Effective desynchronization with bipolar double-pulse stimulation

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This paper is devoted to the desynchronizing effects of bipolar stimuli on a synchronized cluster of globally coupled phase oscillators. The bipolar pulses considered here are symmetrical and consist of a positive and a negative monopolar pulse. A bipolar single pulse with the right intensity and duration desynchronizes a synchronized cluster provided the stimulus is administered at a vulnerable initial phase of the cluster's order parameter. A considerably more effective desynchronization is achieved with a bipolar double pulse consisting of two qualitatively different bipolar pulses. The first bipolar pulse is stronger and resets the cluster, so that the second bipolar pulse, which follows after a constant delay, hits the cluster in a vulnerable state and desynchronizes it. A bipolar double pulse desynchronizes the cluster independently of the cluster's dynamical state at the beginning of the stimulation. The dynamics of the order parameter during a bipolar single pulse or a bipolar double pulse is different from the dynamics during a monopolar single pulse or a monopolar double pulse. Nevertheless, concerning their desynchronizing effects the monopolar and the bipolar stimuli are comparable, respectively. This is significant for applications where bipolar stimulation is required. For example, in medicine and physiology charge-balanced stimulation is typically necessary in order to avoid tissue damage. Based on the results presented here, demand-controlled bipolar double-pulse stimulation is suggested as a milder and more efficient therapy compared to the standard permanent high-frequency deep brain stimulation in neurological patients.

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I. INTRODUCTION

Synchronization processes abound in physics [1,2], chemistry [3], biology [4–6], and medicine [7]. Stimulation is a major experimental tool that is used for investigating and manipulating dynamical processes [1–7]. To study desynchronizing effects of pulsatile stimuli, the concept of phase resetting [4] was extended to populations of noninteracting [8] and interacting [9] oscillators subjected to random forces. For this, limit cycle oscillators are approximated by phase oscillators [3], and desynchronization is caused by stimuli that exclusively affect the phases of the oscillators.

A single pulse of the right intensity and duration desynchronizes a fully synchronized cluster of oscillators if the pulse hits the cluster in a vulnerable phase range which corresponds to only a small fraction (5% or even less) of a period of the oscillation [9]. However, this is tricky to realize under noisy experimental conditions typically encountered in biological systems. What makes single-pulse stimulation even less practicable is that the correct stimulation parameters also depend on the extent of the synchronization of a cluster: A weaker pulse has to be used to desynchronize a weakly synchronized cluster, whereas a stronger pulse is necessary for the desynchronization of a cluster that is in its fully synchronized state. Moreover, not only the strength (i.e., intensity and duration) but also the critical phase at which a pulse has to be administered crucially depends on the extent of synchronization of the cluster [9,10].

For this reason, a double-pulse stimulation technique has been developed which makes it possible to effectively desynchronize a cluster of phase oscillators independently of the cluster's dynamic state at the beginning of the stimulation [10]. The double pulse consist of two qualitatively different stimuli: The first, stronger pulse resets the cluster, so that after the first pulse the cluster restarts in a stereotyped way. The second, weaker pulse is administered after a fixed delay and hits the cluster in a vulnerable state in order to cause a desynchronization. Instead of the first, strong pulse, alternatively, a high-frequency pulse train [11] or a low-frequency pulse train [12] can be used to reset the cluster (for a review see Ref. [12]).

As yet, in all of these theoretical studies the effects of monopolar pulses were investigated [9–12]. In the context of electrical stimulation, a monopolar pulse corresponds to a pulsatile current injection via an electrode. In applications to biological systems, however, it is often necessary to use charge-balanced pulses which guarantee that on average the stimulated tissue is not charged, so that tissue damage can be avoided [6,13]. A charge-balanced stimulation is typically achieved either (i) by means of capacitor driven electronic circuits which control the stimulation in a way that after a monopolar pulse the injected charge smoothly flows back or (ii) by means of bipolar pulses, which consist of two opposite monopolar pulses during which on average there is no net current flow [6,13].

This paper is devoted to the desynchronizing effects of bipolar single pulse and bipolar double-pulse stimulation on a clutser of globally coupled phase oscillators in the presence of noise. The transient dynamics occuring during administration of the bipolar stimuli are compared with the transients related to the monopolar variants. Finally, it will be discussed how to use the results presented here for the model-based development of demand-controlled deep brain stimu-

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lation techniques, which essentially require the use of charge-balanced stimuli.

II. MODEL

Along the lines of a first approximation the dynamics of a population of neurons can be modeled by means of a network of phase oscillators [3,14]. This approach was extensively used, in particular, for investigating spontaneous synchronization processes in populations of oscillatory neurons [3,14]. To study stimulus-induced transient dynamics we consider a cluster of coupled phase oscillators subjected to a stimulus S and to random forces, which is governed by the Langevin equation

$$\dot{\psi}_j = \Omega + \frac{1}{N}\sum_{k=1}^{N} \Gamma(\psi_j - \psi_k) + X(t)S(\psi_j) + F_j(t), \quad (1)$$

where ψ_j denotes the phase of the jth phase oscillator, i.e., the jth model neuron [9]. For the sake of simplicity all oscillators are assumed to have the same eigenfrequency: $\omega_j = \Omega$. The global coupling is a 2π periodic function. For the time being we consider a simple sine coupling of the form

$$\Gamma(\psi_j - \psi_k) = -K\sin(\psi_j - \psi_k), \quad (2)$$

where K is a non-negative coupling constant. This type of coupling is sufficient to explain the basic desynchronization mechanism employed by the bipolar stimulation technique suggested here. The impact of both cosine couplings like $\cos(\psi_j - \psi_k)$ and coupling terms of second and higher order such as $\sin[2(\psi_j - \psi_k)]$, $\sin[3(\psi_j - \psi_k)]$ has already been analyzed in detail in the context of monopolar stimulation techniques [9,12] and will be discussed below.

