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A numerical study of cardiac pacemakers with relaxation oscillators

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Abstract. The cardiac pacemaker is an important device for the proper functioning of the human cardiac system. A modeling to represent the signals from the operation of a pacemaker has been done using a relaxation oscillator, the Van der Pol oscillator, given by a second order differential equation. This paper aims to demonstrate the development of a cardiac pacemaker model based on the modified Van der Pol oscillator to simulate it numerically, in order to analyze the signal in the time domain, as Phase Portrait, and in the frequency domain, as Fourier Transform and Wavelets Transforms, in order to identify the stability of the oscillator and its response in the frequency domain. The numerical integrations performed in this paper were done with the fourth order Runge Kutta method.

Keywords: Peacemakers, Nonlinear Dinamics, Continuous Wavelet Transform, Time Frequence Analises.

1 Introduction

The study of the human body has always been a major effort of understanding and research, due to its vital importance to living things. One of the major organs of the human body is the heart, with increasing studies in recent times. One of the areas of study of the heart is the study of the electrical stimuli that provide the pumping of blood, electrical stimuli that come from the Sinoatrial Node (SA), known as the natural pacemaker, which transmits the stimuli to the other parts of the heart, thus allowing the pumping of blood.

The electrical stimulus in the time domain is known as action potential [6] and in order to represent it through a second-order differential equation (ODE), so that it is possible its numerical simulation and thus its analysis through a nonlinear dynamic perspective, Krzysztof Grudzinski and Jan J. Zebrowski developed a mathematical model [9] based on the model of Van der Pol and Van der Mark [7], this self-excited oscillatory model with a nonlinear damping term. This type of analysis, with a dynamic approach, is not suitable for research at the cellular level, but can be used for the investigation of heartbeats (rhythm). In this work, the classical Van der Pol model and the Grudzinski and Zebrowski model will be numerically simulated, presenting the action potentials with their Phase Portrait, but with a differential, the analysis in the frequency domain (TFA) [2], with the use of well-established tools such as the Fast Fourier Transform and Continuous Wavelet Transform.

The development and analysis of the model will be demonstrated in this article, with its faults and successes, besides a detailed analysis of the model in the frequency domain and the analysis of its temporal response from the Phase Portrait.

2 Action potential

An action potential (AP) is defined as a sudden, rapid and transient change in the resting potential of the membrane that propagates as well as being generated when its membrane is excited above a certain threshold potential where ion channels are activated. This allows ion currents to flow into or out of the cell, thus changing its potential and resulting in the generation of an action potential [3]. The action potential has three phases: depolarization, peak overshoot, and repolarization. There are also other states of the membrane potential related to the action potential. The first is the hypopolarization, which precedes the depolarization, and the second is the hyperpolarization, which follows the repolarization[4].

Hypopolarization is the initial increase in membrane potential to the value of the threshold potential. The threshold potential opens sodium voltaic channels, causing an ion flow. This phase is called depolarization. During depolarization, the interior of the cell becomes increasingly electropositive. This high positivity is called the overshoot peak phase.

After overshoot, the overshoot value of the action potential opens up voltaic channels, reducing the electropositivity of the cell. This is the repolarization phase, whose purpose is to bring the membrane back to its resting potential. Repolarization always leads first to hyperpolarization, a state in which the membrane potential is more negative than the resting potential.

After depolarization (Fig.1) called the diastole period, the cell begins to repolarize, preparing the cell for the next stimulus. The repolarization of the cell corresponds to the refractory period, which can be defined as the time elapsed after the generation of the action potential, and during which the excitable cell is not able to produce a new action potential [6].

