CZECH TECHNICAL UNIVERSITY IN PRAGUE

FACULTY OF BIOMEDICAL ENGINEERING

Department of Biomedical Technology

MASTER THESIS

2016 **Bc. Anna Holubová**

CZECH TECHNICAL UNIVERSITY IN PRAGUE

Faculty of Biomedical Engineering
Department of Biomedical Technology

AUTOMATIC DISCOVERY OF PROBLEMATIC SITUATIONS IN BIOSIGNALS OF PATIENTS WITH DIABETES

Master Thesis

Study Programme: Biomedical and Clinical Technology
Field of study: Biomedical Engineering

Supervisor: *Ing. Jan Mužík, Ph.D.*
Consultant: *MUDr. Jan Brož*

Bc. Anna Holubová

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Zadání diplomové práce

Student:	**Bc. Anna Holubová**
Studijní obor:	Biomedicínský inženýr
Téma:	**Automatizované vyhledávání problematických situací v biologických signálech pacientů s diabetem**
Téma anglicky:	Automatic discovery of problematic situations in biosignals of patients with diabetes

Zásady pro vypracování:

Navrhněte, implementujte a ověřte algoritmy, které umožní automatizované vyhledání problematických situací v záznamech biologických signálů a dalších měřených parametrů pacientů s diabetem 1. typu. Zaměřte se především na signály a parametry jako je kontinuální záznam glykémie, míra fyzické aktivity, dávkování inzulinu, příjem sacharidů či pohyby ve spánku. Algoritmy budou na základě okamžitých hodnot, či odvozených parametrů jako trendy, upozorňovat na situace jako je například včasné upozornění na blížící se hypoglykémii při zvýšené fyzické aktivitě. Algoritmy budou pracovat jak v kauzálním tak nekauzálním režimu. V kauzálním režimu umožní generovat alarmy na základě dat přijímaných v reálném čase a upozorňovat tak na okamžité situace. V nekauzálním režimu umožní ex post vyhledávání potenciálně problematických situací na základě dlouhodobě nasbíraných dat, jako je např. dlouhodobě snížená fyzická aktivita či dlouhodobě zvýšená glykémie apod., a podpoří tak lékaře v rozhodovacím procesu během léčby a edukaci pacienta, ale také přinese možnost edukace pacienta samotného. Algoritmy ověřte na souboru dat získaných v klinické studii ve FN Motol, kterou dodá vedoucí práce, a výsledky porovnejte s manuálním hodnocením lékařem. Tyto výstupy statisticky zpracujte a zhodnoťte.

Seznam odborné literatury:

[1] Rozman, J., Elektronické přístroje v lékařství, ed. 1, Academia, Praha, 2006, ISBN 80-200-1308-3
[2] Rušavý Zdeněk, Brož Jan a kol., Diabetes a sport, ed. 1, Maxdorf, 2012, ISBN 978-80-7345-289-6
[3] Metin Akay, Biomedical Signal Processing, ed. 1, Academic Press, 2012, 377 s., ISBN 0323140149

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Zadání platné do: 20.08.2017

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vedoucí katedry / pracoviště	děkan

V Kladně dne 22.02.2016

Czech Technical University in Prague – Faculty of Biomedical Engineering

Depatment of Biomedical Technology | Academic year: 2015/2016

Diploma Thesis assignment

Student: **Anna Holubová**
Study branch: Biomedical engineer
Title: **Automatic discovery of problematic situations in biosignals of patients with Diabetes**
Title in Czech: Automatizované vyhledávání problematických situací v biologických signálech pacientů s diabetem

Instructions for processing:

The goal is to design, implement and verify algorithms for automated identification of problematic situations in the records of biological signals and other parameters measured in patients with type 1 diabetes. Methods should primary focus on signals and parameters such as continuous glucose monitoring, the level of physical activity, insulin dosing, carbohydrate intake or movements in sleep. The algorithms should be based on instantaneous values, or derived parameters such as trends, highlighting the situation such as early warning of impending hypoglycemia during increased physical activity. The algorithms will work in both causal and non-causal mode. In the causal mode the algorithms will generate alarms based on the data received in real time, and thus, alert to immediate situations. The non-causal mode will allow ex post identification of potentially problematic situations based on previously collected data, e.g. a long-term decreased physical activity or a long-term elevated blood glucose, etc. Final algorithms will not only support the physician in the decision-making process during treatment and education of a patient, but also bring the possibility to educate the patient himself. The algorithms will be validated on a set of data obtained during a clinical trial at the University Hospital in Motol, and will be compared with the results of manual data evaluation made by a doctor. These outputs will be statistically processed and evaluated.

References:

[1] Rozman, J. Elektronické přístroje v lékařství, ed. 1, Academia, Praha, 2006, ISBN 80-200-1308-3.
[2] Rušavý Zdeněk, Brož Jan et al., Diabetes a sport, ed. 1, Maxdorf, 2012, ISBN 978-80-7345-289-6.
[3] Metin Akay. Biomedical Signal Processing, ed. 1, Academic Press, 2012, 377 p., ISBN 0323140149.

Validity of Thesis Assignment: 20. 8. 2017
Supervisor: Ing. Jan Mužík, Ph.D.

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Head of Department

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Dean

In Kladno 23. 02. 2016

Declaration

I hereby declare that I have completed this thesis with the topic “Automatic discovery of problematic situations in biosignals of patients with Diabetes” independently and that I have included a full list of used references. I have no objection to the usage of this work in compliance with the act §60 Zákon č.121/2000 Sb. (copyright law).

In Kladno, 18.5.2016

Acknowledgement

I would first like to thank both my thesis supervisor Ing. Jan Mužík, Ph.D and my consultant MUDr. Jan Brož, for their continuous support, valuable advice they provided to me throughout the whole time of working on my thesis, and also for many opportunities they gave me to assert my interests and improve my skills.

I am also very thanksful to my Norwegian colleagues from NSE, especially Meghan Bradway, for her unfailing support and valuable comments on my thesis, and also to Eirik Årsand, Alain Giordanengo, and others, for their support, friendly attitude, and the possibility to cooperate with them on projects that played essential role both in my thesis and upcoming work.

Another special thanks need to be expressed to all the patients-testers, without whose diligence I would not be able to make an adequate testing of my algorithms, and also to Blanka Zálešáková, for her maximal helpfulness during the data collecting at the University Hospital in Motol.

Finally, I must express my very profound gratitude to my parents, friends, and especially to my boyfriend, for providing me continuous support and encouragement throughout my studies and the whole process of researching and writing my thesis.

Thank you.

Anna Holubová

AUTOMATIZOVANÉ VYHLEDÁVÁNÍ PROBLEMATICKÝCH SITUACÍ V BIOLOGICKÝCH SIGNÁLECH PACIENTŮ S DIABETEM

Abstrakt

Diabetes 1. typu je chronické onemocnění, které vyžaduje od pacientů neustálou kontrolu mnoha parametrů majících vliv na jejich glykémii. Rostoucí výskyt uživatelsky nenáročných mobilních zdravotnických zařízení, představují dostupné a intuitivní řešení pro kontrolu pacientů s diabetem. Na druhou stranu lékaři nejsou schopni analyzovat velké soubory dat během krátké konzultace s pacientem, natož je pak adekvátně edukovat.

Cílem této práce bylo navrhnout, testovat a ověřit algoritmy s využitím dat získaných z mobilních technologií pro léčbu a monitoraci diabetu, které by detekovaly nejčastější chyby a problémy, kterým pacienti čelí. Díky tomu budou moci jak pacienti, tak lékaři učinit odpovídající kroky ke změně denního režimu tak, aby se zabránilo dlouhodobým komplikacím. Prediktivní algoritmy a systémy včasného varování mohou navíc eliminovat akutně nebezpečné situace, které by mohly mít okamžitý dopad na zdraví pacienta.

Používané metody zahrnují tři fáze, kterými jsou 1) určení parametrů a výpočtů, které jsou důležité pro tvorbu algoritmů, 2) provedení klinické studie probíhající ve FN Motol, při níž proběhl doposud sběr dat z 92 krátkodobě monitorovaných pacientů a 5 dlouhodobě monitorovaných pacientů a 3) použití algoritmů a stanovení jejich účinnosti v rámci porovnání výsledků s manuálním hodnocením lékařem.

S ohledem na kauzální funkce byly algoritmy pro automatickou klasifikaci glykémií a údajů získaných z monitorů fyzické aktivity navrženy a testovány na 72 datových souborech měřených pacientů. Algoritmy pro detekci a hodnocení glykemických exkurzí byly navrženy a výsledky z 10 pacientů byly porovnány s výsledky manuálního hodnocení lékařem. Statistické vyhodnocení potvrdilo rozdíl mezi klasifikovanými skupinami analyzovaných dat. Algoritmy pro vyhodnocování před a po-jídelních glykémií a inzulino-sacharidového poměru byly navrženy a úspěšně otestovány na 5 pacientech. Algoritmy určené pro intradenní detekci pacientových chyb byly testovány na 4 pacientech a výsledky byly porovnány manuálním hodnocením lékařem. Algoritmy detekovaly situace hlaních jídel, které byly ve spojení s odpovídající glykémií, nzulinovou a sacharidovou dávkou. Výsledky glykemických detekcí byly v souladu s komentáři lékaře vyjma dvou případů hypoglykémie.

Predikční algoritmy zahrnovaly 1) predikci závažné hyperglykémie, jejíž výsledky korelovaly se subjektivným hodnocením četností výskytu těchto situací u 4 pacientů, a 2) predikci hladiny glukózy v krvi, přičemž algoritmus byl testován a hodnocen na 3 pacientech.

Omezení predikčního algoritmu byla způsobena efektem mnoha faktorů, které nebylo možné monitorovat, a proto vyžaduje hlubší zkoumání. Klasifikační vyžadují dlouhodobé záznamy pro získání požadovaných informací. Detekce problematických situací v denních záznamech ukázala značný potenciál pro možnost podpory rozhodovacích procesů lékaře.

Vytvořené algoritmy budou implementovány do webové aplikace Diani pro zjednodužšení analýzy dat jak pro lékaře, tak pro pacienta.

Klíčová slova

Diabetes 1. typu, problematické situace, algoritmy, mobilní technologie

AUTOMATIC DISCOVERY OF PROBLEMATIC SITUATIONS IN BIOSIGNALS OF PATIENTS WITH DIABETES

Abstract

Type 1 Diabetes is a chronic disease requiring patients to constantly control multiple parameters that have an impact on their glycaemia. The increase in use of more user-friendly mobile health tools presents a solution to better self-manage their diabetes. On the other hand, clinicians are not able to analyse patients' large self-gathered datasets within the brief consultations with patients, let alone educate them properly. Therefore, the aim of this work was to design, test, and verify algorithms that would highlight the most frequent accidental problems that patients face within data extracted from the medical and mobile health tools that patients use for monitoring their diabetes. By identifying these problems and errors, both the patients and clinicians can more effectively make steps toward changing patients´ daily regimens in order to prevent long-term complications. In addition, predictive algorithms and early-warning systems can eliminate acutely dangerous situations.

The methods used include three phases: 1) determining parameters and calculations that are relevant to include in the algorithms, 2) executing clinical trial being run at the University Hospital in Motol, where data from 88 short-term monitored patients and 5 long-term monitored patients have been successfully collected, and 3) applying the algorithms and determining their efficacy by comparing their evaluation to those made by their clinician.

With respect to causal function, algorithms for automatic classification of blood glucose measurement and data extracted from physical activity monitor were designed and tested on 72 datasets of measured patients. Algorithms detecting both inter-day and intra-day glycaemic excursions were designed. Results from 10 patients were compared with manually evaluated datasets made by a clinician and statistical evaluation confirmed a difference between classified groups of analysed data. Algorithms evaluating mealtime glycaemia and insulin-to-carbs ratios were designed and successfully tested on 5 patients. The algorithms designed for intra-day mealtime detection were tested on 4 patients and the results were compared with datasets manually evaluated by clinician. The algorithms detected the main mealtime situations that were connected to corresponding glycaemia, carbs and insulin doses. The algorithm was in accordance with the clinician´s comments on glycaemia but two cases of missed hypoglycaemia.

Prediction algorithms involved prediction of 1) severe hyperglycaemia, of which results from 4 patients correlated with their own subjective evaluation of frequency of hyperglycaemia occurrence, and 2) blood glucose prediction algorithm that was tested and evaluated on 3 patients.

Limitations of the blood glucose prediction were caused by effects of many factors that were not possible to monitor. Thus, further investigation for its proper use is needed. The classification algorithms require long-time datasets in order to determine desired information. Detection of intraday situations showed significant potential for its use as a future decision-support aid.

The algorithms will be implemented in the Diani web application, in order to simplify data analyses for both clinicians and patients.

Key words

Type 1 Diabetes, problematic situations, algorithm, mobile technology

Contents

1. Introduction

Diabetes mellitus is a chronic disease of which incidence increases with time. While its prevalence is more than 400 million adults worldwide, as declared by the WHO [1], the last statistics for the Czech Republic account for more than 400 thousands incidences [2]. Although, Type 1 diabetes represents only 5-10% of the total diabetic population (approx. 8% in the Czech Republic), incidences are still increasing and related therapies bring many obstacles to patients´ daily lives, often accompanied by both acute and chronic complications.

Nowadays, mobile technologies and IT solutions open even more possibilities to help patients with this disease. Insulin delivery systems and blood glucose meters are constantly improved and enable not only the treatment of patients but also the recording, tracking, and analysis of many parameters that need to be controlled for proper self-management.

However, the consequences of dealing with large datasets and the short consultation times in which clinicians have to spend with their patients bring other complications to the scene. It can be; 1) the impossibility of clinicians to evaluate such amount of datasets, 2) inability to find substantial information in there, and/or 3) insufficient education of patients in general.

Therefore, there is a necessity to find solutions for how to efficiently use existing mobile technology for monitoring and extracting data on the most important parameters of proper diabetes therapy. Such information from gathered data can sufficiently support clinicians in a more efficient decision making process. Moreover, nearly real-time tele-monitoring of patients' detailed and daily behavioural and self-management information can allow patients and clinicians to identify problematic situations that would otherwise be unnoticeable.

This thesis aims to find, design and apply the most relevant methods and algorithms that could be used for automatic evaluation of big datasets composed of parameters measured on Type 1 diabetic patients.

First, it was necessary to understand the detailed principles, factors and parameters of the disease, focusing on how they affect an individual's blood glucose level. The most important facts are included in chapter 2. The following chapter looks into state-of-the-art software applications that, in addition to the individual devices enabling patients to track different diabetes-related parameters, constitute even more comprehensive self-management options. These tools help both patients and clinicians to see the relations between each parameter in one place, where all the information can be collected, stored, and available, thereby providing them more possibilities for further data analysis. However, although many of such applications represent a very sophisticated tool for supporting either patients' or clinicians' decision-making, several remaining drawbacks and limitations are highlighted in this work.

In the chapter Methods, I was able to both follow and execute clinical studies and meeting proceedings that focused upon patients´ problematic situations including visually

representations of the data measured on patients. While collecting data measured on real patients, I was continuously analysing them both qualitatively, by visualizing trends and impacts on individuals, and quantitatively, using calculations on the data itself.

The results of these applied stages helped me to define certain problematic situations, which could then be extracted by my own developed algorithms. Studying patient-specific behaviour helped me, in addition, to define such conditions that could increase the chance not only to detect the right situations but also to eliminate the number of missed or invalid ones.

Chapter 5 describes the design and testing periods, which deal with building algorithms and applying methods selected from my investigations on the collected data.

Following the testing phase are the results and data analysis, where I summarized the benefits of my work compared to the current similar systems.

In the phase of the discussion I highlighted the complications I had to deal with when applying my methods, and I also explained both the benefits and limitations of my solutions and made a motion for their potential improvements.

The conclusion details my understanding of the previously mentioned issues that were addressed during my work, as well as the work itself, and suggestions for improvements in the future.

2. Literature review

2.1. Type 1 diabetes mellitus

Type 1 Diabetes mellitus (T1D) is a complex and chronic disease manifested mainly by a disorder of carbohydrate metabolism, and the resulting concentration of blood glucose, caused by complete lack of insulin secretion. Since insulin provides transport of glucose to the cells of some organs, such as muscles and fatty tissue, its deficiency or malfunction leads quickly to hyperglycaemia, i.e. high blood glucose (BG) levels.

The disease is caused by destruction of Beta cells of Langerhans islet in pancreas by one's own immune system. When the disease is fully developed the pancreas no longer able to produce insulin. Therefore, patients with T1D are forced to apply insulin doses subcutaneously using either multiple daily injections (i.e. insulin pens) or continuous subcutaneous insulin infusion (CSII), i.e. insulin pump regimen. [3] Because this disease usually manifests in early childhood or adolescent period, it is known as "juvenile diabetes" [4]. Although, its origin is still not fully understood, both genes and environmental factors are thought to be the main actors. [3]

Untreated or poorly-controlled diabetes can lead to acute complications, such as ketoacidosis, or long-term complications that affects both microvascular and macrovascular system. [3,5]

Microvascular complications include problems with eyes, kidneys, and nerves, i.e. most commonly diabetic retinopathy, nephropathy, and neuropathy. Macrovascular complications affects the cardiovascular, cerebrovascular, and peripheral vascular systems. [3,5]

Besides health complications, lower quality of life, and necessity of lifelong medical assistance, the disease also has a large economic impact on the whole society. [5]

The general goal and requirement for effective treatment and reduction of risk of both acute and chronic complications is keeping BG levels as close the normal range as possible. [6]

2.2. Problematic situations in T1D patients

Keeping BG within target range is not an easy task for T1D patients. It requires all-day self-control not only regarding adhering to treatment recommendations but also in situations that are difficult to predict. Patients are forced to think of each situation that can have an impact on their BG level during a day (e.g. mealtime situations, exercise or any long-lasting trip, stressful situations, illness, or even sleeping, and many others) and check their BG frequently [7]. They are required to treat themselves every moment of their life – estimating medications, operating several medical devices, having a basic mathematical background, and understanding food composition - despite the fact that they may not be either doctors, technicians, mathematicians or nutrition specialists. Moreover, such skills are required for any age bracket.

It is, therefore, obvious that not all patients, or better to say, very few patients are capable of self-managing their diabetes with respect to all of these requirements described above. In fact, human error is a major barrier to proper self-management. Errors can include: poor estimation and bad timing of insulin doses, errors in carbohydrate counting, missed doses of either insulin or carbohydrates, poor rotation of sites for insulin injection, alcohol consumption, unexpected or incorrectly compensated exercise, poor blood glucose monitoring, and many others [8,9,10]. In addition, there are numerous problematic situations that patients cannot predict or react to in time. Some of them can be caused by related illnesses, eating disorders, hypoglycaemia unawareness, stress, menstruation, insulin resistance, malfunction of insulin, temperature, etc. [8,11].

While new technology substantially eases insulin delivery and BG monitoring [9], these innovations bring additional complications. These can include, for instance, obstruction in the insulin set or bent cannula (when using insulin pump), broken needle, low battery or malfunction of a device, low accuracy of BG measuring systems, and in addition, human error related to inappropriate use.

All of these problems mentioned above can have a negative impact on current BG level, leading either to acute complications (sometimes even to death) or to increase their risk of long-term complications. Therefore, searching for particular problems retrospectively in patients' personally-gathered data can highlight the concrete and most frequent accidental problems or errors that patients face. Knowing this, both the patients and clinicians can make adequate steps toward changing patients´ daily regimens in order to prevent long-term complications. In addition, predictive algorithms and early-warning systems, based on certain input parameters and models, can eliminate acutely dangerous situations that could have an immediate impact on a patient´s health. The following section describes the most important factors responsible for changes in BG level and what it means for patients with respect to their therapy.

2.3. Factors affecting blood glucose level

In diabetes, numerous factors are affecting a patient's blood glucose level. While many of them cause the glucose to rise, there are several others that have an opposite effect. However, no one should play more dominant role against the other, but both should be in a balance to keep the BG in a target range. Due to the fact that patients with diabetes have a lack of regulation of their BG provided by their body, they are responsible to balance and regulate effects of all the factors. The following two sections introduce particular factors and explains their action and role with respect to BG changes.

Internal biological factors

- Insulin and other hormones

External behavioural factors

- Carbs
- Physical activity
- Alcohol

Technological and environmental factors

- Temperature
- Obstruction in the insulin delivery system
- Device malfunction

2.3.1. Biological and behavioural factors

The following situations are responsible for increasing BG levels [12]:

- Too much carbohydrates consumed
- Lack of insulin in the body or not enough insulin taken
- Physical inactivity
- Effect of insulin antagonists, such as hormones, caused by the presence of:
    - illness
    - long-term pain
    - stress
    - menstruation
- Dehydration
- Side effects of some medications
- Poor timing of insulin dose with respect to actual BG level and action time of the insulin

Apart from the factors that cause BG to rise, there are several situations that also work to lower BG levels, the most important of which are [12]:

- Not enough carbohydrates consumed
- Too much insulin taken
- Physical activity
- Effect of alcohol elimination
- Side effects of some medications
- Poor timing of insulin dose with respect to actual BG level and action time of insulin

The aims of the next sections are to further explain the principle function(s) of the most impactful factors mentioned above. These sections will also point out why it is important to track not only glucose values but also many other parameters to be aware of dangerous situations as well as to delay or prevent diabetes complications.

Carbohydrate action

As previously described, carbohydrates (carbs) cause blood glucose levels to rise. If the action of insulin is not proportional to the amount of carbohydrates eaten, the BG level increases and is stored in the bloodstream.

However, regarding the effect of carbs on diabetic patients, it is very important to know the type of carbs and the other nutrients that are contained within a given food, the portion size, and when it is eaten with respect to the type of insulin that is administered (see figure 1) and when it is administered. Simple carbs will raise BG levels much faster than complex ones. The same is true for liquid carbs compared to solid carbs. [13]

In order to assess how fast and how much a particular type of food will raise BG after it is eaten, the glycemic index has been established. Its value is derived from the glucose response to carbohydrates of the same amount from different foods. The final value represents the area under the curve of the blood glucose response to different foods. [14]

The frequent occurrence of carbohydrate action on actual BG level represents post-meal spikes that have, however, substantially negative impact on patient´s health. This fact describes the Guideline for management of post-meal glucose [15], published by International Diabetes Association in 2007. Its purpose was to present evidence-based relationship between frequent high values of post-meal blood glucose (PMBG) and development of diabetic complications, based on review of selected reports evaluated by the members of the Guideline Development Committee, and ranked by certain evidence-grading criteria.

Following complications have been described as being associated with post-meal high blood glucose [15]:

- Increased risk of retinopathy
- Increased carotid intima-media thickness
- Oxidative stress, inflammation and endothelial dysfunction
- Decreased myocardial blood volume and myocardial blood flow
- Increased risk of cancer
- Impaired cognitive function in elderly people with type 2 diabetes

It is, therefore, obvious that preventing such glycemic excursions should be on the list of requirements for a good blood glucose management in diabetes.

Insulin action

Insulin is a hormone produced by Beta cells in the pancreas. Its role, when functioning normally, is to help glucose to get into cells so that it can be used to make energy [16]. Therefore, if insulin is released from the pancreas, the corresponding amount of blood glucose is transferred to the cells, and thus, the level of blood glucose is decreasing. If there is too much

insulin in the body, hypoglycaemia becomes a real risk, meaning that the blood glucose level becomes too low to sufficiently support the body's organs, primarily the brain. If no sugar is delivered in such a situation, hypoglycaemia can lead to a coma, and in worst case, death.

However, if there is no insulin to move glucose into the cells, the glucose builds up in the blood. Furthermore, if the kidney's threshold to filter glucose from the blood is reached, the body's only other option is to expel the glucose in the urine. However, since the cells are suffering glucose deprivation and thus are unable to or gain energy, they must find another source, i.e. fat. Unfortunately, when breaking down fatty tissue, dangerous waste products called ketones are created, causing ketoacidosis. This life threatening situation can even lead to death if the body does not get rid of these acidic substances promptly. [16-18]

Another role of insulin is to stimulate the liver to store glucose in the form of glycogen. If the liver is fully saturated by glycogen, insulin stimulates the production of fatty acids. Insulin also then stimulates the accumulation of these fatty acids in fatty tissue [18]. Therefore, higher doses of insulin can cause weight gain. It thus becomes crucial for an individual and their health care team to track and manage the patient's weight.

Insulin therapy involves many different types of insulin for patients with diabetes. The most important features that distinguish one from another type of insulin is the action time. Figure 1 shows different types of insulin and their corresponding action time. By being able to use many different types of insulin, a patient is able to set a personalized regiment of rapid- or long-acting insulin, for example, according to his needs, life style, etc. One of the most common needs and challenges is customizing the timing and amount of carbohydrate consumption to these different insulin types (see Figure 1) in order to achieve BG levels in the normal range. [17]

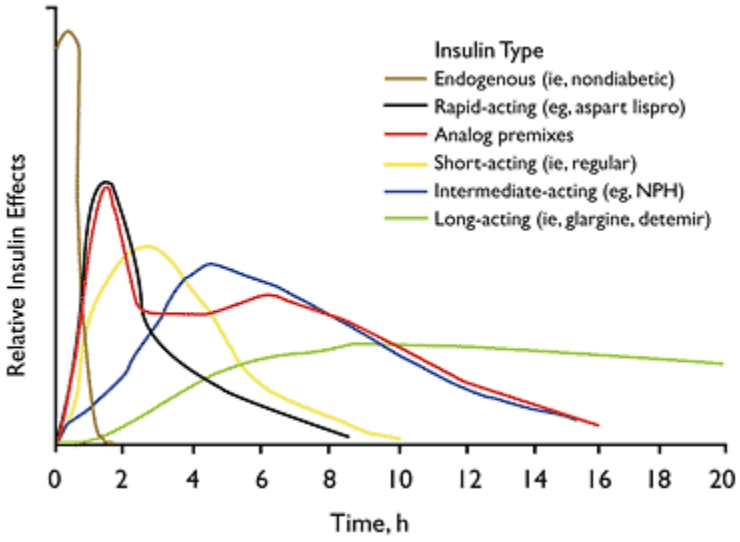

Figure 1: Action times of different types of insulin [19]

Other hormones action

In addition to insulin, there are other hormones responsible for BG fluctuations. In particular, “stress hormones”, such as glucagon, adrenalin, or growth hormone, act as antagonists to insulin, meaning they make BG rise. [20]

Glucagon is normally released by the liver between meals and during the night, in other words, whenever a body does not have an immediate source of glucose from meals. However, in the case of diabetes, normal production of glucagon is disrupted, and as a results, glucagon levels are elevated during meals [16] and when high blood glucose is present [21].

Furthermore, during stressful or emotional situations, glucagon and adrenalin rise, causing even more glucose to be released from the liver. In addition, cortisol and growth hormone are released from suprarenal gland and hypophysis to lower insulin sensitivity of bodily tissues. Therefore, diabetic patients commonly have significant challenges controlling their BG level during stress. [20]

Alcohol action

One of the most dangerous situations for people with diabetes is alcohol consumption, due to the increased risk of hypoglycaemia. The problem is not only that the symptoms of hypoglycaemia and inebriation intensify each other, but also that the body wants to eliminate the alcohol, causing inhibition of the liver’s gluconeogenesis, i.e. glucagon formation. As a result, the liver does not build new reserves of glycogen, which can cause glucose deficiency afterwards and a fast and dangerous drop in blood glucose levels. [22]

Physical activity

Physical activity (PA) plays a crucial role amongst people with diabetes, not only with respect to body weight regulation but also with respect to the regulation of blood glucose levels. The mechanism of glucose utility during physical activity is very complex and varies greatly between people with and without diabetes. [23,24]

During the first 20 minutes of aerobic activity the main source of energy is represented by muscular glycogen. The physiological response to this situation is to lower insulin production via catecholamine secretion (its production is caused by stress situations), and to increase adrenalin and glucagon production. However, in the case of T1D, the body is unable to secrete this insulin and therefore this process is done with administered insulin. During such activity the body’s sensitivity to insulin is rising, meaning that the active insulin in the body from previous insulin doses causes cells to take-up and use glucose, while also replenishing muscular glycogen reserves with glucose from the bloodstream. This is also possible because the increased sensitivity and function of insulin inhibits the increase of the counter-regulatory hormones, glucagon and adrenalin. The synthesis of new glycogen reserves after PA makes the

BG level fall, which can take several hours, depending on the intensity of PA, its duration, and physical training, or fitness, of a given person. [25]

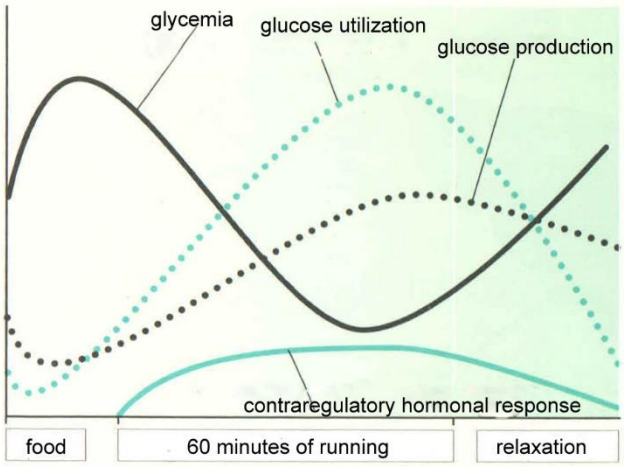

Figure 2: Glucose and hormonal response on aerobic sport. Adapted from [23]

The physiology of anaerobic sports can, on the contrary, lead to hyperglycaemia in T1D and even in people without diabetes. When the lactic threshold is reached, hepatic glucose production is supported by catecholamines, and thus, the BG level is rising. For healthy people, the insulin secretion is increased to regulate this glucose fluctuation. However, for T1D this response does not work, so the glucose level is not pushed down. Therefore, the hyperglycaemia can occur more easily. In turn, couple of hours after an anaerobic activity the glycogen is replenished again, similarly to the aerobic situation, and then the hypoglycaemia can appear. [23,24,26]

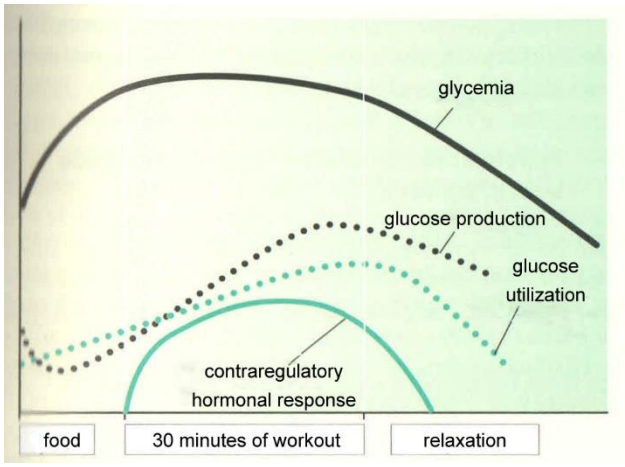

Figure 3: Glucose and hormonal response on anaerobic sport. Adapted from [23].

2.3.2. Technical and physical factors

Not only do the biological factors and dosages of medications have significant impacts on a patient´s blood glucose, but also the factors related to environmental conditions, technical problems with certain devices, or malfunction of both devices and insulin.

With respect to the environmental factors, the most common problem is extreme temperature and its effect on insulin action. Both too high or too low temperature can lead to insulin degradation resulting in constantly high BG readings, which are often not possible to compensate for even when the insulin doses are increased. Therefore, proper storage of insulin and its regular refilling are important to beware of such situations, which becomes increasingly important when considering the use of certain devices to administer the insulin.

Another complication, which causes hyperglycaemia, is if air is presented in the cartridge. It can either be due to a rapid change in temperature or incorrect filling of the cartridge (in case of insulin pumps) that creates these air bubbles. The problem is not the effect of the air itself, but the fact that the volume of insulin dose applied to the body would instead be replaced by the volume of air. Prevention of this negative effect on insulin action includes 1) ensuring similar temperature of the liquid and surroundings to not to even let them emerge, and 2) keeping them on the side of the piston instead of the nozzle (i.e. let the air goes up – see Figure 4A) or squirt them out of the syringe or infusion set.

The occurrence of high blood glucose can be also connected to obstruction within the infusion set of an insulin pump, i.e. the cannula can be bent or blocked by body substances (see Figure 4B). Although, most insulin pumps include a function that generates an alarm when the insulin delivery is stopped by an obstruction (measuring pressure changes in a tube), the success rate is very poor and the response is often too delayed. Prevention of its occurrence is mainly frequent change of the infusion set site and frequent BG measurement during the first hours of a new cannula insertion.

Figure 4: Example of air bubble presented in the infusion set (A) and bent and clogged part of cannula (B).

Last but not least is the potential malfunction of an insulin pen or insulin pump, which can lead to acute hyperglycaemia due to either improper delivery of insulin or its overall discontinuation. The all-in-all lack of insulin distribution that causes the acute hyperglycaemia can result in diabetic ketoacidosis, which can further culminate in a life-threatening situation.

