STABILITY ANALISYS FOR THE FITZHIGH-NAGUMO MATHEMATICAL MODEL

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Abstract. The biological membranes play fundamental roles in many of life's processes. Many of these processes are electrical, and the membrane, is one of the physical states of nerve cells that can be measured in vitro. The flow of various ions through membranes produces electrical currents causing changes in the membrane potential. The pulses observed in the voltage are called action potentials. Here, we are particularly interested in the frequency at which action potentials are generated and what information can be carried by their firing frequency. Various mathematical models have been formulated, describing important features of this kind of problem. All models are electrical circuits of the "flush and fill" kind, where a charge builds up and then is released within a circuit. This paper presents some physical aspects of these processes with special emphasis on a nerve cell's electrical behavior and a special and simplified mathematical model. According to the current literature, the Hodgkin–Huxley (HH) mathematical model published in 1952 by Hodgkin and Huxley is a major success in characterizing the action potential of a squid axon. The Fitzhugh–Nagumo (FH) mathematical model is considered a simplification of the Hodgkin–Huxley (HH) model. This model is a second order ODE and a reinterpretation of the model developed by Hodgkin-Huxley (HH), which deals with the variation in time of quantities, related to the potassium and sodium conductance in the axon. It corresponds to an electrical circuit composed by a linear system coupled to a nonlinear one, involving a tunnel diode in a flush-and-fill circuit. It is also known that Fitzhugh considered the Bonhoeffer-van der Pol (BvP) equation as a simplified alternative mathematical model. This paper analyzes the non-linear dynamics of the Fitzhugh–Nagumo (FN) mathematical model and its stability.

Keywords: Fitshugh-Nagumo model, Stability, Non-Ideal Dynamics

I. INTRODUCTION

The first complete mathematical model of neuronal membrane dynamics was published by Hodgkin and Huxley in 1952. This work fortified the development of quantitative approximations, in order to understand the biophysics mechanism of the action potential generation. The Fitzhugh-Nagumo equation is a simplification of the Hodgkin-Huxley model. However the Hodgkin-Huxley equations are able to reproduce many features of neuronal dynamics, containing several state variables and a large number of empirical constants (Hodgkin, Huxley, 1952).

The Fitzhugh-Nagumo clamped nerve equation is a second order ODE, a reinterpretation itself of the fourdimensional Hodgkin-Huxley dynamic system that deals with the variation in time of quantities those are related with the potassium and sodium conductances in the axon (Cronin, 1987). It corresponds to an electrical circuit composed by a linear system coupled to a nonlinear one, involving a tunnel diode in a flush-and-fill circuit. It is also known that Fitzhugh (Fitzhugh, 1961) considered the Bonhoeffer–van der Pol (BvP) equation as a simplified alternative mathematical model. The differential equations representing the (BvP) model are very similar to those from Van der Pol; these are, in dimensionless form:

$$\dot{x}_{1} = c \left(x_{1} + x_{2} - \frac{x_{1}^{3}}{3} + I \right)$$

$$\dot{x}_{2} = -\frac{1}{c} \left(x_{1} - a + bx_{2} \right)$$
(1)

where \dot{x}_1 represents the membrane's action potential and \dot{x}_2 represents the sodium gating variable. The parameters *a*, *b* and *c* are constants related to the physiological state of the neuron, where *a* is potassium's potential of equilibrium, *b* is sodium's potential of equilibrium, and *c* is the amplitude corresponding to the inverse of a time constant (determining how fast \dot{x}_1 changes relatively to \dot{x}_2). They satisfy the following constraints:

$$1 - \frac{2b}{3} < a < 1$$

$$0 < b < 1$$

$$b < c^{2}$$
(2)

as introduced in (Fukai *et al*, 2000) by modifying the equations of the Van-der-Pol relaxation oscillator (Nagumo *et al*, 1962). Although the variables have no exact physiological interpretation, for suitable parameter values, the qualitative behaviour of \dot{x}_1 is similar to that the voltage variable of the Hodgkin-Huxley equations (Hodgkin, Huxley, 1952) and that of \dot{x}_2 to the "recovery" of gating variables. The variable *I* represent the forcing of the cell by an external stimulus.

