

Estimation of synaptic conductance in the spiking regime for the McKean neuron model ¹

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Abstract

In this work, we aim at giving a first proof of concept to address the estimation of synaptic conductances when a neuron is spiking, a complex inverse non-linear problem which is an open challenge in neuroscience. Our approach is based on a simplified model of neuronal activity, namely a piecewise linear version of the FitzHugh-Nagumo model. This simplified model allows a precise knowledge of the non-linear f-I curve by using standard techniques of non-smooth dynamical systems. In the regular firing regime of the neuron model, we obtain an approximation of the period which, in addition, improves previous approximations given in the literature up-to-date. By knowing both this expression of the period and the current applied to the neuron, and then solving an inverse problem with a unique solution, we are able to estimate the steady synaptic conductance of the cell's oscillatory activity. Moreover, the method gives also good estimations when the synaptic conductance varies slowly in time.

Keywords: synaptic conductance, neuron mode, spiking neuron, piecewise linear system, McKean model, parameter estimation.

MSC2010 classification: Primary 37N25, 70K70; Secondary 34D15, 34C25, 34C26.

1 Introduction

Estimating the synaptic conductances impinging on a single neuron directly from its membrane potential is one of the open problems that needs to be solved in order to understand the flow of information in the brain. The ultimate goal is providing useful methods to deal with experimental data and give trustable estimations of excitatory and inhibitory currents arriving to a neuron. These input estimations constitute an important piece of information to understand the organization of activity in the populations of efferent neurons. In particular, they can shed light to the excitation versus inhibition balance along time in the subjacent network (see the Introduction of Berg and Ditlevsen (2013) and Vich and Guillamon (2015) for specific applications).

Broadly speaking, there are three main obstacles to overcome in order to provide effective solutions to this inverse problem. On one hand, one needs a mathematical model of the target neuron in which the synaptic conductances are well identified (generally, as parameters of the system). Aiming at giving methods as general as possible, the variety of neuron types does not advise to use very specific models, but rather minimal models that capture essential features of neuronal dynamics. This idea has been extensively used in the existing literature (see Borg-Graham et al (1998), Anderson et al (2000), Wehr and Zador (2003), Rudolph et al (2004), Pospischil et al (2009), Bédard et al (2011), Berg and Ditlevsen (2013), among others) assuming that data is following some underlying linear process. Normally, this assumption involves a complementary treatment of the noise present in the data, which is the second main obstacle. Some strategies consists of filtering the data before fitting them to the “minimal model” (see Anderson et al (2000), Borg-Graham et al (1998), among others), some using stochastic linear processes

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in order to obtain the estimations (see Rudolph et al (2004), Pospischil et al (2009), Paninski et al (2012), Berg and Ditlevsen (2013), among others). Other approaches using more sophisticated filtering techniques (see Lankarany et al (2013), Ditlevsen and Samson (2014), Closas (2014), among others). In all these stochastic approaches, linear regression methods and maximum likelihood estimators are in order at some point of the procedure. Despite of some excellent estimations obtained in particular circumstances, special in purely leaky subthreshold regimes, misestimations derived from the use of linear models have also been reported (see Borg-Graham et al (1998), Guillamon et al (2006), Vich and Guillamon (2015)). Therefore, a third challenge, this related to the type of minimal models to use, come into play. The problem is how to deal with the inverse estimation problem when the underlying (deterministic) model is no longer linear. A partial solution for subthreshold regimes with active (nonlinearly behaving) ionic currents has been given in Vich and Guillamon (2015), but no solution for spiking neurons have been yet proposed.

In this work, we provide a first proof of concept to perform estimations of synaptic conductances during spiking activity. We approach this problem by considering the neuronal firing rate, f , as a function of the input current, I ; i.e. the spike frequency f versus the input strength current I function, (known as f - I curve). We have chosen the McKean model, a simplified piecewise linear model of neuronal activity with regular firing, that can be derived from the FitzHugh-Nagumo model (see McKean (1970) and Coombes (2001)). The piecewise linearity of the vector field allows a very precise knowledge of the nonlinear f - I curve by means of standard techniques of non-smooth dynamical systems. In the standard McKean model, we put special emphasis on the synaptic current, $I_{syn}(v)$. We consider the piecewise linear differential system

$$\begin{cases} C\dot{v} = f(v) - w - w_0 + I_{total}, \\ \dot{w} = v - \gamma w - v_0, \end{cases} \quad (1)$$

where $I_{total} = I - I_{syn}(v)$, $I_{syn}(v) = g_{syn}(v - v_{syn})$ and $f(v)$ is the piecewise linear caricature of the cubic FitzHugh-Nagumo function given by

$$f(v) = \begin{cases} -v & v < a/2, \\ v - a & a/2 \leq v \leq (1+a)/2, \\ 1 - v & v > (1+a)/2. \end{cases}$$

Physiologically, the variables of the model are considered to be v , which stands for the membrane potential, and w which represents the recovery property of the neuron. The parameters a , w_0 , v_0 , and $\gamma > 0$ may be considered as conductance properties and combinations of membrane reversal potentials (see Coombes (2001)). The function $f(v)$ determines the outward membrane current at v . In the total input current I_{total} we distinguish two sources: an eventual injected current I , which will be taken constant along the paper, and the synaptic input $I_{syn}(v)$. In the the synaptic input term, v_{syn} symbolizes the reversal potential and $g_{syn} > 0$ is the synaptic conductance. Finally, C is related to the cell membrane capacitance, and is assumed to be small and bounded, that is $0 < C \ll 0.1$. In the numerical simulations, v_{syn} is considered to be the half point between $a/2$ and $(1+a)/2$ to mimic an excitatory synapse.

At a first instance, the synaptic conductance, g_{syn} , is considered to be constant, a fact that can be understood as the synaptic current $I_{syn}(v)$ being a representation of the mean field of the synaptic inputs. Moreover, since C is assumed to be small, the variables evolve with very different velocities and so system (1) can be considered a slow-fast dynamical system, where the variable v is the fast one whereas the variable w is the slow one.

As it has been reported in some previous studies, see Abbott (1990) and Tonnelier and Gerstner (2003), system (1) presents different neuronal behaviours depending on the total amount of constant current that the neuron is receiving. In particular, for $g_{syn} = 0$, authors show that there exist two boundary values I_1^0 and I_2^0 such that, if $I_{total} \leq I_1^0$, the system presents low activity and the membrane potential tends to a silent state, that is, variable v tends to an equilibrium state with low value. Moreover, when $I_1^0 < I_{total} < I_2^0$, the system exhibits a unique isolated periodic orbit, i.e. a limit cycle, and so the

neuron presents an oscillatory behaviour corresponding to a regular firing. Otherwise, if $I_{total} \geq I_2^0$, the neuron tends to a steady high activity, that is, the variable v tends to an equilibrium state with high value, corresponding to a nerve block.

In the present paper, we show that this scenario also persists for $I_{total} = I - I_{syn}(v) = I - g_{syn}(v - v_{syn})$ with $g_{syn} \geq 0$. Since we are interested in the estimation of conductance g_{syn} in spiking regimes, we will focus in the region of the parameter space where the model presents a limit cycle crossing the two switching manifolds $v = a/2$ and $v = (1+a)/2$. Several approximations of the period T of the limit cycle, exhibited by the McKean model (1) with $g_{syn} = 0$ have been recently studied. In Coombes (2008), the period T is computed numerically for different constant inputs I_{total} . In other works, such as Abbott (1990), Coombes (2001), and Tonnelier (2003), the approximation of T has been carried out by considering the singular limit ($C = 0$) of the limit cycle, which consists of segments of orbits from both subsystems, the slow and the fast one. The approximation is then obtained from the total amount of flight times on the slow manifold. We note that this value coincides with the constant term of the power series expansion in C of the period T . More recently, in Fernández-García et al (2015), the authors provide an approximate expression of the period T by taking advantage of the slow invariant manifolds for $0 < C \ll 1$. In this case, T is approximated by computing the flight time of the limit cycle in each lateral region, i.e. in $v < a/2$ and $v > (1+a)/2$, by reducing the flow to the slow manifold; and supposing that the flight time in the central band, i.e. in $a/2 < v < (1+a)/2$, is negligible.

In this paper, we compute an approximated expression, \hat{T} , of the period function, T , which provides two new contributions to the existing literature. The first one is that, instead of approximating the flight time in the lateral regions by reducing the flow to the slow manifold, we compute the exact value of this flight time. The second one is that we consider the flight time in the central region to be non-negligible. As we will show in Section 3.2, numerical evidences support the goodness of the approximated period function in the sense that the absolute error, $|T - \hat{T}|$, is $O(C^\alpha)$, with $\alpha \approx 0.88 < 1$.

This new approximation of the period function denoted by \hat{T} , depends on the parameters of the model, and, in particular, on the synaptic conductance g_{syn} and the applied current I , i.e. $\hat{T}(g_{syn}, I)$. As we prove in this article, the dependence of \hat{T} on the synaptic conductance, g_{syn} , is non-linear but seems to be monotonic for the range of input current values for which \hat{T} has sense; that is, for the input currents that drive the neuron to regularly spiking. Hence, as a consequence of the monotonicity, by knowing \hat{T} and the applied current I (i.e. knowing the $f - I$ curve), one would be able to compute g_{syn} by solving numerically a non-linear equation having a unique solution; and so, estimate the steady synaptic conductance of the neuron, which is the goal of this paper.

We would like to note that, even though some studies consider the synaptic conductances as a constant input, in real experiments synaptic conductances change along time thus causing non-regular spiking. Indeed, we have a non-autonomous system which may have a very complicated dynamics. If the changes in conductances are relatively slow, then we may assume to be “riding” on a periodic orbit with a constant conductance during a certain time window. This fact suggests that each inter-spike interval (ISI), which corresponds to the time between two consecutive spikes, can be a good approximation of T for a specific constant value \tilde{g}_{syn} provided that $g_{syn}(t)$ has a slow variation. Hence, for each ISI we estimate a different steady conductance and so, we obtain a time course estimation of \tilde{g}_{syn} , say $\hat{g}_{syn}(t)$, see Section 4.2.

Furthermore, when the rate of variation of $g_{syn}(t)$ is close to that of V , the estimation $\hat{g}_{syn}(t)$ can be improved by taking advantage of the splitting of \hat{T} into subperiods accounting for the flight times in the lateral and the central regions, see Section 4.3.

The above explained procedure and the results obtained in this article are distributed in the following way. In Section 2, we present the model and revise the main features of its qualitative dynamics, namely the existence and character of equilibrium points, and the conditions on the parameters that ensure the existence of a limit cycle. In Section 3, we present the expression \hat{T} that we obtain as an approximation of the period T , showing numerical evidences that \hat{T} is a monotonically decreasing function of the synaptic conductance g_{syn} . In Section 4, we deal with the estimation procedure, where we are able to infer, in

Section 4.2, a steady synaptic conductance from the cell's oscillatory activity; and, in Section 4.1, we extend the results to a more realistic case, where we present a proof of concept to estimate the full time course of the conductance. The conclusions are presented in Section 5.

2 Qualitative analysis of the model

Let us consider the modified McKean model given by system (1). This system is a non-symmetric continuous piecewise linear system that it is defined in three different regions, being $\{(v, w) \in \mathbb{R}^2; v < a/2\}$ the left region, $\{(v, w) \in \mathbb{R}^2; v > (1+a)/2\}$ the right region, and $\{(v, w) \in \mathbb{R}^2; a/2 \leq v \leq (1+a)/2\}$ the central (or middle) one. Along the paper we will use the symbols L , R and M to refer these regions, respectively.

Observe that system (1) is not globally differentiable but piecewise differentiable. Moreover, since parameter C is assumed to be small, system (1) is endowed with a slow-fast dynamics, being the membrane potential, v , the fast variable, meanwhile the auxiliary variable, w , is the slow one. Notice that the dynamics of system (1) is parameterized by the slow time.

The function $f(v)$ depends piecewise linearly on the parameter v , with different slopes according to the three different zones defined by the model. Therefore the v -nullcline is a piecewise linear function whereas the w -nullcline is a straight line, see Figure 1.

