# Thyrosim Pre-processing Extension:
# Adding Dosing Algorithms for Levothyroxine

**Trevor Davis & Pei-Chun Su**

## Introduction

Supplementing thyroid hormone deficiency with levothyroxine (LT4) has become the standard of care after a total thyroidectomy. A thyroidectomy has become a common treatment for various hyperthyroid diseases; this has led to extensive studies of proper LT4 dosing [1]-[13]. Historically, LT4 dosing is based on the patient's body weight (BW), with the most common oral dose of LT4 being 1.6 $\mu g/kg/day$ [1]-[13]. This dose is assuming that there are no malabsorption problems or ionic supplements being taken for other metabolic imbalances [9]. Using this dosing scheme, some patients are over-prescribed and some are under-prescribed, creating the need for follow up appointments to check thyroid stimulating hormone levels (TSH) [12][13]. T4 levels regulate the amount of TSH in the body and TSH levels between .5-5 mU/L correspond to normal T4 and T3 levels in the rest of the body [1]-[8]. In order to correctly dose patients with proper amounts of LT4 on the first try, researchers have looked in to other correlations between optimal LT4 dosing and other anthropometric measurements including: body surface area (BSA), body mass index (BMI), lean body mass (LBM), sex and age. This project shows the results of a literature search through modern dosing algorithms being developed by various researchers and includes the implementation of these algorithms into a thyroid hormone simulation application called "Thyrosim" [6]-[8].

## Background

### *Lean Body Mass*

The idea that LT4 dosing is stilled based on a simple body weight scaling factor seems rather archaic when one considers the vast amount of research that has been done around thyroid diseases. In fact, LT4 dosing has been shown to be dependent on other factors like BMI, BSA, LBM, sex and age, yet in multiple studies, these factors are shown to be as correlated as BW is to proper dosing [9]-[13]. The most promising parameter that has more closely correlated to LT4 dosing that BW dosing is lean body mass (LBM) calculated by subtracting the body fat from the body weight [10]. This is not surprising because LT4 is processed most in the muscles, liver, gut, brain and thyroid, all of which are comprised in the lean body mass. To our knowledge, lean body mass is the only parameters that has resulted in statistically significant more accurate LT4 dosing when compared to BW dosing [10]. Other studies have found correlations with BMI that match the accuracy of BW dosing but not any that are statistically more accurate [9]. This places lean body mass in a league of its own for LT4 dosing. The one problem that gets in the way of this therapy is the actual calculation of lean body mass.

Lean body mass is technically quantified with dual energy x-ray absorptiometry (DEXA). This imaging modality can distinguish between fat tissue and other tissue allowing the exact LBM to be calculated [10][15][16]. This technique is clinically unrealistic and therefore LBM based dosing has been refuted as a valid LT4 dosing modality. However, Janmahasatian et al. have developed a semi-mechanistic approximation of LBM rooted in bioelectrical impedance analysis. This group began with a connection

between LBM and bioelectrical impedance, and through a series of engineering based assumption about conduction of electricity through the body, connects anthropometric qualities to LBM which can be seen below in Table II. This new algorithm produced results that were accurate with an $r^2$ value of .72 for men, .61 for women and .85 for the combination when viewed as one population [15]. One of the most notable aspects of this new algorithm is its performance at the extremes. Other well accepted LBM algorithms, including James'algorithm (the most widely accepted algorithm) will begin to return negative values for LBM for extremely obese subjects. As shown below in Figure 1, this new algorithm remains accurate at these extremes.

