TAMPERE UNIVERSITY OF TECHNOLOGY

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MODELLING GLUCOSE REGULATORY SYSTEM: ADAPTIVE SYSTEM DYNAMIC APPROACH

Master of Science Thesis

Examiner: prof. Jari Viik
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ABSTRACT

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Keywords: Glucose regulatory system, diabetes, system dynamics, system modelling, adaptive parameter identification

Thesis describes a project that starts from evaluation of simulation programs and ends to testing an individually adaptive glucose regulatory system (GRS) model. Thesis presents a modern adaptive approach to model GRS in order to describe each diabetic's individual causalities. Thesis is divided into three parts; a literature study of diabetes and GRS models, analysis of simulation programs, and building dynamics GRS model and validating it with clinical data.

Validation consists literature data for general GRS model and test data from a pilot diabetic who underwent two-week study period. Data collected included glucose values from two continuous glucose monitors (CGM), fingertip blood glucose measurements, meals and exercises. Adaptive parameter identification was applied to the model during 6 days training period and then blood glucose was estimated for the next 24 hours.

First part of results show that from four simulation programs analyzed, Simulink was the software best meeting Quattro Folia's functional requirements and demanded qualities. Therefore, a general GRS model was built with it. Based on literature review, the best model and parts of models were combined for one general model which was validated to function as in previous studies. Second part of results show that with adequate data, blood glucose can be estimated with decent accuracy. Although the material only consist data from one diabetic subject, it gives an indication that blood glucose could be estimated for others also. However, the precision over population is indecisive.

To conclude, individual diabetic's GRS and its functions can be described with adaptive system dynamic model. The model have multiple possible usages from *in silico* testing to teaching causalities for diabetics or their parents, thus it is useful for research, validation and educational purposes. Its value creators are modularity and wide range of possible usages.

TIIVISTELMÄ

TAMPEREEN TEKNILLINEN YLIOPISTO
Signaalinkäsittelyn ja tietoliikennetekniikan diplomi-insinöörin tutkinto-ohjelma
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Diplomityö käsittelee nykyaikaista adaptiivista lähestymistä ihmisen sokeriaineenvaihdunnan mallintamiseen. Työ on jaettu kolmeen osaan; kirjallisuustutkimus diabeteksestä ja sokeriaineenvaihduntamalleista, simulointiohjelmien analysointi, ja dynaamisen mallin rakentaminen ja validointi. Validointi sisältää niin kirjallisuustietoa kuin myös kliinistä dataa yhdeltä tyypin 1 diabeetikolta kahden viikon pilottijakson ajalta. Materiaali sisälsi kahden sensorimittarin verensokeriarvot, perinteisen verensokerimittarin arvot, ateriatiedot ja liikuntatiedot. Viikko jaettiin kahteen osaan, kuusi ensimmäistä päivää parametrien identifikointia varten ja seitsemäs päivä tulosten testaukseen. Toisin sanoen verensokeria pyrittiin estimoimaan 24 tunnin ajalta edeltävän kuuden päivän perusteella.

Ensimmäinen osa tuloksista osoittaa, että neljästä analysoidusta simulointiohjelmasta, Simulink oli parhaiten Quattro Folian käyttötarkoituksia ja vaatimuksia vastaava. Näin ollen mallinnus tehtiin edellä mainitulla ohjelmalla. Kirjallisuuskatsauksen perusteella valittu yleinen sokeriaineenvaihdunta malli ja mallien osia yhdistettiin kokonaisuudeksi, joka validointiin toimivan fysiologisesti oikein.

Tulokset osoittivat, että riittävällä määrällä yhtenäistä dataa pystytään verensokeria estimoimaan kohtuullisella tarkkuudella. Vaikka materiaalina oli vain yhdeltä diabeetikolta kerättyä dataa, voidaan olettaa, että koejärjestely on toistettavissa onnistuneesti myös muille diabeetikoille. Kuitenkaan estimoinnin tarkkuudesta ei voida antaa arvioita.

Diabeetikon sokeriaineenvaihduntaa voidaan kuvata dynaamisella mallilla, joka adaptoituu yksilön mukaan. Mallia voidaan käyttää esimerkiksi validointiin simulointitesteillä, tutkimuksiin tai diabeetikkojen opetukseeen. Toisin sanoen mallin arvo muodostuu sen modulaarisuudesta ja useista eri käyttökohteista.

PREFACE

In 2009 I came to Tampere University of Technology without any expectations. Yet, I have experienced the best years of my life so far. Even though, it is great to move forward, at the same time it is a pity leave something wonderful behind. Therefore, what better way to finish the school years but a Master of Science thesis: A process, where you first just cross your fingers, then boil the ocean, use your loaf, cut the chase and finally take the bull by the horns and cut the mustard… Then start the next chapter.

I wish to express my gratitude to my supervisor Pekka Lönnroth, PhD, for his guidance throughout the thesis project. Not only he instructed whenever I needed help, but also taught towards analytical thinking.

I would like to thank Harri Okkonen from Quattro Folia Oy for offering a job and a topic for the thesis. This has given a great starting point for my career. I would also like to thank Niina Nippula; Markku Saraheimo, MD, DMSc; Tero Kangas, DMSc for their help in understanding human physiology and diabetes mellitus; Professor Matti Vilkko, PhD, for his effort to teach me more about system dynamics; and Professor Jari Viik, PhD, for advises and examining my thesis. I would also like to thank all the co-workers for all of their efforts, especially those who contributed to questionnaire; and the pilot diabetic, who was willing to participate the study.

Last but not least, I would like to express my gratitude to my dear partner Mira, who tolerated me throughout the thesis process. Without her advices and consoles this thesis might have never been finished.

Tampere, October 1st, 2015

PETTERI VÄISÄNEN

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LIST OF ABBREVIATIONS

A1c	Glycosylated Hemoglobin also HbA1c
ADA	American Diabetes Association
CGI	Clinical Global Impression
CGM	Continuous Glucose Monitoring
CHO	Carbohydrate
CPU	Central Processing Unit
EGP	Endogenous Glucose Production
FDA	Food and Drug Administration
GRS	Glucose Regulatory System
HbA1c	Glycosylated Hemoglobin also A1c
IDF	International Diabetes Federation
IFT	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IVGTT	Intravenous Glucose Tolerance Test
MDI	Multiple Daily Injection
NPH	Neutral Protamine Hagedorn
OGTT	Oral Glucose Tolerance Test
R	Correlation
RMSE	Root Mean Square Error
SI	International System of Units
SMBG	Self-Monitoring of Blood Glucose
STD	Standard Deviation
TDI	Total Daily Insulin
UI	User Interface
UVA	University of Virginia
WHO	World Health Organization

1. INTRODUCTION

In year 1980 WHO Expert Committee on Diabetes Mellitus, estimates that 30 million people have diabetes [1]. In year 2013, International Diabetes Federation (IDF) estimates that there are 382 million people living with diabetes and additional 316 million people with impaired glucose tolerance. Thus, they are at high risk from the disease. In past 30 years the number of diabetics is more than tenfold and by all measures, the number has not reached its peak yet. [2, p.7]

Although diabetes is a widespread and common disease, every individual needs unique care. For instance type 1 diabetic person has to decide every time he eats, whether to have insulin bolus, how many units the bolus should be, when to take it, will I exercise afterwards, etc. In addition, there is also need for basal insulin which basically means that in order to keep the blood sugar in balance person will take one or two additional injections daily. It has been estimated that a person with type 1 diabetes, makes 300 decisions per day that are related to their self-care [3]. Figure 1.1 shows a sketch of the balancing equation that diabetic or diabetic parent undergo around-the-clock. Equation includes elements such as exercise, medication, eating, sleeping, stress, etc. Although doctors and nurses advices patients with the care plan, most of the daily decisions are more or less done based on the individual's understanding of the disease.

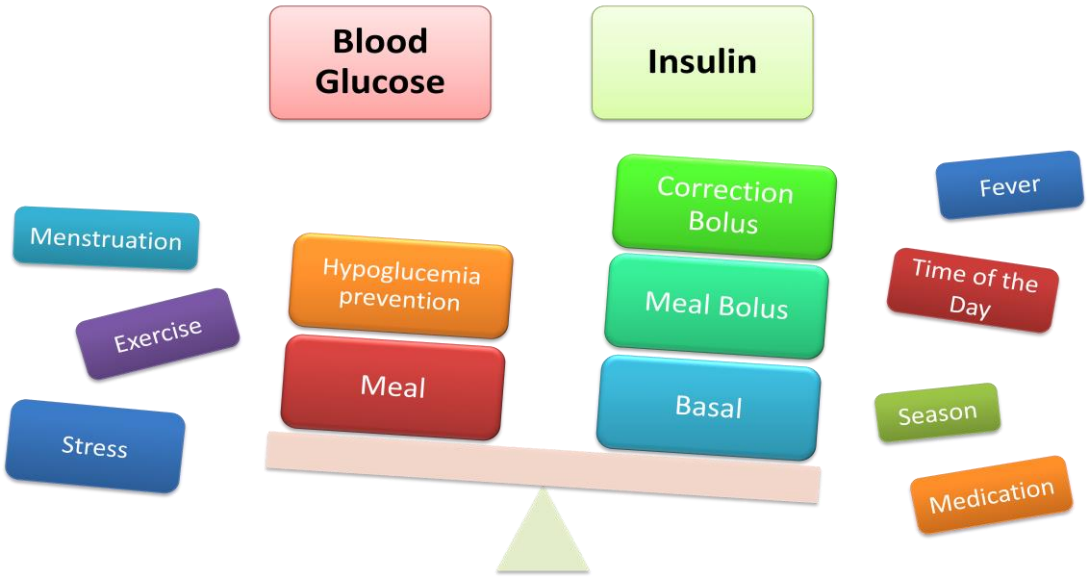

Figure 1.1: The balancing equation that diabetic person is dealing with around-the-clock: Blood glucose is measured and insulin is administered.

The aim is to develop an individual model to every patient's glucose regulatory system to be used as a tool for learning and understanding. Output for patient can be just some simple cause-effect charts or insulin bolus advisor, but doctors can access to all the available data to be able to evaluate how the care plan is succeeding and then make adjustments if necessary. The model should be suitable at least for both type 1 and type 2 diabetes.

Nowadays technology has already shown a great variety of options to measure human body and its functions. Idea is to combine all measurement data and update the older glucose regulatory models to respond the modern technology status.

To summarize, the number of diabetics is increasing so the need for individual care is increasing. Hospitals and clinics are incapable to respond to this growing need and therefore modern models can have a significant influence for diabetic to be able understand how his or her body functions and for care team to be able to react to individual's needs quicker and more efficiently, thus to lead a healthy life with minimum amount of complications.

Chapter 2 of thesis gives a brief overview to diabetes, GRS models and system dynamics. Chapter 3 provides information about materials and methods used in this thesis. Chapter 4 presents results of simulation program selection, dynamic GRS model and individual GRS model. Chapter 5 analyses the results and conclude the thesis. The appendices include further information about parameters and subsystem models build with Simulink.

2. THEORETICAL BACKGROUND

2.1 Diabetes Mellitus

Diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of metabolism resulting from defects in insulin secretion, action, or both [4, p. 2]. Diabetes are generally considered to be divided into two main types; type 1 and type 2 diabetes mellitus.

2.1.1 History of Diabetes

The first known mention of diabetes is from 1552 BCE, when Egyptian physician Hesy-Ra listed remedies to 'passing of too much urine'. The next and more completing description of diabetes was given by Greek physician Aretaes of Cappodocia. He referred diabetes as 'melting down of flesh and limbs into urine'. [5] In the 17th century Dr. Thomas Willis discovered that diabetes can be diagnosed by sampling urine. Sampling was done by tasting the urine and estimating the sweetness of it, but still it took almost 300 years to discover at least somewhat efficient treatment for diabetes and in the early 20th century, Dr. Frederick Allen prescribed low calories diets for diabetics. [6]

Insulin was discovered in the early 1920s by Dr. Frederick Banting. He started injecting insulin to diabetic dogs and moved on to cattle. Dr. Banting and Charles Best with assistance of Prof. John Macleod first tested insulin to themselves and after discovering that there is no significant side-effects, they injected 14-year-old diabetic boy called Leonard Thompson. He was weak and near death, but with insulin shots he managed to regain his strength and appetite. Although insulin will not cure the diabetes, it gives the person possibility to live otherwise normal life and, thus, insulin has become part of everyday life of each type 1 diabetic. In 1923 Dr. Banting and Prof. Macleod were awarded with the Nobel Prize in Physiology or Medicine. After this many studies regarding to diabetes has been published and helping devices such as insulin pump has been invented. [7]

2.1.2 Glucose Metabolism

When human ingest food that includes carbohydrates, glucose is absorbed to blood stream via digestion system. Absorption starts already in mouth, but happens mostly in guts. The glucose appears in blood circulation as a function of time depending also on various factors such as the type of carbohydrate ingested.

Figure 2.1 describes body's causalities. Plasma glucose level controls pancreatic actions. Its alpha or beta cells in the islets of Langerhans releases glucagon or insulin, respectively, which then are connected via portal vein to liver. If glucose level is high, it activates beta cells which triggers insulin secretion that is multi-oscillatory process with rapid pulses and slower so called ultradian oscillations. The length of slow pulse is about 10 minutes and ultradian pulse varies from 50 to 120 minutes. Insulin controls the glucose uptake in muscles and adipose tissue (i.e. fat) and stimulates liver glucose storage. [8]

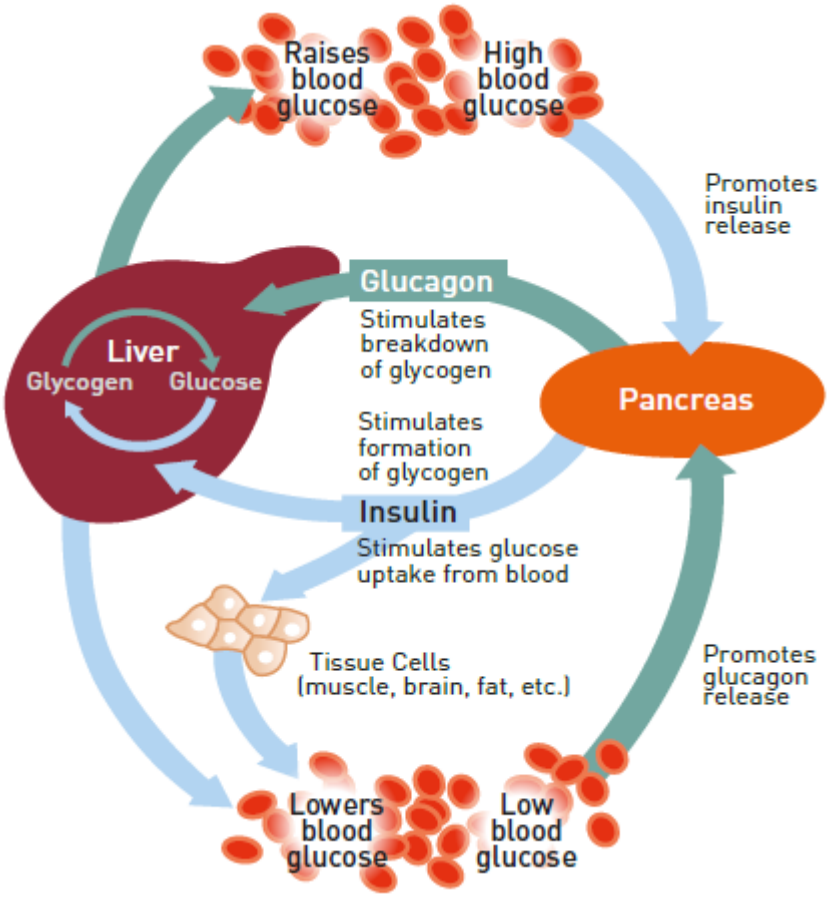

Figure 2.1: Role of pancreas in glucose metabolism [2, p. 27]

If plasma glucose is low, pancreatic response is to release alpha cells that triggers glucagon secretion. Glucagon elevates glucose level by binding to receptors on liver and therefore activating breakdown of glycogen to glucose. [9, p. 217-220]

2.1.3 Medical Aspects of Diabetes Mellitus

Diabetes has two main types, 1 and 2. First, insulin-dependent type 1 diabetes mellitus, usually develops in childhood or in adolescent and is also known as juvenile diabetes. It is mainly caused by autoimmune destruction of beta cells of the pancreas. Beta cells are the only cells that make the hormone insulin that allows glucose to enter the cell, where it is converted into energy. Therefore treatment basically always includes lifelong insulin injections in different combinations. There is no cure for diabetes, at

least yet, discovered and the key component of the treatment is diabetic himself. His daily routine is to act as his own pancreas and, thus, prevent or at least, delay diabetes related complications such as hypoglycemia, hyperglycemia, heart disease, kidney failure, retinopathy, nerve damage, etc. [9, p. 390-430].

The first symptoms of type 1 diabetes mellitus includes increased frequency of urinary, unexplained weight loss, thirst and hunger, all of which are due to too high blood glucose level. Pain in feet, numbness in extremities and blurred vision are usual symptoms also. Severe symptoms are loss of consciousness or severe nausea or even coma. The first assumption is made with mentioned symptoms and it is confirmed usually with plasma glucose measurements. If person's fasting plasma glucose is over 7 mmol/L, he or she most likely have diabetes. Confirmation is done with oral glucose tolerance test (OGTT) that is the most common method to confirm diagnosis of diabetes. In OGTT person ingests 75 grams of glucose and blood sugar is measured two hours after. If glucose is above 11.1 mmol/L, the original assumption is confirmed and person has diabetes. Diagnosis can be also done by measuring person's glycosylated hemoglobin (HbA1c). If HbA1c level is above 6.5 %, person is diagnosed to have diabetes. [4, p. 1; 10, p. 37]

The most common type of diabetes is type 2. It has been estimated that 80-90% of diabetics are type 2 diabetics. It usually occurs in adults due to still unknown reason. Though, there are several important risk factors such as obesity, poor diet, physical inactivity, family history of diabetes, aging, ethnicity, etc. [2, p. 23]

In type 2 diabetes, a person have insulin secretion, but his cells do not use insulin properly. This is called insulin resistance increases. At first, the pancreas secretes more insulin in order to get the glucose into the cells. But, eventually the sugar builds up in blood stream. Type 2 can develop without any of previously mentioned symptoms of type 1 diabetes, but the diagnosis is still done with OGTT or HbA1c measurement. Initial treatment for type 2 is fixing person's diet and exercise, but in some cases insulin boluses are also need. In addition, person can have prediabetes symptoms: impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). These people are at high risk of developing type 2 diabetes, but can prevent it with decreasing saturated fat in food, losing weight 5-10%, daily exercise, etc. [9, p. 455-457]

For type 1 diabetic, treatments first aim is to get enough insulin to cover the basic metabolism so that the cells can use glucose as an energy source. This is done with basal insulin that is usually administered once or twice a day depending on insulin. Figure 2.2 shows the active time of different insulin types. Detemir and glargine are called long-acting insulin and typically used as basal insulin, but also Neutral Protamine Hagedorn (NPH) can be used for same purposes.

