Global Stability and Periodicity in a Glucose-Insulin Regulation Model with a Single Delay

M. Angelova\textsuperscript{1}, G. Beliakov\textsuperscript{1}, A. Ivanov\textsuperscript{2}, and S. Shelyag\textsuperscript{1}
\textsuperscript{1} School of Information Technology, Deakin University Geelong, Australia
\textsuperscript{2} Department of Mathematics, Pennsylvania State University, USA

Abstract

A two-dimensional system of differential equations with delay modelling the glucose-insulin interaction processes in the human body is considered. Sufficient conditions are derived for the unique positive equilibrium in the system to be globally asymptotically stable. They are given in terms of the global attractivity of the fixed point in a limiting interval map. The existence of slowly oscillating periodic solutions is shown in the case when the equilibrium is unstable. The mathematical results are supported by extensive numerical simulations. It is shown that typical behaviour in the system is the convergence to either a stable periodic solution or to the unique stable equilibrium. The coexistence of several periodic solutions together with the stable equilibrium is demonstrated as a possibility.

Keywords: delay differential equations, limiting interval maps, stability analysis, diabetes.

1 Introduction

In this paper we consider a two-dimensional system of differential equations with one time delay which was proposed as a relatively simple mathematical model of the glucose-insulin interaction in the human body \cite{2}. Only a limited number of parameters of the physiologically closed glucose-insulin interaction system are accessible for direct measurements. Therefore, mathematical modelling is required to facilitate the estimation of the narrow physiological range of the glucose-insulin system components \cite{33}. The physiological time delay plays an important part in the regulation and the feedback of the system and determines the important properties of the mathematical description of the model.

The glucose-insulin regulatory system is a key component in the metabolism of the human body. The pancreas and the liver regulate the production of insulin and glucose respectively in order to maintain normal level of the blood glucose. Failure to do this
can result in high blood sugar and diabetes which is related to many other long term health problems. Within this regulation, both rapid (period $\sim 6 - 15$ mins) and ultradian (period $\sim 80 - 180$ mins) oscillations of insulin have been observed [28], along with glucose oscillations (period $\sim 80 - 150$ mins) [29]. The ultradian oscillations were first discovered by Hansen [12] and observed during fasting, meal ingestion, continuous enteral nutrition and constant glucose infusion.

Due to the monotone nature of the nonlinearities involved it is a natural conjecture that some degree of the simplicity in the dynamical behaviour of the solutions should be observed in the model. Such simpler dynamics would be consistent with known behaviours in scalar differential delay equations with monotone nonlinear feedback [25, 26].

The aim of the paper is to justify, both analytically and numerically, that typical behaviour in our system is either the convergence to the unique equilibrium, or the convergence to a stable periodic solution, and better understand the behaviour of the physiological system.

The approach we propose to analyse the system is through a limiting one-dimensional map, which is formally obtained from the original differential delay system when the delay goes to infinity. The resulting interval map is relatively simple: it is given by a monotone decreasing function and can only have a unique fixed point and cycles of period two (which can be either attracting, or repelling, or a combination of the two possibilities).

The dynamics of the limiting interval map largely determine the dynamics of our two-dimensional differential delay system. When the only fixed point of the interval map is globally attracting then the corresponding unique steady state of the delay system is also globally asymptotically stable (for an arbitrary delay $\tau > 0$). However, when the only fixed point of the interval map is repelling the dynamics in the differential delay system are varied and dependent on the delay $\tau$. When the delay is small enough, $0 \leq \tau < \tau_0$ for some $\tau_0 > 0$, the unique equilibrium of the differential delay system is locally asymptotically stable. Note that only the local stability of the equilibrium can be claimed, as examples are possible that the delay system has stable periodic solutions away from the stable constant equilibrium (see an example in Section 4). When the delay becomes large enough, $\tau > \tau_1$ for some $\tau_1 > 0$, then the differential delay system has a slowly oscillating periodic solution. In this case the corresponding characteristic equation of the linearised system about the steady state has a leading pair of complex conjugate solutions $\alpha_0 \pm \beta_0 i$ with the positive real part $\alpha_0 > 0$ and the imaginary part within the interval $\beta_0 \in (0, \pi/\tau)$. This leading eigenvalue makes the slow oscillation in the system typical, in agreement with known results for the case of similar scalar differential delay equations [26, 32].

It is important to note that from the mathematical point of view there is no uniqueness in the model for the stable periodic solution or for the global asymptotic stability of the unique equilibrium. We construct explicit examples of our two-dimensional differential delay system when the coexistence of two stable periodic solutions is observed (Section 4). We also demonstrate the possibility when a stable periodic solution coexists together with the locally stable equilibrium (Section 4). The examples are easily generalised to the case when any finite number of stable periodic solutions can coexist with or without
the locally attracting equilibrium. This multi-stability phenomenon implies the utmost importance of the proper choices of the nonlinearities when the differential delay system is suggested as an actual model of a particular applied problem. For some of such known and available in the literature models we numerically observe the uniqueness of the stable periodic solution and its global attractivity within the admissible set of initial conditions.

The novelty of our approach is that we derive a simple one-dimensional dynamical system (interval map) and use it to determine the global dynamical properties of our dynamical system with delay. The typical dynamical behaviour in our model is also simple - it is the convergence to either a stable periodic solution or to the unique stable equilibrium, or a combination of such behaviours.

The paper is organised as follows. Section 2 describes the foundations of the mathematical problem. In Section 3, we derive the main analytical results, which are then numerically confirmed in Section 4. A concluding summary and a brief discussion are given in Section 5.

2 Preliminaries

2.1 Differential Delay Model and Assumptions

Consider the system of differential equations with delay [2],

\[
\begin{align*}
I'(t) &= f_1(G(t)) - \frac{1}{\tau_0} I(t) \\
G'(t) &= G_{in} - f_2(G(t)) - qG(t)f_4(I(t)) + f_5(I(t - \tau)),
\end{align*}
\]

where \( I \) and \( G \) represent the relative concentrations of insulin and glucose, respectively, \( 1/\tau_0 \) is the insulin degradation rate, \( G_{in} \) is the external glucose input. The function \( f_1 \) corresponds to pancreatic insulin production, dependent on glucose concentration, and \( f_2 \) is the glucose consumption by the brain. The third term in the second equation represents the insulin-dependent glucose utilisation in the muscles, while the last term, \( f_5 \), represents the hepatic glucose production. \( \tau \) is the time delay between plasma insulin production and its effect on hepatic glucose production.

The system is considered under the following assumptions:

(H1) Functions \( f_1(u), f_2(u), f_3(u), f_5(u) \) are non-negative and continuously differentiable for \( u \geq 0 \), with \( f_3 \) defined as \( f_3(u) = qu \) for convenience. Real parameters \( \tau_0, G_{in}, q, \tau \) are all positive;

(H2) \( f_1(u) > 0, f_1'(u) > 0, \forall u > 0, f_1(0) = a_0 > 0 \) and \( \lim_{u \to \infty} f_1(u) = a > 0 \);

(H3) \( f_2(u) > 0, f_2'(u) > 0, \forall u > 0, f_2(0) = 0 \) and \( \lim_{u \to \infty} f_2(u) = b > 0 \);

(H4) \( f_4(u) > 0, f_4'(u) > 0, \forall u > 0, f_4(0) = d > 0 \) and \( \lim_{u \to \infty} f_4(u) = e > 0 \);

(H5) \( f_5(u) > 0, f_5'(u) < 0, \forall u > 0, f_5(0) = h > 0 \) and \( \lim_{u \to \infty} f_5(u) = 0 \).
The assumptions (H1)-(H5) are derived from and justified by the physiological mechanisms of the glucose-insulin interaction in the human body, see e.g. papers [2, 3, 22, 23] for additional details.

The phase space of system (\( \mathbf{I} \)) is defined as \( \mathbb{X} = C([-\tau, 0], \mathbb{R}_+) \times \mathbb{R}_+ \). For arbitrary initial function \( \psi = (\varphi(s), u) \in \mathbb{X} \) the corresponding solution \( x = x(t, \psi) = (I(t), G(t)) \) to system (\( \mathbf{I} \)) can be constructed by the standard step methods [8, 11]. Such solution exists for all \( t \geq 0 \) provided the nonlinearities \( f_1, f_2 \) and \( f_4 \) satisfy a uniform Lipschitz condition on \( \mathbb{R}_+ \), \( |f_k(u) - f_k(v)| \leq L|u - v| \) for all \( u, v \in \mathbb{R}_+ \) and some \( L < \infty, k = 1, 2, 4 \). The latter is the case when their derivatives \( f'_1 \) and \( f'_2 \) are uniformly bounded from above on \( \mathbb{R}_+ \), which we shall be assuming to hold throughout the paper.

