Neural Synchronization at Tonic-to-Bursting Transitions

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Abstract We studied the synchronous behavior of two electrically-coupled model neurons as a function of the coupling strength when the individual neurons are tuned to different activity patterns that ranged from tonic firing via chaotic activity to burst discharges. We observe asynchronous and various synchronous states such as out-of-phase, in-phase and almost in-phase chaotic synchronization. The highest variety of synchronous states occurs at the transition from tonic firing to chaos where the highest coupling strength is also needed for in-phase synchronization which is, essentially, facilitated towards the bursting range. This demonstrates that tuning of the neuron's internal dynamics can have significant impact on the synchronous states especially at the physiologically relevant tonic-to-bursting transitions.

Keywords Neural synchronization · Gap junction · Tonic-to-bursting transition

1 Introduction

Neuronal synchronization is known to play a crucial role in many physiological functions such as information binding [1] and wake-sleep cycles [2] as well as in pathophysiological processes as occurs in Parkinson's disease and during epileptic seizures [3, 4]. Transition to a synchronized state can be associated with the occurrence of bursting activity. For example, thalamocortical neurons synchronize in burst discharges at transition to the sleep, while they show desynchronized tonic activity in waking states [2]. Synchronized discharges during epileptic seizure seem to be related to transitions from tonic firing to burst activity as does synchronized activity in sensory-motor nuclei which generates the tremor of Parkinson's disease [5–7].

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Besides of the impact to neural synchronization, alterations of the firing pattern carry physiologically relevant information. This has been demonstrated for sensory encoding [8] as well as for hormone release, especially for vasopressin secretion from neuroendocrine hypothalamic nuclei which drastically increases when burst discharges are induced [9]. Similar effects can be observed in peripheral glands, e.g. in pancreatic β -cells where physiologically significant insulin secretion depends on the transition to bursts [10]. Indeed, such interdependencies seem to reflect rather general characteristics of neurosecretion including neurotransmitter release. Hence, alterations of discharge pattern which may appear with changed synchronization states can be of high functional relevance.

However, alterations of discharge pattern do not necessarily arise from network effects due to changed neuronal connectivity but also can be caused by alterations of the individual neuron's membrane properties, e.g. by modulation of ionic conductances in response to external stimuli like temperature, osmolarity or ionic concentrations [11]. Even an additional tonic current which may reflect an unspecific synaptic input or the effects of neuromodulators, hormones and drugs can significantly change activity patterns of individual neuron [2] due to the neuron's inherent nonlinearities.

The questions are: To what extent does neuronal synchronization depend on the individual neuron's dynamics, and how does the synchronization state, in turn, affect the neuron's activity patterns? There exist a large number of computational studies that have brought essential new insights into basic principles of synchronization, e.g. [12–18]. Many of these studies, although physiologically motivated, were done with rather general mathematical descriptions of the individual elements and their connectivity. Others considered specific patterns, e.g. synchronization of bursters [12, 19–21], chaotic synchronization [22–24] and synchronization in a tonic firing regime [25]. However, most of these studies have mainly emphasized the impact of the network's connectivity for synchronization, while one would expect that acute information processing is mainly based on alterations of individual neuron membrane conductances due to their synaptic input rather than on changes of the neuronal connectivity.

The goal of the present work is to analyze (1) how the synchronous state changes when individual neurons undergo a transition from the tonic firing to bursting regimes and (2) how the coupling affects the firing pattern of the neurons. Tonic-to-bursting transitions have been observed and analyzed in many systems, for example for a two-dimensional map [26], Hindmarsh–Rose model [27], models of heart interneurons [28] and β -cells [29] etc. We have chosen the Huber/Braun neuron model [30] which is based on Hodgkin–Huxley type algorithms and can reproduce a wide variety of spiking patterns. The original Huber/Braun model exhibits two different types of tonic-to-bursting transitions. The first transition – from the tonic firing regime with prominent subthreshold oscillations – occurs via a period-adding pattern. Synchronization effects at this transition were recently examined by Bahar [25]. We focus on the second type of tonic-to-bursting transition because it seems to be physiologically more relevant in the central nervous system. It occurs via period-doubling bifurcations and includes pacemaker-like tonic firing, bursting and a broad range of chaos in between.

