Tallinn University of Technology
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Predicting hypo- and hyperglycemia

MSc thesis

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Author declaration

I hereby declare that this thesis is the result of my work, and it is not by someone else previously submitted for defense.

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Abstract

Diabetes is a chronic disease that can be characterized by an elevated blood glucose level. A blood glucose level that is elevated for a long period of time can lead to serious complications. To prevent or postpone such complications, a strict control for blood glucose level is needed. In these theses glucose-insulin system model was implemented and tested if it could be used for predicting hypo- and hyperglycemia events. Two approaches were considered. First approach was to use pure glucose-insulin model output to predict hypo- and hyperglycemia events. For this purpose the model performed reasonably well. However it did not detect all the hypoglycemia and hyperglycemia events and it generated a lot of false alarms. Second approach was to use classification to predict hypo- and hyperglycemia events and include glucose-insulin model output into learning data. The classification approach did not generate as many false alarms like predicting from glucose-insulin model and detection accuracy was higher.

Diabeet on krooniline haigus, mida iseloomustab kõrge veresuhkru tase. Veresuhkru taset, mis on kõrge pikka aega võib põhjustada tõsiseid komplikatsioone. Selleks, et vältida või edasi lükata sellise komplikatsioone pidev kontrolli veresuhkru taseme üle on vajalik. Selles töös püütakse glükoosi-insuliini süsteemi mudelit rakendada hüpo- ja hüperglükeemia sündmuste ennustamiseks. Uuritakse kahete lähenemist. Esimene lähenemisviis, mida uuritakse, kasutab puhast glükoosi-insuliini mudeli väljundit selleks, et ennustada hüpo- ja hüperglükeemia sündmusi. Selleks töötas mudel suhteliselt hästi. Samas see ei tuvastatud kõiki hüpoglükeemia ja hüperglükeemia sündmusi ning mudel andis palju valehäireid. Teine lähenemisviis, mida uuriti, oli kasutades klassifitseerimist selleks, et ennustada hüpo- ja hüperglükeemia sündmusi. Selleks, et parandada klassifikaatori õppimise andmeid lisati sinna ka glükoosi-insulini mudeli väljund. Klassifitseerimise lähenemisviis ei tekita nii palju valehäireid nagu ennustamine puhtalt glükoosis-insuliinist mudeli väljundilt ning hüpo- ja hüperglükeemia sündmuste avastamise täpsus oli suurem.

Introduction

Diabetes is a chronic disease that can be characterized by an elevated blood glucose level which can be caused by a lack of insulin production by the pancreas (type I diabetes) or by the body's ineffective use of insulin (type II diabetes). A blood glucose level that is elevated for a long period of time can lead to vascular, neurological or metabolic complications, such as kidney failure, blindness and an increased chance of heart attacks. To prevent or postpone such complications, a strict control for blood glucose level is needed.

There are several factors that affect the blood glucose level, such as carbohydrates intake, insulin injections, exercise and the level of stress. Also there are a number of internal processes, such as absorption and production of glucose by the liver and renal excretion through urine. The large number of factors makes it difficult to predict how the glucose level will behave.

There have been several studies about the prediction of glucose concentration in blood for diabetic patients. There are two main approaches to this problem. First approach is to use complex mathematical models that simulate glucose-insulin system. [3, 14, 9, 15, 4] Second approach is to use existing data and build model from it. [11, 2]

The approach taken in this theses is to implement a mathematical glucose-insulin system model and validate if it could be used for predicting hypo- and hyperglycemia events. AIDA [8] glucose-insulin model was chosen as model to be implementation because it is minimal and has few patient specific parameters and those parameters can be estimated from available data. We investigate, how well the dynamics model of the glycose-insulin system can directly be used to predict hypo and hyperclycemia. In addition we investigate whether the modeled dynamics can be used to improve the outcome of a learning the events from patient specific data.

1 Diabetes

Diabetes mellitus is, according to [20], a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the body, or by the resistance to the insulin produced.

There are two principle forms of diabetes:

- Type 1 diabetes (previously known as insulin-dependent or childhood-onset diabetes) is characterized by a lack of insulin production. According to [13], it results from the autoimmune destruction of the insulin-producing beta cells in the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose.
- Type 2 diabetes (formerly called non-insulin-dependent or adult-onset diabetes) is caused by the body's ineffective use of insulin. It often results from excess body weight and physical inactivity.

Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG), according to [19], are intermediate conditions in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to type 2 diabetes, although this is not inevitable.

Hypoglycemia is a medical emergency that involves an abnormally diminished content of glucose in the blood. Hypoglycemia occurs when blood glucose levels fall below 4 mmol/L [7].

Hyperglycemia is a condition when blood glucose concentration is high. Hyperglycemia occurs when blood glucose level is greater than 7.0 $mmol/l$ when fasting or 11.0 $mmol/l$ 2 hours after meals [6].

Over time, diabetes leads to complications, in particular: diabetic retinopathy, which leads to blindness; diabetic neuropathy, which increases of the risk of foot ulceration and limb loss; and diabetic nephropathy leading to kidney failure. In addition, there is an increased risk of heart disease and stroke with 50% of people with diabetes dying of cardiovascular disease and stroke. [4]

According to [12], globally, as of 2013, an estimated 382 million people have diabetes worldwide. The number of people with type 2 diabetes is increasing in every country. 80% of people with diabetes live in low- and middle-income countries. The greatest number of people with diabetes are between 40 and 59 years of age. 175 million people with diabetes are undiagnosed. Diabetes caused 5.1 million deaths in 2013; every six seconds a person dies from diabetes.

2 Glucose-insulin system

Glucose concentration in body is tightly regulated by a complex neuro-hormonal control system. The main purpose of it is to maintain glucose homeostasis.

Insulin is the primary regulator of glucose concentration in body. It promotes glucose utilization and inhibits glucose production. There are also many counterregulatory hormones at work (i.e., glucagon, epinephrine, cortisol, and growth hormone). Insulin is produced by beta cells in the pancreas and it causes cells to absorb glucose from the blood.

According to [4], the glucose and insulin systems interact by feedback control signals. It means that if a glucose concentration rises (after a meal), beta-cells secrete more insulin in response to increased plasma glucose concentration. Insulin in turn promotes glucose utilization and inhibits glucose production so as to bring plasma glucose concentration back to normal.

Glucose enters into system by absorption in gastro-instestinal track or by endogenous production (mainly by the liver). Glucose is utilized, according to [3], in body by both insulin-independent (e.g., central nervous system and red blood cells) and insulin-dependent (muscle and adipose tissues) tissues and is peripherally cleared primarily by the kidneys.

2.1 Glucose-insulin minimal model

Glucose-insulin model, described in [8], contains three compartments. A single glucose compartment that represents extracellular glucose (including blood glucose) and separate compartments for plasma and active insulin.

Glucose enters into glucose compartment via intestinal absorption and endogenous glucose production (mainly in liver). Glucose is removed by insulin independent glucose utilization (in central nervous system and red blood cells) and by insulin-dependent

glucose utilization (in muscle and adipose tissues). Peripheral and hepatic handling of glucose are dealt with separately in the model. Glucose handling in liver has been modeled in terms of the "net hepatic glucose balance" which is computed as the sum of gluconeogenesis, glycogen breakdown and glycogen synthesis data derived for different blood glucose and insulin levels (table. 2.2).

Insulin enters into plasma insulin compartment only by absorption from insulin injection site and is removed by hepatic degradation. Insulin production by beta cells in the pancreas is assumed to be virtually zero (type 1 diabetes). The activation and deactivation of insulin are assumed to obey first-order kinetics. Active insulin is responsible for glycaemic control.

Glucose excretion by kidneys has been modeled in terms of two patient specific model parameters: the renal threshold of glucose and the creatinine clearance rate.

