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Periodic Modes and Bistability in an Impulsive Goodwin Oscillator with Large Delay ⋆

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Abstract: The impact of time delay on the dynamics of a hybrid model of pulsatile feedback endocrine regulation is investigated. The model in hand can be seen as an impulsive and delayed version of the popular in computational biology Goodwin oscillator, where the feedback is implemented by means of pulse modulation. The value of the time delay is related to the duration of the time interval between the firing times of the feedback impulses. Under the assumption of a cascade structure of the continuous part of the model, the hybrid dynamics of the closed-loop system are shown to be governed by a discrete mapping propagating through the firing times of the impulsive feedback. Conditions for existence and stability of periodic solutions of the model are obtained. Bifurcation analysis of the mapping reveals the phenomenon of bistability arising for larger time delay values but not observed for the smaller ones.

Keywords: Delay systems, Impulse signals, Biomedical systems, Stability analysis, Amplitude modulation, Frequency modulation

1. INTRODUCTION

A mathematical model called "Goodwin oscillator" was first proposed by Goodwin [1965] and developed further by Griffith [1968]. Its intended purpose was to describe oscillatory phenomena in biochemistry. However, over the years, it found broad applications in various fields of mathematical biology. In particular, the Goodwin oscillator was adopted in Smith [1980, 1983] to describe periodic behaviors in endocrine systems and at present is referred to as the Smith model. To capture the episodic nature of pulsatile (non-basal) endocrine feedback, the model was modified in Churilov et al. [2009] by implementing the biologically motivated principles of impulsive control (see e.g. Gelig and Churilov [1998]). Being applied to the testosterone regulation in the human male, the impulsive model demonstrated a good agreement with experimental data in Mattsson and Medvedev [2013] and gave theoretical explanations to some experimentally observed phenomena, including deterministic chaos, Zhusubaliyev et al. [2012].

Starting from the early work of Smith [1983], a time delay was introduced into the Goodwin oscilator to align it with the biological reality (see also Cartwright and Husain [1986], Das et al. [1994], Keenan and Veldhuis [1998], Ruan and Wei [2001], Mukhopadhyay and Bhattacharyya [2004]) and induce sustained oscillations. Similarly, in Churilov et al. [2012, 2013, 2014], a time delay was included into the impulsive Goodwin-Smith model, but rather in order to model the transport phenomena and the time necessary for synthesis of a hormone. In fact, the impulsive Goodwin-Smith model is known to lack equilibria, Churilov et al. [2009].

The main assumption on the delay made in the analysis of Churilov et al. [2012, 2013, 2014] was that the delay value is strictly less than the least time interval between two consecutive firing times of the impulsive feedback. This assumption appears to be satisfied for the testosterone hormonal regulation in the human male (see, e.g., Cartwright and Husain [1986]) but not for pulsatile endocrine loops in general. For instance, in MacGregor and Leng [2005], where hypothalamic control of the growth hormone (GH) secretion is considered, the time delay for the stimulation by GH of the releasable store of somatostatin is estimated to 60 minutes. The experimental data provided by Veldhuis et al. [2000] demonstrate that, for adolescent females, the estimated GH interburst interval is less than an hour, while for young males it is usually greater, but can be less than an hour at certain time intervals. Hence, evidently, the results of Churilov et al. [2012, 2013] are not directly applicable in these cases.

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In this paper, a generalization of the earlier published analysis of periodic solutions in the impulsive Goodwin oscillator with a time delay in the continuous part of the system is considered. The periodicity implies that the firing times of the impulsive feedback repeat themselves modulo the solution period. In contrast with the prior research, the time delay value is allowed to be greater than the least interval between two consecutive feedback firing times. Yet, the delay value is still bounded from above by a double of the latter. To the best of our knowledge, the times delays in pulsatile endocrine systems usefully satisfy this relaxed condition.

The paper is organized as follows. First the notion of finite-dimension reducible time delay systems is briefly reviewed. Then, the impulsive Goodwin-Smith model with delay in the continuous part is revisited under new and relaxed assumptions on the time delay value. A pointwise discrete mapping describing the propagation of the system dynamics from one firing time of the pulse-modulated feedback to another is derived and analyzed. Further, existence and stability of periodic solutions of the model in question (m-cycles) are studied. Finally, the bistability phenomenon arising for larger values of the time delay in the mapping is investigated by bifurcation analysis.

