CarbMetSim: A Discrete-Event Simulator for Carbohydrate Metabolism in Humans

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Abstract

This paper describes *CarbMetSim*, a *discrete-event* simulator that tracks the blood glucose level of a person in response to a timed sequence of diet and exercise activities. *CarbMetSim* implements broader aspects of carbohydrate metabolism in human beings with the objective of capturing the average impact of various diet/exercise activities on the blood glucose level. Key organs (stomach, intestine, portal vein, liver, kidney, muscles, adipose tissue, brain and heart) are implemented to the extent necessary to capture their impact on the production and consumption of glucose. Key metabolic pathways (*glucose oxidation*, *glycolysis* and *gluconeogenesis*) are accounted for in the operation of different organs. The impact of insulin and insulin resistance on the operation of various organs and pathways is captured in accordance with published research. *CarbMetSim* provides broad flexibility to configure the insulin production ability, the average flux along various metabolic pathways and the impact of insulin resistance on different aspects of carbohydrate metabolism. The simulator does not yet have a detailed implementation of protein and lipid metabolism.

1 Introduction

More than 400 million people world wide suffer from diabetes [1]. People with *Type 2 Diabetes* (around 90% of total diabetic population [1]) usually have at least some ability to produce insulin, however their bodies develop *insulin resistance* and hence are not able to react strongly enough to the presence of insulin in blood to keep the *blood glucose level* (BGL) under control. On the other hand, people with *Type 1 Diabetes* cannot produce insulin endogenously at all and hence must receive external insulin regularly. Keeping BGL under control is a constant struggle for people with diabetes. One wrong meal choice may result in very high BGL and an accompanying feeling of sickness for several hours. Persistently high BGL would ultimately cause a number of severe complications such as heart/kidney failure, blindness and limb amputations. Those using external insulin may suffer life threatening hypoglycemic incidents if too much insulin is injected. Physical exercise allows the muscles to use glucose in the blood even in the absence of insulin but exercise activities need to be carefully coordinated with food and medication intake so as to avoid hypoglycemia. For people with Type 1 Diabetes, physical exercise may even worsen the state of hyperglycemia. In general, people with diabetes need help deciding how they should plan their food and exercise activities so as to keep their BGL under control. There is a real need for tools that help diabetic people understand the impact a particular sequence of food and exercise activities would have on their BGL. Continuous BGL monitoring solutions, now offered by a number of vendors, can significantly help but are either not easily available to a vast majority of diabetic people world-wide or are simply too expensive. Clearly, one solution is to build simulation tools that use our vast knowledge of energy metabolism in human beings to give reasonably accurate prediction of the impact of a diet/exercise sequence on some one's BGL. A few such simulators already exist [2, 3] but are geared towards predicting the impact of *individual* meals and are not available in a format that can be freely used by individuals. This paper describes *CarbMetSim* (the **Carb**ohydrate **Met**abolism **Sim**ulator), an *open-source* and freely available [4] simulation software that predicts minute by minute BGL in response to an arbitrary length sequence of food and exercise activities. While the existing simulation tools are based on *continuous time* models that use differential and algebraic equations to describe physiological details,

CarbMetSim is based on a *discrete event* model where the time increments in units (called *ticks*) one minute long. At the beginning of each tick, *CarbMetSim* fires the food/exercise events that need to be fired at this time and directs various simulated body organs to do the work they are supposed to do during this tick. The simulator is currently geared for use by people with Prediabetes and Type 2 Diabetes who follow a fixed medication (including long term insulin) regime prescribed by their physicians. Future versions of the simulator will include a detailed implementation of the impact of short term insulin to allow use by people with Type 1 Diabetes.

CarbMetSim implements broader aspects of carbohydrate metabolism in human beings with the objective of capturing the average impact of various diet/exercise activities on the BGL of people with different levels of diabetes. The simulator implements key organs (stomach, intestine, portal vein, liver, kidney, muscles, adipose tissue, brain and heart) to the extent necessary to capture their impact on the production and consumption of glucose. Key metabolic pathways (*glucose oxidation*, *glycolysis* and *gluconeogenesis*) are accounted for in the operation of different organs. The impact of insulin and insulin resistance on the operation of various organs/pathways is captured in accordance with published research. *CarbMetSim* provides broad flexibility to configure the insulin production ability, the average flux along various metabolic pathways and the impact of insulin resistance on different aspects of carbohydrate metabolism. Thus, it is possible to customize the simulator for a particular user by setting appropriate values to various configurable parameters.

CarbMetSim is not yet a finished product. The protein and lipid metabolism are implemented in a very simplified manner. The simulator does not yet consider monosaccharides other than glucose and assumes that all dietary carbohydrate gets converted to glucose after digestion. The impact of insulin is captured in a simplified manner and other important hormones (e.g. glucagon) are not yet directly modeled. Impact of subcutaneous insulin is not explicitly modeled yet. Only aerobic exercise activities can be simulated at present. Finally, *CarbMetSim* is not yet capable of translating a user's diet/exercise/BGL data into the values of simulation parameters governing the behavior of different organs. The simulator has broad applicability beyond its original purpose described above. For example, it is possible to extend the implementation to study the long term impact of diabetes on various organs or to

predict changes in body weight in response to a diet/exercise regimen.

2 Modeling Carbohydrate Metabolism in Humans - A Literature Review

Existing approaches to model carbohydrate metabolism in human beings can be classified as either *data-driven* or *knowledge-driven* [5]. The data-driven (or *empirical*) models relate a user's recent BGL values along with other relevant information (e.g. diet, exercise, medication and stress) to the user's future BGL values using approaches such as neural networks [6–11] and gaussian models [12]. A number of different neural network models exist including those based on multilayer perceptrons [7, 8], radial basis function [9], wavelets [10], time series convolution [6] and recurrent neural networks [6, 11]. Such models consider the human body to be a *black-box* and do not take in account the physiological aspects of carbohydrate metabolism [13].

Unlike the data-driven models, the knowledge-driven models are based on human physiology. In such models, different factors are treated as different *compartments* that influence each other and are described by a set of differential and algebraic equations [5]. The earliest such models [14–16] involved two *linear* compartments - one for glucose in blood and the other for insulin in blood - such that the rates of appearance/disappearance of glucose/insulin were *linearly* proportional to their level in blood. The next generation of models included *non-linear* rates and consideration of additional hormones (e.g. glucagon) besides insulin [17]. Foster [18] presented a six compartment model, one each for blood glucose, liver glycogen, muscle glycogen, plasma insulin, plasma glucagon and free fatty acids in plasma, and the addition/removal from each compartment happened in a non-linear fashion. Some of the other notable multi-compartment, nonlinear models were those developed by Cerasi [19], Insel [20], Cramp and Carson [21] and Cobelli et al. [22]. These models were increasingly more complex with many physiological details taken in account. Sorensen [23] provides a good overview of the earliest knowledge-based models (and some of the later models described next).

Bergman et al. [24, 25] designed a method to quantify a) the sensitiviy of an

individual's beta cells to his/her BGL and b) the sensitivity of the individual's BGL to insulin level in his/her blood. For this purpose, a *minimally* complex mathematical model was developed that could capture the individual differences in two sensitivities mentioned above. Bergman's *minimal* model has been modified in a variety of ways. Furler et al. [26] introduced modifications to allow for absence of insulin production by pancreas and external insulin infusion. Bergman's model has also been used to study closed [27] and semi-closed [28] loop optimal control algorithms to determine the insulin infusion profile for an individual. Roy and Parker extended Bergman's model to take in account the level of *free fatty acids* in plasma [29]. Bergman's model has also been extended to take in account the impact of physical exercise [30, 31].

Tiran et al. [32] developed a multi-compartment model for glucose circulation where each relevant organ was modeled as a separate compartment. Guyton et al. [33] developed another multi-compartment model consisting of a glucose circulation subsystem (separate compartments for liver glucose, liver glycogen, kidney glucose, brain tissue glucose, brain blood glucose, peripheral (muscles, adipose tissue) blood glucose, peripheral tissue glucose, central (i.e. gastrointestinal tract) blood glucose and central tissue glucose) and an insulin circulation subsystem (separate compartments for liver insulin which represents insulin from pancreatic beta cells, kidney insulin, peripheral blood insulin, peripheral tissue insulin, central blood insulin and central tissue insulin). The model consisted of a total of 32 nonlinear ordinary differential equations (ODEs) with 11 nonlinear ODEs just to model insulin secretion from pancreas [23]. Sorensen [23] presented another physiologically complex, multi-compartment model albeit with a much simplified model for pancreatic insulin secretion. Sorensen's model consisted of a total of 22 nonlinear ODEs of which 11 ODEs were associated with glucose circulation, 10 ODEs with insulin and 1 ODE with glucagon. Parker et al. [34, 35] updated the Guyton/Sorensen models by accounting for uncertainty in parameter values and by including a model for gastric emptying of carbohydrates in a meal [36]. Hovorka et al. [37] developed a multi-compartment model of glucose and insulin kinetics as part of a model predictive controller for subcutaneous insulin infusion for people with Type 1 Diabetes. This model consists of a two-compartment glucose subsystem (accounting for glucose absorption, distribution and disposal), a two-compartment insulin subsystem (accounting for insulin absorption,

distribution and disposal) and an insulin action subsystem (accounting for insulin action on glucose transport, disposal and endogeneous production).

Dalla Man et al. [38] developed a model that related the plasma concentrations of glucose and insulin to various glucose and insulin related rates (the rate of appearance of glucose from the gastro-intestinal tract, the rate at which the glucose is produced by liver and kidney, insulin dependent and independent rates of glucose utilization, the rate of renal extraction of glucose, the rate of insulin secretion by beta cells and the rate of insulin degradation). The parameters of this model were determined using the experimental data collected for 204 normal and 14 Type 2 Diabetic subjects. This model was used to simulate patient behavior in UVA/PADOVA Type 1 Diabetes Simulator [2] aimed at investigating the closed control strategies for insulin pumps. A new version of UVA/PADOVA Type 1 Diabetes Simulator [3] modifies Dalla Man's model by incorporating glucagon secretion/action/kinetics and nonlinear increase in insulin dependent glucose utlization as BGL dips below the normal range.

The *CarbMetSim* simulator presented in this paper is physiologically complex just like the models presented by Tiran et al. [32], Guyton et al. [33], Sorensen [23] and Dalla Man [38]. The key difference is that *CarbMetSim* implements the physiological details in software with various body organs implemented as *objects* whereas the existing models used ODEs to model physiological details. It can be argued that implementing physiological details in software allows for much more complex behavior to be taken in account than what is possible using ODEs. Moreover, it is much easier to modify physiological behavior implemented in software than via ODEs. In that sense, the presented simulator is an improvement over existing ODE based approaches. It is hoped that these benefits coupled with its *open-source* nature will allow *CarbMetSim* to emerge as a popular simulation model of human metabolism for both diabetes research and self-management tools for diabetic people.

3 Key Aspects in *CarbMetSim* Design

In the following, we describe some of the key aspects of *CarbMetSim*'s design.

3.1 Food and Exercise Description

In *CarbMetSim*, a food is described in terms of its serving size and the amount of *rapidly available glucose* (RAG), *slowly available glucose* (SAG), protein and fat per serving. The RAG contents include sugars and the *rapidly digestible* starch (i.e. starch that gets digested in vitro within 20 minutes [39, 40]). The SAG contents include the *slowly digestible* starch (i.e. starch that gets digested in vitro between 20 and 120 minutes [39, 40]). In general, the starch with high amylopectin to amylose ratio is classified as rapidly digestible starch whereas the one with high amylose to amylopectin ratio is classified as slowly digestible starch. The *non-starch polysaccharide* (also known as *dietary fiber*) part of the carbohydrates is currently ignored (even though the fiber contents of the food are known to have an impact on the *gastric emptying*). *CarbMetSim* currently does not have a detailed implementation of the protein and lipid metabolism. However, it does model the impact of protein and fat contents of food on gastric emptying. Hence, the food description should include the total amount of protein and total amount of fat per serving. *CarbMetSim* currently does not characterize protein in terms of its amino acid contents. Since only 3 of the 20 amino acids have *branched chains*, a general assumption is made that 85% of amino acids resulting from protein digestion have *unbranched chains* and the remaining have *branched chains* [41]. In *CarbMetSim*, an exercise activity is described in terms of its intensity in units of *Metabolic Equivalent of Task* or *MET*s, where 1 *MET* is 1 *kcal* of energy expenditure per kg of body weight per hour. *CarbMetSim* can currently simulate only *aerobic* exercises.