It is an easy observation that positive initial data for system (\( \mathbf{I} \)) result in solutions that are positive for all \( t \geq 0 \) (see e.g. [2]). More precisely, if the initial function \( \psi = (\varphi(s), u), s \in [-\tau, 0], \) is such that \( u > 0, \varphi(s) \geq 0 \forall s \in [-\tau, 0] \) and \( \varphi(0) > 0 \) then \( T(t) > 0 \) and \( G(t) > 0 \) holds for all \( t \geq 0 \). It can also be shown that both components \( I \) and \( G \) of all solutions to system (\( \mathbf{I} \)) are bounded above and bounded away from zero. Moreover, a stronger property called the persistence can be established here. It says that positive constants \( m_I, m_G \) and \( M_I, M_G \) can be identified independent of initial functions such that for an arbitrary initial function \( \psi \in \mathbb{X} \) and the corresponding solution \( x(t, \psi) = (I(t), G(t)) \) to system (\( \mathbf{I} \)) there exists a time moment \( T = T(\psi) \) such that the following holds

\[
0 < m_I \leq I(t) \leq M_I < \infty, \quad 0 < m_G \leq G(t) \leq M_G < \infty, \quad \text{for all} \quad t \geq T. \tag{2}
\]

These and other basic properties of the solutions are proved in [2] as Propositions 2.1, 2.2, and 2.4. We will revisit them later in the paper from a different point of view.

### 2.2 Translation to Zero Equilibrium

It was demonstrated in [3] that under the assumptions (H1)-(H5) the system (\( \mathbf{I} \)) has unique equilibrium \( (I_*, G_*) \), \( I_* > 0, G_* > 0 \), where \( I_* = \tau_0 f_1(G_*) \) and \( G_* \) is a unique positive solution of the nonlinear equation \( f_2(G) + qGf_4(\tau_0 f_1(G)) = G_m + f_5(\tau_0 f_1(G)) \).

As a matter of convenience, for various theoretical considerations and computational tasks of this paper it is advantageous to have this equilibrium shifted to the zero equilibrium state \( (I_*, G_*) = (0, 0) \). One of the reasons for this need is that the equilibrium \( (I_*, G_*) \) depends on all the parameters and functions involved in system (\( \mathbf{I} \)). Such shift is achieved by the change of the dependent variables by

\[
x(t) = I(t) - I_*, \quad y(t) = G(t) - G_*.
\tag{3}
\]

System (\( \mathbf{I} \)) is then transformed into the following one:

\[
x'(t) = F_1(y(t)) - \frac{1}{\tau_0} x(t)
\tag{4}
\]

\[
y'(t) = -F_2(y(t)) - q f_4(I_* + x(t)) y(t) - q G_* F_4(x(t)) + F_5(x(t - \tau)).
\]
where $F_1(y) = f_1(y + G_s) - f_1(G_s)$, $F_2(y) = f_2(y + G_s) - f_2(G_s)$, $F_4(x) = f_4(x + I_s) - f_4(I_s)$, $F_5(x) = f_5(x + I_s) - f_5(I_s)$.

Functions $F_1, F_2, F_4$ are strictly monotone increasing and satisfying the positive feedback condition $y \cdot F_i(y) > 0$ for $y \neq 0, i = 1, 2, 4$. Function $F_5(x)$ is strictly decreasing and satisfying the negative feedback assumption $x \cdot F_5(x) < 0$ for $x \neq 0$. System (11) has the unique zero equilibrium $(x, y) = (0, 0)$.

We will perform most of our numerical simulations for systems of type (1). By using appropriate inverse transformations such systems can always be represented in the form of the original system (1).

### 2.3 Linearization and Characteristic Equation

In this subsection we present well-known facts about the unique positive equilibrium of system (1), the linearized system about the equilibrium, and the characteristic equation of the linear system. More related details can be found in papers [3] and [22].

Equilibria of differential delay system (1) are found by solving the nonlinear system

$$ I = \tau_0 f_1(G), \quad f_2(G) + qG f_4(I) = G_m + f_5(I), \quad (5) $$

which reduces to a single scalar equation for $G$: $f_2(G) + qG f_4(\tau_0 f_1(G)) = G_m + f_5(\tau_0 f_1(G))$. It is straightforward to see that the latter has a unique positive solution $G_s > 0$, implying that the original system (1) has a unique equilibrium $(I_s, G_s)$ where $I_s = \tau_0 f_1(G_s)$.

The linearized system about the positive equilibrium $(I_s, G_s)$ has the form

$$ u'(t) = -\frac{1}{\tau_0} u(t) + f_1'(G_s) v(t) $$

$$ v'(t) = -[f_2'(G_s) + qf_4(I_s)] v(t) - qG_s f_4'(I_s) u(t) + f_5'(I_s) u(t - \tau). \quad (6) $$

Note that system (6) is also the linearization of the translated system (1). The characteristic equation of the linear system (6) has the form

$$ (\lambda + \mu_1)(\lambda + \mu_2) + b + a \exp\{-\tau \lambda\} = 0, \quad (7) $$

where $\mu_1 = 1/\tau_0$, $\mu_2 = f_2'(G_s) + qf_4(I_s)$, $b = qG_s f_4'(I_s)f_5'(I_s)$, $a = -f_4'(G_s)f_5'(I_s)$. Since $f_1'(G_s) > 0$, $f_2'(G_s) > 0$, $f_4'(I_s) > 0$ and $f_5'(I_s) < 0$ then $\mu_1 > 0, \mu_2 > 0, b > 0, a > 0$.

The form (7) of the characteristic equation allows us to use known facts about its properties derived elsewhere, see e.g. [1, 3, 22]. The stability/instability of the zero solution of system (6) is determined by the location of the solutions of the characteristic equation (7) in the complex space. If all solutions of the characteristic equation have negative real parts (or are negative themselves) then the zero solution of (6) is asymptotically stable. If there exists a pure imaginary solution of (7) then the zero solution of (6) is unstable. If the characteristic equation (7) has a complex conjugate solution $\lambda = \alpha + i \beta$ with the positive real part $\alpha > 0$ then the zero solution of (6) is unstable. In the latter case there exists the so-called leading pair of complex conjugate solutions $\lambda = \alpha_0 \pm i \beta_0$ of the characteristic equation (7), where $0 < \beta_0 < \pi/\tau$ and $\alpha_0 > 0$. The leading means that $\alpha_0 > 0$ is the largest real part among all solutions of (7). All other complex conjugate solutions $\lambda = \alpha_k \pm i \beta_k, k \in \mathbb{N}$, of (7) satisfy $\alpha_0 > \alpha_1 > \alpha_2 > \ldots$ and $\beta_k \in [2k\pi/\tau, (2k+1)\pi/\tau]$. See Lemma 1 of [1] and Lemma 3 of [6] for more details and proofs.
2.4 Related Interval Maps

In this subsection we recall some basic notions and definitions on interval maps related to the needs of this paper. Comprehensive expositions on the theory of one-dimensional maps can be found in monographs [7, 30].

Given a continuous map \( F : L \to L \) of a closed interval \( L \subseteq \mathbb{R} \) into itself a forward trajectory through an initial point \( x_0 \) is defined as the set \( \{ F^n(x_0), n \in \mathbb{N}_0 \} \) where \( F^n = F \circ F \circ \cdots \circ F \) is the \( n \)-th iteration of \( F \) (\( F^0(x) := x \)). A set \( J \subseteq L \) will be called invariant under \( F \) if \( F(J) \subseteq J \). Note that a proper inclusion is allowed under this definition.

**Definition 2.1.** (i) A fixed point \( x = x^* \) of a continuous map \( F \) of an interval \( L \subseteq \mathbb{R} \) into itself is called attracting if there exists an open interval \( J \subseteq L \) such that \( x^* \in J \), \( F(J) \subseteq J \), and for every point \( x \in J \) one has that \( \lim_{n \to \infty} F^n(x) = x^* \) holds.

(ii) The largest connected interval \( J \subseteq L \) with this property is called the domain of immediate attraction of the fixed point \( x^* \). (iii) A point \( x_0 \) is called period with period \( m \) if \( F^m(x_0) = x_0 \) and \( F^k(x_0) \neq x_0 \) for every \( 1 \leq k \leq m - 1 \). The corresponding set \( \{ x_0, x_1, \ldots, x_{m-1} \} := C_m \) is called a cycle of period \( m \).

Clearly that every point of the cycle \( x_k \in C_m \) is periodic of period \( m \) for the map \( F \); it is also a fixed point for the map \( F^m \).

The following statement is a well-known simple fact in the theory of interval maps. Its proof easily follows from related facts of Section 2.4 in [30].

**Proposition 2.2.** For an arbitrary point \( x \in J \) in the domain of immediate attraction of the fixed point \( x^* \) there always exists a closed finite interval \( L_0 = L_0(x) \subseteq J \) such that \( x \in L_0 \), \( F(L_0) \subseteq L_0 \), and \( \bigcap_{n \geq 0} F^n(L_0) = x^* \).

