Mathematical Biosciences and Engineering

https://www.aimspress.com/journal/mbe

MBE, 21(7): 1790–1824.
DOI: 10.3934/mbe.2025065
Received: 10 January 2025
Revised: 15 March 2025
Accepted: 19 May 2025
Published: 05 June 2025

Research article

Food choices and body weight changes: A mathematical model analysis

Mantana Chudtong[1,2,*] **and Andrea De Gaetano**[1,3,4]

[1] Department of Mathematics, Faculty of Science, Mahidol University, Bangkok 10400, Thailand
[2] Center of Excellence in Mathematics, the Commission on Higher Education, Si Ayutthaya Rd., Bangkok 10400, Thailand
[3] National Research Council of Italy (IRIB-CNR and IASI-CNR), Palermo and Rome, Italy
[4] Dept. of Biomatics, Óbuda University, Budapest, Hungary

* **Correspondence:** Email: mantana.chu@mahidol.ac.th.

Abstract: A short–term stochastic model of minute–by–minute food intake is formulated, incorporating the interaction of appetite, insulinemia, and glycemia in determining the size and frequency of meals. By assuming a person would maintain his or her eating habit over time, we extend the simulation period to several years and explore scenarios based on food choices (high–fiber vs. high–carbohydrate) or appetite suppression. The model coherently predicts increments or decrements in body weight in the long–term when altering appetite in the short–term. Further, the model shows how food type choice, at the same appetite drive and habitual proposed meal size, induces macroscopic changes in body weight over a very few years. The model is innovative in that it connects the minute–by–minute behavior of the individual with long–term changes in metabolic compensation, in insulin sensitivity, in glycemic variability, and eventually in body size, thus helping to interpret the long–term development of Type 2 diabetes mellitus resulting from an unhealthy lifestyle.

Keywords: body weight; mathematical modeling; glycemia; insulin resistance; obesity; energy expenditure; metabolism; ordinary differential equations; food intake

1. Introduction

1.1. Overweight and obesity

According to the World Health Organization (WHO) [1], a person is diagnosed as overweight or obese if body mass index (BMI) exceeds 25 kg/m^2 or 30 kg/m^2, respectively. In 2022, 2.5 billion (43%) of adults were overweight, while 890 million (16%) were affected by obesity. The obesity issue first appeared to be widespread through the USA during the years 1976–1980, subsequently spread-

ing across Westernized countries [2–4]. The global rise in obesity prevalence has risen to epidemic proportions and threatens the health of billions, straining healthcare systems worldwide.

One of the main causes that lead to the rapid rise of obesity, at least over the past 20 years or so [2] is the wide diffusion and availability of cheap ultra–processed foods (UPFs) (i.e., high–calorie foods containing mostly salt, sugar, and fat) in Western countries, especially the USA. From 1970 to 2005, the consumption of total sugars and sweeteners in the US increased by a substantial 19%, mostly driven by the increase in the consumption of corn sweetener, which increased in the same period by 387% [5]. Sugar–loaded beverages have been identified as a major determinant of obesity development [6]: In Morenga et al. [7], sugar–rich food intake was proved to be linked with increased body weight through a meta–analysis. It is thus clear that excess consumption of sugar–rich foods may alter energy balance and lead to overweight and obesity, even in regions with traditionally healthy (vegetable–rich) diets and active lifestyles, such as the Mediterranean or South–East Asia.

Many severe conditions are caused by or at least linked with obesity, such as non–communicable diseases including heart disease, stroke [8, 9], and diabetes, which were the major causes of death in 2019 [10]. Obesity is also linked to musculoskeletal disorders, certain cancers (including endometrium, breast, ovarian, prostate, liver, gallbladder, kidney, and colon cancers) [11, 12], and determines an overall increased risk of death. The COVID–19 pandemic further highlighted this danger, with severe obesity linked to higher intensive care unit (ICU) admission rates [13]. Of particularly concern is the strong association between obesity and Type 2 diabetes mellitus (T2DM) [14, 15], which increases the risk of death even more [16–18]. All this evidence underscores the significant health risks posed by obesity in our society.

It is generally understood that what we eat affects our body size, and thus body mass index (BMI). Factors including cultural habits, social norms, and food preferences, which influence eating style, may indirectly play a major role in controlling body weight and BMI. All of the above factors can lead to overeating, weight gain, and obesity, with attendant insulin resistance. Although (primary) reduced muscle sensitivity to insulin is the main culprit behind Type 2 diabetes (T2DM) [19–22], what we eat can play an important role, since increased body fat deposition can by itself decrease insulin sensitivity [23, 24]. The exact cause–and–effect relationship between overeating and insulin resistance is, however, still being debated [24–27].

1.2. Models Predicting Individual Human Weight Change

Several studies have appeared, modeling long–term body weight change by incorporating various factors, albeit to the exclusion of eating behavior.

One such study is a mathematical model portraying the progression of body weight over time [28] by considering energy intake and energy expenditure as controlling factors and also incorporating the law of energy conservation, data on energy expenditure of fat and lean tissues, and the composition of tissue gained or lost during weight change in building up the model. In 2004, the model was further expanded by including the physical activity factor (PAF) as a control variable [29]. These authors found that energy–based relations between the various factors involved in energy balance help in identifying and quantifying the determinants of energy balance and understanding their interactions as obesity develops.

In 2008, a mathematical model of macronutrient flux balances (fat, protein, and carbohydrates) was proposed to represent the long–term dynamics of human weight change [30]. The study found that for

a fixed food intake rate and physical activity level, the steady state of the body's weight and composition would be reached and could be matched with a unique body weight or a continuum of body weights that were all consistent with the same food intake and energy expenditure rates. Interestingly, existing data on human body weight are not sufficient to distinguish between these two possibilities.

In the same year, Hall et al. [31] developed a mathematical model for the estimation of the expected change in steady–state body weight resulting from a specific alteration in dietary energy intake and, conversely, for the determination of the energy intake adjustments needed to sustain a given body weight change.

Thomas et al. [32] developed a differential equation model of weight change based on the first law of thermodynamics, by incorporating the adaptation of resting metabolic rate, non–exercise activity thermogenesis, and dietary–induced thermogenesis, along with the natural age–related reduction in resting metabolic rate. They modeled resting metabolic rate with an affine function of a power of body mass, based on a statistical model developed by Livingston [33]. A one–dimensional mathematical model of weight change based on the energy balance, along with a relationship between fat–free mass and fat mass, was proposed two years later by Thomas et al. [34] and was calibrated on a large sample collected by the Centers for Disease Control.

In Guo et al. [35], two weight management simulation tools, the National Institutes of Health Body Weight Planner (NIH BWP) and the Pennington Biomedical Research Center Weight Loss Predictor (PBRC WLP), were studied using data originating from the Comprehensive Assessment of Long–term Effects of Reducing Intake of Energy (CALERIE) study. According to the study, following prolonged calorie restriction, the NIH BWP was judged to outperform the PBRC WLP.

Jacquet et al. [36] proposed a mathematical model of weight cycling designed to estimate surplus fat accumulation resulting from repeated dieting, based on principles of body composition's auto–regulated control. In the same year, a model–based predictive control approach for body weight was proposed by other authors [37]. The model determines the energy intake required to reach a predefined target body weight and, given the age of the children, their height, weight, and BMI were predicted using historical observations. In a dietary intervention program, Babajide et al. [38] applied a machine learning method including several machine learning algorithms (linear regression, support vector machine (SVM), random Forest (RF), and artificial neural networks (ANN)) to predict body weight and found that the ANN and RF algorithms outperform other models.

Among all the available contributions mentioned above, only some of the models ([32, 34, 39]) were implemented in the form of web–based applications. These applications are interesting in that they exemplify how mathematical models may be progressively developed until they are sufficiently precise to be applied to the real world. The models and web–based applications mentioned above are all targeted to individual American subjects.

1.3. Population models

Although mathematical models of the evolution of body weight in individual humans are of scientific interest and give us the tools for understanding the relevant physiology, from a policy planning perspective it is useful to explore another class of models: Instead of looking at weight change in a single person, we can study the weight distribution changes of an entire target population.

Lin et al. [40] studied the impact of the taxation policies of the US regarding caloric sweetened beverages on reducing the prevalence of overweight and obesity. The prevalence of obesity predicted

by using Hall's dynamic model [39] was compared with the one using the ubiquitous '3500 calories per pound' static weight loss model, which does not consider changes in energy expenditure over time. The proposed taxation policies were assessed to be less effective when using the dynamic model than when using the static model [41].

Church et al. [42] utilized a dynamic model of population weight change developed by Thomas et al. [32, 34] to study the impact of occupational physical activity on the increase in the prevalence of obesity in the US. They simulated the body weight changes of adults over the past five decades corresponding to the decrease in their occupational physical activity. Their results showed that, given constant energy consumption over time, the model's predictions closely matched the observed average weight of male and female populations. They concluded that the obesity pandemic in the US was indeed almost fully explained by the gradual decline in occupational physical activity. Nonetheless, Hall [43] questioned the model's assumptions, since the variations in energy expenditure are positively correlated with the ones in spontaneous physical activity [32, 34], which may result in overestimating the predicted weight changes.

In Hall et al. [44], a mathematical model of human weight dynamics was validated and was used to investigate whether the increase in average US adult body weight since the 1970s results from changes in the US food supply. They found that the average daily energy intake per capita rose by less than 250 kcal, which was sufficient to generate the obesity pandemic of adults in the US, given that physical activity remained unchanged. This requirement was easily achievable relative to the growth rate of the per capita US food supply, which was approximately three times higher than this amount. Moreover, there has been a steady rise in food waste per capita by 50% since the 1970's, according to data reported by the US Environmental Protection Agency.

1.4. Models for energy expenditure and metabolism

Energy expenditure plays a major role in controlling human body weight. In setpoint theory, it is assumed that every individual possesses a genetically influenced body weight preference, known as the setpoint weight. In a weight loss scenario, the body adapts by decreasing its energy needs in an effort to regain its setpoint weight.

In 2001, a setpoint mathematical model for determining daily energy requirements integrating the metabolic response to human weight loss was proposed by Kozusko et al. [45]. To forecast energy expenditure during weight loss, the model was built on the basis of the setpoint fat–free mass ratio and setpoint energy expenditure, disregarding characteristics such as age, gender, and heredity. Subsequently, the same authors [46] studied weight loss dynamics by introducing a setpoint model of metabolic adjustments in response to diet–driven human weight loss. The model not only incorporates the consumption of fat versus nonfat of an individual but also employs a uniform energy density associated with body weight loss. The simulation results of this model were compared with those obtained using the Harris–Benedict model.

Thomas et al. [47] proposed a dynamic model of energy balance during pregnancy (`http://www.pbrc.edu/the-research/tools/gwg-predictor/`) which helps track weight increases in expectant mothers. Later, Ejima et al. [48] proposed a mathematical model that incorporates both the genetic and non–genetic effects of obesity and used it to predict the prevalence of obesity in the US and UK in 2030.

Hall [49] constructed a mathematical model using the input data based on dietary macronutrient

consumption during periods of semistarvation and refeeding for computing full–body caloric expenditure, *de novo* lipogenesis, and gluconeogenesis, as well as turnover and oxidation of carbohydrates, fat, and protein. In 2020, a system of time–varying differential equations was employed for modeling the metabolic regulation of the human body during weight loss through dieting, exercise, or medication, focusing on changes in three major nutrients and ketone bodies [50]. Supposedly sufficient conditions for safe weight reduction achieved through diet, physical activity, and pharmacological intervention were given.

1.4.1. Food intake models

The study of energy metabolism in humans ought reasonably to start from what we actually ingest. However, while considerable research has been conducted on the mathematical modeling of digestion, absorption, and metabolism (gastric emptying being a prime example), much less attention has been given to modeling eating behavior.

In 1975, Barnwell et al. [51] proposed a model with two decision–making circuits for feeding and satiety. This model considered the interaction between the lateral hypothalamus (stimulating hunger) and the ventromedial hypothalamus (promoting satiety). Feeding was terminated by feedback mechanisms triggered by increased blood sugar levels, body temperature, or stomach distension.

Much later, in 2008, the rate of food intake during a meal was then modeled as normal distribution and was used to examine the differences in dietary patterns between healthy individuals and those with night eating syndrome [52]. In 2009, a system using a Bayesian approach (assuming a uniform prior probability for each meal) was built by Cameron et al. [53] to detect meals and estimate portion sizes in order to facilitate patients to input data for computing insulin dosages.

Balakrishnan et al. [54] proposed a personalized model for Type 1 diabetic children that considered exercise, meals, and insulin interventions. This model aimed to predict adverse events like exercise–induced hypoglycemia. Jacquier et al. [55] developed a model for rats that describes body weight, fat mass, fat–free mass, energy expenditure, and food intake dynamics. Their model suggests that food intake is regulated by available food and hunger, with hunger and satiety triggered by ghrelin and leptin levels, respectively. Finally, Murillo et al. [56] explored the influence of cultural and psychological factors on eating behavior at a population level, even though they did not address the mechanics of how we initiate and stop eating.

In 2021, we proposed an initial complete mathematical model for food intake incorporating both physiological internal factors, such as stomach distension, glycemic variations, and ghrelin dynamics; external factors; cultural habits; and influences on the initiation and continuation of meals, reflecting a combination of hedonic and appetite components [57]. The model was intended to represent the initial input for full–scale simulations of food absorption and metabolism, both in health and disease, considering external (societal) as well as internal (metabolic and psychological) factors.

1.4.2. Models for food digestion and absorption

Clearly, once ingested, food has to undergo digestion and absorption in order for the nutrients to enter metabolism. Another class of models has addressed this topic.

Several reviews of gastrointestinal tract physiology exist, including on the physiology of the absorption of metabolic substrates and other nutrients [58–61].

