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Translational technology in type 1 diabetes to help optimise glycaemic control and sustain behaviour change

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I would like to dedicate this thesis to my loving parents and family...

This work is also dedicated to millions of people who suffer from diabetes...

‘When you reach the end of what you should know,
you will be at the beginning of what you should sense.’

— *Khalil Gobran*

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Abstract

Type 1 diabetes mellitus cases represent 5–10% of all cases of diabetes and these are increasing worldwide. There is no immediate prospect of a cure and managing the disease is the current practice. Poor diabetes management is associated with short-and long-term complications. However, the lifelong burden and complexity of diabetes management result in many patients being unable to achieve the required control targets. Advances in communications technology, wireless networks, cloud computing and storage create new opportunities for implementing comprehensive support solutions to assist in diabetes self-management.

This thesis first investigates current clinical practices via an in-depth retrospective analysis of a novel dataset. This is then used to recommend novel glycaemic targets for enhancing engagement and reducing the exhaustion and anxiety experienced by type 1 diabetes patients. Also, exploiting the glycaemic patterns, HbA1c prediction models are developed to offer quicker and continuous effective feedback on patients' glycaemic control. Furthermore, clustering techniques have been utilised to identify the diurnal patterns of patients, thus automating the configuration of personal factors used in bolus calculators to improve accuracy, context and reduce the burden on patients and clinicians.

Finally, the thesis presents a novel holistic diabetes management platform, developed utilising responsive agile design throughout a two-year clinical pilot trial that involved 78 patients and 10 clinicians at three NHS trust health centres across the UK. The developed technologies resulted in significant improvement in patients' outcome and engagement over the pilot period as measured by HbA1c and usability. These encouraging results are a strong indication that the developed recommendations, models and technologies in this thesis can be adopted in practice and thus provide innovations to improve the lives of type 1 diabetes patients.

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List of Abbreviations

AAMI Association for the Advancement of Medical Instrumentation

ACCORD Action to Control Cardiovascular Risk in Diabetes

ADA American Diabetes Association

ADAG A1c Derived Average Glucose

AG Average Glucose

AGP Ambulatory Glucose Profile

AI Artificial Intelligence

AIC Akaike's Information Criterion

AP Artificial Pancreas

BA Bolus Advisor

BG Blood Glucose

BI Basal Insulin

BMI Body Mass Index

BN Batch Normalisation

CGM Continuous Glucose Monitoring

CHO Carbohydrate

CNN Convolutional Neural Network

CSII Continuous Subcutaneous Insulin Infusion

CV Coefficient of Variation

DAFNE Dose Adjustment For Normal Eating

DCCT Diabetes Control and Complications Trial

DKA Diabetic Ketoacidosis

DVLA Driving and Licensing Agency

eA1c estimated A1c

eAG estimated Average Glucose

EASD European Association for the Study of Diabetes

EHR Electronic Health Record

FBG Fasting Blood Glucose

FCM Fuzzy C-Means

FCN Fully Convolutional Neural Network

FDA Food and Drug Administration

FGM Flash Glucose Monitoring

G-CNN Grouped-Convolutional Neural Network

GAP Global Average Pool

GDM Gestational Diabetes Mellitus

GEE Generalised Estimating Equation

Hb Haemoglobin

HbA1c Haemoglobin A1c

HCP Health Care Provider

HGI Haemoglobin Glycation Index

HTML Hyper Text Markup Language

ICR Insulin to Carbohydrate Ratio

IDF International Diabetes Federation

IFCC International Federation of Clinical Chemistry

IoC Inversion of Control Container

ISF Insulin Sensitivity Factor

ISO International Organization for Standardization

JPA Java Persistence API

JSP Java Server Pages

JSTL JSP Standard Tag Library

MAE Mean Absolute Error

MCDCNN Multi Channel Convolutional Neural Network

MCNN Multi-scale Convolutional Neural Network

MDD Medical Device Development

MDI Multiple Daily Injections

MedAE Median Absolute Error

MPC Model Predictive Control

NHS National Health Service

NICE National Institute for health and Care Excellence

PaaS Platform as a Service

PDA Personal Digital Assistant

pHbA1c predicted Haemoglobin A1c

PID Proportional Integral Differential

PoC Point of Care

QA Quick Acting

RBC Red Blood Cell

RBF Radial Basis Function

RCT Randomised Clinical Trial

ReLU Rectified Linear Unit

REPOSE Relative Effectiveness of Pumps Over MDI and Structured Education

RT-CGM Real Time Continuous Glucose Monitoring

SD Standard Deviation

SMBG Self Monitoring Blood Glucose

SSE Sum of Squared Error

SSL Secure Sockets Layer

STH Sheffield Teaching Hospital

SVM Support Vector Machine

SVR Support Vector Regression

T1D Type 1 Diabetes

TB Time Block

TIR Technical Information Report

UKPDS UK Prospective Diabetes Study

Chapter 1

Introduction

Diabetes mellitus is a chronic disease increasingly becoming more prevalent in the world. There are 451 million people diagnosed with diabetes; it is expected to rise to 693 million people by 2045. Also, it is estimated 179 million people have diabetes but have not been diagnosed yet [4]. In the UK, there are 3.7 million people over the age of 17 diagnosed with diabetes [5]; it is estimated to rise to 5 million people by 2025. The majority of people diagnosed with diabetes have Type 2 diabetes, and only about 10% have Type 1 diabetes.

The main treatment for diabetes is disease management, as opposed to cure. Poor diabetes management is associated with short and long-term complications [6]. In England and Wales, people with diabetes have 34.4% shorter life expectancy compared to their peers with no diabetes. For type 1 diabetes, mortality is 131.1% greater than expected, and for type 2 diabetes it is 32% greater [7]. Diabetes is the most common cause of non-traumatic lower-extremity amputations [8]. Furthermore, pregnancy in diabetic women imposes a higher risk; they are five times as likely to have a pre-term baby and three times as likely to undergo a Cesarean section delivery compared to women without diabetes; their babies are five times as likely to be stillborn, and three times as likely to die in their first month [9]. People with diabetes are as twice as likely to experience episodes of depression that lasts longer compared to people with no diabetes [10]. Hence, the accumulated direct and indirect care cost for diabetes in the UK is £23.7 billion ($\sim$ 10% of the NHS budget). It is predicted to rise to £39.8 billion by 2035/6 ($\sim$ 17% of the NHS budget) [11]. Currently for Type 1 diabetes,

the direct cost is £1bn, and the indirect cost is £0.9bn. The projections to 2035/6 of Type 1 diabetes' direct and indirect costs are: direct cost is £1.8bn and the indirect cost is £2.4bn.

Evidence from different studies demonstrates that intensive diabetes management contributes in reducing the progress of diabetes related complications [12–18]. Diabetes management involves a sequence of education, medication, diet, and healthy lifestyle choices to achieve the expected self-management. The self-management process requires regular collection, compilation, storage, and analysis of data [19, 20].

In the current system for type 1 diabetes, self-management regimen involves patients pricking the side of their finger with a lancet device and placing a drop of blood on a test strip connected to a glucose meter. Then, the glucose reading is used to assess the amount of insulin injected considering their carbohydrates intake and other factors such as physical activity, stress, and illness; it is advised that the blood glucose tests are carried out at least 3-4 times daily by the patient during their lifetime. The patient uses a diary to record the result. It is also recommended to record the dose of insulin injected, carbohydrates consumed and exercise undertaken.

In many clinical centres in the UK, Diasend is used to collect and process patients data from their glucose meter. Diasend is a commercial web-based solution that can be accessed by the health-care team to process patient's data [21]. This system provides a data collection facility and a unified data representation for the supported manufacturers' glucose meter. This is operated in clinics upon the patients' arrival.

The patient visits the health-care team every 3-12 months to assess their diabetes management and to perform examinations such as glycated haemoglobin test, (also known as haemoglobin A1c or HbA1c), and on an annual basis retinal screening, foot checks, blood and urine tests. The health-care team involved include nurses, doctor, and dietitian [22, 23]. The doctor might also refer the patient to the ophthalmologist, cardiologist, nephrologist and psychologist from time to time if needed. This team evaluates the patient's diabetes management by looking into the blood test records, HbA1c and other examinations.

The HbA1c is a measure of the average plasma glucose concentration [24]. This measure provides a better indication of the mean glucose level over the period of 8-12 weeks. It shows

more objectively, how the patient is managing his/her diabetes. Higher levels of HbA1c indicate a poor diabetes management, and are associated with irreversible eye, kidney and nerve damage, which may lead to blindness, dialysis, and lower limb amputations [25–27] .

Various guidelines are published and have shaped the employed practises in clinical procedures of diabetes care [28, 29]. These guidelines include recommendations for the frequency of blood glucose measurement, preprandial glucose targets, postprandial glucose targets, insulin regimen, the frequency of clinical visits, the frequency of HbA1c tests, HbA1c targets and intensity of treatment plans. Additionally, in many hospitals structured educational programmes such as dose adjustment for normal eating (DAFNE) are provided as part of the care plan for patients [30].

Advances in smartphone technology, wireless networks, cloud computing and storage create new opportunities for implementing a comprehensive telehealth solution across the health-care field, especially in diabetes self-management. In addition, the integration of technology to handle our daily tasks is becoming more prevalent. In Great Britain, 99% of adults aged 16 to 44 use online services; 73% of adults aged 25 to 34 downloaded online news, newspapers and magazines. Also, the usage of the Internet has highly increased amongst the older age group. Adults aged 45 to 54 using the Internet to find information on services and goods increased from 74% in 2013 to 84% in 2014 and Internet banking activity has increased from 50% to 62% for the same period [31].

This leads us to challenge the current care practices. It provides the opportunity to adopt modern technological advancement to offer individualised and balanced care plans. Also, it elevates the patient's role in disease management by providing the needed information, potentially improves patient-clinician interaction, follow-up, social support and reducing the care cost.

The following problems and objectives are investigated to facilitate enhanced self-management in people with type 1 diabetes.

1.1 Motivation

Various efforts in proximal technologies (e.g., insulin pumps, continuous glucose monitors) and distal technologies (e.g., web-based platforms and mobile health) have been carried out to help patients and clinicians with diabetes management and treatment adjustments. Nevertheless, there are limitations to the current state-of-the-art. The following describes the limitations and discusses the research objectives; then, it concludes with a thesis outline and a summary of the contributions.

1.1.1 Problem definition

Despite all the efforts of the patients and their health-care team, most patients do not achieve their diabetes management targets. In fact, less than 30% of the type 1 patients achieve the UK's national target for diabetes management [23]. The increasing number of diabetes patients limits the access to diabetes care and diabetes specialists. As a consequence, clinicians have a limited time to interact and follow-up with patients. Social support is key to successful self-management [32].

In addition, the regimen of multiple insulin injections with different doses depending on carbohydrate intake, activity level, and frequent glucose measurements can cause stress and exhaustion that sometimes leads to dose omissions and incomplete compliance. Collateral psychological conditions might further affect the coherence of the planned regimen [33–35]. Moreover, recording, storing, compiling and analysing data requires education, effort and tools to enable both clinicians and patients to understand and assess the state of the patient's diabetes management. Recent studies urge for individualised treatment plans considering the disease stage, benefits, and possible complications [12, 36].

Furthermore, the desired support involves engagement of specialists in different fields who might not always be available across the clinical centres. Likewise, avoiding later complications might be aided by an intervention which enables continuous assessment rather than waiting for the patients to visit the health-care team in 3-6 months to hand in their data and negotiate their diabetes management state [37].

More importantly, type 1 diabetes often remains in the shadow of its bigger counterpart population of type 2 diabetes. Although type 2 shares many acute and long-term complications of type 1 diabetes, it is a very different disease, and does not require as intensive acquisition of self-management skills. The developed solutions require consideration in the design to provide a personalised and structured approach, optimised based on the established intervention techniques specific to each type. However, in both of the medical device industry and research, the broader diabetes population have been considered in the design and development processes [38]. This might provide support and inclusion of the wider diabetes population but does not meet the needs of patients and clinicians that are most times unique to each diabetes type.

Proximal technologies in diabetes such as bolus calculators rely on accurate and continuous adjustments of the underlying set ups [39–41]. Furthermore, these devices fail to provide features to personalise the settings that fits the practical reality of routine changes in the daily life of a patient [42]. Continuous glucose monitoring systems have provided a more reliable data source for patients and clinicians. However, as with self monitoring blood glucose (SMBG) data, the compilation including statistical and graphical inferences remain varied among manufacturers which makes the interpretation, pattern finding, and reflective learning a cumbersome task. There have been various efforts to standardise the views of the presented analyses of the data [43–45]. However, these remain tailored towards clinical use and complicated for the average patient. These shortfalls limit the uptake of proximal technologies for clinical use and hinders the effective communication of the reviewed data between patients and clinicians.

Medical device developers efforts have been somewhat limited in enhancing patients' experience due to the lack of human factor engineering in their design processes [46]. The utilised plan based development life cycles has provided the procedures and factors for compliance with standards and regulations [47]. However, this has often resulted in products that do not meet the needs of the end-users to maximise the benefits and enhance the provided care [48]. Furthermore, there is no established evidence of user-centric design or the efficacy

of the currently used technologies such as telehealth systems in type 1 diabetes management outcomes [38].

Researchers' effort to develop relevant technology related studies such as telehealth in diabetes has been undermined by the rapid shift in the technology landscape [38, 49, 50]. Hence, the prolonged diabetes clinical pilots and trials are at constant risk of potential irrelevance by the time of establishment of the study findings, even possibly being obsolete.

Many proposed methods for decision support and predictions such as the estimation of HbA1c levels are developed and evaluated in studies under burdensome circumstances for patients and/or on a very selective population [51–53]. These impede adapting the methods in clinical practice for wider use and benefit.

Sustaining the improvements gained through structural educational programmes are hampered by the lack of tools to assess current insulin requirements, and psychological support to cater for the continuous demands of everyday life with type 1 diabetes [35, 54]. Therefore, to sustain the patient's engagement and their quality of life, continuous assessment and negotiation of the self-care plan are required [55]. Shortfalls in social support, restricted access to care, and financial constraints result in a disruption in achieving the expected self-management targets [56, 57]. The following objectives are outlined to address the issues raised by advocating the use of telehealth to present a holistic platform that provides user-centred solutions.

1.1.2 Research objectives

In the light of the above, it is deemed necessary to research the major influential aspects of type 1 diabetes management as outlined below:

- **Guidelines and recommendations:** investigating current practices and patients adherence based on SMBG readings. This enables a better understanding of the behavioural and glycaemic patterns to identify pitfalls. Also, to provide recommendations on glycaemic targets to enhance engagement and reduce the exhaustion and anxiety expe-

rienced by type 1 diabetes patients. This requires access to a comprehensive dataset on SMBG data.

- **Clinical outcome measures:** improving on HbA1c prediction to provide a quicker and continuous effective feedback on patients' glycaemic control. The requirement is to provide a solution that is adaptable especially in low adhering patients to treatment guidelines.

- **Proximal technology:** automating the contributing factors in employing technologies such as bolus calculators in glucose meters and pumps that are at patients' disposal to improve accuracy, context and reduce the burden on patients and clinicians. It is desired to develop an applicable method that can be implemented in proximal devices with limited computing power.

- **Distal technology:** developing a holistic diabetes management platform to provide inferences, tools and support through iterative processes to include the end-users for better design.

- **Clinical pilot trial:** evaluating and enhancing the developed technologies to support the DAFNEplus clinical pilot trial technological arm.

Ultimately, the thesis focuses on chronic disease management in adults/adolescents with type 1 diabetes to improve self-care and clinical support. It is aiming to improve glycaemic control, as measured by HbA1c, and reduce the risk of complications. Also, reducing care cost by utilising modern technological advancement in smart-phones, wireless communication and cloud-computing to offer a structured approach to inferences and decision making.

1.2 Methodology and Thesis Outline

To facilitate the exposition of the proposed solutions, the thesis is organised into 7 chapters. Pivotal to satisfying the research objectives is to understand diabetes and its treatment. Hence, Chapter 2 discusses various diabetes types and explores the current treatments and

clinical practices for managing diabetes, especially type 1 diabetes. Since there are many guidelines and recommendations for diabetes management, investigating their conformity and applicability for patients in the current context of health care is explored in Chapter 3. Also, it investigates possible glycaemic control targets based on percentages in-range. Furthermore, it proceeds by looking into patients' behavioural traits under out-of-range glycaemic episodes. To this end, a novel dataset was introduced.

Following the previous analyses, Chapter 4 investigates the glycaemic patterns to identify contributing factors on glycated haemoglobin A1c levels of patients. Artificial intelligence provided the opportunity to further explore the high dimensional time-series data of type 1 diabetes. The models were developed bearing in mind their practicality and applicability in the real world where data are imperfect and sparse.

The work in Chapter 5 identifies diurnal patterns utilising type 1 diabetes generated data to recommend changes in the time settings of the bolus calculators. The performance of the developed model is demonstrated to reach experts' recommendations or exceed it. The chapter progresses by exploring the current limitations and provides solutions utilising the developed model.

Chapters 6 and 7 demonstrates the agile development of a telehealth system in a technology related clinical pilot trial for type 1 diabetes patients. Additionally, it explores the various components of a holistic platform that tackles the challenges in type 1 diabetes care and support factors. It presents the efficacy of the system as measured by the usability and clinical outcomes.

Finally, Chapter 8 provides a résumé of the thesis. It discusses the importance of translational engineering in diabetes care as demonstrated in the presented work. Also, it is seen that the developed work provides a platform that paves the way for further improvement to enhance the data-driven care model, reduce cost and most importantly improve the lives of people with type 1 diabetes. Hence, its consideration for the use in the upcoming DAFNEplus randomised controlled trial.

1.3 Summary of Contributions

The research work presented in this thesis focused on delivering new user-centric and applicable designs, analyses and models whereby the beneficiaries are both the patients and their clinicians. The patient who has to manage the complex needs of diabetes disease throughout their lifetime optimally; and the clinicians to prioritise their effort and resources in an optimal way. The research carried out resulted in the following key contributions:

- A novel dataset of SMBG time-series data of type 1 diabetes patients
- A novel mid-term recommendation targets for glycaemic control based on proportions of glucose ranges
- A novel analysis of patients adherence and glycaemic behaviour
- A novel look into HbA1c and its prediction based on glycaemic patterns
- A novel use of haemoglobin glycation index (HGI) measure and its relationship to the HbA1c prediction
- A novel application of artificial intelligence for HbA1c prediction using time series data of type 1 diabetes patients and their glycaemic patterns
- A novel diurnal pattern recognition based method on SMBG measurement patterns for change in settings of bolus calculators in pumps and glucose meters
- A successful pilot trial using the developed system in the study
- Identification of components of a proprietary telehealth system using an iterative agile development model while meeting the regulation and standards for the pilot trial
- Novel patient centred telehealth system that includes novel structured graphical inference and data interpretation; gamification of components and e-Learning for type 1 diabetes which promotes proactive and data-driven care support model
- Selection of the work carried out in the thesis for the adoption in DAFNEplus randomised controlled trial

1.4 Research Publications

The research presented in this thesis has resulted in the following publications:

- Eissa, M.R., Benaissa, M., Good, T., Hui, Z., Gianfrancesco, C., Ferguson, C. and Elliott, J., 2022. Analysis of real-world capillary blood glucose data to help reduce HbA1c and hypoglycaemia in type 1 diabetes: Evidence in favour of using the percentage of readings in target and coefficient of variation. Diabetic Medicine, p.e14972 [58]. (Chapter 3)

- Glycaemic patterns affect on HbA1c prediction in type 1 diabetes, Diabetes Care Journal. (To be submitted)

- M. R. Eissa, A. Zaitcev, Z. Hui, T. Good, J. Elliott and M. Benaissa, "A Deep Neural Network Application for Improved Prediction of HbA1c in Type 1 Diabetes," in IEEE Journal of Biomedical and Health Informatics, doi: 10.1109/JBHI.2020.2967546 [59]. (Chapter 4)

- M. R. Eissa, T. Good, J. Elliott and M. Benaissa, "Intelligent Data-Driven Model for Diabetes Diurnal Patterns Analysis," in IEEE Journal of Biomedical and Health Informatics, doi: 10.1109/JBHI.2020.2975927. [60] (Chapter 5)

- A holistic platform for diabetes self-management: a case study, IEEE Journal of Biomedical and Health Informatics. (To be submitted)

Chapter 2

Diabetes care

Diabetes mellitus is a chronic disease characterised by a metabolic disorder that results in an increase in the blood glucose levels. It is caused either by the lack of insulin secretion in the blood or an abnormality in the cells' response to the insulin. It can mainly be categorised as Type 1, Type 2 and Gestational Diabetes. In type 1 diabetes, the autoimmune system attacks the responsible cells for insulin production—β-cells—in the pancreas. Hence, patients with Type 1 Diabetes are insulin dependent. In Type 2 diabetes, the insulin level is either insufficient or cells are resistant to the insulin [22, 23]. Gestational diabetes is prevalent in pregnant women and usually is temporary to the pregnancy period.

The treatment for diabetes is to manage the disease. The main goal of diabetes management is to maintain the blood glucose level near normal to avoid complications. These complications can either be short term such as hypoglycaemia (low blood glucose level), hyperglycaemia (high blood glucose level) or long-term such as retinopathy (eyes), cardiovascular disease (heart), peripheral vascular disease and cerebro-vascular disease, nephropathy (kidney), neuropathy (peripheral nervous system). The scope of the review in this chapter is defined as the technologies in diabetes care, including basics of diabetes as a condition. Therefore, a search was performed mostly on the Web of Science Core Collection, and Google Scholar for a combination of terms such as; diabetes, technology, telehealth, telemedicine, type 1, type 2, gestational, insulin, and artificial pancreas.

2.1 Background

The prevalence of Type 1 diabetes is increasing in the world. The rate of incidence varies even amongst neighbouring countries. For example, Finland has a higher incidence than Sweden [1].

Type 1 diabetes is diagnosed by having a fasting blood glucose level of greater than 7.0 mmol/L, and random blood glucose levels of greater than 11.1 mmol/L [61]. Careful diagnosis is crucial for the care-plan to avoid further complications. However, there is a 5-15% possibility of misdiagnosing the patient to Type 2 diabetes in adults [62]. Symptoms such as polyuria, polydipsia, ketosis, weight loss, age below 50-years, BMI below 25 kg/m^2, and personal/family history of autoimmune disease are investigated [23]. A possible candidate of diabetes experiences decreases in the response of C-peptide and an increase in the fluctuation of their blood glucose level. This is associated with substantial loss of the β cells. At this point, the patient is insulin dependent [1](Figure 2.1).

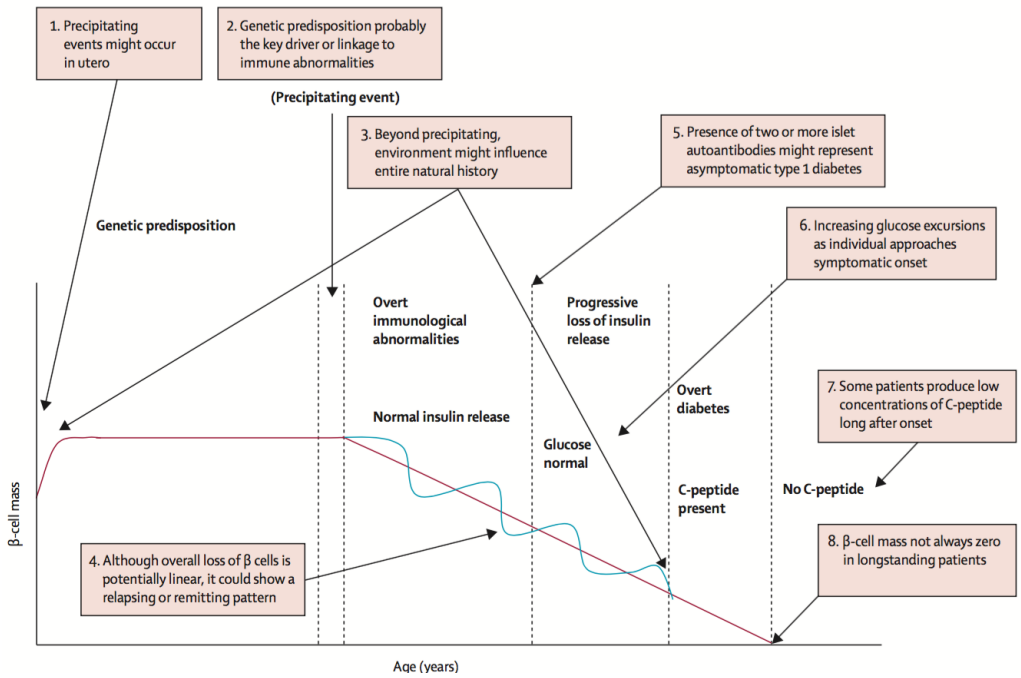


Fig. 2.1 Type 1 diabetes progression through the loss of β cells [1]

The ability to retain β cell function is heterogeneous. Factors as genetic, age and intensity of disease management can influence the process.

2.1.1 Gestational diabetes

Gestational diabetes mellitus (GDM) is a glucose intolerance occurring during pregnancy period [63]. It can be treated either using insulin therapy or diet modification. Also, it is possible that the condition persists after the pregnancy [64]. In some cases, the patient has had diabetes but has not been diagnosed before the pregnancy.

GDM occurrence in England, Wales, and Northern Ireland is one in 250 pregnancy[9]. GDM increases the risk of macrosomia [65]. Macrosomia is the overnutrition of the foetus. The increased transplacental transfer of maternal glucose increases the level of insulin generated by the foetal pancreas. Insulin highly contributes to foetal growth. Moreover, other contributing factors such as insulin resistance and inflammation can be identified by the maternal metabolic environment. These factors increase the excess of glucose, amino acid and free fatty acids [2].

Macrosomia increases the possibility of undergoing a cesarean delivery. Other associated complications can be neonatal hypoglycaemia, jaundice, polycythaemia, and hypocalcaemia [66, 67]. Long-term complications in infants born to mothers with GDM are: maintaining impairment to glucose tolerance, obesity, and lower intellectual performance [68–70]. Figure 2.2 shows the impact of GDM on the infant in different stages.

2.2 Self-management of Diabetes

The disease management of type 1 diabetes includes frequent blood glucose measurement, injection of insulin, healthy diet, and exercise. The patient performs a blood glucose measurement before consuming a meal or snack. Then, the measured blood glucose level can be interpreted as follow:

- Within normal range: Injects insulin regarding their carbohydrate intake using their insulin to carbohydrate ratio.

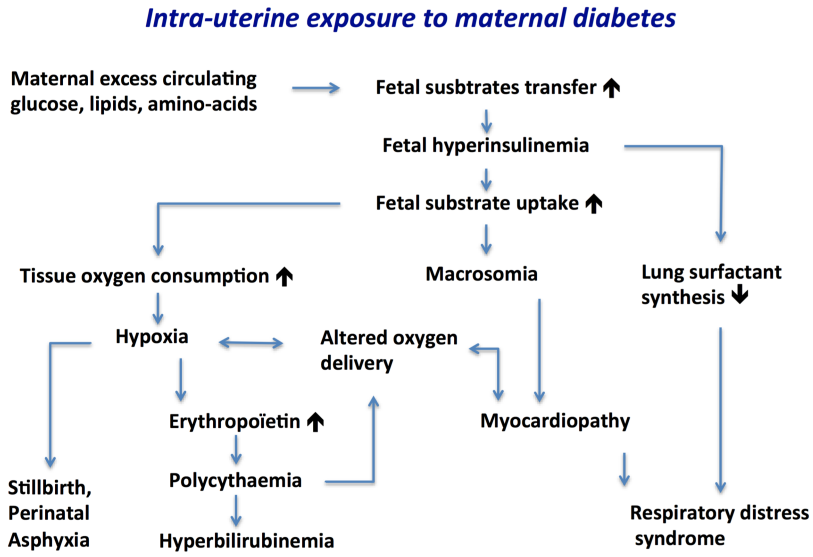


Fig. 2.2 Short-term complications in the offspring [2]

- Above normal range: Injects insulin regarding their carbohydrate intake plus a corrective dose of insulin for their high glucose level
- Below normal range: They consume fast carbohydrate (i.e. "Jelly beans") to correct their glucose level to normal.

On occasions of acute complications such as hyperglycaemia and hypoglycaemia patients perform a further blood glucose test to determine the appropriate action.

2.2.1 Insulin analogue therapy

In Type 1 diabetes, insulin injection is used to replace the lack of production of insulin in the body. Insulin causes glucose influx into the cells using insulin receptors located on the cells. Figure 2.3 shows the release and existence of insulin secretion in the body of a non-diabetic person in response to food consumption. It includes insulin secreted at two rates: basal insulin, and bolus insulin. Basal insulin is present throughout the day to regulate lipolysis and hepatic glucose output. Bolus insulin is released to accommodate the increase in glucose level in the blood by food intake. The bolus insulin is characterised by the magnitude (concentration) and duration (active time). The magnitude is in response to the content of the

meal, and the duration is dependent on the glucose form of the food. Constant adjustment to the insulin is triggered by various factors such as the change in hormones, and activity levels. It is an essential part of the process of maintaining the glucose level in its normal band [71]. The euglycaemia range is between 3.5 to 7.5 mmol/L.

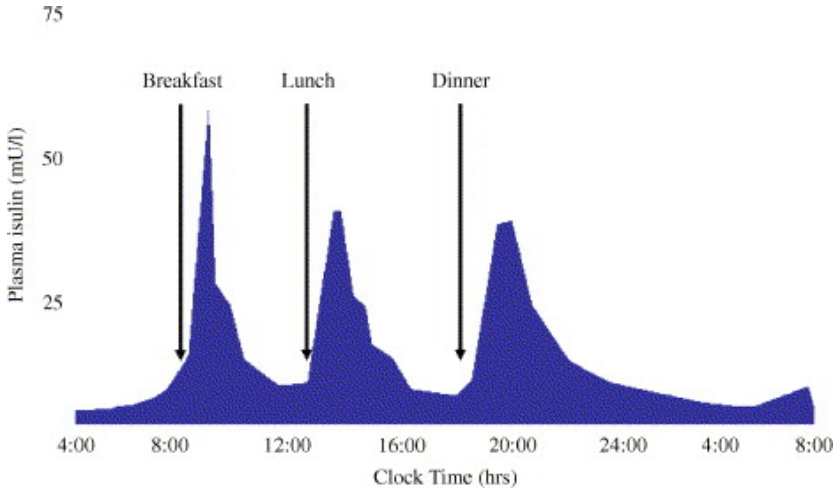


Fig. 2.3 Daily Insulin

This analogy has been used in multiple dose injection (MDI) therapy for diabetes management. However, insulin response varies among different people. A different insulin dose is required for the same amount of carbohydrate intake by various patients. Therefore, individualised insulin to carbs ratio is determined by the clinician and advised to the patient. The patient uses the advised ratio or applies an adjustment to calculate the required insulin dose for their meals. This injection deals with the spikes occurring during mealtimes. The background insulin (long-acting insulin) for the newly diagnosed patient usually starts with $\sim$0.3U/Kg/day and later adjusted to accommodate the patient's need. Throughout the day, constant blood glucose measurement is advised. Thereafter, an insulin dose is injected to maintain the blood glucose level to a targeted range and close to the euglycaemia range. Different insulin products have different responses. Figure 2.4 compares insulin types by their peak effect and the time response. Implicitly, timely injections and blood glucose measurements are vital in MDI therapy [72].

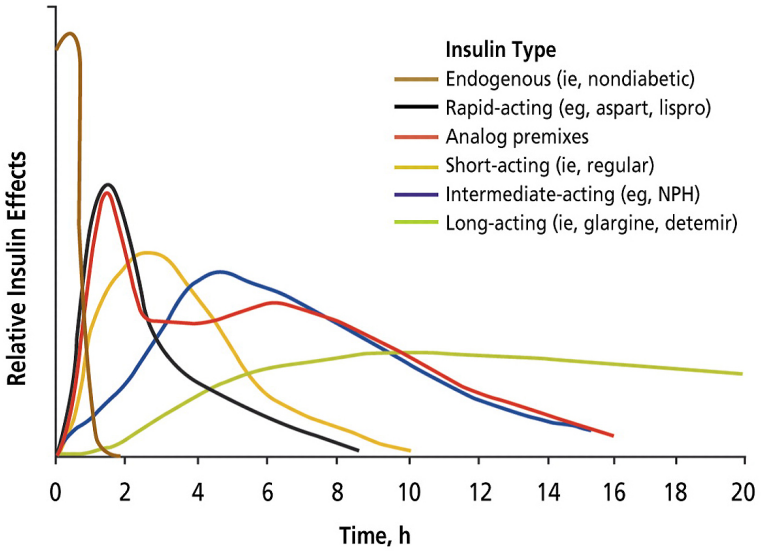


Fig. 2.4 Insulin Comparison

Hyperglycaemia

The injected insulin analogue cannot provide the same action time for insulin of a non-diabetic person. Hence postprandial hyperglycaemia can occur if the insulin injected does not correct for the excess glucose. Also, insulin resistance can cause hyperglycaemia. The resistance of the body to the insulin demands larger doses of insulin injections. Hyperglycaemia is categorised as mild or significant hyperglycaemia based on blood glucose (BG) levels.

Hypoglycaemia

The risks of hypoglycaemia can increase if the timing and the amount of administered insulin are not appropriate. Particularly, this raises concerns on nocturnal glucose levels. Therefore, achieving euglycaemic control might increase the frequency of hypoglycaemia. These are categorised as mild, significant, or severe episodes. In the cases of mild and significant hypoglycaemia, the patient can self-manage the episodes by consuming rapid-acting carbohydrates. However, severe hypoglycaemia, defined as needing the help of a third party to recover, includes confusion, loss of consciousness, seizures and coma.

Diabetes and driving

The driving and vehicle licensing agency (DVLA) outlines the driving license requirements for a person with diabetes [73]. Car and motorcycle drivers are in Group 1 while bus and lorry drivers are in Group 2. The difference in these groups lies in the hypoglycaemia occurrence and frequency of BG monitoring. Group 1 is required to have an adequate awareness of hypoglycaemia. They are allowed to only experience a single episode of severe hypoglycaemia in the preceding 12 months whereas in group 2, full awareness of hypoglycaemia and no episode of severe hypoglycaemia in the preceding 12 months is required. Further for group 2, DVLA requires patients to use glucose meters that can hold 3 months of glucose readings, demonstrate an understanding of the risks of hypoglycaemia and perform two tests a day besides the 2-hour intervals of BG testing while driving or intention of driving. Similarly, DVLA recommends group 1 to perform the 2-hour intervals testing. Patients are required to report changes of their condition and suspend driving if they experience a severe hypoglycaemic episode. These trigger a medical inquiry to assess the eligibility for driving.

2.2.2 Proximal technology

Proximal technologies refer to electronic devices that operate in proximity to patients such as glucose meters and insulin pumps.

Glucose meter

Frequent measurement of blood glucose is an essential part of diabetes self-management. A glucose meter (glucometer) provides the tool to carry out this task. These are regulated by the International Organization for Standardization (ISO) to receive the CE approval. The latest update of the criteria was published in 2013 and the European equivalent of the standard was adopted in 2015 as EN ISO 15197:2015. The ISO:15197:2013 states:

"At least 95% of the system measurement results be within ±0.83 mmol/L of laboratory results at concentrations of $<$ 5.55 mmol/L and within ±15% of laboratory results at

concentrations of ≥5.55 mmol/L". Companies have to comply with the new standards within 36 months [74].

Nowadays, insulin pumps and continuous glucose monitoring (CGM) are increasingly contributing to diabetes care.

Insulin pumps

Insulin pumps contain an insulin reservoir that infuses the insulin continuously under the skin through a tube and cannula [75]. It is also referred to continuous subcutaneous insulin infusion (CSII). Insulin pumps are configurable to administer insulin based on pre-programmed settings. This provides a more accurate method (if the settings are correct) of insulin delivery, particularly at night. For mealtime injections, the user can utilise the bolus advisor provided in the handset of the pumps to aid with calculations. The potential advantages of the pumps are reduced risk of hypoglycaemia and more flexibility in insulin administration.

Continuous glucose monitoring

Continuous glucose monitoring (CGM) utilises sensors that measure the interstitial glucose levels every few minutes (i.e five minutes) [76, 77]. Real-time CGM (RT-CGM) provides alarms in the events of hypoglycaemia and hyperglycaemia [78]. These sensors rely on continuous calibration by capillary blood glucose measurements [79]. Additionally, the active nature of the device (i.e. alarms) can result in irrelevant notifications and be intrusive. Flash CGM (FGM) are factory calibrated and passive that requires patients' scan of the sensor to acquire a BG measurement (such as Freestyle Libre) [80]. FGM are less costly compared to CGMs.

Bolus calculators

Multiple daily injection therapy requires calculation of the insulin dose [39]. The needed dose is calculated based on the preprandial blood glucose, carbohydrate intake, insulin to carbohydrate ratio, insulin sensitivity factor, BG target ranges and insulin-on-board. These parameters increase the complexity of the calculation and can be challenging for people with

low numeracy. Therefore, bolus calculators with predefined settings of the aforementioned parameters can reduce the burden, provide a higher flexibility and increase the confidence in bolus calculation. Bolus calculators are increasingly integrated into glucose meters and pumps. However, to maximise the benefits of the bolus calculators, continuous review of the underlying settings are required [41, 81].

Artificial pancreas

Employing the insulin pump and CGM in a closed-loop scenario introduces new possibilities. This integrated closed-loop system is also referred to as the artificial pancreas (AP). These closed loop solutions therefore require a CGM, an insulin pump, and a control algorithm. The control algorithm regulates the insulin delivery considering the BG levels, pharmacokinetics of the insulin, and the possible absorption rate of carbs for a person. The control algorithms currently developed are either based on model predictive controls (MPC) or proportional integral differential controllers (PID). The main differences between the two approaches are: the way the insulin requirement (e.g. insulin sensitivity, carbs to insulin ratios) is calculated and also the extent in time where glucose levels are predicted. In some systems, the regulation occurs when hypoglycemia is predicted, which triggers a shut down of the insulin supply. In this scenario, since it is solely the scale down of insulin, hyperglycemia is not treated by the algorithm, the closed-loop system is not realised. A complete closed-loop system can be realised when an increase in insulin is also possible. Furthermore, a hybrid approach is used where the person manually summons the amount of injected insulin for carbs, usually using a bolus advisor. Therefore, a fully automated closed-loop system is achieved when the needed insulin for meals is calculated only based on continuously measured glucose levels [82]. The control algorithm is either hosted on the insulin pump or a handheld device. The closed-loop systems can also be categorised based on their use of single hormone supply (i.e. only insulin) or dual hormone (i.e. insulin and glucagon) for regulating BG levels [83].

