Chapter 3

Integrated simulation of the human energy system

In this chapter the mathematical model on which the blood glucose educational simulation model presented in this study is based, will be discussed. The blood glucose subsystem will be subdivided into compartments that will be described mathematically. To verify the model, simulated blood glucose data will be compared to measured blood glucose data from which the accuracy of the model will be determined.

3.1 Introduction

The ultimate goal in biotechnology is to find a way to perform virtual experiments that can speed up the discovery of new medical treatments and reduce the cost of clinical trials (Li and Kuang, 2007; Dalla Man *et al.*, 2006). Consequently, within this field a large body of research is currently dedicated to the development of accurate biochemical and biotechnological simulations – the most salient of which are the works of Bergman (2005); Blanchard *et al.* (1998); Eddy and Schlessinger (2003) and György *et al.* (2010). Whole-body human energy system simulations are scarcer (Kim *et al.*, 2007; Rui and Jing, 2005; Sørensen, 1985). An opportunity therefore exists for developing a simulation model that can successfully predict the whole-body human energy system response, whilst being simple and user-friendly and maintaining an acceptable degree of accuracy.

The human energy system can be isolated and described by means of distinct energy pathways and controls. Therefore, the first step towards simulation of the entire human energy system is the successful implementation of a simulation model for a certain part or subsystem. Due to the vast amount of literature available on the BG subsystem (Ng, 2011; Piątkiewicz and Czech, 2011; Reboldi *et al.*, 2010; Sisley and Sandoval, 2011), it was chosen for simulation purposes as a part of the human energy system. There are several BG-related diseases that will benefit from the development of such a simulation. These include diabetes, obesity, and several proliferative (cancerous and noncancerous) diseases (Albisser and Inhaber, 2010; Borg *et al.*, 2011; Mathews *et al.*, 2011).

3.2 Research design and methods

From a systems point of view, the BG pathway is relatively complex due to the integrated nature of the processes involved (Kim *et al.*, 2007). Simplification of the subsystem was therefore essential in order to solve the system events dynamically within realistic resource constraints. However, the simplified system is still required to simulate realistic glycaemic response to an acceptable degree (Bergman, 2005).

The first step in designing the integrated simulation was to develop a universally applicable unit of measure for foods with known glycaemic indices (GI). The unit should reflect the quality of the foods as well as the quantity of nutrients (carbohydrates, protein, fibre, and so forth) present in the foods. This unit can be applied to determine the amount of energy

released as BG from the food ingested, and therefore predict postprandial BG response (Mathews and Pelzer, 2009).

The **e**quivalent **t**easpoon **s**ugar (—ets) concept was developed for this reason and implemented in the simulation of the BG subsystem. The —ets concept is easy to visualise and simple to implement in food-intake calculations. The derivation of the —ets equations and the verification of these equations are described elsewhere (Mathews and Pelzer, 2009). However, in the following equation the energy value of one teaspoon sugar (—ets) is presented:

$$E_{TeaspoonSugar}\,(\text{in kcal}) = 5\text{ g sugar} = 1\ \text{—ets} = 13\text{ kcal} \qquad (2)$$

Following the —ets concept, the next step was to develop a simulation engine that could be classified as a discrete, deterministic and a dynamic integrated system simulation model. Therefore, an object-orientated construction method was implemented due to the simplicity of using the simulation and the ease with which it could be constructed and expanded.

Background to simulation concepts

Mathematically, compartment models are derived as a combination of fundamental principles and empirical correlations (Teddy *et al.*, 2010). In the case of the BG subsystem simulation model, the simulation procedure and compartment models make use of explicit equations in order to ensure solvability. However, reality cannot be emulated realistically by a virtual model due to the complexity of the BG subsystem, the many factors influencing the subsystem, and intrapatient variability (Dalla Man *et al.*, 2006; Hejlesen *et al.*, 2000; Rutscher *et al.*, 1994). The more detailed the simulation, the more accurate and detailed the required input data has to be. Certain assumptions must be made in order to create a simulation model that is not overly complex (Lehmann and Deutsch, 1998).

The different compartment models contained within the energy subsystem interact in a complex manner with each other, as well as with the control compartments (Kim *et al.*, 2007) and therefore needed to be simplified for the purpose of the simulation (Botha, 2002). Each of the energy compartments (such as the digestion system and the bloodstream), as well as the connection lines and control compartments (RH and CRH) were individually modelled by using the virtual technique of object-oriented programming. A class object was created for

each, incorporating all the properties and methods necessary for solving that compartment dynamically (Osier *et al.*, 1997). The work presented in this chapter is based on the doctoral thesis of CP Botha(2002), with the following chapters as an extension of this work.

Human energy system simulation

The integrated human energy system simulation (depicted in Figure 10) is described in sections consisting of the different compartment models: the digestive system, bloodstream, energy expenditure, primary and secondary storage models, and finally the glucose control compartments.

