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Agnieszka Bartłomiejczyk (Gdańsk)
Beata Jackowska-Zduniak (Warsaw)

Dynamics of a simplified HPT model in relation to 24h TSH profiles.

Abstract We propose a simplified mathematical model of the hypothalamus-pituitary-thyroid (HPT) axis in an endocrine system. The considered model is a modification of the model proposed by Mukhopadhyay and Bhattacharyya in [10]. Our system of delay differential equations reconstructs the HPT axis in relation to 24h profiles of human in physiological conditions. Homeostatic control of the thyroid-pituitary axis is considered by using feedback and delay in our model. The influence of delayed feedback on the stability behaviour of the system is discussed.

2010 Mathematics Subject Classification: Primary: 58F15, 58F17; Secondary: 53C35.

Key words and phrases: Delay differential equations, stability, HPT model.

1. Introduction The thyroid gland (thyroid) is located in the anterolateral lower part of the neck. It is built of two lateral lobes connected by a narrow isthmus and reminds of the shape of a butterfly. When the thyroid is overactive or underactive, it does not hurt and usually does not show any symptoms for a long time. However, the disorders in the work of this gland have an effect on the entire human body. The thyroid gland is responsible regulating for different body functions (including body temperature, body weight, skin integrity, heart rate, breathing, cholesterol levels, muscle strength, menstrual cycle) and control of metabolism. Thyroid gland secretes, inter alia, a thyroxine hormone (T4). The thyroid gland is influenced by hormones produced by two other organs: the pituitary gland and the hypothalamus. The pituitary gland, located at the base of the brain, produces thyroid stimulating hormone (TSH). The hypothalamus, a small part of the brain above the pituitary, produces thyrotropin releasing hormone (TRH). Low levels of thyroid hormones in the blood are detected by the hypothalamus and the pituitary. TRH is released, stimulating the pituitary to release TSH. Increased levels of TSH, in turn, stimulate the thyroid to produce more thyroid hormone, thereby returning the level of thyroid hormone in the blood back to normal. Endocrine hormones have their controls at the biochemical level of cell, but moving information through the bloodstream are also in the subsequent physiological

regulation of feedback loops. It can be easily seen that we have a homeostatic mechanism in the endocrine system. The concept of a negative feedback loop between the thyroid and pituitary glands was proposed as early as in 1940 and established experimentally before 1950, [6]. Regulating work of the endocrine system depends on dynamic inter-relationships between the level of thyroid and pituitary hormones. There are molecular mechanisms involving multiple feedback loops on several levels of organization, different time scales, and varying conditions of their optimum operation. The simplified form of this mechanism is presented in Fig. 1.

