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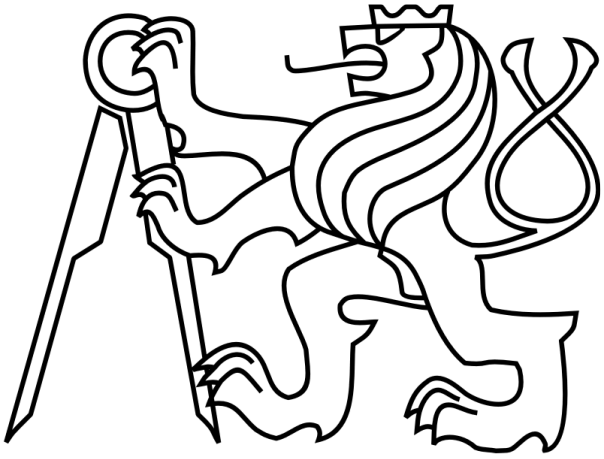

Telemetry Systems for Diabetes Mellitus

DOCTORAL THESIS

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Abstract

Diabetes mellitus (DM) is a chronic disease affecting large numbers of people worldwide and this number is continuously increasing. Self-management is essential for attaining optimal long-term glucose control, and requires careful recording of food intake, glycemic values, insulin doses and other information. Until now, values have usually been recorded in a paper diary. Mobile healthcare and telemedicine provide new possibilities of care models for chronic diseases. There is a big potential to increase adherence to self-management of DM with the use of smartphones and digital therapeutics interventions.

This thesis focuses on two issues:

The first one is the development of a mobile application (app) for DM control and self-management and presents the results of long-term usage of this system in the Czech Republic. The development was based on cooperation with both clinicians and patients. The mobile app was available free-of-charge on Google Play Store from the middle of 2014 until 2019 and suitable users who downloaded the app were selected for the long-term analysis.

The second part of this thesis describes framework for calculation of glycemic variability for Continuous Glucose Monitoring (CGM) data. The Matlab framework implements important measures of glycemic variability and was used for CGM data extraction in several clinical studies. A few requirements for further extension of the functionality such as data filtering or time spent in hypoglycemia have emerged from them.

The thesis shows that the usability of a diabetes mellitus self-management smartphone mobile app and web-based systems could be satisfactory and promising. Nonetheless, some better ways to motivate people with diabetes to participate in self-management are needed. Further studies involving a larger number of patients are needed in order to assess the effect on long-term diabetes management.

Keywords: Diabetes Mellitus; Self-Management; Mobile App; Case Study; Long-Term Data, Continuous Glucose Monitoring, Glycemic Variability

Abstrakt

Diabetes mellitus (DM) je chronické onemocnění, které postihuje velké množství lidí po celém světě, přičemž jejich počet se neustále zvyšuje. Pro dosažení optimální dlouhodobé kontroly glykémie je zásadní samospráva, která vyžaduje pečlivé zaznamenávání příjmu potravy, hodnot glykémie, dávek inzulínu a dalších informací. Dosud se hodnoty obvykle zaznamenávaly do papírového deníku. Mobilní zdravotní péče a telemedicína poskytují nové možnosti modelů péče o chronická onemocnění. Existuje velký potenciál pro zvýšení adherence k samosprávě DM s využitím chytrých telefonů a digitálních terapeutických intervencí.

Tato práce se zaměřuje na dvě problematiky:

První část práce se zabývá vývojem mobilní aplikace pro kontrolu a samosprávu DM a představuje výsledky dlouhodobého používání tohoto systému v České republice. Vývoj byl založen na spolupráci s lékaři i pacienty. Mobilní aplikace byla od poloviny roku 2014 do roku 2019 k dispozici zdarma v obchodě Google Play a pro dlouhodobou analýzu byli vybráni vhodní uživatelé, kteří si aplikaci stáhli.

Druhá část práce popisuje rámec pro výpočet glykemické variability pro data z kontinuálního monitorování glykémie (CGM). Matlab framework implementuje důležité míry glykemické variability a byl použit pro extrakci dat CGM v několika klinických studiích. Z nich vyplynuly požadavky na další rozšíření funkčnosti, například filtrování dat nebo doba strávená v hypoglykémii.

Práce ukazuje, že používání mobilní aplikace pro chytré telefony a webové systémy zaměřené na samosprávu DM by mohlo být uspokojivé a slibné. Přesto je zapotřebí lepších způsobů motivace pacientů s diabetem k účasti na samosprávě. Další studie zahrnující větší počet pacientů jsou nezbytné, aby bylo možné posoudit vliv na dlouhodobou kontrolu diabetu.

Klíčová slova: Diabetes Mellitus; Sebeřízení; Mobilní aplikace; Případová studie; Dlouhodobá data, Kontinuální monitorování glykémie, Glykemická variabilita

Declaration

I declare that this thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institution of tertiary education. Information derived from the published work of others has been acknowledged in the text, and a list of references is given.

Prague, Czech Republic — Václav Burda

April 2022

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Václav Burda, April 2022

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List of Abbreviations

ADRR – Average Daily Risk Range

API – Application Programming Interface

AUC – Area under Curve

BMI – Body Mass Index

BT – Bluetooth

CABG – Coronary Artery By-pass Grafting

CAD – Coronary Artery Disease

CGM – Continuous Glucose Monitoring

CONGA – Continuous Overlapping Net Glycemic Action

CSV – Comma Separated Values

CV – Coefficient of Variation

DiGA – Digital Health Applications (in German: “Digitale Gesundheitsanwendungen”)

DJBL – Duodenal-Jejunal Bypass Liner

DM – Diabetes Mellitus

eHealth – Electronic Health

EU – European Union

GRADE – Glycemic Risk Assessment Diabetes Equation

GV – Glycemic Variability

HbA1c – Glycated Hemoglobin

HBGI – High Blood Glucose Index

HDL – High-Density Lipoprotein

HTTP – Hypertext Transfer Protocol

HTTPS – Hypertext Transfer Protocol Secure

IDDM – Insulin Dependent Diabetes Mellitus

IGC – Index of Glycemic Control

IHD – Ischemic Heart Disease

LBGI – Low Blood Glucose Index

LDL – Low-Density Lipoprotein

LZC – Lempel–Ziv Complexity

MAGE – Mean Amplitude of Glycemic Excursion

mHealth – Mobile Health

mPE – Modified PE

MODD – Mean of Daily Differences

NIDDM – Non-Insulin Dependent Diabetes Mellitus

PDF – Portable Document Format

PE – Permutation Entropy

PHP – PHP: Hypertext Preprocessor (originally Personal Home Page)

REST – Representational State Transfer

RFCOMM – Radio Frequency Communication

ROC – Receiver Operating Curve

SampEn – Sample Entropy

SD – Standard Deviation

SDP – Service Discovery Protocol

SMBG – Self-Monitoring of Blood Glucose

TAG – Triglyceride

US FDA – United States Food and Drug Administration

1 Introduction

Diabetes mellitus (DM) is a chronic life-long progressive metabolic disease affecting over 537 million adults worldwide according to the International Diabetes Federation (Whitehead and Seaton, 2016; Brož *et al.*, 2020). It has been characterized by hyperglycemia due to absolute or relative insulinopenia and accordingly two major types of DM are distinguished: i) Type 1 DM, which is characterized by hyperglycemia due to an absolute deficiency of the insulin hormone produced by the pancreas; ii) Type 2 DM, which is characterized by hyperglycemia due to a defect in insulin secretion usually with a contribution from insulin resistance. It is a disease of high prevalence and is expected to grow significantly in the coming years.

A significant contributing risk factor for developing DM is the global obesity epidemic and as a result, DM is associated with the wide spectrum of risk factors for cardiovascular diseases (Forouhi and Wareham, 2014; Blaslov *et al.*, 2018). Nowadays, the economic impact of the associated healthcare system costs is enormous (Murata *et al.*, 2004). As a result, weight reduction methods have become a field of great medical and scientific interest. Theoretically, it should be a simple matter to achieve weight loss by dieting, producing an energy deficit in which intake is lower than energy expenditure. But practically, successful long-term weight loss maintenance by strategies such as changing dietary habits or increasing physical activity is difficult. This struggle is well illustrated by the typical results in which early weight loss is achieved by most patients, but the weight loss is not kept over the long term (Kassirer and Angell, 1998; Mun, Blackburn and Matthews, 2001).

Another approach is the utilization of pharmacotherapy, which in the context of diabetes can be focused on weight loss, or on glucose control, resulting in weight loss as a side effect (Van Gaal and Dirinck, 2016). However, the long-term outcome is very limited (Mun, Blackburn and Matthews, 2001).

An essential tool of diabetes care is self-management, education, support and motivation that allows all other diabetes interventions to work optimally (Holt *et al.*, 2021). The most frequently reported self-management process was day-to-day decision making related to

self-care, which was a measure of how active and engaged patients were with their own diabetes care (Borries *et al.*, 2019).

Other more aggressive approaches are necessary, especially when a significant weight reduction percentage is required or more serious health consequences are involved. The most successful strategies are based on surgical therapies. The gastric bypass achieves permanent significant long-term weight reduction in most of the patients that have undergone this surgery (Mun, Blackburn and Matthews, 2001; Kothari *et al.*, 2017).

When DM has been diagnosed, in classical treatment an initial consultation is performed and follow-up appointments are set up. A personalized face-to-face approach for visit frequency is recommended and should be annual at least. However, more frequent contact is preferred, especially for recently diagnosed, less involvement or cardiovascular risk patients (Holt *et al.*, 2021). Recently, and especially during the coronavirus pandemic, the usage of telemedicine has been utilized increasingly worldwide and partially has replaced face-to-face visits (Lee and Lee, 2018; Holt *et al.*, 2021). Telemedicine can be defined as "healing at a distance" and is described by the following points: i) using information and communication technologies; ii) providing remote health-care over geographical distance; iii) involving a medical professional on one side and patients on the second side. In addition, the use of telemedicine should be individualized depending on personal needs and limitations. As a result, the telemedicine has a potential to improve self-management, quality of life and treatment of DM (Lee and Lee, 2018; Borries *et al.*, 2019; Timpel *et al.*, 2020).

This thesis describes the development of the Mobiab system for DM self-management. We hypothesized that the use of telemedicine in diabetes care would improve patient self-management processes and clinical outcomes of healthcare. The benefits and impacts of the system usage was explored and analyzed. In order to achieve that, the collection of long-term user's records was gathered and anonymized according to user's agreement provided during the sign-up process. The following part of the thesis is dedicated to the analysis of data from Continuous Glucose Monitoring (CGM). For the analysis Matlab framework that implements several commonly used metrics was prepared. In order, this data analysis was used for a comparison to the newly defined glycemic variability metrics.

1.1 Goals of the Thesis

The overall purpose of this dissertation was to develop a telemedicine system based on the quantitative research and behavioral theory. To accomplish this, the study was composed of two phases. Phase one includes methodological goal of the design and implementation of the telemedicine Mobiab system. Phase two aims at clinical goals of: i) the identification of outcomes on glucose management, quality of life and sustainability of the self-management when using the Mobiab system; ii) the analysis of glycemic variability from continuous glucose monitoring.

1.2 The Structure of the Thesis

The thesis is structured as follows:

Chapter 2 provides an introduction to the topic of the thesis. Namely, section 2.1 gives information on diabetes mellitus and its treatment. Section 2.2 describes eHealth and mHealth technologies and term telemedicine. In section 2.3 there is a subset of available mobile applications for DM self-management.

Chapter 3 provides information on the Mobiab system, Section 3.1 describes the system developed for self-management of DM and its functionalities. Sections 3.2 and 3.3 describe the collected data and results respectively. Sections 3.4 and 3.5 provide discussion and conclusion.

Chapter 4 focuses on continuous glucose monitoring (CGM). Section 4.1 provides an introduction to CGM. Available data and used methods are described in section 4.2. Following sections evaluate achieved results and discussion.

Chapter 5 describes the glycemic variability (GV) and analysis of several nonlinear algorithms. For the analysis the same dataset was used as in the previous chapter.

Chapter 6 concludes the thesis and summarizes the achievements and contributions and offers topics for future work.

2 Background

2.1 Diabetes Mellitus

Diabetes mellitus is a chronic disease affecting large numbers of people throughout the world, and this number is continuously increasing. According to the International Diabetes Federation, there are 537 million adults worldwide diagnosed with DM (Whitehead and Seaton, 2016; Brož *et al.*, 2020). In the Czech Republic in 2020, nearly one million people suffered from this disease, i.e. almost 10% of the population of the country (Brož *et al.*, 2020; SZÚ, 2021). There are two main types of DM (type 1 DM and type 2 DM) and other less common types such as gestational diabetes, prediabetes and others (ADA, 2010).

Type 1 DM. This type is an autoimmune disease, which means that your body attacks itself. It is characterized by an absolute lack of insulin secretion from pancreatic B-cells and it is responsible for approximately 5-10% of the cases. It is usually diagnosed in children and young adults, but it can develop at any age. It used to be known more as "juvenile" diabetes. People with type 1 DM need to inject insulin every day. That is why it is also called insulin-dependent diabetes. The patient has to take some time to adjust to the treatment, but they can still do all the things they like to do. It should be mentioned that type 1 DM is not related to age or overweight, these factors are associated with type 2 DM. (ADA, 2010; Holt *et al.*, 2021).

Type 2 DM. This type is characterized by progressive loss of insulin secretion from B-cells with an underlying background of insulin resistance resulting in hyperglycemia, which further leads to the development of acute and chronic diabetic complications. Type 2 DM accounts for about 90-95% of the cases. Typically, it occurs in middle-aged and older people, although it is increasingly common in children. A risk factor for developing of this diabetes type is an overweight, not enough exercise, family inheritance, higher blood pressure or prediabetes. There is no cure for type 2 DM. However, it can be managed by maintaining a healthy lifestyle, self-management and taking medication if necessary. (ADA, 2010; Riddle *et al.*, 2021).

Gestational Diabetes. The definition of gestational diabetes (GDM) is glucose intolerance of a variable degree diagnosed with onset or first recognition during a pregnancy. Although most cases disappear after giving birth, it is possible that unrecognized glucose intolerance may have preceded or started at the same time as the pregnancy. As the continuing epidemic of obesity and diabetes in population has led to an increasing prevalence of type 2 DM in women of childbearing age, the number of pregnant women with undiagnosed type 2 DM has also increased. Approximately 7% of all pregnancies (between 1% and 14% depending on the population and tests used) are affected by GDM. (ADA, 2010, 2019).

Prediabetes. Having prediabetes means to have higher than normal blood sugar levels. Unmanaged prediabetes can lead to type 2 DM. Prediabetes does not always have symptoms so it is important to be tested for blood sugar levels, especially if the person has risk factors for type 2 DM. Weight reduction, regular exercise and a healthy diet can reverse prediabetes and prevent the development of type 2 DM (Brož *et al.*, 2020).

2.1.1 Diagnosis and Treatment

There are several ways to diagnose diabetes. Each method usually needs to be repeated on the second day to diagnose diabetes: i) A1C test, which measures the average blood sugar level over the past two or three months. The advantage of this method is that there is no need to fast or drink before. The normal value is less than 5.7%, DM is diagnosed on 6.5% or higher value; ii) Fasting Plasma Glucose test that measures fasting blood sugar levels. It requires no food or drink except water for at least 8 hours before taking the test. The normal value is less than 5.6 mmol/l, DM is diagnosed on 6.7 mmol/l or higher value; iii) Oral Glucose Tolerance Test that measures blood sugar levels two hours after drinking a special sugary drink. The normal value is less than 7.8 mmol/l, DM is diagnosed on 13.0 mmol/l or higher value. (ADA, 2010)

The principle of the treatment is to achieve a glycaemia similar to normal glycaemia, the so-called euglycemia. The basis of the treatment is common for all types of diabetes and it contains:

- patient education about diet and exercise,
- glucometers to self-monitor blood glucose,
- patient education about self-monitoring the symptoms of hypoglycemia.

Self-management is essential for attaining optimal long-term glucose control and requires careful recording of food intake, glycemic values, insulin doses and other information. A typical part of self-management is using paper-based protocols or diaries for recording diabetes related values (Donsa *et al.*, 2016). This can be problematic and complicated because the patient has to remember or look up for caloric values. The specific treatment for type 1 DM contains: lifelong insulin injections (combination of short-acting and long-acting), symptom relief and prevention (or delay) of complications by targeting normal blood glucose levels. The treatment for type 2 DM is usually focused on early detection and treatment of complications (eye exam, urine test, foot care) (World Health Organisation, 2013; Holt *et al.*, 2021). An important characteristics of diabetes as a disease is that a proper diet and cooperation with physicians can prevent its serious complications. On the contrary, noncompliance with the given rules can accelerate complications (e.g. atherosclerosis, cardiovascular problems) and can lead to kidney damage or amputation of lower limbs (World Health Organisation, 2013; Riddle *et al.*, 2021).

2.1.2 Gamification in Diabetes Care

The application of gamification involves the use of game elements, design techniques and game mechanics to non-game activities or environments. The idea of gamification is to educate and motivate players to develop personal skills and modify their behavior. The game focuses on our attention, engages the audience, forces people to acquire more effective skills and makes otherwise ordinary tasks more fun. In order to achieve this, many apps use indicators of progress to measure success, share the success and offer rewards to users to keep them self-motivated. For healthcare, gamification is primarily used in applications for health and wellness that relate to the prevention, diagnosis and treatment of disease, managing chronic conditions, or lifestyle modification. (Richards and Caldwell, 2015; Asadzandi *et al.*, 2020)

Games are a new technology that promises to potentially improve adherence to a treatment plan or intervention. In addition, they can be used not only to increase motivation, but also to measure motivation and understand cognitive processes, and to inform and help patients make good health decisions. Therefore, games can be considered to be potentially effective way to promote knowledge from certified and validated sources to development of self-management skills and overall learning experiences among people with diabetes. However, one of the biggest challenges in the treatment of DM is to motivate people with DM to adapt

and adhere to the treatment regimen, which is quite different from the previous habits. (Makhlysheva, Arsand and Hartvigsen, 2015; Richards and Caldwell, 2015).

The literature and analyses suggest that DM management can be achieved and/or improved in several ways: i) through the use of personalized diaries providing feedback to the recorded data; ii) education through games or virtual avatars e.g. virtual pets; iii) balanced reward system that keeps the user motivated; iv) additional use of social networks and interaction between people with the same diagnosis (Makhlysheva, Arsand and Hartvigsen, 2015).

2.2 Telemedicine, eHealth and mHealth

Telemedicine. The first use of term "telemedicine" was noticed in the early 1960s and it can be explained as "healing at a distance". It allows diagnosing and treating patient's disease remotely by using video consultation or other transition of medical information. Internet has brought major changes in the field of telemedicine. The growth of smart devices capable of transmitting high quality images has opened up the option of providing remote healthcare to patients in their homes or workplaces as an alternative to face-to-face visits in primary and specialist care (Nesbitt, 2012; Boyle *et al.*, 2017).

eHealth. The electronic health (eHealth) can be defined as "using information and communication technology for health services and information". Many services or systems such as telemedicine, electronic prescribing, patients web portals (known as IZIP in the Czech Republic) or mobile health can be found under this definition (Thestrup, Gergely and Beck, 2012; Gee *et al.*, 2015).

mHealth. The term mHealth is related with telemedicine and eHealth. It can be described as "using mobile communication for health services and information." Mobile healthcare provides new possibilities of care models for chronic diseases. The mHealth concept covers the evolution of eHealth systems from traditional telemedicine platforms to mobile and wireless configurations (Nesbitt, 2012; Thestrup, Gergely and Beck, 2012).

These tools and care models can contribute to improving the lives of individual patients. The care of a chronic disease should be continuous, available between contact visits and hospitalization and the patient should learn during the care process. However, there are no

data on the impact how mobile technologies influence health outcome (Thestrup, Gergely and Beck, 2012).

At this point, there is a big potential to increase involvement with self-management of DM using smartphones and digital therapeutics interventions. Currently, mHealth represents the focus of various mobile applications that can also reduce barriers to the availability of the healthcare system, e.g. time constraints or limited access to care providers (Adu *et al.*, 2020). Smartphone diabetes apps might have an extensive range, as more than 6.37 billion people in the world use smartphones (Bankmycell.com, 2022), and about 0.5 billion of them already use some mobile app for dieting, physical activities and chronic disease management (Hood *et al.*, 2016).