2.4. Nowadays technology used for diabetes self-management

To be able to deliver proper doses of insulin, monitor all the necessary parameters, and beware of less noticeable dangerous situations, several technical solutions have been made for diabetes self-management during the last couple of decades. Urine glucose tests were replaced by glucometers and continuous glucose monitoring systems (CGMs), and painful and large syringes were replaced by insulin pens and insulin pumps [3]. Continuous innovations in diabetes technology results in improvement of these tools, which have positive impacts on self-management of the disease. On the other hand, at the expense of such rapid development, some challenges also come to the forefront. We could mention the lack of interoperability of different devices due to a lack of standards, or the challenges facing big data complications and questions related to data analysis, or even the acceptance of wearable devices by patients and ubiquitous monitoring [27,28]. Nevertheless, both the innovation and increasingly aging population require new approaches to treating not only diabetes but other chronic diseases as well.

Therefore, mobile medical devices and tele-monitoring systems start to move healthcare from the doctor-centric to the patient-centric focus. The mHealth trend is based on proactively monitoring the patients rather than to react on the consequences. Moreover, this trend attempts to empower patients to monitor and maintain their own health. [29] In fact, patients with

diabetes spend more time as their own doctors, in a sense, than consulting with medical professionals. While they lack the detailed medical knowledge about their body and treatment methods they should follow, they do in fact operate multiple technical devices and other tools on a daily basis that help them sufficiently managing their disease, which requires a sort of proper education itself.

The most common systems used for self-management in diabetes are those enabling insulin delivery, glucose monitoring, and also systems for monitoring and tracking other parameters, such as carbohydrates, insulin dosages or intensity of physical activity. The next sections provide an overview of current technology used in diabetes with respect to particular parameters tracked.

2.4.1. Glucose monitoring systems

A patient's blood glucose (BG) level is the most important parameter they should frequently track to be able to hold BG values within normal range, and if possible, without any significant excursions [3,4]. BG monitoring is also required for proper diagnosis of the type of diabetes, better assessment and prediction of the risk of tissue complications, and also for measuring the effects of added insulin, carbs, physical activity, illness, stress, etc. [3]. Two main glucose monitoring systems are available for self-management of diabetes: glucometers and CGMS.

Self-monitoring of blood glucose (SMBG)

Glucometers, used for SMBG, are absolutely indispensable portable devices for self-checking of BG by patients themselves, at home. Most of the current glucometers are based on an

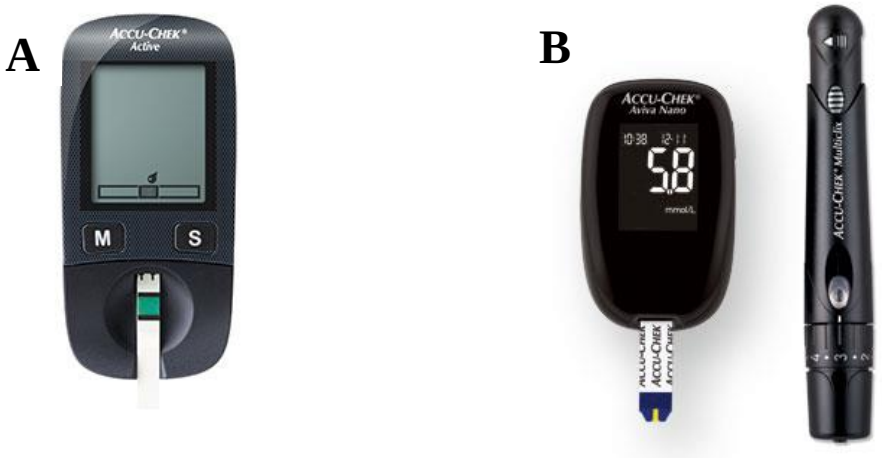

Figure 5: Blood glucose meter based on photometric (A) [30] and electrochemical (B) [31] principle.

electrochemical reaction of capillary blood samples taken most commonly from a finger, or alternative some other specific places on a body, and applied to reagent strips that are then inserted into the machine (Figure 5B) [3] (some devices also works based upon a photometric principle – see Figure 5A [32]). The measurement takes only a few seconds before the value is displayed. Therefore, it is both a user-friendly and time-saving process for the patient.

Today's glucometers also have memory, so the patient can go back in his own history and see the progress of his glycemic values. The physician can also go through the previous measurements to make a summary of how the patient manages his disease.

Medical mobile apps brought a big evolution for the possibility of data displaying and storage. Some newer meters also have the possibility of automatically transferring the data from glucometer to some compatible mobile apps (Figure 6A) [33], or moreover, the mobile app can serve as a display for the device, which is attached to the phone during the measurement (Figure 6B) [34].

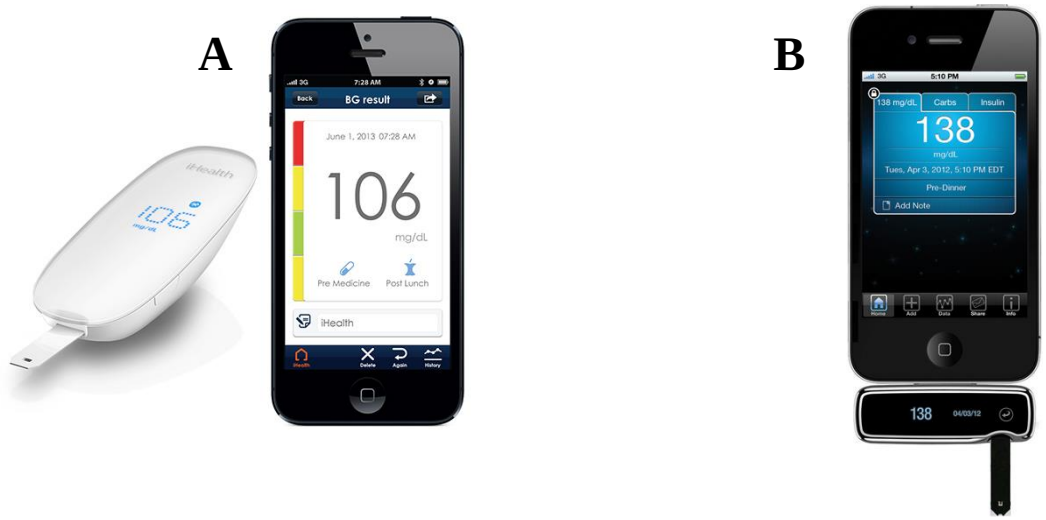

Figure 6: Data transfer of BG values to an app via Bluetooth (A) [33] and data transfer to a phone directly from a connected device (B) [34].

There are also some software products (e.g. Diasend, Accu-chek 360°, OneTouch Dibetes Management Software, iFORA app, etc.) that enable the data to be transferred from given devices to a computer to display the values in a time line, and also perform some statistical analysis.

The most significant disadvantage of the SMBG method (apart from the necessity of performing several BG tests per day, which requires often painful finger pricks) is the fact that the values displayed on a screen only give them static information about actual BG levels, and give no information about its trend. For example, if a patient´s measured value shows 14 mmol/L, the patient does not know if the glucose is stable, raising or falling down. If he decides to apply a correction bolus to push the glucose level down, although in actual fact the glucose is e.g. falling down, the effect of the additional dose of insulin can lead to severe hypoglycaemia. This is, fortunately, not the case when using CGMs.

Continuous glucose monitoring (CGM)

Continuous glucose monitoring systems (CGMs) are based on measuring glucose levels in interstitial fluid under the skin. The device typically consists of a sensor, a transmitter, and a receiver. The sensor is usually a needle-based amperometric enzyme electrode inserted under the skin that monitors glucose oxidation. [3]

The transmitter is attached to the sensor with metal contacts and wirelessly transmits measured data to the receiver, which displays and stores measured values every 1-5 minutes [3]. The whole system is shown on Figure 7. Some insulin pumps also enable communication with given sensors, in which case the pump also works as a receiver.

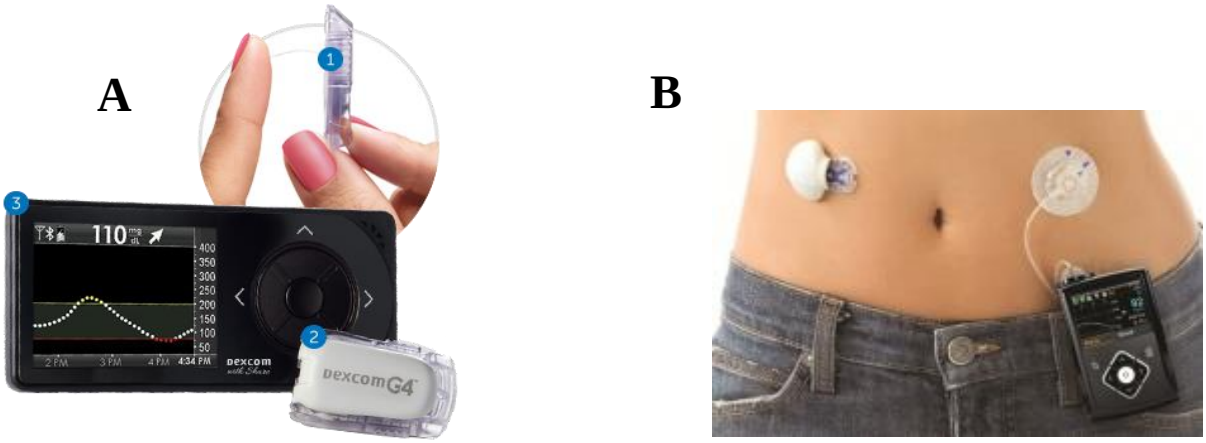

Figure 7: Dexcom´s CGMS (A1 - sensor, A2 - transmitter, A3 - receiver) [*35*] and Medtronic´s CGMS (B) [*36*]

Unlike the SMBG system, the CGM enables the wearer to track BG-value trends. Therefore, one can very easily predict upcoming lows or highs, and see how the glucose fluctuates before and after meals, in a specific phase of a day, during any physical activity or stressful situation, when having an illness, etc.

As is the case for glucometers, CGMs enable data transfer to a computer to see all the data in different representations, statistical evaluation, etc.

There is also the possibility to share a patient's real-time data with their doctor or family members. The Dexcom company recently introduced a new device with Bluetooth technology that enables the wearer to share data with a compatible mobile app [37]

Figure 8: Dexcom G4 Platinum with Share™ [37].

Several studies have shown that using SMBG in connection with Real-Time CGM lowers HbA1c by a significant percentage for most diabetic patients and helps them to better self-manage their disease, compared to SBMG alone [38].

2.4.2. Insulin delivery systems

Other options for diabetes therapy are insulin delivery systems. Nowadays, patients can decide whether to keep on multiple daily injections regimen (MDI) or continuous subcutaneous insulin infusion regimen (CSII). The first type of regimen is enabled by insulin pens, whereas the second one is enabled by insulin pumps. [3,39]

Insulin pens require the patient to manually adjust each insulin dose and insert it under the skin. Some newer pens also have the ability to record the time of their dose administration (Figure 9A) [40]. In addition, some can even communicate via Bluetooth with smartphone and transfer the data to a special mobile app (Figure 9B) [41].

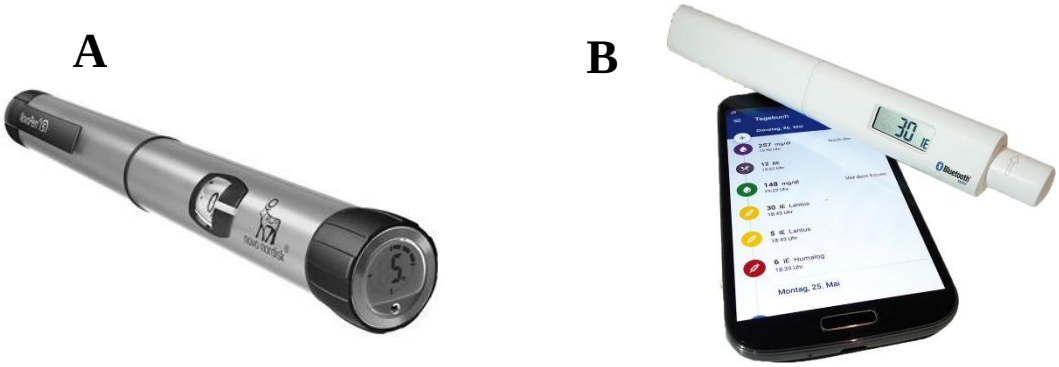

Figure 9: Insulin pen with memory (A) [*40*] and insulin pen with Bluetooth communication (B) [*41*].

Insulin pumps are more sophisticated devices that enable patients to set more precise insulin doses and individual adjustments of basal doses for each hour of the day. There is no need for multiple daily injections because the infusion set is meant to function for 3 days. In addition, there are several functions which help patients with their decision making and proper treatment, such as a bolus calculator, information about bolus-on-board, history of insulin doses, and others. [42]

Some companies also provide a communication between certain CGM sensor and the pump [36] or remote control of the device via a data manager [43]. More recently, sharing data via mobile phone is also possible for some systems.

Figure 10: Roche´s insulin pump with a data manager for remote control (A) [*43*] and Medtronic´s insulin pump with CGMS sharing data with a smartphone (B) [*44*].

The same as for the previous devices, all pumps provide a special software for data transfer and visualisation in the form of graphs, tables with all historical data, statistical evaluation, etc.

2.4.3. Physical activity monitors

It has been already said that physical activity (PA) represents a very important part of patient´s life, not only because of its positive effect on health in general, but also because of the effect it has on insulin sensitivity and blood glucose value.

There are several possibilities available to patients allowing them to track their PA.

One of them can be commercially available activity trackers (such as Fitbit, Garmin, Polar, etc.), that can measure not only step counts, total daily distance or calories burned, but also maximal elevation difference, sleep efficiency, heart rate, and other parameters.

Figure 11: Activity trackers with different functions - Fitbit Surge (A) [45], Polar Loop (B) [46] and Garmin Vivofit (C) [47].

Again, these devices communicate via Bluetooth which enable measured data to be synchronized with a mobile or desktop app, which then displays the data and performs additional analysis.

Figure 12: Dashboard of Fitbit desktop and mobile app. [45].

Patients can also compete with other users or friends, thereby increasing their motivation to be active.

Among insulin pumps currently distributed in Europe or the US, the Cellnovo insulin pump (Figure 13) is probably the only that already has a motion sensor integrated into the device to track a patient´s PA.

Figure 13: Cellnovo insulin pump with activity tracking [48].

With the arrival of MEMS (Micro-Electro-Mechanical Systems) and the ability of smartphones to use them, more and more mobile applications can track a user´s motion. [29,49,50]

While these devices have the motion capturing function as an additional part of for what their initial purpose is, there are mobile devices of which primary function is to track physical activity, as describes the next section.

3. State-of-the-art diabetes software management tools- connecting patients to all collected data

Besides the individual devices that enable patients to track different diabetes-related parameters, there are also various software applications that constitute even more comprehensive self-management options.

Some of the previous sections mention applications in relation to a specific device, but for a patient to be able to see all the relations between each parameter they need to have in one place where all the information can be collected, stored, and available for both patients and physicians. In other words, a patient has benefit from his historical and most recent measured values and registrations by seeing how given situation influence his blood glucose fluctuations, learn from it, and react on possible problems in time.

On the other hand, these comprehensive records of a patient's daily habits can help a physician with decision-making when adjusting a patient´s regimen, as well as well-targeted education, better prediction of health-related complications, etc.

Traditionally, patients are recommended to keep a record of their BG values, carbs and insulin doses and bring these records to each visit of their physician. Therefore, many types of mobile diabetes diaries have been created to make it easier for the patients to adhere to these instructions.

These mobile diaries can be either desktop applications or mobile phone applications that allow users to track their BG values, insulin and carb doses, and other parameters.

3.1. Desktop applications

Nowadays, there are various desktop apps that a patient can choose from based on the preferences of the data interpretation or the device that certain apps support.

The most basic desktop diabetes diary apps usually have some form of a table where each parameter is manually registered. That is the case of the following app on Figure 14.

Datum	Inzulín (U)					Glykémie (mmol/l)								Jídlo (~12 g sach.)						Celkem			
	Bolus				Bazál	v noci	snídaně		oběd		1. večeře		před spaním	v noci	snídaně	svačina	oběd	svačina	1. večeře	2. večeře	Inzulín	jídlo	bolus/sach.	ins./kg
	snídaně	oběd	Večeře	Přídavek			před	po	před	po	před	po												
25.8.13	5,5	4	5	0,5[14:00]	00-06 0.5 06-22 1.0 22-00 0.5		9,2	6,9	4	7,5	6,3	4,9			3,5	0	3	0	3,5	1	35	11	1,36	
26.8.13	5	5	3,5	0,5[13:30]	00-06 0.5 06-22 1.0 22-00 0.5		6,2	6,9	7,2	7,4	3,8	4,9			3,5	1	3	1	3,5	1	34	13	1,08	
27.8.13	5	5	5	0,5[15:00]	00-06 0.5 06-22 1.0 22-00 0.5	3,2			4,9		7,8				3,5		3,5	0,5	3,5		35,5	11	1,41	
28.8.13	5	5	5	0,5[10:00]	00-06 0.5 06-22 1.0 22-00 0.5		6,6	3,3	9,9		6,2	5,1			3	1,5	3,5	0,5	3,5		35,5	12	1,29	
29.8.13	5	5	5		00-06 0.5 06-22 1.0 22-00 0.5		3,4		5,6		8,1	5			4		3,5		3,5		35	11	1,36	
30.8.13	5	5	5		00-06 0.5 06-22 1.0 22-00 0.5		9,8		9,7	8,4	4,7				3,5		3,5		4		35	11	1,36	
31.8.13	5,5	4,5	4,5		00-06 0.5 06-22 1.0 22-00 0.5		13,4	12	2,9	7,2	3,9	2,8	8,8		3,5		3,5		3,5		34,5	10,5	1,38	

Figure 14: Example of a manually completed diabetes diary that is printable from a desktop application Diabetes Diary 1.0.

Better solutions include glucometers, which enable the patient to automatically record blood glucose values that can then be imported into an app for which the given glucometer is compatible. In connection with an insulin pump, information about insulin doses applied by the pump are stored in a device and can be imported into an app as well. However, carb doses are usually registered manually into a glucometer, a pump or its corresponding data manager (see Figure 15).

SOUHRN

Datum	Čas	Glykémie mmol/L	(g)	Inzulín (U) 1	2	3			Poznámky
Pátek	06.03.2015	00:02							
		00:19					1		
		07:01	5,9				1		
		07:02		4,5			1		
		07:16		0,5			1		
		08:10		0,5			1		
		11:02	3,6 H				1		
		12:34		3,0			1		
		15:47		2,0			1		
		19:12	6,1				1		
		19:15		5,0			1		
		19:33		1,0			1		
		22:57		0,4			1		
		23:26							
		23:38					1		
Sobota	07.03.2015	07:33	5,8				1		
		07:34							
		07:34					1		
		07:34		4,0			1		
		07:45		1,0			1		
		08:12		0,5			1		
		10:33		0,5			1		
		12:12	6,7				1		

Figure 15: Example of the SmartPix application, Roche, and the output summary of data imported from a pump.

As we can see on both Figure 14 and Figure 15, the most important parameter is glycemic value, which is clearly shown with a colour corresponding with a level of glycaemia (i.e. normoglycaemia, hypoglycaemia, and hyperglycaemia).

Similarly, the CGMS can save all historical BG readings for several weeks (depending on the particular device and its memory capacity) and one can also manually register additional information about SMBG, meal intake, insulin doses, and PA. Finally, the data can be transferred from the device to a desktop app, where all the information is displayed in a form similar to the previous cases. However, the value added here is the continuous record of BG readings and its graphical interpretation.

Graphs can be either a simple value-by-value graph of BG readings plotted over a period of time or day-long graphs overlapping each other. Both methods have their own meaning. The first one allows an individual to study particular situations in given day in detail. Additional information such as insulin- and carb-dosing and PA, which are manually registered in the device, can also be displayed under the graph (see Figure 16). The second method of interpretation gives an overview of all-day behaviour of a patient. The ratio of all the values that are out of range vs. those within the normal range is clearly visible (see Figure 17). Very often, there is also a significant pattern of a particular part of each day. For example, every day a patient can have the same curve of high readings around meal-times, which might be caused, for example, by wrong insulin-to-carbs ratio of his regimen or by bad timing of an insulin application.

Finally, if a certain insulin pump and CGM are compatible, and the records can be assessed within the same application, all the readings from both the CGM and the pump can contribute to a graphical representation of day-by-day records (see Figure 18).

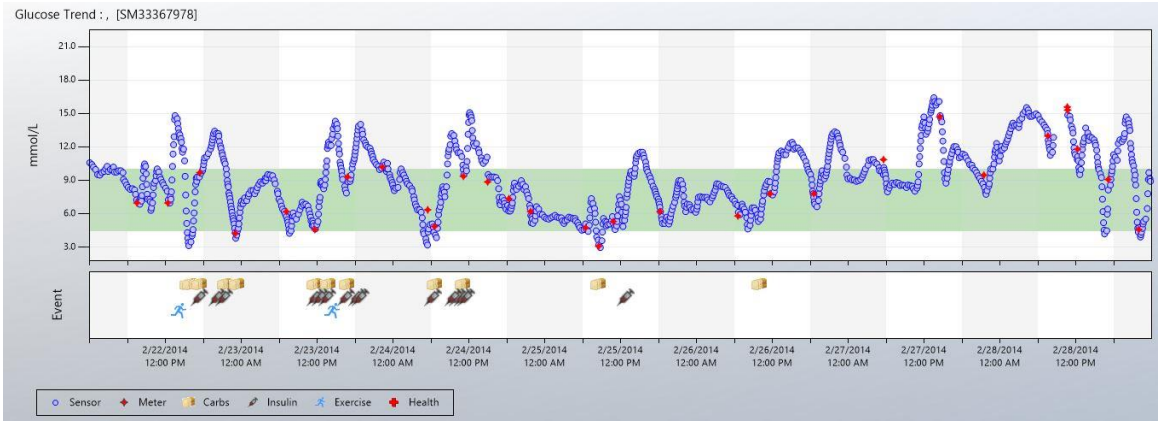

Figure 16: Example of CGM data interpretation from the Dexcom Studio (Dexcom Inc.) desktop application.

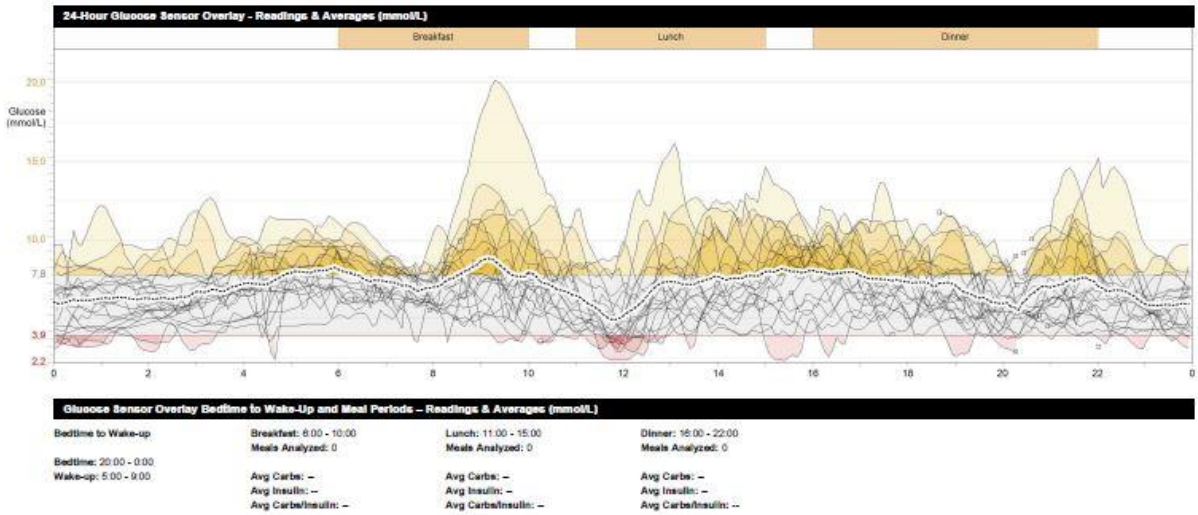

Figure 17: Example of CGM data interpretation from the Carelink Pro desktop application, Medtronic.

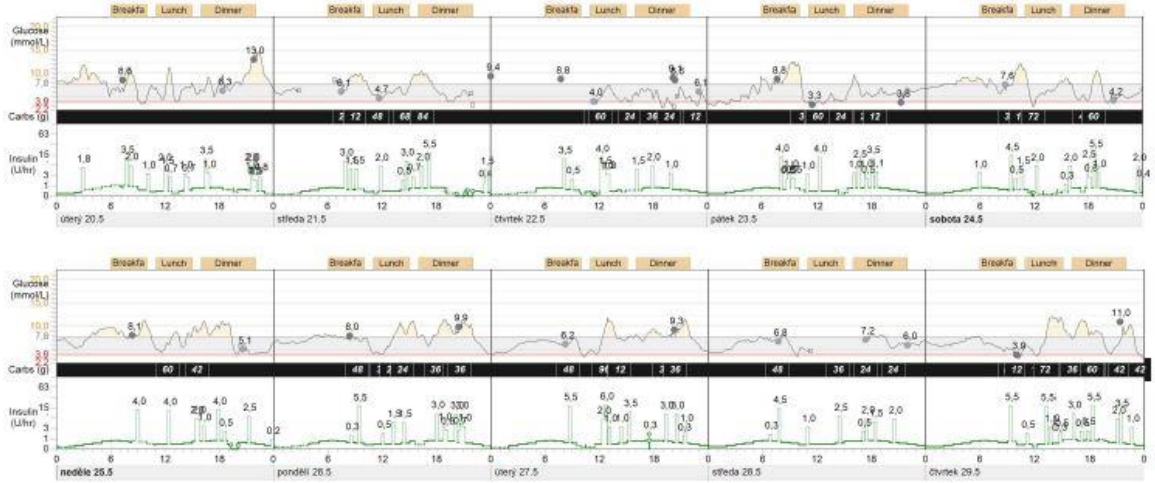

Figure 18: Interpretation of CGM and data together with other patient´s registrations extracted from an insulin pump, Medtronic.

When dealing with data from multiple devices, all of which need to be visualized, analysed, or shared, if possible using only one desktop application, one must consider the concept of compatibility of these data, of which there are several attempts to comply with certain requirements. One of the developers of such a system is Diasend, which enables information from several glucose meters, insulin pumps, CGM systems and mobile apps to be uploaded (Figure 19) [51].

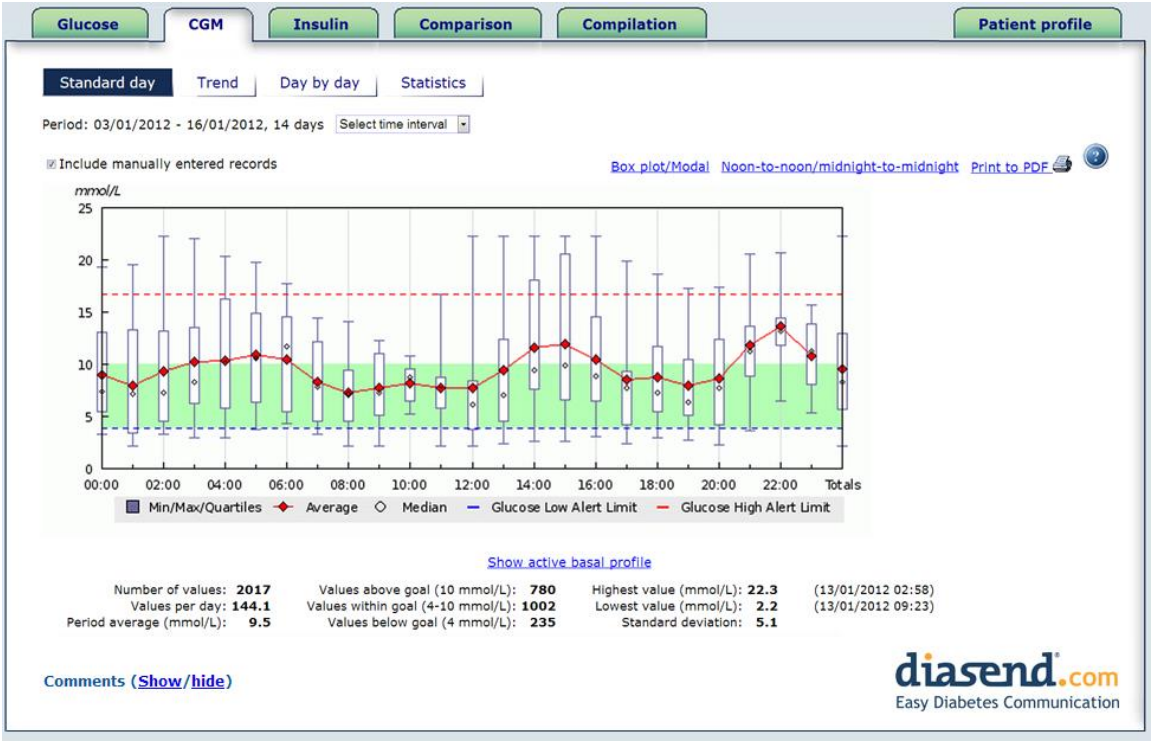

Figure 19: Example of the CGM data interpretation via the Diasend diabetes management software system [51].

Besides that, it is possible to generate and print out different kinds of reports based on the requirements of a healthcare provider (Figure 20).

Moreover, this system provides communication between clinicians and patients via two different portals – a clinical and a personal one. Clinicians can have online access to those patients´ profiles who give them authorization to see their data, and therefore all the data can be stored centrally online. [52]

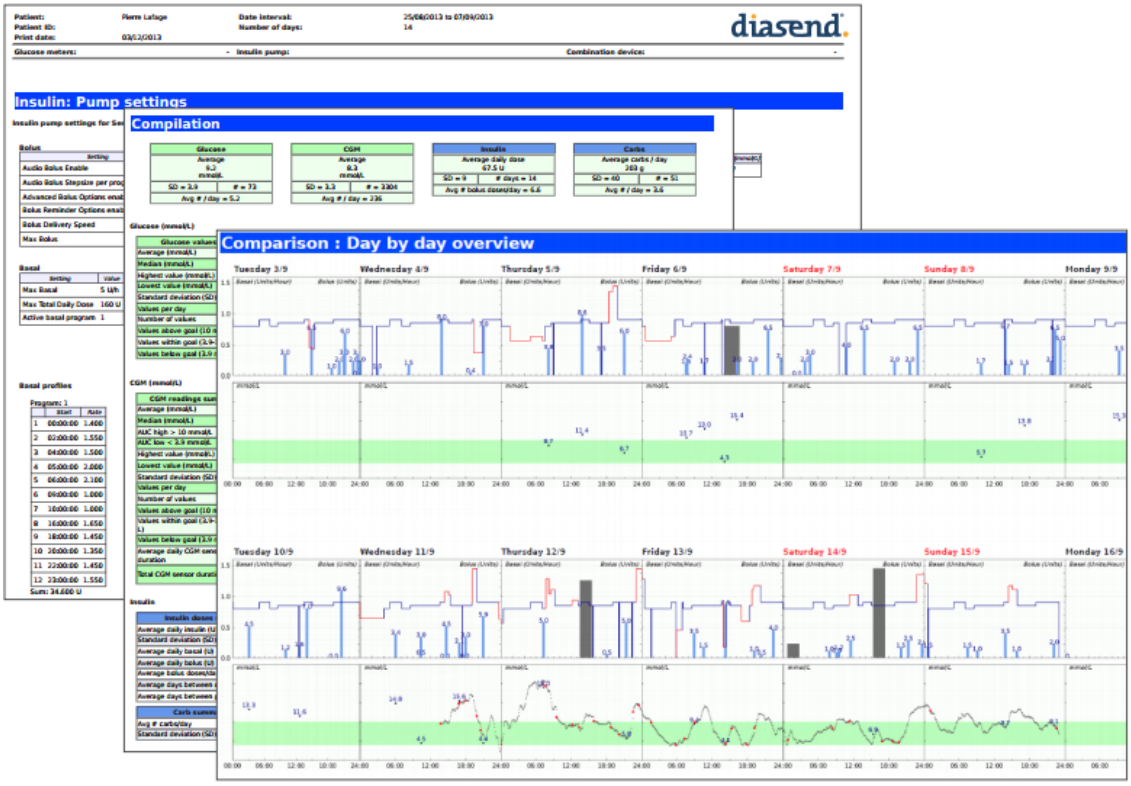

Figure 20: Example of records generated from the Diasend application [52].

