Analysis of the mathematical model describing thyroid-pituitary hormonal transportation by a system of nonlinear ordinary differential equations

Aisha Baididayeva

May 6, 2022

Department of Mathematics, School of Sciences and Humanities
Nazarbayev University
`Supervisor:` Dr. Piotr Sebastian Skrzypacz
`Second Reader:` Dr. Alejandro J. Castro Castilla

Abstract

The main goal of this capstone project is to conduct the analysis of the mathematical model which describes the transportation of the thyroid-pituitary axis of the hormones within the endocrine system. The model is constructed by a system of ordinary nonlinear differential equations that represent the fluctuations of the levels of the concentration of thyroxine hormone in the blood and illustrate its dependency on the concentration of certain enzymes. This capstone project will assess the stability of the system by applying the well-known Routh-Hurwitz criteria, conduct numerical simulations, and use MATLAB with the purpose to visualize the general behaviour of the system. The derivation of the analytical solution separately for normal and degenerate states of the system is also presented in the paper. Lastly, the phenomena of relaxation oscillations that was noticed to take place during the derivation of the analytical solution will be explained. The research has shown that there is a direct correlation between the periodicity in the changes of the levels of thyroxine hormone in the blood and the presence of the symptoms of the schizophrenia. The current capstone project can be improved by modifying the model such that it includes the discrete and distributed delay cases during the transportation process.

1 Introduction

Currently, it has been discovered that unstable concentrations of the certain endocrine hormones like thyroxine and thyroid in the blood stream of a person are the main causes for some physical and psychological diseases [2], [4]. The worst-case scenario caused by such hormonal dis-balance is the development of the periodic catatonic schizophrenia. This mental disorder is cyclic in its nature. In was noted by Danziger and Elmergreen in [13] that the periodic changes in the concentrations of thyroid and thyroxine in the blood and the cyclic occurrences of the schizophrenia's symptoms are directly related. These scientists constructed a first order model by a system of nonlinear ordinary differential equations that reflect the concentrations of thyroxine and thyroid in an organism [2]. This was done by the consideration of enzymes related to these hormones. The primary attention was given to the study of the existence of the periodic solutions to this system of NDEs [14]. The system is as follows:

$$
\begin{aligned}
\frac{dp}{dt} &= c - h\theta - gp \ (\text{for } \theta \leq \frac{c}{h}),\\
\frac{dp}{dt} &= -gp \ (\text{for } \theta \geq \frac{c}{h}),\\
\frac{dE}{dt} &= mp - kE,\\
\frac{d\theta}{dt} &= aE - b\theta.
\end{aligned}
\tag{1}
$$

In table 1 the description of variables presented in the model (1) is given below:

Table 1. The variables and their description.

Variable	**Description of the variable**
p	The concentration of thyrotropin hormone at time, t
E	The concentration of activated enzyme in blood at time, t
θ	The concentration of thyroid hormone at time, t;
b, g and k	Loss constants of the system
a, h and m	Constants that represent the sensitivity of the glands to stimulation and/or inhibition
c	the rate of production of thyrotropin hormone in the absence of thyroid inhibition

The system (1) is the mathematical system suggested by Danziger and Elmergreen in [13] to describe the transportation phenomena. The $p(t)$, $E(t)$, and

$\theta(t)$ are the functions of time t that illustrate the concentrations of such hormones as thyroid, thyrotropin, and enzyme, respectively [8]. The constants g, a, c, b, k, h, m are said to take only strictly positive values [2].

The first equation of the model (1)

$$\frac{dp}{dt} = c - h\theta - gp \text{ (for } \theta \leq \frac{c}{h}),$$

reflects the situation when the concentration of thyroid hormone, which stands for θ, is less than or equal to the control parameter $\frac{c}{h}$. The production rate of the thyrotropin hormone, p, is expected to be equivalent to $c - h\theta$. During the increase in concentration of thyroid hormone, it is seen that the thyrotropin hormone falls down and is destroyed at a rate that is proportional/equivalent to its initial concentration. The notation for thyrotropin is p in the table (1). The further detailed explanation is presented in [13] and [3].

The second equation of the model (1), that stands for

$$\frac{dp}{dt} = -gp \text{ (for } \theta \geq \frac{c}{h}),$$

refers to the concentration of the thyroid enzyme, θ, when its concentration is greater than or equal to the control parameter $\frac{c}{h}$. From the equation, it is noted that the thyrotropin, p, is destroyed at a rate that is proportional to the initial concentration, that is $-gp$ [2].

The equation number three of the model (1), which is

$$\frac{dE}{dt} = mp - kE,$$

provides the information about the concentration of enzyme E. It is produced at a rate that is proportional to thyrotropin, p, and destroyed at a rate that is equivalent to E, namely kE [8].

The fourth equation of the model (1)

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

describes the situation in which the thyroid enzyme, θ is made at a rate that appears to be proportional to E and destroyed at a rate that is equivalent to θ

as stated by J.Cronin [8]

The deeper investigation of the system was done by B.Mukhopadhyay and R.Bhattacharyy in [2] and by J.Cronin in [8]. They, first, stated the assumption about the thyrotropin hormone having an impact on the activation of a thyroid enzyme, θ. Then, when the activation process is done, the thyroxine hormone is produced. As it is seen from the model (1) the concentration of thyroxine is directly dependent on the concentration of the corresponding enzyme, but the dependency on the level of thyrotropin is shown to be indirect in its nature [2].

