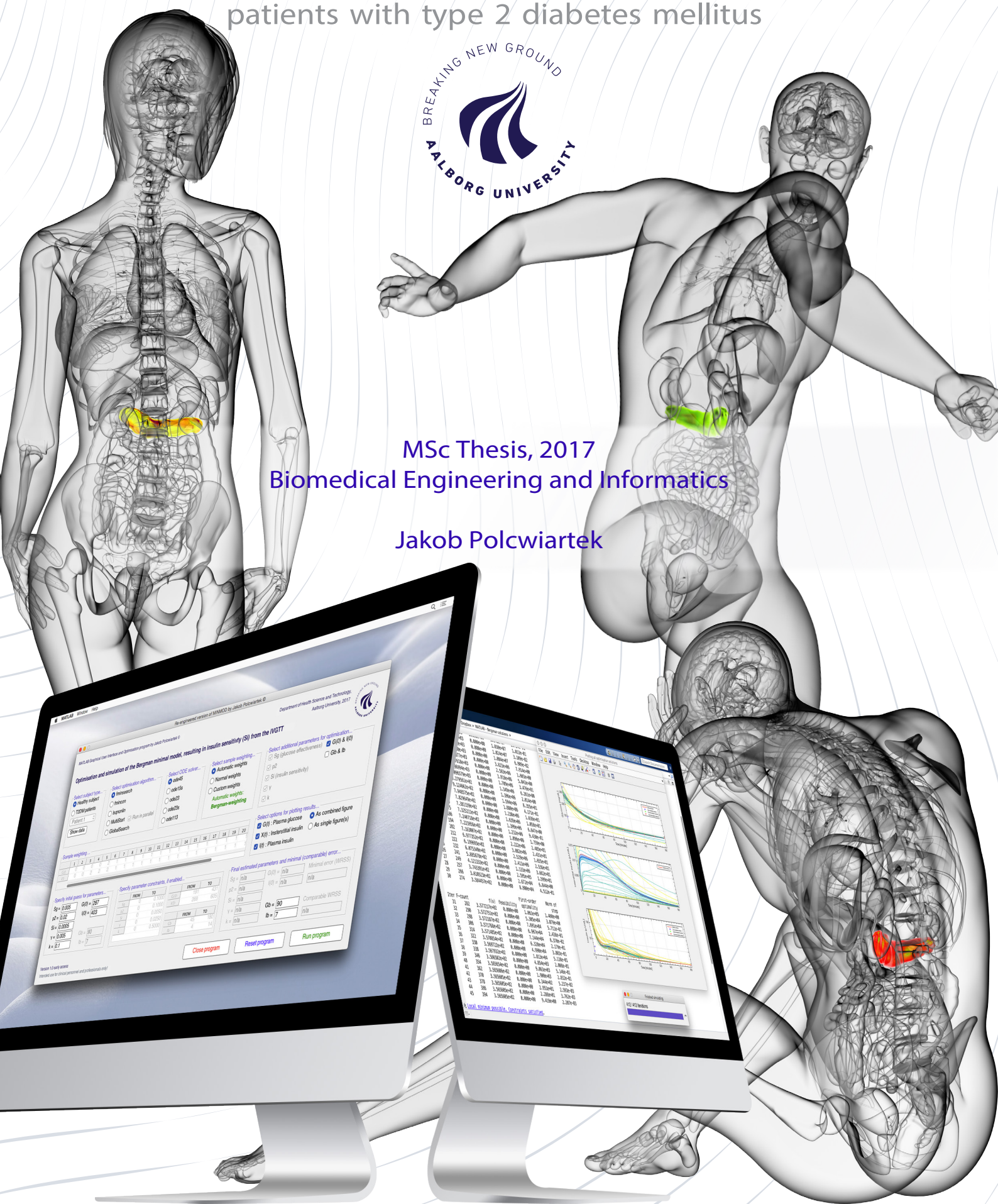
Re-engineered version of MINMOD:

A clinical tool based on physiological modelling of the glucose-insulin system to quantitatively assess insulin sensitivity in healthy subjects and patients with type 2 diabetes mellitus



MSc Thesis, 2017
Biomedical Engineering and Informatics

Jakob Polcwiartek

Colophon

This MSc Thesis was created using LaTeX2e and BibTeX, both obtained from the MacTeX distribution, and edited in the Texpad environment and JabRef reference manager, both with the UTF-8 encoding.

The typesetting is set with pdfLaTeX and the memoir class. The body text is set with 11 pt Charter BT font, while the heading text is set with 14 pt Computer Modern Sans Serif font. The margins of this MSc Thesis are set to 13.2 cm × 24.3 cm for a more comfortable reading.

Graphical representations of data as well as illustrations, are generally vectorised, ensuring high visual quality.

MATLAB® and Adobe® Illustrator®, or combination of both, have been used for this purpose, while Adobe® Photoshop® has been used generally for preparing images to this MSc Thesis.

All figures made in MATLAB® are without a title, since the title is moved to each figure caption including additional information, eventually.

Furthermore, these figures are generally set to a 13 cm width format including 9 pt font with the `printpreview` command and exported to the desired format with the `print` command for final preparation in Adobe® Illustrator®.

This way of handling the figures ensures the exact same scaling and appearance in this MSc Thesis, making the figures confluent with the body text, leading to a greater visual impression and comfortable reading experience.

With regards to the graphic material used in the cover page, the stock photo service, Colourbox has been used via a free student license offered for all students at Aalborg University.

The 5K iMac screens are obtained from Graphic & UI Designer, Ramoti Studio.

Decisions regarding the overall visual appearance of this MSc Thesis, were primarily based on the recommendations given in the Aalborg University design guide from early 2013, providing Aalborg University with a new visual identity.

The overall visual appearance of this MSc Thesis is made by *the author himself*.

Aalborg University

Department of Health Science and Technology

Fredrik Bajers Vej 7 • 9220 Aalborg • Denmark

Re-engineered version of MINMOD:

A clinical tool based on physiological modelling of the glucose-insulin system to quantitatively assess insulin sensitivity in healthy subjects and patients with type 2 diabetes mellitus.

MSc Thesis

Biomedical Engineering and Informatics

Student:

Jakob Polcwiartek

MSc Eng. Student

Supervisor:

Ole Hejlesen

Professor with special responsibilities

Wednesday, 07 June 2017

Week 23

Pages:	100
Printings:	0

Abstract

In the field of biomedical engineering, physiological modelling of the glucose-insulin system may improve understanding of diabetes by e.g. estimating the insulin sensitivity in healthy individuals and patients with prediabetes or type 2 diabetes. The gold standard of measuring insulin sensitivity is the euglyceamic hyperinsulinemic clamp technique, which is rather tedious, invasive, and labour-intensive. A comparable alternative to this is the Bergman minimal model, assessing insulin sensitivity by the intravenous glucose tolerance test (IVGTT). This model has gained much attention in the literature and has been implemented as the PC application MINMOD Millennium, which unfortunately is limited to one optimisation algorithm almost without any level of customisation besides being rather outdated.

Therefore, this MSc Thesis aimed to re-engineer a version of MINMOD, with focus on providing more customisation of the optimisation process to estimate e.g. insulin sensitivity.

A nonlinear least squares (NLS) approach was used together with the Bergman minimal model to develop a PC application in MATLAB (version R2015a). Relevant IVGTT data from the literature was found, extracted, prepared, and implemented into the re-engineered version of MINMOD. This was presented in a graphical user interface (GUI), and the software development process was mainly based on the waterfall model and usability heuristics.

During the software development process, it was possible to re-engineer a version of MINMOD in an aesthetic and minimalistic GUI. Here, it was possible to customise the optimisation process regarding estimates of relevant parameters, including insulin sensitivity, of the Bergman minimal model. Overall, parameter estimates could be replicated and compared with another study found in literature, validating the re-engineered version of MINMOD to some degree. However, more testing is required in order to obtain an even higher degree of validation.

Resumé

Inden for sundhedsteknologi kan fysiologisk modellering inden for glukose-insulinsystemet være med til at øge forståelsen af diabetes, bl.a. gennem estimering af insulinsensitivitet (insulinfølsomhed) for raske personer og patienter med prædiabetes eller type 2-diabetes. Den gyldne standard inden for måling af insulinsensitivtet er den euglykæmiske hyperinsulinæmiske clamp-teknik, som er ret vanskelig og invasiv. Et alternativ til denne er Bergmans minimale model, som kan estimere insulinsensitivtet gennem fortolkning af den intravenøse glukosebelastningstest (IVGTT). Denne model har gennem en årrække vakt stor interesse i litteraturen hvortil, der endvidere er lavet en PC-applikation til (MINMOD Millennium). Denne er desværre begrænset til en enkelt optimeringsalgoritme næsten uden nogen form for brugertilpasning udover også at virke forældet.

Derfor bestræbede dette kandidatspeciale sig på at rekonstruere en version af MINMOD med fokus på mere brugertilpasning af optimeringsprocessen for bl.a. at kunne estimere insulinsensitivitet.

En tilgang med ikke-lineær mindste kvadraters metode (NLS) blev benyttet sammen med Bergmans minimale model til at udvikle en PC-applikation i MATLAB (version R2015a). Relevant IVGTT-data fra litteraturen blev fundet, ekstraheret, processeret samt implementeret i den rekonstruerede version af MINMOD. Alt dette blev samlet og præsenteret i en brugergrænseflade (GUI), mens softwareudviklingsprocessen hovedsageligt var baseret på vandfaldsmodellen samt usability-heuristikker.

Under softwareudviklingsprocessen var det muligt at rekonstuere en version af MINMOD i et æstetisk og minimalistisk GUI. Det var her muligt at tilpasse i optimeringsprocessen mht. estimeringen af relevante parametre, herunder insulinsensitivitet, inden for Bergmans minimale model. Overordnet var det muligt at bekræfte estimeringen af parametrene med andre studier fundet i litteraturen, der validerer den rekonstuerede version af MINMOD til et vist omfang. For at opnå en højere valideringsgrad af programmet, er det dog nødvendigt med flere tests.

Preface

This MSc Thesis has been prepared by Jakob Polcwiartek; an MSc Student in Biomedical Engineering and Informatics affiliated at the Department of Health Science and Technology at Aalborg University.

Reading guide

Remarks on the composition of the MSc Thesis

The overall structure of this MSc Thesis is inspired from the common organisation structure in scientific writing, known as IMRaD (**I**ntroduction, **M**ethods, **R**esults, **a**nd **D**iscussion).

There are, however, some slight naming alterations relative to the IMRaD-template, since the first part in this MSc Thesis takes on a different name, namely Background, since Introduction is better suited as the first chapter. Furthermore, the final part is an additional fifth part labeled as Listings:

I Background
II Methods
III Results
IV Discussion
V Listings

Other remarks

Throughout this MSc Thesis, the term diabetes is used for diabetes mellitus. A list of abbreviations is available on page xi. Before an abbreviation is introduced in parentheses in the text, and hence in the list of abbreviations, the full form of the abbreviated word is written first.

In case of a heading containing an abbreviation, the abbreviation will not be written out. Also, in case when a sentence is beginning with an abbreviation that has already been introduced earlier, the abbreviation will not be written out.

The bibliography style for this MSc Thesis is set to the Vancouver style which is the typical standard used in the field of medicine and biomedical science among others.

This style of referencing is made possible by the package `natbib` that provides numbered references, and also the `unsrtnat` package, ensuring all references in the bibliography to be sorted according to the order in which they appear throughout the MSc Thesis.

A remark regarding the author's method of referring; a reference or a set of references is

- placed inside a sentence and/or left to a punctuation mark, if the sentence itself is based upon the reference or set of references
- placed outside the last sentence in a paragraph, if the paragraph itself is based upon the reference or set of references

When it comes to the numbering of figures, tables, and equations, they are each numbered according to the chapter they belong to, as well as their respective order in which they appear in that chapter.

Acknowledgements

Besides being grateful for invaluable talks with my supervisor, and his understanding, I would also like to thank MSc Lin Wang, who helped me with some ideas in physiologic modelling and optimisation as well as programming in MATLAB.

I do also owe a big thanks to my supportive and beloved family.

Declaration

I, Jakob Polcwiartek, confirm that the work presented in this MSc Thesis is my own.

Where information has been derived from other sources, I confirm that this has been indicated in the thesis to the best of my ability.

Aalborg University, June 7, 2017.

Jakob Polcwiartek
MSc Eng. Student
Biomedical Engineering and Informatics
poltjek@gmail.com

Abbreviations

All abbreviations used throughout this MSc Thesis are listed here alphabetically. By abbreviations, acronyms and initialisms are understood.

DI	disposition index
EEc	eastern european countries
FSIGT test	frequently-sample intravenous glucose tolerance test
GOF	goodness of fit
GUI	graphical user interface
HbA1c	haemoglobin A1c
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IVGTT	intravenous glucose tolerance test
MSE	mean squared error
NEc	northern european countries
NLS	nonlinear least squares
ODE	ordinary differential equation
OGTT	oral glucose tolerance test
RMSE	root mean squared error
SEc	southern european countries
WEc	western european countries
WHO	World Health Organisation
WRSSE	weighted residual summed squared error

Contents

Chapter 1

Introduction

Diabetes, especially type 2 diabetes, is one of the most challenging health issues around the world. In these modern times, it is now considered a global pandemic since not only the people in the western countries are affected. The frequency of type 2 diabetes in many developmental countries are increasing dramatically to a level that equals the western countries. By 2040, it is estimated that globally 642 million people will have diabetes, with 85-90% related to type 2 diabetes. [1]

Although mortality associated with diabetes is nearly doubled relative to individuals without diabetes, morbidity (i.e. burden of disease and complications) also makes a great concern. Particularly, the complications associated with diabetes are multiple and affects not only the patient, but also the society. Patients with major complications such as cardiovascular disease contribute to the majority of the societal costs. [1, 2]

This calls for a discussion on whether it is more cost-effective to focus more on secondary preventive efforts or improve current diabetic treatment strategies. However, it is a combination of both that may be the optimal solution. As diabetes is a very complex disease, it is therefore fought against with a large battery of tools spanning over several interdisciplinary endeavours, such as those depicted in Figure 1.1.

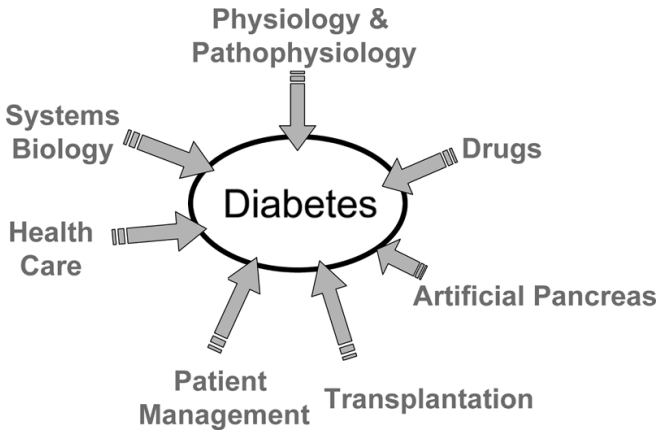


Figure 1.1: *Battery of tools that contribute to control of diabetes. Taken from Cobelli et al. [2].*

Nowadays, in order to address the disciplines of health care and patient management from Figure 1.1, large governing bodies like World Health Organisation (WHO) have implemented screening strategies with cut-off levels and treatment guidelines for diabetes. The main component of screening includes, since 2012 according to Danish College of General Practitioners (DSAM) [3], haemoglobin A1c

(HbA1c) as the primary diagnostic criteria. However, the main problem, as with any binary classifier, is that perfect classification almost never occurs in real life, and therefore, detection of pre-diabetes is complicated. Pre-diabetes is an intermediate condition comprised by impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Particularly, individuals with these pre-diabetic conditions are at increased risk of type 2 diabetes. [2]

In order to obtain better control of diabetes, the individual components of the battery of tools should perhaps be combined more than they are being now, for synergistic effects to happen. For example, a better way to counteract the pre-diabetic conditions, and thereby individuals at increased risk of type 2 diabetes, could be in terms of combining the disciplines of system biology and physiology & pathophysiology from Figure 1.1 on page 1.

In the field of biomedical engineering, physiological modelling of the glucose-insulin system may improve epidemiological research and management of diabetes. This system is one of the most studied in terms of modelling and may be a beneficial contribution to understanding pathophysiology of diabetes and pre-diabetes, thus potentially improving health care and patient management. [2]

The most recognised surrogate marker of diabetes and pre-diabetes remains the insulin sensitivity, as part of the glucose-insulin system. The gold standard in estimating this, is the euglyceamic hyperinsulinemic clamp technique, which is tedious and vary labour-intensive. It is possible to estimate insulin sensitivity in other ways, e.g. via the approach of physiological modelling. In this context, one model, in particular, has gained much attention and popularity, that is the Bergman minimal model developed in the late 1970's by Bergman and colleagues [4–7]. In brief, this model interprets the dynamics of the glucose-insulin system through an intravenous/oral glucose tolerance test (IVGTT, OGTT), which correlates well with the gold standard [2, 6, 7]. By using the concepts of the Bergman minimal model, it may be possible to estimate insulin sensitivity and, consequently, gain more insight into alterations of the glucose-insulin system and pathophysiology of diabetes and pre-diabetes.

Besides, the researchers behind the Bergman minimal model have developed an initial PC application named MINMOD (abbreviation of minimal model), which is described in an article by Pacini and Bergman [5] and later enhanced and described in some detail in [6, 8], where it was referred to as MINMOD Millennium since the 2000's. However, the PC application seems to be outdated and does not offer customisation of the optimisation process. Therefore, a re-engineered version of MINMOD addressing these aspects may be warranted.

To provide the reader with the necessary background, the first part of this MSc Thesis will provide a background of diabetes (i.e. from an epidemiological and pathophysiological standpoint) and of the physiological modelling of the glucose-insulin system. The latter, with focus on assessment of insulin sensitivity from IVGTT, particularly using the Bergman minimal model.

Afterwards, an overview with problem formulation will be provided. Finally, relevant chapters on methods of re-engineering MINMOD, results, discussion, and conclusion will be provided.

Part I

Background

Chapter 2

Epidemiology of diabetes

2.1 Overview of the pandemic worldwide

Diabetes is a global health emergency that is among the largest in the world and of the 21st century. Each year more and more people live with this diabetes, which can result in life-threatening and life-changing complications. In addition to more than the 415 million adults estimated to have diabetes in 2015 worldwide [1], there were 318 million adults with IGT putting them at high risk of developing the condition in the possible near future.

Figure 2.1 illustrates the estimated worldwide situation and per region for both 2015 and 2040.

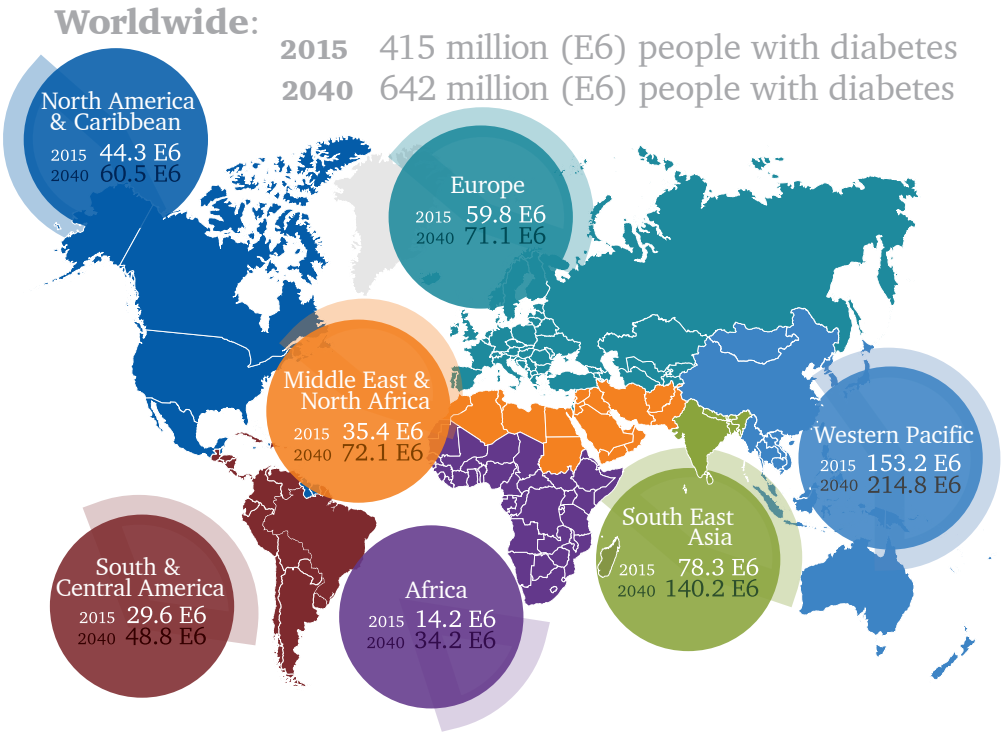


Figure 2.1: *Estimated number of diabetics (20-79 years) worldwide and per region in 2015 and 2040. Numbers are in millions, which is provided with the engineering notation, e.g.* $1 \times 10^6 = 1\text{E}6$. *Adapted from International Diabetes Federation* [1].

According to International Diabetes Federation [1, 9] many countries are still unaware of the social and economic impacts of diabetes. This lack of understanding

is the biggest barrier to effective prevention strategies that could help stop the unavoidable rise of type 2 diabetes.

Despite better awareness, new developments in treatment of type 1 and type 2 diabetes and prevention of type 2 diabetes, leading diabetes organisations across the world report a continuous increase in the number of people with this condition.

2.1.1 The human costs

Diabetes and its complications are major causes of death in most countries. Type 2 diabetes is the most prevalent form of diabetes and has increased alongside cultural and societal changes. International Diabetes Federation [1, 9]

In high-income countries, up to 91% of adults with diabetes have type 2 diabetes. It is estimated by International Diabetes Federation [9] that 193 million people with diabetes have not yet been diagnosed and are consequently at increased risk of developing complications. That makes one in two adults with diabetes 'undiagnosed'. International Diabetes Federation [1, 9]

Furthermore, one in 15 adults is estimated to have IGT, and one in seven births is affected by gestational diabetes, this is a type of diabetes that occurs during pregnancy due to maternal metabolic changes. Both of these conditions are associated with an increased risk of developing type 2 diabetes in later life. International Diabetes Federation [1, 9]

2.1.2 Diabetes in children

Whilst type 1 diabetes is less common, it is still increasing by approximately 3% per year, particularly among children. According to International Diabetes Federation [9], the amount of children with type 1 diabetes exceeded half a million for the first time in 2015.

Around 86,000 children develop type 1 diabetes each year and when insulin is not available e.g. in lower-income countries, the life expectancy for a child with type 1 diabetes is very short.

However, many supportive organisations are counteracting this negative trend. For example 'The Life For A Child' programme of [9] supplies insulin to 17,000 children in 46 countries. [9]

2.1.3 The financial costs

In addition to placing a large financial burden on individuals and their families due to the costs of insulin and other essential medicines, International Diabetes Federation [1] additionally states that diabetes also has a substantial economic impact on countries and national healthcare systems.

Mainly, this is caused by an increased use of healthcare services, loss of productivity, and the long-term support needed to overcome diabetes-related complications, such as kidney failure, blindness, or cardiovascular.

The majority of countries spend between 5% and 20% of their total healthcare expenditure on diabetes. With such a high cost, the disease is a significant challenge for healthcare systems and an obstacle to sustainable economic development. [1, 10]

2.2 Overview of the pandemic in European countries

Figures 2.2 to 2.5 on pages 10–11 show the statistics on comparative prevalences of diabetes and IGT for European countries. Comparative prevalences of diabetes and IGT are described and estimated by International Diabetes Federation [9] in order to be able to compare countries.

The countries in Figures 2.2 to 2.5 have been divided into different parts of Europe, according to the M49 standard for geographic regions defined by United Nations Statistics Division [11]. The list of geographic regions presents the composition of geographical regions used by the Statistics Division in its publications and databases.

❧

The composition for each of Figures 2.2 to 2.5 is the same. That is, the countries are sorted according to the highest average of the comparative prevalences of diabetes and IGT first. In other words, the countries to the most left in each geographic region on Figures 2.2 to 2.5 have the most poor statistics on average, while the countries to the most right have the best statistics on average.

Figures 2.2 to 2.5 have all the same axis properties in common. This has been ensured, so that visual comparison of the statistics can be performed in an easier manner.

Finally, the statistics presented for each part of Europe are compared with values for Denmark as well as the average of the countries in that part of Europe.

❧

For better visual understanding of the statistics presented in Figures 2.2 to 2.5, Figure 2.6 on page 13 summarises the pandemic in Europe with regards to the overall comparative prevalence of diabetes. Similarly, Figure 2.7 on page 13 does the same, just with the comparative prevalence of IGT.

2.2.1 Northern European countries

Denmark is one of the countries included in the geographic region of Northern European countries (NEc), as defined by the M49 standard. As it is illustrated in Figure 2.2 on page 10, Denmark is among the top three countries in this part of Europe, which has the highest comparative prevalence of IGT together with Latvia and Lithuania. The level for these mentioned countries is considerable higher than the rest of the NEc and the NEc average.

❧

The same statistics on the comparative prevalence of diabetes is true for Denmark in this geographic region. Again, Figure 2.2 illustrates that Denmark is the country that is leading this negative statistic, which is the highest among the NEc countries. However, Denmark is not the only country, which has a comparative prevalence of diabetes that is higher than the NEc avarage. Countries like Estonia, Finland, Ireland, and Faroe Islands have higher comparative prevalence than the NEc average.

Countries like Norway, Sweden, and Iceland are better than the NEc average, measured on both comparative prevalence as well as comparative IGT.

2.2.2 Western European countries

As it is illustrated in Figure 2.3 on page 10, the Western European countries (WEc), in general, share the same statistics as NEc (within a reasonable margin, naturally) with regards to the comparative prevalence of IGT. This means the fluctuations, i.e. variations, are less compared to e.g. NEc with respect to the comparative prevalence of IGT.

WEc have all considerably better statistics on comparative prevalence of IGT than Denmark. Among the countries in this geographic region, only Germany and the Netherlands have better statistics on comparative prevalence of IGT relative to the WEc average.

❧

When it comes to comparative prevalence of diabetes, Germany is the most substantial outlier with a level that is considerably higher than the WEc avarege as well as the Danish level, which is higher than the WEc average.

It is only the Netherlands that has statistics better than the WEc average, measured on both comparative prevalences of diabetes as well as IGT.

2.2.3 Eastern European countries

Compared to both NEc and WEc, Eastern European countries (EEc) have more variations with regards to comparative prevalences of diabetes and IGT.

Figure 2.4 on page 11 shows that Poland is the leading country having the poorest statistics on comparative prevalence of IGT. This is not only true for EEc but for all the European countries.

Other EEc like Russia, Belarus, Romania, Ukraine, and Moldova have higher comparative prevalence of IGT than the EEc average on a level that is very similar to the Danish level of comparative prevalence of IGT.

❧

Despite being the leading country with the poorest result of the comparative prevalence of IGT, Poland has a comparative prevalence of diabetes that is just beyond the EEc average.

Russia, Slovakia, Czech Republic, and Hungary have higher levels than the EEc average on comparative prevalence of diabetes. Figure 2.4 reveals that these aforementioned countries, except from Hungary, have higher levels of comparative prevalence of diabetes than Denmark.

Bulgaria has the best statistics among EEc, both on comparative prevalences of diabetes and IGT, which is lover than the EEc.

