Proceedings of the 17th World Congress
The International Federation of Automatic Control
Seoul, Korea, July 6-11, 2008

Bifurcations in a mathematical model of non-basal testosterone production [1]

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Abstract: A recently proposed by the authors impulsive mathematical model of non-basal testosterone secretion of the hypothalamic-pituitary-testicular axis in the male is considered. Conditions for existence of periodic solutions in the model, their parametrization and stability are studied. Parameter bifurcations which lead to periodic oscillations of hormone levels with one or two pulses of gonadotropin releasing hormone (GnRH) in the least period are explored. The feasibility of the periodic mode with two pulses of GnRH is validated using experimental data.

1. INTRODUCTION

Hormones are chemical messengers in distant cell-to-cell communication. Endocrine hormone molecules are secreted directly into the bloodstream. The endocrine system is an integrated system of organs involved in the release of endocrine hormones. In biomedical research, the endocrine network is treated as a complex control system with a large number of feedback loops and feedforward connections, see Murray (2002); Farhy (2004). The feedback loops enable sustained oscillations of hormone levels with amplitudes and frequencies lying within some individual specific limits. To simplify the analysis, the endocrine system is usually decoupled into presumably independent subsystems called axes.

One of the most studied axes regulates the secretion of testosterone (Te) in the male. Besides Te, which is produced in testes, it also includes luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH), secreted in pituitary gland and hypothalamus, respectively. Being secreted in the parts of brain, GnRH and LH are closely related to the neural dynamics, so their secretion is known to be pulsatile, see e.g. Krsmanović et al. (1992). The secretion of GnRH stimulates the secretion of LH which, in its turn, stimulates the production of Te, while Te inhibits the secretion of GnRH and LH, see Veldhuis (1999). The fast responses in Te serum concentration due to the pulsatile secretion of GnRH are referred to as non-basal levels, in contrast to basal levels that exhibit slow diurnal variations related to circadian rhythm.

The mathematical exploration of the GnRH–LH–Te axis has a long history and an ample bibliography. The mathematical models in question can be divided into two classes — simplified deterministic and stochastic simulation models. Stochastic models are usually quite complex and difficult to analyze but produce realistic results in simulations. The work reported in Keenan and Veldhuis (1997), Keenan et al. (2000) presents yet the most complete mathematical model of testosterone regulation. However, the model developed there is too complex to be dealt with analytically using existing mathematical tools. A simplified stochastic model of non-basal Te secretion suggested in Heuett and Qian (2006) originates from a different perspective. Instead of continuous changes in hormone concentration, it reasons in terms of secreted and degraded hormone molecules, i.e. discrete events. Simulation of the model is a random walk on a three-dimensional greed with each dimension corresponding to a hormone in the modeled axis. Similar to the model in Keenan and Veldhuis (1997), Keenan et al. (2000), this model as well exhibits oscillations resembling those observed in experimental data. The authors attribute the oscillatory behavior to the stochastic nature of the approach. An interesting observation made regarding this model is that certain combinations of model parameters lead to an oscillation with a "double pulse" of Te, i.e. a combination of a lager and a smaller one. This closely resembles the 2-cycles studied in the sequel of the present paper.

Simplified deterministic models are more appealing to a control engineer as they have low dynamic dimension and clear structure based on the biochemistry of the involved processes. The main disadvantage of this class of models lies in their poor agreement with experimental studies.

The origin of deterministic models of the GnRH–LH–Te axis goes back to early papers Goodwin (1965), Smith (1980). A number of authors has contributed to further research of these models, including Smith (1983), Cartwright and Husain (1986), Liu and Deng (1991), Das et al. (1994), Ruan and Wei (2001), Murray (2002), Hek et al. (2002), Enciso and Sontag (2004), Mukhopadhyay and Bhattacharyya (2004), Efimov (2005). All these papers have dealt with basal (non-pulsatile) regulation of Te. Lack of stable periodic solutions (see Enciso and Sontag (2004) for an excellent analysis of this) is otherwise a main

[1] This work has been carried out with financial support by The Royal Swedish Academy of Sciences. A. Medvedev was partly supported by Swedish Research Council.

problem with the low-order hormone regulation models of this group, in a sharp contrast with the above mentioned stochastic ones.