The main part of this capstone project consists of four sections, namely stability analysis, derivation of analytical solution, comments on relaxation oscillations and conduction of some numerical simulations. The main results are the derivation of the conditions for the stability of the system based on Routh-Hurwitz criteria, analytical solution for both degenerate and normal states of the system and some numerical simulations on the stability of the system.

2 Stability of the system

In order to conduct the stability analysis of the system (1) of ordinary NDEs the general algorythim presented in [15] by L. Edelstein-Keshet will be followed. The first step is to find the critical points which we label as $Q_0 = (p_0, E_0, \theta_0)$ [2].

Case 1: For $\theta \leq \frac{c}{h}$

First, the following system of equations is required to be solved to find the critical points:

$$\begin{aligned} &c - h\theta - gp = 0, \\ &mp - kE = 0, \\ &aE - b\theta = 0. \end{aligned} \tag{2}$$

From the equation (2), the following is obtained

$$p = \frac{h\theta - c}{-g};\ E = \frac{mh\theta - mc}{-kg};\ \theta = \frac{amc}{amh + kgb}.$$

Second, after conducting some simplifications we are left with the following non-trivial equilibrium point, which is said to be $Q_0 = (p_0, E_0, \theta_0)$, where

$$p_0 = \frac{kbc}{D}$$
$$E_0 = \frac{mbc}{D}$$
$$\theta_0 = \frac{amc}{D}$$

where $D = amh + kgb$ for convenience purposes.

Nest step is the construction of the Jacobian matrix

$$J_Q = \begin{vmatrix} -g & 0 & -h \\ m & -k & 0 \\ 0 & a & -b \end{vmatrix}.$$

Now, we construct the determinant $|J_q - \lambda I|$ in order to find and assess the eigenvalues of the system, that is

$$|J_Q - \lambda I| = \begin{vmatrix} -g-\lambda & 0 & -h \\ m & -k-\lambda & 0 \\ 0 & a & -b-\lambda \end{vmatrix}.$$

Next step is to construct the characteristic equation. Observe the following:

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

It can be observed that the degree of the characteristic equation in (3) is $n = 3$. Thus, solving directly for the roots can be a complicated issue. In order to simplify the calculations, the Routh-Hurwitz criteria will be applied in this case. The definition and algorithm by which this criteria will be used is elaborated by Kaufman and DeJesus in [6]. First, consider the following Hurwitz matrix:

$$\begin{bmatrix} k+g+b & 1 & 0 \\ bdk+mha & gk+bk+gb & k+g+b \\ 0 & 0 & bdk+mha \end{bmatrix}. \tag{4}$$

As it can be noted from the Hurwitz matrix, the principal diagonal minor $\triangle_3$ of (4) is defined as follows

$$\triangle_3 = a_0 \triangle_2,$$

such that a_0 stands for the coefficient before the λ^3 in (3). Now

$$\begin{aligned}\triangle_3 &= \begin{vmatrix} k+g+b & 1 \\ bdk+mha & gk+bk+gb \end{vmatrix} \\ &= (k+g+b)(gk+bk+gb) - bdk - mha \\ &= k^2(g+b) + g^2(k+b) + b^2(k+g) + 2bgk - mha.\end{aligned}$$

According to the Routh-Hurwitz criteria [6], the roots of the characteristic equation (3) are expected to contain a negative real parts if and only if all the principal diagonal minors, namely ($\triangle_n$), of the above constructed Hurwitz matrix (4) take positive values given that $\triangle_3 > 0$ as stated by by Kaufman and DeJesus in their article [6] and in [15] by L. Edelstein-Keshet. The necessary condition is that all coefficients of the characteristic equation need to be positive. Based on the Routh-Hurwitz criteria elaborated and assessed by Kaufman and DeJesus in [6], the system (1) will only be stable in case if

$$k^2(g+b) + g^2(k+b) + b^2(k+g) + 2bgk > mha. \tag{5}$$

and unstable is

$$k^2(g+b) + g^2(k+b) + b^2(k+g) + 2bgk < mha. \tag{6}$$

Case 2: For $\theta \geq \frac{c}{h}$

In this case when $\theta \geq \frac{c}{h}$, there exist another equilibrium point which stands for $Q_0 = (P_0, E_0, \theta_0) = (0, 0, 0)$. This equilibrium point can be described as a trivial one. If to further analyse the explanation of such result by MD.Kamrujjaman et al. in their research concerning the stability of the systems of nonlinear differential equations described in [1] on page 98, the system will be fully not stable when $\theta \geq \frac{c}{h}$.

In was discussed by B.Mukhopadhyay and R.Bhattacharyya in their article [2] that when thyroxine hormone exceeds the value of control parameter $\frac{c}{h}$ then the functioning of pituitary axis in endocrine system will not be proper. As a result, the production of thyroxine will rapidly fall below the value of the threshold of $\frac{c}{h}$.

Then the push-pull feedback mechanism will be turned on [2]. This, indeed, will cause the symptoms of catatonic schizophrenia to activate periodically since the concentration of thyroxine started to go up again. For this reason it is important to keep the ratio of constant external input of thyroxine equivalent to the loss rate not exceeding the threshold value of $\frac{c}{h}$ [2].