2. FD-REDUCIBLE TIME DELAY SYSTEMS

Consider the autonomous system with delayed state

$$\frac{dx}{dt} = A_0 x(t) + A_1 x(t-\tau), \tag{1}$$

where $x(t) \in \mathbb{R}^p$, $A_0, A_1 \in \mathbb{R}^{p\times p}$, and τ is a constant time delay for $t \geqslant 0$, subject to the initial (vector) function $x(t) = \varphi(t)$, $-\tau \leqslant t < 0$.

The following definition was introduced in Churilov et al. [2012, 2013].

Definition 1. Time-delay linear system (1) is called finite-dimension reducible (*FD-reducible*) if there exists a constant matrix $D \in \mathbb{R}^{p\times p}$ such that any solution $x(t)$ of (1) defined for $t \geqslant 0$ satisfies the linear differential equation

$$\frac{dx}{dt} = Dx \tag{2}$$

for $t \geqslant \tau$.

FD-reducibility means that the solutions of time-delay system (1) are indistinguishable from those of a finite-dimensional system of order p on the time interval $[\tau, +\infty)$. The theorem below summarizes the essential properties of FD-reducible systems (see Churilov et al. [2013] for the proof).

Theorem 1. FD-reducibility of system (1) is equivalent to any of the statements (i), (ii):

(i) The matrix coefficients of (1) satisfy

$$A_1 A_0^k A_1 = 0 \quad \text{for all} \quad k = 0, 1, \ldots, p-1. \tag{3}$$

(ii) There exists an invertible $p \times p$ matrix S such that

$$S^{-1}A_0 S = \begin{bmatrix} U & 0 \\ W & V \end{bmatrix}, \quad S^{-1}A_1 S = \begin{bmatrix} 0 & 0 \\ \bar{W} & 0 \end{bmatrix}, \tag{4}$$

where the blocks U, V are square and the sizes of the blocks W and $\bar{W}$ are equal.

Moreover, the matrix D in FD-reduced system (2) for a FD-reducible system (1) is uniquely given by

$$D = A_0 + A_1 \mathrm{e}^{-A_0\tau}. \tag{5}$$

In the special coordinate basis given by (4), system (1) can be rewritten as

$$\frac{du}{dt} = Uu, \tag{6}$$

$$\frac{dv}{dt} = Wu + Vv + \bar{W}u(t-\tau) \tag{7}$$

with $x^{\mathrm{T}} = [u^{\mathrm{T}},\ v^{\mathrm{T}}]$, where $\cdot^{\mathrm{T}}$ denotes transpose. Thus D defined by (5) takes the form

$$D = \begin{bmatrix} U & 0 \\ W + \bar{W}\mathrm{e}^{-U\tau} & V \end{bmatrix}.$$

It is convenient now to, without loss of generality, assume that system (1) is represented in the form of (6), (7).

3. A TIME-DELAY IMPULSIVE SYSTEM

Consider an extension of the impulsive Goodwin-Smith model treated in Churilov et al. [2009] to the class of systems with delayed continuous part:

$$\begin{aligned} \frac{dx}{dt} &= A_0 x(t) + A_1 x(t-\tau), \qquad y = Cx, \\ t_{n+1} &= t_n + T_n, \qquad x(t_n^+) = x(t_n^-) + \lambda_n B, \\ T_n &= \Phi(y(t_n)), \qquad \lambda_n = F(y(t_n)). \end{aligned} \tag{8}$$

Without loss of generality, assume $t_0 = 0$. Here B is a column and C is a row such that $CB = 0$. Let also

$$B^{\mathrm{T}} = \begin{bmatrix} B_1^{\mathrm{T}}, & B_2^{\mathrm{T}} \end{bmatrix},$$

where the dimensions of the vectors B_1, B_2 correspond to those of u, v, respectively.

The continuously differentiable functions $\Phi(\cdot)$, $F(\cdot)$ satisfy

$$0 < \Phi_1 \leqslant \Phi(\cdot) \leqslant \Phi_2, \qquad 0 < F_1 \leqslant F(\cdot) \leqslant F_2,$$

for some constants $\Phi_i, F_i, i = 1, 2$. The latter condition implies that system (8) has no equilibria.

