PERIODIC MODES IN A MATHEMATICAL MODEL OF TESTOSTERONE REGULATION [1]

Alexander Churilov * **Alexander Medvedev** **
Alexander Shepeljavyi *

* *Faculty of Mathematics and Mechanics, St. Petersburg State University, Universitetsky av. 28, Peterhof, 198504, St. Petersburg, RUSSIA,*
e-mail: a_churilov@mail.ru; as@as1020.spb.edu
** *Information Technology, Uppsala University, SE-751 05 Uppsala, SWEDEN, e-mail:* Alexander.Medvedev@it.uu.se

Abstract: Periodic solutions of a recently suggested parsimonious mathematical model of pulse-modulated regulation of non-basal testosterone secretion in the male are studied. The model is of third order, reflecting the three most significant hormones in the regulation loop, but yet is shown to be capable of sustaining periodic solutions with one or two pulses of gonadotropin-releasing hormone on each period. Lack of stable periodic solutions is otherwise a main shortcoming of existing low order hormone regulation models.

Keywords: Biomedical systems, Impulse signals, Oscillation, Limit cycles

1. INTRODUCTION

Hormonal (endocrine) regulation is a complex biological system where hormones, often measured as their serum concentrations, interact via numerous feedback and feed-forward relationships, see (Murray, 2002; Farhy, 2004). Regarding mathematical modeling of hormone dynamics, one considers two general tendencies — hormone clearing from the blood which implies decrease of the serum concentration and hormone secretion which contributes new amounts of the hormone into the blood stream. Clearing rate is basically proportional to the hormone concentration while secretion of a hormone is defined by concentration and dynamics of other hormones. Concentration rise in hormones can either stimulate secretion of a given hormone or inhibit it. In this way, positive and negative feedbacks arise between different hormone concentrations of an organism. The loop of interacting hormones is closed and dynamically stable which guarantees homeostasis, i.e. biological self-regulation. To correct the dynamic behaviors of endocrine systems, exogenous signals can be used, e.g. medication, different kinds of medical treatment, physical activity, special diet, etc.

In the endocrine system of testosterone (Te) regulation in the male, essential role is played by the luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH), also called luteinizing hormone-releasing hormone. While Te is produced in testes, LH and GnRH are secreted in different parts of the brain — hypophysis and hypothalamus, respectively. Therefore the dynamics of LH and GnRH are closely related to the neural dynamics. 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 (Veldhuis, 1999).

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Experimental studies based on high-resolution time assay series reveal (see e.g. (Smith, 1980)) that concentrations of Te and LH in the adult male exhibit oscillative behavior and their exact signal form depends on the individual. Direct measurements of GnRH in the human are difficult to implement due to ethical reasons but experiments on animals confirm that also secretion of GnRH is oscillative and it is furthermore pulsatile, see e.g. (Krsmanović *et al.*, 1992). Oscillations in hormone concentrations are of a broad spectrum. Ultradian harmonics with a period of $1-3$ hours, depending on the individual, are present as well as a circadian rhythm of 24 hours. Chaotic high-frequency variations are superimposed on the low-frequency periodic components resulting in quite complex cumulative signal form.

In this paper, periodic solutions of a recently suggested in (Medvedev *et al.*, 2006) low-order mathematical model of the GnRH–LH–Te axis are studied. The model takes into account the pulsatile nature of GnRH release and is shown to be capable of sustained oscillations. It is further studied and partially validated on LH serum concentration data in (Churilov *et al.*, 2007). First, a brief overview of results related to mathematical modeling of testosterone regulation in the male is provided to highlight the gap filled in by the model in hand. Obtained existence and stability results for periodic solutions of the model are illustrated by simulation.

2. PRELIMINARIES

Secretion of the hormones comprises two components — basal and pulsatile (non-basal). Basal secretion of Te is a slow continuous process and the pulsatile one is directed by episodic release of GnRH.