3 Properties of the system and its solution

Before starting to derive the analytical solution, it is necessary to have some background information about its properties. Our variables p, E, θ in (1) could be referred to as the concentrations of hormones and enzymes in a system (1). The main research interest is in the solutions of the form $[p(t), E(t), \theta(t)]$. In our case $p(t), E(t), \theta(t)$ are denoted as functions, which are non-negative in nature such that all values of t are defined as positive [9]. The next theorem, the proof of which is presented by J.Cronin in [9] and in [5] is of primary importance.

Theorem 1. *If (p_1, E_1, θ_1) appears to be a point in the Euclidean three-space and the value of t is a real number, then there $\exists$ a solution of the form $[p(t), E(t), \theta(t)]$ of (S) such that*

$$[p(t), E(t), \theta(t)] = (p_1, E_1, \theta_1)$$

This solution then is defined to be true for $\forall$ real values of t [9].

One of the requirements for the solutions of the form $[p(t), E(t), \theta(t)]$ is that they are expected to be bounded. This is a necessary limitation because of the control parameter $\frac{c}{h}$. The concentrations need to stay within the range of the fixed bound. If not, then the patient may either pass away or end up receiving a serious health damage caused by the above mentioned hormonal dis-function [2], [5]. The nest important theorem is as follows:

Theorem 2. *Let $E(0) \geq 0, p(0) \geq 0, \theta(0) \geq 0$ then the solution of the system (1) is non-negative and is expected to have a bound.*

Proof. It can be observed that $\frac{dp}{dt} + gp \geq 0$. Therefore, $p(t) \geq 0$ for all $t \geq 0$. Similarly we can expand for $E(t)$ and $\theta(t)$ and we will, thus, obtain $\frac{dE}{dt} - mp + kE \geq 0$ and $\frac{d\theta}{dt} - aE + b \geq 0$. It follows then that $E(t) \geq 0$ and $\theta(t) \geq 0$ for $\forall$ $t \geq 0$. Consider that $\frac{dp}{dt} + gp \leq c$, therefore, $p(t) \leq p_{max}$, and $p_{max} = max\{0, \frac{c}{g}\}$.

Since we know that $p(t), E(t), \theta(t)$ depend on each other, as it is visible in (1), the following appears to be true then: $E(t) \leq E_{max}$, and $E_{max} = max\{0, \frac{mp_{max}}{k}\}$. In addition, $\theta(t) \leq \theta_{max}$, and $\theta_{max} = max\{0, \frac{aE_{max}}{b}\}$ for $\forall\ t \geq 0$. As a result, it can be concluded that the solution of the system (1) does, indeed, have a bound and appears to be non-negative [2]. ■

The Theorem 2 (3) and its results are also supported by the practical clinical evidences that are provided in details in [14]. If there is conducted a procedure of removing the pituitary gland, then:

- c will approach to the zero value.
- p will fall following the exponential pattern as time passes.
- E will behave in a similar was as p while the parameter θ will behave similar to the parameter E.

If there is the case when E is experiencing the dysfunction for the reason of poisoning or issues with the transportation of the iodide enzymes then there is expected a decrease in the production rate of the thyroid. It happens since the concentration of p would be high but not enough to treat the poisoning [14].

4 Analytical solution of the system

Let us formulate a more convenient form of the equations in (1) by introducing the variable changes such that we will apply a dimensionless over-all gain constant K to rewrite our system.

Table 2. The Variables and its description.

Variable	**Description of the variable**
$x = (\frac{g}{h})p$	A new variable that is proportional to p
$y = (\frac{gk}{hm})E$	A new variable that is proportional to E
$C = \frac{c}{h}$	A controlling parameter
$K = (\frac{ahm}{bgk})$	A dimensionless over-all gain constant
$T_1 = \frac{1}{g}, T_2 = \frac{1}{k}, T_3 = \frac{1}{b}$	System time constants

Now, let us consider the new form of the model (1) when we substitute out new variables in:

$$T_1(\frac{dx}{dt}) + x = C - \theta \text{ (for } \theta \le C),$$
$$T_1(\frac{dx}{dt}) + x = 0 \text{ (for } \theta \ge C),$$
$$T_2(\frac{dy}{dt}) + y = x, \tag{7}$$
$$T_3(\frac{d\theta}{dt}) + \theta = Ky.$$

The beginning step in analysing the solution of our rewritten set of equations in (7) is to evaluate the steady-states of the above shown dependent variables, as shown in [14]. To do so, the general algorithm requires to equate the derivatives in (7) to zero and solve [15], [16]:

$$\frac{dx}{dt} = \frac{C - \theta - x}{T_1} = 0 \text{ (for } \theta \le C),$$
$$\frac{dy}{dt} = \frac{x - y}{T_2} = 0,$$
$$\frac{d\theta}{dt} = \frac{Ky - \theta}{T_3} = 0.$$

