ARTICLE IN PRESS
JID: CHAOS [m5G;May 4, 2017;7:53]
Chaos, Solitons and Fractals 000 (2017) 1–7
Contents lists available at ScienceDirect
Chaos, Solitons and Fractals
Nonlinear Science, and Nonequilibrium and Complex Phenomena
journal homepage: www.elsevier.com/locate/chaos

Fractional dynamical behavior of electrical activity in a model of pancreatic β-cells

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ARTICLE INFO

Article history:
Received 18 January 2017
Revised 15 April 2017
Accepted 19 April 2017
Available online xxx

Keywords:
Electrical activity
Fractional β-cells system
Time-domain approach
Chaotic dynamics
Diabetes mellitus

ABSTRACT

The electrical activity of a three dimensional fractional-order model of pancreatic β-cells is numerically studied. The dynamics of the model is understood through the Adams–Bashforth–Moulton predictor corrector scheme, which is a time-domain approach. By considering both integer-order and fractional-order models, we highlight some differences in their dynamics characteristics. It is shown that the fractional model can give rise to chaotic dynamics due to the existence of a Smale horseshoe. Some behaviors related with diabetes mellitus are also reported. The fractional model gets closer to the real biological behavior, thus provides motivation in modeling biological systems with fractional order derivatives.

1. Introduction

One of the biological systems which attracts much attention in biology is the endocrine pancreas. It is here that insulin is secreted into bloodstream in response to an elevation in blood glucose, initiating a cascade of events leading to the uptake of glucose by muscle and adipose tissue. In fact, the metabolism of glucose into the β-cells leads to production of ATP, closure of ATP-sensitive potassium channels (K(ATP)-channels) and electrical activity, which activates voltage-gated calcium channels. The resulting influx of Ca^{2+} leads to insulin release through Ca^{2+}-dependent exocytosis [1]. Like nerve and many endocrine cells, pancreatic β-cells are electrically excitable, producing electrical impulses in response to elevations in glucose. The electrical spiking pattern typically comes in the form of bursting, characterized by periodic clusters of impulses followed by silent phases with no activity [2]. Bursting electrical activity (BEA) is important since it leads to oscillations in the intracellular free Ca^{2+} concentration [3,4], which in turn lead to oscillations in insulin secretion [5]. The synchronization phenomenon that occurs in pancreatic β-cells has been recently studied by generating in-phase BEA in β-cells using a discrete time coupling [6].

Diabetes mellitus, commonly known as diabetes, is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes. Diabetes results in abnormally high blood sugar levels known as hyperglycemia. This is caused by an autoimmune attack on β-cells secreted by the pancreas (Type I) or by the inadequate supply or function of β-cells in counteracting the fluctuations of high and low blood glucose within the body (Type II). Diabetes has become an epidemic with considerable complications such as retinopathy, nephropathy, peripheral neuropathy and blindness [7]. Along the same line, attention has been paid with the increased emphasis on derangements of the sensitivity of tissues to insulin in diverse pathological conditions like diabetes, obesity and cardiovascular diseases [8–10]. Careful diabetes mellitus self-management is essential in avoiding chronic complications that compromise health, and is characterized by many and often not readily observable clinical effects [11]. Therefore, there is an urgent need for improved diagnostic methods that provide more precise clinical assessments and sensitive detection of symptoms at earlier stages of the disease. This may be facilitated by improved mathematical models and tools related to interrelationship dynamics among physiological variables.

For realistic modeling, one improves the existing models, by taking into account the effects that were previously neglected or unknown [12] or by considering various stimulation of existing models [13,14]. This is done in keeping with the progress in the development of pertinent mathematical and numerical methods. Along the same line, recent researches motivated the establishment of strategies taking advantage of fractional calculus in the modeling, the study and the control of many phenomena [15–19].

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http://dx.doi.org/10.1016/j.chaos.2017.04.036
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Although it has a long history, the applications of fractional calculus to physics and engineering are just a recent focus of interest [20,21].

While theoretical studies of electrical patterns in excitable cells have been extensively studied [22,23], fractional (non-integer) mathematical models were developed only recently to provide insight in the electrophysiological patterns observed in excitable cells. In that sense, Mvogo *et al.* [24] showed both analytically and numerically that fractional short impulses in the Hindmarsh–Rose neural network can be in perfect agreement with the typical results reported in most electrophysiological recordings. Their work also suggested that fractional order properties in excitable cells may be advantageous for crucial intuitions into spatio-temporal dynamics, chaos and synchronization. Along the same line, it has been shown that fractional-order differentiation is a fundamental and general way that can contribute to efficient information processing, stimulus anticipation and determination of chaos in neuronal firing [25,33]. Although the BEA on the pancreatic β-cells has been studied extensively [26–32], the previous theoretical studies on the β-cells firing rhythms and modes have been done using integer-order models. To the best of our knowledge there is no report on fractional-order models of β-cells. In this paper, a fractional mathematical model of pancreatic β-cells is studied by looking for qualitative and quantitative explanations on the impact of the fractional order parameter. Interestingly, the fractional model can lead to various dynamical behaviors which can be related to some and often readily observable clinical effects. It is shown that the fractional model can be used to explain the dynamics of β-cells more adequately than other types of differentiation can. Furthermore, it is shown that the fractional model can leads to chaotic behavior as also found recently in fractional neural system [33].

