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Ultradian rhythms in glucose regulation: a mathematical assessment

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Abstract. Glucose regulation is an essential function of the human body which enables energy to be effectively utilized by the brain, organs and muscles. This regulation operates in a cyclic manner, in different periodic regimes. Indeed, ultradian rhythms with a period of 70 to 150 minutes have been clinically observed in healthy patients under various glucose stimulation patterns. Various models of these oscillations in plasma glucose and insulin have shown that the presence of two delays in hepatic glycogenesis and pancreatic insulin secretion provide a pathway for explaining these oscillations. The efficacy of this control is typically reduced in the presence of diabetes. In this contribution, we adopt the presence and the accurate tuning of ultradian rhythms as a criterion for healthy glucose regulation. We then investigate a model with two delays of these ultradian rhythms which incorporates parameters accounting for insulin sensitivity and insulin secretion. Additionally, the effect of diabetic deficiencies on this feedback loop is explored by quantifying the joint contribution of delays and diabetic parameters on the limit cycle of this model, which is generated through a Hopf bifurcation. Strategies for restoring an oscillatory regime in a physiologically appropriate range are discussed. Finally, a simple polynomial model of the oscillations is introduced to give further insight into the influence of each physiological subsystem. The approach provides a quantified relationship between diabetic impairments and the plasma glucose-insulin feedback loop.

INTRODUCTION

In individuals without diabetes, ultradian oscillations in plasma glucose and insulin levels have been clinically observed and described [1]. These have also been detected in patients with diabetes, although they appear to be less controlled, damped and slower [2, 3]. A number of mathematical models, most often in the form of differential equations, have been devised to explain these oscillations in patients without diabetes [4, 5, 6] (see [7] for a review). One of the most important contributions of these studies is the discovery that the generation and sustainability of these oscillations can be explained by the presence of delays in pancreatic insulin secretion and hepatic glucose production [4]. The tuning of the resulting feedback loop therefore strongly depends on the delays which are inherent to production and transport mechanisms entering the regulation of glucose. Deficiencies in basic insulin functions typically break this loop, and may lead to diabetes.

While it can argued that there are five types of diabetes [8], it is broadly accepted that there are two principal ones: Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). T1DM refers to a condition whereby an individual has a much reduced or null ability to secrete insulin. T2DM corresponds to an impaired ability of an individual to utilise insulin to degrade glucose molecules to produce energy and reduce their level in plasma.

It can be seen that Type 1 and Type 2 diabetes have distinct effects on the feedback mechanism. While both types lead to increased blood glucose levels, insulin resistance seen in early stages of T2DM results in higher plasma insulin levels as well as a gradual loss of amplitude in the oscillations [2]. Various strategies for reinstating an oscillatory regime within appropriate healthy physiological ranges for both glucose and insulin are explored by recalibrating parameters. The effects of current therapeutical approaches, such as the use of biguanide medications, are discussed

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along with more recently proposed treatments altering insulin clearance. In particular, the usage of the model has permitted the recovery of healthy regulation through the original objectives of producing a sustained oscillatory regime while stabilising the average glucose levels within a physiologically acceptable range.

To study in more details the influence of each physiological function, we also study a minimal model of the oscillations. This provides a novel technique for estimating the efficacy of glucose regulation in pre- and diabetic individuals.

THE TWO-DELAY MODEL

In this section, we provide the general form of the nonlinear two-delay model under study. It is an adaptation of the one devised and studied in [6, 9, 10] and follows the framework presented in Figure 1. Correspondingly, the system is

