



Predictive Mathematical Models of Weight Loss

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Abstract

Purpose of Review Validated thermodynamic energy balance models that predict weight change are ever more in use today. Delivery of model predictions using web-based applets and/or smart phones has transformed these models into viable clinical tools. Here, we provide the general framework for thermodynamic energy balance model derivation and highlight differences between thermodynamic energy balance models using four representatives.

Recent Findings Energy balance models have been used to successfully improve dietary adherence, estimate the magnitude of food waste, and predict dropout from clinical weight loss trials. They are also being used to generate hypotheses in nutrition experiments.

Summary Applications of thermodynamic energy balance weight change prediction models range from clinical applications to modify behavior to deriving epidemiological conclusions. Novel future applications involve using these models to design experiments and provide support for treatment recommendations.

Keywords Thermodynamic energy balance models · Weight change prediction

Introduction

Predicting weight loss is critical for designing effective weight loss interventions [1, 2], providing accurate weight loss prescriptions for patients [3–5], and evaluating components of energy balance post hoc [6–8]. This need has led to a wide collection of varied weight loss prediction models that differ in how changes in energy storage and energy expenditure are compartmentalized [9•, 10, 11, 12•, 13, 14, 15•, 16, 17].

Early Weight Change Models

In 1958, Max Wishnofsky extended biological conclusions from a combination of Key's Minnesota study and the best existing human subject weight loss data to derive a universal constant rate of weight loss [16]. For this simple regression model, it was assumed that weight loss had no effect on the energy expended during calorie restriction and that the model was only valid for at most a few months. Wishnofsky's analysis determined the rate of weight lost to energy deficit as 1 lb (2.2 kg) per 3500 kcal and is commonly referred to as the 3500 kcal rule [5]. Because of Wishnofsky's model simplicity, weight regulation researchers [18], commercial weight loss programs, and national guidelines continue to apply this simple rule even today extrapolating well past Wishnofsky's original model assumptions [5].

For a few decades after the development of Wishnofsky's model, little quantitative analysis of body weight regulation was conducted. Then in 1970, the pediatrician, Gilbert Forbes, developed the first dose-response model predicting weight loss during starvation [17]. Forbes had an unusual intuitive command of calculus and possibly unknown to him conjectured a curve that is in fact the solution to a second-order linear differential equation:

$$M(t) = c_1 e^{-\lambda_1 t} + c_2 e^{-\lambda_2 t}$$

This article is part of the Topical Collection on *Obesity*

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where $M(t)$ represents body weight on day t of weight loss. Forbes estimated the coefficients c_1 , c_2 and the half-life (eigenvalues), λ_1 , λ_2 from experimental data and then demonstrated the models validated well on two individual subjects undergoing fasting [17].

Thermodynamic Weight Change Models

Early models depended on conjecturing the functional form of the weight change line/curve and then fitting the line/curve to data. As investigators trained in quantitative fields began modeling weight change, incorporating physiological properties that are altered in response to changes in diet or activity became an important foundation for first-principle models. This mechanistic approach starts with the first law of thermodynamics, which can be reduced to what is referred to as the human energy balance equation [19].

The energy balance equation describes the relationship between rate of energy intake and expenditures in humans. If EI , EE , and ES in kcal/day denote the rate of energy intake, energy expenditures, and rate of energy stores respectively, the energy balance equation is formulaically expressed as

$$ES = EI - EE$$

We refer to the models that are derived directly from the energy balance equation above as thermodynamic models. These models incorporate changes in terms of the human energy balance equation that are affected by changes in diet and activity [9••, 10, 11, 12••, 13, 14, 15••]. In this review, we provide an overview of four representative thermodynamic weight change models highlighting their differences and their utility (Table 1).

This presentation is followed by novel applications of these models that range from smart phone clinical applications to evaluation of weight loss effects in pharmacotherapy. The advancement of thermodynamic models in combination with increased collaboration between disciplines has improved predictive accuracy and enhanced innovation in weight loss therapy.

