Thyroid Hormone Homeostasis As a First-Order Control System

Maria Sckaff[1], Jessica Simon[1], Patrick Nguyen[1], Maxwell Pendleton[1], Joe Yuan[1], and Michael Shoga[1]

***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 five-hour period. Other relevant hormones such as thyroxine (T4), triiodothyronine (T3), and their relevant intermediaries were also produced 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 closed-loop transfer function derived presented one stable pole and a -90°phase drop at the resonant frequency, which matched the clearance exponent of TSH.**

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, 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 (HTP) 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 TRH perturbation will affect TSH production and the subsequent T3 production. We also sought to derive the closed-loop transfer function that relates 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.

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C. Relevant Assumptions

First, 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 representative of physiological behavior [2]. This is a safe assumption since the model is only concerned with understanding TSH response to TRH perturbation. Third, nonlinear Michaelis-Menten-Hill kinetics are assumed for the production and release of TSH [2]. This is a common assumption when working with binding enzymes or substrates. Fourth, circadian variation in TSH and TRH release was omitted in the system [2]. This is safe 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 that there are no delays in the production of any hormones. This can be remedied by allowing the simulation to run for at least five hours.

II. Methods

A. Equations

The 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 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].

$$\frac{\partial[TSH]}{\partial t} = \frac{\alpha_S G_H [TRH]}{(D_H + [TRH])(1 + L_S[T_3]_R)} - \beta_S [TSH] \tag{1}$$

$$T_{3R} = \frac{T_{3N}}{T_{3N} + D_R} \tag{2}$$

$$T_{3N} = T_{3C} \frac{1}{1 + K_{31} IBS} \tag{3}$$

$$\frac{\partial T_{3c}(t)}{\partial t} = \alpha_{32} G_{D2} \frac{FT_4(t)}{FT_4(t) + K_{M2}} - \beta_{32} T_{3c}(t) \tag{4}$$

Simply as a means to complete the loop, equations that use the consumption of TSH to produce T4 (which is assumed to happen inside the thyroid) and that use T4 to produce free T4 (FT4) (which is assumed to happen in the bodily tissues) were also considered. These two equations were outlined in equations 5 and 6, respectively, and obtained from published thyroid hormone homeostasis models [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].

$$\frac{\partial T_4}{\partial t} = \alpha_T G_T \frac{TSH(t)}{TSH(t) + D_T} - \beta_T T_4(t) \tag{5}$$

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

For the definition of the other constants seen in equations 1 through 6, refer to the Appendix.

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, biological 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 had a proportional controller ($K_P = 0.01$), deemed appropriate to improve the settling of the system response. The PID controller takes in a target TSH value, which value was 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 will modulate the TRH input considered by the biosystem.

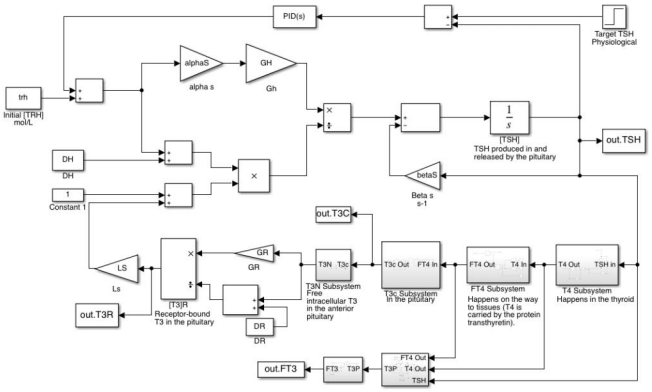

Fig. 1. The Simulink block diagram of the first-order control system.

C. Transfer Function

In developing the control system transfer function, in the format $H(s) = \frac{TSH(s)}{TRH(s)}$, where TSH(s) is the output and TRH(s) is the input, equations 1 through 6 were used as the starting equations. These starting equations were then 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. It was observed that some simplifications were possible after deriving the transfer function and factoring the numerator and denominator of the solution. This yielded a transfer function with a single negative pole, indicating a stable system. The single negative pole produced a phase shift and -90°step in phase at the resonant frequency of $2.3 * 10^{-4}$ Hz in the first order response. This resonant frequency equals the clearance exponent of TSH (β_S). Please refer to the supplemental material for the detailed calculations including the linearized equations, the Laplace transforms, and the steps to obtain the final simplified function showed in equation 8.