Strathe et al. [62] described a mathematical model for the digestion and absorption of nutrients in growing pigs, considering dietary protein, endogenous protein, amino acids, non–amino acid– and non protein nitrogen, lipids, fatty acids, starch, sugars, and dietary fiber. Salinari et al. [63] dealt with glucose absorption in the human. Glucose absorption was also a part of models of glucose–insulin control by our group [64]. Taghipoor et al. [65] developed a model of digestion in the small intestine focusing on dietary fiber. Several other meal absorption models have been proposed [66–68].

1.4.3. Models of the effect of glycemia on appetite

One important factor affecting our eating behavior is the glucose concentration in the blood. Hyperglycemia (high blood glucose concentration) caused by sugar–rich food intake suppresses ghrelin secretion [69] and raises insulin serum concentration; high insulinemia then inhibits dopamine signaling and deters feeding [70–72]. Hyperglycemia is, in any case, effective in reducing food intake, even if it is not clear how much of this effect is mediated by the inhibition of ghrelin production [73].

Advances in glycemia control and treatment strategies have been widely treated [74–77]; within this context, the possible roles of hypo– and hyperglycemia in influencing food intake behavior have also been discussed [78–81]. It is common consensus that hunger is a symptom of hypoglycemia. There is also evidence that hyperglycemia by itself may suppress hunger [82–84]. Even though other contributions [85] doubt the effectiveness of glycemia to regulate hunger, on the whole, it would seem reasonable to include glycemia in a food intake model as a substantial determinant of appetite, very possibly as a mere marker of more complex influences mediated by the appearance of food in the gastrointestinal tract. It should be noted in this regard that hunger due to hypoglycemia is not by itself suppressed by stomach filling (e.g., by drinking water or assuming a large amount of calorie–poor fiber) [86].

With the evidence above supporting how glycemia can trigger or suppress feeding, in the present work, glycemia is assumed to be the representative determinant of appetite. Therefore, in the following, the amount of ingested carbohydrate intake will be converted to its glucose equivalent [87], and the consequent rise in glycemia resulting from glucose absorption into the circulation will be considered as the key determinant of appetite.

1.4.4. Models for glycemic control

Since glycemia plays an important role in our model, it is useful to study glucose homeostasis, i.e., how glycemia is regulated. Extensive research has been done in the mathematical modeling of glucose homostasis, considering different aspects of this complicated physiological control mechanism and given the fact that adequate control of glycemia is necessary to prevent morbidity and mortality [88].

There are several review articles on the mathematical modeling of glucose control [89–92]. One of the most widely used of such models is the so–called ‘minimal model’ of Bergman [93, 94], even though it was shown [95] to suffer from implausible qualitative properties, and it was shown [96, 97] that the statistical parameter estimation scheme originally proposed by the authors [98] was faulty.

Several other contributions appeared over the years: the ‘minimal model’, notwithstanding its problems, was extended to include gastrointestinal absorption [99]. Liu et al. [100, 101] worked on a regulatory system of blood glucose by taking the dynamics of receptors at the molecular level into account; Wu et al. [102] proposed a two–compartmental model in order to account for the oscillatory

behavior of the glucose–insulin system; and Lombarte et al. [103] proposed a model including, blood glucose and insulin concentrations as well as intestinal glucose in rats. Some of these models include lipids in the description of the metabolic response, like in Pratt et al. [104], where experimental data for the ingestion of three mixed composition meals over a 24–h period were used to study the response to a variety of mixed meals in fed and fasted conditions.

The role of other hormones in regulating glucose metabolism has also been studied, particularly regarding incretins, gastrointestinal hormones that enhance insulin secretion by the pancreas in response to a meal. Girard et al. [105] and Holst et al. [106, 107] reviewed the concept of incretins and described the biological effects of GIP and GLP–1 in normal subjects and in patients with Type 2 diabetes mellitus; Kazakos et al. [108] and Holst et al. [109] argued in favor of a possible use of incretin therapy in obesity and diabetes. Zhao et al. [110] proposed a mathematical model to analyze the impact of pulsatile insulin release on postprandial glucose and lipid control. Finally, Masroor et al. [111] developed a model for the homeostasis of glucose through the regulating hormones glucagon and insulin, which could be used for studies on glucagon receptor–targeted therapy as well as on the artificial pancreas. Personalized models of glycaemic control focusing on the effects of physical exercise in body metabolism were studied in [112], while those that account for both food intake and exercise were discussed in [113–116].

Over the past few years, many research groups, including ours, have been active in the mathematical modeling of different aspects of the glucose–insulin control system. Models have dealt with the intravenous glucose tolerance test (IVGTT) [95, 117–119], possibly with delay [96, 120–122]; the oral glucose tolerance test (OGTT) test [123]; the analysis of mixed meals [99]; model–based control of plasma glycemia [124]; the euglycemic hyperinsulinemic clamp (EHC) [125, 126]; islet population pulsatile insulin secretion [127–129]; long–term development of diabetes [130–134]; the glucose–insulin–incretin system [135]; postprandial glucose excursion in diabetics [136]; renal glucose reabsorption [137]; glycemia–structured population models [138]; fractional differential approaches [139, 140]; stochastic gastric emptying and food intake [57, 141]; and reviews [90].

1.5. Goal of the present work

In the quest for a better understanding of the development of obesity in individuals, a mathematical model of body size evolution in humans would be useful. Modeling the changes in body size would help us characterize their determinants and would provide a hitherto missing element in the representation of population–wide insulin resistance and of the development and management of diabetes mellitus. It is to be noted that current mathematical models for the progression of diabetes typically do not consider body habit changes. Conversely, models of weight increase typically assume calorie imbalance over long periods of time, without linking it to its likely daily determinants. A complete model could be used to compare the effectiveness of different approaches to the prevention of obesity.

According to the current existing literature, a mathematical model connecting body weight dynamics to actual daily food intake behavior has not yet been proposed. A useful step forward would thus be to develop such a model, aligned with the clinical, empirical observations [5–7] that indicate how, over the years, simply changing our food choices *ceteris paribus* may significantly affect our body weight.

The purpose of the present work was therefore to build and calibrate a mathematical model of the changes in human body size over several years as determined by daily food intake habits.

2. Materials and methods

2.1. The mathematical model

In this section, we present a mathematical model consisting of time–depending five variables including stomach food content (S), glycemia (G), insulin plasma concentration (I), body weight (W), energy expenditure (Y), and appetite (A). The definitions of each variable are provided below.

In the following, the model variables are presented and discussed in turn. Table 1 summarizes their names, meanings and units of measurement.

t: Time, in minutes (min)

D: Days (days)

D counts the number of whole days since the beginning of the experiment/simulation, starting with Day 1. When its value increases by one (at midnight, zero hours) the meal times and meal amounts for the current (upcoming) day are recomputed.

$$D(t) = ceiling(t/1440), \tag{2.1}$$

where 1440 is the number of minutes in a day.

τ: Time of the day (min)

τ indicates the time of day in minutes. It is used to determine hour–dependent events (such as food intake or sleep patterns).

$$\tau = mod(t, 1440). \tag{2.2}$$

τ_m: Time of the m–th daily meal (min)

τ_m indicates the time of day of the m–th meal (1, breakfast; 2, lunch; 3, dinner) in minutes. It varies randomly from day to day, uniformly between a minimum and a maximum allotted time.

$$\tau_m = \tau_m^{min} + U(\tau_m^{max} - \tau_m^{min}), \quad m \in \{1, 2, 3\}, \tag{2.3}$$

where U is a uniformly distributed random variable, $U \sim \mathcal{U}[0, 1]$.

M_m: Suggested size of m–th daily meal (kcal)

M_m indicates the suggested size of the m–th meal (1, breakfast; 2, lunch; 3, dinner) in kcal. It varies randomly from day to day, uniformly between a minimum and a maximum size. The actual amount of food ingested during the meal depends on the suggested meal size and also on the current appetite of the subject, and it may be smaller or larger than the suggested meal size.

$$M_m = M_m^{min} + U(M_m^{max} - M_m^{min}), \quad m \in \{1, 2, 3\}, \tag{2.4}$$

where U is a uniformly distributed random variable, $U \sim \mathcal{U}[0, 1]$.

λ_{CG}: Propensity (probability rate) of consuming a snack given the current level of glycemia (/min)

λ_{CG} indicates the probability rate or propensity of consuming a snack, given the current glycemic level. It is assumed to follow a decaying sigmoid, achieving a maximum at zero glycemia and falling off to zero with increasing glycemias.

$$\lambda_{CG}(G) = 1 - \frac{G^{\gamma_{CG}}}{G_{C50}^{\gamma_{CG}} + G^{\gamma_{CG}}}. \tag{2.5}$$

S: Stomach food content (kcal)

S is the energy in *kcal* obtained from food in the stomach, or the stomach food content expressed in kcal.

$$\begin{aligned} \frac{dS}{dt} = & - k_{OS}\, S(t) \\ & + A(t) \sum_{D=1}^{N_D} \sum_{m=1}^{3} M_{m,D} \delta(t - t_{m,D}) \\ & + A(t)(C^{min} + U(C^{max} - C^{min}))\chi_G, \\ & S(0) = S_0, \end{aligned} \tag{2.6}$$

where

$m \in \{1, 2, 3\}$ indicates the standard meal (1, breakfast; 2, lunch; 3, dinner).

$D \in \{1, \ldots, N_D\}$ indicates the day.

$M_{m,D} = M_m^{min} + U(M_m^{max} - M_m^{min}), U \sim \mathcal{U}[0, 1]$, indicates the random size of the meal, uniformly distributed between the limits pertaining to the corresponding standard meal.
This means the offered meal is assumed to be uniformly distributed.

$t_{m,D}$ indicates the time of the meal, uniformly distributed between the interval $[6, 9]$ for $m = 1$, $[12, 15]$ for $m = 2$, and $[18, 21]$ for $m = 3$. The meal times are also uniformly and randomly distributed within the usual limits (say, between 6:00 a.m. and 9:00 p.m. for breakfast).

C^{min} and C^{max} are the standard minimum and maximum snack sizes, $U \sim \mathcal{U}[0, 1]$, so that $(C^{min} + U(C^{max} - C^{min}))$ is a uniformly distributed random snack size between C^{min} and C^{max} kcal.

χ_G is the characteristic or indicator function indicating the actual consumption of a snack at time t, depending on its propensity λ_{CG} as a function of glycemia. It is defined in terms of the solution N_G to the Poisson process of parameter λ_{CG}, as follows:

$$\chi_G = \delta(N_G < 1). \tag{2.7}$$

In the course of the numerical simulations, with a (small) time discretization step Δt, we use the approximation $\chi_G \approx (U \leqslant \lambda_{CG}\, \Delta t)$, with U a $[0, 1]$ uniformly distributed random variable sampled at each discretization time step. In the implementation of the algorithm, therefore, the actual probability $P_C(G, \Delta t)$ of consuming a food snack over the next discretization time interval, a probability which depends on the propensity λ_{CG} defined above, on glycemia, and on the length of the interval

$$P_C(G, \Delta t) = 1 - e^{-\lambda_{CG}(G)\Delta t}. \tag{2.8}$$

Notice that we assume that snacking will not happen between 2:00 a.m. and 1 hour after breakfast, thus setting χ_G to zero during that time interval.

The submodel that is relevant to gastrointestinal absorption of nutrients has been kept relatively simple to compensate for the complex representation of the factors influencing food intake.

Z: Relative insulin sensitivity (#)

$Z(W)$ is the level of insulin sensitivity, relative to the baseline value, depending on the current body weight. On the basis of clinical observations [142–146], we assume that the increase in body weight is associated with progressively more severe degrees of insulin resistance

$$Z(W) = 1 - \frac{W^{\gamma_{GIW}}}{W_{GI50}^{\gamma_{GIW}} + W^{\gamma_{GIW}}}. \tag{2.9}$$

G: Glycemia (mM)

G is the current glycemia

$$\frac{dG}{dt} = -Zk_{OGI}IG + k_G + \frac{\rho_{GS}}{V_G}k_{OS}S\ ,\ \ G(t_0) = G_0 \tag{2.10}$$

where ρ_{GS} is the conversion factor between the absorbed glucose–equivalent food, in kcal and mmol of glucose absorbed into the bloodstream.

I: Insulin plasma concentration (pM)

I is the current insulinemia. Insulin secretion by the pancreas is assumed to depend on glycemia nonlinearly (higher glycemic peaks determine proportionally greater insulin secretion)

$$\frac{dI}{dt} = -k_{OI}I + k_{IG}G^2\ ,\ \ I(t_0) = I_0. \tag{2.11}$$

W: Body weight (kg)

W is the current body weight determined by the balance between (a fraction of) what is absorbed from the stomach and current energy expenditure (converted from kcal/day to kcal/min)

$$\frac{dW}{dt} = \rho_{WS}\left(k_{OS}S - \frac{Y}{1440}\right),\ \ W(t_0) = W_0. \tag{2.12}$$

Y: Energy expenditure (kcal/day)

$Y(W)$ is the daily energy expenditure, as a function of the current body weight. An increase in daily energy expenditure is assumed to be determined by an increase in body weight, accounting for the fact that with a heavier mass to move, an increase in metabolism is required

$$Y(W) = Y^{max}\frac{W^{\gamma_{YW}}}{W_{Y50}^{\gamma_{YW}} + W^{\gamma_{YW}}}. \tag{2.13}$$

A: **Appetite (#)**

A is the appetite level assumed to depend merely on glycemia, consistent with the purpose of this study

$$A(G) = A^{max} e^{-\lambda_{AG} G}. \tag{2.14}$$

Figure 1 reveals a schematic diagram of the relationships among the state variables.

