Model of Levothyroxine Treatment for Hypothyroidism

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Abstract— **Understanding the negative feedback loop is essential for evaluating the regulation of a patient's hypothalamic-pituitary-thyroid axis and the effect it has on their health. Hypothyroidism is currently the leading disorder that affects the HPT axis and is caused by the body's failure to produce enough thyroid hormones to regulate the system. Through several key simplifying assumptions, we modeled the treatment of hypothyroidism through Levothyroxine as two ODEs. A Simulink block diagram was then derived from the equations and used to simulate a healthy thyroid, hypothyroidism, and treatment with Levothyroxine. Plots of the secreted hormones adequately represent expected physiology of the HPT axis. The transfer function and the subsequent output and bode plots characterize the response of our system.**

Clinical Relevance— **This simplifies the negative feedback model of the hypothalamic-pituitary-thyroid axis, specifically in the case of primary hypothyroidism with a levothyroxine treatment.**

I. Introduction

A. Hypothalamic-Pituitary-Thyroid Axis

The thyroid is an organ that secretes hormones that control several body functions and is essential for the metabolism and growth/development of the human body. The regulation of the thyroid's function is conducted by the hypothalamic-pituitary-thyroid (HPT) axis which is a neuroendocrine negative feedback-controlled loop between thyroid hormone levels and the hypothalamus and pituitary glands. The hypothalamus initially secretes thyrotropin-releasing hormone (TRH) that travels to the pituitary gland to stimulate the production and secretion of thyrotropin or thyroid stimulating hormone (TSH). TSH then drives the thyroid gland to secrete thyroid hormones with 80% of the hormones released being circulating thyroxine (T4) and 10% being triiodothyronine (T3). T4 can be separated into free T4 and bounded (to proteins in the blood) T4.

Free T4 has no known effects at the nuclear level and currently just serves to be converted to T3 in the liver through deiodination. 80% of all T3 is produced this way. T3 is the more active form that directly acts on the thyroid hormone nuclear receptors of the hypothalamus and the pituitary to suppress the production of TRH and TSH in the negative feedback loop. The produced T3 is essentially compared to a physiological HPT axis setpoint that is different for everyone. When circulating T3 levels are low, the HPT axis is activated to increase both TRH and TSH which will in turn produce more thyroid hormones. When circulating T3 levels are high, the HPT axis's production is then suppressed to allow the thyroid hormones to fall back to a normal value.

While T4 does not directly affect the control of the HPT axis, it does serve an essential role in the clinical study of the system by acting as a clinical surrogate parameter of thyroid hormone levels since it is difficult to properly measure the change in T3 and most of T4, which is easier to measure, is converted to T3 anyways. Physicians will also choose to ignore TRH levels when examining for thyroid disorders since TRH has a very short half-life (5 mins) and is hard to determine the concentration in a research setting. TSH, on the other hand, lasts longer (1 hour) and is also very indicative of the thyroid's status so it becomes one of the benchmarks of evaluating the thyroid's function. Physicians use T4 and TSH levels to diagnose any thyroid problems in patients [1].

B. Hypothyroidism

The most common disorder affecting thyroid function is hypothyroidism which is a class of conditions characterized by plasma concentrations of thyroid hormones that are chronically below normal. Hypothyroidism results from thyroid failure or insufficient thyroid hormone stimulation by the hypothalamus or pituitary gland. Failure of the thyroid gland can be caused by "congenital abnormalities, autoimmune destruction (Hashimoto disease), iodine deficiency, and infiltrative diseases" [2]. About 0.33% of the US population are believed to have some form of hypothyroidism with women and people over the age of 60 more likely to have it. Common symptoms of hypothyroidism include depression, fatigue, weight gain, dry skin, memory impairment, constipation, slowed heart rate, etc. Untreated hypothyroidism can lead to further complications like goiters around the neck, heart problems, mental health issues, etc. Women can also deal with menstrual issues and infertility. Most stages of hypothyroidism can be classified into three types. Primary hypothyroidism is more severe and is characterized by elevated levels of TSH with decreased T3 and T4 levels. Central or secondary hypothyroidism is caused by diseases in the hypothalamus or pituitary gland and the serum levels of TSH and thyroid hormones are similar to primary hypothyroidism. Lastly, subclinical hypothyroidism is milder and is characterized by elevated TSH levels but normal T3 and T4 levels [3].