Finally Figure 2.4 highlights that the Danish level of comparative prevalences of diabetes and IGT are higher than the EEc average.

2.2.4 Southern European countries

Relative to the other parts of Europe, Southern Europe countries (SEc) have on average the poorest statistics on both comparative prevalences of diabetes and IGT. However, this geographic region is that among the four geographic regions containing most amount of countries. Overall, there are less fluctuations as with EEc with regards to comparative prevalences of diabetes and IGT.

As it is showed in Figure 2.5 on page 11, it is considerably remarkable that the SEc can be divided into two categories. That is, one category of countries that

share statistics worse than the SEc average, while the other group of countries share statistics that are better than the SEc average. The statistics referred to here, are both comparative prevalences of diabetes and IGT.

The levels of comparative prevalences of diabetes and IGT are in general considerably high (and higher than the SEc average) for countries like Portugal, Montenegro, Macedonia, Serbia, Bosnia-Herzegovina, and Spain.

Also, these countries have similar statistics to that of Denmark in terms of comparative prevalence of IGT. Likewise, these countries have worse statistics on the comparative prevalence of diabetes than Denmark, though.

The countries in the other group have mostly in common that they share better statistics than the SEc average on comparative prevalences of diabetes and IGT. These countries are primarily Croatia, San Marino, Andorra, Greece, and Italy. These countries, including Albania, have better statistics than Denmark in terms of comparative prevalences of diabetes and IGT.

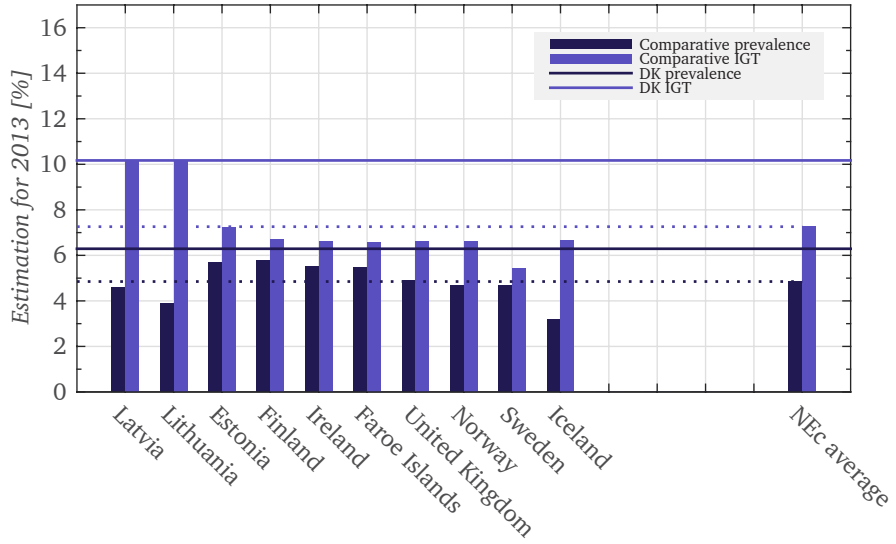


Figure 2.2: *Comparative prevalences of diabetes and impaired glucose tolerance (IGT) for Denmark (DK) and the Northern European countries (NEc). Estimation for 2013. Data were obtained from International Diabetes Federation [9]. Bars represent comparative prevalences of diabetes and IGT. Thin horizontal lines across the graph correspond to similar measures, just for DK. Thin, dashed lines show the NEc average for the same measures.*

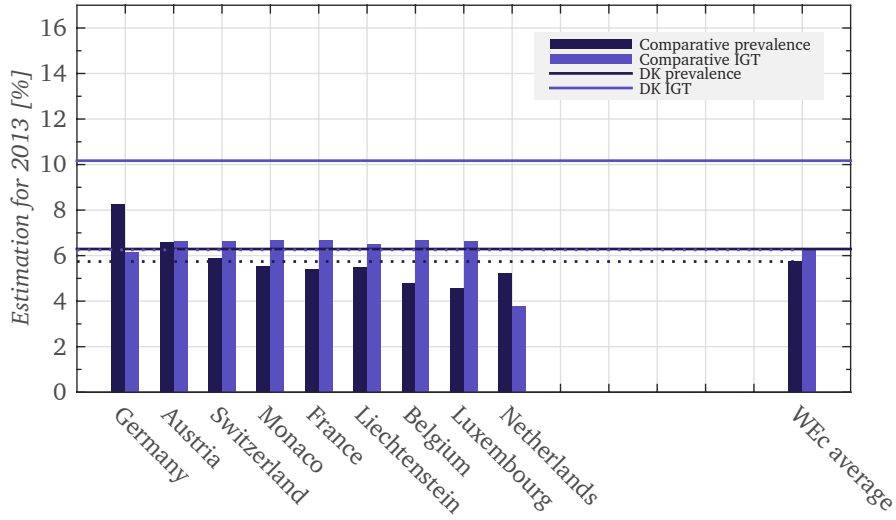


Figure 2.3: *Comparative prevalences of diabetes and impaired glucose tolerance (IGT) for Denmark (DK) and the Western European countries (WEc). Estimation for 2013. Data were obtained from International Diabetes Federation [9]. Bars represent comparative prevalences of diabetes and IGT. Thin horizontal lines across the graph correspond to similar measures, just for DK. Thin, dashed lines show the WEc average for the same measures.*

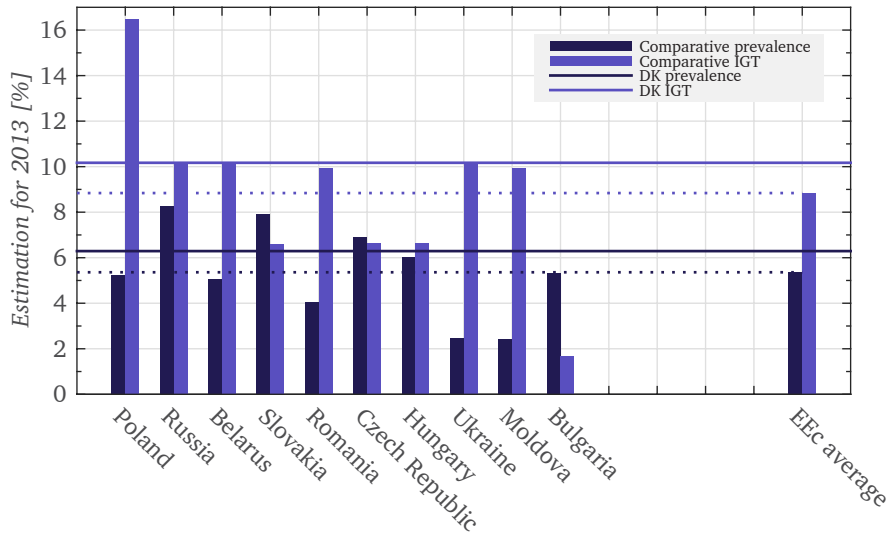


Figure 2.4: *Comparative prevalences of diabetes and impaired glucose tolerance (IGT) for Denmark (DK) and the Eastern European countries (EEc). Estimation for 2013. Data were obtained from International Diabetes Federation [9]. Bars represent comparative prevalences of diabetes and IGT. Thin horizontal lines across the graph correspond to similar measures, just for DK. Thin, dashed lines show the EEc average for the same measures.*

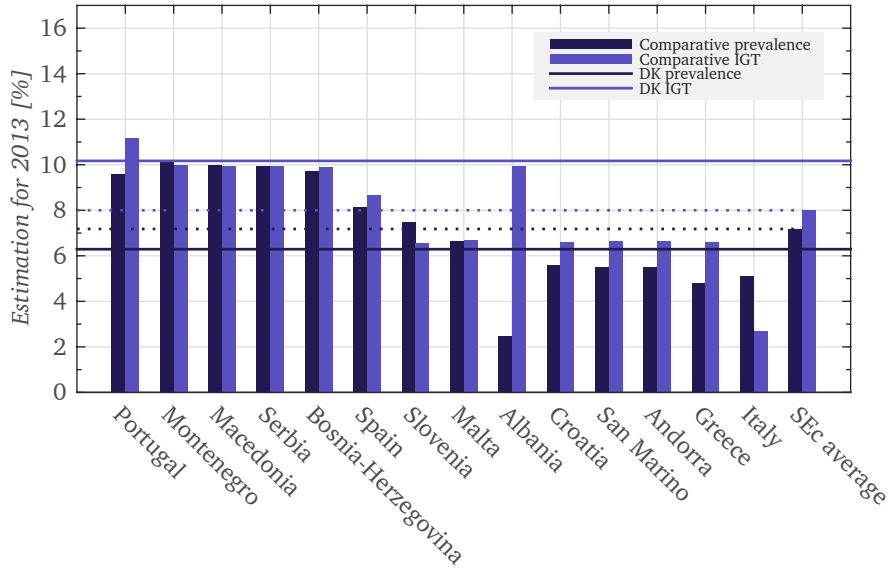


Figure 2.5: *Comparative prevalences of diabetes and impaired glucose tolerance (IGT) for Denmark (DK) and the Southern European countries (SEc). Estimation for 2013. Data were obtained from International Diabetes Federation [9]. Bars represent comparative prevalences of diabetes and IGT. Thin horizontal lines across the graph correspond to similar measures, just for DK. Thin, dashed lines show the SEc average for the same measures.*

2.3 The pandemic in European countries from a Danish perspective

The statistics reviewed in the previous Section 2.2 and Figures 2.2 to 2.5 on pages 10–11, might be too demanding to comprehend because of too much information at once. Therefore, the same information has been rearranged in a more visual context. This is presented in Figures 2.6 to 2.7 on the facing page.

The colourisation of the countries in Figures 2.6 to 2.7 is selected according to whether each country either has:

- higher/worse (red colour),
- lower/better (green colour), or
- the same (orange colour)

statistics on comparative prevalences of diabetes and IGT.

The latter option in the bullet list includes countries with a deviation of ±1 % relative to the level applicable for Denmark.

Figures 2.6 to 2.7 are results of the above-mentioned rearrangement showing the pandemic from a Danish perspective.

Some final notes to make on the Danish comparative prevalences of diabetes and IGT are that the levels are considerably higher than the northern neighbours.

Also, the Danish level on the comparative prevalence of IGT is considerably higher than the averages for NEc, WEc, EEc, and SEc.

Generally, the same applies to the comparative prevalence of diabetes. In this case, the Danish level is only better than the SEc average.

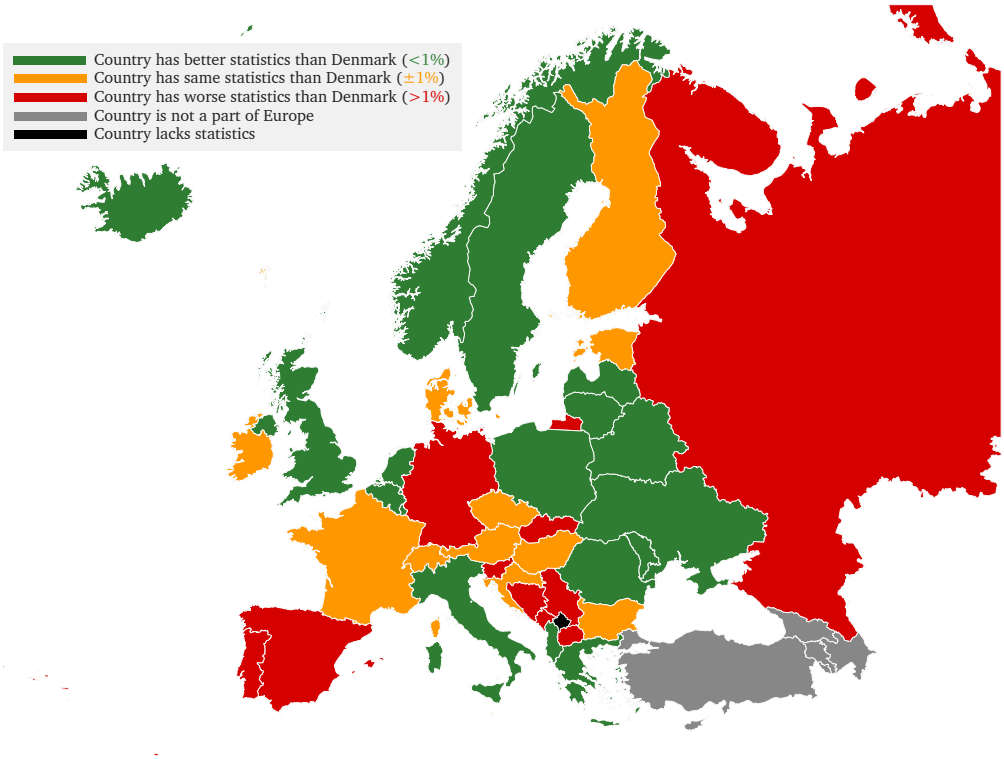


Figure 2.6: *Map with European countries compared to Denmark (DK) on comparative prevalence of diabetes according to the statistics given in Figures 2.2 to 2.5 on pages 10–11.*

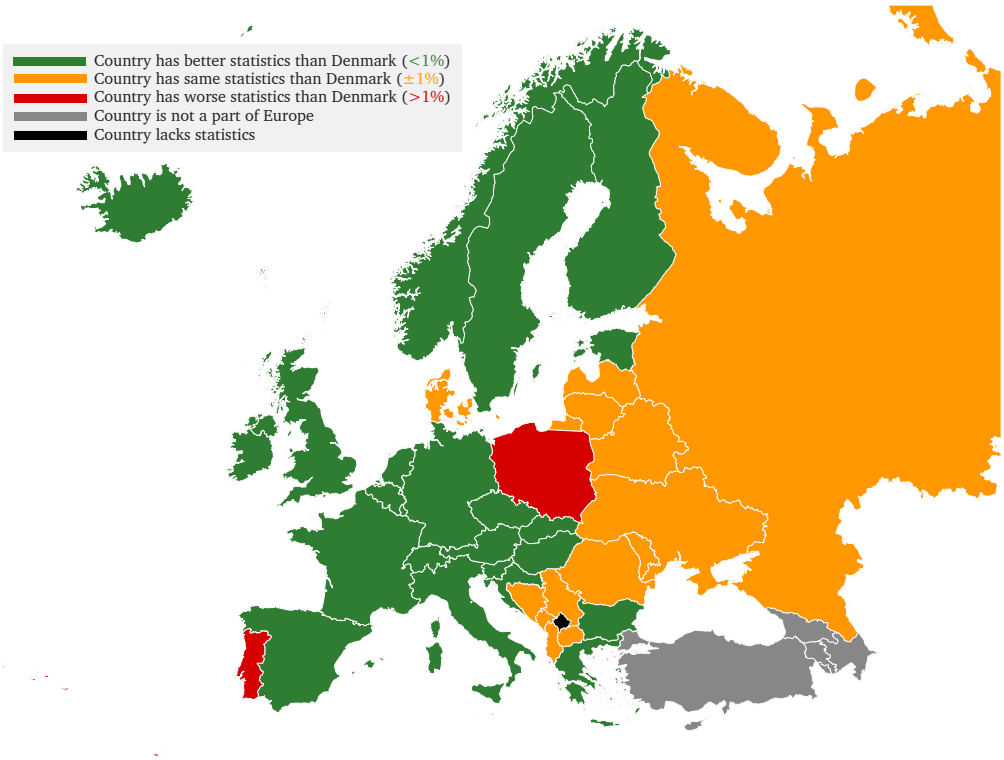


Figure 2.7: *Map with European countries compared to Denmark (DK) on comparative prevalence of impaired glucose tolerance (IGT) according to the statistics given in Figures 2.2 to 2.5 on pages 10–11.*

2.4 Prevalence and incidence of diabetes in Denmark

The situation in Denmark with regards to the statistics on diabetes, has been highly monitored by the Danish National Diabetes Register [12] until late 2015. From that time, Register for Selected Chronic Diseases (*Register for udvalgte kroniske sygdomme* in Danish) (RUKS) undertook the task of monitoring the situation in Denmark.

It is the Danish National eHealth Authority that is responsible for RUKS [13]. Although the period of the epidemiological data is only sampled and presented between the year 1996 and 2012, it is still possible to get an overview of the negative tendency of the development.

Figure 2.8 presents the data of prevalence and incidence of diabetes for people living in Denmark. The data are visualised into three dimensions; namely age groups, time (years), and either prevalence or incidence depicted in thousands ($\times 10^3$).

For better visualisation and comparison, the 3D bar plots in Figure 2.8 on page 16 have been modified by colouring each bar according to its height in each plot.

Furthermore, for easier comparison, the age groups have been sorted in a descending order according to the overall largest average of prevalence and incidence, respectively.

2.4.1 Prevalence

Prevalence is referred to the proportion or measurement of all individuals in a certain region, e.g. country, that have the disease at a specific time.

As presented on Figure 2.8, the age groups, which have the highest prevalence of diabetes in Denmark, are the older groups of people, especially people in the age group of 60-69 years.

This group has a prevalence of approximately 90.000 diabetics in the year of 2012. This is followed by the older age group of people between 70-79 years with approximately 70.000 diabetics in the same year.

The third largest age group, with prevalence of the disease, is the group of people between 50-59 years having nearly 60.000 diabetics.

People, who are older than the age of 80 years, is the fourth largest group on average having nearly 40.000 diabetics.

It is quite remarkable that there is a relative large gap between the age groups 20-29 years and below and age group 30-39 years and above. This may indicate that rather type 2 than type 1 diabetes represent the majority of the prevalence.

2.4.2 Incidence

Incidence is referred to the measurement of the number of new individuals that, at a particular time, have been diagnosed with a disease. Therefore, the incidence can to some degree be regarded as the rate of change of the prevalence.

The bottom part of Figure 2.8 shows the incidence of individuals in Denmark between the year 1997 and 2011.

On average, the age group with individuals between 60-69 years have the highest incidence peaking in 2010. Following this particular group, individuals in both age groups of 70-79 and 50-59 are very similar in fact and among the top three age groups that have a significant higher incidence on average compared to all age groups.

The age groups with individuals between 40-49 years and above 80 years are the 4th and 5th age group in terms of highest incidence, respectively, followed by age groups 30-39, 20-29, 10-19, and 0-9. These four mentioned age groups have the smallest amount of incidence as well as rate of incidence change over time. However, Figure 2.8 shows that there is a slight increase in incidence over the years between 1997 and 2001.

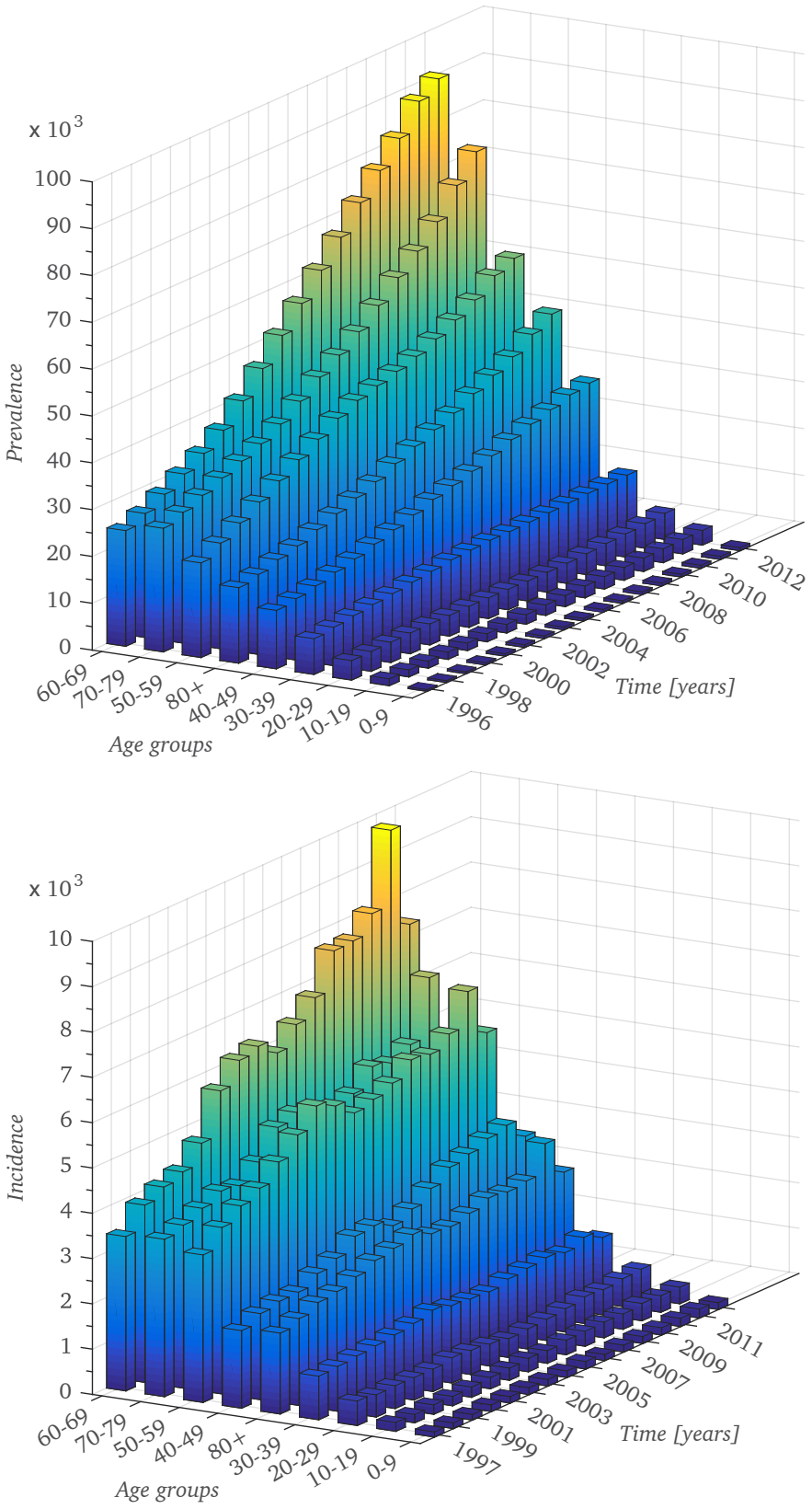


Figure 2.8: *Statistics on prevalence and incidence (upper and lower plot, respectively) of all diabetics in Denmark registered by the Danish National Diabetes Register [12] from 1996-2012. The age groups have been sorted according to the overall highest prevalence and incidence, respectively. Data were obtained from [12].*

2.4.3 Mortality of diabetes in Denmark

If not treated properly, diabetes and its complications can in worst case lead to (premature) death. In most countries this is a huge threat [1].

On a global scale, it is estimated by International Diabetes Federation [1] that the mortality as of 2015 annually is around 5 million, corresponding to what is a little less than the people living in Denmark.

According to [1], estimating the annual number of deaths globally is not an easy task, however. This is for two reasons; (1) more than a third of the countries lack data on diabetes-related mortality and (2) routine health statistics underestimate the number of deaths caused by diabetes. As an example, diabetes-caused cardiovascular complications resulting in death may be wrongly assumed as something else than diabetes.

In Denmark the mortality rate has been monitored by the National Diabetes Register [12] since 1997 where the rate of mortality was nearly two times higher than the rest of the population. Figure 2.9 on page 19 presents the data gathered by [12]. Here it is evident that the mortality rate has been decreasing over the years. Furthermore, it is evident that the mortality rate is higher for men than for women.

Over the years the mortality ratio has fallen for both genders, and was at the time of 2012 about 1.49 on average, indicating that important factors as technology and treatment quality for diabetics in the Danish healthcare sector have been improved considerably.

Since the mortality ratio over the years has been decreasing, means that diabetics are living longer due to better treatment strategies. Despite of this, the negative aspect of this is that the Danish healthcare sector are burdened even more, as expenses rises in order to help the diabetics maintain a good and stable health, which eventually causes greater quality of life for the patients.

The statistics displayed in Figure 2.9 is based on statistics that is known as standardised mortality rate (SMR) [12]. The way SMR is calculated is by standardising the diabetics with respect to rest of the population on parameters like gender and age groups separated by five years, where 85+ is the upper age group.

SMR indicates how many deaths there are among diabetics, compared to the amount of expected deaths if the diabetics had the same mortality rate as the (healthy) population.

2.4.4 Forecasting the future of mortality ratio in Denmark

Since the Danish National Diabetes Register stopped keeping track of the epidemiological statistics with regards to diabetes since 2012, and RUKS only to some degree is maintaining some of the statistics, there are apparently no further statistics on how the mortality ratio in Denmark is going since 2012 [14].

Therefore, basic regression with three simple models has been performed in MATLAB on the data in order to make a simple forecast on the future of mortality rate in Denmark. The forecasting is made with 95 % confidence interval, and is presented in Figure 2.10 on the next page with a histogram analysis of the residuals for each fit in Figure 2.11 on page 20 and a Table 2.1 on page 20 presenting the goodness of fit (GOF) statistics. From Figures 2.10 to 2.11 it seems that, if the improvements in the mortality ratio for diabetics continues as so far, there might be an opportunity that diabetics on average will have a mortality ratio equal to the (healthy) population earliest in 2030 counting on the linear model, solely.

