A DISCRETE-EVENT SIMULATION APPROACH FOR MODELING HUMAN BODY GLUCOSE METABOLISM

by

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ABSTRACT

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Under the Supervision of Associate Professor Mukul Goyal

This document describes CarbMetSim (**Carb**ohydrate **Met**abolism **Sim**ulator), 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 by using the published values of the average flux along these pathways in the operation of different organs. CarbMetSim has the ability to model different levels of insulin resistance and insulin production ability. The impact of insulin and insulin resistance on the operation of various organs and pathways is captured in accordance with published research. The protein and lipid metabolism are implemented only to the extent that they affect carbohydrate metabolism.

To

my parents,

my spouse,

and especially my daughter and son

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Chapter 1

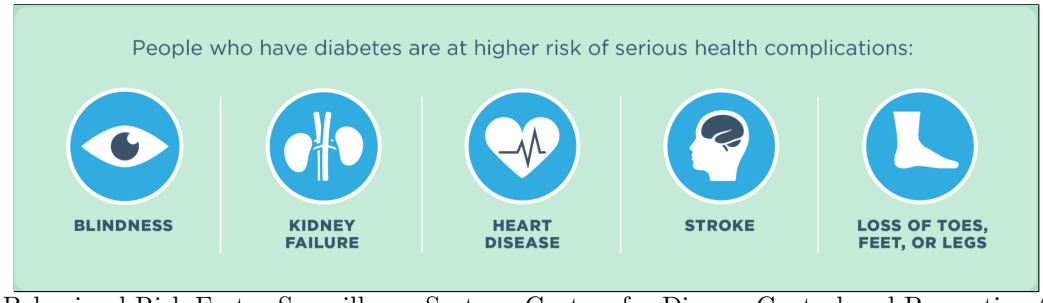
Problem Motivation & Research Objectives

1.1 Background Information

1.1.1 Types and Significance of Diabetes

Diabetes mellitus is a metabolic disorder. It is commonly referred as diabetes. The blood sugar levels are high over an extended period in diabetes. There are several symptoms of this disorder as a result of high blood sugar levels, which include increased thirst and frequent urination [1]. If not treated, diabetes can cause serious health complications such as cardiovascular disease, stroke, chronic kidney disease, foot amputation, and damage to the eyes [2] as presented in Figure 1.1.

Figure 1.1: Health Complications of Diabetes



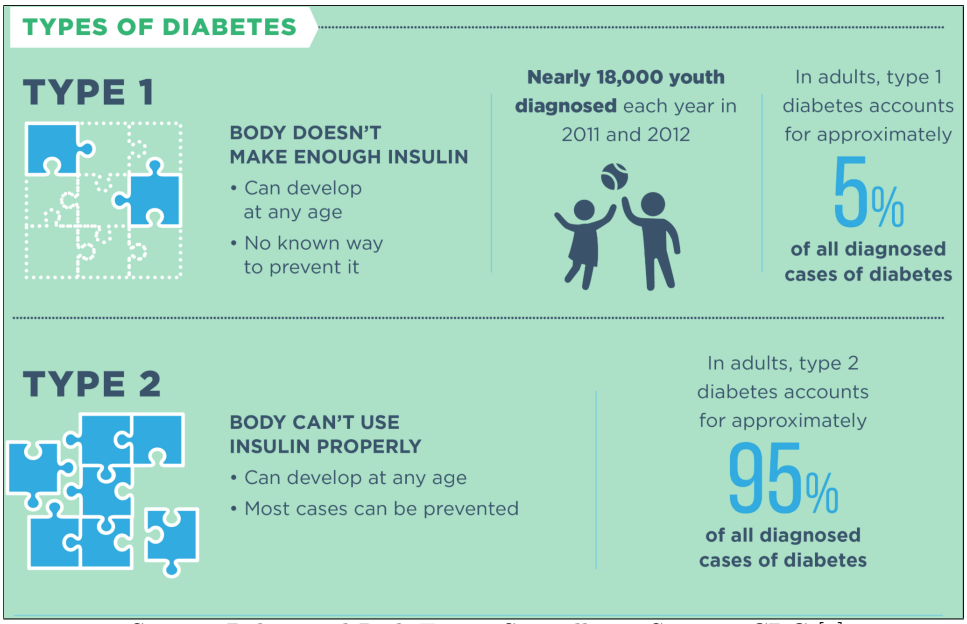
Source: Behavioral Risk Factor Surveillance System, Centers for Disease Control and Prevention (CDC) [2]

The disorder is the result of either not sufficient insulin production by pancreas or the body cells not responding properly to the insulin produced [1]. There are two main types of diabetes mellitus:

- Type 1 DM: In type 1 DM, the pancreas is not able to produce enough insulin. This form can also be referred as "insulin-dependent diabetes mellitus" (IDDM). It can develop at any age. There is not any known way to prevent this form. Nearly 18,000 youth were diagnosed as type 1 diabetes each year in 2011 and 2012 in the U.S. [2]. In adults, type 1 diabetes accounts for approximately 5% of all diagnosed cases of diabetes in the U.S. [2].
- Type 2 DM: In type 2 DM, body cells fail to respond to insulin properly, which is called insulin resistance [1]. As the disease progresses insufficient insulin production by pancreas may also develop [1]. This form can also be referred as "non insulin-dependent diabetes mellitus" (NIDDM). The most common cause is excessive body weight and not enough exercise [1]. It can develop at any age. Most cases can be prevented with an appropriate diet and exercise routine. In adults, type 1 diabetes accounts for approximately 95% of all diagnosed cases of diabetes in the U.S. [2].

Figure 1.2 presents the types of diabetes and their observed frequencies in the U.S.

Figure 1.2: Types of Diabetes and Observed Frequencies in the U.S.



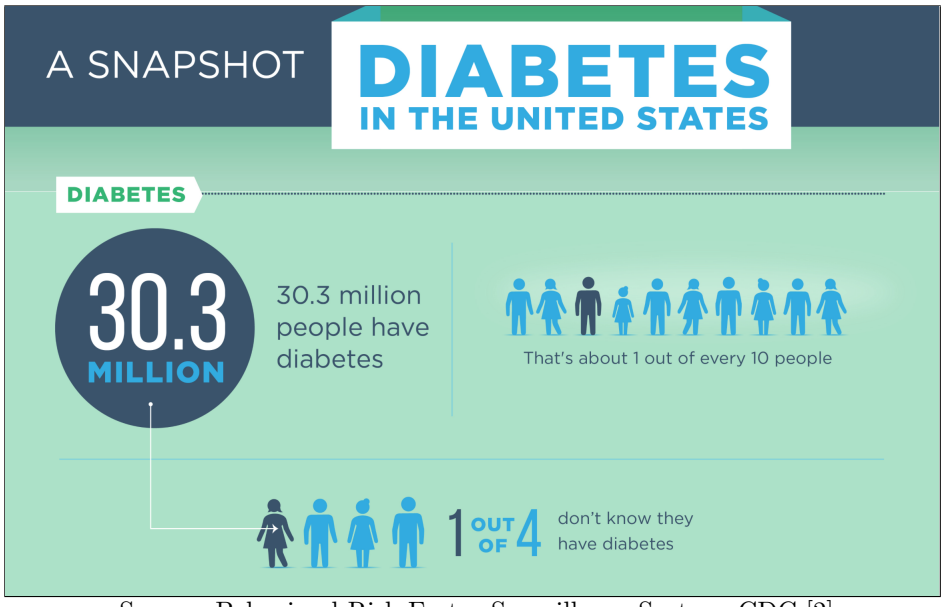
Source: Behavioral Risk Factor Surveillance System, CDC [2]

In 2016, 422 million people were diagnosed as diabetes worldwide, in which in 2013 this number was 382 million, and it was 108 million in 1980 [1]. About 90% of the cases are type 2. 1.5 million deaths in 2012

were resulted from diabetes in the records of World Health Organization (WHO), making it the 8th leading cause of death [1]. On the other hand, another 2.2 million deaths worldwide were attributable to the complications of diabetes (cardiovascular disease, kidney failure, etc.) are often listed as the cause of death rather than diabetes [2]. International Diabetes Federation estimates 8.3% of the global population has diabetes, expected to rise to 9.9% by 2030 [2].

In the United States diabetes is the 7th leading cause of death and may be underreported [2]. Figure 1.3 provides a snapshot of diabetes in the U.S. In the last 20 years, the number of adults diagnosed with diabetes has more than tripled as the American population has aged and become more overweight or obese. Figure 1.4 presents % of U.S. adults who were obese or diagnosed diabetes in 2015 [2]. The patterns of obesity and diabetes suggest a high correlation at alarmingly high levels.

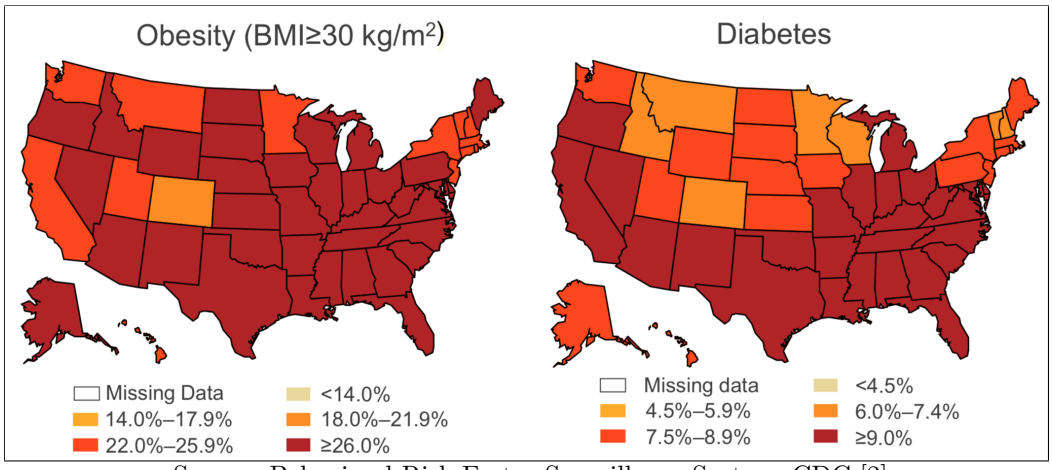
Figure 1.3: A Snapshot of Diabetes in the U.S.



Source: Behavioral Risk Factor Surveillance System, CDC [2]

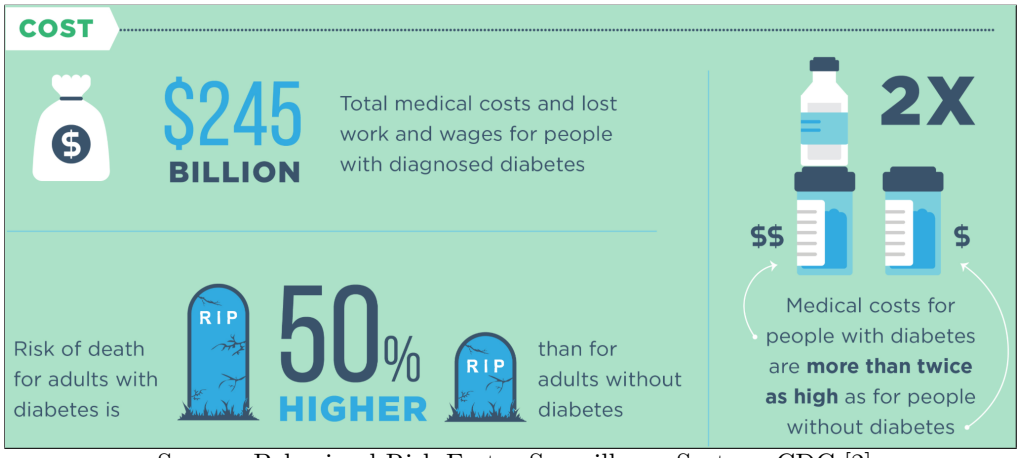
The direct medical costs of diabetes in USA was $176 billion in 2012 with an extra $69 billion cost attributed to disability [2]. Figure 1.5 presents the CDC's estimated cost figures of diabetes in the U.S.

Figure 1.4: % of U.S. adults who were obese or diagnosed diabetes - 2015



Source: Behavioral Risk Factor Surveillance System, CDC [2]

Figure 1.5: Cost of Diabetes in the U.S.



Source: Behavioral Risk Factor Surveillance System, CDC [2]

1.1.2 Physiology of Diabetes

The body obtains glucose from three main sources [3]:

- Intestinal absorption of food
- Breakdown of glycogen, the storage form of glucose in the liver
- Gluconeogenesis (GNG), the generation of glucose from non-carbohydrate substrates (i.e. lactate, amino acids)

Glucose leaves the blood by uptake into tissues for their energy needs. The concentration remains relatively

constant, at close to 90 mg/dl in humans for providing a constant source of energy to the tissues [1]. Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, adipose tissue and muscle [1]. Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen. Table 1.1 presents frequently used physiological terms in diabetes literature.

Physiological Terms	**Explanation**
Metabolic Pathway	Series of chemical reactions occurring in a cell
Metabolic Flux	Turnover rate of molecules through a metabolic pathway
Lactate	Blood substrate that is produced as an end product of glycolysis and can be converted back to glucose when needed
Glycolysis	Oxygen independent metabolic pathway that converts glucose into lactate
Glucose Oxidation	Oxygen dependent pathway that converts glucose into CO_2 and H_2O, produces more energy than glycolysis
Glycogen	Storage form of glucose
Gluconeogenesis (GNG)	Generation of glucose from non-carbohydrate substrates (i.e. lactate, amino acids, fatty acids)
Glycated Hemoglobin (HbA1C)	Average level of blood glucose over the past 2 to 3 months

Table 1.1: Frequently Used Physiological Terms

Insulin is released into the blood by beta cells (β-cells) in the pancreas, in response to increasing levels of blood glucose. Insulin is used by most of the body cells (muscles, adipose tissue, heart, etc.) to absorb glucose from the blood for use as an energy source or for storage [1]. Lower glucose levels result in decreased insulin release from the beta cells and this will cause to the increased breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin. If the amount of insulin available is insufficient, or if cells not responding to the insulin properly (insulin resistance) then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose. When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine [1]. This inhibits reabsorption of water by the kidney, resulting in increased urine production and increased fluid loss [1].

1.1.3 Treatment Methods & Self Management

There is no known prevention for type 1 diabetes. A number of lifestyle factors are known to be important to the development of Type 2 DM:

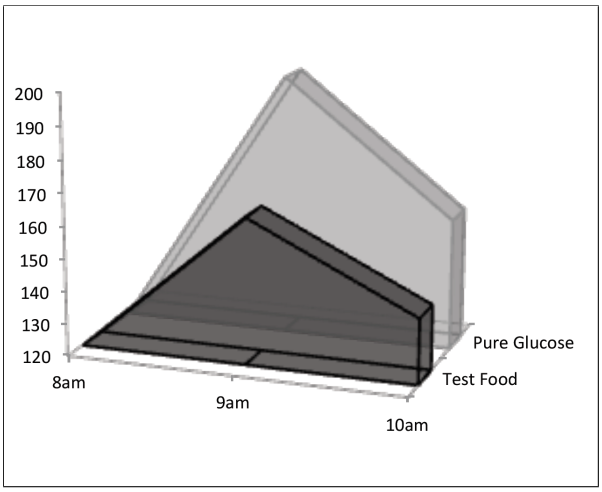
- Obesity (defined by a body mass index of greater than 30),
- Lack of physical activity,
- Poor diet, stress and urbanization.

Type 2 diabetes can often be prevented or delayed by maintaining a normal body weight, engaging in physical activity, and consuming a healthy diet [2]. Management concentrates on keeping BGL as close to normal via healthy diet, exercise, weight loss and medications (insulin infusion for Type 1, oral medications for Type 2). Learning about the disease and actively participating in the treatment is important, since complications are less common and less severe in people who have well-managed blood sugar levels [2].

Higher levels of physical activity (more than 90 minutes per day) reduce the risk of diabetes by 28% [4]. Dietary changes known to be effective in helping to prevent diabetes include maintaining a diet rich in whole grains and fiber, and choosing good fats, such as unsaturated fats found in nuts, vegetable oils, and fish [2]. Limiting carbohydrate rich meals and sources of saturated fat can also help to prevent diabetes [2].

Glycemic Index (GI) is an index that ranks carbohydrates based on their rate of glycemic response (i.e. conversion to glucose within the body) [5]. GI measures the effects of carbohydrates on blood glucose levels. Since sugars and starches are the foods that raise blood glucose levels, carbohydrates are responsible for most of the changes in blood glucose levels. This concept was developed to find out which foods were best for people with diabetes [5]. The glycemic index of a food, as presented in Figure 1.6, is defined as the ratio of: (1) Area under the 2-hour BG curve after eating 50g of carbs of food, and (2) Area under the 2-hour BG curve after eating 50g of carbs of pure glucose [5]. GI uses a scale of 0 to 100, with higher values given to foods that cause the most rapid rise in blood sugar. Pure glucose serves as a reference point, and is given a GI of 100. GI of a food is computed by averaging the area under the 2-hour BGL curve after eating 50g of carbs of food for 10 different test subjects [5]. Therefore, finding out the GI of a specific food is not easy and there are not any other methods to compute it. GI values can be interpreted intuitively as percentages on an absolute scale and are commonly classified as [5] in Table 1.2.

Figure 1.6: Glycemic Index Calculation



Group	GI Range	Sample Foods
No GI	0	meat, fish, eggs, cheese, oil
Low GI	1 - 55	milk, yogurt, apples, berries, broccoli, beans, nuts
Medium GI	56 - 69	mango, raisins, whole-wheat bread, brown rice
High GI	70 - 100	potatoes, watermelon, white bread, rice cereal

Table 1.2: Categories of the Glycemic Index

A low-GI food will release glucose more slowly and steadily, which leads to more suitable postprandial (after meal) blood glucose readings [5]. A high-GI food causes a more rapid rise in blood glucose level and is suitable for energy recovery after exercise or for a person experiencing hypoglycemia (low glucose level) [5]. Several recent studies have shown that individuals who followed a low-GI diet over many years were at a significantly lower risk for developing both type 2 diabetes and coronary heart disease than others [6, 7]. One of the limitations of the current Glycemic Index calculations is for finding the GI of a mixed meal. There are very basic calculation methods, but not proven the accuracy, yet.

1.2 Benefits of Effective Diabetes Management

Management of diabetes is comprised of complex medical decisions regarding goals of care, self-care behaviors, and medical treatments [2]. The main goal is to restore carbohydrate metabolism to a normal state. To achieve this goal, individuals with an absolute deficiency of insulin require insulin replacement therapy, which is given through injections or an insulin pump. Insulin resistance, in contrast, can be corrected by dietary modifications and exercise. Glycemic control is a medical term referring to the typical levels of blood

sugar (glucose) in a person with diabetes mellitus. Much evidence suggests that many of the long-term complications of diabetes result from many years of hyperglycemia (elevated levels of glucose in the blood) [2]. Good glycemic control, in the sense of a "target" for treatment, has become an important goal of diabetes care.

1.2.1 Glycemic Control

Because blood sugar levels vary throughout the day and glucose records are insufficient indicators of these changes, the percentage of hemoglobin which is glycosylated is used as an alternative measure of long-term glycemic control in clinical care of people with diabetes [2]. This test, the hemoglobin A1c or glycosylated hemoglobin, reflects average glucose level over the preceding 2-3 months. In non-diabetic people with normal glucose metabolism the glycosylated hemoglobin is usually 4-6% [2]. As of 2015 the guidelines recommended for an HbA1c of around 7% or a fasting glucose of less than 7.2 mmol/L (130 mg/dL) [2]. Keeping the blood glucose and HbA1c levels within the range recommended can be challenging. That's because many things make blood glucose levels change, sometimes unexpectedly.

For Type 1 diabetics there will always be a need for insulin injections throughout their life. However, both Type 1 and Type 2 diabetics can see dramatic effects on their blood glucose levels through controlling their diet, and some Type 2 diabetics can fully control the disease by dietary modification. As diabetes can lead to many other complications it is critical to maintain blood sugars as close to normal as possible and diet is the leading factor in this level of control. Recent research shows that the first step in diabetes management should be for patients to be put on a low carb (low GI) diet [6, 7]. Patients that are put on a high carb diet find it very difficult to maintain normal blood glucose levels. Patients that are put on a low carb or restricted carbohydrate diet, manage to maintain near normal blood glucose levels and A1cs [6, 7].

High-quality studies established that participation in regular physical activity improves blood glucose control and can prevent or delay type 2 diabetes [4]. The involvements combining physical activity and modest weight loss have been shown to lower type 2 diabetes risk by up to 58% in high-risk populations [4]. There are two well-defined pathways that stimulate glucose uptake by muscle. At rest and in the post-prandial state (after meal) of the body, its uptake by muscle is insulin dependent and serves to replace muscle glycogen stores. During exercise, contractions increase BG uptake to increase muscle glycogenolysis [3]. As the two pathways are distinct, BG uptake into working muscle is normal even when insulin-mediated uptake is impaired in type

2 diabetes. Muscular BG uptake remains elevated in the post-exercise phase, with the contraction-mediated pathway persisting for several hours [3].

1.2.2 Requirement for Decision Support Tools

A growing body of literature suggests that information technology (IT), such as computer, Internet and cellphone technology, holds great promise in enhancing diabetic care [8]. Quality of decisions are enhanced by personalized decision support tools that address patient clinical characteristics and treatment preferences. Individuals are shown to make a dramatic impact on the progression and development of diabetes by participating in their own care. There are some self-management tools and glucose metabolism simulators that help to enhance diabetic care. The details of these models are presented in Chapter 3. All of these tools help to facilitate the decision processes. There is a real need for tools that help diabetic people understand the impact of a particular sequence of food and exercise activities would have on their blood glucose levels (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 worldwide or are simply too expensive. Clearly, one solution is to build simulation tools that use our vast knowledge of energy metabolism in human beings. A few such simulators already exist [9, 10] but are geared towards predicting the impact of individual meals and are not available in a format that can be freely used by individuals.

1.3 Statement of Research Objectives

This document describes CarbMetSim (the **Carb**ohydrate **Met**abolism **Sim**ulator), an open-source and freely available 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 Type 2 Diabetes who follow a fixed medication (including insulin) regime prescribed by their physicians.

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 by using the known average flux along these pathways in the operation of different organs. These average flux values are configurable parameters. The impact of insulin and insulin resistance on the operation of various organs/pathways is captured in accordance with published research. CarbMetSim allows the user to specify his/her ability to produce insulin and the level of insulin resistance on a scale between 0 and 1. Thus, it is possible to customize the simulator for a particular user by setting appropriate values to configurable parameters for the ability to produce insulin, insulin resistance and average flux values for different metabolic pathways in different organs.

1.3.1 Predicting the Impact of a Particular Diet-Exercise Activity

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 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. 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 of a particular sequence of food and exercise activities would have on their BGL.

We have two options to figure out the impact of a particular diet-exercise activity on BGL. First option is the challenging one, in which researchers use healthy or diabetic subjects and test the diet and exercise activity on these individuals to figure out the impacts of them on BGL. Second one is utilizing simulators that mimic glucose metabolism in humans. Since CarbMetSim implements broader aspects of carbohydrate metabolism in human beings, one can easily capture the average impact of various diet-exercise activities on the BGL of people with different levels of diabetes. Even user-specific impact of a particular diet-exercise activity on BGL can be figured out by customizing the simulator for a particular user by setting appropriate values to configurable parameters for the ability to produce insulin, insulin resistance and average flux values

for different metabolic pathways in different organs.

1.3.2 Modeling Types and Levels of Diabetes

As stated above, there are two types of diabetes, Type 1 and Type 2. However, there may be various levels of Type 1 and Type 2 diabetes. There is even a pre-diabetes stage other than these two forms, which the fasting plasma glucose level is changing from 5.6 mmol/L (100 mg/dL) to 6.9 mmol/L (125 mg/dL). Type 2 diabetes has various levels as well. There are people who have diagnosed with type 2 diabetes that have to use insulin, on the other hand some type 2 diabetic people solely use diabetes medication instead of insulin injection, or even there are some levels of type 2 diabetes in which dietary restrictions without any medications and insulin treatment are sufficient to maintain a good glycemic control. In Type 1 diabetes, insulin production levels are changing from one person to another. CarbMetSim allows the user to specify his/her ability to produce insulin and the level of insulin impact on glucose uptake and production rates of organs and tissues on a scale between 0 and 1. Thus, it is possible to customize the simulator for a particular user by setting appropriate values to configurable parameters for the ability to produce insulin, insulin resistance and average flux values for different metabolic pathways in different organs.

By the help of insulin resistance and insulin production levels, how the BGL is changing in different levels of diabetes would be easily identified. For instance, how quickly the BGL is normalized or even not normalized at all in different states of diabetes after glucose level reaching up to very high peak values. These parameters would also help us to understand how insulin and insulin resistance affect individual organs' glucose production and consumption, even we can figure out their effects on flux values for different metabolic pathways in different organs.

1.3.3 Glycemic Index Prediction of Food Varieties

GI is calculated as the incremental area under the curve (iAUC) for blood glucose after consumption of a test food divided by the iAUC of a reference food containing the same amount of carbohydrate. To compute the exact GI of a test food, researchers repeat this process for 10 different test subjects and then the average of all ten GI values would be reported as the glycemic index of the test food. As an example, consider Figure 1.6. This shows the BGL curves for one individual and one test food. Suppose at 8am on day 1, the person ate 50 grams of carbohydrates of pure glucose, and his blood glucose followed the trajectory given by the gray area. Then at 8am on day 2, he ate 50 grams of carbohydrates of a test food we are interested

in measuring the glycemic index of, and his blood glucose followed the trajectory given by the black area. We can then compute that:

$$GI = \frac{Area(TestFood)}{Area(PureGlucose)} \cdot 100 = \frac{60}{100} \cdot 100 = 60 \tag{1.1}$$

Thus for this individual, we compute the glycemic index of the test food to be 60. We can then repeat this for nine other individuals, and the average of all ten GI values would be reported as the glycemic index of the test food. As discussed, computing the GI of a particular food has a long process. Nowadays, there are almost 2000+ foods listed in the literature with their GI values. Computing the GI of a mixed meal such as a dinner that consists of several foods is another dilemma. By knowing the GI values of these many foods , is it possible to calculate the GI of a mixed meal which consists of several foods (with known GI values) or do we still need to follow the process of GI calculation? Current literature provides simple methods to calculate the GI of a mixed meal, for instance, a formula using the GI of individual foods, weighted according to the amount of carbohydrate each food contributes to the meal, has been devised to estimate the GI of whole meals. These methods are not accurate enough for the prediction of GI values of mixed meals. Dodd et al. [11] compared the predicted glycemic index (GI) of 3 mixed meals with the measured GI and showed that predicted GI overestimated measured GI by 22-50%.

It would be easier to calculate the GI of a simple food and a mixed meal by using a tool that simulate glucose metabolism of an averaged person. Since CarbMetSim is 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, GI of a meal or a food can be calculated by the help of CarbMetSim easily without using any test subjects. GI values are arbitrary for normal individuals and diabetic people. Since there are configurable parameters like insulin and insulin resistance in CarbMetSim, GI values of different foods for diabetic people can also be computed. Even user-specific GI values can be found by customizing the simulator for a particular user by setting appropriate values to configurable parameters for the ability to produce insulin, insulin resistance and average flux values for different metabolic pathways in different organs.

1.3.4 Contributions to the Literature

The key contribution of CarbMetSim to the literature is its implementation of the physiological details in carbohydrate metabolism as an object oriented software in which various body organs implemented as software objects whereas the existing models used Ordinary Differential Equations (ODEs) to model physiological details. It can be argued that it is much easier to refine/modify behavior described in software than via ODEs. It is hoped that the ease of modification coupled with the open-source nature of CarbMetSim will allow it to evolve as a fine granularity software model of human metabolism useful for both research as well patient education. CarbMetSim is the first "Comprehensive Model" to use an object-oriented approach modeling physiological details of organs that:

- Dynamically customizes user-specific glucose metabolism parameters (i.e. insulin resistance and production level, metabolic pathway flux rates)
- Incorporates protein and fat effect on carbohydrate digestion
- Differentiates glucose metabolism parameters depending on user's diabetic level
- Addresses several metabolites in the blood (i.e. lactate, alanine, amino acids, GNG substrates) in addition to glucose

CarbMetSim also provides an alternative approach to predict Glycemic Index (GI) values of various foods.

1.3.5 Potential Use of Glucose Metabolism Simulator

CarMetSim is intended to be utilized in:

- Modeling the impact of different kinds of insulin infusion techniques: The insulin infusion process can also be added to the simulator to model type 1 diabetes in which insulin injection is utilized as a treatment method.
- Translating a user's diet/exercise/BGL data into the values of simulation parameters governing the behavior of different organs: CarMetSim can take as input the accumulated records of a person's diet/exercise activities and BGL measurements, then can estimate the rates at which various metabolic pathways operate in different states of the body.
- Providing user-specific real-time guidance on diet and exercise: CarbMetSim can be used to build a smartphone-based tool (or app) that can provide user-specific real-time guidance on diet and exercise.

The real-time guidance, can prove especially helpful to diabetic people. With this feature, the app will be able to suggest a sequence of diet/exercise activities that if followed over the remainder of the day will allow the app's user to achieve the best possible glycemic control no matter what his/her current BGL is.

- Modeling the fat metabolism of human body: With the help of fat metabolism modeling, we can predict changes in body weight in response to a diet/exercise regimen.

Chapter 2

Carbohydrate Metabolism in Humans

2.1 Carbohydrate Digestion and Absorption

2.1.1 Carbohydrate Digestion

Dietary carbohydrate may take different forms. Most meals contain a mixture of simple carbohydrates and complex ones. Complex carbohydrates consist of digestible starch, composed of amylose and amylopectin, as well small amounts of glycogen in animal tissues. Amylose has long chains of glucosyl units joined by α-1,4 links; amylopectin consists of chains of α-1,4-linked glucosyl units, with α-1,6-linked branches similar to glycogen [12]. Resistant starch is another type of starch which could not be digested in the small intestine but can be totally digested in the large intestine. Their chemical structure is very similar to digestible starch, but the polysaccharide chains are in a crystalline state which makes hard for digestion enzymes to access the bonds [12]. Another type of less digestible carbohydrate is non-starch polysaccharide or is known as dietary fiber. Cellulose is one of the main components of the non-starch polysaccharide group.

Starchy foods can be categorized regarding their digestibility, which is described by the rate and the duration of the glycemic response [12]. Predicting and controlling the glucose absorption rates after the ingestion of starchy food takes great attention in the context of worldwide health concerns [12]. Starches consist of

an amount that digests rapidly (rapidly digesting starch), an amount that digests slowly (slowly digesting starch) and that is resistant to digestion (resistant starch) [13]. Resistant starch is described as the portion of starch that is not digested in the small intestine and passes to the large intestine. One of the most widely utilized classification of the starches based on digestibility was suggested by Englyst, Kingman, and Cummings [14]. The classification method is established by the in vitro digestion of starch via modeling stomach and intestinal conditions and calculating glucose release at different times [14]. By the help of this method, different starch fractions are defined as:

- Rapidly digestible starch (RDS): amount of glucose released in 20 min.
- Slowly digestible starch (SDS): amount of glucose released between 20 and 120 min of in vitro digestion.
- Resistant starch (RS): total starch minus amount of glucose released within 120 min of in vitro digestion which can be explained by the following equation:

$$RS = TS - (RDS + SDS) \tag{2.1}$$

  where TS is total starch.

Besides the carbohydrate content of the food, there are several factors that affect the digestion of the carbohydrates. These factors can be classified as starch morphology, amylose to amylopectin ratio, molecular structure, processing techniques (thermal processing, cooking, etc.) and starch modification. The other constituents of the food matrix, such as proteins, lipids and polysaccharides (fibers), play a significant role during processing which affects the final digestibility of carbohydrate [12].

Cooking Effect

Thermal processing during cooking may modify starch structure and this can alter the postprandial reactions [15]. When raw starch molecules are gelatinized during cooking, the disorder of starch structure increases its sensitivity to enzymatic reaction [16]. In many starchy foods, however, a portion of the starch is not fully gelatinized during processing, due to limited water content or inadequate heating. Examples of such foods include breakfast flakes and other baked cereal products. The postprandial responses of foods containing raw or partially gelatinized starches have become the subject of increasing interest in recent years [15], [16], [17]. Starch gelatinization is a process of breaking down the intermolecular bonds of starch molecules by the help of water and heat, allowing the hydrogen bonding sites to preserve more water.

As the degree of gelatinization increased, the RS content decreased [3]. Holm et al. [16] also reported that RS content varied proportionally with degree of gelatinization. The slowly digested starch (SDS) content (0.6-4.2%) varied among the starch samples differing in thermal treatments. The SDS content was decreased by gelatinization [17]. These results suggest that the degree of starch gelatinization is an important determinant for the rate of starch digestion.

