Title
Simulator of Newborn Thyroid Hormone (TH) Dynamics for Optimizing Treatment of Congenital Hypothyroidism (CH)

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Simulator of Newborn Thyroid Hormone (TH) Dynamics for Optimizing Treatment of Congenital Hypothyroidism (CH)

A thesis submitted in partial satisfaction of the requirements for the degree Master of Science in Biomedical Engineering

by

King Chung Ho

2013

ABSTRACT OF THE THESIS

Simulator of Newborn Thyroid Hormone (TH) Dynamics for

Optimizing Treatment of Congenital Hypothyroidism (CH)

by

King Chung Ho

Master of Science in Biomedical Engineering

University of California, Los Angeles, 2013

Professor Joseph J, DiStefano, Chair

Abstract: Congenital hypothyroidism (CH) is a condition of severe thyroid hormone (TH) deficiency present at birth. The current treatment is clear, and straightforward – a daily oral dose of thyroxine (T4). But, knowing precisely how much T4 to give and how to adjust dosages over time is an unsolved major treatment issue. Too much can produce side effects throughout life; too little is not enough to sustain normal growth and development. We developed and quantified a non-linear, multi-compartmental CH neonate model, as an adaptation of an existing simulator of feedback control of human TH levels in children and adults. Using a simulation approach, we found that simulated L-T4 plus L-T3 treatment is better than L-T4 alone treatment and the best treatment for CH babies is 1st 8 μg/kg L-T4, followed by 0.5 μg/kg/day L-T4, with 0.10 μg/kg/day L-T3 over the first month of life – the period for which we had reliable data. Simulation of the standard T4 alone treatment normalized plasma T4 levels, but T3 levels produced from simulated T3 in tissue was >50% less than the normal values.

The thesis of King Chung Ho is approved.

Benjamin M. Wu

Elliot M. Landaw

Joseph J. DiStefano, Committee Chair

University of California, Los Angeles,

2013

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Introduction

The thyroid is a small, butterfly-shaped gland located below the neck [1]. It secretes thyroid hormones necessary for metabolism and growth, i.e. thyroxine (T4) and triiodothyronine (T3) [2, 3]. Thyroid stimulating hormone (TSH) regulates the secretion rate of T4 and T3 via a negative feedback loop. When blood thyroid hormone levels are decreased below normal, the pituitary gland is stimulated to release TSH, which signals the thyroid gland to produce and secrete more thyroid hormone into the bloodstream. The opposite occurs when the thyroid hormone levels are increased. Through this negative feedback system, thyroid hormone levels can always be maintained in the body, facilitating metabolism and growth [5]. If a thyroid fails to work properly, this negative feedback system will break down and it leads to permanent consequences.

Congenital hypothyroidism (CH) is the most prevalent endocrine disorder [1, 4], affecting one in 3000-4000 newborns [10]. Newborns suffering from CH have low blood thyroid hormone levels, despite high blood TSH levels. As a result, they have slower metabolisms and brain development is impeded. It is important to treat hypothyroid newborns with oral thyroid hormones, levothyroxine (LT4). T4 alone treatment is currently recommended [41] and an initial dosage of 10-15 μg/kg/day of L-T_4 should be taken once the diagnosis is confirmed [11]. Dosages are currently established by trial & error for individuals. This is a natural problem for control engineering methodology, and a math model is needed for this purpose. A very severe congenital hypothyroidism condition is thyroid agenesis, when patients have no hormone production and their thyroid hormones level drop quickly after birth [42]. We developed normal and abnormal newborn models, starting with adult and child models [5-7], aiming to help patients with thyroid agenesis and similar disorders.

This new normal model has been fitted to normal newborn thyroid hormone and TSH data [8, 9, 12-15]. It reproduces newborn thyroid hormone levels from 7-28 days, and the CH model has been validated against published CH data [42]. We used this model to determine the best drug treatment for CH babies and found that L-T4 plus L-T3 treatment worked best to restore thyroid hormone levels.

CH Detection and Treatment

All newborns undergo hypothyroidism screening within 2-4 days of birth before discharge from the hospital [23]. There are three current screening strategies: Primary TSH with backup T4 measurements [11], primary T4 with backup TSH measurements [11, 24], and combined primary TSH plus T4 measurements [11]. The first one is the most common. When a newborn has a TSH level > 40mU/L and a low T4 concentration, it is considered to have congenital hypothyroidism [11]. The recommended treatment protocol is 10-15 μg/kg synthetic T4 [24, 25, 27], known as levothyroxine (L-T4), begun within two weeks (0-14 days) after birth [11, 25]. It is expected that the TSH level will be restored after a month [11, 24]. The starting treatment dosage and treatment time are critical for newborn development [26, 27, 39], but there is little evidence supporting the recommended protocol as maximally effective.

Data

Our goal was to develop a model for optimizing the treatment protocol at the earliest possible time postpartum. This requires kinetic data over the first 0-14 days. However, it is difficult to obtain continuous hormone data for the first two weeks of life primarily because newborns are discharged from hospitals within 10 days. After extensive research, we found some useful datasets with different size: single-data point, <5 data points, or a range [8, 15-22, 28-29]. The

most representative datasets were from Fisher *et al.* [8], Uhrmann *et al.* [22], and William *et al.* [38] (Figure 1).

We chose these datasets for three reasons. (1) Each was obtained in the same experimental setting (regions, hospitals, methodology, etc.). (2) Each had small standard errors (Fig.4). (3) The trend in each dataset was consistent with anticipated physiological responses of thyroid hormone regulation. We divided the datasets into two groups: **0-5 days data** (Fisher *et al* 1974 and Uhrmann *et al* 1978), **7-28 days data** (William *et al* 2004).

0-5 day data

Within the first hours birth (<12 hours), TSH surges rapidly and reaches maximum plasma levels at 0.5 hour (~ 80 μU/mL), followed by a slower fall. As a result, T3 and T4 levels are raised. The spontaneous surge may be caused by mode of delivery [31] and cooling after delivery [9]. One hypothesis for the surge is that the fetal hypothalamic–pituitary–adrenal axis is maturing during pregnancy and all molecular activities are "turned on" at delivery, leading to the surge at birth [30, 31]. We could not fit the dataset data in any manner consistent with what was anticipated at later times, probably because the system is changing so much during this very early period.

7-28 day data

T3, T4, and TSH level-off and normal thyroid hormone regulation is established during this period. All levels are maintained within the reference range [11, 22, 40]. We successfully fitted this data, as described later.

