Model and Personal Sensor for Metabolic Tracking and Optimization

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Lincoln Laboratory has developed a novel metabolic fuel model and low-cost breath sensor for measuring, tracking, and enhancing metabolism. The model can predict key metabolic state parameters, including blood glucose levels, available glycogen stores, nutrient substrate utilization, and fat accumulation or depletion, for a given diet and activity profile. It can also predict healthy metabolic responses to a variety of dietary interventions and the onset of medical conditions, such as type 2 diabetes and excessive fat accumulation. The model suggests that the measurement of key metabolic parameters, such as respiratory quotient and energy expenditure, can provide insight into metabolic health and improvements in athletic performance and endurance.

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At the cellular level, metabolism refers to living cells' physical and chemical reactions that produce the energy required for life. These reactions are generally categorized as catabolic (breaking down large molecules to release energy) or anabolic (synthesizing complex molecules to store energy). Humans' very existence is intimately tied to the successful operation of these cellular metabolic processes. Despite the importance of metabolism, most people possess little insight into its function and often have a vague understanding of how dietary intake and activities impact metabolism. Historically speaking, metabolism and nutrition are relatively immature fields of study, and much of what is understood about the complex regulation of cellular metabolism and its relationship to nutrition has been gleaned in just the last half century.

The metabolic processes responsible for converting dietary macronutrients into the chemical energy needed to power biochemical processes were not fully understood until early in the twentieth century, when physiologists Hans Krebs and Fritz Albert Lipmann discovered the citric acid cycle [1]. As understanding of the science behind nutrition and metabolism has evolved, so has the ability to identify and treat metabolic disorders related to dietary imbalances. Despite progress in understanding metabolism, controversies still exist regarding its basic principles, such as the virtues of a low-carbohydrate versus a low-fat diet. Furthermore, even the settled science is slow to influence public policy and health care partly because nutrition education has historically played a minor role in medical training [2]. In a 2006 study,

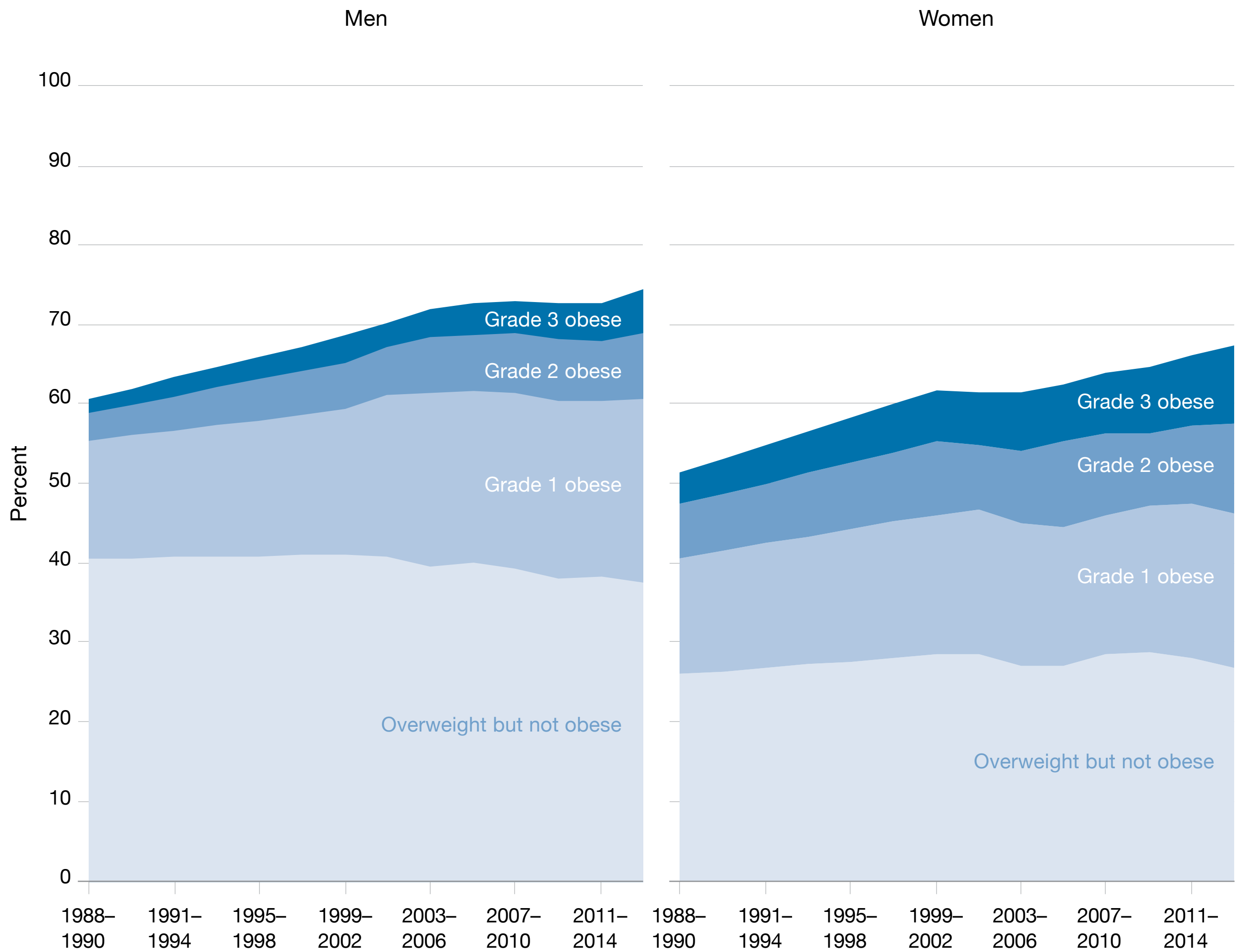


FIGURE 1. The rate of obesity has been increasing in the U.S. population for decades. There has been no consensus regarding how to reverse the trend. Grade 3 obesity is defined as having a body mass index (BMI) > 40. Grade 2 obesity is 40 > BMI > 35; Grade 1 obesity is 35 > BMI > 30; overweight but not obese is 30 > BMI > 25; and healthy is 24.9 > BMI > 18.5 [3].

less than one-third of U.S. medical schools were found to provide adequate nutrition education in their medical training curricula [4].

The relationships between diet, metabolism, socioeconomic status, and debilitating medical conditions, such as type 2 diabetes, are still subjects of active research and debate [5–10]. The lack of consensus is evident from the multitude of different, often antithetical (e.g., low-fat versus low-carbohydrate) diet plans, and degraded or dysfunctional metabolisms among a significant fraction of the U.S. population. According to the Centers for Disease Control and Prevention, in 2016, nearly half of the adults in the United States were either prediabetic (86 million) or diabetic (29 million) [11]. In addition, more than 35 percent of American adults and close to 17 percent of children were obese. As indicated in Figure 1, the percentage of the population affected by metabolic diseases continues to grow [12]. While there are many postulated factors driving the rapid (within one to two generations) growth in obesity, there is neither consensus regarding the root cause nor success in stemming this epidemic.

Metabolic diseases also represent a national security issue across all service branches and phases of a military career, including recruitment, training, deployment, and post-separation from the service. According to a 2015 report, one in three young adults of recruitment age is unqualified for military service because of excessive

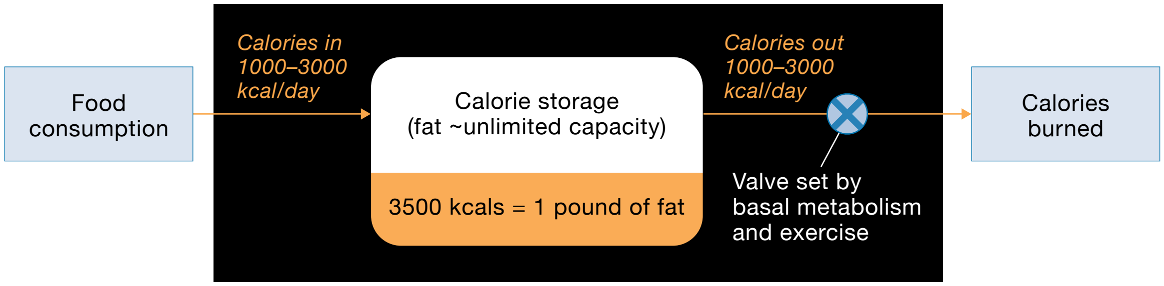


FIGURE 2. The calories-in/calories-out metabolic model helps explain the method of weight gain/loss and is the basis for many weight management strategies. Calories are measured in kilocalories (kcals).

body weight or weight-related disorders [13, 14]. During training and deployment, metabolic fitness levels impact mission readiness, and optimizing a soldier's performance requires matching nutrition to individual metabolic needs [15]. During the later stages of a military career and retirement, avoiding obesity and type 2 diabetes is a concern for the service organizations and aging soldiers. Currently, 15 percent of the patients in Veterans Health Administration hospital care are diabetic, and the Department of Defense spends more than $4 billion per year treating weight-related diseases [16].

The U.S. military has an interest in comprehensive metabolic measurement and tracking systems for optimizing the performance of soldiers under demanding physical conditions and for maintaining soldiers' metabolic health and wellness. It is in this context that Lincoln Laboratory has been developing a novel metabolic model to predict how the body will respond to changes in dietary intake and activity level. The body's response can vary from person to person, with training, and over time; this variability requires measuring individual metabolic parameters to fully personalize the model.

What Is a Metabolic Model, and Why Do We Need One?

To improve public health and optimize physical/mental performance, we must first understand how metabolism varies from individual to individual and how it responds to diet and exercise. An engineering approach to problem solving and optimization often begins with the creation of a system-level model, in which system level implies a model that possesses sufficient fidelity to represent the behavior(s) of interest while keeping complexity to a minimum. For example, if the problem of interest involved modeling the flight dynamics of an aircraft, a parsimonious system model would not include the inner workings of the engines or the individual integrated circuits. Instead, it would include only the salient performance parameters, such as available thrust, lift, or drag, and the control authority to influence all of these factors while omitting the mechanism by which the control was achieved or implemented. To help place our unique metabolic model in context, we review two extremes of metabolic modeling complexity that are frequently invoked in the discussion of metabolism and metabolic health maintenance.

Calories-In/Calories-Out Model

From the general population and from many health professionals, the most common answer to the question "What is the most important metric for managing body weight?" is calories, with the understanding that energy balance is needed for weight maintenance, and an energy deficit is needed for weight loss [17–19]. The calories-in/calories-out (CICO) model, illustrated in Figure 2, captures the essence of the first law of thermodynamics, which states that energy transforms from one form to another but is never created or destroyed.

The model accounts for the fact that if more calories are ingested than expended, the excess calories not excreted are stored (e.g., as glycogen in the liver or muscle tissue or as fat in adipose tissue), resulting in an increase in body weight. Using the CICO model as a base, many weight management strategies emphasize tracking the caloric content of foods eaten and the calories expended while exercising. These weight management plans sometimes include measuring an individual's resting metabolic rate to quantify, rather than estimate, basal metabolic energy needs and to create a more accurate calorie-restricted diet and exercise regimen to achieve the desired energy deficit for weight loss [20].

While the physics of the CICO model are technically correct, the model is insufficient to provide insight into the complex human metabolism. In particular, the CICO model makes no distinction regarding dietary macronutrient composition (fat versus carbohydrate versus protein) or the homeostatic mechanisms inciting hunger or satiety and is thus unable to explain phenomena such as metabolic set points (a preferred or predetermined body weight regulated by a feedback control mechanism) or satiety [21, 22]. For example, a one-liter soda and a small salad both provide about 450 calories. However, the body's response to these two meals is quite different in terms of how the calories are processed, how quickly they become available to meet energy needs, how they impact blood glucose levels, and how much satiety they produce. The CICO model is far too simple to provide useful insight into how the different types of calories[1] we ingest impact metabolic health and performance.

Cellular-Level Models and Utility

At the other extreme of complexity are cellular-level models that seek to represent the microscale processes contributing to metabolism before building them into a holistic human model [23, 24]. However, given that there are tens of trillions of interdependent cells in the human body, micro and cellular models are too detailed for efficient scaling to a whole-body model. What is needed is a model with complexity falling between the CICO model, which fails to account for different macronutrients, and cellular-level models that don't scale well to system-level simulation.

