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A MATHEMATICAL MODEL DESCRIBING THE THYROID-PITUITARY AXIS WITH TIME DELAYS IN HORMONE TRANSPORTATION

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Abstract. In the present paper, a mathematical model, originally proposed by Danziger and Elmergreen and describing the thyroid-pituitary homeostatic mechanism, is modified and analyzed for its physiological and clinical significance. The influence of different system parameters on the stability behavior of the system is discussed. The transportation delays of different hormones in the bloodstream, both in the discrete and distributed forms, are considered. Delayed models are analyzed regarding the stability and bifurcation behavior. Clinical treatment of periodic catatonic schizophrenia is discussed in presence of transportation delays. Numerical simulations are presented to support analytic results.

Keywords: feedback mechanism, distributed time delay, discrete time delay, asymptotic stability, catatonic schizophrenia, hormone therapy

MSC 2000: 34K18, 34K20, 92C30, 92C50

1. Introduction

Thyroid gland, situated in the region of the neck, is considered to be an extremely important endocrine gland in amphibians. Thyroid produces thyroxine, a hormone that contains iodine obtained from the diet. Thyroxine controls the Basal Metabolic Rate (BMR) and also controls metamorphosis in amphibians. The system which regulates the concentration of thyroxine in blood is a negative feedback control mechanism. The anterior lobe of pituitary gland produces the hormone thyrotropin under the influence of the Thyrotropin Releasing Factor (TRF) secreted by the hypothalamus in the brain. Thyrotropin, when it reaches the thyroid gland, activates a thyroid enzyme which, in turn, catalyzes the shedding of thyroxine from the colloidal follicles of the thyroid gland into the blood stream. Such an effect of thyrotropin was observed by Vanderlaan and Greer [17], by Ghosh, Woodbury and Sayers [8] and by

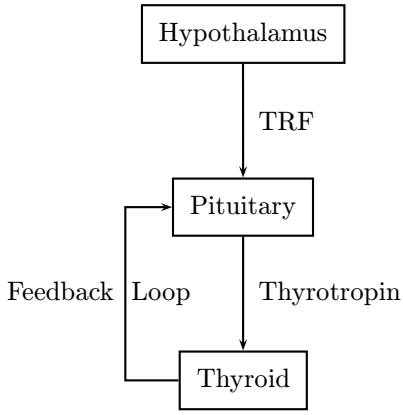
others, who reported that the thyroid of hypophysectomized animals was unable to trap radioactive iodide, and that this ability was restored by the administration of thyrotropin. Though, it is not necessary to identify the enzymes involved, they can be thought to be a peroxidase which oxidizes iodide to iodine, before its incorporation into the thyroxine hormone molecule.

Abnormal steady-state thyroxine level in the blood stream can cause system malfunction leading to various types of physical and mental disorders. Physical disorders include different forms of hypo- and hyperthyroidism. A system malfunction leading to a severe mental disorder is known as periodic catatonic schizophrenia. In this disease, the symptoms vary with remarkably regular periodicity. This has been studied at length by Gjessing et.al. [9], Maeda et.al. [13], Takahaski and Gjessing [16] and others. R. Gjessing established a correlation between the rhythmic changes in the Basal Metabolic Rate (BMR) and the periodic variations in the symptoms of catatonic schizophrenia. Similar correlations between rhythmic changes in the thyroid level and periodic variations in the symptoms have been observed by Richter [15] and Durrell [7]. Since engineering studies of negative feedback systems in electrical circuits show that oscillations often occur in such systems, this suggests to investigate how the thyroid levels change. This was the approach initiated and developed by Danziger and Elmergreen [3]–[6] who set up a system of ordinary differential equations which are assumed to govern, among other quantities, the level of thyroxine in the blood. Then they studied the oscillatory solutions of this system of differential equations. As a treatment of periodic relapsing catatonia, they also analyzed the effect of administering constant doses of thyroxine extract into the system.

In the present paper, we consider the thyroid-pituitary homeostatic mechanism as is proposed by Danziger and Elmergreen [4]. The stability behavior of the system is analyzed and the possibility of occurrence of periodic solutions is looked into. Since there is a spatial separation between thyroid and pituitary gland in the body, time is needed for transportation of thyrotropin and thyroxine between the glands. Consequently, in Section 3 of the paper, instead of taking the transportation of different hormones as an instantaneous process we have introduced distributed time delays into the system to account for the time needed by the hormones to travel from source to destination. In Section 4 of the paper we have replaced distributed delays by discrete ones as the model with distributed delays was unable to explain the phenomenon of periodic fluctuation of different hormones in the blood serum. We also present a numerical study of the system of equations with and without delays to illustrate the analytical results.