Transfer Function:

$$H(s) = \frac{TSH\,(s)}{TRH(s)} \tag{7}$$

$$H\,(s) = \frac{0.0881}{(s + 2.3 * 10^{-4})} \tag{8}$$

III. Results

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

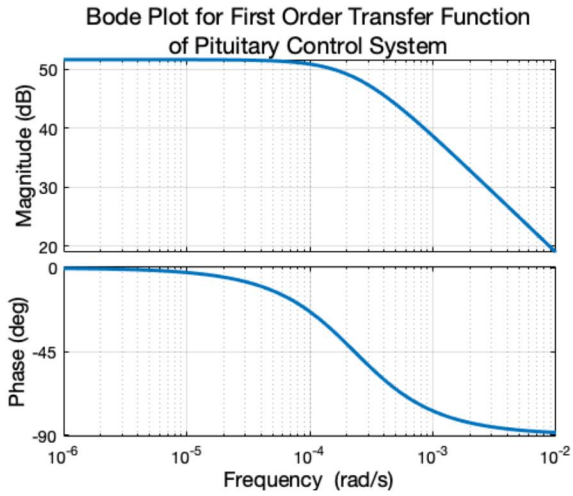

Fig. 2. Bode plot of the first-order transfer function for the control system.

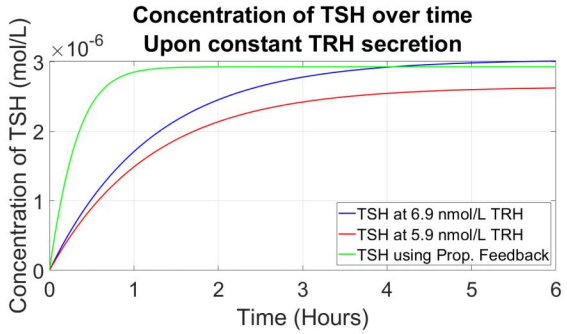

Fig. 3. TSH concentration response using a proportional controller to enhance the biological controller and under different TRH concentrations.

A. Simulation Results

Given a constant input of TRH, the TSH output followed Michaelis-Menten-Hill kinetics and settled at a constant values, which depended on the the TRH input concentration. For an input of 5.9 nmol/L TRH, the output settled at $2.61{*}10^{-6}\mu$mol/L TSH. For an input of 6.9 nmol/L TRH, the output is $3.01 * 10^{-6}\mu$mol/L TSH. 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.

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 both 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]. Note that this ultra-short feedback loop on the regulation of TSH was not included in the model explored in this study.

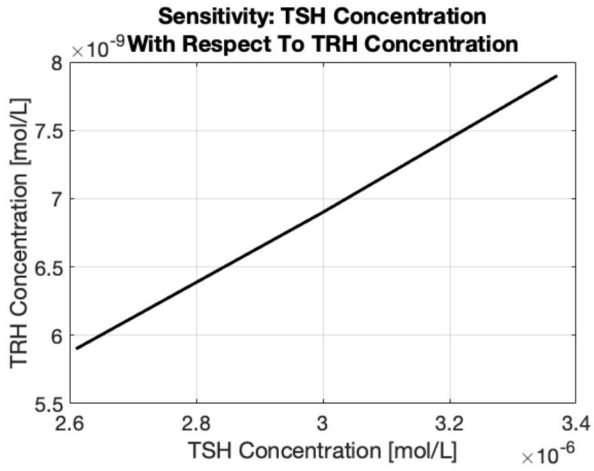

Fig. 4. Sensitivity analysis of the TSH concentration with respect to changes in TRH.

B. Model Sensitivity

Varying the input TRH by increments of one nmol/L between 4.9 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 0.3867 μmol/L of TSH for a nmol/L of TRH. We can expect that the system's TSH will change by approximately 0.39 μmol/L for every nmol/L change in TRH within this approximately linear region.

C. Modeling a Diseased State

Hypothyroidism and hyperthyroidism are characterized by an underproduction and overproduction of T3, respectively. Modeling of thyroid diseases lends itself to the convenience of not needing to account for the source of the error - as damage to the thyroid gland has the same effect as insensitivity to TSH in the thyroid gland. As such, the simplest method to change the system response to TSH is to modify gain as feedback to up-regulate T_{3P} in the T4, FT4, TSH to T_{3P} subsystem. With this, the effect of TSH specifically affects the loop of thyroid hormones, rather than modifying the effects of the conversion of T4 to T3. This allows for the model to account for this possibility of error, since both of these modifications are not feasible to detect in a clinical setting - and clinical practice mostly relies on detecting levels of TSH rather than detecting levels of T3, which is why TSH is used in the definition of error [5]. As such, an error can be defined as the difference between a

target physiological TSH value and the currently held TSH value as the system defines itself. This error can be fed to a PID controller (as modeled in Fig. 1.). The controller output will adjust the physiological TRH concentration, and will be modulated in accordance to the aforementioned target physiological, normal TSH concentration, whose value will serve in correcting for low or high thyroid hormone levels.

