Synchronization-based Parameter Estimation of Neuronal Networks

Sid Visser · Stephan van Gils · Michel van Putten ·
Anton Stoorvogel · Wim van Drongelen

Abstract We study automated parameter searches on single neurons and two cell networks. In order to get round the effects of unknown initial conditions we focus on methods that are based on synchronization of the dynamical system to observed time series. The parameters are estimated with a slow dynamic equation that converges to the best value of the parameter. As this implementation does not require restarts parameters can be estimated real-time. For single cells it is possible to identify conductances of different channels, even when the observed series have a lower resolution than the integration step. Synchronization becomes problematic in two cell networks with a single unidirectional connection, because the sending neuron cannot not be synchronized to a desired state. A new method is developed that is, contrary to other synchronization-based methods, able to estimate network parameters. This method temporarily slows down or speeds up a neuron in order to get the spike timing correct. We show that convergence will not occur because this new method because it has chaotic dynamics. However, we are still able to identify proper values of the parameters as the chaotic attractor has basins of attraction around the optimal parameter values.

1 Introduction

Models of neurons and neuronal networks can provide new physiological insights in the workings of the brain and several brain disorders. A major challenge in computational neuroscience is the correct identification of the various parameters used in these models. An example is epilepsy: some seizures could be induced by changing a single parameter only [10]. Such seizures may be predicted successfully if this parameter can be identified from an EEG. Estimating such parameters requires a detailed model of the neurons and networks that generate the behavior.

Many models exist for single neurons, some are realistic in the sense that they model the flow of ions through the cell membrane whereas others are reduced models, matching only the observable behavior of neurons. The behavior of both model classes is strongly related to the parameters of the models and it is often hard to predict the behavior of a model for a given set of parameters. The inverse problem, finding parameters for a specific type of behavior, is generally even harder. Even though the reduced models have fewer parameters than the conductance-based models, the parameters often lose their physical interpretation, making it hard to compare the parameters with physiological values obtained by experiments. It is therefore desirable to automate parameter searches: an algorithm that would find a set of parameters corresponding to a specific type of behavior. This enables one to distinguish different types of neurons in a better way: instead of comparing the behavior of the cell, the values underlying this behavior can be compared. These concepts of parameter searches, as described above, and some implementations are discussed in [11,9,1].

As neurons are the building blocks of the brain, a proper understanding of their dynamics is required. However, analysis of brain rhythms and related disorders is only possible when networks of neurons are considered, rather than single cells. In this case more parameters appear in the model, e.g. the parameters of the connections between the cells. Physiological values are generally hard to determine with experiments,

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S. Visser
Department of Applied Mathematics,
Twente University,
Enschede, Netherlands
E-mail: s.visser-1@math.utwente.nl

because the number of connections onto a cell is large and the contribution of a single connection can be little. Hence, the parameters required by the model to simulate these connections are hard to identify. To gain a better understanding of the structure of neuronal networks, these parameters are of great interest because they largely determine the rhythms of the network [8, 2]. A goal of this paper is to develop an algorithm that is able to determine values for some of these parameters in small networks, under the condition that limited observations are present: a small number of neurons and for limited time.

A general problem with parameter searches in dynamical systems is that the initial conditions of the system are unknown. Often, this is solved by defining additional parameters that represent these initial conditions. This approach can become problematic when the system is chaotic, because the system is sensitive to the initial conditions, or if the system is large, because the number of initial conditions can easily exceed the number of interesting parameters. A common solution to these problems is to couple the dynamical system to the observed time-series, such that the model is forced to show similar behavior as the observations [5,4,3]. Due to this synchronization, the model becomes independent of its own initial conditions and arbitrary initial conditions can be chosen. As this concept is shown to be effective for estimating parameters of dynamical systems, it will provide a starting point for the methods developed in this article.

2 Methods

2.1 Single cell

To illustrate the implementation and effectiveness of synchronization-based parameter estimation, a single cell consisting of a single compartment is considered first. The results and conditions obtained from this test will be used to expand the concepts of this method to small neuronal networks.

2.1.1 Model decription

A model of a STN cell as developed in [8] is used because it fires intrinsically at a few Hertz without external applied currents. This model is given by:

$$C_m\dot{V} = -I_{\mathrm{leak}} - I_{\mathrm{K}} - I_{\mathrm{Na}} - I_{\mathrm{T}} - I_{\mathrm{Ca}} - I_{\mathrm{AHP}}, \tag{1a}$$

$$I_{\mathrm{L}} = g_{\mathrm{L}}(V - E_{\mathrm{L}}), \tag{1b}$$

$$I_{\mathrm{K}} = g_{\mathrm{K}} n^4 (V - E_{\mathrm{K}}), \tag{1c}$$

$$I_{\mathrm{Na}} = g_{\mathrm{Na}} m_\infty^3(V) h (V - E_{\mathrm{Na}}), \tag{1d}$$

$$I_{\mathrm{T}} = g_{\mathrm{T}} a_\infty^3(V) b_\infty^2(r)(V - E_{\mathrm{Ca}}), \tag{1e}$$

$$I_{\mathrm{Ca}} = g_{\mathrm{Ca}} s_\infty^2(V)(V - E_{\mathrm{Ca}}), \tag{1f}$$

$$I_{\mathrm{AHP}} = \frac{(V - E_{\mathrm{K}})[\mathrm{Ca}]}{[\mathrm{Ca}] + k}, \tag{1g}$$

with membrane potential V, leak current I_{L}, potassium current I_{K}, sodium current I_{Na}, low-threshold T-type Ca^{2+} current I_{T}, high threshold Ca^{2+} current I_{Ca} and a voltage independent afterhyperpolarization current I_{AHP}. Furthermore, the membrane capacity is given by C_m and the specific conductances and reversal potentials for each current are given by g and E respectively. This dynamical system has state variables V, n, h, r and [Ca].

2.1.2 Parameter estimation

The method of dynamic parameter estimation as described in [3] is implemented on this system. We consider the problem in which we want to estimate two parameters of the model (1). For sake of simplicity, two parameters are chosen that appear linearly in the equation of the observed quantity V: the conductances g_{L} and g_{Na}.

