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Bachelor Thesis

A Virtual Type 1 Diabetes Patient

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Statement of Authentication

I hereby declare that the work presented in this Bachelor Thesis has been written by me except of passages that are explicitly acknowledged. I confirm that this work has not been submitted elsewhere in any other form for the fulfillment of any other degree or qualification.

Hamburg, _____

(Tim Wasmuth)

Abstract

Diabetes is one of the most common diseases in the industrialized world, currently affecting more than 371 million people [1]. Especially in the blood glucose regulation in type 1 diabetes, scientists have long been researching various ways to replace the missing and vitally necessary hormone insulin. As a result of the computer age, new opportunities have opened up to explore and develop different treatment methods. The goal is to use devices to mimic the insulin-producing beta cells of the pancreas, as well as to improve the overall quality of life of a type 1 diabetic. The systems that are currently available (artificial pancreas), which consist of a glucose sensor, a controller and an insulin pump, and are used for continuous insulin replacement, are still subject to many limitations. Even today there is no approved system which continuously and automatically regulates blood glucose levels without the need for patient involvement.

A very useful tool for the development of systems such as the artificial pancreas are mathematical models that mimic the physiological behavior of a type 1 diabetic with the help of a suitable software. Such models allow for simulations of different insulin treatment scenarios for training purposes, as well as i.e. the testing of various components of the artificial pancreas previously mentioned. The results of such simulations can be very helpful for the planning and evaluation of clinical trials, with the long-term goal of developing an artificial pancreas. It can also save considerable time and money.

The aim of this thesis is to develop a software (virtual type 1 diabetic patient) that provides for a user-friendly simulation in the range of seconds by using an appropriate mathematical type 1 diabetes model [2]. The software will be constructed so that components such as a controller or glucose sensor can quickly be integrated or replaced in order to test them with the help of various simulations. This should enable a simple and accessible operation of the virtual diabetic with the help of a graphical user interface (GUI), without requiring the user to understand the software.

Keywords: type 1 diabetes, artificial pancreas, mathematical models, simulation, software, seconds, controller, GUI

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Tim Wasmuth

Content

1 Introduction

Since the discovery of diabetes, this disease has been treated in a variety of ways throughout the past centuries. With the progressive development of science, its treatment has been steadily improving. The discovery of insulin in 1922 [3] prevented diabetics who suffered from an absolute insulin deficiency, nowadays referred to as type 1 diabetes, from dying after a short time (since survival is virtually impossible without insulin). In the 21 Century the means of treatment have improved dramatically and continue to improve year by year. Computer-controlled devices have opened up the possibility of creating an artificial pancreas, designed to mimic the natural insulin secretion. Yet fully automated, long-term artificial pancreas' are still not available for commercial use.

Scientists around the world are trying to develop such automated systems for long-term use, by e.g. using the method of computational modeling. With such methods, it is increasingly possible to describe systems and problems as a numerical model. A good model must behave properly in the context of the intended optimization. The challenge is to make such virtual models available for real-life application, in order to see vital research and development of new treatment strategies for Type 1 diabetics.

1.1 Aim of this Thesis

The aim of this thesis is to develop a software that, using an existing mathematical model [2], allows for a simulation of the behavior of a type 1 diabetic regarding his glucose level in the blood and in the interstitial, as well as the simulation of insulin doses and food intake, and which provides for results in the range of seconds with a corresponding graphical display. The software is designed so that it is possible to integrate or replace a controller with the help of methods without having to understand the software in detail. In addition, the application will be made possible through a graphical user interface GUI. With the GUI it will be made possible to administer the virtual patient's insulin and food, to enter patient-specific data, as well as to activate a controller for blood glucose regulation. Moreover, the most important simulation results are presented graphically. Finally, special attention has been given to the design of the GUI with a view to increasing user friendliness and minimizing errors with the simulator. The virtual type 1 diabetic

(simulator) is a useful tool for the *in silico* design and explores various control strategies, such as the artificial pancreas for blood glucose regulation.

In the present thesis, the reader will first be introduced to diabetes. Next, it will be described how the original mathematical model was modified so that the simulation results were outputted in seconds. After this, the design of the simulator will be described and the requirements for the software structure and GUI explained. Finally, it will be demonstrated how the simulator can be used with the GUI.

1.2 Limitations of the Thesis

Within this thesis a verification and validation of the developed software is not possible. The proper use of such a simulator must be completed by the appropriate qualified personnel. All simulation results were not compared with clinical data. The simulations shown at the final of this thesis are merely illustrative of the use of such a simulator using the GUI. The simulations shown in the final statements of the thesis are merely illustrative of the potential use of such a simulator together with the GUI.

2 Theory

2.1 Diabetes

One of the main energy sources for the human body is glucose. Glucose is a degradation product of carbohyhdrates, which are obsorbed by food, and taken up through the intestinal wall into the blood. "*In a healthy person the blood glucose level is maintained between 70-110 mg/dl*" (quote from [4]). Responsible for the blood glucose regulation are two peptid hormones, secreted in the pancreas and called insulin and glucagon.

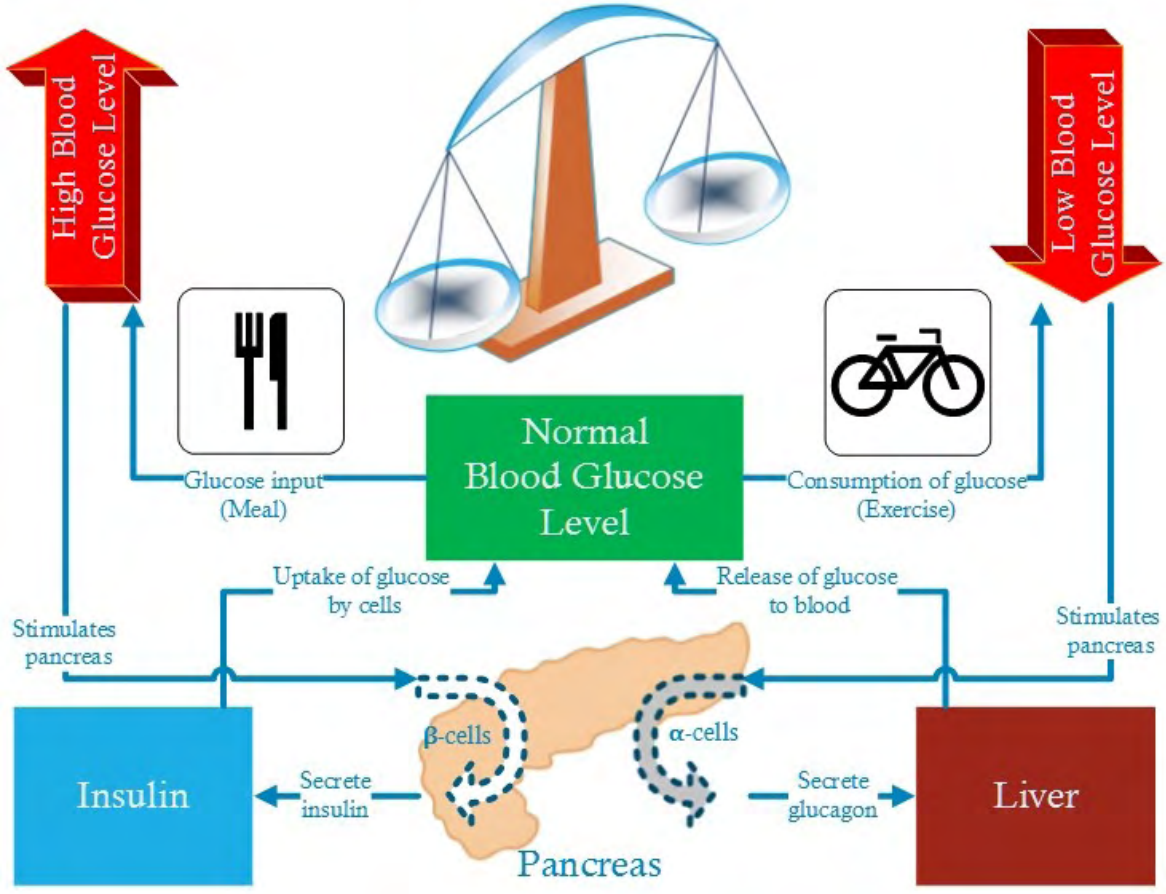


Figure 2.1.1: *The principle of blood glucose regulation.*

With an increasing blood glucose level the pancreas releases insulin, produced in the β-cells of the islets of Langerhans, to stimulate the absorption and degradiation of glucose into the cells in order to bring the level back to a normal range. Otherwise, if the blood glucose level decreases, the α-cells of the islets of Langerhans in the pancreas release glucagon into the blood to stimulate the gluconeogenesis and glucose distribution into the bloodstream by the liver, so as to increase the blood glucose level [5]. In people with diabetes, this regulatory mechanism is disturbed.

Diabetes is a syndrome that is associated with hyperglycemia and glycosuria in which carbohydrates, fat, and protein metabolism are disturbed. It is either an insulin lack or a decreased effect of insulin or a combination of the two [6].

> The American Diabetes Association (ADA) defined Diabetes as: *"a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both"* (quote from [7])

As a consequence, the access of glucose into muscles and other tissues is reduced. Thus the absorption glucose remains in the blood, and also the endogenous glucose regeneration goes on undampedly. Both of these processes ultimately lead to a rise in the blood glucose level [8].

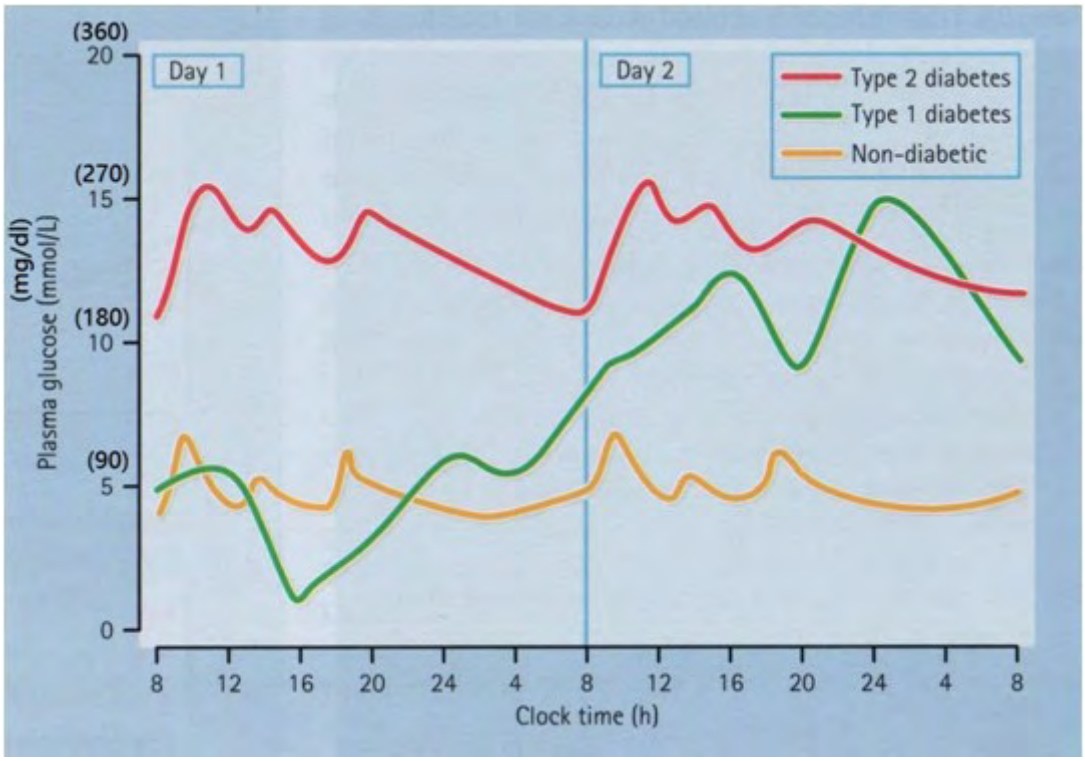


Figure 2.1.2: *Schematic variations of blood glucose concentrations in diabetes and non-diabetes [9].*

There are three principal types of diabetes:

1. Type 1 diabetes
2. Type 2 diabetes
3. Gestational diabetes mellitus

Type 1 diabetes is an autoimmune disease in which the body's immune system attacks and destroys the insulin-producing β-cells of the pancreatic islets. As a result, little or no insulin is produced. Type 2 diabetes is called non-insulin dependent diabetes mellitus

(NIDDM). This type leads to a permanently higher blood glucose (offset), because an insulin resistance and relative insulin deficiency is present. In gestational diabetes mellitus, there are increased blood glucose levels during the pregnancy [10].

In antiquity, the diagnosis was made by a taste test of the urine, because the urine of people with diabetes has a sweet taste with raised blood glucose levels.

> "*Polyuric states resembling diabetes mellitus have been described for over 3500 years. The name 'diabetes' comes from the Greek for a syphon; the sweet taste of diabetic urine was recognized at the beginning of the first millennium, but the adjective 'mellitus'(honeyed) was only added by John Rollo in the late 18th century*" (quote from Tattersal et al. [3])

According to current WHO criteria, there are different methods for the diagnosis of diabetes. Among these are:

- when classic symptoms of hyperglycemia are present and plasma-glucose $\geq 200\, mg/dl$ ($\geq 11\, mmol/l$) is measured
- a fasting plasma glucose level $\geq 126\, mg/dl$ ($\geq 7\, mmol/l$)
- 2 hours after a $75\, g$ glucose drink the plasma glucose $\geq 200\, mg/dl$ ($\geq 11\, mmol/l$)

Is one of these methods fulfilled it must be confirmed by one of the other methods listed in the WHO criteria on a following day [11]. Only authorized glucose measuring devices may be used for the diagnostics.

According to estimates of the IDF more than 371 million people worldwide are currently suffering from diabetes mellitus [1]; 85-95% are type 2 diabetics. Diabetes is one of the most common diseases worldwide.

2.2 Type 1 Diabetes

Humans with type 1 diabetes are dependent on insulin injections every day. Therefore type 1 diabetes is also called insulin-dependent diabetes mellitus (IDDM). The problem is that the pancreas produces insufficient or none of the essential hormone, insulin. As a result the blood glucose level increases to unhealthy levels. It is therefore essentially an autoimmune disease in which the body's immune system attacks and destroys the insulin-producing

β-cells of the pancreatic islets [12]. This process can last for several months to years, until finally all cells are destroyed (see Figure 2.1.1). Today nobody knows exactly what triggers the autoimmune attack.

Insulin is the only hormone which can bring the blood glucose level back into a normal range because it enables the glucose uptake in the cells from the blood plasma (see section 2.1). Without an artificial insulin input, it is currently not possible to survive. Type 1 diabetes patients require lifelong "insulin therapy."

