

Article

Automatic Levothyroxine Dosing Algorithm for Patients Suffering from Hashimoto's Thyroiditis

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Abstract: Hypothyroidism is a condition where the patient's thyroid gland cannot produce sufficient thyroid hormones (mainly triiodothyronine and thyroxine). The primary cause of hypothyroidism is autoimmune-mediated destruction of the thyroid gland, referred to as Hashimoto's thyroiditis. A patient's desired thyroid hormone concentration is achieved by oral administration of thyroid hormone, usually levothyroxine. Establishing individual levothyroxine doses to achieve desired thyroid hormone concentrations requires several patient visits. Additionally, clear guidance for the dosing regimen is lacking, and significant inter-individual differences exist. This study aims to design a digital automatic dosing algorithm for patients suffering from Hashimoto's thyroiditis. The dynamic behaviour of the relevant thyroid function is mathematically modelled. Methods of automatic control are exploited for the design of the proposed robust model-based levothyroxine dosing algorithm. Numerical simulations are performed to evaluate the mathematical model and the dosing algorithm. With the help of the developed controller thyroid hormone concentrations of patients, emulated using Thyrosim, have been regulated under the euthyroid state. The proposed concept demonstrates reliable responses amidst varying patient parameters. Our developed model provides a useful basis for the design of automatic levothyroxine dosing algorithms. The proposed robust feedback loop contributes to the first results for computer-assisted thyroid dosing algorithms.

Keywords: Hashimoto's thyroiditis; HPT-axis; mathematical thyroid model; discrete controller; robust stability



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1. Introduction

Hypothyroidism affects up to 5% of the general population, with an additional 5% remaining undiagnosed and is more common in women than in men [1,2]. Iodine deficiency is the most common cause of all thyroid disorders, but in iodine sufficiency, Hashimoto's thyroiditis is the most common cause of thyroid failure, which results in hypothyroidism [2].

The thyroid gland is a butterfly-shaped gland located in front of our neck. It is responsible for generating the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) mainly. The blood serum concentration of the thyroid hormones is maintained in the human body with the help of the hypothalamic–pituitary–thyroid axis (HPT axis), see Figure 1. The concentration of T_3 and T_4 hormones acts as a negative feedback signal that feeds to the hypothalamus and pituitary gland. Corresponding to this negative feedback, the hypothalamus and the pituitary gland secrete the thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH), respectively. When the concentration of T_4 and T_3 increases, due to this biological closed-loop (HPT-axis), the concentration of TRH and TSH decreases, which results in a decrease in T_4 and T_3 hormone concentrations.

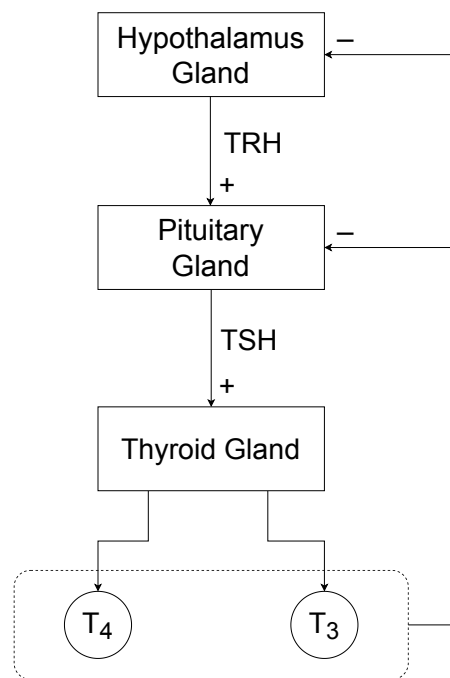


Figure 1. Block diagram of hypothalamic–pituitary–thyroid axis (HPT axis), explaining thyroid hormone regulation in the human body.

1.1. Medical Problem

The thyroid gland consists primarily of follicle cells. These follicle cells are responsible for the production of T_3 and T_4 hormones. When TSH reaches the follicle cells located in the thyroid gland, it starts stimulating follicle cells to produce T_3 and T_4 hormones. In the case of Hashimoto's thyroiditis, the human immune system exerts autoimmunological effects on the thyroid gland including, amongst others, the production of thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb). These antibodies are partially responsible for blocking processes responsible for thyroid hormone production within the follicle cells [3]. This blocking of TSH receptors results in a decrease in T_3 and T_4 hormone concentrations (less than the concentration required by human body, i.e., T_4 and T_3 , 5–12 $\mu\text{g}/\text{dL}$ and 0.8–1.9 ng/mL , [4], correspondingly). Due to the HPT-axis, the hypothalamus and pituitary gland increase TRH and TSH secretion. Hence, the blood serum concentration of TSH exceeds its normal range (i.e., 0.5–5.0 mU/L see e.g., [4]). In the case of Hashimoto's thyroiditis patients are diagnosed with low T_3 and T_4 concentrations and high TSH concentration. The diagnosis of Hashimoto's thyroiditis is usually made by confirming present hypothyroidism (i.e., subclinical hypothyroidism with elevated TSH and decreased thyroid hormone concentrations) in conjunction with elevated TPOAb and TgAb.

Thyroid hormones play a critical role in, e.g., growth and energy metabolism [5]. Therefore, changes in the concentration of thyroid hormones can lead to multiple adverse clinical consequences such as reduced quality of life with symptoms such as fatigue, increased cardiovascular risk and weight gain [6]. A so-called Myxedema coma can be the outcome of a long-standing untreated and severe hypothyroidism [7].

In clinical routine, hypothyroid patients suffering from Hashimoto's thyroiditis usually take levothyroxine (LT_4) oral tablets on a regular, i.e., usually daily, basis. The amount of medication (LT_4 dosage) is regulated by physicians according to the blood serum concentration of TSH , free thyroxine (FT_4) and free triiodothyronine (FT_3), as well as some clinical parameters such as body weight. Therefore, a visit to the physician is required under the current treatment procedure. The frequency of these visits depends on the condition of the patient's thyroid gland (e.g., whether the patient is suffering from overt or subclinical

hypothyroidism) and stages of treatment (i.e., at the initial stages, monthly visits are usually required, later, even once or twice a year is also possible).

This study aims to develop an automated dosage recommendation system that obeys all the requirements of LT_4 dosing (see Section 3.3.1). For the systematic construction of the automated dosage recommendation system, a mathematical model is developed that captures the desired human body parameters. Later, with the help of this developed mathematical model, a mathematical model-based control strategy is designed. Both the model and the control strategy are validated using the Thyrosim model [4,8–10] and numerical simulation framework.

The development of an automated levothyroxine dosage recommendation system will decrease patients' dependency on in-person meetings with physicians. That will eventually lead to an improvement in the current treatment methodology, in which frequent visits to physicians are required (i.e., 4–6 weeks in the initial stages of treatment and twice a year in later stages of treatment).

1.2. Existing Mathematical Models of Human Thyroid Hormone Regulation

A compartment model was developed by Pandiyan [11] to describe thyroid hormone regulation in patients suffering from Hashimoto's thyroiditis. This mathematical model does not encapsulate the effect of exogenously administered thyroxine hormone (LT_4) on patient dynamics, which is the main scope of our study. The mathematical model presented in [12] captures both the effect of LT_4 dosage on TSH and FT_4 dynamics. However, the TSH dynamics is not required in the results presented in this paper.