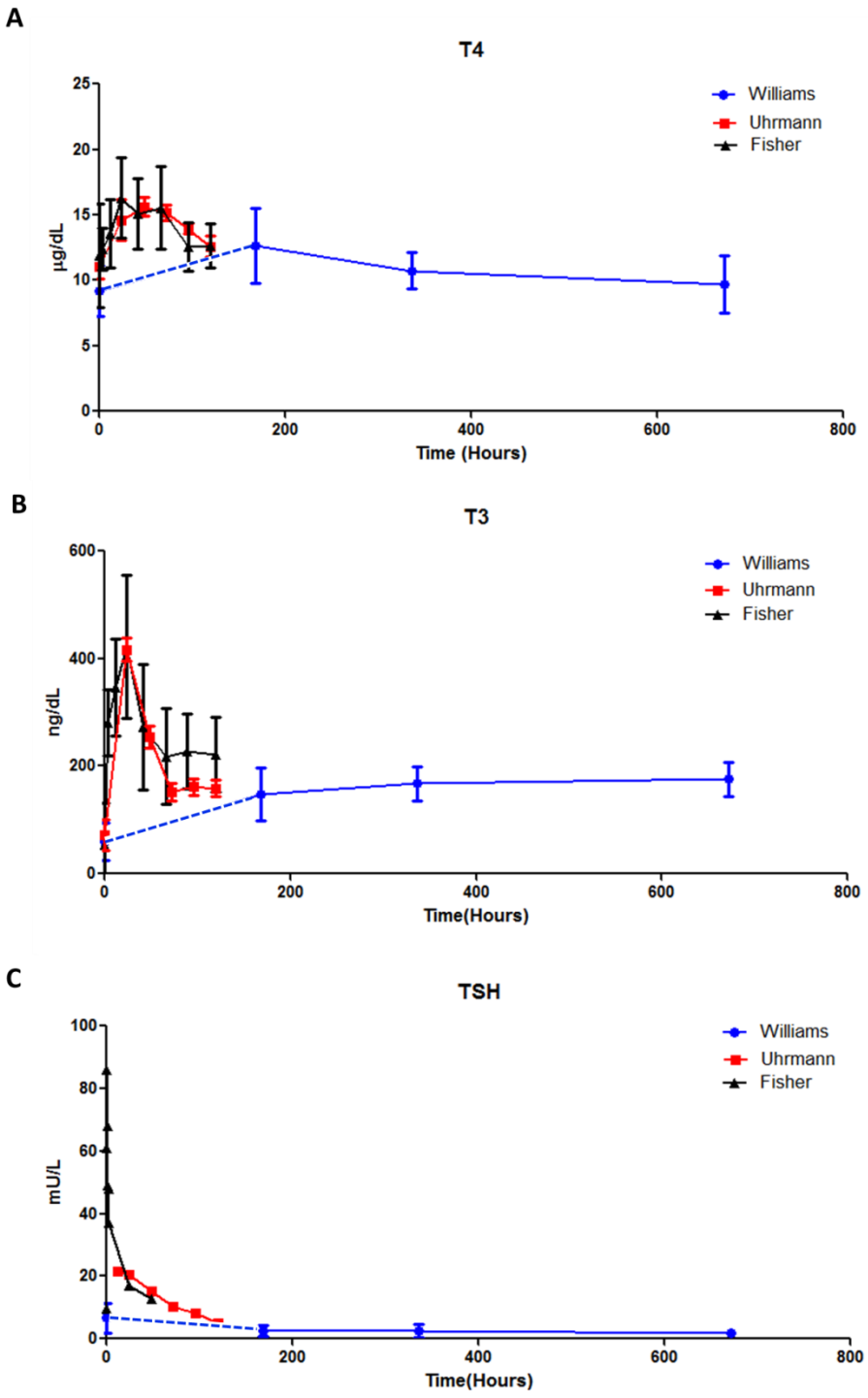

Figure 1. T4, T3, and TSH data in literature [8, 22, 38]. The datasets are similar and demonstrate the negative feedback control of the thyroid hormone regulation system. At birth, newborn TSH levels surge rapidly to the maximum value (~80uU/mL), followed by constant decline. T3 and T4 concentration respond to the rapid surge of TSH via increment in the first 48 hours. After about 120 hours, T3, T4, and TSH level-off.

Model

The baby thyroid hormone regulation model is based on the Eisenberg and co-workers adult model structure [5, 6] (Figure 2), which has three source (hypothalamus, anterior pituitary, thyroid gland) and three sink components (thyroid releasing hormone D&E, thyroid stimulating hormone D&E, thyroid hormone D&E). The adult model has two submodels, i.e. a brain submodel (Figure 3) and a T3&T4 D&E submodel (Figure 4). The baby model also has these submodels (Figure 5), but with more aggregated extravascular tissue compartments for each of T3 and T4 in the T3&T4 D&E submodel. The development details are explained in next section.

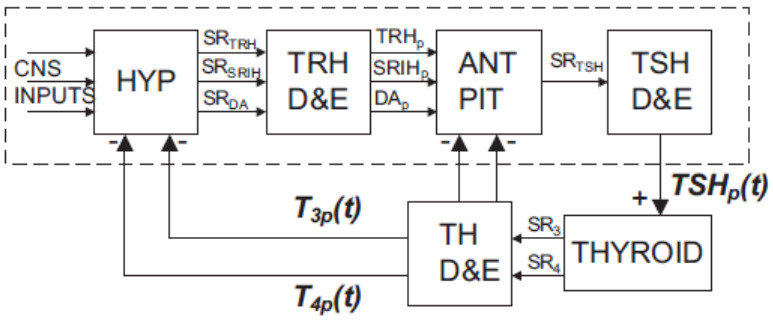

Figure 2. Adult thyroid hormone feedback control system (FBCS). HYP= hypothalamus, TRH = thyroid releasing hormone, ANT PIT = anterior pituitary, TSH = thyroid stimulating hormone, TH = thyroid hormone. It is composed of three sources (organs) and three sinks (distribution and elimination [D&E]) subsystems (submodels). The three sources are HYP, ANT PIT, and thyroid; the three sinks are TRH D&E, TSH D&E, and TH D&E [5, 6].

