Metabolism of mice and men: mathematical modeling of body weight dynamics

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Purpose of review
Dynamic interrelationships between food intake, energy expenditure, energy partitioning, and metabolic fuel selection underlie changes in body weight and composition. A quantitative understanding of these interrelationships is becoming increasingly important given the rise of the worldwide obesity epidemic and the widespread interest in weight management. This review describes how mathematical models offer a quantitative framework for integrating dynamic physiological and behavioral data underlying body weight dynamics in both humans and mice.

Recent findings
Mathematical models have provided important insights regarding the drivers of the obesity epidemic, how metabolism adapts to different diets, the predicted magnitude and variability of weight change, and why mouse models have obesity phenotypes. Because mathematical models are constrained by conservation laws, they can also be used to infer physiological variables that are difficult to measure directly.

Summary
Mathematical models can help improve our understanding of the dynamic energy and macronutrient imbalances that give rise to changes in body weight and composition over time. The model development process can also highlight important knowledge gaps and model simulations can help design and predict the results of key new experiments to fill those gaps.

Keywords
body weight regulation, energy balance, mathematical model

INTRODUCTION

Obesity is known to result from a prolonged period of excess caloric intake over expenditure [1]. This energy balance concept, although more descriptive than explanatory, provides the framework for understanding body weight regulation. Explaining the development of obesity and developing effective therapies requires a quantitative integration of physiological and behavioral data within the energy balance framework [2]. Dynamic mathematical models can help quantify the interrelationships between food intake, energy expenditure, energy partitioning, and metabolic fuel selection that underlie changes in body weight and composition. Recently, mathematical models have been effectively applied to the study of obesity in both mice and men. In this article, I highlight several recent applications of mathematical models to obesity research and describe some insights provided by these models.

MODELS THAT PREDICT HUMAN WEIGHT CHANGE

Mathematical modeling of human body weight dynamics began in the 1970s and a review of the various modeling approaches was recently published [3]. Dynamic models have now reached the level of sophistication required to accurately predict how changes in diet and physical activity affect body weight and body composition over time. For example, building on a steady-state model of human weight change that was calibrated using

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KEY POINTS

- Dynamic interrelationships between food intake, energy expenditure, energy partitioning, and metabolic fuel selection underlie changes in body weight and composition.
- Realistic mathematical models have been developed that accurately predict how changes in diet and physical activity affect body weight and body composition over time.
- Such models offer a quantitative framework for integrating dynamic physiological and behavioral data in both humans and mice.

longitudinal body composition and energy expenditure data [4], Hall *et al.* [5▪▪] recently developed and validated a dynamic simulation model that calculates how factors such as diet and exercise can alter energy expenditure over time and thereby lead to dynamic changes of weight and body fat. A web-based implementation of the model (http://bwsimulator.niddk.nih.gov) provides accurate predictions about how long it will take for different people to reach their weight goals for a given change of diet or physical activity. Perhaps more importantly, the model also calculates the permanent lifestyle changes required to maintain the goal weight. This dynamic model also provides important insights regarding the expected time course, magnitude, and variability of human weight change for people with different initial body composition and physical activity levels [5▪▪,6].

Mathematical models are also beginning to predict the weight changes of entire populations. For example, Lin *et al.* [7▪] estimated the impact of taxation policies for caloric sweetened beverages on the prevalence of overweight and obesity in the USA using the dynamic simulation model of Hall *et al.* [5▪▪]. The authors compared the model-predicted changes in obesity prevalence to predictions obtained using the ubiquitous '3500 Calorie per pound' static weight loss model that does not account for dynamic changes of energy expenditure. The dynamic model simulations predicted that proposed taxation policies will result in a modest decrease in overweight and obesity prevalence that is substantially less than the previously calculated values using the static model [8].

