INSTITUTO SUPERIOR TÉCNICO

An Artificial Bidimensional Model for Bursting Behaviour in Neurons Extended Abstract

by

Pedro Faria

Master Thesis

in the

Departamento de Matemática

Chapter 1

Introduction

Neurons have been known, for a long time, to send and receive electrical signals between them. It is in these signals that the neural code is believed to partially reside. Before attempting to decode them, research first focused on understanding the underlying physical mechanisms that produce them. The axons and dendrites of each neuron constitute the bulk of the network that connects them to each other. Roughly speaking, electrical signals are sent from the neuron's body, or soma, along its axon. It then spreads across the dendritic tree, where it finally reaches a number of other neurons, at their synaptic junctions. This, in turn, stimulates their soma, after which the process may or may not repeat itself.

After realizing that an electrical stimulus at the beginning of the axon (also known as the axon hillock) propagates rather unperturbed until it reaches other neurons, research focused on describing it only there, leaving aside the propagation. The first mathematical description of this phenomenon was put together in what has come to be known as the Hodgkin-Huxley model.

Without dwelling for too long on the intricacies of this model, I decided to make a very brief introduction to the topic, and then jump right away into the core aspects of the thesis. What follows is just a natural way of easing into the subject of continuous models of spiking and bursting behaviour.

1.1 The Hodgkin-Huxley model

In 1952, Alan Lloyd Hodgkin and Andrew Huxley presented an article where they characterized the change (in time) of the membrane potential of a squid giant axon after an initial current impulse of a certain amplitude and duration, injected at a chosen point along the axon. It is the set of differential equations that describe this behaviour that is known as the Hodgkin-Huxley model, although it can also be extended to describe the propagation of the impulse along an axon. This impulse is also known as action potential or spike.

Getting a clear picture of the experiment done by Hodgkin and Huxley is vital to fully grasp the rationale underlying the formulation of the differential equations. Hence, the reader will find a first section below succinctly outlining the procedure they followed, as well as a discussion of the aspects that are more likely to cause confusion when choosing the aforementioned formulation. The other sections delve more deeply into the differential equations themselves. The first of these addresses the concepts of reversal and resting potentials, essential to the development of a realistic model, whereas the second incorporates such concepts into the equations and goes on to fully describe the associated dynamical system.

1.1.1 The Hodgkin-Huxley equations

The simplest **H-H** model is four-dimensional and can be neatly written as five equations, together with the initial values for the so-called 'gate variables', the voltage across the membrane and the fixed values for the amplitude and duration of the injected/total current. The first of the equations can be readily derived from the relation $J = J_{ion}(t) + J_{cap}(t)$. Because the injected current has a specified duration we shall also write it as a function of time, $J(t) = J_{ion}(t)+J_{cap}(t)$. If the membrane is taken to be a capacitor, then $J_{cap}(t) = C\frac{\mathrm{d}V}{\mathrm{d}t}(t)$, where C is its capacitance. This gives us $J(t) = J_{ion}(t)+C\frac{\mathrm{d}V}{\mathrm{d}t}(t)$, which can be rewritten as $\frac{\mathrm{d}V}{\mathrm{d}t}(t) = \frac{J(t)-J_{ion}(t)}{C}$, effectively providing us with the dynamics of V. The second equation describes the dynamics of $J_{ion}(t)$, which is where the non-linearity of the dynamical system partially resides. Two ion species are considered: Na^+(Sodium) and K^+(Potassium). Each gives rise to an ion current, so we get the Sodium current J_{Na} and the Potassium current J_K. Both are functions of time and so we have $J_{ion}(t) = J_{Na}(t) + J_K(t) + J_L$, where J_L is a fixed leakage current, that accounts for an experimental difference between $J_{ion}(t)$ and $J_{Na}(t) + J_K(t)$. And it's in these two ion currents that one finds the non-linear behaviour. Both depend on gate variables and on the voltage across the membrane. The gate variables are three functions with dynamics of their own. They are usually denoted $m(t)$, $h(t)$ and $n(t)$ and take values in [0, 1]. And so the expressions for the currents are $J_{Na}(t) = G_{Na}\, m^3(t)\, h(t)[V(t) - V_{Na}]$ and $J_K(t) = G_K\, n^4(t)[V(t) - V_K]$, where G_{Na} and G_K are maximum conductances for each of the currents, $V(t)$ is the voltage across the membrane at instant t and V_{Na}, V_K are the reversal potentials for Sodium and Potassium, respectively. The only thing left for us to define is the dynamics of each of the gate variables, which further adds to the non-linearity of the system. The specific equations for the dynamics of gate variables are of no consequence to the understanding of these phenomena (at least at the level we are interested in) since they come from experimental fitting, giving little to no clue on the cellular mechanisms that regulate the membrane conductance. The only relevant fact about them is that these dynamics depend on the gate variables themselves and on the voltage. So, the complete **H-H** model can be described by the five equations below (the equations for the dynamics of gate variables remain unspecified), together with the initial values for the gate variables and voltage (which can be found in the relevant literature) and any chosen amplitude and duration for the injected current:

1. $\frac{\mathrm{d}V}{\mathrm{d}t}(t) = \frac{J(t)-J_{ion}(t)}{C}$
2. $J_{ion}(t) = G_{Na}\, m^3(t)\, h(t)[V(t) - V_{Na}] + G_K\, n^4(t)[V(t) - V_K] + J_L$
3. $\frac{\mathrm{d}m}{\mathrm{d}t}(t) = \alpha_m(V(t))(1 - m(t)) - \beta_m(V(t))\, m(t)$
4. $\frac{\mathrm{d}h}{\mathrm{d}t}(t) = \alpha_h(V(t))(1 - h(t)) - \beta_h(V(t))\, h(t)$
5. $\frac{\mathrm{d}n}{\mathrm{d}t}(t) = \alpha_n(V(t))(1 - n(t)) - \beta_n(V(t))\, h(t)$

where

1. $\alpha_m(V) = \frac{0.1\,(25-V)}{e^{\frac{25-V}{10}}-1}$
2. $\beta_m(V) = 4\, e^{-\frac{V}{18}}$
3. $\alpha_h(V) = 0.07\, e^{-\frac{V}{20}}$
4. $\beta_h(V) = \frac{1}{e^{\frac{30-V}{10}}+1}$
5. $\alpha_n = \frac{0.01\,(10-V)}{e^{\frac{10-V}{10}}-1}$
6. $\beta_n = 0.125\, e^{-\frac{V}{80}}$

1.2 Developing a computational tool to explore dynamical systems

Before delving into the details of the models I describe in the thesis, there was one step that had first be taken in order to make the whole process more amenable to dissection. It became clear to me that I would not be getting very far without a computational tool that could speed up my exploration of the topic by giving me immediate intuition and insight into the nature of the models I was entertaining in my mind. For this reason, I set out to create an application that would do just that. It turns out it became somewhat more than that and I think it's fair to say it is a most useful byproduct of this thesis, possibly helpful to anyone working in the field of Dynamical Systems.

The application was written in the *Mathematica* programming language, using the software of the same name. The end result is contained in a notebook named `Dynamical Systems App.nb`, that complements this thesis and which, upon evaluation, returns a user-friendly interface, similar to the one already shown in the application written for the simulation of the Hodgkin-Huxley equations, **HHA**. The notebook contains a detailed description of the application, effectively acting as a user's manual for the software. Henceforth, I shall refer to the application as **DSA** (Dynamical Systems App).

1.2.1 Izhikevich's model and his classification of fundamental properties

Izhikevich developed a hybrid model that captures a great number of neuron properties, with low computational overhead. In his books he goes on to describe these properties. He even identifies 20 that he considers to be fundamental. Figure **??** depicts them.

Here, I describe these properties in a very informal fashion, along with two others that Izhikevich mentions as well.

1. **Tonic spiking -** Through the introduction of a step current, initiate periodic spiking.
2. **Phasic spiking -** Through the introduction of a step current, generate a spike, followed by a convergence to a resting potential.
3. **Tonic bursting -** Through the introduction of a step current, initiate periodic bursting.
4. **Phasic bursting -** Through the introduction of a step current, generate a burst, followed by a convergence to a resting potential.
5. **Mixed mode -** Through the introduction of a step current, get bursting and spiking behaviours together. Namely, generation of a burst, followed by periodic spiking.
6. **Spike frequency adaptation -** Through the introduction of a step current, initiate periodic spiking, whilst observing a relaxation to a final frequency, after the first few spikes.
7. **Class 1 excitable -** Through the introduction of a ramp current, initiate periodic spiking, whilst having its frequency increase with the intensity of the current.
8. **Class 2 excitable -** Through the introduction of a ramp current, initiate periodic spiking, whilst having it be unaffected by an increasing intensity in the current.
9. **Spike latency -** Through the introduction of a current pulse, elicit a spike, albeit with some latency.

10. **Subthreshold oscillations -** Through the introduction of a current pulse, elicit a spike, whilst observing a non-monotonic convergence to the resting potential.

11. **Resonator -** Eliciting spiking only through the introduction of a pulse current with a specific frequency.

12. **Integrator -** Eliciting spiking through an integration in the time variable of the current.

13. **Rebound spike -** Eliciting spiking through a negative pulse current.

14. **Rebound burst -** Eliciting bursting through a negative pulse current.

15. **Threshold variability -** Having negative pulses of current affect the spike generation potential threshold.

16. **Bistability -** Changing from spiking to resting (and vice-versa) through a pulse current.