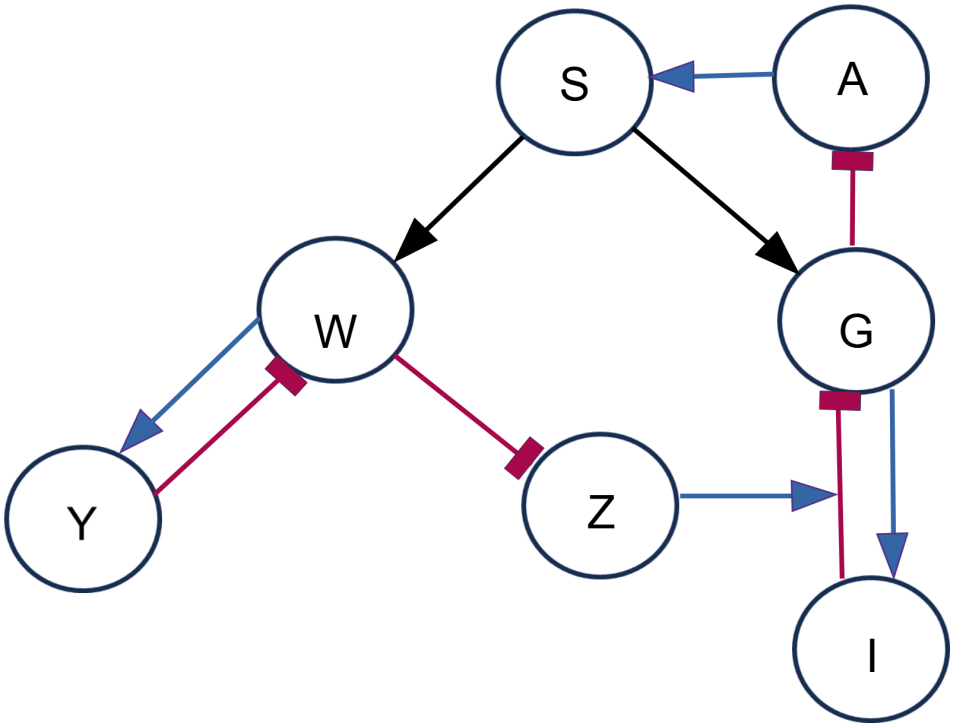

Figure 1. Block diagram of the WeightGain model. Labeled circles correspond to the state variables as defined in the text. Black arrows represent transfer of a substance. Blue arrows represent stimulation or excitation, while red arrows represent inhibition or repression.

2.2. *Software implementation*

The model has been implemented in R [147].

2.3. *Parameter calibration*

Figure 2 shows the assumed relationships between energy expenditure and body weight, between appetite and glycemia, and between insulin sensitivity and body weight. The assumed propensity to snack as determined by (hypo)glycemia and the derived probability of snacking within given time intervals while being kept at 2 mM, 3 mM, 4 mM, and 8 mM glycemia are shown in this figure. All of these relationships reflect the common understanding and are kept unchanged when studying different scenarios.

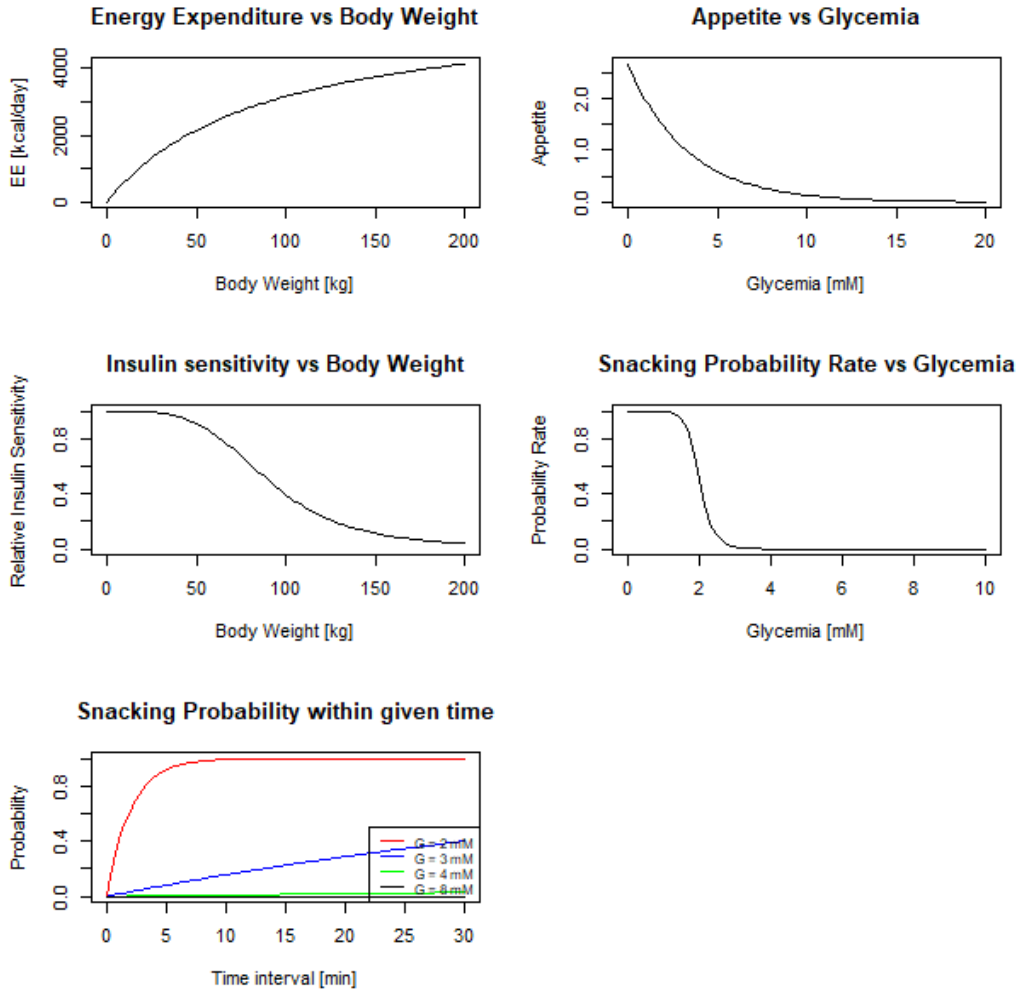

Figure 2. Assumed overall relationships: These basic relationships reflect common physiological and nutritional understanding and are assumed to be the same for all studied scenarios.

Energy expenditure is assumed to increase (nonlinearly) with increasing body weight due to the actual work of moving around a heavier body, as well as to the likely parallel increase in metabolically active muscle mass (Figure 2, upper left panel).

As already mentioned in the Introduction, we take glycemia to be the sole determinant of appetite, neglecting, for this version of the model, other possible influences (hedonic, psychological, social), which may also modify food intake. In fact, we summarize such influences in the concept of baseline appetite (or appetite at zero glycemia), defined as the basic tendency to ingest a given multiple of the proposed calories at each meal: A glutton would be represented as having a high baseline appetite, while anorexia would induce a low baseline appetite. In both conditions, higher glycemia would reduce current appetite, as represented in Figure 2 (upper right panel). It is a common understanding that obese individuals, on average, exhibit some degree of insulin resistance. The normal insulin sensitivity coefficient ($k_O GI$) in the standard $\text{min}^{-1}\text{pM}^{-1}$ units is thus multiplied by a correction factor depending on body weight (Figure 2, center left panel). One possibly important element in the failure to com-

ply with healthy dietary indications is snacking. For the purpose of this investigation, we represent snacking as a continuous–time random process, where the probability of ingesting some extra food depends both on glycemia (the lower the glycemia, the higher the probability rate of having a snack; Figure 2, center right panel) and on the duration of the considered time interval. Figure 2 (lower left panel) shows the computed probability of observing a snack to take place during a time interval as the duration increases for four levels of glycemia maintained during that interval.

Human Energy Requirements Report [148], a meta–analysis of studies that involved a total of 411 men and women from 18 to 64 years of age, showed a modal value for physical activity level (PAL) of 1.60 (range: 1.55 to 1.65) for both men and women [149]. For the most part, the subjects were from affluent societies in developed countries. All were healthy, but 13% of the women and 9% of the men were overweight or obese, with BMI > 30. Typical subpopulations included students, housewives, white–collar or professional workers, and unemployed or retired individuals; only three persons were specifically identified as manual workers. Hence, the authors of the meta–analysis defined the study participants as people with a 'predominantly sedentary Western lifestyle...' (we should however note that '... an expert panel of the International Obesity Task Force (IOTF) suggested a somewhat lower PAL range of 1.50 to 1.55 as being representative of sedentary individuals ...' [148]).

Taking 1.60 as the modal value for PAL in people with a predominantly (but not exclusively) sedentary Western lifestyle, considering a (fit) male individual of 40 years of age, 70 kg body weight and 180 cm height, and applying the coefficients of the simplified Mifflin equations [150]

$$REE_{female}(kcal) = 10 \times BodyWeight(kg) + 6.25 \times Height(cm) - 5 \times Age(yrs) - 161,$$
$$REE_{male}(kcal) = 10 \times BodyWeight(kg) + 6.25 \times Height(cm) - 5 \times Age(yrs) + 5,$$

we obtain a total daily expenditure (TDEE) of 2608 kcal/day. Clearly, obese individuals, very physically active individuals, and younger individuals would have a higher TDEE, and vice versa for very lean, older, and mostly sedentary individuals. These considerations justify the choice of 2600 kcal/day as the baseline TDEE.

In order to justify the choice of stomach emptying half–lives considered, we use Equation (4) from Palumbo et al. [113] and consider an 'average' meal size of 500 mL containing 500 kcal: this would be equivalent to a chicken and vegetable soup with 100 g of chicken, 200 g of mixed vegetables, and a small potato. A calorie–poor, fiber rich meal, such as a lentil and vegetable soup with 50 g of lentils and 150 g of non–starchy vegetables, would contain approximately 250 kcal in a 500 mL volume. Conversely, a calorie–rich meal such as a creamy chicken and avocado soup, with 100 g chicken, half an avocado, and coconut milk would deliver approximately 500 kcal in a volume of 250 mL. All three meals consist of mostly liquid soups, to which, therefore, Eq. (4) from Palumbo et al. would apply, but they would differ markedly in caloric density (1, 0.5 and 2 kcal/mL), thus determining the computed stomach emptying half–lives, respectively, of 36, 23, and 64 minutes. Hence, the choice of portraying a substantial switch in food preferences as going from 60 to 20 minutes for stomach emptying half–life.

3. Results

We explore two scenarios: Scenario 1 (healthy diet baseline) and Scenario 2 (sugar–rich food preference). The quantitative effect of merely changing food preferences on the long–term development of obesity is investigated by conducting simulations over four years.

In the following, the model has been used to quantitatively investigate the effect of merely changing food preferences on the long–term development of obesity.

3.1. Scenario 1

In this scenario, a human subject with a weight of 70 kg following a normal (healthy) diet with a normal baseline appetite is studied. The definition of a healthy diet is the diet consisting of varied and fiber–rich foods such that the stomach emptying half–life is 60 minutes. All other parameters of the simulation have been calibrated so as to reflect the common medical consensus and to determine a stable weight over the course of four years. In this simulation, the offered meal size and meal times are uniformly, randomly distributed within usual limits (say, between 6:00 a.m. and 9:00 p.m. for breakfast), and snacking is not assumed to happen between 2.00 a.m. and 1 hour after breakfast.

Figure 3 shows the time course of stomach contents, glycemia, appetite, and daily total food intake over the course of four years of simulation. Notably, glycemia peaks (postprandially) at around 12 mM, and total daily food intake averages around 2600 kcal, of which around 400 derive from snacking.

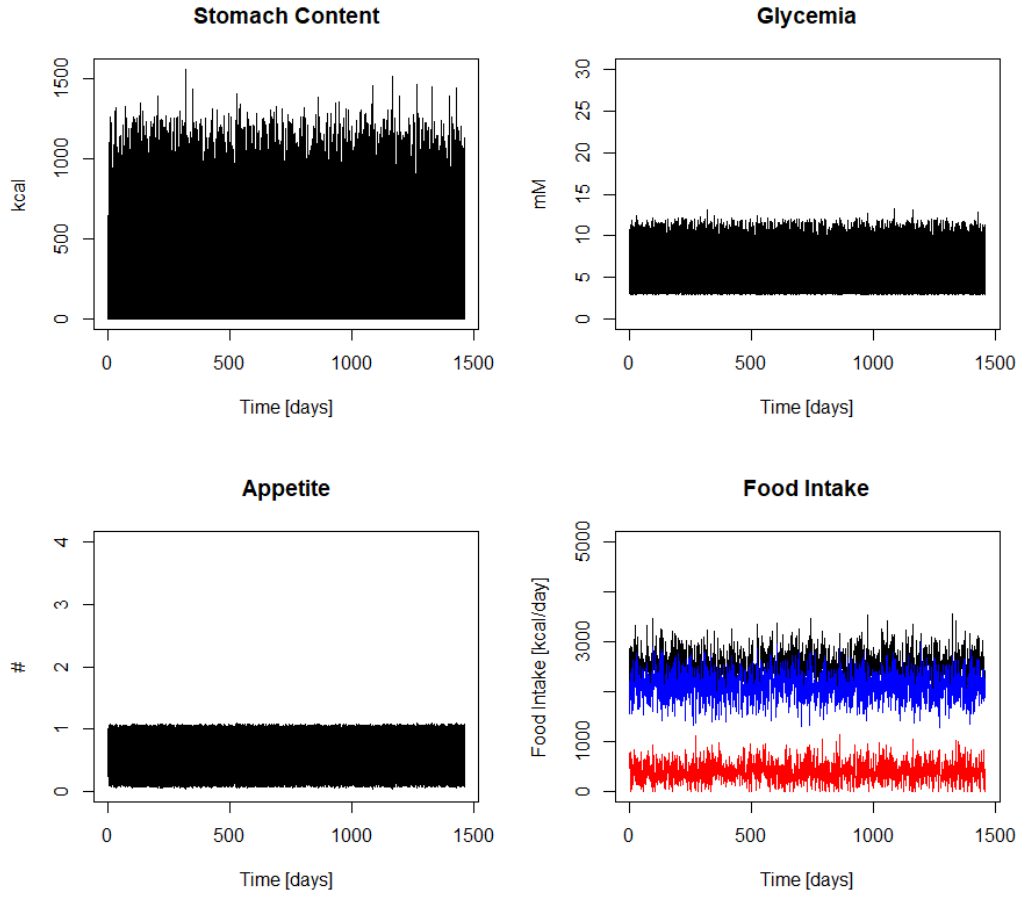

Figure 3. Maintenance of normal body weight: Stomach contents (top left), glycemia (top right), appetite (bottom left) and daily food intake (bottom right: Daily kcal from snacking in red, those from regular meals in blue, and the total in black).