3.2. Mobile applications

Nowadays, smartphones are capable of communicating with several fitness and medical devices. In addition, thanks to the Micro-Electro-Mechanical Systems (MEMS) integration the phone can serve as a sensor itself [53]. In connection with the fact that people usually carry their phone with them most of time and are familiar with its handling, using smartphones can, therefore, be very powerful tool in helping diabetes patients to self-manage their disease.

It has already been said that many of the medical devices used for diabetes treatment can communicate with smartphones. For example, insulin pens, insulin pumps, glucose meters, and activity trackers have been mentioned in previous chapter. This function can be highly useful to support a diabetes diary app.

The diabetes diary in the form of a mobile app is beginning to be a common tool in diabetes self-management. Patients can usually register and track their BG values, insulin doses, carbs, physical activity, even their weight or calories burned on such tools. While, some apps only enable manual registrations, some of them offer, in addition, communication between given mobile devices and the app. This allows for automatic data transfer without the necessity of user-intervention, which can save time and reduce missed registrations or human error when manually entering a registration in an app.

One of these multifunctional apps is, for example, the MySugr app. Apart from the logging of BG values, insulin doses, activity, meals and other notes, the app also enables the user to take pictures of their food portions. Searching in data history, displaying data in a numerical or a graphical format, extracting a printed version of report for a healthcare provider, setting a reminder to check a blood glucose, or sharing data with other users is also possible. The captured data can also be synchronized with Apple Health app to complete all the patient´s health records [53].

Figure 21: MySugr Logbook mobile app portfolio [54].

Besides the diary, mobile apps can be also used for data transfer from medical devices and the data analysis, similar to the desktop apps described in the previous section. Such an example is the Diasend and its connected mobile app (see Figure 22).

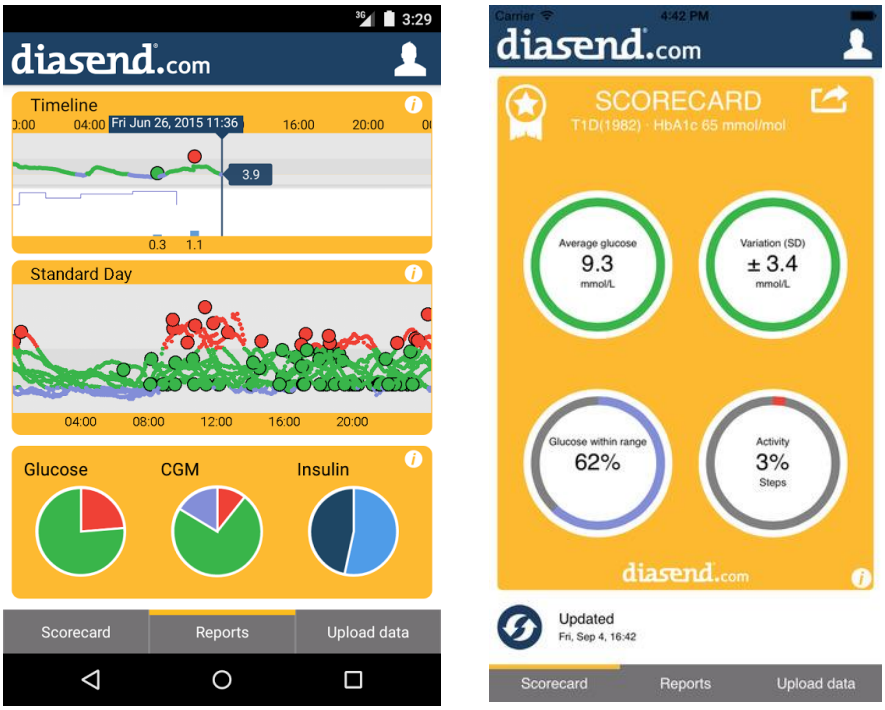

Figure 22: Example of data interpretation via the Diasend mobile application [52].

As we can see, there are many options for both patient and healthcare providers when it comes to transferring data from various devices and apps to a platform that can provide sufficient place to analyse captured data.

Nevertheless, poor interoperability of medical devices on one hand and variety of functions that are either not sufficient or too much advanced and time-consuming to analyse on the other hand, are still an obstacle for doctors when big data and long-time records are presented to him.

Also, there is a lack of predictive functions from previous data that could notify a patient that, for example, a dangerous situation could occur soon.

Therefore, it is required to find a solution that would ensure better interoperability of the most common medical devices used for diabetes treatment and would also extract the most important information from such a big dataset captured by these devices to help healthcare providers with their decision making.

4. Methods

Three consecutive phases are describing the protocol followed for creating, applying and testing the algorithm. In one part of the study, I determined which parameters and calculations that were relevant to include in the algorithm. In parallel, a second part of the study included one major clinical trial being run at the University Hospital in Motol. Finally, the third part involved applying the algorithms and determining their efficacy by comparing their evaluation to those made by clinicians. Further detail about each phase is described below.

4.1. Determining which parameters and calculations should be included in the algorithm

Information about current and clinically accepted technology and software used in traditional diabetes treatment indicates their widely known medical use and established protocols for testing. However, because we included novel mobile devices that lacked such previously established protocols, such as those used for collection of real data during the study at the University Hospital in Motol, it was necessary for me to determine their features, limitations, and type of measured and extractable data these tools were able to provide for further analysis.

By studying the types of data analysis and visualization of both the novel and traditional diabetes technologies, I was better able to understand the most common ways of data interpretation required in medical practice. The methods recruited from my analysis are structured upon each particular parameter as follows:

4.1.1. Blood glucose

Several studies [55-60] have been done to explore blood glucose readings, including finding patterns and formulas that would describe the characteristics of long-term records of BG measurements, among the other descriptive information.

In nowadays practise, clinicians are mostly reliable upon either the registrations of BG values patients bring to the office while having consultation with them, or several desktop or mobile applications providing, besides the simple list of all the BG values, also some deeper analysis of gathered data. With respect to the CGM data, despite nowadays software apps (as described in section 3) helps clinicians to identify BG variability much more in detail, mostly the lack of time obstructs them to analyse the big dataset for each patient they have to consult with.

Therefore, I searched for the methods dealing with the BG analysis, that would 1) follow the best possible standards used for BG evaluation 2) clearly identify patients´ problems related to BG fluctuations 3) enable to reduce time spent on BG data analysis.

The identified methods I used for building my algorithms are further explained in the next paragraphs.

Ambulatory Glucose Profile

The Ambulatory Glucose Profile (AGP) is a method of interpretation of mostly the CGM data, that resulted from an international meeting of diabetes specialists in Tampa, whose purpose was to develop recommendations for standardizing the analysis and visualization of glucose monitoring data [59].

Besides the other parameters, the AGP dashboard describes following parameters as providing relevant information for clinicians:

1) Percentage of blood glucose readings in range
2) Mean glucose exposure for specific time period (daytime, nocturnal…)
3) The average tests per day
4) IQR (interquartile range)
5) Stability of glucose (mean hourly change from the median curve) in mg/dl/h

In addition, to follow the best possible standards the AGP distinguishes 7 categories of BG ranges that should be observed (see Table 1).

Table 1: Glucose categories and their corresponding glucose ranges [59].

Glucose Category	Dangerously High	Very High	High	In Range	Low	Very Low	Dangerously Low
Glucose Range [mmol/L]	> 22.2	13.9 - 22.2	10 - 13.9	3.9 - 10	3.3 - 3.9	2.8 - 3.3	0 - 2.8

These methods for classification of BG ranges as well as the way of the BG data interpretation are convenient to use for either the SMBG data or those measured by CGM.

Calculating Mean Amplitude of Glycemic Excursion (MAGE)

The MAGE index provides yet another way to describe the blood glucose variability. This method is based on calculating the arithmetic mean of blood glucose excursions (i.e. differences between peaks and nadirs) that are bigger than one standard deviation around the mean BG, within a 24-hour period [61,62].

Graphical interpretation of MAGE calculations is exemplified in Figure 23.

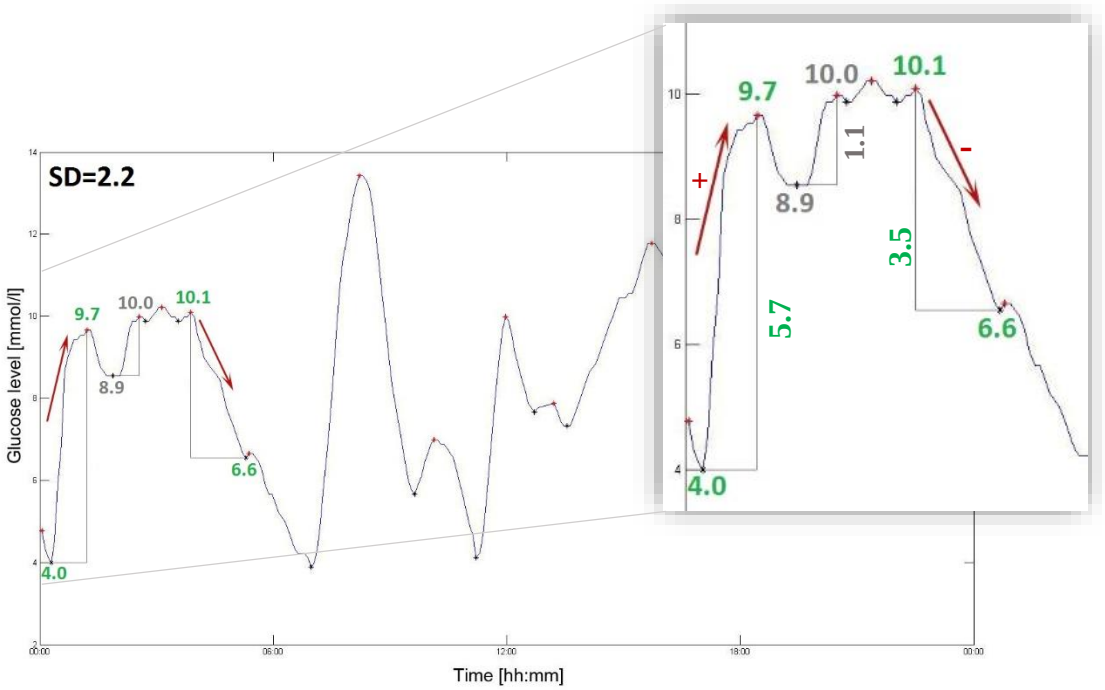

Figure 23: Example of MAGE calculation. The green values differences represent one of the upward and downward trend of the signal that comply with the condition of the difference >1SD. The grey values difference is <1SD and thus this part of the signal is not counted. (Note: the picture´s representation is adapted from [61] and applied on the data from the study at the University Hostpital in Motol).

The method is based on finding all the increases and decreases that comply with the condition of the nadir-peak difference >1SD. The increases are taken to the final calculation of $MAGE^{+}$, i.e. mean amplitude of all the upward glycemic excursion, while the decreases complying the 1SD condition forms $MAGE^{-}$, i.e. mean amplitude of all the downward glycemic excursions [63]. We can also calculate an average of all the excursions, upward and downward, together, forming the average MAGE.

Calculating Mean of Daily Differences (MODD)

The Mean of Daily Differences (MODD) is a parameter computed as a mean absolute value of the differences of glucose values that were measured at the same time within two consecutive days.

Based on my experience, when comparing daily characteristics of CGM measurements of the same patient, we can see that patient´s behaviour, with respect to his daily regimen, is often very similar, and thus, the pattern of the CGM curve is tracking the same line with only some occasional deviations.

Since the MODD allows for the difference in measured blood glucose levels to be measured at the same time of different days, this method is very sensitive and easily influenced if potential irregularities in patient´s mealtimes and insulin schedule occur [64-65].

4.1.2. Insulin

Calculations and methods used to describe an insulin action plays a crucial role mainly in predictive algorithms I aimed to design. The calculations necessary to explain as a part of methods I used are calculation of total daily dose, insulin sensitivity, correction factor, and bolus on board. The next paragraphs describe each particular calculation.

Calculating Total Daily Dose (TDD)

Patients´ frequent lows or highs, which influence significantly their average blood glucose, can be the cause of improper setting of insulin doses. The TDD signifies the total sum of all insulin doses taken per day, which includes all the basal, bolus and correction doses. [42]

The TDD can vary between individuals, ranging from 0.3 to 1.0 IU/kg of patient´s weight [66]. To estimate the average TDD one can first multiply his weight by an average value of IU/kg, i.e. 0.53 in case of adults and 0.44 for children prior to puberty [42].

Apart from its total value it is also required to know the ratio of bolus vs. basal insulin doses per day, whereas the basal dose should form 40-50% of the TDD [66]. Reducing/increasing the TDD and re-calculating the other parameters such as basal dosing, correction and carbohydrate factor (explained in section 2.3) can help to resolve frequent lows/highs.

Since the TDD is one of the parameters used for blood glucose prediction, how good estimated the TDD is can significantly influence the action of insulin on BG changes, and thus, the quality of BG prediction itself.

Calculating Insulin sensitivity (IS)

Insulin sensitivity (IS) is a factor indicating how much insulin we need to move a certain amount of glucose into cells [42]. This parameter varies in individuals and changes during the day based on other factors that either increase insulin sensitivity (i.e. physical activity, some kinds of medicaments, etc.) or decrease insulin sensitivity (i.e. counterregulatory hormones responding on stress, illness, menstrual cycle and others, then another types of illness, some kinds of medicaments, etc.).

Nevertheless, to estimate an average IS factor it is possible to start with an equation [42]:

$$IS = \frac{Weight \cdot 0.53 \frac{IU}{kg}}{TDD}, \qquad (1)$$

where the number 0.53 is an average IS described in the Actual Pump Practices Study (APP) [67], where data from 1020 insulin pumps throughout the U.S. were downloaded and analysed.

Calculating Correction Factor (CorrF)

Another factor related to insulin action on blood glucose is the Correction Factor (CorrF). This parameter indicates how much a patient´s blood glucose drops with each unit of insulin [42].

To estimate the CorrF of each individual, one can use so called "1500 Rule" or "1800 Rule" depending on the type of insulin that is used, i.e. regular or rapid acting insulin, respectively [68]. It means that by dividing 1500 or 1800 by an average TDD, one can approximate the CorrF in mg/dL. To get to the units of mmol/L it requires, in addition, to divide the result by 18. For rapid acting insulin only, we get the following:

$$CorrF = \frac{1800}{TDD}\left[\frac{mg}{dL}\right] = \frac{100}{TDD}\left[\frac{mmol}{L}\right] \quad (2)$$

In the APP study also the CorrF was estimated based on an average of each individual´s CorrF as follows:

$$CorrF = \frac{1960}{TDD}\left[\frac{mg}{dL}\right] = \frac{109}{TDD}\left[\frac{mmol}{L}\right] \quad (3)$$

It was recommended to use the numbers of 1800 or 1500 for frequent high blood glucose readings and numbers like 2200 or 2400 for frequent lows.

Calculating Bolus on Board (BOB)

Bolus on board (BOB, also called active insulin) is such a dose of insulin that remains from recent bolus or correction insulin doses and still lowers patient´s blood glucose [42]. This means that if a patient decides to adjust their blood glucose with their carbs or a correction bolus, he should always count the remaining insulin, if its action is still present.

Most current bolus calculators (for example Medtronic´s Bolus Wizard, Accu-chek Bolus Advisor, and many others) track this parameter and subtract that from the insulin dose that would be normally required if there was no BOB [69].

On Figure 24 we can see the kinetics and dynamics of insulin action. The insulin kinetics represent the presence of insulin in the bloodstream. In contrast, the insulin dynamics represents how the insulin affects the blood glucose level [69].

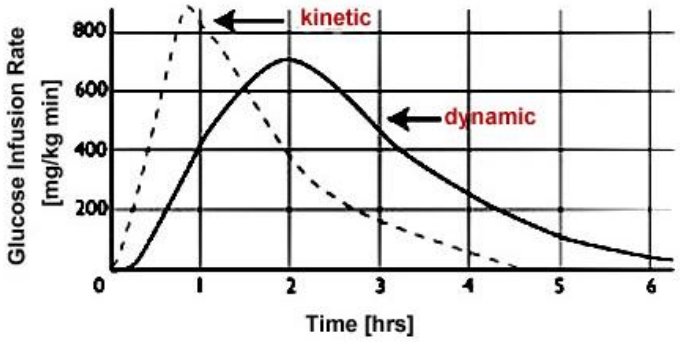

Figure 24: Kinetics and dynamics of insulin action [69].

The amount of active insulin remaining in the body with respect to given insulin dose is listed in Table 2.

Table 2: Hour-by-hour insulin remaining after a dose of rapid-acting insulin (Humalog or Novolog) [70].

Insulin dose	Units left to work after				
	1h	2h	3h	4h	5h
1 IU	0.8	0.6	0.4	0.2	0.0
2 IU	1.6	1.2	0.8	0.4	0.0
3 IU	2.4	1.8	1.2	0.6	0.0
4 IU	3.2	2.4	1.6	0.8	0.0
5 IU	4.0	3.0	2.0	1.0	0.0
6 IU	4.8	3.6	2.4	1.2	0.0
7 IU	5.6	4.2	2.8	1.4	0.0
8 IU	6.4	4.8	3.2	1.6	0.0
9 IU	7.2	5.4	3.6	1.8	0.0
10 IU	8.0	6.0	4.0	2.0	0.0

The duration of insulin action plays a crucial role in not only tracking the BOB but also in the timing of pre-meal insulin boluses, of which poor timing is a common mistake amongst patients.

Calculating pre-meal insulin-action time

It follows that, although the maximum peak of insulin appears in a bloodstream approx. 45 min after injection, its maximum effect appears around 2 hours after injection and then decreases for the next 2 hours until it is fully consumed. Therefore, two conclusions result from these facts. The first one is that patients should take some time after the insulin injection before they start to eat, otherwise the effect of food would be faster than that of the insulin, in which case post-meal spikes appear. The second one is that it is required to remember the BOB if there is another bolus planned within 4 hours of the last one.

Obviously, it is always more convenient and flexible to take a bolus of insulin when one begins to eat than to wait approximately 15-20 [42] minutes (as displayed in Figure 25), between these

two actions. However, the action time of rapid-acting insulin (such as Humalog, Novorapid or Apidra) is often overestimated by patients.

Based on this fact, another efficient method could be to track this insulin-to-carbs time in patients´ data and highlight those situations that could cause post-meal spikes if the patient does not wait long enough.

Having a continuous information about current level of active insulin can effectively support patients in their decision making before an insulin dose is applied, and prevent them mostly from overdosing. Also, this parameter forms, together with the TDD, IS and CorrF, a crucial part of equations that can predict future BG level when calculating the effect of given amount of insulin dose applied.

4.1.3. Carbohydrates

As previously mentioned, the effects of insulin, which acts to reduce BG levels, must be balanced against the impact of carbohydrates, which act to increase BG levels. Therefore, how accurate a patient is with respect to carb boluses accounts for approximately half of the patient's ability to control their blood glucose [42].

However, to be able to estimate correct carb dose for each meal several times per day, it is necessary to have some information about the food itself, including its weight, glycemic index, and other information. If the amount of carbs per given portion is not known, one should be able to calculate a correct dose using a nutrition facts table, a weight scale, or combination of both. All of these calculations are required to use for prediction algorithm I aimed to design.

The next paragraphs explain particular calculations and factors that can be part of prediction algorithms.

Calculating Carb Factor

Apart from the information about the food's composition, each patient should also know his own insulin sensitivity and so called "Carb Factor" (also "insulin-to-carb ratio"), which is the number of grams of carbohydrates that one insulin unit will counteract [42], to ensure that the blood glucose level remains stable after food is eaten.

The Carb Factor's value can be estimated multiplying one´s insulin sensitivity by 10.8, which was the average CarbF in the APP study [42]:

$$CarbF = IS \cdot 10.8\ [g] \qquad (4)$$

Although this parameter is highly individual (the range can vary between 4-30 grams) [71], most patients prefer easy-to-use numbers, such as a factor of 5, whereas the most common insulin to carb ratio is 1 IU = 10 g of carbs. This behaviour was also observed in the Actual Pump Practices Study [67]. Histogram of the Carb Factor settings found in 899 of the pumps is shown on Figure 25.

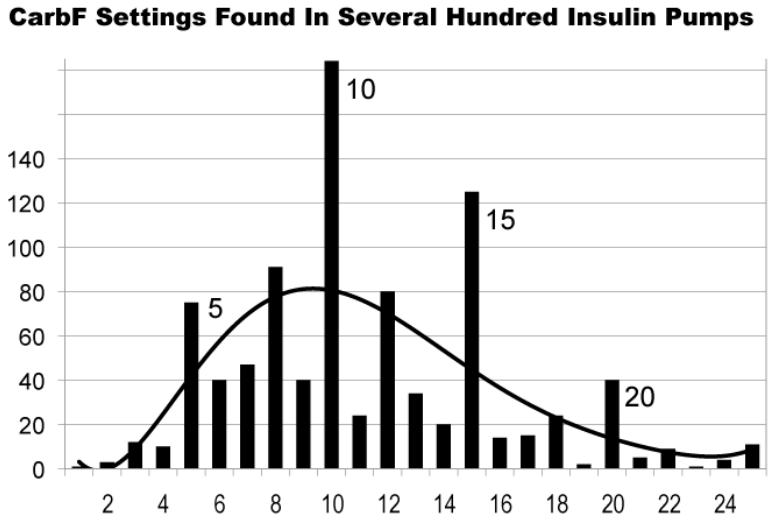

Figure 25: Carb Factor settings found in 899 pumps during the Actual Pump Practices Study [67].

Referencing the Glycemic index (GI)

Glycemic Index is derived from the glucose response to carbohydrates of the same amount from different foods. The final value represents the area under the curve of the blood glucose response to different foods. [14]

Example of such a response to 3 different types of food are shown on Figure 26.

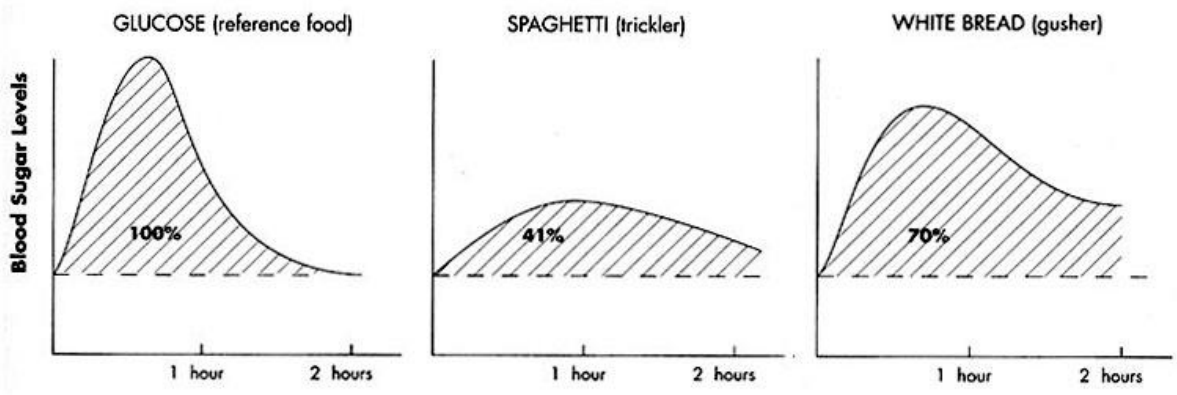

Figure 26: Blood glucose response with corresponding glycemic index of different types of food. Adapted from [72].

Knowing that, we can sort particular types of foods into groups with the same glycemic index. However, many different types of food can have the same glycemic index and the amount of

carbs in the food portion matters, too. Therefore, the Glycemic Load (GL) has been defined to distinguish particular food items and their impact on final blood glucose, re-calculated in grams of carbohydrates as follows [73]:

$$GL = \frac{GI \cdot grams\ of\ carbs}{100}\ [g] \qquad (5)$$

This information can help to predict how much impact certain food will have on blood glucose after its ingestion.

Predicting post-meal spikes

One of the most common causes of significant BG fluctuations, and mainly the cause of very high BG readings, are the post-meal spikes. The reason of their occurrence is mainly bad timing of insulin and inappropriate insulin-to-carb ratio, which means failing in carbohydrates counting [42].

For normal blood glucose tolerance, the glucose level rarely rises above 7.8 mmol/L and gets back to the basal level 2-3 hours after food ingestion [74]. Thus, the ideal scenario for clinicians would be to keep patients´ PMBG as close to this ideal target as possible. However, this is very difficult task to achieve for diabetic patients and they should also be aware of the treatment with respect to risk of hypoglycaemia when trying to control their PMBG [74]. The British National Institute for Health and Care Excellence (NICE) is the British organization that provides many guidelines (official for England and some other states of the UK) including recommendations related to disease prevention and maintaining a good health statement. One of these guidelines [75], specifically NG17, is also focused on diagnosis and management of diabetes, where the recommendation for blood glucose targets includes to advise adults with T1D to aim for:

- Fasting blood glucose in the range of 5-7 mmol/L
- Blood glucose before meals in the range of 4-7 mmol/L
- Post-meal blood glucose (at least 90 minutes after food ingestion) in the range of 5-9mmol/L

Therefore, I these ranges are possible to use when defining conditions for mealtime situations detection and classification of pre-and post-meal BG values.

4.1.4. Physical activity

One of the parameters that has a big impact both on actual blood glucose level as well as on potential delay of long-term complications [24], is physical activity (PA). To estimate or predict the immediate effects of PA on a patient´s blood glucose is difficult, not only because each individual has a unique reaction to different levels of exercise, but also because more than one device is needed to measure an energy expenditure accurately [76-78]. Thanks to current technology and continuous improvement of the accuracy of activity trackers described in

section 2.4.3, there are very effective options for using these data for tracking and evaluating a patient´s physical activity levels. However, despite this technology, this is not a measurable value in clinical practice today, aside from manual registrations of events made by patients often in paper diaries.

Calculating total daily steps

Several studies have been done to explore the level and form of physical activity that should be recommended for health maintenance, both for the general population [76,79] and for patients with diabetes [80,81].

With the arrival of activity trackers and general awareness of the importance of physical activity, the previously recommended amount of 10 000 steps/day is evolving [82].

Based on the previous studies of Tudor-Locke [82,83] the ranges of number of steps per day for different levels of activity have been proposed, as shown on Table 3.

Table 3: Different levels of physical activity with corresponding range of steps [82,83].

Physical activity level	**Steps per day**
Basal activity	<2,500
Limited activity	2,500 – 4,999
Low active	5,000 – 7,499
Somewhat active	7,500 – 9,999
Active	10,000 – 12,500
Highly active	>12,500

Public health guidelines also recommend the inclusion of 30 minutes (at times up to 60 minutes) per day of moderate-to-vigorous physical activity within the daily step counts, of at least in 10 minute bouts, whereby moderately intense levels of activity are considered to be the rate ≥100 steps/min [79]. For youth, this time spent on moderate-to-vigorous activity is suggested to be even higher, that is 60 minutes or more [80].

Due to the fact I found these recommendations as being the most relevant for evaluation of physical activity in T1D patients, I used the above mentioned classification ranges as one of the possible methods for description of patient´s level of physical activity when creating my algorithms.

4.2. Design and completion of clinical trials

In parallel time with phase 1 I followed and executed clinical studies, questionnaires, and meeting proceedings that have been dealing with patients´ problematic situations and methods used to make them visible through the data measured on patients.

4.2.1. Clinical Study protocol

Since April 2014 I was participating on the study at the University Hospital in Motol, of which primary aim was to define relations between patients' physical activity and actual blood glucose levels, among other parameters. The secondary aim was to find the best way how to interpret data collected from the measured parameters (The study was approved by Ethical Committee for Multi-Centric Clinical Trials of the University Hospital Motol – see the ethical committee approval attached in Appendix A).

Defining how active a patient is in a global viewpoint is one piece of information that can help both patients and clinicians better realize how trained patients are, how much physical activity and which level of its intensity patients include in their daily regimen.

However, to define how this parameter influences BG changes is the most required information on one hand, but the most difficult question to answer on the other hand. That is not only due to such individual reaction of each body on particular level of physical activity, but also due to complicated way of its appropriate measurement and, to top it all, in free living conditions.

Therefore, we recruited group of adults among T1D patients to be monitored by CGM (Dexcom G4, Dexcom Inc., or Guardian RT, Medtronic Inc.) in connection with commercial available physical activity monitors (Flex, Fitbit Inc.) to study glycemic reaction on certain intensity of physical activity. Patients were recruited for a sort-term (approx. 1 week) pilot study where patients used activity trackers and CGMs, and some were recruited for further more detailed statistical analysis. Other patients were recruited for long-term monitoring, while using the Fitbit activity tracker, the Diabetes Diary smartphone application, FORA Diamond glucose meter, Pebble smartwatch, and occasionally also CGM. These patients were supervised by a telemonitoring system developed by the Research Center Albertov.

While the clinician provided the medical support for all of the patients, my role was to ensure and process the data collecting from both the short-term and the long-term monitored patients, and provide a technical support for the letter group of patients.

Further description of the method of data collecting is described in the next section.

4.2.2. Data collecting

During the study at the University Hospital in Motol, I was collecting patients´ data to use them for future analysis, to investigate patients´ behaviour, and to test the designed algorithms (as described below). It was necessary to track not only the blood glucose level and physical activity, but also the other parameters such as carbohydrates intake, insulin doses, and in some cases, the sleeping activity.

Each patient with T1D, who came to the diabetologist´s office for a short-term monitoring, agreed to participate in the study and signed corresponding informed consent (see Appendix B), was equipped with the CGM and the Fitbit Flex activity tracker. Some of the patients also received a paper-based diabetes diary.

Patients were expected to wear the devices for approx. one week. I made several appointments with the nurse to instruct her how to operate the activity trackers, in addition to receiving paper-based guidelines for her and the patients. She was also equipped with an internet-connected computer, in which the electronic document of anonymized patients was continuously editing corresponding information about the dates and types of devices they used. Through this computer, the data from the trackers have been synchronized and automatically uploaded to a cloud system for further analysis. The data from CGM monitors were downloaded manually in the office under each patient´s ID. I was visiting the office approximately one to two times a month to collect the anonymized CGM data and upload them to the cloud system.

In order to monitor patients´ diabetes, i.e. the possibility to gather all the measured data, to store them in one place, to visualize them and use them for further analysis and data mining for both patients and clinicians, the Diani web application has been created at the Research Centre Albertov.

This platform stores all parameters measured with the mobile devices patients used, and displays them in a form of diagrams and tables (Figure 27).

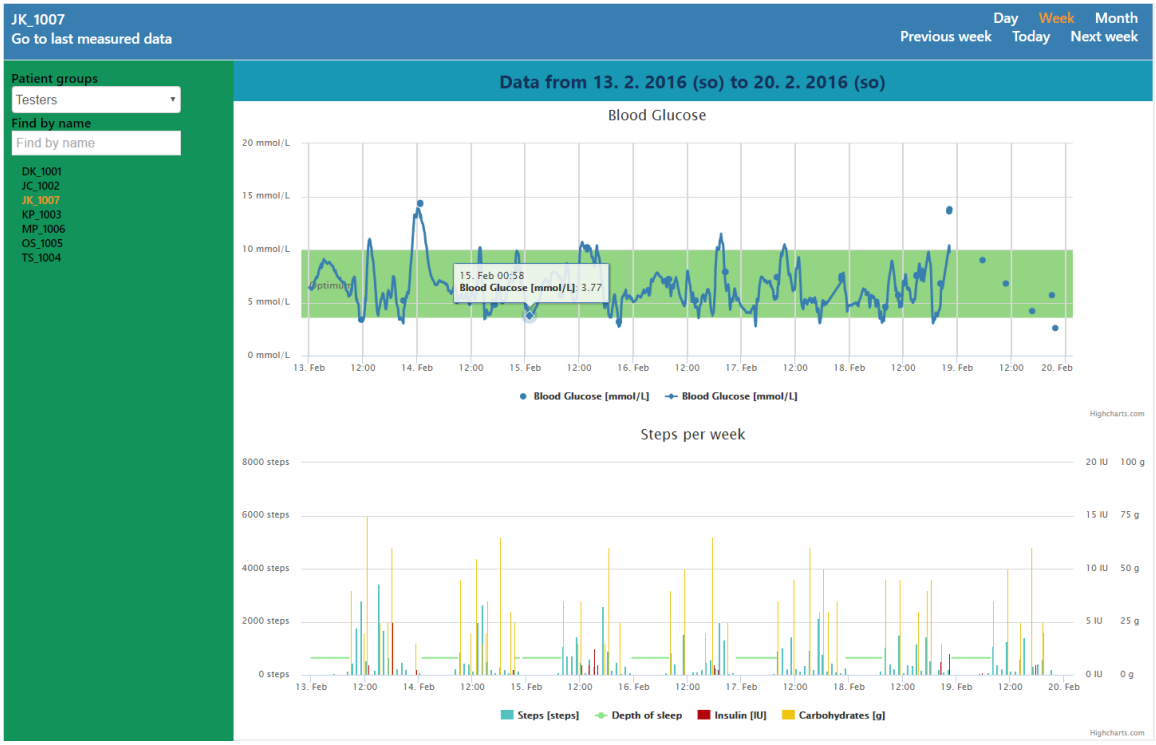

Figure 27: Example of the main screen of the Diani web portal.