2. Description of the model: Stability analysis

In the present study, a mathematical model concerning the thyroid-pituitary system is considered. The anterior lobe of the pituitary gland produces the hormone thyrotropin under the influence of TRF secreted by the hypothalamus. The thyrotropin, in turn, causes the thyroid gland to produce a thyroid enzyme which when activated produces the hormone thyroxine. This hormone has a negative feedback effect on the secretion of thyrotropin from pituitary. This mechanism can be depicted as in the following block diagram.



Similar type of negative feedback mechanism has been studied in various other physiological models by different researchers. Mukhopadhyay et al. [14] considered a mathematical model describing the biochemical interaction of the hormones luteinizing hormone (LH), luteinizing hormone releasing hormone (LHRH) and testosterone (T). The model structure involved a negative feedback mechanism together with transportation and secretion delays of different hormones.

Following Danziger and Elmergreen [4] we assume that the rate of thyrotropin production is reduced by an amount proportional to the blood concentration of thyroxine, and that the rate of loss of thyrotropin is proportional to the existing thyrotropin concentration. As the pituitary gland can produce no output in presence of thyroxine concentration greater than a certain value, we have also included a degenerate form of the equation for thyrotropin production. To describe the mechanism in the thyroid gland, we assume that thyrotropin activates a thyroid enzyme, which when activated produces thyroxine. Thyroxine production, according to this assumption, will depend on the concentration of the activated enzyme and not directly on the level of thyrotropin. We describe a mathematical realization of all these

considerations by the following model:

$$
\begin{aligned}
\frac{\mathrm{d}P}{\mathrm{d}t} &= \begin{cases} c - h\theta - gP & \Big(\text{when } \theta \leqslant \dfrac{c}{h}\Big), \\ -gP & \Big(\text{when } \theta > \dfrac{c}{h}\Big), \end{cases} \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= mP - kE, \\
\frac{\mathrm{d}\theta}{\mathrm{d}t} &= aE - b\theta
\end{aligned} \tag{2.1}
$$

where P, E and θ represent the concentrations of thyrotropin, activated enzyme and thyroxine, respectively, b, g and k represent the loss constants of thyroxine, thyrotropin and activated enzyme, respectively, a, h, m are constants expressing the sensitivities of the glands to stimulation or inhibition; c is the rate of production of thyrotropin in the absence of thyroid inhibition. All constants are assumed to be positive. This model is very useful in the study of causes and clinical treatment of periodic catatonic schizophrenia.

Theorem 2.1. *Let $E(0) \geqslant 0$, $P(0) \geqslant 0$, $\theta(0) \geqslant 0$. Then the solution of the system* (2.1) *is bounded and non-negative.*

P r o o f. We have $\frac{\mathrm{d}P}{\mathrm{d}t} + gP \geqslant 0$. Consequently, $P(t) \geqslant 0$ for all $t \geqslant 0$. The same argument applied consecutively to E and θ yields $E(t) \geqslant 0$, $\theta(t) \geqslant 0$ for all $t \geqslant 0$. We therefore have $\frac{\mathrm{d}P}{\mathrm{d}t} + gP \leqslant c$, hence $P(t) \leqslant P_{\max} = \max\{P(0), \frac{c}{g}\}$, $E(t) \leqslant E_{\max} = \max\{E(0), \frac{mP_{\max}}{k}\}$, $\theta(t) \leqslant \theta_{\max} = \max\{\theta(0), \frac{aE_{\max}}{b}\}$ for all $t \geqslant 0$. This proves the theorem. □

For $\theta \leqslant c/h$, the system possesses a non-trivial equilibrium point, namely, $Q_S = (P_S, E_S, \theta_S)$ where

$$
P_S = \frac{kbc}{D}, \quad E_S = \frac{mbc}{D}, \quad \theta_S = \frac{amc}{D} \quad \text{with} \quad D = amh + gkb. \tag{2.2}
$$

The Jacobian matrix corresponding to this equilibrium point when $\theta \leqslant c/h$ is given by

$$
J_{Q_S} = \begin{pmatrix} -g & 0 & -h \\ m & -k & 0 \\ 0 & a & -b \end{pmatrix}
$$

and the corresponding characteristic equation is

$$
\lambda^3 + (k + g + b)\lambda^2 + (gk + bk + gb)\lambda + (bgk + mha) = 0. \tag{2.3}
$$

Applying the Routh-Hurwitz criteria, the system will be asymptotically stable if

$$k^2(b+g) + g^2(k+b) + b^2(k+g) + 2bgk > mha.$$

Therefore, when

$$mha > k^2(b+g) + g^2(k+b) + b^2(k+g), \tag{2.4}$$

the system will become unstable. If a and m are sufficiently large in comparison with the loss constants then the inequality (2.4) holds. The above analysis indicates that high production rate of the activated enzyme and of thyroxine may be the causes of unstability of the system. Danziger and Elmergreen [4] also showed that the system admits periodic solutions with sustained oscillations in the thyroxine level. The oscillation, together with a high production rate of thyroxine, causes a system malfunction known as periodic catatonic schizophrenia.

