Thyroid Hormone Feedback System

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***Abstract* - The thyroid gland produces hormones that work alongside the hypothalamus's hormones to create a negative feedback system that helps with many body functions. In this paper, we focus on the relationship between the thyroxine (T4) produced by the thyroid and thyroid-stimulating hormone (TSH) produced by the hypothalamus and their ability to regulate metabolism.**

I. INTRODUCTION

The endocrine system is responsible for the maintenance of growth and development, mood, organ functions, metabolism, and reproduction. An essential pathway within this system is the HPT axis, hypothalamus-pituitary-thyroid axis, which specifically, but not only, controls digestion and metabolism through secretion of thyroid hormones. T4 and T3, thyroxine and triiodothyronine, are produced by the thyroid gland in response to the release of thyroid-stimulating hormone (TSH) from the pituitary gland. This pathway begins with the hypothalamus secreting thyroid-releasing hormone (TRH), signaling the pituitary to trigger the production of TSH. Both TSH and TRH are down regulated by T4 and T3 concentrations in the blood, bringing the HPT axis to have a closed negative feedback loop. Since the main role of T4 is to deionize into T3, TSH levels are especially susceptible to change in proportion to the concentration of unbound, or free, T4 [3].

II. ASSUMPTIONS

The goal of our model is to simulate the negative feedback between free T4 concentration and the production of TSH over a period of fasting after eating. As such the final and initial T4 and TSH values should reflect results found in literature. Furthermore, the time constant can be matched with observed results. Values of concentration should also remain positive for the duration of the simulation, as a negative concentration has no physiological meaning. Going off of these knowns, the main assumptions for our system lie in a couple of varying factors.

The general procedure of T4 inhibition begins with the TRH and TSH inhibition via negative feedback from the production of free T4 from the thyroid gland. TRH is produced and released by the hypothalamus causing a release of TSH from the pituitary gland. This reaches the thyroid gland and causes the production of T3 and T4 in both free and bound forms. These molecules serve as the negative feedback control for TRH and TSH, thus reducing their concentrations in the bloodstream which will cause a reduction in the production of T3 and T4.

For our purposes, our analysis lies in the sole ability of T4 to inhibit the release of the TSH hormone. This is a very simplified version of the negative feedback mechanism in the body, but for our purposes it will serve us well in terms of system complexity. Assuming that the analysis of T4 and TSH are the main components of our system, we assume that there is a baseline concentration of both molecules in the blood as well as that the addition of these molecules is through production from either the thyroid or pituitary glands. No other external sources are present in our analysis. We also assume that there are no internal reactions in the blood causing any reductions in T4 or TSH as to preserve numerical data in our designed equations. Additionally, when referring to T4, we mean free T4 molecules in the system, not any bound molecules.

III. DIFFERENTIAL EQUATIONS

Our equation spurs from a mixture of considerations such as the response of TSH to the onset of T4 due to the negative feedback loop of the system. It is important to recognize the starting point of this system is after the onset of TSH, meaning the initial concentration will be much higher than our desired baseline concentration at homeostasis without any excitation event. We can consider a parameter which models this as the change in TSH concentration due to the onset of T4: (Table 1 for variables and constants)

$$Ts(t) = FB(TSH(t) - TSHr) \quad (1)$$

This equation models the difference of our known high value of T4 and subtracts it by our recommended value for T4. Knowing this, we can draft a model equation for change in TSH concentration in terms of $Ts(t)$:

$$dTSH(t)/dt = \alpha Ts(t) - (1/\tau)T4(t) \quad (2)$$

We approach this in terms of a model of rate of change as we aim for our model to be able to have varying rates of change for these molecules. Due to the fact that this system represents a hormone change in chemicals in the bloodstream, it is expected that there would be a bit of noise around the steady state point of the system, which will be shown in the plots for our system. Carrying on from this, we can also draft another equation for T4 concentration varying depending on the TSH reduction as well. It is as follows:

$$dT4/dt = J(t) - rxn(T4(t))(TSh(t)) \quad (3)$$

Here we can now model our rates of change of T4 and TSH based on their decremental decreases in concentration throughout the process of returning T4 and TSH levels back to normal post stimulation. Generating a simulink chart for this process is shown below:

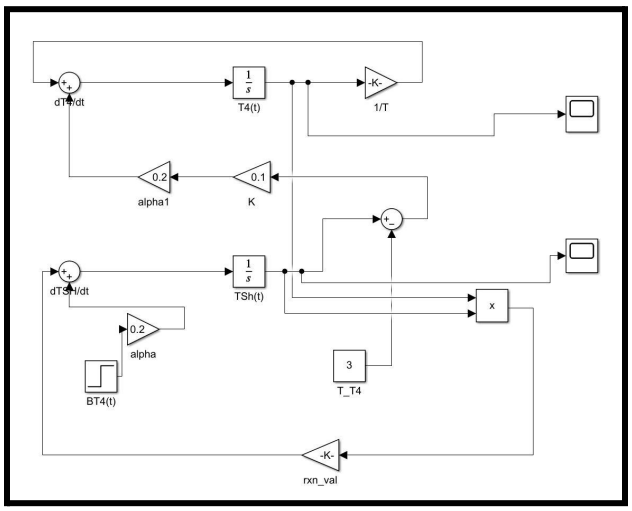

Figure 1: Simulink model for governing equations

Initial conditions can be found on Table 1 as well. The simulated plots for T4 and TSH concentrations are shown below:

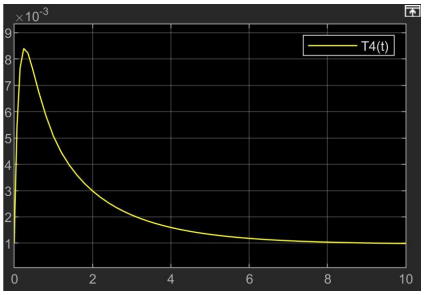

Figure 2: T4 concentration varying with time

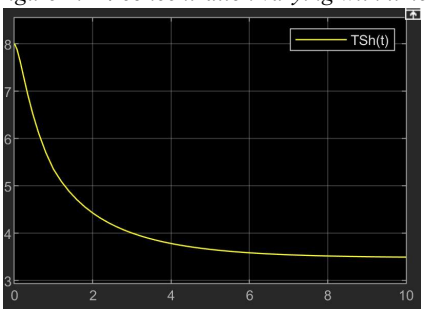

Figure 3: TSH concentration varying with time

The plots are quite accurate with the depiction that we want to occur as the model focuses on the time period after the onset of TSH causing a spike in T4 levels in the blood. This spike then propels the decrease of TSH which in turn causes a T4 concentration decrease, thus mapping out a very accurate depiction of the negative feedback loop of the system.

V. IMPLEMENTING PID CONTROLLER

In addition to our model of the natural negative feedback loop of the thyroid and its hormones, we understand that many individuals suffer from various conditions such as hypothyroidism, or underactive thyroid. This condition results in a lack of production of thyroid hormones, T3 and T4 which can result in a lack of metabolism to produce energy for the body. This being the case, we want to implement a PID control system that will enable us to achieve a free T4 target concentration of 17.7 ng/L [3] as this is the standard lab reference representing optimal levels for healthy metabolism. Thus, for our system we assume the same initial TSH concentration of 8 ng/L and an initial T4 concentration of around 10 ng/L which would be administered for the patient to help promote metabolism.

Since we are considering the thyroid system and its hormonal release which tends to be slower process, we want to consider a delay in our measurements of T4 concentrations which is represented by a first order low pass response:

$$dT4_{meas}/dt = (1/\tau_{meas})(T4(t) - T4_{meas}(t)) \quad (4)$$

Furthermore, we want to implement a combination of a proportional, integral and derivative (PID) control system modeled as:

$$TSh(t) = K_p e(t) + K_i \int_{-\infty}^{t} e(t)dt + K_d \frac{d}{dt} e(t) \quad (5)$$

By doing this, we are able to control the variables Kp, Ki, and Kd in order to increase the response time and reach the target T4 concentration sooner. As a result, we must consider the control objective error which represents our target T4 concentration $T4_{target}(t)$ as shown:

$$e(t) = T4_{meas}(t) - T4_{target}(t) \quad (6)$$

For this system, we also include equations (2) and (3) which represent the change in TSH concentration in terms of $Ts(t)$ and the change in T4 concentration based on the negative feedback loop reaction rate with the presence of TSH. For the application of using our PID control to help individuals with hypothyroidism, we want to first stimulate the production of an initial T4 concentration which would allow use to set a time constant for first-order low pass response of 0.5 sec which will help reach the target concentration of 17.7 ng/L as a faster rate. Additionally, we set our PID parameters as seen in Table 2 while assuming all other parameters remain the same as the natural negative feedback loop previously described.

