

Computing the Vulnerable Phase in a 2D Discrete Model of the Hodgkin-Huxley Neuron

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1. Introduction

In several neurological diseases, like essential tremor, the functions of the brain are severely impaired by synchronized processes, in which the neurons fire in a synchronized periodical manner at a frequency closely related to that of the tremor. Stimulation techniques have been developed to desynchronize these neuronal populations. One such technique is the electrical Deep Brain Stimulation (DBS) (Luders, 2004), (Mayberg, 2005) which is performed by administering a permanent high frequency periodic pulse train to the brain by means of so-called *depth* electrodes. The DBS method was developed empirically, and its mechanism has not yet been understood.

Another stimulation technique is the perturbation with brief stimuli. Clinical results for this technique (some of them are briefly presented in this chapter) prove that a carefully chosen brief pulse applied at a specific time, denoted by the term “vulnerable phase”, can *annihilate* the firing behaviour in the neuron. It is believed that by determining the vulnerable phase of a neuron, the result can be generalized to a population of neurons.

In this context, the first neural model analytically investigated in great detail was the Hodgkin-Huxley (HH) neuron, which exhibits stable periodic solutions for a certain range of constantly applied depolarizing currents.

To study the latter from a variety of perspectives, we shall first present, in Section 1.1, the dynamics of the HH neuron. Then, in Section 1.2, we informally describe its annihilation and stability properties and compare its characteristics with the properties of some of its close “relatives”. Finally, in Section 1.3, we shall describe the HH model from the context of the works of Winfree and Guckenheimer.

1.1 Dynamics of the HH neuron

We present now a few considerations about the dynamical properties of the HH neuron. This neural model can be in one of two states: a resting state and a state that fires in response to certain forms of stimulation. Usually, the neuron is considered to be in a stable mode when it is in a resting state. However, this statement is not universal because there are two stable states associated with this neuron, namely a fixed point and the limit cycle, both of which are stable. One problem to be considered here is the switching of the neuron from one stable mode to the other, which is a phenomenon that can occur without modifying the number and the stability of the equilibria.

Put in a nutshell, we would like to determine if the HH neuron in 2D is controllable (i.e., if it can be driven from a quiescent state to a spiking state and vice versa). However, it turns out that the general system is unsolvable, the latter being a consequence of three well-known fundamental results, namely Hilbert 16-th Problem, the Poincare-Bendixon Theorem and the Hopf Bifurcation Theorem. These three results are cited to prove that an analytic analysis to obtain the exact representation of the separatrix is not feasible. Having achieved this, we proceed to tackle the problem of concern from a topological perspective, and show that the control is achievable by exciting the system with an appropriate pulse. Not only have we proved the existence of this pulse, but also described its characteristics (amplitude, duration etc.).

From a classical system theory point of view, the stable point of a nonlinear dynamical system may disappear or may lose its stability if a control parameter is changed, depending on the type of bifurcation displayed by the system. In our research, the HH neuron is considered to be a dynamical nonlinear system whose stable states are not to be radically changed with regard to its stability. We investigate the case when both stable states, namely the fixed point and the limit cycle, co-exist and remain stable. In addition to the fixed points and limit cycles, a 2D system can also possess homoclinic¹ points, which, in turn, imply the existence of a hyperbolic invariant set on which the 2D system is chaotic.

In this particular situation, the system is bi-stable, without homoclinic points, and, with a carefully chosen synaptic input, it is possible to switch the behaviour from being resting to one which demonstrates spiking, or from being spiking to a resting (spike annihilation) mode. The goal of this research is to describe the properties of the stimulus that can achieve this switching.

This above stimulus, chosen to be a brief pulse of current, is not a control parameter. Its behaviour affects neither the existence of the fixed points or limit cycles, nor their stability. The control parameter is the strength of the constantly applied current and, during our investigation, it is set to be constant. We argue that injecting a constant current into the axon is not equivalent to injecting a brief pulse of current. In the former, the system can go through a bifurcation of the stable state by changing the existence of the stable states or by affecting their stability. In the latter, however, the system can jump to an alternate location in the state space, which is achieved by the system resetting the initial condition. The neuron is driven to a state of "shock", and consequently, the membrane potential instantly switches

¹ It can be advantageous to clarify the concepts of points that are *homoclinic* and *heteroclinic*. We do this by invoking the following definitions essentially from (Devaney, 2003). Let p be a repelling fixed point, with $f'(p) > 1$, namely $|f(x)-p| > |x-p|$. We define a local unstable set at p , denoted as $W_{loc}^u(p)$, to be the maximal open interval in the neighbourhood of p . A point q is said to be *homoclinic* to p if $q \in W_{loc}^u(p)$ and if there exists $n > 0$ such that $f^n(q) = p$ (where $f^n(x)$ is defined as $f(f^{n-1}(x))$). The point q is *heteroclinic* if $q \in W_{loc}^u(p)$ and if there exists $n > 0$ such that $f^n(q)$ lies on a different periodic orbit. If p has a homoclinic point q , p is also so-called "snap-back repeller". Since q , by definition, lies in the local unstable set in the neighbourhood of p , it is possible to define a sequence of pre-images of q , each of which lies closer to p in the local unstable set. Thus, the homoclinic point, q , together with its backward orbit defined by the pre-images and its forward orbit, is called a homoclinic orbit. This orbit has the property that it tends to the fixed point, p , when a "backward iteration" is invoked, and it lands on the same fixed point if a "forward iteration" is invoked.

to a new value. The fixed point, corresponding to the resting state, co-exists with the limit cycle, which corresponds to the spiking state, and the system continues to be bistable. This leads us to the goals of this research: (i) to prove analytically the existence of such stimuli, and (ii) to describe the characteristics of these brief depolarizing shock-stimuli that, when inserted at the appropriate time, can switch the neuron from the spiking to the resting state.