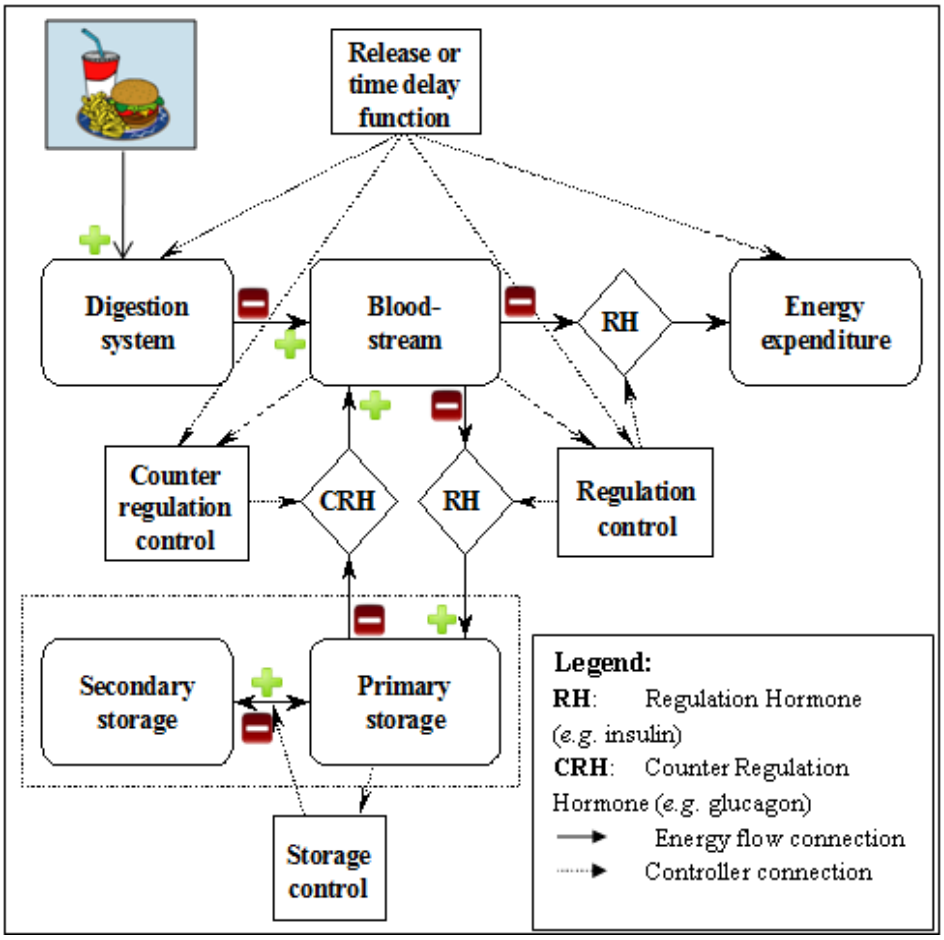

Figure 10: Schematic layout of the integrated human energy simulation model for glucose flow and controller compartments (adapted from Botha, 2002). Rectangles represent the different energy compartments. The storage system is blocked with dotted lines, which consist of two compartments. The solid connection lines indicate the flow of glucose between compartments. The control compartments and connections are presented in this diagram with dotted connection lines to show their interactions with the energy compartments. The + and - signs indicate the glucose increase or decrease of that compartment, respectively.

Digestion system model

The methods for the digestion model mainly consist of calculations to simulate the flow of glucose into the bloodstream due to consumed *ets* (i.e. effective glucose ingested). This glucose flow ($\dot{G}_{Digest}$) is dependent on correction factors and restrictions regarding the specific person being modelled (García-Jaramillo *et al.*, 2010; Lehmann and Deutsch, 1998). This glucose release function can be expressed as follows (Botha 2002; Dalla Man *et al.*, 2007; Mougiakakou *et al.*, 2005; Lehmann and Deutsch, 1998):

$$\dot{G}_{Digest} = f(ets_{Effective}, T_{Meal}, t_{Elapsed}, t_{Digest}) \tag{3}$$

The amount of *ets* used in the analytical function is, however, critically dependent on a combination of both the properties of the food and the metabolic characteristics of the person (Lehmann and Deutsch, 1998). Correction factors for the various influences affecting the effective amount of *ets* were implemented in the methods of the compartment model objects (Dalla Man *et al.*, 2007; Mougiakakou *et al.*, 2005). The following influences were incorporated: the second-meal effect, maximum intake restriction and the uptake duration correction (Botha, 2002).

Bloodstream model

The major purpose of the bloodstream model is to act as the conduit through which the energy (in the form of glucose) is channelled towards, and from the other compartments (Botha, 2002). This compartment stands central in the human energy system model, where it handles all the main energy flows, control connections and feedback loops (Kim *et al.*, 2007; Rui and Jing, 2005; Sørensen, 1985). It comprises a linear storage tank model with two energy in-flow, and two energy out-flow connections.

