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ORIGINAL ARTICLE

A mathematical model of the effects of resistance exercise-induced muscle hypertrophy on body composition

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Abstract

Purpose Current diet and exercise methods used to maintain or improve body composition often have poor long-term outcomes. We hypothesize that resistance exercise (RE) should aid in the maintenance of a healthy body composition by preserving lean mass (LM) and metabolic rate.

Method We extended a previously developed energy balance model of human metabolism to include muscle hypertrophy in response to RE. We first fit model parameters to a hypothetical individual to simulate an RE program and then compared the effects of a hypocaloric diet only to the diet with either cardiovascular exercise (CE) or RE. We then simulated a cohort of individuals with different responses to RE by varying the parameters controlling it using Latin Hypercube Sampling (LHS). Finally, we fit the model to mean data from an elderly population on an RE program.

Conclusion The model is able to reproduce the time course of change in LM in response to RE and can be used to generate a simulated cohort for in silico clinical studies. Simulations suggest that the additional LM generated by RE may shift the body composition to a healthier state.

Keywords Resistance exercise · Dieting · Weight loss · Muscle hypertrophy · Lean mass · Mathematical model

Abbreviations

CE	Cardiovascular exercise
LHS	Latin hypercube sampling
LM	Lean mass
PAL	Physical activity level
RE	Resistance exercise

Introduction

Health complications such as obesity, cardiovascular disease, stroke, and diabetes are in part attributable to the disproportionate allocation of body mass to adipose tissue versus lean body mass. The focus, however, is often on how to reduce body fat rather than on how to increase the lean component of body mass. Obesity interventions in particular tend to focus on reducing overall body weight by reducing energy intake or by increasing energy expenditure through CE. A typical response to these interventions is an initial loss of both FM and LM, with free-living research subjects typically failing to maintain the predicted maximum of weight loss achieved after 6–8 months, gradually regaining weight (Corral et al. 2011; Hall et al. 2011; Shai and Stampfer 2008; Ulen et al. 2008). While physical activity has been shown to aid in long-term weight maintenance (Wing and Phelan 2005), type of activity could be an important consideration, especially for sarcopenic populations. Sarcopenia, the loss of muscle mass and strength that can occur with aging, is implicated in a variety of health issues among the elderly from fractures to increased risk of cardiovascular disease and prediabetes (Scott and Hirani 2016; Srikanthan and Karlamangla 2011). Since RE has been shown to preserve

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LM (Avila et al. 2010; Bryner et al. 1999; Geliebter et al. 1997; Ho et al. 2012; Pavlou et al. 1985; Sanal et al. 2013; Willis et al. 2012) while CE is associated with loss of LM (Ho et al. 2012; Pavlou et al. 1985; Sanal et al. 2013; Willis et al. 2012), it deserves consideration as an ideal type of exercise to improve body composition, especially when combined with a hypocaloric diet or CE.

Here, we extend a mathematical model of human metabolism to include the effects of RE to investigate the impact of this activity on long-term body composition, both alone and when combined with a hypocaloric diet. Many energy balance models of body mass change have evolved over the preceding decades (Alpert 1979, 1990, 2005; Antonetti 1973; Chow and Hall 2008; Christiansen and Garby 2002; Flatt 2004; Hall 2010a; Hall and Jordan 2008; Hall et al. 2007, 2011; Kozusko 2001; Livingston et al. 2001; Navarro-Barrientos et al. 2011; Payne and Dugdale 1977; Song and Thomas 2007; Thomas et al. 2011; Westerterp et al. 1995); and some of these specifically investigate the effects of modulating physical activity level (Christiansen and Garby 2002; Navarro-Barrientos et al. 2011; Thomas et al. 2011; Westerterp et al. 1995). However, in each of these models physical activity is defined as a body weight or BMI-dependent source of additional energy expenditure that is solely a component of total energy expenditure. The production of significant additional LM is unique to RE type physical activity, and the effects of this have not yet been investigated with mathematical modeling. Our simulations support what has been shown clinically that additional LM generated via RE may shift the body composition set point to a healthier state.

We first use this model to conduct a simulated case study comparing the long-term outcomes of a hypocaloric diet alone, dieting with CE, and dieting with RE for a hypothetical individual. We then simulate a cohort of individuals with varying responses to RE. Finally, to further validate the model and its general applicability, we use parameter estimation methods to fit data from an RE study in elderly subjects and perform statistical analyses to evaluate biological feasibility of model results.

Methods

Model background

The regulation of human metabolism and body weight involves a myriad of complex biological processes, but the whole-body system is ultimately governed by the laws of thermodynamics, making mathematical modeling possible. 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 FM or LM, it is possible to predict changes in body mass given an energy surplus or deficit (Hall 2010b). Such an energy-balance model, developed by Hall et al. (Hall 2010a; Hall et al. 2011), consists of five differential equations that describe the storage of glycogen from ingested carbohydrate (Eq. 1), extracellular fluid retention (Eq. 2), adaptive thermogenesis (Eq. 3), and the partitioning of energy stored in the body into FM (Eq. 4) or LM (Eq. 5). These differential equations depend on energy expenditure (Eq. 6) and energy expenditure due to physical activity (Eq. 7). A description of the terms in each equation appears in Appendix A in supplementary material and in the Supplementary webappendix of the original work (Hall 2010a).

