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# A Mathematical Treatment Model and Analysis of Hypothyroidism using Levothyroxine

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**ABSTRACT**

Various models devoted to different facets of diseases, such as prevention, complications, cost-effectiveness measures, and so on, have been developed throughout the previous few decades. Hypothyroidism is caused by an underactive thyroid gland, which produces insufficient thyroid hormones to maintain a normal metabolic rate. Many physical functions, most notably metabolism, are slowed as a result of hypothyroidism. Patients with hypothyroidism are given synthetic thyroxine pills called Levothyroxine to take every day for the rest of their lives. The mathematical model for hypothyroidism therapy with LT4 was discussed in this study, which used a system of ordinary differential equations. The model includes four state variables: LT4 concentration, Thyroid-stimulating hormone (TSH) concentration, functional size of the thyroid gland and TRAb concentration, with twelve parameters. It also analyses the stability of the mathematical model for hypothyroidism. Furthermore, the clinical chart is created based on TSH levels and time. The patient's data collection is used to validate the model description.
**Keywords:** Hypothyroidism, Levothyroxine, Hashimoto Thyroiditis, Ordinary Differential Equations, Stability.

## 1. Introduction

Hypothyroidism is a state of thyroid hormone deficiency and is diagnosed based on elevated serum TSH levels and/or low free thyroxine levels (FT4). Levothyroxine (LT4) has been considered the standard of care for the treatment of hypothyroidism for many years. Although levothyroxine is a safe and effective treatment for thyroid disorders, using too much of it might lead to complications. Levothyroxine is being used as a replacement treatment in hypothyroid patients. This treatment is efficacious when administered orally, has a long serum half-life that permits daily administration, and results in the resolution of the signs and symptoms of hypothyroidism in the majority of patients. Levothyroxine is used to suppress the serum thyroid-stimulating hormone concentration. LT4 is a long-acting drug with a plasma half-life of approximately 7 days, which is regulated by thyroid function, among other factors.

Hypothyroidism is properly described as a condition in which the body is deficient in thyroid hormones and/or the organism's reaction to hormonal actions as a result of this deficiency. Overt hypothyroidism is believed to affect 1–3% of people in Europe and the United States, while subclinical hypothyroidism affects 6–10% of people. Primary hypothyroidism, which is caused by the thyroid gland failing to produce enough thyroid hormones, is the most prevalent classification.To avoid hypothyroidism and improve the efficiency of converting T4 to T3, pituitary stimulation of TSH is used to increase levels of thyroid hormone production. Thyroid hormones, in turn, have a negative feedback effect on pituitary TSH secretion, which prevent it from becoming excessive. The link between TSH and thyroid hormones has been used in modern thyroid test procedures to aid in diagnosis. Subclinical hypothyroidism is defined as an elevated serum TSH level in the presence of free thyroxine (FT4) concentrations that are still within the population reference range, whereas primary hypothyroidism is defined as an elevated TSH concentration combined with an FT4 measurement that is below its range.

According to nationwide data from the National Health Service in the United Kingdom, its prescription has increased over the last 15 years and is expected to increase much more over the next decade[13]. For majority of patients, therapy can be initiated with a full replacement dosage (1.6 μg/kg body weight), which is usually 75 to 100 μg/day for women and 100 to 150 μg/day for men[20]. The goal is to normalize the serum thyroid-stimulating hormone concentration. The treatment goal can be broadly defined as the replacement of a hormone deficiency to return to the former euthyroid state. Aside from its well-known pharmacological features, the actual administration of LT4 as a medication involves the consideration of two primary aspects: detecting the presence of hypothyroidism to assess the indication for therapy and determining the efficacy of subsequent euthyroidism restoration. Substitution with lower doses may be sufficient in the presence of functional residual thyroid tissue. Among other things, biochemical markers should be evaluated for equilibrium, which in the case of TSH, requires a delay of 4 to 6 weeks after starting LT4 or adjusting

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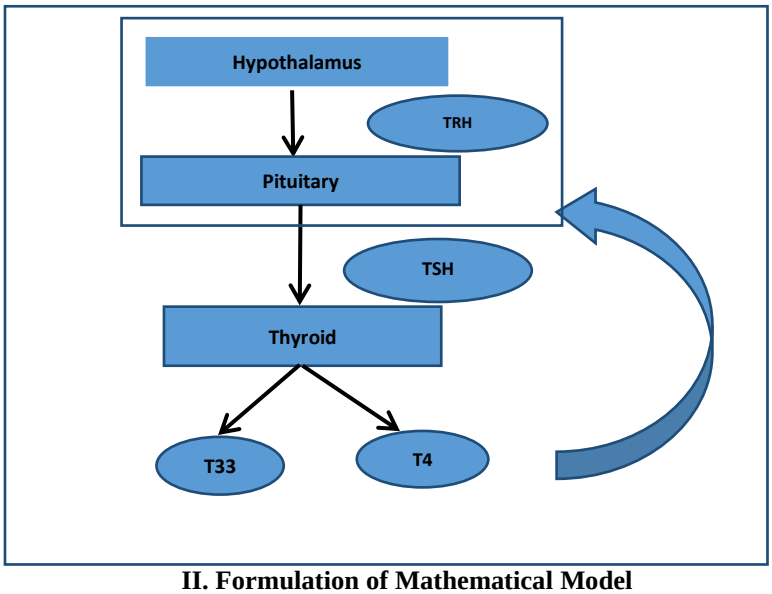
the dose. The volume of LT4 distribution is around 0.2 L/kg, and the metabolic clearance is about 1.32 L/d, with the majority of it occurring in the liver, kidney, brain, and muscle tissue.