This compartment model also makes provision for controller feedback pathways (Liu and Tang, 2008). The feedback pathways are necessary for the complex regulation mechanism to determine what the current BG concentration is at any given time step ($G_{Blood(t)}$) (Liu and Tang, 2008). The bloodstream compartment is the model that contains the set-point variable to which the main control system can act and react.

To dynamically solve the amount of BG energy in the bloodstream compartment at any given time step ($G_{Blood(t)}$), the total flow of glucose energy from the in- and out-flow connections are linearly added to the glucose amount of the previous time step ($G_{Blood(t-1)}$). This calculation is done as follows (Botha, 2002; Kim *et al.*, 2007):

$$G_{Blood(t)} = G_{Blood(t-1)} + \sum_{t=0}^{n} \left(\dot{G}_{Digest} + \dot{G}_{Store-Out} - \dot{G}_{Store-In} - \dot{G}_{Exercise} \right) \Delta t \quad (4)$$

An increase in BG is indicated as positive, while a decrease is denoted by a negative in equation 4. Since *ets* is an appropriate quantity for measuring metabolic energy, $G_{Blood(t)}$ is measured in *ets*. Similarly, *ets* is also used to quantify the flow of glucose energy ($\dot{G}$), and therefore the unit for measuring all the flows in Equation 4 is the time derivative of *ets*, i.e. ets/time.

The only restriction that is placed on the BG value in the bloodstream compartment (G_{Blood}) is that it cannot be negative (less than zero BG concentration). Therefore, whenever Equation 4 yields a value for $G_{Blood(t)} < 0$, the value is artificially reset to zero (i.e. if $G_{Blood(t)} < 0$ then $G_{Blood(t)} = 0$). In that case the two out-flows ($\dot{G}_{Store-In}$ and $\dot{G}_{Exercise}$) are restricted and no glucose energy flows to the compartments connected by those flows.

Energy expenditure model

Energy expenditure in the body can be divided into three major compartments, namely, resting metabolic rate, thermic effect of exercise, and dietary-induced thermogenesis. The energy expenditure compartment uses approximately 20 – 30% of the total energy expenditure of the body (Thain, 2009; Sims and Danforth, 1987). It should be noted that energy can be expended in many organs, muscle tissues, and the nervous system (Rui and Jing, 2005; Lehmann and Deutsch, 1998). The metabolic expenditure of the organs and nervous system is included in the other compartments of the model.

Therefore, only exercise energy expenditure will be seen as energy 'burnt' or expended in the human energy system. It represents the combination of all the compartments that consume glucose energy from the body. The energy expenditure compartment model provides the

simulation of glucose energy flow from the bloodstream ($\dot{G}_{Exercise}$) to any combination of these elements (Botha, 2002).

As long as insulin (the main regulation hormone) is present in the system, the expenditure compartment is able to extract glucose from the bloodstream (Flechsig *et al.*, 2009; Pederson and Saltin, 2006). In the insulin pathway, degradation of insulin is the final step and must be included in the model (György *et al.*, 2011; Franco-Bourland and Méndez-Sánchez, 2011).

Apart from the control hormone consumption, $\dot{G}_{Exercise}$ can never be less than a certain minimum value ($\dot{G}_{Exercise-Min}$). This is because the vital organs require at least a minimum amount of glucose energy ($\dot{G}_{Basal}$) at any given time step in order to sustain life ($\dot{G}_{Basal} \geq \dot{G}_{Exercise-Min}$). The only scenario that might be problematic is if there is too little insulin present in the system to allow for the required flow rate. In this case $\dot{G}_{Exercise}$ is artificially restricted to the minimum flow rate ($\dot{G}_{Exercise-Min}$), i.e. if $\dot{G}_{Exercise} \leq \dot{G}_{Exercise-Min}$ then $\dot{G}_{Exercise} = \dot{G}_{Exercise-Min}$. The basal energy requirement and the minimum $\dot{G}_{Exercise}$ have specific equations that are person-specific and must be calculated per specific patient (Botha, 2002).

Primary and secondary storage model

After ingestion of a meal the digestion system compartment releases glucose energy into the bloodstream compartment ($\dot{G}_{Digest}$). This flow causes the BG concentration of the bloodstream compartment to rise as shown in Figure 11 (Dalla Man *et al.*, 2007; Korach-André *et al.*, 2004). If the energy expenditure compartment does not require glucose, the BG concentration will remain high. This is unacceptable due to the adverse health implications associated with high BG levels (Dittakavi and Ghista, 2001; García-Jaramillo *et al.*, 2010; Kendall-Tackett, 2002).

