Modeling Metabolic Adaptations and Energy Regulation in Humans

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Abstract
Mathematical modeling of human energy regulation and body weight change has recently reached the level of sophistication required for accurate predictions. Mathematical models are beginning to provide a quantitative framework for integrating experimental data in humans and thereby help us better understand the dynamic imbalances of energy and macronutrients that give rise to changes in body weight and composition. This review provides an overview of the various approaches that have been used to model body weight dynamics and energy regulation in humans, highlights several insights that these models have provided, and suggests how mathematical models can serve as a guide for future experimental research.
INTRODUCTION

The emergence of the worldwide obesity epidemic (91) and its public health consequences (101) emphasizes the critical importance of understanding human energy regulation and its effect on body weight and composition. Intense public interest in weight control has led to a proliferation of diet and exercise products, with Americans alone spending tens of billions of dollars per year on these products (14). Media advertisements promise miracle weight loss cures, and every bookshop has an extensive selection of best-selling diet books. Weight loss has even become a form of entertainment, with a proliferation of reality television programs depicting dramatic weight loss interventions.

But despite increased public awareness and investment in obesity research, a great deal of misinformation and confusion remains about the relationship between weight change, nutrition, and energy metabolism. Unfortunately, these misconceptions are not limited to the general public but are also widespread among the professional nutrition and metabolism communities. For example, the so-called 3,500-Calorie-per-pound rule has almost ubiquitously been misused to imply that cutting 500 kcal/d from the daily diet will result in constant weight loss rate of about one pound per week (44). Such prescriptions have been embraced by official health and nutrition organizations around the world (20, 69–71) and have been erroneously used for individual weight loss counseling as well as predicting the potential impact of policy changes on population obesity prevalence (25, 32, 88, 89). Although it is generally acknowledged that weight loss will gradually slow over time as a result of the decreasing energy requirements, the magnitude and time course of the slowing were difficult to determine since this is a dynamic process.

To help address these issues, dynamic mathematical models of human energy regulation and weight change have been developed. Although such modeling began in the 1970s (1, 4, 74, 75), only within the past several years have mathematical models become sufficiently sophisticated to adequately capture the most relevant physiology, guide experimental research, and make accurate weight change predictions (33, 38, 43, 44, 94, 95). This review provides an overview of different approaches to mathematical modeling of body weight change and energy regulation in humans, highlights several insights that these models have provided, and suggests how mathematical models can serve as a guide for future experimental research.
BODY WEIGHT AND BODY COMPOSITION

Body weight is an easily measured quantity that has often been the primary variable of interest in mathematical models of human energy regulation (4, 12, 13, 56, 66). However, body weight is less important than body composition when it comes to health consequences. Thus, many models of human energy regulation have focused on predicting body composition change at some level of detail (1–3, 33, 38, 39, 43, 44, 57, 74, 75, 94, 95, 102, 107).

Figure 1a illustrates the body composition in terms of body fat and fat-free mass in a typical obese man and lean man. Obesity is characterized by a greatly expanded body fat mass but also an increased amount of fat-free mass. Figure 1a also illustrates the chemical composition of the fat-free mass, with water being its greatest component. The absolute masses of body protein and bone mineral are also increased in obesity. Glycogen and cellular solids, such as potassium and nucleic acids, contribute a very small fraction of the fat-free mass.

Body fat, protein, and glycogen comprise the stored energy of the body, and these stores must be mobilized when the diet is insufficient to meet the body’s energy requirements. Figure 1b illustrates the composition of the body in terms of its energy content, with fat stored in adipose tissue providing the overwhelming majority of the available stored energy, especially in obesity. Despite dietary carbohydrate providing the majority of the body’s energy demands on a daily basis, glycogen represents a relatively insignificant store of energy (~2,000 kcal). Body protein represents a substantial amount of energy, but in humans it is not a storage pool in the same sense as adipose tissue triglyceride. Rather, body proteins are functionally important and cannot be depleted by a significant fraction without serious complications and death. In contrast, fat stores represent a considerable energy reserve, and body fat can be depleted to very low levels without substantial functional impairments (30, 61).

Many mathematical models of human energy regulation have represented body fat as well as fat-free mass components (1–3, 33, 38, 43, 44, 57, 74, 75, 94, 95, 102, 107).

Figure 1
(a) The chemical composition of an obese 120 kg man (left) differs from that of a lean 70 kg man (right), primarily as a result of the increased body fat mass. The fat-free mass (FFM) of the body is mostly water, with a significant contribution of protein and bone mineral. Cellular solids and glycogen make up a very small part of the chemical composition of the body. (b) Body energy stores are greatly expanded in the obese man, primarily as a result of the increased body fat mass.
A recent model also includes rapid body water changes as a component of the fat-free mass that can be important contributors to early weight change (44). Only relatively complex computational models have represented the detailed chemical composition of the body (33, 38).