**Definition 2.3.** Let \( x^* \) be an attracting fixed point of a continuous map \( F \). An infinite set of intervals \( \{ L_n, n \in \mathbb{N}_0 \} \) will be called a squeezing sequence of imbedded intervals if the following holds:

\[
L_{k+1} \subseteq L_k, F(L_k) \subseteq L_{k+1}, \text{ and } \bigcap_{k \geq 0} L_k = x^*.
\]

It is evident that the sequence of intervals \( L_k = F^k(L_0), n \in \mathbb{N}_0 \), in Proposition 2.2 is a squeezing imbedded sequence. Given an initial point \( x_0 \) in the domain of immediate attracting it is also clear that a squeezing imbedded sequence of intervals containing its iterations always exists but is not uniquely defined in general.

3 Main Results

3.1 Limiting Interval Map

In this sub-section we derive a limiting interval map for the differential delay system (1) as \( \tau \to \infty \). First we transform system (1) to one with the normalised delay \( \tau = 1 \) by
rescaling the independent variable by \( t = \tau \cdot s \). It is a straightforward calculation then that reduces system \((11)\) to the following form

\[
\frac{1}{\tau} I'(s) = f_1(G(s)) - \frac{1}{\tau_0} I(s) \quad (8)
\]

\[
\frac{1}{\tau} G'(s) = G_{in} - f_2(G(s)) - q G(s)f_4(I(s)) + f_5(I(s - 1)).
\]

By taking the limit as \( \tau \to \infty \) the latter becomes a system of functional difference equations:

\[
I(s) = \tau_0 f_1(G(s)), \quad f_2(G(s)) + q G(s)f_4(I(s)) = G_{in} + f_5(I(s - 1)), \quad (9)
\]

which in turn is further reduced to a single scalar difference equation for the variable \( G \):

\[
f_2(G(s)) + q G(s)f_4(\tau_0 f_1(G(s))) = G_{in} + f_5(\tau_0 f_1(G(s - 1))). \quad (10)
\]

It is easy to see, based on the assumptions \((H1)-(H5)\), that the function \( F \) in the left hand side of equation \((10)\), \( F(G) := f_2(G) + q G f_4(\tau_0 f_1(G)) \), satisfies:

\[
F(0) = 0, F'(G) > 0, \ \forall G \geq 0, \ \text{and} \ \lim_{G \to \infty} F(G) = \infty. \quad (11)
\]

Likewise, the function \( H \) in the right hand side of equation \((10)\), \( H(G) := G_{in} + f_5(\tau_0 f_1(G)) \), satisfies:

\[
H(0) = H_0 > 0, H'(G) < 0, \ \forall G \geq 0, \ \text{and} \ \lim_{G \to \infty} H(G) = H_{\infty} > 0. \quad (12)
\]

Therefore, the inverse function \( F^{-1} \) exists, and equation \((10)\) can be explicitly solved for \( G(s) \) as follows:

\[
G(s) = F^{-1}(H(G(s - 1))) =: \Phi(G(s - 1)), \quad (13)
\]

where the composite function \( \Phi = F^{-1} \circ H \) is defined and continuous on \( \mathbb{R}_+ = \{ G \mid G \geq 0 \} \).

Besides, due to assumptions \((H1)-(H5)\), function \( \Phi(\cdot) \) is continuously differentiable on \( \mathbb{R}_+ \) with

\[
\Phi'(u) < 0 \ \forall u \in \mathbb{R}_+ \ \text{and} \ \lim_{u \to 0} \Phi(u) = \Phi_0 > 0, \ \lim_{u \to \infty} \Phi(u) = \Phi_\infty > 0. \quad (14)
\]

The values \( \Phi_0, \Phi_\infty \) are easily calculated as:

\[
\Phi_0 = F^{-1}(G_{in} + f_5(\tau_0 a_0)), \quad \Phi_\infty = F^{-1}(G_{in} + f_5(\tau_0 a)). \quad (15)
\]

The asymptotic properties of solutions of equation \((13)\) are completely determined by the dynamical properties of the iterations of the interval map \( \Phi \). A comprehensive theory of such equations is given in the monograph \([31]\). All relevant properties on interval maps can be found in monographs \([7, 30]\).

A convenient look at system \((9)\) and equation \((13)\) is via difference equation notations. By denoting \( G(t) := G_n, I(t) := I_n, I(t - 1) := I_{n-1}, n \in \mathbb{N} \) system \((9)\) is rewritten as

\[
f_2(G_n) + q G_n f_4(I_n) = G_{in} + f_5(I_{n-1}), \quad I_n = \tau_0 f_1(G_n).
\]

The difference equation \((13)\) is represented then as \( G_n = \Phi(G_{n-1}), n \in \mathbb{N} \).
3.2 Principal Results

Based on property (14) we can build a sequence of imbedded intervals for map Φ as follows. Set $L_0 := \mathbb{R}_+$ and $L_1 := \Phi(L_0) = \Phi(\mathbb{R}) = [\Phi_\infty, \Phi_0] \subset L_0$. Proceed then recursively as $L_2 = \Phi(L_1) \subset L_1, \ldots, L_{n+1} = \Phi(L_n) \subset L_n, n \in \mathbb{N}_0$. Define the limiting set $L_*$ by $L_* := \cap_{n \geq 0} L_n := [\alpha_*, \beta_*]$.

The set $L_*$ is either a single point or a closed interval with a non-empty interior. In the first case one has that $\alpha_* = \beta_* = G_*$. In the second case the endpoints $\{\alpha_*, \beta_*\}$ form a cycle of period two: $\alpha_* = \Phi(\beta_*), \beta_* = \Phi(\alpha_*), \Phi(L_*) = L_*, G_* \in int(L_*)$.

The sequence $\{L_n\}$ of imbedded interval for the component $G$ generates the sequence of imbedded intervals $\{J_n\}$ for the component $I$ through the first difference equation of system (12) by $J_n := \tau_0 f_1(L_n), n \in \mathbb{N}_0$.

We shall formally distinguish the following subcases for the set $L_*$ and its structure:

(A1) The set $L_*$ is a single point $G_*$. It is the only fixed point of the interval map $\Phi$ which is then globally attracting on $\mathbb{R}_+$: for every initial point $G_0 \in \mathbb{R}_+$ one has $\lim_{n \to \infty} \Phi^n(G_0) = G*$;

(A2) The set $L_*$ is a closed non-empty interval $[\alpha_*, \beta_*], \alpha_* \neq \beta_*$. Then $\Phi(L_*) = L_*$, and $\{\alpha_*, \beta_*\}$ is a cycle of period two, $\alpha_* = \Phi(\beta_*), \beta_* = \Phi(\alpha_*)$, with $G_* \in int(L_*)$. Assume also that the two-cycle is globally attracting: for every initial point $G_0 \in \mathbb{R}_+, G_0 \neq G_*$, its forward iterations converge to the cycle: $\Phi^n(G_0) \to \{\alpha_*, \beta_*\}$ as $n \to \infty$. In addition, it is assumed that the generic condition $\Phi'(G_*) < -1$ holds;

(A3) The set $L_*$ is an interval formed by a cycle $\{\alpha_*, \beta_*\}$ of period two which is locally attracting only. In addition, it is assumed that the condition $\Phi'(G_*) < -1$ holds;

(A4) The set $L_*$ is an interval formed by a cycle $\{\alpha_*, \beta_*\}$ of period two. In addition, the fixed point $G_*$ is locally attracting: there exists an interval $(\gamma_*, \delta_*)$ such that for every initial point $G_0 \in (\gamma_*, \delta_*)$ one has $\lim_{n \to \infty} \Phi^n(G_0) = G*$;

Below we state the principal results of this paper which are essentially dependent and built based on the structure of the limiting sets of the map $\Phi$ as described above by properties (A1) – (A4).

Theorem 3.1. Suppose that in addition to $(H_1) – (H_5)$ assumption (A1) holds. Then for every delay $\tau > 0$ the unique equilibrium $(I_*, G_*)$ of system (14) is globally asymptotically stable: for an arbitrary initial data $\psi = (\varphi, u) \in \mathbb{X}$ the corresponding solution $(I(t), G(t))$ satisfies: $\lim_{t \to \infty} G(t) = G_*, \lim_{t \to \infty} I(t) = I_*$.

Theorem 3.1 is a strong delay independent result about the global asymptotic stability of the unique equilibrium $(I_*, G_*)$ of system (14) with infinite-dimensional phase space based on the global attractivity of the corresponding fixed point in a simple limiting interval map defined by the real-valued function $\Phi$. Theorem 3.1 is proved in subsection 3.3 (as Theorem 3.3).
Theorem 3.2. Suppose that in addition to \((H_1) - (H_5)\) assumption \((A_2)\) holds. Then there exists \(\tau_0 > 0\) such that for every delay \(\tau > \tau_0\) system (1) has a slowly oscillating periodic solution.

The slow oscillation of solutions here means that both components \(I(t)\) and \(G(t)\) are slowly oscillating functions about their respective equilibrium values \(I_\ast\) and \(G_\ast\). Therefore, \(I(t) - I_\ast\) and \(G(t) - G_\ast\) are slowly oscillating functions with their successive zeros separated by a time span larger than the delay \(\tau\). For more complete definitions and statements see details in Subsection 3.4.