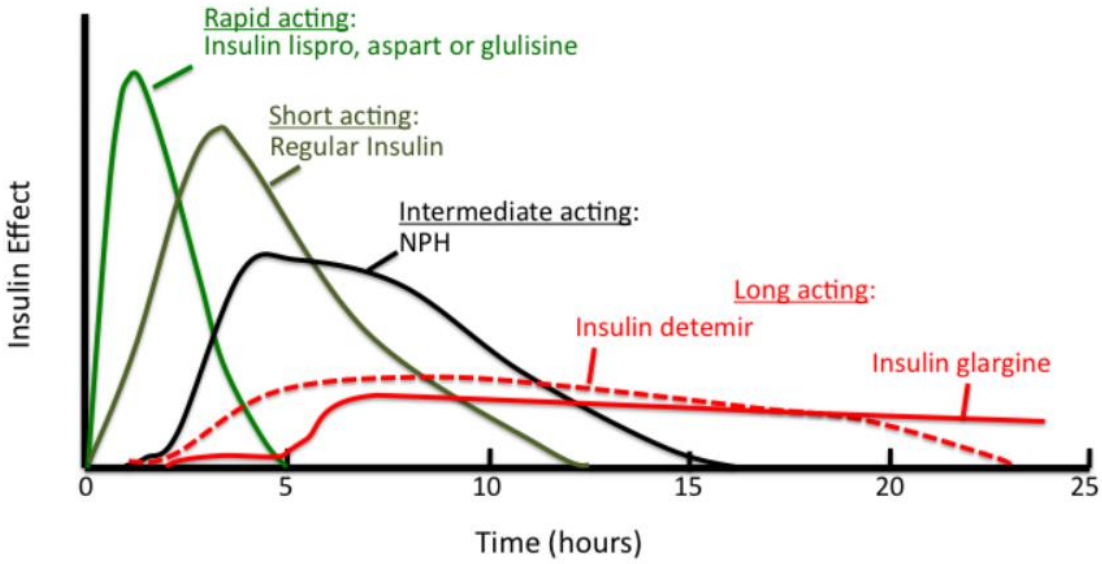

Figure 2.2: Comparison of insulin analog active times [11]

Next aim is to have enough, but not too much, insulin to cover rising plasma glucose level after eating. Nowadays the most common insulin for carbohydrate coverage is rapid-acting insulin such as Aspart, Lispro, etc. Meal time bolus is taken usually 10-20 minutes before eating [12, p. 278-279]. The size of bolus is decided based on the individual's carbohydrate coverage ratio (CHO ratio). It can be calculated as in Equations 2-1, which is also known as 'The Rule of 500'.

$$CHO\ ratio = \frac{500}{TDI} \tag{2-1}$$

where TDI is total daily insulin in international units (IU) and 500 is an average ingested carbohydrates daily. The meal bolus is then calculated as follows:

$$Meal\ Bolus\ = \frac{Total\ grams\ of\ CHO\ in\ the\ meal}{CHO\ ratio} \tag{2-2}$$

In addition to meal bolus, there is a correction bolus. When high plasma glucose is measured, sufficient amount of insulin is administered to scale back the high plasma glucose level. The size of bolus depends on persons insulin sensitivity factor (ISF). It can be calculated with 'The Rule of 1800' as follows:

$$ISF = \frac{1800}{TDI} \tag{2-3}$$

The correction bolus is then

$$Correction\ Bolus = \frac{PG_{measured} - PG_{target}}{ISF} \tag{2-4}$$

where $PG_{measured}$ the measured plasma glucose level and PG_{target} is the target plasma glucose level. Note that both plasma glucose units are now in mg/dl. SI units are mmol/L and the factor from mmol/L to mg/dl is 1/0.055. [13]

Above described are 'rules of thumb' and not intended to be strictly accurate in every situation. Most likely doses need to be modified to meet the individual targets. Also, these are only for rapid-acting insulin and more suitable for type 1 diabetics than type 2. For instance, dawn phenomenon is something that might have to be taken into account when calculating insulin doses. Some persons experience increased plasma glucose in mornings, because liver releases glucose for unknown reasons. One suggested reason is increased level of growth hormone. Anyhow this means that diabetic who experience dawn phenomenon, have to take insulin bolus in morning whether he will eat breakfast or not. In addition, the meal related bolus might need to be injected earlier than usually. [12, p. 293-294]

Another example is the blood glucose level's effect on insulin sensitivity. If blood glucose rises above 12-15 mmol/L, person's insulin sensitivity lowers, thus the person needs more insulin in order to lower the glucose level back to target range. [9, p. 92]

2.1.4 Social and Economic Impact of Diabetes

In past decades diabetes has grown in numbers and the problem is not only in industrialized countries anymore. The economic growth of developing countries have led to increasing numbers of diabetics worldwide and Figure 2.3 shows the global scale of diabetes. IDF has been estimated that people living with diabetes will increase 55 percent by the end of year 2035 which sums up to 592 million diabetic. [2, p. 12]

In Finland, diabetes mellitus is considered as a national disease. The numbers of both type 1 and type 2 diabetes has been growing significantly. From 1997 to 2007 the number of type 1 diabetics has grown 18 percent and the number of type 2 diabetics has grown alarming 77 percent. Small portion of the grown numbers can be explained by increased awareness of disease, thus more persons have been examined to find out if they have diabetes. Yet, undiagnosed diabetes is a common problem in Finland and worldwide. [14]

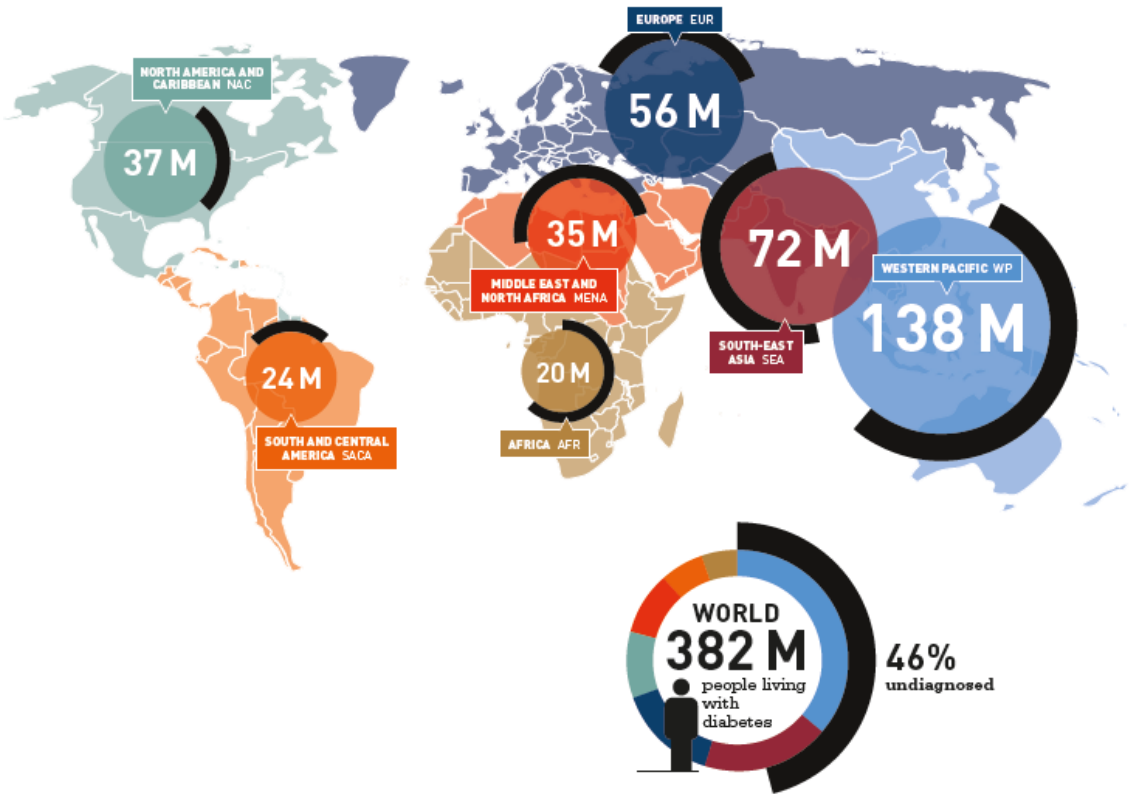

Figure 2.3: People living with diabetes worldwide [2, p. 11]

Diabetes imposes a severe burden on national health systems, countries and individuals and their families. IDF estimates that in 2013, 10.8 percent of total health expenditure worldwide is used to diabetes and all of that is used to treat diabetes not prevent it. The amount of money per diabetic has a huge variety depending where person lives. For instance Norway spent to diabetes healthcare 8 104 € (USD 10 368) per diabetic whereas Somalia and Eritrea spent under 23 € (USD 30). [2, p. 48]

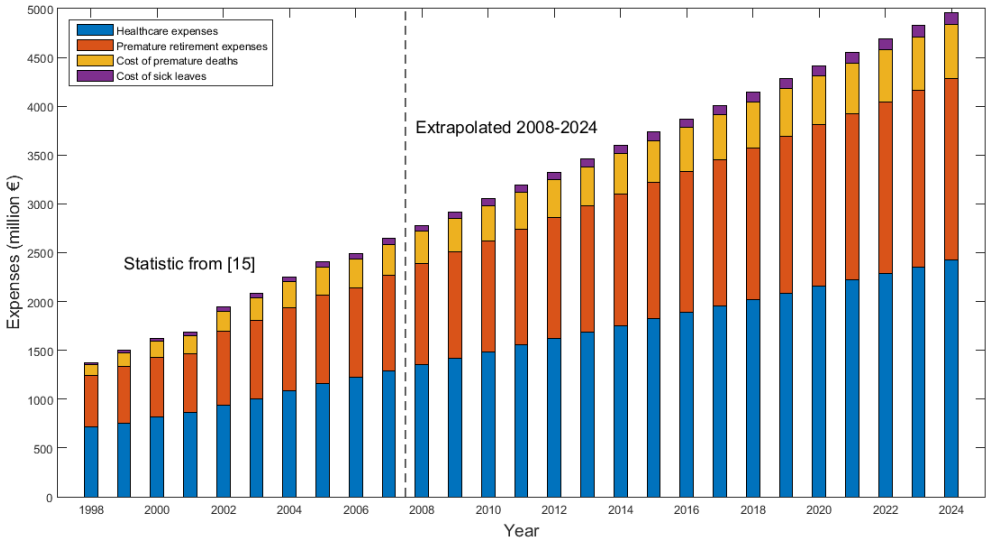

Figure 2.4: Social and economic burden of diabetes in Finland 1998-2007 [15] and estimated continum for 2008-2024.

Figure 2.4 shows the distribution of diabetes expenses in Finland from 1998 to 2024. The largest portions are healthcare and premature retirement expenses that includes loss in man-years and paid pensions. Healthcare cost are mostly diabetes related secondary diseases due to poor diabetes management. Estimations of expenses between 2008 and 2024 is done by linear extrapolation since all four areas had very high linear correlations during the retrospective study done by Jarvala et al. Correlations were 0.9947, 0.9588, 0.9978 and 0.9850 with expenses of healthcare, premature retirement, premature deaths and sick leaves, respectively. In the fit for the cost of premature deaths values before 2004 were extracted since the cause of deaths have been documented only from 1994 and thus, the increase in the start of study was biased. [15]

2.2 Literature Review of Glucose Regulatory System Models

Nowadays diabetes care has progressed towards self-care. Since we all are individuals, one of the most influence aspect of the care is understanding how your body functions. Even though human is very complex system with many unknown variables, different dynamic cause-effect models have been introduced. It has been suggested that modern glucose regulatory system (GRS) models can lead to understanding of pathogenesis and prediction of diabetes mellitus [16].

2.2.1 Minimal Models

Minimal models show the macro-level responses of the system. Those do not include every known substrate or hormone, thus they are insensitive to many micro-level relationships [17]. To understand the glucose system, dynamic data are needed. Therefore quantitative tracer theories has been studied to identify effect of insulin on glucose. Resulting in linear and nonlinear time-variant compartmental models that are shown to be accurate and allowing the use of exponential models to understand the amount of compartments needed to describe the system. Figure 2.5 shows an example of three compartment insulin model from which the compartment 3 controls the basal glucose. [18, p. 1057-1059]

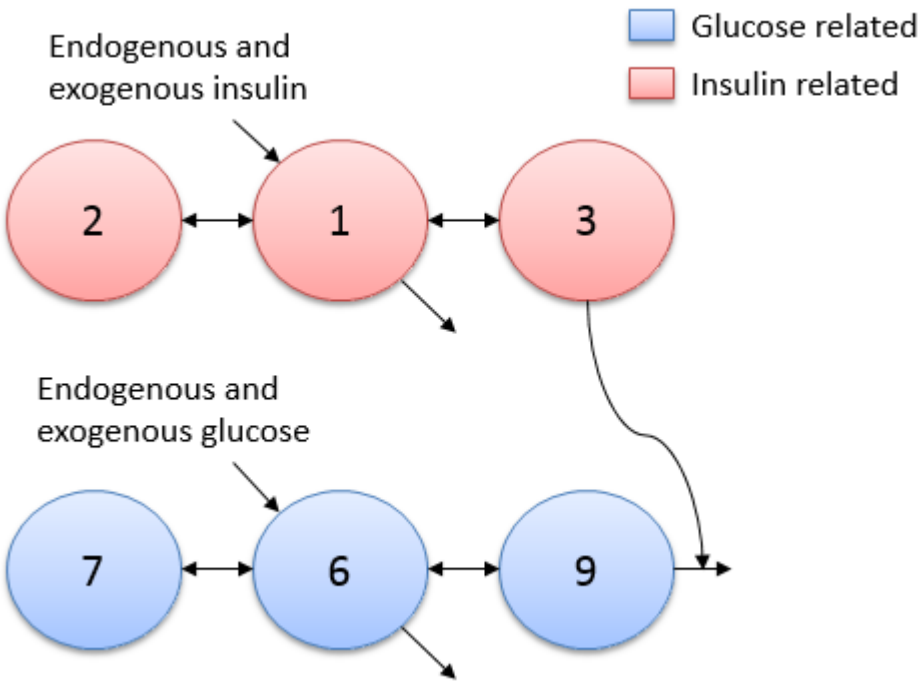

Figure 2.5: Three compartment basal model by P. Insel et al. First three compartments in red are representing the basal insulin model and 6, 7 and 9 in blue the basal glucose model. The insulin mass in compartment 3 controls the glucose loss from compartment 9. Figure is reconstructed from [18, p. 1061].

Later is shown that compartments 1 and 2 can be combined for a single compartment and only a two-compartment model is resolvable after 2-3 minutes of tracer injection [19].

Bergman et al. introduced even simpler model in 1979. This model have been used in clinics to examine body factors such as insulin sensitivity and pancreatic responsiveness; factors that are crucial to understand the etiology of IGT. The problem in making independent measurements of above mentioned factors is the glucose-insulin dynamics and causality of the IGT. As mentioned before the minimum models leaves out feedback loops and therefore it is difficult to hold other aspects of the system constants to isolate the effect of these factors. [20; 21]

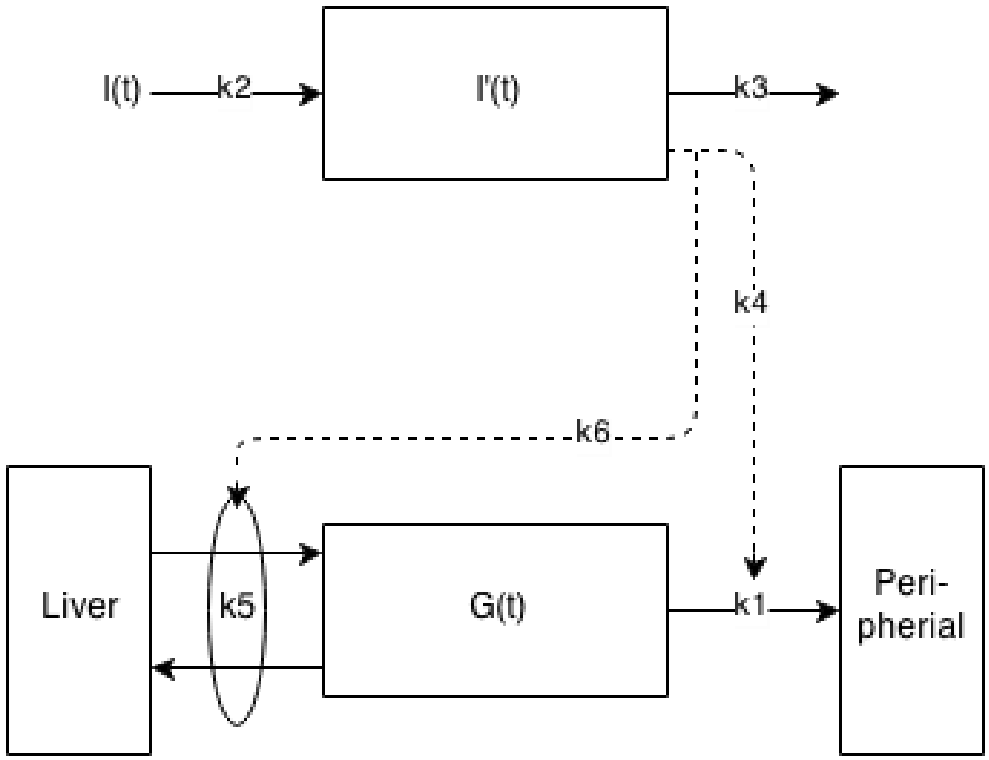

Figure 2.6: Bergman's minimal model 6 that is used to estimate the insulin sensitivity from intravenous glucose tolerance test. Figure was reconstructed from [20, p. 671].

Bergman's study presents seven different glucose-insulin models. Figure 2.6 shows the minimal model which Bergman proved to be the most suitable for estimating the plasma glucose concentration by using plasma insulin as the known input. Parameters are explained in Table 2.1. Model assumes that the remote insulin controls both net hepatic glucose balance and peripheral glucose disposal.

Table 2.1: Symbols and descriptions of variables for Bergman's minimal model shown in Figure 2.6 and presented in Equation 2-5-7.