Thermodynamic Models

Overview

Since all thermodynamic models originate from the first law of thermodynamics, their differences are largely due to how ES and EE are modeled. Simple divisions of ES or EE yield a more tractable model [9••], while more complex divisions reveal more about the underlying mechanisms of human body weight regulation [15••]. The divisions in ES involve compartmentalizing total body mass, W , into sub-energy storage sites (Fig. 1):

$$\begin{aligned} W &= FM + FFM \\ &= FM + (\text{Protein} + \text{Glycogen} + \text{Other (bone, water)}) \\ &= FM + (\text{Glycogen} + \text{Other (protein, bone, water)}) \end{aligned}$$

FM is fat mass and FFM is fat-free mass. Depending on how the modeler determines these divisions changes the number of state variables and sometimes the terms required for EE .

Likewise, EE can be compartmentalized into different expenditures of the human body (Fig. 2). This can range from EE being expressed as a multiple of resting metabolic rate

Table 1 Summary of models, their state variables, the energy expenditure terms, strengths, and limitations

Model	State variables	EE terms	Strengths	Limitations
Antonetti [9••]	M	TEF, PA (as activity level), RMR	Simple, closed form solution	Does not describe changes in body composition
Thomas et al. [20]	FM, FFM	TEF, PA, RMR, SPA	Simple to program, no requirement of baseline PAL knowledge	Does not include exercise intervention effects, does not include macronutrient effects
Flatt [12••]	Glucose/glycogen, FM	PA, RMR, TEF	Focuses on carbohydrate intake	Model equations are unavailable
Hall [15••]	Glucose/glycogen, protein, FM		Highly descriptive impacts of changes in macronutrients on body weight regulation	Challenging to program

CHO, carbohydrates; *EE*, energy expenditure; *FFM*, fat-free mass (kg); *FM*, fat mass (kg); *M*, total body mass (kg); *PA*, physical activity (kcal/day); *PAL*, physical activity level; *SPA*, spontaneous physical activity (kcal/day); *RMR*, resting metabolic rate (kcal/day); *TEF*, thermic effect of food (kcal/day)

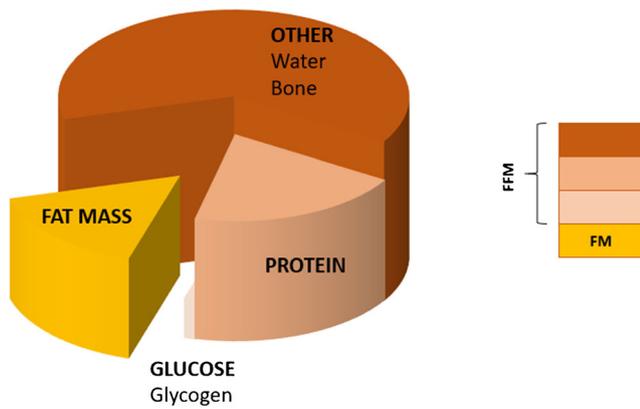


Fig. 1 Partitioning body mass into compartments. Total body mass can be divided into fat mass (FM) and fat-free mass (FFM). FFM can be further divided into protein, glycogen (carbohydrates), and other non-energy contributing components such as water and bone mass

(RMR) to variations in subdivided components such as physical activity (PA), spontaneous physical activity (SPA), and thermic effect of food (TEF). The divisions of EE become even more refined if the state variables correspond to specific macronutrients resulting in a carbohydrate oxidation model, fat oxidation model, and protein oxidation model [15••].

Here, we outline four representative models selected for differences in ES and EE development by defining their state variables, outlining the EE terms, identifying key assumptions, and highlighting the model strengths. A summary of model highlights and differences are presented in Table 1.

The Antonetti Model

Antonetti, motivated by the improper use of the 3500 kcal rule, developed the first thermodynamic model in 1973 [9••]. The sole state variable was total body weight on day *t* of weight change, *W(t)*. In this case, there is no