The impact of an electrical stimulus on a single neuron depends on the phase of the neuron at which the stimulus is administered [15]. Accordingly, the stimulus is modeled by a 2π periodic, time independent function $S(\psi_j) = S(\psi_j + 2\pi)$. First, we assume that the stimulus is of lowest order and defined by

$$S(\psi_j) = I\cos(\psi_j), \quad (3)$$

where I is a constant intensity parameter. The effect of more complex stimuli S, e.g., containing higher order terms such as $\cos(2\psi_j)$ and $\sin(2\psi_j)$, has already been investigated in monopolar stimulation techniques [9,12] and will be discussed below.

Administration of a *monopolar single pulse* is modeled by

$$X(t) = \begin{cases} 1, & \text{stimulus is on at time } t \\ 0, & \text{stimulus is off at time } t \end{cases} \quad (4)$$

[Fig. 1(a)]. In contrast, a symmetrical bipolar single pulse consists of a positive monopolar single pulse and a directly following negative monopolar single pulse, which will briefly be denoted as positive and negative pulse below [Fig. 1(b)]. The parameters of the positive and the negative pulse are identical with respect to all parameters except for the sign of X. In particular, positive and negative pulse have identical

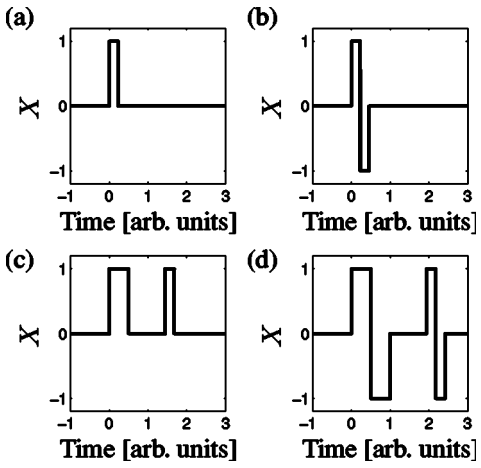

FIG. 1. Time course of X from Eqs. (4) and (5) during a monopolar single pulse (a) [see Eq. (4)], during a symmetrical bipolar single pulse (a) [see Eq. (5)], during a monopolar double pulse (a) [see Eq. (4)], and during a symmetrical bipolar double pulse (a) [see Eq. (4)]. A symmetrical bipolar single pulse consists of a positive and a directly following negative single pulse (b). The positive and the negative pulses are identical with respect to all parameters except for the sign of X. A symmetrical double pulse consists of two symmetrical bipolar single pulses (d): The first bipolar single pulse is stronger [i.e., it is longer and has a higher intensity I from Eq. (3)] and resets the cluster. The second bipolar single pulse follows after a constant delay, is weaker and desynchronizes the cluster by hitting it in a vulnerable state.

intensity I and duration. The duration of the positive and the negative pulse will be denoted as $T/2$, so that the duration of the bipolar single pusle is given by T. Accordingly, the administration of a *symmetrical bipolar single pulse* is modeled by

$$X(t) = \begin{cases} 1, & \text{positive pulse is on at time } t \\ -1, & \text{negative pulse is on at time } t \\ 0, & \text{stimulus is off at time } t. \end{cases} \quad (5)$$

In an experimental application a symmetrical bipolar single pulse would guarantee a charge-balanced stimulation.

The random forces $F_j(t)$ are modeled by Gaussian white noise which obeys $\langle F_j(t)\rangle = 0$ and $\langle F_j(t)F_k(t')\rangle = D\delta_{jk}\delta(t - t')$ with constant noise amplitude D. To study the dynamics of Eq. (1) we first derive the corresponding Fokker-Planck equation which is an evolution equation for the probability density $f(\{\psi_l\},t)$, where $\{\psi_l\}$ stands for the vector $(\psi_1, \ldots, \psi_N)$. $f(\{\psi_l\},t)\, d\psi_1 \cdots d\psi_N$ gives us the probability of finding the oscillators' phases in the intervals $\psi_k \ldots \psi_k + d\psi_k$. In order to simplify the analysis we turn to a more macrospcopic level of description by introducing the average number density $n(\psi,t)$ according to

$$n(\psi,t) = \langle \tilde{n}(\{\psi_l\};\psi)\rangle_t = \int_0^{2\pi} \cdots \int_0^{2\pi} d\psi_1 \cdots d\psi_N \tilde{n}(\{\psi_l\};\psi) f(\{\psi_l\};t), \quad (6)$$

where the number density is defined by $\tilde{n}(\{\psi_l\};\psi) = N^{-1}\Sigma_{k=1}^{N}\delta(\psi-\psi_k)$ [3]. The probability density $f(\{\psi_l\},t)$ provides us with information concerning the phase of each single oscillator. In contrast, $n(\psi,t)$ tells us how many oscillators of the whole population most probably have phase ψ at time t.

With a little calculation we finally obtain the evolution equation for the average number density,

$$\frac{\partial n(\psi,t)}{\partial t} = -\frac{\partial}{\partial \psi}\left\{ n(\psi,t)\int_0^{2\pi} d\psi' \Gamma(\psi-\psi') n(\psi',t)\right\} - \frac{\partial}{\partial \psi} n(\psi,t) X(t) S(\psi) - \Omega \frac{\partial}{\partial \psi} n(\psi,t) + \frac{D}{2}\frac{\partial^2 n(\psi,t)}{\partial \psi^2}, \tag{7}$$

which holds for large N [9]. For the numerical investigation the Fourier transformed model equation (7) was integrated with a fourth order Runge-Kutta algorithm with a time step of 0.0001, where Fourier modes with wave numbers $|k| \leqslant 200$ were taken into account. For a detailed analytical and numerical investigation of Eq. (7) I refered to Ref. [9].

