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Global stability in a model of the glucose-insulin interaction with time delay

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A variety of models on the interaction between glucose and insulin have been suggested over the last 50 years. One, developed by Sturis *et al.* [19], and consisting of six nonlinear ordinary differential equations, has been widely accepted. However, the model has the disadvantage of containing auxiliary variables which have no clinical interpretation. In this paper we study an alternative model which incorporates a time delay explicitly, negating the need for the auxiliary equations. A simplifying assumption of having just one insulin compartment reduces the number of equations still further. We then study the resulting system of two differential delay equations, establishing results on positivity, boundedness, persistence and global asymptotic stability. For the latter, two quite different approaches are employed: comparison principles and Lyapunov functionals. The two approaches provide different sets of sufficient conditions for global stability, so that we investigate different regions of parameter space.

1 Introduction

Over the last 50 years the interaction between glucose and insulin, its regulatory hormone, has been studied by both theoretical and mathematical biologists [1, 5, 8]. Through biological experiments it has been well-established [6, 9, 17, 18] that insulin secretion in the pancreas oscillates on a number of different time scales, ranging from tens of seconds to more than 100 minutes. The oscillations with larger period (80–150 mins) are known as ultradian oscillations and a model developed by Sturis *et al.* [19] (see also Keener & Sneyd [7]) provides a possible mechanism for their origin. This model consists of six nonlinear ordinary differential equations and is detailed in Appendix I (system (4.1)).

Whilst Sturis' model (recently modified by Tolic *et al.* [20] to contain a more sophisticated receptor down-regulation model and receptor modification model) is consistent with observable features of ultradian insulin oscillations, it has the disadvantage of artificially introducing auxiliary variables which have no clinical interpretation. In this article we introduce time delay into the model explicitly, thereby negating the need for the three auxiliary linear chain equations and their associated artificial parameters. In addition, we make the further simplifying assumption that plasma and intercellular insulin are indistinguishable. The original model is thus reduced from six ODEs without delay, to two equations with delay. Li *et al.* [10] proposed a delay model which has certain similarities to the model we propose in this paper, but their model has the delay in the insulin equation.

The model of the present paper was also considered by Engelborghs *et al.* [3]. In fact, they modified it to represent an external system interacting with an internal system in the case of a diabetic patient. They studied the linearised stability of the equilibria and carried out some numerical bifurcation analysis. They extensively investigated several branches of periodic solutions and their stability.

In the present paper, we study the simplified system analytically to determine some of its fundamental properties and, especially, to obtain theorems on the *global* stability of the equilibria. Also, we have aimed to keep the functions f_i (in system (2.1) below) as general as possible, rather than restricting to the particular f_i mentioned in Appendix A. We make only general qualitative assumptions on the f_i; those that are dictated by the need for biological realism. The paper is organised as follows: in § 2 we present our model and some of its basic properties, § 3 addresses global stability, Appendix A summarises the model of Sturis *et al.* [19] and Appendix B lists the properties of the functions f_i used in our model.

2 The model equations and preliminary results

We first modify Sturis' model by explicitly incorporating a discrete delay term into the glucose equation. In this way the three auxiliary variables of Sturis's model representing the delay between plasma insulin and its effect on hepatic glucose production can be dispensed with. To reduce the number of equations still further, we assume there is only one insulin compartment rather than two (i.e. no distinction between plasma insulin and intracellular insulin). Therefore, t_p and t_i in system (4.1) are taken to be equal and we introduce $I = I_p + I_i$. These modifications yield the following model to be solved for $t > 0$:

$$\begin{gathered} dI/dt = f_1(G) - \frac{1}{\tau_0} I, \\ dG/dt = G_{in} - f_2(G) - qGf_4(I) + f_5(I(t-\tau)), \\ I(s) = I_0(s) \geqslant 0, \qquad s \in [-\tau, 0] \qquad \text{with } I_0(0) > 0, \\ G(0) = G_0 > 0, \end{gathered} \tag{2.1}$$

where the functions f_1, f_2, f_4 and f_5 satisfy the assumptions in Appendix B, and $q > 0$ is a constant. Note that there is no function labelled f_3. In fact, $f_3(G)$ is the linear term qG in the second equation. Since Sturis *et al.* [19] took their function $f_3(G)$ to be linear (see the third equation of system (4.1) in Appendix A, and the expression (4.5) for their $f_3(G)$), it seemed more convenient for us to take $f_3(G)$ as qG at the outset, while keeping the other f_i general. We decided to retain the original subscripts on the functions f_4 and f_5 to allow direct comparison with the original paper.

In (2.1), I and G represent the quantities of insulin (mU) and glucose (mg), respectively. Pancreatic insulin production controlled by glucose concentration is represented by the function $f_1(G)$. I/τ_0 is the degradation rate of insulin by the body and $G_{\text{in}} > 0$ represents the input of glucose from outside the system. Glucose uptake by the brain and nerve cells is described by the function $f_2(G)$. Glucose utilization by muscle and fat cells which is dependent on both glucose and insulin concentration is represented by the third term in the second equation of (2.1). The last term in the second equation of (2.1) represents hepatic glucose production which is influenced by insulin.

2.1 Positivity and boundedness

Proposition 2.1 *Let the f_i satisfy the assumptions listed in Appendix B. Then all solutions of the model* (2.1) *exist for all $t > 0$ and are strictly positive.*

Proof Let $(G(t), I(t))$ be a solution of (2.1). If $G(t_0) = 0$ for some $t_0 > 0$, and if t_0 is the first such time, then $\dot{G}(t_0) \leqslant 0$. However, at t_0, the glucose equation becomes

$$\dot{G}(t_0) = \underbrace{G_{in}}_{>0} - \underbrace{f_2(G(t_0))}_{=0} - \underbrace{qG(t_0)}_{=0} f_4(I(t_0)) + \underbrace{f_5(I(t_0 - \tau))}_{>0} > 0.$$

This is a contradiction. Therefore, $G(t) > 0$ for all $t > 0$. By similar reasoning, $I(t) > 0$ for all t. □

Proposition 2.2 *Let the f_i satisfy the assumptions listed in Appendix B. Then all solutions of the model* (2.1) *are bounded.*

Proof First we establish the boundedness of $I(t)$. Solving the first equation of (2.1) for $I(t)$ we have

$$I(t) = e^{\frac{-t}{\tau_0}} I(0) + e^{\frac{-t}{\tau_0}} \int_0^t e^{\frac{s}{\tau_0}} \underbrace{f_1(G(s))}_{\leqslant f_1(\infty)} \, ds \leqslant e^{\frac{-t}{\tau_0}} I(0) + f_1(\infty)\tau_0 \left(1 - e^{\frac{-t}{\tau_0}}\right)$$

and thus $I(t)$ is bounded for all t.

