeds stimulator (4), we have recently proposed in (Montaseri & Yazdanpanah, 2014).

\[
\begin{align*}
\dot{\gamma} &= -k_1 \gamma + k_2 s + k, \\
\dot{s} &= (1 + \tanh[k_3(m_f - k_4)]) (1 - s) - k_5 s,
\end{align*}
\]

To compensate the latency in the impact of the stimulation, we modify the structure of the model (4) to:
\[
\begin{align*}
\dot{\gamma} &= -k_1 \gamma + k_2 s + k, & \gamma(0) = 0, \quad (5a) \\
\dot{s} &= [1 + \tanh(k_3(m_f - k_4))] (1 - s) - k_5 s, & s(0) = 0, \quad (5b) \\
\dot{k} &= k_6 s, & k(0) = 0. \quad (5c)
\end{align*}
\]

Comparing (5) with (4) indicates that the constant parameter \( k \) in (4) now evolves based on the ordinary differential equation (ODE) (5c). In fact, model (5) is a modification of (4) in which \( k \) has an adaptive character. This model makes the second block of the proposed desynchronizing scheme. The adaptive parameter \( k \) has no impact on the \( s \)-dynamics. As explained in (Montaseri & Yazdanpanah, 2014), \( s \) exponentially increases from zero to \( \bar{s} = \frac{M}{M+k_5} \). Thus, \( k \) strictly grows from zero with the growth rate \( k_6 \) which increases the steady state value of \( \gamma \) (recall, \( \bar{\gamma} = \frac{k_1 k_5 \bar{s}}{k_1} \)).

Finally, the stimulation signal or the control law is designed as:
\[
u = -\gamma m_f.
\]

In (6) \( \gamma \) acts as an “adaptive gain”. The stability analysis of the controlled system (2)-(6) will be done in the next section. Here, we simply explain the
mechanism of the designed stimulator. When neurons are synchronized, \( m \) and thus \( m_f \) show large oscillations. Therefore, \( s \) starts increasing exponentially from zero which switches on the evolution of \( k \). The dynamics of \( s \) and \( k \) change the adaptive gain of the controller until it can suppress or desynchronize the collective synchrony. Onset of desynchronization leads to small fluctuations of \( m_f \) which are below the cutoff threshold \( k_4 \). As a result, \( s \) switches off by the rate \( k_5 \) and \( k \) settles down to its steady state value \( \bar{k} \). Consequently, \( s \) is a switch with the cutoff threshold \( k_4 \) and \( k \) is an intermediate gain which controls the steady state value of the adaptive gain \( \gamma \).

Different values of \( \theta \) lead to different collective behaviors. For each, different \( \gamma \) is required to break the collective synchrony. In (Montaseri & Yazdanpanah, 2014), we calculate the upper bound of \( \gamma \) as \(|\gamma| \leq \frac{1}{k_1} \left[ k + \frac{2k_2}{2+k_5} \right] \). So, the adaptive gain depends directly to \( k \). Since the sufficiently large value of \( \gamma \) is required for desynchronization, which is generally unknown, we add the \( \gamma \)-dynamics to propose a self-tuning mechanism for selecting appropriate values of the adaptive gain \( \gamma \). In this mechanism, the adaptive block senses the collective behavior reflected in \( m_f \) and adapts itself such that the desired asynchronous state is achieved.

**Remark 1.** The proposed stimulation signal emerges from the origin (at \( t = 0, \gamma = 0 \) and thus, \( u = 0 \)) then, grows gradually and finally, settles down again at the origin (more exactly, at the level of the noise due to the finite size-effect). During its lifetime it suppresses synchronized oscillations. In the context of neuroscience, the stimulator takes advantages of two important properties: 1) Since the stimulation affects neurons gradually and smoothly, it avoids undesired sudden impacts on the natural behavior of the stimulated neurons. 2) The stimulation is vanishing (or demand-controlled); it means, on the one hand, the maintenance of the desired asynchronous state needs no control efforts; and on the other hand, the stimulation intervention into the living tissue is temporary.

**Remark 2.** The remarkable property of the proposed stimulator is adaptation though vanishing. The adaptation originates from the dynamic (ODE-based) structure of \( \gamma \). In response to variations of system parameters, static controllers with predetermined and constant parameters fail to compensate the changes, whereas self-tuning controllers are able to re-tune their parameters in order to adapt themselves to the new situations. This is the prominent
feature of the proposed adaptive stimulator compared to the feedback and non-feedback-based stimulators (with static gains) presented in the Introduction.