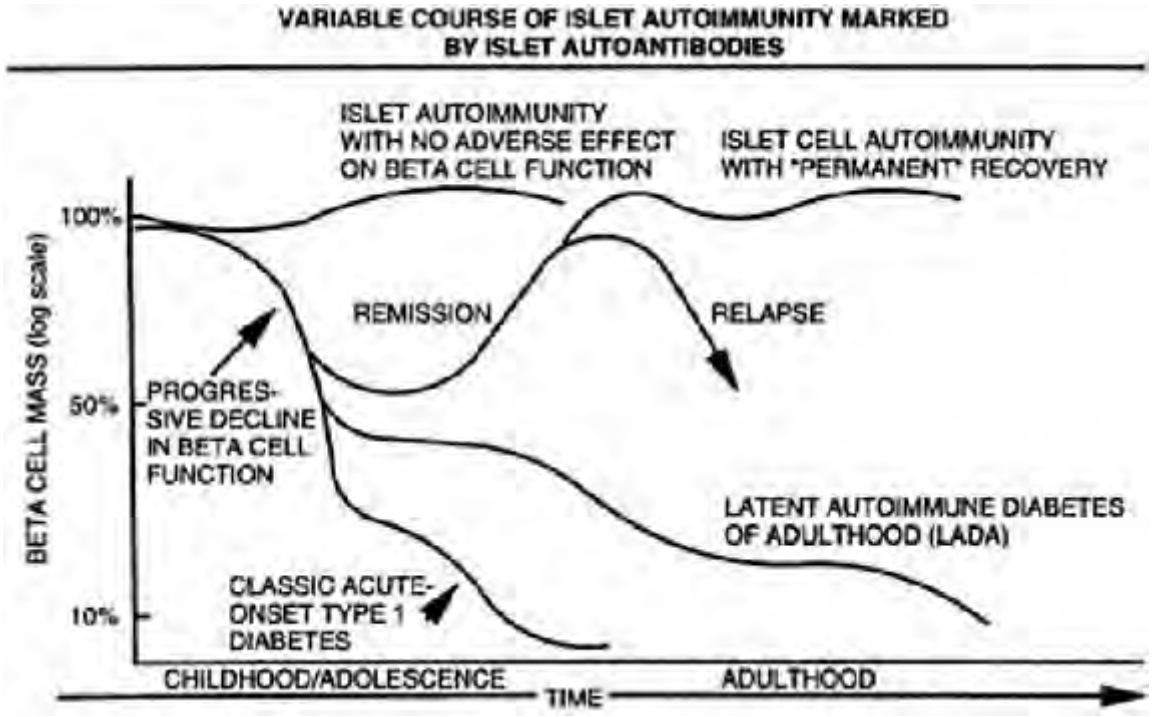


Figure 2.2.1: *"Natural history of the autoimmunity. Some individuals who express islet autoantibodies display no loss of beta-cell mass (top left). More commonly though, individuals with islet autoantibodies exhibit a progressive decline in beta-cell function. Many such individuals will progress to acut-oneset type 1 diabetes that presents in childhood or adolescence. Some individuals will enter a remission phase with improved beta-cell function, whereas others will slowly progress to type 1 diabetes in adulthood (LADA). Permanent remission relapse, or progression to type 1 diabetes after an initial remission are possible clinical courses." [13].*

The IDDM is usually diagnosed in young people but it is also possible to contract it as an adult. In 2004 there were approximately 10-20 Million People with type 1 diabetes worldwide [14]. When one considers the estimates of the International Diabetes Federation [1], then currently over 50 million people could be affected by type 1 diabetes. Characteristic for the manifestation of type 1 diabetes is the pronounced weight loss within days to a few weeks, combined with dehydration, constant thirst, frequent urination, vomiting, sometimes cramps in the calves as well abdominal pain. General symptoms such

as tiredness and weakness, blurred vision and problems concentrating can be added. Secondary diseases due to increased blood glucose levels and acute complications caused by fluctuating blood glucose levels make it difficult to live a healthy life. Untreated type 1 diabetes leads to a permanently elevated fasting blood glucose level over $126\,mg/dl$ [15] and far beyond. This condition is also known as hyperglycemia. On the other hand, in a treated type 1 diabetics it can also lead to low blood glucose levels under $70\,mg/dl$ [16], which is called hypoglycemia, that will be see next section. Both conditions can be very dangerous and therefore it is important to improve blood glucose monitoring constantly. The closer blood glucose levels approximate normal levels the better.

2.3 The Effects of Diabetes

Diabetes is not painful, but the disease brings far-reaching health complications with it. This is valid for type 1 and type 2 diabetics. The occurrence or absence of these complications is crucial for the quality of life and the lifetime of the individual concerned. In the worst cases the complications can lead to hospital admissions, permanent disabilities, and even death. On the one hand there are long-term complications, like chronic diseases, that can result from an increased blood glucose level over an extended period. On the other hand it can cause acute disorders of the blood glucose balance, better known as short-term or acute complications (see table 2.1), which expresses themselves in the form of a hypoglycemia or hyperglycemia. A change in nutrition and lifestyle is necessarily required to achieve an adequate control of the conditions. In addition, it is usually necessary to constantly improve the insulin therapy and also the monitoring of blood glucose to reduce such complications to a minimum.

Complications of diabetes mellitus
Short-term (acute) complications
Diabetic ketoacidosis (DKA) Hyperosmolar non-ketotic acidosis (HONK) Hypoglycemia
Long-term (chronic) complications
Microvascular Retinopathy Nephropathy Neuropathy
Macrovascular Cardiovascular disease (CVD) Peripheral vascular /arterial disease (PVD/PAD) Diabetic foot (associated with PVD/PAD and/or neuropathy)

Table 2.1: *Complications of diabetes mellitus [17].*

2.3.1 Short-Term Complications of Type 1 Diabetes

Short-term complications are the result of acute metabolic imbalances, which are mainly caused by improper insulin infusions, having too much food or missing a meal, exercise, and various other factors. This often affects type 1 diabetics. Among the most significant acute complications are **DKA** and **hypoglycemia** [18]. The problem when type 1 diabetes is diagnosed is that you have to inject insulin every day in accurate amounts. Without insulin replacement DKA leads to death. In contrast, when insulin is used in excessive doses it can cause hypoglycemia and be equally lethal.

DKA is defined as a trias of hyperglycemia, metabolic acidosis and hyperketonemia. The reason for DKA is a relative or absolute lack of insulin. In heavy DKA the blood glucose is significantly higher than $250\,mg/dl$ (often above $350\,mg/dl$) [19]. Clinical features include polyuria, extreme thirst, rapid weight loss, slow and deeper breathing (Kussmaul), pain in the abdomen, blurred vision, nausea, vomiting, and even coma. It is one of the important causes for the morbidity and mortality in type 1 diabetes [20]. For the prevention of DKA the diabetic subject is obliged to manage his diabetes treatment carefully. That means that you have to monitor your blood glucose sufficiently, adjust the right insulin dosage, and be prepared (as much as possible) to counteract DKA. In the case of children, the parents are encouraged to inform themselves about these complications in order to prevent lethal complications.

> *"Approximately 30% of children who present with newly diagnosed type 1 diabetes are ill with DKA"* (quote from [21])

When the blood glucose falls below $70\,mg/dl$ [16], then one talks of **hypoglycemia**. The definition of hypoglycemia is divided into three criteria (called *Whipple's criteria),* which must be satisfied. **F**irst, typical symptoms of hypoglycemia must be present, **s**econdly, an exceedingly low blood glucose level must be measured simultaneously, and **t**hirdly, if symptoms disappear by the ingestion of food [22]. A looming hypoglycemia can be recognized by the following symptoms: perspiration, trembling hands, palpitations, feeling uncomfortable, and ravenous hunger. The typical symptoms for existing hypoglycemia include: difficulties concentrating, feeling tired, difficulty speaking, one's sense of balance may be disturbed, and excessive irritability. The prevention of hypoglycemia is one of the most challenging tasks in achieving a relatively normal blood glucose level. The lower the desired blood glucose level is in the insulin therapy, the more often it can come to hypoglycemia [18]. The state of hypoglycemia can occur very quickly. Mostly in a mild

form, which can be remedied quickly with a glucose-rich drink or food. However, if left untreated and developed into a severe hypoglycemia this can lead to a coma up to the point of death. A training of the patient and an adapted insulin therapy can reduce the risk of hypoglycemia. Specifically nocturnal hypoglycemia can be very dangerous, because one's perceptual ability is reduced. More than half of severe hypoglycemia occurs at night. Therefore continuous glucose measurements can be very helpful.

2.4 Glucose Monitoring in Diabetes

The blood glucose test is used to determine the glucose value in the blood. The results are expressed in milligrams per deciliter (mg/dl) or millimoles per liter ($mmol/l$). This test is needed when you have diabetes, because the body cannot regulate the blood glucose in the usual manner and therefore it is necessary to monitor the blood glucose levels in order to be able to counteract excessively high or low blood glucose levels. The goal for a diabetic must be to keep the blood glucose levels within a healthy range.

> "(...) *measuring metabolic control are for diagnosis of diabetes, for adjusting therapy so as to maintain near-normal blood concentrations of glucose, for detection of the acute complications of hypoglycemia, hyperglycemia and ketoacidosis, and for assessing the risk of later development of tissue complications.*" (quote from [9])

In a **non-continuous monitoring** the blood glucose is typically measured with a capillary blood sample by piercing the skin with a needle. The blood sample is then evaluated with a blood glucose meter (see figure 2.4.1). In type 1 diabetes this is typically done several times a day by the patient himself. This helps to evaluate the effectiveness of their prior insulin dose and to establish their next insulin dose. Yet the true fluctuations in blood glucose levels may not be recognized by conventional capillary self-monitoring of blood glucose [23].

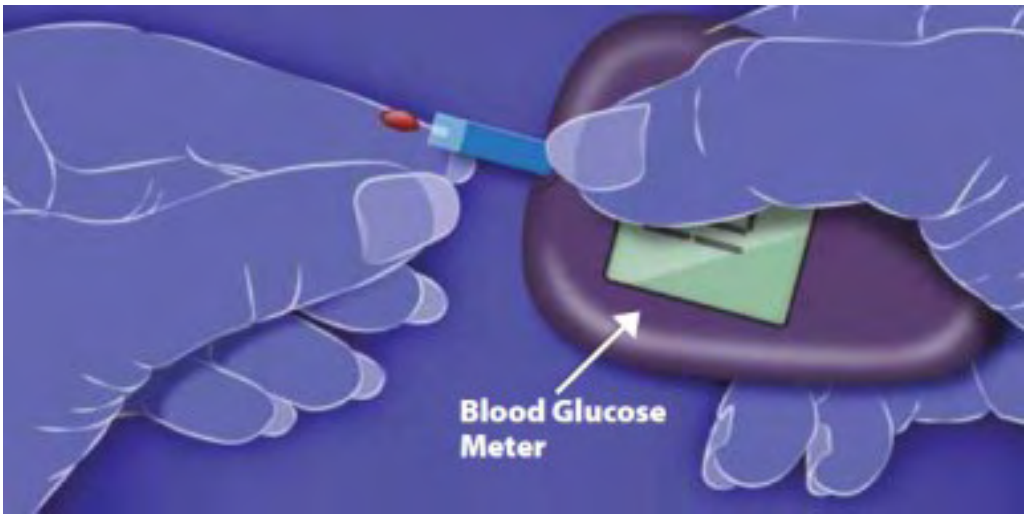


Figure 2.4.1: *Blood glucose monitoring by an blood glucose meter [24].*

With **continuous glucose monitoring systems (CGMS)** it is possible to detect such blood glucose excursions. Furthermore, such systems supply trend information about glucose levels that can help to protect the patient from hyperglycemia or hypoglycemia. Such devices typically have a built-in real-time alarm system that warns the patient when the blood glucose is too low or too high [25]. Especially with nocturnal hypoglycemia it can often prove extremely helpful if not life saving.

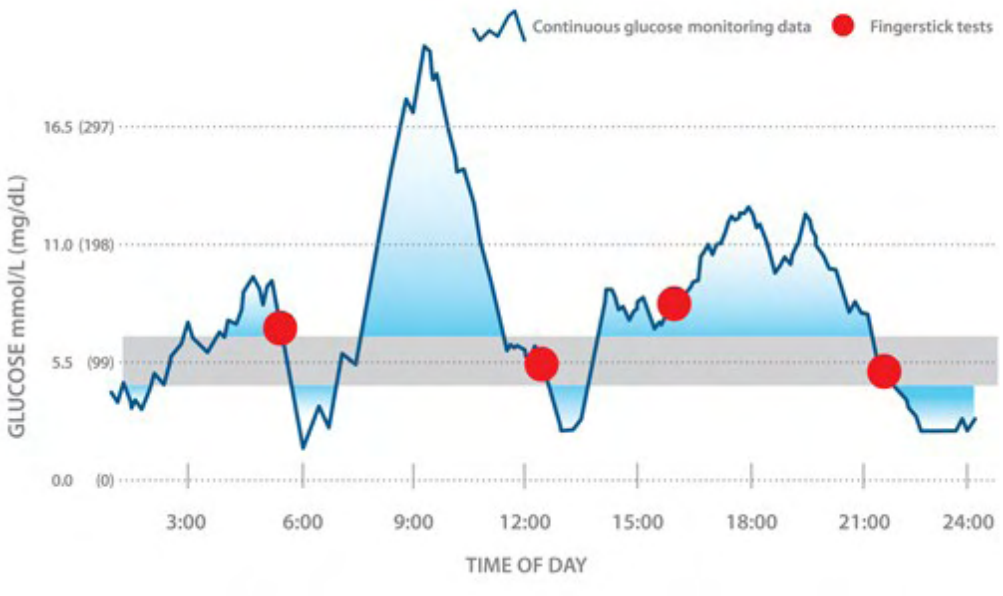


Figure 2.4.2: *Example of continuous and finger-stick glucose monitoring over 24 hours [26].*

These systems consist of a small sensor that determines the blood glucose levels every few minutes, a transmitter, and a monitor, which receives the blood glucose levels.

> *"The currently available CGMS measure blood glucose either with minimal invasiveness through continuous measurement of interstitial fluid (ISF) or with the noninvasive method of applying electromagnetic radiation through the skin to blood vessels."* (quote from [25])

While such systems are a big advance for diabetes therapy and especially for type 1 diabetics they are still in need of improvement since the sensor must be calibrated very carefully and correctly several times a day by a blood sample and must furthermore be changed every few days. These are limitations that can unnecessarily complicate the life of a diabetic since they must be extremely disciplined with the handling of such systems.

An answer to these limitations is e.g. an implantable long-term glucose sensor which is currently under development by a California-based company (GlySens).

> *"The GlySens sensor is designed to allow automated measurements without user interaction and without the inherent variability associated with changing sensor sites every few days."* (quote from [27])

Such glucose monitoring sensors are the basis of safe and comfortably monitored insulin therapy. The combination of glucose sensors that continuously measure levels with an insulin pump offers a potential basis for future closed-loop systems, which provide for artificial pancreas natural insulin secretion [28].

2.5 Insulin Therapy

In contrast to a healthy person, a type 1 diabetic depends on regular insulin injections to survive. Under normal conditions in a healthy individual, insulin is secreted continuously by the pancreas. The secreted amount of insulin is dependent on the blood glucose level. Between meals, when blood glucose levels are around $90\ mg/dl$ [29], insulin is constantly secreted in small amounts (typically at $0{,}1 - 0{,}2\ mU/kg/min \sim 0{,}5 - 1{,}0\ U/h$) [30], also known as basal insulin secretion. During the meals the blood glucose level increases and as a result it comes to a higher insulin secretion (prandial insulin) (see figure 2.5.1), which varies in terms of amount and duration [31].

Different variants of insulin-therapies have been developed in recent few decades for treating diabetes. The goal of treatment is to bring the carbohydrate metabolism and thus the blood glucose levels to a normal level. Insulin doses vary widely between the

individual subjects. The most important factors include body weight, the level of physical activity, and the insulin sensitivity.

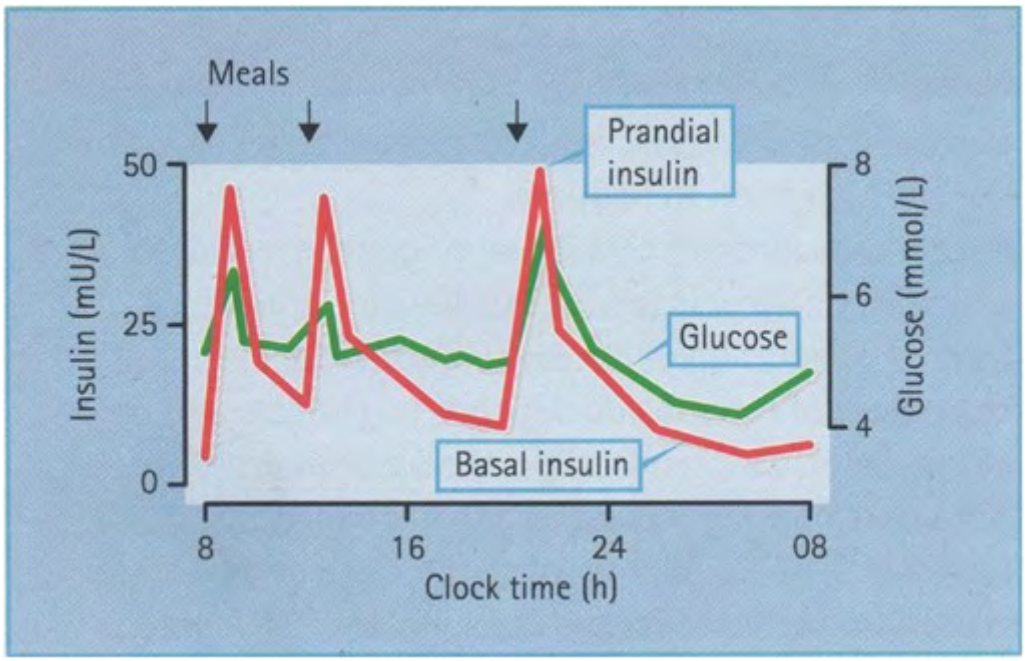


Figure 2.5.1: *"Twenty-four hour profiles of blood insulin and glucose concentrations in non-diabetic subjects. Note the insulin peaks at meals (prandial) and constant delivery between meals (basal level)." [31].*

At the time when people are diagnosed with type 1 diabetes, they must immediately start with insulin-replacement-therapy. During these initial stages the insulin-replacement-therapy is usually "intensified". A distinction is made between **ICT** (intensified-conventional-insulin-therapy), which is also called **MDI** (multiple daily injections) and the **CSII** (continuous-subcutaneous-insulin-infusion therapy).