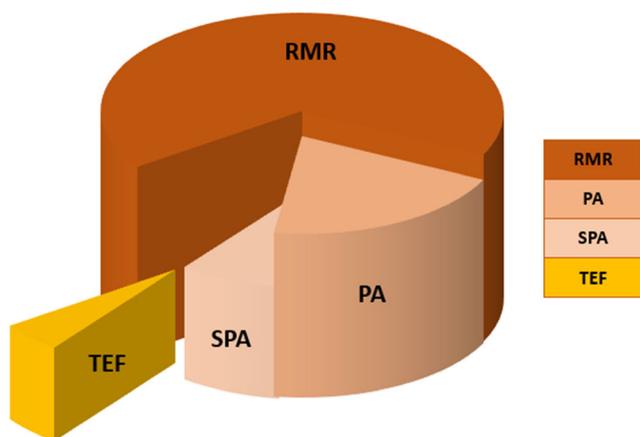


Fig. 2 Partitioning of the compartments that comprise total energy expenditure. Energy expenditure can be divided into resting metabolic rate (RMR), physical activity (PA), spontaneous physical activity (SPA), and the thermic effect of feeding (TEF). RMR can be divided even further into organ-specific metabolic rates

compartmentalization of energy stores into FM, FFM, protein, or glycogen stores (Fig. 1). Antonetti used the energy conversion of 3500 kcal/lb or 7700 kcal/kg [16] to convert the rate of change of body weight with time, thereby correcting Wishnofsky’s model to include the time varying changes in body weight during weight change. To model EE, Antonetti divided EE into the components, RMR, PA, and TEF. Using a RMR model dependent on body surface area, Antonetti derives the nonlinear term for RMR:

$$RMR = K_B W(t)^{0.73}$$

Where the constant K_B is a function of height, age, and gender. TEF is modeled as a direct proportion of EI and PA is modeled as a direct proportion of total body mass, *W(t)*. The proportionality constant reflects an activity level. The values corresponding to categorized levels of activity (sedentary to severe) were provided in the study report [9••].

The resulting differential equation does not have a closed form solution; however, Antonetti, an engineer at IBM, had access to computational power and could numerically integrate the solutions. Antonetti demonstrates the failure of the 3500 kcal rule to capture the nonlinear self-limiting nature of weight loss and successfully compares his model predictions to Ancel Key’s Minnesota Starvation Experiment [21], the only published carefully supervised weight loss study available at the time. Key’s tightly controlled in residence study monitored strict adherence to a constant caloric intake which Antonetti’s model assumes. Antonetti’s model assumes the energy content of weight loss is constant (7700 kcal/kg) and also assumes that all physical activity expenditure is a direct proportion of body weight. The model, however, is simple and easily programmed. In fact, the model was further simplified by substituting a linear regression model for RMR replacing the body surface model [22] which allows for direct integration without need of numerical approximations.

The strength of the model is that it only relies on total body mass at baseline and demographic inputs. It is simple enough to invert and algebraically solve for energy intake during weight change given body weights [22]. However, the simplicity of the model is also a limitation since the model does not provide information regarding macronutrient effects on body weight and expenditure or adiposity.

The Flatt Model

J.P. Flatt presented a thermodynamic model that is distinct from other existing models on two points [12••]. First, the time scale of the model is measured in hours. Flatt wanted to capture dynamic fluctuations of energy balance within the day and then extend the simulation over a few days. Second, Flatt’s model assumes protein stores are relatively constant,

thus yielding no rate of change term in the differential equation model. Additionally, Flatt assumes that energy intake was consumed three times a day through meals. In Flatt's model, *ES* is compartmentalized into glycogen stores and fat stores. Two separate uncoupled differential equations were derived: a carbohydrate balance equation and a fat balance equation. The *EE* term in the model accounts for varying oxidation rates and physical activity. *EI* is a function of carbohydrate and fat intake, food availability, diversity, and palatability estimated parameters. Because of the time scale (hourly), Flatt needed to account for metabolic changes before and after meals. Flatt's model simulates the in vivo influence of insulin in oxidizing carbohydrates and fat after meals.

Flatt validated the dynamics of the model against data from an experiment over two meals where the subject's metabolic response was measured for 9 h after consumption. The model predicted dynamics matched these experimental results.

In a larger sample of 33 subjects, Flatt evaluated the response to changing intake over a 125-day experiment where subjects were placed on provided low-kcal meals for 10 days. These meals were increased by 100 kcal/day and the final 20 days of data were used to validate the model at steady state. The main finding from this model indicates that steady-state fat stores are particularly sensitive to a parameter that mimics the influence of insulin.