In the graphical interpretation section there are two graphs for visualizing patients' data. The upper graph shows the blood glucose data measured either by glucose meter or CGM system, and the lower diagram indicates food and drug registrations, physical and sleeping activity.

Apart from the patients of whose data from the activity tracker, CGM and paper-based diary have been collected, we additionally recruited participants for a long-term test of the system, using the following tools:

1) Dexcom G4 or Medtronic Enlite sensor

These sensors are commonly used in medical practice in the Czech Republic for continuous glucose monitoring, in connection with corresponding receiver or insulin pump. Both are able to register and record blood glucose values in 5-minutes interval. The data downloaded into a special software application were exported manually to .xml format from the Dexcom device and in .csv format from the Medtronic sensor.

Figure 28: CGM systems used for continuous glucose monitoring of the patients. Left picture – Medtronic MiniMed 530G insulin pump with CGM [84], right picture – Dexcom G4 CGM system [37].

2) FORA Diamond Mini glucose meter

This device is used for self-measurement of patients´ blood glucose and is capable of transferring measured data via Bluetooth either to a special application or, in our case, automatically to the Diabetesdagboka mobile application described below.

Figure 29: Glucose meter FOR A Diamond Mini with Bluetooth communication [25].

This functionality ensures that all BG registrations are registered to the Diary and that untruthful and omitted registrations are eliminated [85].

3) Fitbit Flex activity tracker

For physical activity monitoring, our patients were equipped with the Fitbit Flex activity tracker. In addition to other functions (calories burnt, distance walked, etc.), this sensor can track the number of steps taken per minute, and also detect movements in bed when set to sleep-mode. Thanks to the Fitbit API, which allows developers to interact with Fitbit data in their own applications [45], we are able to automatically transfer all the data to the Diani web server.

Figure 30: Fitbit Flex activity tracker used for monitoring patients´physical activity [86].

4) Diabetesdagboka mobile application

This diabetes app was developed by the Norwegian Centre for E-health Research, and its further development and Czech version is supported also by the Research Centre Albertov in the Czech Republic.

As a self-management tool, it enables patient to track their most important parameters. Users can make registrations about their daily food and insulin intake, blood glucose values and physical activity, including the possibility of adding notes to particular logs [53]. If a user checks his blood glucose with the FORA Diamond Mini glucose meter, the values are automatically transferred to the app via Bluetooth. Another function, so called "similar-situations", helps users to search in a history of their own insulin registrations to see the most similar situations to the one they plan to do, and they can decide whether to use the dose offered by the algorithm or not [87].

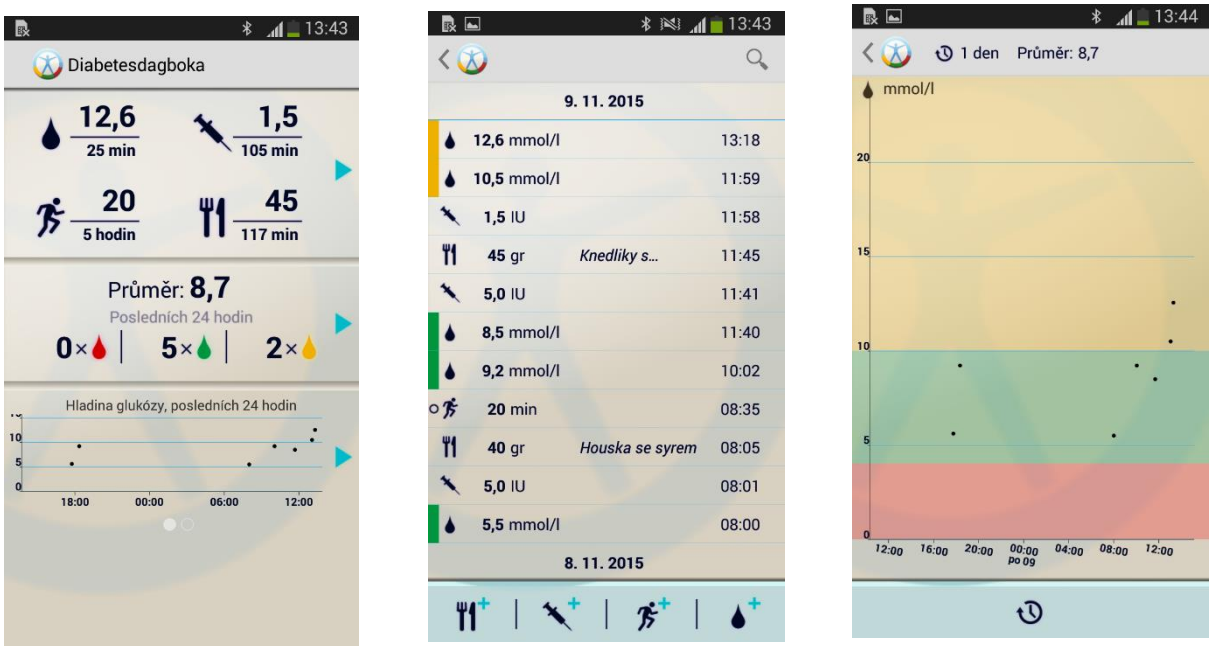

Figure 31: Diabetesdagboka mobile application for tracking patients´ blood glucose measurements, insulin and carb doses, and physical activity [87].

Apart from the logbook, there is also statistical interpretation of blood glucose data, such as average blood glucose for the last 24 hours or 2 weeks, number of blood glucose values within and out-of-target range, etc.

If the patient´s ID is set, Bluetooth, Internet connection and data transfer are enabled, all registrations are automatically uploaded to the Diani web server.

5) Pebble smartwatch

For easier and faster registration to the Diabetesdagboka app, some patients were also equipped with the Pebble smartwatch app that enables users to log each parameter to the diary app with just a few button pushes on the watch.

Figure 32: The Diabetesdagboka app for Pebble watch and its communication with the mobile version of this app. Adapted from [87].

This tool can also help to increase both the adherence of our testers to use the diary and the number of registrations they made. Also, a function that reminds patients to check their blood glucose can higher the frequency of post-meal blood glucose measurements.

All the data that were successfully collected from our study's participants have been uploaded to the server under their ID number, either automatically (mobile app registrations and Fitbit measurements) or manually (CGM data). In order to adapt the current system to medical practice, a function from a generation of the paper-based diabetes diary was implemented to this system as well. Patients who received access to the Diani portal could print out the report from individually selected time periods to show it during a personal consultation with their doctor.

The long-term group of patients received access to this portal together with one clinician. The patients could see only their own data and the clinician could see only his patients' data.

Making this portal accessible for both the patients and the clinician allowed me to gain direct feedback from them about their preferences with respect to the data interpretation, functions that could improve the system and the decision-making, and its user-friendliness.

Unlike the rest of the patients, the long-term patients, in addition, underwent several educational meetings with me to ensure that they understood how to use each particular device correctly. All five patients were requested to contact me whenever some technical problem occurred, in addition to any questions or issues related to the devices´ operations and data monitoring. They could also contact the clinician with respect to health issues.

4.2.3. Meeting proceedings

While collecting the data, I made several appointments, mainly with the clinician who I was participated on the study with, and also with the long-term monitored patients.

During the conversations with the clinician I was able better to understand what clinicians search for in the data collected by patients, how the communication between patients and clinicians works, what are the problems clinicians face with respect to the data and information patients provide them, and which problems the clinician see as the most common but the worst manageable for the patients

In contrary, having discussions with patients helped me to understand their point of view on the disease, what are the biggest struggles and problems that are difficult for them to manage, which mistakes they do the most and what is their typical behaviour with respect to food and insulin administration or handling certain medical device, etc. They also described me their needs and wishes that could support their self-management, if those came true.

Besides these appointments I was also participated in 3 conferences, whereas two of them were connected to treatment and technology in diabetes (ATTD2016, Milano, and 52nd Days of Diabetology, Luhačovice). Thanks to that I got to know the most advanced ways of collecting, analysing, and sharing patients´ data, using mobile technology in diabetes, and many others.

4.3. Applying the algorithms and evaluating their efficacy

The next step was to thoroughly analyse the data measured on real patients both qualitatively, by visualizing trends and impacts on individuals, and quantitatively, using calculations on the data itself 1) to investigate the possibilities and limitations of further data analysis and interpretation, and 2) to study patients´ behaviour under the conditions of real world, and thus, to define the most common problems they are facing while self-managing their diabetes. Evaluations of the data by clinicians and the algorithm were then compared based upon these qualitative and quantitative analysis to compare the effectiveness and accuracy of the algorithm vs. clinician approaches.

The following sections provide a detailed description of my investigation.

5. Results: Algorithms design and evaluation based on collected data

From 92 patients (40 men and 52 women) measured so far for a short-term measurement we processed the first 34 patients (20 women and 14 men) for further statistical analysis of the data from the activity trackers and CGM. Results from the Multiple Regression Analysis and Generalized Additive Model showed, that the relationship between intraday number of steps and blood glucose levels could not be found due to other confounding parameters, such as carbohydrates and insulin doses, which were not gathered from the patients involved. Nevertheless, inversely proportional correlation between average number of steps per day and average blood glucose have been found [88] (see Figure 27).

21 patients also filled in a paper-based diabetes diary, but only 6 of them were using both the CGM and the activity tracker. All of these patients mentioned wore the devices for approx. 5 days, while another 5 patients (2 women and 3 men) were recruited for long-term monitoring, using the Fitbit activity tracker, the Diabetes Diary smartphone application, FORA Diamond glucose meter, Pebble smartwatch, and occasionally also CGM.

After having sufficient amount of data and knowing which methods are relevant to use on them, I started to build the algorithms and apply methods selected from the previous investigations on the data collection.

The results of the three applied stages of the methods presented in section 4 helped me to define those problematic situations that are possible to find in the data we had, and create algorithms that could extract them. Studying patients´ behaviour helped me, in addition, to define cases in which the algorithms fails and the cause of their occurrence.

Some of the designed algorithms and methods used for data interpretation are the components of so called causal functions, which analyse captured data retrospectively, whereas others are included into predictive functions, i.e. those of which results should predict some problematic situation in advance.

I have structured this chapter into sections related to each given parameter, including the design and evaluation of results related to each algorithm component. In addition, I highlighted the facts or methods I was inspired by when developing my own system for data mining.

5.1. Causal functions

One of the possible ways of searching for problematic situations is to analyse captured data retrospectively, i.e. from the patient´s historical registrations, using causal functions. These functions can help to discover how patients manage their diabetes recently and detect potential

problems based on which the patients can either learn from themselves or be re-educated properly by clinicians.

5.1.1. Classification of blood glucose readings

Information about the number of BG readings belonging to corresponding BG ranges is one of the often required features of several programmes used in medical practice. Therefore, I used the classification standard recommended by Bergenstal et al. [59] for automatic classification of BG readings collected from the patients.

Design

After data was extracted, I created the classification algorithm according to the BG ranges defined. To visually interpret the data, I used histograms, which allow both the magnitude and proportion of each range to be represented clearly, as shows Figure 33.

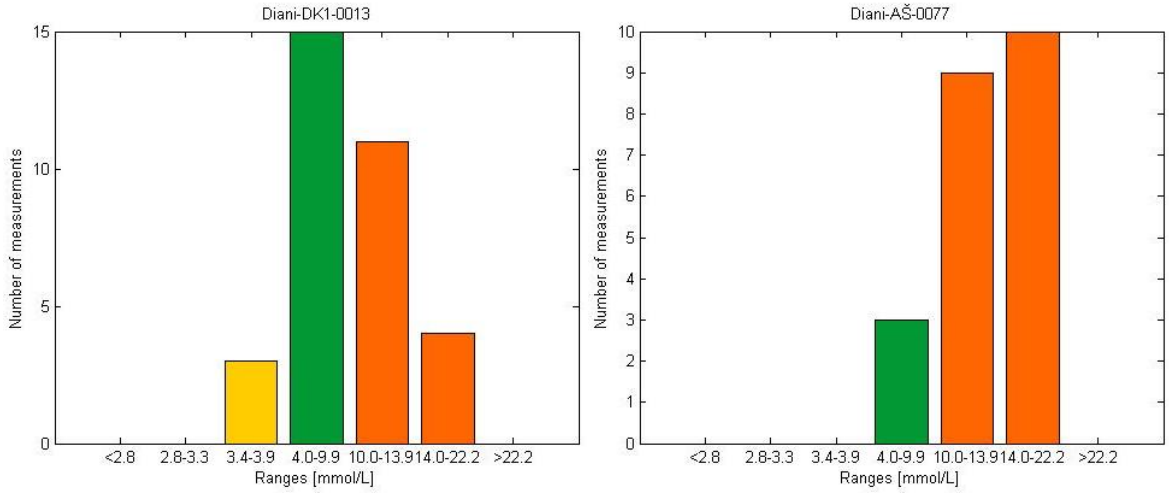

Figure 33: Interpretation of blood glucose data classified into 7 ranges of blood glucose level. The x-axes represent particular blood glucose ranges, while the y-axes represent the number of measurements falling to the given range.

However, to get more into patient´s daily management the distribution per particular weekday can help to discover which day is often problematic, and then to ask what is its cause. Therefore, I made an additional automatic BG classification for particular weekday to see the inter-day differences within a week. An example of two weekday distribution of BG readings of one patient are shown on Figure 34.

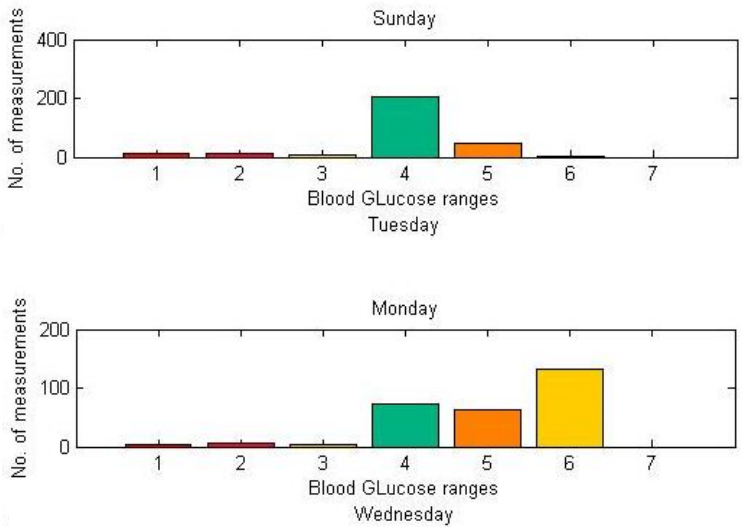

Figure 34: Distribution of blood glucose readings per given weekday. The BG ranges are as follows: 1 - <2.8, 2 – <2.8-3.3), 3 – <3.3 – 3.9), 4 – <3.9 – 10), 5 – <10 – 13.9), 6 - <13.9 – 22.2), 7 - >22.2.

To explore the importance of such data extraction I used weighted averages of BG measurements for each patient, whereby the greatest weight was assigned to the most extreme BG ranges (i.e. extreme lows and extreme highs) and the smallest weight to the target range (see Table 4). In doing this, the more extreme BG values (for both lows and highs) in a patient's data set, which are more related to dangerous situations, become the focus.

Table 4: Weighted coefficient used for each glucose range to describe the correlation between the weighted average throughout the ranges and mean BG, and between the weighted average and HbA1c.

Glucose range [mmol/L]	> 22.2	13.9 - 22.2	10 - 13.9	3.9 - 10	3.3 - 3.9	2.8 - 3.3	0 - 2.8
Weighted coefficient	3	2	1	0	1	2	3

Evaluation

I processed the number of BG readings falling within each range and plotted the weighted average 1) with the average BG for each of a group of 55 patients (Figure 35) and 2) with HbA1c (Figure 36) for each of a group of 52 patients. From the letter group, I excluded first three patients due to extremely low HbA1c compared to the rest of patients. On Figure 36 we can see that the higher the average BG is, the higher the weighted average of number of BG readings falling within particular ranges is, which means that more extreme BG values (either lows or highs) appear in a patient´s BG profile. The correlation of the weighted average with HbA1c shows a similar trend, but the coefficient of determination is much lower comparing to the average BG. However, while HbA1c reflects, simply said, the average BG for the last 2-3

months, the results represent one week of blood glucose readings. Therefore, some patients could achieve better average glycaemia in this short time period despite their higher HbA1c's. Another reason for such results could be increased motivation of some patients to control their BG level more, when wearing the CGM or the actvity tracker during that time. Also, if more low BG readings appears in the data, the weighted average increases, but the HbA1c is reduced.

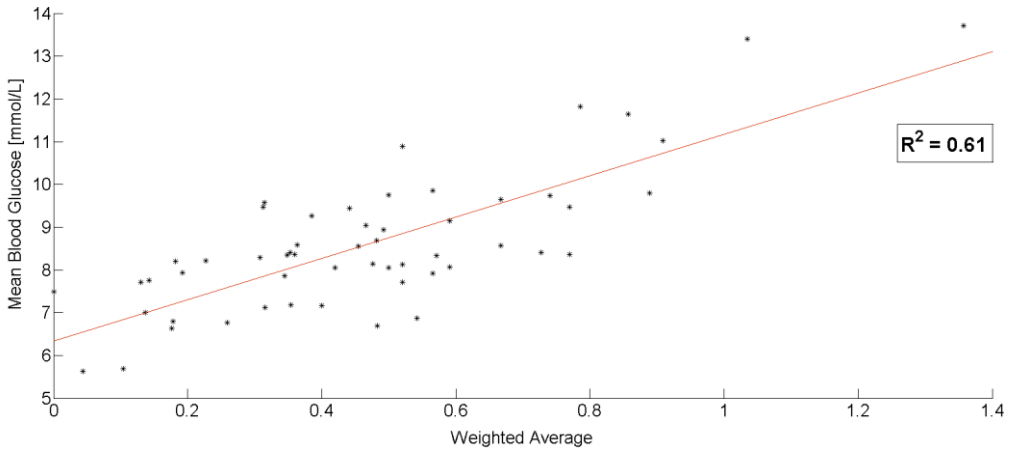

Figure 35: Correlation between the weighted average of blood glucose readings and the average blood glucose level for each patient.

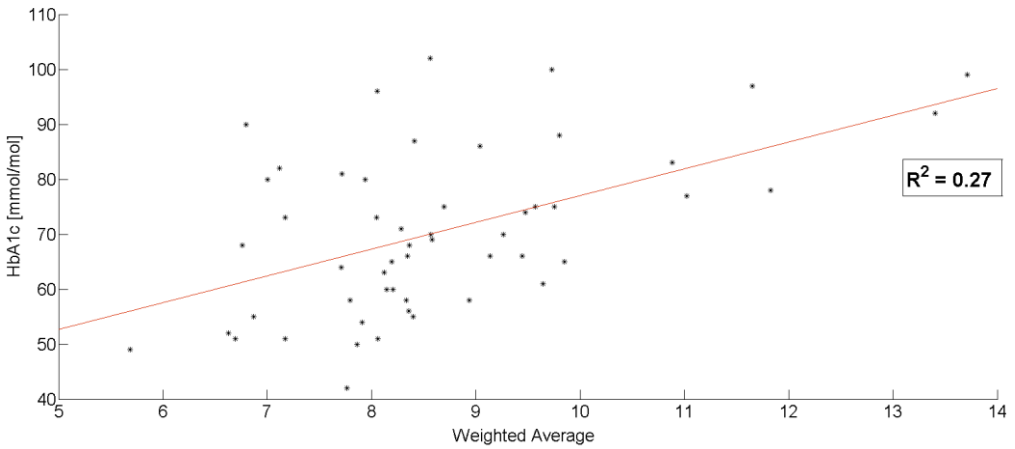

Figure 36: Correlation between the weighted average of blood glucose readings and the HbA1c for each patient.

The type of data interpretation I chose obviously indicates patient´s general BG distribution throughout the whole dataset, whereas the frequency of extreme BG readings and those falling within target range are highlighted, and thus, give a first sight of patient´s potential problems with very dangerous levels of BG values.

On Figure 37 we can see 2 cases of patients, whereas while patient on the left has very similar BG distribution each of the three sampled days, the BG readings of patient on the right are very unstable and differ compared the days between each other. The distribution correlates with

HbA1c, of which value in case of the patient on the left is 31 mmol/L, whereas on the right side there are results of a patient of whose HbA1c is 78 mmol/L.

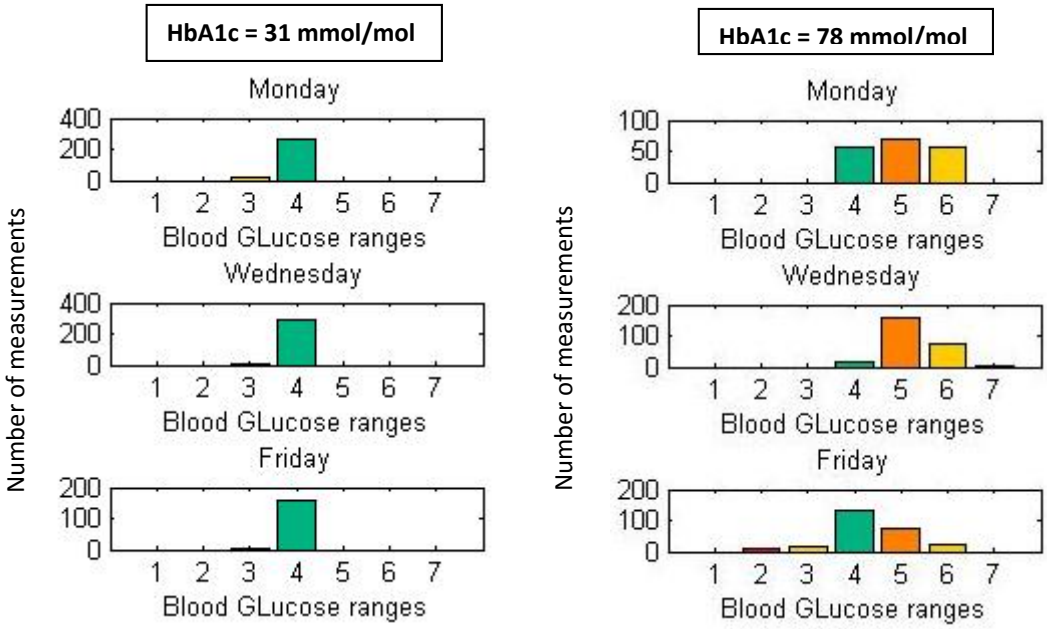

Figure 37: Two different cases of BG distribution for particular weekday. The BG ranges are as follows: 1 - <2.8, 2 – <2.8-3.3), 3 – <3.3 – 3.9), 4 – <3.9 – 10), 5 – <10 – 13.9), 6 - <13.9 – 22.2), 7 - >22.2.

The full Matlab script of the algorithm created together with data from 72 sample patients possible to process is included in the attachment (use the script *bg_readings_weekdays.m* in folder *bg_classification*). Pictures of sampled patients with HbA1c>60 mmol/L and those of which HbA1c<56 mmol/L are available in specific folders on attached CD (see *HighHbA1c* and *LowHbA1c*).

If we make similar distribution with other parameters, such as intensity of physical activity (as is described in the next section) we can get another clue to what causes potential highs or lows on given day.

5.1.2. Classification of total daily steps

Having information about patient´s daily physical (in)activity can help to say more about patient´s daily regimen and discover potential inter-day irregularities in it. An average number of steps taken per day reflects a general information about patient´s lifestyle, engagement in an exercise, or physical activity demands connected to patient´s work. Thus, extracting such information for each weekday can give a view into patient´s daily regimen. Knowing that, one can, on one hand, try to introduce more exercise to some days, or parts of days, in which some activity could effectively reduce regular highs, or try to solve recurrent lows that appears in connection to a high active day.

Design

When I extracted patient´s physical activity data, I classified them into both the ranges of intensity of physical activity recommended in studies [82,83] and corresponding weekdays.

Graphical representation of the output is visualized in Figure 38.

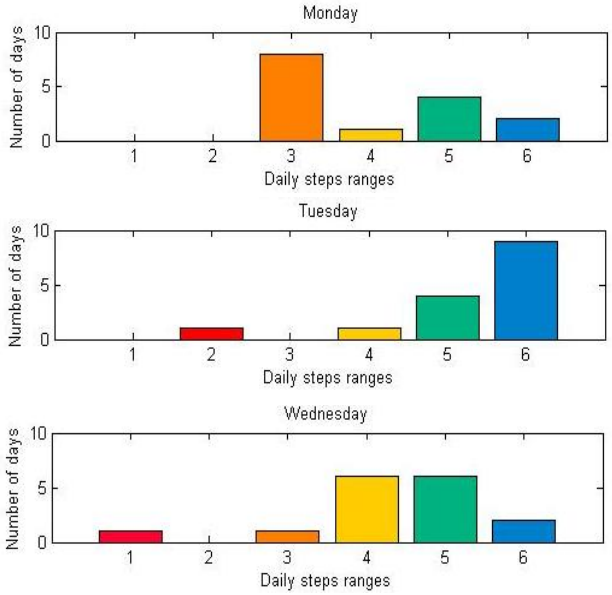

Figure 38: Number of days falling to particular ranges of total daily steps for each weekday. The daily steps ranges are as follows: 1 - <2,500; 2 - <2,500-5,000); 3 - <5,000;7,500); 4 - <7,500;10,000); 5 - <10,000;12,500); 6 - >12,500.

In addition, for each weekday I extracted information about an average number of very active minutes, that means those in which the number of steps was equal or higher than 100/min (Figure 39). This information can pinpoint very active days a patient has the most often weekday(s).

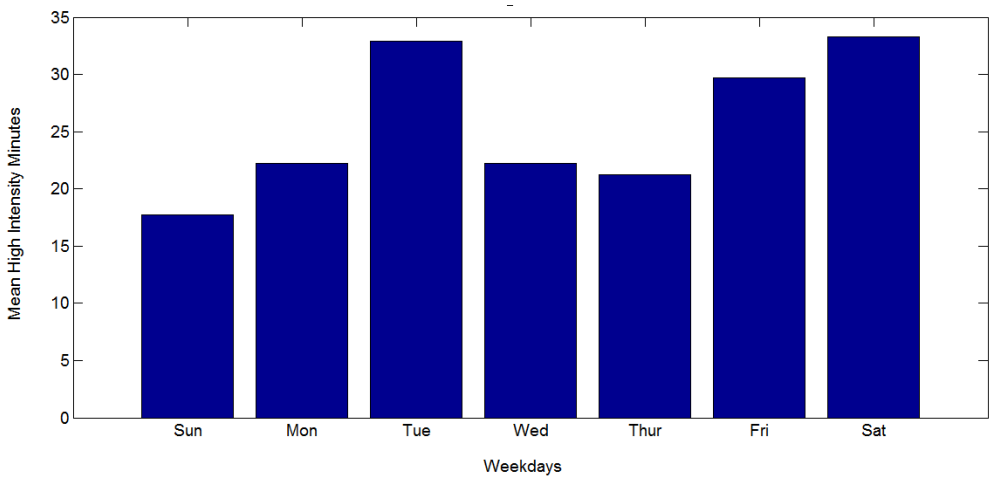

Figure 39: Mean high intensity minutes distribution per each weekday.

In combination with an average BG during this time, or the histogram of BG ranges displayed for particular weekday, it should be possible to discover, for example, the high active days

during which very low BG readings often occurs, or on the other hand, very highs connected with very low activity level.

Evaluation

I processed a database of 72 patients with approx. a week records of CGM and physical activity, using my algorithms created for the BG classification and daily steps classification.

I selected some examples of patients´ weekly profiles, from which we can make some assumptions about how they manage their glycaemia while having certain amount of physical activity.

Two extremes can be shown on Figure 40 and 41, where the first picture shows very inactive patient who, in addition to it, suffers from very unstable and high glycaemia. In the contrary, Figure 42 shows a patient who is highly active and his glycaemia rarely exceeds the upper limit for normal range, but tends to keep BG lower, which leads even to frequent hypoglycaemia.

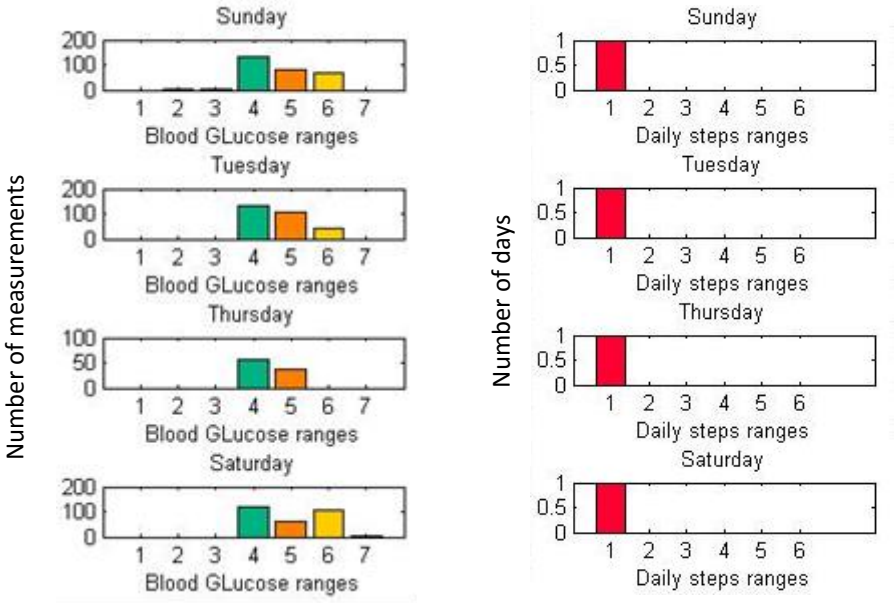

Figure 40: Comparative bar plots - left side displays number of measurements in particular glycemic ranges and the right side displays number of days within particular ranges of intensity of physical activity. In this case the patient has constantly high blood glucose, while being poorly active. The BG ranges are as follows: 1 - <2.8; 2 – <2.8,3.3); 3 – <3.3, 3.9); 4 – <3.9, 10); 5 – <10, 13.9); 6 - <13.9, 22.2); 7 - >22.2. The daily steps ranges are as follows: 1 - <2,500; 2 - <2,500;5,000); 3 - <5,000;7,500); 4 - <7,500;10,000); 5 - <10,000;12,500); 6 - >12,500.

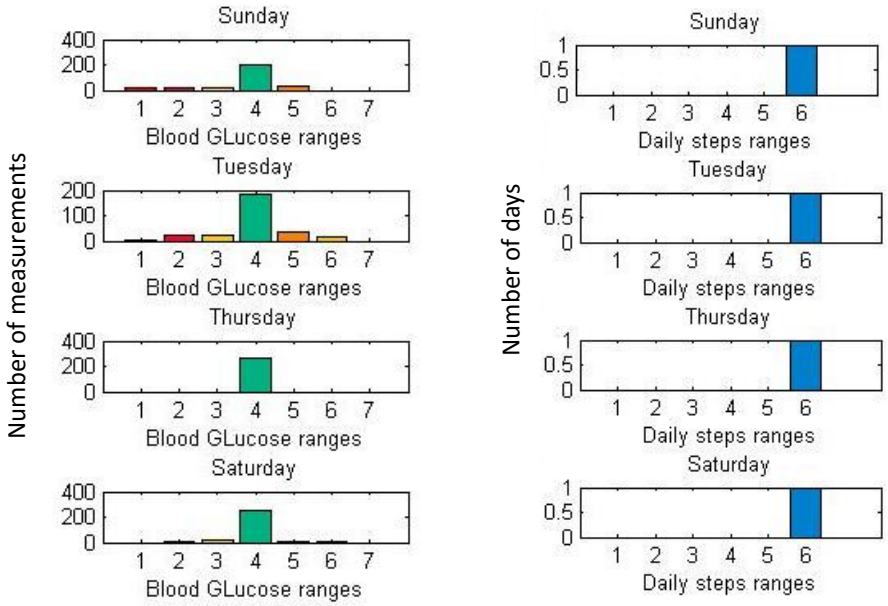

Figure 41: Comparative bar plots - left side displays number of measurements in particular glycemic ranges and the right side displays number of days within particular ranges of intensity of physical activity. In this case the patient has blood glucose almost within normal range but hypoglycaemia occurs, while being highly active. The BG ranges are as follows: 1 - <2.8; 2 – <2.8,3.3); 3 – <3.3, 3.9); 4 – <3.9, 10); 5 – <10, 13.9); 6 - <13.9, 22.2); 7 - >22.2. The daily steps ranges are as follows: 1 - <2,500; 2 - <2,500;5,000); 3 - <5,000;7,500); 4 - <7,500;10,000); 5 - <10,000;12,500); 6 - >12,500.