A pulsatile model for non-basal Te regulation put forward in Medvedev et al. (2006), Churilov et al. (2007a), Churilov et al. (2007b) combines the classical hormone nodal scheme given in Smith (1980) with the model of a GnRH pulse generator proposed for a simulation model in Rasgon et al. (2003). The GnRH producing cells of hypothalamus are considered as a pulse element implementing pulse-amplitude and pulse-frequency modulation, see Gelig and Churilov (1998), where Te is the modulating signal and GnRH is the modulated pulse signal. The pulsatile LH secretion can be seen as the response of the continuous part of the system on the pulse signaling of the hypothalamus. Being very simple in its nature, the model lends itself to mathematical analysis. At the same time, it exhibits sustained oscillations of different signal shapes and accurately explains experimental data, Churilov et al. (2007b).

This paper suggests an explanation to the variability in the pulse signal form observed in non-basal secretion of Te, see e.g. Keenan et al. (2000) via bifurcation theory. It is shown that the origin of oscillations in mathematical models of the GnRH–LH–Te axis lies at the pulsatile nature of the feedback regulation mechanism and not at the choice between stochastic or deterministic modeling of the system. Indeed, all the known models implicitly or explicitly employing the principle of pulsatile feedback (e.g. Keenan and Veldhuis (1997), Keenan et al. (2000), Heuett and Qian (2006) and also Rasgon et al. (2003) for estrogen regulation), oscillate yielding realistic hormone patterns when numerically simulated.

First, existence and stability conditions for periodic solutions in the considered mathematical model are formulated. Then the phenomenon of parameter bifurcation is studied, in particular explicating the changes of periodic mode from one pulse of GnRH in the least period to two pulses of GnRH and back. An experimental data study supports the hypothesis of periodic solutions with two pulses of GnRH in the least period.

2. PULSATILE MODEL

Consider a system of differential equations

$$\begin{aligned} \dot{R} &= \xi(t) - b_1 R, \\ \dot{L} &= g_1 R - b_2 L, \\ \dot{T} &= g_2 L - b_3 T, \end{aligned} \tag{1}$$

where $R(t)$, $L(t)$ and $T(t)$ represent the serum concentrations of GnRH, LH and Te, respectively. Linear functions b_1R, b_2L, b_3T describe clearing rates of the hormones and g_1R, g_2L, $\xi(t)$ are the rates of their secretion, where b_i, g_i are positive numbers.

Equations (1) can be rewritten by using a state space notation. Let us denote $x_1 = R(t)$, $x_2 = L(t)$, $x_3 = y = T(t)$. Then (1) is equivalent to

$$\frac{dx}{dt} = Ax + B\xi(t), \qquad y = Cx, \tag{2}$$

where

$$A = \begin{bmatrix} -b_1 & 0 & 0 \\ g_1 & -b_2 & 0 \\ 0 & g_2 & -b_3 \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}, \quad C^T = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}.$$

The function $\xi(t)$ is described as

$$\xi(t) = \sum_{n=0}^{\infty} \lambda_n \delta(t - t_n), \tag{3}$$

where $\delta(t)$ is the Dirac delta-function. Notice that the δ-functions do not correspond to any biologically meaningful quantity in the model and are employed in order to obtain a compact mathematical description of the pulsatile feedback mechanism. Further, δ-functions are usual in modeling spiking neurons of the brain, Gerstner and Kistler (2002).

Suppose that the GnRH pulse firing times t_n are given by

$$t_{n+1} = t_n + \tau_n, \qquad \tau_n = \Phi(y(t_n)), \tag{4}$$

where $\Phi(\cdot)$ is a non-decreasing function (frequency modulation characteristics), and

$$\lambda_n = F(y(t_n)), \tag{5}$$

where $F(\cdot)$ is a non-increasing function (amplitude modulation characteristic). This reflects the fact that when the concentration of serum Te rises, the pulses of GnRH become sparser and their amplitude (or area) diminishes, see Veldhuis (1999). The functions Φ and F are bounded and positive.