The paper is organized as follows: Section 2 presents the model equations and explains their physiological background, including tonic-to-bursting transition in a single neuron; Section 3 describes the methods by which the simulations were done

and how the synchronization states were determined; Section 4 presents the results showing the different states of synchronization with varying control parameters, the coupling strength and the external tonic current. Finally, in Section 5 we discuss the observed dynamics and their potential relevance for physiological and pathophysiological processes.

2 Model

A model which is capable of demonstrating bursting activity should include slow and fast dynamics [31]. In the case of the Hodgkin–Huxley type model used here, these prerequisites are given by a fast subsystem for spike-generating mechanisms which is combined with a slow subsystem for subthreshold oscillations. The spike-generating subsystem is made up of depolarizing sodium (I_d) and repolarizing potassium currents (I_r). The subthreshold oscillations result from the interaction between slow depolarizing and slow repolarizing currents (I_{sd} and I_{sr}). The slow depolarizing current I_{sd} can represent a persistent sodium current as well as a low voltage activated (T-type) calcium current. The slow repolarizing current I_{sr} is represented as a simplified version of Ca -dependent K -current and depends directly on the slow depolarizing current. These neurons can easily be driven to different dynamic states and firing patterns due to variations in their ionic conductances and/or their activation kinetics as well as by external current injection I_{ext} .

The membrane potential V for each neuron is given by:

$$C_m dV/dt = -I_l - I_d - I_r - I_{sd} - I_{sr} - I_{ext} - I_{couple},$$

with C_m denoting the membrane capacitance. The leakage I_l current is calculated by

$$I_l = g_l(V - E_l). \quad (1)$$

The voltage-dependent ionic currents are expressed in the form:

$$I_i = g_i a_i (V - E_i), i = d, r, sd, sr, \quad (2)$$

where g_i are the maximum conductances, E_i are equilibrium potentials and a_i are activation variables. The fast depolarizing current I_d activates instantaneously:

$$da_d/dt = 0. \quad (3)$$

I_r and I_{sd} activate with first order, voltage-independent time delays τ_i :

$$da_i/dt = (a_{i\infty} - a_i)/\tau_i, i = r, sd, \quad (4)$$

where the voltage dependencies of activation variables are given by sigmoid curves:

$$a_{i\infty} = 1/(1 + \exp(-s_i(V - V_{0i}))), i = r, sd, \quad (5)$$

Fig. 1 Bifurcation diagram of interspike intervals (ISI, ms) for a single neuron with tuning of external current (I_{ext} $\mu\text{A}/\text{cm}^2$). Insets illustrate time series of tonic firing ($I_{ext} = 0$ $\mu\text{A}/\text{cm}^2$), chaos ($I_{ext} = 0.3$ $\mu\text{A}/\text{cm}^2$) and bursting regimes ($I_{ext} = 0.6$ $\mu\text{A}/\text{cm}^2$)

with s_i being the half-activation slopes and V_{0i} , the half-activation potentials. The slow repolarizing current I_{sr} activates and relaxes with the time constant τ_{sr} :

$$da_{sr}/dt = (-\eta I_{sd} - ka_{sr})/\tau_{sr}. \quad (6)$$

The factor η reflects the voltage- and Ca-dependent coupling of I_{sr} to I_{sd} and k is the tuning factor for the relaxation time constant.

Gap junction coupling between neuron 1 and neuron 2 is given in the form:

$$I_{couple} = g_c(V - V_{neighbor}), \quad (7)$$

where g_c is the coupling strength and $V_{neighbor}$ is the membrane potential of the neighbored neuron.

