Chapter 2

Literature survey

Based on published works, this chapter provides an overview of the state-of-the-art simulation models available in this research field. The chapter covers the healthy human energy system as well as the pathophysiology of diabetes mellitus. It then continues to describe possible strategies to help diabetic patients control their blood glucose within a healthy range. The newest technological developments in this area are also described. These include the combination of simulation models of the blood glucose subsystem, continuous blood glucose control and insulin therapy (also known as the artificial pancreas). The most widely used educational models are then briefly described.

2.1 Introduction

For centuries the human physiology and pathogenesis of diseases have been studied. The reason for this is to better understand what happens inside the body and what goes wrong when a disease develops. If this is understood, a cure can be found to prevent people from either getting sick in the future, or curing them when they do get sick.

In the twentieth century the development of the computer opened a new world to scientists. Reality could be simulated to an extent where hypotheses could be virtually tested. Thus, the field of biotechnology came into existence.

The present dilemma is to accurately simulate the human physiology by developing mathematical models that describe the biological pathways and systems inside the body. By simulating the healthy system it might be possible to simulate diseases as well. Therefore, cures can be tested on virtual patients to determine if they might work. This method is less time-consuming, cheaper and safer than clinical trials on human patients.

In this chapter the physiology of the human energy system will be briefly described to explain how the BG subsystem works. This will be followed by an explanation of diabetes and the educational simulation models that currently exist to simulate the BG subsystem and diabetes.

2.2 Human energy system

Energy homeostasis is an essential part of survival in humans, enduring ever-changing internal and external circumstances (Ruiter, 2005). The human energy system operates in the same manner as any other energy balance:

$$Energy_{in} = Energy_{accumulated} + Energy_{generated} + Energy_{expended} \quad (1)$$

Energy intake ($Energy_{in}$) is food that is absorbed by the gut and converted into BG – the main fuel for metabolic processes. $Energy_{expended}$ is the energy expended via exercise and the aforementioned processes. The excessive energy that accumulates in the system ($Energy_{accumulated}$) is stored mainly in the liver or fat cells for later use. $Energy_{generated}$ includes the energy generated in the metabolic pathways of the human energy system.

In this section the energy system will be described in more detail with particular focus on the BG subsystem. The metabolic pathways that regulate this subsystem are complex and have been extensively studied. A simplified overview will be given here.

Blood glucose subsystem

Glucose is the main source of fuel in the body and under normal circumstances it is the brain's only energy source as it stores only minute amounts of glycogen (Mathews *et al.*, 2011), as opposed to the liver and muscle cells (Ruiter, 2005). Therefore, sufficient amounts of BG must be available at all times via circulation to keep the brain alive and healthy. The other main concern is healthy functioning of all other organs in the body (Dittakavi and Ghista, 2001). This requires tight control over the metabolic pathways that regulate the blood glucose level (BGL) and maintain homeostatic stability in the body (György *et al.*, 2010).

The BG subsystem can be divided into compartments that interact with each other to maintain the BGL in a narrow normoglycaemic range of 3.9 – 6.6 mmol/L (György *et al.*, 2010; Thain, 2009). The compartments are connected by means of signalling pathways and control signals that form an integrated control system (Göbel and Langemann, 2011).

For the purpose of this study the system will be divided into the following 'compartments': the bloodstream compartment, the digestive compartment, the energy expenditure compartment, the primary- and secondary storage compartment, and the glucose system control compartment.

Glucose enters the bloodstream by means of food intake (orally). It is absorbed through intestinal glucose absorption when the carbohydrates (CHO) are absorbed from the digested food in the gastrointestinal tract (Dittakavi and Ghista, 2001). Glucose also enters the bloodstream when it is released from the liver, where degradation of glycogen to glucose takes place. The main control mechanism utilised to maintain a healthy BGL is hormonal release from the pancreas.

When BG is low, glucagon is released from the α-cells in the pancreas and initiates the conversion of glycogen to glucose in the liver. This glucose is then released into the bloodstream. If the hepatic (liver) glycogen stores are depleted, fat and muscle cells will also release glucose. If the BGL is too high, β-cells in the pancreas produce insulin. Insulin

initiates the uptake of glucose from the bloodstream by the liver, fat and muscle cells to be stored for later use (Bergman, 2007). This process is illustrated in Figure 4:

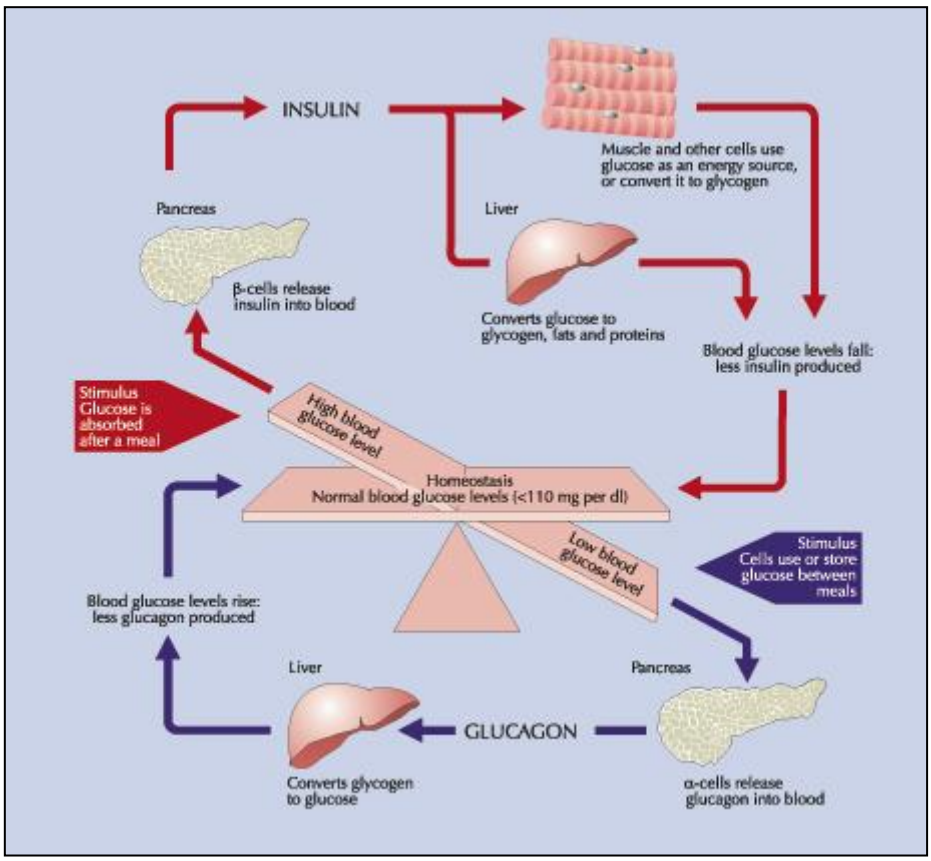

Figure 4: Schematic presentation of the regulatory and counterregulatory effects in the BG subsystem (Hambly, 2011).

There are several diseases associated with the BG subsystem. These include, among others, diabetes, cardiovascular disease, obesity, and several proliferative and nonproliferative (cancerous and noncancerous) diseases. In this study the main focus will be on diabetes: how the disease affects the BG system as well as the complications of this disease.

2.3 Diabetes mellitus

Diabetes mellitus (DM) is a major chronic disease that in general is caused by an insufficiency of the hormone insulin relative to the requirements of the human glucose system (Bellazzi *et al.*, 1995; Thain, 2009). The World Health Organisation (WHO) estimates

that the diabetes population will grow from 245 million people in 2000 to 380 million people by 2030 (György *et al.*, 2011; Piątkiewicz and Czech, 2011).

Type 1 diabetes mellitus (T1DM) – also known as insulin-dependent diabetes mellitus (IDDM) – is characterised by the total destruction of the insulin-producing β-cells in the pancreas (García-Jaramillo *et al.*, 2010; Kovács *et al.*, 2009; Liu and Tang, 2008). The destruction of these cells is caused by an autoimmune response involving cellular and humoral immune pathways (Holt *et al.*, 2010). This results in a high BG (hyperglycaemia) and ketone body concentration (ketosis).

In the long term, this can lead to several micro- and macrovascular complications – blindness, kidney failure, cardiovascular diseases, blood circulatory diseases, and neuropathy, to name a few (García-Jaramillo *et al.*, 2010; Holt *et al.*, 2010; Piątkiewicz and Czech, 2011). Diabetes patients require tight BG control to lower the chances of these long-term complications.

Euglycaemia varies in a narrow range of 3.9 – 6.6 mmol/L (György *et al.*, 2010; Thain, 2009). The slightest change in the BGL at organ level triggers a response to re-establish homeostasis. Hypoglycaemia occurs when the BGL falls below the lower limit of the normoglycaemic range (i.e. 3.9 mmol/L). Hypoglycaemia is the most important limiting factor in achieving accurate BG control (Holt *et al.*, 2010). This leads to a counterregulatory neuroendocrine response to the low BG which involves the pancreas and hypothalamus (Ruiter, 2005; Thain, 2009). The release of glucagon by the pancreas' α-cells will promote glycogenolysis, while the hypothalamus is physiologically and anatomically linked to the pituitary gland that releases cortisol and adrenalin/epinephrine (Thain, 2009). These hormones all play a role in raising the BG concentration to normal levels.