Another recent example of modeling population weight change was performed by Church *et al.* [9▪] who investigated the role of reduced occupational physical activity on the development of the US obesity epidemic. This study used the dynamic mathematical model of Thomas *et al.* [10,11] (http://www.pbrc.edu/the-research/tools/weight-loss-predictor) to simulate the changes in adult body weight corresponding to the calculated decreases in occupational physical activity over the past half century. Assuming that energy intake remained constant over this time, the authors found that the observed increase in the average weight of men and women closely matched the model predictions. The conclusion of Church *et al.* was that the US obesity epidemic was almost fully explained by the progressive decrease in occupational physical activity. However, this conclusion is complicated by the fact that the Thomas weight change model has not been validated for predicting the effects of altered physical activity. There is good reason to believe that the Thomas model overestimates the predicted weight changes because it assumes that changes in any component of energy expenditure are positively correlated to changes in spontaneous physical activity [10,11]. Hence, decreased occupational physical activity was assumed to lead to concomitant decreases in spontaneous physical activity – a property that is highly questionable and significantly limits the model's utility [3].

In contrast, Hall *et al.* [12] employed a validated mathematical model of human weight change to address the question of whether changes in the US food supply could account for the increase in average US adult body weight since the 1970s. The model calculated that an average progressive increase in energy intake of less than 250 kcal per day per person was required to generate the US adult obesity epidemic (assuming no changes in physical activity). This increment in food intake pales in comparison to the rate of increase in the per capita US food supply, which was about triple this amount over the same period. The authors calculated that per capita food waste has progressively increased by 50% since the 1970s such that two-thirds of the increased available food ended up in landfills. This result was mirrored by independent landfill data from the US Environmental Protection Agency.

Thomas *et al.* [13] recently published a useful dynamic energy balance model of gestational weight gain (http://www.pbrc.edu/the-research/tools/gwg-predictor/) that helps expectant mothers and their healthcare providers track pregnancy progress and prescribe the energy intake required to stay within recommendations.

MODELS THAT PREDICT ADAPTATIONS OF HUMAN MACRONUTRIENT METABOLISM

Most mathematical models assume that 'a calorie is a calorie' meaning that the energy content of a diet,

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and not its macronutrient composition, is the primary determinant of weight change [14]. However, a recent computational model of human macronutrient metabolism does not require the 'calorie is a calorie' assumption as the model quantitatively tracks the metabolism of all three dietary macronutrients to simulate how diet changes result in adaptations of whole-body energy expenditure, metabolic fuel selection, and alterations in the major whole-body fluxes contributing to macronutrient balance [15,16▪]. Although the model obeys the first law of thermodynamics, it allows for the possibility that diets with different macronutrient composition can theoretically have differing effects on body weight and composition [17,18]

The macronutrient metabolism model was developed using published data from over 50 human studies and was validated by comparing model predictions with the results from independent-controlled feeding studies, including several that manipulated dietary macronutrient content [16▪]. Despite much previous data on reduced carbohydrate versus reduced fat diets, the model development process revealed a significant knowledge gap: no controlled feeding study has investigated the effects of a selective reduction of dietary carbohydrate versus fat while keeping the other dietary macronutrients at their baseline weight-maintenance values.

Model simulations can be used to address knowledge gaps by helping plan new experiments. For example, subjecting a cohort of 'virtual study participants' to various hypothetical in-silico experiments allows researchers to investigate various protocol designs and predict the anticipated effect size and variability of outcome measurements. The computational model of macronutrient metabolism was used to design a randomized, cross-over diet study to predict the metabolic consequences and body composition changes resulting from a selective isocaloric reduction of dietary carbohydrate versus fat in obese individuals [19]. The model predicted that, while keeping dietary fat and protein at baseline, selective reduction of carbohydrate by ~800 kcal per day resulted in augmented rates of lipolysis and fat oxidation with concomitant reductions in body fat and 24-h respiratory quotient (RQ). In contrast, selective reduction of ~800 kcal per day of dietary fat resulted in no change in the fat oxidation rate or 24-h RQ (Fig. 1). Whereas enhanced fat oxidation with the reduced carbohydrate diet might be expected to lead to greater body fat loss, the net cumulative fat imbalance was predicted to be more negative with the reduced fat diet. These model predictions are now being tested in a clinical research study at the National Institutes of Health [20].

