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Stability analysis of a mathematical model for methimazole dosing in graves' hyperthyroidism: A dynamic approach

Jasmine D and Lavanya G *

Department of Mathematics, Bishop Heber College, (Affiliated to Bharadhidasan University), Trichy,Tamil Nadu, India.

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Abstract

This study explores a novel mathematical model for analyzing methimazole (MMI) therapy in patients with Graves' disease, a common autoimmune cause of hyperthyroidism. The model leverages a system of ordinary differential equations to capture the interplay between key factors: methimazole concentration, thyroid-stimulating hormone (TSH), free thyroxine (FT4) concentration, thyroid-stimulating hormone receptor antibody (TRAb) concentration, and functional thyroid gland size (V). Thirteen parameters account for the underlying physiological processes. Stability analysis were employedby Lyapunov stability theory and LaSalle's principle, to demonstrate the model's asymptotic stability. This implies the system converges towards a steady state under defined conditions. Additionally, a clinically relevant chart is constructed based on FT4 levels and treatment duration.For model validation, patient data is utilized within SimBiology simulations implemented in MATLAB. These simulations offer valuable insights into the dynamic response of hyperthyroidism to MMI treatment. This approach holds promise for future applications in optimizing treatment strategies and facilitating personalized medicine approaches.

Keywords: Hyperthyroidism; Methimazole; Graves' disease; Ordinary Differential Equations; Stability

1. Introduction

Graves disease the most common cause of hyperthyroidism worldwide, is a complex autoimmune diorder with a range of symptoms and complications. The primary cause of death in Graves disease hyperthyroid heart disease, which underscroes the importance of early diagnosis and treatment[11]. The disease is more prevalent in females and can lead to a variety of health issues, including cardiac related complications. Diagnosis and management of Graves disease involve a combination of history taking, laboratory investigations, and treatment options such as anti-thyroid drugs radioactive iodine therapy, and surgery [6]. The incidence of Graves' disease is significant, with 20-50 cases per 100,000 population annually[25].

Graves' disease (GD) is a prevalent autoimmune disorder characterized by hyperthyroidism, a state of excessive thyroid hormone production [4]. The thyroid gland, a butterfly-shaped organ located at the base of the neck, synthesizes and releases thyroid hormones (THs) under the tight regulation of the thyroid-stimulating hormone (TSH) from the pituitary gland [23]. In GD, the immune system malfunctions, leading to the production of thyroid-stimulating immunoglobulins (TSI) or thyrotropin receptor antibodies (TRAbs). In the pathogenesis of Graves' hyperthyroidism, thyroid-stimulating hormone (TSH) receptor antibodies (TRAbs) play a crucial role[1,13,19]. These antibodies mimic the action of TSH, binding to the TSH receptors on the thyroid gland and stimulating it to hyperproduce THs, disrupting the normal homeostatic feedback loop [4,16]. The production of stimulating TSH receptor antibodies, leading to increased thyroid hormone synthesis and secretion, resulting in hyperthyroidism [14,15]. Additionally, TRAbs can cross the placental barrier during pregnancy, affecting both maternal and fetal thyroid function[3]. Free thyroxine (FT4) levels are also elevated in Graves' disease, contributing to the hyperthyroid state. Monitoring TRAbs, along with TSH

* Corresponding author: Lavanya G

and FT4 levels, is essential for diagnosing and managing Graves' disease, as TRAbs are key in distinguishing Graves' hyperthyroidism from other causes of hyperthyroidism[5]. The interplay of TSH, FT4, and TRAbs underscores their significance in the pathogenesis and clinical management ofGraves' hyperthyroidism.Treatment options for Graves' hyperthyroidism include antithyroid drugs, radioiodine therapy, or thyroidectomy, with radioiodine being a well-tolerated and effective choice[22].

Methimazole is the preferred treatment for Graves' hyperthyroidism due to its better side-effect profile. The treatment of Graves' hyperthyroidism has evolved over the years, with methimazole now being the preferred choice due to its better side-effect profile[17]. In critically ill patients, rectal methimazole has been used with similar efficacy to oral administration[27]. Low-dose methimazole has been found to effectively control hyperthyroidism, even after multiple relapses, in patients with normal TRAb concentrations. Long-term low-dose methimazole treatment has also been shown to be effective and safe in preventing relapse in patients with Graves' hyperthyroidism[2]. This is supported by the immunological properties of methimazole, which play a key role in inducing euthyroidism in Graves' disease[7].

.However, in rare cases, patients may be resistant to high doses of methimazole, requiring combination therapy with lithium carbonate, dexamethasone, and inorganic iodine[19]. Studies have shown that a single daily dose of methimazole is effective in inducing euthyroidism in patients with Graves' disease[9,10]. This treatment has also been found to be effective in controlling hyperthyroidism, with a gradual decrease in TSH binding inhibitor immunoglobulin levels[18]. However, the efficacy of this treatment may be influenced by the patient's pretreatment serum concentrations of thyroid hormones, with higher concentrations potentially leading to resistance [7].

Mathematical models play a crucial role in managing hyperthyroidism by optimizing drug dosages and predicting patient outcomes[8,15,26]. These models aid in determining personalized drug dosages, such as anti-thyroid agents like methimazole, through mathematical simulations based on patient-specific data, leading to more efficient and deterministic treatmenapproaches[21,24]. By utilizing ordinary differential equations and machine learning algorithms, these models can predict the progression of hyperthyroidism to euthyroidism, guide treatment schedules, and help maintain optimal thyroid hormone levels within the physiological range. Ultimately, mathematical models offer a promising alternative to traditional trial-and-error methods.

Similarly, Graves' disease was addressed through a set of differential equations. The initial mechanistic model, designed to predict relapse in Graves' disease patients, was constructed using an Methimazole (MMI) is a key component in the treatment of hyperthyroidism, effectively reducing the levels of free thyroxine (FT4) in patients.

