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Mathematical Model for Hashimoto Autoimmune Thyroiditis Disease With steady state

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ABSTRACT

Hashimoto's disease (HT) is the first autoimmune disease that was discovered by Japanese physician Hakaru Hashimoto in 1912. This disease targets the thyroid gland, produces antibodies to it, and then causes deficiency and atrophy in it due to the attack of immune cells on it. The main goal of this work is to study the stability of pre-designed mathematical model described interactions between thyroid cells, lymphocytes TH_{17}, TH_1 and Treg cells and the gut microbiota, hence the model is a nonlinear system consisting of four nonlinear ordinary differential equations. To achieve this goal, all active equilibrium points of the system are found, and hence studied one by one to get the conditions under which the studying point is stable, that is to find a stability point for the system that limits disease complications and immune system activity. Calculating the values of eigenvalues, however, indicates that at least one of them is zero for each point which means the equilibrium points are non-hyperbolic, in this case the linearization method is not effective, therefore Lyapunov method is used. A different Lyapunov function suggested for each point in order to enrich the study.

Keywords: Hashimoto's disease, Mathematical modelling, Autoimmune disease, Thyroid gland, Stability, Lyapunov function.

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نموذج رياضي لمرض هاشيموتو المناعي الذاتي للغدة الدرقية مع حالة الاستقرار

فاطمة صداقة وعبد السلام بوحويش

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ملخص البحث

مرض هاشيموتو هو أول مرض مناعي ذاتي اكتشفه الطبيب الياباني هاكاروهاشيموتو في عام 1912. يستهدف هذا المرض الغدة الدرقية، ويقوم بإنتاج الأجسام المضادة لها، مما يؤدي الى نقصها وضمورها نتيجة هجوم الخلايا المناعية عليها. الهدف الرئيسي من هذا العمل هو دراسة استقرار نموذج رياضي مصمم مسبقا يصف التفاعلات بين خلايا الغدة الدرقية TH_1, TH_{17} والخلايا التنظيمية (Treg) والميكروبات المعوية، وعليه فان النموذج هو نظام رياضي مكون من أربع معادلات تفاضلية عادية غير خطية. ولتحقيق هدف الدراسة، تم إيجاد جميع نقاط التوازن الفاعلة للنظام والشروط اللازمة لاستقرار كل منها، حيث أن محاولة التحكم في تلك الشروط يؤدي الى الحد من مضاعفات المرض ونشاط الجهاز المناعي. نظرا لطبيعة نقاط التوازن فقد تم دراسة استقرارها بطريقة ليبانوف وتم اقتراح دالة ليبانوف مختلفة لكل نقطة بغرض اثراء الدراسة.

الكلمات المفتاحية: مرض هاشيموتو، النماذج الرياضية، الغدة الدرقية، الاستقرار، دالة ليبانوف.

1 Introduction

The immune system is a precise structure of cells that works to attack foreign bodies that infiltrate the body and also repairs and restores tissues after damage [1]. The immune system's attack on the body's tissues is the hallmark of autoimmune dis- eases, where to completely comprehend the underlying mechanisms and interactions amongst the many immune system components, a systems biology approach is required [2]. There are many types of autoimmune diseases, and they vary in severity and intensity

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from one type to another Since many autoimmune illnesses are chronic in nature, patients typically go through phases of remission and activity of the symptoms unique to their particular autoimmune illness [3], the patient also suffers from weight loss, pallor, increased antibodies, and sometimes a high temperature [4]. The loss of tolerance to particular self-antigens is the source of autoimmune inflammation, which can lead to systemic or organ-specific illnesses [5]. Since a large percentage of the population is affected by systemic autoimmune illnesses, which are becoming more common, it is critical to have efficient treatments to manage these long-term conditions.

The highly complex pathophysiology and diverse aetiologies of autoimmune disorders present challenges for research and development (R and D) of innovative therapeutic treatments. There aren't many targeted treatments on the market, but autoimmune dis- eases are becoming more and more common among people all over the world [6]. Regretfully, a number of patients suffering from systemic autoimmune illnesses exhibit minimal or no response to standard synthetic anti-rheumatic medicines and targeted therapy, one of these diseases is Hashimoto's autoimmune disease, which is a disease that causes hypofunction of the thyroid gland due to the attack of lymphocytes on it. [7].