1.2 The HH neuron: the annihilation perspective

The annihilation of the firing activity was predicted theoretically by Teorell (Teorell, 1971) for a two-variable model of a sensory pacemaker. He showed that the annihilation of the firing activity can be achieved by using a small brief test pulse injected into the refractory period, just prior to the system attaining to its firing level. Later, the annihilation of the spike train, by using a carefully chosen stimulus, was predicted by Rinzel² (Rinzel, 1980) and also independently by Best (Best, 1979). Rinzel calculated periodic solutions to the space-clamped HH equations when a depolarizing current was constantly applied. The computational analysis of Best stated that one could “shock” the HH neuron out of the repetitive mode by using a properly timed instantaneous current pulse. In addition, Guttman, Lewis, and Rinzel (Guttman, 1980) experimentally confirmed that repetitive firing in a space-clamped squid axon, merely stimulated by a suprathreshold step of current, can be annihilated by a brief depolarizing or hyperpolarizing pulse of the proper magnitude, applied at the proper phase. After the resting potential of the axon (whose central compartment was bathed in low *Ca* artificial seawater) had reached a steady state, the threshold for repetitive firing was established by a manually triggered stimulation with a step of current, 30 ms in duration, to avoid overstimulation of the axon. Thereafter, a slightly suprathreshold current step of approximately 30 ms duration, was used as a bias in order to initiate the repetitive firing. Upon being excited by this bias current, various magnitudes of brief 0.15 ms perturbations were added at various phases in the period of the response, to investigate the control of repetitive firing. In response to such perturbations, membrane potentials and ionic currents showed damped oscillations that converged towards a steady state. For the non-annihilating perturbations, the repetitive firing of the system resumed with an unaltered frequency, but with a modified phase.

Closely related to the Rinzel model for the HH neuron, is the model due to FitzHugh-Nagumo. Theoretical considerations relevant to the latter have also been derived by Baer and Erneux (Baer, 1986), who studied the phenomena of singular Hopf bifurcations from a basic state to that involving relaxation oscillations. For the model of the FitzHugh-Nagumo neuron, they analyzed the switching from a stable steady state to a stable periodic solution (spike generation) and the reverse situation (spike annihilation). They succeeded in formally explaining both these phenomena.

1.3 The HH neuron: the Winfree/Guckenheimer perspective

The annihilation problem that we have solved for a 2-dimension HH neuron can be viewed from an entirely different perspective. This point of view involves the control of the

² Although the Rinzel model that we have used is a few years old, we do not believe that it is outdated. As far as we know, the Rinzel model is probably the best reported 2-D model for the HH structure. Furthermore, it is also well known that increasing the accuracy of the coefficients does not modify the fundamental dynamics of the neuron.

isochrones of a general dynamical system, and in particular, of networks involving neurons akin to the HH neuron. Historically, the origin of this perspective can be traced to “traditional biology”, where Winfree, in his pioneering papers (Winfree, 1974) and (Winfree, 1977) anticipated the existence of a perturbing stimulus that could affect the dynamics of the system. This hypothesis actually resulted from his initial research on fibrillation, which involves the uncontrolled fluttering of the heart, possibly leading to sudden cardiac death. Later, Winfree applied topological concepts to investigate the effects of involving disturbing stimuli that could change the human biological clock expressed, for example, by alternating sleep-wake cycles at almost-regular intervals. He predicted that in order to generate an arrhythmic pattern, a stimulus should be applied at a specific point in the sleep-wake cycle. Winfree further suggested mathematical models for describing this family of behaviours related to biological clocks, and though these models were very pertinent, they also provided a fertile ground for further research because they raised unforeseen topological questions, that were related to phase resetting.

Winfree's research phenomena were subsequently investigated by Guckenheimer (Guckenheimer, 1975), who, on the other hand, described analytically, using the foundational theory of ordinary differential equations, many of the open problems proposed by the former. In particular, he concentrated on the existence and the properties of the above mentioned “isochrones”. However, while Winfree's interest was related to biological clocks, Guckenheimer's intention was to establish a methodology for analyzing the stability of the limit cycle, which is a component of the dynamics of biological clocks. From this perspective, and based on the so-called assumption of nondegeneracy, Guckenheimer determined the condition for which two points could be isochrones. He concluded that the existence of isochrones is determined by the flow near the limit cycle, and more specifically, formulated the theorems that involve the intersections of the isochrones of a limit cycle and the neighborhood of its *frontiers*.

The followings are the three topics proposed by Winfree, and which Guckenheimer proved analytically in (Guckenheimer, 1975): 1. The properties of the isochrone lines: Guckenheimer showed that these are related to a stable manifold in a dynamical system, this being a special case of the Invariant Manifold Theorem. 2. The topology of a stable manifold of a stable limit cycle: Guckenheimer showed that this determines the dimension of its frontier. 3. The properties of points in the neighbourhood of the frontier that intersects the isochrones.

The last problem involves three distinct directions. The first direction introduced the concept of *open-dense sets* of vector fields. The second investigation included the concept of *generic³ subsets*. The third theorem used the previous results and proved the existence of dense open subsets of vector fields with the property that every neighbourhood of every point in the frontier meets each isochrone of the limit cycles. Guckenheimer also tested his results experimentally. He stated that the results displayed one of the following two phenomena: (i) The destruction of the oscillation entirely, or (ii) The fact that points arbitrarily close to each another lay on isochrones of every point of a limit cycle. In summary, Guckenheimer's work was conducted so as to analytically characterize the second scenario.

To present our work in this perspective, we, first of all, mention that in our research, we analytically investigate the first scenario. Also, we can formally describe the relation between our work and the Winfree-Guckenheimer research, as follows:

³ A subset of a topological space is *generic* if it is a countable intersection of open-dense sets.