$$\rho_G \frac{dG}{dt} = CI - k_G G^2 \tag{1}$$

$$\frac{dECF}{dt} = \frac{1}{[Na]}\left([Na]_{\text{diet}} - \xi_{[Na]}(ECF - ECF_{\text{init}}) - \xi_{CI}\left(1 - \frac{CI}{\text{CI}_b}\right)\right) \tag{2}$$

$$\tau_{AT} \frac{dAT}{dt} = \beta_{AT} \Delta EI - AT \tag{3}$$

$$\rho_F \frac{dF}{dt} = (1-p)\left(EI - EE - \rho_G \frac{dG}{dt}\right) \tag{4}$$

$$\rho_L \frac{dL}{dt} = p\left(EI - EE - \rho_G \frac{dG}{dt}\right) \tag{5}$$

$$EE = \left(K + \gamma_F F + \gamma_L L + \delta BW + TEF + AT + \left(EI - \rho_G \frac{dG}{dt}\right)\left[p\frac{\eta_L}{\rho_L} + (1-p)\frac{\eta_F}{\rho_F}\right]\right) \Big/ \left(1 + p\frac{\eta_L}{\rho_L} + (1-p)\frac{\eta_F}{\rho_F}\right) \tag{6}$$

$$\delta = ([(1-\beta_{TEF})PAL - 1]RMR)/BW \tag{7}$$

Weight-loss trajectory output from this model, which closely matches clinical outcomes, predicts an initial steep drop in both FM and LM, variables F and L, in response to dieting that gradually approaches equilibrium, or weight maintenance, due to the effect of adaptive thermogenesis (AT) which is modeled by Eq. 3 (Hall et al. 2011).

Model development

To model RE-mediated muscle hypertrophy, we have added a term to Eq. 5 resulting in the new differential equation to model change in LM, **less extracellular fluid**, given by Eq. 8.

$$\frac{dL}{dt} = p\left(EI - EE - \rho_G \frac{dG}{dt}\right) + r\frac{L^\alpha}{L^\alpha + H_1^\alpha}\frac{1}{1 + \left(\frac{L}{H_2}\right)^\beta} \tag{8}$$

This term consists of a Hill-type factor for the growth dynamics, which is inhibited by the amount of LM accumulated. The inhibition multiplier was used to capture the later decay in growth rate as the body adapts to the training program.

While the time course of muscle growth varies among different modes of training and total LM gained varies widely among individuals (Hubal et al. 2005; Petrella et al. 2008), studies suggest that for less damaging modes of RE, the rate of muscle hypertrophy is most rapid for the initial 6–15 week periods following the start of a new RE program, followed by a long, slow decline as the body adapts to the exercise (Wernbom et al. 2007). The functional form of Eq. 8 captures these dynamics, as shown in Fig. 1 with the rate of LM gain slowing and eventually decreasing towards zero as it accumulates for a hypothetical individual who has 58 kg of LM before beginning a simulated RE program.

The parameters in the muscle hypertrophy term are not directly measurable, but can be interpreted both mathematically and physiologically. Since r is a scaling parameter, it can be considered the response to dose of RE, where higher frequency, intensity, or volume of training are reflected in higher values of r. The exponent α controls the steepness of the ascent of the curve shown in Fig. 1, or the speed of response to training. Parameter H_1 is defined as the level of LM at which the Hill-type factor is 1/2 and also controls speed of initial response; thus, parameters α and H_1 can be modulated to simulate fast or slow responders. Parameter H_2 is defined as the level of LM at which the multiplicative inhibition factor is 1/2. This parameter plays a large role in magnitude of response and can be considered representative of genetic potential for hypertrophy in response to training. The exponent β controls the steepness of the descent of the curve shown in Fig. 1a, and can be thought of as controlling speed of adaptation to training. By varying these parameters, the predicted time course and magnitude of muscle hypertrophy in response to RE can be modulated to fit data or otherwise conform to physiological expectations. A comparison of model predictions achieved by varying parameters for the same hypothetical individual, with initial conditions corresponding to those of the average US male aged 20–39 years from NHANES 1999–2004 (Borrud et al. 2010), is shown in Fig. 1b. Further modulating the effectiveness of RE is the level of LM as shown in Fig. 1a for the same individual.

To explicitly model changes in total lean body mass including extracellular fluid fluctuations due to changes in dietary sodium and carbohydrate intake, we have added an additional variable, LBM, given by Eq. 9.

$$\frac{dLBM}{dt} = \frac{dL}{dt} + \frac{dECF}{dt} \tag{9}$$

In the absence of dietary changes, $dECF/dt = 0$ and Eq. 9 reduces to Eq. 8. Changes in energy intake or dietary sodium will result in a rapid change in extracellular fluid storage that

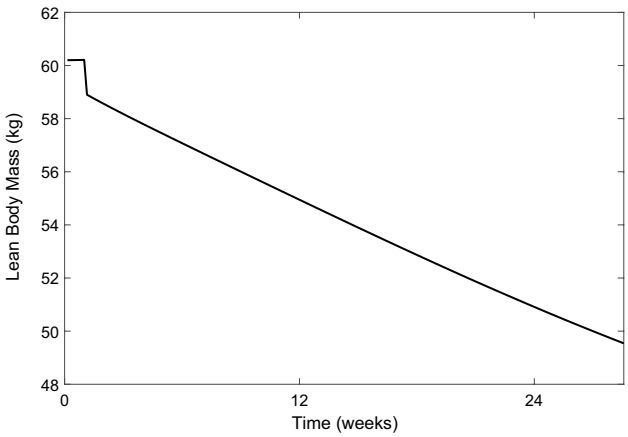

Fig. 2 Effect of an 800 kcal/day decrease in energy intake on total lean body mass