3.2 Modeling Insulin Production

CarbMetSim models insulin production using the following four configurable parameters: *baseGlucoseLevel_*, *highGlucoseLevel_*, *baseInsulinLevel_* and *peakInsulinLevel_*. The *baseGlucoseLevel_* represents the typical fasting BGL and the *highGlucoseLevel_* represents the typical peak BGL the user experiences. Both *baseInsulinLevel_* and *peakInsulinLevel_* parameters assume values between 0 and 1 (with *baseInsulinLevel_* $\leq$ *peakInsulinLevel_*). The *baseInsulinLevel_* represents the insulin level in the blood when the BGL is less than or equal to *baseGlucoseLevel_*. The *peakInsulinLevel_* represents the

ability to produce insulin. A value 1 for *peakInsulinLevel_* means normal insulin production, whereas a value 0 means that the pancreas does not produce any insulin at all (as in people with Type 1 Diabetes). A value x (between 0 and 1) for *peakInsulinLevel_* means that peak insulin production is just x times the normal peak. *CarbMetSim* models the insulin level as a variable *insulinLevel* that assumes values between *baseInsulinLevel_* and *peakInsulinLevel_*. The *insulinLevel* stays at *baseInsulinLevel_* if the BGL is less than or equal to the *baseGlucoseLevel_*. The *insulinLevel* increases linearly from *baseInsulinLevel_* to *peakInsulinLevel_* as the BGL increases from *baseGlucoseLevel_* to *highGlucoseLevel_*. If the BGL increases beyond *highGlucoseLevel_*, the *insulinLevel* stays at *peakInsulinLevel_*.

3.3 Modeling Glucose Transport

Glucose crosses cell membranes using either *active* transporters or *passive* ones. The active transporters, such as *Sodium GLucose coTransporters* (SGLTs) are able to move glucose from a low concentration to a high concentration. The passive transporters, such as *Glucose Transporters* (GLUTs) move glucose from a high concentration to a low concentration. *CarbMetSim* models the operation of active transporters in an organ by specifying the average amount of glucose transferred per minute via active transport. The actual amount transferred is a poisson distributed random variable. The simulator uses *Michaelis Menten* kinetics to determine the amount of glucose transferred in a minute via passive transport. As per the Michaelis Menten kinetics, the rate of transport (V) across a membrane depends on the difference in the substrate concentration (Y) across the membrane in the following manner: $V = V_{max}\frac{Y}{Y+K_m}$, where V_{max} is the maximum rate of transport and K_m is the substrate concentration difference at which the transport rate is half the maximum. The V_{max} value associated with a GLUT transporter in an organ indicates the number of transporters involved. Hence, the simulator treats V_{max} associated with a particular GLUT in a particular organ as a poisson distributed random variable with a configurable mean.

Among the GLUTs, the GLUT4 transporters are of particular importance because they allow the muscles to absorb glucose from the bloodstream. In the resting state, the number of *active* GLUT4 transporters depends on the insulin level in the bloodstream.

However, in people with diabetes, GLUT4 transporters have significantly lower level of activation even in presence of high insulin levels. *CarbMetSim* uses a configurable parameter (*glut4Impact_*) that multiplicatively modifies the V_{max} value associated with GLUT4 transporters. This parameter can be used to model reduced activation of GLUT4 transporters in people with diabetes. The impact of insulin level is captured by multiplying V_{max} with a factor (between 0 and 1) that increases in value with increase in the *insulinLevel*. Currently, the *insulinLevel* itself is used as the value of this factor.

In the exercising state, the physical activity itself is sufficient to activate GLUT4 transporters [42–44] and hence the muscles are able to absorb sufficient glucose from the bloodstream even in the absence of insulin. However, in some people with Type 1 Diabetes with very little insulin in circulation, glucose absorption from the bloodstream is impaired even during a vigorous physical exercise [44–47]. *CarbMetSim* models impaired glucose absorption during physical exercise using a configurable upper limit on the amount of glucose absorbed by the muscles per tick during exercise. This limit can also be modified using another configurable parameter *maxGlucoseAbsorptionInMusclesDuringExerciseImpact_* that multiplicatively modifies the default value of the upper limit.

3.4 Modeling Glycolysis

Glucose serves as a key source of energy for various tissues, which either oxidize it completely or consume it anaerobically via *glycolysis*. Complete oxidation of glucose yields 15 times more energy than anaerobic glycolysis but can only be done if oxygen is available. Tissues with access to plenty of oxygen oxidize glucose for their energy needs whereas others (possibly in the same organ) use glycolysis. Glycolysis results in the generation of lactate, which serves as a key substrate for endogenous glucose production via *gluconeogenesis* (described later).

The following organs in *CarbMetSim* use anaerobic glycolysis as an energy source: *Muscles*, *Liver*, *Kidneys*, *Intestine* and *Blood*. The amount of glucose consumed for glycolysis increases with the glucose availability, which is signaled by the insulin level in the bloodstream. This is modeled in the simulator in the following manner. Each organ using glycolysis as an energy source has two configurable parameters: *glycolysisMin_*

and *glycolysisMax_* (in units of mg of glucose consumed per kg of body weight per minute). At each tick, the organ generates a poisson distributed random number (min) with *glycolysisMin_* as the mean value and *glycolysisMax_* as the maximum value. Then, subject to the glucose availability in the organ, the amount of glucose consumed in a tick for glycolysis is given by: $min + insulinImpact \times (glycolysisMax_ - min)$. Here, *insulinImpact* is a factor (between 0 and 1) that increases in value with increase in the *insulinLevel*. This factor is calculated using a sigmoid function, which is currently the CDF of a normal distribution with a configurable mean and standard deviation. The simulator also uses configurable multiplicative parameters *glycolysisMinImpact_* and *glycolysisMaxImpact_* to modify the values of *glycolysisMin_* and *glycolysisMax_* parameters associated with each organ. These parameters can be used to model the impact of diabetes on glycolysis flux. A fraction (by default 1) of the glucose consumed for glycolysis is converted to lactate, which is added to the *Blood* object.

3.5 Modeling Gluconeogenesis

The liver and kidneys produce glucose via *gluconeogenesis* by consuming lactate, glycerol, glutamine and alanine [40, 48]. Normally, gluconeogenesis occurs when the insulin level is low (i.e. in the *post-absorptive* state). However, diabetic people may experience high gluconeogenesis flux even in the *post-prandial* state when the insulin level is high [49, 50]. In *CarbMetSim*, the *Liver* and the *Kidneys* produce glucose via gluconeogenesis at configured average rates using substrates mentioned above. The impact of insulin on gluconeogenesis flux is modeled by using a multiplicative factor (between 0 and 1) that decreases in value with increase in the *insulinLevel*. By default, this factor has a fixed value 1 because the experimental results [51] we used to determine the default values of various parameters did not show any decrease in gluconeogenesis flux with increase in the insulin level. The simulator does include the code that will allow this factor to be calculated using an inverse sigmoid function (the complementary CDF of a normal distribution with a configurable mean and standard deviation). The simulator uses another configurable multiplicative parameter *gngImpact_* to modify the configured gluconeogenesis flux. This parameter can be used to model the impact of diabetes on gluconeogenesis flux. The simulator currently keeps

track of only the lactate concentration in the blood. It is assumed that the other substrates are always available in sufficient quantity to allow gluconeogenesis to take place in the manner described above.

3.6 Modeling Liver Glycogen Synthesis & Breakdown

In human body, the liver helps maintain glucose homeostasis by storing excess glucose in blood during the post-prandial state (when the insulin levels are high) as glycogen and releasing glucose to the blood during the post-absorptive and exercising states (when insulin levels are low) by breaking down the stored glycogen. Diabetes may effect both glycogen synthesis and breakdown in the liver. The *Liver* object in *CarbMetSim* does glycogen synthesis or breakdown at configured rates modified by two pairs of factors. The first pair of factors models the impact of insulin on glycogen synthesis and breakdown. For glycogen synthesis, this factor (between 0 and 1) increases in value with increase in the *insulinLevel* and is calculated using a sigmoid function, which is currently the CDF of a normal distribution with a configurable mean and standard deviation. For glycogen breakdown, this factor (again, between 0 and 1) decreases in value with increase in the *insulinLevel* and is calculated using an inverse sigmoid function, which is currently the complementary CDF of a normal distribution with a configurable mean and standard deviation. The second pair of factors affecting glycogen synthesis and breakdown, called *liverGlycogenSynthesisImpact_* and *liverGlycogenBreakdownImpact_*, simply modify the configured rates multiplicatively. These factors can be used to model the impact of diabetes on glycogen synthesis and breakdown in the liver.

During the exercising states, the *Liver* object in *CarbMetSim* ramps up the glycogen breakdown so as to meet the increased glucose needs of the exercising muscles and thus maintain glucose homeostasis. The amount of liver glycogen that breaks down per tick during exercise has a configurable upper limit. People with diabetes may have a lower capacity to ramp up glycogen breakdown during exercise than normal people. *CarbMetSim* allows this behavior to be modeled by setting a lower value for the limit on the amount of liver glycogen breakdown per tick during exercise. The user may use another configurable parameter *maxLiverGlycogenBreakdownDuringExerciseImpact_* to multiplicatively modify the default upper limit.

3.7 Modeling Diabetes

As described in the previous paragraphs, *CarbMetSim* uses a number of configurable parameters to model the state of diabetes in a user's body. Parameters *baseGlucoseLevel_*, *highGlucoseLevel_*, *baseInsulinLevel_* and *peakInsulinLevel_* control the insulin production. Parameters *glut4Impact_*, *maxGlucoseAbsorptionInMusclesDuringExerciseImpact_*, *glycolysisMin(Max)Impact_*, *gngImpact_*, *liverGlycogenSynthesis(Breakdown)Impact_*, *maxLiverGlycogenBreakdownDuringExerciseImpact_* and *excretionKidneysImpact_* (described later) can be used to independently model the impact of diabetes on glucose absorption by muscles, glycolysis, gluconeogenesis, liver glycogen synthesis/breakdown and glucose excretion in urine. Additionally, there are configurable parameters (see Table 1) for mean and standard deviation of normal distributions that determine how the insulin level would impact these processes.

Table 1. Configurable parameters (and their default values) for the mean and standard deviation of normal distributions to determine the impact of *insulinLevel* on various metabolic processes.

Parameter	Default Value
insulinImpactOnGlycolysis_Mean	0.8
insulinImpactOnGlycolysis_StdDev	0.2
insulinImpactOnGNG_Mean	Not used
insulinImpactOnGNG_StdDev	Not used
insulinImpactGlycogenBreakdownInLiver_Mean	0.1
insulinImpactGlycogenBreakdownInLiver_StdDev	0.01
insulinImpactGlycogenSynthesisInLiver_Mean	0.9
insulinImpactGlycogenSynthesisInLiver_StdDev	0.1

3.8 Randomization

In the paragraphs above, we have seen several uses of poisson distributed random variables. This pattern is repeated throughout *CarbMetSim* implementation. A poisson distributed random number is used for any quantity that does not have a fixed value and for which only an average value is known. In the subsequent discussion all references to a random variable mean a poisson distributed random variable unless noted otherwise. Future versions of the simulator will allow the use of other distributions as well.