Nagumo (Nagumo et al, 1962) built a circuit using a tunnel diode to the nonlinear element (channel), whose physical representation of the model presented by equations of Fitzhugh (Fitzhugh, 1960) is shown in Figure 1. Since then the "Eq. (1)" become better known as "Fitzhugh-Nagumo model."



Figure 1. The analogical circuit of the Fitzhugh-Nagumo model

The "Fig. 1" shows one of the functions of the fine cellular membrane, that it involves all cells. It allows (or to block) the chemical substance ticket, in accordance with the necessities of cellular metabolism. Between these substances diverse types of ions are meeting. As they possess positive or negative electric load, ions of opposing loads, the long one of the membrane tends to line up it, of one side and another one of it, generating an electric tension through the membrane. In the case of a neuron, this tension is between 60 and 70 mV.

The nervous impulse is caused by a sudden variation of this tension; it is caused by a variation in the concentration of ions, mainly potassium, concentrated inside of the neuron, and sodium, outside. Most of this variation is caused by the potassium transference to the exterior of the cell. The tension at that point of the neuron quickly comes return to the normal, but the variation if it propagates longitudinally (extension of the neuron that loads the nervous impulse), is as a wave. This variation of located tension spreading through the neurons constitutes the nervous impulse.

The extremities of the prolongations (axon and dendrites) of the diverse neurons are connected but not physically; two adjacent extremities remain to a certain distance apart called the synapse. When the nervous impulse arrives in the extremity of an axon or dendrite, chemical substances – the neurotransmitters - are set free inside of the synapse. These substances transmit the electric signal of the impulse for the adjacent cell, making the nervous impulse that is transmitted from cell to cell.

These phenomena constitute the base physical-chemistry of thought, emotions, perception of the five sensations of heat, cold, pain, state. The discharges of epileptic crises have the same nature of the nervous impulses. Such crises depend, therefore, of the balance between chemical substances in the nervous system (Doi and Kumagai, 2001).

In this work, we mention that this paper is organized, as follows: In Section II, we analyzed and discussed equilibrium points of system of Fitzhugh–Nagumo model (FN). In Section III, we analyzed and discussed the stability of the Fitzhugh–Nagumo (FN) mathematical model. In Section IV, we presented the non-linear dynamics of the Fitzhugh–Nagumo (FN) mathematical model. In Section V, we make some concluding remarks about this work and in the final section, we do some acknowledgements and next we list the main bibliographic references used.

2. EQUILIBRIUM POINTS OF SYSTEM.

Richard Fitzhugh and Nagumo JS trying to describe a model that would allow to represent a more accurate and precise characteristics of electrical impulses along the neural membrane, such as the existence of a threshold of excitability and the generation of pulse trains excited by electrical currents external, with several studies, these scientists concluded the following ordinary differential equations to describe what would be observed in the behavior of the phenomenon in question(Assis *et al*, 2010):

$$w' = f(w,a) - v + z$$

$$v' = bw - \gamma v$$
(3)

In this system of equations, the term f(w, a) is a cubic function, described by f(w, a) = v(v - a)(1 - v), the cubic equation is related to the phenomenon of ionic current The term f(w, a) also represents the nonlinearity in the model of Hodgkin-Huxley.

The model in oversized in Eq. (3), gives us a very accurate description of reality biophysics of nerve cells, it also gives us a mathematical idea of the mechanism of neural excitability, the state of rest and other neuro-electrical characteristics easily identifiable in the geometry of phase space (u, w). In effect, this provides a phase space of qualitative explanation of formation and decay of action potential.

A diffusive term was later incorporated into the equation Eq. (3) by Panfilov (Panfilov, A.V., Pertsov, 1984), trying to get better represent the refractory period on the study of reentrant arrhythmias such as ventricular fibrillation.

$$w' = \frac{\partial^2 w}{\partial x^2} f(w, a) - v + z$$

$$v' = \varepsilon(w - \gamma v)$$
(4)

This system of equation has been called reactive-difusive model of Fitzhugh-Nagumo type "Pushchino Kinetics" linear, this model is also called the Fitzhugh-Nagumo model of spatially distributed.

