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TOWARD A UNIVERSAL DESCRIPTION FOR SINGLE NEURON DYNAMICS

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A modo de dedicatoria

Debido a mi infinita egolatría y el gusto por revolcarme en mi mismo, debido a mi infinito amor a las cosas lindas y efímeras como son los sistemas vivos hice esta tesis. No se la dedico a nadie. Pero si tuviera que dedicársela a alguien, dedico esta tesis a este trabajo en si mismo. Redacto estas líneas con el fin de nunca olvidar lo que produjo en mí este trabajo: hizo sentirme vivo en un mundo que no tiene mucho sentido. Redacto estas líneas para que cuando las lea no olvide los sueños que tuve con esta tesis, las duchas eternas haciendo cálculos mentales, lo monotemático que fui con este trabajo este último año y medio en mis conversaciones cotidianas y en mis borracheras, los quasi-orgasmos que sentí los buenos días en el metro de Santiago al pensar de manera enfermiza en este problema. Le dedico esta tesis a esta tesis por que hacerla me hizo ser muy feliz.

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Con respecto a mi tutor Enrique todo esta dicho en la dedicatoria.

Quiero repetir mi agradecimiento a mi esposa Macarena por nuestro amor.

Estudié en el colegio Rogeriano The Angels School de Ñuñoa desde kinder a cuarto medio. Soy escritor, el año 2008 gané el premio especial de poesía Roberto Bolaño para escritores jóvenes otorgado por el Ministerio de Cultura del gobierno de Chile. Estudié Ingeniería en Biotecnología Molecular y Licenciatura en Ciencias con mención en Física en la Facultad de Ciencias de la Universidad de Chile. En ambos egresé como primer alumno de la generación. Con el apoyo de la beca CONICYT y motivado por realizar investigación teórica interdisciplinaria en neurociencia realizé el actual Magister en Ciencias con mención en Física. En unos días mas me voy como becario Fulbright a la Universidad de Chicago a trabajar en neurociencia teórica en el contexto de un Doctorado en Estadística y Matemática aplicada, espero seguir escribiendo en Chicago.

Abstract

Near a bifurcation the behaviour of any physical system is universal (i.e. not depend of its specific details) and is described by a *universal equation* called normal form. These equations are *universality classes*, and very different dynamical systems (near to a given bifurcation) will be described for the same normal form. Although this is mathematically strictly true infinitesimally near of the bifurcation, it occurs often that the qualitative aspects of the behaviour of the system is still given by the normal form even outside of the infinitesimal neighbourhood of the bifurcation point. In this work we will show that the electrical dynamics of a single neuron is a beautiful example of this fact.

At the present time, to describe neuronal dynamics for different types of neurons there exist an overwhelming diversity of thousands of high dimensional nonlinear models. These class of models are called conductance based models (CB models) and are considered the most biophysically realistic models. Despite the huge diversity of types of neurons and models, they display a universal dynamics generically captured by phenomenological models of two variables (for spiking dynamics), and in non generic cases by three variables (for bursting dynamics). But the mathematical mechanisms by which single neurons display this universal behaviour are still not clear.

We analytically show that a CB models that meet the biophysical conditions for spiking are generically in the neighbourhood of the Bogdanov-Takens bifurcation. We numerically confirm that the dynamics displayed by spiking CB models is qualitatively described by the subcritical Bogdanov-Takens normal form (a two variable equation). Furthermore, we found an analytic method to reduce, or transform in the two variable cases, either CB or phenomenological models to an equation with the same form of the subcritical Bogdanov-Takens normal form. We analytically and numerically show that the reduced most famous CB and phenomenological models (Morris-Lecar, Hodgkin and Huxley and generalised FitzHugh-Nagumo model) are actually equivalent to the subcritical Bogdanov-Takens normal form and retain all the qualitative dynamics of the original equations.

We also show that the Triple Zero bifurcation is not generic for CB models, but if these models meet the biophysical conditions for bursting, then they will be in its neighbourhood. Furthermore, we analytically show that the Hindmarsh-Rose model —the most famous phenomenological model for neuronal bursting— can be transformed by a trivial change of variable in almost the Triple Zero normal form.

This results make an advance toward an universal description of single neuron dynamics. Moreover the relevant experimental quantities measured in experiments have a clear link with the proposed mathematical description.

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Introduction

Foreword

We shall start this Introduction to our work presenting our point of view on the way to approach the problem of neuron dynamics of a single neuron. We can do this from the very beginning and without even entering in any details concerning the biophysics involved since we shall adopt a dynamical systems approach and the idea that what one has to look for is a robust behaviour related to the experimental facts and construct from this analysis the simplest possible model satisfying the requirements. The fact is that the robust behaviour of the electrical activity of a single neuron is known and it consists in the presence of global bifurcations of codimension one which lead to the appearance of a limit cycle. These global bifurcations are two dimensional and then we can immediately state that our simplest possible model will have two variables. This is what the geometry tells us. Furthermore it is well known that the Bogdanov-Takens normal form has two variables and has these behaviours. On the other hand one knows through experience that normal forms are almost always easier to analyze than an arbitrary equation and if we can modelize a problem with a normal form it is a good idea to do it. This is exactly what we shall try to do here. First we remark that in codimension one we have only the Andronov-Hopf local bifurcations with two variables but its normal form does not present the global bifurcations. We go then to codimension two and there the only bifurcation with two variables is Bogdanov-Takens. Therefore our guess is that in some sense all models that describe the dynamics of a single neuron must be in the conditions in which the robust behaviour is observed, i.e. near a Bogdanov-Takens bifurcation, and this is exactly what we prove. Since in the experimental setup one moves only the external current one can expect that the two Bogdanov-Takens conditions must be related and then that in the class of models describing neurons this instability arises in some sense with codimension one. We shall see that this is exactly what happens and find that the necessary conditions for the occurrence of this instability are two conditions sindicated as the mechanisms of the excitability. These two conditions are the existence of two time scales (an indication of two variables) and the existence of amplifying and resonant variables. One can of course ask the question of why should one try to do this program since one knows and it is discussed in detail in the literature that the minimal models have two variables. The answer is that proceeding as we propose we can relate the two variables in our two dimensional model to the physical variables of any model with any quantity of variables, although we restrict ourselves here to the conductance based (CB) models since it is widely accepted by

the community of neuroscientists that they give a complete description of the problem. One can also ask if this reduction to two variables is not a consequence of an adiabatic elimination of variables, and the answer is yes in the sense we shall explain in detail in the section devoted to model reduction where we show that we can eliminate adiabatically the fast variables, but not the slow ones, a fact which is corroborated by direct numerical simulation. The result of this last procedure is once again a Bogdanov-Takens type second order equation in the Arnold form. Although the Bogdanov-Takens instability is seldom mentioned in the literature (He et al., 2012) it has always been considered in special cases and not in the sense of being the general mechanism underlying the behaviour of a single neuron. What we have described here is our program. The rest of this thesis is its practical implementation and the proof that our program is a good and successful attempt to understand the universal behaviour of single neuron dynamics. Then to work.

1 Biophysics of single neuron dynamics

In this section we will introduce some fundamental concepts of neuronal biophysics that are necessary to understand the text. Because this is an interdisciplinary work, we will try to reduce the technical biophysical concepts to the minimum which is necessary for our purpose which is to reach a wide audience[1].

All the living cells have an electrical potential difference between their inside and the outside which is called the membrane potential (v). Neurons (a type of cell) have the special feature to respond to certain magnitude of electrical stimulus by a rapid and sharp change of their membrane potential —phenomenon called membrane action potential (see Figure 3)— or (and) having sustained autonomous electrical activity (e.g. pacemaker neurons). The electrical activity in neurons is produced by ionic currents (the four most common ionic species in neurons are: Na^+, K^+, Ca^{2+} and Cl^-) through neuron membranes. The cell membrane is a lipid bilayer which by itself is a poor conductor. But embedded in the neuronal membrane are pore-forming membrane proteins called ionic channels. The ionic channels allow the passage of the ions involved in the electrical activity in neurons and turn then the cell permeable to ions. They selectively allow to pass certain ion species (e.g. Na^+ ionic channels) or more than one type of ion, generating the flux (an actual electrical current) of specific ions through the membrane. The ionic channels involved in the generation of the action potential (called voltage gated ionic channels) change their permeability depending on the membrane voltage, and this dependence with the voltage is nonlinear. In addition to this, a delicate molecular mechanism in which ionic pumps and the hydrolysis of ATP (energy spending) by the cell are involved, maintains constant the difference of each ion species between the inside and the outside of a cell, thus creating electrochemical gradients. These gradients generate an actual electrical potential difference (Hille, 2001) for each ionic species (e.g. v_{Na^+}, v_{K^+}, $v_{Ca^{++}}$ and v_{Cl^-}) called the Nernst potential, and these are the driving forces of neural activity. Therefore, when a neuron is electrically stimulated (by the experimentalist or by the electrical activity of other neurons via synapses) the membrane potential changes and the permeability of the ionic channels vary nonlinearly with the change of the membrane potential. This may cause a time dependent influx or outflux of

[1] If some reader is interested in understand more in deep some aspects of the biophysics or neurophysiology of neurons we recommend the excellent books: Foundations of Cellular Neurophysiology (Johnston and Wu, 1994), Ion Channels of Excitable Membranes (Hille, 2001) and the spanish book Biofísica y Fisiología Celular (Latorre, 1996).

the membrane action potential. Some of these concepts are schematised in the figure 1.

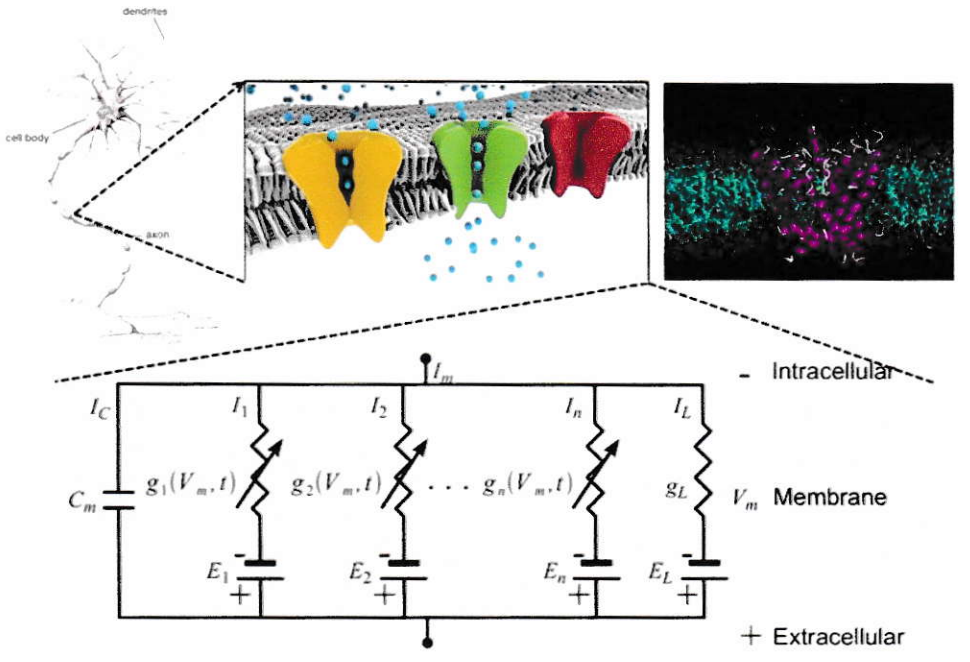


Figure 1: Scheme of a conductance based model. At the top, from left to right: an sketched neuron, a cartoon of the molecular structure of the cell membrane and a picture of a detailed molecular simulation of a ionic channel embedded in the cell membrane. At the bottom: a diagram of a conductance based model, where the cell membrane is represented as a capacitor in parallel to a potential dependent resistance in series with batteries. The resistance represents the conductance of the ionic channels and the different batteries represent the different reversal potentials.

1.1 Conductance based models

The development of a mathematical description for the electrical dynamics of a single neuron[2] begun with the seminal work of Hodgkin and Huxley[3]

[2]Single neuron it refer to a neuron without synaptic connection with other neurons. This imply that their electrical dynamics will be the result of its intrinsic biophysical properties.

[3]See appendix E.1 for the Hodgkin and Huxley model.

(Hodgkin and Huxley, 1952). These authors were the first to show experimentally that the electrical dynamics of neurons can be described by a class of mathematical models called conductance based models (CB models). In these models the electrical properties of the neuron are represented by an equivalent circuit. The circuit consists of three components: (1) conductors in parallel, representing the different ionic channels; (2) batteries, representing the Nernst potential[4] of each ionic species; and (3) a capacitor, representing the ability of the membrane to store charge. An scheme of the equivalent circuit of a CB model is shown at the bottom of the Figure 1. This physical model leads to both an intuitive and a quantitative understanding of how electrical signals are generated in neurons. The differential equation that describes mathematically this kind of circuit is:

$$I = C\frac{dv}{dt} + \sum_{k=1}^{n} I_k$$

This equation physically means that the total current across the membrane (I) is equal to the current stored in the membrane as a capacitor ($C\frac{dv}{dt}$) plus the sum of the current of the ionic channels ($\sum_{k=1}^{n} I_k$). By Ohm's law each ionic channel current is $I_k = G_k(v - v_k)$, where G_k is the average conductance of each ionic channel, and v_k is the Nerst potential of each ionic species. In a microscopic level ionic channels are pore-forming membrane proteins that are closed or open with certain kinetics. Because ionic channels are complex macromolecules, the probability of a ionic channel to be open depends on the fact that different subunits of the ionic channel can be activated and not yet inactivated[5] at a certain time. The dynamical variables which represent the probability that subunits are activated and not inactivated are called gating variables ($m_j(t)$). Then the probability of a ionic channel to be open can be mathematically represented by the product of the probability of each subunit to be active or not inactive ($\prod_j m_j(t)^{p_j}$, e.g. in the Hodgkin and Huxley model the probability of the potassium ionic channel to be open is n^4, where n is the corresponding gating variable). Each gating variable has its own kinetics which depends on the stationary probability to be activated ($m_j^{\infty}(v)$) and the relaxation time of this stationary probability ($\tau_j(v)$), and both quantities are nonlinear functions of the membrane voltage. Therefore in a macroscopic level, if we

[4]Also often called reversal potential.

[5]There are certain subunits that can inactivate a ion channel to be open. One example is the gating variable h of the sodium ion channel in the Hodgkin and Huxley. Where h represent the probability of a certain subunit not inactivate the sodium ion channel.

suppose that each subunit is independent, the average conductance for the ionic channel k is obtained by the product of the maximal conductance g_k of this ionic channel with the probability of this ionic channel to be open, i.e. $G_k = g_k \prod_j m_j(t)^{p_j}$. Then the electrical dynamics of a single neuron can be described by a set of $N+1$ non linear ordinary differential equations (ODEs), the first for the potential (which is just the Kirchhoff law for the equivalent circuit) and then N equations for the N gating variables):

$$\begin{aligned} \dot{v} &= \frac{1}{C}\left[I - \sum_{j=1}^{n} g_j \prod_{l \in w_j} m_l^{p_l}(v - v_j)\right] \\ \dot{m}_j &= \frac{m_j^{\infty}(v) - m_j}{\tau_j(v)} \qquad j = 1, 2 \ldots N \end{aligned}$$

where w_j is a set of indices labelling the gating variables of the j^{th} ionic channel.

In the past decades this class of models has been largely validated experimentally and theoretically (Johnston and Wu, 1994). This models are considered by the scientific community as the more *realistic models*, in the sense that they describe the electrical dynamics of a single neuron using a mathematical description which has a solid biophysical and thermodynamical ground (Hille, 2001).

An experimentally important characteristic time constant is the membrane time. The neurophysiologist define the membrane time as the time relaxation for an small step like electrical stimulus to a neuron in the limit when the neuron has a linear ohmic behaviour. If we consider a CB model for long times and very negative potentials, which in fact is the limit of a linear ohmic behaviour, all the gating variables have relaxed to their stationary state and the stationary probability functions are either 0 or 1. Then the equivalent circuit becomes a simple RC circuit with a capacitance equal to C. If we consider that a set of n_1 gating variables will have a stationary probability equal to 1 for very negative voltages, then the resistance of this circuit will be $R = 1/\sum_{k \in n_1} g_k$. Hence, the membrane time is theoretically defined as $\tau_{\text{membrane}} \equiv C/\sum_{k \in n_1} g_k$.

1.2 Amplifying and Resonant gating variables

To understand the core of the dynamical mechanism through which ionic channels shape the dynamics of the membrane action potential we will introduce the concepts of amplifying and resonant gating variable (Izhikevich,

2010). The amplifying gating variable amplifies voltage changes via a positive feedback loop and the resonant gating variable resists to voltage changes via a negative feedback loop. For a gating variable the property of being amplifying or resonant depends only on the relation between its stationary probability and the sign of the current[6] of the respective ionic channel at a given membrane potential, i.e. if is an outward or an inward current.

In the case of the amplifying gating variable a small depolarizating perturbation will augment the increase of the membrane voltage causing a positive feedback. There are only two possible mechanisms for this positive feedback and they are illustrated in grey boxes in Figure 2: 1) A gating variable with an increasing-with-the-voltage stationary probability and an inward ionic channel current at that voltage (the sign of $v - v_{\text{Reverse}}$ is negative) will be such that a depolarization stimuli will increase the inward current causing the increase of the membrane potential; and 2) A gating variable with a decreasing-with-the-voltage stationary probability and with an outward ionic channel current at that voltage (the sign of $v - v_{\text{Reverse}}$ is positive), will be such that a depolarization stimulus will decrease the outward current causing the increase of the membrane potential.

In the case of the resonant gating variable one has a resistance to voltage changes in the membrane potential. There are also only two possible mechanisms for this negative feedback and they are illustrated in white boxes in Figure 2: 1) A gating variable with an increasing-with-the-voltage stationary probability and an outward ionic channel current at that voltage (the sign of $v - v_{\text{Reverse}}$ is positive), is such that a depolarization stimulus will increase the outward current causing the decrease of the membrane potential; and 2) A gating variable with a decreasing-with-the-voltage stationary probability and with an inward ionic channel current at that voltage (the sign of $v - v_{\text{Reverse}}$ is negative), is such that a depolarization stimulus will decrease the inward current causing the decrease of the membrane potential. The explanation for an hyperpolarization stimulus is similar.

The membrane action potential is an interplay between amplifying and resonant gaiting variables. To get an spike we need a fast amplifying gating variable (e.g. m in the case of the Hodgkin and Huxley model) which produces a positive feedback that rapidly increases the membrane potential and a slower resonant gating variable (e.g. n and h in the Hodgkin and Huxley model) which generates a negative feedback to restore the po-

[6]The convention is that an inward current is negative and depolarize (increase) the membrane potential and an outward current hyperpolarize (decrease) the membrane potential.

tential value. This fast positive feedback/slow negative feedback generate oscillations called tonic spiking. Indeed, a fast inward current that rapidly depolarizes the membrane potential (which implies a fast amplifying gating variable) and a slow outward current (which implies a slow resonant gating variable) which hyperpolarizes the membrane potential, is considered experimentally (Johnston and Wu, 1994; Latorre, 1996) and theoretically (Izhikevich, 2010) the core mechanism of the action potential in the excitable cells, and sometimes as the minimal necessary conditions to have an *excitable behaviour*.

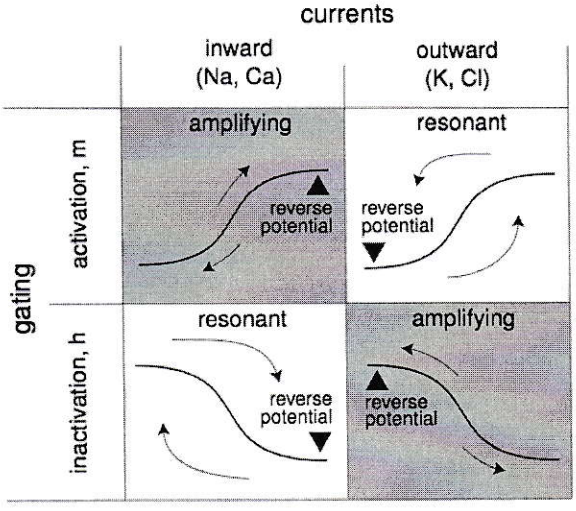


Figure 2: Scheme of how amplifying or resonant gating variables depend on the stationary probability function and the reversal potential. Adapted from the book Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting (Izhikevich, 2010).

2 Diversity of conductances and universality of the dynamics

In the last decades, the detailed electrophysiological and biophysical description of the wide diversity of conductances (Ranjan et al., 2011) led scientists to the possibility of building detailed CB model of almost any neuronal type studied (Carnevale and Hines, 2006). Each different CB model —built using adjustements of parameters with the experimental data— has usually more than twenty nonlinear equations. Different CB models may vary the number

of equations, the specific functions for the stationary probability ($m_j^\infty(u)$) or the relaxation time ($\tau_j(u)$) and the value of the parameters. This has generated in the last decades a massive production of different CB models for different type of neurons or experimental situations, and the development of databases of thousands of different CB models (Peterson et al., 1996). Furthermore, each CB model, depending on the values of the parameters, can produce different firing[7] patterns and there exist databases of up to a million combinations of parameters for a same CB model (Prinz et al., 2003).

2.1 Class I and Class II neurons

Although there exists a huge diversity of type of neurons (and CB models) there is a robust dynamics observed experimentally (and numerically) in almost all of them. This distinctive electrical dynamics observed in neurons is called the *excitable behaviour* of neurons. In 1948 it was Hodgkin who classify this *excitable behaviour* observed in neurons in two major groups (Hodgkin, 1948):

- Class 1 neural excitability. Action potentials can be generated with arbitrarily low frequency, depending on the strength of the applied current. See left of the Figure 3.

- Class 2 neural excitability. Action potentials are generated in a certain frequency band that is relatively insensitive to changes in the strength of the applied current. See right of the Figure 3.

Rinzel and Ermentrout were the first to note the connection between this classification and bifurcation theory (Rinzel and Ermentrout, 1998). They note that class 1 neural excitability is consistent with a Saddle-node homoclinic bifurcation (see Figure 4). On the other hand, they also note that class 2 neural excitability may be consistent with a subcritical Andronov-Hopf bifurcation with a narrow range of bistability[8]. Now many authors which classify membrane properties as class I or class II really mean Saddle-node homoclinic bifurcation and Hopf bifurcation, respectively (Ermentrout and Terman, 2010). It is important to mention that it was shown that the classification is consistent with other (global) bifurcations such as the Saddle homoclinic bifurcation (see Figure 5) or the Big homoclinic bifurcation (see Figure 6)(Izhikevich, 2010; Kuznetsov, 2005).

[7] When a neuron present an action potential the neuroscientist say that it fire or spike.

[8] In fact, in this thesis we will show that this is a more complicated scenario when a big homoclinic bifurcation may led to homoclinc bifurcations of a heteroclinc separatrix.

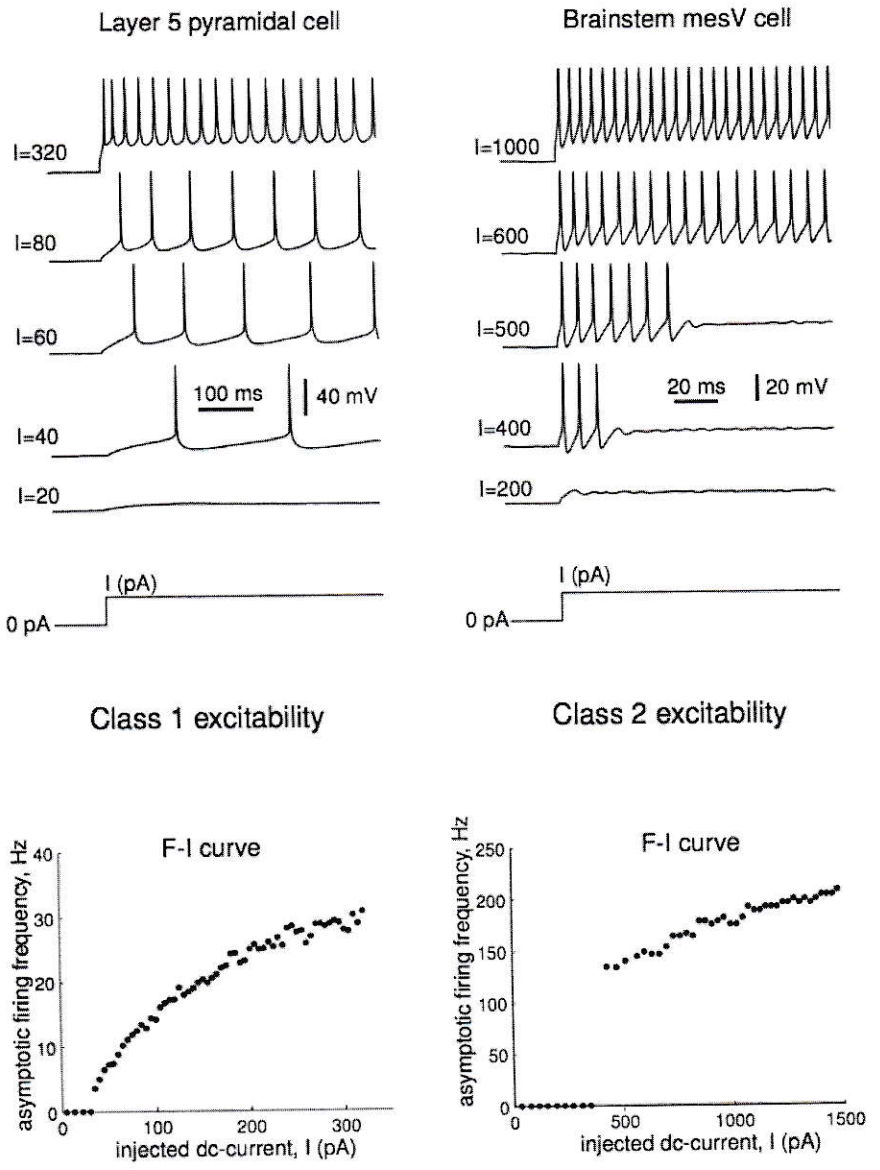


Figure 3: Class 1 and Class 2 excitability. An electrophysiological current clamp experiment where pyramidal neuron (left) and primary visual cortex neurons (right) are subjected to a protocol of steps of DC current. On the bottom we have the corresponding frequency-current (F-I) relations. Adapted from the book Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting (Izhikevich, 2010).

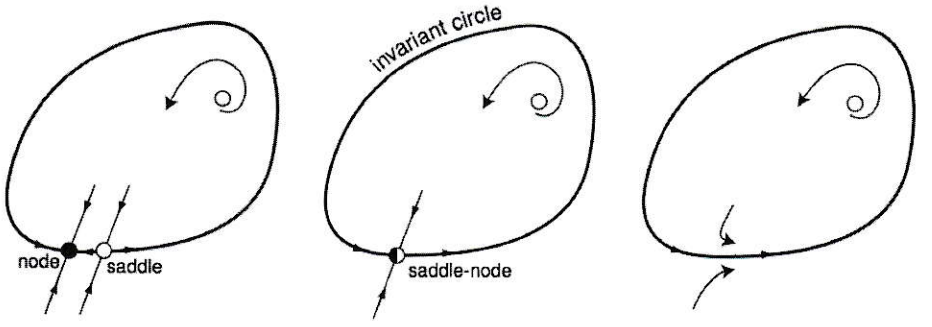


Figure 4: Typical Saddle-node homoclinic bifurcation in a single neuron model. This bifurcation is also called Saddle-node on an invariant circle (SNIC). Adapted from the book Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting (Izhikevich, 2010).

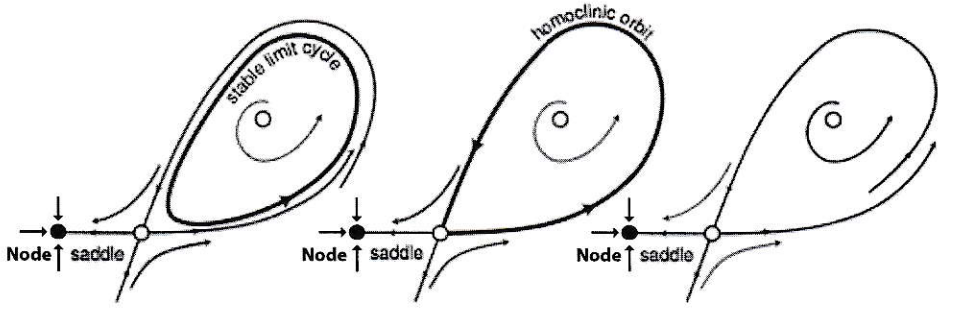


Figure 5: Typical Saddle homoclinic bifurcation in single neuron model. Note that for the bifurcation scenario one needs the saddle fixed point and the homoclinic connection, but in single neuron models there are often involved a node point and an unstable focus as the figure shows. Adapted from the book Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting (Izhikevich, 2010).

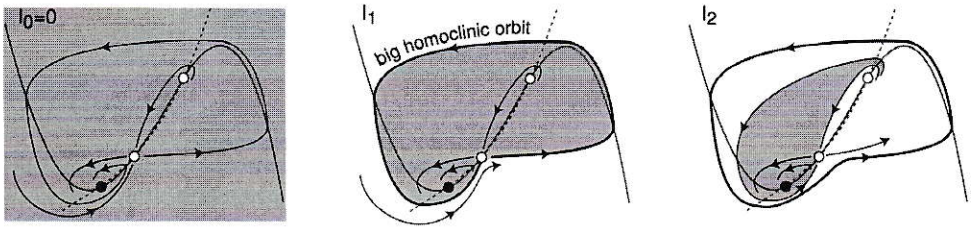


Figure 6: Typical Big homoclinic bifurcation in a single neuron model, the basin of attraction of the stable focus is in grey. Note that the bifurcation scenario occurs when the unstable manifold and the stable manifold connect in the same orbit and the homoclinic orbit formed traps the other ends of the unstable and stable manifolds of the saddle. In single neuron models there are often involved a stable focus and an unstable focus within the homoclinic connection as the figure shows. It also happens often in single neuron models, that after the homoclinic connection appears an heteroclinic separatrix which connects the stable manifold of the saddle point with the unstable focus forms a closed figure which separates the limit cycle and the stable focus, as is showed in the figure. Adapted from the book Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting (Izhikevich, 2010).

2.2 Minimal models

It is interesting that although there is a zoology of firing patterns, with the exception of the very particular dynamics observed in a few neurons called bursting, the dynamics observed in general can be reproduced with models of two differential equations. The literature refer to this models as the *minimal* models for neuronal dynamics because they are the models with the minimal number of variables that reproduce the dynamics observed in neurons. These can be phenomenological models[9] or reduced CB model. Some of the most famous two variable phenomenological models are the FitzHugh-Nagumo model (FitzHugh, 1961), the generalized FitzHugh-Nagumo model (Hindmarsh and Rose, 1982) or the minimal model of Izhikevich (Izhikevich, 2010). On the other hand, the CB models can reduce their dimensions (the number of equations) by different procedures. (Kepler et al., 1992; Izhikevich, 2010) The most common is the adiabatic elimination (Van Kampen, 1985). In fact, there exists also a zoology of two variables reduced CB models, but the most famous is the Morris-Lecar model (Morris and Lecar,

[9]A mathematical phenomenological model is a model that reproduce a phenomena observed in nature but which not have mechanistic ground that correlate the dynamics observed with the physical world.

1981), Appendix D.

3 Motivation and objectives

3.1 Motivation

There is a fundamental theoretical question still not answered: **which are the mathematical mechanisms by which neurons (described by CB models) display an universal[10] dynamics?** To address this question is in some sense to extract the *mathematical essence* of single neurons dynamics from the detailed biophysics (mathematically described by the CB models), and build a theoretical bridge between both.

3.2 Objectives

3.3 General objective

Our general objective is to understand the mathematical mechanisms by which neurons (described by CB models) display their robust dynamics and then to build a universal mathematical description for single neuron dynamics, relating phenomenological models with biophysical detailed CB models.

3.4 Specific objectives

- To study the mathematical structure of CB models. Study the appearance and disappearance of fixed points and the structure of the linear system around them.
- Answer the question: Is there a local bifurcation in CB models which can explain the universal planar dynamics observed in neurons? If yes then the objective is to study the mechanism through which this bifurcation appears naturally and to relate it to the mathematical structure of CB models.
- To study the dynamics of the normal form of this bifurcation and to relate it with the dynamics observed in CB models.

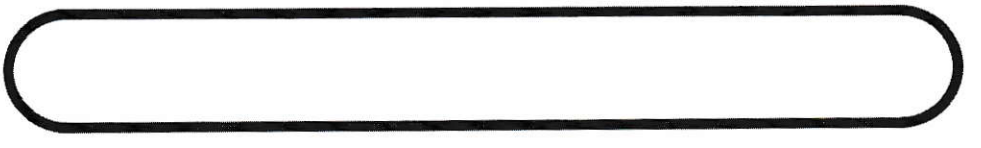
[10] In nonlinear dynamics an universal dynamics is a dynamic appear invariantly in nature under certain circumstances not matter the specific system. As discussed later this universality occur when a system is near to bifurcation.

- To build an interactive software specially costumed for the numerical study the original CB models, the normal form and the theoretical approximations simultaneously and in real time.
- To study how exceptions to this universal planar dynamics, which are not often observed in neurons, such as the bursting dynamics and chaos, can arise in CB models.
- To make biophysical interpretations of our theoretical results.

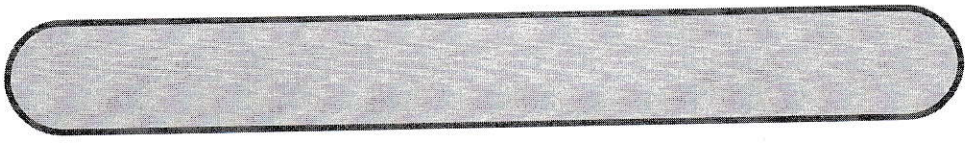
4 Thesis structure

This part (Part I) has introduced the necessary concepts of biophysics and neurophysiology to understand this thesis. In parts II, III and IV we present the results of this thesis. In Part II we characterize the mathematical structure of CB models and obtain an analytical expression for the characteristic polynomial of the linear matrix around a given fixed point. In the part III we use this previous result to show that CB models are generically in the unfolding of the Bogdanov-Takens instability, and show analytically and numerically that the subcritical Bogdanov-Takens normal form successfully describes the *excitable behaviour* observed in neurons. In Part IV we show that a CB model under the necessary biophysical conditions for bursting dynamics is in the unfolding of the Triple Zero bifurcation, and also show that the most famous model for bursting can be transformed to almost the Triple-Zero normal form. In Part V we present the conclusions and perspectives. In the appendices we give the detail of the calculations and the mathematical proofs.