The Thomas Model

Thomas et al. developed a system of differential equations [5, 7, 20] governed by two state variables, kg of FM on day t of weight change ($FM(t)$) and kg of FFM on day t of weight change ($FFM(t)$). $FFM(t)$ represents the sum of protein, glycogen, and the mass of all other non-energy compartments such as water on day t of weight change (Fig. 1). The sum of both state variables yields kg of total body mass on day t of weight change, $FM(t) + FFM(t) = M(t)$ (Fig. 1). The model is further reduced to one dimension by pairing FFM to FM using the algebraic Forbes relationship (6).

Specific terms for energy expenditure are developed for RMR, PA, spontaneous physical activity (SPA), and the TEF (Fig. 2). RMR is modeled using a regression formula reported by Livingston and Kohlstadt [23], while PA is modeled as a direct proportion of body weight. Similar to the Antonetti model, TEF is modeled as a direct proportion of *EI*. SPA is modeled using the experimental conclusions of Levine et al. [24] that found $\Delta SPA = \frac{2}{3} \Delta EE$.

A key model assumption is that physical activity is not raised from baseline beyond weight-related changes; specifically, the model was not developed to predict changes in weight due to exercise interventions.

The simplicity of the model allows for flexible programming for clinical application [25] and inversion to estimate *EI*

that resulted in weight change [7]. The model also does not require an input of physical activity level which may not be truly known for an individual.

The Hall Model

The Hall model [15••, 26] consists of three coupled state equations representing carbohydrate energy balance, fat energy, and protein energy balance. Each equation dissociates at the macronutrient level the metabolic processes from carbohydrate, fat, and protein intake to carbohydrate, fat, and protein oxidation. Since certain amino acids can convert to glucose through the process of gluconeogenesis, glucose can be synthesized to fat (triglyceride) through de novo lipogenesis, and the glycerol portion of triglycerides can be converted to glucose, there exist flows between the compartments and hence the differential equations are coupled.

Numerical simulations of the Hall model yield trajectories for fat, glucose/glycogen, and protein. Body weight can be constructed from these trajectories under assumptions and formulations for components of FFM. Similarly, total energy expenditure can be constructed from all the sub-components of energy expenditure within the model.

The Hall model provides an understanding of the physiology of weight change at the mechanistic level and invites insights into how changes in macronutrient intake may impact different components of body composition and body weight [27].

Applications of Thermodynamic Models

Application of a Thermodynamic Model to Facilitate Dietary Adherence

SmartLoss™ is a weight loss management platform that incorporates electronic measurements of patient body weights and physical activity behavior using electronic scales and accelerometers [25, 28]. Patients undergoing weight loss are provided a personalized weight graph generated from the model of Thomas et al. [20, 29]. Model inputs are degree of energy restriction and patient age, height, baseline weight, and gender. The generated graph is encapsulated in an error "zone" which describes the model variance during validation. Patient daily body weights are automatically extracted from the electronic scales onto their weight graph application delivered on smart phones and identified using color-coded flags as being in the zone or out of the zone. If a weight is out of the predicted zone, the patient is provided additional feedback with a clinician to promote adherence and moving weights back into the zone.

The capacity for SmartLoss to promote adherence was tested in a 12-week randomized controlled trial.

Twenty adults with overweight or obesity were assigned to an energy-restricted intervention of 1200–1400 kcal/day guided by the thermodynamic model in SmartLoss. Twenty adults were assigned to a control group that only received health education via texts on their smart phones. The SmartLoss™ intervention group lost an average of 9.4% of body weight in the 12-week intervention while the control group lost an average of 0.6% of body weight.

The continuous feedback provided by the thermodynamic model enhanced adherence and is now being used for long-term weight loss programs. Guidance by the thermodynamic model is available commercially in the BodyKey SmartLoss™ program delivered by Amway [30].

Food Waste Estimation

Food waste is the difference between food production and food consumption. Hall et al. [31] applied a thermodynamic energy balance model to back-calculate population-wide *EI* from body weights. A Monte Carlo simulation was used to approximate *EI* for each individual in the population and then the values were summed over the population. The resulting quantity is subtracted from USDA published statistics on food availability to estimate total food waste, which the authors found had risen by at least 10% in the last few years. Although this model is limited in applications for an individual, which is noted by the authors, it serves a valuable purpose of being able to provide a reasonable bound based off sound analysis for the food waste problem, which presents both economic and environmental challenges far beyond the obvious.