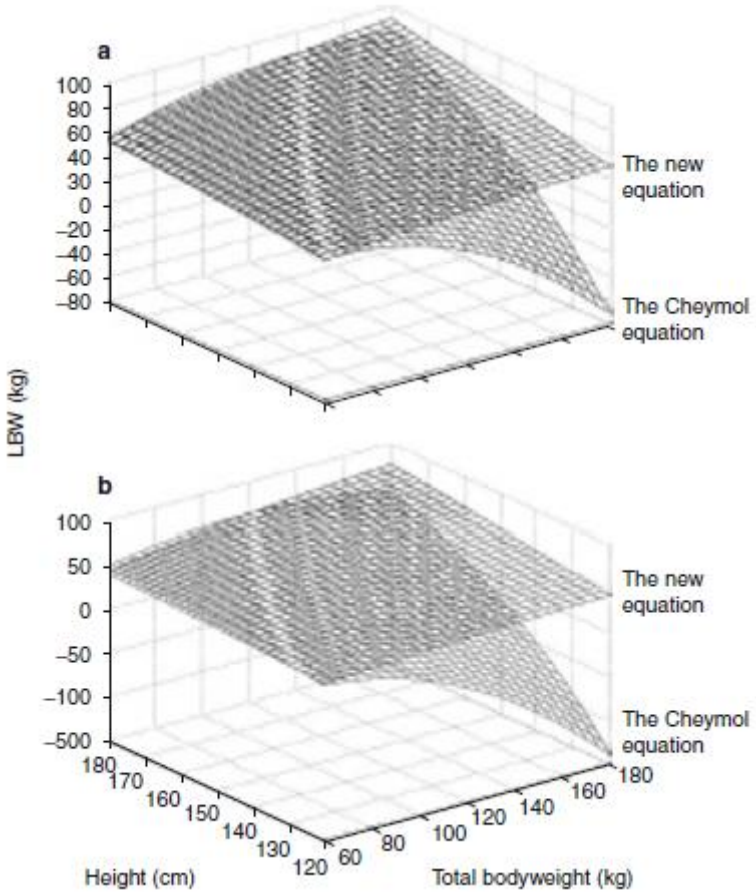



*Figure 1: Above is a depiction of the Janmahasatian algorithm for calculating LBM from anthropometric measurements. This algorithm gives accurate predictions of LBM even at extreme values for height and body weight compared to the James algorithm used by Cheymol [15]. (a) Male, (b) Female.*

Now that there is a clinically feasible method of calculating LBM, these values need to be transformed in dose levels for LT4. Santini et al. have developed a formula to relate these two using LBM values calculated with DEXA to ensure the greatest accuracy of LBM values shown in Equation 1. In this study the correlation of LBM to LT4 dose ($P < .001$, $r = .0667$) was greater than that of the correlation of BW to LT4 dose ($P < .001$, $r = .611$). This correlation is shown below in Figure 2.

