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A Comparison of Obesity Interventions Using Energy Balance Models

Marcella Torres
Virginia Commonwealth University, torresmm@vcu.edu

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

by

Marcella Torres
Master of Science

Director: Angela Reynolds, Associate Professor
Department of Mathematics and Applied Mathematics

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G	stored glycogen	$G(0)$ =0.5 kg
ρ_G	energy density of carbohydrate	0.004 kcal/kg
CI	carbohydrate intake	$CI(t) = 0.6E(t)$ kcal
k_G	calculated constant	$k_G = \frac{CI(0)}{G_{init}^2}$
CI_b	carbohydrate intake at baseline	kcal
G_{init}	glycogen stored at baseline	500 g
$[Na]$	extracellular sodium concentration	3.22 mg/ml
$\Delta[Na]_{diet}$	change in dietary sodium	mg/d
ξ_{Na}	renal sodium excretion	3000 mg/L/d
ξ_{CI}	renal sodium excretion	4000 mg/d
ECF_{init}	extracellular fluid at baseline	kg
AT	adaptive thermogenesis	kcal
τ_{AT}	AT time constant	14 days
β_{AT}	AT parameter	0.14
EI	energy intake	kcal
ΔEI	change in EI from initial input	$\delta = EI(t) - EI(0)$
F	fat mass	kg
L	lean mass	kg
ρ_F	energy density per unit change of fat	9440.7 kcal
ρ_L	energy density per unit change of lean mass	9440.7 kcal
p	energy paritioning function	$p = \frac{C}{C+F}, C = 10.4 \text{ kg} \cdot \frac{\rho_L}{\rho_F}$
TEF	thermic effect of feeding	kcal
δ	energy cost of physical activity	kcal
PAL	physical activity level	dimensionless parameter

Abstract

A COMPARISON OF OBESITY INTERVENTIONS USING ENERGY BALANCE MODELS

By Marcella Torres, Master of Science.

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Virginia Commonwealth University, 2015.

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An energy balance model of human metabolism developed by Hall et al. is extended to compare body composition outcomes among standard and proposed obesity interventions. Standard interventions include a drastic diet or a drastic diet with endurance training. Outcomes for these interventions are typically poor in clinical studies. Proposed interventions include a gradual diet and the addition of resistance training to preserve lean mass and metabolic rate. We see that resistance training, regardless of dietary strategy, achieves these goals. Finally, we observe that the optimal obesity intervention for continued maintenance of a healthy body composition following a diet includes a combination of endurance and resistance training.

Chapter 1

Introduction

Changes in body weight depend on changes in energy intake and energy expenditure. When more energy is consumed as food than is expended in the form of physical work or maintenance of life, the result can be the storage of body fat and, ultimately, obesity. By 2030, over 50% of the US population is expected to be obese, and obesity-attributable disease is projected to rise by 6-8 million cases of diabetes, 5-6.8 million cases of coronary heart disease and stroke, and 0.4-0.5 million cases of cancer [21]. In addition to the human cost, the resulting economic burden is significant, with an estimated 27% of the increase in health-care expenditure between 1987 and 2001 in the US due to increased spending on obese individuals and a predicted doubling of these costs every decade [21].

Developing successful weight loss and weight management strategies is therefore of considerable importance, and mathematical models can predict the outcomes of a variety of obesity interventions such as changes in diet and physical activity. One such dynamic mathematical model of human metabolism was developed by Kevin Hall et al. in [8], and has been validated against clinical weight loss studies of the effects of standard obesity interventions: a low calorie or very low calorie diet sustained for an extended period of time as a stand-alone measure or coupled with endurance training such as jogging. Weight-loss

trajectory output from the model, which closely matches clinical outcomes, predicts an initial steep drop in both body fat and lean mass that gradually approaches equilibrium, or weight maintenance, due to the effect of adaptive thermogenesis. Free-living research subjects typically fail to maintain the predicted maximum of weight loss achieved after 6-8 months, however, and gradually regain weight [8].

An analysis of a wide range of clinical studies suggests that additional interventions can lead to better outcomes. The subject of this thesis is the extension of this model of human metabolism to include the effects of endurance and resistance training on energy partitioning and the use of the extended model to assess the long-term effects of new interventions on body composition over time, including a gradual step decrease in energy intake and various exercise programs.

Chapter 2

Background

The regulation of human metabolism and body weight involve a myriad of complex biological processes, but the whole-body system is ultimately governed by the laws of thermodynamics, making mathematical modeling possible [6]. The law of conservation of energy requires that changes in the body's energy content are due to an imbalance in energy intake and energy expenditure and, since energy is stored in the body as either fat mass or lean mass, it is possible to predict changes in body mass given an energy surplus or deficit [6]. Two such energy-balance models form the basis for the work in this paper, both developed by Hall et al. [7, 8]. The simplified version consists of five differential equations that describe the partitioning of energy stored in the body into fat or lean body mass, adaptive thermogenesis, glycogen storage, and extracellular fluid retention. This chapter provides a summary of the model in Hall et al.

2.1 Glycogen Storage

Carbohydrate consumed in food is stored in the body as glycogen, primarily in the liver and in muscle tissue [10]. Although glycogen dynamics are a complex function of many metabolic processes, glycogen content in the body primarily depends on dietary carbohydrate intake

CI, the first term in Equation (2.1). The glycogen term is quadratic so that carbohydrate intake must be increased three-fold to increase glycogen by a factor of 1.8 [8]. The parameter ρ_G=0.004 kcal/kg, the energy density of carbohydrate, and $k_G = CI_b/G_{init}^2$, where G_{init}=500 g and CI_b is carbohydrate intake at the start of the diet [8].

$$\rho_G \frac{dG}{dt} = CI - k_G G^2 \tag{2.1}$$

2.2 Extracellular Fluid

Extracellular fluid (ECF), or water retained in the body, changes according to dietary sodium intake in Equation (2.2) where $[Na]$ is the extracellular sodium concentration, $\Delta[Na]_{diet}$ is the change in dietary sodium, and $\xi_{[Na]}$ and ξ_{CI} describe the effect of dietary carbohydrate intake on renal sodium excretion [8].

$$\frac{ECF}{dt} = \frac{1}{[Na]}\left(\Delta[Na]_{diet} - \xi_{[Na]}(ECF - ECF_{init}) - \xi_{CI}(1 - \frac{CI}{CI_b})\right) \tag{2.2}$$

2.3 Energy Partitioning

Energy stored in the body is compartmentalized into either lean tissue or fat. Changes in body fat (F) and lean mass (L) depend on energy intake (EI) and energy expenditure (EE) and are modeled in Equations (2.3) and (2.4) [8].

$$\rho_F \frac{dF}{dt} = (1-p)(EI - EE - \rho_G \frac{dG}{dt}) \tag{2.3}$$

$$\rho_L \frac{dL}{dt} = p(EI - EE - \rho_G \frac{dG}{dt}) \tag{2.4}$$

In these equations ρ_F and ρ_L are the energy content per unit change in body fat or lean tissue, respectively, and p is a dimensionless energy partitioning function $p = \frac{C}{C+F}$ with C

a constant [8]. Energy expenditure EE is given by Equation (2.5) where K is a calculated constant, γ_F and γ_L are regression coefficients from models describing the contribution of fat mass and lean mass, respectively, to resting metabolic rate (RMR) [14], and η_F and η_L are the energy expended to change body fat and lean mass.

$$EE = \frac{K + \gamma_F F + \gamma_L L + \delta BW + TEF + AT + (EI - \rho_G \frac{dG}{dt})[p\frac{\eta_L}{\rho_L} + (1-p)\frac{\eta_F}{\rho_F}]}{1 + p\frac{\eta_L}{\rho_L} + (1-p)\frac{\eta_F}{\rho_F}} \tag{2.5}$$

Changes in energy intake result in an immediate change in the energy expended during digestion, with $TEF = \beta_{TEF}\Delta EI$, where $\beta_{TEF} = 0.1$ [8].