Since people with T1DM do not produce endogenous insulin, an external (exogenous) insulin source is required to help regulate their BGLs in the short and long term (Liu and Tang, 2008). Management of T1DM is a complicated and difficult task. The conventional method typically requires several injections of basal- and bolus insulin throughout the day. The treatment should be tailored by a diabetes care provider to each patient according to their diet, lifestyle and exercise regimens. However, even with intensive insulin treatment, severe glycaemic excursions still occur and there is thus a need for an alternative treatment method (Hejlesen *et al.*, 2001).

In recent years a strong focus has been on developing methods to allow tight BG control and administer insulin in the least invasive manner. The focus has shifted to the biotechnology field to assist with this development.

2.4 Information technology and diabetes

Ever since the information technology (IT) sector has taken centre stage in the world of science and technology, research has been done into the possibility of tightening blood glucose control by the application of IT in diabetes care (Lehmann and Deutsch, 1998). Several educational simulation models have been proposed to model and control the glucose-insulin metabolism for normal as well as diabetic patients (Berman *et al.*, 1981; Eddy and Schlessinger, 2003; Flechsig *et al.*, 2011; García-Jaramillo *et al.*, 2010; Kovács *et al.*, 2009).

In general, the models proposed for people with diabetes consist of a mathematical model of the glucose-insulin metabolism, as well as a control loop to simulate the counterregulatory neuroendocrine response of the patient. This is used in conjunction with continuous glucose measurements and insulin therapy to form a closed-loop glycaemic control system. It is known as an 'artificial pancreas' since the control system acts as a substitute for a healthy person's pancreas.

The artificial pancreas is a less invasive method of administering the patient's insulin protocol, while simultaneously controlling the BGL in real-time (Kovatchev *et al.*, 2009). Figure 5 depicts a block diagram of the closed-loop control of the BG system.

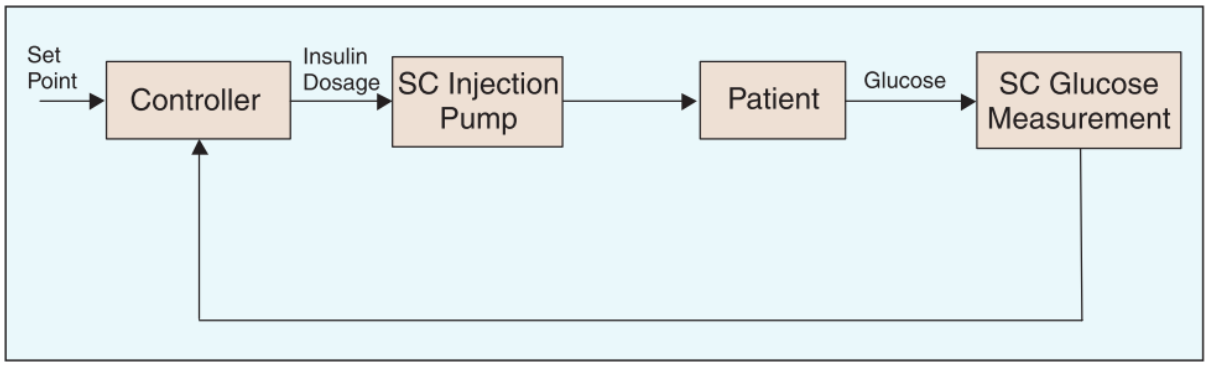

Figure 5: Block diagram of the closed-loop control strategy with subcutaneous (SC) glucose measurement and insulin delivery (Bellazzi *et al.*, 2001).

Different mathematical models can be used to simulate this system: compartmental models (CMs), algorithmic-based models, differential equations, or an object-oriented approach. All of these models contain some uncertainty regarding the postprandial or circadian profile prediction of BGLs. Therefore, many authors have opted to use a combination of these types of models to optimise the accuracy (Sørensen, 1985).

The inter- and intrapatient variability complicates the derivation of the mathematical models due to estimation of the parameters for the models. There is a vast difference in the diabetic population regarding food intake, physical activity, internal and external disturbances, and internal and external circumstances (Teddy *et al.*, 2010). The complexity of the human physiology and the pathogenesis of the disease also complicate the development of these models. The ideal model would be simple, accurate and robust with the least amount of parameters estimated to fit the experimental data. Many models are mathematically very complex with a vast amount of parameters. These parameters were only estimates used to ensure that the simulated results correlated with the experimental data.

People with type 1 diabetes are modelled by excluding the endogenous insulin term of the physiological glucose system's model (Sørensen, 1985). This is where the control strategy comes into play; the control loop acts as part of the artificial pancreas for the patient that will predict the exogenous insulin required by the patient in real-time.