We use I_{ext} in Eq. 1 as a control parameter for tuning our model to different dynamic states. Without an external current ($I_{ext} = 0$ $\mu\text{A}/\text{cm}^2$), the uncoupled model neuron ($g_c = 0$ mS/cm²) operates in a pacemaker-like tonic firing mode (Fig. 1, left inset). Injection of depolarizing, i.e. negative, current leads to an acceleration of the spike generation (shortening of interspike intervals). Accordingly, a positive, hyperpolarizing current decreases the firing rate. However, at a certain point ($I_{ext} = 0.056$ $\mu\text{A}/\text{cm}^2$), a cascade of period-doubling bifurcations leads to chaotic dynamics (Fig. 1, middle inset). With further increasing of current, at $I_{ext} = 0.512$ $\mu\text{A}/\text{cm}^2$, the pattern changes to regular burst discharges (Fig. 1, right inset). A detailed description of a qualitatively similar bifurcation structure of this model, which was obtained with scaling of the ionic activation kinetics, can be found in Feudel et al. [32].

3 Methods

To distinguish between different states of synchronization, we have analyzed the distribution of phase differences between the spike times of the two coupled neurons. The spike times are taken when the membrane potential crosses a -20 mV threshold in the positive direction. The phase difference is calculated by:

$$\Delta\varphi = 2\pi \frac{\tau - t_1}{t_2 - t_1}, t_1 < \tau \leq t_2, \quad (8)$$

where t_1 and t_2 are the times of subsequent spikes of the first (reference) neuron and τ is the spike time of the second neuron [18].

The alterations of synchronization states have been examined as a function of the coupling strength g_c and an external current I_{ext} . In all cases the external current was simultaneously applied to both neurons, so that parameters of the two neurons were identical at any time.

When one of the control parameters was changed, the other one was kept constant. At the beginning of each simulation the system was integrated for 500 interspike intervals to make sure that it comes to stable state. In the course of the simulation the actual control parameter (g_c or I_{ext}) was increased from 0 to 0.03 in steps of 0.0001 mS/cm^2 for g_c or, in the interval from 0 to 0.65, in steps of $0.002 \mu\text{A/cm}^2$ for I_{ext} . At each parameter step the system was integrated for 100 interspike intervals while the distributions of interspike intervals and phase differences were recorded. Examples of such recordings are shown in Fig. 4 and Fig. 5. The same method was used to plot the bifurcation diagram of interspike intervals for the single neuron (Fig. 1) and for the plots of phase difference in Fig. 2.

The two-dimensional map of synchronous states in Fig. 3 was obtained with simulations which were run in both directions, i.e. with tuning of g_c at different constant values of I_{ext} and with tuning of I_{ext} at different constant values of g_c . In each direction about 30 simulations were run with a higher density where significant changes in the phase plots have been observed, e.g. at constant currents in the range of the period doubling bifurcation.

All integrations were performed at random initial conditions using the fourth order Runge–Kutta method with time step of 0.05 ms.

Fig. 2 Phase projections of V_1 vs. V_2 in mV (left panels), plots of phase differences in radians vs time in milliseconds (middle panels) and voltage traces for both neurons (right panels) for different types of activity: **a** out-of-phase ($g_c = 0.001 \text{ mS/cm}^2$), **b** asynchronous ($g_c = 0.005 \text{ mS/cm}^2$), **c** out-of-phase of period four firing ($g_c = 0.01 \text{ mS/cm}^2$), **d** out-of-phase of period four firing ($g_c = 0.02 \text{ mS/cm}^2$), **e** almost in-phase chaotic ($g_c = 0.025 \text{ mS/cm}^2$), **f** in-phase synchronous state ($g_c = 0.03 \text{ mS/cm}^2$). Data are from the tonic firing regime ($I_{ext} = 0.045 \mu\text{A/cm}^2$). Note the zoomed phase plots in **d** and **e**