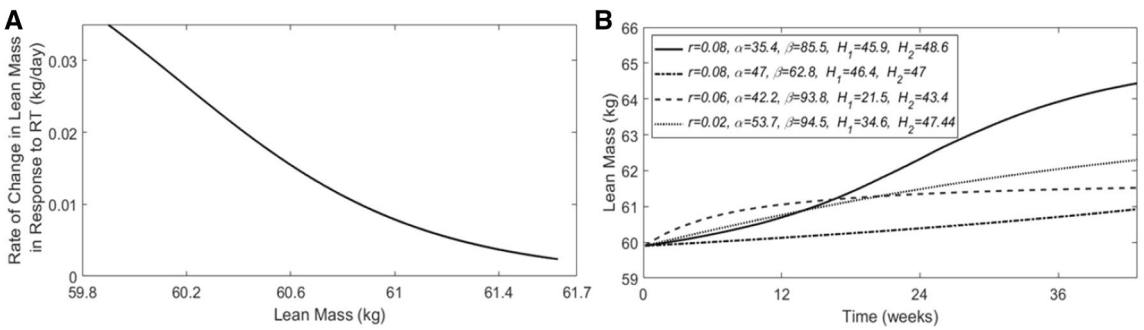

Fig. 1 Model behavior and predictions for initial body measurements corresponding to the average US male (Borrud et al. 2010) performing RE with varying parameter values and energy intakes **a** Daily change in LM in response to RE is plotted against total LM. As LM accumulates the rate of increase slows and approaches zero. **b** Predicted time course of accumulation of LM in response to RE is plotted for different sets of parameter values shown in the legend. Physical activity level, PAL, was set to 1.6 for each simulation in order to compare the effects of varying parameters in the muscle hypertrophy term in Eq. 8

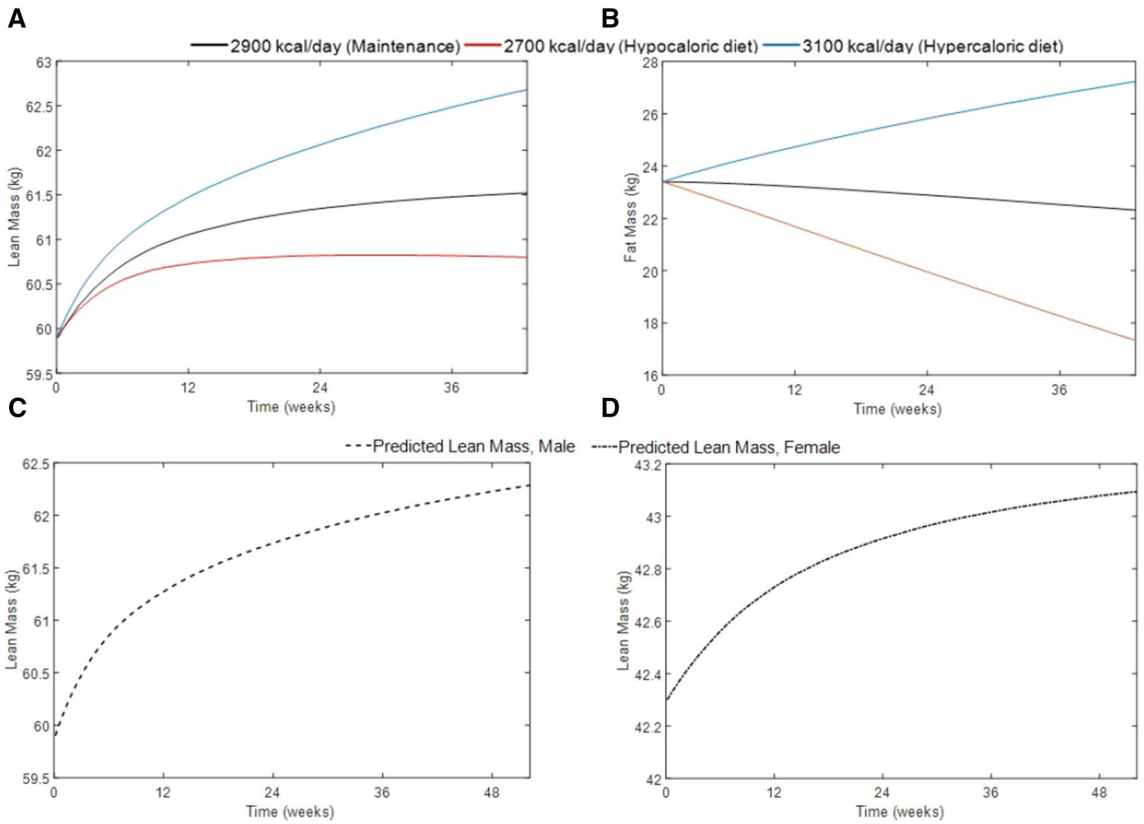

Fig. 3 Effects of initial conditions on model predictions. Initial conditions and parameters used to generate simulations in **a**–**d** are shown in Table 1. **a** A comparison of predicted LM in response to RE for the same parameter set and varying energy intakes: maintenance, a hypocaloric diet, and a hypercaloric diet. Initial body measurements used to generate simulations correspond to those of an average US male aged 20–39 years from NHANES 1999–2004 (Borrud et al. 2010). **b** Predicted FM is compared for the same conditions as in **a**. **c** Predicted LM in response to RE for the average US male on a maintenance energy intake (shown in **a**). **d** Predicted LM in response to RE for an average US female aged 20–39 years from NHANES 1999-*2004 (Borrud et al. 2010)

will shift the predictive curve for LBM up or down slightly as shown in Fig. 2. When dietary changes are modeled here, it is total lean body mass that is shown.

Energy intake will also influence predicted changes in body mass, as shown in the upper panel of Fig. 3 which compares the effects of varying energy intake for the same hypothetical individual and the same model parameters. A hypercaloric diet is predicted to allow for energy storage in both the lean and fat compartments of body mass.Under a hypocaloric diet muscle, hypertrophy is predicted to be inhibited, which is consistent with experimental results (Ballor et al. 1988; Bouchard et al. 2009; Nicklas et al. 2015), and FM is predicted to decrease. Continued maintenance energy intake is predicted to allow for a modest increase in LM at a slight expense of FM. Since energy intake may be an important determinant of muscle hypertrophy in response to RE (Ballor et al. 1988; Bouchard et al. 2009; Nicklas et al. 2015), any uncertainty in the estimation of initial energy intake will influence model predictions.