From the second equation of (2.1) we have

$$\begin{aligned}\dot{G}(t) &= G_{in} - f_2(G) - qGf_4(I) + f_5(I(t-\tau)) \leqslant G_{in} - qG \underbrace{f_4(I)}_{\geqslant f_4(0)} + f_5(I(t-\tau)) \\ &\leqslant G_{in} - qGf_4(0) + \underbrace{f_5(I(t-\tau))}_{\leqslant f_5(0)} \leqslant G_{in} - qGf_4(0) + f_5(0).\end{aligned}$$

Therefore,

$$\limsup_{t\to\infty} G(t) \leqslant \frac{G_{in} + f_5(0)}{qf_4(0)}$$

and also

$$G(t) \leqslant M_G := \max\left\{G(0), \frac{1}{qf_4(0)}(G_{in} + f_5(0))\right\}$$

for all t. The proof is complete. □

Let $(G(t), I(t))$ be a solution of (2.1). Throughout this paper, we define

$$\overline{G} = \limsup_{t\to\infty} G(t),\ \underline{G} = \liminf_{t\to\infty} G(t),\ \overline{I} = \limsup_{t\to\infty} I(t),\ \underline{I} = \liminf_{t\to\infty} I(t).$$

By Propositions 2.1 and 2.2, these quantities are all finite. The following well known *fluctuation lemma* is stated below without proof:

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Lemma 2.3 *Let $f : \mathbf{R} \to \mathbf{R}$ be a differentiable function. If*

$$l = \liminf_{t\to\infty} f(t) < \limsup_{t\to\infty} f(t) = L,$$

then there are sequences $\{t_k\} \uparrow \infty$, $\{s_k\} \uparrow \infty$ such that, for all k,

$$f'(t_k) = f'(s_k) = 0, \lim_{k\to\infty} f(t_k) = L \text{ and } \lim_{k\to\infty} f(s_k) = l.$$

Proposition 2.4 *Model* (2.1) *is uniformly persistent, i.e. solutions are eventually uniformly bounded from above and below.*

Proof If $\underline{I} < \overline{I}$ then, by Lemma 2.3, there exist sequences $\{t_k\} \uparrow \infty$, $\{s_k\} \uparrow \infty$, such that

$$\dot{I}(t_k) = \dot{I}(s_k) = 0, \qquad \lim_{k\to\infty} I(t_k) = \overline{I} \quad \text{and} \quad \lim_{k\to\infty} I(s_k) = \underline{I}.$$

Thus, from the first equation of (2.1), we have

$$0 = \dot{I}(t_k) = f_1(G(t_k)) - \frac{1}{\tau_0} I(t_k)$$

and

$$0 = \dot{I}(s_k) = f_1(G(s_k)) - \frac{1}{\tau_0} I(s_k)$$

for all k.

Let $\varepsilon > 0$ be arbitrary. Then there exists $T_0 > 0$ such that, for all $t \geqslant T_0$,

$$G(t) \leqslant \overline{G} + \varepsilon.$$

Also, there exists an integer k_0 such that $k \geqslant k_0 \Rightarrow t_k \geqslant T_0$ and, therefore,

$$G(t_k) \leqslant \overline{G} + \varepsilon.$$

Hence, for k sufficiently large,

$$0 = f_1(G(t_k)) - \frac{1}{\tau_0} I(t_k) \leqslant f_1(\overline{G} + \varepsilon) - \frac{1}{\tau_0} I(t_k)$$

since f_1 is increasing. Letting $k \to \infty$ and then $\varepsilon \to 0$,

$$\overline{I} \leqslant \tau_0 f_1(\overline{G}). \tag{2.2}$$

In a similar way, we can show using the sequence s_k that

$$\underline{I} \geqslant \tau_0 f_1(\underline{G}). \tag{2.3}$$

Combining (2.2) and (2.3),

$$\tau_0 f_1(\underline{G}) \leqslant \underline{I} < \overline{I} \leqslant \tau_0 f_1(\overline{G}). \tag{2.4}$$

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Recall from the proof of Proposition 2.2 that

$$\overline{G} \leqslant \frac{1}{qf_4(0)}(G_{in} + f_5(0)). \tag{2.5}$$

so that G is bounded above. Note that (2.4) recovers the result that I is bounded above also. We now need to prove that $\underline{G} > 0$ and $\underline{I} > 0$.

If $\underline{G} < \overline{G}$ then there exist sequences $\{t'_k\} \uparrow \infty$, $\{s'_k\} \uparrow \infty$, such that

$$\dot{G}(t'_k) = \dot{G}(s'_k) = 0, \qquad \lim_{k\to\infty} G(t'_k) = \overline{G} \quad \text{and} \quad \lim_{k\to\infty} G(s'_k) = \underline{G}.$$

The second equation of (2.1) then gives, for all k,

$$0 = \dot{G}(s'_k) = G_{in} - f_2(G(s'_k)) - qG(s'_k)f_4(I(s'_k)) + f_5(I(s'_k - \tau)).$$

Let $\varepsilon > 0$. Then there exists $T_2 > 0$ such that, for all $t \geqslant T_2$, $I(t) \leqslant \overline{I} + \varepsilon$. For all k sufficiently large, $s'_k - \tau \geqslant T_2$ and therefore $I(s'_k - \tau) \leqslant \overline{I} + \varepsilon$. Hence, for k sufficiently large,

$$\begin{aligned} 0 &= G_{in} - f_2(G(s'_k)) - qG(s'_k)f_4(I(s'_k)) + f_5(I(s'_k - \tau)) \\ &\geqslant G_{in} - f_2(G(s'_k)) - qG(s'_k)f_4(\overline{I} + \varepsilon) + f_5(\overline{I} + \varepsilon) \end{aligned}$$

since f_4 is increasing and f_5 decreasing. Letting $k \to \infty$ and then $\varepsilon \to 0$,

$$0 \geqslant G_{in} - f_2(\underline{G}) - q\underline{G}f_4(\overline{I}) + f_5(\overline{I}). \tag{2.6}$$

Now suppose, for contradiction, that $\underline{G} = 0$. Substituting this into (2.6) gives

$$0 \geqslant G_{in} + f_5(\overline{I}) > 0,$$

a contradiction. Therefore $\underline{G} > 0$. From (2.4) we now have $\underline{I} > 0$ also. The proof is complete. □

2.2 Equilibria

Let us investigate the equilibria (I^*, G^*) of our system. The first equation of (2.1) gives

$$I^* = \tau_0 f_1(G^*). \tag{2.7}$$

From this, we obtain a single equation for G^*:

$$0 = G_{in} - f_2(G^*) - qG^* f_4(\tau_0 f_1(G^*)) + f_5(\tau_0 f_1(G^*)). \tag{2.8}$$

Define

$$h(G) = G_{in} - f_2(G) - qGf_4(\tau_0 f_1(G)) + f_5(\tau_0 f_1(G)).$$

Then $h(0) = G_{in} + f_5(\tau_0 f_1(0)) > 0$. Also, by the various properties of f_2, f_4 and f_5 listed in Appendix B, it is clear that $h(G) < 0$ for G sufficiently large. It is also straightforward to show that $h'(G) < 0$ for all $G > 0$. Hence there exists precisely one root $G^* > 0$ of (2.8), and therefore there is one equilibrium (I^*, G^*) of (2.1).

3 Global convergence to equilibrium

In this section we shall provide some conditions under which global convergence of solutions to the equilibrium (I^*, G^*) is assured. Our first approach is to use a comparison principle. This approach furnishes a set of conditions which involve the parameter τ_0, but not the delay τ. Our second approach, by use of Lyapunov functionals, yields another set of sufficient conditions which do involve the delay τ, yielding further insight into the behaviour of the system.