In an **ICT** different insulin types are used and given by subcutaneous injections. These include e.g. long- and short-acting insulins. The long-acting insulins (basal insulin) mostly are given in the morning and/or before going to sleep, whereas the short-acting insulins (prandial insulin) are injected before meals to counteract the rising blood glucose levels that result after meals. This therapy attempts to mimic the physiological concentration of insulin over 24 hours as accurately as possible, in order to keep the blood glucose concentration within narrow limits (see Figure 2.5.1).

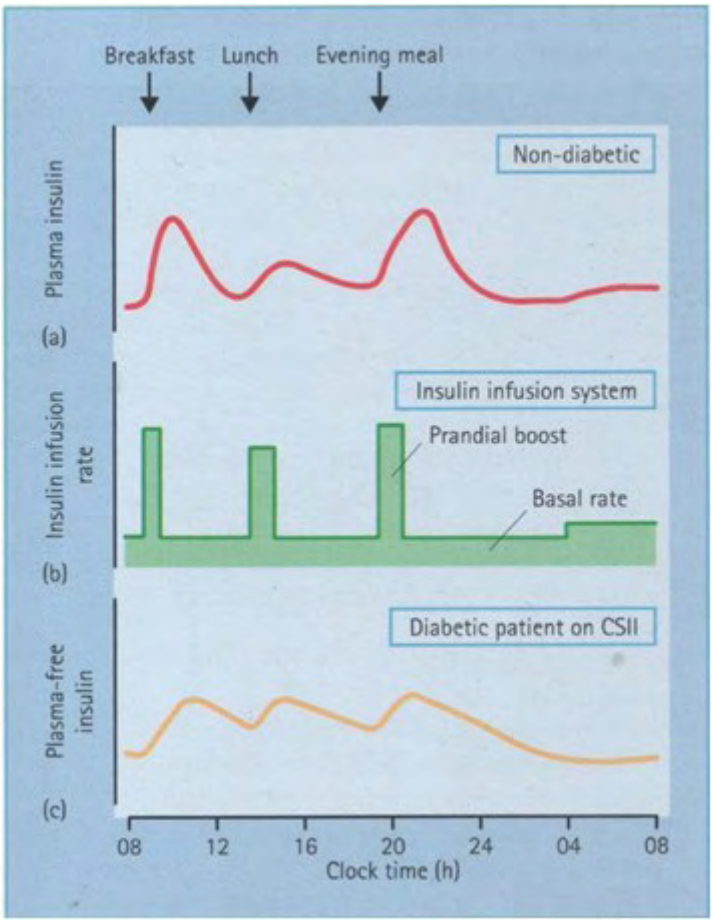


Figure 2.5.2: *"The aim with open-loop insulin delivery systems is to mimic non-diabetic insulin secretion (**a**), by infusing insulin at variable basal rates throughout the 24h, with patient-activated boosts at meals (**b**). (**c**) The plasma free insulin concentrations in a patient treated by continuous subcutaneous insulin infusion (CSII)." [32]*

CSII is a special form of intensified-conventional-insulin-therapy. The treatment principle with the basic-bolus-method is the same, with the difference that only one insulin is used (mostly short-acting) and is not injected a few times a day with a syringe, but rather administered by a pump. By means of a catheter the needle is fixed in the skin and a continuously programmed basal rate is delivered by the pump in order to cover the basic insulin (basal-rate) needs (open-loop). Additional units of insulin are administered before meals by pushing a button (prandial boost) (see Figure 2.5.2). In contrast to the "open-loop-system" just described, the user of a "closed-loop-system" is not responsible for the administration of basal insulin. The goal is to develop a fully-automatic-system (closed loop) for the regulation of blood glucose levels—an "artificial pancreas". For this purpose a continuously measuring glucose sensor is used, an insulin pump, and a controller, which determines how much is to be administered by the insulin pump [33]. So far there is no

closed-loop-system available that regulates for more than a few days, as the necessary long-term glucose sensor is not yet available.

> *"(...)the sensor is key to the implementation of the mechanical artificial beta cell."* (quote from et al. Gough [34])

Patient education and practicing tight control are indispensable prerequisites for the successful application of the above-described forms of intensified therapy. In the Diabetes Control and Complications Trial (DCCT) it was found that a complete break form or slowing of the progression of long-term problems such as retinopathy, nephropathy and neuropathy could be reduced by 35-70% with a properly conducted intensive insulin therapy. The negative side is that the risk of suffering hypoglycemia was increased by 300%. [35].

2.6 Why using virtual models?

Without models, improvements are difficult to achieve, unless one is willing to make large investments for a real-life scenario (like *in vivo* clinical research). A good model must behave properly in the context of the intended optimization. This means it does not correspond to reality or represent a 1:1 process. A distinction is made between real-models, which you can “touch” and virtual-models, which are based on a mathematical algorithm. The translation from real-systems to virtual-models is realized by computational modeling (*in silico*).

These virtual-models mostly describe a system by variables as well as equations that establish relationships between the variables. The simulation time depends on the computing power and the complexity of the model. Yet for most models, the common personal computer is adequate enough to run a simulation, unless it is about simulations of weather forecasts or something similar.

Virtual-models (mathematical models) of the glucose-insulin-metabolism have been developed for the diabetes treatment and research. It can help to better understand the dynamic metabolism of the human body and testing devices during the development phase for the treatment of diabetes. With simulations of such systems the cost and undesirable developments as well as lengthy development times can be minimized. And above all,

experiments on living people can be performed more safely since risk considerations can be detected with simulations.

> *"(...), calculation of optimal insulin dose requirement by real-time experimentation on patients will not be a safe and efficient treatment method. Instead, testing on virtual patients that mimic the real physiological behavior is easy, safe and can help improve the quality of treatment. Virtual diabetic patients can be created by the development of mathematical models that mimic the physiological behaviors related to glucose insulin regulatory mechanism."*
> (quote from [36])

Especially for the development of closed loop systems (artificial pancreas), the testing of such components "*in silico*" for virtual type 1 diabetic patients is needed. Such closed-loop systems essentially consist of three main components. This includes a glucose sensor (see Chapter 2.4), an insulin pump, and a control algorithm (controller) that determines when and how much insulin needs to be administered.

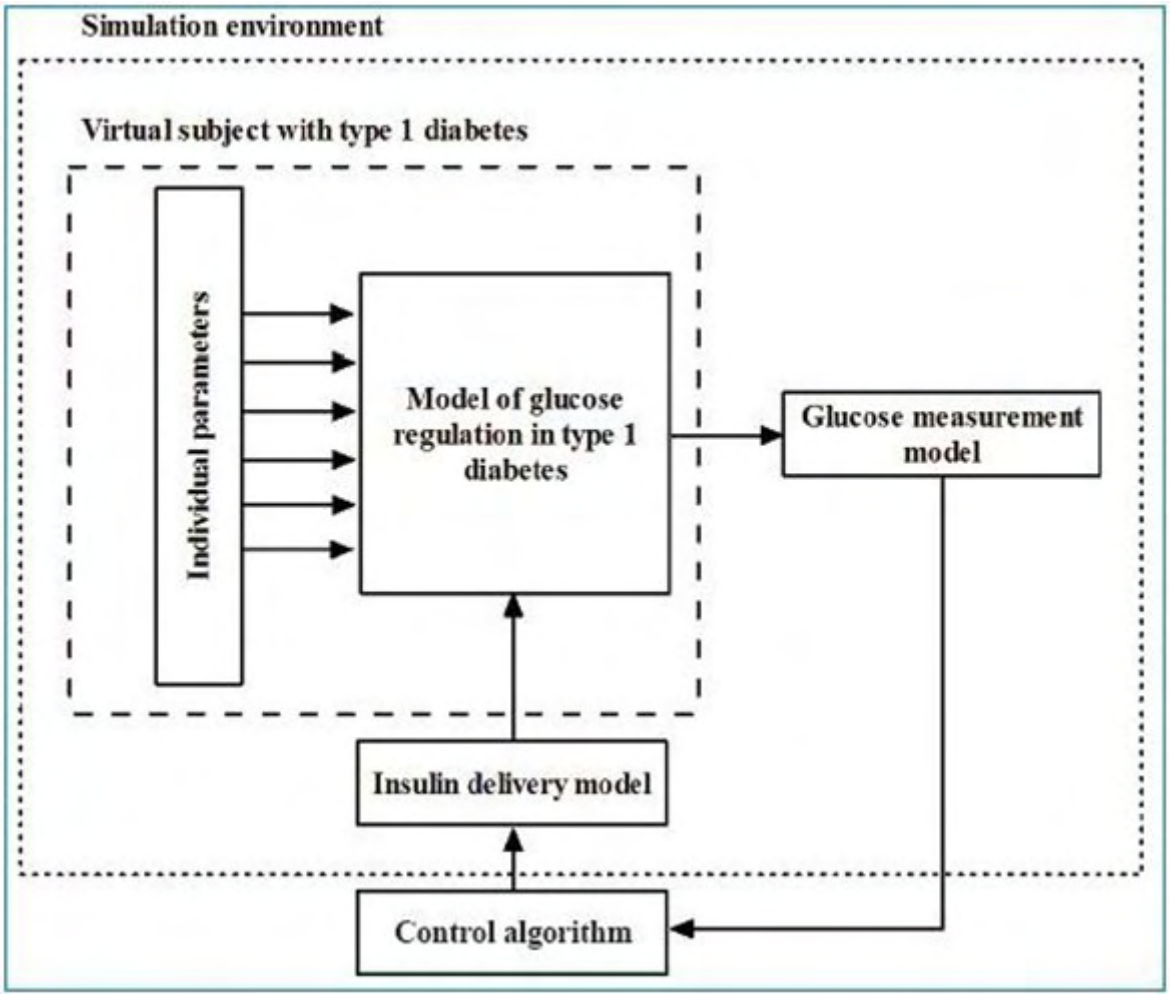


Figure 2.6.1: *Simulation environment of an closed loop system [37].*

3 Approach and Methodology

In this chapter, my approach and methodology will clarified in terms of what is needed and what is used for the implementation and simulation of a virtual type 1 diabetic patient.

3.1 Mathematical Type 1 Models

To elicit a suitable model for implementation and simulation in this thesis, five well-known type 1 diabetes models have been chosen. Below is an overview of each model with a short description.

- **Modified Minimal Model**: The modified minimal model [38] is based on the minimal model (MM) from Richard N. Bergmann [39], [40]. The MM includes three ordinary differential equations (ODE) to describe the plasma glucose, the plasma insulin, and the remote insulin concentration in a healthy subject. Fisher's modifications were made by taking out the pancreatic insulin secretion term and instead adding an exogenous insulin infusion term. The second extension was a exogenous glucose infusion term in the glucose dynamics equation. Both extensions have been made to represent a type 1 diabetic patient.

- **Hovorka Model**: The Hovorka Model as described in [41] consists of three subsystems. The first describes the glucose kinetics, which contains two ODEs (glucose uptake, distribution and disposal). The second one is the insulin subsystem which is used for insulin infusions (insulin uptake, distribution and disposal). The last one describes the insulin actions (insulin action on glucose transport, endogenous production and disposal). In addition to this model there is an associated meal model, which is needed for meal intakes.

- **Parker Model**: The Parker Model [42] is a further development and is more detailed. The glucose sub system includes six differential equations (the original includes eleven) to describe the liver, kidney, heart/lung, periphery and the brain. The insulin system is quite similar. The arterial blood serves as the necessary input for insulin, glucose, and meals servings. The venous blood is the output. This applies for each compartment.

- **Sturis Model**: The Sturis model [43] is comprised of six ODEs and five nonlinear equations. Three of the ODEs describe the plasma glucose, the plasma insulin, and the interstitial insulin concentration. The other three differential equations are used for time delays of plasma insulin to reduce the hepatic glucose production. The five nonlinear equations describe the insulin secretion of the beta cells, the glucose consumption (brain, muscles and fat cells), and the physiologically related delays.

- **Fabietti Model**: The Fabietti model [2] is also based on the MM [39], [40]. The model comprises two main sub systems. One for the glucose kinetics which is split in two compartments for blood glucose and intestinal glucose concentrations, and the second one for the insulin kinetics, which is split in three compartments. The first compartment represents an insulin infusion on a subcutaneous route, the second and the third compartment describe the plasma insulin and the remote insulin concentrations. These are also a related meal model as in the Hovorka model .

3.2 Choice of Mathematical Model

In choosing an appropriate mathematical model various criteria are used in order to ensure the implementation in context of the thesis. The decision is based on the following criteria: "*Complexity of the model*", "*Related meal model*", "*Validated*", "*Modifiability*", "*Topicality*" and "*Accessibility*". In choosing a model a decision matrix was used.

	Complexity of the model	Related meal model	Validated	Modifiability	Topicality	Accessibility
Modified MM	+	−	+	+	+	−
Hovorka Model	+	+	+	−	+	−
Parker Model	−	−	+	−	0	+
Sturis Model	−	−	0	−	0	−
Fabietti Model	+	+	+	+	+	+

Table 3.1: *Decision matrix of mathematical type 1 models.*

Complexity: **(+)** means it is appropriate for the realization in this thesis, **(−)** means it is too complex.

Related Meal Model: **(+)** means there is related meal model, **(−)** means there is no related one, so a implementation of a fitting meal model is needed.

Validated: **(+)** means it is validated by an another study, **(−)** means it is not validated by any study. **(0)** stands for neutral.

Modifiability: **(+)** means the possibility to modifying the model in relation to the workload, **(−)** means that the workload involved is too high.

Topicality: **(+)** means it is an adequate model for R&D in relation to the state of technology (for CSII/artificial pancreas), **(−)** means it is not adequate enough. The remaining models are characterized by neutral **(0)**.

Accessibility: **(+)** means that unrestricted access to the "original" model-datasets is possible by taking into account the procurement costs, **(−)** means there is a limited access.

After extensive evaluation of the decision matrix, the Fabietti model was considered the most appropriate model for implementation and simulation in this thesis. The model is not too complex , there is a related meal model, it is validated, easy to modify in context of the goals of this thesis, provides a good basis for the development and research of new strategies in the diabetes therapy, and the access to the original document is unlimited.

3.3 The used Mathematical Model

The foundation of the Fabietti model is the so-called minimal model (MM), which was developed by Richard N. Bergmann over 25 years ago [39], [40]. The new model used in this thesis is a further development version of the MM, with the feature that this model represents a type 1 diabetic patient in contrast to the MM, which represents a healthy subject [2]. Afterwards the model was validated by another study with data-sets of six (data set 1) and of nine (data set 2) type 1 diabetes subjects with a mean glucose root-mean-square error ($\boldsymbol{G_{rms}}$) of $1.16 \pm 0.43\ mmol\ /l$ (data set 1) and $0.81 \pm 0.20\ mmol/l$ (data set 2) between real blood glucose and simulated profiles [44]. According to this study it is an adequate representation of a type 1 diabetic patient. It allows for the testing of different control strategies for blood glucose regulation systems such as an artificial pancreas, which includes a continuous glucose sensor, an insulin pump, and a corresponding controller, before applying them to people. In addition, a personalized simulation is possible by setting the insulin sensitivity, which is different for each patient.

