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On the dynamical behaviour of a glucose-insulin model

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ABSTRACT

Insulin is a hormone that plays a crucial role in controlling the transport of glucose from the blood to inside the cells. In the pancreas, the insulin is secreted by the β cells, according to the blood glucose concentration, and the interaction of insulin with the glucose is responsible for providing energy to the cells. In this work, we study the dynamical behaviour of a mathematical model, validated by experimental data, that considers the relationship between glucose and insulin concentrations, as well as the role of the β cells. Depending on the control parameters, the model can exhibit periodic and chaotic behaviours. Based on these behaviours, we identify complex structures in the parameter space, namely shrimp-shaped periodic windows immersed in chaotic regions. Furthermore, a parametric perturbation in the parameter related to the rate increase of insulin level secreted by cells can suppress chaos, inducing either periodic or quasi-periodic behaviour. We also investigate the structure of basins of periodic and chaotic attractors in the glucose-insulin system under parametric perturbation; the boundaries between these basins have fractal structures for some control parameters.

1. Introduction

Insulin is a chemical messenger, a well-known hormone, that allows the glucose to enter the cells from the blood stream and be used for energy liberation [1]. In the pancreas, the insulin is secreted by the β cells in response to the blood glucose concentration [2]. Understanding how insulin works with glucose is important for the treatment of diabetes [3,4]. Many scientists carried out research to understand mechanisms involving insulin, glucose, and β cells [5,6].

Over the last 50 years, various studies have considered different mathematical models to investigate the interaction between insulin and glucose [7,8]. In 1972, Grodsky [9] proposed a model to study the phases of insulin release during glucose stimulation patterns. Bajaj et al. [10] developed a nonlinear mathematical model with β cell kinetics and a glucose-insulin feedback system. They analysed the time variations of the insulin and glucose levels. More recently, Shabestari et al. [11] proposed a model for the glucose-insulin system. This model is based on a predator-prey model and considers the interactions between glucose, insulin, and β cells. It exhibits a route to chaos via period-doubling bifurcations.

Chaos, namely sensitivity to initial conditions, has been found in a large number of natural and man-made systems. It is a common dynamical behaviour that appears also in biological systems, such as enzyme reactions [12], biodiversity of plankton [13], the immune system [14], and neuronal networks [15,16]. Experimental data for glucose and insulin values from individual patients, obtained by Kroll [17], showed evidence of a chaotic process. The chaotic behaviour in glucose profiles has also been observed in abnormal conditions, such as disease [18]. Frandes et al. [19] reported that analysis of chaotic features in the glucose dynamics can lead to an understanding of type 1 diabetes mellitus; its understanding can improve control strategies.

In this work, we study the dynamical model proposed by Shabestari et al. [11] for the glucose-insulin regulatory system. We show that the two parameter subspaces exhibit shrimp-shaped

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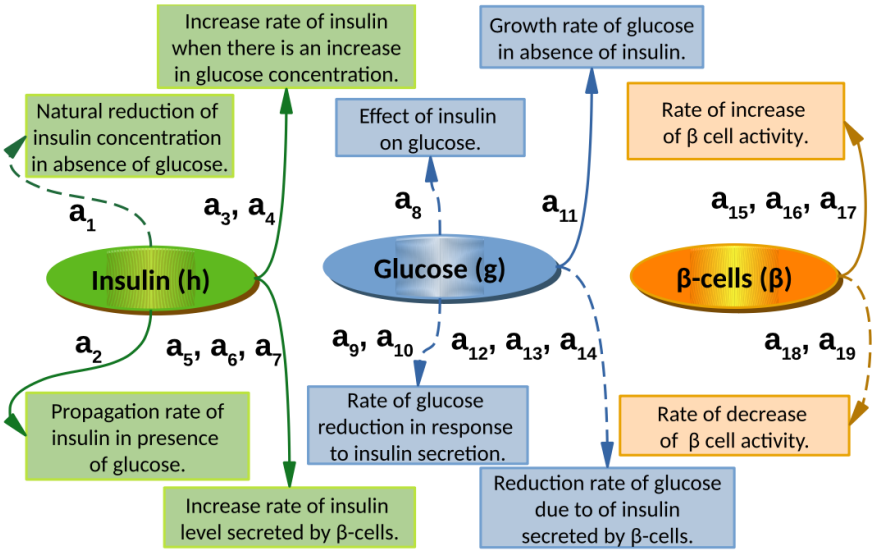

Fig. 1. Schematic representation of the insulin-glucose model, where the solid and dashed lines correspond to the positive and negative terms, respectively, according to Eq. (1).