IV. Conclusion

The main purpose of this study was to understand how TRH perturbation affects TSH production and subsequently 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 further enabled us to understand how the level of concentration of T3 hormone causes diseases such as hyperthyroidism and hypothyroidism and how TSH concentrations different from physiological levels can be remedied. The controller was successful in improving the settling of the TSH concentration, also increasing the rise time and critically damping the response. Upon linearization of the system's differential equations and analysis in the Laplace domain, the closed-loop transfer function $H(s) = \frac{TSH(s)}{TRH(s)}$ presented one negative pole and a stable phase margin at -90°. The single negative pole was introduced at the resonant frequency, which matched the clearance exponent of TSH, β_S. This analysis suggests the system is physiologically stable and well-regulated by the system equations presented earlier.

A. Model Advantages and Limitations

The main advantages of this model is that it is focused in considering the hormonal interaction within the pituitary gland, allowing for a straight-forward analysis of the interaction between TSH and TRH in the HPT axis. This model also provided an insight into the natural physiological controller within the HPT axis and how it could be enhanced. 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 [6]. Some of the model limitations include how the model did not provide 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. 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 [7].

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. IBS, TBG, and TBPA were, respectively, the concentration of intracellular T3-binding substrate, the concentration of thyroxine-binding globulin, and the concentration of transthyretin (T4 transport protein). 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].

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Thyroid Hormone Homeostasis As a First-Order Control System: Supplemental Material

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1 Linearized Forms of Differential Equations

$$\frac{d\left[\widetilde{TSH}\right]}{dt} = \frac{\alpha_s G_H TRH_{ss}}{\left(D_H + TRH_{ss}\right)\left(1 + L_s\left[T_3\right]_{Rss}\right)^2}\left[\widetilde{T_3}\right]_R + \frac{\alpha_s G_H D_H}{\left(D_H + TRH_{ss}\right)^2\left(1 + L_s\left[T_3\right]_{Rss}\right)}\left[\widetilde{TRH}\right] - \beta_s\left[\widetilde{TSH}\right] \tag{1}$$

$$\frac{d\left[\widetilde{T_4}\right]}{dt} = \alpha_T G_T \frac{D_T}{\left(TSH_{ss} + D_T\right)^2}\left[\widetilde{TSH}\right] - \beta_T \widetilde{T_4} \tag{2}$$

$$\frac{d\left[\widetilde{T_{3c}}\right]}{dt} = \alpha_{32} G_{D2} \frac{K_{M2}}{\left(FT4_{ss} + K_{M2}\right)^2} - \beta_{32}\widetilde{T}_{3c} \tag{3}$$

2 Laplace Transforms

$$s\left[\widetilde{TSH}\right](s) = \frac{\alpha_s G_H TRH_{ss}}{\left(D_H + TRH_{ss}\right)\left(1 + L_s\left[T_3\right]_{Rss}\right)^2}\left[\widetilde{T_3}\right]_R(s) + \frac{\alpha_s G_H D_H}{\left(D_H + TRH_{ss}\right)^2\left(1 + L_s\left[T_3\right]_{Rss}\right)}\left[\widetilde{TRH}\right](s) - \beta_s\left[\widetilde{TSH}\right](s) \tag{4}$$

$$s\widetilde{T_4}(s) = \alpha_T G_T \frac{D_T}{\left(TSH_{ss} + D_T\right)^2}\left[\widetilde{TSH}\right](s) - \beta_T \widetilde{T_4}(s) \tag{5}$$

$$s\widetilde{T_4}(s) = \alpha_{32} G_{D2} \frac{K_{M2}}{\left(FT4_{ss} + K_{M2}\right)^2}(s) - \beta_{32}\widetilde{T}_{3c}(s) \tag{6}$$

$$\widetilde{T}_{3N}(s) = \frac{1}{1 + K_{31} IBS}\widetilde{T}_{3c}(s) \tag{7}$$

$$\widetilde{T}_{3R}(s) = G_R \frac{D_R}{\left(T_{3Nss} + D_R\right)^2}\widetilde{T}_{3N}(s) \tag{8}$$

$$\widetilde{FT_4} = \frac{1}{1 + K_{41} TBG + K_{42} TBPA}\widetilde{T}_4(s) \tag{9}$$

3 Transfer Function

$$H(s) = \frac{TSH(s)}{TRH(s)} \tag{10}$$

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4 Plugging in for real values

$$H(s) = \frac{2.8 * 10^{-57} \left(s + 1.1 * 10^{-6}\right) \left(s + 8.3 * 10^{-4}\right)}{2.9 * 10^{-15} \left(2.5 * 10^{-45} s + 2.1 * 10^{-48}\right) \left(s + 1.1 * 10^{-6}\right) + 3.2 * 10^{-56} s \left(s + 1.1 * 10^{-6}\right) \left(s + 8.3 * 10^{-4}\right) + 1.8 * 10^{-85}} \tag{11}$$