3.1 Comparison principle approach

Solving the first equation of (2.1) for $I(t)$, gives

$$I(t) = e^{\frac{-t}{\tau_0}} I(0) + e^{\frac{-t}{\tau_0}} \int_0^t e^{\frac{s}{\tau_0}} f_1(G(s))\, ds.$$

Since we are interested in the asymptotic behaviour of the solutions, we shall neglect the first term in the above. Substituting the remaining expression into the second equation of (2.1), we can recast the original model into the form of a single equation

$$\frac{dG}{dt} = G_{in} - f_2(G) - qGf_4\left(\int_0^t e^{\frac{-(t-s)}{\tau_0}} f_1(G(s))\, ds\right) + f_5\left(\int_0^{t-\tau} e^{\frac{-(t-\tau-s)}{\tau_0}} f_1(G(s))\, ds\right), \qquad t > 0, \tag{3.1}$$

which now requires as initial data:

$$G(s) = G_0(s), \qquad s \in [-\tau, 0] \tag{3.2}$$

where $G_0(s)$ is a prescribed, continuous, non-negative, initial function with $G_0(0) > 0$. Although we have reduced the original system (2.1) to a single equation, this has been done at the expense of now having to deal with *distributed* delay terms. We shall now introduce a definition of sub- and supersolutions appropriate to our problem, and then state a comparison principle which shall be used to prove a theorem on global convergence.

Definition A pair of sub- and supersolutions for (3.1,3.2) is a pair of suitably smooth functions v and w such that:

(i) $v \leqslant w$ for all t;

(ii) v and w satisfy

$$\frac{dv}{dt} \leqslant G_{in} - f_2(v) - qvf_4\left(\int_0^t e^{\frac{-(t-s)}{\tau_0}} f_1(\phi(s))ds\right) + f_5\left(\int_0^{t-\tau} e^{\frac{-(t-\tau-s)}{\tau_0}} f_1(\phi(s))ds\right)$$

$$\frac{dw}{dt} \geqslant G_{in} - f_2(w) - qwf_4\left(\int_0^t e^{\frac{-(t-s)}{\tau_0}} f_1(\phi(s))ds\right) + f_5\left(\int_0^{t-\tau} e^{\frac{-(t-\tau-s)}{\tau_0}} f_1(\phi(s))ds\right)$$

for all functions ϕ such that $v(s) \leqslant \phi(s) \leqslant w(s)$, $s \leqslant t$;

(iii) $v(s) \leqslant G_0(s) \leqslant w(s)$ for all $s \in [-\tau, 0]$.

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We shall employ the following comparison principle, which is a consequence of Theorem 3.4 in Redlinger [14]:

Lemma 3.1 *If there are sub- and supersolutions v and w for* (3.1), (3.2)*, then there exists a unique solution $G(t)$ of* (3.1), (3.2) *such that $v(t) \leqslant G(t) \leqslant w(t)$ for all t.*

Trivially, we have that 0 is a subsolution of (3.1), (3.2). Let us seek a supersolution. Define $\hat{G}$ to be the solution of

$$\frac{d\hat{G}}{dt} = G_{in} - f_2(\hat{G}) - q\hat{G}f_4(0) + f_5(0), \qquad t > 0.$$

Although this is not a delay equation, we do need to define $\hat{G}$ on the interval $[-\tau, 0]$ because of condition (iii) in the above Definition. For $s \in [-\tau, 0)$, we shall take $\hat{G}(s) := \hat{G}(0) := \max\{G_0(\tilde{s}), \tilde{s} \in [-\tau, 0]\}$. Conditions (i) and (iii) of the Definition are then trivially satisfied. Condition (ii) will be satisfied if

$$q\hat{G}f_4(0) - f_5(0) \leqslant q\hat{G}\underbrace{f_4\left(\int_0^t e^{\frac{-(t-s)}{\tau_0}} f_1(\phi(s))\,ds\right)}_{\geqslant f_4(0)} - \underbrace{f_5\left(\int_0^{t-\tau} e^{\frac{-(t-\tau-s)}{\tau_0}} f_1(\phi(s))\,ds\right)}_{\leqslant f_5(0)} \tag{3.3}$$

for all functions ϕ with $0 \leqslant \phi(s) \leqslant \hat{G}(s)$, $s \leqslant t$, and (3.3) holds because of the monotonicity properties of f_4 and f_5. Therefore, $(0, \hat{G})$ is a sub- supersolution pair and thus there exists a unique solution $G(t)$ to (3.1,3.2) such that $0 \leqslant G(t) \leqslant \hat{G}(t)$ for all t.

Our main theorem of this subsection is the following.

Theorem 3.2 *Let the f_i satisfy the assumptions listed in Appendix B, and suppose that the simultaneous equations*

$$G_{in} - f_2(x) - qxf_4(\tau_0 f_1(y)) + f_5(\tau_0 f_1(y)) = 0 \tag{3.4}$$

$$G_{in} - f_2(y) - qyf_4(\tau_0 f_1(x)) + f_5(\tau_0 f_1(x)) = 0 \tag{3.5}$$

have no solution in the first quadrant other than $x = y = G^*$. Then the solution $G(t)$ of (3.1), (3.2) *satisfies*

$$\lim_{t\to\infty} G(t) = G^*.$$

Remark Later, we shall discuss under what circumstances the hypothesis of this theorem is likely to be satisfied.

Proof Let

$$I = \left[\liminf_{t\to\infty} G(t), \;\; \limsup_{t\to\infty} G(t)\right].$$

To prove the theorem, it suffices to show that $I = \{G^*\}$. Now

$$\limsup_{t\to\infty} G(t) \leqslant \lim_{t\to\infty} \hat{G}(t) =: v_0. \tag{3.6}$$

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Therefore, $I \subset [0, v_0]$. Furthermore, v_0 satisfies

$$G_{in} - f_2(v_0) - qv_0 f_4(0) + f_5(0) = 0. \tag{3.7}$$

We now improve the subsolution. Let $\varepsilon > 0$. By (3.6), there exists $t_1 > 1$ such that

$$G(t) \leqslant v_0 + \varepsilon \quad \text{for all } t \geqslant t_1 - 1$$

and there exists $t_2 > t_1 + \tau$ such that

$$\int_{t-t_1}^{t} e^{-s/\tau_0}\, ds < \varepsilon \quad \text{for all} \quad t \geqslant t_2 - \tau.$$

Since $G(t)$ is majorized by $\hat{G}(t)$, and the latter is a monotone function (it satisfies a one-dimensional autonomous ODE), we can say that, for all $t \geqslant -\tau$,

$$G(t) \leqslant \tilde{M}_G := \max(v_0, \max\{G_0(\tilde{s}),\ \tilde{s} \in [-\tau, 0]\}).$$

Introduce the function

$$z^{(1)}(t) = \begin{cases} \tilde{M}_G, & -\tau \leqslant t \leqslant t_1 - 1 \\ v_0 + \varepsilon + (\tilde{M}_G - v_0 - \varepsilon)(t_1 - t), & t_1 - 1 < t < t_1 \\ v_0 + \varepsilon, & t \geqslant t_1 \end{cases}$$

and also the 'cut-off' operator

$$(A^{(1)}G)(t) = \max(0, \min(G(t), z^{(1)}(t))).$$

We see that $G(t) \leqslant z^{(1)}(t)$ for all t since $0 \leqslant G(t) \leqslant v_0 + \varepsilon$ for $t \geqslant t_1 - 1$ and $0 \leqslant G(t) \leqslant \tilde{M}_G$ for all t (in particular for $t < t_1 - 1$). Hence, $A^{(1)}G = G$ and therefore replacing G by $A^{(1)}G$ in the delay terms of equation (3.1) leaves the solution unaltered. Of course, we shall also carry out this replacement in the definition of sub- and supersolutions, with the effect that the functions ϕ in that definition are 'cut off' by the operator $A^{(1)}$. This leads to an improved subsolution.

