Journal of Theoretical Biology 528 (2021) 110853

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

A unified mathematical model of thyroid hormone regulation and implication for personalized treatment of thyroid disorders

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ARTICLE INFO

Article history:
Received 27 October 2020
Revised 26 July 2021
Accepted 28 July 2021
Available online 3 August 2021

Keywords:
Thyroid hormone regulation
Mathematical model
Drug intervention
Hashimoto's thyroiditis
Graves' disease

ABSTRACT

Current clinician practice for thyroid hormone regulation of patients is based upon guesswork and experience rather than quantified analysis, which exposes patients under longer risk and discomfort. To quantitatively analyze the thyroid regulation for patients of different thyroid states, we develop a two-dimensional mathematical model that can be applied to analyze the dynamic behaviors of thyroid hormones with or without drug intervention. The unified model can be employed to study the regulation of TSH (thyroid-stimulating hormone) and FT4 (free thyroxine) for euthyroid (normal thyroid) subjects, Hashimoto's thyroiditis, and Graves' disease patients, respectively. The results suggest that the level of TPOAb (thyroid peroxidase antibody) may be a factor determining whether the patient would progress from euthyroid state to subclinical or clinical hypothyroidism, and that increased TRAb (TSH receptor antibody) may lead Graves' disease to deteriorate from the early stage to overt hyperthyroidism. Given the early blood-test data, we demonstrate the feasibility for healthcare professionals to apply our model in choosing an appropriate dosage regimen for patients to achieve the desired TSH and FT4 levels within a specified time frame. This proposed model has the potential to optimize personalized treatment and shorten the therapeutic time for patients suffering from Hashimoto's thyroiditis and Graves' disease.

1. Introduction

The thyroid is an endocrine gland in the neck that secretes thyroid hormones (Hall, 2010). The thyroid hormones have an extensive impact on the human body. These include metabolic, cardiovascular, developmental, sexual function, sleep and thought patterns. Both the high and low level of thyroid hormones can be detrimental to the body. A remarkable number of people are afflicted by thyroid disorder in the world. According to the American Thyroid Association, greater than 12 percent of the U.S. population is exposed to a thyroid disorder in their lifetime. Nearly 60 percent of those afflicted with thyroid diseases go undiagnosed. Patients' daily lives are greatly affected by thyroid disfunction. The treatment of thyroid diseases primarily relies on the intervention of thyroid hormone production. Both excess and deficiency of drug intervention in thyroid may impose adverse influence in diverse target tissues. In practice, clinicians prescribe the dosage based upon their experience and prior test results of TSH and thyroid hormone levels. Without quantified analysis between the taken dosage and thyroid function, such a trial-and-error strategy takes extensive amounts of time for clinicians to find an optimal drug dosage for each treatment period and thus may expose patients under a longer time of risk and discomfort.

In comparison with commonly used empirical models in the thyroid physiological field, mathematical models have been used to describe thyroid regulation quantitatively, which may have important clinical applications. Norwich and Reiter proposed a homogenous model which used a set of linear differential equations to describe the relationship between the secretion rates of thyroxine and thyroid stimulating hormone (Norwich and Reiter, 1965). DiStefano and Stear described the thyroid hormone regulation with a model involving the hypothalamus (DiStefano and Stear, 1968). In Leow (2007), Leow developed a model providing an explicit expression of TSH as an inverse exponential-power function of FT4, which may explain certain clinical phenomenon observed in the thyroid dysfunctional state. These studies help to depict the relationship among FT4, TSH, and TRH (thyrotropin releasing hormone). More recently, DiStefano, Eisenberg and their collaborators developed a series of models to study thyroid hormone regulation and its applications. In the reference Eisenberg et al. (2006), they developed a nonlinear simulation model of

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https://doi.org/10.1016/j.jtbi.2021.110853
0022-5193/

whole-body regulation mechanisms that involves dynamics of T3, T4, TSH, plasma protein binding, the Hypothalamus-Pituitary-Thyroid (HPT) axis, and extravascular regulatory enzyme systems. Subsequently, they refined the model with the incorporation of a brain submodel and an updated six-dimensional thyroid submodel (Eisenberg et al., 2008). They further modified the comprehensive model in Eisenberg et al. (2008) to study the criteria for testing bioequivalence of LT4 preparations (Eisenberg and Distefano, 2009), optimization of remnant ablation protocols in thyroid cancer (Eisenberg et al., 2010; Ben-Shachar et al., 2012), and central hypothyroidism and circadian rhythm relationships (Eisenberg et al., 2010).

A simpler differential equation model was constructed by Pandiyan to describe the operation of the HPT axis for patients with Hashimoto's thyroiditis (Pandiyan, 2011). The model includes four variables: the functional size of the thyroid gland, the concentration of serum TSH, serum FT4 and serum thyroid peroxidase antibody. In 2018, Pandiyan and collaborators used a similar approach to develop a treatment model for Graves' hyperthyroidism (Pandiyan et al., xxxx). A challenge in the models Pandiyan constructed is the data shortage of patients' functional thyroid gland sizes, as it is unrealistic to order thyroid screen tests for patients per visit. In the same year, Berberich et al. developed a six-dimensional differential equation model of the pituitary-thyroid feedback loop including the component of TSH-stimulated intrathyroidal T3-secretion (Berberich et al., 2018).

Model validation and application are usually challenging for complicated mathematical models that include many biological processes and mechanisms. A critical question pertinent to thyroid modeling is whether there exists a mathematical model that is applicable to different thyroid disorders but only contains variables the values of which can be easily obtained from the general thyroid function test (i.e. test for free T4, plasma TSH and thyroid auto-antibodies levels). A unified model suitable for all thyroid states is also desired to help describe and explain how patients progress from euthyroid state to hypothyroidism or hyperthyroidism. So far a limited number of mathematical models have been proposed to study the abnormality in the thyroid gland (Pandiyan et al., xxxx; Pandiyan et al., 2016; Eisenberg et al., 2006; Eisenberg et al., 2008; Meng et al., 2019). They include a number of variables, some of which may not be validated by available data. In addition, among those models, very few, if any, have investigated the quantitative response of TSH-FT4 dynamics to different plasma concentration of thyroid drugs. Motivated by the above, this work aims to develop a unified and low-dimensional model that can be easily applied in the clinical setting to illustrate the dynamic behavior of TSH and FT4 concentrations for different thyroid disorders with drug intervention. This may facilitate optimal drug dosing for patients by means of the titration regimen.

We establish a two-dimensional ordinary differential equation model to analyze thyroid regulation for euthyroid subjects, Graves' disease patients and Hashimoto's thyroiditis patients. Sensitivity tests on key parameters are performed in the model for the three different thyroid states. Our model is designed upon the HPT axis negative feedback control mechanism, involving only the variables of serum FT4, TSH and autoantibody concentrations. In particular, we focus on the construction of a treatment model for Hashimoto's thyroiditis. With the thyroid function test data from a patient, we apply the Hashimoto's thyroiditis model to predict how serum TSH and thyroid hormone levels change after the patient takes a certain amount of thyroid medicine. The proposed mathematical model may assist clinicians in prompt determination of the optimal length of treatment for a specified dosage which helps accelerate the achievement of euthyroid targets.

2. A unified model for euthyroid and thyroid disorders

We first formulate a thyroid regulation model in a unified form for all thyroid states, and then specify the different parameter settings in the model based on thyroid pathology for euthyroid subjects, Hashimoto's thyroiditis patients and Graves' disease patients, respectively.

The production of triiodothyronine (T3) and thyroxine (T4) is related to thyroid-stimulating hormone (TSH) and thyrotropin-releasing hormone (TRH). The hypothalamus secretes TRH which stimulates the anterior pituitary gland to produce TSH and the TSH in turn stimulates the thyroid to produce T3 and T4. When the thyroid hormones become deficient in blood, TSH is elevated to increase the thyroid hormone secretion. In contrast, excessive thyroid hormones would suppress the TSH level to slow down the thyroid hormone production. The negative feedback control forms a set point of the HPT axis as shown in Fig. 1. It is worth noting that there is a range of set points among different individuals (Andersen et al., 2002). The majority of T3 and T4 are bound to specific transport proteins in blood, and the remainder that can flow freely in the blood are often abbreviated as FT3 and FT4. The lab test of free thyroid hormones evaluates hormone concentration more accurately than the measurement of total T3 and T4, and most of the production of T3 in blood comes from the conversion of T4. For this reason, physicians regard the FT4 as a representative of the plasma level of thyroid hormones in practice (ATA, 2019a; Colledge et al., 2010; Brent, 1994). Additionally, in the clinical setting, TSH is considered as a robust indicator of the thyroid hormone status, eliminating the need of measuring TRH, provided that the hypothalamus-pituitary function of a patient is not damaged (Montoya et al., 1975; Emerson and Utiger, 1975). Hence, clinicians generally assess the thyroid state with the plasma levels of FT4 and TSH, which represent the two variables we construct our differential equation system model with.

We consider the case where there is enough iodine in blood to synthesize hormones and the hypothalamus-pituitary function is intact so that the contribution of the hypothalamus can be abrogated. The euthyroid set points of FT4 and TSH for an individual are assumed to be known, with U representing the euthyroid set point of FT4. Let $\mathrm{TSH}(t), \mathrm{FT4}(t)$ denote plasma concentrations of thyroid stimulating hormone (mU/L) and free thyroid hormone (pg/mL) at time t, respectively. Without drug interference, the rate of change of TSH and FT4 concentrations is equal to their secretion rates minus the excretion rates. We suppose TSH and FT4 decay at a rate in direct proportion to their own plasma concentrations, denoted by d_1, d_2 correspondingly. The FT4 production induced by the thyroid is assumed to be influenced by the blood levels of TSH and anti-thyroid autoantibodies. In general, the levels of these antibodies vary with time for patients with thyroid disorders. Thus, the FT4 synthesis term contains the expression of $p_2(t) * \mathrm{TSH}$, where $p_2(t)$ represents the time dependent FT4 synthesis factor. Moreover, as TSH needs to bind to the TSH receptor to function, we incorporate the factor $1/(s_2 + \mathrm{TSH})$ into the FT4 synthesis term, accounting for the limited rate of receptor recycling. The optimal expression to model TSH secretion should be consistent with the HPT axis negative feedback control mechanism; to this end, we elaborate the design for the TSH secretion term below.