Under assumption \((A_2)\) the cycle \(\{\alpha_\ast, \beta_\ast\}\) is globally attracting on \(\mathbb{R}_+\): for every initial value \(G_0 \in \mathbb{R}_+, G_0 \neq G_\ast\), the sequence of its iterations \(\Phi^n(G_0)\) is attracted by the cycle as \(n \to \infty\). This means that both sequences \(\Phi^{2n}(G_0)\) and \(\Phi^{2n+1}(G_0), n \in \mathbb{N}_0\), are monotone and converge to either \(\alpha_\ast\) or \(\beta_\ast\) (depending on the location of \(G_0\) in relation to the fixed point \(G_\ast\)). To show the existence of a slowly oscillating periodic solution to system (1) we use the standard and well developed techniques of the evjective fixed point theory [8, 11]. To that end the main points we have to show holding true for system (1) are:

(i) Construction of a cone of initial data for system (1) and a non-linear map which maps the cone into itself. The map usually is an appropriately defined shift operator along the solutions;

(ii) Existence of a leading eigenvalue to the characteristic equation (7) with the largest positive real part and the imaginary part within the range \((0, \pi/\tau)\);

(iii) The compactness of the shift operator along solutions of the system starting on the cone.

The outline of the proof of the existence of periodic solutions is given in Subsection 3.4.

Note that in general the evjective fixed point techniques do not address the issue of the uniqueness of the slowly oscillating periodic solution. The existence of periodic solutions can only be proved; the periodic solutions can be non-unique in many cases. This is true for all the classes of delay equations and systems to which they were applied, including our system (1). However, the uniqueness of the globally attracting cycle \(\{\alpha_\ast, \beta_\ast\}\) of period two for the one dimensional map \(\Phi\) seems to yield the uniqueness of a stable slowly oscillating periodic solution to system (1). This fact can only be verified numerically. We have done it for two classes of the nonlinearities \(f_i, i = 1, 2, 4, 5\), used in applications: Hill type functions [14] and exponential functions [23].

Theorem 3.3. Suppose that in addition to \((H_1) - (H_5)\) assumption \((A_3)\) holds. Then there exist multiple choices of the nonlinearities \(f_1, f_2, f_4, f_5\) and of the parameter values \(\tau_0, \tau, q\) such that system (1) possesses at least two slowly oscillating periodic solutions.

The key assumption in \((A_3)\) is that the two-cycle is locally attracting only; therefore, there exists another cycle of period two. Since \(\Phi'(G_\ast) < -1\) the fixed point \(G_\ast\) is repelling. Hence, there exists the minimal cycle of period two, \(\{\gamma_\ast, \delta_\ast\}\), such that the open interval \((\gamma_\ast, \delta_\ast) \ni G_\ast\) is attracted to it. In addition, the inequalities \(\alpha_\ast < \gamma_\ast < G_\ast < \delta_\ast < \beta_\ast\)
functions in the set $X_\tau$. Suppose that map $\Phi$ has a closed finite interval $I_s$. Invariance, Persistence, and Global Asymptotic Stability

Theorem 3.4. Suppose that in addition to $(H_1) - (H_5)$ assumption $(A_4)$ holds. Then there exist multiple choices of the nonlinearities $f_1, f_2, f_4, f_5$ and of the parameter values $\tau_0, \tau, q$ such that system (4) possesses both a slowly oscillating periodic solution and the locally attracting equilibrium $(I_s, G_s)$.

The principal difference between Theorem 3.4 and Theorem 3.3 is that the fixed point $G_s$ is attracting for the map $\Phi$ in the latter (while it was repelling for the former). Therefore, its minimal two-cycle $\{\gamma_s, \delta_s\}$ is one-sided repelling with the interval $(\gamma_s, \delta_s)$ being the domain of immediate attraction of the fixed point $G_s$. This fact makes the equilibrium $(G_s, I_s)$ locally attracting for the system (4). Outside the interval $(\gamma_s, \delta_s)$ the structure of the map $\Phi$ can largely be preserved to be the same as in Theorem 3.3. This would guarantee the existence of a slowly oscillating periodic solution associated with the two-cycle $\{\alpha_s, \beta_s\}$. As in the case of Theorem 3.3 the example can be easily generalized to produce any finite number of slowly oscillating periodic solutions to system (4).

3.3 Invariance, Persistence, and Global Asymptotic Stability

Suppose that map $\Phi$ has a closed finite interval $L = [a, b]$ invariant in the general sense $\Phi(L) \subseteq L \subseteq \mathbb{R}_+$, and let interval $J$ be defined by $J = \tau_0 f_1(L) := [c, d]$. Consider the following subset $X_L$ of the phase space $X$:

$$ X_L = \{ \psi = (\varphi, u) \in X \mid u \in L, \varphi(s) \in J \forall s \in [-\tau, 0] \}. $$

It is easily seen, based of the properties of functions $F^{-1}$ and $H$, that the map $\Phi$ has an invariant interval $L$ such that for an arbitrary initial value $u_0 \in \mathbb{R}_+$ its first iteration under $\Phi$, $u_1 = \Phi(u_0)$ satisfies $u_1 \in L$. Indeed, the interval $L$ can be defined as $L = [F^{-1}(H_\infty), F^{-1}(H_0)]$, where the finite interval $[H_0, H_\infty]$ is the image of the positive semi-axis $\mathbb{R}_+$ under the map $H$. The values of $H_\infty$ and $H_0$ are given as $H_0 = G_{in} + f_5(\tau_0 a_0)$, $H_\infty = G_{in} + f_5(\tau_0 a)$. The corresponding interval $J$ is then defined as $J := \tau_0 f_1(L) = [\tau_0 f_1(F^{-1}(H_\infty)), \tau_0 f_1(F^{-1}(H_0))]$.

The following statement describes the fact that the solutions of system (4) with initial functions in the set $X_L$ remain within this set for all forward times $t \geq 0$. 


Lemma 3.5. (Invariance) Suppose that an initial function \( \psi = (\varphi(s), u_0) \) is such that \( \phi \in \mathcal{X}_L \), where \( L \) is a closed interval invariant under map \( \Phi \). Then the corresponding solution \( x = x(t, \psi) = (I(t), G(t)) \) of system (1) satisfies \( x(t) \in \mathcal{X}_L \) for all \( t \geq 0 \).

Lemma 3.5 shows that when the initial data for system (1) is such that \( G(0) \in L \) and \( I(s) \in J \ \forall s \in [-\tau, 0] \), then the components \( G \) and \( I \) of the corresponding solution to system (1) satisfy the inclusions:

\[ G(t) \in L, \ I(t) \in J \quad \text{for all} \quad t \geq 0. \]

Proof. The proof of Lemma 3.5 can be done by induction in time \( t \) by using the cyclic structure of system (1). We provide its outline below.

Suppose that the initial function \( \psi = (\varphi(s), u_0) \in \mathcal{X} \) for system (1) is given such that \( \phi(s) = I(s) \in J \ \forall s \in [-\tau, 0] \) and \( G(0) = u_0 \in L \). Assume first that \( G(t) \in L \ \forall t \in [0, T] \) for some \( T > 0 \). Then also \( I(t) \in J \ \forall t \in [0, T] \) is satisfied. Indeed, suppose \( t_0 \geq 0 \) is the first time moment of exit of the component \( I \) from the interval \( J \). To be definite assume first that \( I(t_0) = c \) and \( I'(t_0) < 0 \) and \( I(t) < c \ \forall t \in (t_0, t_0 + \epsilon) \) for some \( \epsilon > 0 \). Then \( \tau_0f_1(G(t_0)) \in J = [c, d] \) since \( G(t_0) \in L = [a, b] \). Therefore, \( \tau_0I'(t_0) = -c + \tau_0f_1(G(t_0)) \geq 0 \), a contradiction with \( I'(t_0) < 0 \).

In the case when \( I(t_0) = c \) and \( I'(t_0) = 0 \) there exists a sequence \( \{t_n\} \) of \( t \)-values such that \( t_n \downarrow t_0 \) and \( I'(t_n) < 0, I(t_n) < c \). This would imply that the derivative \( I'(t_n) = (1/\tau_0)[-I(t_n) + \tau_0f_1(G(t_n))] \geq 0 \) is positive in a small right neighborhood of \( t_0 \), a contradiction with \( I'(t_0) < 0 \).

Given \( I(s) = \varphi(s) \in J, \ \forall s \in [-\tau, 0] \) and \( G(0) = u_0 \in L \) we shall show next that \( G(t) \in L \ \forall t \in [0, \tau] \). This is done in a way similar to the reasoning for the component \( I \) above. Assume \( t_0 \in [0, \tau] \) is the first point of exit of the component \( G \) from the interval \( L \). To be specific let \( G(t_0) = b \) and \( G'(t_0) > 0 \) holds. Using the monotone nature of functions \( f_2 \) and \( f_4 \) one sees that \( f_2(G(t_0)) + qG(t_0)f_4((I(t_0))) \leq f_2(b) + qbf_4(b) \). Therefore, \( G'(t_0) \leq G_{\text{in}} + f_2((I(t_0) - \tau)) - f_2(b) - qbf_4(b) \leq 0 \), a contradiction with \( G'(t_0) > 0 \). The case when \( G(t_0) = b, G'(t_0) = 0 \) holds at the first point of exit from interval \( L \) is treated similarly to the analogous case for \( I(t) \) by selecting a sequence \( t_n \downarrow t_0 \) with \( G(t_n) > b \) and \( G'(t_n) > 0 \).