LT4 is synthesized to be the same as the natural hormone, which is often well tolerated when taken properly[20]. Although the drug is effective in treating hypothyroidism, it is more difficult to determine its optimum efficacy in eradicating hypothyroidism and fully restoring euthyroidism as a therapeutic goal. In studies, patients who received LT4 had lower quality-of-life scores than the general population. Underdosing, which does not restore a euthyroid state, or overdosing, which mimics the signs and symptoms of hyperthyroidism, are the most common causes of adverse consequences. After halting and changing the daily LT4 dose, overtreatment symptoms disappear. Although sensitivity to the base formulation is uncommon, interactions with other medications or comorbidities are more common. Injectable and liquid versions are offered for the treatment of severe hypothyroidism as well as resorption issues.

Synthetic levothyroxine is equivalent to T4 released by the thyroid gland. The T4 concentration in tablets, as evaluated by high-pressure liquid chromatography, must be between 90 and 110 percent of the reported dosage, according to the United States Pharmacopeia. Levothyroxine is absorbed about 80% through the gastrointestinal tract and does not alter depending on whether you are hypothyroid or euthyroid[20]. Absorption occurs throughout the human small intestine, however, the rate of absorption slows as it gets farther away. Serum T4 levels peak 2 to 4 hours after intake of levothyroxine (average rise of 10% to 15% over basal values) and stay above this level for up to 6 hours. Because of the time, it takes for T4 to convert to T3, the increase in serum T3 levels after levothyroxine administration is slow.




## II. Formulation of Mathematical Model

A patient-specific treatment model is presented to describe the effect of LT4 treatment in patients with hypothyroidism. The model describes the clinical progression from hypothyroidism to euthyroidism by the treatment procedure. So, The model is constructed with the subsequent key assumptions and state variables.

**Assumptions:**

1. LT4 imitate the action of T4. T4 is the main hormone produced by the thyroid gland, and it raises metabolic rate and decreases TSH produced by the pituitary gland.

2. Absorption of (LT4) occurs primarily in the intestine after oral ingestion. It has a bioavailability of 70%. After an oral dose, the maximum plasma concentration of LT4 is reached about 3 hours later.

3. LT4 is strongly connected to plasma proteins and is distributed throughout the extracellular region of the human body.

4. Approximately 20% of the LT4 dose consumed is eventually removed from the body.

5. The Functional size of the thyroid gland is a concealed compartment in the model.

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**Rate equation 1:**

The rate of change of concentration of LT4 is equated to the dosage given and secretion rate of LT4 minus excretion rate of LT4.

$$\frac{dLT4}{dt} = f_1(LT4, T) - f_2(LT4)$$

Where $f_1(LT4, T)$ and $f_2(LT4)$ represents the secretion and excretion rate of LT4 respectively. We first model the secretion rate of LT4 in equation(1) with two terms, one account for the LT4 dosage given and another for inhibition rate.

$$f_1(LT4, T) = n(t) - \frac{(k_1 T)LT4}{k_a + LT4}$$

The term $n(t)$ denotes the LT4 dosage, next term $k_1$represents maximum uptake rate of LT4 and $k_1 T$ is the maximum saturation rate of LT4.

By using the Menten kinetics, which describes the relationship between affinity constant $k_a$ and the total number of receptors $(k_1)$ on the thyroid gland where $k_a$ described as the concentration of LT4 required for 50% of maximal LT4 inhibitor.

The excretion rate is decreases at a rate propotional to the concentration of LT4 in the blood serum.

$$f_2(LT4) = k_2 LT4$$

$$\frac{dLT4}{dt} = n(t) - \frac{(k_1 T)LT4}{k_a + LT4} - k_2 LT4$$

**Rate Equation 2:**

The rate of change of concentration of TSH is equated to the secretion rate minus excretion rate of TSH.

$$\frac{dTSH}{dt} = g_1(LT4, Ab) - g_2(LT4)$$

Where $g_1(LT4, Ab)$ and $g_2(LT4)$ are the secretion and excretion rate of TSH respectively. Here the functional size of the thyroid gland is neglected purposely, because the active area in the thyroid gland may get smaller as the disease progress in the thyroid gland.

$$g_1(LT4, Ab) = k_3\, Ab - \frac{k_3 LT4}{k_c + LT4}$$

Properties:

Since $\frac{\partial g_1}{\partial LT4} = -\frac{k_3 LT4}{k_c + LT4} < 0$ for all LT4≥0

Then

$g_1(LT4, Ab) = k_3\, Ab - \frac{k_3 LT4}{k_c + LT4} \leq 0$ for all LT4≥0

Remark:

(i) $g_1(0) = k_3\, Ab$

(ii) $\lim_{LT4 \to 0} g_1(LT4, Ab) = k_3\, Ab$ and $\lim_{LT4 \to \infty} g_1(LT4, Ab) = k_3\,(Ab - 1)$

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(iii) $g_1(LT4, Ab)$ is atleast twice continuous.