Fig. 3 The map of synchronous states for two electrically coupled neurons on the plane of parameters: coupling strength (g_c mS/cm²) and external current (I_{ext} μ A/cm²). The panel on the right shows the bifurcation diagram of interspike intervals for uncoupled as well as for in-phase synchronized neurons (the same as on Fig. 1). The letters indicate areas of different synchronous states and asynchronous activity: (a) out-of-phase of period 1, (b) asynchronous, (c), (d) out-of-phase of higher period, (e) almost in-phase chaotic state, (f) in-phase synchronization. The area (m) denotes to a particular area of multistability of asynchronous behavior and in-phase synchronization. The dotted lines indicate the zones of transitions between spiking patterns of individual and in-phase synchronized neurons from tonic firing to chaos (lower lines) and from chaos to bursting (upper lines)

4 Results

According to the distribution of the phase differences, we can distinguish between a diversity of synchronous (out-of-phase and in-phase) and asynchronous states.

The richest dynamics can be observed with tuning of the coupling strength in the tonic firing regime close to the bifurcation to chaos. At $I_{ext} = 0.045$ μ A/cm², the following rhythmic activities can be detected (Fig. 2): asynchronous behavior, out-of-phase, in-phase and almost in-phase chaotic synchronization.

- Out-of-phase synchronization is characterized by a pattern with a constant phase difference ($\Delta\varphi \neq 0, 2\pi$) (Fig. 2a,c,d). The out-of-phase states can be categorized depending on the periodicity of the solution. Firstly, there is the out-of-phase state of period 1 (Fig. 2a) when the phase difference maintains a constant nonzero value (in this example $\Delta\varphi \approx 0.19\pi$). Secondly, there are out-of-phase synchronous states of higher periods (Fig. 2c,d). In Fig. 2c one can see four lines at different constant values of $\Delta\varphi_1 \approx 0.023\pi$, $\Delta\varphi_2 \approx 0.076\pi$, $\Delta\varphi_3 \approx 1.52\pi$ and $\Delta\varphi_4 \approx 1.97\pi$. In the example in Fig. 2c,d there are also four lines, but the values of the phase differences are close to 0 and 2π : $\Delta\varphi'_1 \approx 0.029\pi$, $\Delta\varphi'_2 \approx 0.032\pi$, $\Delta\varphi'_3 \approx 1.962\pi$ and $\Delta\varphi'_4 \approx 1.975\pi$.

- In-phase synchronization is attained when the spikes in both neurons are generated simultaneously ($\Delta\varphi = 0$, Fig. 2f) which only appears when the voltage traces are completely identical. In this situation, when $V = V_{neighbor}$, the coupling current is zero: $I_{couple} = g_c(V - V_{neighbor}) = 0$. Hence, the situation of in-phase synchronized neurons is the same as in uncoupled neurons and, accordingly, also the firing pattern.
- There also exists an almost in-phase chaotic synchronization as shown in Fig. 2e. In this case, the phase differences are distributed within a limited area near 0 and 2π .
- Asynchronous behavior is defined by irregular phase difference distributions as one can see in Fig. 2b.

It is necessary to note that all types of activity, besides the in-phase synchronization, are intimately related to alteration of spiking patterns. Out-of-phase synchronization of higher periods appears when an increasing coupling strength tunes the system towards the period-doubling bifurcation and neurons generate spiking patterns of higher periods. Accordingly, when the neurons exhibit a chaotic spiking pattern, irrespective of whether it is induced by coupling or by current injection, the phase differences will also demonstrate irregular distributions that indicate an asynchronous state. Further discrimination between asynchronous activity and out-of-phase synchronization of chaotic spiking pattern is beyond the scope of this work.

4.1 Diagram of Synchronous Regimes

We have studied transitions between different states of synchronization with increasing coupling strength (g_c) and current injection (I_{ext}). We focus on the general structure rather than on the details of specific bifurcations and particular structures inside the periodic windows of the chaotic activity.

The results are summarized in the map in Fig. 3. The panel on the right shows the bifurcation diagram of interspike intervals for an uncoupled neuron as a function of current injection (similar to Fig. 1). Note that the same bifurcation diagram can be built for coupled neurons in the state of in-phase synchronization.

