Synchronization in Neuronal Networks with Electrical and Chemical Coupling

Reimbay Reimbayev

Georgia State University

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SYNCHRONIZATION IN NEURONAL NETWORKS WITH ELECTRICAL AND CHEMICAL COUPLING

by

REIMBAY REIMBAYEV

Under the Direction of Igor Belykh, Ph.D.

ABSTRACT

Synchronized cortical activities in the central nervous systems of mammals are crucial for sensory perception, coordination, and locomotory function. The neuronal mechanisms that generate synchronous synaptic inputs in the neocortex are far from being fully understood. This thesis contributes toward an understanding of the emergence of synchronization in networks of bursting neurons as a highly nontrivial, combined effect of chemical and electrical connections.

The first part of this thesis addresses the onset of synchronization in networks of bursting
neurons coupled via both excitatory and inhibitory connections. We show that the addition of pairwise repulsive inhibition to excitatory networks of bursting neurons induces synchrony, in contrast to one’s expectations. Through stability analysis, we reveal the mechanism underlying this purely synergistic phenomenon and demonstrates that it originates from the transition between different types of bursting, caused by excitatory-inhibitory synaptic coupling. We also report a universal scaling law for the synchronization stability condition for large networks in terms of the number of excitatory and inhibitory inputs each neuron receives, regardless of the network size and topology. In the second part of this thesis, we show that similar effects are also observed in other models of bursting neurons, capable of switching from square-wave to plateau bursting.

Finally, in the third part, we report a counterintuitive find that combined electrical and inhibitory coupling can synergistically induce robust synchronization in a range of parameters where electrical coupling alone promotes anti-phase spiking and inhibition induces anti-phase bursting. We reveal the underlying mechanism which uses a balance between hidden properties of electrical and inhibitory coupling to act together to synchronize neuronal bursting. We show that this balance is controlled by the duty cycle of the self-coupled system which governs the synchronized bursting rhythm.

This work has potential implications for understanding the emergence of abnormal synchrony in epileptic brain networks. It suggests that promoting presumably desynchronizing inhibition in an attempt to prevent seizures can have a counterproductive effect and induce abnormal synchronous firing.

INDEX WORDS: Dynamical System, Synchronization, Stability, Graph Theory, Neuroscience, Bifurcation Analysis
SYNCHRONIZATION IN NEURONAL NETWORKS WITH ELECTRICAL AND CHEMICAL COUPLING

by

REIMBAY REIMBAYEV

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

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in the College of Arts and Sciences

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DEDICATION

This dissertation is dedicated to my family.
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LIST OF ABBREVIATIONS

- HB - homoclinic bifurcation
- HR - Hindmarsh-Rose neuronal model
- HH - Hodgkin-Huxley model
0.1 Introduction

Neuronal synchrony has been shown to be central to the function and dysfunction of human cognitive processing, memory, and locomotion [16, 17]. Synchrony plays a positive role in hippocampal networks and its disruption due to traumatic brain injury has been shown to severely impair cognitive processing and memory function for many years post-injury [65]. At the same time, synchronized neuronal firing is notoriously known to induce pathological brain states, especially during epilepsy and Parkinson’s tremors [39, 49, 2, 36]. In particular, epilepsy is widely considered a dynamical network disease and is characterized by short bursts of synchronized neuronal activity and long events called seizures. This abnormal synchrony either is localized in a specific area of the brain, yielding a simple focal seizure, or spreads across the whole brain region, usually paralyzing a patient and resulting in a complex generalized seizure [36]. Although, there have been considerable advances in the treatment and understanding of the origin of epileptic seizures, the question of why the vast regions of brain become excitable and susceptible to synchronization remains open.

The emergence of synchronized rhythms in simple and complex networks of spiking and bursting neurons has been extensively studied in the literature [62, 54, 15, 29, 20, 8, 19, 38, 61, 9, 63, 25, 3]. Bursting occurs when neuron activities alternate between a period of quiescence and fast repetitive spiking [46, 57, 28]. There is experimental evidence that epileptic seizures are accompanied by changes in neuronal bursting activities [35, 23] where individual spikes play an important role. In contrast to spiking neurons, whose synchronous behavior is quite simple, coupled bursting neurons are capable of generating various forms of neuronal synchrony. These include synchronization of individual spikes, burst synchronization when only the envelopes of spikes synchronize while the spikes remain unlocked, and complete synchronization. The onset of neuronal synchrony is controlled by a non-trivial interplay between the intrinsic dynamics of individual neurons, the type of synaptic connections, and network architecture.

Electrical and synaptic connections often play different roles in inducing synchronization or anti-phase spiking and bursting [53, 46, 14, 33, 43, 42]. In contrast to slow or delayed inhibitory
connections that favor neuronal synchrony [60, 58, 47, 48, 21], fast non-delayed inhibition is known to promote pairwise anti-phase bursting in a network with purely inhibitory synapses [62]. This is always the case in a pair of spiking neurons with fast non-delayed inhibitory connections, unless each neuron has more than one slow intrinsic variable [47]. It was also demonstrated that weak fast non-delayed reciprocal inhibition can favor the co-existence of in-phase and anti-phase bursting in networks of some bursting cell models; however, the in-phase rhythm is fragile and has a small basin of attraction [30, 31].

The network architecture also plays an important role in synchronization of an inhibitory network. For example, it was shown that even weak common inhibition of a bursting network with strong repulsive inhibitory connections by an external pacemaker neuron can induce synchronization within the network. This common inhibition can win out over the much (e.g., a hundred times) stronger repulsive connections, provided that the pacemaker’s duty cycle, the fraction of the period during which the neuron bursts, is sufficiently long [12]. Inhibitory connections also play various roles in the emergence of synchronous and asynchronous rhythms in neuronal motifs [15, 63, 61, 25]. For example, the presence of a single reciprocally connected pair provides dynamical relaying in neuronal motifs that yields zero-lag synchrony despite long conduction delays [61, 25].

In the first part of the thesis we report a counterintuitive find that fast non-delayed repulsive inhibitory connections can robustly promote synchronization, when added to an excitatory network of square-wave bursting neurons. This synergistic effect is caused by the ability of inhibition to effectively switch the type of network behavior from square-wave [56] to plateau (“tapered”) bursting [28]. Square-wave bursting [46] was named after its shape during a burst which resembles a square wave. Plateau (tapered) bursting is characterized by spikes of decreasing size that turn into a plateau towards the end of the active phase of bursting [28]. Square-wave bursters are difficult to synchronize [29] and their spike synchronization requires strong excitatory coupling, whereas plateau bursters with smaller spikes are more prone to synchrony. The added inhibition causes plateau bursting so that weaker excitatory coupling is sufficient to induce synchrony in the excitatory-inhibitory network. This effect is generic and observed in different models of bursting
neurons. In this study, we choose the Hindmarsh-Rose neuron model as an individual unit of the network. It is important to emphasize that pairwise fast non-delayed inhibition is always repulsive in networks of Hindmarsh-Rose neurons, regardless of coupling strength and initial conditions. Yet, its addition lowers the synchronization threshold much more significantly than strengthening the present excitatory connections due to the combined action of excitatory-inhibitory synaptic coupling and switching to plateau bursting.

While many studies use reduced neuronal models such as phase or relaxation oscillators where the spikes are ignored, our results promote the use of the detailed biophysical models, taking into account neuronal spikes and bursts. The discovered synergistic effect is due to nonlinear interactions of spikes; as a result, it is not observed in networks of the reduced models. Yet, there is experimental evidence that the onset and self-termination of seizures is accompanied by the transition between different types of network bursting activities [23] where the spikes play an important role. Remarkably, the transition to abnormal synchrony corresponds to switching to plateau-like bursting [23].

We use the stability analysis to reveal the general mechanism of the induced synchronization and demonstrate that there is an optimal balance between the excitatory and inhibitory couplings that trigger synchronized bursting. These results are applicable to synchronization in a pair of connected neurons as well as to large networks with mixed excitatory-inhibitory connections. We discover universal scaling laws for the onset and loss of stable synchronization where the synchronization conditions are fully controlled by the number of excitatory and inhibitory inputs each neuron receives, regardless of the network size and topology. The independence of the synchronization conditions in purely excitatory networks of bursting neurons from the details of network architecture, except for the in-degree of each neuron, was reported in [8]. In this work, we show that the inhibition-induced synchrony is also controlled by the number of inhibition inputs to each neuron; however, the scaling law for the synchrony loss is different and involves a ratio of excitatory and inhibitory inputs. These general laws are drastically different from those in linearly coupled networks with positive (attractive) and negative (repulsive) coupling where the synchronization conditions are controlled by the structure of negative connections via the eigenvalues of
the corresponding Laplacian matrix [41, 37, 40].

In the second part, we demonstrate that a similar effect is observed in a network of physiologically-based Hodgkin-Huxley-type models such as the pancreatic $\beta$-cell Sherman model [50], exhibiting square-wave and plateau-type bursting. In the Izhikevich classification [28], square-wave bursters, observed in the Sherman model, correspond to a fold/homoclinic burster. Its main signature is the presence of a homoclinic bifurcation of a saddle in the 2-D fast subsystem. In the following, we will show that the addition of inhibition induces synchrony by making this homoclinic bifurcation disappear and generating plateau-type bursting (Hopf/Hopf bursting, according to the Izhikevich classification).

In the final part of the thesis, we contribute to further understanding of cooperative dynamics in networks of bursting neurons with both gap-junctional (electrical) and inhibitory connections. Many experimental findings indicate the presence of electrical coupling in GABAergic interneurons in the central nervous systems of mammals [32], particularly among neocortical neurons of the same class [24]. Networks of low-threshold-spiking neocortical interneurons with fast inhibitory synapses were found to be connected locally by synchronizing electrical coupling, a phenomenon which may be central to the coordination of strongly-connected cortical subnetworks [4]. Indeed, GABAergic networks in the neocortex are known to control spike timing and influence rhythmogenesis throughout the entire neocortex despite a relatively small number of such inhibitory neurons [22]. Notably, it was shown that both GABA inhibitory currents and gap-junctional coupling are required for synchronized bursting in hippocampal interneurons of the rat [53]. The role of the duty cycle, the fraction of the period during which the neuron bursts, in promoting anti-phase bursting in networks with pairwise inhibitory and gap-junctional connections was previously discussed [13]. It was demonstrated that a short duty cycle can destabilize anti-phase bursting in an inhibitory network, but the addition of electrical coupling can restabilize the anti-phase pattern [13].

We report a non-trivial synchronization mechanism of the combined coupling where electrical and inhibitory connections can synergistically induce synchronized bursting in a range of parameters where electrical coupling alone promotes anti-phase spiking and inhibition induces anti-phase bursting. The synchronization mechanism, where “two wrongs make a right”, is based on the prop-
erties of (i) weak electrical coupling to stabilize burst but destabilize spike synchronization and (ii) inhibition to generally promote anti-phase bursting but stabilize spike synchrony when initial conditions are close. The combined action of the two couplings uses the best of the two worlds to foster synchronized bursting, provided that a balance between the repulsive and attracting components of the combined coupling is preserved. Through analysis and numerics, we demonstrate that this balance is controlled by the duty cycle of the self-coupled system which governs the synchronized bursting rhythm.

This synergistic synchronization effect differs from the ones previously observed in networks with combined chemical and electrical synapses [33, 43, 42]. More specifically, it was shown [33] that a small amount of electrical coupling added to already significant inhibition of the network can increase synchronization more than a very large increase in the synchronizing inhibitory coupling. Notably, each kind of synapse in this network setting [33] alone fosters synchrony, but the resultant effect is much more pronounced. It was also demonstrated [43, 42] that combining electrical synapses with inhibition in a network of spiking cells can enhance synchrony, whereas electrical synapses alone would impede synchronization. For this property to be true, the coupling strength of both electrical and chemical synapses should be sufficiently strong. In this setting, electrical and inhibitory synapses may both foster synchrony, or may compete, with one being an attractive force while the other repulses the cells. In contrast, the synergistic effect reported in Part 3 arises from non-linear interaction of electrical and chemical synapses in a range of coupling strengths where both synapses alone impede complete synchrony. The discovered synergistic effect is due to nonlinear interactions of bursting cells at the level of bursts and spikes and is not observed in networks of spiking cells or reduced phase models of neurons. In this regard, our study along with our previous work [44, 11] promotes the use of the detailed biophysical models that take into account neuronal spikes and bursts.
PART 1

SYNERGISTIC EFFECT OF REPULSIVE INHIBITION IN SYNCHRONIZATION OF EXCITATORY NETWORKS

1.1 Summary

In this part of thesis we show that the addition of pairwise repulsive inhibition to excitatory networks of bursting neurons induces synchrony, in contrast to one’s expectations. Through stability analysis, we reveal the mechanism underlying this purely synergetic phenomenon and demonstrate that it originates from the transition between different types of bursting, caused by excitatory-inhibitory synaptic coupling. This effect is generic and observed in different models of bursting neurons and fast synaptic interactions. We also find a universal scaling law for the synchronization stability condition for large networks in terms of the number of excitatory and inhibitory inputs each neuron receives, regardless of the network size and topology. This general law is in sharp contrast with linearly coupled networks with positive (attractive) and negative (repulsive) coupling where the placement and structure of negative connections heavily affect synchronization.

The layout of this part is as follows. First, in Sec. 1.2, we present and discuss the network model. In Sec. 1.3, we report the main effect observed in a two-cell network with excitatory and inhibitory connections. We also discuss the details of the transition from square-wave to plateau bursting which is caused by the disappearance of a homoclinic bifurcation that governs the type of synchronized bursting. In Sec. 1.4, we derive the variational equations for the stability of the synchronous solution and explain the main synchronization mechanism. We also suggest the universal scaling laws for the stability of synchronization in large networks. Sec. 1.5 gives additional support to the scaling law, controlling the loss of synchrony caused by overly strong inhibition. Finally, in Sec. 1.6, a brief discussion of the obtained results is given.
1.2 The model and problem statement

We consider a network of \( n \) bursting Hindmarsh-Rose neuron models with excitatory and inhibitory connections:

\[
\begin{align*}
\dot{x}_i &= ax_i^2 - x_i^3 - y_i - z_i + g_{\text{exc}}(V_{\text{exc}} - x_i) \sum_{j=1}^{n} c_{ij} \Gamma(x_j) + \\
&\quad + g_{\text{inh}}(V_{\text{inh}} - x_i) \sum_{j=1}^{n} d_{ij} \Gamma(x_j), \\
\dot{y}_i &= (a + \alpha)x_i^2 - y_i, \\
\dot{z}_i &= \mu(bx_i + c - z_i), \quad i, j = 1, \ldots, n.
\end{align*}
\]

(1.1)

Here, \( x \) represents the membrane potential, and variables \( y \) and \( z \) take into account the transport of ions across the membrane through fast and slow ion channels, respectively. The fast synaptic coupling is modeled by the sigmoidal function \( \Gamma(x_j) = 1/[1 + \exp{-\lambda(x_j - \Theta_s)}] \) [54] with the synaptic threshold \( \Theta_s = -0.25 \) [8]. The reversal potentials \( V_{\text{exc}} = 2 > x_i(t) \) and \( V_{\text{inh}} = -2 < x_i(t) \) for any \( x_i \) and any \( t \), i.e. the synapses are excitatory and inhibitory, respectively. Hereafter, the parameters are chosen and fixed as follows: \( a = 2.8, \alpha = 1.6, \lambda = 10, c = 5, b = 9, \mu = 0.001 \) [8, 9]. The connectivity matrices \( C = (c_{ij}) \) and \( D = (d_{ij}) \) define the structure of excitatory and inhibitory connections, respectively; both mutual and unidirectional coupling are allowed. \( g_{\text{exc}} \) and \( g_{\text{inh}} \) are the corresponding synaptic strengths. It is required that all row-sums of \( C \) and \( D \) are equal to \( k_{\text{exc}} \) and \( k_{\text{inh}} \), the property that implies a network where each cell has \( k_{\text{exc}} \) inputs from excitatory neurons and \( k_{\text{inh}} \) from inhibitory ones. This constraint is chosen to ensure the existence of complete synchrony and to allow the use of the stability conditions to reveal the synchronization mechanism. Note that the dynamics of completely synchronized neurons differs from that of an isolated cell and is governed by the self-connected system:

\[
\begin{align*}
\dot{x} &= ax^2 - x^3 - y - z + k_{\text{exc}} g_{\text{exc}}(V_{\text{exc}} - x)\Gamma(x) + \\
&\quad + k_{\text{inh}} g_{\text{inh}}(V_{\text{inh}} - x)\Gamma(x), \\
\dot{y} &= (a + \alpha)x^2 - y, \\
\dot{z} &= \mu(bx + c - z).
\end{align*}
\]

(1.2)

This property is a key ingredient of the synergistic effect discussed in this part of the thesis.
1.3 Two-cell network: inhibition-induced synchronization

We start off with the simplest network where two cells (1.1) are symmetrically coupled through both excitatory and inhibitory connections with $k_{\text{exc}} = 1$ and $k_{\text{inh}} = 1$. From a neuroscientist’s perspective, such a network can be viewed as the interaction between two excitatory neurons with direct excitatory and tertiary synapses [45] where the latter excites the presynaptic terminal of an inhibitory interneuron, allowing inhibition of the other excitatory cell (see Fig. 1.1) [18]. For delayed synapses, however, the dynamics might look different. From a physicist’s perspective, this is a network of two pulse-coupled oscillators with attractive and repulsive connections.