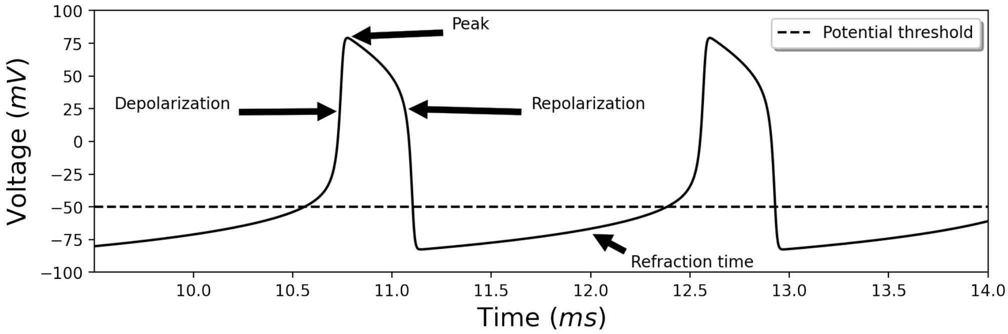

Figure 1. Action potential

3 Equation development

In this section will be presented the natural pacemaker models proposed in the current literature that will be analyzed in the frequency domain. The first model to be analyzed is the Van der Pol model [9], characterized mainly by having an intrinsic frequency that adapts to the frequency of an external signal, proposed at first by Van der Pol and Van Der Mark. This is the characteristic that most closely matches the natural pacemaker of a heart, where the sinoatrial node (SA) is the main node that governs the other nodes of the heart, where these adjust to the rhythm of the main SA node.

The second model is later devised by Grudzinski and Zebrowski Model [3], departing from Van der Pol's model with the presentation of three fixed points in their model due to a nonlinear term.

3.1 Van der Pol Model

The Van der Pol model is a model of a self-excited oscillator exhibiting limit cycles. Regardless of initial conditions, the oscillator is shown to converge to a single limit cycle of given amplitude, the focus found in the action potential of this model.

This type of nonlinear oscillator was used by Van der Pol in studies of vacuum tube circuits in the analyses of early radios [1]. In standard form, it is given by a second-order differential equation, eq.1.

$$\ddot{x} + \mu(x^2 - 1)\dot{x} + x = 0 \tag{1}$$

Analyzing the equation, one can see that it resembles a harmonic oscillator with a nonlinear damping term $\mu(x^2 - 1)$, where μ is the parameter corresponding to the nonlinear term. This term has positive damping for $|x| > 1$, but also has negative damping for $|x| < 1$, i.e. for cases where the amplitude is very large the damping decreases, and in cases where the amplitude is very small the damping amplifies [7]. Rewriting eq.1 to arrive at a result similar to that analyzed by Van der Pol [5], as also to standardize the equations proposed in this paper, one obtains eq. 2. To integrate numerically, the equation is rewritten as being a system of first order differential equations (eq. 3)

$$\frac{d^2x}{dt^2} + \alpha(x^2 - 1)\frac{dx}{dt} + \omega^2 x = 0 \tag{2}$$

$$\begin{cases} v = \dot{x} \\ \dot{v} = \alpha(1 - x^2)v - w^2 x \end{cases} \tag{3}$$

3.2 Grudzinski & Zebrowski Model

The model of Grudzinski & Zebrowski, aims to represent more faithfully the response of the action potential of the sinoatrial node. Their model starts from a modified Van der Pol oscillator [9], with the presence of a Duffing term, which introduces more nonlinearities to the system, arriving at eq. 4.

$$\frac{d^2x}{dt^2} + \alpha(x^2 - \mu)\frac{dx}{dt} + x(x+d)(x+d)/d^2 = 0 \tag{4}$$

Such modifications present in this model are proposed to obtain a phase space that resembles a membrane model of a neuron proposed by Morris-Lecar, which has three fixed points: an unstable focus at $x = 0$, a saddle point at $x = -d$ and a stable node at $x = -2d$. In this equation, the term μ controls the amplitude of the signal, with the saddle manifolds deforming the signal unlike an ordinary Van der Pol oscillator, where this model is biased towards relatively negative values, which at high enough values of μ lead to high oscillation amplitudes, such that they are attracted to the saddle point and then taken to the stable node or unstable focus, depending on its location at the time it passes around the saddle point.

This model where the parameter μ is added has limitations, where the saddle point and the node have an unchanging distance between them. For this, Grudzinski & Zebrowski proposed to introduce a new parameter e, which makes the structure of the phase space present its fixed points at coordinates $x = -d$ and $x = -e$. When e and d are different and have opposite signs, the phase space has a structure similar to that of a Duffing oscillator, an unstable focus and two saddle points, but when the parameters e and d are different and have the same sign, the system has a stable node at $x = -e$, a saddle point at $x = -d$ and an unstable focus at $x = 0$. The change of this parameter E makes it possible to control the depolarization period, since when close to the saddle point the tendency is that the trajectory remains in its vicinity for longer and this causes the period of oscillations to become longer, and when far from the saddle point the trajectory spends less time around this point, thus causing the frequency to increase. With this, it was possible to change the shape of the pulse by parameter α independently of the change of the frequency of oscillations by parameter e, thus allowing a better manipulation of these properties.

