

Solution of a Mathematical Model Describing the Change of Hormone Level in Thyroid Using the Laplace Transform

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Abstract In the present paper, a mathematical model describing the thyroid-pituitary homeostatic mechanism is analyzed for its physiological and clinical significance. The influence of different parameters on the stability behavior of the system is discussed. We have assumed in the present paper that the rate of thyrotropin production is reduced by an amount which is proportional to the blood concentration of thyroxine and also the rate of loss of thyrotropin is proportional to the existing thyrotropin concentration. The stability behavior of the system is analyzed and the possibility of occurrence of periodic solutions is looked into. 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 in the present paper. The solutions of the system of governing equations are obtained by applying the Laplace transform. Also, the nature of the solution is interpreted graphically using the Maple12 technique for both stable and unstable behavior.

Keywords: endocrine glands, hormones, feedback mechanism, schizophrenia

1. INTRODUCTION

The thyroid gets its name from the Greek word for “shield”, due to the shape of the related thyroid cartilage. The thyroid gland is one of the largest endocrine glands. It is also considered to be an extremely important endocrine gland in amphibians. It is situated in the frontal region of our neck.

There are three primary features of the thyroid at the microscopic level:

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1. Follicles: The thyroid is composed of spherical follicles that selectively absorb iodine from the blood for production of thyroid hormones, but also for storage of iodine in thyroglobulin, in fact iodine is necessary for other important iodine-concentrating organs as breast, stomach, salivary glands, thymus etc. Twenty-five percent of all the body's iodide ions are in the thyroid gland. Inside the follicles, colloid serves as a reservoir of materials for thyroid hormone production and, to a lesser extent, acts as a reservoir for the hormones themselves. Colloid is rich in a protein called thyroglobulin.
2. Thyroid epithelial cells (or "follicular cells"): The follicles are surrounded by a single layer of thyroid epithelial cells, which secrete T_3 and T_4 . When the gland is not secreting T_3/T_4 (inactive), the epithelial cells range from low columnar to cuboidal cells. When active, the epithelial cells become tall columnar cells.
3. Parafollicular cells (or "C cells"): Scattered among follicular cells and in spaces between the spherical follicles are another type of thyroid cell, parafollicular cells, which secrete calcitonin.

To describe the mechanism in the thyroid gland, we assume that thyrotropin activates a thyroid enzyme, which when activated, produces thyroxine. Thyroxine production depends on the concentration of the activated enzyme and not directly on the level of thyrotropin. 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. When the level of thyroxine in the blood exceeds a certain value, the anterior pituitary cannot produce any output. As the anterior pituitary cannot produce any thyrotropin in this case, the production of thyroxine decreases, and in the process, when the level of thyroxine falls, the feedback mechanism of the thyroid-pituitary system again starts, which in turn, increases the blood concentration of thyroxine and consequently, the symptoms of catatonic schizophrenia reappears with remarkable periodicity. The system may be stabilized by administering thyroxine extract externally at a constant rate

The thyroid gland releases hormones that regulate the rate of metabolism and affect the growth and rate of function of many other systems in the body. The principal hormones are Tri-iodothyronine(T_3) and Thyroxine (T_4). They are synthesized from both iodine and tyrosine. Up to 80% of the T_4 is converted to T_3 by peripheral organs such as the liver, kidney and spleen. The thyroid also produces calcitonin, which plays a role in calcium homeostasis. Hormonal output from the thyroid is regulated by Thyroid-Stimulating Hormone (TSH)

produced by the anterior pituitary which is regulated by Thyrotropin-Releasing Hormone (TRH) produced by the hypothalamus.

Abnormal steady-state thyroxine level in the blood stream can cause system malfunction leading to various types of physical and mental disorders. Thyroid disorders include-

1. Hyperthyroidism (overactive thyroid gland, excess of Thyroid hormone)
2. Hypothyroidism (underactive thyroid gland)
3. Thyroid nodules (benign thyroid neoplasm, may be thyroid cancers)

All these disorders may give rise to Goiter (enlarged thyroid).

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. Thyroid also produces thyroxine, a hormone that contains iodine obtained from the diet. The system which regulates the concentration of thyroxine in blood is a negative feedback control mechanism. Since engineering studies of negative feedback systems show that oscillations often occur in such systems that suggest investigating the change in thyroid levels. This was the approach initiated and developed by Danziger and Elmergreen (1954, 1956, 1957) who set up a system of ordinary differential equations which are assumed to govern, among other quantities, the level of thyroxine in the blood. They also studied the oscillatory solutions of this system of differential equations.