Studies have tested the integrated closed loop for insulin injection during the night to improve the overnight glycaemic control. It is shown that it can provide a safer and more efficient glycaemic control and reduces the hazard of hypoglycaemia compared to the

traditional insulin pump therapy. But most of the benefit is overnight, as they struggle to cope with carb loads during the day. [84–86].

2.2.3 Distal technology

Distal technology are the systems that offer remote services [38]. These systems can include telehealth (i.e. health delivery via telecommunications), mobile health applications, game-based support, social platforms and patient portals. However, adopting such systems remains challenging. The review of 141 randomised controlled trials (RCTs) in telehealth for chronic disease management identified that the evidence in their effectiveness is inconclusive [87]. These effective (or ineffective) systems seem to be across different diseases. The study also points out that most studies have been conducted in short periods (median of 6 months). This is counter-intuitive to lifelong chronic diseases.

The findings are also mirrored in numerous reviews and meta-analyses carried out in diabetes telehealth [88–95]. In [96], the improved HbA1c in 111 RCTs showed statistically significant but modest levels. Quantified heterogeneity of studies was higher than 60% which points to the bias in the reported results of the studies. In addition, [89] points out the high attrition rate in the studies. [90] presents the need for including marginalised patients of the traditional healthcare in telehealth studies. In [91] affirms the inconclusive evidence on distal technologies and mentions that telehealth studies are mostly tailored towards type 2 diabetes. In [94], the meta-analysis showed that the improvement was not consistent over time; and it indicates the need for studies of long-term effects of telehealth. [97] argues the need for integrating the diabetes data of telehealth systems in electronic health records to provide a consistent workflow for providers and benefit for patients in attempts to increase the usability.

The review of 71 mobile applications and 16 mobile application articles showed most available applications offer the primary features such as medication, blood glucose monitoring, diet management and physical exercise [98]. However, the applications suffered from limitations. From the 71 applications, only 3 of them featured automated data collection. Patients favour automated data entry compared to manual entry, thereby resulting in more

data capture [98]. Most applications did not incorporate educational material. Furthermore, the data was not synced to the patient's record in health-care service for health care providers to access. Another review of 10 salient apps also have concluded that the apps can be beneficial; confirming patients being able to better track their glycaemic control with the emerging trend of utilising smartphones for health support [99, 100].

A recent and more comprehensive review of distal technologies highlights the possible irrelevance and redundancy of the studies due to the shift in the technology landscape [38]. It recognises the significant potential that such changes in technology can also provide. Therefore, methods that can consider the pace of the technology whereby includes data-driven designs utilising machine learning and artificial intelligence capabilities have the potential to transition the current care paradigm in type 1 diabetes.

2.2.4 Structured educational programmes

Educational programmes are utilised to inform the patient about diabetes and its requirements for optimal management. This is to enhance patients knowledge and confidence in insulin self-adjustment and carbohydrate counting. Among such programmes is dose adjustment for normal eating (DAFNE) [30]. DAFNE is facilitated by trained educators on a 5-day course. Currently, more than 70 centres in the UK provide the programme [101].

2.2.5 Influence of lifestyle

Lifestyle is the behavioural patterns of an individual. These patterns are shaped by person's characteristics, social interactions, socioeconomic status and environmental living conditions [102].

Physical activity

The general benefits of activity such as increase in well-being, lower risk of cardiovascular mortality and obesity are transferable to diabetes patients. Also, higher levels of physical activity have been shown to improve HbA1c levels [103, 104]. Exercise increases the insulin

sensitivity which results in lower insulin consumption [105]. However, the evidence of the effect of physical activity in type 1 diabetes is scarce [106]. Therefore, most of the recommendations are based on studies on type 2 diabetes or the general population.

Nutrition

The diet options in type 1 diabetes person remains similar to the non-diabetic person. The meal time injections of the insulin analogue allows for normal eating by adjusting the amount accordingly [107]. This is one of the points promoted by DAFNE to facilitate a non-restrictive diet [30]. However, the risk of an eating disorder is higher among type 1 diabetes patients in comparison to the non diabetic population. This adversely affects the compliance with insulin administration [108, 109].

Alcohol

Alcohol consumption increases the risks of hypoglycaemia. Also, alcohol can influence the ability of self-management. This can result in noncompliance with BG testing and insulin omission. Hence, it can have an adverse effect on glycaemic control and risk of diabetic ketoacidosis (DKA) [110].

Psychological stress

Stress can result in hyperglycaemic episodes [111]. Therefore, increased stress is associated with difficulty in glycaemic control. The change in glucose levels varies among individuals under stress; in some, this change is not noticeable [112].

Socioeconomic status

In type 1 diabetes, higher education and higher income are associated with lower complications such as renal disease and peripheral arterial disease [56]. Higher education level was associated with lower mortality. These associations can be mediated by lower adherence and presence of comorbidities [57].

2.3 Hope vs Hype

The ultimate hope of a diabetes patient is the cure of the disease. Perhaps more attainable hopes are medical procedures that eliminate the burden of the disease or reduce its significance. To this end, many advances in the medical field have shown promising progress. However, the delivery of the information regarding these advancements might have resulted in unrealistic hope among patients and their families [113]. Among these hyped up treatments are:

Prevention of diabetes There is evidence on preventing type 1 diabetes in animal models. However, it is yet to be proven successful in humans [114, 115]. The studies in human beings have been carried out by screening the relatives of type 1 diabetes patients. This is a resource-intensive process since 95% of the relatives would not possess the antibodies [116]. Also, it remains unclear the type of effective intervention to be tested on the identified individuals.

Pancreas transplantation This type of transplantation was started in 1967 which later showed a reasonable improvement in glycaemic control [117, 118]. Combining the pancreas transplantation with kidney transplantation resulted in higher survival rates [119]. As with any transplantation procedure, the associated complications proved challenging; the risks of acute rejection, the need for chronic immunosuppression, infectious complications are among the morbidities of the procedure. More importantly, the recurrence of diabetes cannot be ruled out. Another limiting factor is the shortage of donors that results in a long waiting time. Furthermore, evidence of the risks, benefits and cost-effectiveness of the transplantation remains understudied [120].

Islet transplantation A less invasive alternative to pancreas transplantation is the islet transplantation. Hence, it is associated with reduced risks of morbidity [121, 122]. However, a need for a second islet transplantation or insulin therapy is possible since the transplanted islets can fail to produce insulin. Additionally, the donor shortage is a hurdle to overcome.

β-cell survival Studies have utilised immune interventions to increase the survival rate of the β cells [115]. However, this approach has not shown consistent improvement. The patients experience a transient improvement in the retention of β cells, however the later progressive decline results in similar outcome to the control patients of the studies.

Immune tolerance Evidence of the success of immune tolerance in allergy is established and the efforts to replicate their results in type 1 diabetes are under study. In this treatment, patients are exposed to immune interventions for a period to increase the chances of entering an immune tolerance state. This results in the body ceasing to attack the β cells. In a study, a 6-day intervention resulted in preserving the β cells for 18 months. Also, a lesser insulin need was reported among the intervention group in a 4-year follow-up [123] . Due to the lack of sufficient data and follow-ups, the evidence is yet to be established for the effectiveness of the applied methods. Additionally, immune tolerance is not proven to be successful in other autoimmune diseases.

Artificial pancreas The closed-loop insulin delivery triggered by continuous sensing of the glucose levels is a promising solution. In recent years, improvement in insulin analogues and sensing of interstitial glucose levels has made the solution more viable. However, the delays in glucose sensing and insulin action time remain challenging. This results in the artificial pancreas being costly and ineffective in unexpected situations such as increased activity and meal consumption. Therefore, its use mostly has been for nocturnal control of glucose levels.

2.4 Discussion

Despite the progress made in the medical field, the hope of curing or eliminating the need for intensive self-management remains unreachable. The current research endeavours are promising, but the time needed to achieve these goals is unclear. Hence, alternative solutions for the demanding type 1 diabetes needs are required. Additionally, efforts to help patients

have the least risk of complications will increase their prospect of benefiting from future developments or chances of a cure.

Any technology-related research is required to consider and evaluate the shift in the technology eco-system. The technology is evolving based on Moor's law on a yearly basis. Moor's law states that the increase in the efficiency of technology intertwined with an adjusted reduction in prices make the technology evolve and be affordable [124]. Although it might not be at the same pace, healthcare can use a similar concept to Moors law. This will help the effective translation of technology in healthcare by optimising advancements in technology and reduce costs.

In conclusion, type 1 diabetes patients have to continuously make medical decisions throughout the day. The effective use of technology has the potential to help reduce the burden, educate and provide social support to patients. Patient-centred systems can provide reinforcement of learning, facilitate structured review tools, and if needed, the support of clinicians. This has the potential to promote sustainability of self-care practices gained in the structured educational programmes. Additionally, behavioural modification approaches are needed to encourage patients to engage and adhere to the use and follow-up of the offered technology. The possibility of such systems is becoming more feasible with the current advances in technology. The thesis provides solutions to enhance translational technology in type 1 diabetes self-management by capitalising on these advancements alongside the recent developments on big-data and machine learning techniques.

Chapter 3

Glycaemic Targets and Behaviours

The Diabetes Control and Complications Trial (DCCT)[27] demonstrated the benefits of intensive treatment of type 1 diabetes in reducing the risk of long-term complications. It showed that reducing HbA1c levels is associated with lower rates of diabetes complications, such as eye, kidney and nerve damage. Self-monitoring of blood glucose (SMBG) facilitates adjustments of diabetes treatment. Many guidelines and educational programmes are carried out in the interest of optimising self-management for diabetes patients, as opposed to all adjustments being healthcare professional initiated. Nowadays, SMBG results are utilised to plan nutrition therapy, physical activities, reducing hypoglycaemia, and adjusting insulin doses. Guidelines recommend the performance of SMBG tests before every meal and before bed. Also, these guidelines outline SMBG target ranges before meals and before bed as an intervention measure to try to achieve near-optimal HbA1c levels for diabetes patients.

Structured educational programmes are designed to train patients to perform SMBG tests, estimate carbohydrate intake, administer insulin injections, plan exercise, and deal with glycaemic events such as hypoglycaemia and hyperglycaemia. In addition, patients are educated to self-manage their diabetes by reviewing and amending their treatment regimen regularly. Patients are required to invest a considerable amount of time for their diabetes management. However, adherence and engagement with the guidelines and treatment plans remain challenging. Furthermore, success or failure to achieve better glycaemic control, considering the associated effort can result in stress, and anxiety.

A retrospective analysis of a novel dataset was conducted to evaluate diabetes management in the real world, examining the adherence to the guidelines and diabetes targets. Additionally, more achievable targets and recommendations are explored to possibly increase adherence and engagement of patients; thereby helping to reduce the associated anxiety and stress with diabetes self management.

3.1 Background

Diabetes education is an essential part of diabetes management. It paves the way for patient empowerment and their active informed engagement with the disease. These programmes are designed for patients to attend after 6-12 months of diagnosis [23, 125].

Dose adjustment for normal eating (DAFNE) facilitates patients engagement and empowerment by goal-setting and problem-solving practices throughout a five-day educational course [126]. DAFNE promotes the improved glucose control (HbA1c) by trained educators during the course [127, 128].

The HbA1c test is recommended to be carried out every three to six months [23, 125, 129]. Recently, the aim for the HbA1c level is established as 48 mmol/mol(6.5%) although previously 58 mmol/mol was recommended. Also, National Institute of Health and Care Excellence (NICE) emphasises personalisation of the targets based on the daily activities, comorbidities and history of hypoglycaemia. To achieve the <48 mmol/mol HbA1c target, performing at least four tests a day, before each meal and before bed is recommended. The recommended glycaemic target ranges for SMBG tests are : 5-7 mmol/L before breakfast; 4-7 mmol/L before meals at other times of the day; and 5-9 mmol/L for 90 minutes or more after the meal. Studies have shown an association between increasing the numbers of tests and improvement of HbA1c levels [130–134]. Considering the outlined target ranges, it is implicit to exhibit low variability. There have been studies showing increased variability is correlated with higher HbA1c levels [52, 135–137].

Demands of diabetes can cause emotional stress which affects the patient's glycaemic control, relationships in addition to its psychological ramifications [138, 139]. This can

also occur when doctors and other health care professionals demand unrealistic expectations from patients without fully understanding how difficult it is to achieve stable blood glucose levels at these targets [140]. These can contribute to increased risk of hyperglycaemia and hypoglycaemia in patients.

The over-correction of a hyperglycaemic excursion can potentially cause hypoglycaemia [141]. Furthermore, incorrect treatment and follow up of each hypoglycaemic reading can contribute to the increased risk of a hypoglycaemic reading shortly after the episode. The recommendation for hypoglycaemia treatment is 15 g of fast-acting carbohydrates such as "Jelly babies" followed by a retest in 15 minutes interval until the BG level surpasses 4 mmol/L [142]. However, a recent study suggested a weight based on 0.3 grams of glucose/kg is more effective in treating hypoglycaemic episodes [143].

NICE's recommendations and guidelines are evidence-based and designed to improve diabetes quality of life and reduce acute and long-term complications [23]. Despite the considered benefits of adherence to the guidelines, many patients tend not to follow the therapeutic tasks for various reasons [35, 55]. These reasons can be the burden associated with tighter glycaemic control while perhaps little to no perceived benefit experienced. Some might find the glycaemic targets not realistic to their individual lifestyle and needs. Others might understand the guideline as a recommendation rather than a treatment plan. Fear of recurrence hypoglycaemic of episodes might affect their decision on treatment. A qualitative longitudinal study of post DAFNE experience of patients with blood glucose targets showed that patients find the guidelines and the targets useful, structural and sensible to use [54]. These targets enabled the patients to adjust their insulin doses appropriately. However, patients changed the targets over time. These changes were applied to simplify the targets (easier to remember), more attainable based on their lifestyle, to reduce the associated anxiety, consolidate the feelings of failure and to avoid the possibility of hypoglycaemia. NICE recommends against amending glucose targets [23, 125] even as a treatment for recurrent hypoglycaemic episodes. Hence, it recommends closer monitoring and education as a first step; and on further intervention, incorporating technologies such as pumps or sensors to help with diabetes management.

Additionally, the HbA1c alone is not sufficient to describe the status of diabetes management, especially for short-term (daily) and mid-term (two weeks) periods. More importantly, studies have shown that only about 25% of patients with diabetes have a good understanding of the HbA1c as their diabetes marker [144–147]. There is also an association between this understanding, HbA1c levels and self-care behaviours. Therefore, there is a need for education and other relatable metrics that are easy for patients to understand and track.

There have been efforts to relate the HbA1c with average blood glucose levels to improve the comprehension of the HbA1c test results [51, 135, 148]. The estimated average glucose (eAG) translates the laboratory HbA1c result, reported in mmol/mol or %, to its equivalent average BG levels in mmol/L [51]. The eAG is widely implemented in diabetes management software. However, the accuracy and generalisation of the methods are yet to be established [149]. We also explore the shortfalls of eAG in details in the next chapter.

Alongside eAG additional markers of glycaemic control are reported on diabetes management software. Among these measurements are percentages of hypo, hyper and in-target readings of SMBG. A study reported the percentages of in-target, hypo and hyper levels in 201 type 1 diabetes patients using Medtronic pumps for insulin delivery [3]. The BG data were collected for the period of 14-28 days. The result of the study is presented in the table 3.1. Based on the reported results, the authors suggest a shift of focus from glycaemic target range to proportions in-target. Nevertheless, the thresholds of these proportions whereby various achievable HbA1c levels are obtained remain under-studied, e.g. for users delivering insulin via pens.

TABLE 3.1
SIVASUBRAMANIYAM ET. AL. [3] REPORTED PROPORTIONS OF READINGS IN VARIOUS GLUCOSE RANGES IN DIFFERENT HBA1C GROUPS

	N=201	n=58	n=107	n=36
BG ranges / HbA1c (mmol/L)/(mmol/mol)		<58	58-74	≥75
<4	Hypo(%)	13.8±12.9	8.8±6.4	4.4±3.2
[4-10)	In-Target(%)	57.3±25.4	50.6±11.1	39.9±16.5
≥10	Hyper(%)	28.9±16.5	40.6±12.1	55.6±17.9

3.2 Research Design and Methods

This retrospective analysis was performed to investigate the glycaemic patterns and behaviours of patients in the real world. Due to lack of a publicly available dataset that includes SMBG and HbA1c result of many patients, we decided to generate a novel dataset. Data wrangling algorithms [150] were used to extract sparse data from various sources of data at STH hospital. Due to the varying sources, the data were unstructured, in different formats and missing key entities. Therefore, at first the data were processed manually to a structured format to enable an algorithm to identify the problematic data points (e.g. the key identifier does not match in various sources, and different spelling of the names). After cleaning the data, various data sources were compiled to optimise the raw data for data analysis. Therefore, the algorithm produced an anonymous dataset including capillary blood glucose readings and HbA1c measurements.

The latest HbA1c lab test and the prior 12-week SMBG readings were extracted for the analyses, using participants' data only once. In the event of hypoglycaemia, since participants are advised to retest within 15-20 minutes, any retest after a reading below 4 mmol/L within 30 minutes was excluded from the analyses of frequency of SMBG. In other words, a hypoglycemic measurement, if followed by another reading within 30 minutes was treated as a hypoglycemia episode rather than a hypoglycemia reading. Therefore, measures based on hypoglycemic episodes help avoid the bias that is introduced by the retest due to the clinical need.

The patients were stratified based on the interquartile range of HbA1c; <58 mmol/mol, 58-74 mmol/mol and >74 mmol/mol. Then, the percentages of the readings in various glucose ranges were calculated. Three glucose ranges were defined for the measured BG results: Hyperglycaemia >10 mmol/L, Hypoglycaemia <4 mmol/L and In-target (or In-range) 4-10 mmol/L.

The analysis continued with a more granular sub-levels of HbA1c to avoid bias based on possible sample imbalance in the HbA1c groups; four HbA1c subgroups based on the interquartile ranges were defined: <58 mmol/mol, 58-66 mmol/mol, 67-74 mmol/mol and >74 mmol/mol. To further define BG ranges the hypoglycaemia range was separated in two

groups: significant hypoglycaemia (<3 mmol/L) and mild hypoglycaemia (3-3.9 mmol/L); also, hyperglycaemia was split into two groups of significant hyperglycaemia (>15 mmol/L) and mild hyperglycaemia (10-15 mmol/L).

The analyses performed in this study are divided into two sub-categories of target-ranges and behaviours. In the target-ranges we analysed the followings for each of the HbA1c subgroups:

- Proportions of data in various SMBG ranges: the percentages of the readings in the different ranges of glucose levels were calculated for each HbA1c group. Due to the assumption of independence in various statistical methods only the unique subjects and their latest HbA1c were extracted.
- The effect of significant and mild hyperglycaemia: using the robust linear regression the relationship between the dichotomised hyperglycaemia range with HbA1c was explored.
- The effect of significant and mild hypoglycaemia: using the robust linear regression the relationship between the dichotomised hypoglycaemia range with HbA1c was explored.

In the behavioural category, we analysed:

- Frequency of performing SMBG measurement: we were also interested in the testing behaviour of patients to observe the frequency of BG readings and its effect on different groups. This behaviour is analysed by looking into the relationship with HbA1c, particularly the effect of increasing the number of daily tests.
- Fluctuations in glucose levels: we look at the relationship between HbA1c and variability in BG. We were also interested in the variability of BG measurements of each HbA1c group. We further analysed the effect of variability on BGs on the occurrence of the hypoglycaemia.
- The effect of over-correction of hyperglycaemia on hypoglycaemic episodes: we investigate the effect of hyperglycaemia over-correction on both thresholds of >10

mmol/L and >15 mmol/L in each dichotomised group of the HbA1c. The difference is measured using a Kruskal-Wallis test followed by Dunn's post hoc correction for the significance of the difference between each pair of HbA1c groups.

- The effect of over-treatment of hypoglycaemic episodes: Over-treatment of hypoglycaemia may result in hyperglycaemic events for ranges >10 and >15 mmol/L. These are presented for each HbA1c group and compared for significance using a Kruskal-Wallis test, followed by Dunn's post hoc correction for potential difference between the groups.
- The possible connection of increased hypoglycaemia episodes and hyperglycaemic excursions in different time-blocks: the day is divided into four time-blocks. These time-blocks' start hours are: 00:00, 06:00, 12:00, and 18:00. Then, the data are grouped based on their timestamp for each time-block and the percentages of the results <4 mmol/L for hypoglycaemia are compared in each group. Additionally, the percentages of readings in hyperglycaemia (>10 mmol/L) for each time-block are compared.
- Patients' hypoglycaemic treatment adherence to guidelines: each hypoglycaemia reading and its following glucose reading was grouped to identify the behaviour of the person when a hypoglycaemic episode occurred. A test within a 20 minute time period was counted as a retest, adherence to the guidelines. Then, these adherence of people was categorised to: mostly retest (retest >60% of their hypo results), sometime retest (retest between 15% to 60% of their hypo results) and rarely retest (retest <15% of their hypo result). Thereafter, these results are compared using a Kruskal-Wallis test for the significance of difference.

Also, a sub-analysis was carried out to examine the effect of insulin pumps and DAFNE educational programmes on glycaemic control.

Statistical analysis

The groups were compared where applicable using either Mann Whitney or Kruskal-Wallis tests. Robust linear regression [151] was utilised for the regression analysis to account for

outliers. A hierarchical linear regression was conducted to examine the variance explained by the covariates. Also, when applicable, the logistic regression results are reported.

To be able to carry out the comparison between the HbA1c groups, the independence of the observations is required. Since a patient with more than one test can belong to different HbA1c subgroups, we used the latest HbA1c test and the associated BG readings of each unique user to mitigate any unintended bias in the selection process.

The statistical analyses were carried out in Python (statsmodels 0.9.0) and R (v3.3.3).

3.3 Results

In order to conduct the study, data wrangling algorithms were used to extract sparse data from various sources at STH hospital [150]. This resulted in a comprehensive novel dataset.

3.3.1 Dataset

Anonymised data of 682 type 1 diabetes patient from Sheffield Teaching Hospitals NHS Foundation Trust from the 4th quarter of 2013 to 4th quarter of 2015 were analysed. NHS permission under STH Ref 20586 was granted for the use of the data. The data contained a minimum of one HbA1c test per patient (maximum of 10) with a mean of 2.4 tests (total of 1886 tests). The demographics (means and standard deviation) were: age 46.5 (17.6) years, BMI of 26.5 (5.07) kg/m^2, and diabetes duration of 23.6 (15.2) years. The majority of the population were white European 90.2%. Female patients constituted 51.2% of the population. The mean of glucose levels was 10.5(2.4) mmol/L, the standard deviation of 4.7(1.3) mmol/L and frequency of SMBG 3.67(1.3) times per day. HbA1c levels were 66.4(13.2) mmol/mol.

In this chapter, the latest HbA1c lab test and the associated 12-week SMBG readings were extracted for the analyses. Patients were stratified based on their HbA1c levels.

3.3.2 Percentage in-target

The percentages of the readings in the different ranges of glucose levels were calculated for each HbA1c group. To be able to carry out the statistical comparison and determine the significance of different levels between the groups, the unique subjects and their latest HbA1c was extracted and the results are presented in the table 3.2. As detailed in the table, the three groups are significantly different in their glycaemic control as measured by their percentages of hypo, hyper and in-target glucose readings.

TABLE 3.2
UNIQUE SUBJECTS OF THE POPULATION PERCENTAGES OF GLYCAEMIC TARGETS PER PATIENT. THE KRUSKAL-WALLIS HYPOTHESIS TEST WAS USED FOR DETERMINING THE DIFFERENCE BETWEEN GROUPS.

	N=682	n=176	n=340	n= 166	
BG ranges / HbA1c (mmol/L) / (mmol/mol)		<58	58-74	≥75	p-value
<4	hypo%	8.8±5.7	7.8±5.4	5.17±5.0	<0.0001
[4-10)	in-target%	61.3±15.1	44.8±11.8	30.4±10.1	<0.0001
≥10	hyper%	29.8±14.1	47.2±13.1	64.3±13.1	<0.0001

Figure 3.1 visualises the percentages of various glycaemic ranges in the HbA1c groups. It is evident from the graph that the prevalence of hyperglycaemia increases with increasing HbA1c levels. Also, the occurrence of hypoglycaemic episodes increases as HbA1c levels are lowered.

We divided the glucose levels to a more targeted and granular range. Figure 3.2 outlines the percentages in the new glucose ranges. The groups remain significantly different in their glycaemic percentages of various ranges of glucose levels ($p<0.05$).

As presented in the Figure 3.2, percentages of the significant-hyperglycaemia approximately doubles as the HbA1c progresses in the groups. We investigated the effect of significant hyperglycaemia further by first splitting the HbA1c groups by the interquartile ranges into four groups. This helped reduce possible bias by the presence of imbalanced population size between the groups of HbA1c. Table 3.3 shows the percentage of BG ranges in each group. The groups remain significantly different ($p < 0.05$).

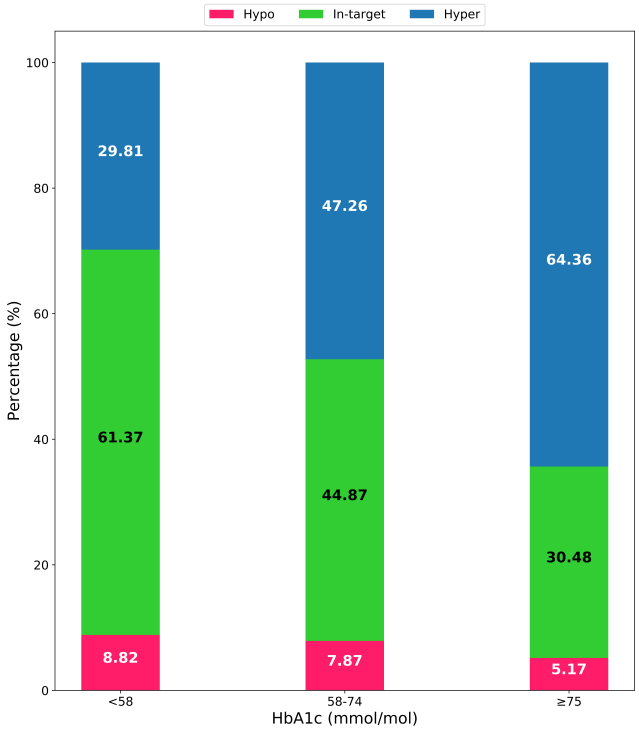


Fig. 3.1 Percentages of readings above, below and in-range

TABLE 3.3
PERCENTAGES OF READINGS IN DIFFERENT GLUCOSE RANGES OF EACH INTERQUARTILE HBA1C GROUP

	N= 682	n=176	n=156	n=184	n=166
BG ranges / HbA1c (mmol/L) / (mmol/mol)		<58	[58-66)	[66-75)	>=75
<3	Significant hypo%	2.5±2.8	2.6±2.7	2.3±3.1	1.5±2.4
[3-4)	Mild hypo%	6.2±3.8	6.3±4.1	4.4±2.9	3.6±3.3
[4-10)	In-target%	61.3±15.0	48.7±11.3	41.2±10.6	30.4±10.0
[10-15)	Mild hyper%	22.2±9.2	28.2±7.5	32.2±7.5	30.0±8.2
≥15	Significant hyper%	7.5±6.6	13.9±8.4	19.7±10.7	34.2±15.0

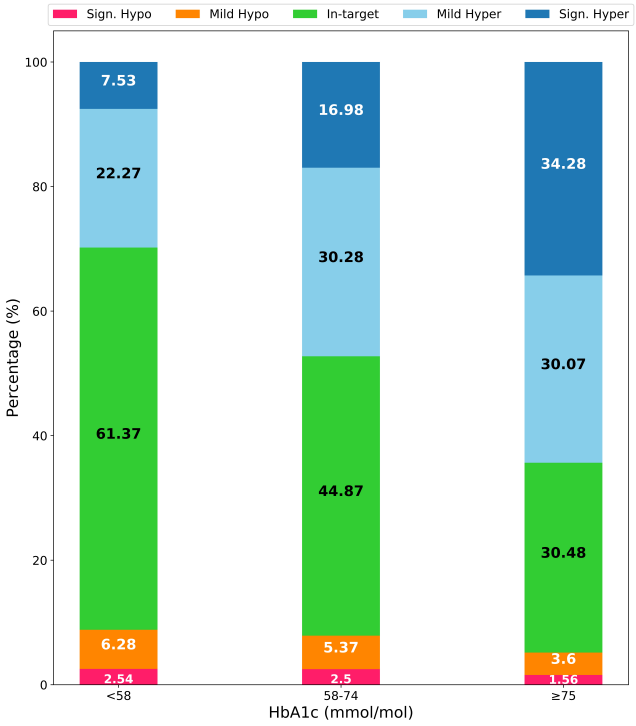


Fig. 3.2 Percentages of readings in significant hyper, mild hyper, significant hypo, mild hypo and in-range

Figure 3.3 shows the percentages of BG ranges in each HbA1c subgroup. As shown in the graph, the similar occurrence of hypoglycaemic episodes in the <58 and 58-64 HbA1c groups is observable. Using Dunn post-hoc test of the groups for hypoglycaemic episodes confirmed this observation (P>0.05).

Furthermore, the regression analysis shows that an increase in the significant hyperglycaemia is associated with an increase in HbA1c levels in all groups (Figure3.4). However, the Figure3.5 shows an increase in percentages of mild hyperglycaemia is associated with an increase in HbA1c levels in the groups except the ≥75 mmol/mol group. In this group, the increase in mild hyperglycaemia is associated with a negative slope of the linear regression line. Utilising Robust regression, a 10% increase in mild hyperglycaemia is associated with the drop of 3.15 mmol/mol in HbA1c levels for the ≥75 HbA1c group (p<0.00001).

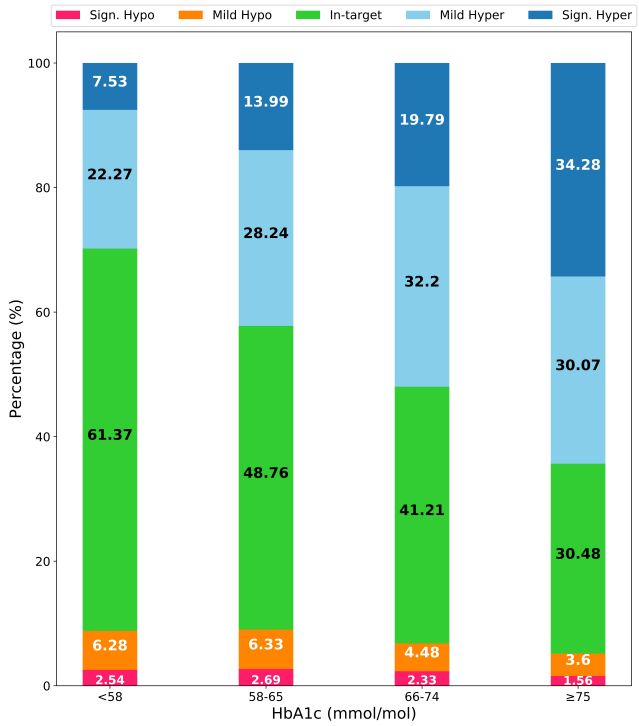


Fig. 3.3 Percentages of readings in significant hyper, mild hyper, significant hypo, mild hypo and in-range in interquartile HbA1c groups

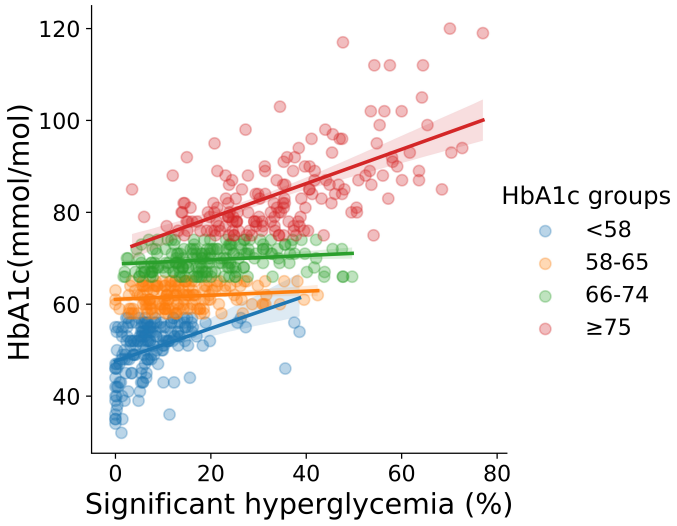


Fig. 3.4 The linear regression of significant hyperglycaemia on each HbA1c group

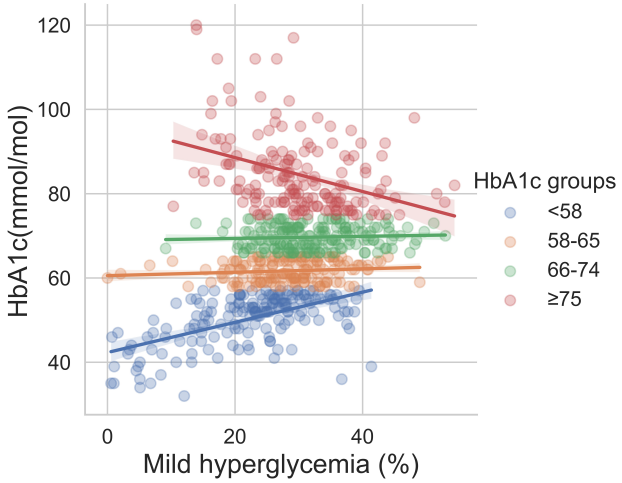


Fig. 3.5 The linear regression of mild hyperglycaemia on each HbA1c group

3.3.3 Fluctuations in BG readings

We were also interested in the variability of blood glucose measurements of each group. Figure 3.6 shows that variability as measured by the standard deviation of the daily blood glucose measurements has a strong positive correlation (0.65) with HbA1c (P<0.00001). Utilising Robust linear regression analysis showed an increase of 1 mmol/L in BG variation results in an increase of 6.63 mmol/mol in HbA1c levels (P < 0.00001). The R^2 of the analysis was 0.42. This indicated that standard deviation is a significant predictor of HbA1c levels.

Figure 3.7 shows the standard deviation of BG measurements in each of the HbA1c groups. The groups are significantly different in their control of variability in the measured glucose readings (p<0.000001). The group <58 has the lowest variability with 3.7 mmol/L; and the variability increases by the increase in HbA1c, where it can be noticed in the group ≥75 reaches about 5.9 mmol/L.

3.3.4 Frequency of BG readings

We were also interested in the testing behaviour of patients to observe the frequency of BG readings and its effect on different groups. Patients' frequency of testing had a weak negative

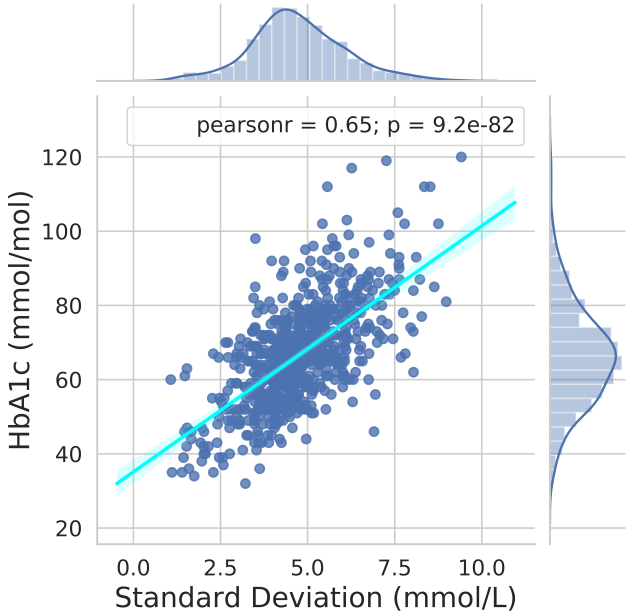


Fig. 3.6 Variability (Standard deviation) VS HbA1c

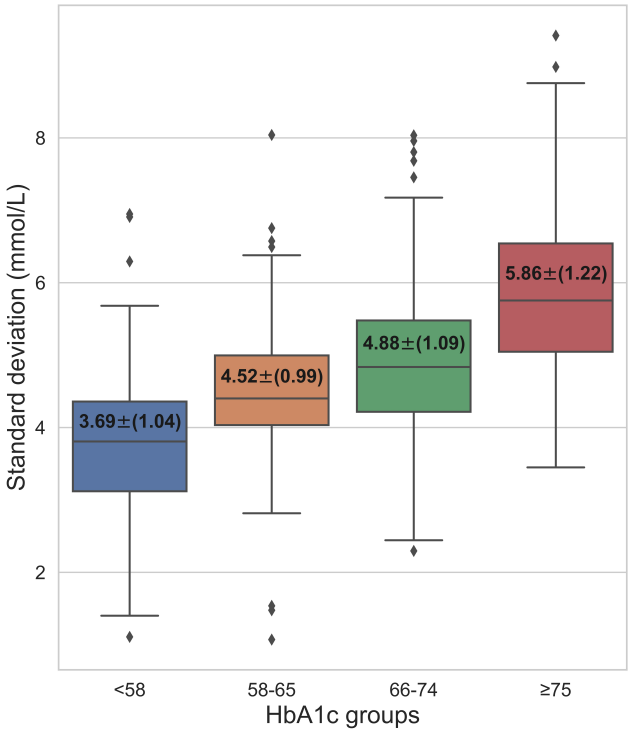


Fig. 3.7 Variation (Standard deviation) in each HbA1c group presented as median and interquartile ranges using boxplot; the numbers in the box are mean(SD)

correlation (-0.23) with HbA1c. This indicated an increase in the frequency of BG tests is associated with decrease in HbA1c levels (Figure 3.8). It is worth noting that about 36% of patients perform less than three tests per day; about 64.9% perform less than four tests per day.

Utilising Robust linear regression analysis showed an increase of one test per day reduces HbA1c levels by 2.3 mmol/mol ($p<0.0001$). However, the frequency of BG measurements has an R^2 of 0.05. This means it can only explain about 5% of HbA1c as an outcome variable. Therefore, we controlled for the significant predictors of HbA1c, i.e. average blood glucose and standard deviation, to investigate the significance of frequency of BG measurements. Despite the inclusion of the controlling factors, the frequency of BG measurements remained significant ($P<0.05$).

