A Simple Model Predicting Individual Weight Change in Humans

Diana M. Thomas\(^1\)* and Corby K. Martin\(^2\) and Steven Heymsfield \(^3\) and Leanne M. Redman \(^2\) and Dale A. Schoeller \(^4\) and James A. Levine\(^5\)

\(^1\)Department of Mathematical Sciences, Montclair State University, Montclair, NJ; \(^2\)Pennington Biomedical Research Center, Baton Rouge, LA; \(^3\)Merck & Company, Rahway, NJ; \(^4\)Department of Nutritional Sciences, University of Wisconsin-Madison; \(^5\)Department of Medicine, Endocrine Research Unit, Mayo Clinic and Mayo Foundation, Rochester, MN

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Excessive weight in adults is a national concern with over 2/3 of the US population deemed overweight. Because being overweight has been correlated to numerous diseases such as heart disease and type 2 diabetes, there is a need to understand mechanisms and predict outcomes of weight change and weight maintenance. A simple mathematical model that accurately predicts individual weight change offers opportunities to understand how individuals lose and gain weight and can be used to foster patient adherence to diets in clinical settings. For this purpose, we developed a one dimensional differential equation model of weight change based on the energy balance equation is paired to an algebraic relationship between fat free mass and fat mass derived from a large nationally representative sample of recently released data collected by the Centers for Disease Control. We validate the model’s ability to predict individual participants’ weight change by comparing model estimates of final weight data from two recent underfeeding studies and one overfeeding study. Mean absolute error and standard deviation between model predictions and observed measurements of final weights are less than 1.8 ± 1.3 kg for the underfeeding studies and 2.5 ± 1.6 kg for the overfeeding study. Comparison of the model predictions to other one dimensional models of weight change shows improvement in mean absolute error, standard deviation of mean absolute error, and group mean predictions. The maximum absolute individual error decreased by approximately 60% substantiating reliability in individual weight change predictions. The model provides a viable method for estimating individual weight change as a result of changes in intake and determining individual dietary adherence during weight change studies.

1. Introduction

The Centers for Disease Control currently estimates that approximately 67% of the US adult population is overweight, with body mass index (BMI) between 25 and 29.9 and 34% is obese (BMI > 30). BMI levels above 25 have been linked to

*Corresponding author. Email: thomasdia@mail.montclair.edu
diseases and health related consequences such as coronary heart disease, type 2 diabetes, cancers (endometrial, breast, and colon), hypertension, dyslipidemia, stroke, liver and gallbladder disease, sleep apnea and respiratory problems, osteoarthritis, and gynecological problems [66]. In fact, it is estimated obesity related diseases currently account for approximately 9.1% of total national health care costs [66].

With such a large proportion of the population considered overweight, mathematical models can provide intuition, insight, and solutions for effective weight loss and weight loss maintenance [2, 4–6, 18, 19, 31, 32, 53, 55]. These differential equation models apply state variables that track the quantity of macronutrients that provide energy, namely, carbohydrates, protein, and fat. The common goal of the models is to predict weight change as a result of changes in dietary intake and/or energy expenditure.

One particular application of weight change models is to foster individual adherence to diets during caloric restriction. Using weight predicted curves, an individual's actual weight loss can be compared to predicted weight loss to test for compliance. Although there are a variety of existing weight prediction models, they either require numerous individual parameter estimates, posing challenges for clinical implementation, or the maximum individual subject error obtained during validation is too high to reliably use for adherence purposes. To fill this knowledge gap, we sought to develop a model that predicts weight change that simultaneously satisfies the following conditions:

1. The model requires minimal input of easily measurable baseline information (age, height, weight and gender).
2. The model predicts final weight during weight loss with a high degree of accuracy (low mean absolute error in predicted weight versus actual weight when tested on individual weight loss data sets).
3. The model provides reliable individual estimates (low standard deviation in the mean absolute error of predicted weight versus actual weight and low maximum absolute error).

The model presented here is the first model to simultaneously satisfy these goals and provides a significant advance in application of weight loss models to clinical settings.

In the next section, we provide a brief history of existing weight change models from the literature followed by the development of our model. Section 3 provides existence and non-negativity of solutions criteria for our developed model. In Section 4 we validate the model’s capacity to reliably predict individual weight change from two recently conducted weight loss experiments and one over-feeding study. We also compare the model results with a recently published model that satisfies our first criterion and show that the developed model provides more reliable and accurate estimates of final individual weight.

2. Model

2.1. History of Dynamic Weight Change Models

One approach to modeling human weight change is to incorporate all reasonable physiological factors in order to reflect reality. This type of model provides insight into how perturbations to any component involved during changes in energy intake ultimately affect weight change. Applying this perspective has led to the carefully developed system of compartmental equations with state variables tracking changes in energy derived from protein, fat and carbohydrates [18, 19]. The Hall
model identifies detailed movement of energy from intake to expenditure providing important information into the mechanisms behind weight change.

The Hall model requires estimation of the amount of grams of protein, carbohydrates and fat a subject consumes per day along with numerous other parameters [18, 19]. In order to reduce the amount of initial data and parameter estimations, several one and two-dimensional models have been developed by applying simplifying assumptions [2, 4–6, 31, 32, 55]. These simplifications are derived by assuming glycogen stores can be modeled by a time averaged constant, resulting in elimination of the carbohydrate mass equation. Elimination of the protein equation is obtained by algebraically correlating fat mass to fat free mass (FFM).

Some models [2, 4–6, 31, 32, 55] either assume that FFM is a linear function of fat mass or assume FFM can be modeled as a time averaged constant. Chow and Hall explored a more sophisticated formulation by coupling the FFM model proposed by the Forbes equation through a two dimensional dynamic model [4]. Forbes conjectured that FFM and fat mass were companions; increases/decreases in fat mass will be followed by increases/decreases in FFM [12]. Based on this hypothesis, Forbes fit mean data for 167 women of similar stature to a log linear regression equation to arrive at what is now known as the Forbes curve:

\[ FFM = 10.4 \ln(F/D) \]

where \( F \) represents fat mass in kg and \( D \approx 2.55 \).