Previously, in Churilov et al. [2012, 2013], the case when $\inf_y \Phi(y) > \tau$, was considered so that

$$T_k > \tau \tag{9}$$

for all $k \geqslant 0$. The analysis carried out in Churilov et al. [2012] indicates that no qualitative changes in the periodic solutions of the model arise for the time delay values bounded by the least time interval between two consecutive firings of the impulsive feedback. In hybrid system (8), such delays can be characterized as small since they do not contribute much to the interaction of the continuous and discrete parts.

In this paper, a less restrictive condition of $2\inf_y \Phi(y) > \tau$ is imposed on the time delay value, resulting in

$$T_k + T_{k-1} > \tau \tag{10}$$

for all $k \geqslant 1$. As it will be shown below, this relaxed condition on the time delay drastically changes the situation. In particular, for larger time delays, dynamical system (1) can exhibit complex nonlinear phenomena such as bistability and quasiperiodic oscillations.

Consider the following four cases as illustrated in Fig. 1:

(i) $T_n > \tau, \quad T_{n-1} > \tau$;

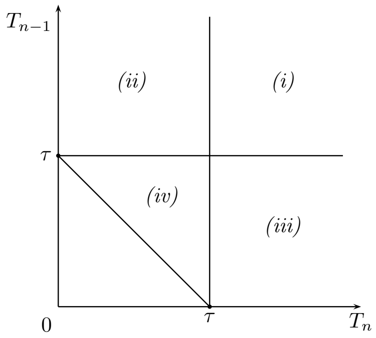

Fig. 1. Four feasible subsets of T_n, T_{n-1}

(ii) $T_n < \tau, \quad T_{n-1} > \tau$;
(iii) $T_n > \tau, \quad T_{n-1} < \tau$;
(iv) $T_n \leqslant \tau, \quad T_{n-1} < \tau, \quad T_{n-1} + T_n > \tau$,

for any $n \geqslant 1$.

The border values $T_n = \tau$ or $T_{n-1} = \tau$ represent the limit cases. Moreover, (10) implies that $T_{n-2} + T_{n-1} > \tau$ for $n \geqslant 2$. Thus, it holds

$$t_{n-2} + \tau = t_n - T_n - T_{n-1} + \tau < t_n. \tag{11}$$

Notice that while the function $x(t)$ jumps at the points t_k, $k = 0, 1, \ldots$, the function $x(t-\tau)$ jumps at the points of the sequence

$$\mathfrak{T} = \{t_k + \tau, \quad k = 0, 1, \ldots\}.$$

From (11), it follows that any time interval $(t_n,\, t_{n+1})$, where $n \geqslant 1$, contains no more than two points of $\mathfrak{T}$, namely $t_{n-1} + \tau$ and $t_n + \tau$.

Thus the conditions (i)–(iv) can be rewritten as follows: the interval $(t_n,\, t_{n+1})$ contains

(i) a single point $t_n + \tau$ from $\mathfrak{T}$;
(ii) no points from $\mathfrak{T}$;
(iii) two points $t_{n-1} + \tau$, $t_n + \tau$ from $\mathfrak{T}$;
(iv) a single point $t_{n-1} + \tau$ from $\mathfrak{T}$.

Define four sets of vector pairs (x, z), where $x \in \mathbb{R}^p$, $z \in \mathbb{R}^p$:

$$\begin{aligned}
\Omega_1 &= \{(x, z) \;:\; \Phi(Cx) > \tau, \quad \Phi(Cz) \geqslant \tau\},\\
\Omega_2 &= \{(x, z) \;:\; \Phi(Cx) \leqslant \tau, \quad \Phi(Cz) \geqslant \tau\},\\
\Omega_3 &= \{(x, z) \;:\; \Phi(Cx) > \tau, \quad \Phi(Cz) < \tau\},\\
\Omega_4 &= \{(x, z) \;:\; \Phi(Cx) \leqslant \tau, \quad \Phi(Cz) < \tau\}.
\end{aligned}$$

Introduce also a map $Q(x, z)$ in the following manner:

(1) $Q(x, z) = Q_1(x)$ for $(x, z) \in \Omega_1$, where

$$Q_1(x) = \mathrm{e}^{D\Phi(Cx)}x + F(Cx)\mathrm{e}^{D(\Phi(Cx)-\tau)}\mathrm{e}^{A_0\tau}B;$$

