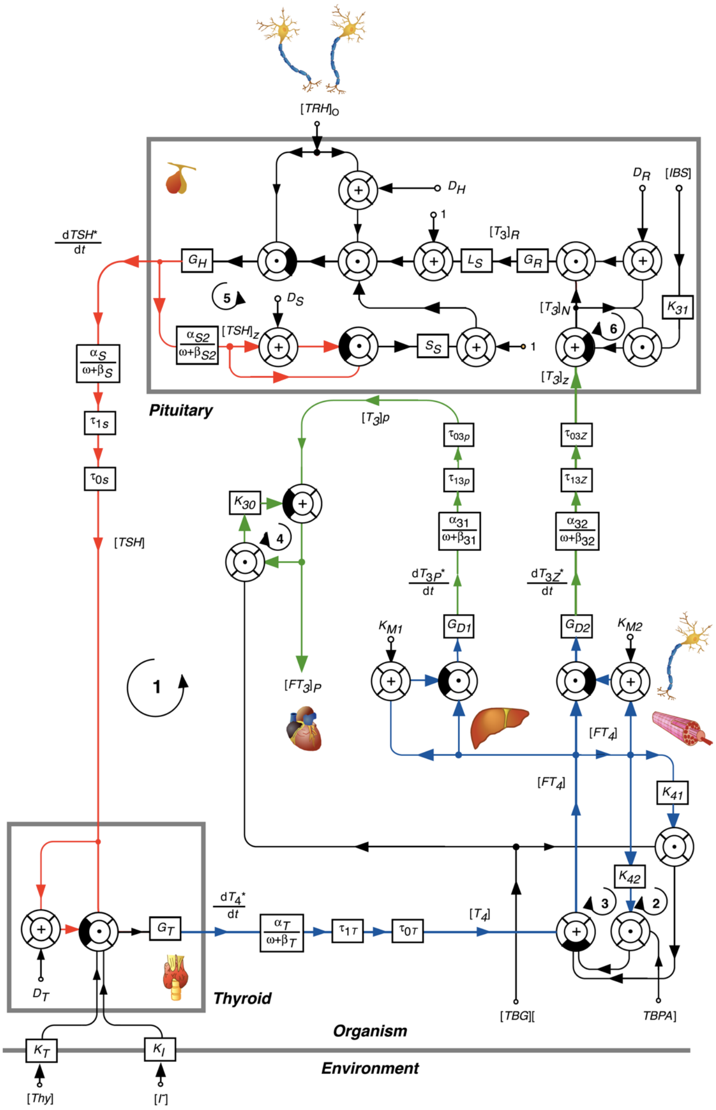
# Documentation of Mathematical Models

## MiMe-NoCoDI Model #10 of Thyroid Homeostasis

### 1 Introduction

This documentation presents the equations forming the foundation of a published model [1-6] of hypothalamus-pituitary-thyroid axis. This model (MiMe-NoCoDI model #10) is based on Michaelis-Menten kinetics and non-competitive divisive inhibition. The numbering of equations is identical to that in Dietrich 2002 [1].

### 2 Processing structure




Information processing structure of model #10 [3]

# 3 Equations of processes, organs and compartments

## 3.1 Plasma Protein Binding (feedback loops #2, #3, #4 and #6)

### 3.1.1 Recursive equation

$$[FT_4] = [T_4] - [BT_4] \tag{3.1}$$

$$[FT_4] = [T_4] - K_{41}[FT_4][TBG] - K_{42}[FT_4][TBPA] \tag{3.2}$$

$[T_4]$: free T4 concentration; $[FT_4]$free T4 concentration; $[BT_4]$: plasma protein-bound T4 concentration. See table for an explanation of additional symbols.

### 3.1.2 Equifinal solution

$$[FT_4] = \frac{T_4}{1+K_{41}[TBG]+K_{42}[TBPA]} \tag{3.3}$$

$$[FT_3]_P = \frac{[T_3]_P}{1+K_{30}[TBG]} \tag{3.4}$$

$[\mathrm{T}_3]_\mathrm{P}$: total T3 concentration in peripheral plasma; $[FT_3]_P$: free T3 concentration in peripheral plasma.