The DPE for this problem takes the following form:

$$\begin{aligned} C_m\dot{V} = {} & -I_{\mathrm{leak}} - I_{\mathrm{K}} - I_{\mathrm{Na}} - I_{\mathrm{T}} - I_{\mathrm{Ca}} \\ & -I_{\mathrm{AHP}} + k(V_{\mathrm{ref}}(t) - V), \end{aligned} \tag{2a}$$

$$\dot{g}_{\mathrm{L}} = \delta_{\mathrm{L}}(V_{\mathrm{ref}}(t) - V)\frac{-I_{\mathrm{L}}}{g_{\mathrm{L}}}, \tag{2b}$$

$$\dot{g}_{\mathrm{Na}} = \delta_{\mathrm{Na}}(V_{\mathrm{ref}}(t) - V)\frac{-I_{\mathrm{Na}}}{g_{\mathrm{Na}}}, \tag{2c}$$

with $k > 0$ the coupling strength that couples the model with the observed data $V_{\mathrm{ref}}(t)$ and δ_{L} and δ_{Na} positive constants. The term $k(V_{\mathrm{ref}} - V)$ that appears in (2a) in addition to (1a) forces V to the observed series V_{ref}. If this force is strong enough, the model will synchronize with the reference series as desired. The choice of the constants δ_{L}, δ_{Na} and k will determine whether the parameters converge or not and if so, what the rate of convergence is. If convergence is possible higher values of k are required, but if k is too large, the rate of convergence of the system decreases [3] Therefore, k is chosen

Fig. 1 Visual representation of the considered network

as a slow monotone increasing variable with an ODE of the form:

$$\dot{k} = \gamma \left(V_{\mathrm{ref}}(t) - V \right)^2 , \tag{3}$$

with γ a positive constant. The coupling depends on the error: whenever the error decreases, due to stronger coupling or better parameters, the coupling term increases slowly in order to allow faster convergence of the parameters than for large k.

All parameters of this system are identical to those used to generate reference series V_{ref}, except the parameters g_{L} and g_{Na} that have to be estimated. Note that other conductances of the cell can be estimated simultaneously with additional equations analogous to (2b).

Even though only the membrane potential of the cell is coupled to the reference series, all state variables of this neuron will synchronize with the unobserved state variables underlying the reference series whenever all conditional Lyapunov exponents (CLEs) are negative [3]. This is due to the fact that the coupling of the membrane potential has an indirect effect on the equations of the other state variables as their equations depend on this quantity. A precise definition of synchronization and the relation with conditional Lyapunov exponents are given in Appendix B. From these definitions follow that synchronization is required in order to guarantee convergence of the parameters: if $V_{\mathrm{ref}} - V \nrightarrow 0$ as $t \to \infty$ then generically $\dot{g}_{\mathrm{L}} \nrightarrow 0$ and the limit $\lim_{t\to\infty} g_{\mathrm{L}}$ does not exist.

2.2 Two cells

Consider two neurons (N1 and N2) without connections. Then their activity is uncorrelated, hence it will be impossible to estimate the parameters of the first neuron with observations of the second neuron only.

Now assume that a single connection between these two neurons is present: N1 fires excitatorily on N2 (see Figure 1). Then a cell recording of N1 contains no information of N2 and only parameters of N1 can be determined. If, on the other hand, a recording of N2 is present then it contains some information of N1 because N1 fires on N2. Even though this additional information is limited, since the recorded postsynaptic potentials do not contain information related to the shape of the action potentials, global firing properties of N1 can still be derived.

2.2.1 Synaptic coupling

Next we give the mathematical description of the connection from N1 to N2. As N2 receives synaptic input from N1, an additional current should be modeled on this neuron, called I_{s}:

$$I_{\mathrm{s}} = g_{\mathrm{s}} s_{\mathrm{N1}} (V_{\mathrm{N2}} - E_{\mathrm{syn}}), \tag{4a}$$

in which s_{N1} represents the synaptic activity of the first neuron given by:

$$\dot{s}_{\mathrm{N1}} = \alpha_{\mathrm{N1}} (1 - s_{\mathrm{N1}}) H_\infty (V_{\mathrm{N1}} - \theta_{\mathrm{N1}}) - \beta_{\mathrm{N1}} s_{\mathrm{N1}}, \tag{4b}$$

with α_{N1} and β_{N1} positive constants and H_∞ a smooth approximation to the Heaviside step function.

2.2.2 Parameter estimation for two cells

Even if it is assumed that all other parameters are known (also those of N1), one can conclude that this is troublesome because of the fact that synchronizing N2 with an observed series will have no influence on N1. Hence, the state of N1 remains unknown and it will therefore be unclear when this neuron fires an action potential on N2. Generally the state of the simulated N1 will be different than the one underlying the reference series of N1. As long as these states differ, convergence of the dynamic parameter to its original value is not possible because $V_{\mathrm{ref}} - V_{\mathrm{N2}} \nrightarrow 0$ and therefore $\dot{g}_{\mathrm{s}} \nrightarrow 0$. To be able to succesfully apply DPE to this problem, an algorithm has to be found that adjusts the state of N1 such that it approaches the state of the unobserved neuron.

The model (1) fires periodically with a few Hertz for given parameters[8]. Whereas the parameters determine the frequency of the neuron, the initial conditions determine the phase. Hence, by changing the initial conditions, the phase of N1 can be adjusted until it matches the unobserved neuron underlying the reference series. This method would require the system to restart several times until the initial conditions corresponding to the correct phase are found. Remark that not just a single number representing the phase has to be found, but values for all state variables have to be identified. If the network is expanded to three or more neurons, the estimation of initial conditions will probably start dominating the problem of finding parameter values. The restarts required for this method are also undesirable, because the system has to be evaluated several times to find proper initial conditions. The simulated time of these simulations has to be long enough allowing N2 to synchronize to the reference series.