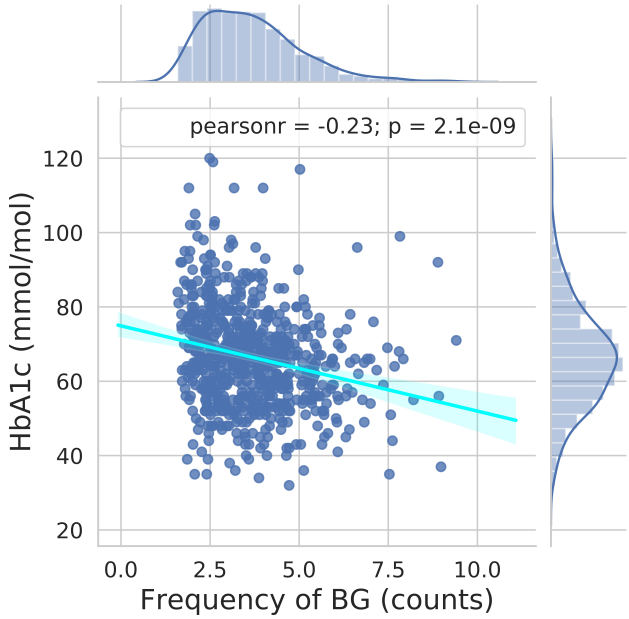


Fig. 3.8 Frequency of BG Measurements VS HbA1c

Furthermore, we analysed the odds of achieving HbA1c levels <58 mmol/mol by increasing the number of tests. Therefore, a logistic regression of the stratified frequency of BG (based on interquartile ranges [2.59,3.47,4.43]) showed an increase in odds of 0.54 when performing more than $\sim$4.5 tests ($p < 0.05$). While increasing the number of tests in each

quartile (i.e. second and third quartile) in comparison to the first quartile (<2.59) the odds increases significantly by 1.4, 1.8 and 2.5 times respectively (Figure 3.9).

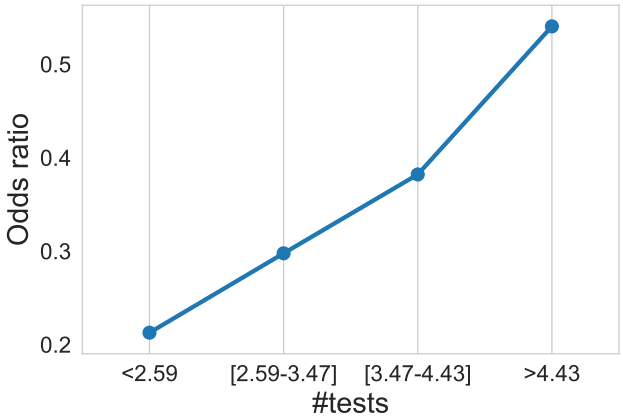


Fig. 3.9 Odds ratio of achieving <58 mmol/mol HbA1c by increasing number of test performed per day based on interquartile ranges

The Figure3.10 shows the frequency of BG measurements for each of the HbA1c groups. The comparison between groups shows a significant difference between the HbA1c groups. Post-hoc analysis revealed that the group $\geq$75 has a significant difference with other groups ($P < 0.00001$); also, the groups <58 and 66-74 were significantly different ($P = 0.015$).

Furthermore, we examined the effect of frequency of BG measurements on variability (Figure 3.11). As shown in the graph, the frequency of measurement has a week negative correlation of 0.19 with the variability. Also, the regression analysis indicates on average an extra test per day reduces the variability by 0.19 mmol/L ($P < 0.05$). The significant correlation and negative coefficient is an indication of improvement of variability control by the increase in BG testing.

3.3.5 Hypoglycaemia

We hypothesised that the frequency of hypoglycaemic episodes is related to the variability in BG readings. We used the coefficient of variance (CV) as a measure of fluctuation, $CV = SD/mean$. The fluctuation in BGs, CV, is strongly correlated with the percentage of hypoglycaemic episodes (<4 mmol/L), r=0.71. As shown in Figure3.12 the relationship is

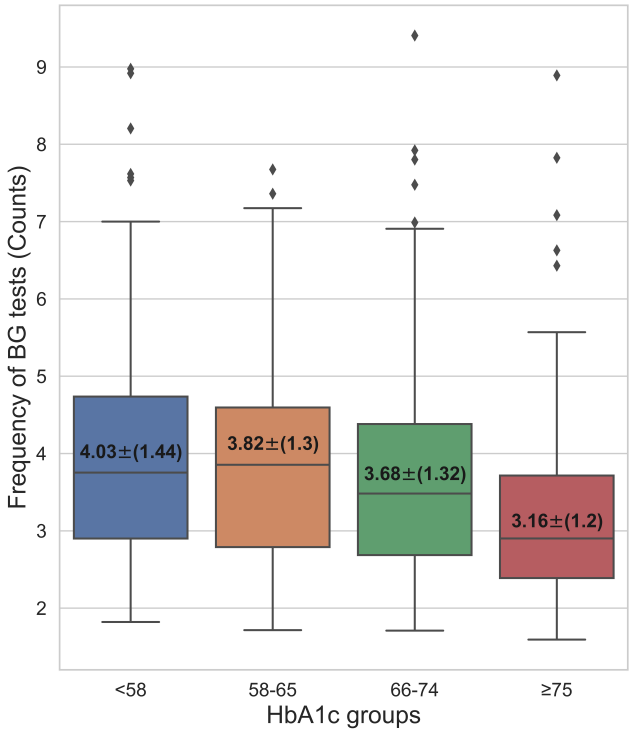


Fig. 3.10 Frequency of BG measurements in each HbA1c group presented as median and interquartile ranges using boxplot; the numbers in the box are mean(SD)

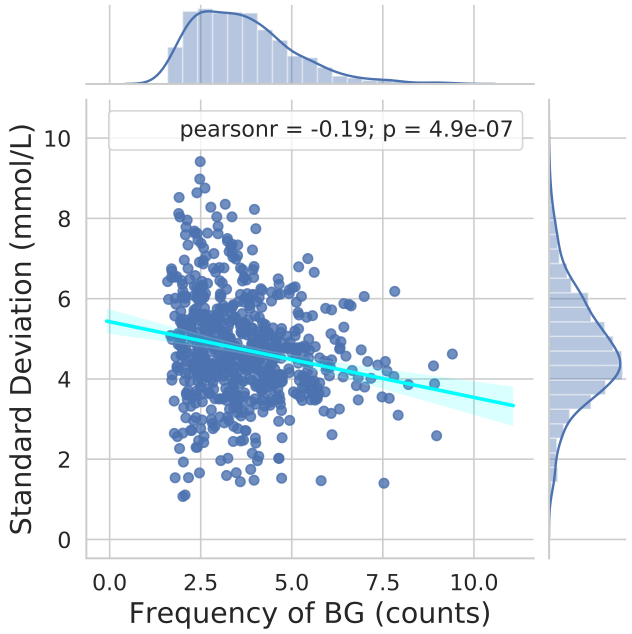


Fig. 3.11 Frequency of BG measurements VS Variability

best described by a quadratic non-linear regression, with the effect of an increase in CV greater the higher the CV. The degree of the polynomial's best fit was determined using ANOVA F-test for different degrees of polynomial regression (a range from 2 to 5 degrees). The p-value of the quadratic was the most sufficient (p=0.0083).

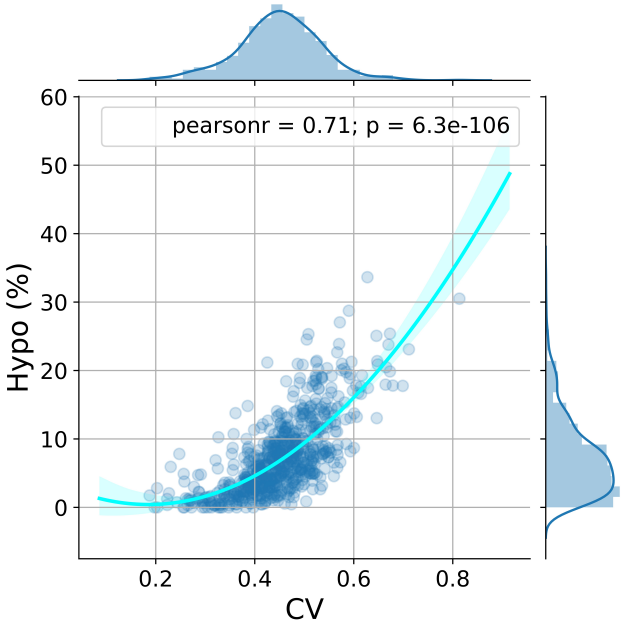
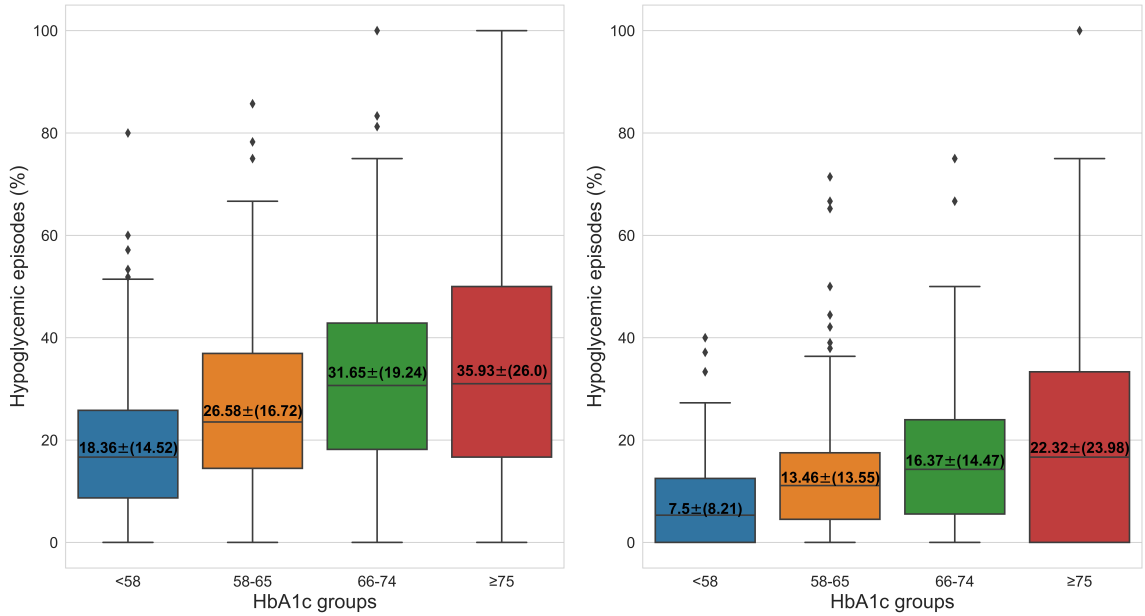


Fig. 3.12 Hypoglycaemia VS Fluctuation

Further to this hypothesis, we examined the prevalence of hypoglycaemic episodes resulting from a rebound of a hyperglycaemic excursion. Figure 3.13a shows the percentages of hypoglycaemic episodes likely resulting from over-aggressive correction of hypers >10 mmol/L in each HbA1c group. Note in the Figure3.3 that the groups <58 and 58-65 have the highest rate of hypoglycaemic episodes; out of those percentages of hypoglycaemic episodes in the groups <58 and 58-65 about 19% and 26% respectively are likely the result of over-aggressive correction of hyperglycaemic excursions.

We investigated further by increasing the hyperglycaemic threshold to 15 mmol/L and to study the effect of higher hyperglycaemic values on patients' reaction. Figure 3.13b shows for the two HbA1c groups (<58 and 58-65), about 8% and 14% respectively of the hypoglycaemic episodes resulted from over-aggressive treatment of hyperglycaemic readings

more than 15 mmol/L. Remember these patients have a lower occurrence of significant hyperglycaemia.

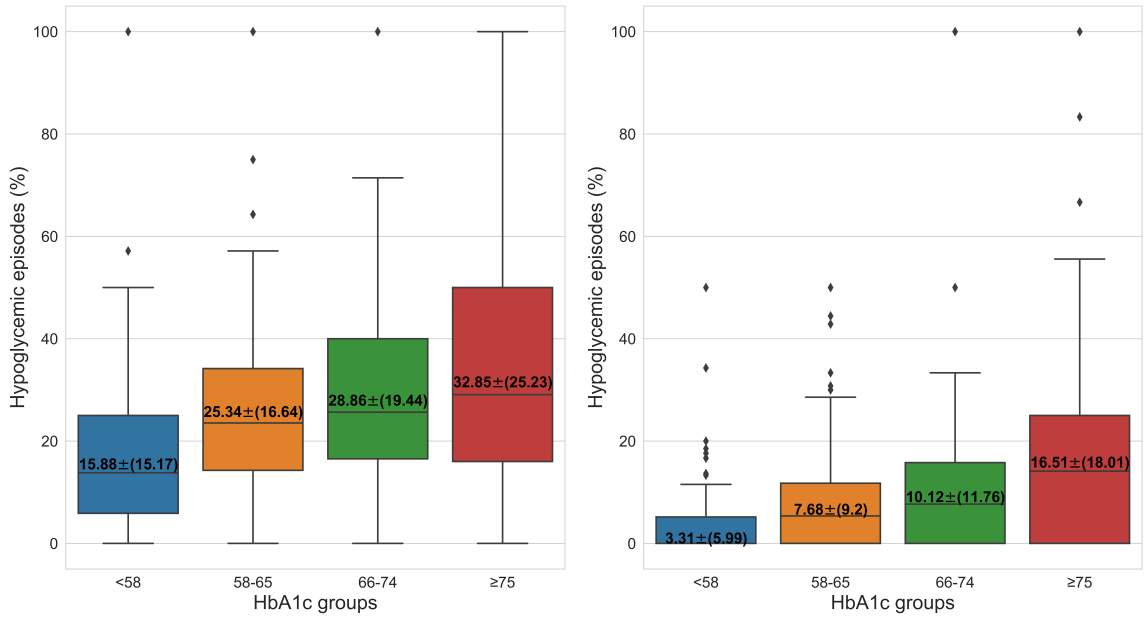


(a) Hypers >10 mmol/L (b) Hyper >15 mmol/L

Fig. 3.13 Percentages of hypoglycaemic episodes resulted from over-aggressive correction of hyperglycaemic excursion

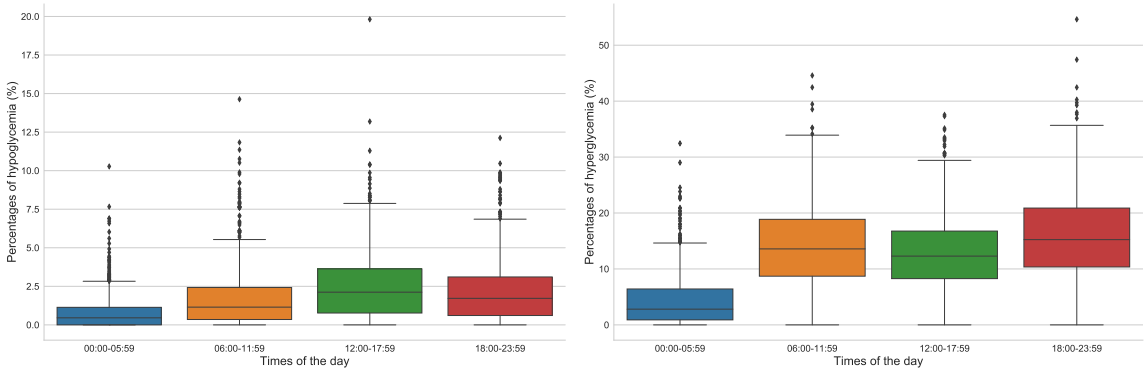
This led us to investigate the reverse of the effect; the prevalence of hypoglycaemic readings resulting in over-treatment behaviour. In other words, the percentages of hypoglycaemic readings ended up with a hyperglycaemia. Figure 3.14a shows that about 29% and 33% of the hypoglycaemic episodes of the HbA1c groups 66-74 and $\geq$75 respectively were likely over-treated to result in hyperglycaemic reading more than 10 mmol/L. Increasing the threshold, about 11% and 17% of the hypoglycaemic episodes of the HbA1c groups 66-74 and $\geq$75 respectively were likely over-treated resulting in a hyperglycaemic reading more than 15 mmol/L (Figure 3.14b).

Figure 3.15 shows the percentages of hypo occurring in different time-blocks of the day. For hypoglycaemia, the post-hoc analysis of the different times of the day shows that the different time-blocks have a significant difference ($p>0.001$). For hyperglycaemia, the post-hoc analysis showed that the time-blocks of 06:00-11:59 and 12:00-17:59 are similar ($p>0.05$) while the rest of the time-blocks are significantly different ($p<0.001$).



(a) Hypers >10 mmol/L (b) Hypers >15 mmol/L

Fig. 3.14 Percentages of hypoglycaemic episodes resulted in a hyperglycaemic excursion by over-treating



(a) Hypoglycaemia (b) Hyperglycaemia

Fig. 3.15 The prevalence of (a) hypoglycaemia and (b) hyperglycaemia throughout different hours of the day

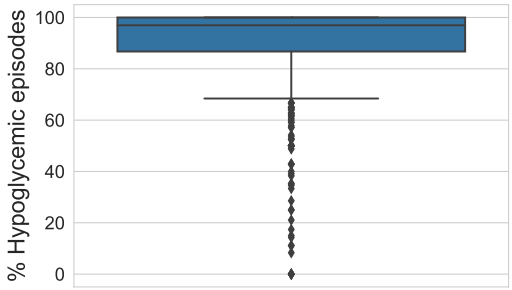
Re-test in the event of hypoglycaemia

The guidelines recommend performing a retest within 15-20 minutes of the treatment of hypoglycaemic reading. As shown in the Figure3.16, the majority of hypoglycaemic readings are not followed by a retest (within 20 minutes). We were interested if a retest will have an effect on reducing hypoglycaemia in the following 24 hours. Therefore, patients are grouped into three categories: Mostly perform a retest (Retest >60% of their hypo), Sometimes retests (Retest between 15% to 60% of their hypos), and rarely retest (<15%). Table 3.4 show the characteristics of these groups. Although their HbA1c levels are the same ($p>0.05$), the mostly retesting group have the lowest prevalence of hypoglycaemic episodes. Notice that the most retesters exhibit the highest variation as well (post-hoc analysis shows significant difference $p<0.025$). The two mostly and rarely retesters have approximately similar age ($p>0.05$).

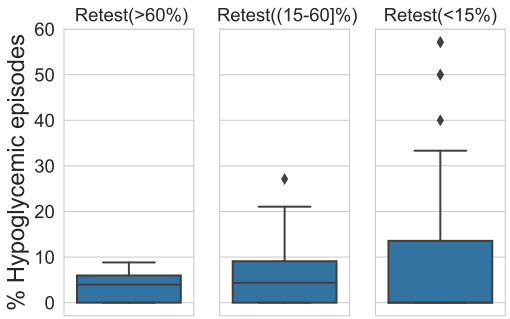
TABLE 3.4
THE CHARACTERISTICS OF RETESTING GROUPS

N=682	n=37	n=135	n=510	
Re-test habits	Mostly	Sometimes	Rarely	P-value
Average BG (mmol/L)	11±3.4	10.5±2.2	10.4±2.3	>0.05
Standard deviation (mmol/L)	4.11±1.5	4.8±1.3	4.7±1.3	<0.01
HbA1c (mmol/mol)	69.6±19.2	65.3±12.7	66.5±13.4	>0.05
Age	47.4±15.4	41.8±16.4	48.3±17.1	<0.001
Sex(male)	40%	45%	50%	>0.05
Hypoglycaemic %	3.69±2.8	7.05±5.4	7.85±5.6	<0.000001

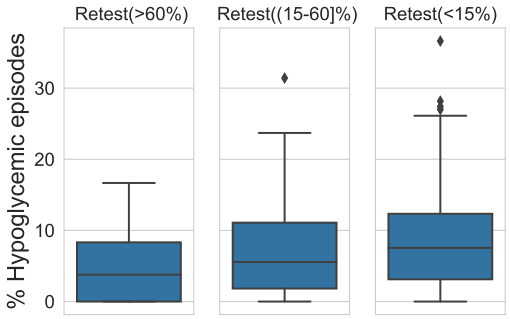
As shown in the Figure3.16b, the hypo retesting among these groups results in approximately similar hypoglycaemic percentages in the following 24 hours ($\sim$similar median, $p>0.05$). However, not retesting among these groups results in a different percentage of hypos in the proceeding 24 hours ($p<0.01$) (Figure 3.16c). The group with the most retesting habit, even if they miss the retest, would experience fewer hypoglycaemic episodes. Similarly, for the group with some retesting habit, experience fewer hypoglycaemic episodes compared to the group with rare retesting. Also, comparing retesting and not retesting of each group, fewer hypo episodes occur except in the last group (Rare retesters).



(a) Hypos without a following retest



(b) Prevalence of hypo in case of retest



(c) Prevalence of hypo in case of no retest

Fig. 3.16 The hypo treatment behaviour **(a)** the percentages of hypoglycaemic readings that was not followed up by a retest **(b)** the percentages of hypoglycaemic episodes occurring the following 24 hours of a hypo reading in the case where the treated hypoglycaemic reading was followed by a retest **(c)** the percentages of hypoglycaemic episodes occurring the following 24 hours of a hypo reading in the case where the treated hypoglycaemic reading was not followed by a retest

3.3.6 Pump vs No-Pump

We also examined the effect of pump on the glycaemic control and behaviour of patients. In the pump users

- The in-target percentage increased by about 3%($p<0.05$)
- The hyperglycaemia percentage decreased by about 3%($p<0.05$)
- The hypoglycaemia percentage increased by 0.5%($p<0.05$)
- The frequency of testing increased by 0.5 test/day($p<0.001$)

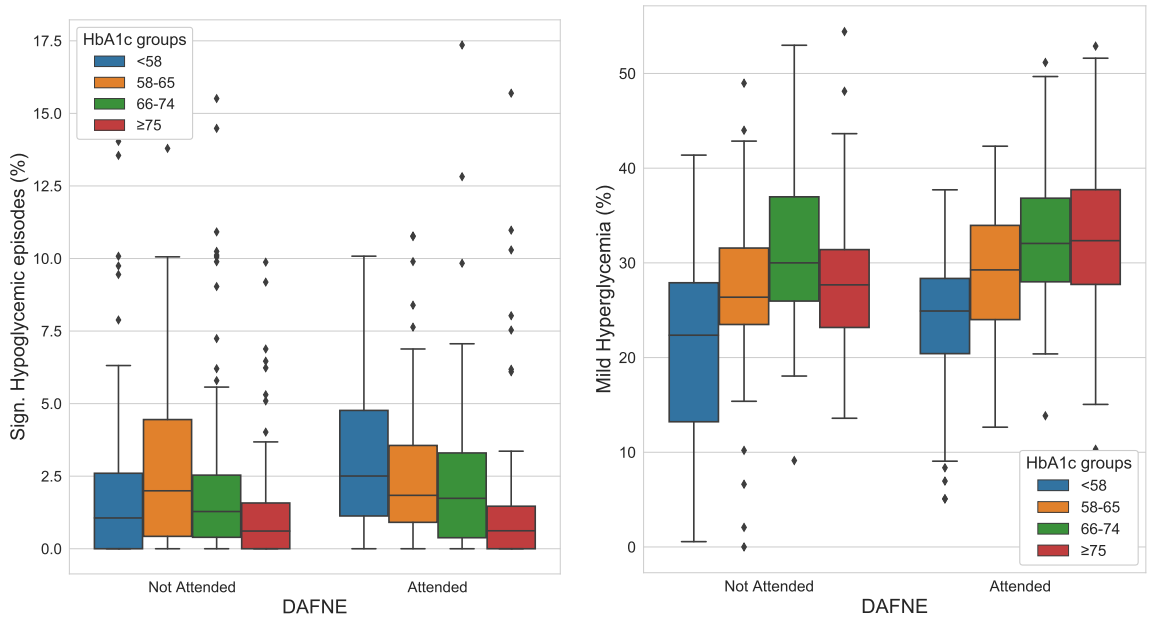
These are statistically significant however the effect is not clinically significant. Also, when the differences are compared in the different HbA1c subgroups, the significance of the differences fade away. In other words, since the differences are small when dispersed among the groups lose their significance.

3.3.7 DAFNE vs Non-DAFNE

Attendance at DAFNE is associated with an increase of the percentage of mild hyperglycaemia and hypoglycaemia (significant and mild). A post-hoc analysis of the HbA1c subgroup shows that this difference is between percentages of significant hypoglycaemia in the HbA1c group <58 of the DAFNE and Non-DAFNE (1.7 median difference, p=0.0014). Also, these results can be explored using their count of significant hypoglycaemia episodes as shown in Figure 3.18. While also an increase in mild hyperglycaemia is notable between HbA1c group of >74 of the DAFNE and Non-DAFNE (5.2 median difference, p=0.0023). These increases are observable consistently at different times of the day.

3.4 Discussion

Data were collected from the 4th quarter of 2013 to the 4th quarter of 2015 to produce a comprehensive novel dataset. This dataset allowed a retrospective analysis of the state



(a) Significant hypoglycaemia (b) Mild hyperglycaemia

Fig. 3.17 DAFNE vs Non DAFNE

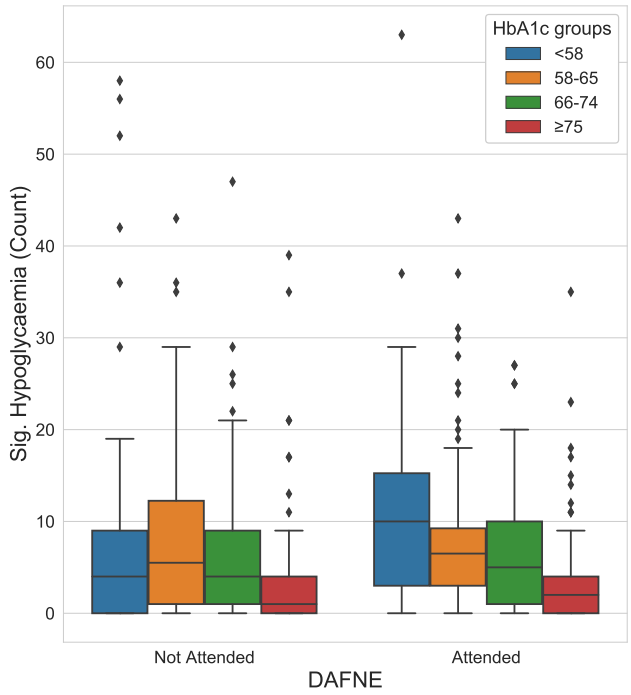


Fig. 3.18 Frequency (count) of BG measurements in significant hypoglycaemia range for each HbA1c group depending on their attendance to DAFNE programme

of glycaemic control of patients and their behavioural adherence to the suggested testing guidelines.

The analyses showed increasing the number of SMBG tests is associated with a significant HbA1c improvement. However, the hierarchical analysis of variance for the explained HbA1c outcome showed that the frequency of SMBG has a low R^2 of (5%) with weak correlation to HbA1c levels. This can be explained by the fact that increasing number of tests needs to improve the quality of action taken by the patient that would result in better control, i.e. less hyperglycaemic excursion while guarding against hypoglycaemic episodes. The standard deviation and average blood glucose, possible measures for glycaemic control, have a strong correlation and significantly higher R^2. Therefore, the recommendation for more frequent testing per day requires improved treatment adjustments by the patient. This study lends weight to the studies which recommend structured education and reinforced learning at appointments to further improve the decision making process on the BG readings undertaken.

The study carried out by Sivasubramaniyam *et al.* suggests a shift of focus from the target range to the proportion in range. However, their conclusion was based on SMBG data for a minimum of 14 days and a maximum of 28 days in pump users only. This is about 16% of the 12-week HbA1c period. Additionally, the study was performed on a small sample, especially in the group with HbA1c >74 mmol/mol there were only 36 patients. Furthermore, the study has not adjusted for hypoglycaemic retests that are recommended by most physicians; hence, it can be assumed that this has resulted in overestimating the percentages of hypoglycaemia and underestimating the hyperglycaemia and in-target percentages. Therefore, the combination of the small sample size, short monitoring period, and hypo-retests' imbalance makes the finding less reliable. The presented analysis of this chapter tackles these shortfalls and provides a better picture of the glycaemic patterns of different HbA1c groups.

Moreover, the shift of focus from the blood glucose targets can be detrimental to patients' glycaemic control. Although patients simplify these targets for their individual needs, they still heavily rely on the target ranges to make momentary treatment decisions on the result of a SMBG test (i.e. insulin for corrections, and exercise preparation). We consider the recommended target ranges as short-term targets that the patients need to aim for in their

day to day glycaemic control practice. Hence, our proposal is not to shift the focus, but to introduce a mid-term (2-4 weeks) glycaemic targets based on proportions in-range that patients can use to assess their glycaemic control. Although anecdotal, the experts in diabetes care have used such views of proportions in their assessment of patients' control as a mid-term measure alongside the HbA1c levels as the long-term measure. However, there has not been a clear definition on the proportions.

Additionally, the experience of patients shows that although they changed the targets, they can still achieve the HbA1c levels <58. This needs to be acknowledged by clinical findings since there is evidence of this as our data shows; pushing patients to higher levels of stringent regimen especially if the clinicians are a specialist or general practitioner who have not deduced such leniency in targets, inadvertently drives patients away and deprive them of access to the needed healthcare support. Therefore, the clinician in primary and specialist care can draw benefits from the presented proportions in-range to have a more realistic assessment and expectation from the patients.

Furthermore, HbA1c alone is not sufficient to describe the status of diabetes management. Also, it is possible that at the time of the clinical appointment the HbA1c test result will not be available. More importantly, only 25% of patients understand the significance of HbA1c which has been shown to affect their glycaemic control [144]. Even if we assume patients understood the HbA1c results, the intervention and treatment adjustments require actions based on patients' goals. Therefore, the proposed mid-term targets are a possible way to simplify the process and provide an objective feedback and tracking of the progress. Also, such guidelines can offer an alternative measure to assess patients' glycaemic control.

The increased occurrence of hyperglycaemia is evident as HbA1c levels increases. In the group with HbA1c level >74, more than 60% of their readings are in hyperglycaemic ranges; and more than half of these readings are in the significant hyperglycaemic range. This results in high exposure to elevated glucose levels; hence the increase in the HbA1c and associated risks. One possible recommendation to this high-risk group is to shift their hyperglycaemic significant ranges to mild hyperglycaemia. Increasing the percentages of mild hyperglycaemia in this group would reduce their HbA1c levels. This is also observable

in the DAFNE patients. Therefore, the education in this group seems to achieve this goal. Our study lends support to such educational programmes, even as an intervention for patients who might have attended such programmes to boost their understanding further. Also, the reduction in significant hyperglycaemic percentages helps to reduce the high variability in the high risk >74 HbA1c group. The reduction in variability positively contributes to improvement in HbA1c levels.

Furthermore, the over-treatment of hypoglycaemia and over-correction of hyperglycaemia creates a cycle that affects patient quality of life. In the groups with HbA1c level >58 mmol/mol, about 30% of their hypoglycaemia are the result of over-correction; and about 30% of their hypoglycaemia are over-treated. Although these groups experience fewer hypoglycaemic episodes, they remain at a higher risk of hypoglycaemia due to this vicious cycle. In the <58 HbA1c group, they seem to be better skilled in the management of such situations which can be a distinguishing factor of their diabetes control. Hence, transferring such skills to higher risk groups can amend their experience and positively change their decision making to manage these situations more objectively. People base their decision on heuristic rapid thinking and the recall of the past events [139].

Analysing the retesting behaviour of patients in the events of hypoglycaemia showed that the majority do not follow the guidelines. Although the average HbA1c levels of retest groups were similar, the mostly retesting group exhibits the lowest percentages of hypoglycaemic episodes, approximately half of the other groups. Additionally, the retesting has a similar effect on the groups in the following 24 hours of the episode. However, those with higher retesting habit when missed the retesting experienced lesser hypoglycaemic episodes in the following 24 hours. In other words, the most retesters' miss of a retest expose them to a lower risk of hypoglycaemia in the following 24 hours. This can be because of their habit; they develop a better awareness of their hypoglycaemia and its treatment. Also, comparing retesting and not retesting of each group, fewer hypo episodes occur except in the rare retesters. This could be justified by considering that the last group (rare retester) does not show a retesting habit; hence, this is a possibility of lower hypoglycaemia or experiencing an accelerated decline in glucose levels. This is more severe than usual and results in the

reoccur of the hypoglycaemic episodes later on. In other words, the retest occurs out of necessity rather than a precautionary measure. These indicate more efforts are needed to help patients with the understanding of benefits and importance of the retesting procedure. Also, a study showed that most adults under-treat their hypoglycaemic episodes [143]. This might contribute to the need for retest and multiple treatments. Hence, the weight based treatment of hypoglycaemic episodes might reduce the need for multiple retests, improve the adherence and reduce the hypoglycaemic episodes in the following 24 hours.

The analyses of the pump users showed a statistically significant increase in the proportion of in-target BGs and the decrease of the proportion out of the target. However, these result in clinically insignificant improvements in the glycaemic control. These findings mirror the findings of the REPOSE study that established the insignificance of the effect of the pump on the patients' diabetes management [101].

In conclusion, the retrospective analyses of data provided an insight into the adherence and behaviour of patients on their management of diabetes. The large dataset produced in the study allowed correlating patterns with clinical outcomes and as a result providing new insight into useful behaviours and less useful practices. Lower levels of HbA1c are achievable even when certain percentages of hyperglycaemia range are present. Also, the cycles of hypoglycaemia over-treatment, and hyperglycaemia over-correction can be detrimental to the glycaemic control, thus lower quality of life. To our knowledge, this is the first study to provide an insight into retesting habits of the patients after a hypolycaemic reading; when a retest post-hypoglycaemia is carried out, it is less likely to experience more hypoglycaemic episodes later on. Also, a novel recommendation of mid-term targets based on proportion in-range is proposed.

Chapter 4

Haemoglobin A1c prediction

Self-monitoring of blood glucose (SMBG) is an integral part of diabetes management. Despite the benefits of adherence to frequent SMBG, many patients do not perform sufficient tests. This incomplete sampling of blood glucose hinders the analysis and review efforts for both patients and healthcare providers alike.

The haemoglobin A1c (HbA1c) is considered the gold standard utilised to assess diabetes management. Current guidelines and treatment plans are heavily influenced by HbA1c test results due to its association with diabetes complications. The availability of a HbA1c test enables a discussion between the patients and their healthcare provider based on the most recent status of their glycaemic control.

Therefore, the study aimed to provide an improved prediction of HbA1c from SMBG and their glycaemic patterns in patients with type 1 diabetes which outperforms established methods despite the porosity of the blood glucose (BG) data.

4.1 Background

Self-monitoring of blood glucose (SMBG) is an integral part of diabetes management. Patients with type 1 diabetes use SMBG to check their blood glucose level and administer quick-acting insulin according to their carbohydrate intake and physical activity level, typically as multiple daily injections of insulin or as multiple boluses from an insulin pump.

Patients are trained to assess their results and adjust their insulin regimes accordingly. Such adjustments are necessary in the events of illness, hypoglycaemia, and hyperglycaemia; for example, performing 15-minute retest(s) in the event of hypoglycaemia to check the resolution of the episode and help prevent recurrence. Furthermore, adherence to SMBG testing is a key factor for patients to avoid asymptomatic hypoglycaemic and hyperglycaemic excursions [129]. Despite the benefits of adherence to frequent SMBG, many patients do not perform sufficient tests [152–154]. This incomplete sampling of blood glucose hinders the analysis and review efforts for both patients and healthcare providers alike. Continuous monitoring of blood glucose is becoming more mainstream, however, due to higher costs compared to SMBG, many healthcare providers lack the adequate financial resources to support the widespread use of it [155]. Therefore, application of methods and statistical analysis, such as HbA1c prediction from sparse SMBG data remains a challenge to overcome.

4.1.1 Why HbA1c?

A haemoglobin assay test was introduced when Rahbar [156] identified an abnormal fast moving haemoglobin band in diabetes patients. Today, HbA1c is the gold standard that is utilised to assess diabetes management [157]. HbA1c defines the percentage of haemoglobin with attached glucose (glycated haemoglobin). The Diabetes Control and Complications Trial (DCCT) [26] and UK Prospective Diabetes Study (UKPDS) [25] emphasised the importance of the HbA1c. These landmark studies established a link between diabetes-related complications and HbA1c. Therefore, HbA1c influences the suggested guidelines and treatment plans. The UK National Institute for Health and Care Excellence (NICE) recommends carrying out a HbA1c test every 3 to 6 months [28]. The HbA1c test result enables a discussion between the patient and the healthcare provider based on their status of glycaemic control. The more recent the result, the more constructive the consultation in terms of the importance of insulin dose adjustment. As a result, some clinics use point of care (PoC) equipment to give a real-time estimate of HbA1c. However, PoC HbA1c is expensive compared to the standard lab measurement; thus its uptake is limited [158].

Levels and duration of haemoglobin exposure to glucose affect the glycation intensity[149]. Therefore, glycaemic patterns such as percentages of readings in the hyperglycaemic, or hypoglycaemic range, and variability in results can express this exposure of haemoglobin to glucose in the analysis of glycaemic control.

4.1.2 Established methods of HbA1c prediction

The A1c derived average glucose (ADAG) study group derived a linear relationship between AG and HbA1c. The estimated average glucose (AG) level is calculated using AG= 1.59 HbA1c - 2.59 [51]. The study received endorsements by the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), International Diabetes Federation (IDF), and International Federation of Clinical Chemists (IFCC) [159]. Therefore, the formula is widely used and its result is often reported alongside HbA1c lab tests.

Although AG is a significant predictor of HbA1c, inter-patient variability is observed. Hence, other studies have considered the effect of the difference in the age of erythrocytes among individuals. The proposed nonlinear models take the mean erythrocyte age as a parameter in the calculations [160]. Furthermore, erythrocyte age can provide an explanation for glucose-independent variations of HbA1c [161–165]. Other studies suggested that SMBG results from the previous 30, 30 to 90, and 90 to 120 days contribute to 50%, 40% and 10% of the HbA1c respectively [166–168]. However, other studies express that high glycation index (HGI) present an imperative indication for glycation variability and its effect on inter-variability among patients with similar AG levels. HGI expresses the difference between the laboratory and the predicted HbA1c. The divergence of the predicted HbA1c conveyed by HGI is a strong predictor of complications in diabetes [169–171].

Kovatchev *et al.* study [172] developed a two-step dynamic model to estimate the HbA1c using a seven-point profile and daily fasting SMBGs. The daily fasting SMBGs are used to predict changes in A1c levels. Whereas, a seven-point profile is generated approximately every month for calibration purposes. Alternatively, an HbA1c lab test measurement can be applied for calibration. The study relied on patients' commitment to perform daily fasting SMBG, and monthly seven-point profile which were reported to cause inconvenience [173].