Moreover, a final change was the exchange of the term $(x^2 - \mu)$ for the asymmetric term $(x - v_1)(x - v_2)$, which allowed the increase in the frequency of generation of the action potential pulses. It is important to stress that it is possible to obtain such changes without changing the maximum value of the action potential, which can be accomplished by simultaneously changing v_1 and v_2. And finally, to preserve the self-oscillatory characteristic of the system v_1 and v_2 must have opposite signs, thus preserving the shape of the phase space, that is, the shape of the action potential. All these changes arrive at a eq. 5, the equation proposed by Grudzinski & Zebrowski. Furthermore, this equation was rewritten in the form of a system of second order ordinary differential equations given by eq. 6.

$$\frac{d^2x}{dt^2} + \alpha(x - v_1)(x - v_2)\frac{dx}{dt} + x(x+d)(x+e)/ed = 0 \tag{5}$$

$$\begin{cases} v = \dot{x} \\ \dot{v} = -\alpha(x - v_1)(x - v_2) - \frac{x(x+d)(x+e)}{ed} \end{cases} \tag{6}$$

4 Numerical solution

The Van der Pol and Grudzinski models given respectively by eqs.(3) and (6). For the simulation, the equations were numerically integrated using the fourth-order Runge-Kutta method, and for plotting the data and subsequent analysis in the time and frequency domain, the signal was defined around the interval t of $100 \geq t \geq 200$ $[s]$, where the system response had the same amount of integer periods in both signals.

For the simulation, the established parameters referring to the Grudzinski model were set being α = 5, d = 3, v_1 = 1, v_2 = -1, and f = 3. To maintain the appropriate ratio of the frequency in the sinoatrial node (SA) we used e

= 12. In relation to the Van der Pol model $\mu = 10$, $\omega = 0.167$ $[Hz]$ was set, and for the initial conditions the value of 1 was used, so that they would present a response similar to the Grudzinski model. All variables and parameters in this paper are dimensionless except for the Van der Pol natural frequency, in addition the magnitude of the period of the oscillations were kept in a range similar to that observed in the physiology observed in Grudzinski's model [10].

The response of the action potential of the classical Van der Pol and Grudzinski models are shown in Figs. 2(a) e 2(b). In an initial analysis, the response of both the Van der Pol model and the Grudzinski model are similar to each other, but when compared with the real action potential, the Van der Pol model presents problems, among which the biggest is the lack of control over the parameters in order to modulate the signal, where by changing the frequency, the waveform also changes. This problem can be mitigated in the Grudzinski model, and the waveform of the Grudzinski model is more similar to a real action potential. For Fig. 2(b),the interval between depolarization and repolarization (Fig. 1) is shortened, compared to the action potential resulting from the Van der Pol, Fig. 2(a). Moreover, the phase space presented in Figs. 2(c) e 2(d) are similar, but the most current model (Grudzinski) presents as the main difference the addition of two fixed points.