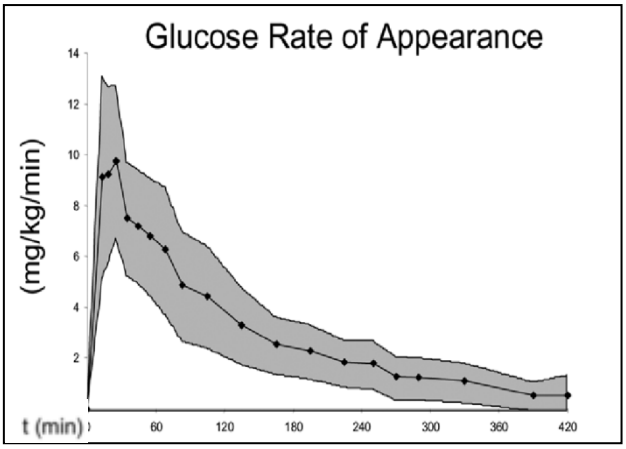

Figure 11: Blood glucose rate of appearance after meal ingestion (Dalla Man *et al.*, 2007).

Therefore, the body has a temporary storage facility to where the glucose can be transferred, and from where it can later be retrieved if necessary (depicted in Figure 12), (Diamond and Echler, 2002; Franco-Bourland and Méndez-Sánchez, 2011; Sims and Danforth, 1987). However, a distinction can be made between short- and long-term storage (Sims and Danforth, 1987). The primary storage (short-term) compartment is where glucose is first stored for easy access (Li and Kuang, 2007). This compartment is very similar to the bloodstream compartment model in that it also comprises a linear ‘storage tank’ model. In the body this storage model is equivalent to the liver (Yoshimatsu and Sakata, 2001).

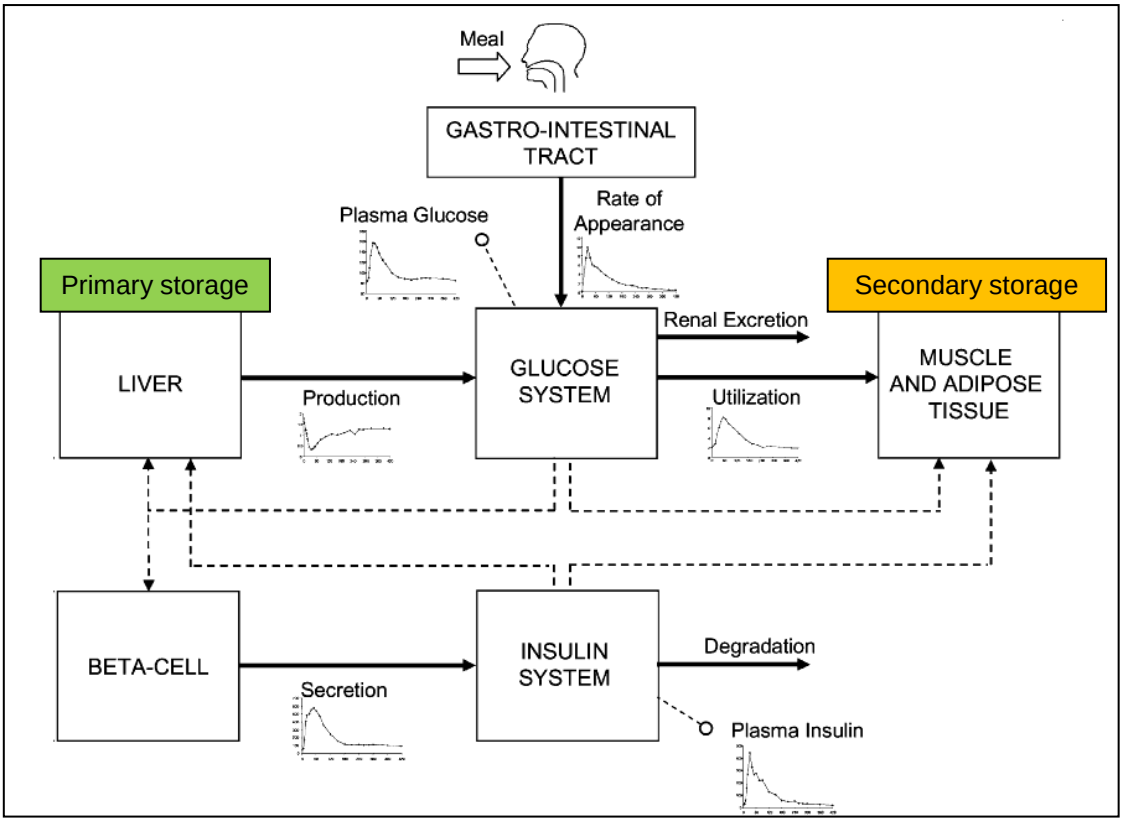

Figure 12: Schematic representation of glucose-insulin subsystem with control system. The solid lines indicate flow of glucose whereas the dashed lines indicate the control pathways between compartments (Dalla Man *et al.*, 2007).