III. SPONTANEOUSLY EMERGING SYNCHRONY

The time-dependent extent of in-phase synchronization is quantified with

$$Z(t) = R(t)\exp[\mathrm{i}\varphi(t)] = \int_0^{2\pi} n(\psi,t)\exp(\mathrm{i}\psi)\mathrm{d}\psi, \tag{8}$$

where $R(t)$ and $\varphi(t)$ are the real amplitude and the real phase of Z, respectively [3,16]. Because of the normalization condition $\int_0^{2\pi} n(\psi,t)\ \mathrm{d}\psi = 1$, the amplitude fulfills $0 \leqslant R(t) \leqslant 1$ for all times t. Perfect in-phase synchronization corresponds to $R=1$, whereas an incoherent state, given by $n(\psi,t) = 1/(2\pi)$, is related to $R=0$. $Z(t)$ corresponds to the center of mass of $n(\psi,t)\exp(i\psi)$, the average number density circularly aligned in the Gaussian plane (Fig. 2).

To study the impact of stimulation, first, the cluster's behavior without stimulation [i.e., $X(t)=0$ in Eqs. (4) and (5)] has to be clarified. Let us assume that the coupling is given by Eq. (2). Noisy in-phase synchronization emerges out of the incoherent state $n=1/(2\pi)$ due to a decrease of the noise amplitude D [3] or, analogously, because of an increase of the coupling strength [9]. When K exceeds its critical value $K^{\mathrm{crit}}=D$, Z from Eq. (8) becomes an order parameter [1] which governs the dynamics of the other, infinitely many stable modes (i.e., frequency components) on the center manifold. In this way a stable limit cycle $Z(t) = Y\exp[i(\Omega + \overline{\Omega})t]$ evolves for $K>D$, where Y is a complex constant, and $\overline{\Omega}$ is a real frequency shift term that depends on model parameters and vanishes if the coupling Γ contains no cosine terms as in Eq. (2) [9].

The cluster's collective dynamics will not only be visualized with the order parameter Z, but also by considering the collective firing. A single firing/bursting model neuron fires/bursts whenever its phase vanishes (modulo 2). Accordingly, the cluster's collective firing is given by the firing density

$$p(t) = n(0,t), \tag{9}$$

which corresponds to quantities registered in neurophysiological experiments such as multiunit activity (MUA), local field potentials (LFP), and magnetic or electric fields measured with magnetoencephalography (MEG) or electroencephalography (EEG).

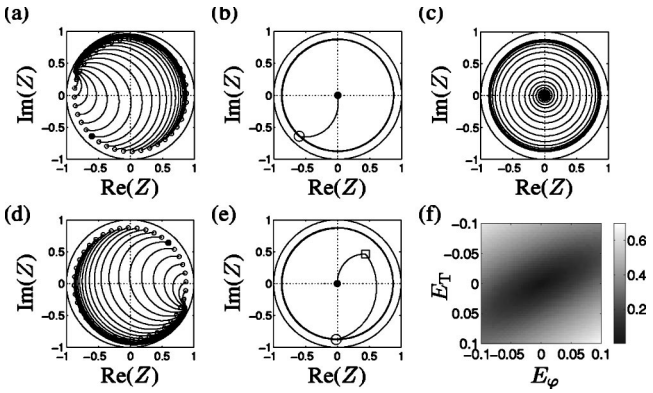

FIG. 2. Trajectory of the order parameter Z from Eq. (8) in the Gaussian plane during and after a monopolar single pulse [(a)–(c)] and during a bipolar single pulse [(d),(e)]. In (a)–(e) the unit circle indicates the maximal range of $|Z|$. Monopolar single pulse: (a) series of identical stimuli with $X(t)S(\psi) = I\cos\psi$ (with $I=7$) administered at different initial phases φ_{B} in the stable synchronized state ("○"). Z approaches its attractor Z_+^{stat} from Eq. (10) for $t\to\infty$. Only the stimulus administered at the vulnerable initial phase ("●") moves Z through the origin. Trajectory of Z before and during (b) and after (c) a desynchronizing monopolar single pulse [parameters as in (a)]. (b) After running on its stable limit cycle (inner circle) in the counterclockwise direction, Z is moved by the pulse into the origin ($Z=0$). Stimulation starts at "○" and ends in "●". (c) After the stimulation the cluster spontaneously spirals back to its stable limit cycle. Symmetrical bipolar single pulse: (d) Series of identical negative pulses with $X(t)S(\psi) = -I\cos\psi$ (with $I=7$) administered at different initial phases φ_{B} in the stable synchronized state ("○"). For $t\to\infty$ Z approaches its attractor Z_-^{stat}. Only the trajectory starting in "●" runs through the origin. (e) Before the bipolar stimulation Z runs on its stable limit cycle (inner circle) in the counterclockwise direction. The positive pulse starts in ("○") and moves Z halfway towards the attractor Z_+^{stat} belonging to the positive pulse shown in (a), so that at the end of the positive pulse Z is located in "□". The directly following negative pulse starts in "□" and moves Z towards the attractor Z_-^{stat} of the negative pulse (d), so that at the end of the negative pulse Z is located in the origin of the Gaussian plane ("●"). (f) The ratio $r = R(t_{\mathrm{E}})/R(t_{\mathrm{B}})$ from Eq. (13) is calculated for a series of stimulations where the normalized phase and amplitude error E_φ and E_T from Eq. (11) and Eq. (12) are varied between -0.1 and $+0.1$. Model parameters: (a)–(f) $\Gamma(x) = -\sin x$, $D=0.4$, $\Omega = 2\pi$, $S(\psi) = I\cos\psi$, $I=7$. Pulse duration $T=0.31$ of the monopolar single pulse in (b), and $T=0.46$ of the bipolar single pulse in (e).