Fiber Effect

Fiber lowers the post-prandial glucose response, but the mechanisms how this happens are not well known yet, however water soluble fiber's high viscosity (thickness) may slow the rate of gastric emptying (movement from stomach to intestine) [18, 19] and decrease small intestinal movements [20], which results in delayed glucose absorption and therefore, a flattened blood glucose response. Ellis et al. [21] studied the effect of adding guar gum (at different concentrations) on the net glucose absorption in growing pigs. Polysaccharide based gums are belong to the water-soluble nonstarch polysaccharides. The pig meals containing guar gum resulted in increased viscosity of jejuna digesta (food that is started to the digestion) along with a significant reduction in the rate of glucose absorption. This postprandial effect of guar gum results because of the gum's capacity to increase the viscosity of digesta within the gastrointestinal tract. This whole phenomenon reduces the rate of digestion and absorption of carbohydrates and therefore lowers the postprandial rise in blood glucose. Kaur et al. [22] studied the presence of galactomannan (a type of water soluble fiber) in the starch mixture that impose limitations on the enlargement of starch granules during gelatinization in the cooked starch pasta because of less availability of water molecules to starch granules. This incomplete gelatinization of starch granules may also increase their resistance towards enzymatic hydrolysis. The fiber derived from different gums increases the viscosity in the food matrix which may increase the overall viscosity of digesta in the gastrointestinal tract. The consequence is the decreasing of the postprandial carbohydrate absorption after ingestion of starchy food. Apart from low rate of starch digestion, the transport of digestion enzymes has also been slowed down through mucosa when gums are present [23]. In addition, it may be difficult to distinguish among the two effects whether decrease in the rate of hydrolysis occur by the inhibition of enzymes or by an increase in the viscosity of gastrointestinal contents. An inhibitory action of very small concentration (0.5%) of galactomannan addition on amylase (digestive enzyme) acting on a range of concentrations of gelatinized starch was observed by Slaughter et al. [24].

Protein Effect

The starch digestion process may be influenced by the existence of protein in the food. Digestibility of the starches with the existence of proteins in several cereal products is significantly influenced by their interaction with each other. The starch digestibility has been observed to be affected by the presence of even small amounts of protein in cereals and other food products [25]. Protein portions such as albumin, globulins and glutens assist in attaching the protein bodies into starch granules that may act as a barrier towards starch digestibility [26]. There are some studies [27] suggest that the structural characteristics of the protein play a role in defining the degree of starch digestion in pasta. They had discovered that the existence of starch-protein interactions in pasta dough may be important for reducing the digestibility of starch in pasta. In vitro digestion studies showed that the concentration of total starch-digestion products was significantly lower for white bread than for gluten-free bread. All-purpose wheat flour is composed of granules with a starch core surrounded by a protein network. The protein network may inhibit the rate of hydrolysis in the small intestine [28].

Another effect of protein on starch digestibility is its effect on insulin secretion. The results of some of the studies suggest that the daily ingestion of at least one high protein meal containing low to moderate amounts of carbohydrate increases insulin secretion and glucose uptake, improving insulin sensitivity. Furthermore, the results indicate that these effects are particularly associated with the consumption of animal protein (i.e. hydrolyzed whey protein), which has a high content of branched-chain amino acids such as leucine, valine and others such as arginine, which leads to improvements in insulin secretion and uptake glucose, since it increases insulin sensitivity [29].

Fat Effect

Starches consist of two molecules – amylose and amylopectin – that connect to form starch granules. Amylose and amylopectin have different characteristics, which determine the different types of starches.Amylose contains 500 to 20,000 molecules of glucose connected in a straight chain. The chain twists into a helix and then two chains bond together, forming a structure that resists the digestive enzymes trying to break the glucose molecules apart. As a result, amylose is slowly digested and absorbed, which is why it's called a slowly digestible starch. Amylopectin is significantly larger than amylose, with a structure made up of millions of glucose molecules that branch out and form a crystalline structure. Its glucose units are easily cleaved during digestion, which makes it a rapidly digestible starch.

The effects of free fatty acids (lauric, myristic, palmitic, stearic and oleic acids, lysolecithin and cholesterol) on the hydrolysis of starch, amylose and amylopectin using amylase and amyloglucosidase have been reported in the literature by Crowe et al. [30]. Around 60% amylose was converted to glucose in 1 h, reaching up to 90% after 6 h. The addition of lauric, myristic, palmitic and oleic acids reduced the enzymatic hydrolysis of amylose by 35%. Fatty acids had no effect on the enzymic hydrolysis of amylopectin, whereas inhibition by fatty acids of the breakdown of whole starch was consistent with only the amylose fraction being affected. Enzymatic resistance of the pure amylose and lipid complexes has also been reported in the literature [31, 32]. With the help of in vitro and in vivo digestibility studies on amylose lipid complexes, Holm et al. [32] observed that complexed amylose is hydrolyzed and absorbed in the gastrointestinal tract to the same extent as free amylose but at a somewhat slower rate. However, the helical amylose-lipid complex cannot explain all effects observed in starch-lipid systems, and the possibility of complexation between amylopectin and lipids must be considered. Evidence is accumulating for complex formation between outer branches of the amylopectin molecule and polar lipids [33].

A study [34] examined the acute effects of coingestion of fat (37.5 g) on the post-prandial metabolic responses to 75 g of carbohydrate which was either slowly absorbed (lentils) or rapidly absorbed (potatoes). Coingestion of fat resulted in a significant flattening of the post-prandial glucose curves, the effect being more pronounced for the rapidly absorbed potatoes. This was probably due to delayed gastric emptying. However, the post-prandial insulin responses to either carbohydrate were not significantly reduced by fat, suggesting that the insulin response to a given glucose concentration was potentiated in the presence of fat.

2.1.2 Glucose Absorption in Digestive System

Monosaccharides are formed by the hydrolysis of the digestible carbohydrates, and then released to the enterocytes, the intestinal absorptive cells, by the enzymes of the brush border membrane. Glucose enters cells via the cell membrane by carrier-mediated diffusion (facilitated diffusion) rather than by free diffusion [3]. There are two families of glucose transporters. The more extensive family includes passive transporters, in which the movement of glucose across cell membranes is only down a concentration gradient. They are called GLUTn, where n is a number differentiating different members. There are 14 members of this family but only five have well-characterized functions [3]. *Michaelis Menten* kinetics are utilized to determine the amount of glucose transferred in a minute via passive transport in the body cells [3] (listed in Table 2.1) . 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. The other family consists of active transporters, in which glucose move up a concentration gradient. These are known as the sodium-glucose cotransporter family, SGLT-n, because sodium ions are cotransported with the glucose [3]. The expression of all these transporters is tissue/organ specific, and their properties are an integral part of the regulation of glucose metabolism in the particular tissue/organ.

Organs/Tissues	**GLUT1**	**GLUT2**	**GLUT3**	**GLUT4**
Brain	X		X	
Blood (Erythrocytes)	X			
Kidney		X		
Liver		X		
Intestine		X		
Muscle	X			X
Adipose Tissue	X			X
Heart	X			X

Table 2.1: Glucose Transporters of Organs/Tissues in Human Body

During the digestion stage, the local concentration of glucose at the luminal surface of the brush border membrane is so high in which maximal absorption rates can be achieved by the help of facilitated diffusion and also active transport. The local concentration of glucose at the luminal side of the brush border membrane may increase up to 200 mmol/l; this can definitely diffuse down a concentration gradient into the plasma, where the glucose concentration, in plasma draining the small intestine, might be 10 mmol/l during the absorptive phase [3]. The glucose transporter GLUT2 moves to the brush border membrane. As the luminal glucose concentration falls, the stimulus for GLUT2 translocation is removed and it recycles back to the intracellular store. Glucose then enter the enterocyte by active transport mediated by SGLT-1; that is, the glucose molecules may be absorbed against a concentration gradient. During the late stages of digestion, active transport guarantees complete capture of almost all the intestinal glucose molecules.

2.2 Metabolic Activities in the Organs and Tissues

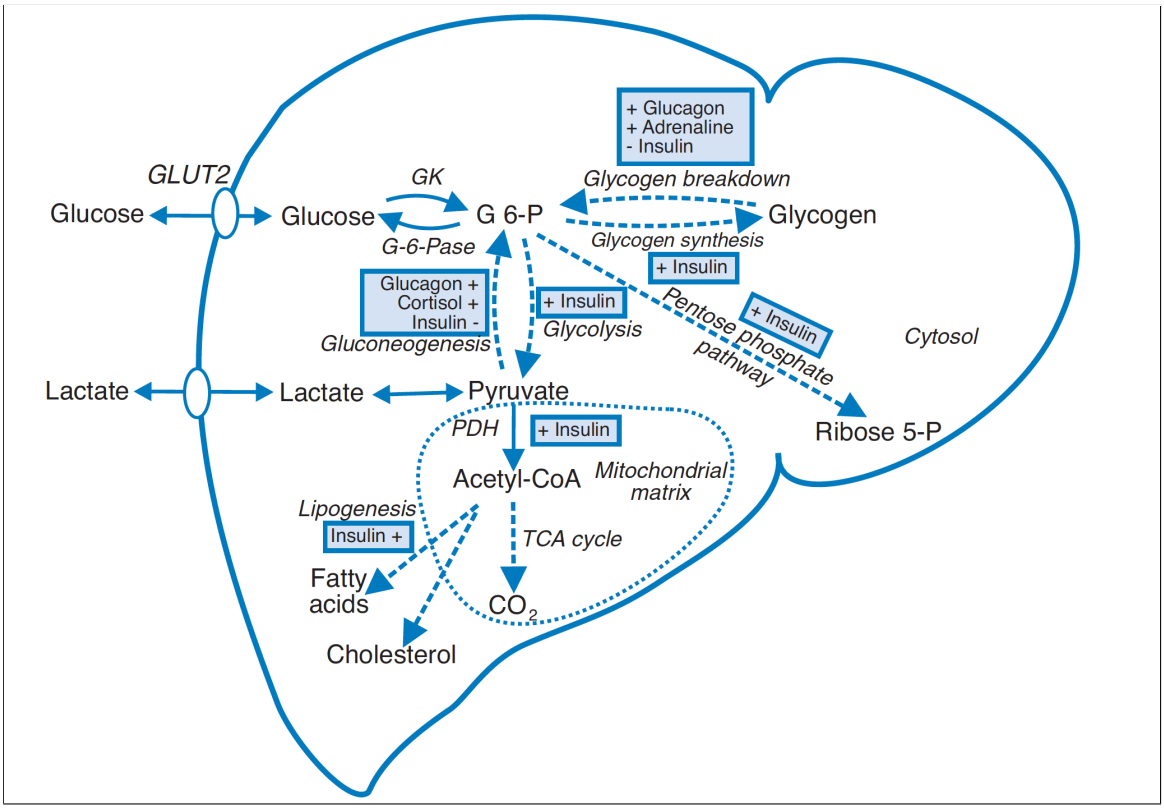
2.2.1 The Liver

It is the first organ to encounter the nutrients which enter the body from the intestine after a meal, therefore it has a major role in energy storage after a meal. This is definitely true for carbohydrate as well; storage and later release of glucose are key functions of the liver. It also has an important role in amino acid metabolism. Although most dietary fat avoids the liver as it enters the circulation, the liver does have significant functions in fat metabolism.

Carbohydrate Metabolism in the Liver

The major pathways of glucose metabolism in the liver, and their hormonal regulation, are summarized in Figure 2.1.

Figure 2.1: Carbohydrate Metabolism in the Liver



Source: Frayn, 2009 [3]

Fed State: After a meal, glucose concentration in portal vein may reach almost 10 mmol/l because glucose is absorbed from the intestine into the portal vein, while the arterial blood glucose concentration is normally around 5 mmol/l [3]. The hepatocytes (liver cells) are therefore exposed to high concentrations of glucose during the absorptive stage. Liver cells have primarily the GLUT-2 type of glucose transporter, which is not responsive to insulin, and has a relatively high K_m for glucose so that it normally functions well below saturation [3]. In addition, there is a high maximal activity (V_{max}) for glucose transport because there are many transporters. This means that the relative glucose concentrations inside and outside the cell determines the rate and direction of movement of glucose across the hepatocyte membrane.

Within the hepatocyte, by the enzyme glucokinase, the phosphorylation of glucose takes place and glucose 6-phosphate is formed which is the initial step in glucose metabolism by any pathway. This enzyme has a high K_m for glucose (12 mmol/l) and is not inhibited by its product, glucose 6-phosphate [3]. It has a high capacity (high V_{max}) and is unaffected, in the short term, by insulin like the GLUT2 transporter. Within the hepatocyte, glucose 6-phosphate may enter either one of the two pathways which are glycogen synthesis and glycolysis. Insulin and glucose both activate the storage of glucose as glycogen. They activate the main regulatory enzyme of glycogen synthesis (glycogen synthase) and inhibit glycogen breakdown (by glycogen phosphorylase). The result is a rapid stimulation of glycogen synthesis and suppression of glycogen breakdown, so that net storage of glycogen occurs. Because insulin is secreted from the pancreas and reaches the liver directly, and because glucose from the small intestine also arrives in the hepatic portal vein, they can bring about precise and rapid coordination of this system. Glucose 6-phosphate can also be metabolized via glycolysis to pyruvate in hepatocytes. This pathway is also activated in fed conditions. Some of the resulting pyruvate may be oxidized directly, some released after conversion to lactate. Most of the energy required by the liver for its multiple metabolic purposes is, however, derived from the oxidation of amino acids and fatty acids rather than glucose.

Fasting State: When the concentration of glucose in the blood falls, glycogen will be broken down for releasing the carbohydrate which is stored in the liver after meals, into the bloodstream. Another significant function of the liver in glucose metabolism is the synthesis of glucose from other substrates, this pathway is called gluconeogenesis. The pathway of gluconeogenesis is the reverse of glycolysis, but there are also some essential differences in the enzymatic steps and these are the points at which regulation occurs. The substrates for gluconeogenesis are lactate, alanine, and glycerol. Other amino acids can also serve as gluconeogenic precursors, although alanine is the most important one. Two major factors control the pathway of

gluconeogenesis: by the rate of substrate supply, and by hormonal regulation of the related enzymes [3].

Generally, gluconeogenesis is stimulated by glucagon and inhibited by insulin while glycolysis is preferred under the opposite conditions. The stimulation of gluconeogenesis by glucagon also happens in part by the help of direct stimulation of the transporters for uptake of substrates (specifically alanine) from the blood into the liver cell. In conditions where glucagon predominates over insulin, the liver will produce glucose 6-phosphate that is directed into release of glucose into the circulation. The processes of glycogenolysis and gluconeogenesis tend to be active at the same time in normal daily life. This is not so in more prolonged starvation, a condition in which gluconeogenesis becomes particularly important since there is little glycogen in the liver to activate.

The increase in the supply of substrate from other tissues can also activate the pathway of gluconeogenesis. The period after physical exercise is a good example, lactate concentration is elevated in the blood after physical exercise, some of which will be reconverted to glucose in the liver. During starvation, an increased concentration of blood glycerol arising from adipose tissue lipolysis will have the same effect. However, there is one common situation in which hormonal factors will be tending to suppress gluconeogenesis while substrate supply increases it. This is the situation after a meal. It is known as the glucose paradox [3]. Under these conditions lactate appears to be the most important substrate for glycogen synthesis. (Lactate must first be converted to glucose 6- phosphate by the pathway of gluconeogenesis). Therefore, hepatic glycogen synthesis after a meal takes place by a combination of the "direct pathway" (glucose uptake, glycogen synthesis) and the "indirect pathway" (uptake of gluconeogenic substrates, particularly lactate, formation of glucose 6-phosphate and glycogen synthesis). The origin of the lactate in this situation is not completely clear. One suggestion is that the small intestine itself metabolizes a proportion of the glucose to lactate during fed state, which passes to the liver through the portal vein [3]. Other tissues may produce some lactate from glucose in the plasma; red blood cells, adipose tissue, and muscle play some part in this [3].

Fat Metabolism in the Liver

The liver can oxidize fatty acids for its energy needs and also synthesize fatty acids for storing excessive amounts of glucose. Fatty acid synthesis from other substrates (specifically glucose) is considered to be very important in coordinating glucose and fat metabolism. The liver may acquire fatty acids in two different

ways: it can take up non-esterified fatty acids from the plasma, like other tissues, and also acquires fatty acids with lipoprotein particles by hepatic receptors. This is specifically important in the period after a meal, when dietary fatty acids reach the liver in the form of lipoprotein particles.

Fatty acids have two major fates within the liver: oxidation or storage. Fatty acids may be oxidized in the liver to produce energy for its metabolic activities. Specifically, gluconeogenesis is fueled by oxidation of fatty acids. If fatty acid oxidation is prevented by using a specific inhibitor, then gluconeogenesis is suppressed; if fatty acid supply to the liver is increased experimentally, gluconeogenesis always increases. The alternative fate for fatty acids absorbed by the liver is esterification with glycerol 3-phosphate to form triacylglycerol and phospholipids. Also, fatty acids synthesized from non-lipid precursors, such as glucose and amino acids, can be esterified to form triacylglycerol and phospholipids. This pathway is stimulated by insulin. Therefore, under conditions when glucose is in excess, some of the glucose is converted to lipids, and in this stage, fatty acids taken up by the liver are also used for triacylglycerol synthesis rather than oxidation. The esterification of fatty acids with glycerol 3-phosphate is itself stimulated by insulin. Thus, in the fed state, the liver tends to store fatty acids as triacylglycerol rather than to oxidize them. Hepatic energy requirements under these circumstances will be met mainly by amino acid oxidation. The hepatic triacylglycerol pool is not a major energy store for the rest of the body (that function is performed by the triacylglycerol stored in adipose tissue) but appears to be a local store for hepatic needs [3].

Amino Acid Metabolism in the Liver

The protein in the body is not continuously accumulated and lost under normal circumstances in adult life [3]. The rate of amino acid oxidation in the body must therefore balance the rate of entry of dietary protein [3]. The liver plays a special role in amino acid oxidation, this has two reasons, first liver is the first organ that receives the dietary amino acids, which enter the circulation via the portal vein, and second it is the only organ capable of eliminating the nitrogen from amino acids, by synthesizing urea [3]. Therefore, amino acid catabolism occurs predominantly in the liver. (An important exception is that of the group of branched chain amino acids, whose catabolism is largely initiated in muscle) Amino acid oxidation provides about half the liver's energy requirements.

Amino acids are not only used for energy production in the liver. They also has a role in the synthesis of glucose (particularly alanine) and of fatty acids. Of course, amino acids also serve as precursors for hepatic

protein synthesis: both proteins required within the liver, and proteins exported into the circulation such as albumin. Catabolism of amino acids by the liver is mainly regulated on a short-term basis by substrate supply. Substrate supply depends in the fed state on the arrival of dietary amino acids, and in the starved state on the net rate of body protein breakdown.

2.2.2 The Brain

The blood supply rate to the brain is so high, about 750 ml/min (50 ml blood per minute per 100 g of tissue) [3]. This high rate of blood flow to the brain reflects its high metabolic rate. The brain oxidizes about 120 g of glucose per day, equivalent to about 2 MJ of energy, or 20% of the whole-body energy expenditure in a typical day [3]. The brain as a whole does not utilize fatty acids and amino acids as a metabolic fuel. Instead it uses almost entirely glucose under normal conditions, although in prolonged starvation it can use another substrate called ketone bodies [3]. The glucose is for the most part completely oxidized, so the brain has an individually high rate of oxygen consumption and carbon dioxide production. In general, the rate of utilization of glucose by the brain is not affected by insulin. Glucose is transported into nerve cells by the glucose transporter GLUT3, which has characteristics that make it particularly suitable for this role [3]. It has a low K_m for glucose transport into the cell so that at normal plasma glucose concentrations it is saturated with substrate [3].

2.2.3 Skeletal Muscle

Glucose Metabolism in Skeletal Muscle

Glucose uptake in skeletal muscle is mainly done by the glucose transporters which are sensitive to insulin. These insulin-sensitive glucose transporters are called GLUT4s. GLUT1 is also expressed in skeletal muscle and plays a role in uptake of glucose at a basal rate. Glucose uptake by GLUT4 has certain characteristics which are relevant to the characteristics of the skeletal muscle. The K_m is within the physiological range of plasma glucose concentrations. In the presence of low concentrations of insulin the maximal activity (V_{max}) of glucose uptake is low. Raising the insulin concentration brings more transporters into action at the cell membrane, and hence increases the V_{max}. Insulin thus increases the rate at which muscle takes up glucose from the blood. The absorbed glucose may be used for glycogen synthesis or glycolysis. As in the liver, insulin stimulates the enzyme glycogen synthase in muscle and inhibits the enzyme glycogen phosphorylase. Thus, when the plasma insulin concentration is high after a meal, glucose will be stored as glycogen in

skeletal muscle. In skeletal muscle, there is also a specific mechanism for stimulation of glycogen synthesis after exercise when the glycogen store has been depleted.

Fatty Acid Metabolism in Skeletal Muscle

Fatty acids are taken up by muscle with two different pathways. These are the plasma non-esterified fatty acids (NEFA), which have appeared from stored triacylglycerol in adipose tissue, and fatty acids transferred as triacylglycerol in lipoprotein particles. Non-esterified fatty acids are taken up across the cell membrane by a specific transport mechanism. Under resting conditions, the rate of fatty acid uptake is usually closely related to the concentration of non-esterified fatty acids in the plasma. Correspondingly, fatty acids within the cell are oxidized in agreement with their rate of uptake. During exercise there is obviously a need to increase the rate of delivery of substrates for oxidation. In the case of fatty acids, this is brought about by increasing the rate of blood flow through muscle. The rate at which blood flows through any particular muscle increases several folds when that muscle is exercising, resulting in the delivery of more fatty acids to the muscle. Experiments with perfused muscle preparations in which the delivery of fatty acids is altered either by altering their concentration or by altering the blood flow show that the rate of fatty acid uptake is largely determined by the delivery rate (i.e., blood flow * concentration).

Apart from the situation of exercise, increased uptake of fatty acids by muscle will occur when the plasma non-esterified fatty acid concentration is raised –for instance, during fasting. Under these conditions the muscle will not need to use so much glucose. Skeletal muscle cannot take up plasma triacylglycerol directly because it is not a molecule that can pass through cell membrane. The fatty acids must first be released from triacylglycerol by the action of an enzyme, lipoprotein lipase, which is present in the capillaries. This process is, therefore, similar to the absorption of triacylglycerol from the intestine. Lipoprotein lipase is also present in other tissues, especially adipose tissue. The fatty acids that are released from triacylglycerol in the capillaries enter the muscle cells, with the same mechanism which plasma non-esterified fatty acids enter. Thereafter, their fate may be either oxidation or re-esterification to replenish the muscle triacylglycerol store.

2.2.4 The Heart

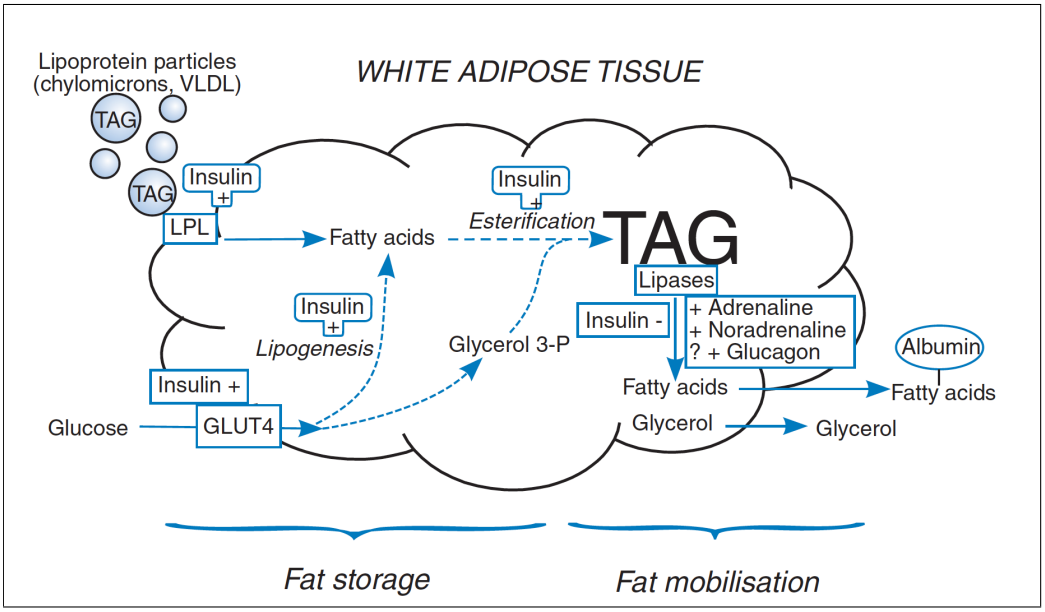
The heart is a good example that utilizes a number of fuels. These include fatty acids and glucose during normal conditions, also ketone bodies during starved conditions [3]. The fatty acids originate both from

the plasma non-esterified fatty acid and from plasma triacylglycerol. It can also take up lactate and oxidize it, via lactate dehydrogenase and the tricarboxylic acid cycle. Its use of the different fuels for its energy needs depends on their concentrations in blood, although its uptake of glucose, by the insulin-sensitive glucose transporter GLUT4, is stimulated by insulin. In fasted conditions, the heart uses mainly fatty acids as oxidative fuel. In fed conditions (high insulin concentrations), the circulating concentrations of these substrates fall, and the heart cells use glucose rather than fat.

2.2.5 Adipose Tissue

The major metabolic role of adipose tissue is the control of storage and release of fat, stored in the form of triacylglycerol and released to the rest of the body in the form of non-esterified fatty acids. Two different aspects of the metabolism of adipose tissue will be considered in this section: the storage of triacylglycerol when there are excess amounts of dietary substrates in the circulation (as after a meal), and the release of fatty acids (fat mobilization) when other tissues in the body require energy, for instance during exercise or after an overnight fast. Both of these are actively regulated all the time; if fat storage is occurring, then fat mobilization is suppressed, and vice versa.

Figure 2.2: Carbohydrate Metabolism in Adipose Tissue



Source: Frayn, 2009 [3]

Fat Storage

Triacylglycerol in adipose tissue comes from two major routes: (1) uptake of triacylglycerol from plasma and (2) de novo lipogenesis, the synthesis of lipid (fatty acids, and hence triacylglycerol) from other sources, particularly glucose. Triacylglycerol is traveled in the plasma via lipoprotein particles. These particles, which carry most of the triacylglycerol, are too big to escape from the capillaries into the interstitial fluid; therefore, the adipocytes cannot take them up directly. There is a significant mechanism to overcome this difficulty. Adipocytes produce the enzyme lipoprotein lipase, which hydrolyzes the triacylglycerol in lipoprotein particles to release fatty acids, which can then diffuse into the interstitial space and so reach the adipocytes. Once taken up to the cells, the fatty acids are esterified to form triacylglycerol, for storage.

The activity of lipoprotein lipase in adipose tissue is stimulated by insulin, secreted in response to an elevation in the blood glucose concentration. Since we rarely eat fat alone, this means that after a typical meal containing both fat and carbohydrate, the uptake of fat into adipose tissue will be stimulated with the increase of insulin. The other potential pathway of fat deposition in adipose tissue is that of de novo lipogenesis, fatty acid production from other precursors (especially glucose). This pathway is the same as that in the liver. It is stimulated by insulin. Thus, again, insulin acts to promote fat storage in adipose tissue.

Fat Mobilization

The mobilization of fat causes the release of fatty acids from the stored triacylglycerol; these fatty acids are liberated into the plasma as non-esterified fatty acids, and therefore they are appeared to be available to other tissues. The mobilization of fat is also called lipolysis since it involves the hydrolysis of stored lipid. Each molecule of stored triacylglycerol produces three fatty acids and one glycerol molecule. The fatty acids mostly leave the cells and enter the plasma as non-esterified fatty acids. The glycerol also leaves the cell because it cannot be utilized for esterification of fatty acids again during fat storage, since adipose tissue almost completely lacks the enzyme glycerol kinase which would be necessary for this.

Lipolysis is inhibited when insulin levels are high. This is a very powerful effect and very rapid, occurring within a matter of minutes of raising the insulin concentration. Thus, insulin not only promotes fat storage, but it also controls fat mobilization. Insulin has a further effect in controlling fat mobilization by stimulating the esterification of fatty acids that are released by the action of hormone-sensitive lipase. Insulin stimu-

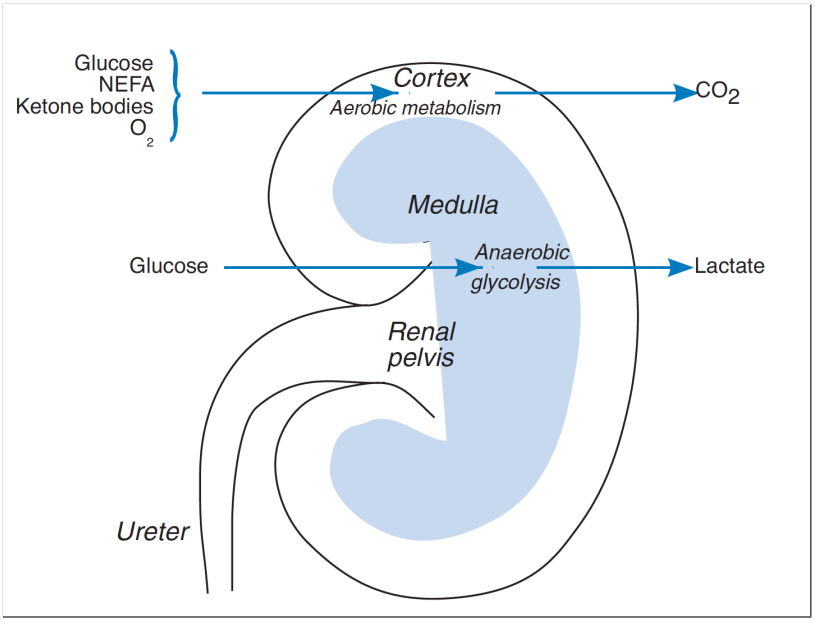
lates this pathway by increasing the delivery of glycerol 3-phosphate. Consequently, insulin both inhibits the activity of hormone-sensitive lipase and cleans up any fatty acids it may liberate by increasing their re-esterification.

Adipocytes will take up excess fatty acids in the short term, we already explained in the previous section, for instance in the period following a meal that contains both carbohydrate (to stimulate insulin) and fat. Normally the uptake of fatty acids after meals will be balanced by fat mobilization in the post-absorptive state (e.g., during the night-time fast) and during exercise, so that in many people the size of the fat stores remains relatively constant over long periods.

2.2.6 The Kidneys

The human kidney has a very important role in glucose metabolism. There are three vital mechanisms which regulate glucose homeostasis: (i) release of glucose into the circulation via gluconeogenesis; (ii) uptake of glucose from the circulation to satisfy its energy needs; and (iii) reabsorption into the circulation of glucose from glomerular filtrate to conserve glucose carbon.

Figure 2.3: Carbohydrate Metabolism in the Kidneys



Source: Frayn, 2009 [3]

Renal Gluconeogenesis

Glucose is released into the blood stream at a rate of approximately 10 μmol/ (kg min) after an overnight fast [35, 36, 37]. This released glucose is from two main sources: around 50% of the released glucose is because of the breakdown of glycogen (glycogenolysis) stored in the liver and the other half is the result of the production of new glucose molecules from substrates such as lactate, glycerol, alanine and other amino acids (gluconeogenesis) by liver and kidneys [35, 36, 37]. The kidney is not capable to release glucose via glycogenolysis [37]. In humans, only the liver and kidney contain substantial amounts of the enzyme glucose-6-phosphatase and therefore are the only organs that are able to perform gluconeogenesis. Nowadays, researchers have confirmed that the human liver and kidneys provide about equal amounts of glucose via gluconeogenesis in the postabsorptive state. Consequently, after an overnight fast, 75-80% of glucose released into the circulation derives from the liver and the remaining 20-25% derives from the kidneys. As the duration of fasting increases, glycogen stores in the liver become further depleted until nearly all the glucose released into the circulation is the result of gluconeogenesis [38, 36]. Consequently, as the duration of fast increases, the amount of overall glucose release from renal gluconeogenesis increases [39]. It is vital to understand that kidney and liver vary in their use of gluconeogenic precursors. Lactate is the principal gluconeogenic substrate in both organs, but otherwise the kidney preferentially uses glutamine [40], whereas the liver preferentially uses alanine [41].

Meyer et al. (2002) [40] demonstrated that, after meal ingestion, overall endogenous glucose release decreases by 61%, with hepatic glycogenolysis almost stopping in the 4- to 6-h period [42] because this period is responsible for replenishment of hepatic glycogen stores. Hepatic gluconeogenesis also decreases by 82% and glucose molecules generated through this pathway are not generally released in the circulation but are largely directed into hepatic glycogen. However, renal gluconeogenesis actually increases by approximately twofold and accounts for 60% of endogenous glucose release in the postprandial period [42]. This has been hypothesized to facilitate the repletion of glycogen stores in the liver [42].