System (2)–(5) has a hybrid nature, because it combines continuous time and discrete time mechanisms. Its solutions sustain jumps $x(t_n^+) = x(t_n^-) + \lambda_n B$. Here $x(t_n^-)$, $x(t_n^+)$ are one-sided limits of $x(t)$ (left and right, correspondingly) at t_n.

Obviously, A is Hurwitz stable and $CB = 0$. System (2)–(5) does not have equilibria because all the modulation characteristics are positive. Since pulse amplitude and frequency are bounded from above by the choice of $\Phi(\cdot)$ and $F(\cdot)$, then all the solutions of (2)–(5) are also bounded.

3. PERIODIC SOLUTIONS AND THEIR STABILITY

Since the processes of endocrine regulation are self-sustained, periodic solutions of system (2)–(5) are especially interesting. In a periodic mode, the original hybrid system can be equivalently replaced by a discrete time system with the help of natural sampling at impulse firing times.

Denote $x_n = x(t_n^-)$, where $x(t)$ is a solution of (2)–(5). Then

$$x_{n+1} = Q(x_n), \tag{6}$$

where

$$Q(x) = e^{A\Phi(Cx)}(x + F(Cx)B).$$

Given a solution of (6), the corresponding intersample behavior (2)–(5) can be completely reconstructed.

Following Zhusubaliev and Mosekilde (2003), a periodic solution is called *m-cycle* if there are exactly m impulses fired on its period. Then each 1-cycle corresponds to a fixed point x^0 of the operator $Q(\cdot)$, i.e.

$$Q(x^0) = x^0 \tag{7}$$

and has the initial condition $x(t_0^-) = x^0$. The periodic solution corresponding to this mode is characterized by the period τ_0 and the pulse amplitude λ_0.

Assume that the numbers b_1, b_2, b_3 are distinct. This assumption is biologically feasible since all the involved hormones have different half-life times. Introduce the numbers

$$\alpha_1 = \frac{1}{(b_2 - b_1)(b_3 - b_1)},$$
$$\alpha_2 = \frac{1}{(b_1 - b_2)(b_3 - b_2)},$$
$$\alpha_3 = \frac{1}{(b_1 - b_3)(b_2 - b_3)}.$$

Obviously $\alpha_1 + \alpha_2 + \alpha_3 = 0$ and two of these numbers are positive, while the third number is negative.

Denote $y^0 = Cx^0$.

Theorem 1. System (2)–(5) has one and only one 1-cycle. The cycle parameters λ_0, τ_0 and y^0 can be evaluated by solving the following system of transcendental equations

$$y^0 = \lambda_0 g_1 g_2 \sum_{i=1}^{3} \frac{\alpha_i}{e^{b_i \tau_0} - 1}, \qquad (8)$$
$$\lambda_0 = F(y^0), \quad \tau_0 = \Phi(y^0).$$

Proof. The proof of the fact that system (8) is uniquely solvable is rather cumbersome and substantially employs the two-diagonal structure of the matrix A. It is omitted for brevity. □

Notice that Theorem 1 says nothing about stability of the solution in question. A 1-cycle in system (2)–(5) would correspond to an equilibrium point of (6). Lyapunov stability of the equilibrium $x_n \equiv x^0$ for discrete time system (6) can be easily studied by linearizing the right-hand of (6) in a neighborhood of x^0. However, the stability properties of discrete system (6) are not necessarily inherited by hybrid system (2)–(5). Because of the jumps, perturbed and unperturbed solutions of the hybrid system can differ significantly. So, a weaker stability notion is to be considered for the hybrid system, namely orbital (Poincaré) asymptotic stability.