Similarity: Both of approaches investigate the stability of a dynamical system, with the goal of controlling it in the neighbourhood of a limit cycle. The control is achievable by exciting the system with an appropriate pulse, which is invoked when the system is in the neighborhood of the limit cycle. Finally, both Guckenheimer and we demonstrate that the characteristics of the limit cycle determine the effect of the excitation.

Difference: Although the similarities between the works exist, it is prudent for us to highlight the dissimilarities. Our first intention is to prove the existence of the stimulus that is able to entirely *destroy* the oscillation -- which is an issue that Guckenheimer has not analyzed. To achieve this, we have used the bi-stability property of the HH neuron, with the goal of annihilating the oscillation, and of forcing the system to move through the stable fixed point. Consequently, we have also investigated analytically the first scenario unearthed by the simulations that Guckenheimer reported. From an analytical point of view, Guckenheimer's work investigated the conditions that maintain the limit cycle to be unaffected by the stimuli. His work is related only to the neighbourhood of the stable limit cycle without investigating a model which contains both a stable limit cycle, a fixed point *and* a region separating them which includes a separatrix - an *unstable* limit cycle. Thus, Guckenheimer has not investigated the effect of adding a stimulus with a goal of forcing the system through separatrix so as to reach the fixed point.

In contrast to the previous pieces of work cited above, which validated experimentally or anticipated theoretically that annihilation is possible, we achieve the following:

1. We formally prove that the problem of spike annihilation has a well defined solution.
2. We formally derive the characteristics of the proposed solution.
3. We demonstrate experimentally the validity of the solution (i.e., by numerical simulations).

All of the results are novel, and we thus believe that our analysis of the HH neuron has practical implications in clinical applications⁴, especially in the case of the desynchronization of neuronal populations.

1.3 Format of the chapter

Section 1 presents an overview of the clinical research related to the problem of spike annihilation in HH neurons. Section 2 contains the dynamical formulation of the problem, namely the bistable neuron, the equations of the system, and its stable and unstable limit cycles. Section 3 investigates the problem of annihilation and presents a formal proof of the existence of the stimulus, and the suggested numerical approach for computing the bifurcation point. Section 4 describes the experiments conducted for determining the properties of the annihilation stimulus, and Section 5 concludes the chapter.

⁴ A few investigations which are applicable to optimizing the characteristics of the stimuli used to annihilate real NNs have been reported. Two renowned investigators, in this field are Dr. Osorio from University of Kansas - Kansas Medical Center, and Dr. McIntyre from Carleton University, in Ottawa, Canada. The former has been praised for his work in the project titled "Safety, tolerability and efficacy of high-frequency periodic thalamic stimulation in inoperable mesial temporal epilepsy" (Osorio et al., 2005), and the latter is well known for his work in low frequency brain stimulations against kindled seizures (Carrington et al., 2007) and (McIntyre et al., 2005). Unfortunately, their more recent results are not published yet.

2. The bistable HH neuron

In this section we investigate the stability-related characteristics of the HH neuron. In the previous section, we stated that the HH neuron can be perceived as a dynamical nonlinear system with two stable equilibria. This is formalized below.

Consider a two-dimensional dynamical system:

$$\frac{dV}{dt} = P(V,R) \quad (1)$$

$$\frac{dR}{dt} = Q(V,R) \quad (2)$$

where $P(V,R)$ and $Q(V,R)$ are polynomials of real variables V and R , and where the corresponding coefficients are real. The fundamental problem associated with the qualitative theory of such systems seems to be the second part of Hilbert's Sixteenth Problem (Gray, 2000), stated as follows:

Specify the configuration and the maximum number of limit cycles that a planar polynomial differential system can have as a function of its degree.

This problem remains unsolved.

It should be mentioned that there are many methods which yield *specific* results related to the study of limit cycles. However, the above general problem has not been solved,⁵ even for the quadratic systems. Rather, we intend to explore, *numerically*, the less general system defined by Equations (3) and (4) proposed by Wilson (Wilson, 1999), which, indeed, approximate the Hodgkin-Huxley neuron:

$$\frac{dV}{dt} = \frac{1}{\tau} [-(a_1 + b_1 V + c_1 V^2)(V - d_1) - e_1 R(V + f_1) + B + \sigma] \quad (3)$$

$$\frac{dR}{dt} = \frac{1}{\tau_R} (-R + a_2 V + b_2) \quad (4)$$

where $a_1, a_2, b_1, b_2, c_1, d_1, e_1, f_1, \tau$ and τ_R are constants⁶, B is the background activity⁷, and σ is an excitation stimulus. Apart from deriving certain specific analytic results, we propose to discover, *numerically*, the number and the positions of the limit cycles.

By introducing Hilbert's Sixteenth Problem as a motivation for the solutions of the system, we argue that the numerical approach to yield the number and the relative positions of the

⁵ Solutions for specific cases of classes of planar differential equations, such as the Lienard equations, systems having homogeneous components of different degree, homogeneous systems perturbed by a constant system, etc. have been reported. Even in these cases, the solutions only yield the number of limit cycles, but not their specific forms.

⁶ In their experiments, Wilson (Wilson, 1999) set the constants as: $a_1=17.81$, $b_1=47.71$, $c_1=32.63$, $d_1=0.55$, $e_1=0.55$, $f_1=0.92$, $a_2=1.35$, $b_2=1.03$, $\tau=0.8$ ms and $\tau_R=1.9$ ms. The stimulus σ was expressed in $\mu A/100$, and V was measured in deci-volts. All these values were assigned to mimic real-life brain phenomena.

⁷ The background activity generates limit cycles in the system. Without this value, the system will converge through the stable spiral point.

limit cycles of the system, described by Equations (3) and (4), is the only reasonable strategy (instead of an analytical one) to tackle the problem.