The excretion rate of TSH is decreases at a rate propotional to the concentration of TSH in the blood serum.

$$\frac{dTSH}{dt} = k_3\, Ab - \frac{k_3 LT4}{k_c + LT4} - k_4\, TSH$$

**Rate Equation:3**

The rare of change of functional size of the thyroid gland is equated to the growth rate minus the destruction rate of the functional thyroid.

$$\frac{dT}{dt} = h_1(TSH, T) - h_2(Ab, T)$$

$$h_1(TSH, T) = k_5 + k_6 \frac{TSH}{T} LT4$$

Where $k_5$ is the basic growth rate of functional thyroid size and $k_6 \frac{TSH}{T} LT4$ represents the growth rate proportional to the ratio of TSH to thyroid size with the influence of LT4.

Remark:

(i) $h_1(TSH, 0) =$ does not exist. This impiles that there is a singularity at T = 0

(ii) $h_1(0, T) = k_5$

The inactivation rate of functional thyroid size is

$$h_2(Ab, T) = k_7 Ab\, T$$

Remark:

(i) If Ab = 0 or T = 0 then $h_2 = 0$.

$$\frac{dT}{dt} = k_5 + k_6 \frac{TSH}{T} LT4 - k_7\, Ab\, T$$

**Rate equation:4**

The rate of change of concentration of antithyroid antibodies is equated to the production rate of antithyroid and elimination rate of antithyroid antibodies.

$$\frac{dAb}{dt} = j_1(LT4) - j_2(Ab)$$

In the same way

$$j_1(LT4) = k_8 - \frac{k_8\, LT4}{k_d + LT4}$$

Where $\frac{k_8\, LT4}{k_d + LT4}$ represents the inhibition rate of antithyroid antibodies due to LT4 dosing.

The natural decompose rate of antithyroid antibodies is

$$j_2(Ab) = k_9\, Ab$$

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$$\frac{dAb}{dt} = k_8 - \frac{k_8\, LT4}{k_d + LT4} - k_9\, Ab$$

**State Variables:**

- LT4(t) = the amount of LT4 $(\mu g)$ per litre of blood serum at time t.
- TSH(t) = the amount of TSH $(mU)$ per litre of blood serum at time t.
- T(t) = the functional size of the thyroid gland (mL) at time t.
- Ab(t) = the amount of Ab (U) per millilitre of blood serum at time t.
- n(t) = the amount of LT4 orally taken per day per litre of body volume.$(\mu g/L/day)$

The model is given below with initial conditions.

$$\frac{dLT4}{dt} = n(t) - \frac{(k_1 T)LT4}{k_a + LT4} - k_2 LT4 \qquad (1)$$

$$\frac{dTSH}{dt} = k_3\, Ab - \frac{k_3 LT4}{k_c + LT4} - k_4\, TSH \qquad (2)$$

$$\frac{dT}{dt} = k_5 + k_6 \frac{TSH}{T} LT4 - k_7\, Ab\, T \qquad (3)$$

$$\frac{dAb}{dt} = k_8 - \frac{k_8\, LT4}{k_d + LT4} - k_9\, Ab \qquad (4)$$

Where $\mathrm{LT4(t)} \geq 0, \mathrm{TSH(t)} \geq 0, \mathrm{T(t)} \geq 0, \mathrm{Ab(t)} \geq 0$ and initial conditions $E_0 = (LT4_0, TSH_0, T_0, Ab_0)$.

In equation (1), the primary term n(t) is time varying, which represents the rate of change of LT4 dosing at time t. The rate of change of LT4 dosing is supposed to be zero when no LT4 is taken. The secondary term, $-\frac{(k_1 T)LT4}{k_a + LT4}$ represents the absorption rate of LT4 by the thyroid gland with maximal saturation rate $(k_1 T)$, which was modeled from the uptake rate with Michaelis-Menten Kinetics. The final term denotes the liquidation rate of the LT4 through non-unique mechanism.

In equation (2), the first term $k_3 Ab$ represents the maximum production rate of TSH due to disorder. The next term $-\frac{k_3\, LT4}{k_c + LT4}$ describes the inhibition of maximum secretion rate of TSH, which depends on the concentration of LT4. The third term $-k_4 TSH$, represents the excretion rate of TSH through uncertain mechanism.

In equation (3), the first term $k_5$ accounts for the basic growth rate of the thyroid gland and second term $k_6 \frac{TSH}{T} LT4$ represents the growth rate proportional to the ratio of TSH to thyroid size with the influence of LT4. The last term, $k_7 AbT$ represents the inactivation rate of functional thyroid size.

In equation (4), the first term represents the maximum production rate of antithyroid antibodies and the second term represents the inhibition rate of antithyroid antibodies due to LT4 dosing. The last term represents the natural decompose rate of antithyroid antibodies.

**III. Stability Analysis**

Two cases arise to check its stability.

**Case (i)**: To Analyse the stability of steady-state for untreated Hypothyroid patients.

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**Case (ii)**: To Analyse the stability of steady-state for patients treated with Levothyroxine.

**Theorem: 1**

*When n(t) and $LT4_0$ is zero, model (1)-(4) with all parameters are positive then there is a only one steady state, that is hypothyroid state in the hyperplane which is asymptotically stable.*

**Proof :**

Let us denote the hypothyroid state as $E_1 = [LT4_1, TSH_1, T_1, Ab_1]$

When n(t) =0 and $LT4_0 = 0$.

