A Personalised and Adaptive Insulin Dosing Decision Support System for Type 1 Diabetes

by

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Abstract

People with type 1 diabetes (T1D) rely on exogenous insulin to maintain stable glucose levels. Despite the advent of diabetes technologies such as continuous glucose monitors and insulin infusion pumps, the majority of people with T1D do not manage to bring back glucose levels into a healthy target after meals. In addition to patient compliance, this is due to the complexity of the decision-making on how much insulin is required. Commercial insulin bolus calculators exist that help with the calculation of insulin for meals but these lack fine-tuning and adaptability.

This thesis presents a novel insulin dosing decision support system for people with T1D that is able to provide individualised insulin dosing advice. The proposed research utilises Case-Based Reasoning (CBR), an artificial intelligence methodology, that is able to learn over time based on the behaviour of the patient and optimises the insulin therapy for various diabetes scenarios. The decision support system has been implemented into a user-friendly smartphone-based patient platform and communicates with a clinical platform for remote supervision.

In-silico studies are presented demonstrating the overall performance of CBR as well as metrics used to adapt the insulin therapy. Safety and feasibility of the developed system have been assessed incrementally in clinical trials; initially during an eight-hour study in hospital settings followed by a six-week study in the home environment of the user. Human factors play an important role in the clinical adoption of technologies such as the one proposed. System usability and acceptability were evaluated during the second study phase based on feedback obtained from study participants.

Results from in-silico tests show the potential of the proposed research to safely automate the process of optimising the insulin therapy for people with T1D. In the six-week study, the system demonstrated safety in maintaining glycemic control with a trend suggesting improvement in postprandial glucose outcomes. Feedback from participants showed favourable outcomes when assessing device satisfaction and usability. A six-month large-scale randomised controlled study to evaluate the efficacy of the system is currently ongoing.

Declaration of Originality

I hereby declare that all content of this thesis is the result of my own work. Therefore, all simulations, software developments and data analysis have been performed by the author, if not stated otherwise in the text. A list of publications that arose from this work can be found in Appendix A. Additional information used from third parties has been referenced accordingly. Any collaborations and assistance are outlined below:

Chapter 3

The concept of using case-based reasoning for insulin recommendations and the methodology for insulin dose adjustments presented in this chapter were established in collaboration with Dr Pau Herrero. The work has been published in two journal papers with the writer of this thesis appearing as co-author.

Chapter 5

The presented clinical study was performed in close collaboration with the medical research team from the Division of Diabetes, Endocrinology and Metabolism, Imperial College London, led by Dr Nick Oliver and Prof. Desmond Johnston. Dr Monika Reddy conducted the clinical studies, analysed the glucose outcomes shown in Table 5.1 b. This data was partly presented at the conferences 'Advanced Technologies and Treatments for Diabetes' in 2015 in Paris and submitted to the journal 'Diabetes Technologies and Treatments' for publication with the writer of this work appearing as co-author. Further clinical support and assistance during the studies was provided by Maria Xenou and Narvada Jugnee.

Copyright Declaration

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Most importantly, massive thanks to my family and friends (you know who you are), for all the unconditional love, encouragement and support I have received, one of the greatest treasures that I can wish for. I am endlessly grateful for this.

Finally, I would like to dedicate the thesis to my parents who always believed in me and encouraged me to follow my dreams.

Contents

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Abbreviations

ABC4D	Advanced Bolus Calculator for Diabetes
AI	Artificial intelligence
AP	Artificial pancreas
AUC	Area under curve
BG	Blood Glucose
CBR	Case-based reasoning
CGM	Continuous glucose monitoring
CF	Correction factor
CT	Control theory
CSII	Continuous subcutaneous insulin infusion
CVGA	Control variability grid analysis
DSS	Decision support system
GI	Glycemic index
GUI	Graphical user interface
HbA1c	Glycated haemoglobin A1c
HBGI	High blood glucose index
IAT	Insulin action time

ILC	Iterative learning control
ICR	Insulin-carbohydrate ratio
IOB	Insulin on board
ISF	Insulin sensitivity factor
IQR	Interquartile range
LBGI	Low blood glucose index
MARD	Median absolute relative difference
MBR	Model based reasoning
MDI	Multiple daily injections
NICE	National institute of clinical excellence
NN	Neural networks
R2R	Run-to-Run control
RI	Risk Index
SD	Standard deviation
T1D/T2D	Type 1 diabetes/Type 2 diabetes
TTP	Time to peak

Chapter 1

Introduction

1.1 Background and Motivation

1.1.1 Diabetes Mellitus

Diabetes mellitus is a chronic condition where the pancreas is unable to produce sufficient insulin in order to keep blood glucose levels within a physiological range [1]. In a healthy body, $\beta - cells$ located in the pancreas produce insulin that enables cells the uptake of glucose from the bloodstream. Glucose is an essential source of energy for the cells within the body and is supplied by carbohydrates contained in the food we eat. Carbohydrates are broken down during meal digestion into mono- and disaccharides, most of which is glucose. There are two types of diabetes. Type 1 diabetes (T1D) is an autoimmune disease, where the $\beta - cells$ are destroyed by antibodies, which results in an absolute deficiency of insulin and leads to elevated blood glucose levels (hyperglycaemia). In type 2 diabetes (T2D), the pancreas is still able to produce insulin but either not sufficient to function properly (relative insulin deficiency) or the cells in the body are not responding to the existing insulin (insulin resistance). Figure 1.1 shows an example of the glucose excursion followed after a meal that contains carbohydrates for healthy individuals and for people with T1D or T2D who rely on exogenous insulin, respectively. In people without diabetes, glucose levels rise slightly after the meal, but usually stay within the defined target range of post-prandial normoglycaemia (i.e. 3.9-10 mmol/l or 70-180 mg/dl [2]). However, if there is not enough insulin available, the glucose in the bloodstream cannot enter the cells and the glucose concentration remains high after the meal. Severe hyperglycaemia can lead to potentially life-threatening diabetic ketoacidosis [3], which occurs when the body switches its main energy source from glucose

to fatty acids and toxic acidic ketone bodies are produced as a by-product. The resulting symptoms of prolonged high glucose levels include polydipsia, polyuria, polyphagia, blurred vision, tiredness and loss of weight.

The onset of T1D is associated partly with genetic predisposition and external triggers such as diet or infections [4], while for T2D there is an additional strong link to lack of exercise and obesity [1]. In early stages of T2D, insulin resistances may be improved with changes in lifestyle, such as weight loss and exercise, whereas later stages require either medications or insulin to lower blood glucose levels. In contrast to early T2D, T1D is not reversible and solely relies on exogenous insulin administration. The World Health Organization (WHO) has reported that an estimate of 171 million people suffered from diabetes in 2000, expecting this number to be doubled in 2030 [5]. T1D accounts for about 10-15 percent of all cases. From a global perspective, diabetes represents a great burden for the health system [6] and its incidence is still increasing for both T1D and T2D.

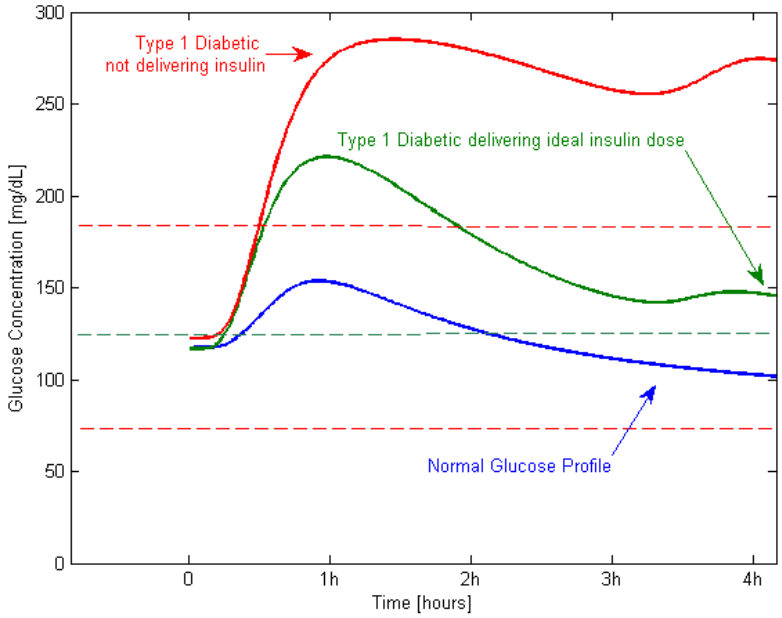

Figure 1.1: Example of a glucose response after a meal for a healthy individual (blue line), a person with T1D on optimal (green line) and suboptimal (red line) insulin therapy

1.1.2 Complications and Treatment

There are several long-term complications that can occur if diabetes is not well managed. Long-term elevated glucose levels may lead to loss of vision, renal failure, cardiovascular diseases, nerve damage and complications during pregnancy. Large-scale randomised studies [2, 7] have shown that it is possible to prevent or delay the onset of complications with intensive diabetes management aiming for tight glycemic control. This involves frequent checks of capillary glucose levels using finger-prick blood glucose meters and the injection of insulin up to six times a day. However, intensive insulin treatment has also been linked to an increased risk of hypoglycaemia (low blood glucose concentration) [8] and hypoglycaemia unawareness (the inability of the body to show symptoms for low glucose levels). Severe hypoglycaemia can lead to seizures, unconsciousness and the 'dead-in-bed' syndrome. Diabetes technologies, such as continuous glucose monitors (CGM) for glucose sensing and continuous insulin infusion pumps (CSII) for insulin delivery, exist and aim to support people with the challenge to achieve optimal glycemic control without recurrent hypoglycaemia. However, these technologies do not provide sufficient decision support to assist people to improve glucose control. A detailed overview of the state-of-the-art and ongoing research in diabetes management will be given in Chapter 2.

1.1.3 Challenges in Diabetes Management

Despite improvements in diabetes technology, people with T1D still struggle to achieve target in glycemic control and prevent long-term complications. The National Diabetes Audit reports that only 27.3% of people with T1D achieved a target HbA1c of less than 7.5% (58mmol/mol), analysing 177.475 patient records between the years 2012 and 2013 [9]. There are several reasons for the low number of people reaching this target. For one, fear of hypoglycaemia [10] has been reported as a factor why people do not deliver enough insulin. Also, people with T1D would need to know the composition of consumed meals and, more importantly, be able to estimate the exact carbohydrate content of the meal. Patient education programmes, also referred to as 'structured education', aim to teach participants how to estimate the amount of carbohydrates and perform insulin dose adjustments. However, only a low percentage (0.9%) [9] of newly diagnosed people are reported to have attended structured education. Calculating an insulin dose also requires basic arithmetic skills and low numeracy among people with T1D is a significant problem [11], which often results in erroneous calculations. Some blood glucose meters and CSII

pumps incorporate simple insulin bolus calculators with the aim to assist people with T1D to perform insulin dosing calculations. Although the clinical benefit of using bolus calculators has been demonstrated [12, 13], their performance remains suboptimal. This is mainly due to the fact that the amount of bolus insulin not only depends on the current blood glucose level (to compensate for initial high or low glucose concentration) and the anticipated amount of carbohydrates but also on various and often unaccounted factors, such as stress, physical activity and the time of the day. These factors are not only subject to the individual but their effect on the insulin sensitivity is also likely to change over time. Some bolus calculators allow to set rules for certain situations (e.g. reduce the amount of insulin by 10% for exercise) but are neither able to assess the outcome of these empirical rules, nor are they able to react to changes in the insulin sensitivity. It is hypothesised that a personalised and adaptive insulin advisory system will provide better glycemic control than state-of-the-art bolus calculators and, thus, has the potential to reduce long-term complications of diabetes.

1.1.4 Proposed Research and Challenges

The aim of this research is the development of a real-time and personalised decision support tool for meal insulin dosing that provides enhanced adaptability and flexibility to current bolus calculators. The hypothesis is that personalised insulin decision support results in improved glycemic control and therefore reduces the onset of secondary diabetes-related complications. Insulin requirements depend on multiple environmental and biological factors, such as exercise or stress, which are likely to change over time. Therefore, the decision support system must be able to adapt to changes in the insulin sensitivity of people with T1D. The work in this thesis proposes the use of Case-Based Reasoning (CBR), an artificial intelligence technique, in order to provide insulin dosing decision support for various meal scenarios (e.g. large dinner after exercise) with the ability to react to changes to insulin sensitivity based on the glycemic outcome of similar scenarios from the past. CBR learns from comparing the current meal scenario to past similar meals. Meal scenarios can be represented through cases, where each case is described through a set of chosen parameters e.g. time of meal, alcohol, exercise before or after the meal. One challenge in this research is to identify key parameters that have an influence on the glucose regulatory system and how they can be represented within a case. Furthermore, the research addresses how such cases can be compared to a current scenario and what solutions (e.g. insulin dosage, injection site and time) can be proposed to the person with T1D. Another research challenge

is how to assess the outcome of the proposed solutions (i.e. glucose excursion after a meal with insulin). Moreover, potential methods need to be investigated to optimise the solution if the glucose outcome is clinically not optimal. The final challenge is to develop a user-friendly, mobile and safe system that implements the decision support algorithm for insulin dosing. The system needs to be able to provide insulin therapy advice in real-time, as well as implement safety features to ensure only clinically safe insulin doses are recommended. Safety features providing risk mitigation and risk control for the proposed advisory system need to be evaluated. Furthermore, a clinical system for remote supervision is required that is able to communicate with the proposed insulin dosing advisory system in order to enable clinical experts to supervise and approve insulin therapy adjustments. The concept of a mobile patient platform providing insulin recommendations that communicates with a clinical supervision platform can be seen in Figure 1.2. Usability and acceptability are key for the adoption of the proposed research and the developed system needs to be easy to use for both clinicians and people with T1D. In order to enhance usability, manual user intervention should be minimised by automatically acquiring necessary features. Eventually, safety and efficacy of the insulin dosing decision support system need to be demonstrated in clinical practice.

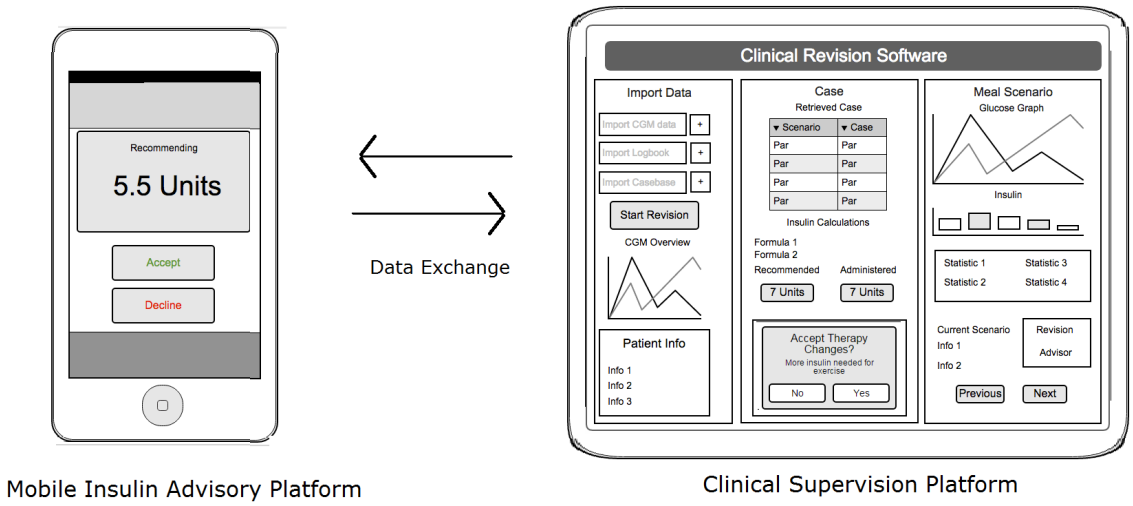

Figure 1.2: Smartphone-based patient platform (left) providing insulin bolus advice and sending data to a clinical platform (right) for remote supervision.

1.1.5 Key Contributions and Findings

Based on the proposed research objectives, this section lists some of the key contributions arising from this work:

- Integration of CBR into a novel insulin bolus advisory system to provide more flexibility and adaptability compared to standard bolus calculators
- Identification of key parameters that have impact on glucose control and how they can be represented within a case
- Implementation and optimisation of the CBR process steps (i.e. retrieval, reuse, revision and retention) for the proposed system
- Development and evaluation of methods for automatic adaptation of the proposed solution, as well as metrics to assess the outcome of insulin recommendations
- Development of a user-friendly decision support system, which includes a mobile patient platform for real-time insulin bolus advice for people with T1D and a clinical platform for remote supervision of performed changes in insulin therapy
- Clinical evaluation assessing safety and feasibility of the proposed insulin dosing advisory system in clinical and real-life setting
- Optimisation of the presented system based on results of clinical trials (i.e. usability, safety, etc.)

1.2 Thesis Organisation

Based on the proposed research objectives, the thesis will be organised in the following sections:

1.2.1 Chapter 1: Background and Motivation

The first chapter introduces the reader to the background of diabetes and explains the need for better decision support in diabetes management, and more specifically, for insulin dosing. The shortcomings of current technologies and therapies are discussed and how the research

proposed in this thesis aims to overcome these limitations and enhances the state-of-the-art insulin therapy. The final part of the chapter describes the challenges of the research and lists research objectives that are addressed in the following chapters.

1.2.2 Chapter 2: Diabetes Management and Decision Support

The second chapter gives an overview of current technologies and decision support in diabetes management. State-of-the-art methods for sensing glucose concentration and insulin delivery, as well as the ongoing research for closed loop control of glucose, are presented. A commercially available decision support tool for insulin dosing, the bolus calculator, will be discussed in more detail. The chapter concludes with the benefits and shortcomings of current bolus calculators and what can be done to improve them.

1.2.3 Chapter 3: Case-Based Reasoning for Insulin Decision Support

Chapter 3 describes the research towards a novel decision support system, which acts as an enhanced insulin advisory system for personalised insulin bolus recommendations.
Initially, the concept of Case-Based Reasoning (CBR) is presented and its potential to improve the performance of the proposed advisory system by enabling it to learn based on past experiences, thus providing more personalised insulin dose recommendations. Key parameters are identified, which influence the glucose regulatory system and can be utilised in CBR to describe meal scenarios in the form of cases. In CBR the process of learning from past experiences follows a four-step cycle (retrieval, reuse, revision and retention of cases) and the implementation of all steps is explained next. Moreover, various methods on how to adapt case solutions are shown, as well as ways to assess the outcome of an insulin advice based on glucose information from continuous glucose monitors. Finally, simulation results are presented from in-silico studies evaluating the performance of the CBR as learning methodology, as well as metrics which can be used for case revision.

1.2.4 Chapter 4: Advanced Bolus Calculator for Diabetes System

This chapter describes the development and evaluation of a CBR-based 'Advanced Bolus Calculator for Diabetes' (ABC4D). The system architecture and the implementation of CBR as the core learning methodology are described. Initial usability and acceptability results of

ABC4D are presented, which have been obtained after ten people with T1D continuously used the system over a period of six weeks.

1.2.5 Chapter 5: Clinical Evaluation

The final goal of the research is to assess the system in clinical and real-life settings used by people with T1D. Chapter 5 will introduce the reader to the various phases of clinical trials, starting with a short safety study in a clinical environment, followed by a six-week feasibility study. Finally, the work towards a large randomised efficacy study in the home setting of people with T1D is described. Based on the results of each trial phase, the insulin bolus advisory system has been optimised and improved. The chapter presents the clinical outcomes and resulting improvements for the first two study phases.

1.2.6 Chapter 6: Outlook and Conclusion

The final chapter provides an outlook on potential future developments and research, as well as summarises and discusses achievements and contributions of the presented research.

1.3 Conclusion

T1D represents a major burden for both individuals with diabetes and more globally for the healthcare system. Current treatment involves intensive self-management, which aims to keep the blood glucose concentration at a constant level. However, the task of maintaining healthy blood glucose levels is challenging and people with T1D often lack structured education and numeracy skills to perform insulin dosing calculations. Yet failure to achieve good glucose control can lead to serious short- and long-term complications, as described in this chapter. The amount of insulin required in order to achieve target control is determined according to the current blood glucose concentration, the quantity of carbohydrates consumed and other factors including time of day, exercise and illness. As many people with T1D struggle to include all this information into their insulin therapy, it is of interest to provide support with intelligent consultations based on available glucose related data. Some commercially available technologies, such as blood glucose meters and insulin pumps, integrate bolus calculators to calculate the amount of insulin needed for a meal but these formulas are very basic and their simplicity leads to several shortcomings. In this research,

an adaptive insulin bolus advisory system for personalised insulin recommendations is presented that aims to outperform state-of-the-art bolus calculators and improve glycemic control of people with diabetes. Even though this research focuses on decision support for people with T1D to optimise the insulin therapy and achieve healthy glucose levels after a meal, the same technology can potentially be used for people with T2D in progressed stages, when relying on exogenous insulin.

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Chapter 2

Diabetes Management and Insulin Dosing Decision Support

The main goal of diabetes management is to keep blood glucose levels within a pre-defined target range. To achieve this, people with T1D rely on exogenous insulin to lower blood glucose levels after meals, while trying to minimise time spent in hyper- and hypoglycaemia (i.e. high and low blood glucose levels). Insulin injections are based on information given by glucose measurements from finger-prick blood samples. The long-term goal of diabetes management is to reduce or control glycated haemoglobin (HbA1c) and to prevent the long complications as described in Chapter 1. The Diabetes Control and Complications Trial (DCCT) was a large-scale study published in 1993 that dealt with the effect of intensive treatment and the progression of long-term complications of T1D. It involved more than 1400 volunteers over a period of 6.5 years and showed that intensive management reduced complications by 50-76% compared to conventional therapy at the expense of increasing the risk of hypoglycaemia [1]. Intensive treatment can be encouraged by providing diabetes education for people with T1D. The National Institute of Clinical Excellence (NICE) recommends structured education (e.g. DAFNE 'Dose Adjustments For Normal Eating' program) to adults that are newly diagnosed with diabetes. This chapter discusses state-of-the-art technologies for diabetes management, such as continuous glucose monitoring systems and insulin infusion pumps, as well as decision support systems (DSS) for both patients and clinicians.

2.1 Glucose Monitoring

2.1.1 Blood Glucose Meters

Intensive diabetes treatment involves multiple daily insulin injections and frequent blood glucose measurements (4-6 times a day). Blood glucose (BG) meters can be used for capturing capillary glucose levels and adjusting the insulin therapy accordingly. Figure 2.1 shows a standard BG meter displaying the glucose value after a measurement. Readings are obtained by piercing the finger using a lancet and applying a drop of blood to a disposable chemical test-strip, which is then inserted into the meter. Standard BG meters use an electrochemical approach where the blood drop on the test strip reacts with glucose oxidase, which acts as a catalyst and produces a current that is proportional to the blood glucose concentration. The result of the measurement is displayed on the screen of the device in either mM/l or mg/dl, depending on the geographical region. Most BG meters provide simple statistics (e.g. mean values over a fixed time period) and allow data export of past readings either via cable or Bluetooth to a computer or smartphone for further analysis.

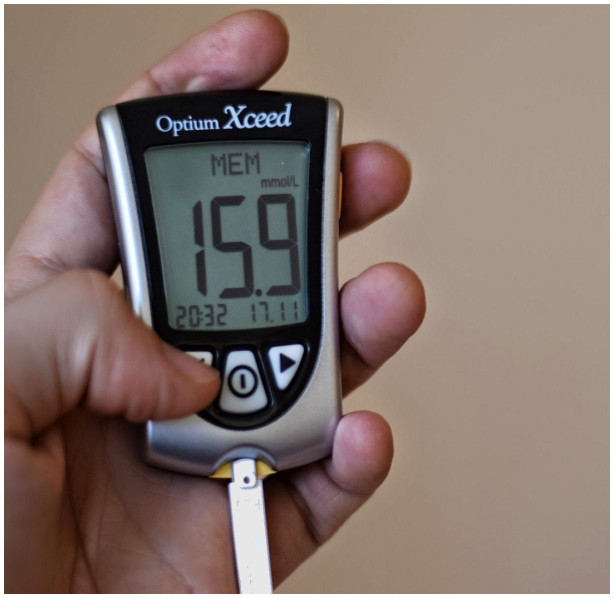

Figure 2.1: BG meter showing the current blood glucose level after a finger-prick measurement.

2.1.2 Continuous Glucose Monitors (CGM)

In contrast to BG meters, which provide only a single reading per use, CGM devices continuously (e.g. every 5 minutes) sample glucose concentration in the subcutaneous tissue from a disposable sensor. CGM systems use an amperometric method to indirectly measure the concentration of glucose. The tip of the inserted sensor contains an enzyme (glucose oxidase) that reacts with the surrounding glucose and produces hydrogen peroxide, which is proportional to the concentration of the glucose and measured by the sensor electrode. The usual lifespan of a sensor is about one week before it needs to be replaced. Glucose measurements performed by a CGM system can be either blinded (data is only available retrospectively after calibration) or real-time. In real-time systems, a transmitter is used to send glucose measurements to an external receiver to display readings and additional glucose related information, e.g. trends and predictions (see Figure 2.2). More recent real-time CGM devices are able to transmit readings directly to a smartphone or insulin pump. The temporary use of retrospective CGM systems can be beneficial to recognise patterns in glucose variations and detect recurring hypoglycaemia for people with hypoglycaemic unawareness. A commonly reported problem with CGM devices is their accuracy compared to blood glucose measurements.

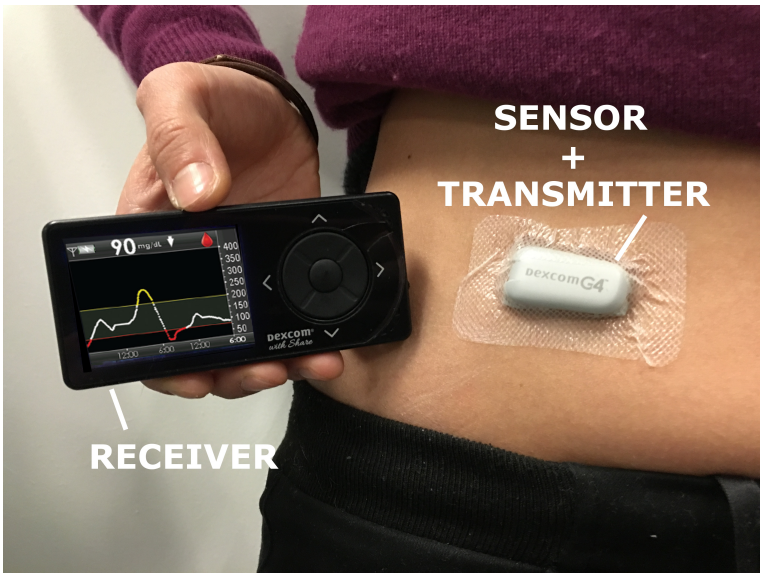

Figure 2.2: Continuous Glucose Monitor (CGM) by Dexcom with a G4 sensor attached to a transmitter (right) sending glucose data in real-time to a body-worn transmitter (left)

As the glucose concentration is measured in the interstitial fluid, readings lag behind changes in blood by several minutes. This lag is even more prominent when glucose concentration changes rapidly [2] (e.g. after a meal or exercise). Although the accuracy of CGM systems improved over the last decade, the majority of CGM systems are not approved to be used as a replacement for blood glucose meters and people with T1D are still advised to use blood glucose measurements before making therapy decisions. In 2015, Dexcom Inc (California, USA) released the G5® Mobile CGM system that allows (in Europe only) the use of the CGM readings for diabetes management decisions, thus eliminating the need for confirmatory finger-prick measurements (capillary glucose testing is still required twice a day for calibrating the system). Multiple studies [3] [4] [5] have shown the benefit of CGM devices to help people with T1D to manage their blood glucose levels and achieve greater average glucose control (HbA1c) without increasing hypoglycaemia.

2.2 Insulin Therapy

2.2.1 Multiple Daily Injections (MDI)

At the moment, the majority of people with T1D use a basal/bolus insulin regime, which requires multiple daily injections of long acting insulin to keep glucose levels within target in fasting condition (basal insulin) and rapid acting insulin to lower the blood glucose levels after each meal (bolus insulin). The amount of basal insulin (e.g. Lantus®, Levemir®) is usually based on the total daily dose (TDD) of required insulin, while meal boluses depend on the meal content. Glucose measurements from blood glucose meters are required before each insulin injection in order to prevent severe hypoglycaemia, if glucose levels are already low. Additional insulin is often given in combination with meal boluses to correct for eventual high glucose levels.

2.2.2 Insulin Pump Therapy

Continuous subcutaneous insulin infusion pumps (CSII) are body worn devices with the size of a pager that are able to deliver insulin to the subcutaneous tissue. Connected to the pump is an infusion set, consisting of a small plastic tube and a soft cannula that is inserted under the patient's skin. CSII pumps can be used as an alternative to multiple daily injections and provide continuous delivery of insulin for intensive insulin therapy, aiming for improved glycemic control. A common reason for people to switch from MDI

to CSII therapy is severe hypoglycaemia, as it allows better tuning of the insulin delivery. Instead of the long-acting insulin for basal, CSII pumps deliver a varied dose of fast-acting insulin continually throughout day and night at a pre-set rate. Furthermore, it is possible to manually set an insulin bolus dose in order to cover a meal. Reported disadvantages are the limitation of physical activity of the patient and the constant reminder that the wearer has diabetes. Several studies have shown the benefit of CSII therapy in T1D over MDI [6].

2.2.3 Combined CGM and Insulin Delivery Systems

In recent years, pump manufacturers presented CSII systems that can communicate with CGM systems (Medtronic REAL-TIME Paradigm® with Medtronic Enlite CGM and Animas Vibe with Dexcom G4® CGM), enabling the user to see recent glucose levels on the display of the pump. In 2009, Medtronic released the Paradigm® Veo™ into the marked that is able to automatically stop the insulin delivery based on low glucose readings from a continuous glucose monitor. The successor of this product, the MiniMed® 640G system, enhanced the feature of suspending the pump by incorporating a prediction algorithm that aims to detect low glucose levels 30 minutes in advance. However, none of the commercially available systems are able to automatically deliver insulin based on CGM readings. Fully automated insulin delivery in a closed-loop fashion is currently investigated by several research groups.

2.3 Artificial Pancreas Systems

The idea of developing closed-loop control of blood glucose concentration exists since the discovery of artificial insulin. In the late 1970s, the Biostator [7] was introduced as a 'Glucose Controlled Insulin Infusion System', which continuously sampled venous blood, measured blood glucose concentration and infused either glucose or insulin intravenously. The amount of insulin was calculated by an algorithm in a computer, which made the Biostator one of the very first in-hospital closed loop systems for glucose control.
A closed loop system with automatic insulin delivery, also defined as an artificial pancreas (AP) system, is based on three core components: the glucose sensor for acquiring new measurements, a control system for calculating the required insulin dose and an infusion pump to deliver the calculated insulin to the human body. Most study groups investigating closed loop control systems utilise algorithms that derive either from control engineering tech-

Figure 2.3: Bio-inspired Artificial Pancreas System [11] (centre) communicating with a continuous glucose sensor (Dexcom G4®) and an insulin pump (Roche ACCU-CHECK®)

niques, e.g. proportional integral derivative (PID) control [8] and model predictive control (MPC) [9], or artificial intelligence techniques, e.g. fuzzy logic [10]. A different approach was proposed by our group [11] using mathematical models to mimic the physiology of the insulin secreting beta-cells. The system, called the Bio-inspired Artificial Pancreas (BiAP) (see Figure 2.3), demonstrated safety and feasibility of the algorithm performing in various clinical settings [12] [13]. While several studies show encouraging results during over-night or fasting periods, post-meal control of glucose is still challenging for algorithms, which is down to the significant delays that occur when sensing glucose and delivering insulin in the interstitial compartment. Control for unannounced meals has been tested but leads to much higher postprandial glucose excursions because of the slow dynamics of current insulin formulations. Therefore, the majority of study groups provide methods to manually announce the size of meals and then deliver a meal insulin bolus based on a patient-specific insulin-carbohydrate ratio (ICR), which describes how much insulin is needed to cover a certain amount of carbohydrates. In this semi-automated mode, the postprandial glycemic outcome greatly depends on the meal bolus. Safety features have been implemented into AP systems to stop the insulin delivery if the drop of glucose levels is predicted to be too low. However, without a counter-regulatory hormone (i.e. glucagon), manual insulin delivery for meals can still lead to hypoglycemic episodes. Therefore, AP systems with meal announcement will still rely on optimal ICR settings to achieve clinically acceptable glucose excursion after meals.

2.4 The Need for Insulin Decision Support

At the moment, parameters ICR and ISF (i.e. insulin-sensitivity factor describing how much insulin is needed to correct for elevated glucose levels) are commonly used by people on MDI or CSII therapy to calculate the amount of insulin needed. These factors are subject dependent and usually defined by clinicians at the time of diagnosis. Many people with T1D use different ICR values for breakfast, lunch and dinner. The reason for this is because of the body's sensitivity to insulin, which is known to vary according to the time of the day. For instance, the 'dawn phenomena' is a commonly experienced effect in people with T1D, describing an increase in insulin resistance in the morning hours, which is due to the release of growth hormones overnight [14].

However, in addition to the time of day, there are many other variables that have impact on the glucose regulatory system and, therefore, on the insulin requirements. One of the main hurdles for people with T1D is to correctly address these and accordingly adjust the insulin therapy. This section discusses a selection of factors that are known to affect the glucose metabolism. A comprehensive list of key factors, their reported effect and how they could be captured and integrated as a parameter within an insulin dosing DSS can be found in Appendix B. Factors are divided into four categories: meal information (e.g. fat content, alcohol, caffeine), biological factors (e.g. hormonal cycle, time of day, sleep) and environmental/other factors (e.g. activity, stress, temperature, smoking). The presented list of parameters affecting glucose levels is based on feedback from patients during focus group meetings (see Chapter 4.4), discussions with the clinical study team, as well as findings in the literature. Following keywords were used for the literature review (databases: MEDLINE, PubMed and PMC): glucose, diabetes, insulin sensitivity, effect, factor, parameter, meal composition, absorption, fat, protein, stress, exercise, hormonal, caffeine, alcohol, environmental and illness.

Meal-related Factors

In addition to the amount of carbohydrates, the composition of a meal can have a great impact on both dosage and the timing/shape of insulin delivery. There is also a reported effect of beverages containing caffeine and alcohol on the glucose control [15] [16].

Glycemic Index Carbohydrate containing food can differ considerably in the glucose response depending on the glycemic index (GI) of the digested food [17]. GI denotes how quickly the blood glucose levels respond after the intake of a meal containing carbohydrates. Consuming food with a high glycemic index results in a greater rise and fall of glucose levels after a meal compared to the postprandial profile after a low-GI meal [18]. High-GI meals are often used for quick recovery of hypoglycaemic episodes.

Fat and Protein Content Current insulin therapies for meal insulin dosing are mainly focused on the carbohydrate intake. However, Wolpert et. al [19] showed in a small population (n=7) of people with T1D that meals with a hight fat content require more insulin and result in higher postprandial glucose levels than meals with identical carbohydrate but lower fat content. Another study [20] in adolescents (n=33) confirmed the increase in glucose excursion for high fat meals and further observed a delayed postprandial rise of glucose.

Caffeine Several studies have shown the effect of caffeine on glucose levels. A review by James Lane [15] analysing existing studies concludes that caffeine (found in coffee, tea and energy drinks) consumed in combination with carbohydrates causes transient insulin resistance resulting in exaggerated glucose and insulin responses for non-diabetics as well as people with T2D. Only little evidence on the effect of caffeine on people with T1D has been collected. Watson et al. report that modest amount of caffeine enhance the intensity of hypoglycaemia warning symptoms [21].

Alcohol Consumption Moderate alcohol consumption is known to affect insulin sensitivity and hepatic glucose output in non-diabetics [22]. For people with diabetes, alcohol is recognised as a risk factor for hypoglycaemia. However, while studies failed to show any acute changes in glucose or insulin concentration after alcohol consumption [23] [24], an increased risk of hypoglycaemia has been reported by several groups the next morning after alcohol consumption in the evening [25] [16].

Biological Factors

Stress and Illness

Illness and stress can cause an increase in the release of hormones, such as cortisol and adrenaline, which reduce insulin sensitivity and can lead to elevated glucose levels [26].

Hormonal Cycle

The effect of the menstrual cycle on glucose control and insulin sensitivity has been demonstrated and literature suggests considering the follicular and luteal phases in the insulin therapy for women with T1D [27].

Environmental and other Factors

Physical Activity

Physical exercise is known to result in a drop of basal plasma insulin concentration [28], amplification of glucose uptake by the working tissue [29] and elevated hepatic glycogenolysis [30]. Thus, energy expenditure before and after a meal is an important parameter for calculating an optimised insulin bolus solution. A simple qualitative value (no, mild or moderate activity) of the parameter can be obtained manually through the user by entering recent and expected activity. Automatic detection of physical activity can be achieved by using data collected from an accelerometer [31, 32] or heart rate monitor, which has been validated as a surrogate for physical activity in people with T1D by Breton [33]. Figure 2.4 shows an implementation of an exercise model utilising heart rate as input and the drop in basal glucose concentration for various intensities. It can be seen that the drop in glucose concentration is still noticeable after 20 hours. Therefore, exercise performed in the evening can potentially still affect the insulin requirements the next morning.

2.5 Decision Support in Diabetes Management

With the advent of information technologies and a vast amount of data available from glucose sensors and insulin pumps, DSS have the potential to assist both patients and clinicians in the complex task of diabetes management.