There are numerous mobile apps dealing with DM. For the term "diabetes", there are more than 200 mobile apps available on the Google Play platform(Veazie *et al.*, 2018). However, despite the large number of apps in this field only few have been evaluated in health outcome studies (Veazie *et al.*, 2018) and just 5 of them have been associated with clinically significant improvements in glycated hemoglobin (HbA1c) (Glucose Buddy, Diabeo Telesage, Blue Star, WellTang, Gather Health) (Veazie *et al.*, 2018). These studies did not assess other parameters, e.g. blood pressure and body weight (Veazie *et al.*, 2018). The authors of one study identified and compared 19 mobile apps in terms of the availability of features for DM self-management (Izahar *et al.*, 2017). Few of them have been designed based on a behavioral model, and endorsed by health care professionals. In addition, it is important to have appropriate integration without compromising user safety and privacy.

The use of mobile apps can improve DM self-management and can contribute to patient education and motivate them to maintain healthy behavior. Furthermore, compared to usual care of DM treatment, m-health solutions present improvements in adherence to medication and glycemic measurements (Bellei *et al.*, 2018). Several small-scale studies have shown promising results in terms of targeting blood glucose, medication intake, weight loss and quality of life (Turner-McGrievy *et al.*, 2013; Arnhold, Quade and Kirch, 2014; Froisland and Arsand, 2015; Huang *et al.*, 2015). To the best of the author's knowledge, there is no published full report on a case study of diabetes self-management over a 5-year period.

2.3 Mobile Apps for DM Treatment

This chapter is devoted to the research of available mobile applications, the features they have, the way they are updated or how popular they are among users. The findings in this research correspond to the facts from 2016 when the research was conducted. The data were the basis for the development of the system proposed and are further supplemented by the current state in which the applications are (compared in Table 2.1).

There are many available mobile applications for a diabetes treatment; however, most of them focus only on a specific function (e.g. logging glycaemia, diet recipes). A few of the mobile applications are more complex and have multiple functions together. They usually contain glycaemia and insulin monitoring and a number of ingested carbohydrates. Activity logging, notes and medicament reminder are included sometimes. If the mobile application contains a food database instead of ingested carbohydrates, then the Czech language is not available. Short reviews of five most downloaded and best rated complex mobile application follow below. Since Android devices cover over two-thirds of the market in the USA and over three-quarters in the five largest European countries, only mobile applications for Android devices are selected.

Table 2.1 - Availability and rating of selected mobile apps.

	Available on Google	**Last update**	**Rating (stars / users)**		**Downloads**	
			2016	**2022**	**2016**	**2022**
MySugr	Yes	31.01.2022	4.6 / 10 620	4.7 / 64 134	500 000 - 1 000 000	Over 1 000 000
Diabetes Connect	Yes	20.12.2020	4.5 / 3 032	4.9 / 4 779	100 000 – 500 000	100 000 – 500 000
Diabetes:M	Yes	10.01.2022	4.7 / 8 599	4.6 / 21 585	100 000 – 500 000	500 000 - 1 000 000
BG Monitor Diabetes	Yes	23.04.2017	4.5 / 465	N/A	10 000 – 50 000	10 000 – 50 000
OnTrack Diabetes	No	29.01.2015	4.4 / 6 015	N/A	100 000 – 500 000	N/A

In December 2018, article "Diabetes Mellitus m-Health Applications: A Systematic Review of Features and Fundamentals" (Bellei *et al.*, 2018) was published. The authors of the article systematically screened and analyzed studies related to the variety of applications aimed at monitoring and treating DM. The objective was to examine the functionality of the apps, the fundamentals of their design and the way the apps were tested. A total of 679 studies

were screened, 39 of which met the inclusion criteria for this study and one from these was our Mobiab system described in Chapter 3. The authors conclude in their research that there is a variety of approaches used in the DM apps, with comprehensive, customizable, and adjusted functionalities for different purposes. In addition, most of the apps are digital logbooks for collecting data on various daily tasks from DM treatment (Bellei *et al.*, 2018).

2.3.1 Review of Selected Mobile Apps

MySugr - Diabetes Logbook

MySugr - Diabetes Logbook is a very popular mobile application with many useful features; however, only basic features are for free. The Pro version with monthly payment adds multiple advanced features (e.g. report for physician, reminders, photo gallery). CGM data integration is available via importing CSV file or instant connection with Accu-Check devices. A motivation element and challenges for personal therapy goals are implemented in the application. As it is shown in Figure 2.1, this application seems well. In 2016, the number of downloads was between 500 thousand and 1 million, the last update was done on 17th August 2016 and the average rating was 4.6 stars given by 10620 users. In 2022, the number of downloads is over 1 million, the last update was done on 31th January 2022; thus, the application still is being developed. The average rating is 4.7 stars given by 64134 users.

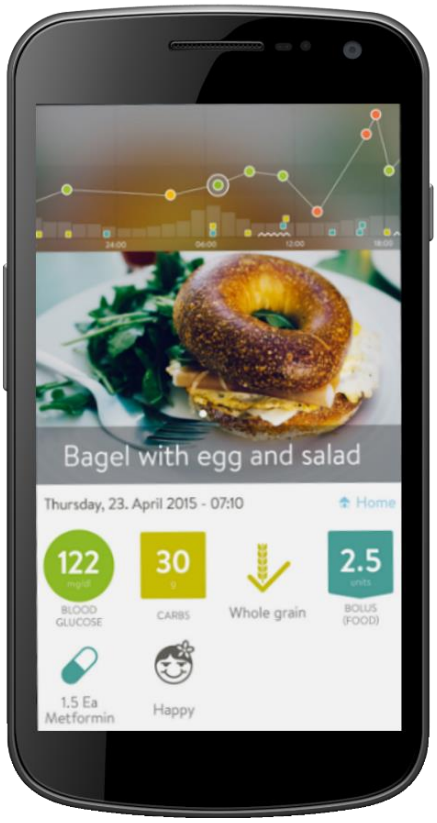

Figure 2.1 - The mySugr - Diabetes Logbook App.

Diabetes Connect

The interesting and simple application Diabetes Connect offers besides basic features also the blood pressure, pulse and weight monitoring as it is shown in Figure 2.2. There is support for exporting reports into a PDF file. Download of the mobile application is for free; however, some advanced features are paid. In 2016, the number of downloads was between 100 thousand and 500 thousand, the last update was done on 22th June 2016 and the average

rating was 4.5 stars given by 3032 users. In 2022, the number of downloads is between 100 thousand and 500 thousand, the last update was done on 20th December 2020 and the average rating is 4.9 stars given by 4779 users. This rating shows very good and increased quality.

Diabetes:M

This mobile application tracks almost all aspects of the diabetes treatment and provides detailed reports, charts and statistics, which are shown in Figure 2.3. They can be shared via an email with a supervising physician. It also supports importing values from various glucometers and insulin pumps via the exported files. However, there is one drawback: in a mobile phone, the design is slightly chaotic and some information is not shown properly. This drawback is balanced by the complexity of the application, to which one needs to get used. In 2016, the number of downloads was between 100 thousand and 500 thousand. The last update was done on 14th August 2016. The average rating is 4.7 stars given by 8599 users and one-star rating was only from 86 users. In 2022, the number of downloads is between 500 thousand and 1 million, the last update was done on 10th January 2022 and the average rating is 4.6 stars given by 21585 users and one-star rating is only from few users.

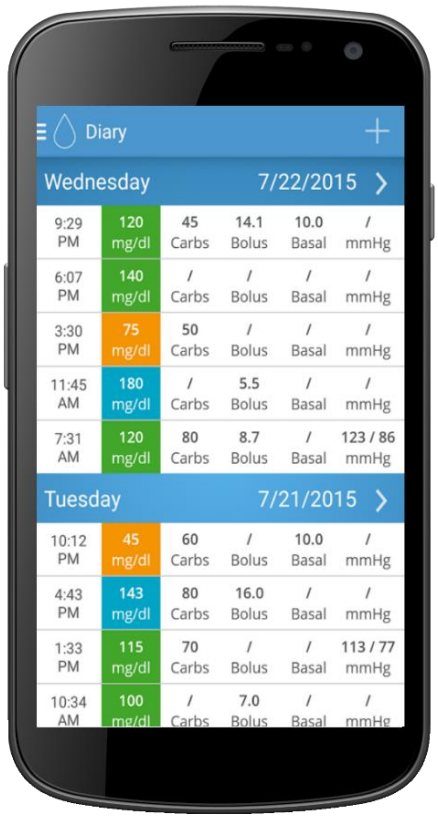

Figure 2.2 - The Diabetes Connect App.

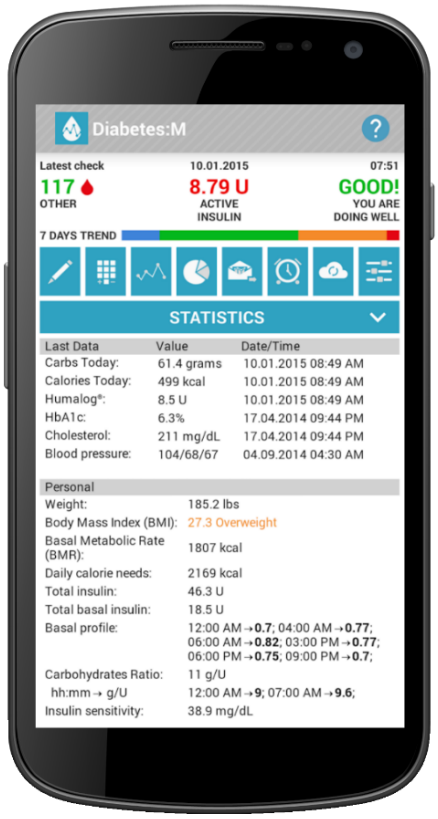

Figure 2.3 - The Diabetes:M App.

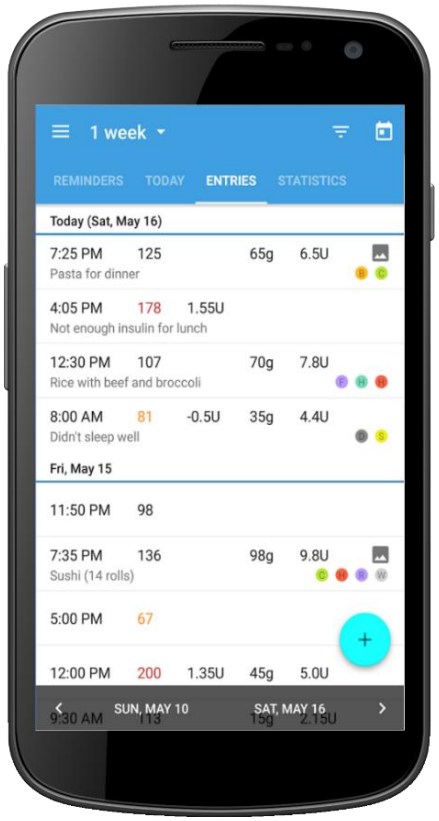

Figure 2.4 - The BG Monitor Diabetes App.

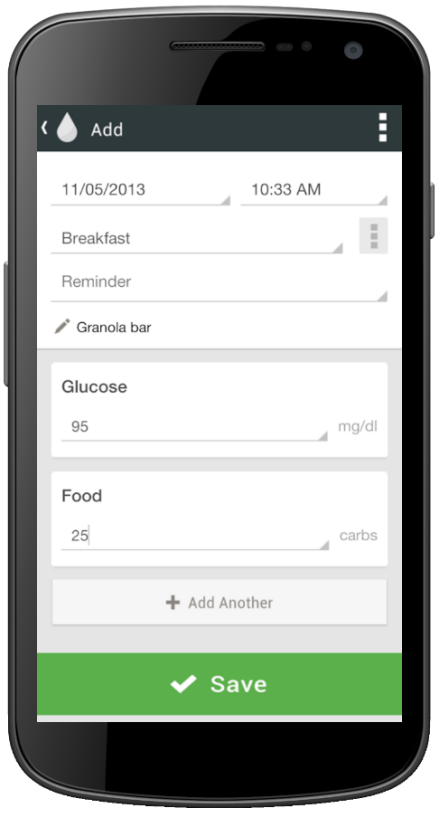

Figure 2.5 - The OnTrack Diabetes App.

BG Monitor Diabetes

This application offers basic logging features for free; advanced features (e.g. food database, backup, import existing data, tagging) are paid. It has an elegant design with a well-arranged overview and statistics as it is shown in Figure 2.4. This mobile application is newer than the previous ones, but is no longer updated. Therefore, the number of downloads is only between 50 thousand and 100 thousand. The last update was done on 23th April 2017. In 2016, the average rating was 4.5 stars given by 465 users and in 2022 the rating is hidden.

OnTrack Diabetes

This application allows easy tracking of everything important for diabetics. The integration of reminders is an advantage. However, a drawback is that it does not contain a food database and an activity logging is only for information without any caloric values. There is an example of adding a new record in Figure 2.5. In 2016, the number of downloads was between 500 thousand and 1 million, the last update was done on 29th January 2015 and the average rating was 4.4 stars given by 6015 users. Unfortunately, the app is no longer available on Google Play, which means that its development has been probably stopped. No reason for this has been found.

3 Diabetes Mellitus Self-Management Telemedicine System

This chapter comments on the development of the mobile app and presents the impact on self-management of people with DM. The presented results were accepted as a journal article in impacted JMIR Diabetes: **V. Burda** *et al.* (2022) 'Managing Diabetes Using Mobiab: Long Term Case Study of the Impact of a Mobile App on Self-Management', Preprint, doi: 10.2196/36675.

3.1 Introduction

The Mobiab system was developed within the context of OLDES (www.oldes.eu), an EU multicenter project involving 4 companies, 2 universities and 2 university hospitals. The OLDES project focused on developing information technology for the purposes of eHealth applications (Novák *et al.*, 2009). We defined the essential requirements for a system based on interviews and discussions with diabetologists from a university hospital in Prague, representatives from the national Czech diabetes association, and patients living with diabetes, who were recruited from an outpatient clinic at the university hospital. This approach enabled us to involve the needs of health professionals and patients during the design and development of the app. Additional information was gathered by searching public scientific databases using the following combinations of keywords: "mobile app", "diabetes", "diabetes management", "patient adherence, empowerment", "mobile health", and "self-management." Several paper-based diabetes diaries were used to define the main functionalities that were to be integrated (Schmocker, Zwahlen and Denecke, 2018).

3.1.1 Architecture and System Functionalities

The Mobiab system offers an alternative to a paper-based diary – an Android mobile application and a web portal aimed at supporting DM self-management. Compared with a paper-based diary, the main benefit is the immediate feedback for inputted data in the form of graphs and basic statistics showing the user's compliance with diet or providing self-monitoring of blood glucose. The Mobiab system was designed in a client-server

architecture with a storage system on the server. Mobiab requires an internet connection on mobile devices. In the beginning, i.e. in 2014, this approach was restricted by lower availability of internet connection (ČSÚ, 2017). However, this is no longer a problem, now that internet connection is much more widely available.

The concept underlying Mobiab consists of a mobile phone app, data collection from medical devices, and data storage (Figure 3.1). All medical data are collected on a mobile phone and are stored on the server. We prepared a prototype of a Bluetooth connection to selected medical devices from ForaCare Suisse AG. The connection works fully automatically – records of measurements are downloaded and are stored without any action by the user. With users' consent, the collected behavior data and medical data are then available on a desktop computer to selected physicians. Common security standards and privacy policies have been followed in the design and development of the Mobiab system. Communication between smartphone or computer and server is encrypted via the HTTPS protocol. After the app download, registration or login is required at first. The login screen requires a unique e-mail address and password to access the app functionality. An expert group consisting of endocrinologists, health researchers, nutrition nurses and app developers provided useful decisions for the design and development of Mobiab.

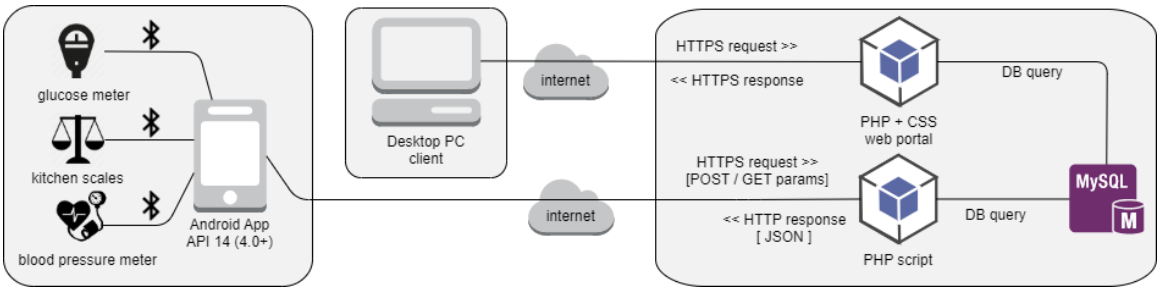

Figure 3.1 - Scheme of system architecture.

On the grounds of the research of mobile applications and the way of DM treatment, the following core requirements for the developed system were defined. These requirements are divided into common and individual demands for the mobile Android application and web-based portal respectively. These are further divided into functional (define what a system is supposed to *do*) and non-functional (define how a system is supposed to *be*). The essential requirements are that the entire Mobiab system (mobile application and web-based portal) uses the PHP scripting language and MySQL as the database layer. In the case of the mobile application, a minimum API version 14 (Android 4.0) was also required.

Common Requirements

Functional requirements:

- The system will allow to create and manage a user accounts.
- The system will be accessible only to logged-in users.
- The system will display detailed information on calorie intake, expenditure (activities performed), glycaemia and insulin dosage for any day.
- The system will show the user information on the daily calorie intake.
- The system will display a graph of the user's glycemic profile.
- The system will allow communication between a user and a physician via messages.

Non-functional requirements:

- The system will be simple and intuitive to use.
- The system will be easy to extend with additional functionality.
- The system will use encrypted communication over HTTPS protocol.

Android Mobile Application Requirements

Functional requirements:

- The system will allow adding, displaying and editing records of consumed food.
- The system will allow adding, displaying and editing records of activity performed.
- The system will allow adding, displaying and editing glycaemia values.
- The system will allow adding, displaying and editing insulin dosage.
- The system will allow communication between a user and a physician via messages.
- The system will implement reminders and gamification features.

Non-functional requirements:

- The system will be implemented in the Java programming language.
- The system will be implemented at least for Android version 4.0 (API Level 14).
- The system can be easily interfaced with other modules and additional applications.
- The system will communicate with the glucometer via Bluetooth protocol.

Web-based Portal Requirements

Functional requirements:

- The system will allow to view graphs of calorie intake, carbohydrate diet compliance, calorie expenditure (activities performed) and glycemic values for any given day.
- The system allows differentiation of user roles: basic user, physician, administrator.
- The system will allow a physician to preview their patients' reports.

Non-functional requirements:

- The system will be accessible via a web interface.
- The system will be implemented in the PHP programming language.

3.1.2 Description of Bluetooth Communication

The Bluetooth (BT) technology in version 1.0 appeared first in devices at the end of the last century in 1999, but its origins date back to 1994. Over time, the technology has evolved to the current version 5.3, which significantly reduces power consumption. Bluetooth transmissions are broadcasting on a radio frequency between 2.402 GHz and 2.480 GHz and thus operate in the free radio band without license fees. This band is further divided into 87 channels that alternate during communication to eliminate possible interference from other devices operating in the same band. The Bluetooth technology is a layered architecture similar to a network interface. A number of protocols then operate on top of it, such as the Service Discovery Protocol (SDP), which allows one device to find available services on another device, or for example the Radio Frequency Communication (RFCOMM), which provides binary data transfer to emulate the serial port known as RS-232, which has a wide range of applications (Zeadally, Siddiqui and Baig, 2019).

Device Communication and Pairing

The communication itself then takes place exclusively between two devices that are paired together. By pairing, the device is able to identify the data being sent from the other device and knows that it is the device that the user has added, thus proving it to be trusted. In order to start pairing, the device to be paired must be switched to the visible mode. In this mode, other devices can find it under a 48-bit MAC address, based on which they can contact the

device for details, and the device will respond to such a call by passing the device name and class, available services and other technical information. This is followed by user action to select the device and initiate the pairing process. The device responses by either requesting a PIN, which it shows on its display, or has a pre-assigned PIN (typically 0000 or 1234). If the user enters the correct PIN, the pairing process is complete and the communication between the devices can begin. (Zeadally, Siddiqui and Baig, 2019).

Integration of Bluetooth Glucometer

For the initial integration with our app, we have chosen the small and lightweight device FORA Diamond Mini Bluetooth (DM30b). This glucometer is commonly available through retailers and is imported to the Czech Republic by the MTE company, which sells it for about 600 CZK including VAT. For this price, the patient gets a Bluetooth glucometer, a sampling pen, 10 lancets for the sampling pen, 10 glucose test strips, a USB cable for charging, a 230V mains charger and a fabric case.

