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Enhancing the Natural Biological Control in the Thyroid Hormone Homeostasis As a First-Order Control System

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***Abstract*— This study explores the natural control system that exists within the pituitary gland. More specifically, this study investigates the regulation of the thyroid stimulating hormone (TSH), released by the anterior pituitary, with regards to the thyroid releasing hormone (TRH), which is released by the hypothalamus. Using appropriate assumptions on the behavior of the hormones, along with relevant boundary conditions, we modeled an output of TSH using constant TRH input over the course of a six-hour period. Other relevant hormones such as thyroxine (T4), triiodothyronine (T3), and their relevant intermediaries were also modeled as a means to complete the natural feedback found physiologically. Due to our boundary conditions, we do not consider the consumption or final function of these hormones since they leave the pituitary gland, our control system; instead, we consider a constant TRH since it is produced by the hypothalamus. Finally, we explore the results of reducing the TRH input while observing the TSH response. We append a short loop controller feedback that uses the TSH output to regulate a TRH input to remedy the reduction of TRH. The open-loop transfer function derived presented three poles at the clearance exponents for T4, TSH, and central T3, with a phase margin of 74.1°, characterizing a stable but slow system that can be improved with a simple proportional control.**

I. Introduction

A. Thyroid Hormone Homeostasis

The thyroid gland plays an important role in regulating the body's metabolism through the production of thyroxine (T4) and triiodothyronine (T3) hormones. These hormones are upregulated by the secretion of thyrotropin-releasing hormone (TRH) by the hypothalamus and thyroid-stimulating hormone (TSH) by the pituitary gland [1]. Physiological feedback-systems use concentrations of T4 and T3 to down-regulate the production of TRH and TSH [1]. The primary use of T4, besides down-regulating the production of TRH and TSH, is to be modified, producing T3 which is the active form of the thyroid hormone taken up by tissues [1]. The body provides a very fine natural controller that regulates the secretion of TSH with respect to free T3 concentration. Having too much or too little T3 hormone can result in either hyperthyroidism or hypothyroidism respectively, which mathematical models have accounted for by altering the thyroid gland secreting capacity accordingly [2].

B. Aim of study

This study aims at investigating the response of TSH to variations in TRH and the natural controller within the hypothalamus-pituitary-thyroid (HPT) axis. Due to the complex nature of the HPT axis, we constrained our system by focusing on the anterior pituitary as our control system, selecting additional boundaries and constraints accordingly. Furthermore, since TRH production is in the hypothalamus, TRH is modeled using a constant source. The consumption of T3 by the tissues was not included in the model since it happens outside of the pituitary. Finally, a portion of the system leaves the pituitary but only as a means to complete the long loop feedback used in TSH regulation. With these constraints in mind, we sought to understand how a perturbation in TRH levels would affect TSH production and the subsequent T3 production. We also sought to derive the closed-loop and open-loop transfer functions that relate the input TRH concentration to the output TSH concentration in the anterior pituitary control system. With this understanding, we modeled a short-loop feedback to improve the recovery of TSH in a diseased state.

C. Relevant Assumptions

First, the TRH level in the hypophyseal portal system is kept constant because it is outside the system boundary. Second, due to the constant TRH, the TSH output is not released in a pulsatile manner which is more representative of physiological behavior [2]. This is a safe assumption since the model is only concerned with understanding TSH response to TRH perturbations. Third, nonlinear Michaelis-Menten-Hill kinetics is assumed for the production and release of TSH [2]. This is a common assumption when working with binding enzymes or substrates [2]. Fourth, circadian variation in TSH and TRH release was omitted in the system [2]. This is a safe assumption since such variations are only present over long (more than 24 hours) periods of time. Fifth, there is noncompetitive inhibition of TSH release by receptor-bound T3 such that all of the receptor-bound plays a role in down regulating TSH [2]. Finally, we assume no delays exist in the production of any hormones. This was remedied by allowing the simulation to run for at least five hours.

II. Methods

A. Equations

Equations were selected from previous published models for the thyroid hormone homeostasis [2] [3]. The first two equations outline the TSH and receptor-bound T3 (T_{3R}) production given TRH and intracellular T3 (T_{3N}) values [3]. The consumption of TSH is taken into account in the

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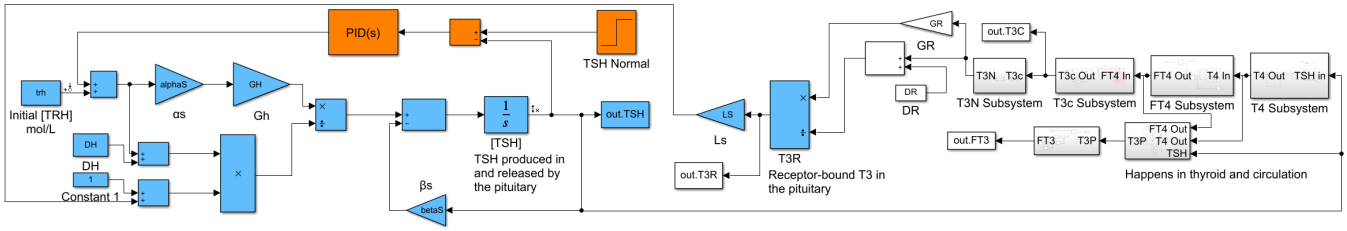