Renal Glucose Utilization

The kidneys utilize approximately 10% of all glucose used by the body in the post-absorptive stage after an overnight fast [35]. The glucose utilization by the kidneys increases after meals. In terms of whole-body glucose usage, normally approximately 45% of ingested glucose is thought to be converted to glycogen in the liver, 30% is taken up by skeletal muscle and later converted to glycogen, 15% is taken up by the brain 5% is

taken up by the adipose tissue and 10% is taken up by the kidneys [35, 42]. The kidney has two important parts, renal medulla and renal cortex. The metabolic fate of glucose is different in these two regions of the kidney. Because of its low levels of oxidative enzymes, the renal medulla must use glucose for its energy requirement and does so anaerobically [35]. Consequently, lactate is the main metabolic end product of glucose taken up in the renal medulla. In contrast, the renal cortex has a high level of oxidative enzymes. Consequently, this part of the kidney does not take up and use glucose very much during post-absorptive state, FFAs act as the main source of energy [35].

Renal Glucose Reabsorption

Another important mechanism in the kidneys that has a great impact on glucose homeostasis is the reabsorption of glucose from glomerular filtrate. Normally, approximately 180 l of plasma are filtered by the kidneys each day [35]. As the average plasma glucose concentration throughout a 24-h period is 5.5 mmol /l (100 mg/dl), 180 g of glucose is filtered by the kidneys each day [35]. In healthy individuals, virtually all of this is reabsorbed into the circulation and the urine is essentially free from glucose. In a given day, the kidneys produce 15-55 g glucose via gluconeogenesis and metabolize 25-35 g glucose [35]. Therefore, in terms of glucose economy, it is clear that renal reabsorption is the primary mechanism by which the kidney influences glucose homeostasis.

2.2.7 Endothelial Cells and Other Cell Types

Blood vessels are lined with a single layer of flat cells, which are called endothelial cells. Some cells in the body normally divide rapidly, or may divide rapidly in certain circumstances. Endothelial cells of the small intestine, or enterocytes, fall into the former category. A common feature of these cells seems to be their dependence on glutamine as a metabolic fuel. This may be because glutamine can act as a nitrogen donor in the nucleic acid synthesis and cell division. In the course of glutamine degradation in the intestinal mucosa, alanine is formed and may be transported to the liver in the hepatic portal vein as a substrate for gluconeogenesis.

2.3 Endocrine Hormones

2.3.1 Insulin

Insulin is a peptide hormone. It is synthesized within the β-cells of the pancreas. Since it has a very significant signaling function, its rate of secretion into the plasma must alter according to the metabolic or nutritional state. The concentration of glucose in the plasma is the most important regulator of the rate of insulin secretion. The β-cell expresses the GLUT2 transporter and the glucokinase similar to the hepatocyte [3]. As in the liver, these help the β-cell to act as a glucose sensor. As the plasma glucose concentration rises, so glucose enters into the β-cell and is phosphorylated, and then enters the glycolytic pathway. This leads to generation of ATP, which regulates events at the cell membrane. Insulin, which is synthesized within the cell and stored in secretory granules, is released into the extracellular space by the regulation of cell membrane. The synthesis of new insulin is also stimulated, and if the elevated glucose concentration continues, insulin secretion will be preserved by increased synthesis and release to the plasma. Glucose is not the only stimulus to insulin secretion. Insulin secretion is also responsive to most amino acids (to somewhat differing extents), so that after a meal containing protein there is a stimulus for net protein synthesis.

Nowadays, considerable interest has been expressed in the effects of fatty acids on insulin secretion. Fatty acids are essential for normal glucose-stimulated insulin secretion; an increase in the fatty acid concentration for a period of one or two hours will cause insulin secretion in response to glucose. However, if elevated fatty acid concentrations are maintained for more than a few hours, the opposite is seen: there is an impairment of insulin secretion. This is associated with an accumulation of triacylglycerol within the β-cell.

Insulin moves free in the bloodstream; it is not bound to a carrier protein [3]. It affects tissues by binding to specific insulin receptors, proteins embedded in cell membranes. Insulin is removed from the circulation after binding to the cell surface insulin receptors. About 70% of the insulin reaching the liver is removed in its first passage [3]. This means that the liver is exposed to much higher concentrations of insulin than other tissues or organs.

2.3.2 Glucagon

Glucagon is a single polypeptide chain of 29 amino acids [3]. In contrast to insulin, glucagon's major action is to raise the blood glucose concentration. It is secreted from the pancreatic α-cells, as the insulin from the β-cells. It responds to both glucose and amino acids. However, unlike insulin, glucagon secretion is suppressed rather than stimulated by a rise in glucose concentration (although it is stimulated by amino acids). Thus, a rise in the plasma glucose concentration will lead to an increased ratio of insulin to glucagon secretion, and a fall in the plasma glucose concentration will lead to an increased ratio of glucagon to insulin. Again, some glucagon is removed on its first passage through the liver, although probably rather less than for insulin.

2.4 Carbohydrate, Fat & Protein Metabolism in Normal Daily Life

2.4.1 Carbohydrate Metabolism

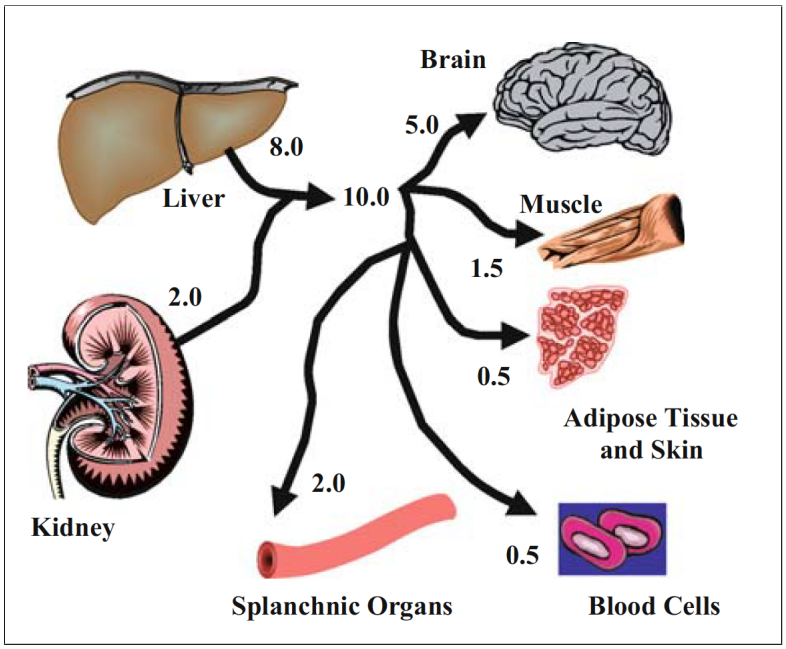
A single meal may contain as an average of 100 g carbohydrate [3]. The volume of blood is about five liters and the glucose concentration about 90 mg/dl, so the amount of glucose in the blood is about 4.5 g. If we consider the amount of glucose in all the extracellular fluid (13 liters), that is about 12 g [3]. Therefore 100 g carbohydrate could elevate the glucose concentration in the blood about eightfold if there were not mechanisms both to inhibit the body's own glucose production and to increase the uptake of glucose into tissues. Furthermore, during night a person does not consume any carbohydrate to provide the energy needs of the body. The body should store glucose and also produce its own glucose for its energy needs whenever needed, for instance during night. By the help of this mechanism, blood glucose levels in the human body would be preserved in a specified range.

The Postabsorptive State

In the post-absorptive state, the rate of turnover of glucose is close to 2 mg/kg body weight/minute, or 130 mg/min (the weight of an average person is 65 kg) entering and leaving the blood stream [3]. Where is this glucose coming from, and where does it go? Glucose metabolism after an overnight fast is illustrated in Figure 2.4. Much of the glucose supplied to peripheral tissues (muscle, adipose tissue, blood cells, etc.)

is reused as lactate, alanine, glutamine and glycerol, which return to the liver and the kidney as substrates for gluconeogenesis. However, a large proportion of the glucose is oxidized, specifically in the brain, and this represents an irreversible loss from the body's store of glucose. In the post-absorptive state, muscle and other tissues (e.g., renal cortex) also oxidize non-esterified fatty acids (NEFA) from the plasma.

Figure 2.4: Glucose Metabolism after an Overnight fast



Source: Shrayyef and Gerich, 2010 [43]

80% of glucose release into the circulation in the postabsorptive state is from the liver [35, 36, 37]. 50% of the glucose entering the plasma is due to glycogenolysis (glycogen breakdown) and the remainder (5.0 μ/kg/min) is due to gluconeogenesis [35] (Figure 2.4). The proportion of gluconeogenesis rapidly increases with the fasting level, as glycogen stores become depleted, gluconeogenesis provides almost all glucose released into the circulation.

The kidney normally contains little glycogen and renal cells that could make glycogen, lack glucose-6-phosphatase. Consequently, all the glucose released by the kidney is the result of gluconeogenesis [44]. The liver releases about four times as much as the kidney in the post-absorptive state. Their contribution (2.5-3.0 μ/kg/min) from gluconeogenesis is the same [44]. However, the proportion of overall glucose release from renal gluconeogenesis increases even further with prolonged fasting.

The liver can be considered to be the only source of glucose due to glycogenolysis. In overnight fasted people, the liver contains about 75 g of glycogen [44]. Thus, if it releases glycogen at a rate of 63 mg/min (5 μ/kg/min), glycogen stores would be totally depleted in about 20 h and the only source of glucose released into the circulation at this point would be gluconeogenesis [44]. It is vital to understand that kidney and liver vary in their use of gluconeogenic precursors. Lactate is the principal gluconeogenic substrate in both organs, but otherwise the kidney preferentially uses glutamine [40], whereas the liver preferentially uses alanine [41] (i.e. see Figure 2.5).

Figure 2.5: Summary of post-absorptive glucose release

	Rate (μmol/kg/min)	% of total
I. Glucose release	10.0	100
A. Hepatic	8.0	80
1. Glycogenolysis	5.0	50
2. Gluconeogenesis	3.0	30
Lactate	1.3	13
Alanine	0.8	8
Other amino acids	0.2	2
Glycerol	0.4	4
Glutamine	0.3	3
B. Renal	2.0	20
1. Glycogenolysis	0	0
2. Gluconeogenesis	2.0	20
Lactate	1.2	12
Glutamine	0.4	4
Glycerol	0.2	2
Other amino acids	0.1	1
Alanine	0.1	1

Source: Shrayyef and Gerich, 2010 [43]

The gluconeogenesis (GNG) precursors result from a variety of tissues. First, lactate comes from those tissues that use glucose almost entirely by anaerobic glycolysis, such as the red blood cells and renal medulla. Note that this constitutes a recycling of glucose; red blood cells, for example, use about 25mg glucose/min and return that amount of lactate to the liver for synthesis of new glucose [3]. Secondly, there will be some breakdown of muscle glycogen releasing lactate and alanine from anaerobic glycolysis. In the post-absorptive state, glycerol arises from the liberation of fatty acids in adipose tissue. The source of the GNG precursor, glutamine, is also skeletal muscle cells. The decreased insulin/glucagon ratio stimulates gluconeogenesis (again, comparing with the previous evening when it was suppressed after a meal).On the disappearance side, the brain uses about 120 g glucose per day or about 80 mg/min, more than half of the total glucose utilization [3]. The remainder is used by a number of tissues including red blood cells, skeletal muscle, renal

medulla, and adipose tissue.

The Fed State

As discussed in the previous sections, the amount of glucose in an average meal would be sufficient to elevate the concentration of glucose in the plasma about eightfold. However, in a normal healthy person, the peak glucose concentration after such a meal is about 7-8 mmol/l, a rise of only 60% at most from the post-absorptive value of 5 mmol/l [3]. By the end of the absorptive period - about five hours after the meal - approximately 25 g of the 100 g of carbohydrate ingested will have been stored and 75 g oxidized [3]. Thus, although glucose oxidation in tissues was increased after the meal, around one-quarter of the glucose in such a meal is stored for later use. Approximately half of the storage will be in the liver and half in other tissues, mainly skeletal muscle. An increase in the concentration of blood glucose can be noticed within about 15 minutes and continues to make a peak at around 30-60 minutes after a moderate meal [3]. The exact timing of a peak depends on factors such as the size of the meal and the amount of complex carbohydrate, fiber, protein, and fat in the meal.

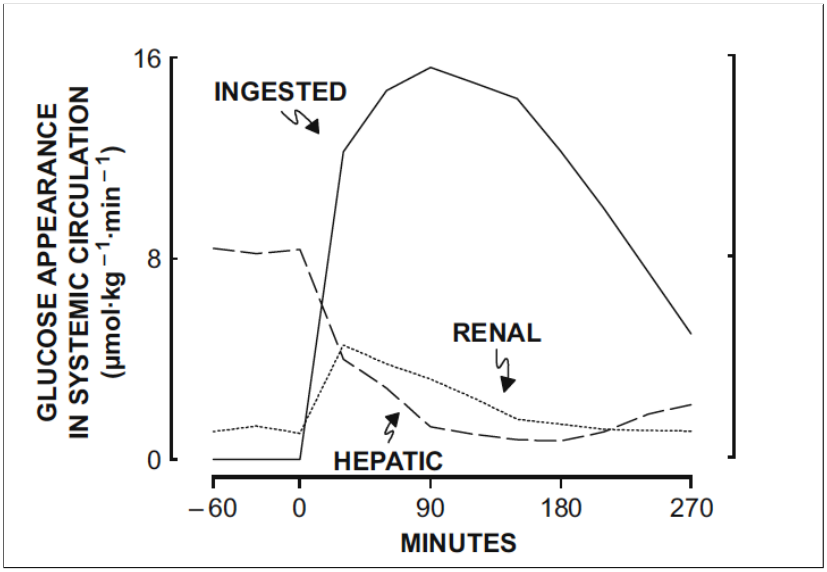
Liver Glucose Metabolism in the Fed State

The liver receives the blood flowing from the small intestine to the hepatic portal vein, and so it encounters the largest change in blood glucose concentration. This indicates to a flow of glucose into hepatocytes from portal vein via the transporter GLUT2. The raise of glucose concentration in hepatocytes, together with the increase in insulin/glucagon ratio, leads to inhibition of glycogen breakdown and stimulus of glycogen storage.

It is also expectable that the pathway of gluconeogenesis would be inactivated by the increase in insulin/glucagon ratio, but this does not occur as expected. There is always an elevation of the blood lactate concentration after ingestion of carbohydrate because of the effect of a switch to partially anaerobic glucose metabolism in a number of tissues, including muscle and adipose tissue. The increase in blood lactate concentration is probably sufficient in itself to maintain the activity of the pathway of gluconeogenesis. The overall effect is that some of the glucose arriving in the blood is used by tissues, released into the blood as lactate, taken up by the liver and converted to glucose 6-phosphate and then glycogen – the indirect pathway of glycogen deposition. It is important to understand that this gluconeogenic flux in fed state does not lead to release of glucose into the blood; the glucose 6-phosphate is instead mainly directed into glycogen synthesis.

The rate of glucose release from hepatocytes (i.e., release of glucose from glycogen and from gluconeogenesis) falls within 1-2 hours after a glucose load or carbohydrate-rich meal (Figure 2.6). This is another mechanism tending to reduce the increase in blood glucose concentration that might otherwise occur. The suppression of liver glucose release falls almost to zero after a pure glucose load. Following a typical meal the suppression is perhaps 30-50% of its fasting value [3]. The difference might be that the presence of fat in the meal slows gastric emptying and delivers glucose more slowly into the circulation.

Figure 2.6: Changes in rates of glucose entry into and removal from plasma after ingestion of a 75 g oral glucose load in normal subjects



Source: Shrayyef and Gerich, 2010 [43]

Glucose Metabolism in Other Tissues in the Fed State

Other tissues are also affected by the modification in insulin concentration. In skeletal muscle and adipose tissue, glucose uptake will be activated by the rise in insulin through increased numbers of GLUT4 transporters at the cell membrane, and by increased usage of glucose within the cell. At the same time, since fat mobilization in adipose tissue is suppressed, the plasma concentration of non-esterified fatty acids drops; this will be discussed in more detail in the next section. Therefore, tissues such as skeletal muscle, which can use either fatty acids or glucose as their energy source, switch to utilization of glucose. Not all the glucose taken up by muscle is oxidized under these conditions; insulin also activates muscle glycogen storage in which muscle glycogen stores will replenish. Thus, after a meal containing carbohydrate, there is a general switch in metabolism to the use of glucose rather than fatty acids, but there is also a major switch to the storage of glucose as glycogen.

In Kidney, renal gluconeogenesis actually increases by approximately twofold and accounts for 60% of endogenous glucose release in the postprandial period [42]. This has been hypothesized to facilitate efficient repletion of glycogen stores in the liver [42]. This can be seen in Figure 2.6.

2.4.2 Fat Metabolism

In this section the regulation of non-esterified fatty acid metabolism in the whole body, along with the fate of fat we eat in the form of triacylglycerol, will be considered. Both triacylglycerol and non-esterified fatty acids are always present in the plasma and, like glucose, they are constantly turning over - being used and replaced. Non-esterified fatty acids turn over very rapidly. Triacylglycerol is present in various forms. The form in which it enters the blood after a meal, chylomicron-triacylglycerol, also has a high rate of turnover. Other forms of triacylglycerol in plasma does not have a high rate of turn over.

Plasma Non-Esterified Fatty Acids

Non-esterified fatty acids enter the plasma only from adipose tissue by the process of fat mobilization. The overall rate of utilization of non-esterified fatty acids from the plasma depends almost entirely on their plasma concentration: the higher the concentration of non-esterified fatty acids, the higher their rate of utilization. Therefore, the concentration of non-esterified fatty acids in the plasma reflects their rate of release from adipose tissue, and also determines the rate of non-esterified fatty acid utilization in other tissues. The plasma non-esterified fatty acid concentration during a normal day is an inverse proportion of the plasma glucose and insulin; when the body is in post-absorptive state, for instance after an overnight fast, the concentrations of glucose and insulin are at their lowest and the concentration of non-esterified fatty acids is at its highest. It can fall noticeably after a carbohydrate meal.

Plasma Triacylglycerol

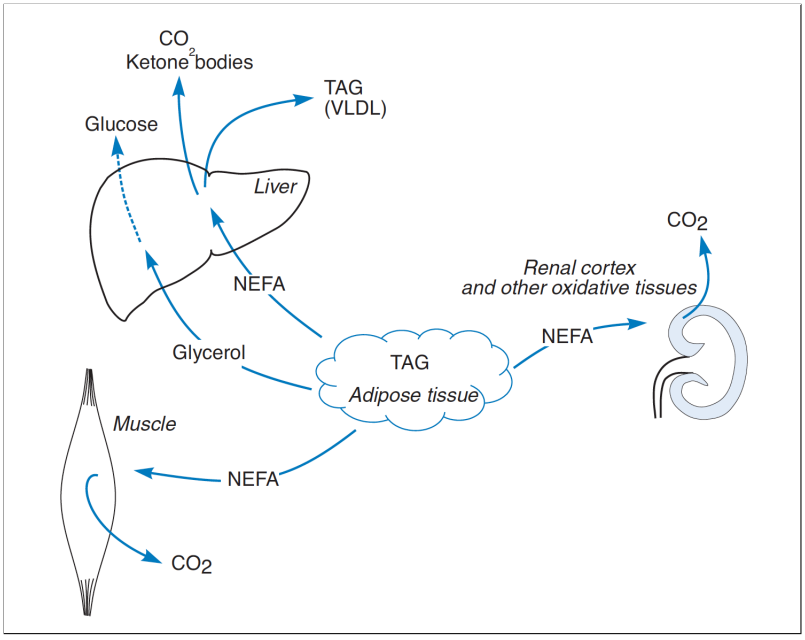
Triacylglycerol is water insoluble and is carried in the plasma in specialized forms, the lipoproteins (the largest of these, the chylomicrons, which transport triacylglycerol absorbed from the small intestine). The total concentration of triacylglycerol in plasma varies extensively between different people, depending on fitness, body build, and genetic influences - but a typical figure after an overnight fast is around 1 mmol/l

[3]. It should be considered that, since each triacylglycerol molecule contains three fatty acids, this is equivalent in terms of energy delivery to a concentration of 3 mmol/l of non-esterified fatty acids.

The Postabsorptive State

After an overnight fast, the concentration of non-esterified fatty acids in plasma is around 0.5 mmol/l [3]. As mentioned above, the total triacylglycerol concentration might be around 1 mmol/l and the chylomicron-triacylglycerol concentration close to zero, usually less than 0.05 mmol/l [3]. The turnover of non-esterified fatty acids in the post-absorptive state involves their release from adipose tissue and their uptake by a number of tissues, mainly skeletal muscle and liver (Figure 2.7). The rate of liberation from adipose tissue reflects mainly the fall in insulin concentration. The rate of non-esterified fatty acid release from adipose tissue is also regulated by the process of fatty acid re-esterification within the tissue. However, the process of re-esterification requires glycerol 3-phosphate produced from glycolysis, and this will be occurring at a relatively low rate, so most of the fatty acids will escape from the adipocyte.

Figure 2.7: Non-esterified fatty acid (NEFA) metabolism after an overnight fast



Source: Frayn, 2009 [3]

The Fed State

The effects of a meal on non-esterified fatty acid and triacylglycerol metabolism are quite different. In this section two different meals will be considered, one of them is a mainly-carbohydrate meal and its effects on non-esterified fatty acid metabolism will be considered. Then we will see how a fatty meal affects the responses.

Non-Esterified Fatty Acid Metabolism After a Meal

As the meal is absorbed, the concentration of insulin in the plasma increases as a result of the rising glucose concentration. Lipolysis (fatty acid release) in adipose tissue will be suppressed as a result of these effects. At the peak of insulin after a typical carbohydrate meal, adipocyte lipolysis will be maximally suppressed. The suppression of lipolysis is not only because of the increase in the insulin level. The rising glucose and insulin concentrations will also increase adipose tissue glucose uptake and glycolysis, and, therefore, production of glycerol 3-phosphate and re-esterification of fatty acids within the tissue. Thus, release of non-esterified fatty acids from adipose tissue will be almost completely suppressed after a carbohydrate-rich meal, and the plasma non-esterified fatty acid concentration will fall significantly.

The fall in plasma non-esterified fatty acid concentration affects the metabolism of tissues that use fatty acids as an oxidative fuel after the overnight fast. Skeletal muscle is a good example. The rate of uptake of non-esterified fatty acids by muscle is a function primarily of fatty acid delivery - that is, plasma concentration and blood flow. On the other hand, when glucose becomes available in the plasma after a meal, its utilization is stimulated by the rise in insulin concentration. As the absorptive phase ends after about 3-5 hours, so insulin concentrations begin to decline, and the fat mobilization is stimulated; plasma non-esterified fatty acid concentrations rise again.

Triacylglycerol

In this section a meal containing both carbohydrate and fat will be considered. The plasma glucose and insulin concentrations will rise as described before, and the release of non-esterified fatty acids from adipose tissue will be suppressed so that their concentration in plasma falls. Dietary fat is almost entirely in the form of triacylglycerol. This is absorbed in the small intestine and processed in the intestinal cells to produce chylomicron particles, which are liberated into the bloodstream through the lymphatic system. This process

is much slower than the absorption of glucose or amino acids, so that the peak in plasma triacylglycerol concentration after a fatty meal does not occur until 3-5 hours after the meal.

Unlike other nutrients dietary fat escapes the liver on its entry into the circulation. In fact, most of the triacylglycerol is removed from chylomicrons in tissues outside the liver, particularly adipose tissue. Adipose tissue contains the enzyme lipoprotein lipase in its capillaries and this is the enzyme responsible for hydrolysis of the chylomicron-triacylglycerol. The activity of lipoprotein lipase is stimulated by insulin, so that it will be increased after the meal. Lipoprotein lipase activity in adipose tissue reaches its peak around 3-4 hours of insulin stimulation [3]. It is surely in coordination with the entry of chylomicron-triacylglycerol into the plasma (which is around 3-4 hours after the meal); this represents another aspect of the significant way in which insulin coordinates metabolism of different fuels in different tissues after a meal.

Lipoprotein lipase in adipose tissue hydrolyses the chylomicron-triacylglycerol, leading to the liberation of fatty acids, which enter the adipocytes and are esterified to form new triacylglycerol for storage. This process is facilitated by the fact that intracellular lipolysis in adipocytes is suppressed after the meal and fatty acid esterification increased by the increased insulin and glucose concentrations (and thus increased glycolytic flux and glycerol 3-phosphate production). Therefore, the concentration of fatty acids will be in favor of their storage rather than diffusion out of the tissue. In this way, the metabolism of triacylglycerol is influenced by the metabolism of glucose and non-esterified fatty acids.

2.4.3 Amino Acid and Protein Metabolism

Amino acids can be oxidized just as glucose and fatty acids. In fact, most of the amino acids we ingest are eventually oxidized [3]. Therefore, at a whole-body level the total oxidation of amino acids per day approximately balances the daily intake of protein, around 70-100 g in the typical Western diet [3]. Amino acid oxidation contributes around 10-20% of the total oxidative metabolism of the body under normal conditions [3]. Unlike fatty acids, amino acids can be converted into glucose. Some examples are alanine and pyruvate.

After eating a meal containing protein, amino acids appear in the portal vein. We believe that these mainly reflect the composition of the meal. However, those leaving the liver in the hepatic vein after a meal show quite different proportions than portal vein. In particular, they are enriched in the three branched-chain amino acids, valine, leucine, and isoleucine. These three essential amino acids constitute about 15% of di-

etary protein but represent about 70% of the amino acids leaving the liver after a meal [3]. The implication is that unbranched amino acids have been favorably preserved in the liver. The branched-chain amino acids are instead favorably removed by muscle after a meal. Therefore, skeletal muscle has the ability to oxidize the branched-chain amino acids.

Another case is the pattern of amino acids leaving muscle and other non-hepatic tissues after an overnight fast; there is always a large predominance of alanine and glutamine, much more than their occurrence in muscle protein. Similarly, it is possible to measure the uptake of amino acids across the liver and intestine, and glutamine and alanine are found to contribute the majority of amino acids taken up. These observations show us that individual amino acids have specific pathways of metabolism in different tissues, some of which we will discuss in the upcoming sections.

Branched-Chain Amino Acids and Muscle Amino Acid Metabolism

The branched-chain amino acids (leucine, isoleucine, and valine) are favorably absorbed by skeletal muscle after a meal. The reason of the stimulated uptake of branched-chain amino acids by skeletal muscle is not only insulin and the increase of its concentration in blood. A number of processes will affect this: transport from plasma to the muscle, release into plasma, utilization for protein synthesis, production from protein breakdown, and loss by degradation [3]. Since they are essential amino acids, means no synthesis from other amino acids, catabolism of branched-chain amino acids take place in muscle, which leads to the release of glutamine and alanine.

Alanine and Glutamine

As these amino acids provide links between amino acid and carbohydrate metabolism, they have a special place in a discussion of energy metabolism. Alanine and glutamine predominate among the amino acids leaving muscle. This is also true of other peripheral tissues including adipose tissue and brain. This ensures that they must be synthesized in these tissues. Alanine and glutamine contain two groups which are amino group and a carbon skeleton group. The amino groups for alanine and glutamine may arise from the amino groups of other amino acids. Where does the carbon skeleton of these amino acids come from? For alanine, the corresponding carbon skeleton is pyruvate, the end-product of glycolysis [3]. Treatments which increase glycolysis usually also increase alanine release. It is most likely that most of the carbon skeleton of the excess alanine leaving peripheral tissues arises from glycolysis. For glutamine, the carbon skeleton comes

from other amino acids rather than pyruvate [3].

Alanine is taken up eagerly by the liver, particularly under conditions of active gluconeogenesis, when its uptake is stimulated by glucagon. Within the liver alanine leaves its carbon skeleton as pyruvate, a substrate for gluconeogenesis. Glutamine is not as good a substrate for hepatic uptake but is removed particularly by the kidney and by the intestinal mucosal cells. In the kidney, it is converted to glucose in the process of gluconeogenesis. In the intestinal cells, glutamine is an important metabolic fuel. The pathway of metabolism leads to production of alanine, which leaves in the portal vein and thus reaches the liver, again as a substrate for conversion to pyruvate and hence glucose. Glutamine is also an important fuel for other rapidly dividing cells [3].

2.4.4 Links Between Carbohydrate, Fat, and Amino Acid Metabolism

Carbohydrate and Fat Metabolism

Lipogenesis means the synthesis of lipid. More precisely, the term de novo lipogenesis means the synthesis of fatty acids and triacylglycerol from substrates other than lipids particularly glucose. Excess carbohydrate can be retained for storage as triacylglycerol since this is the most energy-dense storage compound. The pathway of de novo lipogenesis may occur in both liver and adipose tissue.

Metabolic Interactions Between Fatty Acids and Glucose: the Glucose-Fatty Acid Cycle

The glucose-fatty acid cycle refers to important metabolic interactions between glucose and fat metabolism. These interactions occur in adipose tissue and in muscle; the pancreas is also involved via insulin secretion. In adipose tissue, we have already seen these mechanisms, when the glucose concentration in plasma is high, the plasma insulin concentration increases. Insulin suppresses fat mobilization (the release of fatty acids from adipose tissue). Thus, a high plasma glucose concentration leads to a low plasma non-esterified fatty acid concentration.

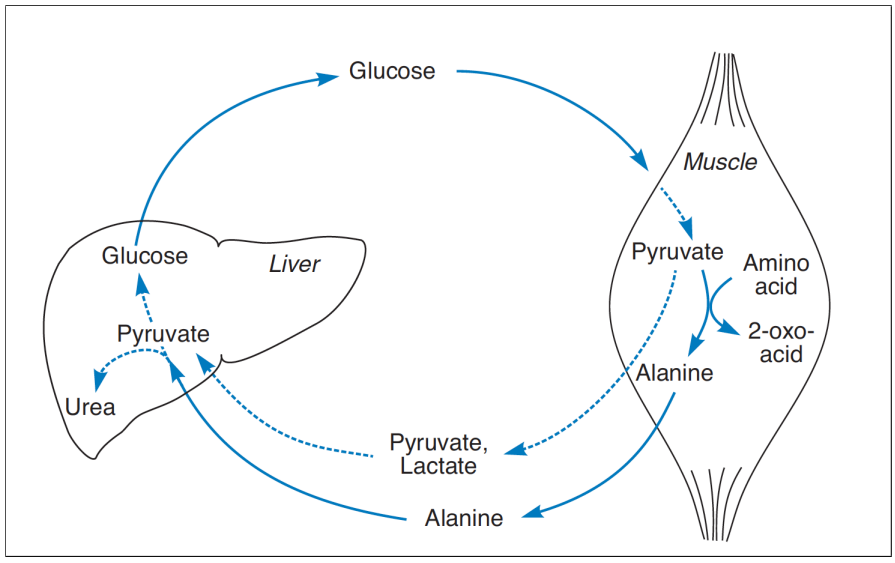
In muscle, the rate at which fatty acids are utilized from plasma is dependent almost entirely on the plasma non-esterified fatty acid concentration. Thus, when additional glucose becomes available in the plasma – after a meal, for instance – the muscle will tend to switch to the use of glucose rather than fatty acids because, firstly, glucose uptake will be stimulated by insulin, and, secondly, the plasma non-esterified fatty

acid concentration will fall and remove that substrate. Between meals (in the post-absorptive phase), the plasma glucose concentration falls a little, insulin secretion decreases, and the plasma non-esterified fatty acid concentration rises. In this situation the body's strategy is to spare the use of carbohydrate for tissues such as the brain which cannot use fatty acids. This is achieved by the fact that oxidation of fatty acids in muscle suppresses the uptake and oxidation of glucose.

Interactions Between Carbohydrate and Amino Acid Metabolism: The Glucose-Alanine Cycle and Gluconeogenesis from Amino Acids

It has already been mentioned that alanine released from muscle may be pyruvate onto which has been transferred an amino group from the breakdown of another amino acid. Pyruvate is a potential precursor for gluconeogenesis. Glucose thus formed in the liver may be released into the circulation, taken up by muscle and, through glycolysis, pyruvate formed. This pyruvate may be transaminated and alanine formed. This has been termed the glucose-alanine cycle. It is very closely related to the glucose-lactate cycle or Cori cycle, described in the 1920s by the Coris (Carl and Gertrude Cori) [3]. These two cycles are illustrated in Figure 2.8. The glucose-alanine cycle provides a clear link between glucose and amino acid metabolism and attracted a lot of attention when it was first proposed by Philip Felig and colleagues [45].

Figure 2.8: The glucose-alanine cycle operates in parallel with the Cori (glucose-lactate) cycle



Source: Frayn, 2009 [3]

But many amino acids can, in principle, be converted to glucose, so that the body's protein reserves, par-

ticularly the bulk of skeletal muscle, could maintain glucose production for a considerable time. Thus, there needs to be a mechanism for transporting the necessary substrates to the liver (the main site of gluconeogenesis). But the glucose-alanine cycle as just outlined does not do this: it merely recycles pyruvate, derived from glucose. It is a means by which muscle glycogen (which cannot lead directly to glucose release from muscle) may lead to release of glucose into the circulation (i.e., from the liver). It also provides a way for the muscle to export amino- nitrogen, liberated from those amino acids whose 2-oxo acids it has oxidized (e.g., the branched-chain amino acids) [3]. The nitrogen will eventually be excreted as urea, which is synthesized in the liver.