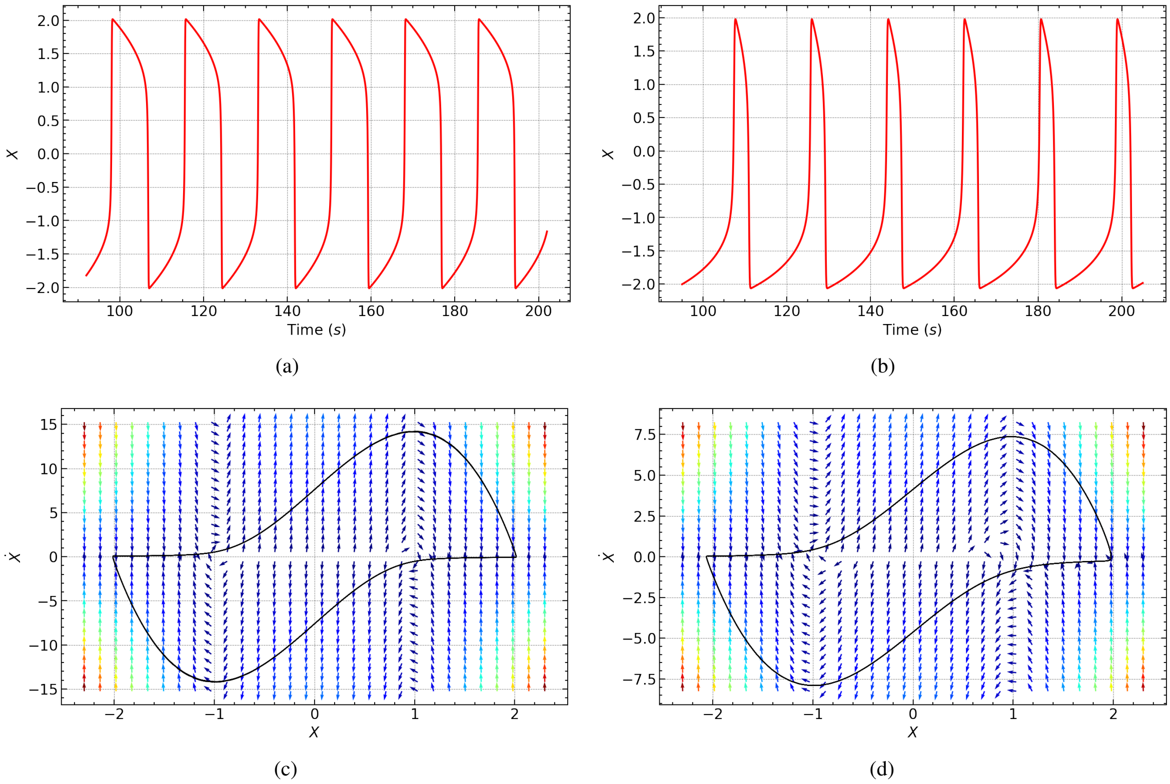

Figure 2. a) Action Potentials (Van der Pol model) b) Action Potentials (Grudzinski model) c) Phase Portrait (Van der Pol model) d) Phase Portrait (Grudzinski model).

Fig.(3), shows the phase space for the Grudzinski model for different initial conditions, where we also have the location of its fixed points, in this case at $x = -12$ have the stable node, at $x = -3$ the saddle point and for $x = 0$ the unstable focus. Around the saddle point it is possible to observe the trajectory followed for different initial conditions and how it slightly deforms the space and the shape of the limit cycle.

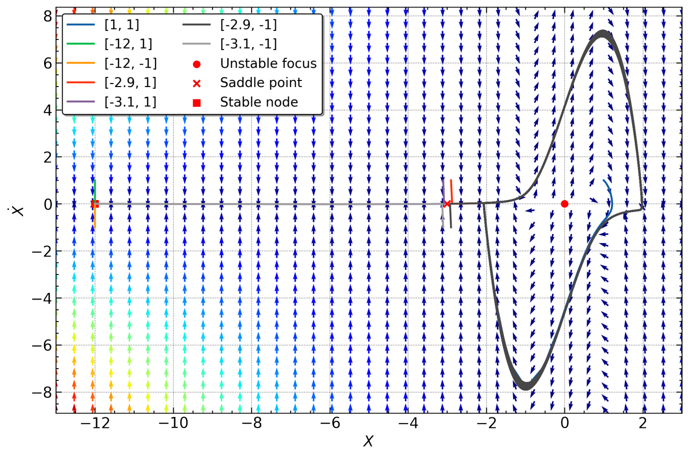

Figure 3. Phase portrait (Grudzinski model) for different initial conditions and fixed points

In Figs. 4(a) e 4(b), the Fast Fourier Transform of the Van der Pol and Grudzinski models are presented, respectively, where due to the models being nonlinear have some effects on the frequency. In the case of the Van der Pol model, several harmonics decaying in amplitude are presented, but in the Grudzinski model, have an unexpected effects, such as frequencies that gather in well-defined blocks and decay in amplitude along the frequency axis, with the use of the Fast Fourier Transform tool, which cannot fully characterize the signal due to the characteristics of the temporal response of the system, which presents harmonics. Figs. 4(c) e 4(d) are the CWT results for each model (using as the mother wavelet the morlet wavelet). In this case, have a total of 6 periods for the analysis of the two models. For the Van der Pol model it is possible to observe in the frequency spectrum a characteristic response of certain structures repeating themselves 12 times, but in the case of the Grudzinski model the structures are larger, repeating themselves a total of 6 times, but with further analysis it is noted that have a pattern similar to that presented in Fig.4(c), as if those structures were clustering in pairs.