In order to make this thesis more pedagogic, specially for readers of other backgrounds than physics or mathematics, we recall the most important mathematical results of a section within this frame:



We also present the particular mathematical expressions of our approach for the Morris-Lecar and Hodgkin and Huxley CB models within this frame:



Part II

Discovering the Mathematical Structure of Conductance Based Models

In this part we will show new general results obtained regarding the mathematical structure of the conductance based model. This results will be key to show our main results regarding these *universal* feature of single neuron dynamics.

5 The conductance based models

As we explain in the previous section, the dynamics of the membrane potential and the different ionic currents across the neuronal membrane is represented by a set of equations called conductance based models or CB models. As also discussed in the introduction this equations have strong biophysical and experimental substrate and reproduce the dynamics measured in any type of neuron of the nervous system. The CB models are a set of ODEs with $N+1$ independent variables. One of the variables represent the membrane voltage u (more precisely $u = u_{in} - u_{out}$ where u_{in} is the potential inside the cell and u_{out} the potential outside), and the other N variables represent the ionic channels gating variables m_j. This kind of systems can be written in a dimensionless form scaling the time and the variables. In this thesis we will refer to these models assuming that this has been done. In order to obtain general results applicable to all conductance based models, we will write the most general form for this set of models. Therefore, a CB model can be written in a general form as follows:

$$\begin{aligned} \dot{u} &= I - G(u, \vec{m}, \vec{\sigma}_T) \\ \dot{m}_j &= \frac{m_j^\infty(u, \vec{\sigma}_j) - m_j}{\tau_j(u, \vec{\sigma}_j)} \qquad j = 1, 2 \dots N \end{aligned} \tag{5.1}$$

As was explained in the section 1, the function $m_j^\infty(u, \vec{\sigma}_j)$ represent the stationary probability of a gating variable m_j to be *activated*, and $\tau_j(u, \vec{\sigma}_j)$ is its relaxation time to this stationary probability. Typically $m_j^\infty(u, \vec{\sigma}_j)$ and $\tau_j(u, \vec{\sigma}_j)$ depend on the potential and also on the same parameters $\vec{\sigma}_j$. The parameter I represents the injected current to the neuron and the function $G(u, \vec{m}, \vec{\sigma})$ represents the total ionic current. This last function depends on the parameters $\vec{\sigma}_T$ and has the general form:

$$G(u, \vec{m}, \vec{\sigma}) \equiv \sum_{j=1}^{n} I_j = \sum_{j=1}^{n} g_j \prod_{l \in w_j} m_l^{p_l}(u - u_j) \tag{5.2}$$

Each I_j represents a ionic current of a generic CB model. The ionic current I_j associated to a ionic conductance j can be written in general as:

$$I_j = g_j \prod_{l \in w_j} m_l^{p_l}(u - u_j) \tag{5.3}$$

where g_j is the maximal conductance and u_j is the reversal potential associated with the j^{th} current. Is important to note that for a given current I_j one has a set of gating variables W_j=$\{m_l, l \in w_j\}$, where w_j is a set of indices. Because each gating variable m_l represents the probability of a specific sub-unit of a given ionic channel j to be open, one cannot have the same gating variable in two different ionic currents. This restriction is based in the very nature of the ionic channels biophysics: the activity of one ionic channel does not directly affect the activity of another ionic channel (indirectly it does through the coupling with the potential u) since their mechanisms of opening and closing are not physically connected (Hille, 2001). This mathematically means that if one has n different ionic channels in a CB model then $W_1 \cap W_2 \cap \cdots \cap W_{n-1} \cap W_n = \phi$. This mathematical expression of a physical consideration will have a key importance to obtain further analytical results. One example of that is the Hodgkin and Huxley model where $G(u, m, n, h) = g_{Na} m^3 h(u - u_{Na}) + g_K n^4 (u - u_K) + g_L(u - u_L)$, and where it is clear that the variables for the sodium current m and h are not involved in the potassium current that have n as their unique gating variable.

5.1 CB model in standard form

We will introduce another form to write the CB models that we shall call *standard form*. If we do the following nonsingular translation $\vec{m} = \vec{m}^{\infty}(u, \vec{\sigma}) + \vec{x}$ the equation 5.1 becomes:

$$\begin{aligned} \dot{u} &= I - G(u, \vec{m}^{\infty} + \vec{x}, \vec{\sigma}_T) \\ \dot{x}_j &= -\frac{x_j}{\tau_j(u, \vec{\sigma})} - \frac{\partial m_j^{\infty}(u, \vec{\sigma})}{\partial u}\dot{u} \qquad j = 1, 2 \ldots N \end{aligned} \tag{5.4}$$

Using the definition 5.2 the total ionic current reads:

$$G(u, \vec{m}^{\infty} + \vec{x}, \vec{\sigma}_T) = \sum_{j=1}^{n} g_j \prod_{l \in w_j} \sum_{k_l=0}^{p_l} \binom{p_l}{k_l} x_l^{p_l - k_l} \left[m_l(u)^{\infty}\right]^{k_l} (u - u_j) \tag{5.5}$$

If we consider long times such that all the gating variables have relaxed ($\vec{x} = \vec{0}$), the ionic current written as 5.5 becomes stationary and will be

the same as the well-known I-v curve studied in electrophysiology (Latorre, 1996). We shall call $f(u, \vec{\sigma}_T)$ this ionic current. It is given by:

$$f(u, \vec{\sigma}_T) \equiv G(u, \vec{m}^{\infty}(u, \vec{\sigma_T}), \vec{\sigma}_T) = \sum_{j=1}^{n} g_j \prod_{l \in w^{(j)}} [m_l(u)^{\infty}]^{p_l} (u - u_j) \quad (5.6)$$

Some examples of this function in well-known models are:

Morris-Lecar model calculation 5.1.

$$f(u) = g_1 m^{\infty}(u)(u - u_1) + g_2 n^{\infty}(u)(u - u_2) + g_3(u - u_3)$$

Details in the appendix D.1

Hodgkin & Huxley model calculation 5.1.

$$f(u) = g_1 m^{\infty}(u)^3 h^{\infty}(u)(u - u_1) + g_2 n^{\infty}(u)^4 (u - u_2) + g_3(u - u_3)$$

Details in the appendix E.1

Note that because all the gating variables have relaxed the function $f(u)$ only depends on the potential u. Now if we define $K(u, \vec{x}, \vec{\sigma}_T)$ as the part of the total current which depends on u and $\vec{x}$, i.e. $K(u, \vec{x}, \vec{\sigma}_T) = G(u, \vec{m}^{\infty} + \vec{x}, \vec{\sigma}_T) - f(u, \vec{\sigma}_T)$, one has:

$$K(u, \vec{x}, \vec{\sigma}_T) = \sum_{j=1}^{n} g_j \prod_{l \in w_j} \sum_{k_l=0}^{p_l - 1} \binom{p_l}{k_l} x_l^{p_l - k_l} [m_l(u)^{\infty}]^{k_l} (u - u_j) \quad (5.7)$$

In the models above one has:

Morris-Lecar model calculation 5.2.

$$K(u,x) = g_1 x(u-u_1)$$

Details in the appendix D.1

Hodgkin & Huxley model calculation 5.2.

$$K(u,x_1,x_2,x_3) = g_1\left\{x_1^3x_2 + 3x_1^2m^\infty(u)x_2 + 3x_1m^\infty(u)^2x_2 + m^\infty(u)^3x_2 + x_1^3h^\infty(u) + 3x_1^2m^\infty(u)h^\infty(u) + 3x_1m^\infty(u)^2h^\infty(u)\right\}(u-u_1) + g_2\left\{x_3^4 + 4x_3^3n^\infty(u) + 6x_3^2n^\infty(u)^2 + 4x_3n^\infty(u)^3\right\}(u-u_2)$$

Details in the appendix E.1

Note that the function $f(u,\vec{\sigma}_T)$ and the function $K(u,\vec{x},\vec{\sigma}_T)$ depend on the same set of parameters $\vec{\sigma}_T$. We define:

$$\beta_j(u,\vec{\sigma}_j) \equiv -\frac{\partial m_j^\infty(u,\vec{\sigma}_j)}{\partial u} \tag{5.8}$$

Due to the form of $m_j^\infty(u,\vec{\sigma}_j)$ which is a strictly incrteasing (or decreasing) function of u one has that $\beta_j(u,\vec{\sigma}_j)$ is strictly positive (or negative).

The equation 5.4 reads now:

$$\begin{aligned}\dot{u} &= I - f(u,\vec{\sigma}_T) - K(u,\vec{x},\vec{\sigma}_T)\\ \dot{x_j} &= -\frac{x_j}{\tau_j(u,\vec{\sigma}_j)} + \beta_j(u,\vec{\sigma}_j)\dot{u} \qquad j = 1,2\ldots N\end{aligned} \tag{5.9}$$

This last equation is a CB model written in its standard form. In this form the reader can see that the dynamics of each gating variable m_j is a exponential decay to its stationary value (which corresponds to $x_j = 0$) plus a perturbation that is the derivative of the potential weighted by the derivative with respect to u of the stationary function. The fixed points $\{u^*,\vec{x}_j\}$ of this equation are:

$$
\begin{aligned}
I &= f(u^*, \vec{\sigma}_T) \\
\vec{x} &= \vec{0}
\end{aligned} \tag{5.10}
$$

and they have a very intuitive physical interpretation: a fixed point in a CB model occurs when all the gating variables have relaxed to their stationary value and when there is no net flux of current through the neuron membrane. It is important to note that mathematically the *location* of the fixed point as functions of the parameters depends only on the function $f(u^*, \vec{\sigma}_T)$. Therefore, in the CB models very important events from the point of view of bifurcation theory as the appearance or disappearance of fixed points depend exclusively of the function $f(u^*, \vec{\sigma}_T)$.

In the figure 7 the lector can see the functions $\tau(u)$, $m^\infty(u)$, $\beta(u)$ and $f(u)$ for the Morris-Lecar and Hodgkin and Huxley model. The functions $\tau(u)$, $m^\infty(u)$, $\beta(u)$ will be qualitatively the same for all CB models or simplified versions of them (Izhikevich, 2010). The function $f(u)$ will have the same shape for very negative or very positive large values for all CB models. In both cases it approximates asymptotically a straight line as it can be seen in figure 7. This is because the functions $m^\infty(u)$ take values of 0 or 1 asymptotically and consequently the function $f(u)$ for $u \to \pm\infty$ will approximate to a straight line whos slope will be the sum the conductances of the currents that do not have a gating variable which goes to zero probability. But it is *in a central interval* (i.e. between the two asymptotic behaviors) of the variation of u where the function $f(u)$ can have different shapes for different models leading to one, three, or in peculiar cases five roots, of the equation $I - f(u^*, \vec{\sigma}_T) = 0$.

The standard forms of the previous models are:

Morris-Lecar model calculation 5.3. Morris-Lecar model in their Standard form:

$$
\begin{aligned}
\dot{u} &= I - f(u) - K(u, x) \\
\dot{x} &= -\frac{x}{\tau(u)} + \beta(u)\dot{u}
\end{aligned}
$$

Details in the appendix D.1

Hodgkin & Huxley model calculation 5.3. Hodgkin and Huxley model in their natural form:

$$\begin{aligned}
\dot{u} &= I - f(u) - K(u, x_1, x_2, x_3) \\
\dot{x_1} &= -\frac{x_1}{\tau_m(u)} + \beta_1(u)\dot{u} \\
\dot{x_2} &= -\frac{x_2}{\tau_h(u)} + \beta_2(u)\dot{u} \\
\dot{x_3} &= -\frac{x_3}{\tau_n(u)} + \beta_3(u)\dot{u}
\end{aligned}$$

Details in the appendix E.1

6 On the linear structure around a fixed point

In this section we shall study the linear system, specifically the structure of the linear matrix, of a CB model in its standard form around a stable fixed point. As Elphick-Tirapegui-Brachet-Coullet-Iooss theorem stated in their famous 1987 paper (Elphick et al., 1987; Haragus and Iooss, 2011; Wiggins, 2003), that the form of all the non linear terms arising in the normal form of any local bifurcation of a stable fixed point is determined by the linear critical part of the system. More explicitly one has to study the system linearized around the fixed point and then study the linear matrix to determine when the fixed point will loose its stability through variation of the parameters. When this happens one says that one is in a critical situation and the number of critical variables is determined by the dimension of the linearly unstable space. The linear matrix restricted to this space completely determines the nonlinear resonant terms which can come in the normal form. The first step then in the reduction to the normal form is to calculate the coefficients of this nonlinear terms since their form is already known. The reduction to the normal form involves a reduction of the number of variables of the original problem to the critical values which are in general quite less (the dimension of the critical space) and one then has to express all the original physical variables in terms of the new critical variables: the functions realizing this are called the ansatz, i. e. the explicit expression of the old physical variables in terms of the critical values which are the ones appearing in the normal form. Normally the linear part of the ansatz, which is determined by the eigenvectors of the critical linear part of the system,

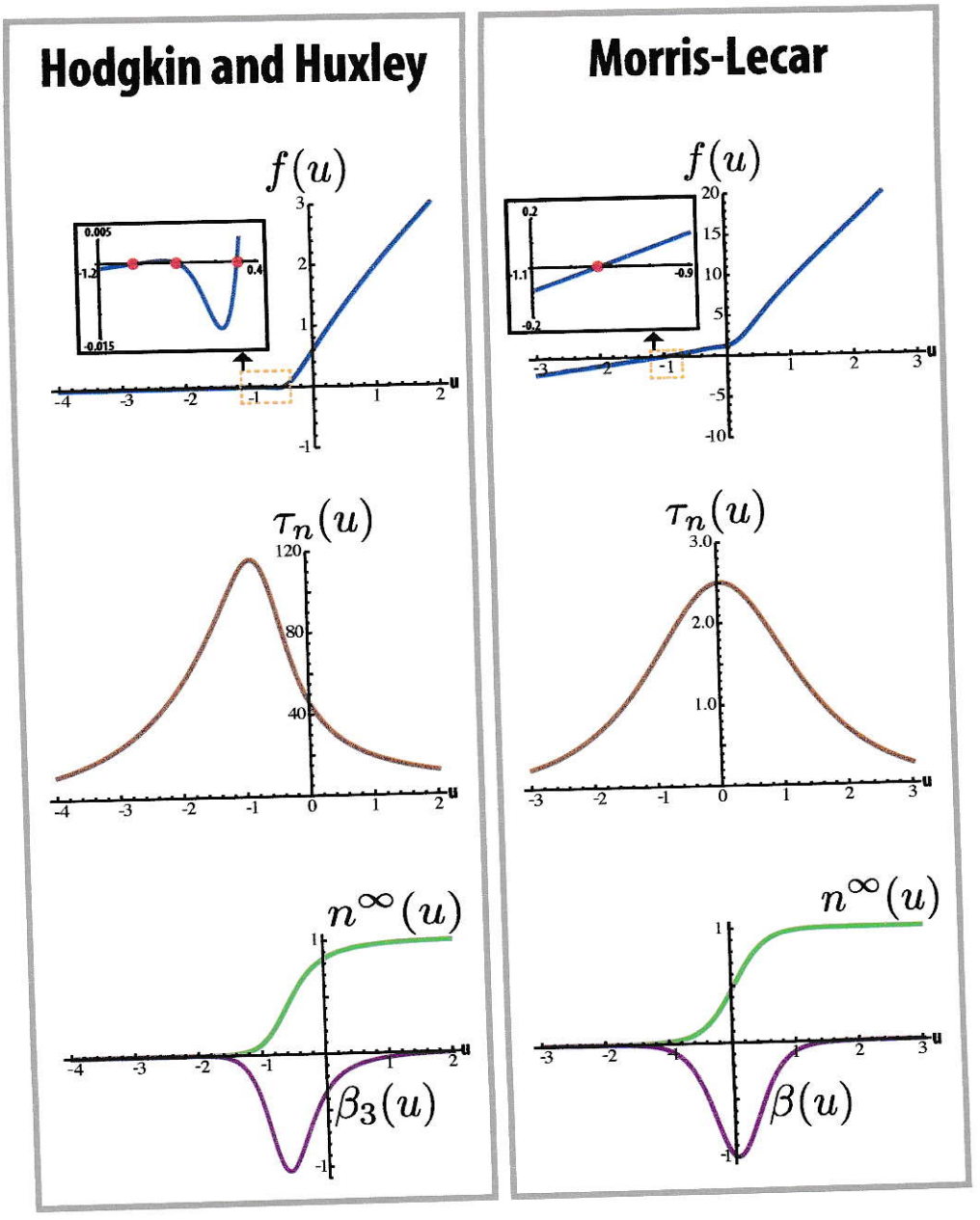


Figure 7: The functions $f(u)$, $n^\infty(u)$, $\beta(u)$ and $\tau_n(u)$ for the Morris-Lecar model (left) and the Hodgkin and Huxley model (right).

gives the relevant physical information relating the physical variables to the ones of the standard normal form, and in that sense one can say that all the specific physical content of the problem is contained in the "ansatz". Once all this has been done the next step is to move away from the critical point varying slightly the parameters around their critical values: this is called the unfolding and it is here that the codimension of the bifurcations appears in a transparent way since it is just the number of independent parameters needed to move away from the critical point in the space of parameters. Therefore is of capital importance in this work — in order to find the *universal equations* or normal form that reproduce the dynamics observed in neurons— to characterise the linear system of a CB model.

We have shown in the previous section that the fixed points must satisfy $\vec{x} = 0$ and $I = f(u, \vec{\sigma}_T)$. This equation for conductance based models has at least one root because the function $f(u, \vec{\sigma}_T)$ for $u \to \pm\infty$ can only have negative slope (because the conductances g_j are always positive quantities) but generically more than one (see figure 7). As also discussed in the previous section, the existence or disappearance of fixed points depends only on the equation $I = f(u, \vec{\sigma}_T)$. Moreover, this fact enables us to choose a root u of this equation as a continuos parameter of bifurcation instead of the parameter I as long as we stay in the same branch of the solution. Taking the last point into account, we will consider a fixed point $(u^*, \vec{0})$, were $I^* = f(u^*, \vec{\sigma}_T)$. Thus, by doing the standard translations in the neighborhood of the fixed point ($\vec{x} = \vec{0} + \bar{\vec{x}}$ and $u = u^* + \bar{u}$) we find that the linear matrix has the form:

$$\mathbb{L} = \mathbb{A} \oplus \left[\vec{\beta} \otimes \vec{M}^T\right] \tag{6.1}$$

Where

$$\mathbb{A}(u^*, \vec{\sigma}_T) = -\begin{pmatrix} 0 & 0 & \dots & 0 \\ 0 & \frac{1}{\tau_1(u^*, \vec{\sigma}_1)} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \frac{1}{\tau_N(u^*, \vec{\sigma}_N)} \end{pmatrix} \tag{6.2}$$

$$\vec{\beta}(u^*, \vec{\sigma}_T) = -\begin{pmatrix} -1 \\ \frac{\partial m_1^\infty(u, \vec{\sigma}_1)}{\partial u} \\ \vdots \\ \frac{\partial m_N^\infty(u, \vec{\sigma}_N)}{\partial u} \end{pmatrix}_{u=u^*} \tag{6.3}$$

$$\vec{M}(u^*, \vec{\sigma}_T) = -\left(\begin{array}{c} \frac{\partial f(u,\vec{\sigma}_T)}{\partial u} \\ \frac{\partial G(u,\vec{x},\vec{\sigma}_1)}{\partial x_1} \\ \vdots \\ \frac{\partial G(u,\vec{x},\vec{\sigma}_N)}{\partial x_N} \end{array} \right)_{u=u^*;\vec{x}=\vec{0}} \tag{6.4}$$

defining:

$$M_s(u^*, \vec{\sigma}_T) \equiv -\left. \frac{\partial G(u,\vec{m},\vec{\sigma}_T)}{\partial m_s} \right|_{u=u^*,\vec{m}=\vec{m}^\infty(u^*,\vec{\sigma_T})} = -\left. \frac{\partial K(u,\vec{x},\vec{\sigma}_T)}{\partial x_s} \right|_{u=u^*,\vec{x}=0} \tag{6.5}$$

which gives

$$M_s = -g_j p_s \prod_{l \in w_j} [m_l (u^*)^\infty]^{p_l - \delta_{l,s}} \, (u^* - u_j)$$

In our models we obtain:

Morris-Lecar model calculation 6.1.

$$\begin{aligned} M_1(u) &= -g_1(u - u_1) \\ M_2(u) &= -g_2(u - u_2) \end{aligned}$$

Note that we considered the equation in Morris and Lecar (1981) before the adiabatic elimination.

Hodgkin & Huxley model calculation 6.1.

$$\begin{aligned} M_1(u) &= -3g_1 m^\infty(u)^2 h^\infty(u)(u - u_1) \\ M_2(u) &= -g_1 m^\infty(u)^3 (u - u_1) \\ M_3(u) &= -4g_2 n^\infty(u)^3 (u - u_2) \end{aligned}$$

and:

$$\alpha_s(u^*, \vec{\sigma}_j) \equiv -\frac{1}{\tau_s(u^*, \vec{\sigma}_j)} \tag{6.6}$$

We shall call the matrices which have the form 6.1 **neuronal matrices.** The neuronal matrices have the form of the direct sum of two matrices: a diagonal matrix $\mathbb{A}$ ($A_{ij} = \alpha_i \delta_{ij}$) plus a matrix $C = \left[\vec{\beta} \otimes \vec{M}^T\right]$ which results from the tensorial product of a column vector $\vec{\beta}$ of components β_j and a row vector $\vec{M}$ of components M_j ($C_{ij} = M_j \beta_i$). In the next section we will prove an important theorem which allows us to find an explicit analytical expression for all the coefficients of the characteristic polynomial of this kind of matrices and consequently for all CB models.

Remark 6.1. The linear matrix of any CB model can be written as:

$$\mathbb{L} = \mathbb{A} \oplus \left[\vec{\beta} \otimes \vec{M}^T\right]$$

Where $\mathbb{A}$, $\vec{\beta}$ and $\vec{M}$ are defined in 6.2, 6.3 and 6.4 respectively.

7 Neuronal matrices and their properties

Here we shall study the properties of the neuronal matrices. In particular we shall find explicit analytical expressions for the coefficients of the characteristic polynomial of these matrices. This result will be fundamental in our argumentation to find a universal equation which describes the generic features of neuronal dynamics, but it has of course an interest per se. The following steps are completely general and depend only on the particular structure of these special matrices.

Definition of Neuronal Matrices 7.1. Given a $n \times n$ diagonal matrix $\mathbb{A}$ and two vectors $\vec{\beta}$ and $\vec{M}$ of n components a Neuronal Matrix $\mathbb{N}$ is defined as:

$$\mathbb{N} = \mathbb{A} \oplus \left[\vec{\beta} \otimes \vec{M}^T\right] \tag{7.1}$$

which can be written in an explicit form as:

$$\mathbb{N} = \begin{pmatrix} \alpha_1 + \beta_1 M_1 & \beta_1 M_2 & \dots & \beta_1 M_n \\ \beta_2 M_1 & \alpha_2 + \beta_2 M_2 & \dots & \beta_2 M_n \\ \vdots & \vdots & \ddots & \vdots \\ \beta_n M_1 & \beta_n M_2 & \dots & \alpha_n + \beta_n M_n \end{pmatrix} \tag{7.2}$$

We shall call the matrix $\mathbb{A}$ the self-interaction matrix and their diagonal components α_j the self-interaction terms. We will called the vector $\vec{\beta}$ the bias vector and its components β_j the bias terms. We will called the vector $\vec{M}$ the interaction vector and their components M_j the interaction terms.

Physical note 7.1. In figure 8 we show an example of the graph representation of a 3×3 neuronal matrix. In this graph representation we note that each i node interact with the other nodes by the terms M_k weighted by its own β_i coefficient. The term β_i is a *bias term* in the sense that its sign depends on the *kind* of interaction with the other nodes, and its value determines the strength of the interaction with all the nodes of the system. This is the reason why we called M_j the interaction terms and β_j the bias term. In the case of CB models this can be interpreted physically saying that at linear order the interaction between a variable x_i with all the variables x_k is via M_k —which qualitatively represents the current associated with the k^{th} ionic channel — weighted by the derivative of their own stationary function β_i. This means that the sign of β_i and its current value is very important in the interaction of the i^{th} gating variable with the complete system. It is also important to note that each node interacts with itself through the α_i plus its own M_i weighted by its own β_i. In the case of neurons the α_i interaction is the inverse of the time of the exponential decay to the stationary value $(-1/\tau_i)$ and the M_i represents the interaction associated with its own ionic current activity wighted by the term $-\frac{\partial m_i(u)^\infty}{\partial u}$.

Theorem 7.1. *Let $\mathbb{N}$ be an $n \times n$ Neuronal Matrix with self-interaction matrix $\mathbb{A}$, bias vector $\vec{\beta}$ and interaction vector $\vec{M}$. Its determinant is given by:*

$$Det(\mathbb{N}) = \prod_{j=1}^{n} \alpha_j + \sum_{i=1}^{n} \beta_i M_i \prod_{s \neq i}^{n} \alpha_s \tag{7.3}$$

The proof is in the section A.1

Corollary 7.1. *The characteristic polynomial $P(\lambda)$ is given by the general*

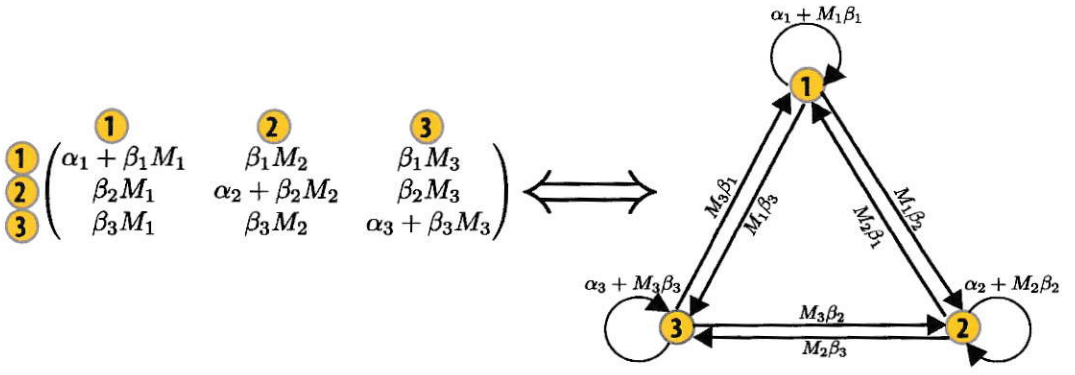


Figure 8: Graph representation the neuronal matrices and their Adjacency matrix.

formula:

$$P(\lambda) = \prod_{j=1}^{n}(\alpha_j - \lambda) + \sum_{i=1}^{n}\beta_i M_i \prod_{s\neq i}^{n}(\alpha_s - \lambda) \tag{7.4}$$

Proof. Using the expression for the determinant of a neuronal matrix proved in the theorem 7.1 and doing the translation $\alpha \to \alpha - \lambda$ we trivially obtain the characteristic polynomial. □

Corollary 7.2. *Each coefficient a_j of the characteristic polynomial $P(\lambda) = \sum_{j=0}^{n} a_j \lambda^j$ of a neural matrix is given by:*

$$a_j = (-1)^j \sum_{l_1\neq l_2\cdots\neq l_j}^{n} \prod_{i\neq l_j}^{n} \alpha_i + \sum_{s=0}^{n}\beta_s M_s \sum_{\hat{l}_1\neq\cdots\neq\hat{l}_{j-1}\neq s}^{n} \prod_{i\neq\hat{l}_{j-1}\neq s}^{n} \alpha_i \tag{7.5}$$

Proof. Using the expression for the characteristic polynomial 7.4 it is easy to verify the previous expression 7.5 for a_j. □

Remark 7.1. The characteristic polynomial of a $n \times n$ Neuronal Matrix with: $\mathbb{A}$ their self-interaction matrix, $\vec{\beta}$ their bias vector and $\vec{M}$ their interaction vector is given by:

$$P(\lambda) = \prod_{j=1}^{n}(\alpha_j - \lambda) + \sum_{i=1}^{n}\beta_i M_i \prod_{s\neq i}^{n}(\alpha_s - \lambda)$$

8 First and second coefficients for the characteristic polynomial of CB models

As we discussed in section 6 the linear matrix ($\mathbb{L}$) of any CB model can be written as:

$$\mathbb{L} = \begin{pmatrix} \alpha_0 + \beta_0 M_0 & \beta_0 M_1 & \dots & \beta_0 M_N \\ \beta_1 M_0 & \alpha_1 + \beta_1 M_1 & \dots & \beta_1 M_N \\ \vdots & \vdots & \ddots & \vdots \\ \beta_N M_0 & \beta_N M_1 & \dots & \alpha_N + \beta_N M_N \end{pmatrix} = \mathbb{A} \oplus \left[\vec{\beta} \otimes \vec{M}^T\right] \tag{8.1}$$

with:

$$\begin{array}{rclrcl} \beta_0 &=& 1 & \beta_j &=& -\left.\frac{\partial m_j^{\infty}(u,\vec{\sigma}_j)}{\partial u}\right|_{u=u^*} \\ \alpha_0 &=& 0 & \alpha_j &=& -\frac{1}{\tau(u^*,\vec{\sigma}_j)} \\ M_0 &=& -\left.\frac{\partial f(u,\vec{\sigma}_T)}{\partial u}\right|_{u=u^*} & M_j &=& -\left.\frac{\partial G(u,\vec{x},\vec{\sigma}_T)}{\partial x_j}\right|_{u=u^*;\vec{x}=\vec{0}} \end{array} \tag{8.2}$$

Then, using expression 7.4 the characteristic polynomial for any CB model can be written as:

$$P(\lambda) = -\lambda\left[\prod_{j=1}^{N}(\alpha_j - \lambda) + \sum_{s=1}^{N}\beta_s M_s \prod_{l\neq s}^{N}(\alpha_l - \lambda)\right] + \beta_0 M_0 \prod_{l=1}^{N}(\alpha_l - \lambda) \tag{8.3}$$

Writing the characteristic polynomial in the form $P(\lambda) = \sum_{k=0}^{N+1} a_k \lambda^k$ we obtain for a_0

$$a_0 = \beta_0 M_0 \prod_{l=1}^{N} \alpha_l = (-1)^{N+1} \left. \frac{\partial f(u, \vec{\sigma}_T)}{\partial u} \right|_{u=u^*} \prod_{l=1}^{N} \frac{1}{\tau_l(u^*, \vec{\sigma}_l)} \tag{8.4}$$

and for a_1

$$\begin{aligned} a_1 = &- \left[\prod_{l=1}^{N} \alpha_l + \sum_{s=1}^{N} \beta_s M_s \prod_{j \neq s}^{N} \alpha_j + \beta_0 M_0 \sum_{i=1}^{N} \prod_{k \neq i}^{N} \alpha_k \right] = (-1)^{N+1} \prod_{l=1}^{N} \frac{1}{\tau_l(u^*, \vec{\sigma}_l)} \\ &+ (-1)^N \sum_{s=1}^{N} \beta_s(u^*, \vec{\sigma}_s) M_s(u^*, \vec{\sigma}_T) \prod_{j \neq s}^{N} \frac{1}{\tau_j(u^*, \vec{\sigma}_j)} \\ &+ (-1)^{N+1} \left. \frac{\partial f(u, \vec{\sigma}_T)}{\partial u} \right|_{u=u^*} \sum_{i=1}^{N} \prod_{k \neq i}^{N} \frac{1}{\tau_k(u^*, \vec{\sigma}_k)} \end{aligned} \tag{8.5}$$

Remark 8.1. The characteristic polynomial of any conductance base model can be written as:

$$P(\lambda) = -\lambda \left[\prod_{j=1}^{N} (\alpha_j - \lambda) + \sum_{s=1}^{N} \beta_s M_s \prod_{l \neq s}^{N} (\alpha_l - \lambda) \right] + \beta_0 M_0 \prod_{l=1}^{N} (\alpha_l - \lambda)$$

With α, β and M defined in 8.2.

Part III

Toward a Universal Description for Single Neuron Dynamics

9 The Bogdanov-Takens Bifurcation

Since the Bogdanov-Takens bifurcation (Bogdanov, 1975; Takens, 1974) will play a central role in what follows we shall make here some general considerations about its principal characteristics. It is a codimension two bifurcation which means that one has to move two parameters of the dynamical system in order to put the system described by the dynamical system at the instability. This instability of an stable fixed point arises as follows: 1) First we are in a situation where the fixed point of interest is stable, i.e. when one linearize around this fixed point and considers the linear terms one has that the matrix defined by the linearization has all its eigenvalues with negative real parts; 2) We move in the space of parameters of the system. Then the eigenvalues of the matrix which are functions of the parameters move and we look for a situation where two eigenvalues go to zero generating in the characteristic polynomial of the matrix an eigenvalue zero of multiplicity two. In order to achieve this one has to impose two conditions on the parameters (codimension two) and generically one will have only one eigenvector, i.e. a Jordan block of order two. However one has to check this last fact separately since in a defined problem the linear matrix can have particular characteristics which can change the scenario. In the case of the conductance based (CB) models which are studied in this thesis we have studied this carefully and we have explicitly calculated the basis vectors which generate the Jordan block. The point in the space of parameters where the double zero is realised is what we call the critical point and when we write the dynamical system for the values of the parameters corresponding to this point we speak of the critical equation (there can be of course a manifold of critical points but this does not change the essential points we want to explain here); 3) The next step is to see what happens around the critical point, i.e. what happens when one in a loose sense crosses the critical point in the space of parameters and when one expects that the eigenvalues which were zero create a positive real part and generate modes which are now linearly unstable. These modes become new variables which are what we call the critical variables and have to be saturated by nonlinear terms and when one is in this region around the critical point one says that one is in the unfolding if the bifurcation; 4) The behaviour of the system in terms of the critical variables in a neighbourhood of the critical point, i.e. is in the unfolding, is what is described by the normal form of the bifurcation, which is the a set of differential equations for the critical variables, in this case two variables. In the normal form we can see how the unstable modes are saturated by nonlinear terms and this balance is precisely what tells us the polynomial

order where we have to stop the nonlinear terms, this of course is seen in the normal form with its unfolding terms. It is also important to remark that we can study in the normal form the appearance of secondary instabilities and the occurrence of global bifurcations and check the self-consistence of what we are discovering. Although the normal form is strictly valid only in a small neighbourhood of the critical point one can expect that it will continue to be valid qualitatively in a much bigger domain of the space of parameters, in fact the region in which no new instability not contained in the normal form appears.