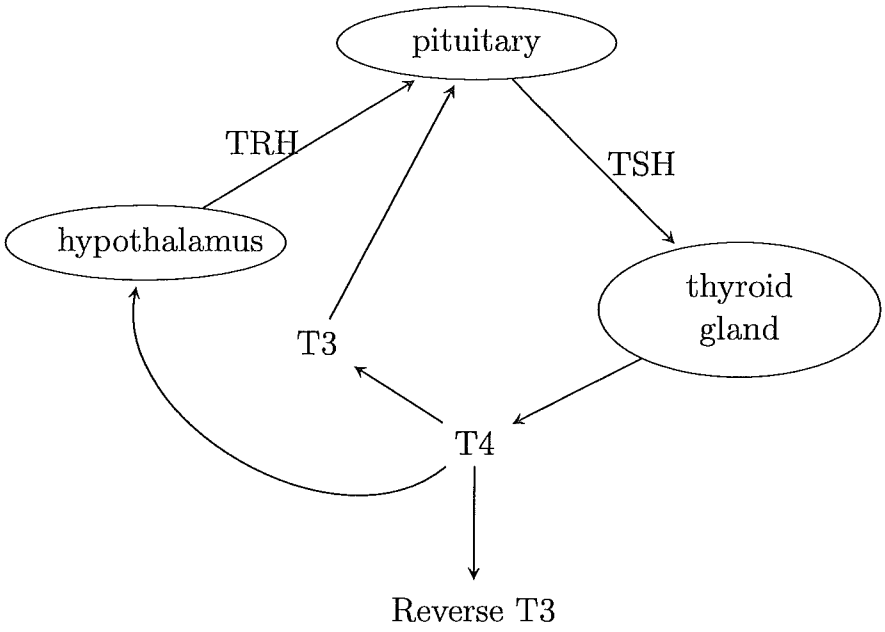

Figure 1: The simplified homeostasis mechanism of thyroidal influences in the absence of thyroid inhibitors, in which arrows indicate the coupling between individual hormones, also negative feedback loops. The output of the thyroid gland is the thyroid hormones (T3 and T4), in which, the free thyroid hormones (FT4 and FT3) are usually sensed by the pituitary gland and/or the hypothalamus to regulate the input of the thyroid gland, TSH.

The above description shows the complexity of the regulation mechanism of the HPT axis, making the interaction between TSH, T4 and FT3 situational and mathematically more complex. We consider the simplified homeostasis mechanism. When there is a high level of thyroxine in blood, it act inhibiting on the pituitary gland and reduces the production of thyrotropin. This reduces the secretion of thyroxine by the thyroid gland and after some time its level in the blood decreases. This is a signal to the pituitary gland to resume production of the tropic hormone and either the cycle repeats, or establishes an equilibrium between thyrotropin and thyroxine hormones. By analogy, a feedback mechanism acts on the hypothalamus, [4, 5, 7]. Irregularity in the synthesis or release of hormones on any of the levels (hypothalamic, pituitary or peripheral) causes a disturbance in hormonal homeostasis and thus the

whole body. The homeostatic mechanism in our system is presented in Fig. 2.

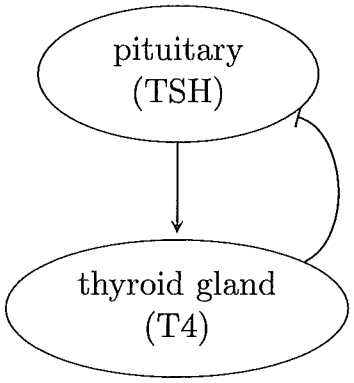

Figure 2: TSH–T4 feedback loop.

In early sixties, it became obvious that hormones such as cortisol, LH and TSH are secreted episodically and with a diurnal variation, each with their specific secretion pattern under physiological conditions. In healthy adults, TSH level remains low during the day and begins to increase before the night. Maximal TSH level is observed soon before sleep, and is independent of the cortisol rhythm and fluctuations in thyroid hormone levels [12]. After the one-set of sleep, TSH levels decrease, which is prevented by keeping the person awake. TSH secretion is partially pulsatile. How TSH pulses are generated is not completely understood. The HPT axis maintains circulating levels of thyroid stimulating hormone and the thyroid hormone in an inverse relationship [9, 12].

2. Mathematical model. For years the Danziger and Elmergreen model has been the most popular model of the thyroid-pituitary homeostatic mechanism [3]. In paper [3], properties of the solutions of the mathematical model for the study of periodic catatonic schizophrenia are studied. In [10], the modified Danziger-Elmergreen model was considered. It is worth noting that the author introduces a discrete delay in feedback, which corresponds to delay which reflects time lags required for transportation of the hormones. The stability of behavior of the system is analyzed and numerical study to illustrate the analytical results is presented. In [11] authors considered the hypothalamus-pituitary as a single unit. The variables TSH, FT4, anti-thyroid peroxidase antibodies (TPOAb) and the functional (active) size of the thyroid gland are considered in the proposed system. The ordinary differential equations are used to reconstruct dynamics of thyroid hormones and the size of thyroid glands during an autoimmune (Hashimoto's) thyroiditis. Author takes into account the coupling of the system but without delay. Particularly, it is important to introduce time delay into this feedback.

