Desynchronization in Networks of Globally Coupled Neurons with Dendritic Dynamics

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Received: 10 April 2006 / Accepted: 4 May 2006 /

Published online: 10 November 2006

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Abstract Effective desynchronization can be exploited as a tool for probing the functional significance of synchronized neural activity underlying perceptual and cognitive processes or as a mild treatment for neurological disorders like Parkinson's disease. In this article we show that pulse-based desynchronization techniques, originally developed for networks of globally coupled oscillators (Kuramoto model), can be adapted to networks of coupled neurons with dendritic dynamics. Compared to the Kuramoto model, the dendritic dynamics significantly alters the response of the neuron to the stimulation. Under medium stimulation amplitude a bistability of the response of a single neuron is observed. When stimulated at some initial phases, the neuron displays only modulations of its firing, whereas at other initial phases it stops oscillating entirely. Significant alterations in the duration of stimulation-induced transients are also observed. These transients endure after the end of the stimulation and cause maximal desynchronization to occur not during the stimulation, but with some delay after the stimulation has been turned off. To account for this delayed desynchronization effect, we have designed a new calibration procedure for finding the stimulation parameters that result in optimal desynchronization. We have also developed a new desynchronization technique by low frequency entrainment. The stimulation techniques originally developed for the Kuramoto model, when using the new calibration procedure, can also be applied to networks with dendritic dynamics. However, the mechanism by which

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desynchronization is achieved is substantially different than for the network of Kuramoto oscillators. In particular, the addition of dendritic dynamics significantly changes the timing of the stimulation required to obtain desynchronization. We propose desynchronization stimulation for experimental analysis of synchronized neural processes and for the therapy of movement disorders.

Key words desynchronization · phase synchronization · phase resetting · dendritic dynamics · deep brain stimulation

1 Introduction

Synchronization processes of the brain have attracted the attention of many scientific fields in the last decades [1–5]. Synchronization of neural activity was proposed as a solution to the binding problem [6, 7]. This problem refers to the question: how is spatially distributed neural activity combined into a single coherent perception? Experimentally it was observed that the firing of neurons coding specific features of a single object in the visual field are synchronized in the gamma band (especially at 40 Hz) [6–8]. Tass [9] has proposed a novel desynchronization-based technique to investigate the binding processes in the visual system.

The present research focuses not only on synchronization under normal conditions, but also on various forms of pathological synchronization. In several neurological diseases such as Parkinson's disease (PD) or essential tremor (ET), brain function is impaired by pathological synchronization processes [10]. For instance, Parkinsonian resting tremor occurs when a population of neurons located in the thalamus and the basal ganglia fires in synchrony [11–13], while under healthy conditions these neurons fire in an uncorrelated manner [14]. Electrical deep brain stimulation (DBS) is the standard treatment for medically refractory PD and ET [15, 16]. This method uses a permanent high-frequency (HF) (greater than 100 Hz), high amplitude periodic pulse train, which is applied via depth electrodes chronically implanted in target areas like the thalamic ventralis intermedius nucleus or the subthalamic nucleus (STN) [15, 16]. HF DBS suppresses the tremor by mimicking the effect of tissue lesioning, e.g., by suppressing neuronal firing [17, 18]. However, the mechanism of HF DBS is not yet fully understood [17]. In addition, there are several drawbacks to this approach, including possible side effects like dysarthria, dysesthesia, and cerebellar ataxia. Moreover, the therapeutic effect of the stimulation often decreases over time [19].

For this reason, novel stimulation techniques are being developed which enable the selective desynchronization of pathologically synchronized processes, in order to shift the dynamics of affected neuronal populations to the physiological mode. Pulse-based desynchronization techniques have been developed and tested in networks of phase oscillators [4, 9, 20–24], as well as in microscopic models of populations of bursting neurons [25].

Phase oscillators are generic oscillators which approximate the dynamics of a large variety of natural oscillators, such as periodically active neurons [2, 26–28]. As yet, the specific contribution of dendritic dynamics to neuronal populations subject to desynchronizing stimulation has not been studied. However, for pulse-based stimulation it is necessary to take dendritic dynamics into account: (1) Dendrites are

abundant in the brain and constitute the hallmark of the interneural communication [29]. (2) Electrical stimulation can have a direct impact on the dendrites [30], or it can influence the dendritic dynamics by stimulation of presynaptic fibers [25, 31]. (3) Individual neurons are capable of exhibiting transient dynamics when exposed to electrical stimulation [32, 33]. These transient dynamics can be attributed to the inertia inherent in synaptic and dendritic dynamics [34–36]. For example dopaminergic neurons in the mammalian brain stem, which are responsible for the maintenance of physiological levels of dopamine in the striatum, display prolonged firing rate transients in response to brief changes in synaptic input [37]. These effects correspond to an effective inertia of the neuron, i.e., the response of the neuron's state to perturbations is not instantaneous, but displays smooth transient dynamics [29].

In this article we incorporate dendritic dynamics into a generic phase oscillator model, and study the dynamics of such neurons as well as of networks of such coupled neurons under different stimulation protocols. Networks of coupled one-dimensional phase oscillators can be used to model networks of synaptically interacting neurons [2, 4, 28]. We show here that dendritic dynamics significantly changes the impact of the stimulation on a single neuron and on networks in the synchronized state. Under medium stimulation amplitude two stable regimes for a single neuron of the network can coexist: the oscillatory regime, where the stimulation alters only the firing rate of the neuron, and the quiet regime, where the neurons stop firing completely. Finally we present a new calibration technique which allows us to choose optimal stimulation parameters for pulse-train-based desynchronization techniques.

2 The Model

In this section we present a brief description of our model of a neuron with dendritic dynamics. A detailed description of this model has been presented by Dolan et al. [38]. The model is an extension of a well-elaborated second order phase-oscillator model originally proposed by Haken as an approximation for the dynamics of a neuron consisting of an axon and dendrite [39]. Our model neuron consists of a single dendrite and an axon (Figure 1a). The dynamics of the dendrite are governed by

$$\dot{\psi}_i(t) = \alpha f(\phi_j(t)) - \gamma \psi_i + \beta \xi(t), \quad (1)$$

where $\dot{\psi}$ denotes the dendritic current. The first term on the right hand side describes the synaptic input from the j th neuron, which is scaled by the synaptic strength α . The response of the dendrite to the synaptic input decays with the constant rate γ , i.e., γ is the damping inherent in the dendrite, and β is the noise intensity. $\xi(t)$ is Gaussian white noise, statistically independent for each neuron, with zero mean and a standard deviation of one. The phase dynamics of the axon is governed by

$$\dot{\phi}_i(t) = c\psi_i(t) + \omega_i, \quad (2)$$

where the currents from dendrite ψ_i are scaled by a constant c and ω_i is a constant driving force. The driving force ω_i causes the neuron to periodically generate a spike with frequency ω_i . Such autonomously firing neurons are found in Parkinson's disease where so-called *no response cells*, located in the thalamus, fire independently

Figure 1 (a) Schematic picture of the model neuron consisting of two parts. The first part is the dendrite and the second is the soma and axon, simulated as single element. (b) The response of the neuron to a short stimulation pulse applied at the phase $\phi = 3/2\pi$ displayed for four values of inertia m . The effect of the stimulation is visualized by means of instantaneous frequency. The stimulation at this phase increases the firing rate of the neuron. Neurons with nonzero inertia display gradual decline of the stimulation effect after the end of the stimulation. For a neuron with zero inertia the stimulation effect immediately disappears (solid line). The stimulus amplitude was $I_{\text{stim}} = 5\omega$ and the duration $T_{\text{stim}} = 0.2$. The neuron's natural frequency parameter was set to $\omega = 2\pi$.

from any kind of sensory input [11–13]. The system described by the above two equations is equivalent to:

$$\ddot{\phi}_i(t) = Af(\phi_j(t)) + \gamma(\omega_i - \dot{\phi}_j(t)) + c\beta\xi(t), \quad (3)$$

where $A = c\alpha$. Corresponding to the above Eqs. (1) and (2), the variable $\ddot{\phi}_i$ represents the dendritic currents.