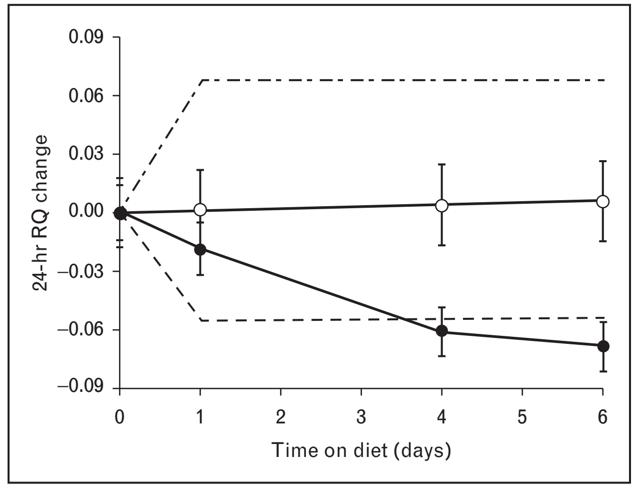

FIGURE 1. Computational model simulations of 24-h respiratory quotient (RQ) change in a cohort of obese 'virtual study participants' engaged in either 6 days of selective restriction of dietary carbohydrate (●) versus an isocaloric selective restriction of dietary fat (○). The error bars correspond to the standard deviations of the simulated 24-h RQ changes resulting from the various subjects having differing initial body fat and baseline energy requirements. The change in food quotient of the reduced fat diet (upper dashed dotted line) and reduced carbohydrate diet (lower dashed line) illustrate that only the reduced carbohydrate diet resulted in a shift in metabolic fuel selection to increase fat oxidation to match the fuel mix of the diet.

MODELS THAT PREDICT FREE-LIVING HUMAN ENERGY INTAKE

Given the importance of energy intake on determining body weight change, it is unfortunate that this variable is so difficult to measure in free-living conditions [21]. Although the doubly labeled water method is the gold standard for estimating the average rate of carbon dioxide production, this measurement is expensive and must be combined with assumptions about average 24-h RQ and measurements of body composition change to estimate average free-living energy intake [22▪]. Recently, dynamic mathematical models have begun to tackle the important problem of estimating changes in human free-living energy intake.

Jordan and Hall [23] demonstrated how a dynamic mathematical model can be used to quantitatively integrate longitudinal body composition data with repeated doubly labeled water measurements to calculate dynamic estimates of average free-living energy intake, energy expenditure,

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as well as 24-h RQ. Furthermore, the study demonstrated how variability in the experimental measurements (the model inputs) influenced the calculated time courses of energy intake, energy expenditure, and 24-h RQ (the model outputs) – a task that would be prohibitively tedious without the aid of a mathematical model. Although this model was applied to data from growing infants over their first 2 years of life [24,25], the methodology is equally applicable to weight gain or loss data in adults.

In the absence of doubly labeled water or body composition data, Hall *et al.* [5▪▪,12] proposed a method for calculating changes in adult energy intake using only repeated body weight measurements along with a dynamic mathematical model of energy metabolism and body composition change [16▪,26▪]. Hall *et al.* [5▪▪,16▪] have recently used such methods to help interpret the results of outpatient weight loss interventions. Weight loss programs ubiquitously result in a period of weight loss that plateaus after about 6–8 months and often followed by slow weight regain [27,28]. Using the longitudinal measurements of body weight, Hall *et al.* applied different mathematical models to estimate the changes of free-living energy intake underlying the typical weight loss, plateau, and regain trajectory. The conclusion was that the plateau was primarily due to a short-lived adherence to the diet intervention that was progressively relaxed to return to the preintervention level within the first year thereby leading to slow regain in subsequent years. Slowing of metabolic rate was found to play a secondary role in the weight plateau and regain trajectory – an interpretation that is a stark departure from the usual explanation that focuses on metabolic slowing as the prime culprit [27,29].