**ENERGY BALANCE**

Most mathematical models of human energy regulation make the assumption that weight change is solely determined by an imbalance between dietary energy intake and the energy expended by the body to maintain life and perform physical work. The theoretical underpinning of this energy balance concept is the first law of thermodynamics, and all energy balance models can be mathematically described by the following equation:

\[
\frac{d}{dt}(\rho BW) = EI - EE, \tag{1}
\]

where the left side of the equation is the rate of change of body energy, with \( BW \) being the body weight and \( \rho \) being an energy density converting between units of metabolizable energy and mass. The right side is the energy imbalance between the body’s energy intake rate, \( EI \), and energy expenditure rate, \( EE \). Any of the terms in the above equation can depend on time, \( t \), as well as other parameters. A conceptual representation of energy balance models is depicted in Figure 2.

A popular, but erroneous, application of the energy balance concept involves the assumption that the energy expended by the body remains relatively unchanged when energy intake deviates from an energy-balanced diet by an amount \( \Delta EI \). In that case, the energy balance Equation 1 gives the following equation for the rate of weight change, assuming a constant value for \( \rho \):  

\[
\frac{dWB}{dt} = \frac{\Delta EI}{\rho}. \tag{2}
\]

In other words, the rate of weight change is a constant and depends only on the magnitude of the diet change, \( \Delta EI \), and the energy density of the weight change, \( \rho \). With the choice of \( \rho = 3,500 \text{ kcal/lb} \), this erroneous equation encapsulates the static 3,500-Calorie-per-pound rule that has been ubiquitously misused to predict weight change (44).

The most serious error of Equation 2 is that the energy expenditure rate does not stay constant but rather dynamically changes. Even the earliest mathematical model of human weight change recognized that dynamic changes in energy expenditure must be taken into account (4), and it is curious that the persistent erroneous use of Equation 2 remains so popular to the present day. The assumption of a constant \( \rho = 3,500 \text{ kcal/lb} \) is also an oversimplification that will be dealt with forthwith.

**Conversion Between Mass and Metabolizable Energy**

A simple translation between the energy imbalance and the rate of weight change, \( dBW/dt \), occurs only if the energy density of the weight change, \( \rho \), is a constant parameter. However, as described above, the body is composed of a variety of chemical constituents with widely varying energy densities. For example, fat has an energy density of about 9.4 kcal/g, whereas protein and carbohydrate have energy densities of about 4.7 kcal/g and 4.2 kcal/g, respectively (64). Other major chemical constituents of the body, water being the most sizable, have metabolizable energy densities of zero. Thus, translating a given energy imbalance to a rate of weight change requires additional assumptions.
about the chemical composition of the weight change.

The historical basis of the common $\rho = 3,500$ kcal/lb assumption can be traced to the idea that body weight changes are primarily due to loss or gain of adipose tissue, which is composed of about 87% triglyceride (110). But we know that body water significantly contributes to overall weight change, especially over the first weeks following a reduced-calorie diet (49). Because body water has no metabolizable energy content, early weight changes have an energy density substantially lower than 3,500 kcal/lb (48). The mathematical models of Hall et al. (38, 44) are the only models to account for these early body water changes in terms of both intracellular and extracellular fluids.

Longer-term changes in body fat are accompanied by changes in lean tissue mass whose metabolizable energy density is significantly less than that of body fat (35). To model these longer-term body composition changes, Forbes (28, 29) hypothesized that the proportion of weight change resulting from lean versus fat tissue is a nonlinear function of body fat. The Forbes hypothesis has since been extended and validated implying that

$$\rho = \frac{M}{\Delta}$$

where $M$ is the mass change and $\Delta$ is the energy imbalance. Application of this model to the energy partition concept reveals that $P$ is a nonlinear function of $F$

$$P = \frac{C}{C + F}$$

where $C = 10.4 \text{ kg} \times \rho_L/\rho_F$, as depicted in Figure 4 (11, 34). The initial value of $P$ can be quite diverse for individuals with very different fat mass, in agreement with the Payne and Dugdale hypothesis. However, the nonlinearity of the Forbes body composition curve suggests that $P$ is not a fixed parameter because it depends continuously on the fat mass, which can change considerably with large weight changes.

