33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Search for the optimal strength of coordinated reset stimulation

Borys Lysyansky, Oleksandr V. Popovych, and Peter A. Tass

Abstract— **The presented computational study is dedicated to the selection of the optimal stimulation strength for coordinated reset (CR) stimulation, developed for an effective desynchronization of pathologically synchronized neuronal ensembles. We studied the parameter space for CR stimulation technique in detail and revealed that CR stimulation can induce cluster states, desynchronized states, and oscillation death. We found that there exists an optimal value of stimulation strength inducing the best desynchronization of the stimulated target population.**

I. Introduction

Synchronization is a fundamental phenomenon and has been found in many interacting systems [1]–[3]. Furthermore, pathological neuronal synchronization is a hallmark of several neurological diseases, e.g., Parkinson's disease (PD) or essential tremor [4]–[14]. Nowadays, high-frequency (HF) electrical deep brain stimulation (DBS) is widely used for the treatment of PD [15]. However, HF DBS may have side effects or be ineffective [16], [17]. During the last decade several desynchronizing stimulation techniques were developed, which are based on the methods of nonlinear dynamics [3], [18]–[21]. The novel stimulation protocols were developed to specifically counteract pathological synchronization by desynchronization and to avoid any strong modifications of the neuronal dynamics, in terms of e.g. blockage of the neuronal firing, as known from HF DBS [22].

During CR stimulation short HF pulse trains are sequentially delivered via several stimulation contacts. This technique demonstrates robust desynchronizing effects [18]. Its impact has been proven experimentally *in vitro* [23]. However, for clinical application the optimal parameter choice for the stimulation is especially important. This problem was addressed for HF DBS [15], but the corresponding question for CR stimulation still remains open. This computational study is devoted to the optimal parameter choice for CR stimulation. The main attention is paid to the stimulation strength, coefficient of signal decay in the neuronal tissue, and the timing properties of the intermittent CR stimulation. The problem of the optimal stimulation strength is of special interest. From the clinical point of view, stimulation should be as mild as possible in order to avoid undesirable side effects, but it should also be strong enough to induce the desired desynchronization. In this study we reveal that an excessively strong CR stimulation may suppress the neuronal activity and lead to an oscillation death, whereas too weak stimulation can be ineffective. Moreover there exists an optimal range of the stimulation strength, where the length of the OFF periods of the intermittent CR stimulation is maximal.

The paper is organized as follows. We introduce the model and stimulation setup in section II. Continuous CR stimulation is investigated in section III, where the main stimulation outcomes like cluster states, desynchronized states, and oscillation death are demonstrated. The intermittent CR stimulation, where the stimulation is alternated by the rest time intervals, is considered in section IV. We verify the results obtained for the phase oscillators on the network of spiking FitzHugh-Nagumo neurons in section V. Discussion of the results is given in section VI.

II. CR stimulation protocol

In the consideration below we pay the main attention to the phase dynamics of the neuronal network subjected to CR stimulation. Under some assumptions, the collective phase dynamics of a neuronal network can be modelled by a system of coupled phase oscillators, see [24], [25]. With such an approach we investigate the well-known Kuramoto model of N globally coupled phase oscillators reflecting the main features of the synchronized behavior of the oscillatory populations [1], [26]

$$\dot{\theta}_j = \omega_j + \frac{C}{N}\sum_{k=1}^{N}\sin(\theta_k - \theta_j),\ j = 1, 2, \ldots, N, \quad (1)$$

where θ_j are the oscillator phases, ω_j give the natural frequencies, and C stands for the coupling strength in the network. Large coupling strength implies synchronization of the ensemble (1) [1], [26]. In order to analyze the extent of synchronization, the order parameters $R_m = N^{-1}\left|\sum_{j=1}^{N}\exp\left(im\theta_j\right)\right|$, where $m \geq 1$ and $0 \leq R_m \leq 1$, will be used [1], [3]. Thus, the fully synchronized state is indicated by a large value of the first order parameter R_1. On the other hand, a desynchronized state with uniform phase distribution is characterized by small values of all order parameters. We assume that the phase oscillators are located on a 1-Dim segment, which also contains N_c equidistantly placed stimulation contacts. According to the CR stimulation

Manuscript received April 15, 2011.