Remark 3. To achieve the desired asynchronous state and its maintenance, the stimulator needs only the measured signal by the recording electrode. To make the control action, there is no any dependency to the neuron parameters except for the frequency of the ensemble $\omega_0$ (used in (3)) which can be easily determined from the data.

Remark 4. Regarding the impact of a stimulation on a neuronal model, the conventional assumption is that the stimulation $u$ affects only the voltage dynamics of the neurons. In this case, fast ion channel conductances ($y_i$) sense impact of $u$ indirectly and through the voltage-mediated interaction. Setting $\theta = 0$, model (2) can retrieve this case. However, here, we add direct impact of $u$ in the $y$-dynamics to highlight the capability of the proposed stimulation in handling not only the indirect but also the direct impact of $u$ on the dynamics of the fast ion channels. In addition, as mentioned before, we consider $\theta \in (-\pi/4, \pi/4)$ to emphasize the dominant role of $u$ on the $x$-dynamics.

Remark 5. The designed stimulator and the previously proposed one in (Montaseri, Yazdanpanah, Pikovsky & Rosenblum, 2013b) (Eqs. (14)-(18)) both are the same in the band-pass filter and the switch mechanism in their structures. While the band-pass filter does the preliminary mission of preparing an appropriate input from the raw measurement, the switch plays an important role in the efficiency of the stimulator. Compared to the stimulator in (Montaseri, Yazdanpanah, Pikovsky & Rosenblum, 2013b), here, the stimulator takes advantages of the dynamic switch with the tunable parameter $K_5$. This parameter is responsible to adjust speed of switching, which can reduce 1) directly the transient time before onset of asynchronous state and/or 2) indirectly the energy of the stimulation signal.

3.2. Applying the adaptive stimulator to the neuronal ensemble

In this subsection, we investigate the capability of the stimulator described by (3)-(6) in desynchronizing the coupled neurons (2). First, we consider Hindmarsh-Rose neurons (2) with spiking activity and $\theta = -\pi/8$. The controller parameter values are: $\omega_0 = 2\pi/3.2$, $\delta = 2\omega_0$, $k_1 = 1$, $k_2 = 1$, $k_3 = 1000$, $k_4 = 0.13$, $k_5 = 10$ and $k_6 = 0.1$. The simulation results are plotted in Fig. 3.
First, consider $t < 250$ in which we select nominal values for the synapse parameters. The stimulator is switched on at $t = 50$. Recall that $X = N^{-1} \sum_{i=1}^{N} x_i$. Figures 3(a),(b) demonstrate that the stimulation changes the synchronous oscillations (reflected in large oscillation amplitude of $X$ and $\dot{X}$) to the asynchronous oscillations (reflected in fluctuation of $X$ and $\dot{X}$). Figure 3(c) depicts the time evolution of the stimulation signal $u$. $u$ increases from zero and when the asynchronous state is achieved, it vanishes to the noise level. Figures 3(e)-(g) show behavior of two arbitrary chosen neurons before, exactly after and some times after applying the stimulation, respectively. Comparison of these figures reveals that the stimulation breaks the synchrony without any undesired effect on the individual neurons.

For $250 \leq t < 450$, we assume that the coupling parameters increase from the nominal values to $C = 0.75$, $V_c = 1.5$ and $x_0 = 0.95$. These new parameters elevate the unstimulated synchrony level to hypersynchronization. Upon incidence, the stimulator starts evolution to compensate the effect of parameters variations and re-stabilize the asynchronous state among neurons. Finally, for $t \geq 450$, we reduce synapse parameters to $C = 0.2$ and $V_c = 1.3$, which means unstimulated neurons are partially synchronized. Similar to the two previous time intervals, the stimulator re-adjust its parameters in order to retrieve the desired asynchronous behavior. These simulation results reveal the robustness of the proposed stimulator to the parameters of coupling which is due to the dynamic (ODE-based) structure of the stimulator.