First mathematically sensible model of the GnRH (LHRH)–LH–Te axis has been suggested in (Smith, 1980). A simplified version of this model (suggesting clearing and secretion rates to be linear) comprises three differential equations

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

where $R(t)$, $L(t)$ and $T(t)$ represent the serum concentrations of GnRH, LH and Te, respectively. The pulsatile nature of GnRH secretion, already discovered at that time (Dierschke, 1970), is not taken into account. Linear functions $b_1 R$, $b_2 L$, $b_3 T$ describe clearing rates of the hormones and $g_1 R$, $g_2 L$, $f(T)$ are the rates of their secretion, where b_i, g_i are positive numbers. The function $f(\cdot)$ is non-increasing and highly nonlinear. In (Smith, 1980), analytical sufficient conditions for (1) to have a stable periodic solution are given. In (Smith, 1983), model (1) has been extended to account for certain biological phenomena. The extended models by Smith have been further studied and followed up on by other researchers (Cartwright and Husain, 1986; Murray, 2002; Enciso and Sontag, 2004; Efimov, 2005). The Smith models and their modifications are illustrative and give an idea about the general tendencies of the considered endocrine system. Unfortunately, they poorly correspond to the experimentally observed behaviors that are far from being periodic and also include irregular components.

Existing stochastic models demonstrate, as a rule, better agreement with clinical data compared to the models with regular dynamics. The most complete model of the GnRH–LH–Te axis, taking into account quite subtle biological considerations, is suggested in (Keenan and Veldhuis, 1998; Keenan *et al.*, 2000). The model has been developed on the basis of LH and Te assays taken from a large number of patients with sampling time of 10 min. Modifications of this model that take into account circadian rhythm and external disturbances can also be found in (Keenan and Veldhuis, 1998; Keenan *et al.*, 2000). The stochastic model is quite complex and involves a significant number of adjustable parameters. This makes it possible to coerce the model into many different kinds of dynamical behavior but, at the same time, makes it the best of the currently available ones at explaining experimental data. On the contrary, a quite simple stochastic model was suggested in (Heuett and Qian, 2006).

3. PULSE MODULATION MODEL

3.1 *Model equations*

As follows from the preceding sections, there is no single broadly accepted mathematical model of testosterone regulation in the male. Furthermore, the biological mechanism of the involved feedbacks is not at all clear, even qualitatively. The pulsatile secretion of GnRH that generally stems from the pulse dynamics of neurons (see (Gerstner and Kistler, 2002)) is studied in (Keenan and Veldhuis, 1998; Keenan *et al.*, 2000; Rasgon *et al.*, 2003; Van Goor *et al.*, 2000; Clément and Françoise, 2005). When the concentration of serum Te rises, the pulses of GnRH become sparser and their amplitude (or area) diminishes (Veldhuis, 1999).

To catch the above described pulsatile feedback mechanism, the GnRH producing cells of hypothalamus can be modeled as a pulse element implementing pulse-amplitude and pulse-frequency

modulation (Gelig and Churilov, 1998). Then 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.

Consider now model (1), where $f(T)$ is no longer a nonlinear function, but rather an operator describing pulse-amplitude-frequency modulation. There are not so many kinds of pulse-amplitude modulation, they are mostly related to the choice of the pulse form, but there is a rich variety of pulse-frequency modulation schemes and some of them are described in (Gelig and Churilov, 1998). Unfortunately, no currently available biological evidence can substantiate the choice of one of the latter. However, it was shown by analyzing biological data that the GnRH pulse modulator resets at the time when a pulse is fired, (Butler *et al.*, 1986).

Let us denote $x_1 = R(t)$, $x_2 = L(t)$, $x_3 = T(t)$. Consider a system

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

where

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

Here b_1, b_2, b_3, g_1, g_2 are positive parameters,

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

where $\delta(t)$ is the Dirac delta-function. Suppose that the 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 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). The functions Φ and F are bounded and positive.

The jump equations are

$$x(t_n + 0) = x(t_n - 0) + \lambda_n B. \tag{6}$$

Obviously, A is Hurwitz stable and $CB = 0$. System (2)–(6) does not have equilibria because all the modulation characteristics are positive. Since pulse amplitude and frequency are bounded from above, then all the solutions of (2)–(6) are also bounded.

4. PERIODIC SOLUTIONS

Since the processes of endocrine regulation are self-sustained, only periodic solutions of system (2)–(6) are treated here. Consider the translation operator along the trajectories $x(t)$ of (2)–(6):

$$Q \ : \ x(t_n - 0) \mapsto x(t_{n+1} - 0).$$

Obviously,

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

Following (Zhusubaliev and Mosekilde, 2003), a periodic solution is called *m-cycle* if there are exactly m impulses of sequence (3) fired on its period.