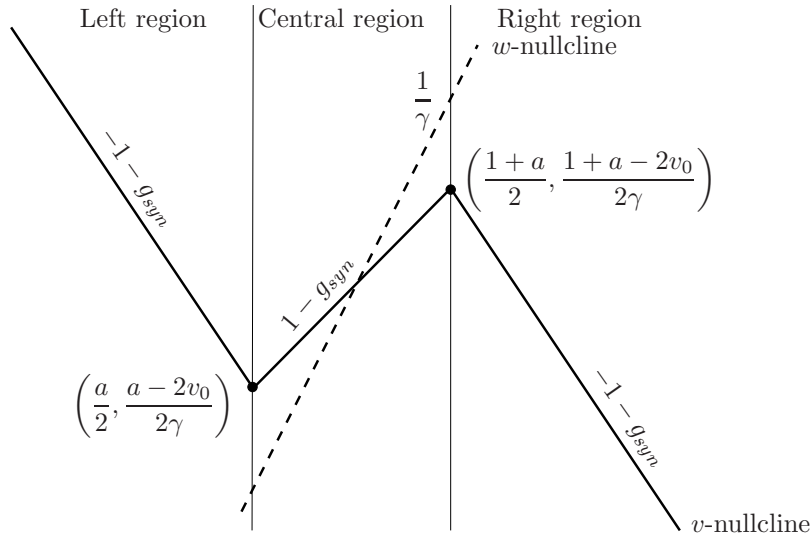


Figure 1: **Representation of the v - and w -nullclines.** The black dotted trace is the v -nullcline of system (1) and the black dashed trace is the w -nullcline. Filled circles describe the switching points, from one region to the other. The expression of the slopes of the nullclines as well as the coordinates of the switching points are also given on the figure.

On the other hand, the determinant and the trace of the model vary across the different regions. In the central region, the determinant is given by $d_M = (\gamma(g_{syn} - 1) + 1)/C$ whereas the trace is $t_M = -((g_{syn} - 1)/C + \gamma)$. In the lateral regions, the determinants and traces are $d_L = d_R = (\gamma(1 + g_{syn}) + 1)/C$ and $t_L = t_R = -((1 + g_{syn})/C + \gamma)$, respectively, where the subscript L stands for the left region and R for the right one. As a consequence, different equilibrium points can coexist in the model and they can also be located in different regions. These facts depend on the value of the external input I and the

synaptic conductance g_{syn} , as it is illustrated in Figure 2, where I_1 and I_2 are defined as

$$\begin{aligned} I_1 &= \left(\frac{a}{2} - v_{syn}\right) g_{syn} + \frac{(\gamma + 1)a - 2v_0 + 2\gamma w_0}{2\gamma}, \\ I_2 &= \left(\frac{a+1}{2} - v_{syn}\right) g_{syn} + \frac{(\gamma + 1)a - 2v_0 + 2\gamma w_0 - \gamma + 1}{2\gamma}. \end{aligned} \quad (2)$$

In fact, $I_j \equiv I_j(g_{syn}; v_{syn}, \gamma, a, v_0, w_0)$, $j = 1, 2$, but we will omit these dependencies to simplify the notation. Note that when $g_{syn} < 1 - 1/\gamma$, lines $I = I_1$ and $I = I_2$ are the subcritical saddle-node-like bifurcations, where two equilibrium points annihilate one each other after they collide.

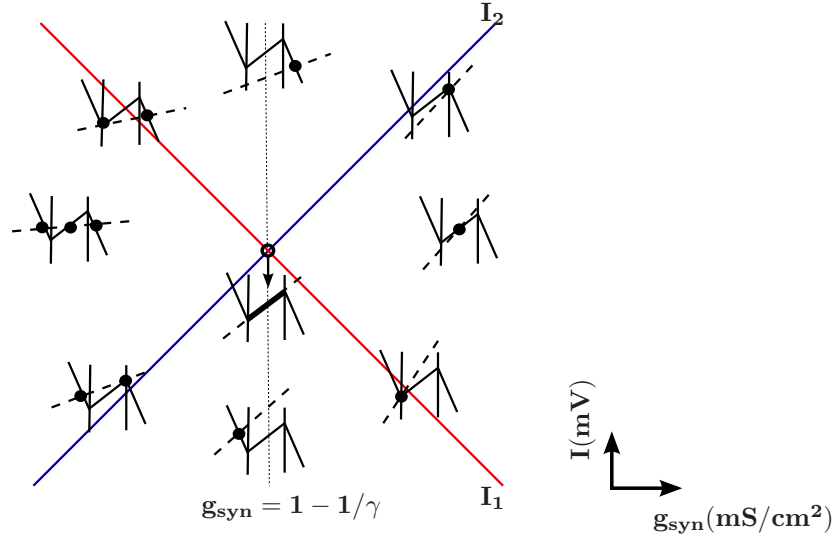


Figure 2: **Location of the equilibrium points.** According to expressions in (2), the solid blue line represents $I = I_2$ whereas the solid red line represents $I = I_1$. The dotted line is $g_{syn} = 1 - 1/\gamma$. Each picture on the figure represents the three different regions of system (1) (left, central and right) separated by vertical segments. The solid piecewise line corresponds to the v -nullcline whereas the dashed line stands for the w -nullcline. The dots on their intersection are the equilibrium points. The different locations and configurations of equilibria follow from Proposition 1 and from the arguments used in its proof.

In the next proposition, we show necessary and sufficient conditions to ensure existence and uniqueness of an equilibrium point of system (1) located in the central region or on either of the two switching manifolds. We point out that, from the arguments used in the proof of this proposition, the rest of possible locations and configurations of equilibrium points given in Figure 2 follows.

Proposition 1. *Let us consider system (1) satisfying that $g_{syn} > 1 - 1/\gamma$ and $I \in [I_1, I_2]$. Then, this system has a unique equilibrium point and it is located*

- a) *in the interior of the central region, if and only if $I_1 < I < I_2$;*
- b) *on the switching manifold $v = a/2$, if and only if $I = I_1$;*
- c) *on the switching manifold $v = (1 + a)/2$, if and only if $I = I_2$.*

Proof. The equilibrium points of system (1) are given by the solutions of

$$-f(v) + \left(g_{syn} + \frac{1}{\gamma}\right)v = \frac{v_0}{\gamma} - w_0 + g_{syn}v_{syn} + I \quad \text{and} \quad w = \frac{v - v_0}{\gamma} \quad (3)$$

where $f(v)$ takes its expression according to the corresponding region. Therefore, we proceed by considering each of the regions separately.

Let us first consider the left region. Since $f(v) = -v$, $g_{syn} \geq 0$ and $\gamma > 0$, the unique solution of system (3) is given by the point $\mathbf{p}_L = (v_L, w_L)$, where

$$v_L = \frac{\gamma(I - w_0 + g_{syn}v_{sys}) + v_0}{1 + \gamma(1 + g_{syn})} \quad \text{and} \quad w_L = \frac{I - w_0 + g_{syn}(v_{syn} - v_0) - v_0}{1 + \gamma(1 + g_{syn})}.$$

Therefore, by imposing that $v_L < a/2$, it follows that \mathbf{p}_L is an equilibrium point in this region if and only if $I < I_1$

In the central region, where $f(v) = v - a$, the unique solution of system (3) is the point $\mathbf{p}_M = (v_M, w_M)$ given by

$$v_M = \frac{\gamma(I - w_0 + g_{syn}v_{syn} - a) + v_0}{1 - \gamma(1 - g_{syn})} \quad \text{and} \quad w_M = \frac{I - w_0 + g_{syn}(v_{syn} - v_0) + v_0 - a}{1 - \gamma(1 - g_{syn})}.$$

Hence, by forcing v_M to lie in the interval $[a/2, (a+1)/2]$, \mathbf{p}_M is an equilibrium point if and only if either of the pair of inequalities

$$g_{syn} > 1 - \frac{1}{\gamma} \quad \text{and} \quad I_1 \leq I \leq I_2; \quad \text{or} \quad g_{syn} < 1 - \frac{1}{\gamma} \quad \text{and} \quad I_2 \leq I \leq I_1,$$

are held. However, notice that the first component of the equilibrium point is exactly $v = a/2$ when $I = I_1$, and so the equilibrium point is located in the left switching manifold. Similarly, when $I = I_2$, the equilibrium point is located in the right switching manifold. Otherwise, i.e. when $I_1 < I < I_2$, the equilibrium point stays inside the central region.

We remark that in the case where $g_{syn} = 1 - 1/\gamma$, if $I = I_1 = I_2$ all points along the central part of the v -nullcline are equilibrium points. This fact is caused by the slopes of v and w nullclines being the same.

Finally, in the right region, i.e. when $f(v) = 1 - v$; the unique solution of system (3) is the point $\mathbf{p}_R = (v_R, w_R)$ given by

$$v_R = \frac{\gamma(I - w_0 + g_{syn}v_{syn} + 1) + v_0}{1 + \gamma(1 + g_{syn})} \quad \text{and} \quad w_R = \frac{I - w_0 + g_{syn}(v_{syn} - v_0) - v_0 + 1}{1 + \gamma(1 + g_{syn})}.$$

Since $g_{syn} \geq 0$ and $\gamma > 0$, by imposing that $v_R > (1+a)/2$, an equilibrium point in this region exists if and only if $I > I_2$.

Hence, we only have an equilibrium point located in the central region when both conditions $g_{syn} > 1 - 1/\gamma$ and $I_1 \leq I \leq I_2$ hold, proving the proposition. \square

Remark 1. *By Proposition 1, when $g_{syn} > 1 - 1/\gamma$ and $I_1 < I < I_2$ system (1) has only one equilibrium point which lies in the interior of the central region. Let us call such point as $\mathbf{p}_M = (p_{v,M}, p_{w,M})$. When each linear system which is part of the vector field is considered to be defined on the full plane, then two more zeros appear: one from the system described in the left zone, $\mathbf{p}_L = (p_{v,L}, p_{w,L})$, and another from the system in the right zone, $\mathbf{p}_R = (p_{v,R}, p_{w,R})$. Under these assumptions, these two points are located in the central region and, even thinking that they have influence on the global dynamics, they are not equilibrium points of system (1). These points are called virtual equilibrium points. Finally, note that when $I = I_1$ or $I = I_2$, \mathbf{p}_M coincides with \mathbf{p}_L or \mathbf{p}_R , respectively.*

Even though the full model is not linear, its behaviour is locally governed by the eigenvalues associated with each one of the linear subsystems. Note that these eigenvalues vary across the three different zones (left, central and right). In each region, there exist two different eigenvalues: one of $O(C^0)$, which is

responsible for the slow dynamics, and denoted by the subscript s ; and another one of $O(C^{-1})$, which is responsible for the fast dynamics, and denoted by the subscript q . These eigenvalues are given by

$$\begin{aligned}\lambda_{s,L} = \lambda_{s,R} &= -\frac{1}{2C} \left(1 + g_{syn} + C\gamma - \sqrt{(1 + g_{syn} - C\gamma)^2 - 4C} \right), \\ \lambda_{q,L} = \lambda_{q,R} &= -\frac{1}{2C} \left(1 + g_{syn} + C\gamma + \sqrt{(1 + g_{syn} - C\gamma)^2 - 4C} \right), \\ \lambda_{s,M} &= \frac{1}{2C} \left(1 - g_{syn} - C\gamma - \sqrt{(g_{syn} - 1 - C\gamma)^2 - 4C} \right), \\ \lambda_{q,M} &= \frac{1}{2C} \left(1 - g_{syn} - C\gamma + \sqrt{(g_{syn} - 1 - C\gamma)^2 - 4C} \right).\end{aligned}$$

They may correspond to either focus or node equilibrium points, depending on the values of the parameters g_{syn} , γ and C . However, for sufficiently small values of C , one can guarantee that all equilibrium points are nodes since all the discriminants are positive when $C = 0$. In fact, all the equilibrium points are nodes if and only if $C \leq C^*$ where

$$C^* = \min \left\{ \frac{2 + \gamma(g_{syn} + 1) - 2\sqrt{1 + \gamma(g_{syn} + 1)}}{\gamma^2}, \frac{2 + \gamma(g_{syn} - 1) - 2\sqrt{1 + \gamma(g_{syn} - 1)}}{\gamma^2} \right\}.$$

In this case, we call $\mathbf{v}_{i,j} = (\lambda_{i,j} + \gamma, 1)$ to the eigenvector associated with the eigenvalue $\lambda_{i,j}$, where $i \in \{s, q\}$ and $j \in \{L, R, M\}$. Notice that the slow motion takes place along manifolds that are defined by the eigenvector associated with the slow eigenvalue. Since the eigenvector depends on the region, we obtain three different slow manifolds. We refer each slow manifold as S_j where $j \in \{L, R, M\}$, which are given by

$$\begin{aligned}S_L &= \left\{ (v, w); v < \frac{a}{2} \quad \text{and} \quad w = p_{w,L} + \frac{v - p_{v,L}}{\lambda_{s,L} + \gamma} \right\}, \\ S_R &= \left\{ (v, w); v > \frac{1+a}{2} \quad \text{and} \quad w = p_{w,R} + \frac{v - p_{v,R}}{\lambda_{s,R} + \gamma} \right\}, \\ S_M &= \left\{ (v, w); \frac{a}{2} \leq v \leq \frac{1+a}{2} \quad \text{and} \quad w = p_{w,M} + \frac{v - p_{v,M}}{\lambda_{s,M} + \gamma} \right\},\end{aligned}\tag{4}$$

where $p_{v,j}$ and $p_{w,j}$ are the first and second components, respectively, of \mathbf{p}_j (see Remark 1).