It is straightforward to see that the solution of (3.1), (3.2) satisfies $G(t) > 0$ for all $t > 0$. Therefore, if

$$\delta_1 = \tfrac{1}{2} \min\left\{G(t) \colon \tfrac{1}{2}t_2 \leqslant t \leqslant t_2\right\}$$

then $\delta_1 > 0$. Define the function v_1 by

$$v_1(t) = \begin{cases} 0, & -\tau \leqslant t \leqslant \frac{1}{2}t_2 \\ \frac{\delta_1}{t_2}(2t - t_2), & \frac{1}{2}t_2 < t \leqslant t_2 \end{cases}$$

$$\begin{aligned} \dot{v}_1 = G_{in} - f_2(v_1) - qv_1 f_4(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0 + \varepsilon)) \\ + f_5(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0 + \varepsilon)), \qquad v_1(t_2) = \delta_1. \end{aligned}$$

We claim that v_1 and $w_1 \equiv \tilde{M}_G$ are sub- and supersolutions for (3.1), (3.2). On $[0, t_2]$ we have $v_1(t) < G(t)$, so the first inequality of (ii) in the definition of a subsolution need only

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hold for $t > t_2$. Therefore, we need to show that $v_1 < \tilde{M}_G$ for all $t \geqslant 0$ and that, for $t > t_2$,

$$qv_1 f_4\left(\int_0^t e^{\frac{-(t-s)}{\tau_0}} f_1\big(\big(A^{(1)}\phi\big)(s)\big)\,ds\right) - f_5\left(\int_0^{t-\tau} e^{\frac{-(t-\tau-s)}{\tau_0}} f_1\big(\big(A^{(1)}\phi\big)(s)\big)\,ds\right)$$
$$\leqslant qv_1 f_4(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0+\varepsilon)) - f_5(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0+\epsilon)) \tag{3.8}$$

for all functions ϕ with $v_1 \leqslant \phi \leqslant \tilde{M}_G$. Note that $A^{(1)}\phi \leqslant z^{(1)}$ and consequently

$$s \in [0, t_1] \Rightarrow \big(A^{(1)}\phi\big)(s) \leqslant \tilde{M}_G,$$
$$s \in [t_1, t] \Rightarrow \big(A^{(1)}\phi\big)(s) \leqslant v_0 + \varepsilon.$$

Thus, for $t > t_2$,

$$\begin{aligned}
&qv_1 f_4\left(\int_0^t e^{\frac{-(t-s)}{\tau_0}} f_1\big(\big(A^{(1)}\phi\big)(s)\big)\,ds\right)\\
&= qv_1 f_4\left(\int_0^{t_1} e^{\frac{-(t-s)}{\tau_0}} f_1\big(\big(A^{(1)}\phi\big)(s)\big)\,ds + \int_{t_1}^t e^{\frac{-(t-s)}{\tau_0}} f_1\big(\big(A^{(1)}\phi\big)(s)\big)\,ds\right)\\
&\leqslant qv_1 f_4\left(f_1(\tilde{M}_G)\int_0^{t_1} e^{\frac{-(t-s)}{\tau_0}}\,ds + f_1(v_0+\varepsilon)\int_{t_1}^t e^{\frac{-(t-s)}{\tau_0}}\,ds\right)\\
&= qv_1 f_4\left(f_1(\tilde{M}_G)\int_{t-t_1}^t e^{\frac{-s}{\tau_0}}\,ds + f_1(v_0+\varepsilon)\int_0^{t-t_1} e^{\frac{-s}{\tau_0}}\,ds\right)\\
&< qv_1 f_4(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0+\varepsilon))
\end{aligned}$$

and, similarly,

$$f_5\left(\int_0^{t-\tau} e^{\frac{-(t-\tau-s)}{\tau_0}} f_1\big(\big(A^{(1)}\phi\big)(s)\big)\,ds\right) > f_5(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0+\varepsilon)).$$

Hence inequality (3.8) is satisfied.

As $t \to \infty$, v_1 tends to a limit $\mu = \mu_1(\varepsilon)$ satisfying the equation

$$p(\mu;\varepsilon) = G_{in} - f_2(\mu) - q\mu f_4(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0+\varepsilon))$$
$$+ f_5(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0+\varepsilon)) = 0. \tag{3.9}$$

Now $p'(\mu;\varepsilon) < 0$ for all $\mu \geqslant 0$. Also, $p(0;\varepsilon) > 0$ and $p(\mu;\varepsilon) < 0$ for sufficiently large μ. Therefore, $p(\mu;\varepsilon) = 0$ has one strictly positive root $\mu = \mu_1(\varepsilon)$ which is a continuous function of ε, and $p(\mu;\varepsilon) > 0$ when $\mu \in (0, \mu_1(\varepsilon))$ and $p(\mu;\varepsilon) < 0$ when $\mu > \mu_1(\varepsilon)$. It follows that

$$\lim_{t\to\infty} v_1(t;\varepsilon) = \mu_1(\varepsilon).$$

We still need to check that $v_1 < \tilde{M}_G$ for all $t \geqslant 0$. Now, using (2.8),

$$p(G^*;\varepsilon) = qG^* f_4(\tau_0 f_1(G^*)) - qG^* f_4(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0+\varepsilon))$$
$$+ f_5(\varepsilon f_1(\tilde{M}_G) + \tau_0 f_1(v_0+\varepsilon)) - f_5(\tau_0 f_1(G^*)).$$

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If we can show $G^* \leqslant v_0$ then $p(G^*;\varepsilon) < 0$. Assume, for contradiction, that $G^* > v_0$. Then from (3.7) and (2.8) it is necessary that

$$0 = \underbrace{f_2(G^*) - f_2(v_0)}_{>0} + \underbrace{qG^* f_4(\tau_0 f_1(G^*)) - qv_0 f_4(0)}_{>0}$$
$$+ \underbrace{f_5(0) - f_5(\tau_0 f_1(G^*))}_{>0},$$

a contradiction. Hence $G^* \leqslant v_0$ and $p(G^*;\varepsilon) < 0$. Therefore $\mu_1(\varepsilon) < G^* \leqslant v_0 \leqslant \tilde{M}_G$. Since v_1 approaches its limit $\mu_1(\varepsilon)$ monotonically, our observations are sufficient to ensure that $v_1 \leqslant \tilde{M}_G$ for all $t \geqslant 0$. So v_1 is a subsolution and, from Lemma 3.1,

$$v_1(t;\varepsilon) \leqslant G(t) \leqslant \tilde{M}_G.$$

Letting $\varepsilon \to 0$ and writing $\mu_1(0) = \mu_1$ we conclude that $I \subset [\mu_1, v_0]$, where μ_1 satisfies

$$G_{in} - f_2(\mu_1) - q\mu_1 f_4(\tau_0 f_1(v_0)) + f_5(\tau_0 f_1(v_0)) = 0.$$