Another way to match the phase of N1 with the unobserved neuron, is to shift the reference series in time. This would require only the identification of a single parameters, i.e. the time shift, rather than the initial conditions of all state variables. However, restarts are still necessary because the reference series cannot be shifted during simulations as gaps may occur whenever the reference series are shifted forward too fast. Furthermore, the variable representing the time shift of the reference series is discrete, because the time series are a discrete-time signal. As it generally is harder to solve discrete optimization problems than continuous problems, this method will not be investigated further.

2.2.3 Temporal scaling

A third way to get the phases right is by temporarily modifying the firing rate of N1. During this period the neuron may fire faster or slower and eventually firing in phase with the unobserved neuron of the reference series. At this moment, the firing rate is set back to its orginal value in order to maintain the synchrony. Adjustments to the firing rate can be made in several ways: either by adjusting the parameters responsible for the firing rate or by modifying the time. As it is unclear which parameters are represent the firing rate and in what manner, the latter approach is chosen. This concept is expanded below.

First, two timelines are introduced: t represents the real (unmodified) time as experienced by N2 and the reference series and let $\hat{t}$ represent the pseudotime that N1 experiences. Chose a function $\tau > 0$ such that the pseudo-time is evaluated as follows:

$$\hat{t}(t) = \int_0^t \tau(u)\,du. \tag{5}$$

Then $\hat{t}(t)$ is a continuous strictly monotone increasing function, hence time cannot stop or be inverted. The fundamental theorem of calculus yields:

$$\frac{d\hat{t}}{dt} = \tau(t). \tag{6}$$

So for a dynamical system $\mathbf{x} \in \mathbb{R}^n$ that is considered on the pseudotime-scale the following holds:

$$\frac{d\mathbf{x}}{d\hat{t}} = \frac{d\mathbf{x}}{dt}\frac{dt}{d\hat{t}} = \frac{d\mathbf{x}}{dt}\frac{1}{\tau(t)} = f(\mathbf{x}, \hat{t}\,), \tag{7}$$

$$\frac{d\mathbf{x}}{dt} = \tau(t) f\left(\mathbf{x}, \int_0^t \tau(u)\,du\right). \tag{8}$$

If applied to an autonomous system (time independent), this reduces to

$$\frac{d\mathbf{x}}{dt} = \tau(t) f(\mathbf{x}). \tag{9}$$

The model (1) of a neuron is such an autonomous system and it is therefore unnecessary to investigate the integral (5).

The function $\tau(t)$, that represents the temporal scaling factor of the dynamical system, is considered next. Even though the behavior of N1 is modified purposely, it is desired to be still “neuron-like” in the sense that action potentials (APs) have a duration close to 1ms. For that reason, τ is bounded from below as well as from above:

$$1 - \eta \le \tau(t) \le 1 + \eta, \qquad 0 \le \eta \le \frac{1}{4}. \tag{10}$$

With τ varying between $\frac{3}{4}$ and $\frac{5}{4}$, the AP durations are still within the physiological range. On the other hand, this speed difference is probably large enough to get the neuron N1 in phase with the unobserved neuron, as well.

The value of the temporal scaling factor of N1 will depend on the error $V_{\mathrm{ref}} - V$ of N2, such that it is 1 whenever the error vanishes. Therefore, a symmetric sigmoidal function is chosen of the following form:

$$\tau_{\pm}(u) = 1 \pm \eta \left(1 - \frac{2}{1 + \exp[u/\sigma_\tau]}\right), \tag{11}$$

with σ_τ a positive parameter. As it is not clear whether the system should speed up or slow down for a given sign of the error, both the ‘+’-variant and the ‘$-$’-variant are considered, representing the increasing sigmoid and decreasing sigmoid respectively. The temporal scaling factor is desired to change slowly, in order to prevent N1 from alternating between speeding up or slowing down whenever the error changes sign often. We introduce a first order differential equation for the factor, having its equilibrium given by (11):

$$\frac{d\tau}{dt} = \mu\left(\tau_{\pm}\left(V_{\mathrm{ref}} - V_{\mathrm{N2}}\right) - \tau\right), \tag{12}$$

with μ a positive constant representing the reciprocal time constant of the temporal scaling factor.

3 Numerical results

3.1 Single cell DPE

Parameters identical as in [8] are used to generate a reference series that will be used as input signal of the parameter search algorithm to determine if the original values of the parameters can be found by the algorithm. To evaluate the DPE on single cells, as described by equations (2), two STN cells are evaluated simultaneously. The first cell has known parameters and produces the reference series used by the second cell that has dynamic parameters. It has the same effect as recording the reference series at the same frequency as the integration time step, i.e. 100kHz. From the results, shown in Figure 2, it is seen that the system converges. Two parameters that appear linearly in the equation of the observed variable are succesfully identified.

Whenever the reference signal is recorded at a lower sampling rate, e.g. 10kHz, it has to be interpolated to obtain a signal of 100kHz as is required by the integrator. Linear interpolation of the data is chosen as it is straightforward. The results obtained with this interpolated signal are shown in Figure 3. The results with the interpolated signal are noticably worse than the DPE with the 100kHz signal. The slower rate of convergence of g_{Na} may be explained by the following: the sodium conductance is best observed during action potentials. However, as action potentials have a duration of 1-2ms only 10-20 measurements per AP are present at a sampling rate of 10kHz. These few data points are not enough to capture every aspect of the AP and the precise value of g_{Na} cannot be derived easily from these misformed APs.