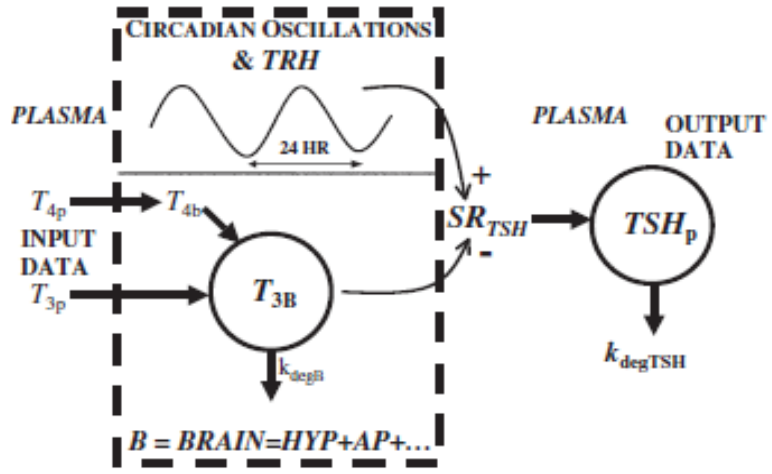

Figure 3. Adult lumped brain submodel for TSH secretion. TSHp is driven implicitly by TRH, and dual suppressor inputs---plasma T3 and T4 concentrations, T3p(t) and T4p(t). This submodel summarizes the TRH secretion, TRH D&E, and TSH secretion from Figure 1 [5,6].

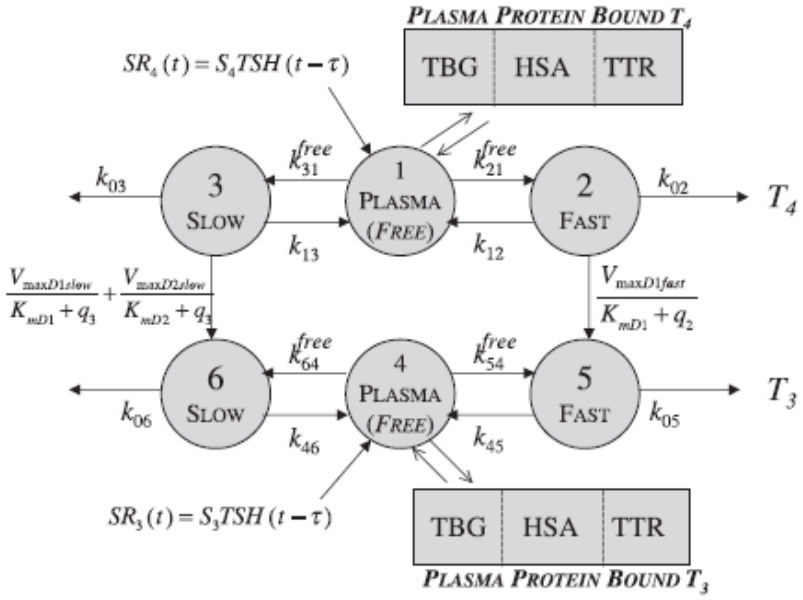

Figure 4. Adult T3 and T4 D&E submodel [5, 6]. This model is reduced-parameter, input-output equivalent, and uniquely identifiable. Compartment 1 represents the free plasma T4 and compartment 4 represents the free plasma T3. There are non-linear, extravascular enzymatic T4 to T3 conversions in this model (from compartment 3 to 6 and from compartment 2 to 5), and the model being used for these rates is Michaelis-Menten (M-M) kinetics. The secretion of T3 and T4 are $SR_3(t)$ and $SR_4(t)$ respectively; the time-delay estimate τ for $SR_3(t)$ and $SR_4(t)$ responses to TSH stimulation that yields the best fit to the closed-loop data [6].

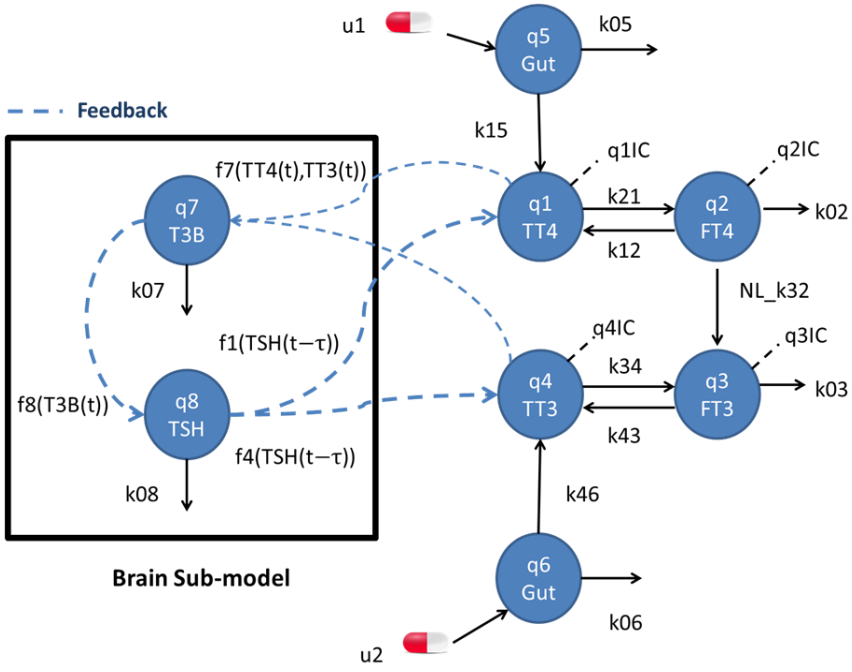

Figure 5. Proposed baby model. The model has a brain submodel and T3&T4 D&E submodel. The T3&T4 submodel contain lumped extravascular enzymatic T4 to T3 conversion (from compartment 2 to compartment 3) and other compartments. The dotted blue lines represent the feedback between T3, T4, and TSH.

Baby Model Construction

The baby model was developed in two steps. The Eisenberg and coworker adult model (Figure 2-4) was used successfully to optimize drug treatment for both normal and hypothyroid adult patients, as described in references [5-8]. We began by attempting to fit it directly to our newborn data, the **0-5 day data**, then **7-28 day data.** The goal was to create a baby model that can simulate thyroid hormone levels in the first month of birth. This was difficult because, (1) for **0-5 day data**, we had no initial conditions for non-vascular tissue compartments, leading to too many unknowns; and (2) the regulation system is maturing in the first few days after birth and some parameters were time-varying during the first few days [30, 31]. The fitting result is shown in figure 6.

To tackle problem (1), we had reviewed >400 articles, but there were no related information. For problem (2), no research had ever explained the exact biological phenomenon at birth and it was hard to determine the parameters that should be time-varying---there were over 30,000 possible combinations of time-varying and constant parameters in the adult model.

We therefore simplified and tuned the model structure to that shown in figure 4, defining it as the baby model (Figure 5 and table 3), and fitted it to the **7-28 day data**. This model fitted the normal baby data very well, as shown in figure 6. Parameter estimation and their variability are given in tables 1 and 2.