Figure 4 shows the time course of body weight, daily energy expenditure, fasting glycemia, and relative insulin sensitivity, none of which change appreciably over four years. Weight is maintained at around 70 kg throughout, while fasting glycemia (the average glycemia in the early hours of the morning before breakfast) is maintained at values around 3.7 mM (66 mg/dL).

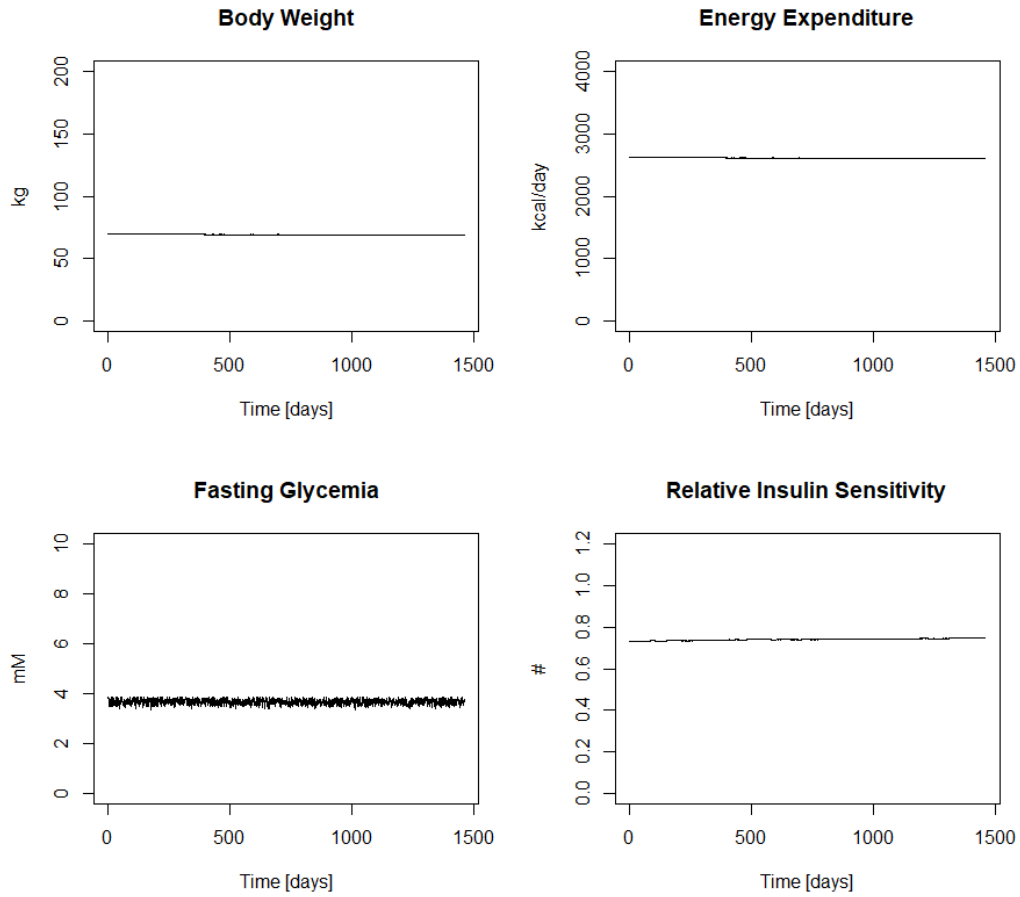

Figure 4. Maintenance of normal body weight:Body weight (top left), daily energy expenditure (top right), fasting glycemia (bottom left), and relative insulin sensitivity (bottom right).

Figure 5 shows the time course of stomach content, glycemia, insulinemia, and appetite over the course of four days. In this stable situation (at normal body weight), glycemic excursions, the corresponding insulinemic peaks, and appetite oscillations are limited.

3.2. Scenario 2

For the second scenario, we simulate an individual with a body weight of 70 kg with the same parameter values as in Scenario 1, except for his/her preference for foods richer in carbohydrates, particularly sugar, such as soft drinks, sweets, and sugary snacks. We assume that with the low level of fibers, fats, and protein in such foods, the rate of digestion is faster and the half–life time of stomach emptying is reduced from 60 to 20 minutes.

Notice that the offered caloric content of meals and snacks is exactly the same as before (but if

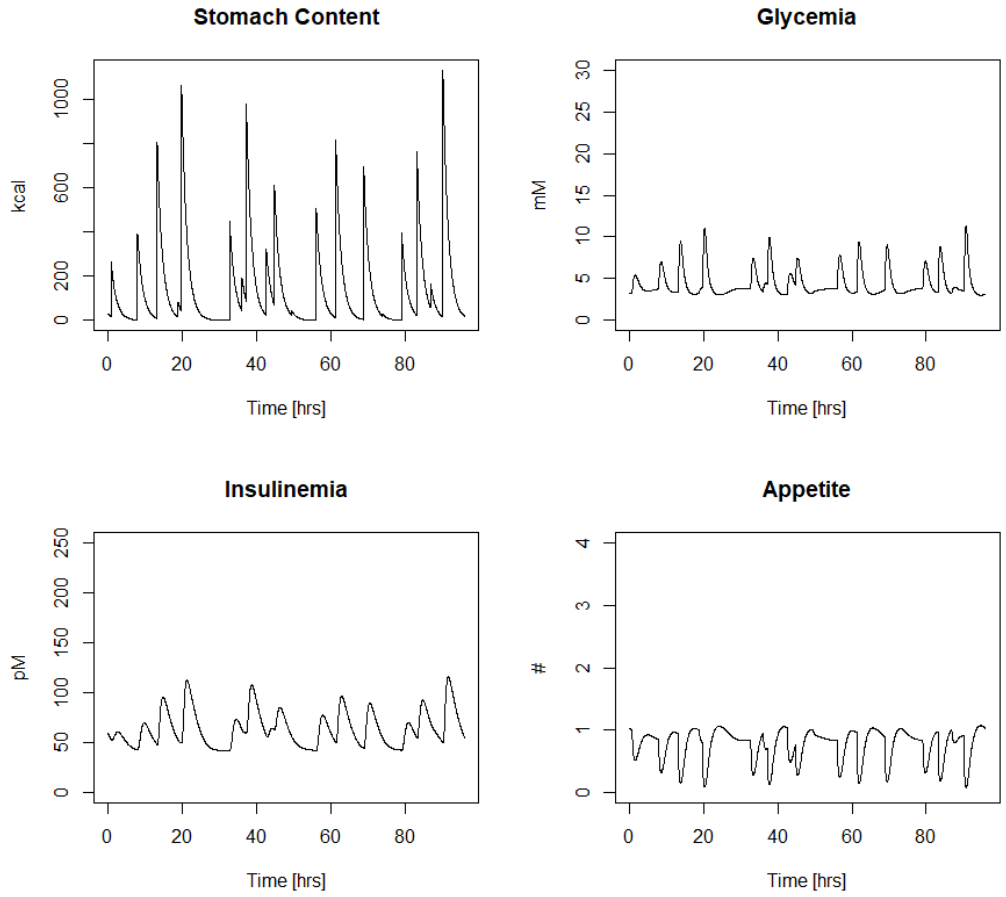

Figure 5. Maintenance of normal body weight: Stomach content (top left), glycemia (top right), insulinemia (bottom left), and appetite levels (bottom right) over the course of four days.

eating with increased appetite, the subject will partake of a larger fraction of the offered meal, possibly greater than 1). In other words, nothing changes except the digestion half–life.

The stomach contents, glycemia, appetite, and daily total food intake over the course of four years for the subject under the second scenario are displayed in Figure 6. Notice that stomach content peaks are only marginally larger than before. Conversely, the glycemic peaks reach 20 mM, a substantial increase, due to the more rapid availability of ingested sugars in the circulation. Appetite peaks are increased, due to the fact that rebound hypoglycemias occur after the rapid elimination of peaking glucose loads (with persistent insulin concentrations).

This is reflected in the much greater contribution of snacking to the total daily food intake: Initially approximately 1700 kcal/day out of a total of 3700 kcal/day, and eventually (at the end of the four years) 1000 kcal/day out of a total of 2900 kcal/day. It should be emphasized that the total caloric intake of a subject depends not only on the offered caloric content of the diet (presumed to be the same throughout our simulations) but also on the level of craving or appetite, leading to more frequent snacking and to larger portions of whatever food is offered at regular meals, hence the variation in total

caloric intake with the same caloric content of meals.

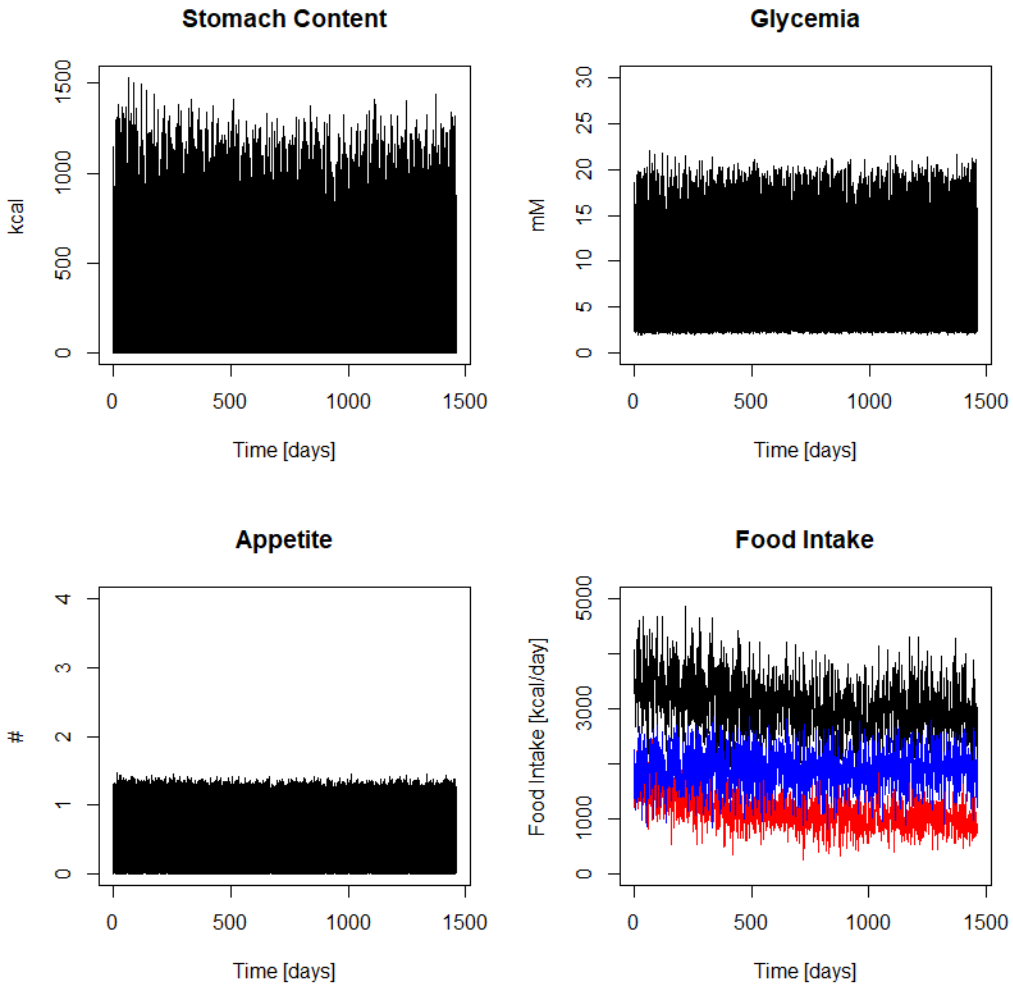

Figure 6. Consequences of unhealthy diet choices: Stomach contents (top left), glycemia (top right), appetite (bottom left), and daily food intake (bottom right: daily kcal from snacking in red, that from regular meals in blue, and the total in black).

In Figure 7, the time course of body weight, daily energy expenditure, fasting glycemia, and relative insulin sensitivity for the subject with unhealthy food intake habits are shown. The subject's weight increases from 70 to about 90 kg within just a couple of years (four years), stabilizing around this higher level. In fact, weight stabilization is caused both by increased energy expenditure and by decreased insulin sensitivity, resulting in higher glycemias with lower appetite levels. Notice, however, that glycemic levels are more variable: Not only are the postprandial glycemic peaks higher (Figure 6 top right panel) but fasting glycemias range from 3 mM to 4.2 mM. In other words, in this situation, the subject is potentially exposed to both hyper– and hypoglycemias. While, quantitatively, the clinical situation depicted in this scenario does not yet reach the severity of overt diabetes, the configuration of the abnormalities is very clear and coincides with the progressive development of Type 2 diabetes mellitus.