Lian & Liang's study [174] has shown compliance with HbA1c test frequency and treatment adjustment reduces complications. Moreover, timely availability of the HbA1c test result is an important factor in avoiding possible complications [175, 176]. Therefore, it is of primary interest of this work to present novel models that enable frequent and real-time availability of predicted HbA1c results utilising only SMBG, without the need for a pre-defined frequency or pattern of SMBG data collection nor additional specific patient behaviours outside their daily routine.

4.1.3 Support vector machines

A support vector machine (SVM) is a supervised binary classification algorithm [177]. An SVM utilises four components to achieve the classification: the separating hyperplane, the maximum-margin hyperplane, the soft margin and the kernel [178]. The maximum margin is optimised to separate the data points by a hyperplane. This hyperplane is represented using support vectors. The SVM classification algorithm can therefore be generalised for continuous values (i.e. regression problem) by introducing convex ε-insensitive loss function to the optimisation objective [179]. This optimisation aims to find an ε-tube that is the 'flattest' considering a trade off between the model complexity and a regression error. Therefore, support vector regression (SVR) utilises a multiobjective function based on the loss function and the geometry of the ε-tube. Also, the support vectors are the data points on the outside of tube boundaries. Additionally, a nonlinear solution by SVR can be deduced utilising kernels. Kernels map the data points to a higher dimension referred to kernel space. These kernels in theory present a solution for separating any data points linearly. However, this approach whereby the dimensions are increased to find a solution is limited to a higher dimension by which the data are mapped. In other words, we cannot always project the data to a very high-dimensional space. The increase in dimensions also increases the variables under consideration resulting in higher dimension curse, which implies exponential expansion of the possible solutions. Therefore, it becomes more difficult to find the optimal solution, if any. Hence, using kernels to find a solution, for either classification or regression, where dimensions are reasonably increased is challenging, and likely requires trial and error.

4.1.4 Convolutional neural network on time-series

Convolutional neural network (CNN) as a deep learning technique can discover features from raw data without the need for engineered features. The feature-based methods depend on the quality of the extracted features outlined by the experts in the field (e.g. healthcare and finance). Therefore, the task of exploring features from raw data such as univariate time-series data is challenging.

Definition 4.1. Univariate time-series: it comprises successive data points measured in specific time periods (regular or irregular). Therefore, a time series can be denoted as $T = \{t_1, t_2, t_3, ...t_n\}$, where n is the length of T.

Although the multi-layer perceptron neural network can discover the underlying features of the data, the number of parameters to be learned is significant, thus an inefficient solution for the high dimensional data. CNN is a specialised artificial neural network which provides better flexibility and scalability techniques by sharing the parameters learned across the network [180, 181]. This becomes useful as the dimensions of the data increases such as the case with the high dimensional multivariate time-series data.

Definition 4.2. Multivariate time-series: it is a combination of multiple univariate time series that are related in time. Therefore, a multivariate time series can be denoted as $M = \{m_{1t}, m_{2t}, m_{3t}, ..., m_{lt}\}$, where l is the number of univariate time-series data.

A typical convolutional layer in CNN comprises of the following components:

Convolutional layer

What particularly distinguishes CNN is the convolutional layer [182]. In this layer, sets of filters (kernels) are convolved with input to produce feature maps. As the name indicates, these filters help locate sets of features in the input layer using the weights of the kernels (Figure 4.1). Therefore, it can be expressed for the input x and output y with kernel k:

$$y_j = b_j + \sum_i k_{ij} * x_i$$

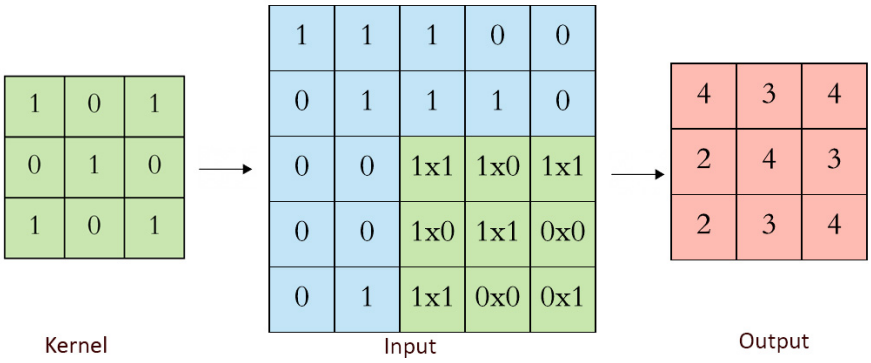


Fig. 4.1 Filter (Kernel) of 3×3 and stride 1 is used to extract local features from the input data

Where $*$ is the convolution operation. As show in the Figure 4.2, the convolution operation is followed by the nonlinear activation function.

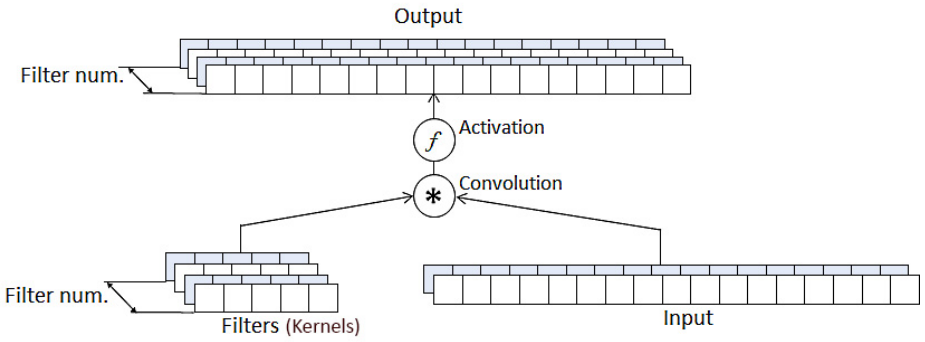


Fig. 4.2 Convolution layer operation

Nonlinear active function It is the key to represent complex models; otherwise, the neural network would perform a linear approximation [183]. The most common non-linear active function is the sigmoid function $\sigma(x) = \dfrac{a}{1+e^{-x}}$, which transforms the input to a range values of [0,1]. In recent years, the rectifier activation function has become more widely used. The rectified linear unit (ReLU) clips any value below zero [184]. Therefore,

$$ReLU(x) = max(0,x) = \begin{cases} 0 & x \leq 0 \\ x & \text{otherwise} \end{cases}$$

Pooling operations Pooling in neural network is a down-sampling process [182]. In this process, array of unit activation are split to smaller arrays. Each smaller array is represented by a unique set of its activation units (Figure 4.3). In essence, it reduces the size of feature

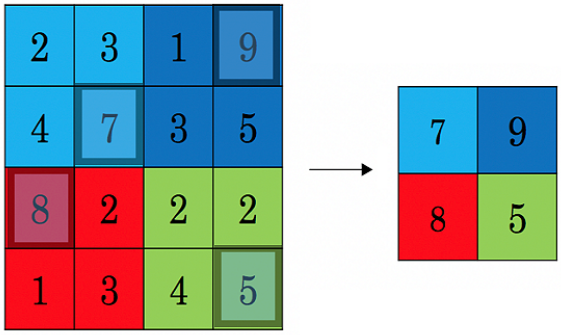


Fig. 4.3 Max Pooling of size 2×2 and stride 2. In each strid the maximum value is chosen as the output

maps of the convolutional layers. In Max-Pooling, the maximally active unit is used for the down-sampling process.

CNN has been mostly utilised in classification problems due to its popular use and high performance in image classification field. Recently, there have been efforts to use the CNN in regression problems but these remain scarce [185]. In both regression and classification, the main task remains to be the learning of features from labelled data. In time-series, the data can be weakly labelled.

Definition 4.3. Weakly labelled data: it is the long successive data points (e.g. time-series) that belong to a single global label.

Techniques used in classification studies for feature learning can be transferred for regression problems. Among these studies, fully convolutional neural network (FCN) [186] was proposed to classify the univariate time-series data. FCN did not perform local pooling; however, it utilised the global average pooling (GAP) [187] to reduce the dimension of the data. The global pooling aggregates the time series data on the entire time dimension, resulting in a drastic reduction of the learning parameters in the network. Time-series data can have features in different scales in time (e.g. daily and weekly). In multi-scale convolutional

neural network (MCNN) [188], subsequences of the time-series are extracted using sliding windows. This provided the ability to learn features in different scales in time. In multi-channel deep convolutional neural network (MCDCNN) [189], the multivariate time-series is unfolded so that each univariate time-series (i.e. channel) is processed independently and in parallel with other channels. These conditional multivariate time series are used to improve the feature learning of the CNN from raw time-series data. In Grouped CNN (G-CNN) [190], the study explored the underlying features of the data by the structural covariance properties of the multivariate time-series. This utilises a clustering technique to group the data points to a certain membership for convolutional operation.

To design an architecture of a functional CNN, in addition to the convolutional layers, the following components are used:

Feed-forward neural network

The computational unit of a neural network is referred to as a neuron, inspired by biological terms of the human brain [183]. These neurons have an input and produce an output. Each unit is associated with weights that are multiplied with the input. Then, these are summed up and a nonlinear activation function is applied. In practice, finding the correct weights for neurons of several layers results in a sufficiently accurate approximation to the solution of many computational problems. A typical feed-forward network is shown in Figure 4.4. Each circle is a neuron with input, its corresponding activation and output. If the input is $x = (x_1 ....x_n)$ then the weight w is multiplied and the bias term is applied as follows

$$z_i = W_i x + b_i$$

Considering the activation function f, we have:

$$y_i = f(z_i)$$

If the input propagates over many layers, such as deep neural networks, it can determine the output using

$$y = f^{(1)}(f^{(2)}(f^{(3)}...(f^{(M)}(z))))$$

Since the output of a layer is the input of another layer, the x and y can be exchanged as shown in the Figure 4.4

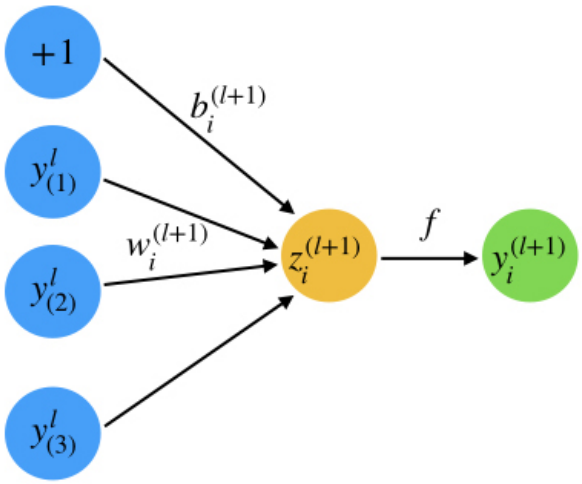


Fig. 4.4 Feed-forward neural network

Fully connected layer

When neurons of a layer are connected to all the neurons of the next layer, they form a fully connected layer. This configuration provides a vector-matrix multiplication of the weights; hence, the association of ith neuron input row to the jth neuron of the output row is determined by the W_{ij}.

Complexity of neural networks

In an attempt to reduce the error in the output (better prediction) of a neural network, the developed models can increase in complexity of their architecture. Also, due to the architecture of neural networks, these complex models require many parameters to be estimated. These raise the issue of over-fitting to the training data.

The following are typical ways to combat increased model complexity in neural networks.

Regularisation Over-fitting can be alleviated using regularisation. A common way to regularise a neural network is to apply a Gaussian (L2), Laplacian (L1) or their combined penalty (Elastic Net [191]) to the learned kernels at different layers. For a cost function J(θ;X,y) with network parameters θ, training set X and targets y the application of Elastic Net regularisation to the j-th layer updates the cost function into:

$$J(\theta;X,y) = J(\theta;X,y) + \lambda 1||w||_1 + \lambda 2||w||_2$$

Drop-out It is the process of randomly dropping neural units along with their connections to avoid overfitting in large networks. In other words, it protects the units of the network from overly co-adapting [192]. The Drop-out in a feed-forward operation can be expressed by

$$r^{(l)} \sim Bernoulli(p),$$

$$x^{(l)} = r(z * y^{(l)})$$

$$z = wx + b$$

$$y = f(z)$$

for any layer l,$r^{(l)}$ is a vector of Bernoulli random variables with probability of 1.

Figure 4.5 shows the change in the network.

Batch normalisation Batch Normalisation facilitates a higher learning rate and allows a leaner initialisation strategy; in some cases, it can eliminate the need for Dropout [193]. This normalisation results in a significant improvement in the speed of the training process. Due to internal covariate shift of layers whereby the complexity of the neural network increases

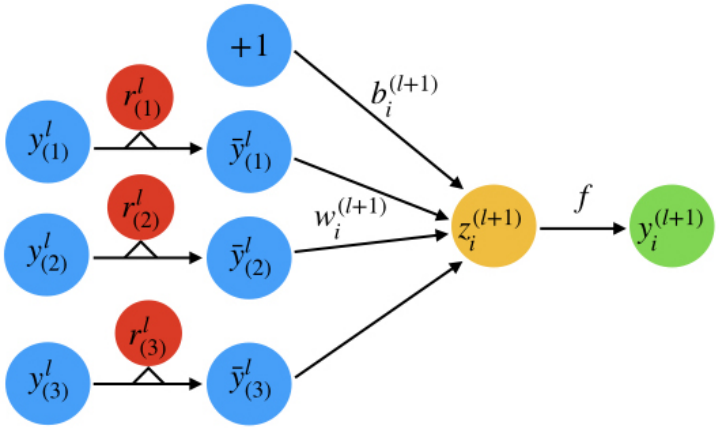


Fig. 4.5 Inclusion of Drop out units (red circles) to combat overfitting of the feed-forward network

as the layers' distribution changes in every training, batch normalisation can combat this effect by applying normalisation utilising mini-batch statistics as follows:

If input $x = (x^1 \ldots . x^d)$, where d is the dimensionality. Then, the normalisation is carried out using the Expectation (E(x)) and Variance (Var(x)) of the training data set:

$$x^k = \frac{x^k - E[x^k]}{\sqrt{Var[x^k]}}$$

To keep the data representation of each layer untouched, the transformation is expressed as an identity transform through pair of parameters γ^k and β^k; this scales and shifts the normalised value as follows:

$$y^k = \gamma^k x^k + \beta^k$$

Therefore the batch normalisation (BN) for a batch of size m transforms the input x to output y as expressed below:

$$BN_{\gamma,\beta} : x_{1\ldots m} \rightarrow y_{1\ldots m}$$

Inception layer The inception layer was introduced in GoogLeNet [194]. In deep neural network, stacking layers to extract local and global features is computationally expensive.

Inception layer can perform the same task in a single layer instead. In other words, the depth of the network is rectified by the increase in width utilising parallel units of convolutional layers. This facilitates applying various filter sizes on the input.

4.2 Research Design and Methods

4.2.1 Dataset

Anonymised data of 682 type 1 diabetes patient from Sheffield Teaching Hospitals NHS Foundation Trust from the 4th quarter of 2013 to the 4th quarter of 2015 were analysed. The data contained a minimum of one HbA1c test per patient (maximum of 10) with a mean of 2.4 tests (total of 1886 tests). The demographics (means and (standard deviation) were: age 46.5 (17.6) years, BMI of 26.5 (5.07) kg/m2, and diabetes duration of 23.6 (15.2) years. The majority of the population were white European 90.2%. Female patients constituted 51.2% of the population. The mean of glucose levels was 10.6(2.4) mmol/L, the standard deviation of 4.7(1.3) mmol/L, frequency of SMBG 3.8(1.3) times per day with the minimum of 2 tests per day, and HbA1c levels of 67.0(13.2) mmol/mol.

4.2.2 Statistical analysis

The features explored in the analysis were as follows. AG was calculated to correspond to each HbA1c test using the preceding three months of SMBG. We defined seven categories of blood glucose (BG) levels; hypo < 4 mmol/L with sublevels of significant-hypo <3 mmol/L, and mild-hypo 3-4 mmol/L; in-target 4-10 mmol/L; hyper >10 mmol/L with sublevels of mild-hyperglycaemia 10-15 mmol/L, and significant-hyper $\geq$ 15 mmol/L. The SMBG checks were grouped into four time-blocks based on their time of the day; midnight (00:00-05:59), morning (06:00-11:59), afternoon (12:00-17:59), and evening (18:00-23:59). For each time block, the percentages of different BG categories were calculated. A further subdivision for weekday and weekend was also created. The variability of SMBG was measured by the standard deviation and standard deviation of the mean. Generalised estimating equation

(GEE) regression [195] was utilised for the analysis to account for the correlated data of subjects with multiple HbA1c tests.

4.2.3 Support vector machine

The statistical analysis provides a linear analysis of the data. It also extracts the meaningful metrics among the features explored. Therefore, SVR is performed on the metrics selected in the statistical analysis for potentially better performance utilising kernels. Three kernels: linear, radial basis function (RBF), and polynomial were used to perform the supervised learning regression. A grid search with 10-fold cross validation was used for hyperparameter optimisation of the kernels. These parameters for the above kernels were set as following: Cs: (0.001, 0.01, 0.1, 1, 10, 100, 1000, 10000); gammas = (1e-4, 1e-3, 0.01, 0.1, 0.2, 0.5, 0.6, 0.9, 100, 1000); degree = (2,3,4,5,6); where C is the regularisation parameter by which a trade off between training error and testing error is achieved, in essence the generalisation of the model; gamma is the Gaussian parameter of the RBF kernel, which represent the potential effect of a data point on the curvature of the boundaries; and degree is the order of the polynomial kernel.

4.2.4 Convolutional neural network

A convolutional neural network (CNN) was used to perform a nonlinear analysis of SMBGs. This processes the data to discover the parameters that define the relationship among different covariates using different layers in the network. Hence, it provides the ability to generalise a model more accurately using the learned parameters from the dataset [196]. This study employs the attributes of a CNN to characterise different glycaemic patterns of patients utilising the daily SMBG readings to predict HbA1c.

The SMBG readings are treated as a sequence of measurements occurring chronologically in time. The time-series of SMBG data points are re-sampled in a thirty-minute resolution using piecewise cubic Hermite interpolation polynomial. To provide more context to the interpolation process, we defined a confidence level between [0,1] for each interpolated

data point. The confidence level of an interpolated data point is one when the data point is an SMBG measure carried out by the patient. Since the minimum active time of a quick acting insulin is about three hours, the confidence level rises from zero in 1.5 hours prior approaching the SMBG measurement and declines to zero in 1.5 hours as the time progresses away from the SMBG measurement. Figure 4.7a depicts the data representation. These

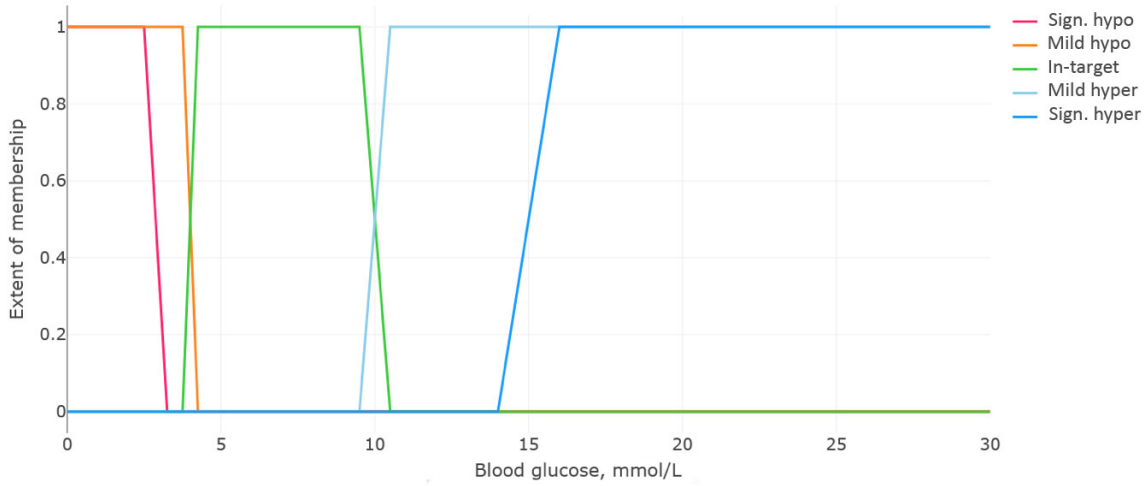
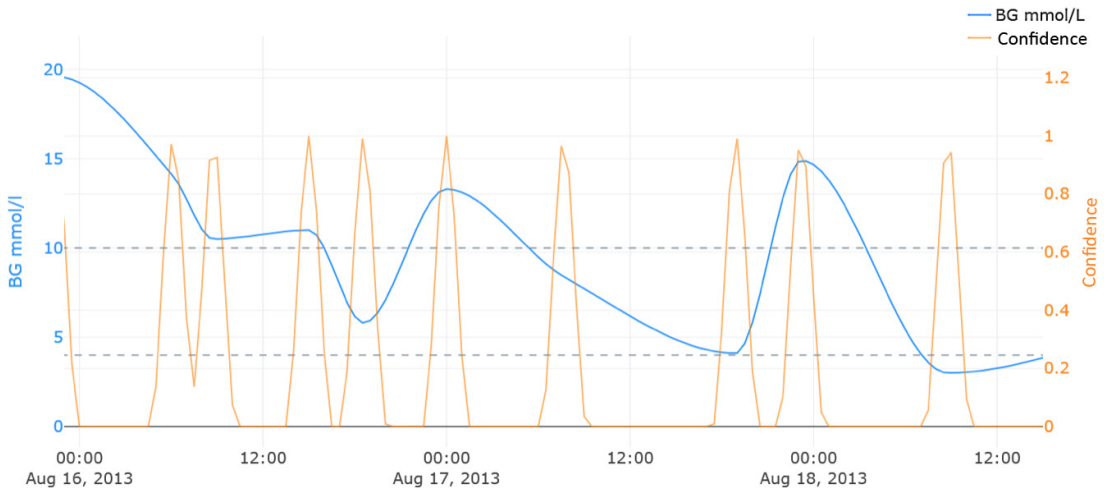


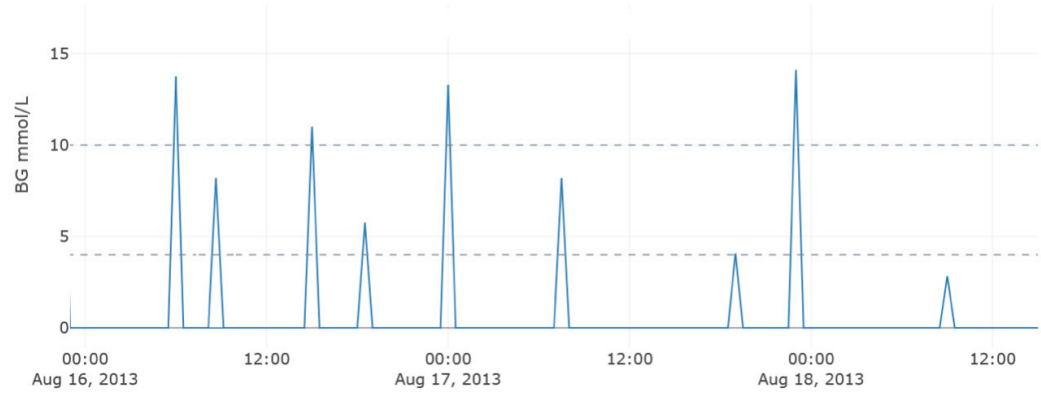
Fig. 4.6 The fuzzy membership functions of the SMBG readings

data combined with interpolated fuzzy SMBG representation are the input to the CNN. The interpolated fuzzy representation was another re-sampling process of the data to provide the network with the meaningful expression of SMBG utilising Fuzzy membership functions of significant hypo, mild hypo, in-target, mild hyper and significant hyper (Figure 4.6). As a result, the time series were transformed into the desired artificial neural network (ANN) input format with: values normalised to [0, 1]; preserved timing and sequential structure; time grid aligned between observations; and meaningful expression of fuzzy BG ranges (Figure 4.7c). Thus, the input for the CNN branch was represented by a 3D tensor $D \in R^{N_e \times T \times N_f}$, where N_e is the number of available epochs, T is their length, and N_f is the number of fuzzy classes employed. Using our dataset and the transformed data, $D \in R^{1886 \times 4032 \times 5}$

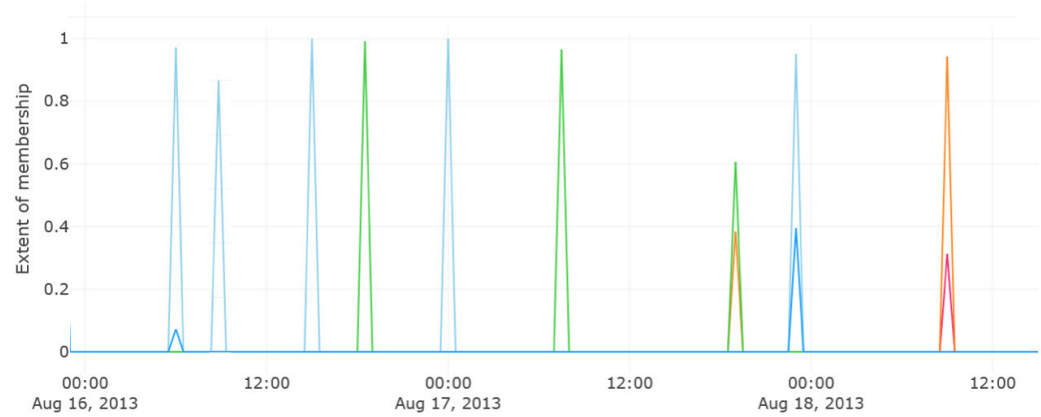
The analyses were carried out in Python (Statsmodels version 0.9.0, Tensorflow [197] and Keras) and R (version 3.3.3). The blood glucose measurements from the 3-month period



(a) Interpolated



(b) Sparse



(c) Sparse fuzzy

Fig. 4.7 The preprocessing of time-series SMBG data to produce the fuzzy sparse representation for the input to the proposed CNN architecture

prior to an HbA1c test were utilised in the analysis of the proposed models. The proposed models are validated using 10-fold cross validation.

4.2.5 Proposed models

First, a linear regression analysis was carried out to identify the significant predictors of HbA1c. The explored covariates represent the glycaemic patterns of individuals to express inter-patient variability alongside AG. Different combinations of covariates are modelled and compared using Akaike's Information Criterion (AIC) [198]. In the analysis of the significant covariates those with p<0.05 were considered, and the final selection made using p<0.01.

Second, we hypothesised that HbA1c prediction improves by utilising HGI as a covariate alongside the AG and glycaemic patterns. A regression analysis was carried out using data from patients with more than one HbA1c test (513 subjects). A HbA1c test and its corresponding period of SMBG were used to identify the patient's HGI group then excluded from onward analysis. The initial estimate of HbA1c was calculated using Hempe *et al.* [199] original formula $HbA1c(\%) = 0.009FBG(mg/dl) + 6.8$, where fasting BG (FBG) is the fasting blood glucose level. In our analysis, FBG was estimated using the mean of the SMBG between the times 06:00 to 10:00 in the morning. The analysis suggested three levels of HGI; low, moderate and high. Consequently, $HGI = HbA1c - (predictedHbA1c)$ was adopted to stratify the patients to groups with the criterion of low HGI $\leq$-0.520mg/dl, moderate HGI 0.520mg/dl to 0.202mg/dl and high HGI >0.202mg/dl. We assumed the patient remains in the defined group over time. Table 4.1 details the characteristics of these groups. The onward analysis used the HGI group as a covariate in the HbA1c prediction to evaluate its contribution.

Third, SVR models were used to explore a better fit of regression results employing a more powerful technique with the kernels. The three explored kernels are linear, RBF and polynomial with combined features selected from the previous two models including the HGI. Finally, a model was designed using CNN to automatically extract features using SMBG readings. The convolutional operations for detecting various glycaemic patterns formed the architecture of the neural network. These glycaemic patterns were inspired by the work

TABLE 4.1
THE CHARACTERISTICS OF POPULATION BASED ON THEIR HGI GROUPS REPORTED AS MEAN(STANDARD DEVIATION)

HGI groups	Low	Moderate	High	p-value
Count (513 individual)	222	147	144	
Age	45.4(16.7)	49.6(16.5)	48.9(19.2)	0.03
BMI (kg/m^2)	26.2(5.0)	26.5(4.8)	27.1(5.9)	0.087
Female	46%	48%	52%	0.413
Mean BG (mmol/L)	9.4(2.1)	10.8(1.9)	11.8(2.2)	<0.0001
Standard deviation (mmol/L)	4.1(1.3)	4.8(1.0)	5.4(1.2)	<0.0001
Frequency of testing	4(1.3)	3.9(1.4)	3.5(1.0)	<0.01
HbA1c (mmol/mol)	57.3(9.7)	69.0(7.9)	78.1(10.9)	<0.0001

done in the first and second proposed models alongside the structured data interpretation carried out by clinicians and patients in practice. To formalise a structured glycaemic pattern detection various levels of patterns, i.e. micro, meso and macro patterns, were investigated utilising the proposed architecture shown in the Figure 4.8. The feature learning of the CNN produced the micro and meso patterns of SMBG data (Figure 4.10). The micro patterns included the episodic glycaemic patterns, time-block glycaemic patterns, and the recurrent patterns on weekly and daily scales. The meso-patterns included the daily and weekly patterns.

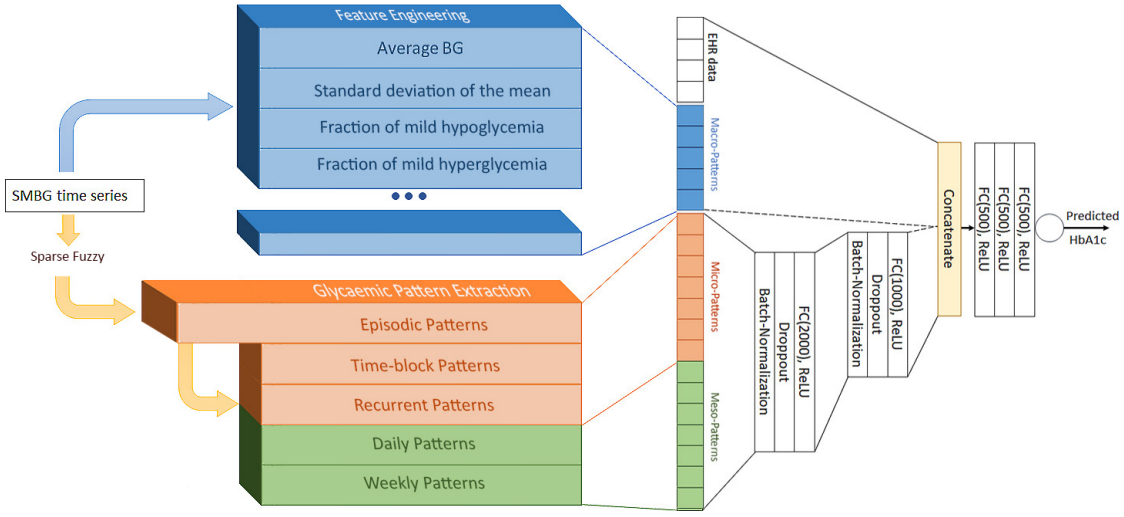


Fig. 4.8 The overview of the proposed model

Episodic glycaemic patterns It refers to episodes that occur during the active time of a single bolus injection. In other words, the decision patterns made by the patient to adjust a glucose value is bound to the active time of the insulin. Considering the interpolated data are in half an hour resolution, we can explore episodic patterns as short as half an hour such as a retest in the event of hypoglycaemia and patterns as long as 8 hours bound to the active time of the bolus insulin. Since we are interested in capturing episodes of varying length (from 0.5 to 8 hours), conventional CNN architecture could be computationally expensive and potentially limiting. Therefore, to avoid increasing the depth of the neural network, we utilised an inception layer to identify the episodic patterns more efficiently. As seen in the Figure 4.9, the logarithmically scaled filters cover the learning of patterns in varying scales. Stacking two of such inception layers can provide patterns of up-to eight-hour time span. The stacked inception layers output 48 channels. These channels are concatenated with the five fuzzy sparse time-series (hypo, hyper, in-target, sign. hypo, and sign. hyper) to produce the identified 53 episodic glycaemic patterns. Due to the time series resolution of half an hour, the three months episodic patterns make up a matrix of 4032×53 elements. Utilising the Maxpool/2 operation the size is reduced to 2016×53.

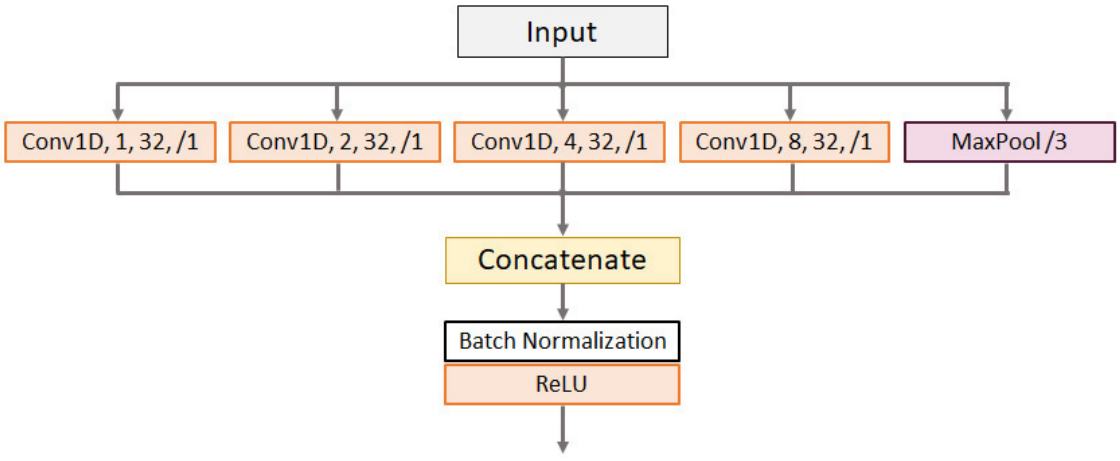


Fig. 4.9 The inception layer of the proposed model with logarithmic scaling convolutional units to extract episodic glycaemic patterns

Time-block glycaemic patterns To have a broader look into the daily patterns of a patient, the day was divided into eight time-blocks. Each time-block contained the average of three hours SMBG measures (minimum active-time of a bolus injection). Since the daily routine of the patients varies, this segmentation of the day helped explore intra-patient patterns. It is worth noting that the starting hour of the day was chosen to be at 3 am instead of 12 am (midnight). This was determined by the analysis of the data using the novel method developed to distinguish the diurnal patterns (the model is presented in the next chapter). The analysis showed that most patients' end of the day overlapped with early hours of the next day. To eliminate this effect, 3 am was an appropriate choice for the start of the day that supported the varying routines of different patients. The network extracted the time-block patterns using filters of size 8×1. Then, the global average pooling produced the average of each time block.

Daily glycaemic patterns Although episodic glycaemic patterns provide a representation of the glycaemic control, it is a detailed analysis of the patterns of SMBGs, here referred to micro-patterns. Therefore, the weighted average of the SMBG measurements of each day produced the average daily profile. This weighted average is calculated using the confidence levels as the weight.

Daily recurrent glycaemic patterns To provide more context to the data, a diagnostic approach to the SMBG readings was utilised to investigate the possible persisting patterns in each time-block. These patterns such as recurrence of hyperglycaemia in a certain time-blocks were extracted using filters of size 2×5. These cover five days of two adjacent time-blocks. Then, average pooling produced the average of each recurrent patterns alongside each time-block.

Weekly glycaemic patterns Further meso-pattern analysis of the SMBG data is carried out by considering weekly glycaemic patterns. Therefore, the 7-days of the week with each day containing eight time-blocks were analysed using 12 filters. These filters span over

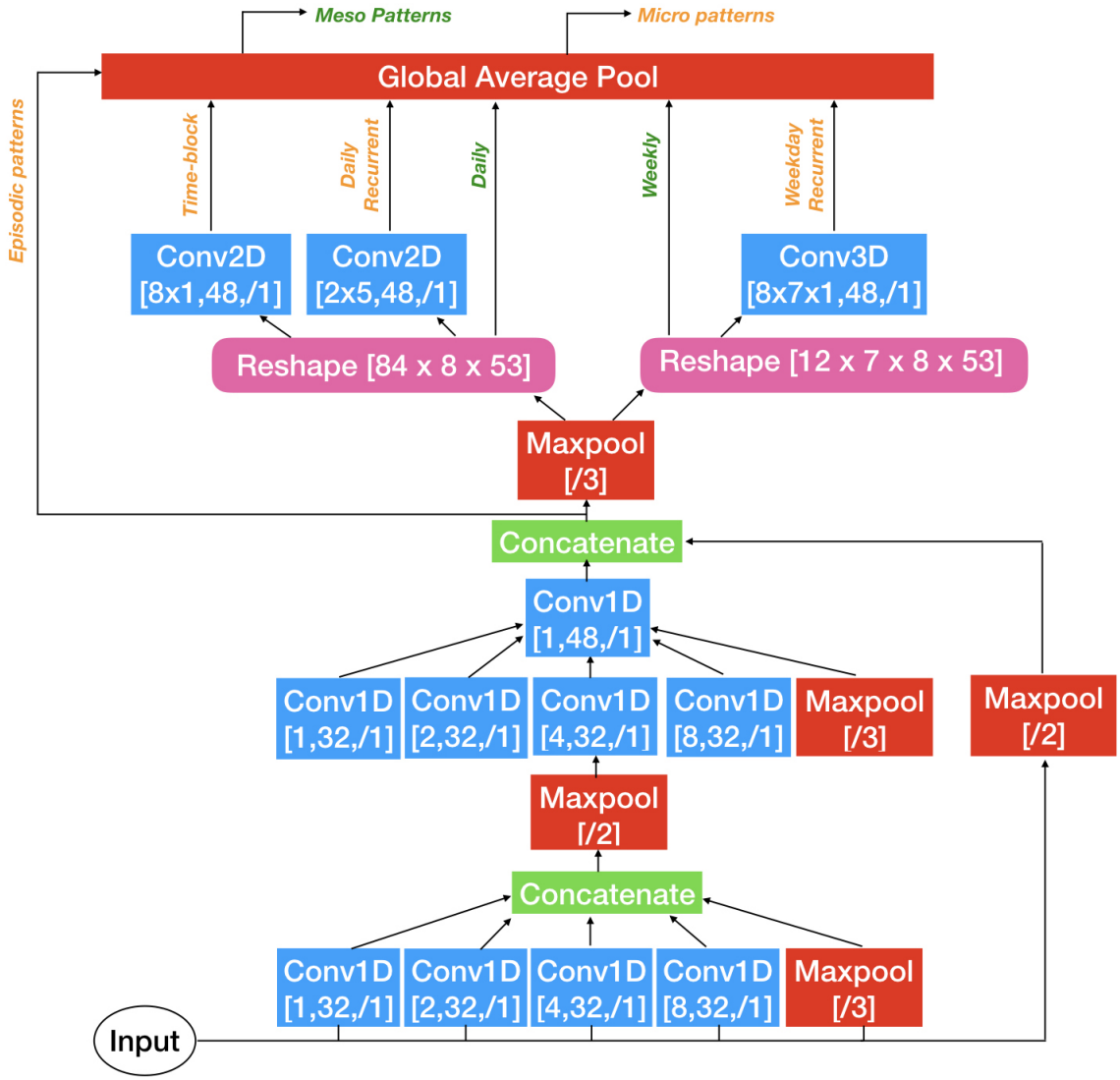


Fig. 4.10 The CNN architecture of the proposed deep neural network model for meso (green) and micro (orange) patterns extraction. The input to the network is the fuzzy sparse data produced in the proprocessing operation. The notations are Conv*x*D[*filter size, number of filters,/strides*], where *x* is the dimensions of the convolution operation; and Maxpool[*/pool size*]

each week of the three months' period of SMBG readings. Then, average pooling is used to generate the average of each week.