Energy expenditure due to physical activity is modeled by in Equation (2.6) as with PAL the physical activity level of the individual, BW current bodyweight, and RMR resting metabolic rate [8].

$$\delta = \frac{[(1-\beta_{TEF})PAL - 1]RMR}{BW} \tag{2.6}$$

RMR was modeled with the Mifflin St. Jeor equation such that

$$RMR = 10 * weight(kg) + 6.25 * height(cm) - 5 * age(y) + 5$$

for males [13].

2.4 Adaptive Thermogenesis

Like friction opposes the movement of a pendulum, adaptive thermogenesis acts in opposition to weight change, bringing energy expenditure into equilibrium with energy intake. In this model, adaptive thermogenesis changes according to perturbations of EI and persists until energy expenditure is equal to energy intake [7]:

$$\tau_{AT}\frac{dAT}{dt} = \beta_{AT}\Delta EI - AT \tag{2.7}$$

where $\beta_{AT} = 0.14$ and $\tau_{AT} = 14$ days, the estimated time constant for the onset of adaptive thermogenesis, is equal to 14 days.

Chapter 3

Adapted Mathematical Model

3.1 Background

Body weight outcomes have traditionally determined the success of an obesity intervention. While body weight is a measure of total mass of the human body including both fat and lean tissue, body *composition* describes the proportion of total mass that is fat versus lean. Fat is stored as adipose tissue in the human body, while lean tissue, also referred to as fat-free mass, is composed of muscle, water, bone, and organs. Fat and lean mass also have differing energy densities, with lean mass weighing more than fat. Two individuals with the same body weight may have vastly different proportions of fat and lean mass. Since obesity is a medical condition defined by an excess of body fat, body composition can provide a measure of obesity whereas body weight may not. Body composition is the outcome of interest here.

3.2 Simplifying Assumptions

The differential equation modeling changes in extracellular fluid, ECF, in response to dietary changes was excluded because $i.$) it does not contribute to fat or lean mass but to total body weight, which is not considered here, $ii.$) dietary sodium intake, which drives

change in ECF, is assumed to depend on carbohydrate intake which is kept constant here and *iii*.) calculations and a review of output of the model in [7] revealed that ECF fluctuates slightly around a baseline according to sodium intake over the time course of weight loss and so can be assumed constant with no effect on model behavior. Units were also converted from joules to calories.

The resting metabolic rate, which is the minimal rate of energy expenditure per unit time while at rest, was calculated in Hall et al. using the Mifflin-St. Jeor equations which depend on age, sex, and height. In this adapted model, RMR was calculated with the Katch-McArdle formula, $RMR = 21.6L + 37$ because it depends only on lean mass [12, p. 266].

3.3 Model Development

The differential equations for glycogen dynamics, energy partitioning, and adaptive thermogenesis were simulated in XPPAUT software [4]. See code in the Appendix. Energy intake was modeled as $EI(t) = EI(0) - 800H(t-1)$ with $H(t-a)$ the Heaviside step function

$$H(t-a) = \begin{cases} 0, & 0 \leq t < a \\ 1, & a \leq t \end{cases} \tag{3.1}$$

which has a value of zero before time $t = a$ and a value of one starting at time $t = a$. The continuous function used to numerically approximate the Heaviside equation in the adapted model is given by

$$h(t-a) = \frac{1}{1 - e^{-20(t-a)}}.$$

This function for energy intake models a diet of 800 kcal beginning on Day 1 and carbohydrate intake $CI(t)$ was assumed to be 60% of $EI(t)$.

Two parameters were calculated such that initially the system is at steady state (weight

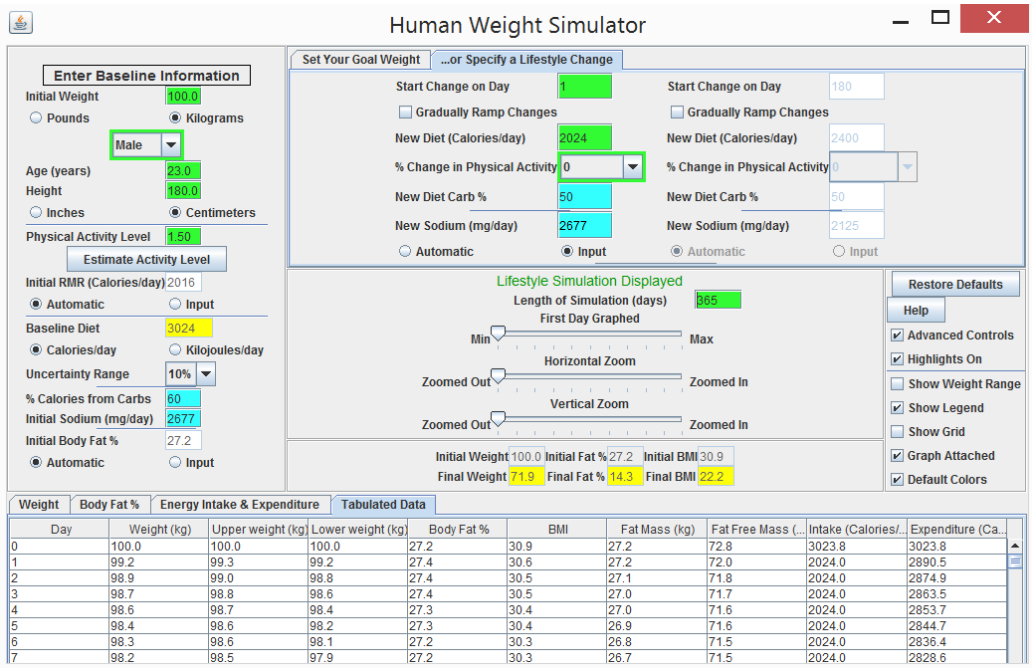

Figure 3.1: **Screenshot of Body Weight Simulator**

maintenance),

$$\frac{dG}{dt} = 0 \Longrightarrow k_G = \frac{CI(0)}{G(0)^2}$$

and

$$EE(0) = EI(0) \Longrightarrow K = EI(0) - \gamma_F F - \gamma_L L - \delta BW.$$

3.4 Validation

The model of Hall et al. has been implemented in Java as a web-based simulation tool shown in Figure 3.1 at http://bwsimulator.niddk.nih.gov/. This provided data output for comparison to the adapted model for validation purposes.