2. MATHEMATICAL MODEL

Quantitative descriptions of endocrine systems in the form of mathematical models have been proposed by Danziger and Elmergreen (1957). We have, in the present paper, assumed 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, following the homeostatic mechanism as discussed by Danziger and Elmergreen (1956). 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 have assumed that thyrotropin activates a thyroid enzyme, which is when activated, produces thyroxine. Thyroxine production, according to this assumption, depends on the concentration of the activated enzyme and not directly on the level of thyrotropin. We can describe a mathematical realization of all these considerations by the following model:

$$\frac{dP}{dt} = \begin{cases} c - h\theta - gP & \left(\text{when } \theta \leq \frac{c}{h}\right) \\ -gP & \left(\text{when } \theta > \frac{c}{h}\right) \end{cases}$$

$$\frac{dE}{dt} = mP - kE$$

$$\frac{d\theta}{dt} = aE - b\theta \tag{2.1}$$

where P , E and θ represent the concentrations of thyrotropin, activated enzyme and thyroxine respectively; g , k and b represent loss rate constants per unit concentration of thyrotropin, activated enzyme and thyroxine respectively; h , m and a are constants expressing the sensitivities of the glands to stimulation (activation) or inhibition (deactivation) rate of the hormone or enzyme; c is the rate of production or activation of thyrotropin in the absence of thyroid inhibition. Since the production rate is not possible, all the constants here are assumed to be positive.

Mathematical model (2.1) describes the steady-state behavior of endocrine systems exhibiting periodicities in component concentrations.

For $\theta \leq \frac{c}{h}$, the system possesses a non-trivial equilibrium point i.e. $Q_s = (P_s, E_s, \theta_s)$ where $P_s = \frac{kbc}{D}$, $E_s = \frac{mbc}{D}$, $\theta_s = \frac{amc}{D}$ with $D = \frac{amh + gkb}{D}$.

It has been proved by Mukhopadhyay and Bhattacharyya (2006) that the system is asymptotically stable if

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

And the system is unstable if

$$k^2(b + g) + g^2(k + b) + b^2(k + g) + 2bgk < mha \tag{2.2}$$

If a and m are sufficiently large in comparison with the loss of constants, then the inequality (2.2) holds. This indicates that high production rate of the activated enzyme and of thyroxine may be the causes of instability of the system. Danziger and Elmergreen (1956) showed that the system admits periodic solutions with sustained oscillations if the thyroxine level is not less than certain value. The oscillation, together with a high production rate of thyroxine, causes a system malfunction which is known as periodic catatonic schizophrenia.

3. MATHEMATICAL SOLUTION

The solution of the system of equations (2.1) has been obtained using the Laplace transform technique.

We write $P_1 = \mathcal{L}(P)$, $E_1 = \mathcal{L}(E)$ and $\theta_1 = \mathcal{L}(\theta)$

Applying the Laplace transform on the system of linear differential equations Erwin Kreyszig, we obtain the subsidiary equations as

$$\begin{aligned} sP_1 - P(0) &= \mathcal{L}(c) - h\theta_1 - gP_1 \quad \text{for } \theta \leq \frac{c}{h} \\ sE_1 - E(0) &= mP_1 - kE_1 \\ s\theta_1 - \theta(0) &= aE_1 - b\theta_1 \end{aligned} \quad (3.1)$$

3.1 STABLE BEHAVIOR

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Following the mathematical model described by Mukhopadhyay and Bhattacharyya (2006), we will assign the values to the parameters $c = 100$, $h = 1$, $g = 1.29$, $m = 8$, $a = 0.6$, $k = 0.97$ and $b = 1.39$ as for the non-delayed system (2.1) with $\theta \leq \frac{c}{h}$ such that equation (2.2) is not satisfied. Also we will assign the value to the equilibrium point i.e. the initial condition as $Q_s = (15, 158, 80)$

System of linear algebraic equations (3.1) are then solved and the values are obtained as

$$\begin{aligned} P_1 &= 15.01 \left[\frac{s^3 + 3.7s^2 + 5.58s + 8.99}{s(s^3 + 3.65s^2 + 4.39s + 6.54)} \right] \\ E_1 &= 158 \left[\frac{(s + 2.94)(s^2 + 0.5s + 2.39)}{s(s + 2.91)[(s + 0.37)^2 + 2.1]} \right] \\ \theta_1 &= 80 \left[\frac{s^4 + 4.84s^3 + 8.47s^2 + 11.11s + 8.34}{s(s + 1.39)(s^3 + 3.65s^2 + 4.39s + 6.54)} \right] \end{aligned} \quad (3.2)$$

To obtain the values of $P(t)$, $E(t)$ and $\theta(t)$, we will take the inverse Laplace transform [6] of each equation in (3.2). Here we require using the result $\mathcal{L}^{-1} \left\{ \frac{1}{s} F(s) \right\} = \int_0^t f(\tau) d\tau$ to each equation in (3.2).