The thyroid gland has a major role in the metabolism process and the balance of human health. It is also responsible for the level of growth in the body [8]. Thyrocyte death is caused by an increase in TH_1 lymphocyte activity, which has been linked to HT at the cellular level. has been discovery that TH_{17}, a novel subgroup of T helper (TH) cells, plays a significant role in thyroid autoimmunity. Research indicates that in many autoimmune illnesses, including HT, TH_{17} cells are in charge of triggering and fostering persistent inflammatory responses.

Furthermore, as in other autoimmune diseases, patients with HT show $T\ reg$ lymphocyte dysfunction and an imbalance between TH_{17} and regulatory T lymphocyte ($Treg$) levels. The genetic predispositions associated with many factors such as prolonged

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selenium deficiency, deficiency of nutrients such as vitamin D, which plays a role in balancing intestinal microbes [9], smoking, drinking alcohol, prolonged stress and psychological distress, persistent infections, exposure to chemicals, and changes in intestinal microbiota are closely linked to thyroid autoimmunity. Studies have shown that the stability of the patient's condition depends on the stability of the immune system, and this is done by suppressing the body's immunity using appropriate treatment methods for the patient. Test results from genetics and cellular immunology may also be utilized to precisely diagnose disease [10].

2 Materials and Methods

In recent decades, mathematical modelling has been actively employed in many scientific and technological domains, particularly in the area of modelling complex systems, which includes living things [11]. A mathematical model was built based on the dynamic interaction between thyrocytes, the immune system, and the gut microbiota, which are represented in a system of four differential equations [8]. The creation of the model also accounts for the fact that thyrocytes proliferate exponentially quickly in the absence of other influences. Furthermore, $TH1$ and $TH17$ lymphocytes have a role in the cellular immune response, influencing thyrocyte proliferation. At this stage, $TH1$ lymphocytes accelerate the inflammatory process of thyrocytes at a rate of γ, whereas $TH17$ cells promote thyrocyte death at a rate of β.

In this research paper, we study the mathematical model in search of stability points, that positively affect the course of interaction between lymphocytes, thyroid cells, and gut microbiota and reduce the risk of disease impact.

Suppression of the immune system is an essential factor in autoimmune diseases, as it reduces the severity of the disease and places the patient in a state of stability and recovery. The following system of differential equations represents a mathematical model of *HT* disease:

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$$\dot{T}(t) = (\alpha - \beta_1)T - \beta T.TH_1 - \gamma T.TH_{17}$$
$$\dot{T}H_{17}(t) = \frac{\emptyset_1 T}{1+T}.TH_{17} + \frac{1}{Treg}.\frac{\emptyset_3 B}{1+B}.TH_{17} - \beta_2 TH_{17}$$
$$\dot{T}H_1(t) = \frac{\emptyset_2 T}{1+T}.TH_1 - \beta_3 TH_1 \qquad (1)$$
$$\dot{B}(t) = \alpha_1 B(1 - \frac{B}{k})$$

where $T(t)$ represents the population of thyrocytes cells, $TH17(t)$ and $TH1(t)$ represents the population of lymphocytes cells, and $B(t)$ represents the population of gut microbiota.
All the variables and parameters used in this model are explained in Table 1.

Table 1. Variables and parameters for Hashimoto autoimmune thyroiditis disease

Variable and parameter	Definition	Unit
$T(t)$	Thyrocytes concentration	cells/mL
$TH17(t)$	$TH17$ lymphocytes concentration	cells/mL
$TH1$	$TH1$ lymphocytes concentration	cells/mL
$B(t)$	Bacteria from gut microbiota	cfu/mL
B	predation rate of $TH1$ lymphocytes on thyrocytes	-
$\beta 1$	Thyrocytes mortality rate	-
$\beta 2$	$TH17$ mortality rate lymphocyte predation rate over thyrocytes	-