Age, height, weight, and physical activity level were input into the simulator, which generated a baseline diet of 3024 kcal. A lifestyle change was specified to start on Day 1 with a new diet of 2224 kcal. This generated tabular data output including body composition. The same initial conditions were simulated in the adapted model, and output for body

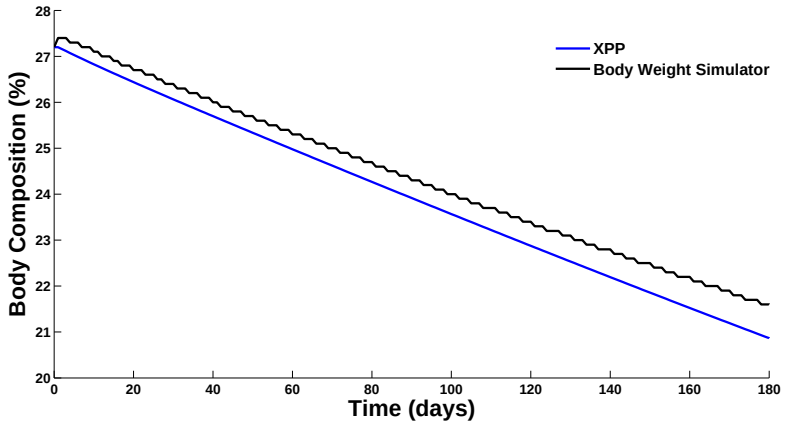

Figure 3.2: **Body Composition Output from Adapted Model versus Body Weight Simulator.** The individual modeled was a 100 kg, 180 cm, 23-year-old sedentary male.

composition was compared. The absence of a model for fluctuations in extracellular fluid in the adapted model that is present in the model of Hall et al. accounts for the relative smoothness of the graph. Given simplifying assumptions in the adapted model, the results were judged to be reasonably close for the time scale over which we wish to examine the effects of weight loss interventions.

Chapter 4

Intervention One: Step Decrease in Energy Intake

4.1 Biological Background

This intervention is a step decrease in energy intake. A periodic step decrease in calories is a technique employed by physique athletes to minimize the effects of adaptive thermogenesis, which rapidly works to brake the initial phase of fast weight loss that occurs with a sudden large drop in energy intake [7]. A second, psychological benefit to the dieter of implementing a step decrease in energy intake as part of an obesity intervention program is that less time overall is spent at a severe calorie deficit, making better adherence to the diet likely.

4.2 Mathematical Model

The Heaviside function in Equation (3.1) was again used in new energy intake function

$$E(t) = EI(0) - 100 \sum_{n=1}^{8} H(t - 1 - 7(n-1)) \tag{4.1}$$

which resulted in eight total decrease decrements of 100 kcal from 3024 kcal to reach the new diet of 2224 kcal as shown in Figure 4.1. In similar fashion, an energy intake function with 29 daily decrements to reach 2224 kcal was written for comparison with the Body Weight Simulator tool [8].

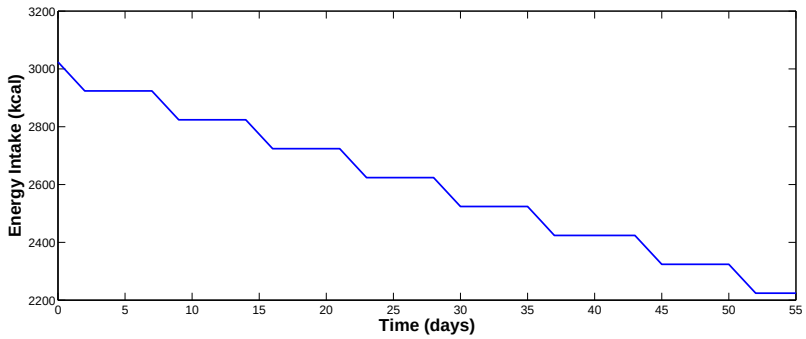

Figure 4.1: **Weekly Step Decrease in Energy Intake.** Energy intake begins at 3024 kcal and decreases weekly by 100 kcal to reach 2224 kcal on Day 51.

4.3 Results

The Body Weight Simulator tool [8] models either a one-time energy intake decrease or a daily step decrease in energy to a specified level and implements a daily decrease in a non-uniform fashion, shown in 4.2. The model of Hall et al. predicts only a slight advantage of <1% body composition to be gained by implementing a one-time initial decrease versus a daily decrement: see Figure 4.3.

Results from the adapted model for a one-time decrease of 800 calories versus a uniform daily or uniform weekly step decrease were compared in Figure 4.4. Similarly to the Body Weight Simulator, there was only a slight <1% lower body composition advantage in a one-time initial decrease of 800 calories versus a gradual decrease.

Adaptive thermogenesis works against weight loss; the calories are negative because AT is being subtracted from total energy expenditure. It is clear from viewing the area between

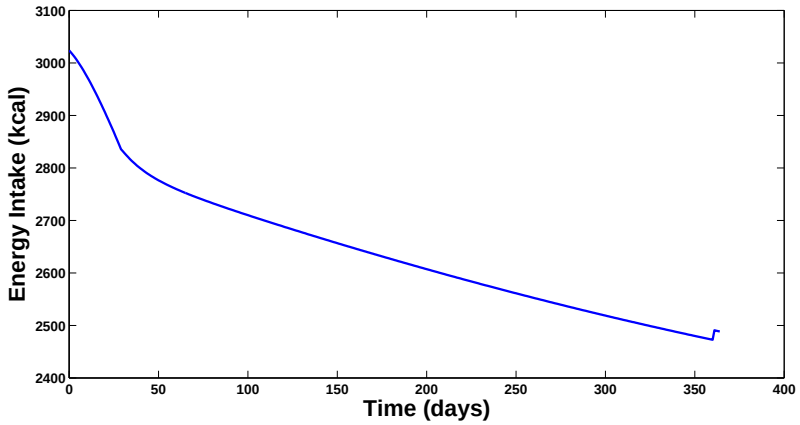

Figure 4.2: **Body Weight Simulator Daily Step Decrease in Energy Intake.** Energy intake at baseline was 3024 kcal with a nonuniform daily decrement to reach a total decrease of 800 kcal on Day 29.

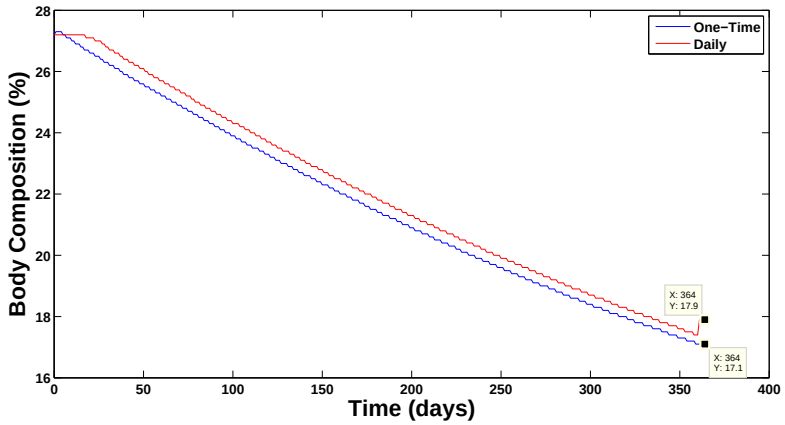

Figure 4.3: **Body Weight Simulator Body Composition Response to Energy Intake Drop, One-Time versus Daily.** The individual modeled was a 100 kg, 180 cm, 23-year-old sedentary male. Energy intake at baseline was 3024 kcal, with either a one-time decrease of 800 kcal on Day One or a daily decrease to reach a total decrease of 800 kcal on Day 29.

the two curves and the x-axis in Figure 4.5 that the total loss of energy expenditure calories is greater for a one-time energy intake decrease, as was expected.