To reveal the capability of the proposed stimulator in adapting to time-variant $\theta$, in the next simulations (Fig. 4), we change $\theta$ as shown in Fig. 4(a). The synapse parameters take the nominal values and the controller parameters are as before. As it can be seen, when the stimulation is applied at $t = 500$, it suppresses the large oscillations of $X$ and $\dot{X}$ (Figs. 4(b),(c)). When $\theta$ varies at $t = 1500$, the mean field and it derivative start growing. The stimulator senses emergence of growing oscillations and adapts itself to the new situation. The adaptation can be observed in Fig. 4(e). However, when $\theta$ increases to zero no adaptation is needed and the stimulator can preserve the asynchronous state using the current value of $\gamma$.

In the next simulation, we aim to compare the designed stimulator with the one proposed in (Montaseri, Yazdanpanah, Pikovsky & Rosenblum, 2013b). To this end, we set $\theta = 0$, $C = 0.4$ and the nominal values for the synapse parameters. In Fig. 5, we regenerate the simulation results under the pre-
viously designed stimulator (shown in the thin red line) and simultaneously plot the simulation results under the proposed stimulator (shown in the thick blue line). As observed, asynchronous state is achieved approximately 50 time units faster under the proposed stimulator. On the other hand, the amplitude of the stimulation signal is smaller compared to the previously proposed stimulation signal. We computed the energy of the stimulation signal by \( E = \int_{t=50}^{t=250} u(t)dt \). We found that the energy of the proposed stimulation signal is \( \frac{1}{8} \) of the previously proposed stimulation. Thus, the tunable desynchronization speed is an outstanding property of the proposed stimulator.

In the last simulation, we set the neurons parameters to obtain chaotic bursting oscillations. In this case, \( \theta = \pi/20 \), coupling parameters have the nominal values and the controller parameters are set to: \( \omega_0 = 2\pi/176 \), \( \delta = 2\omega_0 \), \( k_1 = 1 \), \( k_2 = 1 \), \( k_3 = 1000 \), \( k_4 = 0.03 \), \( k_5 = 0.01 \) and \( k_6 = 0.05 \). The periodic components in \( X \) are suppressed after applying the stimulation. Figure 6(e) reveals that impact of the stimulation is smooth and two arbitrary chosen neurons gradually desynchronize. In addition, comparison of Fig. 6 with Fig. 7 of (Montaseri, Yazdanpanah, Pikovsky & Rosenblum, 2013b) verifies again the fast performance of the proposed stimulator.

4. Stability analysis of the asynchronous state

At the microscopic level, a population of Hindmarsh-Rose neurons (1) consists of \( N \) coupled neurons described by 3\( N \) coupled nonlinear ODEs. Generally, analysis of such a high dimensional system is complicated. To overcome this complexity, one way is to perform the analysis at the macroscopic level, where only the collective motion of the ensemble is considered.

The exact derivation of the macroscopic model from the microscopic dynamics is possible only in exceptional cases (cf. papers (Ott & Antonsen, 2008, 2009)), where individual units of the ensemble are phase oscillators with the sine-coupling. For life systems, such as neuronal systems, with a general coupling, where the model, if known, are approximate, this derivation is not possible. In this case, a transition to synchrony can be viewed as a Hopf bifurcation which is described by the model

\[
\dot{Z} = (\xi + i\omega_0)Z - d|Z|^2Z ,
\]

where \( Z \) and \( \omega_0 \) are the complex amplitude and frequency of the collective mode (mean field), respectively. The positive parameter \( \xi \) represents the
instability of the only equilibrium point $Z = 0$ of the model which means synchronous oscillations of the population.

In this framework, the collective motion of the ensemble of stimulated neurons (2) can be phenomenologically modeled by (Rosenblum & Pikovsky, 2004b; Tukhlina, Rosenblum, Pikovsky & Kurths, 2007):

$$\dot{Z} = (\xi + i\omega_0)Z - d|Z|^2Z + e^{i\beta}u$$

(8)

where the phase shift parameter $\beta$ reflects the uncertainty in the impact of the stimulation $u$ on the collective behavior of the ensemble. In (Rosenblum & Pikovsky, 2004b), authors have shown that $\beta$ inevitably appears in (8) and it depends on the organization of the global coupling, properties of individual units and the way that how the stimulation influences individual neurons. Thus, $\beta$ is related (but not the same as) $\theta$ in (2) and their relation cannot be easily determined. Consequently, $\beta$ is an unknown parameter within $(-\pi, \pi]$.

From the control theory point of view and based on model (8), desynchronization problem means stabilization of $Z = 0$ by designing an appropriate $u$. Therefore, if $u$ is capable of desynchronizing the coupled neurons, then, at the macroscopic level the controlled system (8) will be stabilized at the origin.

