Delay-differential equations for glucose-insulin regulation

Maia Angelova, Sergiy Shelyag

Abstract In this work, a model based on a system of delay differential equations, describing a process of glucose-insulin regulation in the human body, is studied numerically. For simplicity, the system is based on a single delay due to the practical importance of one of the two delays appearing in more complex models. The stability of the system is investigated numerically. The regions, where the solutions demonstrate periodicity and asymptotic stability, are explicitly calculated. The sensitivity of the solutions to the parameters of the model, which describes the insulin production in the system, is analysed.

1 Introduction

Delay differential (and, generally, functional differential) equations (DDEs) and their systems appear in natural and artificial phenomena, when the behaviour of a system explicitly depends both on its current state and its history in some functional form. Among such systems are communication networks, systems of biological and physiological regulations, population growth, infection spread, epidemics and pandemics, devices with actuators and delayed feedback, business cycle models in economics, decision making [1]. Unlike ordinary differential equations and their systems, which are finite-dimensional in phase space, DDEs are infinitely-dimensional. Inclusion of a delay in a dynamical system can lead to rather complicated dynamics, (sometimes unwanted) oscillations and even chaos. Analysis of DDEs is generally more involved, in part due to the structure of the corresponding characteristic equations, and often not allowing for an analytical treatment. Numerical solution of such equations is also not trivial due to propagating discontinuities and strict require-

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ments for interpolation techniques. Nevertheless, in the recent years advances in understanding of DDEs, and analytical and computational approaches to their solution have been achieved.

It is well-known that the chemo-biological process of conversion of insulin into glucose necessarily involves a delay, which also depends on a number of physiological parameters. Only a limited number of these directly involved in glucose-insulin regulation system can be observed directly, and mathematical modelling would help estimate these parameters [2]. Furthermore, the interactions between the sub-systems of the glucose-insulin regulation may be affected by a variety of disorders and diseases, such as diabetes of multiple types [3]. Therefore, further detailed study of the system of the glucose-insulin regulation and its mathematical counterparts is warranted for better understanding of the human physiology.

In this paper, we numerically analyse the behaviour of a system of delay-differential equations, which aims to simulate the interactions in a model of glucose-insulin regulation in the human body. We study only one of the interactive terms of the system in detail (namely, the term, which describes the glucose-sensitive insulin production) and demonstrate the presence of periodic and asymptotically-stable solutions.

2 The Model

The system of delay-differential equations, which describes the glucose-insulin system regulation in human body, was introduced by [4, 5]. Its mathematical properties have been extensively studied for one- or two-delay modifications [3, 4, 6, 7, 8, 9]. We are using one-delay system given below:

$$\begin{aligned} I'(t) &= f_1(G(t)) - \frac{1}{\tau_0} I(t) \\ G'(t) &= G_{in} - f_2(G(t)) - qG(t) f_4(I(t)) + f_5(I(t-\tau)), \end{aligned} \tag{1}$$

Here, I and G are the insulin and glucose blood concentrations, respectively. The first term f_1 in the insulin equation is the insulin secretion caused by glucose intake (the effect of this term on the solution of the system will be studied in a greater detail as an example), the second term is the insulin degradation with the time scale τ_0. In the glucose equation, G_{in} is the constant glucose intake, f_2 is the constant glucose utilisation by the organism, the third term is the glucose utilisation dependent on the insulin concentration, and the fifth term f_5 is the glucose production from insulin, which includes a positive delay τ. The flowchart of the model is given in Fig. 1

The system does not allow for exact analytical solutions, therefore we produce numerical solutions for System (2). Also, we perform solution scans over the parameter ranges to determine whether the System 2 exhibits periodic or asymptotically stable behaviour.