Since the piecewise differential system (1) is locally linear, it can be analytically solved at each region separately, being the local solutions

$$\begin{pmatrix} v(t) \\ w(t) \end{pmatrix} = c_{1,i} e^{\lambda_{s,i} t} \mathbf{v}_{s,i} + c_{2,i} e^{\lambda_{q,i} t} \mathbf{v}_{q,i} + \mathbf{p}_i,\tag{5}$$

where i represents either L , M or R depending on the region being left, central or right, respectively; and

$$c_{1,i} = \frac{v(0) - p_{v,i} - (\lambda_{q,i} + \gamma)(w(0) - p_{w,i})}{\lambda_{s,i} - \lambda_{q,i}}, \quad c_{2,i} = w(0) - c_{1,i} - p_{w,i}.\tag{6}$$

Notice that equation (5) only represents a local expression of the solution of system (1). As long as the orbit, given by a fixed initial condition, remains in one region, this orbit is given by the expression of the solution of the system obtained in this particular region; however, if the orbit crosses to another region, the orbit is given by the corresponding expression obtained in this new region, which depends on the different eigenvalues and initial conditions. Since the vector field defined by system (1) is globally non-linear, system (1) may exhibit limit cycles (see Llibre et al (2013)). In next proposition we give a sufficient condition so that system (1) can have a limit cycle.

Proposition 2. *Consider the following assumptions*

$$g_{syn} > 1 - 1/\gamma, |g_{syn} + C\gamma| < 1 \text{ and } 0 < C \leq C^*.$$

Then,

- a) if $I_1 < I < I_2$, system (1) exhibits a unique limit cycle, this orbit crosses the two switching manifolds $v = a/2$ and $v = (a + 1)/2$, and it is stable.
- b) if $I = I_1$ or $I = I_2$, system (1) exhibits a homoclinic orbit to the equilibrium point \mathbf{p}_M , this orbit is stable from the exterior and delimits an open region which is foliated by homoclinic orbits to \mathbf{p}_M .

Proof. Let us consider system (1) written in its Liénard form. To do that, we make the two different changes of variables. First, we switch to (v, u) through $w = C(u + \gamma v)$ and, second, we introduce (x, y) where $x = 4v - 2a - 1$ and $Cy = 4Cu + C\gamma(2a + 1) - 4I + 2a - 1$ (see Section 2 in Llibre et al (2013)). Then, moving the origin to the point $(0, ((2a + 1 - \gamma v_{syn})g_{syn} + 4w_0)/C)$, the Liénard form of system (1) is given by

$$\begin{cases} \dot{x} = F(x) - y \\ \dot{y} = G(x) - \delta \end{cases}$$

where $\delta = -\frac{1}{C}(2a(\gamma + \gamma g_{syn} + 1) - \gamma + \gamma g_{syn} + 1 - 4v_0 + 4\gamma(w_0 - I - g_{syn}v_{syn}))$,

$$F(x) = \begin{cases} t_L(x + 1) - t_M & x < -1, \\ t_M x & -1 \leq x \leq 1, \\ t_R(x - 1) + t_M & x > 1, \end{cases} \text{ and } G(x) = \begin{cases} d_L(x + 1) - d_M & x < -1, \\ d_M x & -1 \leq x \leq 1, \\ d_R(x - 1) + d_M & x > 1. \end{cases}$$

By Proposition 1, since $g_{syn} > 1 - 1/\gamma$ and $I_1 < I < I_2$, only one equilibrium point exists and it is located in the interior of the central region. Moreover, since $g_{syn} > 1 - 1/\gamma$ and $|g_{syn} + C\gamma| < 1$, the parameters of the functions $F(x)$ and $G(x)$ satisfy that $d_M > 0$, $-d_M < \delta < d_M$, $d_L, d_R \geq 0$, $t_L, t_R < 0$, and $t_M > 0$. Hence, the existence and uniqueness of a limit cycle (isolated periodic orbit) surrounding the equilibrium point is guaranteed by Theorem 1 in Llibre et al (2013).

Finally, since $0 < C \leq C^*$ and $t_M > 0$, the equilibrium point is a repelling node. Consequently, the invariant lines defined by the eigenvectors force the limit cycle to cross the three regions, which ends the proof of the statement (a).

In order to prove the statement (b), let us consider the case where $I = I_1$. Then, let $\mathbf{q}_L = (v_L, w_L)$ and $\mathbf{q}_R = (v_R, w_R)$ be the intersection points of the left and right slow manifolds (see equation (4)) with the vertical lines $v = a/2$ and $v = (1 + a)/2$, respectively; and let $\mathbf{q}_R^{**} = (v_R^{**}, w_R^{**})$ be the intersection point of the w -nullcline with the vertical line $v = (1 + a)/2$, see Figure 3.

In this case, the equilibrium point, \mathbf{p}_M (that exists and it is unique from Proposition 1), coincides with the virtual equilibrium point of the left region, \mathbf{p}_L . Since it is contained in the intersection of S_L and S_M , which are respectively stable and unstable manifolds, the equilibrium point is a saddle node and $\mathbf{q}_L = \mathbf{p}_L$. Moreover, taking into account that $I = I_1$,

$$\mathbf{q}_L = \left(\frac{a}{2}, \frac{a - 2v_0}{2\gamma} \right), \quad \mathbf{q}_R = \left(\frac{1 + a}{2}, p_{w,R} + \frac{1}{\lambda_{s,R} + \gamma} \left(\frac{1 + a}{2} - p_{v,R} \right) \right), \text{ and}$$

$$\mathbf{q}_R^{**} = \left(\frac{1 + a}{2}, \frac{1 + a - 2v_0}{2\gamma} \right).$$

Consider now the closed region delimited by the union of the line segments L_i , $i = 1 \dots 5$, defined as follows:

- i) L_1 denotes the line segment bounded by \mathbf{q}_L and the intersection point of S_R with the line $w = w_L$, which we denote by $\mathbf{q}_{1,R}^*$;

- ii) L_2 denotes the segment of S_R that is bounded by $\mathbf{q}_{1,R}^*$ and \mathbf{q}_R ;
- iii) L_3 denotes the vertical line segment bounded by \mathbf{q}_R and \mathbf{q}_R^{**} ;
- iv) L_4 denotes the line segment bounded by \mathbf{q}_R^{**} and the intersection point of S_L with the line $w = w_R^{**}$, which we denote by $\mathbf{q}_{1,L}^*$; and, finally,
- v) L_5 denotes the segment of S_L that is bounded by $\mathbf{q}_{1,L}^*$ and \mathbf{q}_L .

Looking at the direction of the flow, one can see that the w -component of the flow in L_1 is given by $\dot{w} = v - a/2$, which is positive in the line segment under consideration, and so the flow positively crosses L_1 . Similarly, the w -component of the flow on L_4 is given by $\dot{w} = v - (1 + a)/2$, which is negative in the line segment under consideration, and so the flow positively crosses L_4 . On another hand, segments L_2 and L_5 are contained in the slow manifolds S_R and S_L , respectively; this fact implies that both line segments are invariant under the flow. Finally, notice that the flow positively crosses the line $v = (1 + a)/2$ if and only if $\dot{v} > 0$, and so

$$w|_{v=(1+a)/2} > 1 - \frac{1+a}{2} - w_0 + I - g_{syn} \left(\frac{1+a}{2} - v_{syn} \right).$$

Straightforward calculations show that, for a sufficiently small C , both w_R and w_R^{**} are greater than $w|_{v=(1+a)/2}$, and so the flow crosses the line segment L_3 positively, showing that the closed region obtained by these five segments is a compact set invariant under the flow of system (1); see Figure 3 (left) for a representation of both the invariant region and the direction of the flow. By Poincaré-Bendixson theorem (see for instance Hartman (1982, Th. 4.1)), if there exists a limit cycle in the entering compact set, then there must exist an equilibrium point in its interior. However, the unique equilibrium point lies on the boundary of the closed region. Therefore, there cannot be limit cycles in the interior of the compact set. Consequently, again by Poincaré-Bendixson theorem, the unique α - and ω -limit sets are on the boundary of the closed region. Hence, there exists a continuum of homoclinic orbits from the equilibrium point to itself, with the biggest homoclinic orbit stable.

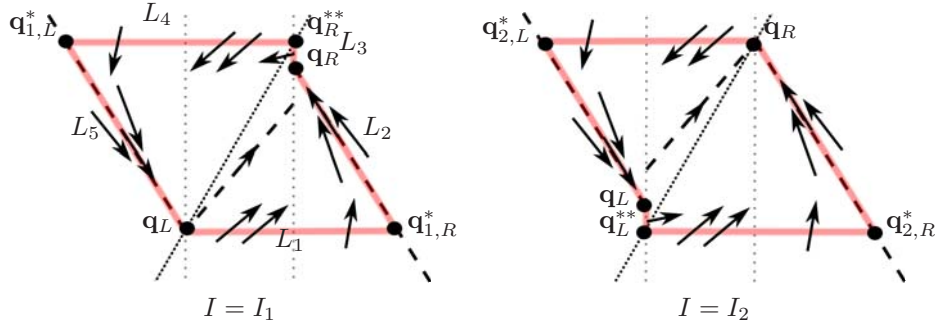


Figure 3: **Invariant region and direction of the flow.** Representation of the invariant regions and the direction of the flow when $I = I_1$ (left) and $I = I_2$ (right). The dashed black lines represent the three slow manifolds, whereas the dotted black line is the w -nullcline. Vertical dotted grey lines represent the two switching manifolds, $v = a/2$ (left line in each subplot) and $v = (1 + a)/2$ (right line in each subplot). The solid red line represents the boundary of each invariant region and the arrows give us information about the direction of the flow. See Proposition 2(b) for more details.

□

Similar arguments can be applied to prove the result when $I = I_2$, where in this case $\mathbf{q}_R = \mathbf{p}_R$. In Figure 3 (right), we depict a representation of the invariant region and the directions of the flow in this case.

Remark 2. *Note that, under the suitable conditions*

$$g_{syn} > 1 - 1/\gamma, \quad |g_{syn} + C\gamma| < 1, \quad I_1 < I < I_2, \quad \text{and} \quad 0 < C \leq C^*, \quad (\text{H})$$

the regular firing behaviour persist for $g_{syn} \geq 0$.

Figure 4 represents the different phase portraits obtained when we change the value of the capacitance (when $C = 0$ and $0 < C \leq C^*$) and also the value of the applied current (when $I = I_1$, $I_1 < I < I_2$, and $I = I_2$). Notice that these configurations are obtained from Proposition 2.

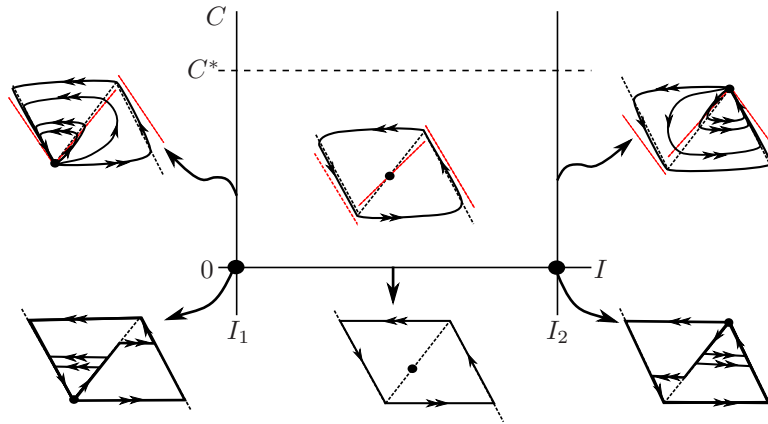


Figure 4: **Bifurcation diagram.** Representation of the bifurcation diagram with the phase portraits of the limit cycles for different values of C and I under conditions $g_{syn} > 1 - 1/\gamma$ and $|g_{syn} + C\gamma| < 1$. The phase portraits are obtained with the following parameter values: $a = 0.25$, $v_0 = 0$, $\gamma = 0.5$, $g_{syn} = 0.2$, $w_0 = 0$, and $v_{syn} = 1/4 + a/2$. The red dotted lines stand for the slow manifolds, whereas the dashed black lines stand for the v -nullcline.

3 Quantitative analysis of the limit cycle period

As we have mentioned in the Introduction, related works such as Tonnelier (2003) and Fernández-García et al (2015), among others, make approximations of the period T of the limit cycle in system (1), where g_{syn} is considered to be identically zero. In this section we present a more accurate approximation of T , which also takes into account the case when g_{syn} is not identically zero. This improvement is, basically, obtained by considering the flight time in the central region and using a better approximation of the flight time in the lateral regions.