![Diagram](image.png)

Figure 1.1. (Left). Possible interactions between two excitatory neurons 1 and 2 with direct excitatory and tertiary synapses. The tertiary synapses mediate inhibition by exciting the presynaptic terminals of inhibitory interneurons at their somas. This network can be viewed as a pair of neurons effectively coupled through both excitatory and inhibitory connections (right). Excitatory (inhibitory) connections are depicted by arrows (circles). The dynamics of the two-cell network is studied in Fig. 1.2.

We use this two-cell network to demonstrate the synergistic effect and clearly describe its stability mechanism. We will then show that the same results carry over to larger networks whose architecture always supports Dale’s law [26] such that synaptic (outgoing) connections from a neuron to other cells are either all excitatory or inhibitory.

Figure 1.2 reveals that there is a broad interval of inhibitory strengths over which the repulsive inhibition compliments attractive excitation in promoting neural synchrony. Notice that the onset of spike (complete) synchronization through boundary $E1$ is accompanied by or close to the transi-
Figure 1.2. (color online). Synchronization in the two-cell network (1.1) as a function of excitation ($g_{exc}$) and inhibiton ($g_{inh}$). (Top panel) The color bar indicates the voltage difference $|x_1 - x_2|$, averaged over the last three bursting periods. The blue (dark) zone (c) corresponds to the zero voltage difference (complete synchronization), appearing from random initial conditions. Observe the effect when a small increase of inhibition from 0 dramatically lowers the synchronization threshold from 1.28 to 0.11. Note that the inhibition desynchronizes the cells in the absence of excitation ($g_{exc} = 0$), independent from the coupling strength and initial conditions. Bifurcation curve $HB$ (white dotted line) corresponds to the transition to synchronized plateau bursting. (Bottom panel) Burst synchronization. The color bar indicates the phase difference between the bursts, $\Delta \phi$, averaged over the last three bursting periods. $\Delta \phi$ ranges from 0 (burst synchrony, blue (dark) color) to 0.5 (anti-phase bursting, red color). Notice a similar effect of burst synchronization, induced by repulsive inhibition.
tion from square-wave to plateau bursting, indicated by the curve \( HB \). The two curves practically coincide up to the values of \( g_{\text{exc}} \approx 0.8 \) such that a significant reduction of the synchronization threshold for \( g_{\text{exc}} \) as much as ten times, observed at the lower values of \( g_{\text{exc}} \) is governed by this transition between the two types of bursting. This transition occurs in both the purely excitatory (Fig. 1.2b) and mixed excitatory-inhibitory connections (Fig. 1.2c). The addition of inhibition to the purely excitatory network, whose synchrony requires a much stronger coupling, makes the cells switch to plateau bursting with smaller spikes which can be synchronized by the weaker excitatory coupling. The blue (dark) synchronization region, bounded by curves \( E_1 \) and \( E_2 \), corresponds to synchronized bursting and indicates a synergistic balance between the excitation and inhibition. Overly strong inhibition destroys synchrony (through boundary \( E_2 \)) and leads to anti-phase bursting, as expected (Fig. 1.2d).

The key component of the synergistic mechanism is the ability of inhibition to induce plateau bursting via the disappearance of a homoclinic bifurcation \( (HB) \) in the 2-D fast subsystem \( (\mu = 0) \) of system (1.2) that governs the type of synchronized bursting. Figure 1.3 illustrates the bifurcation mechanism of this transition from square-wave to plateau bursting. According to the Izhikevich classification [28], square-wave bursting corresponds to fold/homoclinic bursting where the burst termination is determined by a homoclinic loop to a saddle in the fast subsystem. Increasing synaptic coupling in the self-coupled system (1.2), whether excitatory or inhibitory, eventually leads to the disappearance of this homoclinic bifurcation and induces plateau bursting (fold/fold bursting in the Izhikevich classification). This can be achieved by strong excitation (see Fig. 1.2b) or by weaker inhibition (see Fig. 1.2c). The fast \((x, y)\)-subsystem of the self-coupled system (1.2) has the nullcline \( z = h(x) \equiv -\alpha x^2 - x^3 + g_{\text{exc}}(V_{\text{exc}} - x)\Gamma(x) + g_{\text{inh}}(V_{\text{inh}} - x)\Gamma(x) \). The excitatory (inhibitory) coupling moves the nullcline \( z = h(x) \) to the right (left) (see Fig. 1.3). Remarkably, a small shift of the right branch of \( z = h(x) \) towards the synaptic threshold \( x = \Theta_s \) (to the left) caused by weaker inhibition effectively decreases the divergence inside the limit cycle of the fast system, forming the spiking manifold. This causes the limit cycle to shrink in size and makes the homoclinic orbit disappear. At the same time, a much larger amount of excitation is necessary to shift the right branch of \( z = h(x) \) to a far right region where the divergence is small enough for a
Figure 1.3. (color online). Transition from square-wave to plateau bursting in the self-coupled system (1.2), controlling the type of synchronous bursting. (Top). Square-wave burster in the uncoupled network (1.1). The right branch of the fast nullcline \( z = h(x) \) contains two points \( AH1 \) and \( AH2 \) corresponding to supercritical Andronov-Hopf bifurcations. A limit cycle of the fast system (\( \mu = 0 \)) is born from the Andronov-Hopf bifurcation \( AH2 \) and grows in size as \( z \) increases. This family of limit cycles constitutes the spiking manifold which terminates at the homoclinic bifurcation \( HB \) of the saddle point of the fast system, located on the middle branch of \( z = h(x) \). The red dotted curve schematically indicates the route for bursting trajectories. The plane \( x = \Theta_s \) displays the synaptic threshold. (Bottom) Plateau bursting induced by the combination of excitatory and inhibitory coupling (\( g_{exc} = 0.6 \) and \( g_{inh} = 0.25 \)), corresponding to point (c) in Fig. 1.2. The added inhibition leads to the disappearance of the homoclinic bifurcation such that the spiking manifold extends further up and disappears as the limit cycle shrinks to zero amplitude and disappears via the reverse Andronov-Hopf bifurcation \( AH1 \).
similar switch from square-wave to plateau bursting via the disappearance of the homoclinic orbit (see the HB curve in Fig. 1.2(top); the curve is calculated using the bifurcation analysis software CONTENT [1].

Switching to synchronized plateau bursting also shifts the plateau part of the burst to the right from the synaptic threshold (see Fig. 1.3). Due to the choice of the synaptic sigmoidal function \( \Gamma(x_j) \) in (1.1), the coupling between the cells remains continuous during this part of the burst while being pulsatile in the first half of the burst where the spikes cross the synaptic threshold \( \Theta_s \). This might not be the case in cortical networks where the coupling is always pulsatile. Figure 1.2e indicates the region between the stability boundary \( E_1 \), corresponding to the onset of induced synchrony, and the HB curve, indicating the transition to synchronized plateau bursting. This region corresponds to synchronized square-wave bursting where all the spikes cross the synaptic threshold \( \Theta_s \), making the coupling pulsatile for all times. We have also performed numerical simulations of the network (1.1) with the sigmoidal function \( \Gamma(x_i) \), replaced by the Heaviside function \( H(x_i) \), representing realistic fast pulse-coupling. The obtained stability diagrams are similar to the ones of Fig. 1.2 with a slight expansion of the left stability zone bounded by \( E_1 \) along the \( x \) and \( y \) axes, up to the synchronization coupling threshold \( g_{exc} = 1.35 \) in the purely excitatory network (cf. the synchronization threshold \( g_{exc} = 1.28 \) in the network with the sigmoidal function \( \Gamma(x_i) \)). This increase in the coupling comes from the fact that the Heaviside-type pulse-coupling has a weaker impact, compared to the sigmoidal-type coupling. As a result, larger values of \( g_{exc} \) and \( g_{inh} \) are required to achieve the same effect.

1.4 Stability mechanism

1.4.1 Two-cell network

To explain the synchronization mechanism, we use the stability equations for the infinitesimal transverse perturbations \( \xi_{12} = x_1 - x_2 \), \( \eta_{12} = y_1 - y_2 \), \( \zeta_{12} = z_1 - z_2 \) [8]:
Figure 1.4. (color online). Stability function $\Omega(x)$ for synchronized bursting. Panels (a), (b), (c), and (d) correspond to the points (a), (b), (c), and (d) in Fig. 1.2. (a). $g_{\text{exc}} = 0.6$, $g_{\text{inh}} = 0$: Unstable square-wave synchronous bursting (light brown) and the fast nullcline $h(x)$ of the self-coupled system, together with $\Omega(x)$ superimposed on its own scale. The impact of $\Omega(x)$ is not sufficient to stabilize the subthreshold part of the spikes where the coupling is insignificant (to the left from the threshold $\Theta_s$). (b). $g_{\text{exc}} = 1.28$, $g_{\text{inh}} = 0$: The increased excitation makes the impact of $\Omega(x)$ stronger; more importantly it changes the type of synchronous bursting. Notice that the spikes have shifted to the right and moved to the region where the strong coupling is present. (c) $g_{\text{exc}} = 0.6$, $g_{\text{inh}} = 0.25$: The red curve represents the contribution of the excitatory coupling $\Omega_{\text{exc}} = g_{\text{exc}} \Gamma(x) + g_{\text{exc}} (V_{\text{exc}} - x) \Gamma_x(x)$, the light green curve corresponds to that of the inhibitory coupling $\Omega_{\text{inh}} = g_{\text{inh}} \Gamma(x) + g_{\text{inh}} (V_{\text{inh}} - x) \Gamma_x(x)$, and the thick black line indicates the combined curve $\Omega(x) = \Omega_{\text{exc}} + \Omega_{\text{inh}}$. Adding the inhibition decreases the impact of $\Omega(x)$ (cf. with (a) where $\Omega(x)$ equals $\Omega_{\text{exc}}$ in (c)). At the same time, it induces plateau bursting, with the spikes in the region above the threshold, where the coupling is sufficiently strong to synchronize them. (d). $g_{\text{exc}} = 0.6$, $g_{\text{inh}} = 0.9$: Strong inhibition destabilizes synchronous plateau bursting. $\Omega(x)$ has a negative drop in the region, covering the upper knee of the nullcline. As a result, the cells diverge when slowly crawling up this part of the nullcline. Note that synchronous plateau bursting of the self-coupled system is unstable and does not represent the dynamics observed in the network; the cells get locked into anti-phase square-wave bursting (cf. Fig. 1.2d).
\[ \dot{\xi}_{12} = (2ax - 3x^2)\xi_{12} - \eta_{12} - \zeta_{12} - \Omega(x)\xi_{12}, \]
\[ \dot{\eta}_{12} = 2(a + \alpha)x\xi_{12} - \eta_{12}, \]
\[ \dot{\zeta}_{12} = \mu(b\xi_{12} - \zeta_{12}), \]

where \( \Omega(x) = S_1 + S_2, S_1 = (g_{\text{exc}} + g_{\text{inh}})\Gamma(x) \) and \( S_2 = (g_{\text{exc}}(V_{\text{exc}} - x) + g_{\text{inh}}(V_{\text{inh}} - x))\Gamma_x(x) \). Here, \( x(t) \) is the synchronous solution defined via the self-coupled system (1.2). The stability of the zero equilibrium \( \{\xi_{12} = 0, \eta_{12} = 0, \zeta_{12} = 0\} \) of the linearized system (1.3) corresponds to the stability of the synchronous solution in the original network. The function \( \Omega(x) \) represents the contribution of the excitatory and inhibitory coupling; it favors the stability of synchronization when it becomes positive and has a destabilizing impact when it is negative [8]. More specifically, the coupling term \(-\Omega(x)\xi_{12}\) aims at stabilizing the zero equilibrium of system (1.3) when it is positive and tends to destabilize the zero equilibrium when it is negative.

The two terms \( S_1 \) and \( S_2 \), composing \( \Omega(x) \), heavily depend on whether the voltage \( x(t) \) exceeds the synaptic threshold \( \Theta_s \). The first term \( S_1 \) contains the sigmoidal synaptic function \( \Gamma(x) \) and becomes significant for \( x(t) \geq \Theta_s \). Once turned on, the term \( S_1 > 0 \) makes \( \Omega(x) > 0 \) for \( x(t) \geq \Theta_s \) (see Fig. 1.4) and favors the stability for both excitatory and inhibitory coupling as \( g_{\text{exc}} + g_{\text{inh}} > 0 \).

The second term, \( S_2 \), can change sign; the term due to the excitatory coupling \( g_{\text{exc}}(V_{\text{exc}} - x) \) is positive and therefore attractive, whereas the inhibitory one \( g_{\text{inh}}(V_{\text{inh}} - x) \) is negative and repulsive. It contains the derivative \( \Gamma_x(x) \) which has a peak around \( \Theta_s \) and rapidly decaying tails (in the case of the Heaviside function \( H(x_i) \), \( \Gamma_x(x) \) turns into the delta function). Therefore, the term \( S_2 \) switches and remains on for the values of \( x \), close to the threshold \( \Theta_s \) when the spikes cross the threshold. It becomes decisive for the overall sign of \( \Omega(x) \) in a region around the threshold \( \Theta_s \), giving a distinct bell shape to \( \Omega(x) \) (see Fig. 1.4).

When \( x(t) \) drops below the threshold \( \Theta_s \), the cells are practically uncoupled. Our Lyapunov function based analysis of synchronization in excitatory networks [8, 9] suggests that the spikes are the most unstable part of the synchronous solution such that their stabilization via the synaptic coupling yields complete synchronization. The above-threshold part of the synchronous solution
lies in the stability zone as the coupling function $\Omega(x) > 0$, for any combination of $g_{\text{exc}}$ and $g_{\text{inh}}$. Therefore, this part of the solution can be stabilized by making the coupling stronger. At the same time, the subthreshold part of the synchronous spikes is difficult to stabilize as the contribution of the term $S_2$ rapidly decays to zero below from the threshold. Moreover, only excitatory coupling can stabilize the synchronous trajectory in the subthreshold region as it yields the positive peak of the bell-shaped curve $\Omega(x)$ (see Fig. 1.4a). The addition of inhibition lowers this peak and can make it negative (see Fig. 1.4d), making the region around the threshold less stable. Figures 1.4a and 1.4b show that increasing $\Omega(x)$ (via increasing $g_{\text{exc}}$) induces synchrony in the purely excitatory network. However, it requires fairly strong excitation to stabilize the synchronous solution, especially its subthreshold part. Figure 1.4c demonstrates that adding the inhibition has a two-fold effect. It lowers the stabilizing impact of $\Omega(x)$ around and below the synaptic threshold; however, it helps switching the type of synchronous bursting via (1.2), making the spikes shorter and moving them towards the stability region, controlled by the synchronizing term $S_1$. Increasing inhibition typically switches synchronous square-wave bursting to plateau bursting which places the spikes of synchronous bursting into the stability (above-threshold) region that can be in turn effectively stabilized by the excitatory coupling via $S_1$. Therefore, the combination of $g_{\text{exc}} + g_{\text{inh}}$ synergistically induces synchronized bursting within a wide region of parameters $g_{\text{exc}}$ and $g_{\text{inh}}$. Its right stability boundary $E_2$ (cf. Fig. 1.2) corresponds to synchrony loss and is defined by the mutual arrangements between the graphs of $\Omega(x)$ and the nullcline $h(x)$ (Fig. 1.4d). This happens when the upper knee of $h(x)$ falls inside the instability zone where $\Omega(x)$ is negative (cf. Fig. 1.4d). The appendix contains an additional argument for predicting the slope of boundary $E_2$. This estimate $g_{\text{exc}} = 0.78 g_{\text{inh}}$ (see Appendix) coincides remarkably well with the numerically calculated boundary $E_2$ in Fig. 1.2.