All these characteristics will be used extensively in this thesis.

10 The Bogdanov-Takens normal form

When any dynamical system undergoes a local bifurcation, we can write analytically an equation that describes asymptotically for large times the dynamics of the system in the neighbourhood of the bifurcation, this equation is called normal form and it is a universal equation which depends only on the type of local bifurcation. The specific physical case one is studying only determines the values of the coefficients of the terms in the normal form which are monomials of different degrees. The variables of the normal form (the critical variables) are usually much less than the original variables. The original variables are expressed in terms of the variables of the normal form in a formal series which starts with linear terms, when one is in the critical point, followed by quadratic terms, cubic terms, etc. When one moves away from the critical point in the space of parameters, i.e. when one considers the unfolding of the singularity, new correction terms appear in the expressions of the physical variables in terms of the critical variables. Usually the linear terms are the essential ones and most the physics of the problem is there since they give explicitly, at the dominant order, the original physical variables in terms of the variables of the normal form (Elphick et al., 1987; Haragus and Iooss, 2011). Then, very different dynamical systems (near to a given bifurcation) will be described for the same normal form. Although this result is strictly true infinitesimally near of the bifurcation, which is a point in the space of parameters, it occurs often that the qualitative aspects of the behavior of the system is still given by the normal form even if one is outside of the small neighborhood of the bifiurcation point. This just reflects the fact that the qualitative behavior of the system does not change until one finds a new critical point in the space of parameters, i.e. a new bifurcation point. Therefore, we can use this method to understand and

describe qualitatively the dynamics of a particular physical systems when are not strictly in the neighborhood of a particular bifurcation but in certain range of parameters near the critical point.

10.1 The resonant terms

As showed in their famous paper Elphick et al. (1987), using the inner product that the authors define, we can write the adjoint of the homologic operator ($\mathcal{A}(\hat{\mathbb{J}}^c)$) of any dynamical system as the homologic operator of the adjoint of the critical linear matrix, i.e. ($\mathcal{A}(\hat{\mathbb{J}}^c)^\dagger = \mathcal{A}([\hat{\mathbb{J}}^c]^\dagger)$). Therefore, using this inner product and knowing the form of the linear matrix operator in a given basis projected in the critical subspace ($\hat{\mathbb{J}}^c$) we can find all the terms of the normal form of a given bifurcation. When one works in the basis in which the original critical linear matrix is in Jordan form the homologic operator has the form:

$$\mathcal{A}(\hat{\mathbb{J}}^c) = \mathbb{J}^c_{\alpha,\beta} c_\beta \frac{\partial}{\partial c_\alpha} - \hat{\mathbb{J}}^c \tag{10.1}$$

And the the adjoint of the homologic operator $\mathcal{A}(\hat{\mathbb{J}}^c)$ is:

$$\mathcal{A}(\hat{\mathbb{J}}^c)^\dagger = (\mathbb{J}^c_{\beta,\alpha})^* c_\alpha \frac{\partial}{\partial c_\beta} - (\hat{\mathbb{J}}^c)^\dagger \tag{10.2}$$

Where c_α are the variables of the normal form. In the case of Bogdanov-Takens the operator $\hat{\mathbb{J}}^c$ has the form:

$$\mathbb{J}^c = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} \tag{10.3}$$

Then the adjoint of the homologic operator reads:

$$\mathcal{A}(\hat{\mathbb{J}}^c)^\dagger = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} c_1 \frac{\partial}{\partial c_2} - \begin{bmatrix} 0 & 0 \\ 1 & 0 \end{bmatrix} \tag{10.4}$$

Therefore, if the vector $\underline{\chi}(c_1, c_2) = \begin{pmatrix} \chi_1(c_1, c_2) \\ \chi_2(c_1, c_2) \end{pmatrix}$ is an element of the kernel of the adjoint of the homologic operator, then:

$$\begin{aligned} c_1 \tfrac{\partial \chi_1(c_1,c_2)}{\partial c_2} &= 0 \\ c_1 \tfrac{\partial \chi_2(c_1,c_2)}{\partial c_2} &- \chi_1(c1, c2) = 0 \end{aligned}$$

Is straightforward to show that at order m in the components (c_1, c_2) the vector $\underline{\chi}(c_1, c_2)$ has the form:

$$\begin{aligned}\chi_1(c_1, c_2) = &\ c_1\psi^{(m-1)}(c_1)\\ \chi_2(c_1, c_2) = &\ c_2\psi^{(m-1)}(c_1) + \varphi^{(m)}(c_1)\end{aligned}$$

where $\varphi^{(m)}(c_1)$ is a monomial in c_1 of order m and $\psi^{(m-1)}(c_1)$ is a monomial in c_1 of order $m-1$. Therefore, the Kernel of the homologic operator for the Bogdanov-Takens bifurcation written in the Jordan basis is:

$$\text{Kernel}_{BT}\left[\mathcal{A}(\hat{\mathbb{J}}^c)^\dagger\right] = \left\{\psi^{(m-1)}(c_1)\begin{pmatrix} c_1 \\ c_2 \end{pmatrix}, \varphi^{(m)}(c_1)\begin{pmatrix} 0 \\ 1 \end{pmatrix}\right\} \qquad (10.5)$$

To obtain the normal form we must impose the general solubility condition for linear equations of the form $A\vec{x} = \vec{b}$ where A is a linear operator in a finite-dimensional vector space (a matrix), $\vec{x}$ the unknown vector and $\vec{b}$ a given vector. This condition (Fredholm alternative) is that $\vec{b}$ must be orthogonal to the adjoint A^* of A in any nondegenerate scalar product defined in the vector space. In our case we have two critical variables (c_1, c_2) and the original physical variables of the CB models $\underline{V} = (u, x_1, x_2, \ldots, x_N)$ are expressed in terms of (c_1, c_2) in a series of the form $\underline{V} = \underline{U}^{[1]}(c_1, c_2) + \underline{U}^{[2]}(c_1, c_2) + \underline{U}^{[3]}(c_1, c_2) + \ldots$ where $\underline{U}^{[r]}(c_1, c_2)$ is a vector whose components are polynomials of order r in the variables (c_1, c_2), and at each polynomial order r we have to solve the homological equation $\mathcal{A}(\hat{\mathbb{J}}^c)\underline{U}^{[r]}(c_1, c_2) = \underline{I}^{[r]}(c_1, c_2) - \underline{f}^{[r]}(c_1, c_2)$, $r = 1, 2, \ldots$ where $\underline{I}^{[r]}(c_1, c_2)$ is a known vector determined by the previous orders and $\underline{f}^{[r]}(c_1, c_2) = \begin{pmatrix} f_1^{[r]}(c_1, c_2) \\ f_2^{[r]}(c_1, c_2) \end{pmatrix}$ are unknown and in fact they determine the r^{th} polynomial order in the differntial equations of the normal form which are

$$\begin{aligned}\partial_t c_1 &= f_1^{[1]}(c_1, c_2) + f_1^{[2]}(c_1, c_2) + f_1^{[3]}(c_1, c_2) + \ldots\\ \partial_t c_2 &= f_2^{[1]}(c_1, c_2) + f_2^{[2]}(c_1, c_2) + f_2^{[3]}(c_1, c_2) + \ldots\end{aligned}$$

$\underline{I}^{[n]}$ and $\underline{f}^{[n]}$ have the form:

$$\underline{I}^{[n]} = \begin{pmatrix} \sigma_{n,0}^{(1)}c_1^n + \sigma_{n-1,1}^{(1)}c_1^{n-1}c_2 + \cdots\cdots + \sigma_{1,n-1}^{(1)}c_1c_2^{n-1} + \sigma_{0,n}^{(1)}c_2^n \\ \sigma_{n,0}^{(2)}c_1^n + \sigma_{n-1,1}^{(2)}c_1^{n-1}c_2 + \cdots\cdots + \sigma_{1,n-1}^{(2)}c_1c_2^{n-1} + \sigma_{0,n}^{(2)}c_2^n \end{pmatrix}$$

$$\underline{f}^{[n]} = \begin{pmatrix} \nu_{n,0}^{(1)}c_1^n + \nu_{n-1,1}^{(1)}c_1^{n-1}c_2 + \cdots\cdots + \nu_{1,n-1}^{(1)}c_1c_2^{n-1} + \nu_{0,n}^{(1)}c_2^n \\ \nu_{n,0}^{(2)}c_1^n + \nu_{n-1,1}^{(2)}c_1^{n-1}c_2 + \cdots\cdots + \nu_{1,n-1}^{(2)}c_1c_2^{n-1} + \nu_{0,n}^{(2)}c_2^n \end{pmatrix}$$

With $\sigma_{n-j,j}^{(1,2)}$ and $\nu_{n-j,j}^{(1,2)}$ coefficients of the monomial in c_1 and c_2. The functions $(f_1^{[m]}(c_1,c_2), f_2^{[m]}(c_1,c_2))$ are determined by the soulubility condition applied to the linear homological equation through the equations

$$\left\langle \underline{I}^{(m)} - \underline{f}^{(m)}, \psi^{(m-1)}(c_1) \begin{pmatrix} c_1 \\ c_2 \end{pmatrix} \right\rangle = 0 \tag{10.6}$$

$$\left\langle \underline{I}^{(m)} - \underline{f}^{(m)}, \varphi^{(m)}(c_1) \begin{pmatrix} 0 \\ 1 \end{pmatrix} \right\rangle = 0 \tag{10.7}$$

We obtain using the inner product described in Elphick et al. (1987) that for any order we must have:

$$n(\sigma_{n,0}^{(1)} - \nu_{n,0}^{(1)}) + (\sigma_{n-1,1}^{(2)} - \nu_{n-1,1}^{(2)}) = 0 \tag{10.8}$$

$$\sigma_{n,0}^{(2)} - \nu_{n,0}^{(2)} = 0 \tag{10.9}$$

These two last equations can be satisfied in more than one way and we shall use this freedom. Apart from this general feature this two last equations leave an inherent freedom to incorporate to the normal from $\underline{f}^{(m)}$ elements that do not belong to the Kernel of the adjoint of the homologic operator, a freedom which exists in any normal form. In the Bogdanov-Takens bifurcation we have two extreme choices to write the normal form: The Arnold choice and The Takens choice. In the Arnold choice $\sigma_{n,0}^{(1)} = 0$ and $\sigma_{n-1,1}^{(2)} = n\nu_{n,0}^{(1)} + \nu_{n-1,1}^{(2)}$ and $\sigma_{n,0}^{(2)} = \nu_{n,0}^{(2)}$ and the normal form can be written as a perturbed hamiltonian system (Elphick et al., 1987). The other extreme choice is the Takens choice with $\sigma_{n-1,1}^{(2)} = 0$ and $\sigma_{n,0}^{(1)} - = \nu_{n-1,1}^{(2)}/n + \nu_{n-1,1}^{(2)}$ and $\sigma_{n,0}^{(2)} = \nu_{n,0}^{(2)}$. Because in the Arnold choice we gain all the Hamiltonian intuition, in this work we will use the **Arnold form** for the Bogdanov-Takens normal form.

10.2 Arnold form: the subcritical scaling

As we showed in the sections 10.1 the Bogdanov-Takens normal form is written in their Arnold form as:

$$\ddot{u} = F(u,\alpha) - \dot{u}\lambda(u,\beta) \tag{10.10}$$

We will call the function $F(u,\alpha)$ the *force* and the function $\lambda(u,\beta)$ the *friction* (we have written explicitly the two unfolding parameters (α,β)) using the obvious analogy with mechanics. Explicitly:

$$F(u,\alpha) = \alpha + \gamma_2 u^2 + \gamma_3 u^3 + \gamma_4 u^4 + \cdots \quad (10.11)$$
$$\lambda(u,\beta) = \beta + \lambda_1 u + \lambda_2 u^2 + \lambda_3 u^3 + \cdots \quad (10.12)$$

We recall that the unfolding parameters, represent the fact that the normal form has to be written for values of the original parameters in a small neighborhood of the critical point in the space of parameters, in other words α and β are functions of the variation of the original parameters around their values in the critical point, and their number, here two, represents the codimension of the bifurcation. Due to their meaning the values of (α, β) are small since they determine the domain in which we expect the normal form to give not only a qualitative description of the behavior of the system but also a quantitative description. We can define a *potential* $V(u,\alpha)$ such that the force $F(u,\alpha)$ is given by:

$$F(u,\alpha) = -\frac{\partial V(u,\alpha)}{\partial u} \quad (10.13)$$

Where:

$$V(u,\alpha) = -\alpha u - \frac{\gamma_2}{3}u^3 - \frac{\gamma_3}{4}u^4 - \frac{\gamma_4}{5}u^5 - \cdots \quad (10.14)$$

Then we can define the energy of the Bogdanov-Takens normal form as:

$$E(u,\alpha) \equiv \frac{1}{2}\dot{u}^2 + V(u,\alpha) \quad (10.15)$$

If we multiply equation 10.10 by $\dot{u}$ we obtain after a direct calculation:

$$\frac{d}{dt}E(u,\alpha) = -\dot{u}^2\lambda(u,\beta) \quad (10.16)$$

This equation shows that the Bogdanov-Takens normal form does not conserve the energy. Something which is expected since this equation is characterized by a nonconservative dynamics due to the friction term. The reader should note that the Bogdanov-Takens normal form can undergo an *injection* or *dissipation* of energy depending of the sign of $\lambda(u,\beta)$, and this sign can of course change when u changes.

Because the dynamics of the neurons is bounded in the sense that the physical values do not go to infinity in the relevant range of parameters, we want to have the same bounded dynamics in the normal form in order to reproduce with this equation the observed dynamics of the neurons. As it

is discussed in the literature the supercritical normal form of the Bogdanov-Takens is not bounded in the complete phase space and in the whole space of parameters and also does not contain the distinctive global bifurcations observed in neurons as the saddle-node homoclinic bifurcation or the saddle-homoclinic bifurcation (Guckenheimer and Holmes, 2002; Kuznetsov, 2004). This supercritical scaling has a linear friction (with $\lambda(u,\beta) = \beta + \lambda_1 u$). It is clear in the figure 9 that if $-\frac{\beta}{\lambda_1} < u$ the energy of the system can grow without bound in the zone where there is only injection of energy. No matter what is the sign of β or λ_1, there will always exist a range of u between $-\frac{\beta}{\lambda_1}$ and $\pm\infty$, were the energy will grow with a rate that increases lineary with u. This is shown with an example in the figure 9, left graph. Then this scaling forbid the feature that we are looking for: a bounded dynamics in all phase space. Therefore we will look for another scaling where the friction stops the unlimited growth of the variables of the system.

Now, if we consider a quadratic friction (with $\lambda(u,\beta) = \beta + \lambda_1 u + \lambda_2 u^2$) and impose that ($0 < \lambda_2$). As is showed in the figure 9 right graph, is clear that for values $\frac{-\lambda_1 - \sqrt{\lambda_1^2 - 4\lambda_2\beta}}{2} < u < \frac{-\lambda_1 + \sqrt{\lambda_1^2 - 4\lambda_2\beta}}{2}$ there will be only *injection* of energy and is easy to analytically show that one cannot have an stable fixed point in this area. Therefore all the orbits will *scape* from this region but the orbits will not go to infinity, because as soon as they reach the regions $\frac{-\lambda_1 + \sqrt{\lambda_1^2 - 4\lambda_2\beta}}{2} < u$ or $u < \frac{-\lambda_1 - \sqrt{\lambda_1^2 - 4\lambda_2\beta}}{2}$ the system will dissipate energy quadratically with the variable u, and the dynamics will be bounded to a certain region of phase space.

Hence, an scaling of the Bogdanov-Takens normal form which allows a quadratic friction $\lambda(u,\beta)$ with a coefficient λ_2 implying a dissipative behaviour when u goes to $\pm\infty$ (that is $0 < \lambda_2$), will always present a bounded dynamics. Also Kuznetsov show that the Bogdanov-Takens normal form with a quadratic friction presents several global bifurcations, some of which are characteristic of neuron dynamics (Kuznetsov, 2005).

The reader can check that if we try to find the most general scaling: $u \sim \epsilon^s$, $\dot{u} \sim \epsilon^n$, $\alpha \sim \epsilon^r$ and $\beta \sim \epsilon^q$ such that the no term of the equation is of greater order than the quadratic term of the friction $\dot{u}u^2$ (which must be there due to the dissipative dynamics we need in $\pm\infty$) the result is that $n = 3s$, $r = 5s$ and $q = 2s$. Then the subcritical Bogdanov-Takens normal form is:

$$\ddot{u} = \alpha + \gamma_2 u^2 + \gamma_3 u^3 + \gamma_4 u^4 + \gamma_5 u^5 - \dot{u}\left(\beta + \lambda_1 u + \lambda_2 u^2\right) \qquad (10.17)$$

The coefficients are of order: $\alpha \sim \epsilon^5$, $\gamma_2 \sim \epsilon^3$, $\gamma_3 \sim \epsilon^2$, $\gamma_4 \sim \epsilon$, $\gamma_5 \sim 1$,

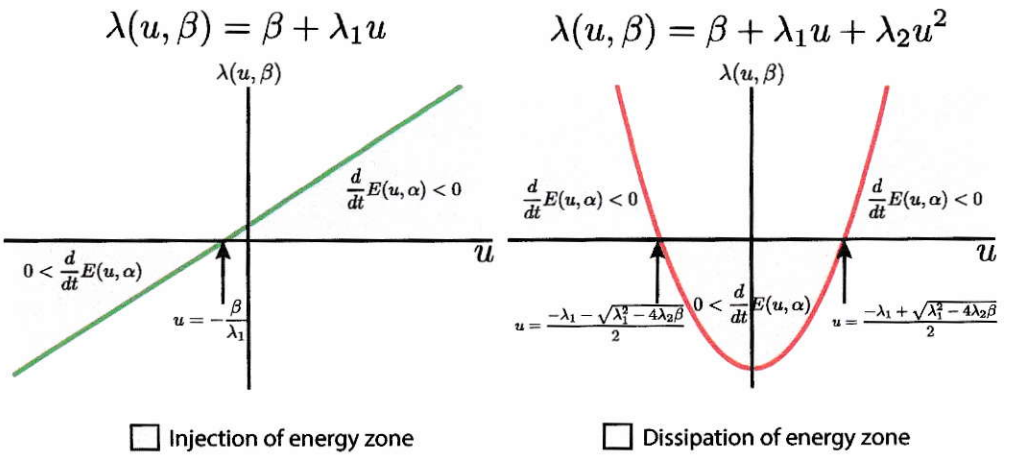


Figure 9: The left graphic shows in green a linear friction curve. The right graphic shows in red a quadratic friction curve with $0 < \lambda_2$. The arrow indicates the points where the friction changes the sign in both cases. In pale red we indicated the region where the system undergoes an injection of energy $0 < \frac{d}{dt}E(u,\alpha)$ and in pale blue the region where the system undergoes a dissipation of energy $\frac{d}{dt}E(u,\alpha) < 0$.

$\beta \sim \epsilon^{2s}$, $\lambda_1 \sim \epsilon^s$ and $\lambda_2 \sim 1$.

Even though the *force* of the Bogdanov-Takens normal form with a sub-critical scaling is quintic as we have shown 10.17 , we will see that in practice in most of the cases a cubic force will be enough to describe the neuronal dynamics. Only peculiar cases, when for example neurons have more than one stable rest potential (Heyward et al., 2001), the dynamics of a single neuron needs a description with a quintic potential.

Remark 10.1. The subcritical Bogdanov-Takens normal form written in the Arnold form reads:

$$\ddot{u} = \alpha + \gamma_2 u^2 + \gamma_3 u^3 + \gamma_4 u^4 + \gamma_5 u^5 - \dot{u}\left(\beta + \lambda_1 u + \lambda_2 u^2\right) \quad (10.18)$$

with the scaling $u \sim \epsilon$, $\dot{u} \sim \epsilon^3$, $\alpha \sim \epsilon^5$ and $\beta \sim \epsilon^2$ and the equation is of order ϵ^5.

10.3 Global bifurcations in the subcritical Bogdanov-Takens normal form

We simulate the subcritical Bogdanov-Takens normal form using the scaling of the coefficients showed in the previous section, with $s = 1$ and $\epsilon = 0.1$. We found all the typical global bifurcations mentioned in the literature for neuron models (Ermentrout and Terman, 2010; Izhikevich, 2010) which are the Saddle-node homoclinic bifurcation, the Saddle-homoclinic bifurcation and the Big homoclinic bifurcation (see section 2).

For the simulations we used our objective-c/COCOA software specially developed by us to deal with neuron models from the point of view of non linear dynamics and normal form theory (see appendix I). In the simulations we calculate analytically and in real time the fixed points (which is a u^* such that $F(u^*, \alpha) = 0$ and $\dot{u} = 0$) and the eigenvalues and eigenvectors of the critical matrix. For the visualization we symbolize with squares the nodes and saddle fixed points and with a circle the focus fixed points. The stable fixed points are purple, the unstable fixed points red and the saddle fixed points dark yellow. The linear stable manifold was coloured blue and the linear unstable manifold coloured yellow. We also show in phase space the force $F(u, \alpha)$ in blue and the friction $\lambda(u, \beta)$ in red. The phase space of the Bogdanov-Takens normal form is naturally the plane $\dot{u}$-u plane.

The figure 10 shows the Saddle-node homoclinic scenario. Before the bifurcation we have three fixed points: an stable node, a saddle and an unstable focus. As it is shown numerically if we follow the orbits in green these two fixed points have an heteroclinic connection. The unstable focus is inside the heteroclinic connection. When we move the parameter α these fixed points collide and the heteroclinc connection becomes a limit cycle, this is the point where the Saddle-node homoclinic bifurcation occurs. The unstable focus remain inside the limit cycle. This scenario was explained in the section 2 as a distinctive bifurcation of class 1 neurons and is the generic

scenario found in the Hodgkin and Huxley model.

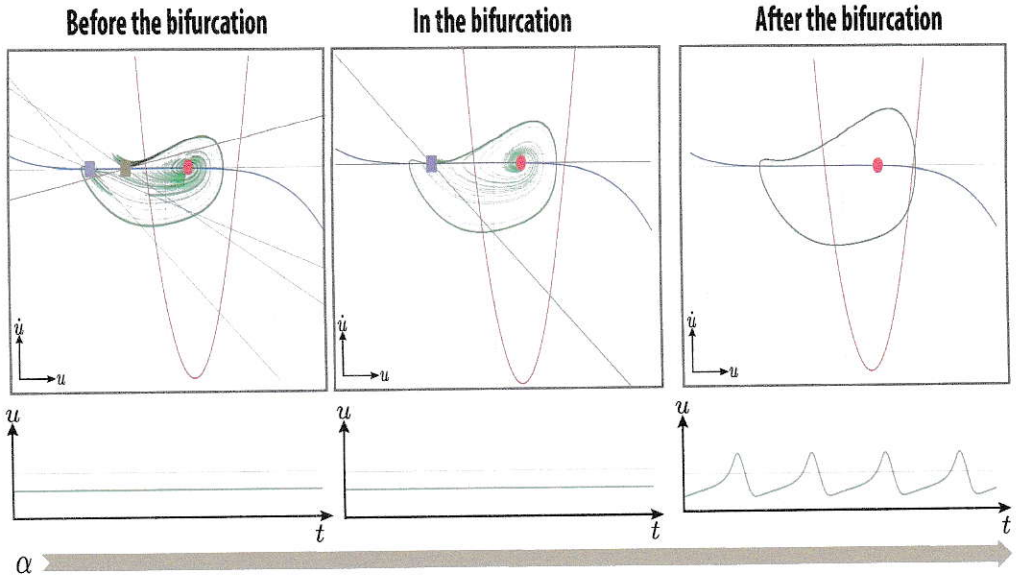


Figure 10: This figure shows the **Saddle-node homoclinic bifurcation** scenario in the subcritical Bogdanov-Takens normal form. On the upper part we show the phase space before the bifurcation, in the bifurcation and after the bifurcation. In the middle we show the graphic of u versus time for long times corresponding to the case above. On the bottom of the figure the brown arrow indicates that the parameter α is increasing.

The figure 11 shows the Saddle-homoclinic scenario in the subcritical Bogdanov-Takens normal form. We have again three fixed points: an stable node, a saddle and an unstable focus. When we move the parameter β the unstable manifold of the saddle fixed point returns getting closer from the stable manifold. When the unstable manifold and the stable manifold connect by the same orbit the Saddle-homoclinic bifurcation occurs, and then the homoclinic connection becomes a limit cycle. The unstable focus stay inside the limit cycle. For the Bogdanov-Takens normal form and for the neuron models also (Ermentrout and Terman, 2010; Izhikevich, 2010), after the bifurcation the limit cycle (marked with 1 in the figure) and the stable node (marked with 2 in the figure) are separated by the stable manifold of the saddle point. Therefore as its shown in the third graph of the figure 11 we have bistability between these two attractors. The Saddle-Homoclinic bifurcation is not necessary to have this bistable scenario, but in the case of the Bogdanov-Takens normal form and in the neuron models this scenario

generically occurs.

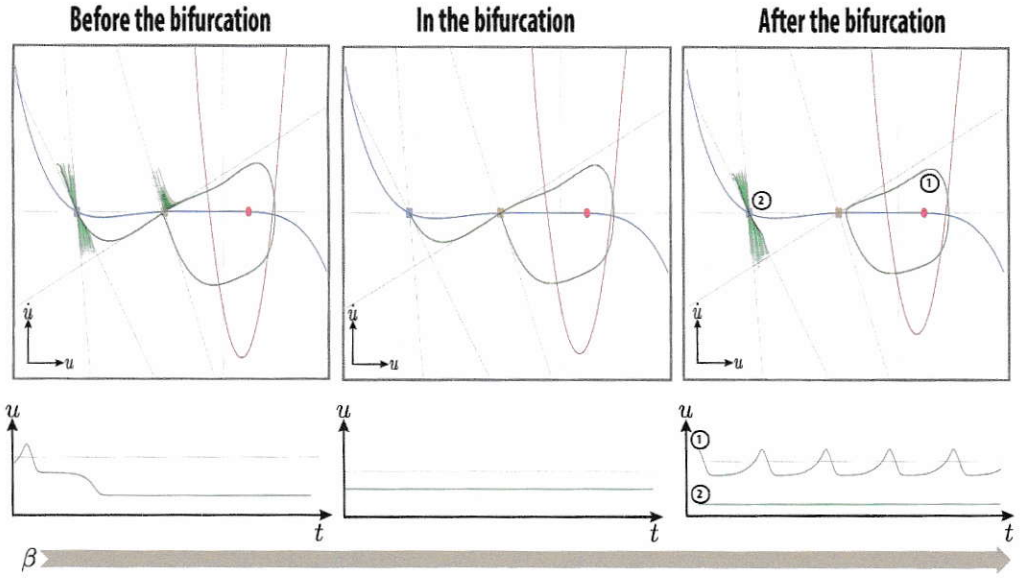


Figure 11: This figure shows the **Saddle-homoclinic bifurcation** scenario in the subcritical Bogdanov-Takens normal form. On the top we show the phase space before the bifurcation, in the bifurcation and after the bifurcation. In the middle we show the graphics of u versus time for long times corresponding with the situations above. On the bottom of the figure the brown arrow indicates that the parameter β is increasing. The two attractors that appear after the bifurcation are marked with the number 1 and 2 in the phase space and in the u versus t graphic.

The figure 12 shows the Big homoclinic scenario in the subcritical Bogdanov-Takens normal form. As in the other two scenarios we have three fixed points: an stable node, a saddle and an unstable focus. When we move the parameter β the unstable manifold of the saddle fixed point returns getting closer to the stable manifold. When the unstable manifold and the stable manifold connects by the same orbit and the homoclinic orbit formed *traps* the other ends of the unstable and stable manifolds of the saddle, then the Big homoclinic bifurcation occurs. This homoclinic connection becomes a limit cycle with the three fixed point inside. The limit cycle is separated of the unstable focus by an heteroclinic separatrix as is shown in the third graphic of the figure 12 in black. The separatrix connect the stable manifold of the saddle point with the unstable focus forming a closed figure. This connection is generic (codimension 0) because it connects an stable manifold (dimension 1) with the unstable manifold (dimension 2) of the focus and in

the mathematical sense it is analogous to the intersection of a line with a plane. This separatrix may suffer a Saddle-homoclinic bifurcation and we finally have: a big limit cycle, a stable focus and a limit cycle separatrix in between. Then moving the parameters this limit cycle could collide and disappear (simulations performed but not shown). Interestingly we found that the big homoclinic scenario showed in the figure 12 led to the other last scenarios described. Together these scenarios are distinctive of the class II neurons.

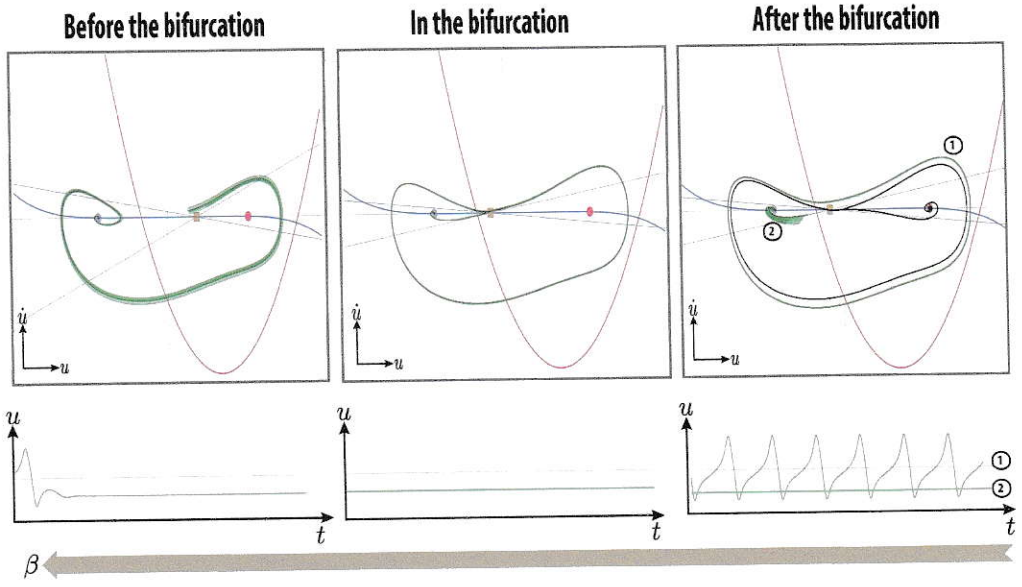


Figure 12: This figure show the **Big homoclinic bifurcation** scenario in the subcritical Bogdanov-Takens normal form. On the top we have the phase space before the bifurcation, in the bifurcation and after the bifurcation. In the middle we show the graphic of u versus time for long times corresponding with each situation. On the bottom of the figure the brown arrow indicates the decrease of the parameter β. The two attractors which appear after the bifurcation are marked with numbers 1 and 2 in the phase space and in the u versus t graphics. The heteroclinic separatrix between these two attractors (simulated using negative time) is showed in black.

11 The Bogdanov-Takens bifurcation in CB models

As we discussed in the previous section to have the codimension two Bogdanov-Takens bifurcation in a dynamical system we must impose that two eigen-

values of the linear matrix must be zero and a Jordan block should arise.

As we discussed in the section 6, to find the linear matrix we consider a fixed point $(u^*, \vec{0})$, were $I^* = f(u^*, \vec{\sigma})$ and $\vec{x} = \vec{0}$. Thus, by doing the standard translations in the neighbourhood of the fixed point ($\vec{x} = \vec{0} + \bar{\vec{x}}$ and $u = u^* + \bar{u}$) we find that the linear matrix has the form 8.1. In this section we will show that by moving two parameters $\vec{\sigma}$ we can reach generically the Bogdanov-Takens bifurcation with the critical matrix $\mathbb{L}^c(u^*, \vec{\sigma^c})$.

11.1 The double zero eigenvalue

In order to have a zero eigenvalue with multiplicity two in the linear matrix, we must impose that the constant term (a_0) and the linear term (a_1) of the characteristic polynomial ($P(\lambda) = \sum_{j=0}^{n} a_j \lambda^j$) must be zero, and then the characteristic polynomial can be written as $P(\lambda) = \lambda^2 \left(\sum_{l=2}^{n} a_l \lambda^{l-2}\right)$.