One can solve for steady state by setting the right hand side of each equation from (1)-(4) equal to zero. Then it yields the following.

$$LT4 = 0$$

$$\text{TSH} = \frac{k_5}{k_4} Ab$$

$$T = \frac{k_5}{k_7 Ab}$$

$$Ab = \frac{k_8}{k_9}$$

We can prove that the hypothyroid state is asymptotically stable, by using the Routh Hurwitz criterion. Consider the Jacobian matrix of this model

$$\text{J} = \begin{vmatrix} \frac{-(k_a k_1 T + k_2 (k_a + LT4)^2)}{(k_a + LT4)^2} & 0 & \frac{-k_1 LT4}{k_a + LT4} & 0 \\ \frac{-k_c k_3}{(k_c + LT4)^2} & -k_4 & 0 & k_3 \\ \frac{k_6 TSH}{T} & \frac{k_6 LT4}{T} & \frac{-k_6\, TSH\, LT4}{T^2} - k_7 Ab & -k_7 T \\ \frac{-k_d k_8}{(k_d + LT4)^2} & 0 & 0 & -k_9 \end{vmatrix}$$

$$\text{J} = \begin{vmatrix} \frac{-k_1 k_5 k_9}{k_7 k_8 k_a} - k_2 & 0 & 0 & 0 \\ -\frac{k_3}{k_c} & -k_4 & 0 & k_3 \\ \frac{k_6 k_3 k_7 {k_8}^2}{k_4 k_5 {k_9}^2} & 0 & \frac{-k_7 k_8}{k_9} & \frac{-k_5 k_9}{k_8} \\ \frac{-k_8}{k_d} & 0 & 0 & -k_9 \end{vmatrix}$$

By solving the characteristic equation of $|J - \lambda I| = 0$, we can find the Eigen values of Jacobian matrix , which is

$$\lambda^4 + a_1 \lambda^3 + a_2 \lambda^2 + a_3 \lambda + a_4 = 0$$

$$\left(\frac{-k_1 k_5 k_9}{k_7 k_8 k_a} - k_2 - \lambda\right) \begin{vmatrix} -k_4 - \lambda & 0 & k_3 \\ 0 & \frac{-k_7 k_8}{k_9} - \lambda & \frac{-k_5 k_9}{k_8} \\ 0 & 0 & -k_9 - \lambda \end{vmatrix} = 0$$

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$$\left(\frac{k_1k_5k_9}{k_7k_8k_a}+k_2+\lambda\right)\left(\begin{matrix}k_4k_7k_8+k_7k_8\lambda+\frac{k_4k_7k_8}{k_9}\lambda+\frac{k_7k_8}{k_9}\lambda^2\\+k_9k_4\lambda+k_9\lambda^2+k_4\lambda^2+\lambda^3\end{matrix}\right)=0$$

where

$$a_1=\frac{k_1k_5k_9}{k_7k_8k_a}+\frac{k_7k_8}{k_9}+k_9+k_4+k_2$$

$$a_2=\frac{k_1k_5}{k_a}+\frac{k_1k_5{k_9}^2}{k_7k_8k_a}+\frac{k_1k_5k_9k_4}{k_7k_8k_a}+\frac{k_2k_7k_8}{k_9}+k_2k_9+k_2k_4+k_7k_8+k_4k_9+\frac{k_4k_7k_8}{k_9}$$

$$a_3=\frac{k_1k_5k_9}{k_a}+\frac{k_1k_5k_4{k_9}^2}{k_7k_8k_a}+k_2k_7k_8+k_2k_4k_9+k_4k_7k_8+\frac{k_2k_4k_7k_8}{k_9}+\frac{k_1k_5k_4}{k_a}$$

$$a_4=\frac{k_1k_5k_9k_4}{k_a}+k_2k_4k_7k_8$$

Since all the parameters from the model are positive, $a_1, a_3, and\ a_4>0$. Let check the criteria : $a_3^2-a_1^2a_4-a_1a_2a_3<0$ to ensure the asymptotical stability of the hypothyroid state inside the plane

$$a_3^2-a_1^2a_4-a_1a_2a_3=-\frac{f}{k_7^3k_8^3k_9^3k_a^3}$$

where f is a function of all parameters.

This completes the proof.

Remark 1: Let$E_2=[LT4_2\ ,TSH_2\ ,T_2\ ,Ab_2]$ be the Euthyroid steady state. Here the analytical description for this is not possible. So we have proved the existence and the stability of the Euthyroid state through qualitative analysis.

**Theorem: 2**

*When n(t) = α > 0, then there is the only one steady state that is euthyroid state* $E_2=[LT4_2\ ,TSH_2\ ,T_2\ ,Ab_2]$*in the positive orthant. Also* $LT4_2\ ,TSH_2\ ,T_2\ ,Ab_2$ *are all decreasing function of α.*

PROOF:

Assume that Euthyroid State as $E_2=[LT4_2\ ,TSH_2\ ,T_2\ ,Ab_2]$

Let n(t) = α > 0, where α is a real number.

To Check the existence of euthyroid state in the positive orthant ,by setting rand hand of (1)-(4) is zero ,which are

$$\alpha-\frac{(k_1T)LT4}{k_a+LT4}-k_2LT4=0\ldots\ldots\ldots\ldots(5)$$

$$k_3Ab-\frac{k_3LT4}{k_c+LT4}-k_4TSH=0\ldots\ldots\ldots\ldots(6)$$

$$k_5+k_6\frac{TSH}{T}LT4-k_7AbT=0\ldots\ldots\ldots(7)$$

$$k_8-\frac{k_8LT4}{k_d+LT4}-k_9Ab=0\ldots\ldots\ldots\ldots\ldots(8)$$

$$\alpha k_a+(\alpha-k_1T_2-k_2k_a)LT4_2-k_2LT4_2^2=0 \qquad (9)$$

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Equation (9) is quadratic equation for $LT4_2$, for which it may have a positive and a negative root for $(\alpha - k_1T_2 - k_2k_a) < 0\ (or)\ > 0$for all parameters are positive. By Descartes' Rule of Signs, we see there is a only one sign change for equation (9), therefore there exist a root for $LT4_2$ in the positive orthant.