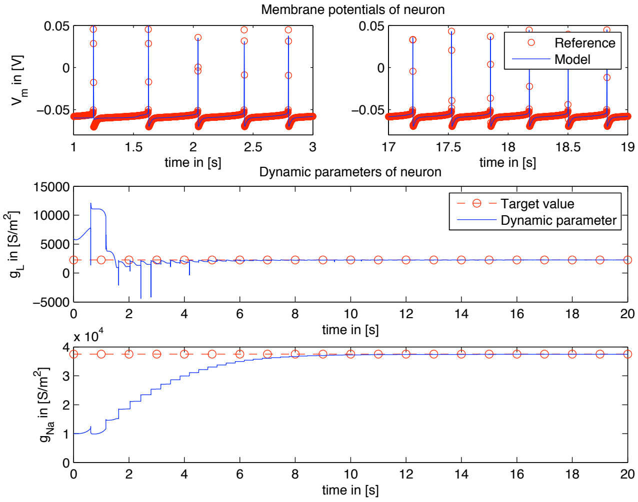

Fig. 2 Results of the DPE when it estimates two parameters, i.e. g_{syn} and g_{Na}, of a single neuron with a reference series of 20s at 100kHz. The top two diagrams show both the reference series and the model synchronized to it at two different time intervals. Note that in the beginning the fit is not perfect: the spikes at 2.5 and 2.8 seconds are not as high as the reference series. Target values of g_{L} and g_{Na} are respectively 2.25e3 and 37.5e3 and initial conditions 6e3 and 10e3. DPE constants used are as follows: $\gamma = 0.01$, $\delta_{\mathrm{L}} = \delta_{\mathrm{Na}} = 10$ and $k(0) = 0$.

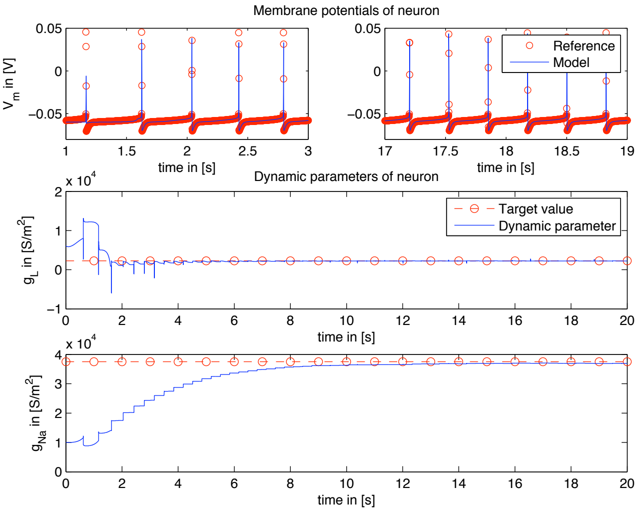

Fig. 3 Results of the DPE when it estimates two parameters of a single neuron with an interpolated reference series of 20s at 10kHz. Note that the convergence of the parameters, especially g_{Na}, is much slower than with the higher sampling rate. Futhermore, the consants and initial conditions used are identical to those in Figure 2.

3.2 Two cell DPE

We consider a two cell network coupled according to(4) and DPE is applied to estimate the synaptic conductance g_{s} that appears linearly in the ODE of the observed quantity V_{N2}. The results of this simulation, using a reference series sampled at 100kHz, are shown in Figure 4. Note that, as predicted in subsection 2.2.2, the regular implementation of DPE fails beacuse N1

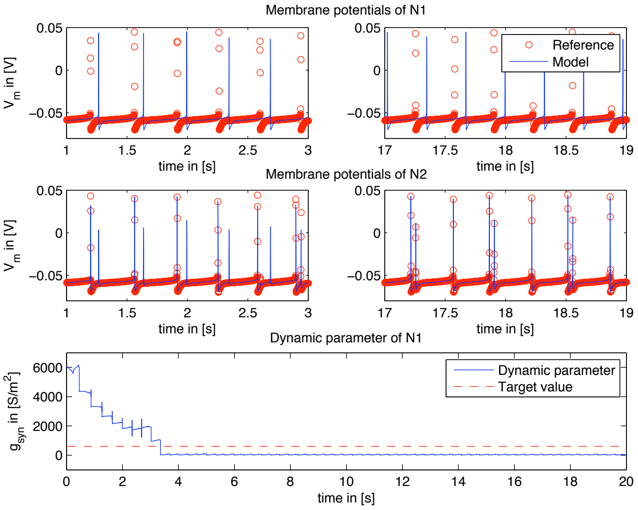

Fig. 4 DPE applied to a network of two cells, but without the temporal scaling factor. Neuron N2 is synchronized with the reference series sampled at 100kHz. No feedback to N1 is present so that its state remains independent with the unobserved neuron of the reference series. The initial condition of g_{s} is 6e3 and its target value is 0.6e3. Other constants are $\gamma = 0.1$ and $\delta_{\mathrm{s}} = 10$.

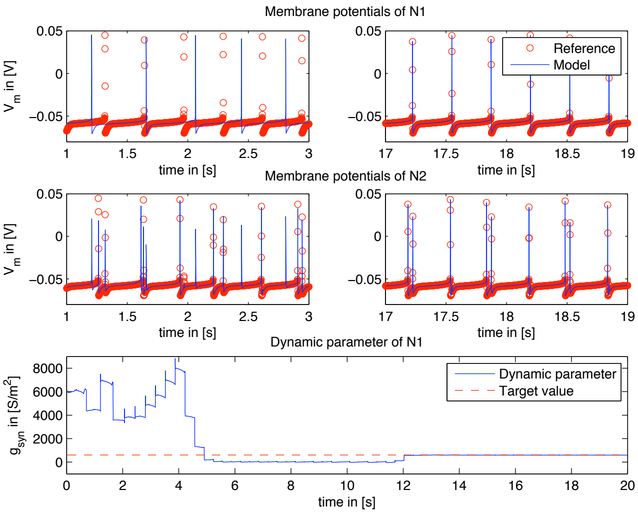

Fig. 5 DPE applied to a network of two cells with the temporal scaling factor. Neuron N2 is synchronized with the reference series sampled at 100kHz. Due to the temporal scaling factor, N1 seems to synchronize with the reference as well.