IV. SINGLE PULSE

A. Monopolar single pulse

Let us first consider the cluster's dynamics during a single monopolar pulse [8,9]. During the monopolar pulse $X(t)=1$, and S from Eq. (3) is constant in time. If the stimulus S is sufficiently strong (i.e., its intensity parameter I is large enough) with respect to the coupling strength, $n(\psi,t)$ tends to a stationary density $n_{\mathrm{stat}}(\psi)$ for $t\to\infty$. The latter is the attractor of Eq. (7), independently of the initial state $n(\psi,0)$ at which the stimulation starts [9]. Correspondingly, the order parameter Z from Eq. (8) is attracted by

$$Z^{\mathrm{stat}}=\int_0^{2\pi} n_{\mathrm{stat}}(\psi)\exp(\mathrm{i}\psi)\mathrm{d}\psi. \tag{10}$$

t_{B} and t_{E} stand for the time of stimulus onset and stimulus end, and $\varphi_{\mathrm{B}}=\varphi(t_{\mathrm{B}})$ denotes the initial phase at which the stimulus administered. In Fig. 2(a) the collective dynamics of the cluster is visualized by plotting the trajectory of Z in the Gaussian plane, where φ_{B} is varied within one cycle $[0,2\pi]$. A desynchronized state corresponds to $Z=0$. Thus, to desynchronize the synchronized cluster, the single pulse has to be administered at a critical (vulnerable) initial phase and it has to be turned off as soon as Z reaches the origin of the Gaussian plane [Fig. 2(b)]. The desynchronized state is unstable. Therefore after the desynchronizing stimulation Z spirals back to its stable limit cycle, so that the cluster becomes synchronized again [Fig. 2(c)].

B. Symmetrical bipolar single pulse

A symmetrical bipolar single pulse consists of a positive and a directly following negative pulse which are identical with respect to all parameters except for the sign of X [Fig. 1(b)]. From Eqs. (3) and (5) it follows that during the positive pulse $X(t)S(\psi_j)=I\cos\psi_j$ holds, so that the Langevin equation (1) reads $\dot{\psi}_j=\Omega+N^{-1}\Sigma_{l=1}^{N}\Gamma(\psi_j-\psi_l)+I\cos\psi_j+F_j(t)$. In contrast, during the negative pulse $X(t)S(\psi_j)=-I\cos\psi_j=I\cos(\psi_j+\pi)$. With this and by applying the transformation $\phi_j=\psi_j+\pi$ $(j=1,\ldots,N)$ to Eq. (1), for the negative pulse we obtain $\dot{\phi}_j=\Omega+N^{-1}\Sigma_{l=1}^{N}\Gamma(\phi_j-\phi_l)+I\cos\phi_j+F_j(t)$, which equals the Langevin equation belonging to the positive pulse. Hence, except for a shift of all phases by π, the dynamics during a negative pulse is identical to the dynamics during a positive pulse.

This difference is illustrated by comparing Z's trajectories belonging to series of simulations where the same infinitely long positive pulse [Fig. 2(a)] or the same infinitely long negative pulse [Fig. 2(d)] is administered at different initial phases, respectively. Rotating the trajectories belonging to the positive pulse by π around the origin of the Gaussian plane yields the trajectories belonging to the negative pulse. Let us denote the attractor from Eq. (10) of the infinitely long positive pulse by Z_+^{stat} [Fig. 2(a)], and the attractor of the infinitely long negative pulse by Z_-^{stat} [Fig. 2(d)]. The two attractors have a phase difference of π, while their amplitudes are identical, $|Z_+^{\mathrm{stat}}|=|Z_-^{\mathrm{stat}}|$.

To desynchronize the cluster of oscillators with a bipolar single pulse, the stimulus has to be administered at the right initial phase, so that Z runs along a zigzaglike trajectory from the stable limit cycle into the origin of the Gaussian plane [Fig. 2(e)] Before the bipolar stimulation Z runs on its stable limit cycle in counterclockwise direction. The positive pulse starts in ("○") and moves Z towards the attractor Z_+^{stat} of the positive pulse [Fig. 2(a)]. At the end of the positive pulse Z has been shifted halfway to Z_+^{stat} and is located in "□". Due to the directly following negative pulse Z is abruptly shifted towards the attractor Z_-^{stat} of the negative pulse [Fig. 2(d)], so that Z darts sideways. At the end of the negative pulse Z is located directly in the origin of the Gaussian plane ("●"). After the bipolar single pulse the cluster resynchronizes [Fig. 2(c)].

Figure 2(f) demonstrates that for a given intensity parameter I, correct values of the duration T, and the initial phase φ_{B} have to be chosen in order to achieve a strong desynchronization. We denote the values of T and of φ_{B} which lead to a maximal desynchronization (i.e., $Z=0$) by T_{crit} and $\varphi_{\mathrm{B}}^{\mathrm{crit}}$. With this we introduce the normalized phase error

$$E_\varphi=\frac{\varphi-\varphi_{\mathrm{B}}^{\mathrm{crit}}}{2\pi} \tag{11}$$

and the normalized duration error

$$E_T=\frac{T-T_{\mathrm{crit}}}{T_{\mathrm{crit}}}. \tag{12}$$

To estimate the extent of desynchronization we define

$$r=\frac{R(t_{\mathrm{E}})}{R(t_{\mathrm{B}})}, \tag{13}$$

i.e., the ratio between the amplitude R of the order parameter at the end of the stimulation and R at the beginning of the stimulation. Fig. 2(f) shows how r depends on E_φ and E_T. Maximal desynchronization ($r=0$) only occurs for vanishing E_φ and E_T. A strong desynchronization with $r\leqslant 0.2$ cannot occur for $|E_\varphi|>0.05$ and $|E_T|>0.05$.