(2) $Q(x, z) = Q_2(x)$ for $(x, z) \in \Omega_2$, where

$$Q_2(x) = \mathrm{e}^{D\Phi(Cx)}x + F(Cx)\mathrm{e}^{A_0\Phi(Cx)}B;$$

(3) $Q(x, z) = Q_3(x, z)$ for $(x, z) \in \Omega_3$, where $Q_3(x, z) = Q_1(x) + R(x, z)$ and

$$R(x, z) = F(Cz)\mathrm{e}^{D\Phi(Cx)}\left[\mathrm{e}^{D(\Phi(Cz)-\tau)}\mathrm{e}^{A_0\tau} - \mathrm{e}^{A_0\Phi(Cz)}\right]B;$$

(4) $Q(x, z) = Q_4(x, z)$ for $(x, z) \in \Omega_4$, where $Q_4(x, z) = Q_2(x) + R(x, z)$.

The map $Q(x, z)$ has the following properties.

Lemma 1. The map $Q(x, z)$ is continuous in the domain of its definition $\Omega = \cup_{i=1}^{4}\Omega_i$.

Proof. From the formulas for Q_i, $i = 1, \ldots, 4$, it is easily seen that for the values of x yielding $\Phi(Cx) = \tau$, one has $Q_1(x) = Q_2(x)$ and so $Q_3(x, z) = Q_4(x, z)$. At the same time, if $\Phi(Cz) = \tau$, then $R(x, z) = 0$, so $Q_1(x) = Q_3(x, z)$ and $Q_2(x) = Q_4(x, z)$. □

Recall that the modulation functions $\Phi(\cdot)$, $F(\cdot)$ are continuously differentiable.

Lemma 2. The partial derivatives of the map $Q(x, z)$ are discontinuous. They have gaps on the surfaces

$$\Pi_1 = \{(x, z) \;:\; \Phi(Cx) = \tau\}, \quad \Pi_2 = \{(x, z) \;:\; \Phi(Cz) = \tau\}.$$

Proof. Let us consider Π_1. Since $Q_1 - Q_2 = Q_3 - Q_4$ for all x, z, it suffices to calculate the partial derivatives of $Q_1 - Q_2$. One has

$$\frac{\partial(Q_1 - Q_2)}{\partial z} = 0.$$

Since $(D - A_0)\mathrm{e}^{A_0\tau} = A_1$, it follows

$$\left.\frac{\partial(Q_1 - Q_2)}{\partial x}\right|_{\Phi(Cx)=\tau} = F(Cx)\Phi'(Cx)A_1BC.$$

Consider Π_2. Similarly $Q_4 - Q_2 = Q_3 - Q_1 = R$ for all x, z and the partial derivatives of $R(x, z)$ calculated on the surface $\Phi(Cz) = \tau$ satisfy

$$\frac{\partial R}{\partial x} = 0, \quad \frac{\partial R}{\partial z} = F(Cz)\Phi'(Cz)\mathrm{e}^{D\Phi(Cx)}A_1BC.$$

□

Introduce the notation $\bar{x}_n = x(t_n^-)$.

Theorem 2. Let $n \geqslant 2$. Then any solution of (8) satisfies the recurrent relationship

$$\bar{x}_{n+1} = Q(\bar{x}_n, \bar{x}_{n-1}). \tag{12}$$

Proof. Omitted for brevity.

Remark. More precisely, if $T_0 > \tau$ then (12) is valid for $n \geqslant 1$. Otherwise, (12) is valid for $n \geqslant 2$. If an initial function $\varphi(t)$, $-\tau \leqslant t \leqslant 0$, is given, then $\bar{x}_0 = \varphi(0)$ and the initial points $\bar{x}_1$ (when $T_0 > \tau$) or $\bar{x}_1$, $\bar{x}_2$ (when $T_0 \leqslant \tau$, $T_0 + T_1 > \tau$) can be obtained by a direct integration of (8).

Introduce $z_n = \bar{x}_{n-1}$ for $n \geqslant 1$. Then (12) can be rewritten in an augmented form as a system of first-order equations

$$\begin{bmatrix}\bar{x}_{n+1}\\ z_{n+1}\end{bmatrix} = P(\bar{x}_n, z_n), \quad P(x, z) = \begin{bmatrix}Q(x, z)\\ x\end{bmatrix}. \tag{13}$$

Let $J(x, z)$ be the Jacobian matrix of $P(x, z)$. Clearly, it holds that

$$J(x, z) = \begin{bmatrix}\partial Q/\partial x & \partial Q/\partial z\\ I_p & 0\end{bmatrix}.$$

In particular, if $(x, z) \in \Omega_1 \cup \Omega_2$, then $\partial Q/\partial z = 0$ and the spectrum of $J(x, z)$ is the union of the eigenvalues of $\partial Q/\partial z$ and of a zero eigenvalue of multiplicity p.

