

Stability Analysis for an Extended Model of the Hypothalamus-Pituitary-Thyroid Axis

Beata Jackowska-Zduniak

Abstract—We formulate and analyze a mathematical model describing dynamics of the hypothalamus-pituitary-thyroid homeostatic mechanism in endocrine system. We introduce to this system two types of couplings and delay. In our model, feedback controls the secretion of thyroid hormones and delay reflects time lags required for transportation of the hormones. The influence of delayed feedback on the stability behaviour of the system is discussed. Analytical results are illustrated by numerical examples of the model dynamics. This system of equations describes normal activity of the thyroid and also a couple of types of malfunctions (e.g. hyperthyroidism).

Keywords—Mathematical modeling, ordinary differential equations, endocrine system, stability analysis.

I. INTRODUCTION

THE paper concerns a research of a secretion system, especially hypothalamus-pituitary-thyroid axis. The thyroid gland is responsible for the operation of virtually all cells of human body and the control of metabolism. Excessive or insufficient production of hormones by thyroid gland can cause a number of abnormalities in the body, including the suppression of physical and mental development. Thyroid gland secretes among others a thyroxine hormone (T4). This secretion is mainly regulated by the hypothalamus-pituitary-thyroid axis. The anterior lobe of pituitary gland produces the hormone called thyrotropin (TSH) which is needed to stimulate the thyroid to produce hormones. In turn, TSH is produced under the influence of the thyrotropin releasing factor (TRF), which is secreted by the hypothalamus. Thyroxine hormone production depends on an activated enzyme, which is activated by the thyrotropin hormone. The simplified mechanism of production of hormones is presented in Fig. 1 (A).

Endocrine hormones have their controls at the biochemical level cell, but moving information through the bloodstream is also in the subsequent physiological regulation of feedback loops. Loop in our model includes the effect of the target organ feedback, both on the hypothalamus and lower intermediate floor secretory-anterior lobe of the pituitary gland. It can be easily seen that we have a homeostatic mechanism in endocrine system. It means the ability to maintain stability of internal parameters in our system. Regulating work of the system consists in the fact that when there is a high level of thyroxine in blood, it operates inhibiting 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

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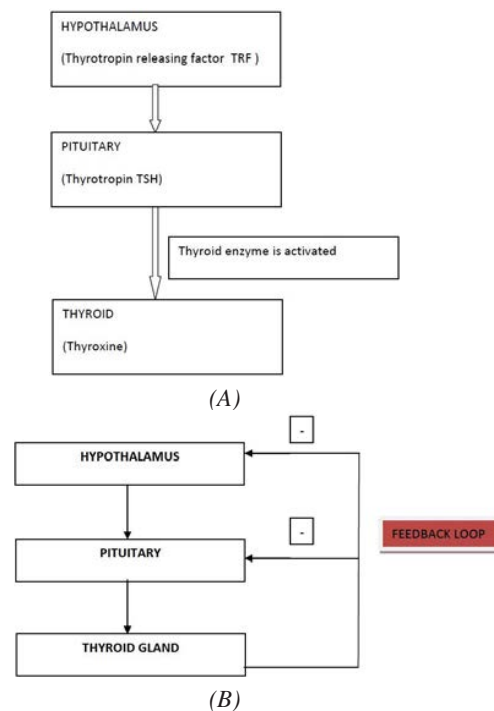


Fig. 1 Sketch of mechanisms in our problem (A) The simplified mechanism of production of thyroid hormones (B) Sketch of the homeostatic mechanism in our problem

gland to resume production of tropic hormone and either cycle repeats, or establishes an equilibrium between thyrotropin and thyroxine hormones. Similarly, it works a feedback mechanism that acts on the hypothalamus [4], [5], [9]. 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. 1 (B).

II. MATHEMATICAL MODEL

Modelling the formation of thyroid hormones is weakly developed area of mathematical biology. For years, the most popular model of the thyroid-pituitary homeostatic mechanism has been the Danziger and Elmergreen model [3]. This model, even though very effective, is not very suitable for studying the dynamics of the system, which is described in view of high dimensionality of the phase space and very broad spatial parameters. Also this system does not include hypothalamus, which is a very important part of the endocrine