At this stage of development, the model does not explicitly account for differences in gender or age; however, differences in initial conditions between these groups are accounted for and may lead to different parameter sets that are group-specific. For example, women tend to have lower body mass and a higher percentage of body fat than males; therefore, parameters that produce physiologically

Table 1 Comparison of initial conditions and parameter values for an average US male versus female aged 20–39 years (Borrud et al. 2010)

	LM (kg)	FM (kg)	Fat %	PAL	r	α	β	H_1	H_2
Male	59.9	23.4	28.1	1.6	0.06	42.2	93.8	21.5	43.4
Female	42.3	28.9	40.6	1.6	0.02	32.1	86.2	25.2	28

reasonable behavior for these relative body measurements will not be the same as for males. Figure 3c, d compares model predictions for an average US male versus an average US female aged 20–39 and the parameter values that generated these predictions are compared in Table 1.

The effect of cardiovascular exercise on energy expenditure was modeled by varying the value of parameter PAL (physical activity level) in Eq. 7 as in Hall et al. (2011). LM has consistently been shown to be the best single predictor of RMR (Cunningham 1991; Johnstone et al. 2005; Mifflin et al. 1990) and, given that LM is likely to change with RE, we chose to model the resting metabolic rate (RMR) with LM-dependent predictive equation RMR = 21.6LM +370 (Cunningham 1991) versus the Mifflin-St.Jeor equations used in Hall et al. (Hall et al. 2011) which depend on age, sex, and height. If RMR is known, it can be treated as a model input, otherwise its estimation will effect model predictions and associated uncertainty can be considered a model limitation. A comparison of predicted change in LM for two different RMR estimations is shown in Fig. 4 for an average US male with initial conditions and parameters given in Table 1.

Mathematical models of biological phenomena such as this also need to be evaluated for robustness. To do this, we need to determine sensitivity of outcomes to perturbations in these parameters, which parameters are most responsible for which outcomes, whether outcomes for a given range of parameter values can be deemed biologically feasible, and if variation of parameters produces expected results. To answer these questions, we combined the uncertainty analysis (sampling using LHS) employed in Section "Simulation of a cohort of study subjects on an RE program"

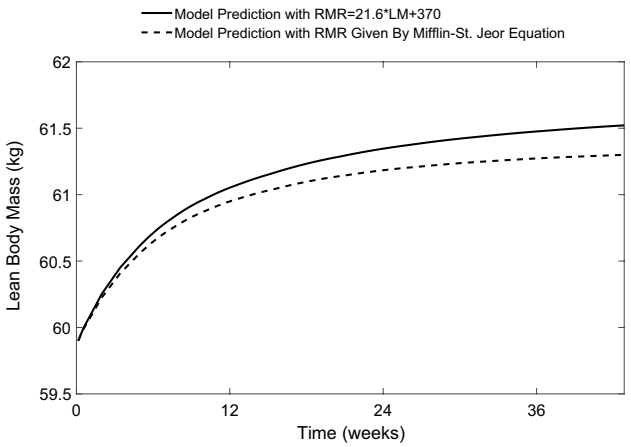

Fig. 4 Comparison of predicted change in LM using predictive equation RMR = 21.6 × LM + 370 (Cunningham 1991) versus Mifflin-St. Jeor equation RMR = 9.99 × Weight + 6.25 × Height − 4.92 × Age+ 166 × Sex(Male = 1, Female = 0) − 161. Initial conditions and parameters used to generate these simulations are the male values given in Table 1

first with sensitivity analysis and then with classification and regression tree methods (CART). Partial rank correlation coefficient results from our sensitivity analysis showed that each parameter in the model has a significant effect on predicted LM, and that correlations between each parameter and predicted LM are consistent with our expectations. A full description of our methodology and results appears in Appendix A in supplementary material. CART methods provide some further insight into how different combinations of parameter values can lead to similar outcomes, which can both guide parameter selection for experiments and also allow us to evaluate biological feasibility. This analysis with accompanying tree diagram is included in Appendix A in supplementary material.

Results

We first fit parameters to an individual in a case study to view results for a simulated RE program and determine whether model dynamics capture expected behavior. We then explore the role of the muscle hypertrophy term in Eq. 8 by varying the parameters controlling it using LHS as seen in (Marino et al. 2008; McKay 1992). LHS is a stratified sampling without replacement method in which each parameter is independently sampled from a statistical distribution in order to create a collection of parameter sets that can each be used to generate model output, thus simulating a variety of responses. This was done both to simulate how an RE program might affect a cohort of individuals and to simulate the variability in response to RE that is seen clinically. Parameter ranges shown in Table 3 were divided into 100 subintervals of a uniform distribution with each subinterval sampled exactly once so that the entire parameter range, including extreme values, was explored. Each combination of six independently sampled parameters is then grouped into a parameter set that is used to generate model output, creating 100 simulated responses to RE for the same initial conditions.

Experiment comparing the effects of a hypocaloric diet only to diet with CE or RE

A hypothetical individual is considered, weighing 100 kg with 27.2% body fat and with a maintenance energy intake level of 3024 kcal/day. Initial conditions and model constants specific to this individual are shown in Table 2 and, while gender is not explicitly modeled, these initial conditions of 100 kg body weight and 72.8 kg LM are more representative of male characteristics. Parameters were selected that produced a moderate response in LM to RE for this individual of about 3 kg gained in one year while in energy balance, consistent with the projected average gain seen

Table 2 Model inputs for experiment comparing the effects of a hypocaloric diet only to diet with CE or RE. Initial conditions are specific to a hypothetical individual weighing 100 kg with 27.2% body fat. Parameters appear in Eq. 8 and were chosen such that a modest LM gain in response to RE was simulated

Name	Description	Value
LM_0	Initial LM	72.8
FM_0	Initial FM	27.2
K	Energy balance constant in Eq. 6	658.8224
k_G	Glycogen constant in Eq. 1	7257.6
PAL	Parameter	1.5
r	Parameter	0.25
α	Parameter	9
β	Parameter	77
H_1	Parameter	66
H_2	Parameter	74