Control strategies for the simulation models

An extensive variety of control strategies has been used in the literature. These strategies, which are briefly discussed in the following sections, include (György *et al.*, 2010):

- Proportional-integral-derivative (PID) controller
- Cascade control
- Soft computing methods (such as neural networks, fuzzy methods and probabilistic computing)
- Adaptive controllers
- Model predictive methods
- H_∞ control
- A combination of the abovementioned strategies

PID: PID is a feedback controller that calculates the error between the set point for a specified process variable and the measured value. The controller then attempts to minimise this error by adjusting the process input variables according to an algorithm containing three terms for the proportional, integral and derivative values, respectively, of the controller (Svrcek *et al*., 2006). Figure 6 shows a block diagram for a PID controller and Figure 7 the typical response of the controller to an input change.

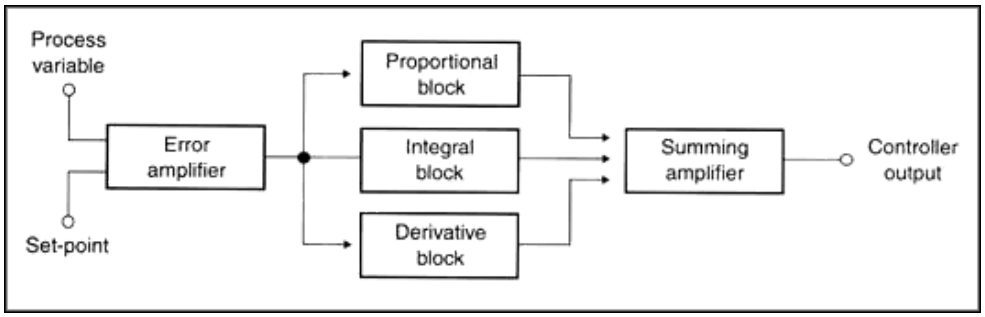

Figure 6: Block diagram of a PID controller (Webb and Reis, 2006).

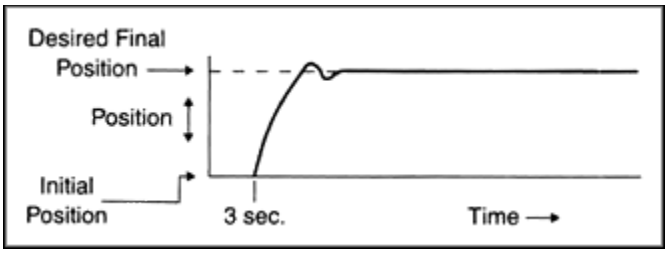

Figure 7: PID controller response to an input change (Webb and Reis, 2006).

Cascade control loop: Two controllers are used together with one feedback loop inside the other. The main advantage of this type of controller is that it yields a better dynamic response. There is a primary- and a secondary controller, with the output from the primary controller acting as set point for the secondary controller and the slave controller controlling the final control element (Svrcek *et al.*, 2006) as depicted in Figure 8. In Figure 9 a comparison between the typical response from a single PID controller and a cascade control loop to an input change is shown. It is evident that the cascade control loop has a much faster response, i.e. returns to the set point faster than a PID controller alone.

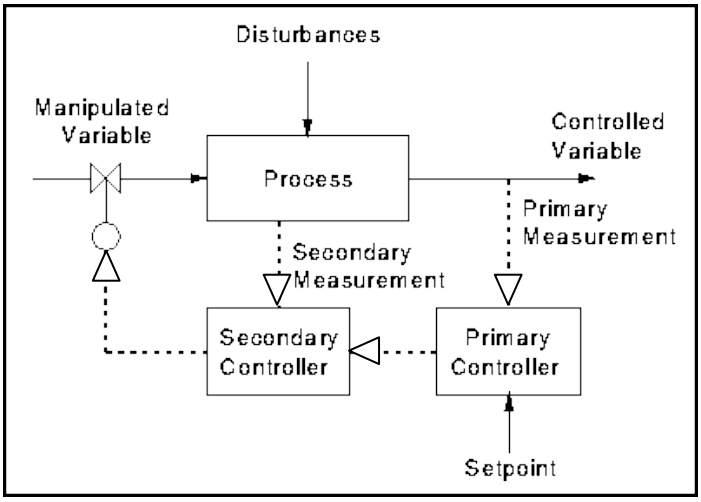

Figure 8: Block diagram of a cascade controller (The ECOSSE IGDS Control Hyper Course, 2011).