As mentioned above, the biggest variety of synchronous states is observed at low current injection when the individual neurons are in a tonic firing regime close to the first period-doubling bifurcation (see also examples in Fig. 2). At weak coupling, there is a narrow range of out-of-phase synchronization of period-1 (a) which is expanded at the transition to chaos within a narrow range of current. With increasing coupling, the out-of-phase state is followed by a broad range of asynchronous activity that covers major areas of the map also in the range of the chaotic spiking pattern. Being originally in the tonic firing mode, the coupled neurons may pass through “islands” of out-of-phase synchronous states of higher periods (c,d) that mainly spread around the first period-doubling bifurcation. With further increase of the coupling strength, the neurons pass through the almost in-phase chaotic state (e) before settling at in-phase synchronization (f).

The almost in-phase chaotic state (e) significantly spreads into the range of the chaotic spiking pattern. It is broadest at the transition of the individual neuron's dynamics to chaos which is also the point at which the highest coupling strength is required to reach in-phase synchronization. It has a maximum value of $g_c \approx 0.0271 \text{ mS/cm}^2$ at an external current of $I_{ext} \approx 0.098 \text{ } \mu\text{A/cm}^2$. The almost in-phase

chaotic state disappears when the neurons are in a tonic firing mode far away from the period-doubling bifurcation.

All through the range of chaotic spiking patterns, the neurons have to pass a state of asynchronous activity (b) before they reach the state of in-phase synchronization (f). However, the coupling strength which is needed for in-phase synchronization is monotonically decreasing with increasing current, i.e. as the neurons approach the regular bursting range. Of particular note is that the parameter constellation at which in-phase synchronization is achieved is different depending on whether the neurons are tuned along increasing coupling strength (solid line) or external current injection (dashed line). These two lines enclose an area of phase multistability (m). Typically, the neurons are synchronized with regard to tuning of the external current earlier than with increasing of the coupling strength.

At the transition from chaos to periodic bursting ($I_{ext} \geq 0.505 \mu\text{A}/\text{cm}^2$, in between the upper dotted lines), the coupling strength that is required for in-phase synchronization drops abruptly. In the regular bursting regime it is close to zero.

Depending on the initial conditions, in-phase synchronization coexists with all other synchronization states. However, outside the areas which here are indicated as in-phase synchronization states, the range of initial conditions at which this state is stable is very small. Examples of multistability are given in Postnova et al. [33] for the tonic firing regime ($I_{ext} = 0 \mu\text{A}/\text{cm}^2$) where in-phase synchronization coexists with two symmetrical out-of-phase states with equal probability at very weak coupling while the probability rapidly goes down with increasing coupling strength.

In this work, we do not focus on the question of multistability but on the elucidation of the major synchronization states at finite coupling strengths which may reflect physiologically more significant and more realistic interactions. Specific emphasis thereby is laid on the interdependencies between the coupling strength and the internal neuronal dynamics. The diagram in Fig. 4 illustrates the distribution of the most probable synchronization states at different constellations of the two control parameters.

Fig. 4 Plots of phase differences ($\Delta\varphi$) between two neurons (*top panel*) and the bifurcation diagram of interspike intervals (ISI *ms*) (*bottom panel*) that are the same for both neurons. Simulations are from the tonic firing regime ($I_{ext} = 0.045 \mu\text{A}/\text{cm}^2$)

These data, irrespective of multistability, clearly elucidate significant differences of synchronization: (1) Two electrotonically coupled neurons are immediately going into in-phase synchronization at any finite coupling strength when they are operating in the bursting range which is in direct neighborhood of the chaotic regime. (2) The same neurons, at the vast majority of initial conditions, will need a significantly higher coupling strength for in-phase synchronization the further they are tuned away from the bursting into the chaotic mode. (3) The highest coupling strength for in-phase synchronization, again not considering the low probability of immediate in-phase synchronization, will be needed around the period-doubling bifurcation.