Consider a periodic solution $x^p(t)$ of (2)–(5) with the initial condition $x^p(t_0^-) = x^0$. Let $\Omega \subset \mathbb{R}^3$ be the positive semi-trajectory corresponding to $x^p(t)$ for $t \geqslant t_0^-$. The solution $x^p(t)$ will be called *stable*, if for any $\varepsilon > 0$ there exists a number $\varepsilon_0 > 0$ such that if $\|x(t_0^-) - x^p(t_0^-)\| < \varepsilon_0$, then $\mathrm{dist}(x(t), \Omega) < \varepsilon$ for all $t \geqslant t_0$. Moreover, there is a neighborhood $\mathcal{D}$ of x_0 such that for each solution $x(t)$ originating from $\mathcal{D}$ at t_0^- the limit relationship

$$\mathrm{dist}(x(t), \Omega) \to 0 \quad \text{as} \quad t \to +\infty$$

is satisfied. Orbital stability of a 1-cycle is readily follows from the Lyapunov asymptotic stability of the corresponding equilibrium of (6). Consider a Jacobian matrix

$$\Psi(x, y) = e^{A\Phi(y)}\big[I + F'(y)BC\big] + \Phi'(y)AQ(x)C.$$

Theorem 2. Suppose that x^0 satisfies (7) and the functions $F(\cdot)$ and $\Phi(\cdot)$ have continuous derivatives $F'(\cdot)$ and $\Phi'(\cdot)$ in a neighborhood of $y^0 = Cx^0$. The 1-cycle with the initial condition $x(t_0^-) = x^0$ is stable if $\Psi(x^0, y^0)$ is Schur stable (i.e. all its eigenvalues lie strictly inside the unit circle).

Proof. Omitted.

For a 2-cycle, the initial condition $x(t_0^-) = x^0$ solves the equation

$$Q(Q(x^0)) = x^0. \qquad (9)$$

Consider a 2-cycle $x^p(t)$ with the pulse parameters τ_0, λ_0, τ_1, λ_1. Denote

$$\hat{x}^0 = Q(x^0), \quad y^0 = Cx^0, \quad \hat{y}^0 = C\hat{x}^0.$$

Theorem 3. Suppose that x^0 satisfies (9). Then parameters of the 2-cycle with the initial value $x(t_0^-) = x^0$ satisfy the following transcendental equations, where $y^0 \neq \hat{y}^0$:

$$y^0 = g_1 g_2 \sum_{i=1}^{3} \alpha_i \frac{\lambda_0 + \lambda_1 e^{b_i \tau_0}}{e^{b_i(\tau_0 + \tau_1)} - 1}, \qquad (10)$$

$$\hat{y}^0 = g_1 g_2 \sum_{i=1}^{3} \alpha_i \frac{\lambda_1 + \lambda_0 e^{b_i \tau_1}}{e^{b_i(\tau_0 + \tau_1)} - 1}, \qquad (11)$$

$$\lambda_0 = F(y^0), \qquad \tau_0 = \Phi(y^0),$$
$$\lambda_1 = F(\hat{y}^0), \qquad \tau_1 = \Phi(\hat{y}^0).$$

If $\hat{y}^0 > 0$ is fixed, equation (10) is uniquely solvable in y^0. If $y^0 > 0$ is fixed, equation (11) is uniquely solvable in $\hat{y}^0$.

Proof. Omitted.

Unlike system (8), solvability of (10), (11) is not guaranteed. In the next section it will be seen that emergence and disappearance of 2-cycles is connected with certain bifurcations of parameters.

If (10), (11) are satisfied, system (2)–(5) has two 2-cycles with the initial values $x(t_0^-) = x^0$ and $x(t_0^-) = \hat{x}^0$, respectively. These 2-cycles have the same trajectory and differ only in the time domain by a constant phase shift.

Theorem 4. Let $F(\cdot)$ and $\Phi(\cdot)$ have continuous derivatives in some neighborhoods of y^0 and $\hat{y}^0$. The 2-cycle with the initial value $x(t_0^-) = x^0$ is stable if the matrix product $\Psi(\hat{x}^0, \hat{y}^0)\Psi(x^0, y^0)$ is Schur stable.

Proof. Omitted.