Let $f(\mathrm{FT4})$ denote the TSH secretion function dependent on the variable FT4. Let p_1 represent the default release rate of TSH from the pituitary when FT4 meets the euthyroid set point value, which implies $f(U) = p_1$. Furthermore, if the plasma has excessive or deficient FT4 than the set point U, the secretion of TSH will be decreased or increased respectively by the pituitary to maintain the homeostasis of thyroid hormone regulation. That is, the func-

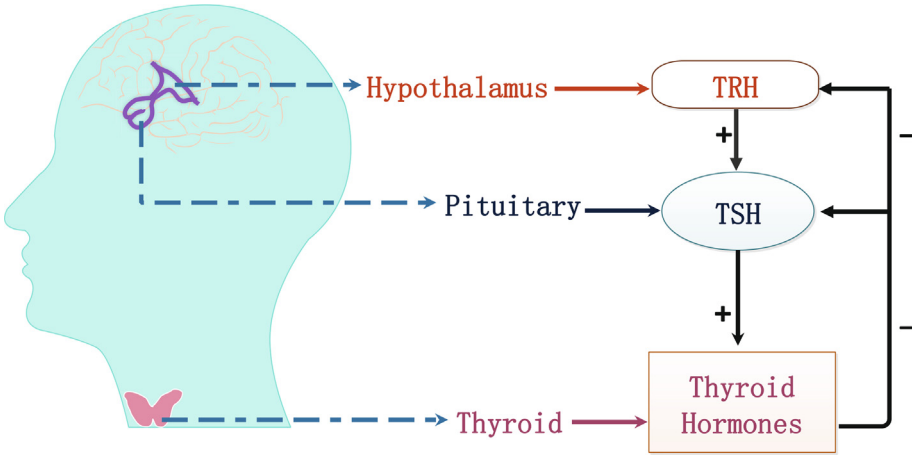

Fig. 1. HPT-axis negative feedback mechanism. When the free T3 and T4 concentrations become lower than their normal set point values, the hypothalamus responds by secreting TRH. This promotes the pituitary gland to produce and secrete TSH into the blood. As a result, thyroid follicle cells are stimulated to secrete T3 and T4. On the contrary, if the plasma levels of free T3 and T4 become higher than the normal range, then the hypothalamus and pituitary gland responds to the high levels of free T3 and T4 by reducing the secretion of TRH and TSH. Consequently, the production of T3 and T4 is slowed down.

tion f should also satisfy $f(U) < p_1$ when FT4 $> U$, and $f(U) > p_1$ when FT4 $< U$. Finally, in the case when the plasma concentration of FT4 is extremely excessive, the pituitary will stop secreting any TSH to protect the thyroid gland. This suggests $\lim_{\mathrm{FT4}\to\infty} f(\mathrm{FT4}) = 0$. To meet all the above properties that $f(\mathrm{FT4})$ possesses, we choose

$$f(\mathrm{FT4}) = p_1 - \frac{p_1(\mathrm{FT4}-U)}{s_1+\mathrm{FT4}} = p_1\frac{s_1+U}{s_1+\mathrm{FT4}}, \tag{1}$$

where $s_1 + 2U$ is the concentration of FT4 causing half the maximum inhibitory effect on the TSH releasing rate controlled by the pituitary.

Therefore, we construct the following system to describe the dynamic behavior of TSH and FT4 for patients:

$$\frac{\mathrm{dTSH}(t)}{\mathrm{d}t} = p_1 - \frac{p_1(\mathrm{FT4}-U)}{s_1+\mathrm{FT4}} - d_1\mathrm{TSH}, \tag{2}$$

$$\frac{\mathrm{dFT4}(t)}{\mathrm{d}t} = \frac{p_2(t)\mathrm{TSH}}{s_2+\mathrm{TSH}} - d_2\mathrm{FT4} + G, \tag{3}$$

where s_2 stands for the concentration of TSH that results in half the maximum synthesis rate of FT4, and G represents the amount of increased or decreased thyroxine levels per unit of time caused by the intake of different thyroid drugs.

It is worth noting that $p_2(t)$ varies with patients in different thyroid states and G takes different values for patients under distinct thyroid treatment strategies. G can also be time-varying due to drug's administration, absorption and excretion. We discuss the evaluation for these two parameters in the following cases:

Case 1) Euthyroid state

In this case, thyroid treatment is not necessary, so G is set to zero. The parameter p_2 is considered to be a constant for a euthyroid individual as the fluctuation of thyroid function caused by the variations of thyroid antibody levels falling within the normal range is negligible. Note that p_2 actually can be calculated by the other parameters in the model as we assume the steady state of the model for healthy people to be their euthyroid set points. By setting the left hand sides of Eqs. (2) and (3) to zero and substituting U for FT4, we obtain

$$p_2 = d_2U\left(1+\frac{d_1s_2}{p_1}\right). \tag{4}$$

Case 2) Hashimoto's thyroiditis

Deficient production of the thyroid hormones is known as hypothyroidism, which is caused by Hashimoto's thyroiditis in most cases. Hashimoto's thyroiditis is an autoimmune disorder that leads to progressive damage to the thyroid gland (Longo et al., 2011). The bio-markers of autoimmune thyroiditis are thyroid peroxidase and thyroglobulin antibodies (TPOAb and TGAb) which attack thyroid peroxidase and thyroglobulin (TPO and TG), respectively (Agrawal, 2012). The increased levels of these thyroid auto-antibodies correlates roughly with the disease severity, and a decreased level correlates with the disease remission (Weetman and DeGroot, 2000). Assays for TPOAb, rather than TGAb, have been proposed to be taken initially for the screening of Hashimoto's thyroiditis. Hence we can regard $p_2(t)$, the growth rate of FT4, as a decreasing function of the TPOAb level for Hashimoto's thyroiditis patients.

The normal reference range for TPOAb is (0–60) U/mL; here we assume that 60 U/mL is the set point of the TPOAb value for patients in view of the fact that the TPOAb levels of most Hashimoto's thyroiditis patients are significantly above the upper bound. Because $p_2(t)$ is always non-negative and the damage to the thyroid caused by excessive TPOAb is constricted by the capacity of the corresponding antibody receptors, we let

$$p_2(t) = \frac{a_1}{1+e^{a_2(\mathrm{TPOAb}(t)-60)}}, \tag{5}$$

where a_1, a_2 are positive constants, and a_1 represents twice the growth rate of FT4 for the patient in the euthyroid state (i.e. TPOAb = 60 U/mL). Thus, by (4)

$$a_1 = 2d_2U\left(1+\frac{d_1s_2}{p_1}\right), \tag{6}$$

which follows that

$$p_2(t) = \frac{2d_2U\left(1+\frac{d_1s_2}{p_1}\right)}{1+e^{a_2(\mathrm{TPOAb}(t)-60)}}. \tag{7}$$

The treatment for Hashimoto's thyroiditis is typically levothyroxine, which is an oral thyroid medicine given daily as the supplement of T4 and is usually suggested to be taken for a lifetime. In the United States, a certain dosage of levothyroxine is often required to be sustained 6–8 weeks by patients with Hashimoto's thyroiditis, before any dose adjustment is made by their doctor ATA, 2019b. Hence, in a certain treatment period for a patient, the increase rate of FT4 in blood converted from the drug can regarded as a positive constant, i.e. $G > 0$. Although implementing drug treatment with a

Table 1
Normal ranges of TSH, FT4, and antibodies.

Variable	Normal Range	Unit	Source
TSH	2.5–4	mU/L	Literature Baloch et al., 2003
FT4	7–18	pg/mL	Literature Baloch et al., 2003
TPOAb	0–60	U/mL	Dataset
TRAb	0–1.75	IU/L	Literature Schott et al., 2009

simple constant G seems deviated from the reality, we have demonstrated in Appendix A that the TSH-FT4 dynamics with an episodic G(t) resemble the one we obtained by incorporating a constant G to the model. Therefore, to avoid introducing another differential equation of G(t) that would inevitably bring more parameters for calibration, we simplify our thyroid hormone regulation model with the reasonable assumption of a constant G.

We further conduct some mathematical analysis for our model in the case of Hashimoto's thyroiditis. The result shows the model has a unique positive steady state which is also globally asymptotically stable. The proofs of the propositions are shown in the Appendix B. The level of TPOAb is assumed to be constant in the proof. The model degenerates to the setting for euthyroid subjects when $G = 0$ and TPOAb $= 60$ U/mL.

Case 3) Graves' disease

An overactive thyroid gland that generates excessive thyroid hormones leads to hyperthyroidism which is commonly associated with Graves' Disease. Graves' Disease is an autoimmune disorder characterized by a circulating TSH receptor autoantibody (TRAb). In principle, TRAb overrides TSH to produce excess thyroid hormones even when free T4 is elevated, leading to a suppressed TSH and causing symptoms of hyperthyroidism (NNIDDK, 2012). In contrast with the effects of antibodies imposed on patients of Hashimoto's thyroiditis, there is a positive relation between the quantity of TRAb and the secretion rate of FT4 for patients with Graves' Disease. Hence we consider $p_2(t)$ as an increasing function of TRAb for Graves' disease patients.

The threshold 1.75 IU/L is usually used for diagnosis, beyond which the patient is considered to have Graves' disease (Schott et al., 2009). Similar as before, we assume 1.75 IU/L as the set point of the TRAb vaule for euthyroid state. Since TRAb has to bound to the TSH receptor to be activated and the total number of TSH receptor in thyroid is limited, we propose

$$p_2(t) = \frac{b_1}{1 + e^{-b_2(\mathrm{TRAb}(t)-1.75)}}, \tag{8}$$

where b_1, b_2 are positive constants, and b_1 represents twice the growth rate of FT4 for the patient in euthyroid state (i.e. TRAb = 1.75 IU/L). Thus, $b_1 = a_1$ and by (6) we have

$$p_2(t) = \frac{2d_2U\left(1 + \frac{d_1 s_2}{p_1}\right)}{1 + e^{-b_2(\mathrm{TRAb}(t)-1.75)}}. \tag{9}$$

Taking antithyroid drugs (ATD) is a common therapy to prevent or suppress the biosynthesis of thyroid hormones. As the dosage patients take during a certain treatment period is fixed, G is considered as a negative constant, that is, $G < 0$ in Eq. (3).

3. Numerical investigations

We perform numerical simulations of the model in the three different thyroid states to illustrate our mathematical analysis and additionally show that the simulation results are consistent with the clinical observations. The normal reference ranges for TSH, FT4, TPOAb and TRAb for adult population (non-pregnancy), are listed in Table 1. We pick an imaginary individual whose set point value of FT4 is designed to be 12.5 pg/mL (i.e. the average of the upper and lower bounds of the FT4 range), and investigate the variations of the TSH and FT4 values with time in different clinical settings.

3.1. Simulation of euthyroid model

Assuming this individual has normal thyroid function, we list the corresponding parameter values in the caption of Fig. 2. We set two abnormal initial states to him, namely thyroid hormones excessive state and deficient state, and investigate the dynamics of his TSH and FT4 levels respectively for the two states as shown in Fig. 2. The simulation result of our euthyroid model demonstrates that for a person with normal thyroid function, the negative

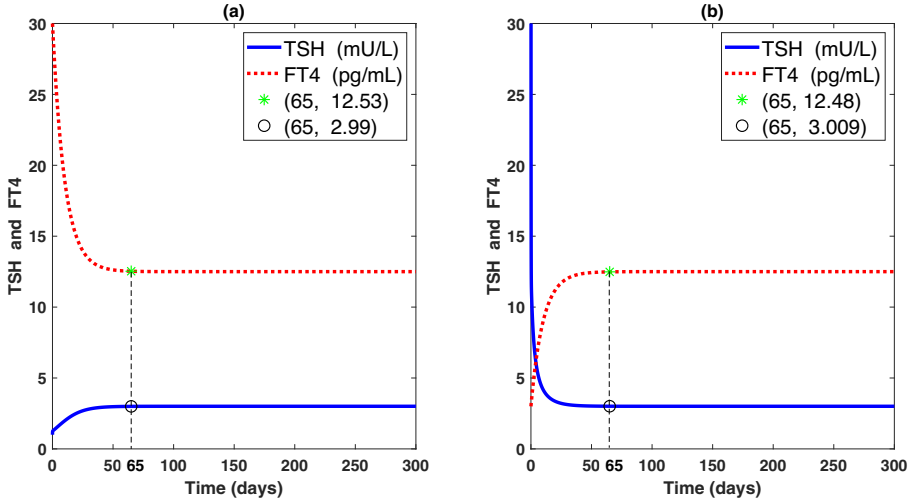

Fig. 2. Dynamics of TSH and FT4 for a euthyroid individual with abnormal initial FT4 and TSH values. (a) An initial state (TSH, FT4) = (30 mU/L, 1 pg/mL), that is, the initial FT4 value is set to be explicitly above its normal range and the initial TSH value lies below its normal range. The system asymptotically goes back to the individual's euthyroid state $(3mU/L, 12.5pg/mL)$ in approximately 65 days. (b) An initial state (TSH, FT4) = (3 mU/L, 75 pg/mL), that is, the individual is assumed to have an initial TSH level sharply above the normal range and an initial FT4 level below its normal range. The system also returns to the individual's euthyroid state in approximately 65 days. The parameter values for (a) and (b) are: TPOAb = 60 $U \cdot mL^{-1}$, U = 12.5 $pg \cdot mL^{-1}$, d_1 = 16.6355 day^{-1} (Pandiyan, 2011), d_2 = 0.099021 day^{-1} (Pandiyan, 2011), p_1 = 50 $mU \cdot L^{-1} \cdot day^{-1}$, s_1 = 0.0434 $pg \cdot mL^{-1}$ (Pandiyan, 2011), s_2 = 0.0021 $mU \cdot L^{-1}$ (Pandiyan, 2011), $a_{.2}$ = 0.01.

