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Thyroid H-P-T-Axis Simulator Equations For Hypothyroid, Euthroid & Mildly-Hyperthyroid Human Adults & Children

(13 ODE's, 12 algebraic terms, 3 outputs & ~56 parameters)

Notes: All mass units are µmol, time units are hours = h, volumes liters = L, unless otherwise noted;

DE ≡ differential equation

Thyroid Secretion & D&E Submodel Equations (Eisenberg 2008)

$\dot{q}_1(t) \equiv \dot{T}_{4P}(t) = SR_4(t) + k_{12}q_2(t) + k_{13}q_3(t) - \left(k_{31}^{free} + k_{21}^{free}\right)FT_{4P}(t) + k_4^{absorb}T_4^{GUT}(t) + u_1(t)$	DE for Plasma T_4 (T_{4P}) (µmol/h)
$\dot{q}_2(t) = k_{21}^{free}FT_{4P}(t) - \left(k_{12} + k_{02} + \dfrac{v_{\max}^{D1fast}}{K_m^{D1fast} + q_2(t)}\right)q_2(t)$	DE for Fast tissue T_4 (µmol/h)
$\dot{q}_3(t) = k_{31}^{free}FT_{4P}(t) - \left(k_{13} + k_{03} + \dfrac{v_{\max}^{D1slow}}{K_m^{D1slow} + q_3(t)} + \dfrac{v_{\max}^{D2slow}}{K_m^{D2slow} + q_3(t)}\right)q_3(t)$	DE for Slow tissue T_4 (µmol/h)
$\dot{q}_4(t) \equiv \dot{T}_{3P}(t) = SR_3(t) + k_{45}q_5(t) + k_{46}q_6(t) - \left(k_{64}^{free} + k_{54}^{free}\right)FT_{3P}(t) + k_3^{absorb}T_3^{GUT}(t) + u_4(t)$	DE for Plasma T_3 (µmol/h)
$\dot{q}_5(t) = k_{54}^{free}FT_{3P}(t) + \dfrac{v_{\max}^{D1fast}q_2(t)}{K_m^{D1fast} + q_2(t)} - \left(k_{45} + k_{05}\right)q_5(t)$	DE for Fast tissue T_3 (µmol/h)
$\dot{q}_6(t) = k_{64}^{free}FT_{3P}(t) + \dfrac{v_{\max}^{D1slow}q_3(t)}{K_m^{D1slow} + q_3(t)} + \dfrac{v_{\max}^{D2slow}q_3(t)}{K_m^{D2slow} + q_3(t)} - \left(k_{46} + k_{06}\right)q_6(t)$	DE for Slow tissue T_3 (µmol/h)
$FT_{3P}(t) = \left(a + bT_{4P}(t) + cT_{4P}^2(t) + dT_{4P}^3(t)\right)T_{3P}(t)$	free T_3 in plasma (µmol)
$FT_{4P}(t) = \left(A + BT_{4P}(t) + CT_{4P}^2(t) + DT_{4P}^3(t)\right)T_{4P}(t)$	free T_4 in plasma (µmol)
$SR_3(t) = S_3TSH_P(t-\tau) \qquad SR_4(t) = S_4TSH_P(t-\tau)$	TH secretion rates (µmol/h), τ is hrs time-delay (Mpy by fractions to adjust secretion rates)

Brain-Pituitary Submodel Equations (Eisenberg 2010)

$\dot{q}_7(t) \equiv T\dot{S}H_P(t) = SR_{TSH}(t) - f_{\deg}^{TSH}TSH_P(t)$	DE for Plasma TSH (µmol/h)
$\dot{q}_8(t) \equiv \dot{T}_{3B}(t) = \dfrac{f_4}{T_{4P}^{EU}}T_{4P}(t) + \dfrac{k_3}{T_{3P}^{EU}}T_{3P}(t) - k_{\deg}^{T_{3B}}T_{3B}(t)$	DE for T_3 in the brain (µmol/h)
$\dot{q}_9(t) \equiv \dot{T}_{3B}^{LAG}(t) = f_{LAG}\left(T_{3B}(t) - T_{3B}^{LAG}(t)\right)$	DE for lagged T_3 in brain (µmol/h)
$SR_{TSH}(t) = \left(B_0 + A_0 f_{CIRC}\sin\left(\dfrac{2\pi}{24}t - \phi\right)\right)e^{-T_{3B}^{LAG}(t)}$	TSH secretion rate (µmol/h) $f_{circ} \equiv 1$ for eu- & hyperthyroid model

$$f_{\deg}^{TSH} = k_{\deg TSH}^{HYPO} + \frac{V_{\max}^{TSH}}{K_{50}^{TSH} + TSH_P(t)}$$ Nonlinear *TSH* degradation rate function (h^{-1})