We develop here a one-dimensional model that incorporates a newly developed FFM – F relationship [54] along with several other terms based on recent experimental observations. We refer the reader to [55] for complete biological details on the full model development and present here a description of the essential components of the model, highlighting the modifications beginning with the energy balance principle.

2.2. The Energy Balance Principle

The energy balance principle discussed in physiology and nutrition literature is based on the application of the first law of thermodynamics to an open system [11]. The human body is considered an open system because energy can be added to the system by input of mass flow in the form of food. The human energy balance equation takes the form,

\[ R = I - E, \tag{1} \]

where \( R \) is the rate of energy stored/lost, \( I \) is the rate of energy intake, and \( E \) is the rate of energy expenditure. The quantities \( R, I, \) and \( E \) are typically measured in kcal/d [27, 41].

2.3. The rate of energy stored/lost: \( R \)

Energy that is not used by the body is stored in the form of glycogen, lipids and protein [24]. Glycogen is a storage molecule of the body’s short-term energy resource, glucose [14]. Because of the regulatory mechanism that works to maintain the glucose/glycogen level in a narrow range, we can model glucose/glycogen energy measured in kcal by a time-averaged constant, \( G \). We remark here that this assumption has been compared successfully to observed data [4].
Lipids (mainly in the form of fatty acids) are the nutrients containing the most energy per unit mass[24]. Unlike glucose, fat can be stored in large quantities for extended lengths of time in the form of triacylglycerols within the adipose tissue spread throughout the human body. Therefore, fat mass is the main long-term energy storage mechanism of the human body. We denote the total kg of fat mass of the body at time \( t \) by the function \( F(t) \).

Protein’s building blocks, amino acids, can be broken down and transformed to glucose to be used for energy through amino acid metabolism [24]. Although there are small amounts of protein stored in the liver, the major portion is contained in the body’s muscle tissue [14]. Protein is a component of \( FFM \) and so we track changes in protein energy through changes in \( FFM \) as discussed previously [4].

As mentioned in the introduction, the two-dimensional model [4] relies on the Forbes \( FFM \) function of fat mass \( (F) \). Specifically, Forbes observed an algebraic relationship between fat mass and \( FFM \) [12] by fitting a log linear curve through mean data for 167 women of similar stature [12],

\[
FFM(t) = 10.4 \ln(F(t)/D)
\]

An analogous male Forbes model was developed using body composition data from approximately 200 men of average stature [54]:

\[
FFM(t) = 13.8 \ln(F(t)/S)
\]

where \( S \approx 0.29 \).

The Forbes model has been established to predict the change in \( FFM \) in numerous weight change studies with a high degree of accuracy for group mean data[17, 54]. It may be tempting to think of the Forbes curve as a trajectory that body composition travels during weight loss, however, the model does not determine change in \( FFM \) by estimating the baseline and final time body composition [54]. The Forbes curve estimates for the change in \( FFM \) rest on the fact that individual data follow a parallel curve of identical slope and in this manner accurately determines change without identifying beginning and endpoints.

As a stand alone equation, the parameter \( D \) can be computed using baseline body composition data to determine the correct translate. It was shown [54] that \( D \) is a reflection of age, height, and race. In addition, the Forbes model has a range of positive fat mass that yields negative \( FFM \) values. Moreover, the intercept of the Forbes model is undefined.

The two dimensional model from [4] successfully incorporates the Forbes model by considering \( F \) and \( FFM \) as state variables and applying the \( p \)-ratio (proportion of body energy mobilized as protein during weight change) derived from the Forbes model [4]. Reduction of the two-dimensional model to a one-dimensional model (Equation 25 [4]) reduces the dimension of the model, but will require calculation of the parameter \( D \).

In order to develop a universal \( FFM \) function that is representative of the current national population, has a biologically realistic intercept when \( F = 0 \), and can be immediately applied for each individual subject in a one dimensional energy balance model, a class of fourth order polynomials of \( FFM \) as a function of \( F \) that considers age, height, gender and race was formulated based on the recently released body composition data collected by the Centers for Disease Control under the The National Health and Nutrition Examination Survey (NHANES). NHANES is a program designed to assess the health and nutritional status of adults and children in the United States. NHANES performs a continuous, nationally representa-
tive health survey of the civilian, non-institutionalized United States population, collecting data on about 5000 persons each year from interviews, physical examinations, and medical tests including bone densitometry. In 1999 NHANES began performing dual energy X-ray absorptiometry (DXA) whole body measurements on survey subjects 8 years old and older in three mobile examination centers. DXA measurements are widely accepted as the gold standard for human body composition measurements. The DXA whole body data obtained from the mobile exam centers was compiled by the NHANES study group and released on the Center for Disease Control (CDC) website [29]. The $FFM$ models developed earlier [54] provided comparable estimates for $\Delta FFM$ to the Forbes model after entering age, height, and gender as initial inputs.

The first major modification to our prior model [55] is the replacement of the linear $FFM$ function of by the $FFM$ functions based on NHANES data. These $FFM$ model terms were statistically determined through a regression analysis [54],

Females:

\[
FFM(t) = -72.1 + 2.5F(t) - 0.04(A_0 + t/365) + 0.7H \\
- 0.002(A_0 + t/365) - 0.01FH - 0.04F(t)^2 \\
+ 0.00003F(t)^2(A_0 + t/365) \\
+ 0.000004F(t)^4 + 0.0002F(t)^3 + 0.0003F(t)^2H \\
- 0.000002F(t)^3H
\]

Males:

\[
FFM(t) = -71.7 + 3.6F(t) - 0.04(A_0 + t/365) + 0.7H \\
- 0.002F(t)(A_0 + t/365) - 0.01F(t)H + 0.00003F(t)^2(A_0 + t/365) \\
- 0.07F(t)^2 + 0.0006F(t)^3 - 0.000002F(t)^4 + 0.0003F(t)^2H \\
- 0.000002F(t)^3H
\]

where $FFM(t)$ represents the kg of $FFM$ on day $t$, $F(t)$ is the kg of fat mass on day $t$, $H$ denotes height in cm, and $A_0$ is baseline age.