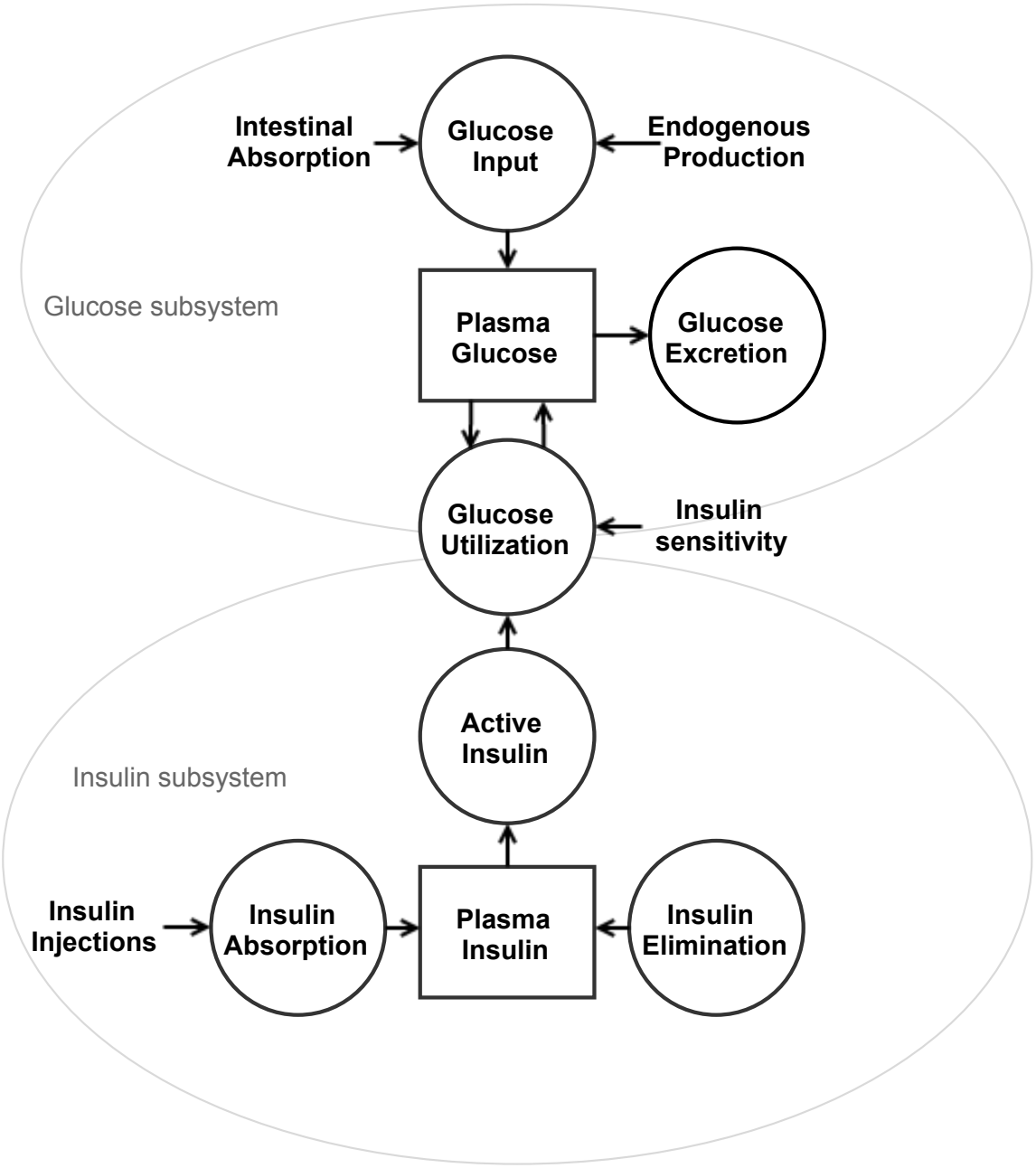

Figure 2.1: Principal components of the glucose-insulin model for simulation of plasma insulin and glucose dynamics. Squares are compartments, circles are actions and arrows indicate interactions.[3]

2.1.1 Insulin dynamics

Change in plasma insulin concentration is modeled as the result of insulin absorption from the subcutaneous tissue and insulin elimination from plasma. These formulas and their descriptions have been taken from [8, 14, 3]. Insulin elimination is assumed to obey first-order kinetics. The possible effects of insulin antibodies are not taken into account.

The change in the plasma insulin concentration, I, is given by the equation:

$$\frac{dI}{dt} = \frac{I_{abs}}{V_i} - k_e \cdot I \tag{2.1}$$

where $k_e$is the first-order rate constant of insulin elimination, I_{abs} is the rate of insulin absorption and V_I (table. 2.3) is the volume of insulin distribution.

The rate of insulin absorption is given by the equation:

$$I_{abs}(t) = \frac{s \cdot t^s \cdot T_{50}^s \cdot D}{t \cdot (t^s + T_{50}^s)^2} \tag{2.2}$$

where$t$ is the time elapsed from the insulin injection, T_{50} is the time at which 50% of the dose, D, has been absorbed and s is a preparation-specific parameter of insulin type (table. 2.1).

Linear dependency of T_{50} on dose is defined as:

$$T_{50} = a \cdot D + b \tag{2.3}$$

where a and b are preparation-specific parameter of the type of insulin (table. 2.1).

Parameter s, a, b define the insulin preparation-specific absorption pattern (see figure 2.5).

Insulin activation and deactivation, I_a, is assumed to obey first-order kinetics.

$$\frac{dI_a}{dt} = k_1 \cdot I - k_2 \cdot I_a \tag{2.4}$$

where k_1 and k_2 (table. 2.3) are first-order rate constants.

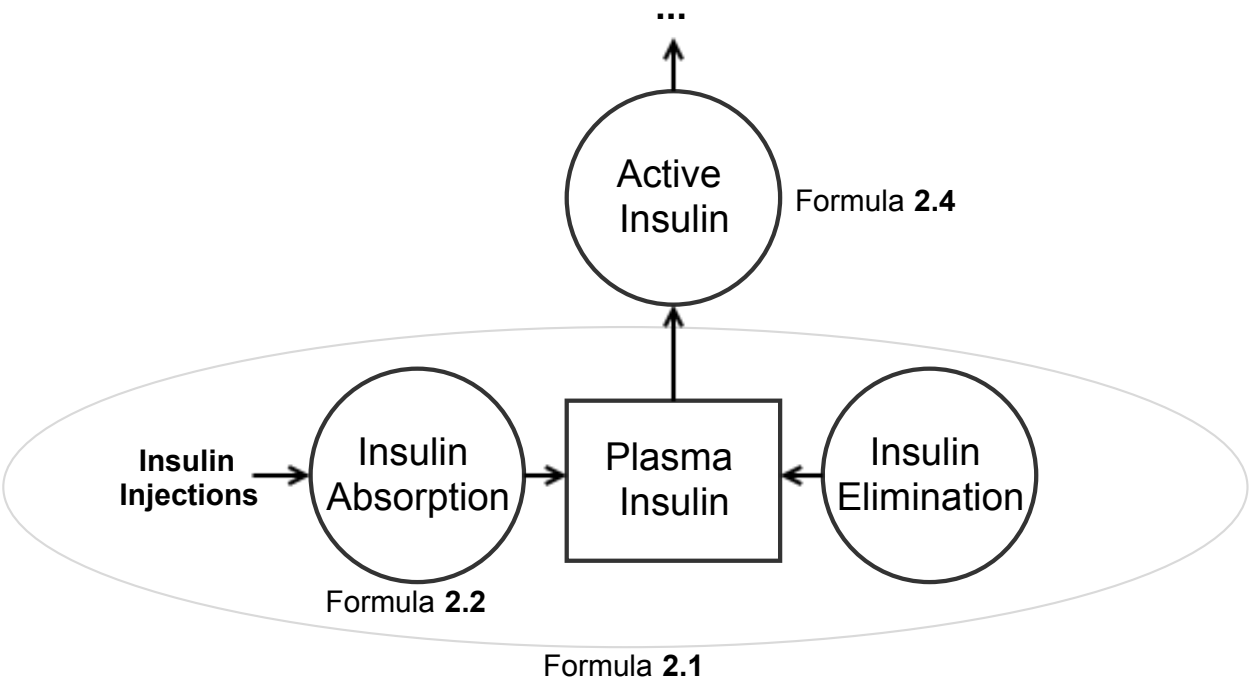

Figure 2.2: Model components of plasma insulin dynamics.