## 3.2 Hypothalamus and Pituitary

$$[TRH]_O = [TRH]_P + \frac{1}{\dot{V}}\frac{dTRH^*}{dt} \tag{3.5}$$

$[TRH]_O$: TRH concentration in hypothalamus-pituitary portal vessel system; $[TRH]_P$: TRH concentration in peripheral plasma; $\dot{V}$: Plasma flow rate in the portal system; $\frac{dTRH^*}{dt}$ : TRH production rate in the hypothalamic PVN.

$$[TSH]_z = \frac{\alpha_{S2}}{\beta_{S2}}\frac{dTSH^*}{dt} \tag{3.6}$$

$[TSH]_z$: central (intrapituitary) TSH concentration; $\frac{dTSH^*}{dt}$ pituitary TSH production rate.

$$\frac{dTSH^*}{dt} = \frac{G_H[TRH]_O}{(D_H+[TRH]_O)(1+L_S[T_3]_R)\left(1+\frac{S_S[TSH]_Z}{D_S+[TSH]_Z}\right)} \tag{3.7}$$

$$[TSH] = \frac{\alpha_S}{\beta_S}\frac{dTSH^*}{dt} \tag{3.8}$$

## 3.3 T4 production, distribution and elimination

$$[T_4] = \frac{G_T\alpha_T[TSH]K_T[Thy]K_I[I^-]}{\beta_T(D_T+[TSH])} \tag{3.9}$$

### 3.4 T3 metabolism in central and peripheral compartments

$$[\mathrm{T}_3]_\mathrm{Z} = \frac{\mathrm{G}_{\mathrm{D2}}\alpha_{32}[\mathrm{FT}_4]}{\beta_{32}(\mathrm{K}_{\mathrm{M2}}+[\mathrm{FT}_4])} \quad (3.10)$$

$[\mathrm{T}_3]_\mathrm{Z}$: intrapituitary total T3 concentration.

$$[T_3]_N = \frac{[T_3]_Z}{1+K_{31}[IBS]} \quad (3.11)$$

$[\mathrm{T}_3]_\mathrm{N}$: intrapituitary unbound T3 concentration; $[IBS]$ concentration of intracellular binding substrate (e.g. CRYM).

$$[T_3]_R = \frac{G_R[T_3]_N}{D_R+[T_3]_N} \quad (3.12)$$

$[T_3]_R$: receptor-bound T3.

$$[\mathrm{T}_3]_\mathrm{P} = \frac{\mathrm{G}_{\mathrm{D1}}\alpha_{31}[\mathrm{FT}_4]}{\beta_{31}(\mathrm{K}_{\mathrm{M1}}+[\mathrm{FT}_4])} \quad (3.13)$$

$[\mathrm{T}_3]_\mathrm{P}$: total T3 concentration in peripheral plasma.

## 4 Predicting the Equilibrium

### 4.1 Ultrashort feedback loop (Brokken-Wiersinga-Prummel loop, loop #5):

$$ax^2 + bx + c = 0 \quad (3.14)$$

$$a = (1 + S_S)\alpha_{S2} \quad (3.15)$$

$$b = D_S\beta_{S2} - \frac{G_H\alpha_{S2}[TRH]_O}{(D_H+[TRH]_O)(1+L_S[T3]_R)} \quad (3.16)$$

$$c = -\frac{G_H D_S\beta_{S2}[TRH]_O}{(D_H+[TRH]_O)(1+L_S[T_3]_R)} \quad (3.17)$$

$$x_{1,2} = -\frac{b}{2a} \pm \frac{\sqrt{b^2-4ac}}{2a} \quad (3.18)$$

Since

$$\frac{\sqrt{b^2-4ac}}{2a} > \frac{-b}{2a} \quad (3.19)$$

one solution is positive and the second solution is negative.