One can then improve this to $I \subset [\mu_1, v_1]$ where v_1 is defined in terms of μ_0. Carrying on with this process (the details are similar to those already presented), one finds that $I \subset [\mu_n, v_n]$ for each $n \in \mathbb{N}$, where (μ_n) and (v_n) are defined by

$$\begin{aligned} G_{in} - f_2(\mu_{n+1}) - q\mu_{n+1} f_4(\tau_0 f_1(v_n)) + f_5(\tau_0 f_1(v_n)) = 0,\\ G_{in} - f_2(v_{n+1}) - qv_{n+1} f_4(\tau_0 f_1(\mu_n)) + f_5(\tau_0 f_1(\mu_n)) = 0. \end{aligned} \tag{3.10}$$

We shall show by induction that

$$0 < \mu_0 \leqslant \mu_1 \leqslant \cdots \leqslant \mu_n < G^* < v_n \leqslant v_{n-1} \leqslant \cdots \leqslant v_1 \leqslant v_0. \tag{3.11}$$

Assuming (3.11) is true (inductive hypothesis), then we need to show

$$\mu_n \leqslant \mu_{n+1} < G^* \tag{3.12}$$

and

$$G^* < v_{n+1} \leqslant v_n. \tag{3.13}$$

We shall show only the former. Now, μ_{n+1} is the root x of

$$F(x) = G_{in} - f_2(x) - qxf_4(\tau_0 f_1(v_n)) + f_5(\tau_0 f_1(v_n)) = 0$$

and therefore (3.12) is satisfied if $F(\mu_n) \geqslant 0$ and $F(G^*) < 0$. Now

$$\begin{aligned} F(\mu_n) &= G_{in} - f_2(\mu_n) - q\mu_n f_4(\tau_0 f_1(v_n)) + f_5(\tau_0 f_1(v_n)) \\ &= q\mu_n f_4(\tau_0 f_1(v_{n-1})) - f_5(\tau_0 f_1(v_{n-1}) + f_5(\tau_0 f_1(v_n)) \\ &\quad - q\mu_n f_4(\tau_0 f_1(v_n)) \qquad \text{(using (3.10))} \\ &= q\mu_n \underbrace{(f_4(\tau_0 f_1(v_{n-1})) - f_4(\tau_0 f_1(v_n)))}_{\geqslant 0} \\ &\quad + \underbrace{f_5(\tau_0 f_1(v_n)) - f_5(\tau_0 f_1(v_{n-1}))}_{\geqslant 0} \\ &\geqslant 0 \qquad \text{since } v_n \leqslant v_{n-1}. \end{aligned}$$

The proof that $F(G^*) < 0$ is similar. Hence (3.12) is satisfied. Similarly, we can show that (3.13) holds, proving (3.11). We can deduce that there exist the limits

$$\mu = \lim_{n\to\infty} \mu_n \quad \text{and} \quad v = \lim_{n\to\infty} v_n$$

and, from (3.10) with $n \to \infty$,

$$\begin{aligned} G_{in} - f_2(\mu) - q\mu f_4(\tau_0 f_1(v)) + f_5(\tau_0 f_1(v)) = 0, \\ G_{in} - f_2(v) - qv f_4(\tau_0 f_1(\mu)) + f_5(\tau_0 f_1(\mu)) = 0. \end{aligned}$$

By the hypothesis of the theorem, these equations have only the solution $\mu = v = G^*$. Since $I \subset [\mu, v]$, it follows that $I = \{G^*\}$ and the proof of the theorem is complete. □

As promised earlier, we shall now discuss the circumstances under which the simultaneous equations (3.4,3.5) are likely to have only the solution $x = y = G^*$. With only the general assumptions on the f_i listed in Appendix B to work with, it is difficult to ascertain precisely the circumstances, but by some simple graphical arguments we can make some very useful comments.

Equation (3.4) defines a curve $y = y(x)$ in the (x, y) plane. Only the first quadrant is of interest. From the properties of the f_i it is easy to see that this curve intersects the x-axis precisely once, but does not intersect the y-axis. Furthermore, by implicitly differentiating (3.4) with respect to x, with $y = y(x)$, we find that

$$y'(x) = \frac{f_2'(x) + qf_4(\tau_0 f_1(y))}{\tau_0 f_1'(y)\{f_5'(\tau_0 f_1(y)) - qxf_4'(\tau_0 f_1(y))\}} \tag{3.14}$$

so that, since f_5 is decreasing, $y(x)$ is always decreasing along the curve. The second equation (3.5) defines a curve that is the mirror image, in the line $y = x$, of the curve we have just been discussing.

The graphs shown in Fig. 1 illustrate two possibilities. In one of these the two curves have only the $x = y = G^*$ intersection while, in the other, there are two additional intersections so that the hypothesis of Theorem 3.2 is not satisfied. On a first glance, what appears to distinguish the two cases is the slopes at the intersection with $y = x$. It is actually not as simple as this; one can imagine that curve 1 could be very steep until just after its intersection with $y = x$, and then suddenly swing round and intersect curve 2 in two further places below $y = x$. However, MAPLE plots of the two curves for the case when the f_i are given by expressions (4.2), (4.3), (4.4) and (4.6) of Appendix A suggest that this never happens and that for all biologically reasonable sets of parameter values it is indeed the slopes at the intersection with $y = x$ that distinguishes the two cases. Examining the slopes at $x = y = G^*$, we require the slope of curve 1 at that point to be less than -1. Equation (3.14) then gives us

$$f_2'(G^*) + qf_4(\tau_0 f_1(G^*)) + \tau_0 f_1'(G^*)\{f_5'(\tau_0 f_1(G^*)) - qG^* f_4'(\tau_0 f_1(G^*))\} > 0. \tag{3.15}$$

These observations suggest that if (3.15) holds then the hypothesis of Theorem 3.2 is satisfied for realistic f_i and for realistic parameter values.

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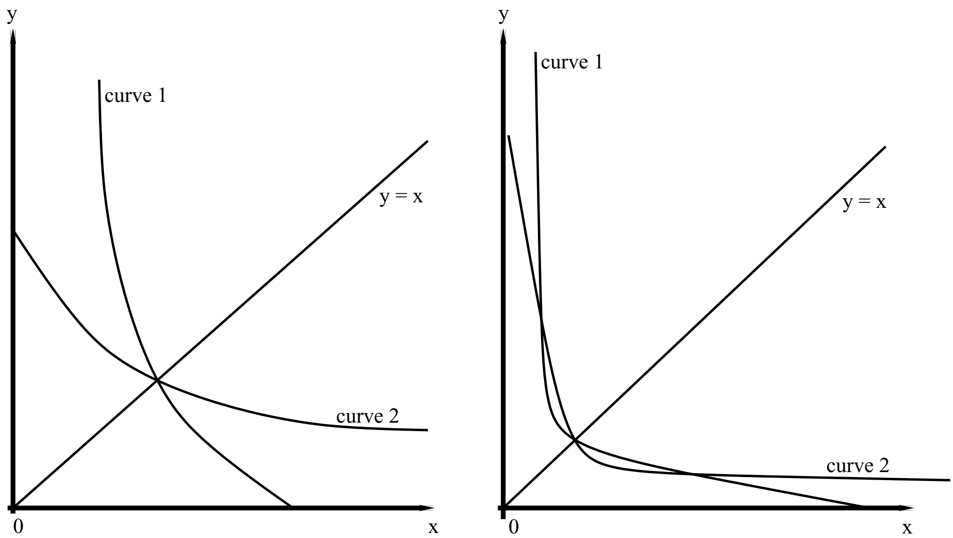

FIGURE 1. Qualitative sketches of the curves defined by equations (3.4) and (3.5) showing two possibilities, only one of which satisfies the hypothesis of Theorem 3.2.