From now on, let us assume that the hypothesis (H) is satisfied. Hence, by Proposition 2(a), the considered model given by system (1) has a unique limit cycle that intercepts the three different regions; and so, the period of the limit cycle can be split into four parts: the first one corresponds to the time that the orbit is contained in the left region; the second part is the time taken by the orbit to cross the central zone from left to right following a counterclockwise movement; the third is the sub-period that the orbit lies in the right region; and, finally, the last part corresponds to the time taken by the orbit to

cross the central part from right to left (see Figure 5). The total period, T , is then the sum of these four sub-periods.

In the singular limit, that is when $C = 0$, the limit cycle does not longer exist. In fact, when C tends to zero, the limit cycle orbit tends to a limit set composed by two line segments on the critical manifold (slow subsystem) plus two more line segments on the stratified flow (fast subsystem), see Figure 4. We refer the reader to Prohens et al (2016) for an overview on piecewise slow-fast dynamics terminology.

Comparing the flight time on the different segments, the one corresponding to the two line segments of the stratified flow can be considered zero with respect to the flight time on the two line segments of the critical manifold. Hence, we consider the flight time on the two line segments of the critical manifold, T_0 , as the limit of T when C tends to zero.

In the following subsections, we first provide an analytical expression approximating the period and then we computationally check the goodness of such approximation.

3.1 An approximation of the period of the limit cycle

In the following proposition we give an approximation, \hat{T} , of the total period. We also show that the singular limit of this expression results to be T_0 .

Proposition 3. *Given system (1) under hypothesis (H),*

- a) *If $C = 0$, the flight time on the two line segments of the critical manifold is $T_0 = T_{0,L} + T_{0,R}$ such that*

$$T_{0,L} = B_0 \ln \left(\frac{\gamma(I - I_1)}{\gamma(I - I_1) + K_0} \right), \quad \text{and} \quad T_{0,R} = B_0 \ln \left(\frac{\gamma(I - I_2)}{\gamma(I - I_2) - K_0} \right) \quad (7)$$

$$B_0 = -\frac{1 + g_{syn}}{(1 + \gamma + \gamma g_{syn})}; \quad K_0 = \frac{(1 - g_{syn})(1 + \gamma + \gamma g_{syn})}{2(1 + g_{syn})}$$

- b) *For a sufficiently small $C > 0$, the period of the unique limit cycle orbit of the system can be analytically approximated by $\hat{T} = T_L + T_{Mu} + T_{Md} + T_R$, where*

$$T_L = \frac{1}{\lambda_{s,L}} \ln \left(\left| \frac{\gamma(I - I_1)}{\gamma(I - I_1) - K_l} \right| \right), \quad T_{Md} = \frac{1}{\lambda_{q,M}} \ln \left(\left| \frac{\gamma(I - I_2) + K_m}{\gamma(I - I_2) + K_{m,d}} \right| \right), \quad (8)$$

$$T_R = \frac{1}{\lambda_{s,L}} \ln \left(\left| \frac{\gamma(I - I_2)}{\gamma(I - I_2) + K_l} \right| \right), \quad T_{Mu} = \frac{1}{\lambda_{q,M}} \ln \left(\left| \frac{\gamma(I - I_1) + K_m}{\gamma(I - I_1) + K_{m,u}} \right| \right),$$

where

$$K_l = \frac{\gamma + \lambda_{q,L}}{2(\lambda_{q,L} - \lambda_{s,L})} (g_{syn}\gamma + \gamma + 2\lambda_{s,L} + 1),$$

$$K_m = \frac{(\gamma + \lambda_{s,M})(g_{syn}\gamma - \gamma + 1) ((g_{syn}\gamma + 1)(\lambda_{s,L} - \lambda_{q,M}) - \gamma(\lambda_{s,L} + \lambda_{q,M}) - 2\lambda_{s,L}\lambda_{q,M})}{2(\gamma + \lambda_{q,M}) ((g_{syn}\gamma + 1)(\lambda_{s,L} - \lambda_{s,M}) - \gamma(\lambda_{s,L} + \lambda_{s,M}) - 2\lambda_{s,L}\lambda_{s,M})},$$

$$K_{m,d} = \frac{(\lambda_{q,M} - \lambda_{s,M})(\gamma + \lambda_{q,M})(g_{syn}\gamma - \gamma + 1)(g_{syn}\gamma + \gamma + 2\lambda_{s,L} + 1)}{2(\gamma + \lambda_{q,M}) ((g_{syn}\gamma + 1)(\lambda_{s,L} - \lambda_{s,M}) - \gamma(\lambda_{s,L} + \lambda_{s,M}) - 2\lambda_{s,L}\lambda_{s,M})},$$

$$K_{m,u} = \frac{(\gamma + \lambda_{q,M})(g_{syn}\gamma - \gamma + 1) ((g_{syn}\gamma + 1)(\lambda_{s,L} - \lambda_{s,M}) - \gamma(\lambda_{s,L} + \lambda_{s,M}) - 2\lambda_{s,L}\lambda_{s,M})}{2(\gamma + \lambda_{q,M}) ((g_{syn}\gamma + 1)(\lambda_{s,L} - \lambda_{s,M}) - \gamma(\lambda_{s,L} + \lambda_{s,M}) - 2\lambda_{s,L}\lambda_{s,M})}.$$

Proof. Let us consider first the singular case when $C = 0$. In this case, since the left term of the first equation of system (1) vanishes, v can be isolated and replaced in the second equation of system (1) obtaining the following non-autonomous linear ordinary differential equations

$$\begin{aligned} \dot{w} &= -(1 + \gamma)w - w_0 - v_0 + I - I_{syn} & \text{if } v < a/2; \\ \dot{w} &= -(1 + \gamma)w - w_0 - v_0 + I - I_{syn} + 1 & \text{if } v > (1 + a)/2. \end{aligned} \quad (9)$$

From this system, the flight time on the two line segments of the critical manifold can be analytically obtained by integrating the \dot{w} equation at each lateral region separately. From the first differential equation in (9), which corresponds to the left region, integrating from $t = 0$ to $t = T_{0,L}$ we calculate the left flight time $T_{0,L}$; and, from the second differential equation, which corresponds to the right region, integrating from $t = 0$ to $t = T_{0,R}$, we calculate the right flight time $T_{0,R}$. Then, we obtain the expressions (7), which proves statement (a).

Consider now the perturbed case, that is when $C > 0$ and small enough. In this situation, it is well-known that the limit cycle evolves exponentially close to the lateral slow manifolds when they intersect the switching manifolds, see Fernández-García et al (2016). The intersection point with the left (resp. right) switching manifold is called \mathbf{q}_L (resp. \mathbf{q}_R), see Figure 5. Therefore, different techniques from the ones used when $C = 0$ are required to find an approximated period.

Since the period can be split into four parts, we can approximate them separately. Let us first approximate the central sub-periods, T_{Md} and T_{Mu} , defined as the bottom and upper sub-periods, respectively. Let $\mathbf{q}_{M,L}$ and $\mathbf{q}_{M,R}$ be the intersection points of the central slow manifold with $v = a/2$ and $v = (1+a)/2$, respectively (see Figure 5 for a representation of these points).

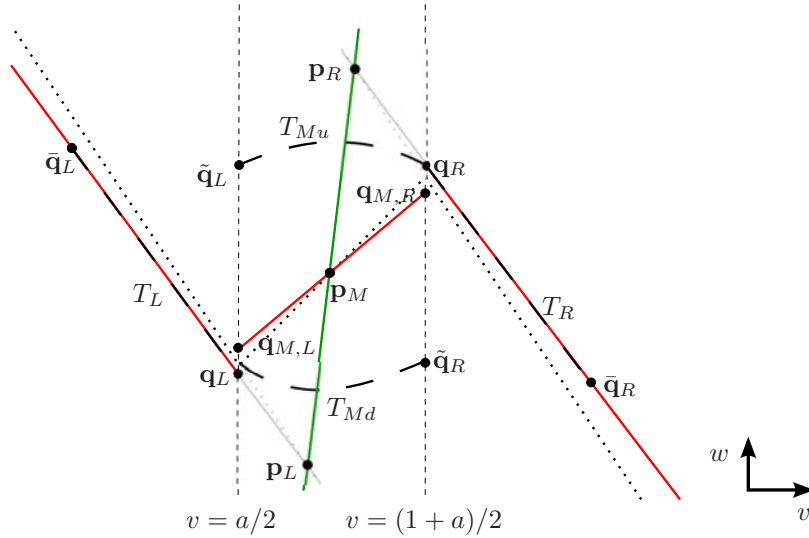


Figure 5: **Key points when $C > 0$.** Representation of all the elements needed to find the expression of the period. The vertical dashed black lines represent the boundaries of the different regions and the rest of dashed black lines illustrate T_L , T_{Md} , T_R and T_{Mu} . The dotted lines represent the critical manifold, whereas the red lines represent the three slow manifolds. These manifolds have been artificially prolonged in grey dotted lines and grey solid lines, respectively, for a better visualization of the virtual singular points. Green line stands for the w -nullcline. See the proof of Proposition 3 for more details.

Since the distance between the slow and critical manifolds of system (1) is of $O(C)$, see Prohens et al (2016), the distance between \mathbf{q}_L and $\mathbf{q}_{M,L}$ is also of $O(C)$. Moreover, the distance between \mathbf{q}_R and $\mathbf{q}_{M,R}$ is also of $O(C)$. In fact, notice that \mathbf{q}_L (resp. \mathbf{q}_R) tends to $\mathbf{q}_{M,L}$ (resp. $\mathbf{q}_{M,R}$) when C tends to zero. The limit cycle follows the left slow manifold very close to it and crosses from the left region to the central one at some point between \mathbf{q}_L and $\mathbf{q}_{M,L}$, exponentially close to \mathbf{q}_L . Similarly, the orbit moves very close to the right slow manifold and crosses from the right region to the central one at some point between \mathbf{q}_R and $\mathbf{q}_{M,R}$, also exponentially close to \mathbf{q}_L (see Figure 4). Hence, since C is close to 0, one can assume that the integral curve through \mathbf{q}_L , which is contained in the central region, will remain in a neighbourhood of the limit cycle, and similarly for the integral curve through \mathbf{q}_R . Therefore, we consider \mathbf{q}_L and \mathbf{q}_R as an approximation of two points where the limit cycle passes through.

Then, consider the central solution of the system, which is given in equation (5) when $i = M$, with \mathbf{q}_L and \mathbf{q}_R as initial conditions. Since the fast eigenvalue $\lambda_{q,M}$ is $O(C^{-1})$ whereas the slow eigenvalue $\lambda_{s,M}$ is $O(C^0)$ and C is sufficiently small, one can suppose that $\lambda_{s,M} = 0$ and, consequently, find an expression of the sub-periods T_{Md} and T_{Mu} . Indeed, under the previous assumptions on the initial conditions, the sub-period T_{Md} corresponds to the piece of orbit that begins at \mathbf{q}_L and ends on the boundary $v = (1+a)/2$ at a point that we call $\tilde{\mathbf{q}}_R$. By imposing that $v(t) = (1+a)/2$ and $\lambda_{s,i} = 0$ in the first component of equation (5) when $i = M$, the sub-period T_{Md} is the result of isolating the time t . That is,

$$T_{Md} = \frac{1}{\lambda_{q,M}} \ln \left(\left| \frac{\gamma(I - I_2) + K_m}{\gamma(I - I_2) + K_{m,d}} \right| \right),$$

where K_m and $K_{m,d}$ are given in the statement of this proposition.

Similarly, the sub-period T_{Mu} corresponds to the piece of orbit that begins at \mathbf{q}_R and ends on the boundary $v = a/2$ at a point that we call $\tilde{\mathbf{q}}_L$. Therefore, following the same procedure as for T_{Md} , we obtain that

$$T_{Mu} = \frac{1}{\lambda_{q,M}} \ln \left(\left| \frac{\gamma(I - I_1) + K_m}{\gamma(I - I_1) + K_{m,u}} \right| \right),$$

where $K_{m,u}$ is described in the statement of this proposition.

Notice that both points $\tilde{\mathbf{q}}_R$ and $\tilde{\mathbf{q}}_L$ can be analytically computed by using the second coordinate of equation (5), since T_{Md} and T_{Mu} are known, and the component v of $\tilde{\mathbf{q}}_R$ and $\tilde{\mathbf{q}}_L$ is $v = (1+a)/2$ and $v = a/2$, respectively. Then, the approximated period on the lateral regions will be the necessary time to travel from $\tilde{\mathbf{q}}_L$ to \mathbf{q}_L for the left sub-period, T_L , and the necessary time to travel from $\tilde{\mathbf{q}}_R$ to \mathbf{q}_R for the right sub-period, T_R .