4. EXISTENCE AND STABILITY OF PERIODIC SOLUTIONS

Consider existence conditions for a periodic solution $x(t)$ of (8) with exactly m impulses in the least period (an m-cycle). Then $x(t)$ is T-periodic with

$$T = T_0 + T_1 + \ldots + T_{m-1} = t_m. \tag{14}$$

The relationship $t_0 = 0$ is utilized above.

With respect to the discrete-time form of the system expressed in (12), suppose that there exists an m-periodic solution $\{\bar{x}_k\}$, such that $\bar{x}_{k+m} = \bar{x}_k$ holds for all k and the vectors $\bar{x}_0, \dots, \bar{x}_{m-1}$ are all different to each other. Then $T_{k+m} = T_k$, $\lambda_{k+m} = \lambda_k$ for all $k \geqslant 0$. Moreover,

$$t_{k+m} = t_k + T, \quad k = 0, 1, \dots \tag{15}$$

The sequence $\{\bar{x}_k\}$ is an m-periodic solution of (12) if its first m terms satisfy the system of transcendental equations

$$\bar{x}_{k+1} = Q(\bar{x}_k, \bar{x}_{k-1}), \quad k = 0, 1, \dots, m-1, \tag{16}$$

where $\bar{x}_m = \bar{x}_0$, $\bar{x}_{m+1} = \bar{x}_1$. In particular, for a 1-cycle, a vector $\bar{x}_0$ can be found as a solution of the equation

$$\bar{x}_0 = Q(\bar{x}_0, \bar{x}_0). \tag{17}$$

Assume that $T_k = \Phi(C\bar{x}_k) \neq \tau, \quad k = 0, \dots, m-1$, to avoid non-smoothness.

Lemma 3. Suppose that a sequence $\{\bar{x}_k\}$ is m-periodic and satisfies (16). Then there exists an initial function $\varphi(t)$, $-\tau \leqslant t \leqslant 0$, such that a solution $x(t)$ of (8) with the initial condition $x(t) = \varphi(t)$, $-\tau \leqslant t \leqslant 0$, is T-periodic with T defined by (14) and satisfies $x(t_k^-) = \bar{x}_k$, $k = 0, \dots$.

Proof. Let the linear part of system (8) be already written in the block matrix form (6), (7). Denote

$$\begin{bmatrix} u_n \\ v_n \end{bmatrix} = \bar{x}_n.$$

Define a function $u(t)$ as

$$u(t) = \mathrm{e}^{U(t-t_k)} u_k, \quad t_{k-1} < t < t_k,$$

$k = 1, 2, \dots$. Obviously $u(t)$ satisfies (6) and $u(t_k^-) = u_k$, $k = 1, 2, \dots$. It is easily seen that since the sequence $\{u_k\}$ is m-periodic and (15) is fulfilled, then the function $u(t)$ is T-periodic for $t \geqslant 0$. Extend $u(t)$ T-periodically for $t < 0$. Set $\varphi_1(t) = u(t)$, $-\tau \leqslant t \leqslant 0$, as an initial function for $u(t)$. Notice that if $\tau > T_0$, the initial function needs to be *discontinuos*. Define

$$\Psi(t) = Wu(t) + \bar{W}u(t-\tau),$$

where the function $u(t)$ is as defined above. Obviously, $\Psi(t)$ is T-periodical for all $t \geqslant -\tau$. Define the function

$$v(t) = \mathrm{e}^{V(t-t_k)} v_k + \int_{t_k}^{t} \mathrm{e}^{V(t-\theta)} \Psi(\theta)\, d\theta$$

for $t_{k-1} < t < t_k$, $k = 0, 1, \dots$. It is easy to check that $v(t)$ satisfies (7) and $v(t_k^-) = v_k$, $k = 1, 2, \dots$. Since the sequence $\{v_k\}$ is m-periodical, $\Psi(t)$ is T-periodical and (15) is satisfied, the function $v(t)$ is also T-periodical. As $v(t)$ is not delayed in equation (7), there is no need in initial conditions for $v(t)$ other that $v(t_0^-) = v_0$. □