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$\beta 3$	$TH1$ mortality rate lymphocyte predation rate over thyrocytes	-
$T\ reg$	$T\ reg$ lymphocyte concentration	cells/mL
$\phi 1$	$T\ H17$ lymphocyte differentiation rate	-
$\phi 2$	$T\ H1$ lymphocyte differentiation rate	-
$\phi 3$	Maximum contribution rate of bacteria to $T\ H17$ lymphocyte	-
$\alpha 1$	Growth rate of bacteria from gut microbiota	-
K	Bacterial carrying capacity in the gastrointestinal trac	bacteria/mL
α	Thyrocytes growth rate	
B	Predation rate of TH_1	
$\boldsymbol{\gamma}$	Induction rate to the cellular apoptosis process	

The conceptual diagram resulting from this cellular dynamic that describes the interaction between thyroid cells, lymphocytes TH_{17}, TH_1 and Treg cells and the gut microbiota, and the model parameters is shown in Fig. 1.

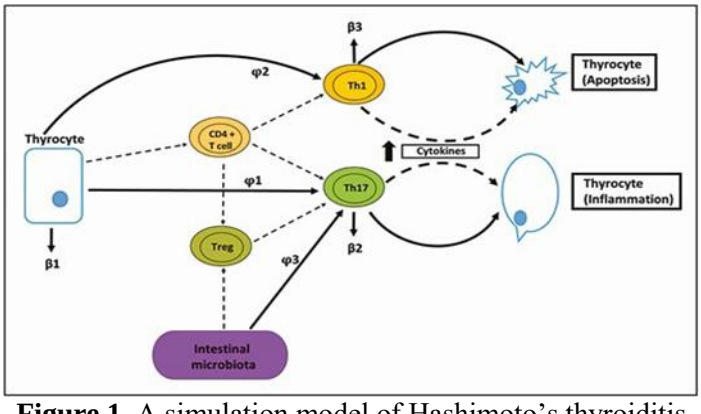

Figure 1. A simulation model of Hashimoto's thyroiditis

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In this diagram, the dashed lines represent the cellular interactions and the solid lines represent the underlying dynamics in the mathematical model.
Thyroid tissue undergoes inflammation and death in response to the growth of TH_1 and TH_{17} lymphocytes, respectively. The connection between effector (TH_{17}) and regulator (*Treg*) lymphocytes is regulated by the gut microbiota, which increases the differentiation of pathogenic $TH17$ lymphocytes and causes inflammation as a result.

3 Stability Analysis

In this section, all active equilibrium points of the system are investigated.

1. Without the TH_{17} population

system (1) will be

$$\dot{T}(t) = (\alpha - \beta_1)T - \beta T.TH_1$$
$$\dot{T}H_1(t) = \frac{\emptyset_2 T}{1+T}.TH_1 - \beta_3 TH_1 \qquad (2)$$
$$\dot{B}(t) = \alpha_1 B(1 - \frac{B}{k})$$

put $\dot{T}(t)$=0, $\dot{T}H_1(t) = 0$, and $\dot{B}(t) = 0$ in (2), then

$$(\alpha - \beta_1)T - \beta T.TH_1 = 0$$
$$\frac{\emptyset_2 T}{1+T}.TH_1 - \beta_3 TH_1 = 0 \qquad (3)$$
$$\alpha_1 B\left(1 - \frac{B}{k}\right) = 0$$

Solving equations (3) simultaneously, gives the T $H17$-free equilibrium

$$P_1 = (\frac{\beta_3}{\phi_2 - \beta_3}, 0, \frac{\alpha - \beta_1}{\beta}, k).$$

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Calculating the values of Jacobian eigenvalues, however, indicates that at least one of them is zero for this point which means it is a non-hyperbolic point, in this case the linearization method is not effective, therefore Lyapunov method is used.
Let $V(t) = TH_{17}$ is the Lyapunov function, and from (3) we have $T = \frac{\beta_3}{\emptyset_2 - \beta_3}, B = k$ then

$$\dot{V}(t) = T\dot{H}_{17}$$

$$= \frac{\emptyset_1 T}{1+T}.TH_{17} + \frac{1}{Treg}.\frac{\emptyset_3 B}{1+B}.TH_{17} - \beta_2 TH_{17}$$

$$= \frac{\emptyset_1\left(\frac{\beta_3}{\emptyset_2-\beta_3}\right)}{1+\left(\frac{\beta_3}{\emptyset_2-\beta_3}\right)}.TH_{17} + \frac{1}{Treg}.\frac{\emptyset_3 k}{1+k}TH_{17} - \beta_2 TH_{17} \quad (4)$$