Using the general expressions 8.4 and 8.5 for the coefficients of the characteristic polynomial, the two general conditions to have two zero eigenvalue are:

$$\begin{aligned} \beta_0 \prod_{i=1}^{N} \alpha_i &= a_0 = 0 \\ \prod_{i=1}^{N} \alpha_i + \sum_{j=1}^{N} \beta_j M_j \prod_{l \neq j}^{N} \alpha_l &= a_1 = 0 \end{aligned}$$

Is very important to notice that the second equations means that the determinant of the $N \times N$ submatrix $\mathbb{L}_{N\times N}$ below must vanish, i.e.

$$\mathrm{Det}(\mathbb{L}_{N\times N}) = \begin{vmatrix} \alpha_1 + \beta_1 M_1 & \beta_1 M_2 & \dots & \beta_1 M_N \\ \beta_2 M_1 & \alpha_2 + \beta_2 M_2 & \dots & \beta_2 M_N \\ \vdots & \vdots & \ddots & \vdots \\ \beta_N M_1 & \beta_N M_2 & \dots & \alpha_N + \beta_N M_N \end{vmatrix} = 0 \quad (11.1)$$

Therefore the two conditions in terms of the functions of the conductance based model are:

$$\begin{aligned} \left.\frac{\partial f(u, \vec{\sigma})}{\partial u}\right|_{u=u^*} \prod_{i=1}^{n} \frac{1}{\tau_i(u^*, \vec{\sigma})} &= 0 \\ \prod_{i=1}^{n} \frac{1}{\tau_i(u^*, \vec{\sigma})} - \sum_{j=1}^{n} \left.\frac{\partial m_j^{\infty}(u, \vec{\sigma})}{\partial u}\right|_{u=u^*} \left.\frac{\partial K(u, \vec{x}, \vec{\sigma})}{\partial x_j}\right|_{u=u^*;\vec{x}=\vec{0}} \prod_{l \neq j}^{n} \frac{1}{\tau_l(u^*, \vec{\sigma})} &= 0 \end{aligned}$$

Since the functions $\tau_j(u,\vec{\sigma})$ are strictly positive the two condition for a zero eigenvalue with multiplicity two become:

$$\left.\frac{\partial f(u,\vec{\sigma})}{\partial u}\right|_{u=u^*} = 0 \quad (11.2)$$

$$\sum_{j=1}^{n} \left.\frac{\partial m_j^{\infty}(u,\vec{\sigma})}{\partial u}\right|_{u=u^*} \left.\frac{\partial G(u,\vec{x},\vec{\sigma})}{\partial x_j}\right|_{u=u^*;\vec{x}=\vec{0}} \tau_j(u^*,\vec{\sigma}) = 1 \quad (11.3)$$

This last result is very important: it is the general condition under which a conductance based model undergoes a double zero bifurcation. If a CB model meets these two conditions we will refer to the linear matrix as the critical linear matrix $\mathbb{L}^c$.

11.2 A Jordan block always arise

We will proof that in the conductance based equations if you have a double zero bifurcation, a Jordan block always will arise and therefore one has a Bogdanov-Takens bifurcation. If we meet the double zero eigenvalue condition for CB models 11.2 and 11.3 the critical linear matrix is written:

$$\mathbb{L}^c = \begin{pmatrix} 0 & \beta_0 M_1 & \dots & \beta_0 M_N \\ 0 & \alpha_1 + \beta_1 M_1 & \dots & \beta_1 M_N \\ \vdots & \vdots & \ddots & \vdots \\ 0 & \beta_N M_1 & \dots & \alpha_N + \beta_N M_N \end{pmatrix}$$

It is immediate to see that the vector $\underline{\chi}^{(0)}$ below is an eigenvector for the eigenvalue 0:

$$\underline{\chi}^{(0)} = \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix}$$

As we remarked in the previous section, the second condition 11.3 is equivalent to impose that the submatrix $\mathbb{L}^c_{N\times N}$ has a determinant equal to zero. If this holds, using a basic linear algebra theorem, there always exists an N component vector $\underline{\tilde{\chi}}^{(1)} = (\tilde{x}_1, \tilde{x}_2 \dots, \tilde{x}_{N-1}, \tilde{x}_N)$ such that:

$$\mathbb{L}^c_{N\times N}\underline{\tilde{\chi}}^{(1)} = 0$$

Then if we consider the vector (ν is arbitrary):

$$\underline{\chi}^{(1)} \equiv \frac{1}{\beta_0 \sum_{j=1}^{N} M_j \tilde{x}_j} \begin{pmatrix} \nu \\ \tilde{x}_1 \\ \vdots \\ \tilde{x}_N \end{pmatrix} \quad \text{with} \qquad \nu \in \mathbb{R}$$

it is easy to see that this vector $\underline{\chi}^{(1)}$ is the second vector of the Jordan basis of the critical matrix $\mathbb{L}^c$ as the following equation trivially shows:

$$\mathbb{L}^c \underline{\chi}^{(1)} = \begin{pmatrix} 0 & \beta_0 M_1 & \dots & \beta_0 M_N \\ 0 & \alpha_1 + \beta_1 M_1 & \dots & \beta_1 M_N \\ \vdots & \vdots & \ddots & \vdots \\ 0 & \beta_N M_1 & \dots & \alpha_N + \beta_N M_N \end{pmatrix} \begin{pmatrix} \nu \\ \tilde{x}_1 \\ \vdots \\ \tilde{x}_n \end{pmatrix} = \frac{\beta_0 \sum_{j=1}^{N} M_j \tilde{x}_j}{\beta_0 \sum_{j=1}^{N} M_j \tilde{x}_j} \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix} = \underline{\chi}^{(0)}$$

We have then proved that the critical matrix of a generic double zero bifurcation in CB models will always have two vectors such that:

$$\begin{aligned} \mathbb{L}^c \underline{\chi}^{(0)} &= 0 \\ \mathbb{L}^c \underline{\chi}^{(1)} &= \underline{\chi}^{(0)} \end{aligned}$$

which is the definition of a Jordan block for a double zero bifurcation. Therefore, we proved that when any CB model undergoes **a double zero bifurcation this bifurcation always will be a Bogdanov-Takens bifurcation.**

Surprisingly **we can found an analytical expression for all the vectors of the Jordan basis for any CB model that undergoes a Bogdanov-Takens bifurcation.** In appendix B we give these expressions explicitly. This last result is very powerful from two different points of views. Mathematically this result allow us to compute the Bogdanov-Takens normal form analytically for a generic CB model, i.e. for any CB model. Physically these analytical expressions enable us to do important biophysics interpretation, since they determine the dominant contribution to the formulas giving the physical original variables in terms of the variables of the normal form. This point will be discussed in the last section of this part.

Remark 11.1. The general conditions for any CB model to have a Bogdanov-Takens bifurcation are:

$$\left.\frac{\partial f(u,\vec{\sigma})}{\partial u}\right|_{u=u^*} = 0$$

$$\sum_{j=1}^{n} \left.\frac{\partial m_j^{\infty}(u,\vec{\sigma})}{\partial u}\right|_{u=u^*} \left.\frac{\partial K(u,\vec{x},\vec{\sigma})}{\partial x_j}\right|_{u=u^*;\vec{x}=\vec{0}} \tau_j(u^*,\vec{\sigma}) = 1$$

An analytical expression for the complete Jordan basis of the critical matrix ($\mathbb{L}^c$) is given in the appendix B.

12 Invariants

It is clear that for any n variables dynamical system evolving with time t the eigenvalues of the linear matrix $\mathcal{L}$ have dimension $[1/t]$. Then the characteristic polynomial $P(\lambda) = \mathrm{Det}(\mathcal{L} - \lambda \cdot 1) = b_n\lambda^n + b_{n-1}\lambda^{n-1} + \cdots + b_1\lambda + b_0$, with $b_n = (-1)^n$, has dimension $\left[1/t^N\right]$ and the coefficients of the polynomial $(b_0, b_1, \ldots, b_N)$ have dimension of $\left[1/t^N\right], \left[1/t^{N-1}\right], \ldots, [1/t], [1]$ respectively. Therefore for any given N variables dynamical system with a dimensionless time $\tilde{t}$ and with a time scaling $\bar{t}$, i.e. $t = \bar{t}\tilde{t}$, the dimensionless eigenvalues of the linear matrix $(\tilde{\lambda}_1, \tilde{\lambda}_2, \ldots, \tilde{\lambda}_N)$ are related to the eigenvalues $(\lambda_1, \lambda_2, \ldots, \lambda_n)$ of the system with dimensions by $\tilde{\lambda}_j = \bar{t} \cdot \lambda_j$ with $j = 1, \ldots n$. Hence, each coefficient of the dimensionless characteristic polynomial $\tilde{P}(\tilde{\lambda}) = (\bar{t})^{-n} P(\lambda) = \tilde{b}_n(\tilde{\lambda})^n + \cdots + \tilde{b}_1\lambda + \tilde{b}_0$ depend as a power law on the time scaling in the form $\tilde{b}_j = \bar{t}^{N-j} b_j, \quad j = 0, 1, \ldots, n$. This shows that physical considerations such as being *near to a bifurcation* is equivalent to $\tilde{\lambda}_k \ll 1$ depends on the election of the time scaling and in particular in our case the statement *near to Bogdanov-Takens* expressed in the form $\tilde{b}_0 \ll 1$ and $\tilde{b}_1 \ll 1$ also depend on the time scaling. On the ther hand the physics cannot depend of the time scaling, and since in a dynamical system the notion of *absolute time* has not physical sense **we must compare characteristic times of the system in order to obtain physical conclusions** (e.j. something is fast of slow compared with what). To take into account this fact in our analysis we will introduce mathematical quantities associated with each coefficient of the characteristic polynomial of the critical linear matrix $(a_0, a_1, \ldots, a_n)$ which will be invariant with respect

to changes in the time scaling. We shall call these quantities invariants. These invariants are quotients of characteristic times of the system or powers of them, and therefore have a deep physical meaning in the sense of dynamical systems. The introduction of this mathematical tools will be of great importance in the analysis of the necessary mathematical conditions for the occurrence of a Bogdanov-Takens instability, and then will be crucial to show our main physical result: that CB models are generically near to Bogdanov-Takens.

Is important that the reader notice that since these quantities will be invariant under time scaling and under the scalings leading to adimensional variables, and consequently **these quantities can be use to compare quantitatively different CB models**. The introduction of invariants in this problem is inspired by old physical scaling ideas (Barenblatt, 1996; Sedov, 1993) the physics of a given system (in our case the dynamics of a single neuron) cannot change with any non-singular change of variables (such as the nondimensionalization and the time scaling in our case). In fact the previous statement underlies the first formulations of the renormalization group in field theory (Tirapegui, 1975) and it will play an important role in our understanding of the single neuron dynamics as it is presented here.

12.1 Invariant associated with a_0

In this section we will obtain the invariant associated with the coefficient a_0. Let us consider the expression 8.4. By the definition 5.6 the function $f(u)$ is given by the following expression:

$$f(u) = \sum_{j=1}^{n} g_j \prod_{l \in w_j} [m_l(u)^{\infty}]^{p_l} (u - u_j)$$

Is important to mention that the derivative of this function for very negative values of the potential ($u \to -\infty$) is the inverse of the nondimensional membrane time constant (see section 1). This is because, as we discussed in the section 5, the function $f(u)$ is actually the nondimensional version of the I-v curve. Hence, if we take into account the time scaling is straightforward to arrive that in fact is the inverse of the nondimensional membrane time constant[11] ($\tilde{\tau}_{\text{membrane}}$). If we study carefully the expression $\left.\frac{\partial f(u)}{\partial u}\right|_{u=u^*}$ using 5.6, we obtain:

[11] $\lim_{u^* \to -\infty} \left[\left.\frac{\partial f(u)}{\partial u}\right|_{u=u^*} \right]^{-1} = \tilde{\tau}_{\text{membrane}}$.

$$\left.\frac{\partial f(u)}{\partial u}\right|_{u=u^*} = \sum_{j=1}^{n} g_j \prod_{l\in w_j} [m_l(u^*)^\infty]^{p_l} +$$

$$\sum_{j=1}^{n} g_j \sum_{l\in w_j} p_l \left[\prod_{r\in w_j} [m_r(u^*)^\infty]^{p_r-\delta_{r,l}}\right] \left.\frac{\partial m_l^\infty}{\partial u}\right|_{u=u^*} (u^* - u_j)$$

Let put our attention in the second term inside the brackets, if we compare with 6.5, we obtain:

$$\sum_{j=1}^{n} \sum_{l\in w^{(j)}} g_j p_l \prod_{r\in w^{(j)}} [m_r(u^*)^\infty]^{p_r-\delta_{r,l}} \left.\frac{\partial m_l^\infty}{\partial u}\right|_{u=u^*} (u^*-u_j) = \sum_{r=1}^{N} M_r(u^*)\beta_r(u^*)$$

and if we define the first term as:

$$\frac{1}{\tau_0(u*)} \equiv \sum_{j=1}^{n} g_j \prod_{l=1}^{N} [m_l(u^*)^\infty]^{p_l}$$

we obtain:

$$\left.\frac{\partial f(u)}{\partial u}\right|_{u=u^*} = \frac{1}{\tau_0(u*)} + \sum_{l=1}^{N} \beta_l(u^*)M_l(u^*) \tag{12.1}$$

and the coefficient a_0 can be written as:

$$a_0 = (-1)^{N+1} \prod_{j=1}^{N} \frac{1}{\tau_j(u^*)} \left[\frac{1}{\tau_0(u*)} + \sum_{l=1}^{N} \beta_l(u^*)M_l(u^*)\right] \tag{12.2}$$

Therefore the invariant associated with the coefficient a_0 can be defined as:

$$\left\|\frac{\partial f}{\partial u}\right\| \equiv a_0 \Big/ \left[(-1)^{N+1} \prod_{j=0}^{N} \frac{1}{\tau_j(u^*)}\right] = 1 + \tau_0(u*) \sum_{l=1}^{N} \beta_l(u^*)M_l(u^*) \tag{12.3}$$

due physical considerations the maximal conductances (g_j) and also the stationary probabilities $(m_l^\infty(u^*))$ are always positive. Then $\tau_0(u^*)$ will always be positive and finite. Furthermore, for very negative values of u^*

the function $\tau_0(u^*)$ will be exactly the nondimensional membrane time constant[12]. On the other hand the τ_j are always positive because there are relaxation times. Therefore $\left[(-1)^N \prod_{j=0}^{N} \frac{1}{\tau_j}\right]$ will never be zero. Then the coefficient a_0 will be equal to zero if and only if only if its associated invariant $\left\|\frac{\partial f}{\partial u}\right\|$ vanishes.

In figure 13 we show the typical shape of the invariant $\left\|\frac{\partial f(u)}{\partial u}\right\|$ as a function of u. Because the functions $\beta(u)$ are decreasing exponentials tending to zero in the limit $u \to \pm\infty$, the value of the invariant tends to 1 ($\lim_{u\to\pm\infty} \left\|\frac{\partial f}{\partial u}\right\| = 1$). This means that the slope of the function $f(u)$ will be constant for very negative or very large values of the injected current. In some central interval between very large negative and very large positive values of u the invariant typically is convex. When the invariant $\left\|\frac{\partial f(u)}{\partial u}\right\|$ is zero the function $f(u)$ has slope zero. Therefore, the zeros of this invariant are the values of u corresponding to certain values of the injected current (via $I^* = f(u*)$) where a saddle-node bifurcation occurs.

Remark 12.1. The invariant associated with the coefficient a_0 is defined as:

$$\left\|\frac{\partial f}{\partial u}\right\| = 1 + \tau_0 \sum_{l=1}^{N} \beta_l M_l \tag{12.4}$$

The coefficient of the characteristic polynomial a_0 will be equal to zero if and only if when its associated invariant $\left\|\frac{\partial f}{\partial u}\right\|$ is zero.

[12]Because $\lim_{u^*\to-\infty} \beta_j(u^*) = 0$, is straightforward to show that: nondimensional membrane time constant $= \lim_{u^*\to-\infty} \left[\frac{\partial f(u)}{\partial u}\Big|_{u=u^*}\right]^{-1} = \lim_{u^*\to-\infty} \tau_0(u*)$.

Morris-Lecar model calculation 12.1. Calculation of the invariant associated with a_0 ($\left\|\frac{\partial f}{\partial u}\right\|$). Using the expression D.12 of the appendix D we obtain:

$$\left\|\frac{\partial f}{\partial u}\right\| = 1 + \tau_0(u*)\left\{g_1 \left.\frac{\partial m^\infty(u)}{\partial u}\right|_{u=u^*} (u^* - u_1) + g_2 \left.\frac{\partial n^\infty(u)}{\partial u}\right|_{u=u^*} (u^* - u_2)\right\} \quad (12.5)$$

with

$$\tau_0(u*) = 1/\left[g_1 \tilde{m}^\infty(u^*) + g_2 n^\infty(u^*) + g_3\right] \quad (12.6)$$

Although Morris-Lecar is described by two dynamical variables (u and x), this model represents the dynamics of a neuron with two gating variables but one of them with a very fast relaxation (Morris and Lecar, 1981).

Hodgkin & Huxley model calculation 12.1. Calculation of the invariant associated with a_0 ($\left\|\frac{\partial f}{\partial u}\right\|$). Using the expressions of the appendix E we obtain:

$$\begin{aligned}\left\|\frac{\partial f}{\partial u}\right\| =& 1 + \tau_0(u^*)\left\{3g_1 m^\infty(u^*)^2 h^\infty(u^*) \left.\frac{\partial m^\infty(u^*)}{\partial u}\right|_{u=u^*} (u^* - u_1)\right. \\ &+ g_1 m^\infty(u^*)^3 \left.\frac{\partial h^\infty(u)}{\partial u}\right|_{u=u^*} (u^* - u_1) \\ &\left.+4g_2 n^\infty(u^*)^3 \left.\frac{\partial n^\infty(u)}{\partial u}\right|_{u=u^*} (u^* - u_2)\right\} \end{aligned} \quad (12.7)$$

with:

$$\tau_0 = 1/\left[g_1 m^\infty(u^*)^3 h^\infty(u^*) + g_2 n^\infty(u^*)^4 + g_3\right] \quad (12.8)$$

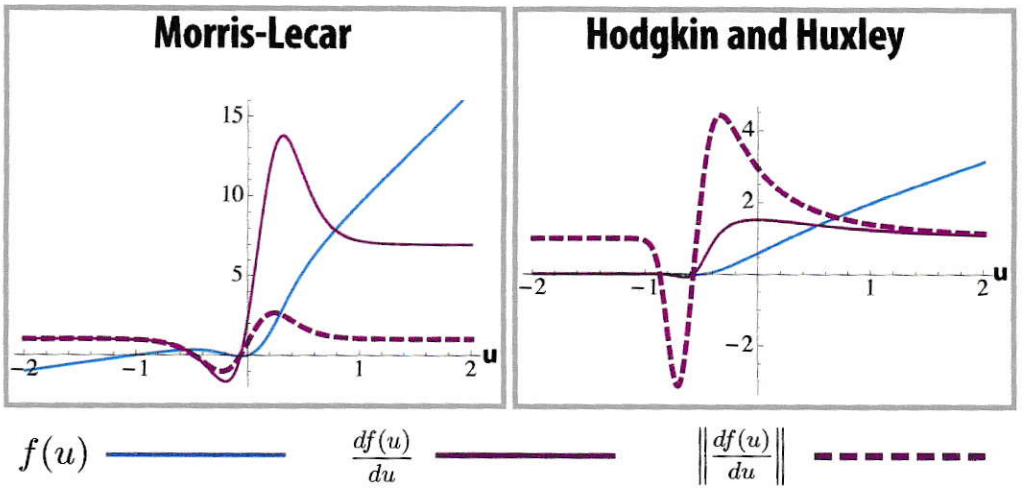


Figure 13: The $f(u)$ function is in blue, the derivative $\frac{\partial f(u)}{\partial u}$ is in solid purple lines and the invariant $\left\|\frac{\partial f(u)}{\partial u}\right\|$ is in dashed purple lines. The figure on the left is the graphic of the invariant for the Morris-Lecar model for relevant values of the parameters. The figure on the right is the graphic of the invariant for the Hodgkin and Huxley model.

12.2 Invariant associated with a_1

In this section we will obtain the invariant associated with the coefficient a_1. Using the expression 8.5 a_1 can be written as:

$$a_1 = -\left\{\prod_{i=1}^{N}\frac{(-1)^N}{\tau_j(u^*)} + \sum_{j=1}^{N}\beta_j(u^*)M_j(u^*)\prod_{l\neq j}^{N}\frac{(-1)^{N-1}}{\tau_l(u^*)} + \prod_{r=1}^{N}\frac{(-1)^N}{\tau_r(u^*)}\sum_{l=1}^{N}\frac{\tau_l(u^*)}{\tau_0(u^*)}\left\|\frac{\partial f}{\partial u}\right\|\right\}$$

Therefore the invariant associated with the coefficient a_1 can be defined as:

$$\|a_1\| \equiv a_1 \Big/ \left[\prod_{i=1}^{N}\frac{(-1)^{N+1}}{\tau_j(u^*)}\right] = 1-\sum_{j=1}^{N}\beta_j(u^*)M_j(u^*)\tau_j(u^*)+\sum_{l=1}^{N}\frac{\tau_l(u^*)}{\tau_0(u^*)}\left\|\frac{\partial f}{\partial u}\right\| \tag{12.9}$$

Note that when $\frac{\partial f}{\partial u} = 0$ (which implies $a_0 = 0$) the coefficient a_1 is exactly the determinant of the $N\times N$ sub-matrix of the linear matrix written explicitly in equation 11.1 . We can define the invariant associated with the determinant of the sub-matrix $\mathbb{L}_{N\times N}$ as

$$\|\mathrm{Det}\mathbb{L}_{N\times N}\| = 1 - \sum_{j=1}^{N} \beta_j(u^*) M_j(u^*) \tau_j(u^*) \tag{12.10}$$

Where:

$$\mathrm{Det}(\mathbb{L}_{N\times N}) = \begin{vmatrix} \alpha_1 + \beta_1 M_1 & \beta_1 M_2 & \dots & \beta_1 M_N \\ \beta_2 M_1 & \alpha_2 + \beta_2 M_2 & \dots & \beta_2 M_N \\ \vdots & \vdots & \ddots & \vdots \\ \beta_N M_1 & \beta_N M_2 & \dots & \alpha_N + \beta_N M_N \end{vmatrix} = \prod_{j=1}^{N} \alpha_j \, \|\mathrm{Det}\mathbb{L}_{N\times N}\|$$

Therefore the invariant associated with the coefficient a_1 can be written as:

$$\|a_1\| = \|\mathrm{Det}\mathbb{L}_{N\times N}\| + \sum_{l=1}^{N} \frac{\tau_l(u^*)}{\tau_0(u^*)} \left\| \frac{\partial f}{\partial u} \right\| \tag{12.11}$$

Because all the τ_j are positive since they are relaxation times, one has that $\left[(-1)^N \prod_{j=1}^{N} \frac{1}{\tau_j}\right]$ will never be zero for finite values of the parameters. Therefore, the coefficient of the characteristic polynomial a_1 will be equal to zero if and only if only if its associated invariant $\|a_1\|$ is zero.

Remark 12.2. The invariant associated with the coefficient a_1 is defined as:

$$\|a_1\| = \|\mathrm{Det}\mathbb{L}_{N\times N}\| + \left\| \frac{\partial f}{\partial u} \right\| \sum_{l=1}^{N} \frac{\tau_l}{\tau_0} \tag{12.12}$$

The coefficient of the characteristic polynomial a_1 will be equal to zero if and only if when its associated invariant $\|a_1\|$ is zero.

Morris-Lecar model calculation 12.2. The invariant associated with a_1 ($\|\mathrm{Det}\mathbb{L}_{N\times N}\|$) is given by:

$$\|\mathrm{Det}\mathbb{L}_{N\times N}\| = 1 - \tau_1(u*)g_1 \left.\frac{\partial m^\infty(u)}{\partial u}\right|_{u=u^*} (u^* - u_1) \qquad (12.13)$$

Hodgkin & Huxley model calculation 12.2. The invariant associated with a_1 ($\|\mathrm{Det}\mathbb{L}_{N\times N}\|$) is given by:

$$\begin{aligned}\|\mathrm{Det}\mathbb{L}_{N\times N}\| =& 1 + 3\tau_1(u*)g_1 m^\infty(u^*)^2 h^\infty(u^*) \left.\frac{\partial m^\infty(u^*)}{\partial u}\right|_{u=u^*} (u^* - u_1) \\ &+ g_1\tau_2(u^*)m^\infty(u^*)^3 \left.\frac{\partial h^\infty(u)}{\partial u}\right|_{u=u^*} (u^* - u_1) \\ &+ 4g_2\tau_3(u^*)n^\infty(u^*)^3 \left.\frac{\partial n^\infty(u)}{\partial u}\right|_{u=u^*} (u^* - u_2)\end{aligned} \qquad (12.14)$$

12.3 Gating Invariants

We will define the gating invariant of a gating variable m_j as:

$$\|m_j\| \equiv \tau_j M_j \beta_j \qquad (12.15)$$

This invariant quantity *extracts* very important features of the impact of a single gating variable in the dynamics of a CB model. First, is easy to notice that **if the gating invariant is negative then the gating variable acts as an amplifier, and if it is positive it acts as resonant** (see section 1.2). This leads us naturally to a sign criteria to designate an amplifier or a resonant gating variable that did not exist until now. An example of a amplifier gating invariant $\|m\|$ for the Hodgkin and Huxley model is showed in the figure 15.

But the gating invariant not only indicates if a gating variable is amplifier or resonant, the magnitude of the gating invariant is tightly related

to the contribution of this gating variable to the dynamics of a certain CB model. In the next sections we will show that the invariant $\|\mathrm{Det}\mathbb{L}_{N\times N}\|$ will be key in the Bogdanov-Takens condition and appears explicitly in the general Andronov form reduction of CB models (see section 15.2). Then, if a gating variable is large or small compare to 1 (as shows the equation 12.13) this is related with the contribution of this gating variable to the invariant $\|\mathrm{Det}\mathbb{L}_{N\times N}\|$, and therefore to the dynamics of a CB model. This can be seen intuitively taking into account that the magnitude of the gating invariant depends on its three components τ_j, β_j and M_j (see as an example the figure 15). If the invariant is large due to a large $\beta_j(u)$, then the function $m_j^\infty(u)$ will be in the u-interval of maximum slope as shown in the figure 15. In this interval, and if the relaxation time is not very fast, an slight change in u will led to abrupt changes of the gating variable m_j and will have a noticeable impact in the dynamics of a CB model. If the invariant is small due to a small $M_j(u)$, this will be because stationary functions $(m_j(u)^\infty)$ involved in $M_j(u)$ have values near to zero, therefore a change in the value of m_j will not have a noticeable influence in the dynamics of the CB model. Finally, if the invariant is large because the function τ_j is large, this leds to a persistent (slow) effect of m_j in the dynamics. In contrast, if it is small due to a small τ_j this generates a transient (very fast) effect of m_j in the dynamics of the CB model. Hence, **if the m_j gating invariant is large in magnitude this gating variable will have a persistent noticeable effect in the dynamics while if it is small the effect will be a transient not noticeable for long times.**

The fact that these gating invariants (as their name indicates) are invariant under scalings of time and of variables allow us to compare quantitatively different gating variables or CB models. This comparison can determine, for example, that one gating variable is *more resonant* (negative and larger in magnitude) than other, or if one CB model has more *amplifier contributions* (the sum of amplifier gating variables) than another.

13 Existence of Bogdanov-Takens in CB models

In this section we shall use the invariants defined in the previous section to study the necessary relations that must fulfill the functions τ_j, β_j and M_j in a CB model to have a Bogdanov-Takens bifurcation. Since these functions are directly related with the biophysics of the ion channels of the CB models, we shall obtain the features and relations between the ion channels which are necessary to have a Bogdanov-Takens bifurcation. We

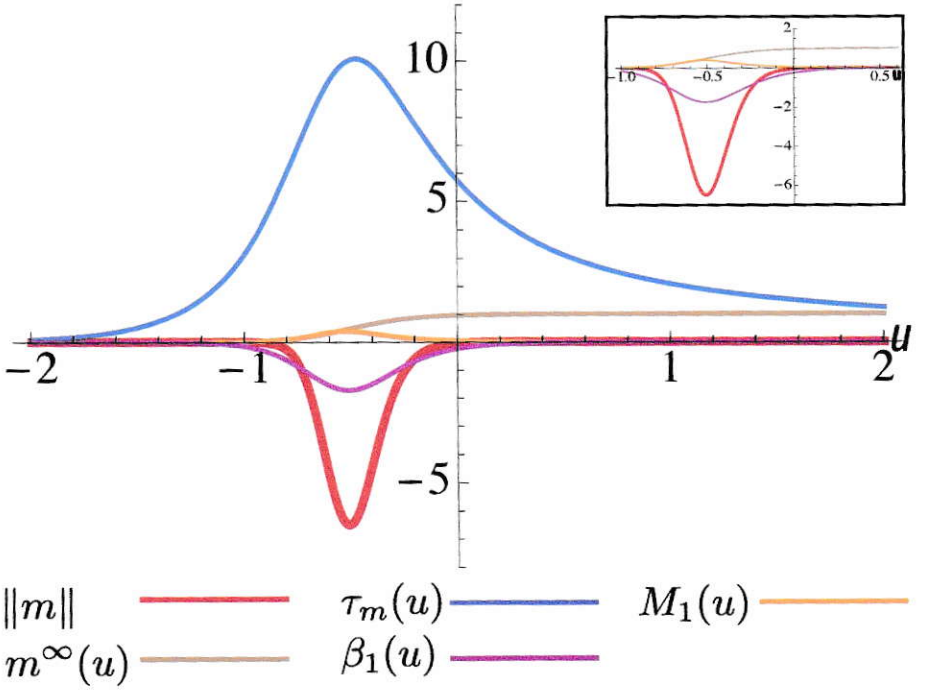


Figure 15: Dependence on u of the m invariant of the Hodgkin and Huxley model and of the different functions on which it depends. In red the invariant $\|m\|$, in brown the stationary probability $m^\infty(u)$, in blue the relaxation time $\tau_m(u)$, in orange the function $M_1(u)$ and in purple the function $\beta_1(u)$. The black rectangle shows a zoom of the graphics. Note that $\|m\|$ is a resonant gating invariant (i.e. negative) for all the values of u.

will also find invariant quantities that are easily interpretable in terms of the biophysics of a single neuron, finding a deep biophysical interpretation to our mathematical expressions. This analysis led us to a remarkable conclusion: the conditions that both experimentalists and theoreticians designate as the minimal necessary conditions to have an *excitable behaviour* (see section 1.2) are the same to have the Bogdanov-Takens bifurcation in a CB model. This conclusion can be considered our main result in this section. In the next section we shall give our arguments to support the following statement: neurons are generically near to a Bogdanov-Takens Bifurcation.

Remark 13.1. From equations 12.4 and 12.12, the two conditions that must fulfill a CB model to undergo a Bogdanov-Takens bifurcation written in terms of their invariants are:

$$\begin{aligned} \left\| \frac{\partial f}{\partial u} \right\| = 1 + \tau_0 \sum_{l=1}^{N} \beta_l M_l &= 0 \\ \|\mathrm{Det}\mathbb{L}_{N\times N}\| = 1 - \sum_{j=1}^{N} \beta_j M_j \tau_j &= 0 \end{aligned} \tag{13.1}$$

13.1 Time scale separation

Using the invariants we will show that one necessary condition to have a Bogdanov-Takens bifurcation in a CB model is to have a time scale separation between at least two sets of characteristics times of the CB models, which are the gating variables relaxation times and the membrane characteristic time. This means physically that **there must exist at least one set of fast variables and another set of slow variables.** We recall that in order to have a Bogdanov-Takens bifurcation the invariants of a CB model must satisfy equations 13.1. Let us assume that we have only one time scale $\bar{\tau}$. This physically means that all ionic channels and τ_0 relax with time scales of the same order. Therefore:

$$\bar{\tau} \sim \tau_j \sim \tau_0 \qquad j = 1, 2 \ldots N$$

Then the conditions for the Bogdanov-Takens bifurcation (equation 13.1)

read:

$$\left\| \frac{\partial f}{\partial u} \right\| = 1 + \bar{\tau} \sum_{l=1}^{N} \beta_l M_l = 0$$

$$\|\mathrm{Det}\mathbb{L}_{N\times N}\| = 1 - \bar{\tau} \sum_{j=1}^{N} \beta_j M_j = 0$$

and then we must have:

$$\sum_{l=1}^{N} \beta_l M_l = -\frac{1}{\bar{\tau}}$$

$$\sum_{j=1}^{N} \beta_j M_j = \frac{1}{\bar{\tau}}$$

These two equations cannot be satisfied simultaneously. However it is clear that equations 13.1 can hold if we have two or more characteristics times (thats it at least $\tau_j \neq \tau_k \quad j,k \in [0,N]$ with $j \neq k$) and then the Bogdanov-Takens conditions may be fulfilled. We have then shown that to have a Bogdanov-Takens bifurcation in a CB model it is necessary to have at least two time scales. Thats means *in practice* that one must have different orders of magnitude for at least two groups of characteristics times, for example differences between the relaxation times of two different gating variables (for example $\tau_j \gg \tau_k$). The necessity of different time scales to have a Bogdanov-Takens bifurcation coincides with one of the two necessary conditions that all the literature suggests for *excitable behaviour* as explained in section 1. In fact it is widely accepted that the fast inward currents (in general sodium currents) are responsible for the initiation of the action action potential and therefore it is almost obvious for the neurophysiologist that the time scales separations is something essential for the *excitable behaviour*. But this is our first step to show the tight relation between the *excitable behaviour* and the Bogdanov-Takens dynamics. To exemplify this we show in figure 16 that this conditions is fulfilled in the Hodgkin and Huxley model (the condition is automatically fulfilled in the Morris-Lecar model since there one assumes that one of the gating variables is very fast and can the be replaced by its stationary value, see Morris and Lecar in 1981).