Insulin type	s	a (h/U^{-1})	b (h)
Regular	2.0	0.05	1.7
NPH	2.0	0.18	4.9
Lente	2.4	0.15	6.2
Ultralente	2.5	0	13

Table 2.1: Standard insulin action times of insulin types [3]

The steady-state insulin profile, I_{ss}, and steady-state active insulin profile $I_{a,ss}$, is given by equations:

$$I_{ss} = I(t) + I(t+24) + I(t+48) \tag{2.5}$$

$$I_{a,ss} = I_a(t) + I_a(t+24) + I_a(t+48) \tag{2.6}$$

It is assumed that three days is enough to reach steady-state.

The equilibrated insulin level with the steady-state active insulin is used when computing the "net hepatic glucose balance" and peripheral glucose uptake.

$$I^*_{eq} = k_2 \cdot I_{a,ss}(t)/k_1 \tag{2.7}$$

I^*_{eq} is the insulin level in equilibrium with $I_{a,ss}(t)$.

2.1.2 Glucose dynamics

Plasma glucose concentration is a summation of several distinct processes that include glucose absorption from the gut, endogenous glucose production, glucose utilization by various insulin sensitive and insensitive tissues and glucose excretion by kidneys. These formulas and their descriptions have been taken from [8, 14, 3].

The change in glucose concentration is given by the equation:

$$\frac{dG}{dt} = \frac{G_{in}(t) + NHGB(t) - G_{out}(t) - G_{ren}(t)}{V_G} \tag{2.8}$$

where G is the plasma glucose concentration, G_{in} is the glucose absorption from the gut, G_{out} is the glucose utilization, $NHGB$ is the "net hepatic glucose balance", G_{ren} is the rate of renal excretion and V_G is the volume of distribution for glucose.

Glucose absorption via the gut wall, G_{in}, is given by the equation:

$$G_{in} = k_{gabs} \cdot G_{gut} \tag{2.9}$$

where k_{gabs} is the rate constant for glucose absorption from the gut (table. 2.3) and G_{gut} is the amount of glucose in gut.

The change of glucose amount in the gut, G_{gut}, after the ingestion of a meal containing C millimoles of carbohydrates (glucose equivalent carbohydrates) is given by the equation:

$$\frac{d(G_{gut})}{dt} = G_{empt} - k_{gabs} \cdot G_{gut} \tag{2.10}$$

where k_{gabs} is rate constant of glucose absorption from the gut and G_{empt} is the rate of gastric emptying.

In the model it is assumed that the rate of gastric emptying has ascending and descending phases and a maximum, after which gastric emptying remains relatively constant.

The period, T_{max}, where gastric emptying is constant and maximum is given by the equation:

$$T_{max_{ge}} = \frac{C - \frac{1}{2}V_{max_{ge}} \cdot 2(T_{asc_{ge}} + T_{des_{ge}})}{V_{max_{ge}}} \tag{2.11}$$

where V_{max}, is the maximum rate of gastric emptying (table. 2.3) and $T_{asc_{ge}}$ and $T_{des_{ge}}$ are the durations ascending and descending phases of the gastric emptying curve.

However in small quantities of carbohydrates gastric emptying curve never reaches its maximum. If amount carbohydrates ingested is below critical level, C_{crit}, $T_{asc_{ge}}$ and $T_{des_{ge}}$ are defined by the equation:

$$T_{asc_{ge}} = T_{des_{ge}} = \frac{2 \cdot C}{V_{max_{ge}}} \tag{2.12}$$

The critical level of carbohydrates ingested, C_{crit}, is defined as:

$$C_{crit} = \frac{(T_{asc_{ge}} + T_{des_{ge}}) \cdot V_{max_{ge}}}{2} \tag{2.13}$$

Gastric emptying, G_{empt}, is given by the equations:

$$G_{empt} = (V_{max_{ge}}/T_{asc_{ge}})/t;\ if\ t < T_{asc_{ge}} \tag{2.14}$$

$$G_{empt} = V_{max_{ge}};\ if\ T_{asc_{ge}} < t \leq T_{asc_{ge}} + T_{max_{ge}} \tag{2.15}$$

$$G_{emp} = V_{max_{ge}} - (V_{max_{ge}}/T_{des_{ge}})(t - T_{asc_{ge}} - T_{max_{ge}});$$

$$if\ T + T_{max_{ge}} \leq t < T_{max_{ge}} + T_{asc_{ge}} + T_{ges_{ge}} \tag{2.16}$$

$$G_{emp} = 0;\ elsewhere \tag{2.17}$$

Glucose utilization, G_{out}, in the model is defined by equation:

$$G_{out}(G, I^*_{eq}) = \frac{G(c \cdot S_p \cdot I^*_{eq} + G_I)(K_m + G_x)}{G_X \cdot (K_m + G)} \tag{2.18}$$

where c is the slope of the peripheral glucose utilization versus insulin line, G_I is the insulin independent glucose utilization, G_x is a reference value for glucose utilization, K_m is Michaelis-Menten constant for enzyme mediated glucose uptake, I^*_{eq} is the equilibrated insulin level and S_p is peripheral insulin sensitivity parameter.

The rate of renal glucose excretion, G_{ren}, in the model is defined by equations:

$$G_{ren} = GFR(G - RTG);\ if\ G > RTG \tag{2.19}$$

$$G_{ren} = 0;\ elsewhere \tag{2.20}$$

where GFR is the glomerular filtration (creatinine clearance) rate and RTG is the renal threshold of glucose.

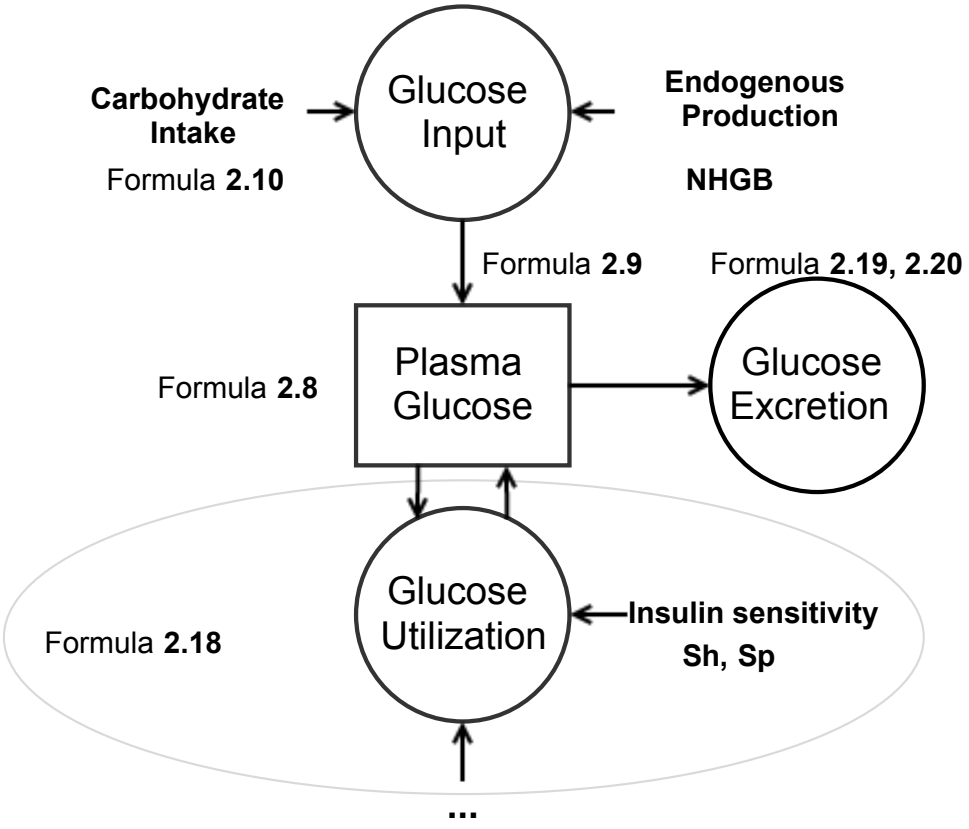

Figure 2.3: Model components of glucose dunamics.