### 4.2 Outer feedback loop (Astwood-Hoskins loop, loop #1):

$$K_2 = \frac{G_T \alpha_T}{\beta_T} \quad (3.20)$$

$$K_3 = \frac{G_{D2} \alpha_{32}}{\beta_{32}(1+K_{31}[IBS])} \quad (3.21)$$

$$K_6 = \frac{1}{2}\frac{1}{(1+S_S)\alpha_{S2}} \quad (3.22)$$

$$K_8 = \frac{\alpha_{S2} G_H [TRH]_O}{D_H+[TRH]_O} \quad (3.23)$$

$$K_9 = D_S \beta_{S2} \quad (3.24)$$

$$K_{11} = \frac{\alpha_S}{\beta_S} \quad (3.25)$$

$$K_{21} = \frac{G_T \alpha_T K_T [Thy] K_I [I^-]}{\beta_T} \quad (3.26)$$

$$K_{22} = \frac{K_{21}}{1+K_{41}[TBG]+K_{42}[TBPA]} \quad (3.27)$$

$$K_{61} = K_6 K_{11} \quad (3.28)$$

$$G_3 = \frac{K_3 G_R}{K_3+D_R} \quad (3.29)$$

$$D_3 = \frac{K_{M2} D_R}{K_3+D_R} \quad (3.30)$$

$$ax^3 + bx^2 + cx + d = 0 \quad (3.31)$$

$$a = \frac{D_3+K_{22}+L_S G_3 K_{22}}{K_{61}} \quad (3.32)$$

$$b = \frac{D_3 D_T}{K_{61}} + 2D_3K_9 + 2K_9K_{22} + 2L_SG_3K_9K_{22} - 2D_3K_8 - 2K_8K_{22} \quad (3.33)$$

$$c = 2[D_3D_TK_9 - D_3D_TK_8 - 2(1+S_S)D_3K_8K_9K_{61} - 2(1+S_S)K_8K_9K_{22}K_{61}] \quad (3.34)$$

$$d = 4(1+S_S)D_3D_TK_8K_9K_{61} \quad (3.35)$$

By introducing the transformation

$$x = y - \frac{b}{3a} \quad (3.36)$$

equation (3.31) can be reduced to

$$y^3 + ry + s = 0 \quad (3.37)$$

with

$$r = \frac{c}{a} - \frac{1}{3}\left(\frac{b}{a}\right)^2 \quad (3.38)$$

$$s = \frac{2}{27}\left(\frac{b}{a}\right)^3 - \frac{1}{3}\frac{cb}{a^2} + \frac{d}{a} \quad (3.39)$$

$$p = \frac{r}{3} \quad (3.40)$$

$$q = \frac{s}{2} \quad (3.41)$$

### 4.2.1 Solution with Cardano's equation

If $p^3 + q^2 > 0$:

$$u = \sqrt[3]{-q + \sqrt{p^3 + q^2}} \quad (3.42)$$

$$v = \sqrt[3]{-q - \sqrt{p^3 + q^2}} \quad (3.43)$$

$$y_1 = u + v \quad (3.44)$$

$$y_2 = -\frac{u+v}{2} + \frac{i}{2}\sqrt{3}(u - v) \quad (3.45)$$

$$y_3 = -\frac{u+v}{2} - \frac{i}{2}\sqrt{3}(u - v) \quad (3.46)$$

### 4.2.2 Solution as casus irreducibilis

If $p^3 + q^2 \leq 0$:

$$\cos\varphi = \frac{-q}{\sqrt{-p^3}} \quad (3.47)$$

$$y_1 = 2\sqrt{-p}\cos\frac{\varphi}{3} \quad (3.48)$$

$$y_2 = -2\sqrt{-p}\cos\left(\frac{\varphi}{3} + 60°\right) \quad (3.49)$$

$$y_3 = -2\sqrt{-p}\cos\left(\frac{\varphi}{3} - 60°\right) \quad (3.50)$$

### 4.2.3 Getting equifinal TSH concentration from the solutions

With equation (3.36) the three solutions for $y$ can be converted to three solutions for $x$. The positive solution represents the TSH concentration that is aimed at in equilibrium. The concentrations for the other hormones within the feedback loop can be calculated from equilibrium TSH concentrations with equations (3.6) to (3.13).