In [13], a mathematical model-based optimal LT_4 and levotriiodothyronine (LT_3) therapy for patients suffering from hypothyroidism was designed. The study addresses the problem of identifying the optimal dosages of LT_4 and LT_3 and analysing the effect of LT_4 monotherapy over LT_4/LT_3 combined therapy on blood serum concentrations of thyroid parameters. A model predictive controller (MPC) is employed as an optimal dosage recommender, which determines the optimal dosage of LT_4 and LT_3 concerning thyroid hormone concentrations. The model used in the MPC control algorithm is presented in [14–16]. In contrast to the model proposed in this paper, this MPC-employing model is much more complex and captures dynamics of human parameters which are typically measured during the regular patient's appointments (e.g., TSH , FT_4). This additionally increases the computational costs of the MPC algorithm. In this paper, it is demonstrated that a control approach which is comparatively less computationally costly is still able to robustly keep the patient's thyroid hormone concentration within the reference range.

Numerical Simulation of Hashimoto Patients Using Thyrosim

Thyrosim is a web application developed by UCLA laboratory. It was designed and developed primarily for researchers, clinicians and others who are interested in thyroid hormone regulation. It is a well-validated simulation of human thyroid hormone regulation [17]. Thyrosim has demonstrated its ability to reproduce a wide range of clinical data studies and can display hormonal kinetic responses to different oral dosages of LT_4 and LT_3 [17]. Thyrosim provides dynamic responses of total thyroxine (TT_4), total triiodothyronine (TT_3), FT_4 , FT_3 and TSH over time, for a 70 kg human [9,10]. It has also been upgraded to predict LT_4 and LT_3 replacement therapy in paediatric patients [8].

Thyrosim is based on a highly complex mathematical model. This mathematical model consists of 13 differential equations and 60 different mainly patient-specific parameters [4,8–10]. Therefore, designing a controller on the basis of this mathematical model is a highly complicated task. This complexity in Thyrosim's mathematical model motivated us to develop a mathematical model of human thyroid hormone regulation, which captures the main FT_4 -dynamics and can be employed as a controller design model.

2. Methods

2.1. Development of an Automated Dosage Recommendation System

This study aims to develop an automated dosage recommendation system for the hypothyroid patients suffering from Hashimoto’s thyroiditis. For designing such an automated dosage recommendation system, a mathematical model of human thyroid hormone regulation has been developed. With the help of this developed mathematical model, a model-based controller was designed. This designed controller will serve as an automated dosage recommendation system. In this study, Thyrosim is employed as a so-called “virtual” patient to validate both the model and the dosing algorithm.

2.2. Simulation of a Patient Suffering from Hashimoto’s Thyroiditis

For simulating a patient suffering from clinical hypothyroidism, the T_4 and the T_3 secretion rates have been adjusted by using the graphical interface provided in the Thyrosim web application (<http://biocyb1.cs.ucla.edu/thyrosim/cgi-bin/Thyrosim.cgi>, accessed on 10 May 2022). The values of T_4 and T_3 secretion rates is 17% of the thyroid gland’s total secretion rate (which demonstrates that the patient is dependent on exogenous administration of thyroid hormones). Correspondingly, the absorption rate of oral LT_4 dosage is set at 83% (the bioavailability of oral LT_4 dosage in hypothyroid patients is slightly more than 80% [18]).

2.3. Validation of Developed Dosing Strategy

With the help of parameter variation in Thyrosim’s mathematical model, 50 different patients are simulated and statistical analysis is performed. All the simulated patients are treated with our developed automated dosing strategy. The developed system should be compatible with all the possible parametric uncertainties and must be able to maintain patients’ FT_4 concentration within the reference range.

3. Results

In this section, the development of the mathematical model-based dosing algorithm is described. In order to evaluate the functioning of this developed dosing algorithm, it is implemented with Thyrosim and simulation-based results are presented.

The results of this study were obtained using MATLAB/Simulink®, version 9.5.0.1298439 (R2018b) on a standard computer (Intel(R) Core(TM) i7-5600U CPU @ 2.60 GHz processor with 8 GB RAM).

3.1. A Control-Oriented Dynamic Model of the Thyroid Gland

A hypothyroid patient suffering from Hashimoto’s thyroiditis is dependent on the exogenous source of T_4 hormones (LT_4 tablets mainly). Therefore, the developed mathematical model needs to capture the effect of exogenous thyroxine (LT_4) on the T_4 dynamics. The well-known Michaelis-Menten equation describes enzyme-substrate relations and has been successfully used for modelling reaction dynamics on an abstract level i.e., without a too detailed description of the considered process [19]. Therefore, the Michaelis–Menten equation [19] is also used for developing this model. The developed mathematical model consists of two state variables. The total blood serum concentration of exogenous T_4 is represented by the state variable x_1 , the variable x_2 captures the total FT_4 concentration in blood serum. The proposed model is given by

$$\frac{dx_1}{dt} = d - k_{exc}x_1, \tag{1a}$$

$$\frac{dx_2}{dt} = \frac{v_{max}TSH}{k_m + TSH} + k_{reac}x_1 - k_{sec}x_2, \tag{1b}$$

where

k_{exc} stands for elimination rate of orally administrated levothyroxine (h^{-1}),

k_{sec} is the natural elimination rate of FT_4 (h^{-1}),

v_{max} represents the maximum rate achieved by the system ($\mu\text{mol/h}$),
 k_m is the Michaelis constant (μmol),
 k_{reac} models the effect of orally administered LT_4 (ppm).

The dosage input d (μmol) is the exogenously infused input rate of oral LT_4 . This exogenous administration of the T_4 hormone has a significant positive effect on the patient’s total thyroxine (TT_4) concentration. The FT_4 concentration in blood serum is approximately 0.02% of TT_4 concentration [20]. Therefore, an increase in TT_4 concentration will also increase the patient’s FT_4 concentration. The patient’s total FT_4 concentration is a combination of FT_4 concentration produced endogenously by the thyroid gland (represented by the Michaelis–Menten equation [19]) and the positive effect of total exogenous T_4 hormone in the blood (with the help of LT_4 tablets). For hypothyroid patients, the half-life of T_4 hormone is 9–10 days [21], which represents the natural elimination rate k_{sec} of FT_4 .

In the developed model, v_{max} , k_m and k_{reac} are patient-specific constants. The values of these parameters must be identified according to the considered patient. As already mentioned above, Thyrosim is regarded as a “virtual” patient. Therefore, the values of these patient-specific parameters are identified with the help of Thyrosim.

3.1.1. Parameter Identification

Some parameters (k_m , v_{max} and k_{reac}) of the developed mathematical model need to be identified with respect to an individual patient. In this section, a least-squares algorithm is used to minimise the cost function, see Figure 2.

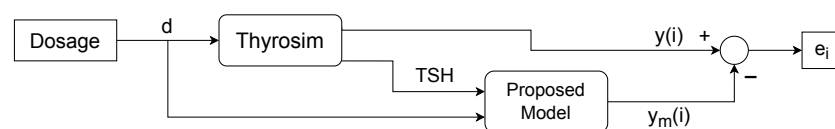


Figure 2. For parameter identification, both models receive the same amount of LT_4 dosage.

$$J(p) = \sum_{i=0}^N e_i^2 \tag{2a}$$

with,

$$e_i = y(i) - y_m(i) \text{ and } P = [k_{reac} \quad k_m \quad v_{max}]^T \tag{2b}$$

where $y(i)$ is the output (FT_4 concentration) by Thyrosim for input dosage d . The signal $y_m(i)$ represents the output (FT_4 concentration) generated by the developed model for the same input dosage d and TSH (an output generated by Thyrosim corresponding to input dosage d) at hour i . The constant N represents the time duration of the performed simulation.