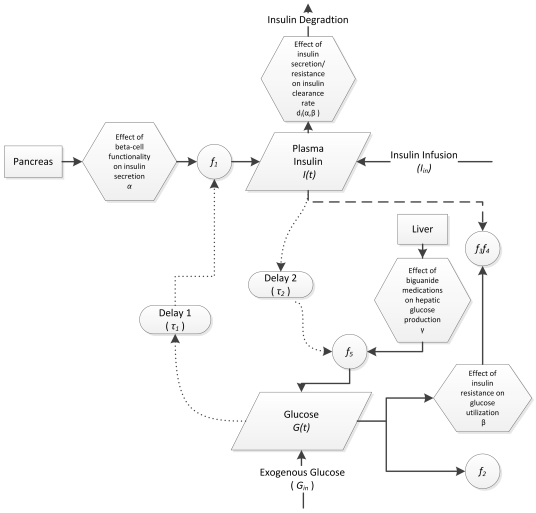

FIGURE 1. Modelling framework of glucose-insulin negative feedback loop at the organ level.

modelled using a set of two delay-differential equations

$$\dot{G} = G_{in} - f_2(G) - \beta f_3(G) f_4(I) + \gamma f_5(I(t-\tau_2)), \quad \dot{I} = \alpha f_1(G(t-\tau_1)) - d_i I, \tag{1}$$

where the phase variables $G(t), I(t)$ correspond to plasma glucose (in mg/dl) and insulin (in mU/l) levels, respectively. All parameters are assumed to be strictly positive. The function f_3 is linear while f_1, f_2, f_4, f_5 are selected as Hill functions of the form

$$f_1(x) = p_1 \frac{x^{h_1}}{x^{h_1} + k_1^{h_1}}, \quad f_2(x) = p_2 \frac{x^{h_2}}{x^{h_2} + k_2^{h_2}}, \quad f_3(x) = p_3 x, \quad f_4(x) = p_{40} + p_4 \frac{x^{h_4}}{x^{h_4} + k_4^{h_4}} \quad f_5(x) = \frac{p_5}{x^{h_5} + k_5^{h_5}}.$$

Thus, as in previous studies [11, 12, 10, 13, 14] the functions f_1, f_2, f_4 are monotonically increasing while f_5 is monotonically decreasing, in line with clinical observations (see [4] and references therein). Under these conditions, it is easily shown that system (1) always possesses a strictly positive steady state $(\bar{G}, \bar{I})$ (see e.g. [9]), satisfying the equations

$$G_{in} - f_2(\bar{G}) - \beta f_3(\bar{G}) f_4(\bar{I}) + \gamma f_5(\bar{I}) = 0, \quad \alpha f_1(\bar{G}) - d_i \bar{I} = 0, \tag{2}$$

which is here assumed to coincide with the basal levels. Parameters for a healthy individual are chosen as in [10], following the fitting of the functions to previously published clinical data using the logit transform, and are shown in Table 1. Using these values, the system is solved numerically using the Bogacki-Shampine algorithm and seen to reproduce oscillations in a physiologically acceptable range (Figure 2). The linearisation of system (1) about the positive steady state $(\bar{G}, \bar{I})$ can be written in matrix form as

$$\begin{pmatrix} \dot{G} \\ \dot{I} \end{pmatrix} = \begin{pmatrix} -A & -B \\ 0 & -d_i \end{pmatrix} \begin{pmatrix} G \\ I \end{pmatrix} + \begin{pmatrix} 0 & 0 \\ D & 0 \end{pmatrix} \begin{pmatrix} G(t-\tau_1) \\ I(t-\tau_1) \end{pmatrix} + \begin{pmatrix} 0 & -C \\ 0 & 0 \end{pmatrix} \begin{pmatrix} G(t-\tau_2) \\ I(t-\tau_2) \end{pmatrix} \tag{3}$$

TABLE 1. Parameter values used for a non-diabetic individual [10, 14].