Net hepatic glucose balance, $NHGB$, is a function of arterial blood glucose concentration AG and plasma insulin level I. Net hepatic glucose balance values according to current effective plasma insulin and arterial blood glucose concentration are given in table 2.2. This table is used when calculating glucose concentration (equation 2.8).

Effective plasma insulin ($S_h \cdot I/I_{basal}$)	$AG \leq 1.1\, mmol\, l^{-1}$	$AG = 3.3\, mmol\, l^{-1}$	$AG \geq 4.4\, mmol\, l^{-1}$
0	291.6	169.0	78.3
1	194.6	114.6	53.3
2	129.3	66.0	-1.7
3	95.7	46.3	-54.3
4	85.0	22.6	-76.0
5	76.3	4.3	85.0
6	69.0	-10.0	-92.0
7	62.0	-25.3	-97.3
8	52.0	-43.3	-101.0
9	48.0	-47.3	-104.0
10	41.7	-49.3	-106.7

Table 2.2: Net hepatic glucose balance ($mmol/h$) as function of the arterial blood glucose concentration AG and plasma insulin level I. S_h is a patient-specific hepatic insulin sensitivity parameter which has normalized value between 0 and 1. [8]

Parameter	
$V_I =$	0.142 (l/kg)
$V_g =$	0.22 (l/kg)
Insulin elimination	
$k_e =$	5.4 (h^{-1})
Insulin action	
$k_1 =$	0.025 (h^{-1})
$k_2 =$	1.25 (h^{-1})
Glucose absorption	
$k_{gabs} =$	1 $(1/h)$
$V_{max_{ge}} =$	120 $(mmol/h)$
$T_{asc_{ge}} =$	0.5 (h)
$T_{des_{ge}} =$	0.5 (h)
Glucose utilization	
$c =$	0.015 $(mmol \cdot h^{-1} \cdot mU^{-1} \cdot l)$
$K_m =$	10 $(mmol/l)$
$G_x =$	5.3 $(mmol/l)$
Renal excretion	
$RTG =$	9.0 $mmol\, l^{-1}$
$GFR=$	100 $ml\, min^{-1}$

Table 2.3: Patient-independent model parameter values

2.2 Model implementation

The glucose-insulin minimal model, described earlier, was implemented in the Java programming language. "The Apache Commons Mathematics Library[16]" was chosen to solve first order differential equations describing the model because it is open source lightweight, self-contained mathematics and statistics library that could be used to quickly solve differential equations.

The model implementation takes patient body weight, insulin doses (U), carbohydrates (g), peripheral insulin sensitivity parameter (S_P), hepatic insulin sensitivity parameter (S_h), simulation start and end time as inputs, and outputs time series of plasma insulin concentration (mU/l), amount of glucose in gut ($mmol$) and blood glucose level ($mmol/l$).

The inputs and the output of the model are shown in Figure 2.4. The inputs are the insulin intake (green circles) and glucose intake (blue circles) and the output is the estimation of blood glucose level (red line).

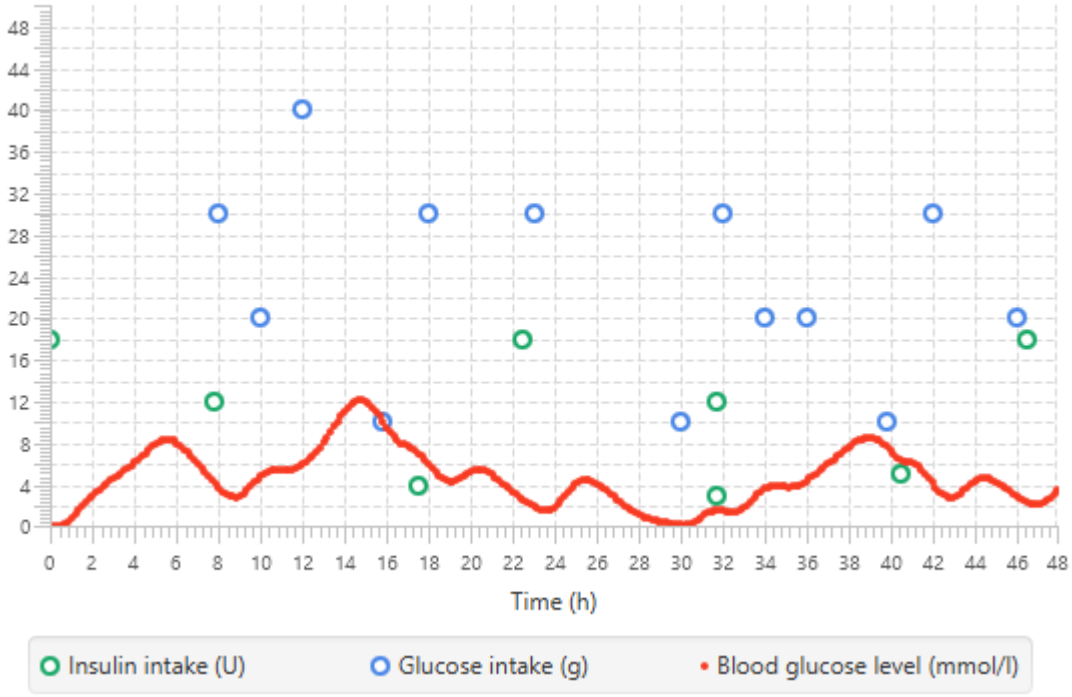

Figure 2.4: The time course of blood glucose simulation. (Body weight is 70 kg, $S_P = 0.5$, $S_h = 0.5$)

In the Figure 2.5 different insulin types are shown.