When the level of thyroxine in the blood exceeds a certain value, namely c/h, the anterior pituitary cannot produce any output. As the anterior pituitary cannot produce any thyrotropin in this case, the production of thyroxine will decrease, and in the process, when the level of thyroxine falls below c/h, the feedback mechanism of the thyroid-pituitary system will again start, which in turn will increase the blood concentration of thyroxine and consequently, the symptoms of catatonic schizophrenia will reappear with remarkable periodicity. The system may be stabilized by administering thyroxine extract externally at a constant rate R where $R > bc/h$ [4]. Physiologically it means that the ratio of constant external input of thyroxine to its loss rate should cross a certain value, namely, c/h, for the stability of the system.

The system of equations (2.1) is integrated numerically using the routine rk45 in Matlab. For $\theta \leqslant c/h$, the results of simulation are shown in Figs. 1–2. Fig. 1 shows the graphs of $P(t)$, $E(t)$ and $\theta(t)$ when $mha < k^2(b+g) + g^2(k+b) + b^2(k+g)$. It is observed from the graphs that all the concentrations exhibit stable behavior. Fig. 2 shows the behavior when (2.4) is satisfied. The graphs, in this case, demonstrate the unstability of different components of the system leading to oscillatory behavior of the solutions which symbolizes the periodic fluctuations of symptoms of periodic schizophrenia.

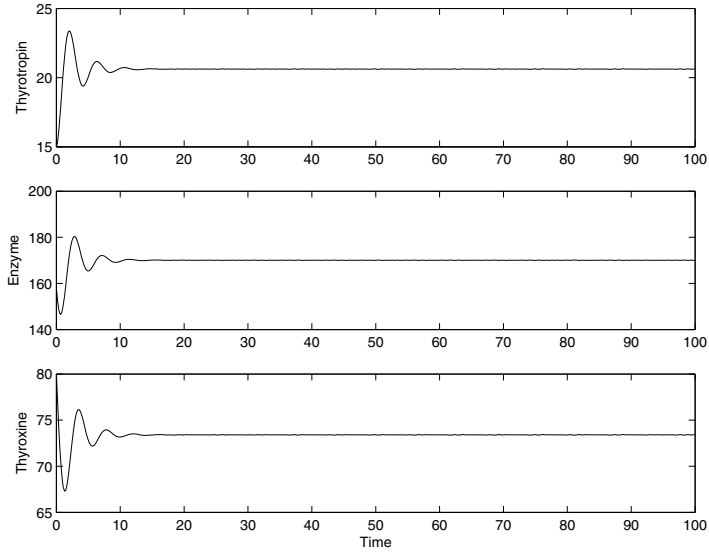


Figure 1. The graphs of $P(t)$ vs. t, $E(t)$ vs. t and $\theta(t)$ vs. t for the non-delayed system (2.1) with $\theta \leqslant c/h$ when (2.4) is not satisfied. Parameter values are $c = 100$; $h = 1$; $g = 1.29$; $m = 8$; $a = 0.6$; $k = 0.97$; $b = 1.39$. Initial conditions are $(P_S, E_S, \theta_S) \equiv (15, 158, 80)$. Stable behavior of solutions is observed.

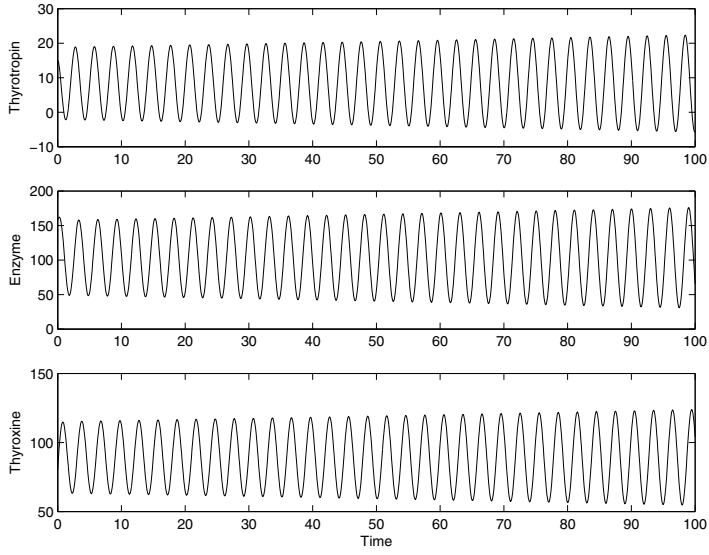


Figure 2. The graphs of $P(t)$ vs. t, $E(t)$ vs. t and $\theta(t)$ vs. t for the non-delayed system (2.1) with $\theta \leqslant c/h$ when (2.4) is satisfied. Parameter values are $c = 100$; $h = 1$; $g = 1.29$; $m = 12$; $a = 1.2$; $k = 0.97$; $b = 1.39$. Initial conditions are $(P_S, E_S, \theta_S) \equiv (15, 158, 80)$. The graphs indicate periodic nature of solutions.