In order for the glucose-alanine cycle to function as a means of transporting amino acid carbon to the liver for gluconeogenesis, the carbon skeleton of the alanine also needs to be formed from an amino acid, not from glucose. In fact there is not a lot of evidence that this occurs, although much effort has been devoted to attempting to demonstrate it. Glutamine may be a more likely carrier of such carbon. Especially in kidney, glutamine is the main gluconeogenesis precursor after lactate. Therefore, glutamine-glucose cycle can be a good example for transporting amino acid carbon to the kidney for gluconeogenesis.

2.5 Exercise

Exercise can be classified into two types, anaerobic and aerobic. Anaerobic exercise is represented by sprinting or weightlifting; it is of short duration but involves great strength [3]. This type will not be considered in this document. Aerobic exercise, on the other hand, involves prolonged exercise but at a lower intensity than can be achieved anaerobically [3]. It is illustrated by running, cycling, swimming, or skiing. Here, since the duration of the exercise is long the energy needs of the body could not be maintained only from the fuels stored within muscle; the fuel stores in the rest of the body (fat in adipose tissue, glycogen in the liver) must also be used. Hence, these substrates must be brought to the muscle in the blood and used for the energy needs of the muscle. The muscle fibers involved in aerobic exercise are mainly the oxidative, Type 1 fibers. It is called aerobic because substrates (fatty acids and glucose) are completely oxidized to maximize efficiency.

2.5.1 Intensity of Exercise

We may measure the rate of whole-body energy expenditure, which will include both external work done and heat produced, by using various units. For instance, this may be measured in watts, however it is more convenient to relate it to the body's resting rate of energy expenditure. The unit MET (abbreviated from metabolic rate) has been invented for this measure. Some typical rates of energy expenditure expressed in this way are given in Table 2.2. One MET is defined as the normal resting metabolic rate (i.e., whole-body energy expenditure); it is about 4.8 kJ/min for a man of average size, and 3.8 kJ/min for a woman of average size. Note that 4.8 kJ/min is 4800/60 = 80 W [3].

Activity	**Energy Expenditure in MET**
Resting (not sleep)	1.0
Sleeping	0.9
Light Housework(e.g. sweeping floor)	2.5
Walking steadily(3 miles/h)	3.5
Heavy Housework (e.g. washing car)	4.5
Dancing	3-7
Swimming	6-11
Jogging	10-12
Squash	12
Marathon Running	18

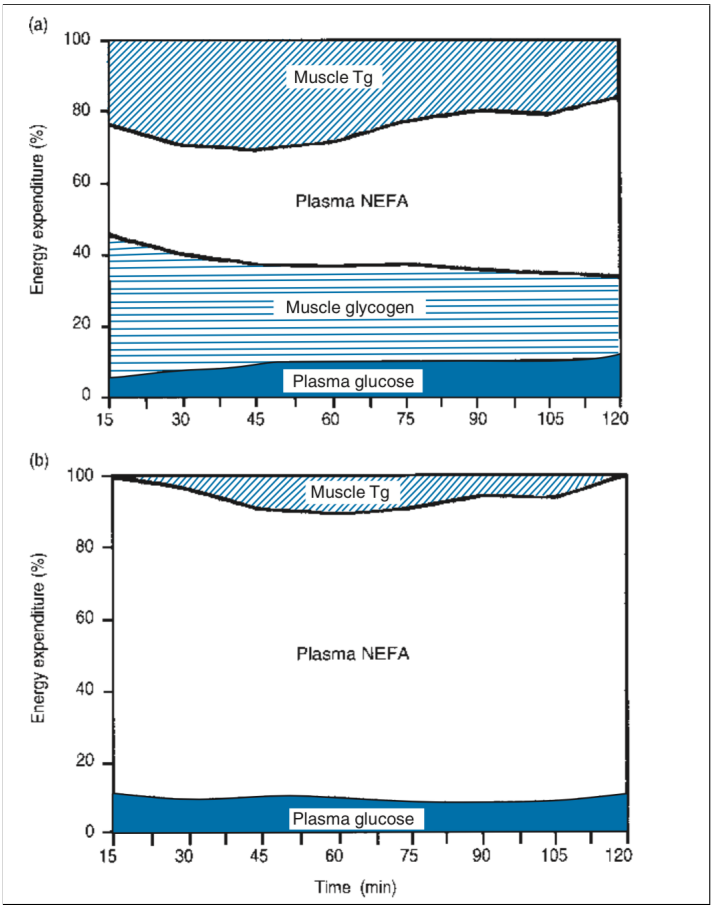
Table 2.2: Energy Expenditure During Various Activities

2.5.2 Metabolic Regulation During Aerobic Exercise

The major fuels used in aerobic exercise vary with the intensity of the exercise and with the duration. In relatively light exercise most of the energy required comes from non-esterified fatty acids delivered from adipose tissue. At higher intensities, carbohydrate tends to predominate early on, fat becoming more important later as glycogen stores are depleted. The carbohydrate used during endurance exercise comes from glycogen stores, both in exercising skeletal muscle and in the liver. In principle, it might also come from gluconeogenesis: exercising muscles always produce some lactic acid, even in aerobic exercise, and this should be a good substrate for hepatic gluconeogenesis. In fact, gluconeogenesis seems to be restricted during exercise, perhaps because blood flow to the liver is restricted as blood is diverted to other organs and tissues (mainly

skeletal muscle). The use of different fuels at different intensities of exercise is illustrated in Figure 2.9. The intensities of exercise are estimated by oxygen consumption, in relation to the maximal rate of oxygen consumption for the individual (VO_2max). Panel (a) shows exercise at 65% VO_2max; 2h at 65% VO_2max is relatively heavy exercise. Panel (b) shows exercise at 25% VO_2max; 2h at 25% VO_2max is relatively light [3]. Figure 2.9 also shows the relative contribution of substrates of the body to energy expenditure.

Figure 2.9: Utilization of different fuels during exercise at two intensities



Source: Romijn et al. (1993) [46], ©American Physiological Society

2.6 Carbohydrate Metabolism in Diabetes Mellitus

Untreated diabetes mellitus is described by extreme thirst and frequent urination. Diabetes mellitus can be divided into two main types. In the first one, the disease usually develops during childhood or adolescence. In this type of diabetes, lack of treatment leads to severe illness; and the only effective treatment is injection

of the hormone insulin. This is known as Type 1 diabetes mellitus or, in older literature, as insulin-dependent diabetes mellitus (IDDM). In the second one, more common form (90% of all diabetes), the disease usually starts later in life - from the mid-thirties. However, Type 2 diabetes can be seen now in younger and younger people. Those who develop this type of the disease are very often overweight. This form of diabetes is known as Type 2 diabetes mellitus or, in older literature, non-insulin dependent diabetes mellitus (NIDDM).

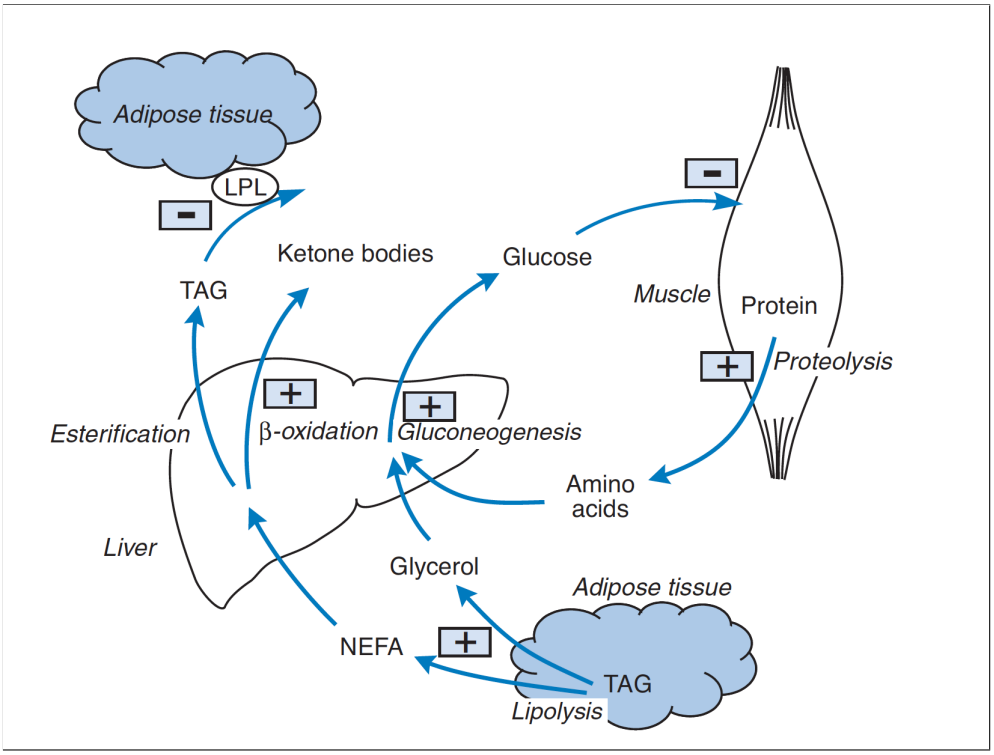
Type 1 diabetes results from destruction of the insulin-secreting cells of the islets of Langerhans. It is clear that the metabolic changes in Type 1 diabetes essentially represent a deficiency of insulin and can largely be treated by injection of insulin. Type 2 diabetes is characterized by a failure of insulin, at relatively normal concentrations, to employ its normal effects: this is the condition known as insulin resistance. Insulin resistance is also an obvious feature of obesity. The generally-accepted hypothesis for the development of Type 2 diabetes with obesity is as follows. When people become obese, their tissues become resistant to the actions of insulin. Therefore, the concentration of glucose in the blood increases and insulin is released in greater quantities from the pancreas. In obese subjects, concentrations of insulin in the plasma, and their response to a glucose load, are thus actually greater than normal.

2.6.1 Alterations in Metabolism in Diabetes Mellitus

Untreated Type 1 Diabetes

The metabolic picture in untreated Type 1 diabetes, outlined in Figure 2.10 , is very much what we might expect from knowledge of the normal role of insulin. There is breakdown of fuel stores and tissues. Lack of insulin leads to a net mobilization of glycogen. Glucagon secretion is increased in this condition. This, together with lack of insulin, leads to increased gluconeogenesis. Thus, hepatic glucose production is increased. In addition, the supply of amino acid substrate for gluconeogenesis is increased because there is net breakdown of tissue protein, especially of the large amount in skeletal muscle. Glucose utilization in tissues in which it is normally activated by insulin, particularly skeletal muscle, is impaired or stopped. This is strengthened by increased availability of fatty acids for oxidation; these will displace glucose as the oxidative fuel by the glucose-fatty acid cycle mechanism. Thus, the concentration of glucose in the blood rises dramatically. The normal resting concentration of around 5 mmol/l may increase to 10, 20, or even 50 mmol/l as the disease progresses [3].

Figure 2.10: The metabolic pattern in untreated Type 1 diabetes



Source: Frayn, 2009 [3]

The increased glucose concentration of the blood, known as hyperglycemia, leads to loss of glucose in the urine. At normal blood glucose concentrations, glucose is not lost by the kidney; it is filtered at the glomerulus and reabsorbed in the proximal tubules. But when the blood concentration rises above about 12 mmol/l, the level known as the renal threshold, reabsorption becomes saturated and glucose spills over into the urine. Lack of insulin leads to unrestrained release of non-esterified fatty acids from adipose tissue, and also to lack of activation of adipose tissue lipoprotein lipase. Thus, adipocytes fail to take up triacylglycerol from the blood, and there is a dramatic net loss of fat from adipose depots. This, together with the breakdown of protein, leads to the catabolic state.

Metabolic Alterations in Type 2 Diabetes

The plasma glucose concentration in Type 2 diabetes varies according to the severity of the condition, but if a patient neglects his or her treatment, it would not be uncommon to find a plasma glucose concentration of 20 mmol/l [3]. The plasma glucose concentration is consistently raised throughout the day, with an impairment of insulin response of skeletal muscle and adipose tissue. In addition, plasma non-esterified fatty acid concentrations may be elevated throughout the day. This elevation of plasma non-esterified fatty acid

concentration may worsen a number of features of the condition, reducing further the ability of insulin to stimulate glucose uptake by skeletal muscle.

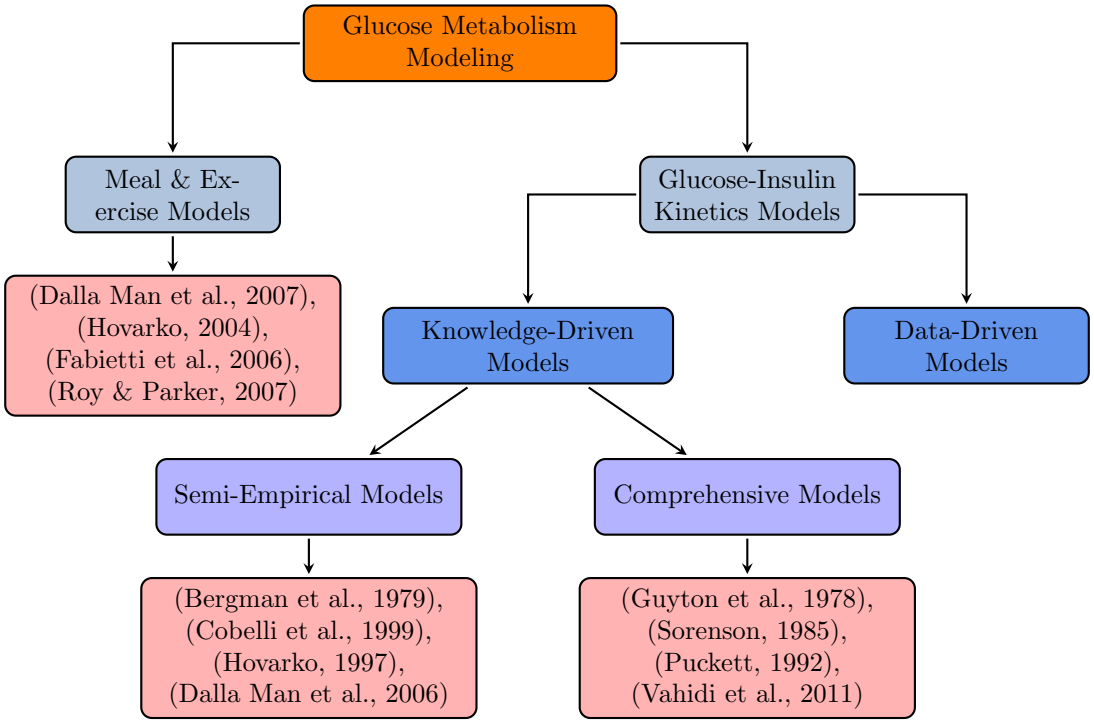
Chapter 3

A Review of Modeling Approaches for Human Body Glucose Metabolism

Blood glucose (BG) regulation in diabetic patients has been examined by researchers for a long time [47]. Various modeling approaches have been implemented with varied complexity ranging from simple data-driven (or empirical) to more detailed knowledge-driven (or conceptual) physiological models [47]. Empirical (or data-driven) models are the black box models, which relate the recently recorded BG values, and other inputs that can influence the BG levels with the output, which is usually the future BG concentration. Generally, the data-driven models are simple. The number of model equations is determined and parameters are estimated on individual basis from experimental data [48]. However, the conceptual models employ general knowledge of the physiology and metabolic processes. Each organ/tissue can be treated as a separate compartment with its own model equations and a detailed description of the metabolic and kinetic processes. These models are more complex and the estimation of the parameters is complicated [47].

The present review provides general information about the BG regulatory models including the description of empirical (data-driven), semi-empirical, and comprehensive models, along with the meal and exercise models, that is presented in Figure 3.1. Finally, the main simulation models that have been used for testing purposes are described.

Figure 3.1: Glucose Metabolism Modeling Approaches



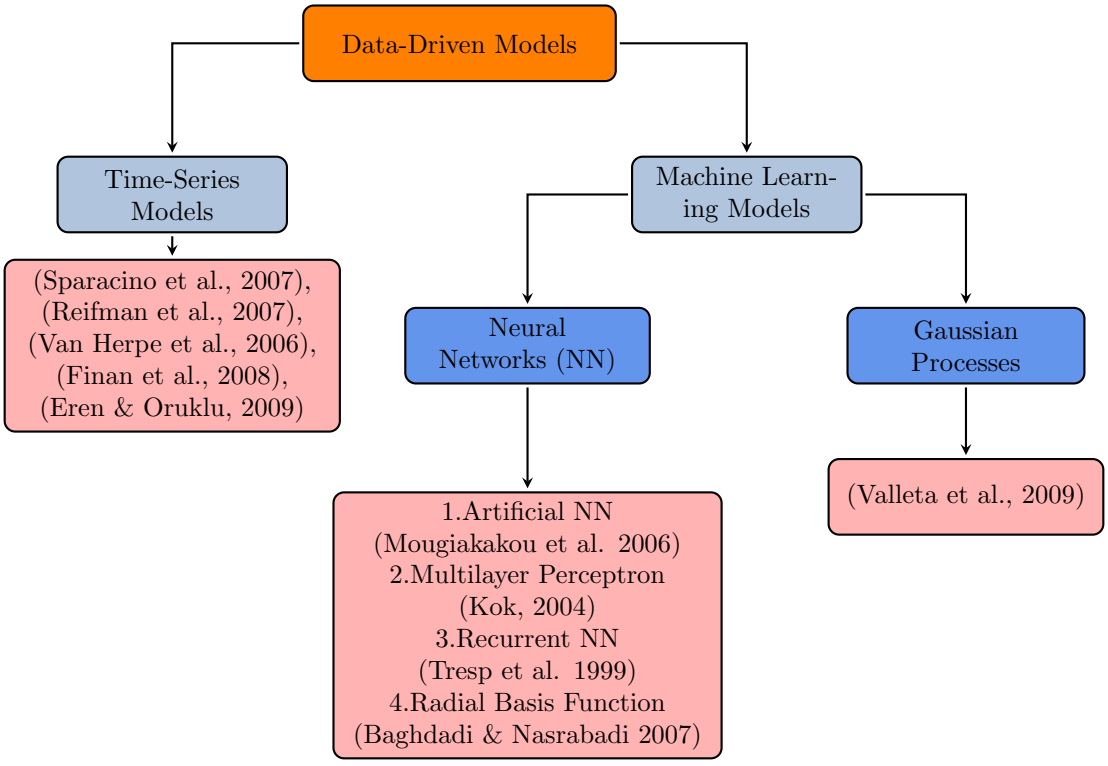
3.1 Data-Driven Models

Data-driven models are the black box models, which relate the input(s) with the output, which is usually BG concentration. In these models, future BG values of a patient will be predicted using recently recorded BG values and other inputs that can influence the BG levels. The most attractive aspect is that simple models predicting BG concentrations can be developed easier than other models, as the model structure is easily identifiable. However, these models cannot provide any understandings on the levels of glucose metabolism in various tissue and organs, as they do not consider any physiology. Also, these models often require the most recent data from patients to predict the BG changes in the near future which may not be practicable due to factors like additional measurement cost, patient's compliance to frequent BG measurements etc. Data-driven models can be classified as presented in Figure 3.2: i) Machine Learning Models and ii) Time-Series Models [48].

3.1.1 Machine Learning Models

The prediction of the glucose as a function of the input variables can be considered as a regression problem. The fact that the relationship between input variables (i.e. medication, diet, physical activity, stress etc.)

Figure 3.2: Data-Driven Models for Glucose Metabolism



and glucose levels is nonlinear, dynamic, interactive and patient-specific [49], requires the application of nonlinear regression models such as artificial neural networks, support vector regression and Gaussian processes. Different types of neural networks have been considered in modeling the blood glucose metabolism, such as multilayer perceptron (MLP) [50, 51, 52], radial basis function (RBF) [53], wavelet [54], time series convolution [49] and recurrent neural networks (RNN) [49, 55]. Additionally, Gaussian processes have derived prominent results regarding glucose prediction [56].

Artificial neural networks (ANN) have been used to forecast the BG levels in T1DM patients. Sandham et al. [57] worked on the prediction of BG concentration in two T1DM patients by using recurrent ANN (RANN). The BG level of past time was used to predict the present/future BG level. The input vector used to predict BG levels in T1DM patients includes: insulin (type, time and site of injection), diet (total carbohydrates (CHO) and meal time), exercise (duration, mobility, strength, endurance, and time), BG level and a vector comprising of other parameters (stress, illness, pregnancy). The prediction results by ANN were found to be very close to the measured values of BG in both patients.

Ghevondian et al. [58] developed a method based on a neural network algorithm for estimating blood glu-

cose levels by using only physiological parameters such as skin impedance and heart rate. Results have shown that an accuracy of 10% was achieved. Tresp et al. [49] studied the application of neural networks to modeling the blood glucose metabolism of a diabetic. They considered recurrent neural networks and time series convolution neural networks that were compared to linear and nonlinear compartment models. They included a linear error model to consider the uncertainty in the system and for managing missing blood glucose observations. The results indicated that best performance was achieved by the combination of the recurrent neural network and the linear error model. Mougiakakou et al. [55] presented two models based on the combination of compartmental models and ANN to simulate the glucose-insulin metabolism in four T1DM children. The insulin kinetics and glucose absorption from the gut were characterized in the form of compartmental models while the glucose dynamics was given by ANN. One model used feed forward ANN (FFANN) and the other used RANN trained with real time recurrent learning algorithm (RTRL). The outputs from compartment models were treated as the inputs of ANN models. The results showed a superior performance by RANN in all the four children.

The Gaussian processes have also been used successfully for the prediction of glucose. More specifically, a Gaussian processes prediction model for type 1 diabetic patients was developed in [56] based on continuous glucose measurements, physical activity information as well as information regarding food intake and insulin injections. The prediction model was evaluated on data collected from 18 patients with type 1 diabetes. Although no quantitative results were provided, it seems that this method can predict glucose in the short-term reasonably well and is able to follow the trends in glucose time series.

3.1.2 Time Series Models

Time series models are yet another category of data-driven models which can be used to develop linear and nonlinear dynamic models by relating the input and output data. Bremer et al. evaluated the ability of empirically developed linear autoregressive (AR) models to predict the future BG values. Results showed that the linear models could predict BG values in a short horizon (of up to 30 min) from the recent past data in both diabetic (T1DM) and non-diabetic patients. Consequently, AR models for predicting BG levels in different prediction horizons were developed by Sparacino et al. [59] and Reifman et al. [60] from continuous glucose data of 28 ambulatory T1DM and 9 T1DM subjects, respectively.

Van Herpe et al. [61] developed an input-output time series model using the data obtained from 41 patients

in an intensive care unit (ICU). A second order autoregressive exogenous input (ARX) model was found to be the optimal model for this data set. In another work, Van Herpe et al. used the data of 15 ICU patients to develop an adaptive input-output time series model by employing the significant input variables identified in their previous study. The new model could make four hours ahead BG predictions. Both models of Van Herpe et al. were found to demonstrate better predicting ability and clinical interpretation of estimated coefficients. Finan et al. [62] developed AR, ARX and autoregressive moving average exogenous input (ARMAX) models using ambulatory data of two T1DM patients. They also developed these models for the data obtained by simulating a T1DM nonlinear physiological model with exogenous insulin and meal disturbances as inputs. The results of this study recommended AR or ARX models for ambulatory data and ARMAX model for the simulated data.

Apart from these regular time series models, Eren-Oruklu et al. [63] have developed subject-specific recursive algorithms for the development of time series models predicting the future BG concentrations. Recently, Eren-Oruklu et al. [64] developed recursive autoregressive moving average model and evaluated the recursive model to further predict the hypoglycemia to provide hypoglycemic alarms. They extended their first model (univariate modeling algorithm) for predicting glucose concentrations [65] to a multivariate model that uses not only the subject's glucose measurements from a CGM device, but also several physiological signals describing a subject's physical activity and emotional conditions that have a significant effect on glucose metabolism.

Aside from the above-mentioned linear data-driven models, some nonlinear models have also been developed. Mitsis et al. [66] developed Volterra-type nonlinear dynamic empirical models with the data obtained from simulation of minimal model (will be explained in the knowledge-driven part). They examined the relation between existing parametric (compartmental) and nonparametric (Volterra type) models. The analytical and simulation results demonstrated the feasibility of obtaining accurate nonparametric models of insulin-glucose dynamics that are generated by widely used parametric models. Since the nonparametric modeling approach did not require prior assumptions about the model structure, it provided the effective means for obtaining accurate patient-specific and data-true models in a clinical context - thus overcoming the limitations of current parametric models. Rollins et al. [67] made significant contributions in developing nonlinear block-oriented Weiner models for T2DM patients. Recently, this group [68] has employed Weiner-block modeling methodology to predict the BG levels in T2DM patients using a large set of strongly correlated noninvasive inputs (nearly 35 sets of input variables related to stress, activity and food).

3.2 Knowledge-Driven Models

The knowledge-driven models can further be categorized as semi-empirical models, and comprehensive models. The semi-empirical models have limited number of equations, in which various organs or tissues in the body are combined into one or more compartments. However, the comprehensive models are highly complex and detailed, in which glucose metabolism of each organ and tissue modeled individually and in detail. The parameters of semi-empirical models are estimated from the data collected via clinical tests, although the parameters of comprehensive models are estimated from the literature.

3.2.1 Semi-Empirical Models

The turnaround in BG regulation modeling happened after Bergman et al. [69, 70] introduced their glucose-insulin kinetics model, which is called minimal model. Their aim is to find out the insulin sensitivity of an individual with the help of mathematical models. They tried to mimic a healthy person with 3 Ordinary Differential Equations (ODEs) for plasma glucose, plasma insulin and remote insulin concentration without considering any external disturbances. The major advantages of this model are its structural simplicity and ability to estimate the significant physiological parameters by using only the BG and plasma insulin data obtained from clinical tests. Earlier approaches of minimal models used intravenous glucose tolerance test (IVGTT) data, but afterwards, as oral glucose tolerance test (OGTT) closely resembles the physiological condition, this model was extended further by incorporating the description for glucose absorption from gut [71]. The resulting model estimates glucose and insulin concentration simultaneously, by considering the feedback relationship between them [71].

The minimal model has met many alterations afterwards. Most of the alterations were based on diabetes, also meal and physical exercise extensions were added to the original model [72, 73, 74, 75, 76, 77]. Another extension was to add a compartment to the glucose kinetics. Glucose kinetics requires at least a two-compartment description [78]. Under modeling the system, i.e., using one instead of two compartments during the highly dynamic IVGTT perturbation, can introduce bias in glucose effectiveness and insulin sensitivity, being over and under-estimated, respectively [79, 80, 81]. A two-compartment glucose minimal model has been proposed [82, 83], but this requires a priori knowledge on the two glucose exchange parameters [78, 84, 85, 86]. By incorporating this a priori knowledge and using a Bayesian Maximum a posteriori estimator, the accuracy of both glucose effectiveness and insulin sensitivity has been shown to improve.

In 2007, Dalla Man et al. [87, 88, 89, 90] developed a new model describing the glucose-insulin kinetics in the postprandial state. Glucose subsystem was modeled as a two-compartmental structure by using two ODEs, one explaining the glucose mass in plasma and rapidly equilibrating tissues and another denoting the glucose mass in slow equilibrating tissues. The insulin subsystem was also represented by a two-compartmental structure with two ODEs for insulin masses in plasma and liver. The model involved four unit metabolic processes, namely, endogenous glucose production (EGP), glucose absorption via gut wall, glucose utilization, and endogenous insulin secretion. The mathematical representation of EGP quantified the effect of insulin and glucose on liver to suppress the EGP. The insulin-dependent (tissues) and independent (brain and erythrocytes) glucose utilizations during meals were modeled based on the results of Cobelli et al. [91, 92]. Finally, the unit process for pancreatic insulin secretion modeled the pancreatic insulin secretion responses with respect to increasing and decreasing glucose concentration.

Dalla Man et al. checked the parameters of the resulting model with a large database of normal subjects and also with a smaller database of T2DM patients. Based on this model, a new simulation software of glucose insulin model (GIM), which could be used to simulate the life of normal, T1DM and T2DM subjects, was developed. This model was modified for T1DM patients by excluding pancreatic insulin secretion term and by including a new model of subcutaneous insulin kinetics. In 2009, Kovatchev et al. [9] developed another simulator (available as ' UVa simulator') for performing in silico preclinical trials in T1DM subjects based on the glucose-insulin model of Dalla Man et al. Food and Drug Administration (FDA) has accepted this simulator as an alternative to animal studies in the preclinical testing of a closed-loop control strategy.

3.2.2 Comprehensive Models

In 1978, Guyton et al. [93] developed a whole-system mathematical model of glucose metabolism in normal man by using current physiologic knowledge about glucose-insulin homeostasis in liver, brain, pancreas, kidney, peripheral tissues, and central vascular organs. The stated organs and tissues in the human body identified as the six compartments in the model. The model structure and the parameters of the model were determined by the available literature at that time and more than 100 intravenous glucose tolerance tests. In 1985, Sorenson [94] revised this model by adding a more complicated mathematical explanation. Then, Parker et al. [95, 96] updated Sorenson's model by adding a meal and exercise input model. The regulatory effects of insulin and glucagon hormones on glucose metabolism are considered in these models.

The Sorensen model contains three main sub-models which represents blood glucose, insulin and glucagon concentrations in the body. Each sub-model is divided into individual compartments representing a specific organ in the human body. The number of compartments in each sub-model is determined by the significance of the organ's job in maintaining the respective solute concentrations. Therefore, the glucose sub-model has six compartments: brain; liver; heart and lungs; periphery (muscles and adipose tissues); gut, which includes the stomach and intestinal system; and kidney. The insulin sub-model has the same six compartments and an additional compartment for the pancreas. The glucagon sub-model treats the whole body as one compartment.

Each compartment is generally divided into three well-mixed spaces representing the capillary blood space, the interstitial fluid space and the intracellular space. Capillary blood space is fed in by arterial blood and drained out by venous blood. The blood components may diffuse through capillary walls to interstitial fluid and from interstitial fluid to intracellular space. For each compartment, sub-compartments are considered where significant transport resistance exists. On the other hand, when the rate of component transport across the cell membrane is not restricted by its respective concentration in the intracellular space, the intracellular space may be omitted.

Model equations include mass balance equations over each sub-compartment for every individual compartment. Since pancreatic insulin production is a complex mechanism which cannot be described by simple mass balance equations, a separate model is considered for the pancreas. The pancreatic insulin release model used in the Sorensen model has been proposed by Landahl and Grodsky [97]. The aim of Landahl and Grodsky's model is to mimic the biphasic behavior of pancreatic insulin secretion in response to a glucose stimulus. The model describes insulin secretion patterns in response to a variety of glucose stimuli, they postulated that insulin granules were not a homogeneous pool. While the threshold hypothesis they introduced (i.e., each granule has a certain glucose threshold above which it releases the content) has gained little support from subsequent experiments, the non-homogeneity of insulin-containing granules pool is today an accepted notion and various beta-cell biology theories have been put forward. Next, we present the general approach employed for the modeling of physiologic processes.

Metabolic rates causing addition or removal of mass were assigned mathematical equations of the general form:

$$r = M^{Glu}(Glu, t) \cdot M^{I}(I, t) \cdot M^{G}(G) \cdot r_{basal} \tag{3.1}$$

r : metabolic rate of mass addition or removal (mass/time)

M^{Glu} : multiplicative effect of glucagon (dimensionless)

M^{I} : multiplicative effect of insulin (dimensionless)

M^{G} : multiplicative effect of glucose (dimensionless)

r_{basal} : basal metabolic rate (mass/time)

This method of representing regulatory effects in terms of separable multiplicative functions is commonly utilized in the modeling of biological processes (Carson et al., 1983). Since hyperbolic tangent functions have been found to be readily suitable for representing the sigmoidal nonlinearities commonly observed in biological data correlation, the rate multiplier functions were generally given the mathematical form:

$$M^{i}(i) = A + B \cdot tanh \cdot [C \cdot (i - D)] \tag{3.2}$$

where the i^{th} multiplier function was fit to clinical data by adjustment of the four constants A, B, C and D.

Physiologic processes affecting glucose mass equations and the substrates affecting the rate of function were listed as follows:

1) Red Blood Cell Uptake - Rate is constant

2) Brain Uptake - Rate is constant

3) Gut Uptake - Rate is constant

4) Peripheral Uptake - Rate is dependent on Peripheral Interstitial Glucose, Peripheral Interstitial Insulin

5) Urinary Excretion - Rate is dependent Kidney Plasma Glucose

6) Hepatic Uptake - Rate is dependent on Liver Glucose and Liver Insulin

7) Hepatic Production - Rate is dependent on Liver Glucose, Liver Insulin, and Plasma Glucagon.