It is true that there are some theoretical results (Gray, 2000), which can be postulated as theorems, that can be applied for two-dimensional nonlinear systems. But their contributions are only qualitative without being capable of describing the *complete* picture of the number and the relative positions of the limit cycles. Thus, in the interest of completeness we mention these formal results that can be used to prove that a system described by Equations (3) and (4) has a limit cycle and a bifurcation point.

In our analytical approach, we propose the following:

1. To identify if in the space of the trajectories of the HH neurons there is only a single area corresponding to the spiking behaviour, and only a single area corresponding to the quiescent behaviour.
2. To identify the curve that separates these two areas - also known as the "separatrix". Observe that the knowledge of the equations of the curve can lead us to determine a stimulus that crosses the boundary, from the spiking state area into the quiescent state area. Since the explicit form of the separatrix is not available (and cannot be determined), we intend to use topological arguments to demonstrate the existence of the excitation sought for.

In this vein, after computing the fixed points and analyzing their stability, we shall further investigate the computation of the limit cycles. The first hurdle encountered is the fact that the stable limit cycle that corresponds to the spiking behaviour has a set of equations that cannot be determined analytically. In addition, the curve that separates the two areas is itself a limit cycle, *albeit* an unstable one, that also can not be computed analytically. Thus, as mentioned earlier, we have opted to prove the existence of the curve that separates the two areas by using only topological arguments. Having achieved this, we shall proceed to solve the original problem, i.e., to prove the existence of the stimulus by using only qualitative aspects of the system. Thus, we shall answer the following: (i) When do the limit cycles occur? and (ii) When is a limit cycle stable or unstable?

To aid us in this endeavour, we shall use the results of the following theorems, first explained informally, and then more formally.

1. **The Poincare-Bendixon Theorem.** This theorem states that if a system has a long-term trajectory in a two dimensional state space limited to some finite-size region, called its *invariant set*⁸, the system has a fixed point or a limit cycle. This theorem works only in two dimensions because only in a two-dimensional domain a closed curve separates the space into a region "inside" the curve and a region "outside". Thus, a trajectory starting inside a limit cycle can never get out of it, and a trajectory starting outside can never enter into it.
2. **The Hopf Bifurcation Theorem.** This theorem describes the birth and the death of a limit cycle. We resort to this result because our task is to prove the existence of an unstable limit cycle (i.e., the separatrix) between the basin of attraction of the attracting fixed point and the basin of attraction of the attracting stable limit cycle. Fortunately, this separatrix, which can only be proven to exist using the Hopf Bifurcation Theorem, is the curve that separates the area that corresponds to the spiking behaviour and the second area that corresponds to the quiescent behaviour.

⁸ Any trajectory starting from a point in this region will stay there for all time.

The reader will observe that as a consequence of these theorems, we can conclude that it is not possible to find the analytical representation of the separatrix, although we can prove its existence.

2.1 Related Theoretical Foundation

The first useful Theorem, due to Poincaré and Bendixon (Hilborn, 2000), defines the conditions for the existence of a limit cycle.

The Poincaré-Bendixon Theorem

1. Consider a system whose long-term motion of a state point in a two-dimensional state space is limited to some finite-size region;
2. Suppose that this region, say R , is such that any trajectory starting within R stays within R for all time⁹.
3. Consider a particular trajectory starting in R . There are only two possibilities for that trajectory:
 - a. The trajectory approaches a fixed point of the system as $t \rightarrow \infty$.
 - b. The trajectory approaches a limit cycle as $t \rightarrow \infty$.

The Hopf Bifurcation Theorem and a supporting result (referred to as Theorem 0) (Devaney, 2003) presented below, define the conditions for the existence of a stable or unstable limit cycle. The following theorems¹⁰ are essentially taken from (Devaney, 2003).

Theorem 0 Consider the family of maps $F_\mu(z) = \mu z + O(2)$ where μ is not a k^{th} root of unity for $k=1, \dots, 5$. Then there is a neighborhood U of 0 and a diffeomorphism L on U such that the map $L^{-1} \circ F_\mu \circ L$ assumes the form $z_1 = \mu z + \beta(\mu) z^2 z' + O(5)$.

Hopf Bifurcation Theorem Suppose F_λ is a family of maps depending on a parameter λ and satisfying:

- i. $F_\lambda(0) = 0$ for all λ .
- ii. $DF_\lambda(0)$ has complex conjugate eigenvalues $\{\mu(\lambda), \mu'(\lambda)\}$ with $|\mu(0)| = 1$ and $\mu(0) \neq k^{\text{th}}$ root of unity for $k=1, \dots, 5$.
- iii. $\frac{d}{d\lambda} |\mu(\lambda)| > 0$ when $\lambda=0$.
- iv. In the normal form given by Theorem 0, the term $\beta(\mu(0)) < 0$.

Then there is an $\varepsilon > 0$ and a closed curve ζ_λ in the form $r=r_\lambda(\theta)$, defined for $0 < \lambda < \varepsilon$ and invariant under F_λ . Moreover, ζ_λ is attracting in a neighborhood of 0 and $\zeta_\lambda \rightarrow 0$ as $\lambda \rightarrow 0$.

It is necessary to mention the following two relevant remarks, taken from (Devaney, 2003):

1. The assumption that $\frac{d}{d\lambda} |\mu(\lambda)| > 0$ when $\lambda=0$ means that the eigenvalues cross from the inside of the unit circle to the outside as λ increases.
2. If we reverse the inequalities (ii), (iii) and (iv) above, the Hopf Bifurcation Theorem still remains valid. However, after the bifurcation, the invariant circle is repelling while the origin is attracting.

The Hopf Bifurcation Theorem indicates that in the parameter space there is a limit cycle. It does not tell us whether this is an unstable limit cycle or an asymptotically stable limit cycle. However, the theorem specifies where in the parameter space we can search to locate a limit cycle behaviour. Thus, although we are not able to provide the equation that describes the limit cycle, we can qualitatively describe it.

