

## ORIGINAL ARTICLE

# How adaptations of substrate utilization regulate body composition

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**Objective:** To elucidate the mathematical relationship between longitudinal changes of body composition and the adaptations of substrate utilization required to produce those changes.

**Design:** We developed a simple mathematical model of macronutrient balance. By using an empirical relationship describing lean body mass as a function of fat mass, we derived a mathematical expression for how substrate utilization adapts to changes of diet, energy expenditure and body fat such that energy imbalances produced the required changes of body composition.

**Results:** The general properties of our model implied that short-term changes of dietary fat alone had little impact on either fat or non-fat oxidation rates, in agreement with indirect calorimetry data. In contrast, changes of non-fat intake caused robust adaptations of both fat and non-fat oxidation rates. Without fitting any model parameters, the predicted body composition changes and oxidation rates agreed with experimental studies of overfeeding and underfeeding when the measured food intake, energy expenditure and initial body composition were used as model inputs.

**Conclusion:** This is the first report to define the quantitative connection between longitudinal changes of body composition and the required relationship between substrate utilization, diet, energy expenditure and body fat mass. The mathematical model predictions are in good agreement with experimental data and provide the basis for future study of how changes of substrate utilization impact body composition regulation.

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**Keywords:** body composition; weight loss; weight gain; mathematical model; substrate utilization

### Introduction

What determines the relative change of body fat and lean mass during weight loss or weight gain? Answering this question has important implications for treatment of obesity as the desired goal is to decrease body fat while preserving lean mass. Alternatively, other conditions of altered body composition, such as anorexia nervosa and cachexia, have the challenge of recovering lean body mass without excessive accumulation of fat.

The concept of macronutrient balance is now accepted as the physiological basis for determining body composition changes.<sup>1–4</sup> However, it remains to be elucidated exactly how longitudinal body composition changes are quantitatively related to the properties of macronutrient balance. Here, we asked the following question: how must substrate utilization

quantitatively adapt to a given energy imbalance to produce the longitudinal body composition changes proposed by Forbes<sup>5</sup>? Addressing this question led to a simple equation that elucidates how interactions between diet, energy expenditure and substrate utilization are quantitatively connected to changes of body composition.

Rather than develop explicit mathematical models of food intake and energy expenditure, our goal was to define the quantitative interactions between these variables, substrate utilization and the resulting changes of body composition. (For a more general model incorporating energy expenditure dynamics we refer the reader to a more complex model of macronutrient metabolism by Hall<sup>6</sup>). Thus, we only considered comparisons to experimental studies, where energy expenditure and food intake were measured and could be used as model inputs. The model then predicts changes of body composition and substrate utilization. This strategy allowed for an explicit mathematical connection to the Forbes body composition data and the resulting equations contained no free parameters thereby avoiding any model fitting procedures. Remarkably, our simple equations accurately predicted the changes of body composition and

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substrate utilization rates during both experimental underfeeding and overfeeding when the measured food intake and total energy expenditure were provided as inputs to the model.

## Methods

Forbes found the following cross-sectional curve of lean body mass (L) versus fat mass (F) and hypothesized that longitudinal changes of body composition during energy imbalance were described by movement along the curve:

$$L = 10.4 \text{Log}_e F + 14.2 \quad (1)$$

with L and F expressed in kg.<sup>5</sup> The following differential relationship was thereby derived for infinitesimal weight changes:

$$\frac{dL}{dF} = \frac{10.4}{F} \quad (2)$$

We began by considering the following macronutrient balance equations:

$$\rho_F \frac{dF}{dt} = I_F - f_F E \quad (3a)$$

$$\rho_L \frac{dL}{dt} = I_L - (1 - f_F)E \quad (3b)$$

where  $E$  is the total energy expenditure rate,  $f_F$  the fraction of the energy expenditure rate accounted for by fat oxidation,  $I_F$  the metabolizable intake rate of fat,  $I_L$  the sum of the metabolizable intake rates of protein and carbohydrate, and  $\rho_F = 9.4$  kcal/g and  $\rho_L = 1.8$  kcal/g are the energy densities of body fat and lean mass changes, respectively.<sup>6</sup> Eq. 3a simply states that the rate of body fat mass change,  $dF/dt$ , results from differences of fat intake and oxidation rates. This assumes that *de novo* lipogenesis is negligible, which is typically true in humans.<sup>7</sup> Eq. 3b is a similar equation for the combination of carbohydrate and protein balances and their impact on the rate of lean body mass change,  $dL/dt$ . Fortunately, combining carbohydrate and protein in this way does not introduce serious errors because both of these macronutrients have similar energy densities.<sup>8</sup> and are associated with similar amounts of water.<sup>9</sup>