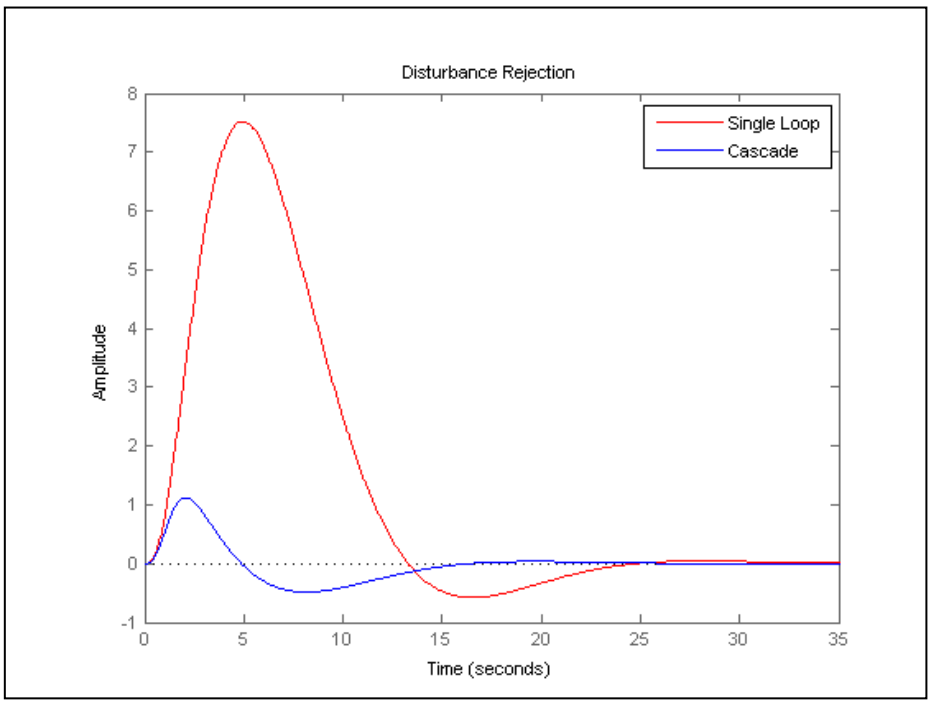

Figure 9: Comparison between response of a single PID controller and a cascade control loop (MathWorks, 2011).

Soft computing methods: Earlier computational techniques could analyse and predict relatively easy problems, but more complex problems and models – such as those found in the biological world – could not be analysed or predicted accurately without oversimplifying the model. Soft computing deals with imprecision, uncertainty, partial truth, and approximation to achieve tractability, robustness and low solution cost. This field includes

fuzzy systems, neural networks, probabilistic computing, and evolutionary computing (Moussa, 2003):

> *Fuzzy systems:* Fuzzy systems are based on the Fuzzy Set theory that was introduced to capture the real world and its uncertainties in programming constructs. Fuzzy sets use linguistic variables to describe and classify certain physical situations. The output of the set is also in a language the operator can understand.
>
> *Artificial neural networks (ANN):* Artificial neural networks are analogous to biological neural networks. ANNs are constructed using programming that simulates neural networks in the human body. ANNs are used to model biological networks for a better understanding, or rather to solve problems or test hypotheses for the real biological system.
>
> *Probabilistic computing:* In probabilistic networks a solution is found for a certain problem by means of measuring the probability of all possible solutions and choosing the one that is most probable. It is based on statistical and mathematical algorithms.
>
> *Evolutionary computing:* Evolutionary computation uses iterative progress, such as growth or development, in a population. This population is then selected in a guided random search using parallel processing to achieve the desired end. Such processes are often inspired by the biological mechanisms of evolution.

Adaptive controller: This type of controller adapts to a controlled system that has uncertain parameters; or is initially uncertain. The controller adapts itself according to varying conditions in the process it is controlling (Bellazzi *et al.*, 1995; Tao, 2003).

Model predictive methods: This type of controller relies on dynamic models of the desired process that needs to be controlled. The model predicts changes in output variables in accordance to changes in the input variables of the modelled dynamic system.

H_∞ *methods of control:* This method is used in control strategies to synthesise a robust performance for a controller. To use the H_∞ method, the control problem needs to be expressed as a mathematical optimisation problem which is then solved by the controller (Kovács *et al.*, 2010).

Together with the mathematical model describing the physiological system, these control methods are incorporated to produce a simulation model that can encourage communication

between patients and their care providers, as well as educate and assist diabetes patients and other interested parties.

2.5 Simulation models

"The form and detail of a mathematical model of a metabolic system and the processes by which it is derived are principally determined by the purposes for which the model is required" (Carson *et al.*, 1981).

This is especially true for mathematical models describing the human biology and metabolic pathways, such as the human energy system. The complexity of human physiology has led to models of varying complexity from the widely known minimal model of Bergman (1981) to the highly complex Sørensen model (1985). Since these two, several models have been developed by implementing certain aspects and improving on these models, or by taking an entirely different approach. Currently, several glycaemia educational simulation models exist, with no two that are exactly the same. Table 1 briefly describes several of the models currently available.