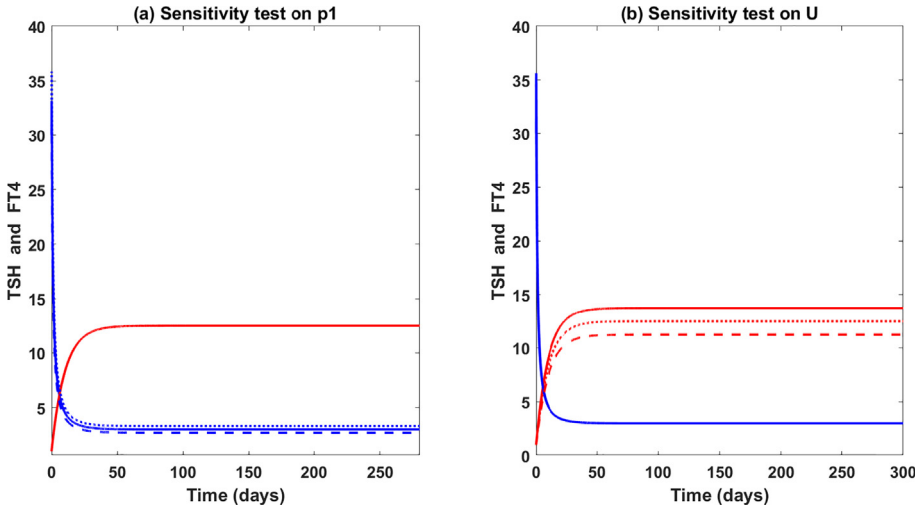

Fig. 3. Sensitivity test on parameters p_1 and U in the euthyroid model. The initial state of (TSH, FT4) is set to (30 mU/L, 1 pg/mL). (a) The TSH release rate varies: $p_1 = 45$ (dashed blue for TSH curve and dashed red for FT4 curve), $p_1 = 50$ (solid blue for TSH and dotted red for FT4), $p_1 = 55$ (dotted blue for TSH and solid red for FT4). The three curves of FT4 overlap as shown in red solid line. (b) The set point value of FT4 varies: $U = 11.5$ (dashed blue for TSH and dashed red for FT4), $U = 12.5$ (solid blue for TSH and dotted red for FT4), $U = 13.75$ (dotted blue for TSH and solid red for FT4). The three curves of TSH overlap as shown in blue solid line.

feedback control mechanism guarantees the thyroid hormone levels stay around its set point value over time, even given significant exogenous interference of two opposite directions. This suggests that the model coincides well with the thyroid physiology. Furthermore, Fig. 2 shows that our system predicts the healthy individual asymptotically recovers in a spontaneous way, from the interfered hormone levels back to the set point values in approximately 65 days, which is consistent with clinical observations.

We perform sensitivity tests on parameters p_1 and U in the euthyroid model, considering the value of d_1 and d_2 can be deduced by half-lives and the value of a_2 has no influence on the dynamics of FT4 in the euthyroid state (figure not shown). In Fig. 3, we examine the effects of different parameter values of p_1 and U on the TSH-FT4 dynamics. When the value of p_1 is varied up to 10 percent, the dynamics of FT4 stay the same and the dynamics of TSH are slighted changed with the steady states staying in the normal reference range. Analogously, as the value of U changes up to 10 percent, the dynamics of TSH remain the same and the FT4 restores to a different set value of U.

3.2. Simulation of Hashimoto's thyroiditis model

Autoimmune thyroiditis features with a complicated disorder caused by a major involvement of genetic and environmental factors. The pathogenic mechanism of Hashimoto's thyroiditis is unclear and controversial even at the current time. Generally, clinicians see three stages of patients with Hashimoto's thyroiditis, namely euthyroidism → subclinical hypothyroidism → clinical hypothyroidism. Subclinical hypothyroidism is defined as the free thyroid hormone levels within the reference range in the presence of high TSH level, while the levels of both thyroid hormones and TSH are abnormal in the clinical hypothyroid state (Biondi and Cooper, 2008). An important question is what leads to the different

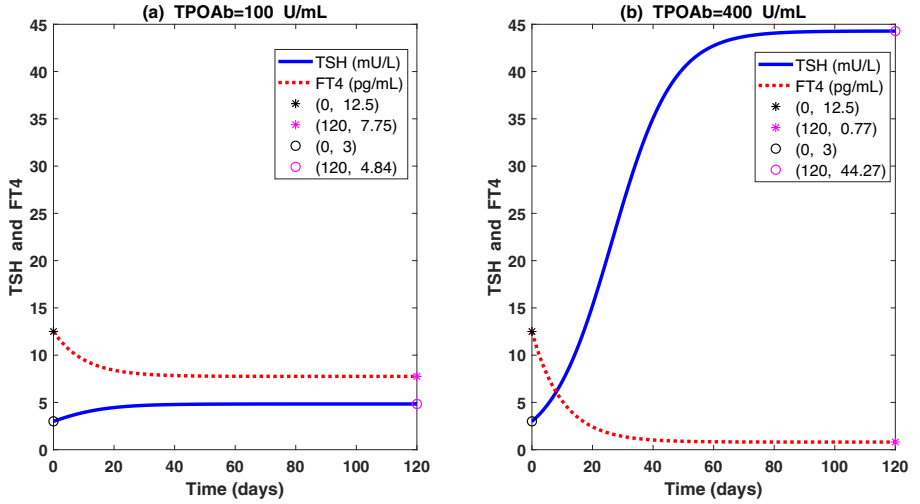

Fig. 4. Dynamics of TSH and FT4 for an untreated patient ($G = 0$) in subclinical and clinical hypothyroidism with initial normal FT4 value. All of the parameters here remain the same as those in Fig. 2, except for the value of TPOAb. The initial conditions are set to be (TSH, FT4) = (3 mU/L, 12.5 pg/mL). Graph (a) shows a patient with TPOAb = 100 U/mL will approach the steady state with (TSH, FT4) = (4.84 mU/L, 7.75 pg/mL) in approximate 60 days, which lies in the stage of subclinical hypothyroidism. Graph (b) shows a patient with TPOAb = 400 U/mL will approach the steady state with (TSH, FT4) = (44.27 mU/L, 0.77 pg/mL) in approximate 80 days, lying in the stage of clinical hypothyroidism.

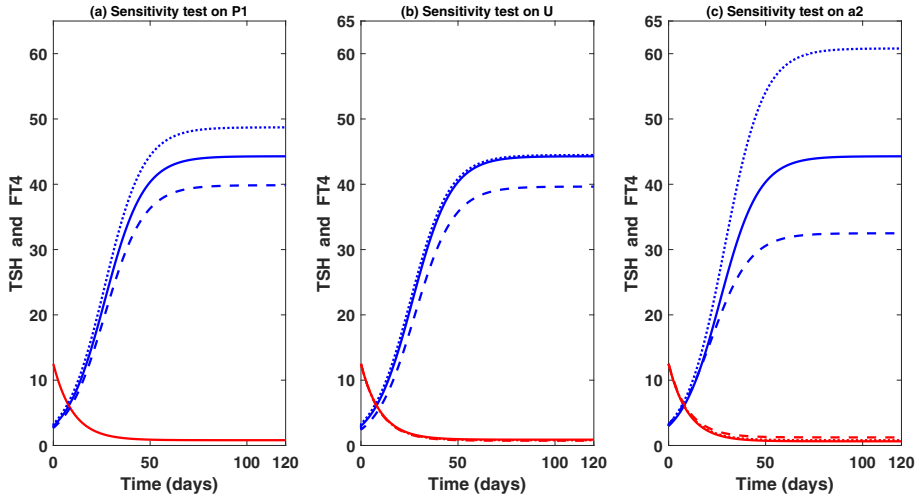

Fig. 5. Sensitivity test on parameters p_1, U and a_2 in the Hashimoto's thyroiditis model. The value of TPOAb is fixed to 400 U/mL. (a) The TSH release rate varies: $p_1 = 45$ (dashed blue for TSH curve and dashed red for FT4 curve), $p_1 = 50$ (solid blue for TSH curve and dotted red for FT4 curve), $p_1 = 55$ (dotted blue for TSH and solid red for FT4). The three curves of FT4 overlap as shown in red solid line. (b) The set point value of FT4 varies: $U = 11.5$ (dashed blue for TSH and dashed red for FT4), $U = 12.5$ (solid blue for TSH and dotted red for FT4), $U = 13.75$ (dotted blue for TSH and solid red for FT4). (c) The TPOAb influence parameter a_2 varies: $a_2 = 0.009$ (dashed blue for TSH and dashed red for FT4), $a_2 = 0.01$ (solid blue for TSH and dotted red for FT4), $a_2 = 0.011$ (dotted blue for TSH and solid red for FT4).

stages of this disease, i.e., is there a factor which can explain the phenomenon that most untreated patients with Hashimoto's thyroiditis go through euthyroidism to subclinical hypothyroidism and then progress to overt hypothyroidism? The simulation result, as shown in Fig. 4, demonstrates that the hypothetical mechanism of our Hashimoto's thyroiditis model helps answer the question. Graph (a) in Fig. 4 shows that an untreated patient with euthyroid initial state would develop to subclinical hypothyroidism over time if his TPOAb value exceeds 40 units over its normal value. Graph (b) illustrates that a clinical hypothyroidism would occur to the same patient with the same initial condition if the TPOAb value is elevated by 340 units. This implies that the increasing TPOAb level over time of untreated Hashimoto's thyroiditis patients may be the answer for our question above.