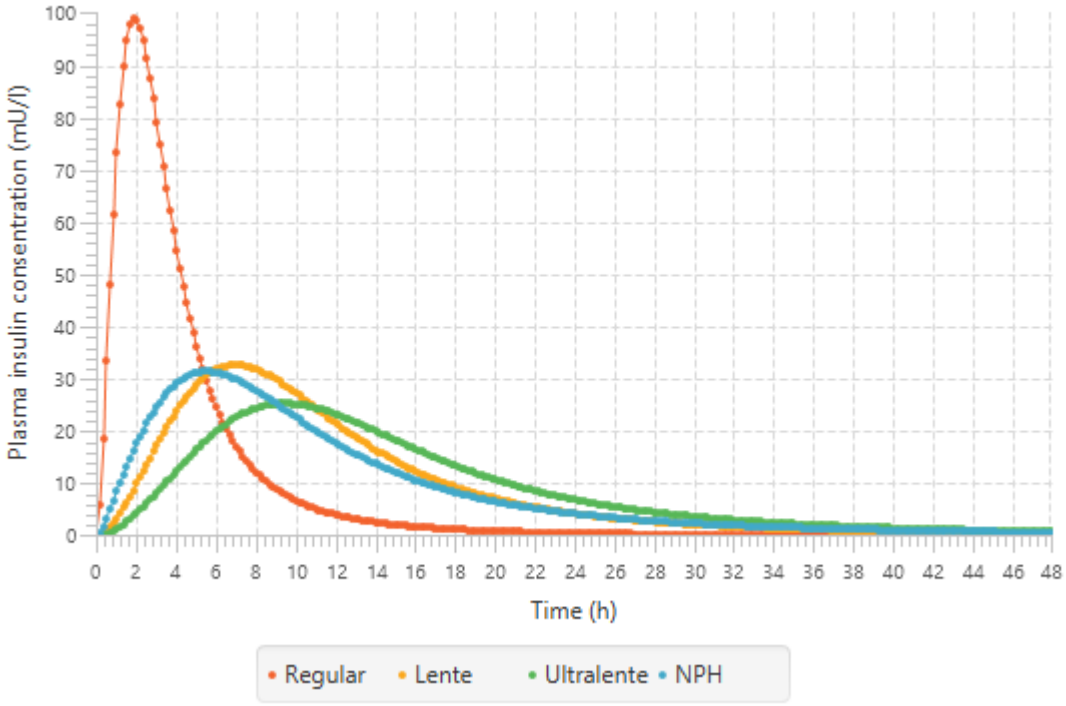

Figure 2.5: The time course of absorption for the different types of insulin after subcutaneous injection of 24 U

Different insulin types have different characteristics:

- Regular or short-acting insulin usually reaches the bloodstream within 30 minutes after injection, peaks anywhere from 2 to 3 hours after injection, and is effective for approximately 3 to 6 hours. [1]
- Lente insulin is an intermediate-acting insulin that starts working about 1.5 hours after it is injected. The effect is maximal between 4 and 8 hours and ends as long as 24 hours after injection. [17]
- Ultralente insulin is a long acting form of insulin. It has an onset of 4 to 6 hours, a peak of 14 to 24 hours, and a duration of 28 to 36 hours. [21]
- NPH Human Insulin which has an onset of insulin effect of 1 to 2 hours, a peak effect of 4 to 6 hours, and duration of action of more than 12 hours. Very small doses will have an earlier peak effect and shorter duration of action, while higher doses will have a longer time to peak effect and prolonged duration. [5]

In the Figure 2.6 comparison of ingested carbohydrates amount is shown. When the ingested amount is small, the gastric emptying function is triangular, when the amount is large it is trapezoidal.

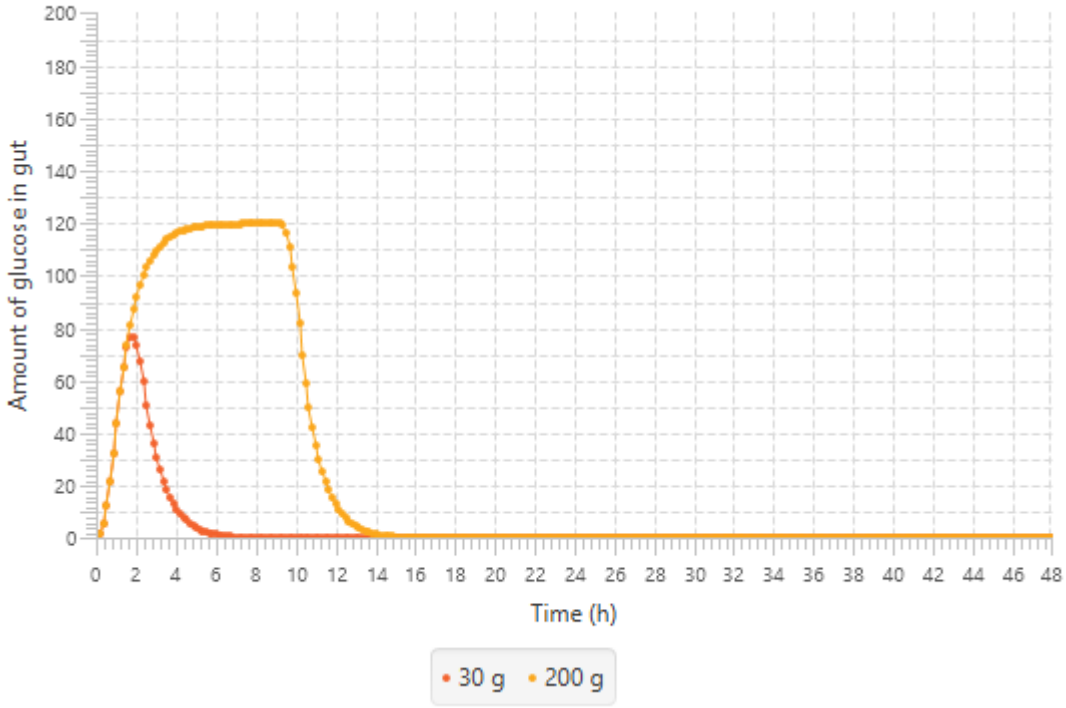

Figure 2.6: The time course of glucose amount in the gut for 30 g and 200 g glucose intake.

2.3 Validating model on collected data

After glucose-insulin model was implemented, it was validated that it could be used for blood glucose simulation using the data inserted by patient. The data that was used for validation was collected during diabetes patients self monitoring pilot project called eMedic [10].

eMedic was a project funded by Central Baltic INTERREG IV A program. The target of the project was to develop new practices for virtual consultation in medicine. The focus was on diabetes and pediatric. eMedic project started in 2011 and ended in April 2014. [10]

The collected data consisted of blood sugar measurements, insulin injections and carbohydrates intake records. What made using this data set difficult was a lot of missing values, which meant that in several cases patient data could not be used. However, in several cases there was sufficient data. Of those patients 4 were chosen.

The first task for simulation was to find values for the patient specific variable S_P (peripheral insulin sensitivity parameter) and S_h(hepatic insulin sensitivity parameter). To find these parameter values the system iteratively tries different values to find best fit between model and real data so that the distance between real measurements and model output is minimal.

The period that was used for simulation was one week. After each simulation error was calculated.

Root-mean-square error was used as error function.

$$RMS(G) = \sqrt{\sum_{i=1}^{n} \frac{(G_{p_i} - G_{m_i})^2}{n}} \tag{2.21}$$

where G_p is model value, G_m is measured value and n is number of data points.

The error function value was minimized during patient specific parameters values search.

2.3.1 Validation results

The found S_P and S_h parameter values for each patient are given in table 2.4.

Patient	S_P	S_h	Average error ($RMS(G)$)
1	1.0	0.4	4.86
2	0.1	0.8	6.06
3	0.0	0.1	5.95
4	0.6	0.0	5.47

Table 2.4: Found S_P and S_h parameter values found for the test patients. (Period: 01.04.2013 - 01.08.2013)

The implemented glucose-insulin model worked using the data inserted by patients and was able to generate values that corresponded to real measured blood glucose values. The minimum root-mean-square error was 4.86 and the maximum was 5.95.

In the Figures 2.7, 2.8, 2.9, 2.10, the results of blood glucose concentration change simulations are shown for each test patient. The simulation period is one week. The

green circles are insulin intake values, blue circles are carbohydrate ingestion, the purple line is glucose-insulin model output and red squares are real measured values.

Patient 1

Test patient 1 had very good data. All the blood sugar measurements, carbohydrates intake and insulin injection records were present and because of that simulations had lowest average error. In the Figure 2.7, we can see that in several points actual measured value is very close to the glucose-insulin model output.