Baby Model Details

i. Lumping the extravascular enzymatic T4 to T3 conversion compartments

Michaelis-Menten (M-M) kinetics were used in the adult model to represent deiodinase D1 and D2 enzymatic interconversions of T4 conversion to T3, in two separate extravascular "fast" and "slow" compartments [6, 30, 31]. These are aggregated (lumped) into one pair of compartments (q2 & q3 in figure 5) in the baby model. The T4-to-T3 conversation rate is now denoted by a non-linear kinetic parameter, NL_k32 (Figure 8), which has VmaxD1 and Km of deiodinase D1.

ii. M-M kinetics for T3, T4 secretion

At birth, T3 and T4 levels increase rapidly to maximum values (first peak) in response to the TSH surge [9, 31]. A second peak follows at 90 hours. This suggests that M-M kinetics in the thyroid gland secretion mechanism: $f1(TSH(t-\tau)\ and\ f2(TSH(t-\tau)$, introducing new variables, V_{max}^{SecT4} , V_{max}^{SecT3}, and KmTSH (Figure 7). K_m^{TSH}, is the TSH concentration at which the

reaction rate is half of V_{max}^{TSH} [33-36]. These new nonlinearities work well in fitting the **7-28 day data**.

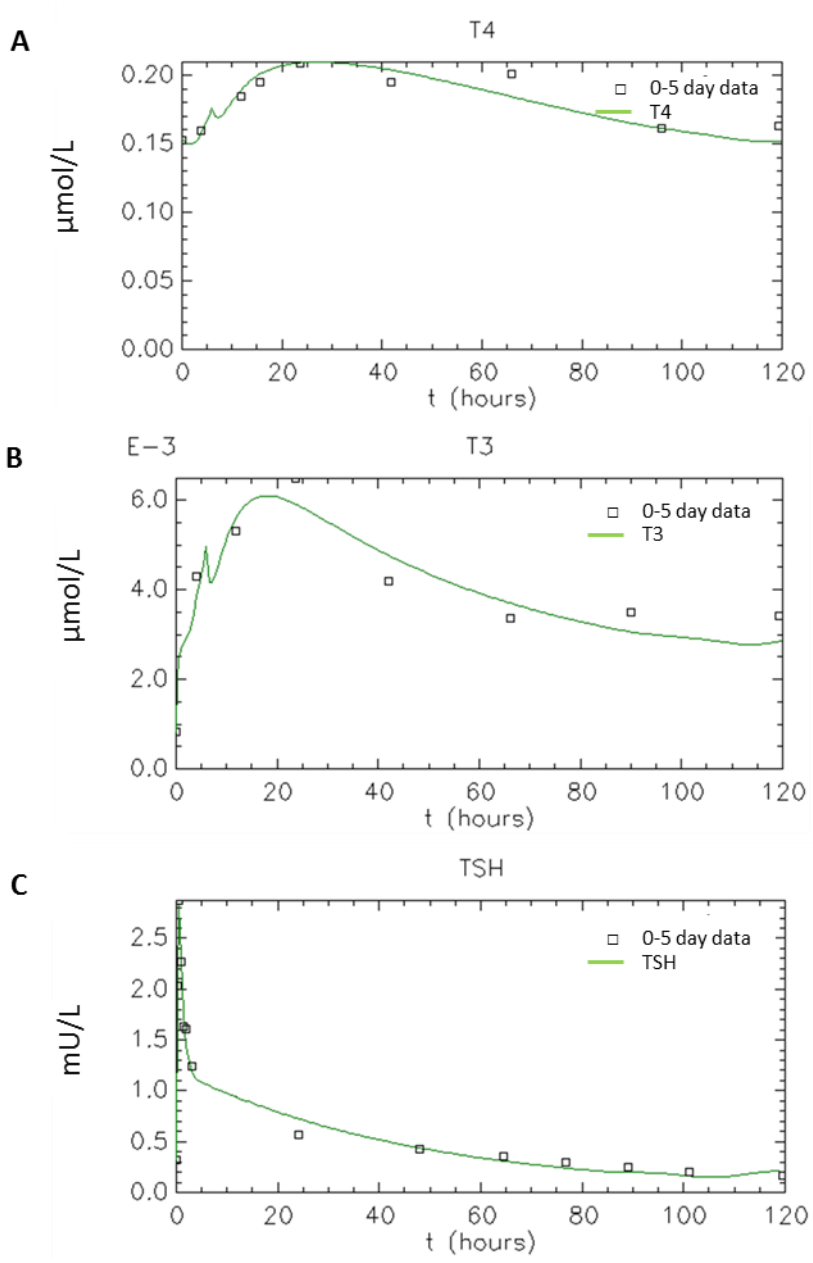

Figure 6. Fitting 0-5 days data using the Eisenberg and coworker adult model. (A) T4 data; (B) T3 data; (C) TSH data. T4 and T3 data were not fitted as well, as we'd like, but the curves followed the data trend. The failure is caused by fast-changing regulation system at birth, and too many unknown parameters.