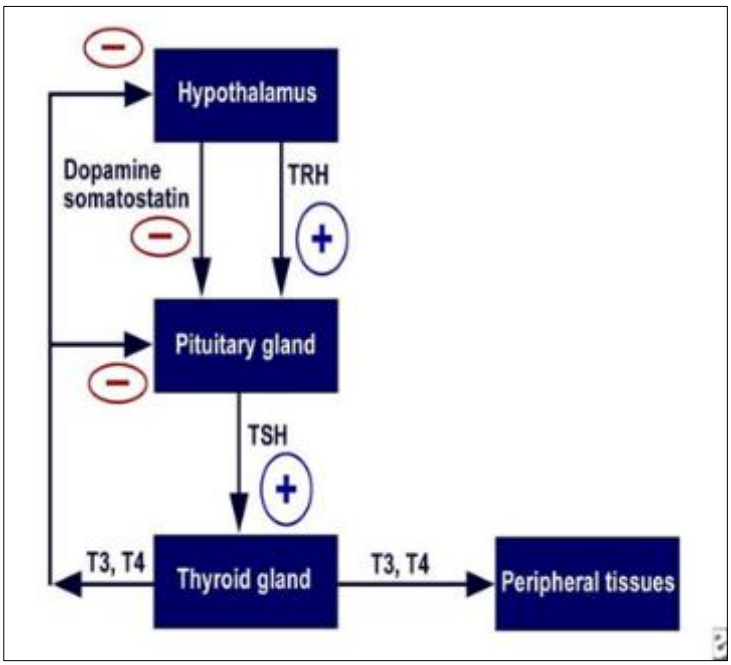

Figure 1 Illustrate the hypothalamic-pituitary-thyroid (HPT) axis, depicts the regulatory interactions between the hypothalamus, pituitary gland, and thyroid gland, and the effects of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) on peripheral tissues.

1.1. Construction of model

Earlier model constructed by Langenstein etal.and Pandiyan et.al for hypothyroid state and hyperthyroid state respectively with ordinary differential equation laid a way to approach the thyroid related diseases by differential equation.Graves disease can be approached in a model of differential equations. Here five compartments are used. Compartments for fT3 and fT4 are subsumed in a single FT4 compartment. Thyroid stimulating hormone is denoted as TSH. The functional thyroid size is described by the compartment T. The amount of antithyroid stimulating receptor antibodies TRAb is described by the Ab compartment. Methimazole (MMI) is describes as another compartment denoted by m.

Variables:

- m(t) denote the concentration of MMI(mg) per litre of blood serum at time t.
- TSH denote the concentration of thyroid-stimulating hormone.
- FT4 denote the amount of FT4 per millilitre of blood serum at time t.
- T(t) denote the the functional size of thyroid gland at t.
- Ab(t) denote the amount of TRAb per millilitre of blood serum at t.
- S(t) denote the amount of MMI taken per day per litre of body volume.

The model for Graves hyperthyroidism with effect of Methimazole (MMI) treatment is given below.

$$\begin{aligned}
\frac{dm}{dt} &= s(t) - \frac{\mu V m}{(K_c + m)} - \delta m \\
\frac{dTSH}{dt} &= k_1 - \frac{k_1(FT4 - U)}{(K_a + FT4)} - \alpha TSH \\
\frac{dFT4}{dt} &= \frac{k_2 VAb}{(K_b + Ab)} + k_3 TSH - \beta FT4 \\
\frac{dV}{dt} &= k_4 + k_5 \frac{Ab}{V} - k_6 Vm \\
\frac{dAb}{dt} &= k_7 - \frac{k_7 m}{(K_d + m)} - k_8 Ab
\end{aligned}$$

This equation (1) describes the rate of change of the concentration of methimazole (m) over time (t).s(t) represents the rate of methimazole administration (external input). $\frac{\mu V m}{(K_c + m)}$ represents the uptake rate of MMI by the thyroid gland with maximal saturation rate (μV). The uptake rate Is modeled with Michealis-Menten kinetics.δ is the natural elimination rate of methimazole.

This equation (2) describes the rate of change of the concentration of thyroid-stimulating hormone (TSH) over time. $\frac{k_1(FT4 - U)}{(K_a + FT4)}$ represents the negative feedback effect of free thyroxine (FT4) on TSH secretion, where FT4-U is the unbound FT4, K_a Michealis-Menten constant for half maximal secretion rate of TSH, and FT4 is the total FT4 concentration. α is the natural elimination rate of TSH.

This equation (3) describes the rate of change of the concentration of free thyroxine (FT4) over time. $\frac{k_2 VAb}{(K_b + Ab)}$ accounts for the secretion rate of free thyroxine, which modeled through the Michaelis-Menten kinetics with the maximum secretion rate as $(k_2 V)$. β is the natural elimination rate of FT4. $k_3 TSH$ represents the stimulatory effect of TSH on FT4 production.

This equation(4) describes the rate of change of the functional size of the thyroid gland (T) over time. k_4 is a constant representing the basal growth rate of the thyroid gland. $k_5 \frac{Ab}{V}$ represents the stimulatory effect of TRAb (Ab) on the growth of the thyroid gland, where k_5 is a constant. $k_6 Vm$ represents the inhibitory effect of methimazole (m) on the growth of the thyroid gland, where k_6 is a constant.

This equation(5) describes the rate of change of the concentration of thyroid-stimulating antibodies (TRAb or Ab) over time. k_7 is the constant production rate of TRAb. $\frac{k_7 m}{(K_d + m)}$ represents the inhibitory effect of methimazole (m) on the production of TRAb, where Kd is a constant. k_8 is the natural elimination rate of TRAb.