Separating $R$ from Equation 1 in the three different components, kg of glucose/glycogen, $FFM(t)$, and $F(t)$ we have

\[
R = c_l \left( \frac{dFFM}{dt} \right) + c_f \frac{dF}{dt}
\]

where $c_l$ is the energy density of $FFM$, $c_f$ is the energy density of fat mass, and the derivative of $FFM$ is taken implicitly. The values of $c_l$ and $c_f$ were obtained from [26, 51] and appear in Table 2.

2.4. The rate of energy intake, $I$

The rate of energy intake, $I$ has been historically difficult to measure [19]. Past dynamic models have assumed that $I$ during weight change is constant and de-
terminated by target energy intake requirements [2, 5, 6, 18, 19, 32, 55]. We now describe the limitations behind this assumption and provide a novel method based on modern technology and measurements to assess \( I \) as a time varying function dependent on an individual subject.

First, baseline intake is determined by applying steady state (zero energy balance) at the conception of the study:

\[
I - E = 0
\]

The gold standard for determining \( E \) is through doubly labeled water (DLW). The technique involves enriching the body water of a subject with an isotope of hydrogen and an isotope of oxygen, and then determining the washout kinetics of both isotopes as their concentrations decline exponentially toward natural abundance levels. It is not feasible to obtain DLW data for every study or individual so we applied individual DLW data from National Academy of Sciences/Institute of Medicine (NAS/IOM) database of over 200 subjects to fit a quadratic regression formula that defines \( E \) as a function of body mass, \( W \). Specifically,

\[
E_F = 0.0278W^2 + 9.2893W + 1528.9 \\
E_M = -0.0971W^2 + 40.853W + 323.59
\]

where the subscript \( F \) represents females and \( M \) represents males.

As stated earlier, when a study prescribes caloric restriction, it is tempting to model \( I \) as the prescription demands. For example, if we prescribe a change in baseline intake \( (\Delta \tilde{I}) \) that is 25% below baseline intake, we would model \( I = \tilde{I} - \Delta \tilde{I} \) where

\[
\Delta \tilde{I} = 0.25\tilde{I}
\]

and \( \tilde{I} \) represents baseline energy intake.

However, compliance to such dietary restrictions are rare. In an analysis of 181 participants placed on popular diets, only one subject in the study was 100% adherent by the end of one year [1]. Furthermore, it has been consistently observed that compliance is a decreasing function of time [1, 7, 25]. To determine \( I \), we applied data from studies which calculated energy intake using DXA measurements of changes in energy stores and DLW measurements of energy expenditures during weight loss. Specific details on these calculations appear in the model validation simulations in Section 4.

2.5. The rate of energy expenditure, \( E \)

The rate of energy expenditure consists of four different quantities; the kcal/day used for dietary induced thermogenesis (DIT), volitional physical activity (PA), basal metabolic rate (RMR), and spontaneous physical activity (SPA) [15]:

\[
E = DIT + PA + RMR + SPA.
\]

DIT is the energy involved in processing food. This consists of digestion, absorption, metallization, storage and transport of ingested food and is estimated to account for 4-15% of total energy expenditure [15]. Although DIT was observed to be sensitive to amount of protein ingested, we do not examine this aspect of DIT [58]. In the case of an aggregated composition of food intake, we assume that DIT
is a direct proportion of the rate of energy intake, $I$, with proportionality constant, $\beta$. In [20], the adjustment to calorie reduction on DIT was examined by multiplying by an adjustment factor. In fact, such an adjustment has also been observed in overfeeding studies by a factor of up to 19% [20, 37]. We model the adjustment by a multiplier that is greater than 1 for the overfeeding case and less than one in the calorie restriction case. As in [20] we absorb the multiplier into one constant $\beta$ with ranges provided in Table 1.

Therefore, the energy expended for dietary induced thermogenesis is

$$\text{DIT} = \beta I.$$ 

By physical activity, PA, we specifically mean volitional exercise such as sports and fitness related activity. PA can accounts for 20-40% of total energy expenditure [15]. Strenuous exercise or starvation cause glycogen stores to deplete [14]. As a result the liver begins to produce ketone bodies as an alternative energy source. Because we are not modeling extreme cases such as starvation, we assume the physical activity is light to moderate and does not deplete glycogen stores. Some PA is what we refer to as weight bearing activity and some of PA is non-weight bearing. Weight bearing activities involve activities that require us to carry our body weight. For example, walking and running are examples of weight bearing activities. As in the two dimensional model [4], we assume that energy used for non-weight bearing activity is negligible.

Thus, the rate of weight bearing exercise is estimated as a direct proportion of body mass and so we model PA by,

$$PA = mW$$

where $m$ is the proportionality constant in kcal/kg/day and $W$, total body mass, is the sum of $FFM$ and $F$.

An individual’s RMR is the rate of energy required to sustain life. RMR is measured in controlled conditions. The subject must be in a relaxed (preferably just having awakened), postabsorptive state (12 hours or more of fasting) [15]. Thus, the direct determination of RMR is not simple. There exists several simple statistical formulas that estimate RMR depending on sex, total body mass, height, and age. These formulas are based on extensive experimental data which was analyzed using predictive regression equations. Although these estimates work well in most situations, they tend not to be as reliable in extreme cases such as obesity [49].

Popular statistical formulas assume that RMR is a linear function of body mass, age, height, and gender [21, 42]. There is evidence that RMR is a nonlinear function of body mass of the form $W^p$ where $0 < p < 1$ [30, 60]. The Livingston-Kohlstadt RMR equations developed using the NAS/IOM database take the form of body mass to a power and provides accurate estimates of RMR when validated against other databases [38]. The Livingston-Kohlstadt formula is a function of a power of body mass and baseline age:

$$RMR_{LK} = (a_i W^p - y_i (A_0 + t/365)),$$  \hspace{1cm} (5)

where $a_M = 293, a_F = 248, p_M = 0.4330, p_F = 0.4356, y_M = 5.92, y_F = 5.09$, $W$ represents body mass, and $A_0$ represents baseline age.