To connect the simplified macronutrient balance equations to Forbes's theory, we divided Eq. 3b by 3a and used Eq. 2 to derive the following expression for the fat oxidation rate:

$$\text{FatOx} \equiv f_F E = \frac{(C/F)I_F - I_L + E}{1 + C/F} \quad (4)$$

where  $C = 10.4 \rho_L / \rho_F$ . Eq. 4 predicts how fat oxidation rates adapt to changes of fat intake, non-fat intake, energy expenditure and body fat mass. These adaptations form the physiological basis of Forbes's hypothesis for longitudinal body composition regulation.

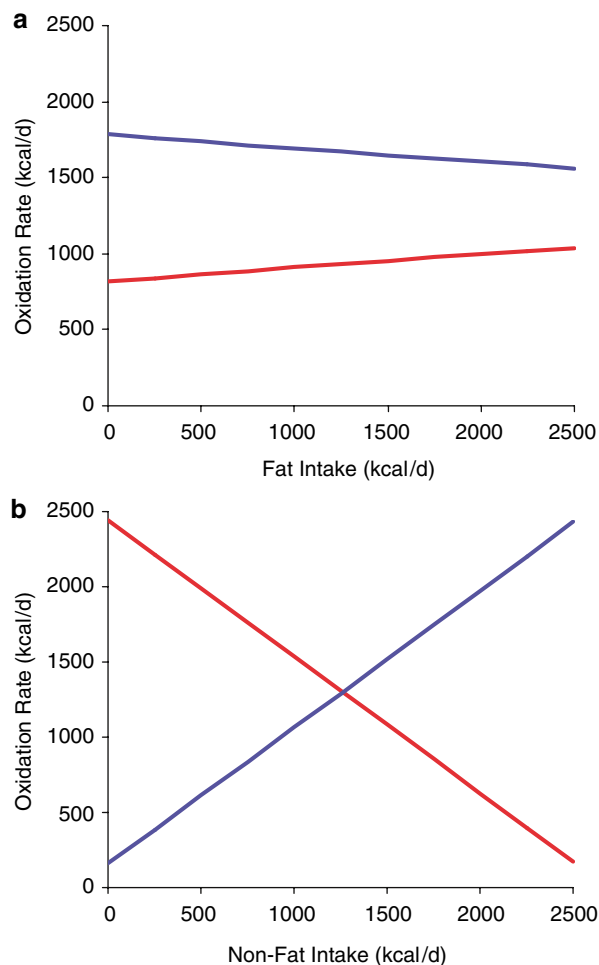
To demonstrate the general properties of Eqs. 3 and 4, we considered an individual with an initial body weight of 65 kg with 31% body fat. The baseline intake rates of dietary fat and non-fat were 900 and 1700 kcal/day, respectively, and the energy expenditure of 2600 kcal/day was held constant. These intake rates were chosen so that the baseline body fat and lean mass were constant. To compare the model directly with experimental overfeeding and underfeeding studies, we altered the initial body composition to match the average physical characteristics of the study subjects and used experimental studies, where both the dietary intake rates as well as the total energy expenditure were measured so that we could directly specify the time courses of  $I_F$ ,  $I_L$  and  $E$  and predict the resulting changes of body composition as well as fat and non-fat oxidation rates.

## Results

Equation (4) has several important physiological implications. The first results from the fact that  $C/F$  is typically small. Therefore, fat oxidation does not change significantly for short-term changes of fat intake relative to the same increment of non-fat intake. This is shown in Figure 1a and b where we plotted the short-term change of fat and non-fat oxidation rates as dietary fat and non-fat were varied. Figure 1a shows that when non-fat intake was fixed at its balanced value of 1700 kcal/day, wide variations of fat intake had little impact on the substrate utilization rates and thereby resulted in substantial fat imbalances. In contrast, Figure 1b shows that alterations of non-fat intake profoundly impacted substrate utilization rates when fat intake was fixed at its balanced value. Again, this resulted in energy imbalances primarily accounted for by changes of body fat.