⁹ R is called an “invariant set” for the system.

¹⁰ The notation $O(k)$ means terms of degree k or more.

To render our theoretical consideration meaningful, in the following, we shall derive:

1. The fixed points of the HH neuron by solving the system of equations described by the isoclines,
2. The Jacobian corresponding to the system described by Equations (3) and (4), at the fixed points,
3. The eigenvalues of the Jacobian, by solving the characteristic equation associated with the Jacobian, and
4. The requirements on the eigenvalues as specified by the *Hopf Bifurcation Theorem* for identifying the limit cycle.

2.2 Computing the fixed points

Consider a system described by Equations (3) and (4). We compute the fixed points by solving the system of equations described by their isoclines. This is formalized in the following Lemma.

Lemma 1 *The fixed points of the HH neuron can be obtained by solving a cubic polynomial equation:*

$$x_3V^3+x_2V^2+x_1V+x_0=0, \tag{5}$$

where: $x_3=-c_1$, $x_2=-(b_1+a_2e_1-c_1d_1)$, $x_1=-(a_1-b_1d_1+a_2e_1f_1+b_2e_1)$, $x_0=a_1d_1-b_2e_1f_1+B$.

Proof From Equations (3) and (4), we see that the system has two isoclines, specified by the

contours: $\frac{dV}{dt} = 0$ and $\frac{dR}{dt} = 0$, which can be written as:

$$\frac{1}{\tau} [-(a_1+b_1V+c_1V^2)(V-d_1)-e_1R(V+f_1)+B]=0, \tag{6}$$

$$\frac{1}{\tau R} (-R+a_2V+b_2)=0. \tag{7}$$

The background activity B is the control parameter β specified in the *Hopf Bifurcation Theorem*.

The fixed points can be computed as solutions of Equations (6) and (7). By substituting R from Equation (7) as $R=a_2V+b_2$, and utilizing this value in Equation (6), we obtain the equation:

$$x_3V^3+x_2V^2+x_1V+x_0=0, \tag{8}$$

where the coefficients x_3, x_2, x_1 and x_0 are as defined in the Lemma statement. Hence the Lemma.

Remarks:

1. The roots for the variable V in Equation (5) can be computed for specific values of B , the background stimulus, which is constantly applied to obtain a bistable neuron.
2. Using the settings of Rinzel and Wilson (Wilson, 1999), assigned to mimic real-life brain phenomena, Equations (6) and (7) become:

$$\frac{1}{\tau} [-(17.81+47.71V+32.63V^2)(V-0.55) -26R(V+0.92)+B]=0 \quad (9)$$

and

$$\frac{1}{\tau R} (-R+1.35V+1.03)=0. \quad (10)$$

The fixed points can thus be computed as solutions of Equations (9) and (10), leading to the resulting cubic polynomial equation:

$$-32.6304V^3 - 64.8632V^2 - 50.6416V+B -14.8424=0 \quad (11)$$

The roots of the Equation (11) are computed for specific values of B , and tabulated in Table 1.

B	Root1	Root2	Root3
0	-0.6979	-0.6449+0.4856i	-0.6449-0.4856i
0.025	-0.6947	-0.6465+0.4854i	-0.6465-0.4854i
0.05	-0.6915	-0.6482+0.4852i	-0.6482-0.4852i
0.06	-0.6902	-0.6488+0.4852i	-0.6488-0.4852i
0.065	-0.6896	-0.6491+0.4852i	-0.6491-0.4852i
0.07	-0.6889	-0.6494+0.4851i	-0.6494-0.4851i
0.075	-0.6883	-0.6498+0.4851i	-0.6498-0.4851i
0.08	-0.6876	-0.6501+0.4851i	-0.6501-0.4851i
0.085	-0.6870	-0.6504+0.4851i	-0.6504-0.4851i
0.1	-0.6850	-0.6514+0.4850i	-0.6514-0.4850i
0.125	-0.6818	-0.6530+0.4849i	-0.6530-0.4849i
0.15	-0.6785	-0.6546+0.4848i	-0.6546-0.4848i
0.2	-0.6720	-0.6579+0.4847i	-0.6579-0.4847i
0.25	-0.6655	-0.6612+0.4846i	-0.6612-0.4846i

Table 1. The roots of the value V variable for the fixed points equation of the HH neuron as a function of B , the background stimulus. The parameters of the neuron are as advocated in (Wilson, 1999)

- To consider the real-life settings, we have also computed the corresponding value of R for all the real values of the roots, V , namely for *Root1* from Table 2. From this Table, we can deduce the range of values for R that is useful in simulating brain-like phenomena. These values will be used later in this paper.

B	Root1(V)	R=R(V)
0	-0.6979	0.0878
0.025	-0.6947	0.0922
0.05	-0.6915	0.0965
0.06	-0.6902	0.0982
0.065	-0.6896	0.0958
0.07	-0.6889	0.1000
0.075	-0.6883	0.1008
0.08	-0.6876	0.1017
0.085	-0.6870	0.1025
0.1	-0.6850	0.1052
0.125	-0.6818	0.1096
0.15	-0.6785	0.1046
0.2	-0.6720	0.1140
0.25	-0.6655	0.1228

Table 2. The values of R obtained for a real root of the fixed points as computed for a particular value of B. The parameters of the neuron are as advocated in (Wilson, 1999)

2.3 Computing the Jacobian

We now consider a Jacobian-based analysis of the HH neuron, formalized in the following Lemma.