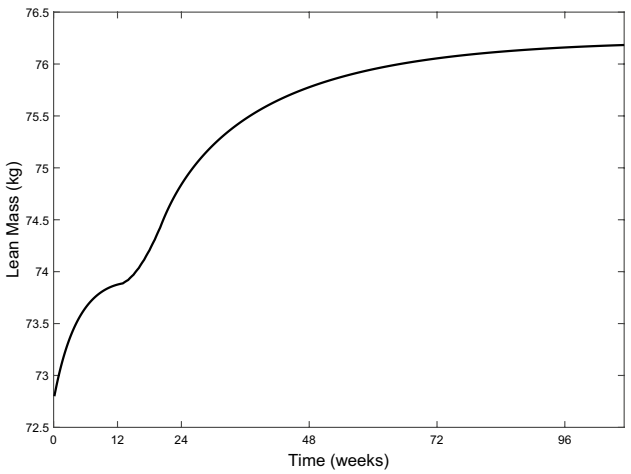

Fig. 5 Change in LM over time in response to RE for a 100 kg individual with 27.2% body fat and a maintenance energy intake of 3024 kcal/day, with a hypocaloric diet consisting of an 800 kcal/day deficit was begun on Day 1 and maintained for 12 weeks followed by a gradual return to 3024 kcal/day over 8 weeks. Parameter values: PAL =1.5, $r = 0.25$, $\alpha = 9$, $\beta = 77$, $H_1 = 66$, $H_2 = 74$

in clinical studies with shorter time periods (Churchward-Venne et al. 2015; Dolezal and Potteiger 1998; Ho et al. 2012; Lo et al. 2011; Stout et al. 2013; Willis et al. 2012; Wilson et al. 2014). Parameter values are listed in Table 2 and the resulting predicted time course of change in LM in response to RE is shown in Fig. 5.

For this hypothetical individual, we simulated a hypocaloric diet consisting of an 800 kcal/day deficit maintained for 12 weeks followed by a gradual return to a pre-diet level of 3024 kcal/day over an 8-week period. This scenario was chosen because it has been shown in clinical studies that subjects on a hypocaloric diet will eventually return to pre-diet energy intake levels (Corral et al. 2011; Saris 2001; Shai and Stampfer 2008; Ulen et al. 2008).

We then compared the effects of a hypocaloric diet with no exercise to the effects of this diet when combined with an ongoing healthy lifestyle change of either CE or RE. The addition of CE was modeled as an increase in PAL that remained constant for the entire time period, simulating light activity such as jogging performed several times per week on an ongoing basis. The addition of RE was modeled with the parameter values shown in Table 2 that produced the accumulation of LM over time shown in Fig. 5. Predicted long-term, three-year body composition outcomes for each of the three scenarios are shown in Fig. 6.

This simulation predicts that a temporary hypocaloric diet will result in an eventual return to the pre-diet body composition, as was predicted in Hall et al. (Hall et al. 2011) and which is supported by clinical study outcomes. The boost in physical activity level that results from continued CE appears to result in maintenance of a lower body composition. The greatest predicted change results from continued RE and its accompanying increase in LM, with a body composition trajectory that continues to decrease. These predictions depend on clamped energy intake after 20 weeks.

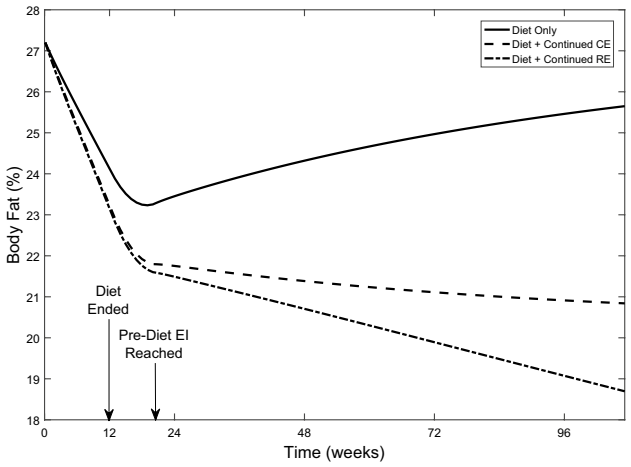

Fig. 6 A comparison of diet and exercise interventions for a 100 kg hypothetical individual with 27.2% body fat and a maintenance energy intake of 3024 kcal/day. In each scenario, a hypocaloric diet consisting of an 800 kcal/day deficit was begun on Day 1 and maintained for 12 weeks followed by a gradual return to 3024 kcal/day over 8 weeks. Diet Only has PAL = 1.5, appropriate for a sedentary individual. Cardiovascular exercise was modeled with an increase in PAL to 1.6, approximating light activity such as several short duration jogs per week. RE was modeled with parameter values PAL=1.5, $r = 0.25$, $\alpha = 9$, $\beta = 77$, $H_1 = 66$, $H_2 = 74$

Simulation of a cohort of study subjects on an RE program

Individual response to RE is known to vary widely among individuals (Leenders et al. 2013; Petrella et al. 2008), with high, low, slow, or fast response to training stimulus possible. To capture physiologically reasonable variation in response to RE, we simulated a cohort of 100 hypothetical individuals with the same initial conditions given in Table 2, yet different responses to RE that were simulated by allowing parameters to vary. This was done using LHS. Parameter ranges sampled from, shown in Table 3, were restricted to ranges that produced physiologically reasonable results for these initial conditions. Statistics calculated on results for the full cohort are shown in Table 4.

A typical clinical study differs from this simulated cohort in that both responses *and* initial conditions vary between individuals. However, it is still possible to evaluate reasonableness of the statistics and mean behavior for this simulated cohort by comparing results to clinical study results for a variety of populations. For example, the mean values for absolute gain in LM and loss of FM seen for our simulated cohort in Table 4 are comparable to results from studies of the effects of RE on young, elderly, or obese individuals (Dolezal and Potteiger 1998; Ho et al. 2012; Lo et al. 2011; Willis et al. 2012). More significantly, a key aspect of the physiology of LM gain that was described in Section "Model development" is reproduced: a rapid initial increase that occurs over approximately the first 12 weeks followed by a greatly reduced response over the following 12 weeks as the simulated cohort adapts to the RE program.