It is important to re-state that the dynamics and type of synchronous bursting $x(t)$ are controlled by the self-coupled system (1.2) and depend on both $g_{\text{exc}}$ and $g_{\text{inh}}$. This property allows the inhibition to induce plateau bursting in the self-coupled system (1.2). The synchronous bursting observed in the self-coupled system (1.2) does not necessarily represent the emergent network dynamics. This synchronous solution can be unstable, especially when $g_{\text{inh}}$ is overly strong as in
Figure 1.5. (color online). Stability diagrams for network synchronization, similar to that of Fig. 1.2. The color bar indicates the mean voltage difference \( \sum_{i=1}^{n-1} \sum_{j>i}^{n} \frac{2}{n(n-1)} (x_i - x_j) \), calculated and averaged over the last three bursting periods. Notice the nearly identical diagrams for pairs of 10-cell irregular and 5-cell regular networks with \( k_{\text{exc}} = 4 \) and \( k_{\text{inh}} = 4 \) (left pair) and \( k_{\text{exc}} = 2 \) and \( k_{\text{inh}} = 4 \) (right pair). Excitatory (inhibitory) connections are depicted by arrows (circles). Excitatory (inhibitory) neurons in the 10-cell irregular networks [with only outgoing excitatory (inhibitory) connections] are denoted by light (dark) circles. The height and width of the left instability zone, adjacent to the \( g_{\text{exc}} \)-axis and corresponding to desynchronized square-wave bursting are inversely proportional to \( k_{\text{exc}} \) and \( k_{\text{inh}} \), respectively (also compare with Fig. 1.2).

Fig. 1.4d. Therefore, the network generates a different stable rhythm; this is typically anti-phase square-wave bursting as in Fig. 1.2d (cf. the two insets for the consistency).

While the onset of inhibition-induced synchronization is typically governed by the transition from square-wave to plateau bursting, the addition of inhibition can also induce synchronized square-wave bursting in a smaller region of parameters (Fig. 1.2e). However, the synchronization mechanism is essentially the same; the inhibition decreases the subthreshold part of the spikes, without changing the type of bursting, and thus facilitates synchronization. Although, fairly strong excitation is required, making the synergistic effect less pronounced.

1.4.2 Larger networks: the scaling laws

The discovered inhibition-induced synchronization phenomenon is also present in larger networks of square-wave bursters (1.1). We demonstrate that the structure of the added inhibitory connections is not important and only the number of inhibitory inputs controls the onset of synchronization, independent from all other details of their network topology. In the context of com-
plex dynamical networks, this unexpected result indicates the drastically different roles of network topology in synchronization of linearly [37, 40] and synaptically coupled networks with attractive and repulsive connections. Figure 1.5 shows that the size of the left desynchronization zone, bounded by the $g_{exc}$ axis and boundary $E1$ (cf. Fig. 1.2), scales down vertically and horizontally by $k_{exc}$ and $k_{inh}$ times, respectively. As a result, the stability boundaries $E1$ for the onset of synchrony are nearly identical for networks of different sizes and topologies, provided that $k_{exc}$ and $k_{inh}$ are uniform for each cell. In support of this claim, we have analyzed a series of different regular and random networks (1.1) with uniform numbers of excitatory ($k_{exc}$) and inhibitory ($k_{inh}$) synapses per neuron. For all simulated networks, numerical results are consistent with the scaling law above. Figure 1.5 demonstrates two representative pairs of networks yielding the largest and smallest regions of inhibition-induced synchronization for all possible network topologies (1.1) with the given number of excitatory and inhibitory inputs. Figure 1.6 summarizes the numerical simulations of different networks with different topologies and shows how the synchronization effect of added inhibition scales with the size of the network.

To show that the scaling laws carry over to larger networks with random coupling matrices, we have simulated a 100-cell random network where each cell receives four excitatory $k_{exc} = 4$ and four inhibitory $k_{inh} = 4$ connections (Fig. 1.7). The network consists of 80 excitatory and 20 inhibitory cells such that the excitatory (inhibitory) cells only have excitatory (inhibitory) outgoing connections, thereby abiding to Dale’s law. Both excitatory and inhibitory coupling strengths are mismatched by adding $\Delta g_{ij} \cdot q$ to $g_{exc}$ and $g_{inh}$ for each existing connection $(i,j)$. The mismatch parameter $\Delta g_{ij}$ is expressed as a percentage of $g_{exc}$ and $g_{inh}$ and kept equal to 5%; the values of the parameter $q$ are chosen randomly from the interval $(-1, 1)$ for each excitatory and inhibitory connection $(i,j)$, yielding a 10% maximum mismatch. The stability diagram supports the scaling law and has a structure similar to the two left diagrams in Fig. 1.5, all corresponding to different network topologies with the uniform number of connections $k_{exc} = 4$ and $k_{inh} = 4$.

To explain the scaling law, we shall return to the transversal variational equations (1.3) written for $n-1$ difference variables $\xi_{ij} = x_j - x_i$, $\eta_{ij} = y_j - y_i$, $\zeta_{ij} = z_j - z_i$, $i,j = 1, ..., n$. The equations for the purely excitatory networks were given in [8] where an analog of the Master
Figure 1.6. (color online). Ratio of the synchronization threshold in the excitatory network without
the inhibition and the minimum synchronization threshold achieved by adding the inhibition, as a
function of the network size $n$, for different values of $k_{\text{exc}}$ and $k_{\text{inh}}$. The ratio of the synchronization
threshold reduction, induced by added inhibition is maximum as much as 12 times for the two-cell
network (compare with Fig. 1.2.) The three curves represent three types of network topology:
rings of cells with local excitatory and inhibitory connections ($k_{\text{exc}} = 2$ and $k_{\text{inh}} = 2$); all-to-all
networks with both excitatory and inhibitory connections ($k_{\text{exc}} = n-1$ and $k_{\text{inh}} = n-1$); and
rings of cells with local excitatory and all-to-all inhibitory connections ($k_{\text{exc}} = 2$ and $k_{\text{inh}} = n-1$).
Notice that the latter topology (local excitation/global inhibition) yields the smallest reduction in
the synchronization threshold for $n > 3$, and therefore has the worst synchronization properties.
Figure 1.7. (color online). (Top) Induced synchronization in a 100-cell randomly generated network with uniform $k_{\text{exc}}=4$ and $k_{\text{inh}}=4$. (Bottom) The network has 80 excitatory (red/light) and 20 inhibitory (blue/dark) cells. The excitatory connections are marked by red arrowed lines; the inhibitory coupling is indicated by blue arrows. Both excitatory and inhibitory coupling strengths are heterogeneous, with randomly distributed mismatch up to 10%. The color bar indicates the mean voltage difference as in Fig. 1.5. The stability diagram is similar to those of the two left diagrams in Fig. 1.5, corresponding to the 5- and 10-cell networks with $k_{\text{exc}} = 4$ and $k_{\text{inh}} = 4$. Complete spike synchronization is impossible in this mismatched network; however, an approximate synchronization with small voltage differences (offsets between the spikes) is robustly present. Various shades of blue and the non-homogeneous structure of the synchronization stability zone correspond to slight voltage offsets due to the parameter mismatch.
Stability Function [41] for synaptically coupled networks (1.1) was used to analyze the stability of the most unstable transverse mode. Unfortunately, the Master Stability Function cannot be applied to mixed excitatory-inhibitory networks in general as it requires simultaneous diagonalization of both the excitatory (C) and inhibitory (D) connectivity matrices. This is impossible in general unless the two matrices commute [27]. In the latter case, the stability equation for the most unstable transverse synchronous mode is the equation (1.3) with a new stability function \( \Omega^{\text{new}}(x) = (k_{\text{exc}}g_{\text{exc}} + k_{\text{inh}}g_{\text{inh}}) \Gamma(x) - g_{\text{exc}}(V_{\text{exc}} - x)\Gamma_x(x)(k_{\text{exc}} + \gamma_{\text{exc}}^2) - g_{\text{inh}}(V_{\text{inh}} - x)\Gamma_x(x)(k_{\text{inh}} + \gamma_{\text{inh}}^2) \), where \( \gamma_{\text{exc}}^2 \) and \( \gamma_{\text{inh}}^2 \) are the second largest eigenvalues of the (commuting) Laplacian connectivity matrices for the excitatory and inhibitory networks, \( C_L = C - k_{\text{exc}}I \) and \( D_L = D - k_{\text{inh}}I \), respectively. The first term in \( \Omega^{\text{new}}(x) \) accounts for the number and strength of excitatory and inhibitory inputs. The last two terms, containing the partial derivative \( \Gamma_x \) and the networks structure via \( \gamma_{\text{exc}}^2 \) and \( \gamma_{\text{inh}}^2 \), only matter for the stability/instability of synchronization in the region of \( x(t) \), close to the synaptic threshold \( \Theta_s \), similar to the two-cell network case. The shift of the nullcline \( h(x) \) and switching from square-wave to synchronous plateau bursting are governed by \( k_{\text{exc}}g_{\text{exc}} \) and \( k_{\text{inh}}g_{\text{inh}} \) via the self-coupled system (1.2). As a result, the spikes of the synchronous bursting solution leave the bell-shaped zone (similar to Fig. 1.4c) such that the contribution of the last two terms in \( \Omega^{\text{new}}(x) \) becomes insignificant for synchronization. This yields the scaling law when the minimum strength of added inhibition \( g_{\text{inh}}^* \), sufficient to induce plateau bursting synchrony is inversely proportional to \( k_{\text{inh}} \), regardless of the network size and structure (compare, for example, \( g_{\text{inh}}^* \approx 0.14 \) in the two-cell network of Fig. 1.2 and \( g_{\text{inh}}^* \approx 0.035 = 0.14/4 \) in the networks of Fig. 1.5 with \( k_{\text{inh}} = 4 \), all calculated at the level \( g_{\text{exc}} = 0.2 \)). Notice that the 5-cell networks of Fig. 1.5 correspond to the commuting excitatory and inhibitory connectivity matrices: global excitation/global inhibition and local excitation/global inhibition. In the case where the connectivity matrices do not commute (the 10-cell networks of Fig. 1.5 and the 100-node network of Fig. 1.7), the eigenvalues of the connectivity matrices cannot be used and the stability function \( \Omega^{\text{new}}(x) \) cannot be derived. A modification of the Connection Graph method [5] that uses graph theoretical reasoning instead of the spectrum of the connectivity matrices can be used to write down a set of similar stability functions. However, the stability argument is essentially the same, the induced
synchronization is governed by the transition to plateau bursting that is in turn controlled by the self-coupled system. Consequently, the same scaling law for the inverse dependence of the induced synchronization threshold on $g_{\text{exc}}$ and $k_{\text{inh}}$ also holds for realistic non-commuting coupling configurations. Our results also indicate that the loss of stable synchrony via the right (inclined) boundary (similar to boundary $E2$ in Fig. 1.2) is governed by a simple condition $g_{\text{exc}} = \alpha \frac{k_{\text{inh}}}{k_{\text{exc}}} g_{\text{inh}}$, where $\alpha$ is a scaling factor, uniform for different topologies with the same ratio $k_{\text{inh}}/k_{\text{exc}}$. As in the two-cell network yielding the slope $g_{\text{exc}} = 0.78 g_{\text{inh}}$, this condition is determined by the shift of the nullcline $h(x)$ such that the upper knee of $h(x)$ moves close to the synaptic threshold $\Theta_s$ and falls into the instability zone (as in Fig. 1.4c).

1.5 Slope of synchrony loss boundary $E2$

This section provides additional support for explaining synchrony loss, caused by overly strong inhibition via the stability boundary $E2$ (see Fig. 1). In addition to the stability argument based on the variational equations (see Sec. IV), we use a more straightforward approach to predict the slope of the boundary $E2$ in the two-cell network.

The network equations (1.1) can be written for the two-cell network as follows:

$$
\begin{align*}
\dot{x}_i &= ax_i^2 - x_i^3 - y_i - z_i + g_{\text{exc}}(V_{\text{exc}} - x_i)\Gamma(x_j) + \\
&\quad + g_{\text{inh}}(V_{\text{inh}} - x_i)\Gamma(x_j), \\
\dot{y}_i &= (a + \alpha)x_i^2 - y_i, \\
\dot{z}_i &= \mu(bx_i + c - z_i), \quad i, j = 1, 2.
\end{align*}
$$

(1.4)

Note that the combined action of two excitatory and inhibitory synapses essentially amounts to that of one synaptic connection with strength $g_{\text{syn}}$ and synaptic reversal potential $E_{\text{syn}}$. The corresponding system reads:

$$
\begin{align*}
\dot{x}_i &= ax_i^2 - x_i^3 - y_i - z_i + g_{\text{syn}}(E_{\text{syn}} - x_i)\Gamma(x_j), \\
\dot{y}_i &= (a + \alpha)x_i^2 - y_i, \\
\dot{z}_i &= \mu(bx_i + c - z_i), \quad i, j = 1, 2.
\end{align*}
$$

(1.5)
The synaptic reversal potential $E_{\text{syn}}$ changes in the range $[-2, 2]$, allowing us to vary the type of the connection from purely inhibitory when $E_{\text{syn}} = -2 < x_i$ for all $x_i(t)$, to purely excitatory when $E_{\text{syn}} = 2 > x_i(t)$. In this setting, changing the coupling strengths $g_{\text{exc}}$ and $g_{\text{inh}}$ in the network (1.4) with fixed $V_{\text{exc}} = 2$ and $V_{\text{inh}} = -2$ is equivalent to changing the values of $g_{\text{syn}}$ and $E_{\text{syn}}$ in the network (1.5). Figure 1.8 shows robust synchronization in an interval of $g_{\text{syn}}$ and $E_{\text{syn}}$. Here, the left stability boundary, indicating the drop of the synchronization threshold from $1.28$ with decreasing $E_{\text{syn}}$ from $2$, corresponds to the boundary $E_1$ in Fig. 1. The vertical stability boundary for synchrony loss at $E_{\text{syn}} = -0.25$ corresponds to the boundary $E_2$ in Fig. 1. The origin of this almost vertically rising boundary, starting roughly at $E_{\text{syn}} = -0.25$ is of no mystery if one realizes that this is also the synaptic threshold $\Theta_s = -0.25$. It is not a coincidence that these two values appear equal. Note that the synaptic connection becomes purely inhibitory when $x_i(t)$ exceeds the reversal potential $E_{\text{syn}}$. Therefore, the part of the synchronous solution lying above $E_{\text{syn}}$ (mainly, the above-threshold part of the spikes) cannot be robustly stabilized. At the same time, when $x_i(t)$ is below $E_{\text{syn}}$, the synapse is excitatory. As Fig. 1.2 suggests, when $E_{\text{syn}}$ is chosen as low as $\Theta_s$, the excitatory action of the synapse is non-existent as the synapse is practically off below the synaptic threshold $\Theta_s$.