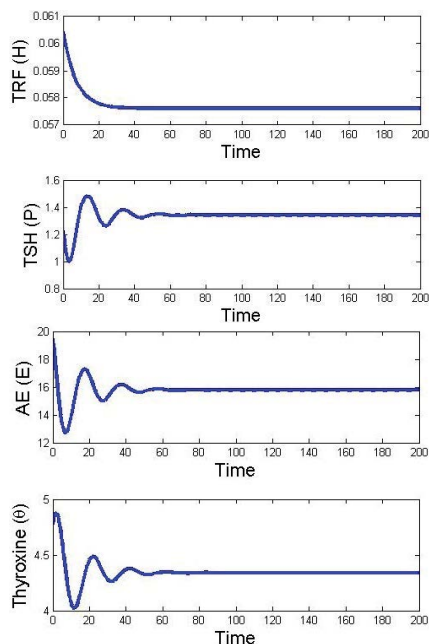


Fig. 2 Concentration of hormones in time, for parameters: $a_1 = 0.008$, $a_2 = 0.14$, $a_3 = 0.00035$, $b_1 = 2$, $b_2 = 0.6$, $c_1 = 47$, $c_2 = 0.2$, $d_1 = 2$, $d_2 = 0.1$, the positive steady state of the system (4) is stable. The parameters have been set so as to solution reflects the actual level of hormones

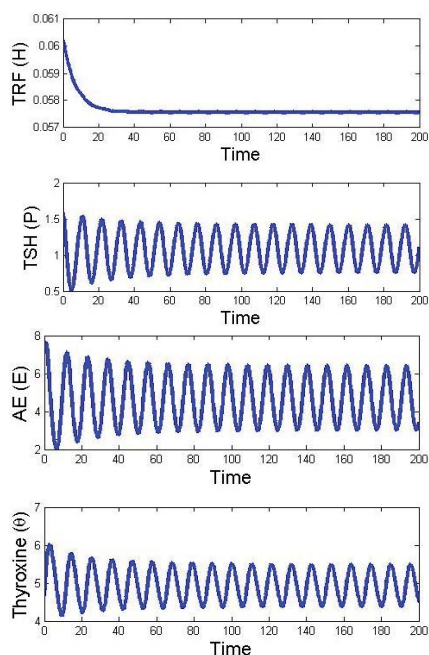


Fig. 3 Concentration of hormones in time, for parameters: a_1, a_2, a_3, b_1, d_2 - reference values, $b_2 = 0.5$, $c_1 = 50$, $c_2 = 0.5$, $d_1 = 20$, instable behaviour of system (4). In all cases we obtain oscillatory behaviour of our system

system. In [7], authors consider system with feedback, but it is also pituitary-thyroid model, which does not include the hypothalamus. It is worth noting that the author introduces a

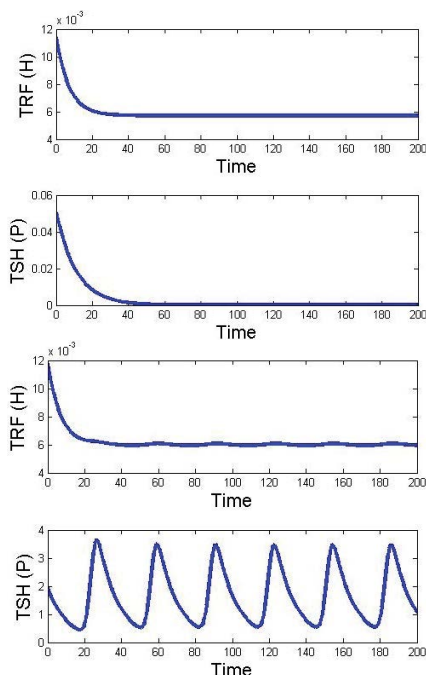


Fig. 4 Concentration of hormones in time, for a_1, a_2, a_3, b_1, d_2 - Reference Values, $b_2 = 0.09$, $c_1 = 47$, $c_2 = 0.2$, $d_1 = 2.1$, $\tau_{1,2} = 0$

discrete delay in feedback, which corresponds to delay which reflects time lags required for transportation of the hormones. In [8], authors also considered the hypothalamus-pituitary as a single unit. Author takes into account the coupling of the system but without delay. Particularly, it is important to introduce a time delay into this feedback. The model in [7] is based on the experimental data, which included a very serious illness, e.g. autoimmune thyroiditis (Hashimoto). The pathological behaviours are modelled in [7] and a very good agreement of the experimental results with the model was obtained. We focus on the model proposed in [8] that reads

$$\dot{P} = c - gP - h\theta(t - \tau_1), \dot{E} = mP(t - \tau_2) - kE, \dot{\theta} = aE - b\theta \quad (1)$$

where $\theta \leq \frac{c}{h}$; P , E , θ represent the concentration of thyrotropin, activated enzyme and thyroxine respectively; b , g , k represent the loss constant s of thyroxine, thyrotropin and activated enzyme; a , h , m are positive constant, 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.