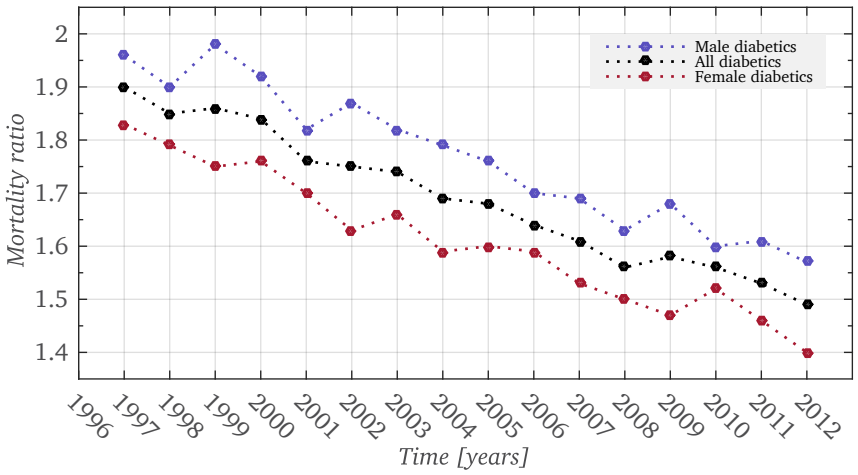


Figure 2.9: *Diabetics mortality ratio in Denmark in relation to the remaining Danish population, from 1997-2012. Linear interpolation is performed automatically between the samples, for each category in the legend. Data were obtained from Det Nationale Diabetesregister [12].*

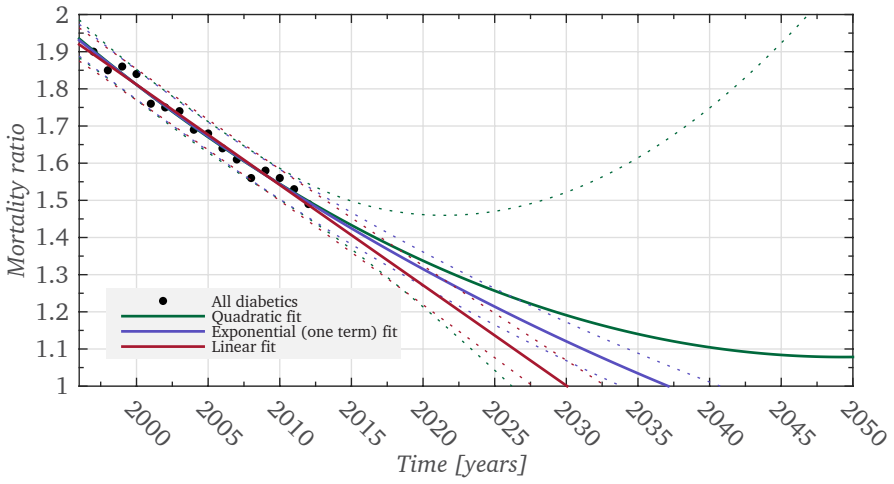


Figure 2.10: *Simple forecast with 95 % confidence intervals (dashed lines) on diabetics mortality ratio in Denmark in relation to the remaining Danish population, based on samples from 1997-2012. The forecast is based on regression of different models which are given in the legend of this Figure. Information on the goodness-of-fit (GOF) statistics of each model is given in Table Table 2.1 on the next page. Data without the simple forecast is obtained from Det Nationale Diabetesregister [12].*

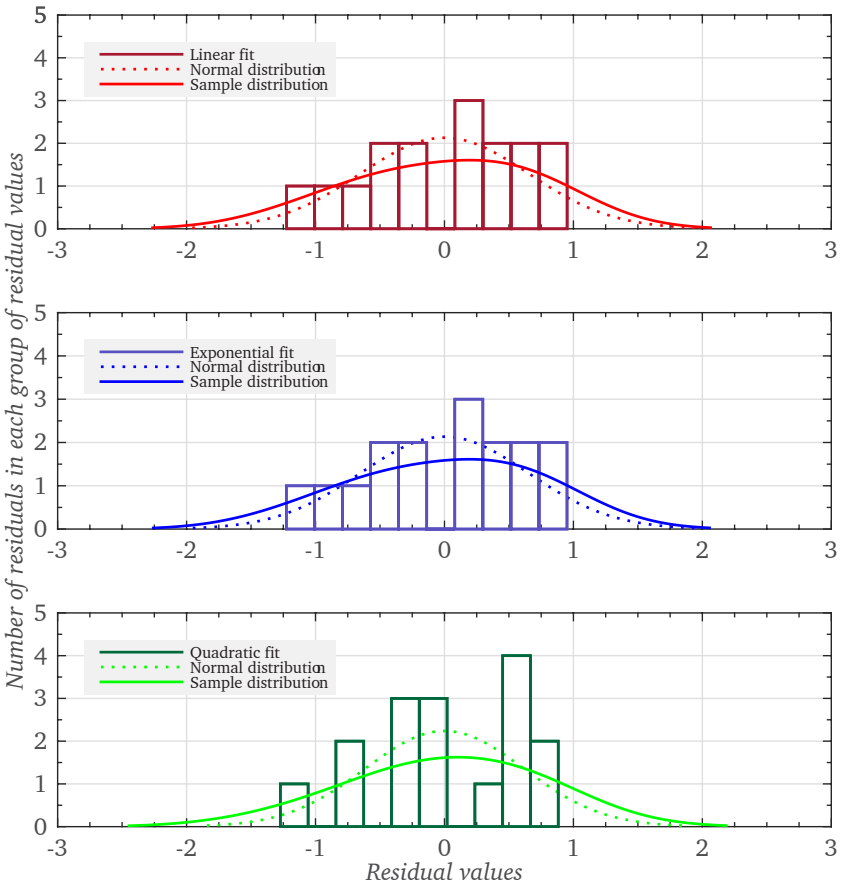


Figure 2.11: *Histogram of the residuals for each fitted model presented in Figure Figure 2.10 on page 19, to look for a roughly normal distribution.*

	Fitting model		
	Linear	Exponential	Quadratic
Summed squared error (SSE)	6.3800	6.3500	5.6602
R-square	0.9812	0.9813	0.9834
Degrees of freedom (DEF)	14	14	13
Adjusted R-square	0.9799	0.9800	0.9808
Root mean squared error (RMSE)	0.6751	0.6735	0.6598

Table 2.1: *Overview of the GOF statistics for the used fitted models in Figure Figure 2.10 on page 19.*

2.5 Societal costs of diabetes in Denmark

Due to the advances in the treatment of diabetes, diabetics are living longer and are having less risk of diabetes-related complications. However, there are increased reported cases of diabetes. Green et al. [15]

The rate of prevalence and incidence of people with diabetes in Denmark is rapidly increasing, as is appears from Figure 2.8 on page 16.

As reported by Green et al. [15], as part of the Danish Diabetes Impact Study 2013, the prevalence of individuals with diabetes has been doubled from the time period between 2000 and 2011. This is cased by a combination of a rise in the incidence rate due to improved diagnosis at the general practitioners and outpatient departments, as well as a fall in the mortality rate for diabetics.

The scenario described above is not only true for Denmark, but can be translated globally or at least to a vast majority of all countries due to the same development.

Diabetes is a 'chronic' disease that is putting a heavy and economic burden on each society [16].

According to the epidemiological statistics, this pandemic keep rising the overall burden as medical care needs to be given to an increasing amount of subjects with diabetes. This is despite that new successful anti-diabetic medicine is being introduced and researched upon – the demand is rising, and will continue so over the years. [1, 9, 14]

It is estimated in a recent article by Sortsø et al. [16] that diabetes has a heavy economical burden for the Danish society of 31.8 billion DKK annually. This amount of expenses is categorised into the following:

- losses of productivity, accounting for 13 billion DKK (approximately 41 %)
- nursing sector, accounting for 6.4 billion DKK (approximately 20 %)
- treatments at general practitioners and outpatient departments at hospitals, accounting for 5.5 billion DKK (approximately 17 %)
- medicine expenses, accounting for a little more than 1 billion DKK (approximately 3 %)

Long-term complications as cardiovascular disease, retinopathy, nephropathy and amputations are not solely devastating for the individual, but also a heavy societal cost.

One in every four patients has complicated long-term complications which by Sortsø et al. [16] is estimated to take up nearly 60 % of the total expenses.

In another article by Sortsø et al. [17], it is approximated that 650.000 individuals in Denmark will have diabetes. For this reason the societal costs will rise to an estimated value of 60 billion DKK which is twice the present societal costs.

The milestone of more than one million diabetics in Denmark will be passed before 2040 from the study by [17], as the number of individuals with diabetes will be 1.2 million. As a consequence of this, societal costs will exceed more than 100 billion DKK.

Chapter 3

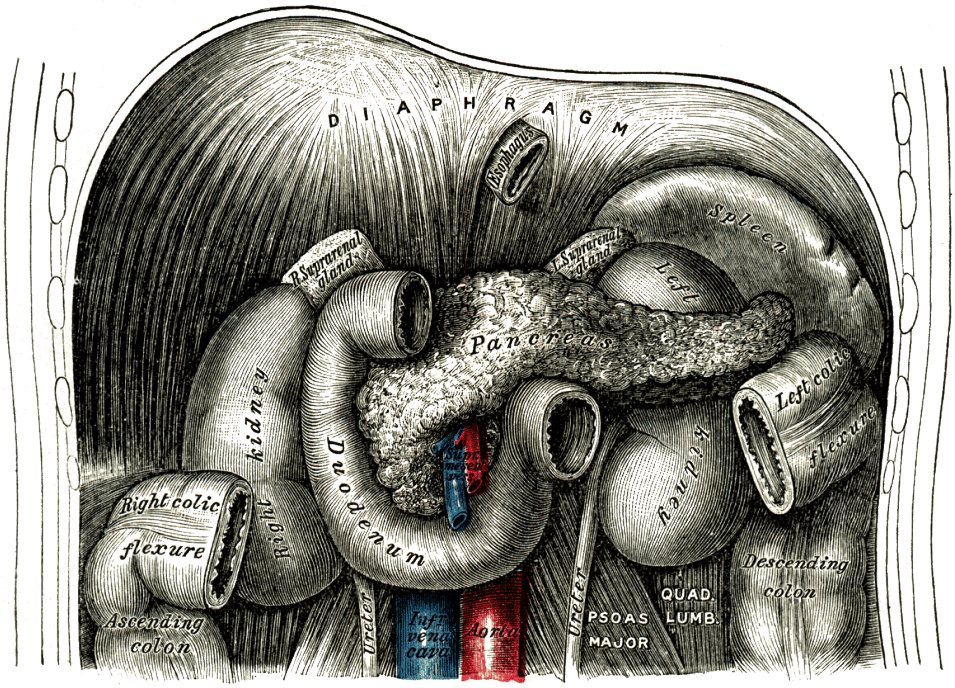
Pathophysiology of diabetes

3.1 The pancreas and its role in maintaining homeostasis

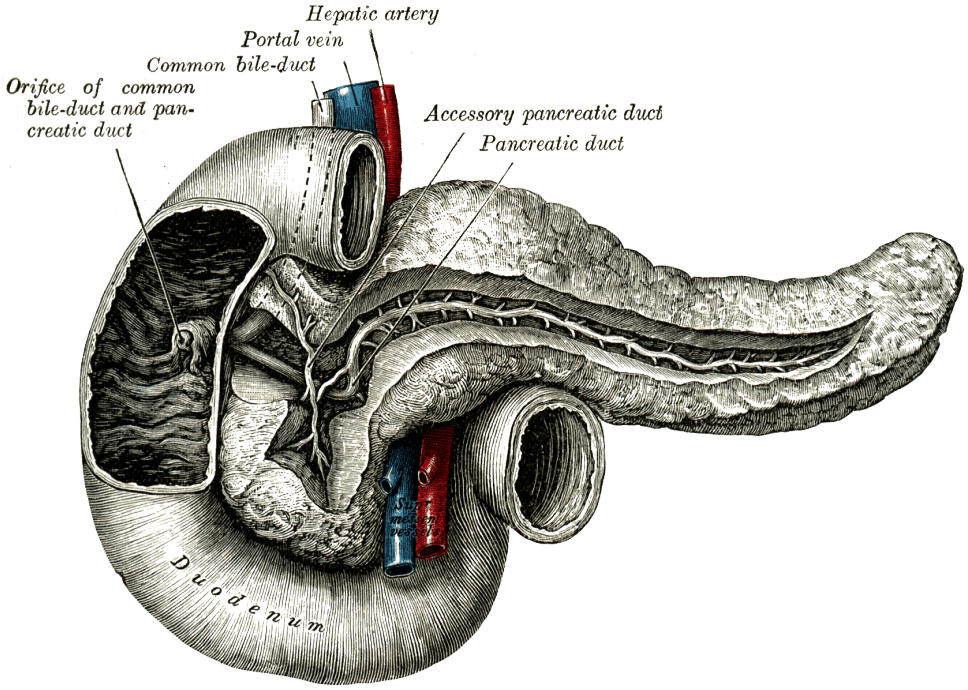
The pancreas is a very important organ and gland within the human body. It is an exocrine organ playing a vital role in the digestive system, but also an endocrine gland playing a vital role in regulating the blood glucose concentration and thereby homeostasis. [18]

The anatomical position of the pancreas in the human body is within the abdominopelvic cavity in the loop between the inferior border of the stomach and the proximal portion of the small intestine. This is illustrated in Figure 3.1(a). The pancreas is slender and pale with a nodular (lumpy) consistency. [18]

In adults, the pancreas is between 20 cm to 25 cm long and weights roughly 80 g as reported by [18] but 65 g, reported by [19], which also reports that the range is between 45 g to 120 g.



(a) Anatomical position of pancreas in the abdominopelvic cavity.



(b) Close-up of the pancreas.

Figure 3.1: *Annotated illustrations of the pancreas in anterior view. Adapted from Gray's Anatomy Premium Edition* [20].

Approximately 99 % of the pancreatic volume consists of gland cells organised in clusters. These are known as *pancreatic acini*. The pancreatic acini are all having ducts attached to them consisting of duct cells, which together with gland cells secrete large amounts of an alkaline fluid, rich on enzymes, reaching the lumen of the digestive track through a network of secretory ducts. [18]

In contrast, the endocrine part of the pancreas consist of tiny cells arranged in clusters, scattered around the exocrine cells mentioned above. These endocrine clusters have a special name, namely *islets of Langerhans* or pancreatic clusters.

Since the earlier mentioned exocrine cells account for roughly 98 % to 99 % of the pancreatic volume, the endocrine cells in the pancreatic clusters account roughly for only 1 % to 2 % of the pancreatic mass. [18, 19]

Despite the small endocrine proportion, the pancreas holds approximately around 1-2 million islets of Langerhans. [18, 21]

The islets of Langerhans are structured in round, sometimes oval, arrangements which are all surrounded and fenestrated by numerous capillaries. The hormone-secreting cells in the pancreatic clusters are divided into five different types, which are displayed in Table 3.1 on the next page. The five cell types are contained in each islet, but in different proportions, however. This is covered in more detail in Table 3.2 on page 27.

Cell type	Hormone(s) produced
α	glucagon
β	insulin, amylin
γ/PP/F	pancreatic polypeptide
δ	somatostatin
ϵ	grehlin

Table 3.1: *Overview of cell types within the islets of Langerhans, and which hormones they are producing. [18, 19, 21]*

α cells

This cell type is responsible for the production of the peptide hormone glucagon. Its function is to raise the blood glucose levels when hypoglycaemia is present. This process can happen due to an increased rate of glycogen breakdown in the liver which in turn release glucose into the bloodstream.

β cells

This cell type is responsible for the production of insulin, which, in contrast to glucagon, lowers the blood glucose. Insulin and glucagon are said to act antagonistic [21].

The reason behind the fall in the blood glucose level happens because insulin stimulates and increases the rate of glucose uptake as well as utilisation by the vast majority of cells in the body. Insulin is essential for cellular nutrient uptake and thus for the survival of the organism [19]. Besides, the liver and skeletal muscle cells intensify the synthesis of glycogen in the liver during an insulin response. Additionally, insulin promotes the absorbed nutrients as fat

❧

Insulin is practically like any peptide hormone proteolytically derived from a precursor molecule known as proinsulin, which is inactive from a biological perspective. In order to become into an biologically active insulin molecule, proinsulin is split into three parts. That is an A and B chain which is connected by two sulfur bridges.

The third part which proinsulin is split into is a C chain referred to as connecting peptide (C-peptide), which together with insulin is released into the bloodstream in an equimolar ratio of 1:1. [19, 22]

As C-peptide is produced and released in equal amounts to insulin, it can therefore be used to assess endogenous insulin secretion, including in patients who are insulin treated. Assessment of insulin secretion is potentially helpful in clinical practice. Thanks to technological advances in assays and collection techniques, the assessment of insulin secretion by using C-peptide has become less expensive, more reliable and available more than ever before. [23]

❧

What is still little known is that the β cells also co-secrete a peptide known as islet amyloid polypeptide (IAPP) which is also referred to as amylin. [18, 19]

Amylin molecules may polymerise from large intra-islet amyloid deposits under pathological conditions which are characteristic for type 2 diabetes and pancreas-

related tumours known as insulinoma. Amylin molecules can also occur in patients with chronic type 1 diabetes as well as in elderly individuals. [19]

γ/PP/F cells

In spite of the fact that this cell type is the least well studied, as reported by Md. Shahidul Islam [19], this islet secrete the hormone pancreatic polypeptide. This is the reason why it is also referred to as the PP cell. The γ cell mass in the pancreatic islets is occupying around 80 % of the cells, especially in the ventral pancreas.

The PP hormone, however, is responsible for inhibiting the contractions of the gallbladder. It also regulates the production of some pancreatic enzymes. It is believed that pancreatic polypeptide helps controlling the rate of nutrient absorption in the digestive tract.

δ cells

δ cells are known to release the polypeptide hormone somatostatin, which is identical to the growth-hormone-inhibiting hormone.

The somatostatin hormone was formerly referred to as somatotropin release-inhibiting factor. The function of this hormone is to inhibit in great extent the release of glucagon and insulin [19]. Another function of somatostatin is that it slows the rate of nutrient absorption from food as well as secretion of enzyme along the digestive tract. [18, 24]

ϵ cells

The ϵ cell produces the hormone grehlin why it is also referred to as the Ghrehlin cell, though. This peptide hormone is the latest cell type that has been discovered. As reported by Md. Shahidul Islam [19], this hormone was first discovered and isolated from rat stomach, and later localised to a specific type of cells in the human adult islet of Langerhans.

Growth hormone release is thought to be related to the grehlin hormone, as well as metabolic regulation, and energy balance. However, more research has to be carried out in order to gain more knowledge about this hormone and its role in the human body. [19]

❧

The knowledge about structure and function of the pancreas is an ongoing science and topic in itself and therefore still in research. This means that new cell types are being discovered and where the physiologic role is still subject to further investigation. [18, 19]

As an example, the ϵ cell type, has been discovered quite recently, of which a small amount only is known. This is also true for γ cell secreting pancreatic polypeptide which is the least well studied hormone among the hormones produced in and secreted by the islets of Langerhans.

❧

The relative proportion of the various endocrine cell types in the human islets can vary considerably from study to study and do also vary depending on where in the pancreas they are located [19]. There is a difference in the proportion depending on if the cells are located anterior or posterior in the pancreas.

Md. Shahidul Islam [19] describes that the proportion of cell types in percentage is distributed as displayed in Table 3.2.

	Islet volume in % (in adult)		
Cell type	Dorsal (posterior)	Ventral (anterior)	Total
α	15-20	<1	15-20
β	70-80	10-20	70-80
γ/PP/F	<1	80	15-25
δ	5-10	2	5-10
ϵ	1	1	1

Table 3.2: *Cell types in the adult human endocrine pancreas with their proportion in volume (%). [19]*

Nonetheless, it is well considered that primarily two cell types are the most important and dominant among all the types in terms of endocrine function. That is, α and β cells. [18]

These two cell types are considered to account for the main key role of the body's blood glucose regulation which is described in more detail in Section 3.2 on the following page.

3.2 Homeostasis and adaptive blood glucose regulation

It is of vital importance for the human body to maintain homeostasis in a variety of different subsystems of which the endocrine is one.

For this particular subsystem, it is crucial to maintain balance within blood glucose concentrations – otherwise the homeostasis will be disturbed. If this happens, it is only a matter of time and extent of the disturbance(s), before symptoms will appear. If no response is triggered, either by the internal adaptive regulation mechanism of the body, or by an external mechanism, different symptoms start appearing. This can cause great danger that can lead to severe internal injuries or in worst case death, if no direct response is established.

Over time, if the efficacy of the adaptive regulatory endocrine subsystem decreases, and the human body can not adapt to that, symptoms will start appearing. If this keeps developing over a longer period of time, without any improvements (or treatments), the acute symptoms will be followed by chronic symptoms and declining quality of life.

Normal blood glucose levels according to [18, 21, 24] are considered to be within 70 mg/dL to 110 mg/dL, corresponding to nearly 4 mmol/L to 6 mmol/L (preprandial). If the blood glucose concentration exceed normal levels, the peptide hormone insulin will be secreted into the bloodstream via pancreatic ducts in the pancreas. Elevated levels of various amino acids, of which arginine and leucine are included, do also trigger a secreting response of insulin, produced by the pancreatic β cells.

As it is illustrated in Figure 3.2 on the next page, homeostasis in the endocrine subsystem can be disturbed in two ways.

A disturbance is made of either rising blood glucose levels, or falling blood glucose levels. Depending on which of the two types of perturbations, the adaptive endocrine system initialises certain hormone secretion leading to different reactions that will restore the homeostasis, eventually.

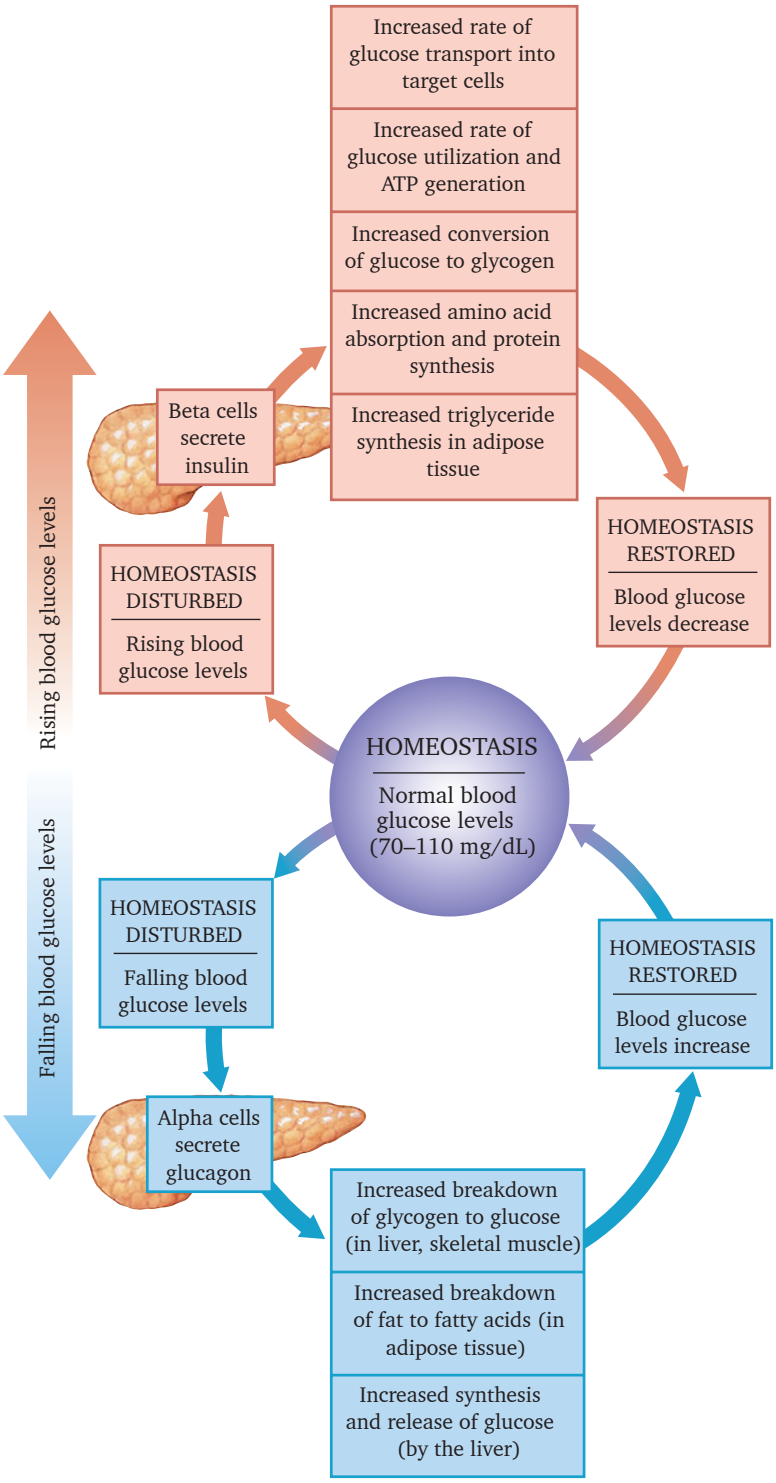


Figure 3.2: *Schematic overview of the regulation of blood glucose concentrations in order to maintain homeostasis. Adapted from Martini et al. [18].*

Rising blood glucose levels

The pancreatic β cells start secreting insulin when levels of blood glucose elevate above the normal range, i.e. 70 mg/dL to 110 mg/dL. The hormone stimulates glucose utilisation to support growth and to build carbohydrate reserves (in terms of glycogen storage in skeletal muscle and liver cells) and subcutaneous lipid reserves (in terms of triglycerides).

As described shortly above, during abundant levels of glucose in the blood, the auto-adaptive regulation mechanisms accelerate the use of glucose, of which circulating glucose levels in the body converge towards normal ranges.

In the following, the main effects of insulin on its target cells, once it has been secreted, will be listed and described briefly. Furthermore, the mechanisms are also illustrated in Figure 3.2 on page 29. [18]

- Increased rate of glucose transport into target cells. Glucose transport proteins are increased in amount, leading to accelerating glucose uptake in the plasma membrane via facilitated diffusion mechanism. Such a mechanism is regulated by a concentration gradient for glucose. Due to this, the energy-rich molecule adenosine triphosphate (ATP) is not required for this.
- Accelerating glucose utilisation (all target cells) and enhanced production of ATP. This effect occurs for two reasons:
  - **1)** The rate of glucose utilisation is proportional to its availability, meaning that when more glucose enters the cell, more is used.
  - **2)** Second messengers activate a key enzyme involved in the initial steps of glycolysis.
- Stimulating formation of glycogen polysaccharide molecules in skeletal muscles and liver cells. When excess glucose enters these cells, it is stored as glycogen.
- Stimulating absorption of amino acids and protein synthesis.
- Stimulating formation of triglycerides in adipose tissue. Insulin stimulates the absorption of fatty acids and glycerol by adipocytes, which store these components as triglycerides. Adipocytes also increase their absorption of glucose, and excess glucose is used in the synthesis of additional triglycerides.

Falling blood glucose levels

As illustrated on Figure 3.2 on page 29, the other scenario that can take place is that of falling blood glucose levels. If this happens, the pancreatic α cells secrete glucagon into the bloodstream. This endocrine hormone mobilises the energy reserves that have been stored in the body, mainly skeletal muscle and liver cells.

The enzyme adenylate cyclase is activated once glucagon binds to a receptor of a target cell's plasma membrane. This enzyme catalyses the conversion of ATP into cyclic adenosine monophosphate (cAMP), which acts as a second messenger of which cytoplasmic enzymes are activated. [18]

The primary effects of glucagon are listed in the following:

- Stimulating the catabolism of glycogen in skeletal muscle and liver cells. As mentioned before, glycogen is a energy-rich polysaccharide molecule. Once glycogen has been broken down into glucose, these molecules are either metabolised for energy in skeletal muscle fibres or released into the bloodstream by liver cells.
- Stimulating the breakdown of triglycerides in adipose tissue. The adipocytes then release the fatty acids into the bloodstream for use by other tissues, mainly for hormone metabolism.
- Stimulating the production and release of glucose by the liver. Liver cells absorb amino acids from the bloodstream, convert them to glucose, and release the glucose into the circulation. This process of glucose synthesis in the liver is called gluconeogenesis.

The results are a reduction in glucose use and the release of more glucose into the bloodstream. Blood glucose concentrations soon rise towards normal ranges.

Pancreatic α and β cells monitor blood glucose concentrations, and they secrete glucagon and insulin independently. However, because the α and β cells are highly sensitive to changes in blood glucose levels, any hormone that affects blood glucose concentrations, indirectly affects the production of both insulin and glucagon. Autonomic activity also influences insulin production: Parasympathetic stimulation enhances insulin release, and sympathetic stimulation inhibits it.

3.3 Brief overview and description of all recognised types of diabetes

Diabetes is a 'chronic' condition that occurs when the body cannot produce enough insulin or cannot use insulin and is diagnosed by observing raised levels of glucose in the blood. Insulin, as mentioned previously, is a hormone produced in the pancreas. It is required to transport glucose from the bloodstream into the body's cells, where it is used as energy. The lack, or ineffectiveness, of insulin in a person with diabetes means that glucose remains circulating in the blood.

Over time, the resulting high levels of glucose in the blood (known as hyperglycaemia) cause damage to many tissues in the body leading to the development of disabling and life-threatening health complications.

The transition from being healthy to developing diabetes is usually not spontaneous.

People with raised blood glucose levels that are not high enough for a diagnosis of diabetes are said to have impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).

These above-mentioned conditions are known as intermediate hyperglycaemia and commonly referred to as pre-diabetes.