Weekdays recurrent glycaemic patterns It is possible to investigate the patterns on different days of the week. In other words, each day of the week over the 3-months period can have recurrent patterns i.e. the Tuesdays' afternoon hypoglycaemic patterns; 48 filters capture such repetitive patterns of the 8 time-blocks based on the day of the week.

The glycaemic patterns were regularised using Drop-out technique to reduce the redundancy in representations and coadaptation of the layers. Later, these sets of features were combined with the engineered features. The engineered features were deduced utilising a similar linear regression analysis of the first proposed model to represent the macro-patterns in SMBG. Since the time-block, daily and weekly glycaemic patterns were handled by the CNN, the generic glycaemic patterns of the entire three months were included, i.e. % of significant hypo, % of significant hyper, % of mild hypo, % of mild hyper, % of in-range, standard deviation, standard deviation of the mean, and average blood glucose. These features were concatenated with electronic health records data such as age, diabetes duration, and sex as the input for the fully connected layers as shown in Figure 4.8.

4.3 Results

The accuracy of the models is measured by Mean Absolute Error (MAE) and Median Absolute Error (MedAE). The methods of Nathan *et al.* [51], and Ladyzensky *et al.* [160] are implemented using our dataset for direct comparison. The reduced data for patients with multiple HbA1c tests was used for the second proposed method (HGI Regression). These are summarised statistically in Table 4.2. The statistical significance between these methods (SVR excluded) were tested using Kruskal-Wallis method, which showed a p-value >0.05.

Figure 4.11 shows the result of the first linear regression. The analysis shows that AG is a significant predictor of HbA1c ($p<0.001$). A unit increase in AG increases HbA1c levels by 2.8 mmol/mol with 95% Confidence Intervals (CI) of [2.3 to 3.3]. In terms of glycaemic

TABLE 4.2

PERFORMANCE COMPARISON OF THE PROPOSED MODELS TO PREVIOUS WORKS. LOWER VALUES OF MEDAE AND MAE IS AN IMPROVEMENT WHEREAS LARGER R^2 IS AN IMPROVEMENT.

	Previous works		This work				
Parameter	Nathan *et al.*[51]	Ladyzensky *et al.*[160]	SVR_{Linear}	$pHbA1c$	$SVR_{Linear-HGI}$	$pHbA1c_{HGI}$	CNN
MedAE	6.8	6.3	5.3	5.3	4.7	4.6	3.4
MAE	8.5	7.6	6.46	6.5	5.5	5.5	4.3
R^2	0.3	0.44	0.62	0.66	0.69	0.76	0.78

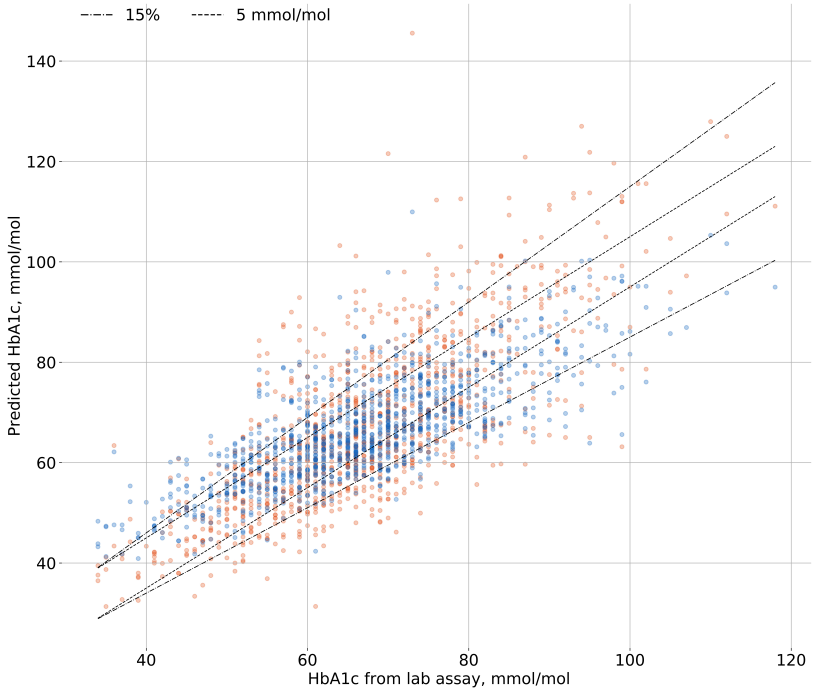


Fig. 4.11 The results of the $pHbA1c$ model (blue) and Nathan's model (orange)

patterns, percentages of morning hyperglycaemia, afternoon hyperglycaemia, and standard deviation of the mean were significant predictors of HbA1c. A 10% increase in the morning hyperglycaemia (MH) results in an increase of 2.0 units of HbA1c with 95% CI [1.1 to 2.9] (p<0.001). A 10% increase in afternoon hyperglycaemia (AH) yields an increase of 1.7 HbA1c units (p<0.01) with 95% CI [0.7 to 2.8]. Furthermore, more variability as measured by 0.1 unit increase in standard deviation of the mean (SDM), results in an increase of 2.2 HbA1c units with 95% CI [1.4 to 3.0] (p<0.001). The adjusted R^2 is 0.66, the median absolute error is 5.3 mmol/mol. In the analysis sex, diabetes duration, and ethnicity were insignificant (p>0.05). However, age was a significant predictor with a p-value of 0.004.

$$\begin{aligned} pHbA1c(mmol/mol) = 2.82AG(mmol/L) + 0.2MH(\%) + 0.17AH(\%) \\ + 22.45SDM(mmol/L) + 0.04age + 22.9 \end{aligned} \tag{4.1}$$

Different HGI groups exhibit significantly distinctive glycaemic patterns. These patterns are investigated and the result of the HbA1c predictive model is shown in Figure 4.12. In

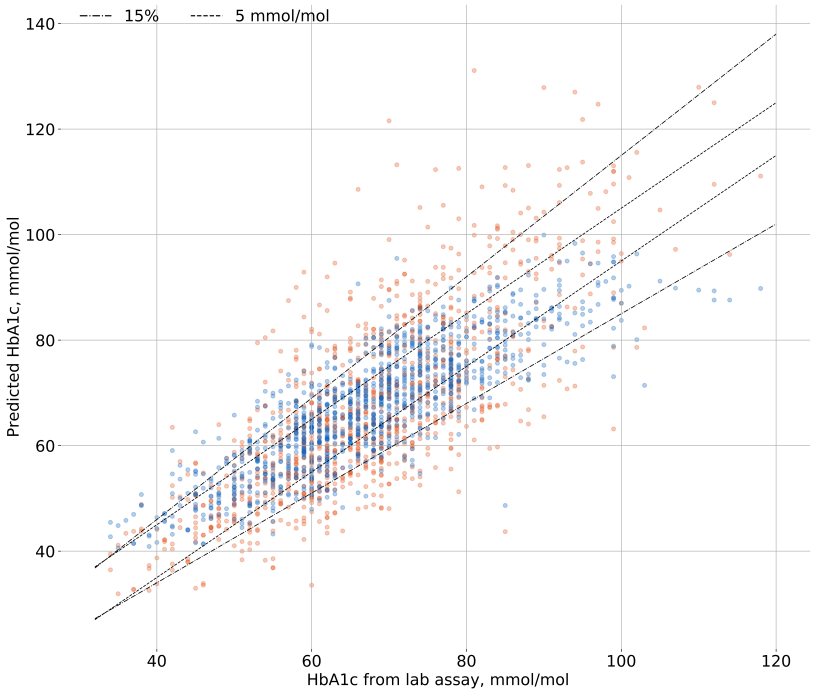


Fig. 4.12 The results of the $pHbA1c_{HGI}$ model (blue) and Nathan's model (orange)

this model, HGI was included as a covariate. The analysis shows that combined AG and HGI are significant predictors of HbA1c (p<0.001). An increase of one unit of AG results in an increase of 2.6 units of HbA1c with 95% CI [2.1 to 3.1]. Also, an increase of 0.1 unit in the standard deviation of the mean on the weekends (SDMW) results in an increase of 0.7 units of HbA1c with CI [0.2 to 1.2] (p<0.001). Furthermore, a 10% increase in mild hyperglycaemia on the weekends (MHW) results in 0.8 units increase in HbA1c with CI [0.2 to 1.4] (p<0.01). The moderate HGI (MHGI) group exhibits a reduction of 4.3 units of HbA1c compared to the high HGI group. Similarly, low HGI (LHGI) group exhibits a reduction of 10.8 units of HbA1c compared to the high HGI group. The adjusted R^2 is 0.76 and the median absolute error is 4.6 mmol/mol. No significant interaction between the HGI groups and covariates observed (p>0.05). In the analysis age, sex, diabetes duration, and ethnicity were insignificant (p>0.05)

$$\begin{aligned} pHbA1c_{HGI}(mmol/mol) = {} & 2.64AG(mmol/L) - 10.84LHGI - 4.34MHGI \\ & + 0.17MH(\%) + 0.08MHW(\%) \\ & + 7.54SDMW(mmol/L) + 36.35 \end{aligned} \tag{4.2}$$

where:

$$LHGI = \begin{cases} 1 & \text{when the patient is in low HGI group} \\ 0 & \text{otherwise} \end{cases}$$

and

$$MHGI = \begin{cases} 1 & \text{when the patient is in moderate HGI group} \\ 0 & \text{otherwise} \end{cases}$$

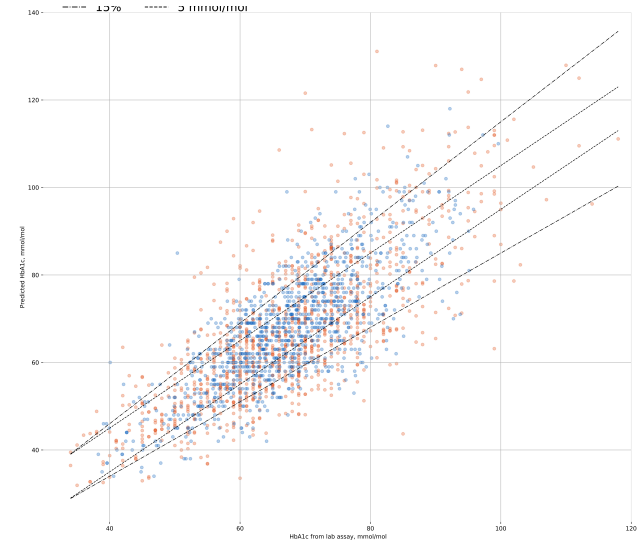
The combination of all the features explored above (except HGI) are employed with SVR ($\varepsilon = 0.01$). Figure 4.13 shows the result for the three kernels. For linear kernel, the optimal C parameter was selected to be 1; for RBF kernel gamma=0.0001, and C=1000 (MAE: 6.4 , MedAE: 5.3, and $R^2 = 0.61$); and for polynomial kernel C=1000, and degree=2 (MAE: 8.2, MedAE: 6.5, and , $R^2 = 0.42$). The linear kernel had the best performance with MAE=6.46,

MedAE=5.3, and , $R^2 = 0.62$. When HGI was included, for the linear kernel the optimal C parameter was selected to be 1; for RBF kernel gamma=0.001, and C=1000 (MAE: 5.5, MedAE: 4.7, and $R^2 = 0.67$); and for polynomial kernel C=1000, and degree=2 (MAE: 8.2, MedAE: 6.5,and $R^2 = 0.44$). The linear kernel had the best performance MAE=5.5, and MedAE=4.7, and $R^2 = 0.69$.

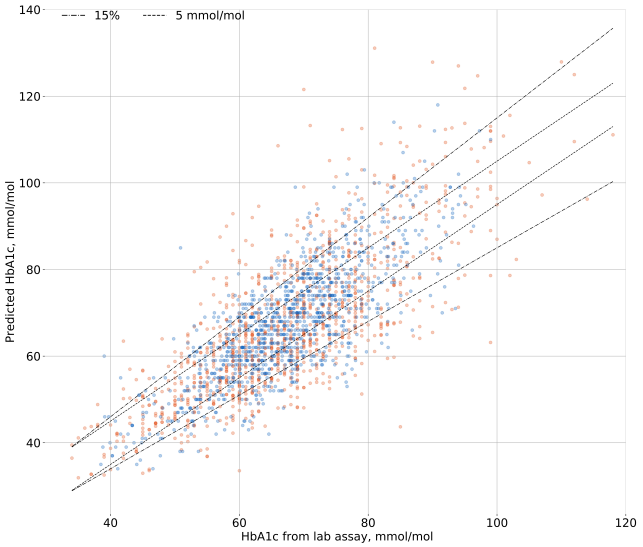
As shown in the Table 4.2, CNN produces the minimum error and highest explained variance. The prediction results of the CNN are shown in Figure 4.14. The analysis for micro-patterns in regression showed that the mild hypo, mild hyper, and the standard deviation of the mean alongside the average blood glucose level were statistically significant ($p < 0.05$). Therefore, these micro-patterns were included as an input to the fully connected layer of the proposed model.

4.4 Discussion

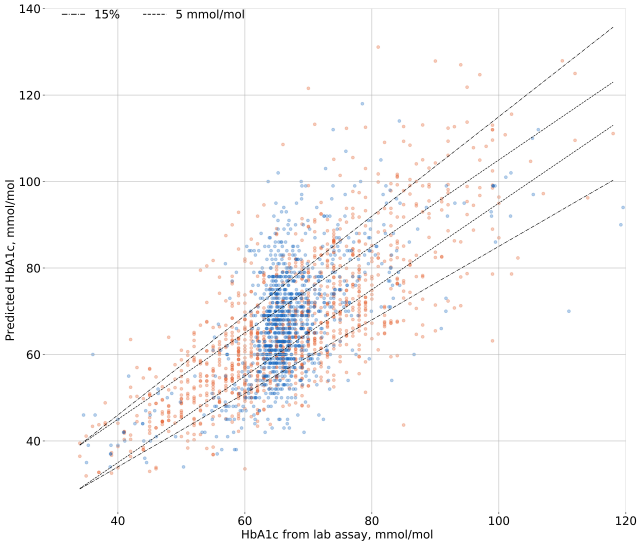
The study of glycaemic patterns as predictors of HbA1c improved the accuracy of the estimated HbA1c. In the linear regression analyses the percentage of hyperglycaemia, glycaemic control at weekends, and during different time-blocks of the day were statistically significant. Also, we utilised CNN to fit a more complex pattern finding model to estimate HbA1c results. The CNN outperformed other models with tighter error margins. The improved results are emblematic of glycaemic patterns in managing diabetes that can influence HbA1c levels. Our first novel model is a regression that incorporates glycaemic patterns alongside AG to better predict the HbA1c. The standard deviation of the mean (SDM) showed that increasing the number of tests and/or reducing variability decreases HbA1c levels. The SDM points out that frequent testing is more representative of diurnal changes in SMBG. In other words, a lower standard deviation of the mean indicates a more precise AG level. This result is in line with findings of other studies [133, 200] and adds further evidence to support easing the limits on providing test strips and an educational programme to improve management of BG levels (i.e. reduce variability). The $pHbA1c$ model included the glycaemic patterns of exposure to high glucose values (percentages of morning hyperglycaemia and afternoon hyperglycaemia)



(a) Linear kernel



(b) RBF kernel



(c) Polynomial kernel

Fig. 4.13 The results of the support vector regression utilising three kernels of linear, RBF and polynomial

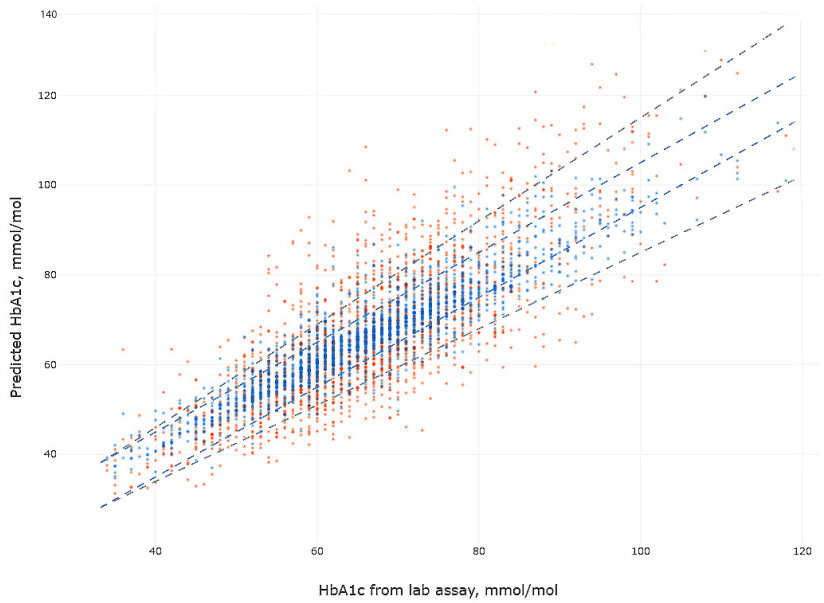


Fig. 4.14 The results of the proposed deep neural network model (blue) and Nathan's model (orange)

to account for the inter-patient variability with similar AG. This emphasises that exploiting glycaemic patterns among patients while controlling for AG improves predicting HbA1c compared to the established methods.

The infrequent sampling of SMBG is a barrier for most established methods to estimate HbA1c using AG. As our data shows, 50% of patients perform less than 3.5 tests a day. The ADAG study [51] derived regression used a selective cohort with stable HbA1c (<1% change in HbA1c) and glycaemic control in their earlier six months. This stable control is more difficult to achieve in type 1 diabetes. Also, ADAG study patients had contributed $\sim$ 2700 combined continuous glucose and SMBG readings for each HbA1c test; non-compliance with the frequency of continuous and SMBG tests resulted in exclusion from the analysis. Layzenski *et al.* [201] model used an in-vitro approach to reproduce the result of the ADAG study. Hence, the same assumption of a selective population applies to their result. In our analysis, the data were obtained from patients in routine clinical practice.

Kovatchev *et al.* [173] two-step dynamic model assumes sufficient blood frequency of at least four tests per day over a week to reconstruct the seven-point profile. Patients may perform four tests a day but not spread them between the main time blocks. A good 'profile

grade' still seems restrictive and was reported by the users as unpleasant. The algorithm also suffers from the initialisation problem: a patient can have a poor week (high hyperglycaemia) or an excellent week (no hyperglycaemia) while it accounts as the starting point for tracking the changes in HbA1c. When applied to our dataset, the surrogate fasting blood glucose still resulted in gaps between days which made the tracking of HbA1c changes impossible.

We examined the hypothesis that the latest month of SMBG contributes 50% more towards HbA1c. The weighted average SMBG did not provide a better model. One explanation could be that this hypothesis might be valid in patients with relatively stable glycaemic control and high frequency of testing. They would have similar patterns and statistics over long periods of time (i.e. three months). Hence, weighting the average blood glucose would not introduce a significant bias toward the latest months and dismissal of the effect on the earlier months; considering the irreversible nature of the glycation of haemoglobin would favour longest-lived Hb.

In the second proposed model, the glycaemic patterns of the first model (AH and SDM) were insignificant. Including HGI in the analysis can explain this insignificance. HGI is calculated from a previously observed HbA1c and adjusted by FBG of the preceding three months. As our assumption that patients follow certain glycaemic patterns over time, the information gained by HGI implicitly includes explained variances of these variables. In other words, patients exhibit patterns trackable across time that HGI can represent. Therefore, the importance of glycaemic patterns shifts toward the glycaemic control on the weekends (i.e. SDMW, MHW). For most patients, weekends represent an atypical glycaemic pattern compared to weekdays that can influence HbA1c levels.

Furthermore, the original HGI formula and cutoff points were applied to account for inter-variability among patients with similar AG. A larger HGI expresses an unusual deviation compared to the population which could be partly related to physiological variability such as red blood cell (RBC) survival and/or variations in glycation rates. Measuring inter-patient physiological variabilities in current clinical practice is difficult. Many factors can cause these variabilities: different variants of haemoglobin (about 7% of the world population), anaemia, blood loss, multiple blood transfusions, and genetic variance in glycation rate. As

the affected population is estimated to be about 5% to 10% [162], HGI which may be used to predict diabetes complications and effectiveness of diabetes treatment [202] could be utilised to express these variabilities. The HGI is an empirical measure derived to express deviation from the expected population's HbA1c. HGI improved the accuracy and explained variance (R^2). This is a novel application of HGI and supports the care considerations and personalisations of the treatment plans for HGI groups as suggested in other studies [169–171, 203]. Especially, subgroup analysis of the ACCORD study has shown that low and moderate HGI groups benefit from intensification of the treatment regime [203]. In contrast, the high HGI group had an adverse reaction to the intensification and were confined with a higher mortality rate [169–171, 203].

Additionally, the $pHbA1c_{HGI}$ model was derived assuming patients would consistently be in the same HGI group. The results show that most patients are consistent. However, patients could improve their diabetes control and associated patterns which results in a change in the HGI group. One way to resolve the issue would be updating the HGI group of a patient in a scheduled manner such as a yearly basis. However, if a patient changes the HGI group frequently, it can indicate HbA1c variability which requires further investigation as it is associated with increased mortality and earlier hospital admission [204].

The proposed deep convolutional neural network similar to the FCN [186] utilises GAP to reduce the sizes of the learned features. Additionally, similar to the work in MCNN [188] and MCDNN [189] varying subsequences (i.e. time-scales) of features in the time-series were explored. Unlike these studies, we utilised the inception layers to accommodate such feature discovery. We utilised a similar concept of G-CNN [190] to provide a membership to the data points (e.g. time-block, episodic patterns). However, unlike the G-CNN, the extra clustering preprocess was mitigated by utilising the knowledge of data in combination with the convolution and max-pooling operations to uncover the relevance of such memberships. The promising results presented adds evidence to the benefits of the CNN for learning the underlying features to improve the predictions in regression problems. To the best of our knowledge, this is the first use of CNN for modelling the HbA1c prediction using raw SMBG data.

One limitation of this study was its observational nature which limits the controlling factors that influence individuals' glycaemic control. Nonetheless, 682 patients is a representative sample, and they received care from the same NHS Trust. Additionally, this is a strength, due to its routine clinical setup rather than an experimental setup which makes the result applicable in clinical practice. As shown, the proposed models outperformed the established methods despite the infrequent glucose testing (minimum of 2 tests per day).

Today's advancement in technology facilitates higher storage and processing power which enables the complex modelling techniques such as CNN to perform with higher accuracy. We speculate more data per patient facilitate personalised prediction models. Also, the recent increase usage of continuous glucose monitoring provides a better opportunity to explore glycaemic patterns associated with HbA1c levels due to its frequent sampling of glucose levels (a sample every $\sim$ 10 minutes).

In conclusion, the individual patterns of glycaemic control affect the analysis of SMBG for prediction of HbA1c. This presents to healthcare providers and patients that HbA1c is more than just the relationship with the average blood glucose. The analysis supports the recommendations that reducing hyperglycaemia, reducing variability, and increasing frequency of SMBG would contribute to improved HbA1c levels. Moreover, implementing the models on a glucose meter or a mobile application could provide prompt availability of the predicted HbA1c and enhance motivation for quicker and more effective intervention. Its application can provide a more personalised consultation and timely feedback on glycaemic control.

Chapter 5

Diabetes diurnal patterns

In multiple dose injection (MDI) therapy, the bolus advisor is utilised to more accurately suggest doses of meal-related insulin based on carbohydrate (CHO) intake, pre-set insulin to carbs ratio (ICR), and insulin sensitivity factors (ISF). One of the advantages of the bolus advisor is that it can take into account active insulin from previous injections when recommending the dose, thus reducing the mathematical load on the users. Diurnal activity routines are influential factors in the recommendations. Therefore, the daily time periods of the routines are required to be identified in order for the BG targets, ICR, and ISF to be optimised. Currently, calculation of these factors relies on self-reporting of daily activity routines including times for meal/snack, exercise, start-of-day, end-of-day, activity periods etc.

The main issues with reporting and adjustments of daily activity routines are self-reporting which is prone to inaccuracy; and in bolus calculators, relying on the use of default settings for daily time periods in devices such as insulin pumps, glucose meters, and mobile applications. Moreover, daily routines are subject to change over periods of time which could go unnoticed due to its usual gradual change. Hence, forgetting to modify the daily time periods could contribute to hypo/hyper blood glucose (BG) readings.

Time-series clustering can be used to achieve the meaningful separation of diurnal patterns by utilising the univariate time-series of self monitoring blood glucose (SMBG) data. The proposed data-driven system identifies the daily time periods and advises the user of any

change. This provides more accurate, granular and personalised daily time patterns. The system segments the day based on the observed routine activities in particular periods of time. Therefore, it has the potential to help provide a more contextual perspective to glycaemic pattern identification. Further improvements on bolus advisor settings are investigated to include week/weekend or even modifiable daily settings. This contributes towards a more personalised experience and flexibility to finely tune the bolus advisor.

5.1 Background

An insulin bolus advisor (BA) is a decision support tool incorporated in many commercial insulin pumps and a few glucose meters to aid with calculating the required units of insulin for injection [39]. Studies have reported the usage of a BA is associated with improvements in HbA1c levels [39, 205–207]. However, this depends on the accuracy of the setup [40]. Each bolus advisor relies on its settings for advising the amount of insulin [41]. The settings in a BA involve the number of time-blocks (TB), periods of time-blocks, insulin sensitivity factor (ISF), insulin to carbohydrate ratio (ICR) and blood glucose (BG) target range. In some BAs, the setting up process begins by first choosing the number of time-blocks in a day. Then, the length of each time-block is specified by choosing the start and end time appropriately, as illustrated in Table 5.1. In other BAs, the number of time blocks and their periods are preset and unmodifiable, thus limiting personalisation.

TABLE 5.1
EXAMPLE BOLUS ADVISOR TIME-BLOCK SETTINGS. EACH TIME-BLOCK DEFINES ISF, ICR AND BG TARGET RANGE.

Time Blocks		Target range		ICR		ISF	
Start time	End time	Lower limit (mmol/L)	Upper limit (mmol/L)	Insulin (U)	Carbohydrates (g)	Insulin (U)	Blood glucose (mmol/L)
00:00	05:29	5	9	1	10	1	3
05:30	10:59	4	7	2	10	1	3
11:00	16:59	4	7	3	10	2	3
17:00	21:29	4	7	2.5	10	1	3
21:30	23:59	5	9	1.5	10	1	3

The ISF is used for correcting an out of range BG reading; whereas CHO ratio is used to determine the required units of insulin for the specified amount of carbohydrates referred as ICR. The glucose targets are preprandial glucose levels defined as a reference for correction insulin calculation.

$$bolus\ insulin = meal\ insulin + correction\ insulin$$

$$bolus\ insulin = \frac{CHO}{ICR} + \frac{Current\ BG - Target\ BG}{ISF}$$

Due to the change in physiological and lifestyle needs of patients, the use of BA for optimal benefit requires attention and close review on a regular basis. Also, trust in the BA is an important factor in patients' engagement with it [42]. If the settings are set correctly, the BA can perform as a helpful tool for insulin administration; otherwise, the settings are inaccurate, the advise given will be suboptimal and lead to more episodes of hypoglycaemia and hyperglycaemia.

The fundamental component of BA settings is the time-blocks. If the time-blocks are not personalised and modified based on the diurnal activities of the patient, the remaining settings of the BA cannot be tuned for optimal usage. These suboptimal settings stemming from inaccurate time-blocks can cause inaccurate insulin dose prediction. A study of 24 individuals using pumps reported that most BAs were set on incorrect settings for patients [208]. Currently, BAs allow for a single setting that is applied for the dose calculations in every day of the week. This is a limiting factor in personalising the BA for the day to day variations of daily routines that exist in real life.

Another study showed that the frequency of adjusting the settings has positively contributed to the glycaemic outcome. Also, continuous adjustments improved the consistency of the usage of BAs [209]. However, manual analysis of the large amounts of SMBG data to identify time-blocks and their corresponding settings is time-consuming and cumbersome. Usually, the applied changes are a reactive intervention at times where glycaemic control is challenging. Furthermore, among diabetes complications is progressive vessel dysfunction

which contributes towards accelerating physical ageing and influential to diurnal physical activities [210]. Hence, automatically tracking patients' diurnal patterns over time is of interest in the presented work.

Studies have utilised a case-based reasoning technique to provide adaptability and personalisation of BAs [211–213]. The advised bolus is calculated based on previously observed measures. This is achieved by defining a similarity measure to identify a close match to the currently inquired insulin dose by comparing to historical data. The results were tested in a simulation and later as a mobile application to evaluate acceptance by users. As of any case-based reasoning system, it requires a huge database of many variant cases and maintenance otherwise its performance is lessened. A neural network (NN) approach is proposed for the personalisation of the BAs in [214]. In the NN approach, continuous glucose monitoring (CGM) and pump data are used alongside individuals' information such as weight, glucose rate of change, and insulin sensitivity to determine the amount of injected insulin for a meal. The method was examined in an in-silico experiment under a single meal, single day, and noise free scenario. In another study [215], various machine learning techniques are utilised in bolus correction factor calculation. The study was limited to reducing the postprandial hypoglycemia occurrences. However, in these proposed methods for BAs, there is no evidence to show a benefit in comparison to current BAs.

In the present study, an intelligent data-driven technique is proposed that enables the clustering of the diurnal activities of people with type 1 diabetes to suggest the number and periods of time-blocks for BA settings automatically. The automated aspect of the technique reduces the burden on both clinicians and patients in terms of effort and time to analyse and understand diurnal patterns for correct setting of time-blocks within BAs. In addition, the proposed approach will allow personalisation of the BA settings in real-time based on data. This to our knowledge is the first attempt at providing real-time recommended settings of BAs that corresponds to a patient's diurnal patterns automatically.

Time series clustering

Clustering is the process of organising objects in groups where members of a group share a common similarity and differ from members of other groups [216]. This is an unsupervised algorithm whereby the structure of the groups is not identified prior to the analysis. Hence, the data are not clearly labelled into groups. The increasing power of storage, data processing and the amount of data generated on a daily basis presents clustering as a useful tool to organise the data in a meaningful manner by discovering the underlying common structure [217]. The focus of the study is on a special type of clustering referred to as time-series clustering. A sequence of nominal data are a temporal series, and the sequence of continuous real value data is a time series. It is a temporal or time series since the observed data are changing chronologically as time progresses. Also, the chronological collection of data results in their complexity in size and high dimensionality [218]. Researchers use time-series clustering to discover rare or frequent patterns in these big data.

Definition 5.1. Time Series clustering: Given a dataset of $D = \{d_0, d_1, d_2, ..., d_n\}$, and process of unsupervised grouping of D into $C = \{C_0, C_1, C_2, ...C_k\}$; such that comparable time-series data grouped together utilising a similarity function is time-series clustering. Therefore, C_i is a cluster, where $D = \cup_{i=0}^{k} C_i$ and $C_i \cap C_j = \varnothing$ for $i \neq j$

Defining an appropriate similarity measure for time series data is difficult. Because, time series data are noisy, include outliers, shifts and are in variable lengths. To help to choose the similarity measure, investigating the type of time-series clustering is the primary process.

- **Whole time-series clustering** is the grouping of sets of a time series based on their similarity. Hence, the entirety of the time series is of interest. The entire time series is compared to other time series and clustered to produce a meaningful structure.

- **Subsequence** clustering is the grouping of subsequences of a longer time series. These subsequences can be from a single or multiple time series extracted using windowing or segmentation algorithms.

- **Time-point clustering** is the grouping of time points based on their closeness in time. This process is similar to segmentation in that it takes the sequential data points and tries to find a meaningful boundary to group them together. However, multiple segments can belong to a single cluster.

Time series clustering has five main components: dimensionality reduction or representation, distance measure, the clustering algorithm, prototype definition and evaluation. The process of clustering requires either all or part of these components.

- **Dimensionality reduction** or representation is the process of manipulating the input data into another space using transformation techniques or re-sampling of the data using a pre-defined function. These transformations or re-sampling helps with reducing the size of the data, simplifying the process of similarity measure, improving the speed of calculation, and most importantly de-noising of the data. Noisy data could result in the clustering of data based on the similarity of their noise rather than the actual data points. Among these representation methods are discrete fourier transform, discrete wavelet transform, singular value decomposition and symbolic approximation.

  Definition 5.2. Time Series representation: Given a set of time-series data points $D = \{d_0, d_1, d_2, ..., d_n\}$, and through the process of transformation $D' = \{d'_0, d'_1, d'_2, ...d'_k\}$; where $k \leq n$, such that two similar series in original form should be similar in transformed form.

- **The similarity measure** is used to compare two objects of time series data. The choice of similarity measure plays an important role in time-series clustering as comparing two irregularly sampled intervals with different lengths is challenging. Also, similarity can be in time, shape and structure of two or more time series. Among distance measures used in time-series clustering are dynamic time warping, Euclidean distance, longest common subsequence, and hidden Markov models based distance measures.

  Definition 5.3. Time Series distance: Given set of time-series data points $D = \{d_0, d_1, d_2, ..., d_N\}$ is time-series with length of N. The distance across all time points

as $dist(d_i, d_j) = \sum_{t=0}^{N} dist(d_{it}, d_{jt})$ where i and j are the indices of time series i and j respectively.

- **Prototypes** Cluster prototype refers to the process of finding a representative member for a cluster. This is especially necessary for some clustering algorithm such as K-means, k-Medoids, Fuzzy C-Means, and Ascendant hierarchical clustering which rely on prototypes for clustering. Most used approaches for determining the prototype is

  - The average: the average of the cluster data points is the prototype. In the case of shape based clustering the average shape using dynamic time warping or longest common subsequence is used as an alternative.
  - The medoid: the centre of the cluster is the prototype
  - The local search prototype: in this approach, the medoid is the starting point (initialisation) for the cluster prototype. Then, it uses the average of the warping path to locate a new prototype. This is similar to determining the centroid in the K-means clustering [219].

  Definition 5.4. Time Series prototype: Given time-series in a cluster $C_i = \{d_0, d_1, d_2, ..., d_n\}$, a prototype R_j objective is to minimise the distance between all cluster members and the prototype(representative member). $E(C_i, R_j) = \frac{1}{n} \sum_{x=0}^{n} dist(d_x, R_j)$

- **Algorithms** Clustering algorithms are divided into six categories: hierarchical, grid based, model based, density based, partitioning and multi-step clustering.

  - Partitioning: This method chooses a prototype for each cluster and performs distance measures to label the data points to a given cluster. Therefore, it needs to specify the intended number of clusters. Among these methods are K-means, K-Medoids, and Fuzzy c-means.
  - Hierarchical: This method utilises agglomerative or divisive algorithms to assign data points to a cluster [220]. The agglomerative algorithm assigns each data point as a cluster; then, merges the clusters in the next level in the hierarchy

(bottom-up approach). Whereas, the divisive algorithm assigns all the data points to a cluster; then, splits the data into more clusters in the next level of the hierarchy (top-down approach). After each split or merge operation, the data point cannot be reassigned. Therefore, hierarchical clustering is usually combined with another algorithm to create a hybrid clustering technique.

  - Grid based: This method divides the space into a grid of cells [221]. Then, the clustering is performed on the cells. This is a grid search (brute-force). Therefore, it is slow. It can also be inaccurate on large datasets due to its dependence on the quality and granularity of the underlying structured cell spaces [222].

  - Model based: This method attempts to recover the original model from sets of data. Therefore, there is an assumption of the underlying distribution of centroids and noise. The uncovered model forms the cluster. Polynomial models, Gaussian mixture models are examples of this technique.

  - Density based: This method defines sub-spaces of high density that are separated with sub-spaces of low density. Therefore, it does not assume any shape or distribution to the data.

  - Multi-step based: In this approach the clustering process is divided in multiple steps. The first step could either be an initial clustering process based on certain distance measure (subclusters) or preprocessing of candidate time-series. Then, these are processed by another clustering method to determine the membership of the data [218, 223].

- **Evaluation** The evaluation of unsupervised techniques is challenging [224]. The clustering evaluation depends on the definition of the cluster in the applied application. Therefore, these methods are likely to be subjective measures. For example, the number of clusters, the size of the clusters and the definition of similarity and outliers are dependent on the subject domain. Hence, the evaluation relies on expert's judgements. Generally, the evaluation measures are broadly divided into two categories as follows:

- External Index: The evaluation is carried out with the aid of external factors such as labelled data or obtained ground truth [225]. These methods are similar to supervised measures for evaluation. Among these methods are purity, entropy and F-measure.

- Internal Index: The evaluation is carried out by measuring the fitness of the cluster in terms of members' own similarity and dissimilarity to members of other clusters. These methods do not rely on external measures. Therefore, these are unsupervised measures that do not require the ground truth. Among these measures are Silhouette index and standard squared error.

5.2 Research Design and Methods

Patient daily measurement records such as BG, carbs, bolus insulin, basal insulin, and ketones are used as inputs to the system. The timestamps of the measurements are extracted and transformed to be features. Therefore, it is an unsupervised machine learning problem of a univariate time series data which would produce clusters in daily time (hours and minutes), as illustrated in Table 5.2. The proposed model is depicted in Fig. 5.1

TABLE 5.2
AN EXAMPLE OF THE UNIVARIATE TIME SERIES DATA OF A PERSON WITH TYPE 1 DIABETES. THESE DATA ARE RECORDED THROUGHOUT A DAY AS AN EVENT AT A CERTAIN TIMESTAMP. ONLY THE GLUCOSE MEASUREMENTS ARE MEASURED USING A GLUCOSE METER AND THE REST OF THE DATA ARE MANUALLY ENTERED BY THE PARTICIPANT. ALBEIT USUALLY USING A USER INTERFACE ON THEIR BG METER.