For integration into the Mobiab system, a separate plugin has been implemented allowing communication between the system and the glucometer. The pairing process is relatively simple and user-friendly. First, it is necessary to switch the glucometer to pairing mode by pressing the small recessed button on the bottom of the glucometer, and pressing repeatedly until the "`PAr`" is visible on the glucometer display, then switch to "`yes`" with the large button and confirm again with the small button. The glucose meter will turn off and start flashing blue and from this time on it is possible to search for a pairing. Next, navigate to App Options in the app, enable using of the Bluetooth glucometer and click on Pair button. After the mobile phone finds the glucometer, click on "`DIAMOND MOBILE`" to signal our intention to connect it to the phone, no PIN code is requested. If we have followed the procedure correctly, a dialogue will pop up on the mobile phone after a while to confirm the whole pairing process.

The developed communication plugin includes a service that runs on the background of the mobile phone and waits for an incoming connection with the glucose meter. With this approach, it is possible to keep the phone for example on a shelf and calmly measure the glucose value and later add a note to the measured values and save them. During the development, we have found out that it is sufficient to be in the same room as the phone during the measurement for the data to be downloaded from the meter into the phone. This

feature provides a good comfort for the user as they do not have to operate the glucometer and the mobile phone at the same time.

3.1.3 Design of the Mobile App

The mobile app consists of individual modules that are independent of each other and need only the basis of the application (Figure 3.2). The main advantage of applying a modular approach is that other functionalities can be added easily, and particular users can select only certain modules that are suited to their needs. For example, patients with type 2 DM and those who do not use insulin can turn off the insulin module. All entered values into the modules are visualized intuitively, and enable the user to monitor the changes continuously. The modules with their main features are described in the following subsections.

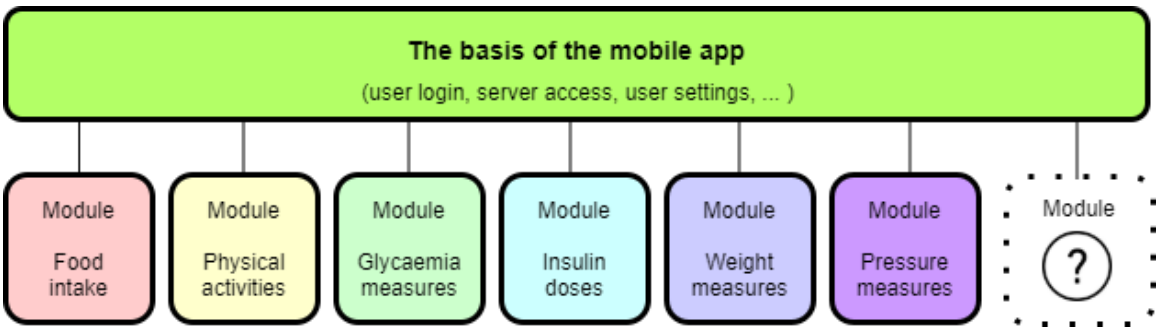

Figure 3.2 - Scheme of the mobile application and individual modules.

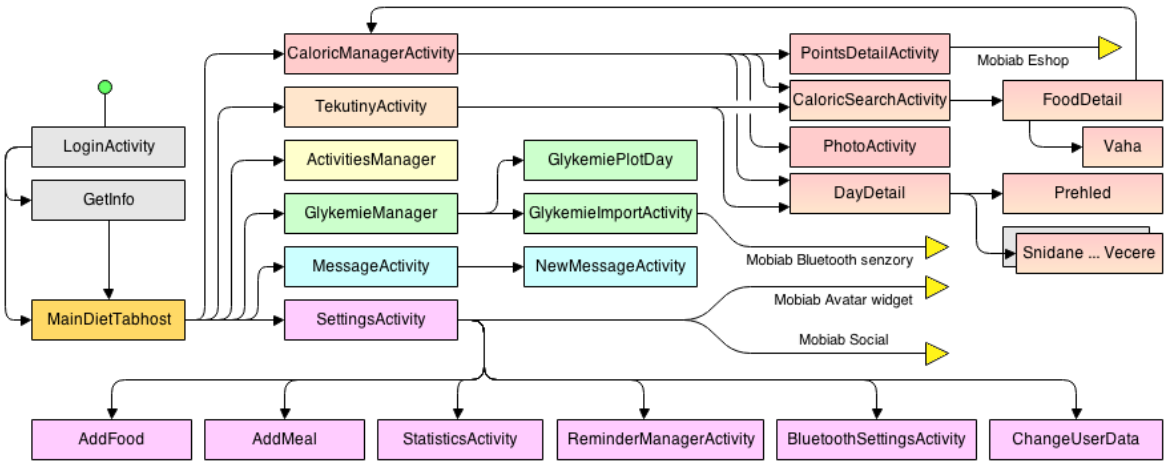

Figure 3.3 - Structure and coherence of Activities in the mobile application.

In our case, implementing modules means adding a link to another activity that represents a functional branch. In Figure 3.3, the different functional branches are color-coded and follow the structure of dividing the application into modules. As can be seen such a module can be implemented within a single activity (*ActivitiesManager*), or it can be broadly branched and later linked to multiple entry points from a signpost (*CaloricManagerActivity*). If modules are implemented in this way, they become a part of the application and the user perceives the application complexly though it is composed of single modules.

From the programmer's point of view, the main advantage of this way of integration is the simplicity of the implementation in the application and once the installation package is created, the module is part of a single installation. This solution is also suitable when the module is part of the main functionality of the application and when we assume that all users who install the application will use it. This has the added benefit of managing only one app (regional availability, price and other app distribution options) in Google Play online store (Android app distribution center).

This solution does not have many disadvantages, but it depends very much on the type of application and module. The biggest disadvantage of bundling all modules together is the size of the whole installation package, and thus of the whole installed application. This could be handled by implementing each module as an additional application. If a user wants to use such a module, they have to install it first before using it. The main app checks if the module is installed, and if it is not, the user is redirected directly to Google Play store for the specific module. After that, everything will already work the same as if the module is integrated directly into the app.

The another possible disadvantage is the higher complexity of the implementation, when each module is programmed as a separate application and it is necessary to properly handle that the application works without these modules and to solve any dependencies between the modules. A further complication is the greater demands placed on the user, as they must install multiple components to achieve the same application performance as if they were installed using only one installation package.

Food Intake and Physical Activities

Food Intake. This is the most complex module, and provides the functionality for recording food that is consumed. Now this module contains a food database with more than 9000 Czech food items. The database has been expanded gradually and checked for data accuracy by other users. There are several approaches to food consumption logging:

- search in the whole database,
- search in favorite items,
- browse all food items and filter by categories,
- browse user's own custom-made meals.

The user enters the amount of food after searching for the specific food item. The timestamp for the consumption and the food category is predefined by the current time; however, this can be changed by the user. To enable the user to change their mind, the description of the nutrition, and the size of the portion (in grams) and the carbohydrates (in grams) are displayed before the final dialog is saved. The changes in values are facilitated by an intuitive visualization of all measured medical data (Figure 3.4). A prototype of kitchen scales with Bluetooth to make weighting of food easier had been created and tested, but this function was hidden due to no available device on the market. Furthermore, on the day detail the user can take a photo or select a photo from gallery and add it to the previously entered meals.

Physical Activities. This module was designed similarly to the food intake module: the database contains more than 400 activities that can be browsed by categories or searched by name. It is necessary to select one activity and to enter the duration of the activity for logging. The caloric expenditure is computed with the user's weight and the duration of the activity. Due to this approach, the computed caloric expenditure may not always match the real expenditure, and should be considered solely as a guide.

Glycemic Monitoring and Insulin Dosage

As the monitoring glycemic values and recording the insulin dosage is an important part of treatment for a person with type 2 DM and type 1 DM respectively, these modules should have a simple design for easy daily usage.

Figure 3.4 - The mobile app: Glycaemia monitoring, Food intake, Insulin doses.

Glycemic Monitoring. The design of the module is intuitive, it has an input part for entering values, e.g. glucose levels, the date and time of measurement and notes. The second part of the module is an overview of the values for the selected day, or a graph for the selected time range (Figure 3.4). In addition, the glucose input module can communicate with the glucose meter (FORA Diamond Mini Bluetooth) via Bluetooth protocol and can download the measured data and allow the patient to attach their note to it, similar to writing down the values in a paper-based diary. The advantage of integration of this module is the synchronization with the web-based portal, which the physician has access to and can immediately see their patients' glycemic data. The added value compared to the paper-based diary is the graphs that show the development of the glycaemia over one or more days.

Insulin Dosage. The insulin applications module is more complex than the previous modules. As shown (Figure 3.4), the user first chooses from three types of insulin (basal, prandial and fast correcting), then selects a specific brand name of insulin (user editable), the number of applied units, and the date and time of application. The overview section is the same as in the Glycaemia Monitoring module.

Other Supplementary Modules

In addition to the main modules described above, several supplementary modules that have supportive effect in DM self-care and self-management are also implemented in the system. An overview and their summary description follow.

Weight and Waist Circumference. Since the diabetic diet, which is a part of the treatment of type 2 DM, is also based on weight reduction, this module is a useful tool for recording weight loss and waist circumference reduction. The user can enter measured values in the same way as measured glucose values in the Glycemic monitoring module.

Blood Pressure Monitoring. As high blood pressure is the most common disease associated with diabetes, the app includes a simple module for logging blood pressure measurements. The design of this module and its usage are the same as the previous ones and differ only in the structure of the input fields.

Knowledge Base. Another module is a small educational knowledge base, like a Wikipedia entry, which contains useful information about DM treatment and self-management. Its content is logically categorized into several sections: information about diabetes, diabetes symptoms, treatments, complications and preventions.

Messaging. A communication module has been implemented in a similar way to the SMS conversation. This approach has several benefits: users are used to this type of messaging; therefore, using it is easy for them. It is then convenient for doctors and patients alike to have the entire history of communication they have written each other. Moreover, if the doctor compliments their patient for exemplary compliance with the limits, the communication module can also have a motivational function. When the communication module is launched, the application retrieves the three most recent

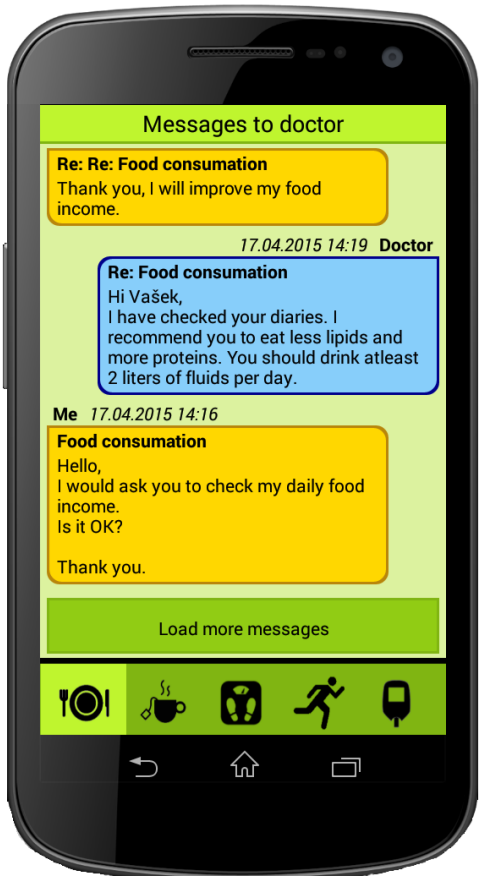

Figure 3.5 - Preview of communication module.

messages that the patient and doctor have sent to each other. The loading of just three messages has been chosen as a compromise between the overall size of the data transferred and the content of the messages that are most interesting to the user. At the bottom of the screen there is a button that allows the user to retrieve more history of their communication. However, this module has not been further developed and practically used, for this reason it is not discussed further more.

User Gamification and Motivation

A special feature implemented in the system is the gamification and motivation support modules. The term of gamification means the use of game elements in a non-game environment. Its principal tools are, for example, points, virtual money, leaderboards, scores, challenges and tasks. The aim is to increase user involvement and motivation to a much greater extent. Virtual games have always motivated players in different ways depending on the nature of the game.

The most common way to motivate is through a score that evaluates the user's performance in the game. As a rule, the higher score, the better. The score is most often increased for tasks completed and the speed of completing them, or conversely it may decrease in case of a longer time taken to finish the tasks. In more complex games, other methods are used, such as virtual money, which can be exchanged for virtual or real items, as well as gaining experience and progressing to other levels, which usually bring more options and different gameplay enjoyment. The main goal of such a concept is to keep the user in the game and to get them to play as much as possible. That is, to keep them in the so-called “flow zone”.

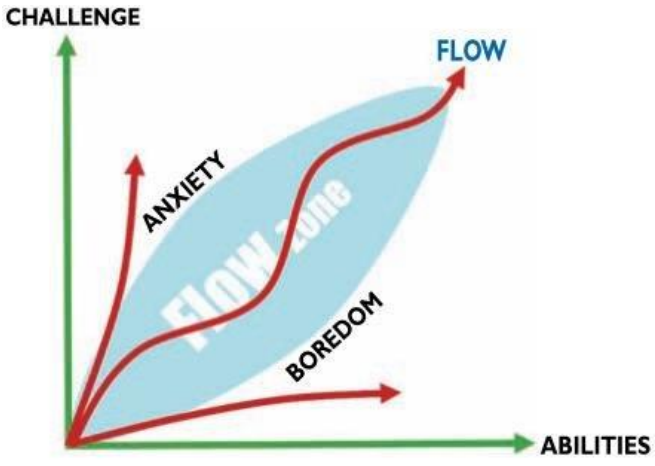

Figure 3.6 - The flow zone in relation to challenge and abilities.[1]

The Figure 3.6 explains the problem, where the flow zone must be challenging enough to keep the player from getting bored, but at the same time not overestimating the player's abilities, because at that point it stops being a challenge for them and they stop playing (Deterding *et al.*, 2011).

[1] https://www.researchgate.net/publication/342529935 (April 2022)

In case of DM self-care this module should motivate users to enter caloric intake, physical activities, glycemic and other values into the app regularly. In the mobile app 4 modules with features aimed at motivating the user to use the mobile application regularly have been implemented:

Animated avatar. Another form of motivation that targets younger users in particular is a home-screen widget that includes a picture of an animal or an object, known as an avatar, which closely recalls the popular Tamagotchi of the 90's. An animated avatar (e.g. a dog or a cat) may be activated and connected with user's profile. This avatar is supposed to personify the user themselves and can have feelings and wishes – it can be hungry, sad or happy depending on the values that the user has entered in the mobile application or web-based portal.

Gamification system. The goal was to implement a scoring system where the user would be rewarded for every performed action that has any sense in support for DM self-management. For each entry, the user gets a certain number of points, and in addition, if the user enters the required information regularly, they will earn bonus points for completing it. By doing so, the user can accumulate a certain amount of points, which can be traded for small real gifts, e.g. blood glucose test strips, or for virtual accessories for the animated avatars. The whole system is set up in the way that each value entered has a different importance and can therefore be scored with a different amount of points. The scoring system is described in Figure 3.7 and is further divided into 4 levels, according to the total continuous time of entering values. This allows the user to move up to a higher level after a certain period of time and thus gain a higher daily bonus if the user still meets the conditions for that level. If the user stops meeting the conditions, the user will drop down one level.

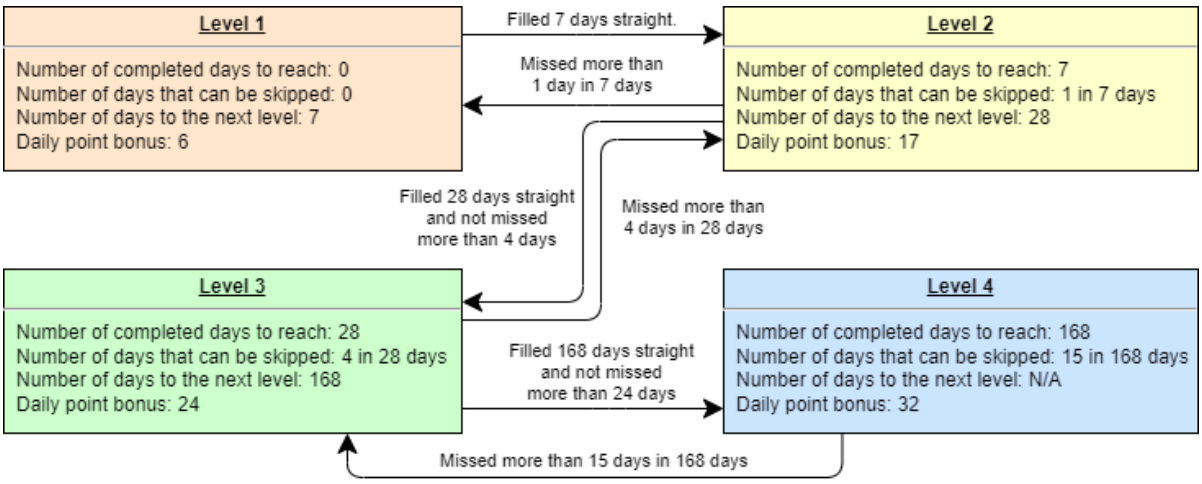

Figure 3.7 - Gamification system score settings.

Reminders. The system checks at a specified time whether expected values have been entered. For example, in the morning the system checks whether breakfast has been entered. If not, the system asks the user to complete the entries. Default reminders can be extended by user-defined ones. This gives the user the ability to add their own reminder as they need or see fit. For example, the user can have defined reminders for glucose measurements so that the user does not forget to measure the high and low glucose profile, or can set additional reminders so that the user takes the necessary medication. The reminder function is enabled by default when the app is installed, but the user has the option to disable all reminders in case they want to save their mobile phone battery more or know that they will not be able to enter data for a certain period of time (for example, during a holiday). Then the notification will appear in the status/navigation bar. With this notification mechanism, it is assumed that the user looks at the phone and actually completes the information that was reminded by the notification.

Facebook Sharing. The use of social networking sites, namely Facebook, to share the results among the users of the application appeared to be an interesting way of motivation. The users could share their results in a managed Mobiab group to show off how they are doing in DM self-management or to communicate with other people with DM. The following objects to share were implemented: i) the achieved results (limits) within the day; ii) adherence to the drinking regime; iii) performed physical activities. However, this module was minimally used, probably due to the older age of the users who did not use social networks that much.

3.1.4 Design of Web-based Clinical Portal

A complementary feature to the mobile application should be web-based clinical portal for physicians and also for the mobile application users. However, the main presumed use-case is the viewing and checking of patient records by a physician. To determine what actions a user can perform, it is necessary to define user roles. The basic division is into logged-in and non-logged-in users to the web portal. Non-logged-in users have the ability to register, log in, or reset a forgotten password. Logged-in users are then divided into three role groups. Basic users have access to the functions of the portal that were defined in common functional requirements. Physicians can view their patients' reports and set new food intake limits. In addition, the physician can use the communication module for reading and sending messages with the patient. Administrators have the ability to delete users and change their roles.

The implementation of the communication module on the web portal is very similar to the mobile application, but with a few differences. As the web portal does not need to save as much screen space as the mobile phone, there is a listing of all messages at one page, along with a form to reply or send a new message. Another difference against the mobile phone and the physician role is the sending of the message itself. If a patient sends a message from a mobile phone or even from a web portal, it is simply stored in the database and can be viewed by the recipient immediately after sending. However, if a physician sends a message via the web portal, a copy of the message is also sent to the patient's email address that was provided in the sign-up process. This functionality was not implemented for physicians to ensure that their email inboxes were not overwhelmed with a series of messages from their patients.

The whole clinical portal is written with pure HTML and CSS and is fully valid (XHTML 1.0 Strict). When deciding on a database system, the choice fell on MySQL. The reason for choosing it is the excellent support in PHP, sufficient speed and wide distribution. To avoid problems with displaying Czech language diacritics, UTF-8 encoding was chosen. For a nicer and clearer appearance of the links, Page Controller is implemented to serve the web pages. The web portal also uses the Google Charts API to render charts using the gchartphp object wrapper and the PEAR Log component to record user actions.

