Cardiac Pacemaker: Fractional Equations and Frequency Analysis

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Abstract. Understanding and researching the human body has been fundamental due to its importance for living beings. As one of the vital organs of the human body, the heart has always been of great academic relevance. One of the areas of study of the heart is the study of the electrical stimuli that provide blood pumping. These electrical stimuli come from the Sinoatrial Node (SA), known as the natural pacemaker, which transmits the stimuli to the other parts of the heart, thus allowing blood to be pumped. A model to represent the signals of a pacemaker has been developed using a relaxation oscillator, the Van der Pol oscillator, given by a second-order differential equation. In this particular study, a more comprehensive investigation is proposed by introducing fractional order differential equations. Varying the order of the system allows for a more refined analysis of the dynamic properties of the Van der Pol oscillator and, by extension, of the cardiac pacemaker modeled by it. This approach is especially relevant considering the complex and non-linear nature of the cardiovascular system. The practical implementation of this model is carried out by means of numerical simulation, using algorithms developed in the Python programming language. This choice of platform allows an efficient and flexible analysis of the resulting signals under different conditions and system parameters. Signal analysis in the time domain is complemented by advanced signal processing techniques in the frequency domain. The Discrete Fourier Transform (DFT), Continuous Wavelet Transform (CWT) are employed to investigate the system's response at different frequencies, providing an in-depth understanding of its stability and dynamic behavior. In addition, the graphical representation of the results using phase spaces provides a visual understanding of the complex interactions between the system components and their dependencies on the model parameters.

Keywords: Cardiac Pacemaker, Action Potential, Fractional Calculus, Frequency Analysis

1 Introduction

Biological systems are complex and depend on coordinated interactions at various scales to achieve proper physiological function. In the heart, complex signaling pathways regulate chemical processes, ion channels mediate flows across membranes and junctions to allow the system to function properly. Although the kinetics of each component can be considered relatively simple, the dynamics of the whole are highly non-linear and difficult to dissect without mathematical modeling and computer simulations [1].

The normal cardiac impulse begins and is conducted by specialized, self-excitable pacemaker cells in the sinoatrial node (SA), a group of cells located in the right atrium, where they spontaneously generate action potentials (AP) that propagate through the conduction system to the ventricles, initiating the contraction necessary for pumping blood. Deficiencies in these intrinsic capacities can lead to disturbances in heart rate and rhythm, accounting for 2 to 17 % of all clinical arrhythmia syndromes [2, 3].

To represent action potentials (AP) by means of a second-order differential equation, thus allowing numerical simulation and analysis from a non-linear dynamic perspective, Krzysztof Grudzinski and Jan J. Zebrowski developed a mathematical model based on the Van der Pol and Van der Mark model, which is a self-excited oscillator with a non-linear damping term [4, 5]. This approach was satisfactory, showing that the relaxation oscillator can be used to model the activity of a cardiac pacemaker, as the model developed recreates experimental results and allows the values of two important physiological variables to be manipulated: the diastolic period and the refractory period.

However, for an advanced approach to modeling complex biological systems, such as the cardiovascular system, this study proposes the use of fractional calculus. This method offers significant advantages when analyzing non-linear systems from a different perspective. The roots of fractional calculus can be found in the correspondence between L'Hopital and Leibniz, where they discussed the meaning of a differentiation of order 0.5. Unlike traditional calculus, which uses derivatives and integrals of integer order, fractional calculus allows the application of non-integer orders. This provides greater flexibility and precision in describing dynamic processes with memory characteristics [6, 7].

In this study, we will be first briefly review the concept of the action potential, as well as the Grudzinski and Zebrowski model and the application of a fractional derivative, focusing on damping and its variation based on the fractional order of the system. The time responses of the action potentials and their phase portraits will be presented, including an analysis in the frequency domain (TFA) based on the fractional order. This will be done using tools such as the Fast Fourier Transform and the Continuous Wavelet Transform (CWT), which offer excellent time-frequency localization [8–10].

2 Action Potential

An action potential (AP) is characterized as a rapid, sudden and transient change in the resting potential of the membrane, which propagates when the membrane is excited beyond a certain threshold, activating ion channels. This phenomenon is crucial for regulating the heartbeat rate, which is governed by the rate of spontaneous action potentials (APs) generated by the sinoatrial node cells (SANC) [11] . The spontaneous generation of APs in SANCs is controlled by a coupled clock system composed of two oscillators: the sarcoplasmic reticulum (SR), acting as a Ca^{2+}, and the surface membrane clock (M clock).