**Energy Partition Models**

To explicitly model body composition change, the energy balance Equation 1 can be written as a pair of equations for the changes in both lean tissue, $L$, and body fat, $F$:

$$\rho_L \frac{dL}{dt} = P(EI - EE)$$

$$\rho_F \frac{dF}{dt} = (1 - P)(EI - EE)$$

Based on assumptions about the chemical composition of lean and fat changes, the energy densities have been estimated to be about $\rho_L = 1.8$ kcal/g and $\rho_F = 9.4$ kcal/g, respectively (35). The energy partition ratio, $P$, ranges between 0 and 1 and determines the proportion of an energy imbalance directed to and from lean versus fat mass. The energy partition concept is illustrated in Figure 3.

The seminal energy partition model of Payne and Dugdale referred to $P$ as the p-ratio, indicating that this factor determines the proportion of an energy imbalance accounted for by body protein changes since they ignored the contribution of glycogen (74, 75). Payne and Dugdale hypothesized that $P$ was a constant parameter whose value could vary between people and could thereby explain variable interindividual weight change for equivalent changes of diet.

Applying the Forbes hypothesis to the energy partition model reveals that $P$ is a nonlinear function of $F$: $P = C/(C + F)$, where $C = 10.4 \text{ kg} \times \rho_L/\rho_F$, as depicted in Figure 4 (11, 34). The initial value of $P$ can be quite diverse for individuals with very different fat mass, in agreement with the Payne and Dugdale hypothesis. However, the nonlinearity of the Forbes body composition curve suggests that $P$ is not a fixed parameter because it depends continuously on the fat mass, which can change considerably with large weight changes.
MACRONUTRIENT BALANCE

In his early twentieth-century textbook, *Food and the Principles of Dietetics*, Robert Hutchison (50) compared the human body to a steam engine, noting that “The building material of food corresponds to the metal of which the engine is constructed, the energy-producers to the fuel which is used to heat the boiler. Where the body differs from the engine is that it is able to use part of the material of its construction for fuel also” (50). A more modern engineering analogy might be an automobile that can run on an arbitrary mixture of different fuels (37). Such a flex-fuel vehicle would allow the driver to fill the tank with whatever fuel was cheaper or more readily available, regardless of what mixture is already in the tank. Although designing a flex-fuel vehicle would be a significant engineering challenge, imagine the additional complexity if the vehicle could have no fuel tank. Rather, the vehicle itself must be composed of its fuel and must continually break down and reconstruct its components. Furthermore, despite the daily turnover of its components and fluctuations of fuel delivery, the composition of the vehicle must remain relatively stable and maintain similar performance characteristics.

Exactly this remarkable engineering feat is accomplished by the human body through its use of the three dietary macronutrients (carbohydrate, fat, and protein) to both fuel metabolism and provide substrates for body constituents. These macronutrients are obtained from the diet, with about 50% of the energy derived from carbohydrate, 35% from fat, and 15% from protein (5). However, these average diet proportions can vary widely from person to person and also from day to day. Complex physiological mechanisms maintain normal functioning of the body despite marked fluctuations of diet quantity and composition.

Figure 4
The Forbes hypothesis for the energy partition ratio, \( P \), as a nonlinear function of the body fat mass.
Figure 5  
Schematic depiction of the simple macronutrient balance concept, where changes in body fat, $F$, are determined by an imbalance between fat intake, $FI$, and fat oxidation, $FatOx$, and changes in lean mass, $L$, are determined by the remaining energy imbalance. EE, energy expenditure; EI, energy intake.

Modeling Macronutrient Balance

Although the molecular, cellular, and physiological mechanisms underlying the regulation of human macronutrient metabolism are exceedingly complex, the whole-body system obeys thermodynamic laws that constrain its dynamics in ways that make the overall system amenable to mathematical modeling (11). For example, macronutrient imbalances between dietary intake and metabolic utilization underlie changes of stored fat, glycogen, and protein and result in changes in the chemical composition of the body. Thus, models of macronutrient balance calculate dynamic changes in the chemical composition of the body as a result of imbalances between intake and utilization of macronutrients (33, 38). The overall body weight change is just the sum of the individual changes in body constituents.

The simplest mathematical model of macronutrient balance and its relationship to body composition change can be expressed as:

$$ \rho_L \frac{dL}{dt} = (EI - FI) - (EE - FatOx) $$

$$ \rho_F \frac{dF}{dt} = FI - FatOx $$

where $FI$ is the energy intake from dietary fat and $FatOx$ is the net energy derived from fat oxidation. The simple macronutrient balance model is conceptually illustrated in Figure 5.

Both energy balance models and energy partition models described by Equations 1 and 3 are special cases of the more general macronutrient balance model (11, 39). For example, when the simple macronutrient balance model is constrained so that $L$ and $F$ follow along the Forbes nonlinear body composition curve, the resulting model is equivalent to the energy partition model described by Equation 3 with the energy partition ratio $P$ shown in Figure 4 (11). Although it is more general than the energy balance and energy partition models, the macronutrient balance model also obeys the first law of thermodynamics.