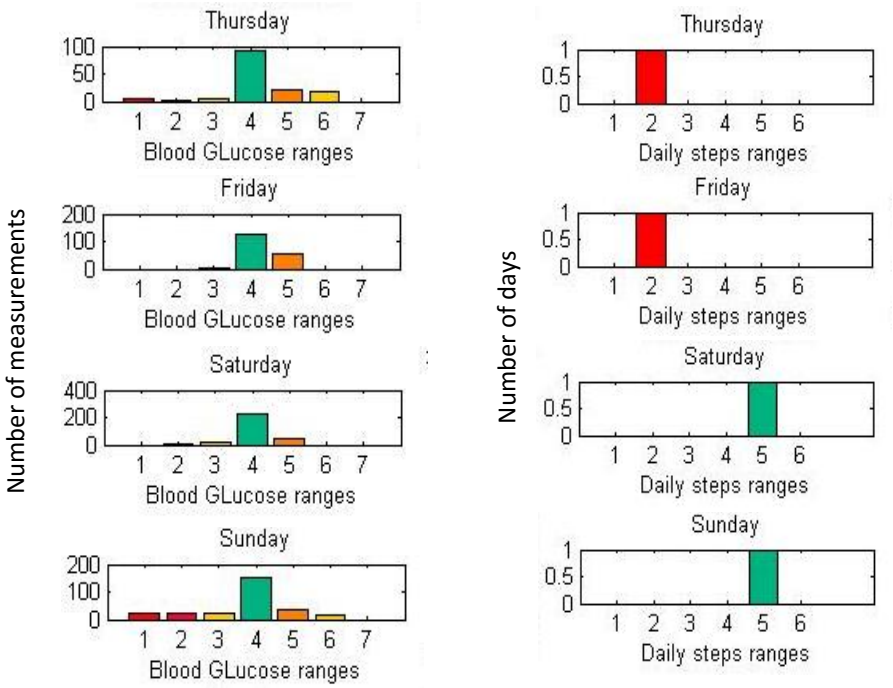

Figure 42: Comparative bar plots - left side displays number of measurements in particular glycemic ranges and the right side displays number of days within particular ranges of intensity of physical activity. In this case as the patient has either low physical activity in connection with more events of hyperglycaemia, or higher physical activity together with more often cases of hypoglycaemia. The BG ranges are as follows: 1 - <2.8; 2 – <2.8,3.3); 3 – <3.3, 3.9); 4 – <3.9, 10); 5 – <10, 13.9); 6 - <13.9, 22.2); 7 - >22.2. The daily steps ranges are as follows: 1 - <2,500; 2 - <2,500;5,000); 3 - <5,000;7,500); 4 - <7,500;10,000); 5 - <10,000;12,500); 6 - >12,500.

Besides mentioned extremes in both glycaemia and intensity of physical activity, there are also examples of inter-day variability, such as the case of the patient on Figure 42.

On the picture we can see that, while being pretty low physical active on Thursday and Friday, the patient has more high BG readings compared to Saturday and Sunday, where the intensity of physical activity is much higher, and at the same time the glycaemia tends to be lower, even falls to more frequent hypoglycaemia.

Last but not least, there are also patients whose glycaemia pattern does not differ with changes of intensity of physical activity. It can be either an example of frequent highs, which indicate that the patient´s overall compensation is poor, or in normal range glycaemia, which indicates the patient is able to self-manage his disease well, despite the changes of physical activity level. This case is represented by Figure 43.

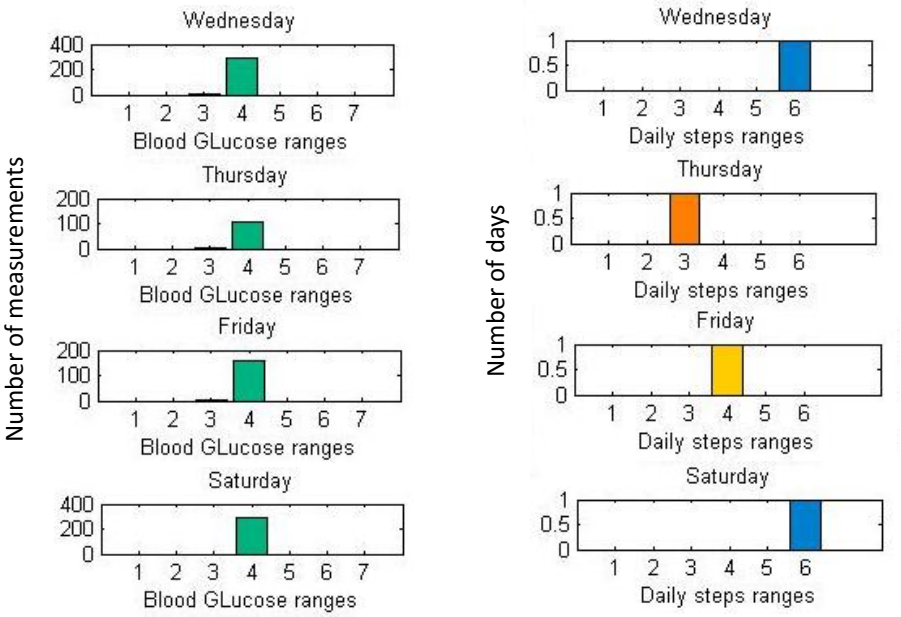

Figure 43: Comparative bar plots - left side displays number of measurements in particular glycemic ranges and the right side displays number of days within particular ranges of intensity of physical activity. In this case the patient´s glycaemia is mostly in range and the glycemic profile on the left does not differ against the intensity of physical activity. The BG ranges are as follows: 1 - <2.8; 2 – <2.8,3.3); 3 – <3.3, 3.9); 4 – <3.9, 10); 5 – <10, 13.9); 6 - <13.9, 22.2); 7 - >22.2. The daily steps ranges are as follows: 1 - <2,500; 2 - <2,500;5,000); 3 - <5,000;7,500); 4 - <7,500;10,000); 5 - <10,000;12,500); 6 - >12,500.

According to the profiles presented it is obvious that there are several patterns in the resulting form of data interpretation that could be useful for both patients and clinicians to better understand not only patient´s general problems with respect to BG values and/or the impact of different levels of physical activity on them, but also to find certain days to focus and analyse in detail.

The full Matlab script of the algorithm created together with data from 72 sample patients possible to process is included in the attachment (use the script *steps_weekdays_classification.m* in folder *steps_classification*).

5.1.3. Classification of glycemic excursions using the MAGE method

Regarding CGM data and their exploration, I chose to use the Mean Amplitude of Glycemic Excursions (MAGE), which is a method that describes BG fluctuations, as explained in section 4.1.1.2. My vision was to find a way of automatic evaluation of glycemic excursion in CGM data, using an algorithm instead of manual searching, which clinicians currently do in case they have sufficient time for a patient.

Design

First step was to find meaningful peaks and nadirs during the 24-hour time record of a given patient. Using the Matlab function for finding global extrema points (*extrema.m*) [89] I identified all peaks and nadirs in the time series (Figure 44).

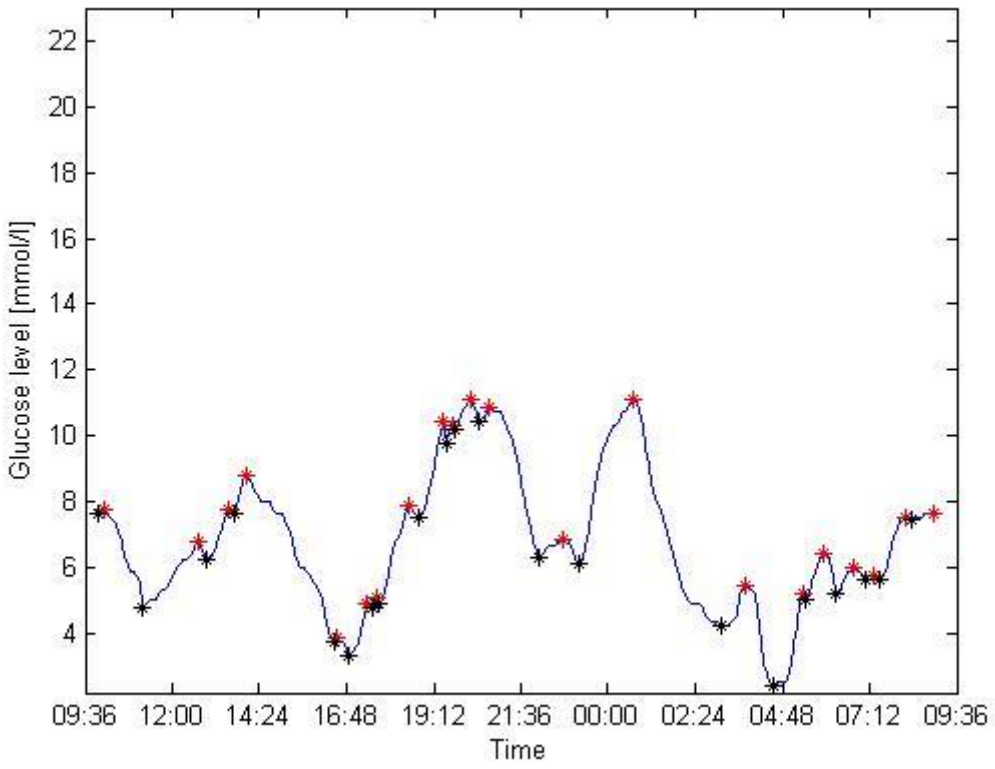

Figure 44: Peaks and nadirs identification in the 24-hour signal extracted frm the CGM.

As we can see in Figure 44, there are many acute peaks. While their amplitude would not fulfil the condition of its value greater than one standard deviation (SD) of average BG of the signal, the combination of these peaks form one dominant peak, the amplitude of which should be

accounted. Therefore, I used a time window to define the duration of which the BG change is not statistically significant for the MAGE calculation.

With this limitation, the algorithm detected only those peaks that were significant with respect to both conditions of time and amplitude (see Figure 45).

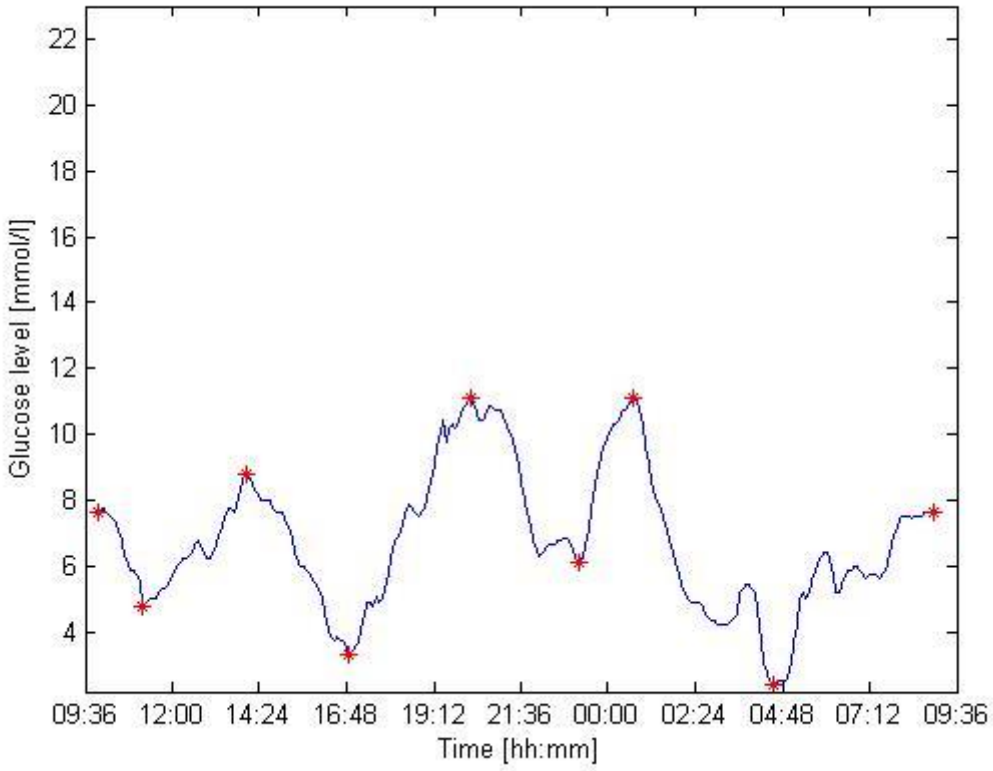

Figure 45: Peaks and nadirs detection using the time window in which the less dominant peaks are reduced.

I defined the MAGE+, MAGE- and the average MAGE values from the data automatically extracted by the algorithm. In addition, I also computed the standard deviation (SD), which dictates the first condition for peaks detection, and the frequency of peak-to-nadir and nadir-to-peak incidences. It is important to identify, for example, when there are a larger number of significant nadir-to-peak incidences together with smaller number of peak-to-nadir incidences and vice versa, whereby the ideal ratio should be obviously 1:1.

Besides that, I choose the sum of absolute differences (SAD) as an additional parameter that can more specifically indicate the total amount of fluctuations.

I processed data from 10 patients, to which I highlighted the parameters mentioned before and applied the corresponding algorithms. In addition, I chose 2 consecutive days for each patient in order to compare the intra-day differences in BG fluctuations.

Example of automatic peaks and nadirs detection of 3 specific sample patients with different BG excursions are shown in Figure 46, whereas for each patient 2 consecutive days are

displayed. In addition, for each of the 3 patients corresponding values of MAGE, numbers of peak-to-nadir and nadir-to-peak excursions detected by the algorithm ($Freq^+$ and $Freq^-$), SAD, SD, mean BG and HbA1c are listed in Table 5.

Table 5: Example of automatic generation of data describing glycemic excursions of CGM records.

Patient ID	Day ID	HbA1c	SD	Mean BG	SAD	MAGE-	Freq-	MAGE+	Freq+	MAGE average
JK1	1	50	4.12	10.17	74.13	-10.29	3	10.82	2	**10.55**
JK1	2	50	3.35	7.57	48.96	-8.16	2	10.05	2	**9.10**
AK1	1	68	1.21	5.91	30.54	-2.17	4	2.49	5	**2.33**
AK1	2	68	3.05	8.07	51.27	-7.88	2	7.33	2	**7.60**
VB3	1	51	1.69	4.53	33.31	-3.89	3	3.97	4	**3.93**
VB3	2	51	1.59	6.43	36.6	-4.55	2	3.19	4	**3.87**

It is obvious that high MAGE signalizes substantial spikes in data, which we can see, for instance, in the results from patient JK1 and compare to those graphs on Figure 46 (A1-A2). Moreover, Figure 46 (B1-B2) shows much smaller BG variability for significantly lower MAGE values of the patient VB3.

Regarding the inter-day variability, we can see that, while having very similar frequency of fluctuations of both patients JK1 and VB3, the values of MAGE belonging to patient AK1 differ, which also proves corresponding glycemic variability displayed on Figure 46 (C1-C2).

To explore which type of useful information can be extracted from such numerical values on one hand and to validate the usefulness of this method itself on the other hand, I needed to choose the gold standard, with which I could compare my results. Therefore, due to the fact that the current and most precise evaluation is considered to be that made by diabetologists or endocrinologists, I gave samples of 2 consecutive days of CMG records from 10 patients to a diabetologist from the University Hospital in Motol, and asked him to evaluate the glycemic excursions of each patient based on his professional medical opinion.

The process of evaluation and its results are described in the next section.

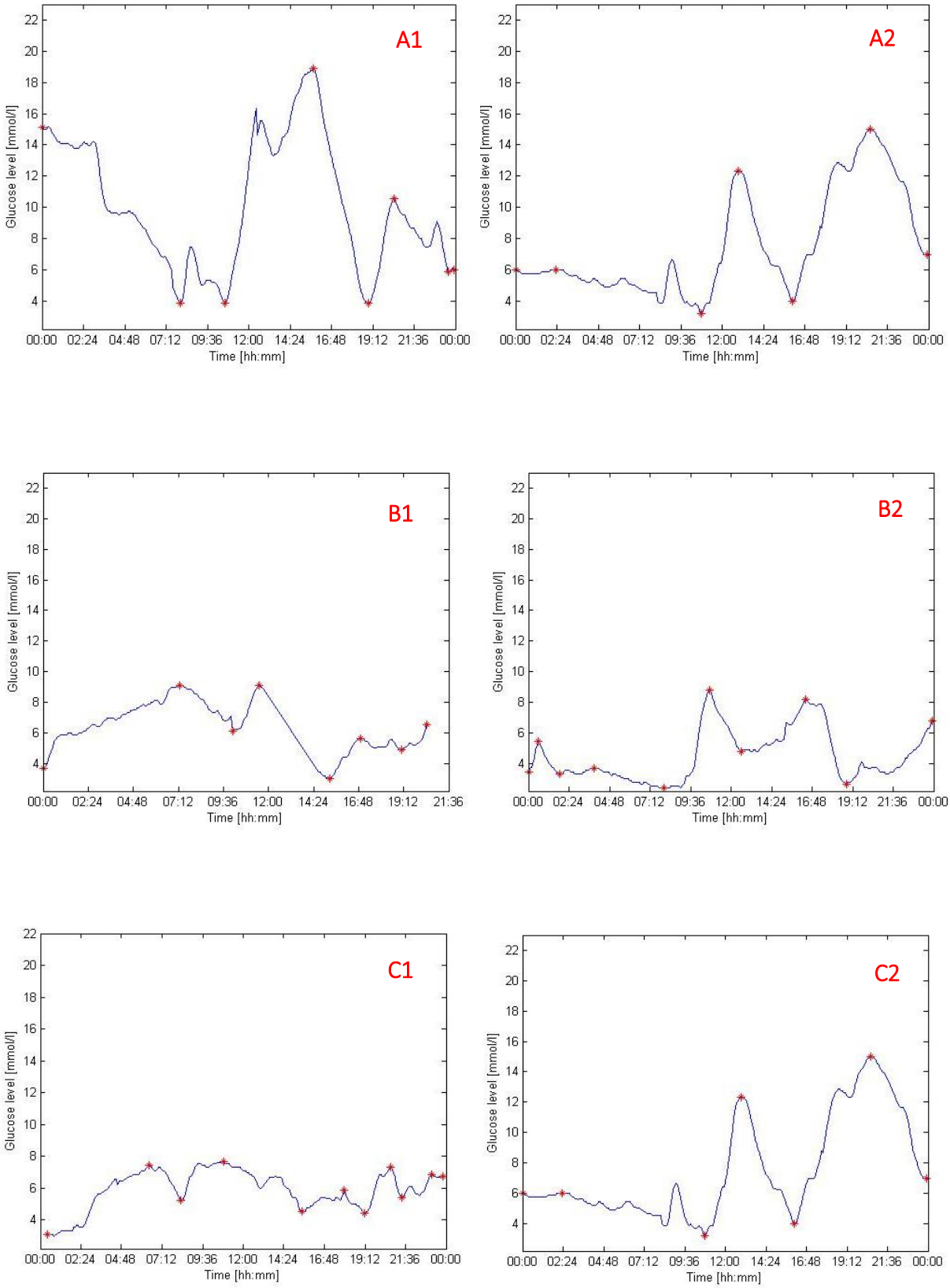

Figure 46: Examples of 2 consecutive days of CGM records of 3 patients with corresponding peaks and nadirs detection.

Evaluation

To evaluate the capacity of glycemic excursion detection, I prepared a document with graphical representation of CGM records from 10 patients in total, whereas each patient´s data were represented by 2 consecutive days of the blood glucose signal. Then I gave it to the clinician and asked him to evaluate glycemic excursions of each patient based on his casual medical practice.

The clinician gave me back the document with his comments and evaluation of the main differences between the 2 consecutive days for each patient, whereas he ranked each graph separately according to 2 following criteria:

1) 1st Variability Index: BG variability from the point of view of the frequency of fluctuations on a scale from 1 to 5 points
2) 2nd Variability Index: BG variability characterized by fluctuations that exceed particular BG range, i.e. class 1 represents BG readings that are fluctuating under the BG level of 10 mmol/L and do not exceed this this value, class 2 means that some of the BG readings cross the line of 10 mmol/L, but do not exceed the level of 15 mmol/L, and into class 3 fall the signals which are exceeding the level of 15 mmol/L.

Having the data ranked according to the classification described above, I added the results to the automatically generated table that was a part of the MAGE evaluation program I have made. All the parameters computed for each patient from the sampled group with corresponding Variability Index matched by the clinician are summarized in Table 6.

Table 6: List of evaluated patients with information about MAGE values and Variability Indices assigned by the clinician.

Patient ID	SD	Mean BG	SAD	MAGE-	Freq-	MAGE+	Freq+	MAGE avg	Variab Index	
									1	2
1	4.12	10.17	74.13	-10.29	3	10.82	2	**10.55**	*3*	***3***
1	3.35	7.57	48.96	-8.16	2	10.05	2	**9.10**	*3*	***3***
2	2.68	6.73	49.26	-6.83	2	5.99	3	**6.41**	*2*	***2***
2	3.23	8.27	75.08	-7.83	4	7.02	4	**7.43**	*3*	***2***
3	3.86	8.62	67.17	-9.33	2	9.55	2	**9.44**	*4*	***3***
3	3.19	9.48	89.37	-4.81	6	5.77	6	**5.29**	*4*	***3***
4	1.21	5.91	30.54	-2.17	4	2.49	5	**2.33**	*1*	***1***
4	3.05	8.07	51.27	-7.88	2	7.33	2	**7.60**	*3*	***2***
5	4.92	12.68	64.64	-11.33	2	7.38	4	**9.35**	*3*	***3***
5	3.80	12.44	51.36	-6.95	3	7.71	2	**7.33**	*3*	***3***
6	1.63	7.48	50.31	-3.50	3	4.94	3	**4.22**	*2*	***1***
6	2.77	8.78	83.38	-6.76	5	7.04	5	**6.90**	*3*	***2***
7	2.67	7.97	74.22	-7.96	2	8.47	3	**8.22**	*3*	***3***
7	5.11	13.15	71.74	-11.74	2	10.46	2	**11.10**	*3*	***3***
8	1.90	7.01	66.52	-6.12	4	4.93	5	**5.52**	*3*	***2***
8	2.05	7.52	65.7	-4.57	5	3.98	6	**4.28**	*3*	***2***
9	2.75	8.38	40.05	-9.77	1	6.37	3	**8.07**	*3*	***2***
9	2.84	10.24	43.76	-6.66	3	6.00	2	**6.33**	*2*	***2***
10	1.69	4.53	33.31	-3.89	3	3.97	4	**3.93**	*2*	***1***
10	1.59	6.43	36.6	-4.55	2	3.19	4	**3.87**	*2*	***1***
11	2.37	9.12	43.64	-6.25	3	4.44	3	**5.35**	*3*	***2***
11	1.83	7.72	35.34	-3.78	3	4.74	3	**4.26**	*2*	***2***
13	2.69	6.13	60.27	-6.89	2	8.22	2	**7.55**	*3*	***2***
13	1.42	5.11	47.47	-2.40	6	3.16	4	**2.78**	*2*	***1***
14	2.17	8.09	64.56	-6.13	4	6.33	4	**6.23**	*3*	***2***
14	1.69	7.43	35.71	-4.03	3	4.41	4	**4.22**	*2*	***2***
15	1.94	6.14	38.12	-3.61	4	4.66	4	**4.14**	-	***1***
17	0.99	7.10	30.66	-2.17	4	2.18	6	**2.17**	-	***1***

As a next step I searched for a correlation between the Variability Indexes assigned by the clinician and the MAGE values computed by my program. Due to a predominant number of samples ranked with the class 3 in case of using the 1st Variability Index, and thus, insufficient number of the samples falling into the other classes, I was not able to find any significant correlation with the MAGE value.

However, when grouping the MAGE values according to the 2nd Variability Index, more samples were assigned to each class to be able to examine whether the 3 emerged groups are significantly different or not. Table 7 summarizes the concrete values falling within particular class.

Table 7: MAGE values grouped according to the clinician´s classification.

Group Number	1	2	3
MAGE values	2.33	6.41	10.55
	4.22	7.43	9.10
	3.93	7.60	9.44
	3.87	6.90	5.29
	2.78	5.52	9.35
	4.14	4.28	7.33
		8.07	8.22
		6.33	11.11
		5.35	
		7.55	
		6.23	
		4.22	
		4.26	
MAGE min	***2.33***	***4.22***	***5.29***
MAGE max	***4.22***	***8.07***	***11.11***
Number of samples	***6***	***13***	***8***

For better illustration of the variability of each group I made a boxplot describing each grouping variable and the distribution of each group (see Figure 47).

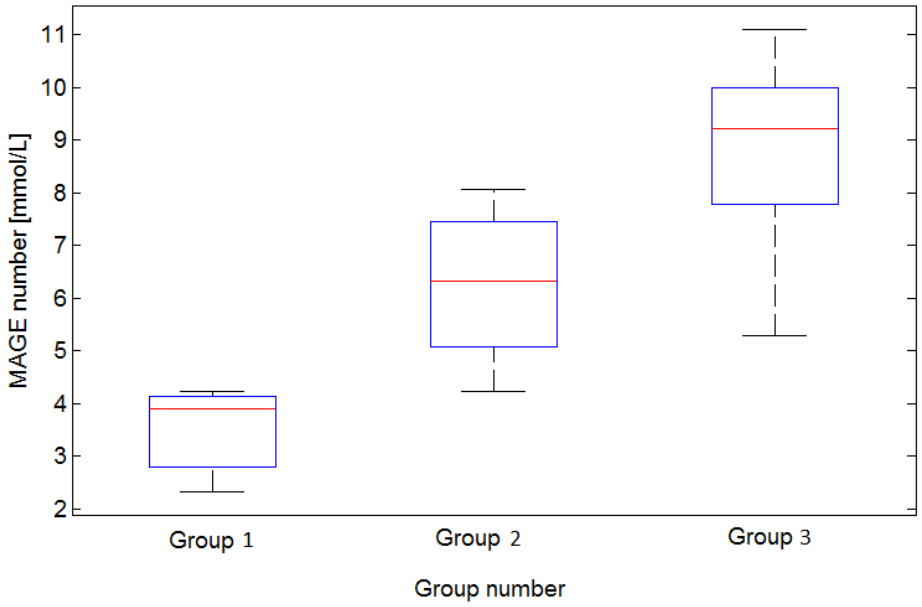

Figure 47: Graphical interpretation of distribution of the groups classifying the MAGE values, with information about median and 25th and 75th percentiles, respectively.

As we can see, the group 1 and group 2 are not crossing each other, while the group 3 overlaps the second group, specifically by 2 values. Since I could not expect a normal distribution of the data, I chose the two-sided Wilcoxon rank sum test as a statistical evaluation method for the data.

I compared the groups between each other using the Matlab function "*ranksum*" to obtain the p-values which indicated whether the null hypothesis of equal medians at the 5% significance level was being rejected or not.

Based on the statistical results for all the three groups, the null hypothesis has been rejected, which means that there is a statistically significant difference between each group, as indicates the results in Table 8.

Table 8: Results of the statistical evaluation using the two-sided Wilcoxon rank sum test.

Compared groups	p-value	h-number
Group 1 vs Group 2	*0.0001*	1
Group 2 vs Group 3	*0.0066*	1
Group 1 vs Group 3	*0.0007*	1

From the results we can conclude that classification of the MAGE values into three ranges as described by the clinician could be a relevant method for an automatic evaluation of glycemic variability.

The final algorithm for MAGE results computation is attached to CD (folder *MAGE*, script *MAGE_auto.m*).

5.1.4. Peaks detection using the MODD method

Design

In case of the MAGE method one is able to judge the intensity of daily excursions and the interday differences of such excursions. However, when it comes to finding the time of the day in which such irregularity occurred and assessment of its significance, this method mostly fails. For that reason, I decided to use, in addition to the MAGE, the Mean of Daily Differences (MODD). This method is based on computation of mean absolute value of the differences of glucose values that were measured at the same time within two consecutive days. The significance of the differences could identify certain time of the irregularity occurrence.

Therefore, I made an algorithm for an automatic computation of differences between 2 consecutive days of the same patient. The main peaks of resulting graph highlight the main differences at corresponding time, as it is shown on Figure 48.

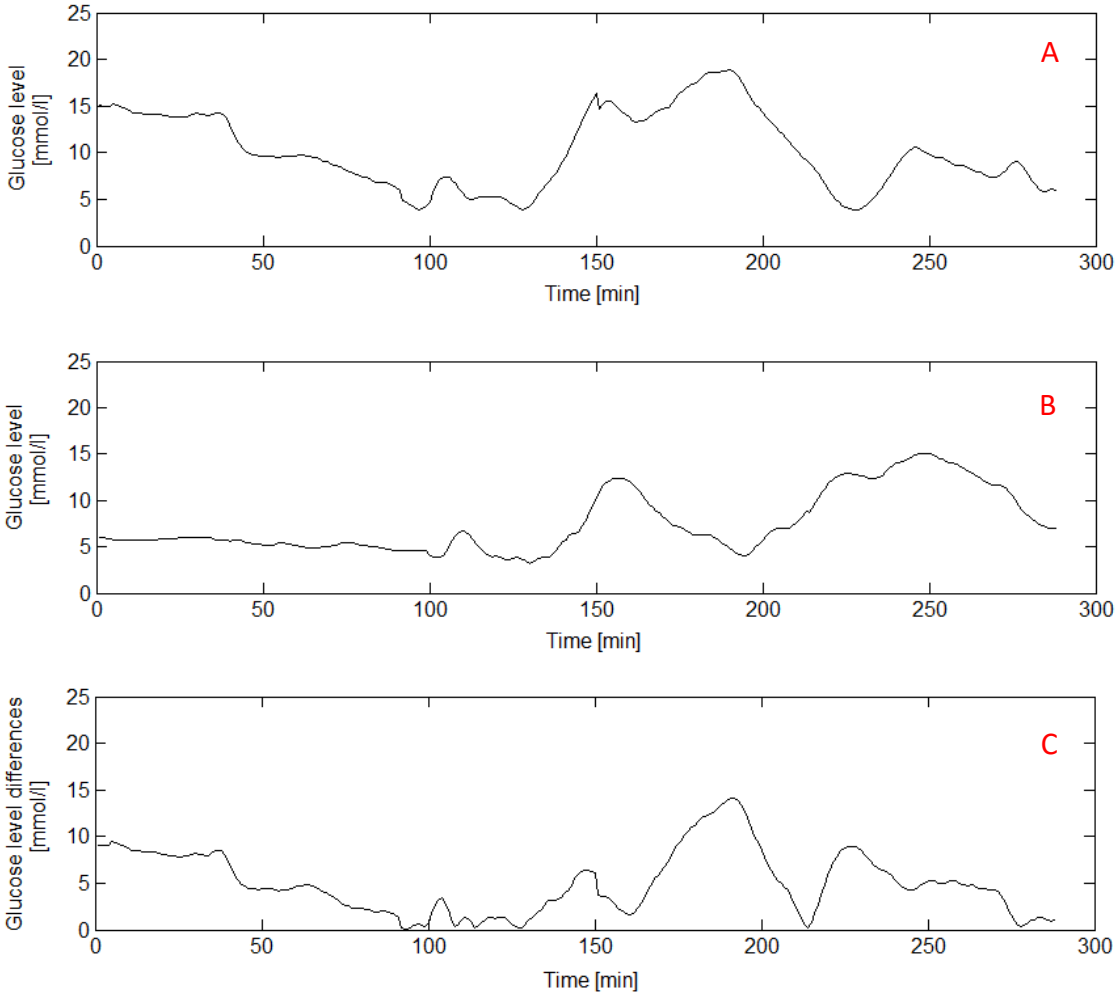

Figure 48: Example of BG difference computed on 2 consecutive days represented by signals A and B. The signal C shows corresponding curve of the difference of the signals A and B.

Using the algorithm for the peaks and nadirs detection for the MAGE computation I detected the peaks signalizing the main inter-day differences at given time. Instead of tracking every peak of its value is bigger than the standard deviation of the signal, I used the MODD value as a threshold for peaks detection (see Figure 49).

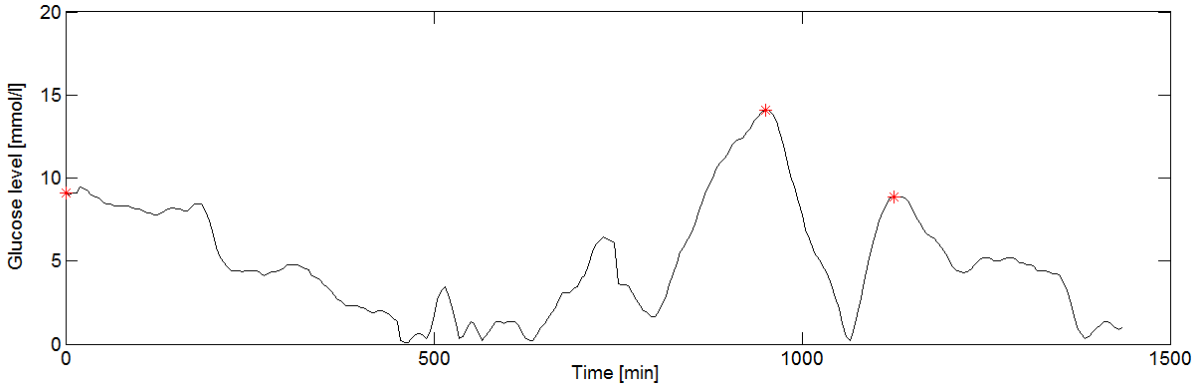

Figure 49: Example of peaks detection using in the signal of inter-day differences.