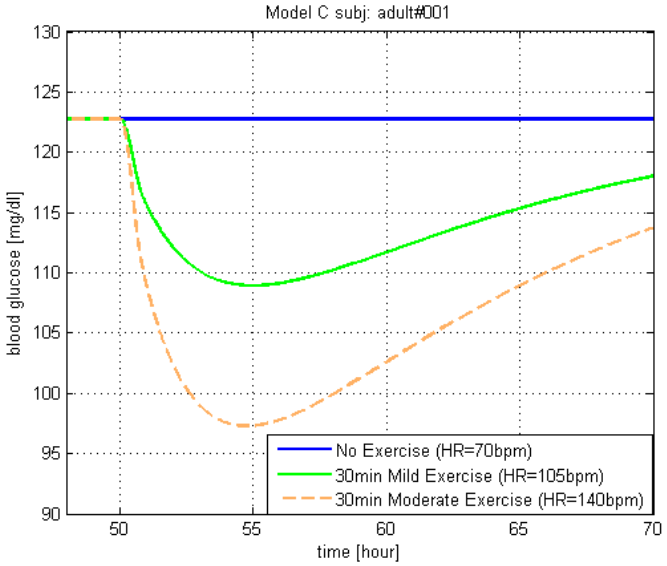

Figure 2.4: MATLAB® simulation of the glucose response after 30 min of mild (HR=105) and moderate (HR=140) exercise compared to resting state (HR=70) utilising exercise model C proposed by Breton [33].

Decision support for clinicians aims at assisting diabetes experts in the management of the chronic disease. The functionality of these systems can range from analysing patient characteristics to supporting the clinical expert in their decision-making of changes to the insulin therapy. So far the focus on DSS for diabetes (both types) has been on providing clinicians with patient-specific assessments or recommendations to aid clinical decision-making [34]. Nilasena et al. [35] used computer-generated reminders to improve physician compliance, while another group [36] showed the clinical benefit of implementing a diabetes electronic management systems (DEMS) and planned care involving guideline implementation and use of clinical information systems. Several telemedicine systems have been investigated to remotely support people with T1D or the clinicians in their decision-making. The Telematic Management of Insulin-Dependent Diabetes Mellitus (T-IDDM) project [37] aimed to assist physicians in the decision-making for insulin therapy adjustments and also allowed remote supervision of patients through tele-monitoring. METABO [38] is another project with the aim to enhance the communication between patients and physicians in order to improve treatment and diagnosis. The system uses a portable mobile device that communicates with the expert control system. However, the patient device does not include any adaptive decision support and a high degree of participation from the medical team is required. Sev-

eral study teams investigated the utilisation of the patient's phone to transmit blood glucose results [39] [40] and receive consultation from the physician via phone [41] [42] or feedback via automated text responses that contain motivational content, estimations of HbA1c or reminders for set goals [43] [44]. The outcome of the studies showed that telemedicine transmission and feedback of information is feasible and acceptable for patients, while real-time access to data is required for insulin dosing adjustments [39].

2.6 Decision Support for Insulin Dosing

Calculating the optimal insulin dosage is key in diabetes management in order to achieve good glycemic control and avoid short and long term complications. The amount of insulin needed to cover a meal depends on the current BG level, target BG, amount of carbohydrates in the meal, the ICR and the insulin-sensitivity-factor (ISF), which describes the drop in glucose for one unit of insulin. Therefore, the ISF is used to add (or remove) insulin for high (or low) glucose levels at the time of meal. While initially patients diligently utilise these factors for calculations, in practice many people with T1D revert back to empirical rules and approximations, which often results in suboptimal glucose control [45].

2.6.1 Bolus Calculators (BC)

Insulin bolus calculators (BC) have been designed to overcome this hurdle and provide more accurate insulin calculations while at the same time improve patient adherence. BCs use a simple formula to calculate the amount of insulin needed for a meal or to correct for elevated BG levels [46] and are commonly integrated into insulin pumps, glucose meters and, more recently, within smartphone applications. Table 2.1 lists input and pre-defined individual parameters, which are commonly used by BCs to calculate a meal bolus dose B as follows:

$$B = \frac{CHO}{ICR} + \frac{G - G_s}{ISF} - IOB, \tag{2.1}$$

where CHO is the total amount of carbohydrate of a meal (gram); ICR is the insulin-to-carbohydrate ratio (gram/IU), G describes the current blood glucose level (mM/l); G_s is the pre-defined glucose setpoint (mMl/l); ISF is the insulin sensitivity factor (mMl/IU) and IOB is the insulin-on-board and denotes how much insulin is still in the body from previous injections. The impact of each parameter will now be explained in more detail:

Carbohydrates (CHO) Carbohydrates are nutrients found in a variety of foods (e.g. potatoes, rice, pasta cereals and sugary drinks). They are converted into glucose by the digestive system and serve as a main energy source for the cells in the body. The more carbohydrates are being consumed, the more insulin is needed to keep glucose levels within target. Therefore, information about the amount of carbohydrates is essential to calculate the insulin dose needed to cover a meal. Nutritional labels on packaged food items or drinks often contain the carbohydrate content, which can help people with diabetes to achieve a better estimation of totally consumed carbohydrates. More recently, many health applications for smartphones incorporate food databases with detailed information about the nutrition of food items and research has investigated the use of meal databases to capture carbohydrate, lipid and protein content [47]. However, meals that are consumed in restaurants or where the meal composition is not known still provide a challenge to accurately guess the correct amount of carbohydrates (see Chapter 1.1.3). Another research team proposed to automatically assess the meal content (e.g. taking a photo of the meal and analyse the content via image processing) but showed only limited success in practice [48]. Currently, there is no reliable automated way to determine the amount of digested food and people with T1D still depend on manually counting the amount of carbohydrates for each meal.

Insulin-Carbohydrate Ratio (ICR) The ICR denotes how much carbohydrates are covered by one unit of insulin. A commonly used formula to estimate the ICR is based on the total daily dose of insulin (TDD), where ICR is determined by dividing the TDD by a factor of 450 or 500 (i.e. 450/500 rule). This factor has been reduced by other research groups to 300, thus providing more conservative ICR values. More recently, Davidson and colleagues proposed following calculations based on the retrospective analysis of 167 pump patients that incorporated the weight (lb) of the individual:

$$ICR = \frac{2.8 * Wt(lb)}{TDD} \tag{2.2}$$

The formula was later slightly adjusted by Walsh after analysis of data from 1020 pumps to:

$$ICR = \frac{2.6 * Wt(lb)}{TDD} \tag{2.3}$$

Estimated ICR values often need to be adjusted for different times of the day and regularly re-adjusted to compensate for changes in insulin sensitivity.

Insulin-Sensitivity Factor (ISF) ISF is used to determine the insulin dose needed to correct for glucose levels outside the target range. More specifically it describes how much glucose levels drop for one unit of insulin. Similar to ICR values, rules or guidelines exist based on the experience of clinical experts to determine the starting point of ISF for an individual. Most rules are based on factors, which are divided by the TDD. Commonly used factors in the literature are 1500, 1800 and 1960 (sometimes rounded to 2000) for mg/dL and 90, 100 and 110 for mmol/l.

Insulin-on-Board (IOB) The estimated amount of bolus insulin on board (IOB or BOB) is based on the individual duration of the insulin-action-time (IAT), which describes how long an insulin bolus from a previous injection is still active in the body. Changing the IAT, therefore, regulates how aggressive or conservative insulin bolus recommendations are after previous insulin injections. Setting the correct IAT is important as an underestimation of IOB could potentially lead to hypoglycaemia when additional insulin although active insulin still remains in the body (i.e. insulin 'stacking'). The calculation of IOB also depends on the function used to describe the decay of active insulin, with linear and curvilinear plots being the ones most commonly used by commercial bolus calculators. Curvilinear plots aim to approximate the pharmacodynamics of insulin formulations while linear plots (Figure 2.5) make the concept of IOB easier to understand for bolus calculator users. Compared to curvilinear plots, linear plots underestimate IOB at the beginning and slightly overestimate the active insulin on board towards the end of the defined IAT. Conversely, curvilinear plots yield in higher IOB in the first 30 minutes after the insulin injections, which aims to replicate the delayed onset of insulin).

Commercial BCs

The first commercial device to incorporate a bolus calculator was the Deltec Cozmo®(Smiths Medical MD, Inc.,St. Paul, MN) in 2002 and since then, most insulin pumps provide some form of bolus advise, either on the pump itself or via a remote handset. More recently, bolus calculators have also been implemented into blood glucose meters (e.g. ACCU-CHEK® Aviva Expert and FreeStyle InsuLinx® Blood Glucose Monitoring System) to assist people with insulin dose calculations who do not use insulin pumps but multiple daily injections as insulin therapy (Figure 2.6). Table 2.2 lists currently available bolus calculators and their features.With the availability of mobile technologies such as smartphones and tablets, there is the potential of integrating meal bolus calculators within commercially available devices.

Table 2.1: Input and patient specific parameters of a standard bolus calculator and their acquisition, usage, dependencies and uncertainties.

Input Parameters	Acquisition	Parameter Usage	Dependencies/ Uncertainties
Glucose Concentration	Manual: User enters value from BG meter or CGM system; Automatic: Glucose value is automatically transmitted and retrieved from BC software	Used to correct for initial Hyper-/ Hypoglycaemia	Dependencies: BG meter, CGM system. Uncertainties: Accuracy and delays when using CGM as glucose input
Amount of Carbohydrates	Manual: User enters estimation of amount of carbohydrates or selects from meal-library; Automatic: e.g. scanning of bar-code of packaged meal	Used to calculate amount of insulin needed to cover the meal	Dependencies: Knowledge of carbohydrate counting Uncertainties: Errors in estimation of carbohydrate content
Patient Specific Parameters	**Acquisition**	**Parameter Usage**	**Dependencies/ Uncertainties**
Insulin-Carbohydrate Ratio	Pre-defined by clinician/endocrinologist	Used to calculate how much insulin is needed to cover a specific amount of carbohydrates	Uncertainties: ICR needs to be adjusted based on changes to the insulin sensitivity
Insulin-Sensitivity Factor/ Correction Factor (ISF/CF)	Pre-defined by clinician/endocrinologist	Used to calculate how much insulin is needed to cover a specific amount of carbohydrates	ISF needs to be adjusted based on factors influencing insulin sensitivity
Insulin Action Time (IAT)	Pre-defined by clinician/endocrinologist	Used to calculate active insulin on board	Dependencies: Type of insulin, insulin injection site, type of insulin, physical activity

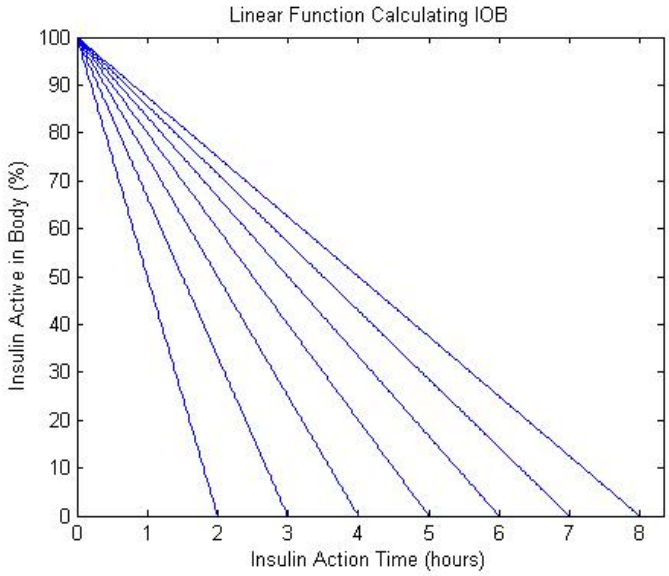

Figure 2.5: MATLAB® simulation showing the linear decay of active insulin in the body for various IAT settings (2-8 hours)

Huckvale et al. systematically reviewed and analysed the clinical suitability of 46 applications (apps) that provide the functionality to calculate an insulin dose for meals. The research team exposed that the majority of insulin calculator apps do not implement any protection for incorrect input or inappropriate use, potentially leading to harmful insulin dose recommendations. The main reason for this is because most of the available dose calculators are not approved by corresponding regulatory authorities, such as the Food and Drug Administration (FDA). In 2013, Volartis (Paris, France) announced the CE-marking of the first insulin dose calculating application Diabeo® [50], which was used in the TeleDiab 1 study [51] [49]. However, the mobile application was not made commercially available.

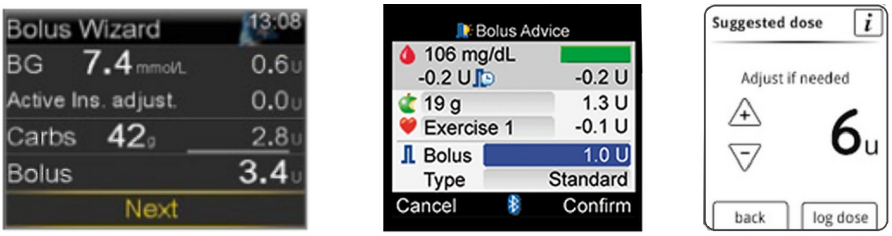

Figure 2.6: Bolus Wizard implemented within the insulin pump of Medtronic's 640G (left), the bolus advisor on ACCU-CHECK®Aviva Expert System from Roche (centre) and the bolus calculator built within the blood glucose meter of Abbott FreeStyle InsuLinx® (right).

In early 2015, Roche Holding AG (Basel, Switzerland) received FDA approval for their diabetes management app ACCU-CHECK® Connect [52], which incorporates an insulin bolus advisor and was later released for Android and iOS compatible devices. Before its first use, the meal bolus advisory function needs to be activated by a healthcare professional.

Benefits of BCs

Several studies demonstrated the clinical benefit of using bolus calculators. In the study presented by Gross et al. [45], the number of correction boluses for elevated glucose levels and the number of times where carbohydrates were needed to recover from hypoglycaemic episodes were reduced. In a paediatric population using insulin pumps, Shashaj et al. [53] demonstrated that the bolus insulin dose calculated using a bolus calculator was more effective in improving pre-and postprandial glycemic control with fewer correction boluses, without differences in the prandial insulin requirements and without restriction to the carbohydrate content of meals. In another study by Garg et al. [54], an insulin guidance software (ACCU-CHEK® Advisor, Roche, Indianapolis, USA) was tested in a crossover study of 12-month duration. The mean HbA1c was significantly lower from 3 to 12 months in the experimental group ($p<0.02$) and an HbA1c reduction of 0.6% was maintained at 12 months in the experimental group. A study by Lepore et al. [55] demonstrated that bolus calculators improve long-term metabolic control and reduce glucose variability in pump-treated subjects with T1D. Finally, Barnard and colleagues [56] reported a reduced fear of hypoglycaemia and improved confidence in dosage accuracy in people with T1D when using bolus calculators.

Limitations of BCs

BC are considered state-of-the-art for insulin dosing decision support. However, they require accurate carbohydrate counting skills and structured diabetes education among people with T1D is limited (see Chapter 1.1.4). Over- or underestimating the amount of carbohydrates can result in potentially dangerous low glucose levels. Current bolus calculators limit the estimation of required bolus insulin for meals to the amount of carbohydrates and omit information about glycemic index or fat content of the meal. However, they provide only limited personalisation and are not able to react to life-style changes that affect the insulin sensitivity and, thus, require intensive and frequent re-adjustments by a clinical expert. Currently, only one bolus calculator(Roche ACCU-CHECK® Expert/Combo/Connect) al-

Table 2.2: List of commercially available bolus calculators implemented in various platforms

Company/Product	Platform	Features	Comments
Animas OneTouch Ping	Insulin Pump	Insulin-Carb.-Ratio, Insulin Sensitivity, Target Glucose Range	BC incorporated in both pump and remote meter
Roche ACCU-CHECK Combo Spirit/Avia Expert	Combo Spirit: Insulin Pump + BG Meter Avia Expert: BG Meter	Insulin-Carb.-Ratio, Insulin Sensitivity, Insulin Action Time, Health Events: Exercise, Illness, Premenstrual	BC incorporated into remote meter; allows adapting insulin dose based on pre-defined percentages for various health events
Roche ACCU-CHECK Connect App	Smartphone	Insulin-Carb.-Ratio, Insulin Sensitivity, Target Glucose Range	Needs to be activated by healthcare professional; connects to BG meter
Medtronic 530G/640G	Insulin Pump	Insulin-Carb.-Ratio, Insulin Sensitivity, Insulin Action Time, Target Glucose Range	CGM Capability
Insulet OmniPod	Pump Handset	Insulin-Carb.-Ratio, Insulin Sensitivity, Insulin Action Time, Target Glucose Range	BC incorporated into remote handset
Tandem t:slim	Insulin Pump	Insulin-Carb.-Ratio, Insulin Sensitivity, Target Blood Glucose, Insulin Action Time	CGM capability (Dexcom G4)
Cellnovo	Pump Handset	Insulin-Carb.-Ratio, Insulin Sensitivity, Target Glucose Range	Bolus advisor integrated in handset, which also acts as glucose meter
Abbott FreeStyle InsuLinx	BG Meter	Insulin-Carb.-Ratio, Insulin Sensitivity, Target Glucose Range	Setup requires access code from health care professional; two modes: Easy mode (breakfast, lunch and dinner) and advanced mode (carb-counting); no IOB information
Thorpe Products Ltd. Calsulin	Standalone Calculator	Insulin-Carb Ratio, Target Glucose, Insulin-Sensitivity Factor physical activity	No information about active insulin; considers intensity of exercise after injection

lows the user to reduce or increase the insulin bolus for stress and exercise. While the inclusion of these parameters is welcome, the changes in the amount of insulin are based on an estimate by the individual user and the performance of the applied adaptation is not evaluated. Moreover, because of their inability to adjust the insulin therapy for the multiple factors described in Chapter 2.4, a more intelligent solution for insulin dosing is needed.

Decision Support Systems (DSS) for Insulin Therapy Adjustments

The potential of decision support for insulin dosing has been advocated since the early 80s [57] where algorithms and techniques from the artificial intelligence domain were used to propose therapy adjustments. The following section lists intelligent systems, which have been proposed for insulin dosing decision support:

BCMC [58] (Better Control Medical Computers, Inc. Ontario, Canada) was one of the first portable microprocessor devices, which implemented an algorithm to adjust the insulin dose to a desired target value set by the physician.

IIAS [59] The IIAS (insulin infusion advisory) system was able to provide real-time estimations of the insulin infusion rate for people on insulin pumps using a non-linear model predictive controller.

DIGS [60] (Diabetes-Insulin-Guided-System by Hygieia, Inc. MI, USA) is an automated decision support algorithm for insulin dose adjustments. In an uncontrolled study the research group demonstrated improvements in glucose control be means of self-monitoring of BG; however the authors note the that the most notable improvement in HbA1c was observed at the end of the run-in phase, which may have been due to the Hawthorne effect [61].

Run-to-Run (R2R) [62] R2R is a method derived from control engineering and exploits the repetitiveness in the process to be controlled. The algorithm relies on two finger-prick measurements after the meal, which limits its practicality.

DIABEO [51] is a smartphone based adaptive bolus advisor with telemonitoring capabilities. The system was assessed in a six-month controlled study in a poorly controlled population with and without the use of tele-consultation. A significant reduction in Hb1Ac over the control group was observed in the intervention group that received tele-consultation.

DIAdvisor [63] aims to assist people with T1D and T2D by showing short-term glucose predictions and providing therapy advice. While presented results are encouraging in terms accurate blood glucose predictions, the system is only suitable for use within a static clinical environment and therefore provides limited mobility.

Suggested Improvements

Based on the presented literature on existing technologies, discussions with the clinical study team and feedback obtained from focus group meetings (see Chapter 4.4), specific requirements for an insulin DSS have been defined that need to be addressed in order to provide maximum clinical efficacy and acceptability. It is hypothesised that an ideal insulin DSS should implement following features:

- Adaptability The DSS should be able to adapt the insulin therapy (or more specifically the patient specific parameters ICR and ISF). This can be either automated or, for safety reasons, semi-automated after approval from a clinical expert.

- Integration of CGM Utilising data from a CGM system helps to capture fluctuations of glucose levels and provides better information for insulin therapy adjustments.

- Multiple Input Parameters The DSS should incorporate multiple inputs that enable the system to have access to information about factors affecting glucose levels (see Chapter 2.4) and perform adaptations to the insulin therapy accordingly.

- Portability Usability is key and a DSS for insulin dosing should be mobile and unobtrusive in order to be easily integrated into the life style of the person with T1D.

- Remote Supervision A system that performs changes to the insulin therapy must ensure that a mechanism is in place that allows remote supervision or approval of suggested adjustments.

The research presented in this work describes the development of an 'Advanced Bolus Calculator for Diabetes (ABC4D)' that was designed to meet all of these criteria and therefore improve over existing technologies. The next chapter introduces the concept of case-based reasoning (CBR) where **multiple input parameters** are used to differentiate between various situations, which include factors that have impact on the insulin requirements (e.g. exercise). In the same chapter, a novel algorithm is presented that **adapts** the insulin bolus calculator parameters ICR and ISF based on the glucose outcome collected with a **CGM** system. The implementation of this algorithm into a **portable** smartphone-based system is described in Chapter 4 along with a clinical platform that allows **remote supervision** of therapy adaptations. Table 2.3 compares the features of the proposed ABC4D system to other existing DSS. While all of the listed systems provided some sort of adaptability, they lack the incorporation of additional input parameters and personalisation.

Table 2.3: Overview of DSSs for insulin dosing compared with the proposed ABC4D system. 'X' indicates that the feature was implemented, '-' that the feature was missing or unknown

DSS Name Approach	Bolus Calc. -	DIAdvisor MBR	BCMC CT	DIGS CT	IIAS MBR/NN	R2R CT	DIABEO CT	**ABC4D** **CBR**
Portability	X	-	X	X	X	X	X	X
Adaptability	-	X	X	X	X	X	X	X
CGM data	-	X	-	-	-	-	-	X
Remote Supervision	-	-	-	-	X	-	X	X
Multiple Parameter Input	-	-	-	-	-	-	-	X

MBR=Model Based Reasoning, CT=Control Theory, NN=Neural Networks, CBR=Case Based Reasoning

2.7 Conclusion

Despite the advent of new diabetes technologies, such as continuous glucose monitors and insulin pumps that support people with T1D to manage their diabetes, maintaining healthy glucose levels still remains a challenging task. The reduction of the complexity of diabetes care is therefore of benefit for both physicians and patients. Insulin bolus calculators aim to assist people with T1D to calculate the amount of bolus insulin needed for a meal and are implemented in insulin pumps, blood glucose meters and smartphone applications. However, bolus calculators do not incorporate any intelligence to revise the glucose outcome and adjust its parameters. Other decision support systems have been discussed that are able to provide insulin dose adjustments, but they lack the utilisation of CGM data or the ability to consider factors (e.g. exercise or alcohol) that impact glucose control after meals. The research in this thesis aims to overcome these shortcomings by presenting a decision support platform that is able to revise and adjust the bolus calculator parameters for various daily life scenarios.

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Chapter 3

Case-Based Reasoning (CBR) for Insulin Dosing Decision Support

3.1 Introduction

This chapter introduces the use of case-based reasoning (CBR) for insulin dosing decision support. First, the concept and motivation of using CBR as a problem-solving methodology is discussed as well as its current use in medicine and diabetes management. Insulin dosing decision support requires detailed understanding about the 'problem' that needs to be solved (i.e. how much insulin is needed for a certain meal to achieve target glucose levels) and the various parameters that have an impact on the insulin requirements of an individual person with T1D. In CBR, a 'problem' is represented by a number of cases within a case base. A problem scenario can be any situation, where insulin is required. The presented system based on CBR will focus on insulin dose recommendations for meals, but the potential of additional decision support will be discussed (i.e. recommending correction insulin boluses or adjustments for insulin basal rates). For meal dosing recommendation, a case contains information about various aspects of the meal scenario (i.e. description of the meal) and environmental factors (e.g. stress, exercise), which are described through a set of parameters. The following chapter discusses potential case parameters and how they can be used within an insulin dosing decision support system.

Another research challenge is the assessment of the glucose outcome for proposed solutions. Using data obtained from continuous glucose monitors, various outcome metrics will be evaluated based on reliability and robustness to sensor noise.

Finally, implementation methods of the CBR learning mechanism are presented, as well as methods on how to adapt the solution of cases (i.e. proposed insulin therapy for a specific meal situation) based on CGM data. The chapter concludes with simulation results evaluating the concept of a CBR-based decision support system using a T1D simulator, which is approved by the Food and Drug Administration (FDA).

3.1.1 Concept and Motivation for using CBR

As discussed in the previous chapter, insulin therapy strongly depends on the specific situation and on various factors affecting the glucose metabolism at the given time. The CBR methodology fits well for this area as here such situations (in CBR called problems) are described and stored within cases in a case base. New arising problems (e.g. a new meal situation where insulin is required) are compared with cases in the case base for similarity and the solution of the most similar case is the proposed. This concept of solving problems in CBR is based on the way what we humans do when making decisions based on our experience. Once a new problem arises, we try to recall whether something similar has happened in the past, and depending on whether the outcome of the solution was successful or unsuccessful, either apply or avoid that solution for the current situation. If we do not have any experience (in CBR this means that no similar case is found), we try a new solution that in our opinion is safe and, while this trial-and-error approach may be not optimal, we hope it will lead to a satisfactory outcome. If the applied solution fails to achieve a good outcome, it can be either revised or discarded. Regardless of the outcome, the new situation can be remembered (stored as a case) for future use.

Case Structure

A newly created case consists of three major parts: the problem description (e.g. high-fat meal with increasing trend of blood glucose), the solution (e.g. amount of insulin units) and the outcome (e.g. mean postprandial glucose excursion).

CBR Learning Cycle

The learning process in CBR has been described by Aamodt and Plaza [1] and is shown in Figure 3.1.

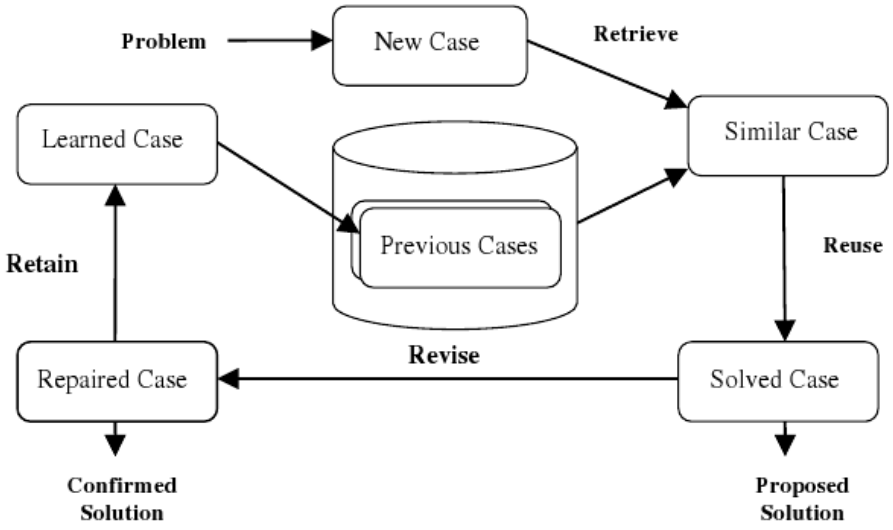


Figure 3.1: Process cycle of CBR

The proposed CBR cycle includes following four steps:

- RETRIEVE the most similar case or cases
- REUSE the information and knowledge in that case to solve the problem.
- REVISE the proposed solution
- RETAIN the parts of this experience likely to be useful for future problem-solving

The first task of the process cycle is to compare the new problem with cases stored in the case base in order to search for the most similar one. The next steps involve modifying the solutions of retrieved cases to fit the current problem (reuse and revision). If the new case is identical with an older one, a simple solution transfer can be performed, otherwise major modifications could be required. The last step is the update of the case base, which can either involve the uptake of a newly learned case or a modification of an existing case.

3.1.2 Successful CBR Applications in Medicine

Many applications of CBR in medicine, for both diagnosis and therapy, can be found in the literature. One of the first CBR systems in medicine was *CASEY* [2], a system designed by P. Koton at the Massachusetts Institute of Technology which combined CBR with model-based reasoning (MBR) in order to diagnose heart failures. The system is built on top of the Heart Failure Program, which is also the source of the cases in the case base, and adds CBR functionality. Koton describes *CASEY* as a system that uses CBR to recall and remember problems that it has seen before, and uses a causal model of its domain to justify re-using previous solutions and to solve unfamiliar problems. *PROTOS* [3] is a CBR-based classification system used for diagnosing hearing disorders. The system learns concepts by retaining exemplars and classifies new cases by matching them to the exemplars.
An example for CBR in medical therapy is *ICONS*, which was designed to prescribe antibiotics to patients in intensive care who have bacterial infections. The prescribed antibiotic regimen should satisfy the medical and economic constraints entered into the system. The *ICONS* system seeks to give advice for a specific, acute medical problem in the form of corrective action.
The use of CBR in diabetes has been centred on prognosis and risk of developing diabetes [4]. The first project to use CBR to recommend an insulin therapy was the T-IDDM project [5], where CBR was integrated within a rule-based reasoning engine and a probabilistic model describing the effects of insulin on blood glucose levels. More recently, the IDSDM project [6] used CBR as primary reasoning modality in a decision support tool for patients on insulin pump therapy, and introduced other factors into the calculations, such as life events that can influence blood glucose levels. However, both systems were focused on providing decision support to the physicians using retrospective data and not real-time decision support for people with T1D.

3.1.3 Advantages of CBR in Diabetes Management

The use of CBR is especially advantageous for applications where not only text-book knowledge is available but where individual experience is an important factor to solve the problem. This is especially true when looking at the glucose profile of individuals with T1D, which all differ from each other and change over time. Because of its adaptive approach (i.e. revision step of the CBR cycle), CBR is flexible in its reasoning such that it can react to changes in

the glucose profile over time and provide new solutions accordingly. This flexibility is a major advantage compared to static decision support techniques such as rule-based reasoning, where the representational knowledge is predetermined and does not change automatically. Arguably, more sophisticated machine learning techniques, such as support vector machines (SVM), offer similar flexibility and can provide the means to differentiate between various diabetes scenarios and optimise the insulin dosage. Compared to other decision support techniques, however, one of the biggest advantages of CBR lies in the transparency of the reasoning on how the decision was created. In addition to providing a solution for a specific problem scenario, CBR can give further information about the most similar retrieved case and its usage history. Furthermore, unlike decision trees and neural networks, relatively little work needs to be performed a priori (e.g. knowledge acquisition or training with data sets) and CBR can start off with little or none initial knowledge. Additionally, CBR is well suited for problem situations that deal with a large amount of uncertainty and parameters that vary with time. Some of the commonly known uncertainties in diabetes management include:

- Accuracy of continuous glucose sensors
- Variable delays in glucose sensing and insulin action time
- Errors in carbohydrate estimation
- Changes in insulin sensitivity

Compared to a fixed set of implemented rules, CBR is able to react to uncertainties or changes over time, where the variability is not uniform distributed (e.g. a drift or offset from the norm). For instance, it is hypothesised that people with diabetes, who struggle with estimating the correct amount of carbohydrates for a meal, will consistently perform a similar error in over-(or under) estimation of the carbohydrate content. Over time, CBR could potentially adapt to this specific situation (e.g. a large breakfast meal, which the user tends to overestimate) and recommend less insulin at the next similar scenario. The final advantage of CBR is that it enables the integration of other techniques into the CBR learning cycle (see Chapter 3.6).

3.2 A CBR System for Insulin Bolus Decision Support

This research proposes to utilise the advantages of CBR and enhance state-of-the-art bolus calculators in order to provide more flexibility and adapt to changes or uncertainties in the environment of the person with diabetes. Situations and variables that are known to have an impact on postprandial glucose levels can be described and stored in cases while the insulin therapy for this specific scenario can be optimised until the glucose outcome proves to be satisfactory.

3.3 Problem Description

One of the main challenges when using CBR for reasoning is how to represent the defined problem situation inside one case. The content of a case strongly depends on the application of CBR. For instance, in a CBR-based bolus advisor system, a case contains all relevant information affecting the glucose profile for a certain situation. The simplest form to represent a case is to assign attribute-value pairs to the parameters and store them in a flat hierarchical structure, thus keeping the knowledge engineering effort at a minimum. Contexts (see 3.6.1) can be used to limit the problem space and therefore to reduce the time of case retrieval.

3.3.1 Case Parameters

As discussed in Chapter 2.4, the optimal amount of bolus insulin depends on various factors e.g. meal amount, current blood glucose level, psychological stress etc., all of which have the potential to be included as parameters within a case. In order to reduce the complexity of an insulin advisory system, only key parameters that influence glycemic control should be considered. A detailed list of biological and environmental factors, their reported effect on the glucose regulatory system and the possible acquisition of the factor, can be found in Appendix B. The list also includes information, whether the parameter needs to be introduced manually (through user elements such as text-fields, check-boxes, slider buttons), or if the information can be automatically obtained without any user intervention (e.g. activity monitor, temperature sensor). While it is of interest to reduce manual user input as much as possible, some factors like stress or illness cannot be captured by sensors and will require manual user input. The selection process of case parameters used during clinical

evaluation of the research is described in Chapters 5.3.3 and 5.4.2
Shepard et al. [7] presented research on the patient's perspective on which parameters they would find useful (thus based on their experience have an impact on the glucose control) and would like to see integrated into a personalised glucose advisory system. Feedback was obtained from 56 adults familiar with technologies such as CGM systems and insulin pumps in several focus group meetings. While most factors, which have already been discussed in this section, were mentioned by focus group participants, additional suggestions included: pregnancy, changes in schedules/routines, shift work or night work, weekend/weekday, travelling/time zones, planned activities in the near future and medical procedures (e.g. surgery).

Additional Potential Case Parameters

Glucose Levels or Range Bolus calculators use information on current blood glucose levels to provide additional insulin at meal time if glucose levels are high. However, absolute glucose levels or their range (i.e. hyperglycaemia) may also be used as a case parameter, as prolonged elevated glucose levels can potentially lead to an increase in insulin resistance [8].

Glucose Rate-of-Change Having access to continuous glucose information offers the possibility to derive further information about the glucose profile, such as calculating the rate of change (ROC) of glucose levels.

Meal size/Size of Dose As the amount of carbohydrates is already being considered within the bolus calculator formula, there is theoretically no need to include the size of the meal as a case parameter. However, this is based on the assumption that the insulin-carbohydrate ratio is 100% linear, something which is unlikely to be the case in reality. Thus, for people who regularly eat meals that vary greatly in sizes, the meal amount could potentially be used as a parameter. An additional effect on the glucose levels for larger meals is also indirectly caused by the size of the insulin dose. Larger insulin doses are recognised to slow down the insulin absorption.

3.3.2 Number, Granularity and Weighting of Parameters

The number and weighting of parameters play a key role in determining how similar a case is to a new meal scenario. In order to accurately describe the problem of insulin dosing for a

meal, the optimal number of parameters is always a compromise between performance and complexity. While a large number of parameters might achieve better personalisation of insulin therapy, the weights (i.e. importance) of chosen parameters need to be considered, which are, as the features themselves, patient specific. Furthermore, the more parameters are defined, the more cases will be created which, in turn, increases the time needed for each case to converge to an optimised solution. Granularity of case parameters describes the level of detail in which parameters are stored in the case-base and used for retrieval. For example, 'physical activity' chosen as a case parameter can be broken down into 'type of exercise', 'intensity', 'duration' etc. While it is hypothesised that finer granularity of a parameter achieves better glucose outcomes after optimisation, it also requires a more detailed understanding on the effect of the parameter on the glucose regulatory system. However, similar to the total number of selected parameters, the use of 'finer-grained' parameters may result in a longer time needed to optimise the solution of an individual case.

3.4 Case Solutions

There are multiple solutions to optimise the postprandial glucose excursion. The most common solutions in the insulin therapy involve changes in the amount of insulin as well as the timing of insulin administration and shape of bolus (when using insulin pumps). Figure 3.2 illustrates which of the presented case parameters have an impact on the insulin sensitivity (amount of insulin) or the insulin absorption (time and shape of insulin).

3.4.1 Amount of Bolus Insulin

If the basal insulin has already been optimised, a possible solution is to recommend the amount of insulin boluses for meals. In this case, the ICR can be used as a possible solution. Required changes to the amount of insulin are usually contributed to factors affecting the insulin sensitivity and have been described in Chapter 2.4.

3.4.2 Timing and Shape of Bolus

Several parameters, which have been discussed, only report little effect on the insulin sensitivity but rather on the absorption time of administered insulin. While people on multiple

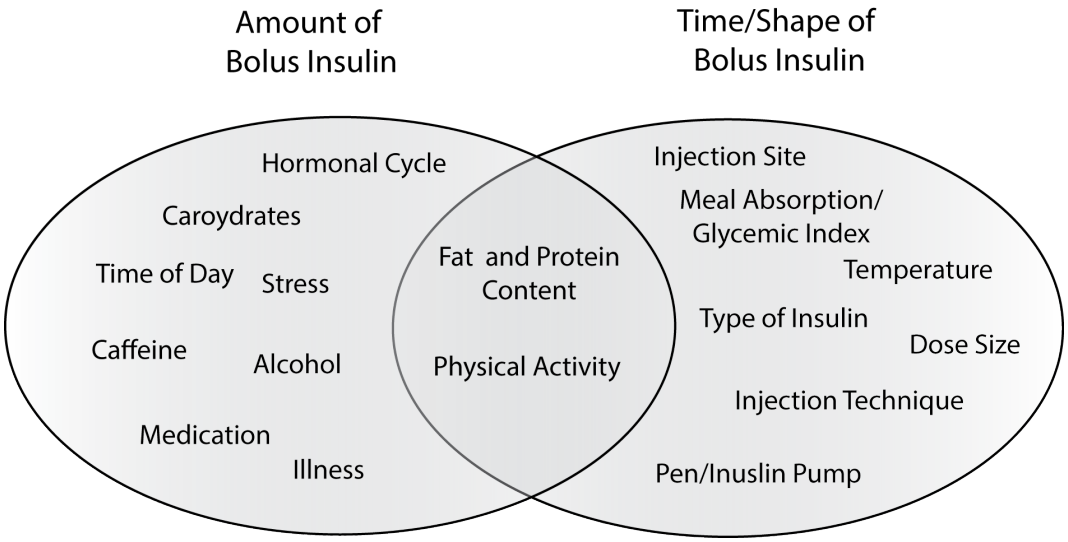


Figure 3.2: Impact of case parameters on the amount (left) and the administration time/shape (right) of the insulin bolus .

daily injections have the option to change the timing of the insulin injection as well as 'splitting' the bolus (e.g. 50% given at the time of meal, the rest of the bolus given at a later time), insulin pumps offer additional types on how the meal bolus can be delivered over time (Figure 3.3). Therefore, a case solution could further propose the timing and shape of the meal bolus, in addition to the amount of insulin to be delivered.