To complete the interpretation of the dynamics of the Fitzhugh-Nagumo system in biophysical, we must perform the following association: the variable v as the voltage across the membrane, the parameter z represents the electrical current applied to the nerve cell, and the variable w as a variable system recovery without specific biophysical meaning.

Examining the Fitzhugh-Nagumo model, we note the crucial fact that the quantities associated to this system of equations are dimensionless. This means that the original equations that make up the Fitzhugh-Nagumo model were scaled in order to make the quantities dimensionless v and w. This is interesting when qualitatively analyzing a dynamic system without a concern with respect to units associated with the quantities involved.

After a few years, scientists Panfilov and Hogeweg (Panfilov, Hogeweg 1993), noted the model of Fitzhugh-Nagumo equation in its classical form, is not very useful for detailed studies of atrial while modeled as breaking the spiral or vortex. (Fiedler-Ferrara *et al*, 2004)

For this reason researchers have suggested modifications of the original equations to favor the occurrence of instabilities of waves which are properties of the model and not due to numerical artifacts. Among various models developed for this purpose include: the continuous model of Aliev-Panfilov (Aliev, Panfilov, 1996), the linear model from Bar-Eiswirth (Bär, Eiswirth, 1993), the linear model of parts of Panfilov, Hogeweg (Panfilov, Hogeweg 1993), among many otherwise exist.

Seeking equilibrium points in the system of differential equations of Fitzhugh-Nagumo, Equal (3) to zero the derivatives dv/dt and dw/dt, and isolate the parameter w in the two equations of the system and we get:

$$w = v (a - v)(v - 1) + I$$
 (5)
 $w = v/c$ (6)

The set of infinite points (w, v) that satisfy Eq. (3), correspond to states in which the voltage applied across the cell membrane, represented by the parameter v, does not vary over time, ie if v a constant, then dv / dt will always be numerically equal to zero, regardless of the value of the applied voltage. If we choose a condition that complies with

this characteristic, then we can say that the membrane will remain indefinitely with the same voltage applied to its structure because it will be in equilibrium.

Similarly, if we choose any point (w, v) that satisfies the Eq. (6), we select a set of states in which the parameter w (variable recovery) is any constant, implying that its derivative is always zero.

Each of these Eq. (5) and Eq. (6) represents a curve in state space w versus v, this system, which in this case corresponds to the graph of two functions w(v). In fact, Eq. (5) represents a third degree polynomial equation and Eq. (6) a straight line without constant terms, ie the line will always pass through the origin of the plans (0.0). The points where these curves intersect correspond to equilibrium points of the system. These curves are called Null isoclines of the system, since they have their first derivatives numerically equal to zero.

You can then check under what conditions are needed for all the parameters of the model guarantees the existence of one, two or three equilibrium point. We also note that the parameter b does not interfere in our analysis, since it will not appear in Eq. (7) and Eq. (8), ie, if we consider the value of b is nonzero, it will not influence the point of system balance.

The number of intersections that occur in the curves under consideration in the plan v versus w depend on the relationship between the inclination angle of the line Eq. (7) and the slope of the inflection point of the cubic function, Eq. (2).

We can find the slope of the cubic function, Eq. (7), calculating their points of inflection for this equal to zero the second derivative of the function w, with respect to v, we find the following value:

$$V = (a + 1) / 3 \tag{7}$$

The slope of the cubic curve, defined by the function w, for this generic value of v, given by Eq. (3), shall:

$$(a^2 - 4a + 1)/3 = M \tag{8}$$

The "Fig. 2" illustrated the three possible situations of equilibrium in the plane v versus w, where the line was identified in Eq. (2) with the color red and the cubic function, Eq. (7), with the blue and highlighted with a black dot equilibrium (intersection of the curves). From the graphs, we can conduct a detailed geometric analysis to analyze the conditions of the occurrence or non-equilibrium system.

By keeping fixed the parameters I and the change of the parameter c has the consequence of change in the slope angle of the line in Eq. (6). Thus, if we set the value and I, just changing the value of c, we get one, two or three intersections, turning straight sets in just one point, the origin. (Fiedler-Ferrara *et al*, 2004)



Figure 2. Phase Portrait (a) one point of intersection. (b) two points of intersection, and (c) three points of intersection.