$$= TH_{17}\left[\frac{\emptyset_1\left(\frac{\beta_3}{\emptyset_2-\beta_3}\right)}{1+\left(\frac{\beta_3}{\emptyset_2-\beta_3}\right)} + \frac{1}{Treg}.\frac{\emptyset_3 k}{1+k} - \beta_2\right]$$

then

$$\frac{\emptyset_1\left(\frac{\beta_3}{\emptyset_2-\beta_3}\right)}{1+\left(\frac{\beta_3}{\emptyset_2-\beta_3}\right)} + \frac{1}{Treg}.\frac{\emptyset_3 k}{1+k} - \beta_2 < 0$$

if

$$\frac{\emptyset_1\left(\frac{\beta_3}{\emptyset_2-\beta_3}\right)}{1+\left(\frac{\beta_3}{\emptyset_2-\beta_3}\right)} + \frac{1}{Treg}.\frac{\emptyset_3 k}{1+k} < \beta_2 \quad (5)$$

Therefore, under **condition** (5) the equilibrium point P_1 is asymptotically stable. The activity of the thyroid gland T in the normal state, and the stability of the intestinal microbiota B and also a decrease in the level of lymphocytes TH_1 responsible for the activity of the disease are shown in Figure 2.

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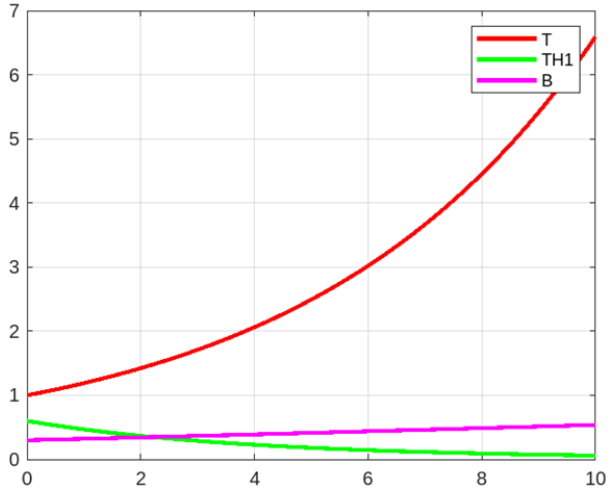

Figure 2. A simulation model of Hashimoto's thyroiditis without TH_{17}

2. Without the TH_1 population

system (1) will be

$$\dot{T}(t) = (\alpha - \beta_1)T - \gamma T.TH_{17}$$

$$\dot{T}H_{17}(t) = \frac{\emptyset_1 T}{1+T}.TH_{17} + \frac{1}{Treg}.\frac{\emptyset_3 B}{1+B}.TH_{17} - \beta_2 TH_{17}$$

$$\dot{B}(t) = \alpha_1 B\left(1 - \frac{B}{k}\right) \qquad (6)$$

put $\dot{T}(t)$=0, $\dot{T}H_{17}(t) = 0$, and $\dot{B}(t) = 0$ in (6), then

$$(\alpha - \beta_1)T - \gamma T.TH_{17} = 0$$

$$\frac{\emptyset_1 T}{1+T}.TH_{17} + \frac{1}{Treg}.\frac{\emptyset_3 B}{1+B}.TH_{17} - \beta_2 TH_{17} = 0 \qquad (7)$$

$$\alpha_1 B\left(1 - \frac{B}{k}\right) = 0$$

Hence, TH_1-free equilibrium is

$$P_2 = (\frac{x}{\phi_1 - x}, \frac{\alpha - \beta_1}{\gamma}, 0, k).$$

where،

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$$x = \frac{\beta_2 - \frac{1}{Treg} \cdot \frac{\phi_3 k}{1+k}}{\phi_1 - (\beta_2 - \frac{1}{Treg} \cdot \frac{\phi_3 k}{1+k})}$$

P_2 is positive equilibrium under the following conditions

$$\frac{1}{Treg} \cdot \frac{\emptyset_3 k}{1+k} < \beta_2 \tag{8}$$

and

$$\beta_2 - \frac{1}{Treg} \cdot \frac{\emptyset_3 k}{1+k} < \emptyset_1 \tag{9}$$