Optimization Problem

For identifying the parameters k_{reac} , k_m and v_{max} , the optimization problem

$$\begin{aligned} &\arg \min_p J(p) \\ &\text{s.t.} \\ &\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix} < p \leq \begin{bmatrix} k_{reac_{max}} \\ k_{m_{max}} \\ v_{max_{max}} \end{bmatrix} \end{aligned}$$

needs to be solved. The implementation of minimization of the cost function $J(p)$ was realized with the Matlab function ‘fminsearch’. The optimization constraints need to be defined in such a manner that the value of estimated parameters must be “realistic” (e.g.,

v_{max} , k_m and k_{reac} must be positive). The identified values of parameters are listed in Table 1.

Table 1. Identified parameters of the proposed model (1a), (1b) for capturing the dynamics of a patient emulated by Thyrosim.

| Constants | Estimation |
|------------|--------------------------------------|
| k_{reac} | 7.25 ppm |
| k_m | $9.504 \cdot 10^3 \mu\text{mol}$ |
| v_{max} | $2.19 \cdot 10^{-4} \mu\text{mol/h}$ |

Model Assessment

A comparison between the FT_4 concentration generated by the proposed model and Thyrosim is presented to assess the quality of the proposed model.

In the assessment of the proposed model, we provided the same amount of dosage to Thyrosim and to the proposed model (1). In Figure 3, both mathematical models received 50 $\mu\text{g/day}$ of dosage in the first month, 80 $\mu\text{g/day}$ in the second month and 110 $\mu\text{g/day}$ in the third month, see Figure 3a. The values of the identified parameters (k_m , v_{max} and k_{reac}) are kept constant throughout the simulation. Thyrosim also captures daily hormonal variations of thyroid hormone parameters. Note that the proposed model in Equation (1) does not replicate these daily hormonal variations of FT_4 concentration, see Figure 3b.

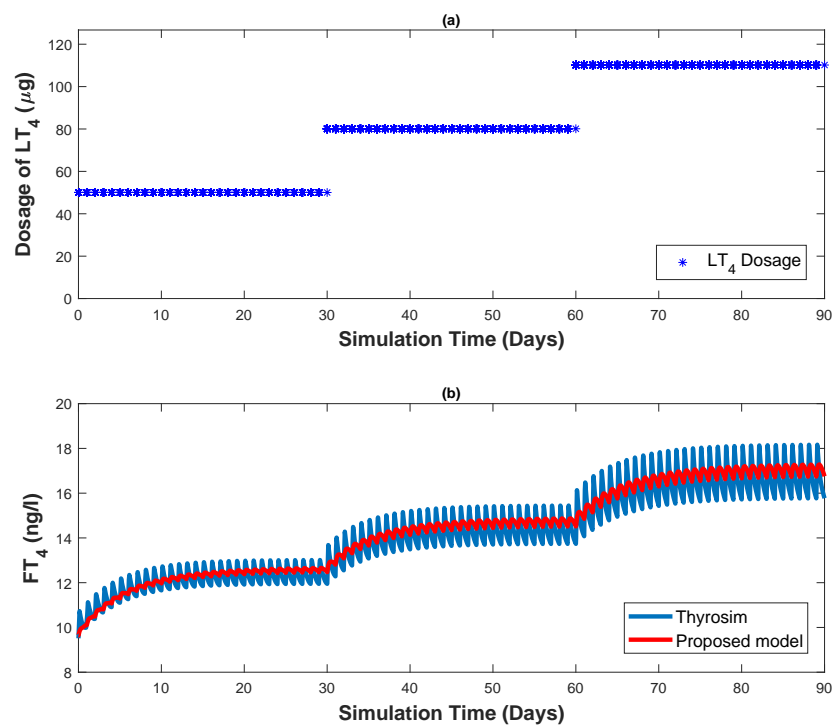


Figure 3. Numerical simulation is used for parameter identification. The same amount of dosage is provided to the proposed model and Thyrosim. A comparison between the two generated outputs (FT_4 concentration generated by Thyrosim and proposed model) is represented.

From the results depicted in Figure 3, it is observable that the FT_4 concentration generated by the proposed model always lies in the range of daily hormonal variations of FT_4 concentration (generated by Thyrosim). As a result, the proposed model can be used as a mathematical model for designing an automated dosage recommendation system for Thyrosim, which prescribes a daily dosage.

3.2. Some Basic Control System-Related Properties of the Model

Analysing control theory-related system properties of the proposed mathematical model is an intended part of controller design. The system's eigenvalues characterize its response to a given input and non-vanishing initial settings of the state variables, whereas controllability describes whether the system can be guided from an arbitrary initial state to a target state over a finite time interval using the actuating signal [22]. The system should be controllable to attain the desired final state by using a controlled input. Note that the proposed model can be rewritten as

$$\dot{x} = Ax + bd + Vp \quad (3a)$$

$$y = c^T x \quad (3b)$$

with,

$$A = \begin{bmatrix} -k_{exc} & 0 \\ k_{reac} & -k_{sec} \end{bmatrix}, \quad b = \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

$$V = \begin{bmatrix} 0 \\ v_{max} \end{bmatrix}, \quad c^T = [0 \quad 1]$$

$$\text{and } p = \frac{TSH}{km + TSH}$$

Some system properties are:

- (a) The eigenvalues of the system are $-k_{exc}$ and $-k_{sec}$, which represent how fast the system will react in response to provided LT_4 dosage;
- (b) Controllability: It can be easily checked that the developed system is controllable. Therefore, it is possible to achieve a certain level of FT_4 concentration in a finite time interval by using a controlled LT_4 dosage.

3.3. Controller Design

This study aims to develop an automated dosage recommendation system that enables us to automate the dosage of LT_4 . Exogenous administration of hormones is a highly sophisticated task. The developed controller must follow all the desired guidelines mentioned in the FPI (full prescription information) of LT_4 dosing (e.g., the dosage must be recommended incrementally, the sampling time must be according to patient condition). Therefore, the designed controller must obey all the following desired requirements:

3.3.1. Requirements for an Automated Dosing Strategy

- (i) The mathematical model (1) consists of different biological parameters that vary from patient to patient. Therefore, a "robust" dosage administration is mandatory;
- (ii) Oral administration of hormones will result in a sudden increment of patient blood serum concentration of FT_4 . Therefore, the designed controller is not allowed to react "too fast";
- (iii) A larger daily dosage exceeding 150 μg in children and 500 μg in adults may produce serious or even life-threatening manifestations of toxicity when administered for longer time periods [23]. Consequently, limitations on the prescribed dosage are essential. Initially, at the beginning of the therapy, a small amount of dosage is prescribed. These dosages are increased incrementally (12.5 μg to 25 μg) until the patient reaches the euthyroid state. Therefore, a defined rate limiter is necessary in the design of an automated dosage recommendation system to control the change in the recommended dosage. Dosages are recommended to the patient with the help of blood serum concentrations of different thyroid hormone parameters (FT_4 , TPOAb, TSH, etc.). Measurement of these parameters initially take place every 4–6 weeks (this sampling time increases in the later stages of treatment, once or twice a year is also possible). Once the parameters are measured, the physician

- recommends an amount of LT_4 dosage. This recommended dosage must be constant until the next measurement of thyroid parameters. Therefore, it is required to design a discrete-time controller with a sampling rate of between 4 and 6 weeks;
- (iv) A dosage above 200 μg per day must require consultation with a physician before recommendation. Therefore, a saturator is an intended part of this proposed dosage recommendation system that saturates dosage above 200 μg per day;
 - (v) Steady-state requirements: When the patient reaches euthyroid state (normal condition of thyroid hormones), the amount of the dosage recommended to the patient should be constant, unless there are some variations in blood serum concentrations of thyroid hormones.