We point out that the units of the coefficients are non-standard as the exponent of body mass is statistically determined. While analysis of data sets indicate that the power of body mass is fractional, the exact fraction is still debated and the
physiological reasoning behind the fractional power is not fully understood at this
time. There are several mathematical explanations, for example, the fractal based
derivation [57], however, the science behind human RMR models is still in its
infancy and the Livingston-Kohlstadt model provides the best known data driven
fractional power formula to date.

It has been observed that calorie restriction results in RMR that is lower than
expected [25, 39]. The expected basal metabolic rate based on body mass in our
model is given by Equation (5). If \( a \) is the percent of metabolic adaptation where
\( 0 \leq a \leq 1 \), then we model the contribution of RMR with adaptation to energy
expenditure by adjusting RMR:

\[
RMR = (1 - a)(a_i W_{pi} - y_i (A_0 + t/365))
\]

Spontaneous physical activity (SPA) is defined as the total energy expended in
activities of daily living, change of posture and fidgeting [61]. During weight gain
due to overfeeding, it was observed that the ratio of the change in SPA to change
in total energy expenditures remained relatively constant [37]:

\[
\frac{\Delta SPA}{\Delta E} = s.
\]

where \( \Delta \) represents final time quantity minus baseline quantity.

SPA is difficult to measure even in highly controlled settings, however, by ex-
anding \( E \) using (4) and applying the linearity of the \( \Delta \) operation we arrive at:

\[
\Delta SPA = s(\Delta DIT + \Delta PA + \Delta RMR + \Delta SPA)
\]

\( \Rightarrow \Delta SPA = \frac{s}{1 - s}(\Delta DIT + \Delta PA + \Delta RMR) \)

Integration over time allows us to solve for \( SPA \) in terms of the remaining energy
expenditure:

\[
SPA = \frac{s}{1 - s} (DIT + PA + RMR) + C
\]

where \( C \) is a constant of integration. The constant \( C \) is determined by solving

\[
SPA(0) = \frac{s}{1 - s}(DIT(0) + PA(0) + RMR(0)) + C
\]

By examining data measured in [34, 35], it was found that baseline SPA is ap-
proximately 32.6\% of baseline energy expenditure determined by DLW; \( SPA(0) = 0.326E(0) \). As a result, we obtain a closed form expression for \( SPA \) in terms of the
other components of energy expenditure. The closed form expression is an increas-
ing function of weight supporting observations that SPA is found to change during
both over-feeding experiments [33, 37] and caloric restriction in obese individuals
[10, 46].

There are only a few overfeeding studies that provide individual DLW, RMR,
and DIT data which presents challenges in locking down the precise value of \( s \).

To estimate \( s \), we analyzed several well known overfeeding studies with published
individual data. Within these published studies, we carefully detailed which data
sets were applicable. Individual subject data was either published or provided by
the author in the overfeeding studies of Bandini [3], Diaz [9], Levine [37], Pasquet
[43], and Siervo [52]. The Pasquet study examined the effects of overfeeding during
Guru-Walla, a traditional Cameroon fattening season. The reported baseline energy expenditures of the Pasquet study were higher than expected when compared to the NAS/IOM regression formulas for E. This was due to increased physical activity of the subjects during the collection of baseline information. Subjects in the study were performing physically demanding agricultural work which raised their baseline energy expenditures and therefore moved them out of energy balance. Thus, calculations of the change in $E$ over time ($\Delta E$) were negative or close to zero for most of the subjects and could not be applied to determine $s$. The Siervo study was unusual as they overfed participants for a period of a few weeks and then allowed a relaxation of the requirements for a few weeks [52]. This process was repeated for three cycles with the amount overfed and the length of the periods increasing. Although baseline and final time energy expenditures were reported, computation of $\Delta E$ was confounded by the non-monotonic feeding pattern. Therefore, we removed the Siervo study from consideration.

Computing the value of $s$ using individual data from Bandini, Levine, and Diaz studies yielded a value of $s = 0.4, 0.67, \text{ and } s = 0.6$ respectively. The Bandini study overfed 13 adolescents for a period of 2 weeks, the Levine study overfed 16 subjects by 1000 kcal/d over baseline requirements for a period of 8 weeks, and the Diaz study overfed 9 male participants 50% over baseline for a period of 42 days. Subjects in the Diaz study conducted both cycling and stepping activity during baseline and overfeeding. Similar to the Pasquet study, baseline energy expenditures for most subjects was higher than expected when compared to the NAS/IOM predictions. The Diaz study, however, continued the stepping and cycling physical activity during the overfeeding study and thus, resulting in positive $\Delta E$ for most subjects. Explanations for the negative $\Delta E$ measurements were due to external circumstances and were not considered in study’s group mean results [9]. Similarly, we restrict our calculation of $s$ to the positive $\Delta E$ measurements. Based on the available current data, we estimate $s$ as the average of the 0.4, 0.6, and 0.67, yielding $s = 0.56$.

Computations of $s$ for the case of caloric restriction indicates that $s = 0.67$ [22, 44, 48, 50].

We now summarize the formulation for $E$:

$$E = RMR + PA + SPA + DIT$$

1. **RMR** is modeled by the Livingston-Kohlstadt equation for $RMR$. Resting metabolic rate travels along the trajectory for weight determined by the differential equation. Age is continuously increased from initial age, $A_0$.

$$RMR = a_i(W(t))^p - y_i(A_0 + t/365),$$

where $a_F, a_M, y_F, y_M$ are the Livingston Kohlstadt parameters subscripted for gender.