The equivalence of Equations 3 and 4 under the constraint of a specified body composition relationship provides a quantitative explanation of how interactions between diet, energy expenditure, and fat oxidation are connected to changes of body composition (11, 39). Hall et al. (39) thereby derived an equation that accurately predicted the observed changes of body composition and metabolic fuel selection during both experimental under- and overfeeding in adult humans when the measured food intake and total energy expenditure were provided as inputs to the model. A similar approach was used to calculate metabolic fuel selection during normal human infant growth and provided the first dynamic picture of how metabolism adapts in concert with changes of diet and energy expenditure to give rise to normal tissue deposition over the first two years of life (51).

Equation 4 represents a simplified version of a more comprehensive computational model of human macronutrient balance and its relationship to body composition change (33, 38). The computational model quantitatively tracks the metabolism of all three dietary macronutrients and simulates 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. The macronutrient balance model is conceptually depicted in Figure 6 and mathematically represented by the following equations describing changes in the body’s energy stores of glycogen ($G$), fat...
(F), and protein (P):

\[
\rho_c \frac{dG}{dt} = CI - DNL + GNG_f + G3P - CarbOx
\]

\[
\rho_F \frac{dF}{dt} = FI + \varepsilon_d DNL - KU_{excr} - (1 - \varepsilon_k) KTG - FatOx
\]

\[
\rho_P \frac{dP}{dt} = PI - GNG_p - ProtOx
\]

where \(\rho_c\), \(\rho_F\), and \(\rho_P\) are the energy densities of carbohydrate, fat, and protein, respectively. The macronutrient intake rates, \(CI\), \(FI\), and \(PI\), refer to the metabolizable energy intake rates of dietary carbohydrate, fat, and protein, respectively. The rates of gluconeogenesis from amino acids and glycerol are indicated by \(GNG_f\) and \(GNG_p\), respectively. The efficiencies of de novo lipogenesis, \(DNL\), and ketogenesis, \(KTG\), are represented by the parameters \(\varepsilon_d\) and \(\varepsilon_k\), respectively. When the ketogenic rate increases, ketones are excreted in the urine at the rate \(KU_{excr}\). Some flux of carbohydrates is provided for the production of glycerol 3-phosphate, \(G3P\), which is used in the synthesis of triglyceride. The oxidation rates \(CarbOx\), \(FatOx\), and \(ProtOx\), sum to the energy expenditure rate, \(EE\), less the small amount heat produced via flux through ketogenic and de novo lipogenic pathways. Turnover of glycogen, fat, and protein and the corresponding energy costs are also included in the model. To account for body water shifts with diets that vary in macronutrient as well as sodium content, the model also tracks intracellular and extracellular fluid changes.

The main model assumptions are that changes of the body’s energy stores are given by the sum of metabolic fluxes entering the pools minus the fluxes exiting the pools. Hence, the computational model obeys the first law of thermodynamics, and the most recent version was developed using published human data from over 50 experimental studies and was validated by comparing model predictions with the results of several controlled feeding studies not used for model development (38). To date, this is the only mathematical model of human metabolism to consider all three dietary macronutrients and accurately simulate the metabolic and body composition changes in response to diet and physical activity changes in a wide variety of subject groups.

**ENERGY EXPENDITURE DYNAMICS**

When diet or physical activities are changed, the body’s metabolic fuel selection and the energy expenditure rate dynamically adapt. All mathematical models designed to accurately predict body weight and composition change must somehow account for these energy expenditure dynamics to avoid the same fatal flaw of the static 3,500-Calorie-per-pound weight loss rule. Figure 7 depicts the energy expenditure components for examples of relatively sedentary lean and obese men. The obese man requires several hundred additional kcal/d to maintain his increased weight compared to the lean man. Although this general dependence of weight on energy expenditure may be captured by a simple model of body weight alone, more realistic models of energy expenditure include its multiple physiological components: the thermic effect of feeding, resting metabolic rate, and physical activity.
Figure 7
The total energy expenditure in relatively sedentary obese and lean men, comprising the thermic effect of feeding, resting metabolic rate, and the physical activity.

Thermic Effect of Feeding
The smallest component of the total energy expenditure rate in humans is the thermic effect of feeding (also called diet-induced thermogenesis or specific dynamic action), defined as the increase of metabolic rate observed for several hours following the ingestion of a meal. The thermic effect of feeding is believed to represent the energy cost of digestion and absorption as well as the storage and metabolic fate of dietary macronutrients (106). Although the precise mechanisms underlying the thermic effect of feeding are not fully understood, there is a clear dietary macronutrient hierarchy in the magnitude of the metabolic rate increase after feeding, with protein causing a greater increment than carbohydrate, which is greater than that of fat. The computational model of macronutrient balance accounts for this hierarchy (33, 38), but all other energy balance and energy partition models ignore the macronutrient effect and assume that the thermic effect of feeding is given by an overall proportion of energy intake, typically ~7%–14%.