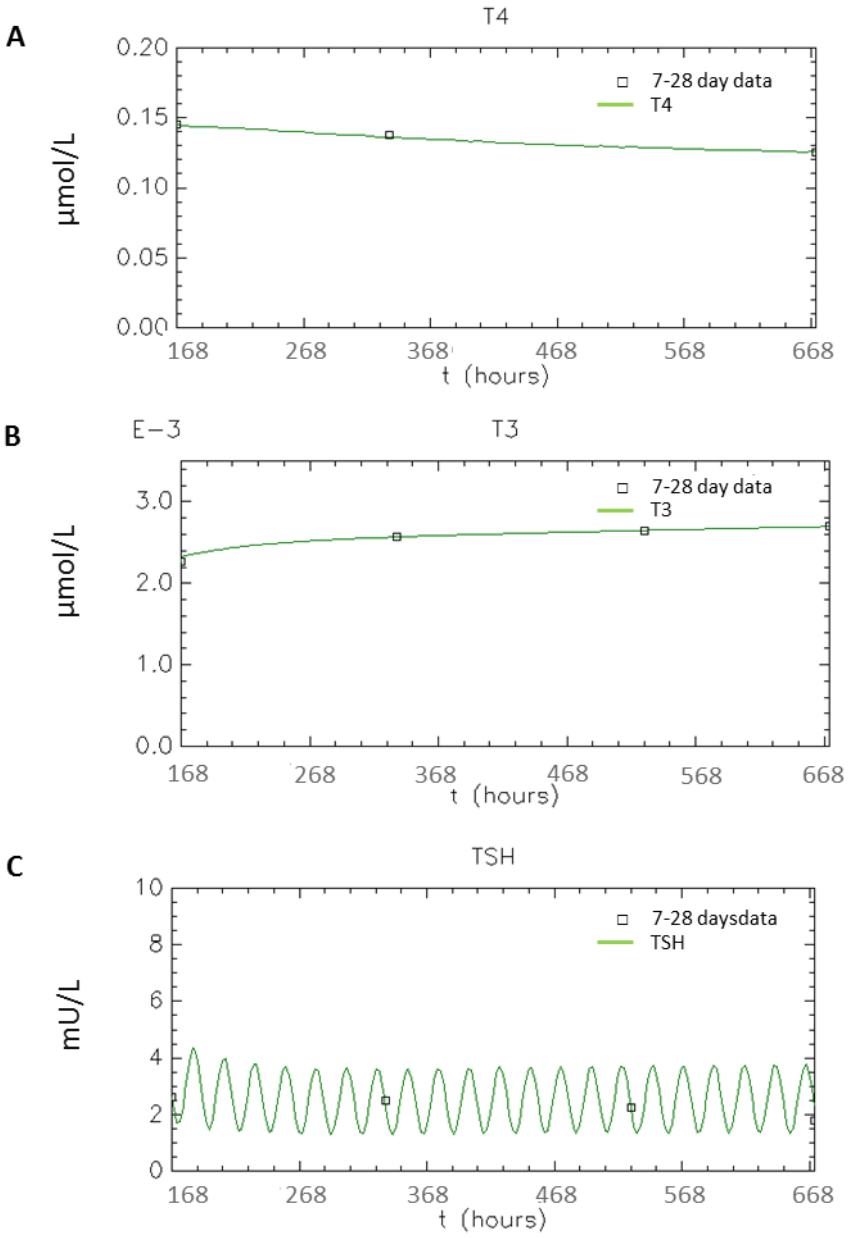

Figure 7. Fitting results for 7-28 days data fitted by our normal baby model. (A) T4 data ; (B) T3 data ; (C) TSH data. We successfully obtained a well-estimated model with well-estimated parameters. This baby thyroid hormones regulation system model was the starting point for our abnormal CH model.

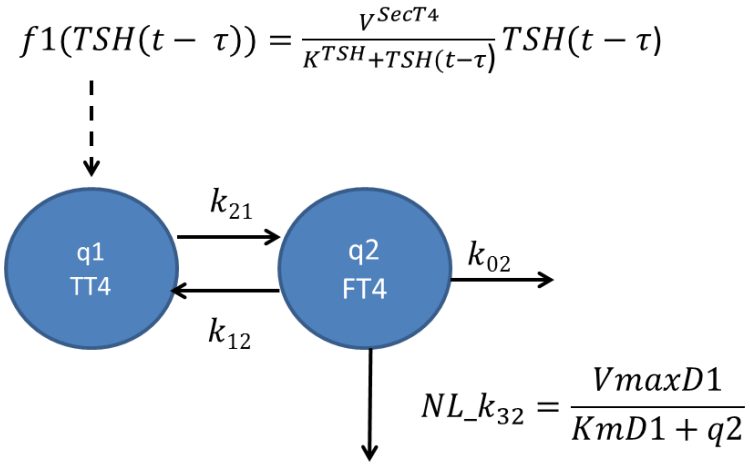

Figure 8. T4 submodel with lumped extravascular enzymatic T4 to T3 conversion. Here, we showed only the T4 submodel with some adjustments; we applied the same changes to the T3 submodel. The T4 submodel, T3 submodel, and brain submodel are combined together to form a model of the baby thyroid hormone regulation system.

Table 1. Parameter values for baby T4-T3 submodel

Parameter	***Units***	***Estimate***	***% CV***	***Source***
V_P	*L*	0.2630	--	[35,36]
V_{TSH}	*L*	0.456	--	[35,36]
K_m^{D1}	*µmol*	2.85	--	[5]
K_m^{TSH}	*µmol*	0.2239	--	[50]
V_{max}^{D1}	*µmol/h*	1.93×10^{-4}	98.7	--
V_{max}^{SecT4}	*µmol/h*	1.49×10^{-4}	36.8	--
V_{max}^{SecT3}	*µmol/h*	7.51×10^{-7}	450	--
A	*unitless*	0.00289	--	[5]
B	$mmol^{-1}$	0.000214	--	[5]
C	$mmol^{-2}$	0.000128	--	[5]
D	$mmol^{-3}$	-8.83×10^{-6}	--	[5]
a	*unitless*	0.00395	--	[5]
B	$mmol^{-1}$	0.00185	--	[5]
C	$mmol^{-2}$	0.000610	--	[5]
D	$mmol^{-3}$	0.000505	--	[5]
k_{02}	h^{-1}	0	--	--
k_{03}	h^{-1}	0.034	127	--
k_{05}	h^{-1}	0.9	--	[6,7]
$k_{0,6}$	h^{-1}	0.9	--	[6,7]
k_{15}	h^{-1}	0.1	--	[6,7]

k_{46}	h^{-1}	0.1	--	[6,7]
k_{12}	h^{-1}	0	--	--
k_{43}	h^{-1}	4.72	1373	--
k_{21}^{free}	h^{-1}	0.7790	32	--
k_{34}^{free}	h^{-1}	1150	1422	--
q1IC	*mol*	0.0174	--	[8,22,38]
q2IC	*mol*	0.3640	--	[8,22,38]
q3IC	*mol*	0.000615	--	[8,22,38]
q4IC	*mol*	0.000272	--	[8,22,38]
τ	*h*	1	--	[5,6,7]
T4eff=T3eff	*unitless*	0 or 1	--	--
Body weight	*kg*	3.5	--	[35]
k22	h^{-1}	N/A	--	k22 = -(k(1,2)+k(0,2)+k(3,2))
k33	h^{-1}	-4.78593	1363	k33 = -(k(4,3)+k(0,3))

Table 2. Parameter values for baby brain submodel

Parameter	***Units***	***Estimate***	***% CV***	***Source***
A_0	*µmol/h*	5.81	--	[6], reduced a factor of 100
B_0	*µmol/h*	11.66	--	[6], reduced a factor of 100
k07=k_{deg}^{T3B}	h^{-1}	0.037	--	[6]
k08=k_{deg}^{TSH}	h^{-1}	0.756	--	[6]
Phiphase	*h*	-3.71	--	[6]
pi	*constant*	3.14	--	--
k_3=k_4	*µmol/h*	0.0776	1.10	--
q7IC	*mol*	4.086	5.66	--
q8IC	*mol*	0.213	--	--
T4ss	*mol*	0.038135	--	[38]
T3ss	*mol*	0.00059701	--	[38]
f_{CIRC}	*unitless*	1	--	[6]
Φ	*h*	-3.71	--	[6]