2. **DIT** is modeled as a direct proportion of time varying intake ($\omega I$). If intake is being increased then there is an increase in the proportion of DIT which is reported from 14-19%. So we have $DIT = \beta I$ where $\beta$ is in the range of $0.075 \leq \beta \leq 0.086$ (determined based on overfeeding or caloric restriction). Baseline $DIT$ is estimated as $0.075I$.

3. **PA** at baseline is determined by applying baseline SPA observed to be around 32.6% of baseline $E$ [34, 35, 37]. Baseline $PA$ is estimated then from $TEE(0) - DIT(0) - SPA(0) - RMR(0)$. If this expression is less than zero, then there is no contribution of physical activity so $PA(0) = 0$. Otherwise $PA(0) = TEE(0) - DIT(0) - SPA(0) - RMR(0)$. We model the dynamic portion of $PA$ by $PA = mW$ where $m = PA(0)/W(0)$ and $W$ is time varying weight.
(4) SPA is modeled by integrating

$$\Delta SPA = s \Delta E$$

where $s = 0.56$ and solving for the constant of integration by applying baseline data.

Combining all expressions obtained for $R, I$ and $E$ and substituting into Equation (1) we obtain the final one dimensional model,

$$c_f \frac{dFFM}{dt} + c_l \frac{dF}{dt} = I - (RMR + DIT + SPA + PA)$$

with initial condition

$$F(0) = F_0 > 0$$

We remark that the state variable of Equation 6 is $F(t)$ since $FFM(t)$ is slaved to $F(t)$ through the NHANES regression formulas. The derivative of $FFM(t)$ on the left hand side of Equation 6 is taken implicitly.
3. Mathematical analysis

In this section we address the existence, uniqueness and non-negativity of solutions to (6). The model (6) when written in the form

$$\frac{dF}{dt} = G(F(t))$$

has a locally Lipschitz right hand side and therefore is guaranteed a unique solution on an interval of existence, $[0, \epsilon)$ where $\epsilon > 0$ [16].

In our analysis, we consider $I$ constant. Individual changes in $I$ during weight loss or weight gain are behavioral and would move to a different trajectory based on the change to $I$ and hence we consider existence and uniqueness of a single trajectory by assuming a constant $I$.

The model defined by Equation 6 is non-autonomous due to the time varying age parameter $A = A_0 + t/365$. Our goal is to first prove existence, uniqueness and non-negative for a related autonomous equation and use differential inequalities to extrapolate the result to our non-autonomous equation.

If we replace the non-autonomous expression $A_0 + t/365$ by $A_0$ in our expenditure term and $\bar{A} = A_0 + \epsilon/365$ in the $R$ term, the modified equation is autonomous. Applying differential inequalities, we can quickly see that the autonomous equation (AE) is a lower bound for (6). Thus, our strategy is to prove non-negativity for the (AE), which guarantees non-negativity for (6) on $[0, \epsilon)$. Finally, to guarantee existence for all time, we prove using contradiction that solutions to (6) do not have finite time blow up.

To prove non-negativity of solutions for the autonomous equation we need to prove that $dF/dt \geq 0$ when $F = 0$. This condition is called the quasi-positivity criteria [40]. If an autonomous differential equation satisfies the quasi-positivity criteria, then the solutions to the equation are non-negative by a result in [40].

In order, to determine what restriction on the parameters will guarantee quasi-positivity, we substitute $F = 0$ into (AE) and calculate the left hand side of AE:

$$= c_l \left( 3.6 \frac{d}{dt} F(t) - 0.002 \left( \frac{d}{dt} F(t) \right) \bar{A} - 0.01 \left( \frac{d}{dt} F(t) \right) H \right) + c_f \frac{d}{dt} F(t)$$

$$= \frac{dF}{dt} (\gamma(\bar{A}, H, c_l, c_f))$$

Similarly, setting $F = 0$ in the right hand side of AE yields a function of parameters

$$\delta(I, A_0, H, \beta, a_i, y_i, C, m)$$

By solving the inequality $dF/dt \geq 0$, we have that quasi-positivity is guaranteed as long as

$$\frac{\delta(I, A_0, H, \beta, a_i, y_i, C, m)}{\gamma(\bar{A}, H, c_l, c_f)} \geq 0$$

(7)

The biological meaning of this condition restricts energy intake to be larger than energy expenditures at zero fat. If we define critical intake to be the intake equal to expenditures at zero fat, the restriction determined by Inequality 7 relates critical intake to minimal energy expenditures from $F$ as a function of age and height [54]. Direct computation of this condition is not elegant but simple using computer
algebra system software. Numerical experimentation with the intake parameter shows that if intake is too low (on the order of below 1000 kcal/d), the restriction on the parameters is violated. This is consistent with the observation from the Minnesota Starvation Experiment that continued reduced intake of 1800 kcal/d for a 24 week resulted in very low BMI surmised to be the near fatal in the Minnesota Starvation Experiment [13]. A separate model describing the dynamics of starvation was previously developed [53] and can be applied to understand lower and zero levels of intake.

To guarantee existence for all time, we only need to show that finite time blow up cannot occur. This is because we have already proved that on the interval of existence the solution is non-negative. If there is a loss of existence, then the solution must blow up. We will assume on the contrary that finite time blow up occurs and arrive at a contradiction.

Let us assume that the restriction on parameters (7) holds. Assume on the contrary that there is a $b_0$ such that the $\lim_{t \to b_0} F(t) = \infty$. Then for some $T > 0$, there is a subsequence $t_k$ with $t_k \to b_0$ and $F(t_k)$ increasing to infinity.

If $F$ increases to infinity, then $W$ also increases to infinity. Moreover, since $E$ is an increasing function of $W$, $E$ also goes to infinity. But then substitution into the right hand side of (6) yields

$$I - E(W(t_k)) \to -\infty$$

which implies $F'(t_k) \to -\infty$ and creates a contradiction. Therefore under condition (7) a nonnegative solution to the initial value problem exists for all time $t \geq 0$.

We summarize these observations in the theorem below:

**Theorem 3.1**: Suppose that the parameters in (6) satisfy the restriction (7). Then a nonnegative unique solution for the equation (6) exists for all $t \geq 0$.