The Ca^{2+} clock works by rhythmically releasing diastolic local Ca^{2+} releases (LCRs) below the cell membrane. The LCRs activate an inward current from the Na^{+}-Ca^{2+} exchanger, which accelerates diastolic depolarization (DD) and activates the M-clock to generate an action potential (AP). As the M clock regulates the influx and efflux of Ca^{2+} from the SANC, it also regulates the Ca^{2+}, forming a coupled clock system [12].

This allows ionic currents to flow into or out of the cell, thus altering its potential and resulting in the generation of an action potential [11]. The action potential has three phases: depolarization, overshoot and repolarization. There are also other states of the membrane potential related to the action potential. The first is hypopolarization, which precedes diastolic depolarization, and the second is hyperpolarization, which follows repolarization[13].

Hypopolarization is the initial increase in membrane potential to the value of the threshold potential. The threshold potential opens the sodium voltage channels, causing an influx of ions. This phase is depolarization and is divided into two phases: early depolarization (early DD) is the beginning of depolarization and late depolarization (late DD) is the end of the process. During this period, represented by the gray triangle, the cell becomes increasingly electropositive, generating a rapid upward movement of the action potential (AP) until it reaches its peak.

After the overshoot, the value of the action potential opens voltage channels, reducing the cell's electropositivity. This is the repolarization phase, the aim of which 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 [11].After depolarization, the cell begins to repolarize, preparing it for the next stimulus. This whole scheme can be seen in Fig.1.

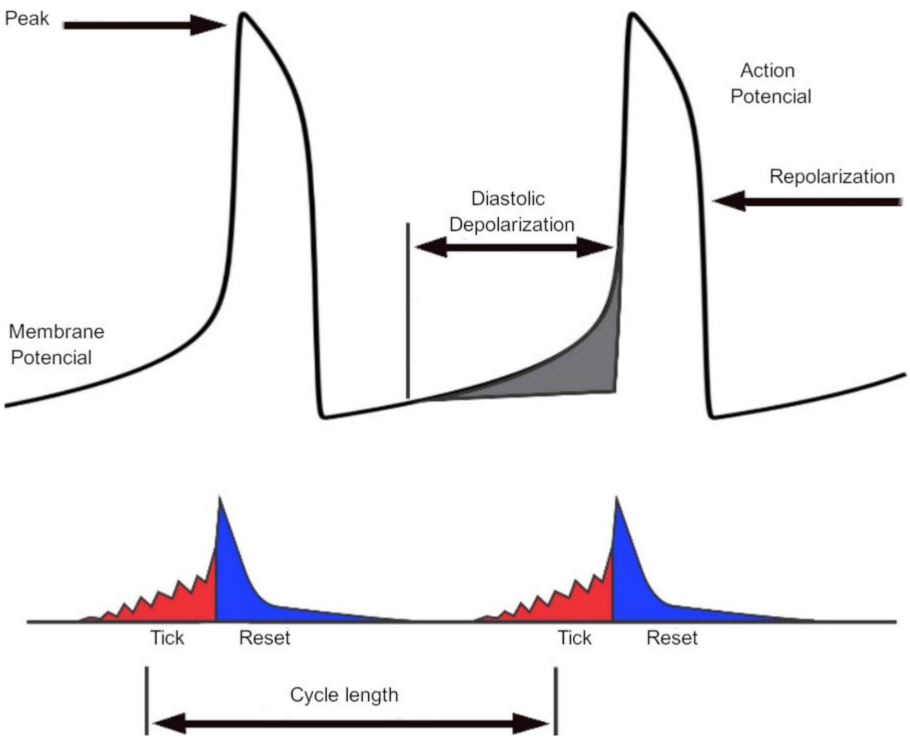


Figure 1. Coupled clock pacemaker system (schematic model adapted from reference [14]).

3 Grudzinski & Zebrowski Model

The Grudzinski Zebrowski model seeks to represent the action potential response of the sinoatrial node, based on a modified Van der Pol oscillator. The Van der Pol model is a model of a self-excited oscillator that exhibits limit cycles. Regardless of the initial conditions, the oscillator converges to a single limit cycle of a given amplitude [4], it was originally used in studies of vacuum tube circuits and can be described by a second-order differential equation represented by eq. (1). This model is characterized by a non-linear damping term that can amplify or attenuate the amplitude of the oscillations [15].

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

To represent the behavior of the sinoatrial node, Grudzinski Zebrowski included a Duffing term, adding more non-linearities to the system represented by the eq. (2).