3.3.2. Selection of the Controller Type

The recommended dosage must be constant between the two diagnoses of patient thyroid parameters (measurement of thyroid gland parameters). Only after the measurement of the thyroid hormones is a change in the recommended amount of dosage possible. Therefore, designing a discrete-time controller is a necessary part of this study. The discrete-time controller’s sampling time must correspond to the patient’s laboratory measurement interval (initially, the diagnosis time is 4–6 weeks, it will increase in the later stages of treatment).

The goal behind designing an automated dosage recommendation is not to achieve a particular FT_4 concentration but to achieve the euthyroid state (9.2 to 16.0 ng/L [24], depending upon patient’s body mass index (BMI) and other parameters such as age or history of chronic disease). Hence, it is recommendable to design a non-integrating discrete-time controller with a sampling time of 30 days (initially, monthly visits to the physician are required).

Calculating the Continuous-Time Transfer Function of the Proposed Model

The proposed model is a so-called linear MISO system (Multi-Input and Single Output). From Equations (3a) and (3b), the output (the Laplace transform of the function $y(t)$) is denoted by $\bar{y}(s)$, i.e., $\bar{y}(s) = \mathcal{L}\{y(t)\}$ $y(t)$ in the Laplacian domain can be computed by

$$\bar{y}(s) = \begin{bmatrix} G(s) & S(s) \end{bmatrix} \begin{bmatrix} \bar{d}(s) \\ \bar{p}(s) \end{bmatrix} \tag{4a}$$

with the transfer functions

$$G(s) = \frac{k_{\text{reac}}}{s^2 + (k_{\text{sec}} + k_{\text{exc}})s + k_{\text{sec}}k_{\text{exc}}} \text{ and } S(s) = \frac{v_{\text{max}}}{s + k_{\text{sec}}} . \tag{4b}$$

The transfer function $G(s)$ is regarded as the plant transfer function and $S(s)$ represents the transfer function capturing the dynamics from TSH to the output y .

If the patient is suffering from clinical hypothyroidism, most of the FT_4 concentration presented in the patient body will be due to the recommended dosage (exogenous infusion of thyroxine). Hence, we assume the effect of TSH disturbance (endogenously produced FT_4) to be negligible.

Discretization of Plant

The patient is allowed to take one tablet of LT_4 per day. Hence, we use the impulse-invariant discretization [25] method for discretizing the plant $G(s)$, which results in the discrete-time transfer function.

$$G(z) = \frac{A(q_2 - q_1)z}{z^2 - (q_1 + q_2)z + q_1 \cdot q_2} \tag{5a}$$

with

$$A = \frac{k_{reac}}{k_{sec} - k_{exc}}, q_1 = e^{-k_{sec} \cdot T_d}, q_2 = e^{-k_{exc} \cdot T_d} \tag{5b}$$

Due to the high sampling time (≈ 28 days), the value of $q_1 \cdot q_2$ is approximately zero, which yields

$$G(z) = \frac{A(q_2 - q_1)}{z - (q_1 + q_2)} \tag{5c}$$

Using, $q_2 - q_1 = p_1$ and $q_1 + q_2 = p_2$ yields

$$G(z) = \frac{A \cdot p_1}{z - p_2} \tag{5d}$$

Designing the Rate Limiter

The patient’s hormone concentration is maintained with the help of a developed dosage recommendation system. Any sudden change in these hormones (e.g., T_4 , TSH etc.) is unaffordable for the patient’s biological condition. The recommended dosage of LT_4 must be adjusted according to the mentioned requirements (see Section 3.3.1). Hence, the development of a designated rate limiter is an intended part of this research. Using the unity feedback loop as depicted in Figure 4 with the transfer function,

$$K_r(z) = \frac{k_r}{z - 1}$$

the rate limitation is realized within the automated dosing algorithm. The parameter k_r is the maximum admissible change in the output (e.g., recommended dosage). Once k_r is defined, the change in output is ensured to not exceed the defined value of k_r (the desired change in recommended dosage 12.5 μg to 25 μg).

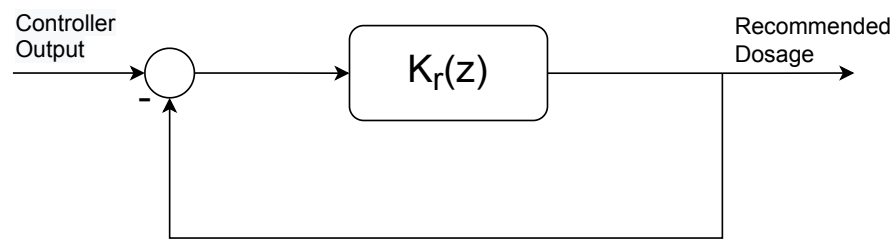


Figure 4. Sketch of the proposed rate limiter to control the rate of change in recommended dosage.

The overall transfer function of the rate limiter describing the dynamics from the controller’s output to the plant’s input is given by

$$K_{rz}(z) = \frac{k_r}{z - \Delta}, \Delta = 1 - k_r.$$

In order to design the controller transfer function $R(z)$, the rate limiter $K_{rz}(z)$ and the plant $G(z)$ are considered as controller design transfer function (total plant in Figure 5).

$$G_p(z) = K_{zr} \cdot G(z) \tag{6a}$$

The values of A , p_1 and p_2 are mentioned in Equation (5a) and

$$G_p(z) = \frac{A \cdot p_1 \cdot k_r}{z^2 - (p_2 + \Delta)z + p_2 \cdot \Delta} = \frac{\mu_0}{z^2 + v_1z + v_0} \tag{6b}$$

$$\frac{\mu(z)}{v(z)} = \frac{\mu_1z + \mu_0}{z^2 + v_1z + v_0} \tag{6c}$$

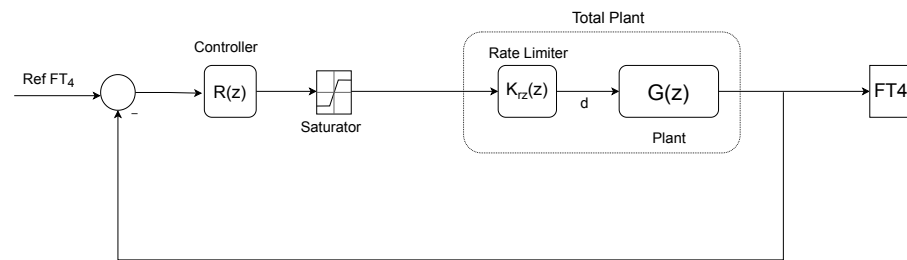


Figure 5. Block diagram of the designed feedback loop including saturator and rate limiter.