After substituting $m = 1/\gamma$, $\sqrt{2D} = c\beta/\gamma$, and introducing coupling and stimulation, we obtain

$$m\ddot{\phi}_j = \omega_j - \dot{\phi}_j + W_j + X(t)S(\phi_j) + \sqrt{2D}\xi_j(t), \quad (4)$$

where m is the effective inertia of the oscillators (which is just inversely proportional to the damping associated with the dendrites), and ω_j is the natural frequency of the j th oscillator (the oscillator will converge to this frequency in the absence of coupling

and stimulation). The phases ϕ_j of the oscillators are normalized to the interval between 0 and 1. The global coupling is implemented as a 2π -periodic function

$$W_j = \frac{K}{N} \sum_{k=1}^N \sin(2\pi(\phi_k - \phi_j)), \quad (5)$$

where K is a non-negative coupling constant. The electrical stimulation of a single neuron shows a phase-dependent response [40, 41], and can be modeled as a periodic function of ϕ . In principle, this could be any periodic function, as determined entirely by the dynamics of the considered neuron. Such a function can be expressed in terms of a Fourier series, and in this preliminary investigation we will use only the first harmonic: a cosine function of lowest order $S_j = I_{\text{stim}} \cos(2\pi\phi_j)$, where I_{stim} is a constant intensity parameter. Switching the stimulation on and off is represented by a step function $X(t)$, such that $X(t) = 1$ when the stimulation is on and $X(t) = 0$ when the stimulation is off. The random forces are modeled by means of Gaussian white noise $\xi(t)$ with amplitude D .

We quantify the extent of time-dependent synchronization by means of a complex order parameter [2]

$$Z(t) = R(t) \exp[2\pi i \varphi(t)] = \frac{1}{N} \sum_{k=1}^N \exp[2\pi i \phi_k(t)], \quad (6)$$

where $R(t)$ and $\varphi(t)$ denote the amplitude and the phase of the complex variable $Z(t)$, respectively. The value range of $R(t)$ is between 0 and 1. In the case of perfect in-phase synchronization $R(t) = 1$, whereas the completely desynchronized state is characterized by $R(t) = 0$. For deeper insight into the dynamics of the network, we also use an additional quantity, the *firing density*, which reflects the collective firing behavior of the network [4]. For this we assume that a single neuron fires whenever its phase vanishes (modulo one). Accordingly the firing density is defined by

$$p(t) = \frac{1}{N} \sum_{k=1}^N \sigma(2\pi\phi_k), \quad \sigma(\phi_k) = \begin{cases} 1 & : \cos(2\pi\phi_k) > c \\ 0 & : \text{otherwise} \end{cases} \quad (7)$$

where N is the number of neurons in the network and ϕ_k is the phase of the k th neuron. The firing threshold c determines when the phase of a neuron vanishes. In our simulations we set $c = 0.975$.

This second order phase oscillator model is a generalization of the well-known integrate and fire neuron to the case of medium to strong coupling, or equivalently, weak damping [42]. This type of second order oscillator model has been studied numerically in the context of phase synchronization [26], phase-frequency synchronization [43, 44], and the emergence of spontaneous oscillations due to time delay and inertia [45, 46].

2.1 Dynamics of a Single Neuron

The dynamics of a single neuron with dendritic dynamics in the absence of noise is governed by

$$m\ddot{\phi} = \omega - \dot{\phi} + X(t)S(\phi), \quad (8)$$

Figure 2 Phase space of a single neuron under continuous stimulation in the absence of coupling and noise. The stable fixed points (foci) are marked with crosses and the unstable (saddle points) with squares. The stable and unstable invariant manifolds of the saddle points are in blue and red, respectively. For better visualization we show three periods of the phase space with borders located at the unstable fixed points. Selected example trajectories are shown with orange dashed lines with a black circle marking the starting point. **(a)** Weak stimulation, $I = 1.2\omega$. The fixed points are present, but the basin of attraction of the stable fixed point is limited only to slow oscillators (inner part of the stable manifold, blue line). All neurons lying on the pre-stimulus periodic trajectory (horizontal line at $\dot{\phi} = 2\pi$) will be attracted by the unstable manifold. **(b)** Medium stimulation, $I = 3.0\omega$. The basin of attraction of the stable fixed point now overlaps with the pre-stimulus periodic trajectory. Depending on the initial stimulation phase the neuron will either be attracted by the stable fixed point, as in the *left* example trajectory, or will follow the unstable manifold, as in the two *right* orange trajectories. **(c)** Strong stimulation, $I = 4.2\omega$. The periodic orbit is destroyed in a homoclinic bifurcation of the unstable fixed point. All neurons are attracted by the stable fixed point. Depending on the initial phase, this will occur within one (*left* trajectory), two (second *left* trajectory), three (third *left* trajectory), or four cycles (*right* trajectory).

where m is the inertia of the oscillator and ω is its natural frequency. The stimulation term is the same as in Eq. (4). Figure 1b displays the response of a single neuron to a short perturbation for different values of inertia m . The response is visualized by means of the instantaneous frequency of the neuron $\dot{\phi}$. Neurons with non-zero inertia values m show smooth decay of the stimulation effect. In contrast, neurons with zero inertia $m = 0$ (equivalent to the standard one-dimensional phase oscillator), immediately restore their frequency to the eigenfrequency. We use the term *phase velocity* to refer to the instantaneous frequency of the neuron $\dot{\phi}$. For our simulations we take the inertia value of $m = 1$ and the eigenfrequency $\omega = 2\pi$.

Figure 2(a–c) shows the stable and unstable invariant manifolds of the single neuron for several stimulation strengths, together with a few trajectories representative of different types of dynamical behavior of the neuron. The stimulated neuron can display two distinct dynamics: (1) *An oscillatory regime* in which the neuron fires with frequencies modulated by the stimulation, and (2) *A quiet regime* where the neuron does not fire, i.e., its phase velocity is equal to $\dot{\phi} = 0$.

For weak stimulation amplitudes $I_{\text{stim}} < \omega$, only the oscillatory regime is present and the phase velocity of the neuron is only slightly perturbed by the stimulation. This trivial case is not shown in the figure.