Symbol	Description	Units
G(t)	Plasma glucose concentration	mg/dl
X(t)	Auxiliary function representing insulin-excitable tissue glucose uptake activity: (k4 + k6) * I'(t)	1/min
I(t)	Insulin concentration	μU/ml
G_0	Basal glucose concentration	mg/dl
I_0	Basal insulin concentration	μU/ml
p_1	Fractional transfer rate: -(k1 + k5)	1/min
p_2	Fractional transfer rate: -k3	1/min
p_3	Fractional transfer rate and conversion factor: (k4 + k6) * k2	$\frac{1/\text{min}^2}{\text{mU/ml}}$
S_I	Insulin sensitivity index	$\frac{1/\text{min}}{\mu\text{U/ml}}$
k1, k2, k3, k4, k5, k6	Constant rate parameters	1/min

The equations of glucose disappearance model are as follows:

$$\frac{dG}{dt} = [p_1 - X] * G(t) - p_1 * G_0 \quad (2\text{-}5)$$

$$\frac{dX}{dt} = p_2 X + p_3 I(t) \quad (2\text{-}6)$$

where the variables are given in Table 2.1.

For individual patient the coefficients of the minimal model are estimates from the intravenous glucose tolerance test (IVGTT) data by allowing the model predict the observed decrease in plasma glucose when the measured plasma insulin is supplied. Insulin sensitivity S_I then is calculated as follows:

$$S_I = \frac{p_3}{p_2} \quad (2\text{-}7)$$

The unit is 1/minute/μIU/ml. Thus, the increase of fractional renal clearance rate of glucose per unit change in the plasma insulin concentration. Although, this approach gives a good estimation of the insulin sensitivity, it is too simple to be an adequate representation of the glucose-insulin system. First, there is no experimental basis that insulin secretion and glucose has a linear relationship. Second, the model does not consider explicitly the complex interactive control of liver glucose production. It has been shown that the model can give negative values for insulin sensitivity in type 2 diabetics [22].

In addition, the model can be used also to estimate insulin secretion responsiveness to glucose both first phase Φ_1 and second phase Φ_2 by predicting the time course of plasma insulin, when above described method is supplied. The first phase insulin release is presented as an insulin bolus entering the plasma compartment at the time of glucose injection. The equation is

$$\Phi_I = \frac{I_0}{n * \Delta G} \quad (2\text{-}8)$$

where I_0 is the first peak of plasma insulin concentration, n is the time constant for insulin disappearance and ΔG is the maximum change in the glucose concentration.

The factor Φ_2 is defined as second phase pancreatic response and is proportional to the degree γ by which glucose exceeds a threshold level h. Thus, insulin secretion can be described by

$$\frac{dI(t)}{dt} = \gamma[G(t) - h] + n * I \quad (2\text{-}9)$$

The model assumes that the rate of rise of second phase is proportional to plasma glucose, thus the second phase responsiveness Φ_2 is the proportionality factor between glucose and the rate of rise. This is also known as minimal model of insulin kinetics. [21]

Bergman and Cobelli have published papers; completing, testing and validating the results of the minimal model [17; 21; 23-26] and in 2009, Cobelli estimated that the minimal model can be found in over one thousand studies [17]. The most important defect in minimal model appears to be the single-compartment representation of the glucose system. According to the American Diabetes Association (ADA) Consensus Development Conference on insulin resistance, minimal model method applied to a frequently sampled IVGTT is one of only two methods that assess peripheral insulin resistance. [27]

2.2.2 Maximal Models

Maximal models are describing the whole glucose regulatory in human body are not generally useful for the quantification of specific metabolic relationships. Their usefulness lies on the system simulation. Most of the models are based on the multi-compartment approach and are challenging to validate against clinical data.

One of the first dynamic glucose regulatory models was Foster's glucose homeostasis model (Figure 2.7). The purpose of the study was to design and experiment new glucose regulatory system in man. It has three subsystems that are plasma glucose, muscle glycogen and liver glycogen of which non-linear relationships were collected from clinical researches found in literature. [28]

The mass balance equation for the model is as follows:

$$\begin{cases} \frac{dGG}{dt} = GLYO + INJ + DIG + LULAC + GLUNEO \\ \quad -GLYS - MU - ATU - NSU - RBCU - U \\ \frac{dGLULIV}{dt} = GLYS - GLYO - GLUB \\ \frac{dPGS}{dt} = MU - PEG - MRLAC \\ \frac{dI}{dt} = ISEC - IDEG \\ \frac{dFFA}{dt} = FFAP - FFAU \\ \frac{dG}{dt} = GSEC - GDEG \end{cases} \quad (2\text{-}10)$$

where the variables can be found in Table 2.2.

Table 2.2: Symbols and descriptions of variables for Foster's glucose regulatory system model that is shown in Figure 2.7 and presented in Equation 2-10.

Abbreviation	Explanation	Unit
ATU	Adipose Tissue Use	mg/min
DIG	Uptake of Glucose from Digestion Rate	mg/min
FFA	Plasma Free Fatty Acid	mg
FFAP	Free Fatty Acid Production Rate	mg/min
FFAU	Free Fatty Acid Utilization Rate	mg/min
G	Plasma Glucagon	µg
GDEG	Glucagon Degradation Rate	µg/min
GG	Plasma Glucose	mg
GLULIV	Liver Glucose	mg
GLUNEO	Gluconeogenesis	mg/min
GLYB	Glucose-6-Phospate Catabolism Rate	mg/min
GLYO	Hepatic Glucose Release	mg/min
GLYS	Hepatic Glucose Phosphorylation	mg/min
GSEC	Glucagon Secretion Rate	µg/min
I	Plasma Insulin	mIU
IDEG	Insulin Degradation Rate	mIU/min
INJ	Intravenous Glucose Infusion Rate	mg/min
ISEC	Insulin Secretion Rate	mIU/min
LULAC	Liver Uptake of Glucose	mg/min
MRLAC	Muscle Release of Lactate	mg/min
MU	Muscle Glucose Uptake Rate	mg/min
NSU	Nervous System Uptake	mg/min
PEG	Muscle Utilization of Glucose for Energy	mg/min
PGS	Peripheral Glucose	mg
RBC'SU	Red Blood Cell Utilization Rate	mg/min
U	Urine Spillage of Glucose	mg/min

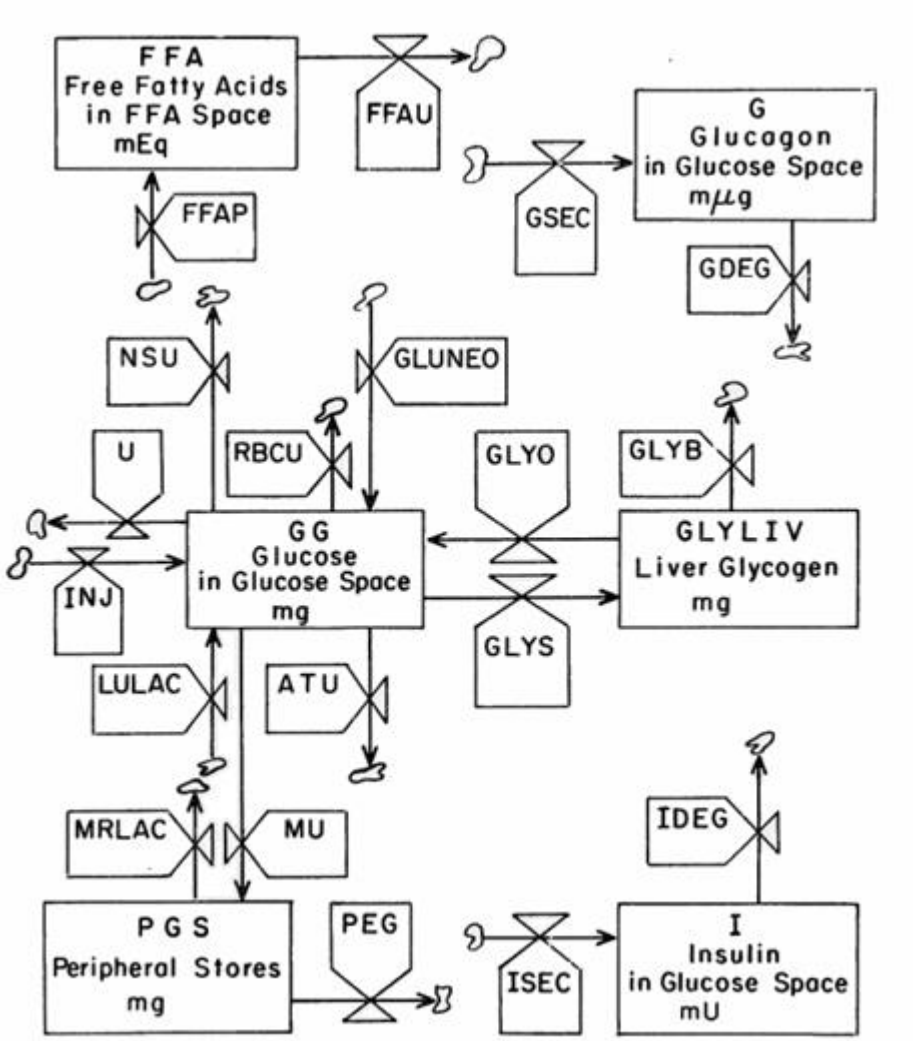

Figure 2.7: Foster's glucose homeostasis model [28, p. 41]. Variables can be found in Table 2.2.

Without going too deeply into the model, it can be said that the unique feature of model is that all the rates are based on the best estimates available from the literature of that era, thus there is no curve-fitting methods used. In addition many of the rates are nonlinear. Model can be used to simulate a human in IVGTT. Also, it performed well in comparison to prediabetes behavior, thus it allows to study different causalities of diabetes. Yet, the model has its down sides. It does not simulate correctly any other response to dynamic stimuli besides IVGTT and its usefulness is therefore limited.

Where Cobelli, Bergman, Foster, etc. [19, 20, 28] concentrated more to compartments and rates between them, Sturis, Li, etc. [29, 31] kept their focus in development of mathematical model that considered the time delays and oscillations in human body. Purpose of these models was to explain the reasons to ultradian oscillation of insulin response, of which are still debated.

In 1991 Sturis et al. [29] developed a parsimonious mathematical model including the major mechanisms involved in glucose regulatory system. The occurrence of insulin and glucose oscillations was found to be dependent on two features: 1.) The time delay

of 30-45 minutes for the effect of insulin on glucose production and 2.) A prolonged effect of insulin dependent glucose utilization. These two characteristics were included in the model, they were able to mimic all the experimental findings such as self-sustained oscillations during constant glucose infusion, postprandial oscillations and increased amplitude of oscillations after increased stimulation of insulin secretion in constant frequency. [29] Later Sturis et al. [30] validated some of their simulated findings with experiments. For instance, it was shown that oscillatory insulin infusion is more efficient in reducing plasma glucose levels than continuous administration. [30]

Li's model has two time delays: insulin response to arise of blood glucose level and endogenous glucose production in liver. Delays were around 6 minutes and 36 minutes, respectively. The results show that both of mentioned delays are necessary for the insulin secretion ultradian oscillation sustainment. In addition, results indicates that endogenous glucose production and related time delay are insignificant in modeling IVGTT. The model can be used to time the insulin injection to the intake of glucose which is one of the key factors in successful insulin therapy. [31; 32]

One can find many good models for one's needs and the list of models could be still continued. The most recognized and sophisticated model was developed by Dalla Man et al. [33] in 2007. Model simulates glucose-insulin response during meal time and in 24-hour glucose-insulin profile and it was constructed from different modules as described in Figure 2.8. [33]

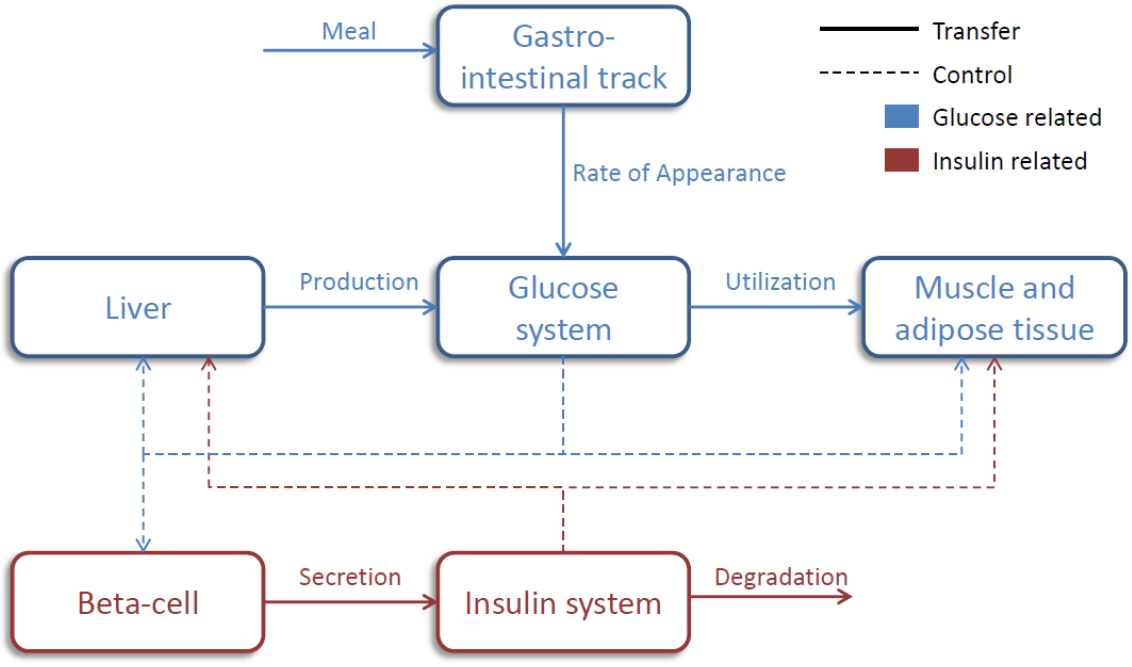

Figure 2.8: Dalla Man et al. glucose regulatory model describing the relations between different subsystems. Glucose related parts are in blue and insulin related in red. Figure was reconstructed from [33, p. 1742].

First subsystem, gastrointestinal track, describes functions of oral glucose absorption. Input to module is an amount of ingested glucose and output is a glucose rate of appearance in plasma. This nonlinear model was tested to perform with good

precision when comparing the results to actual clinical data. Stomach is modeled with two compartments that represent solid and liquid phases, respectively. A single compartment approach is used for gut and a constant rate of intestinal absorption. The relations of model parameters are in Equation 2-11 and the explanations of parameters in Table 2.3. [33; 34]

$$\begin{cases} \frac{dQ_{sto}(t)}{dt} = Q_{sto1}(t) + Q_{sto2}(t) \\ \frac{dQ_{sto1}(t)}{dt} = -k_{gri} * Q_{sto1}(t) + D * d(t) \\ \frac{dQ_{sto2}(t)}{dt} = -k_{empt}(Q_{sto}) * Q_{sto2}(t) + k_{gri} * Q_{sto1}(t) \\ k_{empt}(Q_{sto}) = k_{max} + \frac{k_{max}-k_{min}}{2} * \begin{Bmatrix} tanh[\alpha * (Q_{sto} - b * D)] \\ -tanh[\beta * (Q_{sto} - d * D)] + 2 \end{Bmatrix} \\ \frac{dQ_{gut}(t)}{dt} = -k_{abs} * Q_{gut}(t) + k_{empt}(Q_{sto}) * Q_{sto2}(t) \\ Ra(t) = \frac{f * k_{abs} * Q_{gut}(t)}{BW} \end{cases} \quad (2\text{-}11)$$

The next module describes a glucose system that includes two compartments that describes glucose kinetics. Module's inputs are rate of absorption and endogenous glucose production. Transfer outputs are utilization and when glucose level is above individual threshold limit, renal excretion. Plasma glucose concentration also controls liver glucose production and pancreas beta-cell functions i.e. insulin secretion. Glucose system is divided to two compartments, plasma and tissue glucose. Endogenous glucose production and rate of appearance increases the plasma glucose whereas renal excretion and insulin-independent utilization (glucose uptake by brain and erythrocytes) decreases it. The tissue glucose compartment is related to glucose uptake by muscles and adipose tissue that is controlled with insulin concentration. Between above mentioned two compartments is transfer in both ways depending on individual parameters.

The balance equations are as follows:

$$\begin{cases} \frac{dG_p(t)}{dt} = EGP(t) + Ra(t) - U_{ii}(t) - E(t) - k_1 * G_p(t) + k_2 * G_t(t) \\ \frac{dG_t(t)}{dt} = -U_{id}(t) + k_1 * G_p(t) - k_2 * G_t(t) \\ G(t) = \frac{G_p}{V_G} \end{cases} \quad (2\text{-}12)$$

where parameters are explained in Table 2.3.

Glucose utilization can be divided in two part: insulin-dependent and -independent utilization. Insulin-independent means the part of glucose body needs to keep vital functions going. This basically is constant uptake by brain and erythrocytes. Insulin-dependent glucose is described with Michelis-Menten nonlinear relation as presented by Yki-Jarvinen et al. [35]. Dalla Man et al. obtained similar results which led to following equation:

$$\begin{cases} U_{id}(t) = \frac{V_M(X(t)) * G_t(t)}{K_M(X(t)) + G_t(t)} \\ V_M(X(t)) = V_{m0} + V_{mx} * X(t) \\ K_M(X(t)) = K_{m0} + K_{mx} * X(t) \\ \frac{dX(t)}{dt} = -p_{2U} * X(t) + p_{2U} * (I(t) - I_b) \end{cases} \quad (2\text{-}13)$$

where parameters are explained in Table 2.3. Although, when fitting on clinical data K_{mx} collapsed to zero, thus K_m was not dependent from X any more.

When plasma glucose level exceeds an individual threshold, excretion occurs in kidneys. Process is linearly related with plasma glucose and are modeled as follows:

$$E(t) = \begin{cases} k_{e1} * (G_p(t) - k_{e2}) & if\ G_p(t) > k_{e2} \\ 0 & if\ G_p(t) \leq k_{e2} \end{cases} \quad (2\text{-}14)$$

where parameters are explained in Table 2.3.