The theorem restricts the rate of energy intake to be greater than energy expenditures at zero fat mass, providing lower bounds for energy intake that avoid starvation.

### 3.1. Long-term dynamics

In the case where age is constant, and $I$ is constant, solutions to (AE) converge monotonically to the steady state where intake equals expenditure, $I = E$ [55]. Increases in age act as incremental decreases in energy expenditure which do not allow solutions to completely rest, but force a small pulling away from the steady state of (AE). To see this, we simulated the model with age held constant at $A_0$ alongside the non-autonomous model. One can see the phenomena described in Figure 1.

### 4. Validation and Comparison of the Model

In this section we validate the model using individual data from three studies; two caloric restriction studies and one overfeeding study. Our choice of weight change study to validate the model were defined by three criteria:

1. Baseline data was carefully measured to simulate zero energy balance as closely as possible. No lifestyle changes in physical activity or diet were prescribed during the baseline measurements.
Figure 1. A simulation of individual weight loss for a period of five years with age held constant (dashed curve) and increasing age (solid curve). The y-axis represents weight in kg and the x-axis time in days. Baseline weight, height, and age are 77 kg, 172 cm, and 44 years. The target caloric intake is 2200 kcal/d.

(2) Changes in stored energy were measured during weight change through body composition measurements. These measurements are used to estimate the value of $R$.

(3) Energy expenditures were determined during weight change through DLW measurements. These measurements are used to estimate $E$.

Because it is well known that subject adherence to energy intake are not guaranteed, we can use the estimate of $R$ and $E$ to approximate energy intake:

$$I = R + E.$$  

We also compare the model results to the one dimensional model (Equation 25 [4]):

$$c_l \frac{dFFM}{dt} + c_f \frac{dF}{dt} = I - E$$

applying the energy expenditure regression model from [4]:

$$E = 238.85(0.14FFM + 0.05F + 1.55),$$

$FFM$ is modeled by the Forbes model with $D$ and $S$ set as the average value from [12] and [54], and the derivative of $FFM$ is determined implicitly on the left hand side of the equation. There are several developed one dimensional models that describe weight change [2, 4–6, 31, 32]. A comparison of a differential equation that uses the Forbes model for $FFM$ to other one dimensional models was conducted previously [20] and shown to outperform in predictive power to other one dimensional models in the steady state case. In our own comparisons, the one dimensional equation (Equation 25 [4]) provided more accurate predictions in the dynamic state than the model in [20], therefore we focus our comparison solely to Equation 25 from [4].
Parameters and baseline values that are dependent on individual data are outlined in a table under each simulation. Table 2 provides the values for all universal parameters used in every simulation.

Table 2. Constants that are universal to all numerical simulations of the differential equation model. *The parameter $a$ is zero for overfeeding simulations.

<table>
<thead>
<tr>
<th>Constant</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$s$</td>
<td>underfeeding: $s = 0.67$</td>
<td>[22, 44, 48, 50]</td>
</tr>
<tr>
<td></td>
<td>overfeeding: $s = 0.56$</td>
<td>[3, 9, 37]</td>
</tr>
<tr>
<td>$c_l, c_f$</td>
<td>$c_l = 1100, c_f = 9500$,</td>
<td>[26, 51]</td>
</tr>
<tr>
<td>$a_M, a_F, p_M, p_F, y_M, y_F$</td>
<td>$a_M = 293, a_F = 248, a_M = 0.4330$</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>$p_F = 0.4356, y_M = 5.92, y_F = 5.09$</td>
<td></td>
</tr>
<tr>
<td>$\omega$</td>
<td>$\omega = 0.075$</td>
<td>[58]</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$\beta = 1.19$: overfeeding, $\beta = 1$: caloric restriction</td>
<td>[20, 37]</td>
</tr>
<tr>
<td>$a^*$</td>
<td>$a = 0.02$</td>
<td>[39]</td>
</tr>
</tbody>
</table>

4.1. Caloric Restriction - CALERIE PHASE I study

The Phase I of the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) trial tested the effects of caloric restriction on biomarkers of longevity [23]. Twelve of the CALERIE subjects were placed on a very low calorie diet of 890 kcal/d (LCD), twelve were placed on a low calorie diet of 25% below baseline energy requirements (CR), and twelve were prescribed a combination of caloric restriction (12.5% below baseline energy requirements) and exercise (physical activity increased to 12.5% above baseline total energy expenditure). Thirty of the subjects were overweight and six of the subjects had a baseline BMI classifying them as obese. The 24 subjects that were reducing their weight solely through caloric restriction (CR and LCD) were used to test the validity of our model.

The metabolic adaptation parameter $a$ was determined by comparing the result of regression formulas for the resting metabolic rate to actual resting metabolic rate in the CALERIE Phase I study [39]. The value of $a$ was not calibrated using the dynamical systems model presented here, nor was it computed using the Livingston-Kohlstadt model and is treated as a universal parameter.

Subject energy intake was determined using the energy balance equation. The value of $R$ was estimated by,

$$R \approx c_l \frac{\Delta F}{\Delta t} + c_f \frac{\Delta F}{\Delta t}$$

where body composition changes were measured by DXA. $E$ was measured using DLW and then $I$ was estimated by computing $R+E$. DXA and DLW measurements were collected for all subjects at 4, 12, and 24 weeks. We restrict our attention to the 24 CR and LCD subjects and remark that the 12 combined caloric restriction and exercise subjects would require an extra measurement determining adherence to the exercise prescription.

In order to estimate actual intake as close as possible to known data, we set intake as a piecewise defined step function

$$I = \begin{cases} (1 - c_4)I_0 & : 0 \leq t \leq 28 \\ (1 - c_{12})I_0 & : 28 < t \leq 84 \\ (1 - c_{24})I_0 & : 84 < t \leq 168 \end{cases}$$
where \( I_0 \) is initial intake and \( c_4, c_{12}, c_{24} \) are the individual subjects measured percent decrease from baseline intake at 4, 12, and 24 weeks respectively. The piecewise definition of \( I \) will result in a continuous solution but not one that is differentiable everywhere. This is because we are guaranteed a unique nonnegative solution for each branch of \( I \) by our existence theorem. The continuation along the same trajectory (feeding the end values as initial data for the next leg) guarantees continuity, however, differentiability does not hold since all 19 subjects presented here varied their intake, thereby changing the slope.