Physiologic processes affecting insulin mass equations and the substrates affecting the rate of function were listed as follows:

1) Liver Clearance - Rate is dependent on Liver Insulin

2) Kidney Clearance - Rate is dependent on Kidney Insulin

3) Peripheral Clearance - Rate is dependent on Peripheral Interstitial Insulin

4) Pancreatic Insulin Release - Rate is dependent on Heart and Lung Glucose

Physiologic processes affecting glucagon mass equations and the substrates affecting the rate of function were listed as follows:

1) Plasma Clearance - Rate is dependent on Plasma Glucagon
2) Pancreatic Glucagon Release - Rate is dependent on Heart and Lung Glucose, Heart and Lung Insulin

The parameter values were figured out from the literature and models proposed for a healthy body. These models are not personalized but a general representation. These models for glucose-insulin interactions have been widely used in studying the physiological behavior of type I diabetic patients [96, 98, 99, 100, 101] and type 2 diabetic patients [58] by suitably adjusting the models.

In the early eighties, Cobelli et al. [91, 92] developed a comprehensive physiological model to characterize the glucose, insulin and glucagon kinetics. The glucose and glucagon subsystems are described by one-compartment models. The insulin subsystem is described by five-compartment model. This model also had used mass balance equations for calculating the level of substrates in the compartments and multiplier functions for the metabolic processes.

In 1992, Puckett et al. [102] proposed a multi compartment model structure to explain glucose-insulin interactions at various tissue and organ levels, which is like Sorenson's updated model. However, Puckett's model did not consider the glucagon effect.

Another mathematical model about physiology of diabetes is the Archimedes model developed by Eddy and Chlessinger [103, 104]. The model is written in differential equations, using object-oriented programming. The model includes the pertinent organ systems, more than 50 continuously interacting biological variables, and the major symptoms, tests, treatments, and outcomes. Their main goal is to build a mathematical model of the anatomy, pathophysiology, tests, treatments, and outcomes pertaining to diabetes that could be applied to a wide variety of clinical and administrative problems and that could be validated.

3.2.3 Meal and Exercise Models

The regulation of blood glucose concentration within safe limits in diabetic patients is accomplished by effective dietary planning, physical exercise, and insulin management. Mathematical models describing the effect of diet and exercise on controlling the blood glucose concentration are discussed in this section.

Meal Models

Fisher et al. [74] developed a meal model to explain the rate at which glucose enters bloodstream after intestinal absorption from meal. In oral glucose tests with normal subjects, the plasma glucose level rises quite rapidly (from the rest level) to a maximum in less than 30 min and then falls to the base level after about 2-3 h. Fisher et al. found out the parameters of the equation which specifies the rate at which glucose enters bloodstream by using the oral glucose test values of normal subjects.

Lehmann and Deutsch [105] proposed a meal model to mimic the glucose dynamics starting from oral meal ingestion to glucose absorption into blood. The rate of glucose appearance in gut was modeled by subtracting the rate of glucose appearance in plasma compartment from the rate of gastric emptying. The model represents the duration of period for which gastric emptying is constant and maximal as a function of carbohydrate content in the ingested meal. It assumes that gastric emptying is a trapezoidal function and that intestinal absorption follows first order linear kinetics. Lehmann and Deutsch calculated the parameter values of the meal model from the experimental results of Guyton et al. [93].

In Hovarko's [106] meal model, the gut absorption rate is represented by a two-compartment chain and is dependent on the time-of-maximum appearance rate of glucose in the accessible glucose compartment, the amount of carbohydrates digested, and carbohydrate bioavailability.

Fabietti et al. [107] used a meal model based on Arleth et al. [108] to describe the glucose input via meals. The glucose input from meals was obtained by processing a time dependent input representing the rate of food intake. The gut absorption was split in three terms, each one corresponding to a class of carbohydrates with different absorption rates: sugar (Ag), fast absorption starch (As), and slow absorption starch (Am), as derived from mixed meals, where the presence of different nutrients slows down the absorption of carbohydrates. Ag, As, and Am were obtained mathematically in the form of transfer functions based on the

experimental results of Arleth et al. [108].

All the above models failed in fitting glucose appearance (Ra) into the blood from ingested food satisfactorily [89]. The reason is likely their simplistic structure relative to the complexity of the Ra signal. It is, in fact, well known, for instance, that the gastric emptying of liquids depends nonlinearly on the size of the meal, its energy density and the amount of nutrient in the stomach [109, 110, 111, 112]. Moreover gastric emptying is described as a biphasic process in many studies [111, 113]. Clearly, a linear model does not capture these features. Dalla Man et al. [89], thus, moved to a nonlinear model based on available knowledge on gastric emptying and glucose absorption. A physiological model of glucose intestinal absorption had been developed by Dalla Man et al. [89]. Briefly it describes the glucose transit through the stomach and intestine by assuming the stomach to be represented by two compartments (one for solid and one for triturated phase), while a single compartment is used to describe the gut. The parameters were estimated by the help of the experimental data obtained from labeled oral glucose tolerance test of 41 subjects and labeled mixed meal ingestion of 20 subjects.

Exercise Models

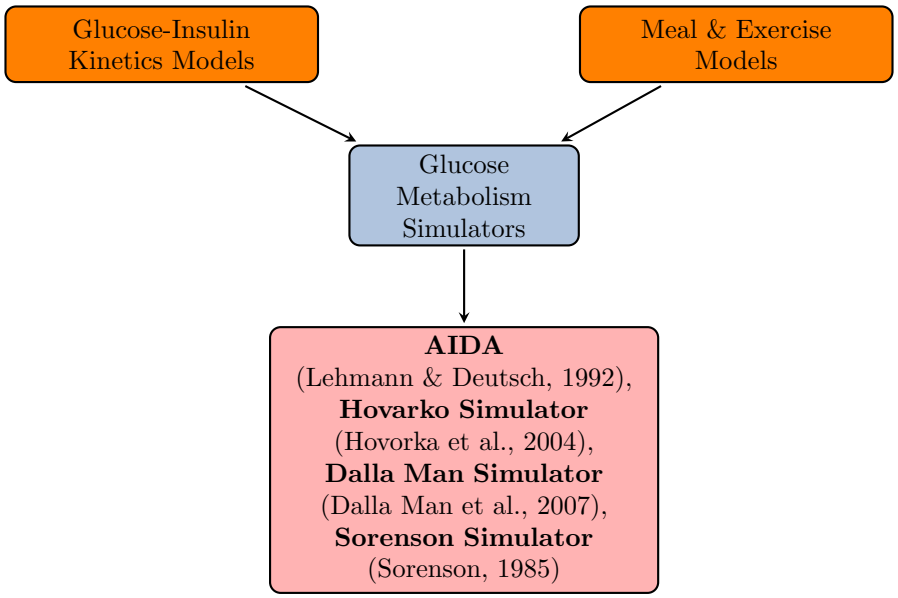
In 2002, Lenart and Parker [114] integrated the effects of exercise into the updated comprehensive model of Sorenson. Their exercise model quantified the exercise level of a person by using percentage of a person's maximum oxygen consumption rate. The influence of exercise on blood flow distribution, peripheral glucose uptake, hepatic glucose production, and insulin uptake has been modeled in the literature. The experimental works of Ahlborg et al. [115] were used to validate the exercise model. This model was mainly developed for introducing mild and moderate intensity exercise effects into the physiological model. The complicated nature of the model makes it difficult to tailor it for a specific patient.

In 2007, Roy and Parker [76] integrated exercise effects into Bergman's minimal model. The extended minimal model consists of three additional variables representing rates of glucose uptake, hepatic glucose production, and insulin removal from the circulatory system because of exercise. The simplistic nature of this new model can help in designing patient specific models for clinical use.

3.3 Simulations

A variety of models, discussed above, have been used to describe the glucose-insulin kinetics and the glucose regulation in subjects with diabetes. Recent research focuses on developing simulation models representing a 'virtual patient'. The Simulation models that will be discussed in this section, consist of a glucose-insulin kinetics model, a meal model and some of them have exercise models. Since we already discussed the specified models, we will summarize the simulation models briefly in this section. The glucose metabolism simulations that are discussed in this section are presented in Figure 3.3.

Figure 3.3: Glucose Metabolism Simulations



3.3.1 AIDA Simulation

AIDA is a diabetes computer program that permits the interactive simulation of plasma insulin and blood glucose proles for teaching, demonstration, and self-learning purposes. It has been made freely available, without charge, on the Internet as a noncommercial contribution to continuing diabetes education. It was launched in 1996 by Lehmann and Deutsch [105]. The model focused on the adjustment of insulin and/or diet in the insulin-treated diabetic patient. The model was followed the principles usually associated with the minimal-model approach, to find a concise mathematical formulation to represent the major physiological systems with the fewest possible parameters. This simulator considered the meal model and the subcutaneous insulin injection, but not the exercise model.

3.3.2 Hovorka Simulation

Hovorka et al. [106] 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 endogenous production). A possible weakness of Hovorka simulation model is its simple representation of glucose absorption from the gut which may need to be refined.

3.3.3 Dalla Man(UVA/PADOVA) Simulation

Dalla Man simulation model [89, 90] is one of the well-known virtual patient models. Dalla Man et al. [89, 90] 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 [9] 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 utilization as BGL dips below the normal range. It has a meal model subsystem, but not an exercise model. As stated before, the model has been accepted by the Federal Drug Administration to replace animal testing of glucose controllers.

3.3.4 Sorenson/Guyton Simulation

Sorensen simulation model [94] belongs to the class of complex physiologically based compartment models. Tiran et al. [116] developed a multi-compartment model for glucose circulation where each relevant organ was modeled as a separate compartment. Guyton et al. [93] 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 [94]. Sorensen [94] 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. [95, 96] 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 [105].

Chapter 4

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

4.1 Introduction

More than 400 million people world wide suffer from Diabetes, around 90% of whom have *Type 2 Diabetes* [1]. People with Type 2 Diabetes 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 *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. The work described in this paper is geared towards people with Type 2 Diabetes and any reference to the standalone term *Diabetes* should be interpreted as meaning *Type 2 Diabetes* unless explicitly noted otherwise.

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 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. 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. A few such simulators already exist [9, 10] 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 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 Type 2 Diabetes who follow a fixed medication (including insulin) regime prescribed by their physicians.

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 by using the known average flux along these pathways in the operation of different organs. These average flux values are configurable parameters. The impact of insulin and insulin resistance on the operation of various organs/pathways is captured in accordance with published research. *CarbMetSim* allows the user to specify his/her ability to produce insulin and the level of insulin resistance on a scale between 0 and 1. Thus, it is possible to customize the simulator for a particular user by setting appropriate values to configurable parameters for the ability to produce insulin, insulin resistance and average flux values for different metabolic pathways in different organs.

CarbMetSim is not yet a finished product. The protein and lipid metabolism are implemented only to the

extent that they affect carbohydrate metabolism. 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 considered. Only aerobic exercise activities can be modeled. 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. The *CarbMetSim* simulator is physiologically complex just like the models presented by Tiran et al. [116], Guyton et al. [93], Sorensen [94] and Dalla Man [89]. The key difference is that *CarbMetSim* implements the physiological details as an *object oriented* software with various body organs implemented as software *objects* whereas the existing models used ODEs to model physiological details. It can be argued that it is much easier to refine/modify behavior described in software than via ODEs. It is hoped that the ease of modification coupled with the open-source nature of *CarbMetSim* will allow it to evolve as a fine granularity software model of human metabolism useful for both research as well patient education.

4.2 Key Aspects in *CarbMetSim* Design

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

4.2.1 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 [14, 3]). The SAG contents include the *slowly digestible* starch (i.e. starch that gets digested in vitro between 20 and 120 minutes [14, 3]). 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* [3]. In *CarbMetSim*, an exercise activity is described in terms of its intensity in units of *MET*s, where 1 MET is 1 kcal of energy expenditure per kg of body weight per hour. The simulator can currently support only *aerobic* exercises.

4.2.2 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 of the user and the *highGlucoseLevel_* represents the typical peak BGL the user experiences. The default values of these parameters are 100 mg/dl and 200 mg/dl. Both *baseInsulinLevel_* and *peakInsulinLevel_* parameters assume values between 0 and 1 (with *baseInsulinLevel_* $\leqslant$ *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_*.

4.2.3 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. The number of *active* GLUT4 transporters depends on the insulin level in the bloodstream (unless the muscles are engaged in vigorous physical exercise). However, in people with diabetes, GLUT4 transporters have significantly less 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.

4.2.4 Modeling Glucose Consumption

Glucose serves as a key source of energy for various tissues, which either oxidize it completely or consume it anaerobically via *glycolysis*. Complete oxidation yields significant 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_* (different organs will have different values for these parameters). At each tick, the organ generates a poisson distributed random number (x) 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

Organ	glycolysisMin_ (μmol/kg/minute)	glycolysisMax_ (μmol/kg/minute)
Blood	0.5	5
Kidneys	0.5	5
Liver	1	16.5
Muscles	1	20
Intestine	0.5	5

Table 4.1: The minimum and the maximum amount of glucose consumed by the simulated organs for glycolysis [42, 118]. 1 μmol of glucose equals 0.1801559mg.

in a tick for glycolysis is given by: $x + insulinImpact \times (glycolysisMax\_ - x)$. Here, *insulinImpact* is a factor (between 0 and 1) that increases in value with increase in the *insulinLevel*. This factor is currently calculated using CDF of a normal distribution with a configurable mean and standard deviation. The simulator also uses a configurable multiplicative parameter *glycolysisImpact_* to modify the *glycolysisMax_* value associated with each organ. This parameter 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. The *glycolysisMin_* and *glycolysisMax_* values associated with various organs are shown in Table 4.1.

4.2.5 Modeling Gluconeogenesis

The liver and kidneys produce glucose via *gluconeogenesis* by consuming lactate, glycerol, glutamine and alanine [3, 42]. 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 [117, 3]. Table 4.2 shows the default values used in the simulator for average gluconeogenesis flux in *Liver* and *Kidneys* using different substrates. The simulator models the impact of insulin on gluconeogenesis flux by multiplying it with a factor (between 0 and 1) that decreases in value with increase in the *insulinLevel*. This factor is currently calculated using the complementary CDF of a normal distribution with a configurable mean and standard deviation. The simulator also uses a 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.

	Liver (μmol/kg/minute)	Kidneys (μmol/kg/minute)
Lactate	2.0	1.1
Glycerol	0.5	0.5
Glutamine	0.5	0.5
Alanine	1.0	0.1

Table 4.2: The gluconeogenesis flux for different substrates in *Liver* and *Kidneys* in post-absorptive state for a healthy person with *insulinResistance_* zero [42].

4.2.6 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 state (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 both glycogen synthesis and breakdown simultaneously at configured rates modified by two factors each. The first factor models the impact of insulin on glycogen synthesis and breakdown. For glycogen synthesis (breakdown), this factor (between 0 and 1) increases (decreases) in value with increase in the *insulinLevel*. For glycogen synthesis (breakdown), this factor is currently calculated using (complementary) CDF of a normal distribution with a configurable mean and standard deviation. The second factor affecting glycogen synthesis (breakdown), called *liverGlycogenSynthesisImpact_* (*liverGlycogenBreakdownImpact_*), simply modifies the configured rates multiplicatively. These factors can be used to model the impact of diabetes on glycogen synthesis and breakdown in the liver.

4.2.7 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_*, *glycolysisImpact_*, *gngImpact_*, *liverGlycogenSynthesisImpact_* and *liverGlycogenBreakdownImpact_* can be used to independently model the impact of diabetes on glucose absorption by muscles, glycolysis, gluconeogenesis and liver glycogen synthesis/breakdown. Additionally, there are configurable parameters that determine how the insulin level would impact these processes.

4.2.8 Modeling Glycemic Index (GI) Calculation

The glycemic index (GI) of a food is defined by the incremental area under the blood glucose curve (IAUC) in 120 minutes after the ingestion of 50 grams of carbohydrates in a test food, expressed as a percentage of the IAUC of an equal amount of a reference food (glucose or white bread). In CarbMetSim, white bread is used as a reference food. IAUC is generally calculated by summing up the areas between the blood glucose level curve and the base glucose level. We use a simple method to calculate the IAUC. Since our model is discrete not continuous, for every tick (minute) we decrement the base glucose level from the current glucose level and sum the decremented values up for the first 120 minutes after the ingestion of 50 grams of carbohydrates in a test food. The same method is used for white bread, and then we get the percentage of the IAUC of the test food to the IAUC of the reference food (white bread).

4.2.9 Randomization

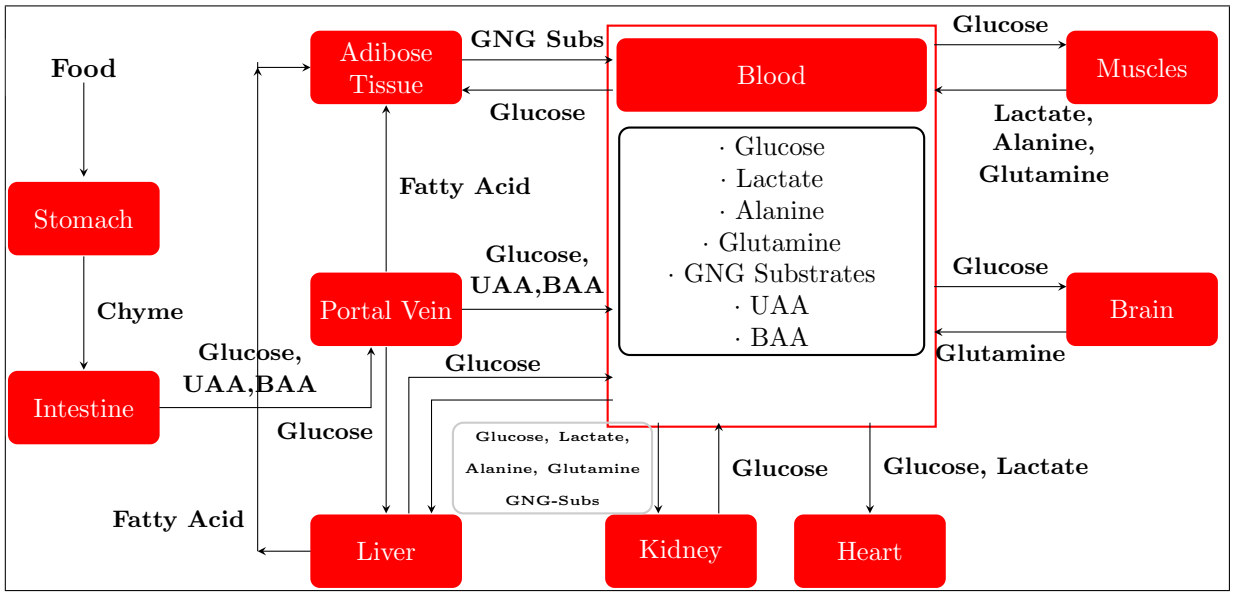
In the paragraphs above, we have seen several uses of poisson distributed random variables. This pattern is repeated throughout *CarbMetSim* implementation. A poisson distributed random number is used for any quantity that does not have a fixed value and for which only an average value is known. In the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

4.3 *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 all the *objects* that together implement the *CarbMetSim* simulator. Figure 4.1 shows an overview of the simulation design. The default values of various parameters listed here were obtained either from the provided references or determined experimentally to

Figure 4.1: A Brief Overview of the Simulation Design



provide best match against published measurements performed on non-diabetic humans [118].

4.3.1 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 reads the description of various foods (their composition in terms of *rapidly/slowly available glucose* (RAG/SAG), protein and fat) and exercise activities (their intensity in units of *MET*s) as well as the values for various parameters affecting the operation of different organs. The *HumanBody* also 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[1]. 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.

[1]The simulation results presented later do not use different parameter values for different body states.

4.3.2 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 Section 4.2.2. Also, some glucose is consumed for glycolysis in the manner described in Section 4.2.4.

4.3.3 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 [12, 109, 112]. 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 [112, 109] and power exponential [119]. Lehmann and Deutsch [105] 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. [87] 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 (formulated in the following equations) 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 100 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 (0.01 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 [109], 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.

$$totalFood = RAG + SAG + protein + fat \tag{4.1}$$

$$CalorificDensity = \frac{4.0 \cdot (RAG + SAG + protein) + 9.0 \cdot fat}{totalFood} \tag{4.2}$$

$$geSlope = 9.0 \cdot \frac{geSlopeMin}{CalorificDensity} \tag{4.3}$$

$$geBolus = geConstant + geSlope \cdot totalFood \tag{4.4}$$

$$ragToChyme = geBolus \cdot \frac{RAG}{totalFood} \tag{4.5}$$

$$sagToChyme = geBolus \cdot \frac{SAG}{totalFood} \tag{4.6}$$

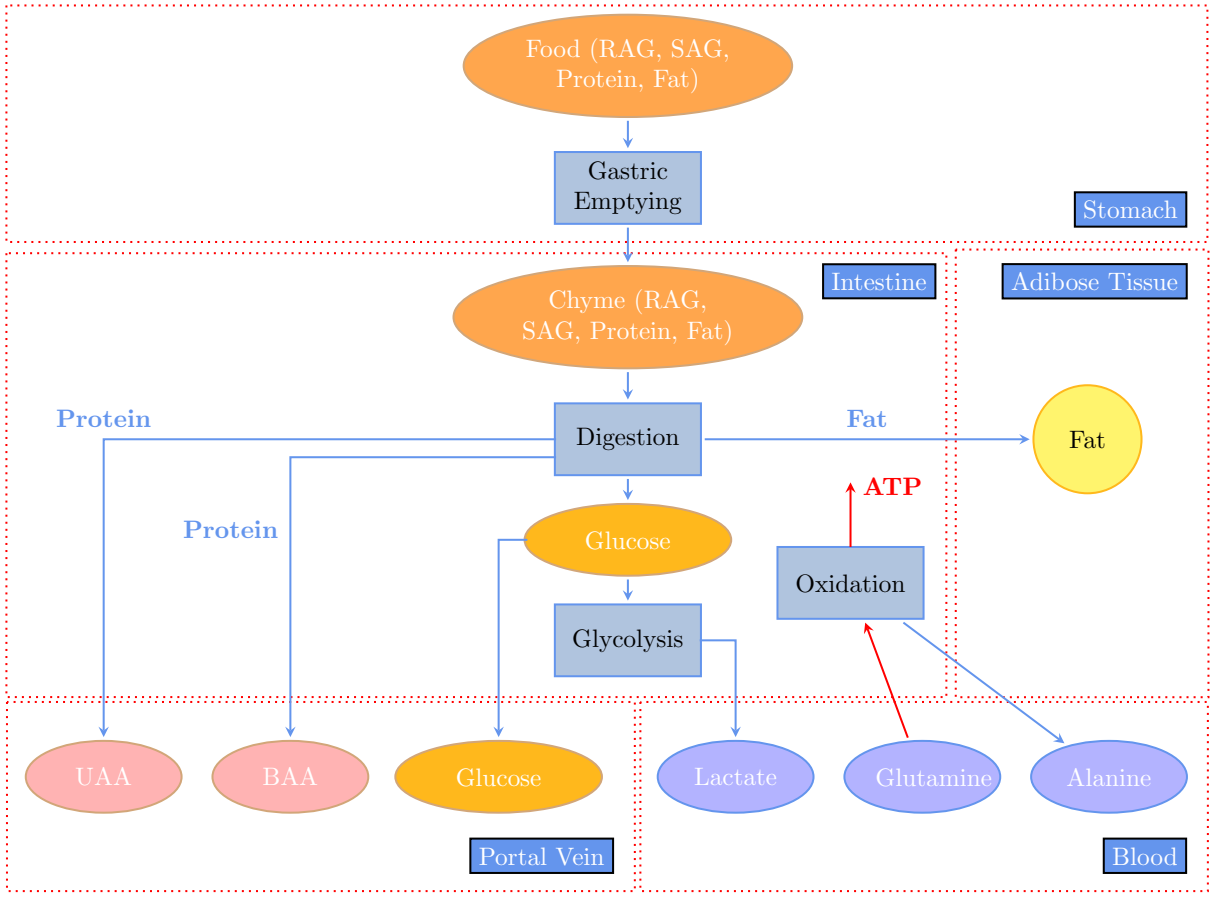
$$proteinToChyme = geBolus \cdot \frac{protein}{totalFood} \tag{4.7}$$

$$fatToChyme = geBolus \cdot \frac{fat}{totalFood} \tag{4.8}$$

4.3.4 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 [3]. However, 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: 5 minutes & 5 minutes for RAG and 60 minutes & 20 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

Figure 4.2: Overview of the Stomach, Intestine & Portal Vein Objects



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.

$$t = t_{current} - t_{foodAdded} \tag{4.9}$$

For RAG Digestion:

$$RAGConsumed = \left[origRAG \cdot 0.5 \cdot \left(erf\left(\frac{t - RAG\_Mean\_}{RAG\_StdDev\_ \cdot \sqrt{2}} \right) - erf\left(\frac{t-1 - RAG\_Mean\_}{RAG\_StdDev\_ \cdot \sqrt{2}} \right) \right) \right] \tag{4.10}$$

For SAG Digestion:

$$SAGConsumed = \left[origSAG \cdot 0.5 \cdot \left(erf\left(\frac{t - SAG\_Mean\_}{SAG\_StdDev\_ \cdot \sqrt{2}} \right) - erf\left(\frac{t-1 - SAG\_Mean\_}{SAG\_StdDev\_ \cdot \sqrt{2}} \right) \right) \right] \tag{4.11}$$

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-1s) and passive (GLUT2s) 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 [3]. 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 1000 mg/minute. The K_m value used is 20 mmol/l by default [3]. 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} = 1000 mg/minute, K_m = 20 mmol/l by default [3]).

Glycolysis: The intestinal cells get some of their energy via glycolysis of glucose to lactate in the manner described in Section 4.2.4. If the glucose in enterocytes (*glucoseInEnterocytes*) is not sufficient, the extra glucose needed for glycolysis comes from the bloodstream (the *Blood* object).

4.3.5 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 glu-

cose 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[2] in the *PortalVein* matches that of *Blood* before the import.
- Glucose transfer takes place from the *Intestine* to the *PortalVein* (as described previously in Section 4.3.4) and then from the *PortalVein* to the *Liver* (as described next in Section 4.3.6).
- 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.

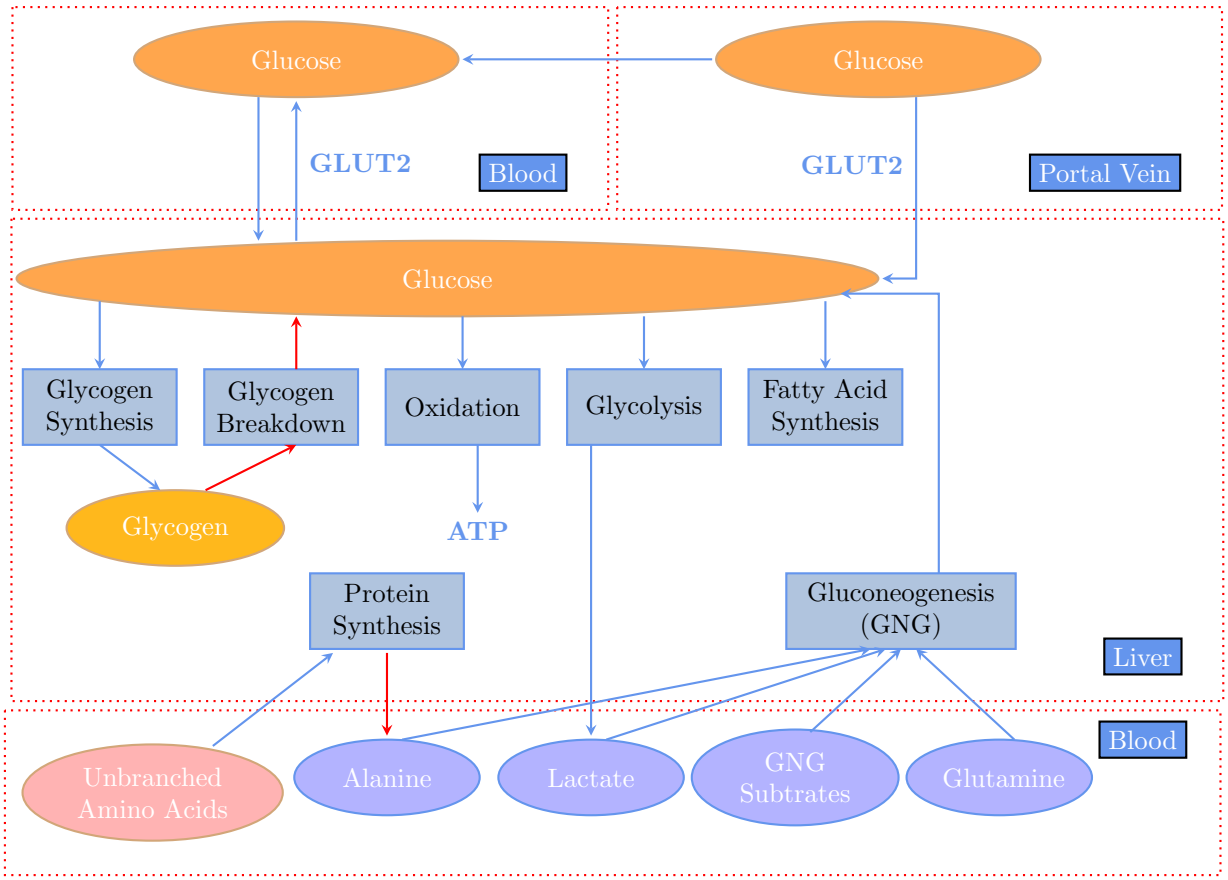
4.3.6 Liver

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 and *gluconeogenesis*, a pathway that also leads to glucose production using substrates like lactate, alanine and glycerol from the bloodstream. The gluconeogenesis flux also increases with the availability of the substrates in the bloodstream even if insulin level is high. Excess glucose is either used for glycogen synthesis (if insulin level is high) or leaves hepatocytes via GLUT2s and possibly other means (if insulin level is low). High insulin levels also cause some of the excess glucose to be converted to lipids. 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 state via glycogen breakdown and gluconeogenesis. Another important aspect of liver oper-

[2]The *PortalVein*'s volume, used to calculate the glucose concentration, is a configurable parameter with default value 5 dl.

ation is its oxidation of *unbranched* amino acids which provides for almost half of liver's energy requirements.

Figure 4.3: Overview of the Liver Object



CarbMetSim implements the liver operation in the *Liver* object. An overview of the liver object can be seen in Figure 4.3. At each tick, the *Liver* does the following:

- *Glucose Absorption/Release:* If the glucose concentration in the *PortalVein* is higher than that in the *Liver*, some glucose will be absorbed in the *Liver* via GLUT2s. Similarly, if the glucose concentration in the *Liver* is higher than that in the *Blood*, some glucose will be released to the *Blood* via GLUT2s. The amount of the glucose absorbed/release is determined using Michaelis Menten kinetics (with default average V_{max}=50mg/kg/min and default K_m=20 mmol/l[3]).

- *Glycogen Synthesis and Breakdown:* Some of the glucose in the *Liver* is converted to glycogen and some of the glycogen is broken down to glucose in the manner described in Section 4.2.6. By default, glycogen synthesis (breakdown) takes place at the maximum rate 76 μmol/kg/min when the *liverGlycogenSynthesisImpact_* (*liverGlycogenBreakdownImpact_*) 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:* The *Liver* consumes some glucose for glycolysis in the manner described in Section 4.2.4.
- *Gluconeogenesis:* The *Liver* produces glucose via gluconeogenesis in the manner described in Section 4.2.5.
- *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*.

4.3.7 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 4.2.4. 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 4.2.5. 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 [44] 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).

4.3.8 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 *branched chain* amino acids absorbed from the bloodstream to meet their energy needs.

Muscles Operation During Rest [3]: In the resting state, the muscles meet most of their energy needs via the oxidation of fatty acids and glucose absorbed from the bloodstream. 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 [120]. The glucose oxidation and glycolysis in muscles under resting conditions increases with insulin level in the bloodstream.

Muscles Operation During Aerobic Activity [3]: The muscles meet about 10% of their energy needs 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 insulin levels while the muscles are engaged in a vigorous physical activity. For moderate and high intensity exercise (more than 3 *MET* in intensity), a fraction of energy requirements is met by oxidation of glucose derived from the glycogen stored in the muscles. Subject to the availability of glycogen stored locally in the muscles, this fraction increases linearly from 0 to 30% of the energy needs as the exercise intensity increases from 3 *MET* to 6 *MET*. For exercise with intensity higher than 6 *MET*, about 30% of the energy needs is met via oxidation of glycogen-derived glucose as long as the muscle glycogen lasts. Another fraction of the energy needs is met by glycolysis of glucose 6-phosphate derived from glycogen stored in the muscles. The glycolysis level increases linearly with exercise intensity. The remaining energy needs are met via oxidation of fatty acids.

Implementation: In *CarbMetSim*, the skeletal muscles are implemented as the *Muscles* object. Currently, the simulator implements response to aerobic exercise only. 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}= 4 mg/kg/minute, default K_m= 5 mmol/l [3]) occurs in the manner described in Section 4.2.3. Also, basal absorption via GLUT1s occurs at a configured rate (by default 1.91 μmol/kg/minute [42]).
- *Glycolysis:* A fraction of the absorbed glucose (determined as described in Section 4.2.4) is consumed via glycolysis and the resulting lactate is added to the *Blood*.
- *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 [3]), some of the absorbed glucose (up to 12μmol/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.