5 Factoring and Simplification

$$H(s) = \frac{2.8 * 10^{-57} \left(s + 1.1 * 10^{-6}\right) \left(s + 8.3 * 10^{-4}\right)}{3.2 * 10^{-56} s \left(s + 1.1 * 10^{-6}\right) \left(s + 2.3 * 10^{-4}\right) \left(s + 8.3 * 10^{-4}\right)} \tag{12}$$

6 Final Transfer Function

$$H(s) = \frac{TSH(s)}{TRH(s)} \tag{13}$$

$$H(s) = \frac{0.0881}{\left(s + 2.3 * 10^{-4}\right)} \tag{14}$$

7 Values of Physiological Constants

Values were obtained from previously published mathematical models of the pituitary-thyroid feedback loop by Berberich and Dietrich [1].

$TRH = 5.9 * 10^{-9}$; [mol/l] TRH-level in hypophyseal portal system.
$TBG = 300 * 10^{-9}$; [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.

$\alpha_S = 0.4; [l^{-1}]$ dilution factor for TSH.
$\alpha_T = 0.1; [l^{-1}]$ dilution factor for T4.
$\alpha_{31} = 2.6 * 10^{-2}; [l^{-1}]$ dilution factor for peripheral T3.
$\alpha_{32} = 1.3 * 10^{-5)}; [l^{-1}]$ dilution factor for central T3.

$\beta_S = 2.3 * 10^{-4}; [s^{-1}]$ clearance exponent for TSH.
$\beta_T = 1.1 * 10^{-6}; [s^{-1}]$ clearance exponent for T4.
$\beta_{31} = 8 * 10^{-6}; [s^{-1}]$ clearance exponent for peripheral T3.
$\beta_{32} = 8.3 * 10^{-4}; [s^{-1}]$ clearance factor for central T3.

$G_H = 13.6 * 10^{-9}; [mol/s^2]$ secretion capacity of the pituitary.
$G_T = 3.4 * 10^{-12)}; [mol/s]$ secretion capacity of thyroid gland.
$G_{T3} = 394 * 10^{-15}; [mol/s]$ gain of the michaelis-Menten-Hill kinetics in the TSH-T3 shunt.
$G_{D1} = 22 * 10^{-9}; [mol/s]$ the maximum activity of type I deiodinase.
$G_{D2} = 4.3 * 10^{-15}; [mol/s]$ maximum activity of type II deiodinase.
$G_R = 1; [mol/s]$ maximum gain of TRBeta receptors.
$D_R = 100 * 10^{-12}; [mol/l]$ damping constant for central T3.
$D_H = 47 * 10^{-9}; [mol/l]$ damping constant of TRH at the pituitary.
$D_T = 4.58 * 10^{-11}; [mol/s * l]$ damping constant of TSH at the thyroid gland.
$L_S = 1.68 * 10^{6}; [l/mol]$ brake constant of long feedback.

$k = 1.67 * 10^{-11}; [mol/s * l]$ the parameter k of the Michaelis-Menten-Hill kinetics that is used to model the TSH-stimulated deiodination inside the the shunt, normalized to [1mU/l].
$K_{31} = 2 * 10^{9}; [l/mol]$ dissociation constant T3-IBS.
$K_{41} = 2 * 10^{10}; [l/mol]$ dissociation constant T4-TBG.
$K_{42} = 2 * 10^{8}; [l/mol]$ dissociation constant T4-TBPA.
$K_{M1} = 500 * 10^{-9}; [mol/l]$ dissociation constant of 5'-deiodinase I.
$K_{M2} = 1 * 10^{-9}; [mol/l]$ dissociation constant of 5'-deiodinase II.

8 Defining the compound constants

Compound constants' definitions were obtained from previously published mathematical models of the pituitary-thyroid feedback loop by Berberich and Dietrich [1].

$$
\begin{aligned}
a_1 &= \frac{G_T \alpha_T}{\beta_T}; \\
a_3 &= \frac{G_{D2} \alpha_{32}}{\beta_{32}}; \\
b_1 &= \frac{1}{1 + K_{41} * TBG + K_{42} * TBPA}; \\
c_2 &= 1 + \frac{K_{M2}}{a_1 * b_1}; \\
c_3 &= D_T \frac{K_{M2}}{a_1 * b_1};
\end{aligned}
\tag{15}
$$

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