Another important consequence of Eq. 4 results from the fact that  $C/F$  changes very little for modest weight changes unless the body fat is very low. This implies that the fat oxidation rate is only weakly influenced by body fat changes for modest weight changes in normal or overweight subjects. Rather, the diet and energy expenditure play a dominant role in determining substrate utilization rates in such circumstances.

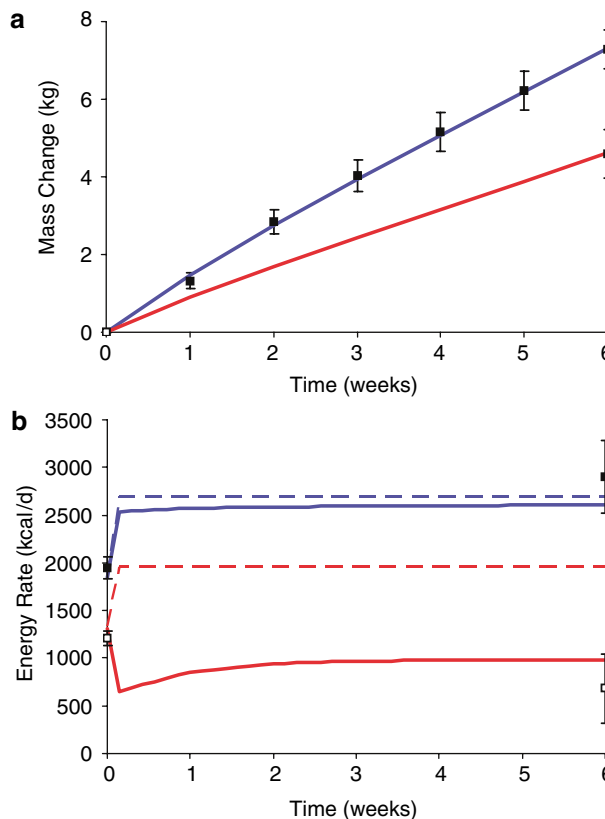
We applied Eqs. 3 and 4 to the overfeeding study of Diaz *et al.*,<sup>10</sup> where 10 subjects were overfed by 50% in excess of maintenance requirements for 42 days. The subjects were young men with an average body weight of 73.4 kg and 21.3% body fat. The energy content of the diet consisted of 12% protein, 42% fat and 46% carbohydrate. Figure 2a demonstrates that the predicted body weight and fat mass changes (blue and red curves, respectively) closely matched the data (closed and open boxes, respectively). Figure 2b illustrates the predicted fat and non-fat oxidation rates (solid blue and red curves, respectively) along with the measured metabolizable dietary intake rates (dashed curves) and measured oxidation rates (boxes). Whereas the predicted



**Figure 1** Short-term adaptations of substrate utilization required by Forbes's logarithmic body composition curve. (a) Changes of dietary fat above cause insignificant changes of fat oxidation (red curve) and non-fat oxidation (blue curve) resulting in large fat imbalances. (b) In contrast, changes of non-fat intake cause robust adaptations of both fat and non-fat oxidation rates that again result in energy imbalances to be primarily accounted for by changes of body fat.

non-fat oxidation increased to reach about 95% of the non-fat intake, fat oxidation was suppressed and accounted for only about 50% of the fat intake. These model predictions agree with the experimental measurements of fat oxidation (open boxes) as well as non-fat oxidation calculated from the difference between the measured expenditure and fat oxidation rates (closed boxes). It is important to emphasize that no parameter fitting was performed to make these comparisons.