Table 1: Simulation models currently available to assist people with type 1 diabetes.

Model name/ Reference	**Description**
Bellazzi *et al.* (1995)	In this model a hierarchical structure is used to control the patient's BGL. The high-level module (HLM) is used to assess a specified insulin protocol provided by the low-level module (LLM) by means of implementing clinical information and medical knowledge. The HLM and LLM communicate continuously. The LLM is used to predict insulin therapy in terms of dosage, timing and type of insulin based on real-time BG measurements and a predefined insulin regimen. The model is optimised to be patient-specific using fuzzy control methods in correlation with open-loop methods. The LLM is evaluated by testing different control strategies for this module. The fuzzy method operating on perfect BGL predictions could control the module best. The model has been assessed on 60 patients with the main target being the telemedicine market.

Table 1 (continued): Simulation models presently available to assist people with type 1 diabetes.

Model name/ Reference	Description
DIABLOG (Biermann and Mehnert, 1990)	This simulation uses predefined virtual patients on either insulin injection therapy or insulin pump therapy. These virtual patients can be accessed to change the carbohydrate (CHO) contents of meals as well as insulin type, dosage and injection schedule. The output is simulated by utilising differential equations to describe delays, such as gut absorption of glucose or insulin action profiles. The model is used as a tool for patients to simulate different dietary and insulin regimens and to observe the simulated effect on BGLs. The model was tested on 22 patients. Out of the patients tested, 20 had positive feedback regarding the use of the model. However, six patients found it unfavourable that the virtual patient's data differed from their own and two found it confusing.
AIDA (Blanchard *et al.*, 1998)	AIDA is a model that takes meals, insulin dose and patient data (that includes hypoglycaemic and hyperglycaemic events) into account, and gives circadian BG and blood insulin (BI) profiles, as well as predicts HbA_{1c} levels. The main purpose of this educational simulation model is to allow patients to observe the change in BGL and insulin levels if certain dietary and insulin therapy adjustments were made. It is an educational tool that uses virtual patients. Input adjustments are made to these virtual patients to better fit the specific patient's data and to observe the changes in the simulated output. To test the simulation, dietary and insulin dose data from 30 TIDM patients were entered into the model. The model parameters for 24 out of 30 patients could be determined. From the data entered the root mean square (RMS) value for the best fit – between observed and predicted data obtained – ranged from 0.8 to 4.6 mmol/L with a mean error of 1.93 mmol/L with a standard deviation of 0.86 mmol/L.
García-Jaramillo *et al.*, (2010)	This simulation is a decision-support system used to optimise a specific patient's postprandial insulin dose using Modal Interval Analysis (MIA). It computes the optimal insulin dose by assessing input such as CHO intake, BG measurements and previous insulin dosages. The model takes into account uncertainty regarding food (CHO) intake and intrapatient variability. The optimal insulin dose and injection time relative to meal times are then calculated using a grid analysis. The model has been validated for preprandial BG values of 5.56, 10 and 13.89 mmol/L. For each scenario evaluated, the insulin protocol computed by the model led to a reduction in risk index in comparison to the protocol determined using heuristic rules.
DEMS (Gorman *et al.*, 2000)	Diabetes Electronic Management System (DEMS) is a program that collects data from T1DM patients, as well as every member of the diabetic care team, and stores it in a database. This information is then used at every patient-care-provider encounter where the input can be updated. The program is designed for ease of navigation, immediate provision of many types of automated generated reports, quality audits, aids with compliance regarding good care guidelines and alerts, advisories, prompts and warnings that guide the care provider. It does not generate output, such as circadian BG profiles, but is rather used to speed up encounters and support care providers according to good diabetic care guidelines. The database contained 34 000 patients' data at time of publication and is used at multiple diabetes care centres.

Table 1 (continued): Simulation models presently available to assist people with type 1 diabetes.