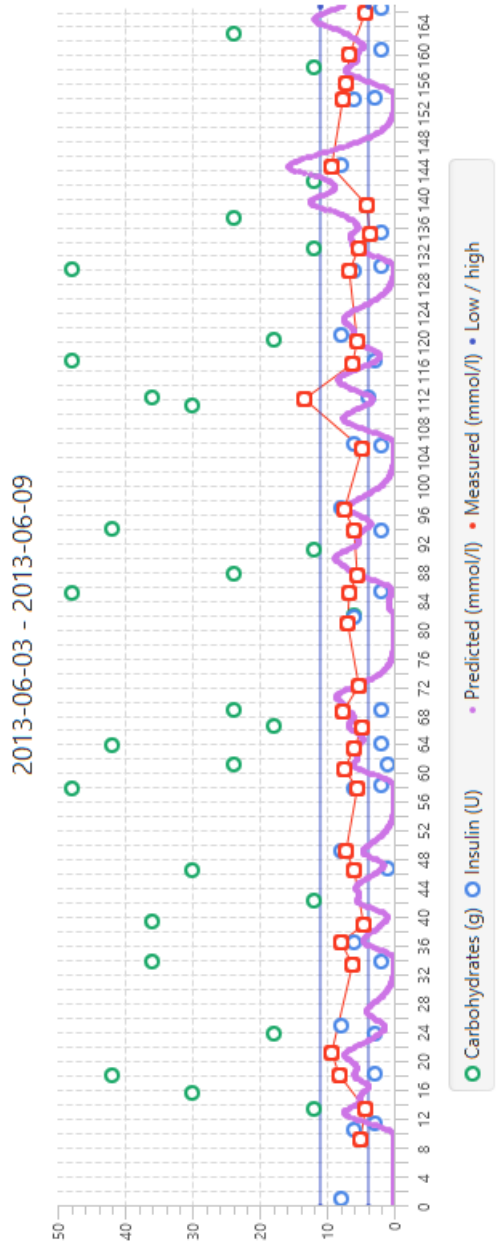

Figure 2.7: The result of simulation of patient 1 blood glucose level.

Patient 2

Patient 2 had most of the blood sugar measurements, carbohydrates intake and insulin injection records. However in some periods data was missing. In case of patient 2 simulated blood glucose values mostly stayed below real measured values.

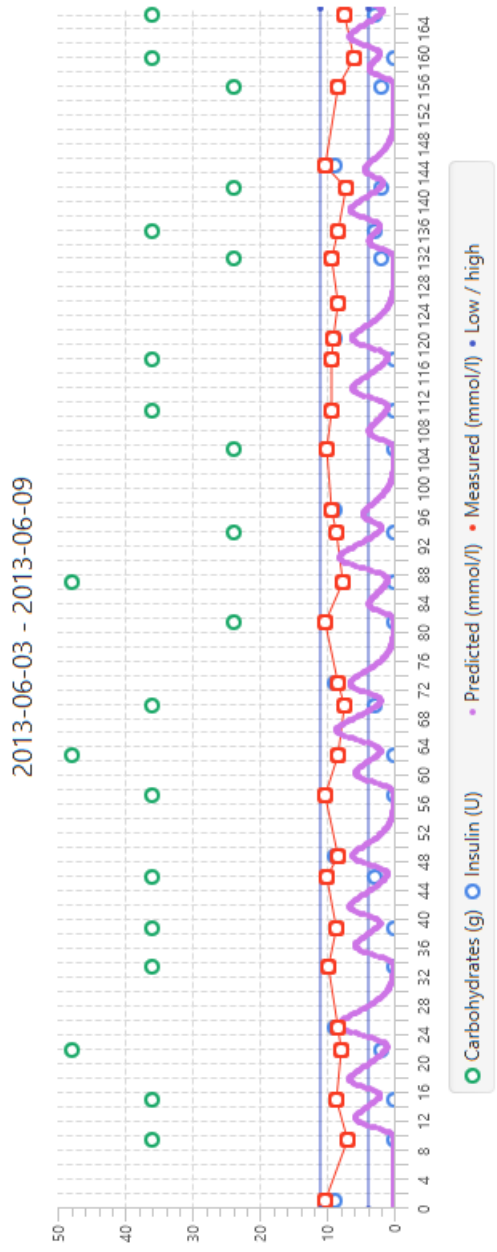

Figure 2.8: The result of simulation of patient 2 blood glucose level.

Patient 3

Patient 3 had most of the blood sugar measurements, carbohydrates intake and insulin injection records present. However in some periods carbohydrates intake data was missing. That meant that simulation failed on those periods. In the Figure 2.9 we can see that from hour 94 to 156 model does not output anything. Because of missing values average error was high.

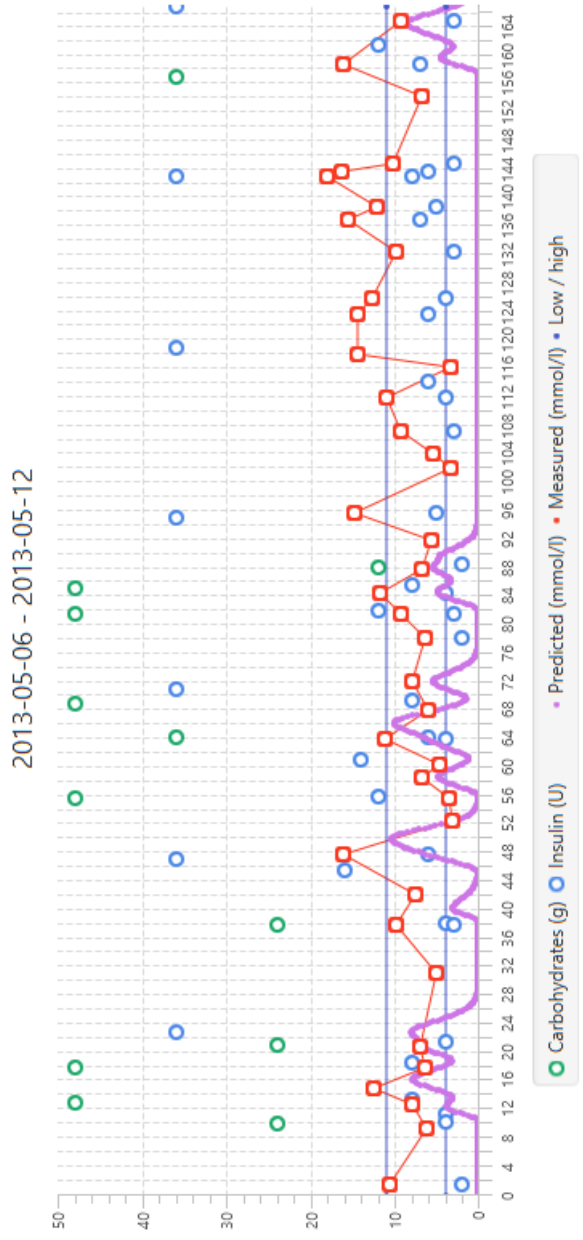

Figure 2.9: The result of simulation of patient 3 blood glucose level.

Patient 4

Patient 4 had all blood sugar measurements, carbohydrates intake and insulin injection records present. Because of that simulations had low average error.