C. Levothyroxine and Treatments

The main form of treatment for most hypothyroidism cases is levothyroxine sodium which is a pure synthetic alternative version of T4. Levothyroxine is available as a generic drug and under various brands with different ingredients. The goal of levothyroxine is to normalize the raised TSH concentrations from the body's insufficiency in producing T4 and T3. The drug is taken as a pill that contains 75 to 100 grams of levothyroxine a day for women and 100 to 150 grams per day for men. After the drug is consumed, absorption occurs in the human small intestine with serum T4 levels beginning to peak at 2 to 4 hours after and remaining at

this level for up to 6 hours. The increase of T3 levels is slower since it requires T4 to be converted to T3 in the liver. Since other drugs may alter the effectiveness of levothyroxine, TSH levels should be monitored more closely in these cases especially in women during pregnancy.

For most patients suffering from primary hypothyroidism, levothyroxine is an adequate treatment that should regulate the body's thyroid hormone levels. The dosage starts off standard (1.6 g/kg body weight) and can be changed after 2 months. Primary hypothyroidism usually means that the patient will have to take levothyroxine for their entire life. Secondary hypothyroidism can still be treated with levothyroxine, but glucocorticoid replacements should be administered first. Patients suffering from subclinical hypothyroidism may require levothyroxine treatment depending on several conditions such as TSH concentration stability, efficacy of thyroid hormones on other tissues, cardiac function, and cognitive function. Nevertheless of the condition, patients suffering from any form of hypothyroidism should still be monitored to control the progression of the disease [4].

II. Methods

A. Equations and Assumptions

The governing equations used to guide our model are

$$(1)\quad \frac{dTSH}{dT} = k(T(t) - T4(t)) - a * TSH(t)$$

$$(2)\quad \frac{dT4}{dT} = a * b * TSH(t) - T4(t) + L(t)$$

In the equations, TSH and T4 represent their respective hormones, T represents the target homeostatic level of T4, L(t) represents a possible input of Levothyroxine, and a, b, and k are gains that represent the rates/ratios that guide physiological production. The first equation describes the rate of change of TSH concentration. The difference between the current T4 levels and target homeostatic levels is positively proportional to the change in TSH levels while the use of TSH to stimulate the thyroid negatively affects the rate of change. The second equation describes the rate of change of T4 concentration. a*b*TSH(t) is the rate of T4 secretion out of the thyroid, accounting for both the rates of TSH stimulation of the thyroid and the thyroid secretion of T4. -T4 represents the T4 loss/use in biological functions, and +L(t) represents the positive rate of change of T4 when Levothyroxine is added to the system. In building this model, we made several key simplifying assumptions. The first is that only total T4 levels regulate the secretion of TRH and TSH in the negative feedback. With this assumption, we are eliminating free T4 and T3 from the system. The second assumption is similar in that we are eliminating and essentially lumping in TRH's consideration in the system into TSH. The main motivation behind these two simplifying assumptions is that when physicians are monitoring and diagnosing hypothyroidism, they only measure T4 and TSH levels in patients as explained. A third assumption that we are making is that TSH only gets consumed in the process of stimulating the thyroid. Likewise, the fourth assumption is that T4 is only lost when feeding back on the system and stimulating the secretion of TSH. Since we are focused on just hypothyroidism, we can assume a closed system where each hormone only reacts to the other. The last assumption we are making is that the relationship between TSH and T4 concentrations is a linear relationship when in physiology, it's typically modeled as an inverse exponential-power relationship [1].

B. Block Diagram

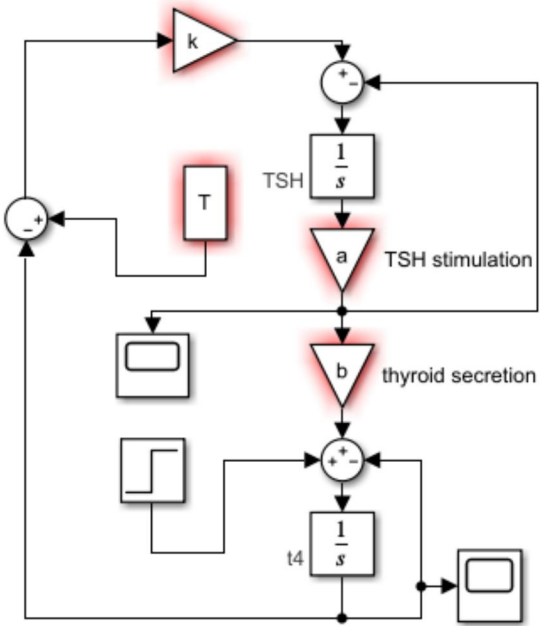

Fig 1. Block Diagram Model of the HPT axis.

To model the hypothalamic-pituitary-thyroid axis, the model sets the target value T to .001mg/L, k to 1mg/(hrL), a to 1 mU/Ls, and b to 1.4 mU/Ls. To model hypothyroidism, the gain constant b is changed to 0, representing the thyroid's failure to secrete T4. To add a Levothyroxine input, the final value of the step input is changed from 0 to a discrete value.