Resting Metabolic Rate
The resting metabolic rate (RMR) corresponds to the energy expended by the body when not performing physical work and is typically the largest contribution to the total energy expenditure rate. Contrary to popular belief, obese people generally have a higher absolute RMR compared to lean people (Figure 7). Readily available clinical measures (e.g., sex, height, weight, and age) have been used along with RMR measurements to generate empirical prediction equations with RMR being an increasing function of body weight, commonly a linear or a power law relationship. Although several mathematical models have used this simplified approach to modeling RMR (4, 94, 95), it has long been recognized that the main contributor to the RMR is the fat-free mass because it comprises the metabolically active tissues of the body (15).

Fat-free mass is elevated in obesity along with the increased body fat mass, which also contributes to increased RMR in obesity. The linear relationship between RMR and fat-free mass is identical in obese and lean people (15, 108). This means that the elevated RMR in obesity is generally in line with what is expected for the body composition of obese people.

Although fat-free mass and, to a lesser extent, fat mass are good predictors of RMR, such models explain only about 70% of interindividual RMR variability, such that for a given body composition the RMR standard deviation is about 300 kcal/d (15, 108). Since there is a large range of specific metabolic rates among various organs that contribute to the fat-free mass (21), some of this residual RMR variability may be due to differences in organ masses. Magnetic resonance imaging methodologies have been used to quantify organ sizes and, using assumptions regarding the organ-specific metabolic rates, RMR prediction equations that sum the individual metabolic rates of various organs explain about 80% of the RMR variability (31, 67, 68). Thus, increasingly detailed knowledge of body composition may improve RMR predictions.
The Payne and Dugdale energy partition model was the first to discriminate between “fast” and “slow” lean tissue contributions to RMR (74, 75). More recently, the computational model of macronutrient balance (38) incorporated how changes in the sizes of various organs affect RMR, assuming linear relationships between changes of fat-free mass and various organ sizes based on cross-sectional data from 110 men and women with body mass index (BMI) between 18 and 37 kg/m² (D. Gallagher, personal communication). Of course, longitudinal organ mass changes with weight gain and loss need not follow the cross-sectional relationships; this possibility requires experimental investigation.

Another potentially important contributor to RMR dynamics involves flux changes through various energy-requiring metabolic pathways. The major macronutrient fluxes of gluconeogenesis, de novo lipogenesis, triglyceride synthesis, and protein turnover all require energy, and these flux rates can be significantly influenced by the energy content of the diet as well as its composition. For example, the breakdown and resynthesis of body fat requires eight molecules of adenosine triphosphate (ATP) per molecule of triglyceride (22), and the flux through this pathway is strongly influenced by dietary carbohydrate via insulin’s inhibition of lipolysis. Similarly, protein synthesis requires four ATP per peptide bond plus one ATP for amino acid transport (6). Such energy-requiring metabolic fluxes have been incorporated into computational models of macronutrient balance (33, 38) and may explain the observed energy cost of tissue deposition that is especially important during growth and weight gain (36).

Physical Activity Expenditure

The physical activities of humans typically involve locomotion, and the energy costs are determined by the duration and intensity of physical activity in proportion to the overall body weight (98). Thus, obese and lean people can have similar daily energy costs for physical activity despite obese people typically being less active. With weight loss, it costs less energy to perform most physical activities, and therefore the physical activity expenditure typically decreases unless the quantity or intensity of physical activity increases to compensate.

All previous mathematical models of human energy expenditure include the body weight effect on physical activity expenditure. Some models further subdivide physical activity expenditure into volitional activities (e.g., exercise) and low-intensity spontaneous physical activity or nonexercise activity thermogenesis (38, 94, 95).

Adaptive Thermogenesis and Metabolic Adaptation

During active weight loss, both RMR and energy expenditure have been observed to decrease to an extent greater than expected based on the measured body weight and composition change (18, 19, 46, 60, 83). Furthermore, this improved energy efficiency appears to persist once energy balance is established at a lower body weight (82), although the magnitude of this persistent effect is smaller than during active weight loss, and its existence has been controversial (26, 104). Conversely, overfeeding and weight gain can result in highly variable increases of energy expenditure that can be greater than expected based on the observed weight gain (62, 63). Collectively, these phenomena have been called adaptive thermogenesis (65, 83) or metabolic adaptation (58, 80). In the case of overfeeding, the term luxuskonsumption has been used to describe adaptive increases in energy expenditure (79).