Let us consider the coordinate system centered at the virtual equilibrium point \mathbf{p}_L and generated by the left eigenvectors $\mathbf{v}_{s,L}$ and $\mathbf{v}_{q,L}$. In this coordinate system $\tilde{\mathbf{q}}_L = \mathbf{p}_L + \bar{c}_1 \mathbf{v}_{s,L} + \bar{c}_2 \mathbf{v}_{q,L}$ and $\mathbf{q}_L = \mathbf{p}_L + c_1 \mathbf{v}_{s,L}$. Let $\bar{\mathbf{q}}_L = \mathbf{p}_L + \bar{c}_1 \mathbf{v}_{s,L}$ be the projection of $\tilde{\mathbf{q}}_L$ on the slow manifold along the direction given by the fast eigenvector $\mathbf{v}_{q,L}$.

The time T_L is computed as the time spent by the limit cycle to go from $\bar{\mathbf{q}}_L$ to \mathbf{q}_L . See Figure 5 for a representation. Then, by isolating t in expression

$$e^{t\lambda_{s,L}} \bar{c}_1 \|\mathbf{v}_{s,L}\| = c_1 \|\mathbf{v}_{s,L}\|,$$

we obtain

$$T_L = \frac{1}{\lambda_{s,L}} \ln \frac{c_1}{\bar{c}_1}.$$

The expressions of c_1 and \bar{c}_1 can be easily obtained from expression (6).

The expression of T_R can be, similarly computed, by considering the expression of the points \mathbf{q}_R and $\tilde{\mathbf{q}}_R$ in the coordinate system centered at the virtual equilibrium point \mathbf{p}_R , and generated by the right eigenvectors $\mathbf{v}_{s,R}$ and $\mathbf{v}_{q,R}$.

Therefore, an expression approximating the period of the limit cycle in system (1) is $\hat{T} = T_L + T_{Md} + T_R + T_{Mu}$, thus proving statement (b). \square

Remark 3. Note that, since $\bar{\mathbf{q}}_L$ is the projection of $\tilde{\mathbf{q}}_L$ on the slow manifold along the direction given by the fast eigenvector $\mathbf{v}_{q,L}$ and system (1) is linear in the left region, the sub-period T_L is the flight time between $\bar{\mathbf{q}}_L$ and \mathbf{q}_L . Similarly, the sub-period T_R is the flight time between $\tilde{\mathbf{q}}_R$ and \mathbf{q}_R .

Remark 4. When C tends to 0, $T_L \rightarrow T_{0,L}$, $T_{Md} \rightarrow 0$, $T_R \rightarrow T_{0,R}$, and $T_{Mu} \rightarrow 0$. Therefore, $\hat{T} \rightarrow T_0$. Moreover, both for $C = 0$ and $C > 0$, the left sub-period tends to infinity when I tends to I_1 . This limit agrees with the fact that, when $I = I_1$, the equilibrium point lies on the intersection of the central slow manifold with the vertical line $v = a/2$; therefore, the orbit reaches the equilibrium point and spends infinite time to escape. Similar arguments explain why the right sub-period tends to infinity when I tends to I_2 .

Remark 5. Notice that, K_l , K_m , $K_{m,d}$, and $K_{m,u}$ in the expression \hat{T} of Proposition 3, have a non-linear dependence on g_{syn} . Moreover, fixing all parameters in the model but keeping the synaptic conductance, g_{syn} , the applied current, I , and the parameter related to the capacitance of the neuron, C , as variable, then the approximated period can be written as the function

$$\hat{T}(C, I, g_{syn}) = T_L(C, I, g_{syn}) + T_{Md}(C, I, g_{syn}) + T_R(C, I, g_{syn}) + T_{Mu}(C, I, g_{syn}).$$

3.2 Goodness of the approximated period function

As we have mentioned in the proof of Proposition 3, in order to approximate the period, we have assumed that the points \mathbf{q}_L and \mathbf{q}_R belong to the limit cycle, because they are exponentially close to the orbit. To see the global effect that this assumption causes, and so the goodness of fit, in Figure 6, we show the relative error of the approximated period function $\hat{T}(C, I, g_{syn})$, first, keeping constant de parameter g_{syn} (panel A); second, keeping constant de capacitance C (panel B); and, finally, keeping constant de applied current I (panel C). The relative errors have been plotted, in all panels, considering the numerical solution of the period, which has been computed using the Newton-Raphson method in each region separately, as well as the actual one (see Appendix B.1 for details on the routine). In panel A we can see how the relative error in the proposed approximation function depends more significantly on the capacitance C than on the applied current I . On the other hand, in panel B, one can see that, when parameter I varies, for a fixed value of g_{syn} , the error is not qualitatively altered, but for larger values of g_{syn} , the relative error significantly increases; see also panel C, where we can better appreciate the errors in g_{syn} as C changes.

Observe that even though $\hat{T}(C, I, g_{syn})$ is defined for all values of C , g_{syn} and I , computing \hat{T} makes sense only under the hypothesis (H), that is, when I lies in (I_1, I_2) and $g_{syn} \in (1 - 1/\gamma, 1 - C\gamma)$. Figure 8 shows the shape of the approximated period function $\hat{T}(C, I, g_{syn})$ in the corresponding domain. As we have mentioned in Remark 4, the period substantially increases when I is close to I_2 and I_1 , tending to infinity. Moreover, the V-shaped domain of the function $\hat{T}(C, I, g_{syn})$ is given by the linear dependence that I_1 and I_2 have on g_{syn} . That is, as we decrease the value of g_{syn} , the value of I_1 is greater whereas the value of I_2 is smaller; consequently, the window where I can move decreases and causes the V-shaped profile.

In Figure 7 we illustrate the asymptotic dependence of the absolute error with respect to C , showing a good linear fit of $\log(|T - \hat{T}|)$ versus $\log(C)$. The slope of this linear fitting provides the order of the absolute error in terms of C . In Panel A we can observe, for different values of g_{syn} , that all traces have an initial slope smaller than one (comparing coloured lines versus the black thick dashed line) and similar to 0.88 (comparing coloured lines versus the black thin dashed line). Hence, our estimation procedure gives an absolute error of $O(C^\alpha)$ with $\alpha \approx 0.88$. In Panel B, we compare the error $|T - \hat{T}|$ with that obtained after avoiding the fast motion and reducing the flow to the slow manifold. We can see that our method reduces the absolute error for any value of g_{syn} .

Remark 6. In Figure 8 we can also see that $\hat{T}(C, I, g_{syn})$ seems to be monotonically decreasing with respect to g_{syn} . Because of the multitude of parameters in the model, we have not been able to give an analytical proof of the monotonicity of \hat{T} . However, computational evidences are given, see Figures 8 and A. Note that, by assuming monotonicity, for a given value T^* of the period, there exists a unique value g_{syn}^* such that $\hat{T}(C, I, g_{syn}^*) = T^*$. In order to avoid possible situations of lost of monotonicity, in the estimation procedure of g_{syn} we have implemented a control to ensure, under some tolerance value, that the derivative of \hat{T} never vanishes.

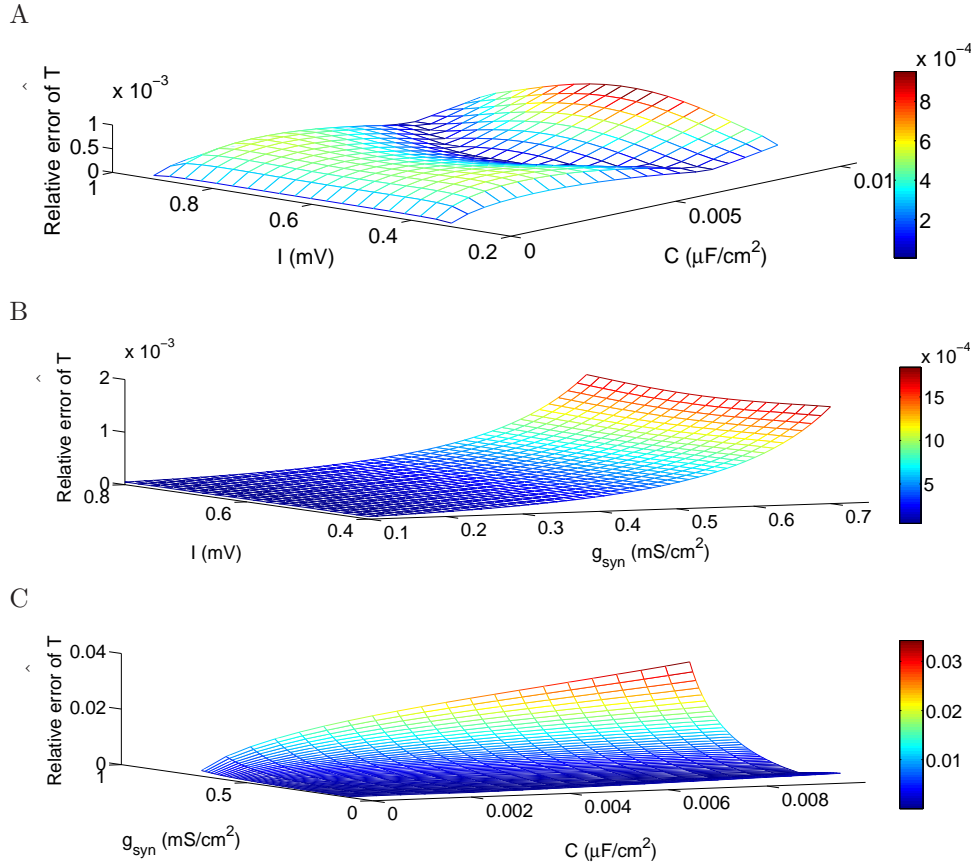


Figure 6: **Goodness of fit of the periodic function $\hat{T}(C, I, g_{syn})$.** Panel A shows the relative error of the period for a fixed synaptic conductance $g_{syn} = 0.2$, panel B shows the relative error of the period when the capacitance is fixed as $C = 1e - 4$, and panel C shows the relative error of the period when the applied current is fixed as $I = (I_1^0 + I_2^0)/2$ such that I_1^0 and I_2^0 are, respectively, the value of I_1 and I_2 corresponding to $g_{syn} = 0$. The relative error of the numerical value obtained using the Newton-Raphson method to the Poincaré map associated with respect to the approximated one using the expression in Proposition 3. The rest of parameters of the model are fixed as $a = 0.25$, $v_0 = 0$, $w_0 = 0$, $\gamma = 0.5$, and $v_{syn} = 0.25 + a/2$.

4 Estimation of the synaptic conductance

In this section we present a method to estimate the steady synaptic conductance from the cell's oscillatory activity. That is, assuming that g_{syn} is constant and knowing the frequency of the spikes for a fixed and constant injected current I , we want to estimate the synaptic current that the neuron is receiving. The procedure will be then extended to estimate the time course of the non-steady synaptic conductance.

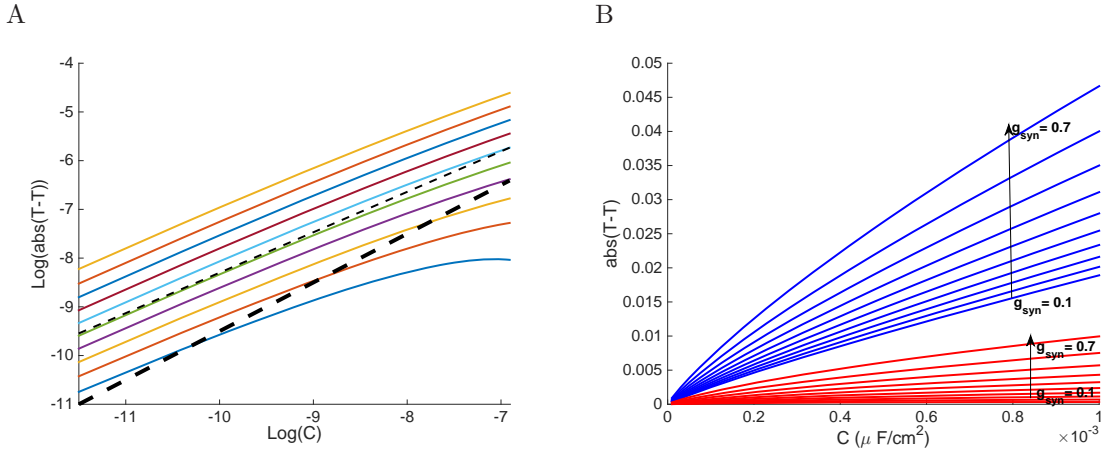


Figure 7: **Asymptotic dependence of the absolute error with respect to C .** Panel A shows the $\log(C)$ versus $\log(|T - \hat{T}|)$ for ten equally spaced values of g_{syn} , moving from 0.1 (bottom coloured trace) to 0.7 (upper coloured trace). Black thick dashed trace stands for a line of slope 1 whereas the thin one stands for a line of slope 0.88. Panel B represents the error $|T - \hat{T}|$ (red traces) and the error obtained after avoiding the fast motion and reducing the flow to the slow manifold (blue traces), for the same different values of g_{syn} . In both panels, the applied current is fixed as $I = (I_1^0 + I_2^0)/2$ such that I_1^0 and I_2^0 are, respectively, the value of I_1 and I_2 corresponding to $g_{syn} = 0$. The rest of parameters of the model are fixed as $a = 0.25$, $v_0 = 0$, $w_0 = 0$, $\gamma = 0.5$, and $v_{syn} = 0.25 + a/2$. The numerical period T has been obtained applying the Newton-Raphson method to the Poincaré map associated with the periodic orbit.