IGT is diagnosed following a glucose tolerance test, most often an OGTT. This involves measuring the blood glucose concentration 2 hours after a drink containing 75g of glucose. In IGT, the glucose level is higher than normal, but not high enough to make a diagnosis of diabetes (i.e. between 7.8 and 11.1 mmol/L (140 to 200 mg/dL)). IFG is diagnosed when the fasting glucose level is higher than normal, but not high enough to make a diagnosis of diabetes (i.e. between 6.1 and 7 mmol/L (110 and 125 mg/dL)).

Raised levels of HbA1c in the non-diabetic range can also be used to identify people at risk of developing type 2 diabetes. Further information on diagnosis of particularly type 2 diabetes using OGTT and HbA1c in clinical practise is provided in the following section.

People with intermediate hyperglycaemia are at increased risk of developing type 2 diabetes. It shares many characteristics with type 2 diabetes, and is associated with advancing age and the inability of the body to use the insulin it produces. Not everyone with intermediate hyperglycaemia develop type 2 diabetes, as lifestyle interventions, such as healthy diet and physical activity, can work to prevent the progression to manifest diabetes.

Overall, there are three main types of diabetes:

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes

Less common types include the following:

- Monogenic diabetes: the result of a genetic mutation, e.g. maturity-onset diabetes of the young (MODY) and neonatal diabetes. An estimated 4% to

13% of diabetes in children is due to monogenic diabetes, according to International Diabetes Federation [9].

- Secondary diabetes, which arises as a complication of other diseases, such as hormone disturbances (e.g. Cushing's disease or acromegaly) or diseases of the pancreas.

3.3.1 Type 1 diabetes

Type 1 diabetes is caused by an autoimmune reaction, in which the body's defence system attacks the insulin-producing beta cells in the pancreas. As a result, the body can no longer produce the insulin it needs. Why this occurs is not fully understood. The disease can affect people of any age, but onset usually occurs in children or young adults. People with this form of diabetes need insulin every day in order to control the levels of glucose in their blood. Without insulin, a person with type 1 diabetes may consequently have a fatal outcome.

As it is described in [1], type 1 diabetes often develops suddenly and can produce symptoms such as the following:

- Abnormal thirst and a dry mouth
- Frequent urination
- Lack of energy, extreme tiredness
- Constant hunger
- Sudden weight loss
- Blurred vision

Type 1 diabetes is diagnosed by an elevated blood glucose level in the presence of the symptoms listed above. In some parts of the world, where type 1 diabetes is less common, the symptoms may be mistaken for other illnesses, and it is therefore essential that the blood glucose is measured when one or more of the above symptoms are present. [9]

Sometimes the type of diabetes is not clear and additional tests are required to distinguish between type 1 and type 2 diabetes or the rarer forms of diabetes.

With daily insulin treatment, regular blood glucose monitoring and maintenance of a healthy diet and lifestyle, people with type 1 diabetes can lead a normal, healthy life. [1]

The number of people who develop type 1 diabetes is increasing. The reasons for this are still unclear, but may be due to changes in environmental risk factors and/or viral infections. [1]

Medication for type 1 diabetes

It is essential that everyone with type 1 diabetes has an uninterrupted supply of high-quality insulin.

There are several different types of insulin available, but as a minimum, regular quick-acting insulin and longer-acting should be available to everyone in all parts of the world. [1]

3.3.2 Type 2 diabetes and pre-diabetes

Type 2 diabetes is the most common type of diabetes (approximately 90 %). It usually occurs in adults, but is increasingly reported in children and adolescents. The number of people with type 2 diabetes is growing rapidly worldwide, and even more than people with type 1 diabetes. This rise is associated with ageing populations, economic development, increasing urbanisation, less healthy diets and reduced physical activity. [9, 18]

In type 2 diabetes, the body is able to produce insulin but becomes resistant so that the insulin is ineffective. Over time, insulin levels may subsequently become insufficient. Both the insulin resistance and deficiency lead to high blood glucose levels.

❧

From [9, 25], the symptoms of type 2 diabetes include the following:

- Frequent urination
- Excessive thirst
- Weight loss
- Blurred vision
- Major cardiovascular events

Many people with type 2 diabetes remain unaware of their condition for a long time because the symptoms are usually less marked than in type 1 diabetes and may take years to be recognised.

However, during this time, the body is already being damaged by excess blood glucose levels. As a result, many people already have evidence of complications when they are diagnosed with type 2 diabetes.

Although the exact causes for the development of type 2 diabetes are still not known, there are several important risk factors. The most important ones are excess body weight, physical inactivity, and poor nutrition. Other factors which play a role are ethnicity, family history of diabetes, past history of gestational diabetes, and advancing age. [9, 25]

Especially, the latter has been depicted in Figure 2.8.

❧

In contrast to people with type 1 diabetes, most people with type 2 diabetes do not require daily insulin treatment to survive. The cornerstone of treatment of type 2 diabetes is the adoption of a healthy diet, increased physical activity, and maintenance of a normal body weight (i.e. non-pharmacological treatment/lifestyle modification).

❧

People with IGT or IFG are at increased risk of developing type 2 diabetes. Especially, IGT shares many characteristics with type 2 diabetes and is associated with advancing age and the inability of the body to use the insulin it produces.

Not everyone with IGT develop type 2 diabetes. A large body of evidence supports the effectiveness of lifestyle interventions, including healthy diet and physical exercise, in preventing the progression to type 2 diabetes. [9]

Lifestyle intervention can lead to normalisation of glucose tolerance in many people with IGT. In case of progression to type 2 diabetes, other treatment than non-pharmacological may be indicated.

Diagnosis of type 2 diabetes

The primary diagnostic biomarker for diabetes is the HbA1c biomarker. In 2011, the World Health Organisation (WHO) has recommended to use HbA1c as a diagnostic criterium with a cut-off threshold $\geq 48\,\text{mmol/mol}$ which corresponds to $\geq 6.5\,\%$. From 2012 these diagnostic criteria have been officially recommended by the Danish Health Authority to be used in outpatient departments.

Other diagnostic measures as fasting plasma glucose (FPG) and 120-min OGTT shall continue to be used as diagnostic criteria, if HbA1c is not possible in a given situation and in patients with gestational diabetes. Here, an oral dosage of glucose (i.e. 75 g) is administered [25]. The diagnostic criteria of diabetes, IFG, and IGT are provided in Table 3.3.

	Venous blood sample (mmol/L)
Diabetes	≥ 7.0
Fasting plasma glucose (FPG)	≥ 11.1
and/or	
120-min value of OGTT	
Impaired glucose tolerance (IGT)	< 7.0
Fasting plasma glucose	7.8–11.0
and simultaneously	
120-min value of OGTT	
Impaired fasting glucose (IFG)	6.1–6.9
Fasting plasma glucose	< 7.8
and simultaneously	
120-min value of OGTT	

Table 3.3: *The diagnostic criteria of diabetes and impaired glucose tolerance measured in the plasma of the venous blood samples. [25]*

The reason why the diagnostic criteria has been changed to use the HbA1c analysis method is due to the following:

- The analysis method behind HbA1c has finally been standardised. This is covered in more detail in the following.
- Low variance (analytically and biologically).
- Fasting prior a diagnostic test is not necessary as in other tests.
- Indicates well chronic hyperglycaemia.
- Better association to cardiovascular disease than FPG.

As explained by Danish College of General Practitioners (DSAM) [25], the choice of using HbA1c forwardly comes with consequences for many patients, as when a patient has been diagnosed once with type 2 diabetes, then that patient is labelled diabetic for the rest of his life. This is regardless whether or not on at some point in the future obtain a level of HbA1c that is beneath the diagnostic cut-off threshold on $\geq 48\,\text{mmol/mol}$ ($\geq 6.5\,\%$).

Medication for type 2 diabetes

A number of oral medications are available to help control blood glucose levels.

Metformin is well-established and one of the most effective. Gliclazide is a sulfonylurea, which increases insulin secretion in type 2 diabetes. Both medications are on the World Health Organization list of essential medicines for type 2 diabetes. They should both be available and accessible to all people with type 2 diabetes worldwide, according to need. [3, 9, 25]

Other commonly used treatments for type 2 diabetes include glucagon-like peptide 1 (GLP-1) analogues (injectable treatments that are not insulin) and dipeptidyle peptidase 4 (DPP4) inhibitors. These treatments both enhance the body's natural response to ingested food, reducing glucose levels after eating. [9]

If blood glucose levels continue to rise, however, people with type 2 diabetes may be prescribed insulin as in type 1 diabetes.

In addition, people with all types of diabetes may need access to medications to control blood pressure and cholesterol levels due to long-term complications of hyperglycaemia. [25]

3.3.3 Major complications caused by diabetes

People with diabetes are at higher risk of developing a number of disabling and life-threatening health problems than people without diabetes.

Consistently, high blood glucose levels can lead to serious diseases affecting the heart and blood vessels, eyes, kidneys and nerves.

People with diabetes are also at increased risk of developing infections. In almost all high- income countries, diabetes is a leading cause of cardiovascular disease, blindness, kidney failure and lower-limb amputation.

The growth in prevalence of type 2 diabetes in low- and middle- income countries means that without effective strategies to support better management of diabetes, it is likely that there will be large increases in the rates of these complications.

Diabetes complications can be prevented or delayed by maintaining blood glucose, blood pressure and cholesterol levels as close to normal as possible. Many complications can be picked up in their early stages by screening programmes that allow treatment to prevent them becoming more serious.

In the following, each of the major complications caused by this non-communicable disease will be described briefly based on [1, 9]. Figure 3.3 illustrates the major complications that can be developed as a result of the lack of regular control.

Eye disease

Many people with diabetes develop some form of eye disease (retinopathy), which can damage vision or provoke blindness in worst case.

Persistently high levels of blood glucose are the main cause of retinopathy. The network of blood vessels that supply the retina can become damaged in retinopathy, leading to permanent loss of vision. Retinopathy however, can become quite advanced before it affects vision, and it is therefore essential that people with diabetes have regular eye screenings. [1, 9, 25]

If detected early, treatment can be given to prevent blindness. Keeping good control of blood glucose greatly reduces the risk of retinopathy.

Oral health

Diabetes can pose a threat to oral health. There is an increased risk of inflammation of the tissue surrounding the tooth (periodontitis) in people with poor glucose control.

Periodontitis is a major cause of tooth loss and is associated with an increased risk of cardiovascular disease. Management of periodontitis is very important in people with diabetes because optimal oral hygiene can prevent tooth loss, facilitate a healthy diet and improve glucose control. [1, 9, 25]

Cardiovascular disease

Cardiovascular disease is the most common cause of death and disability among people with diabetes. The cardiovascular diseases that accompany diabetes include angina, myocardial infarction (heart attack), stroke, peripheral artery disease and congestive heart failure. High blood pressure, high cholesterol, high blood glucose

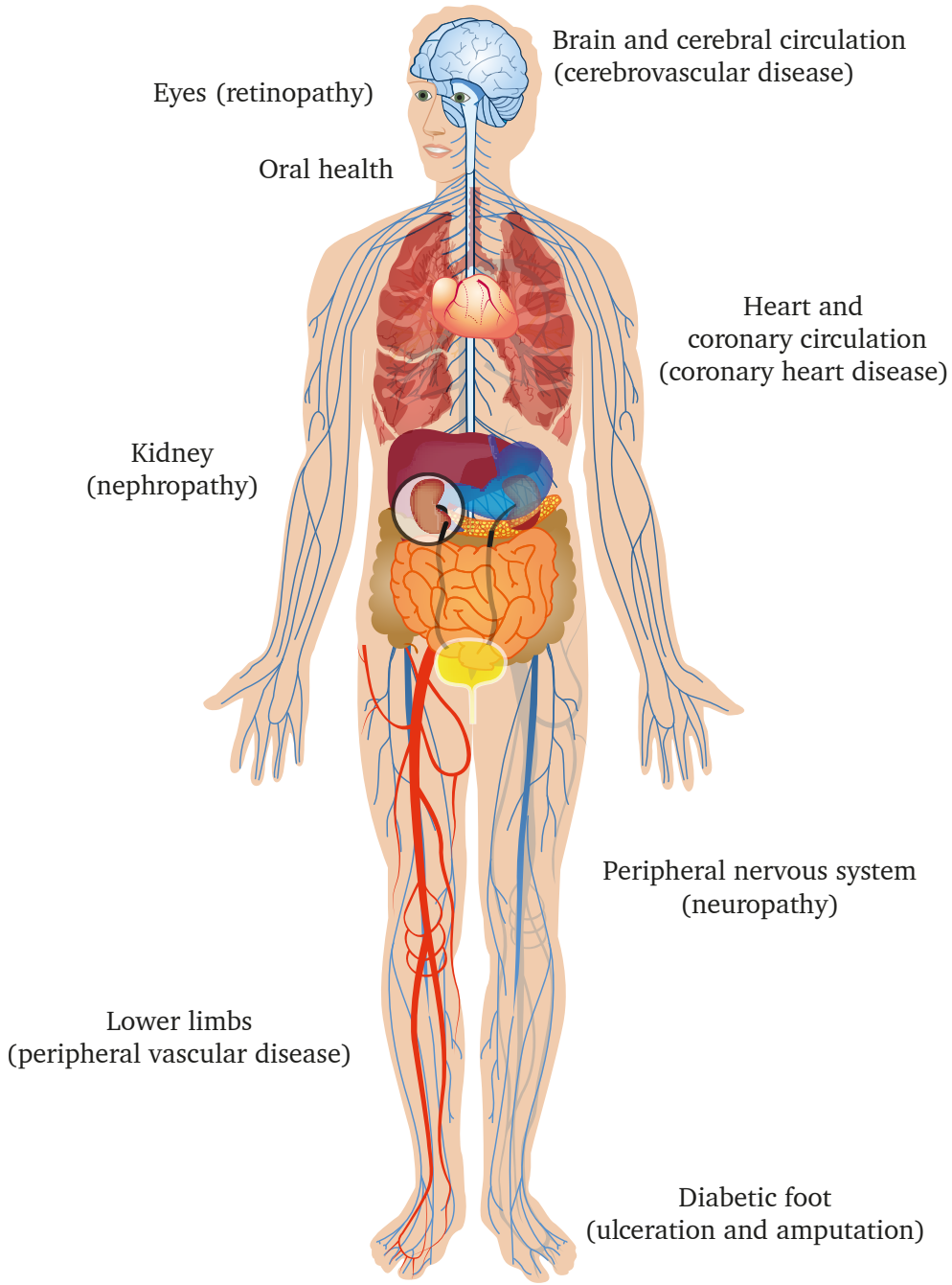


Figure 3.3: *Major complications caused by diabetes. Adapted from International Diabetes Federation* [9].

and other risk factors contribute to the increased risk of cardiovascular complications. [1, 9, 25]

Nephropathy

Kidney disease (nephropathy) is far more common in people with diabetes than in people without diabetes; diabetes is one of the leading causes of chronic kidney disease. The disease is caused by damage to small blood vessels, which can cause the kidneys to be less efficient, or to fail altogether. Maintaining near-normal levels of blood glucose and blood pressure greatly reduces the risk of nephropathy. [1, 9, 25]

Pregnancy complications

Women with any type of diabetes are at risk of a number of complications during pregnancy, as high glucose levels can affect the development of the foetus. Women with diabetes therefore require careful monitoring before and during pregnancy to minimise the risk of these complications. High blood glucose during pregnancy can lead to changes in the foetus that cause it to gain excess size and weight. This in turn can lead to problems during delivery, injuries to the child and mother, and low blood glucose (hypoglycaemia) in the child after birth. Children who are exposed to high blood glucose in the womb are at higher risk of developing type 2 diabetes later in life. [1, 9, 25]

Neuropathy

Nerve damage (neuropathy) also results from prolonged high blood glucose levels. It can affect any nerve in the body.

The most common type is peripheral neuropathy, which mainly affects the sensory nerves in the feet. This can lead to pain, tingling, and loss of sensation. This is particularly significant because it can allow injuries to go unnoticed, leading to ulceration, serious infections, and in some cases amputations.

Neuropathy can also lead to erectile dysfunction, as well as problems with digestion, urination and a number of other functions. [1, 9, 25]

Diabetic foot

As well as nerve damage, people with diabetes can experience problems with poor circulation to the feet, as a result of damage to blood vessels. These problems increase the risk of ulceration, infection and amputation. People with diabetes face a risk of amputation that may be more than 25 times greater than that in people without diabetes.

However, With good management, a large proportion of amputations can be avoided. Even when a person undergoes amputation, the remaining leg – and the person's life – can be saved by good follow-up care from a multidisciplinary foot team. In view of these risks, it is important that people with diabetes examine their feet regularly. [1, 9, 25]

Chapter 4

Physiological modelling of the glucose-insulin system and assessment of insulin sensitivity

As mentioned, the glucose-insulin system is one of the most studied in the field of physiological modelling, with a high clinical implication [2, 7]. The glucose metabolism is a negative feedback mechanism. In a normal individual with a healthy glucose-insulin system, an increase in the blood glucose concentration will cause a counter reaction in which insulin will be secreted from within the pancreatic ducts and into the bloodstream causing the blood glucose concentration to decrease to euglyceamic levels.

In pathophysiology such as type 2 diabetes this is degraded. Initially, this is presented as pre-diabetes, where the function of insulin sensitivity and responsivity of the β cells are being deteriorated. In contrast, the system in type 1 diabetes is altered in another way, where secretion of insulin is gradually impaired. A brief description of the system is depicted in Figure 4.1.

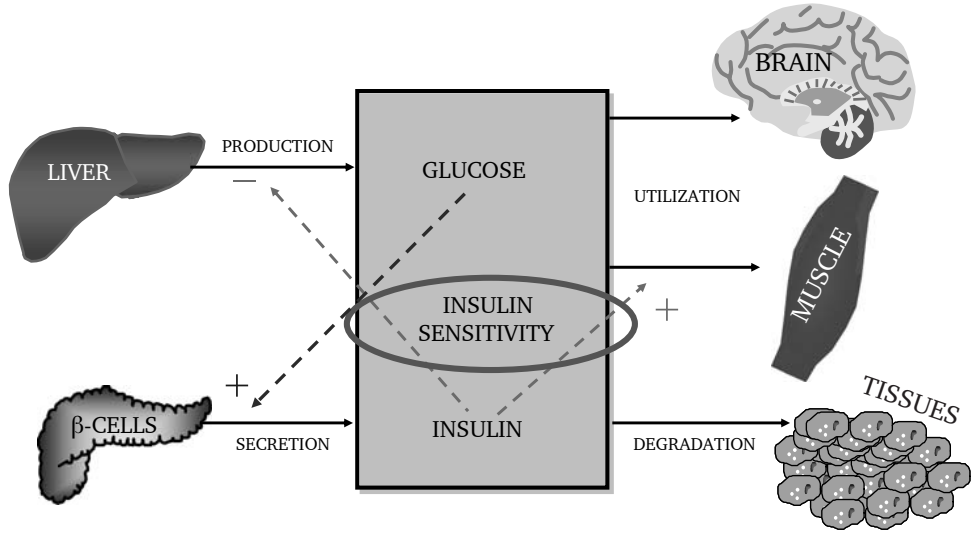


Figure 4.1: *Schematic illustration of the glucose-insulin system. Adapted from [7].*

The relationship between insulin sensitivity and pancreatic responsivity in the glucose-insulin system is a complex one. In [6] this is referred to as the hyperbolic law of glucose tolerance, meaning that pancreatic β cells can compensate for the low peripheral insulin sensitivity in the long term. Individuals that are at risk of developing type 2 diabetes or pre-diabetes operate on a curve that is closer to the origin, as insulin resistance causes an even lesser compensation in the pancreatic

secretion. Bergman [6] introduces a way of measuring the health of the β cells by the introduction of the disposition index (DI). This is a constant of the ability of the β cells adapting to peripheral resistance. The DI is described as the product of insulin sensitivity and insulin secretion as shown in Figure 4.2.

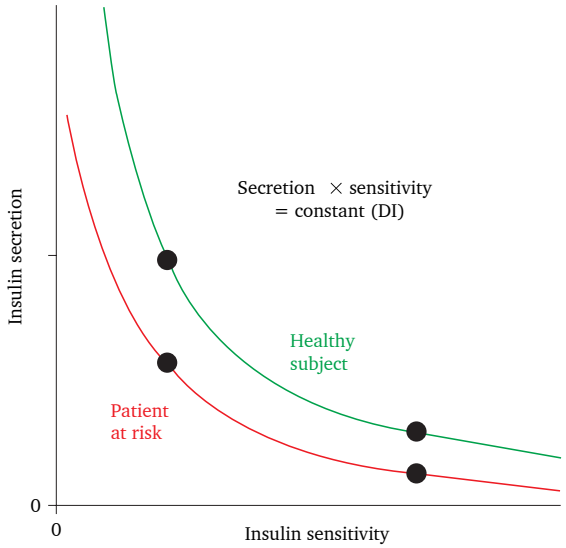


Figure 4.2: *Schematic illustration of the disposition index in the glucose-insulin system introduced by [6], where it was adapted from.*

4.1 Most recognised models in estimating insulin sensitivity

In order to physiologically model and quantitatively understand the glucose-insulin system, dynamic data is, obviously, required. Although HbA1c reflects the average blood glucose level for a limited period (i.e. 8-12 weeks) [18, 21, 24], it does not describe how well or poor the system is responding to perturbations such as a meal.

With an OGTT, however, it is possible to observe how the system responds if more blood samples are being measured frequently. Unfortunately, the OGTT is usually only performed with a measure of the 120-min value for diagnostic purposes. Even if more blood samples were collected and analysed during an OGTT, it would be rather challenging to physiologically model and quantitatively understand the system. Mainly, this is because the gastrointestinal tract should be included in the modelling (see below). [2]

Prior to modelling the system using OGTT, IVGTT was used in the first place, as the glucose-insulin system was generally easier to describe with an IVGTT. Notably, IVGTT is often referred to as FSIGT, meaning that the IVGTT is frequently sampled over a couple of hours. These terms are often used interchangeably.

At the time where the minimal model was proposed by Bergman and colleagues, they proposed to use an IVGTT to estimate insulin sensitivity in the late 1970's. Even though several other methods have been proposed previously, these were more difficult to perform and much more labour intensive and economic expensive [4–7]. Later on, the minimal model that was related to the IVGTT, was optimised

by using the C-peptide instead of insulin concentrations as well as using tracers to obtain even better estimates of parameters included in the model [6, 7].

A comparison between the IVGTT minimal model and OGTT minimal model is illustrated in Figure 4.3.

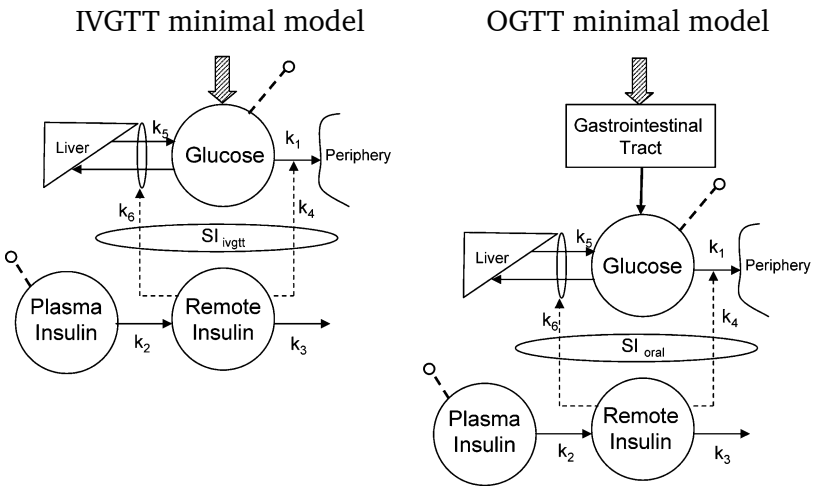
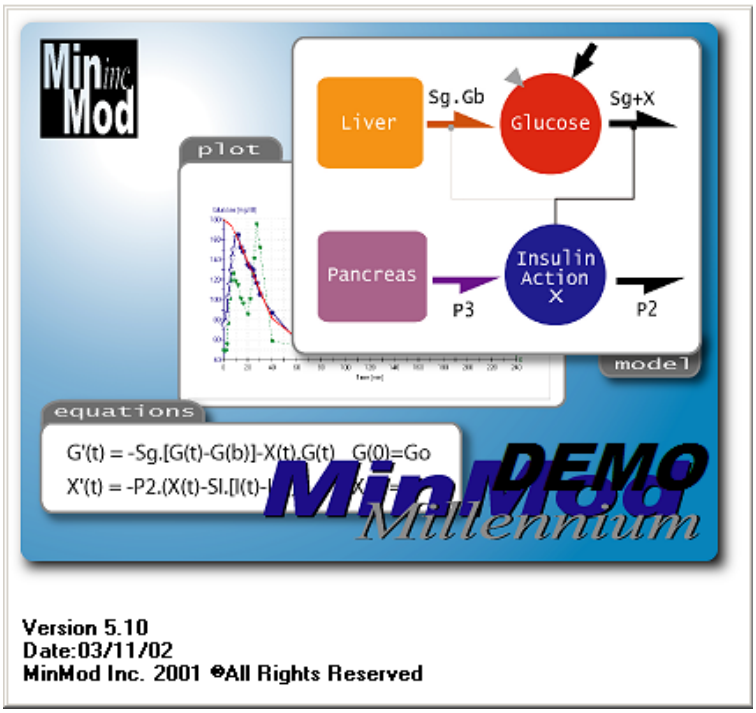
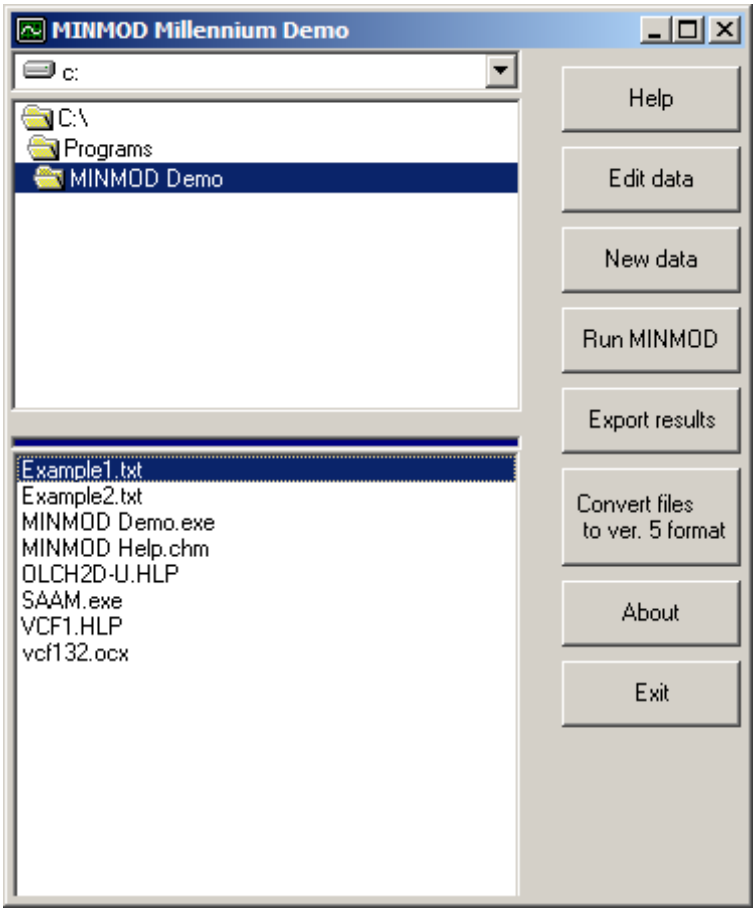


Figure 4.3: *Schematic illustration of IVGTT minimal model and OGTT minimal model. The rate constants, k, are characterised by either material fluxes (solid line) or control actions (dashed lines). Adapted from [2].*

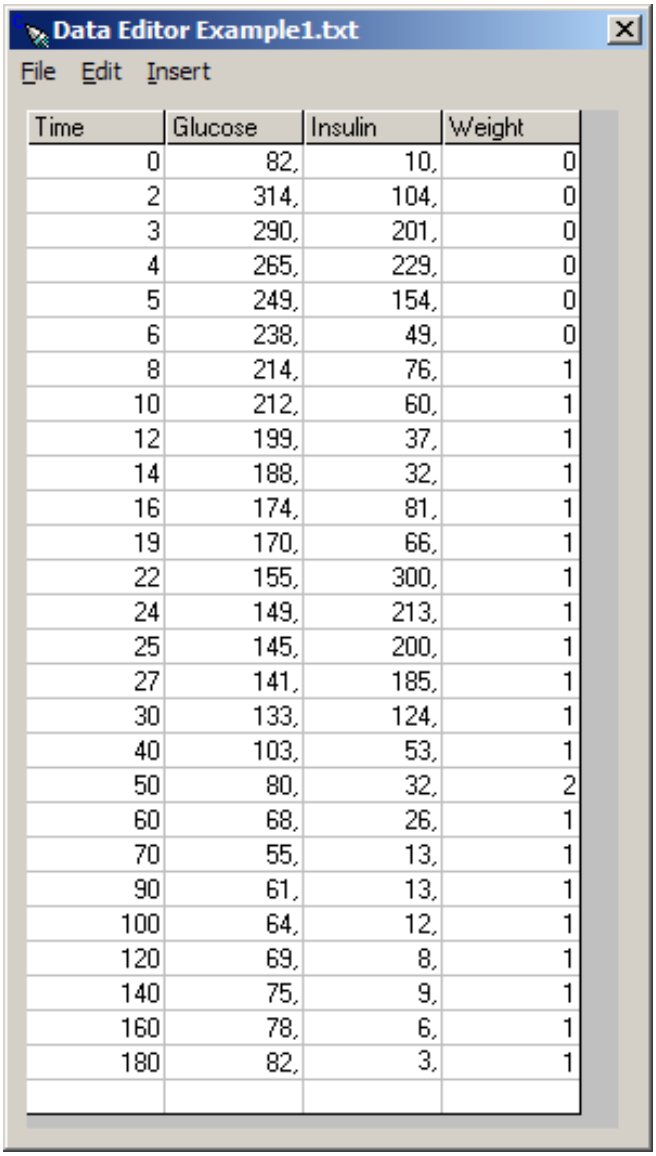
The Bergman minimal model was afterwards implemented as a PC Application named MINMOD around mid 1980's [5], which over the years was maintained and named MINMOD Millennium around the 2000's [6, 8]. It has to be recognised that this PC application seems to no longer being updated even though it has shown to be user-friendly, fast, and highly reliable. Several screen shots of the demo version of MINMOD Millennium are shown in the following.