In contrast with Churilov et al. [2012, 2013, 2014], the consideration here cannot be limited to continuous initial functions. Piecewise continuous initial functions will be treated instead. For a solution $(x(t),\ t_n)$ of system (8) with a piecewise continuous initial function $\varphi(t)$, take a piecewise continuous perturbed function $\tilde{\varphi}(t)$ that is close to $\varphi(t)$, namely such that the L_1-norm

$$\|\tilde{\varphi} - \varphi\|_1 = \int_{-\tau}^{0} \|\tilde{\varphi}(\theta) - \varphi(\theta)\|\, d\theta$$

is small, where $\|\cdot\|$ is the Euclidean vector norm. As previously, let $\bar{x}_n = x(t_n^-)$.

Definition 2. A solution $x(t)$ will be called *stable* if for any $\varepsilon > 0$ there exists a number $\varepsilon_0(\varepsilon) > 0$ such that for the perturbed solution $(\tilde{x}(t), \tilde{t}_n)$ with a piecewise continuous initial function $\tilde{\varphi}(t)$, $\tilde{t}_0 = 0$, and $\tilde{x}_n = \tilde{x}(\tilde{t}_n^-)$ such that $\|\tilde{\varphi}(t) - \varphi(t)\|_1 < \varepsilon_0$, it applies that $\|\bar{x}_n - \tilde{x}_n\| < \varepsilon$ for all $n \geqslant 0$.

A solution $x(t)$ will be called *asymptotically stable* if it is stable and, moreover, there exists a number $\varepsilon_1 > 0$ such that $\|\bar{x}_n - \tilde{x}_n\| \to 0$ as $n \to \infty$, provided that $\|\tilde{\varphi}(t) - \varphi(t)\|_1 < \varepsilon_1$.

Obviously, when $\|\tilde{\varphi}(t) - \varphi(t)\|_1$ is sufficiently small then $\tilde{x}_0$, $\tilde{x}_1$ and $\tilde{x}_2$ are close to $\bar{x}_0$, $\bar{x}_1$ and $\bar{x}_2$, respectively. Thus, the consideration can be limited to local stability of forward orbits of discrete map (16).

The local stability of an m-periodic solution can be explored with help of the product of Jacobian matrices

$$J_m = J(\bar{x}_1, \bar{x}_0) J(\bar{x}_2, \bar{x}_1) \dots J(\bar{x}_m, \bar{x}_{m-1}).$$

by checking its eigenvalues. The solution is stable provided J_m is Schur stable (i.e., all its eigenvalues lie inside the unit circle).

Notice that for $m = 1$ one has $J_1 = J(\bar{x}_0, \bar{x}_0)$. Naturally, the point $(\bar{x}_0, \bar{x}_0)$ belongs either to the region Ω_1, or to the region Ω_4.

5. BIFURCATION ANALYSIS: BISTABILITY

Map (12) governing the propagation of the continuous state variables of hybrid system (8) is highly nonlinear and hard to study analytically. The focus of the bifurcation analysis below is on a specific nonlinear dynamics phenomenon, namely bistability, that arises in the system in hand due to the presence of a larger time delay. Interestingly, bistability is not observed for lower values of the time delay in (8). Bistability, implementing two distinct stable behaviors, appears to be of paramount importance for biological systems (see, e.g., Chaves et al. [2008]).

Following Churilov et al. [2012, 2013], consider an impulsive system with time delay

$$\frac{dx_1}{dt} = -b_1 x_1, \quad \frac{dx_2}{dt} = -b_2 x_2 + g_1 x_1,$$
$$\frac{dx_3}{dt} = -b_2 x_3 + g_2 x_2(t-\tau).$$

Here b_1, b_2, b_3, g_1, g_2, τ are positive parameters. Then, with respect to times delay system (1), it is seen that

$$A_0 = \begin{bmatrix} -b_1 & 0 & 0 \\ g_1 & -b_2 & 0 \\ 0 & 0 & -b_3 \end{bmatrix}, \quad A_1 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & g_2 & 0 \end{bmatrix}$$

and the conditions of Theorem 1 are readily satisfied.