From Equation (8), we get

$$Ab_2 = \frac{k_8k_d}{k_9(k_d+LT4_2)} \tag{10}$$

Here if $LT4_2$ lies in positive orthant ,then $Ab_2$ lies in same positive orthant.

Equation (7) becomes

$$k_7\ Ab_2\ T^2 - k_5T_2 - k_6\ TSH_2\ LT4_2 = 0 \tag{11}$$

By Applying Descarte's Rules to the quadratic polynomial ,there is only one sign change in the equation (11) which shows that the quadratic polynomial has a root in the positive orthant where $LT4_2 > 0\ and\ Ab_2 > 0$

Equation (6) becomes

$$\mathrm{TSH_2} = \frac{\mathrm{k_3\ k_c\ Ab_2}}{\mathrm{k_4(k_c+LT4_2)}} \tag{12}$$

Which also lies in the positive orthant for $LT4_2 > 0\ and\ Ab_2 > 0$

Therefore there exist a unique Euthyroid state $E_2 = [LT4_2, TSH_2, T_2, Ab_2]$ in the positive orthant when α > 0

Then to prove : $TSH_2, T_2, Ab_2$ is all decreasing function

Partially differentiating (9), it becomes

$$\frac{\partial LT4_2}{\partial \alpha} = \frac{\left[k_a+\left(1-k_1\frac{\partial T_2}{\partial c}\right)LT4_2\right]}{k_1T_2+k_2k_a+2k_2LT4_2-c} \tag{13}$$

Partially differentiating (10), it becomes

$$\frac{\partial Ab_2}{\partial \alpha} = -\frac{k_8k_d}{k_9(k_d+LT4_2)^2}\frac{\partial LT4_2}{\partial c} \tag{14}$$

Partially differentiating (11), it becomes

$$\frac{\partial T_2}{\partial \alpha} = -\left[\frac{k_7k_8k_dT^2}{k_9(k_d+LT4_2)^2}\frac{\partial LT4_2}{\partial c} + k_6\left(TSH_2\frac{\partial LT4_2}{\partial c} + LT4_2\frac{\partial TSH_2}{\partial c}\right)\right]\frac{1}{k_5-2T_2k_7Ab_2} \tag{15}$$

Partially differentiating (12), it becomes

$$\frac{\partial TSH_2}{\partial c} = \frac{\frac{\partial Ab_2}{\partial c}(k_3k_c^2+k_3k_cLT4_2)-k_3k_cAb_2\frac{\partial LT4_2}{\partial c}}{k_4(k_c+LT4_2)^2} \tag{16}$$

Substituting (14)-(16) equations in (13)

$$\frac{\partial LT4_2}{\partial \alpha} = \frac{k_a + LT4_2}{(k_1T_2 + k_2k_a + 2k_2LT4_2 - \alpha) - \frac{k_1LT4_2}{k_5 - 2T_2k_7Ab_2}\left(\frac{k_7k_8k_dT_2^2}{k_9(k_d+LT4_2)^2} + k_6TSH_2 - \frac{k_3k_ck_6Ab_2LT4_2}{k_4(k_c+LT4_2)^2} + \frac{k_3k_ck_dk_6k_8LT4_2}{k_9k_4(k_c+LT4_2)(k_d+LT4_2)^2}\right)}$$

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$$\alpha < (k_1T_2 + k_2k_a + 2k_2LT4_2) - \frac{k_1LT4_2}{k_5 - 2T_2k_7Ab_2}\left(\frac{k_7k_8k_dT_2^2}{k_9(k_d+LT4_2)^2} + k_6TSH_2 - \frac{k_3k_ck_6Ab_2LT4_2}{k_4(k_c+LT4_2)^2} + \frac{k_3k_ck_dk_6k_8LT4_2}{k_9k_4(k_c+LT4_2)(k_d+LT4_2)^2}\right)$$

Therefore $\frac{\partial Ab_2}{\partial \alpha}$ ,$\frac{\partial T_2}{\partial \alpha}$ ,$\frac{\partial TSH_2}{\partial c}$ are all negative this gives $LT4_2$ , $TSH_2$ , $T_2$ , $Ab_2$ are decreasing function.

**Theorem: 3**

*The Euthyroid state is asymptotically stable.*

**Proof:**

Let $\overline{LT4} = LT4 - LT4_2$, $\overline{TSH} = TSH - TSH_2$, $\bar{T} = T - T_2$ , $\overline{Ab} = Ab - Ab_2$.