B. Lysyansky is with the Institute of Neuroscience and Medicine – Neuromodulation (INM-7) and Virtual Institute of Neuromodulation, Research Center Juelich, D-52425, Germany (e-mail: b.lysyansky@fz-juelich.de)

O. V. Popovych is with the Institute of Neuroscience and Medicine – Neuromodulation (INM-7) and Virtual Institute of Neuromodulation, Research Center Juelich, D-52425, Germany (e-mail: o.popovych@fz-juelich.de)

P. A. Tass is with the Institute of Neuroscience and Medicine – Neuromodulation (INM-7) and Virtual Institute of Neuromodulation, Research Center Juelich, D-52425 and Department of Stereotaxic and Functional Neurosurgery, University of Cologne, D-50931 Cologne, Germany (corresponding author, phone: +49-2461-612087, fax: +49-2461-611880, e-mail: p.tass@fz-juelich.de)

protocol [3], [18], [19] the stimulation terms $S_j(t)$, which should be added to the r.h.s. of (1), are:

$$S_j(t) = I \sum_{k=1}^{N_c} D(x_j, k)\rho_k(t)P(t)\cos\theta_j. \qquad (2)$$

Here I is the stimulation strength, coefficients $D(x_j, k)$ describe the spatial profile of the stimulation signal, $P(t)$ defines the HF pulse train, and $\rho_k(t)$ are the switching (0-1) functions for the kth contact. Values $D(x_j, k)$ depend on the distance between the stimulation site with coordinate c_k and the oscillator with coordinate x_j [27], see Fig. 1(a)

$$D(x_j, k) = \frac{1}{1 + (x_j - c_k)^2/\sigma^2}, \qquad (3)$$

where σ determines the width of the stimulation profile.

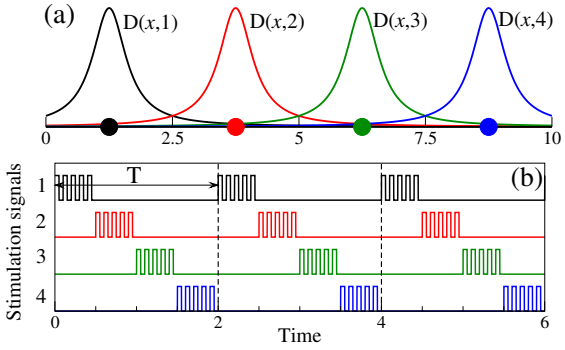

Fig. 1. (a) Spatial profile functions $D(x, k)$, $1 \le k \le 4$ on the segment of length $L = 10$. Stimulation sites are depicted by circles. (b) Stimulation signals for CR stimulation, number of contacts $N_c = 4$ and period $T = 2$.

A CR stimulation protocol implies a sequential application of short HF pulse trains via different stimulation contacts [18], [19]. In the present study we analyze the oscillatory ensemble with mean period $T = 2$, and CR stimulation is also considered to be periodic with the same period. The exemplary time courses of the stimulation signals $\rho_k(t)P(t)$, $k = \overline{1,4}$ are shown in Fig. 1(b). In what follows, the period of HF pulse train is $T_p = 0.05$, i.e. 40 times smaller than the period of the ensemble, and pulse width is taken to be $T_p/2 = 0.025$.

III. Permanent CR stimulation

CR stimulation permanently applied to the synchronized neuronal ensemble can sufficiently change its oscillatory dynamics. In the absence of stimulation, i.e. $I = 0$ in (2), the distribution of the oscillator phases (1) is a narrow peak corresponding to a strong in-phase synchronization. This state is also indicated by a large first order parameter $R_1 \approx 0.98$ [Fig. 2(a)]. If CR stimulation is switched on, other states may emerege: cluster states and desynchronized states. A four-cluster state is reflected by a small first order parameter $R_1 \approx 0.01$ and a large value of the fourth order parameter $R_4 \approx 0.6$ [parameter points **1** in Fig. 2(a),(b)]. The stimulation-induced desynchronized state is characterized by a broad distribution of phases. The corresponding order parameters are also small, $R_1 \approx 0.01$ and $R_4 \approx 0.16$ [parameter points **2** in Fig. 2(a),(b)].

In order to analyze the robustness of the revealed dynamical states, we consider the influence of the stimulation strength I and decay rate σ on the stimulation outcome. The stimulation result is estimated by the values of the time-averaged order parameters $\langle R_1 \rangle$ and $\langle R_4 \rangle$. The corresponding color-coded diagrams are shown in Fig. 2.