The proof can now be completed by induction in \( t \) with a step \( \tau \). Since \( G(t) \in L \ \forall t \in [0, \tau] \) then also \( I(t) \in J \ \forall t \in [0, \tau] \). These values of \( G \) and \( I \) are considered next as new initial data for the same solution to derive the inclusions \( G(t) \in L, I(t) \in J, \ \forall t \in [\tau, 2\tau] \), and so on.

From the proof of Lemma 3.5 it is seen that for every initial data \( \psi = (\varphi(s), u_0) \in \mathcal{X} \) there exists a time moment \( t = t_\psi \) such that the corresponding solution \( x = x(t, \psi) = (I(t), G(t)) \) satisfies

\[ I(t) \in J_0 = \tau_0f_1(\mathbb{R}_+) \quad \text{and} \quad G(t) \in L_0 = \Phi(\mathbb{R}_+). \quad (16) \]

Indeed, if \( I(t_0) \in J_0 \) at some \( t_0 \geq 0 \) then \( I(t) \in J_0 \ \forall t \geq t_0 \), due to reasons in the first part of the proof of Lemma 3.5. Likewise, \( G(t) \in L_0 \ \forall t \geq t_0 \) if \( G(t_0) \in L_0 \) for
some $t_0 \geq 0$. Therefore, one has to consider the possibility that $I(t) \not\in J_0 \forall t \geq 0$ and $G(t) \not\in L_0 \forall t \geq 0$. To be specific assume that $I(t) > \sup J_0$ and $G(t) > \sup L_0$ for all $t \geq 0$ (other options are treated along the same line). Then the respective equations of system (I) imply that $I'(t) \leq 0$ and $G'(t) \leq 0$ for all $t \geq 0$. Therefore, the finite limits $\lim_{t \to \infty} I(t) = I_\infty$, $\lim_{t \to \infty} G(t) = G_\infty$ exist. By applying the limit to both equations of (I) along these components of the solution one sees that ($I_\infty, G_\infty$) satisfies the equilibrium equations:

$$f_1(G_\infty) = \frac{1}{\tau_0} I_\infty, \quad f_2(G_\infty) + qG_\infty f_4(G_\infty) = G_{in} + f_5(I_\infty).$$

Therefore, ($I_\infty, G_\infty$) is the only equilibrium of system (I), so that $I_\infty = I_*$ and $G_\infty = G_*$. This is a contradiction with the inequalities $I_\infty \geq \sup J_0$ and $G_\infty \geq \sup L_0$, since $I_*$ and $G_*$ belong to the interior of the intervals $J_0$ and $L_0$, respectively.

The reasoning above leads to the following

**Proposition 3.6. (Uniform Persistence I)** There are positive constants $0 < m_I < M_I$ and $0 < m_G < M_G$ such that for every initial data $\psi = (\varphi(s), u_0) \in X$ there is a time moment $t = t(\psi) \geq 0$ such that the corresponding solution $x = x(t, \psi) = (I(t), G(t))$ of system (I) satisfies

$$m_I \leq I(t) \leq M_I \quad \text{and} \quad m_G \leq G(t) \leq M_G \quad \forall t \geq t_\psi.$$

Indeed, as it is seen from the above reasoning the values of the constants can be chosen as

$$m_I := \inf\{\tau_0 f_1(\mathbb{R}_+)\}, \quad M_I := \sup\{\tau_0 f_1(\mathbb{R}_+)\}, \quad m_G := \inf\{\Phi(\mathbb{R}_+)\}, \quad M_G := \sup\{\Phi(\mathbb{R}_+)\}.$$

We can now apply an inductive argument to the chain of reasoning preceding Proposition 3.6. Since $I(t) \in J_0$ and $G(t) \in L_0 \forall t \geq t_0 \geq 0$ then $I(t) \in J_1 = \tau_0 f_1(J_0) \subseteq \tau_0 f_1(\mathbb{R}_+) = \tau_0 f_1(L_0)$ and $G(t) \in L_1 = \Phi(L_0) \forall t \geq t_1 \geq t_0$. This is shown exactly the same way as the inclusions (13). By the induction reasoning, there exists a sequence of t-values, $t_0 \leq t_1 \leq t_2 \leq \ldots \leq t_n \leq t_{n+1} \leq \ldots$, such that

$$I(t) \in \tau_0 f_1(L_n) := J_{n+1} \quad \text{and} \quad G(t) \in L_{n+1} := \Phi(L_n) \quad \forall t \geq t_{n+1} \geq t_n, \quad n \in \mathbb{N}_0. \quad (17)$$

The crucial role for the asymptotic behavior of solutions $x(t) = (I(t), G(t))$ is now played by the structure of the set $L_\ast = \cap_{n \geq 0} L_n$. Note that the imbedded sequence of intervals $L_0 \supseteq L_1 \supseteq L_2 \supseteq \ldots \supseteq L_n \supseteq L_{n+1} \supseteq \ldots$, and the limiting set $L_\ast$ were constructed in Subsection 3.2. The following two possibilities can only happen.

(I) The set $L_\ast = [\alpha_\ast, \beta_\ast]$ is a closed interval with non-empty interior. Then points $\alpha_\ast < \beta_\ast$ form a cycle of period two under the map $\Phi$. It is the maximal cycle of period two for the map $\Phi$ in the sense that any other cycle of period two belongs to the open interval $(\alpha_\ast, \beta_\ast)$. Also, the cycle $\{\alpha_\ast, \beta_\ast\}$ is at least one-sided attracting (from above). The latter means that for every initial value $G_0 \in (-\infty, \alpha_\ast)$ one has that $\Phi^{2n}(G_0)$ is an increasing sequence with $\lim_{n \to \infty} \Phi^{2n}(G_0) = \alpha_\ast$. Likewise, for every initial value $G_0 \in (\beta_\ast, \infty)$ the sequence $\Phi^{2n}(G_0)$ is decreasing with $\lim_{n \to \infty} \Phi^{2n}(G_0) = \beta_\ast$. Therefore, in this case, the persistence property of Proposition 3.6 can be essentially improved. Denote the interval $\tau_0 f_1([\alpha_\ast, \beta_\ast]) = [c_\ast, d_\ast]$. The following property holds:
Proposition 3.7. (Uniform Persistence II) For arbitrary initial data \( \psi = (\varphi(s), u_0) \in X \) the following holds for the corresponding solution \( x(t, \psi) = (I(t), G(t)) \)

\[
c_* \leq \liminf_{t \to \infty} I(t) \leq \limsup_{t \to \infty} I(t) \leq d_* \quad \text{and} \quad \alpha_* \leq \liminf_{t \to \infty} G(t) \leq \limsup_{t \to \infty} G(t) \leq \beta_*.
\]

The proof immediately follows from the property (17). In fact, more precise inequalities also hold under the assumptions of Proposition 3.7:

\[
c_* \leq I(t) \leq d_* \quad \text{and} \quad \alpha_* \leq G(t) \leq \beta_* \quad \forall \; t \geq t_* \geq 0.
\]

A proof of the latter requires certain preliminaries and details which cannot be included in the paper due to their length.

(II) The set \( L_* = [\alpha_*, \beta_*] \) is a single point. This implies that \( \alpha_* = \beta_* = G_* \), and that the fixed point \( G_* \) is globally attracting on \( \mathbb{R}_+ \) for the map \( \Phi \). In this case one has that the following global asymptotic stability property holds for system (1).

Theorem 3.8. (Global Asymptotic Stability, also Theorem 3.1) Suppose that the unique fixed point \( G_* \) of the interval map \( \Phi \) is globally attracting: \( \lim_{n \to \infty} \Phi^n(G) = G_* \) for every \( G \in \mathbb{R}_+ \). Then the unique constant solution \( (\tau_0 f_1(G_*), G_*) \) of system (1) is globally asymptotically stable: for arbitrary initial function \( \psi = (G(s), I_0) \in X \) and every delay \( \tau > 0 \) the following holds for the corresponding solution

\[
\lim_{t \to \infty} x(t) = \lim_{t \to \infty} (I(t), G(t)) = (\tau_0 f_1(G_*), G_*).
\]

Again, the proof immediately follows from inclusions (17).

Remark. Note that a uniform persistence property of all solutions of system (1) is also proved in [2], see Proposition 2.4 there. However, our uniform persistence results, given by Propositions 3.6 and 3.7, provide explicit lower and upper bounds for the components \( I \) and \( G \) in terms of one-dimensional map \( \Phi \) (therefore, in terms of functions \( f_1, f_2, f_4, f_5 \) and parameters \( \tau_0, q \)). In fact, the bounds given by Proposition 3.7 are best possible in certain circumstances, e.g. when \( \tau \to \infty \). They are given in terms of the maximum cycle of period two for the map \( \Phi \).