4 *CarbMetSim* Design and Implementation

At the top level, *CarbMetSim* consists of a *SimCtl* (SIMulation ConTroLler) object and a *HumanBody* object. The *SimCtl* object maintains time (*tick*, where each tick is a minute) and contains a priority queue of food/exercise events sorted in order of their firing times. At the beginning of the simulation, the *SimCtl* object reads all the food/exercise events into the priority queue. At each tick, the *SimCtl* object fires the events whose firing time has arrived (by invoking appropriate methods on the *HumanBody* object) and then causes each organ to do its work during that tick (again by invoking a *HumanBody* object method).

In the following, we describe the implementation and operation of various *objects* that together implement the *CarbMetSim* simulator. The default values of various parameters listed here were determined experimentally to provide a close match with published measurements performed on non-diabetic human subjects before and after a meal event [51]. Validation of simulation results against these published measurements is described in Section 5. Table 2 shows the default values for glycolysis related parameters for different organs. Here, the relative contributions of different organs towards overall glycolysis flux were set as suggested in [52, 53]. Table 3 shows the default values for average gluconeogenesis flux in *Liver* and *Kidneys* using different substrates. Here, the relative contributions of different substrates towards overall gluconeogenesis flux were set as suggested in [48]. Various *Impact_* parameters have value 1 by default. Default values of configurable parameters that determine the impact of *insulinLevel* on various metabolic processes are shown in Table 1.

Table 2. The default values for glycolysis related parameters in various organs.

Organ	glycolysisMin_ (μmol/kg/minute)	glycolysisMax_ (μmol/kg/minute)
Blood	0.175	0.7
Kidneys	0.175	0.7
Liver	0.35	3.5
Muscles	0.35	5.25
Intestine	0.175	0.7

1 μmol of glucose equals 0.1801559mg.

Table 3. The glucose production via gluconeogenesis using different substrates in *Liver* and *Kidneys* in post-absorptive state for a non-diabetic person.

	Liver (μmol/kg/minute)	Kidneys (μmol/kg/minute)
Lactate	0.84	0.462
Glycerol	0.21	0.21
Glutamine	0.21	0.21
Alanine	0.42	0.042

1 μmol of glucose equals 0.1801559mg.

4.1 HumanBody

The *HumanBody* object serves as the container for following organ objects: *Stomach*, *Intestine*, *PortalVein*, *Liver*, *Kidneys*, *Muscles*, *AdiposeTissue*, *Brain*, *Heart* and *Blood*. At the beginning of a simulation, the *HumanBody* object does the following:

- It reads the description of various foods: their composition in terms of *rapidly/slowly available glucose* (RAG/SAG), protein and fat.
- It reads the description of various exercise activities: their intensity in units of *MET*s.
- It estimates the maximal rate of glucose consumption (VO_2max, see Section 4.8) associated with the individual being simulated using the tables in Kaminsky et al. [54] given this individual's gender, age and self-assessed fitness level within his/her age group, which are all supplied as simulation parameters.
- It reads other simulation parameters that affect the operation of different organs.

The *HumanBody* contains methods that cause the food to be added to the stomach when *SimCtl* fires a food event and update the energy needs of the body when *SimCtl* fires an exercise event. When an exercise event gets over, the *HumanBody* resets the energy needs to the resting state. Thus, at any given time, the *HumanBody* remembers whether the stomach has some undigested food (*Fed*) or not (*PostAbsorptive*) and whether the body is currently engaged in some exercise (*Exercising*) or not (*Resting*). Accordingly, there are four body states: *Fed_Resting*, *Fed_Exercising*, *PostAbsorptive_Resting* and *PostAbsorptive_Exercising*. Different body states allow

different values to be in effect for the configurable parameters governing the operation of the organs.

As mentioned before, the *HumanBody* object provides a method, which is invoked by the *SimCtl* object at each tick and causes methods to be invoked on individual organ objects that allow the organs to do their work during that tick.

4.2 Blood

The *Blood* object represents the bloodstream and interacts with various organs to exchange glucose, amino acids and other substrates. The *Blood* object maintains the following substrate variables: *glucose*, *lactate*, *branchedAminoAcids* (consumed by muscles, adipose tissue and brain) and *unbranchedAminoAcids*. The *Blood* object also maintains the *insulinLevel* variable discussed earlier and a *fluidVolume_* variable representing the blood volume (5 liters by default). Hormones other than insulin are not currently maintained. At each tick, the *Blood* object updates the *insulinLevel* in the manner described in Seection 3.2. Also, some glucose is consumed for glycolysis in the manner described in Section 3.4.

4.3 Stomach

The gradual emptying of stomach contents into the intestine, also known as *gastric emptying*, is a complex phenomenon affected by a number of factors such as the volume, particle size, viscosity, osmolarity, acidity and nutritional contents of the meal [55–57]. A variety of models have been suggested in the past for the emptying of food from the stomach into the intestine. Many of these models were based on mathematical functions such as exponential [58, 59] and power exponential [60]. Lehmann and Deutsch [36] presented a simple model for gastric emptying of carboydrates in a meal, where the rate of gastric empyting has three phases - a linear increase phase, a constant maximum rate phase and a linear decrease phase. Dalla Man et al. [61] presented a three-compartment model of the gastrointestinal tract where the gastric emptying rate follows a trough-shaped pattern (initially high followed by a non-linear decrease to a minimum value followed by a non-linear increase back to the initial maximum value).

In *CarbMetSim*, when a food event is fired, the eaten food enters the *Stomach*

instantaneously, where its contents are added to any existing stores of RAG, SAG, protein and fat. The simulator currently uses a simple model for gastric emptying where all the food in the stomach is assumed to be in the *chyme* form and the amount of chyme leaking to the intestine each minute consists of one part determined using a poisson distribution (with default mean 500 mg) and another part proportional to the total amount of chyme currently present in the stomach. This proportionality constant increases linearly with decrease in the energy density of the chyme. The minimum value of this proportionality constant (0.03 by default) represents the fraction leaking out of stomach each minute when the chyme consists entirely of fat (with energy density 9.0 kcal/g). On the other hand, the maximum value (9.0/4.0 times the minimum value) represents the fraction leaking out of stomach each minute when the chyme consists entirely of carbs (with energy density 4.0 kcal/g). The nutritional composition of leaked chyme is same as that of chyme present in the stomach. This simple model, inspired from [62], allows us to take in account the fat/protein induced slowdown of gastric emptying. There are many other factors that affect the gastric emptying process (the solid/liquid nature of food, fiber content, osmolarity, viscosity etc.) which *CarbMetSim* currently does not take in account. Thus, a bolus of chyme leaks from the *Stomach* into the *Intestine* every tick (i.e. every minute) until the *Stomach* is empty.

4.4 Intestine

Carbohydrate Digestion: The intestine digests the carbohydrate in the chyme using a number of enzymes to produce monosaccharides such as glucose, fructose and galactose [40]. Currently, the *Intestine* object in *CarbMetSim* converts all the carbohydrate in the chyme to just one monosaccharide - glucose. The *Intestine* receives a bolus of chyme from the *Stomach* every tick as long as there is some food in the *Stomach*. The *Intestine* maintains a list of *Chyme* objects where each object contains the undigested RAG/SAG contents of each bolus received from the *Stomach* and the time when the bolus was received. At each tick, the *Intestine* digests some amount of RAG/SAG from each *Chyme* object. The amount digested from a particular *Chyme* object is determined using normal distributions (default mean & standard-deviation: 2 minutes & 0.5 minutes for RAG and 30 minutes & 10 minutes for SAG) such that most

of the RAG/SAG contents of a bolus are digested within 20 and 120 minutes respectively after the bolus's entry into the *Intestine*. The glucose resulting from digested RAG/SAG is added to the *glucoseInLumen* variable in *Intestine*, which represents the total glucose present in the intestinal lumen. This glucose is processed as described later in this section.

Fat and Protein Digestion: As a chyme bolus enters the *Intestine* from the *Stomach*, its fat contents are simply added to the *AdiposeTissue* and its protein contents are added to a common protein pool in *Intestine*. At each tick, the *Intestine* digests a small amount of this protein (determined as per a poisson distribution with default mean 1mg) and transfers the resulting amino acids to the *PortalVein*. The simulator does not keep track of the amino acid contents of dietary protein and makes a simple assumption that 85% of these amino acids are *unbranched* and the remaining 15% are *branched*.

Glucose Absorption from Intestine to PortalVein: The glucose moves from the intestinal lumen to the enterocytes across the brush border membrane and then from the enterocytes to the portal vein across the basolateral membrane. The transfer from the intestinal lumen to the enterocytes takes place via a combination of active (SGLT-1) and passive (GLUT2) transporters, where the number of GLUT2 transporters in action depends on the glucose concentration on the lumen side. The transfer from the enterocytes to the portal vein takes place solely via passive GLUT2 transporters [40]. The *Intestine* object maintains two variables: *glucoseInLumen* and *glucoseInEnterocytes*, which represent total glucose present in the intestinal lumen and in enterocytes respectively. At each tick, the *Intestine* moves some glucose from *glucoseInLumen* to *glucoseInEnterocytes*. The amount moved has an active transport component (poisson distributed with default mean 30 mg/minute) and a passive transport component determined using Michaelis Menten kinetics (assuming configurable volumes for the lumen and the enterocytes). The V_{max} value used for Michaelis Menten kinetics increases with glucose concentration in the lumen with default maximum value 800 mg/minute. The K_m value used is 20 mmol/l by default [40]. Glucose transport from the enterocytes to the portal vein is modeled by moving some glucose from *glucoseInEnterocytes* to the *PortalVein* at each tick. The amount moved is determined using Michaelis Menten kinetics (average V_{max} = 800 mg/minute, K_m = 20 mmol/l by default [40]).

Glycolysis: The intestinal cells get some of their energy via glycolysis of glucose to lactate in the manner described in Section 3.4. If the glucose in enterocytes (*glucoseInEnterocytes*) is not sufficient, the extra glucose needed for glycolysis comes from the bloodstream (the *Blood* object).

4.5 PortalVein

The portal vein carries blood that has passed through the intestinal tract to the liver. Due to its special status as the conduit from the intestine to the liver, *CarbMetSim* maintains the portal vein as a separate entity (the *PortalVein* object) from rest of the circulatory system (represented by the *Blood* object). The glucose and amino acids resulting from the food digestion in the *Intestine* travel to the *Liver* via the *PortalVein*.

Since the portal vein is a part of the circulatory system, it must have the same glucose concentration as rest of the circulatory system when no new glucose is being received from the intestine. This is achieved in *CarbMetSim* in the following manner. At the beginning of a tick, there is no glucose in the *PortalVein*. During each tick, the following sequence of actions take place:

- The *PortalVein* imports glucose from the *Blood* so that the glucose concentration in the *PortalVein* matches that of *Blood* before the import. The *PortalVein*'s volume, used to calculate the glucose concentration, is a configurable parameter with default value 5 dl.
- Glucose transfer takes place from the *Intestine* to the *PortalVein* (as described previously in Section 4.4) and then from the *PortalVein* to the *Liver* (as described next in Section 4.6).
- Finally, any remaining glucose in the *PortalVein* is moved back to the *Blood*.

All the amino acids received from the *Intestine* into the *PortalVein* during a tick are moved to the *Liver* during that tick itself.

4.6 Liver

The *hepatocytes* in the liver absorb glucose from the portal vein via GLUT2s when the glucose concentration in the portal vein is higher. The absorbed glucose is

phosphorylated to glucose 6-phosphate, which is used either for glycogen synthesis or for glycolysis. Insulin and glucose activate the enzymes associated with glycogen synthesis and inhibit those associated with glycogen breakdown. Insulin also activates glycolysis of glucose 6-phosphate in hepatocytes to form pyruvate, some of which is oxidized and the remaining is converted to lactate and released to the bloodstream. On the other hand, lack of insulin (and presence of glucagon) activates glycogen breakdown (to glucose) as well as gluconeogenesis (which again produces glucose). The gluconeogenesis flux increases with the availability of the substrates (such as lactate, alanine and glycerol) in the bloodstream even if the insulin level is high. Excess glucose in the hepatocytes is either used for glycogen synthesis (if the insulin level is high) or leaves the cells via GLUT2s and possibly other means (if the insulin level is low). High insulin level also causes some of the excess glucose to be converted to lipid. Thus, the liver absorbs glucose during the fed state and uses it for glycogen synthesis and glycolysis. On the other hand, the liver releases glucose to the bloodstream during the post-absorptive and exercising states via glycogen breakdown and gluconeogenesis. Another important aspect of the liver operation is its oxidation of *unbranched* amino acids which provides for almost half of the liver's energy requirements.