Lemma 2 *The Jacobian matrix of the system representing the HH neuron is given by:*

$$J(V,R) = \begin{pmatrix} y_{12}V^2 + y_{11}V + y_{10} & y_{21}V + y_{20} \\ y_{30} & y_{40} \end{pmatrix},$$

where $y_{12} = -\frac{1}{\tau} 3c_1$, $y_{11} = -\frac{1}{\tau} (2b_1 + 2c_1d_1 + a_2e_1)$, $y_{10} = -\frac{1}{\tau} (a_1 + b_1d_1 + e_1b_2)$, $y_{21} = -\frac{1}{\tau} e_1$, $y_{20} = -\frac{1}{\tau} f_1$, $y_{30} = -$

$$\frac{1}{\tau} a_2, \text{ and } y_{40} = -\frac{1}{\tau}.$$

Proof We know from the theory of dynamical systems that the Jacobian matrix of the system is :

$$J(V,R) = \begin{pmatrix} \frac{\partial V(V,R)}{\partial R(V,R)} & \frac{\partial V(V,R)}{\partial R} \\ \frac{\partial R(V,R)}{\partial V} & \frac{\partial R(V,R)}{\partial R} \end{pmatrix}. \text{Evaluating each of these components yields:}$$

$$\begin{aligned} \frac{\partial V(V, R)}{\partial V} &= \frac{\partial \left[\frac{1}{\tau} [-(a_1 + b_1V + c_1V^2)(V - d_1) - e_1R(V + f_1) + B] \right]}{\partial V} = \\ &= \frac{1}{\tau} [-3c_1V^2 - (2b_1 + 2c_1d_1)V - (a_1 + b_1d_1) - e_1R], \\ \frac{\partial V(V, R)}{\partial R} &= \frac{\partial \left[\frac{1}{\tau} [-(a_1 + b_1V + c_1V^2)(V - d_1) - e_1R(V + f_1) + B] \right]}{\partial R} = -\frac{1}{\tau} e_1(V + f_1), \\ \frac{\partial R(V, R)}{\partial V} &= \frac{\partial \left[\frac{1}{\tau_R} (-R + a_2V + b_2) \right]}{\partial V} = \frac{1}{\tau_R} a_2, \\ \frac{\partial R(V, R)}{\partial R} &= \frac{\partial \left[\frac{1}{\tau_R} (-R + a_2V + b_2) \right]}{\partial R} = -\frac{1}{\tau_R}. \end{aligned}$$

However, Equation (7) can be used to eliminate R from the partial derivatives. By achieving this, and omitting the laborious algebraic steps, the result follows.

Remarks:

1. Observe that the Jacobian J is not dependent on B . However, it is clear that J can be evaluated at each fixed point, which, in turn, is dependent on B .
2. Using the same settings of Rinzel and Wilson (Wilson, 1999), the Jacobian matrix of the “real-life” HH neural system becomes:

$$\begin{aligned} J(V, R) &= \begin{pmatrix} \frac{\partial V(V, R)}{\partial V} & \frac{\partial V(V, R)}{\partial R} \\ \frac{\partial R(V, R)}{\partial V} & \frac{\partial R(V, R)}{\partial R} \end{pmatrix}, \quad \frac{\partial V(V, R)}{\partial V} = -122.36V^2 - 74.40V + 10.55 - 32.5R; \\ \frac{\partial V(V, R)}{\partial R} &= -32.5V - 29.9; \quad \frac{\partial R(V, R)}{\partial V} = 0.71053; \quad \frac{\partial R(V, R)}{\partial R} = -0.52632. \end{aligned}$$

As mentioned in the proof of the Lemma, Equation (10) can be used to eliminate R from the partial derivatives and thus, the Jacobian becomes:

$$J(V) = \begin{pmatrix} -122.36V^2 - 118.28V - 22.937 & -32.5V - 29.9 \\ 0.71053 & -0.52632 \end{pmatrix}.$$

2.4 Finding the bifurcation point

We shall now consider the problem of finding the neuron's bifurcation point by using the dynamical matrix of the system. This value of the bifurcation point is used to “set” the neuron so as to render it to be bi-stable.

Theorem 1 *A HH neuron obeying the Equations (3) and (4) has a bifurcation point if and only if a root of the equation*

$$\frac{1}{\tau} [-3c_1V^2-(2b_1+2c_1d_1)V-(a_1+b_1d_1)-e_1R] - \frac{1}{\tau_R} = 0 \text{ satisfies the inequality } V > -f_1 - \frac{1}{e_1} \frac{1}{\tau_R}.$$

Proof It is well known that for the bifurcation point, the roots of the characteristic equation, computed from the Jacobian, are purely imaginary. It is also well known that a quadratic equation $x^2-Sx+P=0$ has imaginary roots if:

Condition 1: $S = 0$,

Condition 2: $P > 0$,

where S and P are the sum and the product of the roots, respectively.

Consider the Jacobian of the HH neuron as given by Lemma 2. Applying Condition 1 to this Jacobian generates the equation:

$$\frac{1}{\tau} [-3c_1V^2-(2b_1+2c_1d_1)V-(a_1+b_1d_1)-e_1R] - \frac{1}{\tau_R} = 0.$$

This equation has two roots, say V_1 and V_2 . The problem now is one of verifying whether V_1 and V_2 satisfy Condition 2. This in turn implies that for V_1 and V_2 :

$$\frac{1}{\tau_R} \frac{1}{\tau} [-3c_1V^2-(2b_1+2c_1d_1)V-(a_1+b_1d_1)-e_1R] + \frac{1}{\tau_R} \frac{1}{\tau} e_1(V+f_1) > 0.$$

We can rewrite this inequality using the observation that V_1 and V_2 are solutions to the

equation corresponding to Condition 1, namely: $\frac{1}{\tau} [-3c_1V^2-(2b_1+2c_1d_1)V-(a_1+b_1d_1)-e_1R] = \frac{1}{\tau_R}$.

Using this relation, Condition 2 becomes: $\frac{1}{\tau} + \frac{1}{\tau_R} \frac{1}{\tau} e_1(V+f_1) > 0$.