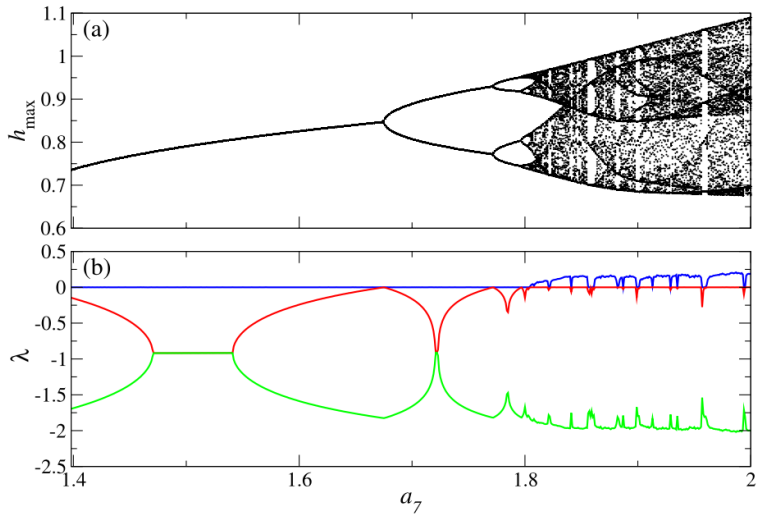

Fig. 2. (a) Bifurcation diagram and (b) Lyapunov exponents for a_7 from 1.4 to 2, where the three colours stand for the three exponents.

structures, which are periodic windows immersed in chaotic regions [20–22]. We analyse the effects of a parametric perturbation in the glucose-insulin model. Parameter perturbation is useful for parameter sensitivity analysis in dynamical systems [23]. In our simulations, we verify that the perturbation is able not only to change the dynamical behaviour, but also to suppress chaos. Depending on the perturbation parameters and which parameter is perturbed, we observe the existence of basin boundaries with fractal structure, whose final state sensitivity is quantified by the uncertainty exponent [24].

This paper is organised as follows. In Section 2, we introduce the glucose-insulin model. In Section 3, we report some results to validate the model, including experimental data analysis for the recognition and acceptance of the model. Section 4 presents our results on the parameter space dynamics and the effects of the parametric perturbation in the system. Concluding remarks are in the final section.

2. The model

We study a glucose-insulin mathematical model proposed by Shabestari et al. [11]. They added a cubic function of variables in a prey-predator model [25] to obtain a nonlinear model that exhibits dependence on the initial conditions. The nonlinear model

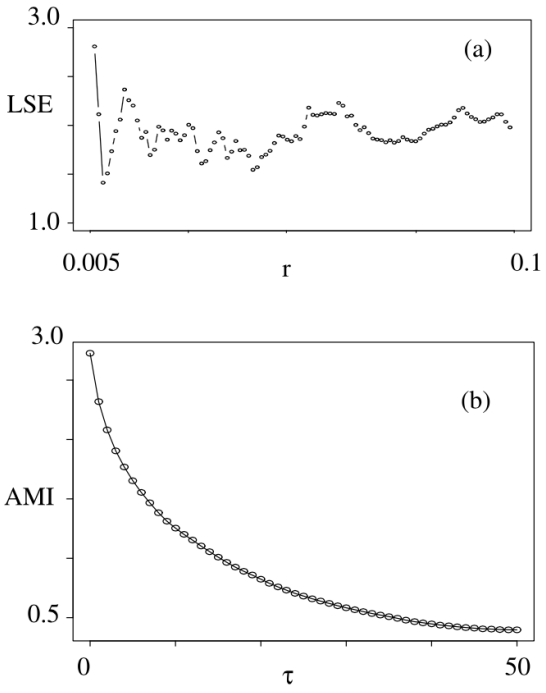

Fig. 3. (a) The local scaling exponents (LSE) as a function of the distance r apart and (b) the average mutual information (AMI) as a function of the time delay for the parameters shown in Table 1.