CarbMetSim implements the liver operation in the *Liver* object. At each tick, the *Liver* does the following:

- *Glucose Absorption/Release:* If the glucose concentration in higher in the *PortalVein* than in the *Liver*, some glucose will be absorbed in the *Liver* via GLUT2s. Similarly, if the glucose concentration is higher in the *Liver* than in the *Blood*, some glucose will be released to the *Blood* via GLUT2s. The amount of the glucose absorbed/released is determined using Michaelis Menten kinetics (with default average V_{max}=50mg/kg/min and default K_m=20 mmol/l [40]).

- *Glycogen Synthesis:* The *Liver* performs glycogen synthesis in the manner described in Section 3.6. By default, glycogen synthesis takes place at the maximum rate 33μmol/kg/min when the *liverGlycogenSynthesisImpact_* parameter has value 1.

- *Lipogenesis:* If the glycogen level exceeds its maximum configured value (equivalent to 120 grams of glucose by default), excess glycogen is converted to fat,

which is stored in *AdiposeTissue*.

- *Glycolysis* and *Gluconeogenesis:* The *Liver* consumes some glucose for glycolysis in the manner described in Section 3.4 and produces glucose via gluconeogenesis in the manner described in Section 3.5.

- *Glycogen Breakdown:* During the resting states, the *Liver* performs glycogen breakdown in the manner described in Section 3.6. By default, glycogen breakdown takes place at the maximum rate 5.5μmol/kg/min during the resting states when the *liverGlycogenBreakdownImpact_* parameter has value 1. During the exercising states, the *Liver* breaks a (poisson distributed) random amount of glycogen (up to a configurable limit which is 30μmol/kg/min by default) so that the resulting glucose along with that generated via gluconeogenesis (in *Liver* and *Kidneys*) meets the current glucose needs of various organs including *Muscles*. It is assumed that the *Muscles* oxidize glucose from the bloodstream in order to meet on average 10% of its energy needs during exercise [63].

- *Amino Acid Consumption:* The *Liver* consumes 93% of unbranched amino acids received from the *PortalVein* and releases the rest (along with all the branched amino acids) to the *Blood* object.

4.7 Kidneys

The kidneys filter the blood and require significant amount of energy for this task. Their outer layer (the *cortex*) is well supplied with oxygen and hence meets its energy needs via oxidation of glucose and fatty acids absorbed from the bloodstream. The inner core (the *medulla*) uses anaerobic glycolysis for energy. The kidneys also generate glucose via gluconeogenesis. *CarbMetSim* implements the kidney operation in the *Kidneys* object. At each tick, the *Kidneys* do the following:

- *Glycolysis:* The renal medulla in *Kidneys* meets its energy requirements via glycolysis, which is implemented in the manner described in Section 3.4. The glucose consumed for glycolysis is absorbed from the *Blood* object and the resulting lactate is released to the *Blood* object.

- *Gluconeogenesis:* The *Kidneys* produce glucose via gluconeogenesis in the manner described in Section 3.5. Lactate and other substrates needed for gluconeogenesis are absorbed from the *Blood* object and the resulting glucose is released to the *Blood* object.

- *Glucose Excretion in Urine:* As the the glucose concentration in *Blood* increases from one threshold (11 mmol/l [52, 64] by default) to another (22 mmol/l by default), the glucose excretion in urine increases linearly from zero to a certain peak level (100 mg/min by default). The simulator supports a configurable parameter *excretionKidneysImpact_* (with default value 1) to multiplicatively modify the amount of glucose excreted per tick in urine.

4.8 Muscles

The skeletal muscles have two types of cells or *fibers*: the *red* fibers oxidize substrates (fatty acids, glucose) absorbed from the bloodstream to meet their energy needs while the *white* fibers rely on glycolysis of glucose 6-phosphate obtained from the glycogen stored within the white fibers for energy. The glucose absorption from the bloodstream occurs mainly via insulin-sensitive GLUT4 transporters with some *basal* level absorption taking place via GLUT1 transporters. The skeletal muscles also use some *branched chain* amino acids absorbed from the bloodstream to meet their energy needs.

Muscles Operation During Rest [40, 47, 65]: In the resting state, the muscles meet $85 - 90\%$ of their energy needs via the oxidation of fatty acids. About 10% of the energy comes from oxidation of glucose and $1 - 2\%$ from amino acids. The glucose is absorbed from the bloodstream using GLUT4 and GLUT1 transporters as mentioned earlier. The absorbed glucose is used for oxidation, glycogen synthesis and glycolysis [66]. The glucose oxidation and glycolysis in muscles under resting conditions increases with the insulin level in the bloodstream.

Muscles Operation During Aerobic Activity [40, 47, 63]: Oxidation of glucose and fatty acids is the main source of energy for exercising muscles. The relative fraction of these substrates used to meet the energy needs depends on the exercise intensity, which in turn is decided based on the rate at which the individual consumes oxygen while doing this exercise. Each individual has a certain maximal rate at which he/she can

consume oxygen. This individual-specific maximal rate, called VO_2max, depends on the gender, age and fitness level of the individual [54]. So, the intensity of an exercise activity can be described by the oxygen consumption rate (as the %age of the individual's VO_2max) associated with this exercise. The exercise intensity can also be described in an individual-independent manner in units of *Metabolic Equivalent of Task* or METs, where 1 MET is 1 $kcal$ of energy expenditure per kg of body weight per hour. By convention, 1 MET is considered equivalent to $3.5ml$ of oxygen consumption per kg of body weight per minute. So, an exercise with a certain intensity in terms of METs may translate to very different intensities in terms of $\%VO_2max$ for different individuals.

Romijn et al. [63] reported that about 10% of the energy needs during aerobic exercise are met by oxidizing glucose absorbed from the blood via GLUT4/GLUT1 transporters. The aerobic activity is sufficient to activate GLUT4 transporters. So, their action is not dependent on the insulin during the aerobic exercise [42–44]. For low intensity (e.g. $25\%VO_2max$) exercise, almost all of the remaining energy needs are met by oxidizing fatty acids [63]. For moderate and high intensity exercise, a significant fraction of energy needs is met by oxidation of glucose derived from the glycogen stored locally in the exercising muscles. Romijn et al. [63] reported about 30% of the energy coming from the oxidation of glucose derived from locally stored glycogen when the intensity of the aerobic exercise was $65\%VO_2max$. Horton [47] reported oxidation of glucose (absorbed from the blood and derived from local glycogen) providing for about 50% and almost 100% of the energy needs when the exercise intensities were $50\%VO_2max$ and $100\%VO_2max$ respectively. Most of the remaining energy needs are met by oxidation of fatty acids [67]. Once the glycogen stored in the liver and the muscles is over, it becomes impossible for the individual to perform very high intensity exercise. A small fraction of the energy needs is met by glycolysis of glucose 6-phosphate derived from locally stored glycogen. The glycolysis level increases linearly with exercise intensity. Finally, a very small fraction of energy needs is met by consuming *branched* amino acids absorbed from the blood [67].

4.8.1 Implementation in *CarbMetSim*

In *CarbMetSim*, the skeletal muscles are implemented as the *Muscles* object. Currently, the simulator implements response to the resting condition and the aerobic exercise only. Specifically, exercise with a significant anaerobic component cannot yet be simulated. Also, it is not yet possible to distinguish among different muscle groups.

At the beginning of a simulation, the *HumanBody* object estimates the VO_2max associated with the individual being simulated using the tables in Kaminsky et al. [54] given this individual's gender, age and self-assessed fitness level within his/her age group, which are all supplied to the simulator as input parameters. When an exercise event is fired, the exercise intensity is translated from the units of *MET*s into $\%VO_2max$. The exercise intensity determines the fraction of the energy needs met via oxidation of glucose derived from locally stored glycogen.

When the *HumanBody* is in *Fed_Exercising* or *PostAbsorptive_Exercising* state during a tick, the *Muscles* object performs the following actions:

- *Oxidation of glucose absorbed from the* Blood*:* The *Muscles* absorb a (poisson distributed) random amount of glucose from the *Blood* (up to a configurable limit which is 30μmol/kg/min by default) so that it can be oxidized to meet on average 10% of the energy needs during this tick. This absorption does not depend on the current *insulinLevel* in the *Blood*.

- *Oxidation of glucose derived from local glycogen:* The exercise intensity (in $\%VO_2max$) is used to determine the fraction of energy needs that will be met by oxidizing glucose derived from locally stored glycogen. As the exercise intensity increases from $0\%VO_2max$ to $100\%VO_2max$, a value between 0 and 0.9 is determined using a sigmoid function (currently, the compressed CDF of a normal distribution) such that exercise intensities $50\%VO_2max$ and $100\%VO_2max$ yield values close to 0.4 and 0.9 respectively. This value is then used as the mean to generate a poisson distributed random value that gives the fraction of energy needs during this tick to be met by oxidizing glucose derived from local glycogen (as long as a sufficient amount of local glycogen is available).

- *Glycolysis:* The glycolysis flux during the tick increases linearly from a (poisson

distributed) random value (with *glycolysisMin_* as the mean) to *glycolysisMax_* as the exercise intensity increases from $0\% VO_2max$ to $100\% VO_2max$. The glucose 6-phosphate consumed for glycolysis comes from locally stored glycogen. The resulting lactate is added to the *Blood* object.

- *Fatty Acid Consumption:* If glucose oxidation and glycolysis described above do not meet the current energy needs, *Muscles* consume fat (representing fatty acids) from the *AdiposeTissue* to meet the remaining energy needs.

When the *HumanBody* is in *Fed_Resting* or *PostAbsorptive_Resting* state during a tick, the *Muscles* object performs the following actions:

- *Glucose Absorption:* GLUT4 based glucose absorption (default V_{max}= 2.7 mg/kg/minute, default K_m= 5 mmol/l $\approx$ 90.08 mg/dl [40]) occurs in the manner described in Section 3.3. Also, basal absorption via GLUT1s occurs at a configured rate (by default zero).

- *Glycolysis:* A fraction of the absorbed glucose (determined as described in Section 3.4) is consumed via glycolysis and the resulting lactate is added to the *Blood* object.

- *Glycogen Synthesis:* If the glycogen store of the *Muscles* is less than a configurable maximum value (by default 15 grams of glycogen per kg of wet muscle weight, which in turn is assumed to be 40% of the initial body weight [40]), a (poisson distributed) random amount of the absorbed glucose (with a configurable mean, 15μmol/kg/min by default) is converted to glycogen.

- *Oxidation:* Remainder of the absorbed glucose is considered consumed via oxidation.

- *Fatty Acid Consumption:* If glycolysis and glucose oxidation described above do not meet the energy needs during the resting state, *Muscles* consume fat (representing fatty acids) from the *AdiposeTissue* to meet the remaining energy needs.

4.9 Adipose Tissue

CarbMetSim does not yet have a detailed implementation of lipid metabolism. Currently, the *AdiposeTissue* object serves as the storage for fat. The *Intestine* object directly adds the fat contents in chyme to the *AdiposeTissue* object. Similarly, the *Liver* object converts excess glycogen to fat to be stored in the *AdiposeTissue* object. The *Muscles* object directly removes fat from the *AdiposeTissue* in accordance with its energy needs.