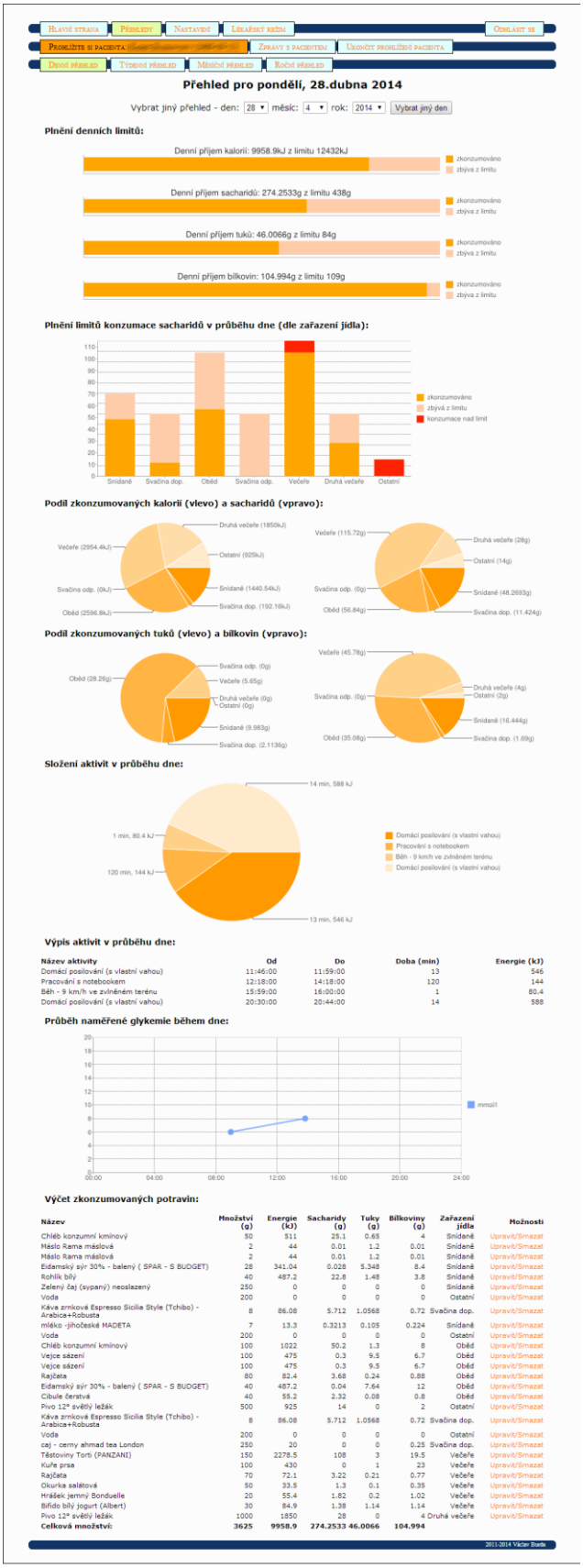

Figure 3.8 - Web-based portal preview.

The overall design should be minimalistic and as functional as possible. This corresponds to the layout, where the menu is at the top of the page and the corresponding content is always below it. Available functions are based on defined requirements: namely reports (daily, weekly, monthly, yearly), doctor-patient communication and profile settings. In addition, a physician mode is available for the physician to view their patients' report. A preview of the whole daily report on web-based portal is shown in Figure 3.8. This report displays in sequence from top to bottom: i) total daily limits met; ii) limits met by phase of the day; iii) the proportion of calories, carbohydrates, fat and protein in each phase of the day; iv) a summary of performed physical activities; v) a graph of measured glucose levels and applied insulin doses; vi) a list of all food entries.

3.2 Data and Methods

Data were collected through Mobiab over a period of 5 years (from January 2016) although Mobiab had been available on Google Play Store from the middle of 2014 only until 2019. No advertisement was used to recruit users, they found the mobile application in an organic reach. All users agreed to use anonymized data for purposes of research and data analysis during sign-up process, which is required for the app usage. Over this period, over 500 users from the Czech Republic used the app for different lengths of time. About 200 users did not report any DM, about 150 users reported type 1 DM and about 175 users reported type 2 DM. Approximately 80% of the users used the mobile app for less than one week. As there are many similar apps, they probably just tried several apps as they were looking for the app that they found most satisfactory. The remaining 20% of the users used Mobiab for a longer time with a decreasing usage trend as it was also noted in (Klasnja *et al.*, 2015). However, of the remaining users, only those who fulfilled at least one of the following conditions were selected for the analysis:

1. at least 3600 records of food intakes,
2. at least 360 records of glycaemia measurements,
3. at least 360 records of insulin doses,
4. at least 1080 records of physical activities,
5. at least 360 records of weight measurements,
6. at least 360 records of pressure measurements.

These conditions were estimated by the expected minimum number of records for each single day, then multiplied by the number of days in the year and slightly rounded. Meeting one of these conditions was considered to provide evidence of long-term usage. More details about users are shown in following tables. Table 3.1 presents the basic user data and the total number of active days. Table 3.2 shows the relationship between the users and the modules they used. For each module, the absolute number of entries and the average number of entries per day are presented.

Table 3.1 - Basic user data and active days.

	Sex	Birth year	Height	DM	Active days
ID 1141	Male	1962	173 cm	Type 2	1749
ID 1196	Male	1960	178 cm	Type 2	1261
ID 1224	Female	1976	162 cm	Type 1	1623
ID 1289	Female	1941	162 cm	No DM	1626
ID 1412	Female	1976	162 cm	Type 2	96
ID 1432	Male	1958	175 cm	Type 1	804
ID 1545	Male	1967	188 cm	Type 2	881
ID 1558	Male	1967	170 cm	Type 2	247

Table 3.2 - Number of records and daily averages.

	Food entries	Glycemic measures	Insulin Doses	Physical activities	Weight measures	Pressure measures
	Daily avg.	Daily avg.	Daily avg.	Daily avg.	Daily avg.	Daily avg.
ID 1141						
	34425	-	-	13515	1690	1478
	19.67	-	-	7.73	0.97	0.85
ID 1196						
	-	1164	-	-	-	-
	-	0.92	-	-	-	-
ID 1224						
	9470	1932	2166	4562	-	449
	5.83	1.19	1.33	2.81	-	0.33
ID 1289						
	15729	-	-	-	-	-
	9.67	-	-	-	-	-
ID 1412						
	-	466	-	-	-	-
	-	4.85	-	-	-	-
ID 1432						
	3757	799	1199	2982	-	-
	5.86	0.99	1.53	4.18	-	-
ID 1545						
	-	857	697	-	-	859
	-	0.97	0.79	-	-	0.98
ID 1558						
	-	538	-	-	-	-
	-	2.18	-	-	-	-

Eight users fulfilled the long-term analysis inclusion criteria. These consisted of 5 males and 3 females. Five of them stated that they had type 2 DM, two users had type 1 DM, and one user was without DM. The average age of all users was approximately 57 years. All 8 users were invited to provide medical records, but only one user (ID 1141) was willing to share them. The interest lay in the development of the following clinical parameters during use of the app: glycated hemoglobin (HbA1c), glycaemia, triglycerides (TAG) and cholesterol: total, Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL). The summary of records for the whole 7 years of the user who provided medical records are presented in Table 3.3. The frequency of the lab's clinical parameters is sufficient to withdraw the conclusion about the patient DM progress (Osborn *et al.*, 2017). In addition to his medical records, user ID 1141 provided personal health state remarks that are presented in the case study results.

Table 3.3 - Selected medical records of the user ID 1141.

	HbA1c (mmol/mol)	**Glycaemia (mmol/l)**	**Cholesterol (mmol/l)**	**LDL (mmol/l)**	**HDL (mmol/l)**	**TAG (mmol/l)**
22.01.2014	-	4.6	4.3	2.82	1.15	1.07
17.04.2016	-	18.17				
26.04.2016	90	7.9	4.17	2.62	1.4	0.85
21.07.2016	36	4.7				
14.11.2016	29	5	4.58	2.39	1.49	0.67
06.03.2017	32	4.8	3.81	1.98	1.66	0.53
17.07.2017	34	4.5	4.05			0.81
23.04.2018	35	5.3	3.73	2.08	1.48	0.51
17.09.2018	34	5	4.11	2.52	1.55	0.73
04.02.2019	-	4.9	3.96	2.54	1.18	0.93
17.06.2019	35	4.9	3.66	2.03	1.46	0.6
04.11.2019	35	5.1	4.26	2.57	1.39	0.99
19.03.2020	36	4.7	3.3	1.65	1.44	0.5
13.07.2020	35	5.1	3.78	2.09	1.44	0.65
13.11.2020	36	5.2	3.77	2.01	1.62	0.64
22.03.2021	35	5.4	3.71	1.98	1.53	0.78

The analysis of the data had to use two approaches, due to missing user medical records; the first approach is an analysis of usage of the application, including any beneficial trends for DM management. The second approach is to make a direct comparison between the medical records and the entered values and trends of the user ID 1141.

In addition, in order to verify the correctness of functioning of the application, it was necessary to test the application among users. The aim of the testing was to verify the functionality of the mobile application, its modules and the web portal, if they were used. A total of 11 participants, who responded to our request for completing an anonymous questionnaire via Google Forms, were included in this testing.

The questionnaire was constructed as a static closed-ended with 5-point rating scale. For each statement, the participant had to choose from: Strongly Agree (SA), Agree (A), Not Sure (NS), Disagree (D), Strongly Disagree (SD). The questions were not mandatory; for example, if the participant had not used the module, they would have skipped the assessment question, answered as Not Available (N/A). The questionnaire included the questions below:

1. The installation and sign-up was done as standard as installing other applications.
2. I was quickly familiar with the design and use of the mobile application.
3. The input of food intake was flawless and the reports are sufficient.
4. The input of physical activities was flawless and the reports are sufficient.
5. The input of glycemic measures was flawless and the reports are sufficient.
6. The input of insulin dosage was flawless and the reports are sufficient.
7. The mobile application worked error-free and as expected.
8. The web-based portal worked error-free and as expected.
9. The overall use was simple and intuitive.

Furthermore, to these close-ended questions, there was dedicated space for any comment about the usage of the system at the end of the questionnaire. The responses to the questions are recorded in Table 3.4, where the columns represent the individual questions and the rows introduce each participant's answers. The responses are then represented by abbreviations according to the scale defined above.

3.3 Results

3.3.1 Adherence Analysis

At first, the long-term food intake was analyzed. Users with ID 1141 and ID 1289 recorded their food intake regularly. They were taking their diet plan strictly and followed energy and sugar intake limits. User with ID 1141 still uses the mobile app, and their performance is described in detail in the following section. Two other users, ID 1224 and ID 1432, enter data irregularly every few days.

Nevertheless, user ID 1224 used the application for over 4 years, and user ID 1432 used it for two years. Interestingly, both of the users have type 1 DM, and they used the app much more regularly for entering glycemic values and insulin dosage than for food intake recording. The glycemic records (Figure 3.9) show a slight decrease in blood glucose levels after a few months of usage of Mobiab.

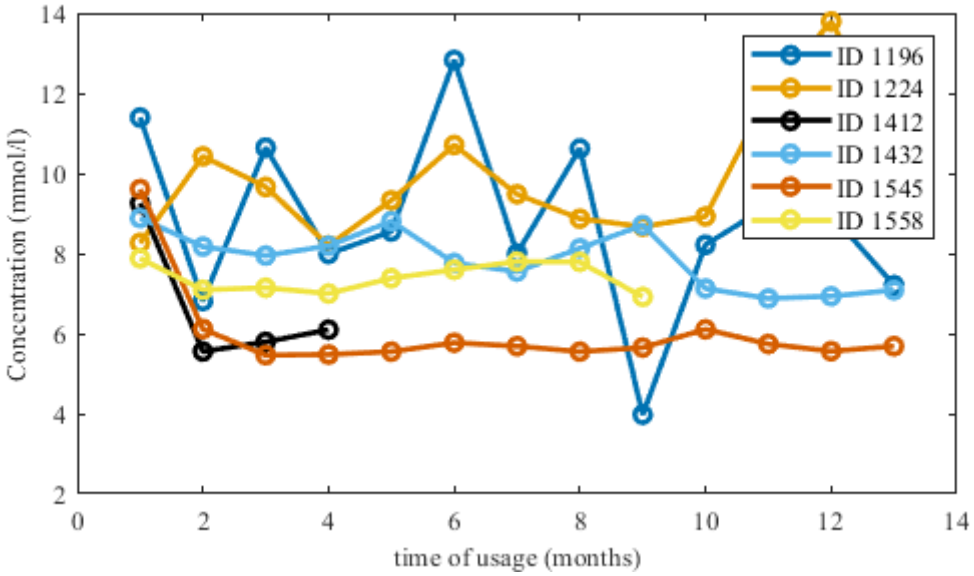

Figure 3.9 - Records of blood sugar in the first year of the app usage.

A more important fact for this study's purposes is that user ID 1224 and user ID 1289 carried out long-term recordings and were engaged for more than 2 years, and user ID 1432 and user ID 1545 were engaged for more than 4 years. Additionally, the other users, ID 1412 and ID 1558, were involved with Mobiab for a shorter time, 3 months and 8 months respectively, but during that time they regularly recorded several measurements per day.

3.3.2 Case Study of a Type 2 DM User

User ID 1141 (male, 60 years old, type 2 DM) was selected for the case study because he was willing to share his medical records and other information about his health and lifestyle. This person was diagnosed as type 2 DM randomly during an emergency examination on 17th April 2016. Before that, he had already been treated for high blood pressure and for hyperlipidemia. After the diagnosis of DM, he was treated with antidiabetic medication (Glucophage XR 500mg) and he was looking for some supporting mobile app. He started dieting and the records show that followed the diet constantly for the whole time that he was using the app. In total, he has entered over 34 000 food records.

Positive results came soon. With regular exercise (stationary exercise bike, walking) he reduced his weight from 127 kg to 84 kg and his waist circumference fell from 141 cm to 107 cm within one year. In the last three years, these values have increased moderately, as of March 2021, his weight was 101 kg, because he was not been able to exercise intensely due to joint pain and he stopped entering new waist circumference values (Figure 3.10). His blood pressure and cholesterol levels also improved and then stabilized (Figure 3.11). All these results are in accordance with his medical records (Figure 3.12).

Unfortunately, the person does not self-monitor blood glucose, and only periodical medical records of his glycemic levels are available (Figure 3.13). Based on the usage quality questionnaire and a semi-structured interview, he was very satisfied with the mobile app and appreciated how easy the app was to use. As of the date of writing this thesis, he is still using the Mobiab app, and he will hit 8 years in April 2022.

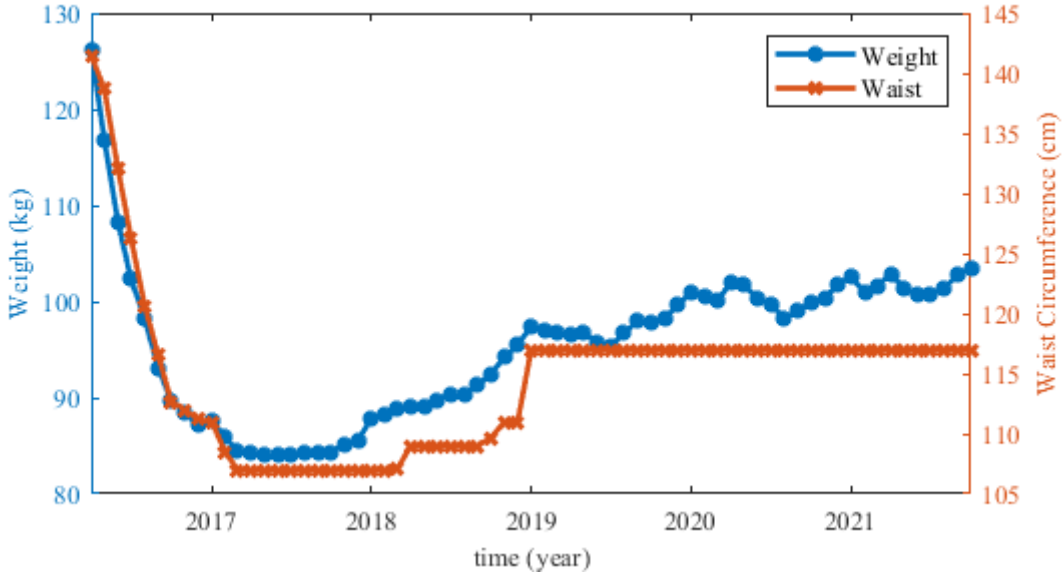

Figure 3.10 - Weight and waist circumference records for the entire period of usage.

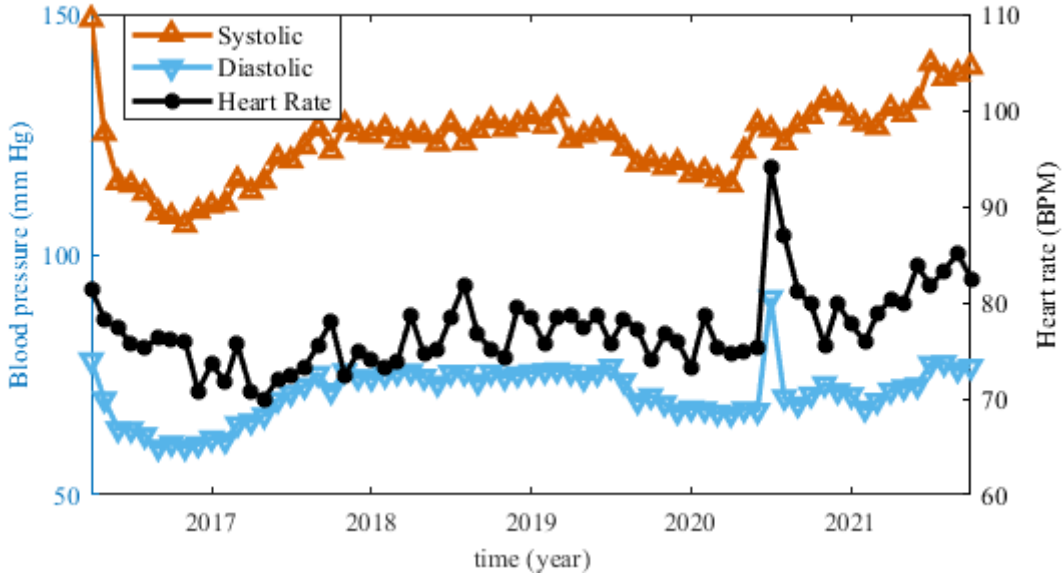

Figure 3.11 - Blood pressure records for the entire period of usage.

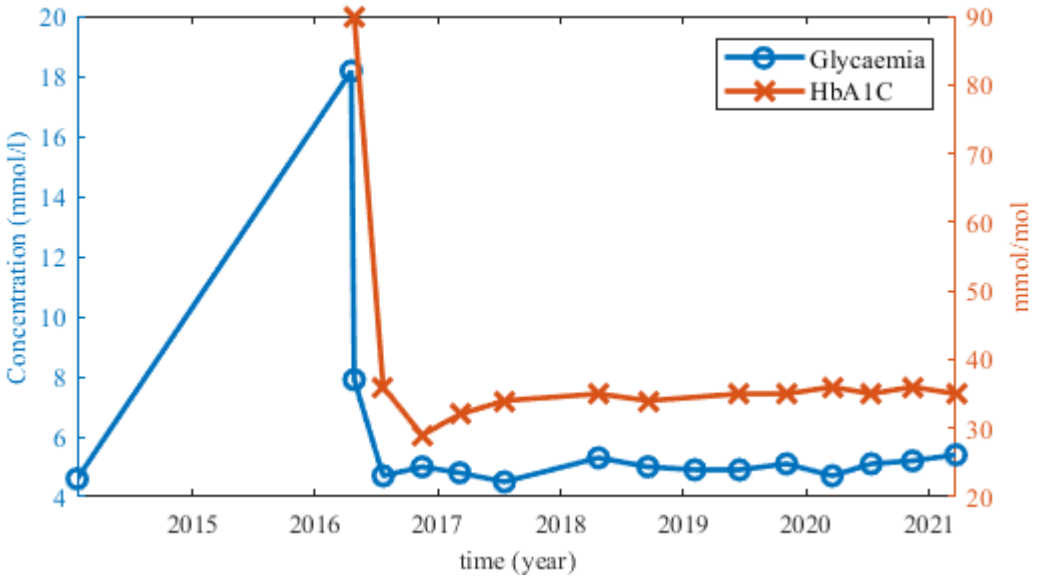

Figure 3.12 - Medical records for HbA1c and glycaemia.