An Engineering Approach to Goldilocks Metabolic Modeling

The genesis of the system model of metabolism introduced here is strongly influenced by the observation that the human body prioritizes maintaining blood glucose concentration within a narrow range [25]. For an average-size adult, controlling blood sugar levels to a nominal value of 100 milligrams/deciliter (mg/dL) translates to a control objective of maintaining about five grams of glucose within the body's entire circulating blood volume. The fact that this level stays fairly constant, regardless of whether carbohydrates are plentiful (300+ grams of carbohydrate per day) or nonexistent (zero grams per day), does not happen by chance. Blood glucose levels must be actively controlled through feedback, and the body employs a system of mechanisms to monitor blood glucose level, signal that the level is out of range, and actively control or correct glucose levels in response to these signals. It is this system control that is captured in our model and drives the observed metabolic behavior.

[1]Note that a food calorie, denoted with an uppercase C, is equivalent to 1,000 of the calories defined in physics and chemistry. To transition between discussions of food calories and energy expenditure, we will employ the physics definition of a calorie, with the understanding that one kilocalorie (kcal) is equivalent to one food calorie.

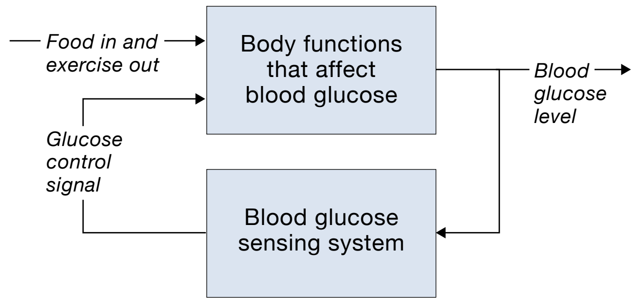


FIGURE 3. This generic blood glucose control model exemplifies a feedback control system and considers the input of food into the body, the energy demands of exercise, and the current blood glucose level to generate a control signal that regulates metabolic homeostasis.

Key Elements of a Metabolic Fuel Model

The body's process for tightly controlling blood sugar is well suited to analysis and modeling techniques developed for feedback control systems. As illustrated in Figure 3, in a feedback control system, the value of the output parameter being controlled (blood glucose) is measured and fed back into the controller. This signal, along with other inputs, is continuously monitored by the controller, which adjusts the available system parameters to achieve the desired output.

System Diagram of the Metabolic Fuel Model

Figure 4 is a block diagram of the metabolic fuel model developed at Lincoln Laboratory. It incorporates dietary inputs, glucose level–sensing functions, glucose control signals, actuators, and the interconnectivity between these elements in a nonlinear feedback control system. For the implementation described in this article, only fats and carbohydrates are considered. Body fat has a role as an energy storage mechanism and, in the model, all consumed fat is initially placed into a storage reservoir with unlimited capacity. In Figure 4, the movement and storage of fat are depicted in red. For digested carbohydrates, storage options are limited and are depicted in yellow, flowing into and out of the bloodstream in the form of glucose. The pancreas monitors the level of circulating glucose and secretes insulin to signal how to dispose of the excess glucose in the bloodstream. Each actuator is represented as a valve that responds to the amplitude of the insulin control signal. The metabolic rate is the sum of valves 2 and 4; the glycogen stores are controlled by valve 1; the macronutrient oxidation ratio is the ratio of valves 2 and 4; and converting glucose to fat, or de novo lipogenesis (DNL), is valve 3.

Also shown in this model is the concept of glucose overflow. When blood glucose becomes extremely high, additional mechanisms manifest in response, such as the kidneys passing excess glucose into the urine and other body tissues accumulating glucose. These responses are not considered actuation mechanisms in the model because they represent disease states.

THE INPUTS: FOOD AND ACTIVITY LEVEL

Food consumption, respiratory gas exchange (breathing), and energy demands (physical and mental activity) represent the body's metabolic interface to the outside world. Food intake, along with existing energy stores, provides the fuel needed to sustain metabolic processes. As much as 70 percent of the metabolic energy required over the course of a day is devoted to sustaining autonomic processes such as breathing, blood circulation, tissue repair and maintenance, digestion, and cognition [26].

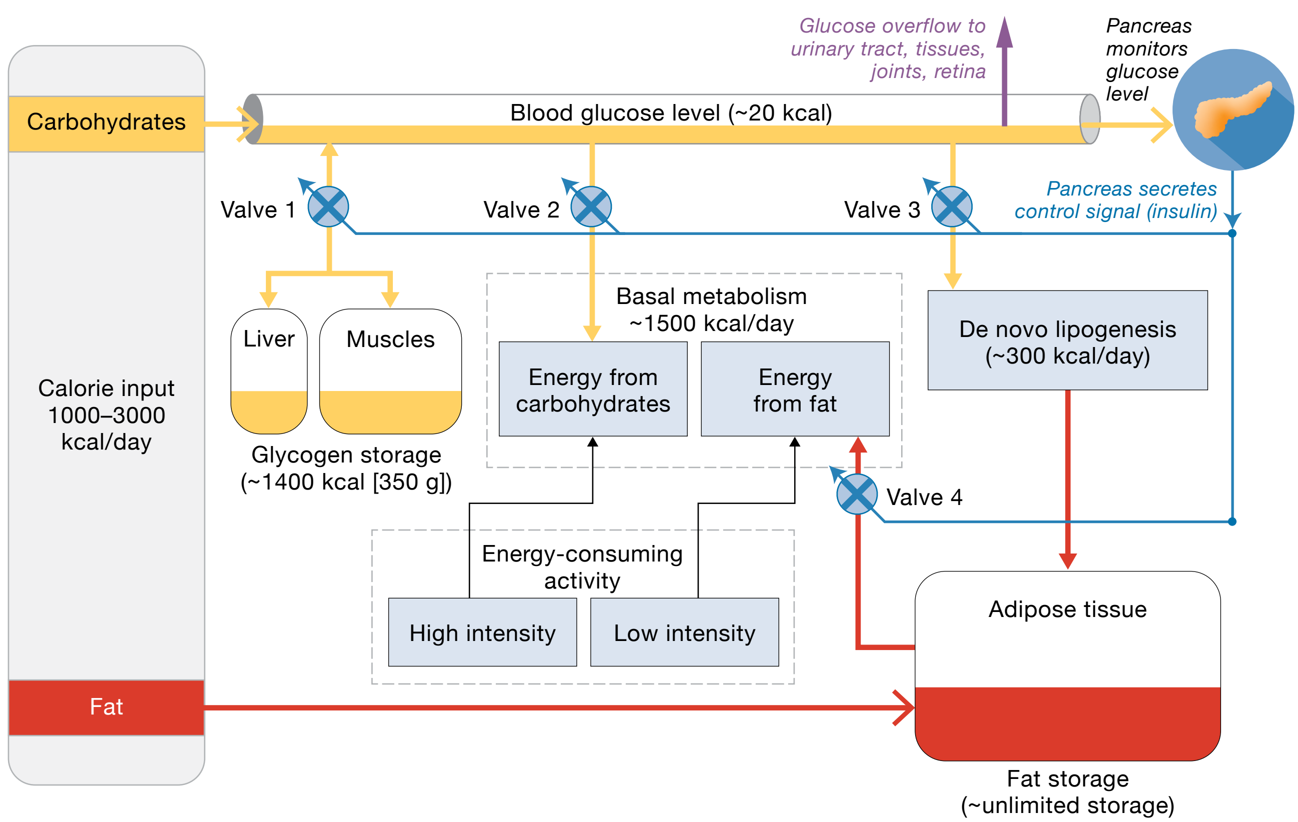


FIGURE 4. The metabolic fuel model features a system-level block diagram of the body's blood glucose feedback control system. The model includes dietary inputs, glucose level–sensing functions, glucose control signals, actuators, and the interaction of all these elements to regulate blood glucose level. Fat is depicted in red, while carbohydrates are depicted in yellow. The arrows represent the path of the calories in an individual, starting with digestion and moving into the body for storage or use.

Individuals also require energy to move about, maintain thermal regulation, and perform daily activities.

Ingesting certain foods, such as simple sugars, may rapidly introduce large quantities of glucose into the bloodstream and place tremendous demands on the blood glucose control system. In contrast, intense exercise may quickly deplete stored and circulating blood glucose, which must be replenished to sustain critical processes such as brain function. In both cases, the key is the rate at which the macronutrients enter and exit the bloodstream.

Food

Fat, carbohydrates, and protein are the three primary macronutrients, and each influences the dynamics of blood glucose circulation differently. For instance, fat does not directly influence the blood glucose concentration, as its digestion does not directly result in the production of glucose. In contrast, highly processed carbohydrates enter the bloodstream primarily as glucose, to be metabolized for energy, stored as glycogen, or converted into fat. Proteins can be converted into glucose through a slower and less efficient process termed gluconeogenesis [27] and are not included in the model of Figure 4.

Carbohydrates have the largest impact on circulating blood sugar and are thus a primary focus of our model. The rate of glucose's appearance in, and disappearance from, blood is critically important. The appearance of glucose in circulation depends on the timing of food consumption, quantity of carbohydrate consumed, rate of carbohydrate digestion and appearance in the blood stream, type of carbohydrate, and energy demands. The glycemic index (GI) is used as a measure of this parameter. Strictly speaking, GI is a measure of the speed with which food is turned into circulating blood glucose and is referenced to raw sugar, which is assigned a glycemic index of 100 [28]. The importance of glycemic response was demonstrated in a recent study in which the blood glucose response to various foods was tracked to establish personalized nutrition plans [29]. Our model allows a different GI to be set for each meal without requiring the GI to be specified for each food. With the addition of blood glucose monitoring, either directly or through an indirect measure such as the respiratory exchange ratio, the model can be tailored to particular individuals and foods. The respiratory exchange ratio is the ratio of the volume of carbon dioxide (CO_2) produced to oxygen (O_2) consumed as measured in the exhaled breath of an individual and indicates the macronutrient mix supplying metabolic energy.

Metabolic energy generation at the cellular level is extremely complex. However, the overall impact of the multistep metabolic processes can be summarized by two relatively simple stoichiometric chemical equations that account for the O_2 consumed and byproducts (CO_2, water [H_2O], adenosine triphosphate [ATP]/energy) produced in the mitochondria per molecule of fuel oxidized.

CARBOHYDRATE BURNING (GLUCOSE)

$$\begin{gathered} C_6H_{12}O_6 + 6O_2 \\ \Downarrow \\ 6CO_2 + 6H_2O + 38ATP(\text{energy}) \end{gathered} \tag{1}$$

$$RQ = \text{moles } CO_2 / \text{moles } O_2 = 6/6 = 1$$

FAT BURNING (PALMITIC ACID) [30]

$$\begin{gathered} C_{18}H_{36}O_2 + 26O_2 \\ \Downarrow \\ 18CO_2 + 18H_2O + 131\,ATP(\text{energy}) \end{gathered} \tag{2}$$

$$RQ = \text{moles } CO_2 / \text{moles } O_2 = 18/26 = 0.7$$

Equation (1) reveals that for every mole of oxygen consumed in the carbohydrate reaction, one mole of carbon dioxide is produced. This 1:1 stoichiometric relationship holds for all carbohydrates represented by $(CH_2O)_n$. For palmitic acid (a typical saturated fatty acid), 18 moles of CO_2 are produced for every 26 moles of O_2 consumed. Thus, the stoichiometry for fat burning (18/26 = 0.7) differs from that for carbs (6/6 = 1). The 0.7 ratio for palmitic acid is typical for many free fatty acids [31]. Therefore, by measuring moles of O_2 consumed and CO_2 produced, the relative fraction of carbohydrates versus fats that the body uses to meet metabolic energy needs is estimated.

The molar ratio between CO_2 produced versus O_2 consumed is called the respiratory quotient, or RQ, and is widely accepted as a key noninvasive indicator of metabolic processes occurring at the cellular level. If all of the oxygen consumed supports carbohydrate oxidation, then RQ is equal to 1, whereas if all the consumed

O_2 supports fat oxidation, the RQ is ~0.7. This simple concept can be extrapolated to an entire organism for which all the CO_2 exhaled and all the O_2 absorbed is measured and ratioed on a breath-by-breath basis to provide a reasonably good approximation of the sum of all the internal cellular chemical reactions. This system-level breath measurement is termed the respiratory exchange ratio, or RER. The RER is not identical to the RQ, but in practice, RER is often very similar to RQ, and the term RQ is frequently used interchangeably with RER [32].