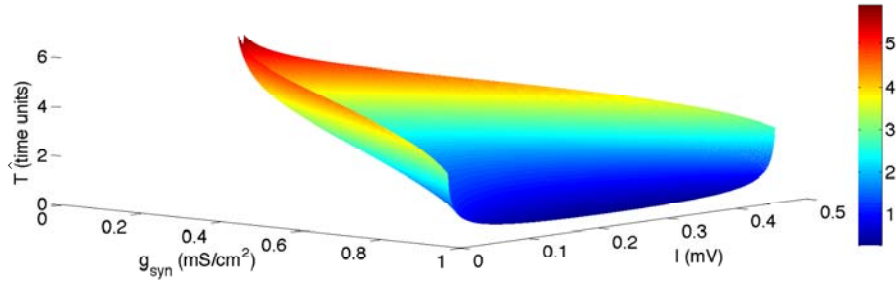


Figure 8: **Shape of the $\hat{T}(C, I, g_{syn})$ function.** This figure shows the shape of the approximated period \hat{T} versus the applied current I and the synaptic conductance g_{syn} . The capacitance has been fixed as $C = 1e - 4$. The rest of parameters of the model are fixed as $a = 0.25$, $v_0 = 0$, $w_0 = 0$, $\gamma = 0.5$, and $v_{syn} = 0.25 + a/2$.

4.1 Estimation of a steady synaptic conductance

Based on the evidences of the monotonicity of $\hat{T}(C, I, g_{syn})$ with respect to g_{syn} (see Figures 8 and A), we assume that there exists a one-to-one correspondence between \hat{T} and g_{syn} . Therefore, applying a specific current, I^* , one can experimentally approximate the corresponding actual period T^* of the

membrane potential v , and so g_{syn} numerically. In other words, knowing the rest of the parameters of the model, a unique possible synaptic conductance g_{syn} can be estimated by solving the implicit equation

$$\hat{T}(C^*, I^*, g_{syn}) = T^*. \quad (10)$$

To solve equation (10), one has to take into account that the logarithmic part of the analytical expression \hat{T} contains an absolute function and, since I_1 and I_2 depend on g_{syn} , we could get up to three possible g_{syn} solutions for a fixed I . However, only one of the three possible solutions for g_{syn} satisfies that $I_1 < I < I_2$. Then, this indetermination can be removed by imposing the additional condition

$$g_{syn} > \max(0, \bar{I}_1, \bar{I}_2), \quad (11)$$

where

$$\bar{I}_1 = \frac{2\gamma I - (\gamma + 1)a + 2v_0 - 2\gamma w_0}{2\gamma(\frac{a}{2} - v_{syn})} \quad \text{and} \quad \bar{I}_2 = \frac{2\gamma I - (\gamma + 1)a + 2v_0 - 2\gamma w_0 - \gamma + 1}{2\gamma(\frac{a+1}{2} - v_{syn})}.$$

When we apply the estimation procedure (10)-(11) to obtain the estimated synaptic conductance, \hat{g}_{syn} , we identify two main sources of error: an error coming from the numerical method used to solve the implicit equation and another error coming from the approximation of the period function, which is at most $O(C^\alpha)$ with $\alpha \approx 0.88$ (see Section 6). To visualize the impact of both error sources and so to test the goodness of the estimation procedure, we show the relative error of the estimated synaptic conductance \hat{g}_{syn} with respect to the actual value of g_{syn} , both using different values of applied currents (see Figure 9(A)), and using different values of the membrane capacitance (see Figure 9(B)). In these plots we estimate different values of the synaptic conductance (from 0.1 to 0.3, equally spaced), each one represented by a different colour trace.

In Figure 9(A) we can see how the estimation of the conductance improves when the applied current is close to I_1 and I_2 . The error of \hat{g}_{syn} takes its maximum at $I = (I_1 + I_2)/2$, where the slope of $\hat{T}(I)$ is minimal (in absolute value). On the other hand, in Figure 9(B) we also observe that the relative error is smaller when the membrane capacitance, C , is smaller; moreover, for small C one can appreciate that this error is notably less than $O(C^\alpha)$ with $\alpha \approx 0.88$. Therefore, we can conclude that the best estimation is done for small values of C and also for values of I close to I_1 or I_2 . In Figure 9(C) we can better appreciate how the error increases for large values of C and for values of I far from I_1 and I_2 . This panel presents the goodness of fit of the synaptic conductance when both parameters C and I change (in this plot, the relative error is represented in absolute value).

4.2 Generalization for non-constant conductance's traces: inter-spike estimation.

In this section, we modify the previous methodology in order to estimate conductance's traces that slowly vary along time, that is, when $g_{syn} = g_{syn}(t)$. Strictly speaking, this leads to a non-autonomous differential system, and the system may not have a limit cycle as for constant g_{syn} . However, for slow changes in the synaptic conductance, even if the limit cycle does not persist, we may assume that the orbits of the system are close to an oscillatory behaviour. Given an inter-spike interval $[t^*, t^* + \tau]$, we propose to apply the associated procedure (10)-(11), that is, solving $\hat{T}(g_{syn}) = \tau$ to obtain an estimated \hat{g}_{syn} on $[t^*, t^* + \tau]$. We summarize this idea in the following procedure:

Procedure 1. Consider a voltage trace $\{v(t), t \in [0, T_{max}]\}$ obtained from the neuron model (1) under an (unknown) synaptic input $\{g_{syn}(t), t \in [0, T_{max}]\}$ and a specific applied current I^* such that they induce spiking activity. We assume that $v(t)$ reaches $N + 1$ peaks (maxima of the trace) and call $\{T^{(k)}\}_{k=1}^N$ the corresponding N inter-spike intervals. Then, the time course of the synaptic conductance $g_{syn}(t)$ can be estimated from next steps:

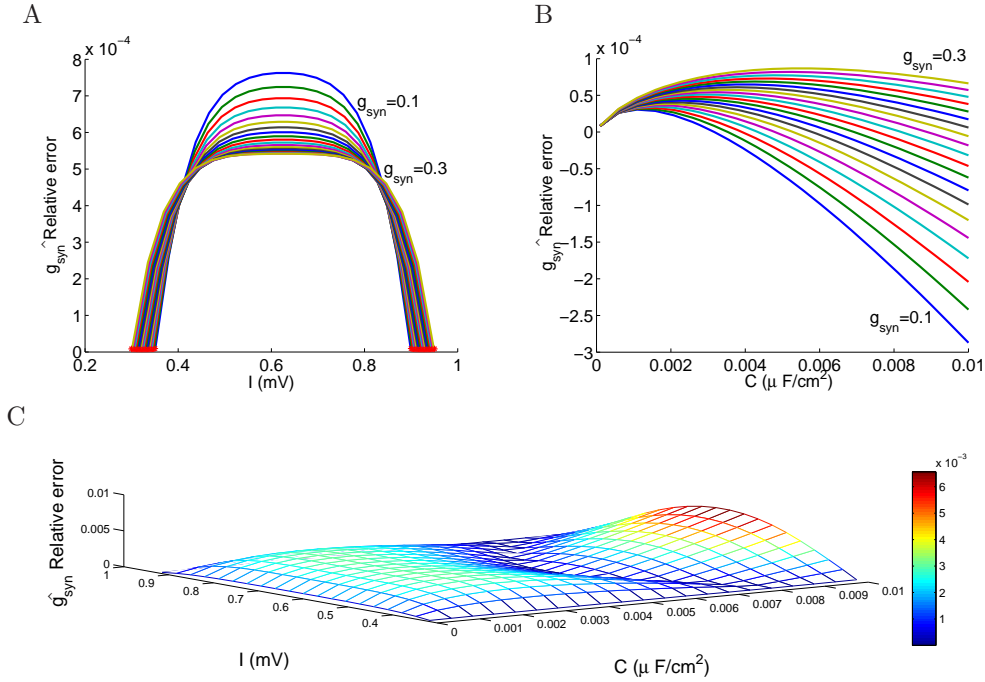


Figure 9: **Goodness of fit of the steady synaptic conductance parameter.** Panels A and B show the relative error caused when we estimate the synaptic conductance. The different traces correspond to different values of g_{syn} equally spaced from 0.1 to 0.3. Panel A represents the relative error versus the applied current for a fixed value of $C = 10^{-4}$, whereas panel B represents the relative error versus the membrane capacitance for a fixed value of $I = I_1 + 10^{-3}$. Red points in panel A represent the values of I_1 (left points) and I_2 (right points) for each g_{syn} . Panel C shows the relative error in absolute value for varying values of the membrane capacitance, C , and the applied current, I , being the actual synaptic conductance $g_{syn} = 0.2$. The rest of parameters are fixed as $a = 0.25$, $v_0 = 0$, $w_0 = 0$, $\gamma = 0.5$, and $v_{syn} = 0.25 + a/2$.

1. For each $T^{(k)}$, $k = 1, \dots, N$, solve (10)-(11) to estimate the corresponding synaptic conductance value, $\hat{g}_{syn}^{(k)}$.
2. Assign at $\hat{g}_{syn}^{(k)}$ the time $t^{(k)}$ corresponding to the $(k + 1)$ -th peak to obtain a set of points $\mathcal{P} := \{(t^{(k)}, \hat{g}_{syn}^{(k)})\}_{k=1}^N$.

As a result of this procedure, we obtain a discrete series of \hat{g}_{syn} values, which are finally interpolated to obtain an approximation of the full time course of $\hat{g}_{syn}(t)$. In the forthcoming examples, we have used cubic spline interpolation. Notice also that we arbitrarily set $t^{(k)}$ as the last time in the corresponding interval; we have tested other choices (e.g., the middle point) and no substantial changes have been observed.

Figure 10 shows some test conductance's traces which have been created in order to obtain scenarios with different spiking intensities. The first two rows present conductance's traces with low frequency oscillations at different phases: the first one presents high amplitude oscillations, $g_{syn}(t) = 0.2 + 0.2 \sin(2\pi t/10)$, and the second one combines small with big oscillations, $g_{syn}(t) = 0.2 + 0.2 \sin(2\pi t/10) + 0.04 \sin(2\pi t/5)$. In both cases we obtain a good estimation of the conductance, according to the high

concentration of points on the vicinity of the identity line in the scatter plots, see panels in the second column of Figure 10. The reconstruction of membrane potential ($v_{rec}(t)$) obtained using the estimated conductance's trace $\hat{g}_{syn}(t)$ as synaptic input show an excellent agreement with the original membrane potential trace, see panels in the last column.