Theorem 2 and Theorem 4 state only local stability of the corresponding cycles. However, numerical experiments show that these cycles are globally orbitally stable.

4. BIFURCATIONS OF PARAMETERS

4.1 Bifurcation diagrams

The values of the model parameters in this section are not biologically motivated but rather chosen to clearly illustrate the dynamical behaviors of the system. The results of this section were obtained by numerical experiments for

$$A = \begin{bmatrix} -b_1 & 0 & 0 \\ 2 & -b_2 & 0 \\ 0 & 0.5 & -b_3 \end{bmatrix}.$$

As follows from Theorem 1 and Theorem 3, the non-zero off-diagonal elements of A influence mainly the amplitudes of the oscillations and not their type. The nonlinearities were taken as

$$\Phi(y) = k_1 + k_2 \frac{(y/h)^2}{1 + (y/h)^2}, \quad F(y) = k_3 + \frac{k_4}{1 + (y/h)^2},$$

where parameters k_1, k_2, k_3, k_4 and h are positive.

Theorems 1 and 3 are illustrated by Figures 1 and 2. From Theorem 3, it follows that each equation of (10) and (11) determines a curve in the plane (y^0, y^1), where $y^1 = \hat{y}^0$. The curve corresponding to (10) is drawn in a solid line, an the curve corresponding to (11) — in a dashed line. The intersection points of the curves correspond ether to a 1-cycle (for $y^0 = y^1$), or to a 2-cycle (for $y^0 \neq y^1$).

The figures were obtained for $b_2 = 0.15$, $b_3 = 0.2$, $k_1 = 60$, $k_2 = 40$, $k_3 = 3$, $k_4 = 2$, $h = 2.7$. In the case $b_1 = 0.03$, the

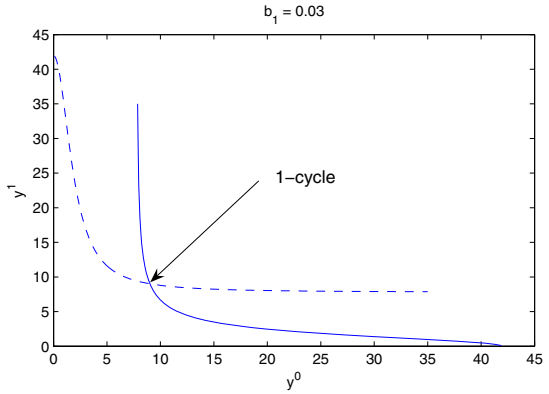

Fig. 1. Graphical solution of equations (10), (11) for $b_1 = 0.03$.

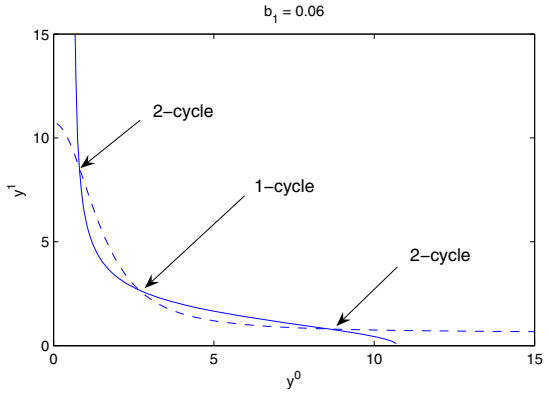

Fig. 2. Graphical solution of equations (10), (11) for $b_1 = 0.06$.

system has no 2-cycles but a unique 1-cycle. In the case $b_1 = 0.06$, the system has both 1-cycle and 2-cycle.

These figures suggest that there is a bifurcation value of b_1, where a 2-cycle emerges. The bifurcation diagram for b_1 is shown in Figure 3. The ordinates of the graph correspond to the fixed points y^0, $\hat{y}^0$. The solid curve shows that the fixed point matches a stable solution, and a dashed curve — an unstable solution. The diagram demonstrates the presence of two bifurcation points. When b_1 increases, a period doubling bifurcation is followed by a period halving bifurcation. Thus the bifurcation diagram forms a non-chaotic "bubble". Similar "bubbles" occur when varying the parameters b_2, b_3, k_1 and h.