Suppose that $x_1(t)$ has jumps at the time instants t_n, $n \geqslant 0$:

$$x_1(t_n^+) = x_1(t_n^-) + \lambda_n, \quad t_{n+1} = t_n + T_n, \tag{18}$$

where

$$\lambda_n = F(x_3(t_n)), \quad T_n = \Phi(x_3(t_n)). \tag{19}$$

In this analysis, the modulation functions are assumed to be the Hill functions

$$\Phi(y) = k_1 + k_2 \frac{(y/h)^p}{1 + (y/h)^p}, \quad F(y) = k_3 + \frac{k_4}{1 + (y/h)^p},$$

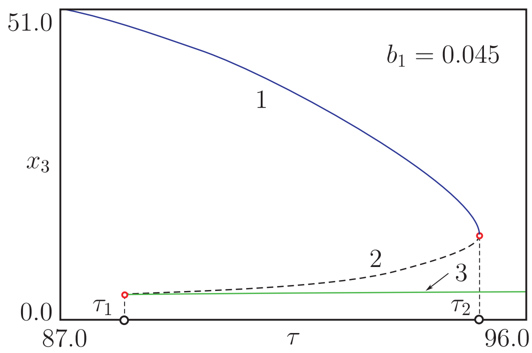

Fig. 2. Bifurcation diagram for $b_1 = 0.045$, illustrating the bistability, i.e. coexistence of two stable 1-cycles of the different types. This coexistence gives rise to hysteretic transitions at the saddle-node bifurcation points τ_1 and τ_2. Here the solid lines denoted by numbers 1 (the blue one) and 3 (the green one) correspond to stable fixed points with $(\bar{x}_0, \bar{x}_0) \in \Omega_1$ and $(\bar{x}_0, \bar{x}_0) \in \Omega_4$, respectively. The dashed line denoted by number 2 corresponds to saddle fixed points $(\bar{x}_0, \bar{x}_0) \in \Omega_1$.

and the parameter values are taken as the follows: $b_1 = 0.045$, $b_2 = 0.15$, $b_3 = 0.2$, $k_1 = 60.0$, $k_2 = 40.0$, $k_3 = 3.0$, $k_4 = 2.0$, $g_1 = 2.0$, $g_2 = 0.5$, $h = 2.7$ and $p = 2$. The time delay τ will be used as a varying parameter ($0 < \tau < 120.0$).

In terms of testosterone (Te) regulation in the male, x_1 is interpreted as the concentration of gonadotropin releasing hormone (GnRH), x_2 as the concentration of luteinizing hormone and x_3 as the concentration of Te. The concentration of GnRH is subject to jumps due to a pulse-frequency and pulse-amplitude modulated feedback from Te implemented by neurons within the hypothalamus (see Evans et al. [2009]) and described by (18), (19). Clearly, the time delay values assumed here lie partly outside of the physiologically motivated range for testosterone regulation and are intentionally selected to include large delays for the purpose of illustrating the arising dynamical phenomena.

Fig. 2 exhibits an example of a one-dimensional bifurcation diagram for the region of bistability obtained by varying the time delay τ, while keeping the other parameters constant. The vertical axis shows the third coordinate of $\bar{x}_0$, where $(\bar{x}_0, \bar{x}_0)$ is a fixed point of map (12).

For the values of the time delay $0 < \tau < \tau_1$, map (12) possesses a single stable fixed point $(\bar{x}_0, \bar{x}_0)$ that corresponds to a 1-cycle in closed-loop system (8). As τ increases, this fixed point undergoes a saddle-node bifurcation at $\tau = \tau_2$ in which the stable node merges with a saddle and disappears. The saddle can be followed backwards in the bifurcation diagram (dashed curve) to the point $\tau = \tau_1$, where it undergoes a second saddle-node bifurcation, and a new stable node is born.

The interval $\tau_1 < \tau < \tau_2$ between the saddle-node bifurcation points τ_1 and τ_2 is a region of bistability where two stable 1-cycles of different types coexist. When crossing the boundaries of the bistability region, the system displays hysteretic transitions from a stable 1-cycle of one type to a 1-cycle of another type and vice versa.