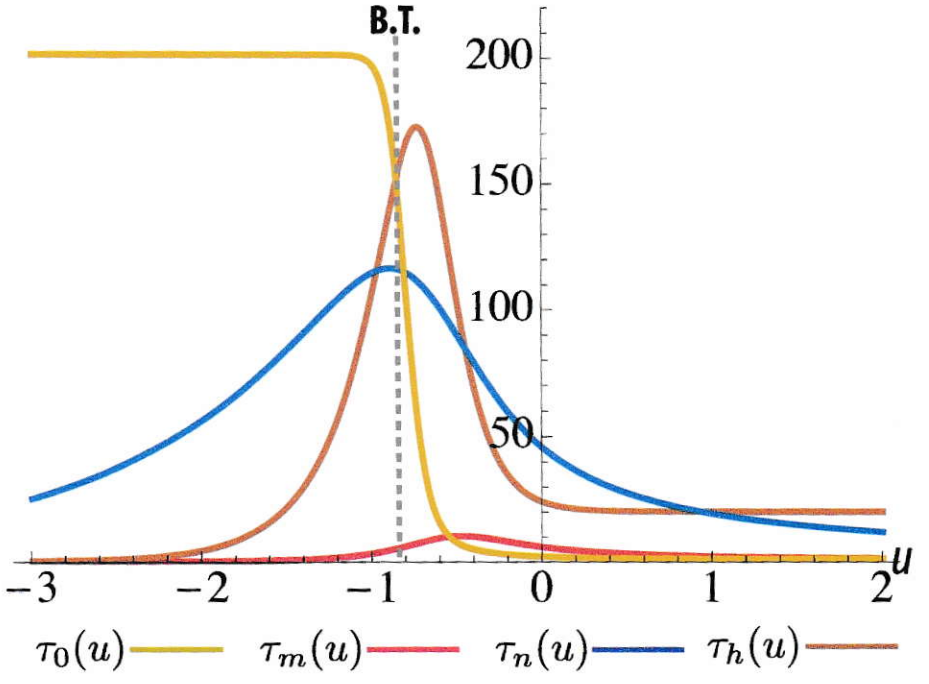


Figure 16: Gating variables relaxation times and τ_0 for the Hodgkin and Huxley model. The grey dashed line with the tag B.T. is centered in the interval of u where the system often undergoes the Bogdanov-Takens bifurcation for several values of the parameters.

13.2 Resonant and Amplifying Variables

As we explain in the section 1.2, we can define amplifying and resonant gating variables, and we showed in section 12.3 that this notion was transparently interpreted in terms of the gating invariants. In this section we will show that **the second necessary condition to have a Bogdanov-Takens bifurcation in a CB model — in addition to time scale separation — is to have at least one resonant and one amplifying gating variable**. Let us assume that in the range of interest for the parameters the system has only one kind of gating variables, i.e. all the variables are either resonant or amplifying. This means mathematically :

$$\text{Sign}\,(\beta_j M_j) = 1 \quad \text{or} \quad \text{Sign}\,(\beta_j M_j) = -1 \qquad \forall j \in N$$

If this is true, then the Bogdanov-Takens conditions written in 13.1 become:

$$\left\| \frac{\partial f}{\partial u} \right\| = 1 + \text{Sign}\,(\beta_j M_j)\,\tau_0 \sum_{l=1}^{N} |\beta_l M_l| \;=\; 0$$

$$\|\text{Det}\mathbb{L}_{N\times N}\| = 1 - \text{Sign}\,(\beta_j M_j) \sum_{j=1}^{N} |\beta_j M_j|\,\tau_j \;=\; 0$$

Then to have a Bogdanov-Takens bifurcation we must have:

$$\text{Sign}\,(\beta_j M_j) \;=\; -\frac{1}{\text{Sign}\left(\tau_0 \sum_{l=1}^{N} |\beta_l M_l|\right)}$$

$$\text{Sign}\,(\beta_j M_j) \;=\; \frac{1}{\text{Sign}\left(\sum_{j=1}^{N} |\beta_j M_j|\,\tau_j\right)}$$

i.e.:

$$\text{Sign}\,(\beta_j M_j) \;=\; -1$$
$$\text{Sign}\,(\beta_j M_j) \;=\; 1$$

These two equations cannot hold simultaneously. Nevertheless it is clear by looking the equations in 13.1 that having at least one resonant and one amplifying gating variable (thats it at least $\text{Sign}\,(\beta_j M_j) \neq \text{Sign}\,(\beta_k M_k) \quad j,k \in$

$[0, N]$ with $j \neq k$) the Bogdanov-Takens conditions may be fulfilled. Therefore we have shown that to have a Bogdanov-Takens bifurcation in a CB model — in addition to time scale separation — it is necessary to have at least one amplifying and one resonant variable. Is very interesting that, as in the previous section, this second necessary condition to have a Bogdanov-Takens bifurcation in a CB model, also corresponds to the the second necessary condition that all the literature suggests for *excitable behaviour* as explained in section 1. As it was explained in this section, it is widely accepted that the fast inward currents (in general sodium currents) that drive a positive feedback, are responsible for the initiation of the action potential and involve amplifying gating variables. On the other hand, it is also widely accepted that the outward currents responsible for the repolarization phase of the action potential (for example potassium currents) involve primarily resonant gating variables. In fact, it is also almost obvious (and widely accepted for the neurophysiologist and also for dynamical system theoretician) that the coexistence of a positive and negative feedback — which means at least an amplifying and a resonant gating variable — is directly related to the oscillating behaviour of neurons and is therefore a necessary condition for *excitable behaviour*. This is our second step to show the tight relation between the *excitable behaviour* and the Bogdanov-Takens dynamics. Figure 14 exemplifies this result in the Hodgkin and Huxley model which has one amplifying gating invariant ($\|m\|$ in red) and two resonant gating invariants ($\|h\|$ in brown and $\|n\|$ in blue).

As a corollary of this result we see that a CB model with one gating variable cannot undergo a Bogdanov-Takens bifurcation.

Remark 13.2. The two necessary conditions for a CB model to undergo a Bogdanov-Takens bifurcation are:

- **There must exist time scale separation.** This mathematically means:

$$\exists j, k \in [0, N] \quad \text{with} \quad j \neq k \quad \text{such that:} \quad \tau_j \neq \tau_k$$

- **There must exist at least one resonant and one amplifying gating variable.** This mathematically means:

$$\exists j, k \in [0, N] \quad \text{with} \quad j \neq k \quad \text{such that:} \quad \text{Sign}\,(\beta_j M_j) \neq \text{Sign}\,(\beta_k M_k)$$

Although the Morris-Lecar model in its usual formulation is described by two dynamical variables (u and x), this model represents the dynamics of a neuron with two gating variables but one of them with a very fast relaxation (Morris and Lecar, 1981). Taking this into account that, in both Morris-Lecar and Hodgkin and Huxley model the two necessary conditions to undergo a Bogdanov-Takens bifurcation (see remark 13.2) are fulfilled. An example of one of the possibilities in the space of parameters to reach the Bogdanov-Takens bifurcation is shown in figure 17 (Morris-Lecar model) and figure 18 (Hodgkin and Huxley model).

13.3 Two time scales gating variables

In this section we will analyse the scenario when the necessary condition exposed in the section 13.1 are fulfilled with two time scales for the gating variables. As a first step we want to prove the statement: **if the two time scales gating variables condition holds, then the sum of the fast invariants must be amplifying and the sum of the slow invariants must be resonant.**

Let us assume that we have two sets of gating variables in a CB model: the fast gating variables with relaxation times of the order of τ_F (set of variables F) and the slow gating variables with relaxation times of the order

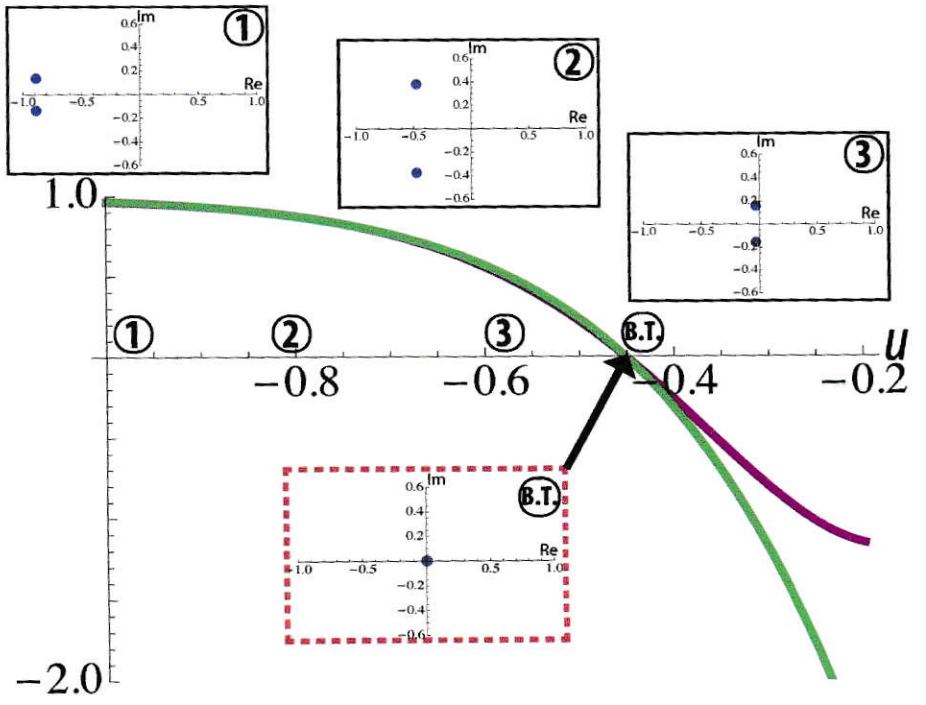


Figure 17: A Bogdanov-Takens bifurcation in the Morris-Lecar model. The $\left\| \frac{\partial f(u)}{\partial u} \right\|$ invariant is shown in purple. The $\|\mathrm{Det}\mathbb{L}_{N\times N}\|$ invariant is shown in green. The graphics in black frames show the eigenvalues of the linear matrix $\mathbb{L}(u, \vec{\sigma}_T^c)$ in the complex plane. The tags 1-3 tags indicate the corresponding values of the variable u. The graphic in a red dashed frame shows the eigenvalues of the linear matrix $\mathbb{L}(u, \vec{\sigma}_T^c)$ in the complex plane when the system undergoes a Bogdanov-Takens bifurcation.

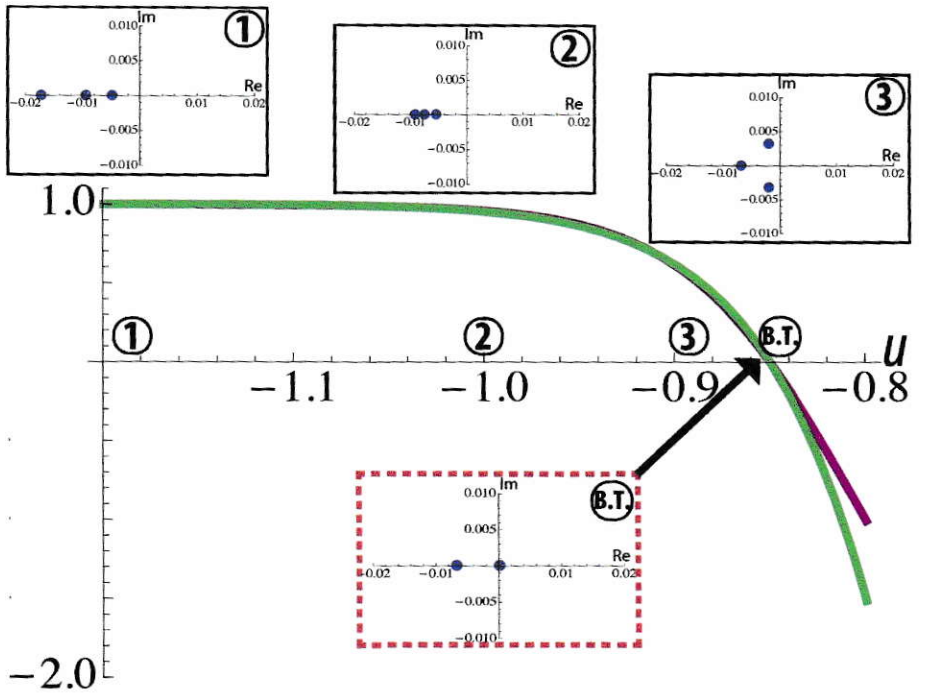


Figure 18: A Bogdanov-Takens bifurcation in the Hodgkin and Huxley model. The $\left\| \frac{\partial f(u)}{\partial u} \right\|$ invariant is shown in purple. The $\|\mathrm{Det}\mathbb{L}_{N\times N}\|$ invariant is shown in green. The graphics in the black frames show the eigenvalues of the linear matrix $\mathbb{L}(u, \vec{\sigma}_T^c)$ in the complex plane. We omit the most negative eigenvalue (far to the left) in order to better visualize the two critical ones. The tags 1-3 indicate the corresponding values of the variable u. The graphic in a red dashed frame show the eigenvalues of the linear matrix $\mathbb{L}(u, \vec{\sigma}_T^c)$ in the complex plane when the system undergoes a Bogdanov-Takens bifurcation.

of T_S (set of variables S). We have then:

$$\begin{aligned} \tau_k &\sim \tau_F & k &\in F \\ \tau_l &\sim T_S & l &\in S \\ \text{with} \quad & \frac{\tau_F}{T_S} \ll 1 \end{aligned} \tag{13.2}$$

Hence, the Bogdanov-Takens conditions in the equation 13.1 are written:

$$1 + \tau_0 \left[\sum_{l \in S} \beta_l M_l + \sum_{k \in F} \beta_k M_k \right] = 0 \tag{13.3}$$

$$1 - T_S \sum_{l \in S} \beta_l M_l - \tau_F \sum_{k \in F} \beta_k M_k = 0 \tag{13.4}$$

If we define:

$$\begin{aligned} BM_S &\equiv \sum_{l \in S} \beta_l M_l \\ BM_F &\equiv \sum_{k \in F} \beta_k M_k \end{aligned}$$

the equations 13.5 and 13.6 become:

$$1 + \tau_0 \left[BM_S + BM_F \right] = 0 \tag{13.5}$$

$$1 - T_S BM_S - \tau_F BM_F = 0 \tag{13.6}$$

Then, after some algebra:

$$BM_S = \frac{1}{T_S} \frac{1 + \frac{\tau_F}{\tau_0}}{1 - \frac{\tau_F}{T_S}} \tag{13.7}$$

$$BM_F = -\frac{1}{T_S} \frac{1 + \frac{T_S}{\tau_0}}{1 - \frac{\tau_F}{T_S}} \tag{13.8}$$

Since $\tau_F / T_S \ll 1$ we can conclude that

$$BM_S > 0 \tag{13.9}$$

$$BM_F < 0 \tag{13.10}$$

This means that if we have two time scales for the gating variables **the sum of fast invariants must be amplifying and the sum of the slow invariants must be resonant**. This is a generic situation widely observed experimentally in neurons and which has been also discussed theoretically (Johnston and Wu, 1994; Izhikevich, 2010). This happens in the Morris-Lecar and in the Hodgkin and Huxley models as shown in figure 14 where the fast gating invariants are amplifying ($\|m\|$ in the Hodgkin and Huxley model) and the slow gating invariants are resonant ($\|m\|$ in the Hodgkin and Huxley and Morris-Lecar model). With further calculations (see appendix C) we can show that the most generic case for a CB model is that τ_0 and the slow time scale are of the same order ($\tau_0 \sim T_S$). The figure 16 shows that within the range u where the Hodgkin and Huxley model undergoes the bifurcation (indicated with a dashed line) this condition holds (the figure shows that $\tau_h(u)/\tau_0 \sim \tau_n(u)/\tau_0 \sim 1$).

14 CM models are in the neighborhood of Bogdanov-Takens

In the previous section we showed that the necessary conditions to have a Bogdanov-Takens instability in a CB model are two: 1) at least two time scales 2) at least one amplifying and one resonant gating variable. As a corollary of this we proved that a CB model with only one gating variable cannot undergo a Bogdanov-Takens bifurcation. We also show that if these two conditions are fulfilled with two sets of fast and slow gating variables, then the sum of the fast invariants must be amplifying and the sum of the slow invariants must be resonant. This last analysis also suggested that the order of magnitude of the membrane time constant is generically of the order of the slow gating variables. Surprisingly all these conditions are pointed out in the literature as fundamental conditions and sometimes as the mechanisms for the *excitable behaviour* observed in neurons (see section 1). In this section we will show that indeed the *excitable behaviour* and the Bogdanov-Takens dynamics are two sides of the same coin. Therefore, at the end of this section it will be very clear that the Bogdanov-Takens behavior is the key mathematical mechanism which gives rise to the observed dynamics of single neurons.

Since the Bogdanov-Takens bifurcation is of codimesion 2, one has to reach a point in a two dimensional space of parameters as it is seen in figure 19, and this means that experimentally one has to tune two knobs in specific points to realize this bifurcation. This scenario does not look likely for single

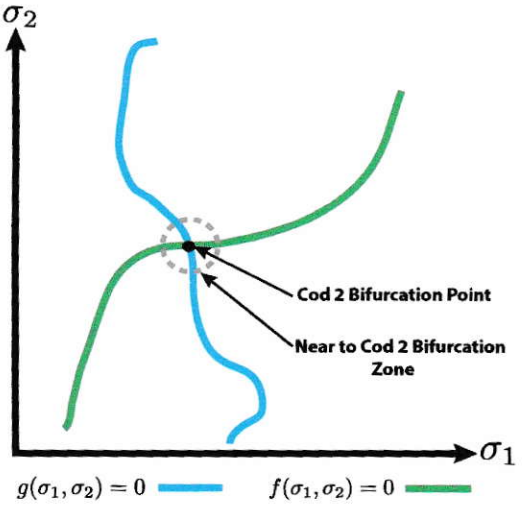


Figure 19: Codimension 2 bifurcation in the space of parameters. The curves $g(\sigma_1, \sigma_2) = 0$ and $f(\sigma_1, \sigma_2) = 0$ are two conditions for two different codimension 1 bifurcations. The intersection in the space of parameters is a codimension 2 bifurcation point.

neuron dynamics where in one of the usual experiments where varying only the magnitude of the injected current it is possible to observe the *excitable behaviour*. One has then the impression that the observed dynamics depends on a codimension 1 mechanism (mathematically a bifurcation) rather a codimension 2 bifurcation such as the Bogdanov-Takens instability. But a the local codimension 1 bifurcation (as Saddle-node and Hopf bifurcation) and their normal forms fail to explain all the phenomenology of the *excitable behaviour* characterised by global bifurcations. Hence, there is a seeming contradiction between the codimension 2 Bogdanov-Takens bifurcation and the apparent codimension 1 mechanism observed experimentally in neurons.

Using our previous results we reconcile this apparent paradox showing that the CB equations are generically *near* to the Bogdanov-Takens bifurcation. In fact their mathematical structure makes —if the necessary conditions for Bogdanov-Takens in remark 13.2 hold— that the first two coefficients of the characteristics polynomial will be very small ($a_0 \ll 1$ and $a_1 \ll 1$). This then leds to the conclusion that generically CB models will be placed in the neighbourhood of a Bogdanov-Takens bifurcation.

In order to show these results let us consider the coefficients a_0 and a_1 of the characteristic polynomial (equation 12.3 and 12.9):

$$a_0 = (-1)^{N+1} \prod_{j=0}^{N} \frac{1}{\tau_j} \left\| \frac{\partial f}{\partial u} \right\| \tag{14.1}$$

$$a_1 = (-1)^{N+1} \prod_{i=1}^{N} \frac{1}{\tau_i} \|a_1\| \tag{14.2}$$

We assume thet the necessary condition of having at least two time scales for the gating variables is fulfilled. Let us assume k fast gating variables with a time scale τ and m slow gating variables with a time scale T, then we can write the equations 14.1 and 14.2 as:

$$\begin{aligned} a_0 &= (-1)^{N+1} \frac{1}{\tau_0 \tau^k T^m} \left\| \frac{\partial f}{\partial u} \right\| \\ a_1 &= (-1)^{N+1} \frac{1}{\tau^k T^m} \|a_1\| \end{aligned}$$

we remind the reader that τ and T are nondimensional characteristic times. As discussed in the section 12 the physics of a system cannot depend of the time scaling, but in order to do physical comparisons (saying for example that a coefficient is small) we must choose a characteristic time to nondimensionalize. This time should be a relevant time of the system, to give physical sense to the words fast or slow. In this case it is quite obvious that a good choice of the time scale to nondimensionalize is the fast variable τ, then something very fast will have times smallest than 1 and slow things will have times greater than 1. Then, if we consider times with a tilde as times with dimensions, the equations become:

$$\begin{aligned} a_0 &= (-1)^{N+1} \frac{\tilde{\tau}^{k+m+1}}{\tilde{\tau}_0 \tilde{\tau}^k \tilde{T}^m} \left\| \frac{\partial f}{\partial u} \right\| = (-1)^{N+1} \left(\frac{\tilde{\tau}}{\tilde{\tau}_0} \right) \left(\frac{\tilde{\tau}}{\tilde{T}} \right)^m \left\| \frac{\partial f}{\partial u} \right\| \\ a_1 &= (-1)^{N+1} \frac{\tilde{\tau}^{k+m}}{\tilde{\tau}^k \tilde{T}^m} \|a_1\| = (-1)^{N+1} \left(\frac{\tilde{\tau}}{\tilde{T}} \right)^m \|a_1\| \end{aligned}$$

We recall that a necessary conditions for Bogdanov-Takens in a CB model is:

$$\frac{\tau}{T} = \frac{\tilde{\tau}/\tau}{\tilde{T}/\tau} = \frac{\tilde{\tau}}{\tilde{T}} \ll 1$$

and we consider also a membrane relaxation time of the order of the slowest variables ($\tau_0 \sim T_S$). We define

$$\epsilon \equiv \frac{\tau}{T} \ll 1$$

Then

$$\begin{aligned} a_0 &= (-1)^{N+1}\epsilon^{m+1}\left\|\frac{\partial f}{\partial u}\right\| \\ a_1 &= (-1)^{N+1}\epsilon^{m}\left\|a_1\right\| \end{aligned}$$

Then if $\left\|\frac{\partial f}{\partial u}\right\|$ is does not diverge one concludes that

$$\begin{aligned} |a_0| &\ll 1 \\ |a_1| &\ll 1 \end{aligned}$$

The functions $\beta_j(u)$ are always finite and decay exponentially for $u \longrightarrow \pm\infty$ and the functions $M_j(u)$ can increase or decrease at most linearly when $\mid u \mid \longrightarrow \infty$. Then because $\tau \ll T$ and $\tau_0 \sim T$, we have

$$\begin{aligned} \lim_{u\to\pm\infty}\left\|\frac{\partial f}{\partial u}\right\| &= 1 \\ \lim_{u\to\pm\infty}\left\|a_1\right\| &= 1+\frac{\tau+T}{\tau_0} \approx 2 \end{aligned}$$

We see then that the invariants as functions of u are both of order one for very large negative and very large positive values of u and in some central interval they take finite values and can vanish. This is shown for the Morris-Lecar and Hodgkin and Huxley models in the figures 13 and 14. It is *then in the central interval* where the invariants can change of sign. Since it is not experimentally seen and physiological plausible that the functions $\beta(u)$ have maximums at large negative values we can expect that the invariants will go monotonically from 1 to zero as it seen in the figures referenced. Hence, from very large negative values of u to the critical value where the invariant is zero (u_0^c for the $\left\|\frac{\partial f}{\partial u}\right\|$ and u_1^c for $\|a_1\|$) both invariant will be of order 1 as it is shown in the figures 17 and 18. Therefore, in the interval $u \in [-\infty, u_0^c]$ the coefficients a_0 will be of order ϵ^m and in the interval $u \in [-\infty, u_1^c]$ the coefficient a_1 will be of order ϵ^{m+1}. The reader may note

that the invariants are zero in two point. But because we are following the stable fixed point root (the positive u fixed point is generically unstable), we only have Bogdanov-Takens for negative values of u.

Since the invariants are finite and remain of order 1 near to the Bogdanov-Takens point and since the products $\beta_j(u)M_j(u)$ and the functions $\tau_j(u)$ will not change abruptly (as they do) as we discuss in the appendix C, the coefficients remain small ($a_0 \sim \epsilon^m$ and $a_1 \sim \epsilon^{m+1}$) in an interval between u_0^c and u_1^c.

Our analysis shows that if we have two time scales for the gating variables the coefficients a_0 and a_1 will be generically very small. This is a very powerful result: this physically means that if a CB model satisfies the necessary condition for the existence of a Bogdanov-Takens instability then the system is automatically in the neighbourhood of the Bogdanov-Takens bifurcation (near as is shown in the figure 19), i.e. in its unfolding. Because the structure of the CB equations, the **necessary conditions for the existence of the Bogdanov-Takens bifurcation becomes sufficient to be in the unfolding of Bogdanov-Takens.** Although mathematically we have a codimension 2 bifurcation, if the conditions of the existence of Bogdanov-Takens holds, it is not necessary to move any parameter to stay in neighbourhood, and the CB models will behave as in the unfolding of the Bogdanov-Takens normal form.

In the next section we clearly show analytically and numerically that if CB models meet the necessary conditions in the remark 13.2, its dynamics are described by the Bogdanov-Takens normal form.

Remark 14.1. If a CB model satisfies the two necessary conditions for the existence of Bogdanov-Takens as described in Remark 12.1 with two time scales for the gating variables this CB model is in the unfolding of Bogdanov-Takens, that is:

$$\begin{aligned} |a_0| &\ll 1 \\ |a_1| &\ll 1 \end{aligned}$$

It is important to note that the previous arguments do not apply to instabilities of higher codimension. We shall see in appendix G that the

triple zero bifurcation (which will have chaotic behavior) is not generic in the sense discussed here for CB models, and in order to have this instability the CB models must fulfill a very specific conditions. We also study carefully the coefficients a_2 and a_3 of the characteristic polynomial and show that they are bigger than a_0 and a_1.

15 CB model reduction

In this section we will explain a method developed to transform any CB model in almost the Bogdanov-Takens normal form in their Arnold form. We say *almost* because this equation will have the form of a perturbed Hamiltonian and will fulfill the subcritical scaling in the relevant range of parameters, but the force and the friction will be written in terms of transcendental functions. This reduced equation will be written in terms of the two variables u and $\dot{u}$. Is important to note that using the analytical expression for the Jordan basis in section 11.2 and in appendix B it is easy to show that these two variables (the potential u and the derivative of the potential $\dot{u}$ of the CB model) are actually the critical variables of the Bogdanov-Takens normal form.

In addition to this remarkable fact, we will say that the reduced equation *preserves the linear structure.* This is not strictly true, because in this method we reduced the number of variables from $N+1$ to 2, therefore we will change the linear matrix and furthermore an *ad hoc* change of variables will break the "neuronal matrix" structure of the linear system. But we preserve two fundamental features of the original CB model that we have shown in the previous sections and which are the key for the *excitability behaviour*: 1) the reduced form will maintain the fixed point condition of the original CB model given by $I^* = f(u^*, \vec{\sigma}_T)$, therefore the appearance or disappearance of fixed points with respect to the parameters will be the same in both the original CB model and their reduced form, 2) the reduced form also preserves the Bogdanov-Takens points of the original equation (thats it $\left\| \frac{\partial f}{\partial u} \right\| = 0$ and $\|\mathrm{Det}\mathbb{L}_{N\times N}\| = 0$).

To do this reduction we will use three assumptions:

1. The difference between the gating variable and its stationary probability is small ($|x_j| \ll 1$).

2. There exists a separation of time scales which leds to two sets of gating variables: the slow set with constant time relaxation T_S and the fast set with constant time relaxation τ_F.

3. The CB model is near to the Bogdanov-Takens bifurcation in the sense that we can use the scaling in the remark 10.1 and then neglect higher order terms with respect to that scaling. In fact, we show in the previous section 14 that if the assumption 2 is fulfilled then we are in the unfolding of the Bogdanov-Takens instability.

In the next section we will show numerically that this reduced equation has the same form and behaviour as the subcritical Bogdanov-Takens normal form with a *cubic-like* force and a *quadratic-like* friction in the relevant range of parameters. But most importantly we will show that this reduced equation has qualitatively the same dynamics of the original CB model, confirming that the dynamics of CB models is qualitatively described by the subcritical Bogdanov-Takens normal form.

15.1 Two time scales model reduction

Consider the most general CB model written in its standard form (see section 5.1):

$$\begin{aligned} \dot{u} &= I - f(u, \vec{\sigma}_T) - K(u, \vec{x}, \vec{\sigma}_T) \\ \dot{x_j} &= -\frac{x_j}{\tau_j(u, \vec{\sigma}_j)} + \beta_j(u, \vec{\sigma}_j)\dot{u} \qquad j = 1, 2 \ldots N \end{aligned}$$

Since $|x_j| \ll 1$ for every j, we shall neglect the higher orders in these variables. Then if we expand $K(u, \vec{x}, \vec{\sigma}_T)$ around the fixed point $(u = u^*, \vec{x} = 0)$ we keep only the linear orders in $\vec{x}$, and using the definitions 6.4 the last equation becomes:

$$\begin{aligned} \dot{u} &= I - f(u) + \sum_{j=1}^{N} M_j(u) x_j \\ \dot{x}_j &= -\frac{x_j}{\tau_j} + \beta_j(u)\dot{u} \qquad j = 1 \ldots N \end{aligned}$$

Now we use the assumption 2): the fast gating variables will have relaxation times of the order of τ_F (set of variables F) and the slow gating variables will have relaxation times of the order of T_S (set of variables S), i.e.

$$\begin{aligned} &\tau_k(u) \sim \tau_F && k \in F \\ &\tau_l(u) \sim T_S && l \in S \\ &\text{with} \quad \frac{\tau_F}{T_S} \ll 1 \end{aligned}$$

For simplicity we shall use the subindices F and S for the functions $\beta_j(u)$ and $M_j(u)$ which are related to the fast and slow gating variables, respectively. Therefore the equations can be written (using an obvious notation)

$$\dot{u} = I - f(u) + \vec{M}_F(u) \cdot \vec{x}_F + \vec{M}_S(u) \cdot \vec{x}_S \tag{15.1}$$

$$\dot{\vec{x}}_F = -\frac{\vec{x}_F}{\tau_F} + \vec{\beta}_F(u)\dot{u} \tag{15.2}$$

$$\dot{\vec{x}}_S = -\frac{\vec{x}_S}{T_S} + \vec{\beta}_S(u)\dot{u} \tag{15.3}$$

If we take the derivative with respect to time of these equations 15.1 we obtain:

$$\ddot{u} = -\frac{\partial f(u)}{\partial u}\dot{u} + \frac{\partial \vec{M}_F(u)}{\partial u} \cdot \vec{x}_F\dot{u} + \vec{M}_F(u) \cdot \dot{\vec{x}}_F + \frac{\partial \vec{M}_S(u)}{\partial u} \cdot \vec{x}_S\dot{u} + \vec{M}_S(u) \cdot \dot{\vec{x}}_S \tag{15.4}$$

where the sign $\cdot$ is the usual euclidean scalar product. Then using the equations 15.2 and 15.8 in 15.4 we obtain:

$$\begin{aligned} \ddot{u} = -\frac{\partial f(u)}{\partial u}\dot{u} + \frac{\partial \vec{M}_F(u)}{\partial u} \cdot \vec{x}_F\dot{u} + \vec{M}_F(u) \cdot \left[-\frac{\vec{x}_F}{\tau_F} + \vec{\beta}_F(u)\dot{u}\right] \\ + \frac{\partial \vec{M}_S(u)}{\partial u} \cdot \vec{x}_S\dot{u} + \vec{M}_S(u) \cdot \left[-\frac{\vec{x}_S}{T_S} + \vec{\beta}_S(u)\dot{u}\right] \end{aligned}$$

We can eliminate adiabatically (Van Kampen, 1985) the fast variables assuming that they are instantaneous. Then we put

$$\dot{\vec{x}}_F \sim 0 \Rightarrow \vec{x}_F = \dot{u}\tau_F\vec{\beta}_F(u) \tag{15.5}$$

and we obtain:

$$\ddot{u} = -\frac{\partial f(u)}{\partial u}\dot{u} + \frac{\partial \vec{M}_F(u)}{\partial u} \cdot \vec{\beta}_F(u)\tau_F\dot{u}^2 + \frac{\partial \vec{M}_S(u)}{\partial u} \cdot \vec{x}_S\dot{u} + \vec{M}_S(u) \cdot \left[-\frac{\vec{x}_S}{T_S} + \vec{\beta}_S(u)\dot{u}\right] \tag{15.6}$$

If we consider now equation 15.1 we can obtain the expression:

$$\vec{M}_S(u) \cdot \vec{x}_S = \dot{u}\left[1 - \tau_F \vec{M}_F(u) \cdot \vec{\beta}_F(u)\right] - (I - f(u))$$

If we replace this expression in equation 15.6 we obtain:

$$\ddot{u} = \frac{I - f(u)}{T_S} - \dot{u}\left(\frac{\partial f(u)}{\partial u} + \frac{1}{T_S}\left\{1 - T_S \vec{M}_S(u) \cdot \vec{\beta}_S(u) - \tau_F \vec{M}_F(u) \cdot \vec{\beta}_F(u)\right\}\right)$$
$$+ \left[\frac{\partial \vec{M}_F(u)}{\partial u} \cdot \vec{\beta}_F(u)\right] \tau_F \dot{u}^2 + \left[\frac{\partial \vec{M}_S(u)}{\partial u} \cdot \vec{x}_S\right] \dot{u}$$

and using the definitions of the invariants in 12.4 and 12.10 the equation becomes:

$$\ddot{u} = \frac{I - f(u)}{T_S} - \dot{u}\left(\frac{1}{\tau_0}\left\|\frac{\partial f(u)}{\partial u}\right\| + \frac{1}{T_S}\left\|\mathrm{Det}\mathbb{L}_{N\times N}(u)\right\|\right)$$
$$+ \left[\frac{\partial \vec{M}_F(u)}{\partial u} \cdot \vec{\beta}_F(u)\right] \tau_F \dot{u}^2 + \left[\frac{\partial \vec{M}_S(u)}{\partial u} \cdot \vec{x}_S\right] \dot{u}$$

Then the CB model becomes:

$$\ddot{u} = \frac{I - f(u)}{T_S} - \dot{u}\left(\frac{1}{\tau_0}\left\|\frac{\partial f(u)}{\partial u}\right\| + \frac{1}{T_S}\left\|\mathrm{Det}\mathbb{L}_{N\times N}(u)\right\|\right)$$
$$+ \left[\frac{\partial \vec{M}_F(u)}{\partial u} \cdot \vec{\beta}_F(u)\right] \tau_F \dot{u}^2 + \left[\frac{\partial \vec{M}_S(u)}{\partial u} \cdot \vec{x}_S\right] \dot{u} \tag{15.7}$$

$$\dot{\vec{x}}_S = -\frac{\vec{x}_S}{T_S} + \vec{\beta}_S(u)\dot{u} \tag{15.8}$$

15.2 CB model in Andronov form

Using the fact that we are near to Bogdanov-Takens we can neglect the term:

$$\left[\frac{\partial \vec{M}_F(u)}{\partial u} \cdot \vec{\beta}_F(u)\right] \tau_F \dot{u}^2$$

Using the subcritical scaling (see remark 10.1) we realise that this term is smaller than the order terms of the Bogdanov-Takens normal form:

$$\left[\frac{\partial \vec{M}_F(u)}{\partial u}\cdot\vec{\beta}_F(u)\right]\tau_F\dot{u}^2\sim\tau_F\epsilon^{6s}\ll\epsilon^{5s}$$

Then the equations becomes:

$$\ddot{u}=\frac{I-f(u)}{T_S}-\dot{u}\left(\frac{1}{\tau_0}\left\|\frac{\partial f(u)}{\partial u}\right\|+\frac{1}{T_S}\left\|\mathrm{Det}\mathbb{L}_{N\times N}(u)\right\|\right)+\left[\frac{\partial \vec{M}_S(u)}{\partial u}\cdot\vec{x}_S\right]\dot{u}$$

$$\dot{\vec{x}}_S=-\frac{\vec{x}_S}{T_S}+\vec{\beta}_S(u)\dot{u}$$

Now the term $\left[\frac{\partial \vec{M}_S(u)}{\partial u}\cdot\vec{x}_S\right]\dot{u}$ is the only term which links together the n_S+2 equations (n_S is the number of slow variables S). This is a non linear term and will only affect nonlinearly the dynamics of the first equation. Furthermore if we are near to Bogdanov-Takens and we use the ansatz (the expression of the physical variables in terms of the critical variables) at linear order (see section 11.2 and the appendix B) we can write

$$\vec{x}_S\sim\dot{u}T_S\vec{\beta}_S(u)$$

and:

$$\left[\frac{\partial \vec{M}_S(u)}{\partial u}\cdot\vec{x}_S\right]\dot{u}\sim\left[\frac{\partial \vec{M}_S(u)}{\partial u}\cdot\vec{\beta}_S(u)\right]\dot{u}^2T_S\sim T_S\epsilon^{6s}\ll\epsilon^{5s}$$

Therefore is fair to neglect this term. Actually in the Morris-Lecar model we have obtained an analytical expression for this term (we can do that in any two gating variable CB model) as a function of u and $\dot{u}$ (see equation D.23) and we have shown numerically that this term qualitatively does not change the dynamics (see section 16.1). Hence, finally, the reduced form of any CB model is:

$$\ddot{u}=\frac{I-f(u)}{T_S}-\dot{u}\left(\frac{1}{\tau_0}\left\|\frac{\partial f(u)}{\partial u}\right\|+\frac{1}{T_S}\left\|\mathrm{Det}\mathbb{L}_{N\times N}(u)\right\|\right)\tag{15.9}$$

Note that this equation has the form of the Bogdanov-Takens normal form in the Andronov form. The force and the friction are:

$$
\begin{aligned}
F(u) &= \frac{I - f(u)}{T_S} \\
\lambda(u) &= \frac{1}{\tau_0} \left\| \frac{\partial f(u)}{\partial u} \right\| + \frac{1}{T_S} \left\| \mathrm{Det}\mathbb{L}_{N\times N}(u) \right\|
\end{aligned}
$$

16 Numerical Results

In the appendices D and E we reduce (transform in the case of Morris-Lecar model since in that case it is just a nonlinear change of variables) the two most famous conductance based models —the Morris-Lecar model and the Hodgkin and Huxley model— to the form in 15.9 using the method developed in the previous section. In the appendix F we show, doing a change of variables, that one of the most famous phenomenological models used to describe the single neuron electrical dynamics, called the generalised Fitzhugh-Nagumo model, (Hindmarsh and Rose, 1982), is actually the subcritical Bogdanov-Takens normal form[13].