To dynamically solve the amount of glucose energy stored in the primary storage compartment for any given time step ($G_{Storage(t)}$), the energy flow to and from the compartment has to be considered. The energy flow rates of glucose into and out of the primary storage compartment ($\dot{G}_{Store-In}$ and $\dot{G}_{Store-Out}$, respectively) at a specific time interval have to be added to the level of glucose at the previous time interval ($G_{Storage(t-1)}$). The sign convention is the same as specified in the bloodstream model. Concerning the flow to the secondary storage ($\dot{G}_{Storage}$), it is considered positive if the glucose energy flows towards the primary storage compartment and negative otherwise (Botha, 2002).

Therefore Equation 5 can be written as (Botha, 2002; Bergman *et al.*, 1981; Sørensen, 1985):

$$G_{Storage(t)} = G_{Storage(t-1)} + \sum_{t=0}^{n} \dot{G}_{Store-Out} - \dot{G}_{Store-In} + \dot{G}_{Storage} \Delta t \qquad (5)$$

There is a zero-flow restriction on this compartment. Therefore, if at any time step $G_{Storage}$ is calculated to be less than zero ($G_{Storage} \leq 0$) then $G_{Storage}$ will be adjusted to zero

($G_{Storage} = 0$). In this case all the glucose energy connections flowing from the primary storage compartment are also reset to zero (Botha, 2002).

Another flow connection – the connection to the secondary storage compartment – is further necessary for active control of the level of glucose energy stored in primary storage ($G_{Storage}$) (Dalla Man, 2007; Liu and Tang, 2008). If at any time interval the primary storage compartment contains more glucose energy than required (glycogen stores are higher than the control set point), the excess glucose is converted into triglycerides (Thain, 2009). This process is called hepatic lipogenesis.

The triglycerides are transferred from the primary- to the secondary storage compartment via the bloodstream. In this case $\dot{G}_{Storage}$ in Equation 5 is negative. Conversely, if the primary storage compartment has too little stored glucose energy; the secondary storage unit is required to supply energy, and $\dot{G}_{Storage}$ is positive.

Glucose energy control system

The control of the human energy system (depicted in Figure 10) is executed through four primary control compartments, namely, an empirical 'release' or 'time-delay' function (Hovorka, 2006; Sturis *et al.*, 1991); a controller unit for the release of the regulation hormone insulin; a controller compartment for the release of counterregulation hormones; and a control strategy to regulate the stored energy level in the primary storage compartment (Kim *et al.*, 2007).

Release or time-delay function

The release function was used to approximate the amount of digested glucose that was 'released' and the time-delay function to approximate the amount of exercise energy 'consumed' at specific time steps (Kim *et al.*, 2007). Empirical measurements for the BG release rate from the digestion system ($\dot{G}_{Digest}$) have yielded a distinctively recognisable response curve (depicted in Figures 13 and 14).

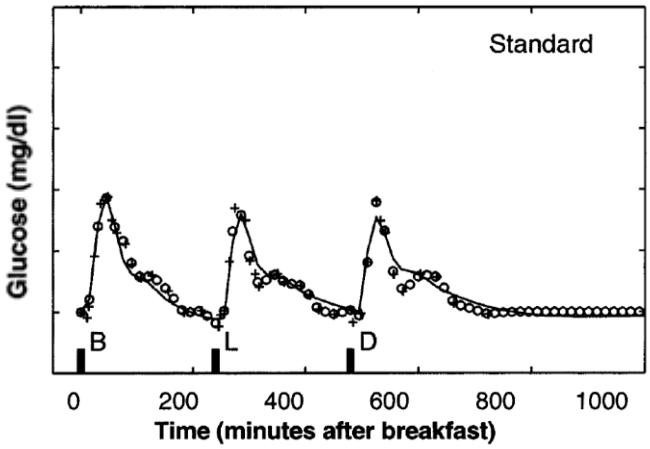

Figure 13: BG response to three separate meals, all containing CHOs (adapted from Holtschlag *et al.*, 1998).

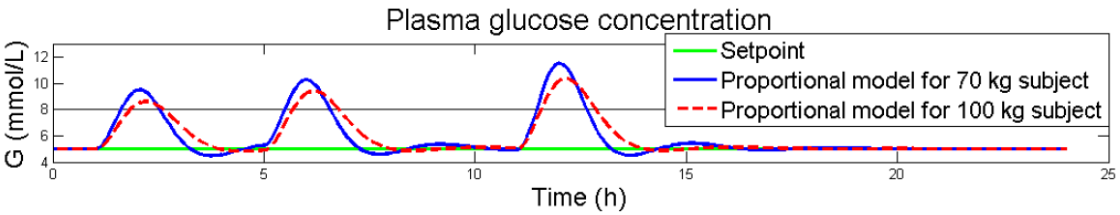

Figure 14: BG response to three separate meals, all containing CHOs (Nærum, 2010).