3.2 Lyapunov functional approach

In the approach to be described in this section, we shall work with the original problem (2.1). The functions f_i shall take the expressions given in Appendix A, and our aim is to study how the global stability of the equilibrium (G^*, I^*) of (2.1) depends on τ_0 and τ. It is inconvenient and unnecessary to carry the exact expressions for the f_i through all the analysis; we shall call upon the actual expressions only as necessary.

Applying the transformation

$$G = G^* + u, \qquad I = I^* + v$$

to system (2.1) gives

$$\begin{aligned}\dot{u} &= -uf_2'(G^* + \theta_2 u) - uqf_4(I^*) - vf_4'(I^* + \theta_4 v)q(G^* + u) + v(t-\tau)f_5'(I^* + \theta_5 v(t-\tau))\\ \dot{v} &= uf_1'(G^* + \theta_1 u) - \frac{1}{\tau_0}v\end{aligned} \tag{3.16}$$

where the θ_i come from applications of Taylor's theorem with remainder, for example,

$$f_2(G^* + u(t)) = f_2(G^*) + u(t)f_2'(G^* + u(t)\theta_1(u(t)))$$

where, for all t, θ_1 is between 0 and 1. We do not need to keep track of the dependence of the θ_i on the state variables or the times at which these are evaluated (for example, $\theta_1(u(t))$ and $\theta_1(u(s))$ shall both appear simply as θ_1 in our analysis). All that we need to know about the θ_i is that they are always between 0 and 1.

In the new system (3.16) the equilibrium of interest is $u = v = 0$. In what follows, u and v are always evaluated at time t except where otherwise shown. In the following analysis,

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we shall several times make use of the inequality

$$xy \leqslant \frac{1}{2}\varepsilon_i x^2 + \frac{1}{2\varepsilon_i} y^2$$

with suitably chosen ε_i. We shall need an upper bound on $G(t)$. Since we are working with the system (2.1), the upper bound given by

$$G(t) \leqslant M_G := \max\left\{G(0), \frac{1}{qf_4(0)}(G_{in} + f_5(0)\right\}$$

is valid here. Define

$$U_1(u,v) = \frac{1}{2}u^2 + \frac{1}{2}\omega v^2 > 0$$

where $\omega > 0$ is to be chosen later. Along the solutions of (3.16),

$$\begin{aligned}
\dot{U}_1 &= -[f_2'(G^* + \theta_2 u) + qf_4(I^*)]u^2 - \frac{\omega}{\tau_0}v^2 - uvf_4'(I^* + \theta_4 v)q(G^* + u) \\
&\quad + \omega uv f_1'(G^* + \theta_1 u) + uvf_5'(I^* + \theta_5 v(t-\tau)) \\
&\quad + uf_5'(I^* + \theta_5 v(t-\tau))[v(t-\tau) - v(t)] \\
&= -[f_2'(G^* + \theta_2 u) + qf_4(I^*)]u^2 - \frac{\omega}{\tau_0}v^2 - uvf_4'(I^* + \theta_4 v)q(G^* + u) \\
&\quad + \omega uv f_1'(G^* + \theta_1 u) + uvf_5'(I^* + \theta_5 v(t-\tau)) \\
&\quad - uf_5'(I^* + \theta_5 v(t-\tau)) \int_{t-\tau}^{t} \dot{v}(s)\,ds \\
&= -[f_2'(G^* + \theta_2 u) + qf_4(I^*)]u^2 - \frac{\omega}{\tau_0}v^2 - uvf_4'(I^* + \theta_4 v)q(G^* + u) \\
&\quad + \omega uv f_1'(G^* + \theta_1 u) + uvf_5'(I^* + \theta_5 v(t-\tau)) \\
&\quad - uf_5'(I^* + \theta_5 v(t-\tau)) \int_{t-\tau}^{t} \left\{u(s)f_1'(G^* + \theta_1 u(s)) - \frac{1}{\tau_0}v(s)\right\} ds \\
&\leqslant -[f_2'(G^* + \theta_2 u) + qf_4(I^*)]u^2 - \frac{\omega}{\tau_0}v^2 \\
&\quad + \frac{1}{2}\left(\varepsilon_1 u^2 + \frac{v^2}{\varepsilon_1}\right) f_4'(I^* + \theta_4 v)q(G^* + u) + \frac{\omega}{2}\left(\varepsilon_2 u^2 + \frac{v^2}{\varepsilon_2}\right) f_1'(G^* + \theta_1 u) \\
&\quad + \frac{1}{2}\left(\varepsilon_3 u^2 + \frac{v^2}{\varepsilon_3}\right) |f_5'(I^* + \theta_5 v(t-\tau))| \\
&\quad + |f_5'(I^* + \theta_5 v(t-\tau))| \int_{t-\tau}^{t} \left\{f_1'(G^* + \theta_1 u(s))|u(s)||u(t)| + \frac{1}{\tau_0}|v(s)||u(t)|\right\} ds \\
&\leqslant -[f_2'(G^* + \theta_2 u) + qf_4(I^*)]u^2 - \frac{\omega}{\tau_0}v^2 + \frac{1}{2}\left(\varepsilon_1 u^2 + \frac{v^2}{\varepsilon_1}\right) f_4'(I^* + \theta_4 v)q(G^* + u) \\
&\quad + \frac{\omega}{2}\left(\varepsilon_2 u^2 + \frac{v^2}{\varepsilon_2}\right) f_1'(G^* + \theta_1 u) + \frac{1}{2}\left(\varepsilon_3 u^2 + \frac{v^2}{\varepsilon_3}\right) |f_5'(I^* + \theta_5 v(t-\tau))| \\
&\quad + \frac{1}{2}|f_5'(I^* + \theta_5 v(t-\tau))| f_1'(C_1 V_g) \int_{t-\tau}^{t} \left\{\frac{1}{\varepsilon_4}u^2(s) + \varepsilon_4 u^2(t)\right\} ds \\
&\quad + \frac{1}{2\tau_0}|f_5'(I^* + \theta_5 v(t-\tau))| \int_{t-\tau}^{t} \left\{\frac{v^2(s)}{\varepsilon_5} + \varepsilon_5 u^2(t)\right\} ds
\end{aligned}$$