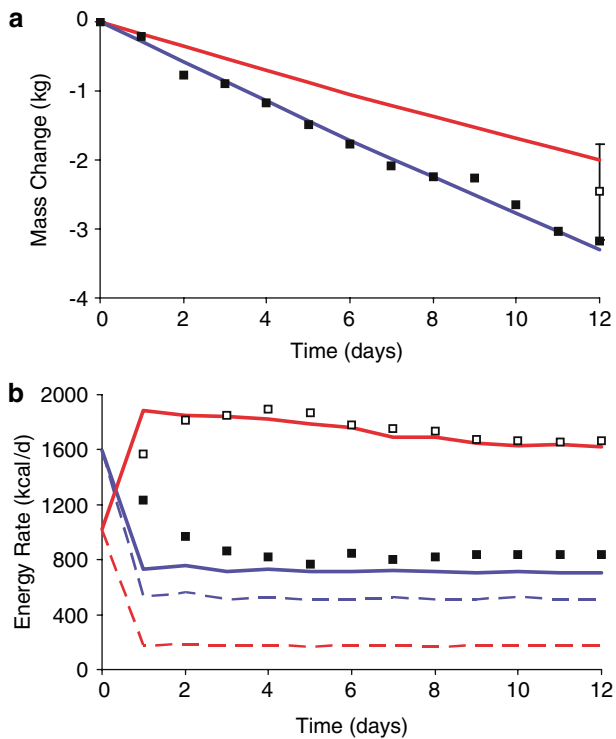
We also simulated an underfeeding study by Jebb *et al.*,<sup>11</sup> where three subjects spent 12 continuous days in a metabolic chamber to assess macronutrient oxidation rates. The subjects were male with an average body weight of 73.7 kg and 23% body fat. The energy content of the diet consisted of 31% protein, 24% fat and 45% carbohydrate. Figure 3a shows that the simulated changes of body weight and fat



**Figure 2** Simulation of the overfeeding study by Diaz *et al.*<sup>10</sup> (a) The predicted changes of body weight (blue curve) and fat mass (red curve) closely matched the data (closed and open boxes, respectively). (b) The predicted changes of fat and non-fat oxidation (solid red and blue curves, respectively) matched the data (open and closed boxes, respectively) in response to the increased rates of fat and non-fat intake (dashed red and blue curves, respectively).

mass closely matched the body composition data. Figure 3b shows that the underfeeding caused increased fat oxidation and suppressed non-fat oxidation in agreement with the data. However, the adaptations of fat and non-fat oxidation observed by Jebb *et al.* occurred more slowly than the predicted oxidation rates, probably reflecting the short-term influence of glycogen reduction, which likely required several days to reach a steady state. As the present model does not directly include glycogen and its impact on substrate oxidation rates, this effect was not predicted.

Finally, we simulated a study by Rumpler *et al.*<sup>12</sup> where eight overweight men (average 96.6 kg and 28% body fat) underwent a 50% energy restriction on either a high-fat (14% protein, 40% fat and 46% carbohydrate) or low-fat diet (14% protein, 20% fat and 66% carbohydrate) for 4 weeks followed by 1 week of the maintenance diet. Figure 4a shows that the predicted changes of body weight (blue curve) and body fat mass (red curve) agreed with the measurements for the low fat diet (closed and open boxes, respectively), and Figure 4b shows the agreement with body composition data



**Figure 3** Simulation of the underfeeding study by Jebb *et al.*<sup>11</sup> (a) The predicted body weight and fat mass changes agreed with the measured changes during 12 days of continuous indirect calorimetry. (b) Apart from the first few days, the predicted oxidation rates matched the data. See Figure 2 for a description of the symbols.

from the high-fat diet. Figure 4c shows that the predicted fat and non-fat oxidation rates (solid blue and red curves, respectively) for the low-fat diet closely matched the experimental data (open and closed boxes, respectively), whereas the model slightly overestimated the fat oxidation rate and underestimated the non-fat oxidation rate during the energy restriction phase of the high-fat diet.