With this we were able to model our PID control system on Simulink and produce the graphs for the concentration of T4 and TSH shown below:

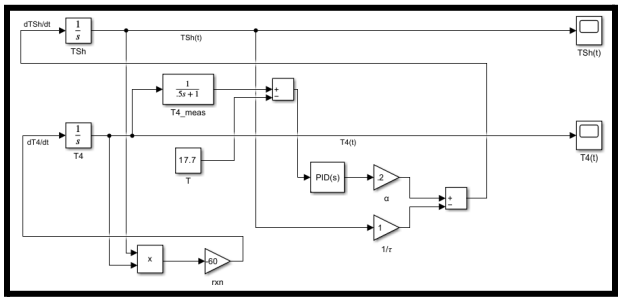

Figure 4: Simulink model for PID controller

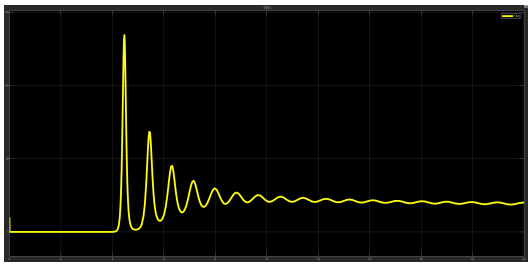

Figure 5: T4 concentration varying with time with PID controller towards a target concentration

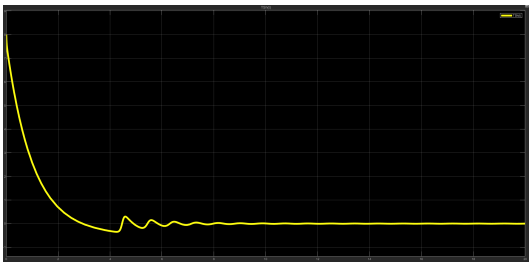

Figure 6: TSH concentration varying with time with PID controller

From the plots shown above representing the concentrations of T4 [top] and TSH [bottom], we can see that a delay is shown due to the system being a hormonal response. However, after about 4 seconds, we see oscillations converging towards a final concentration of the target value for T4 at 17.7 ng/L and close to 0 ng/L for TSH.

V. TRANSFER FUNCTION

$$\frac{\widetilde{T_4}(s)}{\tilde{J}(s)} = \frac{\alpha}{\left(\frac{1}{\alpha \cdot FB}\right)s^2 + \left(\frac{\frac{1}{\tau} + r \cdot T_4}{\alpha \cdot FB}\right)s + \left(\frac{r}{\alpha \cdot FB \cdot \tau} + r \cdot \overline{TSH}\right)} \quad (7)$$

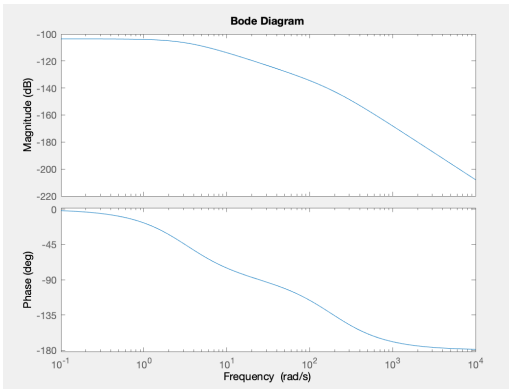

Figure 7: Bode Response of linearized T_4 concentration with respect to input propelling factor

$$\frac{\widetilde{TSH}(s)}{\tilde{J}(s)} = \frac{\alpha\left(s + \frac{1}{\tau}\right)}{s^2 + \left(\frac{1}{\tau} + r \cdot \overline{T_4}\right)s + \left(r \cdot \overline{TSH} \cdot \alpha \cdot FB + \frac{r \cdot \overline{T_4}}{\tau}\right)} \quad (8)$$

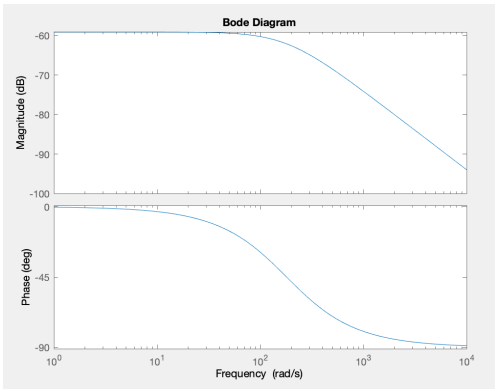

Figure 8: Bode Response of linearized TSH concentration with respect to input propelling factor