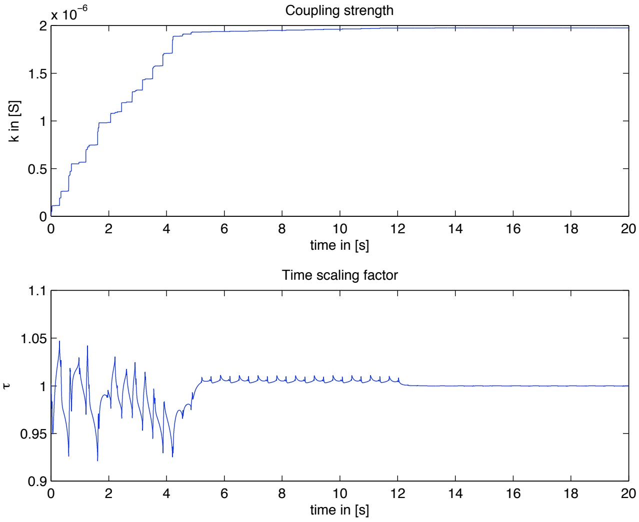

Fig. 6 The results of DPE with the temporal scaling factor τ. Note that the neuron N1 is speeding up until it reaches the correct phase, after which the parameter is identified correctly (see also Figure 5). At this moment, the speed factor drops back to 1 and the coupling strength k increases much slower, suggesting that synchronization occured.

does not synchronize with its state that underlies the reference series (top two plots in Figure 4). This causes N2 to prefer a low synaptic conductance such that it will not fire during synaptic input of N1, preventing additional misfires with respect to the reference series.

Whenever we implement the temporal scaling factor (9) to N1 and use a reference series sampled at 100kHz, we are able to estimate the synaptic conductance of N2. The results are shown in Figure 5 and Figure 6. At first, we notice similar behavior as two cells without the temporal scaling factor: the phase of N1 does not match the reference series and a low synaptic conductance is prefered to prevent additional misfires of N2 that are initiated by synaptic input of N1. At this moment, the temporal scaling factor has an increased value of approximately 1.01 and the phase of N1 approaches the phase of the unobserved neuron. Once a spike of N1 coincides with a spike of the unobserved neuron underlying the reference series the temporal scaling factor drops back to 1 to keep N1 close to this phase. This happens at $t = 12$ in Figure 5 and 6. Furthermore, we note that the coupling strength k increases fast for the first five seconds after which it slows down. This is the time required by N2 to synchronize with the reference series. Once synchronized, small errors between N2 and the reference series will be caused by an incorrect phase of N1. During this period, the coupling strength increases slightly with every misfire. Whenever the phase of N1 matches the phase of the unobserved neuron, no more misfires occur and the coupling strength stops increasing.

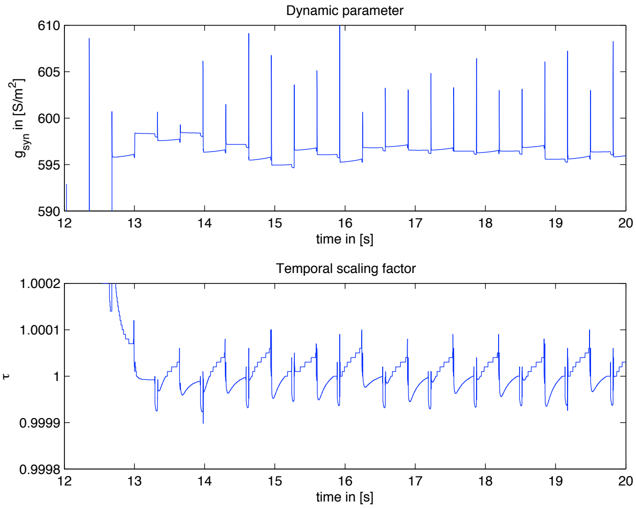

Fig. 7 A detail of the parameter and temporal scaling factor close to their target values of 600 and 1 repectively. Note the irregular oscillations of both variables.

A detail of the final state is shown in Figure 7 and we observe that the converge to the target values is not exponential Furthermore, we note the irregular oscillations of both the parameter and the temporal scaling factor.

4 Analysis

After we have shown numerically that the method of dynamical parameter estimation works on single cells and two-cell networks, we analyze the conditions for convergence. As stated earlier, convergence of the parameter to the correct value is only possible whenever the model synchronizes with the reference time series. By considering the possibilty of a model to synchronize with a time series, we derive a necessary condition for converge of the dynamic parameter.

First we give a formal description of a simplified DPE algorithm from which we derive criteria for synchronization. Thereafter we analyze these conditions for the systems that we described in the previous section.

4.1 Synchronization in DPE

We consider a system $x \in \mathbb{R}^n$ of the form:

$$\dot{x} = f(t, x, p), \tag{13}$$

with $p \in \mathbb{R}^l$ representing the parameters of the system. We assume that the first m components of x are observed with time series and we couple these to a system $y \in \mathbb{R}^n$ that has the same equations as x but different parameters $q \in \mathbb{R}^l$:

$$\dot{y} = f(t, y, q) + K(x - y), \tag{14}$$

The $n \times n$-diagonal matrix K has m entries $k_1, \ldots, k_m > 0$ that correspond with the m observed compoments of x:

$$K = \mathrm{diag}(k_1, \ldots, k_m, 0, \ldots, 0). \tag{15}$$

In the coming analysis we fix all k_i.

We assume that the parameters we want to estimate appear linearly in the equations of of the observed components, hence:

$$\frac{\partial f_i}{\partial p_j}(t, x, p) = \frac{\partial f_i}{\partial p_j}(t, x), \qquad 1 \le i \le m, 1 \le j \le l. \tag{16}$$

To estimate the parameters q we apply an adaptive control mechanism of the form

$$\dot{q} = B \frac{\partial f}{\partial q}(t, y)^T (x - y), \tag{17}$$

in which $\frac{\partial f}{\partial q}$ is the $n \times l$ matrix with partial derivatives of f_i with respect to q_j and B is a $l \times l$-diagonal matrix.