The pole assignment method, see, e.g., [26], is used for designing a discrete-time controller

$$R(z) = \frac{b_1z + b_0}{a_1z + a_0} = \frac{b(z)}{a(z)}. \tag{7a}$$

The closed-loop transfer function of the developed system depicted in Figure 5 is

$$T(z) = \frac{b(z)\mu(z)}{v(z)a(z) + b(z)\mu(z)} = \frac{\mu_T(z)}{v_T(z)}. \tag{7b}$$

Denoting $v_T(z)$ as the is desired characteristic polynomial of $T(z)$, i.e.,

$$v_T(z) = w_3z^3 + w_2z^2 + w_1z + w_0, \tag{7c}$$

the poles of the characteristic polynomial can be placed at desired locations specified by $w(z)$. By solving

$$\begin{bmatrix} v_0 & 0 & \mu_0 & 0 \\ v_1 & v_0 & \mu_1 & \mu_0 \\ v_2 & v_1 & 0 & \mu_1 \\ 0 & v_2 & 0 & 0 \end{bmatrix} \begin{bmatrix} a_0 \\ a_1 \\ b_0 \\ b_1 \end{bmatrix} = \begin{bmatrix} w_0 \\ w_1 \\ w_2 \\ w_3 \end{bmatrix} \tag{7d}$$

the values a_1 , a_0 , b_1 and b_0 and hence the controller $R(z)$ are calculated

When the poles of characteristic polynomial $v_T(z)$ are placed near $z = 0$, then the system will react too fast. That is not recommendable for biological systems. When the poles of $v_T(z)$ are placed near -1 or $+1$, then the developed system has overshoots and it also negatively effects the robustness of the system, which is undesirable. Currently, all the poles of $v_T(z)$ are placed at $z = -0.01$, because at this point, the developed system shows less overshoot and the system is not reacting too fast.

3.3.3. Robustness Analysis of the System

The developed controller must be suitable for all patients and must be able to deal with the possible uncertainties in the parameters of the proposed model (1). In the proposed model, the bioavailability of LT_4 drug is uncertain, which will vary from slightly above 80% to 64% [18] (hypothyroidism slightly above 80% and the under-fastened condition bioavailability of LT_4 decrease to 64%).

To analyse the robust stability of the developed system for the mentioned uncertainty (bioavailability of LT_4) the Jury, Pavlidis theorem [27] is used. This theorem states that the polynomial family $p(z, Q) = \{p(z, q) \mid q \in Q\}$ with $(p(z, q) = a_0(q) + a_1(q)z + a_2(q)z^2 \dots + a_n(q)z^n)$ $p(z, q)$ continuous is Schur-stable if and only if:

- (i) There exists a $q^0 \in Q$ for which the polynomial $p^0(z) = p(z, q^0)$ is Schur-stable;
- (ii) $p(1, q) \neq 0, \forall q \in Q$;
- (iii) $p(-1, q) \neq 0, \forall q \in Q$;
- (iv) $\det S(q) \neq 0, \forall q \in Q$, where $S(q) = X(q) - Y(q)$ and (omitting the dependency on q)

$$X = \begin{bmatrix} a_n & a_{n-1} & a_{n-2} & \dots & a_2 \\ 0 & a_n & a_{n-1} & \dots & a_3 \\ 0 & 0 & a_n & \dots & a_4 \\ \vdots & \vdots & \vdots & \dots & \vdots \\ 0 & 0 & 0 & \dots & a_n \end{bmatrix}, Y = \begin{bmatrix} 0 & 0 & 0 & \dots & a_0 \\ \vdots & \vdots & \vdots & \dots & \vdots \\ 0 & 0 & a_0 & \dots & a_{n-4} \\ 0 & a_0 & a_1 & \dots & a_{n-3} \\ a_0 & a_1 & a_2 & \dots & a_{n-2} \end{bmatrix}$$

where matrix $X(q)$ and $Y(q)$ have $(n - 1)$ rows and $(n - 1)$ columns, n is the order of polynomial $p(z, q)$.

The characteristics polynomial $v(z)a(z) + u(z)a(z)$ of the developed system is

$$a_1z^3 + (a_0 - a_1(p_2 + \Delta))z^2 + [a_1p_2\Delta - a_0(p_2 + \Delta) + Ap_1k_rb_1]z + a_0p_2\Delta + b_0Ap_1k_r).$$

The values of patient-based parameters A, p_1 and p_2 are mentioned in Equations (5a) and (5d). The characteristic polynomial family $\{v_T(z, k_{exc}) \mid k_{exc} \in [0.16, 0.36]\}$ is Schur-stable, if it follows all the mentioned conditions by Jury and Pavlidis [27], i.e.:

- (i) $v_T(z, 0.26)$ is Schur-stable;
- (ii) $v_T(1, k_{exc}) \neq 0, \forall k_{exc} \in [0.16, 0.36]$, see Figure 6a;
- (iii) $v_T(-1, k_{exc}) \neq 0, \forall k_{exc} \in [0.16, 0.36]$, see Figure 6b;
- (iv) $\det S(k_{exc}) \neq 0, \forall k_{exc} \in [0.16, 0.36]$, where $S(k_{exc}) = X(k_{exc}) - Y(k_{exc})$, see Figure 6c.

The characteristic polynomial $v_T(z)$ obeys all the conditions mention by the Jury, Pavlidis theorem, for $k_{exc} \in [0.16, 0.36]$. This is also illustrated by Figure 6. Therefore, the system is robust and stable for the provided parameter uncertainty $k_{exc} \in [0.16, 0.36]$.

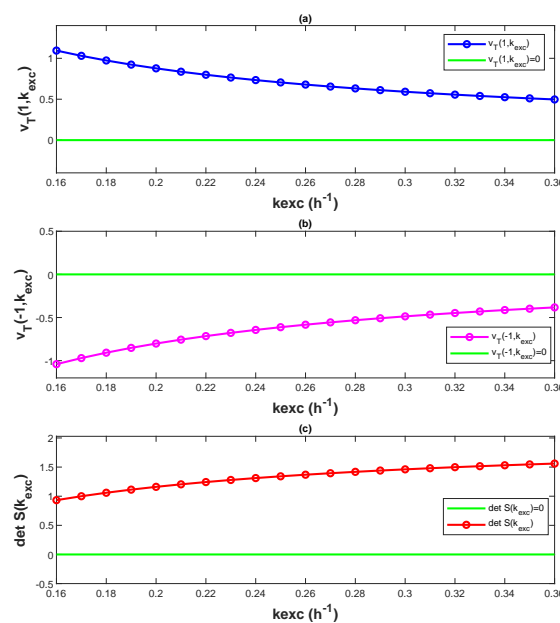


Figure 6. Robust stability analysis of system with Jury, Pavlidis theorem.

3.4. Evaluation of Automated Dosage Recommendation System

The developed automated dosage recommendation system is used to maintain the FT_4 concentration of a patient modelled by Thyrosim, see Figure 7.

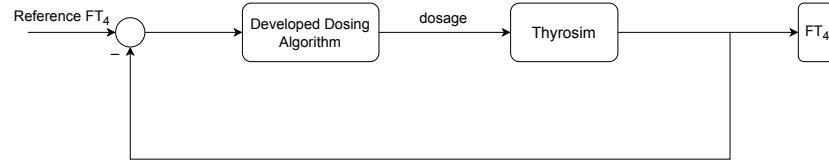


Figure 7. Structure of the implemented simulation setup for evaluating the designed dosing algorithm.