$$LT4\ in\ ug/kg/day\ = 63.323 + 1.521 * (LBM) \qquad Equation\ 1$$

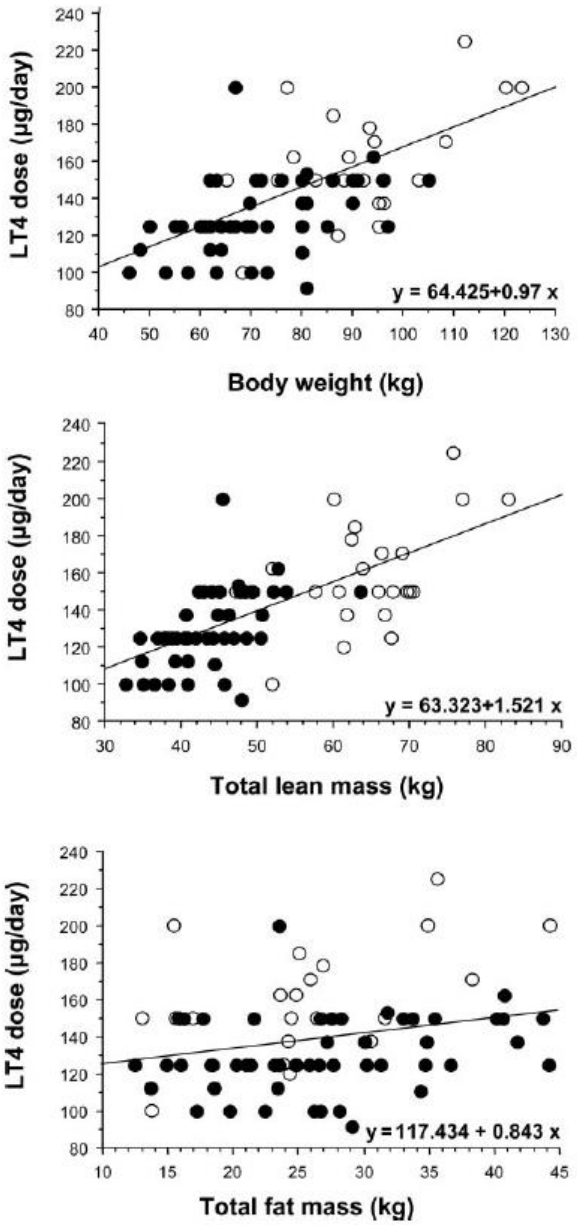



*Figure 2: Above are three graphs showing the correlation of LT4 dosing to body weight, LBM and total fat mass (BW - LBM). BW correlates with P < .001, r = .611, LBM correlates with P < .001, r = .667, Total fat correlates with P = .023, r = .26 [10].*

The algorithm for LBM developed by Janmahasatian et al. has not been used yet to predict proper LT4 doses in patients with total thyroidectomy, but it has been used to predict the clearance of many other drugs [17][18]. Narjoz et al. showed that the Janmahasatian algorithm performed very well when compared to BW algorithms. This group actually modified the algorithm slightly according to a study performed by McLeay et al. who found the body's drug clearance rates to be non-linearly connected to LBM. Using this non-linear adaptation of Janhasatian's algorithm, Narjoz et al. made predictions with a

root mean squared error that was 23% smaller than the root mean squared error based on the non-linear total body weight predictions.

### *Body Mass Index*

Despite the promising potential of LBM based predictions of LT4 dosing, some researchers still think it wisest to ignore LBM based dosing. Initially calculating the exact LBM of a patient using DEXA is too unreasonable a task to do in a clinic for something that isn't necessarily life and death. Even after Janmahasatian et al. developed their formula for LBM calculations, some researchers still think it too unreliable to use this formula in addition to the formula developed by Santini. Doing this would compound the error from two new formula's that have not been clinically tested enough [**9**]. Instead, Donna et al. decided to investigate BMI, defined as the subject weight divided by the square of the height, further to glean any possible predictive power for LT4 dosing.

Multiple studies have been performed to reveal the correlation of BMI to LT4 dosing and many show conflicting results. Despite these confusing reports, clinicians do agree that there is a definite correlation between BMI and proper LT4 doses [9]-[14]. Donna et al. performed an analysis of multiple BW based algorithms, BMI based algorithms and algorithms involving multiple variable (height, weight, sex, age, etc.) and found that the most reliable parameters were BMI and age. These parameters have, practically, the same predictive power for proper dose levels of LT4 as BW based formulas except extremely light weight or obese patients. At these extremes the framework that Donna et al. develop was much more reliable. The comparison of mean values of the optimal LT4 dose based on age and BMI were both statistically significant with F-test and p-values of $F = 4.749$, $p = .01$ and $F = 5.919$, $p = .004$, respectively. A user-friendly nomogram, Table I, was developed that could be easily deciphered by clinicians [9].

*Table 1: This is the nomogram developed by Donna et al. This framework will help accurately dose patients at the extreme high and low ends of BMI and age which was not possible with BW based dosing [9].*

| | *BMI* | | |
|---|---|---|---|
| | *≤ 23* | *23–28* | *> 28* |
| *Age* | | | |
| ≤ 40 | 1.8 | 1.7 | 1.6 |
| > 40–55 | 1.7 | 1.6 | 1.5 |
| > 55 | 1.6 | 1.5 | 1.4 |

BMI in kg/m$^2$; age in years; LT4 dose in $\mu$g/kg/day.