4.10 Brain

The brain meets its energy needs by oxidizing glucose (although under starvation conditions it can also use ketone bodies). The *nerve* cells in the brain use GLUT3 transporters to absorb glucose from the bloodstream. Since the K_m value associated with GLUT3 transporters is quite low, the rate of glucose absorption by the nerve cells does not change much with glucose concentration in the bloodstream (unless it drops way below the normal levels). The brain oxidizes about 120 g of glucose per day, equivalent to absorption of about 83.33 mg of glucose per minute [40, 66]. In *CarbMetSim*, the brain operation is modeled as the *Brain* object which consumes a (poisson distributed) random amount (with mean 83.33 mg) of glucose every minute from the *Blood* object.

4.11 Heart

The heart meets most of its energy needs by oxidizing fatty acids. Depending upon their availability, up to 30% of the heart's energy needs are met by consuming glucose and lactate [68]. A much smaller part of the energy needs is met from amino acids and ketone bodies. The heart uses both GLUT1 and GLUT4 transporters to absorb glucose from the bloodstream. The *Heart* object in *CarbMetSim* models the heart operation. It absorbs a poisson distributed random amount of glucose (with default mean 14 mg/minute [66]) from *Blood* and oxidizes it to meet its energy needs.

5 Validation of *CarbMetSim* For a Meal Event

In order to determine the default values of various configurable parameters for normal subjects and to illustrate *CarbMetSim*'s ability to model carbohydrate metabolism in normal subjects and those with Type 2 Diabetes (T2D) in *post-absorptive* and *post-prandial* phases, we configured the simulator to provide a close match with measurements reported in Woerle et al. [51]. Woerle et al. [51] did extensive measurements on 26 subjects with Type 2 Diabetes and 15 age/weight/sex-matched subjects without diabetes to determine the flux along different pathways for glucose arrival and consumption following a standard meal. The T2D subjects included 16 men and 10 women with following characteristics: age 53 ± 2 years, body weight 93 ± 4 kg, BMI $30 \pm 1 kg/m^2$, body fat 34 ± 3 %, average *HbA1c* 8.6 ± 0.3%. The normal subjects included 7 men and 8 women with following characteristics: age 49 ± 3 years, body weight 89 ± 4 kg, BMI $30 \pm 1 kg/m^2$, body fat 36 ± 3 %. All the subjects consumed a standard breakfast, consisting of 84 g of glucose, 10 g of fat and 26 g of protein, at 10am on the day of the measurements after a fast of more than 14 hours. Measurements were performed for the post-absorptive phase before the breakfast and the post-prandial phase assumed to be six hours in duration after the breakfast.

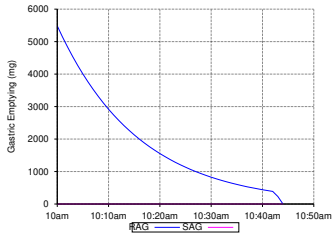
Two sets of simulations were performed using *CarbMetSim*: one for a normal subject and one for a T2D subject (see Table 4). Each set consisted of 30 simulations with different seeds for random number generation. Default values were used for most of the configurable simulation parameters. These values (already reported in the previous section) were set so that the normal subject simulations achieves a close match with measurements reported in [51]. Configurable parameters for which the default values were not used are shown in Table 4. In all the simulations reported in this section and the next, the parameters did not change in value with the body state (although the simulator is capable of using different values for a parameter depending on the body state). For the T2D subject simulations, we used various *Impact_* parameters to modify the default values for various parameters and achieve a close match with results reported in [51]. Simulation parameters *bodyWeight* and *age_* were set to the average values reported for subjects in each category in [51]. Parameters *age_*, *gender_* and *fitnessLevel_* are used to determine VO_2max, the maximal rate of oxygen consumption

for the subject being simulated and will be relevant for simulations reported in the next section. The *baseGlucoseLevel_* and *highGlucoseLevel_* parameters were set to the base and peak BGL values reported in [51] (see Tables 5 and 6). Similarly, the *baseInsulinLevel_* and *peakInsulinLevel_* parameters were set according to the base and peak plasma insulin levels reported in [51]. Each simulation ran for 18 hours of simulated time: from 12am in midnight till 6pm in the next evening with one meal (consisting of 84 g of glucose, 10 g of fat and 26 g of protein) intake event happening at 10am. There were no other events during the simulated time and the simulated subject was already in the post-absorptive state when the simulation started at 12am.

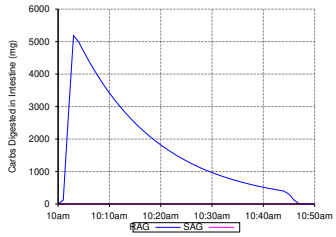
Table 4. Simulation parameters

	Normal	Type 2 Diabetic
age_ (years)	49	53
gender_	0 (male)	0 (male)
fitnessLevel_ (%ile)	50	50
bodyWeight (kg)	89	93
baseGlucoseLevel_ (mg/dl)	85	210
highGlucoseLevel_ (mg/dl)	145	360
baseInsulinLevel_	0	0
peakInsulinLevel_	1.0	0.5
glut4Impact_	1.0	0.5
gngImpact_	1.0	1.46
glycolysisMinImpact_	1.0	6.0
glycolysisMaxImpact_	1.0	0.9
excretionKidneysImpact_	1.0	1.40
liverGlycogenBreakdownImpact_	1.0	1.27
liverGlycogenSynthesisImpact_	1.0	0.8
maxLiverGlycogenBreakdownDuringExerciseImpact_	1.0	0.5
maxGlucoseAbsorptionInMusclesDuringExerciseImpact_	1.0	1.0
insulinImpactGlycogenSynthesisInLiver_Mean	0.9	0.3
insulinImpactOnGlycolysis_Mean	0.8	0.45
insulinImpactOnGlycolysis_StdDev	0.2	0.05

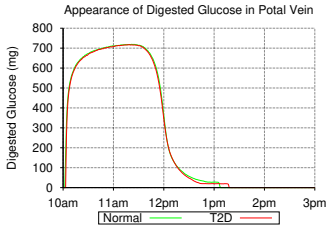
Fig 1 shows the minute-by-minute values of interest in two simulations with a particular seed value (for random number generation): one for the normal subject and the other for the T2D subject. Fig 1a shows that the gastric emptying is complete within 45 minutes of meal intake. The fat contents of the meal was responsible for some of the delay in gastric emptying. Fig 1b shows the rapid digestion of glucose as it arrives in the *Intestine* and Fig 1c shows the appearance of digested glucose in the *PortalVein* as described in Section IV-D. Fig 1d shows the change in BGL throughout the post-prandial phase starting from the post-absorptive levels before 10am.



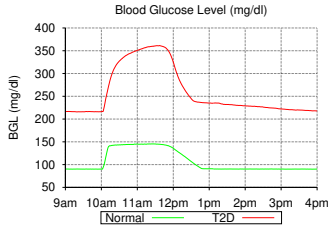
(a) Gastric Emptying (mg/minute)



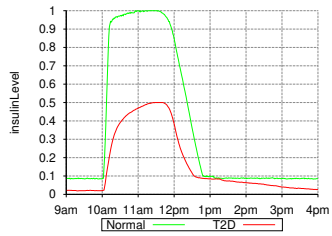
(b) Carbohydrate Digestion in Intestine (mg/minute)



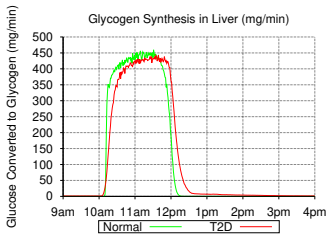
(c) Digested Glucose From Intestine to PortalVein (mg/minute)



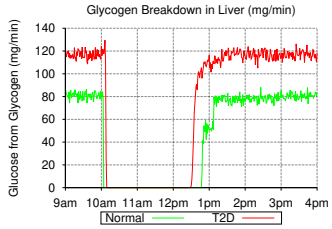
(d) Blood Glucose Level (mg/dl)



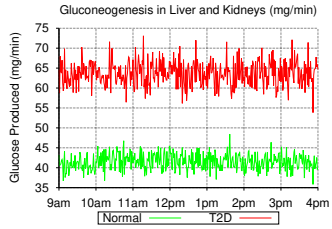
(e) Insulin Level



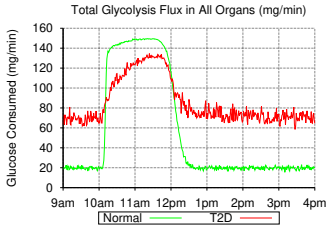
(f) Liver Glycogen Synthesis



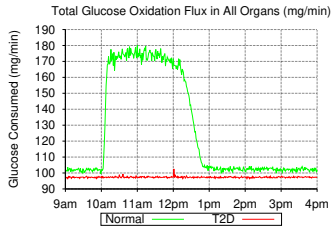
(g) Liver Glycogen Breakdown



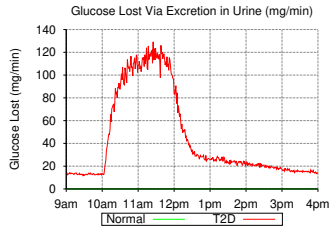
(h) Gluconeogenesis



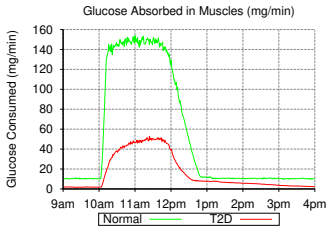
(i) Glycolysis



(j) Glucose Oxidation



(k) Glucose Excretion in Urine



(l) Glucose Absorption in Muscles

Fig 1. Simulating a Meal Event for a Normal and a Subject with Type 2 Diabetes (T2D): Minute-by-minute Values Of Interest In Simulations With a Particular Seed for Random Number Generation.

Post-Absorptive Phase: During the post-absorptive phase (before 10am), the *insulinLevel* (Fig 1e) is low enough to ensure that the glucose production via glycogen breakdown in the *Liver* (Fig 1g) takes place at the peak level, there is no glycogen synthesis in the Liver (Fig 1f) and glucose consumption via oxidation (Fig 1j) & glycolysis (Fig 1i) in various organs is at their minimum levels. Gluconeogenesis

(Fig 1h) takes place in the *Liver* and the *Kidneys*, unaffected by the *insulinLevel* (as reported in [51]), at the configured rates specified in [51] and provides the second source of glucose during the post-absorptive phase. While the minimum glucose oxidation flux is largely determined by the needs of the *Brain* and *Heart*, the configured values for the minimum glycolysis flux are chosen so that total glucose consumption during the post-absorptive phase matches the glucose production during this phase. Another constraint is to make sure that the minimum glycolysis flux is large enough to produce sufficient lactate to allow gluconeogenesis to take place at its configured rate. Accordingly, the *glycolysisMinImpact_* parameter was set to value 6.0 in simulations for the T2D subject and hence the glycolysis flux for the T2D subject during the post-absorptive phase is much higher than that for the normal subject (Fig 1i). Thus, during the post-absorptive phase, total glucose production (glycogen breakdown + gluconeogenesis) is matched closely by the total glucose consumption (oxidation + glycolysis + excretion in urine) and the BGL stabilizes to a value near the *baseGlucoseLevel_*. Since the glycogen breakdown in *Liver* is configured to rapidly slow down with increase in the *insulinLevel*, any temporary mismatch between glucose production and consumption is quickly corrected.