Due to the repeatability of the response curve features, it is therefore suggested that the release of glucose is calculated analytically rather than using time consuming simulation techniques (Botha, 2002). The glucose release rate ($\dot{G}_{Digest}$) can be approximated with the sum of the following two sine curves ($f_1(t)$ and $f_2(t)$). The two functions, which were determined through trial and error methods, are (Botha, 2002):

$$f_1(t) = \sin\left(\frac{2\pi}{t_{total}}(t - t_0)\right) \tag{6}$$

$$f_2(t) = 2\sin\left(\frac{\pi}{t_{total}}(t - t_0)\right) \tag{7}$$

Thus, the following function is proposed for the analytical calculation of $\dot{G}_{Digest}$ (Botha, 2002):

$$\dot{G} = \frac{\pi}{4} \frac{ets_{Effective}}{t_{Total}} \left[\sin\left(\frac{2\pi}{t_{Total}} \left(- t_0 \right) \right) + 2\sin\left(\frac{\pi}{t_{Total}} \left(- t_0 \right) \right) \right] \tag{8}$$

An equivalent equation can also be applied to describe the release function for any substance; as well as the consumption function for exercise expenditure. The release, or time-delay function, not only has control connections with the digestion system and the energy expenditure system, but also with the regulation- and counterregulation controllers.

Regulation hormone controller model

The primary role of the regulation hormone controller is to lower the increasing amount of glucose contained in the bloodstream to an acceptable level (depicted in Figure 15), (Kovács *et al.*, 2011; Liu and Tang, 2009). This is accomplished by releasing the main regulation hormone, insulin ($\dot{I}_{Control}$). Insulin is responsible for activation of the primary storage compartment to absorb glucose energy from the bloodstream (Holt *et al.*, 2010). The insulin level is henceforth lowered to stabilise at the basal insulin level (I_{Basal}).

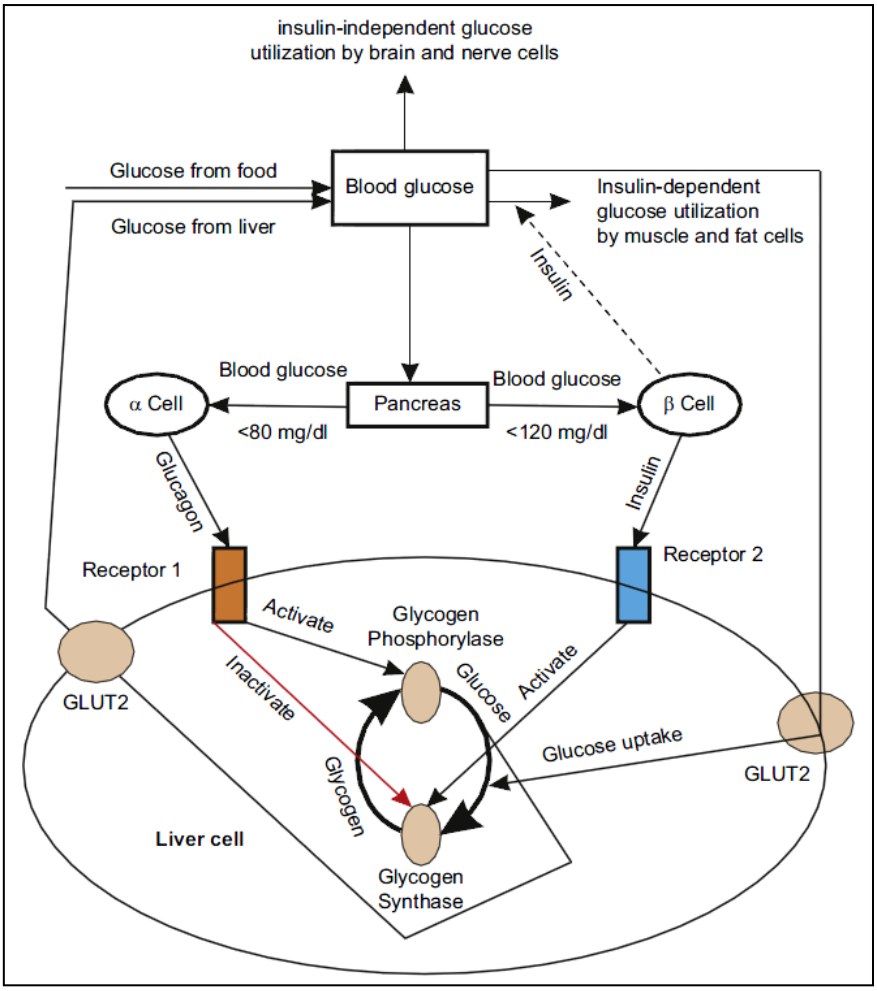

Figure 15: A schematic representation of the simplified BG regulatory system (Liu and Tang, 2009). (GLUT2 = carrier protein that allows passive glucose transport across cell membranes).