Figure 8a shows the amount of dosage prescribed by the developed automated dosage recommendation system. Figure 8b represents the FT_4 concentration generated by Thyrosim for the corresponding amount of dosage. The total time of the simulation is 12 months. For the entire simulation, the reference FT_4 concentration is constant at 13 ng/L. The LT_4 dosage recommended to the patient is varied by 12.5 $\mu\text{g}/\text{month}$. The recommended amount of dosage becomes constant once the patient’s FT_4 concentration settles within the reference range.

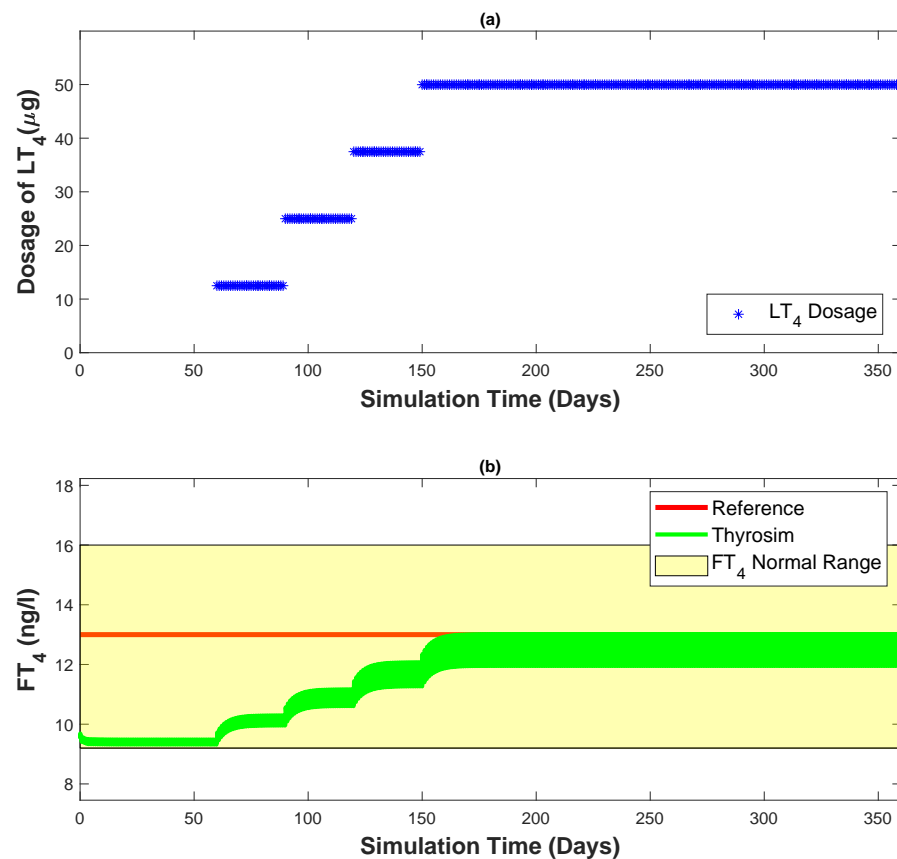


Figure 8. Thyrosim FT_4 concentration is regulated by the developed automated dosage recommendation system (reference FT_4 concentration 13 ng/L), simulation time of 12 months.

In Figure 9a, the amount of dosage prescribed by the developed automated dosage recommendation system is presented. Figure 9b shows the FT_4 concentration generated by Thyrosim for the corresponding amount of dosage. The total time of simulation is three years. The reference FT_4 concentration is 16 ng/L for the first 18 months and in the last 18 months, it decreases to 12 ng/L. The results from Figures 8 and 9 demonstrate that with the help of the developed automated dosage recommendation system, the patient’s

FT_4 concentration is maintained within the reference range. For maintaining the patient’s FT_4 concentration within the reference range, the dosage recommended by the developed automated recommendation system follows all the requirements of LT_4 dosing mentioned in the Section 3.3.1.

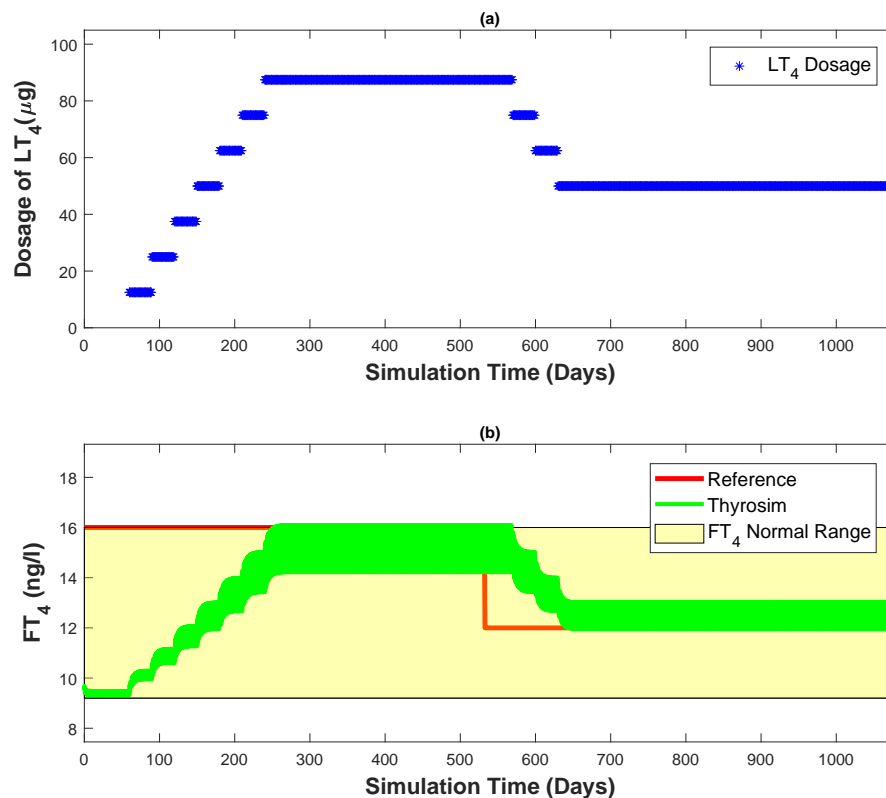


Figure 9. The FT_4 concentration of the patient simulated by the Thyrosim is regulated by the developed automated dosage recommendation system (reference FT_4 concentration 16 ng/L for the first 18 months and for the last 18 months, the reference FT_4 concentration is 12 ng/L).

Statistical Analysis of 50 Patients

In Figure 10, the parameters of the Thyrosim model are varied to simulate 50 different virtual patients. The parameters have varied within their possible range of variation. The designed automated dosage recommendation system has been used to treat all simulated patients. The mean and standard deviation of the patients’ FT_4 concentration and recommended dosage has been calculated monthly. The results reveal that while the variation between the patients’ FT_4 concentrations is high at the beginning of treatment, by employing the developed automated dosage recommendation system in the latter stages of treatment, all patients acquire the FT_4 concentration within the reference range. This demonstrates that with the possible parameter uncertainties, a certain level of FT_4 concentration (within the euthyroid range 9.2–16 ng/L [24]) can be maintained by using the developed automated dosage recommendation system.