In this section we present numerical results which show that this reduced equation has the same qualitative behaviour as the subcritical Bogdanov-Takens normal form with a *cubic-like* force and *quadratic-like* friction in the relevant range of parameters in the case of Morris-Lecar and Hodgkin and Huxley models (because in the case of the generalised Fitzhugh-Nagumo model the result is exact). We will show —as the theory predicts— that the dynamics of this reduced equation has the same local and global bifurcations as the subcritical Bogdanov-Takens normal form studied in section 10.3. We will also numerically show that this reduced equation has qualitatively the same dynamics of the original CB model, confirming that the dynamics of CB models is qualitatively described by the subcritical Bogdanov-Takens normal form.

For the simulations we used our objective-c/COCOA software specially developed by us to deal with neuron models from the point of view of non linear dynamics and normal form theory (see section I).

16.1 The Morris-Lecar model

We simulated simultaneously the Morris-Lecar model (equation D.19), the Morris-Lecar model without the kinetic energy term (equation D.23) and

[13]Note in the appendix F that this model is not the most general form of the subcritical Bogdanov-Takens normal form.

the reduced form of the Morris-Lecar model (equation D.24). With our software we can visualize and perturb interactively the orbits in the same phase space (the $\dot{u}$-u plane). We use green colour to draw the orbits of the original Morris-Lecar model, yellow for the Morris-Lecar without the term in $(\dot{u})^2$ and purple for the Reduced form. Because the three equation have the same fixed points and the same linear matrices when they are linearised around the fixed points, in the software we calculate analytically and in real time the fixed points (thats is a u^* where $I^* = f(u^*)$ and $\dot{u} = 0$) and the eigenvalues and eigenvectors only once. The symbology used for the different classes of fixed points and stable and unstable manifolds is the same that was used in section 10.3. The force $(\frac{I-f(u)}{\tau(u)})$ is the same for the three equations and we plot it in the phase plane in blue. The friction curve will be different for the three models (the original Morris-Lecar model, the Morris-Lecar without the term in $(\dot{u})^2$ and the reduced model in which we neglect also the term $-\frac{I-f(u)}{u-u_1}\dot{u}$ which will always vanish when it is evaluated at a fixed point u^* which is such that $I^* = f(u^*)$). For Morris-Lecar and Morris-Lecar without the term in $(\dot{u})^2$ we plot the friction curve in red and for the reduced model we use magenta.

As the figures 20, 21 and 21 show the forces have a cubic shape (also consistent with a quintic shape) and the friction in both cases (with and without the $-\frac{I-f(u)}{u-u_1}\dot{u}$) has a quadratic shape with slight differences between the two friction curves. As the theory predicts, we found the same global bifurcation scenarios as in the subcritical Bogdanov-Takens normal form (see section 10.3). Interestingly —and also as our general theory predicts— we show numerically that the dynamics does not change qualitatively between the three equations. The figures show how quantitative features such as the specific value of the nondimensional injected current I when homoclinc or heteroclinc bifurcation occur, the shape and period of the limit cycles, the shape of the separatrices change when the parameters vary in the three equations (and must change since in the global bifurcations the nonlinearities play a role). But the simulations show that the qualitative features —as the kind of bifurcations— are the same in the three equations, i.e. they are robust.

The figure 20 shows the Saddle-node homoclinic scenario. Before the bifurcation we have three fixed points: an stable node, a saddle and an unstable focus. We move the nondimensional injected current I and the stable fixed point collides with the saddle and the heteroclinc connection becomes a limit cycle. As it is shown in the third plot of the figure the shape of the three limit cycles are different and have different periods. But because the

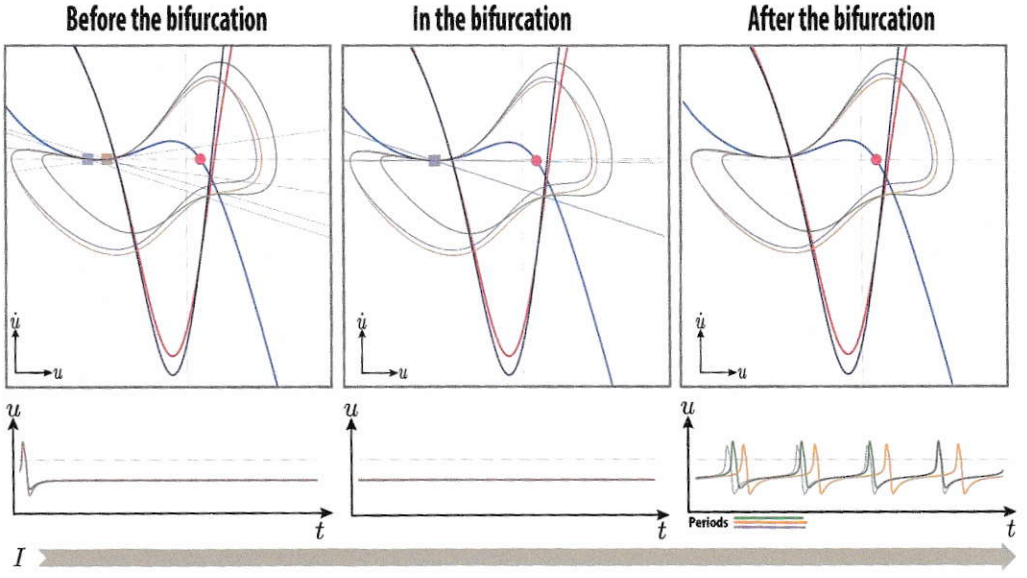


Figure 20: This figure shows the **Saddle-node homoclinic bifurcation** scenario in the Morris-Lecar model (green orbits), the Morris-Lecar model without the $(\dot{u})^2$ term (yellow orbits) and the reduced form of the Morris-Lecar model (purple orbits). On the top we show the phase space before the bifurcation, in the bifurcation and after the bifurcation. In the middle we sow the graphic of u versus time for long times corresponding to each situation. The period of the oscillations is indicated for the three models using with a coloured bar with the previous colour code. On the bottom of the figure the brown arrow indicates the increase of the nondimensional injected current I.

bifurcation is locally a saddle-node bifurcation, and this bifurcation depends locally of the linear system, the Saddle-node homoclinic bifurcation occurs in the same bifurcation point for the three equations.

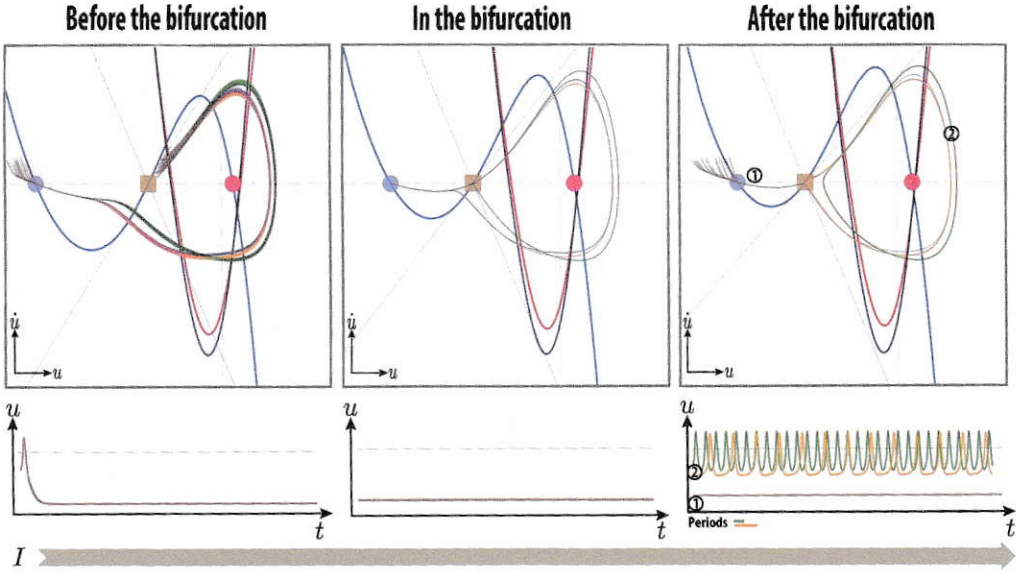


Figure 21: This figure shows the **Saddle-homoclinic bifurcation** scenario in the Morris-Lecar model (green orbits), the Morris-Lecar model without the $(\dot{u})^2$ term (yellow orbits) and the reduced form of the Morris-Lecar model (purple orbits). On the top we show the phase space before the bifurcation, in the bifurcation and after the bifurcation. In the middle we show the graphics of u versus time for long times corresponding with each situation. On the bottom of the figure the brown arrow indicates the increase of the nondimensional injected current I. The two attractors that appear after the bifurcation are marked with the number 1 and 2 in the phase space and in the u versus t graphic.

The figure 21 shows the Saddle-homoclinic scenario. There exist three fixed points: an stable node, a saddle and an unstable focus. When we move the nondimensional injected current I the unstable manifold of the saddle fixed point returns getting closer to the stable manifold. When the unstable manifold and the stable manifold connect in the same homolinic orbit the Saddle-homoclinic bifurcation occurs, and then the homoclinic connection becomes a limit cycle. Because the Saddle-homoclinic is a global bifurcation the specific bifurcation point depends on the nonlinearities and the equations have different bifurcation points (the figure shows that the original Morris-Lecar model bifurcate before the other two). Although the

shape of the limit cycles of the three equations are different we can see that after the bifurcation the same qualitative scenario appears: a limit cycle (marked with 1 in the figure) and the stable focus (marked with 2 in the figure) separated by the stable manifold of the saddle point. Therefore, as it is shown in the third plot of the figure 21, after the bifurcation in the three equations there exists bistability between two attractors.

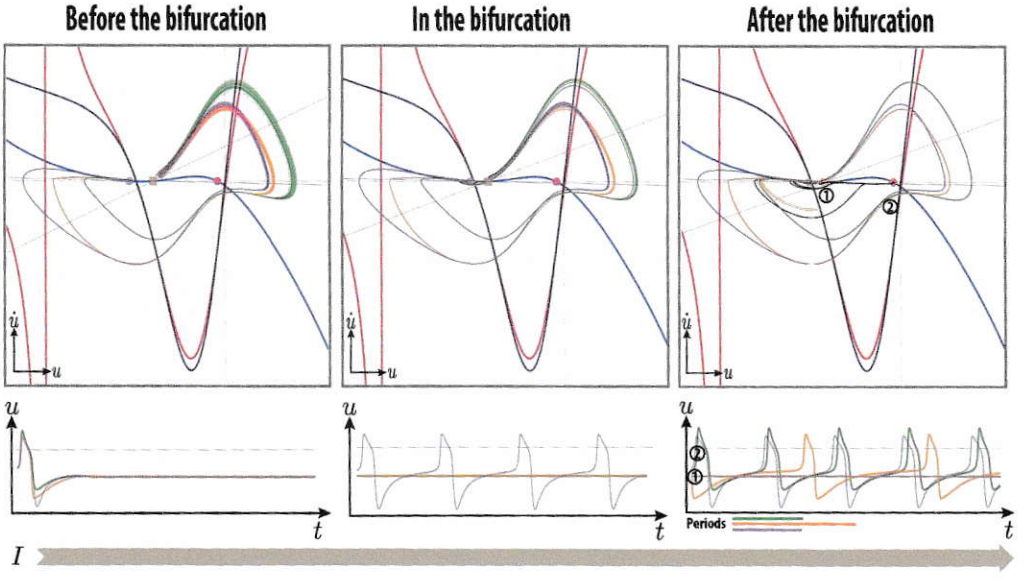


Figure 22: This figure shows the **Big homoclinic bifurcation** scenario in the Morris-Lecar model (green orbits), the Morris-Lecar model without the $(\dot{u})^2$ term (yellow orbits) and the reduced form of the Morris-Lecar model (purple orbits). On the top we show the phase space before the bifurcation, in the bifurcation and after the bifurcation. In the middle we show the graphics of u versus time for long times corresponding with each situation. On the bottom of the figure the brown arrow indicates the increase of the nondimensional injected current I. The two attractors that appear after the bifurcation are marked with the numbers 1 and 2 in the phase space and in the u versus t graphics. The heteroclinic separatrices of the three equations between the two attractors (simulated using negative time) are showed in black.

The figure 22 shows the Big homoclinic scenario. As it is shown in the figure 22 the three equations undergo qualitatively the same scenario described in section 10.3. Interestingly — as the theory predicts— we also found that in the three equations, that moving the parameters the big homoclinic scenario lead to the other scenarios distinctives of class 2 neurons.

Not surprisingly for us, is clear that the dynamics of class 2 neurons is not explained merely by an Andronov-Hopf bifurcation as many authors propose (Ermentrout and Terman, 2010), but by the big homoclinic scenario which led to other homoclinc bifurcations of the sparatrices.

This results are remarkable by itself: we numerically confirm that the Morris-Lecar model is in fact equivalent to the subcritical Bogdanov-Takens normal form. But must importantly, this simulations consistently supports our theoretical results showing that the dynamics observed in the original CB model is explained by the subcritical Bogdanov-Takens normal form.

16.2 The Hodgkin and Huxley model

We have simulated simultaneously the Hodgkin and Huxley model (equations E.17, E.18, E.19 and E.20), the Hodgkin and Huxley model after linearisation of the gating variables (equations E.32, E.33, E.34 and E.35) and the reduced form of the Hodgkin and Huxley model (equation E.46). With our software we can visualize and perturb interactively the orbits in a projection of the phase space (the x_1-u plane) and —in the case of the reduced model— in a transformation of the $\dot{u}$-u phase plane using the relation E.37. Therefore, in this simulations we visualise in the same x_1-u plane the Hodgkin and Huxley model, the model with linearisation of the gating variables (a four variables ODEs) and the reduced form of the Hodgkin and Huxley model (a two variables ODE). We use green to draw the orbits of the original Hodgkin and Huxley model, yellow for the model with linearisation and purple for the reduced form. The three equations have the same fixed points because the fixed points only depend on the $I^* = f(u^*)$ relation. The Hodgkin and Huxley model and the linearised Hodgkin and Huxley model have the same linear matrices and the same eigenvalues and eigenvectors around the fixed points. But in the reduced model the eigenvectors and eigenvalues are not equal to the other models. In practice the nearest to zero eigenvalues will be approximately equal to the nearest to zero eigenvalues of other two models. Hence, in this simulations we will plot the eigenvectors and eigenvalues only for the reduced model. We used the same previous colour and shape symbology for the different classes of fixed points, the stable and unstable manifolds and for the force and the friction functions.

The figure 23 shows that the shape of the limit cycles is quite different for the three equations and also their periods, but the dynamics does not changes qualitatively, and the the three equations undergo a Saddle-node Homoclinic bifurcation. Because the bifurcation is locally a saddle-

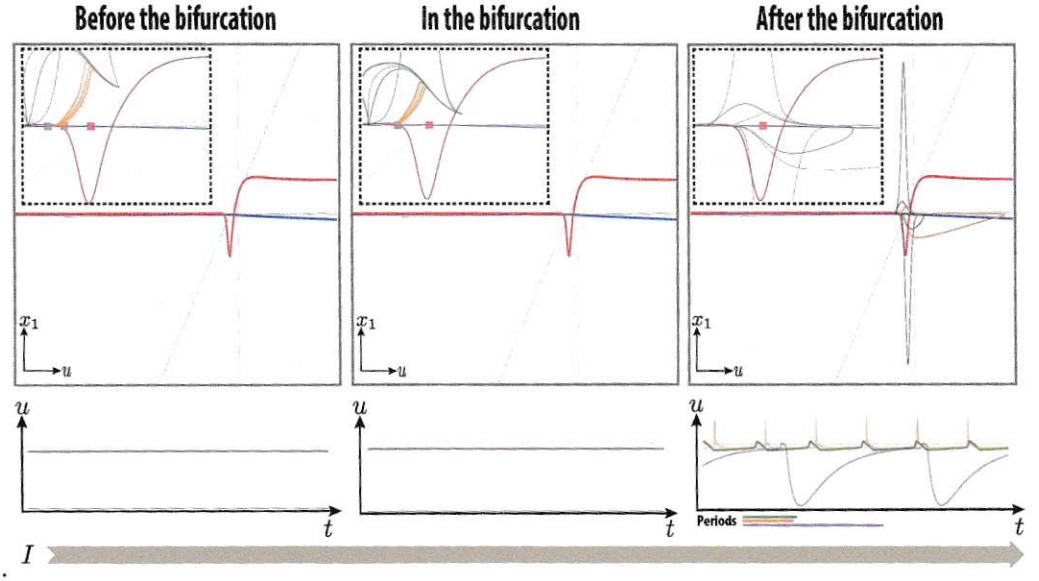


Figure 23: This figure show the **Saddle-node homoclinic bifurcation** scenario in the Hodgkin and Huxley model (green orbits), the linearised Hodgkin and Huxley model (yellow orbits) and the reduced form of the Hodgkin and Huxley model (purple orbits). On the top we show the phase plane before the bifurcation, in the bifurcation and after the bifurcation. In the top left of each phase plane we present in an edge dashed box a zoom of the phase plane. In the middle we show the graphics of u versus time for long times corresponding to each situation. With a coloured bar is we indicate the period of the oscillations for the three models using the same colour code. On the bottom of the figure the brown arrow indicates the increase of the nondimensional injected current I.

node bifurcation, and this bifurcation depends locally on the $I^* = f(u^*)$ curve, the Saddle-node homoclinic bifurcation occurs in the same bifurcation point for the three equations. The fact that the three models have the same qualitative behaviour is a beautiful example the Elphick-Tirapegui-Brachet-Coullet-Iooss theorem (Elphick et al., 1987; Haragus and Iooss, 2011; Wiggins, 2003). This theorem states that the relevant nonlinearities which shapes the qualitative dynamics of a given nonlinear dynamical system only depends of the structure of the linear system. Our numerical result strongly supports the statement because the three systems maintain the same *linear structure* and have the same qualitative dynamics.

16.3 The generalised Fitzhugh-Nagumo model

For completeness we show one example of the simulations performed in the generalised Fitzhugh-Nagumo model. The figure 24 shows the Saddle-node Homoclinic bifurcation scenario using the same symbols and colour codes of the previous simulations. Because (as we showed in the appendix F) this equation is almost the subcritical Bogdanov-Takens normal form (it is in fact less general than the normal form since there is a relation between the coefficient of the highest order nonlinear term in the force and the coefficient of the quadratic term of the friction) this equation will present all the bifurcation scenarios shown in section 10.3.

17 Biophysical interpretations

In this section we pretend to give an outline and a brief discussion of some biophysical interpretations which we found relevant. These interpretations are by no means unique and maybe they are not the most relevant of our theoretical work. We expect that the discussion with the reviewers of this thesis will enrich and open other possible interpretations and experimental applications.

One interesting outbreak interpretation comes from the very *nature* of the normal form approach. As we have previously discussed the qualitative dynamics of any dynamical system near a bifurcation is given by the normal form, but the connection with *the real world* is given by what we call the *ansatz* which is just the set of expressions through which the original physical variables are expressed in terms of the variables of the normal form. In this sense one can say that the physical content of a particular problem is in the *ansatz* which varies from one physical situation to another in contrast to the *normal form which has a universal nature.* Our *ansatz* shows

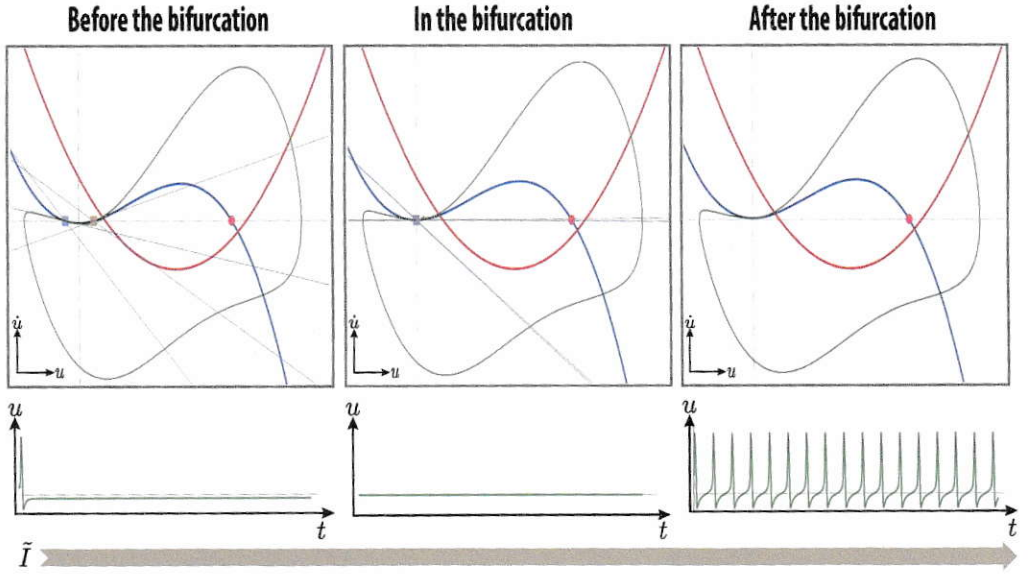


Figure 24: This figure shows the **Saddle-node homoclinic bifurcation** scenario in the generalised Fitzhugh-Nagumo model (green orbits). On the top we show the phase plane before the bifurcation, in the bifurcation and after the bifurcation. In the middle we show the graphics of u versus time for long times corresponding with each situation. On the bottom of the figure the brown arrow indicates the increase of the parameter $\tilde{I}$.

a very interesting feature of CB models, namely that the critical variables, i.e. the variables of the normal form, are the potential u and its derivative with respect to time $\dot{u}$ which have to be considered as independent variables since the normal form is a set of two first order differantial equations. This is very surprising because the variable u is actually the observable measured in the current experiments and $\dot{u}$ is often calculated through widely used data analysis in electrophysiology (Khaliq and Bean, 2008; Yu et al., 2008; Fernandez and White, 2010). Hence, a first important observation is that *the variables of the normal form are the experimentally relevant variables*, something that does not happen very often. As the theory predicts, because the CB models are generically in the neighbourhood of a Bogdanov-Takens bifurcation, the N gating variables of the CB models $(m_1, m_2, \ldots, m_N)$ will be slaved by the critical variables u and $\dot{u}$. Since we are able to calculate analytically the Jordan basis we have the analytical relation between the gating variables $(m_1, m_2, \ldots, m_N)$ and the critical variables (u and $\dot{u}$) at the dominant linear order in the critical variables for any CB model. Explicitly, using expression B.3 and the definitions 6.3 and 6.6 we obtain $(j = 1, 2, \ldots, N)$

$$m_j = m_j^{\infty}(u) - \frac{\partial m_j^{\infty}(u)}{\partial u}\tau_j(u)\dot{u} \tag{17.1}$$

These equations mean that the gating variables are *following* the stationary probabilities $m_j^{\infty}(u)$. The magnitude of the difference between a gating variable and its stationary probability will depend on the magnitude of the associated relaxation time, the variation of the stationary functions $m_j^{\infty}(u)$ on the potential u and the magnitude of the time variations $\dot{u}$ of the potential. The previous equations allow then a clear interpretation which is full of biophysical sense and —as our theory predict— will be approximately true for CB models.

As we mention in the previous sections, the model reduction method captures the qualitative features of the CB models. In that sense it is not a biophysical accurate description but a *qualitative cartoon* of the CB models which captures the essential features of their dynamics. Hence, the reduced equations exhibit the essential biophysical elements needed for the *excitable behaviour* observed in neurons. The interpretation of this equation provides us with a bridge between the excitable dynamics described by the subcritical Bogdanov-Takens normal form and the minimal biophysical elements of a CB model and the relations needed for this *excitable behaviour.*

As it can be seen in the reduced equation 15.9 the force is proportional to the difference between the injected current and the stationary current.

Then our theory suggests that the stationary current actually acts as a *hamiltonian like* force, and zero force *means* zero net current through the neuron.

But most surprisingly for us is the physical interpretation which can be given to the friction. In the hamiltonian dynamics the friction is key to transform a conservative (reversible) system in an out of equilibrium (irreversible) system. It is known that this breaks the $t \longrightarrow -t$ symmetry, a fact that is a fundamental feature shared by all biological systems (Prigogine, 1981). The friction in the equation 15.9 is composed by two terms: the term $\frac{1}{\tau_0}\left\|\frac{\partial f(u)}{\partial u}\right\| = \frac{\partial f(u)}{\partial u}$ and the term $\frac{1}{T_S}\left\|\mathrm{Det}\mathbb{L}_{N\times N}(u)\right\|$. As we we explain in section 5 the derivative respect to the voltage of the function $f(u)$ can be interpreted as the stationary resistance of the neuron membrane for long times. The resistance in electrodynamics is the analog of the friction in classical mechanics since the dissipated energy is proportional to the resistance and the friction, respectively. For large values of the potential ($u \to \pm\infty$) both terms ($\frac{\partial f(u)}{\partial u}$ and $\frac{1}{T_S}\left\|\mathrm{Det}\mathbb{L}_{N\times N}(u)\right\|$) are positive and act as a friction that dissipates energy. In fact it is known that in this conditions the membrane is actually dissipating energy and acting as an ohmic resistance (Latorre, 1996). On the other hand, to maintain the proper constant concentration of ions inside the neuron (concentration that changes in time due to the activity of the ionic channels that selectively permeate the ions inward or outward of the neuron) and maintaining constant the Nernst potential[14] of each different ion, the cells use an active mechanism. By ionic pumps that use ATP (the energy quanta in biology) the cell actually uses energy to maintain the ionic homeostasis (Alberts et al., 2007). By maintaining the reversal potentials is given a determined sign for the functions $M_j(u)$ for u above or below the reversal potential. This energy consumption will be responsible of the zero and negative resistance of neuronal membranes (in a neuronal membrane a very small current can produce a huge change in the potential) characteristic of the active membranes and of the *excitable behaviour*.

This energy consumption of the cell can be represented mechanically in the reduced CB model by the zone where the friction is negative (the injection of energy region in our mechanical interpretation). Interestingly the necessary conditions to have Bogdanov-Takens in CB models (see remark 13.2) will ensure a bounded energy injection region of values of u surrounded

[14]The u_j parameters are nerst potentials or linear combinations of nerst potential of different ion channel. This parameters are also called the reversion potential or the driving force of each ion channel.

by a dissipation energy zone extending to infinity in the reduced CB model if the system is not very far from Bogdanov-Takens[15]. Therefore there exists a beautiful consistence between the bionergetics[16] behind the *excitability behaviour* of neurons and the mechanical energy analysis of the reduced CB model (model that we have shown is equivalent to the subcritical Bogdanov-Takens normal form).

[15]Consider that the invariants have the value of 1 for $u \to \pm\infty$ and the Bogdanov-Takens necessary condition imposes a sign change in both invariants. If this change of sign not happened to far in u the friction will change the sign.

[16]It refer to the field of science that concerns of the energy flow through living systems.

Part IV

Bursting, Chaos and Triple Zero Bifurcation in Conductance Based Models

18 Triple Zero bifurcation in CB models

In the previous section we showed that neurons are poised generically in the neighbourhood of Bogdanov-Takens. Therefore —as we confirmed theoretically and numerically— the single neuron dynamics will be qualitatively described by the subcritical Bogdanov-Takens normal form. An amazing theoretical consequence of this is that this normal form is a two dimensional dynamical system which will not have chaotic behaviour in spite of the fact that the CB models are a set of *very* non linear coupled equation with more than three degrees of freedom (often between 4 to 30 equations) that should led generically to chaotic behaviour (Strogatz, 2001). Therefore, a theoretical prediction of our results is that the observation in single neurons of a chaotic behaviour will be very rare. In fact a chaotic dynamics is rarely observed experimentally in single neurons. But in some occasions it has been reported (Hayashi and Ishizuka, 1992; Makarenko and Llinás, 1998) and also reproduced numerically (Canavier et al., 1990; Innocenti et al., 2007; Laudanski et al., 2010).

On the other hand, the bursting dynamics is a phenomenon observed in single neurons that, in the last decades, attracted a lot of attention of many theoreticians (Coombes and Bressloff, 2005; Izhikevich, 2010; Ermentrout and Terman, 2010). It is characterized by an oscillatory dynamics where two or more spikes are followed by a quiescence period, and where one can see an interplay of fast and a slow oscillations. Although this is not the most generic behaviour, it is observed in some neurons, and can be only be theoretically reproduced with models of at least three dynamic variables (Izhikevich, 2010). Because the subcritical Bogdanov-Takens normal form is a two dimensional dynamical system it fails to capture the bursting phenomenon. Interestingly, it was shown that chaotic dynamics may arise during the transition between the tonic spiking (explained by the Bogdanov-Takens normal form) and the bursting dynamics (Innocenti et al., 2007; Terman, 1991, 1992).

To understand how this non generic dynamics (that may lead to chaos) arises in some particular cases from CB models, we have further investigated the mathematical structure of CB models. In appendix G we showed that the Triple Zero bifurcation (Arneodo et al., 1985) is not a generic bifurcation for CB models. But if a CB model meet the necessary biophysical conditions for bursting (Izhikevich, 2010) thats is: 1) a third very slow gating variable (order of magnitude slowest than T_S), 2) a high threshold gating variable, and this in addition to the necessary conditions for spiking, then the CB model will undergo a Triple Zero bifurcation if there exists three zero eigen-

values. Furthermore, using the calculations in the appendix G and with a similar analysis of the one given in section 14, one can show that if one has this third slow gating variable (in addition to the fast set τ_F and slow set T_S of gating variables) the three first coefficients of the characteristic polynomial will be very small:

$$|a_0| \ll 1$$
$$|a_1| \ll 1$$
$$|a_2| \ll 1$$

and we shall have a Jordan block of order 3. This result shows that, if a CB model meet the necessary biophysical conditions for the bursting dynamics, the system is mathematically within the unfolding of the Triple Zero bifurcation. Therefore in this conditions, the CB model will present all the complex phenomenology contained in the Triple Zero normal form, which consists in three critical variables which give rise to a rich phenomenology that includes chaotic dynamics, and where the Bogdanov-Takens normal form is contained (Arneodo et al., 1985). In addition to this, we recently showed that with a change of variable the Hindmarsh-Rose model (Hindmarsh and Rose, 1984) —the most famous phenomenological model for neuronal bursting— is actually almost the Triple Zero normal form (see appendix H).