In [8], [7] the authors have studied model without hypothalamus. Here, we would like to expand the pituitary-thyroid model and add the equation corresponding to the action of the hypothalamus in the secretory system and we also introduce to this system two types of couplings and delay. Feedback loop in our model includes the effect of the target organ feedback, both on the hypothalamus and lower intermediate floor secretory-anterior lobe of the pituitary gland, which is presented in Fig. 1 (B). The linear model, which is described in [3] can have negative solutions

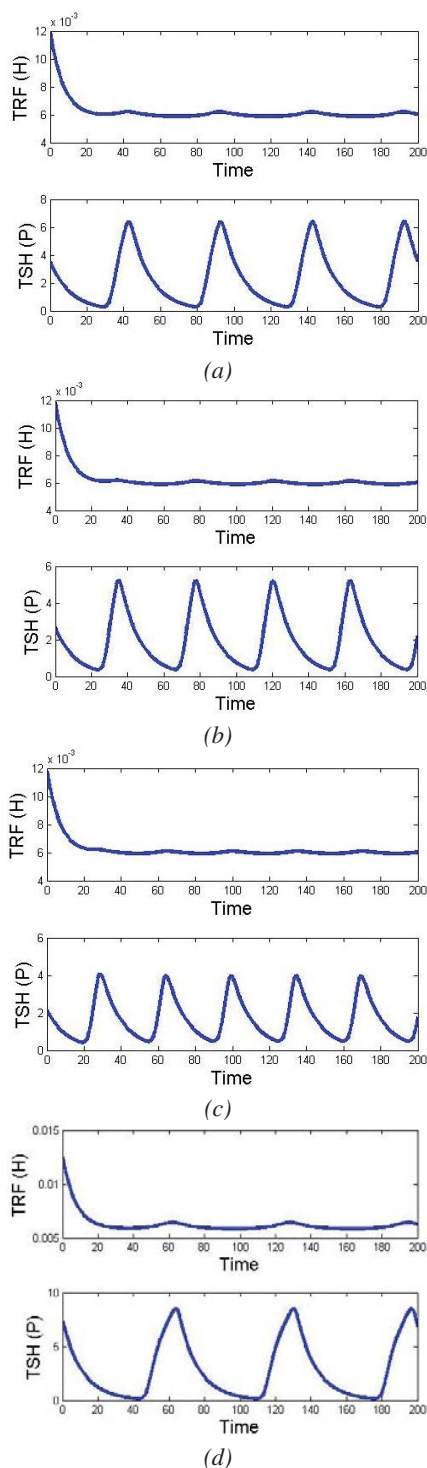


Fig. 5 Concentration of hormones in time, for parameters: $a_1 = 0.008$, $a_2 = 0.14$, $a_3 = 0.00035$, $b_1 = 2$, $b_2 = 0.09$, $c_1 = 47$, $c_2 = 0.2$, $d_1 = 2.1$, $d_2 = 0.1$, the best fitting is in Fig. 5 (c) for $\tau_{1,2} = 0.5$

(The condition below system (1) guarantees non-negativity, but the condition does not need to be preserved), what is a huge problem in describing the biological system (it can