Paper [2] also contains a condition for the global convergence to equilibrium \( (I_*, G_*) \) of all solutions of system (1). It is given by Theorem 3.2 there, which requires that the following system for \( x \) and \( y \)

\[
G_m - f_2(x) - qx f_4(\tau_0 f_1(y)) + f_5(\tau_0 f_1(y)) = 0, \quad G_m - f_2(y) - qy f_4(\tau_0 f_1(x)) + f_5(\tau_0 f_1(x)) = 0
\]

has no solutions \( x > 0, y > 0 \). This is related to our more general and transparent condition of Theorem 3.8 which simply requires that the fixed point \( G_* \) of the map \( \Phi \) is globally attracting. If the later is satisfied then system (18) has no solutions \( x > 0, y > 0 \), since the existence of such a solution would mean that the pair \( x, y \) forms a cycle of period two for the map \( \Phi \), contradicting the global attractivity of its fixed point \( G_* \). In fact, it can be showed, with some additional effort, that under the assumptions imposed on system (1) the only fixed point \( G_* \) of map \( \Phi \) is globally attracting if and only if system (18) has no positive solutions.
### 3.4 Periodic Solutions

In this subsection we outline the algorithm how the existence of periodic solutions for system (1) can be derived. It follows the well established techniques of the ejective fixed point theory, see [8] and [11] for general theoretical basics; we also use some related specific details from papers [1, 6, 15, 16].

The basic components for the existence of periodic solutions are:

1. Construction of a cone of initial functions, and a translation operator on it (Poincare map), such that its fixed points give us slowly oscillating periodic solution. Some of these will have to be verified **numerically**;

2. The instability of the zero solution of the corresponding linearized system. This can be derived from the characteristic equation in terms of the existence of a pair of complex conjugate solutions with positive real part. Known results can be used here with proper harvesting and compilation, e.g. those in [1, 6];

3. The compactness of the nonlinear map constructed in step (1) above. This is rather straightforward derivation based of the boundedness and smoothness properties of the nonlinear functions $f_1, f_2, f_4, f_5$;

4. Application of known results for the existence of periodic solutions for similar systems to our case. In particular, application of the well established ejective fixed point theory to our case;

The proof of existence of periodic solutions to system (1) (or equivalent system (4)) uses well established theory of the ejective fixed point techniques applied to specially constructed maps on subsets of initial functions of the phase space. The subsets are usually cones of the initial functions generating the so-called slowly oscillating solutions, and the related maps are appropriately constructed shifts along corresponding solutions. The general theory of such approach is described in e.g. [8, 11]. In addition we shall use specific cases and results obtained in papers [1, 6, 15, 16].

**Definition 3.9.** (i) Given delay $\tau > 0$ a continuous function $u(t) : \mathbb{R}_+ \to \mathbb{R}$ is called slowly oscillating (with respect to zero) if the distance between any two of its zeros is greater than $\tau$;

(ii) A solution $(I(t), G(t))$ of system (1) is called slowly oscillating for $t \geq 0$ if each of the functions $G(t) - G_*$ and $I(t) - I_*$ is slowly oscillating (with respect to zero in the sense of part (i)).

In case when (ii) holds each of the components $G(t)$ and $I(t)$ is viewed as slowly oscillating function with respect to its constant component of the unique equilibrium $(G_*, I_*)$ of system (1).

We need a sufficient condition which guarantees the oscillatory nature of all solutions to system (1). We can use the corresponding result of paper [6], see Theorem 1 there.
Proposition 3.10. Suppose that nonlinearities $f_1, f_2, f_4, f_5$ are twice continuously differentiable on $\mathbb{R}$ and the characteristic equation (7) has no real solutions. Then all solutions to system (7) oscillate about the positive equilibrium $(I_*, G_*)$.

For the remainder of this subsection we shall assume that the conditions of Proposition 3.10 are satisfied.

**Cone.** Consider the following set of initial functions $K \subseteq X$:

$$K = \{ \psi = (\varphi(s), u) \in X \mid u - G_* \geq 0, \varphi(s) - I_* > 0, \text{ and } \varphi(s) \exp\{1/\tau_0 s\} \uparrow, s \in [-\tau, 0) \}.$$  

$K$ is a cone on $X$.

Proposition 3.11. Suppose that the characteristic equation (7) has no real solutions and the initial function $\psi = (\varphi(s), u) \in K$ is such that $\varphi(s) \geq I_*, \forall s \in [-\tau, 0], \varphi(0) > I_*, u > G_*$. Then the corresponding solution $(I(t), G(t))$ of system (7) is slowly oscillating in the sense that each component $I(t) - I_*$ and $G(t) - G_*$ is slowly oscillating. Moreover,

1. The component $I(t) - I_*$ has a sequence of zeros $\{t_k\}$ such that $0 < t_1 < t_2 < t_3 < \cdots < t_k < t_{k+1} < \cdots$ and $t_{k+1} - t_k > \tau$ for all $k \in \mathbb{N}$. In addition, $I(t) - I_* < 0$ for $t \in (t_{2k-1}, t_{2k-1})$ and $I(t) - I_* > 0$ for $t \in (t_{2k}, t_{2k+1}), k \in \mathbb{N}$;

2. The component $G(t) - G_*$ has a sequence of zeros $\{s_k\}$ such that $0 < s_1 < s_2 < s_3 < \cdots < s_k < s_{k+1} < \cdots$ and $s_{k+1} - s_k > \tau$ for all $k \in \mathbb{N}$. In addition, $G(t) - G_* < 0$ for $t \in (s_{2k-1}, s_{2k-1})$ and $G(t) - G_* > 0$ for $t \in (s_{2k}, s_{2k+1}), k \in \mathbb{N}$;

3. The two sequences of zeros for $I - I_*$ and $G - G_*$ satisfy the following relationship:

$$s_1 < t_1 < s_2 < t_2 < s_3 < t_3 < \cdots < s_k < t_k < s_{k+1} < t_{k+1} < \cdots$$

with $s_{k+1} - t_k > \tau$ for all $k \in \mathbb{N}$.

Main claims of Proposition 3.11 are proved along the lines of similar propositions for other classes of equations; see e.g. [10] for scalar equations, and [15, 16] for systems. We are still missing several details of a rigorous mathematical proof of this proposition; however, we have extensively verified it numerically for various choices of nonlinear functions $f_1, f_2, f_4, f_5$.

**Mapping on Cone.** Proposition 3.11 allows one to define a nonlinear map $F$ on the cone $K$ in the following way. Given initial function $\psi = (\phi(s), u) \in K$ consider the corresponding solution $x = (I(t), G(t)), t \geq 0$, to system (1). Given its second zero $s_2$ consider the first component $I(t)$ at time $s_2 + 1$ as an element $\phi_1(s)$ of the Banach space $C([-\tau, 0], \mathbb{R})$, i.e. $\phi_1(s) := I(s_2 + 1 + s), s \in [-\tau, 0]$. Then $\phi_1(s) > I_* \forall s \in (-\tau, 0]$ and $u_1 := G(s_2 + 1) > G_*$, due to Proposition 3.11. Therefore, the mapping

$$F : \psi = (\varphi(s), u) \mapsto (\varphi_1(s), u_1),$$

maps cone $K$ into itself. The mapping $F$ is well defined for any $\psi \in K$, different from the identical zero. For the trivial initial function $\psi \equiv (I_*, G_*)$ one defines $F((I_*, G_*)) := \psi_1 = (I_*, G_*)$, by the continuity of the map $F$. 

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It is an easy observation that a nontrivial fixed point $\psi_0$ of the map $F$, $F(\psi_0) = \psi_0$, gives rise to a slowly periodic solution of system (11). However, the map $F$ always has zero $\psi - (I_*, G_*) \equiv 0$ as the trivial fixed point (which results in the identical zero solution to system (11) for $\forall t \geq 0$). Therefore, one is interested in finding fixed points of map $F$ which are different from the trivial zero one. This is done by application of the well developed theory of the ejective fixed point theory, which has been applied to various classes of functional differential equations elsewhere.

**Compactness and Boundedness.** An important property required of map $F$ in the ejective fixed point theory is its compactness and boundedness. It is a well known basic fact that if a shift operator along solutions of retarded differential delay equations is compact [8, 11]. The boundedness of $F$ easily follows from the invariance property, Lemma 3.3. One sees that for arbitrary $\psi = (\varphi, u) \in K$ its first image under $F, \psi_1 = (\varphi_1(s), u_1)$ satisfies $\varphi_1(s) \in J_0$ and $u_1 \in L_0$ (where the intervals $J_0, L_0$ are defined earlier). Thus the set $F(K)$ is uniformly bounded from above and below. Alternatively, one can also start with a bounded convex part $K_0$ of cone $K$, requiring that elements $\phi_0 = (\varphi_0(s), u_0) \in K_0$ satisfy $\varphi_0(s) \in J_0 \ \forall s \in [-\tau, 0]$ and $u_0 \in L_0$.