## Discussion

For the first time, we have elucidated the mathematical connection between longitudinal changes of body composition and the adaptations of substrate utilization required to produce those changes. We used Forbes's logarithmic relationship between lean and fat mass to determine how substrate utilization adapts to changes of macronutrient intake, body fat and energy expenditure. Without adjusting any model parameters, the model accurately predicted the experimental measurements of macronutrient oxidation rates and body composition changes during both overfeeding<sup>10</sup> and underfeeding.<sup>11,12</sup>

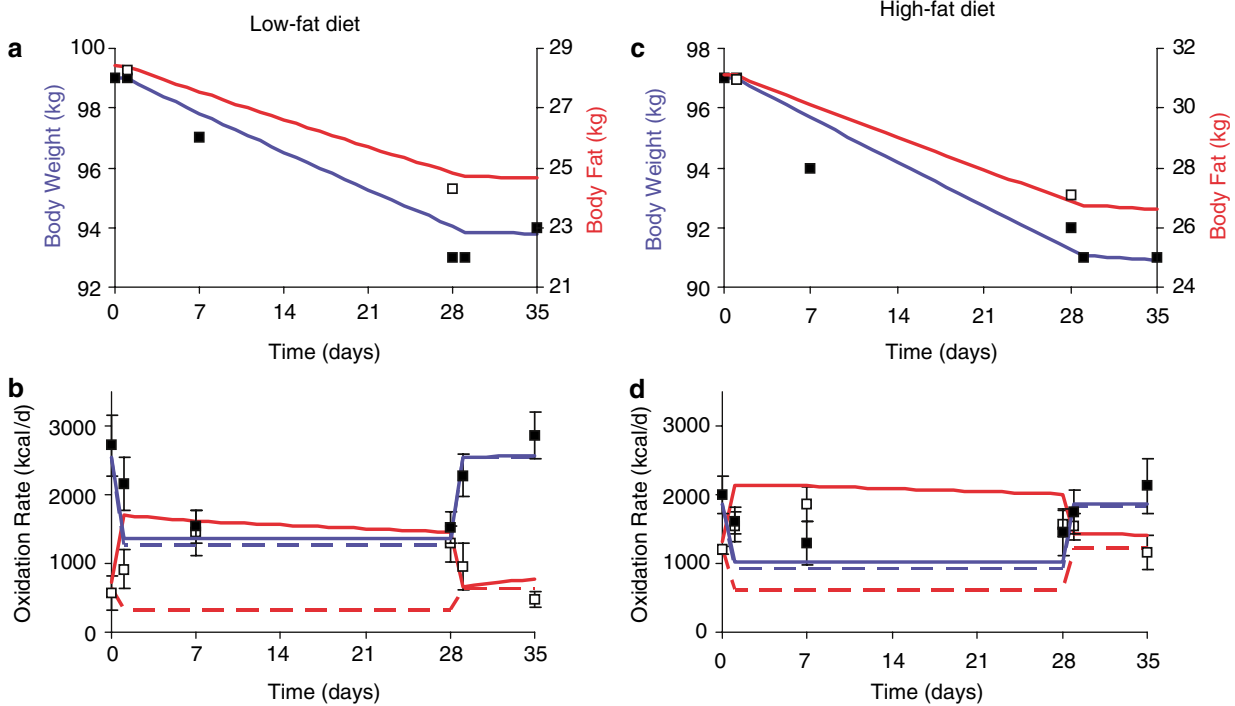
These model predictions were made by using the measured food intake, energy expenditure and initial body composi-

tion as model inputs. We have not explicitly modeled the adaptations of energy expenditure that contribute to determining the absolute rates of macronutrient oxidation. Hall's more complex model of macronutrient metabolism<sup>6</sup> includes a detailed model of whole body energy expenditure, as well as a model of the individual macronutrient balances. For the present study we used measured energy expenditure as a model input and lumped protein and carbohydrate together to minimize the number of model parameters. In fact, the model presented here contains no free parameters because substrate utilization was constrained by Forbes's empirical body composition curve.

The general properties of our model imply that there is a hierarchy of substrate utilization, with dietary fat having little influence on fat and non-fat oxidation rates in comparison with non-fat intake. This result is in general agreement with observations using indirect calorimetry showing that addition of excess dietary fat had little impact on macronutrient oxidation rates in comparison with dietary carbohydrate or protein.<sup>1,13,14</sup> Glycogen changes can impact the macronutrient oxidation rates, but these effects are limited to only a few days after which glycogen achieves a new equilibrium. Therefore, our model responds correctly after that time period as illustrated by comparisons with the macronutrient oxidation data in Figures 3 and 4. Inclusion of glycogen in the present model significantly complicates the mathematical relationship to body composition changes and introduces additional model parameters.