Then 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 $x(t_0 - 0) = x^0$. The periodic solution corresponding to this mode is characterized by the period τ_0 and the pulse amplitude λ_0. Denote $y^0 = Cx^0$.

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.

Theorem 1. System (2)–(6) 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

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

Notice that Theorem 1 says nothing about stability of the solution in question. In the sequel, stability is understood as orbital (Poincaré) asymptotic stability (Hale and Koçak, 1991).

Consider a periodic solution $x^p(t)$ of (2)–(6) with the initial condition $x^p(t_0 - 0) = x^0$. Let $\Omega \subset \mathbb{R}^3$ be the positive semi-trajectory corresponding to $x^p(t)$ for $t \geqslant t_0 - 0$. The solution $x^p(t)$ will be called *stable*, if for any $\varepsilon > 0$ there exists a number $\varepsilon_0 > 0$ such that if $\|x(t_0 - 0) - x^p(t_0 - 0)\| < \varepsilon_0$, 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 $t_0 - 0$ satisfies the limit relationship

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

Notice that the starting time is essential here.

Local stability of a 1-cycle can be checked by linearizing the mapping $Q(x)$ in a neighborhood of the fixed point x^0.

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 $y^0 = Cx^0$. Then the 1-cycle with the inital condition $x(t_0 - 0) = x^0$ is stable if

$$A_1 = e^{A\Phi(y^0)}\big[I + F'(y^0)BC\big] + \Phi'(y^0)Ax^0C$$

is Schur stable (i.e. all its eigenvalues lie strictly inside the unit circle).

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

$$Q(Q(x^0)) = x^0. \tag{9}$$

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 $x(t_0 - 0) = x^0$ satisfy the following transcendental equations, where $y^0 \neq \hat{y}^0$:

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

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

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

Notice that if the above equations are satisfied, system (2)–(6) has two 2-cycles with the initial values $x(t_0 - 0) = x^0$ and $x(t_0 - 0) = \hat{x}^0$, respectively. These 2-cycles have the same trajectory and differ only in the time domain by a phase shift.

It can be shown that if $\hat{y}^0 > 0$ is fixed, equation (10) is uniquely solvable in y^0. On the other hand, if $y^0 > 0$ is fixed, equation (11) is uniquely solvable in $\hat{y}^0$.

Theorem 4. Let $F(\cdot)$ and $\Phi(\cdot)$ have continuous derivatives in some neighborhoods of y^0 and $\hat{y}^0$. Consider the matrix

$$A_2 = \hat{A}_1\hat{A}_2,$$

where

$$\hat{A}_1 = e^{A\Phi(\hat{y}^0)}\big[I + F'(\hat{y}^0)BC\big] + \Phi'(\hat{y}^0)Ax^0C,$$
$$\hat{A}_2 = e^{A\Phi(y^0)}\big[I + F'(y^0)BC\big] + \Phi'(y^0)A\hat{x}^0C.$$

Then the 2-cycle with the initial value $x(t_0 - 0) = x^0$ is stable if A_2 is Schur stable.

5. PIECEWISE LINEAR MODULATION CHARACTERISTICS

Following (Rasgon *et al.*, 2003), consider a special case when $F(\cdot)$ and $\Phi(\cdot)$ are piecewise linear. Namely, let

$$F(y) = \begin{cases} F_2, & 0 \leqslant y < \Delta_1, \\ -k_F y + b_F, & \Delta_1 \leqslant y \leqslant \Delta_2, \\ F_1, & y > \Delta_2, \end{cases}$$

$$\Phi(y) = \begin{cases} \Phi_1, & 0 \leqslant y < \Delta_1, \\ k_\Phi y + b_\Phi, & \Delta_1 \leqslant y \leqslant \Delta_2, \\ \Phi_2, & y > \Delta_2. \end{cases}$$

where

$$0 < F_1 < F_2, \quad 0 < \Phi_1 < \Phi_2, \quad 0 < \Delta_1 < \Delta_2.$$

and k_F, b_F, k_Φ and b_Φ are selected to render continuous functions:

$$k_F = \frac{F_2 - F_1}{\Delta_2 - \Delta_1}, \qquad b_F = \frac{\Delta_2 F_2 - \Delta_1 F_1}{\Delta_2 - \Delta_1},$$
$$k_\Phi = \frac{\Phi_2 - \Phi_1}{\Delta_2 - \Delta_1}, \qquad b_\Phi = \frac{\Delta_2 \Phi_1 - \Delta_1 \Phi_2}{\Delta_2 - \Delta_1}.$$

Thus, the function $\Phi(y)$ is rising from Φ_1 to Φ_2, while $F(y)$ is falling from F_2 to F_1. The functions saturate simultaneously and are constant on two intervals $y \leqslant \Delta_1$ and $y \geqslant \Delta_2$.