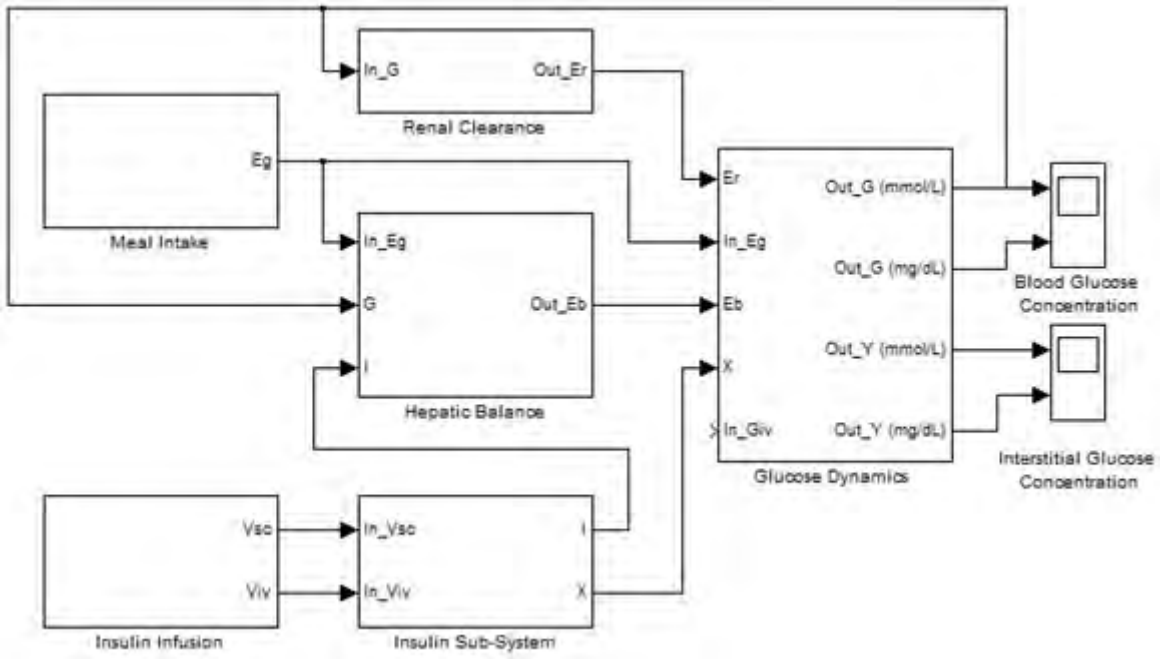


Figure 3.3.1: *Model structure of the used mathematical model.*

The model is split into two main sub-systems. One describes the glucose dynamics, which includes a blood glucose compartment, an intestinal glucose compartment (new) and a renal clearance (new) for hyperglycemic conditions. The other one describes the insulin-kinetics after a subcutaneous or intravenous insulin infusion. In addition to the main sub-systems there is a meal-intake model (new), which describes the glucose-uptake from

different meals into the bloodstream. In addition, a hepatic uptake and release block was inserted (new) to manage the meal intake. A complete model diagram is shown in Figure 3.3.1.

One of the main goals in this thesis is to implement a virtual type 1 diabetic model, whose blood glucose and interstitial *glucose output levels are calculated per second*. This can be e.g. be needed for the development of real-time blood glucose sensors which measure down to the second, or control algorithms which are based on real-time glucose sensor measurements in the range of seconds. A real-time glucose sensor forms the basis of a real-time working closed-loop system. Furthermore, in this thesis an extension is made in the insulin sub system *for concurrent infusion of two different* types of insulin during one simulation. This means that the simulation doesn't need to be interrupted for changing the type of insulin during a simulation. For these goals it was necessary to modify the Fabietti model. The modified mathematical model will be shown in the next sections.

3.3.1 Modifications for a Second Real-Time Based Model and Insulin Infusion

As already mentioned, one of the goals is to modify the existing model so that the output of glucose values in the one second frequency takes place. For this it was necessary to change some dimensions (units) and values of the original *parameters and variables* from existing literature [2], [45], which were based on hours. All variables and parameters of the Fabietti model are listed below (Table 3.2 and 3.3), with the addition that it is specified which data has to be changed (Old vs. New) and what was added.

Symbol	Description	OLD Units	NEW Units	NEW Added
t	time	h	sec	
$V_{sc}(t)$	Rate of insulin subcutaneous infusion, **input**	$\frac{\mu U}{h}$	$\frac{\mu U}{sec}$	○
$V_{iv}(t)$	Rate of insulin intravenous infusion, **input**	$\frac{\mu U}{h}$	$\frac{\mu U}{sec}$	○
$S(t)$	Insulin flow from the subcutaneous to the plasma compartment	$\frac{\mu U}{h}$	$\frac{\mu U}{sec}$	○
$S_1(t)$	Insulin flow from the subcutaneous to the plasma compartment (with regular insulin)	–	$\frac{\mu U}{sec}$	●
$S_2(t)$	Insulin flow from the subcutaneous to the plasma compartment (with Lispro insulin)	–	$\frac{\mu U}{sec}$	●
$I(t)$	Plasma insulin concentration	$\frac{\mu U}{ml}$	–	○
$X(t)$	Insulin concentration in the remote compartment	$\frac{\mu U}{ml}$	–	○
$G(t)$	Blood glucose concentration **output**	$\frac{mmol}{l}$	–	○
$Y(t)$	Glucose concentration in the subcutaneous compartment **output**	$\frac{mmol}{l}$	–	○
$G_{iv}(t)$	Intravenous glucose infusion	$\frac{mmol}{l}$	$\frac{mmol}{l}$	○
$E_g(t)$	Exogenous glucose input in blood	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
E_b	Endogenous glucose input from hepatic balance in blood	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
P_{circ}	Coefficient of the circadian variation of insulin sensitivity	–	–	○
E_r	Renal glucose clearance	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
E_m	Auxiliary variable in the renal clearance description	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
$R_i(t)$	Rate of carbohydrate ingestion during meals **input**	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
A_g	Rate of glucose appearance in blood from sugar	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
A_s	Rate of glucose appearance in blood from fast absorption starch	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
A_m	Rate of glucose appearance in blood from slow absorption starch	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
Q_r	Rate of hepatic glucose release	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
Q_c	Rate of hepatic glucose uptake	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
E_{rel}	Auxiliary variable in the hepatic release description	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○
Q_g	Auxiliary variable in the hepatic uptake description	$\frac{mmol}{h}$	$\frac{mmol}{sec}$	○

Table 3.2: *List of model variables.*

Symbol	Description	OLD Units	NEW Units
K_i	Constant related to the plasma insulin distribution volume	$\frac{\text{ml}}{\text{h}}$	–
T_{xi}	Time constant of insulin infusion in the plasma compartment	h	sec
T_m	Time constant of insulin infusion in the remote compartment	h	sec
T_{i_1}	Time constant of insulin diffusion in the subcutaneous compartment	h	sec
T_{i_2}	Time constant of insulin diffusion in the subcutaneous compartment	h	sec
T_{yg}	Time constant of glucose diffusion from blood to interstitial compartment	h	sec
T_{gy}	Time constant of glucose diffusion from interstitial to blood compartment	h	sec
K_{is}	Sensitivity coefficient in the insulin-dependent glucose metabolism	$\frac{\frac{\text{ml}}{\mu\text{U}}}{\text{min}}$	$\frac{\frac{\text{ml}}{\mu\text{U}}}{\text{sec}}$
V_g	Distribution volume of the blood glucose compartment	l	l
K_{yg}	Rate between the distribution volume of interstitial and blood compartments	–	–
F_s	Starch fraction in the total meal carbohydrate amount	–	–
F_m	Fraction of mixed meal in the starch absorption model	–	–

Table 3.3: *List of model parameters.*

For the purpose of enabling the injection of two different types of insulin (Lispro and regular) during one simulation or to have different types of insulin, which are "fixed" values for a easier handling of the simulator, it was necessary to extended the original input $\boldsymbol{S}$ compartment. This was done by splitting $\boldsymbol{S}$ into $\boldsymbol{S_1}$ and $\boldsymbol{S_2}$ **,** which are then summed up. The first compartment is used for regular and the second one for Lispro insulin injections. This change has no effect on the behavior of the equation $\boldsymbol{S}$, since it is just a sum formulation.

3.3.2 Model Equations

The two main sub-systems - the insulin sub-system and the glucose sub-system - comprise the basis of the entire mathematical model. In addition to these sub-models there is also a related meal model. All equations of each model are shown below.

The Insulin Sub-System

The linear insulin sub-system of our relevant model consist of three compartments, which allows for both a subcutaneous and an intravenous insulin administration. The subcutaneous compartment describes the insulin flow $\boldsymbol{S}$ with a time delay to the plasma compartment after an insulin injection. The time delay depends on the type of insulin. The plasma compartment was modeled to describe the plasma insulin concentration $\boldsymbol{I}$ and the remote compartment shows the insulin concentration in the periphery $\boldsymbol{X}$. If you consider the mathematical system from the insulin flow after a subcutaneous administration up to the plasma insulin compartment as well as the remote insulin compartment, then the insulin sub-system is constructed as follows.

Figure 3.3.2: *Insulin kinetics (sub-system).*

Below you will find the original equation $\boldsymbol{S}$ (equation 1). This equation was split into two equations (equation 2 - 3) - one equation for each type of insulin. In this thesis regular and Lispro insulin are used. Therefore two constants $\boldsymbol{T_{i\_1}}$, $\boldsymbol{T_{i\_2}}$ are needed which describe the time delay of the used insulin and $\boldsymbol{V_{sc\_1}}$, $\boldsymbol{V_{sc\_2}}$ are the rates of administration. Where $-\boldsymbol{S_1}$ and $-\boldsymbol{S_2}$ are the release rates to the plasma compartment.

$$\frac{\boldsymbol{dS}}{\boldsymbol{dt}} = \frac{\mathbf{1}}{\boldsymbol{T_i}} \left(-\boldsymbol{S} + \boldsymbol{V_{sc}}\right) \tag{1}$$

$$\frac{\boldsymbol{dS_1}}{\boldsymbol{dt}} = \frac{\mathbf{1}}{\boldsymbol{T_{i\_1}}} \left(-\boldsymbol{S_1} + \boldsymbol{V_{sc\_1}}\right) \tag{2}$$

$$\frac{dS_2}{dt} = \frac{1}{T_{i\_2}} \left(-S_2 + V_{sc\_2}\right) \quad (3)$$

The plasma compartment represents the plasma insulin concentration I (equation 4), whereby S_1, S_2 and V_{iv} are subcutaneous intravenous insulin inputs and T_{xi} is the time constant of diffusion in the plasma compartment. The parameter K_i is a gain constant, which determines how much insulin in plasma arrives in dependence of the distribution volume.

$$\frac{dI}{dt} = \frac{1}{T_{xi}} \left(-I + K_i(V_{iv} + S_1 + S_2)\right) \quad (4)$$

The third compartment of insulin kinetics describes the insulin concentration X (equation 5) in the remote tissue, and in increasing concentration has a direct influence on the subcutaneous glucose level. The related constant T_m describes the time of diffusion in the remote compartment.

$$\frac{dX}{dt} = \frac{1}{T_m} (-X + I) \quad (5)$$

The Glucose Sub-System

The glucose sub-system is modeled in two non-linear compartments. One compartment represents the blood glucose concentration $\boldsymbol{G}$ (equation 6) and the second one the subcutaneous glucose concentration $\boldsymbol{Y}$ (equation 7).

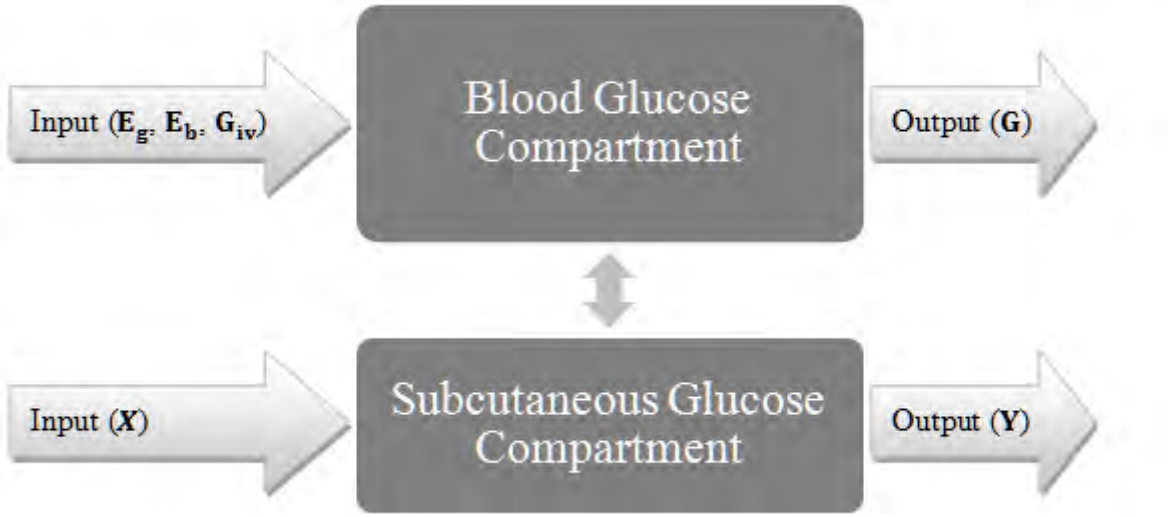


Figure 3.3.3: *Glucose sub systems.*

The blood glucose compartment $\boldsymbol{G}$ involves three inputs. $\boldsymbol{E_g}$ describes the intestinal glucose absorption from meal intakes, $\boldsymbol{E_b}$ the hepatic glucose release rate and $\boldsymbol{G_{iv}}$ can used for an intravenous glucose infusion like the IVGTT (intravenous glucose tolerance test). $\boldsymbol{E_r}$ describes the renal glucose clearance in hyperglycemic conditions (see 8 - 9).

A description of all variables or parameters can be seen in Table 3.2 and 3.3.

$$\frac{dG}{dt} = -\frac{G}{T_{yg}} + \frac{Y}{T_{gy}} + \frac{1}{V_g}\left(-M_i + E_g + E_b + G_{iv}\right) - E_r \qquad (6)$$

$$\frac{dY}{dt} = K_{yg}\left(\frac{G}{T_{yg}} - \frac{Y}{T_{gy}}\right) - K_{is}P_{circ}XY \qquad (7)$$

The subcutaneous glucose concentration is represented by the interstitial compartment $\boldsymbol{Y}$, which includes the insulin sensitivity parameter $\boldsymbol{K_{is}}$. This parameter is needed for a simulation of an individual subject. The insulin sensitivity is different for each subject and

over the course of a day its value will vary considerably. To determine these variations over the course of 24 $hours$ you can use $\boldsymbol{P_{circ}}$. When you simulate with a mean insulin sensitivity value, since the mean value is rich enough for the simulation, you have to set the coefficient of the circadian rhythm to $\boldsymbol{P_{circ}} = 1$. For detailed information the reader is encouraged to see [2], [44].

For hyperglycemic conditions a renal clearance non-linear block (equation 8 - 9) was inserted as a feedback loop (see Chapter 3.3 - Figure 3.3.1).

$$\boldsymbol{E_m = 0.117\left(0.87 + tanh\left(0.0045(G - 175)\right)\right)\frac{1}{3600}} \quad (8)$$

$$\boldsymbol{E_r = \begin{cases} E_m & if\ E_m \geq 0 \\ 0 & else \end{cases}} \quad (9)$$

Hepatic-Balance

To manage the glucose uptake in blood from ingestion of food as well as consumption of glucose by the glucose metabolism a liver was inserted, which is represented as a non-linear block (equation 10 - 14).

$$\boldsymbol{E_b = Q_r - Q_c} \quad (10)$$

$$\boldsymbol{E_{rel} = 0.23 \div I - 0.0027} \quad (11)$$

$$\boldsymbol{Q_r = \begin{cases} 0.0146 & if\ E_{rel} > 0.0146 \\ E_{rel} & if\ E_{rel} \geq E_{rel} \geq 0 \\ 0 & else \end{cases}} \quad (12)$$

$$\boldsymbol{Q_g = \begin{cases} 0.00101G - 0.00417 & if\ 0.00101G - 0.00417 \geq 0.0039 \\ 0.0039 & else \end{cases}} \quad (13)$$

$$\boldsymbol{Q_c = 0.25E_g + Q_g} \quad (14)$$

Meal Model

The meal model describes the gut absorption from ingested meals. Therefore the variable $\boldsymbol{E_g}$ (equation 15) is used to describes the glucose input, and is split into three transfer function's [46], [47] for different gut absorption rates in relation to sugar (equation 16), fast absorption starch (equation 17) and slow absorption starch (equation 18). $\boldsymbol{R_i}$ is the ingestion rate of carbohydrates, $\boldsymbol{F_s}$ is the fraction of starch and $\boldsymbol{F_m}$ is the fraction of mixed meals in the starch.

$$\boldsymbol{E_g = A_g + A_s + A_m} \quad (15)$$

$$\boldsymbol{A_g(s) = (1 - F_s)\frac{16.6}{s^2 + 136.44s + 194.40}R_i(s)} \quad (16)$$

$$\boldsymbol{A_s(s) = F_s(1 - F_m)\frac{467}{s^3 + 15.99s^2 + 74.85s + 83.23}R_i(s)} \quad (17)$$

$$\boldsymbol{A_m(s) = F_sF_m\frac{75.1}{s^4 + 18.30s^3 + s^2114.08 + 258.03s + 97.28}R_i(s)} \quad (18)$$

3.4 Simulation Software

For the analyses of a simulation of dynamic systems like the virtual type 1 diabetic patient an appropriate software is needed. Therefore, a software is required which can simulate the type 1 diabetic model with sufficient accuracy for the target position. Apart from the above application, the available hardware and software is decisive for the choice of the simulator. The appropriate simulation software must be run on a personal computer. Besides numerical computations, the software should also allow the programming of one's own scripts as well a graphical representation.