Parameter	Value	Parameter	Value	Parameter	Value
p_1	210	h_1	2	k_1	58300
p_2	72	h_2	1.8	k_2	1035
p_3	10^{-4}				
p_{4_0}	40				
p_4	900	h_4	1.5	k_4	567.74
p_5	180	h_5	−8.5	k_5	80.16

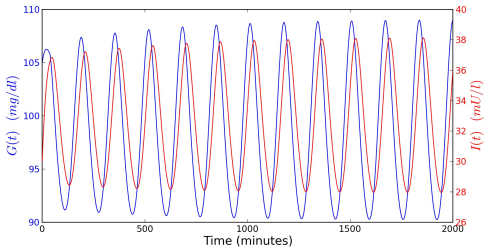

FIGURE 2. Simulation of system (1) using parameter values from Table 1 and the constant initial condition $G(t) = 105, I(t) = 30$ for $t < 0$.

where we introduced the positive quantities

$$A = f_2'(\bar{G}) + \beta f_3'(\bar{G}) f_3(\bar{I}),\ B = \beta f_3(\bar{G}) f_4'(\bar{I}),\ C = -\gamma f_5'(\bar{I}),\ D = \alpha f_1'(\bar{G}). \tag{4}$$

Looking for exponential solutions $(G, I) = (G_0, I_0)e^{\lambda t}$, $\lambda \in \mathbb{C}$, of (3) leads to the following characteristic equation,

$$\lambda^2 + (A + d_i)\lambda + Ad_i + BDe^{-\lambda\tau_1} + CDe^{-\lambda(\tau_1+\tau_2)} = 0. \tag{5}$$

Equation (5) possesses an infinite number of roots, and it is a classical result that they are all contained in a half-plane $\mathrm{Re}\lambda < r$, for some $r \in \mathbb{R}$. Oscillations in the linearised system are the result of a supercritical Hopf bifurcation occurring when a pair of eigenvalues cross the imaginary axis. Hence, we look for roots $\lambda = i\omega$, $\omega > 0$ of (5) which leads to the system

$$-\omega^2 + Ad_i + BD\cos(\omega\tau_1) + CD\cos(\omega(\tau_1 + \tau_2)) = 0, \quad (A + d_i)\omega - BD\sin(\omega\tau_1) - CD\sin(\omega(\tau_1 + \tau_2)) = 0. \tag{6}$$

Expanding the trigonometric functions in (6) and using the fundamental trigonometric identity $\cos^2 x + \sin^2 x = 1$, we obtain that periodic solutions of (3) with frequency ω occurs for delays τ_1 and τ_2 if the following relations

$$(\omega^2 + A^2)(\omega^2 + d_i^2) + D^2(B^2 - C^2) + 2BD\left((Ad_i - \omega^2)\cos(\tau_1\omega) - \omega(A + d_i)\sin(\tau_1\omega)\right) = 0, \tag{7}$$

$$\cos(\tau_2\omega) = \frac{(\omega^2 + A^2)(\omega^2 + d_i^2) - D^2(B^2 + C^2)}{2BCD^2}, \tag{8}$$

are satisfied. Equations (7),(8) define a curve of Hopf bifurcations in the space of delays (τ_1, τ_2). Indeed, for any $\tau_1 > 0$, equation (7) can be solved to obtain $\omega > 0$. In turn, (8) provides a periodic set of values of τ_2, from which we select the smallest positive one. This gives the graph shown in Figure 3. The curve separates the (τ_1, τ_2) into two regions: non-oscillatory (below) and oscillatory (above).

THE EFFECT OF DIABETIC DEFICIENCIES

We now turn to the question of describing the effect of gradually decreasing normal insulin-related functions. As can be seen in Figure 4, T1DM and T2DM diabetes have very distinct effects on the basal levels. On the one hand, values of $\alpha < 1$ lead to a deficiency in the insulin levels which in turn incurs high glucose. On the other hand, values of $\beta < 1$

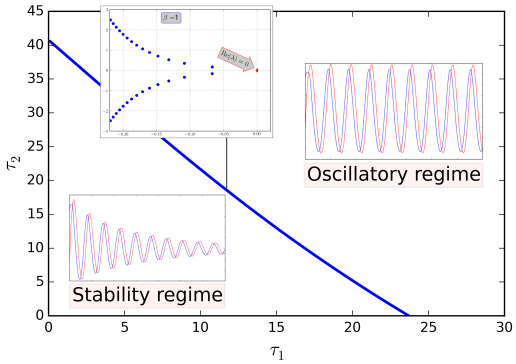

FIGURE 3. Threshold curve (in blue) of supercritical Hopf bifurcations in the space of delays. On the curve, a pair of eigenvalues has null real part.