Lets define a Lyapunov Function

V: $\mathfrak{R}^4 \rightarrow \mathfrak{R}$ by the equation

$$V\left(\overline{LT4}, \overline{TSH}, \overline{T}, \overline{Ab}\right) = \frac{\overline{LT4}^2}{2} + \overline{LT4\ Ab} + \frac{\overline{Ab}^2}{2}$$

Without loss of generality, we see the system (1)&(4) becomes the new coordinates as

$$\frac{d\overline{LT4}}{dt} = -\frac{\overline{LT4\ Ab} + \overline{LT4}\ Ab_2 + LT4_2\overline{Ab}}{f_1 + \overline{Ab}} - k_2\overline{LT4}$$

$$\frac{d\overline{Ab}}{dt} = -\frac{k_8(LT4_2 + \overline{LT4})}{f_3 + \overline{LT4}} - k_9\overline{Ab}$$

(0,0,0,0) is the equilibrium point for the above system. Also V(0,0,0,0)=0 if $\left(\overline{LT4}, \overline{TSH}, \overline{T}, \overline{Ab}\right)$=0,$V\left(\overline{LT4}, \overline{TSH}, \overline{T}, \overline{Ab}\right) > 0$ for all$\left(\overline{LT4}, \overline{TSH}, \overline{T}, \overline{Ab}\right)$ in the positive orthant and

$$\frac{dV}{dt} = \frac{\partial V}{\partial \overline{LT4}}\frac{d\overline{LT4}}{dt} + \frac{\partial V}{\partial \overline{TSH}}\frac{d\overline{TSH}}{dt} + \frac{\partial V}{\partial \bar{T}}\frac{d\bar{T}}{dt} + \frac{\partial V}{\partial \overline{Ab}}\frac{d\overline{Ab}}{dt}$$

$$= -(\overline{LT4} + \overline{Ab})\left\{\frac{\overline{LT4\ Ab} + \overline{LT4}\ Ab_2 + LT4_2\overline{Ab}}{f_1 + \overline{Ab}} + k_2\overline{LT4} + \frac{k_8(LT4_2 + \overline{LT4})}{f_3 + \overline{LT4}} + k_9\right\}$$

<0

Hence the origin is asymptotically stable.

Consequently, the Euthyroid state is Asymtotically stable.

**IV Numerical Simulation:**

We have collected 20 patient data in which we have got some information for steady-state levels of Thyroid stimulating (TSH), thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), Levothyroxine (LT4) loading and maintenance dosage levels, age, and gender. Antibodies are the primary indication for the disease but dosing levels are based only on the values TSH. Units are converted using unitslab for solving purposes. Levothyroxine alteration is required for both replacement and interventional therapy by a variety of diseases or medicines. In these situations, the serum TSH level should be checked more frequently, and the dose of levothyroxine should be adjusted to maintain the TSH levels in the normal range for hypothyroid patients.

In healthy adult hypothyroid patients (under 65 years old), we start levothyroxine therapy with a full replacement dose of about 1.6 μg/kg body weight (or ideal body weight in cases of significant obesity). Most women

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receive between 75 and 100 μg/d, while most men receive between 100 and 150 μg/d. TSH levels in the blood decrease with time and should be examined again after two months of treatment. The longer it takes to get back to normal, the higher the initial serum TSH level. The daily levothyroxine dose can be increased by 25μg if the blood TSH concentration has not returned to normal after four months and the serum-free T4 index has grown, showing compliance. Thyroid function tests are done again in 6 to 8 weeks. Because the metabolic clearance of T4 may increase if hypothyroidism is treated, the serum TSH levels should be tested again 6 months following normalization to ensure that it has stabilized. A serum TSH value below normal in a levothyroxine-treated patient with primary hypothyroidism usually implies over treatment. The serum-free T4 index in patients receiving adequate levothyroxine medication is usually in the upper half of the normal range. However, unless the blood TSH concentration is elevated and problems of bioavailability or compliance occur, a free T4 index measurement is not normally necessary for periodic monitoring of patients receiving a steady levothyroxine dosage.

**Initial Conditions:**

We calculate the initial concentration of LT4 in the blood serum as follows

$$x_0 = \frac{Initial\ dose}{3\ L}$$

where 3L is the volume of distribution in the blood serum.The initial state of TSH and antibodies can be measured at the steady state levels for each patient that can be identified from patient date. The initial state can be also detected from lab report.

Parameters can be calculated from simulation and some of them calculated using half life of the variables.

| **Parameter description Value** | | | |
|---|---|---|---|
| ***Parameter*** | ***Description*** | ***Value*** | ***Units*** |
| $k_1$ | Maximum Uptake rate of LT4 | 2.791 X $10^{-2}$ | μg/(ml *l*day) |
| $k_2$ | Elimination rate of LT4 | 0.1155 | 1/day |
| $k_3$ | Maximum Secretion rate of TSH in the absence of FT4 in the blood | 5000 | mU/(l*day) |
| $k_4$ | Elimination rate of TSH | 16.635 | 1/day |
| $k_5$ | Basic growth rate of functional thyroid size | 0.033 | 1/day |
| $k_6$ | Growth rate of thyroid size proportional to the ratio of TSH with respect to Thyroid size | 1.21 | U/(ml*day) |
| $k_7$ | Inactive thyroid rate | 0.017 | ml/(mg*day) |
| $k_8$ | Maximum production rate of Antithyroid Anitibodies | 6.61 | U/(ml*day) |
| $k_9$ | Elimination rate of Antithyroid Anitibodies | 0.033 | 1/day |
| $k_a$ | Michealis Menten Constant for half maximal uptake rate of LT4 | 0.358 | mg/l |

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| **Parameter description Value** | | | |
|---|---|---|---|
| ***Parameter*** | ***Description*** | ***Value*** | ***Units*** |
| $k_c$ | Michealis Menten Constant for half maximal secrertion rate of TSH | 0.073 | mg/l |
| $k_d$ | Inhibition rate of Antithyroid Anitibodies | 1.8 | mg/l |

TABLE I. APPROXIMATE PARAMETERS V

## V Model Validation:

In this section, we validate the model numerically for finite time and compare it with time course data. Here we have choosen four patient report which has complete data for our work and calculate the needed parameters which is differ from each one. The reference range of TSH for euthyroid state is 2.5 to 4 (mU/L), thyroid gland can be between 15 to 30 (mL) and value of antibodies is zero for non diseased state.