## Methods and Result

After reviewing the various formulas developed in literature we proceeded to implement these formulas into a thyroid simulation compartment-model called Thyrosim [6]-[8]. Three changes were made to existing program. An LBM based dosing function, a BMI based dosing function and various modifications to the compartments of this model were all implemented and are shown in the Appendix. The LBM based dosing function gives the option of using the Janmahasatian's shown in Table II. The

value calculated from the selected formula is inserted into Santini's formula in Equation 1. The BMI does the same but uses height and weight to calculate BMI and chooses a dose based on Table I. Lastly, the LBM or BMI correspond to a specific body type with corresponding volumes of the various compartments. LBM and BMI are used to make crude assumptions about the compartment volumes for the sake of running simulations with these new dose values.

### *Rate parameters modification according to volume or weight ratio*

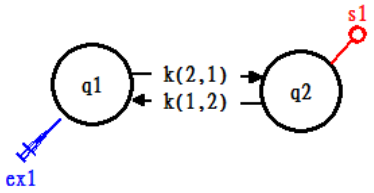



*Figure 3: Compartment model used to quantify new rate term. Model made in SAAM II.*

If the compartments are huge organs/tissues, we assume that the change of output concentration by input compartment should be proportional to the input compartment's volume or weight and proportional to 1/volume or 1/weight of the output compartment. Take two compartment model in Figure 3 as an example, the concentration change rate in q2 is:

$$\frac{dq_2}{dt} = k_{21}\frac{V_{1,R}}{V_{2,R}}q_1 = k'_{21}q_1 \qquad Equation\ 2$$

Where V1R = V1/$V1_{original}$, V2R = V2/$V2_{original}$, and the $V1_{original}$, and $V2_{original}$ is the original volumes of the original model. So we can set k(2,1)' = k(2,1)*V1R/V2R as the modified rate parameter.So according to the compartment model of Thyrosim shown in Figure 4:

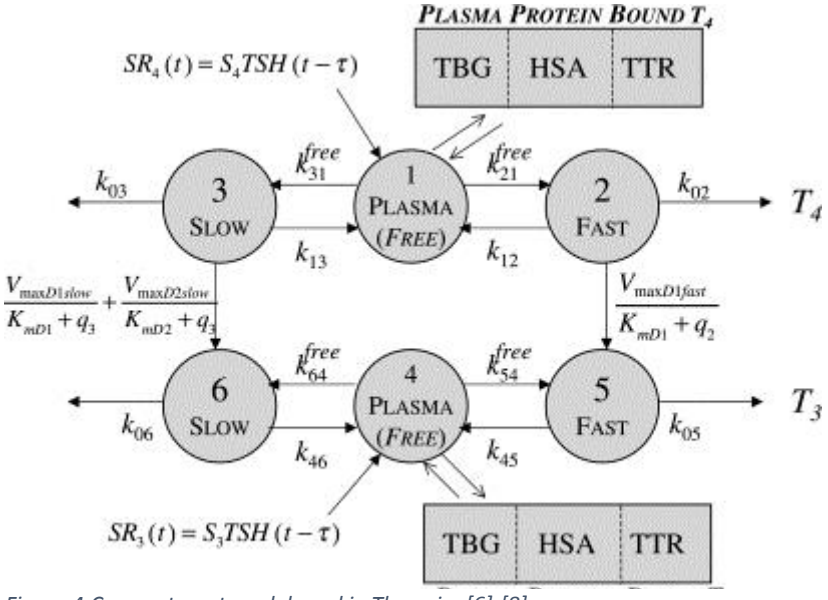



*Figure 4:Compartment model used in Thyrosim [6]-[8].*

The 6 compartments include plasma, Fast tissues, and slow tissues. So if we can estimate the plasma volume and the weight of fast/slow tissues, we can modify all the rate parameters to construct a more valid model.