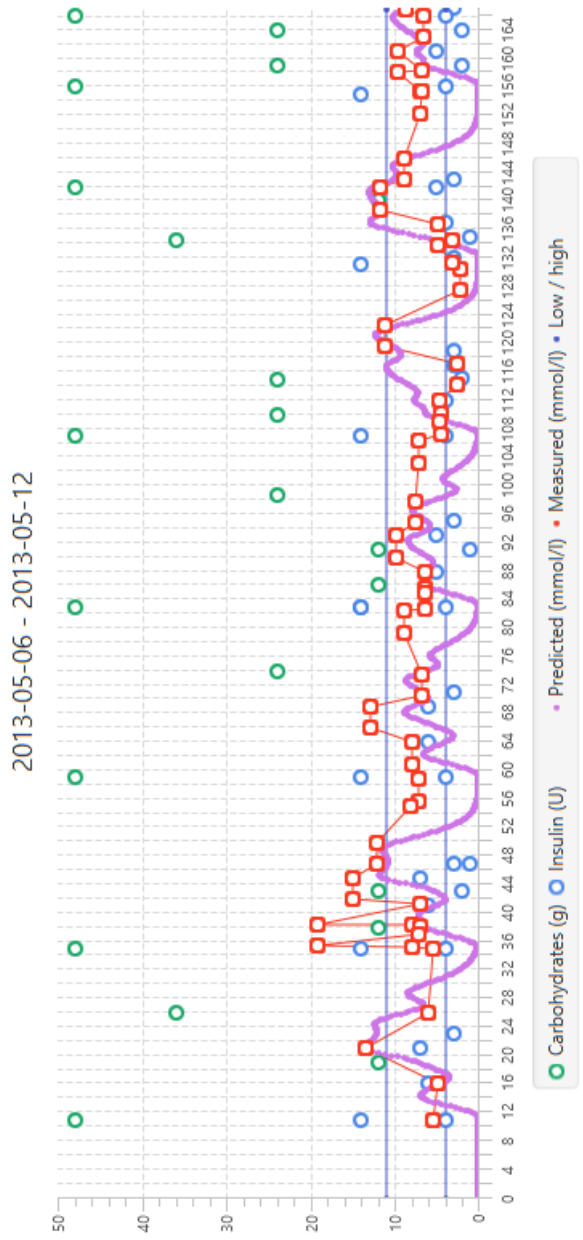

Figure 2.10: The result of simulation of patient 4 blood glucose level.

3 Predicting hypo- and hyperglycemia events

3.1 Prediction using the glucose-insulin model

The first approach that was used to predict hypoglycemia and hyperglycemia event was to use implemented glucose-insulin model output.

The prediction results for each of the test patient are given in tables 3.1, 3.2, 3.3, 3.4. Detected events are correct hypo- or hyperglycemia events that model predicted. Undetected events are hypo- or hyperglycemia events that were not predicted by the model. False alarms are events when model predicted hypo- or hyperglycemia event, but blood sugar level was actually in norm.

Patient 1

In the case of Patient 1, predicting hypoglycemia and hyperglycemia events was successful. Hypoglycemia detection accuracy was 57%, false alarm rate 0.88. Hyperglycemia detection accuracy was 83%, false alarm rate 0.72

Period	Hypoglycemia predicted			Hyperglycemia predicted		
	Detected	Undetected	False alarm	Detected	Undetected	False alarm
01.04 - 07.04	1	0	5	2	0	3
08.04 - 14.04	0	0	2	3	1	2
15.04 - 21.04	0	0	5	1	0	0
22.04 - 28.04	0	0	3	4	0	0
29.04 - 05.05	0	0	1	1	1	3
06.05 - 12.05	1	0	4	3	1	2
13.05 - 19.05	0	0	2	1	1	6
20.05 - 26.05	1	0	0	0	0	7
27.05 - 02.06	0	0	2	1	0	4
03.06 - 09.06	0	1	3	1	0	3
10.6 - 16.06	0	1	1	1	0	4
17.06 - 23.06	0	1	1	1	0	10
24.06 - 30.06	1	0	1	0	0	5
Total	4	3	30	19	4	49

Table 3.1: Patient 1 prediction statistics.

Patient 2

In the case of Patient 2, predicting hypoglycemia and hyperglycemia events was unsuccessful. Hypoglycemia false alarm rate was very high and hyperglycemia detection accuracy was low. Hypoglycemia detection accuracy was 100% and false alarm rate 1. Hyperglycemia detection accuracy was 10% and false alarm rate 0.63

Period	Hypoglycemia predicted			Hyperglycemia predicted		
	Detected	Undetected	False alarm	Detected	Undetected	False alarm
01.04 - 07.04	0	0	10	0	0	0
08.04 - 14.04	0	0	10	0	3	0
15.04 - 21.04	1	0	11	2	8	0
22.04 - 28.04	0	0	13	0	9	0
29.04 - 05.05	0	0	9	0	0	0
06.05 - 12.05	0	0	13	0	0	0
13.05 - 19.05	0	0	7	0	5	0
20.05 - 26.05	0	0	14	0	0	0
27.05 - 02.06	0	0	13	0	3	0
03.06 - 09.06	0	0	14	0	0	0
10.6 - 16.06	0	0	13	0	0	3
17.06 - 23.06	0	0	12	1	0	1
24.06 - 30.06	0	0	11	0	0	1
Total	1	0	150	3	28	5

Table 3.2: Patient 2 prediction statistic

Patient 3

In the case of Patient 3, hypoglycemia detection accuracy was 72% and false alarm rate was 0.62. Hyperglycemia detection accuracy was 34% and false alarm rate was 0.29

Period	Hypoglycemia predicted			Hyperglycemia predicted		
	Detected	Undetected	False alarm	Detected	Undetected	False alarm
01.04 - 07.04	3	2	1	5	4	1
08.04 - 14.04	2	0	1	3	7	1
15.04 - 21.04	3	1	2	3	2	1
22.04 - 28.04	1	1	6	2	5	0
29.04 - 05.05	1	0	3	3	9	0
06.05 - 12.05	3	0	0	1	6	0
13.05 - 19.05	2	1	1	3	2	6
20.05 - 26.05	2	0	4	2	6	0
Total	17	5	28	22	41	9

Table 3.3: Patient 3 prediction statistic

Patient 4

In the case of Patient 4, hypoglycemia detection accuracy was 75% and false alarm rate was 0.37. Hyperglycemia detection accuracy was 39% and false alarm rate was 0.43.

Period	Hypoglycemia predicted			Hyperglycemia predicted		
	Detected	Undetected	False alarm	Detected	Undetected	False alarm
01.04 - 07.04	3	0	0	5	4	2
08.04 - 14.04	0	0	1	3	0	4
15.04 - 21.04	2	2	1	3	0	1
22.04 - 28.04	5	1	1	2	3	2
29.04 - 05.05	3	0	1	3	7	1
06.05 - 12.05	1	1	2	4	4	0
13.05 - 19.05	4	2	1	0	3	4
20.05 - 26.05	4	1	2	3	3	0
27.05 - 02.06	2	2	2	3	2	0
03.06 - 09.06	3	0	2	0	3	2
10.6 - 16.06	3	2	3	1	5	0
17.06 - 23.06	3	0	2	0	4	0
24.06 - 30.06	5	2	4	0	4	4
Total	38	13	22	27	42	20

Table 3.4: Patient 4 prediction statistic

For this purpose glucose-insulin model performed reasonably well. However it did not

detect all the hypoglycemia and hyperglycemia events and it generated a lot of false alarms. This approach seems to work well, if the patient is good at taking notes, e.g. patient 1. When the quality of the data is low, e.g. it has lots of missing values, the error is high. In our experiments periods of missing data where not eliminated because we set up the experiment in such a way that we use all the realistic data during some specific period.

3.2 Predicting using classification

The second approach was to learn from patient previous data and glucose-insulin model output, and use classification to predict hypoglycemia and hyperglycemia events.

The first job was to somehow handle time series. In the given data, the measurements are not aligned in time and there are gaps in measurements. To cope with the misalignment and gaps in the data, the developed system first divides data into samples. Each data sample consists of blood sugar measurement, carbohydrates intake or insulin injection record and next blood sugar measurement. From these samples the system created the learning data set. The first two months of the data were used for training data.

To improve the learning data set, the glucose-insulin model simulation results are included into the learning data set.

We also experimented without including model results into the learning data set. However, since the classifier performed significantly better with the glucose-insulin model results added, here we bring out only the results we got by using the improved learning data set.