This results strongly suggest that the Triple Zero bifurcation explain the bursting dynamics observed in neurons and the transition to chaos in CB models. But because this are preliminary results, we think that we need more theoretical calculations (e.g. to study the invariant to obtain the necessary conditions for the Triple Zero bifurcation in CB models, and also to study with more detail the Hindmarsh-Rose model) and more numerical simulations in order to give a definitive answer. But if our hypothesis is true, we shall be able to say that we can understand all the observed dynamics in neurons with a theory that connects the biophysics of single neurons (in the CB models) with their *mathematical essence* (bifurcations and normal form theory).

Part V
Conclusions and Perspectives

19 Conclusions

Our aim in this work has been to give a unified mathematical description of the behaviour of neuron dynamics as it is observed in current experiments. Since this behaviour is well characterised experimentally our conviction was since the beginning that such a description should exist. This conviction was supported by numerous comments and observations going in that sense in the literature such as the existence of minimal models or the reduction of models.

Our starting point has been the conductance based (CB) models which are universally accepted as models which give an excellent description of what is going on. The problem is of course that we have a huge quantity of these models which differ on the assumptions one makes for a definite situation. The models can differ in the number of variables one uses which depends on how many gating variables one considers important and in the characteristics of each ionic channel. The essential variable that is measured is the potential of the membrane of the cell which can be stationary, can make excursions around a rest stationary state or can have a periodic behaviour.

One of the most common electrophysiological experiments (current clamp experiments) are done varying the electrical current I injected in the neuron and observing what happens to the rest state of the potential. The behaviour which one observes in this procedure is what we call the "generic behaviour of neuron dynamics". Other behaviours, such as bursting, need some kind of "forcing" of the system in the sense that one has to impose conditions on the parameters of the model which put the system in very special conditions which are difficult to observe (they can be found in some special type of neurons). It had been noted by many authors that the generic behaviour can be essentially reproduced by a planar dynamics, i.e. by a dynamical system involving two variables, and many planar models have been constructed and studied.

Our central conclusion here is that the description of the experiments performed as explained in the previous paragraph can be done by a two variables dynamical system: the subcritical normal form of the Bogdanov-Takens bifurcation (0^2 in the notation of Arnold). This certainly looks contradictory since the Bogdanov-Takens bifurcation is codimension two, which means that we have to fix two parameters, and this does not seems to be the case in the description of the experiments we have given. But we have very strong arguments to sustain our conclusion which we shall now summarize:

1. A very complete theoretical discussion of the very special nature of the CB models has led us to the conclusion that when the usual qualitative assumptions accepted to observe the generic behaviour of neurons are satified, namely the existence of two different time scales and two different types of gating variables (one amplifying and one resonant), then the dynamical system, whatever is its dimension, is always in the unfolding of the Bogdanov-Takens (BT) bifurcation and is thus described by the corresponding normal form;

2. A reduction method which can be applied to any CB model satisfying the above mentioned conditions led in a very natural way to a reduced model which is "almost", in a sense that is made precise in the text, the normal form of the subcritical BT bifurcation.

3. We have constructed a special numerical simulator with high interactivity and specially adapted to this problem in all possible ways. In particular we are able to see in the same window and in real time the simultaneous behaviours of the original CB model, the reduced model and the subcritical BT normal form. Moreover we can exhibit the fixed points of the three systems together with their stability and also the linear part of the stable and unstable manifolds of the fixed point, all this in real time. *Our numerical simulations support completely our conclusion* and we can then say that indeed our arguments are correct and the universal description of the generic dynamics of neurons is given by the subcritical BT normal form.

4. When we write the normal form in the Arnold form we have a second order differential equation with a direct mechanical interpretation since it is a Hamiltonian system with non linear friction. We see then in this form the appeareance of two important functions: a nonlinear force (with its corresponding mechanical potential) and a non linear friction. This allows us to discuss the behaviour of neurons in terms of mechanical analogues which are highly intuitive and of direct interpretation.

Finally we have explored the "forcing" of the system and we have concluded that when the conditions given in the literature to have the "non generic" bursting behaviour are satisfied the system is in the unfolding of the triple zero 0^3 bifurcation which has chaotic behaviour as it has been observed experimentally.

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Part VI
Appendix

A Neuronal matrices proves and calculations

A.1 Proof of the theorem 7.1

Proof. We will proof it by induction. For $n = 1$ it is trivial, for $n = 2$ the equation 7.3 reads:

$$\prod_{j=1}^{2} \alpha_j + \sum_{i=1}^{2} \beta_i M_i \prod_{s \neq i}^{2} \alpha_s = \alpha_1 \alpha_2 + \beta_1 M_1 \alpha_2 + \beta_2 M_2 \alpha_1$$

On the other hand the Neuronal Matrix for $n = 2$ reads:

$$\mathbb{N} = \begin{pmatrix} \alpha_1 + \beta_1 M_1 & \beta_1 M_2 \\ \beta_2 M_1 & \alpha_2 + \beta_2 M_2 \end{pmatrix}$$

and its determinant is:

$$\mathrm{Det}(\mathbb{N}) = \alpha_1 \alpha_2 + \beta_1 M_1 \alpha_2 + \beta_2 M_2 \alpha_1$$

Therefore the theorem holds for $n = 2$. Let us assume that the theorem holds for the Neuronal Matrices of $n \times n$ and calculate the determinant of the $n+1 \times n+1$ Neuronal Matrix. We use the Laplace cofactor expansion for matrices and expand in the minors of the first column ($C_{i,1}$) of the Neuronal Matrix. Thus we can write determinant of a $n+1 \times n+1$ Neuronal Matrix as:

$$\mathrm{Det}(\mathbb{N}_{n+1 \times n+1}) = (\alpha_1 + \beta_1 M_1) C_{1,1} + M_1 \sum_{i=2}^{n+1} (-1)^{i+1} \beta_i C_{i,1}$$

Using the hypothesis for $n \times n$ neuronal matrix

$$C_{1,1} = \prod_{j=2}^{n+1} \alpha_j + \sum_{i=2}^{n+1} \beta_i M_i \prod_{s \neq i}^{n+1} \alpha_s$$

we obtain

$$(\alpha_1 + \beta_1 M_1) C_{1,1} = \prod_{j=1}^{n+1} \alpha_j + \sum_{i=1}^{n+1} \beta_i M_i \prod_{s \neq i}^{n+1} \alpha_s + \beta_1 M_1 \sum_{i=2}^{n+1} \beta_i M_i \prod_{s \neq i}^{n+1} \alpha_s$$

Hence, to prove that

$$\mathrm{Det}(\mathbb{N}_{n+1\times n+1}) = \prod_{j=1}^{n+1} \alpha_j + \sum_{i=1}^{n+1} \beta_i M_i \prod_{s\neq i}^{n+1} \alpha_s$$

We must prove now that always

$$M_1 \sum_{i=2}^{n+1} (-1)^{i+1} \beta_i C_{i,1} = -\beta_1 M_1 \sum_{i=2}^{n+1} \beta_i M_i \prod_{s\neq i}^{n+1} \alpha_s$$

If we use matrix row operations and their determinant properties, moving the first raw to the $i-1$ raw of each minor, we get the following expression for each minor

$$C_{i,1} = (-1)^i \begin{vmatrix} \alpha_2 + \beta_2 M_2 & \dots & \beta_2 M_{i-1} & \beta_2 M_i & \beta_2 M_{i+1} & \dots & \beta_2 M_n \\ \vdots & \ddots & \vdots & & \vdots & & \vdots \\ \beta_i M_2 & \dots & \alpha_{i-1} + \beta_{i-1} M_{i-1} & \beta_{i-1} M_i & \beta_{i-1} M_{i+1} & \dots & \beta_i M_n \\ \beta_1 M_2 & \dots & \beta_1 M_{i-1} & \beta_1 M_i & \beta_1 M_{i+1} & \dots & \beta_1 M_n \\ \beta_{i+1} M_2 & \dots & \beta_{i+1} M_{i-1} & \beta_{i+1} M_i & \alpha_{i+1} + \beta_{i+1} M_{i+1} & \dots & \beta_i M_n \\ \vdots & & \vdots & & & \ddots & \vdots \\ \beta_n M_2 & \dots & \beta_n M_{i-1} & \beta_n M_i & \beta_n M_{i+1} & \dots & \alpha_n + \beta_n M_n \end{vmatrix}$$

It is straightforward to note that we can use 7.3 for each $n \times n$ minor obtaining

$$C_{i,1} = \beta_1 M_i \prod_{j\neq i}^{n} \alpha_j \qquad i = 2 \dots n+1$$

Thus, using this expression we obtain

$$M_1 \sum_{i=2}^{n+1} (-1)^{i+1} \beta_i C_{i,1} = -M_1 \beta_1 \sum_{i=2}^{n+1} \beta_i M_i \prod_{j\neq i}^{n} \alpha_j$$

Q.E.D. □

B Analytical expression for the Jordan basis

In section 11.2 we show that the first vector of the Jordan basis is:

$$\underline{\chi}^{(0)} = \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix} \tag{B.1}$$

Therefore, the equation that must be solved to find explicitly the second vector of the Jordan basis is:

$$\mathbb{L}^c \underline{\chi}^{(1)} = \underline{\chi}^{(0)}$$

Then, the explicit linear equations reads:

$$\begin{array}{ccccccccc}
\beta_0 M_1 x_1 & + & \beta_0 M_2 x_2 + & \cdots & \cdots & + \beta_0 M_N x_N & = & 1 \\
(\alpha_1 + \beta_1 M_1) x_1 & + & \beta_1 M_2 x_2 + & \cdots & \cdots & + \beta_1 M_N x_N & = & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & = & \vdots \\
\beta_j M_1 x_1 & + & \beta_j M_2 x_2 + & \cdots & (\alpha_j + \beta_j M_j) x_j \cdots & + \beta_j M_N x_N & = & 0 \\
\vdots & \cdots & \vdots + & \vdots & \vdots & \vdots & = & \vdots \\
\beta_N M_1 x_1 & + & \beta_N M_2 x_2 + & \cdots & \cdots & + (\alpha_N + \beta_N M_N) x_N & = & 0
\end{array} \tag{B.2}$$

Let us number these $N+1$ equations beginning with the first equations as the equation 0 and the last one as equation N. If we perform the following operation with the equations:

$$j) \times \beta_0 - 0) \times \beta_j$$

We find that

$$\alpha_j \beta_0 x_j = -\beta_j$$

Because neither α_j ,β_0 or β_j are singular

$$x_j = -\frac{\beta_j}{\alpha_j \beta_0}$$

And if we choose $\nu = 0$ we find that the second vector of the Jordan basis, which we call $\underline{\chi}^{(1)}$, also belongs to the two dimensional Jordan block subspace and is given by:

$$\underline{\chi}^{(1)} = -\frac{1}{\beta_0}\begin{pmatrix} 0 \\ \frac{\beta_1}{\alpha_1} \\ \frac{\beta_2}{\alpha_2} \\ \vdots \\ \frac{\beta_N}{\alpha_N} \end{pmatrix} \tag{B.3}$$

Is important to notice that if we plug-in the expression (B.3) in the original linear equations (B.2) the equations are fulfilled and are written in terms of the second condition to be in the Bogdanov-Takens Bifurcation 11.3.

Now we have a analytical expression for the two vectors $\underline{\chi}^{(0)}$ and $\underline{\chi}^{(1)}$ and they belong to the Jordan block subspace. To find the other $N-1$ vectors of the Jordan base, let us suppose the most generic case when all the rest of the $N-1$ eigenvalues ($\{\lambda_2, \lambda_3 \ldots \lambda_N\}$) are different. Therefore, the general equation for the $N-1$ vectors is ($l = 2, 3, \ldots, N$):

$$\mathbb{L}^c \underline{\chi}^{(l)} = \lambda_l \underline{\chi}^{(l)}$$

Then the equations are:

$$\begin{array}{ccccc} -\lambda_l x_0^{(l)} + \beta_0 M_1 x_1^{(l)} + & \cdots & +\beta_0 M_N x_N^{(l)} & = & 0 \\ (\alpha_1 + \beta_1 M_1 - \lambda_l) x_1^{(l)} + & \cdots & +\beta_1 M_N x_N^{(l)} & = & 0 \\ \vdots & \vdots & \vdots & = & \vdots \\ \beta_j M_1 x_1^{(l)} + & \cdots (\alpha_j + \beta_j M_j - \lambda_l) x_j^{(l)} & +\beta_j M_N x_N^{(l)} & = & 0 \\ \vdots & \vdots & \vdots & = & \vdots \\ \beta_N M_1 x_1^{(l)} + & \cdots & +(\alpha_N + \beta_N M_N - \lambda_l) x_N^{(l)} & = & 0 \end{array} \tag{B.4}$$

Doing the following operation with the equations:

$$j)\beta_0 - 0) * \beta_j$$

we find that

$$x_j^{(l)} = \frac{\beta_j}{\beta_0} \frac{\lambda_l}{\lambda_l - \alpha_j} x_0^{(l)}$$

Then we find that

$$\underline{\chi}^{(l)} = \frac{\lambda_l x_0^{(l)}}{\beta_0} \begin{pmatrix} 1 \\ \frac{\beta_1}{\lambda_l - \alpha_1} \\ \frac{\beta_2}{\lambda_l - \alpha_2} \\ \vdots \\ \frac{\beta_N}{\lambda_l - \alpha_N} \end{pmatrix} \tag{B.5}$$

Where $x_0^{(l)}$ is a free parameter. Similar to the previous case, if we plug-in the expression (B.5) in the original linear equations (B.4) the equations are fulfilled. But now the expression that arise is written in therms of the analytical general expression of the characteristic polynomial of a conductance based model given in equation (7.5).

C Estimation of the order of τ_0

We will estimate the order of τ_0 assuming the conditions given in section 13.3 . That is assuming that we are in the Bogdanov-Takens point and $\tau_F/T_S \ll 1$. Using the last assumption in the equations 13.7 and 13.8 we can approximate:

$$BM_S \approx \frac{1}{T_S}\left(1+\frac{\tau_F}{\tau_0}\right) \tag{C.1}$$

$$BM_F \approx -\frac{1}{T_S}\left(1+\frac{T_S}{\tau_0}\right) \tag{C.2}$$

We analyze equation C.2. If $T_S/\tau_0 \gg 1$ then BM_F must be large and —due the features of the functions $\beta_j(u)$ and $M_j(u)$— very narrow. This is a singularity for the functions $\beta_j(u)$ and in the CB models generically will not happen. But in section 18 we will show that in this peculiar case (which is unlikely to happen experimentally) the CB models generically undergo a triple-zero 0^3 bifurcation (i.e. an eigenvalue zero with multilicity three and a Jordan block of order 3). Analogously, if $\tau_F/\tau_0 \gg 1$, then using the same argument but with BM_S we conclude that this case must not be generic either. Now, if we consider the case $\tau_F/\tau_0 \sim 1$, equation C.2 becomes

$$BM_F \approx -\frac{1}{T_S}\left(1+\frac{T_S}{\tau_F}\right)$$

and take into account that $\tau_F/T_S \ll 1$ we see that BM_F must be large and this case will not be generic. Now if we consider the case $T_S/\tau_0 \ll 1$, then approximately:

$$\begin{aligned} BM_S &\approx \frac{1}{T_S} \\ BM_F &\approx -\frac{1}{T_S} \end{aligned}$$

And the invariants read

$$\begin{aligned} \left\|\frac{\partial f}{\partial u}\right\| &\approx 1+\frac{\tau_0}{T_S}-\frac{\tau_0}{T_S} \approx 1 \\ \|\mathrm{Det}\mathbb{L}_{N\times N}\| &\approx 1+\frac{\tau_F}{T_S}-\frac{T_S}{T_S} \approx \frac{\tau_F}{T_S} \end{aligned}$$

This result shows that if this case holds then the system will be *far* from Bogdanov-Takens (since $\left\|\frac{\partial f}{\partial u}\right\| \sim 1$), in contradiction with the assumption used in this analysis (we assumed that the system is in the Bogdanov-Takens point). This can be interpreted saying that if the system is in this case, the parameters must be *forced* (in the sense of taking extreme values) to undergo the bifurcation. Finally if $T_S/\tau_0 \sim 1$, we can write approximately:

$$\begin{aligned} BM_S &\approx \frac{1}{T_S} \\ BM_F &\approx -\frac{2}{T_S} \end{aligned}$$

And the invariants:

$$\begin{aligned} \left\|\frac{\partial f}{\partial u}\right\| \approx 1 + \left(\frac{\tau_0}{T_S} - \frac{2\tau_0}{T_S}\right) &\approx 0 \\ \|\mathrm{Det}\mathbb{L}_{N\times N}\| \approx 1 - \left(\frac{T_S}{T_S} - \frac{2\tau_F}{T_S}\right) &\approx \frac{2\tau_F}{T_S} \ll 1 \end{aligned}$$

Using our first assumption that $\tau_F/T_S \ll 1$ the last equations shows that the approximations done in this case ($T_S/\tau_0 \sim 1$) do not deviate much the invariants from the Bogdanov-Takens point (the other assumption for this analysis).

This rough analysis suggest that the only case where we do not need to *force* the parameters to put the functions β or M in extreme values (very large or very small) to undergo Bogdanov-Takens in CB models is when $T_S/\tau_0 \sim 1$. Hence, this must be the generic physical scenario for a realistic CB model that undergo the Bogdanov-Takens bifurcation. The figure 16 shows that within the range u where the Hodgkin and Huxley model undergoes this bifurcation (indicated with a dashed line) this condition hold (the figure shows that $\tau_h(u)/\tau_0 \sim \tau_n(u)/\tau_0 \sim 1$). If we take into account that τ_0 is of the order of the adimensional membrane time constant, then in general the experimental data supports this theoretical estimation.

D The Morris-Lecar Model

D.1 The Model

One of the simplest and well known conductance based model for the generation of action potentials is a model proposed by Kathleen Morris and Harold Lecar (Morris and Lecar, 1981). The model has three channels: a potassium channel, a calcium channel, and a leak. In the simplest version of the model, the calcium current depends instantaneously on the voltage. The Morris-Lecar is representative of the conductance based models that have excitability class 1 and Class 2 (Ermentrout and Terman, 2010) and the global and local bifurcations characteristics of this kind of neuronal dynamics (Tsumoto et al., 2006). The mathematical formulation of the Morris-Lecar model is

$$\dot{v} = \frac{1}{C_m}[I - g_K n(v - E_K) - g_{Ca} m^{\infty}(v)(v - E_{Ca}) - g_L(v - E_L)] \quad \text{(D.1)}$$

$$\dot{n} = \phi \frac{n^{\infty}(v) - n}{\tau(v)} \quad \text{(D.2)}$$

with:

$$m^{\infty}(v) = \frac{1}{2}\left(1 + \tanh \frac{v - V1}{V2}\right) \quad \text{(D.3)}$$

$$n^{\infty}(v) = \frac{1}{2}\left(1 + \tanh \frac{v - V3}{V4}\right) \quad \text{(D.4)}$$

$$\tau(v) = \frac{1}{\cosh \frac{v - V3}{2V4}} \quad \text{(D.5)}$$

To transform the equations to dimensionless equations we can use the scaling:

I	g_1	g_2	g_3	u_1	u_2	u_3	c	a_1	b_1	a_2	b_2
$\frac{I}{g_L\lvert E_L\rvert}$	$\frac{g_K}{g_L}$	$\frac{g_{Ca}}{g_L}$	1	$\frac{E_K}{\lvert E_L\rvert}$	$\frac{E_{Ca}}{\lvert E_L\rvert}$	1	$\frac{g_L}{\phi C m}$	$\lvert E_L\rvert/V_4$	$-V_3/V_4$	$\lvert E_L\rvert/V_2$	$-V_1/V_2$

Table 1: Dimensionless parameters for the Morris-Lecar model.

We scale time as

$$t = \frac{C_m}{g_L}\bar{t}$$

and the variable v as

$$u = \frac{v}{|E_L|}$$

Then the new equations are

$$\dot{u} = I - g_1 n(u - u_1) - g_2 m^\infty(u)(u - u_2) - g_3(u - u_3) \quad \text{(D.6)}$$

$$\dot{n} = \frac{n^\infty(u) - n}{\tau(u)} \quad \text{(D.7)}$$

with

$$m^\infty(u) = \frac{1}{2}[1 + \tanh(a_2 u + b_2)] \quad \text{(D.8)}$$

$$n^\infty(u) = \frac{1}{2}[1 + \tanh(a_1 u + b_1)] \quad \text{(D.9)}$$

$$\tau(u) = \frac{c}{\cosh(\frac{a_1 u + b_1}{2})} \quad \text{(D.10)}$$

Then with a non singular change of variables the equations get a structure that has an important and general interpretation in all models of neurons. We write

$$x = n - n^\infty(u) \quad \text{(D.11)}$$

and define

$$f(u) \equiv g_1 n^\infty(u)(u - u_1) + g_2 m^\infty(u)(u - u_2) + g_3(u - u_3) \quad \text{(D.12)}$$

Then doing the proper calculations that we do for a generic conductance based model in section 5 we obtain

$$\dot{u} = I - f(u) - g_1 x(u - u_1) \quad \text{(D.13)}$$

$$\dot{x} = -\frac{x}{\tau(u)} - \frac{\partial n^\infty}{\partial u}[I - f(u) - g_1 x(u - u_1)] \quad \text{(D.14)}$$

And with the definition 5.8:

$$\beta(u) = -\frac{\partial n^\infty}{\partial u} = -\frac{1}{2} a_1 \text{sech}^2(a_1 u + b_1)$$

the equations finally take the form:

$$\dot{u} = I - f(u) - g_1 x(u - u_1) \tag{D.15}$$

$$\dot{x} = -\frac{x}{\tau(u)} + \beta(u)\dot{u} \tag{D.16}$$

D.2 Morris-Lecar to Andronov

We will reproduce the method developed in section 15.1 in this particular model. Since the Morris-Lecar is a two variables model this will be a change of variable rather than a process of model reduction. In fact, this calculation is very instructive in relation to the general calculations that was performed in 15.1. We begun by doing the time derivative of D.15:

$$\ddot{u} = -\frac{\partial f(u)}{\partial u}\dot{u} - g_1\dot{x}(u - u_1) - g_1 x\dot{u} \tag{D.17}$$

Then using equation D.16 in D.18 we obtain

$$\ddot{u} = -\frac{\partial f(u)}{\partial u}\dot{u} - g_1(u - u_1)\left\{-\frac{x}{\tau(u)} + \beta(u)\dot{u}\right\} - g_1 x\dot{u} \tag{D.18}$$

If we use equation D.15 we have

$$x = \frac{I - f(u)}{g_1(u - u_1)} - \frac{\dot{u}}{g_1(u - u_1)}$$

and if we plug this expression in equation D.18 and if we consider the definitions of the invariants in sections 12 and E.40 we finally obtain:

$$\ddot{u} = \frac{I - f(u)}{\tau(u)} - \dot{u}\left(\frac{I - f(u)}{u - u_1} + \tau_0(u)\left\|\frac{\partial f(u)}{\partial u}\right\| + \frac{1}{\tau(u)}\left\|\mathrm{Det}\mathbb{L}(u)\right\|\right) + \frac{\dot{u}^2}{u - u_1} \tag{D.19}$$

with

$$\tau_0(u) = \frac{1}{[g_1 m^\infty(u) + g_2 n^\infty(u) + g_3]} \tag{D.20}$$

$$\left\|\frac{\partial f(u)}{\partial u}\right\| = 1 + \tau_0(u)\left\{g_1 \left.\frac{\partial m^\infty(\bar{u})}{\partial \bar{u}}\right|_{\bar{u}=u}(u - u_1) + g_2 \left.\frac{\partial n^\infty(\bar{u})}{\partial \bar{u}}\right|_{\bar{u}=u}(u - u_2)\right\} \tag{D.21}$$

and

$$\|\mathrm{Det}\mathbb{L}(u)\| = 1 - \tau(u) g_1 \left.\frac{\partial m^{\infty}(\bar{u})}{\partial \bar{u}}\right|_{\bar{u}=u} (u - u_1) \tag{D.22}$$

Then following the steps of section 15 we can neglect the term $\frac{\dot{u}^2}{u-u_1}$ obtaining

$$\ddot{u} = \frac{I - f(u)}{\tau(u)} - \dot{u} \left(\frac{I - f(u)}{u - u_1} + \tau_0(u) \left\| \frac{\partial f(u)}{\partial u} \right\| + \frac{1}{\tau(u)} \|\mathrm{Det}\mathbb{L}(u)\| \right) \tag{D.23}$$

Using the same arguments of section 15.2 we can neglect the term $\dot{u} \left(\frac{I-f(u)}{u-u_1} \right)$ to obtain finally the reduced form of the Morris-Lecar model

$$\ddot{u} = \frac{I - f(u)}{\tau(u)} - \dot{u} \left(\tau_0(u) \left\| \frac{\partial f(u)}{\partial u} \right\| + \frac{1}{\tau(u)} \|\mathrm{Det}\mathbb{L}(u)\| \right) \tag{D.24}$$

E Hodgkin and Huxley Model

E.1 The Hodgkin and Huxley Model

The Hodgkin-Huxley model is the first conductance based model proposed by Alan Lloyd Hodgkin and Andrew Huxley in 1952 to explain the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon (Hodgkin and Huxley, 1952). They received the 1963 Nobel Prize in Physiology or Medicine for this work. It is widely accepted that this model contain the key biophysical mechanism which give rise to the *excitability behaviour* of most of the neurons. The mathematical formulation of the model is

$$\dot{v} = \frac{1}{C}\left\{\bar{I} - g_{Na}m^3h(v - E_{Na}) - g_K n^4(v - E_K) - g_L(v - E_L)\right\} \quad \text{(E.1)}$$

$$\dot{m} = \frac{m^\infty(v) - m}{\tilde{\tau}_m(v)} \quad \text{(E.2)}$$

$$\dot{h} = \frac{h^\infty(v) - h}{\tilde{\tau}_h(v)} \quad \text{(E.3)}$$

$$\dot{n} = \frac{n^\infty(v) - n}{\tilde{\tau}_n(v)} \quad \text{(E.4)}$$

To transform these equations to a dimensionless form we can use the scaling:

I	g_1	g_2	g_3	u_1	u_2	u_3
$\frac{I}{(g_L+g_K\|E_L\|}$	$\frac{g_{Na}}{g_L+g_K}$	$\frac{g_K}{g_L+g_K}$	$\frac{g_L}{g_L+g_K}$	$\frac{E_{Na}}{\|E_L\|}$	$\frac{E_K}{\|E_L\|}$	-1

Table 2: Relation between the the original and the dimensionless parameters.

The new time scale is

$$t = \frac{C}{g_L + g_K}\bar{t}$$

and we scale the potential variable v as

$$u = \frac{v}{|E_L|}$$

We also consider dimensionless parameters for $m^\infty(u)$, $h^\infty(u)$ and $n^\infty(u)$, as written in tables 3, 4 and 5, respectively. Then these functions read

A_{α_m}	B_{α_m}	A_{β_m}	B_{β_m}	C_{β_m}
$-\frac{\lvert E_L\rvert}{10}$	-3.2	$-\frac{\lvert E_L\rvert}{18}$	$-\frac{57}{18}$	4

Table 3: Dimensionless parameters for $m^\infty(u)$ and $\tau_m(u)$.

A_{α_h}	B_{α_h}	C_{α_h}	A_{β_h}	B_{β_h}
$-\frac{\lvert E_L\rvert}{20}$	$-\frac{46}{20}$	$\frac{7}{100}$	$-\frac{\lvert E_L\rvert}{10}$	-1.6

Table 4: Dimensionless parameters for $h^\infty(u)$ and $\tau_h(u)$.

A_{α_n}	B_{α_n}	A_{β_n}	B_{β_n}	C_{β_n}
$-\frac{\lvert E_L\rvert}{10}$	-3.6	$-\frac{\lvert E_L\rvert}{80}$	$-\frac{46}{80}$	0.125

Table 5: Dimensionless parameters for $n^\infty(u)$ and $\tau_n(u)$.

$$\alpha_m(u) = \frac{A_{\alpha_m}u + B_{\alpha_m}}{e^{(A_{\alpha_m}u+B_{\alpha_m})} - 1} \tag{E.5}$$

$$\beta_m(u) = C_{\beta_m}e^{(A_{\beta_m}u+B_{\beta_m})} \tag{E.6}$$

$$\alpha_h(u) = C_{\alpha_h}e^{(A_{\alpha_h}u+B_{\alpha_h})} \tag{E.7}$$

$$\beta_h(u) = \frac{1}{1 + e^{(A_{\beta_h}u+B_{\beta_h})}} \tag{E.8}$$

$$\alpha_n(u) = \frac{0.1\,(A_{\alpha_n}u + B_{\alpha_n})}{e^{(A_{\alpha_n}u+B_{\alpha_n})} - 1} \tag{E.9}$$

$$\beta_n(u) = C_{\beta_n}e^{(A_{\beta_n}u+B_{\beta_n})} \tag{E.10}$$

and finally

$$m^\infty(u) = \frac{\alpha_m(u)}{\alpha_m(u) + \beta_m(u)} \tag{E.11}$$

$$h^\infty(u) = \frac{\alpha_h(u)}{\alpha_h(u) + \beta_h(u)} \tag{E.12}$$

$$n^\infty(u) = \frac{\alpha_n(u)}{\alpha_n(u) + \beta_n(u)} \tag{E.13}$$

The dimensionless relaxation time of the gating variables (without tilde) are

$$\tau_m(u) = \frac{g_L + g_K}{C\left[\alpha_m(u) + \beta_m(u)\right]} \tag{E.14}$$

$$\tau_h(u) = \frac{g_L + g_K}{C\left[\alpha_m(u) + \beta_m(u)\right]} \tag{E.15}$$

$$\tau_n(u) = \frac{g_L + g_K}{C\left[\alpha_n(u) + \beta_n(u)\right]} \tag{E.16}$$

Thus the new equations will be

$$\begin{aligned}
\dot{u} &= I - g_1 m^3 h(u - u_3) - g_2 n^4 (u - u_2) - g_3(u - u_3) \\
\dot{m} &= \frac{m^\infty(u) - m}{\tau_m(u)} \\
\dot{h} &= \frac{h^\infty(u) - h}{\tau_h(u)} \\
\dot{n} &= \frac{n^\infty(u) - n}{\tau_n(u)}
\end{aligned}$$

By doing the calculations explained in section 5 to transform a generic CB model in its *standard form* we obtain

$$\dot{u} = I - f(u) - K(u, x_1, x_2, x_3) \tag{E.17}$$

$$\dot{x_1} = -\frac{x_1}{\tau_m(u)} + \beta_1(u)\dot{u} \tag{E.18}$$

$$\dot{x_2} = -\frac{x_2}{\tau_h(u)} + \beta_2(u)\dot{u} \tag{E.19}$$

$$\dot{x_3} = -\frac{x_3}{\tau_n(u)} + \beta_3(u)\dot{u} \tag{E.20}$$

with

$$f(u) \equiv g_1 m^\infty(u)^3 h^\infty(u)(u - u_3) + g_2 n^\infty(u)^4 (u - u_2) + g_3(u - u_3) \tag{E.21}$$

and

$$\begin{aligned}
K(u, x_1, x_2, x_3) \equiv g_1 \left\{x_1^3 x_2 + 3x_1^2 m^\infty(u) x_2 + 3x_1 m^\infty(u)^2 x_2 + m^\infty(u)^3 x_2 + x_1^3 h^\infty(u) + \right. \\
\left. 3x_1^2 m^\infty(u) h^\infty(u) + 3x_1 m^\infty(u)^2 h^\infty(u)\right\}(u - u_1) + g_2 \left\{x_3^4 + 4x_3^3 n^\infty(u) + 6x_3^2 n^\infty(u)^2 + \right. \\
\left. 4x_3 n^\infty(u)^3\right\}(u - u_2)
\end{aligned} \tag{E.22}$$

and where we have used the definition 5.8:

$$\beta_1(u) = -\left.\frac{\partial m^{\infty}(\bar{u})}{\partial \bar{u}}\right|_{\bar{u}=u} \tag{E.23}$$

$$\beta_2(u) = -\left.\frac{\partial h^{\infty}(\bar{u})}{\partial \bar{u}}\right|_{\bar{u}=u} \tag{E.24}$$

$$\beta_3(u) = -\left.\frac{\partial n_{\infty}(\bar{u})}{\partial \bar{u}}\right|_{\bar{u}=u} \tag{E.25}$$

with

$$\left.\frac{\partial m^{\infty}(\bar{u})}{\partial \bar{u}}\right|_{\bar{u}=u} =$$

$$-\frac{(A_{\alpha_m}u+B_{\alpha_m})\left(-\frac{A_{\alpha_m}e^{A_{\alpha_m}u+B_{\alpha_m}}(A_{\alpha_m}u+B_{\alpha_m})}{\left(e^{A_{\alpha_m}u+B_{\alpha_m}}-1\right)^2}+\frac{A_{\alpha_m}}{e^{A_{\alpha_m}u+B_{\alpha_m}}-1}+A_{\beta_m}C_{\beta_m}e^{A_{\beta_m}u+B_{\beta_m}}\right)}{(e^{A_{\alpha_m}u+B_{\alpha_m}}-1)\left(\frac{A_{\alpha_m}u+B_{\alpha_m}}{e^{A_{\alpha_m}u+B_{\alpha_m}}-1}+C_{\beta_m}e^{A_{\beta_m}u+B_{\beta_m}}\right)^2}$$

$$+\frac{A_{\alpha_m}}{(e^{A_{\alpha_m}u+B_{\alpha_m}}-1)\left(\frac{A_{\alpha_m}u+B_{\alpha_m}}{e^{A_{\alpha_m}u+B_{\alpha_m}}-1}+C_{\beta_m}e^{A_{\beta_m}u+B_{\beta_m}}\right)}$$

$$-\frac{A_{\alpha_m}e^{A_{\alpha_m}u+B_{\alpha_m}}(A_{\alpha_m}u+B_{\alpha_m})}{(e^{A_{\alpha_m}u+B_{\alpha_m}}-1)^2\left(\frac{A_{\alpha_m}u+B_{\alpha_m}}{e^{A_{\alpha_m}u+B_{\alpha_m}}-1}+C_{\beta_m}e^{A_{\beta_m}u+B_{\beta_m}}\right)} \tag{E.26}$$

$$\left.\frac{\partial h^{\infty}(\bar{u})}{\partial \bar{u}}\right|_{\bar{u}=u} =$$

$$-\frac{C_{\alpha_h}e^{A_{\alpha_h}u+B_{\alpha_h}}\left(A_{\alpha_h}C_{\alpha_h}e^{A_{\alpha_h}u+B_{\alpha_h}}-\frac{A_{\beta_h}e^{A_{\beta_h}u+B_{\beta_h}}}{\left(e^{A_{\beta_h}u+B_{\beta_h}}+1\right)^2}\right)}{\left(C_{\alpha_h}e^{A_{\alpha_h}u+B_{\alpha_h}}+\frac{1}{e^{A_{\beta_h}u+B_{\beta_h}}+1}\right)^2}$$

$$+\frac{A_{\alpha_h}C_{\alpha_h}e^{A_{\alpha_h}u+B_{\alpha_h}}}{C_{\alpha_h}e^{A_{\alpha_h}u+B_{\alpha_h}}+\frac{1}{e^{A_{\beta_h}u+B_{\beta_h}}+1}} \tag{E.27}$$

$$\left.\frac{\partial n^{\infty}(\bar{u})}{\partial \bar{u}}\right|_{\bar{u}=u} =$$

$$-\frac{0.1(A_{\alpha_n}u+B\alpha_n)\left(-\frac{0.1A_{\alpha_n}e^{A_{\alpha_n}u+B\alpha_n}(A_{\alpha_n}u+B\alpha_n)}{\left(e^{A_{\alpha_n}u+B\alpha_n}-1\right)^2}+\frac{0.1A_{\alpha_n}}{e^{A_{\alpha_n}u+B\alpha_n}-1}+A_{\beta_n}C_{\beta_n}e^{A_{\beta_n}u+B_{\beta_n}}\right)}{(e^{A_{\alpha_n}u+B\alpha_n}-1)\left(\frac{0.1(A_{\alpha_n}u+B\alpha_n)}{e^{A_{\alpha_n}u+B\alpha_n}-1}+C_{\beta_n}e^{A_{\beta_n}u+B_{\beta_n}}\right)^2}$$

$$+\frac{0.1A_{\alpha_n}}{(e^{A_{\alpha_n}u+B\alpha_n}-1)\left(\frac{0.1(A_{\alpha_n}u+B\alpha_n)}{e^{A_{\alpha_n}u+B\alpha_n}-1}+C_{\beta_n}e^{A_{\beta_n}u+B_{\beta_n}}\right)}$$

$$-\frac{0.1A_{\alpha_n}e^{A_{\alpha_n}u+B\alpha_n}(A_{\alpha_n}u+B_{\alpha_n})}{(e^{A_{\alpha_n}u+B\alpha_n}-1)^2\left(\frac{0.1(A_{\alpha_n}u+B\alpha_n)}{e^{A_{\alpha_n}u+B\alpha_n}-1}+C_{\beta_n}e^{A_{\beta_n}u+B_{\beta_n}}\right)} \tag{E.28}$$