Endogenous glucose production happens in liver compartment that is controlled by plasma glucose, plasma insulin and portal vein insulin. Plasma glucose signal and portal vein insulin are direct signals, whereas plasma insulin is delayed. Relations are described as follows:

$$\begin{cases} EGP(t) = k_{p1} - k_{p2} * G_p(t) - k_{p3} * I_d - k_{p4} * I_{po}(t) \\ \frac{dI_1(t)}{dt} = -k_i * (I_1(t) - I(t)) \\ \frac{dI_d(t)}{dt} = -k_i * (I_d(t) - I_1(t)) \end{cases} \quad (2\text{-}15)$$

where parameters are explained in Table 2.3. [33]

Insulin is released from the islets of Langerhans in two phases. The first phase is controlled by plasma glucose levels. Both high plasma glucose concentration and fast increase of plasma glucose trigger the first phase release. Second release is glucose-independent slow release of newly formed vesicles. This two phase insulin secretion is modeled as follows:

$$\begin{cases} S(t) = \gamma * I_{po}(t) \\ \frac{dI_{po}(t)}{dt} = -\gamma * I_{po}(t) + S_{po}(t) \\ S_{po}(t) = \begin{cases} Y(t) + K * \frac{dG(t)}{dt} + S_b & if\ \frac{dG(t)}{dt} > 0 \\ Y(t) + S_b & if\ \frac{dG(t)}{dt} \leq 0 \end{cases} \end{cases} \quad (2\text{-}16)$$

and

$$\frac{dY(t)}{dt} = \begin{cases} -\alpha_s * [Y(t) - \beta_s * (G(t) - h)] & if\ \beta * (G(t) - h) \geq -S_b \\ -\alpha_s * [Y(t) - S_b] & if\ \beta * (G(t) - h) < -S_b \end{cases} \quad (2\text{-}17)$$

where parameters are explained in Table 2.3. [36; 37]

Secreted insulin flows from pancreas through portal vein, from which liver separates most of the insulin. In humans, 80 percent of insulin is extracted during the first liver passage and in addition, the mass of secreted insulin pulse controls the hepatic clearance of insulin [38]. Insulin subsystem is modeled similar two compartment model than glucose. First compartment is to describe liver related actions and second compartment to describe plasma actions. These equations are as follows:

$$\begin{cases} \frac{dI_p(t)}{dt} = -\big(m_1 + m_3(t)\big) * I_l(t) + m_2 * I_p(t) + S(t) \\ \frac{dI_p(t)}{dt} = -(m_2 + m_4) * I_p(t) + m_1 * I_l(t) \\ I(t) = \frac{I_p}{V_I} \end{cases} \tag{2-18}$$

where parameter m_3 is

$$\begin{cases} m_3(t) = \frac{HE(t) * m_1}{1 - HE(t)} \\ HE(t) = -m_5 * S(t) + m_6 \end{cases} \tag{2-19}$$

and other parameters are explained in Table 2.3. [33]

Table 2.3: Explained parameters of Dalla Man et al. healthy state simulator. Time-varying parameters are bolded.

Subsystem	Variable	Unit	Explanation
Gastrointestinal Track	**D**	mg	Ingested glucose
	Ra	mg/kg/min	Glucose rate of appearance in plasma
	Q_{sto}	mg	Total glucose mass in stomach
	Q_{sto1}	mg	Glucose mass in liquid phase
	Q_{sto2}	mg	Glucose mass in liquid phase
	Q_{gut}	mg	Glucose mass in intestines
	BW	kg	Body weight
	k_{max}	1/min	Maximum emptying rate
	k_{min}	1/min	Minimum emptying rate
	k_{abs}	1/min	Intestinal absorption rate
	k_{gri}	1/min	Grinding rate
	f	unitless	Fraction of intestinal absorption which actually happens
	α	1/mg	Rate to minimum
	b	unitless	Percentage of dose for which k_empt decreases
	β	1/mg	Rate to maximum
	d	unitless	Percentage of dose for which k_empt increases
	k_{empt}	1/min	Gastric emptying rate
Glucose System	**G_p**	mg/kg	Glucose mass in plasma and rapidly equilibrating tissues
	G_t	mg/kg	Glucose mass in slowly equilibrating tissues
	Vg	dl/kg	Volume of glucose
	k_1	1/min	Rate parameter
	k_2	1/min	Rate parameter
	U_{ii}	mg/kg/min	Insulin-independent utilization
	F_{cns}	mg/kg/min	Glucose uptake by brain and erythrocytes
Muscle and Adipose Tissue	**U_{id}**	mg/kg/min	Insulin-dependent utilization
	X	pmol/L	Remote insulin in interstitial fluid
	V_m	mg/kg/min	Transport rate
	V_{mx}	mg/kg/min / pmol/L	Maximum transport rate
	K_m	mg/kg	Michaelis constant for glucose disposal
	K_{mx}	mg/kg / pmol/L	Maximum for Michaelis constant, thus peripheral insulin sensitivity
	p_{2u}	1/min	Rate of insulin action on the peripheral glucose utilization
	I_b	pmol/L	Plasma insulin in basal state
Kidney	**E**	mg/kg/min	Renal excretion
	k_{e1}	1/min	Glumerular filtration rate

Subsystem	Variable	Unit	Explanation
	k_{e2}	mg/kg	Renal threshold of glucose
Liver	**EGP**	mg/kg/min	Endogenous glucose production
	I_d	pmol/L	Delayed insulin signal
	I_1	pmol/L	First insulin signal
	I_{po}	mg/kg	Amount of insulin in portal vein
	k_{p1}	mg/kg/min	Extrapolated EGP at zero glucose
	k_{p2}	1/min	Liver glucose effectiveness
	k_{p3}	mg/kg/min / pmol/L	Parameter governing amplitude of insulin action, thus hepatic insulin sensitivity
	k_{p4}	mg/kg/min / pmol/kg	Parameter governing amplitude of portal insulin action
	k_i	1/min	Rate parameter
Beta-cell	**S**	pmol/kg/min	Insulin secretion
	γ	1/min	Transfer rate between portal vein and liver
	Y	pmol/kg/min	Secretion because of high plasma glucose
	K	pmol/kg / mg/dl	Pancreatic responsivity to glucose rate of change
	S_b	pmol/kg/min	Secretion in basal state
	α_s	pmol/kg/min / mg/dl	Delay between plasma glucose and insulin secretion
	β_s	1/min	Pancreatic responsivity to glucose
	h	mg/dl	Threshold level of glucose above beta cells initiate to produce new insulin
Insulin System	**I_p**	pmol/kg	Insulin mass in plasma
	I_l	pmol/kg	Insulin mass in liver
	m_1	1/min	Rate parameter
	m_2	1/min	Rate parameter
	m_3	1/min	Rate parameter
	m_4	1/min	Rate parameter
	m_5	min / kg/pmol	Rate parameter
	m_6	unitless	Rate parameter
	HE	unitless	Hepatic extraction of insulin

Although the above described dynamic model is made to describe the healthy person's glucose-insulin regulatory system, it is also used to describe the IGT, IFG and type 2 diabetic metabolism. Dalla Man et al. [33] not only identified the parameters for both groups, healthy and type 2 diabetic person, but also minimized structural uncertainties of each subsystem. They had a vast data of flux concentrations of 204 subjects during triple tracer meal tolerance test. Data consist ingested carbohydrates, Endogenous Glucose Production (EGP), glucose utilization, insulin secretion, plasma glucose concentration and insulin concentration. These were input and output signals

for four unit process models; liver, beta cell, muscle and adipose tissue, and gastrointestinal track. For instance, liver glucose production was numerically identified using EGP as output and plasma glucose and insulin as known inputs. [33]

The same meal simulation model was later used as basis for UVA/PADOVA type 1 diabetes simulator that is included in the first FDA approved *in silico* population. It consists 300 subjects: 100 adults, 100 adolescent and 100 children, and it can be used for instance, to test the insulin pumps' control algorithms. Model is also a substitute for preclinical trials for certain insulin treatments, including artificial pancreas. [39]

Differences compared to previous model are insulin delivery and glucagon subsystems. Glucagon can be considered as an opposite to insulin. When plasma glucose level is below hypoglycemic limit, glucagon elevates the glucose level. Insulin delivery subsystem model depends on the person's insulin in use. Also, different models can be used to describe the delivery. More detailed description of subcutaneous insulin kinetics in Section 2.2.3.

Even though, above described GRS models explains a wide range of causalities in human glucose metabolism, fully explicit model is yet to discover. For instance, acute psychotic stress have been shown to have effect on glucose regulatory system and more detailed to beta cell function and insulin sensitivity which both links to insulin secretion, usage and storage. A clinical global impression (CGI) was used to evaluate the level of psychological stress. The relation between CGI score and insulin sensitivity is inversely correlated ($r = -0.38$, $P < 0.02$) [40]. Thus, model can have many input signals. Usual signals are meal; time and carbohydrate amount and insulin; time, dose and type. These signals produce the good basis, but as described in Section 1, the glucose-insulin balancing equation has many other variables that should be taken into consideration.

2.2.3 Insulin Delivery Models

Since almost all type 1 diabetics and some of type 2 diabetics are treated with insulin injections, maximal GRS models for those includes a subsystem for exogenous insulin delivery. Insulin therapy for type 1 diabetics aims to mimic the pattern of endogenous insulin secretion present in healthy persons. Yet, human insulin is not commonly used in insulin boluses. This is because of absorption of human insulin from subcutaneous depot is impeded by the formation of hexameric macromolecules and it has been shown that insulin analogues such as insulin lispro has better ability to mimic the physiological pattern of insulin secretion. [41]

Eleven different insulin delivery models were evaluated by M. Wilinska et al. [42]. They assessed multiple uncertainties and used experimental data to validate the physiological feasibility of parameter estimates. Data were collected from subjects with type 1 diabetes whom were treated with continuous subcutaneous insulin infusion with insulin lispro (i.e. rapid acting insulin). Their result suggested that the best representation was multi-compartment model with two insulin delivery channels, fast

and slow. In addition, they had a model which assumed that partition of the injected monomeric insulin associates to form dimmers, and thus a state of equilibrium is reached between those two. [42]

Similar monomeric insulin transport model was also presented by Dalla Man et al. [43]. Approach approximates nonmonomeric and monomeric insulin fractions in a subcutaneous space as follows:

$$\begin{cases} \frac{dI_{sc1}(t)}{dt} = -(k_d + k_{a1}) * I_{sc1}(t) + IRR(t) \\ \frac{dI_{sc2}(t)}{dt} = k_d * I_{sc1}(t) - k_{a2} * I_{sc2}(t) \\ R_i(t) = k_{a1} * I_{sc1}(t) + k_{a2} * I_{sc2}(t) \end{cases} \quad (2\text{-}20)$$

where I_{sc1} and I_{sc2} are the amounts of the nonmonomeric and monomeric insulin, respectively. R_i is the rate of appearance of insulin in plasma, k_d rate constant of insulin dissociation, IRR exogenous insulin infusion rate (i.e. injected insulins as a sum of Dirac delta functions), k_{a1} and k_{a2} rate constants of nonmonomeric and monomeric insulin absorption, respectively. [43]

2.3 System Dynamics

System is commonly considered an assemblage of components and dynamics refers to a situation which changes with time, so system dynamics basically means time-varying behavior of connected components or elements. In this case, dynamics are not just mechanical behavior, but also fluid, electrical, thermal, etc. systems. In system dynamics, the idea is to deal with entire process with all the causalities included. [44]

Human body can be considered to be a system: There are identifiable blocks such as organs that affects each other. Although, it is too complicated still to make a model describing the whole body, models of different subsystems can be constructed and validated against clinical data. For instance, heart's functions can be modeled with system dynamics to explain its flow functions or electric functions or combination of both. Therefore, it is quite evident method for engineers to describe GRS with system dynamics as described in Section 2.2 and in fact, all presented models are dynamic systems.

3. MATERIALS AND METHODS

3.1 Simulation Program

Since there are wide range of programs to build a dynamic system, a questionnaire was made to find the most valuable qualities in simulation software before selecting the actual program. In order to get comprehensive results, the questionnaires participants were from software, engineering, research and management divisions of Quattro Folia Oy. Participants were asked to give a value from 1 to 10 to requirements shown in Table 3.1., and add other possible requirements if needed. Values were used to calculate relative weights in decision matrix.

Table 3.1: Demanded quality and functionality requirements in questionnaire.

Functional requirements	Explanation	Unit
Input/Output interfaces	How compatible the software is with others	Number of supported formats
Wide options for features	How many different functions/apps/add-ons the software offers and how complex they are	Number and complexity of features
Easy to learn for developer	How fast you learn to use the software and how good manuals and instructions you get	Tester's opinion
Good future proofs	Is the development of the software still going	Amount of new versions from preceding 5 years
Low price	Total cost of ownership	Price/User and additional costs
Simple to use and maintain	How good the user interface of software is and how easy is to maintain	Tester's opinion
Performance to support multiple users	How much software needs from central processing unit (CPU), memory, disk space etc.	Simulation time, CPU usage, size of the file, etc.
Modularity	How easy is to add and remove parts from the model	Possibility to build modules
Testing possibilities	How easily the model can be tested and validated	Possibility to run in script, test features, etc.
Other	Additional requirement that have not been mentioned	

In order to satisfy the internal customer needs, quality function deployment was used to analyze results. Simplified version of house of quality matrix was build. Requirements of software were analyzed depending on the measurable unit of the requirement. All values were originally between zero to five or normalized to that

range. The values were used in decision matrix to calculate the relative weighted results. Table 3.2 shows the described decision matrix.

Table 3.2: Decision matrix for simulation program evaluation

Demanded quality and Functional requirements	Relative Weight	Weight	Simulation software			
			1	2	3	4
List of internal customer needs	%	Values 1-10	Normalized values 0-5			
		Weighted Result	Sum	Sum	Sum	Sum
		Relative Weighted Result	%	%	%	%

The evaluated simulation programs were MathWorks – Simulink 2014a, Ventana Systems – Vensim PLE 6.3, Simantics System Dynamics 1.8 and Powersim software – Powersim Studio 9 Demo. Although, the programs are popular amongst system dynamics, their functionalities, user-interfaces, designed use, modelling methodology, etc. vary. Thus, the software meeting Quattro Folia's internal customer needs and quality management requirements could be found.

In order to get realistic understanding about the simulation programs, minimal GRS model was built with each software before starting to construct the whole body model. Two requirements were purely based on tester's opinion; is the software easy to learn and simple to use? In addition, the complexity of features and testing possibilities were also partly evaluated by tester.

3.2 Dynamic GRS Model

3.2.1 General GRS Model

Based on literature review, the most suitable dynamic GRS model for Quattro Folia's indented use was selected. The model was built with the simulation program that got the best overall weighted result. Model was constructed for healthy, type 1 and type 2 diabetic person. All model's subsystems were validated against clinical data found in literature. More about validation process in Section 3.2.2. The validated subsystems then were combined in to whole body system. Additional functionalities were also introduced based on physiological needs. For instance, in beta-cell function module a gain block for remaining insulin production was added in order to get comprehensive results.

Since diabetics are treated with wide range of therapies, the constructed model included also choices at least to the most common therapies. Therefore, alternative modules for insulin pump and multiple daily injection (MDI) therapy were built in to model. This also meant the implementation of an insulin delivery subsystem.

3.2.2 Materials for GRS Model Validation

Validation of general healthy person model was done against clinical data found in literature. Each subsystems output was compared to results from Dalla Man et al. [33], where a mixed meal containing 1 ± 0.02 g/kg (x ± SD) of glucose was given to 204 normal subjects with body weight of 78 ± 1 kg. They measured and estimated various fluxes to obtain model-independent results. [33]

In particular, each average flux profile; plasma glucose, insulin, EGP, glucose rate of appearance, glucose utilization and insulin secretion profiles were compared with the simulated results that undergo the same experimental scenario. Thus, 78g of CHO was ingested at t = 0 and simulated fluxes were recorded for the next 7 hours. Root mean square error (RMSE) and Pearson correlation coefficient (R) were calculated.

For insulin delivery subsystem, the validation was done against clinical data from Wilinska et al. [42]. They measured plasma insulin concentration from 7 type 1 diabetic subjects every 30 minutes after 40g CHO ingestion and injection of individually calculated insulin bolus. The continuous insulin infusion rate was 0.86 ± 0.27 IU/h and the bolus prior to the meal was 5.95 ± 2.37 IU. Measured insulin concentration was compared to simulated results by calculating RMSE and correlation from 12-hour period. [42]

3.2.3 Pilot Data and Individual GRS Model

A type 1 diabetic did two 7-day pilots. During this period subject had two continuous glucose monitors (CGM); Dexcom G4 and Medtronic MiniMed Paradigm Veo. Later is a system which includes insulin pump, sensor and MiniLink transmitter that sends the information from sensor to insulin pump. However, CGM was not used to control the insulin pump and thus, the system was not closed-loop insulin delivery system. CGM could only cut off insulin delivery for 2 hours if glucose value was under a preset value. Subject reported also blood glucose measurements from fingertip that were used for CGM calibrations, meals (carbohydrates ingested) and exercises (duration and level) to Quattro Folia's cloud-based personal health record archive.

Both weeks were analyzed as an individual events. Figure 3.1 shows the collected data; blood glucose values in gray, meals in yellow, insulin in green and exercise in orange. In terms of system dynamics and machine learning, the first six days were training data and the last day was test data.

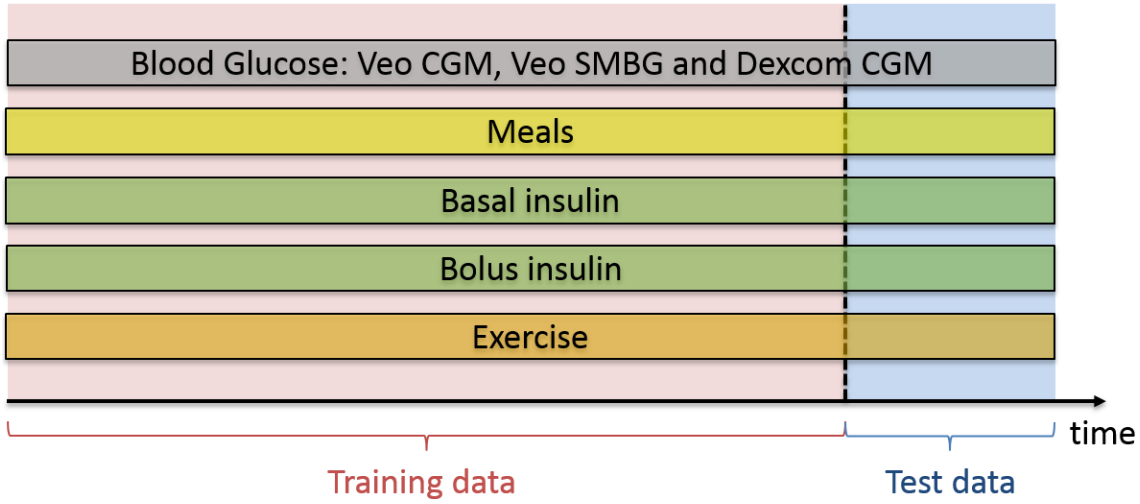

Figure 3.1: Data collected from a week pilot period. Dashed line represents the division to training and test data. Glucose values include continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG) values.

The population based GRS model's parameters were found in literature. They are only averages from previous studies and therefore some of them were individually updated. For instance, the insulin-to-carbohydrate ratio was calculated with the Rule of 500 presented in Chapter 2 Equation 2-1.