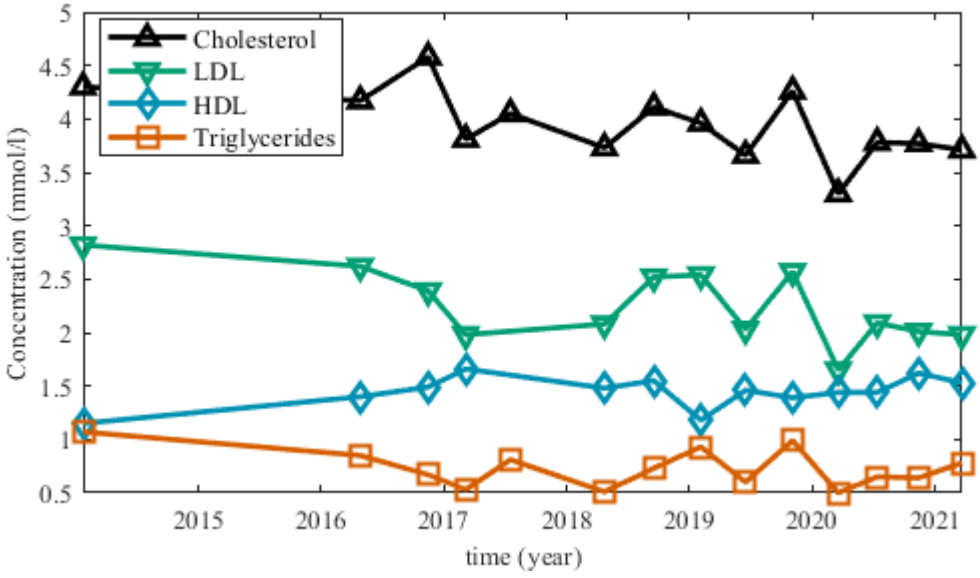

Figure 3.13 - Medical records for cholesterol and triglycerides.

3.3.3 Satisfaction with Usage of the Mobiab

A link to the survey was sent out continuously to active users after one month of their usage of the system. Through a questionnaire completed by 13 users, their feedback on their experience with using the Mobiab system was gained. Due to the guaranteed anonymity, responses cannot be linked to specific users. However, the response rate from the users was quite disappointing, as the request to fill the questionnaire was sent out to a total of 68 users. The responses to the questions are recorded in Table 3.4 and expressed percentages of responses to each question are shown in Figure 3.14.

The results show that users were very satisfied with the ease of installation, which was available in the standard way on Google Play (Q1), and that they became familiar with the design of the app very quickly (Q2). There was also mostly satisfaction with the module for entering glucose measurements (Q5) and also with the module for entering insulin dosage (Q6), although only about a third of respondents used this module. There was also agreement with the overall ease of use (Q9) and the flawless functionality of the mobile app (Q7), but this agreement was not as strong, approximately half of the respondents only expressed agreement. In addition, there was one disagreement, which was expressed by one identical respondent (P-06). The same respondent also did not express agreement with the other questions Q3 and Q4. Approximately three quarters of the respondents who used the module of food intake (Q3) were very satisfied, except for the case mentioned above.

The module for entering physical activities (Q4) appears to be the most problematic. Although it should be useful and interesting for both of the main DM types, it was used by only about two thirds of the respondents and in addition one third of them were not satisfied with it. It is a question about what the problem was; it may be the complexity of the input, where the activity has to be manually selected from quite a large number of options first and then the duration of the activity has to be entered. The fewest respondents, only less than a third, answered the question about the web portal (Q8), they agreed with its functionality but it was not strong agreement.

To summarize the results of the testing, the results were quite positive. More discordant evaluation was given to the module for entering physical activities. The evaluation of the insulin dosage and the usage of the web-based portal, which was rated by only one third of the respondents, should be treated with caution.

Table 3.4 - Responses to usability questionnaire.

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
P-01	SA	A	SA	A	SA	N/A	SA	N/A	SA
P-02	SA	SA	SA	N/A	SA	N/A	SA	N/A	SA
P-03	SA	SA	A	D	SA	N/A	A	A	A
P-04	SA	SA	SA	NS	N/A	N/A	A	N/A	SA
P-05	SA	SA	N/A	N/A	SA	SA	SA	N/A	SA
P-06	SA	A	NS	D	N/A	N/A	D	N/A	D
P-07	A	SA	SA	N/A	SA	SA	SA	N/A	SA
P-08	SA	SA	SA	SA	A	N/A	SA	A	A
P-09	SA	SA	SA	SA	A	A	A	SA	A
P-10	SA	SA	N/A	N/A	SA	A	A	N/A	A
P-11	SA	SA	SA	A	A	N/A	A	A	A
P-12	SA	A	SA	A	SA	N/A	SA	N/A	SA
P-13	SA	SA	N/A	N/A	A	SA	SA	N/A	A

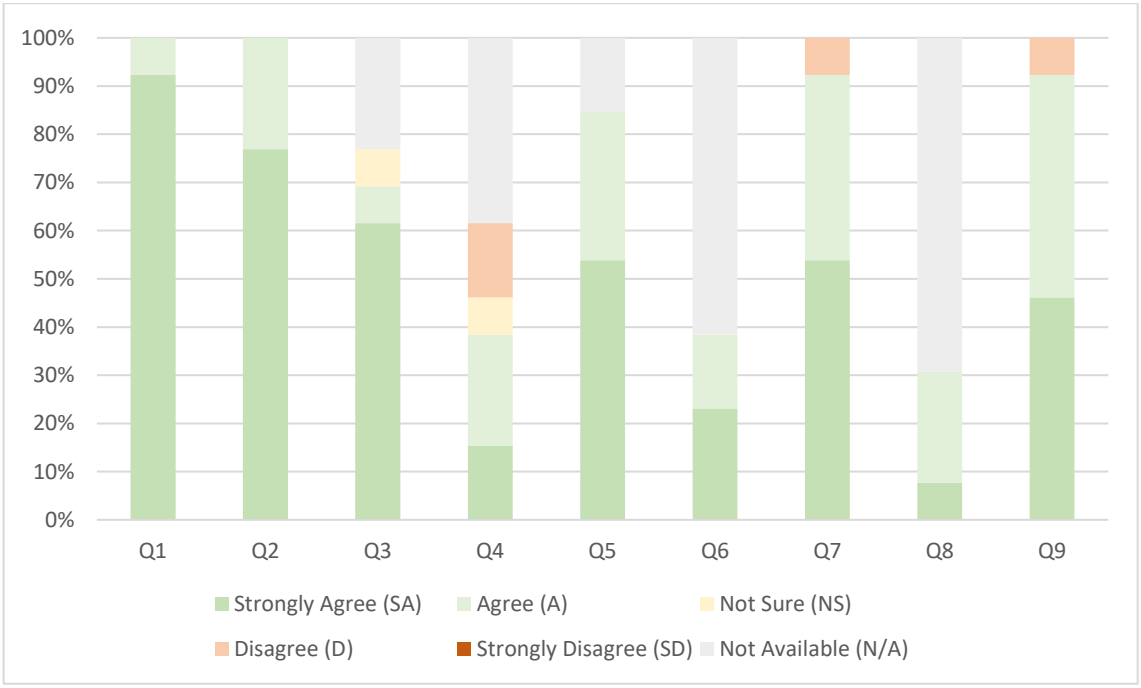

Figure 3.14 - Results of responses to usability questionnaire.

3.4 Discussion

3.4.1 Principal Results

The main goal of the Mobiab system is exploring benefits of long-term usage of such as technology for DM self-management. The system simplifies manual entering and documenting of measured values associated with treatment monitoring and self-management of DM, and provides a user-friendly summary for the patient of their self-management efforts. The Mobiab system contributes to the patient's education and a better understanding of the disease by providing continuous recordings of all important data, including food intake, caloric expenditure, blood glucose levels, insulin dosage, body weight and blood pressure. In addition, it might be argued that the Mobiab system contributes to long term outcomes of DM management as demonstrated in several use cases. Several studies have suggested the usefulness of electronic self-management systems in managing DM. For example, smartphone apps have been shown to improve glycemic control, specifically in younger patients (Hou *et al.*, 2016). Another randomized controlled trial showed that DM intervention using smartphones has led to improved clinical outcomes (Quinn *et al.*, 2011). The US FDA has now approved several (BlueStar) mobile apps for DM management (Quinn *et al.*, 2011). And the new German DiGA scheme has also been approved (Dahlhausen *et al.*, 2021). These data confirm an increasing trend to introduce digital therapeutics intervention into daily clinical practice (Ramakrishnan *et al.*, 2021). A further benefit of smartphone apps is that anonymized data can be collected from a larger population.

The collection of medical data using Mobiab was beneficial to users with both diabetes types. Previously, it was necessary for patients to record medical values manually in a diabetes diary. Using Mobiab, user ID 1141 has already been able to record his food consumption, exercises, weight changes and blood pressure continuously for 1749 days. In addition, the user achieved positive changes in blood glucose levels (Figure 3.12) and weight control (Figure 3.10) within a very short time. Although we cannot quantify the exact contribution of the Mobiab app to these improvements, the benefits for patient ID 1141 have been considerable. A positive impact of the assistance of the mobile app on diet and blood glucose levels were also confirmed in a study focusing on mySugr app benefits (Debong, Mayer and Kober, 2019).

Some systems applied training participants ranging from using telephone (Holmen *et al.*, 2014) to face-face support (Waki *et al.*, 2014). The design of the app followed the user centered design and the final design was also commented by the expert group. At the end no personal training was offered to participants, since it was assumed that the app was easy and intuitive to use. However, the onboarding procedure explaining the main app functionalities started after installing and launching the app.

Only a few technology issues were reported. The main comments steamed from the use of the app without internet connection, mainly at the beginning of the app launch. While there was considerable effort to ensure the whole app functionality without the internet connection by caching all parameters as in the case of earlier systems (Chomutare *et al.*, 2011), after several updates it was decided to remove this feature. This is in line with most of the current solutions based on cloud architecture which requires stable connection to guarantee the smooth operation (Shen *et al.*, 2018). Furthermore, no similar studies analyzed the number of calls that participants or clinicians made for technological support (Whitehead and Seaton, 2016).

The Mobiab dataset is highly variable in terms of the usage of the modules. Not every user used the same set of modules that are shown in Table 1. This is a limiting factor for a complex analysis of the health impacts. However, this variability of usage of the modules should not be classified as an app issue, because it only indicates the well-known highly heterogeneous needs of patients with diabetes (Böhm *et al.*, 2020). The hypothesis that engaged participants used more modules reflecting their higher discipline was not confirmed in our study. Nevertheless, the Mobiab developers will continue to make modules more attractive to users, and convince patients that it would also be beneficial to use a wider range of modules, e.g. to provide overviews of complex data and explain the impacts on the patient's health. We believe that a broad selection of modules is advantageous for patients, thus contributing to personalized DM self-management care which might increase the participants' engagement and long-term outcomes (Grant and Wexler, 2012; Subramanian and Hirsch, 2014; Chen *et al.*, 2018). Furthermore, several studies discussed the usefulness of using Chronic Care Model to improve clinical and behavioral outcomes applying eHealth technology. Consequently, we have identified several improvements that might reduce the burden of the disease and increase engagement by expanding the modular architecture (Castelnuovo *et al.*, 2015; Gee *et al.*, 2015; Tran *et al.*, 2015). Combination of general and tailored educational content might help to cope with medical jargon and misleading

information from different sources. In addition, tracking mood on daily or weekly basis might be important to provide insight for better glycemic control and to prevent depression and diabetes distress (Penckofer *et al.*, 2012; Owens-Gary *et al.*, 2018).

However, there is a concern about placing too much confidence in managing DM using mHealth apps (Faridi *et al.*, 2008; Holmen *et al.*, 2014; Waki *et al.*, 2014). These pilot studies have pointed out that some patients with type 2 DM do not believe in the benefits of these apps resulting in a low level of usage (Waki *et al.*, 2014; Katz, Dalton and Price, 2015; Trawley *et al.*, 2017; Baptista *et al.*, 2019). When discussing self-management of diabetes with the use of a mobile app, several research papers have emphasized the need for education, peer support, interactive content, blood glucose monitoring, dietary tracking, and realistic goal setting (Modave *et al.*, 2016; Peng, Yuan and Holtz, 2016; Boyle *et al.*, 2017; Osborn *et al.*, 2017; Pal *et al.*, 2018). Another important concept for increasing the efficacy of interventions is the establishment of a two-way communication between the patient and care team (Greenwood *et al.*, 2017). We supported this type of communication by developing a stand-alone web-based clinical portal for physicians.

However, the long-term usage of apps developed for managing DM using self-management tools remains low (Trawley *et al.*, 2017). Our own experience suggests that our app can achieve good outcomes, but it is not a straightforward enough to motivate diabetes patients to self-manage their condition consistently in the long term. Long-term engagement with mHealth systems does not necessarily require daily interaction; routine DM management could lead to reduction of using the technology (Klasnja *et al.*, 2015).

Most of the studies referenced to in this paper were single-center pilots validating short-term results of the examined mobile apps. Undoubtedly, more clinical trials with longer follow-up periods are needed to evaluate the long-term effect of diabetes-related mobile apps on glucose management and quality of life, and sustainability of the self-management using the mHealth ecosystem (Doupis *et al.*, 2020). A clinical study for validating the impact of the Mobiab system on patient self-management behavior and for exploring the usability of the system is currently in development.

3.4.2 Limitations

A strong point of this study is the involvement of four patients diagnosed with type 2 DM, two patients with type 1 DM and two patients without DM, each of whom was able to use the system for a long time and to enter a significant amount of data. However, the small number of participants is a limitation of this study. A very small set of users is insufficient to thoroughly test and validate the self-management compliance of the Mobiab system. In addition, even this small number of participants did not use all the modules that the system provides.

Another limitation is the integration of one glucometer only. We implemented seamless glucose data transfer using a specific glucose meter (FORA Diamond Mini Bluetooth) and blood pressure monitor (FORA Active P30 Plus). Technical documentation and cooperation with manufacturers would be needed to connect other devices.

A further limitation is the web-based portal for physicians. Five clinicians in our expert advisory group told us that clinicians already use some commercial software (e.g. Medtronic CareLink), and that the use of different software is an unnecessary complication. The solution would be to have a communication interface to connect the mobile app to an already established systems. Data integration with existing hospital information systems was not implemented as a part of this work, because there was no specification of the communication interface. However, this integration activity remains open for future work, when new versions of the hospital system are incorporated with API functionality.

3.5 Conclusion

The results of this study have shown that the usability of a smartphone mobile app, and server-based systems are potentially satisfactory and promising. The collection of long-term data on diabetes and overall metabolic management can be supported by a modular app such as Mobiab. Our system, based on the needs and requirements of its intended users, has attempted to maximize the potential to enhance self-management and increase user adherence. In this study, eight users evaluated the app functionality in long-term monitoring. A case study has presented and analyzed the particularly successful involvement with the system. However, we cannot yet claim that the Mobiab app has successfully motivated large numbers of people with diabetes to self-manage their condition. An assessment of the

effectiveness of the app in improving self-management over time requires further studies involving a larger number of patients. Some redesign of the mobile app will probably be required due to continuous changes in the development of mobile apps. However, the principles of the modules and functions work well, and will likely be preserved.

4 Continuous Glucose Monitoring and Glycemic Variability

This chapter is based on data, methods and results from several studies in which I have participated by processing continuous glucose monitoring data. (Mraz *et al.*, 2014; Kavalkova *et al.*, 2015; Kaválková *et al.*, 2016). I was focused mainly on the way of data preparation and processing, for which purposes the Matlab framework as described in Data and methods section was created. This is followed by summarization of the results, discussion and conclusions from these articles.

4.1 Introduction

Continuous Glucose Monitoring (CGM) is used for determining levels of glucose over continuous time. The device for monitoring consists of three parts: a disposable glucose sensor, which is worn for a few days, a link from sensor to receiver and an electronic receiver, which displays and records glucose levels. It is necessary to calibrate the device with a traditional blood glucose measurement (finger-stick glucose test) (Cunningham, 2006). Due to measuring blood glucose levels in interstitial fluid, there is a lag in blood glucose values. This lag time is usually about 5 minutes, sometimes up to 10–15 minutes. This can be a problem if the blood glucose level changes rapidly: CGM shows normal range of blood glucose level; however, the patient can fall in hypo/hyper-glycaemia and need a treatment (Wentholt *et al.*, 2005; Cunningham, 2006).

In 2000, when CGM became available, measurement error was more than ±20%, today the error has been reduced to ±10% and accuracy continues to improve (Rodbard, 2016). Changes of blood glucose levels reacting to food, activities, insulin or other factors can be evaluated via CGM. It can help identifying problems in insulin dosing during the time when patient does not take a glucose test – typically during the night. The monitoring device can be equipped with alarms to alert about hypo/hyper-glycaemia. In studies, it was demonstrated that patient's experience with CGM has a positive effect on DM treatment (Deiss *et al.*, 2006; Garg and Jovanovic, 2006; Garg *et al.*, 2006). The effectiveness of CGM

is generally associated with an improvement in the HbA1c level and the benefits are also associated with insulin pumps. Based on CGM data, insulin infusion can be automatically suspended, in response to either observed or predicted hypoglycemic episodes (Vaddiraju *et al.*, 2010; Rodbard, 2016).

Coronary Artery Disease (CAD) is known also as Ischemic Heart Disease (IHD). The risk factors of this disease among other include diabetes and obesity. Patients with type 2 DM have a higher prevalence of CAD. Therefore, a glycemic variability may play an important role in the development of diabetic vascular complications. The factors contributing to the risk of cardiovascular disease include hyperglycemia, oscillations of blood glucose levels and hypertension. That is why effects of glycemic excursions on vascular complications should not be neglected (Tousoulis *et al.*, 2009; Su *et al.*, 2011).

Glucose Variability or Glycemic Variability (GV) is usually defined by the measurement of fluctuations of glucose or other related parameters of glucose homoeostasis over a given interval of time, where the time can be within a day or up to several days (Zhou *et al.*, 2020). GV is still being explored as a potential predictor of DM complications. Although patients may have a similar mean glucose or glycated hemoglobin HbA1c, their daily profile can be with differences and with glucose excursions. So the glucose variability might contribute to improve DM treatment and may have a role in the prediction of hypoglycemia or hyperglycemia (Siegelaar *et al.*, 2010).

As was written in Introduction chapter of this thesis, there are also more aggressive approaches for DM treatment when a significant weight reduction is required, or more serious health consequences are involved. Except for the mentioned gastric bypass, which is an effective and durable approach to target both obesity and type 2 DM but a very invasive procedure with operative risks and possible sequelae, there exists the intermediate possible solution in the implantation of Duodenal-jejunal Bypass Liner (DJBL), also called EndoBarrier (Patel *et al.*, 2013). The DJBL is an endoscopically and reversible implantable device used to noninvasively mimic the effects of gastric by-pass by preventing the contact of chymus with duodenum and proximal jejunum and delivering it in a less digested form to more distal parts of the intestine (Ruban, Ashrafian and Teare, 2018). To simplify it, it is a 60 cm long impermeable fluoropolymer sleeve that can be implanted inside duodenum up to 12 months. Obesity is a central physio-pathological mechanism in type 2 DM, and thus

DJBL has been used to improve metabolic control (Patel *et al.*, 2013; Ramada Faria, Nunes Santos and Simonson, 2017).

4.2 Data and Methods

The data for processing were provided by Third Department of Medicine, Department of Endocrinology and Metabolism, Charles University in Prague. These data were collected between years 2013 and 2015. The patients' basic characteristics about the data are shown in Table 4.1 and are divided into 5 columns: at baseline (Visit 1), during DJBL implantation (Visit 2-4; 1, 3 and 10 months with DJBL) and 3 months after DJBL removal (Visit 5). All participants provided written informed consent before beginning the study. DJBL implantation was implanted in all 30 patients successfully, the mean time for implantation procedure was 18 minutes. No serious adverse events occurred during the study. Mild abdominal pain and nausea after implantation were experienced by 72% of patients during first 14 days after implantation, 33% of patients during the first month and 10% of patients after 1 month. Four patients had to be hospitalized after implantation for 2 days due to nausea or vomiting or for blood sugar monitoring. All of them were discharged without any subsequent problems. The rest of the patients were discharged the following day after the procedure (Kaválková *et al.*, 2016).

Table 4.1 - The baseline characteristics of study subjects.

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Number of subjects	30	30	30	30	28
Body weight (kg)	129.7±4.4	123.9±4.2	118.7±4.2	117.3±4.3	120.3±4.5
Waist circumference (cm)	133.6±2.7	129.4±2.4	125.6±2.6	124.0±2.7	124.3±2.2
BMI (kg/m2)	42.7±1.2	41.0±1.2	39.0±1.2	38.4±1.1	39.0±0.9
Fasting glucose (mmol/L)	12.3±0.7	10.1±0.6	9.54±0.6	8.45±0.5	9.88±0.8
HbA1c (mmol/mol)	75.0±3.4	66.5±2.8	58.4±2.8	55.4±2.5	61.1±3.3

The CGM data then contain 91 measuring periods from 30 participants with type 2 DM, obesity, or body mass index over 30 kg/m2, and their glycated hemoglobin HbA1c was 53 mmol/mol. The body weight and antidiabetic treatment were stable for at least 3 months before the beginning of the study. During the study they were treated only with diet, oral antidiabetics, insulin or some combination of previous. The distribution of participants by sex is: 20 men (58 measuring periods) and 10 women (33 measuring periods) and their age

was between 33 and 65 years. They were examined on five visits: before DJBL implantation (Visit 1), and 1 month (Visit 2), 5 months (Visit 3) and 10 months (Visit 4) after DJBL implantation. Except for two participants, they were examined also 3 months after DJBL removal (Visit 5). Each patient was usually recorded in three or four measuring periods. Each continuous glucose measuring was performed for 7 days and the values were recorded in 5-minute interval. The average number of glycaemia values in measuring period is 1589 (Kaválková *et al.*, 2016).