For typical American diets, the glucose load into the bloodstream is driven by the digestion of carbohydrates. For instance, drinking a sugary beverage might deliver 50 grams of glucose (200 kcal) into the bloodstream within a fraction of an hour of consumption. If the glucose level is not offset in some way (see actuator discussion in later section), blood sugar levels could rise to over 1000 mg/dL (10 times normal) from a single drink. The rate at which high-GI carbohydrates release glucose into the bloodstream establishes a minimum necessary response for the metabolic control system to mitigate high glucose levels.

Activity Level

Understanding the timing, duration, and intensity of physical activity, whether it is part of daily life or formal exercise, is essential to correctly model blood glucose levels. The energy demands that physical activity places on the body, both in terms of intensity and duration, impact the rate of glucose depletion [33]. Low-intensity exercise is primarily fat burning and will have a negligible effect on glucose control. However, high-intensity exercise, which preferentially metabolizes glucose, affects blood glucose turnover and replenishment.

Strenuous exercise can raise metabolic demand to rates greater than 1000 kcal/hour, and much of this energy need is met by the utilization of glucose in neighboring muscle tissue. Typically, this glucose is supplied directly from internal glycogen stores and dietary intake, with both processes having important impacts on the functioning of the control system. High-intensity exercise sustained over a long period of time (e.g., running a marathon) can deplete glycogen stores and severely degrade performance in a phenomenon commonly known as hitting the wall or bonking.

THE SENSING FUNCTION

As an individual eats or exercises, the blood glucose–sensing function of the body detects changes in the circulating blood glucose level and will respond by signaling the body to act in a way to offset departures from nominal. Understanding the details of how insulin and its counterpart, glucagon, broadcast their control signals throughout the body is not essential to correctly model the functional behavior of the control loop. All that is required to implement a control model is to understand that subsystems in the body respond to increasing and decreasing blood glucose levels by adjusting the level of insulin and glucagon control signals, and that there are finite cellular response times associated with the generation of and response to the control signals.

THE ACTUATORS

The mechanisms by which the body responds to glucose control signals are called actuators. The term actuator is adopted from control theory terminology rather than medical terminology. For each actuator, it is important to consider how much capacity it has to offset the rates of glucose's introduction to, and removal from, the bloodstream. Control signals that exceed the actuator capacity limits introduce a nonlinear element to the system behavior and produce complex dynamic responses despite the relatively small number of functional elements in the model. Nonlinear effects are critical to understanding the relationship between type 2 diabetes, obesity, and metabolism. Table 1 lists the four actuators and provides nominal values for the rates of glucose control that they can achieve and the nominal limits (capacity) of their control authority. For each of these four actuators, it is noteworthy that there is a direct connection between the presence of insulin and the rise in the level of actuation, although knowledge of insulin's role in affecting glucose control is not required for understanding the model. Individual variance in the behavior of each of these actuators may change with time, aging, disease, or recent food intake and exercise.

METABOLIC RATE

In response to a signal that blood glucose is elevated, the body can react by increasing the basal metabolic rate to consume more glucose from the bloodstream [34]. This increase in metabolism may be achieved through

Table 1. The Four Primary Actuators Available to Reduce High Blood Glucose Levels and Their Nominal Rate/Capacity Values

CONTROL MECHANISM (ACTUATOR)	ACTUATION METHOD	GLUCOSE CONTROL RATE	CAPACITY LIMIT
Metabolic rate	Burn glucose at a higher rate	Moderate (50 grams/hour)	Maximum metabolic rate (50 grams/hour) [35]
Glycogen stores	Move glucose out of blood	Very high (250 grams/hour) [36, 37]	Glycogen stores (~400 grams typical) [38]
Macronutrient oxidation ratio	Increase burning of glucose for fuel	High (150 grams/hour)	0% reliance on fat (0 grams/hour)
Glucose conversion to fat	Remove glucose by conversion	Moderate (30 grams/hour) [38]	De novo lipogenesis (DNL) rate in liver (30 grams/hour)

a combination of increased body temperature, greater body motion, and other metabolic energy demands. For the purposes of the model, it does not matter how the metabolic rate increase is achieved, only that it occurs and is subject to rate and capacity limits. The metabolic rate cannot be arbitrarily increased in response to the signal, so its control authority to remove glucose is limited to approximately 50 grams/hour (for a nominal basal rate of ~2500 kcal/day [35]).

GLYCOGEN STORES

The body has the ability to store and release glucose outside the bloodstream by converting glucose into the starch-like polysaccharide glycogen, which can be stored in the liver or in skeletal muscle throughout the body. As indicated in Table 1, glycogen storage and release can occur rapidly, with glucose assimilation rates as high as 250 grams/hour [36, 37] and expenditure rates higher than 150 grams/hour [36, 39]. The total glycogen storage capacity in an adult body depends in part on muscle mass and can be as high as 800 grams [38] but is typically about 400 grams [40]. Once these glycogen stores are full, they can no longer serve as a glucose sink. Likewise, when glycogen stores are fully depleted, they cannot release glucose to compensate for declining blood glucose levels. While some carbohydrates, such as fructose, are directly converted to glycogen [41], our simplified model digests and passes all carbohydrates into the bloodstream first. Similarly, the processes of storage and retrieval of glycogen in the liver and muscle are treated identically in this model despite their physiological differences.

MACRONUTRIENT OXIDATION RATIO

While metabolizing fat does not change blood glucose levels, metabolizing glucose directly depletes blood glucose levels. Therefore, shifting the metabolic fuel mix to favor glucose rather than free fatty acids is a favorable control mechanism for reducing high blood glucose levels. Adjusting the fuel mix allows the body to rapidly alter the rates of glucose consumption. Of course, oxidation balance cannot drive the mix beyond the extremes of 0 percent or 100 percent. Furthermore, since the blood/brain barrier inhibits fat as a source of brain fuel, some circulating glucose is necessary to sustain brain function (even for the case of very low-carbohydrate ketogenic diets) [42]. Maintaining cognitive brain function is a primary reason why blood glucose control is a priority in the body's control mechanisms.

CONVERT GLUCOSE TO FAT

Lastly, in terms of glucose disposal mechanisms, the body has the capacity to convert glucose into fat by means of DNL [43], which removes glucose from the blood, thereby reducing excessively high blood glucose concentrations. There is some debate about the maximum achievable DNL rates [44] and the conditions under which DNL occurs in humans; however, measurements indicate that rates of upwards of 500 grams/day are achievable [38]. The DNL process seems to activate as a last resort when the control authority of the three other actuators becomes saturated. There is no direct fat-to-glucose reaction pathway in humans (other than the process of carbohydrates being produced from the small amount of glycerin released during lipolysis).

Validation of the Metabolic Fuel Model

To provide evidence of the validity of the model, we simulated the outcome of a comprehensive 14-day carbohydrate overfeeding study [38]. In the original study, three healthy young men, ages 21 and 22, weighing 62 to 72 kilograms (136.7 to 158.7 pounds), of height 174 to 180 centimeters (5 feet 9 inches to 5 feet 11 inches), and body fat 11 to 14 percent with no family history of diabetes or obesity, participated. The experiment lasted 14 consecutive days. During the first three days, the subjects consumed a high-fat low-energy (HFLE) diet, high in fat and low in carbohydrates, and followed an exercise program. The purpose was to deplete the glycogen stores of the individuals prior to tracking the energy balance over a period of 10 days. Halfway through this energy-restrictive period, the subjects were admitted into a whole room indirect calorimetry chamber, effectively a metabolic monitoring chamber, in which respiratory exchange measurements and controlled feeding were continued for 10 days. After 36 hours in the chamber, the subjects' diet was changed to a high-carbohydrate low-fat diet for the following seven days. During the last two days, while still in the chamber, the subjects received a protein-sparing modified fast (PSMF) diet to begin returning their weight to normal. The subjects then left the respiration chamber but continued to consume the high-fat, low-energy, low-carbohydrate diet for two more days.

Figure 5 shows a dataset from this study that will be interpreted within the context of our model. As shown in Figure 5a, the subjects entered the metabolic chamber with glycogen stores depleted on day 3 and began consuming a high-carbohydrate diet. Initially, excess carbohydrates, beyond those required to meet metabolic energy needs, were converted to glycogen and stored in the liver and muscles. However, by day 5, glycogen stores were nearing their capacity and were unable to absorb all the excess dietary carbohydrates, at which point DNL activated to convert and store excess carbohydrates as fat. Figure 5b shows the corresponding change in the subjects' RQ that indicates the change in metabolic fuel substrate, with a resting RQ = 0.7, implying all fat oxidation; RQ = 1 implying all carbohydrate oxidation; and RQ > 1 implying DNL activity. Figure 5 shows increasing reliance on DNL

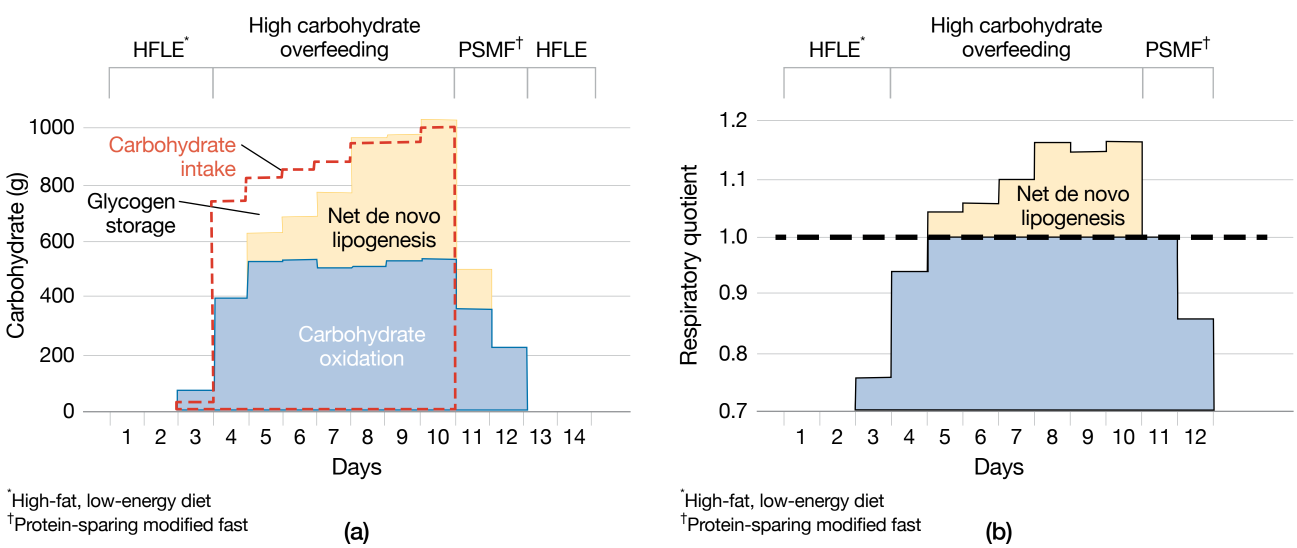


FIGURE 5. A carbohydrate overfeeding study was conducted to evaluate the effects of carbohydrate overfeeding, which led to the filling of glycogen stores and increasing liposynthesis (a), and to determine the respiratory quotient associated with the initial state of glycogen depletion, glycogen saturation, and de novo lipogenesis [38]. These results exemplify the utilization and saturation of the control valves in the theory. The results of this study are compared to the simulation results of the metabolic model.

to manage excess carbohydrates, with as much as ~500 grams/day of carbohydrate disposed via DNL, resulting in an increase of fat stores of about 2.5 pounds over the course of the seven-day low-fat diet (see Figure 6).

An executable version of the metabolic fuel model of Figure 5 was initialized with the data corresponding to the average dietary intake, activity, and physiology of the three subjects in the carbohydrate overfeeding experiment. Unlike the original study, which took 14 days to complete, the simulation of the study was executed in less than one second.