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

The modifications to this model were aimed at obtaining a phase space that resembles the membrane model of a neuron proposed by Morris-Lecar [4]. In this equation, the μ term controls the amplitude of the signal. This model tends towards negative values, an effect that is caused by the stable and unstable manifolds causing the signals to deform in a different way to a traditional Van der Pol oscillator, so that for sufficiently high values of μ, the oscillation amplitudes are high, being attracted to the saddle point and then taken to a stable node or to the unstable focus.

In addition, Grudzinski Zebrowski introduced a new parameter e, which allows the structure of the phase space to be altered by adjusting the position of the fixed points. Depending on the values of e and d, the system can behave similarly to a Duffing oscillator. This change allows you to control the depolarization period and the frequency of the oscillations.

Finally, they replaced the term $(x^2 - \mu)$ by $(x - v_1)(x - v_2)$, which increased the frequency of action potential pulse generation [11]. It is worth noting that these changes can be made without altering the maximum value of the action potential, by simultaneously adjusting v_1 e v_2. To maintain the self-oscillatory characteristic of the system v_1 e v_2 must have opposite signs, thus preserving the shape of the phase space, i.e. the shape of the action potential.

3.1 Grudzinski & Zebrowski fractional model

The modification proposed in this work involves applying fractional damping to the system shown in eq. (2). The change in the Grudzinski equation consists of relating the damping, traditionally associated with velocity (the integer temporal rate of change of the displacement), to the fractional rate of change of the displacement, according to eq. (3), as presented by [16], where the fractional damping was applied to a Duffing system.

$$\frac{d^2x}{dt^2} + \alpha(x - v_1)(x - v_2)\frac{d^qx}{dt^q} + x(x + d)(x + e)/ed = 0. \tag{3}$$

For the numerical integration of the ODE, it is necessary to reduce the second-order equation into a system of first-order equations. In this case, as the objective is to apply the fractional only to the damping, a third equation $w(t)$, is implemented, which allows the separation without changing the order of the system as a whole and will be written in the form of the state space shown in eq. (4), where the nomenclature used in this article is based on [17]. The notation ${}_aD_t^q$ is used to describe this operation, where t and a are the limits of the operation and q is the fractional order of the system, belonging to the set of real numbers [6], where for the case of $q = 1.0$, the response of the integer order system is returned.

$$\begin{cases} {}_LD_t^1 x(t) = y(t). \\ {}_LD_t^q x(t) = w(t). \\ {}_LD_t^1 y(t) = -\alpha(x(t) - v_1)(x(t) - v_2)w(t) - [x(t)(x(t) + d)(x(t) + e)/ed]. \end{cases} \tag{4}$$

The discretization of this system of equations using the Forward Euler method for first-order approximations is described by equations (5-7). This procedure is similar to the one used by [17], where this method is applied to solve fractional differential equations.

$$x(t_k) = x(t_{k-1}) + y(t_{k-1})h. \tag{5}$$

$$x(t_k) = w(t_{k-1})h^q - \sum_{j=1}^{N-1} c_j^{(q)} x(t_{k-j}). \tag{6}$$

$$y(t_k) = y(t_{k-1}) + (((-x(t_{k-1})(x(t_{k-1}) + d)(x(t_{k-1}) + e))/(ed)) - \alpha(x[j] - v_1)(x(t_{k-1}) - v_2)w[i])h. \tag{7}$$

It is worth noting that, to solve the fractional damping system w, eq. (6) is isolated and x is replaced by the definition given in eq. (5), thus obtaining the solution for iteration of w given by eq. (8)

$$w(t_{k-1}) = \frac{1}{h^q}\left[x(t_{k-1}) + y(t_{k-1})h + \sum_{j=1}^{N-1} c_j^q x(t_{k-j})\right]. \tag{8}$$

4 Numerical solution

For comparison with past studies, we chose to use the parameters: α = 5, d = 3, v_1 = 1, v_2 = -1 and e = 12, which are the parameters used in the previous study presented in [18], so the simulations with $q = 1.0$ should follow the response presented in this study. The following initial conditions were adopted $x(0)$ = 0.1 and $y(0)$ = 0.

The simulations in this article were carried out using the Python programming language, where eqs.(5-8), were numerically simulated using the methodology described in [17]. For this simulation, the equations were integrated over an interval of $0 \geq t \geq 200$ s, After refining the mesh, a time step of dt = 0.001 s was chosen. The influence of the fractional order in the system was analyzed by varying the q parameter, which throughout this work will take on the values of: 0.8, 0.9 and 1.0.

The action potential response of Grudzinski's fractional model is shown in Fig.2, for the different fractional orders and, as mentioned above, for the case q = 1 the responses remained with the same dynamics as the full-order model. Initially, it can be seen that the responses remain in the same order of amplitude when the fractional order q, is reduced, with amplitudes in a range close to -2 to 2. This change is accompanied by a reduction in the interval between cycles, which can be seen by the significant change in the time between the two cycles shown on the time axis, which can be useful for modulating the system's frequency.