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$$
\begin{aligned}
&\leqslant -\Big[f_2'(G^*+\theta_2 u)+qf_4(I^*)-\frac{1}{2}\omega\varepsilon_2 f_1'(G^*+\theta_1 u)\\
&\quad -\frac{1}{2}\varepsilon_1 f_4'(I^*+\theta_4 v)q(G^*+u)-\frac{1}{2}\varepsilon_3|f_5'(C_5V_i)|\\
&\quad -\frac{1}{2}\varepsilon_4|f_5'(C_5V_i)||f_1'(C_1V_g)\tau-\frac{1}{2\tau_0}\varepsilon_5|f_5'(C_5V_i)|\tau\Big]u^2\\
&\quad -\left[\frac{\omega}{\tau_0}-\frac{1}{2\varepsilon_1}f_4'(I^*+\theta_4 v)q(G^*+u)-\frac{\omega}{2\varepsilon_2}f_1'(G^*+\theta_1 u)-\frac{1}{2\varepsilon_3}|f_5'(C_5V_i)|\right]v^2\\
&\quad +\frac{1}{2\varepsilon_4}|f_5'(C_5V_i)||f_1'(C_1V_g)\int_{t-\tau}^{t}u^2(s)\,ds+\frac{1}{2\tau_0\varepsilon_5}|f_5'(C_5V_i)|\int_{t-\tau}^{t}v^2(s)\,ds.
\end{aligned}
$$

In the above estimates we have used the fact that $f_1'(G)$ is maximised at $G=C_1V_g$ and that $|f_5'(I)|$ is maximised at $I=C_5V_i$. Similarly, in the following analysis, we shall use that $f_4'(I)$ is maximised at $I=A$, where A is the quantity defined in the statement of Theorem 3.3 below, and that $f_2'(G)\geqslant f_2'(M_G)>0$, since $G(t)$ is bounded by M_G. Now define

$$W_1=\frac{1}{2\varepsilon_4}|f_5'(C_5V_i)||f_1'(C_1V_g)\int_{t-\tau}^{t}\int_{z}^{t}u^2(s)\,ds\,dz$$

and

$$W_2=\frac{1}{2\tau_0\varepsilon_5}|f_5'(C_5V_i)|\int_{t-\tau}^{t}\int_{z}^{t}v^2(s)\,ds\,dz.$$

If $V=U_1+W_1+W_2$, then

$$
\begin{aligned}
\dot V &\leqslant -\Big[f_2'(M_G)+qf_4(I^*)\\
&\quad -\frac{1}{2}\varepsilon_1 f_4'(A)qM_G-\frac{1}{2}\omega\varepsilon_2 f_1'(C_1V_g)\\
&\quad -\frac{1}{2}|f_5'(C_5V_i)|\left(\varepsilon_3+\tau\left(\varepsilon_4 f_1'(C_1V_g)+\frac{1}{\varepsilon_4}f_1'(C_1V_g)+\frac{\varepsilon_5}{\tau_0}\right)\right)\Big]u^2\\
&\quad -\Big[\frac{\omega}{\tau_0}-\frac{1}{2\varepsilon_1}f_4'(A)qM_G-\frac{\omega}{2\varepsilon_2}f_1'(C_1V_g)\\
&\quad -\frac{1}{2}|f_5'(C_5V_i)|\left(\frac{1}{\varepsilon_3}+\frac{\tau}{\varepsilon_5\tau_0}\right)\Big]v^2.
\end{aligned}
$$

For V to be a Lyapunov functional we require $\dot V<0$ when $(u,v)\neq(0,0)$. This is satisfied provided that the square bracketed coefficients of u^2 and v^2 in the above expression are both strictly positive. To maximise the range of τ for which stability is assured, it is clear that we need to minimise $\varepsilon_4+1/\varepsilon_4$, and thus we choose $\varepsilon_4=1$. We shall also choose

$$\varepsilon_5=|f_5'(C_5V_i)|\tau/\omega.$$

We then seek to choose the remaining ε_i and ω so as to have

$$
\begin{aligned}
&f_2'(M_G)+qf_4(I^*)-\tfrac{1}{2}\varepsilon_1 f_4'(A)qM_G-\tfrac{1}{2}\omega\varepsilon_2 f_1'(C_1V_g)\\
&\quad -\tfrac{1}{2}|f_5'(C_5V_i)|\left(\varepsilon_3+2\tau f_1'(C_1V_g)+\frac{\tau^2}{\omega\tau_0}|f_5'(C_5V_i)|\right)>0
\end{aligned}
\tag{3.17}
$$

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and

$$\frac{\omega}{2\tau_0} - \frac{1}{2\varepsilon_1} f_4'(A) q M_G - \frac{\omega}{2\varepsilon_2} f_1'(C_1 V_g) - \frac{1}{2\varepsilon_3} |f_5'(C_5 V_i)| > 0. \tag{3.18}$$

There are various possible choices for the remaining ε_i and ω (and even for the expression for ε_5 above), but most lead to stability conditions that are exceptionally clumsy to state and add little to our understanding. The following theorem arises from particular choices that seem to capture the essence of things.

Theorem 3.3 *Let $f_1(G)$ be given by (4.2), $f_2(G)$ by (4.4), $f_4(I)$ by (4.6) and $f_5(I)$ by (4.3). Also, let*

$$A = \frac{\left(\frac{\beta+1}{\beta-1}\right)^{-\frac{1}{\beta}} C_4 V_i E t_i}{E t_i + V_i}$$

and

$$M_G = \max\{G(0), \frac{1}{q f_4(0)}(G_{in} + f_5(0))\}.$$

Then the positive equilibrium (G^*, I^*) of system (2.1) is globally asymptotically stable for τ_0 and τ sufficiently small that

$$\begin{aligned} &f_2'(M_G) + q f_4(I^*) - 2\tau_0 f_1'(C_1 V_g)(f_4'(A) q M_G + |f_5'(C_5 V_i)|) \\ &\quad - \tfrac{1}{2}|f_5'(C_5 V_i)| \left(2\tau f_1'(C_1 V_g) + \frac{f_1'(C_1 V_g)|f_5'(C_5 V_i)|\tau^2}{(f_4'(A) q M_G + |f_5'(C_5 V_i)|)\tau_0} \right) > 0 \end{aligned} \tag{3.19}$$

(recall $I^* = \tau_0 f_1(G^*)$).

Proof We need to choose ε_1, ε_2, ε_3 and ω so that (3.17) and (3.18) both hold. Let us choose

$$\varepsilon_1 = \varepsilon_2 = \varepsilon_3 = 2\tau_0 f_1'(C_1 V_g).$$

Also, let

$$\omega = \frac{f_4'(A) q M_G + |f_5'(C_5 V_i)| + \xi}{f_1'(C_1 V_g)}$$

with ξ to be chosen. Inequality (3.18) is then satisfied for any $\xi > 0$, while inequality (3.17) now reads

$$\begin{aligned} &f_2'(M_G) + q f_4(I^*) - 2\tau_0 f_1'(C_1 V_g)\left(f_4'(A) q M_G + |f_5'(C_5 V_i)| + \tfrac{1}{2}\xi\right) \\ &\quad - \tfrac{1}{2}|f_5'(C_5 V_i)| \left(2\tau f_1'(C_1 V_g) + \frac{f_1'(C_1 V_g)|f_5'(C_5 V_i)|\tau^2}{(f_4'(A) q M_G + |f_5'(C_5 V_i)| + \xi)\tau_0} \right) > 0. \end{aligned} \tag{3.20}$$

Since (3.19) holds, we can obviously choose $\xi > 0$ so that (3.20) holds. The proof is complete. □

4 Conclusion

The two approaches employed in this paper for establishing sufficient conditions for global convergence to equilibrium have yielded two sets of sufficient conditions which involve

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different parameters of the problem. The conditions generated by the comparison principle approach are somewhat implicit, requiring a certain pair of simultaneous equations to have *only* a certain known solution. Graphical considerations and MAPLE experiments describe the circumstances in which these conditions are likely to hold, suggesting in particular that they hold if the parameter τ_0, which measures the timescale on which insulin degrades, is small. The conditions provided by the comparison principle approach do not involve the parameter τ, which measures the time delay between the appearance of insulin in the plasma and its resultant suppressive effect on the rate of glucose production. If the conditions generated by the comparison principle approach hold, then global stability is assured independently of the value of τ. In situations when a delay is incapable of destabilising an equilibrium however large it is, the delay is sometimes said to be *harmless*.