The provided data were in CSV format exported from Medtronic Diabetes iPro 2 device. In the data file, the first 12 lines are used for the description of measurement. These lines contain related information about the patient, used type of sensor, number of records, time range of measurement and some other descriptions lines. Data recorded from sensor start at 13th line. These data are structured into 17 columns, where the date (2nd column), time (3rd column) and glycaemia value in mmol/l (10th column) are the most interesting and useful. Other columns contain unused raw data from sensor, type of record action, counter or patients' logs (activity, medicament), which are in most cases empty because patients do not use these functions on CGM device.

For the future data processing in Matlab framework it was needed to extract date, time and glycaemia value to accepted format with some restrictions:

- each record is in a new line in this order: date, time, glycaemia value,
- delimiter used between values is |,
- date format: `DD-MM-YY`; day/month can contain only one number,
- time format: `HH:MM:SS`; hour can contain only one number,
- glycaemia value: `XX.X`; one decimal number, dot as decimal point.

Examples of accepted records:

- `24-7-14|10:44:35|9.3`
- `27-10-13|17:53:31|7.4`
- `21-7-14|7:36:16|` (no glycaemia value = record is ignored)

The conversion from data in CSV file format to format accepted by the Matlab framework was done manually with prepared conversion scripts. The reason for this approach was to check each step and ensure that all data had been converted correctly.

4.2.1 Glycemic Variability Implemented Methods

As the data from CGM are generated in such large quantities; thus, a systematic approach to review and interpret these data is needed. Traditionally the HbA1c was considered as the gold standard for evaluation of glycemic control, but GV seems to be a more meaningful measure (Zhou *et al.*, 2020).

There are many of measures of glycemic variability for these purposes; however, there is no universally accepted standard for classifying GV. The easiest way to get an insight into a patient's glucose is Standard Deviation (SD) and Coefficient of Variation (CV). Other frequently used methods include Mean Amplitude of Glycemic Excursion (MAGE), Continuous Overlapping Net Glycemic Action (CONGA) and Average Daily Risk Range (ADRR) (Rodbard, 2009; Weber and Schnell, 2009; Cameron, Donath and Baghurst, 2010; Siegelaar *et al.*, 2010).

For collective evaluation and computing various metric of glycaemic variations, the Matlab framework was developed and implements all of the above metrics. For each metric exists a corresponding method, that can be used separately or together; for one patient or for more patients at once. Batch processing of multiple patients is done by *MultipleLoad* function and the output is a Matlab matrix with evaluated data. The descriptions and formulae of these functions for interpreting the measuring of glycemic variability follow.

Standard Deviation and Coefficient of Variation

As it was mentioned, calculation of Standard Deviation (SD) and Coefficient of Variation (CV) is the easiest way and seems preferable. SD is a statistic that measures the variability or dispersion in a set of values relative to its mean: the lower it is, the closer the values are to the mean. The standard deviation is calculated as the square root of variance by determining each data point's deviation relative to the mean (1). Calculating standard deviation is the easiest way to get a meaning of the glucose variability in an individual patient (Siegelaar *et al.*, 2010).

$$SD = \sqrt{\frac{\sum(x_i - \bar{x})^2}{k - 1}} \qquad (1)$$

x_i = individual observation
$\bar{x}$ = mean of observation
k = number of observation

Additionally, CV can be calculated to correct the mean (2). The coefficient of variation represents the ratio of the standard deviation to the mean, and this is useful especially when two or more sets of data with different measures or values are to be compared. Calculating SD and CV from CGM data seems preferable for the analysis of glycemic variability (Siegelaar *et al.*, 2010).

$$CV = \frac{s}{\bar{x}} \qquad (2)$$

s = standard deviation

$\bar{x}$ = mean of observation

Mean Amplitude of Glycemic Excursion

The Mean Amplitude of Glycemic Excursion (MAGE) algorithm (3) was first proposed and described in the original article by Service et al. in 1970 and is widely used nowadays. It was designed for calculating average size of fluctuations between adjacent peaks and nadirs in one day. MAGE plays a significant role in vascular endothelial dysfunction and cardiovascular events in patients with DM (Akasaka *et al.*, 2017). It was considered to be "a gold standard"; however, there are several significant limitations. The arbitrary definition of peaks and nadirs with 1 standard deviation for 24-hour period is the most limiting. Thus, this has implication when attempting to use it in the CGM analysis (Weber and Schnell, 2009; Cameron, Donath and Baghurst, 2010; Siegelaar *et al.*, 2010).

$$MAGE = \sum \frac{\lambda}{x} \qquad if\ \lambda > v \qquad (3)$$

λ = each blood glucose increased or decreased (nadir to peak or peak to nadir)

n = number of observations

v = 1SD of mean glucose for 24-hour period

The manual procedure to estimate the MAGE value is time consuming and error prone; therefore, an automated method to calculate MAGE from CGM data is particularly needed. In addition, as CGM becomes more attractive and more accessible, the availability of an automated MAGE algorithm provides a research tool for examining the properties of GV and it should facilitate a determination an advantage to indices of GV in terms of its ability to predict adverse outcomes (Baghurst, 2011).

Continuous Overlapping Net Glycemic Action

The Continuous Overlapping Net Glycemic Action (CONGA), published in 2004 by McDonnell et al., seems to be a promising measure of GV which was specifically designed for CGM analysis. The value for CONGA*n* varies systematically with the value of *n*, where *n* is a size of "window" (duration of the time segment) used to compute the GV (Rodbard, 2009). The calculation (4) is described as the difference between the current observation and the *n* hours previous the observation. This is done for each observation after the first *n* hours of observations. This method has benefits of being highly reproducible and in ability to be adjusted for varying time intervals in dependence on the needs of specific issue being addressed and it does not require to identify peaks or nadirs (Weber and Schnell, 2009; Cameron, Donath and Baghurst, 2010; Siegelaar *et al.*, 2010).

$$CONGA_n = \sqrt{\frac{\sum_{t=t_1}^{t_{k^*}} (D_t - \overline{D})^2}{k^* - 1}}$$

k^* = number of observations where there is an observation $n \times 60$ minutes ago

$m = n \times 60$

where $D_t = GV_t - GV_{t-m}$

GV_t = difference between glucose value reading at time t and t minus n hours ago

and $\overline{D} = \frac{\sum_{t=t_1}^{t_k} D_t}{k^*}$

(4)

Low/High Blood Glucose Index

Low and High Blood Glucose Index (LBGI, respectively HBGI) is a measure for representing frequency and extent of low and high blood glucose values. CGM data or data from self-monitoring of blood glucose can be used for computation. Since the basic assumption is that the BG data are represented on a skewed scale, they will be first log-transformed and then the risk index of each value can be calculated (Weber and Schnell, 2009).

$$f(BG) = 1.509 \times [(\ln(BG))^{1.084} - 5.381] \quad \text{if } BG \text{ in mg/DL}$$
$$f(BG) = 1.509 \times [(\ln(18 \times BG))^{1.084} - 5.381] \quad \text{if } BG \text{ in mmol/L}$$

$$rl(BG) = r(BG) \quad if \ f(BG) < 0 \ else \ 0$$
$$rh(BG) = r(BG) \quad if \ f(BG) < 0 \ else \ 0$$

where $r(BG) = 10 \times f(BG)^2$

(5)

Finally, the LBGI and HBGI can be computed as the average of these transformed values:

$$LBGI = \frac{1}{n}\sum_{i=1}^{n} rl(BG_i) \qquad HBGI = \frac{1}{n}\sum_{i=1}^{n} rh(BG_i) \qquad (6)$$

The procedure of data transformation (5) for calculation of LGBI and HGBI is also used as a part of the following Average Daily Risk Range measure.

Average Daily Risk Range

The Average Daily Risk Range (ADRR) algorithm (7) was created by Kovatchev et al. in 2006 in order to describe the notion of glycemic variation more specifically. The ADRR is a valid measure of GV of which score corresponds to a patient's risk for variability: < 20, low risk; 20 – 40, moderate risk, > 40, high risk. A logarithmic transformation of the glucose scale was proposed to be symmetric about 0 and it defines 6.25 mmol/L as the clinical and numerical mean. An important fact for calculating the ADRR value is that it is not necessary to have values from CGM or measurements for each day. It is sufficient to have 14 days with at least 3 values per day during 1 month. The optimal time for risk range evaluation is 1 month with a frequency of 3-5 measurements per day. (Kovatchev *et al.*, 2006; Weber and Schnell, 2009; Patton and Clements, 2013).

$$ADRR = \frac{1}{M}\sum_{i=1}^{M}\left[LR^i + HR^i\right] \qquad (7)$$

where $LR^i = max[rl({x_1}^i), \dots, rl({x_n}^i)]$

and $HR^i = max[rh({x_1}^i), \dots, rh({x_n}^i)]$

for day *i*; *i=1,2,…,M*

The ADRR was developed to quantify the risk of hyperglycemia and hypoglycemia based on the presence of extremely high and low blood glucose levels and it was designed to be equally sensitive to both values: hyperglycemia above 22.2 mmol/l and hypoglycemia below 2.2 mmol/l. This equality distinguishes this algorithm from other known measures of variability, which are more affected by episodes of hyperglycemia than hypoglycemia, due to the inherent asymmetry of both the blood glucose scale and the distribution of blood glucose values observed in people with diabetes. (Weber and Schnell, 2009; Cameron, Donath and Baghurst, 2010; Patton and Clements, 2013).

In addition, the ADRR can address some advantages over CONGA: i) the ADRR has an increased sensitivity to hypoglycemia than other GV measures; ii) the ADDR can be calculated also from self-monitoring of blood glucose (SMBG); iii) there are glucometers available on the market that can automatically calculate the ADRR (Kovatchev *et al.*, 2006). However, there are also disadvantages, for example there may occur a problem with Medtronic CGM devices, which suspend these extreme values and do not record them as a glucose value.

4.2.2 Other Methods for Glycemic Variability

Besides the methods previously described and implemented in the Matlab framework, there is a number of other measures for evaluating the glycemic variability and quality of glycemic management. Their summary, comparison and review were published by David Rodbard in article "Interpretation of Continuous Glucose Monitoring Data: Glycemic Variability and Quality of Glycemic Control" and by Cameron et al. in article "Measuring Glycaemic Variation" (Rodbard, 2009; Cameron, Donath and Baghurst, 2010). Since we have not used these methods in any study and they have not been implemented in the Matlab framework, there is only a brief summary.

Mean of Daily Differences

The Mean of Daily Differences (MODD) is an index of intraday GV. Its calculation is defined as difference between measured glucose values that were obtained at the same time on two following days and under standardized conditions of meals, mealtimes, exercise, and therapy. Furthermore, this measure has modification MODD*d*, where *d* stands for number of days between compared observations, i.e. value and value exactly $d \times 24$ hours later. In comparison MODD*1* is almost perfectly correlated with CONGA*24*. (Rodbard, 2009).

Glycemic Risk Assessment Diabetes Equation

The Glycemic Risk Assessment Diabetes Equation (GRADE) is a function to calculate the risk values for individual glucose concentrations within a glucose profile. It can be easily generated from any blood glucose profile and can be used as a complement to HbA1c to reflect the level of risk associated with GV. The GRADE score is then classified by the percent contribution into three classes: < 70 mg/dL (< 4 mmol/l), hypoglycemia; 70 – 140 mg/dL (4 - 7.8 mmol/l), euglycemia; > 140 mg/dL (> 7.8 mmol/l), hyperglycemia (Hill *et al.*, 2007; Service, 2013).

Index of Glycemic Control

The Index of Glycemic Control (IGC) is the summation of the hypoglycemia and hyperglycemia index, the weighted averages of their respective regions of glycemic status and more weight are given to severe hypo/hyperglycemic values. The IGC shows how far a CGM has diverged from the target glucose levels. Moreover, it has the possible advantage of adjustable parameters and thus it can be set to be more sensitive to the range of severe hypoglycemia than other GV measures (Rodbard, 2009).

Lability Index / HYPO Index

The Lability Index is calculated within a strict 4-week time window and requires at least 2 SMBG values, where each one is within 1-12 hours of each other. The HYPO score is used with the lability index as a non-mathematical approach to quantify the extent of a patient's hypoglycemia. Unfortunately, this measure is not suitable for CGM because of the required fixed time interval and the inability of the index to handle more frequent readings than 1 hour (Cameron, Donath and Baghurst, 2010).

4.3 Results

The framework for Matlab is a very useful tool that enables computation of a large number of measures of glycemic variability as a basis for evaluating studies. It supports several commonly used metrics for interpretation of CGM data. This framework was used for processing CGM data and the results were used in several studies (Mraz *et al.*, 2014; Kavalkova *et al.*, 2015; Kaválková *et al.*, 2016).

The aim of the study "Continuous exenatide infusion improved perioperative glucose control and reduced glycemic variability in cardiac surgery patients: the executive trial" (Mraz *et al.*, 2014) was to find effects of reduction of operation-related hyperglycemia with exenatide infusion. After evaluating CGM data the improvement of perioperative glucose control was showed in comparison to placebo group subjects (average glycaemia 6.1 ± 2.5 vs 6.8 ± 2.8 mmol/l, $p<0.001$; time in range 4.5-6.5 mmol/l was 55.0 ± 3.4 vs 38.6 ± 3.3 %; time above target range 39.7 ± 3.3 vs. 53.5 ± 3.6%, $p<0.01$). Moreover, there was no increased risk of hypoglycemia. Exenatide infusion also reduced glycemic variability (SD 1.4 ± 0.5 vs 2.0 ± 0.6, $p<0.01$; MAGE 2.5 ± 1.1 vs. 3.3 ± 0.9, $p<0.01$) and decreased the need of temporary pacing (16.7 vs 47.4 % of subjects, $p<0.05$). There were no significant

differences in perioperative hemodynamics, but there were differences in postoperative echocardiographic parameters and inotropic medication dosage between groups (Mraz *et al.*, 2014).

From computed CGM data the standard deviation was selected as the primary measure of glycemic variability for the study "Endocrine effects of duodenal-jejunal exclusion in obese patients with type 2 diabetes mellitus". The statistical significance was assigned to $P<0.05$. In the context of DM, the interesting findings from this study are the effect of DJBL on glucose variability and blood pressure which are represented in Table 4.2. The study concludes that DJBL implantation markedly improved blood glucose control, decreased glucose variability and reduced body weight. To check the possibility of longer durability of DJBL after its removal, patients were examined also 3 months after DJBL removal. Decreased body weight and improved blood glucose control persisted with only a slight deterioration. In addition, both the anthropometric and glucose control parameters were noticeably below the baseline values. Another interesting finding is that systolic and diastolic blood pressure was significantly decreased (Kaválková *et al.*, 2016).

Table 4.2 - The influence of DJBL implantation according to CGM data.

	Visit 1 (before DJBL)	**Visit 2 (with DJBL)**	**Visit 4 (with DJBL)**	**Visit 5 (removed DJBL)**
Number of subjects	27	24	24	16
Glucose (mmol/l)	12.3 ±0.7	10.1 ±0.6	8.45 ±0.5	9.88 ±0.8
24-h mean glucose (mmol/l)	10.5 ±0.5	9.49 ±0.5	8.70 ±0.5	9.91 ±0.5
24-h glycemic variability (mmol/l)	2.39 ±0.17	1.89 ±0.14	1.96 ±0.18	2.44 ±0.28
Morning systolic blood pressure (mmHg)	150.2 ±3.7	145.9 ±3.0	143.1 ±3.0	143.6 ±2.5
Morning diastolic blood pressure (mmHg)	92.1 ±1.5	88.2 ±1.8	86.8 ±1.8	87.5 ±1.7

The third study "Ten Months of Treatment with Endoscopic Duodenal-Jejunal By-pass Liner Reduces Glycemic Variability, Increases Serum Fibroblast Growth Factor 19 (FGF19), and Partially Restores the Incretin Effect in Obese Subjects with Type 2 Diabetes Mellitus. Diabetes" analyzed a part of the same CGM data as the previous study. However, only the effect of the implantation of DJBL was examined in this paper. Thus, the partial results are similar, just results after removal of DJBL are missing (Kavalkova *et al.*, 2015).

4.4 Discussion

Evaluation of CGM data for several studies was performed. There was shown the importance of systematic approach to review and interpret these data. There are many measures of glycemic variability. However, it will be important to address some non-linear methods for description of glycemic variability as non-linear process in time. The computation of glycemic variability measures is very simple with the Matlab framework. The most important measures are implemented in the framework; some less frequently used measures might be implemented in the future. An automated conversion of data from various formats would be also done in the next version. The studies have also indicated that a filtering of evaluated data would be useful. Sometimes it is necessary to calculate the measures separately for day and night. It is also interesting to know how long a patient spends in hypoglycemia or in hyperglycemia; thus, this function should be also added into the Matlab framework.

From the studies carried out, the DJBL implantation significantly improved glycemic control, reduced glycemic variability and reduced body weight in obese patients with poorly controlled type 2 DM. The range of reductions in HbA1c and body weight in the "Endocrine effects of duodenal-jejunal exclusion in obese patients with type 2 diabetes mellitus" (Kaválková *et al.*, 2016) study was greater than in the meta-analysis of recently published studies of DJBL implantation, in which HbA1c differences did not reach statistical significance (Rohde *et al.*, 2016). The higher efficacy of DJBL may have been caused by the relatively poor glucose management and higher body weight of the patients at baseline. The results of the study should be also viewed in relation to the lack of a control group that would have undergone a sham procedure. In summary, the published data as well as our data indicate that the antidiabetic and weight loss efficacy of DJBL implantation is much lower compared to bariatric surgery. The other interesting result was a significant reduction in systolic and diastolic blood pressure. This drop was achieved after DJBL implantation after 1 month for systolic blood pressure and after 3 months for diastolic blood pressure. It is also interesting to note that blood pressure remained reduced even 3 months after DJBL removal. (Kaválková *et al.*, 2016).

4.5 Conclusion

The conclusion of the study "Continuous exenatide infusion improved perioperative glucose control and reduced glycemic variability in cardiac surgery patients: the executive trial" (Mraz *et al.*, 2014) was that perioperative administration of exenatide improved glucose control and decreased glycemic variability without increasing the risk of hypoglycemia in subjects undergoing elective coronary artery bypass graft (CABG). Except for the decreased need of temporary pacing, exenatide did not significantly affect parameters of cardiac function (Mraz *et al.*, 2014).

According to the two performed studies "Ten Months of Treatment with Endoscopic Duodenal-Jejunal By-pass Liner Reduces Glycemic Variability, Increases Serum Fibroblast Growth Factor 19 (FGF19), and Partially Restores the Incretin Effect in Obese Subjects with Type 2 Diabetes Mellitus. Diabetes" (Kavalkova *et al.*, 2015) and "Endocrine effects of duodenal-jejunal exclusion in obese patients with type 2 diabetes mellitus" (Kaválková *et al.*, 2016), it is concluded that the implantation of DJBL leads to a lasting reduction of body weight and improvement of all measures of glycemic control. The effects of DJBL on body weight and glucose control mostly persisted 3 months after its discontinuation, while its positive effects on lipids and glucose variability were completely reversed. For these effects, the changes in the incretin system and the increase in fibroblast growth factor 19 (FGF19) may be at least partly responsible (Kaválková *et al.*, 2016).

5 Glycemic Variability Analysis Using Nonlinear Methods

This chapter is based on the journal article in Complexity, which we have published: D. Cuesta-Frau, D. Novák, **V. Burda** *et al.* (2019) 'Influence of duodenal-jejunal implantation on glucose dynamics: A pilot study using different nonlinear methods', doi: 10.1155/2019/6070518. In this chapter most of the text is used as published in the journal. Some subsections are slightly expanded or their structure is modified from the original article.

We hypothesized that DJBL, described in section 4.1, also influences the glucose dynamics in type 2 DM, based on the induced changes already demonstrated in other physiological characteristics and parameters. In order to assess the validity of this assumption, we conducted a quantitative analysis based on several nonlinear algorithms (Lempel–Ziv Complexity, Sample Entropy, Permutation Entropy, and modified Permutation Entropy), well suited to the characterization of biomedical time series. We applied them to glucose records drawn from two extreme cases available of DJBL implantation: before and after 10 months. The results confirmed the hypothesis and an accuracy of 86.4% was achieved with modified Permutation Entropy. Other metrics also yielded significant classification accuracy results, all above 70%, provided a suitable parameter configuration was chosen. With the Leave–One–Out method, the results were very similar, between 72% and 82% classification accuracy. There was also a decrease in entropy of glycaemia records during the time interval studied. These findings provide a solid foundation to assess how glucose metabolism may be influenced by DJBL implantation and open a new line of research in this field.