One of the problems presented by the introduction of the fractional order was the change in the dynamics of the temporal response, where for the parameters presented, there was a marked reduction in the depolarization interval, causing the dynamics of the system to differ from that of a real action potential, which is characterized by well-defined depolarization and repolarization intervals.

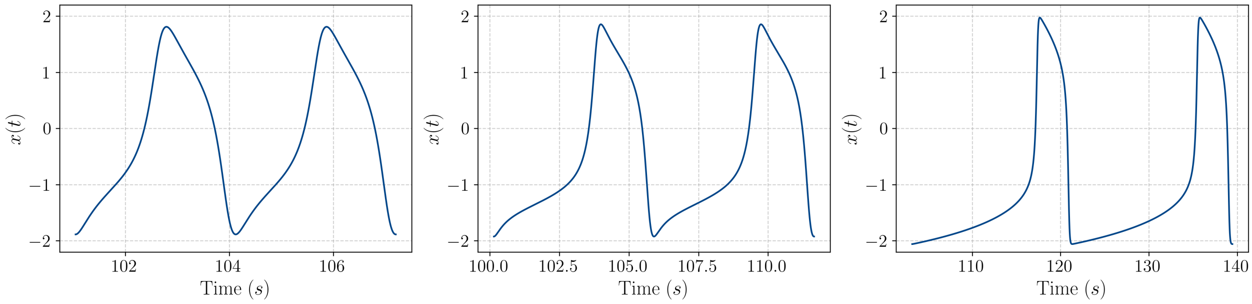


Figure 2. Time response: a) q = 0.8, b) q = 0.9 and c) q = 1.0.

Fig.3, shows the phase space of the system. It shows the change in the dynamics of the rate of change of $x(t)$, which shows a reduction in its amplitude as the fractional order decreases. In addition, there is a rounding-off where previously there was a more rigid dynamic due to the depolarization period.

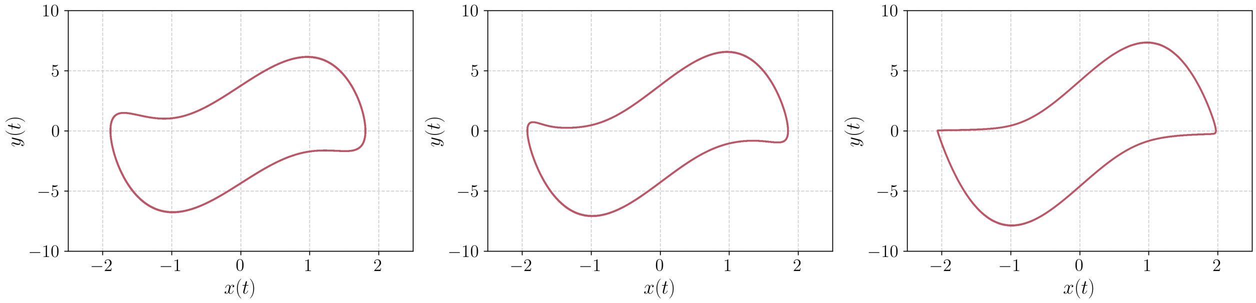


Figure 3. Phase portrait a) q = 0.8 , b) q = 0.9 and c) q = 1.0.

Fig.4, shows the response of x in the frequency domain using discrete Fourier transforms. It shows that as the fractional order decreases, there is an increase in frequency and consequently a reduction in periods. For the cases of q being 0.8, 0.9 e 1.0 the highest peaks in frequency are 0.32, 0.17 e 0.11 Hz respectively. The response, which was initially composed of a double structure of peaks, with harmonics of higher frequency and lower amplitude, stops having this characteristic in its dynamics as q decreases. For the critical case, presented by $q = 0.8$, the suppression of this characteristic becomes more evident, where there is a more dominant amplitude, leading to a drastic change in the system's dynamics, causing the response to become smoother, moving towards more linear oscillations.