Most mathematical models of energy regulation in humans have ignored such adaptive changes in energy efficiency, although several have attempted to account for such effects (33, 38, 41, 43, 44, 46, 56, 57, 72, 94, 95, 107). The energy partition models of Hall et al. (41, 43, 44) incorporated adaptive thermogenesis as an additive term that was a linear function of the energy intake change. In these models, the value of the adaptive thermogenesis parameter
was chosen to match changes in overall energy expenditure measured before and after approximately stable weight loss (43). When active weight loss is followed by subsequent weight stabilization, the change in energy intake required for the weight loss phase is greater than that required for weight stabilization at the reduced weight. Thus, modeling adaptive thermogenesis as a function of the energy intake change has the natural consequence of increasing its magnitude in situations of active weight loss, in agreement with observations (104). A similar approach was used by Westerterp et al. (107), who added an energy expenditure reduction term to account for the effect of the degree of energy imbalance on metabolic rate. In contrast, the energy partition models of Thomas et al. (94, 95) used a constant parameter to model the metabolic adaptation of RMR with weight loss and did not distinguish between active weight loss and weight stabilization. Kozusko (56, 57) considered a set-point model of adaptive thermogenesis as a function of the body weight itself.

Experimental quantification of the adaptive thermogenesis magnitude depends on the definition of the expected values for RMR and total energy expenditure. Typically, cross-sectional regression equations are used to calculate the expected values, using for RMR and total energy expenditure measurements derived either from baseline body composition data in the same subjects (46, 60, 80) or from a separate group of similar subjects (18, 19). But such expected values for RMR and energy expenditure ignore the possible changes in organ size distribution as well as changes in fluxes through energy-requiring metabolic pathways during over- or underfeeding (described above). Whether such considerations can explain the observed changes in energy efficiency is unclear.

Novotny & Rumpler (72) used a mathematical model to investigate the impact of a disproportionate reduction of high-metabolic-rate organs during weight loss and found that such changes could potentially explain the observed reduction of RMR, but the organ sizes were not measured. Conversely, the computational model of macronutrient balance that accounts for alterations of energy-requiring metabolic fluxes as well as organ mass changes required an adaptive thermogenesis model variable to explain the observed average decrease in both RMR and total energy expenditure with weight loss (33, 38). The adaptive thermogenesis model was a linear function of the reduction in energy intake below baseline and was used to suppress the metabolic rate of all organs as well as reduce the energy expended in spontaneous physical activity. The mechanistic basis of such a metabolic adaptation is unclear but may be related to reduced sympathetic drive or blunted thyroid activity, possibly as a result of decreased circulating leptin (58, 81, 83–85, 103).

Interestingly, the adaptive thermogenesis effect was not required to accurately simulate overfeeding and weight gain in the computational model of macronutrient balance (33, 38). Similarly, the energy partition models of Westerterp et al. (107) and Thomas et al. (94, 95) required a metabolic adaptation parameter to explain changes of energy expenditure with weight loss but not weight gain. If correct, such an asymmetry in energy regulation suggests that the body is neutral to overfeeding and weight gain but actively resists weight loss by improving its energy efficiency during underfeeding—much to the dismay of overweight and obese people wishing to lose weight.

INSIGHTS OBTAINED FROM MATHEMATICAL MODELS

Is a Calorie a Calorie? The Effect of Dietary Macronutrients on Body Composition

A topic of great popular interest is the relative effectiveness of weight loss diets varying in macronutrient composition (92). While fully complying with the laws of thermodynamics, macronutrient balance models allow for the possibility that body weight may depend on the diet composition because the energy stored...
per unit mass of carbohydrate, fat, and protein varies considerably, especially when accounting for the intracellular water associated with stored glycogen and protein. Furthermore, dietary carbohydrates have an impact on renal sodium excretion via insulin (16), which results in concomitant changes in extracellular fluid volume. Therefore, when the composition of the diet is altered, transient changes in macronutrient stores and body fluid shifts will result in an expected body weight change even when the energy content of the diet is held constant (99).