For stimulation amplitudes satisfying $\omega < I_{\text{stim}} < H \approx 4.1\omega$ a stable (focus) and an unstable (saddle) fixed point appear in a saddle-node bifurcation (SN) (Figure 3) and both oscillatory and quiet regimes coexist and are stable (Figure 2a,b). The saddle and the focus are determined by the conditions: $\phi_{\text{fix}} = \cos^{-1}(-\omega/I_{\text{stim}})$ and $\dot{\phi} = 0$. The region of bistability extends between the saddle-node bifurcation curve (SN) and the homoclinic bifurcation curve for $m = 1$ (Figure 3, red curve). In the bistable regime for weak stimulation amplitude $\omega < I_{\text{stim}} < I_{\text{crit}} \approx 2.1\omega$ all initial conditions with $\dot{\phi} = 2\pi$ will be attracted by the unstable manifold (black circles in Figure 2a). For these weak amplitudes the basin of attraction of the stable fixed point is limited only to slow phase velocities. Because we will be stimulating a synchronized network, with a natural phase velocity of $\dot{\phi} = 2\pi$, none of those initial conditions will be attracted to the stable fixed point. The bistability will therefore not be apparent for weak stimulation under normal conditions. For stimulation amplitude $I_{\text{crit}} < I_{\text{stim}} < H \approx 4.1\omega$ the basin of attraction of the stable fixed point now overlaps with the initial condition $\dot{\phi} = 2\pi$. For these amplitudes the bistability can be detected

Figure 3 Bifurcation diagram for the saddle node bifurcation (straight line, *SN*) and homoclinic bifurcation curves for Eq. (8) for four inertia values m (lines with markers). When the stimulation amplitude increases, the two fixed points, focus and saddle, are born in a saddle-node bifurcation (*SN*). With further increase of the stimulation, a homoclinic bifurcation of the saddle takes place. The point of the bifurcation depends on the eigenfrequency and the inertia of the neuron. In the region between the *SN*-curve and the homoclinic bifurcation two states, oscillatory and quiet, coexist. Given the parameters used in this paper, the point *H* indicates the stimulation strength for which the bistability disappears. The arrow on the top of the figure points to the eigenfrequency of the neurons in the absence of stimulation.

directly by stimulation of the synchronized network. For initial stimulation phases which are in the basin of attraction of the stable fixed point, the neuron will converge to the quiet regime (left circle in Figure 2b). For initial phases outside of the basin of attraction of the fixed point, the neuron will stay in the oscillatory regime (the middle and the right circle in Figure 2b).

For $I_{\text{stim}} = H$ and $\omega = 2\pi$ the oscillatory regime is destroyed in a homoclinic bifurcation of the unstable fixed point. For stimulation amplitudes satisfying $H \approx 4.1\omega < I_{\text{stim}}$ neurons at all initial phases will converge to the quiet regime (Figure 2c). Depending on the initial stimulation phase the stable fixed point can be reached immediately (the left trajectory in Figure 2c), after one cycle (the second from left trajectory), two cycles (the third from left trajectory) or three cycles (the right trajectory).

The bifurcation diagram in Figure 3 shows the dependence of these three dynamical regimes on the stimulation amplitude I_{stim} and the eigenfrequency ω of the neuron. The appearance of the fixed points is given by the saddle-node bifurcation line (straight line, *SN*) and the destruction of the unstable fixed point is given by the homoclinic bifurcation curves for four inertia values m (lines with markers). The homoclinic bifurcation curves show exponential growth of the required stimulation amplitude I_{stim} with increasing eigenfrequency of the neuron. Higher values of inertia m accelerate these growth rates, i.e., the bistable state, which is located between the saddle-node and the homoclinic bifurcation curves, is destroyed at higher stimulation amplitude for higher m . It is important to note that for increasing eigenfrequency of the neuron ω , even small values of m result in significant regions of bistability. This implies that for neurons oscillating at high frequencies even a minimal dendritic tree

can cause the neuron to have a bistable response to a broad range of stimulation amplitudes, i.e., depending on the phase at the beginning of the stimulation, the neuron may or may not be reset to the fixed point.

2.2 Dynamics of the Network Under Continuous Stimulation

In this section we investigate the impact of continuous stimulation on the synchronization of a network of $N = 100$ globally coupled neurons with dendritic dynamics. Without stimulation, synchronization of the neurons will occur if the coupling strength exceeds a critical value K_c [47]. For $K > K_c$ the neurons form a synchronized cluster, i.e., all neurons have their phases close together, and the network behaves as a single oscillator.

To quantify the impact of stimulation on the network, we monitor the real amplitude $R(t)$ of the order parameter $Z(t)$ and the mean phase velocity $\bar{v}(t)$ for the network as given by

$$\bar{v}(t) = \frac{1}{N} \sum_{k=1}^N \dot{\phi}_k(t), \quad (9)$$

where N is the number of neurons and $\dot{\phi}_k$ is the phase velocity of the k th neuron. The mean phase velocity estimates the mean firing frequency of the neurons in the network. When all neurons are in the oscillatory regime, $\bar{v}(t) \approx \omega = 2\pi$ and when all neurons are in the quiet regime, $\bar{v}(t) \approx 0$. The real amplitude $R(t)$ is used as a measure of network synchrony. Values of $R(t)$ near 1 indicates high in-phase synchronization, whereas desynchronization is indicated by values near 0.

Under continuous stimulation, depending on the stimulation strength, we observe three distinct long-term regimes of the network: *an oscillatory, a quiet and a mixed regime*. These regimes correspond to the behavior of a single neuron under stimulation (see Section 2.1). This is because in the limit since the stimulation term of Eq. (4) is much larger than the coupling and noise terms, the effects of the stimulation dominate the dynamics, so that the behavior of any neuron in the network is well approximated by the behavior of an uncoupled stimulated oscillator. When the stimulation strength is not so strong, the dynamics may be more complicated, but the behavior of the individual oscillators under stimulation can still give relevant insight into this more complicated behavior.

Figure 4 shows the amplitude $R(t)$ of the order parameter, and the mean velocity $\bar{v}(t)$ of the network under permanent stimulation, as a function of both time and the initial phase at which the stimulation was started. The initial phase was varied between 0 and 1, in steps of 0.01. In each case the stimulation is applied when the network is in its natural state, meaning that each neuron is oscillating with its natural frequency.

For subcritical stimulation amplitude $I_{\text{stim}} < 2.1\omega$ (Figure 4a,b), only the oscillatory regime is present. In this regime all neurons continue to oscillate. The stimulation induces only small oscillations in the synchrony measure $R(t)$ and mean velocity $\bar{v}$ of the network. This corresponds well with our observations of the individual oscillators under stimulation, as the basin of attraction of the stable fixed point does not cross the line $\dot{\phi} = 2\pi$ until a stimulation amplitude of $I_{\text{crit}} \approx 2.1\omega$.

Figure 4 Time course of amplitude $R(t)$ (a), (c), (e) and mean network velocity $\bar{v}(t)$ (b), (d), (f) during continuous stimulation, as a function of initial phase of stimulation. (a), (b) Weak stimulation ($I_{\text{stim}} = 1.2\omega$). The stimulation has only a small effect on the synchronization. The network's asymptotic behavior displays only weak oscillations in the amplitude and mean velocity. (c), (d) Medium stimulation ($I_{\text{stim}} = 3.0\omega$). Full desynchronization appears for a broad range of initial phases. These two regions lie at the borders of the oscillatory and quiet regimes of the individual neurons. (e), (f) Strong stimulation ($I_{\text{stim}} = 4.2\omega$). The desynchronization occurs for a broad phase region (0.5–1.0). The location of this region is again at the border of the two operation regimes. In the long-term, the system approaches a fixed point, where all oscillators stop independently of their starting phase. In this case each neuron in the network has been reset to the same phase, where they remain until the stimulus is turned off. As a result, the network is nearly perfectly synchronized, though the neurons are no longer oscillating. The network consists of $N = 100$ globally coupled neurons with $w = 2\pi$. The other parameters used are $m = 1$, $D = 0.07$, and $K = 4\omega$. This set of parameters results in an order parameter magnitude of about $R = 0.85$.