Although calculating the free-living energy intake of groups over time is useful for data interpretation, predicting individual energy intake changes would be extremely valuable for assessing diet adherence during a weight loss program. Thomas *et al.* [30▪] first proposed a computational method for calculating individual energy intake and validated their method using repeated doubly labeled water and body composition measurements. Hall and Chow [26▪] recently introduced a simpler methodology for using longitudinal weight measurements to estimate energy intake changes along with an explicit calculation of the confidence interval of the estimate, a useful metric for assessing individual diet adherence. The method was validated using data from a limited number of participants and, while promising, further validation is required.

MODELS THAT PREDICT MURINE ENERGY EXPENDITURE AND FUEL SELECTION

Mouse models that employ gene knockout technologies have proven to be particularly insightful for identifying molecular mechanisms of body weight regulation. But it is often unclear whether an observed body weight phenotype is a result of altered energy intake, expenditure, or both. Proper understanding of the physiological context by which a molecule exerts its effect on body weight requires knowledge of how food intake, energy expenditure, and fuel selection are dynamically interrelated over several weeks, which is the relevant time scale for mice.

Accurate and frequent measurements of food intake and weight change in mice can be performed over extended periods, but correspondingly frequent measurements of energy expenditure and fuel selection are not currently feasible. Rather, expensive indirect calorimetry systems are increasingly being used to measure energy expenditure and respiratory exchange over periods of only a few days. But measurements made over such limited durations are not ideal, as body weight is determined by the past history of energy and macronutrient imbalance over many weeks. Furthermore, indirect calorimetry systems typically require removing mice from their normal environment, an intervention that can alter their behavior [31]. For example, the indirect calorimetry procedure can cause weight loss mice that had previously been gaining weight in their home cages [32].

To address these issues, Guo and Hall [33] recently developed a dynamic mathematical method based on the law of energy conservation that used the measured body weight and food intake as model inputs to calculate the underlying energy balance and fuel selection dynamics. The model predicted daily energy output, RQ, and net fat oxidation during the development of obesity and weight loss in male C57BL/6 mice consuming various *ad libitum* diets over several weeks while mice were housed in their home cages. Such methods will likely become increasingly important as the challenges of indirect calorimetry in mice are more widely recognized.

MODELS THAT PREDICT MURINE BODY WEIGHT DYNAMICS

A recent mathematical model of mouse metabolism and body weight dynamics was reported by Tam *et al.* [34]. That model focused on the role of leptin to influence both energy intake and energy expenditure through various hypothetical feedback control strategies [35]. Although this mathematical model provided some important theoretical insights

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regarding body weight regulation, it has not been validated by directly comparing its predictions to experimental data and it does not address the issue of metabolic fuel selection.

Guo and Hall [36■] developed a mathematical model based on the principle of energy balance to predict the dynamics of body weight and fat mass in male C57BL/6 mice. Their model of murine energy expenditure included the cost of tissue turnover and deposition, physical activity, diet-induced thermogenesis, and the influence of body composition on metabolic rate. The model was calibrated using previously published data [37] and was validated by comparing its predictions to measurements from an independent study of five groups of male C57/BL6 mice provided *ad libitum* access to either chow or high fat diets for varying periods. The model coefficients relating energy expenditure to body composition also agreed with previous independent estimates [38]. Metabolic fuel selection was predicted to depend on a complex interplay between diet composition, the degree of energy imbalance, and body composition.

This validated mathematical model of mouse energy metabolism provides a novel tool for investigating energy balance relationships. Modification of model parameters will likely be required to appropriately represent other strains of mice, genetic knockouts, or transgenic mouse models. The process of determining the parameter modifications required to accurately simulate different mouse models will provide important quantitative information regarding their integrative metabolic phenotypes and the physiological and behavioral differences between mouse models.

CONCLUSION

An editorial describing the future of biomedical research remarked that ‘formulation of a mathematical model is the ultimate test of understanding. If the model reproduces the behavior of the system under a range of conditions and predicts the consequences of modifications in any component, one can be relatively confident about understanding the system’ [39]. Dynamic mathematical models are now beginning to provide powerful tools to quantitatively integrate physiological and behavioral data within an energy balance framework. Such models have great promise to improve our understanding of the body weight regulation system in both mice and men.

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Conflicts of interest

There are no conflicts of interest.

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