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

- *Oxidation:* The *Muscles* oxidize glucose absorbed from *Blood* or derived from locally stored glycogen to meet a part of the energy needs of the body during exercise (as described earlier in this section).
- *Glycolysis:* Starting from the average minimum value *glycolysisMin_* (by default 1 μmol/kg/minute), the glycolysis flux increases linearly with exercise intensity with peak level *glycolysisMax_* (by default 15 μmol/kg/minute) achieved with exercise intensity 18 METs. 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 energy needs, *Muscles* consume fat (representing fatty acids) from the *AdiposeTissue* to meet the remaining energy needs.

4.3.9 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 remove fat from the *AdiposeTissue* in accordance with its energy needs.

Glucose Absorption: GLUT4 based glucose absorption (default V_{max}= 0.4 mg/kg/minute, default K_m= 5 mmol/l [3]) occurs in the manner described in Section 4.2.3. Also, basal absorption via GLUT1s occurs at a configured rate (by default 0 μmol/kg/min).

4.3.10 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 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 [3, 120]. In *CarbMetSim*, the brain operation is modeled as the *Brain* object which consumes on average 83.33 mg of glucose every minute from the *Blood* object.

4.3.11 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 [3]. 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 some glucose to meet its energy needs during fed state.

Glucose Absorption: GLUT4 based glucose absorption (default V_{max}= 0.4 mg/kg/minute, default K_m= 5 mmol/l [3]) occurs in the manner described in Section 4.2.3. Also, basal absorption via GLUT1s occurs at a configured rate (by default 0 μmol/kg/min).

Chapter 5

Simulation Results & Discussion

In this chapter, simulation results of CarbMetSim are presented and discussed by the help of comparing them with some very well known studies in the glucose metabolism area. Most of the parameters of CarbMetSim are found out in the literature, the ones that are not specifically expressed in the literature are estimated by running the simulations with different levels of values and comparing the results with the studies that are specifically discussed in this chapter. The parameters which are used both for a normal subject and a diabetic subject are listed in Appendix A.

There are 5 sections in this chapter. In the first one, the results of post-absorptive and resting state of CarbMetSim in a normal subject is validated by comparing them with the results of Shrayyef and Gerich, 2010 [43]. The second section discusses the results after glucose load in normal subjects and compares them with the results of Meyer et al., 2002 [42]. Changes in BGL after glucose load, hepatic and renal glucose release rates, and also peripheral glucose uptake rates are discussed in this section of the chapter. The next part discusses the results after a typical meal in normal and diabetic subjects. Specifically the results regarding blood glucose level, insulin level, glucose production and consumption rates, and also total amounts of glucose produced and consumed in some specific tissues and in some specific pathways during postprandial state in normal and diabetic subjects are compared with the ones in the Woerle et al., 2003 [118]. Fourth section is about glycemic index (GI) prediction results and its discussions. The last section discusses the CarbMetSim results of a typical day for a normal subject and a diabetic subject.

5.1 The Results of Post-Absorptive & Resting State in Normal Subjects

Blood glucose level, insulin level, glucose production and consumption rates should be stable in post absorptive-resting state of a non-diabetic subject. In this part of the document, the stableness of Carb-MetSim is presented in addition to the validation of its rates with some well known studies in this area [121, 3, 43]. The results of Gerich et al., Frayn et al., and Shrayyef et al. [121, 3, 43] are very similar regarding blood glucose level, insulin level, glucose production and consumption rates of the post absorptive-resting state. Blood glucose level graphs, glucose production and consumption rates are compared with the listed studies.

5.1.1 Glucose Production

80% of glucose release into the circulation in the postabsorptive state is from the liver [35, 36, 37]. 50% of the glucose entering the plasma is due to glycogenolysis (glycogen breakdown) and the remainder (5.0 μ/kg/min) is due to gluconeogenesis [35] (Figure 5.1). All the glucose released by the kidney is the result of gluconeogenesis [44]. The liver releases about four times as much as the kidney in the post-absorptive state. Their contribution (2.5-3.0 μ/kg/min) from gluconeogenesis is the same. However, the proportion of overall glucose release from renal gluconeogenesis increases even further with prolonged fasting.

The liver can be considered to be the only source of glucose due to glycogenolysis. In overnight fasted people, the liver contains about 75 g of glycogen. Thus, if it releases glycogen at a rate of 63 mg/min (5 μ/kg/min), glycogen stores would be totally depleted in about 20 h and the only source of glucose released into the circulation at this point would be gluconeogenesis. It is vital to understand that kidney and liver vary in their use of gluconeogenic precursors. Lactate is the principal gluconeogenic substrate in both organs, but otherwise the kidney preferentially uses glutamine [40], whereas the liver preferentially uses alanine [41] (i.e. see Figure 5.1).

Figure 5.1: Summary of post-absorptive glucose release

	Rate (μmol/kg/min)	% of total
I. Glucose release	10.0	100
A. Hepatic	8.0	80
1. Glycogenolysis	5.0	50
2. Gluconeogenesis	3.0	30
Lactate	1.3	13
Alanine	0.8	8
Other amino acids	0.2	2
Glycerol	0.4	4
Glutamine	0.3	3
B. Renal	2.0	20
1. Glycogenolysis	0	0
2. Gluconeogenesis	2.0	20
Lactate	1.2	12
Glutamine	0.4	4
Glycerol	0.2	2
Other amino acids	0.1	1
Alanine	0.1	1

Source: Shrayyef and Gerich, 2010 [43]

		Shrayyef and Gerich's Study [43]	**CarbMetSim**
Total Glucose Release		160	154.77
Hepatic	**Total**	128	126.32
	Glycogenolysis	80	78.15
	Gluconeogenesis	48	48.17
Renal	**Total**	32	28.46
	Gluconeogenesis	32	28.46

Table 5.1: Comparison of post-absorptive average glucose production rates (mg/min.) in non-diabetic

Comparison of Glucose Production in the CarbMetSim and in the Shrayyef and Gerich, 2010 [43]

As shown in Table 5.1, the glucose release rates, their proportions in liver and kidney, the amounts from glycogenolysis and gluconeogenesis are significantly similar. The small changes can be caused by different body weights in CarbMetSim and in Shrayyef and Gerich, 2010 [43].

5.1.2 Glucose Utilization

In the post-absorptive state, there is no net storage of glucose; consequently, glucose taken up by tissues is either completely oxidized to CO_2 or released back into the circulation as lactate, alanine, and glutamine

for reincorporation into glucose via gluconeogenesis. Most glucose used by the body can be accounted for by six tissues: the brain (45-60%), skeletal muscle (15-20%), kidney (10-15%), blood cells (5-10%), splanchnic organs (liver, digestive organs, etc.) (3-6%), and adipose tissue (2-4%). Glucose taken up by the brain is completely oxidized whereas that taken up by the kidney, blood cells, splanchnic tissues, and muscle mainly undergoes glycolysis. Recall that most of the body energy requirements are met by oxidation of FFA which compete with glucose as the fuel of choice in certain organs (e.g., skeletal muscles, heart, and possibly kidney).

Figure 5.2: Summary of post-absorptive glucose utilization

	Rate (μmol/kg/min)	% of total
Overall	10	100
Oxidation	∼7	∼70
Glycolysis	∼3	∼30
Tissues		
Brain	5	∼50
Skeletal muscle	2	∼20
Splanchnic organs	1	∼10
Kidney	1	∼10
Adipose tissue	0.5	∼5
Blood cells	0.5	∼5

Source: Shrayyef and Gerich, 2010 [43]

Comparison of Glucose Utilization in the CarbMetSim and in the Shrayyef and Gerich, 2010 [43]

	Shrayyef and Gerich's Study [43]	**CarbMetSim**
Total Glucose Utilization	155	157.5
Oxidation	105	109.7
Glycolysis	50	47.8
Brain	80	83.3
Skeletal Muscle	32	30
Splanchnic Organs	24	23.2
Kidney	16	15
Blood Cells	8	4.8

Table 5.2: Comparison of Post-Absorptive Glucose Utilization (mg/min.) in non-diabetic

As shown in Table 5.2, total glucose utilization rate, its proportions from oxidation and glycolysis, the percentages of various organs are significantly similar in CarbMetSim and in Shrayyef and Gerich, 2010

[43].

5.2 The Results After Glucose Load in Normal Subjects

Studies of glucose homeostasis in humans have generally dealt with the post-absorptive state, i.e., 12-14 h after an overnight fast. However, people usually eat at least three times a day, and assimilation of ingested nutrients takes 5-6 h [122]. The majority of the day, therefore, is spent in the postprandial state. Most studies evaluating postprandial glucose homeostasis have used an oral glucose load because of the convenience of oral glucose tolerance test. In this section, we investigate and compare the results of the literature and the ones of the CarbMetSim after an oral glucose load. The major factors influencing postprandial glucose homeostasis are those that affect suppression of endogenous glucose release and those that affect glucose uptake of tissues (most importantly peripheral tissue glucose uptake). Therefore, changes in BGL after glucose load, hepatic and renal glucose release rates, and also peripheral glucose uptake rates are discussed in this part of the document.

6-hour	Meyer et al. [42]	CarbMetSim
Total Glucose Release	118.2	119
Total Endogenous Glucose Release	43.2	45.8
Total Glycolysis	23	20.7
Total Oxidation	43	43.6
Total Glycogen Storage	44	46.3

Table 5.3: Comparison of total glucose release and disposal amounts (mg) in non-diabetic subjects after 75 gr glucose load

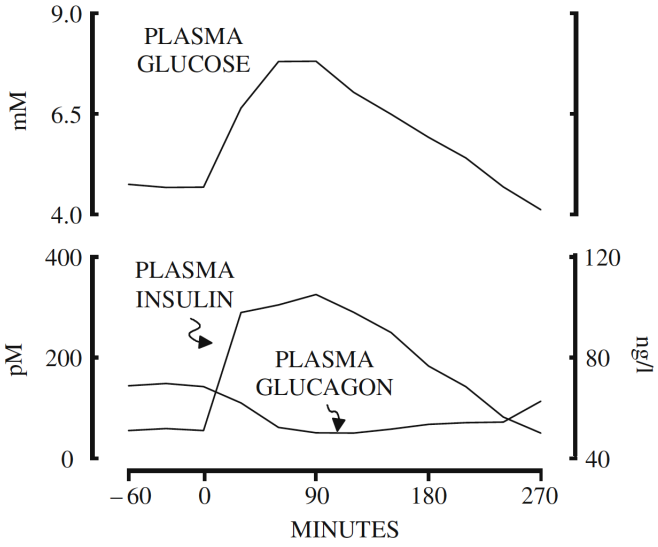
We compare total glucose release and disposal amounts in 6-hours period after ingestion of a 75 g oral glucose load in a normal subject in Table 5.3. Total glucose release, endogenous glucose release, glycolysis, oxidation, and glycogen storage amounts are all satisfying when compared with the amounts in the Meyer et al., 2002 [42].

5.2.1 Changes in BGL

After ingestion of 75 g glucose, plasma glucose levels increase to a peak in 30-60 min, usually not exceeding 7.8 mM (160 mg/dl) and gradually return to or slightly below post-absorptive values by 3-4 h (Figure 5.3). Plasma glucagon concentrations change reciprocally to those of insulin and are generally suppressed by about 50%. Early insulin release (within 30-60 min) plays a critical role in maintaining normal postprandial

glucose homeostasis.

Figure 5.3: Changes in plasma glucose, insulin, and glucagon after ingestion of a 75 g oral glucose load in normal subjects



Source: Meyer et al., 2002 [42]

Comparison of Frayn's [3] and CarbMetSim's BGL Graphs

Figure 5.4: Comparison of the changes in plasma glucose levels after ingestion of a 75 g oral glucose load in normal subjects

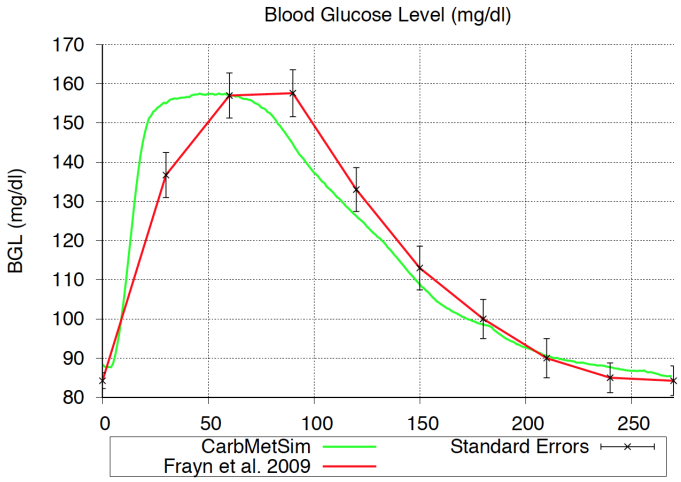


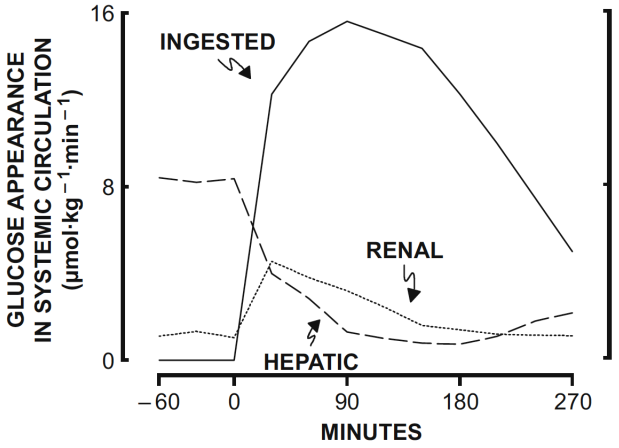
Figure 5.4 shows that CarbMetSim's BGL changes during 6-h period after ingestion of a 75 g oral glucose load in a non-diabetic subject (non-diabetic hypothetical user of the simulator as its parameters are expressed

in Appendix A) is following a very similar pattern that is specified in Frayn, 2009 [3]. Furthermore, Frayn, 2009 [3] is not the only study that validates CarbMetSim regarding BGL changes, as explained in the previous section, the results of the Meyer et al., 2002 [42] follows the same pattern as CarbMetSim, which reaches to the peak value (157 mg/dl) in around the same time period (30-60 min) and also returns to the post-absorptive rates (85 mg/dl) by 3-4 h.

5.2.2 Hepatic & Renal Glucose Release Rates

Endogenous glucose release by the liver decreases rapidly and is suppressed nearly 80-100% during the 5 h postprandial period (Figure 5.5). As a result, nearly 25 g less glucose due to endogenous production reaches the systemic circulation during this interval. In contrast to the liver, recent studies indicate that endogenous renal glucose release is not suppressed and actually increases during this period so that it exceeds hepatic glucose release. This increase in renal glucose release would facilitate more efficient hepatic glycogen replenishment.

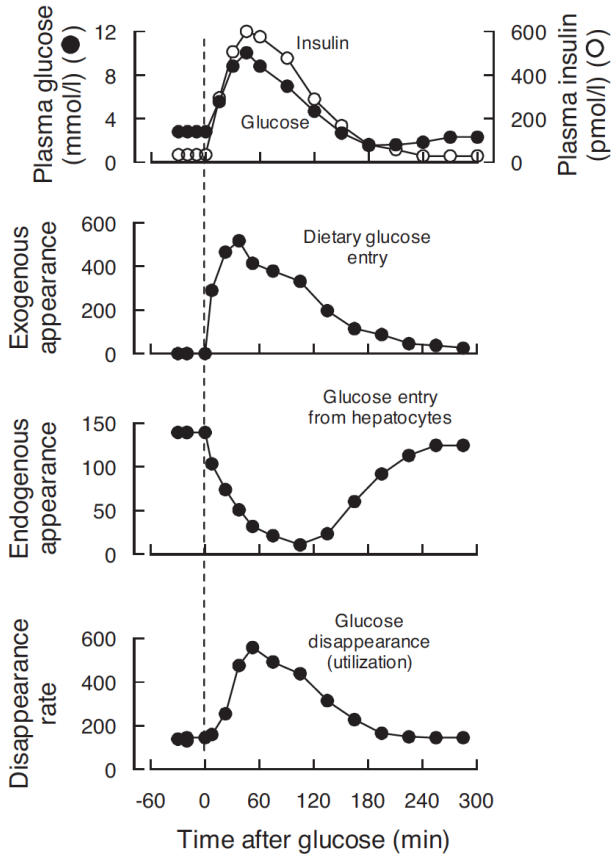
Figure 5.5: Changes in rates of entry of glucose into the circulation from ingested glucose, liver, and kidney



Source: Meyer et al., 2002 [42]

In Frayn, 2009 [3], the pattern shown in Figure 5.5 for the liver glucose release is different after 120 min which is shown in Figure 5.6. There can be some specific reasons that cause the differences after 120 min. CarbMetSim mostly follows a similar pattern with Frayn, 2009 after 120 min.

Figure 5.6: Rates of glucose release from liver, from exogenous (dietary) and endogenous sources in normal subjects before and after drinking 75g glucose in water.



Source: Frayn, 2010 [3]

Comparison of Frayn's [3] and CarbMetSim's Liver Glucose Release Rates

In CarbMetSim, endogenous glucose release from the liver decreases rapidly to almost 0 mg/min from the post-absorptive rate around 125 mg/min and returns back to its post-absorptive rate in around 200 min. The suppression time and returning time to the post-absorptive rate in CarMetSim are earlier than the ones in the Frayn, 2009 [3] and Meyer et al., 2002 [42]. However, the total amount of glucose release to the blood circulation in CarbMetSim, Meyer et al., 2002 [42], and Frayn, 2009 [3] are similar as shown in Table 5.3.

Comparison of Meyer et al.'s, 2002 [42] and CarbMetSim's Renal Glucose Release Rates

As seen in Figure 5.8, renal gluconeogenesis actually increases by approximately twofold after ingestion of a 75 g oral glucose load in normal subjects. It starts with 30 mg/min and increments to the rate of 62

Figure 5.7: Comparison of the changes in liver glucose release rates after ingestion of a 75 g oral glucose load in normal subjects

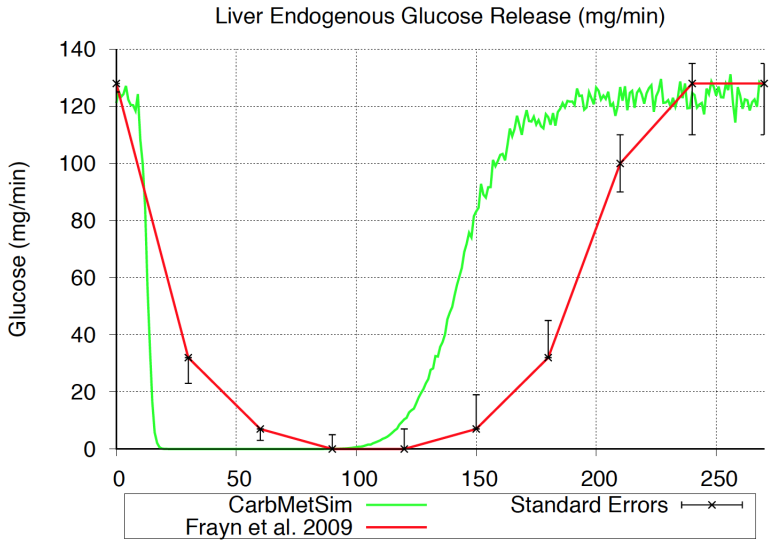
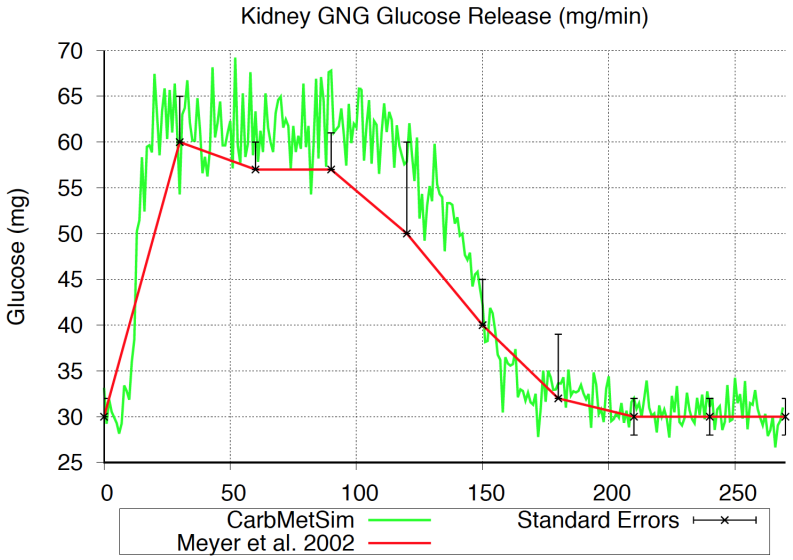


Figure 5.8: Comparison of the changes in renal glucose release rates after ingestion of a 75 g oral glucose load in normal subjects

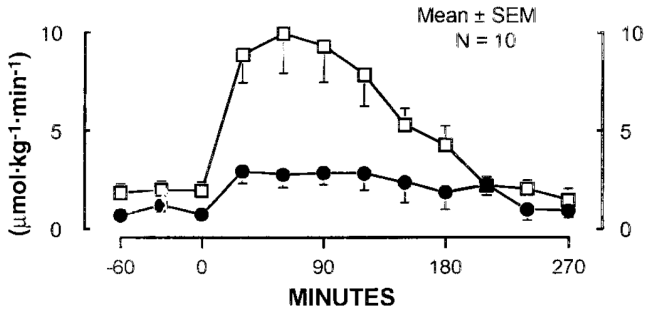


mg/min in 50 minutes, stays there around two hours, and returns to the post-absorptive rate in around 200 min.

5.2.3 Muscle & Renal Glucose Uptake Rates

Muscle glucose uptake averages 1.91 μ/kg/min before glucose ingestion and accounts for 22 % of systemic glucose disposal. During the initial 2 h after glucose ingestion, muscle glucose uptake increases approximately fivefold. Over the 4.5-h postprandial period, it averages 5.72 μ/kg/min accounted for 38 % of systemic glucose disposal. Renal glucose uptake (RGU) before glucose ingestion averages 0.89 μ/kg/min and accounted for 9.4 % of systemic glucose disposal. After glucose ingestion, RGU increases more than threefold to a peak value at 90 min and returns to post-absorptive rates at 240 min.

Figure 5.9: Renal and skeletal muscle glucose uptake, circle represents renal, square muscle



Source: Meyer et al., 2002 [42]

Comparison of Meyer et al.'s [42] and CarbMetSim's Muscle Glucose Uptake Rates

As seen in Figure 5.10, muscle glucose uptake actually increases by approximately fivefold after ingestion of a 75 g oral glucose load in normal subjects. It starts with 35 mg/min and increments to the rate of 200 mg/min in 60 minutes and returns to the post-absorptive rate of 35 mg/min in around 200 min.

Comparison of Meyer et al.'s [42] and CarbMetSim's Renal Glucose Uptake Rates

As seen in Figure 5.11, renal glucose uptake actually increases by approximately threefold after ingestion of a 75 g oral glucose load in normal subjects. It starts with 15 mg/min and increments to the rate of 38 mg/min in 60 minutes and returns to the post-absorptive rate of 15 mg/min in around 200 min.

Figure 5.10: Comparison of the changes in muscle glucose uptake rates after ingestion of a 75 g oral glucose load in normal subjects

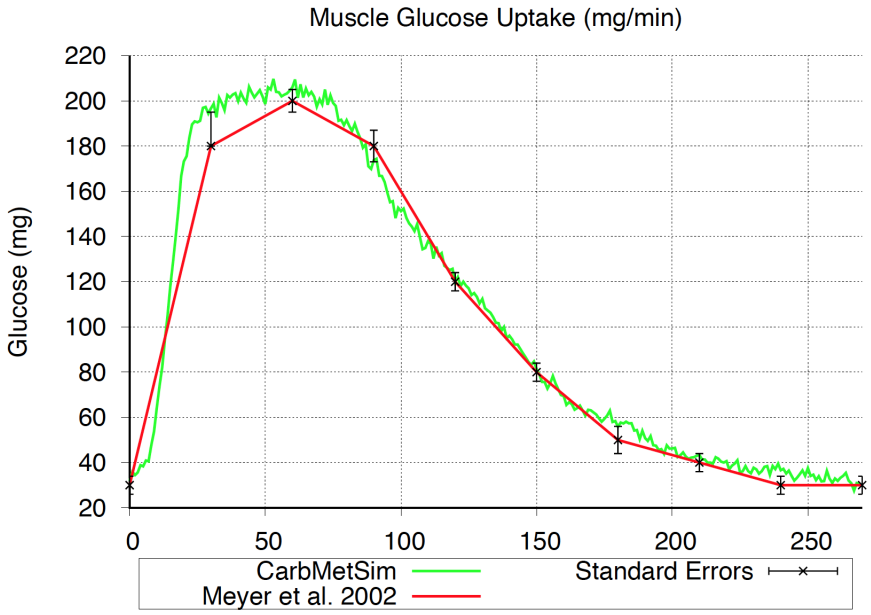
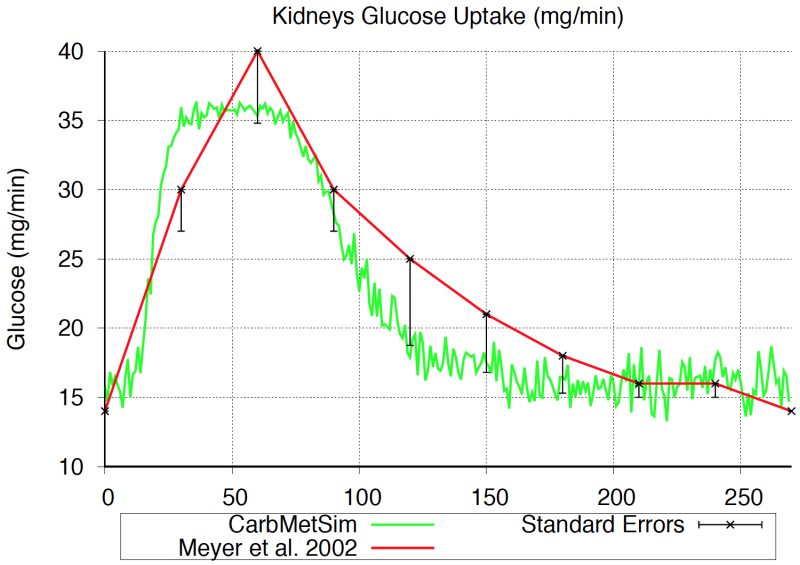


Figure 5.11: Comparison of the changes in renal glucose uptake rates after ingestion of a 75 g oral glucose load in normal subjects



5.3 The Results After a Typical Meal in Normal and Diabetic subjects

Considerable attention has recently been focused on the causes of high blood glucose levels in type 2 diabetic people. One of the well known ones is the study of Woerle et al. [118]. In this section, we analyze and

validate our results with the help of Woerle et al., 2003 [118]. We compare the results of Woerle et al., 2003 with CarbMetSim, furthermore we examine the causes of high blood glucose levels in diabetic subjects by discussing the simulation results. Most of the postprandial analysis in the literature were considered glucose load tests but in this study a mixed meal is considered which makes it more reliable.

In Woerle et al., 2003, 15 healthy subjects (7 men and 8 women, 49 yr of age, 89 kg body wt, BMI 30) with no family history of diabetes mellitus and normal glucose tolerance (according to World Health Organization criteria), and 26 subjects with T2DM (16 men and 10 women, 53 yr of age, 93 kg body wt, BMI 30) are considered as test subjects. At 10 AM, subjects are ingested a meal for 5 min. The size and composition of this meal is designed to simulate a normal breakfast. The size of the meal is 6 kcal/kg, with a composition of 50% carbohydrate, 30% fat, and 20% protein. Various calculation and measurement methods are used to get results regarding blood glucose level, insulin level, glucose production and consumption rates, and also total amounts of glucose produced and consumed in some specific tissues and in some specific pathways during postprandial state in normal and diabetic subjects.

Normal	**Woerle et al. [118]**	**CarbMetSim**
Total Release	78.9	78.9
Meal	58.9	58
Endogenous	20	20.9
Glycogen Breakdown	4.7	7.3
GNG	15.3	13.6

Table 5.4: Comparison of postprandial glucose releases in non-diabetic subjects (mg)

Normal	**Woerle et al. [118]**	**CarbMetSim**
Total Tissue Uptake	107.6	105.1
Total Tissue Glycolysis	67.1	65.2
Oxidative Glycolysis	45.6	44.2
Nonoxidative Glycolysis	21.5	21
Total Tissue Storage	40.5	39.9
Liver Storage	15.3	18.3
Muscle Storage	25.2	21.6

Table 5.5: Comparison of postprandial glucose disposal in non-diabetic subjects (mg)

We compare total glucose release and disposal amounts in 6-hours period after ingestion of a mixed meal in a normal subject and a diabetic subjects in Tables 5.4, 5.5, 5.6, 5.7. Total glucose release, endogenous glucose release, glycolysis, oxidation, and glycogen storage amounts are all satisfying in both non-diabetic

Diabetic	Woerle et al. [118]	CarbMetSim
Total Release	97.8	96.7
Meal	60.9	60
Endogenous	37	36.7
Glycogen Breakdown	10.1	13.4
GNG	26.9	23.3

Table 5.6: Comparison of postprandial glucose releases in diabetic subjects (mg)

Diabetic	Woerle et al. [118]	CarbMetSim
Total Tissue Uptake	107.8	105.7
Total Tissue Glycolysis	61.5	61
Oxidative Glycolysis	32.8	34.5
Nonoxidative Glycolysis	28.7	26.5
Total Tissue Storage	46.3	44.7
Liver	16.1	15
Muscle	30.2	29.7

Table 5.7: Comparison of postprandial glucose disposal in diabetic subjects (mg)

and diabetic subjects when compared with the amounts in the study of Woerle et al., 2003 [118].

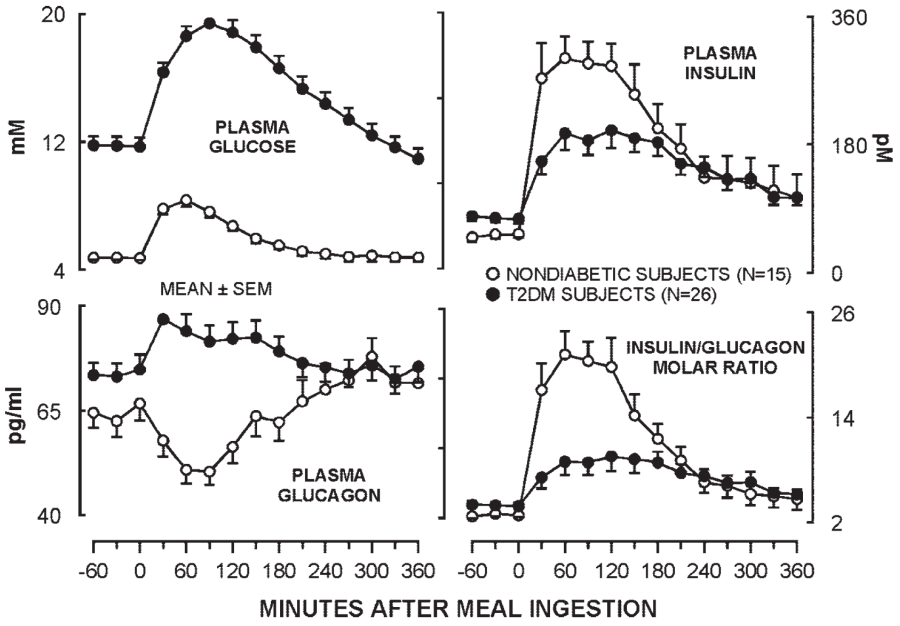
5.3.1 Blood Glucose Level

Diabetic subjects start with greater preprandial plasma glucose concentrations (11.7 vs. 4.7mM) and have more prolonged and greater increases after meal ingestion as shown in Figure 5.12. Consequently, their mean plasma glucose concentration during the 6-h postprandial period is almost three times as great as that of the non-diabetic subjects. Fasting plasma insulin concentrations are greater in the diabetic subjects, an index of insulin resistance is greater in the diabetic subjects. During the initial 90 min after meal ingestion, plasma insulin increases less in the diabetic subjects, averaging 179 vs. 290 pM in the non-diabetic subjects. We do not discuss glucagon in this document since we do not model glucagon effect in CarbMetSim. The units of the values in the figures of the listed studies are different than what we use, so they are all converted to the units that we use to compare them in the same graph.