(a) Splash screen.

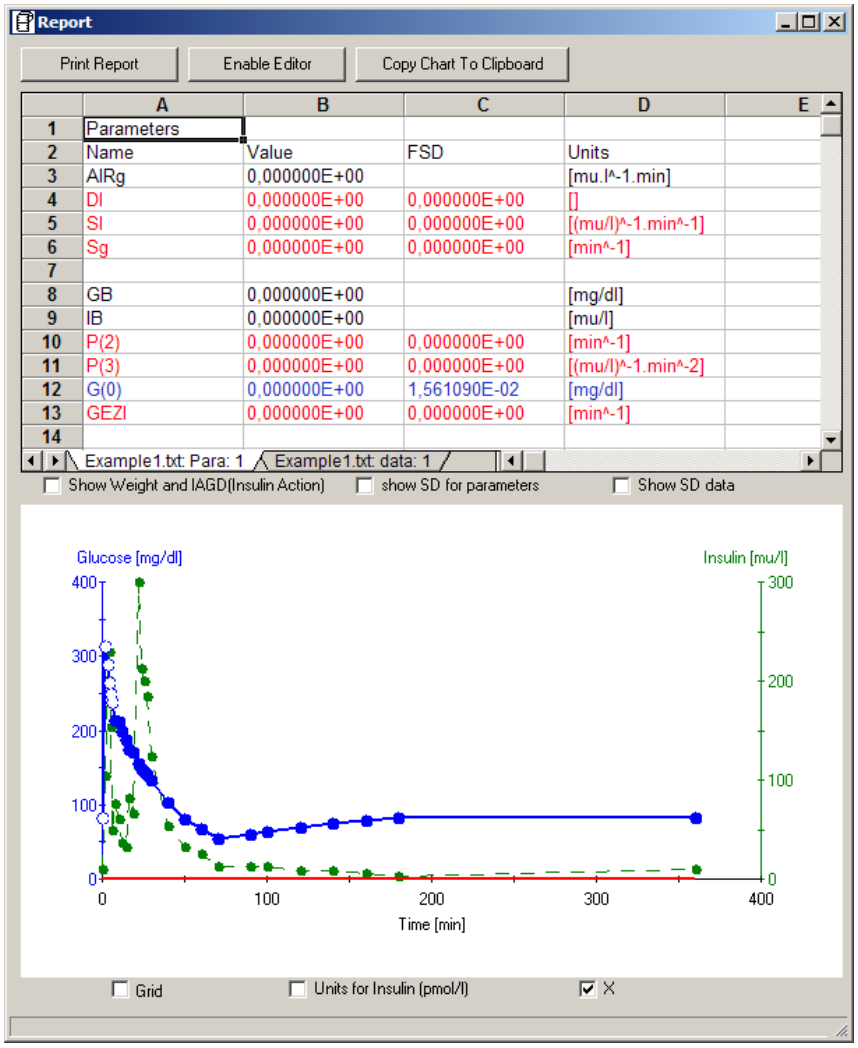


(b) Main overview window.



Time	Glucose	Insulin	Weight
0	82,	10,	0
2	314,	104,	0
3	290,	201,	0
4	265,	229,	0
5	249,	154,	0
6	238,	49,	0
8	214,	76,	1
10	212,	60,	1
12	199,	37,	1
14	188,	32,	1
16	174,	81,	1
19	170,	66,	1
22	155,	300,	1
24	149,	213,	1
25	145,	200,	1
27	141,	185,	1
30	133,	124,	1
40	103,	53,	1
50	80,	32,	2
60	68,	26,	1
70	55,	13,	1
90	61,	13,	1
100	64,	12,	1
120	69,	8,	1
140	75,	9,	1
160	78,	6,	1
180	82,	3,	1

(c) Data editor window.



	A	B	C	D	E
1	Parameters				
2	Name	Value	FSD	Units	
3	AIRg	0,000000E+00		[mu.l^-1.min]	
4	DI	0,000000E+00	0,000000E+00	[]	
5	SI	0,000000E+00	0,000000E+00	[(mu/l)^-1.min^-1]	
6	Sg	0,000000E+00	0,000000E+00	[min^-1]	
7					
8	GB	0,000000E+00		[mg/dl]	
9	IB	0,000000E+00		[mu/l]	
10	P(2)	0,000000E+00	0,000000E+00	[min^-1]	
11	P(3)	0,000000E+00	0,000000E+00	[(mu/l)^-1.min^-2]	
12	G(0)	0,000000E+00	1,561090E-02	[mg/dl]	
13	GEZI	0,000000E+00	0,000000E+00	[min^-1]	
14					

(d) Data analysis window.

Figure 4.4: *Several screen shots from MINMOD Millennium. [6, 8]*

Finally, the gold standard in measuring insulin sensitivity is the euglyceamic hyperinsulinemic clamp, which is performed by couple up a subject into a closed-loop system. This is opened experimentally by maintaining the concentration of plasma glucose to a constant level around 100 μU/mL. Steady state occurs when the infusion rate of glucose is equal to the peripheral uptake of glucose. Usually, this occurs following 90–120 min. Therefore, this is a rather specific measure of insulin sensitivity. A schematic illustration of the method is depicted in Figure 4.5.

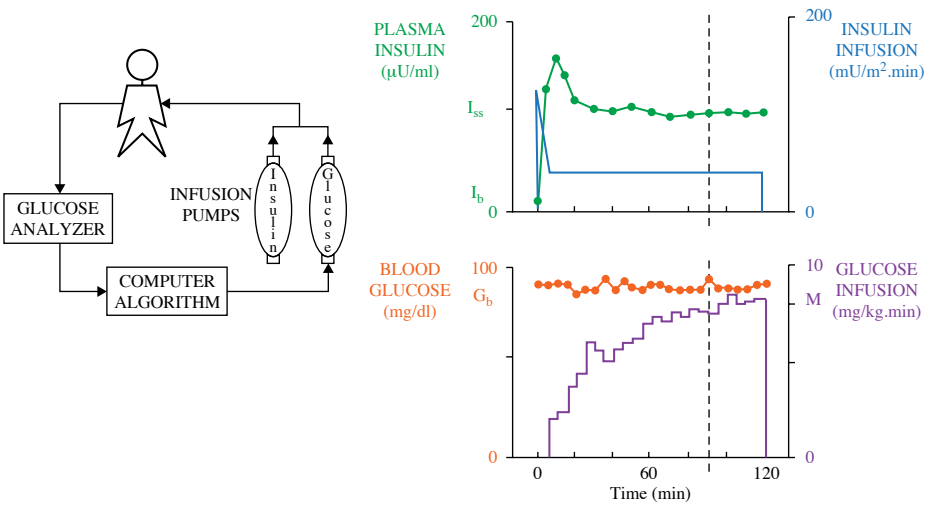


Figure 4.5: *Schematic illustration of the euglyceamic hyperinsulinemic clamp. Adapted from [7].*

However, the method is labour intensive and more expensive than the recommended procedures for screening and diagnosis, but also as a part of epidemiological research of pathophysiology of diabetes. It is also 'nonphysiological' because under normal circumstances, a constantly increased insulin concentration not coordinated with a simultaneously increase in plasma glucose is never experienced. In addition, insulin sensitivity estimated with the Bergman minimal model has shown good correlation with the euglyceamic hyperinsulinemic clamp why it has its popularity over decades. [2, 5, 6, 26]

Chapter 5

Overview with problem formulation

Diabetes is a metabolic condition caused by multifactorial causes. Besides being characterised by hyperglycaemia it is also associated with long-term multi-organ complications that can contribute to decreased quality of life for the individual which is also is a great burden in terms of societal costs. Although several types of diabetes are recognised, the most predominant is type 2 diabetes accounting for approximately 90 % of all diabetes types.

Especially, type 2 diabetes has a complex pathophysiology resulting in several phenotypes, e.g. overt type 2 diabetes vs. pre-diabetes. However, this cannot always be detected using one single blood sample test such as the HbA1c measure. This is because one blood sample has a too low 'information resolution'.

Current screening strategies and guidelines unfortunately have some limitations, which could be improved by using physiological modelling of the glucose-insulin system, i.e. synergistic effects of battery of tools as depicted in Figure 1.1 on page 1. Since late 1970's, a reliable and very often cited modelling approach, that is the Bergman minimal model, has been used in epidemiological research studies to quantitatively assess the level of insulin sensitivity. Although the model is somewhat comparable to the gold standard, the PC application MINMOD Millennium seems to be outdated and does not offer customisation of the optimisation process.

5.1 Problem formulation of the MSc Thesis

How can MINMOD be re-engineered, making it possible to estimate insulin sensitivity in healthy subjects as well as patients with type 2 diabetes from the IVGTT? And how can this be enhanced in a PC application for clinicians allowing more customisation of the optimisation process?

This problem formulation leads to the following solution strategy:

- Use the Bergman minimal model to interpret the IVGTT of healthy subjects and patients with type 2 diabetes
- Use relevant data so that comparisons and validation can be made with similar studies found in literature
- Use different optimisation algorithms to assess important measures of the glucose-insulin system to evaluate each individual's glucose-insulin response
- Use theory of optimisation to develop a PC application made with MATLAB

Part II

Methods

Chapter 6

Data extraction for the re-engineered version of MINMOD

Data for modelling the glucose-insulin system using the Bergman minimal model was extracted from the following study by Pillonetto et al. [27] after finding a similar study trying to estimate insulin sensitivity on patients with type 2 diabetes (n=10) based on an implementation of the Bergman minimal model [28]. This approach was chosen, as there is a limited body of evidence regarding high-quality raw data in the literature.

The process of data extraction was performed by GraphClick version 3.0.3, 2012 for Mac, which is a reverse data extractor. The raw data of glucose and insulin measurements are presented in the following Figure 6.1 on the next page. Figure 6.2 shows how each datum point was extracted. However, before this process, it was necessary to calibrate each of the 10 graphs in order to correctly extract the data.

After this, the data was loaded into Microsoft Excel and prepared for import into MATLAB where further data management and analysis could be carried out. The loaded raw data in Excel is presented in Figure 6.3 on page 56. Another important point is that the coordinates of each glucose and insulin sample are assumed to be most likely collected to the same time instant, i.e. same time interval, why the final time coordinate to each point is an average of the 'same' time coordinate for each glucose and insulin sample. This is shown in Figure 6.4 on page 57.

The last step included rounding the digits to the nearest whole numbers so that eventual error of a wrong interpretation of a point could be prevented. Also, whole numbers are presented in a data set for one healthy individual in [5] which was used as the only data set for a healthy individual. In this way, the data from [27] and [5] were made comparable.

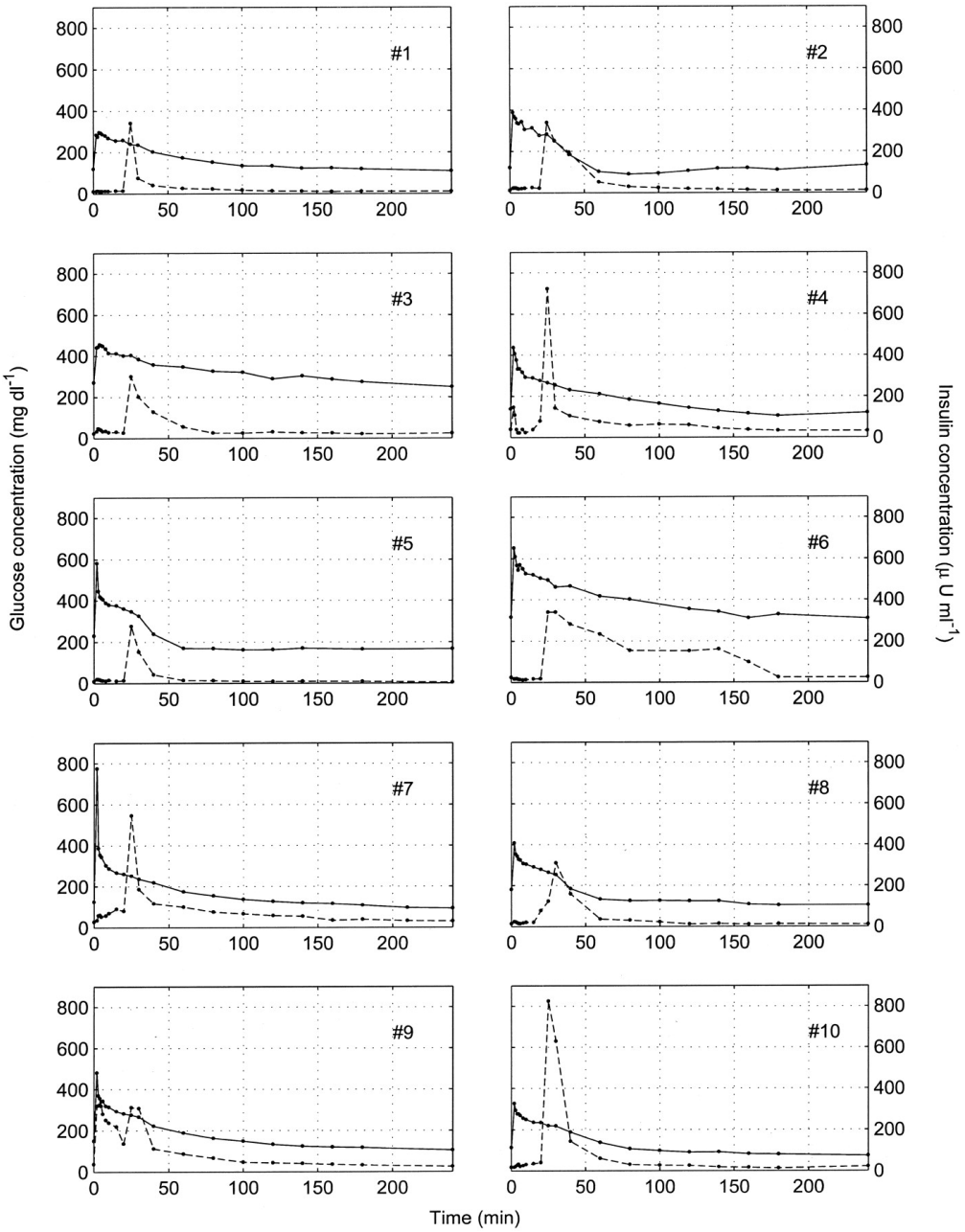


Figure 6.1: *IVGTT data gathered by the study of [27].*

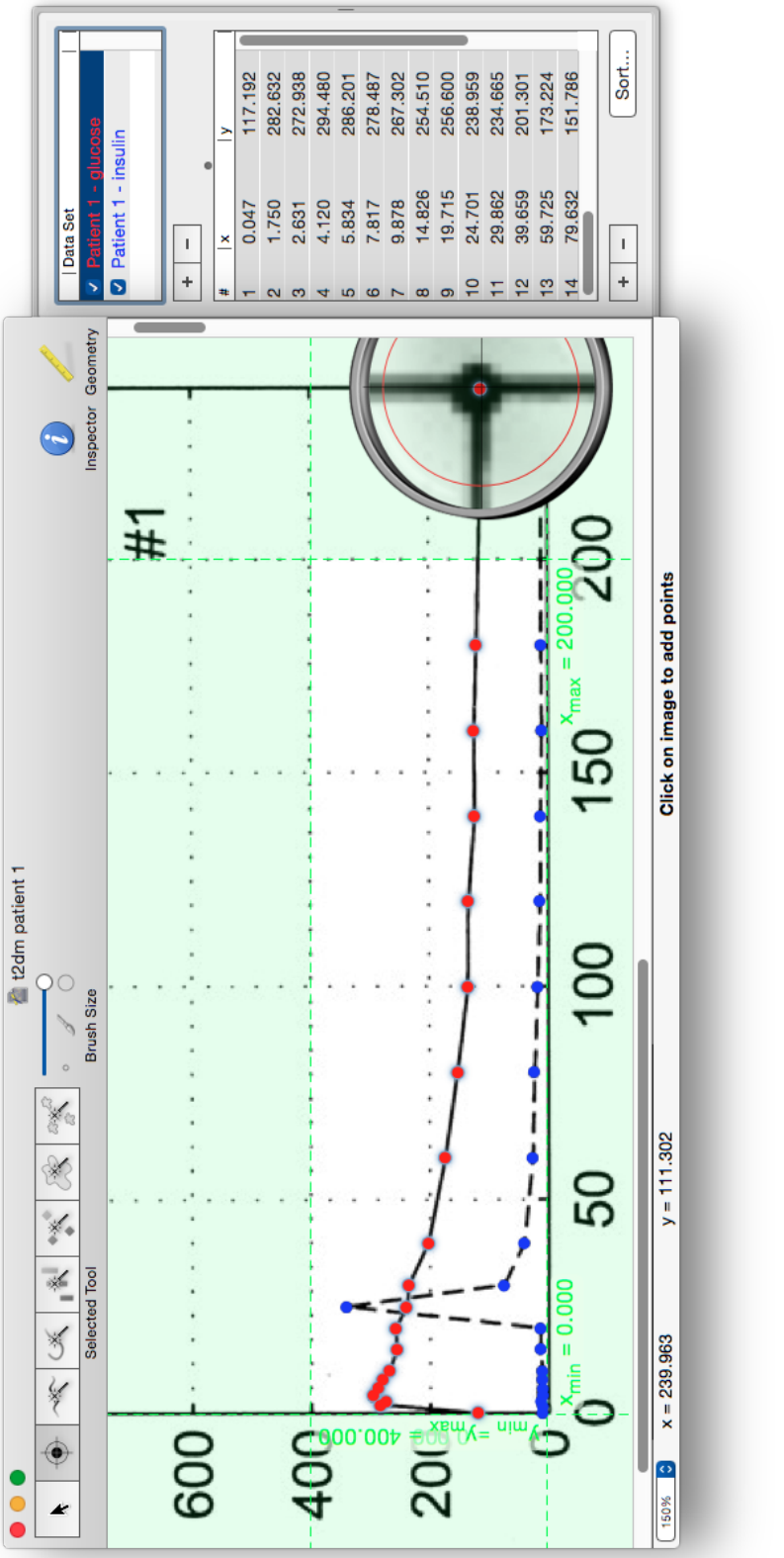
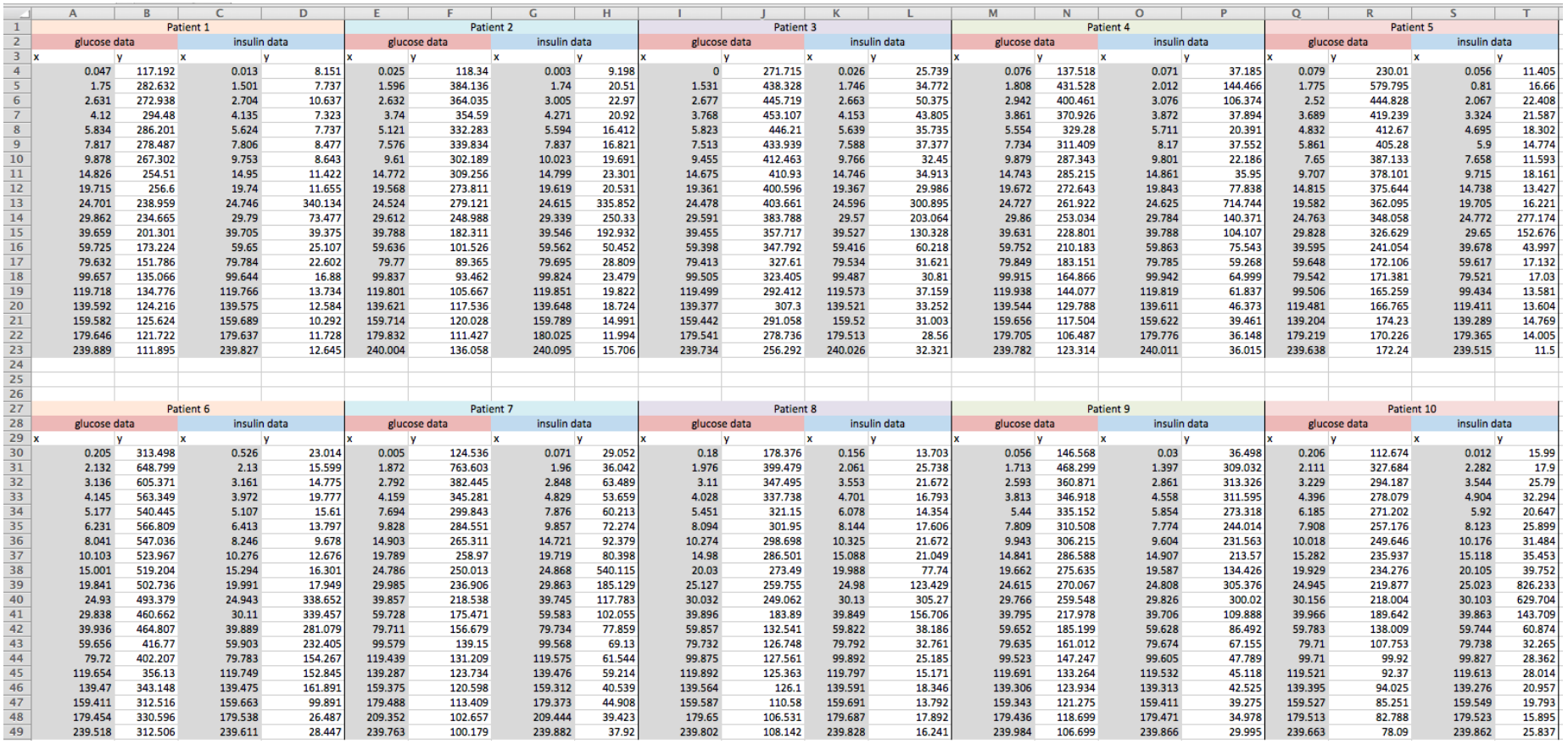


Figure 6.2: *Screen shot of method of data extraction via GraphClick version 3.0.3 for Mac.*