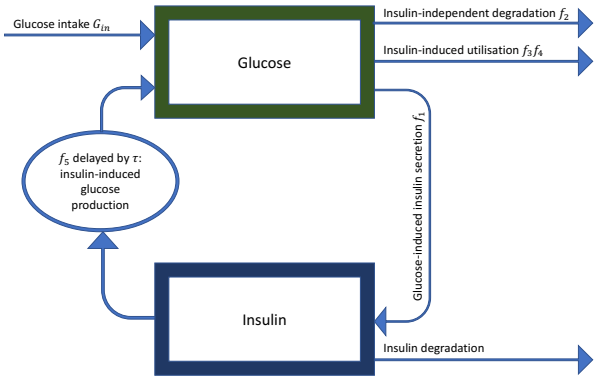

Fig. 1 The flow chart of the model. There are two processes related to production of insulin dependent on glucose concentration and production of glucose dependent on the insulin concentration. These processes create a loop between glucose and insulin compartments in the flow chart. All other processes remove glucose or insulin from the system, or add external glucose through the glucose intake term.

3 Periodic and asymptotically stable behaviour in glucose-insulin regulation system

The IVP system (2) is solved using a 4-th order Runge-Kutta method with an adaptive time step and 4-th order barycentric Lagrange interpolation of the delay term [10]. The numerical solution is therefore 4-th order precise on time. The functions f_1-f_5 are chosen as continuously differentiable, non-negative and Lipschitz-bounded on $\mathbb{R}$, and f_5 also satisfies the negative feedback condition. The functions are chosen as follows (see figure 2): $f_1(u) = a_0 + aH(u)$, $f_2(u) = bH(u)$, $f_3(u) = -qH(u)$, $f_4(u) = d + eH(u)$, and $f_5(u) = h(1 - H(u))$, where

$$H(u) = \frac{u^{N_\mathrm{H}}}{u^{N_\mathrm{H}} + 1} \tag{2}$$

is Hill function. The initial conditions are $I(0) = G(0) = 0$. Also, we set $I(t < \tau) = 0$. The latter choice, as numerical experiments demonstrate, does not change the character of the solution.

Figs. 3 and 4 show examples of the obtained periodic and asymptotically stable solutions, respectively. The parameters chosen to produce the numerical solutions are as follows: $N_\mathrm{H} = 2$, $G_{in} = 1$, $\tau_0 = 1$, $\tau = 5$, $q = 1$, $a_0 = 1$, $b = 1$, $d = 10$, $e = 10$, $h = 100$. Setting the parameter $a = 1$ led to an asymptotically stable solution, while with $a = 10$ the system demonstrated periodic behaviour. Automated differentiation between the periodic and stable solution types represents some difficulty due to

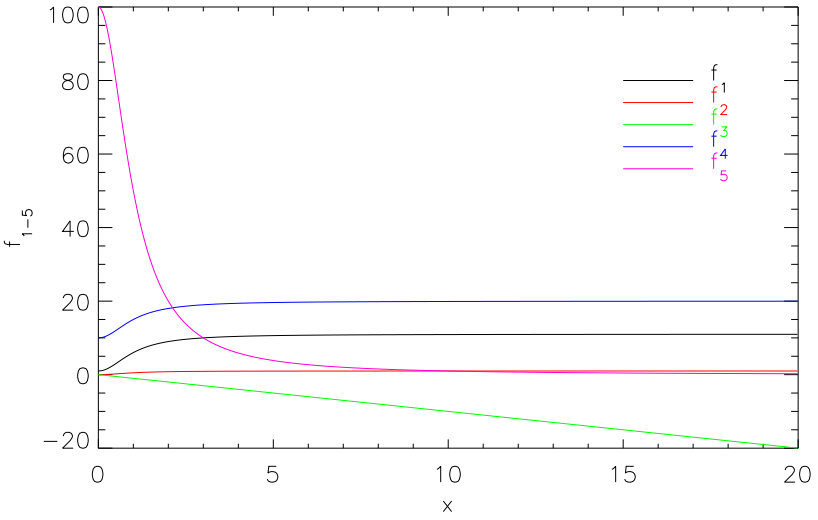

Fig. 2 Functions f_1 - f_5 as used in the numerical solution of System (2).

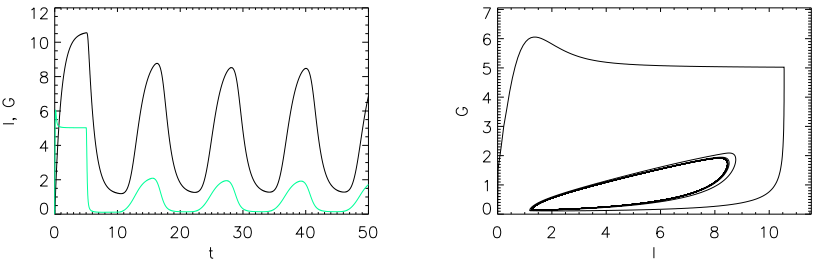

Fig. 3 An example of periodic solution for the system (2). The time evolution of I (black) and G (green) is shown in the left panel. The right panel shows the corresponding phase portrait for the system, plotted for a larger time interval $0 < t < 200$.