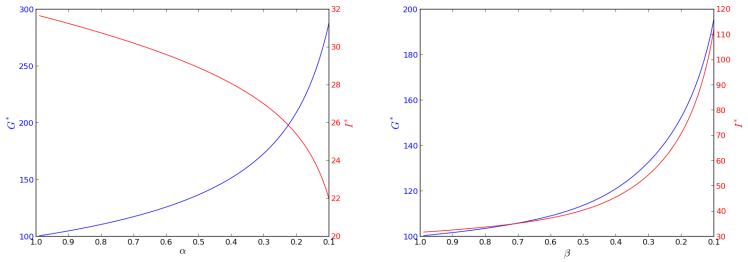

FIGURE 4. Effect of decreasing insulin production capacity (left) and insulin sensitivity (right) on the steady state values.

reduce the ability of the body to take-up glucose, especially in the skeletal muscles, which leads to additional insulin secretion and results in elevated glucose and insulin levels. This is seen in the early phases of Type 2 diabetes, where the phenomenon of insulin resistance gains in importance. With regard to the oscillations, repeating the analysis of equations (7) and (8) for various values of β leads to a sequence of threshold curves in the (τ_1, τ_2) plane. The result is shown in Figure 5 and can be interpreted as follows. Consider an individual with fixed secretion times τ_1 and τ_2. Upon the alteration of insulin sensitivity (value of β), the point (τ_1, τ_2) may fall below or above the new threshold curve. Since decreasing insulin sensitivity (i.e. taking $\beta < 1$) "raises" the threshold curve in the (τ_1, τ_2) plane, we can see that insulin resistance implies a gradual loss of oscillations.

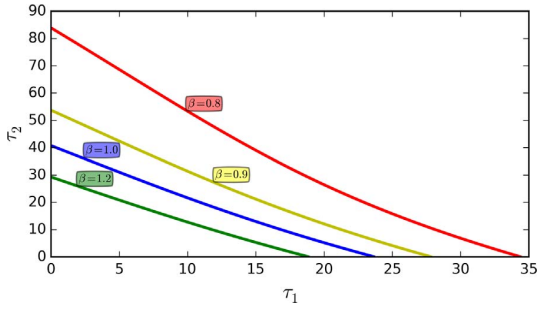

FIGURE 5. Effect of altering insulin sensitivity on the production of an oscillatory regime.

Restoring healthy regulation

Several treatment strategies can be assessed through a recalibration of parameters. These focus on two essential objectives, namely bringing glucose levels within a healthy range and ensuring that they oscillate with an ultradian rhythm. For a given diabetic state, namely for fixed (α,β), we can look at the recalibration of several parameters to achieve this goal. As was shown in [14] and recalled below, recalibrating γ and d_i individually allows us to achieve both goals for a range of diabetic states. We then evaluate the possibility of combining both strategies.

Altering hepatic production

Amongst the most used therapeutical approaches for treating Type 2 diabetes, biguanide medications such as Metformin help in inhibiting the production of glucose by the liver, thus providing an effective mechanism for helping reduce overall glucose levels. Let us consider a situation in which a given level of insulin resistance is present, $\beta < 1$, and investigate under which circumstances the reduction of hepatic glucose allows the value of $\bar{G}$ to be kept constant. Assuming b_2, I_{in} and delays are fixed, equation (2) can be rearranged to obtain the value of γ which enables $\bar{G}$ to be fixed,

$$\gamma = \frac{G_{in} - f_2(\bar{G}) - \beta f_3(\bar{G}) f_4\left(\frac{\alpha f_1(\bar{G})}{d_i}\right)}{f_5\left(\frac{\alpha f_1(\bar{G})}{d_i}\right)}. \tag{9}$$

One can assess whether the resulting pattern is oscillatory by verifying if the point (τ_1, τ_2) falls above the threshold curve. This thus divides the (α,β) domain into three regions, depending on the outcome of this strategy: Oscillatory, non-oscillatory and not-applicable (Figure 6).