Now to study the stability of this point, let $V(t) = TH_1$ is a Lyapunov function, from system (7) and P_2 we have $T = \frac{x}{\emptyset_1 - x}$ then

$$\dot{V}(t) = \dot{T}H_1$$

$$= \frac{\emptyset_2 T}{1+T} TH_1 - \beta_3 TH_1$$

$$= \frac{\emptyset_2 (\frac{x}{\emptyset_1 - x})}{1 + (\frac{x}{\emptyset_1 - x})} TH_1 - \beta_3 TH_1 \tag{10}$$

$$= TH_1 [\frac{\emptyset_2 \left(\frac{x}{\emptyset_1 - x}\right)}{1 + \left(\frac{x}{\emptyset_1 - x}\right)} - \beta_3]$$

if

$$\frac{\emptyset_2 \left(\frac{x}{\emptyset_1 - x}\right)}{1 + \left(\frac{x}{\emptyset_1 - x}\right)} - \beta_3 < 0$$

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Then

$$\frac{\emptyset_2\left(\frac{x}{\emptyset_1-x}\right)}{1+\left(\frac{x}{\emptyset_1-x}\right)} < \beta_3 \qquad (11)$$

Therefore, under **condition (11)**, the equilibrium point P_2 is stable. Figure 3. Figure 3 shows the activity of the thyroid gland T in the normal state, and the stability of the intestinal microbiota B and also shows a decrease in the level of lymphocytesTH_{17} responsible for the activity of the disease.

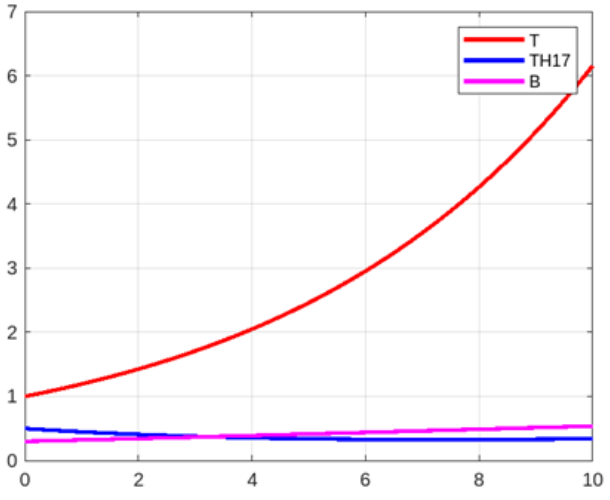

Figure 3. A simulation model of Hashimoto's thyroiditis without TH_1

3. Without the B population, we have

$$\dot{T}(t) = (\alpha - \beta_1)T - \beta T.TH_1 - \gamma T.TH_{17}$$
$$\dot{T}H_{17}(t) = \frac{\emptyset_1 T}{1+T}.TH_{17} - \beta_2 TH_{17} \qquad (12)$$
$$\dot{T}H_1(t) = \frac{\emptyset_2 T}{1+T}.TH_1 - \beta_3 TH_1$$

put $\dot{T}(t)$=0, $\dot{T}H_1(t) = 0$, and $\dot{T}H_{17}(t) = 0$ in (12), then

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$$\begin{aligned}(\alpha-\beta_1)T-\beta T.TH_1-\gamma T.TH_{17}&=0\\ \frac{\emptyset_1 T}{1+T}.TH_{17}-\beta_2 TH_{17}&=0\\ \frac{\emptyset_2 T}{1+T}.TH_1-\beta_3 TH_1&=0\end{aligned} \quad (13)$$

Therefore, *B*-free interior equilibrium point is

$$P_3=(\frac{\beta_2}{\phi_1-\beta_2},TH_{17}^*,\frac{(\alpha-\beta_1)-\gamma TH_{17}^*}{\beta},0).$$

To study the stability, suggest $V(t)=B$ as Lyapunov function, then

$$\begin{aligned}\dot{V}(t)&=\dot{B}\\ &=\alpha_1 B\left(1-\frac{B}{k}\right)\end{aligned} \quad (14)$$

Which is negative, if

$$B>k \quad (15)$$

Therefore, under **condition (15)**, the equilibrium point P_3 will be stable. The activity of the thyroid gland *T* in the normal state, and decrease in the level of lymphocytes TH_1,TH_{17} responsible for the activity of the disease are shown in Figure 4.