1.2. Theorem 1

Using the initial conditions given in equation (1), the solutions $TSH(t), FT4(t), V(t), Ab(t)$ are non-negative for all time $t > 0$

Proof:

To prove the non-negativity of m(t) using the Gronwall-Bellman inequality,

Rewrite the differential equation for m(t) as an integral inequality:

$$m(t) = m(0) + \int_0^t \left[s(t) - \frac{\mu T(t) m(t)}{(K_c + m(t)} - \delta m(t) \right] dt$$

Define $\alpha(t) = m(0) + \int_0^t s(t)dt$ and $\beta(t) = \frac{\mu T(t)}{(K_c + m(t))} + \delta$

Assuming that $m(0) \geq 0$ *and* $s(t) \geq 0$ for all $t \geq 0$, we have:

$$m(t) = \alpha(t) - \int_0^t \beta(t) m(t) dt$$

Apply the Gronwall-Bellman inequality:

$$m(t) \geq a(t) + \int_0^t \alpha(s)\beta(s) exp(\int_s^t \beta(\tau) d\tau) ds$$

To ensure the non-negativity of m(t), we need to show that the right-hand side of the inequality is non-negative for all t ≥ 0.

Since $\alpha(t) = m(0) + \int_0^t s(\tau) d\tau \geq 0$ *and* $\beta(t) = -\left[\frac{\mu V}{(Kc + m(t))} + \delta \right] \leq 0$, the integral term on the right-hand side is non-negative.

Therefore, if $m(0) \geq 0$ *and* $s(t) \geq 0$ *for all* $t \geq 0$, the Gronwall-Bellman inequality implies that

$m(t) \geq 0$ *for all* $t \geq 0$.

1.3. Stability Analysis

THEOREM: 1 When s(t) and m_0 is zero,model (1)-(5) with all parameters are positive then there is a only one steady state, that is hyperthyroid state in the hyperplane which is asymptotically stable.

Proof :

Let us denote the hyperthyroid state as

$$E_1 = [\overline{m}, \overline{TSH}, \overline{FT4}, \overline{V}, \overline{Ab}]$$

When s(t) =0 and m_0 = 0.One can solve for steady state by setting the right hand side of each equation from (1)-(4) equals to zero .then it yields the following.

$$\overline{m} = 0$$

$$\overline{TSH} = \frac{k_1\left(K_a + U\right)}{\alpha\left(K_a + FT4\right)}$$

$$\overline{FT4} = \frac{k_2 VAb + k_3 TSH\left(K_b + Ab\right)}{\beta\left(K_b + Ab\right)}$$

$$\overline{V} = -\frac{k_5 Ab}{k_4}$$

$$\overline{Ab} = \frac{k_7}{k_8}$$

By Routh Hurwitz criterion,we can prove hyperthyroid state is asymptotically stable. Consider the Jacobian matrix of this model

$$J = \begin{vmatrix} -\alpha & -\frac{k_1(K_a+U)}{\left(K_a+FT4\right)} & 0 & 0 \\ k_3 & -\beta & \frac{k_2 Ab}{\left(K_b+Ab\right)} & \frac{k_2 VK_b}{\left(K_b+Ab\right)^2} \\ 0 & 0 & -\frac{k_5 Ab}{V^2} & \frac{k_5}{V} \\ 0 & 0 & 0 & -k_8 \end{vmatrix}$$

The characteristic polynomial is

$$\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0$$

The Routh-Hurwitz criterion states that all the roots have negative real parts if and only if the following conditions are satisfied

$$a_3 > 0, a_0 > 0, a_3a_2 - a_1 > 0, \left(a_3a_2 - a_1\right)a_3 - a_0a_3^2 > 0$$

In our case, the coefficients of the characteristic polynomial are:

$$a_3 = \alpha + \beta + \frac{k_5 \overline{Ab}}{\overline{V}^2} + k_8$$

$$a_2 = \alpha\beta + \alpha\frac{k_5 \overline{Ab}}{\overline{V}^2} + \beta\frac{k_5 \overline{Ab}}{\overline{V}^2} + \alpha k_8 + \beta k_8 + \frac{k_5 \overline{Ab}}{\overline{V}^2} k_8 + \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{(k_2 \overline{Ab})}{(K_b + \overline{Ab})} + \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{(k_2 \overline{V} K_b)}{(K_b + \overline{Ab})^2}$$

$$a_1 = \alpha\beta k_5 \frac{\overline{Ab}}{\overline{V}^2} + \alpha\beta k_8 + \alpha k_5 k_8 \frac{\overline{Ab}}{\overline{V}^2} + \beta k_5 k_8 \frac{\overline{Ab}}{\overline{V}^2} + \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{(k_2 \overline{Ab})}{(K_b + \overline{Ab})} \frac{(k_2 \overline{V} K_b)}{(K_b + \overline{Ab})^2}$$

$$a_0 = \frac{k_1(K_a + U)}{((K_a + \overline{FT4})^2))} k_3 \frac{(k_2 \overline{Ab})}{(K_b + \overline{Ab})} \frac{(k_2 \overline{V} K_b)}{(K_b + \overline{Ab})^2}$$

$$a_3 = \alpha + \beta + k_5 \frac{\overline{Ab}}{\overline{V}^2} + k_8$$

$$> 0$$

$$a_0 = \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{k_3(k_2 \overline{Ab})}{(K_b + \overline{Ab})} \frac{(k_2 \overline{V} K_b)}{(K_b + \overline{Ab})^2}$$