Fig. 1. The Simulink block diagram of the first-order control system. The blue sub-block system is associated with the dynamics from equation (1). The orange sub-block system is associated with the proportional control implemented to enhance the biological control.

concentration of TSH over time. These first two equations were used in modeling the control system inside the anterior pituitary. To calculate T_{3N}, T_{3N} was assumed to depend on the concentration of the central T3 (T_{3C}) and the concentration of intracellular T3-binding substrate (IBS); this relationship is outlined by equation (3) [3]. The concentration of T_{3C} was then assumed to depend on the concentration of free T4, which enters the anterior pituitary from the circulation and is converted into T_{3C}; this relationship is outlined by equation (4) [3].

$$\frac{d[TSH]}{dt} = \frac{\alpha_S G_H [TRH]}{(D_H + [TRH])(1 + L_S T_{3R})} - \beta_S [TSH] \quad (1)$$

$$T_{3R} = \frac{T_{3N}}{T_{3N} + D_R} \quad (2)$$

$$T_{3N} = T_{3C} \frac{1}{1 + K_{31} IBS} \quad (3)$$

$$\frac{dT_{3C}(t)}{dt} = \alpha_{32} G_{D2} \frac{FT_4(t)}{FT_4(t) + K_{M2}} - \beta_{32} T_{3C}(t) \quad (4)$$

As a means to complete the loop, equations that use the consumption of TSH to produce T4 (assumed to happen inside the thyroid) and that use T4 to produce free T4 (FT4) (assumed to happen in the bodily tissues) were also considered. These two equations were obtained from published thyroid hormone homeostasis models (see equations (5) and (6)) [3]. In equation (6), the concentration of FT4 depends also on the concentration of thyroxine-binding globulin (TBG) and the concentration of transthyretin (a T4 transport protein) (TBPA) [3].

$$\frac{dT_4}{dt} = \alpha_T G_T \frac{TSH(t)}{TSH(t) + D_T} - \beta_T T_4(t) \quad (5)$$

$$FT_4 = T_4 \frac{1}{1 + K_{41} TBG + K_{42} TBPA} \quad (6)$$

For the definition of the other constants seen in equations (1) through (6), refer to the Appendix with values obtained from Berberich, Dietrich, Hoermann, and Muller (2018).

B. Block Diagram

The block diagram in Fig. 1 was assembled on Simulink R2020b following the mathematical relationships presented in equations (1) through (6).

A Proportional-Integral-Derivative (PID) controller was added to the block diagram to enhance the natural, physiological controller outlined by equation (1). The natural controller adjusted the TSH concentration based on the concentration of TRH and a T_{3R} input. The PID controller includes a proportional component ($K_P = 0.01$), deemed appropriate to improve the settling of the system response. The PID controller takes in a target TSH value chosen based on the normal physiological range for the TSH concentration. This target TSH value is compared to the TSH produced by the natural controller to produce the parameter error taken by the proportional controller. The proportional controller then outputs the TRH change that modulates the TRH input considered by the biosystem.

C. Transfer Function

The control system's closed loop transfer function was developed in the format $CL(s) = \frac{TSH(s)}{TRH(s)}$, where TSH(s) is the output and TRH(s) is the input, and equations (1) through (6) were used as the starting equations. The starting equations were linearized around the operating point, which in this case was the steady state of each species. For the linearization, small changes around the operating point were assumed for all species. The Laplace transform of the linearized equations was then derived for all species modeled. The linearization of the model then produced a cascade of three first-order sections leading to a transfer function with two zeros and three poles as seen in equation (8). The closed-loop transfer function $CL(s)$ was then converted into the open-loop function $OL(s)$:

$$CL(s) = \frac{TSH(s)}{TRH(s)} = \frac{\alpha_{TRH}(s + \beta_T)(s + \beta_{32})}{(s + \beta_S)(s + \beta_T)(s + \beta_{32}) + \alpha_{T_{3C}} \alpha_{T_4} \alpha_{T_{TSH}}} \quad (7)$$

$$OL(s) = \frac{\alpha_{T_{3C}} \alpha_{T_4} \alpha_{T_{TSH}}}{(s + \beta_S)(s + \beta_T)(s + \beta_{32})} \quad (8)$$

where α_{TRH} is the partial derivative of equation (1) with respect to TRH, α_{T3C} is the partial derivative of equation (4) with respect to T3C, with equations (2) and (3) substituted in, and α_{T4} is the partial derivative of the aforementioned equation with respect to T4. All partial derivatives are evaluated at steady state in the linearization process.