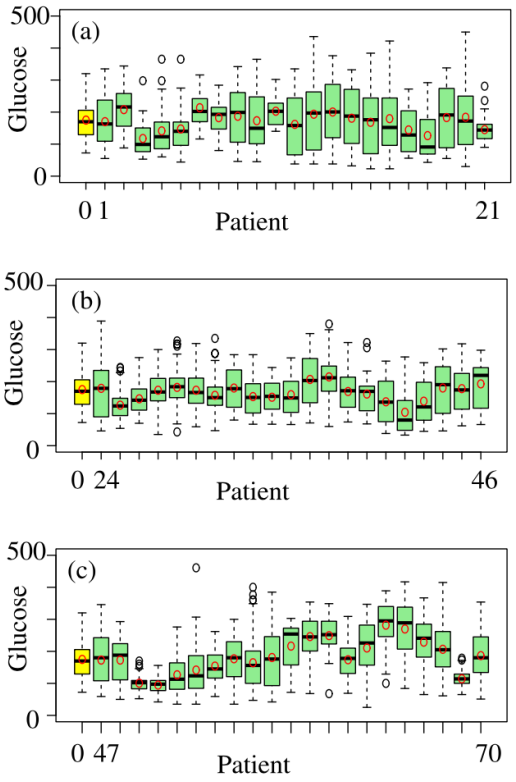

Fig. 4. Boxplot for the glucose-insulin model (yellow box) and experimental data from 70 patients (green boxes) [36]. For the model, we consider the parameters shown in Table 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Description and values of a_n [11].

Description	Parameter	Values
Natural reduction of h concentration in absence of g	a_1	2.04
Propagation rate of h in presence of g	a_2	0.1
Increase rate of h when there is an increase in g	a_3, a_4	1.09, −1.08
Increase rate of h level secreted by β-cells	a_5, a_6, a_7	0.03, −0.06, 2.01
Effect of h on g	a_8	0.22
Reduction rate of g in response to h secretion	a_9, a_{10}	−3.84, −1.2
Growth rate of g in absence of h	a_{11}	0.3
Reduction rate of g due to h secreted by β cells	a_{12}, a_{13}, a_{14}	1.37, −0.3, 0.22
Rate of increase of β cell activity	a_{15}, a_{16}, a_{17}	0.3, −1.35, 0.5
Rate of decrease of β cell activity	a_{18}, a_{19}	−0.42, −0.15
Growth constant rate of h and g	a_{20}, a_{21}	−0.19, −0.56

is a system of three nonlinear differential equations given by

$$\begin{aligned}\frac{dh}{dt} &= -a_1 h + a_2 hg + a_3 g^2 + a_4 g^3 + a_5\beta + a_6\beta^2 \\ &\quad + a_7\beta^3 + a_{20}, \\ \frac{dg}{dt} &= -a_8 hg - a_9 h^2 - a_{10} h^3 + a_{11} g(1-g) \\ &\quad - a_{12}\beta - a_{13}\beta^2 - a_{14}\beta^3 + a_{21}, \\ \frac{d\beta}{dt} &= a_{15} g + a_{16} g^2 + a_{17} g^3 - a_{18}\beta - a_{19} g\beta,\end{aligned} \tag{1}$$

where h, g, and β are the concentration of insulin, glucose, and β cells, respectively. The description of the parameters and values of a_n are given in Table 1 [11]. In Fig. 1, we present a schematic representation of the glucose-insulin model and the parameters a_n $(n = 1,...,21)$, where the solid lines correspond to the positive terms and the dashed lines denote the negative terms, according to Eq. (1).

Fig. 2(a) shows the bifurcation diagram obtained when the maximal dynamic value of insulin ($h_{\max}$) is plotted against a_7, with the latter varying from 1.4 to 2. The parameter a_7 is independent and helps determine the rate at which insulin secretion increases with β cell activity. The diagram exhibits periodic orbits and chaotic attractors, as well as period doubling bifurcation. Shabestari et al. [11] also plotted bifurcation diagrams for a_1, a_7, a_8, and a_{15}. They observed diagrams displaying periodic and chaotic behaviour. The parameters a_1, a_7, a_8, and a_{15} were used to analyse hypoglycemia, hyperinsulinemia, type 2 diabetes, and type 1 diabetes, respectively.