Depending on the value of the parameters used in the system of Fitzhugh-Nagumo (a,c, or I) can get one, two or three crossings (equilibrium points) of the line with the cubic function at the level v from w. If the parameter 1/c is numerically greater than M, there is only one fixed point, otherwise, may present situations with two or three fixed points balance (Guerra et al, 2002)

If you keep unchanged the parameter c, and vary the parameter I (external excitationcurrent) causes a shift of the cubic curve in the direction of the axis w. If the parameter I get a positive addition, the change will be upwards, ie, for a positive w-axis, otherwise offset is to the negative w-axis. (Guerra et al, 2002)

3. STABILITY

In this section, the stability analysis of the nonlinear Fitzhugh-Nagumo model is considered. An equilibrium state x^* is said to be stable if and only if, given $\varepsilon > 0$, there exists $\delta(\varepsilon) > 0$ such that for $||x(0) - x^*|| < \delta(\varepsilon)$, then $||x(t) - x^*|| < \varepsilon$ for all t > 0. Thus, there is a neighborhood of radius δ in the vicinity of equilibrium, so that, for a given initial condition that belongs to the neighborhood, the trajectory corresponding to this initial condition is never away more than a distance ε (Monteiro et al, 2006).

An equilibrium state x^* is said asymptotically stable if and only if there exists a $\delta > 0$, so that for $||x(0) - x^*|| < \delta$ then $||x(t) - x^*|| \to 0$, for $t \to \infty$ (Monteiro et al, 2006).

Finally, if the trend moves away from the neighborhood radius ε in a finite time, the equilibrium is said unstable.

If the system meets some mathematical conditions, we can approximate the area or part thereof of a nonlinear system by a system of linear equations. This process is called linearization of nonlinear systems.

An important note is the fact that only in cases of elliptic points (Real part of eigenvalue $\lambda = 0$) the linear analysis can not be applied because it can bring results in insecure or even erroneous, in which case the terms should be studied higher order system (Monteiro et al, 2006).

Applying the linear approximation method, you can review more quickly and simply the behavior of nonlinear systems, which start in the neighborhood of an equilibrium state. For the system of nonlinear differential equations of first order, f(x, y) and g(x, y).

We get close to the equilibrium state $P = (x^*, y^*)$ the following expansions:

$$\frac{dx}{dt} = f(x, y) = f(x^*, y^*) + \frac{df}{dx}(x - x^*) + \frac{df}{dy}(y - y^*) + \dots$$

$$\frac{dy}{dt} = g(x, y) = g(x^*, y^*) + \frac{dg}{dx}(x - x^*) + \frac{dg}{dy}(y - y^*) + \dots$$
(9)

If we want a more accurate value of dx / dt or dy / dt, we must continue to develop the above expansion in Taylor series with higher order terms. We can then choose a new coordinate system in the plane so that the equilibrium P is changed from its original position for the origin of the system, making our system analysis.

Defining the new variables as:

$$X(t) = x(t) - x^* Y(t) = y(t) - y^*$$
(10)

The approximation above is valid only for points very close to the fixed point $P^* = (x^*, y^*)$ if and only if X(t) and Y(t) describing the local behavior of solutions near P^* , otherwise this approach is false.

The following equations, which is the time domain are determined by:

$$\frac{dX}{dt} = \frac{dx}{dt}$$
 and $\frac{dY}{dt} = \frac{dy}{dt}$ (11)

Neglecting higher order terms of the system of equations (9) and defining $f(x^*, y^*) = g(x^*, y^*) = 0$, we obtain:

$$\frac{dX}{dt} = \frac{df}{dx} \cdot X + \frac{df}{dy} \cdot Y$$

$$\frac{dY}{dt} = \frac{dg}{dx} \cdot X + \frac{dg}{dy} \cdot Y$$
(12)

Using the matrix notation, we can further simplify the problem, and we get the following equality:

$$\frac{dZ(t)}{dt} = AZ(t) \tag{11}$$

where Z(t) is defined as the column vector of state variables of the system and A is a Jacobian matrix.