Solving the system simultaneously we find out that the steady states are as follows:

$$x_s = \frac{C}{1+K},$$
$$y_s = x_s, \tag{8}$$
$$\theta_s = \frac{CK}{1+K}.$$

Since $y_s = x_s$ we can omit y_s and focus only at two steady-states, namely

$$x_s = \frac{C}{1+K}$$

$$\theta_s = \frac{CK}{1+K}$$

From the above it is seen that $C = \frac{c}{h}$ is the one which heavily controlling the steady-state levels of the steady-state solutions of such hormones as thyrotropin and thyroid almost equivalently, as elaborated in details in the work of Danziger and Elmergreen in [14] and in [10] by Pandiyan et al. On the other hand, it can be observed that $K = \frac{amh}{bgk}$ is influencing significantly the x_s state and has not so much impact on the θ_s because of the properties of the fraction. The further investigation of the steady-state levels shows that usually the values that the gain constant K takes are sufficiently high so that it is possible to conduct the following approximation for the convenience purposes [14]:

$$\begin{aligned} \frac{K}{1+K} &= 1, \\ \therefore \theta_s \cong C &= \frac{c}{h}. \end{aligned} \tag{9}$$

This means that the control parameter C is congruent to the level of thyroid hormone, shows how much weak it is as a parameter and makes further considerations of the system and its solution easier.

These above steps illustrate that when the thyroid gland is regulating normally the steady-state level of θ is actually dependent on the values of the following constants c and h [13]. When K takes greater values, then the effects of other constants a, m, b, g, and k are destroyed by the properties of the push-pull feedback mechanism [14], [10].

Let us now consider the situation when a in initial model (1) is expected to be zero. This will imply that the value of K will end up being zero too. Thus, the values of steady-states in (8) will become:

$$\begin{aligned} x_s &= C, \\ \theta_s &= 0. \end{aligned} \tag{10}$$

Thus, this is a mathematical explanation of the fact that conducting an operation on taking away the thyroid gland (thyroidectomy) will lower the concentration of thyroid hormone (θ) but will double the level of thyrotropin (p). Hence, it will not be enough to conduct only the thyroidectomy but inject the thyroid hormone artificially as well [14].

Let us now move on into the derivation of analytical solution and conducts a general procedure of eliminating the x and y from the system in (7). This is a standard procedure described in [15]. We will obtain the following expression for y in terms of θ and its derivative:

$$y = \frac{T_3(\frac{d\theta}{dt} + \theta)}{K},$$
$$\frac{dy}{dt} = (\frac{T_3}{K})(\frac{d^2\theta}{dt^2}) + (\frac{1}{K})(\frac{d\theta}{dt}).$$

For x and its derivative we, in turn, obtain the following:

$$x = (\frac{T_2 T_3}{K})(\frac{d^2\theta}{dt^2}) + (\frac{T_2 + T_3}{K})(\frac{d\theta}{dt}) + \frac{\theta}{K},$$
$$\frac{dx}{dt} = (\frac{T_2 T_3}{K})(\frac{d^3\theta}{dt^3}) + (\frac{T_2 + T_3}{K})(\frac{d^2\theta}{dt^2}) + (\frac{1}{K})(\frac{d\theta}{dt}).$$

By substituting these equations into rewriten model (7) we obtain the following third-order linear differential equations:

$$(\frac{T_1 T_2 T_3}{K})(\frac{d^3\theta}{dt^3}) + (\frac{T_1 T_2 + T_1 T_3 + T_2 T_3}{K})(\frac{d^2\theta}{dt^2}) + (\frac{T_1 + T_2 + T_3}{K})(\frac{d\theta}{dt}) + \frac{\theta}{K} = C - \theta \text{ (for } \theta < C),$$
$$(\frac{T_1 T_2 T_3}{K})(\frac{d^3\theta}{dt^3}) + (\frac{T_1 T_2 + T_1 T_3 + T_2 T_3}{K})(\frac{d^2\theta}{dt^2}) + (\frac{T_1 + T_2 + T_3}{K})(\frac{d\theta}{dt}) + \frac{\theta}{K} = 0 \text{ (for } \theta > C).$$

Thus, by simplifying, we obtain the following result:

$$\begin{aligned} r_3(\frac{d^3\theta}{dt^3}) + r_2(\frac{d^2\theta}{dt^2}) + r_1(\frac{d\theta}{dt}) + (1+K)\theta = KC \text{ (for } \theta < C), \\ r_3(\frac{d^3\theta}{dt^3}) + r_2(\frac{d^2\theta}{dt^2}) + r_1(\frac{d\theta}{dt}) + \theta = 0 \text{ (for } \theta > C). \end{aligned} \tag{11}$$

where the constants represent positive real numbers such that
$r_1 = T_1 T_2 T_3$,
$r_2 = T_1 T_2 + T_1 T_3 + T_2 T_3$,
$r_3 = T_1 + T_2 + T_3$.

The next step will be to find out what is the characteristic equation of this system. If to investigate both equations, it becomes clear that for both cases in (11) the characteristic equation will be:

$$r_3 D^3 + r_2 D^2 + r_1 D + r_0 = 0. \tag{12}$$

where
$D = \frac{d}{dt}$;
$r_0 = (1 + K)$ for the case where $\theta < C$;
$r_0 = 1$ for the case where $\theta > C$.