4.2 Interplay between Synchronous States and Firing Patterns

4.2.1 Tuning of the Coupling Strength

Transitions between asynchronous and different types of synchronous states are associated with changes of firing patterns. Figure 4 shows the evolution of the phase difference (upper diagram) and the corresponding alterations of interspike intervals (lower diagram). Since we consider identical neurons which are mutually coupled, the spiking patterns, at any time, are qualitatively the same in both neurons.

The examples in Fig. 4 are obtained with tuning of the coupling strength for the case when both uncoupled neurons are in the tonic firing regime at a constant value of external current $I_{ext} = 0.045 \mu\text{A}/\text{cm}^2$. At this value, the uncoupled neurons are close to the bifurcation from tonic firing to chaos, where the greatest variety of synchronous activity can also be seen for coupled neurons (see Fig. 3).

Comparison of the phase and interspike interval plots readily reveals that the alterations of spiking patterns are strongly associated with the alterations of the synchronous states as well as with the transition to asynchronous behavior. An irregular firing pattern appears in the asynchronous state, while, in the states of out-of-phase or in-phase synchronization, the neurons demonstrate a periodic pattern. In the state of in-phase synchronization, as mentioned above, the pattern is identical to that of the uncoupled neuron. In the following, we will describe the different states of synchronous and asynchronous behavior and accompanying changes of impulse patterns as they appear with increasing coupling between originally tonically firing neurons.

The coupled neurons first go into out-of-phase synchronization of period one. This does not destroy the regular tonic firing activity (Fig. 4). Nevertheless, the gap-junction coupling has a certain effect on the neuron activity even in this regime. Increasing coupling strength leads to a slight increase of the interspike intervals, i.e. deceleration of the firing rate.

At the transition to the asynchronous behavior, the interspike interval distribution becomes irregular. This transition does not exhibit such a clear period-doubling structure as can be seen in the single neuron dynamics (see interspike interval plot in Fig. 1). Within the asynchronous regime, the range of interspike intervals becomes broader, which is in agreement with a more homogeneous distribution of the phase differences.

At a certain coupling strength ($g_c \approx 0.0091 \text{ mS}/\text{cm}^2$), an abrupt transition back to an out-of-phase state of period-4 takes place. Accordingly, the neurons' firing pattern is changed to period-4 activity. The period-4 out-of-phase state continues over a

broad range of increasing coupling strength until the neurons again abruptly enter the region of asynchronous activity with irregular interspike interval distributions.

The second region of asynchronous behavior is followed by out-of-phase synchronization. It is again a period-4 state but with only tiny deviations of the phase difference from 0 or 2π . With increasing coupling strength, this regime changes to the almost in-phase chaotic synchronization. The phase differences in this regime are even closer to 0 or 2π , but irregularly distributed. These transitions can easily be recognized in the interspike interval plot in Fig. 4, where regions of periodic and chaotic activity are clearly distinguished.

The situation is similar at the transition to in-phase synchronization. While the phase distributions indicate a continuous shift towards 0 or 2π , the interspike interval plot reveals an abrupt transition from chaotic to period-1 activity when the system goes into in-phase synchronization.

4.2.2 Tuning of the Neuron's Intrinsic Dynamics

As indicated in the diagram in the Fig. 3, the synchronous and asynchronous states can also change when the coupling strength is kept constant but an external current is injected which tunes the neurons to different spiking dynamics. The distributions of interspike intervals for the coupled neurons can significantly differ from the distribution for the individual neurons. Figure 5 shows an example for the constant coupling strength of $g_c = 0.013 \text{ mS/cm}^2$ with increasing current. The phase differences (top

Fig. 5 Plots of phase differences (*top panel*) at constant coupling strength ($g_c = 0.013 \text{ mS/cm}^2$) with tuning of the external current I_{ext} in steps of $0.001 \text{ } \mu\text{A/cm}^2$ and (*middle panel*) the corresponding alterations of the interspike intervals (ISI, *ms*). For comparison, the *bottom panel* shows the interspike intervals for uncoupled or in-phase synchronized neurons

panel) and corresponding interspike intervals of the coupled neurons (middle panel) are presented in comparison with the interspike interval distribution of an individual (uncoupled) neuron (bottom panel).