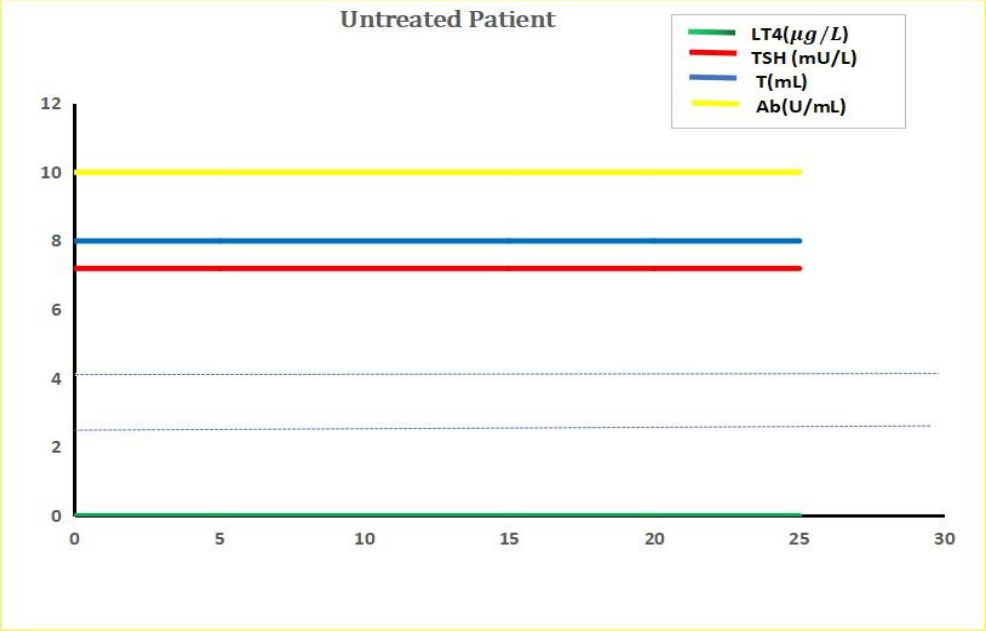


Fig. 2 represent the $E_0$=(0,7.2,8,10), this is the initial report when patient headed for the treatment. Here x axis denote in time ( in days). Without LT4 treatment (i.e., n(t) = 0), shows the patient steady state levels remains the same for 25 days.

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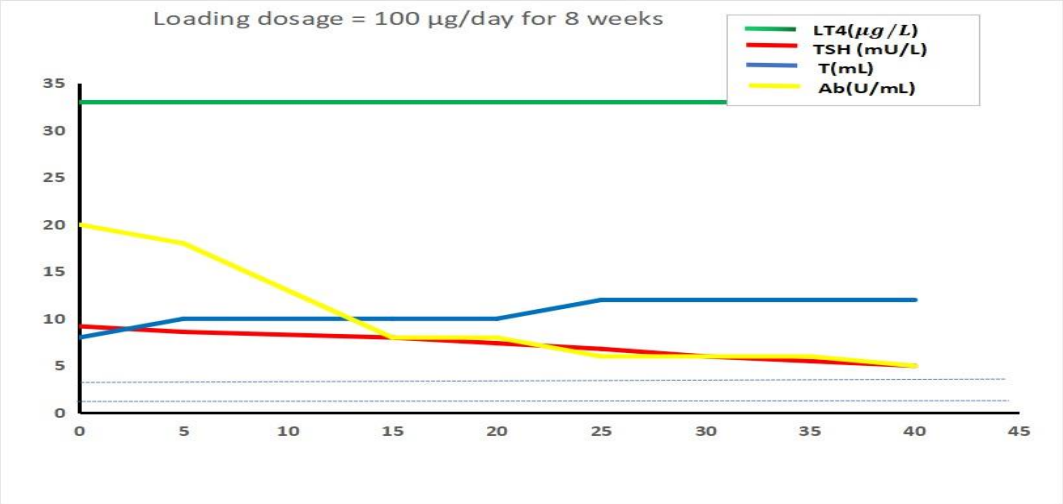


Fig. 3 denote $E_0$= (33,9.2,8,20). Suppose the loading dosage =100µg/day for 6 weeks which results in patients TSH levels close to the normal range. But TSH could not reach the normal range of Euthyroid state which means patient has to continue the treatment for some more days.