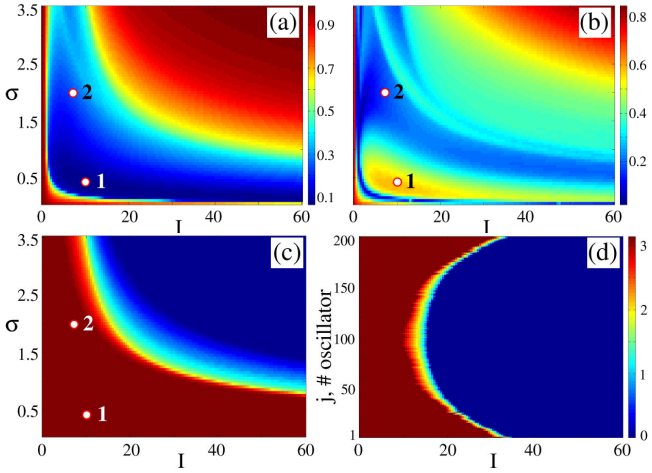

Fig. 2. Dynamical states of ensemble (1), (2) under permanent CR stimulation. The time-averaged order parameters (a) $\langle R_1 \rangle$ and (b) $\langle R_4 \rangle$ versus (I, σ) are encoded in color ranging from blue (small values) to red (large values). Parameter point **1** $(I, \sigma) = (10, 0.4)$ and point **2** $(I, \sigma) = (7, 2)$ are indicated by circles. (c),(d) The averaged frequencies of the stimulated ensembles are encoded in color. (c) The mean of the averaged individual oscillator frequencies $\overline{\Omega} = N^{-1}\sum_{j=1}^{N} \overline{\omega}_j$ is shown versus parameters I and σ. The blue region indicates a parameter values implying oscillation death. (d) Averaged frequencies $\overline{\omega}_j$ of all $N = 200$ oscillators are depicted for fixed $\sigma = 2$ (parameter point **2**) versus varying I. Parameters: $N = 200$, $C = 0.1$, $N_c = 4$, natural frequencies ω_j are Gaussian distributed with mean $\omega_{\text{mean}} = \pi$ and $\sigma_\omega = 0.02$.

The obtained dynamical states are robust with respect to the variation of the parameters I and σ. Indeed, small values of $\langle R_1 \rangle$ (blue domain) indicating an absence of in-phase synchronization are present for a wide parameter range. Note, in the desynchronized regime neurons exhibit an ongoing activity; they are not blocked. It is worth mentioning that small values of σ providing selective stimulation for each contact allow an appearance of cluster states. This mode is indicated by the blue points in Fig. 2(a) and by the green-yellow points in Fig. 2(b), this domain is clearly distinguishable.

Large values of σ admit only a small interval for the stimulation strength I, where the first order parameter R_1 attains small values. In this parameter region both order parameters R_1 and R_4 are small, which is indicative of a desynchronized regime. The parameter points **1** and **2** in Fig. 2 are placed in the corresponding two domains of stimulation-induced cluster and desynchronized states, respectively, and will be used below for illustrative purposes.

If both parameters I and σ are large (right upper corners in diagrams Fig. 2(a),(b)), the values of order parameters are large. This corresponds to the reset-induced synchronization

of the ensemble. The mentioned parameter values guarantee that signal bursts from each of the stimulation contacts affect the whole neuronal population. Such stimulation parameters make permanent CR stimulation resemble the usual HF stimulation, where the entire population is subjected to the same strong impact of the high-frequency pulse train. This strong reset actually stops the normal oscillations of the neurons providing only a low-amplitude high-frequency phase jitter of the oscillators. Being stopped near the phase $\theta = \pi/2$ the oscillators become mutually synchronized, which increases the order parameters. The mentioned oscillation death is clearly illustrated in Fig. 2(c),(d), where the oscillation frequencies are analyzed. The disappearance of oscillations corresponds to the blue domains in these diagrams. One can see that increasing stimulation strength in Fig. 2(d) leads to a progressive oscillation death of the neurons in the ensemble.

An important conclusion is that an excessively strong stimulation suppresses the neuronal oscillations and leads to an oscillation death. Since all oscillators are stopped with nearly the same phase, the order parameters get (artefactually) large although this is, in fact, not a synchronization because the oscillations are stopped. For some fixed σ there exists an optimal value of I leading to a minimal value of R_1 [Fig. 2(a),(b)], which is a sign of optimal desynchronization.