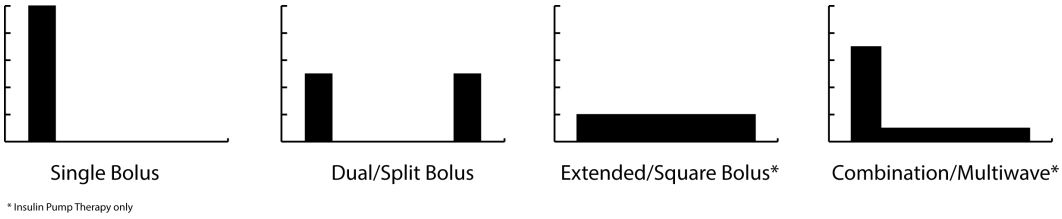


Figure 3.3: Different bolus types for insulin administration.

3.4.3 Other Solutions

Total Daily Dose of Insulin The total daily dose (TDD) of insulin is often used as a starting point for people with diabetes to estimate their basal rate and bolus insulin. While the adjustment of TDD would only provide very general decision support (compared to decision support for specific meals), there is the potential to use TDD as a solution for newly diagnosed people with diabetes, who have no prior knowledge about the insulin-

carbohydrate ratio or insulin-sensitivity factor. Here, cases would only include information that changes over a period of days (interday variability) such as weekday/weekend or illness.

Adjustments to Basal Insulin While the focus of this research is to provide decision support for meal insulin dosing, future work could also provide recommendations to adjust basal insulin. This can be achieved by analysing fasting glucose levels (e.g. during the night). It shall be noted that the adjustment of basal insulin is challenging during meal times if the decision support system already adapts the insulin therapy during that time.

Carbohydrate and Exercise Recommendation Additional to proposing insulin, a decision support system for people with T1D could recommend carbohydrates to correct for low glucose levels (i.e. 'rescue-carbs'), as well as exercise or other behavioural advice (e.g. change of injection site)

3.5 Outcome

The outcome of the proposed solution can either a) solve the problem b) improve, but not solve the problem or c) fail to solve the problem. A clinically acceptable outcome for the meal insulin dosing problem is to achieve safe glucose excursions for meals by bringing postprandial (i.e. from the start of meal intake until 4-6 hours after the meal) glucose levels back to a pre-defined target. While short-time elevated glucose levels are difficult to be avoided due to slow insulin dynamics (the time needed for insulin to lower glucose concentration), the aim is to minimise the time spent in hyperglycaemia without entering the hypoglycaemic zone.

3.5.1 Metrics for Evaluating Outcome

The assessment if a proposed insulin dose was safe and brings glucose levels back into target range is a key element of the decision support system. For the sake of simplicity it is assumed that there is enough time after a meal to evaluate the outcome without any events that alter the glucose profile (e.g. unannounced snack or exercise).

Absolute Post-pranidal Blood Glucose Levels

Most physicians recommend people with T1D to measure glucose levels with a BG meters two hours after the meal, which gives an indication of the effect of the administered insulin dose. However, insulin is active up until 6 hours after administration and a single measurement does not give information about the trend or glucose rate-of-change. So even if the measured glucose levels are within target range, glucose concentrations might still be dropping because of active insulin (insulin-on-board). Two postprandial measurements at different times would help to determine a trend of glucose levels. However, multiple BG measurements during a short period of time might decrease utilisation and would not be adopted by most people with diabetes.

Postprandial Glucose Minimum

Continuous glucose monitor (CGM) data can be used to capture fluctuations between blood measurement samples. One advantage of using CGM devices is the possibility to capture hypoglycaemic events. By analysing the lowest glucose reading for a pre-defined time window after a meal, it is possible to adapt the insulin therapy if the measurement is below or above the target.

Postprandial Glucose Increment

Another method of assessing the outcome of a case would be measuring the glucose increment/rise after a meal, assuming that the glucose increment for meals is linear to the meal size. In case the glucose value should be higher/lower than expected, not enough or too much insulin has been delivered for this meal, respectively.

Time to Peak of Glucose Excursion

A similar method can be used to determine the outcome of a case using the time-to-peak (TTP) of the glucose excursion. If the time of the glucose maximum is earlier or later than expected, too much or too little insulin has been delivered resulting in possible hypo- or hyperglycaemia, respectively. Using retrospective CGM data, the TTP value can be personalised for an individual with T1D. Figure 3.4 shows the graphical representation of the glucose increment and TTP.

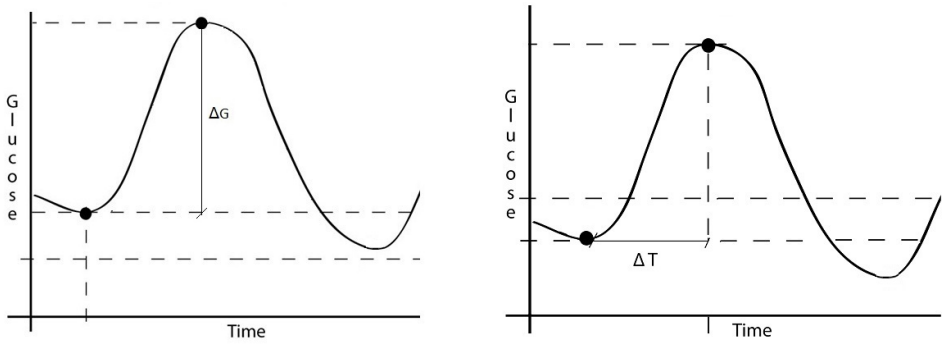


Figure 3.4: Graphical representation of the postprandial glucose increment ΔG (left) and time-to-peak ΔT (right).

Area under Curve

Another metric for evaluating the outcome of an insulin bolus after a meal is to analyse the postprandial area-under-curve AUC (see Figure 3.5 left). The hypothesis is, that AUC is reasonably linear with respect to the amount of ingested carbohydrates which has been proven true in the T1D simulator (see Figure 3.5 right). Thus, for a known glucose area-under-curve AUC_1 corresponding to an amount of carbohydrates CHO_1, it is possible to estimate the area-under-curve AUC_2 corresponding to a carbohydrate load CHO_2 using the following linear relation:

$$AUC_2 = \frac{AUC_1 \cdot CHO_2}{CHO_1}. \tag{3.1}$$

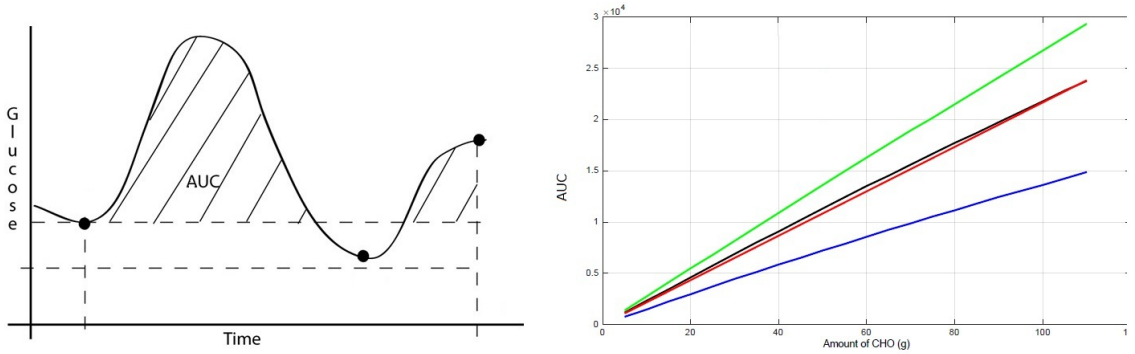


Figure 3.5: Left: Graphical representation of the postprandial glucose area-under-curve (AUC); Right: Linearity of AUC in respect to the amount of carbohydrates. The black line is the measured AUC using an optimised ICR, while the red line is calculated AUC based on a reference AUC. The green and blue lines represent the AUCs for suboptimal ICRs.

3.5.2 In-silico and Clinical Experiments to Evaluate Outcome Metrics

In order to find out which metric is most suitable for revising the outcome of a solution, the previously discussed continuous metrics area-under-curve, glucose increment and time-to-peak have been evaluated. First, the T1D patient simulator [9] was used to find a correlation between the outcome metric and the insulin-to-carbohydrate ratio (ICR). Figure 3.6 shows the setup of the experiment. A fixed meal has been given every 24 hours while increasing the ICR from 50% to 150% of the known optimal value. The optimal ICR was determined *a-priori* for each subject using a meal tolerance test functionality provided by the simulator.

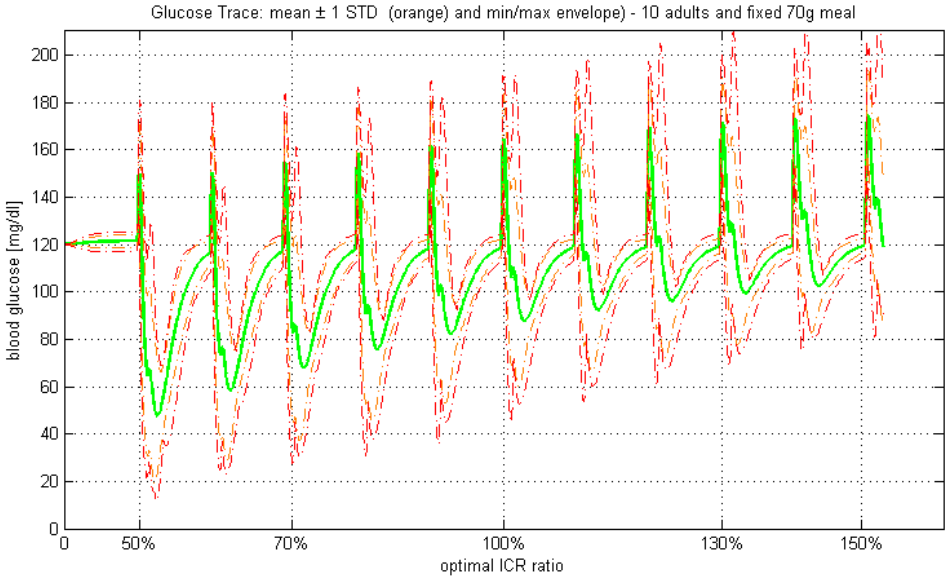


Figure 3.6: Mean glucose trend vs variable insulin-to-carbohydrate ratios for 10 adults given a 70g meal every 24 hours.

Sensitivity of Outcome Metric to Solution

Initially, the correlation between the outcome metric and the ICR has been evaluated. The higher the correlation, the more suitable is the metric for assessing the outcome. An ideal setting is being assumed, thus errors in glucose measurements and carbohydrate counting have been omitted for this experiment. Figure 3.7 shows the results for 10 adults from the virtual population of the T1D simulator. The y-axis for each plot represents the range of the outcome metric, whereas the x-axis denotes the percentage of the optimal ICR. Based on the slope of the regression fit, the metric *area-under-curve* is most sensitive with respect

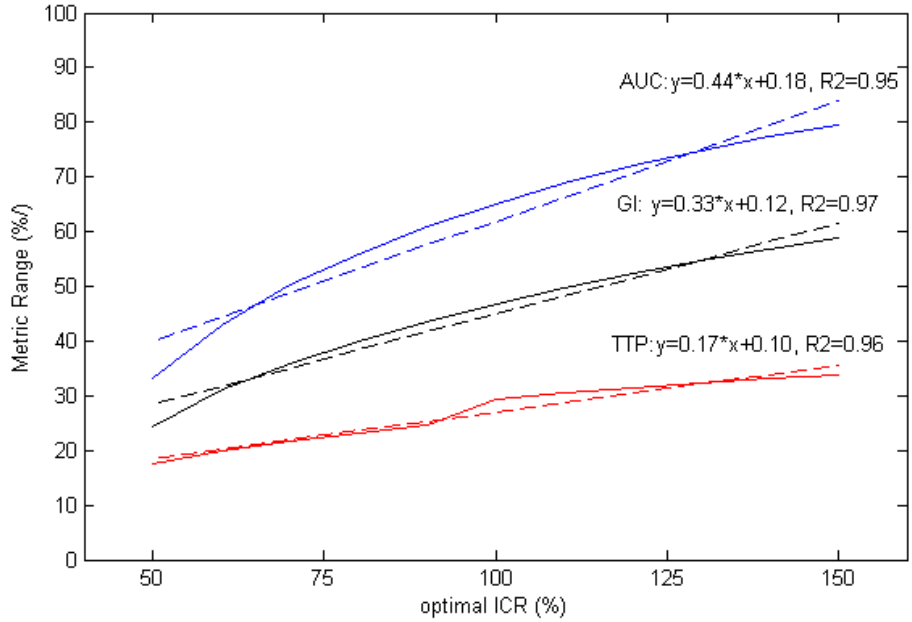


Figure 3.7: Graphical representation of the postprandial glucose area-under-curve (AUC), glucose increment (GI) and time-to-peak (TTP). Solid lines represent the average of 10 adult subjects of the T1D simulator and the dashed lines represent the linear regression fit.

to a change in *ICR* (0.44), followed by the *glucose increment* (0.33) and *time-to-peak* (0.17), respectively. All metrics report to be fairly linear with R^2 values between 0.95 and 0.97.

Robustness of CGM Outcome Metrics to Sensor Error

After showing the correlation of the measured outcome and the solution in ideal conditions, the second experiment deals with the performance of chosen metrics in a more realistic setting. The bottleneck of applications that utilise CGM data is, despite filtering of raw sensor data, the accuracy of glucose readings. For this reason, the metric with most robustness to CGM measurement errors will be advantageous for the performance of an insulin advisory system.

An experiment has been conducted, where postprandial CGM data (Medtronic Guardian REAL-Time with Enlite sensor) and venous glucose data as reference were analysed. Venous glucose concentration was measured every 15 minutes with a YSI (Yellow Spring Instruments) analyser. All data was obtained from clinical trials evaluating the Imperial College Bio-inspired Artificial Pancreas (BiAP) system [10]. Sensitivity to sensor noise of

the outcome metrics has been assessed using 5-hour postprandial glucose values after a 40g breakfast meal from 10 study participants with T1D by calculating the mean absolute relative difference (MARD) between the metric using CGM data and venous glucose data, respectively. The glucose sensor has been calibrated at the time of the meal with the most current YSI reading. A limitation of the experiment is that it does not accurately replicate a real-life scenario. While a manual meal bolus had been given (i.e. meal announcement), the closed-loop controller delivered additional insulin to bring the glucose levels back to target. Further, the experiment was conducted in a clinical environment with only little movement of the study participants. It is hypothesised that movement (e.g. exercise) has a greater impact on the CGM sensor accuracy and leads to different measurements compared to the actual glucose levels.Figure 3.8 shows the results for analysing the differences of four metrics when using YSI glucose values and glucose levels obtained from a CGM system. Area-under-curve, the glucose minima, glucose time-to-peak as well as the relative maximum glucose increment between the meal-time and 5 hours post-meal have been analysed. The metrics area-under-curve, glucose minimum, time-to-peak and glucose increment report differences between YSI and CGM data with a mean MARD of 11.1±13.3%, 12.0 ± 14.9%, 16.1±10.9% and 18.1±14.8%, respectively. None of the metrics showed a statistically significant difference when compared to each other.

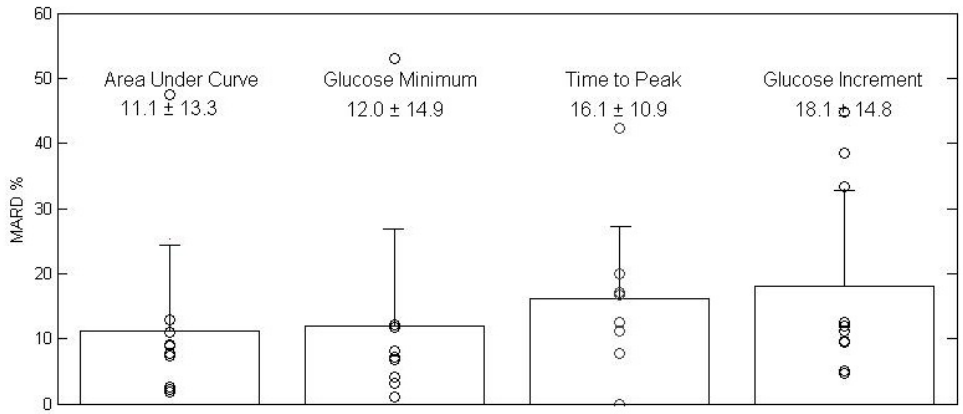


Figure 3.8: The 5-h postprandial MARDs computed for each of the 10 adults are shown, with the mean and SD of each of those MARDs superimposed on the data for the output metrics (differences between metrics are not statistically significant).

3.6 Four Steps of CBR

This section describes methods and algorithms that can be used within the four steps of the CBR cycle. It is important to note that CBR is not a specific technique, but defined as a concept or methodology to solve a problem that can incorporate and combine various techniques from other domains such as machine learning or control engineering. Table 3.1 shows for each CBR step a list of techniques and methods that have been reported in the literature [11] and that are applicable to the proposed insulin advisory system. Methods that can be implemented within each of the CBR steps range from simple rules to sophisticated techniques from the artificial intelligence or machine learning domain. While future work aims to investigate different techniques, the methods for each of the four steps were chosen based on practicality and are now explained in more detail:

Table 3.1: List of potential methods that can be implemented within the CBR steps retrieval, reuse, revision and retention

CBR Step	**Methods**	**Domain**
Retrieve	Classification Algorithms, Similarity Measurement Methods, Fuzzy Logic, Genetic Algorithms, Neural Networks	Machine Learning, Artificial Intelligence
Reuse	Rule-Based Reasoning, Decision Trees, Genetic Algorithms, Neural Networks	Artificial Intelligence
Revision	Control Algorithms, Rule-Based Reasoning, Genetic Algorithms	Control Engineering, Artificial Intelligence
Retention	Fuzzy Logic, Rule-Based Reasoning, Genetic Algorithms, Neural Networks	Artificial Intelligence

3.6.1 Retrieval Step

Initially, each time a problem occurs, the new situation needs to be compared to cases that are stored in the case base for similarity. Similarity is the measure that reflects the strength of the relationship between two or more cases. Retrieval of the most similar case to a current situation can follow either a one-step or two-step retrieval process. Two-step retrieval aims

to narrow down the case base first to a smaller subset of cases (i.e. contexts), which contains only cases that are similar enough for comparison. After finding the most appropriate context (inter-class retrieval), the current problem is only compared for similarity to all cases within the context (intra-class retrieval). The use of contexts improves the retrieving time and further avoids comparisons between cases with low conceptual similarity. As an example, it shall be assumed that a recurrent illness results in a severe temporary change in insulin sensitivity for a person with T1D. If parameter 'illness' (true/false) is not defined as a context, then a scenario where parameter 'illness' is true, is also compared to all cases where parameter 'illness' is false. Therefore, it is possible that a case where 'illness=false' is retrieved if other features show high similarity. Using contexts prevents this problem as the scenario is only compared with other cases within the same subset. If no case exists within the same subset, then a new case with a clinically safe solution is created and added to the case library. Conversely, if more than one case exists for the same context then, in the second retrieval step, similarity measurements determine which case describes best the current situation. Examples for contexts in diabetes management are:

- Type of meal: Breakfast, lunch, dinner.
- Glycemic range: Hypo- , Normo-, Hyperglycaemic range
- Physical activity: no, moderate and intense physical activity.

Techniques from the artificial intelligence domain, such as fuzzy logic, have been successfully utilised in the retrieval of cases. Because only a very small number of parameters is used for the initial evaluation of the presented DSS, simple similarity measurement metrics can be implemented to find the closest case for a new problem. Most potential parameters for insulin dosing decision support are represented in only one dimension e.g. absolute glucose concentration, amount of carbohydrates, etc. Further similarity measurements found in the literature are used for more dimensional parameters or text-based retrieval [12]. Commonly used distance functions in CBR are based on the Euclidean distance, where the distance d is calculated (in the one dimensional space) by the absolute value of the numerical difference of two case parameters (P_x, P_y):

$$d(P_x, P_y) = \sum_{i=1}^{n} \mid (P_{x,i} - P_{y,i}) \mid \tag{3.2}$$

In order to prioritise individual parameters, weights w can be assigned accordingly by:

$$d(P_x, P_y) = \sum_{i=1}^{n} \mid w_i(P_{x,i} - P_{y,i}) \mid \tag{3.3}$$

It shall be noted that some parameters require normalisation in order to make them comparable with each other. Also, the asymmetry of some parameters needs to be considered. As an example, if using absolute glucose levels as a parameter, the definition of the postprandial hyperglycaemic range (>10 mmol/l) is much greater compared to the hypoglycaemic range (<3.9 mmol/l) and the euglycaemic range is not centred within the scale. A difference of 0.5 mmol/l in the hypoglycaemia range is therefore clinically much more significant than the same difference in the hyperglycaemic range. A symmetrisation of the blood glucose measurement scale can be performed to compare cases in a more equitable way [13].

3.6.2 Reuse Step

When a case is successfully retrieved from the case base, two options are possible in order to reuse the solution from the retrieved case. If the retrieved case is similar enough to the current meal scenario, then the case solution can be used without requiring an adaptation. Alternatively, it is possible to temporarily adapt the solution based on pre-defined rules for certain situations. One challenge at the design process of the insulin advisory system is to determine, whether a factor that is known to affect the glucose control is implemented as a case parameter or implemented as a general rule in the reuse-step of the CBR cycle. The utilisation of rules in the reuse-step is beneficial if the effect of the feature is well known or in order to fine-tune the case solution for a specific parameter.

In the second phase of clinical evaluation, exercise was used as a case parameter. If the user with T1D selected exercise (moderate or intense) when requesting an insulin recommendation, the scenario was compared to all existing exercise cases in the case base for similarity, regardless of the selected intensity. However, if the user specifies 'intense' exercise, the solution retrieved from the most similar case containing moderate exercise was slightly adapted to account for the variation in intensity. Based on information from the literature and discussions with the clinician of the study team, a rule was implemented to temporarily increase the retrieved ICR value by ten percent, and therefore provide a more conservative solution compared to less intense exercise. In simulations (see Chapter 3.7), the case solution has been applied without any prior modifications.

3.6.3 Revision

A revision of the solution of a new case is required when the outcome of applying such a solution is not satisfactory. This is even true if the same solution worked for previous situations. The reason for this can be because of changes in the environment or the effect of an unaccounted parameter. For this purpose, it is beneficial to record the number of successful and unsuccessful outcomes in order to determine the need to revise an existing case. While other possible case solutions have been discussed (see Chapter 3.4), the presented research will focus on the revision of ICR as case solution, which regulates the amount of insulin being administered for a carbohydrate containing meal. Dynamic revision methods of insulin therapy found in the literature follow either a knowledge-based approach (e.g. Rule-Based Reasoning) or are based on methods found in control theory.

Rule-Based Adaptation Rule-based Reasoning (RBR) utilises rules that are stored inside a library to update a retrieved case. Parameter values or the solution of a retrieved case are modified once a certain adaptation rule is being satisfied. The T-IDDM project (see Chapter 3.1.2) uses RBR to adjust the insulin therapy and utilises CBR to tune rule parameters in order to individualise the behaviour of the rules.

Control Based Adaptation Another possibility for adjusting ICRs would be the utilisation of an adaptive controller, as the adaptation of a parameter for a repetitive input is well known in control theory. For instance, Iterative Learning Control (ILC) is a control method designed to exploit repetitiveness in the process to be controlled [14]. Its purpose is to enhance performance, using a mechanism of trial and error. Owens et al. [15] used this idea to exploit the repetitive nature of the insulin therapy regimen of diabetics. This algorithm, referred to as Run-to-Run (R2R), uses an update law that corrects the insulin-to-carbohydrate ratio (ICR) for the next day as follows

$$ICR_{k+1} = ICR_k + K(\Psi^r - \Psi_k), \tag{3.4}$$

where ICR_{k+1} is the updated insulin-to-carbohydrate ratio and ICR_k is the one from the previous day. Ψ is the performance measure, where the super-index r represents the reference values and the sub-index k the actual value and K is a tunable gain. The performance

measure is calculated as

$$\Psi = \sqrt{\triangle G_{T_1}^2 + \triangle G_{T_2}^2}, \tag{3.5}$$

$$G_{T_1} = G_{T_1} - G_{T_0}, \tag{3.6}$$

$$G_{T_2} = G_{T_2} - G_{T_0}, \tag{3.7}$$

where G_{T_1} and G_{T_2} are the glucose concentrations at times T_1 (e.g. 60 minutes) and T_2 (e.g. 120 minutes) with respect to the meal intake, and G_{T_0} is the glucose concentration at the time of the ingestion. A pilot clinical study showed the efficacy of this run-to-run algorithm in T1D subjects [16]. More recently, a similar ILC algorithm was proposed by Palerm et al. to adjust basal insulin infusion rates [17].

The utilisation of revision methods from the control engineering domain are specifically of advantage if continuous time-series data exists, such as glucose data from CGM systems. A method utilising CGM glucose data to adapt the ICR parameter based on the Run-To-Run (R2R) controller will be presented in section 3.7.2

3.6.4 Retention Step

After a new case has been generated, or the solution of an existing case has been revised, it is stored in the case base (i.e. retained). Another important aspect of the retention step is the maintenance of the case base. For the developed 'Advanced Bolus Calculator for Diabetes' system (see Chapter 4), simple rules have been implemented which handle the detection and removal of faulty cases or multiple conflicting entries for the same situation.

3.7 In-Silico Studies

This section describes two in-silico studies [18] [19] as a result of the presented research, which have been performed with the UVa/Padvoa T1D simulator. The first study evaluates the performance of a run-to-run based adaptation algorithm utilising CBR and the same algorithm without CBR functionalities. The second in-silico study assesses the performance of an outcome metric used to adapt the bolus calculator parameter insulin-carbohydrate ratio.

3.7.1 UVa/Padova Type 1 Diabetes Simulator

The Uva-Padova Type 1 diabetes simulator [20] is a computer model which has been approved by the Food and Drug administration (FDA) to be used as a substitute for preclinical trials for insulin treatments, such as closed loop insulin delivery algorithms. The commercial version of the T1D simulator is able to emulate meal challenges for a population of 10 adults, 10 adolescents and 10 children. The simulator is based on data from 300 patients and uses 26 parameters to mimic the glucose metabolism.

3.7.2 Evaluation of using CBR for Insulin Decision Support

Although multiple parameters have been identified that have an impact when calculating an insulin dose (Chapter 3.3.1), the utilisation of the simulator for testing the validity of the proposed algorithm limits the number of parameters that can be considered. Following parameters were selected for the in-silico study: time of meal ingestion (breakfast, lunch and dinner) and physical activity (none, moderate and intense). Both parameters were equally weighted and represent changes in the insulin sensitivity. ICR was used as a case solution. The outcome of the solution was the 5-hour postprandial AUC and the minimum postprandial glucose value, both calculated using CGM data (see Figure 3.5). The reference value for AUC was determined individually for each subject in the T1D simulator to tune the controller.

Retrieval and Reuse Steps

The retrieving mechanism based on the euclidean distance function defined as

$$D = \frac{K_{P_1} d_{P_1} + \cdots + K_{P_j} d_{P_j} + \cdots + K_{P_n} d_{P_n}}{K_{P_1} + \cdots + K_{P_j} + \cdots + K_{P_n}}, \tag{3.8}$$

with

$$d_{P_j} = \frac{abs(P_j k - P_j)}{[P_j]}, \tag{3.9}$$

where P_j is a parameter from the current problem, P_{j_k} is the corresponding parameter of the retrieved case k from the case memory, K_{P_j} is a weight associated to the parameter P_j, which allows to assign the importance of a parameter on the retrieving procedure, and $[P_j]$ is the range of feasible values for P_j. Then, the case from the case base corresponding to the minimum distance D is the retrieved case. Reusing the retrieved solution to solve the current problem is done by applying the solution into the bolus calculator formula.

Revision and Retention Steps

For case revision, an extended version of the Run-To-Run (R2R) algorithm [15] has been used that utilises data from a CGM to eliminate the need of the two postprandial measurements. Instead, the postprandial area-under-curve is employed. The update law to adjust the bolus calculator parameters ICR is as follows

$$ICR_{k+1} = ICR_k + K(AUC^r - AUC_k), \tag{3.10}$$

where K is a tunable gain; subindex $k+1$ indicates the updated ICR and subindex k the previous ICR; AUC_k is the postprandial glucose area-under-curve (e.g. at 5 hours) and AUC^r is the reference glucose area-under-curve, which can be determined from retrospective CGM data or from a meal tolerance test. As depicted in Figure 3.5, the AUC is calculated considering the pre-prandial capillarity glucose measurement as the baseline. Figure 3.9 shows an *in silico* example of utilisation of the proposed R2R algorithm, where the ICR of a virtual subject from the T1D simulator is initialized to a non-optimal value and it converges towards to an optimal value and remains stable. The revision step consists of revising the retrieved solution ICR when the obtained outcome $\{AUC, G_{min}\}$ is not considered satisfactory. Then, ICR is revised if $G_{min} < G^L$, where G^L is a safety threshold (e.g. 4 mM/l), then ICR is updated as

$$ICR_{k+1} = ICR_k \cdot \frac{G^L}{G_{min}}, \tag{3.11}$$

or

$$\textbf{if } G^L > G < G^H \;\&\; AUC_k \notin \left[\frac{AUC^r}{Tol}, AUC^r \cdot Tol\right], \tag{3.12}$$

where G^H is a hyperglycaemic threshold (e.g. 10 mM/l) and Tol is a tolerance to avoid unnecessary revisions due to error measurements and uncertainty in the inputs. Then, ICR is updated using the update rule described by Equation 3.10. In order to provide robustness to the algorithm in front of measurement noise and manual input uncertainty (e.g. CHO estimation), Equation 3.12 needs to be satisfied two consecutive times for the same case in order to update ICR. For this purpose, a counter is employed that is increased by 1 each time Equation 3.12 is satisfied and set to zero if not. Finally, parameters ISF (mM/l/IU) is updated based on the correlation with ICR (g/IU) reported in [21]. This correlation is

$$ISF = 4.44 \cdot ICR. \tag{3.13}$$

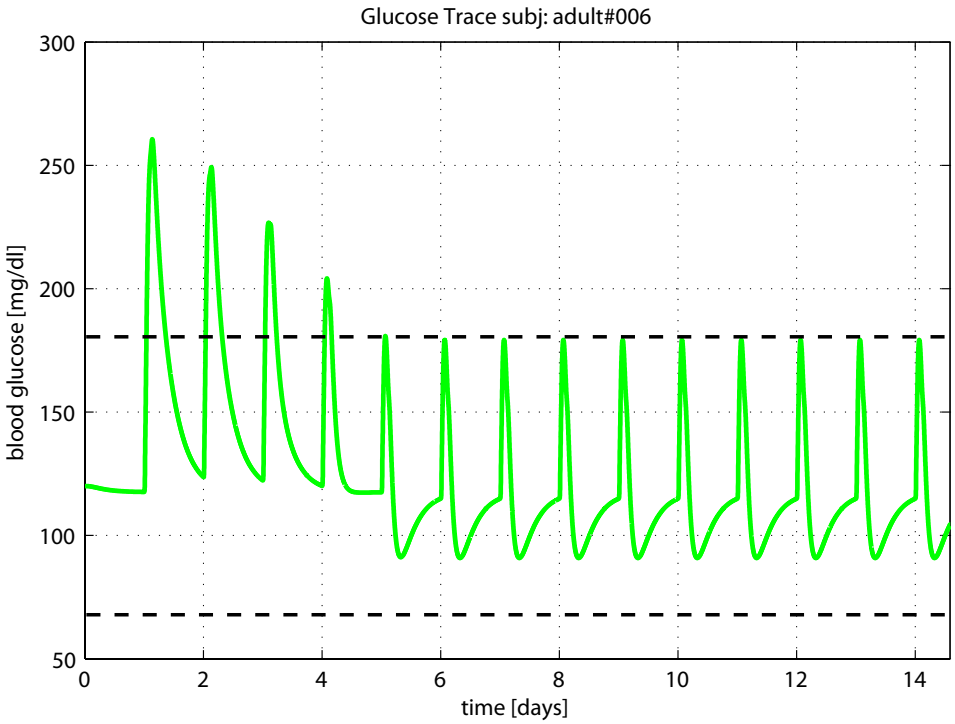


Figure 3.9: Glucose concentration resulting from applying the proposed R2R algorithm over 13 days (single meal) on subject adult 6 of the T1D simulator with an initial non-optimal ICR. Upper and lower dashed lines indicate hyper- hypoglycemia limits.

As safety features, two constraints have been used in order to prevent an excessive update of the solution ICR. The first constraint limits the increment (or decrement) as follows

$$\triangle_{ICR} = min(|ICR_{k+1} - ICR_k|, C \cdot ICR_0), \tag{3.14}$$

$$ICR_{k+1} = ICR_k + S \cdot \triangle_{ICR}, \tag{3.15}$$

$$S = sgn(ICR_{k+1} - ICR_k), \tag{3.16}$$

where C is a tuning constant, sub-index 0 refers to initialisation value, min is the minimum function and sgn is the sign function. The second constraint limits the minimum and maximum values of ICF as follows:

$$ICR_k = min(max(ICR^m, ICR_k), ICR^M), \tag{3.17}$$

where the super-indexes m and M refer to the minimum and maximum values, and min and max are minimum and maximum functions. When the current problem being solved is not found in the case base, a new case is automatically generated based on the current problem and the retrieved case. This case is then incorporated into the case base for further utilisation.

Table 3.2: Variability on meal ingestion time and carbohydrate load

	Breakfast	Lunch	Dinner
Time	[6am, 8am]	[12, 2pm]	[8pm,10pm]
CHO (grams)	[30-50]	[40-70]	[30-60]

In-Silico protocol

A scenario of one-month duration with realistic variability in meal times and carbohydrate intakes was automatically generated. Table 3.2 shows the upper and lower bounds of such variability. Since the T1D simulator does not incorporate intra-subject variability of insulin sensitivity, such changes were artificially introduced by multiplying the insulin delivery (i.e. bolus and basal) by correction gains. Insulin sensitivity was considered to vary along the day following the standard patterns used in clinical practice to adjust basal insulin rates [17] and further to change along the weeks in order to simulate changes in lifestyle such as physical exercise.

Measurement errors and uncertainty

Real-time continuous glucose measurements from the T1D simulator were used to determine G_{min} and AUC values. The capillary glucose measurements (G) were generated by adding a 5% error (uniform distribution) to the plasma glucose value [22] from the T1D simulator. Finally, because it is assumed that people with T1D introduce significant errors when counting carbohydrates, a 20% error (uniform distribution) was considered in the estimation of carbohydrates.

Safety and efficacy measures

The following safety and efficacy measures [23] (presented as mean ± standard deviation) were used: Mean BG (mM/l); percentage of time below target ($BG < 3.9$ mM/l); percentage of time within the $3.9 - 10$ mM/l target range; percentage of time above target ($BG > 10$ mM/l); BG risk index and risk zones of the control variability grid analysis (CVGA) [24].

Results

The algorithm was evaluated during a 1-month scenario and 4 simulation runs. An initial simulation run (Run 1) was carried out using the bolus calculator formula with non-optimal parameters (ICR and ISF) and without any adaptation as a reference. Run 2 consisted of applying the algorithm based on CBR and R2R with a case base containing a unique case with the same solution as the bolus calculator. Run 3 and 4 were like Run 1, but starting from the case base generated in the corresponding previous runs. In order to evaluate the benefit of enhancing the R2R algorithm with CBR compared to the R2R algorithm in a standalone mode, the previously described runs were executed for each one of the algorithm versions.

Tables 3.3 a) and b) show the results corresponding to the 4 runs of the simulations for the R2R adaptation algorithm and for the CBR(R2R) algorithm, respectively. All results are presented as mean ± standard deviation. Improvements in mean blood glucose levels, percentage of time in hyper-/hypoglycaemic range, risk index, as well as percentage in risk zones A+B and D+E of the CVGA, were analysed using a paired t-test with a significance of $p < 0.05$. Although some of the safety and efficacy measures slightly improved with the utilisation of the R2R algorithm in a standalone mode (i.e., mean blood glucose, time in target and risk index), other metrics such as the time spent in hyperglycaemia got worse. When incorporating CBR, all safety and efficacy measures improved, or remain constant, with respect to the previous run when the CBR(R2R) algorithm was employed. A significant reduction can be seen in time spent in hyperglycaemia and time in target, while virtually eliminating hypoglycaemia in both age groups. This narrowing of the glucose window translates also into a significant improvement of the risk index and in the percentage in zone A+B of the CVGA.