	Hour	Minutes	Result	Type
0	0	11	6.3 mmol/L	Glucose
1	0	11	40.0 g	Carbs
2	10	27	15.5 mmol/L	Glucose
3	10	27	3.0 U	Bolus Insulin
4	14	18	7.4 mmol/L	Glucose

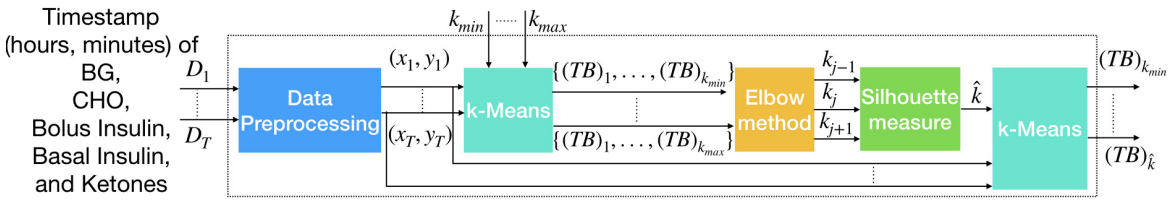


Fig. 5.1 The proposed model to identify diurnal patterns from timestamps of the measurement events of routinely collected data in diabetes including: the data preprocessing, K-means clustering, fitness measurements, and the optimal suggested number of time-blocks

Dataset

The data are the timestamp of a combination of everyday measurements of BG, CHO, bolus insulin, basal insulin and ketones. Data from 70 anonymised Glucollector patients alongside their meter's BA settings were collected. These data were used to produce a logbook view (a sample is in Appendix 1). The logbook included a combination of everyday measurements of BG, carbohydrates, bolus insulin, basal insulin and ketones. The proposed algorithm generated the equivalent BA time-block settings for each logbook. For the application validation of the experiment only two weeks of data was used to match current clinical practice. For the other parts, exploring beyond current limitations, a month of data was used.

5.2.1 Data preprocessing

Pre-processing is an important aspect of the proposed technique to transform the time series data accurately and efficiently. The time series data processed by the algorithm is only the timestamp at which a measurement event has occurred. For modelling and inference of timestamp data, a transformation is needed to be able to apply the common linear methods. Time has a cyclic characteristic. Also, the order of the time is arbitrary, for example, 00:00 can be represented as 24:00. Also, 24:00 and 01:00 are adjacent. It is important to note that someone can have a bedtime of 01:00 which means their natural day overlaps to the next calendar day. This can be a problem when the utilised methods require mathematical operations such as mean.

For example, if an event occurs at 12 am and then at 2 am, the arithmetic mean of these events is $\frac{24+2}{2} = 13$ which on a circular clock has a different direction. These data could be

treated as circular (angular) data and specialised methods could be applied for the analysis. Alternatively, for modelling and inference of such data, a transformation is needed to be able to apply the common linear methods.

One way of transforming the data is using the equations as a pair of (x,y). Although it is denoted as a pair of (x,y), x and y are not bi-variate on a plane. Their relationship is defined by $x^2 + y^2 = 1$. Therefore, these points are strictly located on the circumference of the circle. Hence, they are a Lebesgue measure of zero on the plane [226].

x and y are therefore calculated as such: $x = rcos(\theta)$ and $y = rsin(\theta)$ where r is the distance from the origin and θ is the angle. If the point is on the circumference of a unit circle, then it can be simplified as: $x = cos(\theta)$ and $y = sin(\theta)$. The θ is calculated for timestamp measured in hours as follows:

$$\theta = \frac{2\pi}{24}(hours + \frac{minutes}{60})$$

For example 12:30 would be represented as : $\frac{2\pi}{24}(12+\frac{30}{60}) = 3.27$, $x = -0.99$, and $y = -0.12$. Also, we can show that the mean of the 24:00 and 02:00 would give 01:00 that yields to correct position on the circle.

$$\theta_{24:00} = \frac{2\pi}{24}(12+\frac{0}{60}) = 3.141 \text{ and } x_{24:00} = 1.0, \text{ and } y_{24:00} = 0$$
$$\theta_{02:00} = \frac{2\pi}{24}(2+\frac{0}{60}) = 0.523 \text{ and } x_{02:00} = 0.866, \text{ and } y_{02:00} = 0.5$$
$$\theta_{01:00} = \frac{2\pi}{24}(18+\frac{30}{60}) = 0.261 \text{ and } x_{01:00} = 0.965, \text{ and } y_{01:00} = 0.25$$

To verify:

$$x_{01:00} = \frac{x_{02:00} + x_{24:00}}{2} = \frac{0.866 + 1.0}{2} = 0.965$$

$$y_{01:00} = \frac{y_{02:00} + y_{24:00}}{2} = \frac{0.5 + 0}{2} = 0.25$$

It would be naturally incorrect to consider the change of days as a discontinuous event. For example, the day finishes at 24:00 and it is equally the start of the next day at 00:00.

This periodicity possesses the property of continuity that exists in the cyclic data. In sine and cosine, the end of a period is the beginning of a new period. This is the benefit of using trigonometric sine and cosine predictors for cyclic data. Additionally, the sine and cosine are orthogonal. The orthogonality can be expressed as the lack of correlation between the two functions [227]. In the analysis, it is necessary to avoid a high correlation among the predictor features.

Definition 5.5. Two non zero function $f(x)$ and $g(x)$ are orthogonal on $a \leq x \leq b$ if,

$$\int_a^b f(x)g(x)\,dx = 0$$

Therefore, we can show that the two functions of $sin(\frac{n\pi x}{L})$ and $cos(\frac{n\pi x}{L})$, $n = 0, 1, 2, ...\infty$ are orthogonal by calculating:

$$\int_{-L}^{L} sin(\frac{n\pi x}{L})\, cos(\frac{m\pi x}{L})\,dx = 0$$

Since the integral is the multiplication of an odd (sine) and even (cosine) function, the overall integral is of odd function on a symmetric interval. Therefore, the integral of the product is always zero.

Table 5.3 shows the calculated pair of (x,y); x is calculated using cosine function and y using the sine function outlined above. The angle for these functions are determined using θ based on the timestamp of each measurement in the dataset. After the pre-processing, the common linear methods can be applied to the transformed data. Hence, clustering can be used to identify meaningful diurnal patterns based on measuring patterns of the data recorded.

5.2.2 Clustering for diurnal patterns

The trigonometrically transformed timestamps of the measurement events of each participant are used individually to cluster their day to explore their daily patterns. Among the clustering techniques Gaussian Mixture models, K-means, Fuzzy C-Means, and Spectral Clustering

were investigated. The K-means provided the most robust solution in terms of convergence and cluster identification. K-means is the most popular and it is widely used in practical applications [228]. The K-means is highly efficient and scalable which is desirable for time-series data. The K-means algorithm takes k as an input parameter and starts with k randomly selected centres in the data [229]. The K-means clusters the data into groups through the process of iterative update of the cluster centres, see Procedure K-means(D,k) in Algorithm 1.

Let D be the entire data set for an individual and $D = (d_1, d_2, ..d_t..., d_T)$ where d_t is the transformed timestamp of the event (i.e. d_t is the pair of (x_t, y_t) calculated in the preprocessing) for t-th measurement carried out by the participant. The K-means clustering method is used to find the time-block intervals by solving for the following problem.

$$\min_{(TB)_1,(TB)_2,...,(TB)_k} \sum_{i}^{K} \sum_{d_t \in (TB)_i} ||d_t - E(d_t)||^2$$

where $(TB)_k$ is the k-th time-block; k is the number of clusters; $(TB)_1 \cup (TB)_2 \cup ... \cup (TB)_k = D = (d_1, d_2, ..., d_T)$ and $(TB)p \cap (TB)q = \varnothing$; $||\ ||^2$ is $l2$ norm of a vector and E is expectation over T measurement events. K-means requires the number of clusters to be specified. Usually the performance of the clustering is evaluated using measures such as the Akaike information criterion (AIC), Bayesian information criterion (BIC), Calinski-Harabasz (CH), Davies-Bouldin (DB), Deviance information criterion (DIC), and sum of the squared error (SSE). These measures resulted in various methods to select the optimal number of clusters. Such as split and merge [228], elbow method [230], and silhouette method [231]. Considering

TABLE 5.3
EXAMPLE OF THE TRANSFORMED TIMESTAMPS OF SMBG RESULTS AS PAIRS OF (X,Y)

	Hour	Minutes	x	y
0	0	11	0.0736	0.9972
1	0	11	0.0736	0.9972
2	10	27	0.3710	-0.9286
3	10	27	0.3710	-0.9286
4	14	18	-0.5873	-0.8093

the range for the possible number of clusters in our application is always low (≤ 24, i.e. at most a cluster per hour), it is therefore entirely feasible to run the K-means exhaustively to obtain measures of fitness for the given clusters. Then, numbers of the K selected is based on the measured fitness. In this paper, these measures of fitness are silhouette (mean ratio of intra-clusters) [230] and elbow methods (mean sum of the squared distance) [231] which are combined in a step-wise approach to produce the optimal number of time-blocks.

The Silhouette measurement provides a relative measure by considering the similarity of each data point to its potential cluster and its difference to the points in other clusters. A silhouette value between -1 and 1 is therefore assigned to each data point of a cluster. The average of the calculated silhouette values for all data points of a cluster determines the silhouette measure for a given cluster. A higher value (closer to 1) indicates a well clustered data point. A value near zero represents data points that are near a neighbouring cluster (i.e. the separation from other clusters is poor). A negative value means the data points are poorly clustered and are assigned to an incorrect cluster.

The Elbow method evaluates the standard square error (SSE) for a given range of cluster numbers. The SSE measures how intact the data points are within a cluster. A lower SSE value represents a better cluster. However, after the ideal number of clusters, the improvement in SSE can be negligible. Therefore, in this method, usually the depicted line graph of different numbers of clusters result in a structure where the elbow point represents the optimal number of clusters.

The K-means is first used to produce a set of clusters in the range of 3 to 24 per participant. That is the day is divided into k^* periods varying in length, $k^* = (k_3, k_4, ..., k_{24})$. The elbow method is then deployed to measure the fitness of each cluster k_i , $3 \leq\ i \leq 24$.

In the elbow method the mean sum of the squared distances diminishes as extra clusters are added. Therefore, the optimal number of clusters can be determined by the highest decrease in the gradient of the sums. This optimal number of clusters is the suggested number of time-blocks. However, the elbow method fails at times to clearly identify the optimal number of clusters (i.e. not having a clear elbow point). In this paper, we combine the elbow

method with the silhouette measure to overcome this limitation. The optimal number of clusters, k_j, selected in the elbow method, k_{j-1} and k_{j+1} is used as a guide for calculation of silhouette values to generate the optimal number of time-blocks. For example, if the suggested number of time-blocks from the elbow method is four, the silhouette measures for three, four, and five clusters are calculated. Then, the number of clusters with the highest silhouette value is chosen as the optimal number of clusters ($\widehat{k}$) for the diurnal patterns of the participant, thus the optimal number of time-blocks. The clusters generated by K-means with $\widehat{k}$ as the parameter are the start-time and end-time of the various time-blocks during a single day for an individual.

Algorithm 1 Pseudo code of the proposed algorithm for diurnal patterns

```
Initialize Elbow[]
Initialize k_min, k_max
Initialize D = {d_1, d_2..., d_T} = {(x_1, y_1), (x_2, y_2), ...(x_T, y_T)}
procedure K-MEANS(D, k)
    Randomly initialize cluster means:  μ_1, μ_2, ..., μ_k
    repeat
        for each i do
            c^(i) := arg min_j ||d^(i) − μ_(j)||
        end for
        for each j do
            μ_j := (Σ_{i=1}^m {c^(i)=j} d^(i)) / (Σ_{i=1}^m {c^(i)=j})
        end for
    until convergence
end procedure
for i in k_min to k_max do
    Perform K-means clustering on D data, K-means(D, k_i)
    Elbow.append(mean sum of squared distance of k_i clusters)
end for

Using elbow method find suggested number of clusters k_j at elbow
point
Select k̂ where:
the Silhouette measure is the highest, Max-Silhouette(k_{j-1}, k_j, k_{j+1})
Find the time-blocks as, (TB) = K-means(D, k̂)
```

5.2.3 Application validation

The ground truth of the time-blocks was not available to confirm the results of the algorithm in the BA application. Therefore, the validation process was carried out by recruited experts on real data from participants in the DAFNEplus pilot trial (details of the study is outlined in Chapter 6 and Chapter 7).

Participants

Twelve expert clinicians from DAFNEplus pilot trial centres were recruited to validate the algorithm. Participants included three dietitians, four doctors and five diabetes specialist nurses. The participants are current practising clinicians in their centres and have years of experience in diabetes care.

Experiment

The experiment was conducted as a Turing test [232]. The experts were blind to the source of the time-block settings. Each expert responded to 25 generated cases (12 clinicians/patient, and 13 algorithms). The cases were randomly chosen to avoid any bias and produced a unique combination of cases for each participant. Experts were posed with the question:"*Are the time blocks optimal for the participant; clinically, would you change any of them?*". Then, they responded with agreement or disagreement on each case of the survey. If the participant disagreed with the presented time-block settings, they were asked to suggest one. The experiment was expected to take about an hour to complete.

Statistical analysis

The response of the experiment was agreement or disagreement with the presented time-blocks. For this binary outcome, logistic regression is utilised for the analysis. Each case could have been assessed multiple times by different participants and each participant responded to 25 cases assigned to them. Therefore, to account for these correlations in the response, the generalised estimating equation (GEE) logistic regression was carried out

[195]. In GEE logistic regression of a binary outcome, empirical evidence shows a nonlinear link function is appropriate. Hence, the nonlinear S-shaped logistic response function is employed.

The odds ratio O_R is expressed as log odds of the increased chance of success by an increase of one unit in the predictor [233]. In other words, the exponential of the predictor coefficient of the regression line is the odds ratio. Therefore, the family distribution for GEE is binomial due to the binary outcome variable and logit is the link function.

5.3 Results

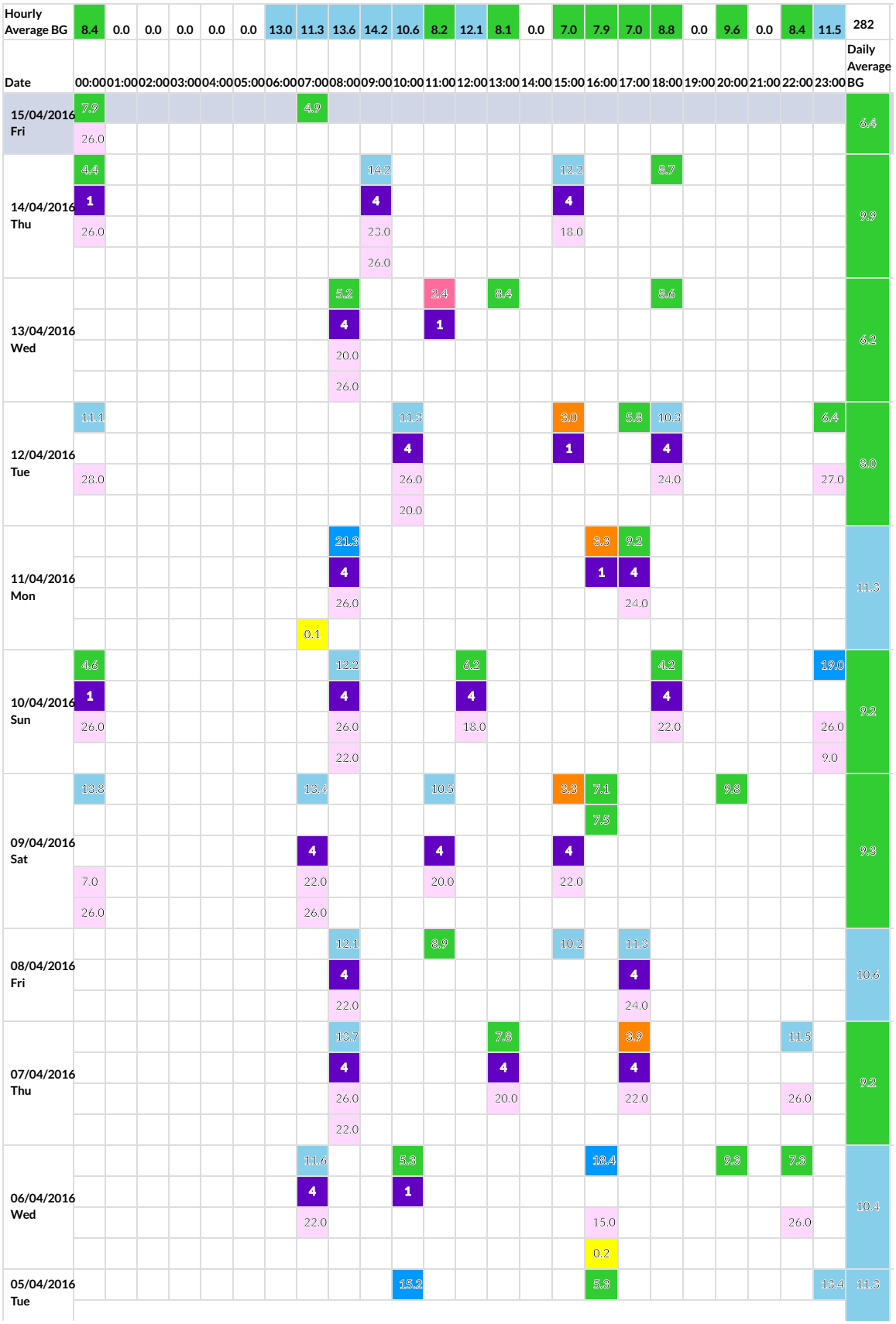
The result of clustering using Gaussian Mixture models (GMM), K-means, Fuzzy C-Means (FCM), and Spectral Clustering are presented in Table 5.4. In the case #204, all the clustering techniques performed similarly, except Spectral clustering where negative silhouette values were present (i.e. some of the points were clustered incorrectly). In the case #203, FCM has its highest silhouette value at 5 clusters unlike the other algorithms, which are 4 clusters. Also, K-means and GMM provided the best results with the highest silhouette values. However, in the case #205, K-means provided a slightly higher silhouette value and some negative results closer to zero compared to GMM. These provided example results are also repeatable on other data. Therefore, the K-means provided the most robust solution in terms of convergence and cluster identification.

TABLE 5.4
EXAMPLE RESULTS OF EXPERIMENTED CLUSTERING ALGORITHM ON THE DATA

Case #		K-means #Clusters	Sil. value	Note	FCM #Clusters	Sil. value	Note	GMM #Clusters	Sil. value	Note	Spectral #Clusters	Sil. value	Note
203	Ideal K-means #clusters	4	0.897		4	0.762	Negative Sil. values	4	.897		4	0.895	Negative Sil. values
	Ideal #clusters other methods				5	0.811	Negative Sil. values						
204		4	0.898		4	.898		4	.898		4	.894	Negative Sil. values
205	Ideal K-means #clusters	6	0.716	Negative Sil. values (near zero)	6	0.692	Negative Sil. values	6	0.706	Negative Sil. values	6	0.697	Negative Sil. values
	Ideal #clusters other methods				3	0.701	Negative Sil. values	6					

K-means clustering was used to group the daily data of T1D patients. The grouping of data produced the time-blocks setting. The algorithm proceeded to cluster the data between three to eight distinctive groups. This range was chosen based on the settings of the Accu-

Chek Expert meter to produce comparable results. The anonymised data of Glucollector users were processed to develop the algorithm. Logbook-282 shows a sample diary of a patient.


Hourly Average BG
8.4 0.0 0.0 0.0 0.0 0.0 13.0 11.3 13.6 14.2 10.6 8.2 12.1 8.1 0.0 7.0 7.9 7.0 8.8 0.0 9.6 0.0 8.4 11.5
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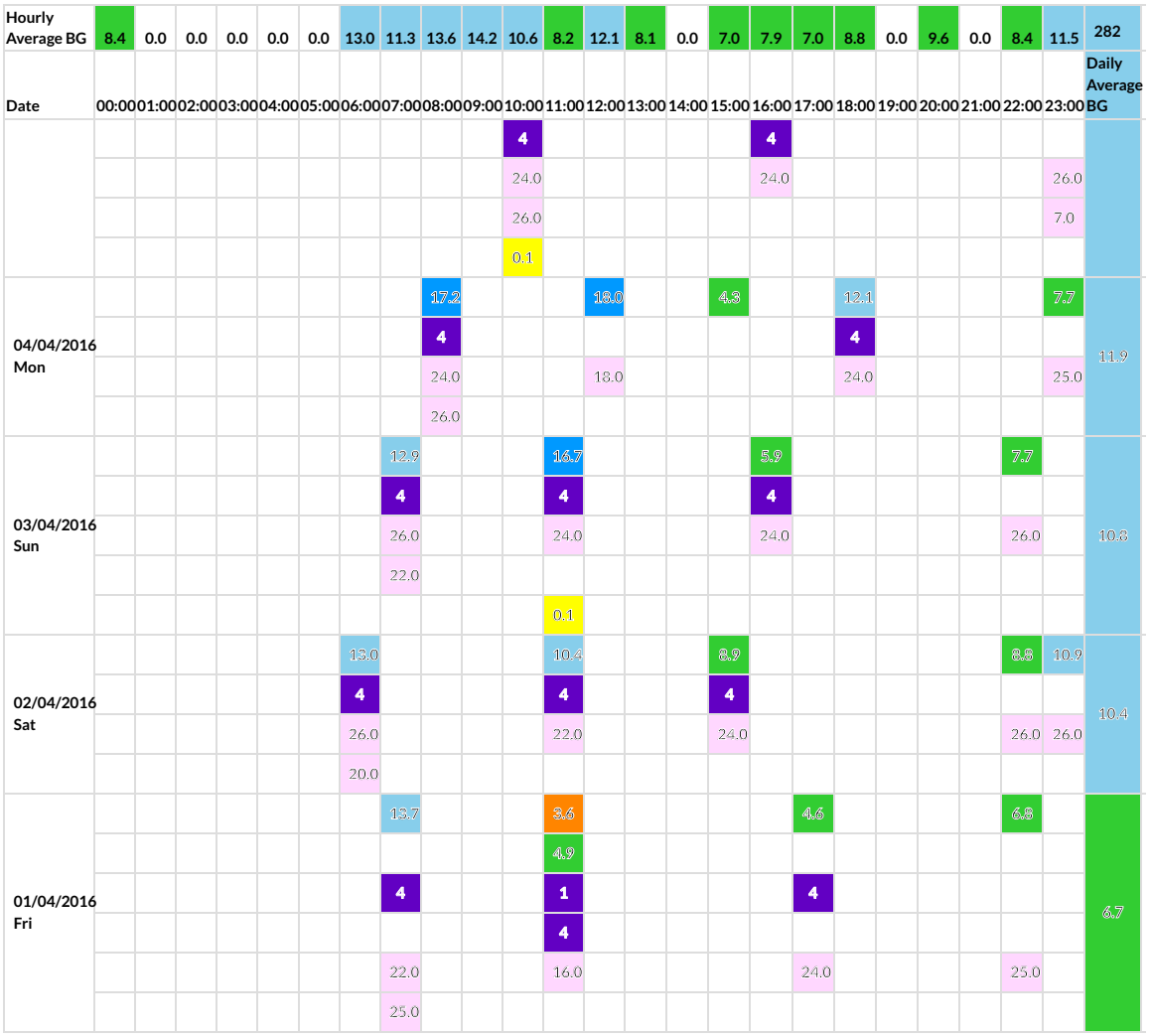
Date
00:00 01:00 02:00 03:00 04:00 05:00 06:00 07:00 08:00 09:00 10:00 11:00 12:00 13:00 14:00 15:00 16:00 17:00 18:00 19:00 20:00 21:00 22:00 23:00
Daily Average BG
15/04/2016 Fri
7.9 4.9
26.0
6.4
14/04/2016 Thu
4.4 14.2 12.2 8.7
1 4 4
26.0 23.0 18.0
26.0
9.9
13/04/2016 Wed
5.2 2.4 8.4 8.6
4 1
20.0
26.0
6.2
12/04/2016 Tue
11.1 11.3 3.0 5.8 10.3 6.4
4 1 4
28.0 26.0 24.0 27.0
20.0
8.0
11/04/2016 Mon
21.3 3.3 9.2
4 1 4
26.0 24.0
0.1
11.3
10/04/2016 Sun
4.6 12.2 6.2 4.2 19.0
1 4 4 4
26.0 26.0 18.0 22.0 26.0
22.0 9.0
9.2
09/04/2016 Sat
13.8 13.4 10.5 3.3 7.1 9.8
7.5
4 4 4
7.0 22.0 20.0 22.0
26.0 26.0
9.3
08/04/2016 Fri
12.1 8.9 10.2 11.3
4 4
22.0 24.0
10.6
07/04/2016 Thu
13.7 7.8 3.9 11.5
4 4 4
26.0 20.0 22.0 26.0
22.0
9.2
06/04/2016 Wed
11.6 5.3 18.4 9.3 7.3
4 1
22.0 15.0 26.0
0.2
10.4
05/04/2016 Tue
15.2 5.3 13.4
11.3



Hourly Average BG	8.4	0.0	0.0	0.0	0.0	0.0	13.0	11.3	13.6	14.2	10.6	8.2	12.1	8.1	0.0	7.0	7.9	7.0	8.8	0.0	9.6	0.0	8.4	11.5	282
Date	00:00	01:00	02:00	03:00	04:00	05:00	06:00	07:00	08:00	09:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00	17:00	18:00	19:00	20:00	21:00	22:00	23:00	Daily Average BG
											4						4								
											24.0						24.0							26.0	
											26.0													7.0	
											0.1														
04/04/2016 Mon									17.2				18.0			4.3			12.1					7.7	11.9
									4										4						
									24.0				18.0						24.0					25.0	
									26.0																
03/04/2016 Sun								12.9				16.7					5.9						7.7		10.3
								4				4					4								
								26.0				24.0					24.0						26.0		
								22.0																	
												0.1													
02/04/2016 Sat							13.0					10.4				8.9							8.8	10.9	10.4
							4					4				4									
							26.0					22.0				24.0							26.0	26.0	
							20.0																		
01/04/2016 Fri								13.7				3.6						4.6					6.8		6.7
												4.9													
								4				1						4							
												4													
								22.0				16.0						24.0					25.0		
								25.0																	

Our Ref:

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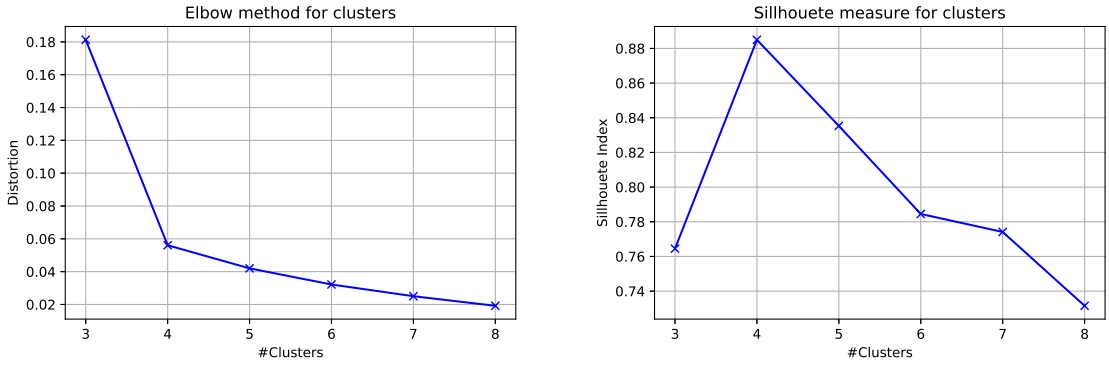
For above diary their meters bolus advisor has the following time block periods.
Clinically, would you change any of them? ***Put tick in chosen box***

☐ No, I wouldn't ☐ Yes, I would

If answered **YES**, please suggest a time for the time block that requires changing to the nearest 30 mins

Existing	**00:00**	**05:00**	**10:00**	**14:30**	**20:00**				
Change	00:00	___:___	___:___	___:___	___:___	___:___	___:___	___:___	___:___



(a) Average distortion (b) Average Silhouette index

Fig. 5.2 An example of internal index measures to evaluate the suitable number of clusters using fitness measures of elbow method and silhouette method. Illustrative plots for test case #231. a) Average distortion in the elbow method resulted from addition of each cluster to the model; b) Average silhouette index of each cluster using the silhouette method.

Then, the algorithm was utilised to search for the periods and the number of time-blocks in the diary. Figure 5.3 shows the visual of silhouette coefficients of the suggested clusters for one participant, as an example. If the number of clusters is three, the silhouettes have an uneven size and the shapes are highly variable. In this case, cluster number 0 has a negative silhouette coefficient. However, if the number of clusters is four, the silhouettes of the clusters have approximately even shapes and they are of the same size. Also, less variability in the shapes is apparent with no negative coefficients in the silhouettes. Increasing the number of clusters to five results in unevenly shaped silhouettes. Similar to three cluster case, the shapes are variable and negative coefficients is observable. Nonetheless, the silhouettes of five clusters are an improvement compared to the three clusters case. However, the silhouettes of the four-cluster outperform the others. The figure 5.2b shows that in the case of four clusters, it has the highest silhouette index. Also, it can be confirmed using the elbow method as shown in figure 5.2a. The elbow of the distortion graph is significant at the fourth cluster. Therefore, four is the ideal number of clusters for the presented diary.

Figure 5.4a shows the histogram of the data in a circular plot. The red lines divide the graph by the algorithm's selected time-blocks. In this example, the graph shows that the data have four clear peaks at around 7, 12, 16 and 22. The algorithm has clustered these peaks with surrounding data points into a separate cluster. Also, this can be observed in the figure

TABLE 5.5
TIME-BLOCK SURVEY AGREEMENT RESULTS

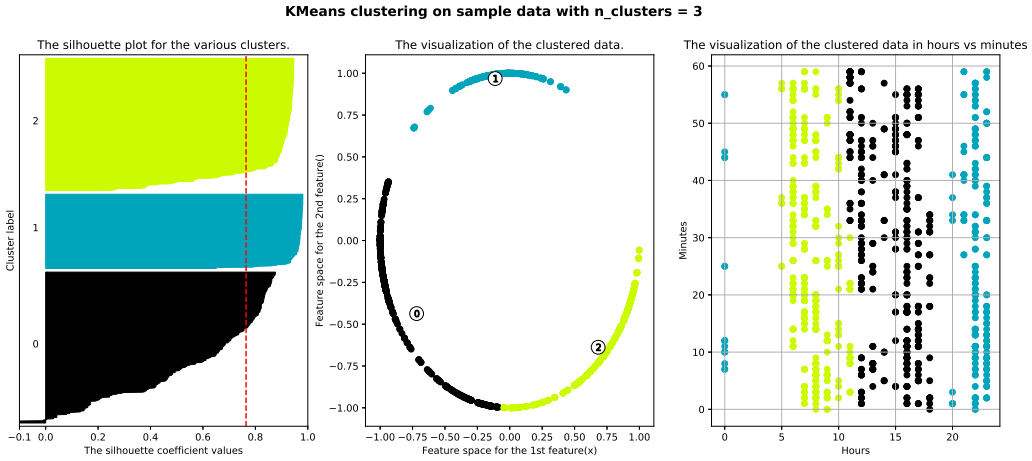
	Agree	Disagree	Total
Algorithm	61 (39.1%)	89	156
Clinician/Patients	52 (36.1%)	92	144
Total	113	187	300

5.4b. The figure shows a histogram of the blood glucose tests in a bar chart. Similarly, the red lines split the time blocks. The peaks and the surrounding data form a bell-like curve in each time-block that can represent a separate pattern in different periods of the day. Furthermore, the daily routine of the patient ends at past midnight around 1 am of the next day. Hence, the algorithm suggests the end of the day be at 01:00 rather than 00:00.

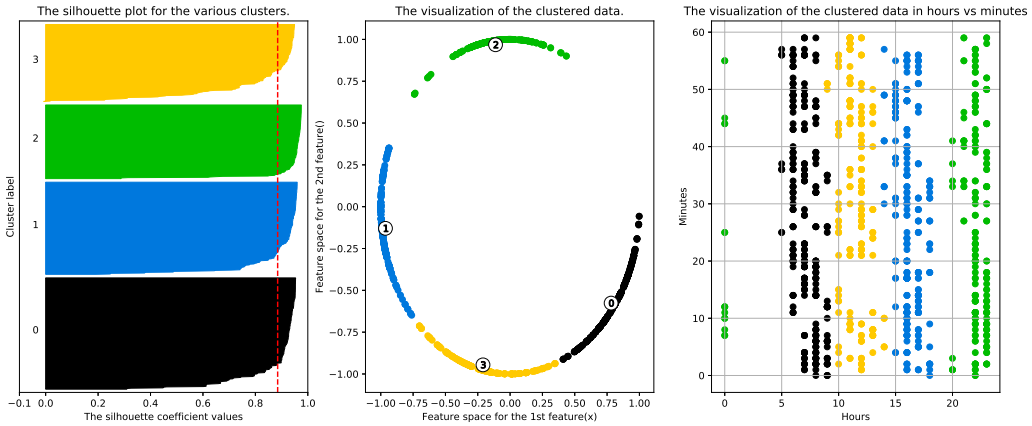
5.3.1 Application validation

The validation process was carried out to determine whether the proposed automated method can substitute the current time and labour intensive practice that people with diabetes or their diabetes healthcare professional need to undertake manually. A Turing test of the algorithm was conducted to validate the suggested time-blocks. The result of the survey is presented in the Table 5.5. The expert respondents agreed with the algorithm's generated time-blocks 39.1% of the time and 36.1% with the clinician/patient generated ones. The percentage of agreements on the algorithm generated time blocks was 3% higher than the clinician/patients generated time-blocks. This slight difference suggests that the algorithm performs better or similar to clinicians. The logistic regression analysis shows that the algorithm's results were agreed more by ~ 0.18 compared to the clinician/patients time-blocks. However, the p-value is higher than 0.05 which suggests the algorithm is similar in performance to the clinicians. This can be investigated by analysing the odds of the agreements. As shown previously, the odds ratio is calculated as follows:

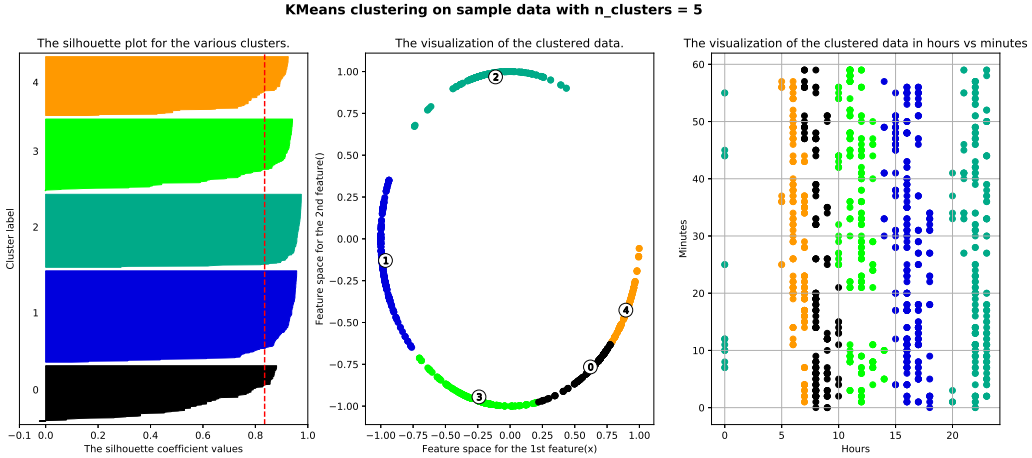
$$O_R = exp(0.18) = 1.197$$



(a) Three clusters

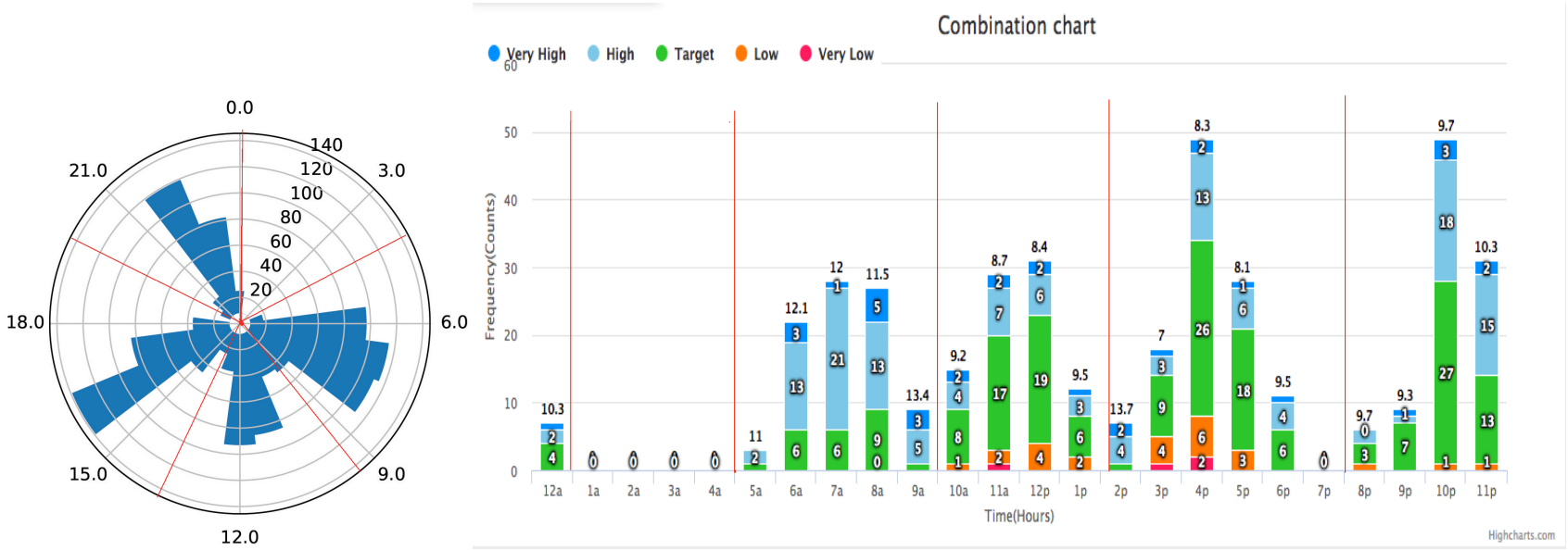


(b) Four clusters



(c) Five clusters

Fig. 5.3 K-means clustering of the logbook-282. Each distinct colour represent the belonging to a cluster. Left graphs: are the silhouettes per cluster with red dashed line showing the average silhouette index. Centre graphs: are the circular representation based on the trigonometric transformed data (x,y); the number labels show the centroid position of the corresponding cluster. Right graphs: are the data in original form and the distribution of the point to different clusters in Hours vs Minutes Cartesian plot.