$$> 0$$

$$a_3 a_2 - a_1 = \left(\alpha + \beta + k_5 \frac{\overline{Ab}}{\overline{V}^2} + k_8 \right) \left(\begin{array}{l} \alpha\beta + \alpha k_5 \frac{\overline{Ab}}{\overline{V}^2} + \beta k_5 \frac{\overline{Ab}}{\overline{V}^2} + \alpha k_8 + \beta k_8 + k_5 k_8 \frac{\overline{Ab}}{\overline{V}^2} + \\ \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{k_2 \overline{Ab}}{(K_b + \overline{Ab})} + \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{(k_2 \overline{V} K_b)}{(K_b + \overline{Ab})^2} \end{array} \right)$$

$$- \left(\alpha\beta k_5 \frac{\overline{Ab}}{\overline{V}^2} + \alpha\beta k_8 + \alpha k_5 k_8 \frac{\overline{Ab}}{\overline{V}^2} + \beta k_5 k_8 \frac{\overline{Ab}}{\overline{V}^2} + \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{k_2 \overline{Ab}}{(K_b + \overline{Ab})} \frac{k_2 \overline{V} K_b}{(K_b + \overline{Ab})^2} \right)$$

$$> 0$$

$$\left(a_3 a_2 - a_1\right) a_3 - a_0 a_3^2 = \left(\begin{array}{l} \left(\alpha + \beta + k_5 \frac{\overline{Ab}}{\overline{V}^2} + k_8 \right) \left(\begin{array}{l} \alpha\beta + \alpha k_5 \frac{\overline{Ab}}{\overline{V}^2} + \beta k_5 \frac{\overline{Ab}}{\overline{V}^2} + \alpha k_8 + \beta k_8 + k_5 k_8 \frac{\overline{Ab}}{\overline{V}^2} + \\ \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{k_2 \overline{Ab}}{(K_b + \overline{Ab})} + \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{(k_2 \overline{V} K_b)}{(K_b + \overline{Ab})^2} \end{array} \right) - \\ \left(\alpha\beta k_5 \frac{\overline{Ab}}{\overline{V}^2} + \alpha\beta k_8 + \alpha k_5 k_8 \frac{\overline{Ab}}{\overline{V}^2} + \beta k_5 k_8 \frac{\overline{Ab}}{\overline{V}^2} + \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{k_2 \overline{Ab}}{(K_b + \overline{Ab})} \frac{(k_2 \overline{V} K_b)}{(K_b + \overline{Ab})^2} \right) \end{array} \right)$$

$$\left(\alpha + \beta + k_5 \frac{\overline{Ab}}{\overline{V}^2} + k_8 \right) - \frac{k_1(K_a + U)}{(K_a + \overline{FT4})^2} \frac{k_2 k_3 \overline{Ab}}{(K_b + \overline{Ab})} \frac{(K_b k_2 \overline{V})}{(K_b + \overline{Ab})^2} \left(\alpha + \beta + k_5 \frac{\overline{Ab}}{\overline{V}^2} + k_8 \right)^2$$

$$> 0$$

Since all these conditions are satisfied for the equilibrium point, then the system is locally asymptotically stable at that equilibrium point.

1.4. Theorem 2

When s(t) = σ> 0, then there is only one steady state that is euthyroid state E_2 in the positive orthant. Also $m_2, FT_{4\,2}, T_2, Ab_2$ are all decreasing function of α.

Proof :

Let s(t) = σ > 0, , where s is a real number. To find the eqilibrium point, set RHS of (1)-(5) as zero.

$$s(t) - \frac{\mu V m}{\left(K_c + m\right)} - \delta m = 0$$

$$k_1 - \frac{k_1(FT4 - U)}{\left(K_a + FT4\right)} - \alpha TSH = 0$$

$$\frac{k_2 VAb}{\left(K_b + Ab\right)} + k_3 TSH - \beta FT4 = 0$$

$$k_4 + k_5 \frac{Ab}{V} - k_6 Vm = 0$$

$$k_7 - \frac{k_7 m}{\left(K_d + m\right)} - k_8 Ab = 0$$

$$\sigma K_c + (\sigma - \mu V - \delta K_c)m - \delta m^2 = 0$$

The eqilibrium point is

$$E_2 = [m^*, TSH^*, FT4^*, V^*, Ab^*]$$

$$m^* = \frac{sK_c - \delta m K_c}{\mu V - s + \delta m}$$

$$TSH^* = \frac{k_1\left(K_a + U\right)}{\alpha\left(K_a + FT4^*\right)}$$

$$FT4^* = \frac{k_1 K_a + U - \alpha TSH^* K_a}{\alpha TSH^*}$$

$$V^* = \frac{k_4 + \sqrt{k_4^2 + 4k_5 k_6 Ab}}{2k_8 m}$$

$$Ab^* = \frac{k_7}{k_8 + \frac{k_7}{Kd + m^*}}$$

Theorem 2. The equilibrium E^* is locally asymptotically stable with some conditions.

Proof. lets denote m as M , TSH as T, FT4 as Fand Ab as A. let consider the positive definite function

$$M = M^* + m, T = T^* + \tau, F = F^* + f, V = V^* + v, A = A^* + a$$

$$U = \frac{1}{2M} m_1 m^2 + \frac{1}{2T} m_2 \tau^2 + \frac{1}{2F} m_3 f^2 + \frac{1}{2V} m_4 v^2 + \frac{1}{2A} m_5 a^2$$