IV. Intermittent CR stimulation

According to the CR stimulation protocol the stimulation signals are delivered intermittently, where several cycles with stimulation (ON cycles) are alternated with the rest time intervals without stimulation (OFF cycles) [18], [19]. During the OFF cycles the stimulation-free ensemble evolves according to its own dynamics, first, to the desynchronized state and then resynchronizes because of the sufficiently strong coupling among the neurons. Therefore, we have to apply CR stimulation repetitively to keep the value R_1 under some small level. In this study we consider the simplest technique of the intermittent $m : n$ stimulation. CR stimulation is switched on during m cycles of length T, whereas the stimulation is switched off during the consecutive n cycles (each of length T either). To quantify the quality of the $m : n$ ON-OFF CR stimulation, we use the maximal value $\langle r \rangle$ of the order parameter R_1 averaged over all OFF-cycles, obtained at each of these intervals. The effect of the

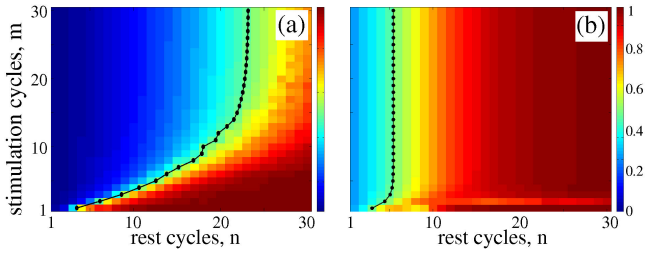

Fig. 3. The averaged maximal value $\langle r \rangle$ of the order parameter R_1 is encoded in color for (a) stimulation parameters inducing a cluster state (point **1** in Fig. 2) and (b) stimulation parameters inducing a desynchronized state (point **2** in Fig. 2). The black curves depict the level $\langle r \rangle = 0.5$.

intermittent $m : n$ stimulation is illustrated in Fig. 3, where the value of $\langle r \rangle$ is shown versus m, n, the characteristic lengths of the intermittent CR protocol. We reveal two important properties: There is a saturation level for the curves $n = n_{\max}(m)$ depicted by the black lines. An increase of m does not result in a further increase of $n_{\max}(m)$ as soon as a limiting value is exceeded. In addition, this saturation level of n is much larger for the clusterizing CR stimulation (Fig. 3(a)) than for the desynchronizing stimulation.

We can also analyze the impact of the stimulation strength for the intermittent stimulation. The effective amount of the stimulation I_{eff} received on average by a single neuron in the stimulated ensemble per time unit will be considered. The diagram in Fig. 4 demonstrates the dependence of the

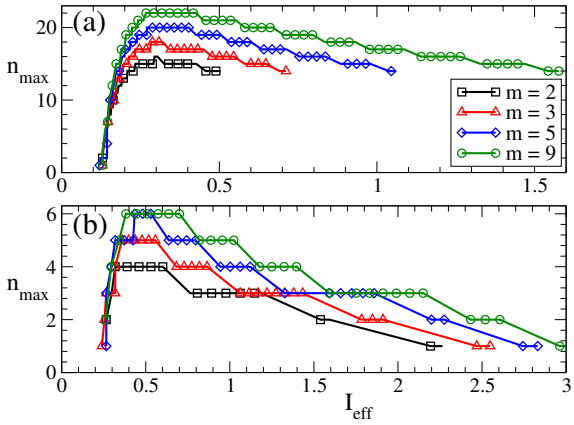

Fig. 4. Optimal protocol for the intermittent CR stimulation. Maximal length $n_{\max}$ of the rest interval providing $\langle r \rangle < 0.5$ versus effective amount of stimulation for the different values of m. (a) Clusterizing CR stimulation for parameter point **1** in Fig. 2. (b) Desynchronizing CR stimulation for parameter point **2** in Fig. 2.

maximal possible length of the OFF-interval $n_{\max}$ on the effective amount of stimulation I_{eff}. Two diagrams are built for several lengths of the active interval m and for the parameter points **1** and **2** from Fig. 2, respectively. We can draw a few important conclusions from this figure. First of all, all curves have clearly observable maxima. This implies that an increase of the stimulation strength can improve the stimulation effect only up to some limit, beyond which stronger stimulation admits only a shorter OFF-interval. In addition, the length of the admissible OFF periods for the clusterizing CR stimulation is much larger than that for the desynchronizing stimulation, compare plots (a) and (b) in Fig. 4.