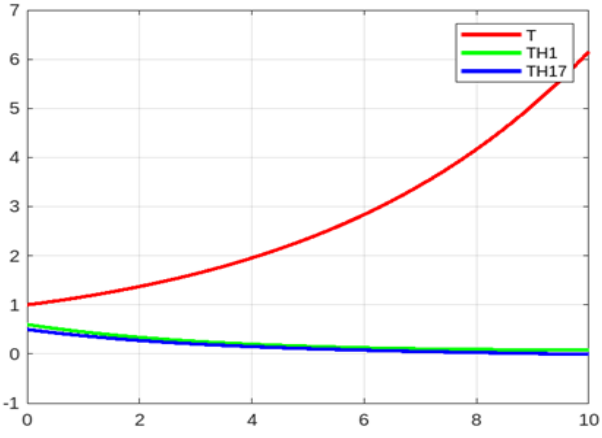

Figure 4. A simulation model of Hashimoto's thyroiditis without *B*

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4 The main equilibrium point,

To study the steady state of system (1), set $\dot{T}(t) = 0$, $\dot{T}H_1(t) = 0$, $\dot{T}H_{17}(t) = 0$ and $\dot{B} = 0$ in (1), we have

$$\begin{gathered}(\alpha - \beta_1)T - \beta T.TH_1 - \gamma T.TH_{17} = 0 \\ \frac{\emptyset_1 T}{1+T}.TH_{17} + \frac{1}{Treg}.\frac{\emptyset_3 B}{1+B}.TH_{17} - \beta_2 TH_{17} = 0 \\ \frac{\emptyset_2 T}{1+T}.TH_1 - \beta_3 TH_1 = 0 \\ \alpha_1 B\left(1 - \frac{B}{k}\right) = 0\end{gathered} \tag{16}$$

The trivial equilibrium point, $P_0(0,0,0,0)$ is always exists. However, solving equations (16) simultaneously, gives the interior equilibrium point

$$T = \frac{\beta_3}{\emptyset_2 - \beta_3},$$
$$\beta TH_1 + \gamma TH_{17} = \alpha - \beta_1,$$

and

$$B = k$$

that is,

$$TH_{17} = \frac{\alpha - \beta_1 - \beta TH_1{}^*}{\gamma}$$

then we can conclude that one-interior equilibrium

$$P^* = \left(\frac{\beta_3}{\emptyset_2 - \beta_3}, \frac{\alpha - \beta_1 - \beta TH_1{}^*}{\gamma}, TH_1{}^*, k\right)$$

which is always exists, if $0 < TH_1{}^* < \frac{\alpha - \beta_1}{\beta}$.

Now we consider a Lyapunov function $V(t) = T$, then

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$$\dot{V}(t) = \dot{T}$$

$$= (\alpha - \beta_1)T - \beta T.TH_1 - \gamma T.TH_{17}$$

$$= (\alpha - \beta_1)T - \beta T.TH_1^* - \gamma T(\frac{\alpha - \beta_1 - \beta TH_1^*}{\gamma})$$

$$= T[(\alpha - \beta_1) - \beta TH_1^* - (\alpha - \beta_1) + \beta TH_1^*] = 0$$

Then P^* is a stable equilibrium point and the trajectories of the system lie on the surfaces in R^4 defined by $V(x) = C$, for constant C. [12].

Figure 5. shows the stability of the disease where we notice the normal activity of the thyroid gland T and the decreased activity of the lymphocytes TH_1,TH_{17} within the permissible rate, with the stability of the intestinal microbiota B.