Statistics calculated on our simulated cohort shown in Table 4 highlight this qualitative behavior, since mean gain of LM over the second twelve week period versus the first twelve week period decreased by 66.4%, a similar decrease to what is seen clinically over a period of 24 weeks (Churchward-Venne et al. 2015; Leenders et al. 2013). The mean of the transients for over time of the full cohort was calculated by averaging the values for LM and FM, respectively, at each time point. Figure 7 shows the time course of LM change for all 100 simulated individuals in the cohort, while Fig. 8 displays the mean of the transients of the full cohort to give an idea of average behavior.

Parameter estimation using data from an elderly population

The ability to select parameters such that experimental results are closely matched can provide model validation. Here, we validate the model's ability to fit data from a study comparing the effects of RE between elderly women and men. RE is known to effectively combat sarcopenia. One meta-analysis of 49 studies and a total of 1328 participants showed an increase of about 1 kg of LM annually after RE versus the decline usually observed for sedentary individuals over 50 (Peterson et al. 2011).

Table 3 Parameter set data

Parameter name	Range	Mean
PAL	1.5–1.6	1.55
r	0–0.5	0.2505
α	2–80	9.001
β	20–80	49.974
H_1	60–74	67.001
H_2	65–75	70

LHS was restricted to these parameter ranges to ensure that physiologically reasonable simulations were generated given initial conditions. Sample means are close to the midpoints we expect for a uniform distribution, so a sample size of $n = 100$ was deemed sufficient

In this study, 60 subjects performed a moderate volume of RE three times per week for 24 weeks with assessments at 0, 12, and 24 weeks (Leenders et al. 2013). To fit mean time course data for the male and female groups in this study, we sought to separately simulate a mean elderly male response and a mean elderly female response. This was done by creating male and female variants of the model using the mean initial LM and FM for each group given in Table 5 as initial conditions and with initial energy intake for each estimated such that a male or female individual with mean values for each characteristic (age, height, weight, body composition) would be in energy balance. The fitting procedure was then performed via ordinary nonlinear least squares using the MATLAB lsqnonlin routine with bound constraints, with bounds placed on the parameter value search that were appropriate for the given initial conditions. This local optimization routine seeks parameters within given bounds that minimize the sum of squared errors between the data and model predictions using a trust region algorithm. Data for both FM and LM were fit simultaneously and the resulting parameter estimates for each group are shown in Table 5. Model output versus mean data for both the male and female groups are shown in Fig. 9.

For the male group, the difference between the predicted and observed LM at 12 and 24 weeks was 0.087 kg and 0.27 kg, respectively, and the difference between predicted and observed FM at 12 and 24 weeks was 0.5 kg and 0.68 kg, respectively. For the female group, the difference between predicted and observed LM at 12 and 24 weeks was 0.14 kg and 0.15 kg, respectively, and the difference between predicted and observed FM at 12 and 24 weeks was 0.3 kg and 0.3956 kg, respectively. Each of these predicted values is within the standard error of measurement of the experimental data.

Table 4 Cohort statistics

Change in Response Variable	12 Week mean	12 Week SD	24 Week mean	24 Week SD
Δ LM (kg)	1.6905	1.8756	2.2114	2.3990
Δ FM (kg)	−0.9463	0.5007	−2.0934	1.1194

Mean and standard deviation calculated for absolute change in LM and FM after 12 and 24 weeks of RE

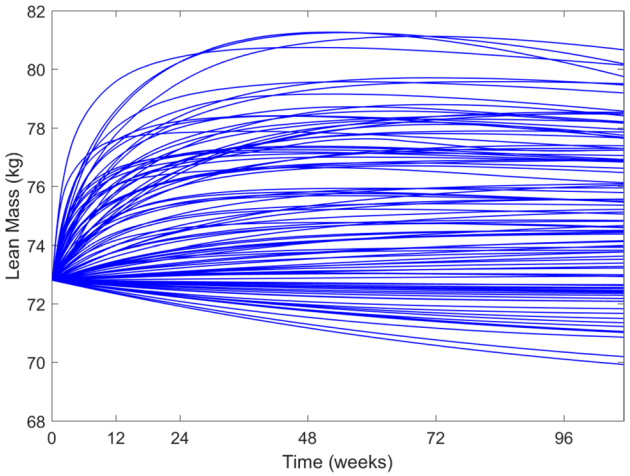

Fig. 7 Change in LM over time in response to RE for a simulated cohort of 100, 100 kg individuals with 27.2% body fat. RE was modeled with parameter values sampled from a uniform distribution with ranges restricted to the values given in Table 3

We then used the parameter estimates that were obtained in fitting mean data for each group in the study (Leenders et al. 2013), shown in Table 5, combined with the associated mean initial conditions to simulate a longer-term scenario in which hypothetical "average" male and female elderly subjects in the study cease RE completely following the 24-week supervised training period. The projected results are shown in Fig. 10. For the hypothetical male, following the cessation of training there is a slight loss of LM until the level of energy intake is sufficiently above that of energy expenditure to cause a second increase. Although initial dynamics are different for the hypothetical female, predicted LM and FM for both hypothetical subjects appear to eventually reach a stable steady state at a new, healthier body composition. These scenarios are only two of many possible outcomes that could be investigated for a variety of hypothetical individuals using this model.