We calculate the Lyapunov exponents by means of Wolf et al. [26]

$$\lambda_i = \lim_{t\to\infty} \frac{1}{t} \log \frac{p_i(t)}{p_i(0)}, \tag{2}$$

where λ_i is the ith Lyapunov exponent and p_i is the length of the ellipsoidal principal axes. The system is chaotic when the value of

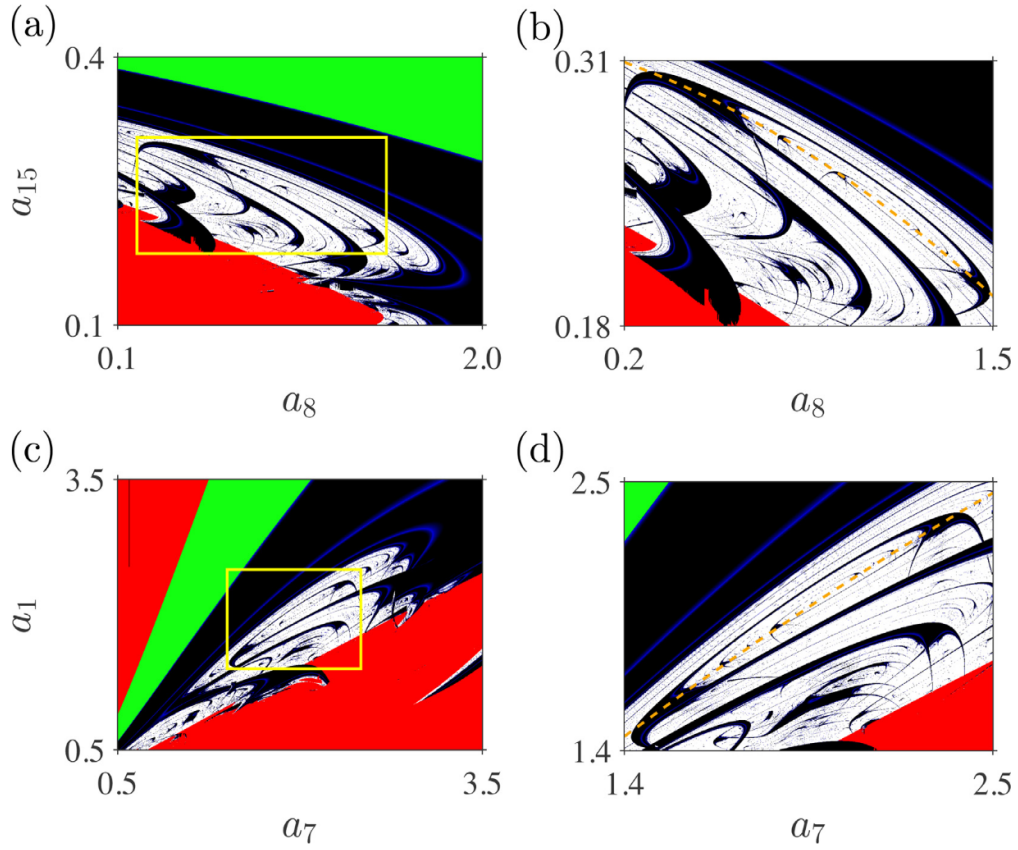

Fig. 5. (a) Parameter space $a_{15} \times a_8$ and (b) magnification (yellow rectangle in the panel (a)) showing periodic attractors (black), chaotic attractors (white), bifurcations (blue), equilibrium points (green), and divergent points (red), where the gold dashed line is given by $a_{15} = 0.32 - 0.04a_8 - 0.03a_8^2$. We consider $a_1 = 2.04$ and $a_7 = 2.01$. (c) Parameter space $a_1 \times a_7$ and (d) magnification (yellow retangle in the panel (c)), where the gold dashed line is given by $a_1 = -0.17 + 1.30a_7 - 0.10a_7^2$. We consider $a_8 = 1.15$ and $a_{15} = 0.24$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the largest Lyapunov exponent λ_1 is positive [27–29]. In Fig. 2(b), the chaotic regions ($\lambda_1 > 0$) end abruptly when periodic windows appear ($\lambda_1 < 0$). For large values of a_7, the system can be chaotic [11]. Large a_7 values are associated with hyperinsulinemia, namely the amount of insulin circulating in the blood is greater than normal. Hyperinsulinemia can lead to the type 2 diabetes [30].