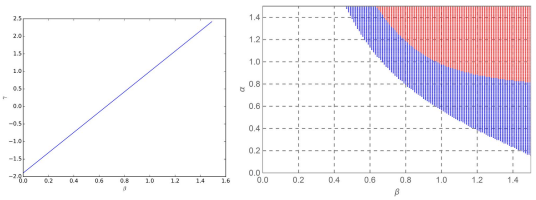

FIGURE 6. Value of γ that stabilises $\bar{G} = 97.87 mg/dl$ (left, for $\alpha = 1$). On the right, the red region in the (α,β) domain corresponds to values for which the resulting solution is oscillatory. The blue area is non-oscillatory, while this strategy cannot be applied in the white zone as it leads to a negative value of γ.

Altering insulin clearance to restore oscillations

A second potential strategy for reinstating an accurate regulation is the retuning of insulin clearance. This possible novel treatment has been recently suggested and clinically evidenced following the discovery of new insulin degradation modulators [15]. Here, we use d_i as a bifurcation parameter, that is for various diabetic states (α,β), we look for values of insulin degradation such that the resulting solution is oscillatory. Furthermore, we verify that the resulting set of values lead to acceptable fasting glucose values, i.e. $70 \leq \bar{G} \leq 110$ for $G_{in} = 0$ (Figure 7). It is clearly seen that for values of $\beta < 0.9$, this strategy cannot be used to recover oscillations.

Combining strategies

Here, we aim to combine both techniques to assess whether a larger range of diabetic states can be successfully recalibrated. We proceed as follows. For fixed values of α,β and delays, we look at whether any value in the ranges $d_i \in [0.01, 0.3]$ and $\gamma \in (0, 1]$ leads to an oscillatory solution with acceptable fasting glucose values. As seen in Figure 8, this combination does extend the range of (α,β) values which can be successfully recalibrated. In particular, even in cases where insulin secretion is relatively low, the retuning of insulin degradation and hepatic production allows to restore an oscillatory regime.

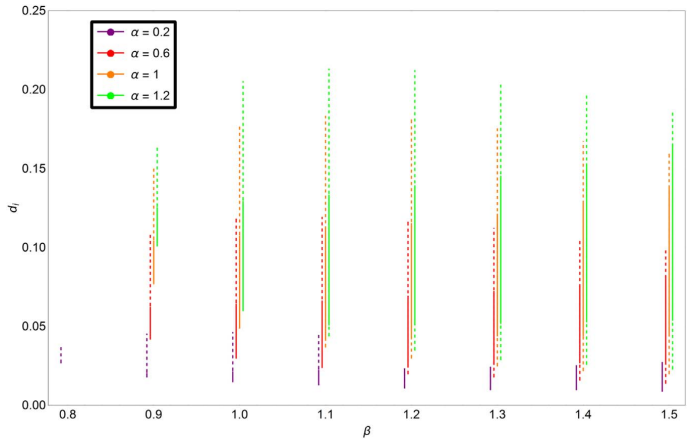

FIGURE 7. Values of d_i leading to oscillatory regulation.

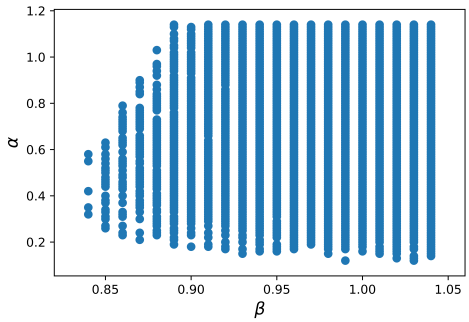

FIGURE 8. Values of α and β for which oscillations can be restored with a healthy fasting basal level using a combined strategy.