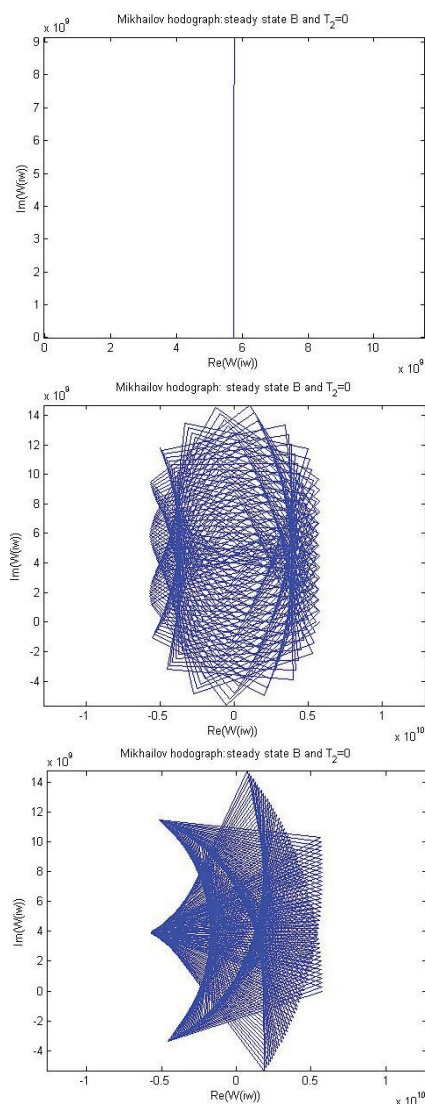


Fig. 6 With increasing delay ($\tau_1 = 0, 10, 15$, $\tau_2 = 0$) the shape of Mikhailov hodographs for B becomes more and more looped

mean that authors have negative values of concentrations of hormones, which is impossible). In our system we introduce the non-linear parts which eliminated this behaviour of system. The non-linear parts are introduced by using a Hill function as a control function of secretion of hormones. The Hill function is often used as an approximation for the input function when the production rate is a function. Hill equations have the following forms:

$$a) f(G) = \frac{(G/T)^n}{(G/T)^n + 1}, b) f(G) = \frac{1}{(G/T)^n + 1} \quad (2)$$

where $T > 0$ is a threshold and $n \geq 1$ is a Hill coefficient. The form (2a) is used as up-regulatory function and (2b) as a down-regulatory function. We also use Hill function to model a feedback control in our system. These feedback loops can driving hormone oscillations. Although the negative feedback

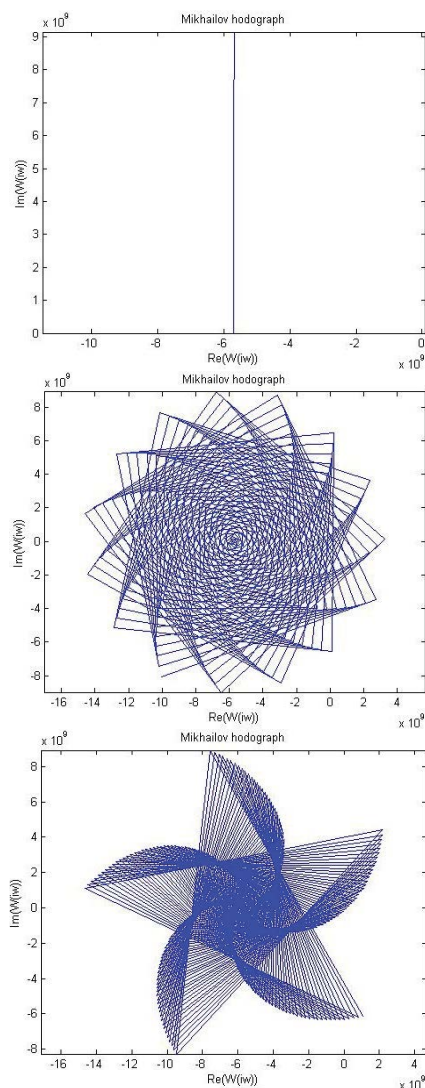


Fig. 7 With increasing delay ($\tau_2 = 0, 10, 15, \tau_1 = 0$) the shape of Mikhailov hodographs for B becomes more and more looped

loop with time delay often generates oscillatory behaviour for sufficiently large delays, the appearance of oscillation is not guaranteed by this kind of terms. Using Hill functions of the form (2), we write the general formula of system that we are going to analyse reads as:

$$\begin{aligned}\dot{H} &= a_1 - a_2 H + \frac{a_3}{(\theta(t - \tau_1)/T_H)^{n_H} + 1}, \\ \dot{P} &= b_1 \frac{(H/T_P)^{n_P}}{(H/T_P)^{n_P} + 1} - b_2 P + \frac{b_3}{(\theta(t - \tau_2)/T_R)^{n_R} + 1}, \\ \dot{E} &= c_1 \frac{(P/T_E)^{n_E}}{(P/T_E)^{n_E} + 1} - c_2 E, \\ \dot{\theta} &= d_1 \frac{(E/T)^n}{(E/T)^n + 1} - d_2 \theta\end{aligned}\quad (3)$$

where we assumed that τ_1 is greater than or equal τ_2 and $a_3 \ll b_3$, we denote concentration of thyrotropin releasing

factor by H , a_1 is the rate of production of thyrotropin releasing factor; a_2, b_2, c_2, d_2 represent the degradation rate of TRF, TSH, activated enzyme, thyroxine respectively; a_3, b_3, b_1, c_1, a are positive constants; τ_1 and τ_2 represent the discrete time delays required for transportation of the hormones.