### *Lean body mass estimation*

*Table 2: The 4 LBM algorithms now included in the functionality of Thyrosim. The best of these is the 4th option, the Janmahasatian Formula [10]-[19]-[21].*

| **The Boer Formula** |
|---|
| Men:eLBM = 0.407weight(kg) + 0.267height(cm) - 19.2<br>Women: eLBM = 0.252weight(kg) + 0.473height(cm) - 48.3 |
| **The James Formula** |
| Men: eLBM = 1.1weight(kg) - 128(weight(kg)/height(cm))$^2$<br>Women: eLBM = 1.07weight(kg) - 148(weight(kg)/height(cm))$^2$ |
| **The Hume Formula** |
| Men: eLBM = 0.32810weight(kg) + 0.33929height(cm) - 29.5336<br>Women: eLBM = 0.29569weight(kg) + 0.41813height(cm) - 43.2933 |
| **Sarayut Janmahasatian Formula** |
| $\text{FFM (male)} = \frac{9.27 \times 10^3 \times \text{BWt}}{6.68 \times 10^3 + 216 \times \text{BMI}}$<br>$\text{FFM (female)} = \frac{9.27 \times 10^3 \times \text{BWt}}{8.78 \times 10^3 + 244 \times \text{BMI}}$ |

### *Plasma Volume estimation*

According to Nadler's formula, the estimation of blood volume is [22]:

*Male: BV(L) = 0.3669 * Ht(meter)^3 + 0.03219 * Wt (kgs) + 0.6041*

*Female: BV(L) = 0.3561 * Ht(meter)^3 + 0.03308 *Wt (kgs) + 0.1833*

And the plasma volume can be calculated by:

$$Vp = (1 - Hct) * BV$$

Where Hct is the hematocrit value (normal range: 0.36~0.5(M), 0.34~0.47(F)). So once we know the height and body weight, we can estimate the value of plasma volume.

### *Fast/Slow tissue weight estimation*

Now we have the lean body mass and blood volume. If we minus the weight of blood from the lean body mass, the remaining weight should be composed of Fast/Slow tissues including bones, muscles, and other proteins. So the weight of Fast + Slow tissues can be calculated by:

$$Ot = LBM\text{-}BV*blood\ gravity$$

And in normal people the blood gravith should be about to 1.060.

Besides, we assume the proportion (Fast tissues : Slow tissues) is the same for every people. So the weight proportion of Fast/Slow tissue to the original model will be the lean body mass proportion. That is,

$$FastW/FastW_{original} = SlowW/SlowW_{original} = LBM/LBM_{original}$$

### *Original model compartment volume/weight estimation*

To valid our new model, we must have the original volume/weight of the original model. Since the model is fit by large amount of patient data, we use some most common values, $BW_{original}$ = 72(kg), $Ht_{original}$ = 178(cm), $Hct_{original}$ = 0.4, gender = male, $Blood\_Gravity_{original}$ = 1.060, then we can estimate the $Vp_{original}$ and original Fast+Slow tissue weight depending on different formula.

### *Simulation*

We try the model for hypothyroidism case. The initial condition is in euthyroid states. After $t = 0^+$, the TSH secretion is adjusted to zero. The dose is started from $t = 0^+$ and is adjusted to a constant T4 injection to the plasma. So the dose D(ug/day) will be transformed to the injection rate = D/24(ug/hr).

We simulate four type of patients, including 175, 150, 75 and 45kg. We only change the body weight variable, and apply the Sarayut Janmahasatian's Formula which is the most accurate LBM estimation method. We compare the simulation result of Santini et al.'s dosing function and Donna et al dosing table.