In our paper we focus on the model proposed in [10], where authors assumed that the rate of thyrotropin production and the rate of loss of thy-

rotropin depends on regulation which was described above as the mechanism of the homeostasis. The model is extended to a degenerate form for the thyrotropin production when the level of thyroxine hormone is to high and the thyrotropine hormone cannot be produced. Authors assumed that the activated enzyme is activated by thyrotropin and then a thyroxine hormone is produced. The described model reads, [10]:

$$\begin{aligned} \dot{P}(s) &= \begin{cases} c - gP(s) - h\theta(s-\tau_1) & \text{if} \quad \theta \leq \frac{c}{h} \\ -gP(s) & \text{if} \quad \theta > \frac{c}{h} \end{cases} \\ \dot{E}(s) &= mP(s-\tau_2) - kE(s), \\ \dot{\theta}(s) &= aE(s) - b\theta(s), \end{aligned} \tag{1}$$

where P, E, θ represent the concentration of thyrotropin, an activated enzyme and thyroxine respectively, b, g, k represent the constant loss of thyroxine, thyrotropin and the activated enzyme, a, h, m are positive constants expressing the sensitivities of the glands to simulation or inhibition, c is the rate of production of thyrotropin in the absence of thyroid inhibition, τ_1 and τ_2 represent the discrete time delays required for transportation of the hormones thyroxine and thyrotropin respectively.

We simplify this model to two equations (for P (in [mU/l]) and θ (in [pmol/l])) for the dynamics of two variables (thyrotropin, thyroxine hormones) because the available literature data with diurnal variation in hormone levels are available for thyrotropin and thyroxine, whereas the activating enzyme is unknown. Hence, we eliminate the equation for this variable.

We estimate the values of parameters in the model based on literature data (see [9, 12]). The results are given in Fig. 3.

Instead of the activated enzyme we add in the second equation additional delay. We also introduce to this system feedback and time lags. Feedback loop in our model includes the effect of the target organ feedback, on the lower intermediate floor secretory-anterior lobe of the pituitary gland, which is presented in Fig. 2.

2.1. Construction of model Our system can be given as:

$$\begin{aligned} \dot{P}(s) &= c - h\min\left\{\theta(s-\tau_P), \frac{c}{h}\right\} - gP(s), \\ \dot{\theta}(s) &= aP(s-\tau_\theta) - b\theta(s), \end{aligned} \tag{2}$$

where P is a concentration of thyrotropin and θ – thyroxine and b, g represent the loss constants of thyroxine and thyrotropin respectively, a, h are positive constants expressing the sensitivities of the glands to the simulation or inhibition, c is the rate of production of thyrotropin in the absence of thyroid inhibition, τ_P and τ_θ represent the discrete time delays required for transportation of the hormones thyroxine and thyrotropin respectively. We

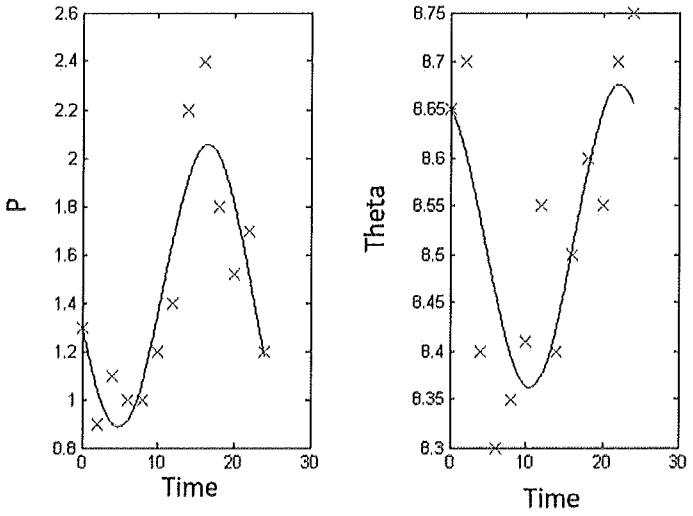

Figure 3: Estimation of parameters based on literature data, [9, 12]. Values of estimation parameters: $c = 3.2407\,\frac{\mathrm{mU}}{\mathrm{l}} \cdot \mathrm{h}^{-1}$, $h = 0.3779\,\frac{\mathrm{mU}}{\mathrm{pmol}} \cdot \mathrm{h}^{-1}$, $g = 0.029\,\mathrm{h}^{-1}$, $a = 0.1540\,\frac{\mathrm{pmol}}{\mathrm{mU}} \cdot \mathrm{h}^{-1}$, $b = 0.0279\,\mathrm{h}^{-1}$.