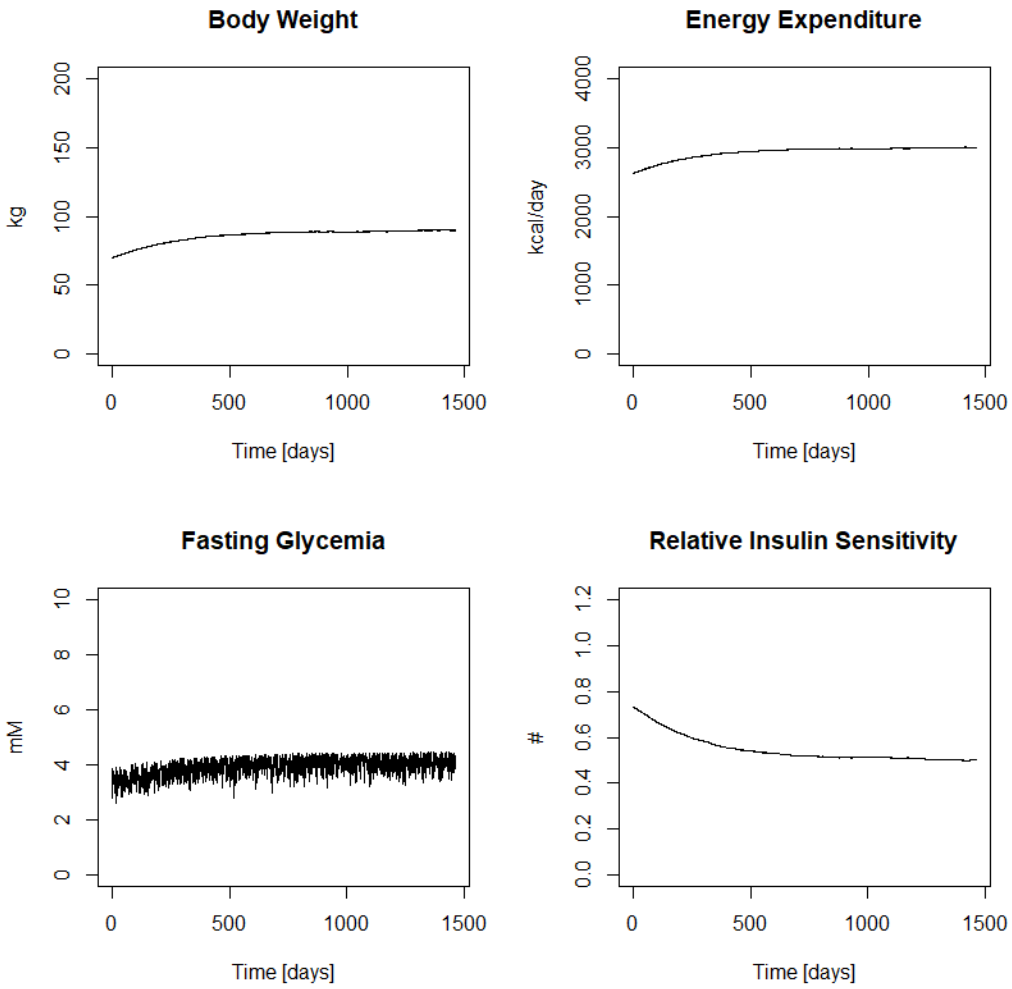

Figure 7. Consequences of unhealthy diet choices: Body weight (top left), daily energy expenditure (top right), fasting glycemia (bottom left), and relative insulin sensitivity (bottom right).

Figure 8 finally shows the time course of stomach content, glycemia, insulinemia, and appetite over the course of four days at the stable regimen after four years of unhealthy eating habits. Glycemic excursions are larger due to the increased proportion of (simple) carbohydrates in the diet, leading to higher insulinemic peaks hence to rebound (relative) hypoglycemias and more sustained appetite overall, with the consequence of more frequent, larger snacks and increased calorie intake.

4. Discussion

It is clear that Western and Westernized societies are undergoing an epidemics of obesity, which represents a major public health concern, with huge economic and human costs. Obesity is a major driver of healthcare spending, since it is clear from epidemiological surveys that obese people are more likely to develop chronic conditions, such as Type 2 diabetes mellitus (T2DM), cardiocirculatory dis-

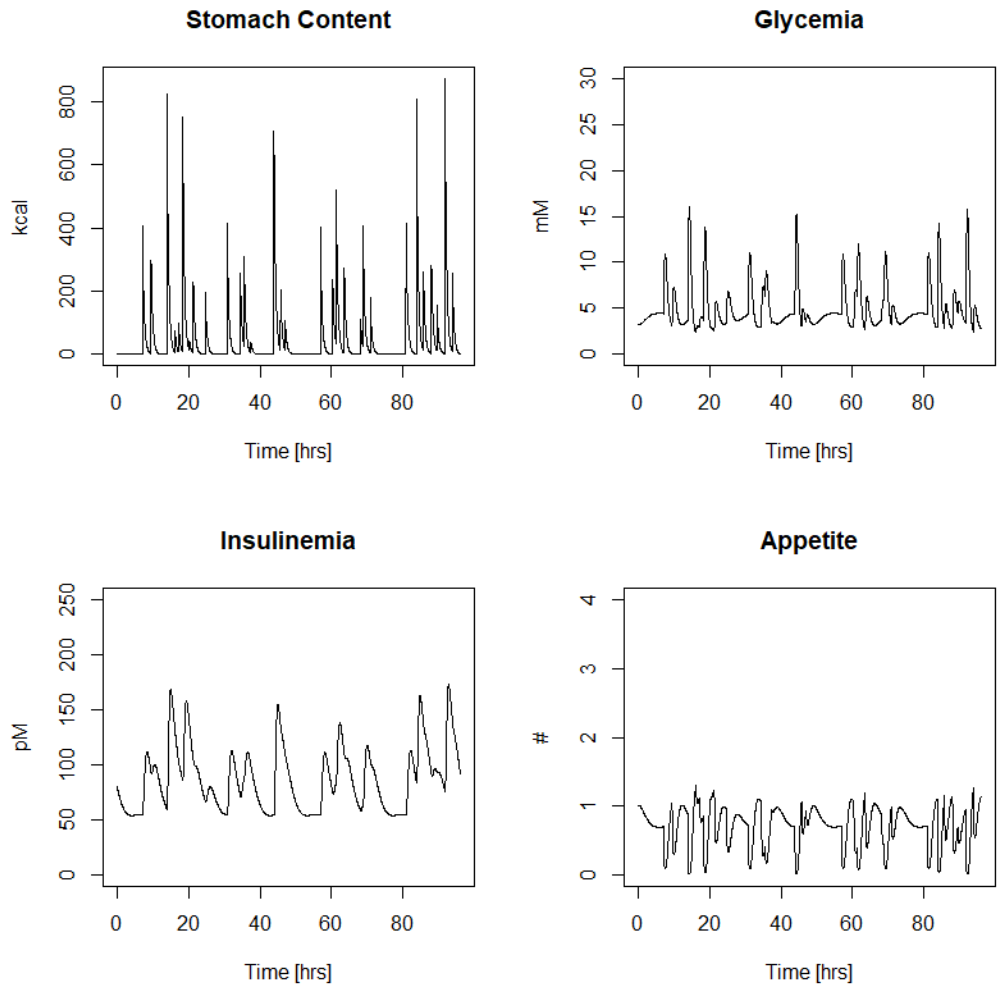

Figure 8. Consequences of unhealthy diet choices: Stomach content (top left), glycemia (top right), insulinemia (bottom left), and appetite levels (bottom right) over the course of four days.

eases, and even some types of cancer, requiring treatment and hospitalization. Furthermore, obesity can also lead to lost productivity due to absenteeism and presenteeism (being at work but not fully functional). Obesity has a major impact on quality of life (QoL): It can limit mobility and make it difficult to participate in daily activities, with attendant feelings of isolation and depression. Among the social determinants of obesity (such as poverty, with a consequent lack of access to healthy food options) an important factor is insufficient health education, leading to poor dietary choices, with reliance on quick–reward foods such as sugary drinks and snacks.

It is generally understood that overeating causes obesity; however, while the effects of obesity are being extensively studied, much less attention has been paid to its causes. A discussion about the psychological and social determinants of overeating would transcend the scope of the present work (the model proposed here does, however, take into account the end–effect of such determinants by quantifying 'appetite', intended as the proportion between the food offered and the actual food consumed, in

terms of calories).

Through the simulation of a model incorporating the common consensus, the present work investigates how dietary choices influence the development of obesity. The main effect which emerges from the numerical implementation of the current model confirms the everyday observation that refined carbohydrates cause rapid spikes in glycemia, followed by rebound hypoglycemia ('crashes'), causing, in turn, a craving for more (sugary) food, thus repeating the cycle, eventually determining substantial increases in calorie intake.

The connection between sugary diets and obesity (with the attendant insulin resistance) is well established in the medical community. However, building robust, meaningful mathematical models for this complex relationship is challenging, due to a number of considerations. First of all, the development of obesity and insulin resistance is influenced by a multitude of factors beyond just dietary preferences: Genetics, physical activity levels, gut microbiome, and even sleep patterns all play a role, and creating a model that accurately captures all these variables is difficult. For these reasons, different people respond differently to diets, and accounting for individual variability complicates the mathematical treatment of the problem. Collecting long–term data is impractical: The longest series of longitudinal observations in (pre–)diabetic patients only span a few years, while we are looking at developments taking place over decades; this lack of comprehensive datasets makes it difficult to validate complex models.

As referred to before, the literature contains mathematical models of energy balance determining weight changes over the years, and models for glycemic control exist. Our group has also contributed a model for the actual initiation and continuation of meals. However, to the best of our knowledge, no models as yet connect the minute–by–minute eating mechanisms and glycemic metabolism with the long–term development of obesity. The present work presents a first attempt to build such a model. It should be remarked that the significance of the conclusions that can be drawn from simulating this model goes beyond establishing quantitatively that a preference for sugary foods determines a very substantial weight increase over the span of a few years. We can, in fact, observe how the representation of the interplay of insulin, glucose, and appetite in this situation gives rise to the hallmarks of prediabetes: Variable glycemias with the possibility of dangerous hypoglycemic episodes, spiking postprandial hyperglycemias (impaired glucose tolerance, IGT), increased fasting glycemias (impaired fasting glucose, IFG), and development of insulin resistance. As such, this model represents a first step towards the quantitative understanding of the development of Type 2 diabetes mellitus on the basis of an unhealthy lifestyle, which is clearly more dangerous when superimposed on genetic predisposition.

One limitation of the present model is that it does not take into account other ways in which sugary foods may increase total caloric intake. For example, by not considering the (possible) contribution of stomach filling to the feeling of satiety, the fact that sugary foods tend to be less filling (packing more calories into smaller volumes), leading to continued eating even after consuming enough calories, is not represented in the model. Also, as mentioned above, psychological determinants are not considered, even though some could actually be modeled: Among these, the fact that sugary foods may activate the reward system in the brain, leading to feelings of pleasure and satisfaction and possibly developing cravings.

Another limitation concerns the fact that the current model only considers the effect of insulin on glycemic control and neglects its role in fat accumulation: Insulin resistance can, in fact, contribute to weight gain by impairing glycogen synthesis (thus increasing fat deposition in the adipocytes).

Expanding the present model to include lipid metabolism would also help us understand, for instance, the consequences of the use of the recently introduced class of anti–obesity drugs: While there is a lot of excitement surrounding these compounds, their affordability and accessibility are major hurdles for large segments of the affected population. A plausible model of the link between determinants of alimentary behavior and long–term weight change effects could help elucidate their mechanism of action and provide for optimal tailored therapy.

We note that mathematical modeling of metabolism is evolving, with the introduction of different techniques to address the complications posed by biological systems. A simple nonlinear ordinary differential equation (ODE) model like the present one assumes well–mixed compartments with deterministic behavior. However, metabolism is inherently stochastic (enzyme activity can fluctuate, hormonal and metabolite concentrations vary), thus making the use of stochastic differential equations (SDEs) appealing. Furthermore, processes are controlled at a variety of levels (with different orders of control) and exhibit memory effects, both of which would justify the use of fractional differential equations (FDEs) and/or delay differential equations (DDEs). While stochastic elements can be introduced in both (FSDE, SDDE), this causes significant estimation problems connected with the inherent non–locality of these systems and the consequent non–Markovianity of the solution processes. All of these issues constitute a very interesting field of investigation for the future.

The end result would be to have a model helping us to forecast body weight in the population over 10–50 years in the future and to comparatively assess the efficacy of possible societal interventions aimed at preventing the obesity epidemics and reducing the attendant healthcare costs. In order to prove the value of this model's application in personalized medicine, validation with independent experimental data should take place in the future.

5. Conclusions

Although it is generally understood that overeating causes obesity (with no need of making recourse to sophisticated computational techniques), the mathematical model presented here can supply quantitative insights to uncover how and why this happens. This first model of the long–term consequences of altered food preferences is of interest by itself and paves the way for improved future representations of overall energy metabolism.

Acknowledgments

The work of Prof. Andrea De Gaetano was supported by the Distinguished Professor Excellence Program of Óbuda University, Budapest, Hungary.

Use of AI tools declaration

The authors declare they have not used artificial intelligence (AI) tools in the creation of this article.

Conflict of Interest

All authors declare no conflicts of interest in this paper.