In practice, when individuals are diagnosed with Hashimoto's thyroiditis, they are most often in the state of clinical hypothyroidism, as the disease symptoms in subclinical state are not obvious enough to bring their attention. Consider the same patient from the last graph (b) in Fig. 4 who has TPOAb $= 400\ U/mL$ and goes from euthyroidism to overt hypothyroidism with a state of $(\mathrm{TSH}, \mathrm{FT4}) = (44.27\ mU/L, 0.77\ pg/mL)$. We suppose a certain dosage of levothyroxine which can be converted as a constant $G = 1$, is given to treat the patient starting at day 120. Fig. 6 shows that the FT4 and TSH levels of the patient will go back to normal with $(\mathrm{TSH}, \mathrm{FT4}) = (3.448\ mU/L, 10.89\ pg/mL)$ after 65 days of drug intervention, which to some extent helps explain the reason that in general, physicians require patients to sustain a dose for 6–8 weeks before making any dosage adjustment.

We notice that it takes approximately 65 days for the patient to approach the steady state levels of TSH and FT4 with the given dosage in Fig. 6. The long period of exposing the patient to deficient thyroxine increases the risk of impairing cells and organs. In particular, patients with very severe hypothyroidism, such as Myxedema, are in life-threatening clinical condition and need immediate and effective treatment to reverse a downhill course. In this case, physicians tend to prescribe patients a large initial

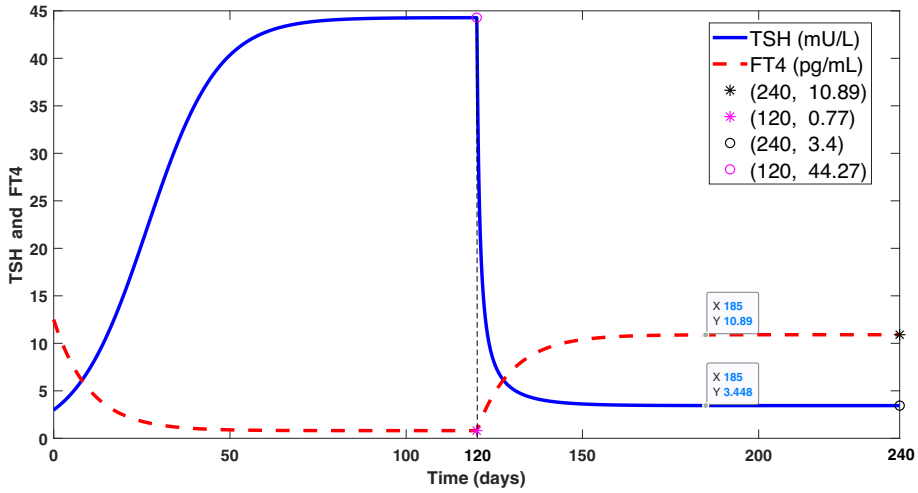

Fig. 6. Dynamics of TSH and FT4 for a patient in Hashimoto's thyroiditis with drug treatment since day 120. Here TPOAb = 400 U/mL, $G = 0$ when $t < 120$ and $G = 1$ when $t \geqslant 120$. All of the other parameters remain the same as those in Fig. 2. Before day 120, the figure is exactly the same as the graph (b) in Fig. 4. Imposed on drug intervention, the steady state achieved before t = 120 is disrupted and a new equilibrium is obtained after a period of variation of thyroid hormone levels. The patient asymptotically approaches a normal level of $(\mathrm{TSH}, \mathrm{FT4})$ = (3.448 mU/L, 10.89 pg/mL) after taking the medicine for 65 days.

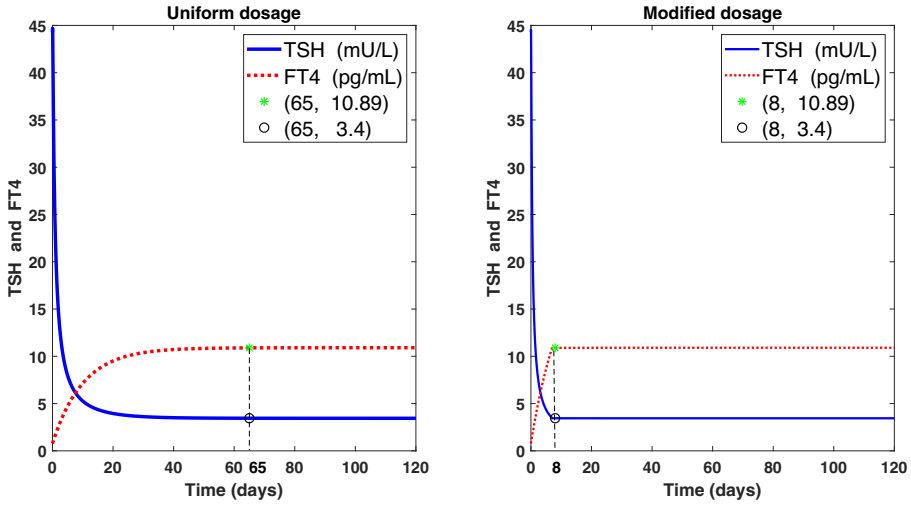

Fig. 7. A comparison between a single fixed dosage and a modified dosage upon the dynamics of TSH and FT4 for Hashimoto's thyroditis treatment. TPOAb = 400 U/mL. All parameters remain the same as those in Fig. 2 except for G. For the left single fixed dosage graph, G is set to be a constant at 1. In the right modified dosage graph, $G = 2$ when $t < 7$ and $G = 1$ when $t \geqslant 7$. The two graphs have the same equilibrium which is approximately (TSH, FT4) = (3.4 mU/L, 10.89 pg/mL), lying in the normal range. However, patients taking the uniform dosage need at least 65 days to get the relatively optimal thyroid state, which suffices to take 8 days to be achieved with modified dosage.

dose of levothyroxine, and then switch to a smaller dosage after a relatively short period of time. Our model simulation in Fig. 7 demonstrates that this strategy is feasible and effective. We maintain choosing the patient with TPOAb = 400 U/mL and $(\text{TSH}, \text{FT4}) = (44.27\ mU/L, 0.77\ pg/mL)$ as the initial state. However, the dosage regimen is changed to a double dosage at the first six days and then returns to the same dose as in Fig. 6 for the following days. The model predicts that with the modified dosage, it takes only 8 days to approach the same level of $(\text{TSH}, \text{FT4}) = (3.4\ mU/L, 10.89\ pg/mL)$. This result of 8 days in comparison to 65 days supports the commonly adopted regimen for treating patients with severe hypothyroidism.

All the previous figures mentioned show that no matter which initial point we start from, our system of the Hashimoto's thyroiditis model always has a unique positive equilibrium which is globally asymptotically stable. This confirms the result of our model analysis.

We have also performed sensitivity tests on parameters p_1, U and a_2 in the Hashimoto's thyroiditis model. As shown in Fig. 5, the dynamics of FT4 are impacted only to a small extent when we vary the values of p_1, U and a_2 up to 10 percent. Moreover, the shifts of the TSH curve corresponding to these respective parameter values only represent the varied severity of Hashimoto's thyroiditis. The TSH-FT4 dynamics with the different parameter values have no effect on the analysis and clinical conclusion obtained from our model work.

3.3. Simulation of Graves' disease model

Similar as hypothyroidism, hyperthyroidism differs in distinct stages with different TSH and FT4 levels (Biondi and Cooper, 2008). It follows to ask: what is the main factor that leads Graves' disease to deteriorate from the early stage to overt hyperthyroidism? Fig. 8 demonstrates that the level of TRAb in the blood

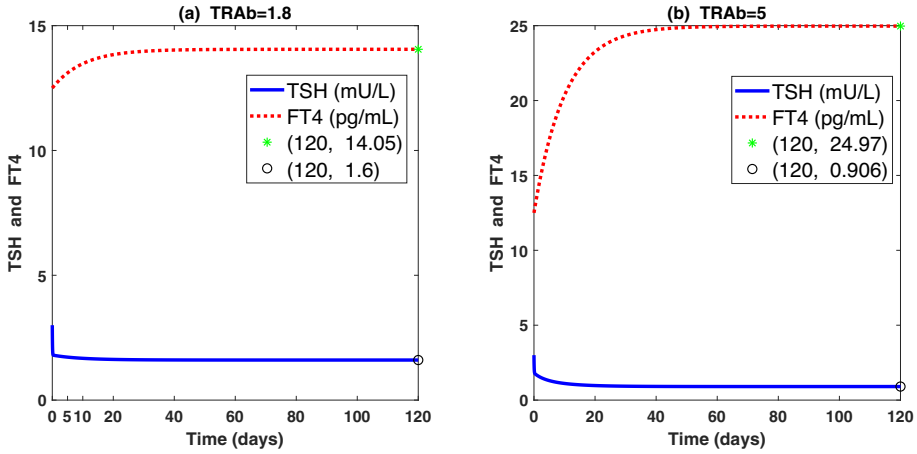

Fig. 8. Dynamics of TSH and FT4 for an untreated Graves' disease patient with abnormal TRAb levels and the same initial normal FT4 value. The initial conditions are set to be (TSH, FT4) = (3 mU/L, 12.5 pg/mL). Graph (a) shows that the thyroid hormone level for a patient with TRAb = 1.8 IU/L will approach the steady state with (TSH, FT4) = (1.6 mU/L, 14.05 pg/mL), where the FT4 value is 1.55 units higher than the initial value. Graph (b) shows that the TSH and FT4 levels of a patient with TRAb = 5 IU/L will approach the steady state with (TSH, FT4) = (0.906 mU/L, 24.97 pg/mL), where the FT4 value exceeds its normal range 6.97 units. The other parameter values are: U = 12.5 $pg \cdot mL^{-1}$, d_1 = 16.6355 day^{-1}, d_2 = 0.099021 day^{-1}, p_1 = 30 $mU \cdot L^{-1} \cdot day^{-1}$, s_1 = 0.0434 $pg \cdot mL^{-1}$, s_2 = 0.0021 $mU \cdot L^{-1}$, b_2 = 5. We chose the value $p_1 = 30$ here to highlight that the FT4 level would change dramatically with a minor change of the TRAb level.