C. Transfer Function

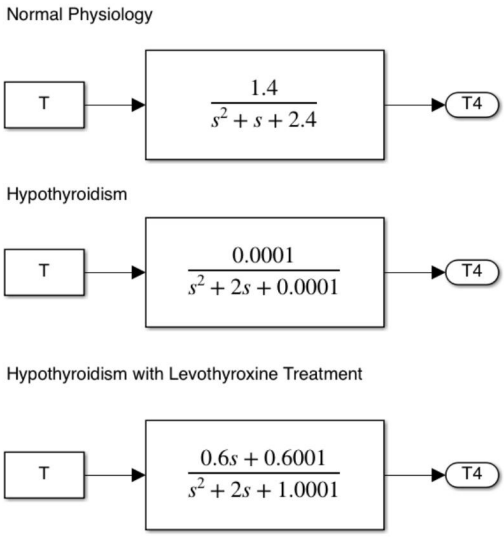

Fig 2. Closed loop (CL) system for the three variations to our model with target T as input and output as T4.

Target value, gain constants, and initial conditions of 0 for TSH and T4 were consistent in all three variations. Changes in the transfer functions of the systems reflect the disrupted thyroid secretion (b = 0) in the second and third models in Fig. 2 and the addition of Levothyroxine in model 3.

III. Results

Our model, given our assumptions about the relationship of certain physiological parameters, adequately describes the system response of the HPT axis. The analytic system reflects the physiological response of the biological system in normal conditions.

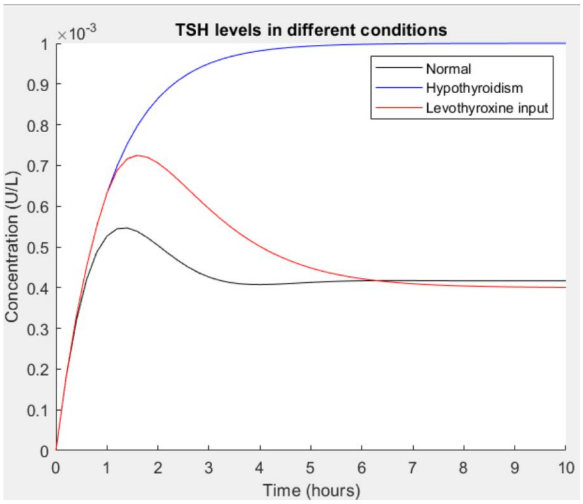

Fig 2: Plot of TSH concentrations over time across three different simulations

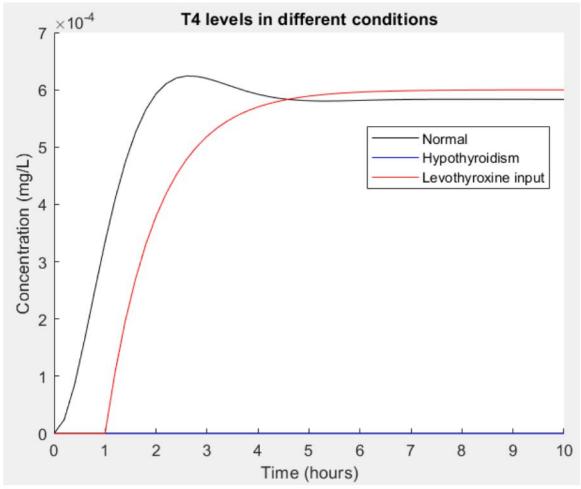

Fig 3: Plot of T4 concentrations over time across three simulations.

With a low initial concentration of T4, the pituitary gland releases TSH, stimulating the thyroid to release T4. This is reflected in the model as a sharp spike in TSH secretion. When T4 levels start to reach homeostatic levels, the effect of the negative feedback on TSH grows, causing the secretion of TSH to drop and levels of TSH to settle to levels that maintain the homeostasis of thyroid hormones. In our model, similar events occur. T4 levels rise steadily, causing TSH secretion to slow and TSH to settle at a constant concentration. There is an overshoot of both TSH and T4 as both concentrations exceed the steady state value before settling. When the parameters are changed to simulate hypothyroidism in our model, thyroid hormone levels never rise from the initial concentration and TSH settles to a much higher level than in other simulations. This reflects the pathology of hypothyroidism as the failure of the thyroid to produce T4 causes an increase in TSH production. With a Levothyroxine or T4 drug input, levels of thyroid hormone should return to normal levels, allowing TSH to settle to normal levels as well. The step function in the model accurately reflects the release of a drug. The model also has a similar speed of response as both the normal biological HPT axis and a drug input in hypothyroidism.