Dietary Compensation During Exercise

It is well known that little or no weight is lost because of exercise interventions [6, 32]. One of explanations for this modest weight loss is that individuals compensate for the additional exercise energy expenditure with increased energy intake. This phenomenon is referred to as dietary compensation [33, 34]. To determine the role of energy intake on modest weight loss during an exercise intervention, Thomas et al. [6] discretized the differential equation model:

$$9500 \frac{dFM}{dt} + 1020 \frac{dFFM}{dt} = EI - EE$$

as:

$$9500 \frac{\Delta FM}{\Delta t} + 1020 \frac{\Delta FFM}{\Delta t} = EI - EE_f$$

where 9500 and 1020 were the energy densities of FM and FFM used in [7] and EE_f is the energy expenditure at final time measured by the doubly labeled water (DLW) method. From the discretized differential equation, *EI* can be algebraically isolated:

$$EI = EE_f + 9500 \frac{\Delta FM}{\Delta t} + 1020 \frac{\Delta FFM}{\Delta t}$$

and calculated using change data. Pre and post intervention data from a 44-week exercise intervention designed to train 32 sedentary individuals was used to calculate EE_f , $\frac{\Delta FM}{\Delta t}$, $\frac{\Delta FFM}{\Delta t}$ where 13 of the subjects had DLW measurements [35]. From this data, 12 of the 13 subjects increased *EI* during the intervention leading to little or no weight loss by end of intervention (Table 2).

Predicting Success in Dietary Weight Loss Interventions

Recently, there have been efforts to identify which participants are likely to succeed in a weight loss study from short term or even baseline data [36]. One important predictor of long-term weight loss success is early dietary adherence [37]. Thermodynamic energy balance models can be used to quantify adherence by estimating the difference between actual versus expected weight loss. Using logistic model inputs of short-term percent weight loss, adherence, and demographic variables, long-term weight loss success can be predicted with good accuracy [38]. These data can then be used to counsel patients early during the intervention while motivation is high. Alternate weight loss therapies such as pharmacotherapy and/or surgery can be advised if the probability of success in response to dietary intervention is low.

Table 2 Change in energy intake during exercise derived using [35]

SS	Baseline EI (kcal/day)	Final EI (kcal/day)	ΔEI (kcal/day)
1	2818	3543	724
2	2594	2987	393
3	2938	3434	496
4	3726	3911	184
5	2508	2993	485
6	3153	3410	258
7	2699	3432	733
8	2484	3240	756
9	2365	2716	352
10	2389	2479	90
11	1887	2731	844
12	2412	2937	524
13	2317	2270	-47

EI, energy intake; *SS*, subject number

Discussion and Conclusions

Because of computational ease of delivery through web-based and smart phone applications, validated thermodynamic energy balance models that predict weight change are increasingly being used in various applications. These models differ from traditional statistically based formulations because they do not require longitudinal weight loss data for model development, relying instead on the first law of thermodynamics. The models can be applied to predict weight change, guide adherence, estimate population-wide effects, and provide physiological insights into underlying mechanisms of weight change.

There are nearly a dozen thermodynamic energy balance models in existence today [9••, 10, 13, 14, 39–43]. Each model differs by time scale, method of division of *ES*, and method of division of *EE*. Here, we outlined differences in four representative models to identify how these divisions of *ES* and *EE* can manifest itself in term development and final model appearance. The variation of models lead to different model strengths ranging from Antonetti's 1973 model [9••] that yields simple predictions of weight change that can be expressed in closed form to the more complex Hall model [15••] that provides macronutrient level insight.

Applications of the models are still emerging. Some applications are in the early stage, for example using the models to intervene when there is a risk identified of potential weight loss clinical trial drop outs has to our knowledge not yet been evaluated. As the obesity/clinical community becomes more familiar and comfortable with thermodynamic energy balance models, we anticipate additional future novel model applications.

Compliance with Ethical Standards

Conflict of Interest Diana M. Thomas is the co-inventor of SmartLoss used in BodyKey. She does not receive any financial compensation for this invention.

Michael Scioletti and Steven B. Heymsfield declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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