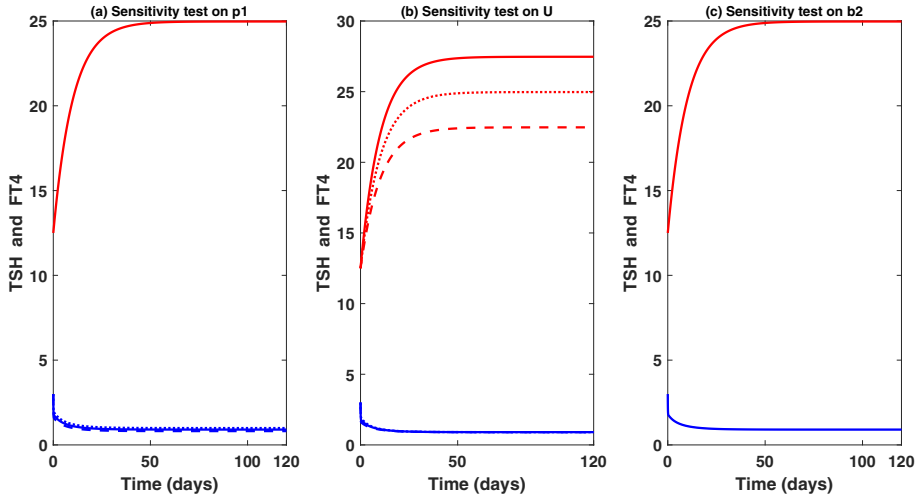

Fig. 9. Sensitivity test on parameters p_1, U and b_2 in the Grave's disease model. The value of TRAb is fixed to 5 IU/L. (a) The TSH release rate varies: $p_1 = 45$ (dashed blue for TSH curve and dashed red for FT4 curve), $p_1 = 50$ (solid blue for TSH curve and dotted red for FT4 curve), $p_1 = 55$ (dotted blue for TSH and solid red for FT4). The three curves of FT4 overlap as shown in red solid line. (b) The set point value of FT4 varies: $U = 11.5$ (dashed blue for TSH and dashed red for FT4), $U = 12.5$ (solid blue for TSH and dotted red for FT4), $U = 13.75$ (dotted blue for TSH and solid red for FT4). The three curves of TSH almost overlap. (c) The TRAb influence parameter b_2 varies: $b_2 = 4.5$ (dashed blue for TSH and dashed red for FT4), $b_2 = 5$ (solid blue for TSH and dotted red for FT4), $b_2 = 5.5$ (dotted blue for TSH and solid red for FT4). The change of TSH-FT4 dynamics on the three different values of b_2 is negligible and the curves overlap in solid lines.

can be an answer. Graph (a) in Fig. 8 illustrates that the FT4 value of a patient with euthyroid initial state would increase by 1.55 pg/mL over time, even if his TRAb value is set to be 0.05 units higher than the normal value 1.75 IU/L. Moreover, if we elevate the TRAb value to 5 IU/L, the FT4 value of the same patient with the same initial conditions would further increase to 6.97 units greater than 18 pg/mL (i.e. the upper bound of the FT4 normal range) over time, as shown in Fig. 8(b).

Unlike hypothyroidism, patients with Grave's disease usually have obvious signs and symptoms, as the overproduced thyroid hormones can significantly influence the body systems in a wide range and seriously impact their daily life. In order to relieve patients' suffering, physicians need to normalize the thyroid hormones of patients as soon as possible and anti-thyroid drugs (ATD) are frequently prescribed at the outset. Consider the same patient from last graph who has TRAb = 5 IU/L and progresses from euthyroidism to overt hyperthyroidism at the level of $(\text{TSH}, \text{FT4}) = (0.906\ mU/L, 24.97\ pg/mL)$. We suppose a certain dosage of ATD, which can be converted to a constant $G = -1.6$ in the Grave's disease model, is given to treat the patient starting at day 120. Fig. 10 shows that the FT4 and TSH levels of the patient will return to a normal value at $(\text{TSH}, \text{FT4}) = (2.54\ mU/L, 8.86\ pg/mL)$ with daily medication treatment.

However, it takes 75 days for the patient to approach the steady state thyroid hormone level with the dosage $G = -1.6$, which implies that this prescription lacks timeliness and effectiveness. The question follows: how can we find a better dosing strategy without exposing the patient to the risk of trial? Our model comes into play and Fig. 11 demonstrates an ideal strategy. We maintain the choice of the patient with TRAb = 5 IU/L and $(\text{TSH}, \text{FT4}) = (0.906\ mU/L, 24.97\ pg/mL)$ as the initial state. However, the dosage regimen is changed to be doubled at the first six days and the same dose as in Fig. 10 for the following days. The Grave's disease model predicts that with the modified dosage, it

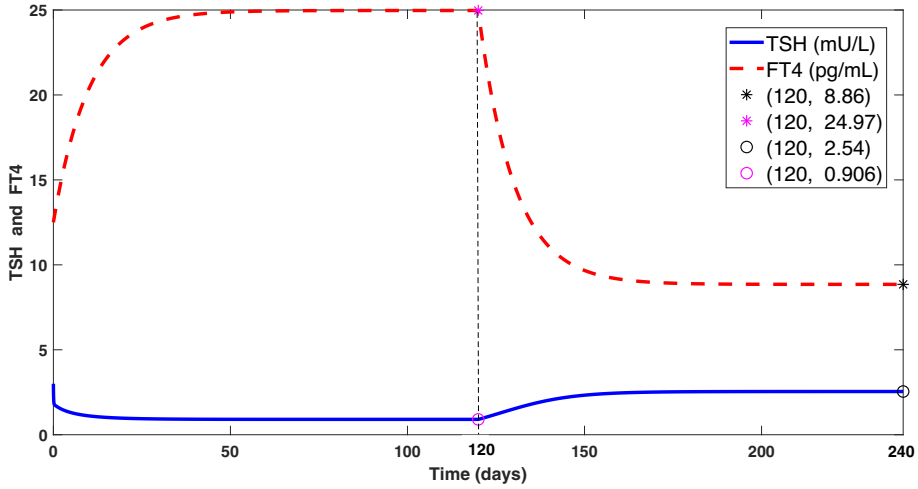

Fig. 10. Dynamics of TSH and FT4 for a patient with Grave's disease under drug intervention since day 120. Here TRAb = 5 IU/L, $G = 0$ when $t < 120$ and $G = -1.6$ when $t \geqslant 120$. All of the other parameters remain the same as those in Fig. 8. Before t = 120, the figure is exact the same as the graph (b) in Fig. 8. Imposed on drug intervention, the steady state achieved before t = 120 is disrupted and a new equilibrium is obtained after a period of variation of thyroid hormone levels. The thyroid hormones of the patient asymptotically approache a normal level of (TSH, FT4) = (2.54 mU/L, 8.86 pg/mL) over time.

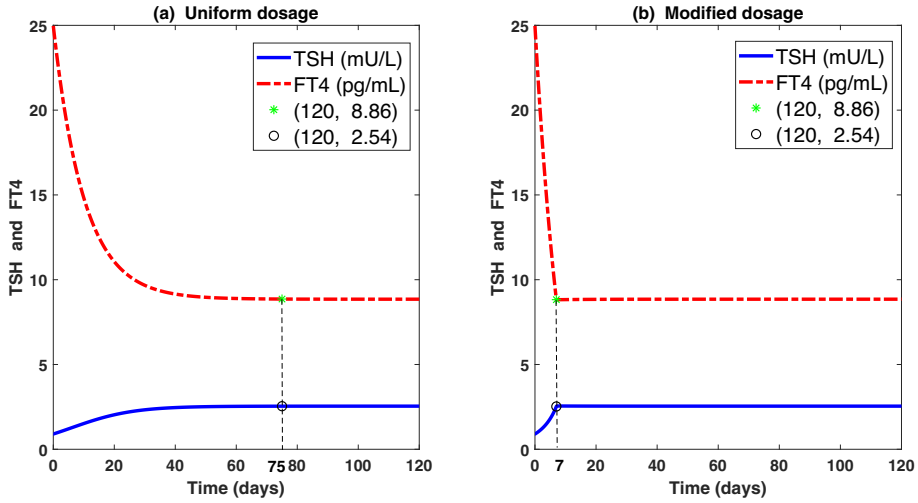

Fig. 11. A comparison between a single fixed dosage and a modified dosage upon the dynamics of TSH and FT4 for Graves' disease treatment. TRAb = 5 IU/L. All the parameters remain the same as those in Fig. 8 except for G. In the left graph (a), G is set to be a constant at -1.6. In the right modified dosage graph, $G = -3.2$ when $t < 7$ and $G = -1.6$ when $t \geqslant 7$. The two graphs have the same equilibrium which is approximately (TSH, FT4) = (2.54 mU/L, 8.86 pg/mL), lying in the normal range. However, patients taking the uniform dosage need at least 75 days to achieve the relatively optimal thyroid state, which suffices to take 7 days to be achieved with modified dosage.

takes only 7 days to approach the same normal level of $(\text{TSH}, \text{FT4}) = (2.54\, mU/L, 8.86\, pg/mL)$.

The sensitivity tests on parameters p_1, U and b_2 in the Graves' disease model are conducted and shown in Fig. 9. The dynamics of TSH and FT4 are influenced insignificantly when we vary the value of p_1 and b_2 up to 10 percent. As the set point value U decreases, the TSH dynamics essentially stay the same and the FT4 trajectory shifts down remaining above the normal range of FT4, which represents a reduced severity of Graves' disease.

Our unified model utilized in different thyroid states reveals an inverse pattern of variation between TSH and FT4 and is accordance with clinical observations. Moreover, our euthyroid model simulation exhibits individual dynamic and static characteristics of the HPT axis. The simulations of the two disease models describe disease trajectories and predict final thyroid state of an individual with different thyroid initial conditions. Most importantly, we showed the feasibility for physicians to apply our model in choosing appropriate dosage regimens for patients.

4. Model fitting to Hashimoto's thyroiditis data

In this section, we show an example of how to estimate individualized parameter values in our model to predict the dynamical behaviors of TSH and FT4 concentrations for a hypothyroid patient (named Patient A, see below) with a few early visit data. As we have limited access to patients' data and it takes frequent blood test data to obtain good parameter estimations for our differential equations system, only one data fitting example is exemplified here. However, the method we use to obtain the estimated parameter values for this patient can be applied to other patients. Given a larger sample of patients' data, we can perform more data analysis in the future.

Patient A has Hashimoto's thyroiditis. The medical record shows that he was prescribed 100 mcg levothyroxine after his first visit to the hospital in Chongqing, China on June 19, 2018, with his blood test data measured to be:

$$\text{TSH} = 86.331 \text{ mU/L}, \quad \text{FT4} = 1.6818 \text{ pg/mL}, \quad \text{TPOAb} = 1600 \text{ U/mL}.$$

He had been taking the same dose daily when his blood concentration data for TSH, FT4, and TPOAb were collected over the next 6, 8, 12, 15, 18, 22 days. Although there is one more set of data points which was collected 204 days from the first visit, the record illustrates that Patient A relapsed for some unknown reason and it is highly possible that he stopped taking the medicine for a certain period before the last visit. Therefore, the last visitation data is excluded from our data fitting.

We have eight parameters in the model (10) after we substitute the parametric expression (7) for $p_2(t)$, shown as follows:

$$\begin{cases} \frac{d\text{TSH}(t)}{dt} = p_1 - \frac{p_1(\text{FT4}-U)}{s_1+\text{FT4}} - d_1\text{TSH}, \\ \frac{d\text{FT4}(t)}{dt} = \frac{2d_2U\left(1+\frac{d_1s_2}{p_1}\right)\text{TSH}}{\left(1+e^{a_2(\text{TPOAb}(t)-60)}\right)(s_2+\text{TSH})} - d_2\text{FT4} + G. \end{cases} \tag{10}$$

We maintain $U = 12.5$ (pg/ml) for all patients. The parameters $s_1 = 0.0434, s_2 = 0.0021$ are chosen from the literature (Pandiyan, 2011), calculated through equilibrium argument. We compute d_1, d_2 by half-lives of TSH and FT4. Since the half-life of TSH is 1 h and approximately 7 days for FT4, we derive.

$$d_1 = 16.6355/day, \quad d_2 = 0.099021/day.$$

We determine the values for the remaining parameters by fitting the system of Eqs. (10) to the TSH, FT4, and TPOAb data of Patient A. In order to fit the parameter a_2, we need the continuous function TPOAb(t). In order to get the explicit expression of TPOAb (t), we apply the least-square algorithm to the TPOAb time-series data. The full medical record shows the TPOAb values of Patient A decrease over time with the minimum value 308 U/mL attained after 204 days from the first visit. We then assume the TPOAb(t) function is in the exponential form

$$\text{TPO}Ab(t) = 308 + b_1e^{-b_2t},$$

where b_1, b_2 are positive constants. The data fitting result for TPOAb gives

$$b_1 = 1304, \quad b_2 = -0.0524,$$

and the TPOAb fitting curve is shown in Fig. 12.