To determine whether the system $[y, q]$ synchronizes with $[x, p]$ we consider the difference z between them:

$$z = \begin{bmatrix} x - y \\ p - q \end{bmatrix}, \tag{18}$$

$$\dot{z} = \begin{bmatrix} \dot{x} - \dot{y} \\ -\dot{q} \end{bmatrix}, \tag{19}$$

$$= \begin{bmatrix} f(t, x, p) - f(t, y, q) - K(x - y) \\ -B \frac{\partial f}{\partial q}(t, y)^T (x - y) \end{bmatrix}, \tag{20}$$

Single cell

parameters	CLEs			
g_{L}	-0.000951	-0.003506	-0.006212	-0.013641
	-0.027785	-3.492551		
$g_{\mathrm{L}}, g_{\mathrm{Na}}$	-0.000509	-0.000885	-0.003595	-0.008101
	-0.026987	-0.126180	-3.384773	

Table 1 The conditional Lyapunov exponents determined for two DPE implementations on a single cell. Note that all CLEs are negative, hence the algorithm synchronizes and identifies the parameters.

upon expanding $f(t, x, p)$ around $f(t, y, q)$, we obtain:

$$= \begin{bmatrix} \frac{\partial f}{\partial y}(t, y, q)(x - y) + \frac{\partial f}{\partial q}(t, y)(p - q) - K(x - y) \\ -B \frac{\partial f}{\partial q}(t, y)^T (x - y) \end{bmatrix}, \tag{21}$$

$$= \begin{bmatrix} \frac{\partial f}{\partial y} - K & \frac{\partial f}{\partial q} \\ -B \frac{\partial f}{\partial q}^T & 0 \end{bmatrix} \begin{bmatrix} x - y \\ p - q \end{bmatrix}, \tag{22}$$

$$= Jz. \tag{23}$$

If we can show that $z \to 0$ as $t \to \infty$, then the model y synchronizes with the reference series x and the parameters q approach the target values p. Clearly, this happens when the system (23) has only negative Lyapunov exponents. Because the orbit of z is mostly determined by y, q and the reference series x, we call these exponents conditional Lyapunov exponents. A proper definition of these exponents in given in Appendix B.

Now that we have shown that a system should have negative CLEs in order to identify its parameters with the above stated DPE algorithm, we consider this condition for the systems described in section 2. From the numerical results obtained in section 3, we know what results we should expect from this analysis.

4.2 Single cell

First we consider the DPE implementation (2) with only a single parameter, namely g_{L}. From numerical simulations we know that DPE is able to estimate one or two parameters in a single cell and therefore we expect that all CLEs of the algorithm are negative.

The linearized system (23) is derived and its spectrum of Lyapunov exponents is determined numerically by the “re-orthonormalization method” [12]. This method is summarized in Appendix A. The results are shown in the first row of Table 1. It turns out that all the Lyapunov exponents of the system are negative, which matches our expectations.

Next we apply the DPE algorithm to a single cell to estimate two parameters: g_{L} and g_{Na}. Numerical results shown in Figure 2 suggest that synchronization occurs

Two-cell network

parameters	CLEs			
g_{syn}	0.000022	-0.000871	-0.000951	-0.003479
	...	-1.722	-6.63	
g_{syn}, τ	0.273469			

Table 2 The conditional Lyapunov exponents determined for two DPE implementations on a two-cell network. The first row represents results results without temporal scaling, the second with.

and thus we expect that all CLEs of this system are negative as well. The values of the CLEs are represented in the second row of Table 1. As expected, all Lyapunov exponents are negative.

Note that the largest CLE in the second case is approximately half of the largest CLE in the first case, indicating that convergence of q to p occurs at a lower rate when more parameters have to be determined.

4.3 Two cells

If we consider the two-cell networks with a single unidirectional connection as described in subsection 2.2 and apply the DPE method without the temporal scaling factor, we fail to identify a single parameter (see Figure 4). This is due to the phase difference of the unobserved neuron between the model and the reference series. Because of this translation symmetry we expect neither convergence nor divergence, hence the largest CLE should be 0.

The numerically determined Lyapunov exponents are shown in Table 2. Not all 12 exponenents are given, only the largest and the smallest are printed to give an impression of the spectrum. The largest CLE turns out to be positive, but small. As this number is close to the expected value 0, we assume that this results is an error of algorithm used to determine the exponents.

Next we analyze the same network, but we apply the temporal scaling factor τ as described in 2.2.3. The dynamical equation of this parameter is of a different form than (17) and therefore loses the Jacobi-matrix of the system (23) its nice form. We use a different algorithm to determine the conditional Lyapunov exponents: one that is able to determine the largest CLE only. This algorithm is described in Appendix A.

The second row of Table 2 contains the numerical evaluation of this largest Lyapunov exponent. Unexpectedly the largest CLE is a positive number, indicating the presence of a chaotic attractor. Therefore we are unable to determine the value of the parameter generically.

From numerical simulations presented in subsection 3.2 we know that the dynamic parameter g_{s} has two prefered values; either 0 or the target value 600. Because of the chaotic nature of the system we can conclude that the DPE method is unstable around both values, but the orbit of the parameter can stay close to these values for arbitrary time as well. This instability of the target values can be observed in the numerical simulations as well, as depicted in Figure 7. Both basins of attraction represent a value of the parameter for which the model shows behavior close to reference series and therefore should both values be considered when estimating parameters from real observations rather than artificial data.

The advantage of having a positive CLE instead of one that equals 0 is that the system becomes chaotic and a much larger part of the parameter space can be explored. These excursions allow us to identify different values of the parameters for which the model behaves similar as the reference series.

5 Discussion

Neurons and small network of neurons play an important role in the generation of rhythms in the brain. An understanding of these rhythms is required to gain better insights in the dynamics of the brain and several disorders. In order to analyze such systems in more detail we have implemented parameter search algorithms on models of a single neuron and two-cell networks.

The method that we have used to identify parameters of different systems is based on synchronization. The concept of synchronizing a model to a reference series reduces the effect of unknown initial conditions because the model is forced to show similar behavior as the time series. Due to this force the model can become independent of its initial conditions, which is required for identifying its parameters successfully.