5.1 Introduction

Glycemic Variability (GV) is a parameter that mathematically defines blood glucose oscillations within a defined time. It turned out that glycated hemoglobin and other parameters used to diabetes compensation do not necessarily reflect a real control of diabetes of all patients. The patients with oscillations of blood glucose from hypoglycemic

to hyperglycemic values with satisfactory glycated hemoglobin represent a typical example of this fact. It was showed that glycemic variability may become an important parameter reflecting the quality of diabetes compensation and the risk of long-term complications. However, further studies are necessary to confirm this prospect (Haluzík, 2012; Fuqua, 2015). Hypoglycemia is a complication of diabetes treatment. Because the main goal of diabetes treatment is lowering blood glucose, occurrence of hypoglycemia is a frequent problem which sometimes has severe consequences such as seizure, coma and death. These complications could be avoided if it was possible to predict hypoglycemia (Siegelaar *et al.*, 2010). Glycemic variability is a feasible candidate because severe hypoglycemia is preceded by disturbances of blood glucose. The authors of the Diabetes Outcomes in Veterans Study suggested that minimizing glycemic variability is a plausible method for offsetting the increased risk of hypoglycemia (Kovatchev *et al.*, 2000; Murata *et al.*, 2004; Siegelaar *et al.*, 2010).

The glucoregulatory system is effectively a complex system, with several acting variables (caloric intake, exercise), a number of active hormones (insulin, glucagon, catecholamine, growth hormone, and incretin), and some well–established feedback and feedforward loops (DeFronzo, 2004; Gagliardino, 2005). The analysis of such a complex physiological system can be addressed using system dynamics characterization methods. Several methods well suited to time series of limited duration were used in this pilot study to characterize the effects of DJBL. Sample Entropy (SampEn) is a robust measure of regularity in sequences (Richman and Moorman, 2000), whilst Lempel–Ziv complexity (LZC) is easy to compute a nonlinear algorithm to estimate the complexity in time series (Zhang, Roy and Jensen, 2001). Permutation Entropy (PE) is another complexity measure introduced in 2002 as a robust method to deal with real-world time series (Bandt and Pompe, 2002). In spite of the proficiency of PE in time series analyses, it neglects equalities within signals. Modified PE (mPE) was proposed to address this shortcoming in the original PE algorithm (Bian *et al.*, 2012).

5.2 Data and Methods

The experimental data of glucose time series were the same as used to assess the endocrine effects of DJBL (Chapter 4.2). There were 91 records from 30 participants with type 2 DM (20 men, 10 women; aged between 33 and 65). This database contained records taken

before implantation (baseline, BL-; 27 records), 1 month after implantation (01M+; 24 records), 10 months after implantation (10M+; 24 records), and 3 months after device removal (03M-; 16 records). Sampling frequency was 5 minutes. The original records in Figure 5.1 were noisy, with missing samples and missing epochs completely at random. Missing values were quite frequent (value spikes down to 0 in the plots). Records representing here 03M- and BL- classes were omitted in the experiments due to their short length.

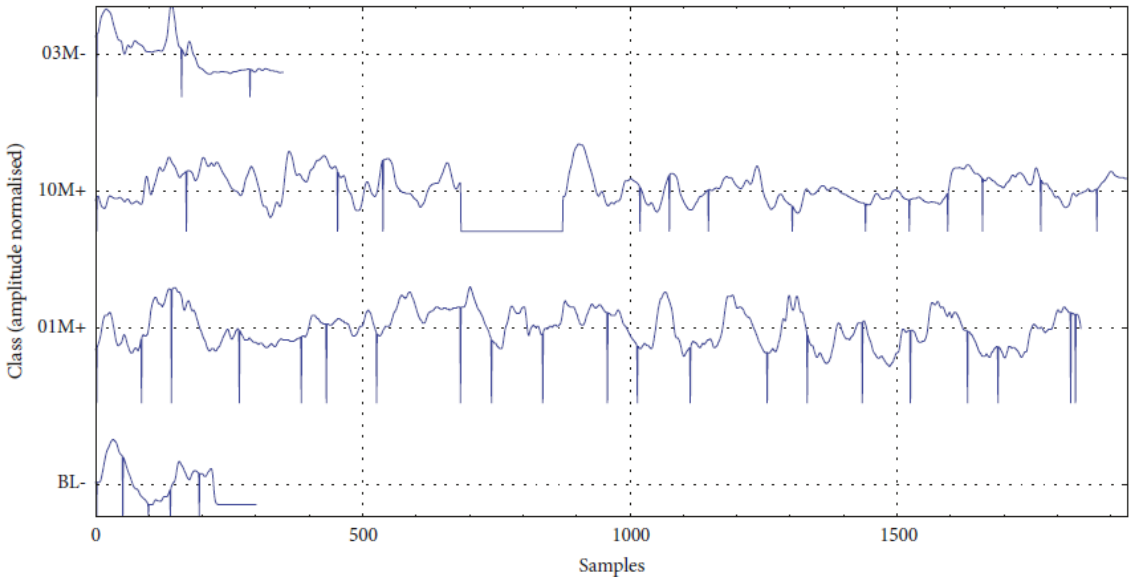

Figure 5.1 - Example of raw glycaemia records from the database.

In order to avoid the influence of these artifacts on the results, missing single samples were linearly interpolated with mean substitution (Masconi *et al.*, 2015). The samples were taken from the central part of the records to avoid border effects. Records with less than 1440 samples (5 days) were excluded from the experiments, since the nonlinear methods used in the analysis are also very sensitive to the number of samples (Yentes *et al.*, 2013). Record was then set to the central 1440 samples, if longer, to also avoid border effects: tissue equilibrium, measuring device configuration, calibration, and stabilization (Weinstein *et al.*, 2007). As a result of all this preprocessing, 60 records out of 91 were finally available, an example shows Figure 5.2.

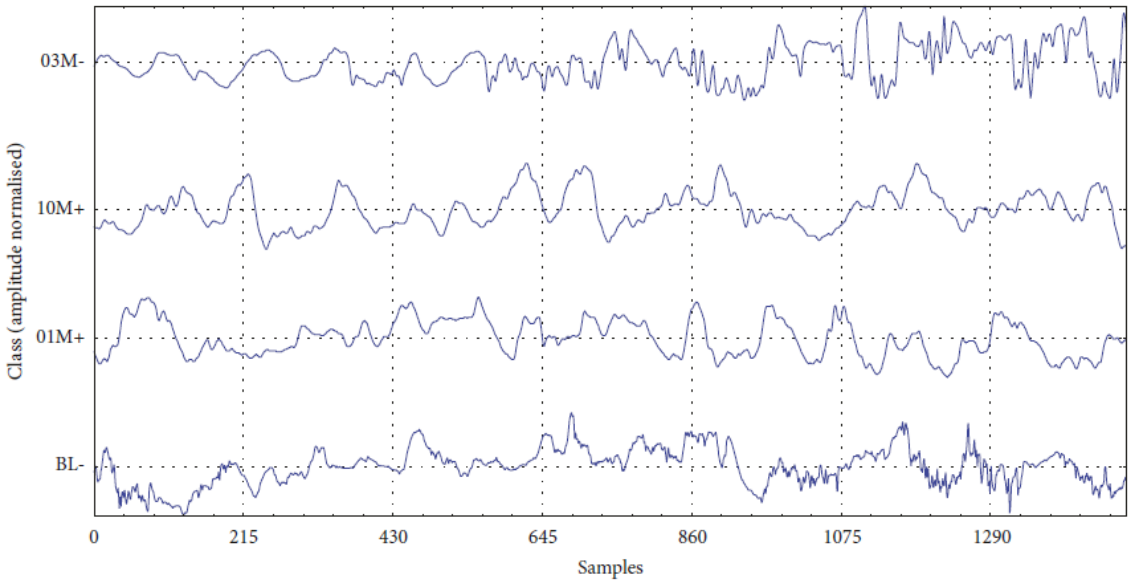

Figure 5.2 - Example of processed glycaemia records from the database.

Nevertheless, these records have not been analyzed yet from a system dynamics standpoint, and our hypothesis was focused first on the two, in principle, most different scenarios: before DJBL implantation (BL-), and just before device removal (10M+). The rationale for this specific selection is that one month after implantation it will arguably be more difficult to find changes in glucose dynamics, due to the time passed. After DJBL removal, the glucose metabolism tends to return to that of the baseline period (de Moura *et al.*, 2015; Kaválková *et al.*, 2016). Furthermore, quantitative endocrine effects seem to confirm that main differences are between these two stages, as shown in Table 5.1. Thus, in this table, 4 out of the 5 physiological features provide significant differences between 10M+ and BL-, giving quantitative support to the study selection. This support is in terms of a significance analysis of these differences obtained using Student's t–test (α = 0.05, sample size of 30, and normality not required (de Winter, 2013)). As shown in the p column, only the differences in hip circumference could not be considered significant. The final experimental set was composed of 11 BL- records (positives P in the classification analysis) of 1440 samples and 11 10M+ records (negatives N) of the same length. These 22 records included the same 11 patients in both classes to ensure a paired test (7 males, 4 females), and the others in these classes were discarded. The dataset is relatively small, but the implantation of DJBL and glucose monitoring for several days is difficult and costly, in terms of workload, time, and resources.

Table 5.1 - Main characteristics and parameters of the complete dataset.

	BL-	**10M+**	p
Body weight (Kg)	129.7 ± 4.4	117.3 ± 4.3	$p = 0.0450$
BMI (km/m2)	42.7 ± 1.2	38.4 ± 1.1	$p < 0.0001$
Glucose (mmol/L)	12.3 ± 0.7	8.45 ± 0.5	$p < 0.0001$
Hip circumference (cm)	132.8 ± 3.5	126.2 ± 2.8	$p = 0.2000$
HbA1c (mmol/mol)	75.0 ± 3.4	58.4 ± 2.8	$p < 0.0001$
HBGI (Variability)	12.8 ± 8.2	7.4 ± 5.1	$p = 0.0367$

Table 5.1 also includes a variability analysis result, the High Blood Glucose Index (HBGI). This index attempts to improve the assessment of glycemic alterations through data transformation and is a well-established tool to estimate the risk of hyperglycemia in diabetic patients. Average long-term blood glucose values are not a very reliable tool for glycemic control, but the analysis of short-term peaks and valleys has proven to have a much more clinical relevance (Weber and Schnell, 2009). HBGI provides an estimation of the hyperglycemia probability for the patients, and its differences have been found to be statistically significant for BL- and 10M+ in this case.

The separability of classes BL- and 10M+ was assessed by means of the Area under Curve (AUC) of the associated Receiver Operating Curve (ROC), AUC–ROC. Statistical analyses based on paired Student's t–test or the Wilcoxon signed rank test, depending on the distribution of the data, were performed to assess the significance of the results. The acceptance threshold was set at $\alpha = 0.05$. Additionally, the classification capability of the results was quantified using the separability, specificity and accuracy classification performance indicators. They were obtained using the closest point to (0,1) in the ROC as the classification threshold. In this framework, positives (P) were assigned to the BL- class, negatives (N) to the 10M+ class, being sensitivity = TP / (TP + FN), specificity = TN / (TN + FP), and accuracy = (TN + TP) / (TN + TP + FN + FP).

5.2.1 Lempel–Ziv Complexity

In order to compute Lempel–Ziv Complexity (LZC) from a time series, the signal must first be converted into a sequence of symbols. In this study, the signal was parsed into a binary

sequence using the median as the threshold (T_d). For an input time series x = $\{x_1, x_2, ..., x_L\}$ of length L, the symbols in the binary sequence $P = \{s_1, s_2, . . ., s_L\}$ are created by:

$$s_i = \begin{cases} 0 \ \ if \ \ x_i < T_d \\ 1 \ \ if \ \ x_i \geq T_d \end{cases} \tag{8}$$

The binary sequence P is then scanned from left to right to identify the different subsequences held within it and a complexity counter c is increased by one every time a new subsequence is found (a detailed description of the algorithm can be found in (Zhang, Roy and Jensen, 2001)). This complexity counter needs to be normalized to obtain a measure of complexity independent of the length of the time series (Lempel and Ziv, 1976):

$$LZC = \frac{c}{L/\log_2 L} \tag{9}$$

LZC captures the dynamics of the time series by reflecting the rate of new subsequences present within it.

5.2.2 Permutation Entropy

Permutation Entropy (PE) is a method measuring the entropy within a time series based on the probability of occurrence of all possible permutations of a certain length within it (Bandt and Pompe, 2002). With the exception of LZC, all other methods used in this study require the selection of values for different input parameters. In the case of PE, the computation relies on the selection of the embedding dimension n and the time delay l. The choice of embedding dimension n is determined by the number of samples available, as the number of permutations must be less than the length of the time series (i.e., $n! \leq L$) (Bandt and Pompe, 2002). In order to compute PE as follows (Bian *et al.*, 2012), embedding vectors need to be created from the original time series as follows:

$$X_i = [x_i, x_{i+l}, \dots, x_{i+(n-1)l}] \tag{10}$$

For each embedding vector, the lowest data point in the embedding vector is assigned a 0, the second lowest 1, and on until all data points in the embedding vector have been replaced with their ranking order. Once all possible embedding vectors in the time series have been

created and ranked, PE can be calculated by applying Shannon's Entropy to quantify the proportion of possible permutations within the time series:

$$\mathrm{PE}(n, l) = -\sum_{A=1}^{k} P_A \ln P_A \tag{11}$$

where k is the number of different subsequence ranked vectors in the original time series and PA is the fraction of the subsequence ranked vectors. A less regular signal will have a greater range of embedding vectors and, therefore, a higher PE.

One limitation of the original PE algorithm is that it ignores any repeated values in the embedding vector, assigning the first repeated value in the vector a lower integer in the ranking than subsequent repeats. This was addressed with the introduction of Modified Permutation Entropy (mPE) (Bian *et al.*, 2012), in which repeated values are given the same ranking value. Then, entropy is evaluated applying Shannon's entropy as is done in PE (Bian *et al.*, 2012).

The outcome of PE will be influenced by the choice of embedding dimension n and delay l. A greater value of n will give a greater possible range of ranking vectors and, therefore, a greater resolution. It has been recommended to use a range of values from n = 3 to 7 but the total number of permutations (given by $n!$) must be less than the length of the original time series (Bandt and Pompe, 2002). However, small embedding dimensions might be too small to accurately track the dynamical changes in a signal (Cao *et al.*, 2004). Hence, PE and mPE were computed with n = 4 to 6. In terms of the time delay, a value of 1 was chosen as this would retain the original relationships between data-points (Bian *et al.*, 2012).

5.2.3 Sample Entropy

Sample Entropy (SampEn) was first defined in (Richman and Moorman, 2000). SampEn starts by creating a set of embedded vectors xi of length m:

$$\mathrm{X}_i = \{x_i, x_{i+l}, \ldots, x_{i+m-1}\} \qquad \text{where } i = 1, \ldots, L-m+1 \tag{12}$$

The distance between subsequences is then defined as $d_{ij} = \max(|x_{i+k} - x_{j+k}|)$, with $0 \leq k \leq m-1$, $j \neq i$. According to a predefined threshold r, two subsequences are considered

similar if $d[X_m(i), X_m(j)] \leq r$. This similarity is quantized for two consecutive subsequence lengths (m and m + 1), with $B_i(r)$ number of j such that $d[X_m(i), X_m(j)] \leq r$, and $A_i(r)$ number of j such that $d[X_m{+}1(i), X_m{+}1(j)] \leq r$. These two values B and A enable the computation of the statistics associated with SampEn:

$$B_i^m(r) = \frac{1}{L-m-1} B_i(r) \qquad A_i^m(r) = \frac{1}{L-m-1} A_i(r)$$
$$B^m(r) = \frac{1}{L-m} \sum_{i=1}^{L-m} B_i^m(r) \qquad A^m(r) = \frac{1}{L-m} \sum_{i=1}^{L-m} A_i^m(r) \tag{13}$$

from which the final value for SampEn can be obtained (for finite time series):

$$SampEn(m, r) = \lim_{N \to \infty} \left(-\log \left[\frac{A^m(r)}{B^m(r)} \right] \right)$$
$$SampEn(m, r, L) = -\log \left[\frac{A^m(r)}{B^m(r)} \right] \tag{14}$$

The length L is usually given by the acquisition stage, but the parameters m and r must be carefully chosen to ensure an optimal performance of SampEn relative to class separability.

The optimal selection of regularity estimators parameters m and r is still an open question. Frequent recommendations suggest adopting a parameter configuration in the vicinity of m = 2 and r = 0.2 (Pincus, Gladstone and Ehrenkranz, 1991). Nevertheless, this selection is lacking in terms of genericity, as many works have already demonstrated (Karmakar *et al.*, 2007; Liu *et al.*, 2011; Yentes *et al.*, 2013; Restrepo, Schlotthauer and Torres, 2014). Although computationally more expensive, we varied SampEn parameters from 1 to 3 for m and from 0.01 to 0.30 for r, in 0.01 steps (r was not multiplied by the standard deviation of the sequences since they were normalized in advance, zero mean, and unitary standard deviation). This enabled us to avoid the possible bias in the results due to the selection of a specific method for SampEn parameter optimization, despite still looking at regions usually recommended for m and r (Pincus, Gladstone and Ehrenkranz, 1991; Richman and Moorman, 2000; Zhao *et al.*, 2015)

5.3 Results

All four methods showed a decrease of complexity between BL- and 10M+ (i.e. decrease of LZC, SampEn, PE, and mPE values). However, for LZC differences between the 2 classes were not significant (see Table 5.5). On the other hand, different combination of input parameters in SampEn, PE, and mPE resulted in significant differences between classes.

The results are expressed in terms of AUC, statistical significance, classification sensitivity, specificity, and accuracy. The threshold for classification was taken as the ROC point closest to point (0,1). These calculations were carried out for all the values in input parameters for which the AUC was at least 0.70. Most of the AUC values fall in the 0.50−0.60 region, with more promising results at low r values (r < 0.10, optimal region), and in the 0.20 zone (suboptimal region). In more detail, the numerical results for the highest AUC region are listed in tables. Table 5.2, Table 5.3 and Table 5.4 show classification analysis results for PE, mPE and SampEn respectively, in terms of highest AUC, including sensitivity (proportion of 10M+ correctly identified), specificity (proportion of BL- correctly identified), and accuracy (proportion of total cases correctly classified), and their significance p. This corresponds to the optimal parameter zone, where some AUC values are above 0.80.

Table 5.2 - Classification analysis results for PE.

n	AUC	p	Sensitivity (%)	Specificity (%)	Accuracy (%)
6	0.7355	0.0244	63.6	90.9	77.3

Table 5.3 - Classification analysis results for mPE.

n	AUC	p	Sensitivity (%)	Specificity (%)	Accuracy (%)
4	0.7438	0.0244	72.7	81.8	77.3
5	0.7769	0.0137	72.7	90.9	81.8
6	0.7851	0.0098	72.7	100	86.4

Table 5.4 - Classification analysis results for SampEn.

m	r	AUC	p	Sensitivity (%)	Specificity (%)	Accuracy (%)
1	0.08	0.7933	0.0427	63.6	90.9	77.3
1	0.09	0.8016	0.0305	72.7	81.8	77.3
1	0.10	0.7933	0.0188	81.8	72.7	77.3
1	0.16	0.7355	0.0648	72.7	72.7	72.7
1	0.19	0.7768	0.0272	81.8	63.6	72.7
1	0.20	0.7272	0.0451	54.5	90.9	72.7
1	0.24	0.7603	0.0472	72.7	72.7	72.7
1	0.25	0.7190	0.0583	72.7	63.6	68.2
2	0.08	0.7603	0.0257	72.7	72.7	72.7
2	0.09	0.8016	0.0289	81.8	72.7	77.3
2	0.10	0.7933	0.0173	81.8	72.7	77.3
2	0.19	0.7520	0.0288	72.7	63.6	68.2
2	0.20	0.6942	0.0609	54.5	81.8	68.2
2	0.24	0.7438	0.0462	72.7	72.7	72.7
3	0.08	0.7933	0.0215	72.7	72.7	72.7
3	0.09	0.8429	0.0271	72.7	90.9	81.8
3	0.10	0.8264	0.0086	90.9	72.7	81.8
3	0.16	0.7355	0.0532	81.8	63.6	72.7
3	0.19	0.7272	0.0236	72.7	63.6	68.7
3	0.20	0.7107	0.0596	45.5	81.8	63.7
3	0.24	0.7355	0.0507	63.6	72.7	68.7
1	0.08	0.7933	0.0427	63.6	90.9	77.3

Table 5.5, Table 5.6, Table 5.7 and Table 5.8 summarize the numerical results for the two classes (BL-; 10M+), including mean and standard deviation (SD). These values were computed using the parameter configuration scheme stated above. It is important to note that some configuration parameters did not yield significant results, such as n = 3 for PE (Table 5.6) and mPE (Table 5.7). As in previous similar studies (D. Cuesta-Frau et al., 2018; David Cuesta-Frau, Miró-Martínez, et al., 2018; David Cuesta-Frau, Varela-Entrecanales, et al., 2018), it seems the greater the embedded dimension n, the better classification performance using PE–based measures.