Comparison of CarbMetSim's and Woerle et al.'s, 2003 [118] BGL graphs in Normal and Diabetic Subjects

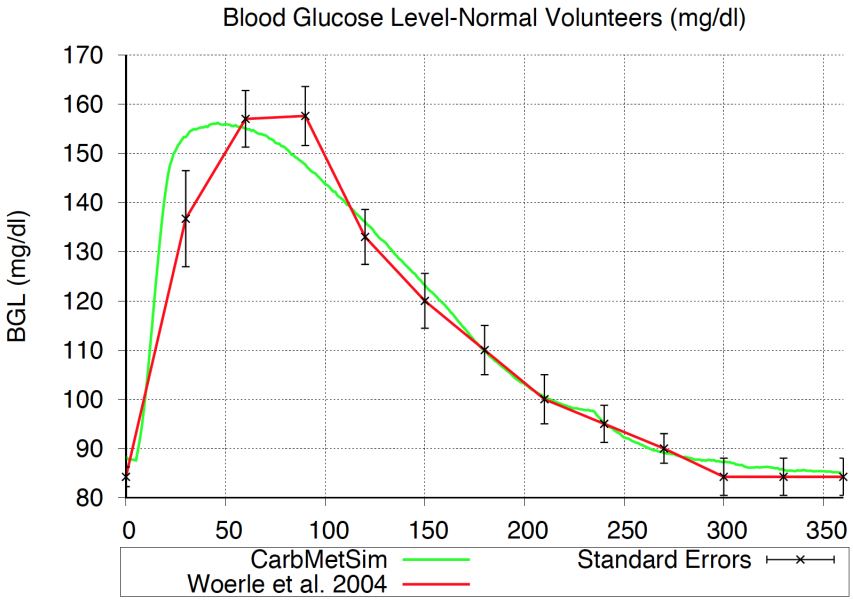
Figure 5.13 shows that CarbMetSim's BGL changes during 6-h period after ingestion of a mixed meal in a non-diabetic subject is following a very similar pattern that is specified in Woerle et al., 2003 [118], which

Figure 5.12: Arterial concentrations of plasma glucose, insulin, and glucagon



Source: Woerle et al., 2003 [118]

Figure 5.13: Comparison of the changes in plasma glucose levels after ingestion of a mixed meal in normal subjects



reaches to the peak value (155 mg/dl) in around the same time period (30-60 min) and also returns to the post-absorptive values (85 mg/dl) by 3-4 h.

Figure 5.14: Comparison of the changes in plasma glucose levels after ingestion of a mixed meal in diabetic subjects

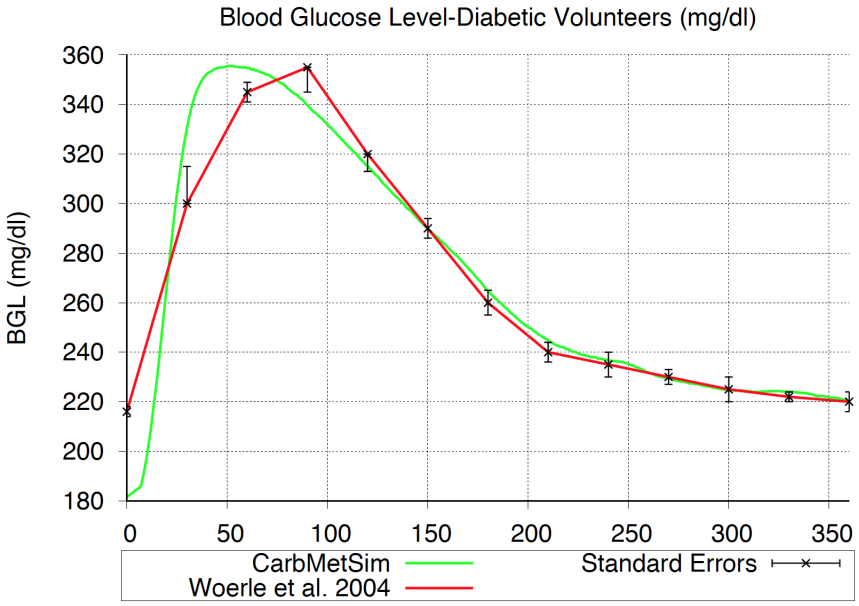
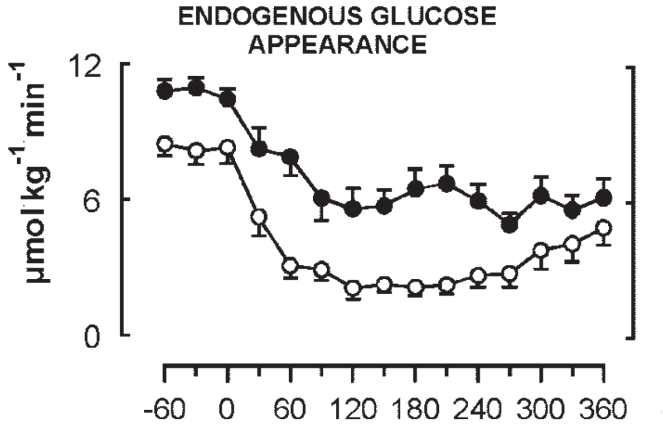


Figure 5.14 shows that CarbMetSim's BGL changes during 6-h period after ingestion of a mixed meal in a diabetic subject is following a very similar pattern that is specified in Woerle et al., 2003 [118], which reaches to the peak value (355 mg/dl) in around the same time period (30-60 min) and also returns to the post-absorptive values (218 mg/dl) by 3-4 h. The starting level of CarMetSim is less than the one in the Woerle et al., 2003 [118], this is because of the greater renal excretion rates in CarbMetSim.

5.3.2 Endogenous Glucose Production

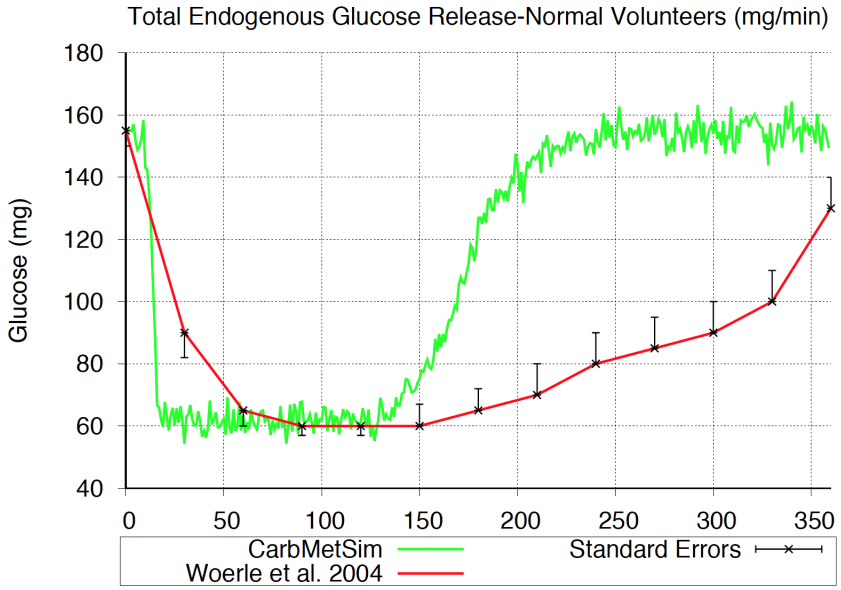
Post-absorptive Endogenous Glucose Release (EGR) is significantly greater in the diabetic subjects. This is attributable to increases in both glycogenolysis and gluconeogenesis. The relative contribution of gluconeogenesis to EGR is comparable in both groups. After meal ingestion, EGR decreases in both groups over the initial 90 min by comparable amounts. But because the diabetic subjects have greater preprandial values, their EGR during this period is almost twice as great as that of the non-diabetic subjects. EGR during the postprandial period is significantly correlated with the changes in plasma insulin.

Figure 5.15: Endogenous glucose release into plasma; filled circle represents diabetic, empty circle represents normal subjects



Source: Woerle et al., 2003 [118]

Figure 5.16: Comparison of the changes in endogenous glucose release rates after ingestion of a mixed meal in normal subjects



Comparison of CarbMetSim's and Woerle et al.'s, 2003 [118] EGR Graphs

Figure 5.16 shows the comparison of the changes in endogenous glucose release rates after ingestion of a mixed meal in normal subjects. CarbMetSim starts from a post-absorptive rate of 155 mg/min and decreases to the value of 60 mg/min in around 20 min, stays there for around 2 hours and returns back to the post-absorptive value of 155 mg/min in 4,5 hours. Post absorptive rates and the suppressed amounts are similar in both graphs, on the other hand in Woerle et al., 2003 [118], the release rate does not return back to the

post-absorptive rate in 6 hours and the suppression time in Woerle et al., 2003 [118] is greater than the one in CarbMetSim.

Figure 5.17: Comparison of the changes in endogenous glucose release rates after ingestion of a mixed meal in diabetic subjects

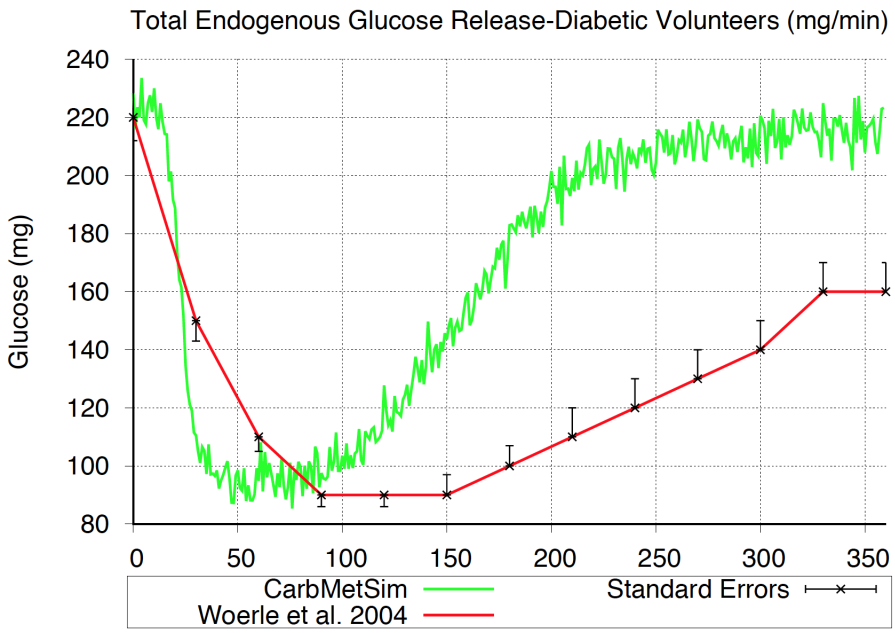
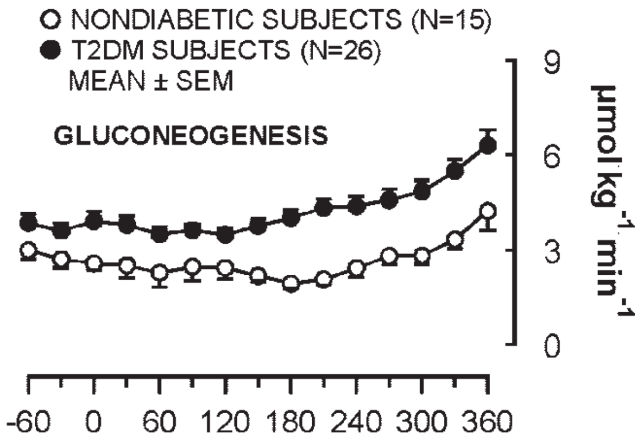


Figure 5.17 shows the comparison of the changes in endogenous glucose release rates after ingestion of a mixed meal in diabetic subjects. CarbMetSim starts from a post-absorptive rate of 220 mg/min and decreases to the rate of 90 mg/min in around 20 min, stays there for around 2 hours and returns back to the post-absorptive value of 220 mg/min in 4,5 hours. Post absorptive rates and the suppressed amounts are similar in both graphs, on the other hand in Woerle et al., 2003 [118], the release rate does not return back to the post-absorptive value in 6 hours and the suppression time in Woerle et al., 2003 [118] is greater than the one in CarbMetSim.

5.3.3 Glucose Production via Gluconeogenesis

During post-absorptive state, glucose production via gluconeogenesis (GNG) is significantly greater in the diabetic subjects. After meal ingestion, gluconeogenesis decreases slightly in both groups over the initial 90 min by comparable amounts. Then, it increases again slightly which reaches to the starting point in both groups as shown in Figure 5.18.

Figure 5.18: Glucose production via Gluconeogenesis



Source: Woerle et al., 2003 [118]

Comparison of CarbMetSim's and Woerle et al.'s, 2003 [118] GNG Graphs

Figure 5.19: Comparison of the changes in glucose production rates via GNG after ingestion of a mixed meal in normal subjects

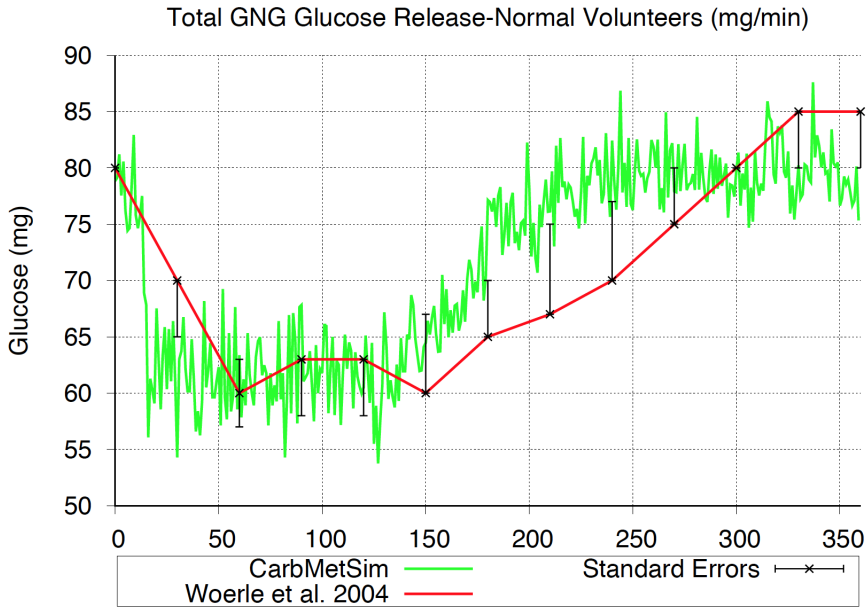


Figure 5.19 shows the comparison of the changes in glucose production rates via GNG after ingestion of a mixed meal in normal subjects. CarbMetSim starts from a post-absorptive value of 80 mg/min and decreases to the value of 60 mg/min in around 20 min, stays there for around 2 hours and returns back to the post-absorptive value of 80 mg/min in 4,5 hours. Post absorptive values, the suppressed amounts, suppression and return times are similar in both graphs.

Figure 5.20: Comparison of the changes in glucose production rates via GNG after ingestion of a mixed meal in diabetic subjects

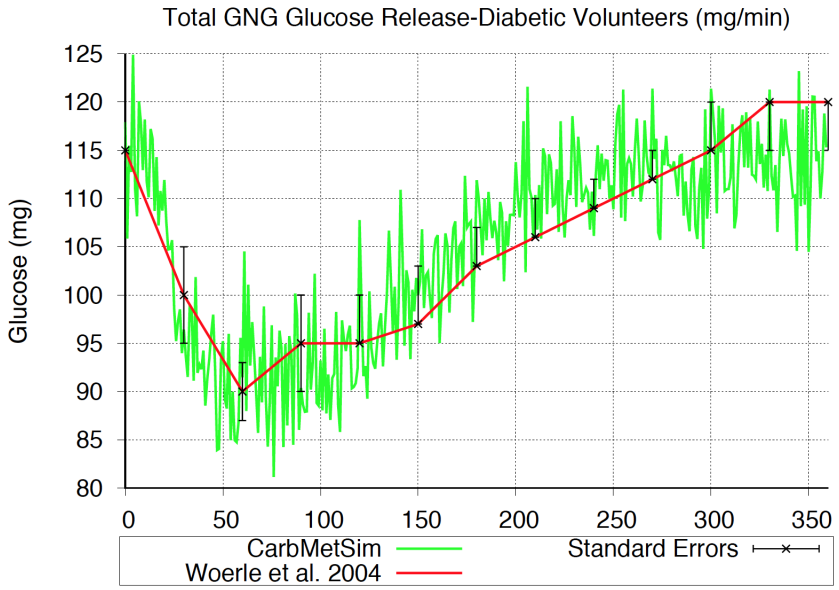
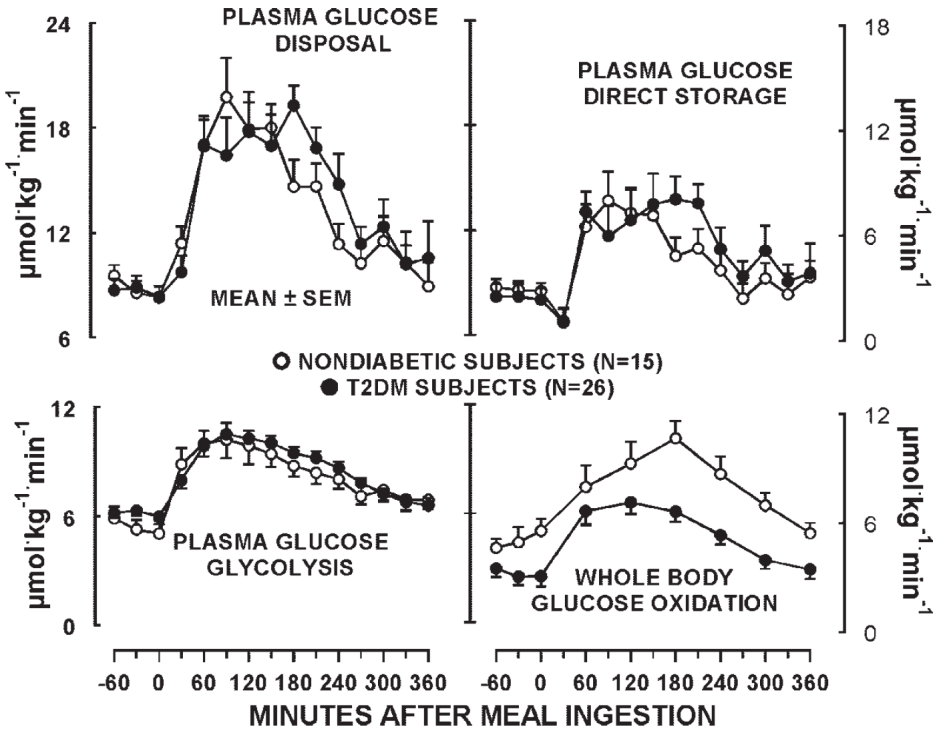


Figure 5.20 shows the comparison of the changes in glucose production rates via GNG after ingestion of a mixed meal in diabetic subjects. CarbMetSim starts from a post-absorptive value of 115 mg/min and decreases to the value of 90 mg/min in around 60 min, stays there for around 2 hours and returns back to the post-absorptive value of 115 mg/min in 4,5 hours. Post absorptive values, the suppressed amounts, suppression and return times are similar in both graphs.

5.3.4 Glucose Storage, Glycolysis and Oxidation in Peripheral Tissues

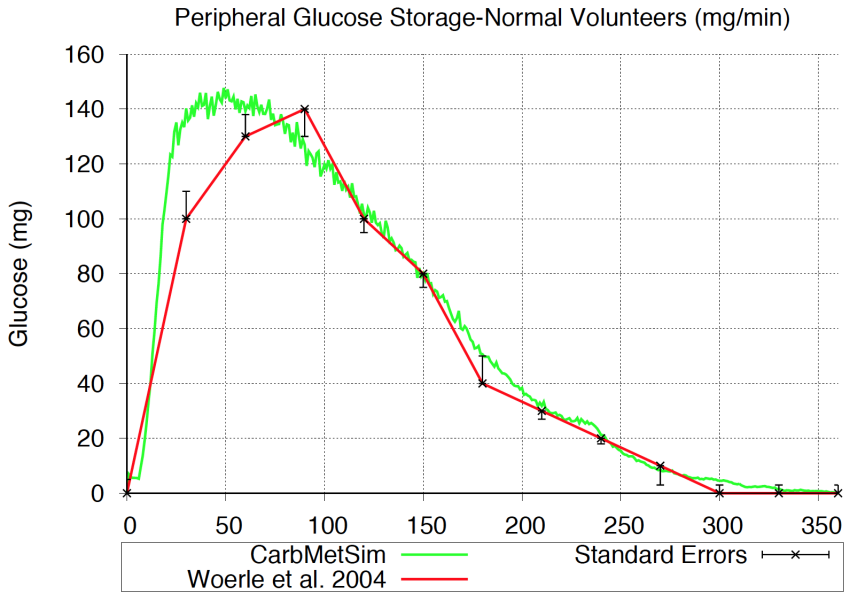
The patterns of glucose storage, total glycolysis, and tissue uptake of postprandial changes in diabetic and non-diabetic subjects are similar. Moreover, during the 6-h postprandial period, peripheral tissue (tissues other than liver and intestine) uptake of glucose, glycolysis, and direct storage are not significantly different in diabetic and non-diabetic subjects (Figure 5.21). The proportion of glucose taken up by peripheral tissues that undergoes glycolysis tends to be lower in diabetic subjects. Postprandial whole body carbohydrate oxidation is also reduced in the diabetic subjects, whereas non-oxidative glycolysis is increased in the diabetic subjects.

Figure 5.21: Peripheral glucose uptake, glycolysis, oxidation and direct storage



Source: Woerle et al., 2003 [118]

Figure 5.22: Comparison of the changes in peripheral storage rates after ingestion of a mixed meal in normal subjects



Comparison of CarbMetSim's and Woerle et al.'s, 2003 [118] Peripheral Storage Graphs

Figure 5.22 shows the comparison of the changes in peripheral storage rates after ingestion of a mixed meal in normal subjects. CarbMetSim starts from a post-absorptive storage rate of 0 mg/min, increments to the rate of 140 mg/min in around 60 min and returns back to the post-absorptive rate of 0 mg/min in 5 hours. Post absorptive rates, the peak amounts, incremental times to the peak values and return times to the post absorptive rates are similar in both graphs.

Figure 5.23: Comparison of the changes in peripheral storage rates after ingestion of a mixed meal in diabetic subjects

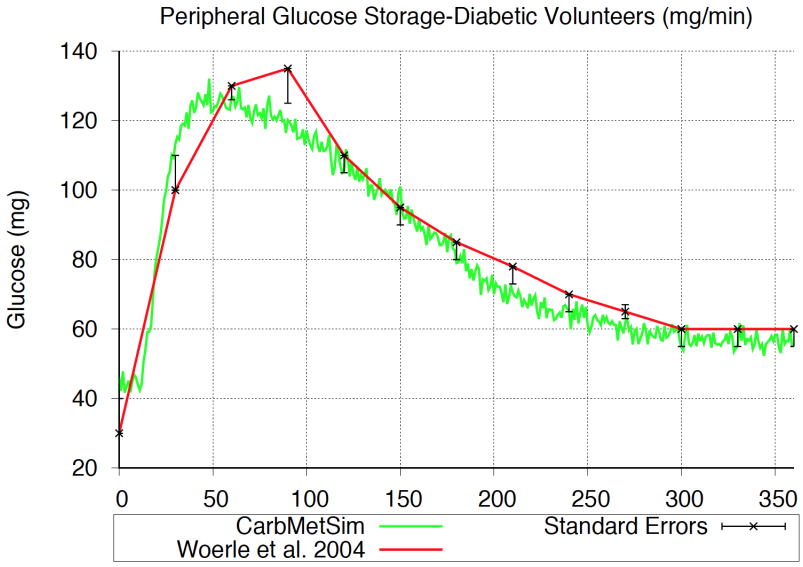
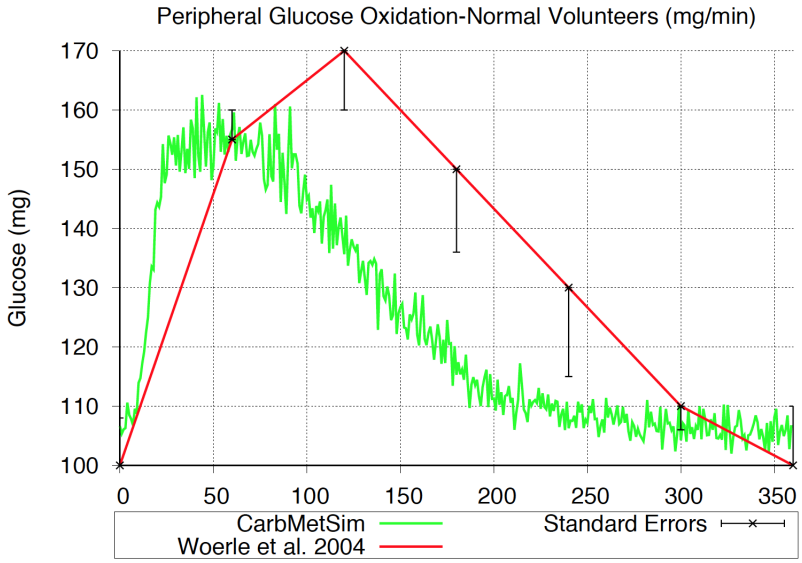


Figure 5.23 shows the comparison of the changes in peripheral storage rates after ingestion of a mixed meal in diabetic subjects. CarbMetSim starts from a post-absorptive storage rate of 40 mg/min, increments to the rate of 140 mg/min in around 60 min and returns back to the post-absorptive rate of 60 mg/min in 5 hours. Post absorptive rates, the peak amounts, incremental times to the peak values and return times to the post absorptive rates are similar in both graphs.

Comparison of CarbMetSim's and Woerle et al.'s, 2003 [118] Peripheral Oxidation Graphs

Figure 5.24 shows the comparison of the changes in peripheral oxidation rates after ingestion of a mixed meal in normal subjects. CarbMetSim starts from a post-absorptive oxidation rate of 105, increments to the rate of 160 mg/min in around 60 min and returns back to the post-absorptive rate of 105 mg/min in 3.5 hours. Post absorptive rates and return times to the post absorptive values are similar in both graphs. On

Figure 5.24: Comparison of the changes in peripheral oxidation rates after ingestion of a mixed meal in normal subjects



the other hand, peak values, incremental times to the peak values are close but not very similar.

Figure 5.25: Comparison of the changes in peripheral oxidation rates after ingestion of a mixed meal in diabetic subjects

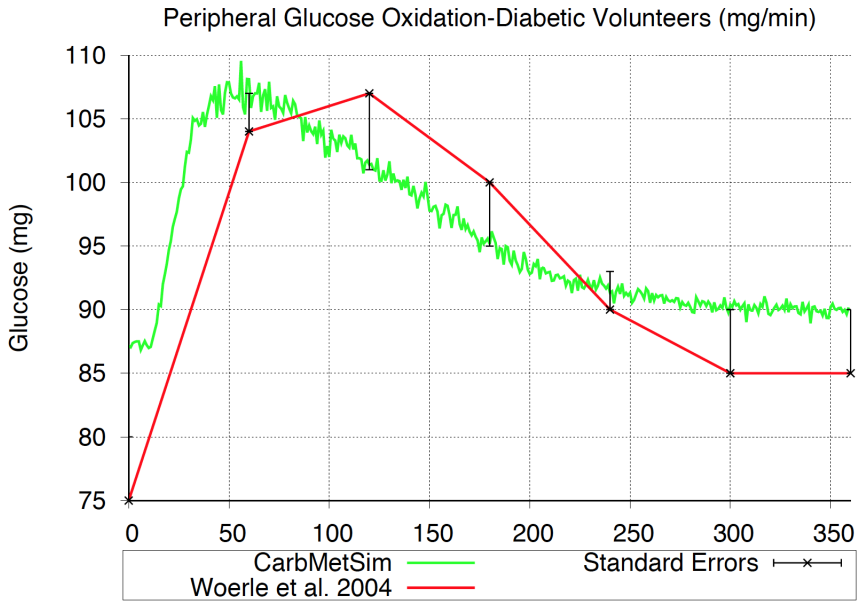


Figure 5.25 shows the comparison of the changes in peripheral oxidation rates after ingestion of a mixed meal in diabetic subjects. CarbMetSim starts from a post-absorptive oxidation rate of 87 mg/min, increments to

the value of 107 mg/min in around 60 min and returns back to the post-absorptive rate of 90 mg/min in 3.5 hours. Post absorptive rates, the peak amounts, incremental times to the peak values and return times to the post absorptive rates are similar in both graphs. The only difference is their starting rates.

Comparison of CarbMetSim's and Woerle et al.'s, 2003 [118] Peripheral Glycolysis Graphs

Figure 5.26: Comparison of the changes in peripheral glycolysis rates after ingestion of a mixed meal in normal subjects

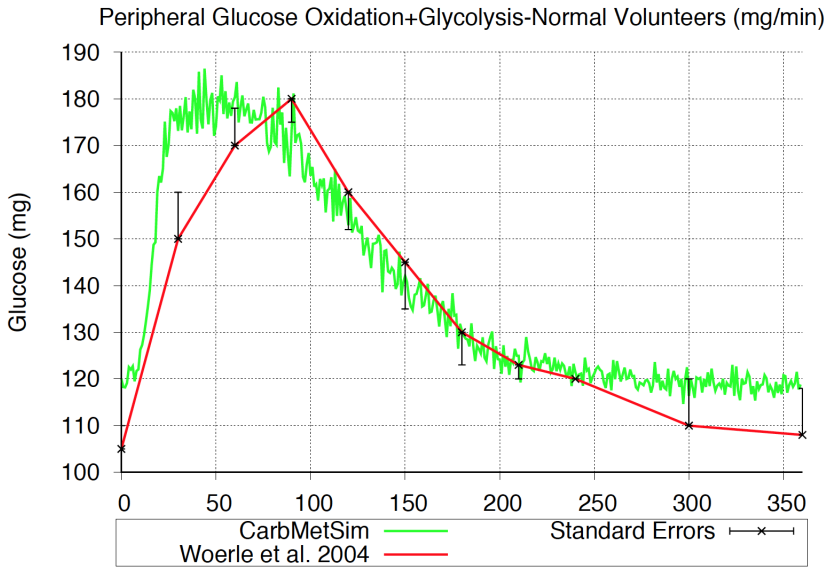
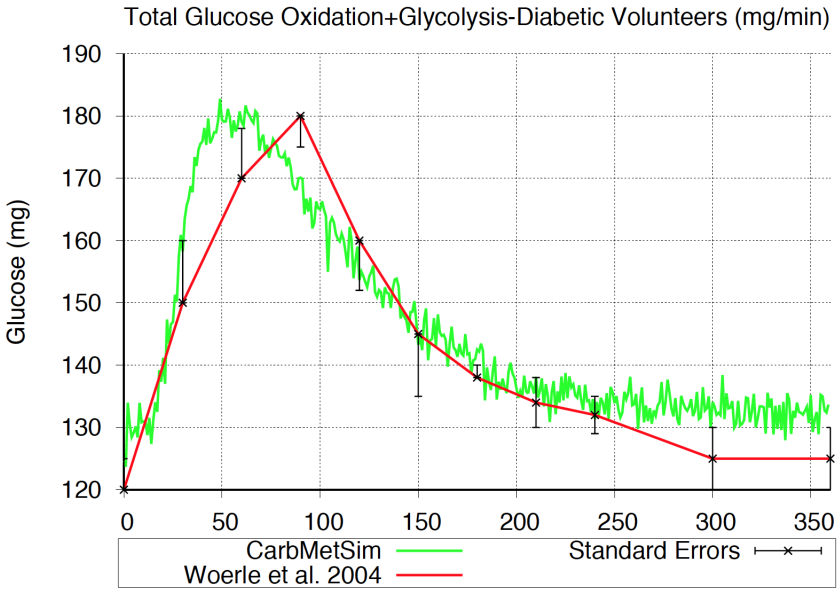


Figure 5.26 shows the comparison of the changes in peripheral glycolysis rates after ingestion of a mixed meal in normal subjects. CarbMetSim starts from a post-absorptive glycolysis rate of 120 mg/min, increments to the value of 180 mg/min in around 60 min and returns back to the post-absorptive rate of 120 mg/min in 3.5 hours. Post absorptive rates, the peak amounts, incremental times to the peak values and return times to the post absorptive rates are similar in both graphs.

Figure 5.27 shows the comparison of the changes in peripheral glycolysis rates after ingestion of a mixed meal in diabetic subjects. CarbMetSim starts from a post-absorptive glycolysis rate of 130 mg/min, increments to the value of 180 mg/min in around 60 min and returns back to the post-absorptive rate of 130 mg/min in 3.5 hours. Post absorptive rates, the peak amounts, incremental times to the peak values and return times to the post absorptive rates are similar in both graphs.

Figure 5.27: Comparison of the changes in peripheral glycolysis rates after ingestion of a mixed meal in diabetic subjects



5.4 Glycemic Index Prediction Results

Glycemic Index (GI) prediction of 30 foods and comparison of the predicted values with the values listed in the literature are examined in Table 5.8. Table 5.9 provides the GI prediction errors, such as mean and median of the absolute percentage errors, furthermore quarters and maximum of them. It is really complicated to find an exact value of the GI for a typical food even in the literature. There are several factors which affect GI of foods. The protein, fat, fiber amounts of the food and the different cooking times are the major factors to see different values of GI even in various studies of the literature. For instance, especially for plain pasta there are more than 5 different GI values listed in the well known studies. We tried our best to find the most accurate values to compare our results with. Our prediction results are very accurate for some of the foods. However, we can improve the accuracy of CarbMetSim by adding fiber and cooking effects to the gastric emptying model of the simulator in the future.