(a) The circular histogram

(b) Bar chart histogram

Fig. 5.4 The histogram of a diary. The red lines represent the time separation between time-blocks. Illustrative plot for test case #231. a) The circular histogram of the measurement events on a clock that starts at 0 hours (zero degrees) to 24 hours (360 degrees); b) The bar chart histogram of the frequency of the daily measurement events in an hourly basis for a nominal day

Therefore, it is ~ 1.2 times as more likely to agree with the algorithm's suggested time-blocks (confidence interval of [0.69 - 2.07]). However, the confidence interval of the odds ratio includes one which suggests a similar odds of agreement between the algorithm and clinician/patients time-blocks. Therefore, the generalisation that the algorithm outperforms the clinicians/patients generated time-blocks is not conclusive. Nonetheless, the analysis of the results shows that the algorithm suggestion is as good as the clinicians/patients time-blocks suggestions, if not better.

5.3.2 Beyond current limitations

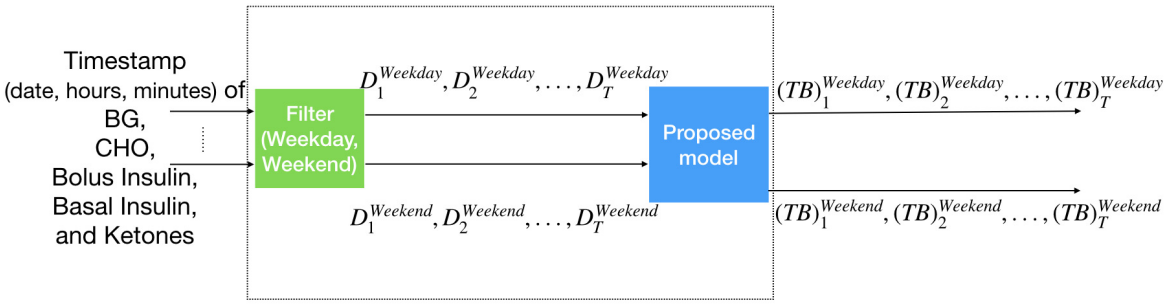
Currently, the BA only allows for a single setting that is applied for every day of the week. This is a limiting factor towards personaliation of the BA. Also, this can impact glycaemic control greatly if the day to day routine of the patient is variable.

Incorrect time-block settings can lead to incorrect insulin doses. At the moment, the patient has to actively remember that their BA settings are not suitable for that day's activity or situation and apply an increment or decrement of the recommended dose by some percentage. Our proposed method is a viable solution to automate a more personalised and suitable settings based on patients' measured patterns. A filtering is added to the proposed model in Fig. 5.1 that can be used to accommodate the changing nature of day to day activities. In this thesis day to day and weekday to weekend personalisation patterns for people with type 1 diabetes are analysed, see Fig. 5.5. The following experiments are based on a period of one month of the collected data.

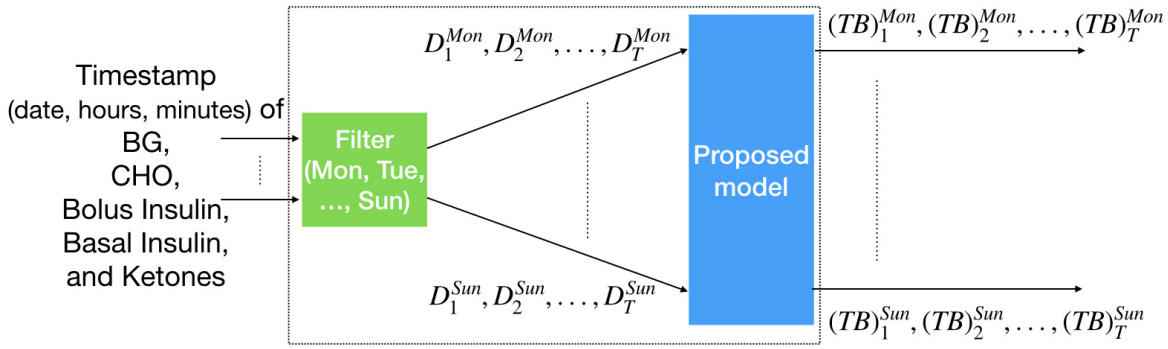
Weekdays vs Weekend

One approach to provide the flexibility is to accommodate different routines by allowing different settings between for example the work days (Monday to Friday) and the weekends (Saturday and Sunday). Therefore, a modification to the algorithm was applied to carry out the experiment.

The modified algorithm is a multi-step operation. First, it categorises the data to weekdays and the weekends. Then, it processes each category to identify diurnal patterns accordingly.



(a) Weekdays vs. weekend proposed model

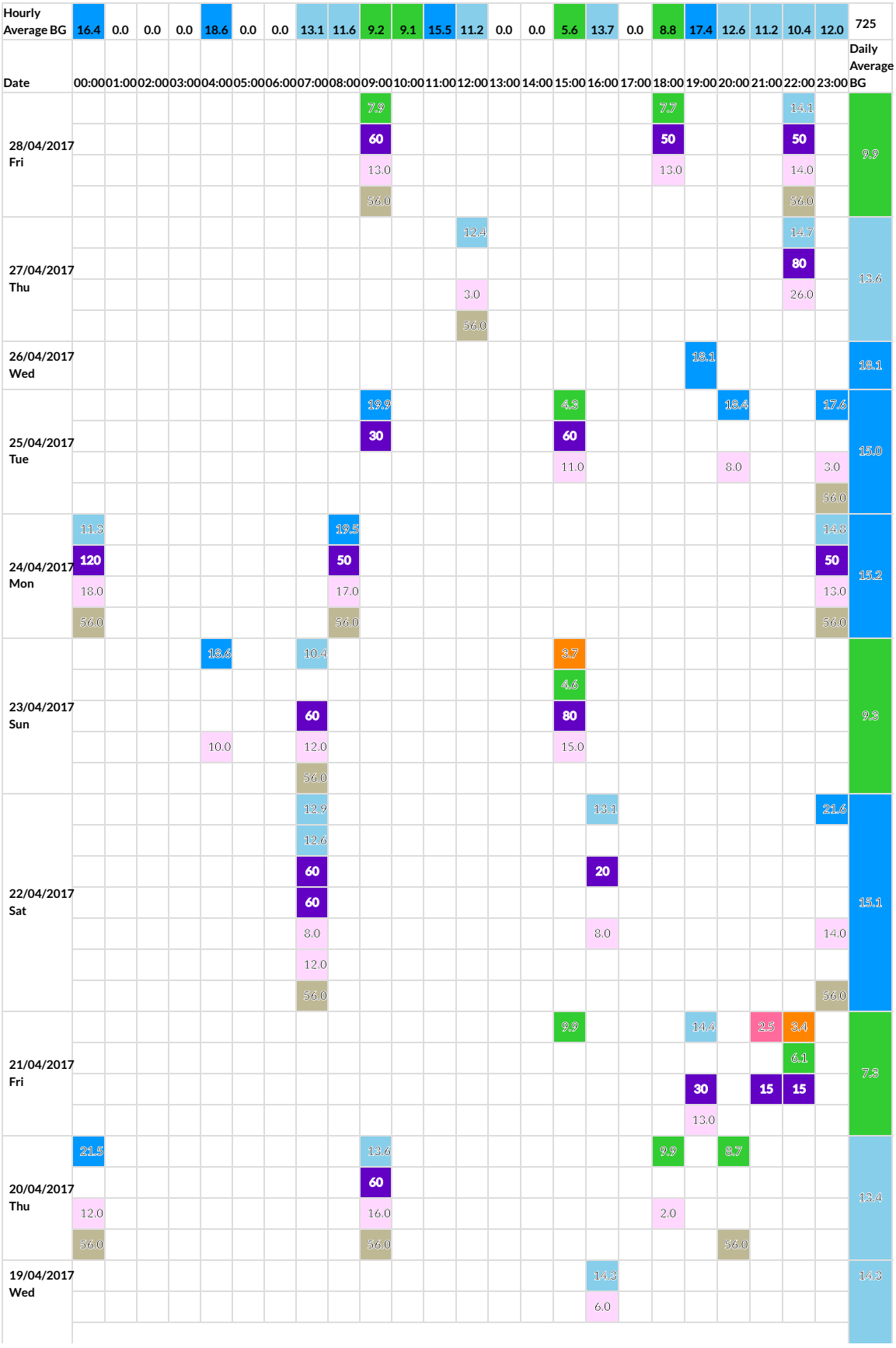


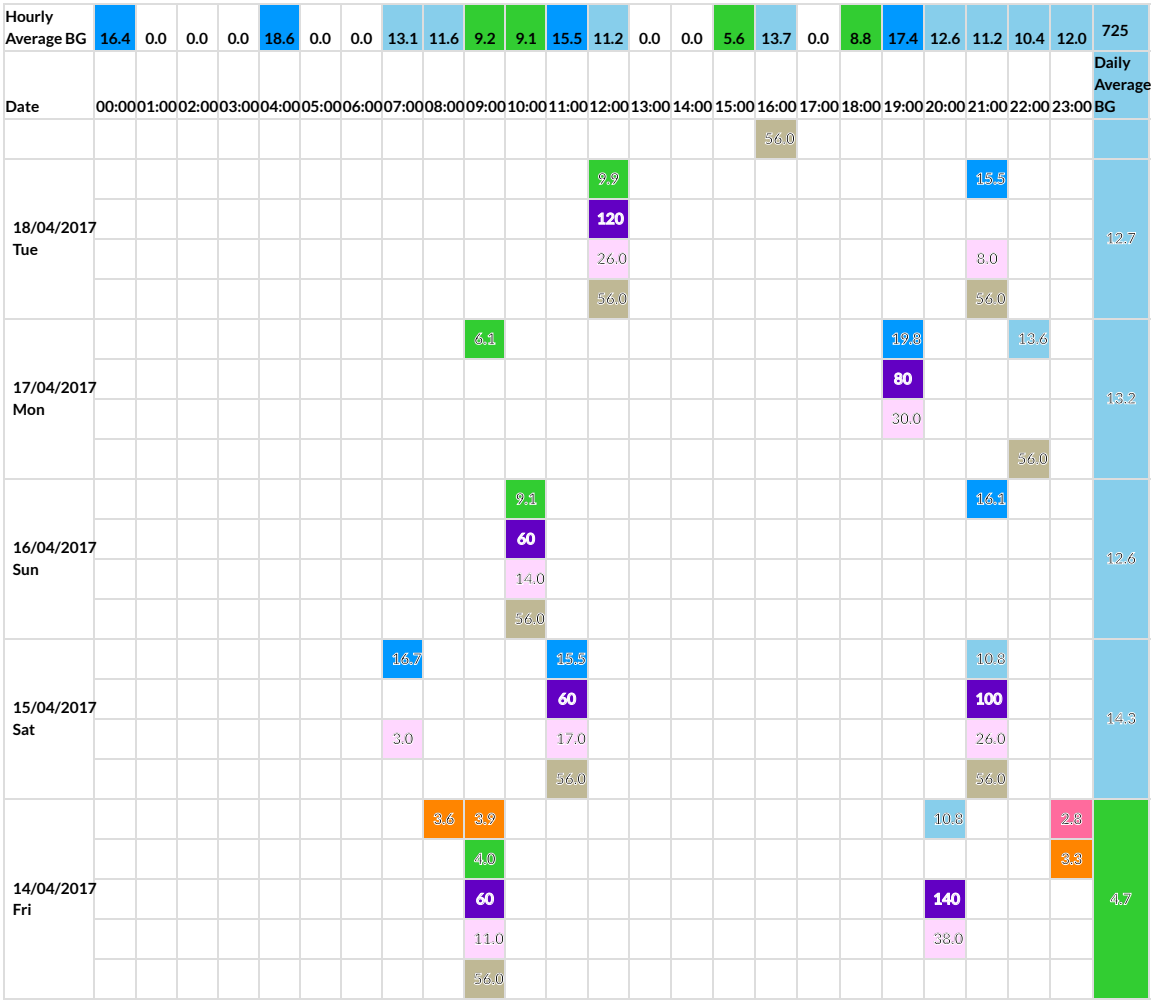
(b) Days of the week proposed model

Fig. 5.5 Addition of filtering into the pre-processing of the proposed model to facilitate beyond current practices and overcome the limitations for personalising the BAs. a) Weekday vs weekend model where data are filtered to accommodate change of routine between weekdays and weekends; b) Days of the week proposed model where each day of the week is personalised for its specific routine patterns.

An example of a diary is presented in the logbook-725. The modified algorithm was utilised to discover diurnal patterns during the weekdays and weekends. The identified time-block settings are presented in the table 5.6. The example shows that a 3.5 hours accumulated time difference arises between weekdays and weekends time-blocks; such a significant time-difference would be missed otherwise, leading to incorrect BA settings and therefore incorrect insulin doses. For example, if the ICR of TB2 is 2 U:10 g but the ICR of TB3 is 1 U: 10 g, then if the person uses the weekday setting for the weekend for an injection at 10 am (on weekdays, 10 am is in TB2), the person would inject twice the insulin dose needed, which is clinically significant and may be harmful.

Also, the result of the algorithm is shown in the figure 5.6. Looking at the histogram of the graphs, it can be noticed that the frequency of data in the morning time-block (TB2) is similar during the week and the weekend, with slight delay in the start of the morning on the weekends. However, the rest of the day, the frequency of data is much lower relative to the TB2 and there is a slight variation in the start and end of the time-blocks between weekday and the weekend. These are more apparent in the TB5 and TB6. For the afternoon time-block (TB4), the weekend has a longer span and relatively more activity in comparison to the weekdays.


Hourly Average BG
16.4 0.0 0.0 0.0 18.6 0.0 0.0 13.1 11.6 9.2 9.1 15.5 11.2 0.0 0.0 5.6 13.7 0.0 8.8 17.4 12.6 11.2 10.4 12.0 725
Date
00:00 01:00 02:00 03:00 04:00 05:00 06:00 07:00 08:00 09:00 10:00 11:00 12:00 13:00 14:00 15:00 16:00 17:00 18:00 19:00 20:00 21:00 22:00 23:00 Daily Average BG
28/04/2017 Fri
7.9 60 13.0 56.0
7.7 50 13.0
14.1 50 14.0 56.0
9.9
27/04/2017 Thu
12.4 3.0 56.0
14.7 80 26.0
13.6
26/04/2017 Wed
18.1
18.1
25/04/2017 Tue
19.9 30
4.3 60 11.0
18.4 8.0
17.6 3.0 56.0
15.0
24/04/2017 Mon
11.3 120 18.0 56.0
19.5 50 17.0 56.0
14.8 50 13.0 56.0
15.2
23/04/2017 Sun
18.6 10.0
10.4 60 12.0 56.0
3.7 4.6 80 15.0
9.3
22/04/2017 Sat
12.9 12.6 60 60 8.0 12.0 56.0
13.1 20 8.0
21.6 14.0 56.0
15.1
21/04/2017 Fri
9.9
14.4 30 13.0
2.5 15
3.4 6.1 15
7.3
20/04/2017 Thu
21.5 12.0 56.0
13.6 60 16.0 56.0
9.9 2.0
8.7 56.0
13.4
19/04/2017 Wed
14.3 6.0
14.3



Our Ref:

725

For above diary their meters bolus advisor has the following time block periods.
Clinically, would you change any of them? ***Put tick in chosen box***

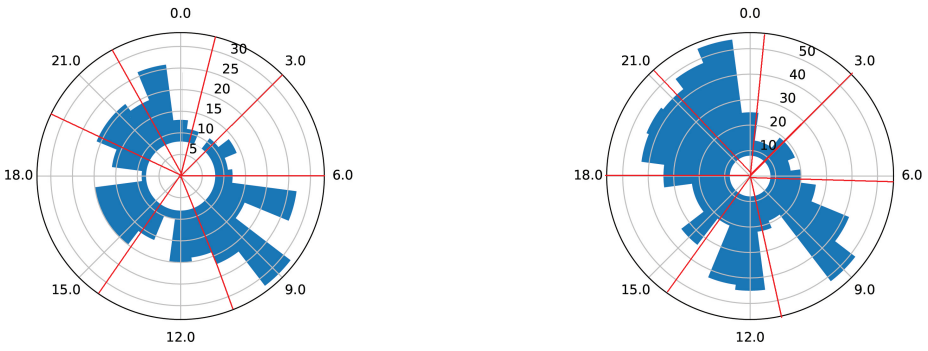
☐ No, I wouldn't ☐ Yes, I would

If answered **YES**, please suggest a time for the time block that requires changing to the nearest 30 mins

Existing	**00:00**	**06:30**	**12:00**	**18:00**	**22:30**				
Change	00:00	___:___	___:___	___:___	___:___	___:___	___:___	___:___	___:___

TABLE 5.6
AN EXAMPLE OF TIME-BLOCKS BASED ON WEEKDAYS VS WEEKEND FOR THE TEXT SUBJECT #224

	TB1	TB2	TB3	TB4	TB5	TB6	Silhouette index
Weekend	03:00	06:00	10:00	14:00	19:00	22:00	0.741
Weekday	03:00	06:30	11:00	14:30	18:00	21:30	0.756



(a) Weekend (b) Weekdays

Fig. 5.6 An example of the circular histogram of the weekdays and weekends of a diary. The red lines show the separation hours of the time-blocks suggested by the proposed algorithm for test case #224. a) Weekends measurement patterns; b) Weekdays measurement patterns

Days of the week

Another approach to provide a more personalised BA, is to allow different settings for different days of the week. Similar to weekday vs weekends experiment, a modified algorithm was utilised to cluster the diary data into time-blocks.

This is a multi-step operation. First, it categorises the data to days of the week. Then, processes each day to identify diurnal patterns accordingly. The suggested time-blocks of the algorithm is shown in the table 5.7. The patient exhibits a different routine based on their logbook data. The different days of the week can have a different number of time-blocks and starting hours.

TABLE 5.7
TIME-BLOCKS BASED ON DIFFERENT DAYS OF THE WEEK

Day	TB1	TB2	TB3	TB4	TB5	Silhouette index
Monday	05:00	10:00	12:00	15:00	20:00	0.930
Tuesday	05:00	07:00	12:00	16:00	21:00	0.949
Wednesday	———	07:00	12:00	16:00	20:00	0.950
Thursday	05:00	10:00	12:00	16:00	21:00	0.978
Friday	05:00	10:00	12:00	16:00	20:00	0.986
Saturday	05:00	10:00	12:00	17:00	21:00	0.980
Sunday	05:00	09:00	12:00	16:00	21:00	0.981

Figure 5.7 shows the circular histogram of the days of the week for logbook-620. The exception of Tue and Wed, the rest of the week looks similar in measuring patterns. Especially in the peak hours of those days (i.e. 5, 10, 12, and 18). However, Tuesdays show a less active morning routine and more active afternoons. While Wednesdays show a less active midday period.

Recall that due to current limitations the patient has to actively apply a corrective percentage to accommodate his/her change of routines between days. This can adversely affect their glycaemic control. We can examine such effects by the provided context from the algorithm's recommended time-blocks. For this diary, the presented time-blocks for Tuesdays and Wednesdays are very different from other days of the week. By a closer look at the diary, it can be observed that the patient manages his/her BG levels relatively well (mostly green)

in the hours of TB2 and TB3 in days other than Tue and Wed. However, the Tue and Wed seem to be more challenging for the patient with many out of range BGs. This indicates a possible change in the routine e.g. less activity in those days. Possibly, different settings for Tue and Wed would be suitable to accommodate the change in the routine. As illustrated, such details and context are provided in seconds using the proposed model. This can be presented to patients as a recommendation to clarify their routine based on their data and encourage them to review the diary in such a context.

Hourly Average BG	0.0	0.0	0.0	0.0	0.0	12.6	12.3	0.0	13.3	0.0	6.8	0.0	7.4	10.7	0.0	0.0	8.2	8.4	5.2	6.6	3.8	8.2	8.6	0.0	620
Date	00:00	01:00	02:00	03:00	04:00	05:00	06:00	07:00	08:00	09:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00	17:00	18:00	19:00	20:00	21:00	22:00	23:00	Daily Average BG
20/05/2017 Sat							12.3																		12.3
							55																		
							8.0																		
							8.0																		
19/05/2017 Fri						9.8					8.5		4.7					3.8	5.0				13.2		7.5
						55					20		80						60						
						6.0							7.0						6.0				2.0		
						8.0																	8.0		
18/05/2017 Thu						16.8							5.9				8.2	5.4					8.3		8.9
						55							80					65							
						9.0							8.0					7.0							
						8.0																	11.0		
17/05/2017 Wed									17.6					11.8					4.2				5.3		9.7
									55					70					100						
									9.0					9.0					10.0						
									8.0														11.0		
16/05/2017 Tue									10.3					6.3				12.4					4.5		8.4
									60					80				125							
									7.0					8.0				15.0							
									8.0														11.0		
15/05/2017 Mon						13.4					7.4		7.7					7.6			3.8		7.5		7.9
						60					10		60					100							
						9.0							6.0					11.0							
						8.0																	11.0		
14/05/2017 Sun						17.5							5.8							6.6			10.2		10.0
						55							70							80					
						9.0							6.0							8.0					
						8.0																	11.0		
13/05/2017 Sat						11.9					5.7		7.8						3.7				14.2		8.7
						55					30		55						90						
						8.0							6.0						8.0				2.0		
																							11.0		
12/05/2017 Fri						12.8					8.8		5.1						3.4			7.5			7.5
						55					10		95						90						
						8.0							9.0												
						8.0																11.0			
11/05/2017 Thu						15.2					9.2		6.9					8.2					8.4		9.6
						55					10		65					40							
						9.0							7.0					5.0							

Hourly Average BG	0.0	0.0	0.0	0.0	0.0	12.6	12.3	0.0	13.3	0.0	6.8	0.0	7.4	10.7	0.0	0.0	8.2	8.4	5.2	6.6	3.8	8.2	8.6	0.0	620
Date	00:00	01:00	02:00	03:00	04:00	05:00	06:00	07:00	08:00	09:00	10:00	11:00	12:00	13:00	14:00	15:00	16:00	17:00	18:00	19:00	20:00	21:00	22:00	23:00	Daily Average BG
						8.0																	11.0		
10/05/2017 Wed									13.3				15.0						4.7				8.3		10.3
									60				90						80						
									8.0				12.0						8.0						
									9.0														11.0		
09/05/2017 Tue									12.1					14.1				13.1				2.9			12.3
									60					80				70							
									8.0					11.0				10.0				1.0			
									8.0													11.0			
08/05/2017 Mon						6.3					5.2		9.5						5.7				5.0		6.3
						55					30		40						110				10		
						5.0							4.0						11.0						
						8.0																	11.0		
07/05/2017 Sun						13.2					4.7		7.2						8.8			7.1			8.2
						55					30		40						60						
						8.0							3.0						7.0						
						8.0																11.0			
06/05/2017 Sat						9.0					4.6		5.5						3.3				9.6		6.7
																			8.2						
						55					30		75						80						
						6.0							8.0						9.0						
						8.0																	11.0		

Our Ref:

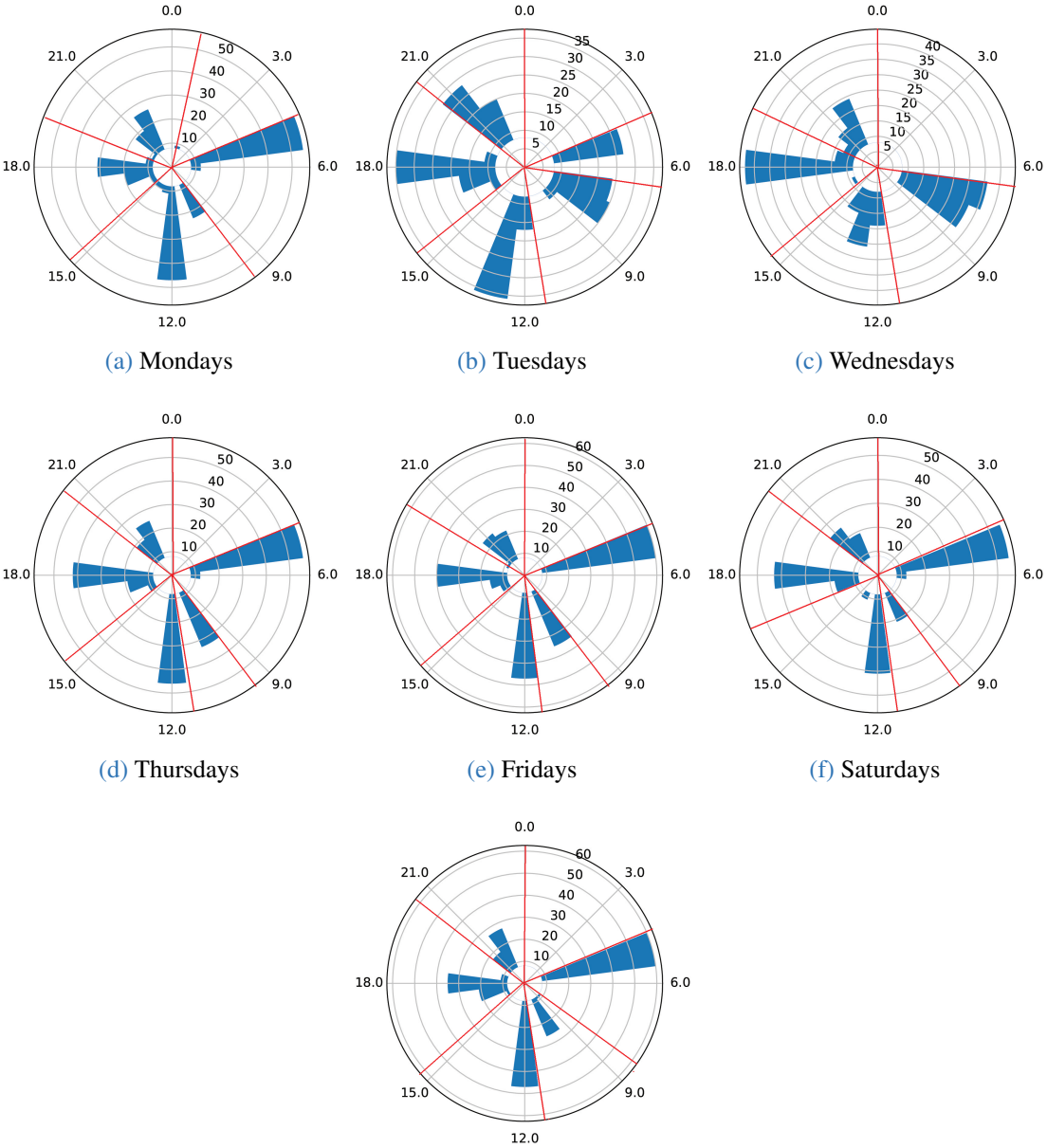
620

For above diary their meters bolus advisor has the following time block periods.
Clinically, would you change any of them? ***Put tick in chosen box***

☐ No, I wouldn't ☐ Yes, I would

If answered **YES**, please suggest a time for the time block that requires changing to the nearest 30 mins

Existing	**00:00**	**05:00**	**08:00**	**12:00**	**16:00**	**20:00**			
Change	00:00	___:___	___:___	___:___	___:___	___:___	___:___	___:___	___:___



(a) Mondays (b) Tuesdays (c) Wednesdays

(d) Thursdays (e) Fridays (f) Saturdays

(g) Sundays

Fig. 5.7 Daily cyclic histogram of the diary from logbook-620 over one month. The red lines split the time periods based on the suggested time-blocks for each day of the week.

5.4 Discussion

The proposed method applies a clustering technique to detect diurnal patterns in the time series data of the T1D patients. The time-stamp of the daily measurements of BG, carbs, bolus insulin, basal insulin and ketones were extracted and transformed. Predictors in terms of sine and cosine are orthogonal and periodic. Therefore, they were adopted to transform the univariate time series data of T1D patients. Then, K-means clustering was utilised to recognise the diurnal patterns and suggest the numbers and periods of time-block settings of the BA. The developed method aids elimination of the error-prone self-reporting practice and automates the suggestions based on the real-time change detected in the daily routines. Up to date and accurate BA settings are crucial to maximising the benefits of BA as a decision support tool.

We compared the results of the proposed method to the clinicians' suggested time-blocks. These clinician-generated time-blocks acted as the control group in the conducted survey. Furthermore, the cases were allocated in a random and dynamic fashion instead of a set and static one. This enabled investigation of a higher number of unique cases (Overall 300 cases, 51 unique cases compared to 25 otherwise).

Our proposed intelligent system of routinely collected data has similar accuracy to an expert that can automatically process vast amounts of individual data to efficiently adjust TBs in real-time. These prompt adjustments can contribute to the accuracy of the underlying settings and therefore improved utilisation of the BAs, which is known to improve glycemic control [209].

5.4.1 Underlying context of glycemic patterns

The data-driven suggested time-blocks can help to provide more context to the diabetes data. Diurnal patterns can provide clues and drive the conversation to specific actions that influence the glycaemic management. For patients, clinical appointments are limited and time constrained. Maximising available contexts to the collected data is timesaving. Manual analysis and pattern finding of a large amount of data to suggest the BA settings are

challenging and time-consuming. As in the conducted survey, it was expected to take about an hour to analyse the time blocks. This was to assess two weeks data on an organised diary. However, many respondents fed back that it required a longer time. For some respondents, it took about three hours to complete. Therefore, there is a need for a system to aid with decision making.

Additionally, the presented method enables tracking changes in daily routines. A study showed that diabetes patients with painful neuropathy are more active in the evening and less active in the morning compared to those without neuropathy. Also, the study found that temporal and chronic factors of diabetes are associated with altered diurnal rest-activity rhythmicity [210]. The proposed method has the potential to facilitate a thorough and reliable analysis of changes in the daily activity of patients, therefore, empowering patients with a more complex and variable daily routine to use the suggestions as a guide to adapt promptly.

Furthermore, our proposed model only uses the timestamp; therefore, including other data events such as exercise and circadian rhythms would help the algorithm to divide the day even more appropriately, especially when the data are closely dispersed naturally. Recording of such data events can also contribute to improved contextual information.

5.4.2 Do experts agree?

The expert respondents to the survey agreed about 36% of the time with the clinicians/patient time blocks and 39% with the proposed algorithm's suggestions. The analysis of the odds of agreement showed a slight favourability in choosing the algorithm. Nonetheless, in both cases of clinician and algorithm generated time-blocks, the agreement is lower than expected. This is potentially an indication of variation in the approach. The respondents to the survey were asked to present their suggestions of the time-block settings if they did not agree with the presented one. Observing the respondents time-block suggestions, one hypothesis for the variation and lower agreement is that the discrepancy stems from the fact that patients daily routines can change from one day of the week to the other. More importantly, one generic time-block setting cannot include all the variations in the diurnal patterns. The expert respondents had different approaches in assessing each case. In some

cases, a change in the ratios was accounted as a trigger for a new time-block where in other cases, the glycaemic patterns. Additionally, glycaemic control at different times of the day can influence the decision. By looking at a diary through these approaches, it could result in different settings. If it is the glycaemic control, the problematic hours (frequent hyperglycaemia, or hypoglycaemia) are a possible time-block. If it is based on glycaemic patterns, the change in the patterns during the day is the separating criteria. Certainly, a change in ratios necessitates a change in time-blocks. Experts' clinical experience seems to have resulted in a practical approach to the problem of finding the diurnal patterns and possibly a subjective one. Patients with a more routine lifestyle are more likely to spot a more generic pattern in their diary. However, a more varying routine can pose a challenge and varying decision depending on the approach.

5.4.3 Standardised vs weekday settings

In some cases, a patient is recommended to replicate glycaemic control of their better days of the week i.e. *"whatever you do on Tuesday and Wednesday do, on the other days"*. This can potentially be from the generic settings of the BA that suits certain days of the week and not the others. Such recommendations indicate the need for more flexibility in settings options. Additionally, the time and resources of the clinicians are limited. The manual personalisation of the BA to more granular settings requires a higher engagement and analysis. This can be time-consuming. The proposed method can process a diary with longer periods and produce a personalised daily time-blocks in a matter of seconds.

This especially applies to the difference between the daily routines of the weekdays and weekends. In pumps, this can be accounted for to a certain degree by having different basal profiles. For those on MDI, different amounts of background insulin (e.g., because more or less active at weekends) can be utilised. Alternatively, the exercise settings can be set to reduce the dose (e.g. -33%) to account for the change in the ratio. These require active participation and judgement of the patients for every insulin injection. Patients have to always remember their settings which can deter users from modifying them. These drawbacks can contribute to limiting the uptake of the BA as an assisting tool for dose calculation. However,

utilising the proposed method can automate the process by filtering the data by days, or weekdays and weekend to suggest more suitable time-block settings.

5.4.4 Participant awareness vs data

From the clustered data, many patients' natural day overlaps with the early hours (e.g. 2 am) of the next day. This is rarely observed in the healthcare/patient time-block settings. It can be seen in the data that patients make glycaemic decisions that relate to their last time-block of the day in the early hours of the next day. Hence, the algorithm usually includes these data points to the last time-block setting of the day. In many cases presented in the survey, the respondent agreed with this overlap. However, this does not seem to be applied in practice. One explanation can be because most of the time-blocks are set in consultation with the patient that might overlook those early hours of the day. This high precision is one of the benefits of using a clustering technique for identifying the time-blocks that can be translated to practice in the clinics to reflect the findings.

5.4.5 Other methods and related works

As shown in the figure 5.4b, the divided time blocks of glucose data represent a combination of bell curves which suggests a mixture of Gaussian models. Hence, we tested this hypothesis; in many cases, the Gaussian mixture model clustering produced identical results to K-means. However, this model-based clustering has a scalability issue and its performance suffered when the clusters are close to each other.

To our knowledge, the presented method is the first to attempt a data-driven model to automate the process of diurnal patterns for recommending and tracking time-block settings of BA in diabetes. The closest work to partially improve BAs was presented in the case-based reasoning models. However, these studies are mostly limited to CGM, whereas the proposed method applies to any diabetes data irrespective of the type (e.g. glucose, carbs, insulin or a combination of the three). Also, the studies attempt a new approach to the bolus advisor which is not evident to provide any benefits over current bolus advisors. From the patient

perspective, it is a 'black box' that relies on previous cases to suggest an insulin dose. Hence, the focus is on the insulin patterns rather than diurnal patterns that can define patients daily routine. This does not provide context and the ability to use the settings to review patterns of glycaemic control.

Furthermore, our proposed model can be applied to continuous glucose monitoring data without any modification when other modalities are recorded. In CGM, BG timestamps are uniformly spaced and driven by the sensor rather than the participant's patterns, thus clustering would only be on the other recorded data such as carbs, basal insulin, bolus insulin, and ketone timestamps.

In conclusion, the proposed K-means method improves the accuracy of time-block settings, provides context to data, reduces the review time and potentially improves the engagement and adherence to the BA. Furthermore, it could be implemented in pumps and glucose meters to provide on-set auto adjustment.

Chapter 6

Glucollector: Agile development in healthcare research

The rising cost of health-care alongside budget cuts, in a highly regulated industry, makes the lengthy clinical studies more financially expensive and burdensome. Technology-related academic medical research in T1D faces the risk of becoming obsolete due to the technological ecosystem evolving and moving on by the time of establishing the intended evidence [38, 50]. Therefore, the need for alternative methods of design for technology-related clinical pilots and trials that accommodate change and evolve with the up to date technological ecosystem is apparent [50].

Companies in non-regulated industries have been rapidly adopting agile design methodologies to improve efficacy, reduce costs and embrace a culture of rapid change. However, regulated industries such as the medical device industry have embraced agile development process only moderately. The agile prioritising of the end-user over processes and delivering working software over comprehensive documentation can be challenging in the regulated medical technology sector.

This chapter provides a detailed description of the development and validation of the Glucollector system as a proof of concept for the use of agile principles in designing a successful pilot study to improve technology translation in diabetes care.

6.1 Telemedicine

Implementing telemedicine, healthcare delivered using telecommunications, in healthcare faces technical and systematic difficulties. The lack of computer training and limitation in accessing computers can deter the use of telemedicine for both patients and clinicians. Privacy and security concerns can be a red flag for many users. Furthermore, power outage or malfunction of the hosting server can slow or even stop the access to the data. Moreover, training, practice code, and technical support are essential to ensure the quality of service. In diabetes, it needs to support multiple glucose meter vendors for convenience. These can delay the implementation and increase the cost of the system [234]. Additionally, the evolving and vibrant technological landscape has proven to be a challenge in the face of traditional development models whilst meeting the standards and the requirements of regulatory bodies [49, 50, 235].

6.1.1 Development Models

The traditional development process relies on outlining details of the requirements at the very beginning of the development [236]. Then, a thorough planning phase is followed to set out the design and procedures in place. Afterwards, the procedures are implemented, tested and changes are applied. This sequential development is known as the waterfall. This procedure benefits from well structured, focused and measured effort, since the scope of the work appears to be known in advance. However, capturing all the requirements for the project at the start is difficult [237]. Moreover, any change after the project starts demands the re-evaluation of the requirements and re-iteration from early stages of development. This creates cost and jeopardises the effectiveness of the final product in meeting all the requirements in the specified time-frames. Especially if the intent is an innovative product, specifying all the potential details at the start is an onerous task and likely impossible. This results in an extended development cycle whereby usability may be ignored and the end product is not fit for the purpose, e.g. impractical and out-dated [238].

Similarly, the V-shaped development is a sequential model; after completing one phase of the development, the next is processed [239]. The model heavily relies on testing to ensure meeting the requirements. It has a higher emphasis on testing than the waterfall model. The testing plan process begins with system test planning, proceeds to integration test planning and finalised by unit test planning [240]. Due to these test plannings, it is more likely to succeed compared to the waterfall model. However, it suffers from the same issues as the waterfall. The implementation occurs at the end and it does not provide a clear plan for any problem detected during testing. Hence, any change would have a knock-on effect and results in delays and cost [241].