We show in the next section that the construction of our model allows to generate oscillations, even if there is feedback without delay. It can be caused by high Hill coefficients in our control function (large non-linearity). However, oscillations may be generated also when we have feedback with non-zero delay.

A. Results: The Model without Delay

We first consider the case of our model in which τ_1, τ_2 equals 0. It is given by as:

$$\begin{aligned}\dot{H} &= a_1 - a_2 H + \frac{a_3}{\theta + 1}, \quad \dot{P} = b_1 \frac{H^3}{H^3 + 1} - b_2 P + \frac{b_3}{(\theta/5)^{10} + 1}, \\ \dot{E} &= c_1 \frac{(P/5)^2}{(P/5)^2 + 1} - c_2 E, \quad \dot{\theta} = d_1 \frac{(E/30)^2}{(E/30)^2 + 1} - d_2 \theta\end{aligned}\quad (4)$$

For the numerical analysis of the discussed system a numerical model was created using Matlab. In Fig. 2, we can observe that the steady state of the system is stable. The set of parameters are given in the description of figures.

For parameters $a_1 = 0.008$, $a_2 = 0.14$, $a_3 = 0.00035$, $b_1 = 2$, $b_2 = 0.6$, $c_1 = 47$, $c_2 = 0.2$, $d_1 = 2$, $d_2 = 0.1$, we obtain following values of concentration of hormones: $TRF = 0.057$, $TSH = 1.34$, $AE = 15.8$, $\theta = 4.33$. The normal reference ranges of TRF , TSH , $FT4$ are 0.05-0.25 U/ml, 0.3-5.0 U/ml and 0.8-3 ug/dL [2]. We have similar values of concentration of hormones as in clinical data. However, we must mention the important observation between the two clinical variables is that the TSH changes on the order of hours and FT4 changes on the order of days in the blood.

In Fig. 3, we have unstable behaviour of considered system (4).

B. Results: The Model with Delay

Now we consider system (4) with delays. Results from some simulations were used to analyze the influence of feedback loops ($a_3 \neq 0, b_3 \neq 0$) with delay on behaviour of our system (4). We analyze how feedback loops with delays influence the behaviour of (4). According to theory the feedback loops in endocrine system try to regulate the value of concentration of thyroxine hormone. If we have a small value (close to zero) of thyroxine (hyperthyroidism), we try to increase the value of the concentration of hormone in the system by using feedback, which is shown in Fig. 4. These results confirm that feedback is a regulation function of our system. The range of concentration of TSH in result adding feedback is similar to physiological range of this hormone, 0.5-3.8 U/dL. We obtain a periodic behaviour of our system.

In Fig. 5, we analyze influence change of delay for solution of this model, the parameters are a_1, a_2, a_3, b_1, d_2 - reference values, $b_2 = 0.09$, $c_1 = 47$, $c_2 = 0.2$, $d_1 = 2.1$ and delays $\tau_1 = 4, \tau_2 = 1, \tau_1 = 2, \tau_2 = 0.5, \tau_1 = 0.5, \tau_2 = 0.5$,

$\tau_1 = 10, \tau_2 = 5$, respectively. We can see in Fig. 5 that delay can regulate the oscillation amplitude. We can get oscillations corresponding exactly to the physiological range of concentrations of the hormone, TSH.

Two conclusions can be drawn from the plots illustrating the model (4). The first one is that we can see that in the modified model with delay; the oscillation amplitude is changing when delay changes. This is caused by the delay; similar results were obtained in [1].

Important is the fact that when we regulate a system using feedback with delay, we know that there is high concentration of thyroxine in the blood so delay has a small value. Because the time that information about the concentration of the hormone in the blood needs to get to the hypothalamus (and pituitary) is very short.

