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# *Supplementary Material*: Mathematical modeling of the pituitary-thyroid feedback loop: role of a TSH-$T_3$-shunt and sensitivity analysis

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## S1 DIFFERENTIAL EQUATIONS OF THE EXTENDED MODEL

In the following, the differential equations of the extended model presented in Section 2 of the main article are described. Since the equilibrium values of this system are of particular interest for the parameter estimation of $G_{D1}$, $k$, and $G_{T3}$, we also show how to compute the equilibria depending on the parameters. The model can be expressed via the following system of five coupled nonlinear delay differential equations:

$$\frac{dT_4}{dt}(t) = \alpha_T \cdot G_T \cdot \frac{TSH(t-\tau_{0T})}{TSH(t-\tau_{0T}) + D_T} - \beta_T \cdot T_4(t) \tag{S1}$$

$$\begin{aligned}\frac{dT_{3P}}{dt}(t) = \alpha_{31} \Bigg( & G_{D1} \cdot \frac{FT_4(t)}{FT_4(t) + K_{M1}} + G_{D2} \cdot \frac{FT_4(t)}{FT_4(t) + K_{M2}} \\ & + G_{T3} \cdot \frac{TSH(t)}{TSH(t) + D_T} + G_{D1} \frac{T_{4,th}(t) \frac{TSH(t)}{TSH(t)+k}}{K_{M1} + T_{4,th}(t) \frac{TSH(t)}{TSH(t)+k}} \\ & + G_{D2} \frac{T_{4,th}(t) \frac{TSH(t)}{TSH(t)+k}}{K_{M2} + T_{4,th}(t) \frac{TSH(t)}{TSH(t)+k}} \Bigg) - \beta_{31} \cdot T_{3P}(t)\end{aligned} \tag{S2}$$

$$\frac{dT_{3c}}{dt}(t) = \alpha_{32} G_{D2} \cdot \frac{FT_4(t-\tau_{03Z})}{FT_4(t-\tau_{03Z}) + K_{M2}} - \beta_{32} \cdot T_{3c}(t) \tag{S3}$$

$$\begin{aligned}\frac{dTSH}{dt}(t) = & \\ & \frac{\alpha_S G_H \cdot TRH(t-\tau_{0S})}{(TRH(t-\tau_{0S}) + D_H)\left(1 + S_S \cdot \frac{TSH_z(t-\tau_{0S})}{TSH_z(t-\tau_{0S}) + D_S}\right)(1 + L_S \cdot T_{3R}(t-\tau_{0S}))} \\ & - \beta_S \cdot TSH(t)\end{aligned} \tag{S4}$$

$$\frac{dTSH_z}{dt}(t) = \frac{\alpha_{S2} G_H \cdot TRH(t-\tau_{0S2})}{(TRH(t-\tau_{0S2}) + D_H)\left(1 + S_S \cdot \frac{TSH_z(t-\tau_{0S2})}{TSH_z(t-\tau_{0S2})+D_S}\right)(1 + L_S \cdot T_{3R}(t-\tau_{0S2}))} - \beta_{S2} \cdot TSH_z(t) \tag{S5}$$

where

$$\begin{aligned} T_{4,th} &= G_T \cdot \frac{TSH}{TSH + D_T} \cdot \frac{s}{l} \\ FT_3 &= T_{3P} \cdot \frac{1}{1 + K_{30} \cdot TBG} \\ FT_4 &= T_4 \cdot \frac{1}{1 + K_{41} \cdot TBG + K_{42} \cdot TBPA} \\ T_{3N} &= T_{3c} \cdot \frac{1}{1 + K_{31} \cdot IBS} \\ T_{3R} &= G_R \cdot \frac{T_{3N}}{T_{3N} + D_R} \end{aligned} \tag{S6}$$

