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

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Introduction

- The thyroid hormones, triiodothyronine (T3) and thyroxine (T4), 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. Greater than 12 percent of the U.S. population is exposed to a thyroid disorder in their lifetime.

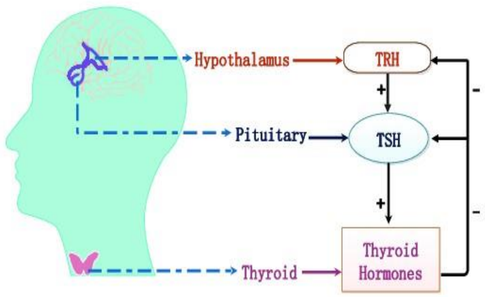


Figure 1: HPT-axis negative feedback mechanism.

Motivations

- Both excess and deficiency of drug intervention in thyroid may impose adverse influence in diverse target tissues. 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.
- So far a limited number of mathematical models have been proposed to study the abnormality in the thyroid gland. They include a number of variables, some of which may not be validated by available data. Among those models, very few have investigated the quantitative response of TSH-FT4 dynamics to different plasma concentration of thyroid drugs.
- 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.

Our work

- We establish a two-dimensional ordinary differential equation model to analyze thyroid regulation for euthyroid subjects, Graves' disease patients and Hashimoto's thyroiditis patients.
- Our model is designed upon the HPT axis negative feedback control mechanism, involving only the variables of serum FT4, TSH and autoantibody concentrations. 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.

Unified model for euthyroid and thyroid disorders

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

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

U: The set point value of FT4.

P_1: The default release rate of TSH from the pituitary when FT4 meets the euthyroid set point value.

G: The amount of increased or decreased thyroxine levels per unit of time caused by the intake of different thyroid drugs.

The FT4 synthesis factor $p_2(t)$ varies with patients in different thyroid states:

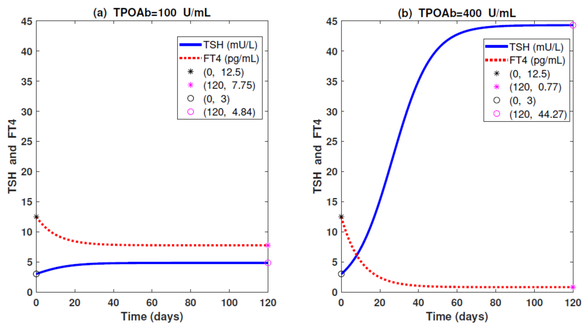
I. Euthyroid state $\quad p_2 = d_2U(1 + \frac{d_1 s_2}{p_1}).$

II. Hashimoto's thyroiditis $\quad p_2(t) = \frac{2d_2U(1 + \frac{d_1 s_2}{p_1})}{1 + e^{a_2(\mathrm{TPOAb(t)}-60)}}$

III. Graves' disease $\quad p_2(t) = \frac{2d_2U(1 + \frac{d_1 s_2}{p_1})}{1 + e^{-b_2(\mathrm{TRAb(t)}-1.75)}}.$

Results

Figure 2: Dynamics of TSH and FT4 for an untreated patient (G=0) in subclinical and clinical hypothyroidism with initial normal FT4 value.



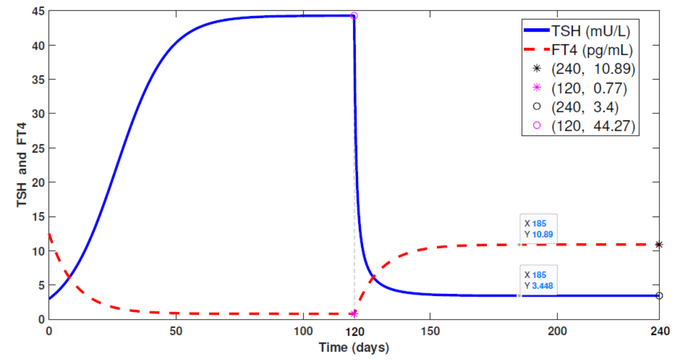


Figure 3: Dynamics of TSH and FT4 for a patient in Hashimoto's thyroiditis with drug treatment since day 120.

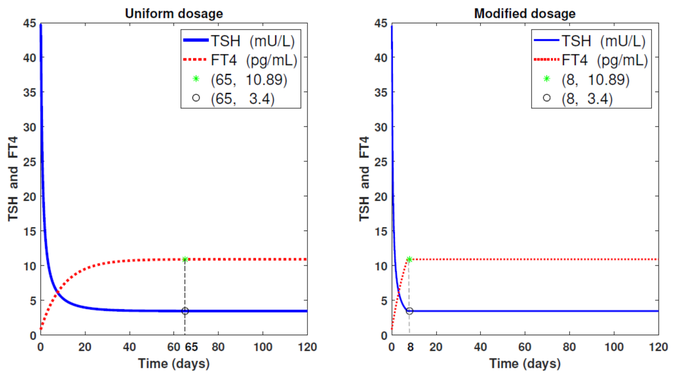


Figure 4: A comparison between a single fixed dosage and a modified dosage upon the dynamics of TSH and FT4 for Hashimoto's thyroiditis treatment

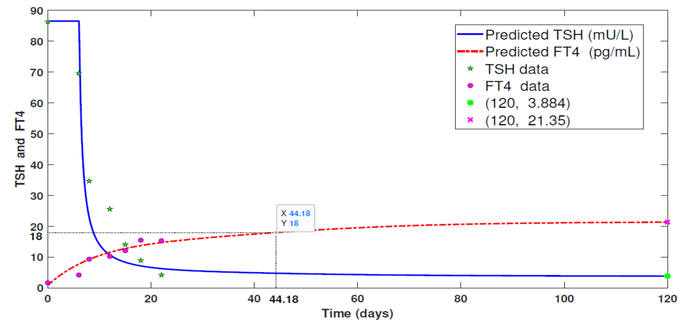


Figure 5: Data fitting to both the TSH and FT4 levels of Patient A with Hashimoto's thyroiditis.

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