The rest of the paper is organized as follows: in Section 2, we first present the standard model of β-cells with integer-order derivative and discuss on the dynamical behaviors. In Section 3, the fractional mathematical model is introduced and the numerical scheme is presented. The numerical results are presented and discussed with emphasis on the biological implications. Section 4 concludes the paper.

2. Integer-order model of β-cells

The modeling of bursting oscillations in β-cells is an interesting topic and several models have been proposed and studied with the purpose of understanding the system better. The first mathematical model for such bursting oscillations has been proposed by Chay and Keizer [26]. Since that, several authors have proposed more revised and refined models with results consistent with physiology [27–32]. The mathematical model implemented throughout this paper has been proposed by Pernarowski [30,31]. The main characteristic of this model is that it presents fast and slow variables which can model different behaviors of β-cells, such as: an active β-cell, which is considered to be a regular cell with active and silent phases of insulin releasing; an inactive cell, which corresponds to cell that no longer produce oscillations; and continuous spiking β-cells, commonly refereed to cells which are isolated from the cluster. As the other models, it is a singularly perturbed system that consists of a two-dimensional fast subsystem (FS) and at least a one-dimensional slow subsystem (SS). The model is described by the following set of equations:

$$\begin{aligned} \frac{dx}{dt} &= f(x) - y - z, \\ \frac{dy}{dt} &= x^3 + f(x) - 3x - y - 3, \\ \frac{dz}{dt} &= \varepsilon(\beta(x - u_\beta) - z), \end{aligned} \tag{1}$$

where x is the membrane potential, y is a channel activation parameter for the voltage-gated potassium channel, and z denotes the concentrations of agents which regulate the BEA, such as intracellular calcium and concentration of calcium in the endoplasmic reticulum and ADP. The function $f(x)$ has the following form:

$$f(x) = \frac{-a}{3}x^3 + a\mu x^2 + (1 - a(\mu^2 - \eta^2))x. \tag{2}$$

In this section, all the results have been obtained by a numerical integration of Eq. (1) through the fourth-order Runge Kutta computational scheme with time-step $\Delta t = 10^{-2}$ and with the following initial conditions:

$$x(t=0) = -1.345, \;\; y(t=0) = 0 \;\text{ and } z(t=0) = 1.4.$$

Moreover, in the whole paper, it is considered the standard parameters values of the Pernarowski model (1) which are recalled hereafter [30]:

$$a = \frac{1}{4}, \;\; \mu = \frac{3}{2}, \;\; \beta = 4, \;\; \varepsilon = 0.0025.$$

Using this specific values, depending on η and u_β, the system exhibits square-wave bursting which is analogous to the BEA in the pancreatic β-cells.

Fig. 1 summarizes the different behaviors which can be obtained in the classical Pernarowski model (1) according to the values of η and u_β. Indeed, by considering two specific values of each parameter η and u_β, namely $\eta = \frac{3}{4}$, $\eta = 1$, $u_\beta = -0.954$ and $u_\beta = -2$, it is plotted the time series of x, y and z:

- for an active cell [Figs. 1(a)–(c)] defined when $u_\beta = -0.954$ and $\eta = \frac{3}{4}$.
- for a continuous spiking β-cell [Figs. 1(d)–(f)] when $u_\beta = -0.954$ and $\eta = 1$
- for an inactive cell [Figs. 1(g)–(l)] obtained when u_β is adjusted to $u_\beta = -2$ and $\eta = \frac{3}{4}$ [(g)-(i)] or $\eta = 1$ [(j)–(l)].

For an active cell, that is for $u_\beta = -0.954$, when $\eta = \frac{3}{4}$, it is seen in Fig. 1.(a) that the membrane potential x is triggered due to the levels of glucose in the blood. Fig. 1.(b) shows the channel activation parameter for the voltage-gated potassium channel y, and Fig. 1(c) shows the concentration of calcium z. Then, when the concentration of calcium z, due to the levels of glucose in the blood increases, the membrane potential and the channel activation parameter for the voltage-gated potassium channel y exhibit an active phase with square-wave bursting. The generation of bursts is characterized by an alternation between a silent phase and a phase of rapid oscillation whose duration seems to have a great importance in the regulation of blood glucose [41,42]. Moreover, when u_β remains unchanged and η is increased up to $\eta = 1$, it is observed a different behavior which corresponds to continuous spiking β-cells. This case, which is reported in Fig. 1(d)–(f), shows that as the parameter η varies, the system always present an electrical activity. The burst gives way to continuous spiking or beating. This spiking activity is represented by fast oscillations in the form of spikes. This is commonly attributed to isolated cells [43] and sometimes to cells belonging to clusters with a reduced number of cells in it [44].

By contrast, in Fig. 1(g)–(l), the parameter u_β has been changed to $u_\beta = -2$, while the two previous values of η have been considered, namely $\eta = \frac{3}{4}$ and $\eta = 1$. In this case the system given by Eq. (1) models the response of an inactive cell [30]. This is appreciated from Fig. 1(g)–(l). These figures show the behavior of the system due to this change of parameter u_β for both values of η. Whatever the value of η, after a transient, the system evolves towards a stable state. This is one of the main problems on nonfunctional β-cells.