Complexity of model affected parameter identification. Since our pilot data were collected from routine everyday life, it did not include values such as plasma insulin concentration, EGP, etc. Therefore, unit process model and forcing function strategy for parameter identification could not be used. Other options such as linearization of the problem was discussed with Professor Matti Vilkko from Department of Automation Science and Engineering at Tampere University of Technology, but the conclusion was that the complexity of model made it impossible without further studies with system dynamics. To give an idea of the complexity, a model of an automatic transmission controller for vehicle consists of 1 differential equation, 9 algebraic equations and 6 parameters [45], where the selected combination of models consists of 16 differential equations, 14 algebraic equations and 47 parameters.

First, the basal level was approximated to correspond with the subject's basal level. An independent algorithm estimated the base level of the subject's blood glucose and then set the parameter k_{p1} in EGP subsystem to correspond the subject's basal level.

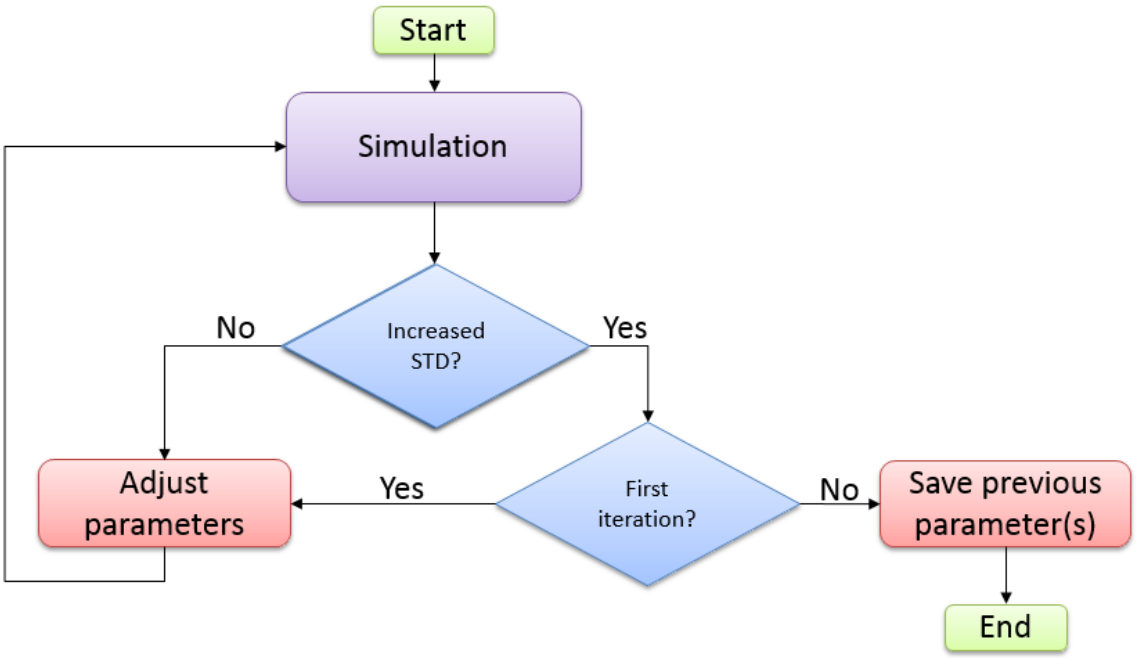

Figure 3.2: Decision chart of adaptive parameter identification algorithm for steady state

The parameter identification to find the steady state was made with fine tuning with simple algorithm and repeated simulations as described in Figure 3.2. All the input parameters were constant during the following method. First, the reference standard deviation (SD) was calculated. Next, the basal levels of the following parameters; I_l, I_p, I_{con}, G_p, G_t, EGP, I_{sc1} and I_{sc2} were adjusted, and then the previous SD was compared to the latest results. If SD was reduced, values were adjusted again and another simulation was made. This was repeated until the SD was same or greater as previous and then the previous parameters were saved. If the first calculated SD was increased, the starting values were adjusted to another direction and the best fitting value was identified with same procedure.

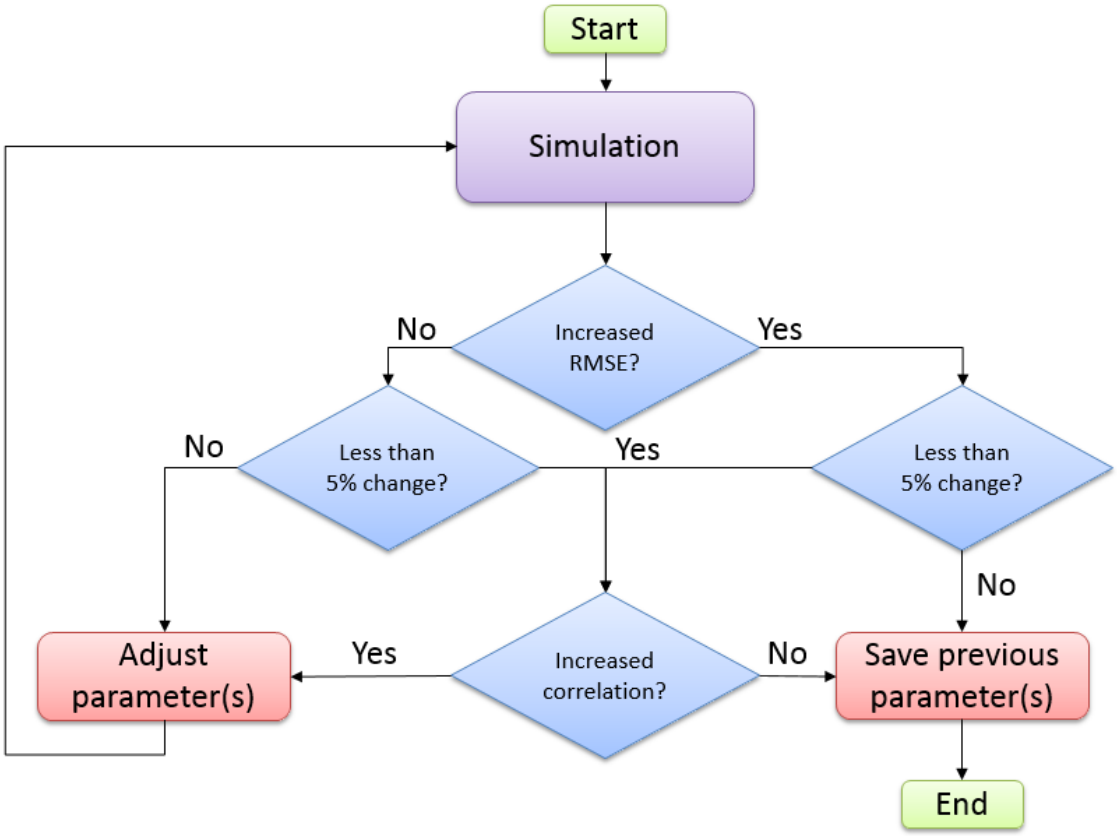

Figure 3.3: Decision chart of adaptive parameter identification algorithm for any parameter or parameters.

Similar adaptive parameter identification algorithm as the algorithm for steady state was used to adjust any parameter or parameters. Figure 3.3 shows the algorithm's decision chart. First, the reference RMSE and correlation were calculated. Next, the parameter was adjusted, and then the previous RMSE and sometimes correlation were compared to the latest results. If RMSE was reduced, values were adjusted again and another simulation was made. This was repeated until the RMSE was greater and then the previous parameters were saved. If the first calculated RMSE was increased, the starting values were adjusted to another direction and the best fitting value was identified with same procedure. In addition, if the improvement in RMSE was not significant, the correlation was also evaluated. Based on the change in correlation, parameters were adjusted again or previous parameters were saved.

Insulin related actions were adjusted with four measurable parameters; amplitude, onset time, peak time and duration. The last three are parameters which averages insulin manufacturers report but can vary between users. Amplitude was used to adjust hepatic and peripheral insulin sensitivity, k_{p3} and V_{mx}, respectively. Onset time was sought with independent algorithm which calculated difference between time of administered insulin and time when glucose change rate went to negative. This was done in sections where bolus was taken to correct too high blood glucose and there was no upcoming meals. When bolus and meal were timed at the same time, the peak time of insulin bolus was analyzed with an algorithm that identified the peak from CGM data and sought

matching peak from simulated blood glucose data. The time differences between these peaks were used to adjust the insulin peak time. Last, the insulin duration was adjusted to match the active time of insulin bolus, thus the time when glucose change rate was close to zero after the peak. Average insulin active times can be also found in Figure 2.2.

Since above represented algorithms are based on correlation and RMSE, the simulation output fit to CGM data was evaluated with R to RMSE ratio that was designed to be used in this study only. Higher the ratio was, better the fit was. This also proofs the concept of algorithms, if parameter identifications steps are improving the training accuracy. Ratio was only use to compare simulation steps.

4. RESULTS

4.1 Comparison of Simulation Programs

Figure 4.1 shows the minimal GRS model build with Simulink 2014b Academic license. The model had to be constructed from single blocks such as integrator, thus it was logical to build the model from equations, but at the same time understanding of causalities between compartments got more difficult to perceive.

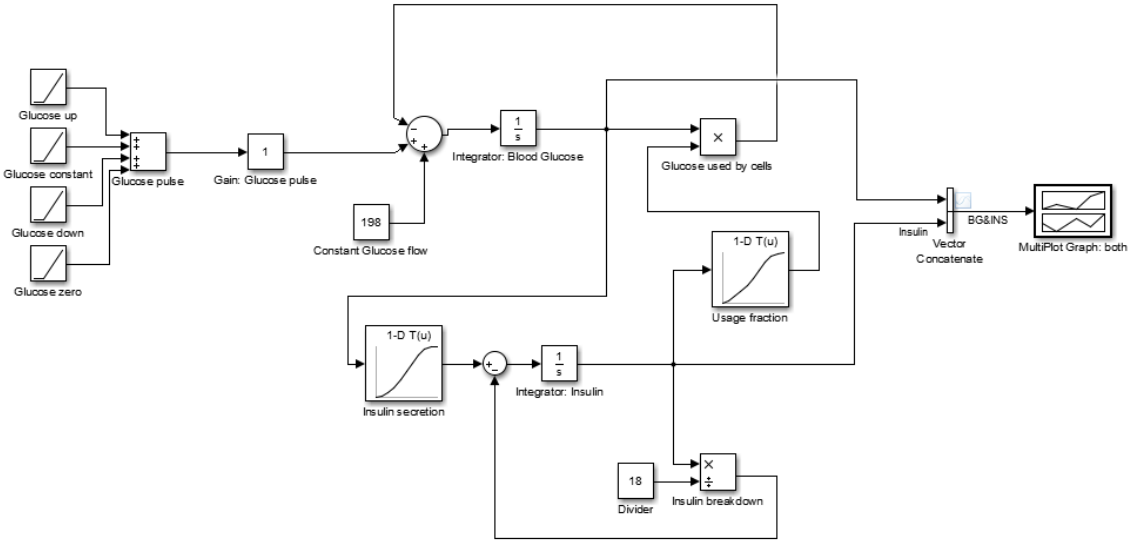

Figure 4.1: Simple glucose regulatory system model build with Simulink

Simulink's manuals, instructions and helps are well documented and they were easy to understand. Because Simulink is widely used, instructional sites and video tutorials can also be found. Simulink could not be used without MATLAB and this offered multiple opportunities: Different input and output formats were supported; the simulation could be run in script, thus testing, multiple user support and modularity were improved.

MathWorks have released a new version of MATLAB and Simulink twice-a-year and there has been significant improvements included. For instance, in 2014b version has been implemented a simulation data inspector which enabled the recording of different signals between the simulations. Therefore, it was easy to compare the signals when developing the model functionalities and modules.

As mentioned above, Simulink is a MATLAB add-on, therefore the price of Simulink includes also MATLAB's price. In addition, Simulink product family includes add-ons also for real-time simulation, testing, verification, validation, etc. These are individually sold extras that are not included the evaluated price.

Second tested simulation software was Ventana Systems Vensim PLE 6.3. Program was easy to use and the minimal GRS model was fast to build. Figure 4.2 shows the model from which the causalities of GRS are simple to understand. The user interface was simple and required only a little time to understand.

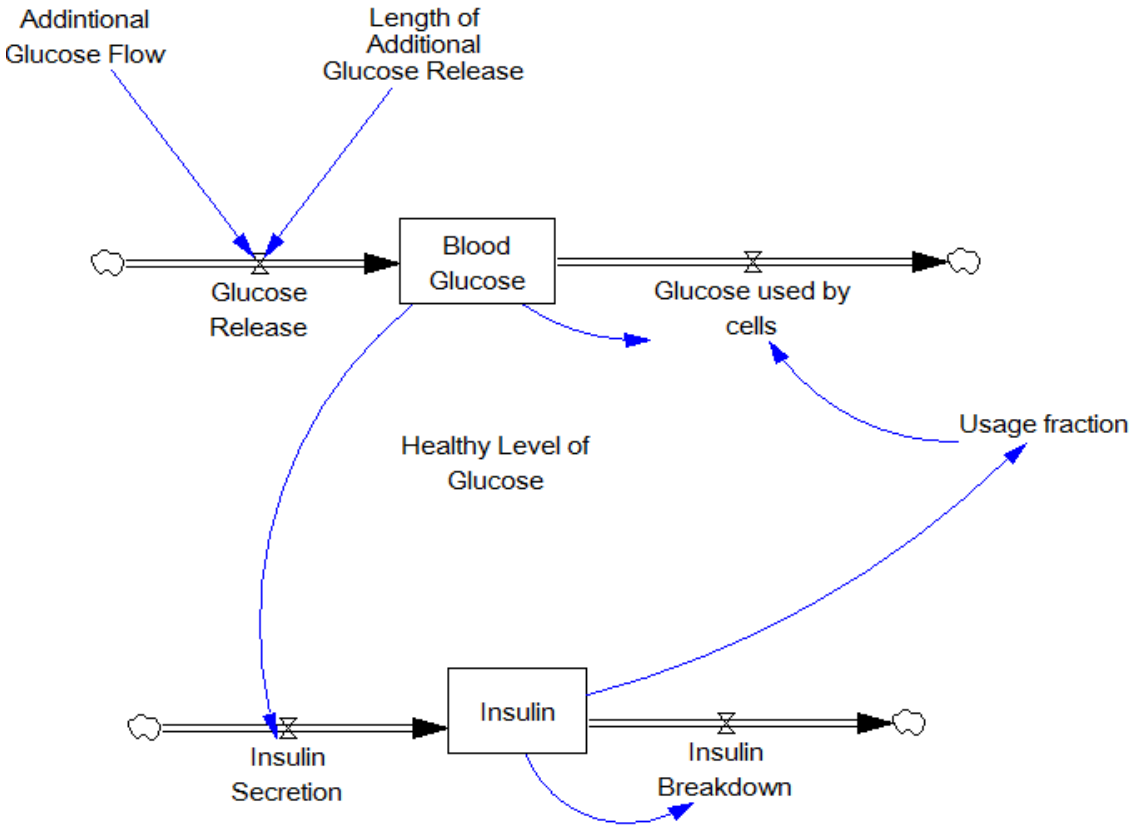

Figure 4.2: Simple glucose regulatory system model build with Vensim

Import and export formats were limited, thus interfaces with other programs was poor compared to Simulink. Although, worth mentioning is that commercial license offered better data connectivity. Ventana Systems has only released four version from preceding 5 years and there has not been any major improvements. Model could not be run in script or loop which made it hard to test and especially, would have made it hard to implement the model for multiple users. Also, there was no possibility to build individual modules. Although, the tested software was a free version, it lacked significantly in needed requirements.

Next tested software was Simantics which is an open platform for modelling and simulations. Its performance should be excellent with data triple engine on the server side. At the same time it was developed to be scalable and reliable which were definitely an advantages for Quattro Folia's planned use of the model. The build GRS model in Figure 4.3 resembles the model build with Vensim in Figure 4.2, thus the modelling view and structures are similar to Vensim. Yet, Simantics was not as easy to learn and simplicity of the program was the worst of all four. For instance, the end-user wiki was clumsy to use and it took a lot of time to start to build the actual model. If

compared to Simulink which was also hard to get into, the manuals and instructions of Simantics were not as explicit as in Simulink.

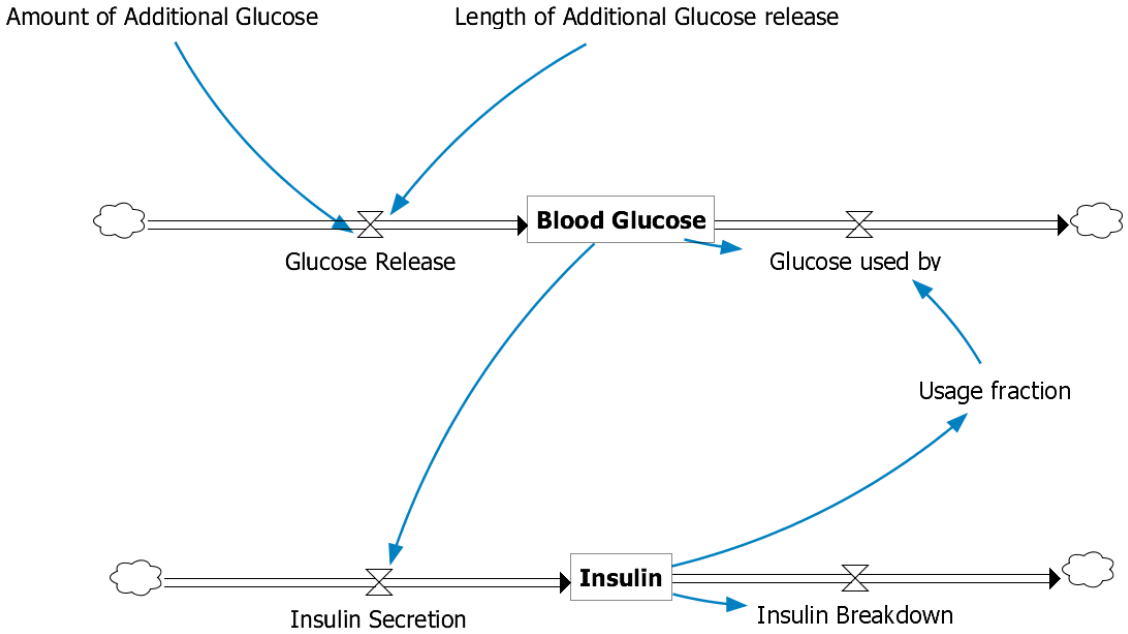

Figure 4.3: Simple glucose regulatory system model build with Simantics

The amount of features was low in Simantics and testing features or possibility to run in a script were missing. Also the modularity and compatibility to other programs or formats were weak. The best thing in Simantics was the price. It was free. This also raises questions about the future developments and certainty of the new versions or updates. Nevertheless, if software is stable already and its functionalities are meeting the Quattro Folia's needs, it could be used years even without updates.