We observe that the highest decrease in synchrony $R(t)$ occurs where the mean velocity $\bar{v}(t)$ changes from slow (dark stripes) to high (bright stripes). This relationship can be understood by tracking the responses of single neurons to stimulation. Before stimulation the phases of neurons in the cluster have their phases close together. Due to noise they are not identical but distributed in some narrow interval around $\varphi(t)$. Since the effect of the stimulation depends on the phase of the neuron, each neuron in the cluster is influenced by the stimulation slightly differently. Neurons with phases located at positions where the phase response curve $S(\phi)$ from Eq. (4) is positive will be accelerated and neurons with phases located where $S(t)$ is negative will be slowed down. The maximal acceleration will be achieved when all neurons have their phases in the positive region of $S(t)$, whereas the maximal deceleration will take place when all neurons have phases in the negative region of $S(t)$. Between these two regions $S(t)$ has its maximal positive gradient ($\phi = 0.75$). When the cluster is at this position the velocities of the oscillators will be spread the most. The leading neurons in the cluster will be accelerated, whereas the neurons at the end of the cluster will be decelerated. This will lead to spread of the phases and hence to the decrease of synchrony for the cluster. At the opposite transition, from the accelerating to decelerating region of $S(t)$, the stimulation will push the velocities closer together, i.e. it will synchronize the cluster even more.

When the stimulation amplitude exceeds $I_{\text{crit}} \approx 2.1\omega$ (Figure 4c,d) all three regimes are present. For initial phases centered around $\varphi = 0.75$, the network will stay in the oscillatory regime. This corresponds to the behavior of the individual oscillator under stimulus where the initial conditions at the time when the stimulus starts lie within the basin of attraction of the oscillatory regime. In this regime the stimulation causes oscillations in $R(t)$ and $\bar{v}$ due to the same mechanism as in the case of subcritical stimulation. For phases centered around $\varphi = 0.25$, the entire network goes to the quiet regime, i.e., all neurons stop oscillating completely. This corresponds to the behavior of the individual oscillator under stimulus where the initial conditions at the start of the stimulus lie within the basin of attraction of the stable fixed point. The mean velocity of the network in this regime is $\bar{v} = 0$ and $R(t) \approx 1$. In a narrow initial phase range between the above quiet and oscillatory regimes, a mixed regime exists. In this regime, the population is split into two groups. One portion of the neurons go to the quiet regime, and the other part continues to oscillate. This results in strong oscillations of the amplitude of the order parameter. Maximal oscillations are visible for initial phases where 50% of the neurons go to the fixed point and 50% continue to oscillate. The amplitude of the order parameter then oscillates between full desynchronization ($R = 0$) and full synchronization ($R = 1$) during each cycle, as these two portions of the network go from being exactly out of phase to exactly in phase.

With increasing stimulation strength the basin of attraction of the quiet regime expands. At the stimulation amplitude $I_{\text{stim}} = H \approx 4.1\omega$, the oscillatory regime disappears, and all initial stimulation phases result in the quiet regime. This corresponds to the case of stimulation of individual oscillators where the homoclinic bifurcation occurs, and all initial conditions go to the stable fixed point [38].

There is a broad range of initial phases for which waves of brief desynchronization occur (Figure 4e,f). Here, approximately half of the neurons are quickly captured by the fixed point and the other half require one or more additional cycles before being captured.

2.3 Dynamics of the Network Under Finite Length Stimulation

Since many real applications do not allow for the use of persistent stimulation, due to significant alteration of the dynamics of the system, and to other possible side-effects, we are interested in a stimulation strategy that works on demand. Such a stimulation should desynchronize the network for as long as possible by means of short pulses, and should be applied only when needed.

Unfortunately, we are not able to instantaneously determine the desynchronizing impact of a finite-length stimulation from the state at the end of the stimulation, as can be done for the one-dimensional model [2, 4]. The reason for this complication is that the post-stimulus behavior of the network depends not only on the amplitude $R(t)$ and phase $\varphi(t)$ of the order parameter, but also depends on the phase velocity distribution of the oscillators at the end of the stimulation. Figure 5 shows an example of the time course of the amplitude $R(t)$ during and after the stimulation. This behavior can be understood by looking at the mechanism of how the stimulation works. The stimulation acts on the phase velocities, and when the slope of the phase-response curve $S(\phi)$ is positive, it induces a dispersion of the velocity distribution. This causes the phases of the oscillators to spread over time as the velocity distribution broadens. At the end of the stimulation, the velocities are spread out and, hence, the phases continue to diverge further until the velocities, due to the damping and coupling, return to their own eigenfrequencies. This means that the network starts to resynchronize after a small time lag after the stimulation is turned off.

To deal with this, we evaluate the network order parameter $Z(t)$ over a fixed period of time after the end of the stimulus and introduce a *mean amplitude* parameter given by

$$\bar{R}(t_{\text{end}}, t_{\text{cal}}) = \frac{1}{t_{\text{cal}}} \int_{t_{\text{end}}}^{t_{\text{end}} + t_{\text{cal}}} R(t) dt, \quad (10)$$

where t_{end} is the time at which the stimulation is terminated, and t_{cal} denotes the interval over which the mean is calculated. The mean amplitude provides a measure of the overall quality of the desynchronization and also helps us to determine the optimal combination of starting phase ϕ_B , stimulus amplitude, and length of stimulus.

Figure 6 shows the mean amplitude $\bar{R}$ (a, c, and e), and standard deviation of the phase velocity distribution (b, d, and f), for three different stimulation strengths, which are representative of three different types of stimulation-induced dynamics of the network. Weak stimulation with amplitudes around $I_{\text{stim}} = 1.5\omega$ can cause full desynchronization of the network for a broad range of initial phases (Figure 6a,b), in contrast to the case of continuous weak stimulation, where only a very narrow range of initial phases result in desynchronization. This weak stimulation induces a significant spreading of the velocity distribution when the stimulation is turned off just after the network has passed the region of steepest positive slope of the phase-response curve. This fact is responsible for the striped regions of desynchronization in Figure 6a. For initial phases smaller than 0.75 some time is required for the network to reach the region of strongest positive phase response. The length of the required stimulation time for initial phases between 0.25 and 0.75 is proportional to about two times the phase difference between the initial phase and 0.75 (that is, the slope of the stripes is around -0.5).