As described in Section 2 in the main text, the novelty of the presented model is the inclusion of intrathyroidal $T_3$ production, depicted by the three blocks "T1D", "T3 Synthesis" and "T2D" in Figure 1 in the article. This results in the last three terms inside the bracket on the right hand side of Equation (S2). Concerning the $TSH$-stimulated deiodination (corresponding to the last two terms inside the bracket on the right hand side of Equation (S2)), the following comments are in order. First, the thyroidal $T_4$ concentration, $T_{4,th}$, is modeled as a zero-th order process, i.e., given by (S6). This is a valid approximation under the assumption that the thyroidal $T_4$ production is fast compared to peripheral $T_4$ distribution. Second, the stimulation of the deiodinases by $TSH$ is modeled by the additional multiplicative term $TSH/(TSH + D_T)$. This can be derived as follows. The considered deiodination is an enzymatic reaction and can be modeled as many basic enzymatic reactions by

$$\mathrm{d} + \mathrm{T_{4,th}} \rightleftharpoons \mathrm{dT_{4,th}} \longrightarrow \mathrm{d} + \mathrm{T_3}, \tag{S7}$$

compare, e.g., [1]. Here, $d$ is the (activated) deiodinase concentration and $dT_{4,th}$ is the concentration of an intermediate complex between the deiodinase and thyroidal $T_4$. Using the quasi-steady-state assumption[1] for the complex $dT_{4,th}$, such a reaction scheme can be approximated by the well-known Michaelis-Menten-Hill kinetics $G_{D1}T_{4,th}/(K_{M1} + T_{4,th})$ with appropriate constants $G_{D1}$ and $K_{M1}$, see, e.g., [1]. The activation/stimulation of the thyroidal deiodinases by $TSH$ is now modeled by a reaction of the form

$$\mathrm{d}' + \mathrm{TSH} \rightleftharpoons \mathrm{d},$$

[1] In case that this assumption does not hold, approximation by a Michaelis-Menten-Hill kinetics might not be valid and other modeling approaches might be required, compare, e.g., [2].

where $\mathrm{d}^{'}$ is the concentration of an inactive form of deiodinase. Combining this equation with (S7) and using again the quasi-steady-state assumption (both for deiodinase activation and the complex $dT_{4,th}$) results in the term appearing in (S2), i.e.,

$$G_{D1}\frac{T_{4,th}\frac{TSH}{TSH+k}}{K_{M1}+T_{4,th}\frac{TSH}{TSH+k}}$$

for some constant $k > 0$.

We note that an interesting topic for future work would be to include a more precise model of the thyroid and thyroidal $T_4$ production, e.g., a compartmental model including membrane transporters, or modeling the dynamics of the second messenger $cAMP$.

The numerical values of the parameters for the model (S1)–(S5) are listed in Section S3. In order to obtain the equilibrium hormone levels of the system (S1) - (S5), we set all of the derivatives in equations (S1) - (S5) to zero and solve the resulting equations for the corresponding hormone values. Due to the complex structure and the many parameters of the system, this is rather cumbersome but straightforward, as outlined in the following.

After defining some intermediate parameters

$$a_1 = \frac{\alpha_T G_T}{\beta_T},\ \ a_3 = \frac{\alpha_{32} G_{D2}}{\beta_{32}},\ \ b_1 = \frac{1}{1+K_{41}TBG+K_{42}TBPA}$$
$$c_2 = 1+\frac{K_{M2}}{a_1 b_1},\ \ c_3 = D_T\frac{K_{M2}}{a_1 b_1}$$

and plugging $T_4$ from equation (S1) into (S3), one arrives at

$$T_{3c} = a_3\frac{TSH}{c_2 TSH + c_3}.$$

This can then be inserted into (S5) which, after performing some algebraic computations, leads to

$$TSH = \frac{g_1 TSH_z^2 + g_2 TSH_z + g_3}{g_4 TSH_z^2 + g_5 TSHz + g_6}, \tag{S8}$$

where we again define intermediate parameters as follows:

$$a_5 = \frac{\alpha_{S2} G_H}{\beta_{S2}},\ b_3 = \frac{1}{1 + K_{31} IBS},\ c_1 = \frac{TRH}{TRH + D_H},\ d_2 = L_S G_R b_3 a_3,$$
$$d_3 = b_3 a_3 + c_2 D_R,\ d_4 = c_3 D_R,\ d_5 = d_2 + d_3,\ d_6 = 1 + S_S,\ f_1 = c_1 a_5,$$
$$g_1 = -d_4 d_6,\ g_2 = f_1 d_4 - d_4 D_S,\ g_3 = f_1 d_4 D_S,\ g_4 = d_5 d_6,\ g_5 = -f_1 d_3 + d_5 D_S,$$
$$g_6 = -f_1 d_3 D_S,\ g_7 = \frac{\alpha_{S2} \beta_S}{\beta_{S2} \alpha_S}.$$