Therefore MATLAB was chosen in this work because the software package includes everything that is needed to achieve the set objectives. For one, MATLAB offers the possibility to implement the mathematical type 1 diabetic model with one's own script and to solve it with an appropriate ordinary differential equation (ODE) solver in a numerical way. On the other hand, it is possible to create a custom graphical user interface (GUI), which is also a main goal of this thesis. MATLAB is a proprietary high level programming language and is one of the most common programs for scientific, numerical computing. The name MATLAB stands for Matrix and Laboratory. As the name suggests, it is based on interactive systems of matrixes. In the following chapter you can see how the mathematical model was implemented in MATLAB (Version R2012a).

3.5 Blood Glucose Regulation

With this virtual type 1 diabetic model it is possible to simulate the blood glucose regulation with insulin in open loop, semi-closed loop, and closed loop conditions. Open loop conditions mean that you can use the insulin infusion inputs $\boldsymbol{V_{sc}}$,$\boldsymbol{V_{iv}}$ (see Chapter 3.3.2 equation 2-3) at self-defined times for insulin boluses like in the ICT (see Chapter 2.5) to show what the glucose level course of a type 1 diabetic subject can look like over a certain period. Alternately, you can analyze the blood glucose reactions after insulin injections. Semi-closed loops mean that a controller closes the loop only for an automatic basal insulin delivery but that before meal intakes you have to additionally inject insulin boluses by yourself. Closed loop conditions means you add a controller (closing the loop) between glucose sensor and insulin pump, which automatically decides how much insulin needs to be delivered as a basal rate and boluses before meals in dependence on the current blood glucose or subcutaneous glucose value. A fully automatic blood glucose regulation

(closed loop) system consists of three main components - the glucose sensor, an insulin pump and a controller, which determines how much insulin is required by the insulin pump to keep the blood glucose level at a healthy level. In Figure 3.5.1 you can see a principal control schema. For simplification in later simulations with this model one could call the glucose sensor the model output $\boldsymbol{Y}(t)$ respectively $\boldsymbol{G}(t)$ and the controller a insulin pump which is connected with the insulin inputs ($\boldsymbol{V_{sc}}$ or $\boldsymbol{V_{iv}}$).

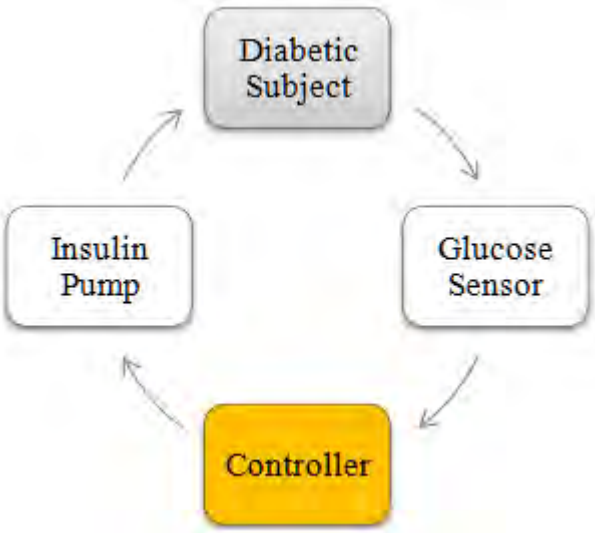


Figure 3.5.1: *Closing the loop with an controller.*

With the virtual type 1 diabetic patient it is possible to test such control strategies. In the next section we will describe a self-made controller to show how you could use the insulin infusion term $\boldsymbol{V_{sc}}$ or $\boldsymbol{V_{iv}}$ or rather connect it. This is not an attempt to design a perfect controller which you can use in real life but is meant to illustrate what it is like to add a controller to the virtual type 1 diabetic model and what a controller does to keep the blood glucose level within a specific range.

3.5.1 Example: Connecting a Self-Made Controller

The control algorithm (controller) used here consists of a nonlinear block (equation 19) working with an *if else* condition. As of a defined threshold value of blood glucose or interstitial glucose the controller triggers the insulin delivery. In order to adjust the insulin the *if else* loops were built staggered. Thus, there are several thresholds for the glucose concentration. This means that the higher the threshold value the more insulin is administered. The decisive factor here is that the controller only administers insulin when the blood sugar rises. Therefore, an additional condition has been incorporated to prevent the administering of insulin when the patient's blood glucose decreases. In this condition,

the difference of two consecutive blood glucose values is formed. Is the result positive, insulin is administered, whereas in the case of a negative result no insulin is delivered. The administrated quantity/sec of insulin must be adapted to each individual patient. For this purpose the inputs $\boldsymbol{V_{iv}}$, $\boldsymbol{V_{sc\_1}}$, $\boldsymbol{V_{sc\_2}}$ can be used.

In this case we use the "measurements" of the interstitial glucose compartment $\boldsymbol{Y}$ $(mmol/l)$ and $\boldsymbol{V_{sc}}$ $(microU/s)$ for the insulin administration:

$$\boldsymbol{Vsc} = \begin{cases} \boldsymbol{1200\ if\ Y \geq 5.0} \\ \boldsymbol{1400\ if\ Y \geq 6.5} \\ \boldsymbol{0} \qquad \boldsymbol{else} \end{cases} \tag{19}$$

4 Design of the Simulator

This chapter will first show the necessary requirements for the software architecture and graphical user interface, thereby highlighting the structure of the software design. Thereafter a short description of the use and functionality of this software is given. Finally the graphical user interface is presented.

4.1 Requirements for the Software Architecture and Graphical User Interface

To ensure an easy, safe, and extended use of the virtual type 1 diabetic patient, the following demands were made to the software and graphical user interface (GUI):

- **Interchangeability of the individual functionalities.** Usage of methods for the possibility for an easy interchangeability of functionalities (components), so that the software can be used flexibly. This allows, for example, to connect an alternative controller (control algorithms) for the insulin delivery only with changing the method **controller()**.

- **Separation between GUI and program code.** Due to the separation between the actual program flow of the mathematical model and the GUI another GUI with low or higher functionality for student or scientist can be adapted to the main function.

- **Usability through self-explanatory software.** The user interface (UI) can be operated without training because important information is mediated by, for example, mouse-over functionalities.

- **Customizability to local units.** It should be an option to adjust the outputted glucose or subcutaneous glucose results because two different units ($mmol/l$ or *mg/dl*) are used among the experts community.

- **Error handling when using the GUI.** With the improper entering of values in the available edit field (for example a character instead of a number), an error message has to be displayed. Moreover, the edit field is highlighted in color and a warning signal is given.

4.2 Software Design

For the purpose of attaining compatible software, the system is divided into different methods. For this purpose, a main function is utilized to which all other programs are linked and in which the actual computing operations of the mathematical model, controller, or other added functions take place. Thus, it is possible to change the values of all variables and parameters of the whole model in the main function. By structuring the software in such a way, a separation between graphical user interface and the actual calculation of the model, as well as the incorporation of other components like a controller or sensor is made possible. In the following Figure 4.2.1 you can see a simplified illustration of the entire software structure.

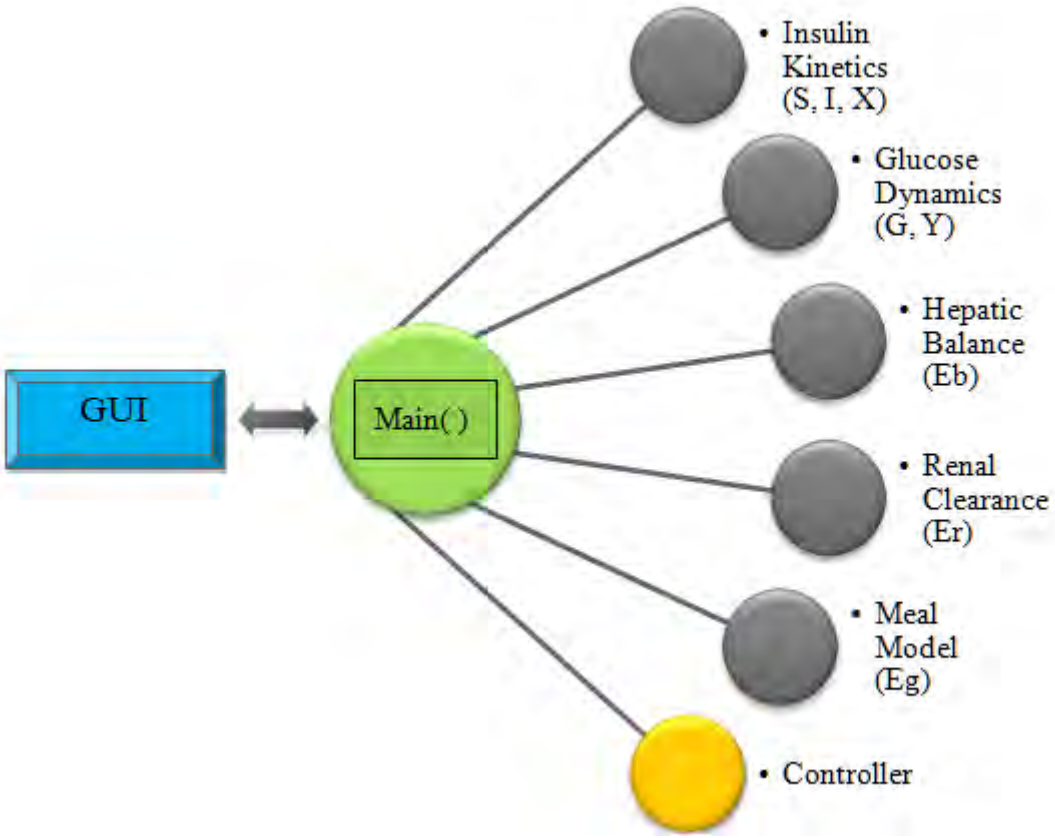


Figure 4.2.1: *Illustration of the software structure.*

The method **main()** which is the main part of the program is marked green. The methods marked gray represent the real mathematical model of the type 1 diabetic subject and the related meal model (see section 3.3.2 equation 1-18). The yellow one describes the controller (see 3.5.1 equation 19). The GUI (blue) sends the input parameters' respective values to the main program and this runs the individual computational operations (gray and

yellow), which then passes back the results of the simulation to the GUI for a graphical representation.

4.2.1 Use of Methods in the Type 1 Diabetic Model

In this section you will find a short description of the main function related to its use, functionality, as well as links to all other methods.

The whole system is based on a network of matrices. Every variable of the mathematical type 1 diabetes model and of the controller-method obtains its own value-matrices. These matrices are filled after every run (loop) with values, which means that in the next line the new value is written. The main method (**main()**) manages these matrices by initializing it, filling it with values, obtaining values from it, and passing them on to the respective method. The actual calculations, that is the solving of the differential equations and state events (*if else*) of the model, can be controlled by the method **main()** and carried out.

```
1   %TIM WASMUTH TYPE 1 DIABETIC MODEL - MAIN FUNCTION - ©2013
2   function [t_matrix,g_matrix,y_matrix,i_matrix,vsc_matrix_reg,vsc_matrix_lispro,eg_matrix]
3
4   %------------------------------------------------------------------------
5   %----------VARIABLES AND PARAMETER(VALUES) OF THE DIABETIC MODEL----------
6   %------------------------------------------------------------------------
7   vsc_matrix = 0 ; %Matrix for subcutaneous insulin injections (default-values '0')
8   viv_matrix = 0; %Matrix for intravenous insulin injections (default-values '0')
9   t_matrix = 0; %Matrix for time
10  s_matrix = 0; %Matrix for s
11  s_matrix_lispro = 0; %Matrix for s_lispro
12  s_matrix_reg = 0; %Matrix for s_reg
13  i_matrix = 0; %Matrix for i
14  x_matrix = 0; %Matrix for x
15  y_matrix = 0; %Matrix for y
16  g_matrix = 0; %Matrix for g
17  giv_matrix = 0 ;%Matrix for giv
18  eg_matrix = 0 ;%Matrix for eg
19  ag_matrix = 0; %Matrix for ag
20  as_matrix = 0;%Matrix for as
21  am_matrix = 0;%Matrix for am
22  eb_matrix = 0; %Matrix for eb
23  ti_lispro = 547.2;
24  ti_reg = 5472;
25  txi = 6516;
26  ki = 0.0202;
27  t_m = 8820;
28  kyg = 0.952;
29  tgy = 698.4;
30  tyg = 698.4;
31  vg = 9.91;
32
33  Fortschritt=0;
```

Figure 4.2.2: *Initialization of matrices and parameters in main().*

Initialization of matrices and parameters. In Figure 4.2.2 a cutout of the main method (**main()**) is shown. First, the variables of the matrices are initialized. These are necessary for the calculations of the respective equations of the mathematical model. Then these are

marked for better orientation with a **_matrix** (underscore). The actual calculations performed are outsourced, i.e. not found in the main function **main()**. Since the system provides the output values of the various equations at one second intervals, the matrices are filled with values in a simulation at one second intervals. The resulting parameters of the mathematical model are initialized and defined in the main function method **main()** as well, so that they can be controlled by **main()** and needn't be changed under each separate method.

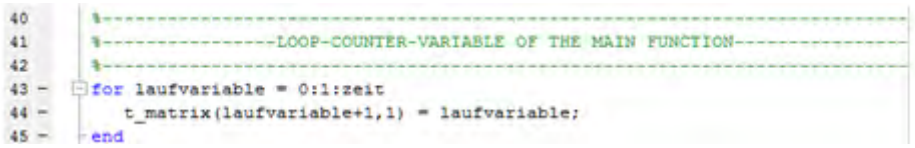


Figure 4.2.3: *Loop counter variable in main().*

Loop counter variable. For the synchronization of different processes during the simulation a matrix is initialized with the aid of the global variable **zeit**. The rows of the matrix (**t_matrix**) contain the values from zero up to the input simulation time (**zeit**). A run (loop) of the whole system equals one second, in other words, the counter-variable (control variable) counts up every second. The number of iterations is determined later through the simulation time.