Post-Prandial Phase: The post-prandial phase in these simulations begins with the meal intake at 10am. The BGL begins to rise (as shown in Fig 1d) with the arrival of the digested glucose in the *PortalVein*. Increase in the BGL causes the *insulinLevel* to increase (Fig 1e) which rapidly brings glycogen breakdown in the *Liver* to a halt (Fig 1g). However, the influx of digested glucose ($\approx$ 700 mg/minute at peak) is more than sufficient to compensate for the halt in glycogen breakdown (peak value $\approx$ 120 and 80 mg/minute for T2D and normal subjects respectively) and the BGL (and hence the *insulinLevel*) continues to rise. Glucose production via gluconeogenesis (Fig 1h) continues as before unaffected by the increase in the *insulinLevel* (as reported in [51]). In the simulation for the normal subject, increase in the *insulinLevel* causes a proportional increase in the GLUT4 activation and hence in the glucose absorption by *Muscles* (Fig 1l). The glucose absorbed by the *Muscles* is consumed via glycolysis and oxidation. Since the glycogen stores in the *Muscles* are already full, none of the absorbed glucose is stored as glycogen in the *Muscles*. Increased oxidation flux seen in Fig 1j between 10am and 1pm in the normal subject is mainly due to the increased

glucose oxidation in the *Muscles*. Impaired GLUT4 activation in the T2D subject (caused by *glut4Impact_* value 0.5) means that the diabetic *Muscles* are not able to absorb as much glucose as the normal *Muscles* (Fig 1l). Also, almost all of the glucose absorbed by the diabetic *Muscles* is consumed via glycolysis (since the oxidation flux shown in Fig 1j does not show any rise in the post-prandial phase for the T2D subject). This is because of the much higher value of the minimum glycolysis flux in the T2D subject than for the normal subject (caused by the *glycolysisMinImpact_* parameter having value 6.0 for the T2D subject and 1.0 for the normal subject). Increase in the *insulinLevel* causes glycolysis flux to increase in other organs too (Fig 1i). The peak glycolysis flux for the T2D subject is configured to be little less than that for the normal subject (by setting *glycolysisMaxImpact_* to 0.9 for the T2D subject) so as to achieve a close match with reported results in [51] for the total glycolysis flux between 10am and 4pm (see Table 6). As the BGL approaches the *highGlucoseLevel_* (and *insulinLevel* approaches the *peakInsulinLevel_*), glycogen synthesis in the *Liver* starts and quickly ramps up to its peak level (see Fig 1f) thereby significantly slowing down any further increase in BGL. For the T2D subject, a significant amount of glucose is also lost via excretion in urine (see Fig 1k). Thus, BGL stays around the *highGlucoseLevel_* as long as the digested glucose is appearing in the *PortalVein* at the peak rate. As the digested glucose appearance in the *PortalVein* slows down, the BGL begins to drop and the glycogen synthesis in the *Liver* quickly comes to a halt thereby slowing down the rate at which the BGL falls. Decrease in BGL also causes decrease in the glycolysis flux, the glucose absorption by the *Muscles* and the glucose excretion in the urine, which further slows down the rate of BGL decrease. As BGL approaches the *baseGlucoseLevel_*, the glycogen breakdown in the *Liver* quickly ramps up to prevent any further decrease in the BGL and another post-absorptive phase begins.

Comparison with Measurements from Woerle et al. [51]: Tables 5 and 6 show the key measurements from [51] for normal and T2D subjects respectively along with the corresponding results from the simulations. The simulations were configured to use the post-absorptive (peak) glycogen breakdown and gluconeogenesis flux values reported in [51]. With appropriate settings for other configurable parameters (Table 4), the post-absorptive BGLs in the simulations were close to the values reported in [51] for both normal and T2D subjects. The simulations were configured to ensure that the

insulinLevel does not have any impact on gluconeogenesis flux (as reported in [51]). Accordingly, the gluconeogenesis flux in simulations 90 minutes after the breakfast was same as that before the breakfast matching the numbers reported in [51]. The glycogen breakdown 90 minutes after the breakfast was still substantial in [51] but had completely halted in the simulations. Overall, the peak post-prandial BGLs in simulations matched the ones reported in [51]. Total glucose produced/consumed along various pathways in the simulations for the normal subject during 6 hours after the breakfast was similar to values reported in [51]. The only exception was glycogen breakdown. It is clear from Fig 1 that the post-prandial phase in simulations was over by 1pm and hence glycogen breakdown happened at the peak level between 1pm and 4pm (Fig 1g). Apparently, this was not the case during measurements reported in [51] and the average glycogen breakdown flux during 6 hours after the breakfast was quite low. This combined with the fact that the glycogen breakdown was still substantial 90 minutes after the breakfast (when insulin levels were at their peak) means that glycogen breakdown process is relatively slow in reacting to the insulin levels. We observed a similar mismatch between the simulation results for the T2D subject and the values reported in [51] for total glycogen breakdown during 6 hours after the breakfast. Also, for the T2D subjects, [51] reported somewhat higher total gluconeogenesis flux during 6 hours after the breakfast (26.9 ± 2.2 g) than what we observed in the simulations (22.894 ± 0.011 g). Since gluconeogenesis flux in the simulation had same values during both post-prandial and post-absorptive phase, higher total flux reported in [51] means that gluconeogenesis flux actually increased during the post-prandial phase (perhaps due to higher availability of gluconeogenesis substrates). The simulator currently does not support increase in gluconeogenesis flux due to increased availability of substrates. Other results for T2D subjects in [51] were quite similar to what we observed in the simulations. Overall, it can be said that the simulation results closely matched those reported in [51] for both normal and T2D subjects.

6 Validation of *CarbMetSim* for Exercise Events

Carbohydrate metabolism during and after an exercise event has been extensively studied for both normal and diabetic subjects [44, 47, 69–72]. As described in Section

Table 5. Normal Subjects: Key Measurements From Woerle Et Al. [51] and Corresponding Results From 30 Simulations with Different Seeds.

	Woerle et al. [51]	Simulations
	Before Breakfast	
BGL	4.7 ± 0.1 mM (84.6 ± 1.8 mg/dl)	90.14 ± 0.01 mg/dl
Glycogen Breakdown	$5.5 \pm 0.6\mu$mol/kg/min (88.1 ± 9.6 mg/min)	81.34 ± 0.43 mg/min
Gluconeogenesis	$2.6 \pm 0.2\mu$mol/kg/min (41.6 ± 3.2 mg/min)	40.29 ± 0.32 mg/min
	90 Minutes After Breakfast	
Plasma Insulin	290 ± 29 pM	1
Glycogen Breakdown	$1.3 \pm 0.6\mu$mol/kg/min (20.8 ± 9.6 mg/min)	0 mg/min
Gluconeogenesis	$2.6 \pm 0.2\mu$mol/kg/min (41.6 ± 3.2 mg/min)	41.40 ± 0.42 mg/min
Peak Post-prandial BGL	8 mM (144 mg/dl)	145.54 ± 0.04 mg/dl
	Total Glucose Consumed/Produced During 6 Hours After The Breakfast	
Gluconeogenesis	15.3 ± 1.2 g	15.004 ± 0.007 g
Glycogen Breakdown	4.3 ± 1.7 g	14.802 ± 0.006 g
Glucose Excretion in Urine	0.7 ± 0.4 g	0 g
Oxidation	45.6 ± 2.6 g	46.977 ± 0.007 g
Glycolysis	21.5 ± 2.2 g	21.851 ± 0.004 g
Glycogen Storage	40.6 ± 3.6 g	44.974 ± 0.008 g

Before Breakfast Simulation Results Were Observed at 9.59AM. All Values Expressed as *Mean ± Std Error*.

Table 6. Subjects with Type 2 Diabetes: Key Measurements From Woerle Et Al. [51] and Corresponding Results From 30 Simulations with Different Seeds.

	Woerle et al. [51]	Simulations
	Before Breakfast	
BGL	11.7 ± 0.6 mM (210.6 ± 10.8 mg/dl)	216.51 ± 0.12 mg/dl
Glycogen Breakdown	$7.0 \pm 0.4\mu$mol/kg/min (117.2 ± 6.7 mg/min)	115.67 ± 0.61 mg/min
Gluconeogenesis	$3.8 \pm 0.3\mu$mol/kg/min (63.6 ± 5 mg/min)	63.21 ± 0.53 mg/min
	90 Minutes After Breakfast	
Plasma Insulin	179 ± 19 pM	0.5
Glycogen Breakdown	$3.8 \pm 0.7\mu$mol/kg/min (63.6 ± 11.7 mg/min)	0 mg/min
Gluconeogenesis	$3.8 \pm 0.3\mu$mol/kg/min (63.6 ± 5 mg/min)	62.73 ± 0.45 mg/min
Peak Post-prandial BGL	20 mM (360 mg/dl)	361.11 ± 0.10 mg/dl
	Total Glucose Consumed/Produced During 6 Hours After The Breakfast	
Gluconeogenesis	26.9 ± 2.2 g	22.894 ± 0.011 g
Glycogen Breakdown	10.1 ± 1.2 g	24.437 ± 0.012 g
Glucose Excretion in Urine	17.4 ± 2.7 g	17.722 ± 0.011 g
Oxidation	32.8 ± 2.8 g	35.059 ± 0.002 g
Glycolysis	28.7 ± 2.2 g	31.637 ± 0.012 g
Glycogen Storage	46.3 ± 3.3 g	46.802 ± 0.009 g

Before Breakfast Simulation Results Were Observed at 9.59AM. All Values Expressed as *Mean ± Std Error*.

4.8, glucose oxidation plays a major role in meeting energy needs during physical exercise. The exercising muscles get the glucose they need by breaking down locally stored glycogen and by absorbing glucose from the bloodstream. The glucose absorption from the bloodstream does not depend on the insulin levels since the physical exercise itself is sufficient to activate GLUT4 transporters [42–44].

In case of normal people, physical exercise inhibits insulin secretion [65, 73–76] and promotes secretion of other hormones such as glucogon [65, 75–77]. These changes allow the liver to break sufficient glycogen to meet the increased glucose needs. So, as long as

glycogen is available in the liver and in the exercising muscles, the glucose production via glycogenolysis (in the liver and the exercising muscles) and gluconeogenesis (in the liver and kidneys) generally matches the glucose consumption by exercising muscles (and other organs) and the blood glucose level stays in the normal range [44, 47]. The blood glucose level will drop once the glycogen stores have been exhausted and gluconeogenesis alone is not sufficient to match the glucose consumption by the exercising muscles. In case of people with Type 2 Diabetes or insulin-treated Type 1 Diabetes, physical exercise fails to sufficiently reduce insulin level in the blood and as a result the glycogen breakdown in the liver may not be sufficient to meet the additional glucose needs [78]. Thus, the blood glucose level may drop significantly during physical exercise. Finally, people with Type 1 Diabetes with too little insulin in their system may experience an increase in BGL (which was already high before the exercise) when they indulge in physical exercise. This may happen because the secretion of glucagon and other hormones during exercise increases glucose production via glycogen breakdown in the liver to a rate much higher than the impaired rate at which the exercising muscles absorb glucose in some people with Type 1 Diabetes [44–47].

In order to demonstrate *CarbMetSim*'s ability to simulate the impact of aerobic physical exercise, we performed three sets of simulations each involving a subject doing aerobic physical exercise for 1 hour at different intensity levels (3, 5, 7 and 9 *MET*s). The first set simulated a normal subject and the second set simulated a subject with Type 2 Diabetes (T2D). The simulation parameters defining these two subjects are shown in Table 4 (under the headings *Normal* and *Type 2 Diabetic* respectively). The meal event response simulations reported in the previous section were performed on the same subjects. The *age_*, *gender_* and *fitnessLevel_* parameters (that were not used in the meal response simulations) were used to determine the maximal rate of glucose consumption (VO_2max) for these subjects [54] and translate the exercise intensities from *MET*s to $\%VO_2max$ (see Table 7). The T2D subject had 0.5 as the value for *maxLiverGlycogenBreakdownDuringExerciseImpact_* parameter. Thus, for the T2D subject, the upper limit on the rate of liver glycogen breakdown during exercise was half the value for the normal subject. The third set simulated a subject with Type 1 Diabetes (T1D) with no insulin in circulation and impaired muscle glucose absorption during exercise. This subject had same values for most of the configurable parameters

as the T2D subject. In particular, the (VO_2max) value (and hence the values in terms of $\%VO_2max$ for different exercise intensities) was same for both T1D and T2D subjects we simulated. These two subjects differ in terms of the following parameters:

- *peakInsulinLevel_*: This parameter had values 0 and 0.5 respectively for T1D and T2D subjects. In other words, the T1D subject was not capable of producing any insulin at all.