Without current injection, the uncoupled neurons are in the tonic firing regime. In contrast, the coupled neurons exhibit irregular interspike interval distributions according to the irregular distribution of phase differences. With increasing current injection, irregular pattern of both phase differences and interspike intervals disappear. The coupled neurons enter the out-of-phase state with period-4 discharges. At this level of current injection, the uncoupled neuron still exhibits tonic period-1 activity.

At slightly higher current values, where the uncoupled neuron is in period-2 activity, the coupled neurons go back to chaotic discharges with irregular distribution of phase differences. The neurons stay in this regime for a broad range of external current.

Transitions between the different synchronization states and firing patterns occur abruptly, which is also true for the transition to in-phase synchronization. In the state of in-phase synchronization, the interspike interval plots of the two coupled neurons and of the uncoupled neuron become identical. In this case, the system goes into in-phase synchronization already at the external current of $I_{ext} = 0.218 \mu\text{A}/\text{cm}^2$ which is far within the chaotic regime. Accordingly, there is a broad range of external current within which the chaotic pattern is synchronized in-phase. This is maintained when the firing pattern finally changes to burst discharges.

5 Discussion

We have used a computational approach to examine how alterations of individual neurons' rhythmic patterns can interfere with neural synchronization and how the transition between different synchronous and asynchronous states modifies the impulse pattern. This study was based on experimental and clinical data which indicate that synchronization goes along with significant modification of the impulse patterns [1, 6, 7]. Specific emphasis was laid on the transition from tonic firing to burst discharges which seems to be of particular physiological and pathophysiological relevance.

It has recently been demonstrated in a computational study with two electrically-coupled Hindmarsh–Rose model neurons [24] that the firing pattern of coupled neurons can significantly differ from that of the isolated neurons as long as the neurons are not in-phase synchronized. This study also has shown, with examples of tonic, bursting and chaotic activity, that the coupling strength which is needed for in-phase synchronization is highest in the period-1 or period-2 tonic firing range, a little bit lower in the chaotic range and even relatively high in the example for the period-2 bursting range.

In the present study, we have systematically analyzed the transitions between different synchronous states as a function of coupling strength and current injection. In contrast to the above-mentioned simulations, we have used a Hodgkin–Huxley type model, where each parameter has a clearly defined biological correlate.

Our results demonstrated that isolated examples for different impulse patterns do not provide a complete information about transitions between synchronous states.

Even within a range of qualitatively identical impulse patterns, these transitions can appear at different parameter values (Fig. 3). This is most obvious for the range of chaotic activity within which the critical coupling strength for in-phase synchronization significantly decreases when the neurons are tuned towards to the range of periodic bursting.

The situation is similar for the tonic firing mode within which the coupling strength that is necessary for in-phase synchronization also decreases when the neurons are tuned away from the transition to chaos. The system seems to be most resistant against synchronization around the period-doubling bifurcation from tonic firing to chaos. This is also the range where a diversity of synchronous behavior can be observed.

The fact that strong diffusive coupling is needed for stable in-phase synchronization in the periodic tonic firing regime may appear counterintuitive. However, it is known that electrotonic coupling does not necessarily lead to immediate in-phase synchronization in more complex oscillators as it is also described, for example, for other models with spike generation [13, 34].

The neurons which are coupled here can certainly be classified as more complex oscillators. Remarkably, the most complex dynamics seem to develop just when the activity of the uncoupled neurons appears most simple, i.e. when they are in the regular tonic firing mode. The spike activity appears to be generated by a simple pacemaker which, however, is not the case. Although the subthreshold oscillations cannot be seen in the voltage traces, the subthreshold currents, of course, have not disappeared. When they are blocked, the neurons will be silent [30]. The subthreshold currents are still needed for spike generation and, inversely, they are periodically driven by the voltage deflections of the spikes through their full activation range. Hence, there are strong interactions between the different activation variables which apparently react very sensitively to additional input from a neighboring neuron and on its phase. In any case, the mechanisms which generate this type of tonic firing are completely different from that of a simple pacemaker which periodically triggers a spike when a threshold is reached and then resets.