Four of the measured parameters from the study are compared to the simulation output in Figure 6. The solid curves represent the daily average metabolic values measured for the three individuals involved in the study. The dotted curves represent the values predicted by the simulation model given the feeding and exercise schedules followed during the study. The largest disparity between the simulation and the actual study results is in the predicted value of RQ during the days in which DNL was active. The disparity is due in part to the fact that the RQ associated with DNL is dependent on the type of fat synthesized and can vary from 2.75 to 9. For an example, see Equation (4) on page 128. A significant point of agreement between the study data and the model-based simulation data is that the simulated RQ rose above 1 on day 5, predicting the onset of DNL on the day it was observed in the actual experiment.

The relatively close agreement between the published data and the simulated output provides compelling evidence that, without resorting to detailed modeling of cellular metabolic pathways and processes, the impact of dietary macronutrients and exercise on metabolism can be captured by this system-level feedback control model.

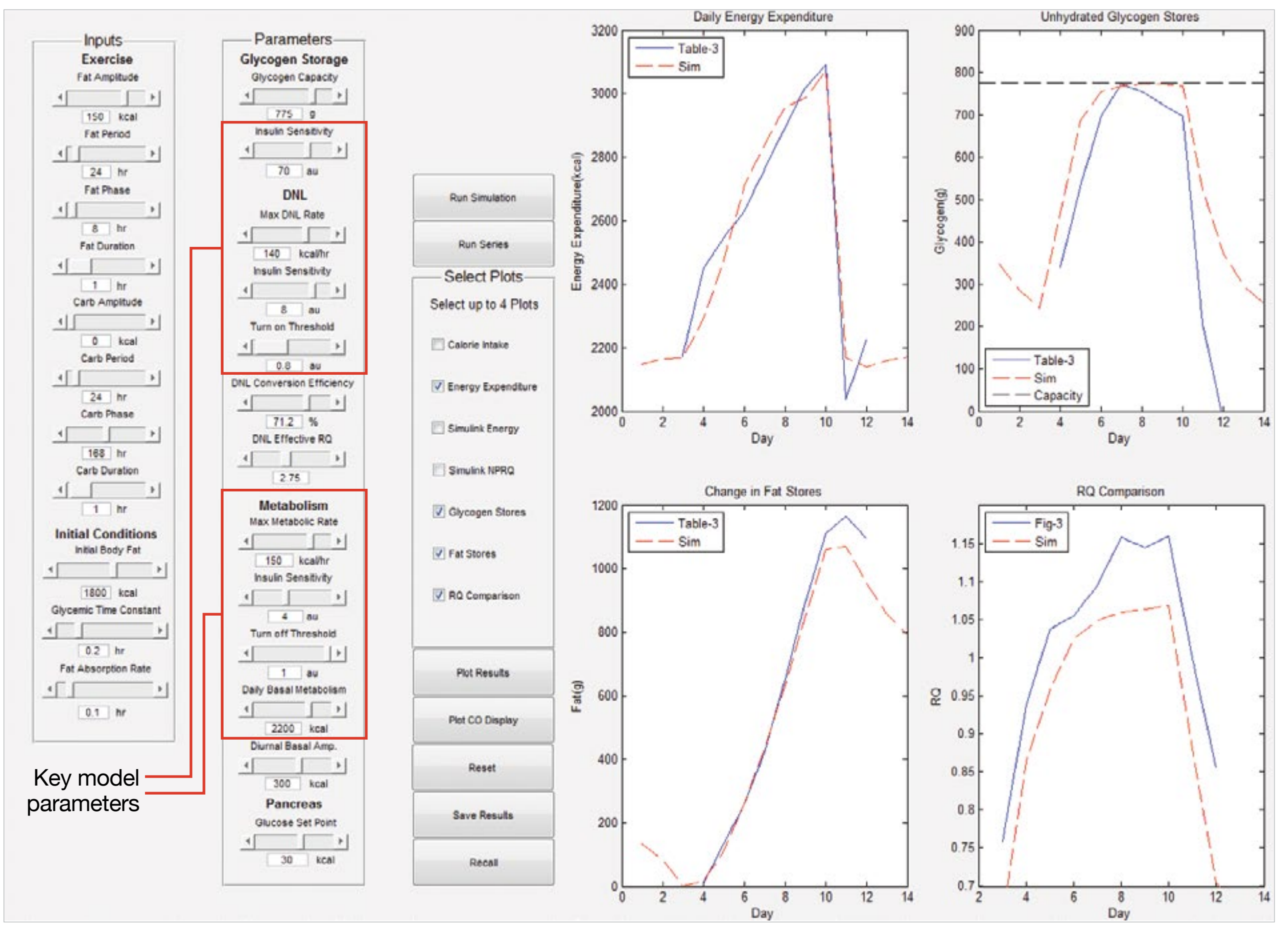


FIGURE 6. The metabolic model simulation inputs and prediction performance showed a high agreement with the results of the published overfeeding study, indicating that the metabolic model is a promising system for predicting the real-life impact of diet and exercise on metabolism. The key tunable parameters of the model are highlighted in the red boxes.

Implications of the Metabolic Fuel Model

Applying control systems theory to model human metabolism provides a powerful simulation tool for predicting the metabolic response (blood glucose level control, fuel usage, glycogen storage, fat storage, and insulin level control) that an individual will exhibit over a wide range of diets and activity profiles.

The realization that blood glucose control is a critical function that takes precedence over other functions of the homeostatic control system, such as body weight stabilization and energy balance, can lead to a view of the causes and treatments for excess body weight and type 2 diabetes that is different from the view typically encountered. Table 2 compares and contrasts some of the implications drawn from the metabolic fuel model to commonly held views [45].

Utility of the Metabolic Fuel Model

To illustrate one of many possible applications of the metabolic fuel model, we simulated a diet experiment. The simulation provided insight into why a dietary model that only considers calories, and not the macronutrient composition of those calories, is inadequate for understanding and managing body weight.

For one week, the simulated subject was fed a high-carbohydrate diet with a caloric ratio of 80 percent carbohydrates to 20 percent fats. A glucose-tolerance test, consisting of an injection of 100 kcal of glucose (equivalent to drinking about eight ounces of soda) over a 10-minute span, was administered to the simulated test subject. After injection of the glucose into the bloodstream, the four actuators, shown in the block diagram in Figure 4, were monitored as the glucose spike induced by the sugary soda was cleared to restore the baseline blood glucose concentration.

In the second week, the same simulated subject was fed a diet consisting of the same number of calories as the first week, but with a low carbohydrate ratio (20 percent carbohydrates and 80 percent fats). The same glucose injection was repeated. The glucose recovery results corresponding to the two feeding regimens are summarized in Figure 7, and the results show markedly different responses to the same glucose challenge.

- The glucose clearance time is 50 percent longer following the high-carbohydrate/low-fat diet.
- There is evidence of what has been termed insulin resistance in the high-carbohydrate diet (it takes three

Table 2. Implications about Various Medical Conditions Drawn from the Metabolic Fuel Model versus Commonly Encountered Views about the Same Conditions

METRIC/RESPONSE	CONVENTIONAL VIEW	MODEL VIEW
Obesity	Contributor to type 2 diabetes [46, 47]	Two of four mechanisms that the body employs to avoid becoming diabetic lead to obesity
High insulin levels	Caused by insensitivity to insulin (insulin resistance)	Root cause is chronically overwhelming the four glucose control processes
Diet for weight loss	Requires overt control of energy balance (calorie intake/expenditure)	Requires active avoidance of macronutrient imbalance (carbohydrate overconsumption)
Exercise for weight loss	Low-intensity exercise is best because it is fat burning	Choose exercise to counteract macronutrient imbalance (e.g., high-intensity exercise to counteract carbohydrate overconsumption)
Feedback for guiding weight loss intervention	On-demand body weight measurements (scale)	On-demand metabolic state measurements (e.g., RQ, insulin, etc.)
Excess body weight trend in the population	Root causes are inactivity and overeating	Root causes are historical changes in dietary macronutrient mix that subvert homeostatic control loops

times more insulin to clear the glucose after consuming the high-carbohydrate/low-fat diet).

- The DNL process activated for the high-carbohydrate/low-fat diet to convert and store excess glucose as fat.
- There was a reduced capacity for converting glucose into glycogen following the high-carbohydrate/low-fat diet.
- There was a reduced opportunity to dispose of excess blood glucose by means of fat burning on the high-carbohydrate/low-fat diet.
- There was a prolonged and exacerbated period of low blood sugar following glucose clearance on the high-carbohydrate/low-fat diet.

The results in Figure 7 also suggest how the promotion of low-fat (consequently, high-carbohydrate ratio) diets over the past 40+ years may have contributed to the dramatic rise in obesity. As shown by the simulation, even small amounts of dietary fat may be stored to reduce high blood sugar levels by preferentially using glucose to meet energy demands (resulting in fat storage in adipocytes). In the case of high-carbohydrate diets, DNL is also more likely to be activated to convert the excess carbohydrates into stored fat.

Diabetes and the System Model

A principal characteristic of diabetes is an impaired ability to properly control blood glucose concentration. Because the foundation of the metabolic fuel model presented here is blood glucose control, the model has direct applicability to understanding the underlying causes of diabetic behavior. In the case of type 1 diabetes, from the metabolic fuel model perspective, the impairment is in the sensing system. For type 1 diabetics, despite an elevation in blood glucose, the feedback signal is very weak or nonexistent and not fed to the four actuation mechanisms. Without the ability to produce insulin and broadcast the control message, the actuators are never enabled despite having ample capacity to control blood sugar. When insulin is injected into the bloodstream, the full set of actuation mechanisms are activated to control blood glucose levels. Maintaining the precise level of insulin required to balance incoming glucose is very difficult to achieve and requires constant monitoring of blood glucose level. Understanding the feedback mechanisms may help type 1 diabetics better manage their blood sugar in response to different dietary and exercise inputs.

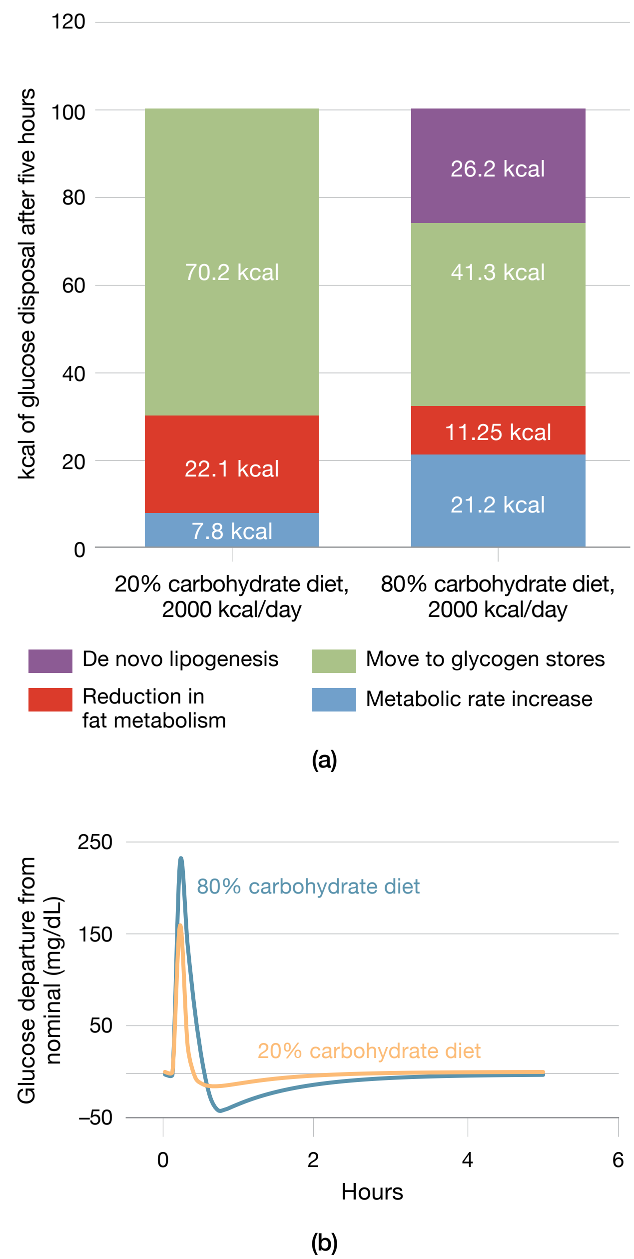


FIGURE 7. This figure shows the results of simulated glucose infusions following low-carbohydrate and high-carbohydrate diets. The four colors correspond to the four glucose disposal mechanisms discussed in Table 1 (a). For the same calories during the week preceding the glucose infusion, the low-fat diet resulted in a less desirable metabolic response, including fat gain through de novo lipogenesis, and higher elevated glucose levels followed by a longer low blood sugar event (hypoglycemia) (b).