3. Stability analysis in presence of distributed delays

In this section, we consider the Danziger Elmergreen model (2.1) together with distributed delays [12] caused by the transportation time taken by different hormones in the blood plasma due to the spatial separation of the anterior pituitary and the thyroid gland. As it is not usually possible to determine the past history of the release of hormones, the delays are assumed to be continuous in nature. We assume that the hormone thyrotropin which stimulates the thyroid gland at time t, was released by the pituitary gland s time units ago, where s is distributed according to a probability distribution $F_1(s)$, called the delay kernel, given by $F_1(s) = \beta \exp(-\beta s)$. Similarly, it is assumed that the delay in the hormone thyroxine is distributed as $F_2(s) = \alpha \exp(-\alpha s)$. The model (2.1) with these distributed delays takes the form

$$
\begin{aligned}
\frac{\mathrm{d}P}{\mathrm{d}t} &= \begin{cases} c - h\left[\displaystyle\int_{-\infty}^{t} \alpha \mathrm{e}^{-\alpha(t-s)}\theta(s)\,\mathrm{d}s\right] - gP & \left(\theta \leqslant \dfrac{c}{h}\right), \\ -gP & \left(\theta > \dfrac{c}{h}\right), \end{cases} \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= m\left[\int_{-\infty}^{t} \beta \mathrm{e}^{-\beta(t-s)}P(s)\,\mathrm{d}s\right] - kE, \\
\frac{\mathrm{d}\theta}{\mathrm{d}t} &= aE - b\theta
\end{aligned}
\tag{3.1}
$$

where $\alpha, \beta > 0$.

The equilibrium point of the system (3.1) is the same as that of the system (2.1) and is given by (2.2). We first consider the case $\theta \leqslant c/h$. Let

$$
\begin{aligned}
X &= \int_{-\infty}^{t} \alpha \mathrm{e}^{-\alpha(t-s)}\theta(s)\,\mathrm{d}s, \\
Y &= \int_{-\infty}^{t} \beta \mathrm{e}^{-\beta(t-s)}P(s)\,\mathrm{d}s.
\end{aligned}
\tag{3.2}
$$

With these substitutions, the system (3.1) reduces to

$$
\begin{gathered}
\frac{\mathrm{d}P}{\mathrm{d}t} = c - hX - gP, \qquad \frac{\mathrm{d}E}{\mathrm{d}t} = mY - kE, \\
\frac{\mathrm{d}\theta}{\mathrm{d}t} = aE - b\theta, \qquad \frac{\mathrm{d}X}{\mathrm{d}t} = \alpha\theta - \alpha X, \\
\frac{\mathrm{d}Y}{\mathrm{d}t} = \beta P - \beta Y.
\end{gathered}
\tag{3.3}
$$

The Jacobian matrix of the system (3.3) is given by

$$J = \begin{pmatrix} -g & 0 & 0 & -h & 0 \\ 0 & -k & 0 & 0 & m \\ 0 & a & -b & 0 & 0 \\ 0 & 0 & \alpha & -\alpha & 0 \\ \beta & 0 & 0 & 0 & -\beta \end{pmatrix}.$$

According to the Routh-Hurwitz criteria, the necessary and sufficient condition that all the eigenvalues have negative real parts are

$$\begin{gathered} \operatorname{tr} J < 0, \qquad \det J < 0, \\ \operatorname{tr} J \times M_2 - |J| < 0 \end{gathered} \tag{3.4}$$

where M_2 is the sum of second order principal minors of the Jacobian matrix J.

Now,

$$\begin{aligned} \operatorname{tr} J &= -[g + k + b + \alpha + \beta] < 0, \\ |J| &= -\alpha\beta[kgb + ahm] < 0, \\ \operatorname{tr} J \times M_2 - |J| &= (-g - k - b - \alpha - \beta)(\alpha\beta kb + gb\alpha\beta \\ &\quad + gk\alpha\beta + gkb\beta + gkb\alpha) + \alpha\beta gkb + \alpha\beta ahm. \end{aligned} \tag{3.5}$$

From (3.5) it is clear that $\operatorname{tr} J \times M_2 - |J|$ can be positive only if a and m are sufficiently large in comparison with α, β, b, g, k. As large values of a and m signify high production rate of both the activated enzyme and thyroxine, this situation implies that the blood concentration of thyroxine will increase and will soon exceed the value c/h. Under this situation the model with distributed delay will assume the form

$$\begin{aligned} \frac{\mathrm{d}P}{\mathrm{d}t} &= -gP, & \frac{\mathrm{d}E}{\mathrm{d}t} &= mY - kE, \\ \frac{\mathrm{d}\theta}{\mathrm{d}t} &= aE - b\theta, & \frac{\mathrm{d}Y}{\mathrm{d}t} &= \beta P - \beta Y. \end{aligned} \tag{3.6}$$

Solving (3.6) explicitly for θ we get

$$\theta = A\mathrm{e}^{-gt} + B\mathrm{e}^{-kt} + C\mathrm{e}^{-bt} + D\mathrm{e}^{-\beta t}$$

where A, B, C, D are constants involving system parameters. As $t \to \infty$, we have $\theta \to 0$. So after a finite time, the thyroxine concentration (θ) will stay below c/h forever. Thus it is not possible to analyze the case when the thyroxine level goes

beyond the limit c/h using the present model. Consequently, we consider a clinical modification of the model.