V. DOUBLE PULSE

A. Monopolar double pulse

The monopolar double pulse consists of two monopolar single pulses separated by a pause [Fig. 1(c)] [10]. The first pulse resets the cluster, whereas the second pulse causes a desynchronization as explained in Sec. IV A. In the stable synchronized state before the double pulse, Z runs on its limit cycle [Fig. 3(b)]. The first pulse is stronger compared to the second pulse, i.e., the first pulse is longer and/or has a larger intensity parameter I. Therefore during the first pulse Z is quickly attracted by the corresponding attractor Z^{stat} [Figs. 3(a),3(b)]. Independently of the initial dynamical state at which the first pulse is administered, at the end of the first pulse Z is sufficiently close to Z^{stat} [Fig. 3(b)]. During the pause between the first and the second pulse Z relaxes to its stable limit cycle in a stereotyped way [Fig. 3(c)]. The sec-

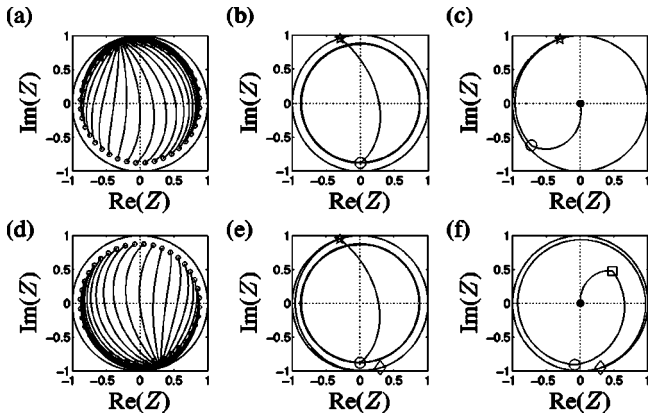

FIG. 3. Trajectories of Z from Eq. (8) are plotted in the Gaussian plane (same format as in Fig. 2). *Monopolar single pulse*: (a) Series of identical positive pulses with $X(t)S(\psi)=I\cos\psi$ (with $I=21$) administered at different initial phases φ_B in the stable synchronized state ("○"). (d) Series of identical negative pulses with $X(t)S(\psi)=-I\cos\psi$ (with $I=21$) administered at different initial phases φ_B in the stable synchronized state ("○"). In both cases Z approaches the corresponding attractors $Z_+^{\rm stat}$ (a) and $Z_-^{\rm stat}$ (d) for $t\to\infty$. Compared to Figs. 2(a),2(d) the intensity I is larger here ($I=21$ vs $I=7$ in Fig. 2), so that a quick reset is achieved, i.e., Z reaches its attractor rapidly. A *monopolar double pulse* consists of a stronger, resetting monopolar single pulse [parameters as in (a)] and a weaker, desynchronizing monopolar single pulse [parameters as in Fig. 2(a)]. (b) Trajectory of Z before and during the first pulse of the double pulse. The first pulse is administered at "○" and forces Z to the corresponding attractor $Z_+^{\rm stat}$ ("⋆"). (c) After the first pulse Z relaxes from the attractor towards its stable limit cycle. The second pulse of the monopolar double pulse starts at "○" and moves Z into the origin ("●"). A *bipolar double pulse* consists of a stronger, resetting bipolar single pulse [parameters as in (a) and (d)] and a weaker, desynchronizing bipolar single pulse [parameters as in Fig. 2(e)]. (e) Trajectory of Z before and during the first bipolar pulse of the bipolar double pulse. Before the stimulation Z runs on its stable limit cycle (inner circle) in the counterclockwise direction. The positive pulse is administered at "○" and forces Z to its attractor $Z_+^{\rm stat}$ ("⋆"). The directly following negative pulse then moves Z to the attractor $Z_-^{\rm stat}$ ("◇"). (f) At the end of the first bipolar pulse Z is located sufficiently close to $Z_-^{\rm stat}$ ("◇"). During the pause between first and second bipolar pulse Z relaxes back to its stable limit cycle. The desynchronizing bipolar pulse [with parameters as in 2(e)] moves Z along a zigzag trajectory: The positive pulse starts in "○" and moves Z to "□", the directly following negative pulse shifts Z into the origin ("●"). Model parameters: (a)–(f) $\Gamma(x)=-\sin x$, $D=0.4$, $\Omega=2\pi$, $S(\psi)=I\cos\psi$. $I=21$ in (a), (b), (d), and (e). $I=7$ in (c) and (f). Pulse duration $T=0.5$ in (b), $T=0.4$ in (c), $T=1$ in (e), and $T=0.48$ in (f).

ond pulse is administered at the right initial phase so that Z is moved into the origin of the Gaussian plane, the desynchronized state [Fig. 3(c)]. After the second pulse Z spirals back to its stable limit cycle as shown in Fig. 2(c).

B. Symmetrical bipolar double pulse

The symmetrical bipolar double pulse consists of two bipolar single pulses separated by a pause [Fig. 1(d)]. Similar to the monopolar double pulse, the first bipolar single pulse performs a reset, whereas the second bipolar single pulse desynchronizes the cluster as explained in the former section. The first bipolar single pulse is stronger compared to the second bipolar single pulse, which means that the first bipolar single pulse is longer and/or has a larger intensity parameter I. Before stimulus adminitration Z runs on its stable limit cycle [Fig. 3(b)]. The first bipolar single pulse performs a *double reset*: Independently of Z's initial conditions, the resetting positive pulse shifts Z towards the corresponding attractor $Z_+^{\rm stat}$ [Figs. 3(a),3(e)], in this way achieving a first reset. The directly following resetting negative pulse then moves Z towards the opposite attractor $Z_-^{\rm stat}$ [Figs. 3(d),3(e)], so that Z undergoes a second reset. After this zigzaglike reset Z is sufficiently close to $Z_-^{\rm stat}$, and Z consequently restarts in a stereotyped manner: During the pause between the first and the second bipolar single pulse Z tends to its stable limit cycle [Fig. 3(f)]. The second bipolar single pulse is administered after a constant delay and hits the cluster in a vulnerable state, so that a desynchronization is achieved as explained in Sec. IV B. After the stimulation induced desynchronization the cluster resynchronizes: Z spirals back to its stable limit cycle [Fig. 2(c)].