$$f_{LAG} \equiv k_{LAG}^{HYPO} + \frac{2T_{3B}^{11}(t)}{K_{LAG}^{11} + T_{3B}^{11}(t)}$$ Nonlinear lag-time function for T_{3B} in brain (h^{-1}

$$f_4 \equiv k_3 + \frac{5k_3}{1+e^{2T_{3B}(t)-7}}$$ Nonlinear rate function for T_4 transport into & conversion of T_4 to T_3 in brain (h^{-1})

$$f_{CIRC} \equiv 1 + \left(\frac{A_{\max}}{A_0 e^{-T_{3B}^{LAG}(t)}} - 1\right)\left(\frac{1}{1+e^{10T_{3B}^{LAG}(t)-55}}\right)$$ Circadian rhythm saturation function (h^{-1})
$f_{circ} \approx 1$ for eu- & mild hyper model

2-Compartment Gut Input Submodels (Mak et al. 1973; Eisenberg et al. 2008)

$\dot{q}_{10}(t) \equiv \dot{T}_4^{PILL}(t) = -k_4^{dissolve} T_4^{PILL}(t), \quad T_4^{PILL}(0) \equiv T_4 Dose$	DE for L-T_4 pill dissolution in gut (μmol/h)
$\dot{q}_{11}(t) \equiv \dot{T}_4^{GUT}(t) = k_4^{dissolve} T_4^{PILL}(t) - \left(k_4^{excrete} + k_4^{absorb}\right) T_4^{GUT}(t)$	DE for absorbable L-T_4 in gut (μmol/h)
$\dot{q}_{12}(t) \equiv \dot{T}_3^{PILL}(t) = -k_3^{dissolve} T_3^{PILL}(t), \quad T_3^{PILL}(0) \equiv T_3 Dose$	DE for L-T_3 pill dissolution in gut (μmol/h)
$\dot{q}_{13}(t) \equiv \dot{T}_3^{GUT}(t) = k_3^{dissolve} T_3^{PILL}(t) - \left(k_3^{excrete} + k_3^{absorb}\right) T_3^{GUT}(t)$	DE for absorbable L-T_3 in gut (μmol/h)

3 Measured Outputs

$y_{T_{4P}}(t) \equiv y_1(t) \equiv T_{4P}(t)/V_P = q_1(t)/V_P$ μmol/L $\rightarrow 777q_1(t)/10V_P$ μg/dL	Plasma T_4 concentration
$y_{T_{3P}}(t) \equiv y_4(t) \equiv T_{3P}(t)/V_P = q_4(t)/V_P$ μmol/L $\rightarrow 651q_4(t)/V_P$ μg/L	Plasma T_3 concentration
$y_{TSH_P}(t) \equiv y_7(t) \equiv TSH_P(t)/V_{TSH} = q_7(t)/V_{TSH}$ μmol/L $\rightarrow 5.6q_7(t)/V_{TSH}$ mU/L	Plasma *TSH* concentratio

Parameter Values for 3 Conditions: (1) Adult Eu- & Mildly Hyper- (same #s); (2) Adult Hypo-; and (3) Child Hypothyroid

Note: Unless otherwise specified, parameter values are for both children & adults

Parameter	*Units*	*Estimate*	*% CV*	*Source*
ϕ	*h*	-3.71	1.04	Eisenberg 2008
A_0	*μmol/h*	581	61.4	Eisenberg 2008
B_0	*μmol/h*	1166	60.7	Eisenberg 2008
$k_3 = k_4$	*μmol/h*	0.118	6.43	Eisenberg 2008
f_4 range	h^{-1}	0.118-0.708	--	Eisenberg 2010
$k_{\deg}^{T_{3B}}$	h^{-1}	0.037	12.6	Eisenberg 2008
V_P *(kids)*	*L*	1	-	Ben-Shachar 2011
V_P *(adults)*	*L*	3.2	-	Eisenberg 2008
V_{TSH} *(kids)*	*L*	2.5	-	Ben-Shachar 2011
V_{TSH} *(adults)*	*L*	5.2	-	Eisenberg 2008