We will assume

$$\begin{aligned} F_1(s) &= 15.01 \left[\frac{s^3 + 3.7s^2 + 5.58s + 8.99}{s^3 + 3.65s^2 + 4.39s + 6.54} \right] \\ G_1(s) &= 158 \left[\frac{(s + 2.94)(s^2 + 0.5s + 2.39)}{(s + 2.91)[(s + 0.37)^2 + 2.1]} \right] \\ H_1(s) &= 80 \left[\frac{s^4 + 4.84s^3 + 8.47s^2 + 11.11s + 8.34}{(s + 1.39)(s^3 + 3.65s^2 + 4.39s + 6.54)} \right] \end{aligned} \quad (3.3)$$

to be the functions of s i.e. $F(s)$ whose $f(t)$ is to be calculated. Simplifying (3.3) using the partial fractions, we will get the form

$$\begin{aligned}
 F_1(s) &= 15.01 - \frac{1.05}{s + 2.91} + 1.8 \left[\frac{s + 0.37}{(s + 0.37)^2 + 2.1} \right] + \frac{12.69}{\sqrt{2.1}} \left[\frac{\sqrt{2.1}}{(s + 0.37)^2 + 2.1} \right] \\
 G_1(s) &= 158 + \frac{4.74}{s + 2.91} - 37.92 \left[\frac{s + 0.37}{(s + 0.37)^2 + 2.1} \right] + \frac{37.92}{\sqrt{2.1}} \left[\frac{\sqrt{2.1}}{(s + 0.37)^2 + 2.1} \right] \\
 H_1(s) &= 80 + \frac{507.2}{s + 1.39} - \frac{392}{s + 2.91} - 131.2 \left[\frac{s + 0.37}{(s + 0.37)^2 + 2.1} \right] - \frac{481.5}{\sqrt{2.1}} \left[\frac{\sqrt{2.1}}{(s + 0.37)^2 + 2.1} \right]
 \end{aligned}
 \tag{3.4}$$

To obtain $f(t)$, we will apply the inverse Laplace transform on both the sides of each equations in (3.4), we will get

$$\begin{aligned}
 f_1(t) &= 15.01\delta(t) - 1.05e^{-2.91t} + 1.8e^{-0.37t} \cos(\sqrt{2.1}t) + 8.75e^{-0.37t} \sin(\sqrt{2.1}t) \\
 g_1(t) &= 158\delta(t) + 4.7e^{-2.91t} - 37.92e^{-0.37t} \cos(\sqrt{2.1}t) + 26.15e^{-0.37t} \sin(\sqrt{2.1}t) \\
 h_1(t) &= 80\delta(t) + 507.2e^{-1.39t} - 392e^{-2.91t} - 131.2e^{-0.37t} \cos(\sqrt{2.1}t) - 332.07e^{-0.37t} \sin(\sqrt{2.1}t)
 \end{aligned}
 \tag{3.5}$$

where $\delta(t)$ is the Dirac delta function.

Integrating each equation in (3.5) between the limit 0 and t and also using the result that integration of $\delta(t)$ from 0 to ∞ is one, we will get

$$\begin{aligned}
 P(t) &= 20.61 + 0.36e^{-2.91t} - 5.96e^{-0.37t} \cos(\sqrt{2.1}t) - 0.28e^{-0.37t} \sin(\sqrt{2.1}t) \\
 E(t) &= 170.3 - 1.63e^{-2.91t} - 10.67e^{-0.37t} \cos(\sqrt{2.1}t) - 28.87e^{-0.37t} \sin(\sqrt{2.1}t) \\
 \theta(t) &= 73.55 - 364.89e^{-1.39t} + 134.71e^{-2.91t} + 236.63e^{-0.37t} \cos(\sqrt{2.1}t) - 30.08e^{-0.37t} \sin(\sqrt{2.1}t)
 \end{aligned}
 \tag{3.6}$$

The solution of the system (2.1) which does not satisfy (2.2) is given by equations in (3.6).