Figure 5 The transient effects of the stimulation. The trajectories of $Z(t)$ plotted in the Gaussian plane before, during, and after the stimulation, and after the full desynchronization was reached, as well as the firing density $p(t)$ and the amplitude of $Z(t)$. **(a)** The order parameter $Z(t)$ is running on its stable limit cycle (inner circle in counterclockwise direction). At the right initial phase $\phi = 0.589$ the stimulation is turned on, and after $T = 0.225$ it is turned off. The stimulation starts at ‘*’ and ends at ‘o’. During the stimulation, the trajectory of $Z(t)$ shows only a small displacement toward the zero of the Gaussian plane. After the end of the stimulation, $Z(t)$ continues to approach the zero of the Gaussian plane, and at $t = 1.65$ it reaches the origin. **(b)** After the origin is reached the network spontaneously spirals back to its stable limit cycle. For clarity, this figure is shown zoomed in to a small region around the origin of the Gaussian plane. **(c)** Firing density $p(t)$ of the network. The black rectangle at the bottom shows the duration of the stimulation. When desynchronization of the network is achieved, the phases of the network become approximately uniformly distributed, and the firing density becomes nearly constant (with $p \approx 0.1$). As the network resynchronizes, the oscillations in the firing density grow. **(d)** The time course of the amplitude of $R(t)$ before, during, and after the end of the stimulation. At the time point $t_{\text{beg}} = 0$ the stimulus is turned on. At this time the network is fully synchronized $R(t) = 0.95$ and it has the phase $\phi(t_{\text{beg}}) = 0.589$. At the time point $t_{\text{end}} = 0.225$ the stimulation is turned off. Due to the dendritic dynamics, the network continues to desynchronize further until it reaches the minimal amplitude $R(t) \approx 0.005$ at about $t = 1.65$. Then it starts to resynchronize. After about 60 cycles it is synchronized again. The vertical line and arrow t_{cal} marks the upper time boundary for the computation of the mean amplitude parameter. Model parameters: $I_{\text{stim}} = 4.5\omega$, stimulation duration $T = 0.225$, and all others the same as in Figure 4.

Figure 6 The effect of finite-time stimulation visualized by means of the mean amplitude parameter $\bar{R}$ (a), (c), (e) and the velocity deviation at the end of the stimulation (b), (d), (f). To obtain the mean amplitude, $\bar{R}$, for each combination of phase and stimulation length a single simulation was run and the amplitude of the order parameter, after the end of the stimulation, was averaged over 30 cycles. The X axis is the stimulation length, and the Y axis is the phase at which stimulation began. The average amplitude is given by the gray scale in (a), (c), and (e). In (b), (d), and (f), the gray scale indicates the velocity deviation in units of rad/cycle. (a) and (b) Weak stimulation ($I = 1.2\omega$). Desynchronization can be induced for a broad range of initial phases when the stimulation has appropriate length. (c) and (d) Medium stimulation ($I = 3.0\omega$). For a short stimulation length, desynchronization can be achieved for a very broad range of initial phases. Additionally, there exist two narrow phase ranges centered around $\phi_B = 0$ and $\phi_B = 0.5$ where strong desynchronization occurs independent of stimulus length. For stimulation lengths longer than four cycles, and the range of initial phases between 0.1 and 0.4, no desynchronization can be induced. (e) and (f) Strong stimulation ($I = 4.2\omega$). Full desynchronization occurs for almost all starting phases when the stimulation length does not exceed four cycles. For longer stimulation all initial conditions are attracted to the stable fixed point, and desynchronization is not induced. Other parameters are the same as in Figure 4.

In Figure 6b we can observe a doubling of the stripes of high velocity deviation compared to the number of stripes of desynchronization in Figure 6a. The stripes of high velocity deviation which do not lead to desynchronization are induced by a stimulation that is turned off just after the network has passed the region of maximal negative slope of the phase-response curve. The neurons in the front of the cluster are slowed down, whereas the neurons at the end of the cluster are accelerated. This distribution will cause the neurons to become more synchronized.

A medium strength stimulation (Figure 6c,d) induces complete desynchronization in two narrow phase ranges located around $\phi_B = 0.0$ and $\phi_B = 0.5$ that are independent of the length of the stimulation. This effect is intimately connected with the dynamics observed during the continuous stimulation (Figure 4c,e). In the two bands of full desynchronization (Figure 4c,e) the stimulation induces a very strong velocity spread. Between these two bands a region of desynchronization can be observed with the same dynamics as in the case of weak stimulation (i.e., the stimulus is turned off shortly after the network passes the steepest part of the phase-response curve).

Strong stimulation ($I_{\text{stim}} > H$) generates a broad region in both phase (0–0.5) and time (0–4 cycles) of complete desynchronization. In this case, the strong stimulation induces a very large velocity spread over both the positive and negative slopes of the phase-response curve. This is in contrast to the case of the one-dimensional oscillator, where stimulus during the negative slope portion of the phase-response curve always results in increased synchronization. For weak stimulus strengths, when the stimulation is applied in the negative slope of the phase-response curve, leading oscillators get slowed down, and trailing oscillators are speeded up. This naturally moves them together, causing an increase in synchronization analogous to the case for the one-dimensional model. But for a strong stimulus, the velocity change induced is so great that the leading oscillators get pushed back behind the trailing ones, and the trailing ones get pushed ahead of the leading ones, thus resulting in essentially the same condition that exists when the stimulus is applied during the positive slope of the phase-response curve.

2.3.1 Calibration Techniques, How to Find Optimal Stimulation Parameters

In the previous sections we have shown the possibility of desynchronization of the network for the right stimulation parameters. For desynchronization-based applications, for example deep brain stimulation, one needs an effective and quick way to determine the optimal stimulation parameters. In a calibration procedure one must estimate at least the following four parameters: pulse type, amplitude, length of the stimulation, and starting phase φ_B . Since our model is of second order and the stimulation acts on the velocities, the calibration technique from [20] must be modified in order to account for resulting transient effects. In this section we describe in detail two main effects which the dendritic dynamics have on the response of the network to stimulation: delayed desynchronization and velocity distribution effects on resynchronization time. A modification of the calibration technique is then presented.

2.3.2 Delayed Desynchronization due to Dendritic Dynamics

As can be seen in Figure 5, the network does not start to resynchronize at the end of the stimulation, as is the case for the one-dimensional phase oscillator

Figure 7 Delayed phase resetting curves (dPRC) for $I_{\text{stim}} = 4.5\omega$ and stimulation length of 0.2. **(a)** A dPRC at the beginning of the stimulation. **(b)** A dPRC just before the stimulus is turned off. At this point only a vertical shift of the dPRC is present (due to the length of the pulse). The form of the dPRC changes only marginally, indicating that no transition from type one to type zero phase resetting has occurred. As the effect of the stimulation evolves over time, the form of the dPRC starts to change **(c)–(f)** and a transition from phase resetting type one to phase resetting type zero **(e)–(f)** can be observed. **(g)** The time evolution of the amplitude of the order parameter (in units of ω^* rad/cycle) over a period of 19 cycles for different initial velocity distributions. The image is composed of gray-scale-coded time courses from 100 simulation, in which the initial velocity deviation of the network have been varied in equal steps (see section 2.3.3 for explanation)

model, but instead becomes more desynchronized after the stimulation ends. Full desynchronization is reached after some time delay, and only then does the network begin to resynchronize again. If the pulse is too long, the network will desynchronize to a much lower extent and it will not cross the origin of the Gaussian plane.