Table 3.3: Evaluation of R2R a) without and b) with the use of CBR during four runs. Each run represents a one-month scenario with three meals per day. Mean glucose levels, percentage time in hyper/hypoglycaemia, risk indices as well as risk zones A+B and D+E are presented for each run.

a) R2R in standalone mode

10 adults	mean BG (mM/l)	% time <3.9 mM/l	% time >10 mM/l	% time in target	risk index	% A+B	% D+E
Run1	8.7±0.7	0.3±0.5	24.6±11.5	75.2±11.7	5.4±2.2	44.5±10.7	1.9±3.3
Run2	8.8±1.2	0.1±0.2	25.6±16.5	74.3±16.5	5.9±3.9	45.0±15.3	2.6±4.8
Run3	9.1±1.8	0.0±0.1	27.0±20.9	73.0±20.9	6.9±6.2	45.1±18.3	4.0±7.6
Run4	9.2±2.2	0.0±0.0	28.2±22.7	71.8±22.7	7.7±7.6	44.5±18.6	4.7±9.2
p value	0.34	0.17	0.51	0.52	0.28	1	0.19
10 adolesc.							
Run1	9.4±1.1	0.0±0.0	36.5±17.8	63.5±17.8	7.8±3.5	38.1±16.2	3.1±2.6
Run2	9.2±1.3	0.1±0.3	34.8±19.1	65.1±19.0	7.3±3.8	40.6±18.8	2.6±2.8
Run3	9.3±1.4	0.1±0.1	35.2±19.8	64.7±19.7	7.5±4.0	40.3±19.7	3.0±3.5
Run4	9.3±1.4	0.1±0.1	35.3±20.2	64.6±20.2	7.4±4.0	39.7±20.4	2.7±3.5
p value	0.53	0.19	0.69	0.7	0.52	0.59	0.16

b) R2R in combination with CBR

10 adults	mean BG (mM/l)	% time <3.9 mM/l	% time >10 mM/l	% time in target	risk index	% A+B	% D+E
Run1	8.7±0.7	0.3±0.5	24.6±11.5	75.2±11.7	5.4±2.2	44.5±10.7	1.9±3.3
Run2	8.6±0.8	0.1±0.2	23.2±12.3	76.7±12.3	5.1±2.5	47.2±13.4	1.6±3.1
Run3	8.4±0.9	0.0±0.1	20.1±13.4	79.9±13.3	4.7±2.5	51.1±14.5	1.5±3.0
Run4	8.3±0.9	0.0±0.0	18.1±13.4	81.9±13.4	4.3 ±2.5	52.7±15.1	1.2±3.0
p value	0.031*	0.17	0.0032*	0.0029*	0.012*	0.019*	0.29
10 adolesc.							
Run1	9.4±1.1	0.0±0.0	36.5±17.8	63.5±17.8	7.8±3.5	38.1±16.2	3.1±2.6
Run2	9.2±1.2	0.0±0.0	33.5±18.7	66.5±18.7	7.2±3.6	41.9±17.7	2.7±2.6
Run3	9.1±1.2	0.1±0.2	31.6±19.3	68.3±19.2	6.6±3.6	42.7±18.3	2.1±2.1
Run4	9.0±1.3	0.0±0.0	31.2±19.2	68.8±19.2	6.4±3.6	43.3±19.5	1.4±1.8
p value	0.0056*	-	0.017*	0.017*	0.0021*	0.014*	0.011*

*Significant with p <0.05

3.7.3 Evaluation of a Metric for Adapting ICRs

The same simulation environment (T1D simulator) was used to evaluate a method to adjust the solution of a case (i.e. bolus calculator parameter ICR). Variability was added in order to provide a more realistic scenario by introducing uncertainty in meal absorption, insulin absorption, insulin sensitivity, as well as in glucose measurements [19].

Adaptation metric

The proposed metric utilises the correlation between ICR and ISF stated in [25] and expressed by

$$ISF = \frac{1960 ICR}{2.6W}, \tag{3.18}$$

where W is the subject's weight in pounds. Then, by replacing Equation (3.18) into the standard bolus calculator formula and isolating ICR, it is possible to calculate the adjusted ICR required to deliver the insulin dose ($B + IOB + B_{add}$) that brings G_{min} into the glycemic target range. That is

$$ICR(k+1,m) = \frac{CHO(k,m) + \frac{G_c(k,m) - G_{sp}}{\frac{1960}{2.6W}}}{B(k,m) + IOB(k,m) + B_{add}(k,m)}, \tag{3.19}$$

where index $k+1$ denotes the updated value for the next day. The corresponding $ISF(k+1,m)$ is then obtained by applying Equation 3.18.

Study Design

Although three cases have been created for various meal times (i.e. breakfast, lunch and dinner) to cope with intra-day variations in insulin sensitivity, further cases could not be created as the simulator does not incorporate perturbations such as physical exercise, illness or stress. The performance of the algorithm has been compared to a standard bolus calculator without adaptation in a 3-month scenario.

Table 3.4: Comparison of three bolus calculator cases (i.e. breakfast, lunch and dinner) with and without parameters adjustment on a cohort of 10 virtual adults and 10 virtual adolescents. Results are expressed as mean±SD.

(a) 10 virtual adults

	mean BG mM/l	BG∈[3.9,10]mM/l % time	BG<3.9mM/l % time	BG>10mmol/L % time	LBGI –
No adjust	7.2 ± 0.7	87.2 ± 13.9	2.7 ± 4.0	10.1 ± 10.5	1.1 ± 1.3
Adjust	7.4 ± 0.6	90.1 ± 8.9	0.4 ± 0.7	9.4 ± 8.8	0.3 ± 0.2
p-value	0.03*	0.5	0.03*	0.92	0.002*

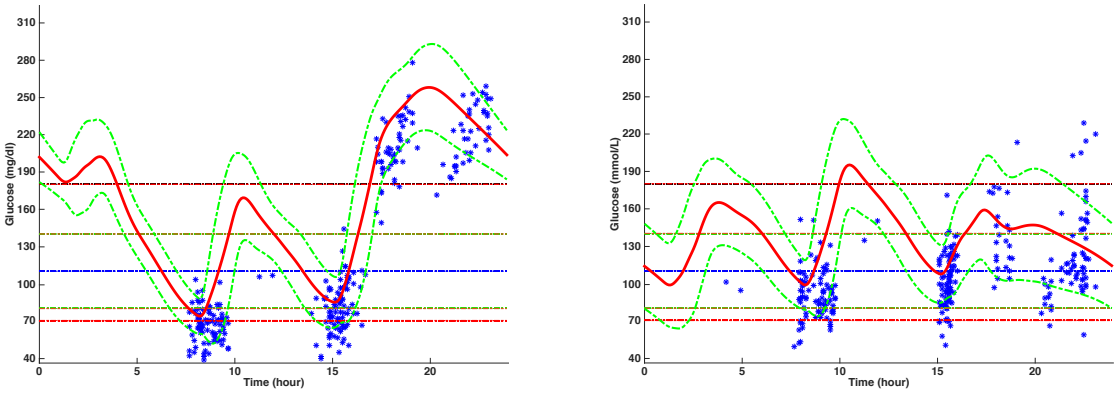
(b) 10 virtual adolescents

	mean BG mM/l	BG∈[3.9,10]mM/l % time	BG<3.9mM/l % time	BG>10mmol/L % time	LBGI –
No adjust	8.8 ± 0.9	61.7 ± 16.8	7.1 ± 7.4	31.2 ± 12.3	2.0 ± 2.2
Adjust	8.8 ± 1.1	73.3 ± 18.3	1.3 ± 2.4	25.3 ± 16.6	0.7 ± 1.4
p-value	0.92	0.16	0.02*	0.37	0.05*

*Statistically significant $p \leq 0.05$

Results

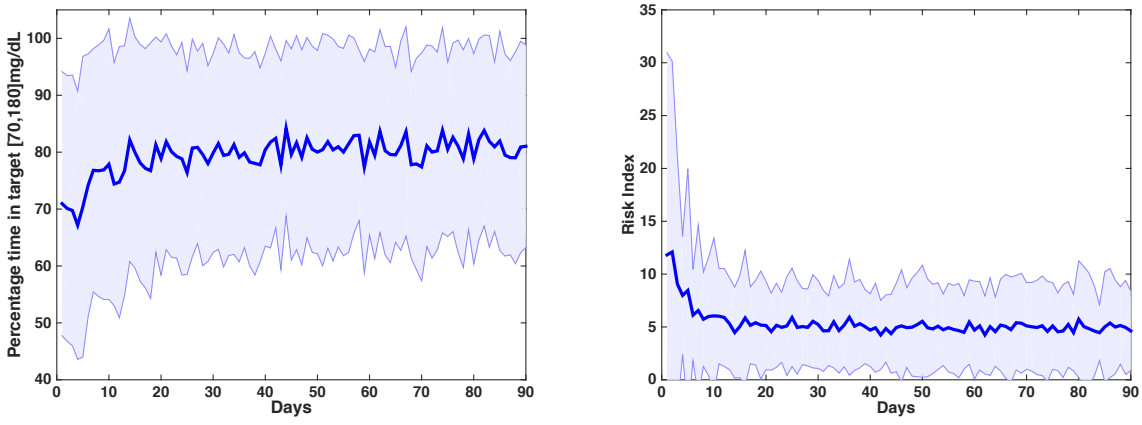
Table 3.4 shows simulation results comparing the glycemic outcomes employing three cases (i.e. breakfast, lunch, dinner) with and without case parameter adaptation on a cohort of 10 virtual adults (Table 3.4a) and on a cohort of 10 virtual adolescents (Table 3.4b). In summary, the proposed adaptation method statistically improved ($p \leq 0.05$) all glycemic metrics evaluating hypoglycaemia on both virtual cohorts: percentage time in hypoglycaemia and low blood glucose index (LBGI). Figure 3.10 shows a graphical example of a 3-month simulation run of the bolus calculator without and with adaptation mechanism on an adolescent subject. The minimum postprandial CGM values (G_{min}) represented by blue dots, are more concentrated in the glycemic target range $[G_l, G_h]$ when using the adaptation metric compared to non-adaptive bolus calculator. Figure 3.11 displays the mean of percentage time in target (i.e. 3.9 -10 mM/l) and the mean of risk index along the 3-month simulation corresponding to the bolus calculator with parameters adjustment for adults and adolescents combined. On average, the adaptation metric converges in about 20 days and remains stable along the rest of the simulation. While in-silico results of improvements in glycemic control are encouraging, the new metric also has a practical advantage compared to other metrics such as area-under-curve as it does not require any reference or initial tuning. Therefore the proposed metric has the potential to be integrated in the CBR revision step of the proposed decision support system.



(a) Bolus calculator without adaptation.

(b) Bolus calculator with adaptation.

Figure 3.10: Graphical representation of a 3-month simulation run of the bolus calculator without and with adaptation mechanism on an adolescent subject. From down to top, horizontal lines represent: hypoglycaemic threshold; low target bound (G_l); mid target zone (G_{sp}); high target bound (G_h); and hyperglycaemic threshold. Red solid line is the mean blood glucose and dashed green lines represent the standard deviation. Blue dots represent the minimum postprandial CGM values (G_{min}).



(a) Percentage time in target (mean± SD).

(b) Risk Index (mean± SD).

Figure 3.11: Population mean of percentage time in target (i.e. [3.9,10] mM/l) (a) and population mean of risk index (b) along the 3-month simulation corresponding to the bolus calculator with parameters adjustment. Solid line represents mean values and shaded area the standard deviation.

3.8 Discussion

When using CBR for insulin dosing decision support, the selection and representation of case parameters are crucial for achieving optimal results. Many factors have been discussed in the previous chapter to have an impact on glycemic control. However, incorporating a vast number of parameters results in a longer time needed to populate the case-base, as the number of possible cases rises exponentially with each additional parameter. Adding more parameters may also require additional manual user input, if a parameter cannot be captured by sensors (e.g. illness), thus potentially reducing the usability of the insulin advisory system. Therefore, the number of case parameters is always a compromise between usability and convergence time of the CBR algorithm.
Several methods exist for retrieving cases and finding the best match. Because of the small number of parameters used for simulations and first clinical prototype, the weighted average distance function was used. Algorithms to adapt the insulin-carbohydrate ratio have been presented, but their performance is limited based on the assumption that insulin therapy is a repetitive process [16] or that frequent blood glucose measurements are available that may restrict the applicability [15]. In simulations, an extended version of the R2R algorithm has been used that utilises data from a CGM system to eliminate the need of the two postprandial measurements. The performance of assessing the outcome of a proposed insulin dose is crucial for this research. A positive outcome of a solution means that the solution can be remembered for future situations. Conversely, a negative outcome would mean that the solution needs to be updated (i.e. more or less insulin will be delivered next time for this situation) - thus accuracy of the metric determining the outcome is important. Various glucose outcome metrics utilising continuous glucose data have been evaluated, showing good sensitivity and robustness against sensor noise in simulations as well as when applying the metrics on clinical data. One of the metrics (AUC) had been used for in-silico trials, evaluating the use of CBR for insulin dosing and achieving encouraging results in postprandial glucose control for 10 virtual adults and 10 adolescents. However, utilising AUC as a metric requires an ideal reference; something which proves to be difficult to determine in practice. Figure 3.12 shows two post-meal glucose excursions measured with a CGM system for two meals with the same recorded amount of carbohydrates. Although this data was recorded by the same study participant in a similar setting (i.e. two breakfast scenarios within the same week) and the same amount of insulin was delivered, a noticeable difference in AUC can be seen. The late rise of glucose observed in AUC 2 suggests that this difference can be due to the meal composition or preparation. While the T1D simulator

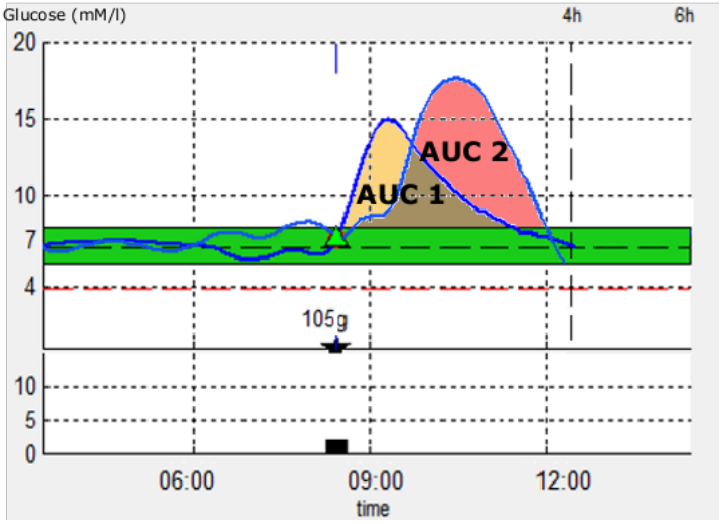


Figure 3.12: Two postprandial glucose excursions measured with a CGM sensor for one study participant. Although similar settings (same amount of carbohydrates during breakfast), a noticeable difference in AUC can be observed.

incorporates CGM sensor noise, it is not able to simulate different meal absorption profiles, which would affect the AUC. Therefore, another metric has been evaluated based on the postprandial minimal glucose concentration, which showed similar robustness against sensor noise compared to AUC when analysing clinical CGM data. The performance of the metric was further evaluated during extensive in-silico trials with realistic variability and uncertainty [19].

3.9 Conclusion

This chapter introduced the reader to the concept of CBR and its possible incorporation into a novel decision support system for individualised insulin dosing. CBR utilises cases to describe and differentiate various meal scenarios. Multiple factors affecting glucose control have been identified that can be used as case parameters as well as possible solutions to adapt the insulin therapy. In-silico studies and analysis from clinical data have been performed to evaluate the best way to assess the performance of proposed solutions with continuous glucose data. Finally, this chapter presented encouraging simulation results on the concept of using CBR for insulin decision support as well as a novel metric for adapting the case solution (i.e. insulin-carbohydrate ratio).

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Chapter 4

An Advanced Bolus Calculator for Diabetes (ABC4D) System

4.1 Introduction

The final goal of this research is the development of a user-friendly system that helps people with diabetes with the insulin decision making in an effortless way. This chapter describes the implementation of the previously presented CBR based decision support algorithm into an 'Advanced Bolus Calculator for Diabetes' (ABC4D). ABC4D provides real-time meal bolus advice for people with T1D on their smartphone, as well as integrates a clinical platform that allows experts (e.g. endocrinologists) to supervise and approve automatically proposed changes to the insulin therapy. This chapter presents the concept and architecture of the CBR-based system, which comprises a patient and a clinical platform.
Human factors are key in the adoption of decision support systems and the design and usability, therefore, play a crucial part. The aim when designing systems that are frequently used (i.e. multiple times a day) is to reduce manual user interaction as much as possible in order to seamlessly integrate the system into the lifestyle of the person with diabetes. Several design prototypes are presented in this chapter, which have been used in various phases of the clinical trials presented in Chapter 5. Before the start of each study phase, we held focus group meetings with people with T1D and implemented their feedback in the design process of the system used in the clinical studies. Also, the expert software for remote monitoring and approval of insulin therapy changes was optimised for each trial phase in collaboration with our clinical study team. Finally, the chapter present initial results assessing system usage, usability and acceptability of the whole ABC4D system

during a feasibility study. The ABC4D architecture, as well as the results presented in this chapter, have been published here [1] [2].

4.2 System Concept

The concept of ABC4D is shown in figure 4.1. The main user (person with diabetes) enters input parameters through a mobile platform (e.g. smartphone) and receives insulin bolus advice for meals. In periodic intervals, all data used by ABC4D (e.g. CGM data, insulin advice, case base) is sent to a clinical platform, where all cases that have been used undergo revision. After all proposed case adaptations have been approved by a clinical expert, the updated case base is sent back to the patient platform. For practicality reasons, case revisions can be performed periodically (e.g. weekly). Periodic revisions also have the advantage to filter out potential outliers if a case has been used more than once. Prior to the start of the development of ABC4D, the following requirements have been set for the two platforms:

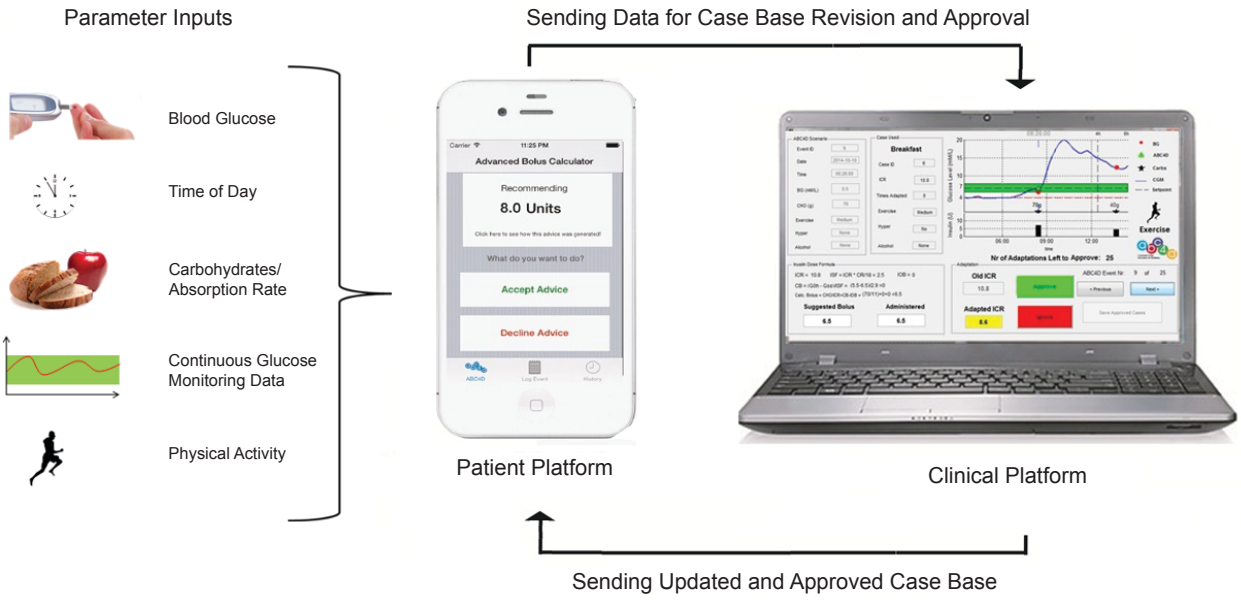

Figure 4.1: Concept of ABC4D showing input parameters of the patient smartphone platform (left), which periodically sends data to the clinical platform (right) for approval of case revisions.

4.2.1 Requirements on the Patient Smartphone Platform

- Real-time insulin advice for meals that can be accepted or declined by the user
- User-friendly interface to capture diabetes events such as glucose measurements, exercise, insulin injections
- Event and glucose visualisation in form of a table view as well as through graphs and charts
- Display basic statistics for various time windows (e.g. average, minima and maxima glucose levels)
- Easy data export to clinical expert via email for remote supervision

4.2.2 Requirements on the Clinical Revision Platform

- Access and maintenance of patient profiles holding demographics and other data needed for revision e.g. email address and smartphone ID
- Import of CGM, logbook and case base data
- Provide general overview of CGM data
- Detailed information for each insulin bolus recommendation

  - Used case, parameters and solution

  - Information on whether advice was accepted or not

  - Show reason for declined advice and alternative insulin delivery

  - Graph showing postprandial glucose profile and additional information (e.g. meals and snacks, correction insulin, exercise, comments)

  - Navigation and control buttons to switch between cases and accept or ignore proposed case adaptation

- Function to approve cases which have been adapted multiple times (e.g using the average of all adaptations)
- Automated summary of revision and adapted cases
- Sending updated case base to patient platform via email

4.3 ABC4D System

The proposed ABC4D system comprises a patient platform consisting of a smartphone application and a computer-based clinical platform (see Figure 4.2). The patient platform allows manual user input of relevant glucose-related data and provides real-time bolus advice. The clinical platform allows a clinical expert to easily analyse and accept changes to the insulin therapy proposed by the CBR algorithm.

4.3.1 Integration of the CBR Process Cycle

In order to warranty patient safety, the proposed platform separates the CBR cycle into two parts. The first part, comprising the retrieval and adaptation steps, is integrated into the patient advisory platform; while the second part, containing the revision and the retention steps, is performed within the clinical platform. The functional separation of the CBR cycle ensures that only clinically safe adaptations are performed. Both platforms have access to the case base, which is synchronised after each revision.

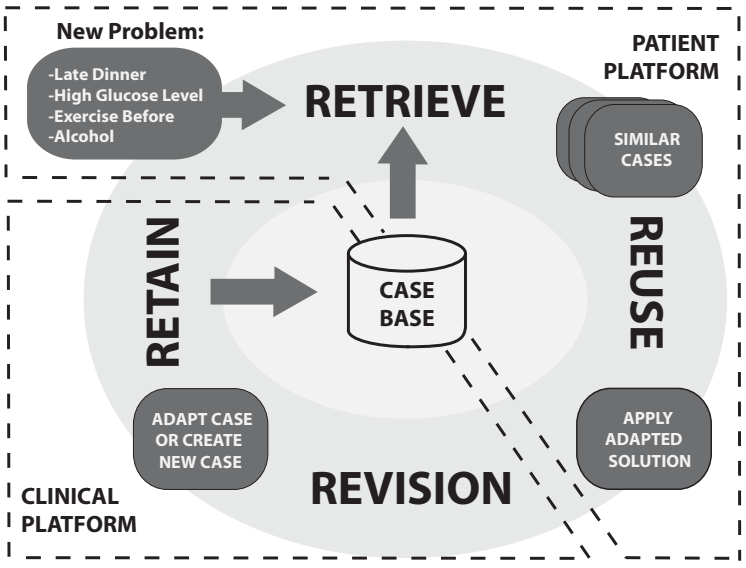

Figure 4.2: CBR functionalities split into the patient and clinical platform

4.3.2 System Architecture

Figure 4.3 shows the software system architecture of both the patient advisory and clinical supervision platforms. The main difference in the structure of the architecture between the two platforms lies in the algorithm layer. The algorithm layer of the patient platform contains the bolus calculator formula as well as CBRs retrieval and reuse steps, while the same layer of the clinical platform implements the revision and retention steps of the CBR cycle.

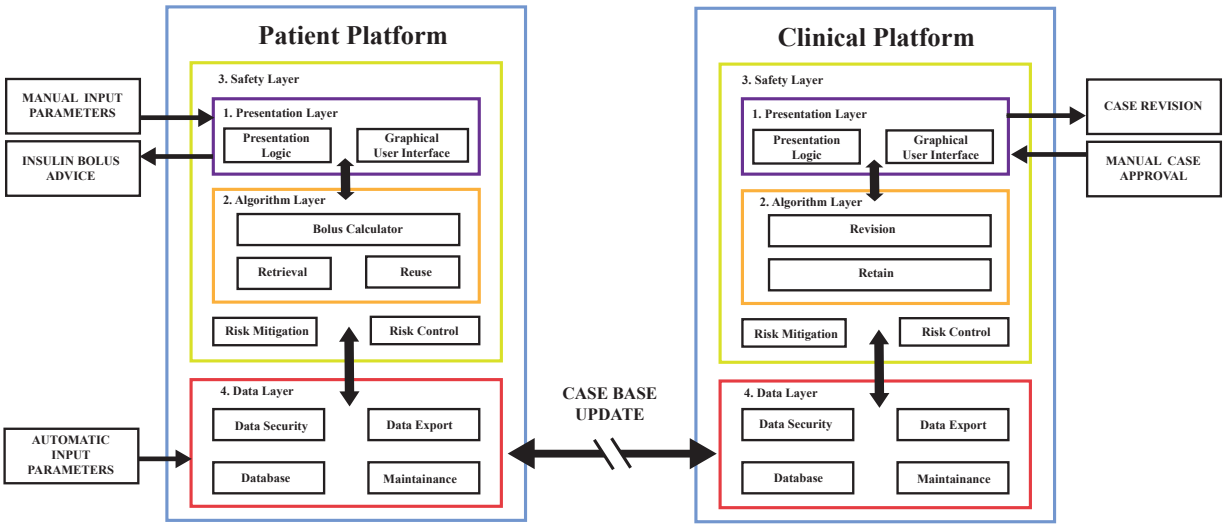

Figure 4.3: Software architecture and user interaction of the ABC4D patient platform (left) and clinical platform (right).

ABC4D Patient Smartphone Platform (PSP)

The system architecture of the ABC4D patient smartphone platform (PSP) is structured as follows:

1. The presentation layer holds the logic for the graphical user interface, which is responsible for retrieving manual input parameters and presenting requested bolus recommendations to the patient.

2. The algorithm layer contains the retrieval and reuse steps of the CBR cycle and the bolus calculator formula. Whenever the user requests a new bolus advice, the

retrieval algorithm compares the current scenario with existing cases in the case base and returns the solution (i.e. bolus calculator parameters) and, if necessary, adapts the retrieved solution to the current scenario (reuse step). The bolus calculator formula uses this solution to calculate the recommended insulin dose, which is sent to the presentation layer for visualisation through the graphical user interface.

3. The safety layer implements risk mitigation and risk control measures to ensure maximum safety of the system. Risk mitigation is implemented to ensure that only safe (i.e. physiological) values are entered via the user interface and to verify each parameter retrieved from the database. Risk control limits the maximum amount of insulin to be advised which can be pre-defined for each user by the clinical expert.

4. The data layer is responsible for storage, maintenance, security of data stored in the local databases, as well as providing secure transmission to the clinical platform. The data layer contains three databases: 1) An event-database which contains log book entries and information about all glucose related user entries and insulin requests; 2) a case database (i.e. case base) containing all generated cases and information about their usage and 3) a settings-database to store security information, patient details and personal settings. The data layer also manages access to automatic input parameters (e.g. exercise information through external accelerometer.)

ABC4D Clinical Revision Platform (CRP)

The clinical revision platform is structured as follows:

1. The presentation layer is responsible for the graphical user interface of the clinical revision platform. It allows the clinician to import the log book and cases retrieved from the patient platform, as well as additional data (e.g. CGM data) required by the revision algorithm. During the revision process, the user interface displays glucose graphs, meal information, selected parameters (e.g. exercise) and retrieved cases used for each scenario where an insulin advice has been requested. A suggested adaptation to the solution of the retrieved case is presented to the clinical expert who needs to approve or decline each case adaptation.

2. The algorithm layer holds the revision and reuse steps of the CBR algorithm. The revision algorithm calculates adaptations to the solution of each case that has been

used. After all case adaptations have been revised, the approved cases are updated into the case base of the patient platform (retain step).

3. The safety layer of the clinical revision platform ensures that all essential data have been imported and checks the databases for validity. In order to avoid overly aggressive adaptations, safety constraints limit the maximum allowed change to a case solution by a pre-defined percentage.

4. The data layer is responsible for synchronising and storing data that has been uploaded from the patient platform. It contains a duplicate of all databases from the phone in addition to usage information and historical data from previous case adaptations.

4.4 System Design and Human Factors

Usability and human factors are key for the adoption of decision support systems that require frequent user interaction such as the proposed ABC4D platform. In order to get feedback on the system design from end-users (i.e. people with T1D), we have organised two focus group meetings through the Imperial College Patient and Public Involvement Panel at the NIHR/Wellcome Trust Imperial CRF Hammersmith Hospital. The first focus group meeting was held between the first and second phase of the clinical evaluation of ABC4D (see Chapter 5). The next meeting was organised after finishing the second study phase, where ABC4D was used in the home setting for over six weeks, and before the start of the final study phase. Figure 4.4 shows the evolution of changes to the user interface of the patient smartphone platform performed after each study phase. It shall be noted that the first version of the software looks rather 'crowded' and contains different input elements, while the latest software version (right) is more consistent in the choice of user elements and provides improved clarity for glucose and carbohydrates input fields.

Focus Group Meeting 1

Five people with T1D attended the focus group meeting (2 female, 3 male with an average age of 51 $\pm$ 15 years). The objective of the meeting was to get feedback on the choice of case parameters for the second trial phase and on input methods of the ABC4D-PSP graphical user interface (GUI). Participants were happy with the selection of case parameters exercise, alcohol and meal absorption. Users were asked about types of manual input and

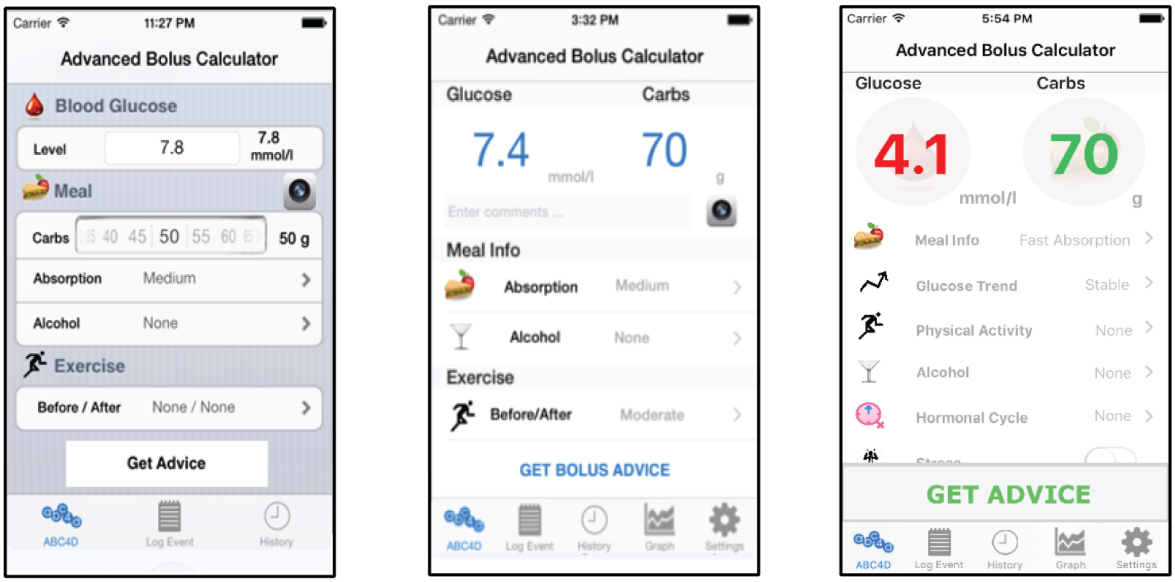

Figure 4.4: Evolution of the graphical user interface for the ABC4D patient smartphone platform from study phase 1 (left) to phase 3 (right)

visualisation of glucose data. Based on participant's feedback, the following changes have been implemented in the GUI prior the start of the next study phase: Simplification of the main menu, changing the input methods for entering carbohydrates and glucose levels (i.e. changing scroll wheel to numeric keypad) and adding explanatory text that informs the user in detail on how recommendations have been generated.

Focus Group Meeting 2

The second focus group meeting was organised before the start of the final study phase and was attended by four people with T1D (2 female, 2 male with an average age of 53 $\pm$ 17 years). The objective was to review and get feedback on the ABC4D-PSP software, which was used during the six-week study. Furthermore, participants were asked about additional user input or case parameters and the integration of other technologies such as continuous glucose monitors and smartwatches. The outcome of the second focus group meeting lead to changes in the design of the GUI as seen in Figure 4.4 (right).

4.5 System Implementation

This section describes the system implementation of the patient smartphone platform (ABC4D-PSP) and the clinical revision platform (ABC4D-CRP). The user manuals for both platforms, which was used during the second phase of clinical evaluation (Chapter 5.3) can be found in Appendix D.

4.5.1 Patient Smartphone Platform (PSP)

The ABC4D-PSP is built on the presented architecture [1] and has been implemented in an off-the-shelf smartphone (Hardware: iPhone 4S, Apple Inc. California; Programming Environment: X-Code/Objective-C; Database: SQLite3). Figure 4.5 (left) shows the main screen of the smartphone application used for requesting a new recommendation. It contains input elements to enter manual parameters (i.e. amount of carbohydrates, meal absorption,

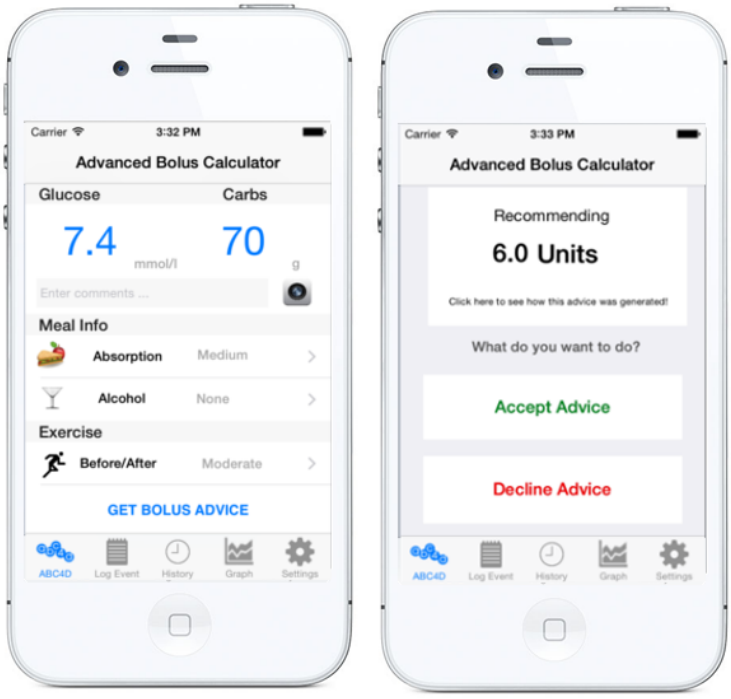

Figure 4.5: Main screen of ABC4D patient platform used during the second study phase to enter manual input parameters and request an insulin advice (left); display of an insulin bolus recommendation with the option of accepting or declining the advice, or to request more information on how the advice has been generated (right).

current blood glucose level, alcohol consumption and exercise) and a button for requesting insulin bolus advice. The insulin recommendation is then presented to the user via a graphical user interface (see Figure 4.5 (right)). Each recommendation needs to be accepted or declined manually, while the latter option requires the user to input the actual insulin dose that has been delivered. Users could give reasons for declining bolus advice through selecting one of following checkboxes:

- Too much insulin
- Too little insulin
- Other/Manual user comment

Declined recommendations by the user were used for revision. However, instead of the solution of the retrieved case, the solution proposed by the user is revised and adapted if the outcome was non-optimal. All user input and recommendations are locally stored in a relational database management system (i.e. SQLite3) on the phone. This enables the user to have access to past glucose information and recommendations at all times. Data essential for case revision can be exported as an Excel (Microsoft) file and sent encrypted via email to the clinical expert.

4.5.2 Clinical Revision Platform (CRP)

The clinical revision platform has been implemented in MATLAB (The MathWorks, Inc) and is designed to run on a desktop computer. It implements the revision algorithm based on [3] which has been described in the previous chapter.
At the start of the software, the clinical expert is asked to select a patient (or create a profile for a new patient) and the date of revision. Next, logbook and case base data from the patient platform as well as the CGM data for the revision period need to be uploaded. If all data was imported successfully, an overview of the glucose data for the revision period is shown to the user.

Example of a Case Revision

Figure 4.6 shows an example of a revision for a breakfast case. The main screen used for the revision contains following elements:

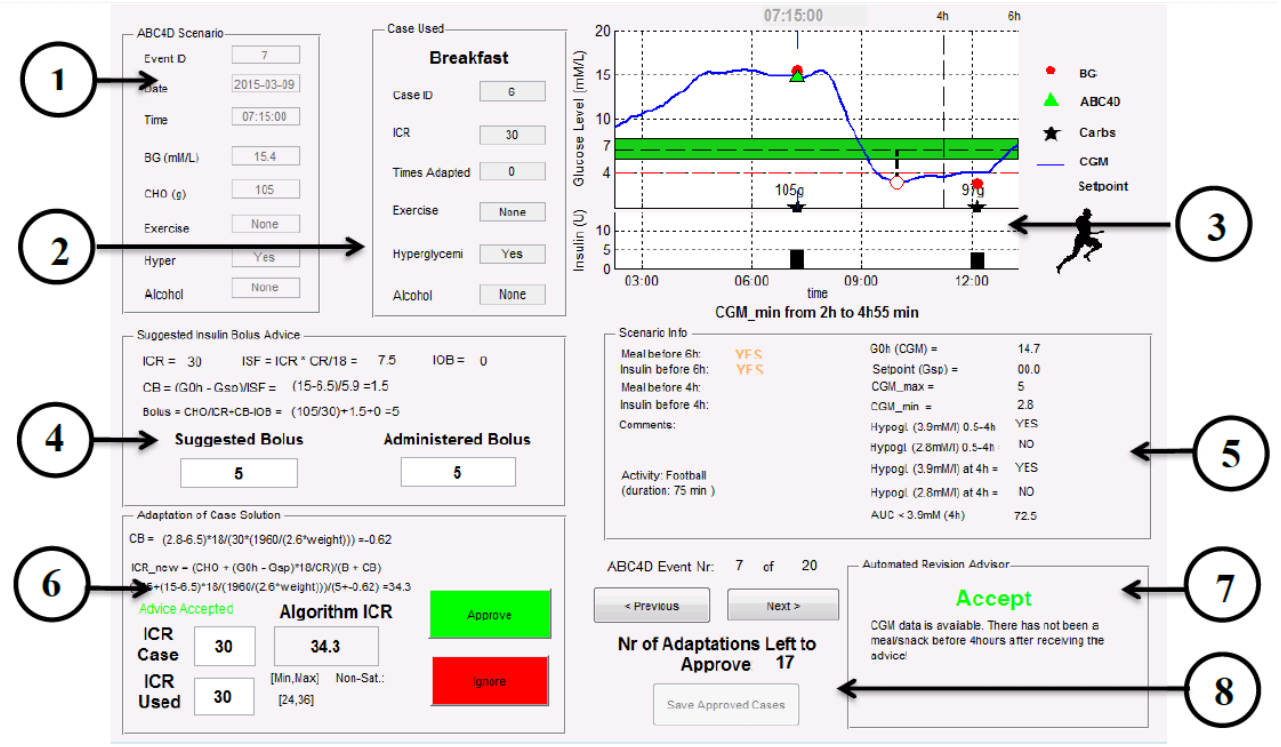

Figure 4.6: Clinical revision software reviewing a breakfast scenario with exercise and proposing an adaptation to the insulin-carbohydrate-ratio (ICR) of a case.