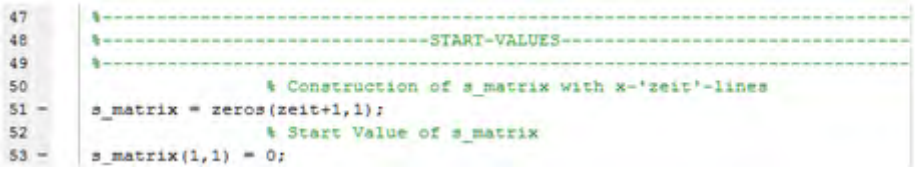


Figure 4.2.4: *Start value for the s_matrix in main().*

Initial conditions. For the execution of the different methods ($\boldsymbol{S}$, $\boldsymbol{X}$, $\boldsymbol{I}$, $\boldsymbol{Y}$, $\boldsymbol{G}$, $\boldsymbol{E_b}$, $\boldsymbol{E_r}$, $\boldsymbol{E_g}$) of the mathematical model and the controller an initial value is set in the associated matrices. The initial value (start value) is the first value that is written into the respective matrix. For this, a matrix with x rows and columns must be created first. In Figure 4.2.4 you can see how for the mathematical function $\boldsymbol{S}$ (see 3.2.2 equation 1-3), which describes the flow of insulin to plasma after a subcutaneous injection, first a matrix (**s_matrix**) with x rows (**zeit+1**) and one column is designed for the value of $\boldsymbol{S}$ and filled with zeros with the aid of the method **zeros()**. In this process the number of rows depends on the simulation time **zeit**. Thereafter, the start value for the **s_matrix** (in this case zero) is set. This ensures that in the actual function $\boldsymbol{S}$ only zeros are passed on when no insulin is administrated.

```
107   %------------------------------vsc_reg-----------------------------------
108                   % Construction of vsc_matrix with x-'zeit'-lines
109 - vsc_matrix_reg = zeros(zeit+1,1);
110             %--DIFFERNT INSULIN INJECTIONS - SUBCUTANEOUS (Regular Insulin)
111   % Dosage of VSC -> Dosage(when,microU/sec,run-time,zeit(Globale
112   % Zeitvariable)
113   %
114 - vsc_matrix_reg = vsc_matrix_reg+dosierung(vsc_reg_t_1,vsc_reg_d_1,vsc_reg_l_1,zeit);
115 - vsc_matrix_reg = vsc_matrix_reg+dosierung(vsc_reg_t_2,vsc_reg_d_2,vsc_reg_l_2,zeit);
116 - vsc_matrix_reg = vsc_matrix_reg+dosierung(vsc_reg_t_3,vsc_reg_d_3,vsc_reg_l_3,zeit);
117   % vsc_matrix_reg = vsc_matrix_reg+dosierung(6200,900,6000,zeit);
```

Figure 4.2.5: *Principle of insulin administration in main().*

Model inputs. For the subcutaneous or intravenous administration of insulin ($\boldsymbol{V_{sc}}$ and $\boldsymbol{V_{iv}}$), as well as for food intake ($\boldsymbol{R_i}$) value-matrices are once again needed. Figure 4.2.5 shows how for the subcutaneous administration of insulin with regular insulin a matrix **vsc_matrix_reg** is first produced. In this connection the row count is once again orientated to the global counter variable **zeit**. With the method **dosierung()** we can define how a dosage takes place by defining start time (**vsc_reg_t**), dose (**vsc_reg_d**), and the duration (**vsc_reg_l**). The method then provides an already filled matrix with the same number of rows as in the **vsc_matrix_reg** back and is then summed up with it. In **main()** up to three dosages of regular insulin (**vsc_reg**) via the GUI can be made (line of 114-116). The dosage can also be alternatively set in **main()** without the GUI (line of 117).

```
267     %Calling the current blood glucose value at the current time
268 -   g = g_matrix(laufvariable,1);
269     %Computation of blood glucose concentration
270 -   result_matrix_bloodglucose = bloodglucose(t0,tf,g,y,tyg,tgy,vg,mi,eg,eb,giv,er);
271 -   result_g_single = result_matrix_bloodglucose(3,2);
272 -   g_matrix(laufvariable+1,1) = result_g_single;
```

Figure 4.2.6: *Calling in main().*

Calling and computing of values from linked methods (model equations). The three Figures 4.2.6, 4.2.7 and 4.2.8 show how with the differential equation for the blood glucose value $\boldsymbol{G}$ a linkage of **main()** to other methods exists by checking the values, and how these can be computed externally as a consequence.

In the method **main()** (Figure 4.2.6), the current value will first be written at the time *laufvariable* from $\boldsymbol{G}$ into the variable *g*. After this the method **bloodglucose()** is retrieved. Time variables (*t0, tf*), constant parameters (*tyg*, *tgy*, *vg*, *mi*) and current values (*g*, *y*, *eg*, *eb*, *giv*, *er*) at time *laufvariable* are delivered. The result of **bloodglucose()** is the matrix *result_matrix_bloodglucose*. The next *g*-value is in the 3rd row in column 2 and is stored in the variable *result_g_single*. This variable is then written into the next row of the matrix *g_matrix* to be able to access it in the next run (loop).

```
1   function result = bloodglucose(t0,tf,g,y,tyg,tgy,vg,mi,eg,eb,giv,er)
2
3   % ----------------- Solving of the differential equation ------------------
4   tm = t0+0.5;
5   % Calling the Differential Equation with the Methode ode45 like Simulink
6   [t,x] = ode15s(@bloodglucose_deqn,[t0 tm tf],g,[],y,tyg,tgy,vg,mi,eg,eb,giv,er);
7   result = [t,x];
```

Figure 4.2.7: *Linked method - bloodglucose().*

In the method **bloodglucose()** (Figure 4.2.7) we begin by building the auxiliary variable *tm*. This auxiliary variable corresponds to a half second and is later required for the method **ode15s()**. The method **ode15s()** is provided by MATLAB, which solves differential equations. All the previously mentioned values are passed on to the **ode15s()**, whereas *bloodglucose_deqn* is the actual ODE [48]. The result is a matrix with three rows and two columns and includes the values at the time points *t0*, *tf* and *tm*. This matrix is then returned to it (return value).

```
1   function result = bloodglucose_deqn(t,g,y,tyg,tgy,vg,mi,eg,eb,giv,er)
2
3   % actual differential equation
4   gdot = -(g/tyg) + (y/tgy) + (1/vg) * (-mi + eg + eb + giv) - er ;
5
6   % Vector as the return value
7   result(1,1) = gdot ;
```

Figure 4.2.8: *Linked method - bloodglucose_deqn().*

The ODE of blood glucose ***G*** is stored in **bloodglucose_deqn()** (see Figure 4.2.8).

```
285 -       vsc_help=controller(y);
286         %Auswählen zwischen regulär und lispro
287 -       vsc_matrix_lispro(laufvariable+1,1)=vsc_matrix_lispro(laufvariable+1,1)+vsc_help;
```

Figure 4.2.9: *Controller interface in main().*

Controller interface. The Controller is selected with the method **controller()**. This method is passed on to the current subcutaneous glucose value ***Y***. The result is a value for subcutaneous insulin injection. This value is then in this case added to the next subcutaneous insulin injection value (with Lispro) in the matrix *vsc_matrix_lispro*.

The advantage of using an interface is that the controller can be used without knowledge of other program operations and program structures, and can be easily replaced by another controller. This allows any MATLAB programmer to write a new controller and integrate it. The programmer only needs to write a new method that is then called **controller()**. This receives the handover value *y* and must deliver *vsc_help* as the output value.

4.3 The Graphical User Interface (GUI)

The graphical user interface allows the application software just described (Virtual Type 1 Diabetic Model), consisting of **main()** and all the associated methods, to be controlled by dialog boxes and edit fields without having to deal with the program code. On the other hand, simulation results are summarized and presented graphically in order to analyze them after a simulation.

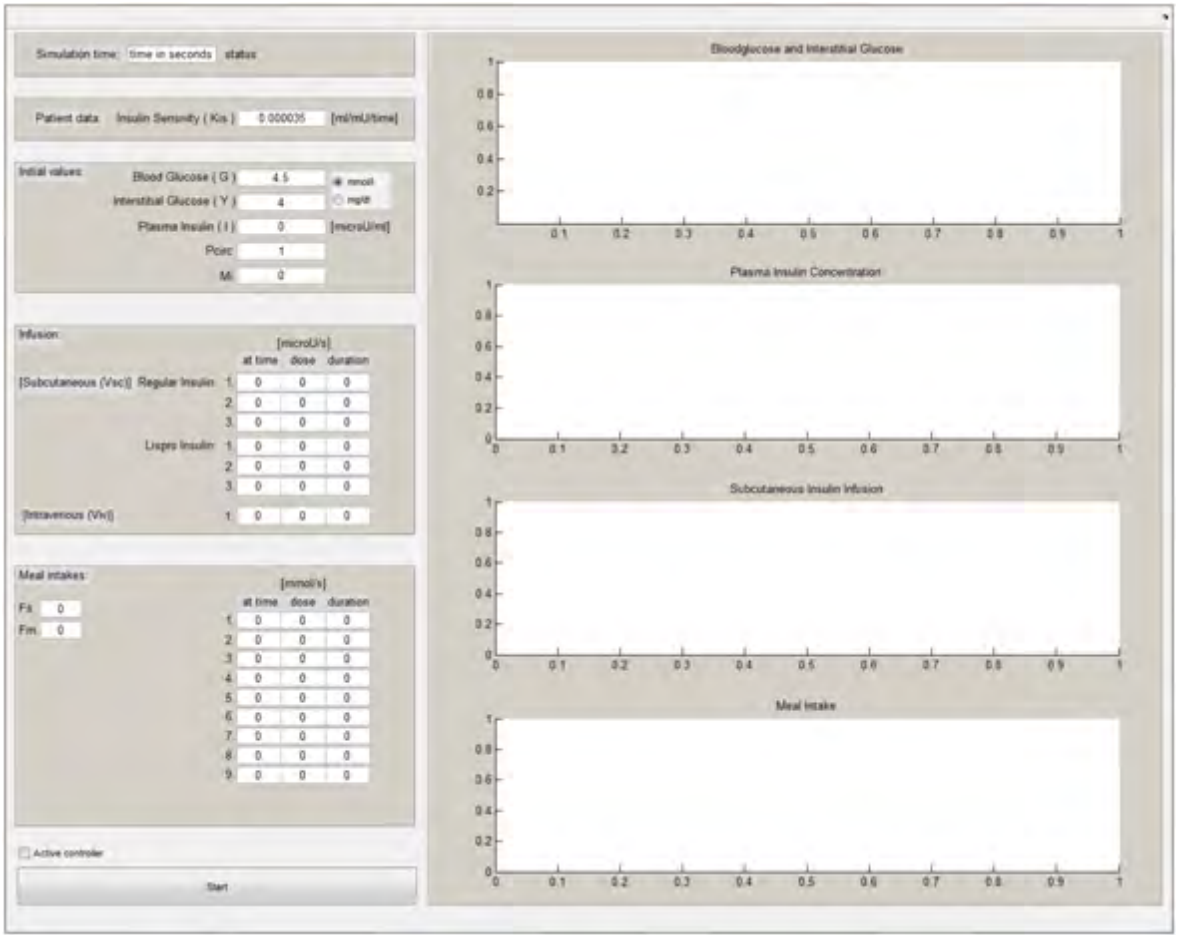


Figure 4.3.1: *The **G**raphical **U**ser **I**nterface.*

In Figure 4.3.1 you can see the entire surface of the GUI. The left side is divided into five sections. In these sections are located the edit fields and dialog boxes that operate the simulator. Below the five sectors is the activation-box for the integration of the controller as well as the start-button for the simulation. For relevant input parameters the following sections have been implemented in the GUI: 1) Simulation time. 2) Insulin sensitivity coefficient ($\boldsymbol{K_{is}}$) for the individual patient. 3) Initialization values for ($\boldsymbol{G}$, $\boldsymbol{Y}$, $\boldsymbol{I}$, $\boldsymbol{P_{circ}}$, $\boldsymbol{M_i}$). 4) Subcutaneous insulin injections with Lispro or regular insulin and intravenous. 5) Food intake for several meals during a simulation.

On the right, the simulation results of the blood glucose level $\boldsymbol{G}$ and subcutaneous glucose concentration $\boldsymbol{Y}$ ($mmol/l$ or mg/dl), the plasma insulin concentration $\boldsymbol{I}$ ($microU/ml$), the subcutaneous administration $V_{sc}(microU/s)$ with Lispro or regular insulin and the food supply $E_g(mmol/s)$ are displayed graphically among themselves. An accurate evaluation of the graphical simulation results can be obtained with the help of a cursor, including its respective function value at time *t*. The function graphs are color-separated if multiple graphs are in one plot.

4.3.1 Usability and Self-Explanatory Software

To ensure the usage of the simulator without requiring the user to be incorporated into the software, mouse-over functionalities in addition to the labeling of each edit field in the GUI were also implemented [49]. The functionality is simple. If you move the mouse cursor over an edit field a text box appears with instructions regarding what to enter in the appropriate field. Thus, a simple application of the simulator is guaranteed. In Figure 4.3.2 the mouse-over functionality for the input field "simulation time" is shown by the mouse and was performed using the input field.

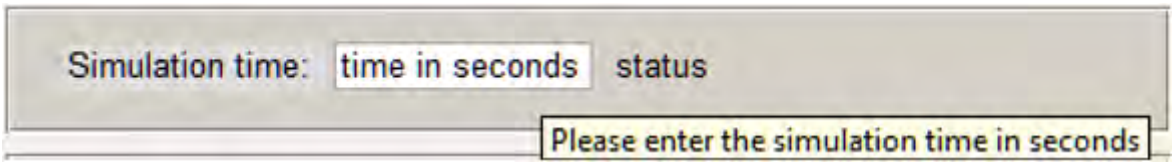


Figure 4.3.2: *Mouse-over functionality.*

Usability describes the quality of operationality. The usability of devices and software in the field of biomedical engineering is an important point. The user of the equipment and software is the focal point. The goal is the simple and straightforward usability of each product, as well as ensuring adequate functionality. Thus, the usability is determined by the factors influencing usability and functionality [50].

To make the use of the GUI as clearly as possible, edit fields and selection windows for the operation of the simulator have been implemented on one side (left). The graphic simulation results were placed on the other side (right). Thus, there is a clear (visual) separation between the user interface and the simulation results.

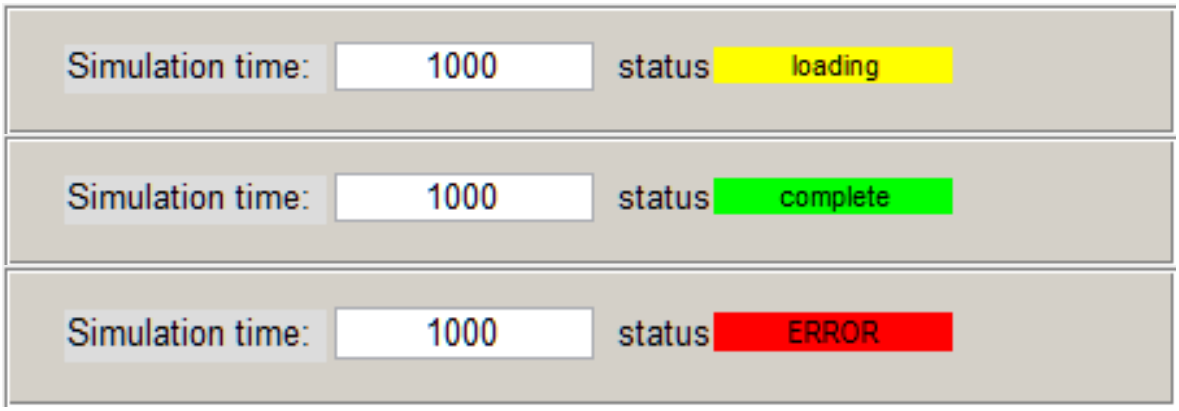


Figure 4.3.3: *Different status messages.*

In addition, the GUI has been provided with a progress bar so that the user detects whether the simulation has been completed or is still in progress and/or whether there is an error (see Figure 4.3.3).