Rank	Food Name	iAUC	Predicted GI	Actual GI	Abs. % Error
1	White Bread	5239.53	100	100	0.00%
2	Frozen Pea	3938.83	75	74	1.59%
3	Weetabix Cereals	5573.74	106	109	2.40%
4	Ryvita Crispbread	4836.30	92	95	2.84%
5	Wholemeal Bread	5024.42	96	99	3.14%
6	Potato	5097.66	97	101	3.67%
7	Pasta Macaroni	3485.40	67	64	3.94%
8	Haricot Beans	2238.00	43	45	5.08%
9	Brown Rice (Long)	4122.82	79	83	5.20%
10	Oatmeal Biscuits	4335.96	83	78	6.10%
11	Marrowfat Peas	3320.96	63	68	6.79%
12	Rich Tea Biscuits	4515.78	86	80	7.73%
13	Kidney Bean	2370.80	45	42	7.73%
14	Kidney Beans (Canned)	3571.60	68	74	7.88%
15	Buckwheat Cereals	3548.77	68	74	8.47%
16	Water Biscuits	5174.44	99	91	8.52%
17	Shredded Wheat Cereals	4632.52	88	97	8.85%
18	Parboiled Rice	3829.43	73	67	9.09%
19	White Rice Long	4550.23	87	96	9.54%
20	Pasta Spaghetti	3854.48	74	67	9.80%
21	Digestive Biscuits	3871.07	74	82	9.90%
22	Oat Bran Cereals	3936.32	75	84	10.56%
23	Rice Krispies	5476.19	105	117	10.67%
24	Chickpea (Canned)	3526.30	67	60	12.17%
25	Sweetcorn Cereals	5142.42	98	87	12.81%
26	Puffed Wheat Cereals	4996.26	95	110	13.31%
27	Potato Crisps	4488.88	86	74	15.77%
28	Porridge Oats Cereals	4453.45	85	71	19.71%
29	Pinto Beans	3802.96	73	60	20.97%
30	Instant Potato	4787.13	91	116	21.24%

Table 5.8: Glycemic Index Prediction Results of 30 Foods

5.5 Comparison of a Typical Day for Diabetic and Non-Diabetic Subjects

In this section we consider two hypothetical users, one normal and one diabetic, in which their related parameters are listed in Table 5.10. Table 5.11 represents the specifications of a typical day. Blood glucose

	Abs. % Error
Mean	8.85%
1st Quar.	5.11%
Median	8.50%
3rd Quar.	10.64%
Max	21.24%

Table 5.9: Glycemic Index Error Calculation

	Normal Person	Diabetic Person
bodyWeight	65 kg	65 kg
baseGlucoseLevel_	100 mg/dl	150 mg/dl
highGlucoseLevel_	150 mg/dl	350 mg/dl
insulinResistance_	0	0.5
insulinPeakLevel_	1	0.5

Table 5.10: Simulation parameters for two hypothetical users

and insulin levels, glucose production and utilization rates of both normal and diabetic subjects are considered and compared using CarbMetSim. The results show clearly that average blood glucose level of a diabetic person in a typical day is almost threefold of the non-diabetic person's. The post-absorptive insulin level of the diabetic person is higher than the non-diabetic one, whereas the postprandial insulin level of the diabetic is almost half of the insulin level of the non-diabetic. By comparing the glucose production and utilization rates of both a normal and a diabetic person, we clearly understand that the reason of the high blood glucose levels in the diabetic one is the insulin effect on the insulin dependent pathways in glucose metabolism. Insulin dependent pathways are glycogen synthesis and glycogen breakdown in liver and muscles, glucose uptake in peripheral tissues (mostly dependent on GLUT4s for the transport of glucose), glycolysis, and endogenous glucose release from liver and kidney. We see from the simulation results that the gluconeogenesis in liver and kidney, and also glycogenolysis in liver have higher rates in various states of the body. Glucose uptake by peripheral tissues is decremented in diabetic subjects which causes higher glucose levels. The decreased insulin levels is not the only reason of the increased endogenous glucose release and decreased glucose uptake by some tissues, the insulin resistance of the peripheral tissues is another factor that should be considered to understand the reasons of high blood glucose levels. Another significant result of CarbMetSim that we should consider is the effect of the exercise on blood glucose levels in both diabetic and normal subjects. During exercise, the blood glucose levels of diabetic and non-diabetic subjects decrease significantly even the insulin level is less and the insulin resistance level is greater than the normal one.

	RAG	SAG	Protein	Fat	Dur.	Intensity
Breakfast (8am)	25g	30g	25g	20g		
Lunch (1pm)	40g	40g	30g	25g		
Snack (4pm)	30g	10g	5g	15g		
Walk (6pm)					30min	5 MET
Dinner (8pm)	40g	40g	30g	25g		
Total	135g	120g	90g	85g		

Table 5.11: Simulated events

Figure 5.28: Blood Glucose Level (mg/dl)

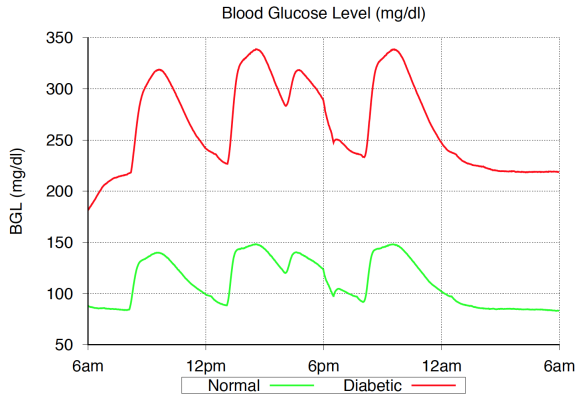


Figure 5.29: Insulin Level

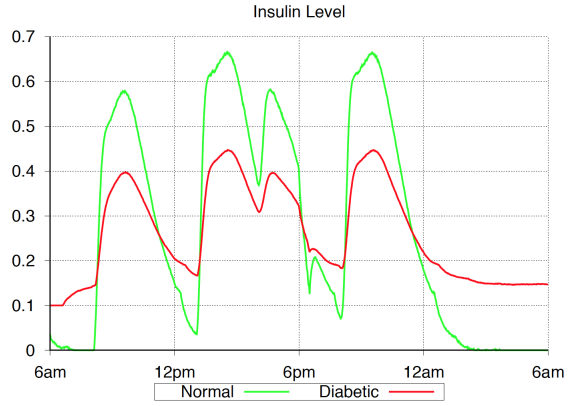


Figure 5.30: Digested Glucose Release (mg/min)

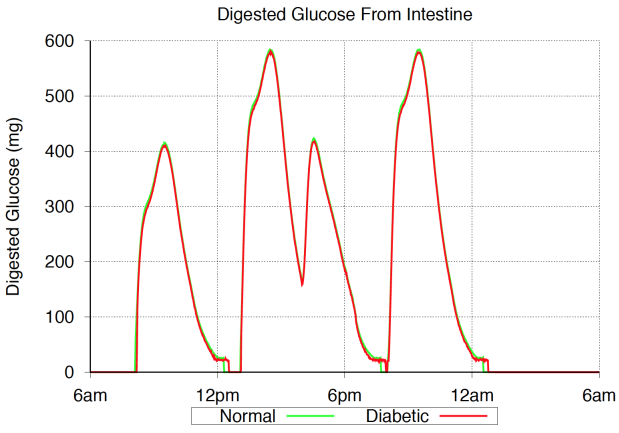


Figure 5.31: Glucose Produced From Liver Glycogen Breakdown (mg/min)

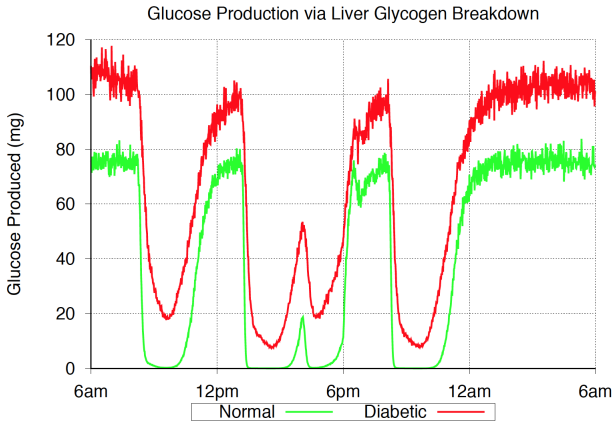


Figure 5.32: Liver GNG (mg/min)

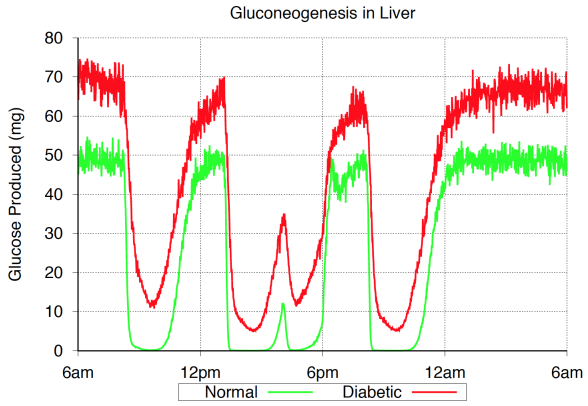


Figure 5.33: Liver Glycogen Synthesis (mg/min)

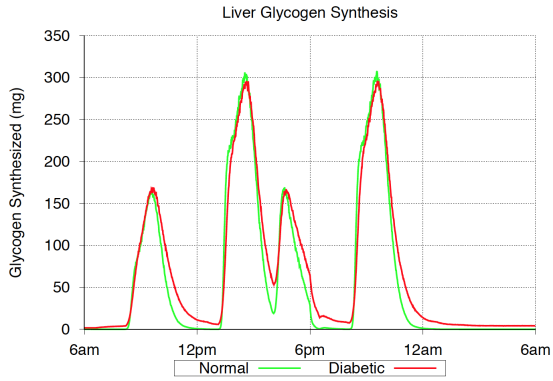


Figure 5.34: Liver Glycogen Amount (mg)

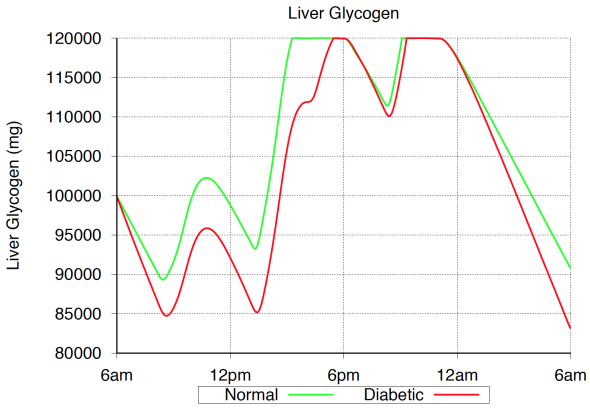


Figure 5.35: Liver Glycolysis (mg/min)

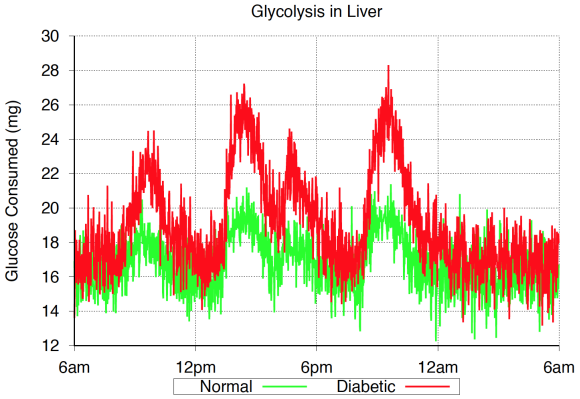


Figure 5.36: Muscle Glucose Uptake (mg/min)

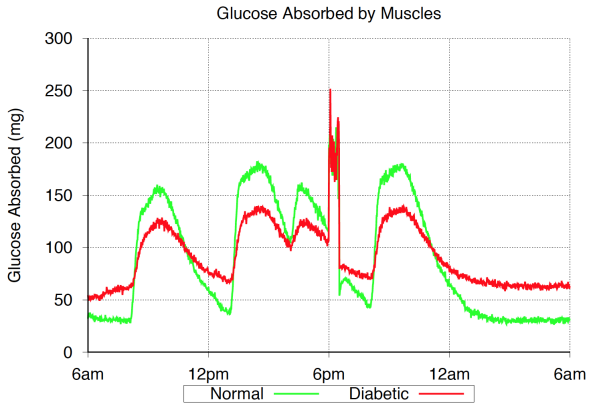


Figure 5.37: Muscle Glycolysis (mg/min)

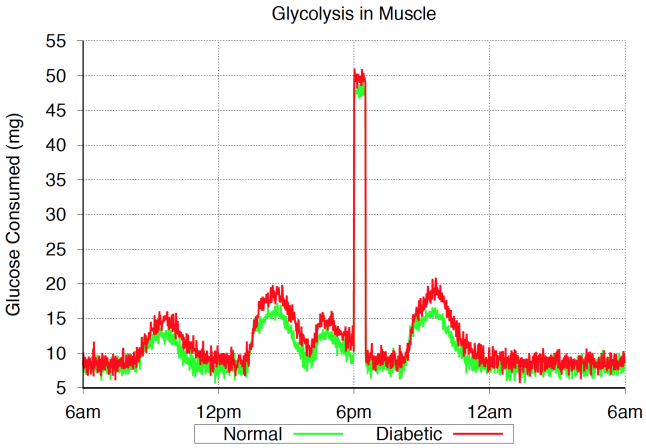


Figure 5.38: Kidney GNG (mg/min)

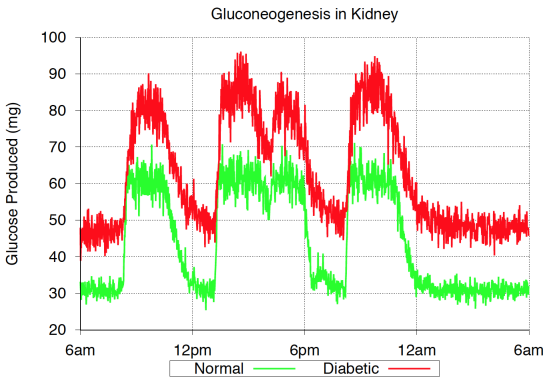


Figure 5.39: Kidney Glycolysis (mg/min)

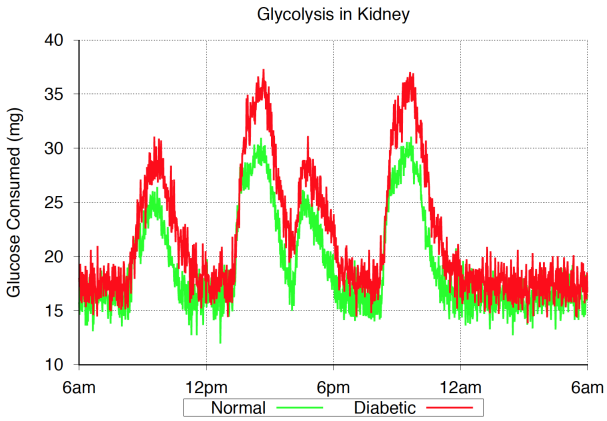


Figure 5.40: Kidney Excretion in Urine (mg/min)

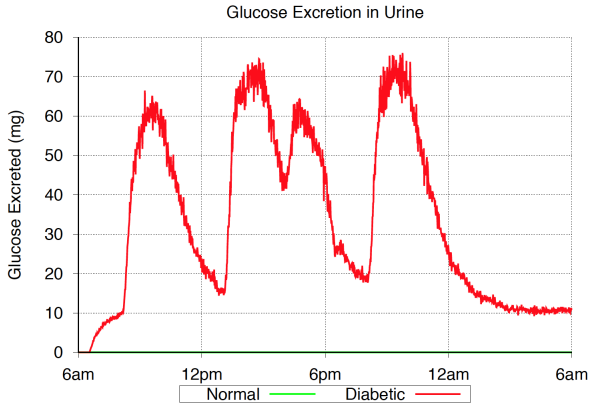
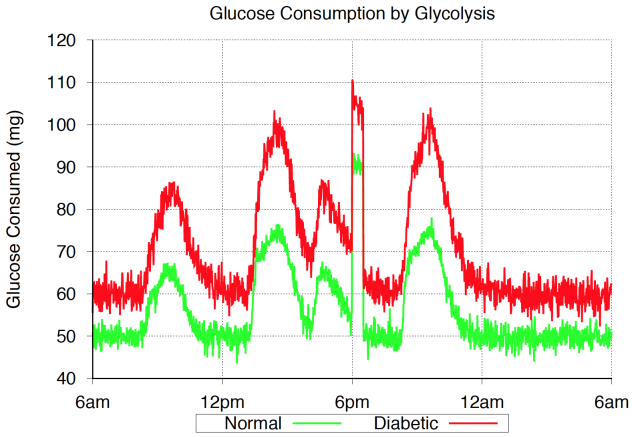


Figure 5.41: Total Glycolysis (mg/min)



Chapter 6

Conclusions

6.1 Significance of Decision Support Tools in Diabetes Management

More than 400 million people world wide suffer from Diabetes, around 90% of whom have *Type 2 Diabetes* [1]. People with Type 2 Diabetes 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 *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 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. 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.

6.2 Specifications of Existing Models

Existing approaches to model carbohydrate metabolism in human beings can be classified as either *data-driven* or *knowledge-driven* [47]. 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 [49, 51, 52, 53, 54, 55] and gaussian models [56]. A number of different neural network models exist including those based on multilayer perceptrons [51, 52], radial basis function [53], wavelets [54], time series convolution [49] and recurrent neural networks [49, 55]. Such models consider the human body to be a *black-box* and do not take in account the physiological aspects of carbohydrate metabolism [48].

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 [47]. The earliest such models [123, 124, 125] 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 [126]. Foster [5] 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 [127], Insel [128], Cramp and Carson [129] and Cobelli et al. [91]. These models were increasingly more complex with more and more physiological details taken in account. Sorensen [94] provides a good overview of the earliest knowledge-based models (and some of the later models described next).

Bergman et al. [69, 70] 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 the two sensitivities mentioned above. Bergman's *minimal* model has been modified in a variety of ways. Furler et al. [72] 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 [73] and semi-closed [74] 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 [75]. Bergman's model has also been extended to take in account the impact of physical exercise [76, 77].

Tiran et al. [116] developed a multi-compartment model for glucose circulation where each relevant organ was modeled as a separate compartment. Guyton et al. [93] 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 [94]. Sorensen [94] 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. [95, 96] 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 [105]. Hovorka et al. [106] 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 endogenous production).

Dalla Man et al. [89] 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 [9] aimed at investigating the closed control strategies for insulin pumps. A new version of UVA/PADOVA Type 1 Diabetes Simulator [10] modifies Dalla Man's model by incorporating glucagon secretion/action/kinetics and nonlinear increase in insulin dependent glucose

utilization as BGL dips below the normal range.

6.3 Contributions of CarbMetSim to the Literature

The *CarbMetSim* simulator presented in this document is physiologically complex just like the models presented by Tiran et al. [116], Guyton et al. [93], Sorensen [94] and Dalla Man [89]. The key contribution of CarbMetSim to the literature is its implementation of the physiological details in carbohydrate metabolism as an object oriented software in which various body organs implemented as software objects whereas the existing models used Ordinary Differential Equations (ODEs) to model physiological details. It can be argued that it is much easier to refine/modify behavior described in software than via ODEs. It is hoped that the ease of modification coupled with the open-source nature of CarbMetSim will allow it to evolve as a fine granularity software model of human metabolism useful for both research as well patient education. CarbMetSim is the first "Comprehensive Model" to use an object-oriented approach modeling physiological details of organs that:

- Dynamically customizes user-specific glucose metabolism parameters (i.e. insulin resistance and production level, metabolic pathway flux rates)
- Incorporates protein and fat effect on carbohydrate digestion
- Differentiates glucose metabolism parameters depending on user's diabetic level
- Addresses several metabolites in the blood (i.e. lactate, alanine, amino acids, GNG substrates) in addition to glucose

CarbMetSim also provides an alternative approach to predict Glycemic Index (GI) values of various foods.

6.4 Validation Methods & Results

Simulation results of CarbMetSim are presented and discussed by the help of comparing them with some very well known studies in the glucose metabolism area. Most of the parameters of CarbMetSim are found out in the literature, the ones that are not specifically expressed in the literature are estimated by running the simulations with different levels of values and comparing the results with the studies that are specifically discussed in the previous chapter.

The results of post-absorptive and resting state of CarbMetSim in a normal person is validated by comparing them with the results of Shrayyef and Gerich's Study [43]. Blood glucose level, insulin level, glucose production and consumption rates should be stable in post absorptive-resting state of a non-diabetic person. The stableness of CarbMetSim is presented in addition to the validation of its rates with some well known studies in this area [121, 3, 43]. The results of Gerich et al., Frayn et al., and Shrayyef et al. [121, 3, 43] are very similar regarding blood glucose level, insulin level, glucose production and consumption rates of the post absorptive-resting state. Blood glucose level graphs, glucose production and consumption rates are compared with the listed studies and we find out that the values are significantly similar to the existing rates listed in the studies of Gerich et al., Frayn et al., and Shrayyef et al. [121, 3, 43].

The results after glucose load in normal subjects are discussed and compared with the results of Meyer et al. [42]. Changes in BGL after glucose load, hepatic and renal glucose release rates, and also peripheral glucose uptake rates in normal subjects are validated by the results of Meyer et al. [42].

The results after a typical meal in normal and diabetic subjects are discussed to see the effects of a typical meal on the glucose metabolism of the normal and diabetic subjects. Specifically the results regarding blood glucose level, insulin level, glucose production and consumption rates, and also total amounts of glucose produced and consumed in some specific tissues and in some specific pathways during postprandial state in normal and diabetic subjects are compared with the ones in the study of Woerle et al. [118]. The results of both normal and diabetic subjects match very well with the study of Woerle et al. [118].

Glycemic Index (GI) prediction of 30 foods and comparison of the predicted values with the values listed in the literature are also examined. Our prediction results are very accurate for some of the foods. We can improve the accuracy of CarbMetSim by adding fiber and cooking effects to the gastric emptying model of the simulator in the future.

6.5 Limitations & Future Work

CarbMetSim is not yet a finished product. The protein and lipid metabolism are implemented only to the extent that they affect carbohydrate metabolism. 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 considered. Only aerobic exercise activities can be modeled. 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 in the forth chapter. It can be utilized in:

- Modeling the long term impact of diabetes on various organs.
- Modeling the impact of different kinds of insulin infusion techniques: The insulin infusion process can also be added to the simulator to model type 1 diabetes in which insulin injection is utilized as a treatment method.
- Translating a user's diet/exercise/BGL data into the values of simulation parameters governing the behavior of different organs: CarMetSim can take as input the accumulated records of a person's diet/exercise activities and BGL measurements, then can estimate the rates at which various metabolic pathways operate in different states of the body.
- Providing user-specific real-time guidance on diet and exercise: CarbMetSim can be used to build a smartphone-based tool (or app) that can provide user-specific real-time guidance on diet and exercise. The real-time guidance, can prove especially helpful to diabetic people. With this feature, the app will be able to suggest a sequence of diet/exercise activities that if followed over the remainder of the day will allow the app's user to achieve the best possible glycemic control no matter what his/her current BGL is.
- Modeling the fat metabolism of human body: With the help of fat metabolism modeling, we can predict changes in body weight in response to a diet/exercise regimen.

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APPENDIX

CarbMetSim Configuration Parameters

	Default Values for Subjects	
Parameters	**Non-Diabetic**	**Diabetic**
insulinPeakLevel_	1	0.5
glut4Impact_	1	0.8
liverGlycogenBreakdownImpact_	1	1.4
liverGlycogenSynthesisImpact_	1	6
gngImpact_	1	1.4
glycolysisImpact_	0.15	0.6
insulinImpactOnGlycolysis_Mean	0.7	0.7
insulinImpactOnGlycolysis_StdDev	0.2	0.2
insulinImpactOnGNG_Mean	0.3	0.3
insulinImpactOnGNG_StdDev	0.1	0.1
insulinImpactGlycogenBreakdownInLiver_Mean	0.3	0.3
insulinImpactGlycogenBreakdownInLiver_StdDev	0.1	0.1
insulinImpactGlycogenSynthesisInLiver_Mean	0.8	0.8
insulinImpactGlycogenSynthesisInLiver_StdDev	0.2	0.2
bodyWeight_	89 kg	93 kg

Table 6.1: Human Body Object Configuration Parameters

Parameters	**Default Value**
glycogenMax_	120 gr
glucoseToGlycogen_	4.7 * 0.1801559 mg/kg/min
glycogenToGlucose_	76 * 0.1801559 mg/kg/min
glycolysisMin_	0.1801559 mg/kg/min
glycolysisMax_	10 * 0.1801559 mg/kg/min
glycolysisToLactateFraction_	1
gngFromLactate_	0.762 * 2.0 * 0.1801559 mg/kg/min
gngFromGlycerol_	0.762 * 0.5 * 0.1801559 mg/kg/min
gngFromGlutamine_	0.762 * 0.5 * 0.1801559 mg/kg/min
gngFromAlanine_	0.762 * 1 * 0.1801559 mg/kg/min
fluidVolume_	12 dL
Glut2Km_	20*180.1559/10.0 mg/deciliter
Glut2VMAX_	50 mg/kg/min

Table 6.2: Liver Object Configuration Parameters

Parameters	Default Value
glycogenMax_	0.4* bodyWeight_*15000.0 mg
volume_	250 dL
basalGlucoseAbsorbed_	1.91 * 0.180155 mg/kg/min
glucoseOxidationFraction_	0.5
baaToGlutamine_	0
glycolysisMin_	0.5 * 0.1801559 mg/kg/min
glycolysisMax_	11.0 * 0.1801559 mg/kg/min
glucoseToGlycogen_	12.0 * 0.1801559 mg/kg/min
Glut4Km_	5*180.1559/10.0 mg/deciliter
Glut4VMAX_	4 mg/kg/min

Table 6.3: Muscle Object Configuration Parameters

Parameters	Default Value
geConstant_	100
geSlopeMin_	0.01

Table 6.4: Stomach Object Configuration Parameters

Parameters	Default Value
fluidVolumeInEnterocytes_	3 dL
fluidVolumeInLumen_	4 dL
Glut2Km_In_	20*180.1559/10.0 mg/dL
Glut2VMAX_In_	1000 mg/min
Glut2Km_Out_	20*180.1559/10.0 mg/dL
Glut2VMAX_Out_	1000 mg/min
sglt1Rate_	30 mg/min
glycolysisMin_	0.5*0.1801559 mg/kg/min
glycolysisMax_	2*0.1801559 mg/kg/min
aminoAcidsAbsorptionRate_	1 mg/min
glutamineOxidationRate_	1 mg/min
glutamineToAlanineFraction_	0.5
RAG_Mean_	5 min
RAG_StdDev_	5 min
SAG_Mean_	60 min
SAG_StdDev_	20 min

Table 6.5: Intestine Object Configuration Parameters

	Default Values for Subjects	
Parameters	**Non-Diabetic**	**Diabetic**
fluidVolume_	50 dL	50 dL
glycolysisMin_	0.5 * 0.1801559 mg/kg/min	0.5 * 0.1801559 mg/kg/min
glycolysisMax_	2 * 0.1801559 mg/kg/min	2 * 0.1801559 mg/kg/min
baseGlucoseLevel_	85 mg/dl	200 mg/dL
highGlucoseLevel_	180 mg/dL	360 mg/dL
minGlucoseLevel_	40 mg/dL	40 mg/dL
HighLactateLevel_	4053.51 mg	4053.51 mg

Table 6.6: Blood Object Configuration Parameters

Parameters	**Default Value**
Glut4Km_	5*180.1559/10.0 mg/dL
Glut4VMAX_	0.4 mg/kg/min

Table 6.7: Adipose Tissue Object Configuration Parameters

Parameters	**Default Value**
glycolysisMin_	0.1801559 mg/kg/min
glycolysisMax_	20*glycolysisMin_ mg/kg/min
gngFromLactate_	0.872 * 1.1 * 0.1801559 mg/kg/min
gngFromGlycerol_	0.872 * 0.5 * 0.1801559 mg/kg/min
gngFromGlutamine_	0.872 * 0.5 * 0.1801559 mg/kg/min
gngFromAlanine_	0.872 * 0.1 * 0.1801559 mg/kg/min
glutamineConsumed_	0 mg/min
reabsorptionThreshold_	11*180.1559/10 mg/dL
glucoseExcretionRate_	100/(11*180.1559/10) mg/dl

Table 6.8: Kidney Object Configuration Parameters

Parameters	**Default Value**
glucoseOxidized_	83.333 mg/min
glucoseToAlanine_	0
bAAToGlutamine_	0

Table 6.9: Brain Object Configuration Parameters

Parameters	**Default Value**
basalGlucoseAbsorbed_	0 mg/min
Glut4Km_	5*180.1559/10.0 mg/dL
Glut4VMAX_	0.4 mg/kg/min
lactateOxidized_	0

Table 6.10: Heart Object Configuration Parameters

CURRICULUM VITAE

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EDUCATIONAL HISTORY

- Fall 2012 - May 2018: Ph.D. in Biomedical and Health Informatics, College of Engineering & Applied Science, University of Wisconsin-Milwaukee (CGPA: 4.00/4.00)
- 1999 - 2005: B.S. in Computer Science, Middle East Technical University, Ankara, Turkey (CGPA: 3.10/4.00)

PAPERS UNDER REVIEW

- Aydas, B., Gazaleh H., Khunlertkit T. ,Goyal M. (2018). "*CarbMetSim: A Discrete-Event Simulator for Carbohydrate Metabolism in Humans*" *IEEE Journal of Biomedical & Health Informatics*
- Bahado-Singh R., Yilmaz A., Aydas B. (2018) "Deep Learning Accurately Predicts Gestational Age at Birth in Amniotic Fluid Metabolomics Data" *Journal of Proteomics*

WORKING PAPERS

- "Markov Model and Machine Learning Approaches for Predicting Length of Stay in Hospital and Readmission within 30 Days in Diabetic Patients" with Goyal M., Khunlertkit T.
- "A Stochastic Model for Variations in Blood Glucose Levels" with Goyal M., Gazaleh H., Khunlertkit T.
- "Integrated Nurse Staffing and Scheduling with Patient Acuities and Dynamic Patient Movements in a Pediatric Intensive Care Unit" with Aydas O.T., Ross A.D.
- "A Two-Stage Stochastic Integer Programming Approach for Short-Term Nurse Schedule Adjustments" with Aydas O.T., Ross A.D.

CONFERENCE PRESENTATION

- 11/2016 - INFORMS Annual Meeting 2016, Nashville, TN. "A Simulation of Glucose Metabolism for

Predicting Blood Glucose Level" with Gazaleh H. & Goyal M..

TEACHING EXPERIENCE

- Fall 2016 - CS 557 - *Introduction to Database Systems*: (Teaching Assistant) (Learning objectives: (1) The conceptual to physical data modeling process, (2) Entity Relationship Diagramming (ERD) techniques, (3) Advanced Data Definition Language (DDL) and Data Manipulation Language (DML), (4) Big Data Analytics, SQL, NoSQL, and Hadoop.).
- Fall 2016 - CS 150 - *Survey of Computer Science*: (Teaching Assistant) (a non-superficial survey of the modern computer and computer science in general).
- Fall 2016 - CS 395 - *Social, Professional and Ethical Issues*: (Teaching Assistant) (Social, professional and ethical issues that arise in computing).
- Spring 2016 - CS/EE 710 - *Artificial Intelligence*: (Teaching Assistant) (AI programming, search techniques, knowledge representation and acquisition, expert systems and machine learning techniques).
- Spring 2016 - CS 747/657 - *Human-Computer Interaction*: (Teaching Assistant) (Design and use of computer technology, focusing on the interfaces between users and computers).
- Spring 2016 - CS 315 - *Introduction to Computer Organization and Assembly Language Programming*: (Teaching Assistant) (Number systems, arithmetic and Boolean operations, digital computer organization, assembly and machine language programming).
- Spring 2014, Fall 2017 - CS 250(201) - *Introductory Computer Programming*: (Teaching Assistant) (Introduction of basic programming skills using a structured high-level language, JAVA).

PROGRAMMING SKILLS

- Programming Languages
  - C/C++/JAVA/Lisp/Python/SQL
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  - MIPS Assembly Language Programing using QtSpim.
- Statistical Computing & Data Mining

- R (R Foundation for Statistical Computing, Vienna, Austria)
- SAS®(SAS Institute Inc., Cary, NC)
- WEKA (http://www.cs.waikato.ac.nz/ml/weka/)

HONORS & AWARDS

- 2016 - Graduate Assistance in Areas of National Need (GAANN) Fellowship, Biomedical and Health Informatics, University of Wisconsin-Milwaukee.
- 2016 - Chancellor's Graduate Student Award, Biomedical and Health Informatics, University of Wisconsin-Milwaukee.
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