Model name/ Reference	Description
Dalla Man *et al.* (2007)	This model was built to simulate a normal person's glucose-insulin metabolism, but was also modified to simulate that of a patient with type 1 diabetes. The model includes the glucose and insulin subsystems, and model parameters and unit models to predict postprandial BG and insulin for a mixed meal. The model was tested on 204 normal patients who ingested three different tracers with the meal for comparison to the model's predictions. A type 1 diabetic was simulated by excluding the endogenous insulin from the model and incorporating both open- and closed-loop insulin infusion strategies. The model does not include counterregulation hormones.
ANFIS (György *et al.*, 2010)	This model consists of a continuous glucose monitor (CGM), an insulin pump and a control loop to simulate closed-loop control of the human BG system. A molecular model is adapted to a control algorithm that is based on an Adaptive Neuro-Fuzzy Inference System (ANFIS) which can naturally be divided into three different subsystems. These subsystems include the transition subsystem of glucagon and insulin, the receptor-binding subsystem and the BG system. The model is tested by using a glucose absorption curve from another source (Korach-André *et al.*, 2004). The model can predict BG and BI profiles for original glucose intake, faster absorption and more glucose intake for people with type 1 diabetes. The model is robust in terms of disturbances and controlled the BGLs for the aforementioned three scenarios within the normoglycaemic range.
Bolus Calculator – Medtronic MiniMed (Gross *et al.*, 2003)	This is a bolus insulin calculator designed for a Personal Digital Assistant (PDA) for improved control over postprandial glycaemic excursions in patients with type 1 diabetes. The PDA is pre-programmed with a specific patient's insulin sensitivity factors, carbohydrate-to-insulin ratios, and target BG levels. The patient then enters the preprandial BG measurements, the total CHO content of the meal, and an appropriate insulin dose. It is proven in the paper that this bolus calculator controls postprandial BG just as well as standard bolus techniques. The bolus calculator is patented. 49 patients with type 1 diabetes were enrolled in a study to test the calculator. Significantly less correction insulin boluses for hyperglycaemia, and more CHOs to counter hypoglycaemia, were administered with the bolus calculator than when the calculator was not used.
DiasNet (Hejlesen *et al.*, 2001)	This is a BG-simulation program that is available on the Internet. It is a CM that incorporates a Casual Probalistic Network to handle uncertainties in, for example, BG measurements. The model includes the glucose in the blood and gut as functions of various other organs. This tool is used by patients and clinicians for education and communication. It uses inputs, such as meal and insulin data, to estimate model parameters for a specific patient and then simulates BG and BI circadian profiles. It allows the patient to predict changes in BGLs by changing insulin type and doses as well as CHO intake. The tool also has an optimisation function that can optimise the insulin protocol for specific data input. The model has been evaluated in five small clinical studies.

Table 1 (continued): Simulation models presently available to assist people with type 1 diabetes.

Model name/ Reference	Description
Montani *et al.* (2003)	In this model a multi-modal reasoning (MMR) approach is used to implement Case-based Reasoning (CBR), Rule-based Reasoning (RBR) and Model-based Reasoning (MBR). The model implements rules and cases to profile the patient while a new probabilistic model of the patient's metabolic behaviour is used to derive and optimise a new insulin therapy. This model is a decision-support system. A cost estimate parameter is used to eliminate probable therapies. The model has been tested on real and simulated patients' data. The statistical accuracy is undetermined, but the results were encouraging and the MMR approach has since been implemented in a telemedicine-based trial.
Archimedes Glycaemia Simulator (Eddy and Schlessinger, 2003)	The Archimedes model is a broad-based model built on a patient-specific basis. The extent of the model covers multiple diseases including diabetes and its complications, as well as biological details, care processes and logistics, recourses, and cost-of-care systems. The glycaemia simulator is only a part of the greater model and includes meals, physical exercise (to an extent) and insulin treatments. The output of the model includes circadian BG profiles and insulin dose predictions. The model is extensive and includes a wide variety of variables that most models do not. In a total of 71 out of 74 validation exercises conducted in 18 trials, there were no statistically significant differences between the results calculated by the model and the results observed during the trial ($r = 0.97$).
Mougiakakou *et al.* (2005)	This model implements a combination of CMs and Recurrent Neural Networks (RNNs) trained with Real-time Recurrent Learning (RTRL) algorithms. There are three CMs: one for short-acting insulin, one for long-acting insulin and one for the meal input data, all from the patient, in order to predict glucose released from the gut. The BG measurements of the patient are also required as input to the model. The output from these CMs is fed to an RNN. The output from the RNN in turn simulates BGL predictions based on the input for patients with type 1 diabetes. For comparison reasons, two strategies were used: Free-run (FR) and Teacher-forming (TF). The model was tested using data from type 1 diabetic patients for 59 days (275 BG measurements). This data was used as a training set for the model. The next 10 days (45 BG measurements) were used as a testing set. The results show the mean absolute difference and the standard deviation (for both strategies) between simulated- and measured BG data as FR: 33 ($\sigma = 24$) and TF: 35 ($\sigma = 28$).
KADIS® (Rutscher *et al.*, 1994)	KADIS® is a decision-support system with the following main objectives: evaluation of patient data, analysis of this data, and simulation of BG and BI profiles on a daily basis. It uses a mathematical model of which the parameters can be specified for a specific patient based on certain diagnostic tests on the patient. The model can also predict BG and BI circadian profiles in accordance to dietary, therapeutic and exercise adjustments. Inputs to the model include meals, insulin dose, type and means of administration, as well as physical exercise. KADIS® was tested by physicians on outpatients. An increase in metabolic control was achieved within three months of using the decision-support system. HbA_{1c} levels were reduced by 0.62% ± 0.20% and normoglycaemia increased by approximately 3 hours/day.