Applying this in our work, we have the matrix of linearization for the Fitzhugh-Nagumo model considering I = 0, without external excitation current and also considering a fixed point in the neighborhood (v_0 , w_0), we have:

$$A = \begin{bmatrix} \frac{\partial V}{\partial v} & \frac{\partial V}{\partial w} \\ \frac{\partial W}{\partial v} & \frac{\partial W}{\partial w} \end{bmatrix}$$

$$A = \begin{bmatrix} -3(v_0)^2 + 2(a+1)v_0 - a & -1 \\ b & -bc \end{bmatrix}$$
(12)

Therefore, working a little our system of Fitzhugh-Nagumo equations, we linearized point very close to equilibrium, as will be shown below:

$$\frac{dZ(t)}{dt} = AZ(t)$$

$$\begin{bmatrix} dv/dt \\ dw/dt \end{bmatrix} = \begin{bmatrix} -3(v_0)^2 + 2(a+1)v_0 - a & -1 \\ b & -bc \end{bmatrix} \begin{bmatrix} v \\ w \end{bmatrix}$$

$$\frac{dv}{dt} = (-3(v_0)^2 + 2(a+1)v_0 - a)v_0 - w$$

$$\frac{dw}{dt} = bv - bcw = b(v - cw)$$
(13)

The behavior of the system under consideration is integrally related to the eigenvalues of the matrix representing the linearized system.

Analyzing the two eigenvalues corresponding to the matrix of the linearized system, we can easily classify them from the pair of eigenvalues found with the change of parameters.

According to Equations (13), the system eigenvalues $\lambda_{1,2}$ are:

$$\lambda_{1,2} = -\left(\frac{a+bc}{2}\right) \pm \frac{\sqrt{(a-bc)^2 - 4b}}{2}$$
(14)

Analyzing these eigenvalues analytically, we can study in detail the states of equilibrium exist for this particular situation:

1) If the eigenvalues $\lambda_{1,2}$ are real numbers, the condition must be satisfied that $(a - bc)^2$ is numerically greater than or equal to 4b

2) If the eigenvalues are negative, one has to fulfill the condition that $(a + bc) > \sqrt{((a - bc)^2 - 4b)} > 0)$.

3) If the eigenvalues are positive, one has to fulfill the condition that $(a + bc) < \sqrt{((a - bc)^2 - 4b)}$, and simultaneously $\sqrt{((a - bc)^2 - 4b)} > 0$

4) If the eigenvalues are complex numbers of the form A + Bi, we have to satisfy the condition that $(a - bc)^2 < 4b$ and simultaneously the condition that a + bc is different from 0.

In all situations described above, and with a mathematical development of equations and inequalities mentioned meeting the initial conditions: b > 0, c being greater than or equal to zero, and external excitation current I = 0, we have the steady state (v_0 , w_0) = 0 is always asymptotically stable in the system.

We must emphasize that all our analysis has been developed for the case that there is no external current stimulus on the membrane, ie I = 0. Under these conditions, the experiments show that the physiological resting potential behaves like an attractor, ie, if there is a small external excitation in the membrane potential, will have as an immediate response to recovery and return to its initial value, a fact shown in our analysis shows a behavior that will always be stable.

We should also pay attention to the character of local stability analysis obtained by a linearization: the solutions are approximate solutions, valid for short distances around the equilibrium point.

4. NON-LINEAR DYNAMICS.

In this section, in order to carry out numerical integrations of the Fitzhugh-Nagumo system, we use Simulink (Matlab)®. A block diagram of the Fitzhugh-Nagumo system is shown in "Fig. 3".



Figure 3. The SIMULINK® model for numerical simulation of the Fitzhigh-Nagumo system.

In the current literature, there are some studies on the model (Hoppensteadt, 1986) and "Fig. 4" illustrates the behavior of the Fitzhugh–Nagumo mathematical model, by using "typical" numerical values for the parameters I = 0.5, a = 0.7, b = 0.8 and c = 0.8.

The equilibrium point of the dynamical system is $P^* = (1.44842, -0.93553)$. The system eigenvalues are $\lambda = -0.8690 \pm 0.8646i$. The negative real part indicates that the system is stable, therefore the equilibrium point P is a stable focus and the trajectories described an orbit spiral converged to the point.