3. Model validation

3.1. Local scaling exponents and average mutual information

Ginoux et al. [18] computed the Lyapunov exponent, the correlation dimension, and the average mutual information (AMI) of glucose for a database of ten type 1 diabetes patients. For each patient, the blood glucose continuous variations were recorded during fourteen consecutive days. They observed positive a maximal Lyapunov exponent. The values of the correlation dimension varied between 1.20 and 2.61, and the AMI did not have a local minimum. To compare the time series generated by the glucose-insulin model with the database of glucose from ten patients, we compute the correlation dimension and the AMI for the parameters shown in Table 1. For these parameters, the maximal Lyapunov exponent is positive. Fig. 3(a) shows the local scaling exponents (LSE) as a function of the distance r apart, where we find the correlation dimension equal to 1.42. The LSE is defined as the local slopes of the correlation sum curves [31].

In Fig. 3(b), we plot the AMI as a function of the time delay. The AMI quantifies the dependence between pairs of variables [32]. We verify that the value of the correlation dimension computed using the time series from the model is in the interval obtained from the database of ten patients. We also observe that the AMI has the same behaviour as the one reported from the database [18]. To compute the LSE and AMI, we use the "nonlinearTseries" [33], which is a R package for nonlinear time series analysis.

3.2. Boxplot of experimental data

The boxplot is a graphical technique that displays the distribution of quantitative data and allows the comparison among variables [34]. It gives information on how the values in a data are spread out and about the skewness [35]. We compute the boxplot for the diabetes data sets provided by Kahn [36]. The data are from diabetes mellitus, in which the patients are insulin deficient. We consider the data recorded for the pre-breakfast blood glucose measurements.

In Fig. 4, the green boxes show the results from the experimental data of 70 patients, while the yellow boxes exhibit the results for the glucose-insulin model. The red circles correspond to the av-

erage glucose, the center black lines denote the median, and the vertical box size is the interquartile range (IQR) given by the difference between the third Q_3 and first Q_1 quartiles. The lower L_l and upper L_u limits (vertical dashed line) are calculated by

$$L_l = Q_1 - 1.5\,\mathrm{IQR} \tag{3}$$

and

$$L_u = Q_3 + 1.5\,\mathrm{IQR}, \tag{4}$$

respectively. We observe that the yellow box not only present the same behaviour as the green boxes, but it is also within the lower and upper limits of the green boxes. Therefore, we verify an agreement between the results from the glucose-insulin model with experimental data.

We consider the parameters shown in Table 1 to generate the model data. For the comparasion between experimental data and model, we multiply the data from the model by 170.8, which is the average glucose of the experimental data.

4. Dynamical behaviour

4.1. Glucose-insulin model

We compute the largest Lyapunov exponent value to characterise the dynamic behaviour of the model in the parameter spaces $a_{15} \times a_8$ (Fig. 5(a) and (b)) and $a_1 \times a_7$ (Fig. 5(c) and (d)). The parameters a_1, a_7, a_8, and a_{15} are related to hypoglycemia, hyperinsulinemia, type 2 diabetes, and type 1 diabetes, respectively [11].

Fig. 5 displays the two dimensional parameter space showing different dynamic behaviours: periodic attractors (black), chaotic attractors (white), bifurcations (blue), equilibrium points (green), and divergent points (red). Inside the periodic regions there are period-doubling bifurcations. We find regions with points that diverge, namely, values of a_1, a_7, a_8, and a_{15} in which the solution goes to an attractor at infinity. In Fig. 5(b) and (d), the magnifications exhibit periodic windows, known as shrimps [37,38], immersed in chaotic regions.

In Fig. 5(b) and (d), the equations of the gold dashed lines are written as $a_{15} = 0.32 - 0.04a_8 - 0.03a_8^2$ and $a_1 = -0.17 + 1.30a_7 - 0.10a_7^2$, respectively. By means of these equations, we compute the parameter space $a_7 \times a_8$, as shown in Fig. 6(a), in which is considered the simultaneous variation of four parameters. The parameter space displays different dynamical behaviours, as well as shrimp structures. We see in the magnification (Fig. 6(b)) that the shrimps have different sizes and intersections among their structures. The red cross corresponds to the point where it is observed the highest Lyapunov exponent value.