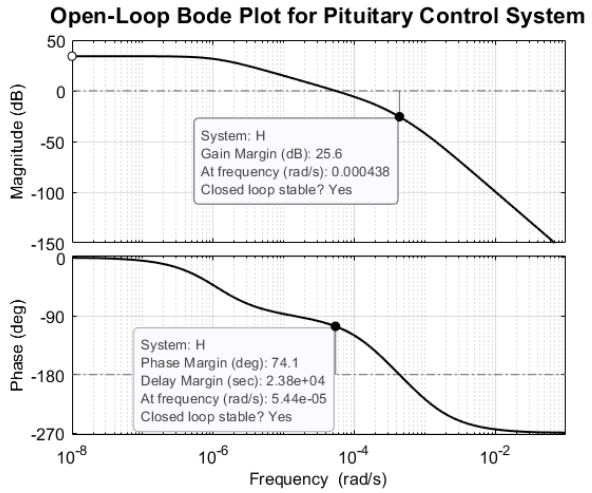

Fig. 2. Bode plot of the open loop transfer function for the control system. Poles are $\beta_T = 1.1 * 10^{-6} Hz$, $\beta_S = 2.3 * 10^{-4} Hz$, and $\beta_{32} = 8.3 * 10^{-4} Hz$

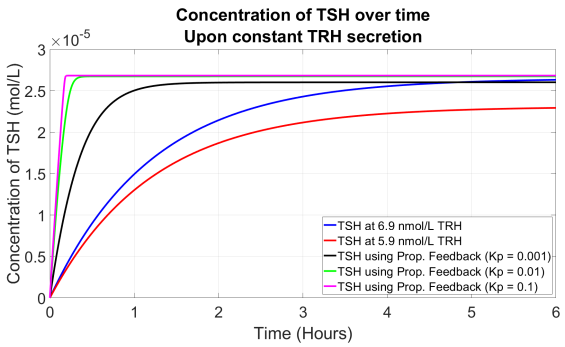

Fig. 3. TSH concentration response using a proportional controller to enhance the speed, rise time, and steady-state error of the biological controller (Kp = 0.001, Kp = 0.01, and Kp = 0.1) and under different TRH concentrations.

III. Results

The concentration of TSH over time was modeled upon different values for a constant TRH source as well as under a TRH source modeled through a PID controller proportional feedback, serving to enhance the natural biological controller. The proportional controller used successfully improved the mid-frequency response of the biological controller, while improving also the settling by critically damping the system response (see Fig. 3).

A. Open-Loop Model

Open-loop analysis of the model is completed using equation (8). As seen in Figure 2, the system is stable with a phase margin of 74.1°and a gain margin of 25.6 dB. Three poles are observed in this open-loop model, occurring at 1.1e-6 Hz, 2.3e-4 Hz, and 8.3e-4 Hz respectively. The DC gain error is 1.93% for the corresponding open-loop gain.

B. Simulation Results

The TSH concentration settled at slightly higher values as the input TRH concentration increased. The TSH concentration also experienced a higher rise time with an increased TRH input concentration. This difference could be due to the imperfection of the natural biological feedback controller and common variations in TSH physiological values for different individuals; that is, the upper limit of the TSH concentration varies amongst individuals both under healthy and pathological conditions [4]. The vagueness in the upper limit for TSH presents a challenge in the analysis of the TSH settling values [4]. However, the incorporation of an ultra-short feedback loop in which the TSH concentration regulates the TSH release could also adjust the settling values of TSH and increase the sensitivity of TSH to given TRH inputs [2] [3]. This ultra-short feedback loop on the regulation of TSH was not included in the model explored in this study.

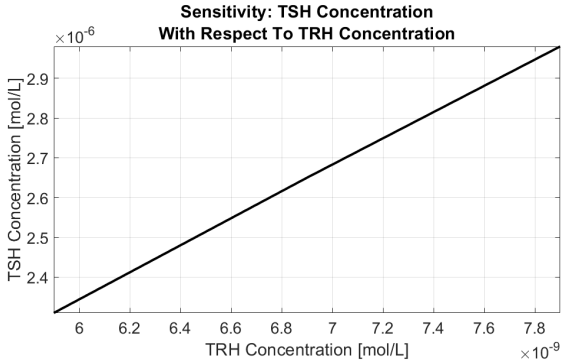

Fig. 4. Sensitivity analysis of the TSH concentration with respect to changes in TRH.