The parameters chosen for the model allow it to achieve similar steady state values and response times as the HPT axis. As seen in Figure 3, the concentration of TSH in both a normal simulation and a hypothyroidism simulation with an input of Levothyroxine reaches a steady state value around .45 mU/L, within the range of healthy TSH levels of .4-4 mU/L [5]. Similarly, in Figure 4, T4 levels in both the normal simulation and a hypothyroidism simulation with an input of Levothyroxine reach a steady state around 600 pg/L, within the range of health total T4 levels [4]. However, the steady state value for TSH under hypothyroidism, while higher than the other simulations, is still within the range of healthy TSH levels. Like the release of hormones and the release of drugs, the timescale for the complete response of T4 and TSH happens in the timescale of hours. Drug input, in particular, has an accurate timeline, as the drug and the model show a peak in T4 levels between two to four hours after the initial drug release. One limitation of just using a single step input is that the decrease in T4 levels after 6 hours is not described in the model. The system adequately and efficiently models the HPT axis in normal conditions, in hypothyroidic conditions, and in conditions with treatment of hypothyroidism via Levothyroxine.

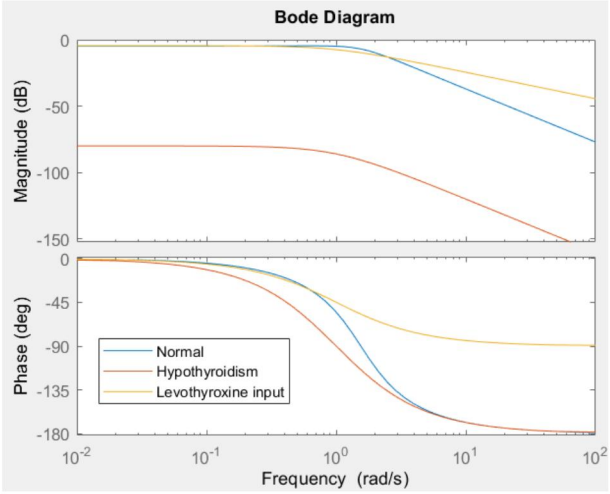

Fig 4. Bode plot describing the closed loop system

Our system has some limitations. The transfer functions and system response in Figures 2, 3, and 4 indicate

that our system is close to a critically damped response but not quite there. Overshoots in the normal TSH and T4 levels are characteristic of an underdamped system. The healthy model with poles of (-1±1.18j) indicate the same. With poles at 0 and -2 our system for hypothyroidism represents an overdamped system. Characteristics of such a system is the longer time taken to reach steady state which can be seen from the TSH response for hypothyroidism. The system response is also underdamped for the levothyroxine treatment of hypothyroidism and has poles of (-1±0.01j). This response is evident from the initial overshoot in TSH prior to the effect of Levothyroxine taking place and settling T4 and TSH levels closer to normal. The poles of our system lie in the region of convergence of the complex plane indicating that the response in each scenario does decay and eventually converge to steady state. The Bode plot in Figure 5 is informative of the phase margin, steady-state gain, and poles of the system. Our phase margins could be improved. Our steady-state gain is less than 1 in all scenarios. Adding an integral controller could help reduce steady-state error and improve system response at low frequencies. Also, derivative control could lower rise time and thereby improve high frequency response [6].

When deriving our parameters for the different gain values, we initially took an experimental approach backed by our understanding of the physiology of the system. While our parameters and the corresponding outputs adequately model the response of the HPT axis in various conditions, analysis of our transfer functions, output response, and bode plots demonstrate that further improvement is needed to reach an ideal system. Identifying correct gains to better reach a critically stable system that also resulted in an output response that made physiological sense was an iterative process.

IV. Conclusion

Our mathematical representation accurately models the hypothalamic-pituitary-thyroid axis. The model simplifies the biological system while still maintaining the correct TSH response to low initial values of T4. In addition, our system is able to describe the effects of the introduction of a T4 substitute like Levothyroxine into the system.

Further steps that can be taken include expanding the system to model TRH and T3 concentrations. Another possible direction is to create a PID controller to improve the frequency response.

Our simulation could be improved upon to illustrate the physiological response to Levothyroxine treatments and thereby aid clinical treatments. Simulation can show how long it will take for the patient to respond to the drug. Novel treatments such as continuous dosage of drugs vs intermittent dosage can be explored, and the differences can be more easily understood via simulation and at no risk to patients. Lack of personalized treatment, in regard to rates of stimulation of the thyroid by TSH and thyroid hormone secretion, which vary from individual to individual, is a disadvantage of simulation. However, it can greatly improve translational research with less risk and lower costs.

Acknowledgment

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