Finally, I exported values and times of occurrence of the peaks from selected patients, and used the results for evaluation of success rate of this method with the manually evaluated records made by the clinician, as described in the next section.

The final algorithm for peaks detection using MODD is attached to CD (folder *MODD*, script *MODD_auto.m*). In the same folder the final table with all the results is attached as well (see *PeakDiffTab.xlsx*).

Evaluation

When using the MAGE method, we can obtain the information about patient´s intensity of fluctuations throughout the whole one day. However, to be able to compare manual evaluation of the inter-day irregularities with an automatic evaluation method, I used my algorithms based on the MODD method to compare whether the automatic peak detection is able to find at least those problematic situations that have been matched by the clinician in the same document as the MAGE evaluation have been made (see example in Appendix C or the full file on CD – *evaluation_excursions.pdf*). Besides the variability evaluation the clinician commented using the ranking scale, he also made a comparison between the 2 consecutive graphs and marked some places with the following letters: 1) 'VR', which means a big difference, 2) 'ZR', which means significant difference, and 3) 'O', which means that the signals are quite similar.

I used the results with the detection of the main daily differences from the automatically generated table, that is a part of the MODD evaluation program I have made, to compare it with the differences highlighted by the clinician. The final comparison is described in Table 9.

As we can see, all the significant inter-day differences highlighted by the clinician were detected automatically as well. In addition, another more than a half of the rest excursions in the daily difference signals was detected by the program due to its meeting the condition of the minimum threshold of the MODD value calculated for each dataset. The two main reasons why the clinician did not highlight more of the situations detected by the program was that he mostly matched only the maximum differences between the day, which were marked as "VR" (i.e. big difference), and only the data from the last patient in the Table were described with the two rest classes explained above the text (i.e. "ZR" as a significant difference, and "O" as similar). Considering the last proper evaluation of the patient "AH", we can see that the maximum value marked as "VR" was matched as the maximum value detected by the program. Although the next smaller difference marked as "ZR" was matched by the program as the third biggest value, it is necessary to consider that the values of the second and the third biggest differences are almost the same, and thus, very hard to be distinguished with sole observation made by clinicians. Finally, the situations marked as "O", which means the parts of the signals were similar, were not detected by the program, which means it complied its purpose.

Table 9: Peaks of the main daily differences automatically detected by the algorithm. The highlighted values signalize cases that were matched by the clinician.

Patient ID	Patient No.	Time	Diff value	Max Diff	Min Diff	MODD
JK1	1	0:00	9.1	14.1	8.9	5.0
	1	15:50	**14.1**			
	1	18:45	8.9			
LB2	2	1:35	7.0	14.2	6.3	3.4
	2	9:40	**6.3**			
	2	14:45	**14.2**			
	2	20:50	6.8			
MH1	3	3:05	10.8	10.9	5.8	4. 8
	3	9:30	5.8			
	3	16:50	**10.9**			
	3	23:05	6.3			
AK1	4	0:25	3.7	9.1	3.7	3.2
	4	2:25	5.7			
	4	4:00	5.6			
	4	8:20	**9.1**			
	4	21:25	5.4			
MK4	5	0:00	2.9	9.5	2.9	2.6
	5	9:40	**9.5**			
	5	16:55	5.0			
DK1	7	0:00	**9.9**	11.4	8.6	6.1
	7	1:45	**8.6**			
	7	3:40	**11.4**			
	7	17:10	8.7			
	7	20:50	10.2			
AH	14	0:00	2.2	8.1	2.2	2.2
	14	8:10	**8.1**			
	14	11:55	3.0			
	14	15:35	6.1			
	14	23:45	**5.9**			
					Total number differences detected by program	***24***
					Total number differences matched by clinician	***11***
					Sum of matched differences	***11***
					Number of mismatched differences	***0***

5.1.5. Mealtime situations detection

My aim was to find certain mealtime situations in the datasets from which to extract important factors that could clearly indicate how a given patient manages these parts of their daily regimen. Although several applications, usually those connected to a blood glucose meters or insulin pumps, can analyse, for example, pre- and post-meal glycaemia, a user often has to sign manually what event he plans to do (such as glycaemia measured before or after breakfast, lunch, dinner, night time, and others). However, accepting the fact that not many patients are sufficiently willing to register any additional information, it was required to define an algorithm that would be able of an automatic detection of mealtime situations in the datasets, while having the information about BG values and corresponding doses of insulin and carbs only, without any additional notes. Furthermore, signing those situations could help clinicians to better orientation in datasets, when being concerned to the substantial information that describes patients´ self-management.

Design

To detect those situations that would be relevant for making decisions about the treatment, the following parameters were needed to consider when creating the algorithm:

- Time of pre-meal BG, post meal BG, insulin injection and carbs intake together with the times between particular parameters. This would be used to detect the right meal situation and ensure that the post-meal BG is not affected by other circumstances.
- Time between carb intake and post-meal BG record, to ensure that certain post-meal BGs belong to the right range.
- Missing registrations that would make correct evaluation impossible.
- Multiple insulin injections and carbs registrations between pre-meal and post-meal BG records that are distributed in certain time intervals and have an impact on the following postprandial BG.
- Insulin-to-carbs ratio that can, in some cases, highlight missing registrations, or that can be used for evaluation of patients´ estimated insulin and carbs doses.

Based on these conditions and knowledge about carbs and insulin action, I determined corresponding time intervals between each parameter, as described in the following flowchart on Figure 50.

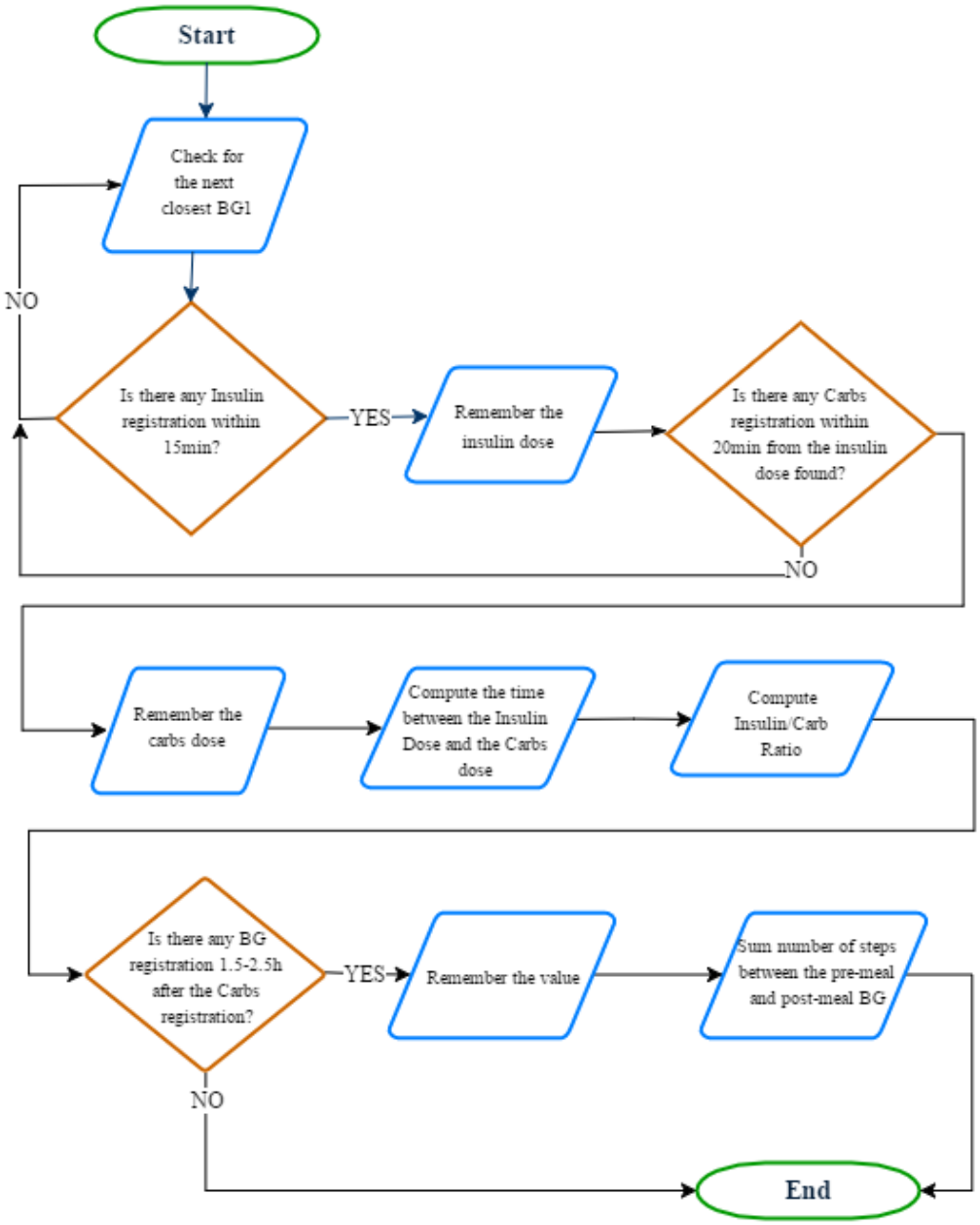

Figure 50: Flowchart describing the process of data extraction to be used for pre- and post-meal analysis.

After the designed algorithm was applied on the dataset, we extracted those data that complied with the conditions required to obtain relevant information about patient´s mealtime management. Table 10 includes the information we extracted in connection with an explanation of the importance of each of them.

Table 10: List of information extracted from the database and the reasons for extraction of given information.

Information extracted from the database	**Reason for its extraction**
Time and value of pre-meal blood glucose	Identification of the daily period and pre-meal BG levels
Time and value of post-meal blood glucose (if exists)	Identification of the daily period and post-meal BG levels
First insulin dose and the time of its application	Identification of an insulin dose situation
First Carbs dose and the time of its consumption	Identification of a carbs dose situation
Time between the pre-meal BG and the first insulin dose applied	Relevance of the pre-meal BG value
Time between the first insulin dose applied and the first carbs consumption	Defining how long patients wait for an insulin action before they start to eat
Sum of insulin registrations considered to be part of the same mealtime situation	To eliminate invalid interpretation of full mealtime dose of insulin
Sum of carbs registrations considered to be part of the same mealtime situation	To eliminate invalid interpretation of full mealtime dose of carbs
Insulin-to-carbs Ratio calculated from the first carbs and insulin dose only	To eliminate potential errors in summing inadequate additional carbs or insulin registrations
Insulin-to-carbs Ratio calculated from the sum of carbs and insulin doses detected	To compare with the Insulin-to-carbs ratio from the first insulin and carbs registrations and choose the most relevant information
Number of steps taken between pre-meal and post-meal BG	Factor of physical activity for evaluation of BG fluctuations

In a global context, this information helped me to extract 1) the most relevant information used from patients´ own datasets as an ideal model for them to learn from, and 2) some patterns related to patients´ behaviour that could indicate potential frequent mealtime problem, such as unstable pre- and post-meal BG readings or patient´s pattern of an insulin-to-carbs ratio throughout a day.

The next sections describe concrete types of data extraction and interpretation when focusing on the global viewpoint.

1) Pre- and post-meal BG

Design

One of the essential information relevant from the global viewpoint are the ranges of BG values before and after each mealtime throughout some period of time. Therefore, I classified the data into time intervals for breakfast (5-10h), lunch (11-14h) and dinner (17-21h) episodes. Following the Guidelines from NICE and their recommendation for pre and post-meal BG ranges [75], I applied the classification on the data from each episode to get final groups of data. Then I calculated a percentage of BG values falling within certain times before and after the main mealtimes, i.e. breakfast, lunch and dinner time.

Evaluation

I used my algorithm to be tested on data from 5 patients recruited for the long-term monitoring. Resulting graphical interpretation of pre- and post-meal BG values are presented in Figure 51.

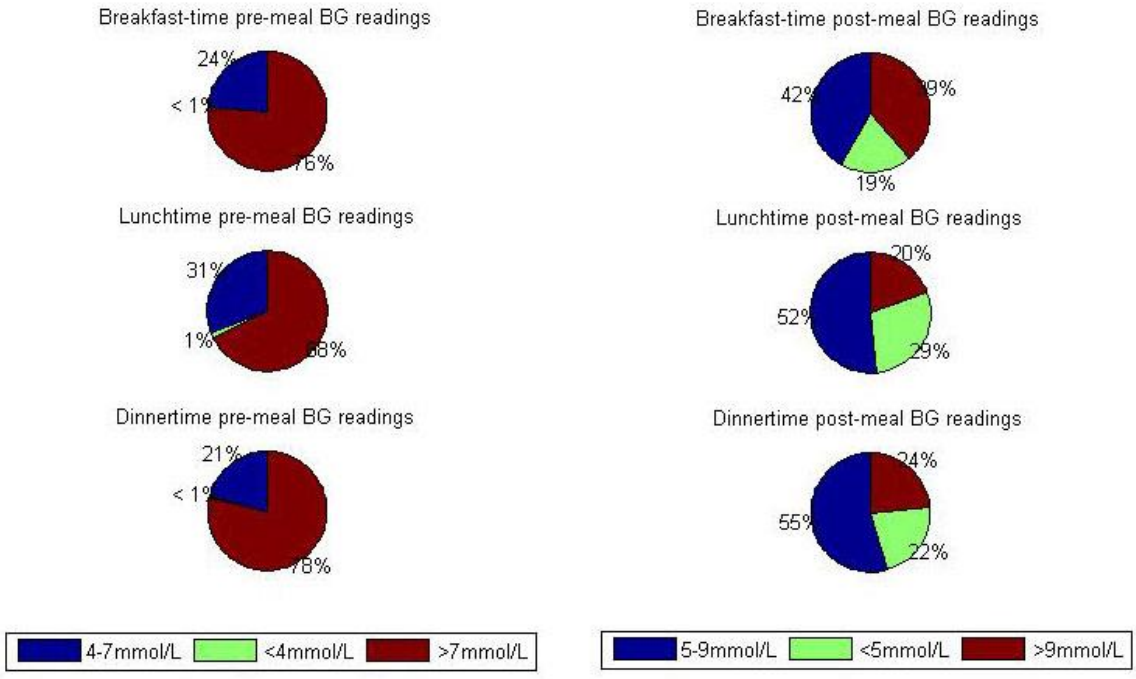

Figure 51: Distribution of blood glucose values before and after breakfast, lunch and dinner time.

Having this information both the clinician or the patient can see the main pattern of patient´s behaviour around given daily period with respect to BG values. For example, Figure 51 clearly shows that the patient has often higher BG before meal on one hand, but frequent lows after the meal episode. That might indicate that he attempts to lower pre-meal highs with correction boluses, which can lead to low blood glucoses afterwards in case the insulin doses are inappropriate.

All the results from selected patients are possible to generate using the designed Matlab script uploaded on CD attached (use the script *mealtime_bg.m* to run the program).

2) Insulin-to-Carbs ratio

Design

Apart from the mealtime BG readings, it is important to track insulin-to-carb ratio. This parameter dictates how many carbohydrates are covered by 1 unit of insulin. It means that improper ratio used for any meals can lead either to hypoglycaemia or hyperglycaemia, depending on its value. Moreover, as the insulin sensitivity varies during a day, the insulin-to-carb ratio should be estimated according to these changes.

Therefore, to explore how a given patient manages his insulin and carbs dosing, I extended the algorithm for mealtime data extracted for pre and post-meal BG readings, and defined the following conditions, which allowed me to find situations in which patients estimated the ratio correctly:

1) Premeal BG in target range, above range, and under the target range
2) Postmeal BG in target range
3) No physical activity between consecutive BG measurements
4) No additional insulin and carbs doses too far from the mealtime situation, but still falling within the time period observed

From the results of the selected data, I grouped the findings by time segments for which I calculated an average insulin-to-carb ratio. Example of resulting interpretation is displayed on Figure 52 (green bars).

After that, I took the same steps on the insulin-to-carb ratios, where the pre-meal BG was above target range, and grouped the results, as shows the same Figure 52 (dark red bars).

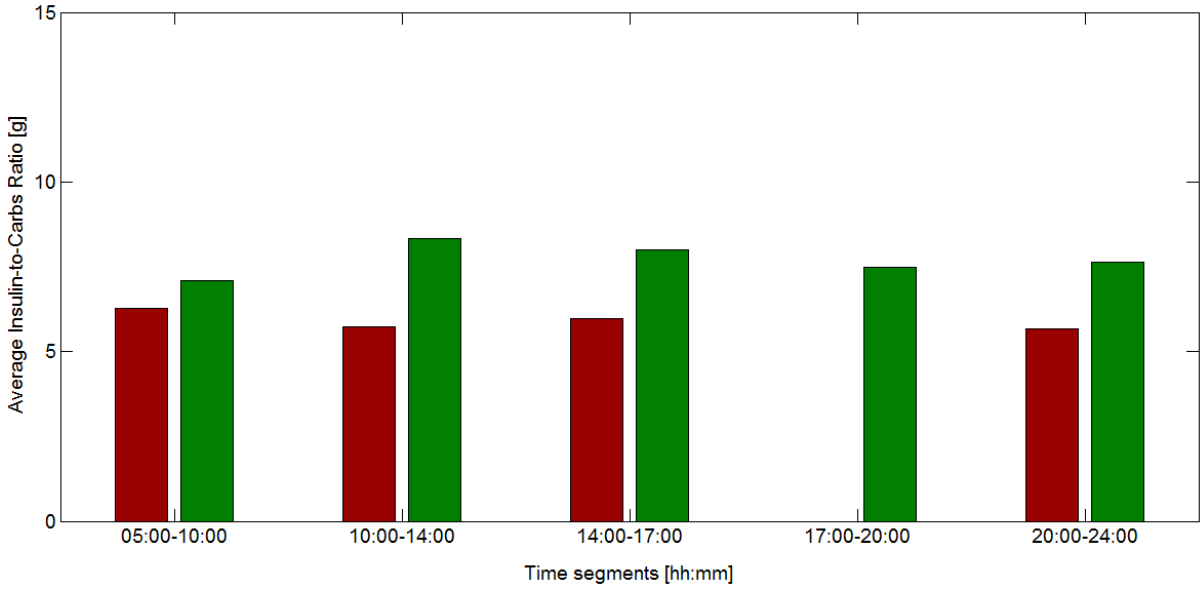

Figure 52: Example of the changes in the insulin-to-carbs ratio throughout a day. The green bars indicate the ratios when pre-meal blood glucose is within target range, whereas the dark red bars indicate the ratios when pre-meal blood glucose is above target range.

Evaluation

I run the program for 5 long-term monitored patients and got results about their insulin-to-carbs ratio throughout a day. Looking at Figure 52, we can see the green bar chart that represents insulin-to-carbs ratios of those situations when both pre- and post-meal average BG fall within the target values, the dark red distribution is significantly lower. This signifies behaviour of the patient to lower high BG with correction bolus, which results in lower insulin-to-carbs ratio. Moreover, comparing each time range, we can notice that there are more attempts to lower BG values in the second time range when compared to the breakfast time.

All the results from selected patients are possible to generate using the designed Matlab script uploaded on the CD attached (use the script *ins_to_carbs_ratio.m* to run the program).

3) Intra-day problems analysis

From a detailed viewpoint, the information extracted from the database, together with the patterns found, enabled me to define further conditions which would evaluate particular day and summarized the main problem that occurred there.

Design

While the global viewpoint can help to discover mostly patient´s regular habits on various conditions, such as high, low or in target BG level, different intensity of physical activity, or various time period, the role of a detailed viewpoint is to detect and highlight certain problems that occur within particular day.

This is, however, the crucial role of a clinician, i.e. to manually evaluate day-by-day records of patient´s registrations (if there are any reliable), make assumptions about patient´s self-management and consult detected problems with a patient. The next step is then to make decision about certain education the patient needs in order to dispose the problems.

Naturally, the implication of that is requirement of sufficient amount of time that is, unfortunately, often not possible to manage by clinicians.

Therefore, having a general information about patients´ habits and patterns found in their registrations, together with the information extracted from the database, my idea was to use all of these information and define further conditions which would evaluate particular patient´s day and summarize the main problems that occurred there. In addition, all of this performed as close as clinicians do. Summary from such algorithm could be a decision support tool that would not only shorten the time spent on the data-mining, but also highlight those situations that might be omitted by clinician´s manual performance.

Therefore, while in case of the mealtime situations detection in section 6.1.1. I defined such conditions that ensured finding mostly the ideal mealtime situations (that is, for example, when glycaemia is measured in certain times), in case of finding as many situations as possible I needed to change the conditions in order to obtain adequate feedback about what happened in certain day and time.

The main changes I applied on the algorithm described in section 6.1.1. were related to time intervals between each registration I wanted to detect. Detailed description of the algorithm´s process describes the following flowchart on Figure 53.

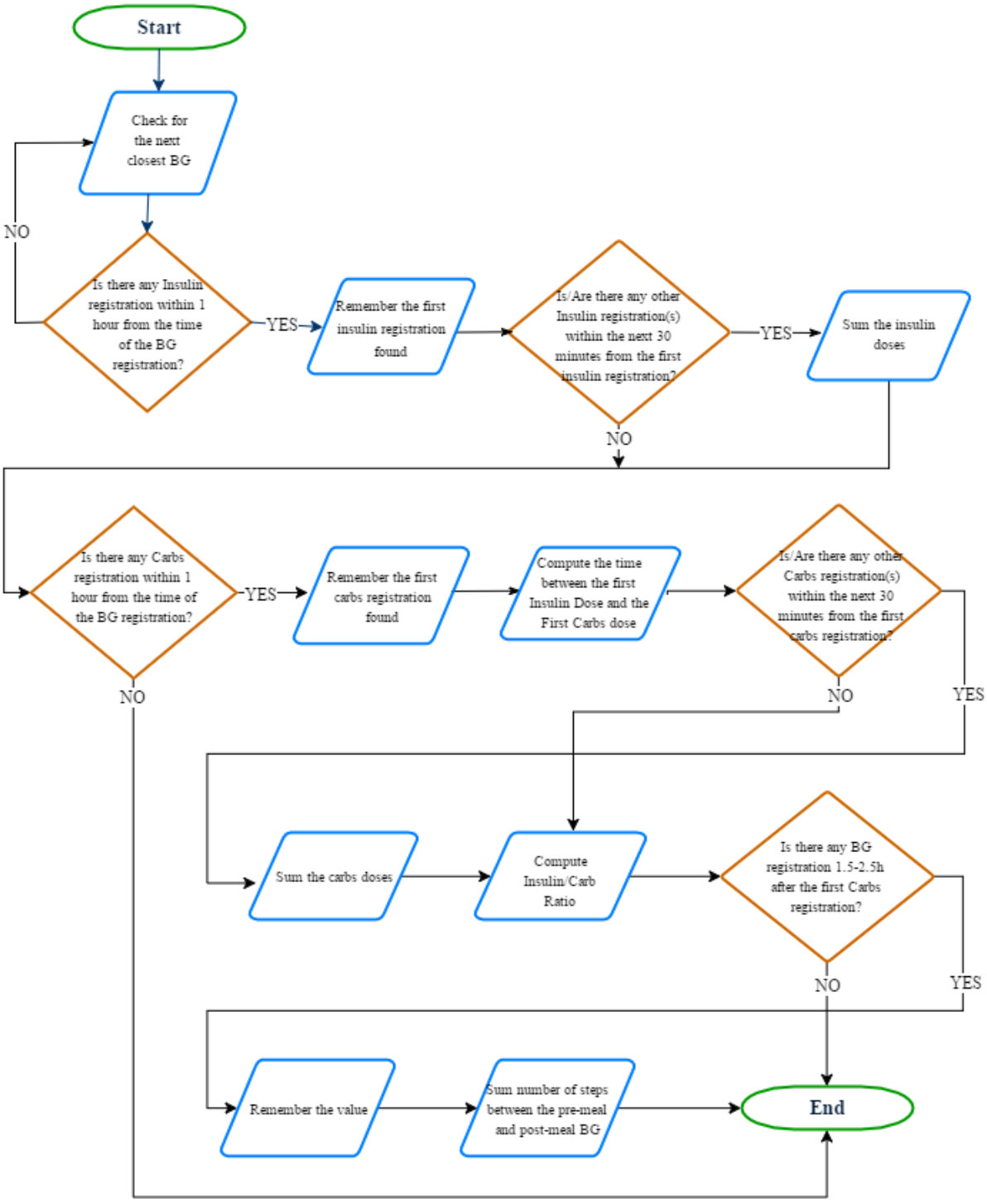

Figure 53: Flowchart describing the process of mealtime situations detection.

Using the data extracted from the database I design the algorithm generating occurrence of concrete problematic situations upon defined conditions. Table 11 summarizes defined conditions and corresponding outputs in case the algorithm meets the condition.

Table 11: List of situations described upon defined conditions.

1.	**Mealtime episode**	
Condition	**Output**	**Situation meaning**
5:00 ≤ BG time < 10:00	1	Breakfast
10:00 ≤ BG time < 14:00	2	Lunch
17:00 ≤ BG time < 21:00	3	Dinner
Other time	0	Other
2.	**Mealtime blood glucose ranges**	
Condition	**Output**	**Situation meaning**
BG>22.2 mmol/L	6	Dangerously high
13.9 mmol/L < BG ≤ 22.2 mmol/L	5	Very high
10 mmol/L < BG ≤ 13.9 mmol/L	4	High
3.9 mmol/L < BG ≤ 10 mmol/L	3	In range
3.3 mmol/L < BG ≤ 3.9 mmol/L	2	Low
4 mmol/L < BG ≤ 10 mmol/L	1	Very low
BG < 2.8 mmol/L	0	Dangerously low
3.	**Fasting blood glucose ranges**	
BG>10 mmol/L	4	High
7 mmol/L ≤ BG ≤ 10 mmol/L	3	Elevated
4 mmol/L ≤ BG ≤ 7 mmol/L	2	In range
BG < 4 mmol/L	1	Low
4.	**Insulin-to-Carbs Ratio (=I-C)**	
10 > BG(i-1) > 3.9 ∧ BG(i) > 10 ∧ 8 < I-C < 12	1	Carbs counting fail
10 > BG(i-1) > 3.9 ∧ BG(i) <3.9 10 ∧ 8 < I-C < 12	2	PA/too much insulin/lack of data registrations
BG(i-1) > 10 ∧ BG(i) > 10 ∧ 8 < I-C	3	Carb counting Fail/too less Insulin
5.	**Correction Bolus**	
BG >10 ∧ ∃ Insulin dose>0 ∧ ∃ Carbs dose=0	4	Correction bolus

As we can see in Table 11, the 1st section classifies data into groups upon defined mealtime ranges. While this condition has already been implemented on data during their extraction from the database, I kept the results from the extracted file when importing the data to the Matlab.

The 2nd and the 3rd sections are dedicated to a data classification upon defined blood glucose ranges. While the 2nd section considers ranges of the mealtime situations, the 3rd one is related to the fasting BG, which means the first blood glucose after a sleeping time and on an empty stomach. The fasting BG information were extracted from the database separately, based on the condition to find the first BG between 5a.m. and 10a.m.

Section no. 4 deals with both the condition of mealtime BG and the insulin-to-carbs ratio. Carbs counting fail is a result of detected in range pre-meal BG but high post-meal BG, while the insulin-to-carbs ratio is in typical patient´s range. (Note: the range for "normal" insulin-to-carbs

ratio can be individualized when using the results from patient´s throughout a day ratio levels). Similarly, having in range pre-meal BG and low post-meal BG, whereas the insulin-to-carbs ratio is in typical range, the conclusion of the algorithm is a problem with either physical activity occurrence, insulin overdosing, or missing some registrations that had an impact on low post-meal BG. In contrary, having high both pre-meal and post-meal BG and insulin-to-carbs ratio lower than is normal, the result from the algorithm is evaluated as carbs counting fail or not enough insulin. (Note: it means that the patient reacted on pre-meal high with increased insulin dose, which could be, in addition, a signal that the patient might not plan any physical activity of high intensity).

Finally, since from the database we extracted also the situations when blood glucose was measured and there was an insulin dose but not any carbs dose (you can follow the flowchart in Figure 53), I used these results for addition condition saying that if the BG was high and there was an insulin dose detected without any carbs dose in connection, sign this situation as a correction bolus.

After my application of defined conditions on the extracted data I got the results for each patient included to the evaluation process, whereas each day of given patient contained set of situations the algorithm found as those meeting corresponding condition. Having that, I was able to proceed to the evaluation part, in which my results were compared with data manually evaluated by clinician.

The algorithm for extraction of the data from the database and the algorithm detecting concrete situations are both attached to CD (see folder *inter_day_detections,* files *database_data_extract.sql*). Results from the database extraction and applied algorithm are possible to see using the scripts or extracted files attached (see *database_data_extract.xlsx, FastingBGExp.xlsx, DataExp.xlsx*).

Evaluation

In order to investigate whether the situations detected by my algorithm were assigned correctly and deduced relevant conclusions about patient´s problematic days, I asked the clinician to manually evaluate data from 4 selected patients based on his professional medical opinion. He got an access to all available information about patients´ registrations (i.e. graphical interpretation of BG readings, insulin and carbs registrations, and physical activity) together with tables containing detailed time of each event and value of corresponding parameter.

When he gave me back his evaluation in a form of pictures of each patient´s days with his own comments (see sample in Appendix D, full document is attached to CD in folder *intra_day_detections*), I compared what my algorithm deduced from the information available with the clinician´s comments, and made a conclusion about all the matches and mismatches. Examples of the type of evaluation is shown in Figure 54, more samples of the evaluation are shown in Appendix E.

Time	Glycemia (G) Carbs(C) Insulin (I)	Value G [mmol/L] C [g] I [IU]	Clinician´s Evaluation		Algorithm´s Evaluation		Numbered Excursions	Comments
Day 1								
6:47	**G**	4.4	**NA**		**In range<4,10> Fasting BG In range**		**1**	The clinician´s notes on this day were: "*Optimal glycemia + one "mistake". Based on the execusion, and since no other data are available, I would say that it must have been a mistake related to carbs counting* ". The algorithm detected the same situation with similar evaluation (#3), whereas the the optimal glycemias are interpreted with their correct classification
6:47	C	30						
7:07	I	3						
12:32	**G**	6.7	**NA**		**In range<4,10>**		**2**	
12:34	C	35						
12:34	I	3.5						
12:54	C	20						
12:54	I	2.5						
14:33	**G**	12	**High**	**Bad Carbs Counting**	**High <10,15>**	**Mistake in Carb Counting/Missed registration**	**3**	
14:34	I	1						
15:01	C	8						
15:01	I	0.5						
18:21	**G**	7.5	**NA**		**In range<4,10>**		**4**	
18:27	C	30						
18:27	I	4.5						
18:43	C	8						
18:44	I	0.5						
20:53	C	8						
20:53	I	1						
21:37	G	8.5						

Figure 54: Example of the comparison process between the algorithm´s and clinician´s matches on one patient´s day.

Based on my analysis of 14 days in total, the algorithm was able to detect all the main mealtime situations containing information about glycaemia, carbs and insulin doses. Regarding the BG matches, the algorithm was in accordance with the clinician´s comments on glycaemia but two case of missed hypoglycaemia. This was caused by the fact that these values were not included into mealtime situation.

With respect to the comments on glycaemia mentioned by the clinician, all of them were in accordance, except from 2 cases of missing notes about physical activity that might cause present lows, one case in which the clinician commented bad carbs counting but the algorithm mentioned patient´s reaction on high with correction bolus, and one comment of clinician that a missed food registration might be the cause of present high, whereas the algorithm assigned that situation to patient´s attempt to lower high with correction bolus.

From the general perspective, it was obvious that each day commented by the clinician as being "ideal" was marked by the algorithm with in-range mealtime glycaemia only, without any other problematic detections. Therefore, besides the conclusions about non-problematic day detection, this observation could be also used for detection of all the days in which the patient managed the disease well. Such days could then form some kind of an "ideal template" for the patient to learn from.

5.2. Predictive functions

While searching for particular problems retrospectively in patients' personally-gathered data can highlight the concrete and most frequent problems that patients deal with or errors they make, predictive algorithms and early-warning systems, based on certain input parameters and models, can eliminate acutely dangerous situations that could have an immediate impact on a patient´s health. Therefore, I designed and tested two types of algorithms that could predict some problematic situation. One of them is a severe hyperglycaemia detection that can be

mostly caused by technical problem on an insulin delivery system (as described in section 2.3.2.), and the second is a blood glucose prediction algorithm, that could form a basis of some early-warning alarms.