The Lyapunov functional approach leads to a sufficient condition for global stability that involves the parameter τ, and therefore the role of τ is discovered to some extent. Again, the conditions are sufficient but not necessary. Note that in the Lyapunov functional approach we have used the expressions for the functions f_i that previous investigators have used (see Sturis *et al.* [19]). However, in fact only certain particular properties of these functions are used, most notably, the maximum values of their derivatives.

The sufficient conditions for global stability produced by the two approaches cease to hold in precisely the circumstances in which other investigators have noted that oscillations appear. It is known (see, for example, Keener & Sneyd [7]) that a sufficiently large infusion of glucose (G_{in} large) can cause oscillations. Raising G_{in} has the effect of raising G^*, as can be seen by examining the function $h(G)$ defined in § 2.2. Raising G^* has the effect of violating inequality (3.15) which comes from the comparison principle approach.

Raising G_{in} has the effect of raising M_G and I^* and therefore, eventually, of violating condition (3.19) which is the condition for stability generated by the Lyapunov functional approach (note that f_2' and f_4 are uniformly bounded). On the other hand, the conditions predict convergence to the equilibrium if $f_1'(G^*)$ is small (comparison principle approach) or $f_1'(C_1V_g)$ is sufficiently small (Lyapunov functional approach). This implies that there will be no oscillations if insulin production (stimulated by glucose) is low.

Appendix A

The model proposed by Sturis *et al.* [19] is

$$
\begin{aligned}
\frac{dI_p}{dt} &= f_1(G) - E\left(\frac{I_p}{V_p} - \frac{I_i}{V_i}\right) - \frac{I_p}{t_p},\\
\frac{dI_i}{dt} &= E\left(\frac{I_p}{V_p} - \frac{I_i}{V_i}\right) - \frac{I_i}{t_i},\\
\frac{dG}{dt} &= G_{in} - f_2(G) - f_3(G)f_4(I_i) + f_5(x_3),\\
\frac{dx_1}{dt} &= \frac{3}{t_d}(I_p - x_1),\\
\frac{dx_2}{dt} &= \frac{3}{t_d}(x_1 - x_2),\\
\frac{dx_3}{dt} &= \frac{3}{t_d}(x_2 - x_3).
\end{aligned} \tag{4.1}
$$

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In this system, I_p, I_i and G represent the quantities of plasma insulin (mU), intercellular insulin (mU) and glucose (mg) respectively. The equations are written in terms of the total amounts of these quantities. All the parameters and functional relations in the model are based on the results of independent experiments. Appropriate values for the parameters can be found in Tolic *et al.* [20].

The model contains three separate compartments: glucose in the plasma and intercellular space, insulin in the intercellular space and insulin in the plasma. It can be regarded as having two time delays. The time lag between the appearance of insulin in the plasma and its inhibitory effect on hepatic glucose production (see Bradley *et al.* [2]) is modelled as the three-stage linear filter (x_1, x_2, x_3) and is measured by t_d. Additionally, there is a delay related to the fact that the physiological action of insulin on the utilization of glucose is regulated by the intercellular insulin rather than the plasma insulin [12], whereas glucose has a direct effect on plasma insulin. Mathematically, one could solve the second equation for I_i in terms of I_p and the first equation would then take the form of a distributed delay equation.

The first equation represents insulin being secreted by the pancreas into the plasma, where it is either degraded by the kidneys/liver or transported into the intercellular space. V_p is the distribution volume for insulin in plasma and V_i is the effective volume of the intercellular space. Insulin exchange between the two compartments is a linear function of the concentration difference between the compartments $(\frac{I_p}{V_p} - \frac{I_i}{V_i})$ with rate constant E. In addition, there is linear removal of insulin from the plasma by the kidneys and the liver, with rate constant $\frac{1}{t_p}$. Pancreatic insulin production controlled by glucose is described by

$$f_1(G) = \frac{R_m}{1 + \exp\left(\frac{1}{a_1}\left(C_1 - \frac{G}{V_g}\right)\right)} \tag{4.2}$$

which has been fitted to experimental results ([11] & [17]). The second equation of model (4.1) represents the accumulation of intercellular insulin via exchange with the plasma compartment and its degradation in muscle and adipose tissue at a rate $\frac{1}{t_i}$. The third equation models glucose being supplied to the plasma at an exogenously (uptake from food or intravenous glucose infusion) controlled rate G_{in}. The influence of insulin on hepatic glucose production, as determined by Rizza *et al.* [16] is described by

$$f_5(I) = \frac{R_g}{1 + \exp\left(\alpha\left(\frac{I}{V_i} - C_5\right)\right)}. \tag{4.3}$$

Glucose utilization is represented by two terms: $f_2(G)$ which describes insulin-independent utilization (glucose uptake by the brain and nerve cells) and $f_3(G)f_4(I_i)$ which describes insulin-dependent glucose utilization (glucose uptake by muscle and fat cells). These functions are given by

$$f_2(G) = U_b\left(1 - \exp\left(\frac{-G}{C_2 V_g}\right)\right), \tag{4.4}$$

$$f_3(G) = \frac{G}{C_3 V_g}, \tag{4.5}$$

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$$f_4(I) = U_0 + \frac{U_m - U_0}{1 + \left(\frac{I}{C_4}\left(\frac{1}{V_i} + \frac{1}{Et_i}\right)\right)^{-\beta}}, \qquad \beta > 1. \tag{4.6}$$

The functions (4.4), (4.5) and (4.6) are all determined by experimental data. (See Rizza *et al.* [16] and Verdonk *et al.* [21]).

Appendix B

Throughout the paper, the functions f_1, f_2, f_4 and f_5 satisfy:

$$f_1(G) > 0 \quad \forall \quad G > 0,\ f_1'(G) > 0 \quad \forall \quad G > 0,\ f_1(0) > 0 \text{ and } f_1(G) \to a \text{ as } G \to \infty,$$

where $a > 0$ is constant;

$$f_2(G) > 0 \quad \forall \quad G > 0,\ f_2'(G) > 0 \quad \forall \quad G > 0,\ f_2(0) = 0 \text{ and } f_2(G) \to b \text{ as } G \to \infty,$$

where $b > 0$ is constant;

$$f_4(I) > 0 \quad \forall \quad I > 0,\ f_4'(I) > 0 \quad \forall \quad I > 0,\ f_4(I) \to d \text{ as } I \to 0,$$

where $d > 0$ is constant, and $f_4(I) \to e$ as $I \to \infty$

where $e > 0$ is constant;

$$f_5(I) > 0 \quad \forall \quad I > 0,\ f_5'(I) < 0 \quad \forall \quad I > 0,\ f_5(0) > 0 \text{ and } f_5(I) \to 0 \text{ as } I \to \infty.$$

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