We know that τ and τ_R are time constants, being positive. We make a convention that e_1 is also a positive constant. With these considerations, Condition 2 can be rewritten in a new

form as: $V > -f_1 - \frac{1}{e_1} \frac{\tau}{\tau_R}$. The theorem follows since whenever these constraints are satisfied,

we obtain purely imaginary roots.

Remarks:

1. As before, using the same settings of Rinzel and Wilson (Wilson, 1999), Condition 1 applied to the Jacobian generates the equation $-122.36V^2-118.28V-22.937-0.52632=0$, whose roots are -0.6879 and -0.2788 . It is easy to verify whether either of these roots satisfy the constraint specified by Theorem 1. Observe that the first root, $V=-0.6879$,

satisfies the *Condition 2* that is equivalent to $V > -0.9361$, implying that the HH neuron has a bifurcation point.

2. From Equation (11), we can compute the value of B that corresponds to the root $V=0.6879$. This value¹¹, of $B=0.0777$, generates a bifurcation in the system.
3. The second root, -0.2788 , does not have any biological significance, being distant from the resting potential of the neuron.
4. The values of the roots (and the corresponding stability consequences) are tabulated in Table 3 as a function of B . Examining this table, we can conclude (using the notation of the *Hopf Bifurcation Theorem*) that $\alpha=0.0777$. Thus, if $B < 0.0777$ (namely, $\beta < \alpha$) the system has a stable spiral point. If $B > 0.0777$, the stable spiral point becomes unstable and the system has a stable limit cycle. The value $B = 0.0777$ is a subcritical or hard Hopf bifurcation point. The system has an unstable limit cycle for $B < 0.0777$, and this is a point that is not observable in the real world due to its instability. It is only possible to *detect* the *consequences* of its presence.

B	V_{equilib}	λ_1	λ_2	
0	-0.6979	- 0.2565+2.2485i	- 0.2565-2.2485i	S
0.025	-0.6947	- 0.1731+2.2534i	- 0.1731-2.2534i	S
0.05	-0.6915	- 0.0909+2.2554i	- 0.0909-2.2554i	S
0.06	-0.6902	- 0.0579+2.2555i	- 0.0579-2.2555i	S
0.065	-0.6896	- 0.0909+2.2554i	- 0.0909-2.2554i	S
0.07	-0.6889	- 0.0909+2.2554i	- 0.0909-2.2554i	S
0.075	-0.6883	- 0.0100+2.2548i	- 0.0100-2.2548i	S
0.08	-0.6876	+0.0075+2.2543i	+0.0075-2.2543i	U
0.085	-0.6870	+0.0225+2.2537i	+0.0225-2.2537i	U
0.1	-0.6850	+0.0721+2.2514i	+0.0721-2.2514i	U
0.125	-0.6818	+0.1504+2.2456i	+0.1504-2.2456i	U
0.15	-0.6785	+0.2299+2.2372i	+0.2299-2.2372i	U
0.2	-0.6720	+0.3825+2.2138i	+0.3825-2.2138i	U
0.25	-0.6655	+0.5300+2.1820i	+0.5300-2.1820i	U

Table 3. Eigenvalues of the Jacobian computed from the real root of the fixed point equation obtained with particular values of the background stimulus B . Last column describes the stability of the fixed points, namely S (stable) and U (unstable)

¹¹ The more exact value is 0.07773267 and it is obtained for $V=-0.687930$ and $R=0.101295$. The Largest Lyapunov exponent for this Hopf bifurcation is $1.000287e-002$. For his neural model, Cooley et al. (Cooley et al., 1965) found a value of 0.0765 (7.65 μA) for the value of B . By increasing the stimulus further, he obtained finite trains of shortening duration, and finally, at higher intensities, claimed to obtain the annihilation.

2.5 The Stable and Unstable Limit Cycles

If we consider B to be a control parameter, we can analytically compute the fixed point, which, for certain values of σ , leads to a *spiral stable point* and, for other values of σ , leads to an *unstable spiral point*. The behaviour around a specific value, namely the change of the stability of the fixed point, induces the concept of a *subcritical (hard) Hopf bifurcation*.

Let us focus on the issue of the limit cycles themselves. By plotting the evolutions of the numerical solutions of the system (Equations (3) and (4)), we discover that for the settings of Rinzel and Wilson (Wilson, 1999), there is a stable limit cycle to the right of the bifurcation point. To identify a hypothetical unstable limit cycle, we can modify the system's equations to make time run "backwards". The modification, which consists of rendering the sign of the two constants, τ and τ_R , to be negative, changes the unstable limit cycle to become asymptotically stable. In this way, by using a numerical method, we can identify the position of a second limit cycle, which happens to be unstable. The stable spiral point is surrounded by this unstable limit cycle which, in turn, acts as a *separatrix* defining a basin of attraction for the stable point.

In Figures 1 and 2 we present the stable and unstable limit cycles, together with the isoclines

$\frac{dV}{dt}=0$ and $\frac{dR}{dt}=0$. The trajectory starts at the point indicated by '1' and follows the

arrowed curves. Observe that in the case of Figure 1, the trajectory of the HH neuron follows the stable limit cycle, and in Figure 2, the trajectory follows the unstable limit cycle. Figure 3 depicts the bifurcation diagram. When B is increased from the resting value, the steady state remains asymptotically stable and the spikes are generated only after the bifurcation point is reached by increasing the value of B . In other words, the HH neuron indicates spiking at $B = 0.0777$, and the spiking process continues for all values of $B > 0.0777$.