Table 1 (continued): Simulation models presently available to assist people with type 1 diabetes.

Model name/ Reference	Description
Rui and Jang (2005)	This is a CM of glucose metabolism at organ level based on research of CHO metabolism. The model includes compartments for the liver, kidney, brain, interstitial fluid, pancreas, circulatory system and other tissue CHO metabolism. The model is incorporated into a multi-element, nonlinear cardiovascular model and simulated CHO metabolism for several situations. It was tested by simulating a BG response to 20 g of injected glucose and comparing this to experimental data from literature. The results of measured- vs. simulated BG data are accurate to within approximately 8mg/dl for 150 minutes after the glucose injection. A bolus insulin administration was also simulated, but the accuracy is undetermined.
Dittakavi and Ghista (2001)	This model of the combined gastrointestinal tract and the BG control system is derived from differential equations. The model was developed to simulate the BG regulation control for diabetic patients after the oral glucose tolerance test (OGTT). This test implies a single oral bolus administration of glucose. The model is rate-controlled by the rate of glucose absorption in the gut. The model was tested on healthy people and diabetic patients to determine its accuracy. It was found that the model is sufficiently accurate and will be used in differential diagnosis of diabetes as well as determining the risk for diabetes. They quantified insulin intolerance in a parameter, which if evaluated, will determine the risk of diabetes.
Sørensen (1985)	This is a very extensive model; it covers the entire body's BG and insulin system. The model divided the body into the following compartments: brain, heart and lungs, liver, gut and periphery. The amount of differential equations (22), as well as parameters (42), used to describe the organ and tissue compartments is an indication of the complexity of the model. It also takes into account all the rate-controlling steps in the metabolic pathways – such as the rate of transport for insulin from the β-cells to the receptors on other cells, or the rate of glucose uptake by any one of the compartments as defined above. The model was tested using intravenous glucose tolerance test (IVGTT) data to compare to simulated results. The model was extremely accurate in predicting BG and BI response.
MinMod *Millennium* (Boston *et al.*, 2007)	This is an updated version of the Bergman MinMod model (Pacini and Bergman, 1986). This simulation is based on the Bergman minimal model that estimates two key factors in the BG subsystem: glucose effectiveness (S_G) and insulin sensitivity (S_I). The model can also calculate several other parameters associated with this system and it has been shown that the estimation of these parameters with MinMod is very accurate. This update of the original model was assessed and updated to "be Windows-based, have a simple interface, and be automatic, accurate, repeatable, reproducible, and concordant with prior versions of MINMOD". The Millennium model was tested on 131 subjects taking the frequently sampled intravenous glucose tolerance test (FSIGTT). The model produced identified estimates of S_I and S_G for all 131 subjects with a standard deviation of less than 0.5.

Table 1 (continued): Simulation models presently available to assist people with type 1 diabetes.

Kim *et al.*, 2007	This is a whole-body compartmental model of the body's metabolism. The following compartments are included in the model: brain, liver, gastrointestinal tract, heart, skeletal muscle, adipose tissue and 'other tissues'. Each compartment is mathematically derived from mass balances and the metabolic pathways taking place. The glucose-insulin system was also incorporated to determine the hormonal response of this system during exercise. The model was validated by comparing simulated results to experimental results. The model can predict several parameters that are difficult to measure directly, such as dynamic hepatic glycogenolysis and gluconeogenesis. This is a valuable tool to use in experimental studies to predict parameters that cannot be measured directly.

2.6 Conclusion

The human energy system is a complex combination of metabolic pathways and interactions at molecular, cellular and organ level. The BG subsystem is an intrinsic part of the energy system and has been studied for centuries to understand how it works, and the diseases related to this system.

The increase in the number of diabetes mellitus cases over the last decade is alarmingly high and has been classified by the WHO as an epidemic. Due to the severity of the complications of diabetes, a strong focus has been placed on education of the public on the matter, as well as improving therapies and tools to help diabetics regulate their BGL.

Several simulation models have been developed to virtually simulate the BG system and diabetes. The main goal is to test insulin protocols and hypotheses developed on virtual patients rather than real patients. This is less dangerous, time-consuming and expensive than clinical trials performed on real diabetes patients.

The problem with existing models is that they do not use an integrated approach to incorporate all the external and internal influences on the BG system. These influences include food intake, exercise, stress, alcohol, and regulation- and counterregulation hormones. The human physiology is an integrated system that has to adapt to all external and internal changes to maintain internal homeostasis.

To accurately simulate reality, the model has to represent reality as close as possible. Therefore, an integrated approach is required for the BG subsystem. In the following chapters an integrated educational simulation model will be presented and described.

2.7 References

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