This is the key observation for predicting the slope of the stability boundary $E_2$ in the original network (1.1). We return to the network (1.1) and notice that for the overall impact of the excitatory and inhibitory connections to be robustly synchronizing, the overall input to the $i$-th cell, $g_{\text{exc}}(V_{\text{exc}} - x_i)\Gamma(x_j) - g_{\text{inh}}(V_{\text{inh}} - x_i)\Gamma(x_j)$ must remain positive. Rewriting this condition yields $\frac{g_{\text{exc}}V_{\text{exc}} + g_{\text{inh}}V_{\text{inh}}}{g_{\text{exc}} + g_{\text{inh}}} - x_j > 0$, as $\Gamma(x_j) \geq 0$. Notice that the first term plays a role of the reversal potential $E_{\text{syn}}$ in the network (1.5). Therefore, according to Fig. 7, $\frac{g_{\text{exc}}V_{\text{exc}} + g_{\text{inh}}V_{\text{inh}}}{g_{\text{exc}} + g_{\text{inh}}}$ cannot exceed $E_{\text{syn}} \approx \Theta_s = -0.25$ for synchronization to remain stable. This yields the following condition on the stability boundary $g_{\text{exc}} = \frac{\Theta_s - V_{\text{inh}}}{V_{\text{exc}} - \Theta_s}g_{\text{inh}}$, written in terms of the parameters of the original network (1.1). Plugging in the values of the parameters $V_{\text{inh}} = -2$, $V_{\text{exc}} = 2$, and $\Theta_s = -0.25$, one gets $g_{\text{exc}} = 0.78g_{\text{inh}}$. This condition predicts the slope of the boundary line $E_2$ remarkably well. This argument also carries over to larger networks and supports the scaling law for synchrony loss: $g_{\text{exc}} = \alpha \frac{V_{\text{inh}}}{k_{\text{exc}}} g_{\text{inh}}$. 
1.6 Conclusions

In this part of the thesis, we have discovered the synergistic effect of combined attractive excitation and repulsive inhibition in promoting bursting synchrony. Remarkably, the addition of the inhibitory coupling lowers the synchronization threshold much more significantly than strengthening the present excitatory connections. The effect is generic and observed in other Hodgkin-Huxley-type models of square-wave bursting cells, including Sherman models [50] with $V_{\text{exc}} = 10 \text{ mV}$, $V_{\text{inh}} = -75 \text{ mV}$, $\Theta_s = -40 \text{ mV}$. The effect is also independent from the choice of the synaptic interaction model, ranging from the instantaneous pulsatile coupling to a fast dynamical synapse [58]. While fast non-delayed inhibition can lead to the co-existence of synchronous and anti-phase bursting in some bursting models [30] when the coupling is weak, typically comparable to the small intrinsic parameter of the individual neuron, a significant synergistic effect is only observed in a range of coupling where the inhibition is purely repulsive and strong to change the type of bursting. Our preliminary results show that inhibition also promotes burst synchrony in realistic networks with a highly heterogenous structure of connections, where spike or approximate synchrony is impossible. Our study has potential implications for understanding the emergence of
abnormal synchrony in epileptic brain networks. An epileptic patient is normally (i.e., except for during a seizure) in a desynchronized state which might correspond to the instability region to the left of the $E_1$-border in Fig. 1.2. Our results suggest that promoting presumably desynchronizing inhibition in an attempt to prevent the patient’s seizures can have a counterproductive effect and induce abnormal synchronous firing in the excitatory-inhibitory brain network. Brain networks have been also shown to evolve their functional topology during epileptic seizures [36]. In light of this, our results on the role of network connectivity, identifying network topologies with the highest and lowest resilience of abnormal synchronized bursting can give insights into how seizures self-terminate and into how to control epileptic networks.

Outside of Neuroscience, negative pairwise repulsive interactions were previously shown to have a positive effect on synchronization in linearly coupled networks, where negative interactions by themselves tend to destabilize synchronous states, but can compensate for other instabilities [40]. However, this intriguing phenomenon, where the structure of negative connections heavily affects the synchronization, is conceptually different from the one reported in this study.
PART 2

WHEN TRANSITIONS BETWEEN BURSTING MODES INDUCE NEURAL SYNCHRONY

2.1 Summary

In this part of the thesis, we continue to study the synchronization of bursting cells that are coupled through both excitatory and inhibitory connections. We extend our results (Part 2) on networks of Hindmarsh-Rose bursting neurons [11] to coupled Sherman $\beta$-cell models and show that the addition of repulsive inhibition to an excitatory network can induce synchronization. We discuss the mechanism of this purely synergetic phenomenon and demonstrate that the inhibition leads to the disappearance of a homoclinic bifurcation that governs the type of synchronized bursting. As a result, the inhibition causes the transition from square-wave to easier-to-synchronize plateau bursting, so that weaker excitation is sufficient to induce bursting synchrony.

The layout of Part 2 is as follows. First, in Sec. 2.2, we introduce the network model and the Sherman cell model as its individual unit. We show that the uncoupled cell model exhibits square-wave bursting and discuss the generation mechanism. Then, in Sec. 2.3, we introduce the self-coupled system that governs the type of synchronous bursting. We show that the self-coupled system switches from square-wave to plateau bursting with an increase in the excitatory and/or inhibitory couplings. This property is then used in Sec. 2.4 to analyze the variational equations for the transverse stability of the synchronous bursting solution, defined through the self-coupled system. Several stability arguments are given to explain the synergetic, synchronizing effect of combined excitation and inhibition. In Sec. 2.5, similar transitions to synchronized plateau-bursting are shown in a network with a varying reversal potential. Finally, in Sec. 2.6, a brief discussion of the obtained results is given.
2.2 The network model

We consider the simplest network of two coupled Sherman models [51] with both excitatory and inhibitory connections:

\[
\tau \frac{dV_i}{dt} = F(V_i, n_i, S_i) + g_{\text{exc}}(E_{\text{exc}} - V_i)\Gamma(V_j) + g_{\text{inh}}(E_{\text{inh}} - V_i)\Gamma(V_j),
\]

\[
\tau \frac{dn_i}{dt} = G(V_i, n_i) \equiv n_\infty(V_i) - n_i,
\]

\[
\tau_s \frac{dS_i}{dt} = H(V_i, S_i) \equiv S_\infty(V_i) - S_i, \quad i, j = 1, 2.
\]

(2.1)

Here, \(V_i\) represents the membrane potential of the \(i\)th cell. Function \(F(V_i, n_i, S_i) = -[I_{Ca}(V_i) + I_K(V_i, n_i) + I_S(V_i, S_i)]\) defines three intrinsic currents: fast calcium, \(I_{Ca}\), fast potassium, \(I_K\), and slow potassium, \(I_S\), currents:

\[
I_{Ca} = \bar{g}_{Ca} m_\infty(V_i) (V_i - E_{Ca}), \quad I_K = \bar{g}_K n_i (V_i - E_K), \quad I_S = \bar{g}_S S_1 (V_i - E_K),
\]

The gating variables for \(n_i\) and \(S_i\) are the opening probabilities of the fast and slow potassium currents, respectively, and

\[
m_\infty(V_i) = [1 + \exp((-20 - V_i)/12)]^{-1},
\]

\[
n_\infty(V_i) = [1 + \exp((-16 - V_i)/5.6)]^{-1},
\]

\[
S_\infty(V_i) = [1 + \exp((-35.245 - V_i)/10)]^{-1}.
\]

Other intrinsic parameters are \(\tau = 20, \tau_s = 10000, \bar{g}_{Ca} = 3.6, E_{Ca} = 25 \text{ mV}, \bar{g}_K = 10, E_K = -75 \text{ mV}, \bar{g}_S = 4\).

The cells are identical and the symmetrical synaptic connections are fast and instantaneous. The parameters \(g_{\text{exc}}\) and \(g_{\text{inh}}\) are the excitatory and inhibitory coupling strengths. The reversal potentials \(E_{\text{exc}} = 10 \text{ mV}\) and \(E_{\text{inh}} = -75 \text{ mV}\) make the synapses excitatory and inhibitory, respectively as \(E_{\text{exc}} > V_i (E_{\text{inh}} < V_i)\) for all values of \(V_i(t)\). The synaptic coupling function is
modeled by the sigmoidal function \( \Gamma(V_j) = 1/[1 + \exp\{-10(V_j - \Theta_s)\}] \). The synaptic threshold \( \Theta_{syn} = -40 \text{ mV} \) is set to ensure that every spike in the single cell burst can reach the threshold (see Fig. 2.1). As a result, a spike arriving from a presynaptic cell \( j \) activates the synapse current (through \( \Gamma(V_j) \) switching from 0 to 1) entering the postsynaptic cell \( i \). Unless noticed otherwise, we will keep the above parameters fixed and only vary the synaptic strengths \( g_{exc} \) and \( g_{inh} \).

The presence of the large parameter \( \tau_S = 10000 \) on the left hand side of the \( S \)-equation makes the system (2.1) slow-fast such that the \( (V_i, n_i) \)-equations represent the 2-D fast “spiking” subsystem for the \( i \)th cell; the \( S_i \)-equation corresponds to the slow 1-D “bursting” system. Therefore, we use the standard decomposition into fast and slow subsystems; the types of bursting that can exist in the uncoupled cell systems (2.1) with \( g_{exc} = 0 \) and \( g_{inh} = 0 \) are defined by the \( S \)-parameter sequences of phase portraits of the 2-D fast system. This analysis has been performed for a similar pancreatic cell [59] and revealed different types of bursting such as square-wave, plateau and pseudo-plateau bursting [55]. Figure 2.1 illustrates the standard sequence of phase portraits in the uncoupled systems (2.1) with \( g_{exc} = 0 \) and \( g_{inh} = 0 \), giving rise to square-wave bursting.

The equilibrium point on the upper branch of the nullcline \( h_i(V) \) in the 2-D fast subsystem undergoes a supercritical Andronov–Hopf bifurcation for \( S = S_{AH1} \), softly giving rise to a stable limit cycle that encircles the unstable point and forms the spiking manifold for \( S_{AH1} < S < S_{HB} \). Its upper edge is defined by a homoclinic bifurcation at \( S = S_{HB} \). Here, the stable limit merges into a stable homoclinic loop and disappears. For the given location of the slow nullcline \( S_{\infty}(V) \), the trajectories jump down to the lower branch of the fast nullcline, creating square-wave (fold/homoclinic) bursting. A more detailed analysis of the phase portraits’ sequences and bifurcations leading to square-wave bursting in other cell models such as the Hindmarsh-Rose model can be found in [52, 9].

### 2.3 Self-coupled system and its burster

Each cell in the network (2.1) receives one inhibitory and one excitatory input from the other cell, therefore the network system (2.1) has an invariant manifold \( D = \{V_1 = V_2 = V(t), \ n_1 = n_2 = n(t), \ S_1 = S_2 = S(t)\} \), that defines complete synchronization between the cells.
Figure 2.1. Square-wave burster of the uncoupled Sherman models (2.1). The fast system displays a supercritical Andronov-Hopf bifurcation at $S = S_{AH1}$ and a homoclinic bifurcation (loop) at $S = S_{HB}$. The spiking manifold is composed of limit cycles in the fast system and terminates at the homoclinic bifurcation HB. The intersection of the fast ($h(V)$) and slow ($S_\infty(V)$) nullclines indicates a unique saddle point $O$ of the full system. The red dotted arrows show the route for bursting in the full system. The plane $V = \Theta_s$ displays the synaptic threshold above which the presynaptic cell can influence the postsynaptic one.
Synchronous dynamics on the manifold $D$ is defined by the self-coupled system:

$$
\tau \frac{dV}{dt} = F(V, n, S) + g_{exc}(E_{exc} - V)\Gamma(V) + g_{inh}(E_{inh} - V)\Gamma(V), \\
\tau \frac{dn}{dt} = G(V, n) \\
\tau \frac{dS}{dt} = H(V, S).
$$

(2.2)

Note that the synchronous dynamics differs from that of the uncoupled cell as the former is governed by a system with extra coupling terms. Moreover, the synchronous dynamics and the type of bursting depend on the coupling strengths $g_{exc}$ and $g_{inh}$. There are critical coupling strengths $g_{exc}$ and $g_{inh}$ at which square-wave bursting in the self-coupled system (2.2) turns into plateau-type bursting, depicted in Fig. 2.2. This happens through the disappearance of the homoclinic bifurcation in the self-coupled system (2.2) due to increased coupling strengths. In the following, we will show that the disappearance of the homoclinic bifurcation (HBD) practically coincides with the onset of stable synchrony in the system (2.1). While excitation alone is able to transform square-wave into plateau-type bursting at some high values of $g_{exc}$, inhibition does so more effectively and its addition lowers the combined coupling strength $g_{exc} + g_{inh}$.

### 2.4 Stability of synchronization: a synergetic effect of inhibition and excitation

The stability of synchronization in the network (2.1) is equivalent to the stability of the invariant manifold $D$. The variational equations for its infinitesimal transverse perturbations $\Delta V = V_1 - V_2$, $\Delta n = n_1 - n_2$, and $\Delta S = S_1 - S_2$ read [8, 11]:

$$
\tau \frac{d\Delta V}{dt} = F_V(V, n, S)\Delta V + F_n(V, n, S)\Delta n + F_S(V, n, S)\Delta S - \Omega(V)\Delta V \\
\tau \frac{d\Delta n}{dt} = G_V(V, n)\Delta V + G_n(V, n)\Delta n \\
\tau \frac{d\Delta S}{dt} = H_V(V, S)\Delta V + H_S(V, S)\Delta S, \quad \text{where}
$$

(2.3)
Figure 2.2. Plateau-type burster of the self-coupled model (2.2), governing the synchronous network dynamics. Note the disappearance of a homoclinic bifurcation in the fast system due to the synaptic coupling. The stable limit cycle of the fast system disappears through a reverse Andronov-Hopf bifurcation at $S = S_{AH2}$, ending the spiking manifold. The red dotted curve shows the route for plateau-type bursting. The non-smooth part of the fast nullcline at $V = \Theta_s$ is due to the synaptic coupling, turning on when the trajectory jumps up to the spiking manifold and crosses the threshold $\Theta_s$. The coupling strengths $g_{exc} = 0.14$ and $g_{inh} = 0.06$ correspond to the point $b$ in the 2-D diagram of Fig. 2.3.

$$\Omega(V) = (g_{exc} + g_{inh}) \Gamma(V) + (g_{exc}(E_{exc} - V) + g_{inh}(E_{inh} - V)) \Gamma_V(V). \quad (2.4)$$

Here, the partial derivatives are calculated at the point $\{\Delta V = 0, \Delta n = 0, \Delta S = 0\}$; and $\{V(t), n(t), S(t)\}$ is the synchronous bursting solution defined through the system (2.2). Note that the synaptic coupling function $\Gamma(V)$ along with its derivative $\Gamma_V(V) = \frac{\lambda \exp\{-\lambda(V - \Theta_s)\}}{(1+\exp\{-\lambda(V - \Theta_s)\})^2}$ is non-negative. Hence, the contribution of the first term in (2.4), $-(g_{exc} + g_{inh}) \Gamma(V) \Delta V$ is stabilizing for the zero fixed point of the variational system (2.3), corresponding to synchronous bursting. On the other hand, the contribution of the second coupling term in (2.4) can be destabilizing when $g_{inh}(E_{inh} - V)$ exceeds $g_{exc}(E_{inh} - V)$, making the second term overall negative. Note that increasing the inhibitory coupling $g_{inh}$ makes this term more negative and, therefore, promoting desynchronization as one would expect. However, Fig. 2.3 indicates that the addition of inhibition to an excitatory network induces synchronization in a fairly wide range of the inhibitory
strength $g_{\text{inh}}$. Note that increasing $g_{\text{inh}}$ first lowers the synchronization threshold and weaker excitation synchronizes the cells (e.g., from $g_{\text{exc}} = 0.18$ in the absence of inhibition to $g_{\text{exc}} = 0.07$ for $g_{\text{inh}} = 0.07$). At the same time, the inhibition cannot induce robust synchronization by itself (see the $x$-axis in Fig. 2.3a, which corresponds to the desynchronizing role of inhibition in the absence of excitation).

Figure 2.3. (a) The stability diagram for synchronization in the two-cell network (2.1). Blue (dark) zone corresponds the zero voltage difference ($V_1 - V_2$) and indicates the synchronization region. Note the unexpected effect when an increase of the inhibitory coupling from 0 to 0.07 significantly lowers the synchronization threshold from about 0.18 to 0.07. Notice that the inhibition desynchronizes the cells in the absence of excitation ($g_{\text{exc}} = 0$). The red dashed curve indicates the disappearance of the homoclinic bifurcation (HBD) in the 2-D fast subsystem; it corresponds to the transition from square-wave to plateau bursting and practically coincides with the stability boundary between asynchronized and synchronized bursting. (b) Top: Typical out-of-phase voltage traces, corresponding to the red (“out-of-phase”) zone. Bottom: synchronization of plateau bursting in the blue (“sync”) parameter region.

What is the cause of this highly unexpected phenomenon? It is worth noticing that when complete (spike) synchronization occurs in the purely excitatory network (2.1) with $g_{\text{inh}} = 0$, square-wave bursting, observed in the unsynchronized network (2.1) at lower values of $g_{\text{exc}}$, turns into plateau bursting (see Fig. 2.3b). This happens when the excitatory coupling is strong enough to change the type of bursting via the disappearance of the homoclinic bifurcation in the fast subsystem of (2.2). The important ingredient of the inhibition-induced synchronization in the network is that the inhibition changes the type of bursting much more effectively than the excitation (see
Fig. 2.3a. Consequently, a much smaller amount of the combined force \((g_{\text{exc}} + g_{\text{inh}})\) is necessary for synchronization.