A more important consideration is whether body fat mass depends on the macronutrient composition of the diet. Proponents of low-carbohydrate diets for weight loss emphasize the ability of dietary carbohydrate to influence adipose tissue fat storage via circulating insulin (92). Therefore, it is claimed that body fat changes depend primarily on dietary carbohydrate and not the energy content of the diet. Macronutrient balance models allow for this possibility, but energy balance and energy partition models assume that “a calorie is a calorie” (8) and therefore all equivalently reduced energy diets should lead to identical body fat loss regardless of their macronutrient composition. However, this assumption is not an obvious or necessary consequence of the first law of thermodynamics because the more general macronutrient balance models allow for an effect of diet composition while also obeying the law of energy conservation. In fact, to achieve an independence of body fat on the macronutrient content of the diet requires a robust physiological control system to precisely adapt metabolic fuel selection to the diet composition (37). Nevertheless, most inpatient studies with adequately controlled diets have shown little impact of diet composition on body weight and fat mass changes (55, 59, 100, 105, 111, 112), but there are notable exceptions (52, 77, 78). Thus, it remains to be determined whether the physiology regulating metabolic fuel selection can fully adapt to diet composition over extended time periods without resulting in body fat mass changes.

Another argument against the concept that “a calorie is a calorie” is that the diet composition can have a significant impact on the flux pattern through various energy-requiring metabolic pathways and may thereby affect the body’s energy expenditure rate (23, 24). Despite the attractive theoretical possibility of a significant “metabolic advantage” of one diet over another, simulations using a computational model that includes the contributions of energy-requiring metabolic fluxes (38) suggest that the overall effect of diet composition on energy expenditure appears to be relatively modest, especially when dietary protein is unchanged. Specifically, the model predicts that large isocaloric exchanges of dietary carbohydrate and fat will result in energy expenditure changes of around 100 kcal/d. These model results agree with experimental observations (86), and therefore the assumption that a “calorie is a calorie” may be a reasonable first approximation over relatively short time periods. However, even small differences in energy expenditure and macronutrient balance can theoretically lead to significant differences of body weight and composition if the diets are maintained over long periods. A 100 kcal/d difference in energy expenditure alone could lead to an initial body fat imbalance of about 10 g/d. Using current body composition methods, it would require a sustained period of about 100 days to detect such a difference in body fat. Nevertheless, this possibility requires further investigation.

Behavioral Adaptations to Energy Imbalance

Energy imbalance and weight change can influence behaviors that directly affect energy intake and/or expenditure. For example, outpatient weight loss interventions geared to reducing energy intake typically result in a period of weight loss that plateaus after about six to eight months, followed by slow weight regain (47, 90). The well-known deficiencies in assessing free-living energy intake (97, 109) make it extraordinarily difficult to interpret such results, and mathematical models have...
recently been proposed to address this difficulty by estimating changes of free-living energy intake using longitudinal measurements of body weight (38, 40, 96). Such models have shown that the typical weight loss, plateau, and regain trajectory was likely due to short-lived adherence to the prescribed diet that was progressively relaxed over the first year to return to the preintervention level (38, 44). Thus, an energy imbalance resulting in transient weight loss leads to an eventual adaptation of behavior to return to the original lifestyle.

Another example of a behavioral adaptation to energy imbalance is the compensatory changes in energy intake when a physical activity program is added. In particular, engaging in many weeks of supervised exercise leads to a wide range of individual weight changes, with some people gaining weight and others having greater-than-expected weight loss (7, 10, 53, 54). These results imply that volitional physical activity can have a wide range of effects on energy intake and/or other components of total energy expenditure.

Under- and overfeeding may also significantly influence physical activity expenditure, especially nonvolitional spontaneous physical activity (62, 63). This effect is very difficult to model because of the highly variable interindividual response. Thomas et al. (94, 95) attempted to account for the average change in spontaneous physical activity in the presence of this variability. However, the mathematical equation used to model this effect has two constraints on its use. First, the model is not applicable during prolonged substantial underfeeding because the equation allows for the possibility of negative values for the spontaneous physical activity expenditure that is not physiological. Second, the model requires that changes in any other component of total energy expenditure are positively correlated to changes in spontaneous physical activity. For example, increased volitional physical activity or exercise in the Thomas model necessarily results in an increased spontaneous physical activity. Such an effect would not apply to people where added exercise results in fatigue and a corresponding reduction in subsequent spontaneous physical activity. Hence, application of the model of Thomas et al. requires a priori knowledge of the highly variable response characteristics of the individual.

The highly variable behavioral adaptations to energy imbalance pose a significant challenge for modeling individual weight changes. Rather than attempting to directly simulate these behavior changes, models that start by assuming no effect might be used to help estimate the magnitude of any behavioral adaptations by measuring the difference between the measured and model-predicted weight change. Furthermore, models that can quantitatively integrate physiological data collected during the intervention may be used to better characterize behavioral adaptations in the overall context of energy and macronutrient balance.