Differentiating the above function with respect to time t, we have

$$\frac{dU}{dt} = -\frac{1}{2} a_{11} m^2 + a_{14} mv - \frac{1}{3} a_{44} v^2 - \frac{1}{2} a_{11} m^2 + a_{15} ma - \frac{1}{3} a_{55} a^2$$
$$-a_{22} \tau^2 + a_{23} \tau f - \frac{1}{3} a_{33} f^2 - \frac{1}{3} a_{33} f^2 + a_{34} fv - \frac{1}{3} a_{44} v^2$$
$$-\frac{1}{3} a_{33} f^2 + a_{35} fa - \frac{1}{3} a_{55} a^2 - \frac{1}{3} a_{44} v^2 + a_{45} va - \frac{1}{3} a_{55} a^2$$

$$\dot{U} = -m_1 \left(\frac{\mu V K_c}{\left(K_c + M^*\right)^2} + \delta \right) m^2 - m_1 \left(\frac{\mu V^* K_c}{K_c + M^*} \right) m\tau - m_2 (\alpha) \tau^2 - m_2 \left(\frac{k_1 (K_a + U)}{\left(K_a + F^*\right)^2} \right) \tau f - m_3 \left(k_3\right) \tau f - m_3 \left(\beta\right) f^2$$
$$-m_3 \left(\frac{k_2 A^*}{K_b + A^*} \right) fv - m_3 \left(\frac{k_2 V^* K_b}{\left(K_b + A^*\right)^2} \right) fa - m_4 \left(k_6 V^*\right) mv - m_4 \left(k_6 M^* + k_5 \frac{A^*}{V^{*2}} \right) v^2 - m_4 \left(\frac{k_5}{V^*} \right) va$$
$$-m_5 \left(\frac{k_7 K_d}{\left(K_d + M^*\right)^2} \right) ma - m_5 k_8 a^2$$

$\dot{U}$ will be negative definite

$$m_1 \left[\left(\frac{\mu M^*}{\left(K_c + M^*\right)} \right) + m_4 k_6 V^* \right]^2 < \frac{2}{3} m_4 \left(\frac{\mu V^* K_c}{\left(K_c + M^*\right)^2} + \delta \right) \left(k_6 M^* + k_5 A^* \right)$$
$$\left[m_3 k_3 - m_2 \frac{k_1 (K_a + U)}{\left(K_a + F^*\right)^2} \right]^2 < \frac{4}{3} \alpha\beta m_2 m_3$$
$$\left[m_3 \frac{k_2 A^*}{\left(K_b + A^*\right)} \right]^2 < \frac{4}{9} m_4 \beta \left(k_6 M^* + k_5 \frac{A^*}{V^{*2}} \right)$$
$$m_3 \left[\frac{k_2 V^* A^*}{\left(K_b + A^*\right)^2} \right]^2 < \frac{4}{9} m_5 k_8 \beta$$
$$m_3 \left[\frac{k_5}{V^{*2}} \right]^2 < \frac{4}{9} m_5 k_8 \left(k_6 M^* + k_5 \frac{A}{V^{*2}} \right)$$
$$m_5 \left[\left(\frac{k_7 K_d}{\left(K_d + M^*\right)^2} \right) \right]^2 < \frac{2}{3} m_1 k_8 \left(\frac{\mu M^*}{\left(K_c + M^*\right)} + \delta \right)$$

Now $m_1 = 1, m_3 = 1, m_4 = 1$

" $\dot{U}$ will be negative definite provided the above conditions are satisfied and hence E^* is globally asymptotically stable."

1.5. Theorem 3

The equilibrium E^* is globally asymptotically stable with some conditions.

Proof. lets denote TSH as T, FT4 as Fand Ab as A. let consider the positive definite function

$$U=\frac{1}{2}m_1\left(M-M^*\right)^2+\frac{1}{2}m_2\left(T-T^*\right)^2+\frac{1}{2}m_3\left(F-F^*\right)^2+\frac{1}{2}m_4\left(V-V^*\right)^2+\frac{1}{2}m_5\left(A-A^*\right)^2$$

Differentiating the above the function with respect to time t, we have

$$\frac{dU}{dt}\le m_1\left(m-m^*\right)\dot{m}+m_2\left(T-T^*\right)\dot{T}+m_3\left(F-F^*\right)\dot{F}+m_4\left(V-V^*\right)\dot{V}+m_5\left(A-A^*\right)\dot{A}$$

$$\begin{aligned}\dot{U}=&-m_1\left(\frac{\mu VK_c}{\left(K_c+M\right)^2}+\delta\right)\left(M-M^*\right)^2-m_1\left(\frac{\mu VK_c}{K_c+M}\right)\left(M-M^*\right)\left(T-T^*\right)-m_2(\alpha)\left(T-T^*\right)^2\\&-m_2\left(\frac{k_1(K_a+U)}{\left(K_a+F\right)^2}\right)\left(T-T^*\right)\left(F-F^*\right)-m_3\left(k_3\right)\left(T-T^*\right)\left(F-F^*\right)-m_3\left(\beta\right)\left(F-F^*\right)^2\\&-m_3\left(\frac{k_2A}{K_b+A}\right)\left(F-F^*\right)\left(V-V^*\right)-m_3\left(\frac{k_2VK_b}{\left(K_b+A\right)^2}\right)\left(F-F^*\right)\left(A-A^*\right)\\&-m_4\left(k_6V\right)\left(M-M^*\right)\left(V-V^*\right)-m_4\left(k_6M+k_5\frac{A}{V^2}\right)\left(V-V^*\right)^2-m_4\left(\frac{k_5}{V}\right)\left(V-V^*\right)\left(A-A^*\right)\\&-m_5\left(\frac{k_7K_d}{\left(K_d+M\right)^2}\right)\left(M-M^*\right)\left(A-A^*\right)-m_5k_8\left(A-A^*\right)^2\end{aligned}$$