For classification K* classification algorithm was used from Weka[18] data mining library. K* classification algorithm was chosen because it performed best of the algorithms tried. We also tried classification algorithms like, e.g. Naïve Bayes, DTNB (a decision table/naive bayes hybrid classifier), J48 (a decision tree classifier), SMO (a support vector classifier), and used cross-validation to assess their performance.

Implementation of the solution described in [11, 2] was not evaluated within the current MSc thesis because of the extended development effort required.

The prediction results for each of the test patient are given in tables 3.5, 3.6, 3.7, 3.8. Detected events are correct hypo- or hyperglycemia events that model predicted. Undetected events are hypo- or hyperglycemia events that were not predicted by the

model. False alarms are events when model predicted hypo- or hyperglycemia event, but blood sugar level was actually in norm. In the brackets is the result of predicting using glucose-insulin model.

Patient 1

In the case of Patient 1, hypoglycemia detection accuracy was 17%, false alarm rate 0.5. Hyperglycemia detection accuracy was 78%, false alarm rate 0.22.

Period	Hypoglycemia			Hyperglycemia		
	Detected	Undetected	False alarm	Detected	Undetected	False alarm
06.05 - 12.05	0 (**1**)	1 (**0**)	**0** (4)	2 (**3**)	2 (**1**)	**0** (2)
13.05 - 19.05	**0** (0)	**0** (0)	**0** (2)	**1** (1)	**1** (1)	**0** (6)
20.05 - 26.05	**0** (1)	1 (**0**)	**0** (0)	**0** (0)	**0** (0)	**1** (7)
27.05 - 02.06	**0** (0)	**0** (0)	**0** (2)	**1** (1)	**0** (0)	**0** (4)
03.06 - 09.06	**0** (0)	**1** (1)	**0** (3)	**1** (1)	**0** (0)	**0** (3)
10.6 - 16.06	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)	0 (4)
17.06 - 23.06	0 (0)	1 (1)	0 (1)	1 (1)	0 (0)	0 (10)
24.06 - 30.06	1 (1)	0 (0)	0 (1)	0 (0)	0 (0)	1 (5)
Total	1 (**3**)	5 (**3**)	**1** (14)	7 (**8**)	3 (**2**)	**2** (41)

Table 3.5: Patient 1 prediction statistic. In the brackets is the result of predicting using glucose-insulin model.

Patient 2

In the case of Patient 2, hypoglycemia detection accuracy was100%, false alarm rate 0%. Hyperglycemia detection accuracy was67%, false alarm rate 0.25.

Period	Hypoglycemia			Hyperglycemia		
	Detected	Undetected	False alarm	Detected	Undetected	False alarm
06.05 - 12.05	**0** (0)	**0** (0)	**0** (13)	**0** (0)	**0** (0)	**1** (0)
13.05 - 19.05	**0** (0)	**0** (0)	**0** (7)	**3** (0)	**2** (5)	**0** (0)
20.05 - 26.05	**0** (0)	**0** (0)	**0** (14)	**0** (0)	**0** (0)	**0** (0)
27.05 - 02.06	**0** (0)	**0** (0)	**0** (13)	**3** (0)	**0** (3)	**0** (0)
03.06 - 09.06	**0** (0)	**0** (0)	**0** (14)	**0** (0)	**0** (0)	1 (**0**)
10.6 - 16.06	**0** (0)	**0** (0)	**0** (13)	**0** (0)	**0** (0)	**0** (3)
17.06 - 23.06	**0** (0)	**0** (0)	**0** (12)	**0** (**1**)	**1** (**0**)	**0** (1)
24.06 - 30.06	**0** (0)	**0** (0)	**0** (11)	**0** (0)	**0** (0)	**0** (1)
Total	**0** (0)	**0** (0)	**0** (97)	**6** (1)	**3** (8)	**2** (5)

Table 3.6: Patient 2 prediction statistic. In the brackets is the result of predicting using glucose-insulin model.

Patient 3

In the case of Patient 3, hypoglycemia detection accuracy was 14%, false alarm rate 0. Hyperglycemia detection accuracy was 30%, false alarm rate 0.6.

Period	Hypoglycemia			Hyperglycemia		
	Detected	Undetected	False alarm	Detected	Undetected	False alarm
06.05 - 12.05	0 (**3**)	3 (**0**)	**0** (0)	**4** (1)	**3** (6)	2 (**0**)
13.05 - 19.05	0 (**2**)	3 (**1**)	0 (1)	2 (**3**)	3 (**2**)	**5** (6)
20.05 - 26.05	1 (**2**)	1 (**0**)	**0** (4)	0 (**2**)	8 (**6**)	2 (**0**)
Total	1 (**7**)	7 (**1**)	**0** (5)	**6** (6)	**14** (14)	9 (**6**)

Table 3.7: Patient 3 prediction statistic. In the brackets is the result of predicting using glucose-insulin model.

Patient 4

In the case of Patient 4, hypoglycemia detection accuracy was 71%, false alarm rate 0.32. Hyperglycemia detection accuracy was 36%, false alarm rate 0.63.

Period	Hypoglycemia			Hyperglycemia		
	Detected	Undetected	False alarm	Detected	Undetected	False alarm
06.05 - 12.05	**2** (1)	**0** (1)	**0** (2)	2 (**4**)	6 (**4**)	3 (**0**)
13.05 - 19.05	**6** (4)	**0** (2)	2 (**1**)	**1** (0)	**2** (3)	6 (**4**)
20.05 - 26.05	**4** (4)	**1** (1)	**1** (2)	0 (**3**)	6 (**3**)	**2** (0)
27.05 - 02.06	**3** (2)	**1** (2)	**1** (2)	**4** (3)	**1** (2)	**0** (0)
03.06 - 09.06	**3** (3)	**0** (0)	**2** (2)	**1** (0)	2 (3)	5 (**2**)
10.6 - 16.06	1 (**3**)	4 (**2**)	**2** (3)	**1** (1)	**5** (5)	**0** (0)
17.06 - 23.06	0 (**3**)	3 (**0**)	4 (**2**)	**1** (0)	**3** (4)	**2** (0)
24.06 - 30.06	**6** (5)	**1** (2)	**0** (4)	**4** (0)	**0** (4)	**1** (4)
Total	**25** (23)	**10** (12)	**12** (18)	**14** (11)	**24** (28)	19 (**10**)

Table 3.8: Patient 4 prediction statistic. In the brackets is the result of predicting using glucose-insulin model.

The classification approach did not generate as many false alarms like predicting from the glucose-insulin model did. In the case of patient 3, detection accuracy was lower compared to predicting from the glucose-insulin model. However in case of patients 1, 2 and 4 the detection accuracy was higher.

4 Conclusion

In these theses the glucose-insulin system model was implemented and tested if it could be used for prediction of hypo- and hyperglycemia events. The AIDA [8] glucose-insulin minimal model was chosen as model to be implementation. The implemented model was also tested that it could handle the data inserted by real patient.

Two approaches were considered for predicting hypo- and hyperglycemia events.

The first approach was to use the pure glucose-insulin model output for prediction of hypo- and hyperglycemia events. For this purpose the implemented model performed reasonably well. However it did not detect all the hypoglycemia and hyperglycemia events and it generated a lot of false alarms.

The second approach was to use classification to predict hypo- and hyperglycemia events and include glucose-insulin model results into the learning data. The classification approach did not generate as many false alarms like predicting from glucose-insulin model and detection accuracy in some test cases was higher.

Recommendations

Overall, the glucose-insulin system model can be used for prediction of hypo- and hyperglycemia events. However some future work is required before it can be used in real life. The implemented glucose-insulin model does not include process of insulin production by beta cells in the pancreas and physical activity model. Including those factors could make model accurate and might bring false alarm rate down.

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Nomenclature

homeostasis Homeostasis is the property of a system in which variables are regulated so that internal conditions remain stable and relatively constant