K_m^{D1fast}	*μmol*	2.85	-	Eisenberg 2008 fixed
K_m^{D1slow}	*μmol*	95	-	Eisenberg 2008 fixed
K_m^{D2slow}	*μmol*	0.075	-	Eisenberg 2008
$v_{\max}^{D1fast}$	*μmol/h*	9.99×10^{-3}	30.6	Eisenberg 2008
$v_{\max}^{D1slow}$	*μmol/h*	6.63×10^{-4}	6.27	Eisenberg 2008
$v_{\max}^{D2slow}$	*μmol/h*	7.46×10^{-4}	6.27	Eisenberg 2008
S_3	h^{-1}	3.36×10^{-4}	6.49	Eisenberg 2008
S_4	h^{-1}	1.74×10^{-3}	7.4	Eisenberg 2008
τ	*h*	8	-	Eisenberg 2008
k_4^{absorb}	h^{-1}	0.88	2.2	Eisenberg 2008
$k_4^{dissolve}$	h^{-1}	1.3	-	Eisenberg 2008
$k_4^{excrete}$	h^{-1}	0.12	16.3	Eisenberg 2008
k_3^{absorb}	h^{-1}	0.88	7.2	Eisenberg 2008
$k_3^{dissolve}$	h^{-1}	1.78	32.0	Eisenberg 2008
$k_3^{excrete}$	h^{-1}	0.12	7.2	Eisenberg 2008
A	*unitless*	0.000289	--	Eisenberg 2006
B	$mmol^{-1}$	0.000214	--	Eisenberg 2006
C	$mmol^{-2}$	0.000128	--	Eisenberg 2006
D	$mmol^{-3}$	-8.83×10^{-6}	--	Eisenberg 2006
a	*unitless*	0.00395	--	Eisenberg 2006
b	$mmol^{-1}$	0.00185	--	Eisenberg 2006
c	$mmol^{-2}$	0.000610	--	Eisenberg 2006
d	$mmol^{-3}$	-0.000505	--	Eisenberg 2006
k_{02} *(kids)*	h^{-1}	0.0114	17.0	Ben-Shachar 2011
k_{12} *(kids)*	h^{-1}	0.523	19.2	Ben-Shachar 2011
k_{13} *(kids)*	h^{-1}	0.0514	28.8	Ben-Shachar 2011
k_{21}^{free} *(kids)*	h^{-1}	2275	14.4	Ben-Shachar 2011
k_{31}^{free} *(kids)*	h^{-1}	255	36.0	Ben-Shachar 2011
k_{02} *(adults)*	h^{-1}	0.0189	25.7	Eisenberg 2006
k_{12} *(adults)*	h^{-1}	0.868	18.3	Eisenberg 2006
k_{13} *(adults)*	h^{-1}	0.108	12.4	Eisenberg 2006
k_{21}^{free} *(adults)*	h^{-1}	1503	31.2	Eisenberg 2006
k_{31}^{free} *(adults)*	h^{-1}	584	16.6	Eisenberg 2006
k_{54}^{free}	h^{-1}	2043	--	Eisenberg 2006
k_{64}^{free}	h^{-1}	127	--	Eisenberg 2006
k_{05}	h^{-1}	0.207	12.8	Eisenberg 2006
k_{45}	h^{-1}	5.37	16.3	Eisenberg 2006
k_{46}	h^{-1}	0.0689	4.79	Eisenberg 2006
A_{max}	*mmol/h*	2.37	61.4	Eisenberg 2010

$k_{\deg TSH}^{HYPO}$	h^{-1}	0.53	--	Eisenberg 2010
K_{LAG} *(kids)*	*unitless*	6.5	--	Ben-Shachar 2011
K_{LAG} *(adults)*	*unitless*	5	--	Eisenberg 2010
k_{LAG}^{HYPO}	h^{-1}	0.0034	5.87	Eisenberg 2010
K_{50}^{TSH}	*μmol*	23	--	Eisenberg 2010
T_{3P}^{EU} *(kids)*	*nmol/L*	2.6	--	Elmlinger 2001
T_{4P}^{EU} *(kids)*	*nmol/L*	100.8	--	Elmlinger 2001
T_{3P}^{EU} *(adults)*	*μmol*	0.006	--	Eisenberg 2010
T_{4P}^{EU} *(adults)*	*μmol*	0.29	--	Eisenberg 2010
$V_{\max}^{TSH}$	h^{-1}	0.037	12.6	Eisenberg 2010
Next 4 params	*are for*	*linearized*	*model*	
k_{21}	h^{-1}	0.544	31.2	Eisenberg 2006
k_{31}	h^{-1}	0.211	16.6	Eisenberg 2006
k_{54}	h^{-1}	9.24	13.7	Eisenberg 2006
k_{64}	h^{-1}	0.573	6.20	Eisenberg 2006

Equation and Parameter NOTES

(1) $u_1(t)$ and $u_4(t)$ in the first and fourth equations are exogenous IV inputs of T_4 and T_3. They are normally zero, but are needed for structural identifiability analysis and IV simulation studies.

(2) Parameters k_{03} and k_{06} are shown in red in the equations. They are assumed to be approximately zero in adult and children models: degradation (other than to T_3) and elimination of T_4 in slow compartments (mostly muscle) are assumed negligible compared to T_4 conversion to T_3.

(3) ICs on the ODEs are not included here. To get ICs, run the model to steady state with normal SR_3 and SR_4 values and use the results to set ICs and the first $\tau = 8$ hr results for representing the 8 hr delay in the loop. For parameter estimation, the ICs are functions of the parameters to be estimated. These need to be evaluated and used as constraints on the search.