## 5 Parameters

Table: Constant parameters of the model [1–3, 6]

| Symbol | Explanation | Value |
|---|---|---|
| $G_H$ | Secretory capacity of the pituitary | 817 mIU/s |
| $D_H$ | Damping constant (EC50) of TRH at the pituitary | 47 nmol/l |
| $G_T$ | Secretory capacity of the thyroid gland | 3.4 pmol/s |
| $D_T$ | Damping constant (EC50) of TSH at the thyroid gland | 2.75 mIU/l |
| $G_{D1}$ | Maximum activity of type I deiodinase | 28 nmol/s |
| $K_{M1}$ | Dissociation constant of 5'-deiodinase I | 500 nmol/l |
| $G_{D2}$ | Maximum activity of type II deiodinase | 4.3 fmol/s |
| $K_{M2}$ | Dissociation constant of 5'-deiodinase II | 1 nmol/l |
| $G_R$ | Maximum gain of TRβ receptors | 1 mol/s |
| $D_R$ | EC50 for central T3 | 100 pmol/l |
| $S_S$ | Brake constant of TSH ultra-short-feedback | 100 l/mIU |
| $D_S$ | EC50 for TSH at the pituitary | 50 mIU/l |
| $\alpha_R$ | Dilution factor for peripheral TRH | 0.4 l-1 |
| $\beta_R$ | Clearance exponent for TRH | 2.3 e-3 s-1 |
| $\alpha_S$ | Dilution factor for TSH | 0.4 l-1 |
| $\beta_S$ | Clearance exponent for TSH | 2.3 e-4 s-1 |
| $\alpha_T$ | Dilution factor for T4 | 0.1 l-1 |
| $\beta_T$ | Clearance exponent for T4 | 1.1 e-6 s-1 |
| $\alpha_{31}$ | Dilution factor for peripheral T3 | 2.6 e-2 l-1 |
| $\beta_{31}$ | Clearance exponent for T3P | 8 e-6 s-1 |
| $\alpha_{32}$ | Dilution factor for central T3 | 1.3 e5 l-1 |
| $\beta_{32}$ | Clearance exponent for central T3 | 8.3 e-4 s-1 |
| $\alpha_{S2}$ | Dilution factor for pituitary TSH | 2.6 e5 l-1 |
| $\beta_{S2}$ | Clearance exponent for central TSH | 140 s-1 |
| $K_{30}$ | Dissociation constant T3-TBG | 2 e9 l/mol |
| $K_{31}$ | Dissociation constant T3-IBS | 2 e9 l/mol |
| $K_{41}$ | Dissociation constant T4-TBG | 2 e10 l/mol |
| $K_{42}$ | Dissociation constant T4-TBPA | 2 e8 l/mol |

## 6 References

1. Dietrich JW. Der Hypophysen-Schilddrüsen-Regelkreis. Entwicklung und klinische Anwendung eines nichtlinearen Modells. Vol 2. Berlin: Logos-Verlag 2002. ISBN 9783897228504.

2. Dietrich JW, Tesche A, Pickardt CR, Mitzdorf U. Thyrotropic Feedback Control: Evidence for an Additional Ultrashort Feedback Loop from Fractal Analysis. Cybernetics and Systems 2004; 35:315-331. doi 10.1080/01969720490443354.

3. Dietrich JW, Landgrafe G, Fotiadou EH. TSH and Thyrotropic Agonists: Key Actors in Thyroid Homeostasis. Journal of Thyroid Research 2012; 2012:351864. doi 10.1155/2012/351864.

4. Hoermann R, Midgley JE, Larisch R, Dietrich JW. Is pituitary TSH an adequate measure of thyroid hormone-controlled homoeostasis during thyroxine treatment? European Journal of Endocrinology 2013; 168:271-280. doi 10.1530/EJE-12-0819.

5. Midgley JE, Hoermann R, Larisch R, Dietrich JW. Physiological states and functional relation between thyrotropin and free thyroxine in thyroid health and disease: in vivo and in silico data suggest a hierarchical model. Journal of Clinical Pathology 2013; 66:335-342. doi 10.1136/jclinpath-2012-201213.

6. Dietrich JW, Landgrafe-Mende G, Wiora E, Chatzitomaris A, Klein HH, Midgley JE, Hoermann R. Calculated Parameters of Thyroid Homeostasis: Emerging Tools for Differential Diagnosis and Clinical Research. Frontiers in Endocrinology 2016; 7:57. doi 10.3389/fendo.2016.00057.