1) **Scenario Information:** Shows all information and user inputs of the current meal scenario where ABC4D has been used for bolus advice

2) **Retrieved Case:** Shows the retrieved (most similar) case to the current scenario, its parameters and its solution (i.e. ICR)

3) **Postprandial Glucose Excursion:** Shows a detailed graph of the current meal scenario including glucose data from the CGM device (blue line) and BG meter (red dots), as well as meal information, delivered insulin and exercise.

4) **Suggested Bolus Advice:** Shows the calculation on how the bolus advice has been calculated (suggested bolus) and if the user followed the advice (i.e. administered bolus)

5) **User Comments and Statistics:** Analyses the logbook data and indicates if a meal or correction bolus has occurred within a pre-defined time window (i.e. 4 and 6 hours). Comments entered by patients are displayed here. Postprandial statistics can be seen on the right.

6) **Adaptation of Case Solution:** Here the revision algorithm calculates the new solution

based on the postprandial outcome (Algorithm ICR).
7) **Automated Revision Advisor:** Automatically analyses the glycemic outcome and provides a suggestion to the clinical expert on whether to approve or ignore this scenario for revision. For instance: In case the user administered additional insulin or consumed another meal with insulin within 4 hours after the bolus advice, then this scenario will be excluded for revision as it is not clear if a potential bad glycaemic outcome was the result of the initial bolus advice or because of the user intervention. However, cases solutions are still revised in scenarios when participants consumed carbohydrates without administration of insulin to correct for hypoglycaemia.
8) **Navigation Control:** Enables the expert to switch between ABC4D scenarios. The number below shows how many cases are left to be revised.
After the revision of the cases has been completed, the software shows a summary of all adapted cases to the clinician. If one case has been used and revised multiple times, an average of all adaptations is calculated which, in turn, needs to be manually approved. Finally, the case base on the patient platform needs to be updated. This can be performed either on the phone itself through an authorised settings menu or remotely via email.

4.6 System Usage

The usage of ABC4D has been analysed during phase 2 of the clinical trial described in Chapter 5 where 10 adults used the ABC4D-PSP over a period of six weeks.

4.6.1 Usage of ABC4D-PSP

Number of Recommendations and Logbook Entries Table 4.1 shows the ABC4D usage of all subjects (n=10) participating in the six-week pilot study. On average, 115±21 insulin recommendations have been requested of which 103±28 (90%) were accepted by the participants. For the majority of all declined recommendations participants found the proposed insulin dose was not enough (64%), while for 32% of all declined advice participants felt the insulin dose was too much. No reasons were provided by the user for the remaining 4% of declined advice.While participants used the log book function of the application less in the last week of the study ($p<0.05$), no statistically significant change was observed when analysing the average number of requested bolus recommendations when comparing the initial study week with the last week.

Table 4.1: Usage of the patient platform during the six weeks pilot study. Values are mean ± standard deviation. Above: Total number of bolus advice requested, average number of bolus advice requests per day in the first and final study week and total number of accepted and declined bolus recommendations. Below: Total number of logbook entries, average number of logbook entries per day as well as usage time in the first and final study week, respectively.

N^o Bolus Advices	Bolus Advice/Day		N^o Accepted Advices	N^o Declined Advices
	Week 1	Week 6		
115±21	2.9±0.4	2.7±0.6	103±28(90%)	12±14(10%)

N^o Logbook Entries	Logbook-Entries/Day		Usage Time (s)	
	Week 1	Week 6	Week 1	Week 6
121±83	4.1±2.9	2.3±1.9*	100±63	62±36**
*p <0.05	**p <0.01			

Usage Time The mean time spent for requesting a bolus advice using the application (i.e. time from opening the software until closing it) was 100±63 seconds in the first week. This value was significantly ($p<0.01$) reduced to 62±36 seconds in the last week.

Usage of Case Parameters Because of the limited study time, only a small number of case parameters were selected: meal time, exercise, alcohol, meal absorption and hyperglycaemia. While parameter exercise was Boolean (None/Yes), additional information about the intensity (moderate/intense) was considered in the re-use step of the CBR cycle by adding a pre-defined percentage to the case solution (i.e. insulin-carbohydrate-ratio). Parameter 'hyperglycemia' was automatically assigned, when blood glucose levels at meal time were above 15 mM/l. Case parameter 'time of meal' was automatically obtained by retrieving the system clock of the phone when an insulin advice had been requested. Out of all used cases, 30.9±6.4% were assigned to breakfast, 34.8±3.8% to lunch and 34.2±5.7% to dinner. Parameter 'hyperglycaemia' was observed in 8.5±10.4% of all case retrievals. Exercise was the most frequently manually entered parameter with 8.4±6.3 %, followed by alcohol (5.5±6.0%) and absorption rate (1.8±2.1%) of all retrieved cases.

Table 4.2: Results of clinical revision platform analysing proposed bolus recommendations

N^o of total meal scenarios available	1149
N^o of scenarios eligible for revision	754
N^o of approved revisions by clinician	723 (96%)
N^o of declined revisions by clinician	31 (4%)

4.6.2 Usage of ABC4D-CRP

Table 4.2 shows the use of the clinical revision software, which has been used periodically during the six-week study to revise the outcome of bolus recommendations. A total of 1149 bolus recommendations have been imported to the revision platform of which 754 advice were eligible for revising the outcome of the cases. Other bolus advice were ignored for revision because of either missing glucose sensor data or exclusion criteria of the adaptation metric (e.g. a user has given additional insulin or consumed a snack shortly after the advice received). Out of all eligible imported bolus advice, 723 (96%) proposed adaptations were approved by the physician and uploaded to the patient platform. Only 4% of all proposed adaptations have been declined manually by the clinician, which was due to either human error (e.g. wrong value entered by patient) or artefactual sensor data.

4.7 User Acceptance and Usability Results

User acceptance of ABC4D-PSP was evaluated within the second phase of the clinical study (see Chapter 5) based on the feedback from subjects that participate in the clinical trials. The study team developed an acceptability questionnaire (see Appendix C) to assess how user-friendly and acceptable the whole system is for everyday use and what can be done to we can improve it. The questionnaire has been divided into two sections. The first part assesses the ABC4D software and the user interface, whereas the second part aims to evaluate the usability of the whole system (the ABC4D application running on a smartphone + continuous glucose monitoring on a regular basis). In total, the questionnaire includes 24 questions and one text field for additional comments.

Results Feedback obtained from the focus group meeting lead to changes in the graphical user interface of the patient platform. Implemented changes included: Simplification of the

Table 4.3: Results of the acceptability/usability questionnaire of patient platform (n=10)

	Strongly Agree	Agree	Neither Agree Nor Disagree	Disagree	Strongly Disagree
Acceptability Questions					
I trusted the insulin dose advice generated by ABC4D.	2	6	0	2	0
The use of continuous glucose monitoring was acceptable.	4	6	0	0	0
Using ABC4D for insulin calculation caused more anxiety.	0	3	0	4	3
Overall, I would be happy to use ABC4D system for bolus calculation.	6	3	0	1	0
Usability Questions					
The ABC4D main screen is clear and was easy to read.	5	5	0	0	0
Entering data on the screen was straightforward.	6	4	0	0	0
Using ABC4D for insulin calculations was time consuming.	3	2	1	3	1
I would consider the ABC4D app user-friendly.	5	5	0	0	0

main menu, changing the input methods for entering carbohydrates and glucose levels (i.e. changing scroll wheel to numeric keypad) and adding explanatory text that informs the user in detail on how recommendations have been generated. Table 4.3 shows the outcome of the questionnaire assessing system usability and acceptability after completion of the six-week study. The majority of people considered the ABC4D platform as user-friendly, to trust the generated advice and to be happy to use the platform. However, some participants reported that using ABC4D for insulin bolus advice was more time consuming compared to their conventional calculation.

User Perception on Selected Case Parameters

Usability plays a key role in the adoption of decision support systems for insulin dosing and implemented case parameters can only demonstrate their efficacy when frequently used. We hypothesise that case parameters, which need to be entered manually in the system, will more likely be selected if they are perceived as useful or important to the person with diabetes. Therefore we asked study participants after completion of the study for their opinion on selected manual case parameters. Feedback was obtained through a non-validated questionnaire about the perception of participants on the importance of selected case parameter. Eight out of ten participants stated that it would be useful to add additional information about case parameters alcohol and exercise. While users could choose between two levels of intensities, the inclusion of type and duration of exercise was highlighted as a potentially useful additional feature. Participants further pointed out that they would like to differentiate between type and amount of consumed alcohol.

4.8 Discussion

Human factors are key components to ensure adherence of patients and clinicians to information technologies for therapeutic purposes. For maximum performance, decision support systems for insulin dosing need to be as user-friendly as possible for both patients and clinicians. This is why end users were involved from the beginning in the design and the development phase of the proposed system. There is a wide scope for integrating the developed ABC4D system into routine diabetes management as it has been designed to be used by either people on multiple daily injections or on insulin pump therapy. Insulin pumps allow greater fine-tuning by setting hourly basal rates and are able to deliver doses with high accuracy (0.1 units or less), while people using insulin pens need to round the dose up or down to the nearest unit or half-unit. Depending on the insulin therapy, the developed ABC4D system rounds to the nearest value which can be delivered by the technology used. Initial acceptability results obtained from a six-week study are encouraging with almost 90% of all bolus recommendations have been accepted by the participants. The difference in usage of the patient platform between the first and last study week has been highlighted in Table 4.1. Participants used the logbook less frequent at the end of the study phase to enter daily diabetes-related events (e.g. snacks, exercise or stress). However, the number of insulin advice requests did not significantly change over the study period. Further findings

show, that the time needed to request an insulin advice was significantly reduced in the last week compared to the start of the study. As the software did not provide a function to re-use previously entered manual inputs (e.g. library of profiles), this reduction results from the learning curve of the user to enter data more efficiently when becoming more familiar with the software. Nevertheless, some participants still found the use of ABC4D too time-consuming compared to their conventional way of calculating the insulin dose. To address this, future work could see the system being integrated into a blood glucose meter or insulin pump to reduce the number of manual user inputs. Also, pre- and post-meal physical exercise could be measured using existing commercial devices such as heart rate monitors or accelerometers (e.g. Fitbit Inc, San Francisco, CA, USA) as study participants stressed to find this parameter of importance. This has been confirmed when analysing the overall usage of case parameters during the study. Cases including information about exercise and alcohol were frequently selected, while parameter 'absorption rate' was used least often by participants. The reason for the little usage may be because of the additional effort needed to analyse the glycemic index of the meal and the effectiveness of the parameter could be evaluated again, if it is automatically obtained e.g. through a pre-programmed meal-library.

Safety, as well as perceived safety, are other key aspects for the adoption of ABC4D. The proposed separation of the CBR cycle into a patient platform for advice retrieval and a clinical platform for supervision ensures patients that all changes of their insulin therapy are approved by a clinical expert. After completion of the study, 80 % participants stated that they trusted the insulin advice which was generated by ABC4D (Table 4.3). A decision support system that would automatically adapt the insulin therapy without approval by a clinical expert might receive less acceptance by patients. However, we show in our pilot study that 96% of all proposed adaptations have been approved by the clinical experts which indicates the potential of further automation and reduced remote supervision.

It is important to note that the presented platform can utilise various algorithms for each of the CBR steps. While the ABC4D system can potentially hold other revision algorithms that do not rely on CGM data (e.g. postprandial capillary measurements [4]), the algorithm implemented in the presented system uses retrospective CGM data to learn from previous case outcomes and further adapt the bolus calculator parameters. However, even without CGM, the patient platform is able to provide real-time bolus advice. In this scenario, the revision and retain steps will not be performed. For long-term usage, and once the bolus calculator parameters have been optimised, CGM could be used periodically (e.g. one

month every four months) to adapt to changes in the user's environment. This is important as CGM sensors are expensive and some users may not want to continuously use CGM for longer periods. The overall clinical performance of the system will be discussed in the next chapter.

4.9 Conclusion

This chapter presented the implementation of a CBR-based 'Advanced Bolus Calculator for Diabetes' (ABC4D). ABC4D comprises a patient platform consisting of a smartphone application and a computer-based clinical platform. The patient platform allows manual user input of relevant glucose-related data and provides real-time insulin bolus advice. In order to guarantee that only clinically safe adaptations are being performed, the clinical platform allows remote supervision by a diabetes expert who can approve changes to the insulin therapy proposed by the case-based reasoning algorithm. We have evaluated the usability of the patient platform and have shown promising results from a pilot study, where ten people with T1D used the ABC4D system continuously over six weeks.

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Chapter 5

Clinical Studies Evaluating Safety, Feasibility and Efficacy

The final outcome of the research is to progress towards a system that is accepted by both patients and clinicians and is able to demonstrate improvements in glycemic control. The 'Advanced Bolus Calculator for Diabetes' (ABC4D), based on the system architecture presented in the previous chapter, is currently being evaluated in three study phases (Figure 5.1). The first two study phases have been completed and the results [1] [2] are presented in this chapter, while the third study phase is currently on-going at the time of writing. Safety, usability and acceptability have been the main focus in the first two trial phases, while the last study phase evaluates the clinical efficacy of the system. The three phases of the study are structured as follows:

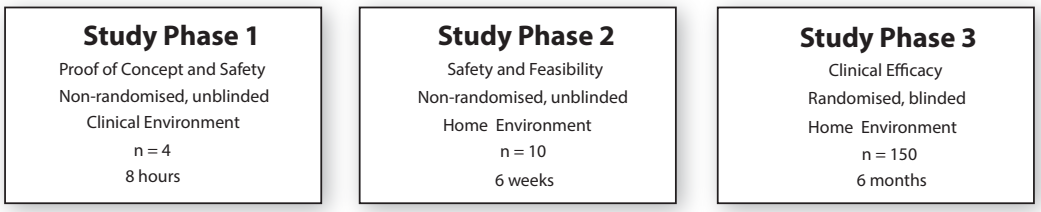

Figure 5.1: Study phases to evaluate safety, feasibility and efficacy of the presented 'Advanced Bolus Calculator for Diabetes'

5.1 Clinical Evaluation of ABC4D - Study Phases

5.1.1 Study Phase 1 - Proof of Concept

Phase 1 was a clinical ambulatory 'run-in' study of one-month duration in a small group of people with T1D to register the individual's physiological variables influencing the glucose through the mobile interface and different monitoring devices (e.g. glucose meters and CGM systems). Safety was assessed by measuring post-prandial glucose for hypo- and hyperglycaemia for two meal challenges (i.e. breakfast and lunch) in a controlled clinical environment.

Study Outcome Primary outcome was the frequency and severity of post-prandial hypoglycaemic episodes within 2 hours of insulin administration.

5.1.2 Study Phase 2 - Safety and Feasibility

The objective of the second phase of the study was to demonstrate safety and technical proof of concept of the ABC4D system in the subject's own environment before commencing to a large-scale efficacy study. Ten adults with T1D on multiple daily injections have been recruited for this study phase. As the number of participants was small, the study was not randomised and there was no comparison or control group. The sample size was comparable to other technology transfer studies and aimed to provide robust clinical validation and safety data. The study was not powered to show a change in the primary or secondary outcomes compared with usual care but is an assessment of a new technology.

Study Outcome Primary outcome was the frequency and severity of post-prandial (0-4 hours) hypoglyaemica, while secondary outcomes included post-prandial glucose at 60 and 120 minutes, post-prandial area-under-curve (AUC) at 120 minutes, glycaemic risk indices and glycaemic variability.

5.1.3 Study Phase 3 - Clinical Efficacy

The last phase of the study is currently ongoing and includes a large cohort of subjects with T1D over 6 months to test the clinical efficacy of ABC4D. In contrast to the first two study phases, this is a randomised study with an intervention group and a control group. The intervention group uses the ABC4D patient platform where the implemented CBR algorithm adapts the insulin therapy over time. Subjects are blinded to which group they belong to. Participants in the control group use the same ABC4D platform for requesting insulin recommendations. However, the CBR learning algorithm has been disabled, thus the software acts as a standard bolus calculator. The reason for introducing a control group is based on the hypothesis that the use of CGM alone and an electronic logbook can already lead to improvements in glycaemic control. Also, the Hawthorne effect (alteration of the behaviour of participants when being observed by a study team) can be eliminated as the improvement would be noticeable in both study groups. In order to estimate the number of participants needed to demonstrate significant changes in outcomes, a power calculation has been performed. The calculation was based on a population mean HbA1c of 7.9% with a standard deviation of 1.1. Results showed that 150 subjects with T1D (75 in each study group) are required to demonstrate an HbA1c difference of 0.6% with an alpha level of 0.05 and 90% power (two-tailed). In contrast to the first two study phases, both people on multiple daily injections and insulin pump therapy are allowed to participate in the study.

Study Outcome The primary endpoint of the study will be changes in HbA1c at the end of the 6 month period. Secondary outcomes will include changes in HbA1c after 3 months, glucose variability, fasting glucose, weight, 24-hour insulin requirement and frequency and severity of hypoglycaemia

5.2 Study Phase 1 - Proof of Concept and Safety in Clinical Environment

The trial was designed to demonstrate safety of ABC4D when used for two meals consumed at the clinical research unit at the NIHR/Wellcome Trust Imperial Clinical Research Facility. Further objectives were to get initial feedback from participants using the system through a non-validated questionnaire and to use collected data for the development of the clinical revision platform.

5.2.1 Participants

Four people with T1D (3 female and 1 male, with an average age of 38±18 years and duration of diabetes of 14±12 years) participated in the first evaluation phase of ABC4D. All study participants have had structured diabetes education in the past.

5.2.2 Study Protocol

Participants were advised to take their basal insulin as normal leading up to the study day. They attended the research facility fasting at 08:00 with a standardised breakfast (40g) given at 08:30 and a standardised lunch (50g) at 12:30. After a short induction to the software at the beginning of the trial, the participants estimated the amount of carbohydrates and calculated the insulin bolus dose for each meal using the ABC4D smartphone platform and delivered the proposed insulin subcutaneously (Novorapid or Humalog) in the anterior abdominal wall, immediately before the meal. Participants were closely supervised by the study team. Throughout the study period (08:30-16.30) venous blood was sampled every 15 minutes during the first 2 hours after each meal and every 30 minutes for the remaining time. Blood samples were analysed immediately for glucose concentration using a glucose analyser YSI 2300 (Yellow Springs Instrument, Yellow Springs, OH, USA). If signs of hypoglycaemic episodes appeared at any stage, the ABC4D study would have been terminated. After 8 hours, participants could leave the unit and continue with their usual insulin treatment. Before leaving, each study participant was asked to complete a usability and acceptability questionnaire.

5.2.3 ABC4D System

Only the ABC4D patient smartphone platform (ABC4D-PSP) was used for this first study phase. As ABC4D-PSP was used by participants only for two meals, there was no case revision performed. However, the collected data was used as a basis for the development of the ABC4D clinical revision platform (ABC4D-CRP), which was used in the next study phase.

5.2.4 Results

All four participants completed phase 1 of the study. No episodes of hypoglycaemia (<3.9 mM/l) or technical (software) faults occurred during this trial visit. All insulin dose recommendations were accepted by the study participants. Figure 5.2 shows the average post-prandial glucose concentration sampled with the YSI 2300 glucose analyser. Administered insulin was 5.5 ± 2.5 Units and 4 ± 1 Units for breakfast and lunch, respectively. Lowest recorded glucose levels were 5.4 ± 1.5 mM/l after breakfast and 10 ±2.4 mM/l after lunch. The higher post-prandial glucose excursion for lunch may be due to a conservative insulin dosing regime and a slight underestimation of the carbohydrate content 47±2.5g (50g exact). The estimation of carbohydrate amount for breakfast was 40±4g.

5.2.5 Conclusions From Study Phase 1

This was the first time the ABC4D patient smartphone platform was used by people with diabetes. The aim was to learn how the user interacted with the system and get further user feedback. Provided insulin recommendations were safe and did not result in low post-prandial glucose levels. All data (i.e. glucose levels, carbohydrates and insulin dose) was stored locally on the phone and has been used to build onto the clinical revision platform needed for the next study visit. Study participants were free to decline the advice if they did not feel comfortable with the proposed insulin dose, however, all proposed insulin advice were accepted. The high acceptance rate of insulin recommendations can be contributed to the 'safe' study environment and a conservative initial tuning of the cases but will be further evaluated in the next study phase.

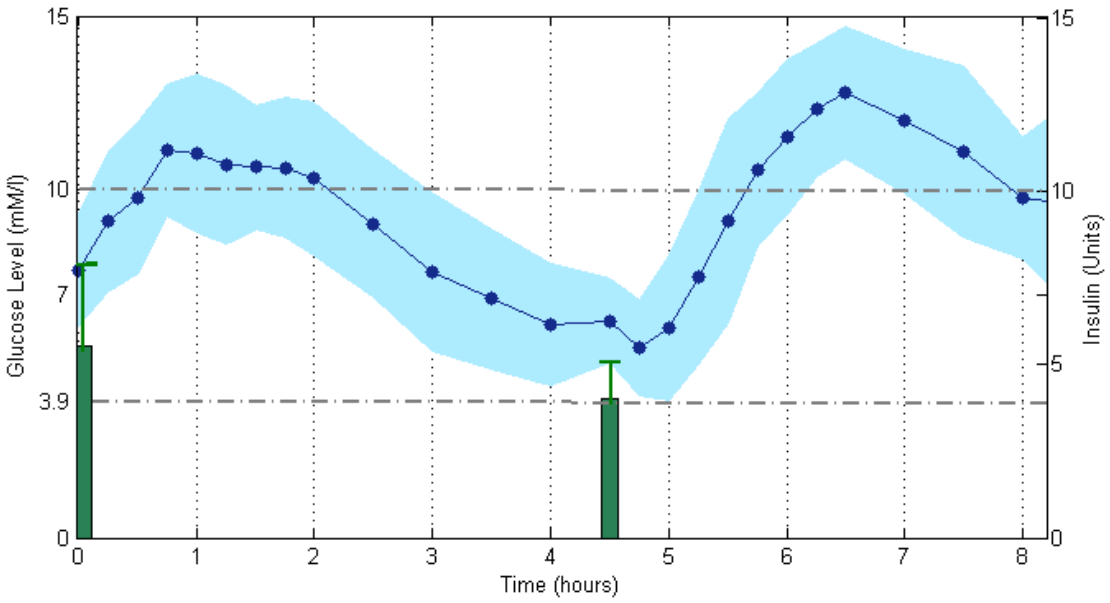

Figure 5.2: Mean glucose concentration (n=4) measured by the YSI 2300 analyser (blue dots) and standard deviation, with insulin (green bars) being delivered for breakfast and lunch.

5.3 Study Phase 2 - Safety and Feasibility in Home Setting

The second evaluation phase was a non-randomised open-label study where participants used the ABC4D for bolus calculations over a six week period in their normal environment. The research objective was to assess safety, feasibility and usability of the whole ABC4D system. Safety was assessed by measuring post-prandial glucose for hypo- and hyperglycaemia. Participants wore a retrospective CGM (Enlite sensor, iPro2, Medtronic) throughout the study. Recorded glucose data was downloaded every week allowing the research team to update the algorithm's case base with new cases from the preceding week. The algorithm automatically retrieved new cases, but adaptations were approved manually by a clinical expert.

5.3.1 Participants

Ten adult participants with T1D were recruited from the diabetes clinics at Imperial College Healthcare NHS Trust. Inclusion criteria were >18 years of age, diagnosis of T1D for >1 year, on MDI using a basal-bolus insulin regime, structured education completed, HbA1c

<86mmol/mol and no history of severe hypoglycaemia (defined as needing 3rd party assistance) in the previous year. Exclusion criteria included recurrent severe hypoglycaemia, pregnancy, breastfeeding, enrolled in other clinical trials, active malignancy or under investigation for malignancy, Addisons Disease, gastroparesis, autonomic neuropathy, concomitant use of GLP-1 analogues and gliptins, visual impairment and reduced manual dexterity. Informed written consent was obtained. As part of screening, participants underwent one week of blinded CGM and their insulin settings (ICR, ISF and basal insulin dose) reviewed by the study team. All participants were provided with a half-unit pen (Echo pen (Novo Nordisk) for insulin aspart, the Junior Star (Sanofi) for insulin glulisine or the Humapen Luxura HD (Lilly) for insulin lispro) for their rapid-acting insulin injections as the insulin bolus advice is rounded to the nearest half unit.

5.3.2 Study Protocol

Participants attended the clinical research facility on day 1 of the study and the iPro2 CGM (Medtronic) was inserted according to manufacturers instructions. The ABC4D patient smartphone platform was initialised with three basic cases (i.e. breakfast, lunch and dinner) with the existing ICR as a solution. People participating in the study were given instructions to perform blood glucose measurements fasting, pre-meal and pre-bed. They were also encouraged to avoid correction boluses for 2 hours post-meal unless clinically indicated (i.e. blood glucose >15mM/l or ketosis). An ABC4D user guide, outlining how to enter the data in the app and how to use the logbook feature, was given to all participants. Participants then attended the clinical research facility at the end of each week over the next 6 weeks for the revision of the case-base.

5.3.3 ABC4D System

Selection of Case Parameters

Because of the short duration of the presented study, only a limited number of case parameters were selected. Criteria for case parameters to be included were the frequency of usage and the impact on glucose control. The final choice on which parameters to include was made based on discussions with the medical study team and feedback from the focus group meetings (see Chapter 4.4). Chosen case parameters were: time of meal, meal absorption rate, physical exercise, alcohol consumption and hyperglycemia.

Initialisation and Parameter Weighting

At the start of the study, the case base was initialised with three cases for each state of the context 'time of day' (i.e. breakfast, lunch, dinner). Initial solutions of the cases were the ICRs, which participants used prior to the study and were optimised by a clinical expert based on data collected from a run-in period of one week. Also, the amount of basal insulin was revised before the start of the study. The weights for each parameter were pre-defined as equal (i.e. 1) and remained static throughout the duration of the pilot study.

Case Retrieval

In this phase of ABCD, cases were retrieved via the k-nearest neighbour (k-NN) classifier to find the most similar case when compared to the current meal scenario. Only the solution of the closest case has been considered for the retrieval step (i.e. k=1). The similarity of the best match was calculated by the weighted arithmetic mean of the distance between the parameters of the current situation and those of the retrieved case.

Case Revision

At each study visit, data from the smartphone ABC4D application was transferred to a study desktop computer and the CGM data was uploaded to the Medtronic Carelink iPro software. All data was then imported and synchronised using the clinical revision platform allowing visualisation of glucose data and the corresponding logbook data for all meal scenarios where ABC4D was used, as well as information about the applied case solutions. Finally, each proposed adaptation to the case solution was manually approved prior to updating the case base in the smartphone ABC4D application.

Cases were not included for revision if any of the following events occurred: a post-prandial snack/meal ingested within 4 hours, correction bolus taken within 4 hours or insufficient CGM data (minimum requirement was 6 hours of CGM data post-meal). However, if a snack/meal coincided with glucose levels of <3.9mmol/l within 4-hours of the meal bolus it was assumed this was an intervention for correction of hypoglycaemia and therefore included for revision. Scenarios, where participants declined the ABC4D bolus recommendation were included for revision.

Case Retention

In order to ensure safety, a case needs to be revised at least twice in order for the case solution to be adapted. The final solution of the case is then calculated based on the average of all adaptations.

Safety constraints

Safety constraints included saturation of the case adaptation to ± 20% of the existing ICR and a maximum threshold for any recommended insulin dose. IOB was pre-set to 5 hours for all participants and was not changed. Only correction boluses were considered in the computation of IOB to avoid conservative insulin recommendations in the event of multiple meals close together. The case base was not accessible to the participant at any point. While the clinical revision platform automatically recognised if a case adaptation should be approved or declined, for safety, each case adaptation was manually approved by the study team. Each week the CGM sensor (Enlite, Medtronic) was then replaced. All CGM data was blinded to the participants throughout the study.

5.3.4 A Case Study

Figure 5.3 shows the evolution of adaptations to the solution of a single case (breakfast, medium absorption, no alcohol or exercise) for one study participant. Each graph represents one study week and shows an overlay of pre- and postprandial glucose levels for chosen breakfast scenarios, which were similar in size and where the user accepted the proposed insulin dose. The case solutions (i.e. ICRs) used for insulin recommendations are shown at the top of the graph. Week 1 started with the optimised ICR value after the run-in period by the clinician (i.e. ICR = 30 g/U). If the minimum post-prandial glucose level was outside the green target range, then the metric implemented in the revision step of the CBR cycle calculated a new case solution based on the difference to glucose setpoint (here 6.5 mM/l). In this example, it can be seen that the ICR values were increased during each study week, converging to a more conservative insulin therapy for this case. The proposed insulin dose for a similar sized meal was 3.5 units and 2 units in the first and last study week, respectively. While one scenario in week 5 showed the post-prandial glucose minimum in target, the overall case solution was still increased as the final case solution is calculated based on the average of individual case adaptations.

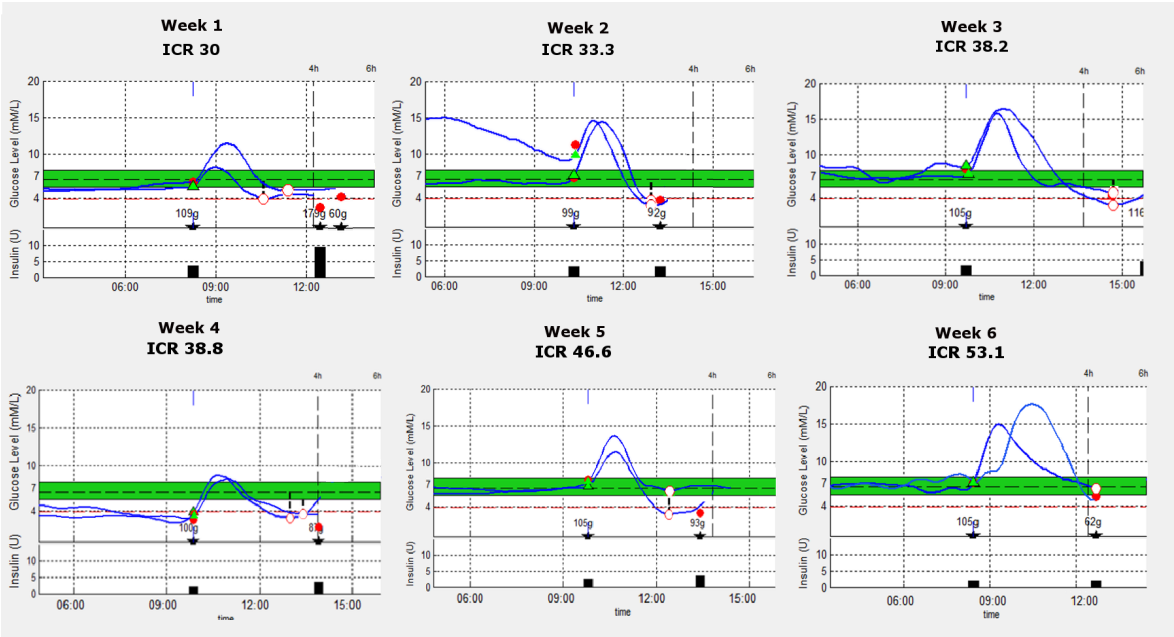

Figure 5.3: Evolution of changes to the insulin-carbohydrate ratio (ICR) for a breakfast case after each study week. Each graph shows glucose levels for two similar breakfast scenarios (above) and the amount of administered insulin proposed by ABC4D (below). The blue line represents the glucose concentration measured with a continuous glucose monitor and is displayed until 6 hours after the meal or until a new meal scenario occurs. Red dots are glucose measurements from a blood glucose meter, while white circles represent the post-prandial glucose minima used for adaptation.

5.3.5 Results

Ten adults with a mean (SD) age 47 (17), duration of diabetes 25 (16) and HbA1C 68(16) mmol/mol (8.4 (1.5) %) completed the study. The primary outcome was the number of post-prandial hypoglycaemic (<3.9mmol/l) episodes. Secondary outcomes were percentage time in glucose target range (3.9 - 10.0mmol/l), euglycaemia (3.9 - 7.8mmol/l), hypoglycaemia (<3.9 mmol/l) and hyperglycaemia (>10.0 mmol/l), mean sensor glucose, post-prandial area-under-the-curve (AUC) and glycaemic risk measures of low blood glucose index (LBGI) and high blood glucose index (HBGI). Overall glycaemic outcomes from week 1 were compared to week 6 using the paired t-test (for normally distributed data) or the Wilcoxon matched-pairs signed-rank test (non-normally distributed data). The number of created cases has been analysed as well as the individual effect of parameters exercise and alcohol on the case solution (ICR) and post-prandial glucose control. During the study, retrospective CGM data was used for case revision, thus information about the glucose trend was not

available at the time of the meal. As the final study phase will incorporate real-time CGM, glucose rate-of-change at mealtime could be used as a potential case parameter. With the retrospective glucose data available from the six-week study, we have evaluated the effect of glucose rate-of-change (ROC) before mealtime (15-0 min before) on the post-prandial glucose.

Primary and Secondary Glucose Outcomes The overall post-prandial glycaemic outcomes comparing week 1 to week 6 of the study are outlined in Table 5.1 a). Although not statistically significant, more than a two fold reduction in the number of post-prandial hypoglycaemic episodes was observed. There was no significant difference in area-under-the-curve (AUC) or mean post-prandial glucose. The mean (SD) number of post-prandial rescue carbohydrate required for hypoglycaemia was 0.7 (0.9) at week 6 compared with 1.8 (1.7) at baseline (p=0.06) and the number of postprandial correction boluses taken for hyperglycaemia was 0.6 (0.8) versus 0.1 (0.3) (P=0.06), in week 1 and week 6 respectively. The overall changes in percentage time spent in target range, hypo- and hyperglycaemia, mean glucose and LBGI and HBGI are outlined in 5.1 b). The small reduction in hypo- and hyperglycaemia did not reach statistical significance. No episodes of severe hypoglycaemia requiring third party assistance occurred during the study.

Changes in Insulin-Carbohydrate-Ratios Table 5.2 shows the mean change (week 1 vs. week 6) in ICRs of cases used for breakfast, lunch and dinner, as well as for cases that include parameters alcohol, exercise and hyperglycaemia. Parameter meal absorption rate was not included in this analysis because of its little usage. Cases including only exercise or alcohol yield less insulin delivery at the end of the study compared to cases without the parameter. The resulting post-prandial outcome (30min-6 hours after meal) showed a slight reduction in the number of hypoglycaemic events (<3.9 mM/l) per participant for cases with parameter alcohol and exercise in the final three weeks of the study. Although presented changes are not statistically significant, the trend to reduce hypoglycaemia indicates the importance of analysed case parameters. For cases, where blood glucose levels were high at meal-time (case parameter hyperglycaemia), the mean ICR was slightly reduced compared to lower glucose levels, thus more insulin was proposed towards the end of the study. In spite of the insulin therapy being more aggressive, this did not negatively affect the number of hypoglycaemic events with 0.4±0.5 and 0.2±0.4 events in week 1-3 and week 4-6, respectively.

Table 5.1: a) Post-prandial glycaemic outcomes (median (IQR)) in week 1 and week 6, b) Changes in glycaemic outcomes between week 1 and week 6 (n=10). Data are expressed as median (IQR). The p-values are calculated for differences between week 1 and week 6.

a) Postprandial glucose	**Week 1**	**Week 6**	**p Value**
Hypoglycaemic episodes within 4 hour post-prandially	3.5(1.7-5.2)	1 (0-5)	0.2
Hypoglycaemic episodes within 6 hour post-prandially	4.5(2.0-8.2)	2 (0.5-6.5)	0.17
Post-prandial AUC 2hrs	1118 (996-1292)	1117 (1091-1425)	0.5
Post-prandial AUC 4hrs	2095 (1860-2559)	2080 (1927-2597)	0.7
Post-prandial glucose 60 min (mM/l)	9.6 (8.1-10.3)	8.6 (8.4-12.4)	0.7
Post-prandial glucose 120 min (mM/l)	9.3 (7.0-10.6)	8.6 (7.6-10.9)	0.5

b) Overall Glucose	**Week 1**	**Week 6**	**p Value**
% time spent in <2.8 mM/l	0.8 (0.0-3.6)	0.4 (0.0 - 3.5)	0.5
<3.3 mM/l	2.3 (0.1-5.7)	1.2 (0.3 - 5.9)	0.7
<3.9 mM/l	5.0 (0.7-9.2)	3.6 (0.6 - 9.8)	0.7
3.9 - 7.8 mM/l	35.5 (25.7-40.7)	39.8 (29.1 - 46.7)	0.8
3.9 - 10 mM/l	55.0 (50.1-56.7)	60.9 (46.5 - 72.2)	0.9
>10 mM/l	40.5 (26.3 - 47.3)	36.9 (18.0 - 43.1)	0.5
>15 mM/l	9.3 (2.8 - 15.3)	5.5 (2.1 -19.3)	0.8
Mean Glucose (mM/l)	9.5 (8.3 - 10)	9.1 (8.1 - 10.2)	0.7
LBGI	4.3 (2.8-8.0)	2.8 (2.3-8.6)	0.9
HBGI	12.9 (8.6-14.6)	11.9 (5.8 - 17.7)	0.7

Number of Cases Figure 5.4 shows the growth of the case base through the six-week pilot study. On average, 11.6±3.5 cases were created by the end of the study which is half of the maximum possible number of cases (i.e. 24). The majority of cases was created within the first week of use. Throughout the rest of the study the case base grew steadily, but fewer cases were created compared to the initial week.