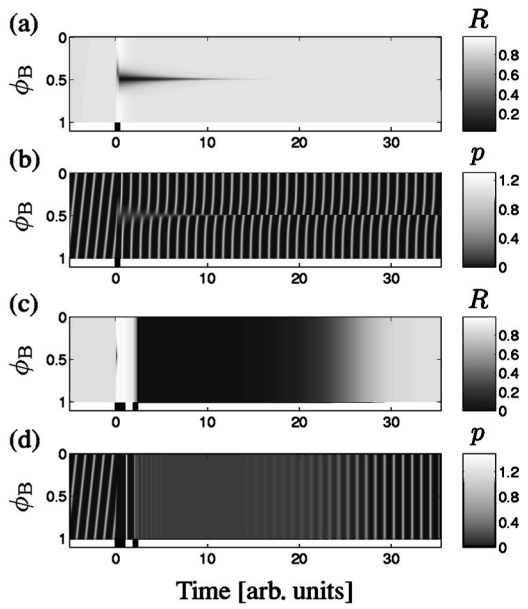

FIG. 4. Time course of the amplitude R of the order parameter from Eq. (8) [(a),(c)] and the firing density $p(t)=n(0,t)$ [(b),(d)] before, during, and after a bipolar single pulse [(a),(b)] and a bipolar double pulse [(c),(d)], where $\phi_B=\varphi_B/(2\pi)$ mod 1, the normalized phase of the order parameter Z at the beginning of the stimulation, is varied within one cycle. Stimulation starts at $t=0$. At the bottom of each plot bipolar pulses are indicated by bars. In (a),(b) and (c),(d) same parameters as in Figs. 2(e) and 3(e),3(f), respectively.

VI. VULNERABILITY TO STIMULATION

Figure 4 shows how a bipolar single pulse and a bipolar double pulse affect a cluster in its stable synchronized state, where φ_B, the phase of the order parameter Z at the beginning of the stimulation, is varied within one cycle $[0,2\pi]$.

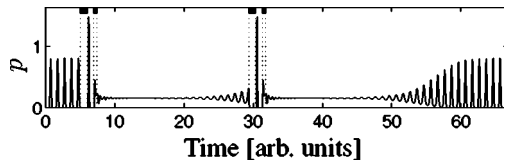

FIG. 5. Time course of the firing density p. Two successively administered bipolar double pulses with identical parameters are administered. The first one desynchronizes the cluster, whereas the second blocks the resynchronization. Model parameters as in Fig. 4. Begin and end of bipolar pulses are indicated by dotted vertical lines connected by shaded regions at the top.

We consider R, the amplitude of the order parameter and the firing density $p(t)$. The bipolar single pulse causes a desynchronization only provided it hits Z at or close to a vulnerable phase φ_B^{crit} [Figs. 4(a),4(b)]. In contrast, the bipolar double pulse causes a temporary desynchronization, no matter at which initial phase it is administered [Figs. 4(c),4(d)].

VII. DEMAND-CONTROLLED DESYNCHRONIZATION

The bipolar double pulse explained in Sec. V B desynchronizes a cluster independently of its initial dynamic state. For this reason a bipolar double pulse can be used to effectively block the cluster's resynchronization. Whenever the cluster tends to resynchronize, the same bipolar double pulse is administered in order to prevent the cluster from resynchronization (Fig. 5). In this way an uncorrelated firing can be maintained. The larger the coupling strength K, the more often a bipolar double pulse has to be administered to cause a desynchronization.

VIII. DEMAND-CONTROLLED DEEP BRAIN STIMULATION

In several neurological diseases such as Parkinson's disease or essential tremor brain function is severely impaired by pathological synchronization of neuronal firing. Parkinsonian resting tremor appears to be caused by a cluster of neurons located in the thalamus and the basal ganglia which fire synchronously at a frequency similar to that of the tremor [19,20]. For instance, in the anterior nucleus of the ventrolateral thalamus there are the so-called no-response cells which are neither modulated by somatosensory stimuli nor by active or passive movements [20]. These cells fire rather periodically in an intrinsic manner, regardless of any feedback signals. In contrast, under physiological conditions the neurons in this cluster fire incoherently [21]. In patients with Parkinson's disease (PD) this cluster acts like a pacemaker and activates premotor areas (premotor cortex and supplementary motor area) and the motor cortex [7,21,22], where the latter synchronize their oscillatory activity [23]. Similarly, essential tremor also appears to be caused by a central cluster of synchronously firing neurons, which is located in different brain areas compared to PD [24].

In patients with advanced PD or with essential tremor who do not respond to drug therapy any more, depth electrodes are chronically implanted in target areas like the thalamic ventralis intermedius nucleus or the subthalamic nucleus with millimeter precision [13]. Up to now, electrical deep brain stimulation (DBS) is performed by administering a permanent high-frequency (>100 Hz) periodic pulse train via the depth electrodes. DBS at high frequencies suppresses the neuronal activity of the pacemakerlike cluster which, in turn, suppresses the peripheral tremor [13].

High-frequency DBS has been developed empirically, mainly based on observations during stereotactic surgery [13]. The mechanism by which DBS at high frequencies suppresses pathological rhythmic activity has not yet been clarified in detail. The permanent high-frequency stimulation basically mimics the effect of tissue lesioning by suppressing neuronal firing [13,25]. DBS is reversible and has a much lower rate of side effects than lesioning with thermocoagulation [26]. However, permanent high-frequency stimulation is an unphysiological input which may cause an adaptation of the stimulated neuronal networks. This may be one of the reasons why in a number of patients the stimulation amplitude has to be increased in the course of the treatment in order to maintain a therapeutic effect. As a consequence of the increased stimulation strength, neighboring areas may be affected due to current spread, which leads to severe side effects such as dysarthria, dysesthesia, cerebellar ataxia.

For this reason a different therapeutic approach with mild and efficient stimulation techniques based on stochastic phase resetting [9] has been suggested: Instead of simply suppressing the neuronal firing in the pacemakerlike cluster, the novel stimulation techniques aim at desynchronizing the pacemaker's pathologically synchronized firing in a demand-controlled way [10–12]. Accordingly, Eq. (1) models the effect of stimulation on the pacemakerlike cluster. In other words, instead of stopping the driving force, I suggest to desynchronize it, so that it is no longer able to entrain other brain areas like premotor areas and the motor cortex.