While the metabolic fuel model does not provide any new insight into the cause of type 1 diabetes, the model is particularly useful in providing insights into the management and avoidance of type 2 diabetes. In type 2 diabetes, the body is also unable to adequately control blood glucose levels. However, unlike type 1 diabetes, type 2 diabetes results not from a malfunction of the insulin signal generation system but rather from a problem with the control mechanisms. Typical insulin levels with type 2 diabetes are much higher than normal, yet the blood glucose control actuators do not respond strongly enough to the elevated insulin signal to effectively control the glucose levels. This condition is referred to as insulin resistance and suggests that the actuators need higher signal levels than previously required to achieve proper blood glucose control. However, there is no universal agreement or consensus regarding the root cause of this apparent loss in insulin sensitivity.

The metabolic fuel model offers a coherent explanation of the precursors to, and root cause of, the symptoms of type 2 diabetes. If all of the four actuation mechanisms incorporated in the model are functioning at their full capacity, then the presence of higher levels of insulin will have a minimal effect on the rate at which glucose is cleared from the blood. Consequently, symptoms of type 2 diabeties will be observed (insulin resistance), and there will be high levels of both glucose and insulin. Blood glucose control fails when the control authority available in the actuators is less than the rate of glucose appearance in the bloodstream or, put another way, if too much sugar is in the blood and no actuator capacity is left to remove it. This interpretation of type 2 diabetes implicates the macronutrient content ingested, as opposed to a degradation of the glucose processing mechanisms, as the root cause of diabetic symptoms. Any individual whose actuation mechanisms cannot keep up with the rate at which carbohydrates are being absorbed will exhibit diabetic symptoms. Changes to the available food supply that increase consumption of carbohydrates and high-GI foods challenge the available control authority of a great fraction of the population. The metabolic fuel model explanation for the origins of type 2 diabetes does not require postulating or explaining the appearance and mechanism of insulin resistance, nor does it preclude the development of insulin resistance over time in response to chronic carbohydrate overloading.

Conversely, the metabolic fuel model suggests that if carbohydrate consumption is reduced to a level compatible with the individual's control authority, the symptoms of type 2 diabetes will quickly disappear. There is ample evidence in the literature that carbohydrate reduction can successfully reverse the progression of type 2 diabetes [5, 48–50]; however, the science is not settled [51].

Obesity and the Metabolic Fuel Model

The motivation for creating the metabolic fuel model was to functionally express the mechanisms involved in the body's response to changes in blood glucose concentration. However, the insights provided by the metabolic fuel model extend well beyond blood glucose control, including how these blood glucose control mechanisms impact long-term changes in body weight.

Contradicting the view that obesity is the primary cause of insulin resistance and the onset of type 2 diabetes [45, 46, 52], the metabolic fuel model suggests an alternative sequence of events. The model reveals that when the body is struggling to reduce the blood glucose level, it will stop burning fat and, in some situations, convert excess blood glucose into fat (DNL) in an attempt to keep up with the rate of glucose input. If, through dietary choices, an individual is constantly releasing high levels of glucose into the bloodstream, one predictable consequence of these control mechanisms, as summarized in rows three and four of Table 1, is an increase in stored fat. The metabolic fuel model further suggests that for an overweight individual seeking to reduce body weight through a low-fat high-carbohydrate diet, the metabolic response of the body to control circulating blood glucose acts in opposition to the desired fat burning, resulting in weight gain rather than weight loss.

The metabolic fuel model can also be used to predict an individual's response to a given diet and, in particular, how the response varies with the number of calories, the macronutrient mix, the GI, and the duration and intensity of exercise. Tuned to an individual, the model can be used to determine what dietary intake and nutrient mix will ensure that the blood glucose control does not override the body's hormonal signals related to weight control, enabling the individual to preferentially burn dietary and stored fat rather than carbohydrates to meet metabolic energy needs.

Metabolic Sensing

The metabolic fuel model provides a framework for understanding the impact of macronutrient imbalances on weight management, obesity, and type 2 diabetes, and also provides a means of predicting the impact of diet and exercise on an individual's metabolic health and performance. To apply the model to a particular individual or class of metabolically similar individuals, standard physiological data such as age, gender, weight, and height can be used to estimate basal metabolic rate, glycogen stores, and responses to exercise. However, to tune the model to a particular individual or class of individuals, such as athletes or military trainees, measurement of the individuals' metabolic responses to diet and exercise is required.

Metabolic Fuel and Energy Measurement Confounds

While the stoichiometric relationships described by Equations (1) and (2) are relatively straightforward, proper interpretation of the measured values of O_2 consumption and CO_2 production requires awareness of a number of temporal and physiological confounds. For example, CO_2/bicarbonate buffering in the bloodstream can lead to previously buffered CO_2 being released during hyperventilation, and CO_2 is also released during the conversion of glucose to fatty acids and anaerobic energy production. Each of these confounds can result in RER measurements greater than 1, so the equivalence between cell-level metabolism (RQ) and the molar ratio of breath gases (RER) needs to be applied with caution [31, 32, 53]. Alcohol is another confound since it cannot be stored and its disposal is a priority. So, as with carbohydrate overconsumption, alcohol may further suppress the metabolism of dietary fats. However, unlike that of carbohydrates, the RQ of alcohol is less than 0.7, so the metabolization of alcohol pushes the RQ down rather than up.

Protein is not a preferred source of metabolic energy but, when present in excess, the amino acids are processed and stored as glucose or ketones. The nitrogen waste that is liberated in the process is converted to urea in the urea acid cycle and eliminated through the urine. The RQ for proteins is nominally 0.85, midway between the RQ for fats and carbohydrates. Consequently, while protein can serve as a source of metabolic energy, the bias it introduces when neglected in the estimate of fat versus carbohydrate oxidation is typically a small portion of total calories consumed. If necessary, the average contribution of protein to metabolic energy can be ascertained by collecting and analyzing the nitrogen content of the subject's urine.

Equations (1) and (2) not only establish which type of fuel is being used, but they also enable estimation of the amount of energy created in each reaction. Given the RQ and the volume of O_2 consumed, the energy expenditure (EE) can be estimated from the Weir equation [54], where EE is the total energy expenditure and VO_2 is the time-dependent volumetric rate of oxygen consumption.

$$EE\left(\frac{\text{kcal}}{\text{day}}\right)=\left[3.9+1.1\times RQ\right]\times 1.44\times VO_2\left(\frac{\text{mL}}{\text{min}}\right) \tag{3}$$

Note that because RQ is normally between 0.7 (all fat) and 1 (all carbohydrate), the accuracy of EE calculated from the Weir equation is dominated by the accuracy of the VO_2 measurement. A completely erroneous estimate of RQ (e.g., an RQ estimate of 1 when the true value is 0.7) results in less than a 7 percent error in the estimate of expended energy, provided the VO_2 value is correct. However, errors in RQ and VO_2 may be correlated, resulting in a compounding effect on the error in the energy estimate.

The EE and RQ are both useful quantities for the metabolic fuel model. The measurements required to compute RQ and EE enable the calculation of additional parameters of interest, such as the VO_2, respiration rate, breath volume, and metabolic equivalent of task (MET).

RQ as an Indicator of Macronutrient Mix

Figure 8 shows the nominal range of RQ levels and its relationship to metabolism for measurements of physically active and resting subjects. When the body is inactive, metabolic demand is mostly driven by breathing, blood circulation, body temperature control, and other autonomic processes. As the voluntary activity level increases, these autonomic metabolic demands are overshadowed by muscle demand, and the basal metabolic energy needs are overshadowed by the substrate balance needed to meet the proportionally greater muscle energy demand. According to Equations (1) and (2), an RQ of 0.7 implies that all of the calories are supplied through fat combustion, whereas an RQ = 1 implies that calories are being supplied exclusively from glucose. Figure 8 implies that resting RQ is driven primarily by the available mix of circulating macronutrients, whereas the preferred fuel (fats versus carbohydrates) during exercise is driven primarily by exercise intensity [55]. When the RQ is between 0.7 and 1, the metabolic fuel substrate is a combination of carbohydrates and fats. A resting RQ greater than 1 indicates that DNL (conversion of glucose into triglycerides) is occurring. The RQ associated with DNL depends upon the specific form of fat conversion. For example, the conversion of glucose to a fat (palmitoyl-stearoly-oleoyl-glycerol) is given by the stoichiometric chemical equation

$$
\begin{gathered}
27\,C_6H_{12}O_6 + 24\,\mathrm{ATP} + 6O_2 \\
\Downarrow \\
2\,C_{55}H_{104}O_6 + 24\,\mathrm{ADP} + 52\,CO_2 \\
\mathrm{RQ} = \text{moles } CO_2 / \text{moles } O_2 = 52/6 = 8.7
\end{gathered}
\tag{4}
$$

The RQ of 8.7, when averaged with the total RQ across all cells, results in a whole body RQ >1.

A resting RQ greater than 1 also implies that fat burning has largely ceased, and all of the metabolic fuel is coming from carbohydrates. Alternately, an RQ above 1 produced during strenuous activity indicates that the oxidation needs of muscle exceed the oxygen supply and that anaerobic reactions are occurring. The anaerobic glycolysis does not require an O_2 input to the stoichiometry and temporarily skews the RQ calculations to higher values [56]. After exercise, the resulting pH drop from lactic acid production shifts the bicarbonate buffer system toward releasing stored CO_2 into the exhaled breath. Recognizing and understanding the physiology of confounds such as anaerobic glycolysis is important when one performs breath-based (i.e., RER or RQ) energy measurements that assume aerobic metabolism.

As shown in the metabolic fuel model in Figure 4, there is a relationship between RQ, EE, and the metabolic actuators. The state of three of the four actuator values can be inferred by measuring EE and RQ. If the resting RQ is above 1, indicating high blood glucose levels, the model predicts that valve 4 (fat burning) is completely closed and valves 2 (carb burning) and 3 (DNL) are open, allowing for only carbohydrate oxidation and conversion into fat. When the homeostatic control system is operating normally, the resting RQ indicates the ratio of fat to carbohydrate oxidation, and therefore the RQ is isomorphic to knowing the flow relationship between valve 4 to valve 2. From Equation (3), the total number of calories metabolized is given by the sum of carbohydrate and fat oxidation. This energy flow is captured in valves 2 and 4. Therefore, calculations of RQ and EE unambiguously define the settings of valves 2, 3, and 4 in the metabolic fuel model, leaving only the available glycogen storage capacity uncertain.

Weight management protocols frequently focus on calorie consumption as the only metric of consequence. The model of Figure 4 shows that a more complete understanding of metabolic state and macronutrient imbalances can be achieved by measuring and tracking the dynamics of both RQ and EE.

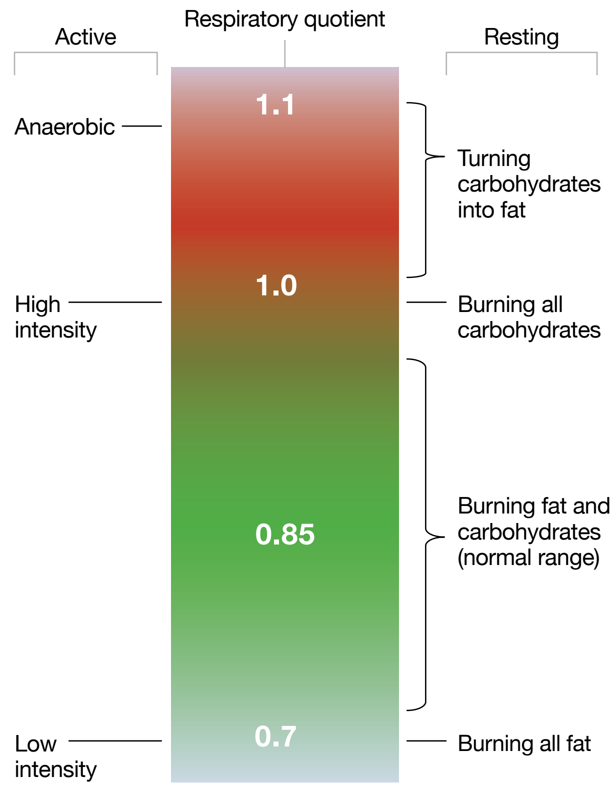


FIGURE 8. This figure shows the normal range of the respiratory quotient (RQ) and its significance for resting versus physically active measurements. Resting RQ is primarily driven by the available mix of circulating macronutrients, whereas the preferred fuel during exercise is driven primarily by the intensity of exercise.