VI. DISCUSSION

A. Selecting a Template (Heading 2)

When observing the differential equation plots, for the purposes of our simulation, our results depict the overall trend of the negative feedback loop present in the thyroid hormone biosystem. As seen in Figure 2, the spike in T4 concentration is due to the already high TSH concentration shown at the start of Figure 3. It takes about 7-8 seconds for both systems to return to normal levels after the end of the stimulation event. Such is expected as well. Due to the influx of T4 into the bloodstream, we see an immediate decay in the concentration of TSH in the blood. This produces the expected reduction in T4 production since TSH is responsible for T4 production in the first place.

B. System Behavior/Stability

In order to analyze the response of the system and its respective stability the system was linearized and assumed to be representative of the system over most biologically realistic

parameters. The concentration of T_4 and TSH were analyzed through calculation of their transfer functions with respect to the input propelling force J(t) and can be found in eqs 4 and 5 respectively. Their stability was then analyzed with bode analysis and the responses of T_4 and TSH are shown in figures 7 and 8 respectively. The response of T_4 with respect to J was shown to have no zeros and two negative poles at -3.2351 rad/s and -186.7649 rad/s. This response indicates that the response of T_4 to a propelling force of TSH is always stable. The response of TSH with respect to J was shown to have one zero at -10 rad/s and two poles at -10.0247 rad/s and -179.9753 rad/s. As seen by the bode plot in figure 8, the pole at -10.0247 rad/s cancels the zero at 10 rad/s, and shows a response of a first order low pass filter. This response also indicates that the response of TSH concentration to a propelling factor J is always stable.

C. Similarity to Measured Data

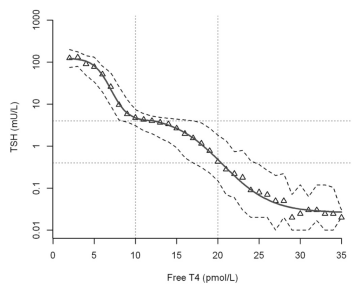

Figure 9: Measured data observing the relationship between T4 concentration and TSH concentration.

As seen in figure 9, it has been physiologically observed that a higher concentration of free T4 corresponds to a lower concentration of TSH. The exact relationship between these two variables has shown to vary with a variety of factors, but overall the trend remains consistent. This behavior does make sense, as there is a negative feedback between the concentration of T4 and the production of TSH. As more T4 hormone is produced, there is a greater negative impact on the production of TSH. The experimentally determined relationship between T4 and TSH is shown to differ across the 12 pmol/L T4 mark, and shows an overall trend which is close to inverse log linear [2]. Our simulation follows this trend, as when T4 concentration increases, TSH concentration decreases as a result.

E. Sources of Error

The simulation does not take into account several factors involved in this feedback loop such as the role of TRH in the production of TSH, the production and conversion of T4 hormones into T3 hormones, or the conversion between free and bound states. Instead the biological system is modeled as a consumption reaction in which TSH is consumed in the production of T4 hormone. For this reason any change of these unaccounted factors could result in a shift in TSH and T4 concentrations that would not be seen in this simulation.

The parameters used in this model are also specific for any patient and would have to be experimentally determined in order to provide a simulation that is representative of their specific state.

D. Comparison to Physiologic Experimentation

The use of simulation provides easier situational testing with an increased range of possible situations. Physiologic experimentation requires the use of patients who experience a specific condition and are willing to provide their data for study. The use of patients also requires large amounts of testing and can only provide discrete data, while a simulation can be used to fill in the gaps. A simulation is limited however in that it is only an estimation of what is happening physiologically and needs verification to confirm its accuracy. In this way this simulation is useful because it can provide information for predictions into thyroid function, and what might occur when implementing relevant changes.