observe that:

$$\bar{P} = \frac{bc}{ah + bg}, \quad \bar{\theta} = \frac{ac}{ah + bg}$$

is a unique steady state. First, we reduce the number of parameters by scaling the functions and time in our equations:

$$P = \frac{cb}{ah}x, \quad \theta = \frac{c}{h}y, \quad t = bs, \quad \tau_1 = b\tau_P, \quad \tau_2 = b\tau_\theta$$

and introducing new constants:

$$\frac{ah}{b^2} = \alpha, \quad \frac{g}{b} = \beta.$$

Then our system (2) can be put in the dimensionless form

$$\begin{aligned} \dot{x}(t) &= \alpha(1 - \min\{y(t - \tau_1), 1\}) - \beta x(t), \\ \dot{y}(t) &= x(t - \tau_2) - y(t), \end{aligned} \tag{3}$$

where the dot represents the derivative with respect to the dimensionless time t. Moreover, we impose the initial condition

$$x(t) = \varphi_P, \quad y(t) = \varphi_\theta, \quad \text{for} \quad t \in [-\tau_M, 0], \tag{4}$$

where the functions φ_P and φ_θ are non-negative and continuous on the interval $[-\tau_M, 0]$, $\tau_M = \max\{\tau_1, \tau_2\}$.

2.2. Basic properties of model We consider the dimensionless model (3). Due to the fact that the right-hand side of (3) is locally Lipschitz continuous with respect to the variables (x, y), we conclude that the solution to (3) exists locally and is unique. Moreover, the form of system (3) guarantees the non-negativity of the solution.

From the above observations we obtain the following result.

THEOREM 2.1 (LOCAL EXISTENCE, UNIQUENESS AND NON-NEGATIVITY) If the initial functions defined by (4) are non-negative then there exists a unique and non-negative solution to (3)–(4) defined for all forward time.

Let $\mathbb{C}(I, \mathbb{R})$ denote the set of continuous functions defined on the interval I with values in $\mathbb{R}$.

THEOREM 2.2 (INVARIANT SET) The set

$$\Omega = \left\{(x, y) \in \mathbb{C}\left([-\tau_M, 0], \mathbb{R}\right) : 0 \leq x(t) \leq \frac{\alpha}{\beta}, 0 \leq y(t) \leq \frac{\alpha}{\beta},\ t \in [-\tau_M, 0]\right\}$$

is invariant under the evolution of system (3).

PROOF Since $y(t) \geq 0$ for all $t \geq -\tau_2$, the first equation of system (3) yields

$$\dot{x}(t) + \beta x(t) \leq \alpha.$$

Thus,

$$x(t) \leq \frac{\alpha}{\beta} + \left(x_0 - \frac{\alpha}{\beta}\right) e^{-\beta t},$$

where $x_0 = \varphi_P(0)$. Finally, we get

$$x(t) \leq \max\left\{\frac{\alpha}{\beta}, x_0\right\}$$

for $t \geq 0$. By a similar argument, we obtain

$$y(t) \leq \max\left\{\frac{\alpha}{\beta}, x_0, y_0\right\},$$

where $y_0 = \varphi_\theta(0)$, which completes the proof. ∎

REMARK 2.1 From the existence of the invariant set Ω we can deduce the global existence of the solutions to system (3).

3. Asymptotic behaviour of system We start with calculating of the steady state of system (3):

$$\bar{x} = \frac{\alpha}{\alpha + \beta}, \quad \bar{y} = \frac{\alpha}{\alpha + \beta}.$$

Now we formulate and prove the main result.

THEOREM 3.1 (i) If $\alpha < \beta$ then the steady state $(\bar{x}, \bar{y})$ of system (3) is locally asymptotically stable for $\tau_1, \tau_2 \geq 0$.

(ii) If $\beta < \alpha$, then exists a critical value τ_{cr} such that the steady state $(\bar{x}, \bar{y})$ of system (3) is stable for all $\tau_1 + \tau_2 < \tau_{cr}$, and unstable for all $\tau_1 + \tau_2 > \tau_{cr}$, where

$$\tau_{cr} = \frac{1}{\omega_0} \arctan \frac{(1+\beta)\omega_0}{\omega_0^2 - \beta} \tag{5}$$

and

$$\omega_0 = \sqrt{\frac{-(1+\beta^2) + \sqrt{(1-\beta^2)^2 + 4\alpha^2}}{2}}. \tag{6}$$

Moreover, for $\tau_1 + \tau_2 = \tau_{cr}$ periodic solutions arise with period close to $2\pi/\omega_0$.