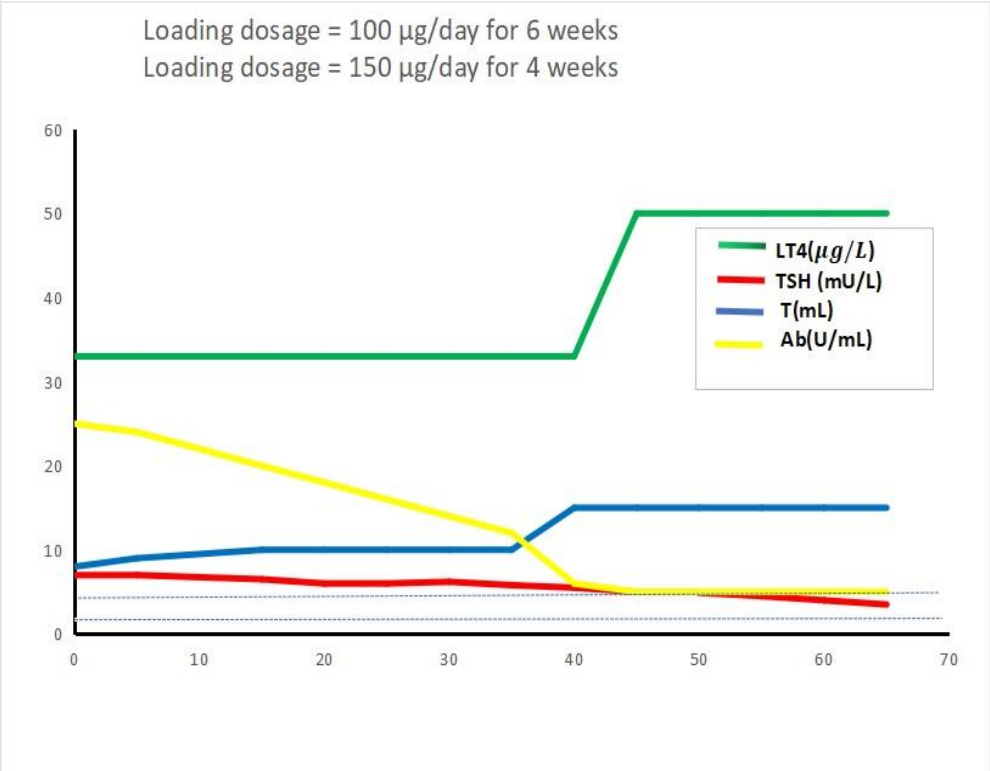


Fig. 4 denote $E_0$= (33,7,10,25). Suppose the loading dosage =100µg/ day for 6 weeks and raising the dosage as 150µg/ day for next four weeks which results in patients TSH levels close to the normal range. In above figure the value of TSH is nearing to the normal reference range, whitch means the patient heading to the Euthyroid state.

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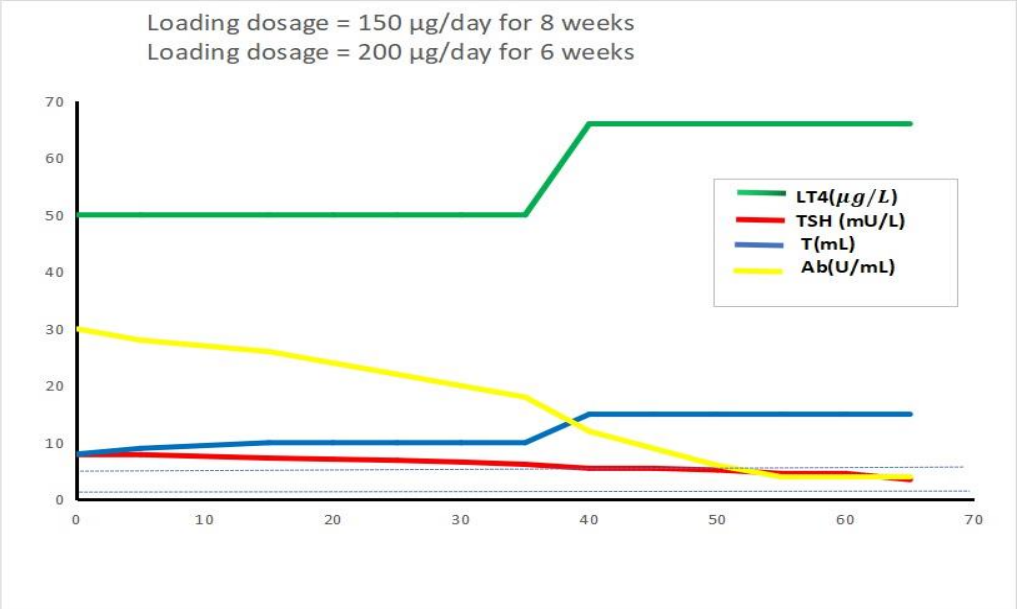


Fig. 5 denote $E_0$= (50,7.9,6,30). Suppose the loading dosage =150µg/ day for 8 weeks and raising dosage is 200µg /day for 6 weeks which results in patients TSH levels close to the normal range also antibodies are getting reduced by this treatment. By this the patient achieved the euthyroid state.

## VI. Conclusion

We created a mathematical model for hypothyroidism patients to characterise the time course of tsh levels following levothyroxine(LT4) medication and TSH levels within the physiological range (0.4 to 2.5 mU/l) with the optimal maintenance dosage plan. Our aim is to describe the natural history of hypothyroidism with LT4 treatment, as well as restore TSH levels with the proper dosage and schedule. The model was created in the form of four variable, systm of ordinary differential equations with twelve parameter. LT4 concentration, Thyroid stimulating hormone (TSH) concentration, TRAb concentration and thyroid's functional size are the state variables. Some paramet the nature of hypothyroidism ers were discovered using patient data, while the rest was obtained from the literature. Since the nature hypothyroidism differs from patient to patient, each patient's treatment with LT4 is unique.The proper dosage loading is crucial in maintaining a normal TSH value,because overdosing can lead to hyperthyroidim. Undershooting, Overshooting and relapses might all be avoided using methodolgy. In the essence, the model canpredict when to suspend the medication, which helps with determinig how muchLT4 to take orally over time. To validate the model, we collected data from four hypothyroid individuals. With the right LT4 dose schedule, clinical transition from hypothyroidism to euthyroidism can be accomplished quickly.

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