To further understand this effect, we introduce *delayed phase resetting curves* which give us a convenient way to visualize the network dynamics. Traditional phase resetting curves (PRC) show the phase at the end of the stimulation φ_E plotted against the stimulus starting phase φ_B . The critical set of stimulation parameters is connected with a change in a particular topological property of the PRC, the *winding number* [5, 48]. The winding number is defined as the net number of times that φ_E runs through one full cycle from 0 to 1 while φ_B runs through one full cycle from 0 to 1 (the winding number can also be interpreted as an average gradient of PRC over one full cycle of φ_B). In the network consisting of neurons with dendritic dynamics, the phase at the end of the stimulation φ_E does not represent the full impact of the stimulus. To account for this fact, we now introduce *time-delayed phase resetting curves* (dPRC(t)). In order to construct a single delayed phase resetting curve, we evaluate the phase φ_E at given time t after the end of the stimulation, and introduce a new notation for this $\varphi_E(t)$. Now the traditional phase at the end φ_E is equal to $\varphi_E(0)$, i.e., the phase is evaluated at time $t = 0$ after the end of the stimulation. We construct dPRC(t) as a set of phases $\varphi_E(t)$ plotted against the starting phase φ_B . We will use dPRC(t)s for the calibration of the stimulation.

Figure 7a–f shows delayed phase resetting curves for a network of 100 neurons with stimulation strength $I_{\text{stim}} = 4.5\omega$ and stimulation length 0.2. For small delay t (evaluation time point), the $\varphi_E(t)$ are close to φ_B , with some small shift in the vertical direction (Figure 7a,b). In this case the winding number is equal to one. When the delay t exceeds $t_{\text{crit}} \approx 0.4$, the $\varphi_E(t)$ do not run through the full cycle, and the dPRC(t)s change their topological properties and have winding number equal to zero. For any combination of parameters to be critical, this transition from a winding number of one to a winding number of zero must be observed in one of the dPRC(t)s. The change of the winding number from one to zero implies the existence of a trajectory of $Z(t)$ which runs through the origin of the Gaussian plane [5]. Such a trajectory will thus result in complete desynchronization of the network. This fact will be of crucial importance to the calibration method described below.

2.3.3 Velocity Distribution Effects on Resynchronization Time

The second important aspect which must be considered in the search for the optimal stimulation parameters is the distribution of the phase velocities at the point of complete desynchronization, i.e., the velocities of the neurons when their phases are equally distributed over the whole phase range and the order parameter $Z(t)$ is equal to zero. This is because a fully desynchronized network will resynchronize faster when there is a range of phase velocities at the time of full desynchronization, than when the neurons all have approximately the same phase velocity [38].

To better understand the influence of the velocity distribution on the resynchronization, numerical simulations have been performed with a set of preselected initial conditions, such that the phases of the neurons are uniformly distributed at the beginning of the simulation. The initial phase velocities are selected from a normal distribution with mean equal to the natural frequency of the neurons. This represents

the network shortly after an optimal stimulus was applied, when the system is maximally desynchronized. We then varied the standard deviation of the velocity distribution in order to see how the broadness of the velocity distribution affects the amount of time required for resynchronization.

We can see from Figure 7g that the strongly desynchronized state lasts longer for a δ -like distribution of velocities, whereas for broader distributions the resynchronization time becomes smaller. This is because the uniformly distributed phases, combined with a δ -like velocity distribution at the eigenfrequency of the oscillators, constitutes a fixed point in the phase space of the network [38]. This fixed point is unstable, but when the system is at that fixed point, the effect of the coupling vanishes. As the neurons begin to cluster together, the coupling becomes more effective. The time required for this clustering should therefore be maximized. Of course, for very broad velocity distributions (greater than 0.4 in our simulations), the resynchronization takes a very long time. This is also due to the inertia in the system. Neurons which are moving much faster than the natural frequency will take a long time to slow down to their natural frequency, which they must do in order for synchronization to be achieved. Likewise, oscillators moving much slower than the natural frequency (or even backwards) will take a long time to speed back up to the natural frequency. This is not ideal, though. Not only does such a stimulus require a great deal of energy (something we are trying to minimize), but in the case of real neurons such strong stimuli are likely to drastically alter the dynamics. For example, unlike our model neurons, a real neuron cannot oscillate with a negative frequency. Nor can it fire at arbitrarily high rates. Such broad velocity distributions are therefore not very representative of real neural dynamics. Thus, the optimal stimulation parameters should be chosen to induce a complete desynchronization, and additionally to cause the standard deviation of the velocities at the point of complete desynchronization to be near to zero.

2.3.4 The modified calibration technique

Taking these effects of dendritic dynamics into account, we propose the following modification of the calibration technique from [9]. We begin by applying a stimulus of fixed strength and duration to the neural population at random times (each separated by enough time for the effects of the previous stimulus to wear off). The instantaneous phase of the neural population can then be estimated from the experimental data (for example, by means of band-pass filtering and Hilbert transformation [4]). We can then construct delayed phase-resetting curves, and see whether a transition from winding number one to zero occurs. If it does not, then we repeat the stimulation with different combinations of stimulation strength and duration until we find a combination for which this transition occurs. From these delayed phase-resetting curves we can then determine the starting phase of the stimulation which will result in complete desynchronization of the population.

This combination of stimulation parameters will desynchronize the population, but may not be the optimal parameters for maintaining desynchronization for a long time with a minimal energy expenditure. To optimize our parameters further, we then repeat the above procedure for progressively weaker stimuli and shorter durations, until the transition no longer occurs. This allows us to find the parameters that will desynchronize the population with a minimal expenditure of energy,

and will result in a very narrow distribution of velocities at the time of complete desynchronization.

3 Phase-Independent Desynchronization

In this section we investigate several stimulation techniques that have been proposed for phase-independent desynchronization of a neural network, and compare them to single-pulse stimulation. Our goal is to determine the most effective technique that requires minimal stimulation strength for desynchronization of the network.

3.1 Single Pulse

As shown in previous sections, for fixed stimulation length the single-pulse stimulation induces desynchronization only for a small range of initial phases. Let us consider the desynchronizing effect of a single pulse on a network in the synchronized state. The stimulation parameters are chosen from the data in Figure 6 as follows: initial phase $\varphi_B = 0.65$, amplitude $I_{\text{stim}} = 4.5\omega$, and stimulation duration $t_{\text{stim}} = 0.2$. Before the stimulation, the order parameter $Z(t)$ runs on its limit cycle. During a pulse which is applied at the optimal initial phase, the network starts to desynchronize. The stimulus is turned off before the network fully desynchronizes. $Z(t)$ then reaches the origin of the Gaussian plain with some delay. Since the desynchronized state is unstable, $Z(t)$ then spirals back to its limit cycle (Figure 5b). To keep the network in the desynchronized state, the stimulation must be periodically readministered. The crucial aspect of single-pulse stimulation is that each pulse must be administered at the critical phase. When the pulse is applied at other phases, it results in the network resynchronizing more quickly, or may even cause the network to become more synchronized than in the unperturbed state (Figure 8a). As a consequence, in order for the single-pulse stimulation to be effective, online monitoring of the network state is required. This is a highly complicated and energy-demanding technical task. To overcome this problem, compound stimulation techniques have been developed [9, 20, 22, 49].