Danziger and Elmergreen [4] suggested a treatment of schizophrenia by administering exogeneous thyroid extract into the system at a constant rate. They showed that if $R > bc/h$ (where R is the constant rate at which thyroxine is administered) the system is asymptotically stable and the thyroxine level in blood is slightly higher than that found in a normal system. In such a case, some improvement will occur to the condition of the patient.

We assume the amount of thyroxine administered to depend on θ, the existing thyroxine concentration of the system. This ensures the administration of the most appropriate amount of hormone at any particular instant. For simplicity, we consider this administration to be a linear function of θ, namely, $R_1\theta + R_2$. Then, the modified system will be

$$
\begin{aligned}
\frac{\mathrm{dP}}{\mathrm{dt}} &= -gP, \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= m\left[\int_{-\infty}^{t} \beta \mathrm{e}^{-\beta(t-s)} P(s)\,\mathrm{d}s\right] - kE, \\
\frac{\mathrm{d}\theta}{\mathrm{d}t} &= aE - b\theta + R_1\theta + R_2.
\end{aligned} \tag{3.7}
$$

Considering the second substitution in (3.2) the above system will reduce to

$$
\begin{aligned}
\frac{\mathrm{d}P}{\mathrm{d}t} &= -gP, & \frac{\mathrm{d}E}{\mathrm{d}t} &= mY - kE, \\
\frac{\mathrm{d}\theta}{\mathrm{d}t} &= aE - b\theta + R_1\theta + R_2, & \frac{\mathrm{d}Y}{\mathrm{d}t} &= \beta P - \beta Y.
\end{aligned} \tag{3.8}
$$

The only equilibrium point of this system is $\left(0, 0, \frac{R_2}{b-R_1}, 0\right)$. The roots of the characteristic equation of the Jacobian matrix corresponding to (3.8) are $-g$, $-k$, $R_1 - b$ and $-\beta$. The equilibrium point will exist if $b > R_1$. Now for $b > R_1$, all characteristic roots are negative and consequently, the system is asymptotically stable. Therefore, for asymptotic stability of the system we should have

$$
\frac{R_2}{b - R_1} > \frac{c}{h}. \tag{3.9}
$$

Thus, the symptoms of catatonic schizophrenia will disappear when the ratio of the constant part of the administration function (R_2) to the net loss of thyroxine ($b - R_1$) will exceed a certain value c/h.

4. Stability analysis for the model with discrete delay

In this section, we consider the Danziger Elmergreen model with discrete time delays for transportation of different hormones. The model in this case will be

$$\begin{aligned}
\frac{\mathrm{d}P}{\mathrm{d}t} &= \begin{cases} c - h\theta(t-\tau_1) - gP & \left(\theta \leqslant \dfrac{c}{h}\right), \\ -gP & \left(\theta > \dfrac{c}{h}\right), \end{cases} \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= mP(t-\tau_2) - kE, \\
\frac{\mathrm{d}\theta}{\mathrm{d}t} &= aE - b\theta
\end{aligned} \tag{4.1}$$

where τ_1 and τ_2 represent the discrete time delays required for transportation of the hormones thyroxine and thyrotropin, respectively. The equilibrium point of the system (4.1) will be the same as that of the system (2.1). We analyze the model by dividing it into two cases.

Case I: $\theta \leqslant c/h$.

The characteristic equation will be

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 + A_4\mathrm{e}^{-\lambda\tau} = 0 \tag{4.2}$$

where

$$\begin{aligned}
&A_1 = g + k + b, \qquad A_2 = gk + gb + kb, \\
&A_3 = kbg, \qquad A_4 = ahm, \qquad \tau = \tau_1 + \tau_2.
\end{aligned} \tag{4.3}$$

Let

$$\lambda = p + \mathrm{i}q \tag{4.4}$$

be a root of the equation (4.2). Substituting (4.4) into (4.2) and separating the real and imaginary parts we get

$$\begin{aligned}
p^3 - 3pq^2 + A_1(p^2 - q^2) + A_2p + A_3 + A_4\mathrm{e}^{-p\tau}\cos q\tau = 0, \\
3p^2q - q^3 + 2pqA_1 + A_2q = A_4\mathrm{e}^{-p\tau}\sin q\tau.
\end{aligned} \tag{4.5}$$