For the sake of comparison, we refer to the model presented here as the Heymsfield model. At 24 weeks of calorie restriction, the Heymsfield model predicts the mean 24 week weight as 73.9 kg versus the actual mean observed weight of 72.6 kg (Table 1). Simulations of the one dimensional model in [4] yield a mean weight of 72.6 kg. Error between each subjects individual final predicted and observed weight at 24 weeks was computed by

\[
\psi_i = |W_{\text{actual},i} - W_{\text{estimate},i}|
\]

where the subscript \( i \) denotes subject number, and \( W_{\text{actual},i} \) represents the measured weight, and \( W_{\text{estimate},i} \) represents the model predicted weight for subject \( i \). We refer to the mean absolute error as the mean of the set of \( \{\psi_i\}_{i=1}^{19} \).

The mean absolute error in predicting individual final weight for the Heymsfield model was 1.8 ± 1.3 kg whereas the one dimensional model (Equation 25 [4]) was 4.5 ± 3.3 kg. The Heymsfield model predicted final body mass consistently with a maximum absolute error of 4.3 kg. Model reliability is also substantiated by the low standard deviation in the mean absolute error for the Heymsfield model. In terms of individual predictions, the one dimensional model (Equation 25 [4]) yielded a maximum absolute error of 12 kg and predictions for 9 subjects produced absolute error over the maximum absolute error held by the Heymsfield model. Individual subject final measured 24 week weight and model predictions for both the Heymsfield model and the one dimensional model (Equation 25 [4]) appear in Figure 2.

Subjects were provided with all food using an infeeding paradigm during the first 12 weeks of the study which appeared to affect the level of adherence to the prescribed restrictions in intake. Direct inspection of individual weight predictions against measured data at 4 weeks, 6 weeks, 12 weeks, and 24 weeks, revealed although the weight loss trend was modeled well by the adherence measurements, the initial drop of weight appeared higher than predicted by the model. Moreover, subjects appeared to adhere at the 24 week measured adherence percentages for a few weeks after infeeding was discontinued.

We surmised that subjects may have been highly compliant during the inception of the study with compliance decreasing over time. To test this assumption, we modeled intake by a piecewise defined step function applying the assumption that subjects were 100% compliant for the first 28 days (represented by the percentage \( c_0 \)), followed by a decrease in intake to the observed adherence numbers \( c_4 \) for \( 28 \leq t \leq 60 \). We then assumed that participants attempted to match their infeeding behavior at home for a few weeks after infeeding was discontinued. This is reflected by a decrease in intake to by the measured percentage \( c_{12} \) for \( 60 < t \leq 100 \). Finally,
Figure 2. The 24-week body mass in kg (y-axis) is plotted for each individual calorie restricted subject (x-axis) for actual CALERIE PHASE I measurements (square), Heymsfield model predictions (solid circle) and one dimensional Chow-Hall model predictions (solid triangle). [23].

Table 4. Baseline information used to simulate model compared to data in [23].

<table>
<thead>
<tr>
<th>Baseline/Parameter</th>
<th>Method Obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMR</td>
<td>Livingston-Kohlstadt</td>
</tr>
<tr>
<td>$A_0$</td>
<td>Provided from study data</td>
</tr>
<tr>
<td>$H$</td>
<td>Provided from study data</td>
</tr>
<tr>
<td>$W'(0)$</td>
<td>Provided from study data</td>
</tr>
<tr>
<td>$F'(0)$</td>
<td>Heymsfield Model; Estimated using NHANES FFM formula [54]</td>
</tr>
<tr>
<td>$F(0)$</td>
<td>1-D Chow-Hall model; Estimated using Forbes model</td>
</tr>
<tr>
<td>$FFM(0)$</td>
<td>Obtained from $W(0)$-$F(0)$</td>
</tr>
<tr>
<td>$c_2, c_3$</td>
<td>Obtained from study data</td>
</tr>
</tbody>
</table>

after 100 days, intake decreased to the adherence percentages measured at 168 days:

$$I = \begin{cases} 
(1 - c_0)I_0 & : 0 \leq t \leq 28 \\
(1 - c_4)I_0 & : 28 < t \leq 60 \\
(1 - c_{12})I_0 & : 60 < t \leq 100 \\
(1 - c_{24})I_0 & : 100 < t \leq 168 
\end{cases}$$

Applying the intake step function, we discover a remarkable fit to the individual observed measurements. The mean absolute error in prediction for the Heymsfield model reduces to $1.5 \pm 1.6$ kg. The one dimensional Chow-Hall model predictions remain relatively similar to the previous case with a mean absolute error of $4.6 \pm 2.7$ kg.

A sample simulation for a single subject describing the impact of each definition of intake (full compliance, adherence data applied, full compliance is temporarily attained followed by the measured adherence values) is depicted in Figure 3.

4.2. The Racette study

To compare the effects of exercise and composition of reduced energy intake, twenty three obese women were assigned to four groups; control, exercise, low carbohy-
drate and low fat. A 12 week weight reduction phase followed a 5-week baseline measurement period. A third phase, where subjects maintained their weight reductions was also conducted, however, for the purposes of model validation we are solely interested in the 12-week weight reduction phase. Total daily energy expenditure was measured at baseline and twelve weeks using doubly labeled water and body composition was determined at baseline and at the end of the weight reduction period using underwater weighing. From these two measurements, we estimate actual intake as \( R + E \) where \( R \) is determined by

\[
R = c_l \Delta FFM/84 + c_f \Delta F/84
\]

and \( E \) is given by DLW measurement at 12 weeks. We restricted our analysis to the 13 subjects who were assigned to the high fat or low carbohydrate diets.