3.2 Composite Desynchronizing Stimuli

To effectively desynchronize the network without online phase monitoring, several composite stimulation techniques have been developed, including double-pulse stimulation [20, 21], high-frequency entrainment followed by a desynchronizing stimulus [22], and low-frequency entrainment followed by a desynchronizing stimulus (*Soft Phase Resetting*) [9, 23]. These new techniques are based on the following principle. The stimulation is split into two different epochs. During the first epoch we have to put the network to a known *controlled state*. Before the first epoch, in the synchronized stable state, $Z(t)$ runs on its limit cycle. During the first stimulation epoch $Z(t)$ quickly converges towards its attractor $Z^{\text{stat}}(t)$, which is the state the network would converge to under persistent stimulation, and, depending on the stimulation used, may be a fixed point, or limit cycle. At the end of the first epoch, regardless of the initial phase, $Z(t)$ will be very close to $Z^{\text{stat}}(t)$. During the pause between the epochs, $Z(t)$ will relax to its unperturbed limit cycle in a stereotyped

Figure 8 The time course of the firing density before, during, and after stimulation for each of the stimulation methods. **(a)** Single pulse: a pulse is applied at the critical phase of the network (first black line), which desynchronizes the network. Later, as the network resynchronizes, a pulse is applied at a randomly selected phase. This fails to desynchronize the network, because the stimulation did not occur at the vulnerable phase. **(b)** Double pulse: a strong pulse is used to push the network to the quiet regime. A fixed time later, a desynchronizing pulse is administered. When the system begins to resynchronize, the process is repeated. In this case the system is again desynchronized, even though the process was performed at arbitrarily chosen times. **(c)** Low frequency pulse stimulation: a strong low frequency stimulus is applied, which also forces the network to the quiet regime. As with the double-pulse technique, the system can then be desynchronized with a single pulse applied with a fixed delay. This is accomplished with much less energy than the double pulse. **(d)** Soft phase resetting: a sequence of very strong, but very short pulses is applied with a frequency close to that of the network. This puts the network into a state where the neurons continue to fire, but in a very desynchronized way. Once this state is reached, another stimulus is applied which is timed so as to create an optimal distribution of phase velocities. This method gives the longest period of desynchronization, with a minimal expenditure of energy. The stimulation parameters were: **(a)** The initial phase for the first pulse $\varphi_B = 0.55$ and randomly selected for the next, the stimulation amplitude $I_{\text{stim}} = 6.5\omega$, and the length of the pulses $T_{\text{stim}} = 0.35$. **(b)** The amplitude of the resetting pulse $I_{\text{rst}} = 8.0\omega$, the length of the resetting pulse $L_{\text{rst}} = 7.0$. The amplitude of the desynchronizing pulse $I_{\text{stim}} = 6.5\omega$, and the length of the pulse $T_{\text{stim}} = 0.5$ applied after a delay $\tau = 1.01$. **(c)** The entrainment amplitude $I_{\text{entr}} = 8.0\omega$, the length of the entrainment is $L_{\text{entr}} = 7.0$, the frequency of the pulses in the train is $F_{\text{entr}} = 6.0$ Hz, and the length of the pulses in the train is $T_{\text{entr}} = 0.1$. The amplitude of the desynchronizing pulse $I_{\text{stim}} = 6.5\omega$, the length of the pulse is $T_{\text{stim}} = 0.35$ applied after a delay $\tau = 1.01$. **(d)** $I_{\text{entr}} = 15.0\omega$, $L_{\text{entr}} = 6.67$, $F_{\text{entr}} = 0.9$ Hz, $T_{\text{entr}} = 0.075$, $I_{\text{stim}} = 4.5\omega$, $T_{\text{stim}} = 0.22$ and $\tau = 0.9$. The network parameters are $K = 4\omega$, $D = 0.07$, and size $N = 500$.

way. The second stimulation epoch starts when $Z(t)$ is at the selected optimal initial phase, which due to the stereotyped behavior will happen after some predetermined delay, and so the second stimulus will push $Z(t)$ towards the origin of the Gaussian plane. The network will then start to resynchronize again. We can then periodically measure the state of the network, and when the synchronization is over some given value the procedure can be repeated.

There are several techniques for putting the network to a *controlled state* (hard reset [20, 21], high frequency pulses, [22], and low frequency pulses [9, 23]). In the following section we will apply selected compound stimulation techniques to the synchronized network of neurons with inertia.

3.2.1 Double Pulse

The double pulse consists of two single pulses with a pause in between. The first pulse is very strong, and should reset the network to a stereotyped state. Each neuron is reset to its fixed point. The network as a whole is then strongly synchronized, with order parameter $Z(t) \approx Z^{\text{stat}}$, where $Z^{\text{stat}} = R^{\text{stat}} \exp(i\varphi_{\text{stat}})$ with $R^{\text{stat}} = 1$ and $\varphi_{\text{stat}} = \phi_{\text{fix}} = \cos^{-1}(-\omega/I_{\text{stim}})$.

With some delay after the first stimulus is turned off, the second one is applied. The second pulse will therefore always hit the network in the vulnerable phase, and hence $Z(t)$ will be forced to move toward the zero of the Gaussian plane. Before $Z(t)$ reaches the zero of the Gaussian plane the stimulation is turned off, so as to result in optimal desynchronization as described in Section 2.3. The stimulation parameters are chosen in such a way that when $Z(t)$ reaches zero the network has minimal variability in phase velocity.

The dynamics of the network is visualized by the means of the amplitude $R(t)$ of the order parameter (Figure 9a) from Eq. (6) and the firing density $p(t)$ (Figure 8b). As can be seen in Figure 9a, full desynchronization of the network is induced for all initial phases.

3.2.2 Low Frequency Pulse

The low frequency pulse is also composed of two stimulation epochs with a pause in between. In the first epoch a train of short pulses with low frequency (less than 10 Hz, but greater than the eigenfrequency) is applied. $Z(t)$ is again shifted to $Z^{\text{stat}}(t)$, but unlike the double pulse case, the transition occurs over several cycles. An advantage compared to the double pulse, though, is that only a fraction of the energy is required to put the network into the stereotyped state. After a small time delay after the end of the first epoch, the desynchronizing pulse, with the same parameters as in the double pulse case, is applied. The firing rate of the network is strongly quenched during the first epoch, due to the neurons all being forced to the quiet regime (Figure 8c), and after the desynchronizing pulse is applied, the system is completely desynchronized independently of the initial phase (Figure 9b).

Since the model does not have a fast time scale, the effect of entrainment frequencies over 10 Hz is approximately the same as that of continuous stimulation (tested by numerical simulations, results not shown). Hence the effects of high frequency stimulation are well approximated by continuous stimulation. Compound stimulation methods which use a high-frequency pulse train for the first epoch are

Figure 9 Time course of the amplitude of $Z(t)$ from Eq. (6) before, during, and after a double pulse (a), low frequency pulse (b), and soft phase resetting (c), where φ_B denotes the phase at the beginning of the stimulation. (a) Double pulse stimulation: the first pulse forces the network to the quiet regime (all neurons stop firing). When the first pulse ends, then system begins to resynchronize in a stereotyped way, so that the second pulse always catches the network at its vulnerable phase, thereby desynchronizing the network independently of the initial phase. (b) Low frequency pulse stimulation: results are qualitatively the same as for the double pulse stimulation, but with a much lower energy expenditure. (c) Soft phase resetting: a sequence of pulses at approximately the same frequency as the network, causes the network to go to a cycle which oscillates between partial and full desynchronization. A final pulse is then applied which results in the network being fully desynchronized with the optimal phase velocity distribution. The stimulation parameters are the same as in Figure 8.

thus essentially equivalent to the double-pulse method (for this model), and thus will not be discussed further here.