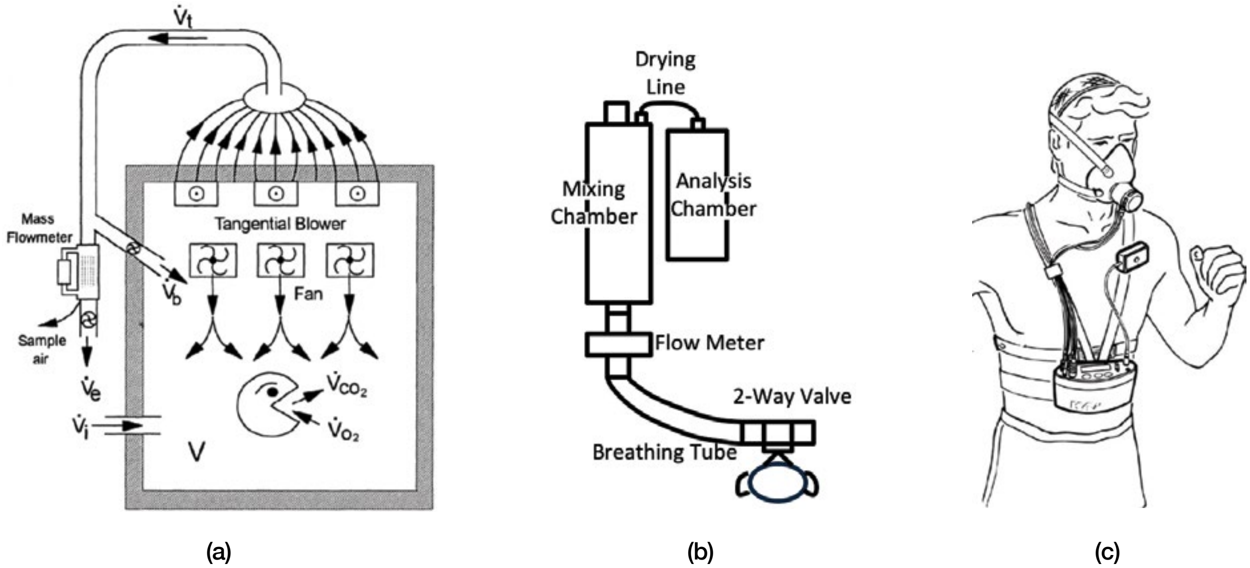


FIGURE 9. This illustration shows diagrams of the three different metabolic sensor classes, including a whole room calorimeter design (a) [57], a mixing chamber apparatus employed in single-user laboratory measurement systems (b) [58], and a breath-by-breath instrument designed to support mobile use (c) [59].

Traditional Methods of Measuring the Respiratory Quotient and Energy Expenditure

In general, three classes of systems are available for measuring RQ and EE. Each is described briefly in the following sections and represented schematically in Figure 9. Understanding the traditional methods of indirect calorimetry provides a context for understanding the distinctive features of a novel prototype sensor that significantly reduces the cost and complexity of traditional measurement methods.

WHOLE ROOM INDIRECT CALORIMETRY

Whole room indirect calorimetry involves isolating the subject in a small room, typically 10,000–20,000 liters in volume, and precisely measuring both the gas composition of fresh makeup air flowing into the room and the volume flow and gas composition of the exhaust air, as illustrated in Figure 9a [60]. The whole room indirect calorimetry approach allows for an unencumbered range of movement and activity within the room, which facilitates the study of exercise, sleep, and other specific activities over long intervals of time, typically on the order of days. Because a 20,000-liter whole room calorimeter corresponds to a volume of more than 20,000 breaths under resting conditions, it may take hours for new breaths to diffuse, mix, and produce a sufficiently strong signal to be measured [57, 61]. Transient events with durations of less than a few hours are difficult to measure reliably, and the mass spectrometer needed to measure the very small changes in room air composition attributed to changes in consumed O_2 and exhaled CO_2 is quite expensive. More importantly, not all activities of interest to the military or athletes can be conducted in a 20,000-liter room.

MIXING CHAMBER IMPLEMENTATIONS (METABOLIC CARTS)

A mixing chamber (integrated breath sensor) employs a breath-mixing chamber with a nominal volume of three to four liters to capture one or more exhaled breaths from the subject even during periods of exercise involving large tidal (total) volumes. The chamber is designed so that as each new breath is exhaled, it mixes with the previously expired breaths while displacing a proportional amount of the existing breath sample mixture from the chamber. The mixed breath in the chamber is continuously sampled by a pump and sent through series-connected, high-speed (20 or more measurements per second) gas sensors to measure the changing concentrations of O_2 and CO_2. The measurements provide a moving average of the test subject's RQ and EE, with effective averaging time determined by the volume of the mixing chamber relative to the tidal volume of each breath. Since the gas concentrations of each breath exhaled into the mixing chamber are not diluted by room air, the gas sensors in the metabolic cart implementation can be smaller, cheaper, and less sensitive than those required for whole room indirect calorimeters. Mixing chamber–based breath measurements have the advantage of providing a temporal resolution on the order of a couple breaths, and the entire measurement system can be placed on a mobile cart (or metabolic cart) and wheeled to treadmills or other activity areas to perform clinical or lab measurements on demand. The ownership and operating costs of a metabolic cart are significantly lower than those of a whole room indirect calorimeter. However, metabolic carts generally require wall plug power, and their interface and overall size and cost confine their use to research laboratories and clinics, making them impractical for field studies and too expensive for widespread personal ownership.

BREATH-BY-BREATH IMPLEMENTATION (MOBILE SENSORS)

Portable sensors for field use generally employ a breath-by-breath measurement technique. In a breath-by-breath system, the user wears a mask capable of capturing and measuring the entire exhale (main stream) volumetric flow rate by means of a spirometer, while a pump continuously samples a fraction (side stream) of the respiratory flow and delivers the sampled gas to a series-connected pair of fast (25–50 samples/second) O_2 and CO_2 sensors that measure gas concentration many times during each breath cycle. The 25- to 50-hertz sampling rate is required because, for intense exercise, a complete inhale/exhale breath cycle can be as short as one second. Software then pairs the sample-by-sample measurements of volume flow rate with gas concentration measurements that have been corrected for the time delays associated with sequential measurement of the gas concentrations. The software computes a continuous series of differential volume elements that, when integrated, enable computation of volume flow rates for O_2 consumed and CO_2 exhaled as a function of time. Rapid, on-the-fly measurement of CO_2 and O_2 eliminates the requirement for a mixing chamber and enables metabolic estimation with a temporal resolution limited only by the time constants of the gas concentration sensors. Eliminating the mixing chamber produces a compact portable sensor that can be used outside a laboratory setting and addresses a larger range of use cases. However, the measurements of flow and gas composition must be performed rapidly, and for a given aliquot of gas, the flow, O_2, and CO_2 measurements all occur at slightly different times. Consequently, calibration of breath-by-breath systems requires precise time alignment of the instantaneous flow measurements with the sequential gas concentration measurements, each of which is made at a slightly later time. The need for time coherence among all three sensors may be difficult to maintain over a variety of environmental conditions and activity levels, and verifying calibration in the field is difficult without supporting calibration equipment. The high sample rate requires fast gas sensors that increase the system power consumption and cost. One of many applications for breath-by-breath mobile sensors is metabolic measurement of athletes as they train (some sensors have even been adapted for use by swimmers). However, the high cost and calibration complexity make breath-by-breath sensors unattractive for large-scale group studies or personal ownership.

Prototype Personal Metabolic Sensor

Both the Army and the Marines are interested in measuring RQ and EE in the field on a cohort of dozens of soldiers as they conduct a variety of load-bearing activities over the course of many hours or days. To make concurrent metabolic field measurements for dozens of soldiers affordable, the individual sensors must be low cost and easy to use without extensive training. The sensor must also be sufficiently small and lightweight to minimize impact on the normal functions performed by the soldiers. Low cost, ease of use, and small size are also attractive qualities for athletic use of the sensor in schools and sports programs and for personal ownership and metabolic health tracking.

Cost, size, weight, and power are often invoked as the primary metrics for comparing mobile systems that perform a similar function. However, because the power required by a mobile sensor over the period of operation translates into battery weight, the comparison can be reduced to just three parameters: cost, size, and weight (CSaW). Figure 10 compares the CSaW of Lincoln Laboratory's prototype sensor under development, named the Carbon-dioxide/Oxygen Breath and

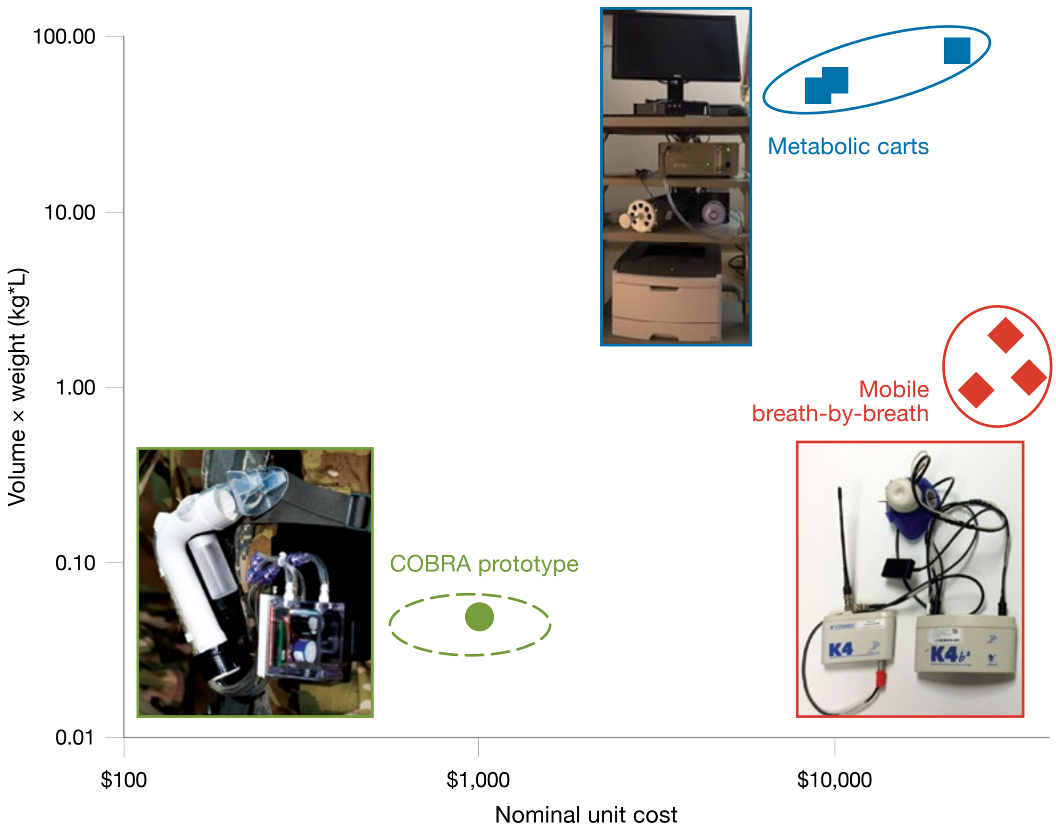


FIGURE 10. The prototype COBRA sensor has lower volume, weight, and estimated cost in comparison to commercially available metabolic carts and mobile metabolic sensors.

Respiration Analyzer (COBRA), to nominal values of CSaW associated with representative commercial metabolic carts and mobile sensors.

We achieved the significant reduction in CSaW of the prototype COBRA sensor by means of a novel passive proportional breath-sampling scheme [62–65] that eliminates the need for mechanical pumps or valves and replaces the conventional multiliter mixing chamber with a miniature mixing chamber that is about 100 times smaller. Relative to the breath-by-breath measurement technique, the passive proportional sampling technique enables the use of slower, less expensive gas sensors. Consequently, the total combined cost of the constituent O_2, CO_2, and flow sensors in single unit quantities is less than $250, and this cost is expected to be reduced in production with volume purchasing.