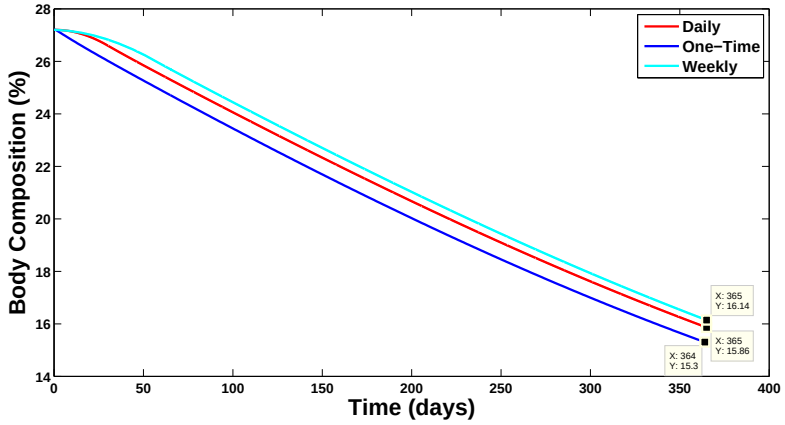

Figure 4.4: **Adapted Model Body Composition Response to Energy Intake Drop.** The individual modeled was a 100 kg, 180 cm, 23-year-old sedentary male. Energy intake at baseline was 3024 kcal, with either a one-time decrease of 800 kcal on Day One, a daily decrease of 27.586 kcal to reach a total decrease of 800 kcal on Day 29, or a weekly decrease of 100 kcal to reach a total decrease of 800 kcal on Day 51.

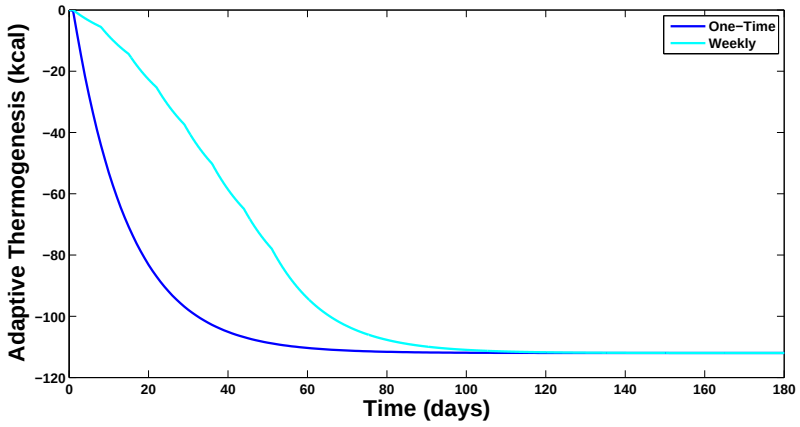

Figure 4.5: **Adapted Model Adaptive Thermogenesis with Energy Intake Decrease One Time versus Weekly.** Area under the curves gives total negative energy expenditure.

Chapter 5

Intervention Two: Physical Activity

5.1 Background

This intervention added resistance training (RT) and endurance training (ET). RT, also called strength training, is a type of anaerobic exercise that uses resistance in the form of weights or body weight to produce muscular contractions which increase muscle size and strength. Anaerobic training increases the quantity and activity of key enzymes controlling glucose catabolism, a type of carbohydrate metabolism [12, p.460]. ET, also called aerobic exercise or cardiovascular training, is exercise that increases endurance by improving the capacity for respiratory control. Examples of ET include running and cycling. Aerobic training increases fat metabolism during rest and sub-maximal exercise and increases carbohydrate metabolism during maximal exercise, and the effects of the latter are greater than from anaerobic training [12, p.460].

5.1.1 Effects of Endurance and Resistance Training on Fat and Lean Mass

While lean mass gained by fit non-dieting individuals varies widely, for untrained individuals on a low calorie (1200 kcal per day) or very low calorie diet (800 kcal per day), lean mass

was found to be at least almost completely preserved with RT. In one study of two groups on a very low calorie diet, the group that performed ET lost an average of 4.1 kg of lean mass over 12 weeks versus only 0.8 kg lost in the RT group [2]. Resting metabolic rate (*RMR*) was also preserved in the RT group in this study, while decreasing significantly for the ET group. Similar results were obtained in [16]: "lean body tissue was almost completely preserved in the exercised group, as the source of energy to meet the energy needs of the dieting individuals was shifted almost entirely to triglyceride utilization". Another study of adults aged 65 and up showed a slight gain in lean mass for a RT group versus a significant loss in the comparison group that performed no exercise at all - both groups were dieting [1].

ET, however, is associated with lean mass loss, even without dieting [9, 16, 20, 23] and, because fat metabolism is also promoted with aerobic exercise, total weight lost is greater than with RT. Success of a weight-loss program has long been judged by total body weight lost rather than improved body composition, which may be the reason that cardiovascular exercise is often the sole type of physical activity in most weight loss intervention programs as it is judged to be more effective by this measure.

However, the addition of energetically expensive lean tissue that results from RT should produce better body composition outcomes, with a lower percentage of body fat and a higher resting metabolic rate. Since cardiovascular exercise during dieting is associated with greater loss of fat at the cost of lean mass while RT is associated with preservation or gain of lean mass[2, 5, 9, 16, 20, 23], a combination of both types of training may achieve an optimal balance of fat loss and lean mass preservation. This possibility was explored here.

5.1.2 ET and Physical Activity Level

Physical activity in the form of cardiovascular exercise causes weight loss primarily through an increase in energy expenditure [8]. Physical activity level (*PAL*) is an indicator of daily

energy expenditure due to physical activity. The *PAL* scale shown in Table 5.1 describes different levels of physical activity and their associated values.

Category	PAL value
Sedentary	1.4
Light (walking 1 time per week)	1.5
Moderate (walking $\geq$ 1 time per week)	1.6
Active (intense sport $>$ 1 time per week)	1.7
Very Active (strenuous sport $\geq$ 3 times per week)	1.9

Table 5.1: *PAL* **Value Scale.** A simple value scale that is used to quantify level of energy expenditure due to physical activity.Values are the same as those used in the Body Weight Simulator from Hall et al.