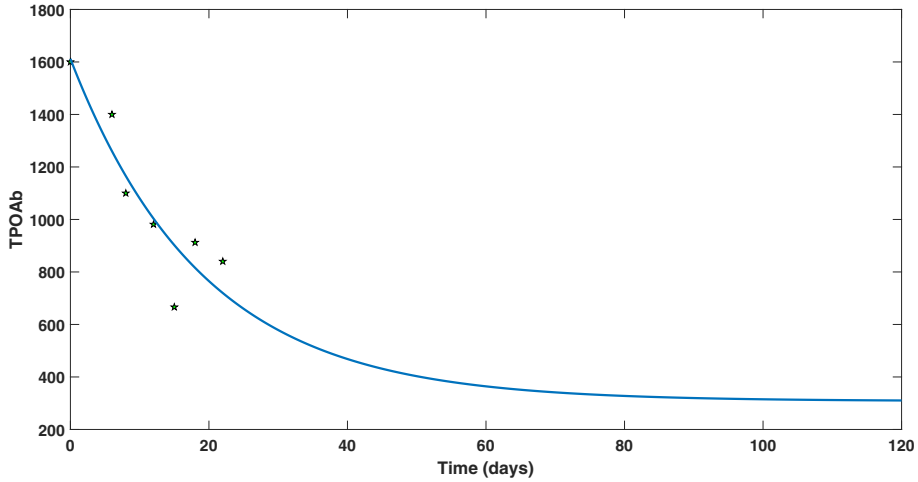

Fig. 12. Data fitting to the TPOAb data using an exponentially decreasing function with the minimum value 308, as recorded in Patient A.

We perform data fitting to the system (10) by the commercial software package Berkeley Madonna. The parameter estimates are based on the best fitting that achieves the minimum root mean square (RMS) between model prediction and the data, which is calculated using the following formula.

$$RMS = \sqrt{\frac{\sum_{i=1}^{n}\left[\left(TSH(t_i) - \widehat{TSH}(t_i)\right)^2 + \left(FT4(t_i) - \widehat{FT4}(t_i)\right)^2\right]}{2n}}$$

In the formula, $TSH(t_i)$ represents the TSH level at time t_i predicted by the model and $\widehat{TSH}(t_i)$ is the corresponding data at t_i. $FT4(t_i)$ and $\widehat{FT4}(t_i)$ are defined similarly. In the clinical scenario, thyroid function test data show that patients with mild thyroid disorders can recover their FT4 and TSH to the expected baseline levels relatively fast in a coupled fashion with drug treatment. However, hypothyroid patients with severe departure of initial FT4 and TSH values away from their normal ranges can still have persistent elevation of serum TSH even when FT4 has recovered sometimes for weeks. This phenomenon is termed as *hysteresis* which has been noted for decades Leow, 2016. The first data points of Patient A reveals that he was in severe hypothyroidism, and indeed, a hysteresis pattern for TSH is observed during our data fitting process. Hence, to obtain a better fitting result, we assume TSH levels are affected by the FT4 levels achieved 6 days ago, which is the time between the first two measurements. A favorable fitting result is presented in Fig. 13 and the individualized parameter values are estimated to be

$$p_1^* = 110, \quad a_2^* = 0.00529, \quad G^* = 1.6.$$

We note that $G^* = 1.6$ corresponds to the 100 ug dose of levothyroxine which Patient A had been taking. In Fig. 13, our model predicts that the patient's FT4 level will exceed the normal range after taking the dose for 45 days. Thus, the doctor needs to reduce the dosage applied to Patient A before Day 45 to avoid overshooting. This highlights the feasibility of using our model for clinical decision-making.

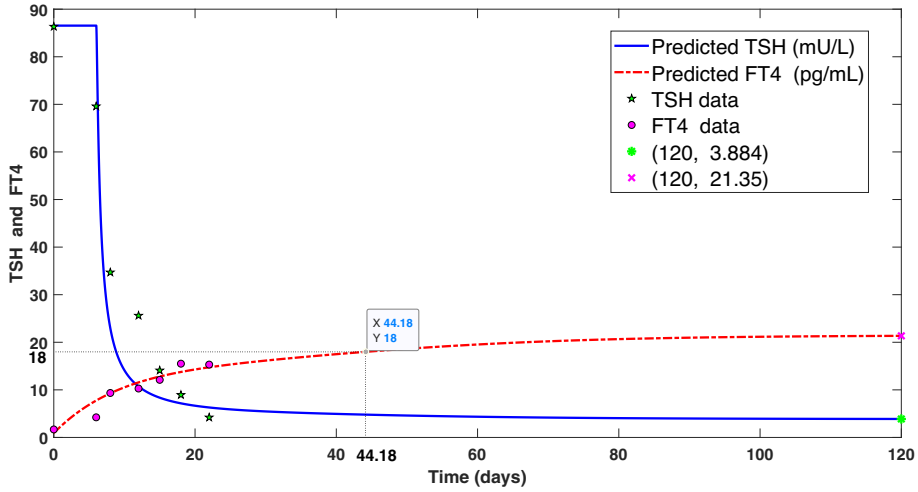

Fig. 13. Data fitting to both the TSH and FT4 levels of Patient A. Here we set the initial TSH level equal to the first TSH data point value and then fit the initial FT4 value, p_1, a_2, and G to the TSH, FT4 data sets of Patient A. Furthermore, in consideration of hysteresis, we assume that there is a delay of 6 days (i.e. the time between the first two measurements) in the reduction of TSH as the level of FT4 increases. We obtain $p_1^* = 110, a_2^* = 0.00529, G^* = 1.6$ and the initial value $FT4^* = 0.915$. The fitting curves derived from these estimated parameter values show that Patient A will asymptotically approach a level of (TSH, FT4) = (3.884 mU/L, 21.35 pg/mL) after taking the 100 ug dose of levothyroxine for 4 months.

5. Discussion

In the pursuit of analyzing the dynamic behaviors of thyroid hormones for patients with different thyroid states with or without drug intervention, a mathematical model based on a two-dimensional ODE system was developed to explain thyroid regulation for different thyroid disorders. The unified model is able to describe the regulation of TSH and FT4 for euthyroid subjects, Hashimoto's thyroiditis patients, and Graves' disease patients respectively. The sensitivity tests on important parameters in different thyroid states demonstrate the robustness of the model. In our model, the time dependent FT4 synthesis factor $p_2(t)$ was chosen to be a specific function of TPOAb or TRAb antibody depending on different thyroid disorders. Berberich et al. also mentioned that the thyroid's secretory capacity (denoted by G_T, see Ref. Berberich et al. (2018)) can affect the equilibrium concentrations of TSH and T4 using a complicated model. However, the stated correlation between G_T and thyroid function in Berberich et al., 2018 is descriptive, without illustrating how G_T is changing and how the dynamics of thyroid hormones for a specific patient are influenced by the variation of G_T and the initial thyroid functional state. Applying mathematical analysis to the Hashimoto's thyroiditis model, we proved the model always has a unique steady state and the equilibrium is globally asymptotically stable, which suggests it is feasible to control hypothyroidism with the T4 supplement drug.

Our euthyroid model demonstrated that for a person with normal thyroid function, the negative feedback control mechanism guarantees the thyroid hormone levels stay around its set point values over time, even given significant exogenous interference of two opposite directions. The simulation results of the Hashimoto's thyroiditis model showed that the level of TPOAb may be an important factor determining whether patients would progress from euthyroid state to subclinical or clinical hypothyroidism. The dynamics of TSH and FT4 in the Hashimoto's thyroiditis model illustrated that it takes approximately 65 days for the patient to reach steady state levels of TSH and FT4 with a fixed dosage. This result supports the procedure that physicians generally require patients to sustain a dose for 6–8 weeks before making any dosage adjustment. Additionally, the simulation results of our Graves' disease model reveal that the TRAb level might lead Graves' disease to deteriorate from the early stage to overt hyperthyroidism.

The current trial-and-error strategy for clinicians to find an optimal drug dosage for patients with thyroid disorders is time-consuming and may expose patients under a long time of risk and discomfort. Given the parameter values in our individualized model for a specific patient, our model was able to exhibit how the TSH and FT4 levels change over time with a certain drug dose. Two examples illustrated that the model can help clinicians design better dosage regimens which drastically shortens the required time to attain the same target thyroid hormone levels for patients with Hashimoto's thyroiditis and Graves' disease. This shows the feasibility for physicians to apply our model in choosing an optimal dosage that leads to the desired FT4 and TSH levels over a predetermined duration.

A data fitting example of a patient with Hashimoto's thyroiditis was exemplified for model comparison with some thyroid function test data. The predicted FT4 curve suggests it is not appropriate for the patient to keep taking the same dose for more than 45 days. A similar method can be applied to Graves' disease patient's data to obtain the individualized parameter values. Due to limited access to patients' data, we were not able to provide more data fitting examples for our model. Nevertheless, it is clear that given more visitation data for a certain patient during a period, the parameter values in our model can be estimated by computerized algorithms. Clinicians can employ our model to predict treatment outcome, adjust drug dosage, and develop a personalized therapeutic strategy.

For convenience, the simulations of our model are based on the assumption that the levels of thyroid auto-antibodies maintain as a constant instead of varying as a time-dependent function. A numerical simulation of the Hashimoto's thyroiditis model with a specific function of TPOAb(t) is demonstrated in Appendix A, the result of which shows the use of constant antibody levels in our model has no apparent effect on investigating the dynamic trend of the HPT system. Our model construction is based on the hypothesis that the levels of auto-antibodies in patients with Hashimoto's thyroiditis and Graves' disease determine the stimulating rate of TSH. There may exist other factors affecting the secretion rate of FT4 such as the functional size of the thyroid gland (Carlé et al., 2009). However, a model taking more factors into account will need more data for parameterization and model validation. In this study, we aim to establish a relatively simple modeling framework that only requires the data of the readily measured and commonly used variables (i.e. free T4, TSH and auto-antibodies) to facilitate the clinical application.

In view of the limited data available for the pharmacokinetics of thyroid drugs, we also incorporate drug treatment to the model via a constant additive drug input, which simplifies the illustration of TSH-FT4 dynamics given different levels of drug intake. To demonstrate that the simplified drug incorporation to the model has little impact on the dynamics of thyroid hormones, we present the comparison of thyroid hormone dynamics between constant G and episodic G integrated to the Hashimoto's thyroiditis model in Appendix A. More data on the drug concentration over time and its treatment effectiveness, when available, will support the incorporation of more comprehensive pharmacokinetics and pharmacodynamics models into our model.

In summary, this study establishes a low-dimensional modeling framework that has a unified form explaining different thyroid disorders and in the meantime can also be applied to study the thyroid hormone regulations with drug treatment. The model has the potential to assist healthcare professionals in rapid determination of the optimal length of treatment for a specified dosage which helps accelerate the attainment of euthyroid targets.

CRediT authorship contribution statement

Boya Yang: Conceptualization, Methodology, Formal analysis, Writing - original draft. **Xi Tang:** Data curation, Writing - original draft. **Michael J. Haller:** Methodology, Writing - review & editing. **Desmond A. Schatz:** Methodology, Writing - review & editing. **Libin Rong:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This work is supported by the NSF grant DMS-1950254 (LR).