The developed automated LT_4 dosing algorithm sampled with a fixed sampling time (e.g., 28 days). In real-world scenarios, physicians may choose to adjust the recommended amount of LT_4 dosage for patients at different time intervals (e.g., 4–6 weeks in the initial phase of the treatment, and in the later stages, even twice a year is also possible). Furthermore, the proposed mathematical model (1) does not account for the effects of thyroid antibody concentrations (TPOAb and TgAb) on the system’s dynamics. To encapsulate the effects of these antibody concentrations (TPOAb and TgAb) on the dynamics of the system, further investigation is required.

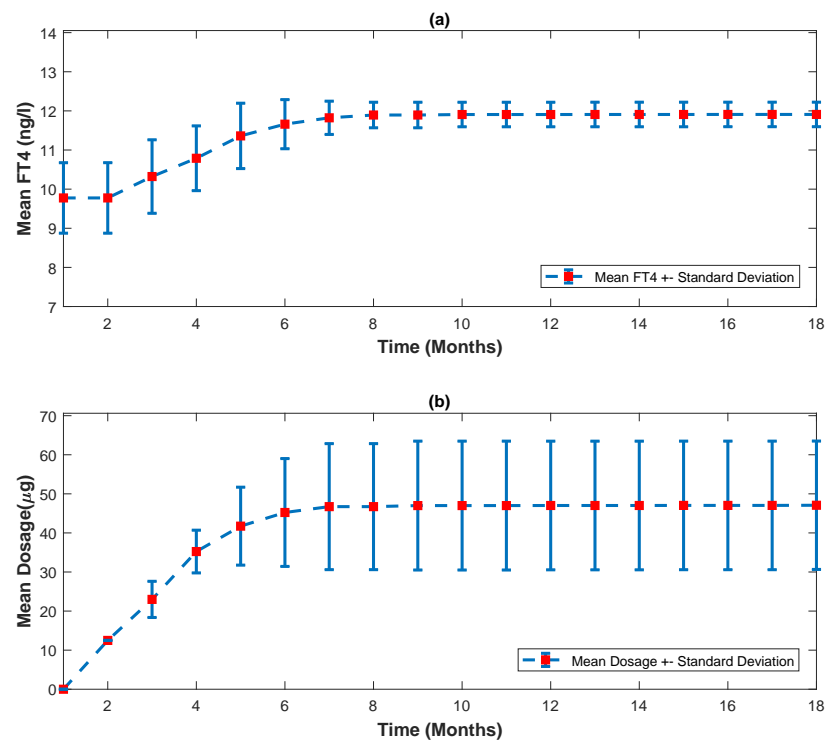


Figure 10. With the help of parameter variation in Thyrosim’s model, 50 patients are simulated. The developed automated dosage recommendation system is used to treat the patients. The mean and standard deviation of the patients’ FT_4 levels, as well as the recommended dosage, are presented.

4. Discussion

The scope of this study is to develop an automated dosage recommendation system that prescribes a daily dosage of LT_4 to hypothyroid patients. With the help of the prescribed dosage, patients can maintain their thyroid hormone concentration within the euthyroid state. The recommended dosage must follow all the requirements of LT_4 dosing (see Section 3.3.1). In our model, the reference range of FT_4 concentration is 9.2–16 ng/L (mean 12.9 ng/L [24]), the developed dosage recommendation system must be able to maintain the patient’s FT_4 concentration within the reference range.

In Figure 8, the reference concentration is set at 13 ng/L. The proposed controller is a non-integrating discrete-time controller. As a result, the system’s output will have a steady-state error. However, the goal is not to reach a specific reference concentration; rather, a FT_4 concentration within the reference range is suitable for the patient’s biological condition. Figure 8a represents the dosage recommended by the controller. The recommended dosage follows the mentioned requirements (see Section 3.3.1). Initially, a small amount of the dosage (e.g., 12.5 µg) is recommended by the developed controller. Later, the recommended dosage is incremented with monthly increments of 12.5 µg. When the FT_4 concentration of Thyrosim attains a value within the reference range, the recommended dosage becomes constant (as mentioned in FPI) with no fluctuations. Figure 8b represents the FT_4 concentration of Thyrosim for the corresponding amount of dosage. With the help of the recommended dosage generated by the developed controller, the FT_4 concentration of Thyrosim is increased slowly after reaching the desired concentration (within the reference range of FT_4 concentration) Thyrosim’s FT_4 concentration becomes constant (as demanded in Section 3.3.1).

In Figure 9, the reference FT_4 concentration varies over time (e.g., first 18 months 16 ng/L, last 18 months 12 ng/L). Figure 9a represents the dosage recommended by the controller. In the first 18 months, a constant increment of 12.5 µg/month in dosage is observable. When Thyrosim FT_4 concentration reaches a value within the reference FT_4 concentration, the dosage recommended by the controller gets constant. In the last 18 months, the refer-

ence FT_4 concentration is decreased to 12 ng/L. Consequently, the dosage recommended by the developed controller decreases with a decrement of 12.5 $\mu\text{g}/\text{month}$. When Thyrosim's FT_4 concentration attains a value within the reference FT_4 concentration, the recommended dosage by the controller becomes constant. This demonstrates that the system fulfils the steady-state requirement (recommended dosage must be constant after reaching the desired FT_4 concentration "euthyroid state"). Correspondingly, Figure 9b the FT_4 concentration generated by Thyrosim varies according to the recommended dosage by the controller. When Thyrosim FT_4 concentration attains a value within the reference FT_4 concentration (for both times, initially, 16 ng/L and later 12 ng/L), it becomes constant with no fluctuations. This demonstrates that the developed automated dosage recommendation system adheres to the LT_4 dosage administration guidelines (see Section 3.3.1). Thyrosim's FT_4 concentration can be maintained within the reference range by employing this proposed automated dosage recommendation system.

The biological parameters of patients are different from patient to patient. The proposed automated dosage recommendation system must be able to deal with possible parametric uncertainties and recommend the dosage that obeys all LT_4 prescription guidelines (see Section 3.3.1). In Figure 10, a statistical analysis is performed to assess the developed system's capability in dealing with possible parameter uncertainties. The Thyrosim model has 60 biological parameters that can be varied within their possible range of variation. This parameter variation in the Thyrosim model is used to simulate 50 different patients. In Figure 10a, at the beginning of the treatment, the difference between patients' FT_4 concentration is high, as the biological conditions of patients can be different. As treatment progresses, the standard deviation between patients' FT_4 concentration decreases, and in the final phases of treatment, the standard deviation between patients' FT_4 concentration has been minimized with the help of the dosage recommended by the developed automated dosage recommendation system. Correspondingly, in Figure 10b, the standard deviation in recommended dosage is low at the beginning of the treatment. Patients with different biological conditions require different amounts of dosage to achieve reference FT_4 concentration, therefore, the standard deviation in the recommended dosage increases as treatment progresses. Thus, a reference FT_4 concentration is maintained in different patients (simulated by Thyrosim) using the developed automated dosage recommendation system.

Note that the results presented in this study are based on simulation only. Consequently, in a next step, data from real patients need to be incorporated and a clinical validation of the proposed approach is required.

5. Conclusions

In this study, an automated dosage recommendation system has been developed that provides LT_4 dosage to hypothyroid patients suffering from Hashimoto's thyroiditis. The simulation-based results reveal that the developed system can maintain patients' FT_4 concentration (emulated by Thyrosim) within the reference range. The statistical analysis of 50 different patients illustrates that despite variation in biological parameters, the proposed system can maintain patients' FT_4 concentration within the reference range. The findings of this study provide a good basis for the development of an automated dosage recommendation system that could minimize the necessity for in-person interactions with medical professionals.