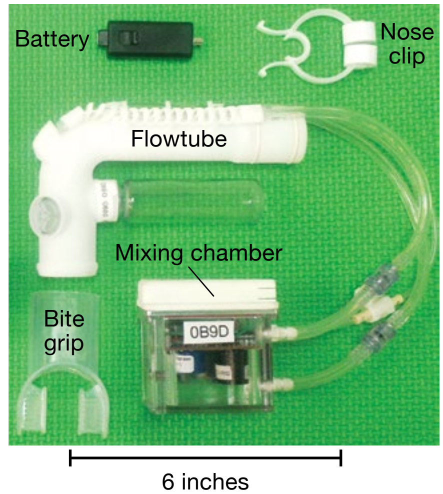
The prototype COBRA sensor system is shown in Figure 11. Figure 11b shows the COBRA sensor in use with a chest harness to enable hands-free operation. The mixing chamber currently employs a GoPro bayonet mount. The chest harness is only one of many GoPro-compatible mounting options, including shoulder mounts, backpack strap mounts, and helmet mounts, that enable the users to select mounting options that are best suited to the units' intended use.

Passive Proportional Side Stream Sampling Innovation

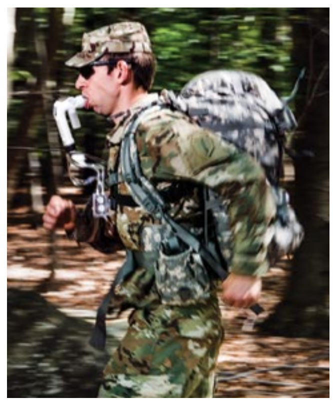
As shown in Figure 11a, to record data with the COBRA sensor, the user simply begins breathing through the flow tube in which the inhale and exhale breaths pass through a specially designed internal geometry. Upon exhale, the flow tube creates a positive pressure difference between the entrance and exit ports of the flow tube. The positive pressure difference diverts a small fraction of exhaled breath into the mixing chamber in proportion to the volumetric flow rate of the exhaled breath. Additionally, the location of the high- and low-pressure sample ports on the flow tube creates a null pressure difference during inhale when gas is flowing in the opposite direction.

The result is that the flow tube acts as a diode, diverting exhaled breath into the mixing chamber for analysis while preventing ambient air from diluting the mixing chamber contents during inhale. A plot of the gas collection percent versus the average flow rate through the flow tube is shown in Figure 12. The tight clustering of the samples over a wide range of expiratory flow rates (i.e., over a wide range of exercise intensity) is evidence that the volume of gas diverted to the mixing chamber at any instant is proportional to the instantaneous exhale flow rate. As a result, the sample diverted to the mixing chamber preserves the constituent gas ratios in the exhale breath, and the sample is a proportional fraction of the entire exhale volume. Similarly, the tight clustering of samples during inhale and the relatively small proportionality constant indicate minimal dilution effects over a wide range of flow rates despite the absence of a valve on the mixing chamber.

This passive proportional sampling technique [62–65] enables more than a hundredfold reduction in the volume of the mixing chamber relative to that of whole breath–integrating metabolic carts while avoiding the need for fast gas sensing required in breath-by-breath systems. In addition, the time to collect and mix samples from several breaths is commensurate with the measurement time constants of low-cost miniature gas sensors. The passive proportional gas collection technique preserves the temporal relationship between



(a)



(b)

FIGURE 11. The lightweight and easy-to-use design of the COBRA sensor system includes a rechargeable battery, nose clip, and bite grip (a). The COBRA sensor is compatible with GoPro camera-mounting harnesses, enabling hands-free metabolic measurement during exercise (b).

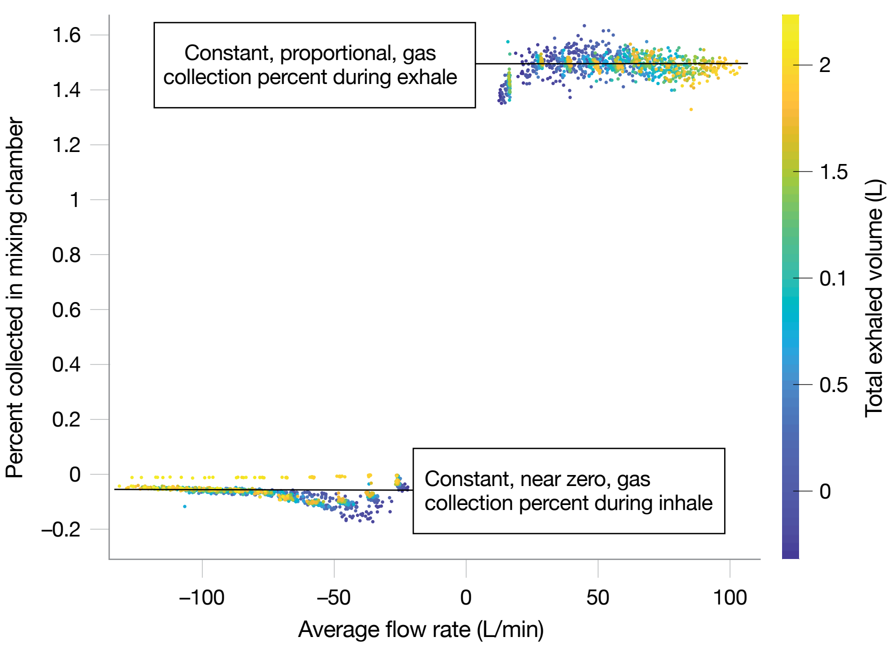


FIGURE 12. This plot reveals the proportional sampling and diode features of the Carbon-dioxide/Oxygen Breath and Respiration Analyzer flow tube design. These data show that the fraction of gas collected in the mixing chamber during an exhale is proportional to instantaneous flow rate over a wide range of flow rates, resulting in a relatively constant sampling fraction of 1.5 percent of the total exhale gas volume. Additionally, the negative flows, which represent dilution during inhale, are relatively small, typically less than 0.1 percent.

gas concentration and volumetric flow without requiring the high-speed gas sensors or large mixing chambers of existing commercial systems.

COBRA Data Products and Validation

In the COBRA sensor, flow and gas composition data are collected in real time and stored internally for later download. In addition, data can be processed by the sensor to produce derived data products and passed via a Bluetooth low-energy wireless connection to an Android device for real-time display. Data from metabolic measurements are presented in two different formats, either as a series of panel plots or as a Microsoft Excel–compatible spreadsheet. Data products include instantaneous flow, respiration rate, tidal volume, minute volume, VO_2, VCO_2, RQ, and EE. Three examples of the many available data products are shown in Figure 13.

The plots in Figure 13 correspond to an interrupted time series of three different levels of exercise intensity from one subject, with the walking data appearing first, followed by the jogging data and finally the running data. Each panel shows a different data product, with the EE in the top panel, RQ in the second, and the volumetric flow

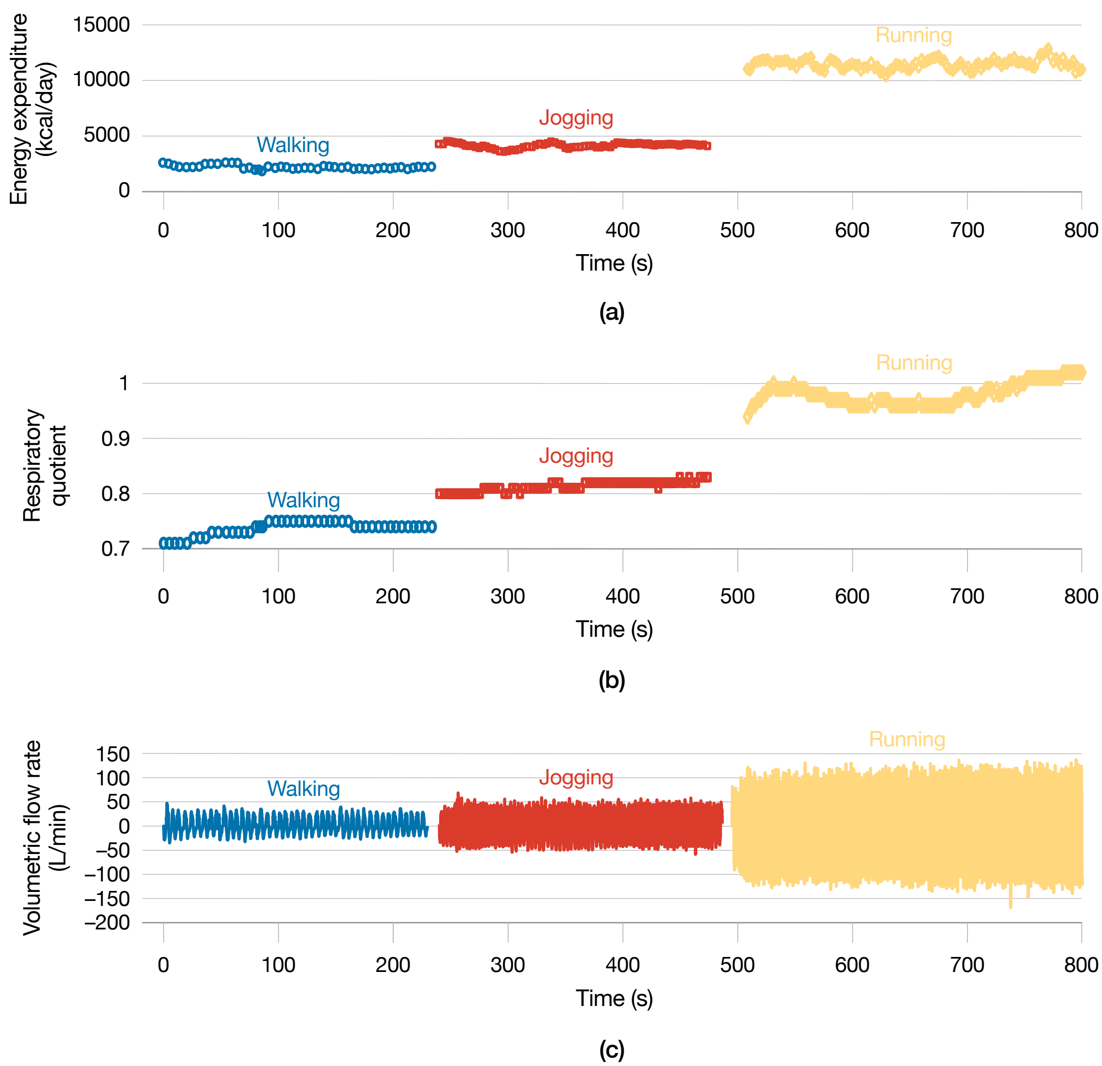


FIGURE 13. Three different sample sets of data were collected with the COBRA sensor. Walking resulted in a respiratory quotient (RQ) ~0.75 and energy expenditure (EE) ~2200 kcal/day (a); jogging resulted in RQ ~0.80 and EE ~4400 kcal/day (b); and running resulted in RQ ~1 and EE ~12,000 kcal/day (c). The changes in RQ reveal how metabolic fuel preference shifts to glucose in response to the higher-intensity exercise.

rate in the third. The flow measurement is performed at 18–20 hertz to provide the resolution needed to resolve the breath profiles, and the other measurements are presented in the form of average numbers over the course of a whole breath. The data presented as breath-by-breath data are not truly breath-by-breath measurements because the time constants associated with the mixing chamber and gas sensors are larger than the duration of an average breath. Consequently, the RQ and energy expenditure data represent a moving average over two to eight adjacent breaths, depending upon respiration rate and tidal volume.

One important aspect to observe across the three exercise intensities is the change in the dynamic range of the flow and energy estimates. For walking flow measurements, the peak flow rate is around 30 liters/minute; however, as the exercise intensity increases, the peak flow rates increase to upwards of 150 liters/minute. In general, the peak flow rate may increase to more than 400 liters/minute during maximal exertion and can be less than 10 liters/minute for resting measurements of individuals with small lung capacity. Designing a reliable passive proportional sampling scheme for this large dynamic range is a challenge. To ensure accuracy and rapid speed of measurements at both ends, the current prototype employs a low-volume-rate flow tube for resting and low-intensity exercise measurements, and a high-volume-rate flow tube for moderate to intense exercise or exertion.