3.3 Soft Phase Resetting

The soft phase resetting (SPR) technique is also based on the application of two qualitatively different stimuli. The first stimulus induces a soft reset by means of a periodic pulse train, where the entraining frequency is close to the natural frequency of the network [9, 23]. During the course of the entrainment the influence of the initial dynamic state at the beginning of the stimulation decays while the network performs several periods of oscillation. The second stimulus is a single pulse which hits the network in a vulnerable phase and desynchronizes it.

For low-amplitude stimulation, soft phase resetting works in this model very analogously to the one-dimensional phase oscillator model. The neurons all lock to the stimulus, thereby putting the network into a stereotyped state. A second pulse can then be used to desynchronize the network exactly as in the case for single pulse stimulation, with the advantage being that instead of having to monitor the network so as to catch it at its vulnerable phase, we will now know exactly when the network will be in this state. Because the only aspects of this which differ from the one-dimensional model have already been covered in our treatment of single pulse stimulation, no further results for this are shown here.

As the stimulation strength increases (again with stimulation frequency near the eigenfrequency of the neurons), the effects of soft phase resetting in a network of coupled neurons with dendritic dynamics becomes quite different from in the one-dimensional phase oscillator model. In this case, the first epoch induces strong oscillatory desynchronization. The pulse parameters are selected in such a way that each pulse induces a very strong velocity spread, i.e., each pulse induces a short but strong desynchronization. For example, we use single pulses with $I_{\text{stim}} = 21\omega$ and very short duration $t_{\text{stim}} = 0.075$. The attractor of this stimulation is an elliptical stable limit cycle $Z^{\text{LFD-stim}}$ which crosses the origin of the Gaussian plane and has a maximal distance to the origin smaller than 0.5. During the pulse train, after the point of maximal desynchronization has been passed, the network starts to resynchronize again very quickly (due to the strong velocity spread). But before the network significantly resynchronizes, the next pulse of the train will hit the network and desynchronize it again. After six such pulses we have sufficient control over the network for all starting phases, i.e., the phase of the network is synchronized with the stimulation. In the second epoch, after some predetermined delay, the second pulse is administered. It does not directly desynchronize the network, but instead just adjusts the distribution of velocities to an optimal value. This velocity distribution will cause the network to become fully desynchronized, and at the point of complete desynchronization the velocities will have only a minimal spread and the resynchronization will thus occur at the minimal speed. The advantage to this over the low-amplitude soft phase resetting technique is that here the neurons fire in an uncorrelated way during the first epoch. The desynchronization during the first epoch is not perfect, and we can observe low amplitude oscillations in the firing rates at the harmonics of the natural frequencies, but, as can be seen in Figure 8d, the overall firing rate of the network is still very low during the entrainment period.

4 Discussion

As a next step towards developing new desynchronization-based experimental techniques for brain research, we have applied basic phase-resetting techniques to a neuron model with dendritic dynamics, which is known to be an important aspect of neural dynamics [29–31, 34]. Formally the dendritic dynamics in our model corresponds to the inertia of the oscillator. These extensions leave much of the qualitative aspects of the desynchronization process intact, but introduce several phenomena not seen in the one-dimensional model:

Bistability: In the case of medium stimulation amplitudes the oscillatory and quiet regimes coexist both for individual neurons, and also in the network, i.e., at

some phases at which stimulation is started the neurons will fire whereas at other phases they will stay quiet. The region of bistability depends on the inertia and the eigenfrequency of the neuron. For neurons oscillating at high eigenfrequencies even very small inertia values result in broad regions of bistability. At the level of the network, this dynamical property of the neurons results in strong oscillations of the amplitude of the order parameter, when medium continuous stimulation within a narrow range of initial phases is applied. This bistability plays a crucial role in the mechanism by which the various desynchronizing stimulation techniques affect the network.

Delayed desynchronization: The inertia inherent in the dendritic dynamics results in delayed desynchronization. This means that the maximal desynchronization of the network is reached with a certain time lag after the stimulation is turned off. This is a consequence of the stimulation acting not on the phases but on the velocities of the neurons. This means that the standard phase-resetting curves are no longer applicable for the calibration, because the state of the network cannot be described by a single parameter. Inducing desynchronization therefore does not imply that optimal desynchronization has been achieved. The resynchronization time depends both on the uniformity of the distribution of the phases, and also on the distribution of the phase velocities at that time. To account for these effects in real applications, we have modified the standard calibration technique [9] in order to reliably determine the optimal combination of stimulation parameters. First, one must find a critical combination of stimulation amplitude and length which induces desynchronization, and then adjust these parameters so as to minimize the broadness of the velocity distribution at the time when desynchronization occurs. Similar delayed desynchronization effects have been observed experimentally in systems of coupled electrochemical oscillators [49]. In this case, a single electrical pulse was applied to a system of 64 electrochemical oscillators. When the stimulation was applied at a critical phase of the system, strong desynchronization was observed. As with the model we have presented here, the maximal desynchronization occurs with some delay after the end of the stimulus. Zhai et al. observe that the one-dimensional phase oscillator model is thus not suitable for describing the response of such a system to a desynchronizing stimulus. Our results here indicate that the two-dimensional model we have presented may also be useful for modelling such electrochemical oscillators.

Several stimulation techniques which were originally developed for the one-dimensional model were successfully applied to networks of neurons with dendritic dynamics. For these pulse-based techniques a long entrainment period (5–6 cycles) is required in order to achieve sufficient control over the network. As a possible solution for this complication, a soft phase resetting stimulation technique with short pulses of strong amplitude has been proposed. In the entrainment epoch the network is kept in a strongly desynchronized state, and the subsequent mild pulse adjusts the velocity distribution to a value which will induce full desynchronization for as long as possible.

In addition to the applications to deep brain stimulation treatment of movement disorders mentioned previously, the pulse-based desynchronization techniques described here may also be useful for the effective suppression of brain rhythms, for example by sensory stimulation. One possible application might be the suppression of the gamma rhythm in order to test its functional relevance [9]. Another promising

application might be the suppression of the theta rhythm, since its functional relationship is also still under debate [51, 52]. Prominent oscillations in the theta range (4–8 Hz) have been observed in rodents during spatial navigation [53–55]. The assumed functional role of theta oscillations in rodents is to provide a reference frame for neural coding, in which the position is represented by the phase in the theta cycle [54, 56]. Sustained oscillatory activity in the theta range can also be found in human EEG and MEG measurements [50, 57, 58]. Tesche and Karhu have observed stimulus-locked theta oscillations during a working memory (WM) Sternberg task [59]. The subjects had to memorize from one to seven numbers during an encoding sequence. After each sequence, with a short delay, the subjects decided whether the test probe was in the previous sequence (in-set) or not (out-of-set). A strong phase reset of the theta rhythm was detected after each item from the sequence and after the probe. The duration of theta oscillations after the in-set probe is correlated with the number of items in the encoding sequence. The desynchronization techniques presented here may be used for experimental stimulation to suppress theta activity in order to study the role of the theta rhythm in human memory processes. For this, the sequence of items to be memorized, and the probe, have to both be presented with appropriate timing and intensity, so that the theta rhythm will be suppressed. This might allow a selective study of the role of theta activity in encoding and recognition in the human brain.

Acknowledgements The authors would like to thank Prof. Lutz Schimansky-Geier and Prof. Yuri L. Maistrenko for very useful discussions. This work was supported by the European Union through the Network of Excellence BioSim, Contract No. LHSB-CT-2004-005137.

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