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
1	Patient 1				Patient 2				Patient 3				Patient 4				Patient 5			
2	glucose data		insulin data		glucose data		insulin data		glucose data		insulin data		glucose data		insulin data		glucose data		insulin data	
3	x	y	x	y	x	y	x	y	x	y	x	y	x	y	x	y	x	y	x	y
4	0.047	117.192	0.013	8.151	0.025	118.34	0.003	9.198	0	271.715	0.026	25.739	0.076	137.518	0.071	37.185	0.079	230.01	0.056	11.405
5	1.75	282.632	1.501	7.737	1.596	384.136	1.74	20.51	1.531	438.328	1.746	34.772	1.808	431.528	2.012	144.466	1.775	579.795	0.81	16.66
6	2.631	272.938	2.704	10.637	2.632	364.035	3.005	22.97	2.677	445.719	2.663	50.375	2.942	400.461	3.076	106.374	2.52	444.828	2.067	22.408
7	4.12	294.48	4.135	7.323	3.74	354.59	4.271	20.92	3.768	453.107	4.153	43.805	3.861	370.926	3.872	37.894	3.689	419.239	3.324	21.587
8	5.834	286.201	5.624	7.737	5.121	332.283	5.594	16.412	5.823	446.21	5.639	35.735	5.554	329.28	5.711	20.391	4.832	412.67	4.695	18.302
9	7.817	278.487	7.806	8.477	7.576	339.834	7.837	16.821	7.513	433.939	7.588	37.377	7.734	311.409	8.17	37.552	5.861	405.28	5.9	14.774
10	9.878	267.302	9.753	8.643	9.61	302.189	10.023	19.691	9.455	412.463	9.766	32.45	9.879	287.343	9.801	22.186	7.65	387.133	7.658	11.593
11	14.826	254.51	14.95	11.422	14.772	309.256	14.799	23.301	14.675	410.93	14.746	34.913	14.743	285.215	14.861	35.95	9.707	378.101	9.715	18.161
12	19.715	256.6	19.74	11.655	19.568	273.811	19.619	20.531	19.361	400.596	19.367	29.986	19.672	272.643	19.843	77.838	14.815	375.644	14.738	13.427
13	24.701	238.959	24.746	340.134	24.524	279.121	24.615	335.852	24.478	403.661	24.596	300.895	24.727	261.922	24.625	714.744	19.582	362.095	19.705	16.221
14	29.862	234.665	29.79	73.477	29.612	248.988	29.339	250.33	29.591	383.788	29.57	203.064	29.86	253.034	29.784	140.371	24.763	348.058	24.772	277.174
15	39.659	201.301	39.705	39.375	39.788	182.311	39.546	192.932	39.455	357.717	39.527	130.328	39.631	228.801	39.788	104.107	29.828	326.629	29.65	152.676
16	59.725	173.224	59.65	25.107	59.636	101.526	59.562	50.452	59.398	347.792	59.416	60.218	59.752	210.183	59.863	75.543	39.595	241.054	39.678	43.997
17	79.632	151.786	79.784	22.602	79.77	89.365	79.695	28.809	79.413	327.61	79.534	31.621	79.849	183.151	79.785	59.268	59.648	172.106	59.617	17.132
18	99.657	135.066	99.644	16.88	99.837	93.462	99.824	23.479	99.505	323.405	99.487	30.81	99.915	164.866	99.942	64.999	79.542	171.381	79.521	17.03
19	119.718	134.776	119.766	13.734	119.801	105.667	119.851	19.822	119.499	292.412	119.573	37.159	119.938	144.077	119.819	61.837	99.506	165.259	99.434	13.581
20	139.592	124.216	139.575	12.584	139.621	117.536	139.648	18.724	139.377	307.3	139.521	33.252	139.544	129.788	139.611	46.373	119.481	166.765	119.411	13.604
21	159.582	125.624	159.689	10.292	159.714	120.028	159.789	14.991	159.442	291.058	159.52	31.003	159.656	117.504	159.622	39.461	139.204	174.23	139.289	14.769
22	179.646	121.722	179.637	11.728	179.832	111.427	180.025	11.994	179.541	278.736	179.513	28.56	179.705	106.487	179.776	36.148	179.219	170.226	179.365	14.005
23	239.889	111.895	239.827	12.645	240.004	136.058	240.095	15.706	239.734	256.292	240.026	32.321	239.782	123.314	240.011	36.015	239.638	172.24	239.515	11.5
24																				
25																				
26																				
27	Patient 6				Patient 7				Patient 8				Patient 9				Patient 10			
28	glucose data		insulin data		glucose data		insulin data		glucose data		insulin data		glucose data		insulin data		glucose data		insulin data	
29	x	y	x	y	x	y	x	y	x	y	x	y	x	y	x	y	x	y	x	y
30	0.205	313.498	0.526	23.014	0.005	124.536	0.071	29.052	0.18	178.376	0.156	13.703	0.056	146.568	0.03	36.498	0.206	112.674	0.012	15.99
31	2.132	648.799	2.13	15.599	1.872	763.603	1.96	36.042	1.976	399.479	2.061	25.738	1.713	468.299	1.397	309.032	2.111	327.684	2.282	17.9
32	3.136	605.371	3.161	14.775	2.792	382.445	2.848	63.489	3.11	347.495	3.553	21.672	2.593	360.871	2.861	313.326	3.229	294.187	3.544	25.79
33	4.145	563.349	3.972	19.777	4.159	345.281	4.829	53.659	4.028	337.738	4.701	16.793	3.813	346.918	4.558	311.595	4.396	278.079	4.904	32.294
34	5.177	540.445	5.107	15.61	7.694	299.843	7.876	60.213	5.451	321.15	6.078	14.354	5.44	335.152	5.854	273.318	6.185	271.202	5.92	20.647
35	6.231	566.809	6.413	13.797	9.828	284.551	9.857	72.274	8.094	301.95	8.144	17.606	7.809	310.508	7.774	244.014	7.908	257.176	8.123	25.899
36	8.041	547.036	8.246	9.678	14.903	265.311	14.721	92.379	10.274	298.698	10.325	21.672	9.943	306.215	9.604	231.563	10.018	249.646	10.176	31.484
37	10.103	523.967	10.276	12.676	19.789	258.97	19.719	80.398	14.98	286.501	15.088	21.049	14.841	286.588	14.907	213.57	15.282	235.937	15.118	35.453
38	15.001	519.204	15.294	16.301	24.786	250.013	24.868	540.115	20.03	273.49	19.988	77.74	19.662	275.635	19.587	134.426	19.929	234.276	20.105	39.752
39	19.841	502.736	19.991	17.949	29.985	236.906	29.863	185.129	25.127	259.755	24.98	123.429	24.615	270.067	24.808	305.376	24.945	219.877	25.023	826.233
40	24.93	493.379	24.943	338.652	39.857	218.538	39.745	117.783	30.032	249.062	30.13	305.27	29.766	259.548	29.826	300.02	30.156	218.004	30.103	629.704
41	29.838	460.662	30.11	339.457	59.728	175.471	59.583	102.055	39.896	183.89	39.849	156.706	39.795	217.978	39.706	109.888	39.966	189.642	39.863	143.709
42	39.936	464.807	39.889	281.079	79.711	156.679	79.734	77.859	59.857	132.541	59.822	38.186	59.652	185.199	59.628	86.492	59.783	138.009	59.744	60.874
43	59.656	416.77	59.903	232.405	99.579	139.15	99.568	69.13	79.732	126.748	79.792	32.761	79.635	161.012	79.674	67.155	79.71	107.753	79.738	32.265
44	79.72	402.207	79.783	154.267	119.439	131.209	119.575	61.544	99.875	127.561	99.892	25.185	99.523	147.247	99.605	47.789	99.71	99.92	99.827	28.362
45	119.654	356.13	119.749	152.845	139.287	123.734	139.476	59.214	119.892	125.363	119.797	15.171	119.691	133.264	119.532	45.118	119.521	92.37	119.613	28.014
46	139.47	343.148	139.475	161.891	159.375	120.598	159.312	40.539	139.564	126.1	139.591	18.346	139.306	123.934	139.313	42.525	139.395	94.025	139.276	20.957
47	159.411	312.516	159.663	99.891	179.488	113.409	179.373	44.908	159.587	110.58	159.691	13.792	159.343	121.275	159.411	39.275	159.527	85.251	159.549	19.793
48	179.454	330.596	179.538	26.487	209.352	102.657	209.444	39.423	179.65	106.531	179.687	17.892	179.436	118.699	179.471	34.978	179.513	82.788	179.523	15.895
49	239.518	312.506	239.611	28.447	239.763	100.179	239.882	37.92	239.802	108.142	239.828	16.241	239.984	106.699	239.866	29.995	239.663	78.09	239.862	25.837

Figure 6.3: *Screen shot of raw data presented before the cleaning process.*

55	Rounding digits																			
56																				
57			Patient 1				Patient 2				Patient 3				Patient 4				Patient 5	
58		mean time	glucose	insulin		mean time	glucose	insulin		mean time	glucose	insulin		mean time	glucose	insulin		mean time	glucose	insulin
59		0	117	8		0	118	9		0	272	26		0	138	37		0	230	11
60		2	283	8		2	384	21		2	438	35		2	432	144		1	580	17
61		3	273	11		3	364	23		3	446	50		3	400	106		2	445	22
62		4	294	7		4	355	21		4	453	44		4	371	38		4	419	22
63		6	286	8		5	332	16		6	446	36		6	329	20		5	413	18
64		8	278	8		8	340	17		8	434	37		8	311	38		6	405	15
65		10	267	9		10	302	20		10	412	32		10	287	22		8	387	12
66		15	255	11		15	309	23		15	411	35		15	285	36		10	378	18
67		20	257	12		20	274	21		19	401	30		20	273	78		15	376	13
68		25	239	340		25	279	336		25	404	301		25	262	715		20	362	16
69		30	235	73		29	249	250		30	384	203		30	253	140		25	348	277
70		40	201	39		40	182	193		39	358	130		40	229	104		30	327	153
71		60	173	25		60	102	50		59	348	60		60	210	76		40	241	44
72		80	152	23		80	89	29		79	328	32		80	183	59		60	172	17
73		100	135	17		100	93	23		99	323	31		100	165	65		80	171	17
74		120	135	14		120	106	20		120	292	37		120	144	62		99	165	14
75		140	124	13		140	118	19		139	307	33		140	130	46		119	167	14
76		160	126	10		160	120	15		159	291	31		160	118	39		139	174	15
77		180	122	12		180	111	12		180	279	29		180	106	36		179	170	14
78		240	112	13		240	136	16		240	256	32		240	123	36		240	172	12
79																				
80																				
81																				
82																				
83			Patient 6				Patient 7				Patient 8				Patient 9				Patient 10	
84		mean time	glucose	insulin		mean time	glucose	insulin		mean time	glucose	insulin		mean time	glucose	insulin		mean time	glucose	insulin
85		0	313	23		0	125	29		0	178	14		0	147	36		0	113	16
86		2	649	16		2	764	36		2	399	26		2	468	309		2	328	18
87		3	605	15		3	382	63		3	347	22		3	361	313		3	294	26
88		4	563	20		4	345	54		4	338	17		4	347	312		5	278	32
89		5	540	16		8	300	60		6	321	14		6	335	273		6	271	21
90		6	567	14		10	285	72		8	302	18		8	311	244		8	257	26
91		8	547	10		15	265	92		10	299	22		10	306	232		10	250	31
92		10	524	13		20	259	80		15	287	21		15	287	214		15	236	35
93		15	519	16		25	250	540		20	273	78		20	276	134		20	234	40
94		20	503	18		30	237	185		25	260	123		25	270	305		25	220	826
95		25	493	339		40	219	118		30	249	305		30	260	300		30	218	630
96		30	461	339		60	175	102		40	184	157		40	218	110		40	190	144
97		40	465	281		80	157	78		60	133	38		60	185	86		60	138	61
98		60	417	232		100	139	69		80	127	33		80	161	67		80	108	32
99		80	402	154		120	131	62		100	128	25		100	147	48		100	100	28
100		120	356	153		139	124	59		120	125	15		120	133	45		120	92	28
101		139	343	162		159	121	41		140	126	18		139	124	43		139	94	21
102		160	313	100		179	113	45		160	111	14		159	121	39		160	85	20
103		179	331	26		209	103	39		180	107	18		179	119	35		180	83	16
104		240	313	28		240	100	38		240	108	16		240	107	30		240	78	26

Figure 6.4: *Screenshot of cleaned and prepared data ready for implementation into MATLAB.*

Chapter 7

The Bergman minimal model in the re-engineered version of MINMOD

7.1 Overview of the model

7.1.1 The FSIGT

As mentioned in Chapter 4 on page 41, there are mainly two factors controlling glucose tolerance – these are:

- insulin sensitivity
- pancreatic responsivity/secretion

In the article from 1986, Pacini and Bergman [5] proposed a method for measuring these two factors. In order to do so, they used computer analysis of a FSIGT test.

A typical FSIGT test is conducted on a fasting subject where a single intravenous injection of glucose into the bloodstream is carried out. The volume of injected glucose is set to 0.3 $\frac{g}{kg}$ of body weight according to Pacini and Bergman [5]. The subject's fasting period should be at least 8 hours. After a short period of time of the injection, blood samples are collected at regular intervals of time.

Finally, when the FSIGT test has come to an end, the blood samples are analysed post hoc in a laboratory for content of glucose and insulin to the instances of time, in which they where sampled.

Figures 7.1 and 7.2 display results from a healthy subject's glucose and insulin responses during a FSIGT test.

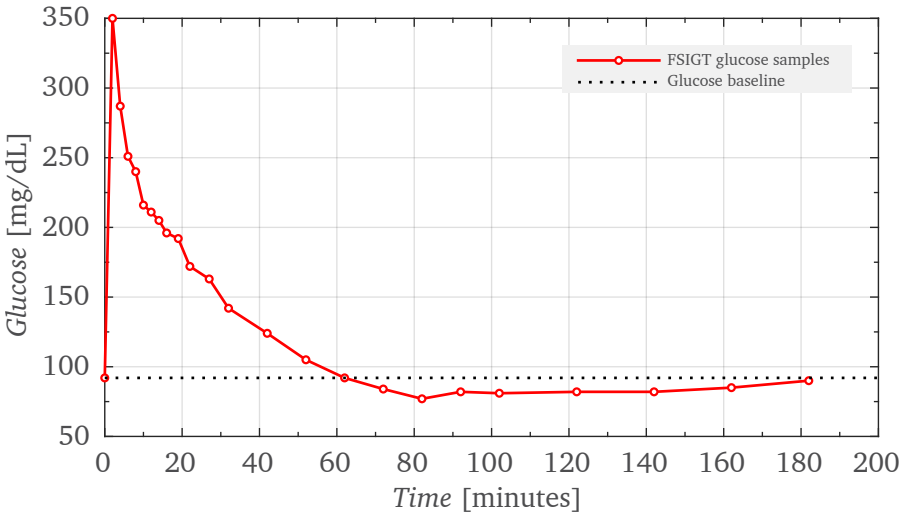


Figure 7.1: *Glucose response from a healthy subject during a FSIGT test. Data from [5].*

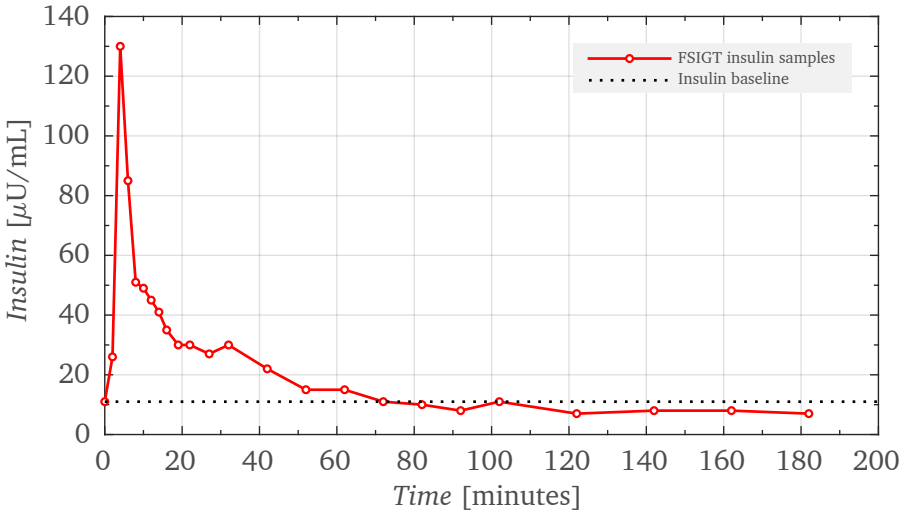


Figure 7.2: *Insulin response from a healthy subject during a FSIGT test. Data from [5].*

The measured glucose and insulin contents from the FSIGT test are important in that they are a measurement of glucose disappearance and insulin kinetics, respectively. This is of great importance for healthcare professionals and scientist in that they it makes it possible to analyse the subject with regards to diabetes-related conditions.

In the article by Pacini and Bergman [5], the authors performed analysis of several FSIGT tests by developing the MINMOD computer program (updated to MINMOD Millennium over the years) for computer analysis of conducted FSIGT tests. During the analysis of an individual FSIGT test, MINMOD is able to estimate the most optimal model parameters to that specific FSIGT test, and conclude whether or not

the results are in the normal healthy range.

7.1.2 Parameter estimation

The estimation of parameters in MINMOD is performed by the utilisation of the weighted nonlinear least squares method, which minimises the weighted residual summed squared error (WRSSE) between the measured values and model predicted values to each data point. This is carried out with the following equation:

$$\arg\min_{\mathbf{P}\in\mathbb{R}^+} S(\mathbf{P}) = \sum_{i=1}^{N} \mathbf{W}[Y(t_i) - f(t_i, \mathbf{P})]^2, \tag{7.1}$$

where the vector of parameters $\mathbf{P}$ should include non-negative values, that is $\mathbf{P} \in \mathbb{R}^+$. In this context, Equation (7.1) has been 'modified' into the physiological modelling framework, where negative parameters do not make much sense.

Also, Equation (7.1) includes a factor $\mathbf{W}$, which is the weight and is given by:

$$\mathbf{W} = \frac{1}{\sigma^2(t_i)}. \tag{7.2}$$

However, this weight factor $\mathbf{W}$ should only be used when sampling multiple measurements to each data point, since the variance or squared standard deviation $\sigma^2(t_i)$ adjust the weight for the samples measured at t_i. This means that the weight for samples measured at t_i having a big variance will be weighted less than samples having a small variance which in turn will be weighted more.

The optimal for this procedure of weighting is if the multiple samples to t_i are normally distributed or close to such a distribution.

In a situation where only single measurements to each sampled data point is the case, the weight factor $\mathbf{W}$ is a N-sample long vector $\mathbf{W}(t_i)$:

$$\mathbf{W}(t_i) = [w_1 \;\; w_2 \;\; \ldots \;\; w_N]^{\mathrm{T}}. \tag{7.3}$$

In the case with single measurements, Equation (7.1) becomes:

$$\arg\min_{\mathbf{P}\in\mathbb{R}^+} S(\mathbf{P}) = \sum_{i=1}^{N} \mathbf{W}(t_i)[Y(t_i) - f(t_i, \mathbf{P})]^2, \tag{7.4}$$

where:

- N is the number of sampled data points
- t_i is the discrete time to which FSIGT sampling occurred
- $Y(t_i)$ is the measured function to each time t_i
- $f(t_i, \mathbf{P})$ is the model-computed function, fitting the sampled data points and depending on the n-long parameter vector $\mathbf{P} = [p_1 \;\; p_2 \;\; \ldots \;\; p_n]^{\mathrm{T}}$

Introducing the 'comparable WRSSE'

Equations (7.1) and (7.4) are equations that are used very often in the field of optimisation, because they are very powerful. However, it is possible to make Equation (7.4) even more powerful assuming that one keeps varying the weight vector in order to obtain a better optimisation of a given problem.

In a situation like this, it does not make any sense to compare one numerical instance of Equation (7.4) with another instance of this very same equation, because the weighting has been changed. Therefore, the author of this MSc Thesis suggests to modify Equation (7.4) in a way that makes is possible to compare multiple numerical instances of the WRSSE from which the weight vector has been modified each time. This yields the following equation describing the comparable WRSSE:

$$\arg\min_{\mathbf{P}\in\mathbb{R}^+} \langle S(\mathbf{P})\rangle = \frac{S(\mathbf{P})}{\sum_{i=1}^{N}\mathbf{W}(t_i)} \tag{7.5}$$

$$= \frac{\sum_{i=1}^{N}\mathbf{W}(t_i)[Y(t_i)-f(t_i,\mathbf{P})]^2}{\sum_{i=1}^{N}\mathbf{W}(t_i)}, \tag{7.6}$$

where $\langle S(\mathbf{P})\rangle$ is the standardised WRSSE, which can be seen as a score, allowing comparisons between all possible iterations of optimisations to be made, taking into account dynamic changes to the weight vector.

A special case is obtained from Equations (7.5) and (7.6) when all data points are weighted equally with the value 1. In this particular case when $\mathbf{W}(t_i) = 1$, then $\sum_{i=1}^{N}\mathbf{W}(t_i) = N$ why Equations (7.5) and (7.6) happen to be the arg min of the Mean Squared Error (MSE):

$$\arg\min_{\mathbf{P}\in\mathbb{R}^+} \text{MSE} = \frac{1}{N}\sum_{i=1}^{N}[Y(t_i)-f(t_i,\mathbf{P})]^2\,. \tag{7.7}$$

Besides MSE, which is a reasonable measure of a fit, and therefore applicable as a cost function that is object to minimise, there is also the Root Mean Squared Error (RMSE). This is likewise a GOF-measure and explains the average residual error where the MSE is an expression of the average residual error squared.

As the name suggests $\text{RMSE} = \sqrt{\text{MSE}}$. Taking the square root of Equation (7.7) yields the RMSE:

$$\arg\min_{\mathbf{P}\in\mathbb{R}^+} \text{RMSE} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}[Y(t_i)-f(t_i,\mathbf{P})]^2}. \tag{7.8}$$

Going back to the comparable WRSSE in Equation (7.6) which is analogous to the MSE in Equation (7.7), the same analogue to the RMSE in Equation (7.8) can be made by taking the square root of the comparable WRSSE:

$$\arg\min_{\mathbf{P}\in\mathbb{R}^+} \langle S(\mathbf{P})\rangle = \sqrt{\frac{\sum_{i=1}^{N}\mathbf{W}(t_i)[Y(t_i)-f(t_i,\mathbf{P})]^2}{\sum_{i=1}^{N}\mathbf{W}(t_i)}}. \tag{7.9}$$

A final note with regards to the denominator in Equations (7.5) and (7.6) as well as in Equation (7.9) has to be explained in more detail as this modification can be considered as an enrichment to the standard used MSE and RMSE.

The denominator $\sum_{i=1}^{N} \mathbf{W}(t_i)$ can basically be object to 3 scenarios depending on how a measured data point to each time measurement t_i is being weighted. That is when:

$$\sum_{i=1}^{N} \mathbf{W}(t_i) > N \tag{7.10}$$

$$\sum_{i=1}^{N} \mathbf{W}(t_i) = N \tag{7.11}$$

$$\sum_{i=1}^{N} \mathbf{W}(t_i) < N \tag{7.12}$$

In the first scenario in Equation (7.10) when the sum of the weights is larger than the number of samples N this results in a smaller number of which the square root has to be taken. This leads to an even smaller number. In this scenario, the error will be smaller than the RMSE which in the first sudden impulse appear to be reasonable.

This scenario has a downfall, however. If all samples, as an example, are weighted equally and twice as much, there should not be any positive effect in the parameter estimation although that the error itself will be reduced.

A more reasonable scenario is the second one presented in **??**. Here, the sum of weights is equal to the number of sampled points.

In this particular situation it might be possible to distribute the weighting scheme in such a way that the denominator in Equation (7.9) is smaller compared to N, leading to a smaller comparable WRSSE and therefore a better fit and estimation of the parameters.

In the last scenario in **??**, where the sum of weights is smaller than the amount of samples N, it is unlikely that the fit and parameter estimation will be good compared to the RMSE.

This is due to a smaller value in the denominator, resulting in a larger comparable WRSSE.

7.1.3 Equations in the (modified) Bergman minimal model

The Bergman minimal model consists of 3 ordinary differential equations (ODEs) with respect to time t, which are interconnected. Each of the ODEs represents a compartment. That is, a compartment for the plasma glucose, interstitial insulin, and plasma insulin. These ODEs are provided in the following, with Newton's dot notation instead of Leibniz's notation.

The ODE for the plasma glucose is given by:

$$\begin{aligned}\dot{G}(t) &= p_1\left[G_\mathrm{b} - G(t)\right] - X(t)G(t),\\ G(t_0) &= G_0,\end{aligned} \tag{7.13}$$

and the ODE for the interstitial insulin is given by:

$$\begin{aligned}\dot{X}(t) &= -p_2 X(t) + p_3\left[I(t) - I_\mathrm{b}\right],\\ X(t_0) &= 0,\end{aligned} \tag{7.14}$$

where:

- t is the independent model variable time in [min].
- t_0 is the time of injection.
- $G(t)$ is the plasma glucose concentration in $\left[\frac{\mathrm{mg}}{\mathrm{dL}}\right]$.
- G_b is the basal plasma glucose concentration in $\left[\frac{\mathrm{mg}}{\mathrm{dL}}\right]$.
- $X(t)$ is the interstitial insulin activity in $\left[\frac{1}{\mathrm{min}}\right]$.
- $I(t)$ is the plasma insulin level in $\left[\frac{\mu\mathrm{U}}{\mathrm{mL}}\right]$.
- I_b is the basal plasma insulin level in $\left[\frac{\mu\mathrm{U}}{\mathrm{mL}}\right]$.

There are 6 unknown parameters in Equations (7.13) and (7.14) that need to be estimated, these are p_1, p_2, p_3, G_b, G_0, and I_b besides the parameters that are given later in Equation (7.22).

The glucose effectiveness S_G is simply defined as:

$$S_\mathrm{G} = p_1, \tag{7.15}$$

and the insulin sensitivity S_I is defined as the relationship between the parameters p_3 and p_2, that is:

$$S_\mathrm{I} = \frac{p_3}{p_2}. \tag{7.16}$$

With the information provided in Equation (7.15), Equation (7.13) can be rewritten to:

$$\begin{aligned}\dot{G}(t) &= S_\mathrm{G}\left[G_\mathrm{b} - G(t)\right] - X(t)G(t),\\ G(t_0) &= G_0,\end{aligned} \tag{7.17}$$

while the information provided in Equation (7.16) makes it possible to rewrite Equation (7.14) to:

$$\begin{aligned}\dot{X}(t) &= p_2\left\{S_\mathrm{I}\left[I(t) - I_\mathrm{b}\right] - X(t)\right\},\\ X(t_0) &= 0.\end{aligned} \tag{7.18}$$

The rewriting of Equation (7.14) to Equation (7.18) is carried out in the following way, by first rewriting Equation (7.16):

$$\begin{aligned} S_{\mathrm{I}} &= \frac{p_3}{p_2} \quad \Leftrightarrow \\ p_3 &= p_2 S_{\mathrm{I}}. \end{aligned} \tag{7.19}$$

Now, having Equation (7.14) written again:

$$\begin{aligned} \dot{X}(t) &= -p_2 X(t) + p_3 [I(t) - I_{\mathrm{b}}], \\ X(t_0) &= 0, \end{aligned}$$

it is possible to substitute p_3 from Equation (7.14), in terms of Equation (7.19), resulting in the following expression:

$$\begin{aligned} \dot{X}(t) &= -p_2 X(t) + p_2 S_{\mathrm{I}} [I(t) - I_{\mathrm{b}}], \\ X(t_0) &= 0. \end{aligned} \tag{7.20}$$

Now, factoring the terms which, on the right-hand side, include p_2 in the above Equation (7.20), and then having them rearranged, yields Equation (7.18):

$$\begin{aligned} \dot{X}(t) &= p_2 \{-X(t) + S_{\mathrm{I}} [I(t) - I_{\mathrm{b}}]\} \\ &= p_2 \{S_{\mathrm{I}} [I(t) - I_{\mathrm{b}}] - X(t)\}, \\ X(t_0) &= 0. \end{aligned}$$

The last ODE in the Bergman minimal model for the plasma insulin, is given by Pacini and Bergman [5] to:

$$\begin{aligned} \dot{I}(t) &= \gamma [G(t) - G_{\mathrm{b}}]\, t - k I(t), \\ X(t_0) &= 0, \end{aligned} \tag{7.21}$$

but modified by A. Kartono [29] to the following:

$$\begin{aligned} \dot{I}(t) &= \begin{cases} \gamma [G(t) - G_{\mathrm{b}}]\, t - k [I(t) - I_{\mathrm{b}}] & \text{if } G(t) > G_{\mathrm{b}} \\ -k [I(t) - I_{\mathrm{b}}] & \text{if } G(t) \leq G_{\mathrm{b}} \end{cases}, \\ I(t_0) &= I_0, \end{aligned} \tag{7.22}$$

since insulin enters the plasma insulin compartment at a rate γ that is proportional to the product of time t and the concentration of glucose $G(t)$ above the basal plasma glucose concentration G_{b}.

If $G(t)$ equals or drops below G_{b} at time t, then the rate of insulin entering the plasma compartment γ is zero.

Insulin is cleared from the plasma compartment at a rate k that is proportional to the amount of insulin in the plasma compartment.

[29]

Furthermore, Pacini and Bergman [5] describe that the pancreas typically shows a biphasic response in a situation when glucose levels rises very rapidly like in the

FSIGT test. The parameters given in Equations (7.21) and (7.22) give two new parameters ϕ_1 and ϕ_2 when combined in the following manner:

$$\phi_1 = \frac{I_{\max} - I_b}{k\,(G_0 - G_b)}, \tag{7.23}$$

where $I_{\max}$ is the maximum value of the first peak in the insulin release.

$$\phi_2 = \gamma \times 10^4. \tag{7.24}$$

From the 3 ODEs that now have been presented to this point, there are up to 9 parameters in total that need to be estimated. These are:

- S_G
- p_2
- S_I
- γ
- k
- G_0 (initial condition)
- I_0 (initial condition)
- G_b (basal glucose level)
- I_b (basal insulin level)

A simple estimate of the two latter parameters in the list above, G_b and I_b, is to use the first or last blood sample, as its value according to [5, 28].