The last tested simulation software was Powersim Studio 9 Demo which user interface was quite pleasant. It was easy to get into and the basic features were simple to find. The build model shown in Figure 4.4 looks similar to Vensim and Simantics. Unlike other programs, Powersim offered possibility to the build model as equations which was a great way for understanding system dynamics and validating that the built model was as it was in equations.

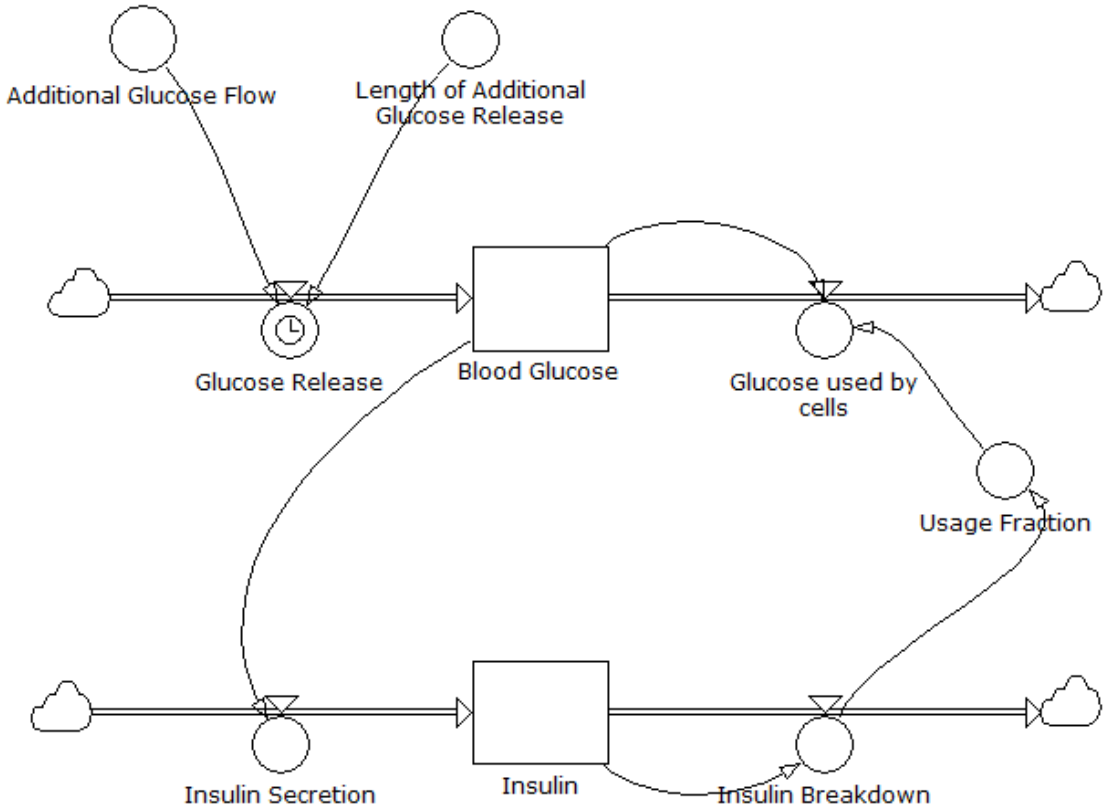

Figure 4.4: Simple glucose regulatory system model build with Powersim

But as Vensim and Simantics, Powersim lacked in amount of supported formats and its testing possibilities and multiple user support were weak, thus it did not have possibility to run in script nor it could be exported to other programs as an independent function or block. Also, Powersim was the most expensive program of these four and it has not have as many new releases or updates from preceding 5 years as has others.

Table 4.1: Decision matrix for evaluating simulation programs. Weights are calculated according to the results of questionnaire. Bolded values are the best in each row. *Row values are normalized between 0-5.

Demanded quality and Functional requirements	Relative Weight	Weight	Simulation software			
			Simulink	Vensim	Simantics	Powersim
Input/Output interfaces*	10.43	6.80	**5.0**	0.2	0.0	0.4
Wide options for features	10.12	6.60	**5.0**	2.5	0.0	2.5
Easy to learn for developer	9.82	6.40	1.0	**5.0**	4.0	4.0
Good future proofs*	11.66	7.60	**5.0**	0.7	2.1	0.0
Low price*	11.96	7.80	0.0	0.0	**5.0**	0.0
Simple to use and maintain	10.12	6.60	2.0	**3.0**	1.0	**3.0**
Performance to support simultaneous users*	10.43	6.80	**5.0**	0.5	0.0	0.0
Modularity	12.88	8.40	2.0	**3.0**	**3.0**	**3.0**
Testing possibilities	12.58	8.20	**5.0**	2.0	1.0	3.0
		Weight	**216.4**	120.4	120.9	114.3
		Relative Weight	**37.83**	21.05	21.13	19.99

Table 4.1 shows the results of decision matrix. Simulink was superior at input/output interfaces and multiple user support. It offered wide range of import and export options and possibility to run in script makes testing possibilities simpler. Also options for features, future proofs and testing possibilities were better than in other evaluated programs. Furthermore, Simulink had the highest relative weight.

4.2 General Dynamic GRS Model

The general GRS model was selected based on literature review. One model was superior in terms of validation. Dalla Man et al. [33] used wide range of flux data to parameter identification. As mentioned in Section 2.2.2, they had data from 204 subjects and the unit process model consist four compartments; liver, gastrointestinal track, muscle and adipose tissue and beta cell. Model was also used basis for the first Food and Drug Administration (FDA) approved *in silico* population. Therefore, the first build model was same as shown in Figure 2.7 and described in Equations 2-11 to 2-19.

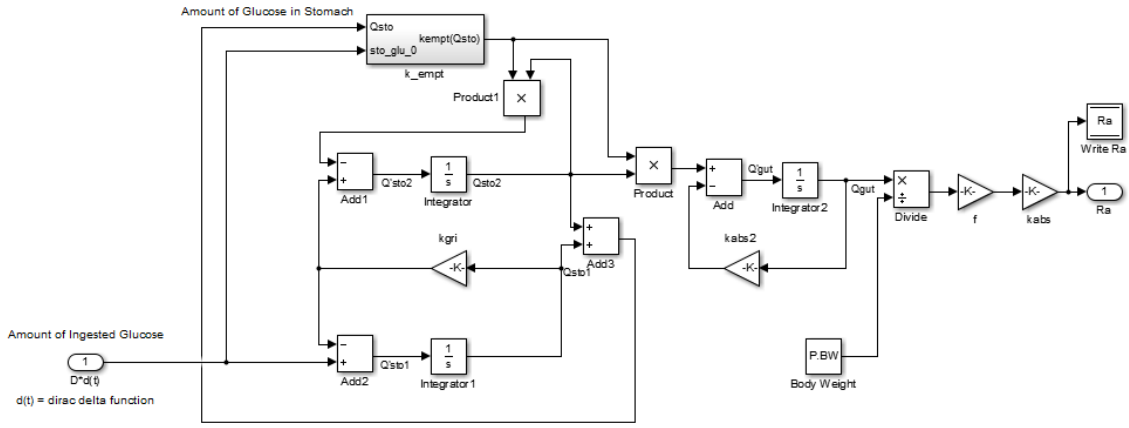

Figure 4.5: Gastro-intestinal track subsystem modeled with Simulink and described in Equation 2-11. Gray block, k_empt, is another subsystem that describes the nonlinear function of gastric emptying.

For the sake of space, here is only shown one example how the subsystems are modeled with Simulink. Figure 4.5 shows how the dynamic Equation 2-11 is represented in Simulink. Input signal is the amount of ingested glucose D at time t. After various grinding and absorption processes in stomach and guts the subsystem output, glucose rate of appearance in plasma, is generated and added to plasma glucose compartment in glucose subsystem. Above described subsystem is the gastrointestinal track in Figure 4.8.

Validation was done against clinical data and Figure 4.6 shows the results from literature compared to the model's subsystem outputs. The gray are represents mean ± 1 standard deviation (STD) and as can be seen in the Figure, the inter-subject variability is high especially in plasma insulin concentration and in endogenous glucose production.

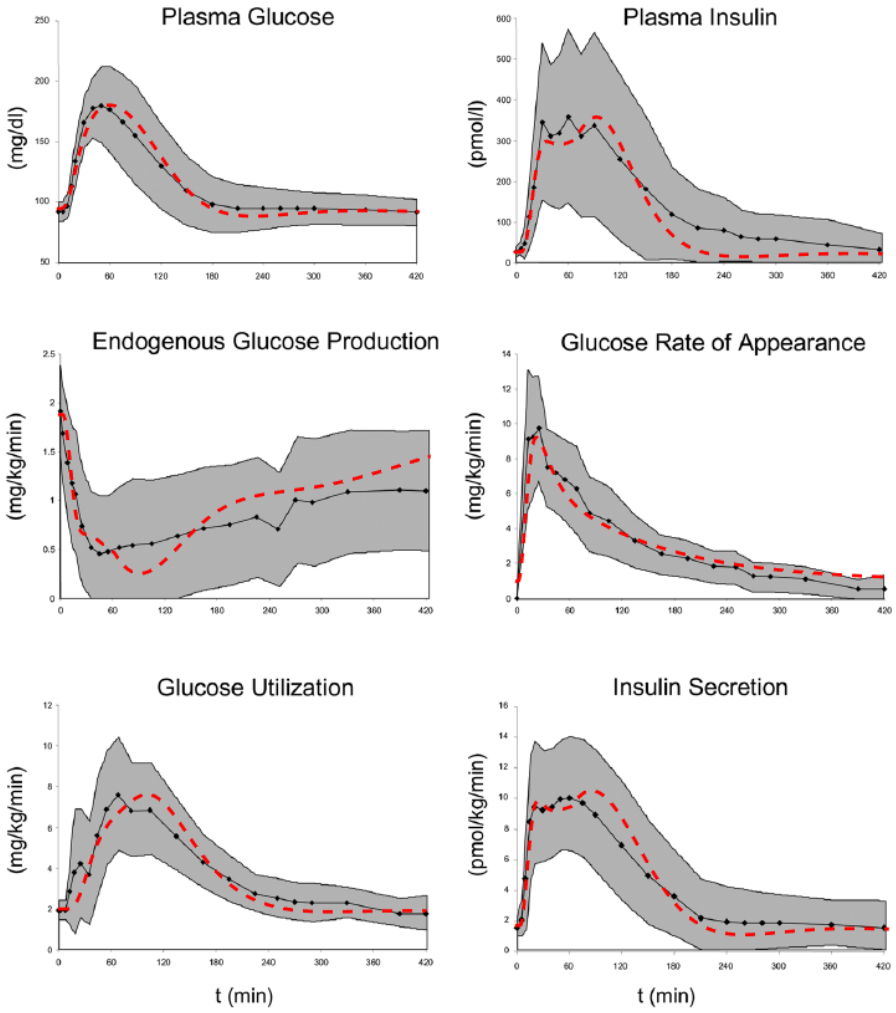

Figure 4.6: Simulation data (in red) superimposed on clinical data from 204 subjects (gray area represents mean ± 1 STD range). [33, p. 1741]

Error with the clinical averages and simulated data is shown in Table 4.2. RMSE is relatively small and correlations are very high in each of the six examined signals. Here, plasma glucose unit is now in mg/dl in order to compare the results and superimpose the figure. Later, the plasma glucose unit is changed to mmol/L that is the SI unit.

Table 4.2: Root mean square error (RMSE) and correlation (R) between simulated and clinical average data from [33].

Signal (unit)	RMSE	R
Plasma Glucose (mg/dl)	6.46	0.99
Plasma Insulin (pmol/L)	54.18	0.97
EGP (mg/kg/min)	0.90	0.95
Rate of Appearance (mg/kg/min)	1.33	0.81
Glucose Utilization (mg/kg/min)	0.32	0.86
Insulin Secretion (pmol/kg/min)	0.97	0.97

The same GRS model be used to describe those type 2 diabetics who do not use additional insulin. Average parameters are in Appendix I. For insulin treated diabetics, an insulin delivery subsystem had to be included. Here, a two-compartment subcutaneous insulin transport model described in Equation 2-20, was used, because the parameter identification was done with a largest amount of subjects, thus statistically it was the most relevant. In addition, insulin injection had three options: bolus, basal or continuous insulin infusion via insulin pump. Yet, the option with insulin pump only enabled open-loop and not closed-loop control algorithm. Thus, there was no feedback loop to control the insulin pump's insulin delivery. In addition, the remaining insulin production can be adjusted, but with type 1 diabetics it is usually zero.

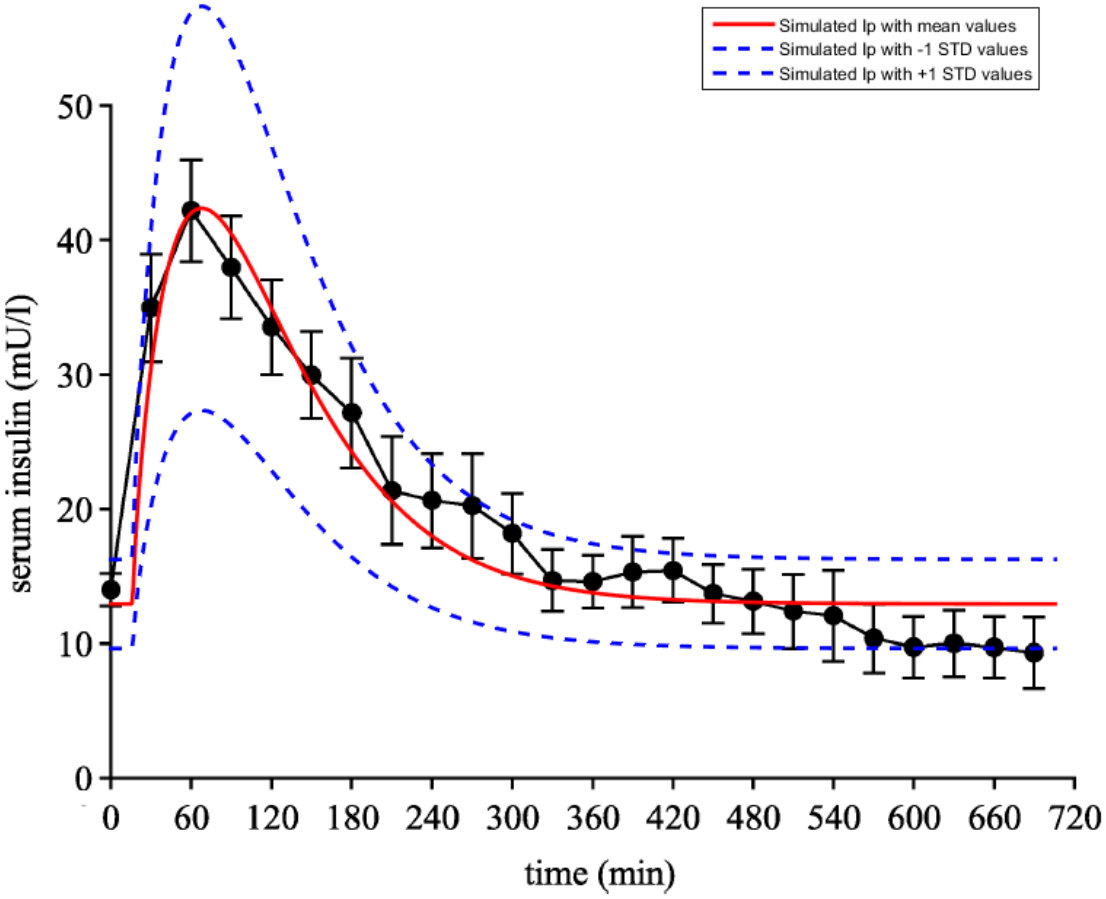

Figure 4.7: Simulation data superimposed on clinical plasma insulin (Ip) concentration from 7 type 1 diabetic subjects. Black circles are mean values with ±1 STD. [42, p. 7]

Insulin delivery model was also validated against clinical data. Figure 4.7 shows the comparison with plasma insulin concentration after the meal and simulated insulin concentration (in red) with the same ingested CHO and injected bolus. In addition, simulation was also done with ±1 STD error in continuous insulin infusion and prandial bolus. These are plotted in dashed blue line. RMSE and correlation between simulated and clinical average data were 41.21 pmol/L and 0.97, respectively.

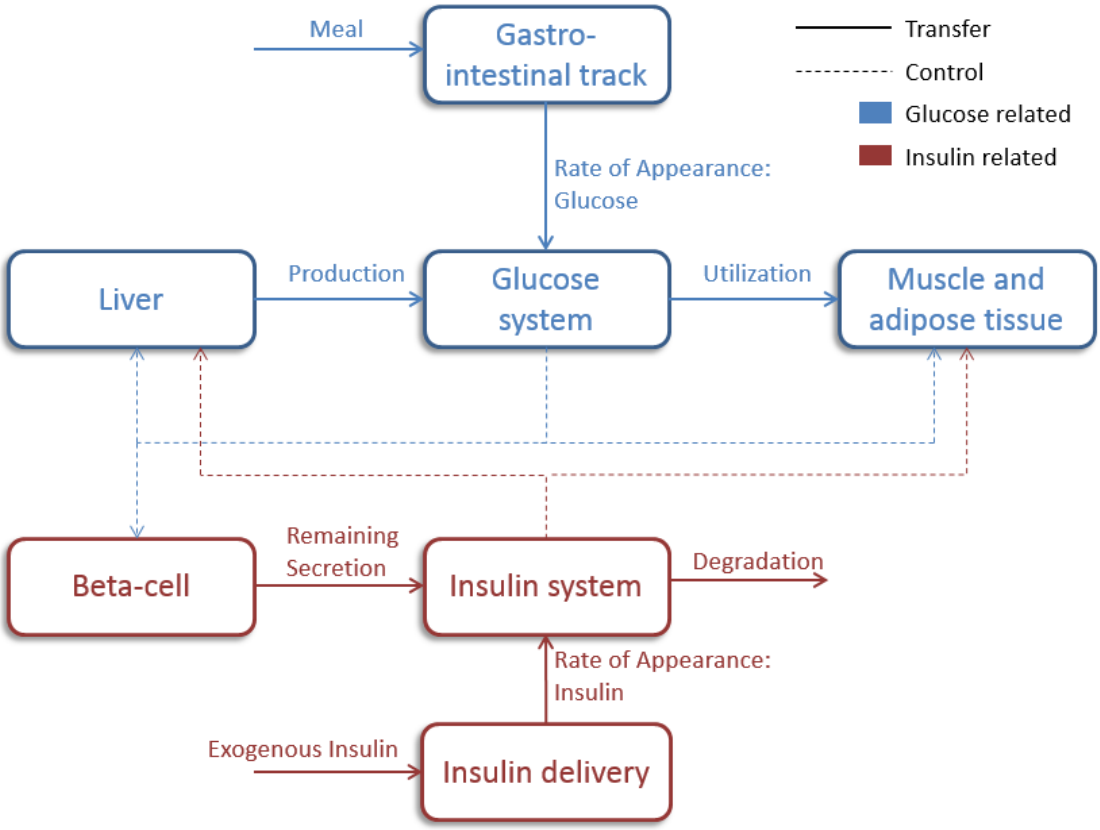

Figure 4.8: Dalla Man et al. glucose regulatory model with the insulin delivery model added. Glucose related parts are in blue and insulin related in red.