**Ejectivity.** The ejectivity of map $F$ can be determined in terms of a linear operator calculated on specific eigenvalues of the linearized system (6) [8, 11]. It has a closed form in a general case [16]. In lower dimensions of scalar equations or delay systems of two equations the property of ejectivity is eventually reduced to the existence of solutions of the characteristic equation (7) with positive real part and the imaginary part within the range $(0, \pi/\tau)$ [11].

We shall show next that for all sufficiently large delays $\tau$ the characteristic equation (7) has a pair of complex conjugate solutions $\alpha_0 \pm i\beta_0$ with the positive real part $\alpha_0 > 0$ and the imaginary part $\beta_0$ satisfying $0 < \beta_0 < \pi/\tau$. This would imply the ejectivity of the above map $F$.

It is more convenient to rewrite the characteristic equation (7) in an alternative form by rescaling the time $t = \tau \cdot s$ to get the normalized delay $\tau = 1$ (see subsection 3.1 system (11)). One derives the following

$$(\varepsilon \lambda + \mu_1)(\varepsilon \lambda + \mu_2) + b + a \exp\{-\lambda\} = 0,$$

(20)

where $\varepsilon = 1/\tau > 0$ is a small parameter when $\tau > 0$ is large enough. By setting $\varepsilon = 0$ one gets the equation $\mu_1\mu_2 + b + a \exp\{-\lambda\} = 0$, which has a pair of complex conjugate solutions $\lambda = \alpha_0 \pm i\pi$, where $\alpha_0 = \ln[a/(\mu_1\mu_2 + b)] > 0$. Consider now the characteristic equation (20) for small $\varepsilon > 0$. By Rouché’s Theorem it has a pair of complex conjugate solutions $\lambda_\varepsilon = \mu(\varepsilon) \pm i\nu(\varepsilon)$ such that $\mu(\varepsilon)$ is close to $\alpha_0 > 0$ and $\nu(\varepsilon)$ is close to $\pi$. We shall show that $\nu(\varepsilon) < \pi$ for all sufficiently small $\varepsilon > 0$. One rewrites the characteristic equation (20) for the solution $\lambda_\varepsilon$ in the form

$$(\varepsilon \mu + \mu_1 + \varepsilon \nu i)(\varepsilon \mu + \mu_2 + \varepsilon \nu i) + b + a \exp\{-\mu\}(\cos \nu - i \sin \nu) = 0.$$

and considers its imaginary part:

$$\varepsilon \nu(2 \varepsilon \mu + \mu_1 + \mu_2) - a \exp\{-\mu\} \sin \nu = 0.$$
By differentiating the last equation with respect to \(\varepsilon\) and setting \(\varepsilon = 0\) one finds
\[
\nu'(0) = -\frac{\pi(\mu_1 + \mu_2)}{\mu_1 + \mu_2 + b} < 0,
\]
which proves that \(\nu(\varepsilon) < \pi\) for all sufficiently small \(\varepsilon > 0\), since \(\nu(0) = \pi\).

### 3.5 Multiple Periodic Solutions

We will demonstrate numerically the existence of multiple solutions using the system \((1)\). We start with linear functions \(F_1, F_2,\) and \(F_4\), which contain a constant function \(f_4\). The only non-linear function is then \(F_5(x) = F(x)\), which is monotonically decreasing (see system \((21)\) below). The two-dimensional system of this type is simply looking close in a sense to a single scalar differential delay equation where the non-uniqueness of slowly periodic solutions is known by several publications \([17, 27]\). Having derived multiple periodic solutions for system \((21)\) we will perturb it by the arctangent function to produce a system of type \((25)\) which will have the same two periodic solutions, however they are slightly perturbed compared with those in system \((21)\).

With the first step, the system \((4)\) becomes
\[
\begin{align*}
x'(t) &= -\frac{1}{\tau_0} x(t) + a_1 y(t) \\
y'(t) &= -a_2 y(t) - a_4 x(t) + F(x(t - \tau)),
\end{align*}
\]
where \(a_i > 0\) for \(i = 1, 2, 4\). Here, we will consider two appropriate choices of the monotonically decreasing \(F(x)\) designed as follows:
\[
F(x) = \begin{cases} 
f(x), & x \in [0, M] \\
-x, & x \in [M, \frac{\pi}{2}] \\
-\frac{\pi}{2} - A \arctan[k(x - \frac{\pi}{2})], & x > \frac{\pi}{2} \\
-F(-x), & x < 0.
\end{cases}
\]
\[(22)\]

where, \(A > 0\) and \(k > 1\) are positive arbitrary constants. For this definition, \(M\) is the solution of the \(\arctan(x) = x\) equation. Therefore, the function \(F\) is continuous (not in \(C^1\)) and odd by construction.

Another choice of function \(F\) is as follows:
\[
F(x) = \begin{cases} 
-B x^{2n+1}, & |x| \leq 1, \quad B > 0 \\
-B - A \arctan[k(x - 1)], & x \geq 1 \\
-F(-x), & x \leq -1.
\end{cases}
\]
\[(23)\]

The function plots are shown in Fig. 1. These choices allow us to demonstrate the presence of multiple periodic solutions of different types. The first choice (Equation \((22)\) leads to two different periodic solutions, while the second choice (Equation \((23)\) to attracting...
We verify Theorem 3.1 numerically in Section 4. We make a small modification to system (21) so that it can be viewed as the original system of the form (4).

We change the function $f_4$ from a constant to a monotonically increasing function with $0 < d = f_4(0) < \lim_{x \to \infty} f_4(x) = e > d$. For $f_4(u)$ one can choose:

$$f_4(u) = \epsilon (A + B \arctan(u)), \; u \in \mathbb{R},$$

where $A, B$ and $\epsilon > 0$ are constants, and $A > \frac{\pi}{2} B$.

We consider an intermediate system (between (4) and (21)), as follows:

$$x'(t) = - \frac{1}{\tau_0} x(t) + a_1 y(t)$$
$$y'(t) = -a_2 y(t) - f_4(x(t)) y(t) - \delta B \arctan(x(t)) + F_5(x(t - \tau)),$$

where $\delta$ is a constant comparable to $\epsilon$ and $F_5$ is chosen as $F(x)$ from equations (22) and (23).

By replacing the constants $a_1$ and $a_2$ in equation (25) with non-linear piecewise continuous functions, linearly proportional to the argument in the argument range within the range of the periodic solutions and equal to constants outside this range, and by replacing $F_5(x)$ outside the range of $x(t)$ by a symmetric smooth nonlinearity with a finite limit $\lim_{x \to \infty} F(x) = -F_\infty = -\lim_{x \to -\infty} F(x)$ for an appropriate $F_\infty > 0$, the system (25) is converted back to the original form (4).

Remark. The existence of any number of stable slowly oscillating periodic solutions can be achieved in two different ways.
(i) An analogous construction to that of function $F(x)$ given by (22) can be continued on the interval beyond the amplitude of the second large periodic solution. Indeed, given $A > 0$ and $k > 1$ such that the second periodic solution exists, one finds the unique value $M_1 > \pi/2$ such that it solves the equation $\frac{\pi}{2} + \arctan[k(x - \pi/2)] = x$. Then one defines function $\tilde{F}, x \geq 0$, such that $\tilde{F} \equiv F(x)$ for $x \in [0, M_1]$ and $\tilde{F} = -M_1 - A_1 \arctan[k_1(x - M_1)]$ for $x \geq M_1$, and $\tilde{F}(x) = -\tilde{F}(-x)$ for $x < 0$. Exactly as with $F(x)$ given by (22) it can be showed for the modified $\tilde{F}(x)$ that there exists $k_1^0$ large enough such that system (25) has three slowly oscillating periodic solutions, with the amplitude of the largest one greater than $M_1$. This procedure of additional modification of $F(x)$ in (22) can be continued step-by-step further so that one can obtain any finite number of stable slowly oscillating periodic solutions. If the procedure is applied to function $F(x)$ given by (23) then one derives any number of stable periodic solutions together with the locally stable equilibrium.

(ii) It is known that the existence of stable (hyperbolic in general) slowly oscillating periodic solutions persists under small continuous perturbations of the non-linear right hand side (functions $F, F_5, f_4, \arctan(\cdot)$ and constants $a_1, a_2, a_4, \tau_0$ for systems (21) and (25)) [20, 21]. Therefore, if the nonlinearity $F$ in (22) is replaced, in sufficiently small neighborhood $|x| < \delta$ of $x = 0$, by an arbitrary and small function $\tilde{F}$, and remains the same outside the small vicinity, $|x| \geq \delta$, then the two stable slowly oscillating periodic solutions will persist, having changed only a little. The replacement of $F(x)$ for $|x| < \delta$ can be done in such a way that the resulting function $\tilde{F}(x)$ is monotone decreasing there (therefore, it is monotone decreasing for all $x \in \mathbb{R}$). We now consider function $F(x)$ by (22) on the interval $[-M_1, M_1]$ where $M_1$ is defined above in part (i). Rescale it next to the interval $[-\delta, \delta]$ by $\tilde{F}(x) = (\delta/M_1)F(M_1 \delta x)$. We now use the above $\tilde{F}$ to replace the original $F$ in the delta neighborhood of $x = 0$. The resulting nonlinearity is now such that the corresponding system (25) has four stable slowly oscillating periodic solutions: two are the perturbed original periodic solutions, and the other two are small scaled original periodic solutions placed in the $\delta$-neighborhood of $x = 0$. This procedure can be repeated any finite number of times.