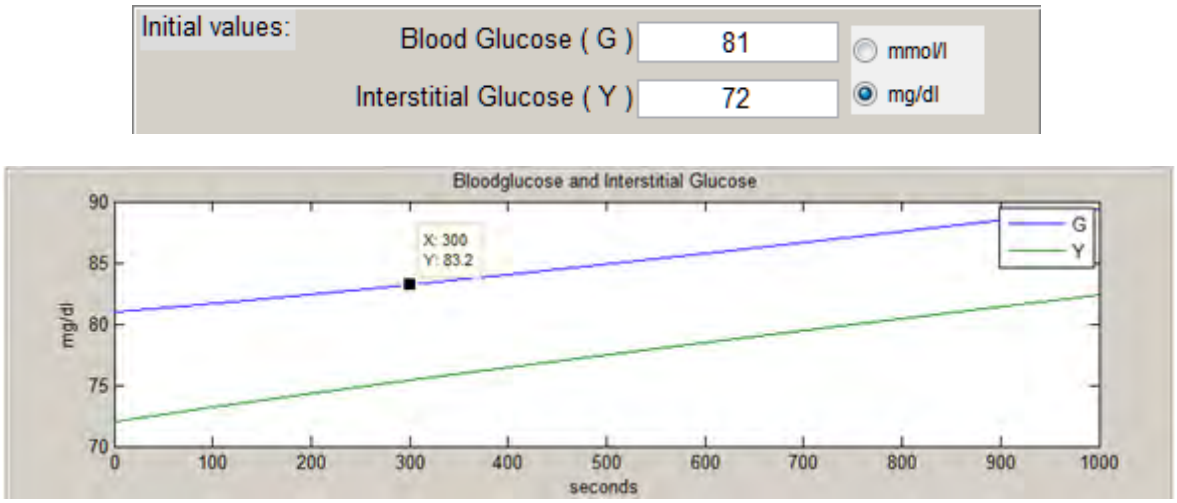


Figure 4.3.4: *Choice of the unit mg/dl.*

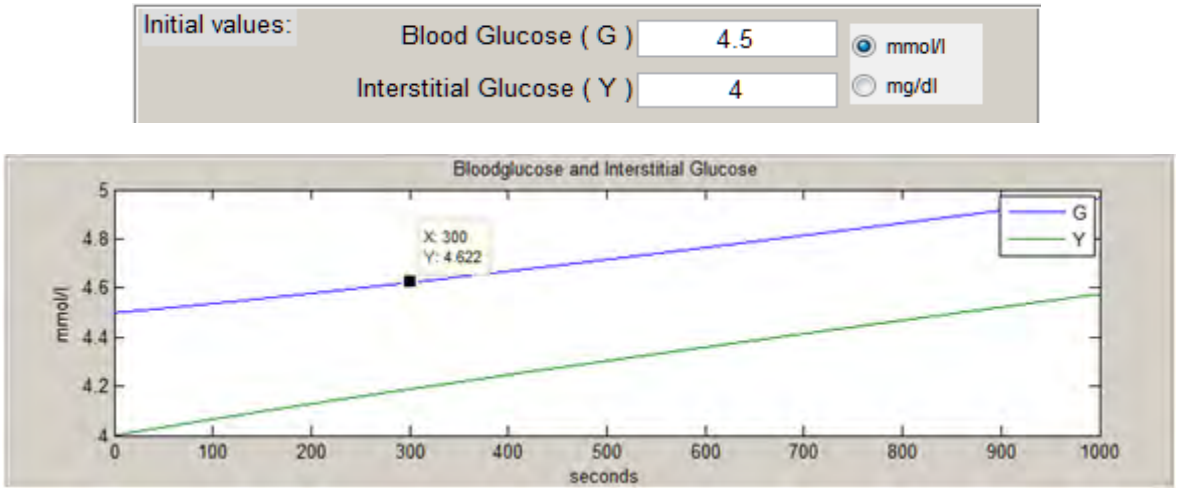


Figure 4.3.5: *Choice of the unit mmol/l.*

Another feature is the selection of the units $mmol/l$ or mg/dl for the blood glucose $\boldsymbol{G}$ and in the interstitial glucose $\boldsymbol{Y}$ level. The selection refers to the initial values to be entered, as well as the graphical simulation results of $\boldsymbol{G}$ and $\boldsymbol{Y}$. This is necessary since these units are used internationally and therefore a conversion no longer necessary for the users themselves. It is also possible to let the mouse cursor display the values of the simulation results by clicking them. In Figure 4.3.4 the glucose units were simulated in mg/dl and in Figure 4.3.5 in $mmol/l$ for purposes of illustration. As can be clearly seen in this Figures, the blood sugar curve $\boldsymbol{G}$ is selected by the cursor and the corresponding x and y coordinates (blood glucose level at time t) were issued.

4.3.2 Error Handling

In addition to general usability in the operation of the simulator, error handling has an important role. This involves the avoidance of errors or detecting the cause of the error. Of course you can use the simulator without error handling. Yet in this it is difficult to determine whether a fault has arisen in the entering process, where the error occurred, and what the cause of the error might be. In the following Figure 4.3.6 a part of the error handling of the GUI is illustrated.

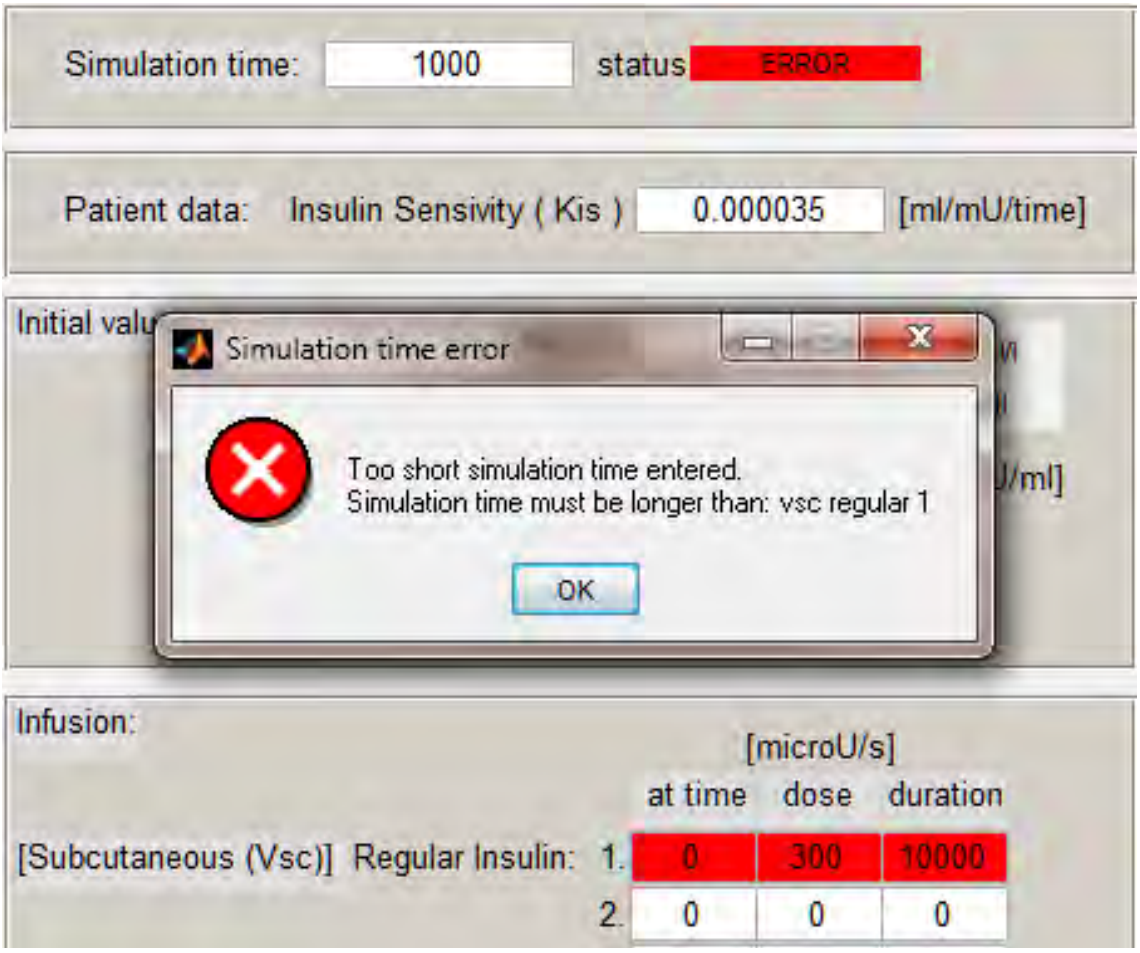


Figure 4.3.6: *GUI error handling.*

It can be seen that in the edit field (simulation time) a simulation time of 1000 $seconds$ was entered. In addition, a duration of 10,000 $seconds$ was selected for subcutaneous insulin administration. Since the simulation time is shorter than the duration of the insulin, an error message is generated. In addition, if an error occurs the status message "ERROR" is displayed and the corresponding fields are highlighted in red.

5 Using the Simulator

The following sections are only meant to demonstrate how the simulator with the help of the GUI can be operated and how the results of simulation are presented graphically in seconds.

First, it is shown how the system responds when no insulin is administered to a type 1 diabetes patient and no additional food is supplied. After that it will be illustrated how different doses of insulin (subcutaneous and intravenous) can be administered manually and how it is possible to have two different types of insulin such as Regular insulin (short acting) and Lispro (rapid acting) injected subcutaneously. Thereafter it is shown how in addition to the administered insulin, food can be supplied in the form of carbohydrates. Finally, it is demonstrated how a closed loop system is simulated, by activating the self-made Controller in the GUI.

To obtain the most realistic simulation results possible with respect to the insulin doses, the following patient's data was entered from the literature in the **main()** (see Chapter 4.2.1 Figure 4.2.2) and insulin sensitivity coefficient ($\boldsymbol{K_{is}}$) in the GUI. All used parameter values for the simulations you can see in table 5.1.

Symbol	Description	Units	Values
K_i	Constant related to the plasma insulin distribution volume	$\frac{ml}{sec}$	0.0202
T_{xi}	Time constant of insulin infusion in the plasma compartment	sec	6516
T_m	Time constant of insulin infusion in the remote compartment	sec	8820
T_{i_1}	Time constant of insulin diffusion in the subcutaneous compartment (with regular insulin)	sec	5472
T_{i_2}	Time constant of insulin diffusion in the subcutaneous compartment (with Lispro insulin)	sec	547.20
T_{yg}	Time constant of glucose diffusion from blood to interstitial compartment	sec	698.40
T_{gy}	Time constant of glucose diffusion from interstitial to blood compartment	sec	698.40
K_{is}	Sensitivity coefficient in the insulin-dependent glucose metabolism	$\frac{\frac{ml}{\mu U}}{sec}$	0.000035
V_g	Distribution volume of the blood glucose compartment	l	9.91
K_{yg}	Rate between the distribution volume of interstitial and blood compartments	–	0.95
F_s	Starch fraction in the total meal carbohydrate amount	–	0.00
F_m	Fraction of mixed meal in the starch absorption model	–	0.00

Table 5.1: *Parameter values for simulation.*

5.1 Simulation without External Inputs

The following example is intended to show how the virtual type 1 diabetes patient behaves without externally supplied insulin doses and food intake. In principle, the glucose metabolism is hereby simulated without insulin kinetics and meal intakes.

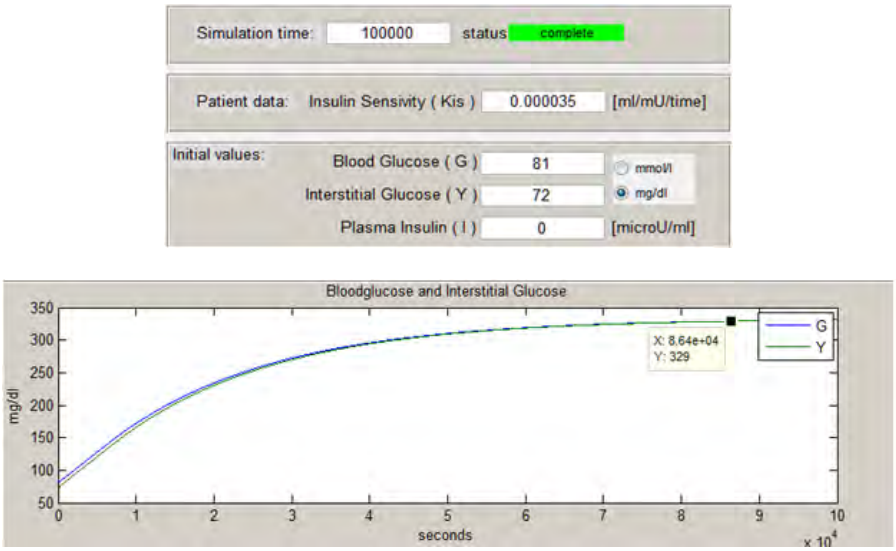


Figure 5.1.1: *Rising blood and subcutaneous glucose levels over 24 hours.*

In the GUI, a simulation time of 100,000 $seconds$ ($>$ 27 $hours$) was entered and the initial values for the subcutaneous glucose level $\boldsymbol{Y} = 72\ mg/dl$ and for the blood glucose level $\boldsymbol{G} = 81\ mg/dl$ (see Figure 5.1.1) were selected. The insulin sensitivity coefficient ($\boldsymbol{K_{is}}$) has no influence on the simulation result, since no insulin is administered. The graphical simulation results of blood glucose are located after 86,400 $seconds$ (24 $hours$) at 329 mg/dl and would come closer to the limit of 330 mg/dl in the course. Thus it is shown that the simulator simulates a typical hyperglycemia of a type 1 diabetic in the case of absolute insulin deficiency [51]. The renal clearance is responsible for the associated hyperglycemia (see Chapter 3.3.2 equation 8-9).

5.2 Simulation with Basal Insulin Injections

The following examples show how a constant intravenous insulin dose or multiple subcutaneous injections can be administered (basal rates), to keep the blood glucose $\boldsymbol{G}$ at a certain level ($90 - 110\ mg/dl$) without food intakes. The basal insulin rate is the basic need of insulin and covers about 50% of the whole daily insulin requirement. For the used patient data a basal rate of about $26\ U/day$ is necessary. Basal rates can vary greatly depending on the patient. The simulations are only for illustrative purposes to demonstrate how the simulator can be operated.

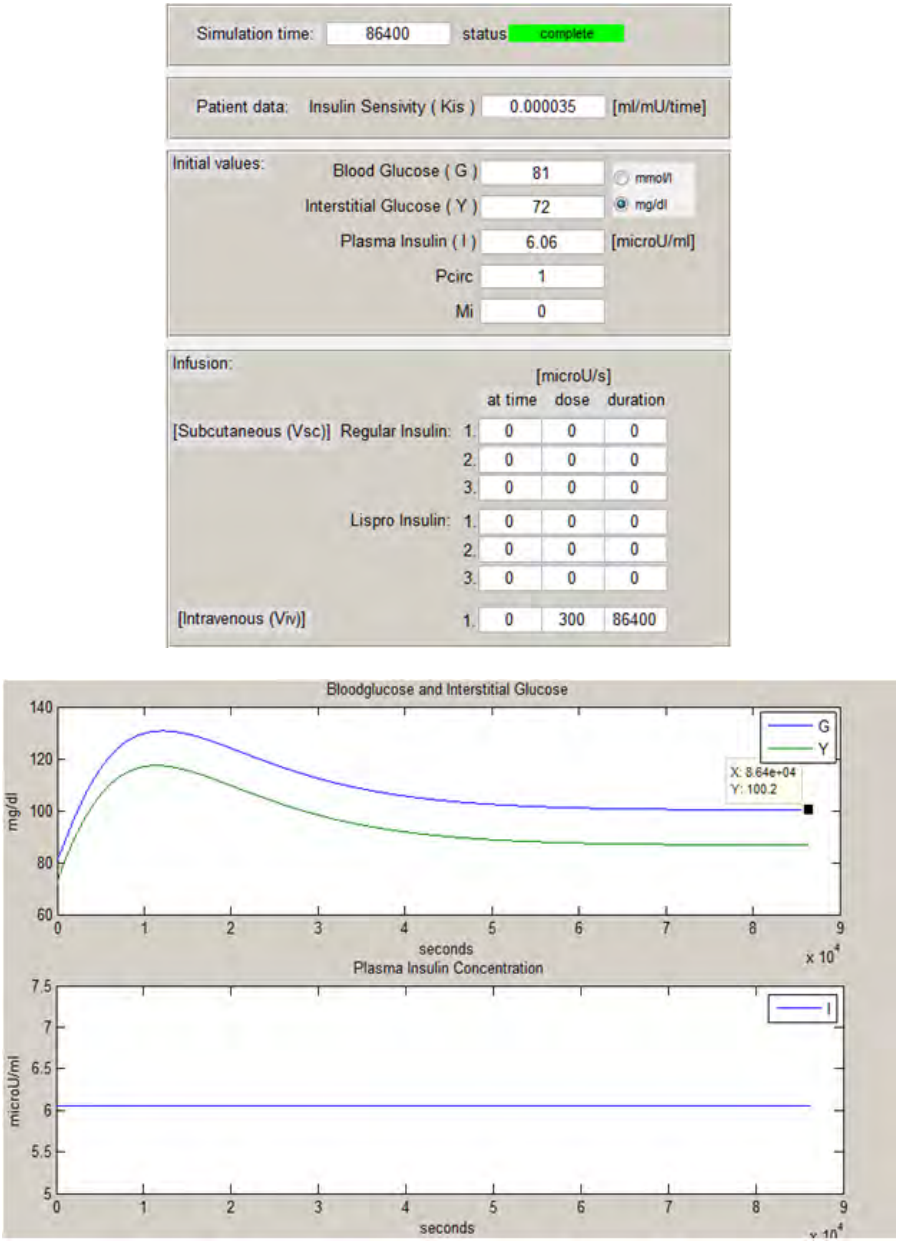
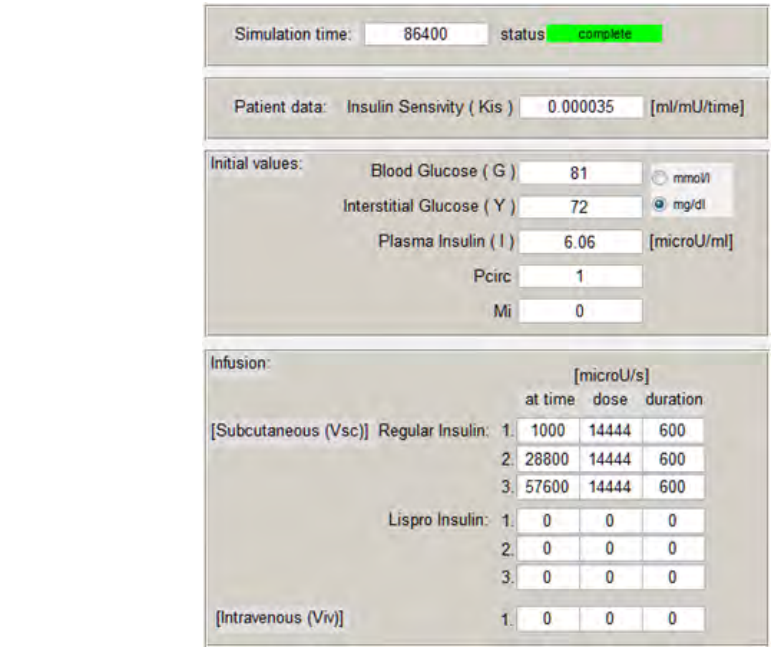


Figure 5.2.1: *Constant intravenous basal infusion.*

In Figure 5.2.1 a constant dose of insulin was administered intravenously ($\boldsymbol{V_{iv}}$). The administered basal rate of 300 $microU/sec$ corresponds to 26 U/day. It can be seen how over the course of the day the blood glucose $\boldsymbol{G}$ reaches a constant value (steady state) of 100 mg/dl.