All validated subsystems were combined to the GRS model that is shown in Figure 4.8 which is similar to Figure 2.8. Difference is an insulin delivery subsystem. Transfer and controlling signals are marked in solid and dashed lines, respectively. Red represents insulin related actions and blue glucose related. The exogenous insulin input with insulin pump is a sum of continuous insulin infusion and boluses. For MDI therapy, the exogenous insulin has two signals; one for basal and one for bolus injections. Both of the signals depends on the type of administered insulin, thus the onset, peak and acting time can be adjusted.

4.3 Individual GRS Model and Parameter Identification

Collected data from pilot weeks 1 and 2 to consist; 20 and 14 meals, 36 and 33 bolus, and 34 and 28 SMBG measurements, respectively. RMSE and correlation of two glucose profiles; mean of CGMs and simulated blood glucose, are shown in Table 4.3 and includes training and test results for both of the individual pilot weeks.

Table 4.3: Simulation error and correlation for two independent pilot weeks. Weeks are divided into training (1st-6th day) and test data (7th day).

Simulation	Week 1				Week 2			
	Train		Test		Train		Test	
	RMSE (mmol/L)	R	RMSE (mmol/L)	R	RMSE (mmol/L)	R	RMSE (mmol/L)	R
Original	7.716	0.170	9.066	-0.173	9.360	0.019	10.559	0.418
1	4.683	0.195	5.507	0.060	5.457	-0.010	5.216	0.560
2	4.380	0.204	3.630	0.306	4.786	-0.028	3.727	0.466
3	4.229	0.220	3.964	0.293	4.389	-0.044	2.825	0.446
4	4.141	0.226	3.311	0.277	4.715	0.011	2.593	0.587
5	3.992	0.245	3.542	0.185	4.612	0.003	2.604	0.571
6	3.744	0.285	3.640	0.241	4.520	0.019	2.631	0.527
7	3.646	0.285	2.809	0.292	4.322	0.011	2.761	0.587

Figures 4.9 and 4.10 shows model input parameters and simulated blood glucose (simBG) in time. Input parameters were meals, bolus and basal insulins. Note that ingested carbohydrates are divided by 10 to fit the values in the same axis. Subplot A is the initial simulation without any parameter adjustment and C the best fit. Test data, right from dashed vertical line, shows the 24-hour blood glucose prediction. In addition, SMBG measurements are plotted also.

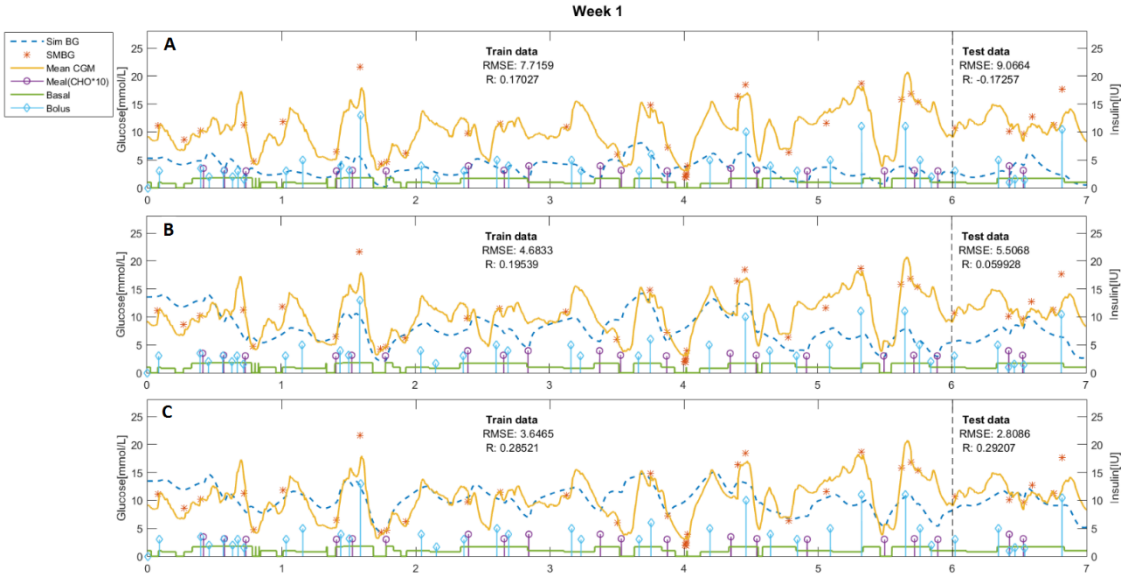

Figure 4.9: Pilot week 1 recorded and simulated data. Plots from top to down: A is the initial simulation without any parameter adjustment; B is simulation 1, where the first parameter kp1 is adjusted and steady state sought by adjusting basal values of I_l, I_p, I_{con}, G_p, G_t, EGP, I_{sc1} and I_{sc2}; C is the last simulation number 7, thus the best parameter identification achieved.

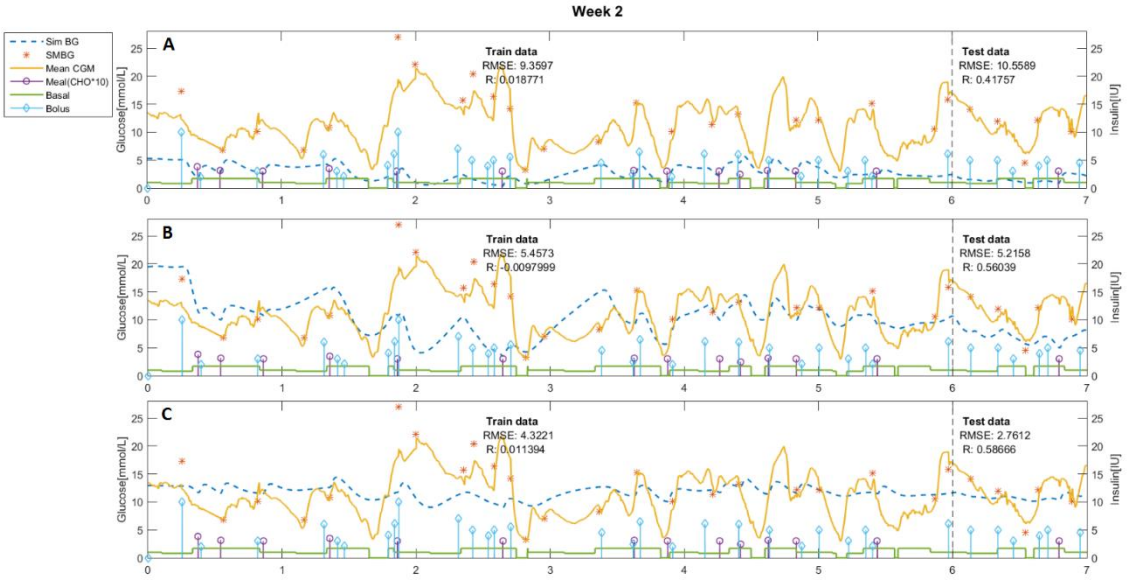

Figure 4.10: Pilot week 2 recorded and simulated data. Plots from top to down: A is the initial simulation without any parameter adjustment; B is simulation 1, where the first parameter kp1 is adjusted and steady state sought by adjusting basal values of I_l, I_p, I_{con}, G_p, G_t, EGP, I_{sc1} and I_{sc2}; C is the last simulation number 7, thus the best parameter identification achieved.

During the parameter identifications, 7 steps was used to obtain the best fit. In total of 22 parameters were adjusted. For both weeks those parameters were kp1, I_l, I_p, I_{con}, G_p, G_t, EGP, I_{sc1}, I_{sc2}, BW, remaining insulin production, TDI, m_2, kp_2, kp_3, Km, p2U, ke_1 and ke_2 and insulin onset time. For first week also parameter ka_1 was adjusted. Some of the parameters were adjusted in multiple steps to obtain the best result. All the adjusted parameters were verified to be within physiological limits. For instance, there could not be negative values for insulin sensitivity as in Bergman's model. Other parameters were kept untouched. For instance, changing of insulin related parameters; amplitude, peak time and duration, with the proposed algorithms did not improve test results.

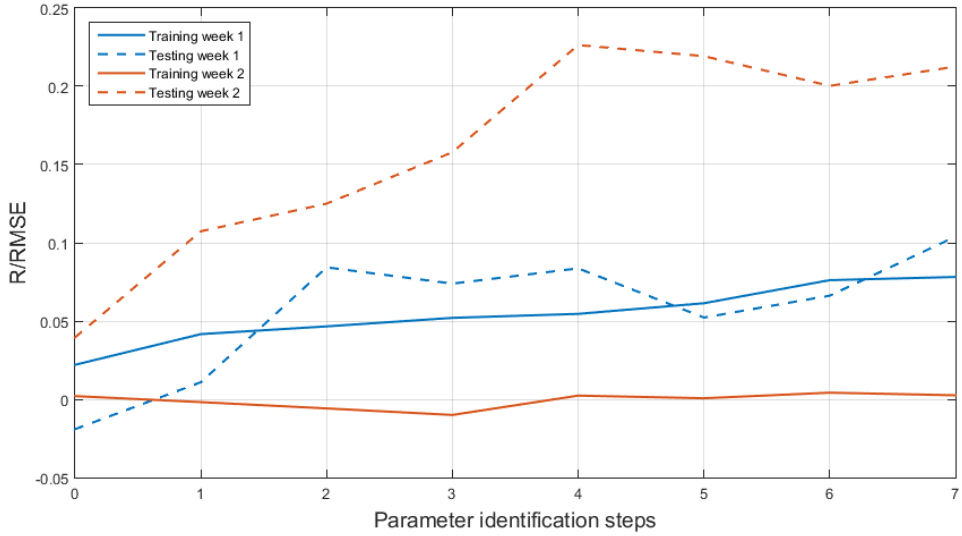

Figure 4.11: Correlation (R) divided by RMSE after parameter identification steps. Solid and dashed line represents training and test data, respectively.

Figure 4.11 shows the improvement of R to RMSE ratio during the training and testing period. During the training period the ratio should be improved constantly in order to get better parameter identification. Testing period is only allowed to use as an independent period, thus it is not known during the training period but only predicted after the training period.

5. DISCUSSION AND CONCLUSION

Based on questionnaire, Quattro Folia Oy demanded simulation software that was easy to test and had good modularity. They also required low price and good future proofs. Minimal GRS model was built with four programs and Simulink had the highest relative weight according to decision matrix in Table 4.3, thus it was the best program for Quattro Folia's criterions and therefore the maximal GRS model was built with it. One of the key factors was the testing possibilities that were the best in Simulink. In addition, the program enables comprehensive understanding of system dynamics, whereas other simulation programs are easier to learn and use, but lack in testing, future proofs and features.

Maximal GRS model was then built and validated with Simulink. Table 4.2 shows the simulated general GRS model correspond with the clinical data; decent RMSEs and very high correlations. Only the glucose rate of appearance exceeded the 1 STD limit, but this was only after 6 hours after the meal. Similarly, insulin delivery model was shown to correspond with clinical data in Figure 4.7. RMSE was in acceptable range and correlations was very high. Only a small time difference can be seen at the start of simulation, since insulin delivery system here included insulin onset time which was based on rapid acting insulin average, thus delay was initially 15 minutes. Apart from first 20 minutes, plasma insulin concentration falls within the 1 STD limits. Also, insulin delivery system was made for MDI and insulin pump therapy.

For first pilot week retrospective analyses, Table 4.3 shows the improvement of both RMSE and R during the parameter identification (i.e. training period). The same continuous improvement can be seen in Figure 4.11 where the R to RMSE ratio increases constantly and the best test results also was obtained with the best parameter identification results. For second week the lack of input data, particularly meal data, resulted in low correlation during the training. Although, test data in Figure 4.11 shows improved R to RMSE ratio, the result are not applicable. Figure 4.10 part C shows how the variance of simulated blood glucose has decreased which ultimately led almost constant simulated blood glucose. User reported only 14 meals in seven days and in three of those days had only a single meal. In order to get realistic parameter identification results, model needs to have input data which elevates and reduces the blood glucose, thus input data must include both meals and insulins, respectively.

One solution could be to have a shorter pilot period. Model parameter identification could be done in one day or in 7 hours as Dalla Man et al. did [33] and then have a test period of the same length. This way even amount of ingested carbohydrates could be more accurate, since in this case it was based only on user's estimation. The exact glycemic load of meal could be predefined and have even the blood glucose

measurements done with finger stick measurements, which brings us to the next error in the setup.

Training period assumes that the reference CGM signal is without an error, thus the best possible simulated blood glucose can be as good as the CGM blood glucose estimation is. Since CGMs has their own independent algorithms to estimate blood glucose based on glucose measured from interstitial fluid, reference CGM signal here was chosen to be the mean of both devices.

Yet, there has been recent report showing that CGM results could be improved in retrospective [46]. For future development, an implementation of this or similar method would be direct improvement to simulation results. Also, the better parameter identification itself would improve the results. This should be discussed further with system dynamics experts such as Professor Matti Vilkko.

Since the model does not incorporate intrasubject variability of parameters such as insulin sensitivity, future physiological development ideas are to include the dawn phenomenon and high blood glucose effect on insulin sensitivity discussed in Section 2.1.3. Latter especially in this case could have improved the results significantly, since the pilot user was relatively long periods over high blood glucose limit (i.e. over 12 mmol/L). This can be observed from Figures 4.9 and 4.10. Also, the effects of stress that were discussed in the end of Section 2.2.2 would be relevant idea to take into account and furthermore, implement in the model. Unfortunately, an explicit model describing the effects of stress to GRS has not yet presented. Similar to stress, the effects of exercise should be included to model also. Recent publication have shown a promising results how to implement exercise subsystem to GRS model [47], and actually it is the next subsystem to be implemented in the model.

In conclusion, the simulation program best meeting Quattro Folia's criterions was Simulink and maximal GRS model was built and validated with it. General GRS model was then adapted to correspond a pilot user's physiological values. Parameter identification worked with extensive and intact input data, and blood glucose prediction for 24 hours showed low correlation and relatively small error for the test period. Yet, statistically more reliable results could be obtained with greater test subject amount. Model have possible usages from *in silico* testing to teaching causalities for diabetics, thus it is useful for research, validation and educational purposes.

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APPENDIX 1: Parameters for GRS Model from Literature

TABLE I
MODEL PARAMETERS OF THE NORMAL AND TYPE 2 DIABETIC SUBJECT

Process	Parameter	Normal Value	Type 2 Diabetic Value	Unit
Glucose Kinetics	V_G	1.88	1.49	dl/kg
	k_1	0.065	0.042	min^{-1}
	k_2	0.079	0.071	min^{-1}
Insulin Kinetics	V_I	0.05	0.04	l/kg
	m_1	0.190	0.379	min^{-1}
	m_2	0.484	0.673	min^{-1}
	m_4	0.194	0.269	min^{-1}
	m_5	0.0304	0.0526	min ·kg/pmol
	m_6	0.6471	0.8118	dimensionless
	HE_b	0.6	0.6	dimensionless
Rate of Appearance	k_{max}	0.0558	0.0465	min^{-1}
	k_{min}	0.0080	0.0076	min^{-1}
	k_{abs}	0.057	0.023	min^{-1}
	k_{gri}	0.0558	0.0465	min^{-1}
	f	0.90	0.90	dimensionless
	a	0.00013	0.00006	mg^{-1}
	b	0.82	0.68	dimensionless
	c	0.00236	0.00023	mg^{-1}
	d	0.010	0.09	dimensionless
Endogenous Production	k_{p1}	2.70	3.09	mg/kg/min
	k_{p2}	0.0021	0.0007	min^{-1}
	k_{p3}	0.009	0.005	mg/kg/min per pmol/l
	k_{p4}	0.0618	0.0786	mg/kg/min per pmol/kg
	k_i	0.0079	0.0066	min^{-1}
Utilization	F_{cns}	1	1	mg/kg/min
	V_{m0}	2.50	4.65	mg/kg/min
	V_{mx}	0.047	0.034	mg/kg/min per pmol/l
	K_{m0}	225.59	466.21	mg/kg
	p_{2U}	0.0331	0.0840	min^{-1}
Secretion	K	2.30	0.99	pmol/kg per (mg/dl)
	α	0.050	0.013	min^{-1}
	β	0.11	0.05	pmol/kg/mirn per (mg/dl)
	γ	0.5	0.5	min^{-1}
Renal Excretion	k_{e1}	0.0005	0.0007	min^{-1}
	k_{e2}	339	269	mg/kg

Part 1: Average parameters for GRS model [33]

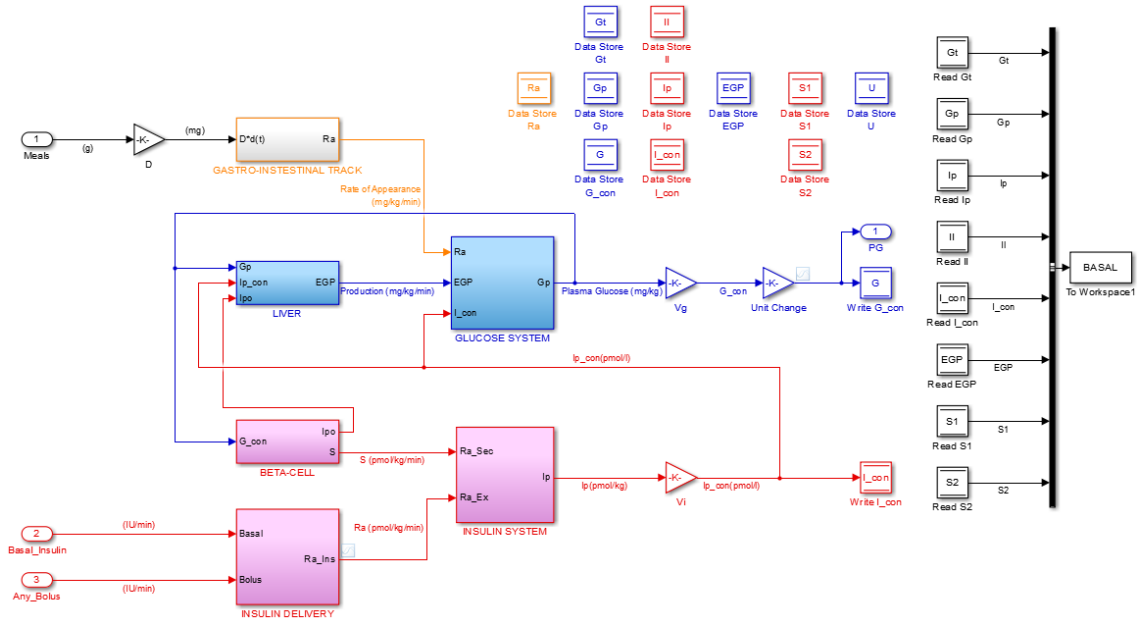
Table 1.
Parameters of Subcutaneous Insulin Kinetics, Glucose Sensor Delay, and PID Controller