The next step is to simplify and factor the characteristic equation in (12):

$$(D - q)((D - z)^2 + w^2). \tag{13}$$

where q, z and w are presented as the functions of the coefficients. Thus, the roots of the characteristic equation in (13) appear to be

$$D_1 = q,$$
$$D_{2,3} = z \pm iw.$$

where w is either real or imaginary.
The general solution will be then as follows:

$$\theta = \theta_s + Se^{qt} + Me^{zt} sin(wt + \phi). \tag{14}$$

where S, M, ϕ vary depending on the initial conditions.

Worth noting that all the constants depending on the conditions put on the value of θ differ for the solution (14):

θ_s for the case $\theta < C$ will be as shown in 8 $\theta_s = \frac{CK}{1+K}$;
θ_s for the case $\theta > C$ will be as shown in 10 $\theta_s = 0$;
r_0 as well differs for both $\theta > C$ and $\theta < C$ cases because q, z, w will have different values;
Due to stability concerns regarding the system in general, it is also required $\lim \theta$ as t goes to infinity needs to approach θ_s [14].

5 Relaxation Oscillations and Periodicity

Let us rewrite our model (1) as shown below:

$$
\begin{aligned}
&\frac{dp}{dt} + gp = c - h\theta \ (\text{for } \theta \leq \frac{c}{h}),\\
&\frac{dp}{dt} + gp = 0 \ (\text{for } \theta \geq \frac{c}{h}),\\
&\frac{dE}{dt} + kE = mp,\\
&\frac{d\theta}{dt} + b\theta = aE.
\end{aligned} \tag{15}
$$

Before we move on, it is necessary to introduce two definition of *degenerate state* of the model [1], which will be referred to frequently.

Definition 1 *Degeneration of the model* is presented in a form of a so-called piece-wise linear comprising of a system of linear equations, what is observed in [1]. These equations are expected to unstable in the normal state and stable in the other - degenerate state, as introduced in their paper [12] by Danziger and Elmergreen.

In other words we can separate our initial model (1) into two different systems, where the normal system set will be:

$$
\begin{aligned}
&\frac{dp}{dt} + gp = c - h\theta \ (\text{for } \theta \leq \frac{c}{h}),\\
&\frac{dE}{dt} + kE = mp,\\
&\frac{d\theta}{dt} + b\theta = aE.
\end{aligned} \tag{16}
$$

and the degenerate system set will be:

$$
\begin{aligned}
&\frac{dp}{dt} + gp = 0 \ (\text{for } \theta \geq \frac{c}{h}),\\
&\frac{dE}{dt} + kE = mp,\\
&\frac{d\theta}{dt} + b\theta = aE.
\end{aligned} \tag{17}
$$

We are interested in the periodic and oscillatory solutions. Further we will proceed with finding the solution for two states, normal and degenerate separately. Before it is done, let us introduce the criteria for the condition that we will need to consider in order to ensure that we will have a sustained oscillations for the systems of order $n > 2$ taken from the paper [12]:

1. at least one or more of the roots for the normal state of the system (16) are expected to have a positive real part [12], [7];
2. all the roots for the degenerate state of the system (17) are expected to have negative real parts [12];
3. the steady-state concentrations for the degenerate system (17) are lower than the concentrations of the degeneration; [12], [7].

In this (16) state of the system, the roots fulfilling the first criteria above would push the system to enter an unstable phase. Then the concentrations of p, E, θ are going to increase. This would take place until the system would enter the stable degenerate phase [12].

Then, in this (17) state the system would fulfill the second criteria above. As a result, the concentrations are going to decrease until the system will again enter an unstable normal state [7].

Now, consider the following characteristic equation for the normal state (16):

$$\begin{vmatrix} (D+g) & 0 & h \\ -m & (D+k) & 0 \\ 0 & -a & (D+b) \end{vmatrix} = 0 \tag{18}$$

According to the criteria for the existence of the oscillatory behaviour in a system, we need to have, as it is stated in the first criteria, at least one root that has a positive real part [12], [17]. Recall that our characteristic equation will look like this:

$$R_0 D^3 + R_1 D^2 + R_2 D + R_3 = 0 \tag{19}$$

According to the Routh-Hurwitz criteria that we stated in the Stability Analysis section 2, this will be true only if the coefficients $R_0 R_3 > R_1 R_2$, see [6] and section 2 for the application of the Routh-Hurwitz criteria.

For the degenerate system (17) we need all roots to have negative real pars, as stated in the second criteria [12]. Note that it is, indeed, true, since the degenerate case differs from normal only in a part where $c - h\theta = 0$. Therefore, $c = h = 0$. Thus, by considering the new characteristic equation it becomes evident that roots will have negative real parts, namely $r_1 = -g$, $r_2 = -k$, $r_3 = -b$.

As we discussed previously, the characteristic equation will be as [12]. The factored form will be as in [13]. Now, let us rewrite two solutions for θ derived earlier differently.

Thus, for normal case, our solution will become:

$$\theta_{norm} = \theta_s + c_{31}e^{qt} + e^{zt}[c_{32}e^{iwt} + c_{33}e^{-iwt}]. \tag{20}$$

and for the degenerate case:

$$\theta_{deg} = c'_{31}e^{-gt} + c'_{32}e^{-kt} + c'_{33}e^{-bt}. \tag{21}$$

Here, the relaxation oscillations would take place and the solutions are going to alternate with each other. Let us introduce the definition of the relaxation oscillation first, which was eloborated in details by J.Grasman in [7] and by B. Van der Pol in [17].