Consider a solution $x(t)$ of (2)–(6). The solution $x(t)$ will be called *saturated*, if all the values

$$y_n = Cx(t_n - 0), \quad n = 0, 1, \ldots, \tag{12}$$

belong to the saturation intervals of $F(y)$ and $\Phi(y)$. The solution $x(t)$ will be called *semi-saturated*, if some of the values (12) belong to the saturation intervals, and some do not.

Theorem 5. Any saturated m-cycle is stable.

The piecewise linear character of Φ, F enables a systematic analysis of saturated periodic solutions of model (2)–(6). Direct calculations yield the following saturation conditions.

Theorem 6. A saturated 1-cycle exists iff one of the following inequalities holds:

$$g_1 g_2 F_2 \sum_{i=1}^{3} \frac{\alpha_i}{e^{b_i\Phi_1} - 1} \leqslant \Delta_1,$$

$$g_1 g_2 F_1 \sum_{i=1}^{3} \frac{\alpha_i}{e^{b_i\Phi_2} - 1} \geqslant \Delta_2.$$

From Theorem 1 it follows that the 1-cycle is unique.

Theorem 7. A saturated 2-cycle exists iff $y^0 \neq \hat{y}^0$ and

$$\min\{y^0, \hat{y}^0\} \leqslant \Delta_1, \quad \max\{y^0, \hat{y}^0\} \geqslant \Delta_2,$$

where

$$y^0 = g_1 g_2 \sum_{i=1}^{3} \alpha_i \frac{F_2 + F_1 e^{b_i \Phi_1}}{e^{b_i(\Phi_1+\Phi_2)} - 1},$$
$$\hat{y}^0 = g_1 g_2 \sum_{i=1}^{3} \alpha_i \frac{F_1 + F_2 e^{b_i \Phi_2}}{e^{b_i(\Phi_1+\Phi_2)} - 1}.$$

5.1 *Simulation results*

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.

Consider piecewise linear $F(\cdot)$ and $\Phi(\cdot)$ with

$$\Delta_1 = 1.5,\ \Delta_2 = 4,\ \Phi_1 = 60,\ \Phi_2 = 100,$$
$$F_1 = 3,\ F_2 = 5.$$

As an example, consider different types of behavior arising from variation of the element b_1 in the matrix of the linear part

$$A = \begin{bmatrix} -b_1 & 0 & 0 \\ 2 & -0.15 & 0 \\ 0 & 0.5 & -0.2 \end{bmatrix}.$$

This corresponds to alternations in the clearing rate of GnRH.

(1) For $b_1 \leqslant 0.03$ the system has a stable saturated 1-cycle ($\lambda_n = 3$).
(2) For $b_1 = 0.04$ the system has an unstable unsaturated 1-cycle and two stable semi-saturated 2-cycles with the same trajectory (saturation with $\lambda_n = 3$).
(3) For $0.05 \leqslant b_1 \leqslant 0.08$, the system has an unstable unsaturated 1-cycle and two stable saturated 2-cycles.
(4) $0.09 \leqslant b_1 \leqslant 0.11$ the system has an unstable unsaturated 1-cycle and two stable semi-saturated 2-cycles (saturation with $\lambda_n = 5$).
(5) For $b_1 \geqslant 0.12$ the system has a stable saturated 1-cycle ($\lambda_n = 5$).

The intervals $(0.03, 0.04)$ and $(0.11, 0.12)$ contain the values of b_1, for which a period-doubling bifurcation takes place, (Zhusubaliev and Mosekilde, 2003).

In Fig. 1 the two sets of points with the coordinates (y^0, y^1), $y^1 = \hat{y}^0$, satisfying (10), (11) are shown. Their intersection point with $y^0 = y^1$ corresponds to a 1-cycle (see (8)), and two intersection points with $y^0 \neq y^1$ correspond to 2-cycles.