- *maxLiverGlycogenBreakdownDuringExerciseImpact_*: This parameter had values 1 and 0.5 respectively for T1D and T2D subjects. So, the T1D subject had same capacity to break liver glycogen during exercise as the normal subject but the T2D subject had only half this capacity.

- *maxGlucoseAbsorptionInMusclesDuringExerciseImpact_*: The T2D subject had value 1 for this parameter and hence had the same muscle glucose absorption capacity during exercise as the normal subject. The T1D subject had value 0.5 for this parameter and hence his muscle glucose absorption capacity during exercise was only half of that of the normal subject.

Simulations involving a particular subject doing exercise at a particular intensity were repeated 30 times with different seed values for random number generation. Each simulation ran for 12 hours of simulated time: from 12am in midnight till 12pm in the next afternoon with one exercise event taking place from 10am to 11am. There were no other events during this time and the simulated subject was already in the post-absorptive state at 12am when the simulation started.

Table 7. The Maximal Rate of Glucose Consumption (VO_2max) and Exercise Intensity in $\%VO_2max$ for Simulated Subjects

	VO_2max ml/kg/min	Max Possible Intensity	**Exercise Intensity (in $\%VO_2max$)**			
			3 METs	5 METs	7 METs	9 METs
Normal	37.8	10.8 METs	27.78 %	46.30 %	64.81 %	83.33 %
T1D/T2D	32.6	9.3 METs	32.21 %	53.68 %	75.15 %	96.63 %

Table 8 shows the mean and standard deviation (calculated for 30 simulations performed with different seed values) for the BGL of the normal subject at specific time instants during exercise at different intensity levels. It is clear from these numbers that the simulated normal subject was able to maintain glucose homeostatis throughout the one hour exercise duration for all intensity levels. Fig 2 shows the minute-by-minute

values of interest in normal subject simulations with a particular seed value. Fig 2a confirms that the BGL value hovered around the *baseGlucoseLevel_* throughout the exercise duration at all intensity levels. As shown in Fig 2b, the glycogen breakdown in the *Liver* increased in proportion to the exercise intensity to meet the elevated glucose demands on the *Muscles* during exercise. The configured upper limit on glucose production via liver glycogen breakdown during exercise was 30μ mol/kg/min, which, for a body weight of 89 kg, translates to about 481 mg/min. It is clear from Fig 2b that this limit was not reached for the simulated exercise intensities and the *Liver* was able to break sufficient glycogen to maintain glucose homeostasis during exercise. Fig 2c shows the dwindling glycogen storage in the *Liver* before, during and after the exercise. As shown in Fig 2f, gluconeogenesis flux in the *Liver* and *Kidneys* was not impacted by the exercise or its intensity. As currently implemented, *Muscles* meet about 10% of their energy needs by oxidizing glucose absorbed from the *Blood*. For a person with body weight 89 kg, the exercise intensities 3, 5, 7 and 9 *MET*s translate to energy needs of 4.45, 7.42, 10.38 and 13.35 kcal/min respectively. Considering that oxidation of 1 g of glucose generates 4 kcal of energy, the *Muscles* would need to absorb on average 111.25, 185.41, 259.58 and 333.75 mg of glucose every minute from the *Blood* in order to meet 10% of the energy needs during exercise at intensities 3, 5, 7 and 9 *MET*s respectively. As shown in Fig 2e, this is indeed what seems to be happening in the simulations. Fig 2d shows the glycogen breakdown in the *Muscles* to meet a fraction of the energy needs. As discussed earlier in Section 4.8, the fraction of energy needs met via oxidation of glucose derived from the glycogen stored locally in the *Muscles* increases with exercise intensity. Exercise at intensity 3 *MET*s was merely $27.78\% VO_2max$ for the normal subject (Table 7). The average glycogen breakdown in the *Muscles* during this exercise was about 130 mg/min, which provided enough glucose to meet just about 11.7% of the energy needs. On the other hand, exercise at intensity 9 *MET*s was $83.33\% VO_2max$ for the normal subject (Table 7) and the average glycogen breakdown in the *Muscles* during this exercise was about 2849 mg/min, which provided enough glucose to meet about 85.4% of the energy needs. This is in accordance with expectation.

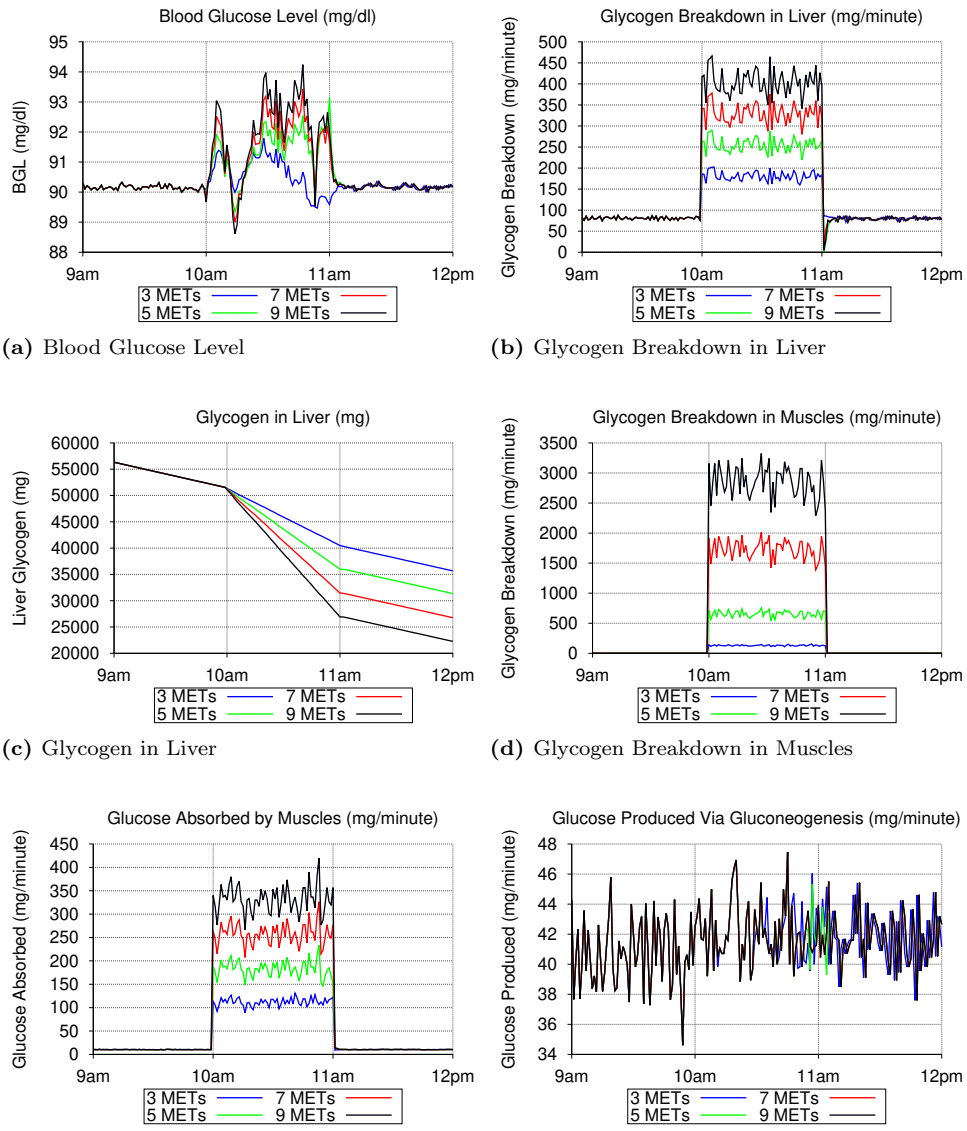
Table 9 shows the mean and standard deviation (calculated for 30 simulations performed with different seed values) for the BGL of the T2D subject at specific time instants during exercise at different intensity levels. These numbers show that, for this

Table 8. Simulating a Normal Subject Doing Exercise: Blood Glucose Levels At Specific Moments During Exercise.

	Time Since the Beginning of Exercise		
Exercise Intensity	15 minutes	30 minutes	59 minutes
3 METs	89.94 ± 0.81 mg/dl	89.99 ± 1.05 mg/dl	90.42 ± 1.77 mg/dl
5 METs	89.82 ± 1.59 mg/dl	90.02 ± 2.11 mg/dl	90.43 ± 3.40 mg/dl
7 METs	89.69 ± 2.18 mg/dl	89.96 ± 2.79 mg/dl	90.35 ± 4.01 mg/dl
9 METs	89.39 ± 2.80 mg/dl	89.73 ± 3.58 mg/dl	89.85 ± 5.29 mg/dl

30 Simulations Were Performed For Each Intensity Level Using Different Seeds. The Results Expressed as *Mean* ± *Std Deviation*.

subject, the BGL dropped with time during the physical exercise at intensities higher than 3 *MET*s. These numbers also show that the drop in BGL was proprotional to the exercise intensity for a given exercise duration. In fact, it was not possible for the subject to finish one hour of exercise at intensity 9 *MET*s. After about 51 minutes of exercise at intensity 9 *MET*s, the T2D subject's BGL dropped below 40 mg/dl level, which is considered a fatally low BGL and caused the simulation to terminate. These results can be explained by the fact that the T2D subject had a lower limit on the rate of liver glycogen breakdown during exercise than the normal subject. Hence, the T2D subject's liver was not able to break sufficient glucose to meet the muscles needs during exercise at intensities higher than 3 *MET*s and hence the BGL fell with time during exercise at these intensities. Fig 3 shows the minute-by-minute values of interest in the T2D subject simulations with a particular seed value. Fig 3a confirms the drop in BGL with time during exercise. In T2D subject simulations, the limit on the glucose production via glycogen breakdown in the *Liver* during exercise was 15μ mol/kg/min, which, for a body weight of 93 kg, translates to about 251 mg/min. Fig 3b shows that the glycogen breakdown in the *Liver* during exercise was capped at this value for exercise intensities greater than 3 *MET*s. As shown in Fig 3f, about 63 mg/min of glucose was produced via gluconeogenesis in the *Liver* and *Kidneys* unimpacted by the exercise duration or its intensity. As mentioned before, *Muscles* meet about 10% of their energy needs by oxidizing glucose absorbed from the *Blood*. For a person with body weight 93 kg, the exercise intensities 3, 5, 7 and 9 *MET*s translate to energy needs of 4.65, 7.75, 10.85 and 13.95 kcal/min respectively. Considering that oxidation of 1 g of glucose generates 4 kcal of energy, the *Muscles* would need to absorb on average 116.25, 193.75, 271.25 and 348.75 mg of glucose every minute from the *Blood* in order to meet



(a) Blood Glucose Level

(b) Glycogen Breakdown in Liver

(c) Glycogen in Liver

(d) Glycogen Breakdown in Muscles

(e) Glucose Absorption in Muscles

(f) Gluconeogenesis in Liver and Kidneys

Fig 2. Simulating a Normal Subject Doing Exercise At Different Intensity Levels: Minute-by-minute Values Of Interest In Simulations With a Particular Seed for Random Number Generation.

10% of the energy needs during exercise at intensities 3, 5, 7 and 9 *MET*s respectively. Fig 3e shows glucose absorption by *Muscles* taking place at these levels in the simulations. If the glucose requirements of other organs (e.g. the *Brain* and the *Heart* absorb on average 83.33 and 14 mg/min of glucose respectively from the *Blood*) are added to this, it is clear that the glucose production via liver glycogen breakdown and gluconeogenesis did not meet the glucose needs of various organs and hence the BGL

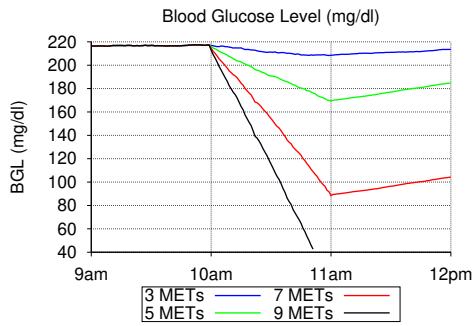
fell during exercise.