Furthermore, the initial conditions given in Equations (7.17) and (7.22) need to be specified. These are G_0 and I_0, respectively. If it is not possible to estimate these initial conditions, they will act as parameters which extend the parameter vector to 7 parameters.

7.1.4 Numerical solution and optimisation of the (modified) Bergman minimal model

In order to solve the system of ODEs provided in Equations (7.17), (7.18) and (7.22) on page 64 and on page 65, respectively, simultaneous integration of each ODE is required.

It is of common nature that real-life problems that can be described by an ODE or system of ODEs (or other kinds of differential equations for that matter), are too complicated or too time consuming to solve analytically. For this reason it is preferable to solve the given problem numerically through an iterative approach with help of a computer, which has been done in this situation.

In this particular situation the problem does not only consist of solving the system of the interconnected ODEs, but also simultaneously find and optimise the parameters by Equation (7.3) on page 61 which minimises the total error, that is the WRSSE, by finding the optimal set of parameters leading to the best possible fit to some given data points.

Finding the optimal set of parameters can be rather problematic, difficult, and time consuming. However, this depends typically on the dimensionality of the given problem. The problematic, difficult, and time consuming nature is proportional to

the dimensionality of the parameter vector – and thereby the n-dimensional error space surface – but also to some extent the problem itself. Figure 7.3 illustrates clearly the challenges of finding the global minimum, leading to the smallest WRRSE.

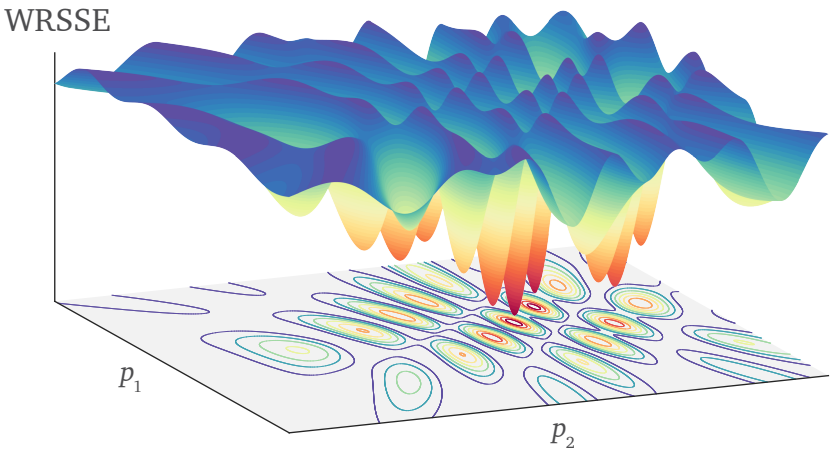


Figure 7.3: *An example illustrating what a* 3*-dimensional error space surface can look like for a tough optimisation problem with two parameters* p_1 *and* p_2*. Modified from* [30].

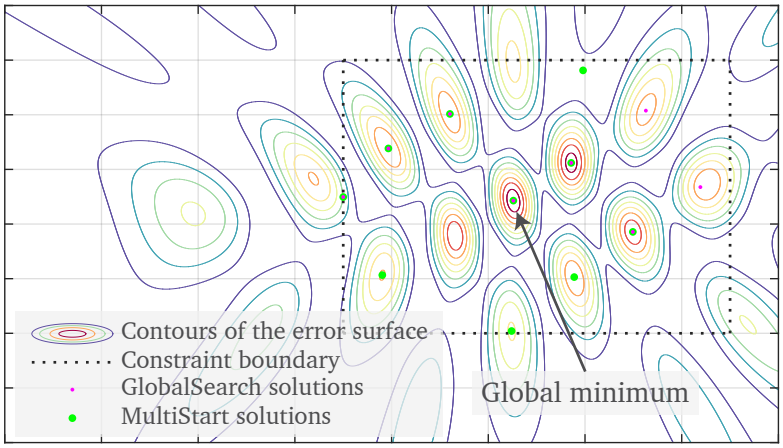


Figure 7.4: *GlobalSearch and MultiStart results within constrained bounds in MATLAB, applied on the error surface in Figure 7.3. Modified from* [30].

When solving optimisation problems numerically in MATLAB, it is possible to choose among several solvers depending on the type of the objective function and constraint type. Table 7.1 lists all available options.

Constraint type	*Objective type*				
	Linear	**Quadratic**	**Least squared**	**Smooth nonlinear**	**Nonsmooth**
None	n/a	`quadprog`	`lsqcurvefit`, `lsqnonlin`	`fminsearch`, `fminunc`	`fminsearch`, *
Bound	`linprog`	`quadprog`	`lsqcurvefit`, `lsqlin`, `lsqnonlin`, `lsqnonneg`	`fminbnd`, `fmincon`, `fseminf`	`fminbnd`, *
Linear	`linprog`	`quadprog`	`lsqlin`	`fmincon`, `fseminf`	*
General smooth	`fmincon`	`fmincon`	`fmincon`	`fmincon`, `fseminf`	
Discrete	`intlinprog`	*	*	*	*

Table 7.1: *MATLAB solvers by type of objective and constraint. The * means relevant solvers are found in the MATLAB Global Optimization Toolbox functions like e.g.* `MultiStart` *and* `GlobalSearch`*. Modified from* [31].

The numerical solution and optimisation of the (modified) Bergman minimal model is carried out by in-build functions in MATLAB that need to be called. When it comes to solving ODEs, MATLAB has build-in numerical solver for different situations as shown in Table 7.2. All the numerical solvers in MATLAB are highly specialised and most of the solvers have adaptive step size to obtain a numerical solution with acceptable accuracy. However, these numerical solvers are essentially based on the Euler method which is the simplest numerical ODE-solver.

Numerical solver	**Order of accuracy**	**When to use**
ode45	Medium	Most of the time. This should be the first solver to try.
ode23	Low	For problems with crude error tolerances or for solving moderately stiff problems.
ode113	Low to high	For problems with stringent error tolerances or for solving computationally intensive problems.
ode15s	Low to medium	If ode45 is slow because the problem is stiff.
ode23s	Low	If using crude error tolerances to solve stiff systems and the mass matrix is constant.
ode23t	Low	For moderately stiff problems if you need a solution without numerical damping.
ode23tb	Low	If using crude error tolerances to solve stiff systems.

Table 7.2: *Build-in numerical solvers of ODEs in MATLAB. The algorithms used in the ODE solvers are varying according to order of accuracy. Adapted from [32].*

Chapter 8

Re-engineering MINMOD

8.1 Software development process

When developing software applications, a traditional approach is using the so-called waterfall model. This model is sequential in which the development process is flowing steadily downwards through several phases as depicted in Figure 8.1. The waterfall model is highly structured and can proceed through the development phases one by one.

The downfalls of this way of developing software is that it does not allow any high degree of reflection during the stages. Once an application has been developed and being evaluated, it might be a challenge to go back in the phases and make potential changes. [33]

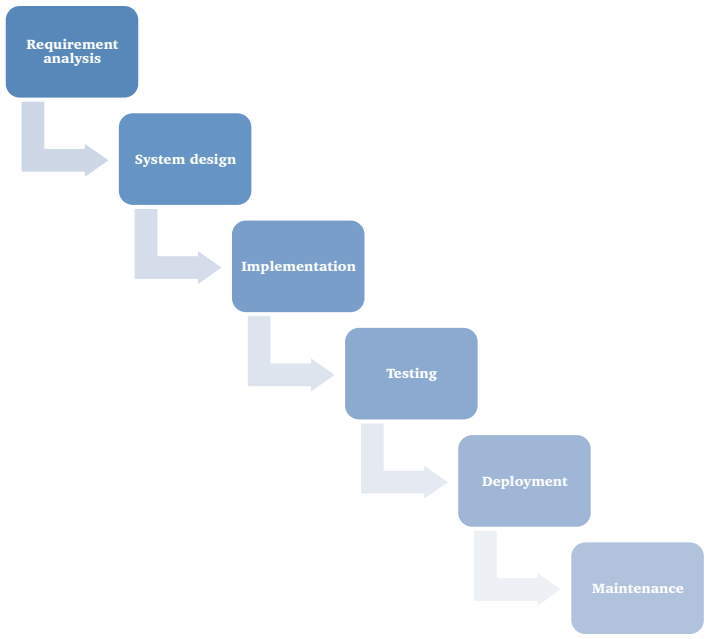


Figure 8.1: *Schematic illustration of the waterfall model in the software development process. Based on [33].*

Initially, the re-engineered version of MINMOD is inspired by the MINMOD Millennium as described in Chapter 4 on page 41. In order to carry this out, requirements of the system were specified resulting in clear and minimalistic design of the graphical user interface (GUI) in MATLAB (phases 1–2). Here, it was also required that it should be possible for the user to customise how the overall optimisation process of the data could be performed. Afterwards, small subprograms/units controlling the

overall settings of the application were developed separately, joined, and tested for correct functionality (phases 3–4). Finally, as this application has not been officially released, phases 5–6 have not been applicable at this stage.

8.2 Usability heuristics for GUI design

Regarding GUI design, Jakob Nielsen [34] is among the leading experts in the field of evidence-based user experience research. Following many years of research, 10 usability heuristics have been proposed as shown in Table 8.1. What needs to be understood by the term heuristics is that they represent broad rules of thumb that are positive to account for during application development rather than being specific and strict usability guidelines. By acknowledging these heuristics, there is a good possibility of eliminating a vast majority of errors potentially leading to negative evaluation of an application.

Heuristic #	Title
1	Visibility of system status
2	Match between system and the real world
3	User control and freedom
4	Consistency and standards
5	Error prevention
6	Recognition rather than recall
7	Flexibility and efficiency of use
8	Aesthetic and minimalist design
9	Help users recognise, diagnose, and recover from errors
10	Help and documentation

Table 8.1: *10 heuristics in usability for GUI design according to [34].*

These 10 heuristics have also been accounted for when developing and implementing the re-engineered version of MINMOD. Notably, some were considered more important and relevant than others, thus not included here.

Heuristic 1 was addressed by using dialogues that tends to inform the user about what is going on.

Heuristic 3 was accounted for by clearly giving the user the possibility of terminating an option if this was chosen by mistake (i.e. emergency exit). Thereby, the option may be leaved without having to go through an extensive exit dialogue.

Heuristic 5 was addressed by making it possible for the user to only select few options at a time (i.e. step-by-step activation and deactivation of other panels with options).

Both heuristics 7 and 8 were partly met by creating an aesthetic and minimalistic design, making it easy and possible for the experienced user to speed up the interaction, besides being easy to use for the novice user.

As the application is still not deployed but only presented in its preliminary software cycle, the last two heuristics have not yet been addressed due to low priority.

Part III

Results

Chapter 9

Results

9.1 Presentation of the re-engineered version of MINMOD

Following data extraction of IVGTT, description of the Bergman minimal model, and software development in MATLAB (version R2015a), a GUI with the re-engineered version (1.0 early access) of MINMOD was first crafted as shown in Figure 9.1 on the following page via the existing `guide` tool. The main screen of the application is shown in MATLABs `guide` tool, offering a variety of GUI components. The final result is shown in Figure 9.2 on page 75.

The main screen of the application is based on the nine categorised panels, where step-by-step activation and deactivation of certain options is possible for the optimisation process for the user. The application is made up in such a way that the order of selecting a given panel does not matter, making the panels independent of each other.

Panel 1 shows the options for selecting the subject type. It is possible to choose either a healthy individual or a patient with type 2 diabetes. If the latter is selected, a dropdown menu is activated allowing the user to select among the 10 patients described in Chapter 6 on page 53.

Panel 2 shows algorithms that have been implemented into the program and that are responsible for optimising the parameters in panels 5, 7, and 9. This is done by minimising the WRSSE described in Section 7.1.2 on page 61. The default option to achieve the optimal parameters in the Bergman minimal model is fminsearch.

Panel 3 is responsible for options that are related to the numerical optimisation algorithms. Here, the default is ode45, which is the 4th order Runge-Kutta method.

Panel 4 represents the options with regards to the weighting scheme of the data points given in panel 1. The default option is the one with automatic weights that has been provided in [5, 28].

Panels 5, 7, and 9 shows which parameters need to be optimised. Especially, in the fifth panel, it is possible to select all nine parameters to be estimated which are covered in more detail in Section 7.1.3 on page 64. The default setting is seven parameters, though.

Panel 6 gives option on how the final results should be plotted. It is possible to select the solution curves as a combined figure or single figure for those that are selected. All three solution curves are selected per default and plotted in a single figure together with the samples from panel 1.

Panel 8 is an important panel, giving the user the option of narrowing down the optimisation process by instructing the algorithms from panel 2 to search for the best solution in the provided parameter intervals. In this panel, three groups are existing which are controlled by the settings provided in panel 5.

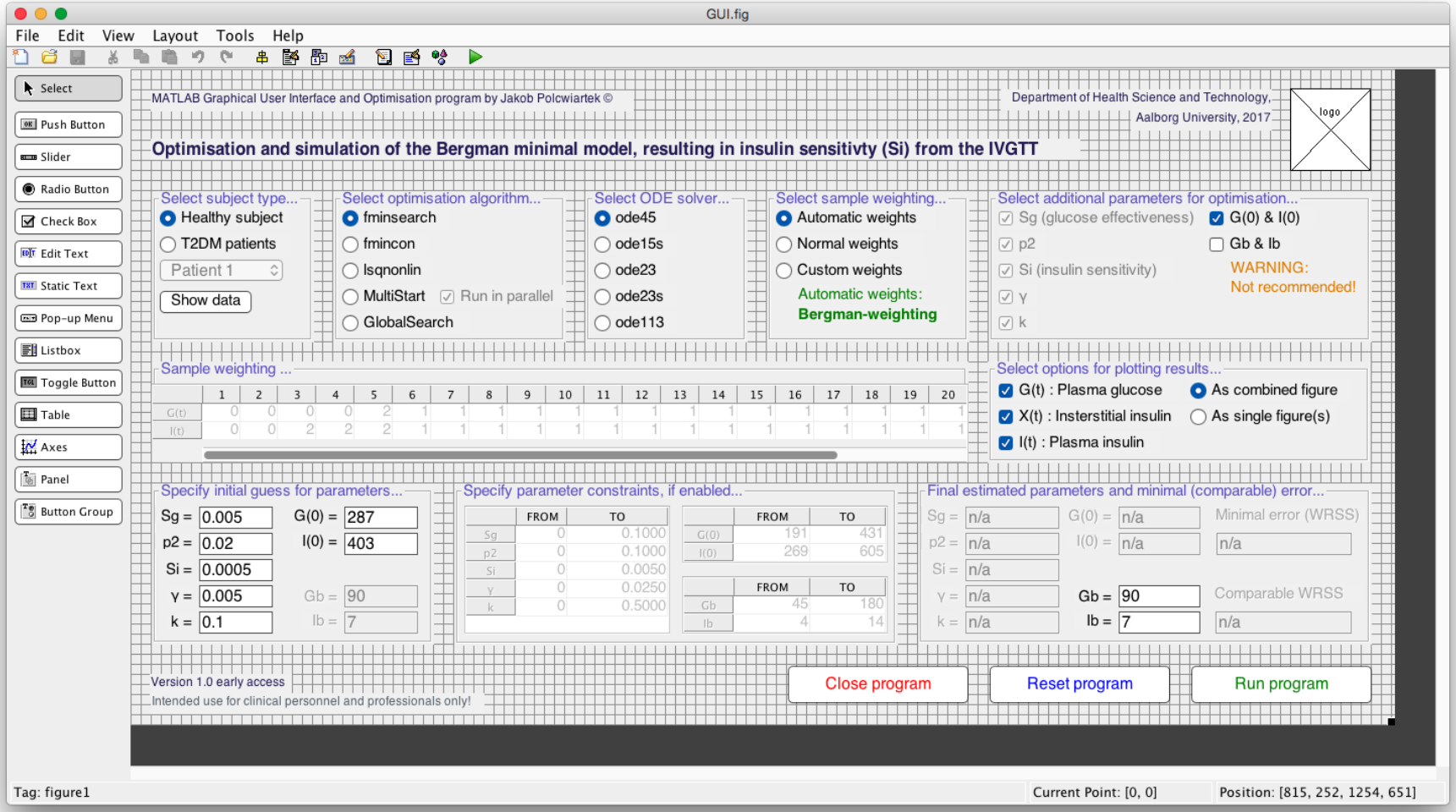


Figure 9.1: *Screen shot of the layout process with the main components of the Re-engineered version of MINMOD via the* `guide` *tool in MATLAB.*

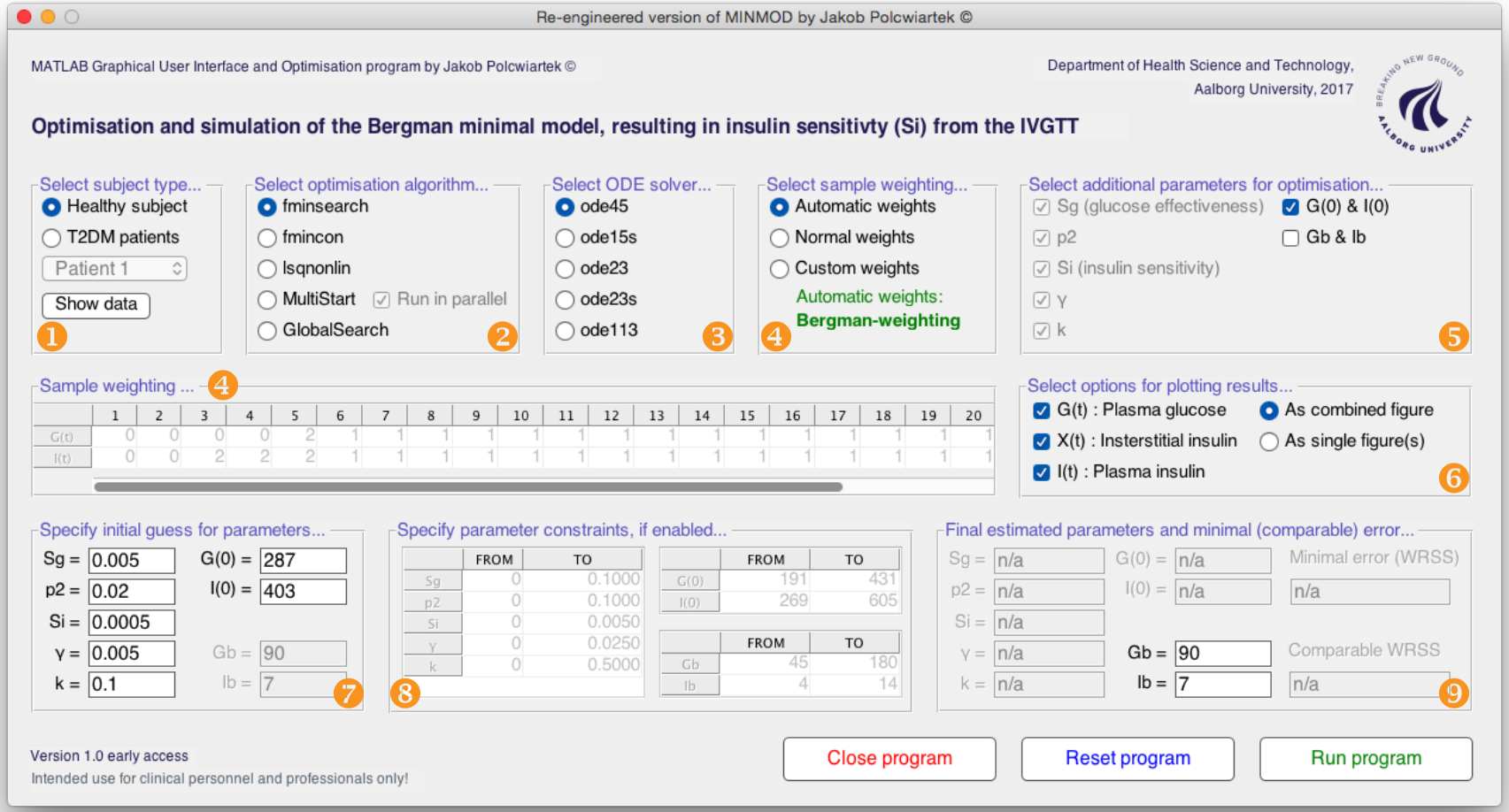
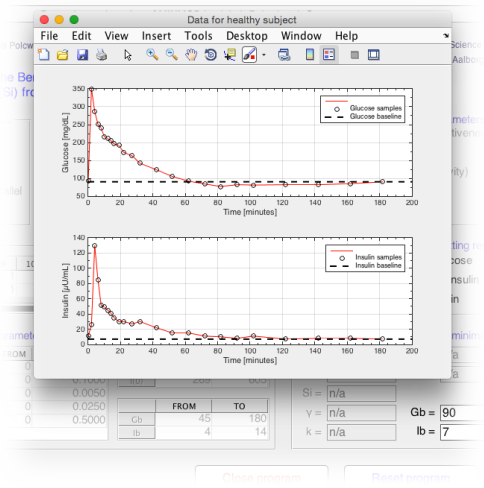
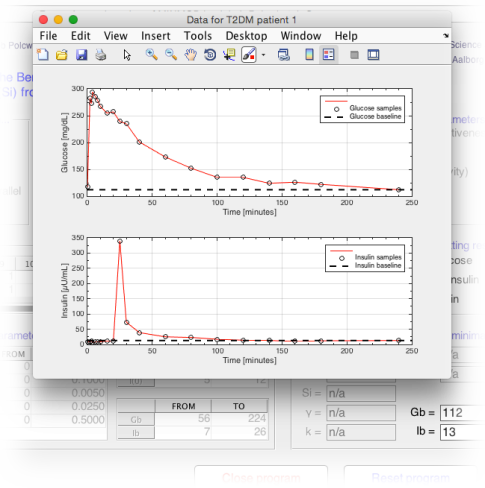


Figure 9.2: *Screen shot of Re-engineered version of MINMOD (Version 1.0 early access) on opening with default options.*

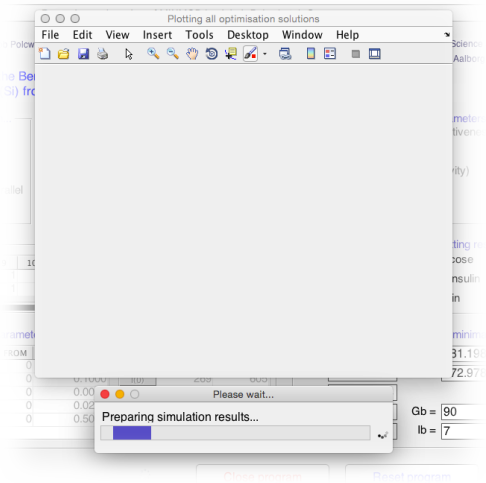
The program is seen running in Figure 9.3 on the next page, subdivided into parts (a–g). When panel 1 is selected, the possibility of inspecting the data for the selected subject is given (a–b). After choosing among the options in panels 2–9, the program is initially preparing simulation results from the entire optimisation process (c–e). During the simulation, the user is successively informed by a loading bar. When the simulation is finished, last operations regarding the Bergman minimal model are depicted (f). Finally, the user will be asked what to do next (g).



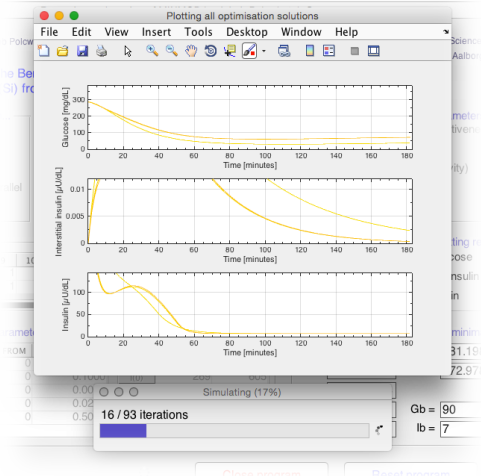
(a) Data inspection of a healthy subject.



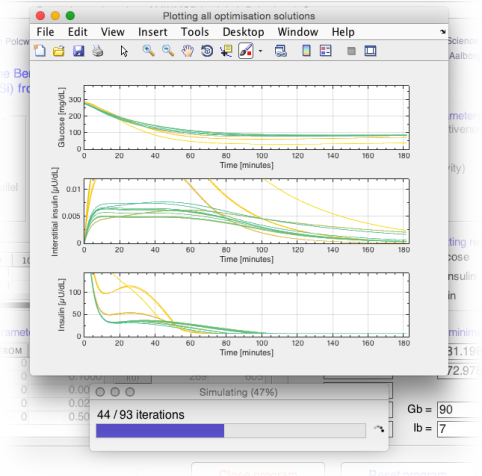
(b) Data inspection of a type 2 diabetes patient.



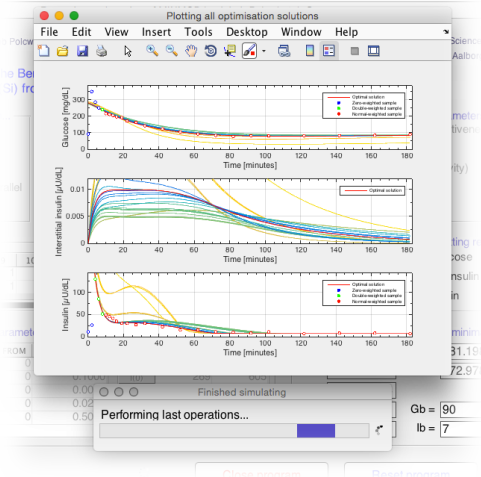
(c) Preparing simulation results which are about to begin.



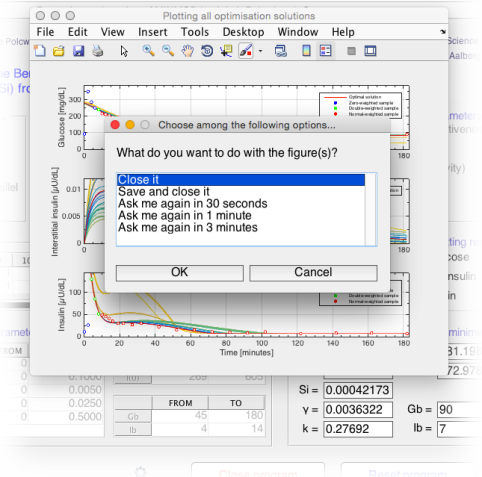
(d) Simulation running.



(e) Simulation running.



(f) Simulation finished. Performing last operations in background.



(g) Window prompting user on next action.

Figure 9.3: *Several screen shots from Re-engineered version of MINMOD.*

9.2 Parameter estimates from IVGTT data

The re-engineered version of MINMOD is used to analyse the IVGTT data provided in Chapter 6 on page 53. Thereby, a solution of the Bergman minimal model will be presented for each patient with type 2 diabetes (n=10).