Table 3. Baby Model Equations

Equation	Physical Meaning
$\dot{q_1}(t) = \mathrm{k12q2}(t) + \mathrm{k15q5}(t) - \mathrm{k21q1}(t) + \mathrm{f1}(\mathrm{TSH}(\mathrm{t}-\tau))$	Plasma Total T4
$\dot{q_2}(t) = \mathrm{k21q1}(t) - (\mathrm{k12} + \mathrm{k02} + \mathrm{q32})\mathrm{q2}(t)$	Free T4
$\dot{q_3}(t) = \mathrm{NL\_k32q2}(t) + \mathrm{k34q4}(t) - (\mathrm{k43} + \mathrm{k03})\mathrm{q3}(t)$	Free T3
$\dot{q_4}(t) = \mathrm{k43q3}(t) + \mathrm{k46q6}(t) - \mathrm{k34q4}(t) + \mathrm{f2}(\mathrm{TSH}(\mathrm{t}-\tau))$	Plasma Total T3
$\dot{q_5}(t) = -(\mathrm{k05} + \mathrm{k15})\mathrm{q5}(t) + \mathrm{u1}$	Gut for L-T4 absorption

,where u1 is the amount of L-T4	
$\dot{q_6}(t) = -(\mathrm{k06} + \mathrm{k46})\mathrm{q6}(t) + \mathrm{u2}$,where u2 is the amount of L-T3	Gut for L-T3 absorption
$\dot{q_7}(t) = -(\mathrm{k07})\mathrm{q7}(t) + \mathrm{f7}(\mathrm{TT4(t)}, \mathrm{TT3(t)})$	Brain T3
$\dot{q_8}(t) = -(\mathrm{k08})\mathrm{q8}(t) + \mathrm{f8(T3B(t))}$	TSH
$\mathrm{k21} = \mathrm{k21free} * (\mathrm{A} + \mathrm{B} * \mathrm{q1}(t) + \mathrm{C} * \mathrm{q1}(t)^2 + \mathrm{D} * \mathrm{q1}(t)^3)$	T4 binding
$\mathrm{k34} = \mathrm{k34free} * (\mathrm{a} + \mathrm{b} * \mathrm{q1}(t) + \mathrm{c} * \mathrm{q1}(t)^2 + \mathrm{d} * \mathrm{q1}(t)^3)$	T3 binding
$\mathrm{f1}\big(\mathrm{TSH(t} - \tau)\big) = \frac{V_{max}^{SecT4}}{K_m^{TSH} + \mathrm{TSH(t} - \tau)} \mathrm{TSH(t} - \tau) * \mathrm{T4eff}$, where T4eff = T4 secretion fraction	T4 production
$\mathrm{f4}\big(\mathrm{TSH(t} - \tau)\big) = \frac{V_{max}^{SecT3}}{K_m^{TSH} + \mathrm{TSH(t} - \tau)} \mathrm{TSH(t} - \tau) * \mathrm{T3eff}$, where T3eff = T3 secretion fraction	T3 production
$\mathrm{NL\_k32} = \frac{V_{max}^{D1}}{K_m^{D1} + q2(t)}$	Conversion from T4 to T3
$\mathrm{F3} = \frac{k46}{k46 + 06}$	Fraction of T3 being absorbed
$\mathrm{F4} = \frac{k15}{k15 + 15}$	Fraction of T4 being absorbed
$\mathrm{f7(TT4(t), TT3(t))} = \frac{k4}{T4ss} \mathrm{TT4(t)} + \frac{k3}{T3ss} TT3(t)$, where T4ss and T3ss are the T4 and T3 steady state values respectively.	Brain T3 secretion
$\mathrm{f8}\big(\mathrm{q7(t)}\big) = (B_0 + A_0 f_{CIRC} \sin\left(\frac{2 * pi * t}{24} - \phi\right)) * e^{-q7(t)}$	TSH secretion

Congenital Hypothyroidism Model

The goal of the project is to optimize treatment protocols for hypothyroid newborns and therefore we needed a congenital hypothyroid (CH) model. The CH model mimics a hypothyroid newborn that has a malfunctioning thyroid gland and produces little or no thyroid hormones, leading to high TSH levels [4, 9, 10, 11, 26, 40]. It is implemented from the normal model in figure 5 by setting the T4 and T3 secretion rates zero, i.e. f1(TSH(t-τ))=0 and f4(TSH(t-τ))=0, mimicking a hypothyroid newborn with a thyroid gland disorder. In the CH model (Figure 9), T4 and T3 have very low initial values, which are the leftovers from maternal-transfer before birth [42], and TSH remains high because there is not enough T4 and T3. The simulated T4 level follows an exponential decay, similar to published data (Figure 10) [42].