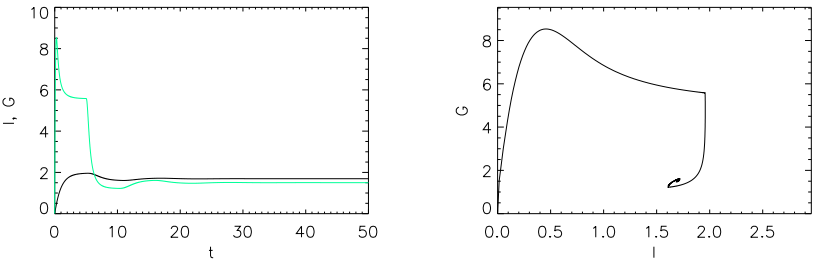

Fig. 4 Same as in Fig. 3, but for an asymptotically stable solution for the System (2).

the *a priori* unknown solution period and the time scale of amplitude decrease of the solution oscillations. This is done as follows. First, all the local extrema of the solution are located. If the number of local extrema is less than 4 (corresponding to two periods, if solution is periodic), then the solution is assumed to be stable. Otherwise, solution values are found at the positions of the solution extrema. Then, the even and odd pairs of these values are compared, and, if the difference between them is greater than some value, the solution is assumed to be stable. All other solutions are assumed periodic.

This is further demonstrated in Fig. 5, which shows solution types for System (2) on a range of scanned parameters. The scan was performed over a number of values for the Hill parameter N_{H}, a range of the delays $\tau = 0.1 - 10$ and the parameter $a = 0 - 10$. All other parameters are as used above for solution of the system (2). We also note that the system exhibits asymptotic stability over the whole range of the used parameters for the smaller values of $N_{\mathrm{H}} = 0.5,\ 1$. Only a part of the scanned parameter space is shown in the figure. The figure clearly demonstrated that the stronger the non-linearity of the Hill functions in $f_1 - f_5$ is, the wider the range of delays τ and parameter a leads to oscillatory behaviour of the solution.

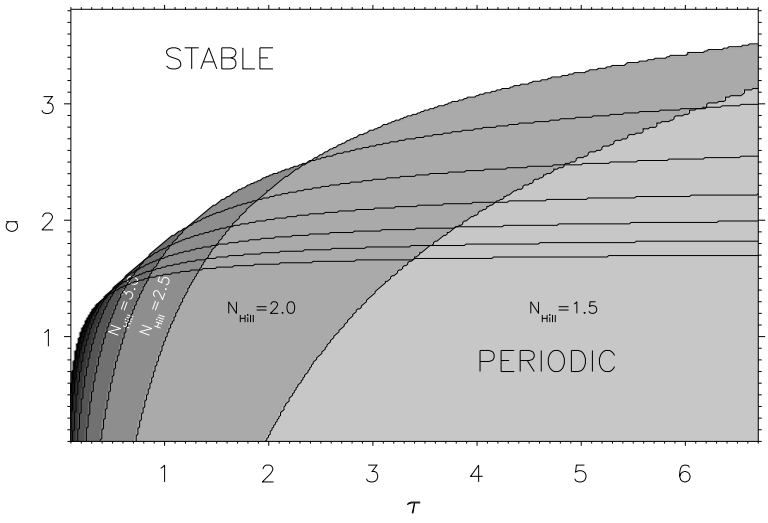

Fig. 5 Solution types obtained from numerical solution of the system (2) over a range of τ and a parameters for different values of Hill parameters N_{H}.

A scan over a range of values of the glucose intake G_{in} has also been performed for the different non-linearity indexes of the Hill function. Two-dimensional scan of the solution types, which also includes the parameter a, is shown in Fig. 3. The figure shows that, again, the stronger non-linearity (steepness) in the Hill functions provokes oscillatory behaviour in System (2) solutions. However, with the increase

of the amplitude of the non-linear part in $f_1 = a_0 + aH(u)$, the region, where periodic solution occur, shrinks.