From equations (S4) and (S5), we can also conclude that $TSH_z = g_7 TSH$. Now, plugging this into (S8), we finally arrive at a cubic equation in $TSH$:

$$m_1 TSH^3 + m_2 TSH^2 + m_3 TSH + m_4 = 0 \tag{S9}$$

where

$$m_1 = g_4 g_7^2,\ m_2 = g_5 g_7 - g_1 g_7^2,\ m_3 = g_6 - g_2 g_7,\ m_4 = -g_3$$

Solving this cubic equation yields three (complex-valued) solutions for the equilibrium level of $TSH$. In practice, it turns out that for the most common parameter settings, there is, indeed, only one solution that is real-valued and positive and therefore physically reasonable.

Now, one can simply plug this solution for $TSH$ into equations (S1), (S2), (S3), and (S5) to solve for the other steady-state values. Since the equilibrium value of free peripheral $T_3$ is of particular interest for the parameter identification, we state the formula for its computation, depending on the parameters $G_{T3}$, $k$, and $G_{D1}$.

$$\begin{aligned} FT_{3,eq}\left(G_{T3}, k, G_{D1}\right) = b_2 \frac{\alpha_{31}}{\beta_{31}} \Bigg[ & G_{T3} \frac{TSH}{TSH + D_T} \\ & + G_{D1} \left( \frac{T_{4,th} \frac{TSH}{TSH+k}}{K_{M1} + T_{4,th} \frac{TSH}{TSH+k}} + \frac{FT_4}{FT_4 + K_{M1}} \right) \\ & + G_{D2} \left( \frac{T_{4,th} \frac{TSH}{TSH+k}}{K_{M2} + T_{4,th} \frac{TSH}{TSH+k}} + \frac{FT_4}{FT_4 + K_{M2}} \right) \Bigg] \end{aligned}$$

where

$$b_2 = \frac{1}{1 + K_{30} TBG}$$
$$T_{4,th} = G_T \frac{TSH}{TSH + D_T}$$

It can be seen that $FT_{3,eq}\left(G_{T3}, k, G_{D1}\right)$ is affine in $G_{D1}$ and $G_{T3}$ for a fixed value of $k$ and given the equilibrium concentrations of $TSH$ and $T_4$, which can be computed independently of $G_{D1}$ and $G_{T3}$. This fact is used in the parameter identification in the main article.

In the dynamic simulations of the model shown in Section 3 of the main text, we observe that the stationary hormone levels are slightly higher than the equilibrium value $FT_{3,eq}$ computed above. This is due to the following. For our dynamic simulation, the $TRH$ concentration arriving at the pituitary has a circadian oscillation with additional stochastic noise with a log-normal distribution, as discussed in detail in [3]. On the other hand, for the parameter identification described in Section 2 of the main text, a constant (equilibrium) value for $TRH$ was assumed. The presence of the additional log-normally distributed noise causes an offset in $TSH$ (its mean value increases by approximately 17%) which in turn results in the observed slight increase in $FT_3$ levels. The transient increase in $FT_3$-levels, which can be observed in both plots in Figure 3 of the main text, is a result of this additional noise and the chosen initial conditions for the simulation.

## S2 FORMAL DEFINITION OF SENSITIVITY ANALYSIS

The purpose of this section is to formally define the first-order sensitivity matrix of a system of ordinary differential equations (ODEs) w.r.t. several parameters, following the exposition in [4]. As stated in Section 4 in the main article, we consider ODEs of the form

$$\dot{x}(t) = f(t, x, p), \quad x(t_0) = x_0. \tag{S10}$$

where

- $t \in I$ denotes time, where $I$ is some closed interval $I = [t_0, t_1]$ on which the solution $x$ to (S10) is defined
- $p \in \mathbb{R}^m$ denotes the $m$-dimensional parameter vector
- $x : I \times \mathbb{R}^m \to \mathbb{R}^n$ denotes the solution to (S10), i.e. $x(t, p)$ is the value of the system state at time $t$ for a given parameter $p$
- $x_0 \in \mathbb{R}^n$ is the system's initial value
- $f : I \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$ is a continuous vector field that is continuously differentiable w.r.t. $x$ and $p$