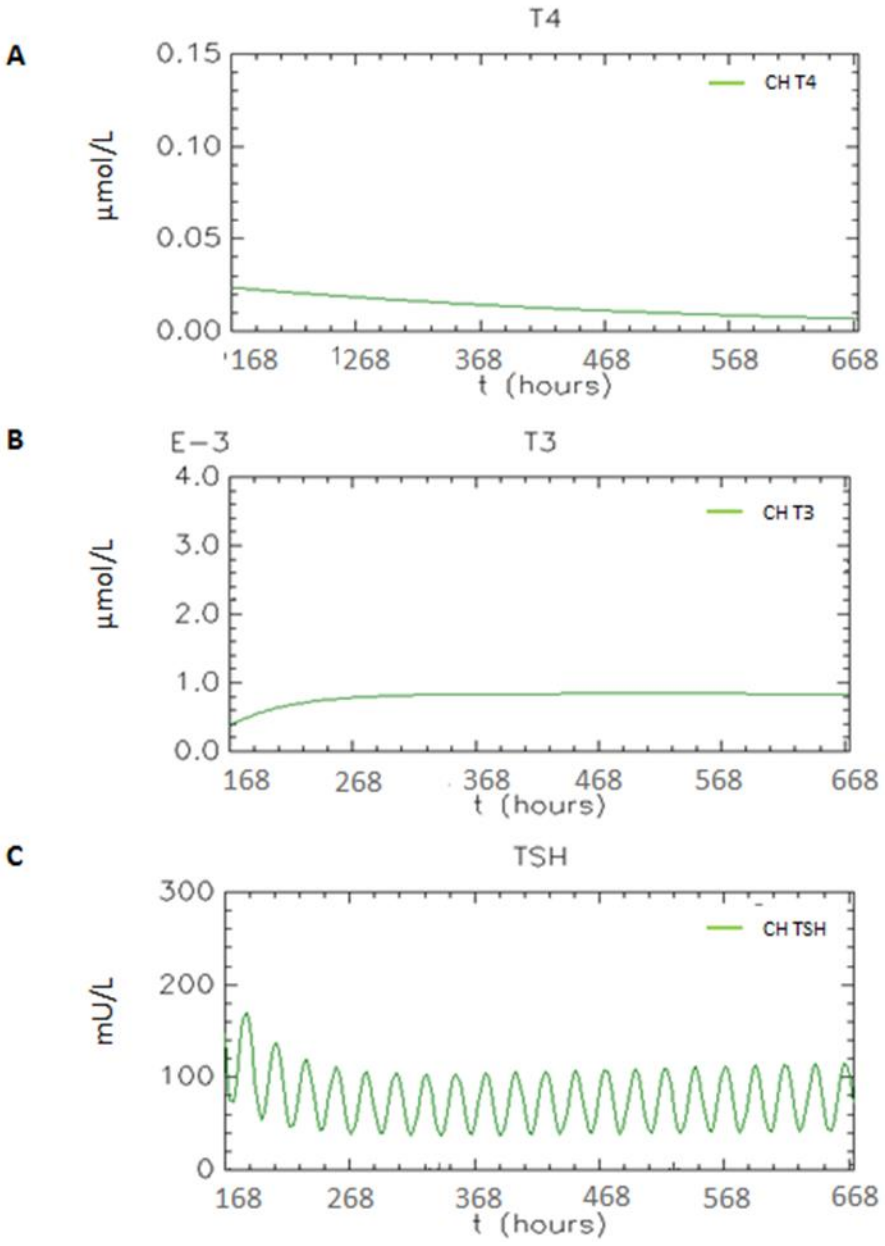

Figure 9. Simulated CH model responses with zero T4 and T3 secretion. (A) CH T4; (B) CH T3; (C) CH TSH. T4 is dropping because there is no hormone secretion. T3 levels do not go to zero, but instead level-off, because there is still some conversion of T4 to T3 in non-thyroidal organs. It is expected that T3 will eventually go to zero. TSH levels remain high because of low T4 and T3 values.

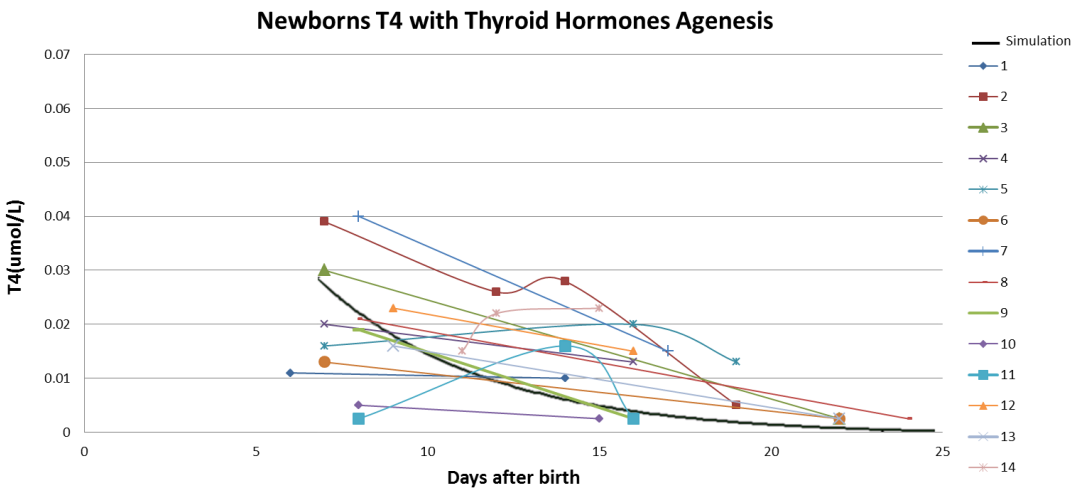

Figure 10. Simulated T4 responses (black line) superimposed on published hypothyroid newborn data [42]. The simulated T4 has very low initial values, hormone remaining in baby blood from maternal-transfer before birth [42]. It follows an exponential decay, similar to the published data.

Thyroid Hormones Replacement Treatment Protocols

There are two possible treatment protocols for congenital hypothyroidism: levothyroxine (L-T4) alone treatment and L-T4 plus liothyronine (L-T3) treatment. The normal gland secretes both, but most T3 is produced from T4 in non-thyroidal organs. In the past decade, the majority of research supported the L-T4 alone treatment [11, 41, 44, 46], and a few supported L-T4 plus L-T3 treatment [48, 49]. Debate about these treatments' efficacy is still on-going. Two main objectives for our treatment optimization using the baby model are: (1) to restore thyroid hormone levels to the normal range (Table 4) as quickly as possible and; (2) to determine which treatment is better.

A primary CH baby has little or no endogenous thyroid hormones secretion since the first day of birth. His/her thyroid hormone levels are the leftover from maternal transfer before birth [42]. Therefore, T4 and T3 levels are low but not zero in the 7^{th} day after birth, and an initial high dose of L-T4 is needed. One question is whether L-T3 is also necessary [45, 47]. Our simulation

results suggest that L-T4 plus L-T3 treatment works best (Figure 11). Based on our model, the optimized L-T4 dosage is found to be 8μg/kg/day L-T4 on the 1st day, followed by 0.5μg/kg/day on the 2nd day and beyond. Our model simulation also suggests that a small amount of L-T3 works combined with L-T4, namely 0.10μg/kg/day (Table 5).

Treatment Details

To speed up early recovery of T4 levels, and maintain them afterwards, we hypothesize the correct treatment pattern for T4 alone therapy should be high dose treatment with L-T4, followed by lower doses. We, therefore, began by searching different initial high T4 doses. We tried different amounts for the first daily dose: 4μg/kg (Method1), 6μg/kg (Method 2), 8μg/kg (Method 3) and 10 μg/kg (Method 4) (Figure 11). We found that 10μg/kg dose was too high and 4μg/kg was too low. The best amount was 8μg/kg, and it restored T4 levels closest to the data.

A single high dose of L-T4 was not enough to maintain normal T4 levels over the long term. We tried different doses for subsequent daily treatment and found that 0.5μg/kg/day gave the best result (Figure 11).

L-T4 + L-T3 Treatment

Researchers have debated about the need of L-T3 in CH treatment [11, 41, 44-49]. Our simulation results suggest that a small amount of L-T3 helps restore T3 levels (Figure 11). Method 1 and Method 2 are L-T4 alone treatment while Method 3 and Method 4 are L-T4 plus L-T3 treatment. With 0.10μg/kg/day additional L-T3 (Method 3 & Method 4), T3 levels are restored quickly within a few days, while T3 levels in Method 1 & Method 2 increase too slowly. The result clearly shows that L-T3 helps restore CH baby T3 levels, at least over the first 28 days.