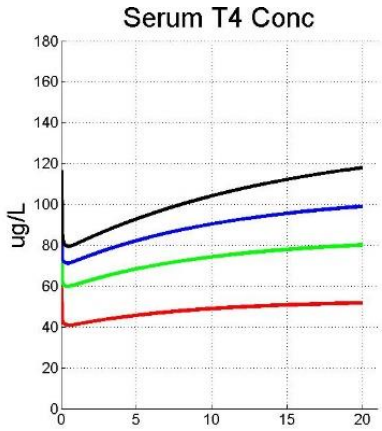
**Test patient model**

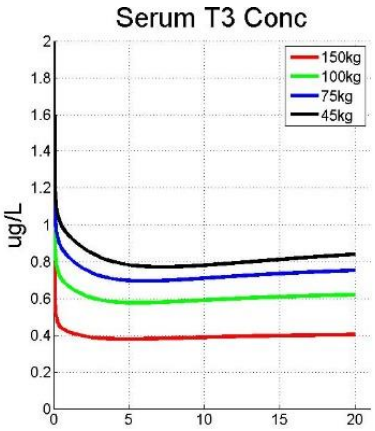
| | BW (kg) | Height (cm) | Age | Hct | Blood Gravity | Lean body mass(kg) | Blood Volume (L) | Plasma Volume (V) | Fast+Slow tissue weight |
|---|---|---|---|---|---|---|---|---|---|
| Obese | 150 | 175 | 25 | 0.4 | 1.060 | M:80.56<br>F:67.07 | M:7.40<br>F:7.05 | M:4.44<br>F:4.23 | M:72.72<br>F:59.60 |
| Normal | 75 | 175 | 25 | 0.4 | 1.060 | M:58.08<br>F:47.12 | M:4.98<br>F:4.57 | M:2.99<br>F:2.74 | M:52.77<br>F:42.27 |
| Slim | 45 | 175 | 25 | 0.4 | 1.060 | M:42.33<br>F: 33.74 | M:4.02<br>F:3.58 | M:2.41<br>F:2.15 | M:38.07<br>F:29.95 |