In order to illustrate the differences between the classes studied better, a Leave–One–Out test (David Cuesta-Frau, Miró-Martínez, et al., 2018) was applied using the data presented in Table 5.8. The classification threshold was set at the optimal SampEn value at which the classification accuracy was maximal. For both classes, there were 3 misclassified instances.

Therefore, the overall classification accuracy using the Leave–One–Out cross validation was 72.7%. As expected, the performance was lower than using all the records, but still very significant. This method was also applied to the Modified Permutation Entropy results in Table 5.7, when n = 6. In this case, there were 2 misclassified instances, achieving a classification accuracy of 82%.

Table 5.5 - Lempel–Ziv Complexity individual results.

Subject	**BL-**	**10M+**
1	0.2113	0.1676
2	0.1530	0.1749
3	0.0947	0.1311
4	0.1676	0.1530
5	0.1822	0.1239
6	0.2842	0.1457
7	0.1384	0.1530
8	0.1239	0.1457
9	0.1093	0.1020
10	0.1822	0.1384
11	0.1457	0.1676
mean ± SD	0.1629 ± 0.0528	0.1457 ± 0.0214

Table 5.6 - Permutation Entropy individual results.

	n = 3		n = 4		n = 5		n = 6	
Subject	**BL-**	**10M+**	**BL-**	**10M+**	**BL-**	**10M+**	**BL-**	**10M+**
1	1.5131	1.1105	2.4970	1.5694	3.5541	2.0522	4.5778	2.5522
2	1.1824	1.1688	1.6784	1.6891	2.1995	2.2423	2.7291	2.7994
3	1.1279	1.1341	1.6425	1.5961	2.1819	2.0835	2.7465	2.5888
4	1.2189	1.1447	1.8155	1.6146	3.4558	2.1075	3.1213	2.6170
5	1.1358	1.1672	1.6402	1.6812	2.1761	2.2046	2.7335	2.7255
6	1.5166	1.1369	2.5011	1.5947	3.5701	2.0686	4.5942	2.5614
7	1.1220	1.1154	1.6156	1.5780	2.1372	2.0690	2.6745	2.5696
8	1.1527	1.1451	1.6876	1.6734	2.2577	2.2221	2.8539	2.7863
9	1.0638	1.1926	1.5742	1.7023	2.0880	2.2140	2.6170	2.7293
10	1.1453	1.1244	1.6538	1.5727	2.1947	2.0412	2.7450	2.5038
11	1.1117	1.0477	1.5838	1.4787	2.0904	1.9190	2.6209	2.3806
mean	1.2082	1.1352	1.8083	1.6136	2.4460	2.1113	3.0921	2.6194
STD	0.1566	0.0380	0.3475	0.0674	0.5607	0.0992	0.7512	0.1286
p	0.1475		0.0830		0.0420		0.0244	

Table 5.7 - Modified Permutation Entropy individual results.

	n = 3		n = 4		n = 5		n = 6	
Subject	**BL-**	**10M+**	**BL-**	**10M+**	**BL-**	**10M+**	**BL-**	**10M+**
1	1.2301	0.9643	1.0896	0.7487	0.9834	0.6330	0.8655	0.5554
2	1.0249	0.9643	0.7971	0.7544	0.6723	0.6400	0.5899	0.5624
3	1.0423	1.0017	0.8249	0.7732	0.7040	0.6524	0.6221	0.5727
4	1.0570	1.0163	0.8500	0.7793	0.7328	0.6570	0.6524	0.5764
5	1.0029	1.0459	0.7879	0.8193	0.6727	0.6934	0.5950	0.6086
6	1.2328	1.0098	1.0879	0.7781	0.9837	0.6512	0.8738	0.5672
7	1.0468	1.0345	0.8252	0.8043	0.7048	0.6793	0.6239	0.5958
8	1.0517	1.0625	0.8359	0.8426	0.7106	0.7179	0.6281	0.6333
9	1.0296	1.0224	0.8266	0.7944	0.7080	0.6682	0.6271	0.5849
10	1.0172	1.0273	0.8024	0.7876	0.6856	0.6590	0.6036	0.5731
11	1.0093	1.0180	0.7913	0.7954	0.6703	0.6709	0.5910	0.5895
mean	1.0677	1.0152	0.8650	0.7888	0.7480	0.6657	0.6611	0.5836
STD	0.0828	0.0302	0.1123	0.0272	0.1180	0.0244	0.1048	0.0225
$\boldsymbol{p}$	0.1748		0.0244		0.0137		0.0098	

Table 5.8 - SampEn individual results.

	$m = 3, r = 0.09$		$m = 2, r = 0.25$	
Subject	**BL-**	**10M+**	**BL-**	**10M+**
1	0.5020	0.3604	0.2972	0.2304
2	0.4304	0.3668	0.1667	0.2384
3	0.3730	0.4253	0.1639	0.1643
4	0.4354	0.3909	0.2069	0.1562
5	0.4862	0.3874	0.2337	0.1984
6	0.6553	0.2854	0.3584	0.1250
7	0.4030	0.3541	0.1414	0.1797
8	0.3798	0.3709	0.1602	0.1530
9	0.3021	0.2585	0.1112	0.1666
10	0.4130	0.3449	0.2151	0.1710
11	0.3906	0.3079	0.2126	0.1957
mean	0.4337	0.3502	0.2061	0.1799
STD	0.0914	0.0489	0.0714	0.0337
$\boldsymbol{p}$	0.0073		0.0234	

5.4 Discussion

Our results show that it is possible to identify the effects of DJBL in the dynamics of glycaemia records with nonlinear analysis methods. A significant decrease in entropy (estimated with SampEn, PE, and mPE) of glycaemia records from BL- to 10M+ was observed. Complexity, quantified with LZC, also decreased in 10M+, but differences were not significant.

There is no gold standard for the unsupervised selection of parameters m and r for SampEn calculations, despite the numerous efforts in this regard (Sheng Lu *et al.*, 2008; Mayer *et al.*, 2014; Zhao *et al.*, 2015). In order to leave no stone unturned, we adopted a maximalist strategy where a wide range of values were tested. As a result, this parameter analysis for SampEn provided an optimal combination with m = 3 and r = 0.09. In this case, the AUC was maximal, AUC = 0.8429, with significant (reject hypothesis) classification capabilities between BL- and M10+ (sensitivity = 72.7%, specificity = 90.9%, and accuracy = 81.8%). However, there were other values for m, with r in the vicinity of 0.09, that also yielded good significant accuracy. In fact, the results seem to be almost independent of m.

The optimal value of r (r = 0.09), falls practically within the usually recommended interval, $r \in [0.1, 0.25]$ (Pincus, Gladstone and Ehrenkranz, 1991). There is another region of acceptable results for r = 0.19. These specific values seem to be related to the resolution of the measurements, which was 0.1 mmol/L and the dissimilarity measure ($d < 0.1$, and $d < 0.2$). As for the m parameter, significant performance was achieved in all tested cases.

As it is also the case with SampEn, there is no consensus on the choice of input parameter values for the calculation of PE and mPE. However, some guidelines exist and were followed in this pilot study. Firstly, the delay was equal to 1 to guarantee that no down-sampling of the original time series would occur. Secondly, the embedding dimension determining the size of the permutation vectors was selected taking into account its upper limit (Bandt and Pompe, 2002) and the reported results showing that small embedding dimensions could fail to identify changes in the dynamics of a signal (Cao *et al.*, 2004).

Therefore, a range of values from n = 4 to 6 was tested, with results showing that greater values of n lead to better discrimination between both classes. The highest accuracy was observed with n = 6 for both PE (77.27%) and mPE (86.36%), with the latter outperforming SampEn. It is worth noting that the entropy of glucose time series estimated with PE and

mPE decreases from class BL to 10M+ for all subjects but two, but the subjects where this decrease is not observed are different for both methods. Furthermore, our results suggest that mPE is a more accurate method to characterize subtle differences in glucose time series than PE.

Despite the analysis limitations due to small database size, records length, and artifacts, the results confirmed there are differences between BL- and 10M+ records that can be associated with changes in the underlying glucose dynamics after DJBL implantation. With a high degree of accuracy (86.4%), it was possible to correctly distinguish between the two classes. As far as we know, this is the first evidence in this classification context beyond variability and it opens a new perspective for the research of the DJBL implantation effects.

The results are consistent. For most of the cases where AUC was relatively high (AUC > 0.75), the hypothesis was rejected and the classification accuracy was higher than 70%. The opposite also holds true when no significant difference was apparent. Namely, there is a good correlation among all the features used to assess the classification capabilities; there were no antagonistic results (AUC > 0.75 with $p > \alpha$).

5.5 Conclusion

We explored the possible influence on the glucose dynamics of DJBL implantation using several nonlinear methods. The best results were obtained with mPE calculated with an embedding dimension of 6 and with SampEn with input parameter values m = 3 and r = 0.09, although many other parameter configurations yielded suboptimal but relevant results. A similar approach was followed in other previous works related to blood glucose (Crenier *et al.*, 2016) or body temperature time series (Cuesta *et al.*, 2007).

The performance of the method proposed could arguably be enhanced using other methods of theoretically better consistency (Chen *et al.*, 2009). For instance, other modifications of PE can be considered, like fine-grained PE, based on incorporating the size of the differences between data–points into permutations and not just ranking them from smallest to largest (Xiao-Feng and Yue, 2009), or the weighted PE, based on weighting permutation patterns depending on the amplitudes of their constituent data–points (Fadlallah *et al.*, 2013). Other effects should be studied, such as the influence of the artifacts, the characterization of the time–of–day variations (chronobiology), and the possible differences

between other stages of the DJBL implantation. The availability of a validated set of methods for glucose dynamics assessment will arguably become a powerful tool for the study of disease onset and progression.

In summary, the DJBL implantation does alter the glucose metabolism of the subjects, and these changes can be detected by an analysis as the one proposed in this paper. This analysis may increase the clinical uses of the new information gathered. Additionally, there is room for improvement in terms of more accuracy and/or more classes.

6 Summary and Future Work

In the thesis presented, the mobile app and web-based portal for support of DM self-management have been designed and implemented, as it is described in Chapter 3. The system was designed with principles of telemedicine using mHealth and eHealth approaches (Chapter 2.2) and is based on an analysis of the features of similar mobile applications available at the time of early development (Chapter 2.3). In addition, data from users who had been using the application for a long time were evaluated. The most active patient is a user who has records for more than 7 years and still uses the system. The results are potentially satisfactory and promising; however, a small set of users poses limits to validate effectiveness of DM self-management using the Mobiab system. Furthermore, a Matlab framework for extracting and evaluating data gained from continuous glucose monitoring sensors has been created. These data have been processed and the calculated GV measures have been used in several studies and articles (Chapter 4) and in addition, the same data were used for comparison of new glycemic variability methods (Chapter 5).

6.1 Thesis Contributions

- I have implemented working telemedicine Mobiab system that contains Android mobile application and web-based portal for desktop computers. The Android app was available on Google Play Store from the middle of 2014 only until 2019. In this period over 500 users from the Czech Republic downloaded and used the app for different lengths of time. From this usage the data were obtained for the analysis of using this system, especially long-term data over one year were interesting.
- I have analyzed the usage of the Mobiab system from the user's records and it has been discovered how users use the Mobiab system and what the main advantages and shortcomings of this system are. A strong point is that users are able to use the system for a long time and enter a significant amount of data. However, a small number of total users is a limitation factor to test and validate the self-management compliance of the Mobiab system.

- A useful Matlab framework for CGM data analysis has been implemented. It consists of a method for data extraction from Medtronic format and five standard metrics used for glucose variability description.
- We successfully explored the possible influence on the glucose dynamics of DJBL implantation using several nonlinear methods. This analysis may increase the clinical uses of the new information gathered.

6.2 Future Work

Based on the results of this thesis, following steps in the future work need to be addressed:

- The redesign of mobile app is necessary to meet the current design principles according to new Android standards. Then it will be possible to republish the app on Google Play. Additionally, the cross-platform development to support Apple devices should be considered.
- Support for more blood glucose meters and other Bluetooth devices across several manufacturers have to be implemented.
- Integration with commercial software (e.g. Medtronic CareLink) is proving to be necessary because the use of another web-based portal for a clinician is an unnecessary complication. Interfaces such as REST API with specific connection module or export in required formats should be prepared.
- More long-term data should be collected to confirm the effect of using the Mobiab system in comparison with the patients that do not use the system.
- The Matlab framework for extracting CGM data could be improved for fully automatic data extraction and evaluation of different input devices and file formats.
- In the explored nonlinear methods there is an occasion for improvement in terms of more accuracy and/or more classes and also other effects should be studied, such as the influence of the artifacts, the characterization of the time–of–day variations (chronobiology), and the possible differences between other stages of the DJBL implantation.

6.3 List of Candidate Publications

Author contribution are given based on the V3S database. Citation counts according to ISI Web of Science (WoS) are valid as of 24th of April 2022.

6.3.1 Impacted Journals Publications Related to the Thesis

Burda, V.; Mráz, M.; Schneider, J.; Novák, D., 'Managing Diabetes Using Mobiab: Long Term Case Study of the Impact of a Mobile App on Self-Management', *JMIR Diabetes*, Accepted – in print.

IF 5,43: Q1; Contribution: 80 %

Colás, A.; Vavrela, M.; Mráz, M.; Novák, D.; Cuesta-Frau, D.; Vigil, L.; Beneš, M.; Pelikánová, T. et al., 'Influence of glucometric 'dynamical' variables on duodenal-jejunal bypass liner (DJBL) anthropometric and metabolic outcomes', *Diabetes/Metabolism Research and Reviews*. 2020, 36(4), ISSN 1520-7552.

JCR 2020 - IF 4,88: Q2; Contribution: 9.09 %; 1 WoS citations

Cuesta-Frau, D.; Novák, D.; **Burda, V.**; Abasolo, D. et al., 'Influence of duodenal-jejunal implantation on glucose dynamics: A pilot study using different nonlinear methods', *Complexity*. 2019, 2019 ISSN 1076-2787.

JCR 2019 - IF 2,46: Q2, Contribution: 9.09 %; 0 WoS citations

Cuesta, D.; Novák, D.; **Burda, V.**; Molina-Pico, A.; Vargas, B.; Mraz, M.; Kavalkova, P.; Benes, P. et al., 'Characterization of Artifact Influence on the Classification of Glucose Time Series Using Sample Entropy Statistics', *Entropy*. 2018, 20(871), ISSN 1099-4300.

JCR 2018 - IF 2,42: Q2; Contribution: 20 %; 0 WoS citations

Kavalkova, P.; Mraz, M.; Trachta, P.; Klouckova, J.; **Burda, V.**; Novák, D. et al., 'Endocrine effects of duodenal-jejunal exclusion in obese patients with type 2 diabetes mellitus', *Journal of endocrinology*. 2016, 231(1), 11-22. ISSN 0022-0795.

JCR 2016 - IF 4,71: Q1; Contribution: 10 %; 26 WoS citations

6.3.2 Conference Reports Related to the Thesis

Burda, V.; Novák, D.; Schneider, J., 'Evaluation of diabetes mellitus compensation after one year of using Mobiab system', In: *38th International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) 2016*. New York: IEEE, 2016. p. 6002-6005. ISSN 1557-170X. ISBN 978-1-4577-0220-4.

Contribution: 75 %; 0 WoS citations

Burda, V.; Novák, D., 'Mobiab System for Diabetes Mellitus Compensation', In: *INTERNATIONAL WORKSHOP ON COMPUTATIONAL INTELLIGENCE FOR MULTIMEDIA UNDERSTANDING*. Praha: Czech Technical University in Prague, 2015. ISBN 978-1-4673-8457-5.

Contribution: 50 %; 1 WoS citations

Burda, V.; Novák, D., 'Diabetes Mellitus Compensation Using Mobile Technology', In: *Proceedings of the 2nd Conference on Mobile and Information Technologies in Medicine*. Praha: ČVUT v Praze, Fakulta elektrotechnická, 2014, ISBN 978-80-01-05637-0.

Contribution: 60 %

Mraz, M.; Lips, M.; Klouckova, J.; Dobias, M.; **Burda, V.**; Novák, D. et al., 'CONTINUOUS EXENATIDE INFUSION IMPROVED PERIOPERATIVE GLUCOSE CONTROL AND REDUCED GLYCAEMIC VARIABILITY IN CARDIAC SURGERY PATIENTS: THE EXECUTIVE TRIAL', *Diabetes Technology and Therapeutics*. 2015, 17 A14-A15. ISSN 1520-9156.

JCR 2015 - IF 2,20: Q3; Contribution: 10 %; 0 WoS citations

Kavalková, P.; Mráz, M.; Trachta, P.; Haluzíková, D.; Lacinová, Z.; Beneš, M.; Vlasáková, Z.; **Burda, V.** et al., 'Ten Months of Treatment with Endoscopic Duodenal-Jejunal By-pass Liner Reduces Glycemic Variability, Increases Serum Fibroblast Growth Factor 19 (FGF19), and Partially Restores the Incretin Effect in Obese Subjects with Type 2 Diabetes Mellitus', *Diabetes*. 2015, 64(64), A64. ISSN 0012-1797.

JCR 2015 - IF 8,78: D1; Contribution: 8.33 %; 0 WoS citations

Mraz, M.; Anderlova, K.; Krejci, H.; **Burda, V.**; Novák, D.; Drapalova, J.; Soupal, J.; Fajmon, M. et al., 'RELATIONSHIP BETWEEN GLYCEMIC VARIABILITY, GLUCOSE CONTROL AND LONG-TERM COMPLICATIONS IN PATIENTS WITH DIABETES MELLITUS', *Diabetes Technology and Therapeutics*. 2013, 15 A68. ISSN 1520-9156.

JCR 2013 - IF 2,29: Q3; Contribution: 9.09 %; 0 WoS citations

Mráz, M.; Kavalková, P.; Trachta, P.; Haluzíková, D.; Lacinová, Z.; Křížová, Z.; Beneš, M.; Vlasáková, Z. et al., 'Ten months of treatment with endoscopic duodeno-jejunal bypass liner reduce glycaemic variability and partially restore the incretin effect in obese type 2 diabetic subjects', *Diabetologia*. 2015, 58(58), S438. ISSN 0012-186X.

JCR 2015 - IF 6,21: D1; Contribution: 7.69 %; 0 WoS citations

Haluzik, M.; Lips, M.; Drapalova, J.; Mraz, M.; Dobias, M.; Kopecky, P.; Lindner, J.; **Burda, V.** et al., 'Continuous Exenatide Infusion Improved Perioperative Glucose Control and Reduced Glycaemic Variability in Cardiac Surgery Patients: The EXECUTIVE Trial, *Diabetologia*. 2014, 57(57), S371-S372. ISSN 0012-186X.

JCR 2014 - IF 6,67: Q1; Contribution: 9.09 %; 0 WoS citations

6.3.3 Impacted Journal Publication and Selected Conference Reports Unrelated to the Thesis

Lukavská, K.; Novák, D.; **Burda, V.**; Prokop, J. et al., 'Improving Adherence to an eHealth Program: A Randomized Controlled Trial Comparing Reminders by Text Message with E-mail**',** *JMIR mHealth and uHealth*. 2022, ISSN 2291-5222.

JCR 2020 - IF 4,77: Q1; Contribution 12.5 %

Lukavská, K.; **Burda, V.**; Lukavský, J.; Slussareff, M.; Gabrhelík, R., 'School-Based Prevention of Screen-Related Risk Behaviors during the Long-Term Distant Schooling Caused by COVID-19 Outbreak', *International Journal of Environmental Research and Public Health*. 2021, 18(16), ISSN 1660-4601.

JCR 2020 - IF 3,39: Q1; Contribution: 20 %; 2 WoS citations

Kulhánek, A.; Gabrhelík, R.; Novák, D.; **Burda, V.**; Brendryen, H., 'eHealth Intervention for Smoking Cessation for Czech Tobacco Smokers: Pilot Study of User Acceptance', *Adiktologie*. 2018, 2018(2), 81-85. ISSN 1213-3841.

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