Till now in all modeling studies only monopolar pulses have been used [9–12]. The results presented here show that at least in a phase oscillator network bipolar pulses are equally suitable for the design of demand-controlled double-pulse stimulation. Based on these results and using a network of phase oscillators as a simple model for a neuronal population [14], I suggest to try to use demand-controlled DBS for the therapy of neurological diseases like Parkinson's disease or essential tremor. To this end, the depth electrode has to be used for both stimulation and registration of the feedback signal, i.e., the local field potential (LFP), which in the model corresponds to the firing density p defined by Eq. (9). A desynchronizing bipolar double pulse is administered only and whenever the pacemaker-like cluster becomes synchronized, put otherwise, whenever its LFP exceeds a critical value (Fig. 5). Note, that the first and the second bipolar single pulse of the bipolar double pulse are delivered to the same site. The goal of this approach is to effectively block the resynchronization and, hence, keep the firing as close to the physiological (i.e., uncorrelated) firing mode as possible. Instead of the LFP registered via the depth electrode one could alternatively use an epicortical electrode measuring the neuronal electrical activity in cortical areas (e.g., premotor areas or the motor cortex) which are sufficiently strongly

synchronized with the target area stimulated via the depth electrode.

IX. DISCUSSION

In this study it was shown that a bipolar single pulse with the right intensity and duration desynchronizes a synchronized cluster of phase oscillators provided the stimulus is administered at a vulnerable initial phase φ_B^{crit} of the order parameter. Furthermore, it was shown that a bipolar double pulse consisting of a first, resetting and a second, desynchronizing bipolar pulse desynchronizes the cluster independently of the cluster's dynamical state at the beginning of the stimulation.

The dynamics of the order parameter Z during the bipolar single- and double-pulse stimulation is different from Z's dynamics during monopolar single- and double-pulse stimulation (Figs. 2 and 3). Nevertheless, with respect to their desynchronizing effects the monopolar and the bipolar stimuli are comparable. A bipolar single pulse desynchronizes only if it hits the cluster close to the vulnerable phase φ_B^{crit} [Figs. 2(f) and 4(a),4(b)]. The same holds for a monopolar single pulse [9]. In contrast, a bipolar double pulse desynchronizes the cluster, regardless of the dynamical state at which it is administered [Figs. 4(c),4(d)]. Thus, a bipolar double pulse can be used to block the resynchronization effectively (Fig. 5). Again, the same is true for a monopolar double pulse.

The fact, that monopolar and bipolar stimuli are exchangeable concerning their desynchronizing effects, is important for all applications where bipolar stimulation is more favorable. For example, in medical and physiological applications charge-balanced stimulation is typically required in order to avoid tissue damage.

The reset attained by means of the first, stronger bipolar pulse of the bipolar double pulse guarantees, that a desynchronization is caused independently of the initial dynamical state of the cluster (see Secs. V B, VI, and VII). The first bipolar pulse shown in Figs. 3–5 consists of a positive and a negative monopolar pulse which both are so strong, that they reset the cluster even when applied alone. Consequently, a reset is already achieved after the positive pulse, i.e., the order parameter Z is sufficiently close to the attractor Z_+^{stat} of the positive pulse ["$\star$" in Fig. 3(e)]. In other words, during the first bipolar pulse the cluster undergoes a double reset: The first reset occurs at the end of the positive pulse, the second reset at the end of the negative pulse.

If in an experimental application such a strong reset cannot be performed or should be avoided in order to protect the stimulated system from damage, alternatively a resetting bipolar pulse with reduced strength (i.e., with reduced intensity I and/or duration T) can be used. In this case both the positive and the negative pulse of the first bipolar single pulse alone perform only an imperfect reset, while the combination of the two is strong enough to reset reliably. Accordingly, after the positive pulse there is still a certain distance between Z and the attractor Z_+^{stat} of the positive pulse, and this distance depends on the initial dynamical state at the beginning of the stimulation. Nevertheless, after the negative pulse Z is sufficiently close to the corresponding attractor Z_-^{stat} independently of the initial dynamical state, so that positive and negative pulse together reset the cluster in a stereotyped manner.

All bipolar single pulses used in this study have a $(+,-)$ structure, meaning that their first pulse is a positive pulse, whereas their second pulse is negative (Fig. 1). Instead of bipolar single pulses with a $(+,-)$ structure, one can also use bipolar single pulses with a $(-,+)$ structure, where the first pulse is negative and the second pulse is positive. The exclusive use of stimuli that have a $(-,+)$ structure corresponds to replacing $X(t)\rightarrow -X(t)$ in Eq. (5), which in turn is equivalent to the transformation $\phi_j \rightarrow \phi_j + \pi$ (see the reasoning in Sec. IV B). Except for this transformation the dynamics of the cluster remains unchanged.

Interesting alternative options, however, ensue from mixing $(+,-)$ and $(-,+)$ stimuli. To illustrate this, let us again dwell on the dynamics of the order parameter Z during the bipolar double pulse [Figs. 3(e),3(f)]. After the first, resetting bipolar pulse Z is located in the attractor of the negative pulse Z_-^{stat}. During the pause between the first and the second bipolar pulse Z has to run through nearly one period before the desynchronizing, second bipolar pulse can be administered [Fig. 3(f)]. Such a long pause in between the first and the second bipolar pulse may be a disadvantage in experimental applications, since this pause is a period of time where fluctuations or unforeseen external influences can alter the cluster's dynamical state in a way that the desynchronizing impact of the second bipolar pulse gets spoiled. To avoid such a long pause, we can replace the first bipolar pulse with $(+,-)$ structure by a $(-,+)$-bipolar pulse. Consequently, at the end of the first bipolar pulse Z is located in Z_+^{stat} ["$\star$" in Fig. 3(e)]. During the pause between first and second bipolar pulse Z then runs through less than half a period before the second, desynchronizing $(+,-)$-bipolar pulse starts [in "$\bigcirc$" in Fig. 3(e)]. In this way the pause between the two bipolar stimuli is reduced by more than a factor of 2. Furthermore, since Z then does no longer cross the positive x axis during the pause, there is no strong burst of firing in between the two bipolar pulses any more (see Fig. 5). Obviously, the cluster's transient reaction during stimulation crucially depends on the pattern of consecutive $(+,-)$ and/or $(-,+)$ stimuli.