Why is plateau bursting easier to synchronize? Why does inhibition not desynchronize plateau oscillations as it seems to have an apparent dystabilizing effect due to the second term in (2.4)?

These questions have been answered for networks of Hindmarsh-Rose models in [11] and Part I of this thesis; here, we give additional details and adapt the main arguments to the network of Sherman models (2.1), representing realistic Hodgkin-Huxley-type cell models. Figure 2.4 answers these questions by revealing the dynamics and stability of synchronous bursting via the variational system (2.3) and self-coupled system (2.2), describing the synchronous solution \(V(t)\), whether stable or unstable. Figure 2.4a (top) shows the synchronous solution of the self-coupled system (2.2), which is unstable as the coupling is not sufficiently strong (see the corresponding point \(a\) in Fig. 2.3). The contribution of the coupling term \(\Omega(V)\) to the stabilization of the synchronous solution is depicted in Fig. 2.4a (bottom). When the voltage is above the synaptic threshold \(\Theta_s\), only the first (stabilizing) term \((g_{\text{exc}} + g_{\text{inh}})\Gamma(V)\) [8] as \(\Gamma(V)\) becomes close to 1. The second term is only essential for the values of \(V\), close to the threshold \(\Theta_s\) as the derivative \(\Gamma_V(V)\) is close to the delta function at \(V = \Theta_s\). There is practically no coupling between the cells when \(V\) is below the synaptic threshold \(\Theta_s\). The previous analysis of synchronization in excitatory networks of square-wave bursting cells by means of Lyapunov functions [8, 9] suggests that the stabilization of spikes via the coupling \(\Omega(V)\) amounts to stabilizing the entire synchronous trajectory, including its subthreshold part.

Notice that the lower part of the spikes lies below the synaptic threshold \(\Theta_s\) (to the left from \(\Theta_s\) in Fig. 2.4a (top)) where the synchronizing impact of \(\Omega(V)\) is insignificant (to the left from \(\Theta_s\) in Fig. 2.4a (top)). Therefore, there is no synchronization for these values of \(g_{\text{exc}}\) and \(g_{\text{inh}}\). Figure 2.4b corresponds to synchronized bursting, induced by stronger inhibition (point \(b\) in Fig. 2.3). In fact, increasing the inhibition has a two-fold effect. It lowers the peak of \(\Omega\) at \(V = \Theta_s\) (Fig. 2.4b), making the contribution of the coupling smaller. However, at the same time it is capable of changing the type of bursting such that the spikes of plateau bursting almost entirely lie in the region above the threshold where the coupling term \(\Omega\) stabilizes the (most unstable) spiking part of the trajectory.
Hence, the inhibition-induced transition to plateau bursting makes synchronization stable. When the inhibition becomes stronger than the excitation (see the 45° line in Fig. 2.3), synchronization loses its stability. Note that the coupling $\Omega$ no longer favors the stability of synchronization at $V = \Theta_s$ as it has a negative peak (Fig. 2.4c). Moreover, the excessive inhibition pushes the right branch of the nullcline $h(V)$ to the left so that the synchronous trajectory experiences this negative, desynchronizing impact for a long time while crawling along the nullcline up to the right upper knee (see the non-smooth part of the nullcline in Fig. 2.4c). This results in desynchronization and the onset of asynchronous bursting in the network.

Figure 2.4. The role of inhibition in the stability and type of synchronous bursting. Cases (a), (b), and (c) correspond to points $a$, $b$, and $c$ in Fig. 2.3. (a) Top: The unstable synchronous solution and the fast nullcline $h(V)$ of the self-coupled system (2.4). Bottom: The coupling term $\Omega$ is not strong enough to stabilize the synchronous solution, especially the subthreshold part of the spikes where the coupling is absent. (b) Increasing the inhibition shifts the part of the nullcline $h(V)$ above the threshold closer to the threshold $V = \Theta_s$. However, it makes the amplitude of spikes smaller and leaves the spikes in the region above the threshold where the coupling effectively synchronizes the spikes. Notice the transition from square bursting to plateau bursting. (c) Excessively strong inhibition dominating over excitation has a desynchronizing effect. It still forms plateau bursting in the self-coupled system, governing synchronous bursting, but it creates a vertical part of the nullcline $h(v)$ at $V = \Theta_s$. The bursting trajectory has to follow this part of the nullcline for a while when the cells experience a strong desynchronizing impact (notice the negative peak of $\Omega$ at $V = \Theta_s$) and get desynchronized.
2.5 The role of the reversal potential

In this section, we show that similar transitions from square-wave to plateau bursting and windows of induced synchronization also can be observed in the network (2.1) where the excitatory and inhibitory connections \( I_{\text{syn}} = g_{\text{exc}}(E_{\text{exc}} - V_i)\Gamma(V_j) + g_{\text{inh}}(E_{\text{inh}} - V_i)\Gamma(V_j), \ i, j = 1, 2 \) are replaced with two synaptic connections \( I_{\text{syn}}^i = g_{\text{syn}}(E_{\text{syn}} - V_i)\Gamma(V_j), \ i, j = 1, 2. \) Depending on the value of the reversal potential \( E_{\text{syn}} \), these synaptic connections can be excitatory or inhibitory or be of a mixed type when \( E_{\text{syn}} \) lies somewhere in between the two extremes 10 mV and −75 mV. To some extent, decreasing \( E_{\text{syn}} \) from 10 mV amounts to increasing the inhibitory connections in the original network (2.1). Figure 2.5 shows the dependence of the synchronization threshold coupling \( g_{\text{syn}} \) on the reversal potential \( E_{\text{syn}} \). There is an optimal range of \( E_{\text{syn}} \) close to the synaptic threshold \( \Theta_{\text{syn}} = -40 \) mV and corresponding to significantly improved synchronizability of the network. The vertical boundary of this synchronization region around \( \Theta_{\text{syn}} = -40 \) mV corresponds to the \( 45^\circ \) line in Fig. 2.3a. In fact, the coupling becomes purely inhibitory for the values \( V_i > E_{\text{syn}} = \Theta_{\text{syn}} \) as the factor \( (E_{\text{syn}} - V_i) < 0 \), and therefore the spikes cannot be robustly synchronized.

2.6 Conclusions

Different types of bursting have significantly different synchronization properties. While square-wave bursters are known for their high resistance to spike synchronization, elliptic and plateau-like bursters are much easier to synchronize and require a weaker coupling strength. Typically, fast non-delayed excitation promotes synchronization of bursters while fast non-delayed inhibition desynchronizes them. Although, counterexamples of synchronizing fast non-delayed inhibition in the weak coupling case have been reported [30]. In this Part, we have shown that the onset of spike synchronization in a network of bursting cells is accompanied by transitions from square-wave to plateau bursting. These transitions can be effectively enhanced by the addition of inhibition to a bursting network with excitatory connections. As a result, the inhibition, that desynchronizes the cells in the absence of excitation, plays a synergetic role and helps the excitation to make synchronization stable. In our study, we have chosen the pancreatic \( \beta \)-cell Sherman
Figure 2.5. The stability diagram for synchronization in the network (2.1) with synaptic connections $I_{\text{syn}}^i = g_{\text{syn}}(E_{\text{syn}} - V_i)\Gamma(V_j)$, $i, j = 1, 2$. Similar to Fig. 2.3a, the red dashed curve displays the transition from square-wave to plateau bursting via the disappearance of the homoclinic bifurcation in the fast subsystem. This transition boundary coincides remarkably well with the onset of synchronized bursting. Notice the drop in the coupling strength $g_{\text{syn}}$, necessary for inducing synchronization in a window around $E_{\text{syn}} = -40 \text{ mV}$. This window corresponds to the window of induced synchronization in Fig. 2.3a.

model, which exhibits various types of bursting and is capable of switching between them as a building block for the two-cell network. Our preliminary study shows that the reported synergetic effect of combined excitation and inhibition is also present in larger networks of bursting Sherman models with network topologies admitting complete synchronization. The role of network topology on synchronization of other bursting cell models such as the Hindmarsh-Rose models has been studied for excitatory networks [8] and for excitatory-inhibitory networks [11], indicating that the number of incoming excitatory and inhibitory connections is often the crucial quantity. A detailed stability analysis of complete synchronization and other phase-locked rhythms in large excitatory-inhibitory networks of Sherman models remains a subject of future work.
PART 3

WHEN TWO WRONGS MAKE A RIGHT: SYNCHRONIZED NEURONAL BURSTING
FROM COMBINED ELECTRICAL AND INHIBITORY COUPLING

3.1 Summary

In this part of the thesis we study the emergence of synchronization in networks of bursting neurons as a highly non-trivial, combined effect of electrical and inhibitory connections. We report a counterintuitive find that combined electrical and inhibitory coupling can synergistically induce robust synchronization in a range of parameters where electrical coupling alone promotes anti-phase spiking and inhibition induces anti-phase bursting. We reveal the underlying mechanism, which uses a balance between hidden properties of electrical and inhibitory coupling to act together to synchronize neuronal bursting. We show that this balance is controlled by the duty cycle of the self-coupled system which governs the synchronized bursting rhythm.

The layout of this Part is as follows. First, in Sec. 3.2, we describe the individual neuron and network models. In Sec. 3.3, we report the synchronization effect observed in the simplest two-cell network with electrical and inhibitory connections. We also use Poincaré return maps to demonstrate how the number of co-existing phase-locked states changes as a function of the inhibitory coupling strength. Then, we employ a slow-fast decomposition of the networked system to isolate the impacts of the electrical and inhibitory coupling on the emergence of synchronized bursting. In Sec. 3.4, we introduce the variational equations for the stability of the synchronous bursting solution and explain the main synchronization mechanism via the calculations of averaged synaptic terms and their dependence on the duty cycle of synchronous bursting. In Sec. 3.5, we demonstrate that the synergistic effect is also present in larger networks and identify network topologies with the highest and lowest resilience of synchronized bursting. Section 3.6 contains a rigorous proof of the stabilizing role of strong electrical coupling in synchronization of bursting Sherman cells. Finally, in Sec. 3.7, a brief discussion of the obtained results is given.
3.2 The network model

We consider a network of $N$ Hodgkin-Huxley-type neuronal models [50] with electrical and inhibitory synapses:

$$\tau \frac{dV}{dt} = F(V_i, n_i, S_i) + g_{el} \sum_{j=1}^{N} c_{ij}(V_j - V_i) + g_{inh}(E_{inh} - V_i) \sum_{j=1}^{N} d_{ij}\Gamma(V_j),$$

$$\tau \frac{dn}{dt} = G(V_i, n_i) \equiv n_\infty(V_i) - n_i, \quad (3.1)$$

$$\tau_s \frac{dS}{dt} = H(V_i, S_i) \equiv S_\infty(V_i) - S_i, \quad i, j = 1, ..., N.$$

The intrinsic dynamics of the $i$th cell is represented by the membrane potential $V_i$, and the gating variables $n_i$ and $S_i$ are the opening probabilities of the fast and slow potassium currents, respectively. Function $F(V_i, n_i, S_i) = -[I_{Ca}(V_i) + I_K(V_i, n_i) + I_S(V_i, S_i)]$ describes three intrinsic currents: fast calcium, $I_{Ca}$, persistent potassium, $I_K$, and slow potassium, $I_S$, currents such that

$$I_{Ca} = \bar{g}_{Ca} m_\infty(V_i) (V_i - E_{Ca}), \quad I_K = \bar{g}_K n_i (V_i - E_K), \quad I_S = \bar{g}_S S_1 (V_i - E_K).$$

According to the Hodgkin-Huxley formalism, the steady-state values for the activation and inactivation of the fast and slow currents are represented by the Boltzmann equations as functions of $V_i$,

$$m_\infty(V_i) = [1 + \exp((-20 - V_i)/12)]^{-1},$$

$$n_\infty(V_i) = [1 + \exp((-16 - V_i)/5.6)]^{-1},$$

$$S_\infty(V_i) = [1 + \exp((-35.245 - V_i)/10)]^{-1}.$$  

Other intrinsic parameters are chosen and fixed as follows $\tau = 20$ (ms), $\tau_S = 10000$ (ms), $\bar{g}_{Ca} = 3.6$ (nS), $E_{Ca} = 25$ (mV), $\bar{g}_K = 10$ (nS), $E_K = -75$ (mV), and $\bar{g}_S = 4$ (nS). The individual unit of the network (3.1), the Sherman cell model [50], was originally introduced to mimic the electrical activity of a pancreatic $\beta$-cell. This model is known to exhibit different types of bursting such as square-wave, plateau, and pseudo-plateau bursting [59], and is often used as a generic Hodgkin-
Huxley-type model to describe neuro-computational properties of bursting neurons and networks [28]. In the given set of parameters, the uncoupled cell generates square-wave bursting [46] (see 3.1). The presence of the large parameter $\tau_S = 10000$ (mV) makes the system (3.1) slow-fast such that the $(V, n)$-equations represent the 2-D fast “spiking” subsystem; the $S$-equation corresponds to the slow 1-D “bursting” system. The dynamics is centered around nullcline $h_\infty$ of the fast $(V, n)$-subsystem. The intersection between $h_\infty(V)$ and the nullcline $S_\infty(V)$ of the slow $S$-subsystem yields a saddle fixed point [44].

The cells are identical, and the coupling strength of the electrical ($g_{el}$) and inhibitory ($g_{inh}$) synapses is uniform for each type of coupling. The electrical coupling between cells $i$ and $j$ is modeled via the difference between the membrane potentials $V_i$ and $V_j$. In order to make the chemical synapse inhibitory, the reversal potential is chosen at the level $E_{inh} = -75$ (mV), such that $E_{inh} < V_i(t)$ for all permissible values of $V_i$. The inhibitory coupling is instantaneous and non-delayed; a smooth approximation of the Heaviside function is used to model the synaptic coupling function $\Gamma(V_j) = 1/[1 + \exp\{-10(V_j - \Theta_s)\}]$ [54]. The synaptic threshold $\Theta_s = -40$ (mV) is chosen such that spikes in the single cell burst can cross the threshold (see 3.1). Therefore, a spike in presynaptic cell $j$ activates the synaptic current entering postsynaptic cell $i$ (via $\Gamma(V_j)$ switching from 0 to 1).

In (3.1), $N \times N$ connectivity matrices $C = (c_{ij})$ and $D = (d_{ij})$ describe the network structure of the electrical and inhibitory synapses, respectively. The electrical coupling matrix $C = (c_{ij})$ is symmetric as the electrical coupling is always undirected such that $c_{ij} = c_{ji}$ and $c_{ij} = 1$ if neuron $i$ receives an input from neuron $j$. The nodes of the electrical network may have different in-degrees and receive a different number of inputs. The inhibitory coupling matrix $D$ can be asymmetric such that both mutual and unidirectional couplings are allowed. As in matrix $C$, $d_{ij} = 1$ if neuron $i$ receives an input from neuron $j$; however, $d_{ii} = 0$. We require the connectivity matrix $D$ to have all row-sums equal to $k_{inh}$. This property implies that each cell on the inhibitory network receives $k_{inh}$ inputs from other cells and this number is uniform for each cell. This requirement is a necessary condition for the existence of the synchronization subspace $M = \{V_1 = \ldots = V_N = V(t), \; n_1 = \ldots = n_N = n(t), \; S_1 = \ldots = S_N = S(t)\}$, that defines complete synchronization.
between the cells. The dynamics of completely synchronized cells is governed by the following system:

\[
\tau \frac{dV}{dt} = F(V, n, S) + k_{\text{inh}} g_{\text{inh}} (E_{\text{inh}} - V) \Gamma(V), \quad \tau \frac{dn}{dt} = G(V, n), \quad \tau \frac{dS}{dt} = H(V, S). \tag{3.2}
\]

It is worth noticing that the synchronous behavior differs from that of the uncoupled cell with \(g_{\text{inh}} = 0\) and \(g_{\text{el}} = 0\) due to the presence of the additional inhibitory synaptic term. As the electrical coupling disappears when \(V_i = V_j\), the electrical coupling term is not present in system (3.2). As a result, changing the strength of inhibitory coupling can change the synchronous dynamics. In the following, we will show that these changes, induced by moderately weak inhibitory coupling, result in small variations of the duty cycle of synchronous bursting in system (3.2) and lead to stable synchronization.