5.2 Resistance Training and Lean Mass Gain

Strenuous activity in the form of RT triggers a variety of responses in the body, such as hormonal changes, growth factors, and temperature changes that in turn alter the activity of signal transduction pathways that regulate gene expression during muscle growth, causing an increase in muscle mass [18]. While the time course of muscle growth varies among different modes of training and total lean mass gained varies widely among individuals, studies suggest that for less damaging modes of RT, the rate of muscle hypertrophy is most rapid for the initial 6-15 week period following the start of a new RT program, followed by a long, slow decline as the body adapts to the exercise [22].

5.3 Mathematical Model

The effect of cardiovascular exercise on energy expenditure was modeled by varying the value of parameter *PAL* in Equation (2.6). We modeled the lean mass gain in response to RT with the addition of a multiplicative inhibition function to Equation 2.4 resulting in the new

differential equation to model total change in lean mass given by Equation 5.1.

$$\frac{dL}{dt} = p(EI - EE - \rho_G \frac{dG}{dt}) + r \cdot \frac{L^a}{L^a + u^a} \cdot \frac{1}{1 + \left(\frac{L}{d}\right)^b} \tag{5.1}$$

(5.1) This equation consists of a Hill-type term for the growth dynamics, which is inhibited by the lean mass. The inhibition multiplier was used to capture the later decay in growth rate as the body adapts to the training program.

The exponent a controls the steepness of the ascent of the curve and the exponent b controls the steepness of the descent. The parameter u is defined as the level of L at which the Hill term is 1/2. The parameter d is defined as the level of L at which the multiplicative inhibition term is 1/2. While u and d control the dynamics of lean mass gain, the response to dose of RT is controlled by parameter r, with higher frequency, intensity, or volume of training reflected in higher values. These training variables were not considered separately because it has been shown that varying levels of each, combined in a variety of ways, can produce equivalent results [15, 17, 19, 22].

5.4 Results

5.4.1 Validation

Predicted changes in body fat and lean mass gain were compared to experimental data from the STRRIDE AT/RT randomized trial comparing the effects of 8 months of ET, RT, and a combination program including both types of training (CT) on these variables [23]. The close agreement between the model predictions and the data for each group, with parameter values falling within expected ranges, provides some validation of the model.

A comparison of experimental outcomes and predicted outcomes following 8 months of RT only is shown in Table 5.2. Experimental data used for comparison were mean values

of the group with n=44 [23]. Model parameters were set to r=0.0195 kg/day, u=54.92 kg, d=56.5 kg, a=7, and b=8. The r value that produced a predicted change near to the mean was judged reasonable, as several similar studies [3, 9, 11, 20] showed average gains in lean mass of 0.002 to 0.033 kg/day.

Variable	**Baseline (Std. Dev)**	**Experimental Change (Std. Dev)**	**Predicted Change**
Lean Mass (kg)	54.4 (13.3)	1.09 (1.54)	1.105
Fat (kg)	34.3 (9.12)	-0.26 (2.16)	-0.361

Table 5.2: **RT Validation.** Change is from baseline after 8 months of RT. Experimental data includes mean values and standard deviation with n=44 [23]. Model parameters were set to r=0.0195 kg/day, u=54.92 kg, d=56.5 kg, a=7, and b=8.

Similarly, experimental outcomes and predicted outcomes following 8 months of ET only were compared, with results shown in Table 5.3. Experimental data includes mean values and standard deviation with n=38 [23]. Subjects assigned to this group performed an average of 17 minutes per day of cardiovascular activity, which can reasonably be described as a light to moderate activity level. The parameter *PAL* produced a predicted change in fat mass near to the mean experimental value when set to 1.5526, which is in the light-moderate range.

Variable	Baseline (Std. Dev)	Experimental Change (Std. Dev)	Predicted Change
Lean Mass (kg)	53.3 (8.71)	-0.1 (1.22)	-0.511
Fat (kg)	34.7 (7.89)	-1.66 (2.67)	-1.664

Table 5.3: **ET Validation.** Change is from baseline after 8 months of ET. Experimental data includes mean values and standard deviation with n=38 [23]. Model parameter *PAL* was set to 1.5526.

Finally, a comparison of experimental outcomes and predicted outcomes following 8 months of a combined program (CT) is shown in Table 5.4. Experimental data includes mean values and standard deviation with n=37 [23]. Subjects assigned to this group performed an average of 37 minutes per day of combined training, which can reasonably be described as a light to moderate activity level. Model parameters were set to PAL=1.553, r=.01826 kg/day, u=51.6 kg, d=58.4 kg, a=7, and b=8.

Variable	Baseline (Std. Dev)	Experimental Change (Std. Dev)	Predicted Change
Lean Mass (kg)	54 (9.59)	0.81 (1.38)	0.79
Fat (kg)	34.9 (8.92)	-2.44 (2.97)	-2.45

Table 5.4: **CT Validation.** Change is from baseline after 8 months of CT. Experimental data includes mean values and standard deviation with n=37 [23]. Model parameters PAL=1.553, r=.01826 kg/day, u=51.6 kg, d=58.4 kg, a=7, and b=8.

5.4.2 Sensitivity Analysis

The effect of small perturbations in parameters r, u, and d, and PAL on lean and fat mass after a simulated 8-month training period was examined to determine the impact of these changes on model behavior with results shown in Table 5.5. Changes in lean and fat mass after 8 months of training were very small in response to small perturbations in parameters r, u, and d and reasonable for a 10% variation in PAL, therefore the model is not overly sensitive to slight fluctuations in parameter values.

Variable % Change	**Change in Lean Mass (kg)**	**% Change in Lean Mass**	**Change in Fat (kg)**	**% Change in Fat**
r **+ 10**	0.1102	0.2	-.0361	-0.1
r **- 10**	-0.1103	-.2	0.0359	0.1
u**,** d **+ 10**	-0.1617	-0.29	0.0450	0.15
u**,** d **- 10**	-0.1208	-0.22	0.0425	0.13
PAL**+ 10**	-1.331	-2.5	-3.971	-12
PAL**- 10**	1.29	2.3	4.111	12.44

Table 5.5: **Model Sensitivity to Changes in r, u, and d.** Parameters were changed from baseline values r=0.0195, u=57.8, and d=56.5 used for validation against experimental results for RT only, with u and d change in tandem to meet requirement that $u>d$. Parameter PAL was changed from baseline value PAL=1.5526 used for validation against experimental results for RT only.