E.2 Hodgkin and Huxley model reduction

We will reproduce the method developed in section 15.1. Let us suppose that $x_1, x_2, x_3 \ll 1$, then:

$$K(u, x_1, x_2, x_3) \approx -M_1(u)x_1 - M_2(u)x_2 - M_3(u)x_3$$

where:

$$M_1(u) = -3g_1 m^\infty(u)^2 h^\infty(u)(u - u_1) \quad \text{(E.29)}$$
$$M_2(u) = -g_1 m^\infty(u)^3 (u - u_1) \quad \text{(E.30)}$$
$$M_3(u) = -4g_2 n^\infty(u)^3 (u - u_2) \quad \text{(E.31)}$$

As its clear in the figure 16 in the Hogkin and Huxley model we have one fast gating variable (x_1 corresponding to the m variable) and two slow gating variables (x_2 and x_3 corresponding to h and n respectively). We will consider that $\tau_m(u)$ is of the order of some τ_F and consider τ_h and τ_n of the order of some T_S, and perform all the calculations described in general in section 15.1. It will be not qualitatively important how to approximate the specific values of τ_F and T_S, for example we can approximate its values by doing the average in an interval of u of $\tau_m(u)$ for τ_F and of τ_h and τ_n for T_S. But the important matter is —as it actually happens in the Hodgkin and Huxley model— that there must exist two sets of gating variables with differents time scales $\tau_m(u) \sim \tau_F$ and $\tau_h(u) \sim \tau_n(u) \sim T_S$, that meet the condition $\tau_F / T_S \gg 1$. Then the Hodgkin and Huxley model becomes

$$\dot{u} = I - f(u) + M_1(u)x_1 + M_2(u)x_2 + M_3(u)x_3 \quad \text{(E.32)}$$
$$\dot{x_1} = -\frac{x_1}{\tau_F} + \beta_1(u)\dot{u} \quad \text{(E.33)}$$
$$\dot{x_2} = -\frac{x_2}{T_S} + \beta_2(u)\dot{u} \quad \text{(E.34)}$$
$$\dot{x_3} = -\frac{x_3}{T_S} + \beta_3(u)\dot{u} \quad \text{(E.35)}$$

If we take the time derivative of equation E.32 we obtain

$$\ddot{u} = -\frac{\partial f(u)}{\partial u}\dot{u} + x_1\frac{\partial M_1(u)}{\partial u}\dot{u} + M_1(u)\dot{x_1} + x_2\frac{\partial M_2(u)}{\partial u}\dot{u} + M_2(u)\dot{x_2} + M_3(u)\dot{x_3} + x_3\frac{\partial M_3(u)}{\partial u}\dot{u} \quad \text{(E.36)}$$

Because x_1 is a fast variable we can do an adiabatic elimination supposing that x_1 is instantaneous

$$\dot{x}_F \sim 0 \Rightarrow x_1 = \dot{u}\tau_F\beta_m(u) \tag{E.37}$$

Then equation becomes

$$\ddot{u} = -\frac{\partial f(u)}{\partial u}\dot{u} + \tau_F\beta_1(u)\frac{\partial M_1(u)}{\partial u}\dot{u}^2 + x_2\frac{\partial M_2(u)}{\partial u}\dot{u} + M_2(u)\dot{x_2} + M_3(u)\dot{x_3} + x_3\frac{\partial M_3(u)}{\partial u}\dot{u} \tag{E.38}$$

Using equations E.34 and E.35 we obtain

$$\ddot{u} = -\frac{\partial f(u)}{\partial u}\dot{u} + \tau_F\beta_1(u)\frac{\partial M_1(u)}{\partial u}\dot{u}^2 + x_2\frac{\partial M_2(u)}{\partial u}\dot{u} + M_2(u)\left\{-\frac{x_2}{T_S} + \beta_2(u)\dot{u}\right\} + M_3(u)\left\{-\frac{x_3}{T_S} + \beta_3(u)\dot{u}\right\} + x_3\frac{\partial M_3(u)}{\partial u}\dot{u} \tag{E.39}$$

From equation E.32 we have

$$M_2(u)x_2 + M_3(u)x_3 = \dot{u} - [I - f(u)] - \tau_F M_1(u)\beta_1(u)\dot{u}$$

and using this last equation in E.38 we obtain

$$\ddot{u} = \frac{I - f(u)}{T_S} - \dot{u}\left(\frac{\partial f(u)}{\partial u} + \frac{1}{T_S}\left[1 - \tau_F M_1(u)\beta_1(u) - T_S M_2(u)\beta_2(u) - T_S M_3(u)\beta_3(u)\right]\right) + \tau_F\beta_1(u)\frac{\partial M_1(u)}{\partial u}\dot{u}^2 + \dot{u}\left\{x_2\frac{\partial M_2(u)}{\partial u} + x_3\frac{\partial M_3(u)}{\partial u}\right\} \tag{E.40}$$

If we consider the definitions of the invariants in section 12 the equation E.40 becomes

$$\ddot{u} = \frac{I - f(u)}{T_S} - \dot{u}\left(\frac{1}{\tau_0(u)}\left\|\frac{\partial f(u)}{\partial u}\right\| + \frac{1}{T_S}\left\|\mathrm{Det}\mathbb{L}(u)\right\|\right) + \tau_F\beta_1(u)\frac{\partial M_1(u)}{\partial u}\dot{u}^2 + \dot{u}\left\{x_2\frac{\partial M_2(u)}{\partial u} + x_3\frac{\partial M_3(u)}{\partial u}\right\} \tag{E.41}$$

Finally the Hodgkin and Huxley model is written as

$$\ddot{u} = \frac{I - f(u)}{T_S} - \dot{u}\left(\frac{1}{\tau_0(u)}\left\|\frac{\partial f(u)}{\partial u}\right\| + \frac{1}{T_S}\left\|\mathrm{Det}\mathbb{L}(u)\right\|\right) + \tau_F\beta_1(u)\frac{\partial M_1(u)}{\partial u}\dot{u}^2$$
$$+ \dot{u}\left\{x_2\frac{\partial M_2(u)}{\partial u} + x_3\frac{\partial M_3(u)}{\partial u}\right\} \tag{E.42}$$

$$\dot{x_2} = -\frac{x_2}{T_S} + \beta_2(u)\dot{u} \tag{E.43}$$

$$\dot{x_3} = -\frac{x_3}{T_S} + \beta_3(u)\dot{u} \tag{E.44}$$

with the constraint

$$M_2(u)x_2 + M_3(u)x_3 = \dot{u} - [I - f(u)] - \tau_F M_1(u)\beta_1(u)\dot{u} \tag{E.45}$$

E.3 Hodgkin and Huxley to Andronov

Fallowing the same steps as in 15.1 we finally arrive to the reduced form of the Hodgkin and Huxley model:

$$\ddot{u} = \frac{I - f(u)}{T_S} - \dot{u}\left(\frac{1}{\tau_0(u)}\left\|\frac{\partial f(u)}{\partial u}\right\| + \frac{1}{T_S}\left\|\mathrm{Det}\mathbb{L}(u)\right\|\right) \tag{E.46}$$

F Generalised Fitzhugh-Nagumo Model

The generalized FitzHugh-Nagumo model proposed in Hindmarsh and Rose (1982) can be written as:

$$\dot{x} = I + f(x) - y \tag{F.1}$$
$$\dot{y} = g(x) - y \tag{F.2}$$

with:

$$f(u) = -ax^3 + bx^2 \tag{F.3}$$
$$g(x) = -c + dx^2 \tag{F.4}$$

Taking the derivative with respect to time of the first equation

$$\ddot{x} = \frac{df(x)}{dx}\dot{x} - \dot{y}$$

and using equation F.2 we obtain

$$\ddot{x} = \frac{df(x)}{dx}\dot{x} - g(x) + y$$

We use now equation F.2 to obtain

$$y = I + f(x) - \dot{x}$$

Therefore the generalized FitzHugh-Nagumo model becomes

$$\ddot{x} = I - [g(x) - f(x)] - \dot{x}\left\{1 - \frac{df(x)}{dx}\right\}$$

and using F.3 and F.4 we have

$$\ddot{x} = I - \left[-c + dx^2 - (-ax^3 + bx^2)\right] - \dot{x}\left\{1 - (-3ax^2 + 2bx)\right\}$$

which can finally be written in the form

$$\ddot{x} = I + c - \left[ax^3 + (d-b)x^2\right] - \dot{x}\left\{3ax^2 - 2bx + 1\right\}$$

and if we define $\tilde{I} = I + c$ the equations reads

$$\ddot{x} = \tilde{I} - \left[ax^3 + (d-b)x^2\right] - \dot{x}\left\{3ax^2 - 2bx + 1\right\}$$

This equation has the form of the subcritical Bogdanov-Takens normal form in its Andronov form with a cubic force and a linear friction (see remark 10.1). Note that because we have 5 parameters instead of the six of the subcritical Bogdanov-Takens normal from (three in the force and three in the friction), this model is not the most general form of the subcritical Bogdanov-Takens normal form.

G Triple Zero conditions in CB models

In this appendix we will show that the triple zero bifurcation is not generic in CB models. But under certain conditions that the literature claim are the minimal necessary conditions for bursting (a third very slow time scale with a sharp stationary probability) a CB model actually will undergo the Triple Zero bifurcation. Using the general expression 8.3 for the characteristic polynomial we obtained that the three zero eigenvalues conditions are:

$$a_0 = \beta_0 \prod_{i=1}^{N} \alpha_i = 0 \tag{G.1}$$

$$a_1 = \prod_{i=1}^{N} \alpha_i + \sum_{j=1}^{N} \beta_j M_j \prod_{l \neq j}^{N} \alpha_l = 0 \tag{G.2}$$

$$a_2 = \sum_{q=1}^{N} \prod_{i \neq q}^{N} \alpha_i + \sum_{j=1}^{N} \beta_j M_j \sum_{r \neq j}^{N} \prod_{l \neq j \wedge l \neq r}^{N} \alpha_l = 0 \tag{G.3}$$

But in addition to the three zero eigenvalues we need to have a Jordan block with multiplicity three:

$$\begin{aligned} \mathbb{L}^c \underline{\chi}^{(0)} &= 0 \\ \mathbb{L}^c \underline{\chi}^{(1)} &= \underline{\chi}^{(0)} \\ \mathbb{L}^c \underline{\chi}^{(2)} &= \underline{\chi}^{(1)} \end{aligned} \tag{G.4}$$

Where $\mathbb{L}^c$ is the critical matrix of a CB model and $\underline{\chi}^{(0)}$, $\underline{\chi}^{(1)}$ and $\underline{\chi}^{(2)}$ the critical vectors of the Jordan basis.

Theorem G.1. *If in a CB model the characteristic polynomial has an eigenvalue zero of multiplicity three (conditions G.1, G.2, G.3) we need a new condition in order to have the* 0^3 *bifurcation.*

Proof. The critical matrix is of the form

$$\mathbb{L}^c = \begin{pmatrix} 0 & \beta_0 M_1 & \beta_0 M_2 & \dots & \beta_0 M_N \\ 0 & \alpha_1 + \beta_1 M_1 & \beta_1 M_2 & \dots & \beta_2 M_N \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & \beta_N M_1 & \beta_N M_2 & \dots & \alpha_N + \beta_N M_N \end{pmatrix} \tag{G.5}$$

In section 11.2 we show that the first vector of the Jordan basis of this matrix is:

$$\underline{\chi}^{(0)} = \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix} \tag{G.6}$$

Therefore, to find the second vector of the Jordan basis

$$\mathbb{L}^c \underline{\chi}^{(1)} = \underline{\chi}^{(0)}$$

we must satisfy the equations (where $(x_0^{(1)}, x_1^{(1)}, \ldots, x_N^{(1)})$ are the components of $\underline{\chi}^{(1)}$)

$$\begin{array}{ccccccc}
\beta_0 M_1 x_1^{(1)} + & \beta_0 M_2 x_2^{(1)} + & \cdots & \cdots & +\beta_0 M_N x_N^{(1)} & = 1 \\
(\alpha_1 + \beta_1 M_1) x_1^{(1)} + & \beta_0 M_2 x_2^{(1)} + & \cdots & \cdots & +\beta_1 M_N x_N^{(1)} & = 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & = \vdots \\
\beta_j M_1 x_1^{(1)} + & \beta_j M_2 x_2^{(1)} + & \cdots & (\alpha_j + \beta_j M_j) x_j^{(1)} \cdots & +\beta_j M_N x_N^{(1)} & = 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & = \vdots \\
\beta_N M_1 x_1^{(1)} + & \beta_N M_2 x_2^{(1)} + & \cdots & \cdots & +(\alpha_N + \beta_N M_N) x_N^{(1)} & = 0
\end{array} \tag{G.7}$$

Let us number the $N+1$ equations with 0 for the first one and N for the last one. If we perform the following operation with the equations

$$j) \times \beta_0 - 0) \times \beta_j$$

we find that

$$\alpha_j \beta_0 x_j^{(1)} = -\beta_j$$

Since neither α_j or β_0 are singular we obtain $(j = 1, 2, \ldots, N)$

$$x_j^{(1)} = -\frac{\beta_j}{\alpha_j \beta_0}$$

We note that $x_0^{(1)}$ remains as a free parameter since it does not appear in the equations. We put $\sigma \equiv -\beta_0 x_0^{(1)}$ where σ is now free. Then the second Jordan vector reads

$$\underline{\chi}^{(1)} = -\frac{1}{\beta_0}\begin{pmatrix} \sigma \\ \frac{\beta_1}{\alpha_1} \\ \frac{\beta_2}{\alpha_2} \\ \vdots \\ \frac{\beta_N}{\alpha_N} \end{pmatrix} \tag{G.8}$$

If we calculate explicitly G.13 using G.8 we found that the conditions G.2 for the three zero bifurcation must hold. Therefore our result is consistent and we have shown that we must have a Jordan block of order 2.

To find the third vector of the Jordan basis we must solve

$$\mathbb{L}^c \underline{\chi}^{(2)} = \underline{\chi}^{(1)}$$

The explicit linear equations reads (where $(x_0^{(2)}, x_1^{(2)}, \ldots, x_N^{(2)})$ are the components of $\underline{\chi}^{(2)}$)

$$\begin{array}{ccccccc}
\beta_0 M_1 x_1^{(2)} + & \beta_0 M_2 x_2^{(2)} + & \cdots & \cdots & +\beta_0 M_N x_N^{(2)} & = & \sigma \\
(\alpha_1 + \beta_1 M_1) x_1^{(2)} + & \beta_0 M_2 x_2^{(2)} + & \cdots & \cdots & +\beta_1 M_N x_N^{(2)} & = & -\frac{\beta_1}{\alpha_1 \beta_0} \\
\vdots & \vdots & \vdots & \vdots & \vdots & = & \vdots \\
\beta_j M_1 x_1^{(2)} + & \beta_j M_2 x_2^{(2)} + & \cdots & (\alpha_j + \beta_j M_j) x_j^{(2)} \cdots & +\beta_j M_N x_N^{(2)} & = & -\frac{\beta_j}{\alpha_j \beta_0} \\
\vdots & \vdots & \vdots & \vdots & \vdots & = & \vdots \\
\beta_N M_1 x_1^{(2)} + & \beta_N M_2 x_2^{(2)} + & \cdots & \cdots & +(\alpha_N + \beta_N M_N) x_N^{(2)} & = & -\frac{\beta_N}{\alpha_N \beta_0}
\end{array} \tag{G.9}$$

If we perform the same previous operations ($j = 1, 2, \ldots, N$)

$$j) \times \beta_0 - 0) \times \beta_j$$

we find that

$$\alpha_j \beta_0 x_j^{(2)} = -\beta_j \left(\frac{1}{\alpha_j} + \sigma \right)$$

Since neither α_j or β_0 are singular

$$x_j^{(2)} = -\frac{\beta_j}{\alpha_j} \left(\frac{1}{\alpha_j} + \sigma \right)$$

where again $x_0^{(2)}$ is a free parameter that we will call $\nu \equiv -x_0^{(2)}$. Then the third Jordan vector reads

$$\underline{\chi}^{(2)} = -\begin{pmatrix} \nu \\ \frac{\beta_1}{\alpha_1}\left(\frac{1}{\alpha_1}+\sigma\right) \\ \frac{\beta_2}{\alpha_2}\left(\frac{1}{\alpha_2}+\sigma\right) \\ \vdots \\ \frac{\beta_N}{\alpha_N}\left(\frac{1}{\alpha_N}+\sigma\right) \end{pmatrix} \tag{G.10}$$

If we calculate explicitly G.9 with G.10 in order to verify the consistency with the third condition for the zero eigenvalue of multiplicitly three G.2 we arrive to the equation

$$\sum_{j=1}^{N} \frac{M_j \beta_j}{\alpha_j^2} = 0 \tag{G.11}$$

This equation is independent of the conditions for the zero eigenvalue of multiplicity three (conditions G.1, G.2, G.3) then we must impose a fourth condition to have a Jordan Block of order 3. Therefore, generically in a CB model a zero eigenvalue of multiplicity three will have a Jordan block of order 2 and we conclude that the Triple Zero bifurcation does not occur automatically in CB models (as it is the case for the Bogdanov-Takens bifurcation which is the reason to call it "generic" in the context of the CB models).

Q.E.D. □

Theorem G.2. *We discuss now the conditions for a CB model to undergo a triple 0 bifurcation* 0^3 *if (conditions G.1, G.2, G.3) hold. A way to have the* 0^3 *bifurcation (triple Zero with a Jordan block of order 3) is to have a gating variable* k *which fulfills:*

- *Its relaxation time is very slow:*

$$\alpha_k \to 0 \Leftrightarrow \tau_k \gg 1$$

- *Its stationary probability function is very sharp or far from the half stationary probability voltage*[17]*:*

$$\beta_k \sim 0$$

[17]This is consistent with the high threshold ion channels.

Proof. Then the critical matrix will look like

$$\mathbb{L}^c = \begin{pmatrix} 0 & \beta_0 M_1 & \beta_0 M_2 & \dots & \beta_0 M_N \\ 0 & \alpha_1 + \beta_1 M_1 & \beta_1 M_2 & \dots & \beta_2 M_N \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & \beta_N M_1 & \beta_N M_2 & \dots & \alpha_N + \beta_N M_N \end{pmatrix} \tag{G.12}$$

It is trivial to realize that the first vector of the Jordan basis of this matrix is

$$\underline{\chi}^{(0)} = \begin{pmatrix} 1 \\ 0 \\ \vdots \\ 0 \end{pmatrix}$$

Therefore, to find the second vector of the Jordan basis

$$\mathbb{L}^c \underline{\chi}^{(1)} = \underline{\chi}^{(0)}$$

we must satisfy the linear equations

$$\begin{array}{cccccc} \beta_0 M_1 x_1^{(1)} + & \beta_0 M_2 x_2^{(1)} + & \dots & \dots & +\beta_0 M_N x_N^{(1)} & = 1 \\ (\alpha_1 + \beta_1 M_1) x_1^{(1)} + & \beta_0 M_2 x_2^{(1)} + & \dots & \dots & +\beta_1 M_N x_N^{(1)} & = 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & = \vdots \\ & & & & 0 & = 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & = \vdots \\ \beta_N M_1 x_1^{(1)} + & \beta_N M_2 x_2^{(1)} + & \dots & \dots & +(\alpha_N + \beta_N M_N) x_N^{(1)} & = 0 \end{array} \tag{G.13}$$

Numbering the $N+1$ equations from 0 to N we perform the same operation as before ($j = 1, 2 \dots, N, j \neq k$)

$$j) \times \beta_0 - 0) \times \beta_j$$

we find that

$$\alpha_j \beta_0 x_j^{(1)} = -\beta_j$$

Since neither α_j or β_0 are singular

$$x_j^{(1)} = -\frac{\beta_j}{\alpha_j \beta_0}$$

where now $x_0^{(1)}$ and $x_k^{(1)}$ are free. Then the second Jordan vector reads

$$\underline{\chi}^{(1)} = -\frac{1}{\beta_0} \begin{pmatrix} -\beta_0 x_0^{(1)} \\ \frac{\beta_1}{\alpha_1} \\ \vdots \\ \frac{\beta_{k-1}}{\alpha_{k-1}} \\ -\beta_0 x_k^{(1)} \\ \frac{\beta_{k+1}}{\alpha_{k+1}} \\ \vdots \\ \frac{\beta_N}{\alpha_N} \end{pmatrix} \tag{G.14}$$

If we calculate explicitly G.13 using G.14 we find that the condition G.2 for the 0^3 bifurcation must hold. But we also found that we must fulfill

$$x_k^{(1)} = 0$$

If we will call $\sigma \equiv -\beta_0 x_0^{(1)}$ then the second Jordan vector reads:

$$\underline{\chi}^{(1)} = -\frac{1}{\beta_0} \begin{pmatrix} \sigma \\ \frac{\beta_1}{\alpha_1} \\ \vdots \\ \frac{\beta_{k-1}}{\alpha_{k-1}} \\ 0 \\ \frac{\beta_{k+1}}{\alpha_{k+1}} \\ \vdots \\ \frac{\beta_N}{\alpha_N} \end{pmatrix} \tag{G.15}$$

To find the third vector of the Jordan basis we must solve

$$\mathbb{L}^c \underline{\chi}^{(2)} = \underline{\chi}^{(1)}$$

Then, the explicit linear equations reads

$$
\begin{array}{cccccccc}
\beta_0 M_1 x_1^{(2)} + & \beta_0 M_2 x_2^{(2)} + & \cdots & \cdots & +\beta_0 M_N x_N^{(2)} & = & \sigma \\
(\alpha_1 + \beta_1 M_1) x_1^{(2)} + & \beta_0 M_2 x_2^{(2)} + & \cdots & \cdots & +\beta_1 M_N x_N^{(2)} & = & -\frac{\beta_1}{\alpha_1 \beta_0} \\
\vdots & \vdots & \vdots & \vdots & \vdots & = & \vdots \\
\beta_k M_1 x_1^{(2)} + & \beta_k M_2 x_2^{(2)} + & \cdots & (\alpha_k + \beta_k M_k) x_k^{(2)} \cdots & +\beta_k M_N x_N^{(2)} & = & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & = & \vdots \\
\beta_N M_1 x_1^{(2)} + & \beta_N M_2 x_2^{(2)} + & \cdots & \cdots & +(\alpha_N + \beta_N M_N) x_N^{(2)} & = & -\frac{\beta_N}{\alpha_N \beta_0}
\end{array}
\tag{G.16}
$$

If we perform the same operation as above

$$
j) \times \beta_0 - 0) \times \beta_j
$$

We find that:

$$
\begin{aligned}
x_0^{(2)} &= \text{Free} \\
x_j^{(2)} &= -\frac{\beta_j}{\alpha_j}\left(\frac{1}{\alpha_j} + \sigma\right) \\
x_k^{(2)} &= \text{Free}
\end{aligned}
$$

Then third Jordan vector reads:

$$
\underline{\chi}^{(2)} = -\begin{pmatrix}
-x_0^{(2)} \\
\frac{\beta_1}{\alpha_1}\left(\frac{1}{\alpha_1} + \sigma\right) \\
\vdots \\
\frac{\beta_{k-1}}{\alpha_{k-1}}\left(\frac{1}{\alpha_{k-1}} + \sigma\right) \\
-x_k^{(2)} \\
\frac{\beta_{k+1}}{\alpha_{k+1}}\left(\frac{1}{\alpha_{k+1}} + \sigma\right) \\
\vdots \\
\frac{\beta_N}{\alpha_N}\left(\frac{1}{\alpha_N} + \sigma\right)
\end{pmatrix}
\tag{G.17}
$$

If we calculate explicitly G.16 using G.17 we find that the condition G.3 for the 0^3 bifurcation must hold but also found that we must have

$$
x_k^{(2)} = \frac{1}{M_k} \sum_{j \neq k}^{N} \frac{M_j \beta_j}{\alpha_j^2}
$$

If we will call $x_0^{(2)} \equiv -\nu$ then the third Jordan vector reads:

$$\underline{\chi}^{(2)} = - \begin{pmatrix} \nu \\ \frac{\beta_1}{\alpha_1}\left(\frac{1}{\alpha_1}+\sigma\right) \\ \vdots \\ \frac{\beta_{k-1}}{\alpha_{k-1}}\left(\frac{1}{\alpha_{k-1}}+\sigma\right) \\ -\frac{1}{M_k}\sum_{j\neq k}^{N}\frac{M_j\beta_j}{\alpha_j^2} \\ \frac{\beta_{k+1}}{\alpha_{k+1}}\left(\frac{1}{\alpha_{k+1}}+\sigma\right) \\ \vdots \\ \frac{\beta_N}{\alpha_N}\left(\frac{1}{\alpha_N}+\sigma\right) \end{pmatrix}$$

We find then that we can have a Jordan Block of order 3. In addition we have obtained an explicit expression for each vector of the Jordan critical basis. Therefore, if the conditions in the theorem G.2 hold a CB model generically undergo a Triple Zero 0^3 bifurcation.

Q.E.D. □

H Hindmarsh-Rose to *almost* Triple Zero normal form

The Hindmarsh-Rose model (Hindmarsh and Rose, 1984) reads:

$$\dot{x} = y + \phi(x) - z + I \tag{H.1}$$
$$\dot{y} = \psi(x) - y \tag{H.2}$$
$$\dot{z} = r\left[s(x - x_R) - z\right] \tag{H.3}$$

With:

$$\phi(x) = ax^2 - x^3 \tag{H.4}$$
$$\psi(x) = 1 - bx^2 \tag{H.5}$$

Let us define:

$$\alpha \equiv rs$$
$$\beta \equiv -r$$
$$\gamma \equiv -rsX_R$$

Then the model is

$$\dot{x} = y + \phi(x) - z + I \tag{H.6}$$
$$\dot{y} = \psi(x) - y \tag{H.7}$$
$$\dot{z} = \alpha x + \beta z + \gamma \tag{H.8}$$

If we take the derivative of equation H.6 we obtain:

$$\ddot{x} = \dot{y} - \dot{z} + \frac{\partial \phi(x)}{\partial x}\dot{x}$$

Using H.7 and H.8 in this equation we obtain:

$$\ddot{x} = \psi(x) - y - (\alpha x + \beta z + \gamma) + \frac{\partial \phi(x)}{\partial x}\dot{x} \tag{H.9}$$

If we use equation H.6 we have:

$$-y = \phi(x) - z - \dot{x} + I$$

Using this equation H.9 can be written as

$$\ddot{x} = (I - \gamma) + [\psi(x) + \phi(x) - \alpha x] + \left[\frac{\partial \phi(x)}{\partial x} - 1\right] \dot{x} - (\beta + 1)z \qquad \text{(H.10)}$$

If we take the derivative H.10 with respect to time we obtain

$$\dddot{x} = \left[\frac{\partial \psi(x)}{\partial x} + \frac{\partial \phi(x)}{\partial x} - \alpha\right] \dot{x} + \left[\frac{\partial \phi(x)}{\partial x} - 1\right] \ddot{x} + \frac{\partial^2 \phi(x)}{\partial x^2} \dot{x}^2 - (\beta+1)\dot{z} \quad \text{(H.11)}$$

Using the equation H.6 in H.12 we obtain:

$$\dddot{x} = \left[\frac{\partial \psi(x)}{\partial x} + \frac{\partial \phi(x)}{\partial x} - \alpha\right] \dot{x} + \left[\frac{\partial \phi(x)}{\partial x} - 1\right] \ddot{x} + \frac{\partial^2 \phi(x)}{\partial x^2} \dot{x}^2 - (\beta+1)\left(\alpha x + \beta z + \gamma\right) \qquad \text{(H.12)}$$

From H.10 we have:

$$-(\beta + 1)z = \ddot{x} - (I - \gamma) - [\psi(x) + \phi(x) - \alpha x] - \left[\frac{\partial \phi(x)}{\partial x} - 1\right] \dot{x}$$

If we use this expression in H.12 we obtain:

$$\dddot{x} = \left[\frac{\partial \psi(x)}{\partial x} + \frac{\partial \phi(x)}{\partial x} - \alpha\right] \dot{x} + \left[\frac{\partial \phi(x)}{\partial x} - 1\right] \ddot{x} + \frac{\partial^2 \phi(x)}{\partial x^2} \dot{x}^2$$
$$+ \beta \left(\ddot{x} - (I - \gamma) - [\psi(x) + \phi(x) - \alpha x] - \left[\frac{\partial \phi(x)}{\partial x} - 1\right] \dot{x} \right) - (\beta + 1)\alpha x - (\beta + 1)\gamma$$

If we order the terms finally we obtain:

$$\dddot{x} = -(\beta I + \gamma) + \beta \left[\psi(x) + \phi(x) - \frac{\alpha}{\beta} x\right] + \left[\frac{\partial \psi(x)}{\partial x} + (1 - \beta)\frac{\partial \phi(x)}{\partial x} + (\beta - \alpha)\right] \dot{x} \qquad \text{(H.13)}$$
$$+ \left[\frac{\partial \phi(x)}{\partial x} + (\beta - 1)\right] \ddot{x} + \frac{\partial^2 \phi(x)}{\partial x^2} \dot{x}^2$$

This is almost the Triple Zero normal form (Arneodo et al., 1985).

I Some words about the simulations software

Within the collaboration with Professor Pierre Coullet of the Universit de Nice Sophia-Antipolis, we developed from the scratch an interactive simulator specially suited for neuron models from the point of view of non linear dynamics and normal form theory. The software was developed in objective-c/COCOA. With this software it is possible to observe orbits of different equations in the same phase space (i.e. different steps in the reduction of one equation), calculate and visualize in real time the fixed points, calculate and visualize stable and unstable manifolds, visualize separatrices and more. This software is interactive in the sense that we can perturb the system and observe the behaviour after the perturbation in real time. An snapshot of the software is shown in the figure 25.

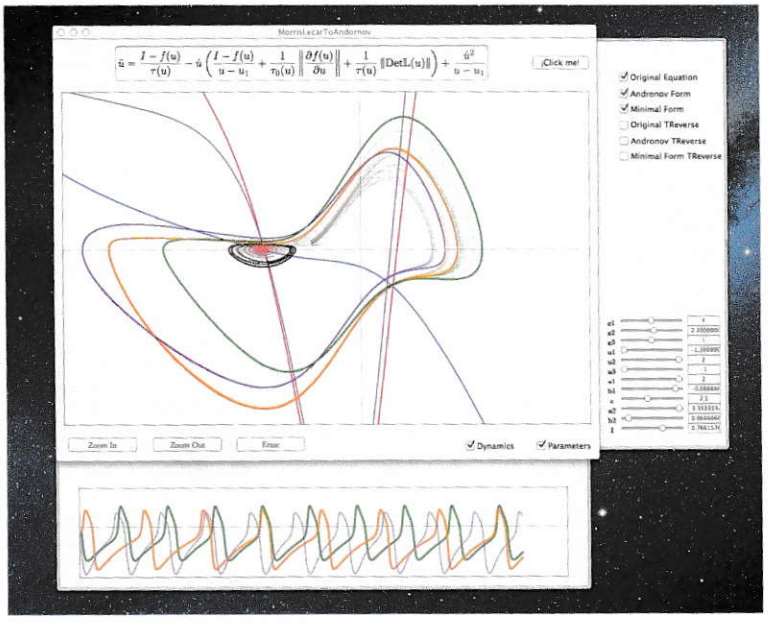

Figure 25: Snapshot of the simulations software.