A SIMPLE POLYNOMIAL MODEL

In this section, we describe the behaviour of a minimal model which provides a simpler basis for studying the oscillations. This model is given as a 2-variable system with one delay

$$\dot{G} = A - a_1 G - a_2 G I, \quad \dot{I} = b_1 G(t-\tau)^2 - b_2 I. \tag{10}$$

Here again, all parameters are assumed to be strictly positive. This model has also been studied in [16], as a limiting case of a novel model with a distributed delay. The constant A contains both the glucose infusion and the hepatic glucose production, which is here assumed to be constant. The steady state of (10) satisfies the equations

$$a_2 b_1 \bar{G}^3 + a_1 b_2 \bar{G} - b_2 A = 0, \quad \bar{I} = \frac{b_1}{b_2}\bar{G}^2, \tag{11}$$

which always possess a strictly positive solution by Descartes' rule of signs. The characteristic equation of the linearisation of (10) can be written as

$$\lambda^2 + (a_1 + a_2\bar{I} + b_2)\lambda + b_2(a_1 + a_2\bar{I}) + 2a_2 b_1 \bar{G}^2 e^{-\lambda\tau} = 0. \tag{12}$$

Proceeding as previously, looking for purely imaginary roots $\lambda = i\omega$, $\omega > 0$ leads to the system

$$-\omega^2 + 2a_2 b_1 \bar{G}^2 \cos(\omega\tau) + b_2(a_1 + a_2\bar{I}) = 0, \quad (a_1 + a_2\bar{I} + b_2)\omega - 2a_2 b_1 \bar{G}^2 \sin(\omega\tau) = 0, \tag{13}$$

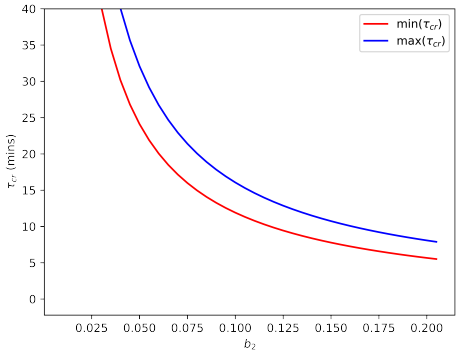

FIGURE 9. Range of values of τ_{cr} which can be attained by varying a_1 and a_2 for each given value of b_2. Here, we used the fixed values $\bar{G} = 97.87\ mg/dl$ and $\bar{I} = 30\ mU/l$. Any value of τ above the range leads to an oscillatory solution.

or equivalently,

$$\cos(\omega\tau) = \frac{\omega^2 - b_2(a_1 + a_2\bar{I})}{2a_2b_1\bar{G}^2}, \quad \sin(\omega\tau) = \frac{(a_1 + a_2\bar{I} + b_2)\omega}{2a_2b_1\bar{G}^2}. \tag{14}$$

Equations (14) imply that ω must be a root of the following quartic polynomial

$$\omega^4 + \omega^2\left((a_1 + a_2\bar{I})^2 + b_2^2\right) + b_2^2\left(a_1 - a_2\bar{I}\right)\left(a_1 + 3a_2\bar{I}\right) = 0, \tag{15}$$

which has roots

$$\omega = \pm\sqrt{\frac{-\left((a_1 + a_2\bar{I})^2 + b_2^2\right) \pm \sqrt{\left((a_1 + a_2\bar{I})^2 + b_2^2\right)^2 - 4b_2^2\left(a_1 - a_2\bar{I}\right)\left(a_1 + 3a_2\bar{I}\right)}}{2}}. \tag{16}$$

In order for equation (15) to possess one positive root, one needs to have

$$a_1 < a_2\bar{I}.$$

This gives a criterion for an oscillatory solution to exist. The positive root ω is associated with a critical delay value τ_{cr} for which an oscillatory solution occurs. This value is obtained from (14) as

$$\tau_{cr} = \frac{1}{\omega}\left(\arccos\left(\frac{\omega^2 - b_2(a_1 + a_2\bar{I})}{2a_2b_1\bar{G}^2}\right) + 2k\pi\right), \tag{17}$$

where $k \in \mathbb{Z}$ is the smallest integer such that (17) defines a positive value. Larger values of k gives successive values of τ_{cr} for which stability switches may occur in the linear system. However, for the nonlinear system (10), it is numerically observed that oscillations are present whenever $\tau \geq \tau_{cr}$.