The findings that these neurons are not so easy to synchronize when they operate in the periodic tonic firing mode while they immediately synchronize in the periodic burst mode may have important physiological and pathophysiological implications. The simulation results fit perfectly with experimental and clinical observations that the transition to a synchronized state is often associated with a transition to burst discharges. Why do these neurons not synchronize in the tonic firing mode? Essentially for the same reasons as in our model: the tonic activity is not generated by a pacemaker but by complex interactions between subthreshold oscillations and spike-generation which prevents an easy synchronization.

It is again within the tonic firing range that the most pronounced alteration of the firing pattern appears when the synchronous state changes. Indeed, there are significant differences between the impulse patterns of coupled and uncoupled neurons also in the chaotic range where coupled neurons may exhibit a less clear bifurcation structure and a less structured interval distribution but still remain in a chaotic regime. In contrast, for the originally tonically firing neuron, qualitative changes can be observed. It can go from the original tonic firing of period-1 to firing at higher periods and even into irregular activity with quite different interspike interval distributions. Hence, the information which may be transmitted by the impulse

pattern can significantly change depending on the synchronous (or asynchronous) state.

One of the major outcomes of our study is the demonstration that in-phase synchronization can be obtained without any changes of the coupling strength simply by tuning the neurons towards the regime of burst discharges. In this way, in-phase synchronization can be obtained already deep within the range of chaotic dynamics. Here the critical value for in-phase synchronization depends on the coupling strength. In the bursting range, the neurons immediately go into in-phase synchronization at all values of coupling strength except very tiny values. This is contradictory to the results with the HR-model which have been reported [24] but have been illustrated only with a single example which was taken from the period-2 bursting regime. This is remote from the period-5 burst activity which we have analyzed here and which occurs in close proximity to the range of chaotic activity.

Altogether these simulation studies have revealed significant interdependencies between the activity patterns of individual neurons and coupling strength. We have shown that the neurons can pass through a diversity of synchronous states and asynchronous behavior depending on the coupling strength as well as on the individual neurons' dynamics. We also have demonstrated that the neurons can be driven through different states up to in-phase synchronization without changes of the coupling strength but with only alteration of neuronal dynamics due to external current injection. The data, additionally, have revealed that alterations of the synchronous behavior are closely associated with alterations of the activity patterns which can have quite different temporal structures compared to the isolated neurons. The fact that these model neurons easily synchronize in the periodic bursting mode but not, as expected, in the periodic tonic firing mode indicates that our principal assumptions about the underlying neuronal dynamics, may be rather close to physiological and pathophysiological reality where similar phenomena have been observed. This provides a promising basis for further elucidation of clinically possible interventions not only with regard to neuronal connectivity but also at the level of neuronal control parameters, e.g. with specific blockers of identified ion channels, which can modify the individual neuron's dynamics.

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Appendix

Below the detailed set of model parameters are listed:

Equilibrium potentials: $E_{sd} = E_d = 50$, $E_{sr} = E_r = -90$, $E_l = -60$ mV;

Ionic conductances: $g_l = 0.1$, $g_d = 0.91$, $g_r = 1.21$, $g_{sd} = 0.15$, $g_{sr} = 0.24$ mS/cm²;

Membrane capacitance: $C_m = 1$ (μ F/cm²). This gives a passive time constant $\tau_M = C_m/g_l = 10$ ms;

Activation time constants: $\tau_r = 16$, $\tau_{sd} = 80$, $\tau_{sr} = 160$ ms;

Slopes of steady state activation: $s_d = s_r = 0.25$, $s_{sd} = 0.09$ mV⁻¹;

Half activation potentials: $V_{0d} = V_{0r} = -25$, $V_{0sd} = -40$ mV;

Coupling and relaxation constants for I_{sr} : $\eta = 0.012$, $k = 0.17$.

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