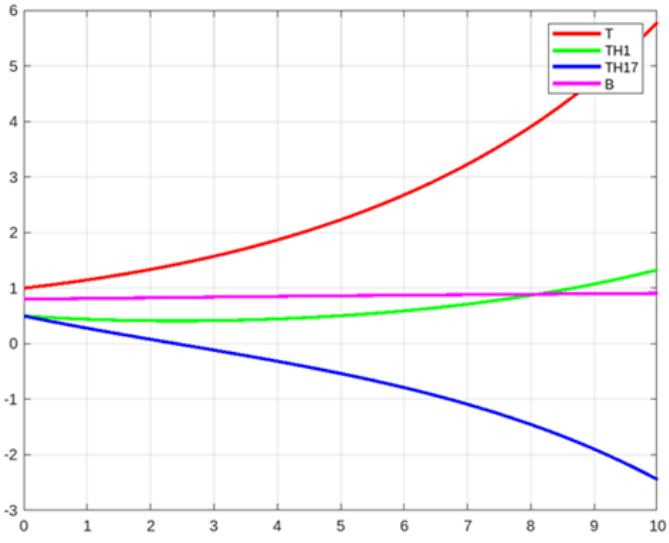

Figure 5: A simulation model of Hashimoto's thyroiditis

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5 Conclusion

In this study, we highlight finding stability points for the mathematical model (1), which represents a model that simulates Hashimoto's immune disease, as stopping the disease activity and stabilizing the patient's condition depends entirely on inhibiting the immune system represented by the TH_1, TH_{17} lymphocytes responsible for attacking the thyroid cells. From Model (1), a set of stability points was deduced, the most important of which is the main point P^*, which includes all the cells that represent the HT disease. The importance of the point P^* and its stability play a major role in inhibiting the disease activity, as it keeps the T cells from dying by reducing the high rate of β_1, which is the rate of death of the thyroid cells, and inhibiting γ, which is the rate of induction of the process of death of the HT cells, as the TH_1, TH_{17} lymphocytes are responsible for the activity of the immune cells that incite and develop chronic inflammatory responses in many autoimmune diseases, including HT. Also, the balance of the rate $\alpha 1$ which is the growth rate of intestinal bacteria has an important role in the development of HT disease, as the loss of balance in the number of intestinal bacteria B leads to a disturbance in the immune system and an increase in TH_{17} cells, which is one of the causes of autoimmune diseases. Mathematical models can be used to identify people who are at high risk of developing autoimmune diseases, to forecast the occurrence of diseases in the future, and to support health-care decisions.

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APPENDIX

MATLAB Codes

Figure 2.

```
% Parameters
alpha = 0.3;      % Parameter alpha
beta1 = 0.1;      % Parameter beta1
beta = 0.05;      % Parameter beta
phi2 = 0.1;       % Parameter phi2
beta3 = 0.3;      % Parameter beta3
alpha1 = 0.1;     % Parameter alpha1
k = 1.0;          % Carrying capacity

% Initial conditions
T0 = 1.0;         % Initial concentration of T
TH10 = 0.6;       % Initial concentration of TH1
B0 = 0.3;         % Initial concentration of B

% Time function
f = @(t, y) [
    (alpha - beta1) * y(1) - beta * y(1) * y(2);
% dT/dt
    (phi2 * y(1) / (1 + y(1))) * y(2) - beta3 *
y(2); % dTH1/dt
    alpha1 * y(3) * (1 - y(3) / k) % dB/dt
];

% Time span
tspan = [0 10];

% Initial conditions vector
y0 = [T0; TH10; B0];

% Solve ordinary differential equations
[t, y] = ode45(f, tspan, y0);
```

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```
% Plot results
figure;
plot(t, y(:, 1), 'r', 'LineWidth', 2); % T
hold on;
plot(t, y(:, 2), 'g', 'LineWidth', 2); % TH1
plot(t, y(:, 3), 'm', 'LineWidth', 2); % B
xlabel('');
ylabel('');
legend('T', 'TH1', 'B');
title('');
grid on;
```

Figure3

```
% Parameters
alpha = 0.3;      % Parameter alpha
beta1 = 0.1;      % Parameter beta1
gamma = 0.05;     % Parameter gamma
phi1 = 0.1;       % Parameter phi1
phi3 = 0.5;       % Parameter phi3
beta2 = 0.4;      % Parameter beta2
alpha1 = 0.1;     % Parameter alpha1
k = 1.0;          % Carrying capacity
Treg = 0.5;       % Regulation time constant

% Initial conditions
T0 = 1.0;         % Initial concentration of T
TH170 = 0.5;      % Initial concentration of TH17
B0 = 0.3;         % Initial concentration of B