Table 9. Simulating a Subject With Type 2 Diabetes Doing Exercise: Blood Glucose Levels At Specific Moments During Exercise.

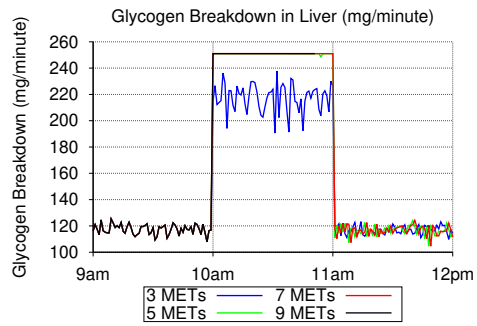
	Time Since the Beginning of Exercise		
Exercise Intensity	15 minutes	30 minutes	59 minutes
3 METs	213.09 ± 1.10 mg/dl	210.60 ± 1.02 mg/dl	206.64 ± 1.14 mg/dl
5 METs	202.77 ± 1.30 mg/dl	191.91 ± 1.78 mg/dl	170.80± 3.22 mg/dl
7 METs	183.54 ± 2.20 mg/dl	154.47 ± 3.45 mg/dl	97.05 ± 4.18 mg/dl
9 METs	163.76 ± 2.69 mg/dl	115.54 ± 4.05 mg/dl	

30 Simulations Were Performed For Each Intensity Level Using Different Seeds. The Results Expressed as *Mean* ± *Std Deviation*. Exercise At Intensity 9 METs Led to Simulation Termination (Due To BGL Falling Below 40 mg/dl) Before The *59 Minutes* Stage.

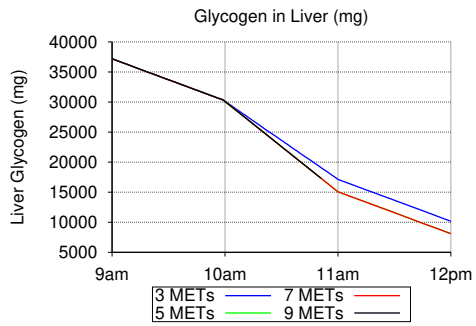
Table 10 shows the mean and standard deviation (calculated for 30 simulations performed with different seed values) for the BGL of the T1D subject (with impaired glucose absorption during exercise by the muscles) at specific time instants during exercise at different intensity levels. For exercise intensities 3 and 5 *MET*s, this subject was able to complete one hour of exercise without any significant change in his BGL. One hour of exercise at intensity 7 *MET*s caused a small increase in BGL. The subject's BGL increased significantly during one hour of exercise at intensity 9 *MET*s. The results for exercise at intensities 7 and 9 *MET*s were caused by the impaired glucose absorption during exercise by the subject's *Muscles*. Unlike the T2D subject simulated earlier, this T1D subject had a normal limit on the rate of glycogen breakdown in the *Liver* during exercise but the maximum rate at which his *Muscles* could absorb glucose during exercise was only half that of the normal/T2D subjects. Thus, the *Liver* ramped up the glycogen breakdown during exercise (actually caused by a decrease in insulin level and an increase in glucagon level) and released the glucose thus produced to the bloodstream but the *Muscles* were not able to absorb the glucose as they should have and hence the BGL increased. Fig 4 shows the minute-by-minute values of interest in the T1D subject simulations with a particular seed value. Fig 4a confirms the trends described above regarding the change in BGL during exercise at different intensity levels. It is also interesting to note that the BGL creeped back slowly to its pre-exercise level once the exercise is over. This happened for all exercise intensities except 9 *MET*s. As shown in Fig 4c, exercise at intensity 9 *MET*s left the glycogen store in the *Liver* completely exhausted soon after the completion of the exercise, which caused a steep



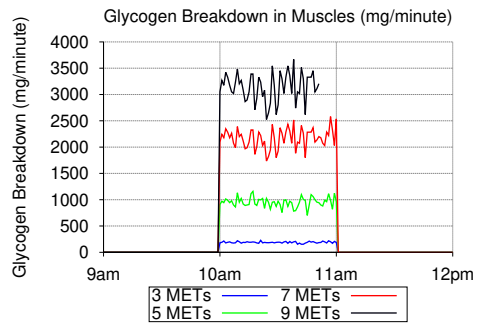
(a) Blood Glucose Level



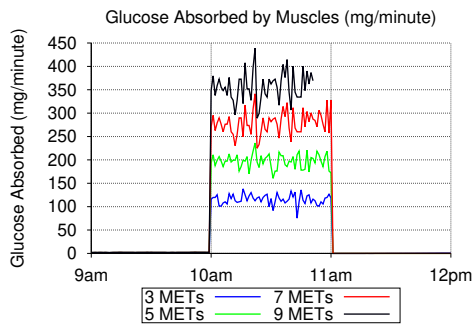
(b) Glycogen Breakdown in Liver



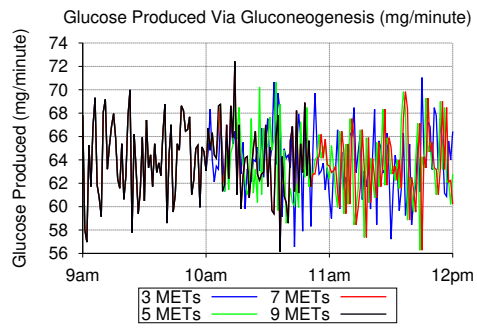
(c) Glycogen in Liver



(d) Glycogen Breakdown in Muscles



(e) Glucose Absorption in Muscles



(f) Gluconeogenesis in Liver and Kidneys

Fig 3. Simulating a Type 2 Diabetic Subject Doing Exercise At Different Intensity Levels: Minute-by-minute Values Of Interest In Simulations With a Particular Seed for Random Number Generation.

drop in the BGL as shown in Fig 4a. Since the T1D subject had normal liver glycogen breakdown during exercise, the *Liver* was able to ramp up the glycogen breakdown in proportion to exercise intensity (Fig 4b). Glycogen breakdown in the *Muscles* (Fig 4d) and gluconeogenesis in the *Liver* and the *Kidneys* (Fig 4f) happened in the expected manner. In the T1D subject simulations, the limit on the glucose absorption by *Muscles* during exercise was 15μ mol/kg/min, which, for a body weight of 93 kg, translates to

about 251 mg/min. Fig 4e shows that this limit restricted the glucose absorption by *Muscles* for exercise intensities 7 and 9 *MET*s, which caused BGL to creep up during exercise at these intensities. The increase in BGL was much more prominent for exercise at intensity 9 *MET*s because the glucose production via liver glycogen breakdown was much higher at this intensity than at 7 *MET*s (Fig 4b).

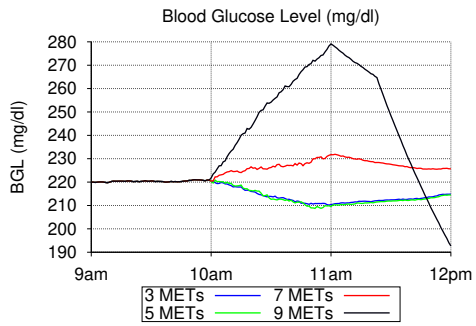
Table 10. Simulating a Subject With Type 1 Diabetes and Impaired Muscle Glucose Absorption Doing Exercise: Blood Glucose Levels At Specific Moments During Exercise.

	Time Since the Beginning of Exercise		
Exercise Intensity	15 minutes	30 minutes	59 minutes
3 METs	216.12 ± 1.17 mg/dl	213.18 ± 1.09 mg/dl	208.53 ± 1.17 mg/dl
5 METs	216.22 ± 1.85 mg/dl	212.96 ± 1.95 mg/dl	208.55± 2.75 mg/dl
7 METs	221.75 ± 1.78 mg/dl	222.84 ± 2.29 mg/dl	225.48 ± 2.62 mg/dl
9 METs	238.58 ± 1.81 mg/dl	253.55 ± 2.42 mg/dl	276.37 ± 2.89 mg/dl

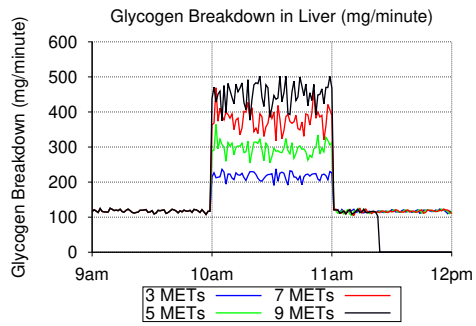
30 Simulations Were Performed For Each Intensity Level Using Different Seeds. The Results Expressed as *Mean* ± *Std Deviation*.

7 Conclusion

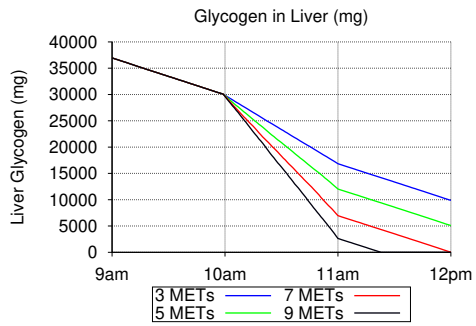
This paper described *CarbMetSim*, a discrete event simulator that models the carbohydrate metabolism in human beings and allows tracking of a user's BGL in response to a timed sequence of diet and exercise activities. The paper also validated *CarbMetSim*'s behavior in response to meal and exercise events and demonstrated its ability to simulate the metabolic behavior of both normal and diabetic subjects. Our future work on *CarbMetSim* will include expanding its functionality to correct some of its current limitations identified towards the end of Section 1 and building web/smartphone apps that will allow diabetes patients to use the simulator. *CarbMetSim* can also serve as the underlying engine for a variety of diabetes self management and education tools. With its open source nature and ease of modification/extension, *CarbMetSim* also has a good potential to emerge as a popular simulation framework for diabetes research.



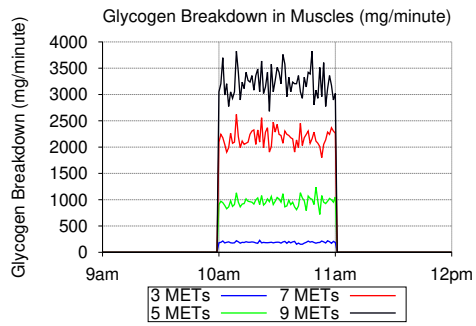
(a) Blood Glucose Level



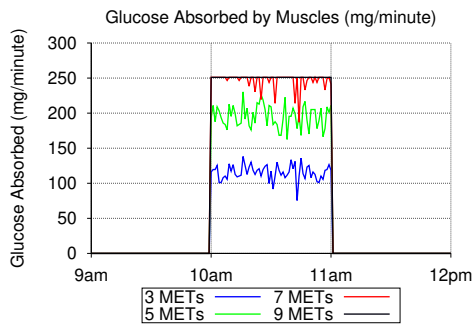
(b) Glycogen Breakdown in Liver



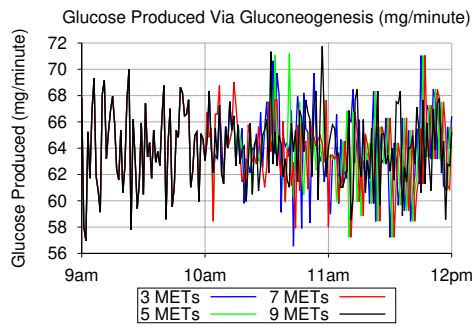
(c) Glycogen in Liver



(d) Glycogen Breakdown in Muscles



(e) Glucose Absorption in Muscles



(f) Gluconeogenesis in Liver and Kidneys

Fig 4. Simulating a Type 1 Diabetic Subject With Impaired Muscle Glucose Absorption Doing Exercise At Different Intensity Levels: Minute-by-minute Values Of Interest In Simulations With a Particular Seed for Random Number Generation.

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