5.2.1. Severe hyperglycaemia detection

It has been already described in section 2.3.2 that often in connection to an insulin pump several technical complications can occur. It can be related to cannula obstruction, which is mostly caused by its bending or blockage with body substances, or even malfunction or insulin itself. Therefore, these situations that mostly result in severe hyperglycaemia are required to be detected in order to both monitor frequency of the incidences and directly warm a patient about their presence in time.

Design

Based on personal experiences described by the patients and my direct observation of these situations in the datasets, I defined following conditions that should be able to detect such events in a reasonable height of probability:

- At least 2 consecutive BG registrations higher than 17 mmol/L
- No decrease of BG under this threshold even with an insulin bolus delivery

The final algorithm describes the flowchart on Figure 55.

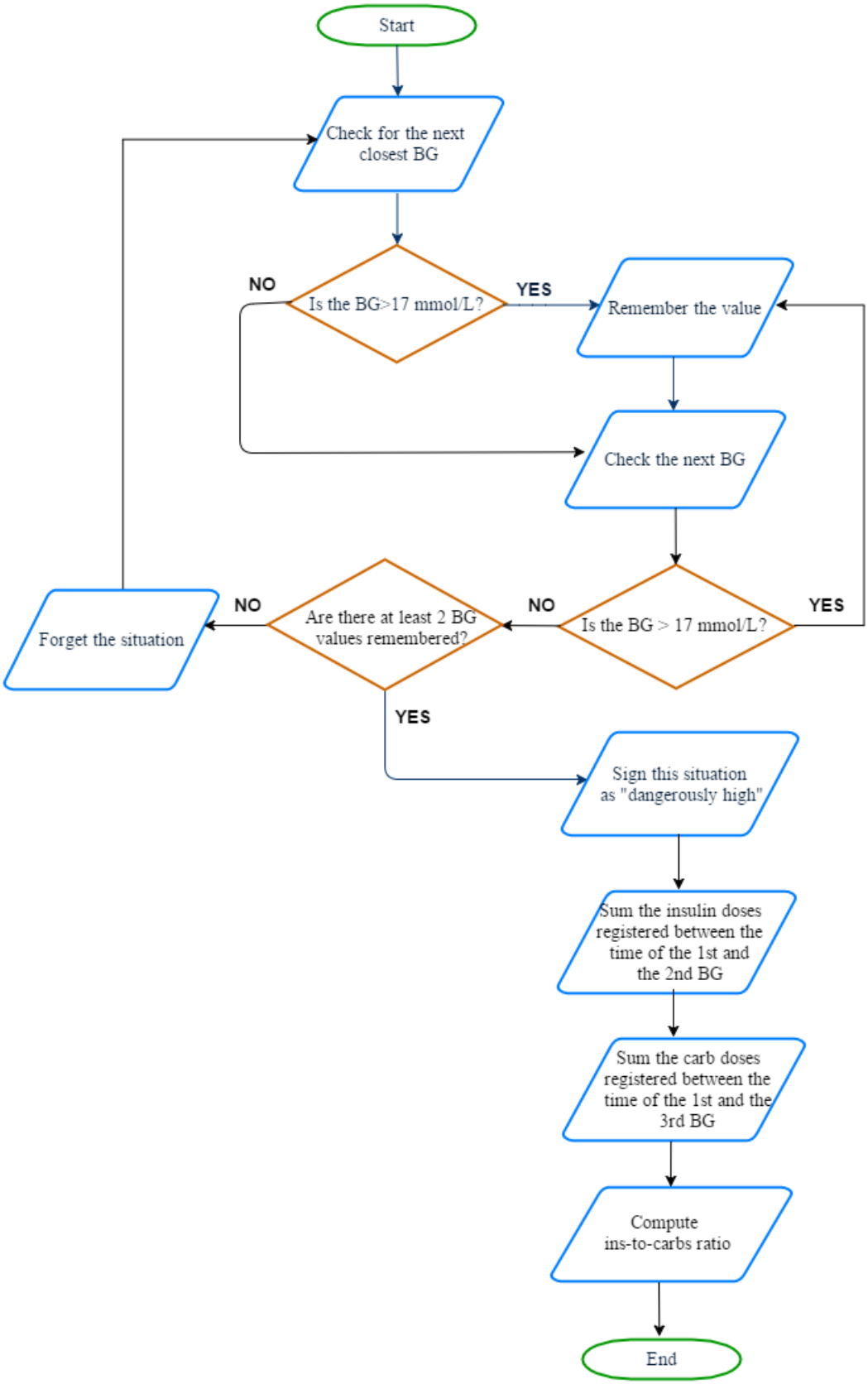

Figure 55: Flowchart describing the algorithm for detection of severe hyperglycaemia situations.

The algorithm designed has been applied on the whole database of our patients and resulted in detection of situations in case of both long-term and short-term measured patients.

Evaluation

I made a computation of an average number of events detected in certain month of long-term patients in whose data severe hyperglycaemia has been observed (See Table 12).

Table 12: Number of days detected per month in the dataset of each of the four patients selected for evaluation of the algorithm.

Patient 1		**Patient 2**		**Patient 3**		**Patient 4**	
Month	**No. of days detected**	**Month**	**No. of days detected**	**Month**	**No. of days detected**	**Month**	**No. of days detected**
10/2015	1	03/2016	2	03/2016	1	01/2016	1
09/2015	0	02/2016	1	02/2016	1	02/2016	0
08/2015	1	01/2016	3	01/2016	2	03/2016	0
07/2015	0	12/2015	4	12/2015	0		
06/2015	0	11/2015	1	11/2015	2		
05/2015	1	10/2015	3	10/2015	1		
04/2015	1	09/2015	1	09/2015	2		
02/2015	3						
	0.9		***2.1***		***1.3***		***0.3***

Since there were no comments made by the patients regarding each situation detected, I decided to ask them directly for their own personal feeling of the frequency of occurrence of such situations. Getting a feedback from all of them, I compared response of each patient with his/her average of detected situations per month. Table 13 displays final results with the comparison.

Table 13: Resulting comparison of number of severe hyperglycaemia occurrence caused by the technical problems on cannula, with the computed average of its occurrence per month for each patient.

Patient no.	**Personal feeling of occurrence**	**Computed average of occurrence per month**
1	Approx, once per 1-2 month	0.9
2	Several times per month	2
3	Approx, 2 times per month	1.3
4	Approx, once per 2-3 month	0.3

As we can see, for each case the patient´s personal feeling of frequency of the occurrence of such problematic situations significantly correlates with the results computed from the automatic detection. Therefore, this method could be a good tool for both the in time notification for the patient and long-term monitoring of frequency of its occurrence.

5.2.2. Blood glucose prediction

Using simple formulas described in sections 4.1.2. and 4.1.3 we are able to roughly suspect an effect of either given insulin dose or amount of carbs on current BG level, while no other factors are considered. However, using such tools for blood glucose prediction that is rather close to the future could be an effective additional tool for, let´s say, tracking a patient while being one step ahead.

One problematic situation I met as being often mentioned by patients is a fear of hypoglycaemia when an insulin dose is taken and patients are waiting for its action before they start to eat. Although the time patients take between the insulin administration and eating is one of the crucial factors affecting post-meal spikes, most of them are not able to adhere to it due to either very unstable eating habits or the fear they might forget to eat in time, often when being in a hurry or disturbed by working stuff.

Therefore, one of my ideas was to use a tool that would track patient´s registrations and whenever an insulin dose applied would appear in the app, some predictive algorithm would consider what happened in the recent past with respect to previous doses (i.e. remaining BOB, carbs and physical activity) and the most recent BG measured, to decide whether the patient is likely to have low – that might be a case for carbs early-warning reminder, or the dose is most likely to be a correction bolus that does not require any reminder, which would be more bothering than supportive for the patient. The same principle could be also applied, for example, on physical activity logs that would not be supported by any carbs.

However, the initial question for me was how truthful such algorithms could be to use them as an additional module for reminders. Thus, I attempted to create an algorithm for BG prediction when using the basic formulas presented, and add some other parameters, such as physical activity, to the system. The next aim was to investigate how reliable it can be if considering its usage as a personal tool for patients.

Design

To be able to predict a patient's level of glycaemia, it was first necessary to know the reaction of the patient´s body to a given amount of food and insulin dose. This means we must know the input parameters, the CarbF and the CorrF, for which calculations required information about the patient´s weight, insulin sensitivity and TDD. Certainly, we also need the initial BG value to know the starting point of the prediction.

My initial idea was to consider only the effect of insulin and carbs without any other factors having impact on the final BG level. Based on that, the expected BG value should be counted as follows:

$$BG_{out} = BG_{in} - BG_{inz} + BG_{carb} \quad (6)$$

where BG_{out} is the predictive BG value, BG_{in} is the initial BG value, BG_{inz} is the level of BG by which the initial BG is decreased due to insulin action, and BG_{carb} is the level of BG by which the initial BG is increased due to the carbs´ action.

The BG_{carb} can be derived from the CarbF, defined as a number of carbs that 1IU covers. Thus, if we divide total amount of carbs intake by the CarbF, we should obtain the amount of insulin needed to cover this dose. Recalculation of the insulin dose into the BG level by which the initial BG would be elevated when eating certain dose or carbs, we can multiply requiring insulin dose by CorrF:

$$BG_{carb} = \frac{CD}{CarbF} \cdot CorrF \tag{7}$$

where *CD* is the carb dose planned to take.

Similarly, the BG_{inz} can be derived from the CorrF, defining how much glycaemia drops after injection of 1IU. Thus, the final calculation is done when multiplying CorrF by the total amount of insulin that will lower current BG:

$$BG_{inz} = ID \cdot CorrF \tag{8}$$

where *ID* is the insulin dose planned to take.

However, if there is any insulin on board (BOB), meaning insulin still in action from the previous insulin dose, this BOB dose value should be added to the current insulin dose. After the modification of the equation (8) we get:

$$BG_{inz} = (ID + BOB) \cdot CorrF \tag{9}$$

In addition, at the time of the BG prediction there could be some BOB as a rest of the ID from the previous bolus dose injected, that will not influence this predictive value we want to calculate, but will lower the future one when it starts to act. Therefore, it is necessary to subtract this dose that is not affecting the BG currently calculated yet.

For the BOB estimation I used Table 2, from which we can observe that the initial insulin dose is decreasing by 20% (or 1/5) each hour. Then, we can declare that

$$BOB = ID - h \cdot \frac{ID}{5} \tag{10}$$

where *h* means the time between the ID injected and the time of investigation.

Substituting the equations (7), (8) and (9) into the formula (6) we obtain the final prediction formula:

$$BG_{out} = BG_{in} - \left(ID + BOB_{prev} - BOB\right) \cdot CorrF + \left(\frac{CD}{CarbF} \cdot CorrF\right) \tag{11}$$

After some editing and substitution by formula (10) we gets:

$$BG_{out} = BG_{in} - \left(ID + \left(ID_{prev} - h_{prev} \cdot \frac{ID_{prev}}{5}\right) - \left(ID - h \cdot \frac{ID}{5}\right) - \frac{CD}{CarbF}\right) \cdot CorrF \qquad (12)$$

Finally, using the formulae (1), (2) and (3) for substitution of the IS, CorrF and CarbF, we write the final formula:

$$BG_{out} = BG_{in} - \left(ID + \left(ID_{prev} - h_{prev} \cdot \frac{ID_{prev}}{5}\right) - \left(ID - h \cdot \frac{ID}{5}\right) - \frac{CD}{\frac{Weight \cdot 0.53}{TDD} \cdot 10.8}\right) \cdot \frac{100}{TDD} \qquad (13)$$

For better illustration, let us assume a patient, 67 kg, TDD = 40 IU, checked his BG with a result of 8 mmol/L. Based on his experience, he ate 45 g of carbs in a meal and he had injected 7 IU before he started to eat. Now, he wants to know what his BG level will be in 2 hours. However, 2.5 hours ago he had a snack for which he injected 3 IU, so there is likely to be some resting BOB from the previous dose as well as some insulin that is not going to lower the BG until the time of prediction.

Using the information above, we can calculate his CarbF, CorrF and BOB as follows:

$$CarbF = \frac{Weight \cdot 0.53}{TDD} \cdot 10.8 = \frac{67 \cdot 0.53}{40} \cdot 10.8 = 9.5877 \text{ g}$$

$$CorrF = \frac{100}{TDD} = \frac{100}{40} = 2.5 \frac{\frac{\text{mmol}}{\text{L}}}{\text{IU}}$$

$$BOB = \left(ID - h \cdot \frac{ID}{5}\right) = 7 - 2.5 \cdot \frac{7}{5} = 3.5 \text{ IU}$$

$$BOB_{prev} = ID_{prev} - h_{prev} \cdot \frac{ID_{prev}}{5} = 3 - 2 \cdot \frac{3}{5} = 1.8 \text{ IU}$$

This result means that the patient:

- Needs approx, 9.6 g of carbs to cover 1 IU
- His BG drops by 2.5 mmol/L with each 1 IU,
- From the starting 7IU he injected for the meal the dose of 3.5 IU will still not affect the, BG after 2.5 hours from the time of injection,
- 1.8 IU will lower the predicted BG from the insulin dose in the past

Substituting these calculations into the formula (13) we can estimate the future BG as follows:

$$BG_{out} = BG_{in} - \left(ID + BOB_{prev} - BOB - \frac{CD}{CarbF}\right) \cdot CorrF =$$

$$= 8 - \left(7 + 1.8 - 3.5 - \frac{45}{9.5877}\right) \cdot 2.5 = \mathbf{6.5\ mmol/L}$$

I first tested the algorithm on a selected day of one of two patients whose data include all-day registrations and who are well compensated and educated about carbs and insulin dosing. Figure 56, illustrating the algorithm, shows that the prediction works pretty well until the time of the last registration of carbs when the BG rapidly dropped compared to the predicted one.

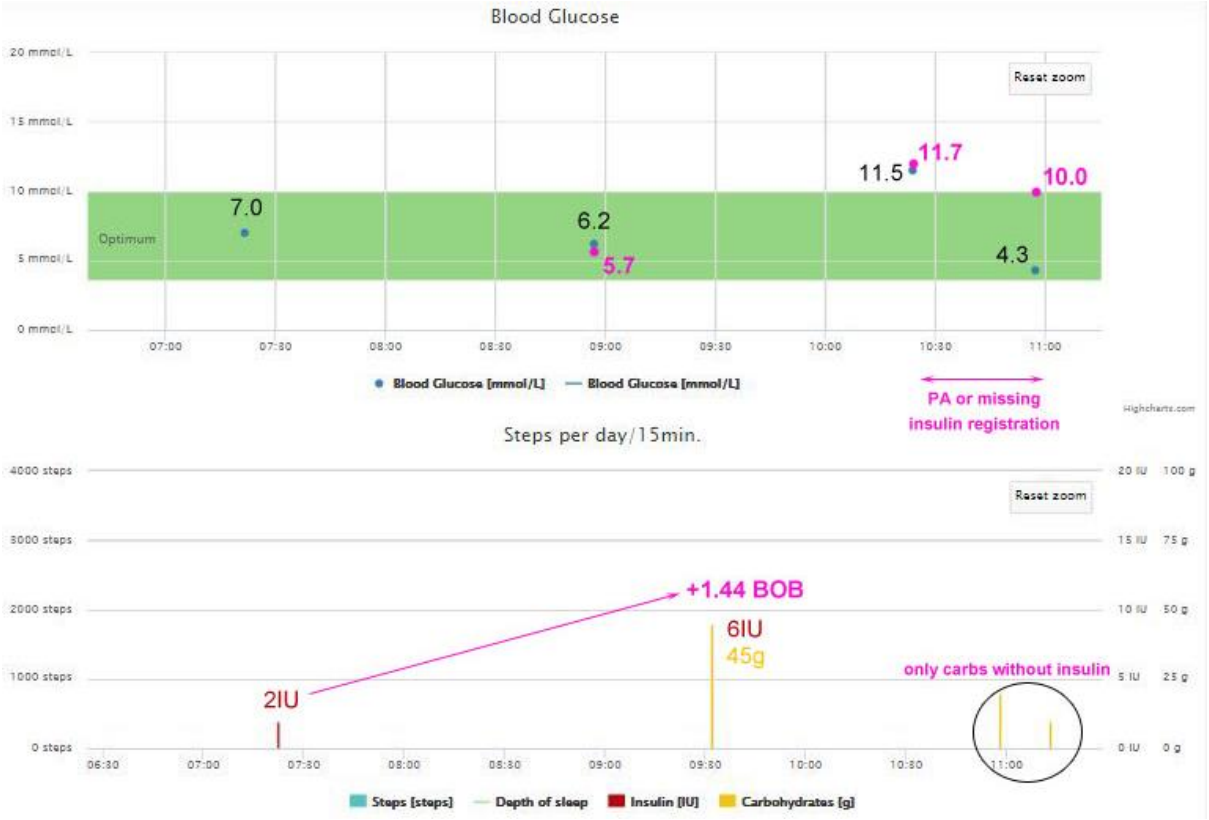

Figure 56: Illustration of how the blood glucose prediction works on one part of a day of one sampled patient.

Based on the last registrations of food without any insulin boluses, it is very probable that the BG reduction was caused by some level of physical activity.

Therefore, to reduce the errors affected by this parameter and having some data measured by the Fitbit activity tracker, I tried to estimate a correlation between the average number of steps taken per some period of time and the BG drop. To do this, I used my own data to search for those situations with different intensity of physical activity where CGM measurements are also presented. Another condition was to include only those events in which no reduction of insulin delivery and no carbs intake before or during the activity was applied. This eliminated possible errors caused by the effect of these additional parameters on BG during the activity.

I used in total 7 situations for which the average number of steps per 5 minutes was calculated together with the average drop of BG. Finally, plotting these data we can see on Figure 57 that there is a statistically significant correlation (R^2=0.91) between these two parameters and the shape is almost linear.

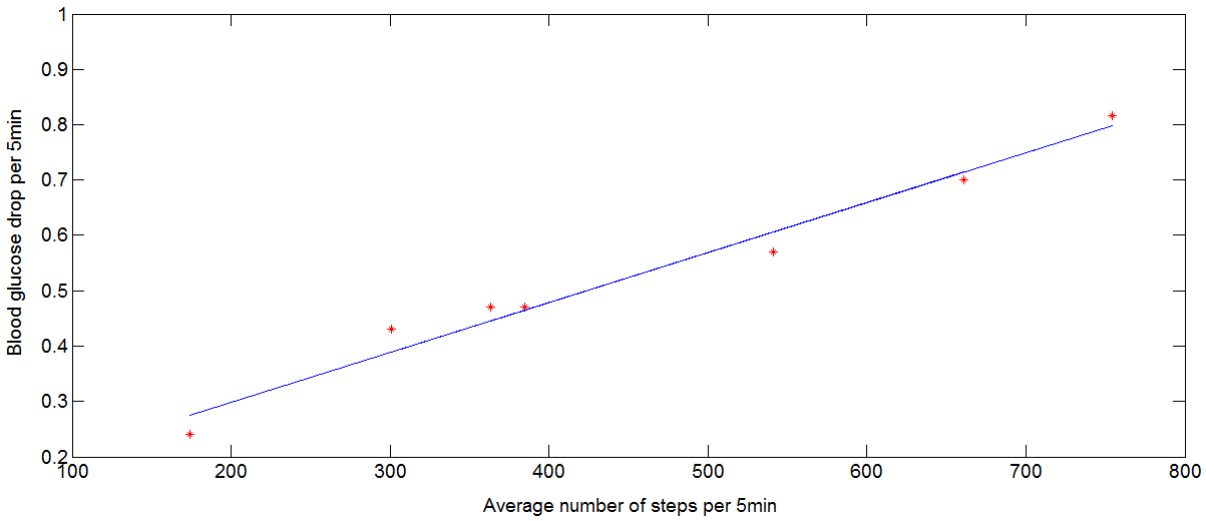

Figure 57: Correlation between the average number of steps per 5min with the blood glucose drop per 5 min, using data from one patients.

Although the BG drop with respect to physical activity is very individual, I tried to introduce this parameter into the BG prediction algorithm as a starting formula that can be adjusted during the testing phase.

Since the step-by-step prediction worked in some parts of data pretty well, in case the registrations were done properly by patients, I decided to make the predictive calculation fully automatic. To do that, it was necessary to find a function for insulin action and carbohydrates action. For that purpose, I used the insulin action model for rapid-acting insulin based on Figure 1, and made a model with the possibility to change its action time and shape. In case of the carbs action modelling, the biggest problem was the fact that there is no information about glycemic index of food registration in the data, which plays a crucial role in post-meal glycemic trend. As a compromise, I modelled something between the carbs action models displayed on Figure 25 to model glycemic reaction on given amount of carbs. On Figure 26 we can see that in all the three cases the maximum glycemic response appears within the first 1 hour. Therefore, I first set the carbs action duration to 60-minutes and modelled a Gaussian curve with the possibility to change its shape and duration time, as in the case of the insulin model. For the physical activity integration, I used the function from my experiment describing dependence of the average number of steps taken per 5 minutes and corresponding BG drop per the same time.

Both the insulin and carbs action curves are displayed on Figure 58.

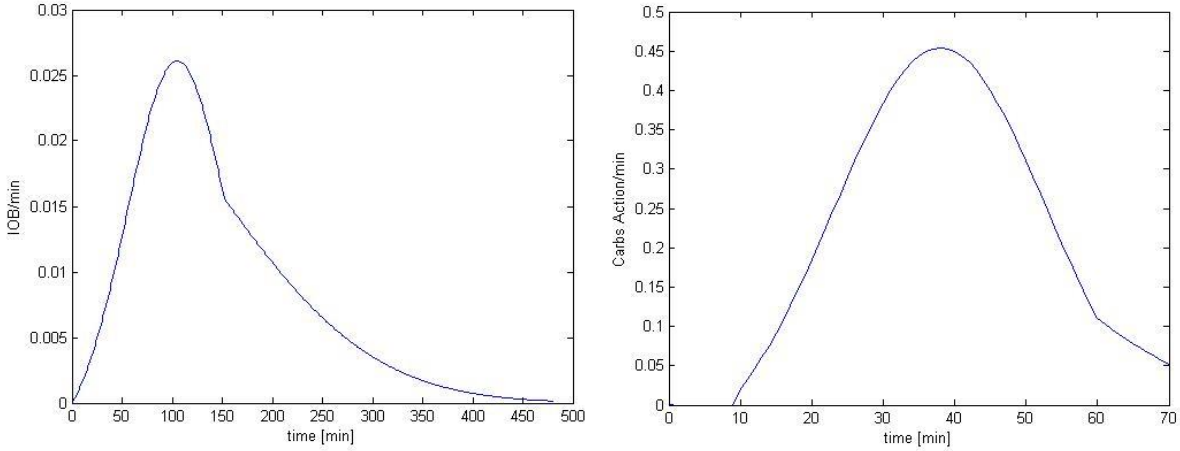

Figure 58: Insulin action curve and carbs action curve modelled for blood gluose prediction algorithm.

Having that, I was able to import data from the database and order each column of certain parameter by time into a minute-by-minute segments.

Illustration of a minute-by-minute modelling of carbs, insulin and physical activity action for one selected day is presented on Figure 59.

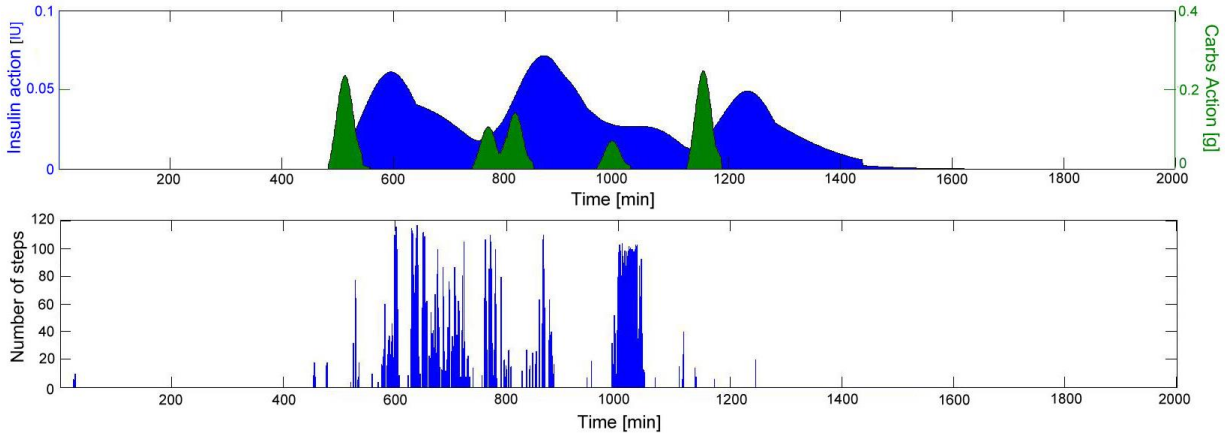

Figure 59: Illustration of a minute-by-minute modelling of carbs, insulin and physical activity action for one selected day.

Finally, I applied the previous computations for BG prediction used for the step-by-step prediction to get the automatic computation of BG values throughout a day.

The script of the algorithm is attached to CD (folder *bg_prediction*, file *bg_prediction.m*).

Evaluation

I tested the designed algorithm on 3 sampled patients, whose I supposed they register all the parameters properly and are well educated about carb counting.

During the testing phase the physical activity formula I used was first lowering the BG significantly, and thus, I set the condition of accepting only those active minutes that were higher than 100 steps. I also tried to change some parameters, such as IS or time of carbs or insulin duration, to find the best input parameters that would fit to each testing datasets.

I computed the mean absolute error, its maximum and minimum value, and standard deviation for all the three patients, as displayed in Table 14.

Table 14: Resulting table for 3 testing samples of patients´ data, including number of BG values, mean, maximum and minimum absolute error (AE) and standard deviation (SD).

Patient no.	No. of BG measurements	Mean AE [mmol/L]	SD	Max AE [mmol/L]	Min AE [mmol/L]
1	19	1.75	1.65	6.04	0.03
2	13	2.09	2.02	6.40	0.30
3	18	1.68	1.75	6.70	0.20
Mean		***1.80***	***1.79***		

From the results we can see that either the mean absolute error (mean AE) nor the mean standard deviation (SD) exceeded 1.8 mmol/L.

Tables 15-17 show the results from selected days of the 3 patients. We can see that, in some days, the predicted value is very similar to the measured one, for example day #1. However, there are often full days or only particular cases within one day that are significantly different. As an example, we can look at the day #4 of patient 1 on Table 15, where the predicted values are all similar but one BG in the evening is highly different. This is a typical example of unexpected factor that might appear around the time the BG was measured, but was not registered by any device. The same can be with an insulin dose that was not registered, but let the predicted BG to be higher than actually was. Going back to the case mentioned above, it might have been any additional dose of carbs that prevented BG from being low, or overestimated physical activity the algorithm worked with.

Table 15: Comparison of measured and predicted BG of Patient 1.

Patient 1					
day	**hour**	**minute**	**BG measured**	**BG predicted**	**Absolute error**
1	7	47	**11.9**	-	
	12	12	**11.3**	***9.7***	*1.59*
	15	49	**10.0**	***8.9***	*1.06*
	18	34	**5.8**	***7.1***	*1.36*
	21	2	**10.5**	***9.3***	*1.27*
2	6	10	**12.0**	-	
	8	38	**14.8**	***15.8***	*1.08*
	10	3	**12.0**	***10.3***	*1.69*
	11	1	**12.2**	***13.4***	*1.22*
	13	35	**11.9**	***14.4***	*2.48*
	15	9	**10.8**	***7.8***	*2.99*
	18	47	**13.8**	***8.6***	*5.14*
	21	53	**13.8**	***13.7***	*0.03*
3	7	58	**4.0**	-	
	10	52	**7.8**	***4.2***	*3.56*
	12	13	**6.0**	***6.1***	*0.05*
	14	51	**5.9**	***5.3***	*0.55*
	17	46	**5.1**	***4.3***	*0.72*
4	6	4	**8.3**	-	
	9	45	**7.8**	***6.2***	*1.61*
	11	36	**6.5**	***6.0***	*0.51*
	19	13	**5.3**	***-0.8***	*6.04*
	22	54	**5.5**	***5.2***	*0.28*

Table 16: Comparison of measured and predicted BG of Patient 2.

Patient 2					
day	**hour**	**minute**	**BG measured**	**BG predicted**	**Absolute error**
1	5	39	**8.2**		
	10	16	**7.9**	***10.2***	*2.3*
	13	30	**3.1**	***3.3***	*0.3*
	16	36	**9.7**	***11.1***	*1.4*
	20	9	**6.7**	***1.0***	*5.7*
	22	52	**8.7**	***7.9***	*0.7*
2	2	0	**7.5**		
	7	39	**7.9**	***7.5***	*0.4*
	9	52	**9.5**	***10.9***	*1.4*
	11	0	**5.5**	***4.0***	*1.5*
	13	16	**11.9**	***12.7***	*0.8*
	14	18	**8.0**	***1.6***	*6.4*
	18	1	**3.2**	***0.9***	*2.2*
	19	42	**11.5**	***11.8***	*0.3*
	22	51	**3.2**	***7.0***	*3.8*

Table 17: Comparison of measured and predicted BG of Patient 3.

Patient 3					
day	**hour**	**minute**	**BG measured**	**BG predicted**	**Absolute error**
1	0	53	**9.0**	***5.2***	*3.8*
	8	49	**7.0**	***0.3***	*6.7*
	8	55	**6.5**	***7.0***	*0.4*
	10	51	**7.5**	***6.8***	*0.7*
	11	52	**4.0**	***4.9***	*0.9*
	12	3	**3.0**	***3.7***	*0.7*
	13	14	**8.0**	***5.0***	*3.0*
	14	15	**12.5**	***10.7***	*1.8*
	14	40	**13.0**	***12.7***	*0.2*
	15	17	**10.0**	***9.6***	*0.4*
	15	38	**5.0**	***8.3***	*3.3*
	16	28	**5.0**	***5.6***	*0.6*
	18	21	**10.0**	***8.9***	*1.1*
	19	21	**8.5**	***8.0***	*0.5*
	20	28	**6.0**	***4.9***	*1.1*
	22	18	**5.3**	***4.4***	*0.9*
	22	53	**5.5**	***5.1***	*0.4*
	0	53	**9.0**	***5.2***	*3.8*

However, significant impact on BG differences also had the type of food I was not able to track. How big impact given food can have on predicted BG mainly depends on its glycemic index together with related time of measurement. Moreover, there are many other factors I was not able to take into account when using this prediction algorithm, such as stress or illness, which both are very dominant factors that make glucose to raise.

Another thing is variability of basal dose of insulin, of which effect was covered by the TDD only. In this regard, we have to distinguish the basal dosing of insulin pump users vs. those injecting insulin with pens. While the insulin pump users are able to set variable insulin profiles (hour-by-hour dosing of insulin) and adjust doses upon their daily regimen, insulin pens users cannot change the effect of a dose once it is administered to the body. Therefore, introducing more precise settings for patients with respect to the basal dose could significantly improve the algorithm.

Last but not least, I should mention missed registrations, that have obviously the biggest impact on resulting BG, and also inaccuracy of glucometers, of which values can differ up to 20% [90] (but the difference can be even higher if the blood is contaminated by various substances during the blood measuring phase).

Despite all these factors described above, we can see that in all the three cases of prediction, at least the trend of BG changes is maintained. I believe that if the adherence to register all the necessary parameters is kept, and the patient is educated enough to estimate carbs dosing (and if possible, provide the information about glycemic index), the prediction can be a helpful tool for patients, for example, as a reminder to eat after certain time the insulin dose I administered.

6. Discussion

Searching for patient´s problematic situations from data measured in the real world is an effective way of helping patients with diabetes. However, when trying to implement such system I was working on into practice, it is also necessary to count with the barriers, imperfections and untruthful data we have to deal with.

Apart from many technical complications and barriers I was facing during the data-collection phase or when building the algorithms, a very common issue was a loss of data. During the data collecting phase at the University Hospital in Motol, there was a loss of data from the activity trackers due to both patients' inability to properly follow instructions and technical problems at the doctor´s office. Another common issue was that sensors were often accidently pulled out of a patient´s body, which meant additional loss of data.

While this was mostly solved with time, another problem appeared in relation to insufficient communication or misunderstandings between the technical and medical personnel. Some of the patients that got the CGM and activity tracker did not obtain the diabetes diary, and vice versa. The implications of that were missed parameters necessary for testing the algorithms. However, the data from patients that were asked to make registrations about carbs, insulin doses, daily activities, and others, were in the form of a paper-based diary, which complicated the post-processing of data digitization. Nevertheless, thanks to the long-term testers, I was able to not only get valuable data on the parameters that were gathered and monitored, but also to communicate with the patients themselves, and to see their subjective viewpoint issues related to their self-management. Similarly, the chance to consult with clinicians helped me to understand the other side of diabetes treatment and monitoring. Thus, searching for and understanding the problems straight from the "sources", i.e. both patients and clinicians, gave me the opportunity to improve my algorithms and customize them based on each groups' needs.