% Time function
f = @(t, y) [
    (alpha - beta1) * y(1) - gamma * y(1) * y(2);
% dT/dt
```

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```
    (phi1 * y(1) / (1 + y(1))) * y(2) + (1 /
Treg) * (phi3 * y(3) / (1 + y(3))) * y(2) - beta2
* y(2); % dTH17/dt
    alpha1 * y(3) * (1 - y(3) / k) % dB/dt
];

% Time span
tspan = [0 10];

% Initial conditions vector
y0 = [T0; TH170; B0];

% Solve ordinary differential equations
[t, y] = ode45(f, tspan, y0);

% Plot results
figure;
plot(t, y(:, 1), 'r', 'LineWidth', 2); % T (red)
hold on;
plot(t, y(:, 2), 'b', 'LineWidth', 2); % TH17
(blue)
plot(t, y(:, 3), 'm', 'LineWidth', 2); % B
(purple)
xlabel('');
ylabel('');
legend('T', 'TH17', 'B');
title('');
grid on;
```

Figure4

```
% Parameters
alpha = 0.3;      % Parameter alpha
beta1 = 0.1;      % Parameter beta1
beta = 0.05;      % Parameter beta
gamma = 0.05;     % Parameter gamma
```

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```
phi1 = 0.1;       % Parameter phi1
phi2 = 0.1;       % Parameter phi2
beta2 = 0.4;      % Parameter beta2
beta3 = 0.3;      % Parameter beta3

% Initial conditions
T0 = 1.0;         % Initial concentration of T
TH10 = 0.6;       % Initial concentration of TH1
TH170 = 0.5;      % Initial concentration of TH17

% Time function
f = @(t, y) [
    (alpha - beta1) * y(1) - beta * y(1) * y(2) -
gamma * y(1) * y(3); % dT/dt
    (phi1 * y(1) / (1 + y(1))) * y(3) - beta2 *
y(3); % dTH17/dt
    (phi2 * y(1) / (1 + y(1))) * y(2) - beta3 *
y(2); % dTH1/dt
];

% Time span
tspan = [0 10];

% Initial conditions vector
y0 = [T0; TH10; TH170];

% Solve ordinary differential equations
[t, y] = ode45(f, tspan, y0);

% Plot results
figure;
plot(t, y(:, 1), 'r', 'LineWidth', 2); % T (red)
hold on;
plot(t, y(:, 2), 'g', 'LineWidth', 2); % TH1
(green)
```

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```
plot(t, y(:, 3), 'b', 'LineWidth', 2); % TH17
(blue)
xlabel('');
ylabel('');
legend('T', 'TH1', 'TH17');
title('');
grid on;
```

title(”); grid on;

Figure5

```
% Model equations
alpha = 0.25;
beta1 = 0.05;
beta = 0.092;
gamma = 0.05;
phi1 = 0.05;
phi2 = 0.05;
phi3 = 0.5;
beta2 = 0.5;
beta3 = 0.5;
alpha1 = 0.09;
k = 1.0;
Treg = 0.7;

% Initial conditions
T0 = 1.0;
TH10 = 0.5;
TH170 = 0.5;
B0 = 0.2;

% Time function
f = @(t, y) [
(alpha - beta1) * y(1) - beta * y(1) * y(2) -
gamma * y(1) * y(3);
```

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```
(phi1 * y(1) / (1 + y(1))) * y(3) + (1 / Treg) *
(phi3 * y(4) / (1 + y(4))) * y(3) - beta2 * y(3);
(phi2 * y(1) / (1 + y(1))) * y(2) - beta3 * y(2);
alpha1 * y(4) * (1 - y(4) / k)
];

% Time span
tspan = [0 10];

% Initial conditions
y0 = [T0; TH10; TH170; B0];

% Solve ordinary differential equations
[t, y] = ode45(f, tspan, y0);

% Plot results
figure;
plot(t, y(:, 1), 'r', 'LineWidth', 2);
hold on;
plot(t, y(:, 2), 'g', 'LineWidth', 2);
plot(t, y(:, 3), 'b', 'LineWidth', 2);
plot(t, y(:, 4), 'm', 'LineWidth', 2);
xlabel('');
ylabel('');
legend('T', 'TH1', 'TH17', 'B');
title('');
grid on;
```