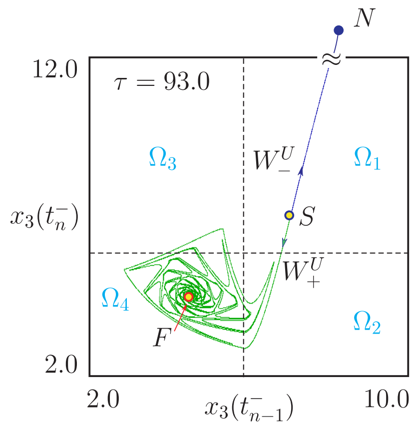

Fig. 3. Two-dimensional projection of the phase portrait in the region of multistability. A stable node N that corresponds to a 1-cycle with $(\bar{x}_0, \bar{x}_0) \in \Omega_1$ coexists with a stable focus F that corresponds to a 1-cycle with $(\bar{x}_0, \bar{x}_0) \in \Omega_4$. Here S is a saddle related to a 1-cycle with $(\bar{x}_0, \bar{x}_0) \in \Omega_1$. $W_\pm^U$ are the unstable manifolds of the saddle S. The stable manifold of the saddle S separates the basins of attraction of the coexisting stable fixed points N and F. Here $\tau = 93.0$ and $b_1 = 0.045$.

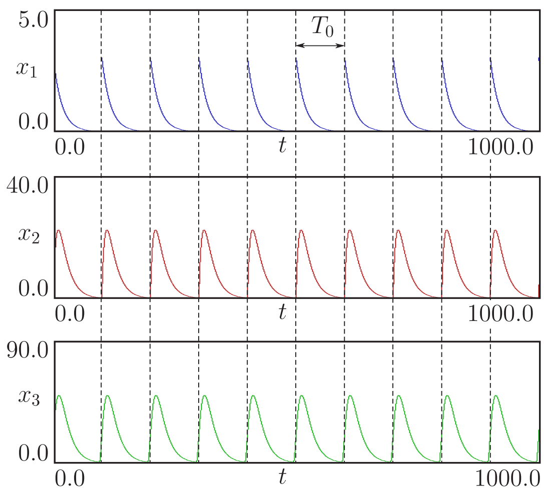

Fig. 4. Temporal variations of $x_1(t)$, $x_2(t)$ and $x_3(t)$ for a 1-cycle related to a stable node N with $(x_0, x_0) \in \Omega_1$, $T_0 \approx 99.3$. $\tau = 92.4$ and $b_1 = 0.05707$. This solution coexists with the stable 4-cycle (see Fig. 5).

Fig. 3 displays a two-dimensional projection of the trajectories of map (12) for a value of τ from the interval $\tau_1 < \tau < \tau_2$.

Stable cycles of different periodicity can also coexist in the model. To illustrate this fact, Fig. 4 and Fig. 5 depict temporal variations of the continuous state variables $x_1(t)$, $x_2(t)$ and $x_3(t)$ for the coexisting 1- and 4-cycles, respectively.

CONCLUSIONS

An earlier formulated hybrid mathematical model of pulsatile feedback endocrine regulation is considered for large values of the time delay. The notion of large time delays is defined with respect to the distance between firing times of

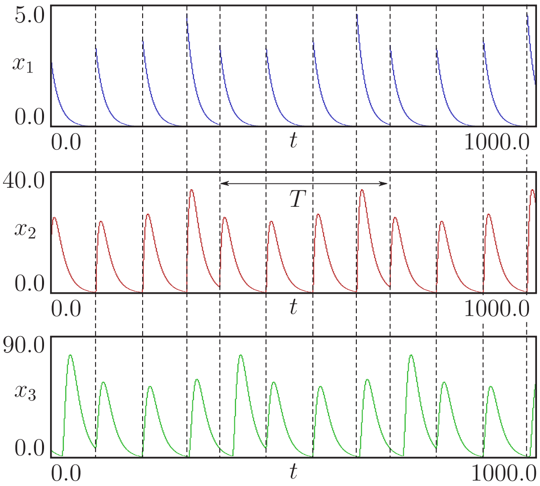

Fig. 5. Temporal variations of $x_1(t)$, $x_2(t)$ and $x_3(t)$ for a stable 4-cycle with $T_0 \approx 95.06$, $T_1 \approx 95.86$, $T_2 \approx 89.50$ and $T_3 \approx 67.86$. Here T is the period of this motion: $T = T_0 + T_1 + T_2 + T_3$, $\tau = 92.4$ and $b_1 = 0.05707$.

the feedback. Under the assumption of cascade structure of the continuous dynamics, a pointwise mapping describing the propagation of the continuous and delay-free part of the system through the firing time instants of the impulsive feedback is derived. Existence and stability of the periodic solutions of the hybrid model are investigated analytically. Bifurcation analysis of the pointwise mapping suggests that, in contrast with the previously treated case of smaller time delays, large values of the time delay in the endocrine loop can lead to e.g. bistability.

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