It can be shown (cf. [4]) that if the system (S10) has a unique solution $x(t, p_0)$ over $I$ for some fixed (nominal) parameter vector $p_0$, then it also has a unique solution $x(t, p)$ for all parameter variations $p$ sufficiently close to $p_0$, i.e. for all $p$ such that $\|p - p_0\|$ is sufficiently small. Thus, we can define the sensitivity matrix $S : I \to \mathbb{R}^{n \times m}$ as the matrix of partial derivatives of the components of $x$ w.r.t. to the components of $p$:

$$(S(t))_{ij} = \left.\frac{\partial x_i(t, p)}{\partial p_j}\right|_{(t, p_0)} \tag{S11}$$

Note that, indeed, this matrix describes how sensitive each state component is w.r.t. variations in one component of the parameter vector $p$ around some nominal value. According to [4], $S(t)$ can be computed by solving the following system of ODEs:

$$\begin{aligned} \dot{x}(t) &= f(t, x, p_0) \\ \dot{S}(t) &= \left[\frac{\partial f(t, x, p)}{\partial x}\right]_{p=p_0} \cdot S + \left[\frac{\partial f(t, x, p)}{\partial p}\right]_{p=p_0} \\ x(t_0) &= x_0, \quad S(t_0) = 0 \end{aligned} \tag{S12}$$

This approach can easily be extended to time-varying parameter vectors which is needed in the modeling of the pituitary-thyroid feedback loop due to the sinusoidal circadian rhythm of $TRH$.

## S3 NUMERICAL PARAMETER VALUES FOR THE IMPLEMENTATION OF THE PRESENTED MODEL

| Symbol | Description | Value | Origin |
|---|---|---|---|
| $TBG$ | Concentration of thyroxine-binding Globulin | $300\ nmol/l$ | [5] / well-known reference value |
| $TBPA$ | Concentration of Transthyretin | $4.5\ \mu mol/l$ | [5] / well-known reference value |
| $IBS$ | Concentration of intra-cellular $T_3$-binding substrate | $8\ \mu mol/l$ | Estimated from $TBG$-level, corrected for intra-cellular $T_3$-accumulation (according to values from [6]) |
| $TRH$ | $TRH$-level in hypophyseal portal system | $6.9\ nmol/l$ | [7] |
| $G_H$ | Secretory capacitiy of the pituitary | $817\ mU/s$ | Calculated according to values from [8] and [9] |
| $D_H$ | Damping constant ($EC_{50}$) of $TRH$ at the pituitary | $47\ nmol/l$ | [10] |
| $\alpha_S$ | Dilution factor for peripheral $TSH$ | $0.4\ l^{-1}$ | Reciprocal value of the volume of distribution for plasma volume of $2.5\ l$ |
| $\beta_S$ | Clearance exponent for peripheral $TSH$ | $2.3 \cdot 10^{-4} s^{-1}$ | Calculated from plasma half-life of 50 min ([11, 12]) |
| $L_S$ | Brake constant of long feedback | $1.68\ l/\mu mol$ | Calculated from clinical data of hyperthyroid patients |
| $G_T$ | Secretory capacity of thyroid gland | $3.4\ pmol/s$ | [12] |
| $D_T$ | Damping constant ($EC_{50}$) of $TSH$ at the thyroid gland | $2.75\ mU/l$ | [13] |

**Table S1.** Numerical parameter values for the implementation of the presented model of the HPT axis, adopted from [14] - part 1.