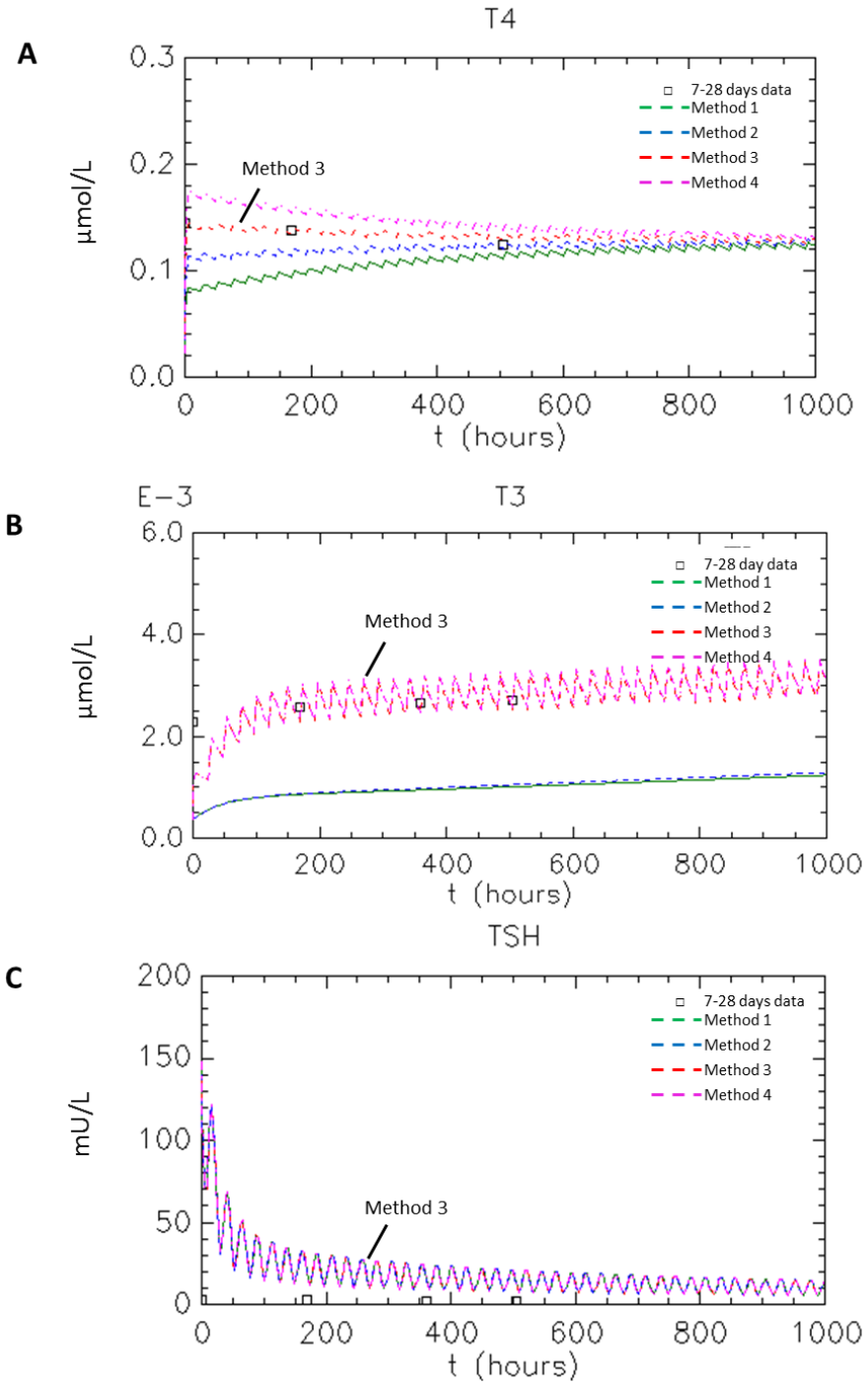

Figure 11. Comparison of Different Simulated L-T4 plus L-T3 treatment Protocols with L-T4 alone Treatment Protocols. Method 1: 1st 4µg/kg + daily 0.5 µg/kg L-T4; Method 2: 1st 6µg/kg + daily 0.5 µg/kg L-T4; Method 3: 1st 8µg/kg + daily 0.5 µg/kg L-T4 with daily 0.10 µg/kg L-T3; Method 4: 1st 10µg/kg + daily 0.5 µg/kg L-T4 with daily 0.10 µg/kg L-T3. (A) T4 levels; (B) T3 levels; (C) TSH levels. Method 3 restores simulated T3, T4 and TSH quickly.

Table 4. **Newborn Thyroid Hormone Reference Range [11, 22, 40]**

T4	0.0643μmol/L – 0.14μmol/L
T3	0.000768μmol/L – 0.0023041μmol/L
TSH	<7.5 mU/L

Table 5. **Best Predicted Treatments with L-T4 plus L-T3 for babies about 3.5kg at birth [35]**

L-T4	L-T3
1st day: 8μg/kg = 28 μg /day 2nd and beyond: 0.5μg/kg = 1.75 μg/day	0.10μg/kg = 0.35 μg/day

Recommendations

Based on our simulation results, Method 3 is the best treatment protocol for restoring T3, T4, and TSH quickly to normal values. In general, the dosage should be slightly different when babies suffer from different degree of congenital hypothyroidism, but the treatment pattern should still be the same: high dose of T4 at the beginning, followed by lower dose of T4, supplemented by small amounts of T3.

It is to be noted that the maintenance L-T4 dose of 0.5μg/kg/day in our results is much less than the usually accepted protocol maintenance dosage of about 10μg/kg/day [11] – although standard protocols do not include additional T3. This is an anomaly that remains to be resolved.

Summary

We developed baby thyroid hormone regulation models to simulate thyroid hormone levels in the first month following birth, for both normal and CH babies. We fitted the normal model to literature data (Fisher *et al.* [8], Uhrmann *et al.*[22], and William *et al.* [38]), and validated the CH model (zero thyroid hormone secretion) against literature data [42]. We used an ad hoc

simulation methodology to improve hormone replacement therapy for this model and found that L-T4 plus L-T3 treatment is superior to L-T4 alone treatment. The best treatment is 8μg/kg/day L-T4 on the 1st day, followed by 0.5μg/kg/day, T4 on the 2nd day and beyond, all combined with 0.10μg/kg/day L-T3 beginning on day one. Our next steps would be to compare our protocol with more literature findings as they become available.

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