Comparing (1) with (7) shows that the neuron states $(x_i, y_i, z_i)$ in the $\mathbb{R}^3$ space are mapped to $(X = \text{Re}(Z), Y = \text{Im}(Z))$ in the $\mathbb{R}^2$ space. This map cannot be easily determined. In the $\mathbb{R}^2$ space, we reformulate the measured signal $m = N^{-1}\sum_{i=1}^{N}\dot{x}_i$ as $m = \cos \psi \dot{X} + \sin \psi \dot{Y}$, where $\psi$ describes the distribution of $m$ vs $(\dot{X}, \dot{Y})$.

The complete set of equations for the closed-loop system reads as:

$$\dot{X} = \xi X - \omega_0 Y - dX(X^2 + Y^2) - \gamma \delta \cos \beta \nu_2,$$  

(9a)

$$\dot{Y} = \omega_0 X + \xi Y - dY(X^2 + Y^2) - \gamma \delta \sin \beta \nu_2,$$  

(9b)

$$\dot{\nu}_1 = \nu_2,$$  

(9c)

$$\dot{\nu}_2 = \cos \psi \dot{X} + \sin \psi \dot{Y} - \omega_0^2 \nu_1 - \delta \nu_2,$$  

(9d)

$$\dot{\gamma} = -k_1 \gamma + k_2 s + k,$$  

(9e)

$$\dot{s} = [1 + \tanh (k_3 (m_f - k_4))] (1 - s) - k_5 s, \quad m_f = \delta \nu_2,$$  

(9f)

$$\dot{k} = k_6 s.$$  

(9g)

At the first step of analysis, we study linear stability of the only equilibrium point $(X, Y, \nu_1, \nu_2) = (0, 0, 0, 0)$ in the absence of the adaptive block, i.e. for
fixed value of $\gamma$. So, we consider linearization of (9a)-(9d). To find stability regions, we follow the similar method used in (Montaseri, Yazdanpanah, Pikovsky & Rosenblum, 2013b). On stability borders, the eigenvalues $\lambda$ of the state matrix $A$ are purely imaginary, i.e., $\lambda = i\Omega$ (see Appendix A for details). Thus, one can find the stability borders on the plane $\beta - \gamma$ in a parametric form as functions of $\Omega$. In Fig. 7, we plot the stability regions in the $\beta - \gamma$ plane for four arbitrary values of $\psi$. The parameters values are: $\xi = 0.1$, $\omega_0 = 2\pi/3$ and $\delta = 2\omega_0$. However, Sine $\gamma$ is a positive gain, stability subregions located in the lower half plane are not feasible and their borders are drawn by dashed lines.

Figure 7 starts from $\psi = 0$ where $m_f$ is composed of only $\dot{X}$, then $\psi$ increases to generate $m_f$ which mainly consists of $\dot{X}$ and $\dot{Y}$ (panels (b), (c), respectively) and finally in panel (d) $m_f = \dot{Y}$. As it can be seen, for each value of $\psi$ there is a region in the $\beta - \gamma$ plane such that if the controller adaptive gain $\gamma$ is selected in, the proposed stimulator can stabilize the simulated system at the origin for some values of $\beta$. Therefore, the stability is guaranteed 1) for some $\beta$s (and thus some $\theta$s) depending on the value of $\psi$ and 2) for sufficiently large $\gamma$. In other words, if the adaptive gain is strong enough, it can desynchronize (2) for some $\theta$s. Simulation results done in the Subsection 3.2 reveal that the desired asynchronous state is achieved for the assumed $\theta$s (recall the assumption $\theta \in (-\pi/4, \pi/4)$).