References

1. Obesity and overweight, URL https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. N. J. Temple, The origins of the obesity epidemic in the USA–lessons for today, *Nutrients*, **14** (2022), 4253. https://doi.org/10.3390/nu14204253
3. S. Bleich, D. Cutler, C. Murray, A. Adams, Why is the developed world obese?, *Annu. Rev. Public Health*, **29** (2008), 273–295. https://doi.org/10.1146/annurev.publhealth.29.020907.090954
4. M. Ng, T. Fleming, M. Robinson, B. Thomson, N. Graetz, C. Margono, et al., Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the global burden of disease study 2013, *Lancet (London, England)*, **384** (2014), 766–781. https://doi.org/10.1016/S0140-6736(14)60460-8
5. H. F. Wells, J. C. Buzby, Dietary assessment of major trends in U.S. food consumption, 1970–2005. URL http://www.ers.usda.gov/publications/pub-details/?pubid=44220.
6. Y. Ritze, G. Bárdos, J. G. D'Haese, B. Ernst, M. Thurnheer, B. Schultes, S. C. Bischoff, Effect of high sugar intake on glucose transporter and weight regulating hormones in mice and humans, *PLOS ONE*, **9** (2014), e101702. https://doi.org/10.1371/journal.pone.0101702
7. L. T. Morenga, S. Mallard, J. Mann, Dietary sugars and body weight: Systematic review and meta-analyses of randomised controlled trials and cohort studies, *BMJ*, **346** (2013), e7492. https://doi.org/10.1136/bmj.e7492
8. H. Gu, S. Shao, J. Liu, Z. Fan, Y. Chen, J. Ni, et al., Age- and sex-associated impacts of body mass index on stroke type risk: a 27-year prospective cohort study in a low-income population in China, *Front. Neurol.*, **10** (2019). https://doi.org/10.3389/fneur.2019.00456
9. K. Cheng, Health oriented lifelong nutrition controls: Preventing cardiovascular diseases caused by obesity, 2020, URL /paper/Health-Oriented-Lifelong-Nutrition-Controls%3A-Caused-Cheng/e8ba816f29502370121f6c44217d019fcbae0223.
10. K. Mc Namara, H. Alzubaidi, J. K. Jackson, Cardiovascular disease as a leading cause of death: how are pharmacists getting involved?, *Integr. Pharm. Res. Pract.*, **8** (2019), 1–11. https://doi.org/10.2147/IPRP.S133088
11. N. Taghizadeh, H. M. Boezen, J. P. Schouten, C. P. Schröder, E. G. E. de Vries, J. M. Vonk, BMI and lifetime changes in BMI and cancer mortality risk, *PLoS ONE*, **10**. https://doi.org/10.1371/journal.pone.0125261
12. K. Bhaskaran, I. Douglas, H. Forbes, I. dos Santos-Silva, D. A. Leon, L. Smeeth, Body-mass index and risk of 22 specific cancers: A population-based cohort study of 5·24 million UK adults, *The Lancet*, **384** (2014), 755–765. https://doi.org/10.1016/S0140-6736(14)60892-8
13. M. Kalligeros, F. Shehadeh, E. K. Mylona, G. Benitez, C. G. Beckwith, P. A. Chan, et al., Association of obesity with disease severity among patients with coronavirus disease 2019, *Obesity*, **28** (2020), 1200–1204. https://doi.org/10.1002/oby.22859
14. A. Golay, J. Ybarra, Link between obesity and type 2 diabetes, *Best Pract Res. Clin. Endocrinol Metab.*, **19** (2005), 649–663. https://doi.org/10.1016/j.beem.2005.07.010

15. A. S. Al-Goblan, M. A. Al-Alfi, M. Z. Khan, Mechanism linking diabetes mellitus and obesity, *Diabetes Metab. Syndr. Obes.*, **7** (2014), 587–591. https://doi.org/10.2147/DMSO.S67400

16. A. S. Barnes, The epidemic of obesity and diabetes, *Tex. Heart Inst. J.*, **38** (2011), 142–144. URL `https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3066828/`.

17. N. A. Roper, R. W. Bilous, W. F. Kelly, N. C. Unwin, V. M. Connolly, Cause-specific mortality in a population with diabetes: south tees diabetes mortality study, *Diabetes Care*, **25** (2002), 43–48. https://doi.org/10.2337/diacare.25.1.43

18. M. Tancredi, A. Rosengren, A.-M. Svensson, M. Kosiborod, A. Pivodic, S. Gudbjörnsdottir, et al., Excess mortality among persons with type 2 diabetes, *NEJM*, **373** (2015), 1720–1732. https://doi.org/10.1056/NEJMoa1504347

19. R. A. DeFronzo, R. C. Bonadonna, E. Ferrannini, Pathogenesis of NIDDM: a balanced overview, *Diabetes Care*, **15** (1992), 318–368. https://doi.org/10.2337/diacare.15.3.318

20. A. D. Baron, G. Brechtel, P. Wallace, S. V. Edelman, Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans, *Am. J. Physiol. Endocrinol Metab.*, **255** (1988), E769–E774. https://doi.org/10.1152/ajpendo.1988.255.6.E769

21. R. A. DeFronzo, D. Tripathy, Skeletal muscle insulin resistance is the primary defect in type 2 diabetes, *Diabetes Care*, **32** (2009), S157–S163. https://doi.org/10.2337/dc09-S302

22. R. A. DeFronzo, The triumvirate: -cell, muscle, liver: A collusion responsible for NIDDM, *Diabetes*, **37** (1988), 667–687. https://doi.org/10.2337/diab.37.6.667

23. E. Archer, C. J. Lavie, J. O. Hill, The contributions of 'diet', 'genes', and physical activity to the etiology of obesity: contrary evidence and consilience, *Prog. Cardiovasc. Dis.*, **61** (2018), 89–102. https://doi.org/10.1016/j.pcad.2018.06.002

24. E. Archer, G. Pavela, S. McDonald, C. J. Lavie, J. O. Hill, Cell-specific "competition for calories" drives asymmetric nutrient-energy partitioning, obesity, and metabolic diseases in human and non-human Animals, *Front. Physiol.*, **9** (2018), 1053. https://doi.org/10.3389/fphys.2018.01053

25. A. V. Greco, G. Mingrone, A. Giancaterini, M. Manco, M. Morroni, S. Cinti, et al., Insulin resistance in morbid obesity: reversal with intramyocellular fat depletion, *Diabetes*, **51** (2002), 144–151. https://doi.org/10.2337/diabetes.51.1.144

26. O. T. Hardy, M. P. Czech, S. Corvera, What causes the insulin resistance underlying obesity?, *Curr. Opin. Endocrinol. Diabetes Obes.*, **19** (2012), 81–87. https://doi.org/10.1097/MED.0b013e3283514e13

27. C. Roberts-Toler, B. T. O'Neill, A. M. Cypess, Diet-induced obesity causes insulin resistance in mouse brown adipose tissue: DIO causes BAT insulin resistance, *Obesity*, **23** (2015), 1765–1770. https://doi.org/10.1002/oby.21134

28. E. Christiansen, L. Garby, Prediction of body weight changes caused by changes in energy balance, *Eur. J. Clin. Invest.*, **32** (2002), 826–830. https://doi.org/10.1046/j.1365-2362.2002.01036.x

29. E. Christiansen, L. Garby, T. I. A. Sørensen, Quantitative analysis of the energy requirements for development of obesity, *J. Theor. Biol.*, **234** (2005), 99–106. https://doi.org/10.1016/j.jtbi.2004.11.012

30. C. C. Chow, K. D. Hall, The dynamics of human body weight change, *PLoS Comput. Biol.*, **4** (2008), e1000045. https://doi.org/10.1371/journal.pcbi.1000045

31. K. D. Hall, P. N. Jordan, Modeling weight-loss maintenance to help prevent body weight regain, *Am. J. Clin. Nutr.*, **88** (2008), 1495–1503. https://doi.org/10.3945/ajcn.2008.26333

32. D. M. Thomas, A. Ciesla, J. A. Levine, J. G. Stevens, C. K. Martin, A mathematical model of weight change with adaptation, *MBE*, **6** (2009), 873–887. https://doi.org/10.3934/mbe.2009.6.873

33. E. H. Livingston, I. Kohlstadt, Simplified resting metabolic rate-predicting formulas for normal-sized and obese individuals, *Obes. Res.*, **13** (2005), 1255–1262. https://doi.org/10.1038/oby.2005.149

34. D. M. Thomas, C. K. Martin, S. Heymsfield, L. M. Redman, D. A. Schoeller, J. A. Levine, A simple model predicting individual weight change in humans, *J. Biol. Dyn.*, **5** (2011), 579–599. https://doi.org/10.1080/17513758.2010.508541

35. J. Guo, D. C. Brager, K. D. Hall, Simulating long-term human weight-loss dynamics in response to calorie restriction, *Am. J. Clin. Nutr.*, **107** (2018), 558–565. https://doi.org/10.1093/ajcn/nqx080

36. P. Jacquet, Y. Schutz, J.-P. Montani, A. Dulloo, How dieting might make some fatter: modeling weight cycling toward obesity from a perspective of body composition autoregulation, *Int. J. Obes.*, **44** (2020), 1243–1253. https://doi.org/10.1038/s41366-020-0547-1

37. A. Peña Fernández, A. Youssef, C. Heeren, C. Matthys, J.-M. Aerts, Real-time model predictive control of human bodyweight based on energy intake, *Appl. Sci.*, **9** (2019), 2609. https://doi.org/10.3390/app9132609

38. O. Babajide, T. Hissam, P. Anna, G. Anatoliy, A. Astrup, J. Alfredo Martinez, et al., A machine learning approach to short-term body weight prediction in a dietary intervention program, *Computational Science – ICCS 2020*. Lecture Notes in Computer Science, Springer International Publishing, Cham, 2020, 441–455.

39. K. D. Hall, G. Sacks, D. Chandramohan, C. C. Chow, Y. C. Wang, S. L. Gortmaker, et al., Quantification of the effect of energy imbalance on bodyweight, *Lancet (London, England)*, **378** (2011), 826–837. https://doi.org/10.1016/S0140-6736(11)60812-X

40. B.-H. Lin, T. A. Smith, J.-Y. Lee, K. D. Hall, Measuring weight outcomes for obesity intervention strategies: the case of a sugar-sweetened beverage tax, *Econ. Hum. Biol.*, **9** (2011), 329–341. https://doi.org/10.1016/j.ehb.2011.08.007

41. T. A. Smith, *Taxing Caloric Sweetened Beverages: Potential Effects on Beverage Consumption, Calorie Intake, and Obesity*, DIANE Publishing, 2010, Google-Books-ID: 3hBCqYKh0JQC.

42. T. S. Church, D. M. Thomas, C. Tudor-Locke, P. T. Katzmarzyk, C. P. Earnest, R. Q. Rodarte, et al., Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity, *PLOS ONE*, **6** (2011), e19657. https://doi.org/10.1371/journal.pone.0019657

43. K. D. Hall, Metabolism of mice and men: mathematical modeling of body weight dynamics, *Curr. Opin. Clin. Nutr. Metab. Care*, **15** (2012), 418–423. https://doi.org/10.1097/MCO.0b013e3283561150

44. K. D. Hall, J. Guo, M. Dore, C. C. Chow, The progressive increase of food waste in America and its environmental impact, *PLOS ONE*, **4** (2009), e7940. https://doi.org/10.1371/journal.pone.0007940

45. F. P. Kozusko, Body weight setpoint, metabolic adaption and human starvation, *Bull. Math. Biol.*, **63** (2001), 393–403. https://doi.org/10.1006/bulm.2001.0229

46. F. P. Kozusko, The effects of body composition on setpoint based weight loss, *Math. Comput. Model.*, **35** (2002), 973–982. https://doi.org/10.1016/S0895-7177(02)00064-X

47. D. M. Thomas, J. E. Navarro-Barrientos, D. E. Rivera, S. B. Heymsfield, C. Bredlau, L. M. Redman, et al., Dynamic energy-balance model predicting gestational weight gain, *Am. J. Clin. Nutr.* , **95** (2012), 115–122. https://doi.org/10.3945/ajcn.111.024307

48. K. Ejima, D. M. Thomas, D. B. Allison, A mathematical model for predicting obesity transmission with both genetic and nongenetic heredity, *Obesity (Silver Spring)*, **26** (2018), 927–933. https://doi.org/10.1002/oby.22135

49. K. D. Hall, Computational model of in vivo human energy metabolism during semistarvation and refeeding, *Am. J. Physiol. Endocrinol. Metab.*, **291** (2006), E23–37. https://doi.org/10.1152/ajpendo.00523.2005

50. D.-M. Li, T.-N. Guo, Q. Wang, B. Chai, R.-X. Zhang, D.-M. Li, et al., Quantitative analysis of body metabolism regulation model in the process of weight loss, *AIMS Math.*, **5** (2020), 2500–2525. https://doi.org/10.3934/math.2020165

51. G. M. Barnwell, F. S. Stafford, Mathematical model for decision-making neural circuits controlling food intake, *Bull. Psychon. Soc.*, **5** (1975), 473–476. https://doi.org/10.3758/BF03333304

52. R. C. Boston, P. J. Moate, K. C. Allison, J. D. Lundgren, A. J. Stunkard, Modeling circadian rhythms of food intake by means of parametric deconvolution: results from studies of the night eating syndrome, *Am. J. Clin. Nutr.*, **87** (2008), 1672–1677. https://doi.org/10.1093/ajcn/87.6.1672

53. F. Cameron, G. Niemeyer, B. A. Buckingham, Probabilistic evolving meal detection and estimation of meal total glucose appearance, *J. Diabetes Sci. Technol.*, **3** (2009), 1022–1030. https://doi.org/10.1177/193229680900300505

54. N. P. Balakrishnan, L. Samavedham, G. P. Rangaiah, Personalized mechanistic models for exercise, meal and insulin interventions in children and adolescents with type 1 diabetes, *J. Theor. Biol.*, **357** (2014), 62–73. https://doi.org/10.1016/j.jtbi.2014.04.038

55. M. Jacquier, F. Crauste, C. O. Soulage, H. A. Soula, A predictive model of the dynamics of body weight and food intake in rats submitted to caloric restrictions, *PLOS ONE*, **9** (2014), e100073. https://doi.org/10.1371/journal.pone.0100073

56. A. L. Murillo, M. Safan, C. Castillo-Chavez, E. D. C. Phillips, D. Wadhera, Modeling eating behaviors: The role of environment and positive food association learning via a ratatouille effect, *MBE*, **13** , 841–855. https://doi.org/10.3934/mbe.2016020

57. M. Chudtong, A. D. Gaetano, A mathematical model of food intake, *MBE*, **18** (2021), 1238–1279. https://doi.org/10.3934/mbe.2021067