Weight Change Variability Due to the Uncertainty in Baseline Energy Requirements

Calculating the energy imbalance generated by a given diet requires knowing the energy requirement to maintain the baseline body weight. Unfortunately, even the specialized and expensive doubly labeled water method cannot measure the initial energy requirements of a free-living individual with a precision better than ∼5% (87). The uncertainty of the baseline energy requirements translates to an expected interindividual variability of weight change even if adherence to a prescribed diet is perfect (44). This is a fundamental limitation on a model’s ability to precisely predict the body weight time course of an individual. For example, assuming a ±150 kcal/d uncertainty in the initial energy expenditure requirements, the dotted curves in Figure 8a illustrate the minimum expected weight gain variability during a study intending to overfeed subjects by 500 kcal/d above baseline energy requirements. In this example, the energy partition model of Hall et al. (44) was used to simulate multiple runs of the same 70-kg “virtual study subject,” assuming
Greater Weight and Body Fat Gain in Obesity for the Same Increment in Energy Intake

Another source of weight change variability results from physiological differences that are captured by mathematical models of human energy regulation. For example, Figure 8b illustrates the predicted average weight change for a 500 kcal/d increase of daily energy intake in both a 120 kg man and a 70 kg man using an energy partition model (44). Although the average weight gain over the first year is comparable, it takes longer for the 120 kg man to reach half of the maximum weight change compared with the 70 kg man, and both men require several years to begin to stabilize at a new weight plateau. Mechanistically, these different average weight change predictions result from the nonlinear relationship between body fat and the fraction of weight change accounted for by increased lean tissue. Thus, persons with higher initial body fat have a greater fraction of their weight change attributable to increased body fat versus lean tissue. Because body fat contributes less than lean tissue to RMR and overall energy expenditure, the person with higher initial body fat must gain a greater amount of weight to achieve a new state of energy balance (37, 43, 44).

This finding of increased weight gain in obese versus lean individuals for the same increment of energy intake is shared by all mathematical models that include nonlinear body composition changes as well as the differential effect of lean versus fat tissue on RMR (37, 43, 44, 102). It is also a feature of models where energy expenditure increases sublinearly with body weight (4, 94, 95) because the same weight change at a higher initial body weight results in a smaller change of energy expenditure. In other words, a sublinear increase of energy expenditure with increased body weight indirectly reproduces the nonlinear body composition effect on RMR. This results in increased predicted weight gain for the same increment in energy intake for people with greater initial weight.

These mathematical model predictions that the same increment of energy intake leads to increased weight gain in overweight and obese people may help explain the observed increased positive skewness of the U.S. population’s BMI distribution over time (27). In other words, if the same average increase in energy intake were
added to all individuals across BMI categories, then mathematical models predict that more weight would be gained in people with larger BMIs, thereby pushing out the upper tail of the BMI distribution with time. Whether this effect is sufficient to explain the evolving shape of the BMI distribution is an intriguing question.

CONCLUSIONS AND FUTURE DIRECTIONS

In the physical sciences, there is a long history of developing mathematical models that quantitatively describe past data and predict the results of key new experiments. Such quantitative models have been relatively rare in the biomedical sciences, possibly because biological systems are highly complex, and defining the important variables is often difficult. Fortunately, models of human energy regulation and macronutrient metabolism are constrained by conservation principles and knowledge of the main metabolic pathways that contribute to whole-body imbalances.

A guiding principle when developing a mathematical model is to target its complexity to the class of phenomena that the model is intended to address. Mathematical models of human energy regulation and body weight dynamics have ranged in complexity from detailed computational models that accurately simulate dynamic changes in macronutrient metabolism and body composition to overly simplified static weight loss models that fail to capture the most basic features of body weight dynamics. Most other models fall between these extremes and have been used to provide important insights regarding human energy regulation and body weight change.

Despite significant progress, much work remains for improving and expanding the existing mathematical models of human energy regulation and body weight change. For example, the anatomical location of body fat, especially in visceral adipose tissue, has profound clinical importance, and mathematical models have only just begun to capture the relationship between body fat changes in various depots during weight loss and gain (42, 45). Furthermore, even the most detailed computational models of macronutrient metabolism implicitly represent the effect of hormones such as insulin, but an explicit representation of organ systems along with concentrations of hormones and metabolites would be desirable—especially on shorter time scales so that the response to individual meals could be simulated (17, 73). Conversely, capturing the dynamics of energy regulation and body composition change during aging as well as during childhood and adolescent growth (9) will require extending current mathematical models to operate on much longer time scales.

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” (76). As highlighted in this review, much progress has been made on integrating past research on human nutrition and metabolism into self-consistent and predictive mathematical models of energy regulation and body composition change. Such models can highlight knowledge gaps, integrate metabolic data within a broader context of knowledge, and make testable predictions, thereby helping design new experiments. Indeed, the best mathematical models will never replace experimental research but rather will be used to help design the key experiments that, in turn, will help improve the mathematical models and our understanding of the human energy regulation system.

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