In the shrimps, the periodic windows are organised along some distinguished directions and exhibit self-similarity. The shrimp orientation depends on the stability conditions of the model [39]. At the boundaries of a shrimp, small changes in the parameter value are enough to induce relevant alterations in the dynamic behaviour [40]. Due to the existence of shrimps, it is possible to control chaotic behaviour by considering the values of parameters within the periodic windows [41].

4.2. Parametric perturbation

Parametric perturbations can be used to analyse the parametric dependence of biological systems [42–44]. With this in mind, we consider a parametric perturbation according to the alteration, $a_i \to a_i(1 + \eta\cos(\Omega t))$, to study its effect on the dynamic changes in the glucose-insulin model, where η and Ω correspond to the amplitude and frequency, respectively.

Fig. 7 displays the maximum insulin values ($h_{\max}$) by varying η from 0 to 0.2 and applying the parametric perturbation to different

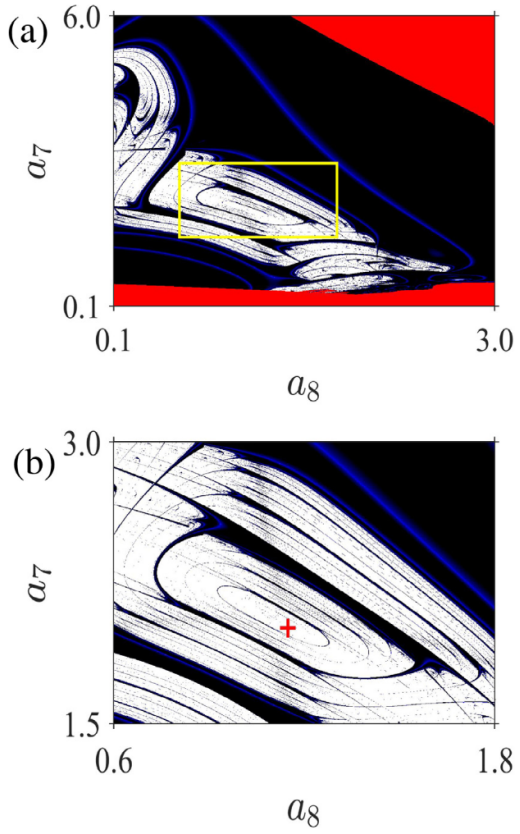

Fig. 6. (a) Parameter space $a_7 \times a_8$ and (b) magnification (yellow rectangle in the panel (a)) showing periodic attractors (black), chaotic attractors (white), bifurcations (blue), and divergent points (red), where the red cross indicates the highest Lyapunov exponent value. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

parameters. We choose the parameters given by the red cross indicated in Fig. 6(b). Considering the perturbation in a_1 (Fig. 7(a)) and a_7 (Fig. 7(b)) for $\Omega = 3$ and $\Omega = 1.6$, respectively, we conclude that the chaotic behaviour can be suppressed for η greater than about 0.1. For the perturbation in the parameter a_8 with $\Omega = 4.1$, the increase of η leads the system dynamics to undergo a change from chaos to period-three, as shown in Fig. 7(c). The chaotic behaviour is suppressed when the parametric perturbation is considered in a_{15} for $\Omega = 1$ and η greater than about 0.05. Therefore, the chaos in the glucose-insulin system can be suppressed by means of parametric perturbations.

We compute examples of basins of attraction for the glucose-insulin model. Fig. 8(a) and (b) display the basins of attractions for initial conditions $g(0) \times h(0)$ without and with a parametric perturbation applied in the parameter a_7, respectively. We consider a parametric perturbation with $\eta = 0.18$ and $\Omega = 1.6$. The black points correspond to the initial conditions of the trajectories that converge toward periodic attractors, while the white region corresponds to the initial conditions whose trajectories asymptote to the chaotic attractors. The red points denote the initial conditions of trajectories that asymptote to an attractor at infinity.