Figure 3.1. Square-wave bursting in the uncoupled Sherman model (3.1) with \(g_{\text{inh}} = 0\) (nS) and \(g_{\text{el}} = 0\) (nS). (Main graph). The dotted curve schematically indicates the route for the bursting solution. The plane \(V = \Theta_s = -40\) (mV) corresponds to the synaptic threshold. (Insert). Corresponding time series of square-wave bursting.
3.3 Tug-of-war synchronization effect of combined coupling

We begin with the simplest network (3.1) where two cells are symmetrically coupled through electrical and inhibitory connections with $k_{\text{inh}} = 1$. We will study this two-cell network to reveal the synergistic effect of combined coupling and describe its stability mechanism. We will then demonstrate that this effect is also present in larger networks and discuss the role of network structure.

3.3.1 Multistability and emergent synchronized bursting

Figure 3.2 demonstrates the onset of synchronized bursting in the two-cell network as a function of the electrical ($g_{\text{el}}$) and inhibitory ($g_{\text{inh}}$) coupling strengths. Figure 3.2 (top row) indicates that a strong electrical coupling, exceeding a threshold value $g_{\text{el}} \approx 0.18$, synchronizes the cells in the absence of inhibition ($g_{\text{inh}} = 0$). The addition of inhibition to the strong electrical coupling impedes complete synchrony, as one would expect, and gradually increases the threshold value of electrical coupling $g_{\text{el}}$. Section 3.6 contains a rigorous derivation of an upper bound for the electrical coupling threshold, required for stable synchronization in the absence of inhibition. This analytical bound is very conservative and yields the synchronization threshold at $g_{\text{el}} = 3.925$ compared to the actual threshold $g_{\text{el}} \approx 0.18$ (see Fig. 3.2). However, it rigorously proves that the electrical coupling always promotes synchronization when it reaches the threshold value. Surprisingly, there is a range of much weaker electrical coupling $g_{\text{el}} \in (0, 0.02)$ (see Fig.3.2 (bottom row)) where the electrical coupling alone always impedes synchronization but the addition of inhibition can yield complete synchrony.

The fact that increasing the electrical coupling within the range $g_{\text{el}} \in (0, 0.02)$ makes the synchronization solution more unstable is verified via the calculation of the largest transversal Lyapunov exponent of the synchronous solution which is positive and monotonically increases within the interval $g_{\text{el}} \in (0, 0.02)$ (see Fig. 3.3) (the details on the calculation of the transversal Lyapunov exponent are given in Sec. 3.8). Note that, once the electrical coupling becomes stronger and lies beyond this coupling interval, its repulsive force becomes attractive and promotes
Figure 3.2. The combined effect of electrical and inhibitory synapses on complete synchronization in the two-cell network. The color bar indicates the voltage difference $\Delta V = |V_1 - V_2|$ (mV), averaged over the last three bursting periods. Black (blue) zone corresponds to the zero voltage difference (complete synchronization). Dark grey (red) color indicates anti-phase bursting with the maximum voltage difference (around 40mV). (Top row). Established phase locking from initial conditions where the first cell is in the active spiking phase while the second is silent (left) and initial conditions close to complete synchrony (right). (Bottom row). Zoom-ins of the corresponding top diagrams. Coexistence of synchronized and anti-phase bursting. The scattered black (blue) regions (left figure) correspond to the onset of complete synchronization from the unfavorable initial conditions. The synchronization effect is much more pronounced when the cells start from close initial conditions, as indicated by the black (blue) tongue-shaped region (right figure). Parameters corresponding to points A ($g_{inh} = 0.0001; g_{el} = 0.0001$ (nS)); B ($g_{inh} = 0; g_{el} = 0.01$ (nS)); C ($g_{inh} = 0.01; g_{el} = 0.01$ (nS)); D ($g_{inh} = 0.01; g_{el} = 0$ (nS)); E ($g_{inh} = 0.02; g_{el} = 0.01$ (nS)); and F ($g_{inh} = 0.01; g_{el} = 0.02$ (nS)).
synchrony, ultimately stabilizing complete synchrony at the threshold value \( g_{el} \approx 0.18 \).

Figure 3.3. Largest transversal Lyapunov exponent \( \lambda_\perp \) for the stability of the synchronous solution in the two-cell network with purely electrical connections \( (g_{inh} = 0) \). Positive (negative) values indicate instability (stability) of synchronization. Increasing \( g_{el} \) from 0 first makes the electrical coupling desynchronize the cells within a range of moderate coupling (see the zoomed region \( g_{el} \in (0, 0.02) \), where the dependence of \( \lambda_\perp \) on \( g_{el} \) is monotonic). Any further increase in \( g_{el} \) beyond 0.04 makes the electrical coupling synchronizing, as the Lyapunov exponent becomes less positive. The zoomed region corresponds to the heatmap in Fig. 3.2 (bottom row).

Figures 3.2 (bottom row) also demonstrates that inhibition alone can foster or destabilize complete synchrony, depending on the coupling strength and initial conditions. When one cell is initially in the spiking phase, and the other is in the quiescent - inactive state, inhibition also impedes synchrony and promotes anti-phase bursting in the absence of electrical coupling (see the dark grey (red) color area adjacent to the \( g_{inh} \)-axis in Fig. 3.2 (bottom left)). When both cells start close to each other, inhibition can promote complete synchrony via the mechanism of nonlinear interaction between the spikes, described in [30, 31]. For this property to be true, the inhibitory coupling must be weak such that \( g_{inh} \in (0, 0.008) \) (see the dark (blue) tongue-shaped region adja-
cent to the $g_{\text{inh}}$-axis in Fig. 3.2 (bottom right)). Further increase of $g_{\text{inh}}$ makes the inhibition desynchronizing, independent from the initial conditions. Remarkably, the combination of the electrical and inhibitory coupling, where each synapse alone impedes complete synchrony, can promote synchrony, regardless of the initial conditions (see the dark (blue) areas in Fig. 3.2 (bottom row)), even though the synchronization effect is much more pronounced when the cells start from close initial conditions. Figure 3.2 (bottom right) illustrates the synergistic effect, when “two wrongs make a right,” at point C, which corresponds to the combined attractive action of the repulsive electrical and inhibitory coupling. Note the instability of synchronization at points B and D, where the electrical and inhibitory coupling alone destabilizes complete synchrony. We are especially interested in the transition from point B via point C to point E. This transition along the horizontal line $g_{\text{el}} = 0.01$ corresponds to a route where the repulsive electrical coupling first competes with the weak synchronizing inhibition (within the range $g_{\text{inh}} \in (0, 0.008)$), then acts synergistically with the repulsive inhibition to promote synchrony (point C), and finally cooperates with the repulsive inhibition in a linear fashion to promote anti-phase bursting (point E). Similarly, the transition from D via point C to point F along the vertical line $g_{\text{inh}} = 0.01$ is accompanied by the transition from anti-phase bursting at point D to complete synchrony at point C, and back to out-of-phase bursting at point F. Here, increasing $g_{\text{el}}$ from 0 makes the electrical coupling alone more repulsive (Fig. 3.3); yet, it yields a region of stable synchrony when combined with the (repulsive) inhibition at $g_{\text{inh}} = 0.01$. Thus, the same forces can switch their stabilizing and destabilizing roles, similar to playing tug of war. In addition to the co-existence of complete synchrony and anti-phase bursting, the combined coupling can also induce multiple co-existing phase-locked states, as shown in Fig. 3.4.

Our goal is to explain this counterintuitive synergistic effect and reveal the properties of the coupled system (3.1) which make the combined coupling attractive. Toward this goal, we will first use Poincaré return maps for the phase differences between two interacting cells to reveal the existence of multistable phase-locked states and their dependence on the strength of electrical and inhibitory coupling (see Sec. 3.8 for the details of how the phases are introduced and calculated). Figure 3.4 (left column) illustrates how the phase differences between two cells stabilize after forty
Figure 3.4. Poincaré maps for the evolution of the phase difference in the two-cell network and the corresponding voltage traces. Initial phase differences $\Delta \phi_n$ (horizontal axes) vs. the phase differences after $k$ bursts $\Delta \phi_{n+k}$, with $k = 40$. The phase difference is normalized to 1, where the zero phase difference $\Delta \phi = 0$ corresponds to complete synchrony and $\Delta \phi = 0.5$ indicates anti-phase bursting. Intersections of the graph $\Phi(\Delta \phi)$ (solid curve) with the diagonal (dashed) line yield phase-locked states. Graphs A, B, C, and E correspond to points A, B, C, and E in Fig. 3.2. (A). Weak electrical and inhibitory synapses yield multiple phase-locked states as fixed points of the phase map. These include stable anti-phase bursting (star), complete synchrony (solid circle), and an unstable state at $\Delta \phi_n \approx 0.015$ which separates the attraction basins of the stable states. Note a much larger attraction basin of anti-phase bursting. Arrowed lines on the cobweb diagram illustrate the convergence to the anti-phase state from a given initial condition (left column). Voltage traces of co-existing anti-phase bursting and complete synchrony (right column). (B). Electrical coupling induces phase-locking with a small phase difference between the bursts; however, the spikes within the bursts are in anti-phase. (C). Stable complete synchronization with a large basin of attraction. (E). Phase-locking with $\Delta \phi \approx 0.4$, close to anti-phase bursting. The cloud of dots rather than a baseline phase-shift curve originates from varying duty cycles of the cells and numerical difficulties in identifying the initial ratio of the burst period over the phase shift to the terminal ratio of the same quantities.
bursts. The number of bursts to skip ($k = 40$) is chosen large enough to avoid transient stages. Note that the $B - C - E$ transition (cf. Fig. 3.2) originates from the phase-locked state where the electrical coupling alone tends to establish burst synchrony; at the same time, it promotes anti-phase spiking (see Fig. 3.4B). Increasing the inhibition up to point $C$ (cf. Fig. 3.2) helps to synchronize the spikes within the bursts (see Fig. 3.4C). Further increase in $g_{\text{inh}}$ up to point $E$ destabilizes complete synchrony and establishes a phase-locked state close to anti-phase bursting (see Fig. 3.4E). Remarkably, while being destabilizing for complete synchronization when acting alone, the impact of electrical and inhibitory coupling is different. The electrical coupling promotes (destabilizes) burst (spike) synchrony, whereas inhibition does the reverse and fosters spike synchrony and impedes burst synchrony. This suggests how the combined action of both coupling can stabilize complete synchrony. To further validate this observation and isolate the impact of the electrical and inhibitory coupling, we will use a slow-fast decomposition of the two-cell coupled system (3.1).

3.3.2 Insight from the slow-fast decomposition

To better understand the action of electrical and inhibitory coupling on the dynamics of two cells during two distinct phases of active spiking and quiescence, we employ the slow-fast property of square-wave bursting and dissect the network dynamics into the fast and slow components (see Fig. 3.5). We choose and fix the slow variable $S$ at some level $S = 0.18$, which corresponds to the middle of the spiking phase (see Fig. 3.1). This yields the fast $(V_i, n_i)$ systems ($i = 1, 2$), which are coupled via the electrical and inhibitory coupling and mimic the interaction between the cells during the spiking phase of both cells. Similarly, decreasing the time constant $\tau$ for the second variable $n_i$, we effectively get rid of all the spikes and turn the coupled system into a two-relaxation-oscillator network. This network aims at reproducing the cooperative dynamics of the full system (3.1) during the stage when one cell is active while the other is inactive. In this setting, the active cell keeps the inhibition on such that the inactive (inhibited) cell is kept at the inactive state as long as the active cell is in the spiking phase, causing anti-phase bursting.

This slow-fast decomposition reveals striking differences between the impacts of the elec-
trical and inhibitory synapses on synchronization in the networks of fast and slow subsystems (Fig. 3.6). In the given range, the electrical synapses always repel the spikes and attract their envelopes (bursts) (compare the circle from the left diagram with the triangle from the right one). At the same time, the inhibitory connections bring the spikes together but push the bursts apart (compare the square with the diamond from the diagrams). While the heatmaps of Fig. 3.6 can slightly differ, depending on the value of $S$ (not shown), they remain qualitatively the same and indicate the same effect. Combined together, the two seemingly counter-actions of electrical and inhibitory synapses make up a rich multistable pattern in the full system and induce the synchronization mechanism that we have called a “tug of war.”

Figure 3.5. Transformation of the full coupled system into two subsystems: fast (left) and slow (right). Fixing the slow variable $S$ at a given value, $S = 0.18$, turns the coupled system into a network of interacting tonic spiking cells. This fast system accounts for the interaction in the full system when both cells are in the spiking phase. Ignoring the spikes transforms the coupled system into a network of two slow relaxation oscillators, which mimics the interaction between the cells at the level of bursts (envelopes of spikes).

### 3.4 Stability mechanism: why does the duty cycle matter?

To better quantify the stability mechanism and reveal the property of the coupled system that controls the stability of complete synchronization, we use the stability equations for the infinitesimal transverse perturbations $\Delta V = V_1 - V_2$, $\Delta n = n_1 - n_2$, $\Delta S = s_1 - s_2$ [8]:

$$
\tau \frac{d}{dt} \Delta V = F_V(V, n, S) \Delta V + F_n(V, n, S) \Delta n + F_S(V, n, S) \Delta S - \left[ g_{inh} \Omega(V) + 2g_{el} \right] \Delta V \\
\tau \frac{d}{dt} \Delta n = G_V(V, n) \Delta V + G_n(V, n) \Delta n, \quad \tau \frac{d}{dt} \Delta S = H_V(V, S) \Delta V + H_S(V, S) \Delta S,
$$

(3.3)
Figure 3.6. The effect of electrical and inhibitory synapses on the synchronization properties of the dissected, fast (left) and slow (right) subsystems. Electrical and inhibitory synapses play opposite roles in promoting synchrony in the fast and slow subsystems. When isolated, electrical synapses promote anti-phase spiking in the coupled fast system (left column) and synchrony in the slow system (right column). Inhibitory coupling induces spike synchrony in the fast subsystem and fosters anti-phase bursting in the slow one. (Top row). Heatmaps and color-coding are similar to those of Fig. 3.2. The circle and the triangle correspond to point $B$ in Fig. 3.2. The square and diamond indicate point $D$ in Fig. 3.2. (Bottom row). The corresponding voltage traces.

where $\Omega(V) = S_1 + S_2$ with $S_1 = \Gamma(V)$ and $S_2 = (E_{\text{inh}} - V)\Gamma_V(V)$ is due to the contribution of the inhibitory coupling. Here, $\{V(t), n(t), s(t)\}$ denotes the synchronous solution which corresponds to the self-coupled system (3.2), $\Gamma_V(V)$ is the partial derivative of $\Gamma(V)$ with respect to $V$. The stability of the completely synchronous solution corresponds to the zero fixed point $\{\Delta V = 0, \Delta n = 0, \Delta S = 0\}$ of the variational equations (3.3). The function $\Omega(x)$ promotes the stability of synchronization when it becomes positive and has a destabilizing impact when it is negative [8].

The two terms $S_1$ and $S_2$, composing $\Omega(V)$, play opposite roles in stabilizing synchronization. The first (stabilizing) term $S_1 \geq 0$ remains turned on when the voltage $V(t)$ is above the synaptic threshold $\Theta_s$. The second (destabilizing) term $S_2 \leq 0$ contains the derivative $\Gamma_V(V)$, which has a negative peak around $\Theta_s$ (in the case of the Heaviside function, $\Gamma_V(V)$ turns into the negative delta
Figure 3.7. Stabilizing and destabilizing components of the inhibitory coupling. (Top). Voltage trace of twelve-spike synchronous bursting. The horizontal line indicates the synaptic threshold $\Theta_s = -40$ (mV), above which the inhibition activates. (Middle). The synaptic term $S_1 \geq 0$, which promotes spike synchrony, is turned on during the duration of a spike. (Bottom). The destabilizing synaptic term $S_2 \leq 0$ is on during instances when the voltage crosses the synaptic threshold.