Using Maple12, the graphs of $P(t)$, $E(t)$ and $\theta(t)$ versus time t has been obtained and are shown as below –

3.2 UNSTABLE BEHAVIOR

Again following the mathematical model described by Mukhopadhyay and Bhattacharyya (2006), we will assign the values to the parameters as $c = 100$, h

1, $g = 1.29$, $m = 12$, $a = 1.2$, $k = 0.97$ and $b = 1.39$, for the non-delayed system (2.1) with $\theta \leq \frac{c}{h}$ such that equation (2.2) is satisfied. Also we will assign the value to the equilibrium point i.e. the initial condition as

System of linear algebraic equations (3.1) are then solved and the values are obtained as

$$\begin{aligned} P_1 &= 15.01 \left[\frac{s^3 + 3.7s^2 + 0.74s + 8.97}{s(s^3 + 3.65s^2 + 4.39s + 16.14)} \right] \\ E_1 &= 158.04 \left[\frac{s^3 + 3.82s^2 + 4.9s + 10.55}{s(s^3 + 3.65s^2 + 4.39s + 16.14)} \right] \\ \theta_1 &= 80 \left[\frac{s^4 + 6.02s^3 + 13.45s^2 + 27.76s + 25.01}{s(s^4 + 5.04s^3 + 9.46s^2 + 22.24s + 22.43)} \right] \end{aligned} \quad (3.7)$$

To obtain the values of $P(t)$, $E(t)$ and $\theta(t)$, we will take the inverse Laplace transform Murray R. Spiegel of each equation in (3.7). Here we require using the result $\mathcal{L}^{-1} \left\{ \frac{1}{F(s)} \right\} = \int_0^t f(\tau) d\tau$ to each equation in (3.7).

We will assume

$$\begin{aligned} F_1(s) &= 15.01 \left[\frac{s^3 + 3.7s^2 - 0.74s + 8.97}{s^3 + 3.65s^2 + 4.39s + 16.14} \right] \\ G_1(s) &= 158.04 \left[\frac{s^3 + 3.82s^2 + 4.9s + 10.55}{s^3 + 3.65s^2 + 4.39s + 16.14} \right] \\ H_1(s) &= 80 \left[\frac{s^4 + 6.02s^3 + 13.45s^2 + 27.76s + 25.01}{s^4 + 5.04s^3 + 9.46s^2 + 22.24s + 22.43} \right] \end{aligned} \quad (3.8)$$

to be the functions of s i.e. $F(s)$ whose $f(t)$ is to be found. Simplifying (3.8) using the partial fractions, we will get the form

$$\begin{aligned} F_1(s) &= 15.01 + \frac{10.36}{s + 3.65} - 9.61 \left[\frac{s}{s^2 + 4.39} \right] - \frac{41.88}{\sqrt{4.39}} \left[\frac{\sqrt{4.39}}{s^2 + 4.39} \right] \\ G_1(s) &= 158.04 - \frac{45.83}{s + 3.65} + 72.7 \left[\frac{s}{s^2 + 4.39} \right] - \frac{184.91}{\sqrt{4.39}} \left[\frac{\sqrt{4.39}}{s^2 + 4.39} \right] \\ H_1(s) &= 80 - \frac{0.8}{s + 1.39} + \frac{24.8}{s + 3.65} + 54.4 \left[\frac{s}{s^2 + 4.39} \right] + \frac{13.6}{\sqrt{4.39}} \left[\frac{\sqrt{4.39}}{s^2 + 4.39} \right] \end{aligned} \quad (3.9)$$

Now we will apply the inverse Laplace transform on both the sides of each equation in (3.9), we will get

$$\begin{aligned} f_1(t) &= 15.01\delta(t) + 10.36e^{-3.65t} - 9.61\cos(\sqrt{4.39}t) - 19.94\sin(\sqrt{4.39}t) \\ g_1(t) &= 158.04\delta(t) - 45.83e^{-3.65t} + 72.7\cos(\sqrt{4.39}t) - 88.05\sin(\sqrt{4.39}t) \\ h_1(t) &= 80\delta(t) - 0.8e^{-1.39t} + 24.8e^{-3.65t} + 54.4\cos(\sqrt{4.39}t) + 6.48\sin(\sqrt{4.39}t) \\ &\quad + 25.9\sin(\sqrt{4.39}t) \end{aligned} \tag{3.10}$$

where $\delta(t)$ is the Dirac delta function.