For the bifurcation values, the spectrum of the Jacobian $\Psi(x^0, y^0)$ reaches the unit circle at the point -1, so the 1-cycle either loses or restores its stability.

4.2 Circadian oscillations

Hormonal secretion is governed by a biological clock, which has a 24-hour cycle called circadian rhythm. Clinical experiments exhibit that the serum concentration of Te attains its maximum at 4–6 AM, then drops by 15–70 % in the evening and rises again at the nighttime sleep, see Keenan and Veldhuis (1998). Another feature observed in clinical practice is variability of pulse shapes, see Keenan et al. (2000), which directly influences the modeling of non-basal secretion.

The latter fact can be explicated by bifurcations in the proposed model. Note that the signal form for GnRH pulses is usually assumed and not derived from the model

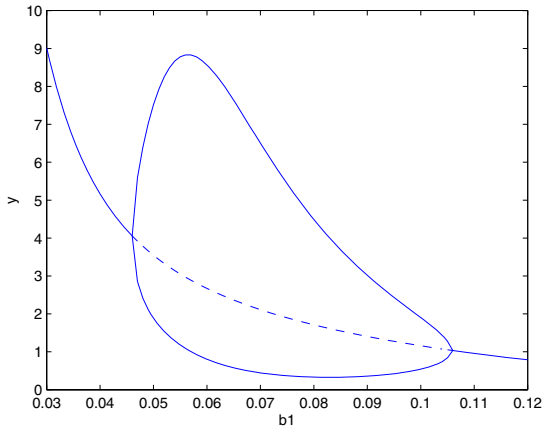

Fig. 3. Bifurcation diagram for b_1

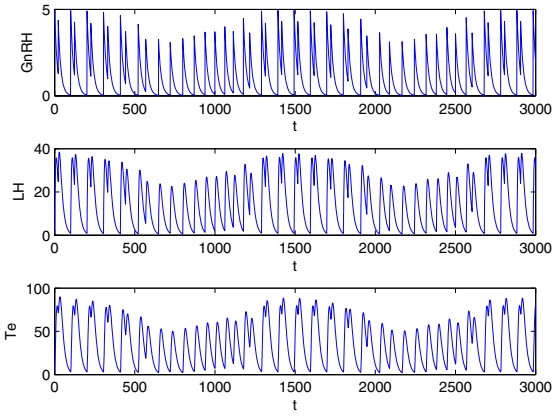

Fig. 4. Graph of a solution with a circadian rhythm taken into account

structure. Suppose that some of the model parameters periodically vary passing through their bifurcation points. Then the system comes from 1-cycle to 2-cycle and *vice versa*. In clinical experiments, a couple of adjacent pulses fired in a 2-cycle can look as a single pulse of highly asymmetric shape, Churilov et al. (2007b).

As an example, consider the results of computer simulation depicted in Figure 4. There, the model with the previously assumed set of parameters, $b_1 = 0.06$, and

$$h(t) = 7 + 6.5\,\cos(2\pi t/1440)$$

is simulated. Notice that time is measured in minutes.

5. EXPERIMENTAL RESULTS

In medical literature, it is an established thesis that pulses of GnRH from hypothalamus cause pulses of LH secretion in pituitary in a nearly uniformly one-to-one ratio, Veldhuis (1991). In a typical endocrinological study, pulses of GnRH and LH are counted using a pulse detection algorithm run on a hormone concentration time series, as in the classical CLUSTER algorithm by Veldhuis and Johnson (1986). Pulses are recognized over a sliding window as significant increases followed by significant decreases. In this way, minor pulses can be missed due to slow sampling or regarded as nuisance. Furthermore, the pulse signal form has to be assumed.