In order for a stability change of the system to take place, the real part of λ should be zero, that is, one of the characteristic roots is purely imaginary. Let τ_0 be the

value of τ such that $p(\tau_0) = 0$ and $q(\tau_0) = q_0$. Putting these values of p and q in (4.5) we obtain

$$\begin{aligned} A_1 q_0^2 - A_3 &= A_4 \cos(q_0 \tau), \\ -q_0^3 + A_2 q_0 &= A_4 \sin(q_0 \tau). \end{aligned} \tag{4.6}$$

Combining the equations in (4.6) we get a cubic in q_0^2 as follows:

$$\begin{aligned} &\Psi(q_0^2) \equiv (q_0^2)^3 + (A_1^2 - 2A_2)(q_0^2)^2 + (A_2^2 - 2A_1 A_3) q_0^2 + A_3^2 - A_4^2 = 0, \\ &\Psi(q_0^2) \equiv (q_0^2)^3 + B_1 (q_0^2)^2 + B_2 q_0^2 + B_3 = 0. \end{aligned} \tag{4.7}$$

Obviously, $B_1 > 0$, $B_2 > 0$. So equation (4.7) will have a positive root only when $B_3 < 0$, that is, $A_3^2 - A_4^2 < 0$, which equivalently implies $kgb < ahm$.

From (4.6) it follows that the system will undergo a stability change when τ, the sum of different transportation delays, crosses any one of the values given by

$$\tau_n = \frac{1}{q_0} \tan^{-1} \Big[\frac{A_2 q_0 - q_0^3}{A_3 - A_1 q_0^2} \Big] + \frac{n\pi}{q_0}, \quad n = 0, 1, 2, 3 \ldots \tag{4.8}$$

Differentiating (4.5) with respect to τ at $\tau = \tau_0$ we get

$$\begin{aligned} E \frac{\mathrm{d}p}{\mathrm{d}\tau}\Big|_{\tau=\tau_0} - F \frac{\mathrm{d}q}{\mathrm{d}\tau}\Big|_{\tau=\tau_0} &= G, \\ F \frac{\mathrm{d}p}{\mathrm{d}\tau}\Big|_{\tau=\tau_0} + E \frac{\mathrm{d}q}{\mathrm{d}\tau}\Big|_{\tau=\tau_0} &= H \end{aligned} \tag{4.9}$$

where

$$\begin{aligned} E &= A_2 - 3q_0^2 - A_4 \tau_0 \cos(q_0 \tau_0), \\ F &= 2A_1 q_0 - A_4 \tau_0 \sin(q_0 \tau_0), \\ G &= q_0 A_4 \sin(q_0 \tau_0), \\ H &= A_4 q_0 \cos(q_0 \tau_0). \end{aligned} \tag{4.10}$$

From equations (4.9), simple algebra reveals that

$$\frac{\mathrm{d}p}{\mathrm{d}\tau}\Big|_{\tau=\tau_0} = \frac{GE + HF}{E^2 + F^2}. \tag{4.11}$$

Now,

$$GE + HF = \frac{\mathrm{d}}{\mathrm{d}q_0^2} \Psi(q_0^2).$$

Since q_0^2 is the only positive root of equation (4.7), we have

$$\frac{\mathrm{d}p}{\mathrm{d}\tau}\Big|_{\tau=\tau_0} \neq 0.$$

Consequently, by the Hopf bifurcation theorem [10], the system will undergo a Hopf bifurcation as τ crosses any one of the values given by (4.8) provided that

$$\frac{kbg}{ahm} < 1.$$

Case II: $\theta > c/h$.

The analysis of this case is similar to that of the distributed delay model and gives the same qualitative result.

A numerical study of the delayed system (4.1) is performed and the results are shown in Figs. 3–6. For $\theta \leqslant c/h$, the system exhibits interesting dynamical behavior depending upon the delay parameter. It is found that for $kbg/amh \leqslant 1$, different hormones and the enzyme will exhibit stable behavior when τ, the sum of different system delays, is less than 0.9 (Fig. 3). When τ exceeds this value, the system gradually changes its behavior from stable to unstable nature. Such a change in the stability behavior of the system is depicted in Fig. 4. This changing behavior ultimately leads to periodic fluctuations of concentrations of different system components as is shown in Fig. 5. Fig. 6 shows the limit cycle arising out of this periodic fluctuations.