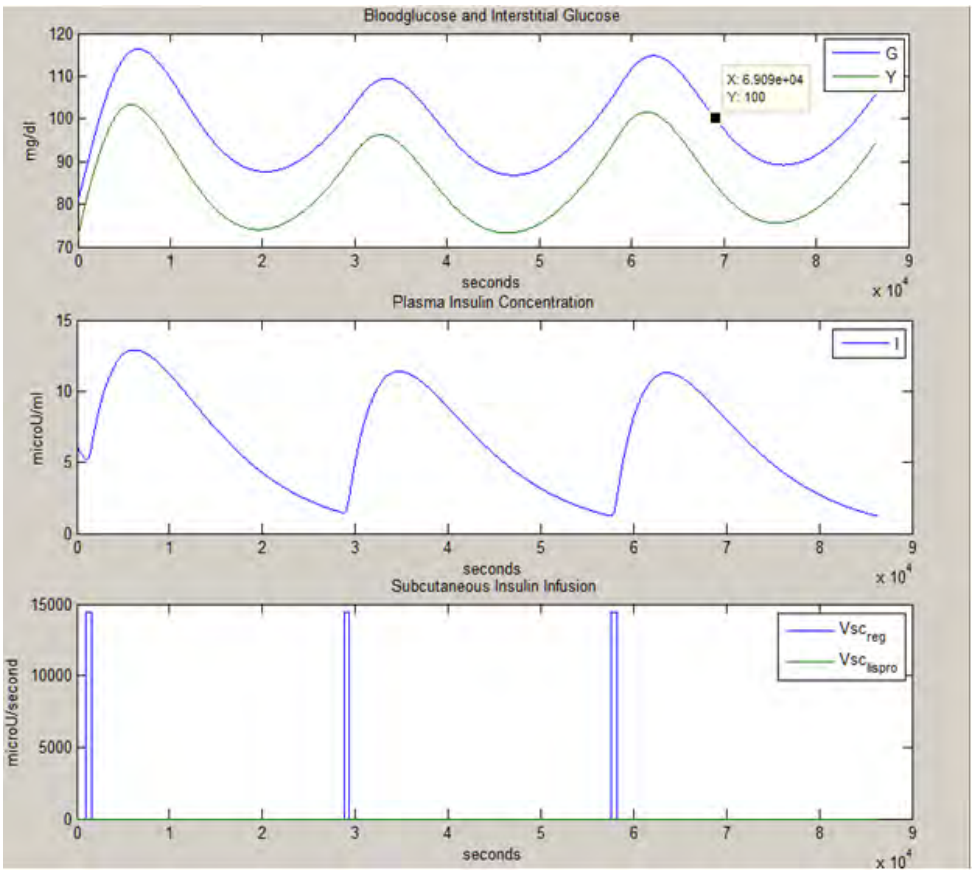


Figure 5.2.2: *Three subcutaneous injections with regular insulin.*

In Figure 5.2.2, the basal rate of $26\ U/day$ was divided in three subcutaneous injections ($\sim 3 \times 8.7\ U$) with regular insulin (short acting). The injections were each administered over $600\ seconds$ ($\sim 14{,}444\ microU/sec$). It is particularly obvious how after a subcutaneous injection with regular insulin the plasma insulin concentration increases sharply, and how after reaching the maximum value slowly decreases. The effect of one injection corresponds to about 8 hours. This results in blood glucose levels $\boldsymbol{G}$ between $90 - 115\ mg/dl$.

5.3 Simulation with Meal Intakes

The following section will show how in addition to injecting insulin the necessary nutrition can also be supplied in the form of carbohydrates. With the GUI it is possible to be administered up to nine different meals during a simulation. For illustrative purposes, only one food intake of $50\ g$ Carbohydrates (CHO) as pure sugar ($\boldsymbol{F_s} = 0$) is simulated, to show how as a result the blood glucose level increases. The factor $\boldsymbol{F_s}$ describes the proportion of the administered CHO's starch and the factor $\boldsymbol{F_m}$ the proportion of mixed meal in the starch absorption.

There were problems with the meal model simulation (Figure 5.3.1). The food was administered at $t = 50{,}000$ seconds over $180\ seconds$ since in this region of the blood glucose level by intravenous insulin administration (basal insulin) it almost reaches its steady state of $100\ mg/dl$ and thus the blood sugar increase is hardly falsified by the ingested food. The rise of blood glucose level of about $40\ mg/dl$ is not realistic. Normally, the blood glucose level in the case of an intake of $50\ g$ ($\sim 416\ mmol$) of pure sugar would rise stronger. In addition, the blood glucose level increases abruptly, rather than delaying the increase. The error probably lies in the transfer functions (see Chapter 3.3.2 equation 16-18) of the meal model.

A clarification of the error would exceed the scope of this thesis. The mathematical model was modified so that the simulator produces the blood glucose values in seconds, in contrast to the original model [2], where this happens in hourly intervals. The transfer functions of the meal model could therefore not be suitable for the seconds-based model and would have to be adapted in order to realistically simulate a food supply of CHO's.

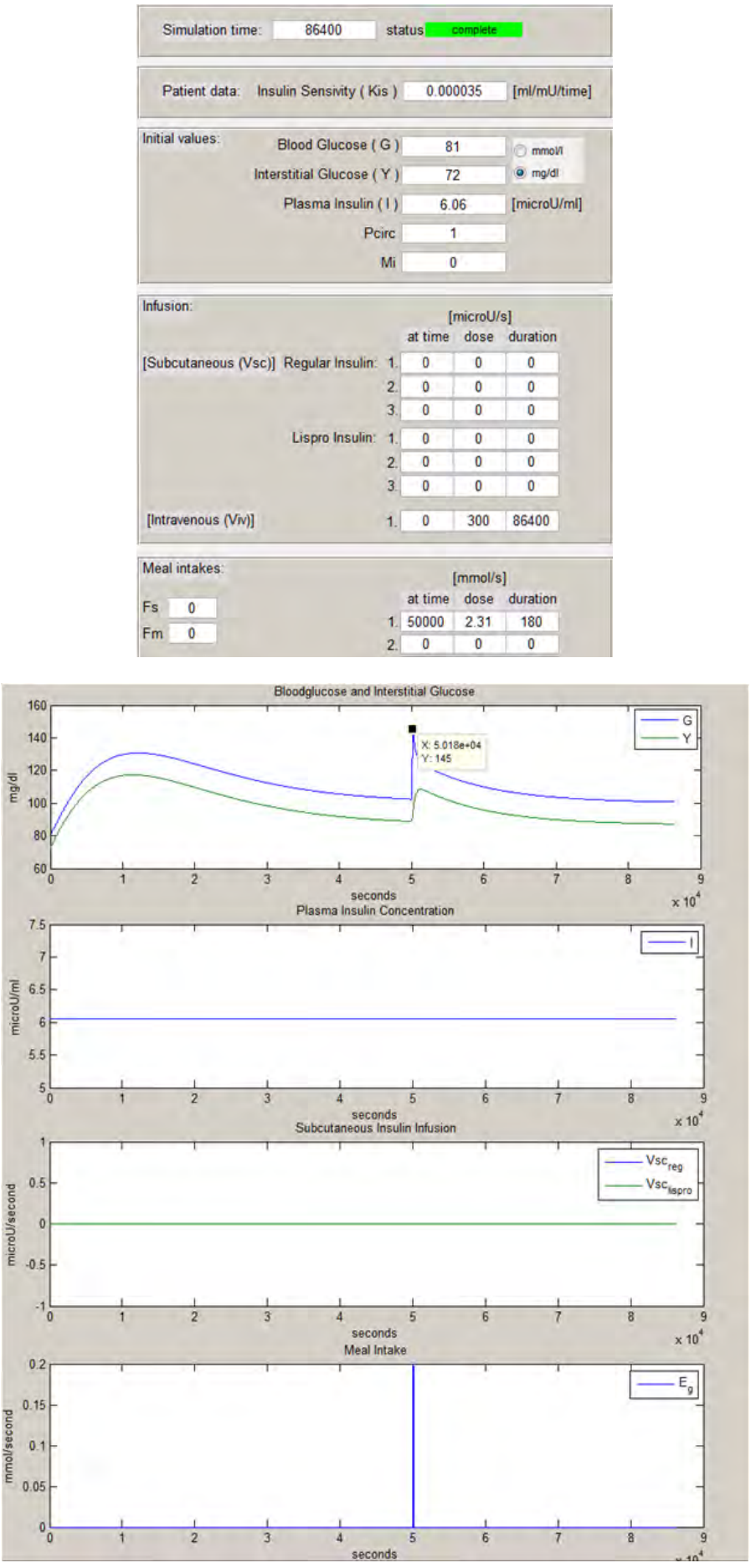


Figure 5.3.1: *Meal intake (50 g CHO's) and intravenous basal infusion.*

5.4 Simulation with the Controller

Finally, it is demonstrated how a closed loop system operates under the integrated controller (see Chapter 3.5.1). The controller automatically decides when and how long a certain amount of insulin has to be administered in order to keep the blood glucose values within narrow limits ($90 - 110\ mg/dl$). In this simulation, Lispro insulin (rapid acting) was used and the controller is based on the subcutaneous glucose value $\boldsymbol{Y}$, as is common in an artificial pancreas (closed loop system). This is approximately the same rate as in the previous simulations.

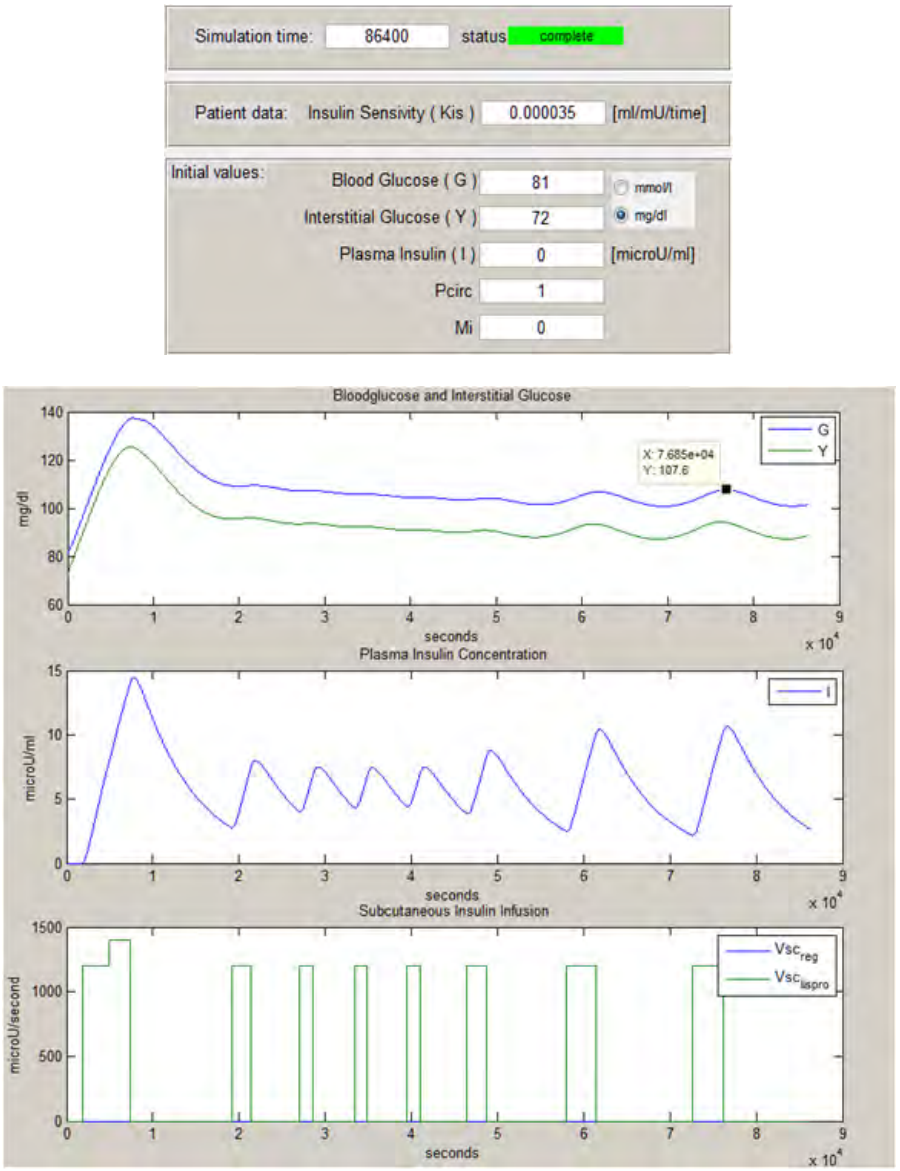


Figure 5.4.1: *Closed loop simulation with the controller.*

In Figure 5.4.1 it is clearly visible that the controller is triggered when the interstitial glucose value $\boldsymbol{Y}$ rises and is greater than or equal to 90 mg/dl. As a result, 1200 $microU/$

sec of Lispro insulin are administered until the next trigger threshold of $117\ mg/dl$ is reached and then administered at a higher dose of $1400\ microU/sec$. Overall, the controller has given $26.5\ U/day$ of basal insulin. This is approximately the same rate of insulin as in the previous simulations. In addition, the controller administers different doses at irregular intervals until the target blood glucose value (steady state) of $90 - 110\ mg/dl$ at $t\ = 55{,}000\ seconds$ ($\sim 15 - 16\ hours$) is achieved. As a result, the controller delivers an even dosage of insulin in regular intervals after reaching the target blood glucose value in order to maintain the blood glucose value (steady state) between $90 - 110\ mg/dl$.

6 Conclusion

6.1 Achieved Status

The necessary modifications for a seconds-based virtual type 1 diabetic patient (simulator) have been successfully carried out on the mathematical model, with the exception of one point. There are still problems associated with the meal model. The food supplied to the virtual patient through the meal model does not correspond to reality. I expect that the error is located in the associated transfer functions.

The written software and associated implementations of components of the mathematical model, as well as the controller, were also successfully carried out by using MATLAB. The simulator is therefore operable. Furthermore, the integration and interchangeability of methods are ensured through the software design.

Finally, the developed graphical user interface (GUI) was completed for the operation of the simulator and is fully functional. A user-friendly and correct application of the simulator is therefore secured.

6.2 Future

The present simulator is a prototype. An evaluation and validation of the simulator is not part of this thesis and should be performed as a next step towards utilization of this simulator in future research. This should include a comparison between the measured data and the simulated patient data. In addition, the related meal-model needs general revision.

7 List of Figures

8 List of Tables

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A Appendix

Used Software:

- Microsoft Word Professional 2007
- Microsoft Visio Professional 2013
- MATLAB R2012a

Contents of the CD:

- Bachelor Thesis (PDF)
- Simulation Software (MATLAB File's)
- Internet Sources (PDF)