Glucose Rate of Change A total of 649 meal scenarios have been analysed. Glucose rate of change (ROC) was categorised into three trends (falling, stable or rising). The effect of ROC trends on the minimum post-prandial (2-6 hours) glucose concentration was evaluated. For the majority of analyzed meals (53.9%), glucose ROC was stable (-0.5 mg.dl-1.min-1 to <+0.5 mg.dl-1.min-1) at mealtime, for 29.6% above +0.5 mg.dl-1.min-1 and for 16.5% below -0.5 mg.dl-1.min-1, respectively. For 7.5% of meals with a falling glucose

Table 5.2: Evolution of case solutions (ICRs) of cases with parameters alcohol, exercise and hyperglycaemia after the six-week study (above) and number of hypoglycaemic events for weeks 1-3 and 4-6 for used case parameter (below)

a) Changes in ICR	**Insulin-Carb.-Ratio (1U/g)**		
Time of Day	**Week 1**	**Week 6**	**p Value**
Breakfast	12.2 ± 7.0	15.3 ± 14.1	0.5
Lunch	11.3 ± 3.4	13.2 ± 6.2	0.4
Dinner	10.8 ± 3.3	10.8 ± 3.0	0.9
Parameter			
Alcohol	10.5 ± 3.6	11.1 ± 4.1	0.2
Exercise	13.1 ± 3.1	14.6 ± 8.0	0.4
Hyperglycaemia	12.5 ± 3.0	10.6 ± 4.1	0.1

b) Hypogl. (<3.9 mM/l)	**Nº Hypoglycaemic Events**		
Parameter	**Weeks 1-3**	**Weeks 4-6**	**p Value**
Alcohol	0.4± 0.1	0.3 ± 0.0	0.7
Exercise	0.9 ± 0.1	0.5 ± 0.1	0.2
Hyperglycaemia	0.4 ± 0.5	0.2 ± 0.4	0.4

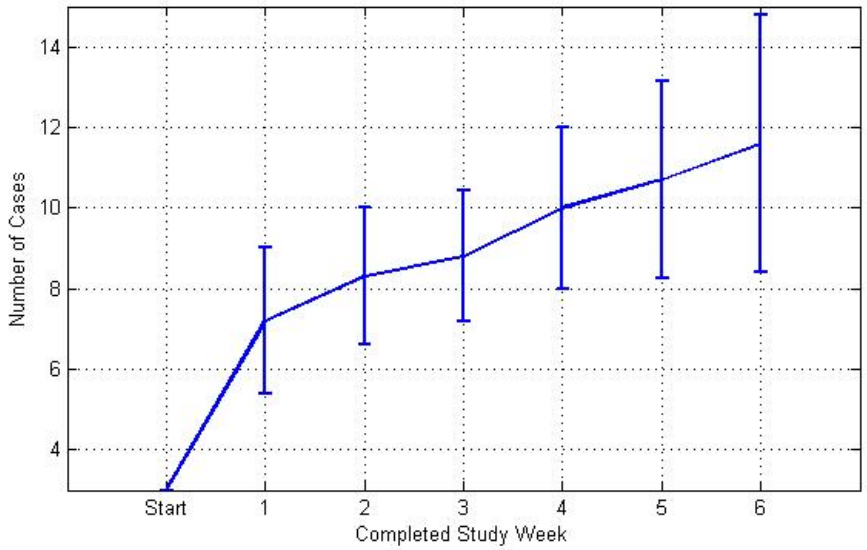

Figure 5.4: Graph showing number of cases (mean ± standard deviation) in the case base for each study week.

trend, active insulin from previous insulin administrations was recorded. The post-prandial minimum mean glucose levels were 106±52 mg.dl-1, 115±55 mg.dl-1, 128±56 mg.dl-1 for falling, stable and rising glucose trends at meal times, respectively. The reported difference of minimum glucose levels for rising and stable glucose ROC was significant with p=0.01.

5.3.6 Conclusions From Study Phase 2

In the six-week study, the ABC4D adaptive bolus calculator provided safe insulin recommendations and maintains glycaemic control with a trend suggesting improvement in post-prandial glucose outcomes. Observed changes of the insulin-carbohydrate ratios for cases including exercise and alcohol information give a positive indication of the clinical effectiveness of parameters exercise and alcohol. Retrospective analyses of the results show that including information about glucose rate-of-change for a real-time continuous glucose monitor could potentially improve glycemic control.

5.4 Study Phase 3 - Large Scale Randomised Controlled Efficacy Study

The final study phase is a large-scale randomised controlled blinded study where participants use the ABC4D patient smartphone platform over a period of 6 months. The aim of the study is to evaluate the efficacy of ABC4D with real-time CGM (RT-CGM) compared to state-of-the-art care with RT-CGM. State-of-the-art care has been defined as MDI or CSII therapy while using a standard bolus calculator implemented in insulin pumps or glucose meters to calculate the amount of insulin for meals.

5.4.1 Study Design

In order to provide a fair comparison, the study is blinded to the participants and both study groups (intervention and control) use the ABC4D patient smartphone platform to calculate the insulin dose for meals. While the ABC4D software in the intervention group implements the CBR algorithm with the capability to automatically adapt the insulin therapy, the ABC4D software used by people in the control group acts as a standard bolus calculator (without CBR adaptation). During the study, all participants have continuous access to real-time CGM data (Dexcom G5), which shows current and past glucose data on the phone.

After a run-in period of one month to allow users to accustom to the RT-CGM, participants are randomised into either the intervention or control group. While the availability of real-time CGM alone is anticipated to show improvements in the glycaemic control, this benefit will be also noticeable in the control group. In order to ensure safety for all study participants, follow-up visits are scheduled at one and three months after study start where a clinician can manually perform changes to the insulin therapy. This is particularly of importance for the control group as here the insulin-carbohydrate ratio is not adjusted by the CBR algorithm. The primary outcome in the last study phase is the change in HbA1c after 6 months.

5.4.2 Case Parameters

All case parameters from the second phase have been included. Because of the longer study duration, more parameters have been added, some of which occur less frequent and were therefore omitted in the previous study phase (e.g. illness or hormonal cycle). Additionally, based on the results of the analysis from the second phase (see section 5.3.5) and the availability of real-time CGM, parameter 'glucose rate-of-change' was introduced. Table 5.3 shows the list of case parameters included in the study and their discretised states. All participants were asked at the beginning of the study to define a personalised parameter, which can then be selected among the pre-defined parameters on the main screen of the ABC4D smartphone application.

5.4.3 Case Revision

All used cases are revised at the end of each week throughout the study. In the beginning, all individual case adaptations are approved by the study team (as in study phase 2) before moving to a semi-automatic process where only a summary of performed adaptations requires approval. Update of case adaptations is performed via email, where an encrypted file sent as an attachment synchronises the case base on the patient platform. A confirmation of the successful update is sent back to the research team. The end of the study envisages fully automated case adaptations with the research team being informed in advance of planned therapy changes with the potential to overwrite or decline proposed changes. The use of RT-CGM also allows glucose data of study participants to be synchronised with a web-based diabetes management system in real-time. This provides remote supervision and prevents any potential system faults despite safety measures.

Table 5.3: List of case parameters used for the third study phase, their discrete states and default values

Parameters	Discrete States	Default State
Time of Day	Breakfast, Lunch, Dinner	-
Exercise	None/Moderate/Intense	None
Alcohol	None/Little/Some	None
Stress	None/Yes	None
Illness	None/Yes	None
Hormonal Effect (only for female participants)	None/Low Glucose/High Glucose	None
Glucose Rate of Change	Not Available/Falling/ Stable/Rising	Not Available
Meal Absorption	Slow/Medium/Fast	Medium
High Fat Content	No/Yes	No
Hyperglycemia (>7.8 mM/l	No/Yes	-
Personalised Parameter	No/Yes	No

5.4.4 Preliminary Results

At the time of writing, four participants have completed the run-in phase of one month and have been randomised into either control (n=2) or intervention (n=2) study group.

5.4.5 Cases in Case Base

The average number of cases in the case base of the two participants in the intervention group was 66 ± 25 after one month. This is significantly larger than the number of cases observed in the second study phase after the same time interval (10 ± 2), which is due to the greater selection of implemented case parameters.

5.4.6 Personalised Parameter

Before the start of the study, participants have been asked to name a daily life scenario that, in their experiences, causes changes to the glucose levels and which they would like to see integrated within the ABC4D system. Following parameters have been chosen by the four study participants as their 'personal' parameter after discussions with the study team:

- Eating Out
- Cooking
- Lack of Sleep
- Working Late

The rationale behind the first two parameters (eating out and cooking) is that the mentioned scenarios provide a challenge to estimate the correct amount of carbohydrates. While one participant struggles to analyse the meal content when eating in a restaurant, another person stated that tasting the food during cooking may be the reason for higher glucose levels during this process. Other study participants named lack of sleep and late night work as a reason for glucose levels to be out of range.

5.5 Discussion

After testing the performance of the developed DSS in simulations in the previous chapter, the clinical evaluation aims to demonstrate the effectiveness of the system under real-life conditions. Initial study phases focused on the safety of the insulin advisory system. No severe hypoglycaemic events occurred after receiving an insulin dosing advice during the first two study phases. The performance of the system under real-life conditions was first tested in the second trial phase where ten study participants continuously used ABC4D for meal insulin dosing advice for six weeks. Results of this study suggested a trend to reduce hypoglycaemia (both post-prandial and overall) and improve time in target (3.9-10mmol/l) with no increase in hyperglycaemia. However, the differences observed between week 1 and week 6 did not reach statistical significance. The reason for this can be contributed to the small population size of the study, which was not powered. Additionally, only a limited number of case parameters have been considered in phase 2 and omitted factors with impact on the glucose control could result in continuous adaptation of case solutions. Figure 5.5 shows the glucose control over 24 hours for an individual study participant during the second trial phase, comparing the initial study week (purple) with subsequent study weeks (green) after performed adaptation. It can be seen that the glucose control already improved in the third study week, while the fourth week showed increased variations in glucose levels during the night and morning as well as hypoglycaemia in the fifth study week due to changes in the subject's environment or other unaccounted parameters. Therefore, the number of

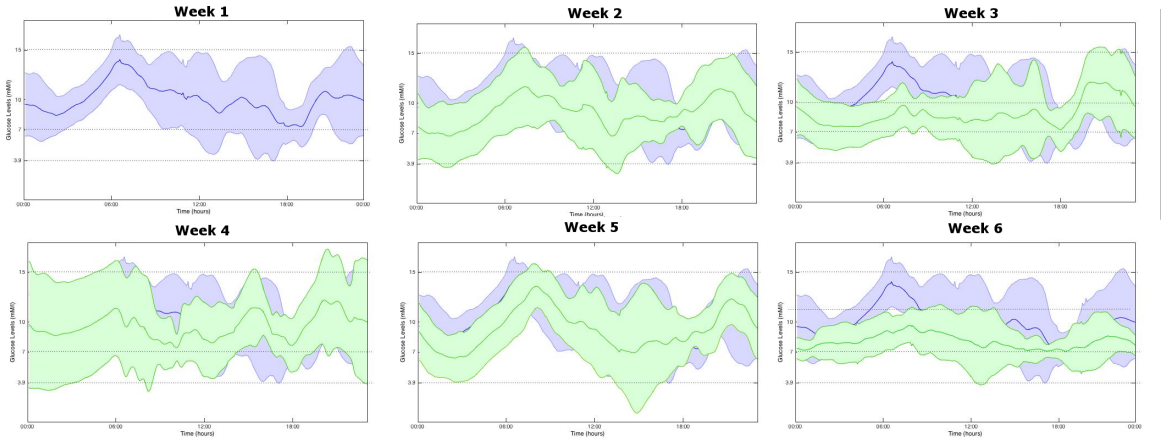

Figure 5.5: Evolution of average glucose levels (± SD) during 24 hours comparing the initial week (purple) with each subsequent week (green).

parameters was increased for the last study phase from five to eleven, aiming to capture more factors affecting the glucose control. Interim analysis performed during the third study phase showed that the inclusion of additional parameters results in a much larger number of cases retained in the case base. In order to ensure safety, all case adaptations were approved by the study team in the first two study phases. To reduce the workload, a more automated revision process has been implemented for the third study phase. As a safety feature, a web-based diabetes management platform provides real-time glucose data for remote supervision.

5.6 Conclusion

This chapter discussed the clinical evaluation of the 'Advanced Bolus Calculator for Diabetes' system in three phases. The first study demonstrated proof of concept in a clinical environment, while the second study evaluated safety and feasibility of the system over six weeks in ten people with diabetes in their normal environment. As the second study was a non-randomised trial without a control group, no major conclusions can be drawn from the glycaemic outcomes measured. However, the safety of the overall system was demonstrated and initial results are encouraging, indicating improvements in glycemic control, which is currently being further evaluated in the third study.

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Chapter 6

Outlook and Discussion

6.1 Future Work and Outlook

This section provides an outlook on future work and technologies to further enhance the presented insulin advisory platform. It further includes the author's vision about current technologies that could be integrated into the ABC4D system to improve its usability, performance and adherence.

6.1.1 Case-based Reasoning Algorithm: Additional Features

Case Parameters

Initial results from the second phase of clinical evaluations confirmed the clinical importance of the parameters mentioned in the literature, such as physical exercise and alcohol consumption, which is consistent with the views and perceptions of participants obtained through a questionnaire on the system's usability. Further parameters that could be integrated into the ABC4D system are listed in Appendix B. Future versions of ABC4D could allow clinicians to select case parameters that are most relevant to a patient through the clinical user interface while leaving out parameters that are not of relevance to the user. For instance, a person with T1D who does not drink alcohol could omit this parameter.

Case Retrieval Methods

The presented CBR algorithm in this thesis uses K-Nearest Neighbours (KNN) to find the most similar case in the case-base. However, there are several other similarity measurement metrics that can be found in the literature [1] and could be investigated (e.g. use of fuzzy logic case retrieval [2]).

In the presented clinical trials, case parameters are equally weighted for case retrieval. The reason for the inability to fine tune them was due to the lack of clinical data. With the realisation of longer clinical trials, it is possible to assign weights to parameters accordingly.

Case Adaptation Methods

Case adaptation is very domain specific and there is no universal method that can be applied. In the second phase of the clinical evaluation a rule-based method has been used to adapt the solution of a retrieved case to the current scenario (e.g. if retrieved solution corresponds to moderate exercise and current scenario has intense exercise, then the ICR is increased by 20%). Other adaptation techniques could be investigated [3].

Case Revision Methods

Although the current metric for case revision has been proven to be effective, both in silico and in vivo, other revision metrics exist that could be considered. For example, area-under-the-curve (AUC) below and above target range in a predefined time window (e.g. 4 hours post-prandially) could be used.

Additional Bolus Calculator Parameters

Current bolus calculator use following parameters: the insulin-carbohydrate ratio (ICR), the insulin sensitivity factor (ISF) and the insulin action time for insulin on-board estimation (IOB). Additional parameters could be taken into account if more information about the meal composition is available. For example, these parameters could be the type of bolus (square bolus, dual bolus, etc.). For insulin pump users, the reduction of basal insulin could be considered for physical exercise. Insulin action time for IOB calculations is currently considered as a constant parameter. However, it is possible to automatically adapt

the parameter based on the analysis of glucose excursions. The bolus calculator can also potentially incorporate an estimation of 'carbohydrates-on-board'.

Correction Bolus Recommendations

The insulin dosing decision support system presented in this thesis has been designed to recommend meal insulin boluses only. However, it could also be used for recommending correction boluses in between meals. If real-time CGM is available, the user could be automatically notified about the need for a correction bolus.

Carbohydrate and Exercise Recommendation

In addition to providing insulin recommendations, future versions of the system could incorporate carbohydrate recommendations for hypoglycaemia prevention and exercise recommendation for hyperglycaemia treatment (instead of a correction bolus). Real-time CGM would be required for this feature.

6.1.2 Technology Integration

Currently, the ABC4D patient software runs as a stand-alone application on a smartphone and does not communicate in real-time with any external device (e.g. glucose sensors or insulin pumps). The integration of ABC4D into a blood glucose reader would enable direct access to glucose readings. Alternatively, the insulin recommender can be implemented into the handset of an insulin pump, which would allow automatic delivery of insulin if recommendations are accepted by the user. In case the decision support tool is not integrated into a blood glucose meter or an insulin pump, then direct communication of ABC4D with these commercially available devices would enhance its usability. Blood glucose measurements can be sent from the meter to the ABC4D software and would therefore reduce manual user input. Interfacing ABC4D with a real-time CGM could also enable the user to receive predictive hypo- and hyperglycaemic alarms. Further methods to potentially enhance usability and performance of ABC4D are discussed now:

Automated Acquisition of Parameters (e.g. Exercise or Stress)

Several minimally intrusive activity monitors are currently available in the market (e.g. Fitbit, Inc., CA, USA). Integrating one of these activity monitors into ABC4D would allow automatic detection and quantifications of parameters such as exercise and psychological stress. This automation could significantly reduce the need for manual user input. It is important to remark that the precision of these devices does not need to be very high and only a rough estimation is sufficient (e.g. intense exercise for a short duration). In order to differentiate between physical activity and stress, concurrent sensors are needed. For example, a heart rate monitor might show an increase in heart rate but the accelerometer indicates no physical activity. This could be a sign of stress, but also could be due to a workout on a static bike if the accelerometer is worn on the wrist. A solution to this problem could be asking the user if the change in heart rate is stress related or if there was any kind of activity that was undetected by the accelerometer.

Web-based Platform for Automated Revision

Future work could also see the CBR revision algorithm implemented into a secured web-based platform to automate the revision process and enable remote access to the data for clinicians and patients. Clinicians could retrieve historical data and react to changes performed by the algorithm. Patients would have access to personal historical data and past insulin recommendations. The platform would also enable easier communication between the clinical team and the patients. Social media could potentially motivate users to adhere to the therapy by setting personal goals (e.g. percentage of time in target over a week) on the mobile app and sharing them online.

Interfacing with other Mobile Devices (e.g. Smartwatch)

Another way to enhance usability and promote interaction with the ABC4D patient platform is to utilise functionalities of other mobile devices, such as smartwatches. The ABC4D smartphone application can be paired and connected via Bluetooth to the smartwatch (e.g. Apple Watch, Apple Inc. or Moto 360, Motorola Mobility), which can access and synchronize the data from the smartphone application. The menu on the watch is controlled either via swipe or touch gestures. According to feedback from people with diabetes in focus group meetings, users would be interested in seeing past recommendations and glucose levels

on the watch or receive notifications and reminders. Sensors that are in-built within the watch (e.g. accelerometer, heart rate data) can be used to detect physical activity and stress. Figure 6.1 shows a prototype version of ABC4D interacting with a smartwatch for requesting insulin dose recommendations, which has been developed during this work [4]. The smartwatch displays glucose information that is synchronised via the smartphone and communicates with a CGM system in order to provide alarms if glucose levels are predicted to be out of target range.

Figure 6.1: Smartwatch version of the 'Advanced Bolus Calculator for Diabetes' communicating with the ABC4D patient smartphone platform and synchronising data from a CGM system.

Integration of a Meal Library

Next generations of ABC4D could be linked up with existing meal libraries, which contain detailed information about the composition of the meals. Alternatively, ABC4D users could create their own personalised meal library. The library can potentially be co-created personally or remotely with the help of a dietician in the set-up phase of the software. The integration of a meal library would allow consideration of parameters such as meal absorption, fat and protein content.

Integration with an Artificial Pancreas

Long-term research goals in diabetes management include the development of technologies such as the artificial pancreas, which intends to totally, or partially, remove the person with diabetes from the decision-making process so that insulin dosing can be calculated and administered with no user intervention. However, due to the slow pharmacodynamics of current insulin formulations, artificial pancreas systems still require pre-meal boluses to achieve good post-prandial glycaemic outcomes. Therefore ABC4D could potentially be integrated into an artificial pancreas for pre-meal insulin dosing.

6.2 Summary and Discussion

People with T1D rely on frequent glucose measurements and insulin injections in order to avoid long-term diabetes-related complications. Calculating how much insulin is required to bring glucose levels back to a target range is a complex task and the challenges involved have been outlined in this work.

From the user's perspective, the two main challenges are the estimation of the meal content and the time and effort needed to perform the insulin dose calculation (either mental arithmetic or typing into a calculator). Over- or underestimation of the carbohydrate amount is frequent and associated with higher daily blood glucose variability in people with T1D [5]. Newly diagnosed patients are encouraged to attend structured education, which involves carbohydrate counting, however, it has been reported that less than one percent of diagnosed people have undergone such training programme [6]. Providing support through technology by integrating meal databases or automatically estimating the meal content through image processing has been investigated, but the proposed methods are so far limited by practicality [7]. Another group proposed the use of a smartphone application that utilises content from a meal database to capture carbohydrate, lipid and protein content and therefore report better meal estimations [8].In order to support people with T1D with the second challenge (performing the insulin dosing calculations) diabetes technology devices such as blood glucose meters or insulin pumps have incorporated insulin bolus calculators for meals and correction boluses. Although bolus calculators rely on manual user input (e.g. amount of carbohydrates, blood glucose levels) and therefore may take up more time than mental arithmetic (or approximations), the clinical benefit of these simple tools has been

proven [9]. One reason for this is, apart from helping with arithmetic, that they often take into account the residual active insulin within the body and therefore propose less insulin shortly after meals. The calculations performed by standard bolus calculators are based on the patient's specific insulin-carbohydrate ratio (ICR) and insulin sensitivity factor (ISF).

From a clinical point of view, the greatest challenge is the optimal adjustment of these individual parameters (i.e. ICR and ISF), mostly because these factors vary during the day, are influenced by external factors e.g. exercise, stress and are also known to change over longer periods of time. It has been shown that, because of the dynamic nature of insulin therapy, frequent insulin dosing adjustments are required, not only to improve but to maintain glucose control [10]. At present, these parameters are re-adjusted when patients attend their diabetes clinic appointments. Insulin dose adjustments are made based on available glucose information e.g. HbA1c levels and blood glucose records. While these measures can help to assess the overall glucose profile, they do not provide information about fluctuations and the variability of the glucose data, most importantly hypoglycemic episodes. Continuous glucose monitoring can help to capture otherwise unnoticed hypoglycaemia and provide more detailed information to perform therapy adjustments. However, as the glucose data is reviewed retrospectively, it can be difficult to perform adequate therapy adjustments if clinical visits are scheduled infrequently [11]. For this reason, proposed therapy changes are kept mostly general (e.g. reduction of basal insulin or the total daily dose of insulin) and rarely include changes to daily life situations such stress, illness or exercise, all of which have an impact on the glucose regulatory system.

The research described in this thesis tries to tackle this challenge by proposing personalised insulin dosing support that is able to differentiate between the aforementioned daily life scenarios. It extends existing research of automatically adjusting the insulin therapy [11] [12], by individually adapting the ICRs for various scenarios that have an impact on glucose levels. The use of CBR for this application has been shown to be well suited as it enables these scenarios to be represented within cases inside a case base. It is important to note that the concept of CBR only tells us 'what' to do and not 'how' to do it. Therefore CBR should not be seen as a technology such as rule-based reasoning or neural networks, but rather as a methodology that can utilise any of the technologies from the artificial intelligence or control engineering domain [13]. Moreover, the proposed decision support system integrating CBR as a learning methodology incorporates techniques from multiple domains. For instance, the concept of k-nearest neighbour or other classification methods are commonly

used in machine learning, while the methods discussed to adjust ICR values are based on techniques derived from control engineering (e.g. iterative learning control). Although beyond the scope of this thesis, future work can further investigate different techniques for each step of the CBR process cycle (see Chapter 6.1).

One of the research objectives outlined in the first chapter was to identify parameters that can be incorporated into the insulin decision support system. Multiple factors that can be used as case parameters have been discussed in Chapter 3.1.1 and listed in Appendix B. Initial results of the second clinical study described in Chapter 5.2 were encouraging. However, in order to demonstrate a clinically significant improvement in glucose control (e.g. reduction in HbA1c), a longer study duration is needed as well as a greater selection of case parameters to cover all factors influencing the post-prandial glucose control.

When selecting case parameters, a decision must be made on how detailed or abstract case parameters are being defined. For practicality reasons, this research only uses observable factors (e.g. exercise, stress) to describe the effect on the glucose regulatory system. As these terms are very abstract and general, it shall be noted that parameters also could describe the effect on the glucose metabolism on a more detailed level. As an example, instead of using the general term 'stress' as a parameter, a more detailed term describing the effect of stress to the body could be used (e.g. a rise in stress hormones adrenaline or cortisol). For instance, cortisol plays a role in hepatic gluconeogenesis and increases insulin resistance [14]. The advantage of using cortisol instead of stress as a case parameter is that it can be linked to various other factors such as sleep deprivation and caffeine [15]. It would then be possible to define labels (e.g. stress, sleep deprivation) within the graphical user interface that can be selected by the user, which would eventually trigger the single case parameter 'high cortisol'. However, while this approach can potentially reduce the number of case parameters, the complexity may be increased when considering that selected labels (or a combination of labels, such as sleep deprivation and caffeine) have a different impact on cortisol levels.

One of the major advantages of using CBR as learning methodology for this application is that the exact effect (or the combination of effects) of a factor does not need to be known. The CBR based advisory system simply observes the final effect on the glucose level and sees all intermediate steps as a 'black-box'. This also enables the personalisation of the decision support system, one of the research objectives outlined in this thesis, by includ-

ing individual case parameters, which are chosen by the patient in the set-up phase of the insulin bolus advisor. In the last study phase, presented in Chapter 5, study participants could choose and name one parameter, which they think would describe an effect on their post-prandial glucose.

A crucial step in this research is the revision of used cases and the adaptation of case solutions (e.g. ICR). Several methods to assess the outcome of adaptations and to perform insulin dose adjustments have been proposed (see Chapters 3.5.1, 3.6.3 and 3.7), while the adaptation algorithm used during clinical studies has been validated in-silico [16] using the FDA-accepted T1D simulator.

After demonstrating the efficacy of the algorithms in simulations, a mobile and user-friendly system was designed that incorporates all presented techniques within the CBR process cycle. Acceptability and usability are key for the adoption of the insulin advisory system and the developed 'Advanced Bolus Calculator for Diabetes' (ABC4D) has been designed with patients being involved from the beginning of the design process through multiple focus group meetings as well as feedback obtained from questionnaires at the end of each study phase. The system implementation and usability of the presented methodology in clinical practice showed encouraging results evaluating the usability and acceptability for both patients and clinicians [17].

The implemented ABC4D system has been used in three phases of clinical evaluation, which have been described in Chapter 5. The objective of the first study was to assess the proof-of-concept in the clinical environment, while the second study phase evaluated the safety of ABC4D in the normal environment of the user over six weeks. As safety was a priority in this study, the research team approved therapy changes on a weekly basis. While frequent (e.g. weekly) manual revisions may not be practical for clinical adoption, presented results (Chapter 4.2.1) show that a more automated revision process is feasible and can achieve similar performance compared to clinical experts. By providing appropriate remote supervision, it is possible to minimise user intervention by a clinical expert. The automated revision process is currently under investigation in the third study phase evaluating the efficacy of ABC4D. This final study phase is a six-month randomised controlled blinded study and has been designed to evaluate the efficacy of ABC4D with a change in HbA1c at 6 months as the primary outcome.

In conclusion, the work outlined in this thesis demonstrated a novel personalised and adaptive insulin advisory system that aims to outperform state-of-the-art bolus calculators by providing more flexibility and individualised therapy. First results of clinical evaluation in the home environment of people with T1D showed that the developed ABC4D system is able to automatically perform safe insulin adjustments. It has been further demonstrated that the concept of CBR can be used as an intelligent tool to assist people in the decision making for insulin dosing therapy. A large randomised controlled study to prove the clinical efficacy is currently under way.

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Appendix A

Publications arising from this work

Journal Papers and Book Chapters

An Advanced Bolus Calculator for Type 1 Diabetes - P Pesl, P Herrero, M Reddy, M Xenou, N Oliver, P Georgiou - Book chapter: Wireless Medical Systems and Algorithms: Design and Applications; ISBN-10: 1498700764; Publisher: CRC Press - February 2016

An Advanced Bolus Calculator for Diabetes: System Architecture and Usability Results - P Pesl, P Herrero, M Reddy, M Xenou, N Oliver, D Johnston, C Toumazou, P Georgiou - Article: IEEE Journal for Biomedical and Health Informatics, vol.20, no.1, pp.11-17 01/2016

Case-Based Reasoning for Insulin Bolus Advice: Evaluation of Case Parameters used in a six-week Pilot Study - P Pesl, M Reddy, N Oliver, D Johnston, C Toumazou, P Herrero, P Georgiou - Article: Journal of Diabetes Science and Technology (Epub ahead of print), vol.99, 2016

Clinical Safety and Feasibility of the Advanced Bolus Calculator for Type 1 Diabetes (ABC4D) based on Case-based Reasoning: A 6-week Non-randomised Single-arm Pilot Study - M Reddy, P Pesl, M Xenou, C Toumazou, D Johnston, P Georgiou, P Herrero, N Oliver - Article: Diabetes Technologies and Treatment (Epub ahead of print), vol.99, 2016

Method for Automatic Adjustment of an Insulin Bolus Calculator: In Silico Robustness Evaluation under Intra-Day Variability - P Herrero, P Pesl, J Bondia, M Reddy, N Oliver, P Georgiou, C Toumazou - Article: Computer Methods and Programs in Biomedicine, vol. 119, no.1, pp.1-8 02/2016

Advanced Insulin Bolus Advisor Based on Run-To-Run Control and Case-Based Reasoning - P Herrero, P Pesl, M Reddy, N Oliver, P Georgiou, C Toumazou - Article: IEEE Journal of Biomedical and Health Informatics vol.19, no.3, pp.1087-96 05/2015

Conference Abstracts and Poster Presentations

Live Demonstration: Smartwatch Implementation of an Advanced Insulin Bolus Calculator for Diabetes - P Pesl, P Herrero, M Reddy, N Oliver, D Johnston, C Toumazou, P Georgiou - Conference: International Symposium on Circuits and Systems, Montreal, 05/2016

Performance of an Automated Revision Algorithm for a Personalised Bolus Advisory System - P Pesl, P Herrero, M Reddy, N Oliver, D Johnston, C Toumazou, P Georgiou - Conference: Diabetes Technology Meeting, Bethesda 10/2015

Clinical Pilot Study Assessing the Post-Prandial Outcome of An Advanced Bolus Calculator for Diabetes when used for Meals with Exercise and Alcohol - P Pesl, M Reddy, N Oliver, D Johnston, C Toumazou, P Herrero, P Georgiou - Conference: Diabetes Technology Meeting, Bethesda 10/2015

Clinical Safety Evaluation of an Advanced Bolus Calculator for Type 1 Diabetes (ABC4D) - M Reddy, P Pesl, M Xenou, N Jugnee, C Toumazou, D Johnston, P Georgiou, P Herrero, N Oliver - Conference: Advanced Technologies and Treatments for Diabetes 2015, Paris; 02/2015

Acceptability of a Patient and Clinical Platform of an Advanced Bolus Calculator for Type 1 Diabetes (ABC4D) P Pesl, P Herrero, M Reddy, M Xenou, N Jugnee, N Oliver, D Johnston, C Toumazou, P Georgiou - Conference: Advanced Technologies and Treatments for Diabetes, Paris 02/2015

Parameter Tuning of a Case-based Reasoning Algorithm for Insulin Dosing Decision Support - P Pesl, P Herrero, M Reddy, N Oliver, M El-Sharkawy, D Johnston, P Georgiou, C Toumazou - Conference: Advanced Technologies and Treatments for Diabetes, Paris 02/2013

Effect of Continuous Glucose Sensor Noise on Three Postprandial Metrics - P Pesl, P Herrero, M Reddy, N Oliver, M El-Sharkawy, D Johnston, P Georgiou, C Toumazou - Conference: Diabetes Technology Meeting, San Francisco 10/2013

Live demonstration: An advanced bolus calculator for diabetes management - A clinical and patient platform - P Pesl, P Herrero, M Reddy, N Oliver, D Johnston, C Toumazou, P Georgiou - Conference: IEEE Biomedical Circuits and Systems Conference, Lausanne pp.175-175, 22-24 Oct. 2014

Mobile-Based Architecture for an Insulin Dosing Decision Support System - P Pesl, P Georgiou, N Oliver, P Herrero, M El-Sharkawy, C Toumazou - Conference: Diabetes Technology Meeting 10/2011

Other Journal Publications

Metabolic Control With the Bio-inspired Artificial Pancreas in Adults With Type 1 Diabetes: A 24-Hour Randomized Controlled Crossover Study - M Reddy, P Herrero, M El-Sharkawy, P Pesl, N Jugnee, D Pavitt, IF Godsland, G Alberti, C Toumazou, DG Johnston, P Georgiou, N Oliver - Journal of Diabetes Science and Technologies (Epub ahead of print), 2015

Feasibility Study of a Bio-Inspired Artificial Pancreas in Adults with Type 1 Diabetes - M Reddy, P Herrero, M El-Sharkawy, P Pesl, N Jugnee, D Pavitt, [...], DG Johnston, P Georgiou, N Oliver - Diabetes Technology and Therapeutics, vol 16, no 9, 2014

Appendix B

Factors Affecting Glucose Levels

Table B.1: Effect of meal-related, biological and environmental parameters on the glucose regulatory system and the possible integration into an insulin decision support system. Bolus calculator parameters (e.g. carbohydrates) are not included.

Meal Factors	**Reported Effect**	**Parameter Acquisition**
Meal Absorption	Changes in insulin absorption [1]	Manual entry of meal type
Alcohol	Effect on insulin sensitivity and hepatic glucose output [2] Increased risk of hypoglycaemia next morning [3]	Type and quantity of alcohol need to be manually announced by user
Fat Content	Increased insulin resistance [4] Elevated glucose excursion [4] [5] Delayed rise in postprandial glucose [5]	Manually entered by retrieving information from packaged food items; Automatic acquisition through food databases
Protein Content	Increased glucose excursion, delayed rise in postprandial glucose and protective effect against hypoglycemia [5]	Manually entered by retrieving information from packaged food items; Automatic acquisition through food databases
Caffeine	Decrease in insulin sensitivity [6] Increase in post-prandial glucose (T2D) [7] Enhance the intensity of hypoglycemia warning symptoms (T1D) [8].	Manually entered by user

Biological Factors	**Reported Effect**	**Parameter Acquisition**
Time of Day	Changes in insulin sensitivity Increased insulin resistance in the morning ("dawn phenomena")	Automatic: Date and time can be obtained from system time
Illness Stress	Increase in the release of hormones such as cortisol and adrenaline, which reduce insulin sensitivity [9]	Manually announced by user
Hormonal Cycle	Changes in insulin sensitivity [10]	Manually announced by user
Sleep (lack of)	Impaired diabetes control Greater insulin resistance [11]	Automatic by sleep tracker and accelerometer or manually announced by user

Environmental/ Other Factors	**Reported Effect**	**Parameter Acquisition**
Exercise/ Physical Activity	Drop of basal plasma insulin concentration [12] Amplification of glucose uptake by the working tissue [13] Elevated hepatic glycogenolysis [14]	Manual: User enters type and duration of activity Automatic: Physical activity monitor Heart rate monitor Temperature sensor
Type of Insulin Injection Site	Insulin Absorption	Manually announced by user
Amount of insulin	Larger boluses remain longer in the body compared to smaller doses [15]	Manually announced by user
Temperature	Decrease of insulin absorption for rising temperatures [16]	Manually announced by user or automatic by temperature sensors

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Appendix C

ABC4D Questionnaire

Acceptability questionnaire

Advanced Bolus Calculator for Type 1 Diabetes (ABC4D)

The aim of this questionnaire is to assess how user-friendly and acceptable the ABC4D is for everyday use and how we can improve it. For each statement/question please circle the answer you agree with the most. Please use the space at the end of the questionnaire to write any additional comments you may have about the ABC4D.

Section 1: The ABC4D application

The main ABC4D main screen is clear and easy to read

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

The colour scheme used on the screen is acceptable

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

The symbols used for glucose, meal and exercise are acceptable

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

The size of the buttons on the touch-screen are acceptable

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Entering data on to the screen eg. capillary blood glucose (from fingerprick testing), amount of carbohydrate and/or exercise was straightforward

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

There were enough options to describe the type of meal (slow, medium and fast absorption) you were about to have

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

There were enough options to describe the type of exercise (intensity: none, medium, intense) that you had done or were about to do

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Having to enter alcohol intake with meals was inconvenient

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

It would be useful to be enter additional information such as type of alcohol(beer, wine, spirit) and type of exercise (running, aerobic class, weight training etc.)

Please specify:……..

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

The capillary blood glucose and meal information was saved and displayed in an easy-to - understand format

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

It was useful to be able to access the previous data of my capillary blood glucose and meals

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Overall, I would consider the ABC4D application user-friendly/easy to use

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Section 2: The ABC4D system as a whole (the ABC4D application running on a smartphone + continuous glucose monitoring on a regular basis)

The verbal instructions given on how to use the ABC4D system at the first consultation were sufficient

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

The written user guide on how to use the ABC4D was sufficient

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

The need for regular continuous glucose monitoring(having a glucose sensor attached for a week) to optimise the ABC4D algorithm was acceptable

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Using the ABC4D for insulin calculation was more time-consuming than using my standard method of bolus calculation

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Using the ABC4D for insulin bolus calculation caused more anxiety than when using my standard method of bolus calculation

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

I was/would be reluctant to use the ABC4D in the following situations:

While at work

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

When travelling abroad

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Before/after exercise

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

When eating out

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

When consuming alcohol

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

When feeling unwell

Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

I trusted the insulin dose recommendation generated by the ABC4D

None of time	Some of the time	Not sure	Most of the time	Each time

Prior to accepting the insulin dose recommendation by the ABC4D I used the feature to check how the advice was generated

None of time	Some of the time	Not sure	Most of the time	Each time

Overall, I would be happy to use the ABC4D system for bolus calculation

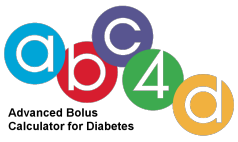
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

Please provide any additional comments that you feel will be useful for us to improve the ABC4D system:

Thank you very much for your time and comments!