Parameters for model simulations are provided in Table 5 and individual subject results for the observed, Heymsfield model, and one dimensional Chow-Hall model (Equation 25 [4]) appear for each of the 13 subjects in Figure 4. Similar to the CALERIE study, the one dimensional Chow-Hall model predicted mean group results accurately with a mean final weight of 85.3 ± 9.3 kg, however the maximum mean absolute error was 11.1 kg as opposed to the Heymsfield model which yielded maximum absolute error of 4.3 kg. Mean absolute error in prediction for the Heymsfield model was 1.7 ± 1.2 kg and mean absolute error for the one dimensional Chow-Hall model was 2.9 ± 3.0. We again note the low standard deviation in mean absolute error for the Heymsfield model indicating low variance in the error for individual subject predictions.

4.3. Overfeeding

For model validation purposes in the case of overfeeding, we apply overfeeding data from 22 subjects who increased their caloric intake to 1000 kcal/d over baseline requirements for a period of 8 weeks[34, 35]. Similar to the caloric restriction studies, subject compliance was determined using the energy balance equation; namely \( R \) was measured by DXA, \( E \) was measured through DLW and then \( I \) was estimated...
Figure 4. The 12-week body mass in kg (y-axis) is plotted for each individual calorie restricted subject (x-axis) for actual Racette study measurements (square), Heymsfield model predictions (solid circle) and one dimensional Chow-Hall model predictions (solid triangle) [44].

Table 5. Baseline information used to simulate model compared to data in [44].

<table>
<thead>
<tr>
<th>Baseline/Parameter</th>
<th>Method Obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMR</td>
<td>Livingston-Kohlstadt</td>
</tr>
<tr>
<td>$A_0$</td>
<td>Provided from study data</td>
</tr>
<tr>
<td>$H$</td>
<td>Provided from study data</td>
</tr>
<tr>
<td>$W(0)$</td>
<td>Provided from study data</td>
</tr>
<tr>
<td>$F(0)$</td>
<td>Heymsfield Model: Estimated using NHANES $FFM$ formula [54]</td>
</tr>
<tr>
<td>$F'(0)$</td>
<td>1-D Chow-Hall model: Estimated using Forbes model</td>
</tr>
<tr>
<td>$FFM(0)$</td>
<td>Obtained from $W(0)-F(0)$</td>
</tr>
<tr>
<td>$I$</td>
<td>Provided from study data</td>
</tr>
</tbody>
</table>

Table 6. Baseline information used to simulate model compared to data in [34, 35].

<table>
<thead>
<tr>
<th>Baseline/Parameter</th>
<th>Method Obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMR</td>
<td>Livingston-Kohlstadt</td>
</tr>
<tr>
<td>$A_0$</td>
<td>Provided from study data</td>
</tr>
<tr>
<td>$H$</td>
<td>Provided from study data</td>
</tr>
<tr>
<td>$W(0)$</td>
<td>Provided from study data</td>
</tr>
<tr>
<td>$F(0)$</td>
<td>Heymsfield Model: Estimated using NHANES $FFM$ formula [54]</td>
</tr>
<tr>
<td>$F'(0)$</td>
<td>1-D Chow-Hall model: Estimated using Forbes model</td>
</tr>
<tr>
<td>$FFM(0)$</td>
<td>Obtained from $W(0)-F(0)$</td>
</tr>
<tr>
<td>$I$</td>
<td>Used IOM/NAS regression formula (4)</td>
</tr>
</tbody>
</table>

by computing $R + E$. From these measurements, it was determined that subjects were on average 98% compliant to the 1000 kcal/d overfeeding prescription. Input parameters and baseline information appear in Table 6. Results of the simulations show that the Heymsfield model predicts with a mean absolute error of $2.5 \pm 1.6$ kg the actual weight at 8 weeks and the one dimensional Chow-Hall model predicts with a mean absolute error of $5.5 \pm 2.1$ kg.

In summary, the Heymsfield model predictions of weight during weight change had very good agreement with actual measured weights Figure 6. Figure 6 depicts the plot of individual actual final weight from all three studies considered here
Figure 5. The 8-week body mass in kg (y-axis) is plotted for each individual overfed subject (x-axis) for actual measurements (square), Heymsfield model predictions (solid circle) and one dimensional Chow-Hall model predictions (solid triangle) [34, 35].

Figure 6. Final measured body mass in kg (y-axis) plotted against the Heymsfield model predicted body mass in kg (x-axis) for subjects in all three studies. (y-axis) against model predictions.
5. Conclusion

Our previously developed model [55] was modified by coupling the differential equation to the FFM functions of fat mass developed in [54]. The revision results in improved predictions of final individual weight for three weight change studies. Comparison of the model to other one dimensional models demonstrates that the model provides improved predictions of individual final weight for both caloric restriction and overfeeding studies. The model also yields an increase in reliability measured through very low standard deviation of the mean absolute error and a reduction by over 60% in the maximum absolute error.

As part of our efforts to validate the model using data from weight change studies that also collected measurements of subject compliance, it is confirmed that subject dietary adherence to study prescriptions are not guaranteed. Additional challenges presented by our analysis of overfeeding studies indicates a need for more tightly controlled overfeeding studies where baseline data is obtained as close to energy balance as possible, overfeeding is a consistent and constant, and compliance to the prescription is determined.

The model presented here can be applied in a clinical setting by simulating the expected rate of weight change (and final weight) of participants engaging in dieting or overfeeding and comparing to observed weight change. Differences in model predictions and observed weight change identify the need for clinical intervention to foster adherence.

To this date, validation of models of weight change focused on model accuracy for predicting group mean data. In order to apply models in a clinical setting, reliable and valid individual-level predictions are required. Importantly, the model reported herein provides accurate estimates for both group-level and individual-level data, demonstrating the ability to use the model to accurately predict individual patients weight loss and objectively measure adherence to calorie prescriptions.

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