$\dot{U}$ will be negative definite

$$\begin{aligned}&\left[m_1\left(\frac{\mu M}{\left(K_c+M\right)}\right)+m_4k_6V\right]^2<m_1m_4\left(\frac{\mu VK_c}{\left(K_c+M\right)^2}+\delta\right)\left(k_6m+k_5\frac{A}{V^2}\right)\\&\left[m_3k_3-m_2\frac{k_1(K_a+U)}{\left(K_a+F\right)^2}\right]^2<\alpha\beta m_2m_3\\&\left[m_3\frac{k_2A}{\left(K_b+A\right)}\right]^2<m_4\beta\left(k_6M+k_5\frac{A}{V^2}\right)\\&m_3\left[\frac{k_2VA}{\left(K_b+A\right)^2}\right]^2<m_5k_8\beta\\&m_3\left[\frac{k_5}{V^2}\right]^2<m_5k_8\left(k_6M+k_5\frac{A}{V^2}\right)\\&m_5\left[\left(\frac{k_7K_d}{\left(K_d+M\right)^2}\right)\right]^2<m_1k_8\left(\frac{\mu M}{\left(K_c+M\right)}+\delta\right)\end{aligned}$$

Now $m_1=1, m_3=1, m_4=1$

$\dot{U}$ will be negative definite provided the above conditions are satisfied and hence E^* is globally asymptotically stable."

2. Numerical Simulation

Graves' hyperthyroidism patients data was collected with the details of steady state levels of free thyroxine (FT4), free triiodothyronine (FT3), thyroid receptor stimulating antibodies (TRAb), thyroglobulin antibodies (TgAb), Methimazole (MMI) loading and maintenance dosage levels.Depending upon FT4 and FT3 levels the antithyroid drug (MMI) is advised fot treatment . Based on the levels of FT4, MMI loading dosage started with six, four, three or two tablets per day for one or two months. The treatment would last till the patient achieved the normal range of FT4.After patients achieved euthyroidism, MMI therapy would be stopped and patients were all asked to check their FT4 levels periodically to avoid relapses of hyperthyroidism. After stopping therapy, relapses may occur for some patients. If relapses occur, then MMI therapy would be administered again.

With twelve positive parameters and a dose (rate) function *s(t)* in this model, we have to determine the numerical values for these parameters and a function via patients data, thyroid literature and equilibrium argument of hyperthyroidism state. A summary of theparameter estimates can be found in Table 2. In Eq. (1), we first calculate the dose function *s(t)* = *c* based on the loading dosage schedule information and bio-availability of MMI *(f* = 93%*)*. Typically, dosing schedule of a patient is obtained from the data. Suppose the loading dosingschedule is 30 mg/day for 45 days for the average man with body volume 59.71 L, then

$$s(t) = \begin{cases} \dfrac{0.93 \times 30\ mg/day \times 45\ days}{59.71L} = 21.027 mg/L & \text{if } 0 \le t \le 45 \\ 0 & \text{otherwise} \end{cases}$$

The study by Huang G et al. investigated the relationship between the dosage of methimazole (MMI) and its intrathyroidal concentration. Their results showed that as the MMI dosage increased from 5 to 15 mg/day, the intrathyroidal levels of MMI increased correspondingly. However, when the dosage exceeded 15 mg/day, there was no significant further increase in the intrathyroidal concentration. This observation suggests that the intrathyroidal concentration of MMI reached saturation at a dosage of 15 mg/day, indicating that this dosage represents the maximum uptake rate or the maximum saturation rate of MMI within the thyroid gland. Suppose the normal functional ize of the thyroid gland in hyperthyroidism is $V_0 = 30$ ml

Then the value $\mu = \dfrac{15}{30 \times 59.71} = 0.008374$ was estimated. The value of δ was estimated using the optimization technique in MATLAB with lower bound 0.5 and upper bound 3. The value of k_1 and U are taken from the litereture[yang].

The rate of elimination of TSH is calculated using chemical half-life in equation, By neglecting the secretion rate in second Equation of (1) it becomes, $\dfrac{dTSH}{dt} = -\alpha TSH$

The solution of this equation is,

$$TSH(t) = TSH(0)e^{-\alpha t}$$

Where TSH(0) is the initial value of TSH in the blood. The half-life is the period of time it takes for the concentration or amount of a substance in the body to be reduced by half of its initial value.

By TSH half life,

$$\frac{1}{2}TSH(0) = TSH(0)e^{-\alpha(1\text{ hr})}$$

$$\alpha = \frac{\ln(2)}{1\text{ hr}} = 16.635/day$$

The parameter Ka was the half maximal inhibition concentration of TSH is estimated using the optimiation technique in MATLAB.

$$\frac{dFT4}{dt} = \frac{k_2 VAb}{(K_b + Ab)} + k_3 TSH - \beta FT4$$

The stimulatory effect of TSH on FT4 production are calculated using optimization technique in MATLAB by setting the lower bound and upper bound with the help of the initial values and known parameter.

The elimation rate of FT4 is estimated in the same way as TSH. The half life of FT4 is 7 days. Then the value of beta is estimated as 0.0990/day.

$$\frac{dV}{dt} = k_4 + k_5 \frac{Ab}{V} - k_6 Vm$$

The basic size of thyroid gland was taken from the literature and the value of k5 and k6 were simulated using the simbiology in matab

The maximum TRAb t production rate is given in Eq. (5). More accurately, in the absence of MMI treatment, the parameter estimate of $k_7 = k_8 w_0$. The death rate of TRAb, denoted by the parameter k_8, was computed as $k_8 = 0.035$ 1/day, based on the assumption that it is exponential in the model. The half-maximal inhibitory concentration of the TRAb (Michalies-Menten constant), or parameter kb, can be calculated using the fmincon technique, with an upper bound of 12 and a lower bound of 3.