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References

1. Meng, Z.; Liu, M.; Zhang, Q.; Liu, L.; Song, K.; Tan, J.; Jia, Q.; Zhang, G.; Wang, R.; He, Y.; et al. Gender and Age Impacts on the Association Between Thyroid Function and Metabolic Syndrome in Chinese. *Medicine* **2015**, *94*, e2193. [[CrossRef](#)] [[PubMed](#)]
2. Chiovato, L.; Magri, F.; Carlé, A. Hypothyroidism in Context: Where We've Been and Where We're Going. *Adv. Ther.* **2019**, *36*, 47–58. [[CrossRef](#)]
3. Fröhlich, E.; Wahl, R. Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. *Front. Immunol.* **2017**, *8*, 521. [[CrossRef](#)] [[PubMed](#)]
4. Eisenberg, M.C.; Santini, F.; Marsili, A.; Pinchera, A.; DiStefano, J.J. TSH Regulation Dynamics in Central and Extreme Primary Hypothyroidism. *Thyroid* **2010**, *20*, 1215–1228. [[CrossRef](#)] [[PubMed](#)]
5. Dietrich, J.W.; Tesche, A.; Pickardt, C.R.; Mitzdorf, U. Thyrotropic Feedback Control: Evidence for an Additional Ultrashort Feedback Loop from Fractal Analysis. *Cybern. Syst.* **2004**, *35*, 315–331. [[CrossRef](#)]
6. Klein, I. Unusual Manifestations of Hypothyroidism. *Arch. Intern. Med.* **1984**, *144*, 123. [[CrossRef](#)]
7. Chaker, L.; Bianco, A.C.; Jonklaas, J.; Peeters, R.P. Hypothyroidism. *Lancet* **2017**, *390*, 1550–1562. [[CrossRef](#)]
8. Ben-Shachar, R.; Eisenberg, M.; Huang, S.A.; DiStefano, J.J. Simulation of Post-Thyroidectomy Treatment Alternatives for Triiodothyronine or Thyroxine Replacement in Pediatric Thyroid Cancer Patients. *Thyroid* **2012**, *22*, 595–603. [[CrossRef](#)]
9. Eisenberg, M.; Samuels, M.; DiStefano, J.J. Extensions, Validation, and Clinical Applications of a Feedback Control System Simulator of the Hypothalamo-Pituitary-Thyroid Axis. *Thyroid* **2008**, *18*, 1071–1085. [[CrossRef](#)]
10. Eisenberg, M.; Samuels, M.; DiStefano, J.J. L-T4 Bioequivalence and Hormone Replacement Studies via Feedback Control Simulations. *Thyroid* **2006**, *16*, 1279–1292. [[CrossRef](#)]
11. Pandiyan, B.; Merrill, S.J.; Benvenga, S. A patient-specific model of the negative-feedback control of the hypothalamus-pituitary-thyroid (HPT) axis in autoimmune (Hashimoto's) thyroiditis. *Math. Med. Biol.* **2013**, *31*, 226–258. [[CrossRef](#)]
12. Yang, B.; Tang, X.; Haller, M.J.; Schatz, D.A.; Rong, L. A unified mathematical model of thyroid hormone regulation and implication for personalized treatment of thyroid disorders. *J. Theor. Biol.* **2021**, *528*, 110853. [[CrossRef](#)]
13. Wolff, T.M.; Dietrich, J.W.; Müller, M.A. Optimal Hormone Replacement Therapy in Hypothyroidism—A Model Predictive Control Approach. *Front. Endocrinol.* **2022**, *13*, 992. [[CrossRef](#)] [[PubMed](#)]
14. Wolff, T.M.; Veil, C.; Dietrich, J.W.; Müller, M.A. Mathematical Modeling of Thyroid Homeostasis: Implications for the Allan-Herndon-Dudley Syndrome. *bioRxiv* **2022**. [[CrossRef](#)]
15. Dietrich, J.W. Der Hypophysen-Schilddrüsen-Regelkreis: Entwicklung und Klinische Anwendung eines Nichtlinearen Modells. Ph.D. Thesis, Institut für Medizinische Psychologie der Ludwig-Maximilians-Universität München, München, Germany, 2001. [[CrossRef](#)]
16. Berberich, J.; Dietrich, J.W.; Hoermann, R.; Müller, M.A. Mathematical Modeling of the Pituitary–Thyroid Feedback Loop: Role of a TSH-T3-Shunt and Sensitivity Analysis. *Front. Endocrinol.* **2018**, *9*, 91. [[CrossRef](#)]
17. Han, S.X.; Eisenberg, M.; Larsen, P.R.; DiStefano, J. THYROSIM App for Education and Research Predicts Potential Health Risks of Over-the-Counter Thyroid Supplements. *Thyroid* **2016**, *26*, 489–498. [[CrossRef](#)] [[PubMed](#)]
18. Colucci, P.; Yue, C.S.; Ducharme, M.; Benvenga, S. A Review of the Pharmacokinetics of Levothyroxine for the Treatment of Hypothyroidism. *Eur. Endocrinol.* **2010**, *9*, 40. [[CrossRef](#)]
19. Johnson, K.A.; Goody, R.S. The Original Michaelis Constant: Translation of the 1913 Michaelis–Menten Paper. *Biochemistry* **2011**, *50*, 8264–8269. [[CrossRef](#)]
20. Schussler, G.C. The Thyroxine-Binding Proteins. *Thyroid* **2000**, *10*, 141–149. [[CrossRef](#)] [[PubMed](#)]
21. Roberts, G.W. Taking care of thyroxine. *Aust. Prescr.* **2004**, *27*, 75–76. [[CrossRef](#)]
22. Ogata, K. *Modern Control Engineering*, 3rd ed.; Prentice Hall: Upper Saddle River, NJ, USA, 1997.
23. Nygaard, B.; Saedder, E.A.; Dalhoff, K.; Wikkelse, M.; Jürgens, G. Levothyroxine Poisoning—Symptoms and Clinical Outcome. *Basic Clin. Pharmacol. Toxicol.* **2015**, *117*, 280–285. [[CrossRef](#)]
24. Park, S.Y.; Kim, H.I.; Oh, H.K.; Kim, T.H.; Jang, H.W.; Chung, J.H.; Shin, M.H.; Kim, S.W. Age- and gender-specific reference intervals of TSH and free T4 in an iodine-replete area: Data from Korean National Health and Nutrition Examination Survey IV (2013–2015). *PLoS ONE* **2018**, *13*, e0190738. [[CrossRef](#)] [[PubMed](#)]
25. Jackson, L. A correction to impulse invariance. *IEEE Signal Process Lett.* **2000**, *7*, 273–275. [[CrossRef](#)]

26. Chen, C. *Analog and Digital Control System Design: Transfer-Function, State-Space, and Algebraic Methods*; Holt, Rinehart and Winston Series in Electrical Engineering; Saunders College Pub.: Philadelphia, PA, USA, 1993.
27. Jury, E.; Pavlidis, T. Stability and Aperiodicity Constraints for System Design. *IEEE Trans. Circuit Theory* **1963**, *10*, 137–141. [[CrossRef](#)]

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