Control	Parameter	Value	Unit
Subcutaneous insulin kinetics	k_d	0.0164	min^{-1}
	k_{a1}	0.0018	min^{-1}
	k_{a2}	0.0182	min^{-1}
Glucose sensor delay	T_d	10	min
PID controller	K_p	0.032	pmol/kg/min per mg/dl
	T_D	66	min
	T_I	450	min

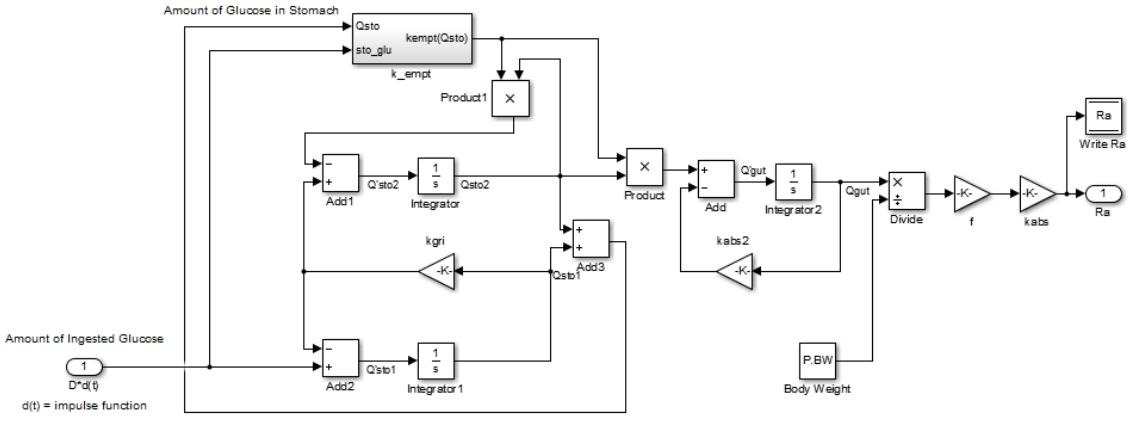
Part 2: Insulin delivery subsystem average parameters[48]

APPENDIX 2: Full GRS Simulink Model

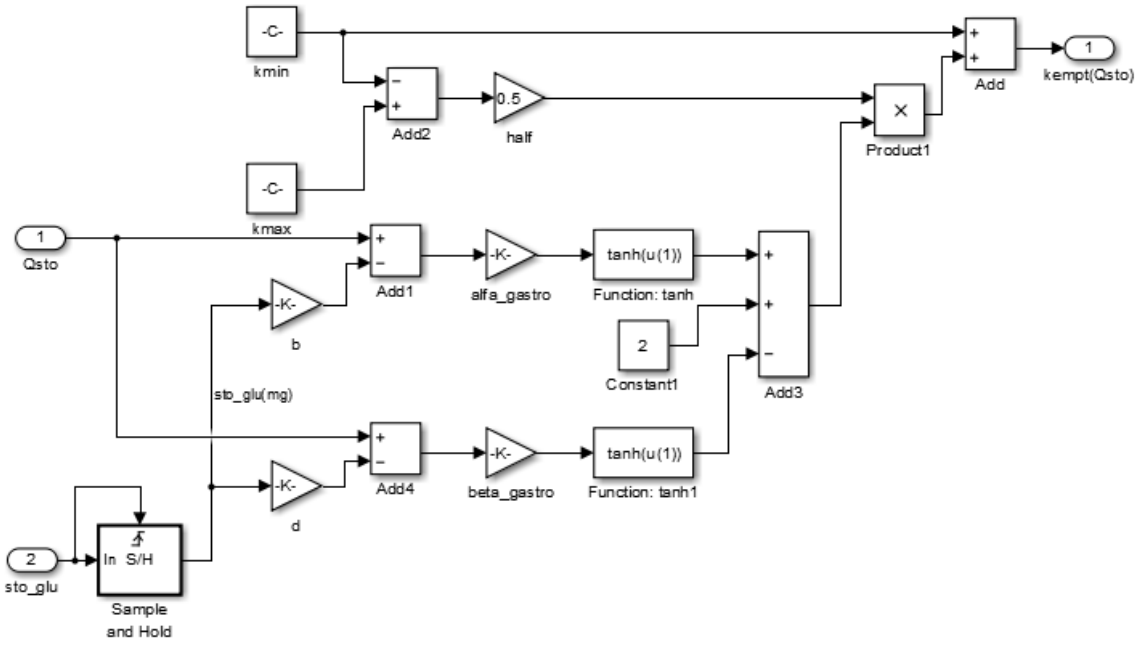
Screen capture 1: Model view at the top layer



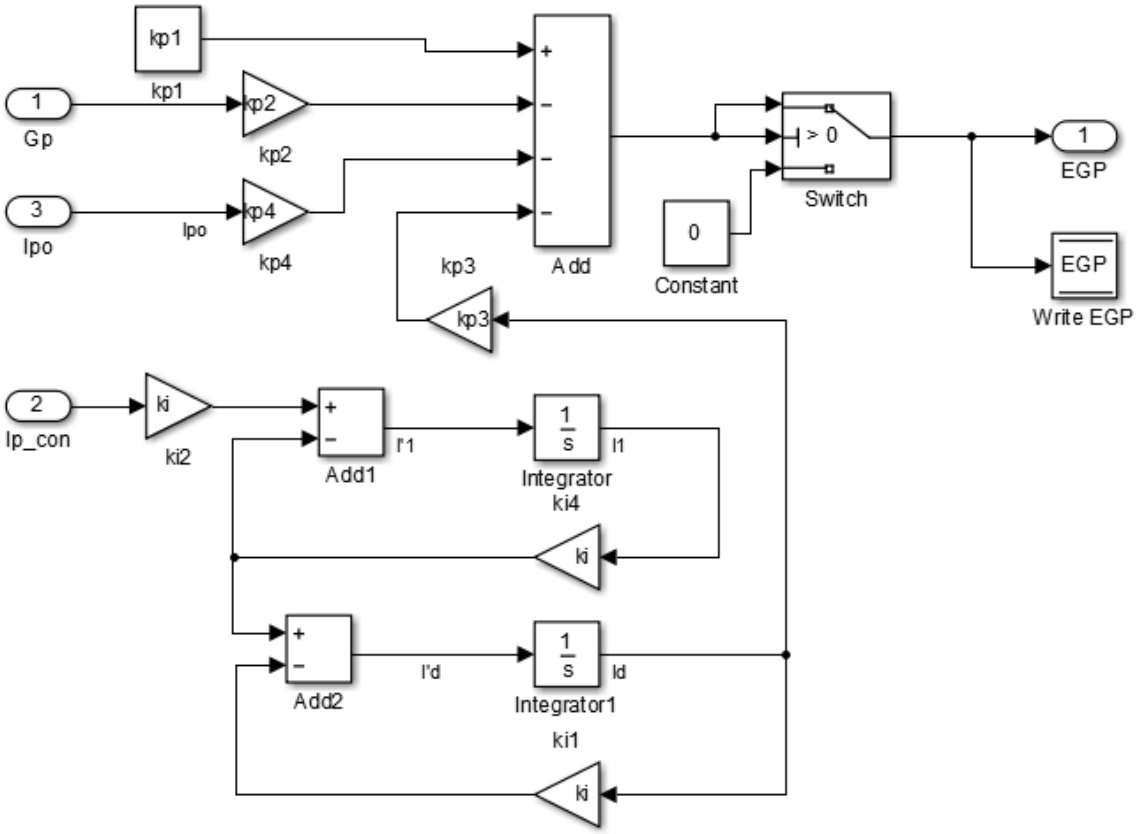
Screen capture 2: Subsystem HUMAN at second layer of the model



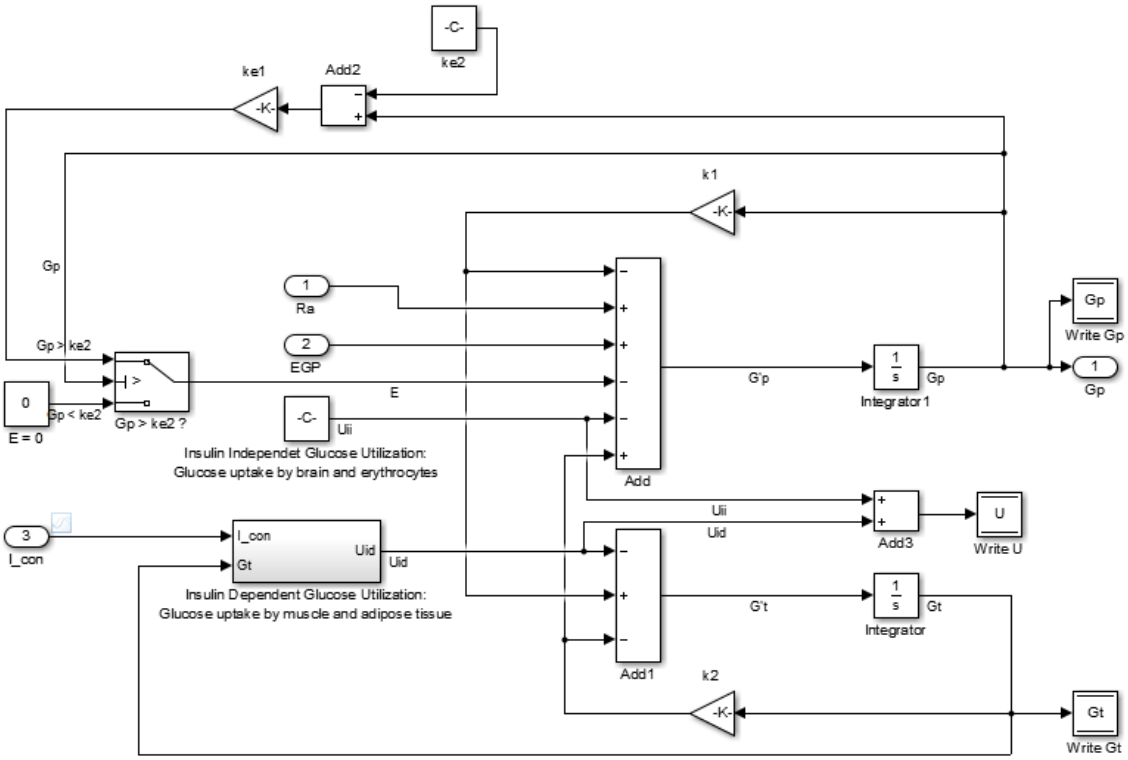
Screen capture 3: Subsystem GASTROINTESTINAL TRACK at third layer of the model



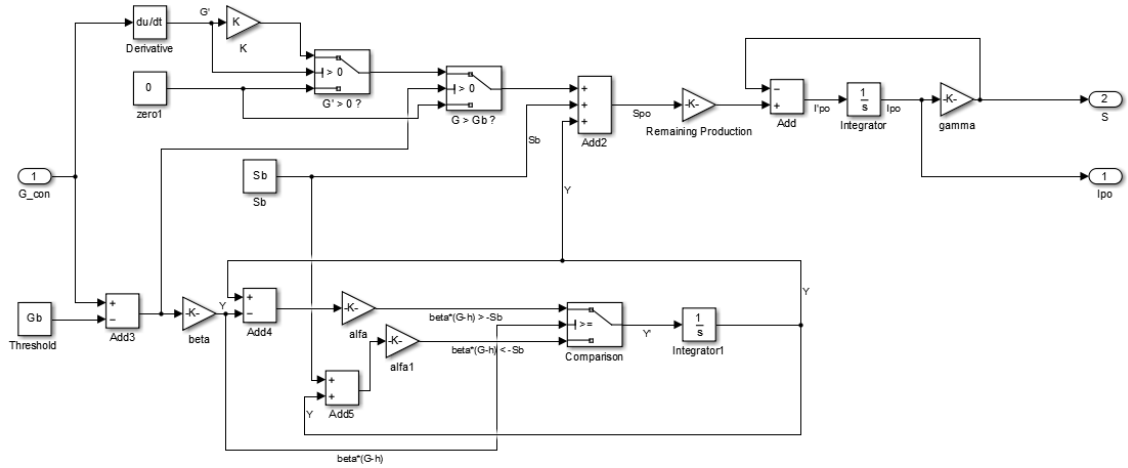
Screen capture 4: Subsystem k_empt at fourth layer of the model



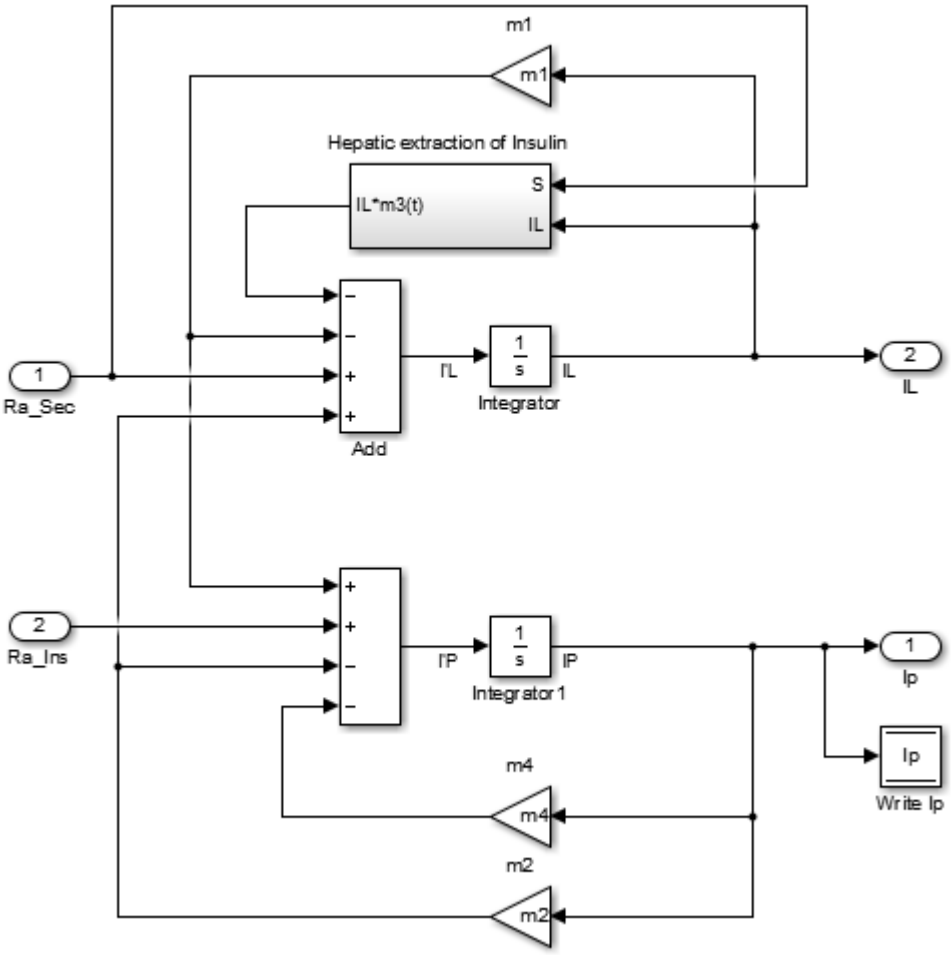
Screen capture 5: Subsystem LIVER at third layer of the model



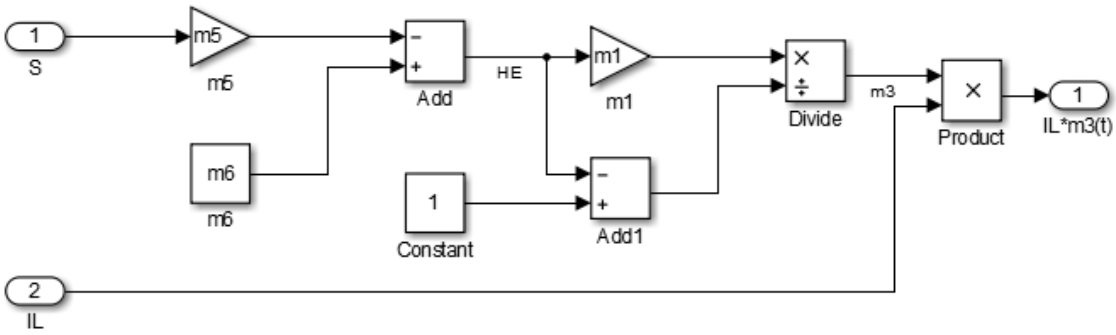
Screen capture 6: Subsystem GLUCOSE at third layer of the model



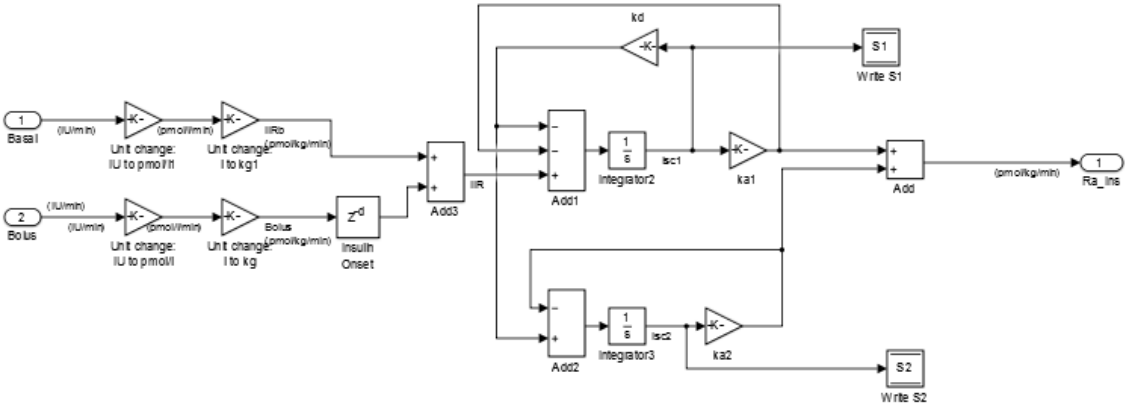
Screen capture 7: Subsystem BETA-CELL at third layer of the model



Screen capture 8: Subsystem INSULIN at third layer of the model



Screen capture 9: Subsystem Hepatic extraction of Insulin at fourth layer of the model



Screen capture 10: Subsystem INSULIN DELIVERY at third layer of the model