To characterise the basin boundaries, we calculate the uncertainty exponent δ, which is related to the phase space dimension D in the z-dimensional section through the equation $\delta = D - d$, where d is the box-counting dimension of the boundary. To do

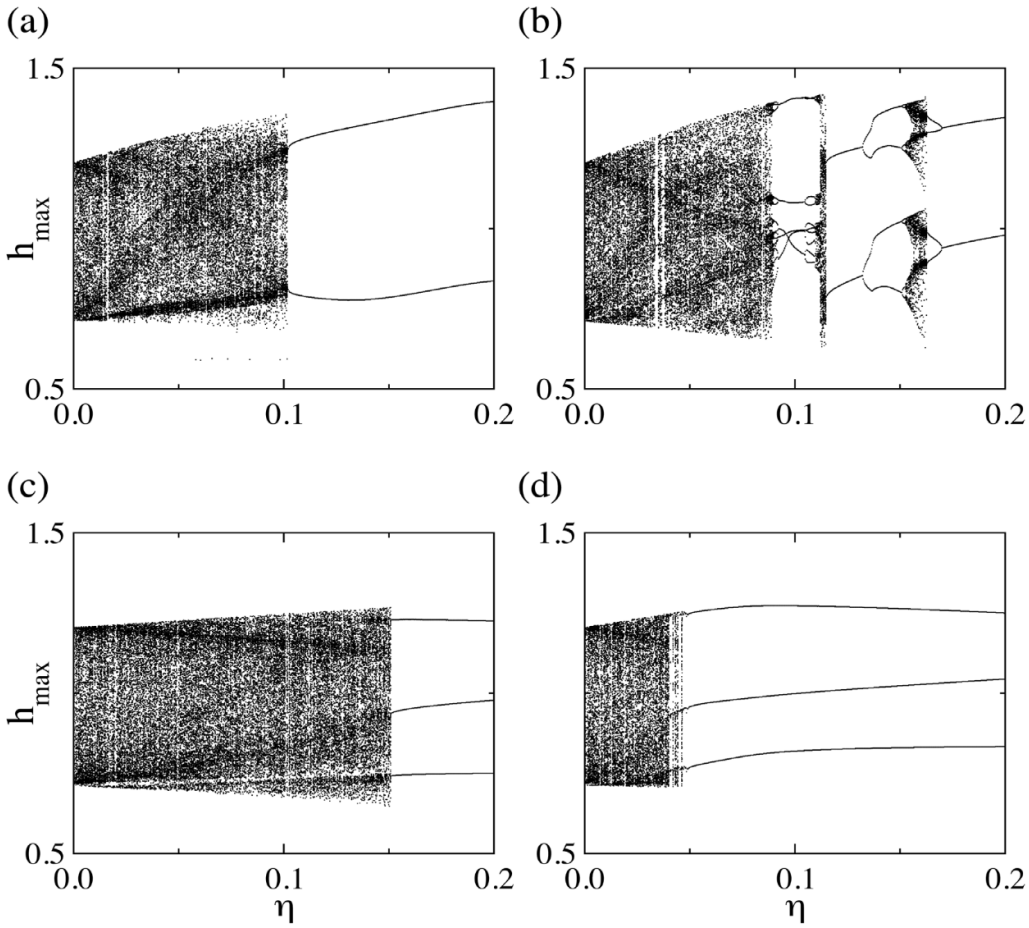

Fig. 7. h_{max} versus η when applying a parametric perturbation in (a) a_1 for $\Omega = 3$, (b) a_7 for $\Omega = 1.6$, (c) a_8 for $\Omega = 4.1$, and (d) a_{15} for $\Omega = 1$. We consider $a_1 = 2.04$, $a_7 = 2.01$, $a_8 = 1.15$, and $a_{15} = 0.24$, according to the red cross indicated in Fig. 6(b).

that, we compute the fraction of trajectories $f(\varepsilon)$ that are generated by uncertain initial conditions, where ε is the radius of a circle of initial conditions. The values of $f(\varepsilon)$ scale as a power law with ε as [24]

$$f(\varepsilon) \sim \varepsilon^{\delta}. \tag{5}$$

Fig. 8(c) shows $f(\varepsilon)$ as a function of ε for the same parameters used in Fig. 8(b) (green square). The red line corresponds to the linear fitting in the log-log plot with $\delta = 0.134$. As a result, we find $d = 2 - \delta = 1.866$, indicating that the basin boundary has a fractal structure.