Now, we consider the dynamics of $\gamma$ i.e., Eqs. (9e)-(9g) and investigate its interaction with subsystem (9a)-(9d). Compare to the previous analysis, in this case, $\gamma$ has a dynamic. Suppose a typical scheme of a stability region for an arbitrary $\psi$ is depicted in Fig. 8. Let, $\beta$ is unknown -but within the acceptable range according to the stability region- which is denoted by $\beta^*$. Our aim is to show that $\gamma$ follows a trajectory similar to the one plotted in Fig. 8. At $t = 0$, $\gamma(0) = 0$. So, $\gamma$ starts evolution from the initial point $A$. As stated in (Montaseri & Yazdanpanah, 2014), the only equilibrium point of (9e) is globally exponentially stable. Therefore, when $s$ receives $m_f$ it starts growing which forces $k$ and thus $\gamma$ to increase. This increase continues until $\gamma$ reaches point $B$ on the stability border. Since then, $m_f$ decreases. When $m_f$ gets less than the cutoff threshold, the term $1 + \tanh (k_3(m_f - k_4))$ vanishes and thus, $s$ converges to zero. In this time interval, the growth rate of $k$ speeds down. When $s$ switches off, $k$ stops evolution and is locked at $\bar{k}$. Finally, $\gamma$ settles down to the value $\bar{\gamma}$ which is shown by the point $C$. Consequently, through an adaptive mechanism, $\gamma$ is forced to increase gradually until it enters the stability region and it remains there for all future
times. In the stability region, the controller \( u = -\bar{\gamma} m_f \) vanishes to zero which means that maintenance of the desired asynchronous state needs no control effort.

5. Conclusion

In this paper, we proposed an adaptive deep brain stimulator for the purpose of desynchronizing a synchronized neural ensemble. The proposed feedback stimulator has the following properties: 1) It has a self-tuning adaptive mechanism. The necessity of adaptation can be explained based on the model (8) which requires knowledge of parameters \( \xi, \omega_0 \) and \( \beta \). \( \omega_0 \) can be easily specified from the data, while \( \xi \) and \( \beta \) cannot be determined \textit{a priori}, and should be either estimated through a trial and error process or by an adaptive mechanism. 2) The stimulation has a vanishing nature. So, maintenance of the desired asynchronous state needs no control effort. 3) The impact of the stimulation on the stimulated neurons is smooth and temporary. Simulation results and the linear stability analysis reveal that the stimulator can overcome the uncertainty in the parameter \( \beta \) (or \( \theta \) in (2)).

Our research was motivated by recent studies related to neuroscience. We demonstrated capabilities of the proposed stimulator in desynchronizing populations of spiking and bursting neurons. However, the proposed stimulator can be used in other applications of the desynchronization problem and not only in neuroscience. This claim is verified in Section 4, where the stability analysis is done based on the generic model (8). This model describes the collective oscillation mode of all self-sustained oscillators (including Hindmarsh-Rose oscillators) close to the Hopf bifurcation.

Uncovering the mechanistic underpinnings of DBS and/or proposing efficient replacement for DBS are the main goal of theoretical studies. However, no one can ignore the present gap between the theoretical results and their clinical verification and confirmation. This gap was highlighted in (Dovzhenok, Park, Worth & Rubchinsky, 2013). There, the delayed feedback stimulation was applied to the computational model of the basal ganglia network (proposed in (Park, Worth & Rubchinsky, 2010, 2011)). Despite the good performance of the delayed feedback stimulation when applied to the fully synchronized network, it could not adapt itself to the realistic case of partially synchronous regime and, therefore, it failed. Theoretically, the adaptive property of the proposed stimulator in this study is expected to be a solution to this challenge. We investigate this expectation by applying
the proposed stimulation to the partially synchronized neurons. The simulation results reveal the capability of the proposed stimulator to cope with not only fully (hyper) synchronized ensemble but also the partially synchronized one. However, further discussion about results of considering a more realistic network model and type of coupling is left as a problem for ongoing researches.

Appendix A. Computing the stability border

For the state matrix $\mathcal{A}$ of Eqs. (9a)-(9d), the characteristic equation reads:

$$
\lambda^4 + (\gamma \delta \cos(\psi - \beta) + \delta - 2\xi)\lambda^3 + (\omega_0 \gamma \delta \sin(\psi - \beta) - \xi \gamma \delta \cos(\psi - \beta) - 2\xi \delta + 2\omega_0^2 + \xi^2)\lambda^2 + (\xi^2 \delta + \omega_0^2 \delta - 2\xi \omega_0^2)\lambda + \omega_0^4 + \xi^2 \omega_0^2 = 0
$$

(A.1)

The stability regions in the $\beta - \gamma$ plane correspond to the condition $Re(\lambda) < 0$. The borders of the regions are calculated by $Re(\lambda) = 0$. Therefore, substituting $\lambda = i\Omega$ in (A.1) and separating the real and imaginary parts, give:

$$
\Omega^4 + (-\omega_0 \gamma \delta \sin(\psi - \beta) + \xi \gamma \delta \cos(\psi - \beta) + 2\xi \delta - 2\omega_0^2 - \xi^2)\Omega^2 + \omega_0^4 + \xi^2 \omega_0^2 = 0,
$$