## Result

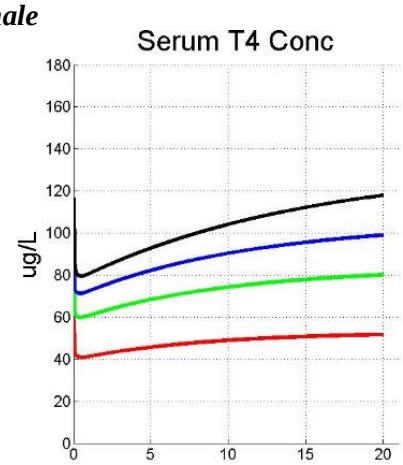
***Santini et al.'s Method***

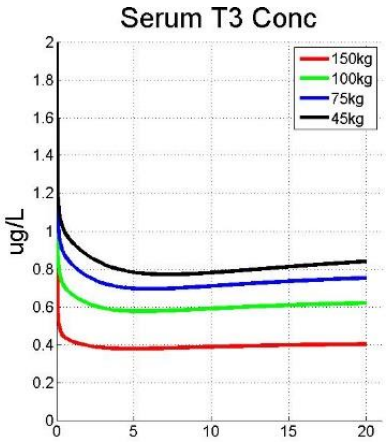
***Male***



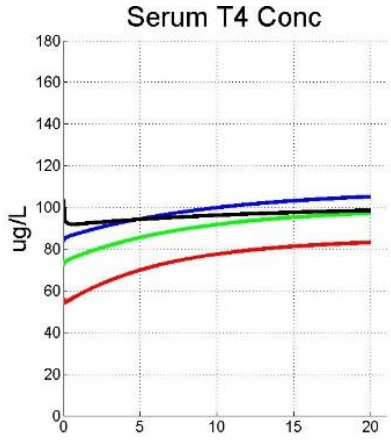

***Female***

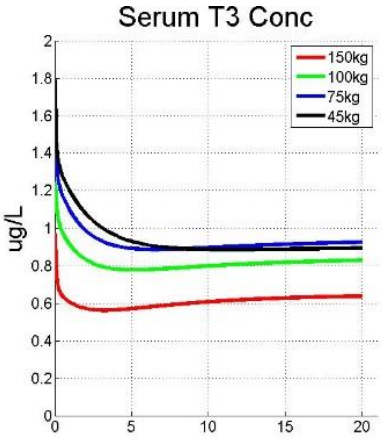


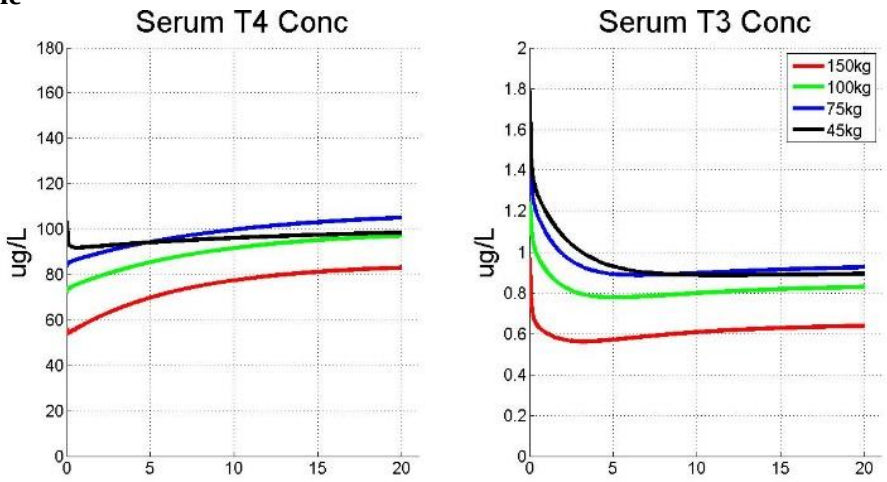

**Donna et al's method**

**Male**



**Female**




Serum T4 normal range: 46~120 ug/L
Serum T3 normal range: 0.6~1.8 ug/L

In the Santini et al.'s method simulation, the steady state concentration fall out of the normal range in the extreme obese (175kg) case both for male and female. Besides each case's steady state are far separated. Instead, when using Donna et al's method every case reach a steady state with the normal concentration range even for extreme case. And concentrations of steady states are closer. This suggest that Donna et al's method which considering BMI and age is a better dose estimation method, at least in our rebuilt model.

## Discussion and Summary

In this project, we modified the Thysim app to generate a more valid model for T4 T3 concentration simulation. This model can be applied to various patient case, with variables including weight, height, age, gender, Hct, and blood gravity. We compared two estimation T4 dose algorithm, including the Santini et al.'s method and the Donna et al's method for hypothyroidism case. The Donna et al's method yield a better simulation result that serum thyroid concentration of every patient fell into the normal range and the steady state have less variance in our modified model. Compared to the Santini et al's method which only considering about lean body mass, Donna et al's method take age into account, that younger patient with higher metabolizing rate should have higher dose to maintain the concentration.

There is still many improvement we should make to apply this model. Such as, in our model we assume the weight proportion (Fast tissue weight: Slow tissue weight) is the same for every people, but this is not the truth. People should have different tissue composition, such as athletics should have more muscle component compared to normal people. So we should generate another formula which can estimate the weight proportion of fast and slow tissue, so the rate parameters will be more accurately modified. Besides, we do not have feed data to fit our model and compare the simulation and real world case. For further study, we should fit this model with data recordings not only including the serum T3 T4 TSH dose, but also the body weight, height, gender, age, hct, and blood gravity as additional variables.

## Appendix

Code has been sent in a zip-file to Dr. DiStefano.

## Work Assignment

**Trevor Davis**

Literature search for lean body mass calculation and levothyroxine dosing

Algorithm application

Report writing: Introduction/Background

**Pei-Chun Su**

Literature search for lean body mass calculation and levothyroxine dosing

Algorithm application/Code writing/Experiment

Report writing: Method and Result/Discussion and Summary

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