"Fig. 4-d" is not exhibited the appearance of chaos, because it has a Lyapunov exponent negative: $\lambda_1 = -0.85$

"Fig. 5" illustrates the behavior of the Fitzhugh–Nagumo mathematical model, by using numerical values for the parameters I = 0.5, a = 0.7, b = 0.1 and c = 0.8.

All images contained in "Fig. 4, 5 and 6", were simulated and designed by the authorin the software (Matlab) \Box 2010.



Figure 4. (a) Time History for x_1 . (b) Time History for x_1 . (c) Portrait Phase (x_1, x_2) and (d) Dynamics of Lyapunov expoents.



Figure 5. (a) Time History for x_1 . (b) Time History for x_1 . (c) Portrait Phase (x_1, x_2) and (d) Dynamics of Lyapunov expoents.

The equilibrium point of the dynamical system is $P^* = (0.84437, -1.44370)$. The system eigenvalues are $\lambda = 0.1185 \pm 0.6867i$. The negative real part indicates that the system is unstable, therefore the equilibrium point P is an unstable focus and the trajectories described an limit cycle. "Fig 4-d" illustrated the periodic behavior periodic ($\lambda_I = 0.006$).

The "Fig. 6" illustrates the behavior of the Fitzhugh–Nagumo mathematical model, by using numerical values for the parameters I = 0.3, a = 0.01, b = 0.5 and c = 0.2.

The equilibrium point of the dynamical system is $P^* = (0.39020, -0.38039)$. The system eigenvalues are $\lambda = 0.3489 \pm 0.2261i$. The negative real part indicates that the system is unstable, therefore the equilibrium point **P** is an unstable focus and the trajectories described an orbit spiral converged to the limit cycle and in "Fig. 6-d" is not exhibited the appearance of chaos, because it has a Lyapunov exponent negative: $\lambda_I = 0.02$.



Figure 6. (a) Time History for x_1 . (b) Time History for x_1 . (c) Portrait Phase (x_1, x_2) and (d) Dynamics of Lyapunov expoents.

5. CONCLUSION

One of the functions of the fine cellular membrane, involved in all cells, is to allow (or to block) the chemical substance, in accordance with the requirements of cellular metabolism. Between these substances diverse types of ions meet. As they possess a positive or negative electric load, ions of opposing loads along the membrane tend to line up on either side, generating an electric tension through the membrane. A nervous impulse is caused by a sudden variation of this tension, caused by a variation in the concentration of ions, mainly potassium, concentrated inside the neuron, and sodium outside. Most of this variation is caused by the potassium transference outside the cell. The tension in that point of the neuron quickly comes back to the normal one, but the variation propagates along the axon (extension of the neuron that loads the nervous impulse), as a wave. This variation of the tension spreading through the neurons constitutes the nervous impulse. The extremities of the prolongations (axon and dendrites) of the diverse neurons are connected - in reality, they do not connect physically; two adjacent extremities remain at a certain distance, the small space between them called is called the synapse. When the nervous impulse occurs in the extremity of an axon or dendrite, chemical substances—the neurotransmitters—are set free inside the synapse. These substances transmit the electric signal of the impulse for the adjacent cell, making the nervous impulse to be transmitted from cell to cell. These phenomena constitute the basic physics-chemistry of thought, of emotions, of perception of the five feelings and sensations of heat, cold, pain, etc. As the involved discharges in epileptic crises have the same nature as the nervous impulses, such crises depend on the balance between chemical substance present in the nervous system. In this work, a dynamics of the Fitzhugh-Nagumo model proposed (Fitzhugh, 1960; 1961, Nagumo et al, 1962) is investigated and we verified the behavior stable. If there is indication of chaos in the system in question, we can relate them physically with epileptic seizures, where we could not control impulses, not seeking it shapes its instability.

6. ACKNOWLEDGMENTS

The authors thank all the support of the Fapesp (Proc. N° 2010/13116-9), Fundesp (Proc N° 00746/10-DFP) and Prope/UNESP (Programa Primeiros Projetos, Edital n° 005/2010-PROPE).

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