Characteristic dynamical features of monopolar stimuli are passed on to bipolar stimuli, because bipolar stimuli are combinations of consecutively administered monopolar stimuli. Let us consider the most important aspects.

The right stimulation parameters are reliably determined in an experimental application with calibration procedures that have been developed for the monopolar single-pulse stimulation [9] and the monopolar double-pulse stimulation [10]. These procedures work in the same way for the bipolar stimulation techniques presented here: A series of test stimuli is administered. To extract a quantity that corresponds to the phase φ of the order parameter Z from Eq. (8), the phase of the dominant Fourier mode is extracted out of the experimental data with bandpass filtering and Hilbert transform, and, finally, the correct parameters are obtained with phase

resetting curves. The Hilbert transform s_H of a signal s is generated by a filter which causes a phase shift of $\pi/2$ for all frequencies. Applying such a filter yields the instantaneous phase ψ and amplitude A of s according to $s(t)+s_H(t)=A(t)\exp[i\psi(t)]$ [29].

The bipolar stimulation techniques presented in this paper can also be used for desynchronizing cluster states, which are complex synchronized states, where a population of coupled oscillators breaks into distinct clusters, each consisting of phase-locked oscillators [17,18]. Cluster states may even occur in networks of globally coupled oscillators [18]. In model equation (1) noisy clustering may emerge due to coupling terms of higher order like $\Gamma(x)=-K_m\sin(mx)$ (with $K_m>0$). Increasing K_m above its critical value mD causes an m-cluster state, which consists of m equidistant clusters, where all individual oscillators have the same frequency [9]. For example, increasing K_2 above its critical value $2D$ gives rise to a two-cluster state, where two clusters are synchronized in antiphase. Synchronized states of this kind appear to be important in the context of neurological diseases [23,27]. For supercritical coupling $K_m>mD$, the order parameter is given by

$$Z_m(t)=\int_0^{2\pi} n(\psi,t)\exp(\mathrm{i}m\psi)\mathrm{d}\psi \qquad (14)$$

[9,28]. Note that Z_1 is equivalent to the order parameter Z defined by Eq. (8). Z_m runs on a limit cycle and has to be desynchronized as illustrated in Figs. 2 and 3. For monopolar stimulation techniques it has already been shown that this most effectively achieved with a stimulus S containing terms of mth order, e.g., $S(\psi)=I\cos(m\psi)$ [9–12]. These results are also valid for bipolar stimuli, because the latter are made up of monopolar stimuli. Accordingly, also in the case of bipolar single-pulse and bipolar double-pulse stimulation, stimulation terms of mth order are favorable for a quick and strong desynchronization.

In this study we considered a stimulus of first order, i.e., a stimulus $S(\psi_j)$ containing only terms with $\sin(\psi_j)$ and/or $\cos(\psi_j)$. Instead of the stimulus $S(\psi_j)=I\cos(\psi_j)$ defined by Eq. (3) we can, alternatively, use the general form of a first-order stimulus: $S(\psi_j)=I\cos(\psi_j+\gamma)$ with constant γ. Such a stimulus leads to the same stimulation mechanisms as explained above. This can easily be seen by replacing ψ_j by $\psi_j+\gamma$ and using the same arguing as in Sec. IV B.

Applying a stimulus which additionally contains terms of higher order, e.g., $S(\psi_j)=I_1\cos(\psi_j+\gamma_1)+I_2\cos(2\psi_j+\gamma_2)$ with constant parameters I_1, I_2, γ_1, and γ_2, to the model investigated here, causes a desynchronization in terms of a quenching of the order parameter Z from Eq. (8) in the same way as explained in Secs. IV B and V B, provided that the right stimulation parameters are used. The additional stimulation term of second order $I_2\cos(\psi_j+\gamma_2)$, however, gives rise to an excitation of the amplitudes of higher order terms Z_m from Eq. (14), in particular, of Z_2 and Z_4, so that $|Z_2|$ and $|Z_4|$ are larger after the stimulation than before. During the transient after the stimulation the vanishing order parameter Z damps the excited modes Z_2 and Z_4, so that Z_2 and Z_4 quickly relax to zero, and the strongest uniform desynchronization occurs with a delay after the end of the desynchronizing stimulation. The order parameter-induced damping of excited modes is due to the slaving principle [1]. This desynchronization mechanism has been studied in detail in monopolar stimuli [9,10] and holds equally in bipolar stimuli.

In a first approximation a phase oscillator can be used as a simple model for a rhythmically active neuron [14]. Accordingly, model equation (1) serves a simple model for a population of globally interacting neurons subjected to stimulation and random forces [9]. Based on the results presented here I, hence, suggest to try to perform demand-controlled electrical deep brain bipolar double pulse stimulation for the therapy of neurological diseases characterized by pathologically synchronized neuronal activity perturbing brain function. In contrast, standard DBS aims at mimicing the effect of tissue lesioning by simply suppressing neuronal firing [13,25]. As, for instance, in Parkinson's disease the uncorrelated firing is the physiological mode of functioning in the relevant brain area, the demand controlled block of the resynchronization in that area (Fig. 5) might be the milder and more effective therapy which would aim at reestablishing the physiological function instead of totally suppressing the neuronal firing in that particular target area.

Model-based novel DBS techniques may be more effective and may influence the affected neuronal dynamics in a more subtle way. Correspondingly, statistical physics may contribute to the development of therapies that avoid severe side effects. For this, along the lines of a top-down approach microscopic models have to be investigated which take into account all relevant neurophysiological features such as the dynamics of single ion channels, the anatomy of synaptic interactions, transmission delays, etc. Since microscopic models of this kind are much more complicated than a model of globally coupled phase oscillators, the dynamical mechanisms studied in the more macroscopic models will form a necessary basis and starting point for the study of microscopic models.

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