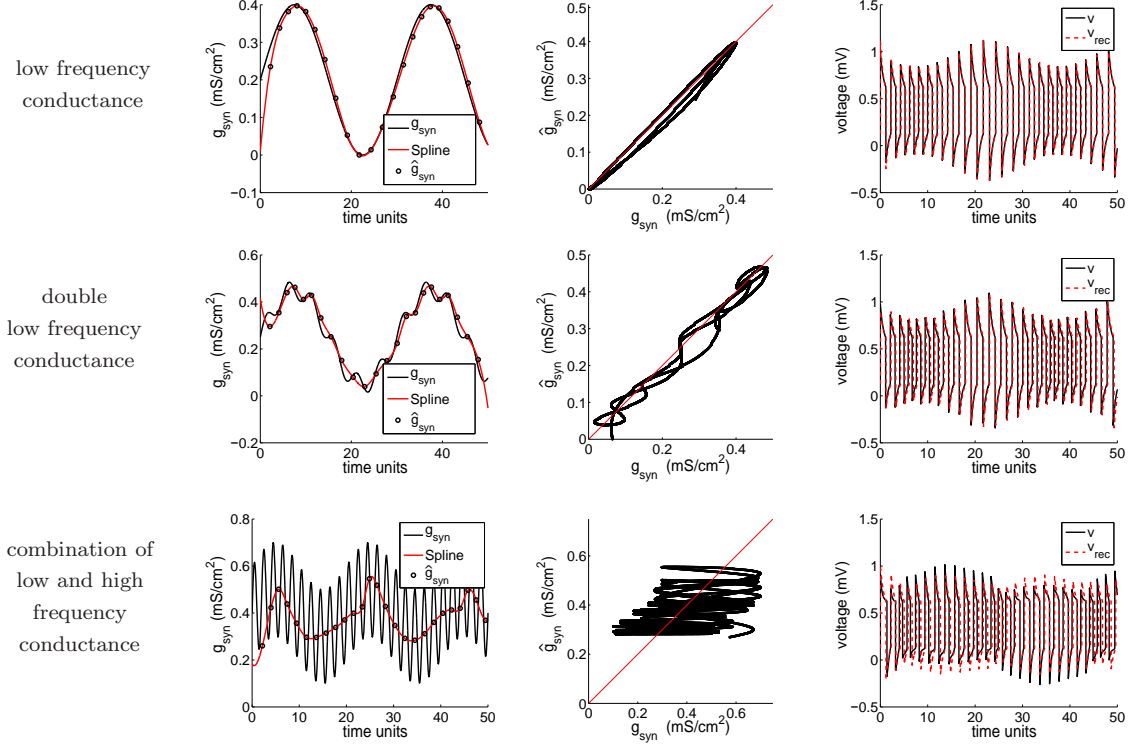


Figure 10: **Goodness of fit of the synaptic conductance time course for different functions of g_{syn} .** The first column shows the estimated values of the discretization of g_{syn} (black dots) and the cubic spline interpolation of them (red solid line). The black line corresponds to the actual value of the synaptic conductance at each time. The second column represents the scatter plot of the actual versus the estimated synaptic conductance after the interpolation. The red line is the identity line as a reference to observe the goodness of the estimation. The third column shows a comparison of the voltages computed using the actual conductance (solid black trace) and the estimated conductance (dotted red trace). Parameters are $a = 0.25$, $v_0 = 0$, $\gamma = 0.5$, $w_0 = 0$, $v_{syn} = 0.25 + a/2$, $C = 0.001 \mu F/cm^2$, and $I = 0.625 \mu A/cm^2$.

In the last row of Figure 10, we consider a new conductance's trace where both frequency and amplitude of the small oscillations have been changed respect to the results in the second row, $g_{syn}(t) = 0.4 + 0.2 \sin(2\pi t/2) + 0.1 \sin(2\pi t/20)$. In the left panel we can observe that the estimated conductance does not match with the actual ones, where the fast oscillations have not been captured. However, on the reconstruction of the membrane potential (see $v_{rec}(t)$ in right panel on the last row), the frequency is captured, the amplitude of the spikes is not, and a small delay is presented.

From Figure 10, we conclude that for a slowly varying synaptic conductance, the method proposed in Procedure 1 gives estimates the time course of the synaptic conductance with small errors and reproducing

the membrane potential with high accuracy. However, confronted to abrupt changes, the performance of the method weakens and can only track the mean time course of synaptic conductance, whereas the membrane potential is still well reconstructed.

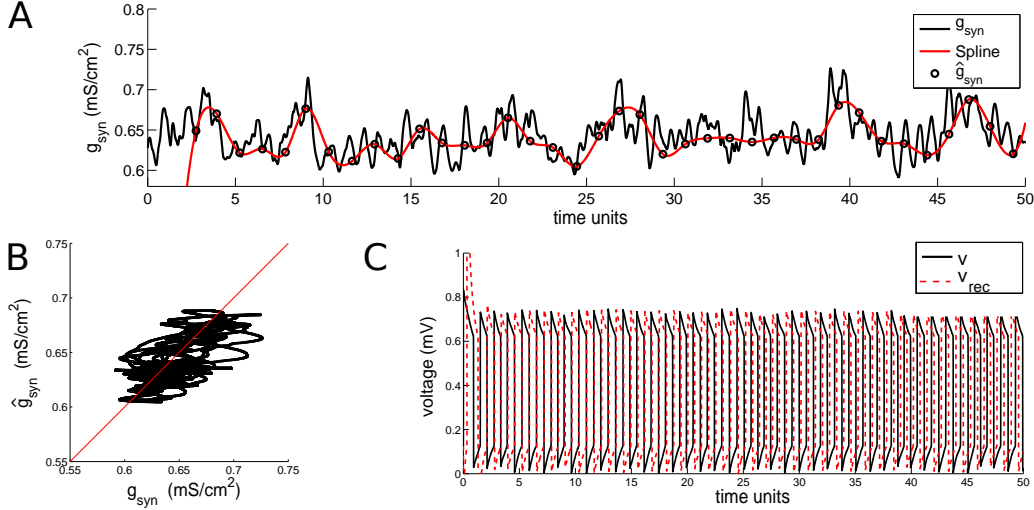


Figure 11: **Goodness of fit of the time course of synaptic conductance based on inter-spike intervals.** Panel A shows the estimated values of the discretization of g_{syn} (black dots) and the cubic spline interpolation of them (red solid line). The black line corresponds to the actual trace of synaptic conductance. Panel B represents the scatter plot of the actual versus the estimated synaptic conductance after the interpolation. The red line in Panel B is the identity line, left as a reference to observe the goodness of the estimation. Panel C shows a comparison of the voltages computed using the actual conductance (solid black trace) and the estimated conductance (dotted red trace). Parameters are $a = 0.25$, $v_0 = 0$, $\gamma = 0.5$, $w_0 = 0$, $v_{syn} = 0.25 + a/2$, $C = 0.001 \mu F/cm^2$, and $I = 0.625 \mu A/cm^2$.

To test the estimation of the conductance’s course in a more realistic case, in Figure 11, we use a 1 *ms* conductance’s traces obtained from a computational network that models layer 4C α of primary visual cortex (see McLaughlin et al (2000) and Tao et al (2004)). Panel A shows how the estimated conductance follows the trace of the actual ones but, as we can also see in Figure 10, higher oscillations are not well captured. We can corroborate this fact in panel B, where we show that the actual and the estimated conductance is poorly correlated (the coefficient of correlation is approximately 0.12). In panel C we compare the voltage computed using the actual conductance’s traces and the estimated ones (after interpolation). One can appreciate a small time shift of order 0.1 *ms* that remains almost constant along the time sequence.

4.3 Generalization for non-constant conductance’s traces: estimation based on the sub-periods

In the previous section we have seen that for quickly varying conductance, we cannot obtain good estimations. These misestimations are partly due to the fact that we are assuming the conductance to be stationary in a quite long time window. To reduce the errors and to better capture the oscillations of the synaptic conductance, in this section we present a more accurate way to estimate $g_{syn}(t)$ by taking advantage of the approximated expression of each sub-period (the time spent in each region)

separately in terms of g_{syn} , obtained in the proof of Proposition 3(b). We denoted these sub-periods as T_L, T_{Mu}, T_{Md}, T_R . Similarly, for any monodromic trajectory of system (1), not necessarily periodic, we can split the trajectories into pieces lying only on one of the three regions. We denote by τ_ξ the time spent in region ξ to go from $v_{\xi,1}$ to $v_{\xi,2}$, where ξ stands for L, Md, Mu or R , and the crossing points $v_{L,1} = v_{L,2} = v_{Md,1} = v_{Mu,2} = a/2$, $v_{R,1} = v_{R,2} = v_{Md,2} = v_{Mu,1} = (1+a)/2$. We understand that regions Mu and Md are both the central region. With this notation, we present a refined version of the estimation procedure given in Procedure 1.

Procedure 2. Consider a voltage trace $\{v(t), t \in [0, T_{max}]\}$ obtained from the neuron model (1) under an (unknown) synaptic input $\{g_{syn}(t), t \in [0, T_{max}]\}$ and a specific applied current I^* such that they induce spiking activity. We assume that the voltage trace describes N oscillations in the time interval $[0, T_{max}]$ and we define $\{\tau_\xi^{(k)}\}_{k=1}^N$ as the time spent to go from $v = v_{\xi,1}$ to $v = v_{\xi,2}$ in the k -th oscillation, where ξ stands for L, Md, Mu or R . Then, the time course of the synaptic conductance $g_{syn}(t)$ can be estimated by following the next steps:

1. For each $k = 1, \dots, N$ and $\xi \in \{L, Md, Mu, R\}$, solve

$$T_\xi(C^*, I^*, g_{syn}) = \tau_\xi^{(k)},$$

in terms of g_{syn} , under the constraint (11), and call the solution $\hat{g}_{syn}^{\xi,k}$.

2. Define the set $\mathcal{P} = \{(t^{\xi,k}, \hat{g}_{syn}^{\xi,k}); \xi = L, Md, Mu, R, k = 1, \dots, N\}$, where $t^{\xi,k}$ is the time when the k -th oscillation crosses $v = v_{\xi,2}$.

As for Procedure 1, we finally interpolate the points of \mathcal{P} to obtain an approximation of the full time course of $\hat{g}_{syn}(t)$. Note that using Procedure 2 we can extract a more accurate discretization of the conductance's trace, as we can see in Figures 12 and 13. If we compare the results from those obtained by using Procedure 1, for instance comparing the last row of Figure 10 to Figure 12, we observe how all the oscillations of $g_{syn}(t)$ are captured both in frequency and amplitude; concerning the reconstructed voltage in panel C, note that the delay detected when using Procedure 1 has been washed out with Procedure 2. For *in silico* data, see Figure 11(A) and Figure 13(A), we can also appreciate an improvement of the estimation when using Procedure 2 even though the improvement is more evident when conductance changes abruptly. Hence, using Procedure 2 we can capture more oscillations.

When we apply Procedure 2 to the data obtained from the more realistic input to a single cell in visual cortex, see Figure 13, the agreement between $g_{syn}(t)$ and $\hat{g}_{syn}(t)$ improves notably. This fact is reflected more clearly in panel A (compared to the same panel in Figure 11) rather than in the scatter plot of panel B, where it is difficult to tell a higher concentration of points around the identity line. Even though in this case the synaptic conductance is not perfectly estimated along time, we do capture the accurate mean conductance ($\text{mean}(g_{syn}) = 0.6350$ and $\text{mean}(\hat{g}_{syn}) = 0.6381$).

5 Discussion

Difficulties to estimate synaptic conductance when the ionic channels of the postsynaptic cell are activated have been extensively reported in the literature (see for instance Borg-Graham et al (1998), Guillamon et al (2006), Vich and Guillamon (2015), and the references therein). The standard approach of filtering the membrane potential and then fitting the filtered data to a linear model seems to work only in subthreshold regimes with no active ionic currents. In these low-activity regimes it has also been shown that quadratic models improve the estimations in a significant way. In spiking regimes, however, one has to face a greater challenge since the magnitude of ionic currents is far bigger than the magnitude of the synaptic currents. We need, then, a method that is able to disentangle the ionic activity from

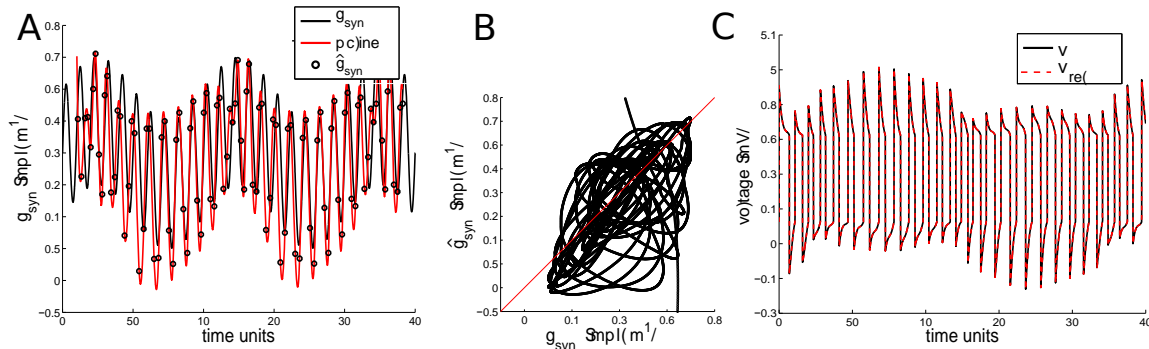


Figure 12: **Goodness of fit of the synaptic conductance time course for the combination of low and high frequency conductance.** Panel A shows the estimated values of the discretization of g_{syn} (black dots) and the cubic spline interpolation of them (red solid line). The black line corresponds to the actual value of the synaptic conductance at each time. Panel B represents the scatter plot of the actual versus the estimated synaptic conductance after the interpolation. The red line is the identity line as a reference to observe the goodness of the estimation. Panel C shows a comparison of the voltages computed using the actual conductance (solid black trace) and the estimated ones (dotted red trace). The other parameter values are $a = 0.25$, $v_0 = 0$, $\gamma = 0.5$, $w_0 = 0$, $v_{syn} = 0.25 + a/2$, $C = 0.001 \mu F/cm^2$, and $I = 0.625 \mu A/cm^2$.

the synaptic one and, at the same time, to extract, from the original recordings, a data set that can be useful to estimate the synaptic input that the cell is receiving. In this manuscript, we have presented a proof of concept of how such methods can be constructed; that is, how non-linear estimation methods can be implemented in order to estimate synaptic conductance in spiking regimes. Our method relies on the knowledge of the $f - I$ curve of the cell, a nonlinear trait that accounts for the activity of ionic channels involved in the spike generation. The proposed methodology does not take into account other features that could make the estimation more complex, like noise in the system or having other type of nonlinearities.