The graphs of the transition from the unstable mode with single pulse on the period to the stable mode with a double pulse on the period are shown in Fig. 2. A trajectory corresponding to a 2-cycle is depicted in Fig. 3. Notice the prominent discontinuous behavior of the model along GnRH axis, due to the pulse-modulated feedback.

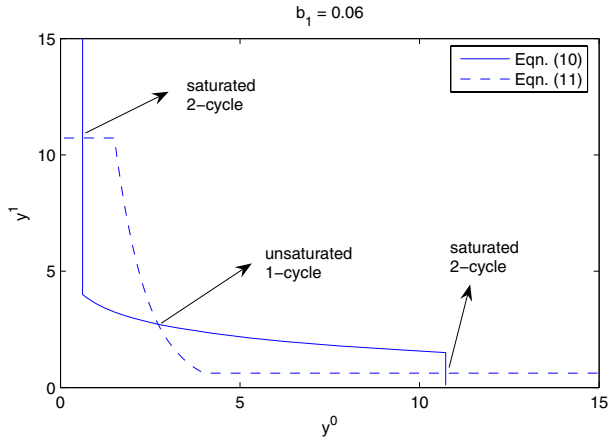

Fig. 1. Graphical solution of equations (10), (11).

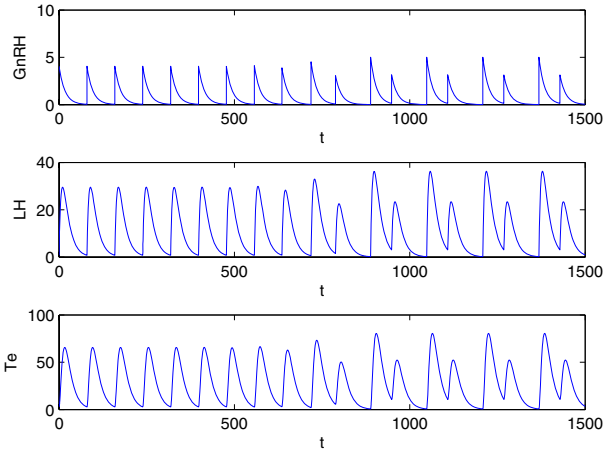

Fig. 2. Periodic solution for $b_1 = 0.06$. An unstable 1-cycle evolves to a stable 2-cycle.

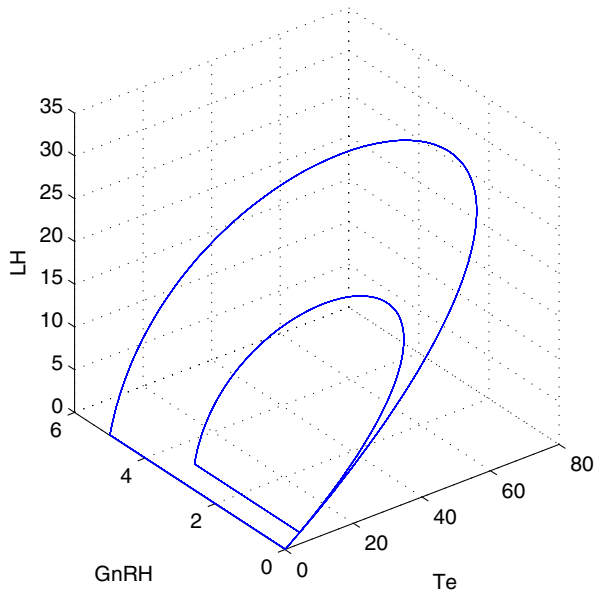

Fig. 3. The trajectory of a 2-cycle.

6. CONCLUSIONS

The process of pulsatile endocrine regulation can suitably be described by means of pulse-modulated systems. A simple dynamic model of GnRH–LH–Te axis in the male is suggested and shown to produce stable periodic solutions with one or two GnRH pulses on the period. A deeper biological insight into the feedback mechanisms of Te regulation by means of GnRH is needed to achieve realistic signal profiles in the involved hormone serum concentrations.

In clinical or experimental data, the regularity of hormone oscillations is heavily perturbed by many impacting factors. Both the amplitudes and periods of GnRH pulses are subject to significant variations which are often described as stochastic. However, the underlying dynamics of the GnRH–LH–Te axis can probably be explained by simple deterministic models, provided they take into account the feedback mechanism of hormonal regulation.

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