PROOF First, we observe that the characteristic function has the following form

$$W(\lambda) = \det \begin{bmatrix} -\beta - \lambda & -\alpha e^{-\lambda\tau_1} \\ e^{-\lambda\tau_2} & -1 - \lambda \end{bmatrix}.$$

Then, the characteristic equation reads

$$\lambda^2 + (1+\beta)\lambda + \beta + \alpha e^{-\lambda\tau} = 0, \tag{7}$$

where $\tau = \tau_1 + \tau_2$. It is easily seen that for $\tau = 0$ all roots of the above equation have a negative real part, so the steady state is asymptotically stable. It is worth pointing out that the switches of stability occur when a pair of complex conjugate roots crosses the imaginary axis. For this purpose, we write quasi-polynomial $W(\lambda)$ in the following form

$$W(\lambda) = P(\lambda) + Q(\lambda)e^{-\lambda\tau},$$

where $P(\lambda) = \lambda^2 + (1+\beta)\lambda + \beta$ and $Q(\lambda) = \alpha$. Now we try to find purely imaginary characteristic roots, i.e. we solve the equation $W(i\omega) = 0$. To do this, we define the auxiliary function

$$F(\omega) = |P(i\omega)|^2 - |Q(i\omega)|^2 = \omega^4 + \omega^2(1+\beta^2) + \beta^2 - \alpha^2.$$

If $\beta > \alpha$ then $F(\omega) > 0$ for all $\omega \in \mathbb{R}$. In consequence the steady state is stable for $\tau \geq 0$, which completes the proof of (i). If $\beta < \alpha$ then, there exists a unique simple positive root of the polynomial $F(\omega)$ given by the formula

$$\omega_0 = \sqrt{\frac{-(1+\beta^2) + \sqrt{(1-\beta^2)^2 + 4\alpha^2}}{2}}.$$

It is easy to check that $F'(\omega_0) > 0$. Hence, there exists τ_{cr} such that system (3) is stable for $\tau = \tau_1 + \tau_2 < \tau_{cr}$ and unstable for $\tau = \tau_1 + \tau_2 > \tau_{cr}$ (compare [1, 2, 8]). Moreover, substituting $\lambda = i\omega_0$ in (7) and separating the real and imaginary parts, we get

$$\sin(\omega_0 \tau_{cr}) = \frac{(1+\beta)\omega_0}{\alpha} \quad \text{and} \quad \cos(\omega_0 \tau_{cr}) = \frac{\omega_0^2 - \beta}{\alpha} \tag{8}$$

and in consequence the critical value of time delay is given by (5). The proof is completed. ∎

REMARK 3.1 Due to the fact that the function $F(\omega)$ has exactly one positive zero we conclude that no more stability switches are possible. The stability of the steady state depends on the sum of delays. Moreover, there are oscillations of constant amplitude for $\tau_1 + \tau_2 = \tau_{cr}$.

Now, we present the graphs of solutions to the non-rescaled system (2) for different values of time delays and the rest of parameters as given in the caption of Fig. 3. For these parameters we calculate the critical value of time delay, i.e. $\tau_{cr} = 0.1457$. In Fig. 4 we show the behaviour of solutions to (2) in the case without delay.

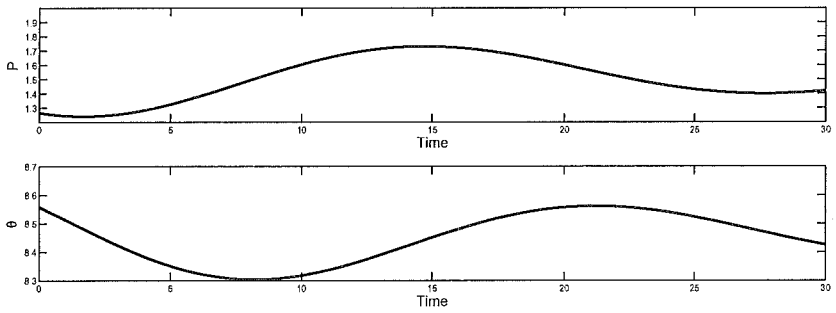

Figure 4: Trajectories of solutions to (2) for reference parameters – case without delay.