V. Spiking neurons under CR stimulation

In this section we verify some results, obtained for the phase Kuramoto ensemble (1), (2), in the network of spiking FitzHugh-Nagumo (FHN) [28] neurons. The considered model reads

$$\begin{aligned} \dot{v}_j &= v_j - \tfrac{1}{3}v_j^3 - w_j + 1 + I_j^{(syn)} + I_j^{(stim)}, \\ \dot{w}_j &= \varepsilon_j(v_j + 0.7 - 0.8w_j), \\ \dot{s}_j &= \frac{2(1-s_j)}{1+\exp(-10v_j)} - s_j, \qquad j = 1, 2, \ldots, N, \end{aligned} \tag{4}$$

where the variable v_j corresponds to the membrane potential of neuron j, s_j models the post-synaptic potential generated by the cell [29], ε_j defines the frequency of oscillations. Neurons are supposed to be coupled via chemical synapses. We consider the excitatory coupling which is implemented by $I_j^{(syn)}$ being a sum of all synaptic inputs to the cell, namely $I_j^{(syn)} = C(V - v_j)N^{-1}\sum_{k=1}^{N} s_k$. Since the coupling is excitatory, the value of the reversal potential is taken as $V = 2$. C is the coupling strength, and we consider $C = 0.1$.

The external stimulation current $I_j^{(stim)}$ delivered to the oscillator j is modelled as $I_j^{(stim)} = I\sum_{k=1}^{N_c} D(x_j, k)\rho_k(t)P(t)$. The functions D, ρ_k, and P are similar to the functions in section II. The HF pulse train $P(t)$ has the period $T_p = 1$ and pulse width $T_p/2 = 0.5$. As revealed by Fig. 5(a), the dependence of

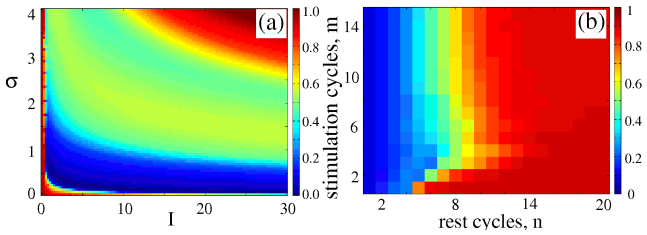

Fig. 5. Desynchronizing effect of (a) permanent CR stimulation versus parameters (I, σ) and (b) intermittent ON-OFF CR stimulation versus parameters (m, n) on the FHN neuronal ensemble (4), where the order parameters $\langle R_1 \rangle$ and $\langle r \rangle$ are encoded in color in plots (a) and (b), respectively. Parameters: $N = 200$, $N_c = 4$.

the first order parameter R_1 on (I, σ) is very similar to those for the Kuramoto model, see Fig. 2. Indeed, small values of σ provide quite a wide interval for the stimulation strength I suppressing the system synchronization, whereas a larger σ demands a more precise tuning of I. Large I and σ also induce an oscillation death as found for the phase oscillators, see section III. The diagram for R_4 is not shown here, but it is also similar to the picture for the phase oscillators. For example, the blue domain in Fig. 5(a) also corresponds to the cluste states with large values of R_4.

The diagram in Fig. 5(b) illustrates the quality of the intermittent $m : n$ ON-OFF CR stimulation versus (m, n). It is built for the values of (I, σ) providing strong clustering, $(I, \sigma) = (5, 0.4)$, see also Fig. 5(a). The diagram is similar to that in Fig. 3 built for the phase oscillators. Thus, the conclusions drawn for the phase ensemble can straightforwardly be applied to the neuronal ensemble of spiking neurons. This supports the robustness and broad applicability of the desynchronizing CR stimulation.

VI. Discussion

In the present study we investigated the parameter space of CR stimulation. Different stimulation-induced dynamical states like cluster states, desynchronized states, and oscillation death were revealed as outcome of the CR stimulation. We have also identified the existence of the optimal parameter values providing the best desynchronization. The optimal choice of the stimulation parameters, in particular, stimulation strength is important for clinical applications. We found that CR stimulation which is either too weak or too strong may not effectively counteract the pathological synchronization in the stimulated network. We have also disentangled the relation between the maximal length of the rest interval n and the stimulation strength I as well as the length of the stimulation interval m. The obtained theoretical results may contribute to an optimal stimulation parameter choice in experimental and clinical studies of the desynchronizing CR stimulation.

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