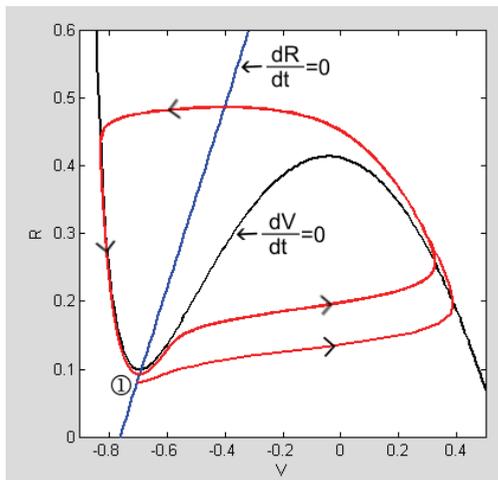


Figure 1. The phase space representing the *stable* limit cycle and the resulting isoclines

$\left(\frac{dV}{dt}=0 \text{ and } \frac{dR}{dt}=0\right)$ obtained by using Rinzel and Wilson settings for the HH neuron. The starting point, (represented by '1') is $V_0=-0.7$, and $R_0=0.08$. In addition, $B=0.08$

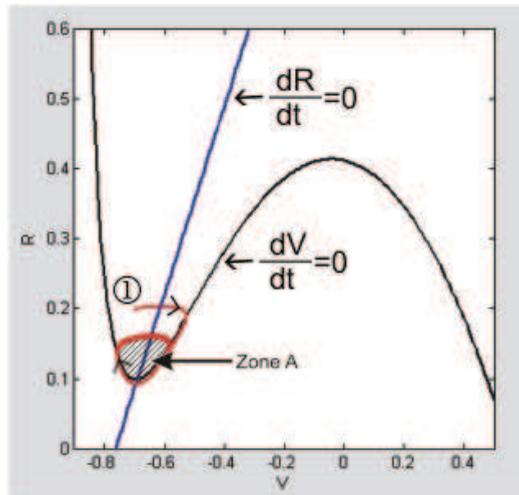


Figure 2. The phase space representing the *unstable* limit cycle and the resulting isoclines ($\frac{dV}{dt} = 0$ and $\frac{dR}{dt} = 0$) obtained by using Rinzel and Wilson settings for the HH neuron. The starting point, (represented by '1') is $V_0 = -0.7$, and $R_0 = 0.2$. In addition, $B = 0.08$

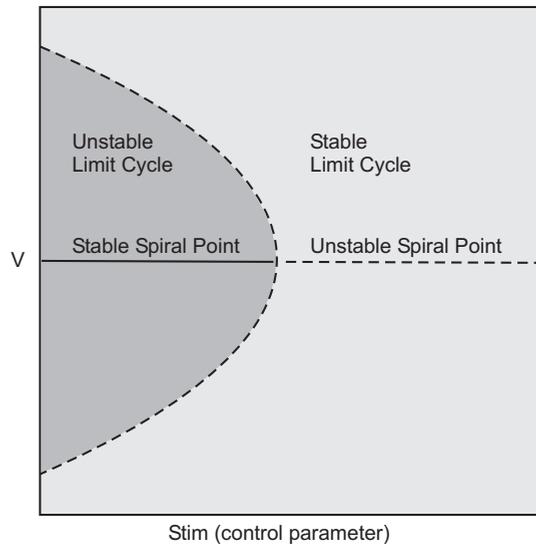


Figure 3. The bifurcation diagram for the system specified in Figures 1 and 2. The variable B is the control parameter. We consider B as a background stimulus that generates a bi-stable neuron

3. The problem of annihilation

The problem of the annihilation of spikes for the HH neuron involves moving the state of the system, by using a pulse stimulus, from outside a particular zone (denoted as $Zone_A$) to being inside $Zone_A$, where $Zone_A$ is a basin of attraction of the stable spiral point which is described by an unstable limit cycle. For example, if the system is characterized by the settings specified by Rinzel and Wilson (Wilson, 1999), $Zone_A$ is contained in the region given by $V \in [-0.6, -0.8]$ and $R \in [0.1, 0.15]$, as depicted in Figure 2. Figure 4 contains all the steady states of the system, including the stable spiral point, and the stable and unstable limit cycles.

The success of the annihilation process depends on four crucial issues:

1. What should be the initial point (V, R) for the system to exhibit annihilation?
2. When should the pulse stimulus, σ , be applied to the system to annihilate it?
3. What should the amplitude of the pulse stimulus be for the annihilation to be achieved?
4. What should the duration of the pulse stimulus be for the annihilation to be achieved?

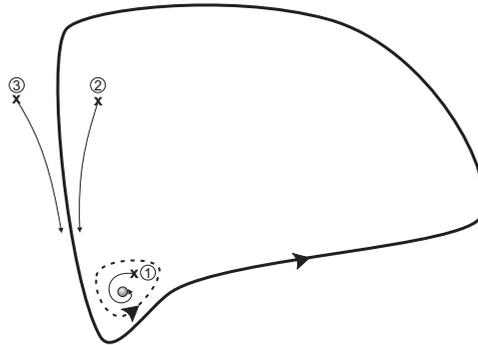


Figure 4. The stable fixed point, the stable limit cycle, and the unstable limit cycle (the *separatrix* given by the dashed line) are represented together. If the system starts in State 1, it will move towards the stable fixed point. If it starts in State 2 or State 3, it will converge to the stable limit cycle

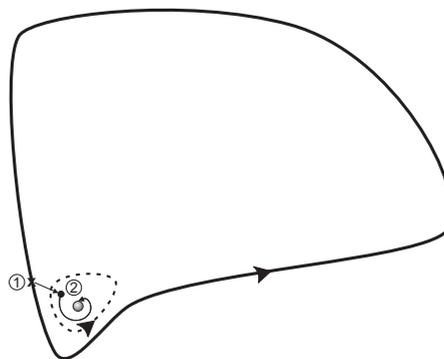


Figure 5. The annihilation process for the system specified in Figures 1 and 2. If the system starts in a carefully chosen configuration at State 1 on the stable limit cycle, the system can be driven to State 2 by applying a carefully chosen stimulus. From this state, it will then go to the stable fixed point

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