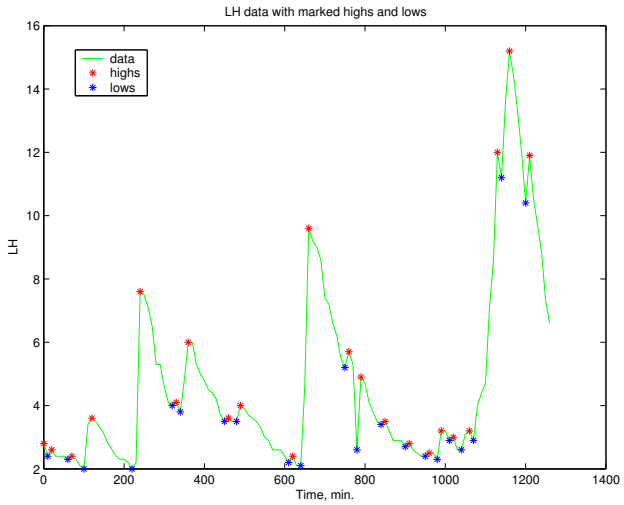

Fig. 5. Changes in LH serum concentration observed in a patient during a day. Highs and lows of the signal are marked to facilitate localization of impulses.

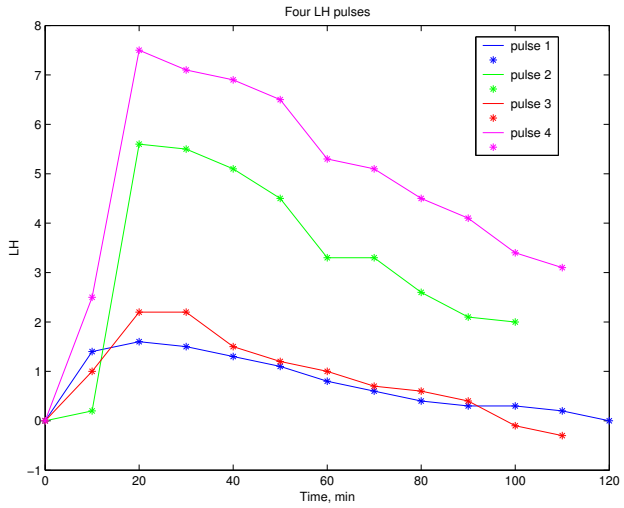

Fig. 6. Four pulses of LH extracted for the data set. Notice similar pulse signal form.

In this section, it is demonstrated that the signal form predicted by the model studied in this paper for the case of two pulses of GnRH on the least period is consistent with LH serum concentration data observed in a young human male at a sampling time of 10 min, see Fig. 5. The data set was kindly provided by Prof. Veldhuis of Mayo Clinic. In the data set, both the slow (basal) trend related to circadian rhythm and pulses caused by non-basal hormone secretion are visible. Four pulses of LH have been studied, each comprised of more than 10 measured points and assayed from the same patient, see Fig 6. All of them have similar signal form that can be explained as LH secretion stimulated by two consequent GnRH pulses.

In the model, the amplitude and onset time of GnRH pulses are governed by weighted δ-functions generated by the impulse feedback controller, see (3). Assuming that the periodic mode has two pulses of GnRH in the least period T and setting $t = 0$ at the beginning of a period, gives two weighted δ-functions produced on each period by the impulse controller in the mathematical model

$$\Theta(t) = \lambda_0 \delta(t) + \lambda_1 \delta(t - t_1).$$

Table 1. Parameter estimates for LH pulse caused by two GnRH pulses

data set	*estimates*				
	$\hat{b}_1$	$\hat{b}_2$	$\hat{t}_1$	$\hat{g}_1$	$\hat{\lambda}_1$
pulse 1	0.07	0.033	89	0.23	0.04
pulse 2	0.075	0.023	60	0.75	0.1
pulse 3	0.075	0.033	72	0.32	0.05
pulse 4	0.076	0.017	60	0.87	0.08