Definition 2 *Relaxation Oscillation* can be described as a limit cycle of some singularly perturbed system that is dynamical. It is a system of NDE, where within the occurrence of a cycle at least one of the system leaves and comes back to the some agreed manifold $M^{(\epsilon)}$ [17], [7].

Let us apply this definition to our case and explain why relaxation oscillation will take place in the solution of our model:

- At case when $\theta < c/h$ he pair of complex roots of the solution for the normal state cause a formation of a periodic term that has an amplitude which is following positive exponential path;

- Then θ would eventually hit the concentration value of our control parameter c/h;
- Then the rate of change of θ will be in a positive range and will continue increasing until it reaches certain maximum that is bigger than the control parameter c/h;
- As $\theta > c/h$ the degenerate solution would take place and θ would decrease and reach zero steady state until the value of control parameter, namely c/h is achieved;
- The rate of change of θ will be in a negative range and will keep decreasing until it will reach some minimum that is lower than the control parameter $\frac{c}{h}$;
- When the $\theta < c/h$ again the solution for normal state will apply and all the steps above would again repeat;

6 Numerical Results and Discussions

The MATLAB programming platform has been used for the visualization of the results using some numerical techniques. Two cases, stable and unstable, of the model (1) considering $\theta \leq \frac{c}{h}$ and $\theta \geq \frac{c}{h}$ were assessed. The results are summarised in the following figures 1, 2, and 3.

First, the behaviour of the system when the condition of (5) was satisfied were considered. All necessary values for the parameters of the model (1) including the values for initial conditions, and some loss and gain constants were used from the data presented in [2]. On the Figure 1 there are depicted the graphs of $p(t), E(t), \theta(t)$ vs time such that $k^2(g+b)+g^2(k+b)+b^2(k+g)+2bgk > mha$. It can be noted on the Figure 1, the trend of all hormones and enzymes is stable, as we expect them to be.

Next step is to consider this criteria of stability (5). The only adjustment that was made was to alter the values of m and a such that $m = 8$ and $a = 0.6$

Assessing the results from Figure 2, it can can be observed that it illustrates the functions of $p(t)$, $E(t)$, and $\theta(t)$ vs time for the system (1) such that $\theta \leq \frac{c}{h}$ having the (5) criteria being met. The production rates and concentrations of

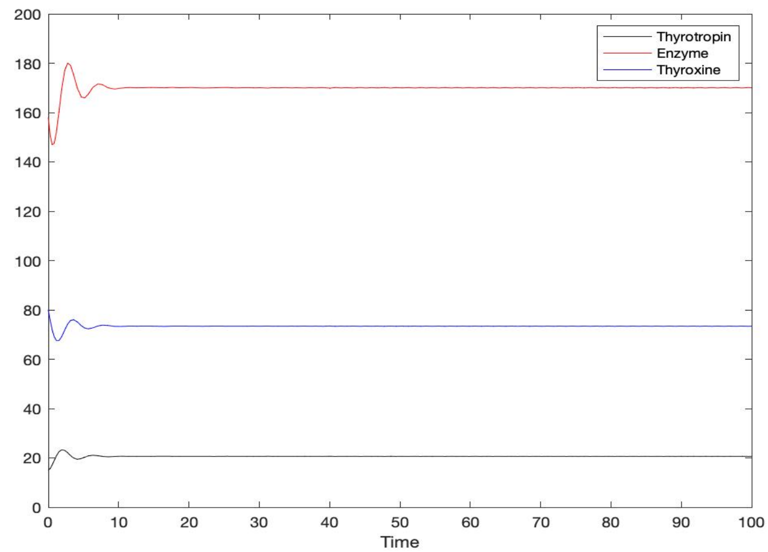

Figure 1: The graphs of $p(t)$, $E(t)$, and $\theta(t)$ vs. time for the system of ODE (1) when $\theta \leq \frac{c}{h}$ given the (5) is met. Parameter values were taken from [2]: c = 100; h = 1; g = 1.29; m = 8; a = 0.6; k = 0.97; b = 1.39. Initial conditions are $(p_0, E_0, \theta_0) = (15, 158, 80)$.

hormones and enzymes are not stable here. There can be noted some oscillations being present and they appear to be periodic in their nature. Thus, it can be concluded that these cycles, indeed, reflect the behaviour of the symptoms of the catatonic schizophrenia [2].

Looking at the Figure 3 we can see that it represents the graphs of $p(t)$, $E(t)$, and $\theta(t)$ vs time for the system (1) with $\theta \geq \frac{c}{h}$ when the (6) condition is met. As we can observe from the section that discusses the stability criteria for both $\theta \leq \frac{c}{h}$ and $\theta \geq \frac{c}{h}$ cases, the numerical results meet our expectations.

We expect in a degenerate mode the creation of thyroxine hormone will go down [2], [12], [14]. Since our numerical simulation does not incorporate in this case the alternating solution of the normal state, the system will just reach the value of zero [2]. The further numerical simulations incorporating both normal and degenerate states' solution can be further developed in the future projects.