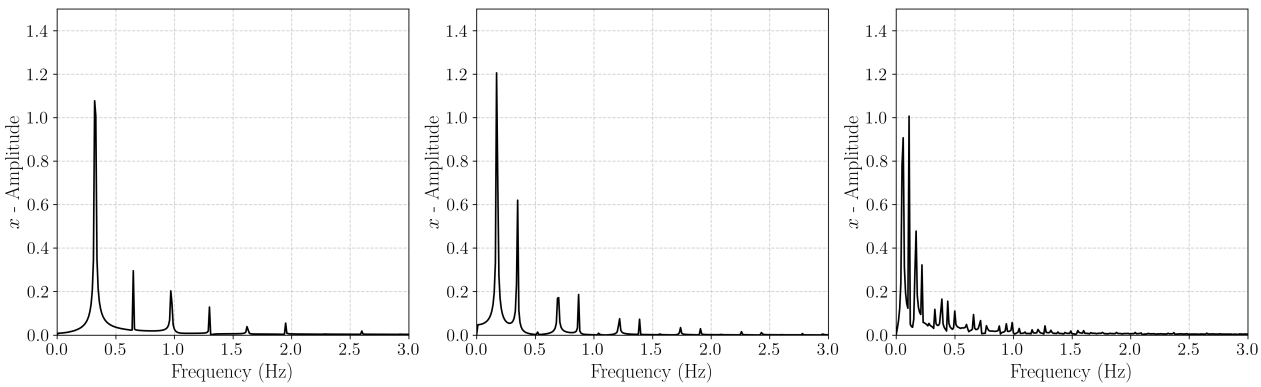
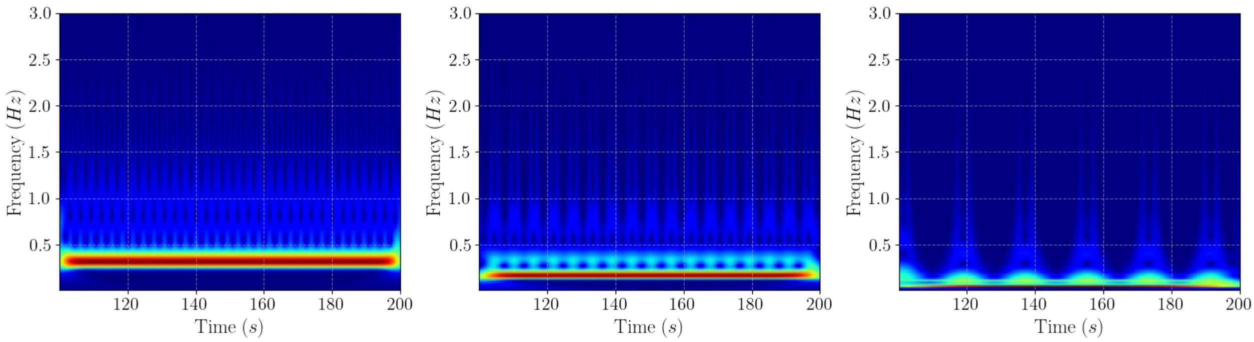


Figure 4. Fast Fourier transform: a) q = 0.8 , b) q = 0.9 and c) q = 1.0.

To better characterize this frequency dynamics, the Continuous Wavelet Transform (CWT) tool is used, which makes it possible to observe the change in frequency over time from the instantaneous frequency. The CWT responses for the three cases presented can be seen in Fig.5. For the $q = 1.0$ case, it can be seen that there is a certain pulsation around a certain interval, where the system shows certain spaced structures, repeating a total of 6 times. For $q = 0.9$ there is more of a fixed frequency and the appearance of different structures that are more widely spaced, a total of 17 times. Finally, in the case of $q = 0.8$ the dominant frequency appears even more clearly, with its harmonics having a higher frequency but an even lower influence, showing dominance around the main frequency.



(a) (b) (c)

Figure 5. Continuous wavelet transform: a) q = 0.8 , b) q = 0.9 and c) q = 1.0

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5 Conclusions

This paper presents an analysis of the implementation of a fractional order derivative in a natural pacemaker model based on Grudzinski's model. Where the influence of this implementation is observed in the time and frequency domain.

The model proposed by Grudzinski resembles the action potential of a natural pacemaker. However, for the purposes of broader studies, it is not suitable, as it is a rigid model in terms of frequency. By adding a fractional damper to the system, it becomes possible to change this frequency, but the dynamics of the system also change. The introduction of a fractional order derivative makes it possible to change the system's frequency, but also alters the signal's dynamics. In this study, the fractional model still presents some difficulties, namely the change in the shape of the action potential as the fractional parameter varies, which means that the system does not maintain the shape of the fixed pulse.

In this study, the implementation of the fractional order showed a change in the depolarization and polarization intervals, where reducing the fractional order showed the loss of these well-defined periods for the parameters presented. A significant change can also be seen in the frequency domain analysis, where reducing the fractional order showed clear changes in the signal structure presented by the discrete Fourier transforms. As this is a non-stationary system, analysis in the time-frequency domain using continuous wavelet transforms also provided a better understanding of the system based on the variation in frequency over time.

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