Discussion

We have extended the Hall et al. energy balance model (Hall et al. 2011) of human metabolism to include muscle hypertrophy in response to RE with the addition of the muscle hypertrophy term in Eq. 8. Statistical analyses were

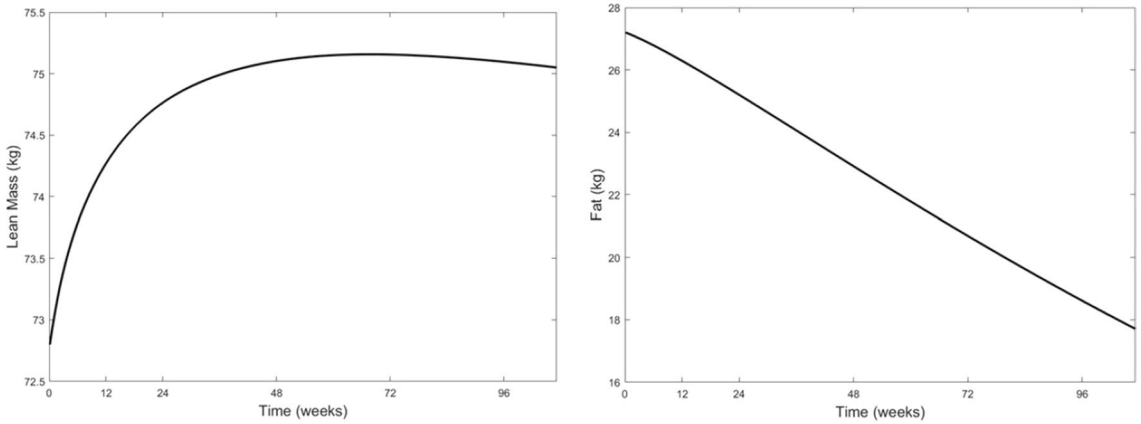

Fig. 8 Mean of the transients for LM and FM of the full cohort

Table 5 Initial conditions and parameter estimates for group data

Group	LM (kg)	FM (kg)	Fat %	PAL	r	α	β	H_1	H_2
Men	62.2	19.3	22.6	1.6	0.5	18.14	100	8.07	60.79
Women	42.5	21.2	32.1	1.6	0.21	2.37	99.94	13.48	42.16

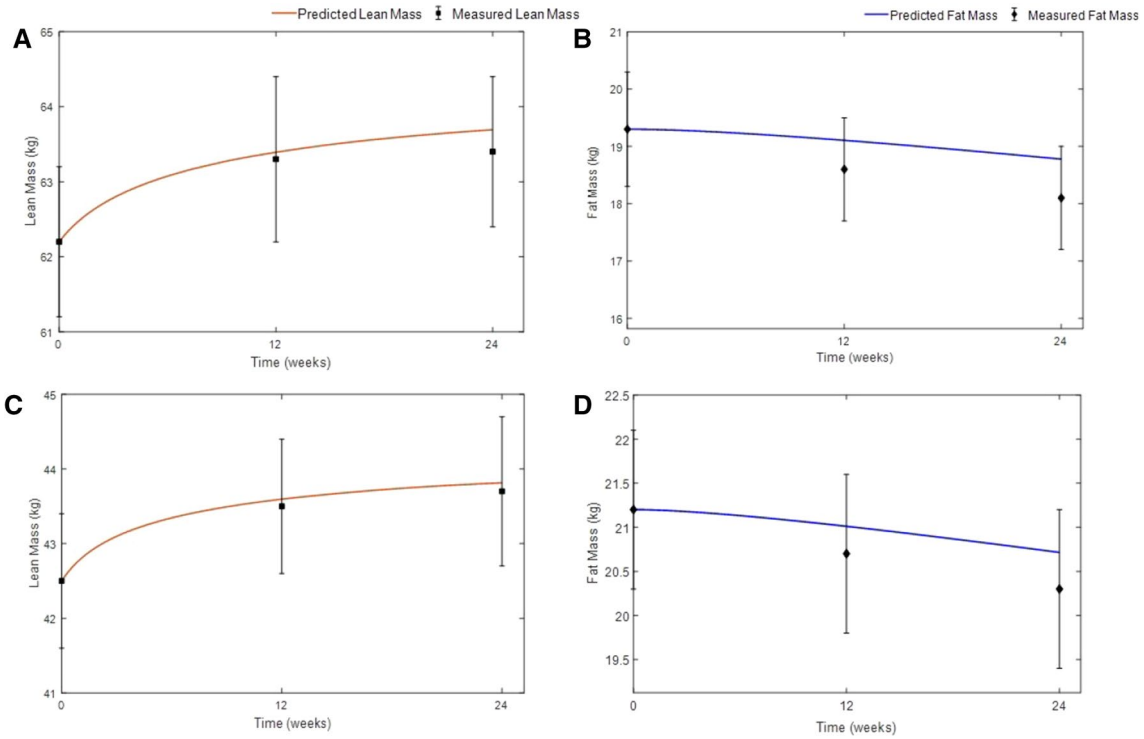

Fig. 9 Predicted and measured body mass during a trial comparing the effects of a moderate volume RE program on elderly men and women (Leenders et al. 2013). **a** Predicted and measured average LM with SEM for 29 elderly men. **b** Predicted and measured average FM with SEM for 29 elderly men. **c** Predicted and measured average LM with SEM for 24 elderly women. **d** Predicted and measured average FM with SEM for 24 elderly women

performed, with results given in Appendices B and C in supplementary material, that provide support for the biological interpretation of the parameters given in Section "Model development". We also determined that, for selected parameters, the model is able to reproduce a key aspect of the physiology of RE: a fast initial rate of response over the first 12 weeks of a training program that slows over the following 12 weeks as the body adapts.

A simulated case study comparing the effects of a hypocaloric diet alone versus combined with CE or RE followed by a resumption of pre-diet energy intake levels showed that the increased energy expenditure from LM gained in response to RE could lead to better long-term body composition outcomes. The modest gain in LM from RE leads to an energy expenditure of 3084 kcal/day. This is sufficiently above energy intake to produce continued fat loss. Higher energy expenditure from moderate CE gives an energy expenditure of 3030 kcal/day, barely above pre-diet energy intake levels. A hypocaloric diet alone with no exercise results in a new, lower energy expenditure of 3003 kcal/day due to the energetically expensive LM lost during the period of reduced energy intake, and an eventual FM regain. Additionally, the boost in energy expenditure that results from increased LM due to RE or increased calories burned due to CE offsets the effect of adaptive thermogenesis, which works in opposition to the maintenance of a new, lower body weight (Trexler et al. 2014). It is known that a majority of individuals on a weight loss diet eventually return to higher energy intake levels leading to a regain of weight lost (Corral et al. 2011; Saris 2001; Shai and Stampfer 2008; Ulen et al. 2008). A way to combat this could be the addition of an RE program with the support and education necessary to make it an ongoing lifestyle change.