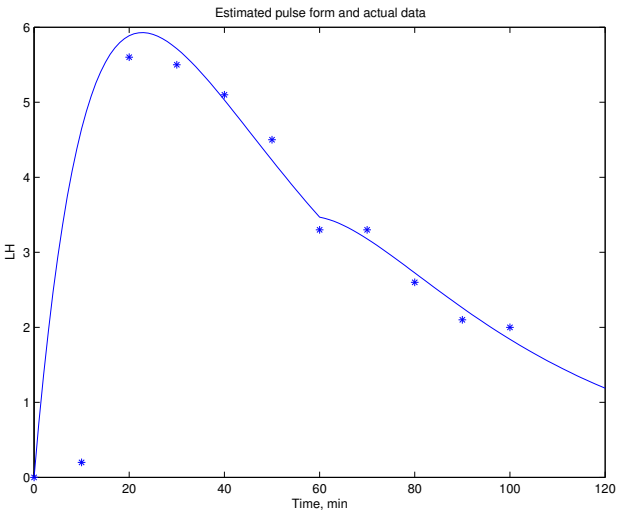

Fig. 7. LH pulse model with parameters from Table 1 (solid line) compared to the identification set `pulse 2` (asterisks)

This results in the following evolution in the concentration of GnRH

$$R(t) = \lambda_0 e^{-b_1 t}, \qquad 0 \leqslant t < t_1,$$
$$R(t) = \eta(b_1) e^{-b_1 t}, \eta(x) = \lambda_0 + \lambda_1 e^{x t_1}, \quad t_1 \leqslant t < T,$$

and that of the measured model output LH

$$L(t) = \frac{\lambda_0 g_1}{b_2 - b_1}(e^{-b_1 t} - e^{-b_2 t}), \qquad 0 \leqslant t < t_1,$$
$$L(t) = \frac{g_1}{b_2 - b_1}\left(\eta(b_1) e^{-b_1 t} - \eta(b_2) e^{-b_2 t}\right), \quad t_1 \leqslant t < T.$$

Since GnRH concentrations cannot be measured in the human, the problem of evaluating the model parameters b_1, b_2, g_1, λ_0, λ_1 from experimental data involves deconvolution. From the equations above, it becomes clear that λ_0 and g_1 cannot be estimated separately from measurements of LH but only in a product. Therefore, the values of λ_0 and λ_1 cannot neither be estimated but only their ratio. Here it is assumed that $\lambda_0 = 1$. As already mentioned, the value of g_1 does not influence the type of oscillations in the model but only their amplitude.

Model parameters have been estimated from the data set using standard nonlinear least squares, a method commonly applied for deconvolution, and the obtained estimates are summarized in Table 1. A typical estimation result is illustrated in Fig. 7 showing a fair model fidelity. Without the second GnRH pulse which is 10% of the first one in this case, the almost constant concentration of LH in the interval between $t = 60$ min and $t = 70$ min would be difficult to explain.

As shown in Churilov et al. (2007b), the present sampling time of 10 min. yields undersampled data sets and the accuracy of estimates cannot be expected to be high. This agrees well with the results in Veldhuis et al. (1986) where it is concluded from stochastic analysis that a sampling

time of 2–3 min is necessary to capture 90% of all LH pulses. Besides, the very coarse mathematical modeling applied to obtain the model at hand allows for significant model uncertainty which in its turn unavoidably leads to parameter estimation errors.

The oscillations in endocrine regulation are severely perturbed by many contributing factors and it is clearly visible from the parameter estimates in Table 1. First of all, the estimate $\hat{b}_1$ corresponding to the clearing rate of GnRH varies least. However, according to Keenan and Veldhuis (1998), GnRH has to clear out much faster than LH, while the values of $\hat{b}_1$ and $\hat{b}_2$ are of the same order. This is probably a consequence of undersampling making the fast GnRH dynamics poorly observed in the experimental data.

6. CONCLUSIONS

Parameter bifurcations in a mathematical model of non-basal testosterone secretion are studied. The paper provides a mathematical explanation to impulsive and oscillative effects in the male reproductive axis. Existence and stability conditions for periodic solutions in the considered mathematical model are formulated. Experimental data validate the existence of a periodic mode with two pulses of gonadotropin releasing hormone in the least period.

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