C. Effect of an External Proportional Controller

With the additional proportional control enhancing the biological controller, an input of 5.9 nmol/L TRH produced an output of $2.93 * 10^{-6} \mu$mol/L TSH (see Fig. 3). The addition of the proportional controller improved the settling time of TSH, which also reached the target value in less time (decreased rise time). The incorporation of the PID controller enabled TSH to reach the target value in under two hours compared to the original model in which TSH took more than five hours to settle. As Kp increased from 0.001 to 0.1, the rise time decreased accordingly.

D. Model Sensitivity

Varying the input TRH by increments of one nmol/L between 5.9 nmol/L to 7.9 nmol/L allowed for measurement of the system sensitivity. Using the TSH values at steady state from each input of TRH, we plot the output against the input and obtained an approximately linear curve. The slope of the curve is 355 mol/L of TSH for one mol/L of TRH. We can expect that the system's TSH will change by approximately 0.355 μmol/L for every nmol/L change in TRH within this approximately linear region.

IV. Conclusion

The main purpose of this study was to understand how TRH perturbation affects TSH production and subsequently

informs potential changes in the concentration of the T3 hormone. A natural, biological controller surfaced as an integral part of the homeostasis model, where TSH concentration was driven by TRH and T_{3R}; however, this controller presented a slow response. Thus, we expanded the study to also enhance the biological controller in the pituitary, which regulates the concentration of TSH from a difference between TRH and T_{3R} terms in the linearized equation for changes in TSH concentration with time. This helped us understand how TSH concentrations that are different from physiological levels can be remedied. The external controller was successful in improving the settling of the TSH concentration, decreasing the rise time and critically damping the response. Upon linearization of the system's differential equations and analysis in the Laplace domain, the open-loop transfer function presented three negative poles and a stable phase margin at 74.1°. The three negative poles were introduced at the resonant frequencies, which matched the clearance exponent of T4, β_T, TSH, β_S, and central T3, β_{32}. This analysis suggests the system is physiologically stable and well-regulated by the system equations presented earlier.

A. Model Advantages and Limitations

The model here explored considered the hormonal interaction within the pituitary gland, allowing for a straightforward analysis of the interaction between TSH and TRH in the HPT axis. This model provided an insight into the natural physiological controller within the HPT axis and how it could be enhanced for speed. This insight can be used in further research to explore other natural controllers and model them to be enhanced via a control systems approach - including both the controllers of the hormones themselves and of the hormone transport systems [7]. An extension of the model to include integral and derivative controllers would boost the DC gain, further reducing the steady-state error, and improve the high-frequency response, respectively. For the model here explored, these additions were deemed negligible compared to the efficacy of the proportional controller in critically damping the system's response and lowering the rise time. Some of the model limitations include the lack of an exit point for the T3 hormone produced by the thyroid gland. The control system model also did not actively show the consumption of T3 and T4 by bodily tissues, which could be incorporated into the control system to serve as an additional model sink for the concentration of T3 and T4. Further research can also aim at providing more mathematically detailed models for the hormone interactions in the biological system to help develop novel targets or strategies for the improvement of the thyroid homeostasis under deficient thyroid hormone signaling [8].

APPENDIX

The α_S, α_{32}, and α_T are dilution factors for TSH, T3c, and T4, respectively. The β_S, β_{32}, and β_T are clearance exponents for TSH, T3c, and T4, respectively. The G_H and G_T are the secretion capacities of the pituitary and the thyroid gland, respectively, while the G_{D2} is the maximum activity of type II deiodinase. The D_H, D_R, and D_T are damping constants for pituitary, T3c, and TSH at the thyroid gland, respectively. The K_{31}, K_{M2}, K_{41}, and K_{42} are dissociation constants for T3-IBS, of 5'-deiodinase II, T4-TBG, and for T4-TBPA, respectively. The L_S was the brake constant of long feedback. All values were obtained from published studies considering both clinical data and physical quantities [3]:

- $TBG = 300{*}10^{-9}; [mol/l]$ concentration of thyroxine-binding globulin.
- $TBPA = 4.5 * 10^{-6}; [mol/l]$ concentration of transthyretin (T4 transport protein).
- $IBS = 8 * 10^{-6}; [mol/l]$ concentration of intracellular T3-binding substrate.
- $L_S = 1.68 * 10^{6}; [l/mol]$ brake constant of long feedback.
- $D_H = 47 * 10^{-9}; [mol/l]$ damping constant of TRH at the pituitary.
- $D_T = 4.58 * 10^{-11}; [mol/s * l]$ damping constant of TSH at the thyroid gland.
- $G_H = 13.6 * 10^{-9}; [mol/s^2]$ secretion capacity of the pituitary.
- $G_T = 3.4{*}10^{-12}; [mol/s]$ secretion capacity of thyroid gland.
- $\alpha_S = 0.4; [l^{-1}]$ dilution factor for TSH.
- $K_{M2} = 1 * 10^{-9}; [mol/l]$ dissociation constant of 5'-deiodinase II.

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