58. A. Hinsberger, B. K. Sandhu, Digestion and absorption, *Curr. Pediatr.*, **14** (2004), 605–611. https://doi.org/10.1016/j.cupe.2004.08.004
59. A. D. Jackson, J. McLaughlin, Digestion and absorption, *Surgery (Oxf)*, **27** (2009), 231–236. https://doi.org/10.1016/j.mpsur.2009.03.003
60. I. Campbell, Digestion and absorption, *Anaesth. Intensive Care Med.*, **13** (2012), 62–63. https://doi.org/10.1016/j.mpaic.2011.11.001
61. P. R. Kiela, F. K. Ghishan, Physiology of intestinal absorption and secretion, *Best Pract. Res. Clin. Gastroenterol.*, **30** (2016), 145–159. https://doi.org/10.1016/j.bpg.2016.02.007
62. A. B. Strathe, A. Danfær, A. Chwalibog, A dynamic model of digestion and absorption in pigs, *Anim. Feed Sci. Technol.*, **143** (2008), 328–371. https://doi.org/10.1016/j.anifeedsci.2007.05.018
63. S. Salinari, A. Bertuzzi, G. Mingrone, Intestinal transit of a glucose bolus and incretin kinetics: a mathematical model with application to the oral glucose tolerance test, *Am. J. Physiol. Endocrinol. Metab.*, **300** (2011), E955–965. https://doi.org/10.1152/ajpendo.00451.2010
64. A. D. Gaetano, S. Panunzi, A. Matone, A. Samson, J. Vrbikova, B. Bendlova, et al., Routine OGTT: a robust model including incretin effect for precise identification of insulin sensitivity and secretion in a single individual, *PLOS ONE*, **8** (2013), e70875. https://doi.org/10.1371/journal.pone.0070875
65. M. Taghipoor, G. Barles, C. Georgelin, J. R. Licois, P. Lescoat, Digestion modeling in the small intestine: impact of dietary fiber, *Math. Biosci.*, **258** (2014), 101–112. https://doi.org/10.1016/j.mbs.2014.09.011
66. E. D. Lehmann, T. Deutsch, A physiological model of glucose-insulin interaction in type 1 diabetes mellitus, *J. Biomed. Eng.*, **14** (1992), 235–242. https://doi.org/10.1016/0141-5425(92)90058-s
67. A. Roy, R. S. Parker, Dynamic modeling of exercise effects on plasma glucose and insulin levels, *J. Diabetes Sci. Technol.*, **1** (2007), 338–347. https://doi.org/10.1177/193229680700100305
68. R. Hovorka, V. Canonico, L. J. Chassin, U. Haueter, M. Massi-Benedetti, M. Orsini Federici,et al., Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes, *Physiol. Meas.*, **25** (2004), 905–920. https://doi.org/10.1088/0967-3334/25/4/010
69. B. K. Mani, K. Shankar, J. M. Zigman, Ghrelin's relationship to blood glucose, *Endocrinol.*, **160** (2019), 1247–1261. https://doi.org/10.1210/en.2019-00074
70. R. D. Palmiter, Is dopamine a physiologically relevant mediator of feeding behavior?, *Trends Neurosci.*, **30** (2007), 375–381. https://doi.org/10.1016/j.tins.2007.06.004
71. D. P. Figlewicz, S. B. Evans, J. Murphy, M. Hoen, D. G. Baskin, Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat, *Brain Res.*, **964** (2003), 107–115. https://doi.org/10.1016/S0006-8993(02)04087-8
72. D. P. Figlewicz, P. Szot, M. Chavez, S. C. Woods, R. C. Veith, Intraventricular insulin increases dopamine transporter mRNA in rat VTA/substantia nigra, *Brain Res.*, **644** (1994), 331–334. https://doi.org/10.1016/0006-8993(94)91698-5
73. J. Vartiainen, Ghrelin, obesity and type 2 diabetes : Genetic, metabolic and epidemiological studies, *University of Oulu*, Place: University of Oulu.

74. J. L. Jameson, L. J. D. Groot, *Endocrinology: Adult and Pediatric, E-Book*, Elsevier Health Sciences, 2015, Google-Books-ID: xmLeBgAAQBAJ.

75. D. A. Schatz, M. Haller, M. Atkinson, *Type 1 Diabetes, An Issue of Endocrinology and Metabolism Clinics of North America, E-Book*, Elsevier Health Sciences, 2010, Google-Books-ID: nu2IxmYJkjkC.

76. J. Morales, D. Schneider, Hypoglycemia, *AJM*, **127** (2014), S17–S24. https://doi.org/10.1016/j.amjmed.2014.07.004

77. C. Kenny, When hypoglycemia is not obvious: Diagnosing and treating under-recognized and undisclosed hypoglycemia, *Prim. Care Diabetes*, **8** (2014), 3–11. https://doi.org/10.1016/j.pcd.2013.09.002

78. G. Cheney, *Medical Management of Gastrointestinal Disorders*, Year Book, 1950, Google-Books-ID: nwiyAAAAIAAJ.

79. M. M, *How to Manage Your Diabetes and Lead a Normal Life*, Peacock Books, 2008, Google-Books-ID: bavxjgZa2NIC.

80. R. K. Bernstein, Hunger–a common symptom of hypoglycemia, *Diabetes Care*, **16** (1993), 1049. https://doi.org/10.2337/diacare.16.7.1049a

81. L. C. Perlmuter, B. P. Flanagan, P. H. Shah, S. P. Singh, Glycemic control and hypoglycemia, *Diabetes Care*, **31** (2008), 2072–2076. https://doi.org/10.2337/dc08-1441

82. B. Schultes, K. M. Oltmanns, W. Kern, H. L. Fehm, J. Born, A. Peters, Modulation of hunger by plasma glucose and metformin, *J. Clin. Endocrinol. Metab.*, **88** (2003), 1133–1141. https://doi.org/10.1210/jc.2002-021450

83. B. Schultes, A. Peters, M. Hallschmid, C. Benedict, V. Merl, K. M. Oltmanns, et al., Modulation of food intake by glucose in patients with type 2 diabetes, *Diabetes Care*, **28** (2005), 2884–2889. https://doi.org/10.2337/diacare.28.12.2884

84. H. A. J. Gielkens, M. Verkijk, W. F. Lam, C. B. H. W. Lamers, A. A. M. Masclee, Effects of hyperglycemia and hyperinsulinemia on satiety in humans, *Metab. Clin. Exp.*, **47** (1998), 321–324. https://doi.org/10.1016/S0026-0495(98)90264-5

85. B. Schultes, A.-K. Panknin, M. Hallschmid, K. Jauch-Chara, B. Wilms, F. de Courbière, et al., Glycemic increase induced by intravenous glucose infusion fails to affect hunger, appetite, or satiety following breakfast in healthy men, *Appetite*, **105** (2016), 562–566. https://doi.org/10.1016/j.appet.2016.06.032

86. G. H. Anderson, D. Woodend, Consumption of sugars and the regulation of short-term satiety and food intake, *Am. J. Clin. Nut.*, **78** (2003), 843S–849S. https://doi.org/10.1093/ajcn/78.4.843S

87. J. M. McMillin, Blood Glucose, *Clinical Methods: The History, Physical, and Laboratory Examinations* (eds. H. K. Walker, W. D. Hall and J. W. Hurst), 3rd edition. Butterworths, Boston, 1990. URL `http://www.ncbi.nlm.nih.gov/books/NBK248/`.

88. S. J. Russell, F. H. El-Khatib, M. Sinha, K. L. Magyar, K. McKeon, L. G. Goergen, et al., Outpatient glycemic control with a bionic pancreas in type 1 diabetes, *N. Engl. J. Med.*, **371** (2014), 313–325. https://doi.org/10.1056/NEJMoa1314474

89. A. Boutayeb, A. Chetouani, A critical review of mathematical models and data used in diabetology, *Biomed. Eng. OnLine.*, **5** (2006), 43. https://doi.org/10.1186/1475-925X-5-43

90. P. Palumbo, S. Ditlevsen, A. Bertuzzi, A. De Gaetano, Mathematical modeling of the glucose-insulin system: A review, *Math. Biosci.*, **244** (2013), 69–81. https://doi.org/10.1186/1475-925X-5-43

91. A. Mari, A. Tura, E. Grespan, R. Bizzotto, Mathematical modeling for the physiological and clinical investigation of glucose homeostasis and diabetes, *Front. Physiol.*, **11** (2020), 575789. https://doi.org/10.3389/fphys.2020.575789

92. B. Huard, G. Kirkham, Mathematical modelling of glucose dynamics, *Curr. Opin. Endocrinol. Metab. Res.*, **25** (2022), 100379. https://doi.org/10.1016/j.coemr.2022.100379

93. R. N. Bergman, G. Bortolan, C. Cobelli, G. Toffolo, Identification of a minimal model of glucose disappearance for estimating insulin sensitivity, *IFAC Proc. Vol.*, **12** (1979), 883–890. https://doi.org/10.1016/S1474-6670(17)65505-8

94. G. Toffolo, R. N. Bergman, D. T. Finegood, C. R. Bowden, C. Cobelli, Quantitative estimation of beta cell sensitivity to glucose in the intact organism: a minimal model of insulin kinetics in the dog, *Diabetes*, **29** (1980), 979–990. https://doi.org/10.2337/diab.29.12.979

95. A. De Gaetano, O. Arino, Mathematical modelling of the intravenous glucose tolerance test, *J. Math. Biol.*, **40** (2000), 136–168. https://doi.org/10.1007/s002850050007

96. S. Panunzi, P. Palumbo, A. De Gaetano, A discrete single delay model for the intra-venous glucose tolerance test, *Theor. Biol. Med. Model.*, **4** (2007), 35. https://doi.org/10.1186/1742-4682-4-35

97. S. Panunzi, A. De Gaetano, G. Mingrone, Advantages of the single delay model for the assessment of insulin sensitivity from the intravenous glucose tolerance test, *Theor. Biol. Med. Model.*, **7** (2010), 9. https://doi.org/10.1186/1742-4682-7-9

98. G. Pacini, R. N. Bergman, MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test, *Comput. Methods Programs Biomed.*, **23** (1986), 113–122. https://doi.org/10.1016/0169-2607(86)90106-9

99. C. Dalla Man, R. A. Rizza, C. Cobelli, Meal simulation model of the glucose-insulin system, *IEEE Trans. Biomed. Eng.*, **54** (2007), 1740–1749. https://doi.org/10.1109/TBME.2007.893506

100. W. Liu, F. Tang, Modeling a simplified regulatory system of blood glucose at molecular levels, *J. Theor. Biol.*, **252** (2008), 608–620. https://doi.org/10.1016/j.jtbi.2008.02.021

101. W. Liu, C. Hsin, F. Tang, A molecular mathematical model of glucose mobilization and uptake, *Math. Biosci.*, **221** (2009), 121–129. https://doi.org/10.1016/j.mbs.2009.07.005

102. Z. Wu, C. K. Chui, G. S. Hong, S. Chang, Physiological analysis on oscillatory behavior of glucose–insulin regulation by model with delays, *J. Theor. Biol.*, **280** (2011), 1–9. https://doi.org/10.1016/j.jtbi.2011.03.032

103. M. Lombarte, M. Lupo, G. Campetelli, M. Basualdo, A. Rigalli, Mathematical model of glucose–insulin homeostasis in healthy rats, *Math. Biosci.*, **245** (2013), 269–277. https://doi.org/10.1016/j.mbs.2013.07.017

104. A. C. Pratt, J. A. D. Wattis, A. M. Salter, Mathematical modelling of hepatic lipid metabolism, *Math. Biosci.*, **262** (2015), 167–181. https://doi.org/10.1016/j.mbs.2014.12.012

105. J. Girard, The incretins: From the concept to their use in the treatment of type 2 diabetes. Part A: incretins: concept and physiological functions, *Diabetes Metab.*, **34** (2008), 550–559. https://doi.org/10.1016/j.diabet.2008.09.001

106. J. J. Holst, C. F. Deacon, T. Vilsbøll, T. Krarup, S. Madsbad, Glucagon-like peptide-1, glucose homeostasis and diabetes, *Trends Mol. Med.*, **14** (2008), 161–168. https://doi.org/10.1016/j.molmed.2008.01.003

107. J. J. Holst, T. Vilsbøll, C. F. Deacon, The incretin system and its role in type 2 diabetes mellitus, *Mol. Cell. Endocrinol.*, **297** (2009), 127–136. https://doi.org/10.1016/j.mce.2008.08.012

108. K. Kazakos, Incretin effect: GLP-1, GIP, DPP4, *Diabetes Res. Clin. Pract.*, **93** (2011), S32–S36. https://doi.org/10.1016/S0168-8227(11)70011-0

109. J. J. Holst, C. F. Deacon, Is there a place for incretin therapies in obesity and prediabetes?, *Trends Endocrinol. Metab.*, **24** (2013), 145–152. https://doi.org/10.1016/j.tem.2013.01.004

110. G. Zhao, D. Wirth, I. Schmitz, M. Meyer-Hermann, A mathematical model of the impact of insulin secretion dynamics on selective hepatic insulin resistance, *Nat. Commun.*, **8** (2017), 1–10. https://doi.org/10.1038/s41467-017-01627-9

111. S. Masroor, M. G. J. van Dongen, R. Alvarez-Jimenez, K. Burggraaf, L. A. Peletier, M. A. Peletier, Mathematical modeling of the glucagon challenge test, *J. Pharmacokinet. Pharmacodyn.*, **46** (2019), 553–564. https://doi.org/10.1007/s10928-019-09655-2

112. M. C. Palumbo, M. Morettini, P. Tieri, F. Diele, M. Sacchetti, F. Castiglione, Personalizing physical exercise in a computational model of fuel homeostasis, *PLoS Comput. Biol.*, **14** (2018), e1006073. https://doi.org/10.1371/journal.pcbi.1006073

113. M. C. Palumbo, A. A. de Graaf, M. Morettini, P. Tieri, S. Krishnan, F. Castiglione, A computational model of the effects of macronutrients absorption and physical exercise on hormonal regulation and metabolic homeostasis, *Comput. Biol. Med.*, **163** (2023), 107158. https://doi.org/10.1016/j.compbiomed.2023.107158

114. J. Deichmann, S. Bachmann, M. Pfister, G. Szinnai, H.-M. Kaltenbach, A comprehensive model of glucose-insulin regulation including acute and prolonged effects of physical activity in type 1 diabetes, *bioRxiv*, 2021.06.09.447693. https://doi.org/10.1101/2021.06.09.447693

115. N. E. López-Palau, J. M. Olais-Govea, Mathematical model of blood glucose dynamics by emulating the pathophysiology of glucose metabolism in type 2 diabetes mellitus, *Sci. Rep.*, **10** (2020), 12697. https://doi.org/10.1038/s41598-020-69629-0