Appendix D

ABC4D User Manuals



User Manual (Patient)

for

ABC4D Patient Smartphone Platform (ABC4D-PSP)

Software Version *v1.7*

Prepared by Peter Pesl

Center for Bio-Inspired Technology, Imperial College London

Table of Contents

1. Introduction

1.1 Intended Use of the Manual

This document explains the usage of the 'Advanced Bolus Calculator for Diabetes - Patient Smartphone Platform' (ABC4D-PSP) after it has been setup by the clinical expert. The main functionality of the ABC4D-PSP is to provide real-time personalised insulin bolus recommendations for people with type 1 diabetes (T1D). Further, the software can be used to record diabetes related events e.g. blood glucose (BG) meter readings, correction boluses or exercise. There are no restrictions on whether the person with T1D uses multiple daily injections or insulin pump therapy. The software works in combination with a continuous glucose monitor (CGM).

2. Instructions for Use

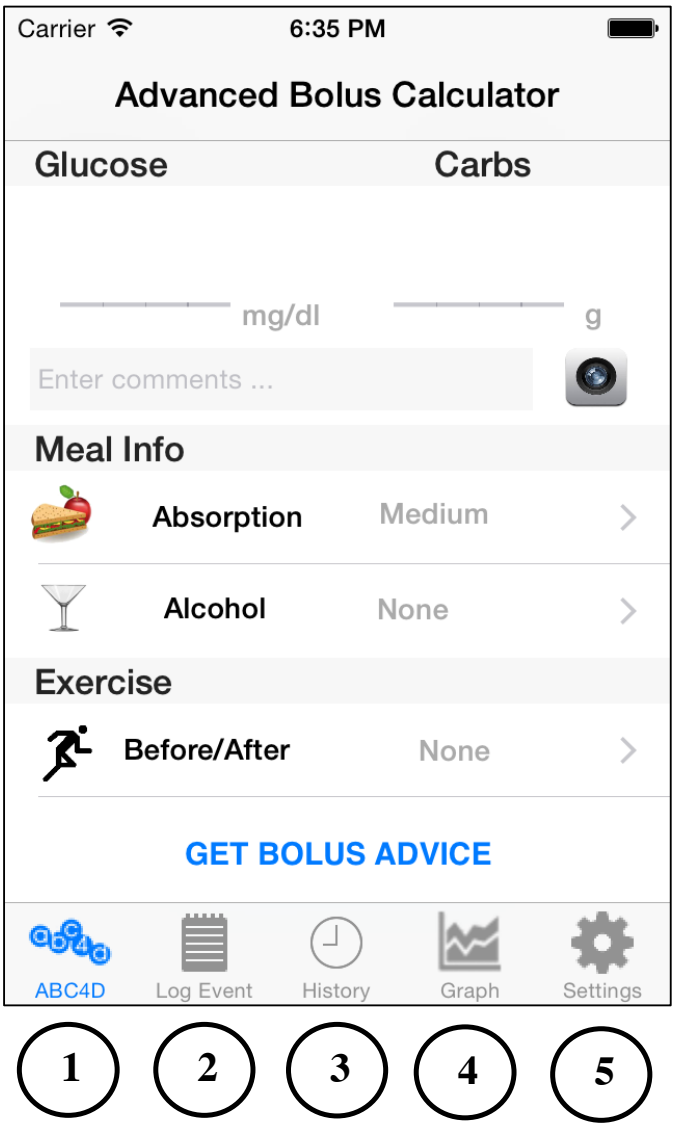
Note: This device should be operated in accordance with the instructions given by your clinician, even if your clinician's advice differs from the instructions outlined below.

2.1 Getting started:

Insulin dose advice can be requested through the ABC4D application on the smartphone.

Open the application on the smartphone by tabbing on the 'ABC4D' icon  on the home screen. The ABC4D logo appears while the application is loading. After successfully launching the software, the main user interface is shown on the screen (*Figure 1*).

Figure 1: Main Screen of ABC4D



1) ABC4D: Main screen that appears when app is opened - used to request insulin bolus advice

2) Log Event: Used to log additional diabetes events e.g. correction boluses, snacks, exercise

3) History: Displays all past recommendations and logbook events in a table

4) Graph: Analyses and shows blood glucose meter entries in a graph

5) Settings: General settings about the user and advanced settings for the clinical expert (password protected)

2.2 Input options for insulin dose recommendations:

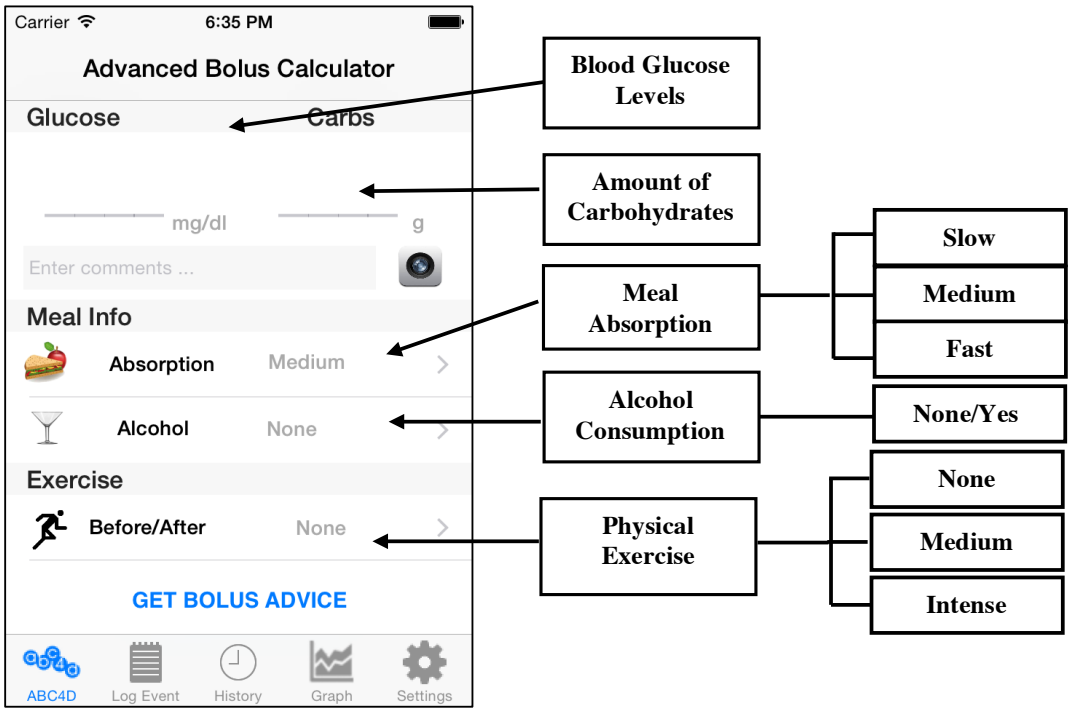
Once the ABC4D app has been started and the main screen appears, it is ready to give insulin bolus advice for meals. *Figure 2* shows the input options available for insulin dose recommendations. The following information is needed to receive an advice.

1) Blood Glucose Information: Glucose information at meal time is required which can be obtained from a standard blood glucose meter. The units of the blood glucose levels can be changed in the settings tab. Note that you will not be able to request an advice without entering a valid glucose value.

2) Meal Information: Also, an estimation of the amount of carbohydrates to be consumed is required. Additional information about the meal absorption and alcohol consumption can be selected below.

3) Exercise Information: Optionally, information about any exercise before or after the meal can be entered via the touch screen on the phone.

Figure 2: Input options for insulin dose recommendations

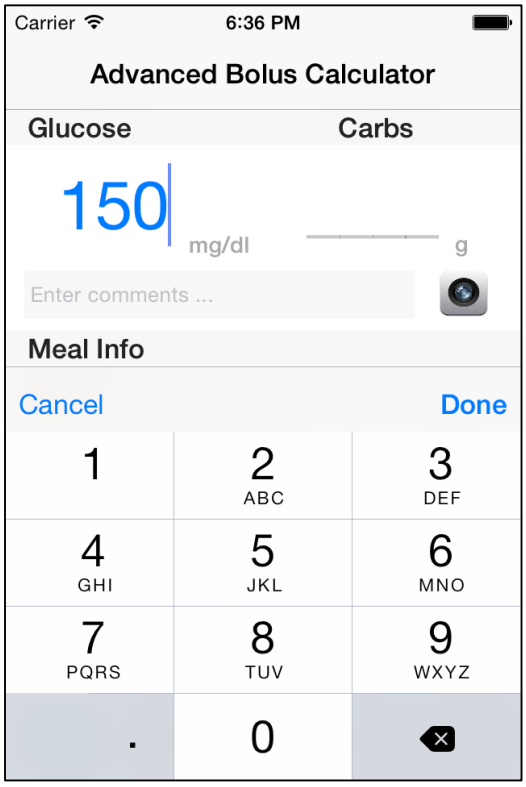


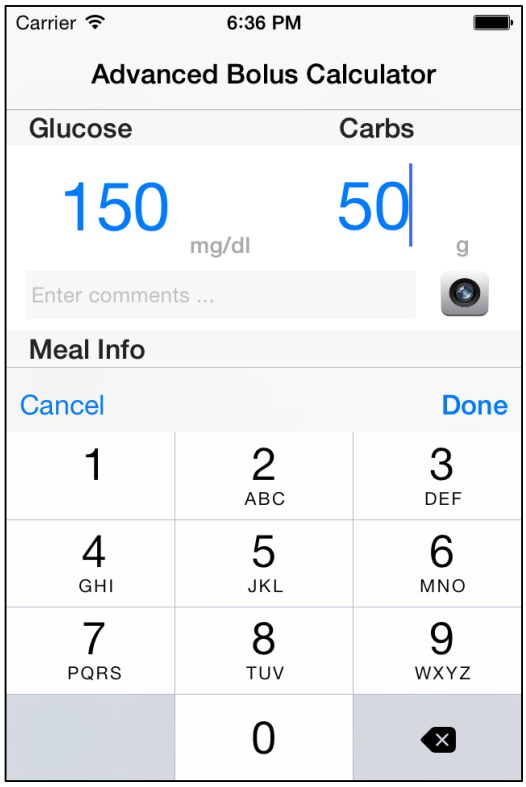
2.1 Requesting Insulin Bolus Advice

When used: For every meal that requires insulin and where the user would like to receive a bolus advice.

How to request an insulin advice:

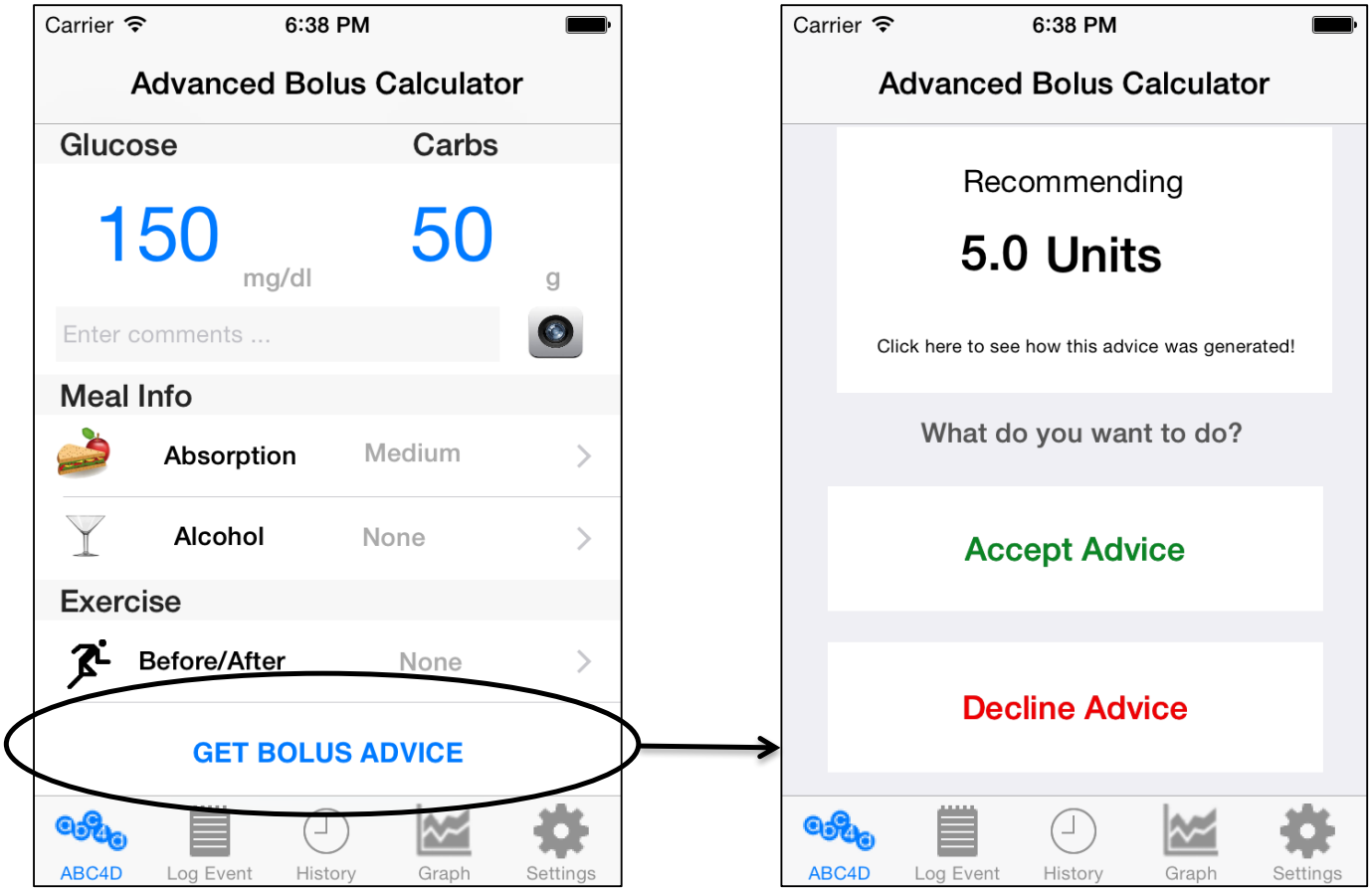
1) Enter glucose levels and estimated amount of carbohydrates (grams)



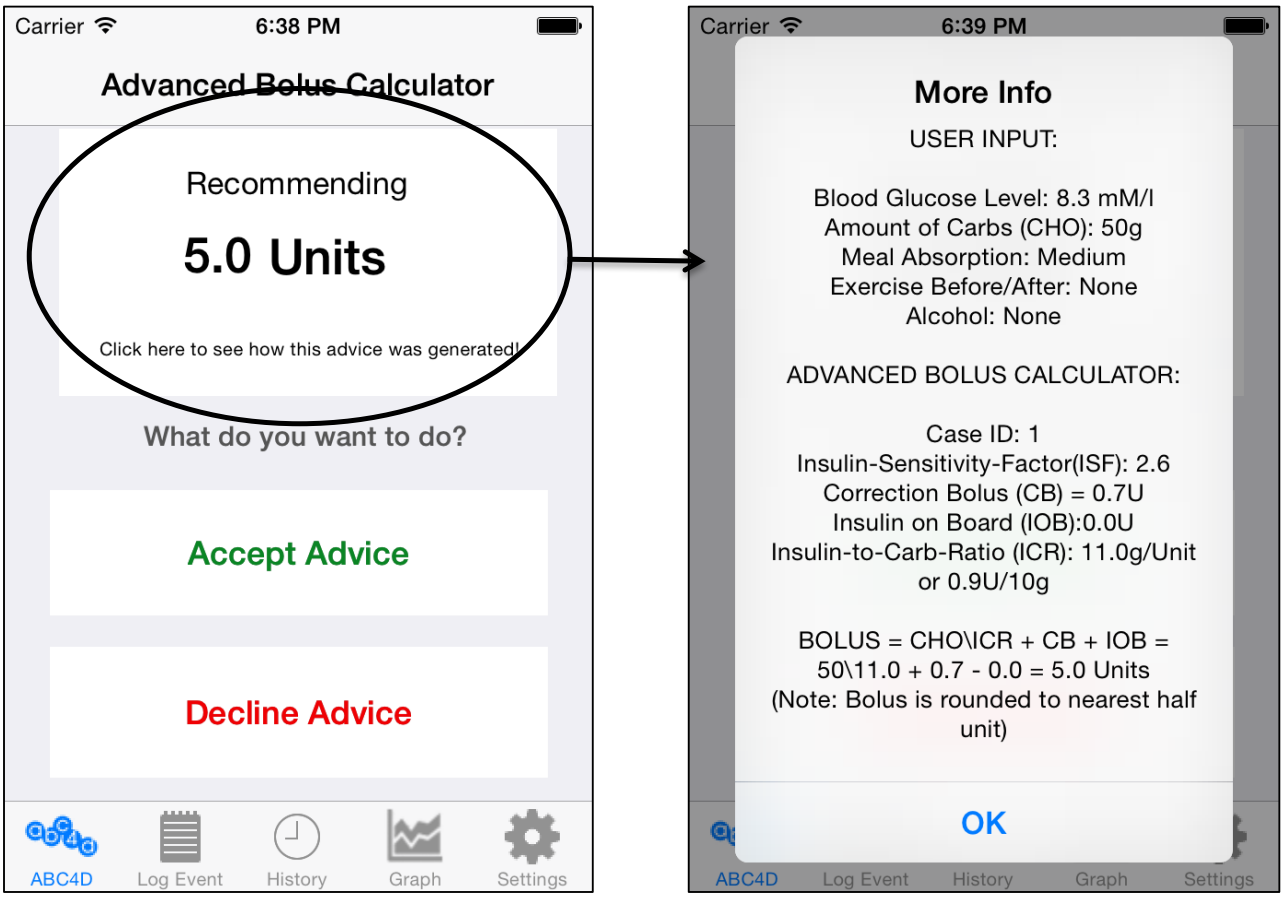


2) Optionally change parameters absorption rate, alcohol and exercise (default values: medium, none, none)

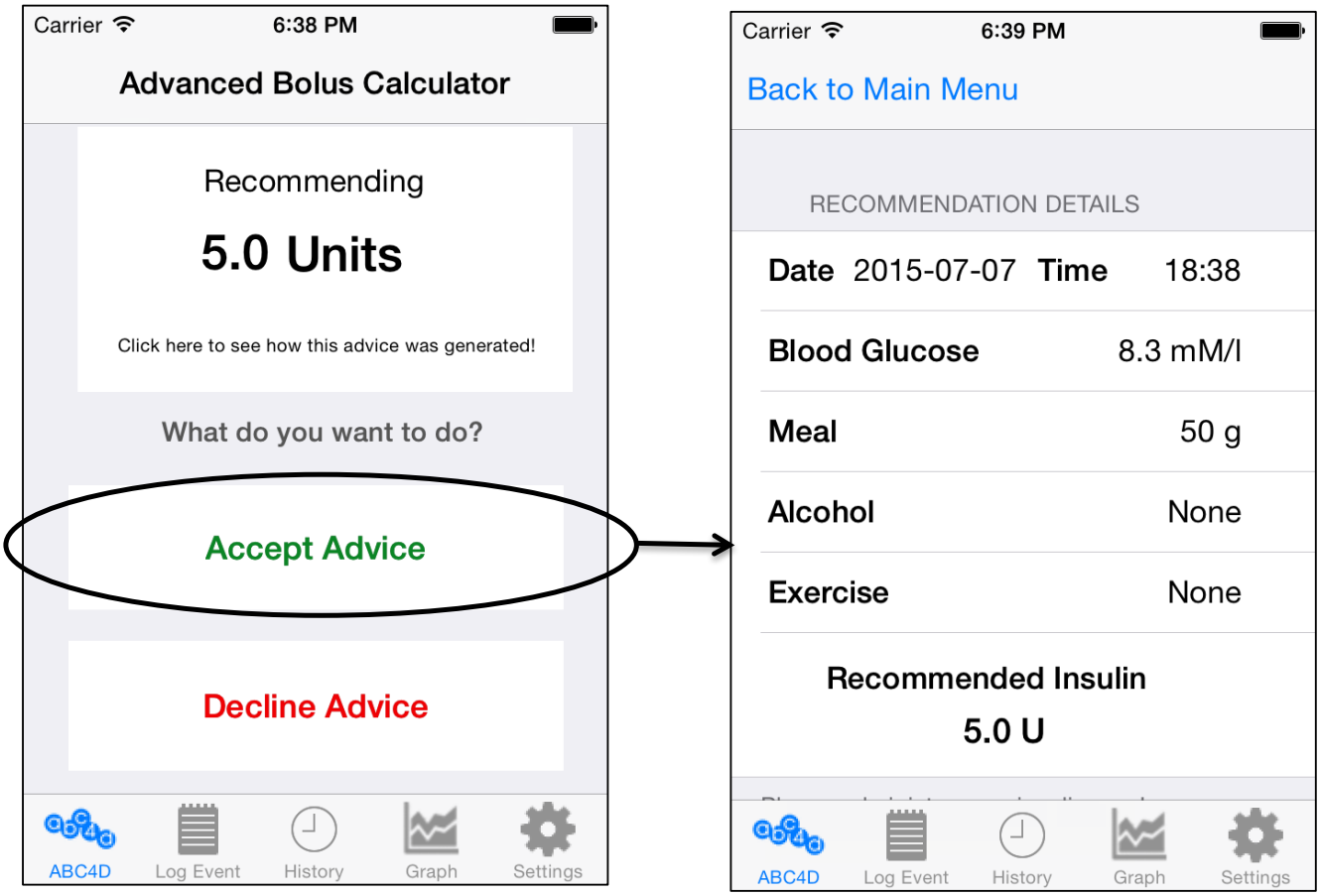
3) Finally, press the button *Get Bolus Advice* to receive an insulin recommendation



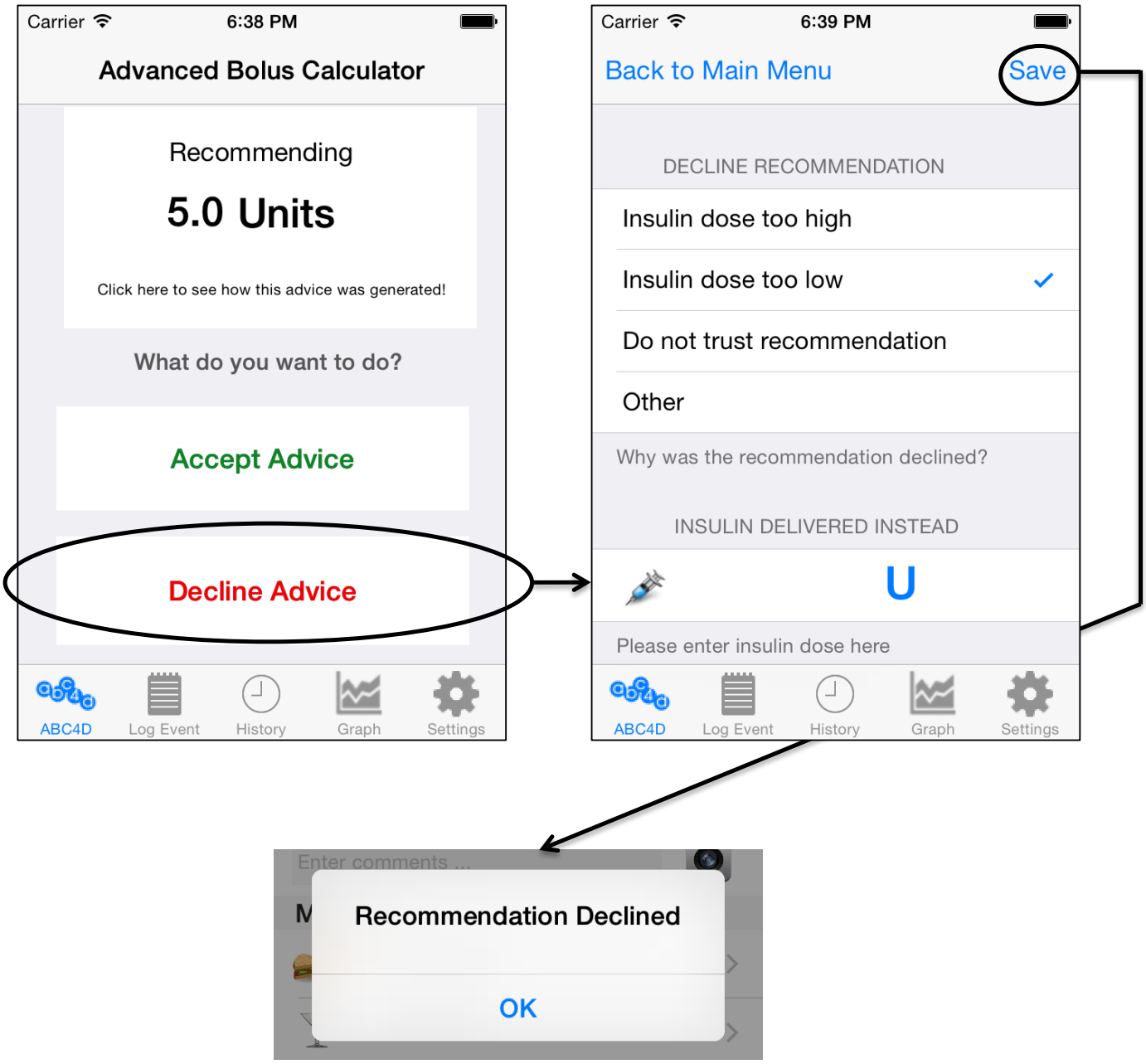
4) Request information about bolus advice (optionally)



5) Accept Advice

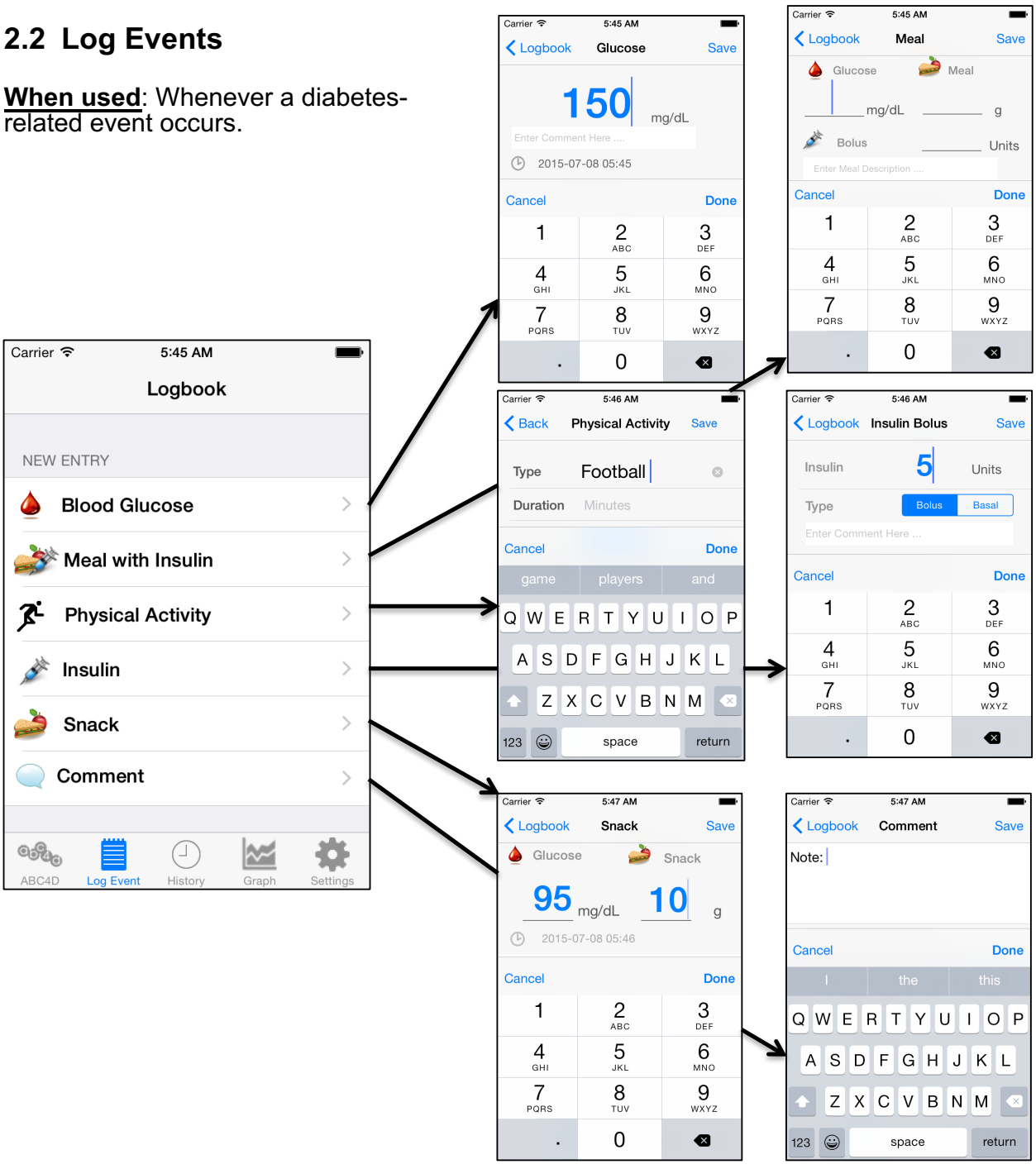


6) Decline Advice



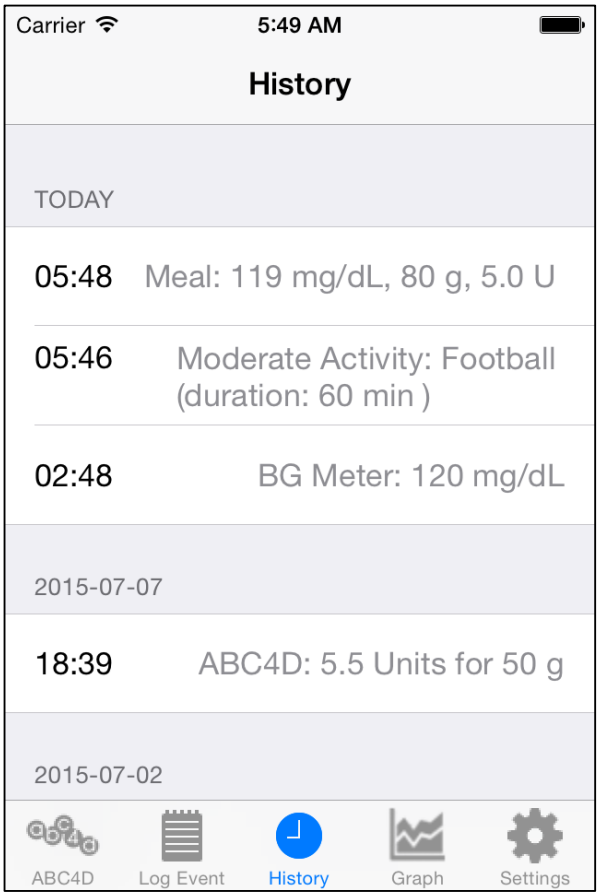
2.2 Log Events

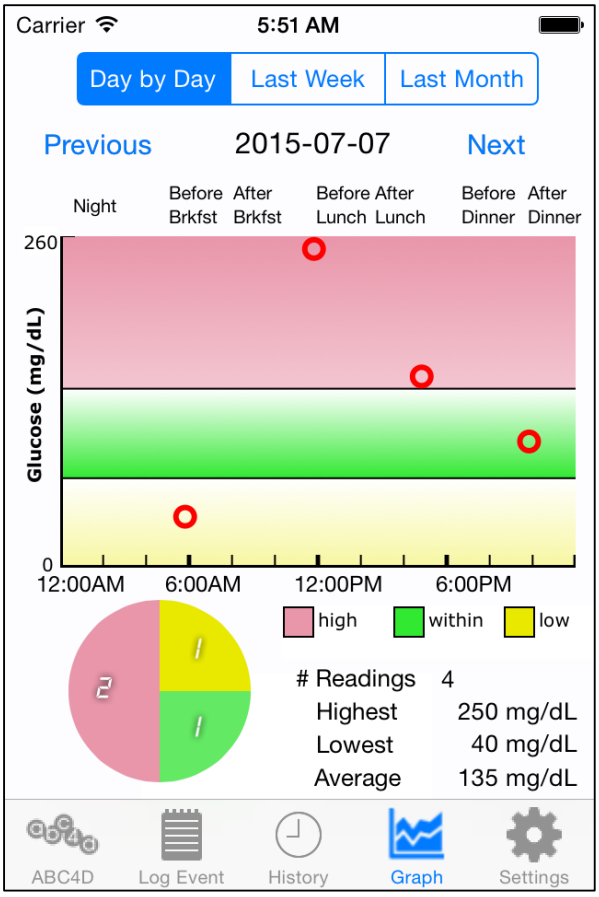
When used: Whenever a diabetes-related event occurs.



2.3 History/Graph

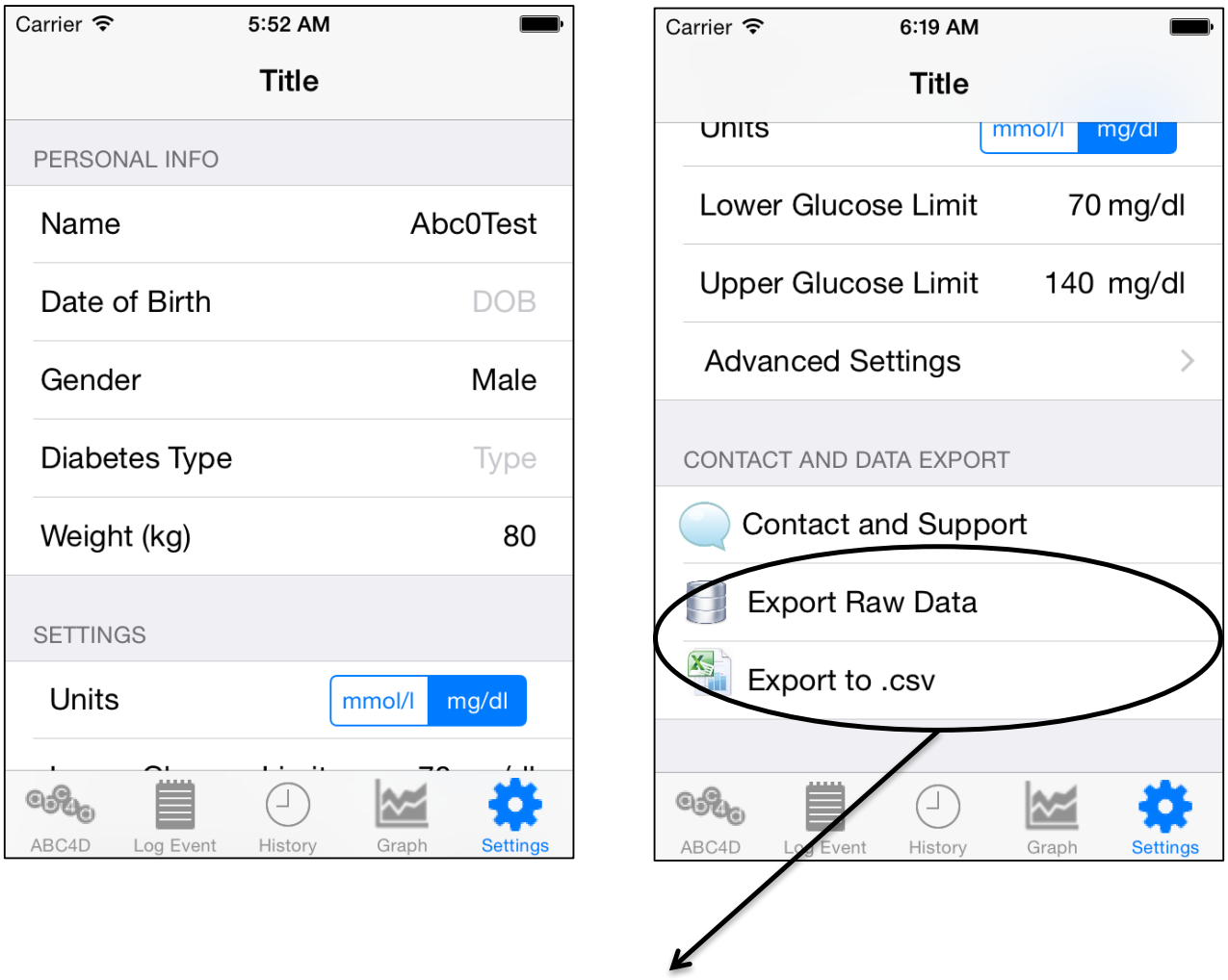
When used: For the user to review entered information and past recommendations



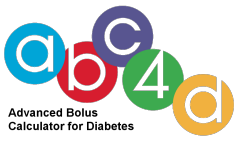


2.4 User Settings

When used: In case the user wants to change settings (e.g. changing units form mM/L to mg/dL) and to send logbook/ case-base to clinical expert. The user needs to be informed by the clinical expert when this is required.



Data export of logbook and case-base sent to clinical expert for case revision



User Manual (Expert)

for

ABC4D Clinical Revision Platform (ABC4D-CRP)

Software Version *v2.61*

Prepared by Peter Pesl

Center for Bio-Inspired Technology, Imperial College London

Table of Contents

Revision History

Name	Date	Reason For Changes	Version
Software Update	14/10/2014	Re-Structuring Variables and Implementation of Adaptation Revision Advisor	*V2.0*
	28/10/2014	Automatic Integration of Pending Cases Enhanced and Improved Screenshot Capture	*V2.1*
	06/11/2014	Fixed Screenshot Error in Summary Window Fixed Bug when timestamp of imported data showed 00:00:00	*V2.2*
	12/11/2014	Added comment textbox in summary window Auto-generate folder for each revision week and for storing screenshots and summary	*V2.3*
	19/11/2014	Start including declined recommendations when the outcome was in target	*V2.41*
	26/11/2014	Including declined recommendations even when outcome was not in target. Fixed minor bug of naming screenshot files	*V2.5*
	03/12/2014	Fixing issue when user selects intense exercise	*V2.5.1*
	01/06/2015	Added functionality to add new patient	*V2.6*

1. Introduction

1.1 Getting Started

This document contains a user manual for the ABC4D Clinical Revision Platform (ABC4D-CRP). This manual is intended for the expert reviewing case-adaptations proposed by the revision algorithm used for the clinical trial assessing the 'Advanced Bolus Calculator for Diabetes' (ClinicalTrials.gov Identifier: NCT02053051)

1.2 MATLAB Version

The software has been designed and implemented using Matlab 2012b. To ensure maximum compatibility it is advised to use the same version or higher. In order to use the software, following essential files need to be inside the working directory of the software.