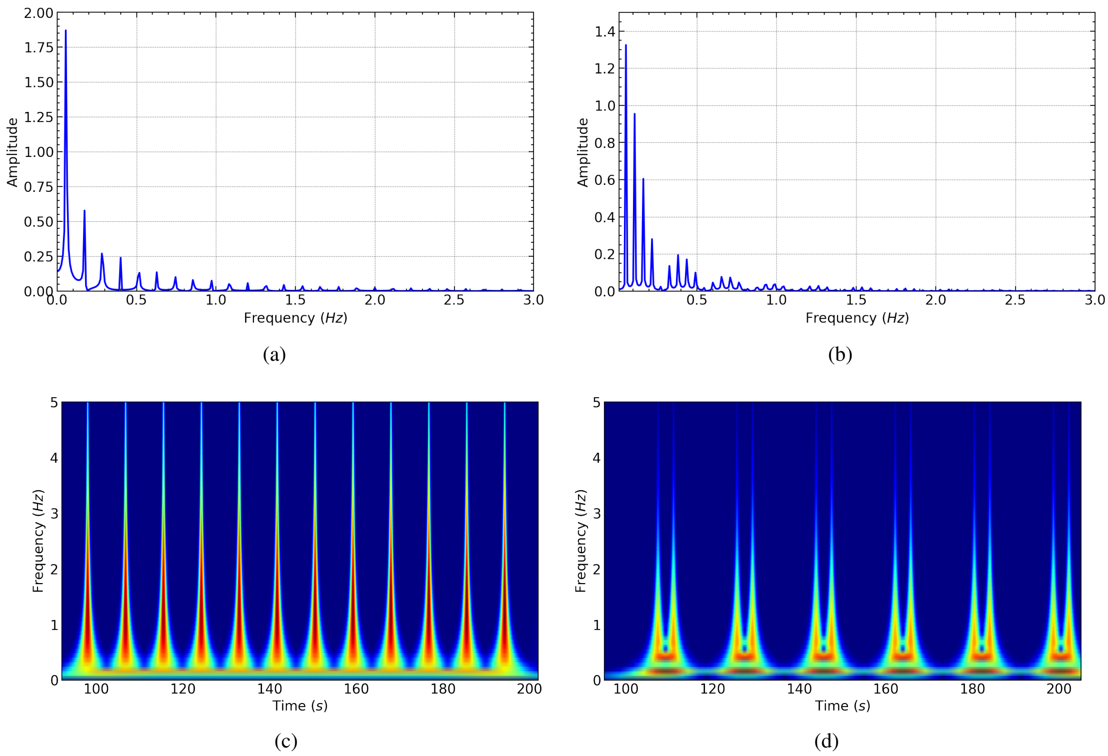

Figure 4. a) Fast Fourier Transform (Van der Pol model) b) Fast Fourier Transform (Grudzinski model) c) Continuous Wavelet Transform (Van der Pol model) d) Continuous Wavelet Transform (Grudzinski model).

5 Conclusion

In this paper a brief review of the natural pacemaker models from Van der Pol oscillators has been presented, in addition, an analysis in the time and frequency domain that is missing in the general literature for Van der Pol oscillators has also been presented.

The model proposed by Van der Pol is a model that resembles the action potential of a natural pacemaker, however, for general study purposes it is not suitable as it is an unchanging model. Grudzinski & Zebrowski presented a more satisfactory model in the context of studies of a natural pacemaker, as it introduces new parameters that make possible the best modulation of the signal, thus becoming closer to the goal of mathematically modeling a real action potential. Even with its similarity to the real model, it still has some impasses, among them the fact that it cannot adapt to the frequency of the real model keeping the pulse format fixed.

In the time-frequency analysis it was initially observed from the discrete Fourier transforms the appearance of harmonics in both models, but in the case of the Grudzinski & Zebrowski model the harmonics are condensed into groups of 4. Moreover, using CWT's, a method that presents a good visualization both in the time and frequency domain, there is the appearance of structures due to these harmonics and their change in time, in the Van der Pol model there are 12 equally spaced structures, however in the Grudzinski model there is the junction of structures in pairs having 6 structures in total.

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