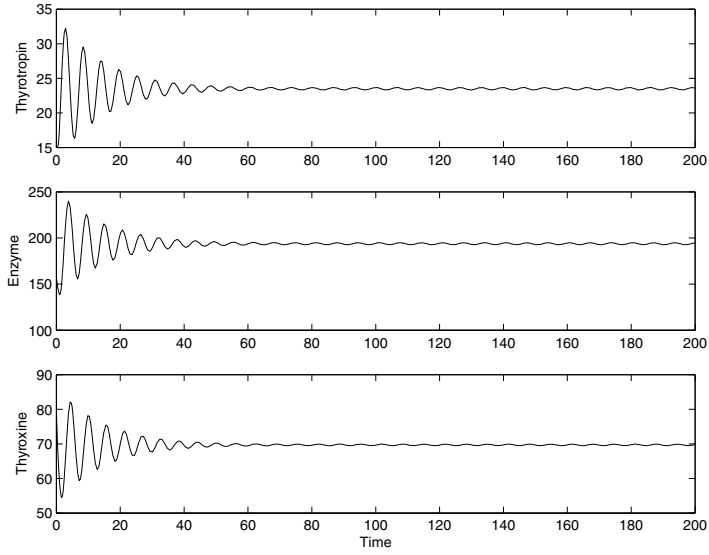


Figure 3. The graphs of $P(t)$ vs. t, $E(t)$ vs. t and $\theta(t)$ vs. t for the delayed system (4.1) with $\theta \leqslant c/h$. Parameter values are $c = 100$; $h = 1$; $g = 1.29$; $m = 8$; $a = 0.5$; $k = 0.97$; $b = 1.39$; $\tau = 0.8$. Initial conditions are $(P_S, E_S, \theta_S) \equiv (15, 158, 80)$. Different system components exhibit stable behavior.

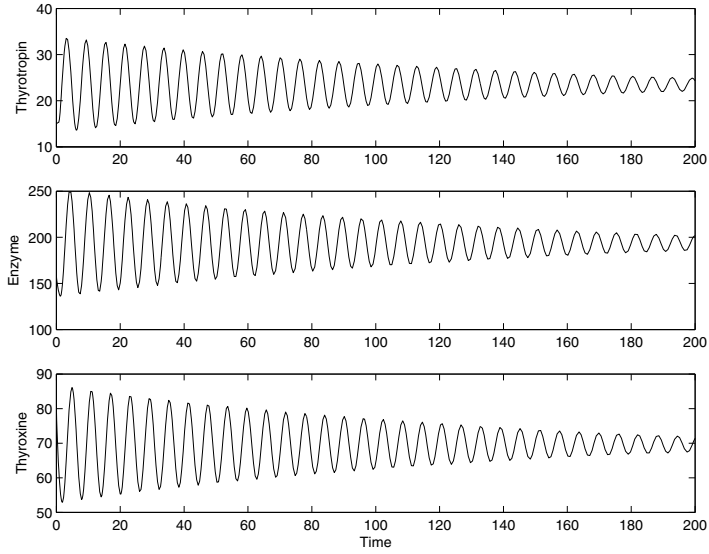


Figure 4. The graphs of $P(t)$ vs. t, $E(t)$ vs. t and $\theta(t)$ vs. t for the delayed system (4.1) with $\theta \leqslant c/h$. Parameter values are $c = 100$; $h = 1$; $g = 1.29$; $m = 8$; $a = 0.5$; $k = 0.97$; $b = 1.39$; $\tau = 0.96$. Initial conditions are $(P_S, E_S, \theta_S) \equiv (15, 158, 80)$.

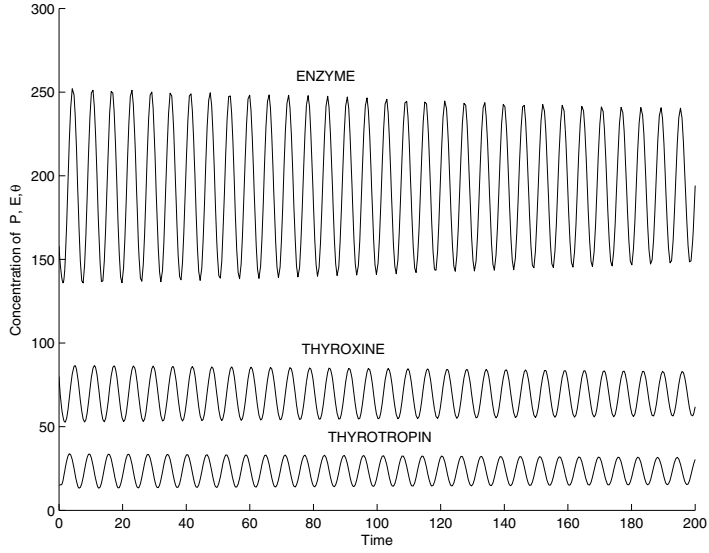


Figure 5. The graphs of $P(t)$ vs. t, $E(t)$ vs. t and $\theta(t)$ vs. t for the delayed system (4.1) with $\theta \leqslant c/h$. Parameter values are $c = 100$; $h = 1$; $g = 1.29$; $m = 8$; $a = 0.5$; $k = 0.97$; $b = 1.39$; $\tau = 1.0$. Initial conditions are $(P_S, E_S, \theta_S) \equiv (15, 158, 80)$. Different system components exhibit periodic oscillations.