Furthermore, we have estimated the parameters of the model with a first order dynamical equation that converges to a value as the time evolves. This limit value is the best value of the parameter. We have shown that this method is not able to identify parameters accurately when the model fails to synchronize with the reference series. We have analyzed several models on their ability to synchronize with a reference series and we have derived a necessary and sufficient condition for synchronization when the unknown parameters appear linearly in the equations of the observed components: all conditional Lyapunov exponents of the system should be strictly negative.

We have considered a single STN cell of which only recordings are available of its membrane potential and we have implemented the described parameter search algorithm for this system and we have estimated the conductances of two channels, parameters that appear linearly in the equation of the observed component, accurately. Further analysis has shown that all conditional Lyapunov exponents of the system are negative, as is required for convergence.

Next we have defined a two-cell network for which synchrization is impossible by definition: between the two cells of this network is a single unidirectional synaptic connection. Whenever time series are available of the receiving neuron we can synchronize these series to that neuron, but we fail to synchronize the sending neuron. Even if we assumed the easiest case in which both neurons are oscialltors with a fixed period, synchronization is still impossible because the largest CLE of the system is 0. Numerical simulations have confirmed that this method fails to identify the synaptic conductance, a parameter that appears linearly in the equation of the observed component.

In order to estimate this parameter, we have developed a new method that temporarily modifies the firing rate of the unobserved neuron and we have considered it on neurons that fire periodically with a known frequency. Depending on the difference of the time series and the coupled neuron we speed up or slow down the unobserved neuron by multiplying all its dynamical equations with a scalar. We call this scalar the temporal scaling factor. By definition this factor lies in the range $[0.75, 1.25]$ such that the action potentials of the neuron still have a physiologically correct duration.

We have studied the effects of this factor both numerically and analytically. Simulations have shown that it this temporal scaling factor enables the method to come close to the original value of the parameter. Exponential convergence, however, was not the case as both the dynamic parameter and the temporal scaling factor kept oscillating irregularly. This result matches with the analysis we have performed: the largest CLE of the system is a positive number, indicating the presence of a chaotic attractor. From the results of the numerical simulations we have found that this attractor has two basins of attraction: one around the target value of the parameter and one around 0. The latter value corresponds with the case in which the synaptic conductance is 0 and no spikes of the sending neuron are transfered. This results seems quite natural: if you are unable to match the action potentials initiated by the synaptic input because the phase of the sender is incorrect, it is better to neglect this synaptic input to prevent such misfires.

Even if synchronization and convergence are not possible due to the chaotic nature of the system, this method is still valuable. The orbits of these chaotic dynamics are likely to cover a much larger part of the phase space than the other methods, yielding more information of the system and possibly identifying different sets of parameters that show similar behavior of the model.

The effectiveness of this chaotic parameter estimation needs to be studied for larger systems. It is likely that the basins of attraction grow wider and may eventually intersect each other, yielding a more complex attractor. Furthermore, the new method has to be analyzed for systems in which the neurons fire irregularly. In this case the time spent on the attractor around the target value may become very small, making it hard to identify the basins of the attractor.

A different aspect that has to be analyzed as well is the effect of noise. Even in small system that synchronize with the reference series in the abscence of noise, noise will prevent synchronization and the dynamic parameter will be noisy as well. In some cases it might suffice to determine the mean value of this parameter, but this might fail in other cases.

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A Lyapunov exponents

A.1 Description

The Lyapunov exponents (LEs) of a dynamical system determine the growth rates of pertubations of an orbit. We state the following definition for a Lyapunov exponent.

Definition 1 *For any norm* $||\cdot||$ *a Lyapunov exponent* λ *satisfies*

$$||x(t) - y(t)|| \approx e^{\lambda t}||x(0) - y(0)||, \tag{24}$$

with $x(t)$ *and* $y(t)$ *both orbits of the system* f *and a sufficiently small initial separation* $||x(0) - y(0)||$.

As the value of λ depends on the direction of the initial separation, a whole spectrum of Lyapunov exponents exists. The number of LEs equals the number of dimensions of the phase space as this the number of independent directions in this space.

Clearly, if all Lyapunov exponents of the system are negative the orbits of x and y will close each other such that $||x(t) - y(t)|| \to 0$ as $t \to \infty$. On the other hand, if one of the LEs is positive the orbits of x and y are unstable with respect to each other. If in this case $x(t)$ and $y(t)$ remain bounded for all time a chaotic attractor exists in the bounded domain, because no asymptotically stable limit points or limit cycles exist in the domain due to the positive LE.

A.2 Numerical calculation

Now that we have defined a Lyapunov exponent and considered some of its properties, we will consider the numerical approximations of these exponents. First we describe an algorithm that is able to determine the largest LE only. Thereafter a more advanced algorithm is given that enables one to approximate the complete spectrum of Lyapunov exponents.

A.2.1 Largest Lyapunov exponent

If the direction of the initial separation is chosen arbitrarily, it is likely to have a component along the direction corresponding to the largest LE. When we evaluate the distance between both orbits (the original and the perturbed) after some time, it will be dominated by the largest Lyapunov exponent as the contribution of the other LEs is much lower. This concept can be used to determine the largest Lyapunov exponents numerically.

At a certain point x_0 in the phase space we add a small perturbation of size d_0 and we obtain y_0, hence $||x_0 - y_0|| = d_0$. Some time t_1 later the state of the system and the perturbation are x_1 and y_1 respectively and the separation is given by definition 1:

$$d_1 = ||x_1 - y_1|| \approx d_0 e^{\lambda_1 t_1}, \tag{25}$$

in which λ_1 represents the largest LE. We obtain an approximation of the largest Lyapunov exponent of the form

$$\lambda_1 \approx \frac{1}{t_1} \ln \frac{d_1}{d_0}. \tag{26}$$

As such a single evaluation estimates the Lyapunov exponent at a small part of the attractor only, this procedure has to be repeated several times until the "local" Lyapunov exponents of the attractor are determined. Furthermore, no guidelines exist for the initial separation d_0 and the time t_1. If t_1 is too large the perturbation y_1 may deviated too fat from to its original orbit x_1 to give you information about the neighbourhood of x, whereas a too small t_1 could yield cases in which the system has not be evaluated long enough for λ_1 to dominate the final separation d_1.