Table 1 Approximate Parameters value with units

	description	**values**	**Units**
μ	Maximum Uptake rate of MMI	0.008374	mg/(ml *day)
δ	Elimination rate of MMI	1.942	1/day
k_1	Rate constant for TSH stimulation	30	$mU / L * day$
k_2	Maximum Secretion rate of FT4	0.1190	$mU / L * day$
k_3	stimulatory effect of TSH on FT4 production.	0.5	
k_4	Basic growth rate of thyroid gland	0.5472	$pg / mL^2 * day$
k_5	Proportional rate of TRAb to the size of thyroid gland	0.2567	$U / mL * day$
k_6	Inactivation rate of thyroid gland due to MMI	0.01168	$U / mL * day$
k_7	Production rate constant for TRAb	0.7340	$1/day$
k_8	Decay/clearance rate of TRAb	0.0280	$1/day$
K_a	Michealis-Menten constant for half maximal secretion rate of TSH	0.0434	$1/day$

K_b	Michealis-Menten constant for half maximal secretion rate of FT4	0.05	$1/day$
K_c	Michealis-Menten constant for half maximal uptake rate of MMI	0.0038	mg/L
K_d	Inhibition rate of TRAb	1.5700	mg/L
α	Elimination rate of TSH	16.635	$pg/mL^2 * day$
β	Elimination rate of FT4	0.099021	$1/day$

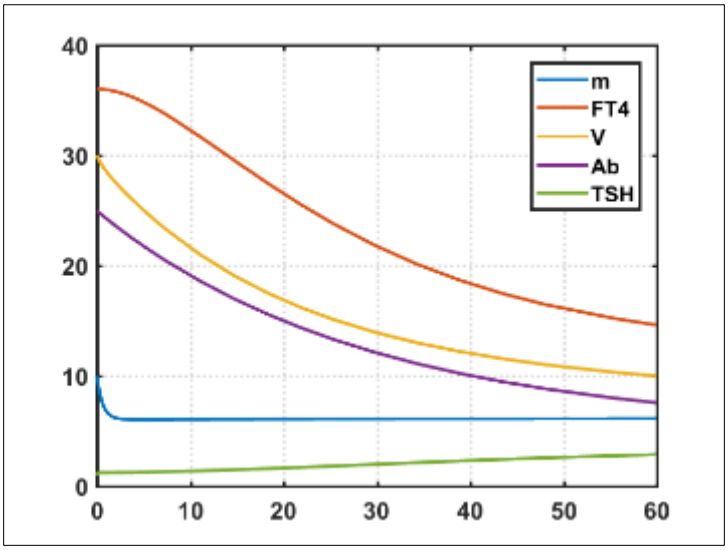

Figure 2 With E0 = (10, 0.965, 36, 30, 25), suppose the loading dosage = 30 mg/day is given for 60 days which results in patient's FT4 levels within the normal reference range

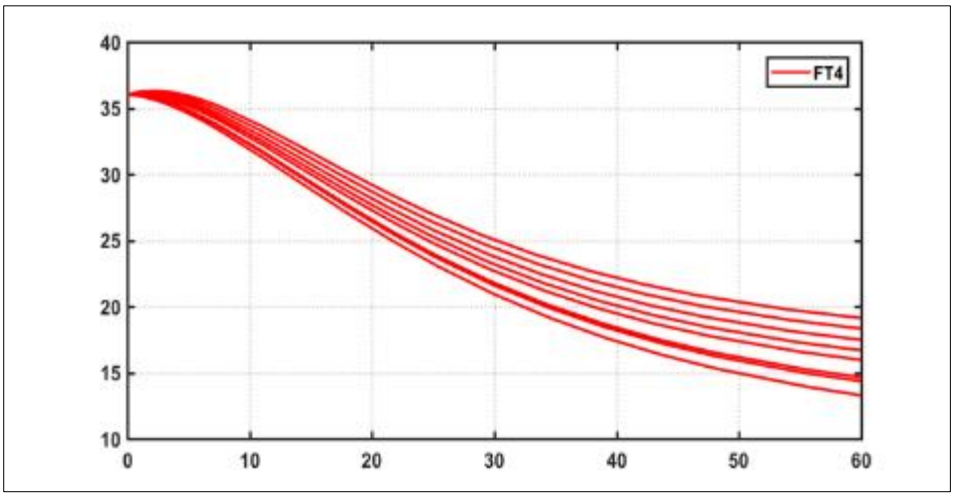

Figure 3 Depicts the dynamics of FT4 by varying the parameter values. The iniitial values and other parameters are remains same

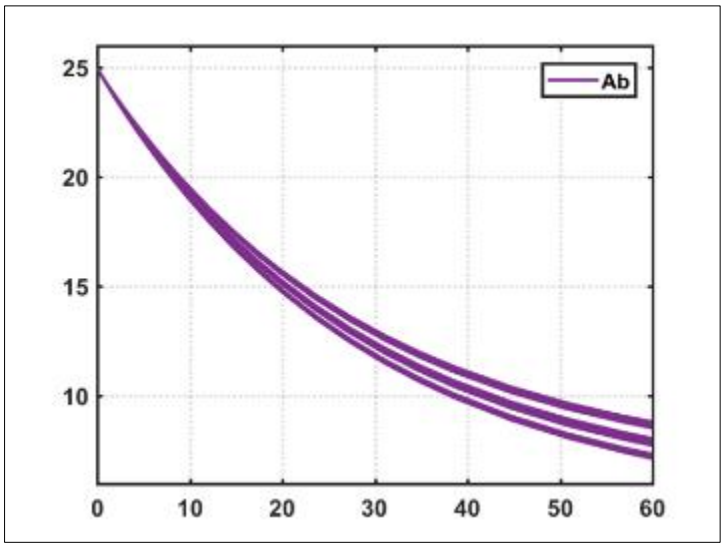

Figure 4 Depicts the dynamics of Ab by varying the parameter values. The iniitial values and other parameters are remains same