5.4.3 Comparison of Body Composition Outcomes Among Training Programs

In the next chapter we examine body composition outcomes for an obesity intervention program that include both exercise and diet. It is also interesting to compare outcomes for the same individual with changes in exercise program only. The time-course of change in fat,

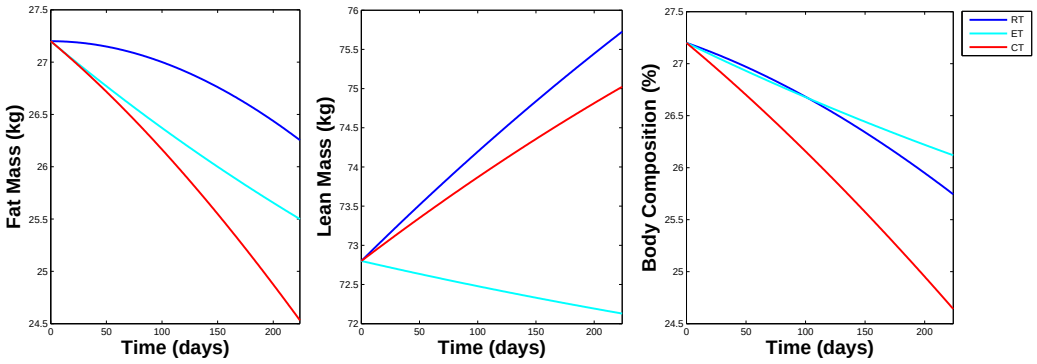

Figure 5.1: **Comparison of Body Composition Time-Course Among Training Programs.** The individual modeled was a 100 kg, 180 cm, 23-year-old male.

lean mass, and body composition for 8 months of simulated RT, ET, and a combined program is compared in Figure 5.1. As expected, fat loss is greater for cardiovascular versus RT, yet more lean mass is lost which, interestingly, results in the worst body composition outcome among the three programs. RT, considered widely to be sub-optimal for fat loss, actually results in the greatest gain in lean mass and a better ultimate body composition than ET. The beneficial effects of lean mass and metabolic rate retention do not become apparent until around 100 days into the diet; prior to that point, ET appears most effective. As metabolic rate begins to slow midway through the diet due to lean mass lost, fat loss slows as well, shown in the inflection of the ET curve in the left graph of Figure 5.1. At this point in the diet, fat loss with RT picks up speed resulting in the reversal of positions of ET and RT in the right graph. Maximum fat loss is ultimately achieved with a combined program because of the higher amount of energetically expensive lean mass and preservation of metabolic rate that results from RT in addition to the energy expended through cardiovascular activity. This makes the combined training program optimal for improving body composition in the long-term.

Chapter 6

Case Study

A low calorie diet is often associated with a significant loss of lean mass and a decrease in resting metabolic rate (*RMR*) and ET, the most commonly used exercise intervention, often only exacerbates the effect [2]. Here we evaluate the relative effectiveness of different dietary approaches and exercise interventions for a single individual with 100 kg total mass and body composition of 27.2% with the ultimate goal of maximizing fat loss while preserving lean mass and metabolic rate.

It was shown in Section 4.3 that a step decrease in energy intake has a slight metabolic benefit that minimizes the difference in body composition outcome versus a one-time initial decrease, with a gradual decrease resulting in only about 0.5-1% greater ultimate body composition. This is negligible given the psychological benefit to the gradual dieter, who will take two months of very gradual progress to achieve a calorie deficit that the drastic dieter will have already endured for that entire period, making it likely that the former approach would lead to greater adherence to the diet. Both strategies are shown in the included figures, as the psychological benefit and improved adherence to a gradual diet is difficult to prove or quantify. The intervention that is clearly beneficial in these comparisons, however, is exercise.

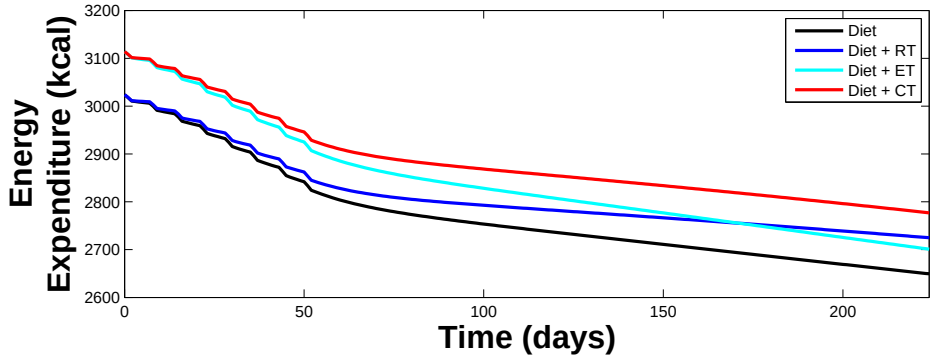

Figure 6.1: **Comparison of Energy Expenditure Time-Course Among Training Programs Coupled with Gradual Diet.** The individual modeled was 100 kg with body composition of 27.2%. Energy intake was initially 3024 kcal and decreased by 100 kcal per week for 8 weeks to reach 2224 kcal.

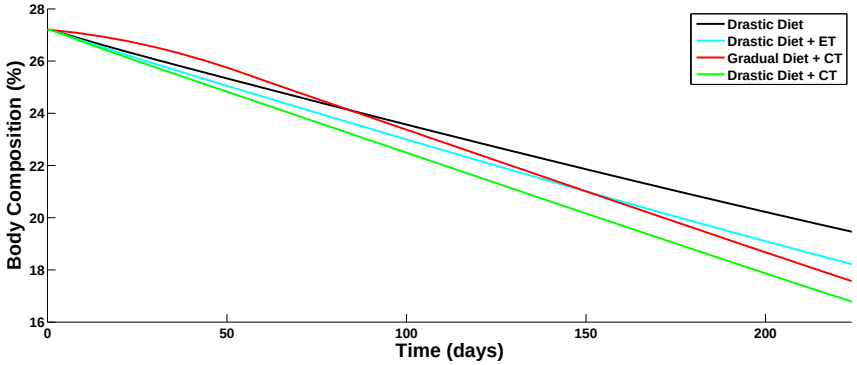

Figure 6.2: **Comparison of Body Composition Among Standard and Proposed Optimal Interventions.** The individual modeled was 100 kg with body composition of 27.2%.

A comparison of daily energy expenditure among diet and diet coupled with RT, ET, or CT shown in Figure 6.1 demonstrates the additional metabolic benefit of including resistance training in an obesity intervention strategy. Diet coupled with either RT or CT both lead to higher energy expenditure in the long term than the two standard clinical interventions of either diet alone or diet with ET. A comparison among body composition outcomes for the two standard interventions of a one-time initial drastic decrease in energy intake, either alone or with ET, and a one-time or gradual decrease with CT, shown in Figure 6.2, demonstrates the relative effectiveness of the addition of RT and ET to either dietary scheme.