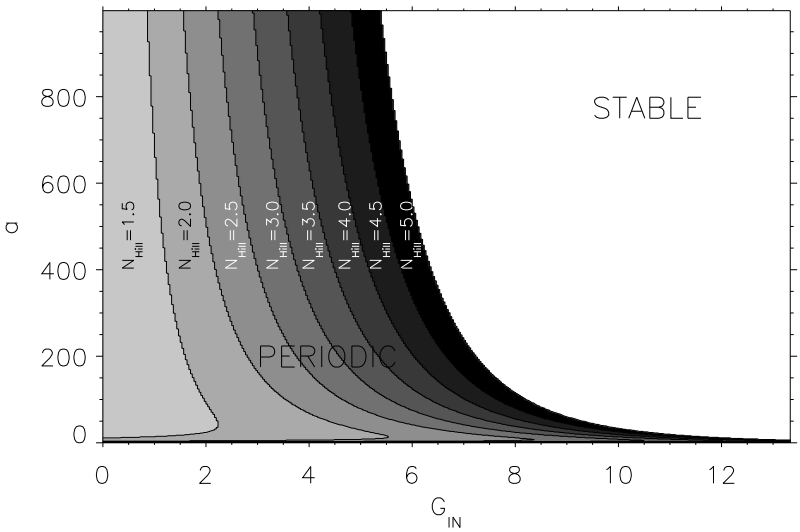

Fig. 6 Solution scan of System (2) on the glucose intake G_{in} and parameter a for a range of the non-linearity indices N_H.

Another scan has been performed on the parameter a_0 and G_{in} (shown in Fig. 3). Again, the oscillatory region widens in G_{in} and shrinks in a_0 if the non-linearity in the Hill functions increases.

4 Conclusions

In this work we studied the stability of the DDE system, which describes a model of glucose-insulin regulation system. We analysed the dependence of the solution types (periodic or asymptotically stable) on the parameters of the glucose-dependent insulin production. We have shown that the stronger the nonlinearity in the Hill functions, which describe the components of the glucose-insulin regulation system, the wider the parameter range (which includes the delay parameter) for which the oscillatory behaviour is observed.

Further study is required for precisely diagnosing the behaviour of the system and connecting it to the physiologically measurable parameters. Also, mathematically, the system of glucose-insulin regulation exhibits both periodic and asymptotically stable solutions. However, normally, only periodic behaviour of the insulin and glucose concentrations is observed in the test environments. It would be interesting to

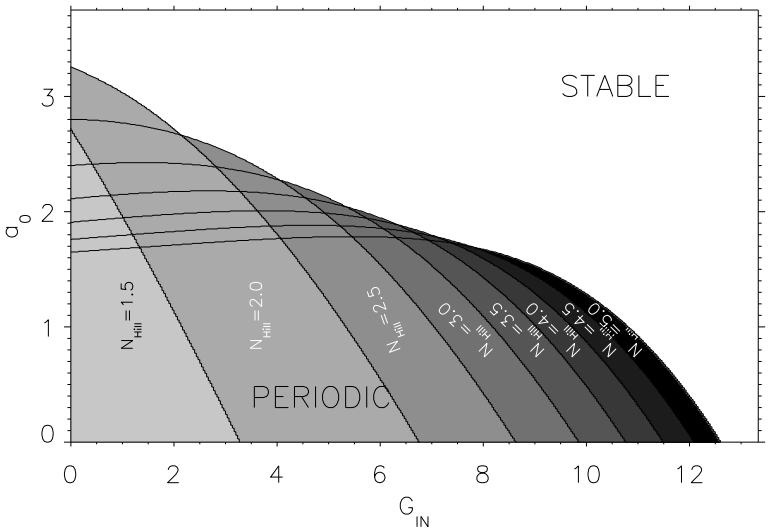

Fig. 7 Solution scan of System (2) on the glucose intake G_{in} and parameter a_0 for a range of the non-linearity indices N_H.

get a better insight into the existence of physiological equivalents of the asymptotically stable solutions of the System (2).

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