In order to calculate the level of insulin present in the system at any time interval, the insulin level at the previous time interval is added to the changes in insulin due to the various processes, such as insulin secretion and insulin consumption. This leads to the equation that calculates the total amount of insulin in the system at time step (t) (Botha, 2002):

$$I_{Control\,(t)} = I_{Control\,(t-1)} + \sum_{t=0}^{n} \left(\dot{I}_{Control} + \dot{I}_{Injected} - \dot{I}_{Exercise} - \dot{I}_{Storage} \right) \Delta t \qquad (9)$$

If a type 1 diabetic's energy system is simulated, $\dot{I}_{Control}$ is zero because the person is unable to secrete insulin for BG control (Holt *et al.*, 2010; Kovács *et al.*, 2011). Strategies concerning the control of injected insulin in people with type 1 diabetes, as well as in non-diabetic people, have been derived and will be discussed in a future paper.

Counterregulation hormone control model

The main purpose of the counterregulation hormones is to raise BG levels by releasing stored glucose from the storage system (Jiang and Zhang, 2003). The storage system consists of several hormones, such as glucagon, cortisol, growth hormone, etc., that all act to ensure elevation of BG levels whenever it is required (Holt *et al.*, 2010; Lucidi *et al.*, 2002). To simplify this control model in the simulation, the effects of all the control regulation hormones are combined into one virtual hormone.

Storage control model

A third controller, with a step control strategy (depicted in Figure 16), is used to regulate the flow of glucose energy between the primary and secondary storage compartments ($\dot{G}_{Storage}$) (Levermore, 2000). Due to the unavailability of measurements and the relative simplicity of a step controller, this strategy was chosen. The regulation of $\dot{G}_{Storage}$ is direct in that no hormones or induced control is required. When the liver glycogen stores are filled, the synthesis of triglycerides in the liver may begin from glycogen and amino acids (Thain, 2009). This induces the flow of energy from the primary to the secondary storage compartment.

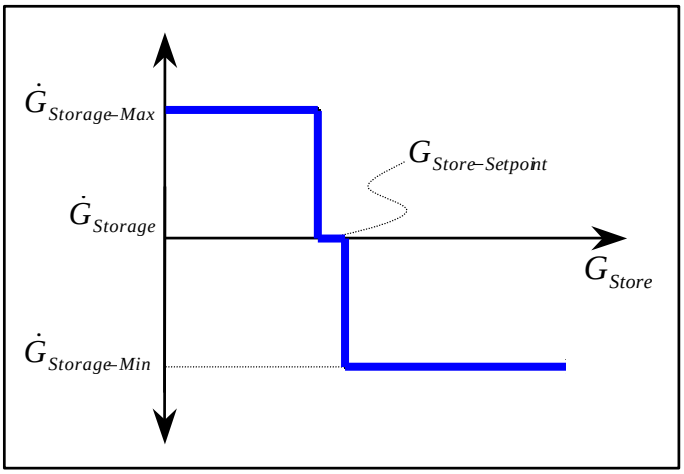

Figure 16: Step control strategy for the storage system controller compartment (adapted from Botha, 2002)

Verification of simulation

The simulation model's prediction accuracy was verified by performing a variety of case studies on the simulation, and comparing the simulation results with the measured results. Measurement data, used to verify the simulation model, was collected over a series of separate trials. The trials included long- and short-term trials to verify the versatility of the simulation. The original objectives of many of these trials were wide-ranging and not aimed at the verification of this study specifically. This, however, is not a disadvantage, but rather an advantage, since the acquisition of the data represents glycaemic responses due to many everyday influences (Botha, 2002).

The test subjects were subdivided into two categories: a diabetic group and a healthy persons group. A separate simulation model was constructed for each person based on a few of the trials the person performed. That model was then unique to each of the specific people. It is important to note that not all the trial data obtained for the subject was used for the model construction phase. The model was solved to simulate the specific person's BG response in reaction to a variety of external influences. Verification of the model was then accomplished by comparing the simulated results to the measured results obtained from the trials.

3.3 Results

The first set of simulations was performed over an entire day. The result was an integrated BG response due to various inputs such as ingested food, exercises done, second-meal effects, waking effects, long- and short-acting insulin injections, stress situations, etc. that were logged and provided to the simulation model as external influences experienced at specific times of the day. The results are presented in Figure 17.

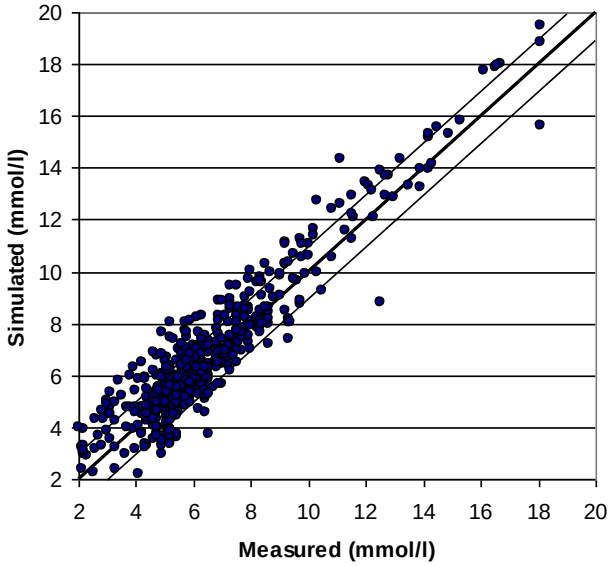

Figure 17: Comparison between measured and simulated data for the whole-day simulations. The thin, solid diagonal lines on both sides of the x = y line is the 1 mmol/L error band (Botha, 2002).