It was mentioned earlier that free-living research subjects in clinical studies typically

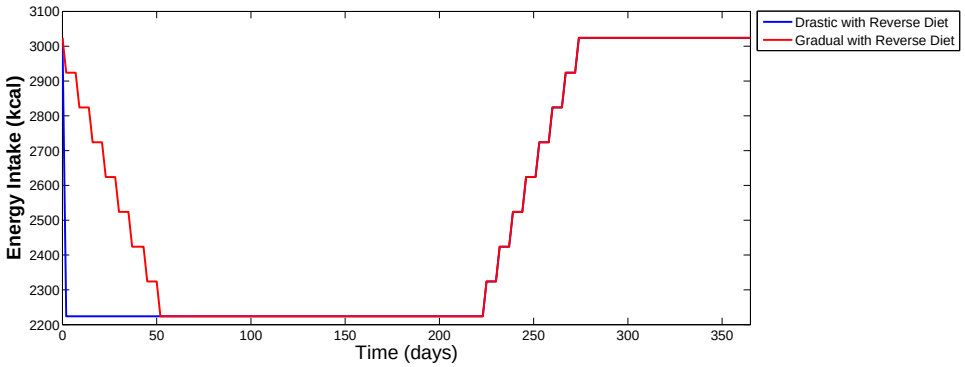

Figure 6.3: **Energy Intake Time-Course Through Maintenance, Diet, and Reverse Diet.** Energy intake decreased from 3024 kcal daily, the initial level required for weight maintenance, to 2224 kcal daily for the diet. Gradual decrease is shown in the blue curve, an initial total decrease is shown in red. Both diets then gradually returned to maintenance level.

fail to maintain the predicted maximum of weight loss achieved after 6-8 months, gradually regaining much of the weight lost[8]. This is because a decreased metabolic rate and a lower level of lean mass at the end of the diet, when the individual begins to increase calories, can often lead to a regain of the fat that has been lost [8] because energy intake is increasing while energy expenditure has decreased. An obesity intervention that is successful in the long-term will preserve as much lean mass and metabolic rate as possible in addition to causing fat loss so that an individual can maintain their improved body composition when normal eating is resumed. Ideally, the exercise program would then continue as part of a healthy lifestyle change.

To simulate a return to a normal diet after 8 months of reduced calories, energy intake was gradually increased up to pre-diet levels. The individual in this case study initially consumed 3024 kcal daily to maintain their weight and then decreased by 800 calories to 2224 kcal daily. Beginning at Day 224, the diet was reversed with an increase of 100 kcal weekly back up to the initial maintenance level of 3024 kcal daily; the time-course of energy intake is shown in Figure 6.3. An obesity intervention followed by a return to normal eating with the healthy lifestyle change of continued exercise was simulated for the case study

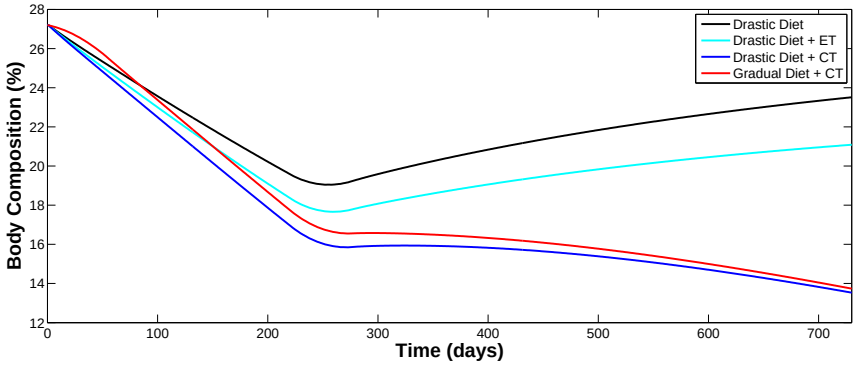

Figure 6.4: **Body Composition Outcomes Following Obesity Interventions.** Energy intake decreased from 3024 kcal daily, the initial level required for weight maintenance, to 2224 kcal daily for the diet, and then gradually returned to maintenance level after 273 days which was then maintained. Exercise interventions continued for the entire period.

individual with: an 8 month diet phase with CT followed by a reverse diet phase and then 15 months of continued CT at energy intake levels that previously led to maintenance of an obese body composition. A comparison of body composition in Figure6.4 shows a striking contrast between predicted results for the standard interventions of either drastic diet or drastic diet and ET and the proposed optimal interventions that include a combination of RT and ET exercise. It is clear that the standard interventions ultimately lead to a return to pre-diet body composition levels, as seen in clinical studies. Whether a gradual or drastic diet is implemented, the addition of a moderate CT program leads to continued improvement in body composition even after resuming an energy intake level that initially maintained an unhealthy body composition. Once a desired body composition is reached, the individual could increase energy intake until energy balance is achieved and the new, healthier body composition is maintained.

Chapter 7

Conclusion

There is a clear need for alternatives to standard obesity interventions that often have poor outcomes. We have extended an energy balance model of human metabolism developed by Kevin Hall et al. to examine the effects of two alternative interventions, a gradual diet and resistance training, on ultimate body composition. A new energy intake function modeling a step decrease in calories consumed was added to simulate a gradual diet and lean mass dependant growth with self inhibition to model lean mass gain in response to resistance training was added to the differential equation modeling change in lean mass to simulate a resistance training program. Predicted outcomes were then validated against experimental data. Finally, full simulations of obesity interventions including diet, exercise, and a return to normal energy intake were compared to determine relative effectiveness in reducing body composition in the long-term.

We observed that there is a slight advantage to a drastic diet versus a gradual diet and that there is a metabolic benefit that results from increased lean mass due to moderate resistance training. This increased energy expenditure appears to eventually exceed energy expended during endurance training, in part due to the loss of lean mass that occurs in response to that activity, which is the standard exercise intervention employed today. A comparison

of two-year outcomes for simulated standard and proposed interventions supports results from clinical studies that a return to normal energy intake causes eventual weight regain following standard interventions, while also indicating that a continued healthy lifestyle change of moderate endurance and resistance training may lead to the maintenance of a new, healthy body composition.

It remains to examine how energy intake decrement size or frequency of decrement may influence the relative effectiveness of a gradual diet as compared to a drastic diet. A closer examination of the effects of endurance training and resistance training on energy expenditure is also needed for further information about optimal amounts of each to include in a combination training program. Additionally, more research on adaptive thermogenesis may ensure accurate representation of long-term behavior in the model so that it is possible to investigate when, if ever, a new stable equilibrium of body composition maintenance is achieved following proposed interventions and at what new higher energy intake level that occurs. These continued efforts can assist in the development of a recommended obesity intervention with a greater likelihood of positive outcomes.

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Appendix A

XPPAUT Code

A.1 Validation Model

```
#Models ONE decrease in calories beginning at day 1
#energy intake functions
  h(t)=1/(1+exp(-20*t))
#One decrease of 100 kcal
  EI(t)=EI0-800*h(t-30)
  CI(t)=.6*EI(t)
#glycogen storage, units in kg
  dG/dt=(CI(t)-k*G^2)/.004
#adaptive thermogenesis, units in kg/day
  dAT/dt=(.14*(EI(t)-EI0)-AT)/14
#thermic effect of feeding, units in kg
  TEF=.1*(EI(t)-EI0)
#energy expenditure
  EE(t)=(E+3.107*F+21.989*L+(.9*PAL-1)*(21.6*L+370)+TEF+AT
```

```
   +(EI(t)-(CI(t)-k*G2^))*((.1073)*(2/(2+F))+
   .018987))/(1+.1073*(2/(2+F))+.018987)
#energy partitioning equations
   dF/dt=(1-2/(2+F))*(EI(t)-EE(t)-(CI(t)-k*G2^))/9440.727
   dL/dt=(2/(2+F))*(EI(t)-EE(t)-(CI(t)-k*G2^))/1816.444
init G=.5,F=27.2,L=72.8
par k=7257.6,EI0=3024,PAL=1.5,E=658.8224
   @ bound=10000, TOTAL=365, METH=stiff
   done
```