Appendix A

Thyroid hormone regulation model with time-varying drug concentration:

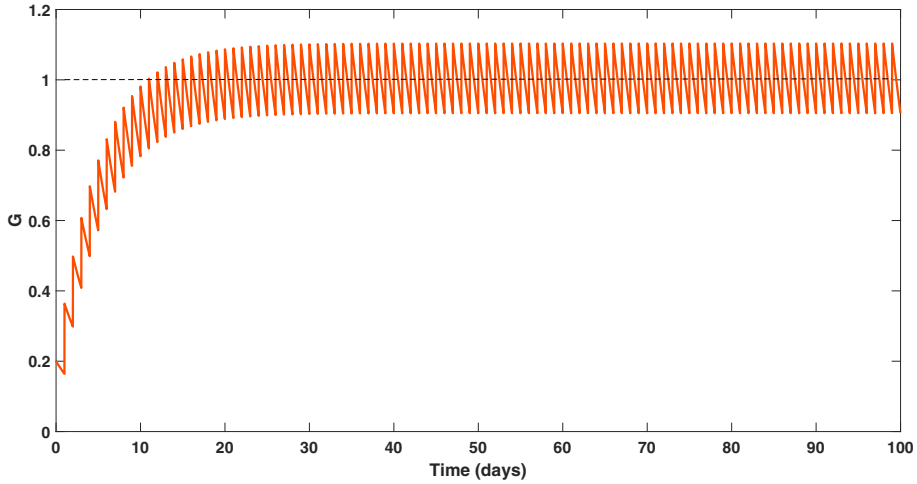

Fig. 14. Dynamics of G(t) with continuous maintenance dose on each day. See Appendix A for the equation and solution. Parameter values are $G(0) = 0.2$ and $k = 0.2$.

$$\begin{cases} \frac{\mathrm{dTSH}(t)}{\mathrm{d}t} = p_1 - \frac{p_1(\mathrm{FT4}-U)}{s_1+\mathrm{FT4}} - d_1\mathrm{TSH}, \\ \frac{\mathrm{dFT4}(t)}{\mathrm{d}t} = \frac{p_2(t)\mathrm{TSH}}{s_2+\mathrm{TSH}} - d_2\mathrm{FT4} + G, \\ \frac{\mathrm{dG}}{\mathrm{dt}} = -\mathrm{kG}, \quad \mathrm{t} \notin \mathbb{Z}^+, G(0) = G_0; \\ G(i^+) - G(i^-) = G_0, \quad i \in \mathbb{Z}^+. \end{cases}$$

Here k represents the clearance rate of the drug and $G(0)$ stands for blood concentration of the loading dose. The drug is taken daily.

Solving the impulsive differential equation for $G(t)$, we obtain

$$G(t) = G_0 \frac{1-e^{(i+1)k}}{1-e^k} e^{-kt}, \text{ for } i \leqslant t \leqslant i+1 \text{ where } i = 0, 1, 2, \cdots$$

The dynamics of G(t) are shown in Fig. 14.

We present the comparison of thyroid hormone dynamics between constant G and episodic G incorporated to the Hashimoto's thyroiditis model, as shown in Fig. 15. Notably, when the average value of the periodic G agrees with the constant G, the TSH-FT4 dynamics with varying G resemble the one we obtained by simply incorporating a constant G to the model. It is worth mentioning that there are oscillations for the FT4 curve with a periodic G(t) but they are hardly noticeable due to the scale of the vertical axis.

In the model simulations (e.g. Fig. 4), we used constant autoantibodies values to avoid the difficulty of choosing a specific antibody function. In the situation that TPOAb levels vary with time, we may assume the TPOAb value increases with time from an initial normal value, which is a reasonable assumption for untreated patients with hypothyroidism. Letting $TPOAb(t) = 60 + \frac{340t}{t+50}$ and applying the TPOAb function with the same parameter values as that in Fig. 4, we obtain the results shown in Figs. 16 and 17. As these two figures illustrate, if we set the TPOAb function to increase slowly from a normal value 60 U/mL to approach the value 400 U/mL, the dynamics with time-varying TPOAb resemble the one with fixed TPOAb = 400 U/mL and the close proximity of the two steady states is clearly presented.

Furthermore, zooming in the figure of thyroid hormone dynamics with time-varying TPOAb, as shown in Fig. 17(b), we can observe that the patient would develop subclinical hypothyroidism after Day 19 when the TPOAb exceeds 93.6 units over its normal value. Clinical hypothyroidism would occur to the patient after Day 31 when the TPOAb value is elevated by 130.1 units. Comparing the results obtained with a fixed TPOAb value and the one with time-varying TPOAb level, we perceive that whether setting TPOAb as a constant or a variable with time does not affect the application of our model to study the regulation of TSH and FT4.

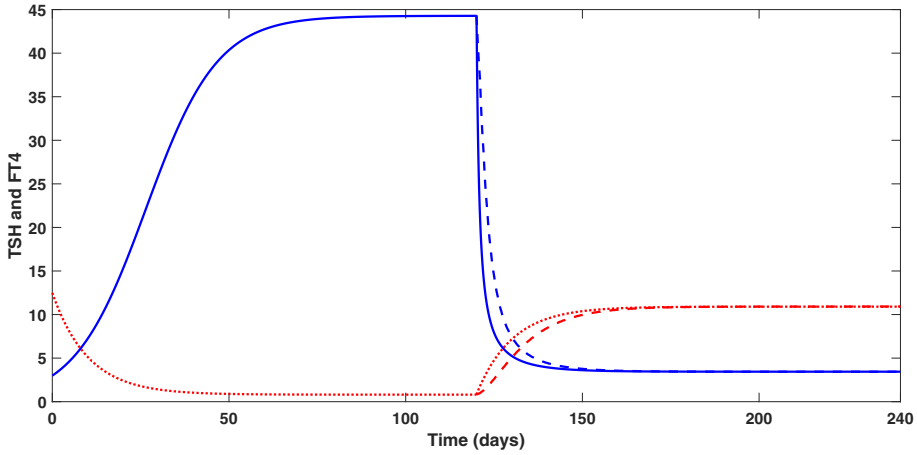

Fig. 15. Comparison of thyroid hormone dynamics between constant G and episodic G incorporated to the Hashimoto's thyroiditis model. The solid blue and dotted red lines represent the TSH-FT4 dynamics with the same parameter values taken in Fig. 6 (where G = 1). The dashed blue and dashed red lines stand for the TSH and FT4 dynamics respectively, incorporated with the varying G shown in Fig. 14.

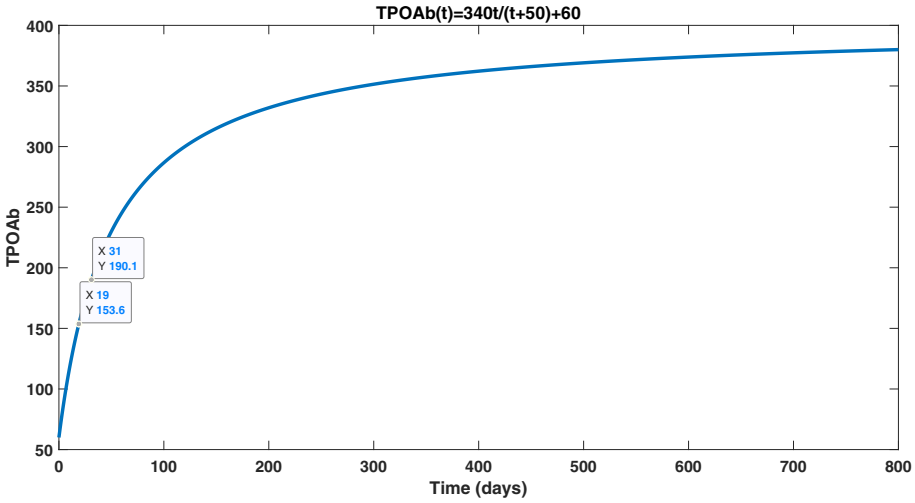

Fig. 16. Increasing function of TPOAb(t) with the horizontal asymptote at 400 U/mL, designed for simulation.

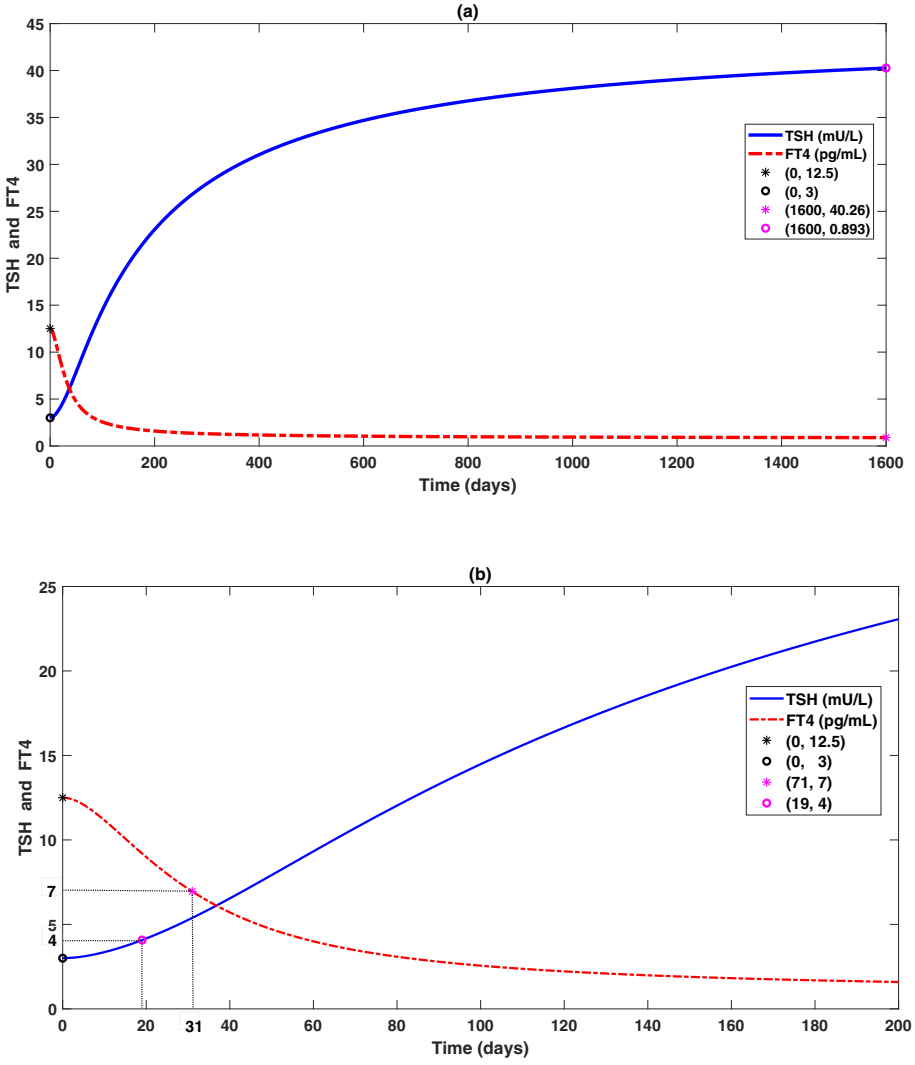

Fig. 17. Thyroid hormone dynamics with $TPOAb(t) = \frac{340t}{(t+50)} + 60$ plotted in Fig. 16. All the other parameter values remain the same as those in Fig. 4. Graph (b) is the zoomed-in figure of graph (a).