Another major challenge was to maintain patient adherence to use all the devices and register necessary parameters. Although many of the data-gathering processes were automatic, and thus, not bothersome for the patients (i.e. automatic transfer of data from the activity trackers to a cloud, automatic transfer of BG values to the Diary app, and upload of CGM data to a cloud mediated by me), the manual carbs and insulin dose registrations were often problematic for them to consistently enter. In addition, inadequate carbs counting or missing logs negatively influenced the results of the evaluation process. In order to improve their adherence, I attempted to support them via social media and allowed them to contact me whenever they had any technical or other problems that I could solve.

Moving from the phase of data-collection to the methods I used for identifying particular problems in the data, including the glycaemia and physical activity classification, I mainly followed clinicians' recommendations. The participating clinicians widely uses a method of comparing multiple parameters between each day to find either some patterns in patient´s daily

regimen or irregularities when the patient's data does not follow the typical pattern as one would suspect. However, regarding physical activity, I did not find any other system that would make such type of data interpretation, and thus, the evaluation method I used should be taken under deeper investigation and further tested by clinicians to make a conclusion about its relevance.

Interestingly, using the MAGE and MODD method, I was able to classify CGM signals into groups defining the severity of glycemic excursions, as well as to find certain unstable episodes or irregularities when comparing more days instead of treating only one day as independent of others. While searching for descriptions of this method in the literature review, I found that there was no concrete classification of CGM records using certain scaling of the coefficients computed. However, I was able to distinguish selected samples of data upon classification used by the clinician. The only problem was the 1st Variability Index he used to describe BG variability from the point of view of the frequency of fluctuations on a scale from 1 to 5 points. This type of scaling did not reflect any significant concordance with the results generated by the algorithm. This could be caused by very individual evaluation of each CGM record by the clinician. In some cases of apparently the same signals the indices ranked by the clinician were different, and vice versa. However, it needs to consult the ranking possibilities with clinicians more in detail and to gain a better understanding of what they search for in the signals the most, and perhaps a wider scaling than only the three classes, in order to find better ways of evaluating variability.

With respect to detecting the main peaks of the difference signal, the algorithm I designed did not miss any differences signed by the clinician. In fact, it detected some additional peaks that were considered to be, based on defined conditions, relevant to highlight as potentially dangerous situations or habits. To this point, certain levels of differences, that would sufficiently meet clinicians´ scale of what is and what is not essential to mark, must be defined so that no useless data is displayed to the clinician when making decisions. However, the clinician also made mistakes including incorrectly classifying some samples or not discovering excursions that were at least as significant as other signals that were matched by him. Therefore, I see the potential to reduce human errors when using automatic data evaluation.

Mealtime situations represent the most important part of my work. It has been already said that the mealtime peaks are the ones that, once arise, are not easily reduced and often leads to the other extreme, i.e. low BG. This results in a BG signal that resembles a so called "roller coaster". The effects of the carbs and insulin are often difficult to predict for the patients, due to not only unusual food intake or inadequate carb-counting, but also incorrect timing of both carbs and insulin, split-doses or missed doses. All of these cases were included when searching for patterns in patients' data to design the algorithm for mealtime detection. Although many software applications enable patients to track pre- and post-meal BG, patients are additionally required to note what certain BG values represent for the patients themselves. For example, a patient has to select that the current BG was measured before breakfast, etc. Therefore, my aim was to detect these situations without the necessity of noting any additional mealtime

information by only searching for: certain patterns in the patient´s data, common meal-time behaviours, times between particular registered parameters, and others.

Starting with searching for those mealtime situations that would be "ideal" for proper evaluation, I received only a few samples from some of the patients, although the amount of the dataset was large. However, this helped me to realize that there are not as many "ideal" situations, simply because patients do not often follow the instructions of their doctor. Nevertheless, I used these data to discover the most relevant information about the patient, such as the typical insulin-to-carbs ratio throughout a day, or a general pattern of patient´s pre- and post-meal glycaemia.

Despite the fact there are not many matches for these strictly defined situations, I extracted as many information about patients' eating habits as possible. In doing so, I aimed to help the patients with their better education when showing them their self-management mistakes, and the clinicians for faster evaluation of large datasets, and again, reducing human error in cases when parameters are difficult to evaluate manually.

Statistical evaluation of mealtime situations in datasets made by my algorithm in comparison with the manual evaluation made by the clinician was pretty difficult to process, mainly due to such variability in clinician´s comments. On the other hand, these results were a very substantial feedback for me in what else to search in the data, which information is essential, and also the overall way of clinician´s thinking when making decisions. With respect to the evaluation itself, the algorithm works well when finding mealtime glycaemia, correction boluses, and mistakes in carbs counting. Two missed hypoglycaemia, that were missed only due to the fact they were not a part of mealtime situation, can be easily improved with additional algorithm that extracts these values under specified range from the database. What should be incorporated into the algorithm more is mainly the physical activity indicator and number of daily carbs and insulin registrations with corresponding amount of doses. Also, defining such conditions that would track also those mealtime situations that are not connected to checked glycaemia could help to reduce missed detections.

Regarding sleeping activity that was also possible to track using the activity tracker, I was not able to find any patterns in there due to insufficient amount of data. Therefore, I did not include this parameter into any of the algorithms presented.

Finally, regarding the predictive algorithms I chose, my aim was to follow not only the past of the patient, but also to be a step ahead and help the patient either to better decide about what is planning to do (such as an impact of given amount of food or insulin on his future BG), or warm him in cases he is not able to detect a problem that might appear. The predictive algorithm for dangerous highs that appear often in case of patients who use insulin pump and there is an obstruction in cannula, worked well if considering the comparison of patient´s subjective feeling of the frequency of its occurrence. In case of the predictive algorithm, there were many other factors we were not able to monitor, both individual and global ones, which pose a

negative impact on predictive values. Some of them could be added to the system to improve its accuracy, such as heart rate monitor, or simply some defined notes about certain situations registered to the diary by patients. However, in this case we have to consider the fact that any additional registrations patients are required to make can lower the adherence to use these helping tools. Speaking about the algorithm itself, one of the main complication I faced was the carbohydrates modelling, which needs to be improved in the way of including variable types of the model for different types of Glycemic Index. However, this would require an additional action of patients to register not only the amount of carbs into their dairy, but also the information about Glyemic Index of a food they eat. Also, since the sensitivity on insulin fluctuates throughout a day, it would be also required to use a function that would count with this fact, maybe if using the insulin-to-carbs ratio profile I made from the most relevant information of some patients, as described in section 5.1.5. However, from what I have already processed, the algorithm I designed seems to be a good starting point for short-time prediction that could be incorporated to some early-warning systems and reminders. Nevertheless, patients would have to be educated very well about correctness of its results with respect to their potential invalid food and drug registrations and other factors that are not possible to be covered by the system.

Despite the fact there are still several complications related to detection algorithms used in this work, and thus, proposals for their improvement, their potential to be used in medical practise as a decision support tool seems to be obvious.

7. Conclusion

Detection of problematic situations in Type 1 Diabetes - related data gathered from patients' own mobile technologies can sufficiently support clinicians in conducting a more efficient decision making process. Moreover, nearly real-time tele-monitoring of T1D patients' detailed and daily behavioural and self-management information can allow both patients and clinicians to identify problematic situations that would otherwise be unnoticeable.

Therefore, I designed, implemented and verified the most relevant methods and algorithms to be used for automatic evaluation of big datasets from Type 1 diabetic patients composed of parameters gathered via mHealth and clinical sources.

The algorithms that I created to evaluate causal impacts of one's diabetes and self-management were those that classified blood glucose readings and total daily steps. In doing so, patients and clinicians can better understand not only a patient´s general problems with respect to BG values and the impact of different levels of physical activity, but also to identify certain days and situations upon which to focus for improvement through more detailed analysis.

With respect to the variability of blood glucose values, I built the algorithm for automatic evaluation of CGM data using the MAGE method. After classifying resulting MAGE values into 3 groups, based upon the level of blood glucose variability defined by clinician, I verified that there was a statistically significant difference between the groups. This demonstrates that this algorithm can be used for decision-support purposes by providing automatic evaluation of glycemic variability.

To compute the inter-day differences at a given time, I designed an algorithm that automatically computes differences between 2 consecutive days of the same patient in connection with peaks detection. Comparing the differences matched by the clinician with those detected by the algorithm allowed me to verify the ability of my system to be used for an automatic detection of inter-day differences.

The main part of my investigation was focused on mealtime situations. I was able to detect and visualize information about 1) pre-meal and post-meal blood glucose values within a given part of a day, and 2) changes in insulin-to-carbs ratio throughout a given day. To display a more detailed point of view, I built an algorithm for automatic evaluation of intra-day situations defined by certain conditions: 1) the most relevant information used from patients´ own datasets as an ideal model for them to learn from, and 2) some patterns related to patients´ behaviour that could indicate potential frequent mealtime problem, such as unstable pre- and post-meal BG readings or patient´s pattern of an insulin-to-carbs ratio throughout a day. When comparing the effectiveness and accuracy of the algorithm vs. clinician approaches, we found that my algorithm was able to detect all the main mealtime situations containing information about glycaemia, carbs and insulin doses. Regarding the blood glucose levels that were categorized

by severity, the algorithm was in accordance with the clinician´s comments on glycaemia, in case of 4 evaluated patients, but two cases of missed hypoglycaemia.

In addition to the causal algorithms, predictive algorithms were built in order to eliminate acutely dangerous situations. I designed and tested two types of algorithms, i.e. a severe hyperglycaemia detection algorithm and a blood glucose level prediction algorithm. The results from the first one correlated with the patient´s personal feeling of the hyperglycaemia occurrence. The latter one was able to follow the trends of blood glucose changes and could form a basis for early-warning alarms. However, these must be further explored and refined.

The algorithms will be implemented in the Diani web application, in order to simplify data analyses for both clinicians and patients.

For the future, I would like to focus on the intra-day detection of problematic situations and the possibility to use these and other detection algorithms as a comprehensive self-educational tool for patients. In effect, such a tool would allow patients to receive continuous feedback about their recent actions while using their own data and “ideal” templates extracted from the most from their own situations in which they were in the best control.

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List of Abbreviations

APP	Actual Pump Practices Study
App	Application
BG	Blood Glucose
BOB	Bolus on Board
CarbF	Carbohydrates Factor
Carbs	Carbohydrates
CGM	Continuous Glucose Monitoring
CorrF	Correction Factor
CSII	Continuous Subcutaneous Insulin Infusion
GI	Glycemic Index
GL	Glycemic Load
HbA1c	Glycosylated Hemoglobin
HCP	Healthcare Professional
IS	Insulin Sensitivity
MAGE	Mean Amplitude of Glycemic Excursions
MEMS	Micro-Electro-Mechanical Systems
NICE	The British National Institute for Health and Care Excellence
PA	Physical Activity
PMBG	Post Meal Blood Glucose
SAD	Sum of Differences
SD	Standard Deviation
SMBG	Self-monitoring of Blood Glucose
T1D	Type 1 Diabetes
TDD	Total Daily Dose

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Appendix A

Ethical committee approval

Research grant of the **Czech-Norwegian Research Programme (CZ09)**

The Programme Operator of the Czech-Norwegian Research Programme is the Ministry of Education, Youth and Sports of the Czech Republic.

Applicant: Assoc Prof.Denisa Janíčková Žďárská, MD. and assoc Prof. Jan Brož, MD.

Title: **Influence physical activity and other parameters to compensation of diabetes mellitus - options of telemonitoring and a computerized data processing.**

The approval conforms to the national laws of the Czech Republic where the research is carried out.

January 17, 2014, Prague, Czech Republic

Ethical committee official (signature & stamp):

MUDr. Vratislav ŠMELHAUS

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Appendix B

Informovaný souhlas s účastí v klinickém výzkumu

Informace o výzkumném projektu	
Název projektu:	**Vliv fyzické aktivity a dalších parametrů na kompenzaci diabetes mellitus – možnosti telemonitoringu a počítačového zpracování dat v rámci expertního systému**
Řešitelé projektu:	As. MUDr. Denisa Janíčková Žďárská
Vedoucí projektu:	As.MUDr. Jan Brož
Instituce:	Interní klinika 2. LF UK a FN Motol Praha, V Úvalu 84, 150 06 Praha
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1. Účel výzkumné studie

Vážená paní, vážený pane,

Byl/a jste požádán/a o účast ve studii zabývající se sledováním změn koncentrace glukózy a kompenzace diabetu v závislosti na fyzické zátěži, množství a typu sacharidů v jídle. Cílem studie, v níž Vám nyní nabízíme účast, je zjistit jak se tyto parametry projevují v glykemických exkursích a dle nich přesněji specifikovat potřebné změny dávkování inzulínoterapie či perorálních antidiabetik. Získané poznatky mohou být též využity k vytvoření simulačních programů sloužících v budoucnosti k edukaci pacientů s diabetes mellitus.

2. Procedury

Po zařazení do studie budete požádán/a, abyste absolvoval/a následující program. Budete vybavení náramkem, který sleduje vaši fyzickou aktivitu a inteligentním mobilním telefonem. Do mobilního telefonu budete zaznamenávat údaje o době jídla, množství v něm obsažených sacharidů, době spánku, probuzení, začátku a konce zaměstnání, interkurentních onemocněních. Data budou automaticky online přenášena do centrálního úložiště. Zde budou analyzována a na základě jejich analýzy Vám může být doporučena změna terapie, popřípadě zvýšení či snížení míry fyzické aktivity.

Pro některé části studie budete vybaveni i kontinuálním monitorem glykémie, který umožňuje přesnější sledování koncentrace glukózy.

3. Možná rizika a diskomfort

Celkově účast ve studii a podstoupení vyšetřovacího programu představuje pouze minimální riziko zdravotních komplikací. Toto riziko je dáno povahou jednotlivých vyšetření a studijních úkonů.

Náramek Fit bit: je plastový náramek, který se nasazuje na zápěstí a automaticky registruje míru fyzické aktivity. Jeho použití nepřináší žádná popsaná zdravotní rizika.

Inteligentní mobilní telefon: v něm je uložená aplikace pro zadávání výše uvedených parametrů. Její obsluha je jednoduchá, nicméně vkládání dat si bude vyžadovat určitou, byť minimální, míru Vaší pozornosti.

Zavedení odběrové stříkačky pro odběr vzorku krve: je běžným úkonem při odběrech krve či podání medikamentů. Komplikace se objevují zřídka: může dojít k podráždění cévní stěny infúzním roztokem či k poškození cévy při zavádění či odstraňování kanyly. Toto se projeví rozvojem drobného výronu krevního (modřiny), podobně jako při odběru krve ze žily. Vzácněji se může

rozvinout zánět žil, který se projeví zarudnutím a bolestivostí v místě vpichu. Tento stav není závažný, představuje spíše diskomfort a většinou s léčbou (mast) do týdne odezní bez následků. **Zavedení senzoru kontinuální monitorace koncentrace glukózy.** Senzor tvoří teflonová trubička o velikosti 6x0,7 mm, která se zavádí do oblasti břicha. Signál ze senzoru je bezdrátově přenášen na monitorovací zařízení. Přístroj, který umožňuje sledovat změny koncentrace glukózy v pětiminutových intervalech.

4. Další nakládání s biologickými vzorky a získanými elektronickými daty

V průběhu studie Vám budou postupně odebrány vzorek žilní krve k vyšetření glukózy popřípadě inzulínu či C peptidu (marker hladiny inzuínu), popřípadě adrenalinu, glukagonu, růstového hormonu, GLP-1 a GIP a další běžných biochemických vyšetření.Vzorky budou rozděleny a vyšetřeny v laboratoři FN Motol, některé z nich budou zamrazeny a zpracovány později ve specializovaných laboratořích.Vzorky budou anonymizovány a mimo řešitelský tým nebude možno identifikovat pacienty, kterým vzorek patří.

Ve vzorcích nebudou prováděny žádné analýzy jaderné genetické informace. Dárci vzorků se s řádným ukončením Vašeho vyšetřovacího protokolu vzdávají vlastnických práv vůči odebranému materiálu.

Elektronická data o sledovaných parametrech budou uložena v centrálním sběrném pultu. Data tam budou uložena anonymně a jejich identifikaci s ohledem na konkrétní osobu bude moci učinit pouze řešitelský lékařský tým.

5. Obecný přínos výzkumu

Výsledky výzkumu mohou mít přímý a okamžitý dopad na klinickou praxi. Slouží k přesnějšímu míry fyzické aktivity a dalších parametrů, dle nichž lze přesněji nastavit dávku inzulínu popřípadě perorálních antidiabetik.

6. Osobní přínos účasti ve studii

Pro Vás osobně vyšetření, která podstoupíte, přinesou lepší orientaci v posunech glykémie v souvislosti s mnoha parametry (především intenzitou fyzické zátěže), a tak umožní lepší vhled do léčby Vašeho onemocnění. Dozvíte se i o citlivosti Vašeho těla na fyzickou zátěž, což Vám pomůže při předcházení hypoglykémií v běžném životě.

7. Lékařská péče pro případ akutních komplikací

V případě rozvoje akutní komplikace v souvislosti s vyšetřovacím programem je Vám naše pracoviště připraveno poskytnout odbornou lékařskou pomoc.

8. Důvěrnost informací

Vaše totožnost ve studii bude důvěrná. Výsledky výzkumu, včetně informací z dotazníků či laboratorních dat mohou být publikovány pro vědecké účely, avšak nebudou obsahovat jakoukoli identifikaci s Vaší osobou. I přes to mohou být data včetně identifikace účastníků přezkoumána etickou komisí či příslušnými inspekcemi. V takovém případě se na tyto údaje vztahuje zákonná povinnost lékařského tajemství.

9. Ukončení studie

Je na Vás, zda se této studie zúčastníte či nikoli. Jakákoli nová zjištění, která by vyvstala v průběhu vyšetřování a která by mohla ovlivnit Vaši ochotu pokračovat ve studii, s Vámi budou komunikována. V případě, že se rozhodnete odstoupit ze studie před jejím skončením, nebudete nijak penalizován/a. Pouze Vás žádáme, abyste toto rozhodnutí zavčasu komunikoval/a s řešitelem projektu. Vaše účast může být ukončena ze strany řešitele v případě nově zjištěného zdravotního rizika či v případě Vaší neohlášené nepřítomnosti v době plánovaného vyšetření.

10. Další informace

Tým řešitelů je Vám připraven poskytnout jakékoli další doplňující informace.
as. MUDr. Jan Brož
Mail: zorb@seznam.cz
Tel.: 224434001

11. Autorizace

Potvrzuji, že jsem si přečetl/a výše uvedené, že mi řešitelé podali dostatek informací o projektu, a že mi byly zodpovězeny veškeré mé otázky. Všemu jsem dobře porozuměl/a a dobrovolně se zúčastňuji tohoto výzkumného projektu. Jsem si vědom/a, že tento souhlas mě nezbavuje žádných zákonných práv v případě pochybení či odborného selhání kohokoli, kdo tuto studii provádí. Jsem si vědom toho, že se mohu kdykoli svobodně rozhodnout vzít svůj souhlas s účastí ve studii zpět.

Tento formulář bude podepsán ve dvou kopiích, z nichž jedna zůstane v mých rukou.

Řešitel projektu: as.MUDr. Jan Brož,

Podpis řešitele projektu:

Jméno účastníka:

Podpis účastníka:

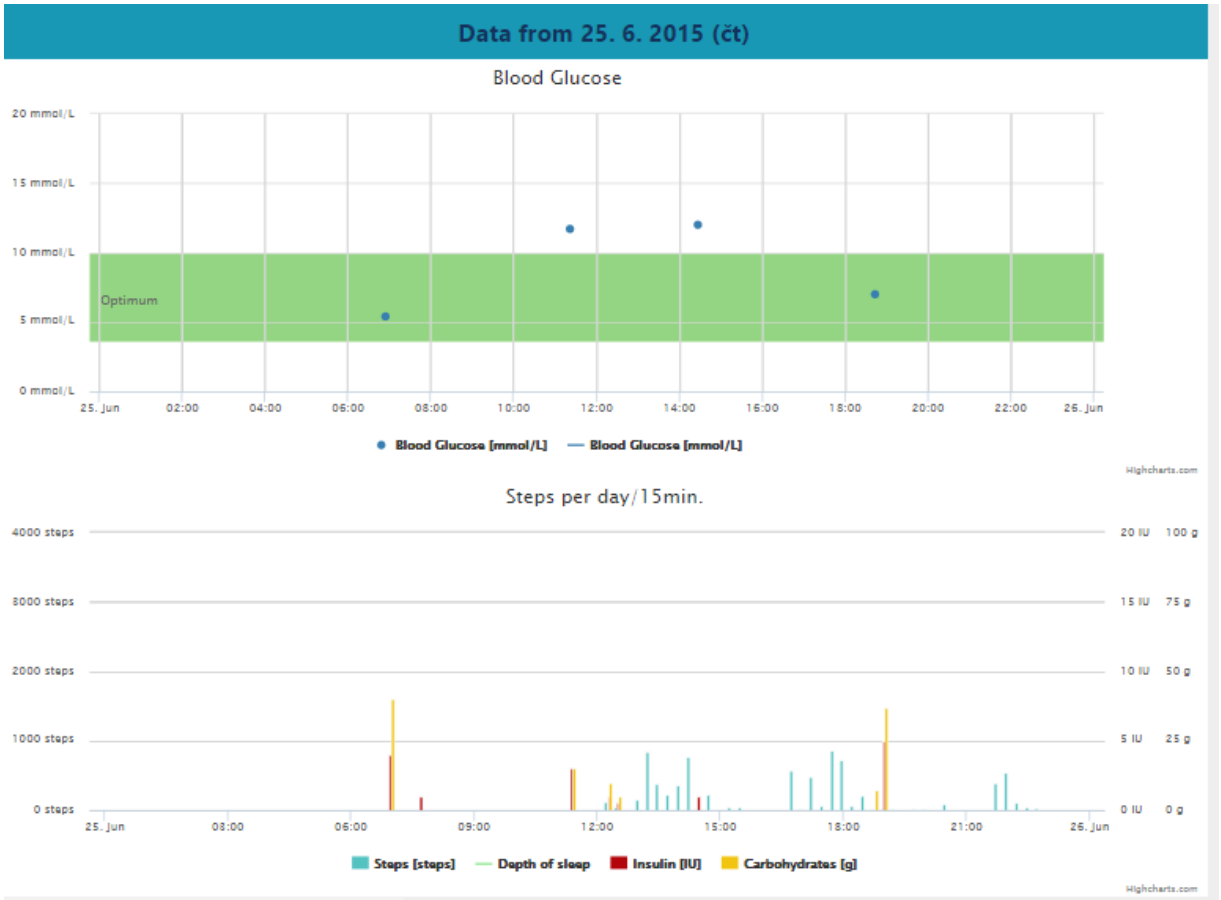
V Praze dne:

Appendix C

TOTO JE HEZKÉ, ÚPLNĚ STEJNÝ VZOREC
DK1
AH1
Glucose level [mmol/l]
Time
00:00 02:24 04:48 07:12 09:36 12:00 14:24 16:48 19:12 21:36 00:00
VR
VR
0
0
VR
2 2R

Appendix D - Example no. 1

Tady už jsou dvě hodnoty nad 10, opět platí, že ten vzestup v poledne nelze s ohledem na absenci poznámek vyložit jinak než chybu v odhadu sacharidů. Stejně tak jako v prvním případě by se tady doktor zeptal pacienta, jestli něco zvláštního nedělal (stres). Pacient si to většinou nepamatuje, takže se to nijak nedořeší.[1]



Time	Blood Glucose [mmol/L]
25. 6. 2015 6:55	5,4
25. 6. 2015 11:22	11,7
25. 6. 2015 14:28	12,0
25. 6. 2015 18:44	7,0

Time	Carb [g]
25. 6. 2015 6:57	40
25. 6. 2015 11:23	15
25. 6. 2015 12:17	10
25. 6. 2015 12:30	5
25. 6. 2015 18:46	7
25. 6. 2015 18:59	37

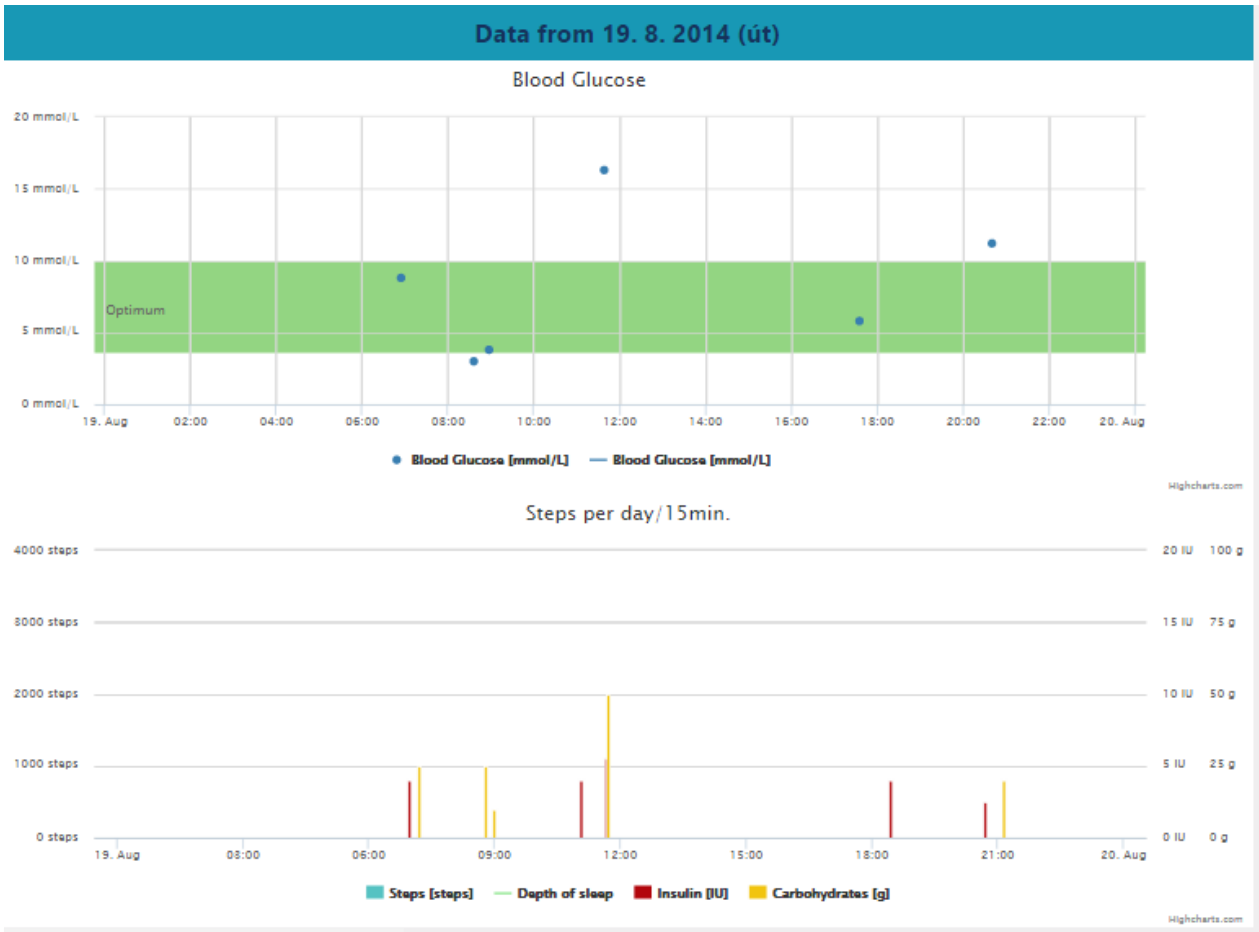
Time	Insulin [IU]
25. 6. 2015 6:57	4,0
25. 6. 2015 7:42	1,0
25. 6. 2015 11:22	3,0
25. 6. 2015 12:17	1,0
25. 6. 2015 12:30	0,5
25. 6. 2015 14:28	1,0
25. 6. 2015 18:59	5,0

Time	Steps
25. 6. 2015 0:00	0
25. 6. 2015 0:15	0
25. 6. 2015 0:30	0
25. 6. 2015 0:45	0
25. 6. 2015 1:00	0
25. 6. 2015 1:15	0
25. 6. 2015 1:30	0
25. 6. 2015 1:45	0
25. 6. 2015 2:00	0
25. 6. 2015 2:15	0
25. 6. 2015 2:30	0
25. 6. 2015 2:45	0

[1] *"Here, we can already see 2 BG values above 10 mmol/L, and again, due to the absence of other notes, the raise in BG level at noon can be understood as a mistake in carbs counting. The same as in the previous case, the doctor would ask the patient whether he/she experienced any unusual situation (such as stressful one). The patient usually doesn´t remember that, so nothing is solved afterwards."*

Appendix D - Example no. 2

Více inzulínu k snídani s ohledem na poměr v porovnání s prvním dnem, proto hypo.[2]



Time	Blood Glucose [mmol/L]
19. 8. 2014 6:54	8,8
19. 8. 2014 8:36	3,0
19. 8. 2014 8:57	3,8
19. 8. 2014 11:39	16,3
19. 8. 2014 17:35	5,8
19. 8. 2014 20:40	11,2

Time	Carb [g]
19. 8. 2014 7:09	25
19. 8. 2014 8:43	25
19. 8. 2014 8:56	10
19. 8. 2014 11:39	50
19. 8. 2014 21:06	20

Time	Insulin [IU]
19. 8. 2014 6:57	4,0
19. 8. 2014 11:03	4,0
19. 8. 2014 11:39	5,5
19. 8. 2014 18:26	4,0
19. 8. 2014 20:41	2,5

Time Steps

[2] "*More insulin for breakfast when compared to the previous day could cause the hypoglycaemia*."

Appendix E – Example no. 1

Time	Glycemia (G) Carbs(C) Insulin (I)	Value G [mmol/L] C [g] I [IU]	Clinician´s Evaluation		Algorithm´s Evaluation		Numbered Excursions	Comments
Day 2								
6:55	**G**	**5,4**			**In range** **Fasting BG In range**		**1**	Commenting this day the clinician says: "*Here, we can already see 2 BG values above 10 mmol/L, and again, due to the absence of other notes, the raise in BG level at noon can be understood as a mistake in carbs counting. The same as in the previous case, the doctor would ask the patient whether he/she experienced any unusual situation (such as stressful one). The patient usually doesn´t remember that, so nothing is solved afterwords.* " Reading the algorithm results we can see the match of the two elevated BG values (#2 and #3). However, while the first excursion connects patient´s mistake to a bad carbs counting, as the clinicians does, the second excursion is connected to the information obout treating high BG with correction bolus instead
6:57	C	40						
6:57	I	4						
7:42	I	1						
11:22	**G**	**11,7**	**High**	**Bad Carbs Counting**	**High**	**Mistake in Carb Counting/Missed registration**	**2**	
11:22	I	3						
11:23	C	15						
12:17	C	10						
12:17	I	1						
12:30	C	5						
12:30	I	0,5						
14:28	**G**	**12**	**High**	**Bad Carbs Counting**	**High**		**3**	
14:28	**I**	**1**			**Correction Bolus**			
18:44	**G**	**7**	**NA**		**In range**		**4**	
18:46	C	7						
18:59	C	37						
18:59	I	5						

Appendix E – Example no. 2

Day 3								
12:20	**G**	5	NA		**In range**		**1**	Here, the clinician observed the situation with high BG in the evening (#2), which was also matched by the algorithm, but he was unable to make a decision about its cause due to lack of information about food consumption, as he comments on it: "*information about dinner is missing* "
12:20	I	5						
13:00	C	50						
15:17	I	4,5						
18:47	**G**	17,5	High	**Missing dinner registration**	**Very High >15**	Mistake in Carb Counting/Missed registration	**2**	
18:48	I	7						
18:53	C	35						
22:25	G	9,9						
Day 4								
8:13	**G**	4,5	NA		**In range** **In range Fasting BG**		**1**	The clinician´s notes on this day were: "*Very nice day, here, it is evident that the patient is able to manage the disease if he/she makes more efforts* ", whereas the algorithm highlighted the premeal BG values falling within the target range only.
8:20	I	3						
8:37	C	35						
9:59	G	9,3						
11:26	**G**	7,5	NA		**In range**		**2**	
11:28	I	5						
11:50	C	30						
17:41	**G**	9,7	NA		**In range**		**3**	
17:42	I	4,5						
18:27	C	35						
18:32	G	11,3						
20:47	G	6,2						
22:44	G	8,2						