A.2 Intervention One Model

```
#Models decrements of 100 calories per week beginning at Day 1
   #energy intake functions
   h(t)=1/(1+exp(-20*t))
# 8 decreases of 100 kcal
   EI(t)=EI0-100*(h(t-1)+h(t-8)+h(t-15)+h(t-22)+h(t-29)+
   h(t-36)+h(t-44)+h(t-51))
   CI(t)=.6*EI(t)
#glycogen storage, units in kg
   dG/dt=(CI(t)-kG*G2^)/.004
#adaptive thermogenesis, units in kg/day
   dAT/dt=(.14*(EI(t)-EI0)-AT)/14
#thermic effect of feeding, units in kg
   TEF=.1*(EI(t)-EI0)
#energy expenditure
```

```
   EE(t)=(K+3.107*F+21.989*L+(.9*PAL-1)*(21.6*L+370)+TEF+AT+
   (EI(t)-(CI(t)-kG*G2^))*((.1073)*(2/(2+F))+
   .018987))/(1+.1073*(2/(2+F))+.018987)
#energy partitioning equations
   dF/dt=(1-2/(2+F))*(EI(t)-EE(t)-(CI(t)-kG*G2^))/9440.727
   dL/dt=(2/(2+F))*(EI(t)-EE(t)-(CI(t)-kG*G2^))/1816.444
init G=.5,F=27.2,L=72.8
par kG=7257.6,EI0=3024,PAL=1.5,K=658.8224
   @ bound=10000, TOTAL=365, METH=stiff
   done
```

A.3 Intervention Two Model

```
#Model used for parameter fitting by comparison to study Effects
of aerobic training and/or resistance training on body mass and
fat mass in overweight or obese adults
#values set to match study mean baseline values for body composition,
energy intake, lean and fat mass
#energy intake functions
   h(t)=1/(1+exp(-20*t)) #no diet EI(t)=EI0
   CI(t)=.4*EI(t)
#glycogen storage, units in kg
   dG/dt=(CI(t)-kG*G2^)/.004
#adaptive thermogenesis, units in kg/day
   dAT/dt=(.14*(EI(t)-EI0)-AT)/14
#thermic effect of feeding, units in kg
```

```
   TEF=.1*(EI(t)-EI0)
#energy expenditure
   EE(t)=(K+3.107*F+21.989*L+(.9*PAL-1)*(21.6*L+370)+TEF+AT+
   (EI(t)-(CI(t)-kG*G2̂))*((.1073)*(2/(2+F))+
   .018987))/(1+.1073*(2/(2+F))+.018987)
#resistance training
#energy partitioning equations
   dF/dt=(1-2/(2+F))*(EI(t)-EE(t)-(CI(t)-kG*G2̂))/9440.727
   dL/dt=(2/(2+F))*(EI(t)-EE(t)-(CI(t)-kG*G2̂))/1816.444+
   r*((Lâ/(Lâ+uâ))*(1/(1+(L/d)b̂)))
init G=.5,F=34.3,L=54.4
par kG=3214.4,EI0=2009,PAL=1.5,K=165.4643,
r=0.0195,u=54.92, d=56.5,a=7,b=8
aux RT=r*((Lâ/(Lâ+uâ))*(1/(1+(L/d)b̂)))
aux BC=F/(F+L)
@ bound=10000, TOTAL=224, METH=stiff, dt=1
done
```

A.4 Case Study Model

```
#Model used to simulate a diet phase followed by a reverse diet
that returned to initial energy intake levels
#energy intake functions
   h(t)=1/(1+exp(-20*t))/par #either drastic or gradual diet could
be selected by commenting out or in energy intake functions
   #drastic:
```

```
  EI(t)=EI0-800*h(t-1)+100*(h(t-224)+h(t-231)+h(t-238)+h(t-245)+
  h(t-252)+h(t-259)+h(t-266)+h(t-273))
  #or gradual:
  EI(t)=EI0-100*(h(t-1)+h(t-8)+h(t-15)+h(t-22)+h(t-29)+h(t-36)+
  h(t-44)+h(t-51))+100*(h(t-224)+ h(t-231)+h(t-238)+h(t-245)+
  h(t-252)+h(t-259)+h(t-266)+h(t-273))
  CI(t)=.4*EI(t)
#glycogen storage, units in kg
  dG/dt=(CI(t)-kG*G^2)/.004
#adaptive thermogenesis, units in kg/day
  dAT/dt=(.14*(EI(t)-EI0)-AT)/14
#thermic effect of feeding, units in kg
  TEF=.1*(EI(t)-EI0)
#energy expenditure
  EE(t)=(K+3.107*F+21.989*L+(.9*PAL-1)*(21.6*L+370)+TEF+AT+
  (EI(t)-(CI(t)-kG*G^2))*((.1073)*(2/(2+F))+
  .018987))/(1+.1073*(2/(2+F))+.018987)
#resistance training
#energy partitioning equations
  dF/dt=(1-2/(2+F))*(EI(t)-EE(t)-(CI(t)-kG*G^2))/9440.727
  dL/dt=(2/(2+F))*(EI(t)-EE(t)-(CI(t)-kG*G^2))/1816.444+
  r*((La^/(La^+ua^))*(1/(1+(L/d)^b^)))
init G=.5,F=34.3,L=54.4
par kG=3214.4,EI0=2009,PAL=1.5,K=165.4643,
r=0.0195,u=54.92, d=56.5,a=7,b=8
aux BC=F/(F+L)
```

```
aux INTAKE=EI0-800*h(t-1)+100*(h(t-224)+h(t-231)+h(t-238)+h(t-245)+
   h(t-252)+h(t-259)+h(t-266)+h(t-273))
   #for drastic diet, or EI(t) for gradual diet @ bound=10000,
TOTAL=224, METH=stiff, dt=1
done
```

Vita

Marcella Torres was born on October 27, 1981 in Omaha, Nebraska and is a United States citizen. She is married to Derek Tresize with whom she has two children and with whom she co-owns a personal training, fitness coaching, and nutrition counseling business in Richmond, Virginia and with whom she has co-authored a guide to nutrition and fitness training for bodybuilding competitions.

Marcella earned a Bachelor of Science in Mathematical Sciences with a concentration in Applied Mathematics and a minor in Physics from Virginia Commonwealth University in 2007. While an undergraduate, Marcella was a member of the University Honors program, served as president of the Society of Physics Students, was a member of Sigma Pi Sigma Physics Honor Society, received two National Science Foundation Scholarships and a Bijan K. Rao Department of Physics scholarship for the highest GPA in the department, and completed a summer research fellowship in medical physics at the Medical College of Virginia before graduating Magna Cum Laude. She also worked as a math tutor and teaching assistant throughout this period, and as a research assistant in the solid state physics laboratory of Dr. Alison Baski from 2005 to 2007.

Following her undergraduate degree, Marcella worked full time as an actuarial associate for three years, passing three actuarial examinations in probability theory, financial mathematics, and mathematical economics before entering graduate school.While pursuing her Master of Science degree in Applied Mathematics, she taught several sections of college

algebra and worked as a large lecture teaching assistant in multivariate calculus.