17. **Depolarizing after-potential -** Clear from picture.

18. **Accommodation -** Having a neuron stay at rest while slowly increasing the injected current, but being able to fire a spike with a short and weaker pulse.

19. **Inhibition-induced spiking -** Eliciting spiking through the introduction of a negative step current.

20. **Inhibition-induced bursting -** Eliciting bursting through the introduction of a negative step current.

21. **Spike frequency modulation -** Controlling the spiking frequency with the intensity of the injected current.

22. **Flip -** Changing from resonator to integrator and back with the introduction of appropriately timed current pulses.

This concludes chapter 1. I have now laid out the foundations for developing the core ideas in this thesis.

Chapter 2

An Artificial Planar Burster

Because bursting seems to have a periodic nature, suggesting that in its simplest form no chaotic behaviour is involved, it becomes natural to ask the question: since chaos in continuous dynamical systems is known to emerge only when the dimension is at least three, is it possible to have a two-dimensional continuous system showing bursting activity? If so, how hard is such an example to come by, whilst at the same time being capable of exhibiting other well-known and expected properties? Sure enough, a planar limit cycle attractor corresponding to periodic bursting activity would not look like the kind of curve one sees when inspecting the phase portrait of a system with periodic spiking. What, then, would its shape be?

Taking a toy example from Eugene Izhikevich's book as a starting point I set out to answer these questions. In particular, I set myself the goal of coming by with an artificially constructed continuous (and even differentiable) bidimensional dynamical system that could not only burst but also capture as many as possible of the fundamental properties described by Izhikevich. Only then would I be able to say that I had created a decent artificial planar burster. In chapter 2 of the thesis I took the reader through the steps I myself had to follow in order to achieve this goal, culminating in an elementary theoretical analysis and exposition of the plethora of behaviors extractable from my model.

2.0.1.1 Putting the model together

Now comes the time to get all the pieces together and build the model. This process requires a certain amount of experimenting and fitting to get the core parameters right. Even then, to show some of the behaviors we want, we will need to go back to those same core parameters and fiddle with them slightly.

Chapter 3

Analysis of Properties and Behaviours

3.1 Bifurcation analysis

3.1.1 Bifurcations of equilibria

The model developed in chapter 2 of the thesis, or at least the instances we considered, have one equilibrium only, that can change its position either through changes in parameter d (stretching or compressing $vpol(x)$) or in the position of the $\dot{y}$-nullcline. Being it a straight line and since the y-component of the field in question does not vary along the y-direction, the only changes in position that one needs to consider to get a new equilibrium (once d is fixed) are horizontal shifts of the $\dot{y}$-nullcline.

We are not interested so much in classifying the bifurcations as we are in identifying the types of hyperbolic equilibria that can occur. Even though these two things are almost the same for codimension-1 bifurcations of equilibria, they involve quite distinct amounts of effort in the case of bifurcations of higher codimension. Here, these do not concern us. To exhibit the behaviours we care about we only need to know the local and linear nature of the equilibria.

3.1.2 Bifurcations of limit cycles

There was not a rigorous treatment of the limit cycle bifurcations that can occur in the model. Nevertheless, I believe the experiments that have been done using the **DSA** are convincing enough to make some observations on the likely nature of such bifurcations. What I tried to show was that, while shifting the $\dot{y}$-nullcline to the left, until the equilibrium ceases to be unstable and becomes stable, the cycle can disappear in one of two ways:

1. It gradually shrinks as one approaches the value α (at which the equilibrium becomes stable), disappearing precisely at that value, when its radius becomes zero.
2. It shrinks slightly as one approaches the same bifurcation value as above, but remains relatively fixed at a certain radius. As one crosses the bifurcation value, the equilibrium becomes stable and an unstable cycle emerges from it, with a radius that starts at zero and grows until it collides with the bigger stable limit cycle. These two annihilate and the stable equilibrium remains as the only attractor.

3.2 Properties and behaviours

We were now able to present the core results of this thesis. Each of the next sections displays a set of properties and behaviours that, in most cases, have an analogous example in Izhikevich's list of most fundamental properties. It was not my objective to be exhaustive and exhibit a whole plethora of behaviours, which could certainly be obtained by combining many of the properties we can get. All of the behaviours can be found in the thesis.

Chapter 4

Conclusion

Coming up with an artificial bidimensional planar burster does, if nothing else, fill in a theoretical gap. Competing, efficiency-wise, with other realistic models that are available was never my intention. But it helps to know just how far one can push the boundaries of what is possible to do with a bidimensional model, while still getting decent results. I think this thesis does that. Additionally, the computational tools developed, either for numerical simulation or for theoretical analysis, illustrate the benefits of having an approach that explores avenues other than the classical, only using pen and paper. In a sense, this is what this text gradually became, an exercise in computer aided research.