A.2.2 Spectrum of Lyapunov exponents

To determine the entire spectrum of Lyapunov exponents more advanced algorithms are required, such as proposed in [12,7]. We summarize the method described in [12] below.

First the linearization of the system around its orbit is considered:

$$\dot{z} = J(x)\, z, \tag{27}$$

in which z represents a relative perturbation of the system x and $J(x)$ the Jacobi-matrix of the system evaluated at x. As shown earlier every initial perturbation will in the long term be affected by the largest LE and corresponding direction only. Therefore we introduce another perturbation which is perpendicular to the first direction and therefore independent of the largest Lyapunov exponent. Every time we normalize the system, we also orthogonalize the directions. As this second direction is independent of the largest LE, it will orient itself slowly in the direction of the largest remaining LE and we are able to estimate the exponent along this direction.

Continuing in this manner we define a total of n orthogonal directions corresponding with the n Lyapunov exponents and we orthonormalize the perturbations regularly such that the direction of the i-th perturbation is orthogonal to all $i - 1$ previous directions. This orthonormalization is determined with the Gram-Schmidt process.

Unlike with the algorithm presented in subsubsection A.2.1 the time between the re-orthonormalizations is not too important because the perturbations point in a direction that is independent of other Lyapunov exponents it is not necessary to "wait long enough" for the dominating term.

B Synchronization of dynamical systems

Two different methods exist to synchronize dynamical systems to time series. The first method, called "feeding", substitutes (or feeds) the time series in the in the corresponding equations of the dynamical system, thereby reducing the size of the system. The method of "coupling" synchronizes a model by forcing it to show similar behavior as the time series: the model is coupled to the time series (much like a spring). Both methods are summarized below.

B.1 Feeding method

First we define a continuous time dynamical system $u \in \mathbb{R}^n$ of the form:

$$\dot{u} = f(t, u), \tag{28}$$

We split this system into two subsystems $u = [w, x]$ with $w \in \mathbb{R}^m$ and $x \in \mathbb{R}^{n-m}$:

$$\dot{w} = g(t, w, x), \qquad \dot{x} = h(t, w, x), \tag{29}$$

such that w corresponds with the observed quantities of the time series. Next, consider a system $y \in \mathbb{R}^{n-m}$ that is similar to x, hence:

$$\dot{y} = h(t, w, y). \tag{30}$$

Generally, y will have a different orbit than x due to different initial conditions.

Definition 2 *A system of the following form:*

$$\dot{w} = g(t, w, x), \quad \dot{x} = h(t, w, x), \quad \dot{y} = h(t, w, y), \tag{31}$$

synchronizes if $x - y \to 0$ as $t \to \infty$ independent of initial conditions. Hence, the orbit of w contains enough information to approximate the phase $[w, x]$ of the system with $[w, y]$.

We analyze the difference $z = x - y$ between both systems to state whether synchronization of this form is possible:

$$\begin{aligned}
\dot{z} &= \dot{x} - \dot{y}, && (32)\\
&= h(t, w, x) - h(t, w, y), && (33)\\
&\approx h(t, w, x) - \left(h(t, w, x) + \frac{\partial h}{\partial x}(t, w, x)(y - x) \right), && (34)\\
&= \frac{\partial h}{\partial x}(t, w, x) z. && (35)
\end{aligned}$$

in which $\frac{\partial h}{\partial x}$ represents the Jacobi-matrix of h with respect to x.

A closer look at (35) reveals that we basically linearize around the orbit $[w(t), x(t)]$ to see if it attracts other nearby orbits. Convergence to this orbit is possible whenever all eigenvalues of the Jacobi-matrix in (35) have negative real part. As the Jacobi-matrix changes in time, the eigenvalues are undefined and we have to consider the Lyapunov exponents of the system. We state the following theorem [6]:

Theorem 1 *Synchronization occurs if and only if all Lyapunov exponents of the system*

$$\dot{y} = h(t, w(t), y). \tag{36}$$

are negative. The Lyapunov exponents of the subsystem (36) are refered to as "Conditional Lyapunov Exponents" (CLEs) of the system (28).

B.2 Coupling method

Define a continuous time dynamical system $x \in \mathbb{R}^n$:

$$\dot{x} = f(t, x). \tag{37}$$

If we have observations of the first m coordinates of x, we can add a feedback term to couple system $y \in \mathbb{R}^n$ to x:

$$\dot{y} = f(t, y) + K(x - y), \qquad K = \mathrm{diag}(k_1, \ldots, k_m, 0, \ldots, 0), \tag{38}$$

with $k_i, i = 1 \ldots m$ positive coupling constants.

Definition 3 *A system of the form (37), (38) synchronizes if $x - y \to 0$ as $t \to \infty$ independent of initial conditions.*

Next we consider the difference $z = x - y$ between the model y and the reference series x:

$$\begin{aligned}
\dot{z} &= \dot{x} - \dot{y} && (39)\\
&= f(t, x) - f(t, y) - K(x - y) && (40)\\
&\approx f(t, y) + \frac{\partial f}{\partial y}(t, y)(x - y) - f(t, y) - K(x - y) && (41)\\
&= \left[\frac{\partial f}{\partial y} f(t, y) - K \right] z, && (42)
\end{aligned}$$

in which $\frac{\partial f}{\partial x}$ represents the Jacobi-matrix of f with respect to x.

As with the feeding method (previous subsection), we have to consider the Lyapunov exponents of this system. We state that the following theorem:

Theorem 2 *The system (38) synchronizes if and only if its Lyapunov exponents are negative. These Lyapunov exponents are refered to as conditional Lyapunov exponents (CLEs).*

B.3 Final remarks

Note that the conditional Lyapunov exponents of a system x quantify the attraction of orbits of the coupled system y to the orbit of x. For instance, the system x may have positive Lyapunov exponents, implying chaotic dynamics, but it can still synchronize with a system y. The Lorenz system is an example of such a system [6,3].