The metabolic response to each of these three different levels of exercise intensity is evident in these data. In the case of walking, the RQ is dominated by slow twitch muscular processes, which are typically fat burning. In this particular case, the subject has an RQ of 0.75, or a molar mix of 17 percent carbohydrates and 83 percent fats. As the subject transitions to jogging, more glycogen from the skeletal tissue is used for energy production, and the RQ increases to 0.80 while the EE increases from about 2200 to 4400 kcal. As the exercise intensity further increases to a run, glucose becomes the preferred fuel and dominates the macronutrient selection, raising the RQ to 1. These data exemplify the transition in metabolic fuel preference as a function of exercise intensity. The transition points and the values of RQ and EE, paired with the exercise information, can be used to assess individual fitness and track changes in fitness and endurance over time.

The U.S. Army Research Institute of Environmental Medicine has conducted a rigorous independent evaluation of the COBRA sensor with 12 volunteers. The testing included a series connection between the COBRA sensor and a gold-standard metabolic cart that ensured that the same test subject's metabolism was presented to both sensors during a measurement cycle. Results of this testing indicated that over a range of activity levels from resting to walking, jogging, and running, the COBRA produces EE and RQ measurements consistent with those of the reference metabolic cart [66].

Applications

TRAINING AND PERFORMANCE TRACKING

For high-performance athletes or military personnel, optimally matching dietary macronutrients to the demands of a specific activity can improve performance and increase the likelihood of successful completion of the activity. In endurance athletic events, matching nutrition to performance needs is already standard practice in the form of carbohydrate or glycogen loading [58], but this practice often results in overconsumption of carbohydrates to ensure maximization of glycogen stores, with excess carbohydrates being converted to fat and stored.

However, to better predict an individual's available energy resources for longer time periods and to properly account for the activity demands and dietary intake, a metabolic model is necessary. Dietary tracking and exercise simulation can be employed to estimate an athlete's initial energy reserve state. The COBRA sensor can then be used to monitor which nutrients are actually selected to meet metabolic energy needs and estimate the individual's future nutritional needs. The information available from the metabolic fuel model and simulation may be used alone or in conjunction with other physiological models to improve performance predictions and assess the benefits of training. One possible example of coupling metabolic and physiological models is estimating a distance runner's performance. A 2010 study used the level of exertion and glycogen storage state to predict the maximal running distance of a person [67]. The COBRA sensor reports both VO_2 and RQ, which are the correlated measures of exertion recommended in the study [67], and the metabolic fuel model predicts glycogen storage on the basis of previous diet and exercise. The information provided by the sensor and the model allows individuals training for an endurance event to predict how far they can expect to run at different running speeds and intensities. The COBRA sensor data are invaluable for guiding different training regimens or deciding on an optimal pace to run a race.

This reasoning can be extended to address needs in the military. For example, a mission may require demanding physical exertion over the course of many days in a location where resupply is challenging. In such a situation, it would be beneficial for decision makers to know which soldiers operate efficiently on calorie-dense fatty food and which soldiers require high-carbohydrate food to maintain the required performance levels. Measurements of RQ and EE during training sessions provide the information for commanders to know which soldiers preferentially select which type of fuel substrate when executing various tasks and levels of exertion. With this knowledge, the commander can select soldiers exhibiting a preference for energy from fat oxidation for missions with difficult resupply. Conversely, for short-lived intense physical tasks, a soldier may need to be capable of exerting maximal metabolic output, in which case a diet that assures adequate glycogen stores is essential. The best way to optimize soldier selection and nutrition for the job at hand is to measure each soldier's metabolic profile and capacities.

The U.S. Army's recruitment and retention has historically relied on a one-size-fits-all fitness assessment of candidates that is independent of their eventual roles. Soldier 2020 is an Army program taking a more discerning approach, with the goal of developing specific fitness standards based on the role that the individual fills [68]. These standards will be informed with awareness of the metabolic costs of particular jobs and quantitative metabolic measurements of the soldiers who successfully occupy the roles. The Soldier 2020 system will likely ease fitness requirements for some specialties while still maintaining the rigor and high standards currently in place for the necessary roles. For instance, a recruit who wants to work in the field still requires a high level of physical fitness, whereas soldiers working at desk jobs could have their standards reduced. The job-specific fitness requirements could help commanders better retain and recruit high-functioning soldiers for specific needs.

QUANTIFYING INDIVIDUAL METABOLISM

In addition to improving military training and readiness, the COBRA sensor and metabolic fuel model can be employed to improve the metabolic health of the civilian population on a broad scale. Specific to the military, the physical health and well-being of soldiers have come under increased scrutiny as the rate of obesity in the military has monotonically increased over the past several years [69]. The rise of obesity has raised the washout rate of soldiers unable to meet fitness requirements and has also elevated health care expenses [16]. Studies have shown that health maintenance, rather than intervention after a person becomes pathogenic, mitigates the risk of such events. However, implementing a health maintenance regimen can be challenging, especially to ensure that individuals follow prescribed diets and exercise regimens. Additionally, very little feedback is available to allow individuals to know if they are doing enough, or even doing the right thing, to achieve weight loss or weight maintenance goals. A system model to predict the impact of dietary and exercise choices on the body and a sensor to provide on-demand feedback and confirm progress are previously unavailable tools for planning and confirming health maintenance and weight management regimens.

A typical practice for weight management studies or intervention is to record activity levels, food consumption, and body weight over the course of weeks or months. Personal tracking and estimation of food calories is challenging to do accurately, and body weight is highly variable, requiring days or weeks to confirm the impact of day-to-day diet and exercise choices. Body weight measurements can be deceptive, as body mass composition depends on water retention, muscle mass, fat, glycogen stores, digestive state, and many other difficult-to-quantify variables. The metabolic fuel model helps to visualize the consequences of eating a certain macronutrient mix or engaging in a particular exercise rather than trying to quantify feeling better or tracking confounding weight changes. Because the metabolic fuel model incorporates macronutrient type and quantity, dietary frameworks (e.g., low fat versus low carbohydrate) can be utilized to gain an understanding of the impact of specific macronutrients and exercise regimens rather than simply tracking calories apart from macronutrient composition. While weight change is often tracked as the only measure of success, our sensor provides on-demand feedback of metabolic fuel substrate to indicate whether the subject is staying in fat-burning mode or fat-storing mode. Furthermore, the model shows how blood insulin and glucose levels (quantities that are linked to feelings of hunger or satiation) are impacted by macronutrient and exercise choices [70, 71]. The COBRA sensor reliably evaluates metabolic indicators and provides a more complete context to help validate the model and understand how dietary choices are affecting metabolism on a day-to-day or even hour-by-hour basis [61].

If, rather than dietary advice, a specific metabolic state—such as ketosis (extreme restriction of carbohydrates) or glycogen loading (extreme consumption of carbohydrates)—is sought, a measurement of the RQ informs the users where they are on the carbohydrate versus fat fuel substrate spectrum. If their goal is to move toward a ketogenic state, an RQ measurement will establish whether fat is the preferred metabolic fuel or if the body is relying primarily on carbohydrates to meet energy demands. On the other end of the spectrum, a resting measurement of RQ greater than 1 would indicate that fat burning is being suppressed in favor of carbohydrate metabolism and that excess carbohydrates are being converted into fats.

Future Work

FIELD TESTING

As noted earlier, the traditional methods of metabolic measurement, whole room indirect calorimetry or treadmill testing with a metabolic cart, are expensive and do not reflect the actual conditions under which soldiers operate in the field. In conjunction with the metabolic fuel model, providing COBRA sensors to soldiers in the field will enable the collection of metabolic data over a range of workloads and environmental conditions. The COBRA sensor data will help quantify the impact of environmental factors on energy expenditure and better inform the development of doctrine and training manuals to avoid excessive heat strain, glycogen depletion, and other undesirable performance degradations.

SINGLE-SUBJECT EXPERIMENTS AND CLINICAL STUDIES

The low-size, -weight, and -power metabolic sensor, along with other physiological status monitors such as heart rate and continuous glucose monitors, promises to enhance the value of clinical studies by providing a low-cost, simple-to-use sensor for monitoring RQ and EE in natural living conditions. For example, a handheld metabolic sensor, communicating with a camera-equipped smartphone to document meal composition and an activity monitor to record exercise, enables the collection of a much richer dataset for clinicians and researchers to use in quantifying the impact of diet and exercise on metabolic health.

There are a number of single-subject experiments planned to provide a preliminary assessment of the value of the metabolic sensor in helping individuals achieve various metabolic fitness and health goals.

EARLY TYPE 2 DIABETES DETECTION AND INTERVENTION

Prediabetes is defined by a fasting blood glucose level between 100 and 125 mg/dL. According to the metabolic model described earlier in this article, a normally functioning endocrine system strives to keep blood sugar below 100 to 110 mg/dL at all times. A primary mechanism for achieving this regulation in the face of carbohydrate overconsumption is to defer the oxidation of fats and preferentially oxidize glucose to meet metabolic energy needs. Consequently, a persistently high resting RQ, particularly in the post prandial, or fasting state, would seem to be indicative of excessively high blood glucose levels. If so, routine resting RQ measurement may provide an early indication of prediabetes. In the case of confirmed prediabetic or type 2 diabetic individuals, rather than making multiple capillary blood glucose measurements each day to check for high blood sugar, a noninvasive RQ measurement in the middle range may be sufficient to ensure blood glucose levels are not high and thus avoid the need to draw a capillary blood sample for testing.

The efficacy of RQ measurements as a noninvasive means of identifying high blood glucose levels can be tested by instrumenting subjects with a continuous glucose monitor, intentionally raising blood sugar levels through manipulation of dietary macronutrients, and quantifying the correlation between high resting RQ and high blood glucose levels. A study with 16 subjects examined this thesis using a whole room indirect calorimeter to collect data for 24 hours [61]. Demonstration of a consistent correlation over a longer period of time would justify a larger study to establish the consistency of the correlation between resting RQ and blood glucose levels over a range of ages, gender, activity, and dietary habits.

GUIDANCE FOR WEIGHT MANAGEMENT PROTOCOLS

The traditional approach to weight management is to estimate calories associated with food intake and activity, create an energy-deficient diet, and monitor progress toward weight loss goals with a scale. Not surprisingly, this approach fails much of the time for several reasons. As noted earlier, counting food calories and estimating activity calories is fraught with error, and body weight may fluctuate by several pounds or more a day depending upon hydration state, glycogen stores, and digestive state.

Rather than a one-size-fits-all formulaic CICO diet for weight loss, the metabolic model and sensor provide the quantitative tools to tailor macronutrient intake and exercise activity to increase the likelihood of achieving weight loss and weight management goals. In particular, a quantitative measurement of RQ may prevent dieters from deceiving themselves about the success of efforts to balance dietary macronutrients and the effectiveness of their exercise regimen by providing real-time feedback. The COBRA sensor enables on-demand RQ measurement throughout the day to assess the impact of dietary and exercise choices on the goal of staying in the fat-burning zone.

RQ-ONLY SENSOR

At least half of the volume of the COBRA sensor is devoted to making the flow measurements necessary to compute energy expenditure and related flow metrics, such as tidal volume and VO_2. However, considering the spectrum of potential applications for the metabolic fuel model, knowledge of energy expenditure is not always necessary. In particular, for detecting chronically high blood glucose levels and providing guidance on how dietary macronutrient imbalances impact fuel substrate selection, energy expenditure data are not required.

By removing the requirement to measure volumetric flow rates and focusing only on resting RQ, a number of simplifications can be made to the COBRA sensor, the breath sampling protocol, and the processing. The flow tube can be made smaller, and the four tubes connecting the flow tube to the mixing chamber can be reduced to a single tube. Because the RQ is a ratio of the measured CO_2 concentration to O_2 concentration for a fixed volume, it is no longer necessary to capture all of the exhaled breath, eliminating the need for a nose clip. The best measure of RQ comes from the deep alveolar lung exchange, so it is only necessary to sample the end tidal portion of the breath. Consequently, an RQ-only sensor can be made smaller and in a form factor compatible with connection to a smartphone for battery power, processing, and display of the measured data.

An RQ-only sensor would reduce the cost of manufacturing and the operational power, further reducing the barriers to personal ownership by a broad segment of the population.

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