Figure 3.8. Largest transversal Lyapunov exponent $\lambda_\perp$, the duty cycle of synchronous bursting, and the averaged synaptic terms $<S_1 + S_2>$ as a function of the inhibitory coupling (electrical coupling $g_{el} = 0.01$ is fixed; this diagram corresponds to the $B - C - E$ route in Fig. 3.2). The dotted line (left figure) is zero and hence represents the transition to stable synchrony, which occurs when $\lambda_\perp < 0$. The sign of $\lambda_\perp$ changes at the values $g_{inh} \approx 0.009$ and $g_{inh} \approx 0.017$, which bound the stable region (see Fig. 3.2) and are indicated by the vertical lines in each plot. The duty cycle of the self-coupled system (3.2), which governs the synchronous solution, reaches its minimal values within the stable region (top right diagram). The shorter duty cycle yields maximal values of the synaptic terms $S_1 + S_2$ averaged over one period of oscillations (bottom right diagram), such that the overall stabilizing effect of the inhibitory coupling can stabilize the synchronous solution. The sharp drop (rise) in the size of the duty cycle (synaptic terms) is due to the addition of one spike in the burst.
function). Hence, the term $S_2$ switches and remains on for the values of $V$ close to the threshold $\Theta_s$ when the spikes cross the threshold (see Fig. 3.7). Thus, the terms $S_1$ and $S_2$ compete with each other to stabilize and destabilize the completely synchronous rhythm.

The contribution of the electrical coupling to the stability of the variational equations is always favorable due to the negative term $-2g_{el}\Delta V$. As we seek to quantify the $B - C - E$ transition (see Fig. 3.2) where the electrical coupling is fixed, we study the changes in the overall dynamics of the variational equations (3.3) as a function of the averaged contribution of the inhibitory synaptic terms $S_1$ and $S_2$ (see Fig. 3.8). However, it is important to emphasize that, once the phase difference between the cells is no longer infinitesimal, the variational equations lose their credibility. As a result, the role of the electrical coupling for non-infinitesimal voltage differences cannot be assessed from the variational equations. As the phase map and slow-fast decomposition analysis suggest, this role is destabilizing for spike synchrony.

It is also important to stress that increasing the inhibitory coupling strength $g_{inh}$ from 0 along the $B - C - E$ route changes the dynamics of the self-coupled system (3.2) and alters the duty cycle of synchronous bursting in a nonlinear fashion (Fig. 3.8). This change turns out to be the critical quantity which shifts the balance between the competing terms $S_1$ and $S_2$. As a result, a shorter duty cycle maximizes the averaged contribution of the resultant force $S_1 + S_2$ and induces complete synchronization.

### 3.5 Larger networks

The combined effect of electrical and inhibitory coupling is also present in larger networks (3.1). Figure 3.9 presents stability diagrams for synchronization in four-cell networks with different network structures of electrical and inhibitory connections. Our previous results on synchronization in excitatory-inhibitory networks [11] suggest that the structure of the added inhibitory connections is not important and only the number of inhibitory inputs controls the onset of synchronization, independent from all other details of their network topology. However, this is only true if the synchronizing excitatory connections are strong enough and form a connected graph which involves all the cells [11].
Figure 3.9. Stability diagrams for network synchronization in four-cell networks, similar to the heatmaps of Fig. 2. The corresponding topologies illustrated underneath each figure; spring-like (solid circle) lines indicate electrical (inhibitory) connections. The color bar depicts the mean voltage difference \( \frac{1}{n} \sum_{j=1}^{n} \frac{1}{n(n+1)} (V_i - V_j) \) (mV), calculated and averaged over four bursting periods. The dark blue bounded region represents complete synchrony. Note the maximal area of stable synchrony in the network with both local electrical and inhibitory connections (bottom left figure); this indicates that the combined synergistic effect is strongest in sparse configurations with connected graphs.
As Fig. 3.9 indicates, the sparse network topology with both local electrical and inhibitory connections (bottom left) has the maximal horizontal and vertical size of the stability region. Notice that each cell in this network receives two inhibitory inputs such that $k_{\text{inh}} = 2$. Similarly to the above-mentioned scaling law in excitatory-inhibitory networks [11], the horizontal size of the stability region in network configurations, where the combined effect is observed (the three networks in the top row), is inversely proportional to the number of incoming inhibitory connections $k_{\text{inh}}$. For example, the network with both global electrical and inhibitory connections (top left network) has the stability region whose horizontal size scales down by a factor $3/2$ to offset the effect of increasing the number of inhibitory inputs, $k_{\text{inh}}$, from two (as in the locally connected network with the maximal stability region) to three (as in the fully connected four-cell network). This scaling law originates from the self-coupled system (3.2) which governs the synchronous rhythm via the term $k_{\text{inh}} g_{\text{inh}} (E_{\text{inh}} - V) \Gamma(V)$, whose impact remains the same as long as the quantity $k_{\text{inh}} g_{\text{inh}}$ is preserved.

At the same time, the interplay between network structures of electrical and inhibitory connections and its impact on the stability of synchronization are highly non-trivial. Figure 3.9 demonstrates that global electrical connections should be compensated for by global inhibitory connections to enlarge the stability region (compare the top left and top right network configurations). Note that the bottom middle and bottom right networks do not exhibit the combined synchronizing effect in the region where inhibition is repulsive. Indeed, only two electrical connections in the bottom middle network of Fig. 3.9 can not burst synchronize all four cells, such that repulsive inhibition induces anti-phase bursting between the left and right sides of the network. The global structure of electrical connections in the bottom left network does induce burst synchrony [not shown]; however, the sparse directed inhibitory coupling is insufficient to overcome the impact of electrical coupling and synchronize the spikes. As a result, the combined effect cannot be achieved.

To show that the combined effect of electrical and inhibitory coupling appears in neural networks with complex topologies, we have simulated a 30-cell random network where each cell receives eight inhibitory connections ($k_{\text{inh}} = 8$) whereas the number of electrical connections varies from one cell to another (Fig. 3.10). The uniform node in-degree of the inhibitory connec-
Figure 3.10. (Bottom). Thirty-cell random network with electrical and inhibitory connections. The structure of directed inhibitory connections (thin (blue) lines) is random, with a constraint on the uniform node degree $k_{\text{inh}} = 8$. Undirected electrical connections (thick (red) lines) are randomly generated; the node degree ranges randomly from 1 to 15. (Top). The stability diagram and color coding are similar to those of Fig. 9. Notice the presence of the combined effect of electrical and inhibitory coupling.
tions ($k_{\text{inh}} = 8$) is preserved to guarantee the existence of the completely synchronized solution. Node degrees of the electrical connections do not affect this condition, and, therefore, were chosen freely. Figure 3.10 (top) demonstrates the emergence of stable synchrony as a result of the synergistic interaction between the electrical and inhibitory coupling. Notice that the size of the stability zone (black (blue) region) has shrunk, compared to the four-cell networks of Fig. 3.9. This is due to the increased node-degree of the inhibitory network and the above-mentioned scaling law.

The detailed analysis of the interplay between synchronization and the network structure of electrical and inhibitory connections is beyond the scope of this work. This analysis can be based on the variational equations, similar to (3.3), and the application of the Connection Graph method [5, 7, 6], which uses Lyapunov functions and graph theoretical reasoning.

3.6 The synchronizing role of strong electrical coupling

Here, we rigorously prove that strong electrical coupling never changes its synchronizing role as long as it exceeds a synchronization threshold. We derive a rigorous upper bound on the strength of electrical coupling sufficient to induce globally stable synchronization in the two-cell network (3.1) in the absence of inhibitory connections.

**Theorem 3.6.1.** Complete synchronization in the network (3.1) of two mutually coupled cells with only electrical synapses is globally asymptotically stable if $g_{el} \geq g^*$, where $g^* = \frac{1}{8(E_{Ca} - E_K)}[g_K^2 + g_S^2 + 4g_{Ca} \max(m'_\infty)(E_{Ca} - E_K)^2]$.

**Proof.** It can be seen from system (3.1) that each single cell with or without connections has an absorbing domain: $0 \leq n, S \leq 1, E_K \leq V \leq E_{Ca}$ such that any trajectory will eventually converge to this domain. Henceforth, we can assume that all the values of our system variables are inside this absorbing domain.

Similar to (3.3), we introduce the differences $\Delta V = V_1 - V_2, \Delta n = n_1 - n_2, \Delta S = s_1 - s_2$. As we target the global stability of synchronization, these differences do not have to be infinitesimal as in (3.3). Therefore, we obtain the following difference equation system from system (3.1) with
\( g_{\text{inh}} = 0 : \)

\[
\begin{align*}
\tau \Delta \dot{V} & = F(V_1, n_1, S_1) - F(V_2, n_2, S_2) - 2g_{el}\Delta V, \\
\tau \Delta \dot{n} & = G(V_1, n_1) - G(V_2, n_2), \\
\tau \Delta \dot{S} & = H(V_1, S_1) - H(V_2, S_2).
\end{align*}
\]

(3.4)

To have the explicit presence of \( \Delta V, \Delta n, \) and \( \Delta S, \) we apply the mean value theorem such that

\[
\begin{align*}
F(V_1, n_1, S_1) - F(V_2, n_2, S_2) &= F_V(\tilde{V}, \tilde{n}, \tilde{S})\Delta V + F_n(\tilde{V}, \tilde{n}, \tilde{S})\Delta n + F_S(\tilde{V}, \tilde{n}, \tilde{S})\Delta S, \\
G(V_1, n_1) - G(V_2, n_2) &= G_V(\tilde{V}, \tilde{n})\Delta V + G_n(\tilde{V}, \tilde{n})\Delta n, \\
H(V_1, S_1) - H(V_2, S_2) &= H_V(\tilde{V}, \tilde{S})\Delta V + H_S(\tilde{V}, \tilde{S})\Delta S,
\end{align*}
\]

(3.5)

where \( \tilde{V} \in [V_1, V_2], \tilde{n} \in [n_1, n_2], \) and \( \tilde{S} \in [S_1, S_2]. \) Strictly speaking, the values of \( \tilde{V}, \tilde{n}, \) and \( \tilde{S} \) in the partial derivatives of functions \( F, G, \) and \( H \) are not the same. However, we will later bound them by the same conservative quantity, so we keep this abused notation.

Calculating the partial derivatives and regrouping terms in (3.4) yields

\[
\begin{align*}
\tau \Delta \dot{V} &= - [g_{Ca}(m'_{\infty}(\tilde{V})(\tilde{V} - E_{Ca}) + m_{\infty}(\tilde{V})) + g_K\tilde{n} + g_S\tilde{S} + 2g_{el}]\Delta V \\
&\quad - g_K(\tilde{V} - E_K)\Delta n - g_S(\tilde{V} - E_K)\Delta S, \\
\tau \Delta \dot{n} &= n'_{\infty}(\tilde{V})\Delta V - \Delta n, \\
\tau \Delta \dot{S} &= S'_{\infty}(\tilde{V})\Delta V - \Delta S.
\end{align*}
\]

(3.6)

In order to prove the global asymptotic stability of synchronization, it suffices to show that the origin of system (3.6) \( \Delta V = \Delta n = \Delta S = 0 \) becomes globally stable when \( g_{el} \) exceeds some critical value. To this end, we construct a Lyapunov function in the following form:

\[
W(t) = \frac{\tau \Delta V^2}{2(E_{Ca} - E_K)^2 \Delta V} + \frac{\tau \Delta n^2}{2} + \frac{\tau \Delta S^2}{2},
\]

where parameter \( E_{Ca} \) is always greater than \( E_K. \) The exponent 2.5 is chosen to minimize the bound on the synchronization threshold.

We need to show that the derivative of this quadratic form with respect to the trajectories of
system (3.6) is negative everywhere except of the origin. Thus,

\[
\dot{W} = -[g_{Ca}(m'_\infty(\bar{V})(\bar{V} - E_{Ca}) + m_\infty(\bar{V})) + g_K n + g_S \tilde{S} + 2g_{el}] \frac{\Delta V^2}{(E_{Ca} - E_K)^2} - g_K \frac{\tilde{V} - E_K}{(E_{Ca} - E_K)^2} \Delta n \Delta V - g_S \frac{\tilde{V} - E_K}{(E_{Ca} - E_K)^2} \Delta S \Delta V + n'_\infty(\bar{V}) \Delta n \Delta V - \Delta n^2 + S'_\infty(\bar{V}) \Delta S \Delta V - \Delta S^2.
\]

This quadratic form simplifies as follows

\[
\dot{W} = -[A \Delta V^2 + B \Delta n \Delta V + C \Delta S \Delta V + \Delta n^2 + \Delta S^2],
\]

where

\[
A = \frac{1}{(E_{Ca} - E_K)^2} [g_{Ca}(m'_\infty(\bar{V})(\bar{V} - E_{Ca}) + m_\infty(\bar{V})) + g_K n + g_S \tilde{S} + 2g_{el}],
\]

\[
B = \frac{1}{2} [g_K \frac{\tilde{V} - E_K}{(E_{Ca} - E_K)^2} - n'_\infty(\bar{V})],
\]

\[
C = \frac{1}{2} [g_S \frac{\tilde{V} - E_K}{(E_{Ca} - E_K)^2} - S'_\infty(\bar{V})].
\]

To prove that the quadratic form \(-\dot{W}\) is positive definite, we use the Sylvester Criterion:

1). \(A > 0\); 2). \(\begin{vmatrix} A & B \\ B & 1 \end{vmatrix} > 0\); 3). \(\begin{vmatrix} A & B & C \\ B & 1 & 0 \end{vmatrix} > 0\). \(\text{(3.7)}\)

All the conditions are satisfied if the last one is true: \(A - B^2 - C^2 > 0\). From which, it follows that

\[
g_{el} > g^* = \frac{1}{8(E_{Ca} - E_K)} [g_K^2 + g_S^2 + 4g_{Ca} \max(m'_\infty)(E_{Ca} - E)^2],
\]

where we have used the absorbing domain bounds \(\tilde{V} = E_{Ca}, \tilde{n} = 1\), and \(\tilde{S} = 1\).

The theoretical estimate for the synchronization threshold bound is conservative \(g_{el} > 3.925\) compared to the numerically computed bound \(g_{el} \approx 0.18\) shown in Fig. 3.2. However, it guarantees that the electrical coupling remains synchronizing as long as it exceeds the synchronization threshold.

We point the reader to the connection graph method [5, 7, 6], which allows us to use the
bound $g^*$ for the two-cell network to calculate the critical value of electrical coupling sufficient for globally stable synchronization in large $N$-cell networks (3.1) with arbitrary topologies of electrical connections in the absence of inhibition. The following proposition is a direct application of the connection graph method [5] to the network (3.1) with only electrical connections.

**Theorem 3.6.2.** Complete synchronization in the network (3.1) of $N$ electrically coupled Sherman models without inhibitory connections ($g_{\text{inh}} = 0$) is globally asymptotically stable if for every edge $k$ on the connection graph associated with the connectivity matrix $C$

$$g_{el} > \frac{2g^*}{N} b_k,$$

where $g^*$ is the bound given in theorem A.1 for the two-cell network and the quantity $b_k = \sum_{j > i;\ k \in P_{ij}} |P_{ij}|$ is the sum of the lengths of all chosen paths $P_{ij}$ which pass through a given edge $k$.

**Proof.** The proof directly follows from that of the main theorem of the Connection Graph Method [5].

More details on the calculation of graph quantity $b_k$ for a given network topology are given in [5, 10].
3.7 Conclusions

In this part of the thesis, we have discovered a highly nonlinear effect of combined electrical and chemical synapses in promoting synchronization of bursting cells in a parameter region where each type of synapse alone destabilizes synchronization. This unexpected effect where “two wrongs make a right” is caused by a sudden decay in the duty cycle of synchronous bursting. This change can induce stable synchronization as a result of the separable and counter-balancing effect of both coupling types on the slow (bursting) and fast (spiking) subsystems, corresponding to potassium and calcium ion channels. More precisely, fairly weak electrical coupling stabilizes burst synchronization but repels the individual spikes, whereas the inhibition does the opposite, promoting spike synchrony when the phases of the cells are close to each other and destabilizing burst synchronization when one of the cells is in an inactive state. The duty cycle controls a fragile balance between the two opposite forces, such that shorter duty cycles with a longer quiescent period increase the stabilizing impact of the electrical coupling in establishing burst synchronization. By the same token, these short duty cycles maximize the impact of inhibition in stabilizing spike synchrony. This dependence is non-trivial and increasing the inhibitory strength changes the duty cycle of synchronous bursting via the self-coupled system in a nonlinear fashion. The observed combined effect is not limited to networks of bursting Sherman cells but is also present in, for example, coupled Purkinje neuron models [34], capable of generating square-wave bursting. Our preliminary studies also indicate that synchronized bursting induced by the combined coupling persists under small parameter mismatch, including the intrinsic parameters and coupling strength. This study reinforces our work presented in Parts 1 and 2, in which it was shown that the addition of strong pairwise repulsive inhibition to excitatory networks of bursting neurons can induce synchrony due to the transition between different types of bursting. Remarkably, the addition of the inhibitory coupling can promote synchronization much more significantly than strengthening the present excitatory connections. In contrast to excitatory-inhibitory networks studied in Parts I and II where the excitatory connections are synchronizing, the combined effect of electrical and inhibitory coupling reported in this work originates from two types of connections which are
both repulsive. Our studies of neuronal synchronization form a basis for understanding the counter-intuitive dynamics of bursting networks, which may yield meaningful insight into the phenomenon of pathological synchrony in epileptic networks. Epileptic seizures are strongly associated with a synchronized state of certain brain networks. Our results suggest that promoting normally repulsive inhibition in an attempt to prevent seizures can have an unintended effect of inducing pathological synchrony.
APPENDIX: NUMERICAL METHODS AND MATLAB CODES

3.8 Codes used in Part 1

For numerical calculations was used MATLAB, multi-paradigm numerical computing environment and fourth-generation programming language. Below presented a MATLAB code for the network of \( n \) Hindmarsh-Rose cells connected through excitatory, \( C \), and inhibitory, \( C_{inh} \), connectivity matrices (adjacency matrices). It follows by the code for drawing nullclines of the single Hindmarsh-Rose system. For integration of the system of differential equations it is used the standard MATLAB ODE solver - \texttt{ode45} (Dorman-Prince method with adaptive step size).