(A.2a)

$$
\Omega^3 (-\gamma \delta \cos(\psi - \beta) - \delta + 2\xi) + (\xi^2 \delta + \omega_0^2 \delta - 2\xi \omega_0^2) \Omega = 0.
$$

(A.2b)

Since $\Omega = 0$ provides no solution, we divide (A.2b) by $\Omega \neq 0$. Thus, we solve (A.2a) and (A.2b) to obtain $\gamma$ and $\beta$ as:

$$
\gamma = \frac{1}{\delta \omega_0 \Omega^2} \sqrt{T_1^2 \omega_0^2 + (\xi T_1 + T_2)^2},
$$

$$
\beta = \psi - \cos^{-1} \left( \frac{T_1}{\delta \gamma \Omega^2} \right),
$$

(A.3)

where

$$
T_1 = \delta(\xi^2 + \omega_0^2 - \Omega^2) - 2\xi \omega_0^2 + 2\xi \Omega^2,
$$

$$
T_2 = \Omega^4 + \omega_0^2(\xi^2 + \omega_0^2) + \Omega^2(2\xi \delta - 2\omega_0^2 - \xi^2).
$$

(A.4)

It is easy to check that if the point $(\beta, \gamma)$ belongs to the stability borders, then the points $(\beta \pm 2k\pi, \gamma)$ belong to the stability borders as well.


Figure 1: (Color online) Asynchronous (a),(b) and synchronous (c),(d) oscillations in a population of $N = 200$ Hindmarsh-Rose neurons (1) for the spiking activity (a), (c) and bursting activity (b),(d).
Figure 2: (Color online) The schematic representation of the controlled neuronal population. The LFP, related to the mean field of the population, is measured by the recording electrode. The controller consisting of two main blocks generates the control signal $u$ which is fed back to the system via the field application electrode.
Figure 3: (Color online) Desynchronization in the ensemble of spiking Hindmarsh-Rose neurons (2) with $\theta = -\pi/8$ and three different levels of synchronization (intermediate synchronization $C = 0.6$, hypersynchronization $C = 0.75$ and partial synchronization $C = 0.2$). (a)-(c) The mean field $X$, its derivative and the control signal $u$, respectively. (d) Time evolution of the adaptive gain $\gamma$. The behavior of two arbitrary chosen neurons for $C = 0.6$, (e) before, (f) exactly after, and (g) some times after applying the stimulation.
Figure 4: Suppressing synchrony in the ensemble of spiking Hindmarsh-Rose neurons (2) in the presence of the time-variant parameter $\theta$. (a) When $\theta$ changes from $\pi/4$ to $-\pi/5$, (e) the adaptive variable starts to evolve, so that (d) the stimulation adapts itself to the new value of $\theta$ and suppresses (b) the mean field and (c) its derivative. However, for variation of $\theta$ from $-\pi/5$ to 0 no adaptation is needed and the stimulator can preserve the desired asynchronous state based on the current value of the adaptive gain.
Figure 5: (Color online) Comparison of synchrony suppression in the ensemble of spiking Hindmarsh-Rose neurons (2) under the proposed stimulator (thin red line) and the one designed in (Montaseri, Yazdanpanah, Pikovsky & Rosenblum, 2013b) (thick blue line). (a) The mean fields, (b) the control signals $u$ and (c) the adaptive variable $\gamma$. 
Figure 6: (Color online) Suppression of synchrony in the ensemble of chaotic bursting Hindmarsh-Rose neurons (2) with $\theta = \pi/20$. (a)-(c) The mean field, its derivative and the control signal $u$, respectively. (d) Time evolution of the adaptive variable $\gamma$. (e) Transition from synchrony to asynchrony illustrated with two arbitrary chosen neurons.
Figure 7: Stability regions of the controlled system (9a)-(9d) consist of closed sub-regions; here they are shown for four different values of $\psi$. 

\[ \psi = 0 \] 
\[ \psi = \frac{\pi}{3} \] 
\[ \psi = \frac{\pi}{6} \] 
\[ \psi = 0 \]
Figure 8: The typical stability region and the trajectory followed by $\gamma$ for an arbitrary $\psi$. 