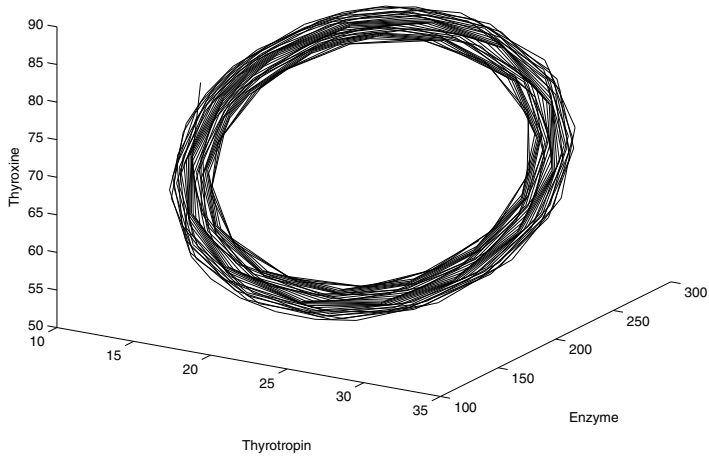


Figure 6. The phase portrait for the delayed system (4.1) with $\theta \leqslant c/h$ exhibiting limit cycle arising out of Hopf bifurcation. Parameter values are $c = 100$; $h = 1$; $g = 1.29$; $m = 8$; $a = 0.5$; $k = 0.97$; $b = 1.39$; $\tau = 1.0$. Initial conditions are $(P_S, E_S, \theta_S) \equiv (15, 158, 80)$.

5. Discussion

The work of Dangizer and Elmergreen showed a correlation between various conditions of catatonic schizophrenia and the blood concentration of thyrotropin and the thyroid hormone thyroxine. Their work emphasizes the utility of mathematical representation of the endocrine control system. The feedback aspects of the thyroid-pituitary homeostatic mechanism make an analogy with this and perhaps other physiological phenomena on the one hand and feedback amplifiers on the other hand possible. A basic difference in the philosophy of study in these fields arises from the fact that from the engineering point of view, the main thrust is on synthesis whereas from the endocrinological point of view the primary aim is the analysis of a system in which measurements are difficult and numerical values of parameters are either unknown or known with little accuracy.

In the thyroid-pituitary feedback system considered here, since the solutions are bounded, the patients' symptoms will never be worse than a certain level [1], [2]. The stability analysis with instantaneous transportation of different hormones revealed that high production rate of activated enzyme (m) and thyroxine (a) may be the causes of unstability of the system. Numerical simulation of the system (2.1) established the significance of the parameters m and a in controlling the stability criteria of the system.

To make the model of Danziger and Elmergreen more realistic, we have modified it by incorporating time lags [11] needed for transportation of different hormones from source to destination. In Section 3 of the paper, we have taken the transportation delay to be a distributed one, as it is not usually possible to know the past history of hormone release. The analysis in this section demonstrated that the system remains unstable for a very rare situation, namely when the generation rate of the hormone thyroxine is very high. Moreover, this unstable state of the system is seen to be transient. Therefore, the periodic oscillation of the thyroxine level in the bloodstream cannot be explained when the time lag is of a continuous nature.

In view of the above, we have considered discrete time delay instead of distributed delay in Section 4 of the paper. Our study in this section showed that with discrete transportation delay, the system will undergo a Hopf bifurcation which results in periodic fluctuation of the thyroxine level in the blood. Thus the discrete time delay is able to explain the phenomenon of periodic oscillation of blood concentration of thyroxine and hence the reappearance and disappearance of symptoms of periodic catatonic schizophrenia. Numerical simulation of the delayed model reaffirms the remarkable periodic behavior of the system. From these simulations we have obtained a critical value of the delay parameter (which is the sum of the two system delays considered) below which the system exhibits stable behavior. When this critical value is exceeded, a gradual increase in oscillation of different concentrations is observed which ultimately leads to perfectly periodic oscillations of different system components. In the literature of biological delay systems, distributed time delays are considered to be more general than discrete delays. But interestingly, our analysis in this paper showed that in some situations discrete delays are much more realistic than distributed delays. This assertion is amply demonstrated in this case, by the fact that discrete delays are able to explain the practical phenomenon of the periodic nature of symptoms of schizophrenia. Furthermore, since the time taken by any particular hormone to travel from source to destination in the body through the bloodstream is fixed for an individual, the choice of discrete delay should be preferred over distributed delay in the mathematical models describing hormone dynamics.

Danziger and Elmergreen suggested a treatment of the disease by administering thyroid extract at a constant rate into the system. As the thyroxine level in any individual changes continuously with time, administering thyroid extract at a constant rate to such a system could not be a realistic clinical treatment. Thus we have modified the mode of the treatment by allowing thyroxine administration to depend upon the existing thyroxine concentration of the system. The analysis with the above modification revealed that the disease may be cured by allowing the ratio of the constant part of administered thyroxine (R_2) to the net loss of thyroxine from the system ($b - R_1$) to exceed a certain value c/h.

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