3.8.1 MATLAB codes

```matlab
function dU = netInh(t,U)

global g_syn
global g_inh
global C
global Cinh

%nnumber of neurons
n = length(U)/3;

X = reshape(U,[n 3]);

%First have to name the function. dX and X are vectors.

%Give values for all constants.
```

\[ a = 2.8; \]
\[ alfa = 1.6; \]
\[ c = 5; \]
\[ b = 9; \]
\[ mu = 0.001; \]
\[ theta = -0.25; \]
\[ V = 2; \]
\[ k = 50; \]
\[ lambda = 10; \]
\[ V_{inh} = -2; \]

\[ gmma = \frac{1}{1 + \exp(-lambda \cdot (X(:,1) - theta))}; \]

\[%dX = [dx, dy, dz]\]

\[ dX(:,1) = a\cdot X(:,1)^2 - X(:,1)^3 - X(:,2) - X(:,3) - g_{syn} \cdot (X(:,1) - V) \cdot (C \cdot gmma) - g_{inh} \cdot (X(:,1) - V_{inh}) \cdot (C_{inh} \cdot gmma); \]
\[ dX(:,2) = (a + alfa) \cdot X(:,1)^2 - X(:,2); \]
\[ dX(:,3) = mu \cdot (b \cdot X(:,1) + c - X(:,3)); \]

\[ dU = \text{reshape}(dX, [n*3 1]); \]
clc

close all

% Parameters
a = 2.8;
apha = 1.6;
c = 5;
b = 9;
mu = 0.001;
theta = -0.25;
V_exc = 2.9
V_inh = -2;
lambda = 10;

k_exc = 4;
gamma_exc = -5
gamma_inh = -1.382
k_inh = 2;
g_exc = 0.2;
g_inh = 0.7;

Gamma = @(x)[1./(1+exp(-lambda.*(x-theta)))];
Gamma_x = @(x)[(lambda*exp(-lambda.*(x-theta)))./((1+...exp(-lambda.*((x-theta)))).^2)];
Omega = @(v1)[k_exc*g_exc*Gamma(v1)-g_exc.*(V_exc-v1)...*Gamma_x(v1).*((k_exc+gamma_exc)+k_inh*g_inh*Gamma(v1)-...g_inh.*(V_inh-v1).*Gamma_x(v1).*((k_inh+gamma_inh)));
Fast_Null = @(x)[-x.^3-alpha*x.^2+(k_exc*g_exc*(V_exc-x)...+k_inh*g_inh*(V_inh-x)).*Gamma(x)];
Slow_Null = @(x)[b*x+c];
HR_selfcoupled = @(t,x)[ a*x(1)^2-x(1)^3-x(2)-x(3)... 
+ (k_exc*g_exc*(V_exc-x(1))+k_inh*g_inh*(V_inh-x(1)))*... 
Gamma(x(1)); (a+alpha)*x(1)^2-x(2); mu*(b*x(1)+c-x(3))];
[ts,vs] = ode45(HR_selfcoupled,[0:0.05:1000], [1 0.5 1.2]);

x=-3:0.05:2;
f_null = Fast_Null(x);
g_null = Slow_Null(x);
Omega_fun = Omega(x);
figure(1)
plot(x,f_null,'g','LineWidth',2)
xlabel('x')
ylabel('z')
hold on
plot(x,g_null,'b','LineWidth',2)
plot(vs(9200:end,1),vs(9200:end,3),'b','LineWidth',1);
plot(x,Omega_fun,'r','LineWidth',2)
line([-2 2],[0 0])
line([theta theta],[-3 3])
axis([-2.5 2 -1 2.5])
hold on

3.9 Codes used in Part 2

3.9.1 MATLAB codes

function Y = ode4(odefun,tspan,y0,varargin)
if `~isnumeric(tspan)`
    error('TSPAN should be a vector of integration steps.');
end

if `~isnumeric(y0)`
    error('Y0 should be a vector of initial conditions.');
end

h = diff(tspan);
if any(sign(h(1)) * h <= 0)
    error('Entries of TSPAN are not in order.')
end

try
    f0 = feval(odefun,tspan(1),y0,varargin{:});
catch
    msg = ['Unable to evaluate the ODEFUN at t0,y0. ',lasterr];
    error(msg);
end

y0 = y0(:);  % Make a column vector.
if `~isequal(size(y0),size(f0))`
    error('Inconsistent sizes of Y0 and f(t0,y0).');
end

neq = length(y0);
N = length(tspan);
Y = zeros(neq,N);
F = zeros(neq,4);

Y(:,1) = y0;
for i = 2:N
    ti = tspan(i-1);
    hi = h(i-1);
    yi = Y(:,i-1);
    F(:,1) = feval(odefun,ti,yi,varargin{:});
    F(:,2) = feval(odefun,ti+0.5*hi,yi+0.5*hi*F(:,1),varargin{:});
    F(:,3) = feval(odefun,ti+0.5*hi,yi+0.5*hi*F(:,2),varargin{:});
    F(:,4) = feval(odefun,tspan(i),yi+hi*F(:,3),varargin{:});
    Y(:,i) = yi + (hi/6)*(F(:,1) + 2*F(:,2) + 2*F(:,3) + F(:,4));
end
Y = Y.';
% Largest Lyapunov Exponent for Sherman cells coupled
% mutually through an inhibitory chemical coupling
% Reimbay Reimbayev, GSU, 2014 // Aug.25/2014

close all
clear all
clc
tic

%parameters of the model
k =10;
Theta =-45;
V_in =-75;
NumberPoints=11;

%initial conditions
x0 = [-30 0.2 0.17]; options=odeset('RelTol',1e-5);
g_ins=linspace(0,0.02,NumberPoints);
Lambda=zeros(1,NumberPoints);
for i=1:NumberPoints;
    disp(i);
    g_in=g_ins(i);
    %synchronous solution
    Sherman = @(t,x)[(3.6*(25-x(1))/(1+exp((-20-x(1))/12))-10*x(2)*(x(1)+75)-4*x(3)*(x(1)+75)-g_in*(x(1)-V_in)/(1+exp(-k*(x(1)-Theta))))/20;
                      (1/(1+exp((-16-x(1))/5.6)))-x(2))/20;
\[
\frac{1}{1+\exp\left(-\frac{35.245-x(1)}{10}\right)}-x(3)\] /10000;
\]

%transient solution
[t,v] = ode45(Sherman,[0 4000], x0);
if i==1||i==NumberPoints; figure; plot(t,v(:,1));end;

%self-coupled system with variational equations
% Sherman self loop with variational equations
ShermanVar = @(t,x)[(3.6*(25-x(1))/(1+exp((-20-x(1))/12))-10*x(2)*(x(1)+75)-4*x(3)*(x(1)+75)...-
\quad \frac{g_{in}*(x(1)-V_{in})}{(1+exp(-k*(x(1)-Theta)))}/20; \]
\[
\frac{1}{1+\exp\left(-\frac{16-x(1)}{5.6}\right)}-x(2)\] /20;
\[
\frac{1}{1+\exp\left(-\frac{35.245-x(1)}{10}\right)}-x(3)\] /10000;
\[
(3.6*\left(\frac{-1}{1+\exp\left(-\frac{20-x(1)}{12}\right)}+\frac{1}{12}\cdot (25-x(1))\right)\exp\left(-\frac{20-x(1)}{12}\right)/(1+\exp\left(-\frac{20-x(1)}{12}\right))^2)*x(4)...-
\quad -10*(x(2)*x(4)+x(5)*(x(1)+75))-4*(x(3)*x(4)+x(6)*(x(1)+75))...-
\quad \frac{g_{in}*(1/(1+exp(-k*(x(1)-Theta)))-(x(1)-V_{in})*k*exp(-k*(x(1)-Theta))/(1+exp(-k*(x(1)-Theta)))^2)}{20; \]
\[
\frac{1}{5.6}\exp\left(-\frac{16-x(1)}{5.6}\right)/(1+\exp\left(-\frac{16-x(1)}{5.6}\right))^2)x(4)/20;
(0.1*\exp\left(-\frac{35.245-x(1)}{10}\right)/(1+\exp\left(-\frac{35.245-x(1)}{10}\right))^2)*x(6)/10000; \]
\]
\[
^2\cdot x(4)-x(6)\] /10000];

v0=zeros(1,6); v0(1:3)=v(end,:); d=0.01;...

v0(4)=d;% perturbation d on variation V

%running the system again but this time with all
% the variational equations
T=0.5; M=8000; S=0; dt=0.1;

for index=1:M
[t,v] = ode45(ShermanVar,[0:dt:T],v0); v1 = v(end,:);
\[ S = S + \log(\text{norm}(v_1(4:6)/d)); \]
\[ v_0 = v_1; ~ v_0(4:6) = v_0(4:6)/\text{norm}(v_0(4:6)) \times d; \]
end

\[ \text{Lambda}(i) = S/(M \times T); \text{disp}(\text{Lambda}(i)); \]
end

figure(10)
plot(g_ins, Lambda);
toc
3.10 Codes used in Part 3

3.10.1 Phase difference

The phase difference $\Delta \phi_n$ used for the Poincaré maps in Fig. 3.4 was introduced via a time delay between the $n$th onsets of bursting in the two cells. The time delay was normalized over the full period of bursting oscillations such that $\Delta \phi_n = 0$ corresponds to complete synchrony and $\Delta \phi_n = 0.5$ indicates anti-phase bursting. The phase of bursting in either cell is reset to zero when the voltage of the cell increases from its quiescent state to reach an auxiliary threshold $\Theta_{aux} = -50$ (mV). The auxiliary threshold $\Theta_{aux} = -50$ (mV) is chosen such that it lies between the minimum values of spikes and the quiescent state. Therefore, the time when the voltage of the reference cell increases from its quiescent state and crosses this threshold is the time for the onset of bursting. More details on the calculations of the phase differences and the Poincaré maps using this procedure can be found in [31].

3.10.2 Transversal Lyapunov exponent

Transversal Lyapunov exponents for the stability of synchronization correspond to eigenvectors transversal to the synchronization subspace $M$. When all $N - 1$ transversal Lyapunov exponents are negative, an initial synchronization error converges to zero, yielding stable synchronization. The largest transversal Lyapunov exponent $\lambda_\perp$ shown in Figs. 3.3 and 3.8 was calculated from simulated time-series data of the variational equations (3.3) via the orbit separation algorithm [64] and the standard fourth-order explicit Runge-Kutta method of numerical integration.

3.10.3 MATLAB codes

```matlab
% phaseifferencePlotter m-file
load onePeriodSherman;
vv = onePeriodShermanSys;
tt = onePeriodShermanTime;
periodTime = tt(end);
```
maxIndex = length(tt);
stepSize = 200;
grid = 1:stepSize:maxIndex;
numberPoints = length(grid);
disp(numberPoints);
phaseDiff = zeros(1, numberPoints);
v0 = vv(1, :);
g_in = 0.0;
eps = 0.01;

options = odeset('AbsTol', [1e-8, 1e-10, 1e-10, 1e-8, 1e-10, 1e-10], ...
'RelTol', 1e-10);
options2 = odeset('AbsTol', [1e-8, 1e-10, 1e-10, 1e-8, 1e-10, 1e-10], ...
'RelTol', 1e-10, 'Events', @crossUpEvent);

parfor ii = 1: numberPoints;
    disp(ii);
    vl = vv(grid(ii), :);
    vv0 = [v0, vl];
    [~, v] = ode15s(@shermanCoupled, [0:0.01:4000], vv0, ...
                 options, g_in, eps);
    vv0 = v(end, :);
    [t, v, te, ve, ie] = ode15s(@shermanCoupled, [0:0.1:100000], ...
                               vv0, options2, g_in, eps);
    times1 = te(ie == 1); % jump ups for the 1-st cell
    times2 = te(ie == 2); % jump ups for the 2-nd cell
    if times1(end) > times2(end)
        phaseDiff(ii) = (times1(end) - times2(end)) / ...
    end
end
\[(\text{times1(end)} - \text{times1(end-1)})\];

else

    \quad \text{phaseDiff(ii)} = (\text{times1(end)} - \text{times2(end-1)})/...
    \quad (\text{times1(end)} - \text{times1(end-1)});

end

disp(\text{phaseDiff(ii)})

end

plot(grid/maxIndex,phaseDiff,'.').
saveas(gcf,'Bprc_morePoints.fig')
% shermanPhase-a-la_Sajia
close all
clear all
clc
tic

load onePeriodSherman;
vv = onePeriodShermanSys;
tt = onePeriodShermanTime;
periodTime = tt(end);
maxIndex = length(tt);
stepSize = 200;
grid = 1:stepSize:maxIndex;
numberPoints = length(grid);
disp(numberPoints);

g_in = 0.01;
eps = 0.01;

upLine = zeros(1, numberPoints);
downLine = upLine;

options = odeset('AbsTol', [1e-8, 1e-10, 1e-10, 1e-8, 1e-10, 1e-10], ... 'RelTol', 1e-10, 'Events', @crossUpEvent);
k = 0; d = 1000;
parfor k = 1: numberPoints;
    disp(k);
    ii = grid(k);
v0=vv(ii,:);  
vUp=v0;  
vDown=v0;  
diff1=0;  
diff2=0;  
jj=ii;  
while diff1<0.01 && abs(ii-jj)<22900;  
    jj=jj+d;  
    v1=vv(mod(maxIndex+jj,maxIndex)+1,:);  
    vUp=[v0,v1];  
    [t,v,te,ve,ie] = ode15s(@shermanCoupled,[0:0.1:100000],...  
        vUp,options,g_in,eps);  
    times1=te(ie==1); % jump ups for the 1-st cell  
    times2=te(ie==2); % jump ups for the 2-nd cell  
    diff1=min(abs([times2(end)-times1(end),times2(end)-...  
                  times1(end-1),times2(end-1)-times1(end),times2(end-1)...  
                  -times1(end-1)])/times1(end)-times1(end-1)));  
    if diff1<0.01; upLine(k)=upLine(k)+d; end;  
end  
jj=ii;  
while diff2<0.01 && abs(ii-jj)<22900;  
    jj=jj-d;  
    v2=vv(mod(maxIndex-jj,maxIndex)+1,:);  
    vDown=[v0,v2];  
    [t,v,te,ve,ie] = ode15s(@shermanCoupled,[0:0.1:100000],...  
        vDown,options,g_in,eps);  
    times1=te(ie==1); % jump ups for the 1-st cell  
    times2=te(ie==2); % jump ups for the 2-nd cell
diff2 = min(abs([times2(end)-times1(end), times2(end-1)-times1(end-1), times2(end-1)-times1(end)])/(times1(end)-times1(end-1)));
if diff2 < 0.01; downLine(k) = downLine(k) - d; end;
end
end
figure(1)
title('First Approximation g= %')
plot(tt(grid)/periodTime, upLine/10/periodTime, 'b', tt(grid)/...
periodTime, downLine/10/periodTime, 'b');
toc
REFERENCES

[1] CONTENT is available on its main developer’s webpage (Yu.A. Kuznetsov): http://www.staff.science.uu.nl/kouzn101/CONTENT.