The process of choosing parameters in the minimal model (10) can be addressed by requiring that it produces oscillations around a fixed basal state $(\bar{G}, \bar{I})$. The insulin degradation term b_2 has been numerically estimated in the narrow range $[0.05, 0.3] min^{-1}$ [17], with a value of $b_2 = 0.06$ being regarded as typical. Fixing $(\bar{G}, \bar{I})$ and, for instance b_2, equations (11) imply that A and b_1 are given by

$$A = \frac{1}{b_2}\left(a_2b_1\bar{G}^3 + a_1b_2\bar{G}\right), \quad b_1 = b_2\frac{\bar{I}}{\bar{G}^2}. \tag{18}$$

The parameters a_1 and a_2 can be chosen such that oscillations are present for a physiologically relevant value of the critical delay τ_{cr}. For different values of b_2, one can numerically compute the range of achievable values for τ_{cr} using equation (17). This gives the graph shown in Figure 9. As observed in [16], the model leads to slightly higher values of τ_{cr} than in the two-delay model (1), although it is comparable with the value one obtains when formally setting $\tau_2 = 0$ in (1) (see Figure 3). This highlights the importance of both delays in generating a negative feedback loop. Nevertheless, this approach provides a model able to replicate the nonlinear oscillations within an appropriate physiological range (Figure 10).

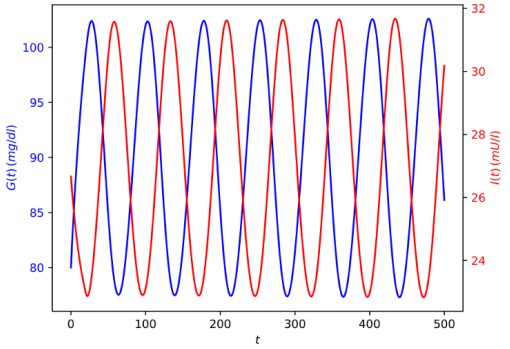

FIGURE 10. Oscillations described by the minimal model (10).

CONCLUSIONS

The regulation of glucose is an essential feature of the human body and ultradian oscillations have been observed under a variety of conditions. The role of observed oscillations in glucose levels is subject to debate. However, similarly to the feedback mechanisms present in the HPA axis [18], it could be argued that oscillatory glucose levels ensures that the strain on pancreatic cells is not continuous.

Stochastic effects may also play an important role in this mechanism. Of particular relevance, the uncertainty and fluctuations on parameter values can have an effect on the obtained solution. For instance, insulin sensitivity (β) is known to be influenced by a large number of factors such as fatigue and stress, as well as a circadian rhythm. Incorporating these effects into the insulin sensitivity term, for instance using a sinusoidal circadian rhythm and a 5% normally distributed random noise leads to a fluctuating pattern (Figure 11). Further quantification of these phenomena is needed to provide additional insight into the insulin resistance dynamics.

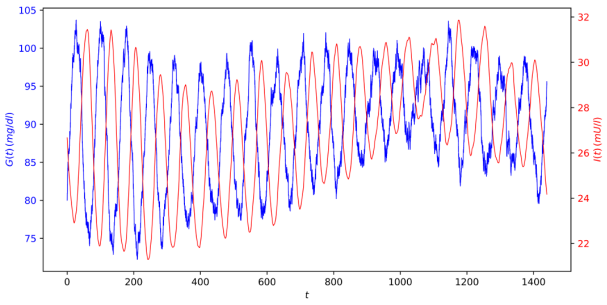

FIGURE 11. Stochastic simulation of the minimal model when β is assumed to include a sinusoidal circadian variation and 5% random fluctuations.

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