There is much debate surrounding the weight loss potential of diets differing in macronutrient content.<sup>15,16</sup> When our model was applied to data from a weight loss study comparing the effects of a low-fat diet with a high-fat diet,<sup>12</sup> the substrate utilization rates were quite different during weight loss despite the similar caloric contents of the diets. Because of the ability to adapt macronutrient oxidation to the diet composition, the two diets generated similar degrees of weight loss and body fat reduction. Whether this holds for other diets, such as low-carbohydrate and high-protein diets, is presently unclear because reliable estimates of food intake, energy expenditure and macronutrient oxidation have yet to be made during weight loss with such diets.

Previous investigators have recognized the importance of substrate utilization adaptations as a major determinant of body composition regulation.<sup>1-4</sup> Here, we extended these concepts to relate quantitatively the longitudinal body composition changes with adaptations of substrate utilization. Although Forbes's logarithmic body composition relationship was used for illustrative purposes in the present study, the same analysis could be applied to any function relating longitudinal changes of lean mass to fat mass. In particular, different individuals or groups may be characterized by different body composition curves. These differences will be reflected by how substrate utilization adapts to dietary changes as defined by our analysis. It is intriguing to speculate that the reverse might also be true:



**Figure 4** Simulation of the underfeeding study by Rumpler *et al.*<sup>12</sup> The predicted body weight and fat mass changes agreed with the measured changes during the low-fat diet (a) as well as the high-fat diet (b). The predicted oxidation rates closely matched the data during the low-fat diet (c), but the predicted fat oxidation rate was slightly higher than the data during the energy restriction phase of the high-fat diet (d). See Figure 2 for a description of the symbols.

that measurement of substrate utilization differences may predict differences in longitudinal body composition changes.

In particular, if we assume that the general form of Forbes's curve is correct, but that different groups or individuals may be characterized by different values of the constant  $C$ , then Eq. 4 can be solved for the value of this constant:

$$C = \frac{F[(1 - f_F)E - I_L]}{f_F E - I_F} \quad (6)$$

Interestingly, the state of macronutrient balance results in an undetermined value for  $C$  because both the numerator and denominator of Eq. 6 are zero. However, suitable short-term dietary perturbations along with measurements of the resulting macronutrient oxidation rates could result in an experimental determination of  $C$  and thereby predict an individual's longitudinal body composition relationship before significant changes of body composition have occurred. Future work will address this possibility.

Several investigators have proposed mathematical expressions that describe the interrelationships between body fat and lean mass. For example, Payne and Dugdale,<sup>17</sup> Christiansen and Garby,<sup>18</sup> and Krietzman<sup>19</sup> proposed that the composition of weight change is a constant for a given individual. Dulloo and Jacquet<sup>20</sup> suggested that the composition of a body weight change depends on the initial fat mass, in agreement with the observations of Forbes.<sup>5</sup>

Recently, Hall<sup>21</sup> showed that Forbes's theory of body composition further implies that the relative change of body fat and lean mass also depends on the magnitude and direction of the weight change. Others have proposed complex calculations involving the degree of energy imbalance and percent body fat.<sup>22</sup> These theoretical descriptions of the factors impacting fat and lean mass interrelationships do not address the underlying mechanism of macronutrient balance.

Our model has taken a step beyond previous descriptions of body fat and lean mass interrelationships by connecting the body composition changes with adaptations of substrate utilization. Although our model shows that diet plays a dominant role in determining substrate utilization rates, we have not modeled food intake regulation as there are insufficient data in humans to construct accurately such a model. Rather, we compared the model predictions with experimental data where the food intake was controlled and used as a model input. Finally, although our model predicts how substrate utilization adapts to changes of diet, energy expenditure and body fat, we have not specified the physiological mechanisms for these adaptations. Clearly, diet and body fat impact many metabolic processes including, whole body lipolysis, glucose disposal, de novo lipogenesis and nitrogen balance.<sup>3,4,23</sup> Future work will investigate more complex models of macronutrient metabolism<sup>6</sup> to better understand the physiological control of

substrate utilization in the context of body composition regulation.

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