The patients with type 2 diabetes were selected (panel 1). Afterwards, the optimisation algorithm `lsqnonlin` was selected (panel 2). This was done as this is the same algorithm (Levenberg–Marquardt) found in the MINMOD Millennium. The ODE solver was selected to the default (panel 3) as this is the standard option one should use according to [32]. Custom weights were afterwards selected (panel 4) and the first five $G(t)$ samples weighted 0, and the 10 first $I(t)$ samples were weighted 0. This was done (1) as the the Bergman minimal model does not account for the first 8-10 minutes [5] as the intravenous bolus injection of glucose has to be equally distributed in the blood, and (2) the insulin response is delayed in the patients. Finally, the optimisations and simulations were based on default initial guesses for parameters (panel 7), except the values of $G(0)$ and $I(0)$ which in [5] is described to be based on the value of the 5th sample. The results of the parameter estimates are presented in Table 9.1 and based on the above described.

Patient #	S_I $10^{-4}\mathrm{min}^{-1}/\mu\mathrm{U\ mL}^{-1}$	S_G $10^{-2}\mathrm{min}^{-1}$	p_2 min^{-1}	G_0 mg/dL
1	1.42	1.49	0.0745	300.0
2	1.66	1.10	0.0640	332.0
3	3.58	0.50	0.0200	446.0
4	0.61	1.38	0.0277	329.0
5	1.99	1.42	0.0377	413.0
6	2.82	0.50	0.0200	540.0
7	0.76	1.17	0.0290	300.0
8	1.44	1.38	0.0601	321.0
9	0.91	1.62	0.0356	335.0
10	1.42	1.42	0.0531	271.0

Table 9.1: *Estimated parameters from using the nonlinear least squares (NLS) approach on patients with type 2 diabetes with IVGTT data. S_I: insulin sensitivity, S_G: glucose effectiveness, p_2: rate parameter, G_0: glucose at $t = 0$.*

Part IV

Discussion

Chapter 10

Discussion

10.1 Objectives and key findings

This MSc Thesis sought to describe, analyse, and implement a well-established physiological model of the glucose-insulin system, the Bergman minimal model. This was done by developing a PC application in MATLAB.

The model is an approved non-invasive alternative to the gold standard for estimating insulin sensitivity both in healthy subjects and patients with type 2 diabetes. Furthermore, the model has potential to also express the pancreatic responsivity.

The key findings were that it was possible to re-engineer a licensed software, MINMOD, that is based on the Bergman minimal model. The re-engineered version was able to reproduce similar estimates of the parameters, including insulin sensitivity, based on the same IVGTT data that was presented in the literature [5, 28]. In addition, the re-engineered version contained several optimisation algorithms not previously reported. This is considered highly relevant in that it might be possible to obtain better solutions (i.e. not running into the $S_I = 0$ problem) than those presented in the original version of MINMOD and MINMOD Millennium described in late 1980's and early 2000's, respectively.

It is however necessary to carry out more optimisation tests with regards to certainly validate the re-engineered version of MINMOD, of which Monte Carlo simulations could be a great way of providing distributions of parameter estimates, by varying the inputs of the IVGTT data slightly observing how the changes affects the final estimates of the parameters.

10.2 Importance of the re-engineered version of MINMOD

MINMOD Millennium is the latest PC application since 2000's, providing interpretation of IVGTT data, using physiological modelling of the glucose-insulin system formulated as the Bergman minimal model. Both the model and the application has been referred to several places in the literature, and particularly by some of the leading researchers in this field [2, 5–8, 35–37]. However, the development of the re-engineered version of MINMOD has shown that it is possible to re-engineer, that is, redesign and restructure an existing technology into a new framework. In addition, it was possible to obtain same good or at least similar optimisation results as presented in the literature by other researchers.

Based on published IVGTT data from [27], there is a rather good correspondence between the parameter estimates regarding validation (compare Table 9.1 on page 78 with Table 10.1 on the next page).

Patient #	S_I $10^{-4}\text{min}^{-1}/\mu\text{U mL}^{-1}$	S_G 10^{-2}min^{-1}	p_2 min^{-1}	G_0 mg/dL
1	0.92 (20)	1.54 (14)	0.015 (21)	297.9 (2.3)
2	1.51 (3)	2.1 (10)	0.072	381.6 (23)
3	0.22 (148)	1.33 (19)	0.00495 (402)	444.13 (1.3)
4	0.86 (23)	0.97 (17)	0.007 (37)	315.6 (2.2)
5	2.1 (5)	0.87 (29)	0.098 (14)	409 (2.3)
6	0.14 (186)	1.33 (12)	0.0074 (176)	563 (1.6)
7	0.98 (353)	1.5 (10)	0.0016 (460)	315 (1.5)
8	0.99 (7.6)	0.9 (16)	0.3 (30)	323.8 (1.7)
9	0.52 (128)	1.7 (4.9)	0.0011 (147)	353.9 (1.4)
10	0.58 (10)	0.84 (19)	0.027 (8)	263 (2.2)

Table 10.1: *Estimated parameters from using the nonlinear least squares (NLS) approach on patients with type 2 diabetes with IVGTT data. Numbers in parentheses show precision of the estimate expressed as a percent coefficient of variation. S_I: insulin sensitivity, S_G: glucose effectiveness, p_2: rate parameter, G_0: glucose at $t = 0$.*

By plotting a box plot, shown in in Figure 10.1, of the insulin estimates for both studies, as well as the differences between published estimates and those presented in Table 9.1 on page 78 of the insulin sensitivity values (S_i), there is a rather fair correspondence for most of the patients, as shown in Figure 10.2 on the facing page. This reflects that the re-engineered version of MINMOD has been implemented sufficiently. However, there are two substantial outliers when observing the differences between the two studies depicted in Figure 10.2 on the next page (i.e. patients 3 and 6).

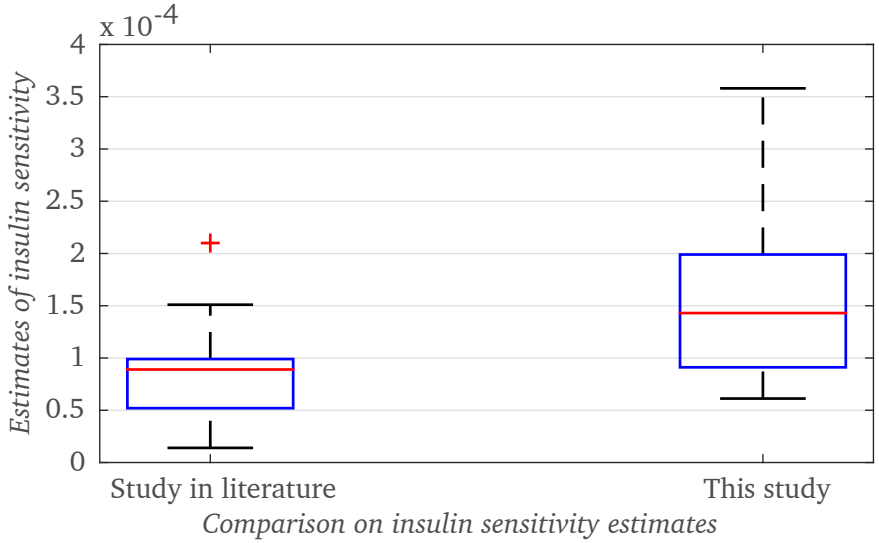


Figure 10.1: *This box plot shows how well the estimates published in [27] and the parameter estimates in the re-engineered version of MINMOD overlap.*

With the box plot it is possible to observe that the estimates of the insulin sensitivity in this study are generally higher than those presented in [27] which are shown in Table 10.1. Also, it is observable that a higher median value and higher

values of the whiskers of the box plot are present.

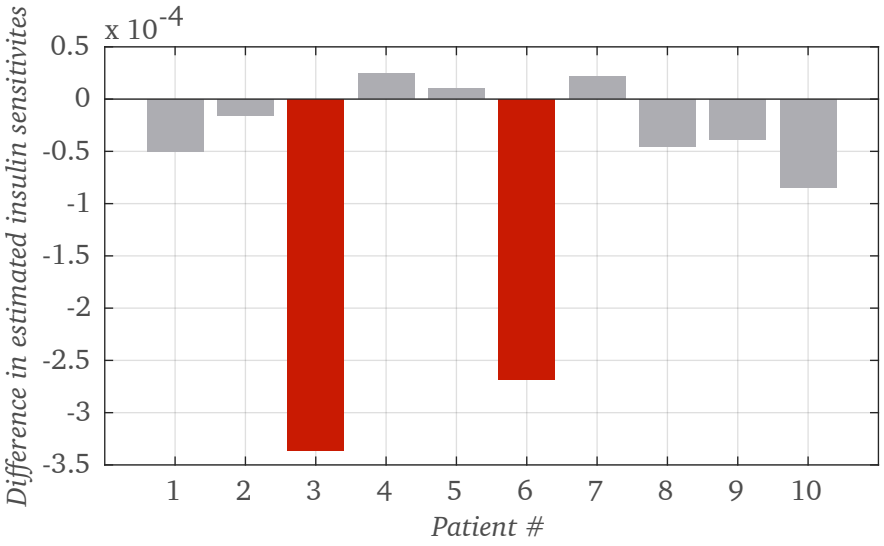


Figure 10.2: *This plot shows the the differences between the estimates published in [27] and the parameter estimates in the re-engineered version of MINMOD.*

These two outliers can also be recognised in the solution curves of the optimisations processes as shown in Figures 10.3 and 10.4 on the current page and on the following page.

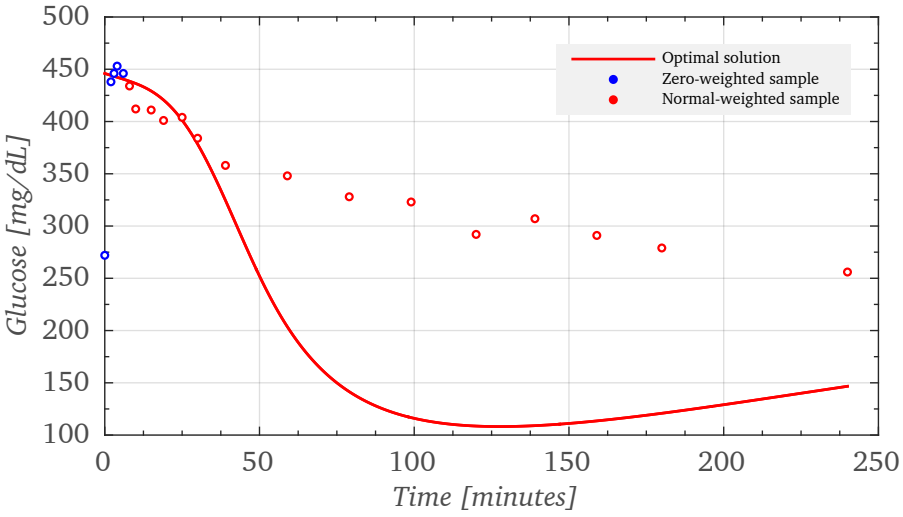


Figure 10.3: *'Optimital solution' for patient 3 with* `lsqnonlin`.

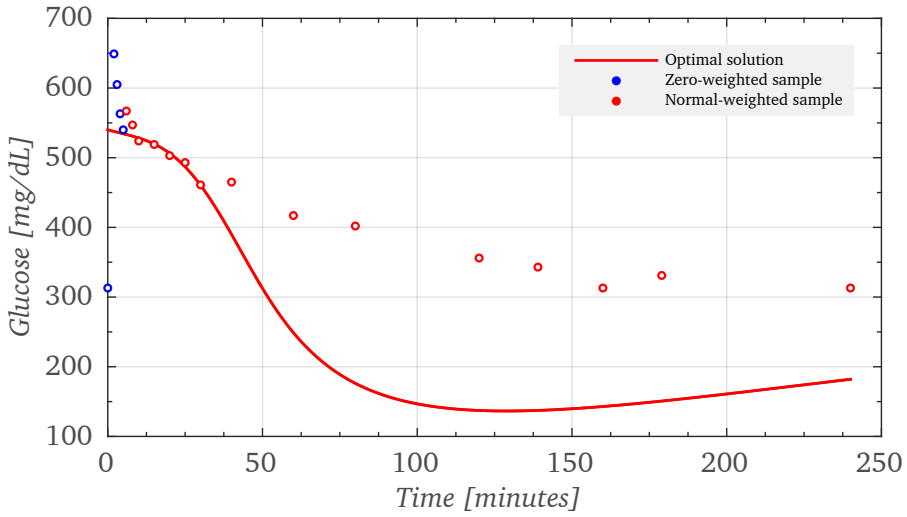


Figure 10.4: *'Optimital solution' for patient 6 with* `lsqnonlin`.

Eventual deviations in final parameter estimates reflects uncertainties caused by a relative broad range of options selected prior the optimisation process. For example, by choosing custom weights in panel 4 in Figure 9.2 on page 75, this has a huge impact on the final parameter estimates, as some data points can be ignored or oversampled, leading to different estimates of parameters. The same may be influenced by the optimisation algorithms shown in panel 2 concurrent with the choice of initial guessing for parameters in panels 7 and 8, if applicable in the latter panel.

Generally, the problem with current parameter estimates in published literature as well as with the MINMOD Millennium is that only few options are available for selection for the user. The point of reference (i.e. how these options have been carried out) is limited regarding documentation and poorly described prior to presentation of the final parameter estimates for the 10 patients with type 2 diabetes with data on IVGTT [27]. This makes it difficult to perform an 1:1 comparison on performances here. In contrast, it is made clear in [5] how IVGTT data for the single healthy subject was weighted and how values were assigned as to the initial parameter estimates.

That IVGTT data only was available from 11 subjects, including one single healthy subject and 10 patients with type 2 diabetes, from the literature, raises another point to be discussed. Lack of large IVGTT dataset available in the literature compromised the potential of using the re-engineered version of MINMOD. Also, the assumption of the extraction of IVGTT data from the literature was based on the fact that data are complete and free of noise. However, human data extraction via software can cause wrong or biased data unintended.

Importantly, one specific reported problem with MINMOD is that insulin sensitivity is not estimated optimally in patients with type 2 diabetes [27]. The optimisation algorithm in MINMOD uses a nonlinear least squares (NLS) approach, which is the same in the re-engineered version of MINMOD. However, the optimisation algorithm in MINMOD is based on only one single optimisation method, which is the Levenberg–Marquardt algorithm. However, besides implementing this algorithm (lsqnonlin in the application), the re-engineered version of MINMOD further holds

the advantage of including other advanced optimisation algorithms giving the user other, and possibly better, estimates of the parameters. It is not only the MINMOD which fails in providing reasonable estimates of patients with type 2 diabetes, but also software packages as e.g. SAAM II or ADAPT. These have similar challenges which in [27] calls for a replacement of parameter estimation method of NLS to Bayes estimation to overcome the so-called $S_I = 0$ problem.

One way to overcome this problem can be by replacing the IVGTT minimal model (i.e. Bergman) with the OGTT minimal model [2]. Although the Bergman minimal model is a popular alternative to the gold standard, euglyceamic hyperinsulinemic clamp, it is undermodelling the glucose-insulin system by underestimating the insulin sensitivity. The rationale by replacing the minimal model of IVGTT to OGTT is because it is important to measure the insulin sensitivity from a more physiologically stable setting.

10.3 Improvements of the re-engineered version of MINMOD

10.3.1 Application and GUI design

Even though the waterfall model was used in the software development process, a heuristic evaluation as a part of the testing phase of the early access version could help to identify strengths and weaknesses. The 10 usability heuristics were highly considered during the design and implementation process stage, making it easy for the user to work with the application.

However, as it can be observed from the application, some decisions are less optimal. For example, there is currently no option to load any IVGTT data externally, limiting the application to the IVGTT data files that were originally included as part of the implementation phase. See panel 1 in Figure 9.2 on page 75. It is also considered relevant to provide an export function after the optimisation process has ended, where the parameter estimates are provided with information about under which settings they were estimated.

Secondary, the choice of plotting all optimisation iterations should be optional and thereby not the standard. See part (d–f) in Figure 9.3 on page 77. Mainly, this is because optimisation algorithms using many iterations to search for the optimal set of parameters can potentially cause memory problems and thereby a slow-down of the system. Providing more options in this regard, could increase the speed of the application, benefitting the user.

Improving the existing GUI according to the new Application Designer available in MATLAB (introduced in R2016a) which makes it more convenient to create GUIs with tabs [38]. This has a significant advantage, in that the features of the program can be ordered in a more convenient and subtle way.

Finally, the above discussed points call for a discussion of the applied method behind the software development process using the waterfall model. It can be considered that another approach that is more agile could lead to increased prevention of 'errors', as the agile approach runs the waterfall model in several iterations [33].

10.3.2 Other modelling approaches

The re-engineered version used the traditional approach of NLS for all the optimisation algorithms, as shown in panel 2 in Figure 9.2 on page 75. However, there are some challenges with regards to using the Bergman minimal model to estimate insulin sensitivity in patients with type 2 diabetes, often referred to as the $S_I = 0$ problem.

Another challenge described in the literature is that of underestimation of the insulin sensitivity with the traditional approach. Consequently, it might be considered to use the so-called Bayes approach [27, 39]. This has shown to cope well with the problems of under- and overestimation of some parameters that occurs using the traditional NLS approach. As shown in Figure 10.5, it is evident that the Bayes provides non-negative estimates and convincing intervals allowing for physiological meaningful interpretation compared with the NLS. However, compared to the traditional approach, the Bayes is computationally more demanding [39].

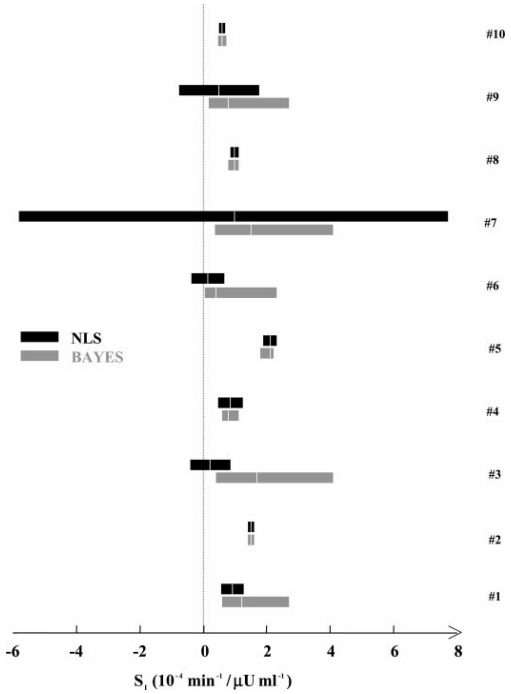


Figure 10.5: *Overview of the Bayes (grey boxes) compared with the NLS (black boxes) approach. The estimated parameter is the insulin sensitivity for the 10 patients with type 2 diabetes. Taken from [27].*

Chapter 11

Conclusion

The Bergman minimal model is a popular alternative to the gold standard in physiological modelling to interpret IVGTT data to assess insulin sensitivity. This has been implemented in a PC application named MINMOD (Millennium).

In this MSc Thesis it can be concluded that it was possible to re-engineer a version of MINMOD, allowing the user to customise the optimisation algorithm process regarding estimates of relevant parameters of the Bergman minimal model.

Overall, parameter estimates could be replicated and compared with another study found in literature, validating the re-engineered version of MINMOD to some degree. However, more testing is required in order to obtain an even higher degree of validation.

Part V

Listings

List of figures

List of tables

Bibliography

[1] International Diabetes Federation. *IDF Diabetes Atlas, 7th edition*. International Diabetes Federation, Brussels, Belgium: International Diabetes Federation, 7th edition, 2015. URL http://www.idf.org/diabetesatlas. ISBN: 978-2-930229-81-2.

[2] C. Cobelli, C. Dalla Man, G. Sparacino, L. Magni, G. De Nicolao, and B.P. Kovatchev. Diabetes: Models, Signals, and Control. *IEEE Reviews in Biomedical Engineering*, 2:54–96, 2009. doi: 10.1109/RBME.2009.2036073. URL https://doi.org/10.1109%2Frbme.2009.2036073.

[3] Danish College of General Practitioners (DSAM). *Insulinbehandling af patienter med type 2-diabetes – herunder vejledning om hjemmemonitorering af blodsukker og hypoglykæmi*. Dansk Selskab for Almen Medicin (DSAM), 2012. Klinisk vejledning for almen praksis.

[4] Richard N. Bergman, Ziya Y. Ider, Charles R. Bowden, and Claudio Cobelli. Quantitative estimation of insulin sensitivity. *American Journal of Physiology*, 236:E667–E677, 1979.

[5] G. Pacini and R. N. Bergman. MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. *Computer Methods and Programs in Biomedicine*, 23:113–122, 1986.

[6] R. N. Bergman. Minimal Model: Perspective from 2005. *Hormone Research*, 64:8–15, 2006.

[7] Claudio Cobelli and Ewart Carson. *Introduction to modeling in physiology and medicine*. Elsevier Science & Technology, 2011. ISBN 978-0-12-160240-6.

[8] Boston RC, Stefanovski D, Moate PJ, Sumner AE, Watanabe RM, and Bergman RN. MINMOD Millennium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test. *Diabetes Technology and Therapeutics*, 2003.

[9] International Diabetes Federation. *IDF Diabetes Atlas, 6th edition*. International Diabetes Federation, Brussels, Belgium: International Diabetes Federation, 6th edition, 2013. URL http://www.diabetesatlas.org/resources/previous-editions.html. ISBN: 2-930229-85-3.

[10] Mary E. Cox and David Edelman. Tests for Screening and Diagnosis of Type 2 Diabetes. *Clinical Diabetes*, 27(4):132–138, October 2009.

[11] United Nations Statistics Division. Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and

other groupings. Website, October 2013. URL http://unstats.un.org/unsd/methods/m49/m49regin.htm#europe. URL accessed: February 2014.

[12] Det Nationale Diabetesregister. Tal på diabetes 1996-2012. Website, 2011. URL http://www.ssi.dk/Sundhedsdataogit/Dataformidling/Sundhedsdata/Diabetes.aspx. URL accessed: December 2013.

[13] Sundhedsdatastyrelsen. Udvalgte kroniske sygdomme og svære psykiske lidelser, 2016. URL http://esundhed.dk/sundhedsregistre/uks/Sider/uks.aspx.

[14] Diabetesforeningen. Det Nationale Diabetesregister, 2016. URL http://www.diabetes.dk/presse/diabetes-i-tal/det-nationale-diabetesregister.aspx.

[15] Anders Green, Camilla Sortso, Peter Bjodstrup Jensen, and Martha Emneus. Incidence, morbidity, mortality, and prevalence of diabetes in Denmark, 2000-2011: results from the Diabetes Impact Study 2013. *Clinical epidemiology*, 7:421–30, 2015.

[16] Camilla Sortsø, Anders Green, Peter B. Jensen, and Marta Emneus. Societal costs of diabetes mellitus in Denmak. *Diabetic Medicine*, 33(7):877–885, oct 2015. doi: 10.1111/dme.12965. URL https://doi.org/10.1111%2Fdme.12965.

[17] Camilla Sortsø, Martha Emneus, Anders Green, Peter B. Jensen, and Thomas Eriksson. Societal costs of diabetes mellitus 2025 and 2040 – forecasts based on real world cost evidence and observed epidemiological trends in denmark. *Modern Economy*, 06(10):1150–1166, 2015. doi: 10.2147/CLEP.S88577. URL https://doi.org/10.4236%2Fme.2015.610109.

[18] Frederic H. Martini, Judi L. Nath, and Edwin F. Bartholomew. *Fundamentals of Anatomy & Physiology*. Pearson, 9th edition, 2012.

[19] Md. Shahidul Islam, editor. *Islets of Langerhans*. Springer Netherlands, 2015. doi: 10.1007/978-94-007-6686-0. URL https://doi.org/10.1007%2F978-94-007-6686-0.

[20] Luke Allen. Gray's Anatomy Premium Edition. App Store, August 2015. App version 1.5 downloaded from the Mac App Store.

[21] Adolf Faller and Michael Schuenke. *The Human Body – An Introduction to Structure and Function*. Thieme, 2004.

[22] Yoshifumi Saisho. Postprandial C-Peptide to Glucose Ratio as a Marker of β Cell Function: Implication for the Management of Type 2 Diabetes. *International Journal of Molecular Sciences*, 17(5):744, may 2016. doi: 10.3390/ijms17050744. URL https://doi.org/10.3390%2Fijms17050744.

[23] A. G. Jones and A. T. Hattersley. The clinical utility of c-peptide measurement in the care of patients with diabetes. *Diabetic Medicine*, 30(7): 803–817, jun 2013. doi: 10.1111/dme.12159. URL https://doi.org/10.1111%2Fdme.12159.

[24] Stefan Silbernagl and Agamemnon Despopoulos. *Color Atlas of Physiology*. Thieme, 6th edition, 2009.

[25] Danish College of General Practitioners (DSAM). *Type 2-diabetes – et metabolisk syndrom*. Dansk Selskab for Almen Medicin (DSAM), 2012. Klinisk vejledning for almen praksis.

[26] Ralph A. DeFonzo, Jordan D. Tobin, and Reubin Andres. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *American Journal of Physiology*, 1979.

[27] Gianluigi Pillonetto, Giovanni Sparacino, Paolo Magni, Riccardo Bellazzi, and Claudio Cobelli. Minimal model SI=0 problem in NIDDM subjects: nonzero Bayesian estimates with credible confidence intervals. *American Journal of Physiology – Endocrinology and Metabolism*, 282(3):E565–E573, 2002.

[28] Piers W. Lawrence. *Parameter estimation techniques for insulin-glucose models*. Honours thesis, Department of Mathematics and Statistics, University of Canterbury, 2008. URL http://people.cs.kuleuven.be/~piers.lawrence/papers.html.

[29] A. Kartono. Modified minimal model for effect of physical exercise on insulin sensitivity and glucose effectiveness in type 2 diabetes and healthy human. *Theory in Biosciences*, 132(3):195–206, 2013.

[30] MathWorks. Maximizing Monochromatic Polarized Light Interference Patterns Using GlobalSearch and MultiStart, 2015. URL http://se.mathworks.com/help/gads/examples/maximizing-monochromatic-polarized-light-interference-patterns-using-globalsearch-and-multistart.html. URL Accessed: September 2015.

[31] MathWorks. Optimization Toolbox™– User's Guide, 2015. URL http://se.mathworks.com/help/releases/R2015b/pdf_doc/optim/optim_tb.pdf.

[32] The MathWorks, Inc., 2015. URL http://se.mathworks.com/help/releases/R2015b/matlab/ref/ode45.html.

[33] tutorialspoint. SDLC – Software Development Life Cycle, 2017. URL https://www.tutorialspoint.com.

[34] Jakob Nielsen. 10 Usability Heuristics for User Interface Design. *NN/g Nielsen Norman Group*, 1994. URL https://www.nngroup.com/articles/ten-usability-heuristics/.

[35] R. N. Bergman, L. S. Phillips, and C. Cobelli. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. 68:1456–1467, 1981. ISSN 0021-9738.

[36] R. N. Bergman. Lilly lecture 1989. toward physiological understanding of glucose tolerance. minimal-model approach. 38:1512–1527, 1989. ISSN 0012-1797.

[37] Claudio Cobelli, Chiara Dalla Man, Morten G. Pedersen, Alessandra Bertoldo, and Gianna Toffolo. Advancing our understanding of the glucose system via modeling: a perspective. *IEEE Transactions on Biomedical Engineering*, 61(5), 2014. doi: 10.1109/TBME.2014.2310514.

[38] What's New, 2017. URL https://se.mathworks.com/products/matlab/whatsnew.html.

[39] Kim E. Andersen and Malene Højbjerre. A population-based bayesian approach to the minimal model of glucose and insulin homeostasis. 24: 2381–2400, 2005. ISSN 0277-6715. doi: 10.1002/sim.2126.