The accuracy of the simulations is defined as the amount of data points that fall within a certain error band when compared to the measured data. For the whole-day simulations a 1.0 mmol/L error band was considered to be acceptably accurate and 70.7% of the data falls within this error band.

Simulation models were furthermore constructed for all the test subjects that participated in the short-term trials. Three different types of isolated disturbance simulations were performed. The results are presented in Figures 18 – 20.

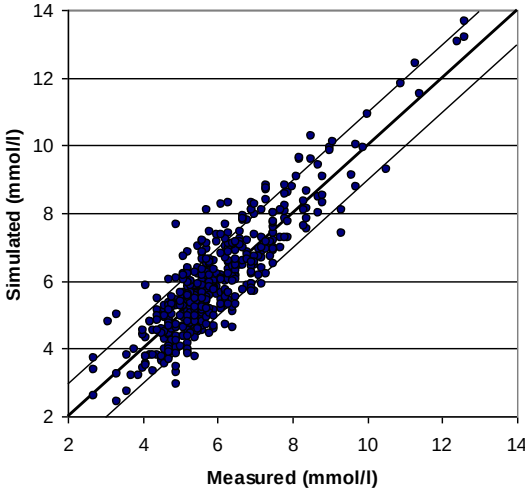

Figure 18: Comparison between measured and simulated data for the isolated food simulations (Botha, 2002).

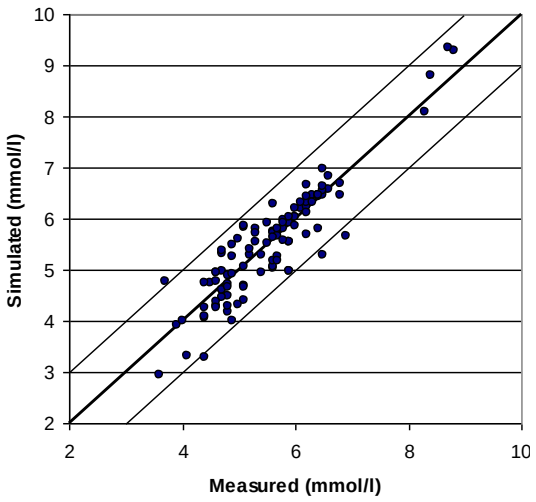

Figure 19: Comparison between measured and simulated data for the isolated exercise simulations (Botha, 2002).

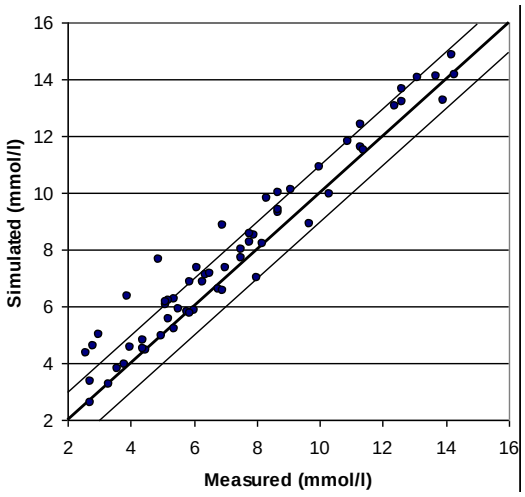

Figure 20: Comparison between measured and simulated data for the isolated insulin simulations (Botha, 2002).

Simulations for the healthy subjects included a wide range of food tolerance tests as well as some exercise response tests. The diabetic simulation verifications were done for BG response due to ingested food, exercises and also for short-acting insulin response. Again an error of ±1.0 mmol/L was deemed to be acceptable. For all three different types of isolated disturbances the simulation was more than 80% accurate according to the error band.

3.4 Conclusion

The newly developed –ets concept for quantifying glucose energy flow in the human body provides the basis on which the simulation model of human BG subsystem is built. Its simplicity and easy implementation contributes to the success and accuracy of the simulation.

The results from the simulation model for the short-term trials were above 70%, within the 1 mmol/L error band, whilst the long-term trial results were above 80%. The accuracy of all the simulations suggests that the simulation model and its results may yet be implemented for various applications.

The dynamically integrated simulation model provides a method for predicting the BG response due to various external influences. This is significantly faster and less expensive than conducting experiments on clinical trial subjects.

3.5 References

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