We have exemplified the general idea with a simple model, the McKean model (1), a piecewise linear version of the FitzHugh-Nagumo system, that allows us to perform analytical computations and give a very accurate approximation of the $f - I$ curve. The strategy proposed is easily extendable to other models or cell types, where the goodness of the estimations will mainly depend on the accuracy achieved in computing the $f - I$ curve. More precisely, for the McKean model (1), we have restricted to the situation where it exhibits an oscillatory behaviour; given a constant value of g_{syn} , we provide an approximation $\hat{T} = \hat{T}(C, I, g_{syn})$ of the period T such that $|T - \hat{T}| = O(C^{0.88})$, which includes the dependence on g_{syn} . This approximation has been obtained by taking into account the flight time of the fast and the slow sub-periods. Assuming the parameter g_{syn} to be constant in time, our results show excellent estimations for small values of C (the parameter related to the capacitance) and also for those values of I that are close to the boundaries of the oscillatory regime (see Figure 9). We think that the method could be tested in dynamic-clamp experiments in which the neuron can be first driven to a spiking regime that can be further modulated by a current injection of type $g_{syn}(v - v_{syn})$, with g_{syn} constant.

The estimation procedure has been also extended to a more general and realistic context, where we estimate the time course of variable synaptic conductance. In Figure 10 we show estimations obtained from three different prescribed inputs: a sinusoidal drive, an oscillatory drive with two low frequencies and a combination of both low and high frequencies. We observe fairly good estimations of synaptic

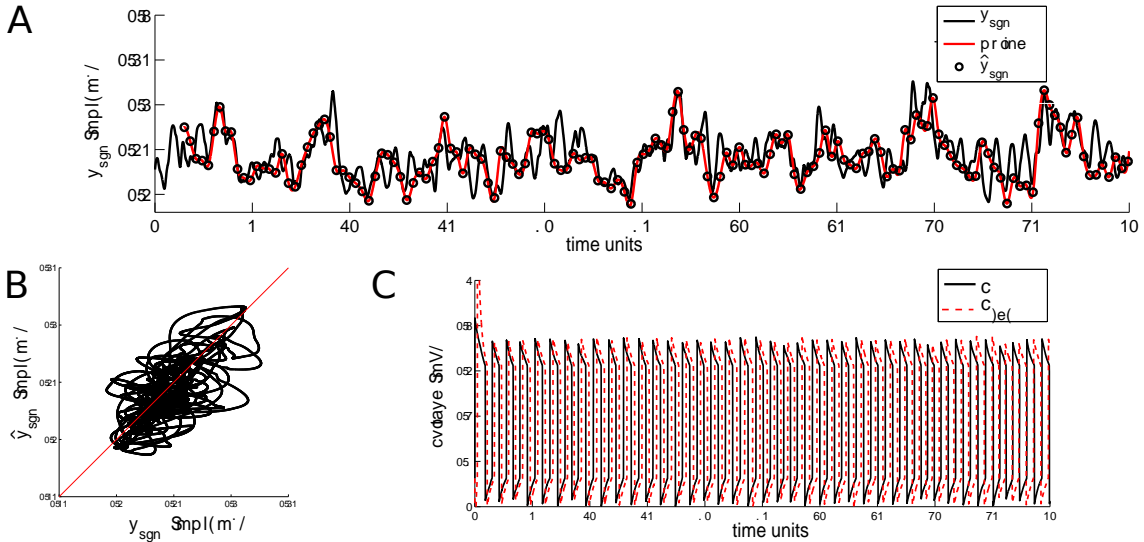


Figure 13: **Goodness of fit of the synaptic conductance time course when we consider the sub-periods separately.** Panel A shows the cubic spline interpolation of the estimated values of the discretization of $g_{syn}(t)$ (red solid line) and the actual value of the synaptic conductance (black solid line) given as in Figure 11. Panel B represents the scatter plot of the actual versus the estimated synaptic conductance after the interpolation. The red line in Panel B is the identity line as a reference to observe the goodness of the estimation. Panel C shows a comparison of the voltages computed using the actual conductance (solid black trace) and the estimated ones (dotted red trace). The other parameter values are $a = 0.25$, $v_0 = 0$, $\gamma = 0.5$, $w_0 = 0$, $v_{syn} = 0.25 + a/2$, $C = 0.001 \mu F/cm^2$, and $I = 0.625 \mu A/cm^2$.

conductance in the first two cases, but the addition of a high frequency makes the estimations impoverish. In general, frequencies of the conductance's changes higher than the spike frequency are difficult to estimate. The reconstructed voltage using the estimated conductance (see $v_{rec}(t)$ in the last column in Figure 10) always exhibits a good agreement, meaning that it is not a suitable detector for good estimations. When we inject a stereotypical synaptic input to a single cell in visual cortex taken from a realistic model of V1 (see Figure 11), the estimation captures the overall conductance profile but does not match at a smaller scale. In realistic inputs, the conductance's time-scale is variable, being very short in some moments. Thus, we can only get a good estimation on average.

In order to check the influence of high frequency synaptic inputs, we have improved our method by refining the sampling, taking advantage of the knowledge of the sub-periods T_L , T_{Md} , T_{Mu} and T_R , thus enlarging the sampling set by a factor of 4. Figure 12 compared to the last row of Figure 10 confirms the predicted improvement. For the realistic input, however, we appreciate only a slight improvement (see Figure 13 compared to Figure 11).

Summing up, we have shown the viability of the approach based on the use of the $f - I$ curve in order to estimate synaptic conductance in spiking regimes. We have also examined the drawbacks of this proof of concept, but nevertheless we think that our proposal brings up positive results that open new research lines which we aim to address:

- The gain obtained when increasing the sampling indicates that introducing more Poincaré sections to estimate flight times in shorter intervals would be a good strategy to cope with high frequency synaptic inputs. Extending this reasoning to the limit, we plan to add to the model a third differ-

ential equation modelling the dynamics of the synaptic conductance. This would allow to obtain good estimations in a more general context and provide a scheme to be applied to experimental data.

- The scheme need to include both excitatory and inhibitory terms. We have only considered one type of synaptic input. In the examples, we have chosen $v_{syn} = 1/4+a/2$, a value that could be attributed to excitatory synapses. However, a key aspect in estimating conductance is to differentiate between excitation and inhibition. We think that this step is feasible within the frame of the McKean model.
- The methodology needs to be tested in other conductance-based models with more realistic ionic channels. This extension will require to get approximate expressions of the period in terms of g_{syn} , a challenging problem that can be successfully treated by adapting existing formulas for the period of limit cycles close to bifurcation points, see for instance Gasull et al (2005).
- Combine the new methodology for spiking regimes with existing estimations for subthreshold oscillations. This issue connects again with bifurcation diagrams since an ideal method should apply to a variable synaptic input that sweeps the I parameter range from excitable to spiking regimes and vice versa. It also opens an interesting question about the influence of the type of bifurcation (Hopf, saddle-node on invariant curve,...) on the goodness of the estimations.

A Evidences of the monotonicity of \hat{T} .

In Figure 14 we represent the function $\hat{T}(g_{syn})$ (panel A) and the derivative $\partial\hat{T}/\partial g_{syn}$ (panel B) for the set of parameter values used in all the numerical computations, except for the applied current which varies (different colours) in the range of existence of limit cycles. It is worth to note, see for instance panel B, that for all the applied currents considered we have that $\partial\hat{T}/\partial g_{syn} < 0$. In all the results given above, we use this numerical evidence together with an on-line check that the derivative does not vanish to ensure that the solution we get from equation (10) is unique.

B Numerical methods

In the numerical computations, to solve (10) we need the time spent on some trajectory, T^* , that has to be computed numerically. We have computed these values by integrating the orbits and determining the intersection points with the corresponding Poincaré section using both the Newton-Raphson method and the bisection method with a tolerance $TOL = 1e - 11$ (see Appendix B.1 for more details of the routine). The same methods have been used to estimate the synaptic conductance g_{syn} with tolerance $TOL = C^2$.

In order to integrate the differential piecewise linear system we have used the Runge-Kutta 7-8 method with tolerance $TOL = 1e - 8$ and a maximal step size $h_{max} = 1e - 1$. We have used the `edo78` function of Matlab[®].

Finally, we have used the `spline` function of Matlab[®] to compute the cubic spline interpolation used to construct the continuous time course of the estimated synaptic conductance in Procedure 1 and Procedure 2.

B.1 Routine to compute the numerical period

Consider the solution (5) of the model given by the piecewise differential system (1).

- Let $x_0 = (\frac{a}{2}, w_0) = \mathbf{q}_L$, $\bar{T}_0 = 0$ be the initial condition.

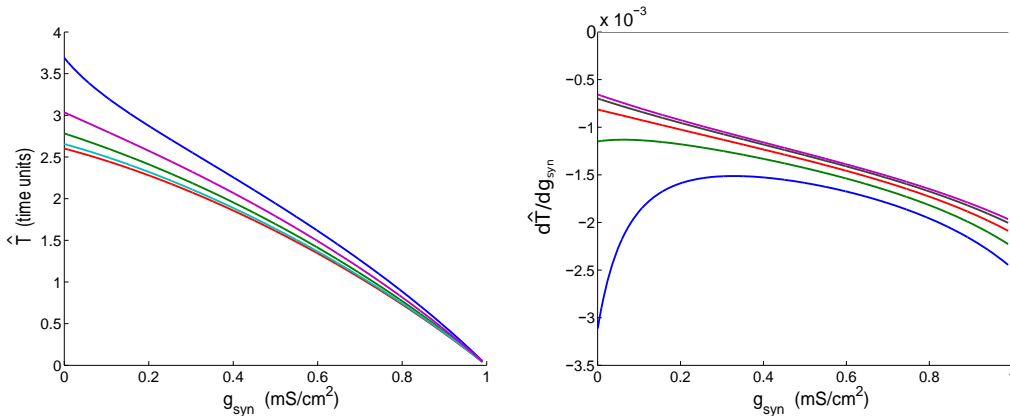


Figure 14: **Monotonicity of $\hat{T}(C, I, g_{syn})$ with respect to g_{syn} .** This figure shows different plots representing the approximated period \hat{T} and its derivatives versus the synaptic conductance g_{syn} for different values of the applied current. We depict $\hat{T}(g_{syn})$ in panel A and the first derivative $\partial\hat{T}/\partial g_{syn}$ (coloured lines) in panel B, together with the line $d\hat{T}/dg_{syn} = 0$ (gray line). The different coloured lines, in all panels, stand for different applied currents, namely $I_{app} \in [0.4, 0.5, 0.6, 0.7, 0.8]$. The rest of parameters of the model are fixed as $C = 1e-4$, $a = 0.25$, $v_0 = 0$, $w_0 = 0$, $\gamma = 0.5$, and $v_{syn} = 0.25 + a/2$.

1. Let x_0 be the initial condition and compute T_{Md} as a zero of the equation $v(t) - \frac{1+a}{2}$. Then, knowing $t = T_{Md}$, we can compute $w_1 = w(T_{Md})$, and so we obtain a new point $x_1 = (\frac{1+a}{2}, w_1)$.
 2. Let x_1 be the initial condition and compute T_R as a zero of the equation $v(t) - \frac{1+a}{2}$. Then, knowing $t = T_R$, we can compute $w_2 = w(T_R)$, and so we obtain a new point $x_2 = (\frac{1+a}{2}, w_2)$.
 3. Let x_2 be the initial condition and compute T_{Mu} as a zero of the equation $v(t) - \frac{a}{2}$. Then, knowing $t = T_{Mu}$, we can compute $w_3 = w(T_{Mu})$, and so we obtain a new point $x_3 = (\frac{1+a}{2}, w_3)$.
 4. Let x_3 be the initial condition and compute T_L as a zero of the equation $v(t) - \frac{a}{2}$. Then, knowing $t = T_L$, we can compute $w_4 = w(T_L)$, and so we obtain a new point $x_4 = (\frac{a}{2}, w_4)$.
 5. Compute $\bar{T} = T_L + T_{Md} + T_R + T_{Mu}$
- b) If $|w_0 - w_4| < TOL$ or $|\bar{T}_0 - \bar{T}| < TOL$, DONE: the numerical period is \bar{T} . Otherwise, let $x_0 = x_4$, $\bar{T}_0 = \bar{T}$, and repeat steps 1-5. we have considered $tol = 1e-10$ for this step.

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