C. Equilibrium State and Stability in the Model

Now, we turn to the analysis of steady states for the parameters; $a_1 = 0.008, a_2 = 0.14, a_3 = 0.00035, b_1 = 2, b_2 = 0.5, c_1 = 50, c_2 = 0.5, d_1 = 20, d_2 = 0.1$. We calculated steady states of (3) without delays. For simplicity, we assume that T_H, T_P, T_R, T_E, T and n_H, n_P, n_R, n_E, n equal 1. We obtain three steady states: A=(0.0568732, -0.000488202, -0.0488441, -10.2705), B=(-1.00473, -0.0000498653, -0.00498678, -1.00235), C=(0.057156, 0.226749, 18.4837, 189.735). We used in our calculation a Grobmann-Hartman theorem about linearization [6]. The Jacobi matrix for the system of ODE has the form:

$$\begin{bmatrix} -a_2 & 0 & 0 & a_3 \\ \frac{1}{(1+H^*)^2} & -b_2 & \frac{-1}{(1+\theta^*)^2} & 0 \\ 0 & \frac{1}{(P^*+1)^2} & -c_2 & 0 \\ 0 & 0 & \frac{1}{(E^*+1)^2} & -d_2 \end{bmatrix}$$

Taking into account above formula we obtain: A and B are unstable and C is always stable steady state. Now, we turn to study possible stability switches due to the presence of delays. It is possible to check stability using the Mikhailov criterion:

Let a function $W : \mathbb{C} \rightarrow \mathbb{C}$ be of the form

$$W(z) = \sum_{k=0}^m A_k(z)^{-h_k z},$$

where $0 = h_0 < h_1 < \dots < h_m, A_k(z) = \sum_{j=0}^{n_k} a_{jk} z^j, a_{jk} \in \mathbb{C}, n_0 \geq 1$ and $n_k < n_0$, for $k = 1, \dots, m$. If $W(z)$ has no zeros on the imaginary axis, then all roots of W lie in the open left half-plane of the complex plane if and only if $\Delta = n_0 \frac{\pi}{2}$, where Δ denotes the change of the argument of $W(i\omega)$ when ω increases from 0 to ∞ .

Now, we use this theorem to check stability of the steady states of (3). After the linearization system at $(H^*, P^*, E^*, \theta^*)$ the characteristic quasi-polynomial has the following form:

$$W(\lambda) = \lambda^4 + (a_2 + b_2 + c_2 + d_2)\lambda^3 +$$

$$+ (a_2 d_2 + a_2 b_2 + a_2 c_2 + b_2 d_2 + c_2 d_2 + b_2 c_2)\lambda^2 + -\alpha\beta\gamma\xi^{-\lambda\tau_1} \\ + (a_2 b_2 d_2 + a_2 c_2 d_2 + a_2 b_2 c_2 + b_2 c_2 d_2)\lambda + a_2 b_2 c_2 d_2 + \\ + a_2 z \gamma \xi^{-\lambda\tau_2} + z \gamma \lambda \xi^{-\lambda\tau_2}$$

where $z = \frac{1}{(\theta^*+1)^2}, \alpha = -\frac{a_3}{(\theta^*+1)^2}, \beta = \frac{b_1}{(H^*+1)^2}, \gamma = \frac{c_1}{(P^*+1)^2}, \xi = \frac{d_1}{(E^*+1)^2}$.

The curve drawn by the vector $W(i\omega) = (Re(W(i\omega)), Im(W(i\omega)))$ in the complex plane, when ω increase from 0 to ∞ , is called Mikhailov hodograph.

The change of the shape of Mikhailov hodographs with increasing τ_1 for B steady state is shown in Fig. 6. The change of the shape of Mikhailov hodographs with increasing $\tau_2 = 0, 10, 15$ for B steady state is shown in Fig. 7. The Mikhailov criterion implies that for A and C steady states then it does not change stability with increasing delay (τ_1, τ_2). For both steady states that the shape of hodographs becomes more and more looped but the total change of argument of $W(i\omega)$ remains the same. But when we check B steady state, the stability switches with increasing τ_1, τ_2 can occur (see Figs. 6 and 7 (Mikhailov hodograph)).

III. CONCLUSIONS

Principal aim of this work is to present a mathematical model describing the secretion system HPT using ODEs with feedback loops. According to control theory the feedback loops in endocrine system, we tried to regulate value of concentration of thyroxine hormone. We used Hill functions to simulate the feedback process. Our model exhibits oscillatory behaviour, even if time delay is not present. Numerical analysis suggest that periodic solution to model (4) can be observed for large values of the Hill coefficient (i.e. fast switch) and sufficiently large delay. We can see also that feedback with delay has impact on quantitative behaviour of our system (Mikhailov hodograph). In this work, usage of the presented model allowed to reproduce physiological behaviour. The system is able to generate correct results for feedback even if the concentration of TSH is almost zero (modeling hyperthyroidism). The problems are different time scales used for description of concentration of each hormones as well as different units (some are defined by mass while others by volume).

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