4 Numerical Analysis

Analytical investigation of systems of delay-differential equations and, in particular, System (1), with biologically-inspired functions and experimentally measured parameters, is usually very difficult or impossible. Therefore numerical methods have to be employed to study the details of behaviour of the glucose-insulin regulation models [9]. Li, Kuang and Mason [23] performed numerical analysis of a two-delay glucose-insulin regulation system to analyse the dependence of bifurcations in the system on delays. This model utilised functions $f_1 - f_5$ in their exponential forms with experimentally determined constants. [14, 13] performed numerical analysis of a similar system with more complex Hill functions, allowing for more realistic modelling of the physiological mechanisms of glucose-insulin regulation. They also studied the sensitivity of the solutions to the values of Hill
parameters used and performed simulations, which represented glucose-insulin regulation disorders, namely both Type 1 and Type 2 diabetes. Here we also use numerical analysis to further clarify some of the analytical results, obtained in the previous sections.

There are two main points we aim to demonstrate numerically. First, we demonstrate usability of equation (10) in diagnostics of the solution behaviour of system (1). Then we revisit the statement on relative insignificance of the actual forms of functions $f_1 - f_5$ in comparison to their shapes.

4.1 Numerical Methods

To confirm the results obtained in the previous sections, we produce numerical solutions for systems (1), (4), (25) and equation (10). Furthermore, some of the theoretical concepts and results in Section obtained in Section 3 cannot be proven analytically, therefore we use numerical methods to verify their validity.

The initial value problem of system (1) is solved using a 4-th order Runge-Kutta-Fehlberg method with an adaptive time step. The solution examples and their corresponding phase portraits are shown in Figures 3 and 4, which represent a periodic and an asymptotically stable solutions, respectively.

The delay term in the system is interpolated using Lagrange polynomials in their barycentric form [5]. This method demonstrates 4-th order self-convergence for sufficiently small time steps for both periodic and asymptotically stable solutions and a wide range of delays (see Figure 5).

To demonstrate applicability of the limiting interval map analysis, described in Subsection 3.1, we numerically solve Equation (10). The solution of the (implicit with respect to $G(s)$) difference equation (10) is preferential for numerical treatment as does not require numerically inverting a function on an arbitrary range of its argument, despite equation (13) being mathematically simpler and providing an explicit solution for $G(s)$.

Since the functions $f_1-f_5$ are monotonic, numerical solution of the difference equation (10) for $G(s)$ does not represent difficulties, and a simplest bisection method has been implemented. To distinguish numerically the solution types is also straightforward, as the period of the solution (if such period exists) is always 2 by construction. A solution is considered periodic for a large integer $s$ if $|G(s+2) - G(s)| < \epsilon$ and $|G(s+1) - G(s)| > \epsilon$, where $\epsilon = 10^{-3}$ is a constant, which determines precision.

The solution of Equation (10) either exhibits an asymptotic stability, which corresponds to the asymptotically stable regime for any delay $\tau$ in the system (1), or an oscillatory function with a period 2. The latter case corresponds to the periodic solution of system (1), which exists for the delay $\tau$ greater than some critical value $\tau_c$, determined numerically from the full solution of the system (1) given a set of its parameters. If $\tau < \tau_c$, the system shows a stable solution. Examples of equation (10) solution are shown in Fig. 2.

Other advantages of Equation (10) in comparison to the original system (1) are that it does not explicitly contain the delay value, neither require a priori knowledge of the oscillation period (if present) and the solution derivatives. It is, therefore, beneficial to
Figure 2: Examples of periodic (green) and asymptotically stable (black) solutions of Equation (10).
numerically analyse G-I system behaviour using this equation.

4.2 Numerical Demonstration of Multiple Periodic Solutions and Slow Oscillations

To further verify Theorem 3.1 we solve the system (25) numerically. The piecewise functions $f_1$ and $f_2$, constructed as described above, and $f_4$ as in Equation (24), are used in the calculation. Two different cases are considered for $F(x)$, as given in Equations (22) and (23), leading to different solution types. In Figure 8, examples of the solutions are shown. Transition between the different solutions of system (25) occurs in a very narrow range of the initial conditions $x(t = 0) = y(t = 0)$. Figure 6 demonstrates the solution amplitude (left panel) and the solution period (right panel) for $x(t = 0) = y(t = 0) = \{1.59, 1.61\}$. This figure also shows that there is a small effect (2%) of the initial condition on the period of oscillations, with the transition occurring at the same value as the transition between the amplitude of the solutions.

On the other hand, the time delay $\tau$ determines the period $T$ of oscillations. This is illustrated in Figure 7 where the dependence of ratio of the delay $\tau$ to the oscillation half-period $2\tau/T$ vs $\tau$ is shown. For all reasonable from the practical point of view values of $\tau$, $T \gtrsim 2\tau$. This confirms the existence of slow oscillations for this system. To remind, an oscillation is considered to be a slow oscillation if the period $T > \tau$. As system (25) mimics the behaviour of the original system (1), this shows that the time delay to a great extent determines the period of the oscillations and slow oscillations occur.
Figure 4: Same as in Fig. 3 but for an asymptotically stable solution to the system (1).

Figure 5: Dependence of the absolute global mean $L_1$ error on the time step for the employed numerical scheme. To demonstrate the precision order, the red dashed lines correspond to the power laws with the provided indices. Blue and black dash-dotted curves show Euler integration of the system with 4-th order Lagrange-interpolated delay term for $I$ and $G$, respectively. The solid curves show the 4-th order Runge-Kutta integration.
Figure 6: Demonstration of multiple solutions of the system (25) with $F$ as defined by equation (22). Left panel: dependence of the amplitude of the solution on the initial value $x(t=0) = y(t=0)$. Right panel: dependence of the period of the solution on the initial value $x(t=0) = y(t=0)$.

5 Conclusion

In this paper we performed an analytical and numerical study of the two-dimensional system of delay-differential equations with a single delay, which describes the glucose-insulin regulation system in humans. The aim of the paper was to demonstrate applicability of limiting interval maps to provide information on the system behaviour and to demonstrate the existence of slowly oscillating periodic solutions when the equilibrium is unstable.

The model of Bennett and Gourley [2, 3, 4], on which this paper is based, includes one delay - namely the delay between plasma insulin production and its effect on hepatic glucose production. This model was selected to demonstrate the power of limiting interval maps method.

The method not only reproduced the results obtained in [2, 3, 4], but also showed the behaviour of the system with a choice of physiological functions $f_i$, with specific attention on $f_5$. We investigated the behaviour of the system with $f_5(u)$ chosen as monotonically decreasing function of the variable $u$ and showed that this specific choice leads to multiple oscillating or stable solutions. We demonstrated that depending on the careful choice of functions $f_1 - f_5$ (which still satisfy all the conditions H1-H5), non-uniqueness of the solutions can be achieved.

The model with single delay has been succeeded by a number of more sophisticated models with two delays [23, 22, 24, 14], which involve control loops containing muscle [19] or effect of diabetes type I or II [13]. However, as one of the delays is always significantly larger than the other, a system with one delay is a very good approximation of the real system.

Constructing the nonlinear maps, we have found a difference equation, which repre-
Figure 7: Dependence of the ratio of the delay $\tau$ to half-period of the solution of system (25) with $F_5$ as defined by equation (22) on the delay $\tau$, which confirms the slowly oscillating solution property.
Figure 8: Numerical demonstration of multiple periodic solutions of the two-dimensional system. Top and bottom rows show examples of multiple solutions for systems (21) and (25), respectively. Left and right columns demonstrate multiple periodic and periodic/attractive equilibrium solutions, produced by functions $F$, defined by equations (22) and (23). Green curves correspond to $G(t)$ and black curves correspond to $I(t)$. The delay $\tau = 5$ is used for all solutions in the plot.
sents the dynamics of the system in the large delay limit, which has the potential for diagnostics of the solution types without the need to solve the full system of differential equations with one delay.

The paper shows the elegance and efficiency of the limiting interval maps in solving systems of differential equations with one delay. Furthermore, using this method, we revealed the existence of multiple slow oscillating or globally stable solutions.

Thus, the paper shows the potential of this method for solving complex problems in mathematical physiology and is generally applicable for the systems of nonlinear differential equations with a single delay.

5.1 Author Contributions

MA proposed the idea for the investigation. AI developed the theoretical aspects of the paper. SS produced the numerical results. GB contributed to the numerical aspects of the paper. All authors contributed to writing up the manuscript.

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