116. H. Kurata, Virtual metabolic human dynamic model for pathological analysis and therapy design for diabetes, *iScience*, **24** (2021), 102101. https://doi.org/10.1016/j.isci.2021.102101

117. R. N. Bergman, Y. Z. Ider, C. R. Bowden, C. Cobelli, Quantitative estimation of insulin sensitivity., *Am. J. Physiol. Endocrinol. Metab.*, **236** (1979), E667. https://doi.org/10.1152/ajpendo.1979.236.6.E667

118. A. Mukhopadhyay, A. De Gaetano, O. Arino, Modeling the intra-venous glucose tolerance test: a global study for a single-distributed-delay model, *DCDS-B*, **4** (2004), 407. https://doi.org/10.3934/dcdsb.2004.4.407

119. J. Li, M. Wang, A. De Gaetano, P. Palumbo, S. Panunzi, The range of time delay and the global stability of the equilibrium for an IVGTT model, *Math. Biosci.*, **235** (2012), 128–137. https://doi.org/10.1016/j.mbs.2011.11.005

120. D. V. Giang, Y. Lenbury, A. De Gaetano, P. Palumbo, Delay model of glucose–insulin systems: Global stability and oscillated solutions conditional on delays, *J. Math. Anal. Appl.*, **343** (2008), 996–1006. https://doi.org/10.1016/j.jmaa.2008.02.016

121. C.-L. Chen, H.-W. Tsai, Modeling the physiological glucose–insulin system on normal and diabetic subjects, *Comput. Methods Programs Biomed.*, **97** (2010), 130–140. https://doi.org/10.1016/j.cmpb.2009.06.005

122. P. Palumbo, P. Pepe, S. Panunzi, A. De Gaetano, Time-delay model-based control of the glucose-insulin system, by means of a state observer, *European J. Control*, **6** (2012), 591–606. https://doi.org/10.3166/EJC.18.591-606

123. A. De Gaetano, S. Panunzi, A. Matone, A. Samson, J. Vrbikova, B. Bendlova, et al., Routine OGTT: a robust model including incretin effect for precise identification of insulin sensitivity and secretion in a single individual, *PLOS ONE*, **8** (2013), e70875. https://doi.org/10.1371/journal.pone.0070875

124. P. Palumbo, G. Pizzichelli, S. Panunzi, P. Pepe, A. De Gaetano, Model-based control of plasma glycemia: Tests on populations of virtual patients, *Math. Biosci.*, **257** (2014), 2–10. https://doi.org/10.1016/j.mbs.2014.09.003

125. U. Picchini, A. De Gaetano, S. Panunzi, S. Ditlevsen, G. Mingrone, A mathematical model of the euglycemic hyperinsulinemic clamp, *Theor. Biol. Med. Model.*, **2** (2005), 44. https://doi.org/10.1186/1742-4682-2-44

126. U. Picchini, S. Ditlevsen, A. De Gaetano, Modeling the euglycemic hyperinsulinemic clamp by stochastic differential equations, *J. Math. Biol.*, **53** (2006), 771–796. https://doi.org/10.1007/s00285-006-0032-z

127. P. Palumbo, A. De Gaetano, An islet population model of the endocrine pancreas, *J. Math. Biol.*, **61** (2010), 171–205. https://doi.org/10.1007/s00285-009-0297-0

128. A. De Gaetano, C. Gaz, P. Palumbo, S. Panunzi, A unifying organ model of pancreatic insulin secretion, *PLOS ONE*, **10** (2015), e0142344. https://doi.org/10.1371/journal.pone.0142344

129. A. De Gaetano, C. Gaz, S. Panunzi, Consistency of compact and extended models of glucose-insulin homeostasis: the role of variable pancreatic reserve, *PLOS ONE*, **14** (2019), e0211331. https://doi.org/10.1371/journal.pone.0211331

130. B. Topp, K. Promislow, G. deVries, R. M. Miura, D. T. Finegood, A model of beta-cell mass, insulin, and glucose kinetics: pathways to diabetes, *J. Theor. Biol.*, **206** (2000), 605–619. https://doi.org/10.1006/jtbi.2000.2150

131. A. De Gaetano, T. Hardy, B. Beck, E. Abu-Raddad, P. Palumbo, J. Bue-Valleskey, et al., Mathematical models of diabetes progression, *Am. J. Physiol. Endocrinol. Metab.*, **295** (2008), E1462–1479.

132. P. C. Fletcher, P. J. Kenny, Food addiction: A valid concept?, *Neuropsychopharmacology*, **43** (2018), 2506–2513. https://doi.org/10.1038/s41386-018-0203-9

133. T. Hardy, E. Abu-Raddad, N. Porksen, A. De Gaetano, Evaluation of a mathematical model of diabetes progression against observations in the Diabetes Prevention Program, *Am. J. Physiol. Endocrinol. Metab.*, **303** (2012), E200–E212. https://doi.org/10.1152/ajpendo.00421.2011

134. A. De Gaetano, T. A. Hardy, A novel fast-slow model of diabetes progression: Insights into mechanisms of response to the interventions in the diabetes prevention program, *PLOS ONE*, **14** (2019), e0222833. https://doi.org/10.1371/journal.pone.0222833

135. P. Toghaw, A. Matone, Y. Lenbury, A. De Gaetano, Bariatric surgery and T2dm improvement mechanisms: A mathematical model, *Theor. Biol. Med. Model*, **9** (2012), 16. https://doi.org/10.1186/1742-4682-9-16

136. C. C. Y. Noguchi, E. Furutani, S. Sumi, Enhanced mathematical model of postprandial glycemic excursion in diabetics using rapid-acting insulin, *2012 SICE AC.*, 2012, 566–571.

137. A. De Gaetano, S. Panunzi, D. Eliopoulos, T. Hardy, G. Mingrone, Mathematical modeling of renal tubular glucose absorption after glucose load, *PLOS ONE*, **9** (2014), e86963, https://doi.org/10.1371/journal.pone.0086963

138. A. Borri, S. Panunzi, A. De Gaetano, A glycemia-structured population model, *J. Math. Biol.*, **73** (2016), 39–62. https://doi.org/10.1007/s00285-015-0935-7

139. S. Sakulrang, E. J. Moore, S. Sungnul, A. De Gaetano, A fractional differential equation model for continuous glucose monitoring data, *Adv. Differ. Equ.*, **2017** (2017), 150. https://doi.org/10.1186/s13662-017-1207-1

140. S. Panunzi, A. Borri, L. D'Orsi, A. DeGaetano, Order estimation for a fractional Brownian motion model of glucose control, *Commun. Nonlinear Sci. Numer.*, **127** (2023), 107554. https://doi.org/10.1016/j.cnsns.2023.107554

141. J. Yokrattanasak, A. De Gaetano, S. Panunzi, P. Satiracoo, W. M. Lawton, Y. Lenbury, A simple, realistic stochastic model of gastric emptying, *PLoS ONE*, **11** (2016). https://doi.org/10.1371/journal.pone.0153297

142. Y. T. Wondmkun, Obesity, insulin resistance, and type 2 diabetes: Associations and therapeutic implications, *Diabetes Metab. Syndr. Obes. Targets Ther.*, **13** (2020), 3611–3616. https://doi.org/10.2147/DMSO.S275898

143. B. B. Kahn, J. S. Flier, Obesity and insulin resistance, *J. Clin. Invest*, **106** (2000), 473–481. https://doi.org/10.1172/JCI10842

144. L. Pénicaud, M. F. Kinebanyan, P. Ferré, J. Morin, J. Kandé, C. Smadja, et al., Development of VMH obesity: In vivo insulin secretion and tissue insulin sensitivity, *Am. J. Physiol.*, **257** (1989), E255–260. https://doi.org/10.1152/ajpendo.1989.257.2.E255

145. S. Virtue, A. Vidal-Puig, Adipose tissue expandability, lipotoxicity and the metabolic syndrome–an allostatic perspective, *BBA*, **1801** (2010), 338–349. https://doi.org/10.1016/j.bbalip.2009.12.006

146. D. S. Ludwig, C. B. Ebbeling, The carbohydrate-insulin model of obesity: beyond 'calories in, calories out', *JAMA Intern. Med.*, **178** (2018), 1098–1103. https://doi.org/10.1001/jamainternmed.2018.2933

147. R Core Team, *R: a Language and Environment for Statistical Computing*, R Foundation for Statistical Computing, Vienna, Austria, 2023, URL `https://www.R-project.org/`.

148. U. N. UNIVERSITY, *Human energy requirements Report of a Joint FAO/WHO/UNU Expert Consultation*, 1, 2004.

149. A. E. Black, W. A. Coward, T. J. Cole, A. M. Prentice, Human energy expenditure in affluent societies: An analysis of 574 doubly-labelled water measurements, *Eur. J. Clin. Nutr.* , **50** (1996), 72–92.

150. M. D. Mifflin, S. T. St Jeor, L. A. Hill, B. J. Scott, S. A. Daugherty, Y. O. Koh, A new predictive equation for resting energy expenditure in healthy individuals, *Am. J. Clin. Nutr.*, **51** (1990), 241–247. https://doi.org/10.1093/ajcn/51.2.241

Tables

The model's variables and parameters are summarized in Tables 1 and 2.

Table 1. Model Variables.

VarID	Variable	Units	Meaning
0	t	min	Time in minutes
1	D	days	Days
2	τ	min	Time of the day in minutes
3	τ_1	min	Time of first daily meal (breakfast)
4	τ_2	min	Time of second daily meal (lunch)
5	τ_3	min	Time of third daily meal (dinner)
6	M_1	kcal	Suggested size of first daily meal (breakfast)
7	M_2	kcal	Suggested size of second daily meal (lunch)
8	M_3	kcal	Suggested size of third daily meal (dinner)
9	λ_{CG}	/min	Probability rate of assuming a snack given the current glycemia
10	P_{CG}	#	Probability of assuming a snack during the next time interval
11	S	kcal	The stomach's food content
12	Z	#	Relative insulin sensitivity
13	G	mM	Glycemia
14	I	pM	Insulin plasma concentration
15	W	kg	Body weight
16	Y	kcal/day	Energy expenditure
17	A	#	Appetite

Table 2. Model Parameters.

VarID	Parameter	Units	Meaning	Value
0	t_0	min	Starting time for numerical integration	0
1	t_{end}	min	Final time for numerical integration	525600
2	t_Δ	min	Time integration step	2
3	t_{10}	min	Initial time of first meal (breakfast)	450
4	t_1^{min}	min	Lower bound of random time for first meal	360
5	t_1^{max}	min	Upper bound of random time for first meal	540
6	t_{20}	min	Initial time of second meal (lunch)	750
7	t_2^{min}	min	Lower bound of random time for second meal	660
8	t_2^{max}	min	Upper bound of random time for second meal	840
9	t_{30}	min	Initial time of third meal (dinner)	1170
10	t_3^{min}	min	Lower bound of random time for third meal	1080
11	t_3^{max}	min	Upper bound of random time for third meal	1260
12	M_{10}	kcal	Initial size of first meal (breakfast)	600
13	M_1^{min}	kcal	Lower bound of random size for first meal	450
14	M_1^{max}	kcal	Upper bound of random size for first meal	650
15	M_{20}	kcal	Initial size of second meal (lunch)	1000
16	M_2^{min}	kcal	Lower bound of random size for second meal	700
17	M_2^{max}	kcal	Upper bound of random size for second meal	1300
18	M_{30}	kcal	Initial size of third meal (dinner)	1000
19	M_3^{min}	kcal	Lower bound of random size for third meal	700
20	M_3^{max}	kcal	Upper bound of random size for third meal	1300
21	γ_{CG}	#	Exponent of the Hill function relating snacking probability rate to glycemia	10
22	G_{C50}	mM	Glycemia of half-maximal snacking probability rate	2
23	C^{min}	kcal	Lower bound of random size for snacks	0
24	C^{max}	kcal	Upper bound of random size for snacks	300
25	t_C^{last}	min	Time of last allowed snack of the day	120
26	$t_{C\Delta}^{first}$	min	Time delay after first meal before snacking is allowed	60
27	$t_{OS}^{1/2}$	min	Half-life of stomach contents	60
28	S_0	kcal	Initial stomach contents	0

VarID	Parameter	Units	Meaning	Value
29	γ_{ZW}	#	Exponent of the Hill function relating daily energy expenditure to body weight	4
30	W_{Z50}	kg	Body weight of half-maximal daily relative insulin sensitivity	90
31	k_{OG}	/min	Glucose elimination rate at baseline insulinemia	0.02
32	ρ_{GS}	mmol/kcal	Conversion factor kcal of absorbed food to mmol absorbed glucose	0.486111
33	G_0	mM	Baseline glycemia at t_0	3.5
34	k_{OI}	/min	Insulin elimination rate	0.005
35	I_0	pM	Baseline insulinemia at t_0	35
36	ρ_{WS}	kg/kcal	Weight increase in kg per kcal net energy gain	5.55556e-05
37	W_0	kg	Baseline body weight at t_0	70
38	Y^{max}	kcal/day	Maximal energy expenditure with increasing body weight	6000
39	γ_{YW}	#	Exponent of the Hill function relating daily energy expenditure to body weight	1
40	W_{Y50}	kg	Body weight of half-maximal daily energy expenditure	90
41	Y_0	kcal/day	Baseline energy expenditure at t_0	2200
42	A^{max}	#	Maximal appetite level (at zero glycemia)	2.66
43	λ_{AG}	/mM	Rate of exponential decrease in appetite with increasing glycemia	0.3
44	h	m	Height of the subject	1.75
45	D_{end}	days	Final simulation day	365
46	V_G	L	Glucose distribution volume	14
47	k_{OGI}	/min/pM	Insulin sensitivity, insulin-dependent glucose elimination rate	0.000571429
48	k_G	mM/min	Net glycemia increase rate	0.07
49	k_{OS}	/min	Food absorption rate from gut	0.0115525
50	k_{IG}	pM/min/(mM^2)	Glycemia-dependent insulin secretion rate (nonlinear)	0.0142857
51	A_0	#	Baseline appetite at t_0	0.930834

AIMS Press