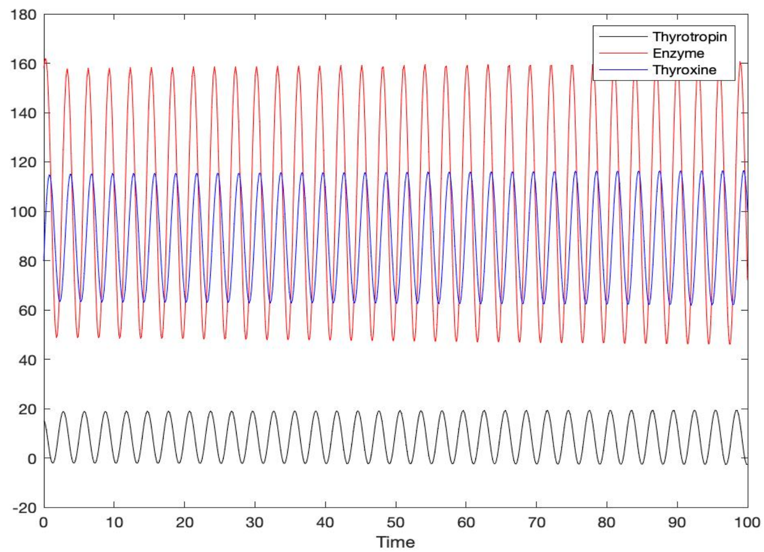

Figure 2: The graphs of $p(t)$, $E(t)$, and $\theta(t)$ vs. time for the system of ODE (1) when $\theta \leq \frac{c}{h}$ when the (6) is satisfied. Parameter values were taken from [2]: c= 100; h = 1; g = 1.29; m = 12; a = 1.2; k = 0.97; b = 1.39. Initial conditions are $(p_0, E_0, \theta_0) = (15, 158, 80)$.

Algorithm 1 MATLAB script for the DEdeffe.m file

```
function[Ddv]=DEdeffe(I,D)

% IV, I, IVsolt - Independent variables
% DV, D, Dvsolt - Dependent variables

c=100; %defining the parameters
h=1;
g=1.29;
m=12;
a=1.2d;
k=0.97;
b=1.39;

p=D(1);
E=D(2);
q=D(3);

%derivatives of dependent variable w.r.t independent variables

Ddv =[c-h*q-g*p;
m*p-k*E;
a*E-b*q];
end
```

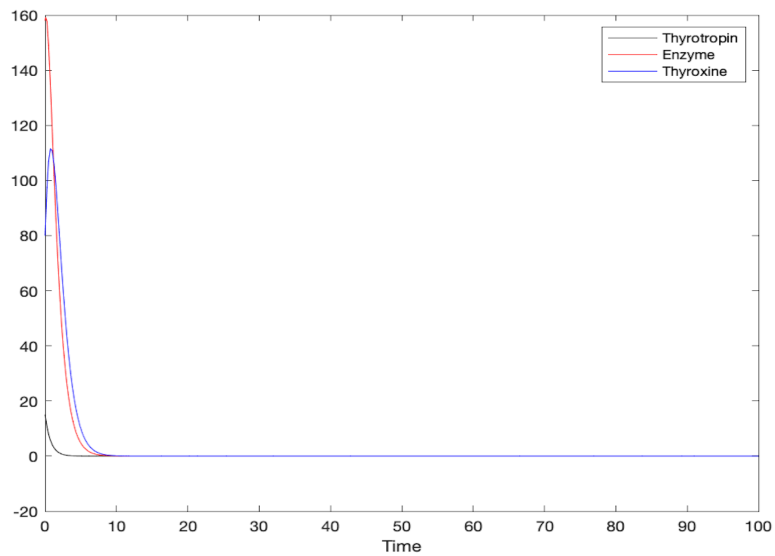

Figure 3: The graphs of $p(t)$, $E(t)$, and $\theta(t)$ vs. time for the system of ODE (1) when $\theta \geq \frac{c}{h}$ when the (6) is satisfied. Parameter values were taken from [2]: c= 100; h = 1; g = 1.29; m = 12; a = 1.2; k = 0.97; b = 1.39. Initial conditions are $(p_0, E_0, \theta_0) = (15, 158, 80)$.

Algorithm 2 MATLAB script for the DEdefRun.m file

```
domain=[0 100];
IC1=15; %defining the Initial Conditions
IC2=158;
IC3=80;

IC=[IC1 IC2 IC3];

[IVsolt, DVsolt] = ode23('DEdeffe', domain, IC);

%plotting the graphs of the solutions

plot(IVsolt, DVsolt(:,1), 'k')
hold on
plot(IVsolt, DVsolt(:,2), 'r')
plot(IVsolt, DVsolt(:,3), 'b')
legend('Thyrotropin','Enzyme','Thyroxine')
xlabel('Time')
```

This system of ordinary NDEs (1) is not the most efficient and precise one but rather represent a simpler version of a transportation of hormones in endocrine system. It can be improved by considering the possible discrete and distributed delays during the transportation and adjusted accordingly.