Appendix B

Proposition 1. *The Hashimoto's thyroiditis model has a unique positive steady state* $(TSH^*, FT4^*)$.

Proof. By the definition of steady state, $(\mathrm{TSH}^*, \mathrm{FT4}^*)$ satisfies the following system of equations:

$$\begin{cases} 0 = p_1 - \frac{p_1(\mathrm{FT4}-U)}{s_1+\mathrm{FT4}} - d_1\mathrm{TSH}, & (11) \\ 0 = \frac{p_2\mathrm{TSH}}{s_2+\mathrm{TSH}} - d_2\mathrm{FT4} + G. & (12) \end{cases}$$

Solving (12), we get

$$\mathrm{FT4} = \frac{\frac{p_2\mathrm{TSH}}{s_2+\mathrm{TSH}} + G}{d_2}. \quad (13)$$

Substituting (13) into (11), we obtain

$$c_1\mathrm{TSH}^2 + c_2\mathrm{TSH} + c_3 = 0, \quad (14)$$

where $c_1 = d_1(p_2 + s_1d_2 + G), c_2 = d_1s_2(s_1d_2 + G) - p_1d_2(s_1 + U)$, $c_3 = -p_1s_2d_2(U + s_1)$.

It is clear that c_1 is positive and c_3 is negative, so the Eq. (14) has a unique positive root

$$\mathrm{TSH}^* = \frac{p_1d_2(s_1+U) - d_1s_2(s_1d_2+G) + \sqrt{(p_1d_2(s_1+U) - d_1s_2(s_1d_2+G))^2 + 4p_1d_2d_1s_2(s_1+U)(p_2+s_1d_2+G)}}{2d_1(p_2+s_1d_2+G)}.$$

Substituting TSH^* back into (13), we can get $\mathrm{FT4}^*$. □

Proposition 2. *The steady state* $(TSH^*, FT4^*)$ *for the Hashimoto's thyroiditis model is locally asymptotically stable.*

Proof. We first linearize the model near the steady state $(\mathrm{TSH}^*, \mathrm{FT4}^*)$. The Jacobian matrix is

$$J = \begin{pmatrix} -d_1 & -\frac{p_1(s_1+U)}{(s_1+\mathrm{FT4})^2} \\ \frac{p_2s_2}{(s_2+\mathrm{TSH})^2} & -d_2 \end{pmatrix}.$$

Observing that

$$Det(J(\mathrm{TSH}^*, \mathrm{FT4}^*)) = d_1d_2 + \frac{p_1p_2s_2(s_1+U)}{(s_2+\mathrm{TSH}^*)^2(s_1+\mathrm{FT4}^*)^2} > 0$$

and

$$TrJ = -(d_1 + d_2) < 0,$$

we conclude that the equilibrium $(\mathrm{TSH}^*, \mathrm{FT4}^*)$ is locally asymptotically stable. □

Proposition 3. *The steady state* $(TSH^*, FT4^*)$ *for the Hashimoto's thyroiditis model is also globally asymptotically stable.*

Proof. To begin, we use Dulac's criterion to rule out the possibility of periodic orbits or graphics for the model and then we apply the Poincaré-Bendixson Theorem to show all the trajectories of the model converge to the equilibrium $(\mathrm{TSH}^*, \mathrm{FT4}^*)$ (Martcheva, 2015). □

Lemma 1. *The Hashimoto's thyroiditis model does not possess periodic orbits or graphics.*

Set

$$\begin{aligned} \frac{d\mathrm{TSH}(t)}{dt} &= p_1 - \frac{p_1(\mathrm{FT4}-U)}{s_1+\mathrm{FT4}} - d_1\mathrm{TSH} = f(\mathrm{TSH}, \mathrm{FT4}), \\ \frac{d\mathrm{FT4}(t)}{dt} &= \frac{p_2\mathrm{TSH}}{s_2+\mathrm{TSH}} - d_2\mathrm{FT4} + G = g(\mathrm{TSH}, \mathrm{FT4}). \end{aligned}$$

Let $Z = \mathbb{R}^2_+$. It is clear that Z is open and simply connected. Also f and g are continuously differentiable on Z. Choose $D \equiv 1$, then

$$\frac{\partial(Df)}{\partial\mathrm{TSH}} + \frac{\partial(Dg)}{\partial\mathrm{FT4}} = (-d_1) + (-d_2) < 0,$$

since both d_1 and d_2 are positive. Thus, by Dulac-Bendixson Criterion (Martcheva, 2015), the model does not possess periodic orbits or graphics.

Lemma 2. *All trajectories of the Hashimoto's thyroiditis model is constrained in a bounded region of* $\mathbb{R}^2_+$.

The equations of the model can be rewritten as

$$\begin{aligned} \tfrac{d}{dt}(\mathrm{TSH} + s_2) &= \tfrac{p_1(s_1+U)}{s_1+\mathrm{FT4}} - d_1(\mathrm{TSH} + s_2) + d_1s_2, \\ \tfrac{d}{dt}(\mathrm{FT4} + s_1) &= -\tfrac{p_1s_2}{\mathrm{TSH}+s_2} - d_2(\mathrm{FT4} + s_1) + (p_1 + s_1d_2 + G). \end{aligned}$$

We observe that

$$s_2 > \frac{p_2s_2}{p_2 + s_1d_2 + G}.$$

By changing of variables with $x = \mathrm{TSH} + s_2$ and $y = \mathrm{FT4} + s_1$, we consider the differential equations:

$$\frac{dx}{dt} = \frac{A}{y} - ax + \alpha = P(x, y) \quad (15)$$

$$\frac{dy}{dt} = -\frac{B}{x} - by + \beta = Q(x, y) \quad (16)$$

where the constants are all positive with

$$\frac{\alpha}{a} > \frac{B}{\beta} \quad (17)$$

First, we show

$$\liminf_{t\to\infty} x(t) \geqslant \frac{\alpha}{a} > 0.$$

From Eq. (15), we have

$$\frac{d}{dx}e^{at}x(t) = \frac{Ae^{at}}{y(t)} + \alpha e^{at}.$$

Thus,

$$\begin{aligned} e^{at}x(t) &= x(0) + \frac{\alpha}{a}e^{at}(1 - e^{-at}) + \int_0^t \frac{Ae^{as}}{y(s)}ds \\ &> x(0) + \frac{\alpha}{a}e^{at}(1 - e^{-at}), \end{aligned} \quad (18)$$

and this implies

$$x_* := \liminf_{t\to\infty} x(t) \geqslant \frac{\alpha}{a} > 0. \quad (19)$$

From Eq. (16), we have

$$\frac{d}{dx}e^{bt}y(t) = -\frac{Be^{bt}}{x(t)} + \beta e^{bt}.$$

Thus,

$$e^{bt}y(t) = y(0) + \frac{\beta}{b}e^{bt}(1 - e^{-bt}) - \int_0^t \frac{Be^{as}}{x(s)}ds < x(0) + \frac{\beta}{b}e^{bt}(1 - e^{-bt}),$$

which yields

$$y^* := \limsup_{t\to\infty} y(t) \leqslant \frac{\beta}{b}.$$

Next, we will prove

$$y_* := \liminf_{t\to\infty} y(t) > 0 \quad \text{and} \quad x^* := \limsup_{t\to\infty} x(t) < \infty.$$

Let $O := \{(x(t), y(t)) : 0 \leqslant t < \infty\}$ be an orbit lying in the first quadrant. Let $Z = \{0 \leqslant t_1 < t_2 < t_3 < .. < t_n < ..\}$ be the sequence of points in $[0, \infty)$ such that $y\prime(t_j) = 0, j = 1, 2, \ldots$. The set Z may be an empty set. We observe

$$\inf_{t\geqslant 0} y(t) = \min\{y(0), y(t_1), y(t_2), \ldots, y(t_n), \ldots\}.$$

If Z is an empty set or a finite set, clearly $\inf_{t\geqslant 0} y(t) > 0$.

Suppose Z is an infinite set (this situation will occur if (x_c, y_c) is a spiral point). Then $\{t_n\}$ is an increasing sequence tending to ∞. From (17) and (19),

$$\frac{B}{\beta} < \frac{\alpha}{a} \leqslant x_*,$$

we can choose an $\bar{x}$ with $\frac{B}{\beta} < \bar{x} < x_*$ and let $\bar{y}$ be the intersection of the vertical line $x = \bar{x}$ and the hyperbola $by = -\frac{B}{x} + \beta$. Since $\bar{x} > B/\beta$, we see that $\bar{y} > 0$. Since $\bar{x} < x_*$, there exists some $\bar{t}$ such that

$$x(t) > \bar{x}$$

for all $t \geqslant \bar{t}$ and this implies that the orbit $O_{\bar{t}} := \{(x(t), y(t)) : \bar{t} \leqslant t < \infty\}$ lies on the right hand side of the vertical line $x = \bar{x}$ and which, in turn, implies that the intersections of $O_{\bar{t}}$ with the hyperbola $by = -\frac{B}{x} + \beta$ all have their y-coordinates greater than $\bar{y}$. Hence, we deduce that

$$y(t_j) \geqslant \bar{y}$$

for all $t_j \geqslant \bar{t}$. We choose j_0 such that $t_j \geqslant \bar{t}$ for all $j \geqslant j_0$. Then

$$\inf_{t\geqslant 0} y(t) = \min\{y(0), y(t_1), y(t_2), \ldots, y(t_{j_0})\} > 0.$$

To show $x^* < \infty$, we choose $0 < y_0 < y_*$. Then there exists some t_* such that

$$y(t) > y_0$$

for all $t \geqslant t_*$. Then, from (18), we have

$$\begin{aligned} e^{at}x(t) &= x(0) + \tfrac{\alpha}{a}e^{at}(1 - e^{-at}) + \int_0^t \tfrac{Ae^{as}}{y(s)}ds \\ &= x(0) + \tfrac{\alpha}{a}e^{at}(1 - e^{-at}) + \int_0^{t_*} \tfrac{Ae^{as}}{y(s)}ds + \int_{t_*}^t \tfrac{Ae^{as}}{y(s)}ds \\ &< x(0) + \tfrac{\alpha}{a}e^{at}(1 - e^{-at}) + \int_0^{t_*} \tfrac{Ae^{as}}{y(s)}ds + \int_{t_*}^t \tfrac{Ae^{as}}{y_0}ds \\ &= x(0) + \tfrac{\alpha}{a}e^{at}(1 - e^{-at}) + \int_0^{t_*} \tfrac{Ae^{as}}{y(s)}ds + \tfrac{A}{ay_0}e^{at}\left(1 - e^{-a(t-t_*)}\right). \end{aligned}$$

From the above, we deduce that

$$x^* = \limsup_{t\to\infty} x(t) \leqslant \frac{\alpha}{a} + \frac{A}{ay_0} < \infty.$$

Therefore, combining Lemma 1 with Lemma 2, we conclude that all trajectories of the Hashimoto's thyroiditis model converge to the steady state $(\mathrm{TSH}^*, \mathrm{FT4}^*)$. □

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