We also simulated a cohort of individuals with varying responses to RE by sampling parameters from a uniform distribution using LHS to capture known variation in individual response. This demonstrates how the model presented here could be used to simulate clinical studies for hypothesis testing or experimental design.

To further validate the model, we used parameter estimation methods to fit data from an RE study and performed statistical analyses to evaluate biological feasibility of model results. The parameter estimates shown in Table 5, when considered along with the sensitivity analysis results in Appendix B in supplementary material, seem to be reasonable in the context of known biology. Versus the male group, the female group has a lower r value (corresponding to a lower overall gain), a lower α value (corresponding to slower overall response), a higher H_1 value (corresponding to a somewhat delayed response), and a lower H_2 value

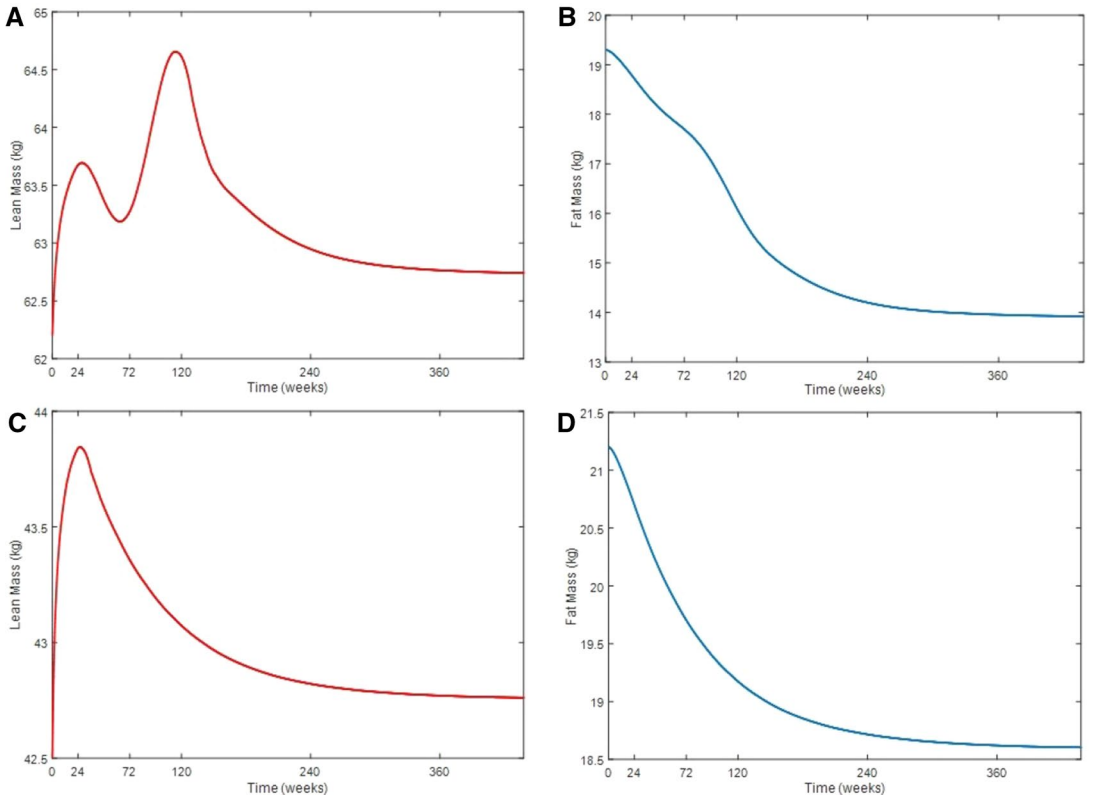

Fig. 10 Model predictions of long-term change in LM and FM following 24 weeks of RE. Parameter estimates obtained in fitting the model to mean data from elderly subjects completing an RE program for 24 weeks (Leenders et al. 2013) were then used to simulate a long-term scenario: cessation of RE after 24 weeks. **a** Predicted average LM for the male group. **b** Predicted average FM for the male group. **c** Predicted average LM for the female group. **d** Predicted average FM for the female group

(corresponding to a lower potential for gain given lower initial LM). Both groups have a high β value corresponding to quick adaptation to RE that could result in a lower level of gain over time which would not be unexpected for elderly trainees.

Our predictions for LM and FM at 12 and 24 weeks were within the standard error of measurement for the data, yet it would be ideal to have more than three longitudinal data points. Additionally, we have had to make assumptions regarding energy intake given the free-living status of the research subjects. It is possible that better fits could be achieved with more knowledge about energy intake of subjects over the course of the study. However, given the relative closeness of fit for both LM and FM achieved with these limitations, one can see how group and patient-specific parameters could be estimated and then used to simulate different diet and exercise strategies. It is not currently established that there are inherent differences in response to RE between groups such as young or old, or male and female; fitting this model to data from different groups and comparing parameter estimates could provide some intuition in this area.

Conclusion

Stability analysis performed on this model could provide insight into how the addition of LM from RE affects body weight set point. This model could also be further refined to include additional physiological responses to varying energy intake and exercise such as hormonal effects and even the response to specific styles of training such as high intensity interval training, a type of CE which is also known to have a positive effect on metabolism and increase LM. Submodels that are specific to populations could also be developed; for example, the addition of a muscle loss term to account for sarcopenia could produce an elderly specific model. Since this model is unique in its inclusion of response to resistance-type exercise, it can now be used to perform in silico testing of this type of exercise as part of a simulated obesity or sarcopenia intervention.

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