VII. CONCLUSION

With our design, we are successfully able to analyze the naturally occurring negative feedback system that enables the thyroid and its hormones to regulate body functions. With the addition of a PID controller, we are able to use this analysis and develop a way for individuals with conditions that inhibit their production of T4 for metabolism to be able to produce enough. As seen from Figure 5, we are able to successfully implement a PID controller to help reach a target T4 concentration as TSH levels decrease to around 0. This makes sense due to the fact that as T4 increases, there will be a decrease in TSH as it becomes limited due to the natural negative feedback system that exists with these hormones. By setting our PID parameters to the values shown in Table 2, we are able to successfully represent the measurement delay that makes the closed-loop system response unstable as a negative closed-loop feedback with a faster response time due to our tau value. With the addition of the derivative control, we are able to convert the system to stable as it converges toward the target T4 concentration. Furthermore, with the integral control, we are able to have the system response become smooth with the low pass filter that acts as an integrator for our system. As shown, the implementation of our PID control system to the naturally occurring negative feedback system of the thyroid and its hormones can help individuals who suffer from conditions negatively impacting the thyroid's ability to produce T4 for the body to metabolize materials for energy. By controlling the PID parameters, and the time constants, we are able to speed up production of T4 in the bloodstream to a specific target concentration to allow for proper metabolism and healthy energy production.

VIII. REFERENCES

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APPENDIX

Variables	values
$T4(0)$ = Initial T4 concentration	0.001 ng/L
$TSh(0)$ = Initial TSH concentration	8 ng/L
FB = feedback parameter	0.1
$TSHr$ = Resting T4 concentration	3 ng/L
α = 1/Blood Volume	0.2/L
rxn, r = reaction rate	-60 L/(sec*ng)
τ = time constant	0.1 seconds
J = propelling factor for system	1 ng/L

Table 1: Values for simulink simulations

Variables	values
$T4(0)$ = Initial T4 concentration	10 ng/L
$TSh(0)$ = Initial TSH concentration	8 ng/L
τ_{meas} = time constant for first-order low pass response	0.5 second
K_p = proportional control parameter	0.1 L/sec
K_i = proportional control parameter	0.01 L/sec^2
K_d = proportional control parameter	0.1 L

Table 2. Values for the PID control system including different initial T4 and TSH concentration, τ_{meas}, and PID parameters.

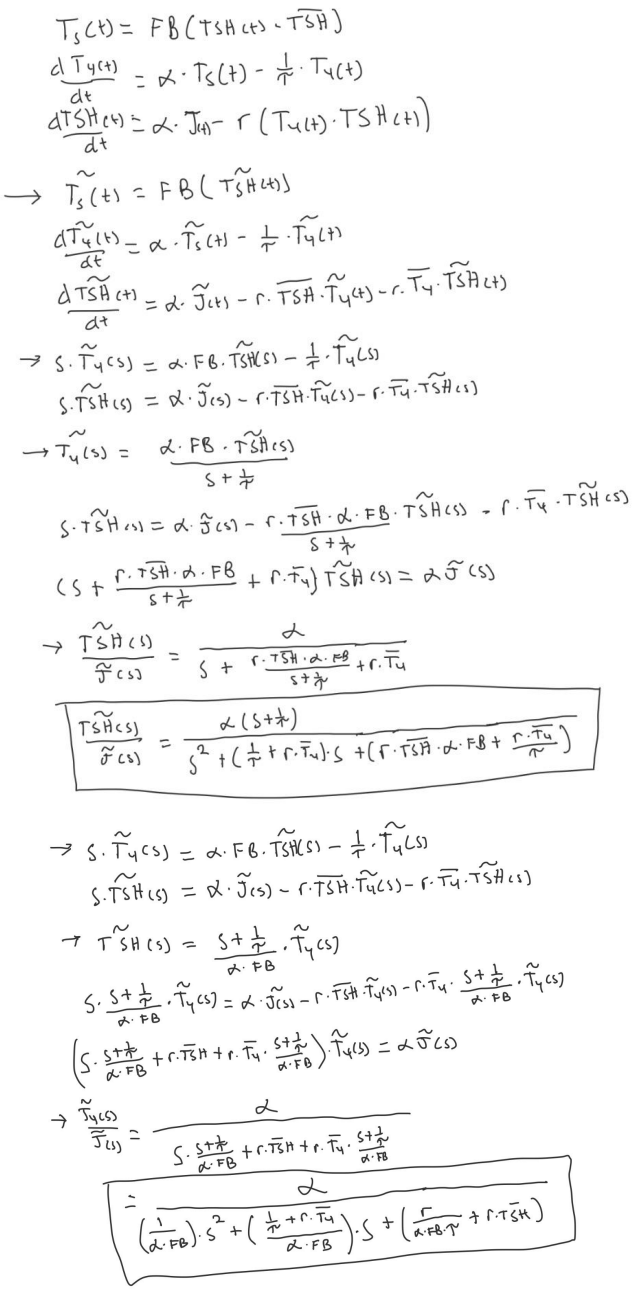

Figure 10. Calculation of Transfer functions