In the next figures (Fig. 5 and Fig. 6), we present the behaviour of solutions to (2) for $\beta < \alpha$. In this case we observe that the steady state of our system (2) is stable for all $\tau_1 + \tau_2 < \tau_{cr}$, see Fig. 5.

For $\tau_1 = \tau_2 = 5$, i.e. in the case when $\tau_1 + \tau_2 > \tau_{cr}$, according to Theorem 3.1 the steady state is unstable and moreover there exists periodic solutions. In Fig. 6 we present projections of trajectories of the solution to (2) in the plane (P, θ) and we observe the undumping oscillations confirming our analytical results.

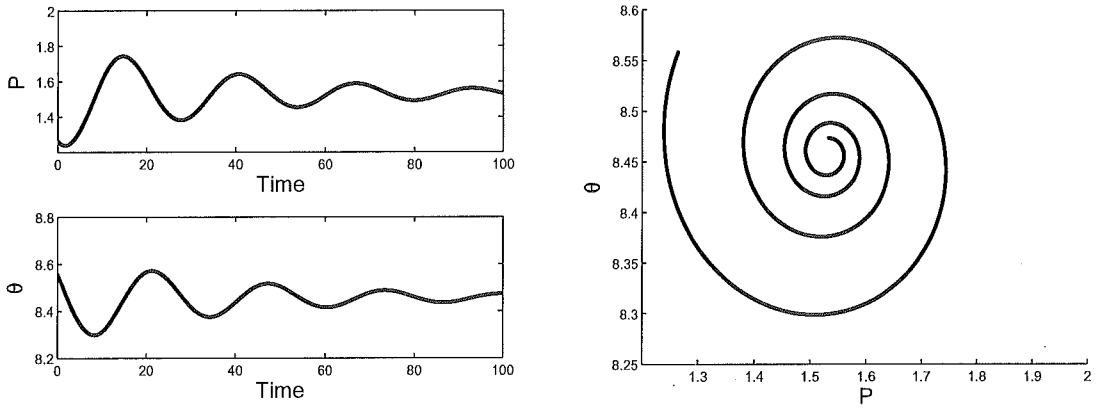

Figure 5: The level of hormones in time [h] (left side). Solutions to (2) in the plane (P, θ) for the case with delays (right side): $\tau_1 = 0.01$, $\tau_2 = 0.1$ and for reference parameters. In this case $\tau_1 + \tau_2 < \tau_{cr}$, so the steady state is stable.

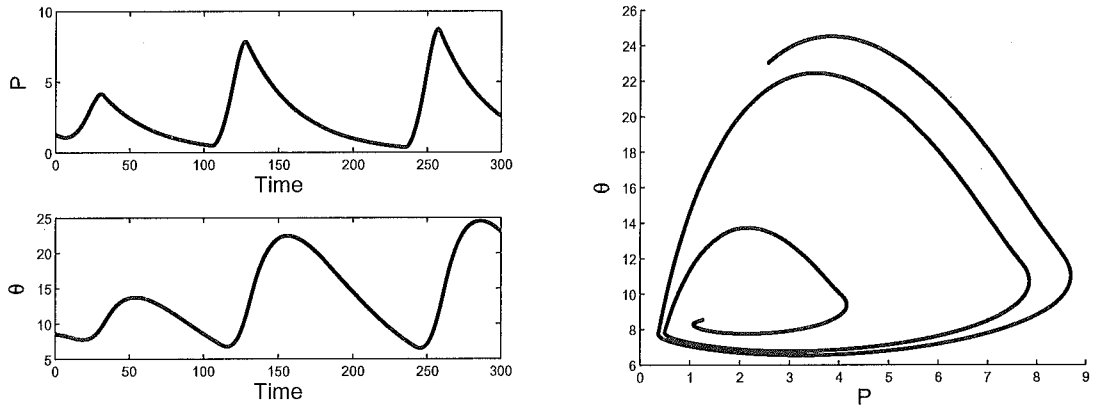

Figure 6: The level of hormones in time [h] (left side). Solutions to (2) in the plane (P, θ) for the case with delays (right side): $\tau_1 = \tau_2 = 5$ and for reference parameters. In this case $\tau_1 + \tau_2 > \tau_{cr}$, so the steady state is unstable.