7 Conclusions and Outlooks

This capstone project focused on the mathematical analysis of the thyroid-pituitary axis in the hormonal transportation within the push-pull feedback mechanism presented in the model (1). During the study of this topic, it was found that there exist a direct correlation between the symptoms of the catatonic schizophrenia and concentrations of thyroid, thyroxine, and thyrotropin hormones and enzymes in the blood stream of a patient [9]. Based on the stability analysis conducted in section (2), if the values of such constants as m and a that stand for some activated enzymes are high then the system enters an unstable phase [2]. The deeper investigation of the stability of the system was conducted by applying a well-known Routh-Hurwitz criteria when considering two cases where θ was taking greater or lower values than the threshhold $\frac{c}{h}$. The results showed that it is required for hormones no to exceed the value of a control parameter in order to avoid a fatal end of a patient that could be caused by a serioud hormonal dysfunction [8].There were conducted several numerical simulations to visualise the behaviour of a system (1) during the stable and unstable phases. The role of the parameters m and a has been proven to be crucial in maintaining the push-pull feedback mechanism of the hormone transportation stable for both cases of normal and degenerate states of the initial fourth order system of ordinary NDEs. The analytical solution for both normal and degenerate cases have been derived using the reduction techniques so that our nonlinear system was reduced to the set of two linear third order differential equations. Further investigation and research showed that both solutions of the system alternate with each other causing the relaxation oscillation to occur. The current model can be improved by incorporating the phenomena of the discrete and distributed delays during the transportation that may take place because of other hormones and enzymes [2], [11].

8 Acknowledgement

I would like to express my sincere gratitude to my supervisor, Professor Piotr Sebastian Skrzypacz, for all the help, support, and guidance during the completion of this capstone project and the second reader Professor Alejandro J. Castro Castilla for all the useful feedback and comments. I would also like to thank capstone course coordinators, Professor Achenef Tesfahun and Professor Adilet Otemissov, for thought-provoking questions, suggestion, and useful comments during the weekly capstone sessions. In addition, I wish to acknowledge the contribution of all the mathematicians, scientists, and scholars, whose works I referenced and who have studied and developed this topic in their research work.

References

[1] MD.Kamrujjaman et al. "Stability analysis and numerical solutions of a competition model with the effects of distribution parameters." In: *Bangladesh Academy of Sciences* 43.1 (2019), pp. 95–106.

[2] B.Mukhopadhyay and R.Bhattacharyya. "A mathematical model describing the thyroid-pituitary axis with time delays in hormone transportation". In: *Applications of Mathematics* 51.6 (2006), pp. 549–564.

[3] James R. Brannan and William E. Boyce. *Differential Equations. An Introduction to Modern Methods and Applications.* Third Edition. Laurie Rosatone, 2015.

[4] J. Cronin. "Biomathematical Models of Schizophrenia". In: *A Journal of Progress in Neurosurgery, Neurology and Neurosciences: Neurological Research* 1.1 (2016), pp. 87–99.

[5] J. Cronin. "Mathematical Aspects of Periodic Catatonic Schizophrenia". In: *Bulletin of Mathematical Biology* 39.2 (1977), pp. 187–199.

[6] E.X.DeJesus and C.Kaufman. "Routh-Hurwitz Criterion in the Examination of Eigenvalues of a System of Nonlinear Ordinary Differential Equations." In: *Physical Review A* 35.12 (1987), pp. 5288–5290.

[7] J. Grasman. "Relaxation Oscillations". In: *Meyers R. (eds) Mathematics of Complexity and Dynamical Systems. Springer* 3.10 (2012), pp. 1475–1488.

[8] J.Cronin. "A mathematical model for catatonic schizophrenia." In: *Bulletin of Mathematical Biophysics* 36.11 (1976), pp. 706–714.

[9] J.Cronin. "The Danziger-Elmergreen theory of periodic catatonic schizophrenia." In: *Bulletin of Mathematical Biophysics* 35.11 (1973), pp. 689–707.

[10] Balamurugan K. Pandiyan. "A patient-specific model of the negative-feedback control of the hypothalamus–pituitary–thyroid (HPT) axis in autoimmune (Hashimoto's) thyroiditis". In: *Mathematical medicine and biology: a journal of the IMA* 31.3 (2014), pp. 226–258.

[11] L. Kenneth L. Cooke and Z. Grossman. "Discrete delay, distributed delay and stability switches". In: *Journal of mathematical analysis and applications* 86.2 (1982), pp. 592–627.

[12] L.Danziger and G.L.Elmergreen. "Mathematical Models of Endocrine Systems". In: *Bulletin of Mathematical Biophysics* 19.13 (1957), pp. 9–18.

[13] L.Danziger and G.L.Elmergreen. "Mathematical theory of periodic relapsing catatonia." In: *Bulletin of Mathematical Biophysics* 16 (1954), pp. 15–21.

[14] L.Danziger and G.L.Elmergreen. "The Thyroid-Pituitary Homeostatic Mechanism." In: *Bulletin of Mathematical Biophysics* 18 (1956), pp. 1–13.

[15] L.Edelstein-Keshet. *Mathematical Models in Biology.* First Edition. Random House, New York, 2005. ISBN: 978-0-89871-554-5.

[16] H. DeSai M. Mulla. "Solution of a Mathematical Model Describing the Change of Hormone Level in Thyroid Using the Laplace Transform". In: *Mathematical Journal of Interdisciplinary Sciences* 2.1 (2013), pp. 99–108.

[17] B. Van der Pol. "LXXXVIII. On Relaxation-Oscillations". In: *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science* 2.11 (1926), pp. 978–992.