2. Starting a new Revision

2.1 Opening Software in MATLAB

All files needed to run the software are included in the folder "ABC4D Clinical Revision Platform".

- Open MATLAB
- Navigate to the directory containing the ABC4D Revision software
- Double-click on "ABC4D_Revision_Software.m"
- Press the green arrow (RUN) on the top of the script to start the software.

2.2 Selecting Subject and Week

After starting the software, a window appears (*Figure 2*) to enter details about the revision.

- First, select the Patient ID using the drop down menu box on the top
- Then select the current week of the revision.
- Enter the name of the clinical expert performing the revision.

2.3 Initial Setup for New Patient

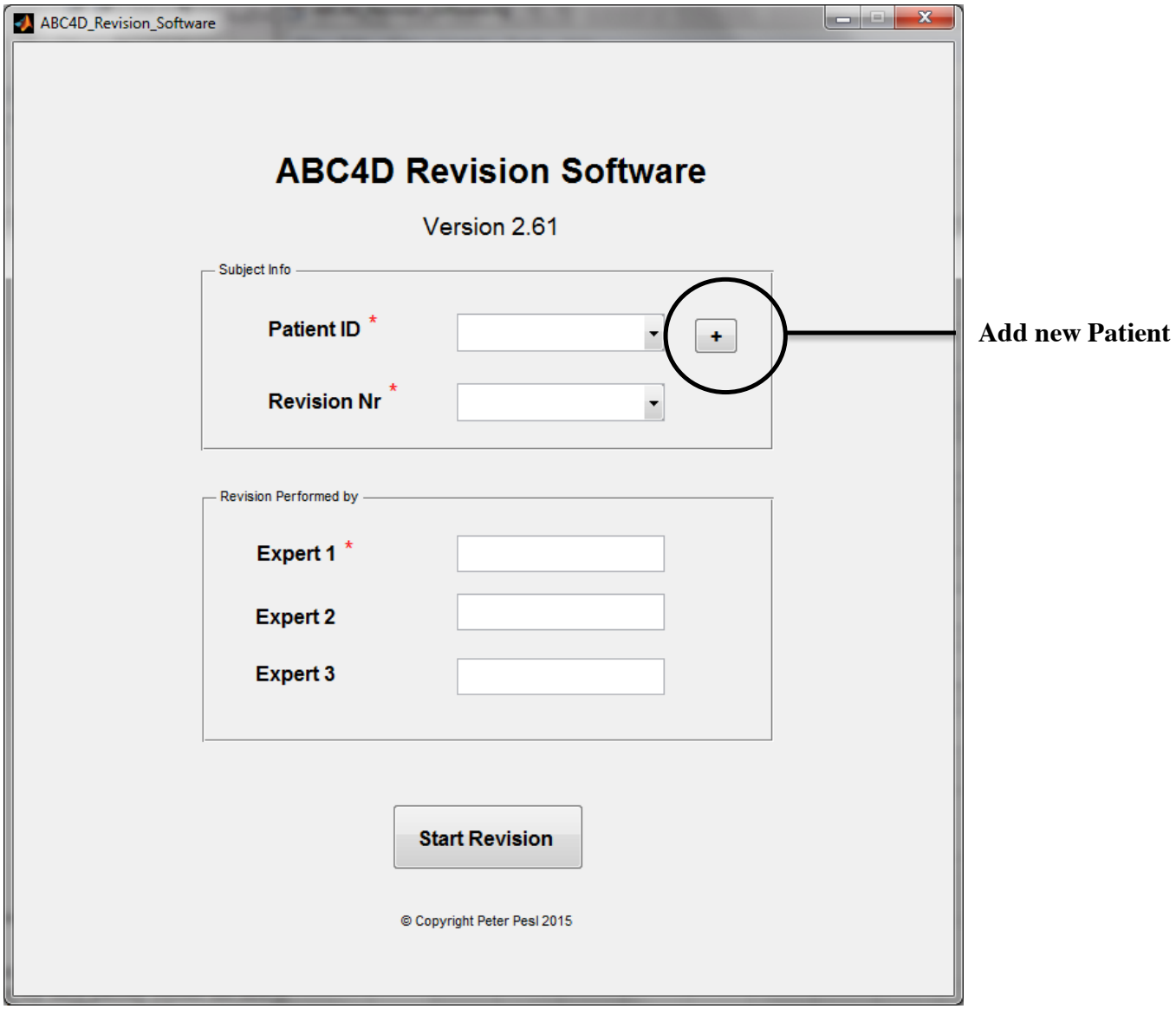


Figure 1 – ABC4D-CRP Start Window

First, a new patient profile needs to be added into the revision software. This has to be done only once for each patient before the first revision. In order to add a new patient click on the "+" symbol next to the Patient ID text-field (Figure 2).

2.4 Adding New Patient

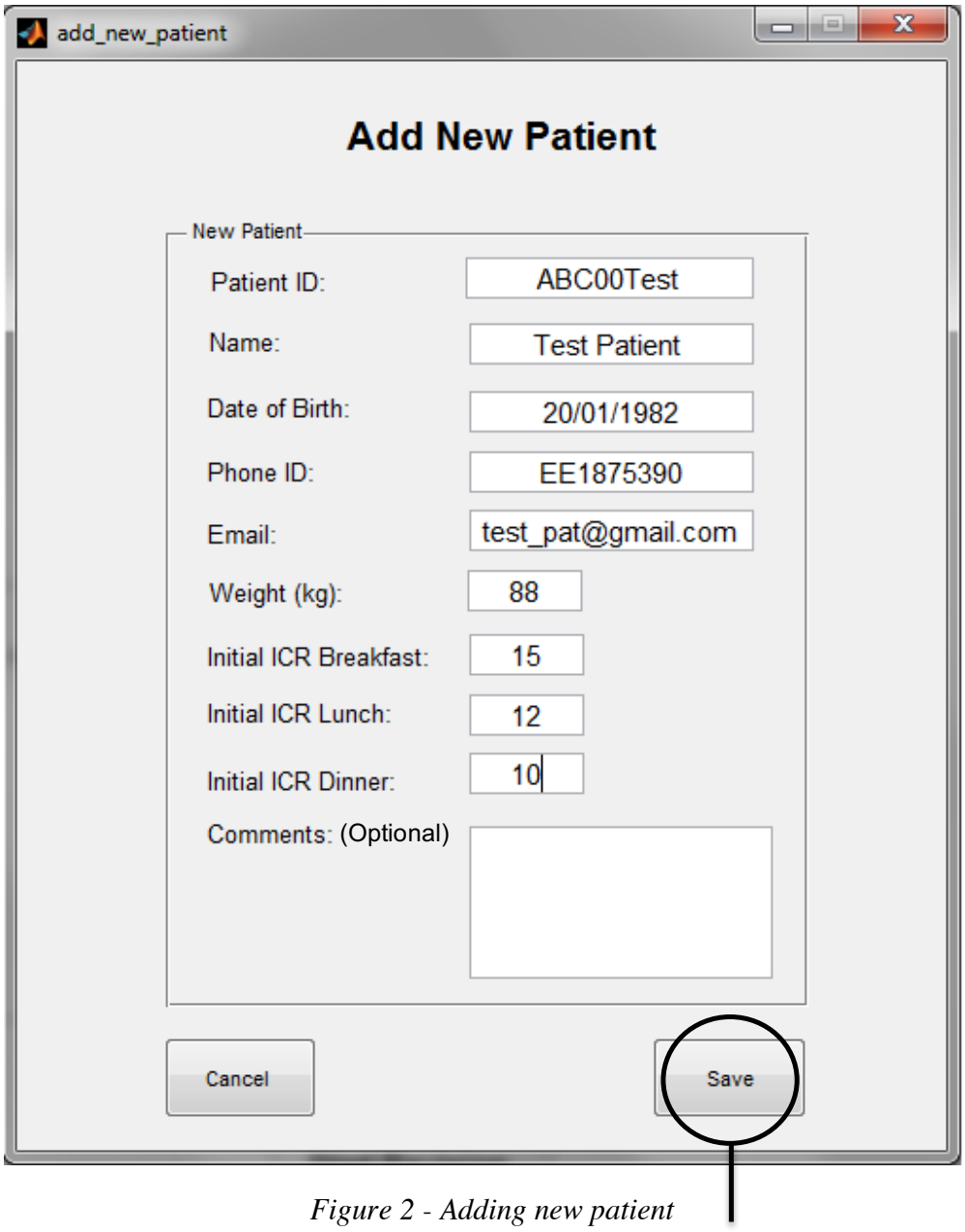


Figure 2 - Adding new patient

All text-fields except the comment text-box are required to be filled. Initial ICRs need to be identical to the once entered in the ABC4D-PSP. Pressing 'Save' adds the new patient to the ABC4D-CRP.

2.5 Entering Revision Info

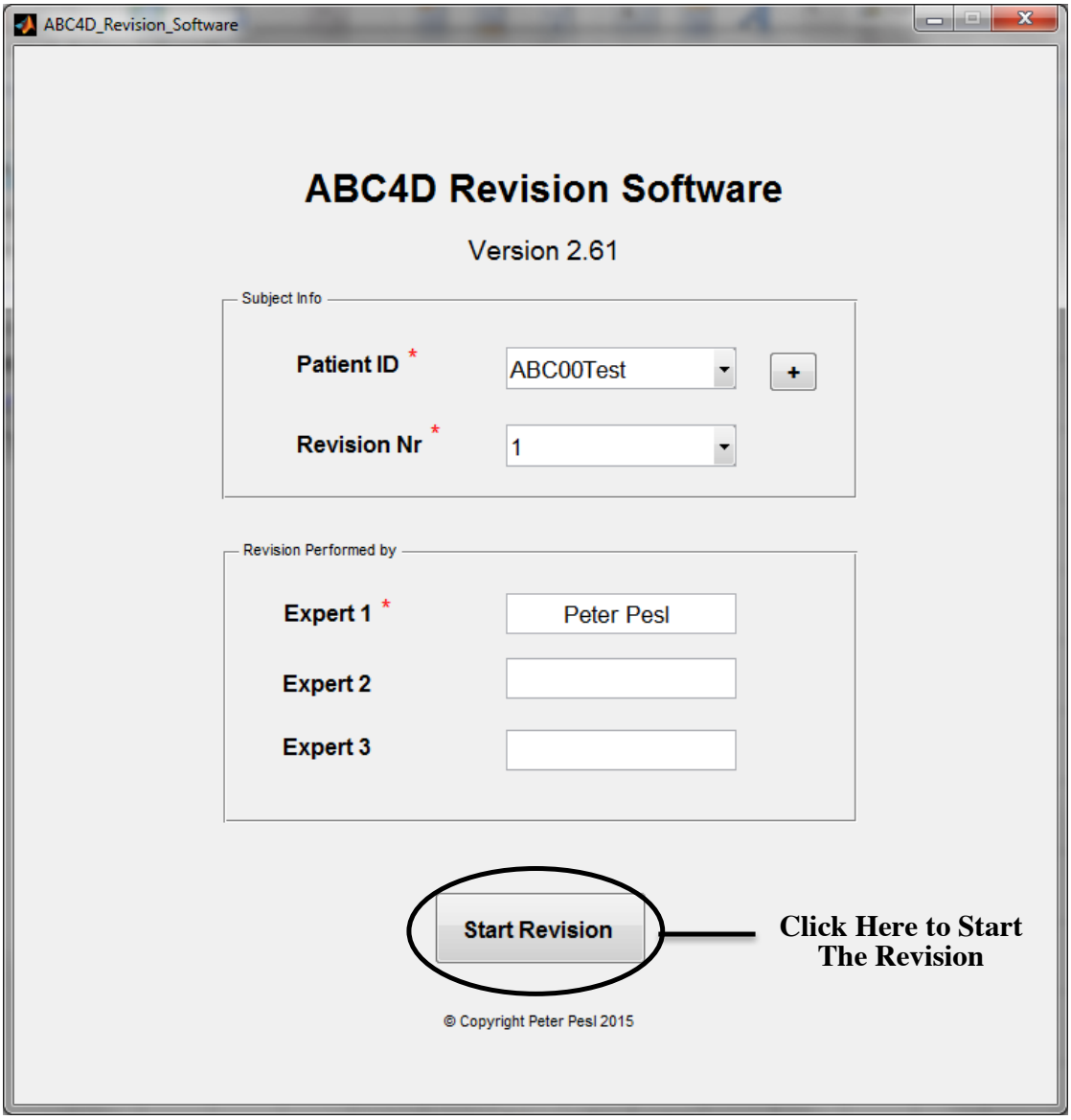


Figure 3 – Starting the revision

Figure 3: After a new patient has been added successfully added to the CRP, it can be selected here through the drop-down menu. Text-fields “Patient ID”, “Revision Nr” and at least one “Expert” need to be selected before being able to start the revision process.

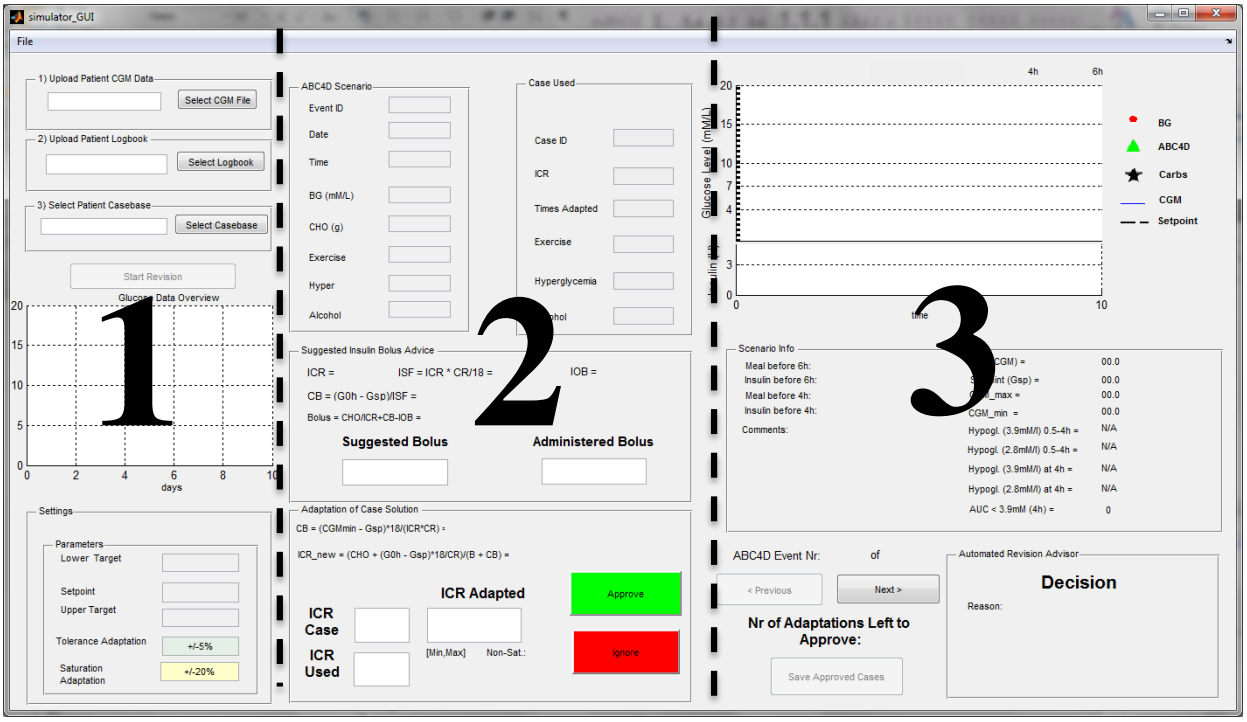


Figure 4 – ABC4D-CRP Main Screen

2.6 Clinical Revision Software

After pressing the button “Start Revision” the main revision software window appears (Figure 4). The main graphical user interface is divided into three parts:

1. On the left, an overview of the continuous glucose data is shown as well as general settings and parameters which have been imported from the phone
2. In the centre, the clinical expert sees detailed information about the currently selected scenario and its closest matching case (top). The suggested and administered bolus is shown in the middle, while the suggested adaptation and the review buttons for accepting/ignoring cases for revision are located at the bottom
3. The right side of the main screen shows a detailed plot containing CGM and events data (i.e. carbohydrates, blood glucose levels, exercise information, etc) as well as statistics about the currently selected meal scenario. The bottom of the screen shows navigation buttons to switch to the previous/next ABC4D meal scenario (left) and a clinical decision support tool, which analyses all data and gives advice to the clinical expert on whether the current scenario is eligible to be used for adaptation or not (right).

2.6.1 1) Uploading Data from CGM and Phone

First, data from the CGM and the ABC4D-PSP (phone) need to be uploaded. For this, the three panels on the top left of the screen are used (Figure 5).

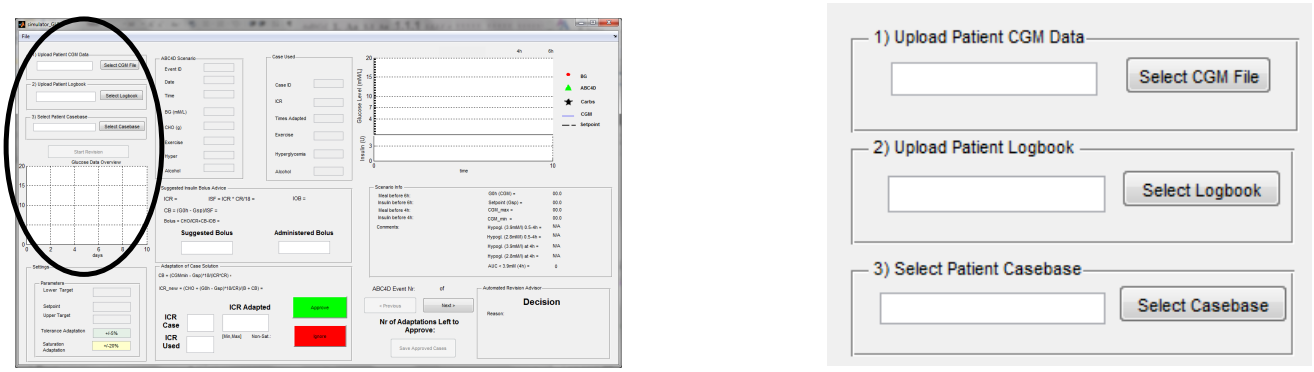


Figure 5 – Uploading Data from CGM and Phone

Following files need to be selected:

1. Upload Patient CGM Data (*.xls): (works for Medtronic iPro/iPro2) This file contains the blinded continuous glucose data and can be downloaded and exported to .xls via the iPro Carelink website: https://carelink.minimed.eu/ipro/hcp/login.jsf After successful upload, an overview of the glucose data appears below (Figure 6).

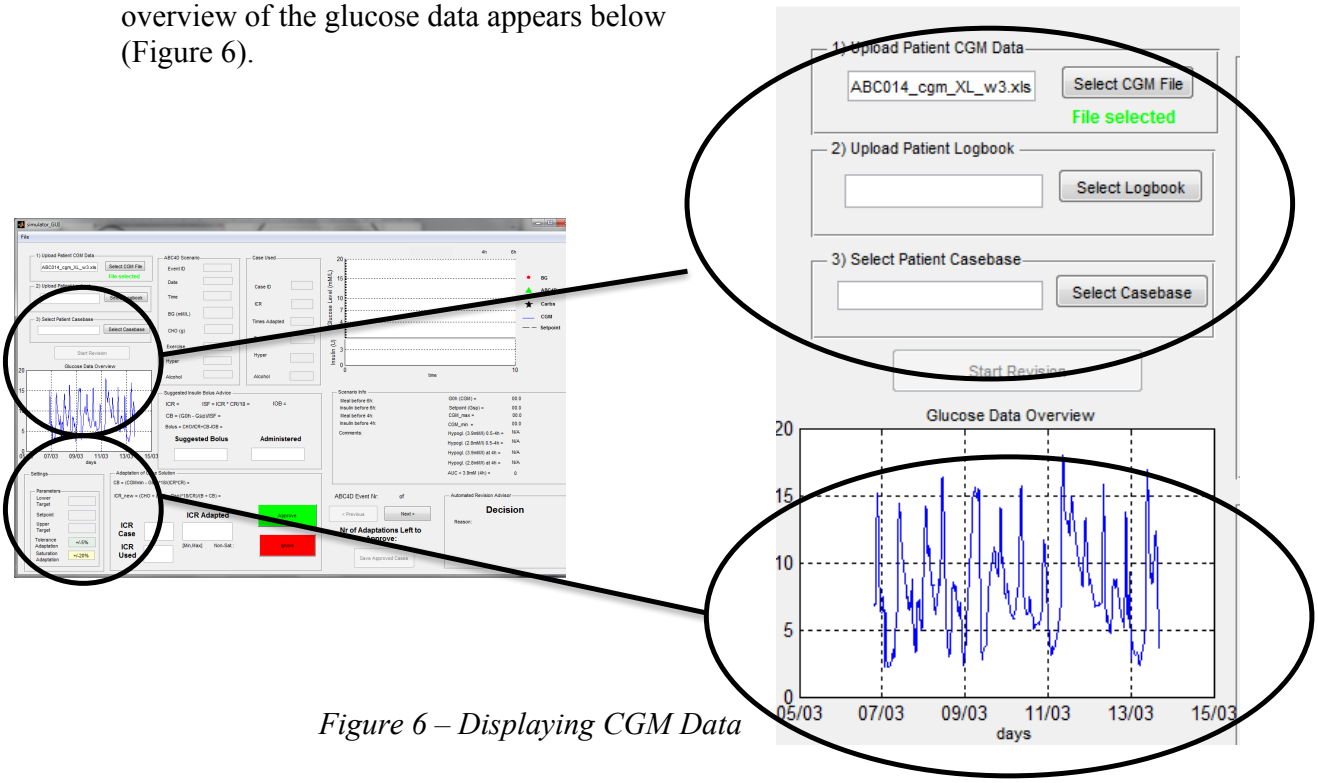


Figure 6 – Displaying CGM Data

2. Upload Patient Logbook file (*.csv): This file contains logbook events and settings from the ABC4D Patient Platform.

3. Upload Patient Casebase (*.csv): This file contains the current case base of the Patient Platform

Files needed for 2) and 3) are exported from the Patient Platform via Settings -> Export to .csv on the phone (see Manual of Patient Platform for more details). After selecting all three files the button 'Start Revision' is enabled and the revision process can be started (Figure 7).

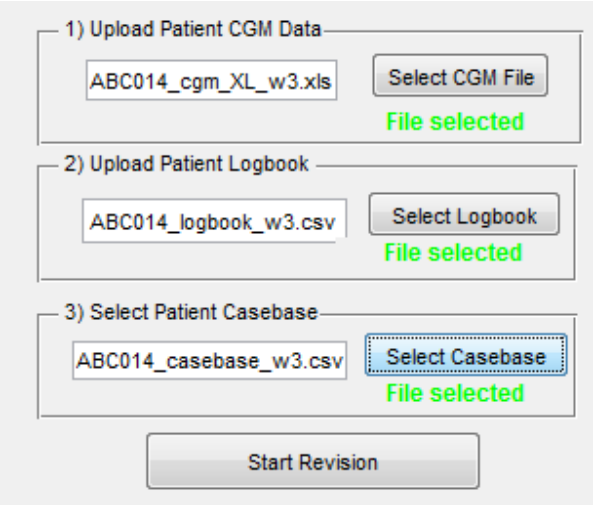
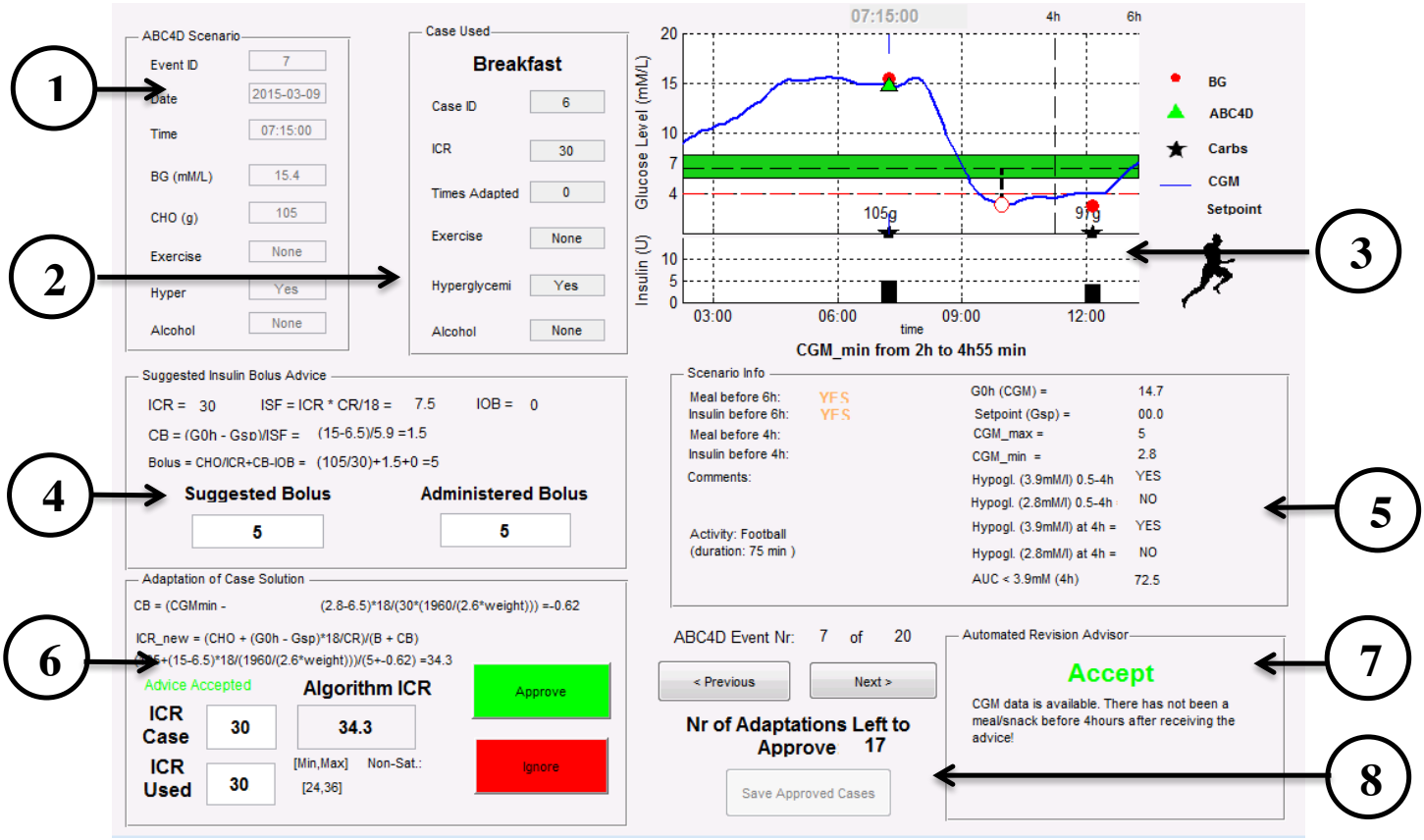


Figure 7 – Successful Data Import

2.7 Accepting/Ignoring Adaptations

Next, each case which has been used for an insulin recommendation will be revised by the algorithm. Adaptations proposed to the ICRs need to be either accepted or ignored by the expert (Figure 9). The old and suggested insulin-carbohydrate-ratio as well as two buttons (Approve/Ignore) are located at the bottom of the main GUI. After either approving/ignoring the proposed adaptation, the clinical expert can move on to the next scenario using the navigation buttons on the right. It shall be noted that each decision can be undone using a checkbox which appears after pressing approve or ignore.

Figure 9 – Main Screen after Data Import



1) **ABC4D Scenario:** Shows all information and user inputs of the current meal scenario where ABC4D has been used for bolus advice
2) **Retrieved Case:** Shows the retrieved (most similar) case to the current scenario, its parameters and its solution (i.e. ICR)
3) **Post-prandial Glucose Excursion:** Shows a detailed graph of the current meal scenario including glucose data from the CGM device (blue line) and BG meter (red dots), as well as meal information, delivered insulin and exercise.
4) **Suggested Bolus Advice:** Shows the calculation on how the bolus advice has been calculated (suggested bolus) and if the user followed the advice (i.e. administered bolus)
5) **Scenario Details/Statistics:** Analyses the logbook data and indicates if a meal or correction bolus has occurred within a per-defined time window (i.e. 4 and 6 hours). Comments entered by patients are displayed here. Post-prandial statistics can be seen on the right.
6) **Adaptation of Case Solution:** Here the revision algorithm calculates the new solution based on the post-prandial outcome (Algorithm ICR).
7) **Automated Revision Advisor:** Automatically analyses the glycemic outcome and provides a suggestion to the clinical expert on whether to approve or ignore this scenario for revision.
8) **Navigation Control/Save Revision:** Enables the expert to switch between ABC4D scenarios. The number below shows how many scenarios are left to be approved/ignored. After all scenarios have been revised, the 'Save Approved Cases' button is enabled.

2.8 Finishing Revision

After reviewing (accepting/ignoring) all ABC4D scenarios, the button "Save Approved Cases" is being enabled (Figure 10).

Figure 10 – Finished Revision

2.9 Including Pending Case-Base

An adapted case is only then updated into the case-base of the patient platform if the case has been revised and approved at least twice in order to avoid initial outliers. If a case has been used only once for this patient, then it is not used to update the case-base but will be remembered for the next revision phase. Cases that have been revised and approved only once will be saved in a pending case-base. After pressing the 'Save Approved Cases' button, a dialog box appears confirming pending cases for this patient from previous revisions that will be included in the case-base update.

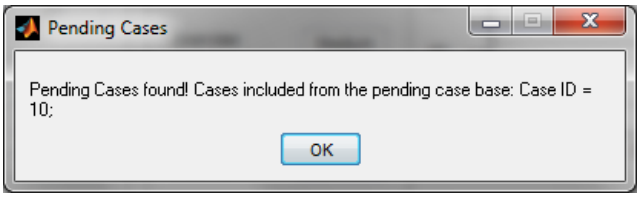


Figure 11 – Completed Revision

2.10 Merging Multiple Adapted Cases

After including pending cases, all multiple adapted cases will appear. An average value of all adaptations is shown at the bottom which needs to be approved for each adaptation (Figure 12).

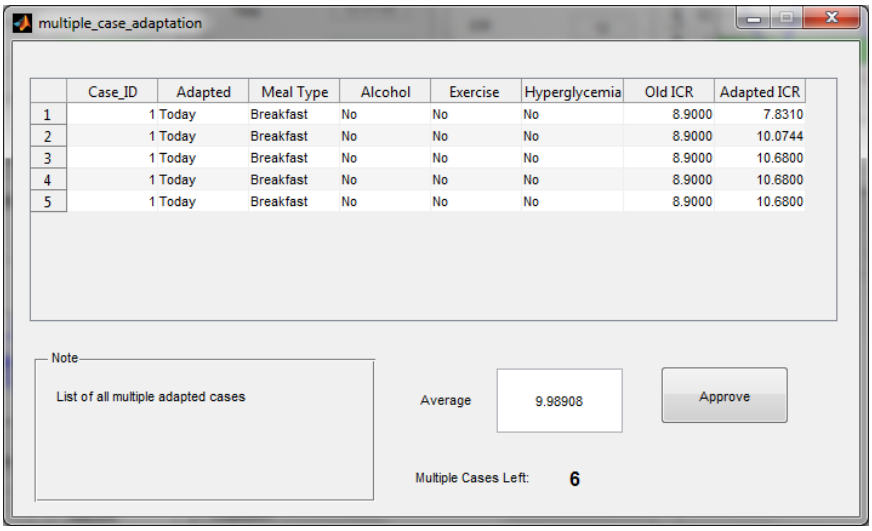


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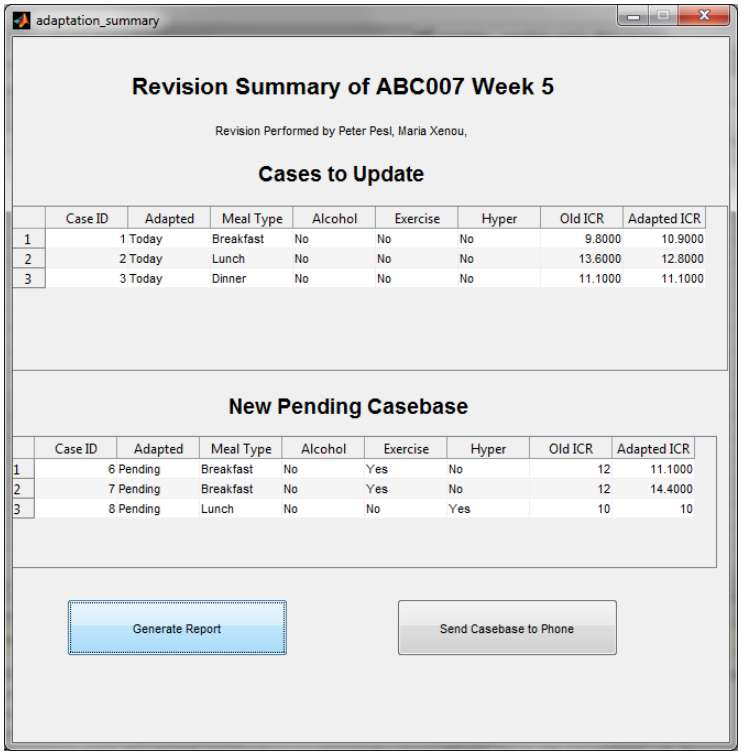
Figure 12 – Multiple Case Adaptation

2.11 Revision Summary and Case-base Update



The summary window appears in this window which displays all adapted cases as well as pending cases for the revision. The clinical expert can also add comments about the revision. The new case-base can either be updated manually on the or by pressing the button “Send case base to Phone” (beta). A message-box will appear to confirm the correct phone and user account before the adapted case base will be sent to the specified phone.

2.12 Generating Automated Report

Pressing “Generate Report” will automatically open a new Microsoft Word document and write a summary report about the adaptations being made including a table with the current case-base.

Appendix A:

Information about essential MATLAB Files

SubjectID_Info.mat

In order to be used by the revision software, for each subject, a .mat file (named patient_ID_info.mat) containing essential information about the revision is required. The .m file is automatically created using the ABC4D Revision software and located in the folder \ABC4D Revision Software 2.61\data. A list of all available patients can be found in the .mat file subjects.mat

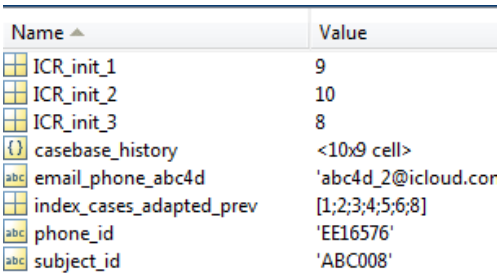


Figure 1: Structure for Subject file used for Revision

- *ICR_init1-3*: These are the initial insulin-carb-ratios used by the subject at the start of the trial
- *Casebase_history*: This cell structure contains all past adaptations performed by a revision expert
- *Email_phone_abc4d*: String containing the email address of the phone which holds the case base to be updated
- *Index_cases_adapted_prev*: Array showing Case_IDs which have been adapted previously
- *Phone_id*: String containing a unique identifier for the phone used for the subject
- *Subject_id*: String holding the id of the patient using ABC4D

2.13 General Adaptation Rules

For phase 2 of the clinical trials case adaptations are accepted if:

- No meal/insulin event occurs after the advice and 4hours
- A snack occurs for correcting a hypoglycaemic event (<3.9mM/l)

For phase 2 of the clinical trials case adaptations are ignored if:

- CGM data is missing
- A meal/insulin event occurs before 4 hours (and CGM_min > 3.9mM/l for meals)
- Meal is smaller than 15g

Automated Revision Advisor

Note: For better readability some system functions are not displayed here.

```
  % CASE: CGM DATA MISSING -> IGNORE
   if(length(glucose_data.glucose_2_to_6h)<40)
    string_reason = [string_reason,'CGM data is missing. No revision
possible!'];

  %CASE:Snack < 15g  -> IGNORE
  elseif(CHO<15)
  string_reason = [string_reason,'Meal is smaller than 15g so will be
excluded!!!'];

  %CASE: Event before 2h   -> IGNORE
 elseif(first_cho_insulin_event<120)
  string_reason = [string_reason,'There has been a meal/insulin between 0h-2h
after advice. Even if there was a hypo, its not clear it was because of the
ABC4D recommendation.No revision possible!'];

 %CASE:Snack before 4hours without hypo -> IGNORE
  elseif(meal_event_before_4h==1&&min_CGM_2_6h>=3.9)
  string_reason = [string_reason,'There has been a meal/snack before 4hours
after receiving the advice and CGM_min was above 3.9mM (no hypo)!'];

%CASE:Snack before 4hours without hypo    -> IGNORE
  elseif(insulin_event_before_4h==1&&min_CGM_2_6h>=3.9)
  string_reason = [string_reason,'There has been insulin delivered before 4hours
after receiving the advice and CGM_min was above 3.9mM (no hypo)!'];

%CASE:Snack before 4hours with hypo -> ACCEPT
  string_reason = [string_reason,'There has been a meal/snack before 4hours
after receiving the advice but CGM_min was below 3.9mM (hypo)!'];

 else  -> ACCEPT
  string_reason = [string_reason,'CGM data is available. There has not been a
meal/snack before 4hours after receiving the advice!'];

 end
```