5. Conclusions

Insulin is a hormone produced by the β cells in the pancreas and controls the glucose levels. Its main function is to allow glucose to enter the cells and to be used for energy. The lack of insulin production or insulin resistance leads to type 1 or type 2 diabetes, respectively. Experimental and analytical methods have been used to investigate how insulin and glucose work together.

In this work, we study a glucose-insulin system proposed by Shabestari et al. [11], in which cubic functions were added to a prey-predator model. Due to these functions, the model is nonlinear and can exhibit chaotic behaviour. The model has parameters related to interactions between insulin, glucose, and β cells. Depending on the parameters, it is possible to study different disorders, for instance, hypoglycemia and hyperinsulinemia. With regard to the parameters, we find domains with islands of periodicity within a chaotic sea, known as shrimp structures. We observe shrimps of different size and intersections among their structures. The parameter changes that, in the model, give transitions between different dynamic structures, may suggest pharmacologic or other strategies for controlling insulin and glucose dynamics.

We consider a periodic parametric perturbation to study the parametric dependence of the glucose-insulin system. We verify that the chaotic behaviour is suppressed for different amplitude and frequency of the perturbation. In our simulations, we uncover basins of attraction whose boundaries have fractal structures in the glucose-insulin system under parametric perturbations.

The fractal structure provides us the knowledge about the lack of predictability related to the dynamical system. Moreover, the fractal basin boundaries are responsible for the emergence of long chaotic transients, as well as the death of chaotic attractors [45]. In future works, we plan to propose a new mathematical model using as a base the observed fractal structures.

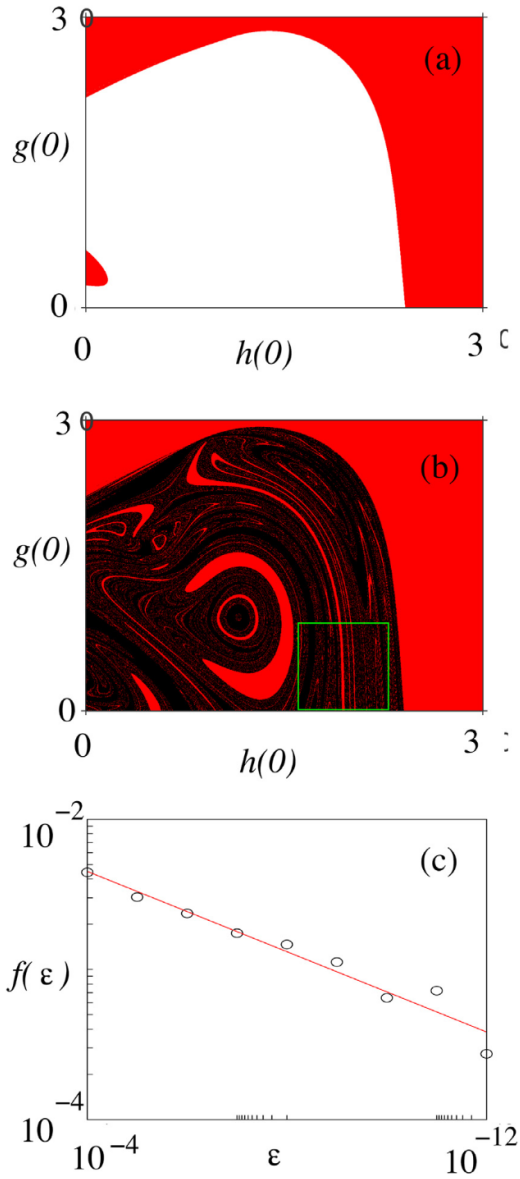

Fig. 8. Basin of attraction $g(0) \times h(0)$ for the chaotic glucose-insulin model, where we consider (a) without parametric perturbation and (b) a perturbation with $\eta = 0.18$ and $\Omega = 1.6$ in the parameter a_7. We use $\beta(0) = 1.03$, $a_1 = 2.04$, $a_7 = 2.01$, $a_8 = 1.15$, and $a_{15} = 0.24$. The trajectories can asymptote to periodic attractors (black), chaotic attractors (white), or an attractor at infinity (red). (c) Fraction of trajectories $f(\varepsilon)$ as a function of the uncertainty ε for the basin of attraction shown in the panel (b) (green square). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Credit author statement

All authors discussed the results and contributed to the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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