Integrating equations in (3.10) between the limit 0 and t and using the result that integration of $\delta(t)$ from 0 to ∞ is one, we will get

$$\begin{aligned} P(t) &= 8.35 - 2.84e^{-3.65t} + 9.5\cos(\sqrt{4.39}t) - 4.58\sin(\sqrt{4.39}t) \\ E(t) &= 103.55 + 12.5e^{-3.65t} - 41.93\cos(\sqrt{4.39}t) + 34.62\sin(\sqrt{4.39}t) \\ \theta(t) &= 89.3 + 0.58e^{-1.39t} - 6.79e^{-3.65t} - 3.09\cos(\sqrt{4.39}t) + 25.9\sin(\sqrt{4.39}t) \end{aligned} \tag{3.11}$$

The solution of the system (2.1) which satisfies (2.2) is given by equations in (3.11).

Using Maple12, the graphs of P(t), E(t) and $\theta(t)$ vs. time t has been obtained and are shown as below –

4. CONCLUSION

It can be observed from figure1 that the concentrations show stable behavior. The graphs in figure2 demonstrate the unstability of different components of the system leading to oscillatory behavior which symbolizes the periodic fluctuations and shows the symptoms of periodic schizophrenia.

From equations in (2.1), it can also be observed that when the level of thyroxine in the blood exceeds $\frac{c}{h}$, the anterior pituitary cannot produce any thyrotropin. As a result the production of thyroxine is decreased and when this level falls below $\frac{c}{h}$, the feedback mechanism of the thyroid-pituitary system starts working, which in turn increase the blood concentration of thyroxine and consequently, the symptoms of catatonic schizophrenia may reappear with remarkable periodicity. This system may be stabilized by administering

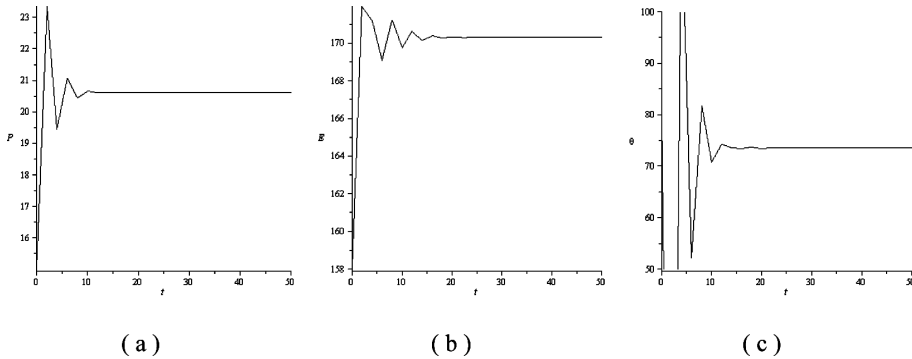


Figure 1: Graphs exhibit the stable behavior of all the concentrations for the non-delayed system: (a) $P(t)$ vs. t (b) $E(t)$ vs. t (c) $\theta(t)$ vs. t .

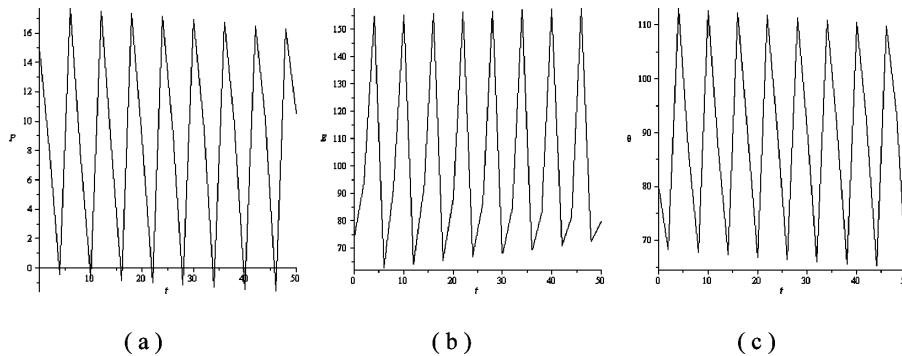


Figure 2: Graphs exhibit unstable behavior of all the concentrations for the non-delayed system: (a) $P(t)$ vs. t (b) $E(t)$ vs. t (c) $\theta(t)$ vs. t .

thyroxine extract externally at a constant rate which should be greater than $\frac{bc}{h}$ i.e the ratio of constant external input of thyroxine to its loss rate should cross a certain value for the stability of the system

USE AND SCOPE

The thyroid-pituitary feedback system considered in the present paper, may help to control the patient's symptoms and may prevent the situation from getting worse than a certain level. The stability analysis with instantaneous transportation of different hormones reveals that high production rate of activated enzyme and thyroxine may be the cause of instability in the system.

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The present work can be further extended to the case of discrete or distributed delays due to time transportation by different hormones in the bloodstream.

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