4. Summary. The aim of this work is to propose a mathematical model describing the secretion system HPT using DDEs with a feedback loop. According to the control theory the feedback loops in the endocrine system try to regulate the value of concentration of the thyroxine hormone. The considered model is a modification of the model proposed by Mukhopadhyay and Bhattacharyya in [10]. We simplified this model to two equations (for P and θ), because we have medical data for the dynamics of two variables (thyrotropin, thyroxine hormones) in the circadian cycle. It is very difficult to obtain data for the activated enzyme, hence we eliminate the equation for this variable. In this work usage of the proposed model allowed to show that we have non-negative solutions of our system what is not prevented in [10]. The quality of a mathematical model depends on how well the model developed on the the-

oretical side and if it agrees with results of repeatable experiments. The lack of agreement between the theoretical mathematical model and experimental measurements often leads to mistakes such as even negative solutions. The analysed system keeps local stability which is very important for mathematical models used for a description of medical phenomena.

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Dynamika modelu HPT w relacji z 24h zapisem TSH.

Agnieszka Bartłomiejczyk i Beata Jackowska-Zduniak

Streszczenie W pracy zapropnowano uproszczony model matematyczny osi podwzgórze-przysadka-tarczyca (HPT). Rozważany model jest modyfikacją modelu zaproponowanego przez Mukhopadhyay i Bhattacharyya w [10]. Nasz układ równań różniczkowych z opóźnieniem modeluje oś HPT w odniesieniu do profili 24h u ludzi w warunkach fizjologicznych. Kontrolę homeostazy osi tarczyca-przysadka uwzględnia się za pomocą sprzężenia zwrotnego z opóźnieniem, które jest zadane w naszym modelu. W pracy omówiono również wpływ sprzężenia zwrotnego z opóźnieniem na zachowanie stabilności układu.

Klasyfikacja tematyczna AMS (2010): 58F15, 58F17; 53C35.

Słowa kluczowe: równania różniczkowe z opóźnieniem, stabilność, model HPT.

Dr. Agnieszka Bartłomiejczyk took her M.Sc. and Ph.D. at the Faculty of Mathematics and Computer Science of Nicolaus Copernicus University in Toruń. She is currently an Assistant Professor at the Faculty of Applied Physics and Mathematics of Gdańsk University of Technology. She works on the development of the mathematical methods which could be useful in the sphere of applications. Her recent research interests focus on mathematical modelling in biology and chemistry including investigation of gene expression and structured population. She is the editor of three volumes of the monograph *Mathematical methods in applications*. She is a reviewer for many interdisciplinary papers submitted to international journals such as Topological Methods in Nonlinear Analysis, Mathematical Biosciences and Engineering, International Journal of Control. She has been very active in organizing conferences and workshops under the project of the Center for Applications of Mathematics. She also collaborates with Warsaw Biomat Team.

Beata Jackowska-Zduniak received the M.Sc. degree in mathematics from Cardinal Stefan Wyszynski University, Poland, in 2007, the M.Sc. degree in physics from Warsaw University of Technology, Poland, in 2008 and the Ph.D. degree in mechanics from Military University of Technology, Poland, in 2011. She is currently an assistant professor of Warsaw University of Life Sciences, Poland. Her research interests include dynamical systems, biological modeling, delayed differential equations and mechanics.

Agnieszka Bartłomiejczyk
Gdańsk University of Technology
Faculty of Applied Physics and Mathematics
Gabriela Narutowicza 11/12, 80-233 Gdansk, Poland
E-mail: agnbartl@pg.edu.pl

Beata Jackowska-Zduniak
Warsaw University of Life Sciences SGGW
Faculty of Applied Informatics and Mathematics
Nowoursynowska 159, 02-776 Warsaw, Poland
E-mail: beata_jackowska_zduniak@sggw.pl

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