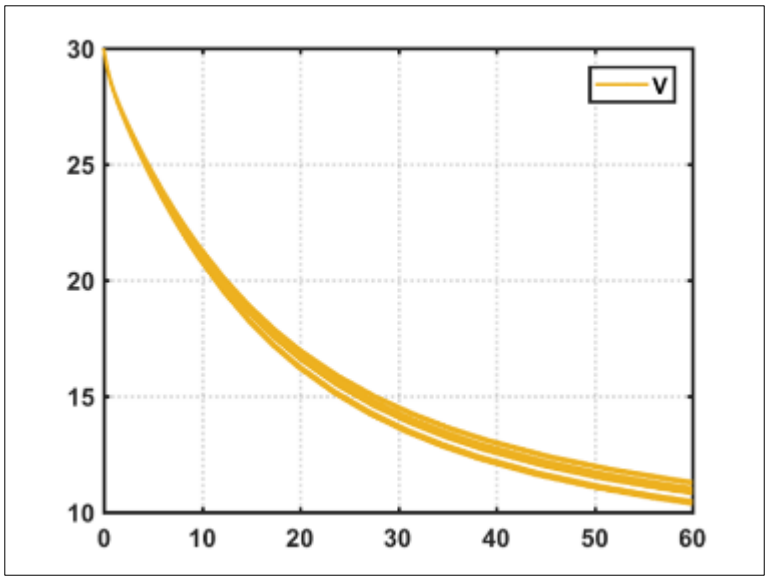

Figure 5 Depicts the dynamics of V by varying the parameter values. The iniitial values and other parameters are remains same

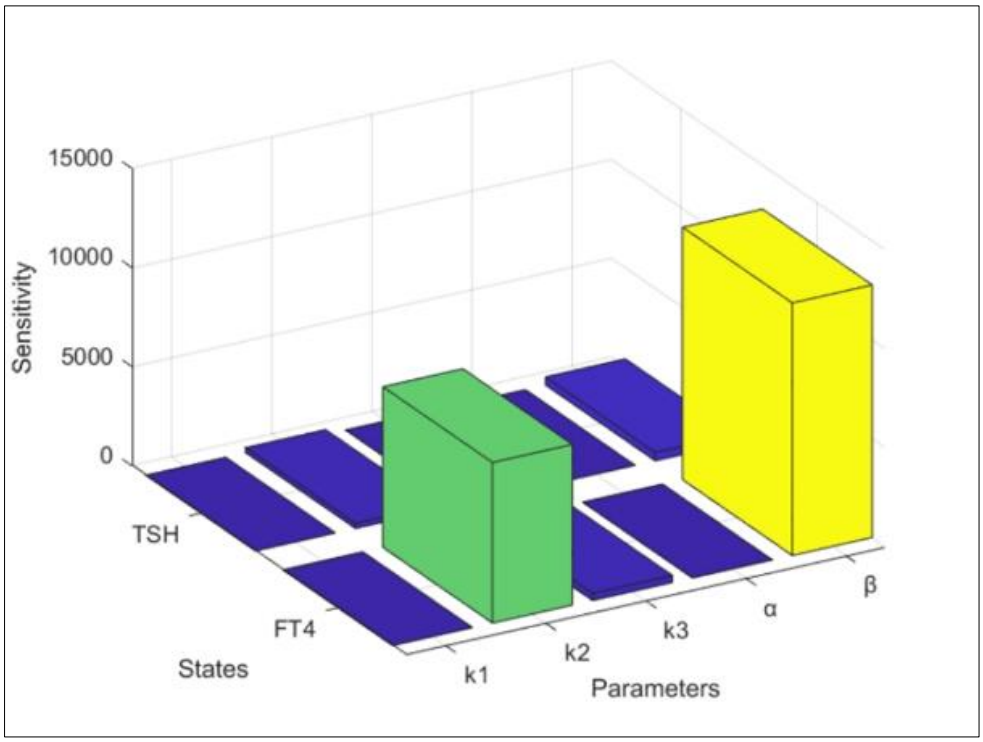

Figure 6 The local sensitivity of all variables with respect to a set of parameters using the SimBiology Toolbox for Matlab of the proposed model with initial conditions E0 = (10, 0.965, 36, 30, 25).

3. Conclusions

Hyperthyroid patient without taking a treatment that is no dosage of MMI,then there is a only one steady state corresponding to hyperthyroidism, which is asymptotically stable. After the initiation of MMI treatment, that is s(t) = c > 0 the hyperthyroidism steady state is moving on the monotonic decreasingtowards subclinical hyperthyroidism and then euthyroidism. Once patients achieve euthyrodism, the maintenance dosage is prescribed to maintain FT4 values within the normal reference range. The value of treatment parameter c is determined in accordance with loading or maintenance dosages, treatment time period and body volume of patients. The initial concentration of MMI is estimated from the loading dosage of MMI.

One way to use the model is to run an experiment on clinical dosing amount and schedules. By keeping the dosing MMI amount constant throughout the treatment period and varying the dosing schedule, can actually check to see if that assumption ever results in hypothyroidism. Also by keeping the dosing schedule constant say every day for some period of time and varying the dosing amount from high to low doses each day. After reaching the lowest dosage amount, restart the dosage amount from high to low doses again. In this way, we can actually check to see if that assumption results in sub clinical hyperthyroidism, euthyroidism or hypothyroidism.

Another way to use to model is to find the response rate of thyroid gland to different concentrations of MMI in the blood serum. Finally,This model is constructed to analyse the time course of FT4 levels after administration of Methimazole (MMI) and to control FT4 levels within the normal rangewith an appropriate maintenance dosage schedule in Graves'disease. This model takes the form of differential equation with four variables namely concentration of MMI , concentration of Free Thyroxine - FT4, and concentration of TRAb and the functional size of the thyroid gland with thirteen parameters.We analyse the stability of the model and validate with data of a patient.This model can also used to predict the discontinuation of the treatment without relapsing.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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