| Symbol | Description | Value | Origin |
|---|---|---|---|
| $\alpha_T$ | Dilution factor for $T_4$ | $0.1\ l^{-1}$ | Reciprocal value of the volume of distribution (the latter from [15]) |
| $\beta_T$ | Clearance exponent for $T_4$ | $1.1 \cdot 10^{-6} s^{-1}$ | Calculated from plasma half-life of 7 days ([16, 15]) |
| $K_{M1}$ | Dissociation constant of 5'-deiodinase I | $500 nmol/l$ | [15] |
| $\alpha_{31}$ | Dilution factor for peripheral $T_3$ | $2.6 \cdot 10^{-2} l^{-1}$ | Reciprocal value of the volume of distribution (the latter from [15]) |
| $\beta_{31}$ | Clearance exponent for peripheral $T_3$ | $8 \cdot 10^{-6} s^{-1}$ | Calculated from plasma half-life of 24 h ([15]) |
| $G_{D2}$ | Maximum activity of type II deiodinase | $4.3\ fmol/s$ | Calculated from pituitary $T_3$-level ([17]) |
| $K_{M2}$ | Dissociation constant of 5'-deiodinase II | $1\ nmol/l$ | [18] |
| $\alpha_{32}$ | Dilution factor for central $T_3$ | $1.3 \cdot 10^{-5} l^{-1}$ | Calculated from volume of distribution $7.6 \mu l$ |
| $\beta_{32}$ | Clearance-Exponent for central $T_3$ | $8.3 \cdot 10^{-4} s^{-1}$ | Calculated from intra-cellular half-life of 15 min [19] and [20]) |
| $\alpha_{S2}$ | Dilution factor for pituitary $TSH$ | $2.6 \cdot 10^{-5} l^{-1}$ | Calculated from volume of distribution $3.8 \mu l$ |
| $\beta_{S2}$ | Clearance exponent for pituitary $TSH$ | $140\ s^{-1}$ | estimated corresponding to half-life of $5s$ |
| $D_R$ | Damping constant for central $T_3$ | $100\ pmol/l$ | [21] |
| $G_R$ | Maximum gain of TR$\beta$ receptors | $1\ mol/s$ | Value unknown, normalized to 1 (magnitude of feedback is determined by $L_S$) |
| $S_S$ | Brake constant of ultrashort feedback | $100\ l/mU$ | Determined according to values from [22] |
| $D_S$ | Damping constant for $TSH$ inside the pituitary | $50\ mU/l$ | Determined according to values from [22] |

**Table S2.** Numerical parameter values for the implementation of the presented model of the HPT axis, adopted from [14] - part 2.

| Symbol | Description | Value | Origin |
|---|---|---|---|
| $K_{30}$ | Dissociation constant $T_3$-$TBG$ | $2 \cdot 10^9 l/mol$ | [12] |
| $K_{31}$ | Dissociation constant $T_3$-$IBS$ | $2 \cdot 10^9 l/mol$ | Value unknown, adapted to extra-cellular dissociation constant |
| $K_{41}$ | Dissociation constant $T_4$-$TBG$ | $2 \cdot 10^{10} l/mol$ | [12] |
| $K_{42}$ | Dissociation constant $T_4$-$TBPA$ | $2 \cdot 10^8 l/mol$ | [12] |
| $\tau_{0S}$ | Peripheral delay for $TSH$ | $120\ s$ | Derived from circulation time |
| $\tau_{0S2}$ | Pituitary delay for $TSH$ | $3240\ s$ | Derived from period of $TSH$-pulses (data from [23, 24]) |
| $\tau_{0T}$ | Delay for $T_4$ | $300\ s$ | Estimated according to circulation and diffusion times |
| $\tau_{03Z}$ | Delay for pituitary $T_3$ | $3600s$ | Derived from [25] |

**Table S3.** Numerical parameter values for the implementation of the presented model of the HPT axis, adopted from [14] - part 3.

| Model Configuration | Parameter | Value |
|---|---|---|
| (1) no shunt | $G_{T3}$ | - |
| | $G_{D1}$ | $27.5\ nmol/s$ |
| | $k$ | - |
| (2) full $TSH$-$T_3$-shunt | $G_{T3}$ | $394\ fmol/s$ |
| | $G_{D1}$ | $22\ nmol/s$ |
| | $k$ | $1\ mU/l$ |

**Table S4.** Numerical parameter values for the implementation of the presented model of the HPT axis - parameters identified via least squares estimation. $G_{T3}$ is the gain of the Michaelis-Menten-Hill kinetics in the $TSH$-$T_3$-Shunt, $G_{D1}$ describes the maximum activity of type I deiodinase. The parameter $k$ of the Michaelis-Menten-Hill kinetics that is used to model the $TSH$-stimulated deiodination inside the shunt was normalized to $1\frac{mU}{l}$. There are two different model configurations for which we separately identified the parameters: The model from [14] without the $TSH$-$T_3$-shunt (1), and the model including the full shunt as described in the main article (2). For version (2), the optimal parameters cannot be determined uniquely. In this case, the above values correspond to a peripheral contribution to the $T_3$ production of approximately $80\%$, as described in Section 2 in the article.

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