Software engineers introduced agile development as an iterative process to tackle the aforementioned pitfalls of traditional development models. In recent years, many institutions and companies are replacing waterfall with agile development [242]. The Agile manifest [243] presents its values and method as follows:

*" **Individuals and interactions** over processes and tools*
***Working software** over comprehensive documentation*
***Customer collaboration** over contract negotiation*
***Responding to change** over following a plan*
That is while there is value in the items on the right it values the items on the left more."

Therefore, the aim is to deliver a product that quickly adapts to the changes and needs of the user while maintaining quality within the constraints of the project such as cost, time, and features.

The possibility of combining traditional models with agile development has been investigated in a few studies suggesting a better outcome [244–246]. A more comprehensive proposal of these studies is the AV-Model [47]. The study suggests that the V-model can act as the foundation for the development. Then, the analysis of the agile practices is carried out to enable the adoption of iterative concepts in different stages of the V-Model. Also, some processes would solely be carried out by V-model and some in combination utilising iterative cycles. Therefore, this process would mitigate the rigid nature of the V-Model and

provides more flexibility in the development. However, a risk identification stage is added to determine the priority in which components of the project to be carried out.

Standards and regulations

Medical device development is a highly regulated industry. Therefore, every medical device produced is advised to follow the recommended standards. Also, it is necessary to meet the required regulations. In 2007 the European Union introduced an amendment referred to as 2007/47/EC that defined medical technology as: *"Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings"*

Therefore, software on its own is required to be registered as a medical device under the medical device directive (MDD) regulations. Additionally, in the same amendment Annex IX defined the categories of different medical devices where it states an active medical device is: *"Any medical device operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices. Stand-alone software is considered to be an active medical device."*

Based on these definitions and regulations, the developer is required to demonstrate the safety and efficacy of the medical device. This includes a specification representation of the intended device before the start of the development. Additionally, a detailed documentation of the followed development processes is also required. However, the regulatory bodies do not specify any development lifecycle as part of regulations and left the choice to the developers. The US food and drug administration's (FDA) General Principles of Software Validation states: *"This guidance recommends an integration of software lifecycle management and risk management activities. Based on the intended use and the safety risk associated with the*

software to be developed, the software developer should determine the specific approach, the combination of techniques to be used, and the level of effort to be applied. While this guidance does not recommend any specific life cycle model or any specific technique or method, it does recommend that software validation and verification activities be conducted throughout the entire software lifecycle"

Later IEC 62304:2006 reiterated by stating: *"This standard does not prescribe a specific life cycle model. The users of this standard are responsible for selecting a life cycle model for the software project and for mapping the processes, activities, and task in this standard onto that model."*

Since it is recommended to follow the validation and verification throughout the software life cycle, the plan-based developments seem a good fit for the purpose. Hence, these models and, in particular, the V-model have been widely utilised for the development process. Due to drawbacks of the plan based development models, efforts to introduce agile to the medical device development has been made. However, there are challenges in adopting Agile in safety-critical areas such as the medical field [247].

Agile development can be challenging due to its minimal documentation. The regulators require sufficient levels of documentation for traceability. Documentation in agile is usually carried out lightly and is limited. Therefore, consideration based on the principles of agile is needed. Agile development advances by delivering the proposed requirements. Hence, it can facilitate the documentation as a requirement [246, 248].

Also, flexible requirements of Agile can pose further challenges. Safety-critical applications prefer set requirements without changes, if possible, whereas agile promotes change [249, 250]. In essence, its requirements usually begin with unstructured user stories. This is significantly different from the detailed requirements presented in plan-based development. However, safety-critical devices may require many changes throughout their lengthy development process. Therefore, the unstructured user stories can be formulated to a formal requirement specifications [251]. Also, the frequently changing functional requirements can be separated from the more stable safety requirements, and hence their documentation too.

Another challenge is the iterative and incremental cycles of the development, which are the core of Agile development. In each iteration or increment, the impact of the changes made becomes difficult to assess on the entirety of the system. Some studies suggest the breakdown of the requirements on iterations help with granular understanding, and thus a more informed solution can be developed [252].

Agile is a test driven development. Hence, the tests are usually developed at the start. In many instances, these tests are written before the development commences. Automated testing can therefore be used in such circumstances. This approach is different from plan-based development, which performs its tests at the end of the development cycle. The plan-based tests can help to verify the end product. Therefore, agile first tests need more scrutiny to potentially perform their intended use for verification [253].

A recent review [247] introduced a model by which five links between the aforementioned challenges were established; traceability of requirements, securing safety with flexible requirements, incremental and iterative testing, light test documentation, and incremental and iterative validation and verification of safety. To be able to address the challenges of Agile development, these links also need investigation. The review also acknowledges the sparse evidence of the agile development in critical-safety fields. This sparsity may be due to recent introduction of agile in these fields. Therefore, more studies, critical reviews, and empirical evidence such as trials of new solutions in agile are needed. The next section outlines the few experimental evidence available in the literature for medical device development.

Agile in medical device industry

Rasmussen *et al.* presented an experience report on their use of agile [254]. They compared projects pre and post agile adoption. The two projects, ARCHITECT i2000 and m2000 were developed by traditional and agile development processes, respectively. These software medical devices were classified as Class-III, the most stringent category in MDD. Although these projects are not of the same complexity, an estimate of the corresponding details is reported. m2000 took 24 months to complete and was launched within 17 months. Whereas, ARCHITECT i2000 took 54 months to launch and resulted in many complaints and changes

afterward. m2000 required 24 full-time equivalent (FTE) employees while ARCHITECT i2000 required 100 FTEs. If ARCHITECT i2000 was developed using agile, Abbott estimated a reduction of 20% to 30% in both duration and headcount. Also, Abbott estimated 35% to 50% overall cost saving that could have been achieved on an agile production of ARCHITECT i2000.

Also, Medtronic published two articles outlining their experience adopting agile methodologies [255, 256]. They closely monitored the reduction in the amount of rework, the increase in speed and efficiency in processing the product backlogs. They also surveyed their employees (28 team members) to measure the success of their adoption. The survey result showed an overall improvement noticed by the employees including quality assessment, quicker detection of bugs, and enhanced achievement of the requirements. However, they noticed a shortfall (68% agreement) integrating with other functional teams; they expected this as other teams were not run on agility.

A mapping study investigated the extent of agile in research reports for medical devices. The result found in the period between 2002 and 2012, only five studies utilised agile for their development [47]. Also, this was recognised by the experts in the Association for the Advancement of Medical Instrumentation (AAMI) that resulted in a technical information report (TIR) for agile in medical device development in 2012. TIR45:2012 is a guideline that explores the features of agile and its feasibility in the regulated medical industry to meet the standards and regulations. However, AAMI TIR45:2012 was a theoretical proposal for the ways that agile can be adapted to meet the regulations.

Additionally, medical device manufacturers avert from employing human factor engineering [46]. Manufacturers consider the process to be too resource intensive; the analysis of the data produced in the process is cumbersome and costly. The ways to integrate these analyses in the development process is unclear and time-consuming. In their development process, manufacturers perceive the option not to be viable and out of reach.

Interviews with 11 medical device manufacturers showed that the consulted users are usually higher senior healthcare staff rather than the intended users of the device; it is preferred to consult more senior staff who are mostly decision makers in health care [46].

These staff have a limited overlap with users of the device. They mostly employ the users to verify the device to meet the external standards rather than contributing to its development. Some manufacturers have expressed the view that ethical approval is a hindrance to recruiting users to conduct research. Hence, informal discussions with clinical staff is a quicker, viable and more efficient option.

Focus groups and interviews were conducted to assess the effectiveness of telehealthcare in meeting the needs of the end user [48]. The findings of the study mirrored the results of the interviews of the medical device manufacturers. The interviews revealed the missing early involvement of end-users in the design and development processes. These focus groups emphasised the lack of good design principles which undermines the consideration of aesthetic appeal, functions and usability of devices.

6.1.2 Current research

For many years researchers have studied the effect of technology on diabetes healthcare often with the main focus on the end-user outcomes. These outcomes are evaluated in terms of improvement and satisfaction of end-users using rigorous and statistically significant measures. However, these studies tend to become obsolete due to the prolonged period of the studies and not adapting to the changes in the technology [38, 50, 257, 258]. Therefore, the relevance of the findings is undercut and certainly, their adoption in practice is almost impossible. For example, a study was conducted to investigate the effect of mobile technology in improving diabetes management [259]. They used iBGStar, a glucose meter that attaches to the iPhone. This glucose meter was the first of its kind as it is attached to the phone as an add-on and seamlessly communicated to an app to provide the result and statistical information. The study was initiated in 2012 and the results were published in 2017. In 2012 —the same year of the study— Apple changed their interface on the iPhone and the device of the study became unusable. Sanofi, the manufacturer of the glucose meter and the funder of the study discontinued the production of the glucose meter. Similarly, another study used PDAs to help with logging of data and food information. This study began in 2009 and published in 2014. At the time of the publication, PDAs were a thing of the past.

The R3 research study acknowledges the need for adaptive research and points out that the health system has a 10-year lag in IT implementations [50]. R3 suggests a change in protocols and providing rapid and responsive learning for RCTs. For example, running sets of smaller and shorter N-of-1 trials and utilising Bayesian analyses to provide a generalisation of the combined results of the studies, or using more within-group designs where the same subject acts as the control subject to simplify the study procedures, additionally, improving the involvement of wider stakeholders to increase the relevance of the research. However, these suggestions have not been utilised or implemented in practice as far as the published literature is concerned.

The research in this chapter utilises an agile methodology to develop a telemedicine system in type 1 diabetes. This helps to establish a holistic design that values change, patients and clinicians collaboration and interactions during lengthy periods of clinical studies. A novel patient-centred platform (Glucollector) was designed and evaluated during a two-year multi-centre clinical pilot trial. The Glucollector platform provides tools, visual analytics and data analysis to improve diabetes management and engagement of type 1 diabetes patients and clinicians. Glucollector and its development process provide a proof of concept on how technology oriented diabetes research can be readily translated into practice.

6.2 Research Design and Methods

The process of developing the Glucollector platform involved many iterations. At first, we surveyed the patients at Sheffield Teaching Hospital (STH) to understand their internet usage on different systems outside the clinic. Also, the survey explored the possibility of adopting telehealth for managing and providing support in diabetes management.

Afterwards, we interviewed health-care providers, and patients at STH to investigate currently used systems and discuss potential improvements. Interviews occurred in two phases: in the first phase, familiarity with workflow and patient-clinician engagement was observed over a few clinic visits. In the second phase, interviews explored the description and questions about the technological needs of the system to enhance diabetes care for patients.

A thematic analysis [260] of the interviews and observations was carried out to identify the requirements. At this stage, the development began, and we required patient involvement to include the end-users in the development process. Also, it was decided to use the developed system in the DAFNEplus pilot trials.

The DAFNEplus clinical pilot trial was a non-randomised, mixed method study aimed at modifying the existing DAFNE programme by including behavioural change, structural follow-up support, and use of technology to benefit both patients and clinicians. The DAFNEplus programme was developed, piloted and refined under the program grants (IRAS 208842; IRAS 214683).

6.2.1 Volunteers

Three cohorts were recruited to provide feedback on the system. The University of Sheffield (UoS) volunteers, DAFNE graduates at STH, and DAFNEplus multicentre pilot clinical trial attendees were recruited to use the system.

UoS volunteers

Patients at the UoS were invited in January of 2016 to volunteer to pilot the system for two weeks. 11 (6 females) volunteers attended an introductory meeting to register and familiarise themselves with Glucollector. The registered volunteers could upload, view and analyse their data for the intended period. Volunteers were requested to give feedback on their usage, issues and possible improvements. Feedback was provided on web-pages using the online feedback system integrated onto Glucollector. At the end, volunteers filled in a usability questionnaire and commented on their usage of the system.

DAFNE graduates at STH

Patient and clinician volunteers at STH were recruited in October of 2016 to test the system usage and acceptability (12 patients and 5 clinicians). This provided the opportunity to test the system under its intended environment (i.e. patients' home, and clinics). The setup of

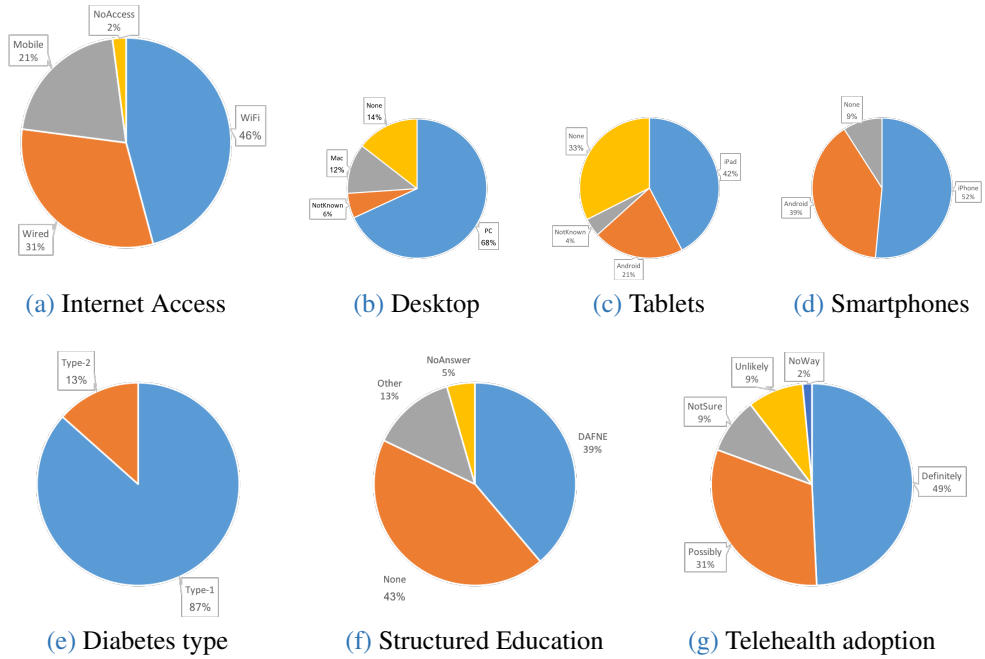
previous recruitment was utilised to process the volunteers. The registered patients were DAFNE graduates who have had diabetes for a few years. These volunteers were recruited for two purposes in the development process: first, they provided feedback on the latest changes in the system before the initial start of the DAFNEplus clinical pilot trial. Second, they acted as the pilot population for the changes and improvements on Glucollector in parallel with the patients in the DAFNEplus pilot trial. These patients were experienced in DAFNE self-management and volunteered to provide feedback on the functions of Glucollector. They also helped prepare us for the pilot trials in terms of system set-up, etc.

DAFNEplus multicentre clinical pilot participants

In October 2016, the DAFNEplus pilot trial recruited 66 patients and 10 clinicians across three centres in the UK at STH in Sheffield, King's College London in London, and Norwich and Norfolk Hospital in Norwich. These centres are experienced in delivering the DAFNE education programme. Hence, they were chosen to be among testing sites in the NHS. The inclusion criteria for participants were: Adults (>17 years), diabetes length of > 6 months (post-honeymoon period), using multiple daily injection (MDI) therapy, able to attend the course days over five weeks and take part in the follow-up. Exclusion criteria were: Insulin pump therapy, high HbA1c (>108 mmol/mol), pregnancy, exhibiting severe diabetes complications (e.g. blindness, renal dialysis, etc), suffer from an eating disorder, lack of language proficiency (speak, listen, understand and read in English); and unable to provide written consent.

6.3 Results

The Glucollector is being designed for the diabetes population. A survey was conducted at STH and was completed on voluntary basis by people attending clinical appointments at the Diabetes centre. This was to confirm the assumption that patients have the willingness and ability to use a technology-based intervention such as DAFNEplus. The summary of their responses is: 87% of the respondents had T1D, and about 52% graduated a structured



(a) Internet Access (b) Desktop (c) Tablets (d) Smartphones

(e) Diabetes type (f) Structured Education (g) Telehealth adoption

Fig. 6.1 Internet use and acceptability of telehealth system among diabetes patient

education for diabetes management. The majority, about 80%, will use telehealth. Also, the majority accessed the internet through various devices; 80% desktop computers, 54% tablets, and 90% smartphones.

6.3.1 Requirement gathering and analysis

The first phase of requirement gathering was observing the clinical workflow. The observed workflow was: patients are referred to the diabetes unit at STH. Then, patients arrange their appointments to visit the diabetes specialist. Patients are asked to bring a record of their SMBG results in a handwritten diary and/or their blood glucose meter. The clinicians downloaded the data in the glucose meter at the clinic upon the arrival of the patients. If the download was successful, the clinician can view the data recorded on the meter in a digital logbook combined with statistics such as average blood glucose, percentages of hypoglycaemia and hyperglycaemia. Clinicians expressed the view that the system is intermittent and sometimes it was not possible to download the data from the glucose meter. The clinician reviews the data when the patients start their appointment. During the review,

the clinician asks questions to better understand the progress and gain more context on the patients' glycaemic control.

The second phase of requirement gathering was the interviews conducted with patients and clinicians. These were recorded for thematic analysis and the following themes were identified:

- One place for viewing all the data rather than using various software and applications to achieve the task would be desirable. The data should be combined to be presented in harmony with other contexts. This would help to view, analyse and communicate the data efficiently.

- Clinicians access to the data and efficient streamlining of the clinical workflow. Data availability as per upload of patients to facilitate a proactive role for the clinicians. This can provide the support to set certain agendas to discuss before the appointments at the clinic to maximise the benefits of face-to-face meetings.

- Consistency with diabetes structured educational programme, such as DAFNE. Sets of common views, and frameworks for both patients and clinicians to enable remote clinical appointments (i.e. phone appointments). This facilitates seamless communication due to the common set of panels and information.

- The possibility of support services from clinical and technological aspects. Secure communication with clinicians to offer feedback and answer questions asked by patients. Additionally, engineering help and support in using technology at home.

- A reliable access to data with easy to navigate and review structure. Hence, presenting the information in an organised and contextual fashion to ease the reviewing process.

- Support for a reliable source of reference for carbohydrate intake. Facilitating a food diary to provide more context to the recorded SMBG readings by patients.

- Pattern recognition facilities through statistical information and trends presented to aid with treatment decision making and progress tracking.

- Pattern recognition facilities through visual analytics to communicate the information efficiently. Facilitating a structured review process for both patients and clinicians.

- Availability of data-driven information and educational material based on a structured educational programme such as DAFNE to provide reinforcement learning of the related subjects.

6.3.2 Glucollector agile development

Figure 6.2 shows the agile life-cycle adopted for Glucollector development. The users are stakeholders of the system which included patients, doctors, dietitians, diabetes specialist nurses, and psychologists. In the iterative process of agile, we included risk assessment whereby the deliverables were ranked in priority order to meet the deadlines for the design. This meant that high risk, high priority deliverables were performed at early stages of the development. The supervisory team were involved in risk assessment ensuring conformity to the regulations. Any regulatory aspect was considered a part of the development process and was added to the sprint backlogs.

The Glucollector was developed including the clinicians and patients in two-week cycles of development sprints through subsets of sprint backlogs. At the start of testing, the hospital provided a few glucose meters to populate the system with real data from patients. After a few iterations, the first version of the system was ready and tested in four different outpatient clinics at STH. This testing provided feedback on the usability and reliability of the system under clinical use. Consequently, we introduced incubation cycles in the development process. The incubation periods were between two to five days depending on the importance, complexity, and the number of applied changes to the design or functions. Clinicians and patients received notifications on the updates and used the system for testing. This improved the quality and quantity of the provided feedback to the research team regularly. In the early stages of the development, only clinicians were involved in the incubation period. After a few iterations, the second version of the Glucollector was produced. At this point, it interested us to test the system with patients outside the clinic. As the recruitment progressed, the patients

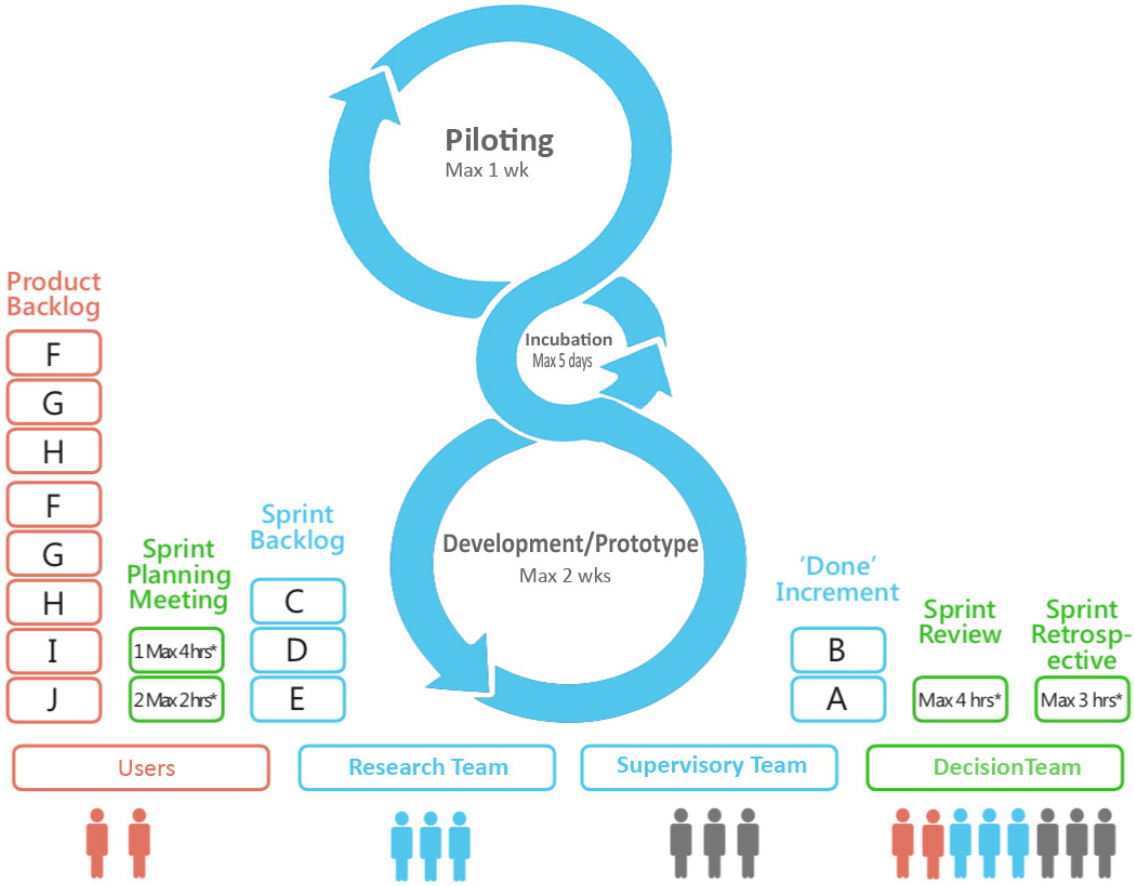


Fig. 6.2 Glucollector agile life cycle

in the incubation cycles included a subset of experienced DAFNE graduates. They were usually the more engaged users since we were looking for quick and concise feedback. After the changes were applied based on the feedback, the piloting commenced.

In most cases, the pilot version of the new features was only shown to the DAFNE graduates cohort. Later as the time progressed, a subset of the DAFNEplus cohort was involved. These subsets were the early groups of DAFNEplus who were familiar with the Glucollector. The piloting process lasted for a maximum period of one week. Then, the introduced features were refined and made available to the users on the Glucollector.

Technical feedback

Patients were involved in enhancing and introducing features on Glucollector. They provided feedback utilising the built-in online system. This feedback was intended for technology related matters. This included comments on features, bug reports and feature requests. These feedback were mostly gathered during incubation and pilot periods of the introduced features. Overall, we have received 336 comments; this is equivalent of about one comment every two days.

The requested features and suggestions were taken and further improvements were carried out in the iterative process of agile to adapt to users' needs and wants. Through this iterative process, there have been many additions and modifications to the system. Figure 6.3 shows the frequency and the load of the applied changes over time. Overall, there was about 1.5 change every two days. Interestingly, this is close to the frequency of patients feedback and requests. This constituted git addition of 149,879 lines of codes and modification of further 60,740 lines of codes. The Glucollector is built with total of 82,990 lines of code.

TABLE 6.1
THE INTRODUCED FUNCTIONS OF THE GLUCOLLECTOR UTILISING THE AGILE DEVELOPMENT

Year	Date	Activity
2015	22-May	initial commit
		Authentication

Table 6.1 continued from previous page

Year	Date	Activity
		Registration
		Mysql integration
		Connection pooling
	25-May	Error handling / profile
	26-May	Role-Based Authorisation
	27-May	Visualisation improvement summary
		Caseload management
		Two factor authentication
	03-Jun	Forms validation
		Java 8
		Logging
		Maven
	05-Jun	Production and development profiles
		Spring security
	18-Jun	Exercise collection integration
	20-Jul	Date selection for logbook view
		Jawbone integration
		Visualisation bar charts and bubble charts
		Navigation improvement
	24-Aug	Auditing
		x509 authentication
		Full charts
		HbA1c visualisation
	31-Aug	Fitbit integration
		UI improvement
	September- October	UI improvement

Table 6.1 continued from previous page

Year	Date	Activity
		Visualisation improvement
		Rest APIs
	05-Nov	Introducing colour coding
	29-Nov	Front end devices integration
2016	05-Feb	Change to colour scheme
		Improved usage logging
		Front end devices end-end integration
	22-Mar	Feedback forms on every page
		Automating user identification through meter
	30-Mar	Granular option for display such as carbs, ketones etc
	18-Apr	Random user generator
		Improved authorisation based on different clinical roles
	07-May	Improving Feedback mechanism
	26-May	Preparing for Trial
	31-May	Performance improvement
		Caseload sharing
	10-Jun	Introducing more statistical information on the data
		Performance improvement
	20-Jun	UI Improvement (Look and feel of the pages)
	27-Jun	UI improvement
		Logging improvement
		Help introduction
	30-Jun	Logbook view improvement based on feedback
		Colour Scheme correction
	02-Aug	Hourly charts
		ANON website

Table 6.1 continued from previous page

Year	Date	Activity
	08-Aug	Daily average added to logbook
		Logbook UI improved by table layout
		Percentage bar chart
	Aug-11	Monthly and quarterly Summary chart
	12-Aug	Weekday Bubble chart
	23-Aug	Nodes to collect daily readings of multiple modalities
	02-Sep	Logbook view improvement
	18-Oct	Bolus Advisor
		Helpdesk users
	03-Nov	Visualisation improvement
		Patient prioritisation (Scoring)
		Validations across views for user input
		Secure communication added
	09-Nov	Improving the emailing
		UI improvement adding easy access period 72 hours etc
	11-Nov	Commenting on data enable
	14-Nov	Day view chart and timeline improved
	15-Nov	HbA1c predicting introduced
		HbA1c Visualization improved
	17-Nov	Adding tags to readings
		Improving helpdesk
	22-Nov	Improving readability
		Help and tooltips on the pages
	30-Nov	Device based viewing experience
	02-Dec	Carb Centre Initiated
		Carbsand cals db is added

Table 6.1 continued from previous page

Year	Date	Activity
2017	20-Jan	Carbs centre modifying added carbs
		Pending unattached dishes to carb readings
	24-Jan	Favourite meals
		Help content for Carb Centre
	26-Jan	Carb Challenge
	27-Jan	Carb Challenge improvement
	31-Jan	Improved carb centre search
	04-Mar	UI and Performance improvement
		Scatter plots introduced
	06-Mar	UI improved logbook view rows for each modality
	08-Mar	CGM improvement on logbook view
		Improve logbook view date selections
		Dot plot bug fix
	09-Mar	Day chart bug fix
	13-Mar	UI improvement logbook view
		Bug fix with REST Api
	20-Mar	Schedule based notification system
	23-Mar	Improved carb centre interaction with logbooks view
	30-Mar	Bug fix with user id in the URL
		Reading data validation improvement
	26-Apr	Dashboard view improvement and bug fixes
	09-May	Dashboard view improvement Charts
	10-May	Dashboard UI improvement
		PIN security improved
		Comments API for mobile applications
	11-May	Bolus on board on the full chart

Table 6.1 continued from previous page

Year	Date	Activity
		Dashboard UI improvement
	12-May	Displaying comments on the full chart
	17-May	Dashboard improvement related to time blocks
		Fullchart bolus on board improvement
	30-May	Dashboard UI improvement
		Proxy for static content access
	19-Jun	Comments API improvement
	21-Jun	Static content improvement
	29-Jun	PIN bug fixed
	03-Jul	Full chart bug fix
		Improved registration
		Monthly Reminder
	04-Jul	Email formatting improved
		Dashboard UI for handheld devices improved
	25-Jul	Dashboard charts improvement
		Clinician dashboard scoring improvement
		Caseload UI improvement
	05-Aug	Fitbit integration with logbook view
	06-Aug	HbA1c prediction based on three months
		Dashboard update insulin and carbs chart
		Dashboard optimisation
	08-Aug	Caching bug fix
		Colour scheme for summary table
	09-Aug	Caching improvement for performance optimisation
	14-Aug	E-learning rewrite and initialisation
		Improved TDD display on dashboard

Table 6.1 continued from previous page

Year	Date	Activity
		Help content improvement
		Improved summary table
	15-Aug	Caseload management improvement
	16-Aug	Improving comment on the readings
	18-Aug	Performance improvement
	26-Aug	Performance improvement
		Bug fix in security
	28-Aug	Site wide UI improvement
	01-Sep	Charts performance improvement
		REST Api improvement
		Improved UI on Dashboard
	02-Sep	Bug Fix for Scoring on dashboard and caseloads
		Charts Performance improvement
	07-Sep	Adding daily comments on the logbook view
		Adding readings manually by the clinicians
		TDD improvement
	08-Sep	Bolus advisor view improved
	22-Sep	Introducing time-block based dot-chart
		REST API for healthcare feedback
	25-Sep	Box fix and code improvement
		Improved Fitbit integration
		Sickday help flowchart
		TDD Algorithm update
	26-Sep	Sickday rules update
		Modification to time-block based dot charts
	05-Oct	TDD Algorithm improvement

Table 6.1 continued from previous page

Year	Date	Activity
	11-Oct	Logbook view improvement
	15-Oct	Logbook view improvement
	16-Oct	HbA1c prediction bug fix
	01-Nov	Improved flags association from different meters
		Logbook view improvement
	11-Nov	TDD bug fix
		Star rating on the dashboard
		UI improvement
	15-Nov	Review toolbar improvement
		UI improvement relevant to the sidebar
		UI improvement colour schemes
	28-Nov	Views improvement across handheld devices
	04-Dec	HbA1c prediction bug fix
2018	28-Jan	User activation improvement

As shown in the Table 6.1, many of the features and functions of the Glucollector were made through many iterations, mostly followed by the agile cycles in Figure 6.2. For example, the development of the Carbs centre (its function is detailed in the next chapter) started in December 2016 and then through feedback cycles, it was modified on 20th January to facilitate amending added carbs and pending unattached meals to a reading in the logbook; then on 24th January, a list of favourite meals and help content on the carbs centre was added. On the 26th January, Carbs challenges from carbs centre was introduced, and then on 27th January carbs challenges were improved. Finally, on 31st January the search for meals were modified to be optimised and tolerate misspellings. As can be seen, the iteration at times needed a lengthier period, (although this might have been influenced by the Christmas period), however, sometimes a lesser feedback period such as a day is recorded. The above is not a safety critical function. Total daily dose (TDD) calculation where patients use this total

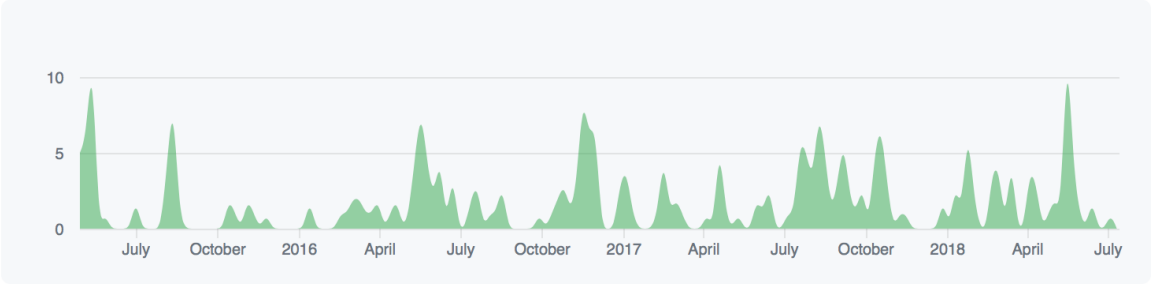


Fig. 6.3 Number of git commits (changes) over the development period of Glucollector

to adjust their insulin intake between basal and bolus, and in particular during sick days is a safety critical function. TDD was first introduced on 7th September, then through various feedback and internal testing with the upcoming data, on 25th September, a modification was made to optimise the algorithm in tolerating changing start-of-day or the odd injections of the basal at different hours than the usual during a day. Then, on 5th October, a bug in the code was fixed; and on 11th November the user interface and messages displayed for the TDD information were improved. This safety critical had a longer feedback period and also an internal testing was continuously ran on the upcoming data to ensure safety. This extra task of internal testing was not needed for non-critical functions. Therefore, through these iteration improvement to user interface (UI) and introduced functions was continuously made, which enable the design of the Glucollector system.

6.3.3 Glucollector system

The Glucollector is a novel web application which leverages the system to become a platform and support different functions efficiently, securely, and in a timely manner. As shown in Figure 6.4, the Glucollector was designed to improve the patients' access to care and enable efficient streamlining of clinical work. The core of the architecture is the patient in the inner most circle to represent the patient centric design. The patient centred design in turn enhances the utilisation and engagement by the patient. The Glucollector therefore improves the link between patients and clinicians that eventually benefits both the patients and clinicians. Glucollector receives data from the WithCare+ front-end (developed in Electronic

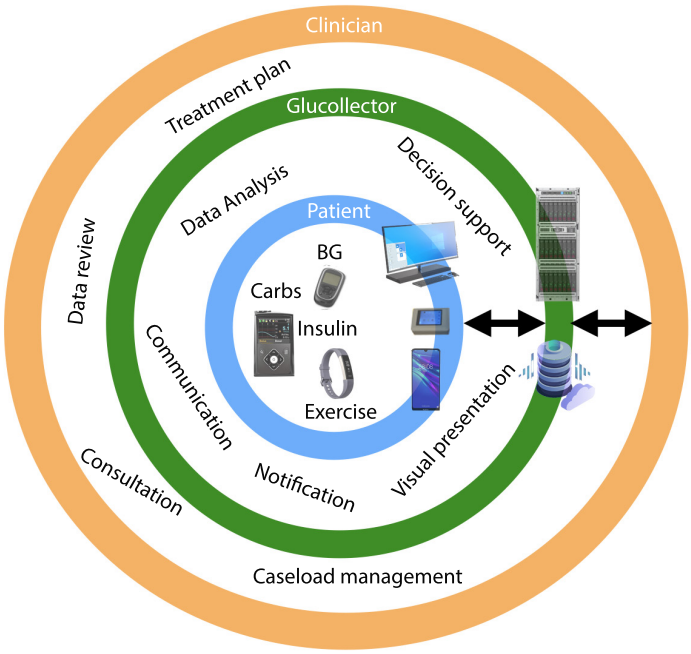


Fig. 6.4 General architecture of the Glucollector

and Electrical Engineering Dept, The University of Sheffield) and related third parties to format, analyse and present them in a meaningful and intelligent fashion to the users of the system. Users take measurements of blood glucose levels using their glucose meters and also record other relevant data (e.g. insulin and carbs) manually to the meter. These data are then interrogated by the WithCare+ front-end, formatted and transmitted over the internet to the cloud service for the Glucollector system. The Glucollector presents these data for inference and review, while also performing data analysis to help with decision making. The functional architecture of the Glucollector is detailed in the next chapter.

The Spring framework [261] was adopted to build the system. It is a Java based open source framework that utilises inversion of control container (IoC) [262].

The development architecture

The Glucollector development architecture is designed to divide the functions of the system in a modular fashion so it could be scalable considering its use case. Figure 6.5 shows the modules and their dependencies to implement the architecture.

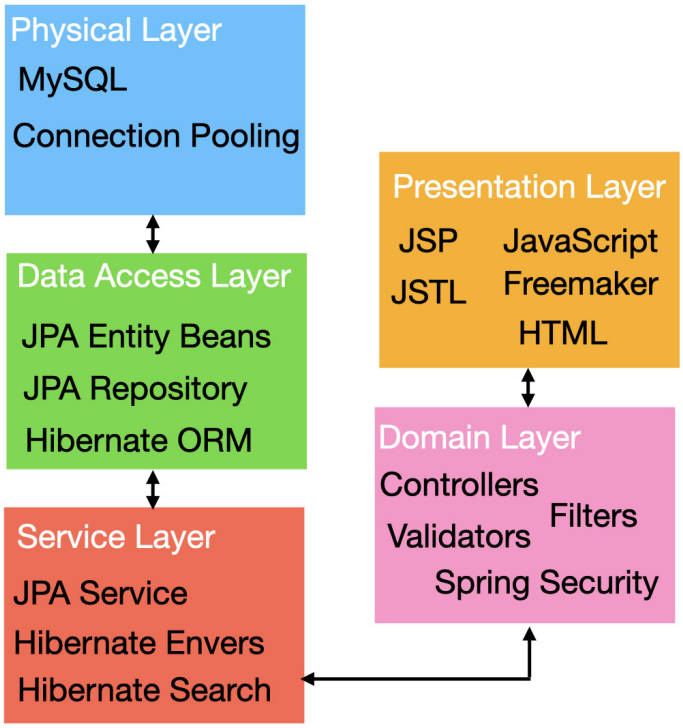


Fig. 6.5 The development architecture of the Glucollector

Presentation Layer This layer provides interfaces that enable users to access data, perform operations, and utilise different functionality. In this project, JavaServer Pages (JSP), JavaServer Pages Standard Tag Library (JSTL), Apache Tiles, and freemaker are used to produce the required Hypertext Markup Language (HTML) and Java-Script codes. Controllers are responsible for creating models that will be embedded into the web-page for dynamic contents.

Service Layer This layer provides tools for accessing transactions, connecting to different modules, and initiate data access calls. It buffers the domain layer from underlying complications.

Domain Layer This is where the logic of the required request is processed. It uses resources such as services, models, validators and a security module to complete a response.

Data Access Layer This layer provides an interface to the physical layer. The requested data are passed to the upper layers. It validates the data request and issues the appropriate queries. Spring Data Java Persistence API (JPA) implements JPA and handled using Hibernate Framework.

Physical Layer This is the layer that persists the data and files. MySQL is utilised to implement the layer.

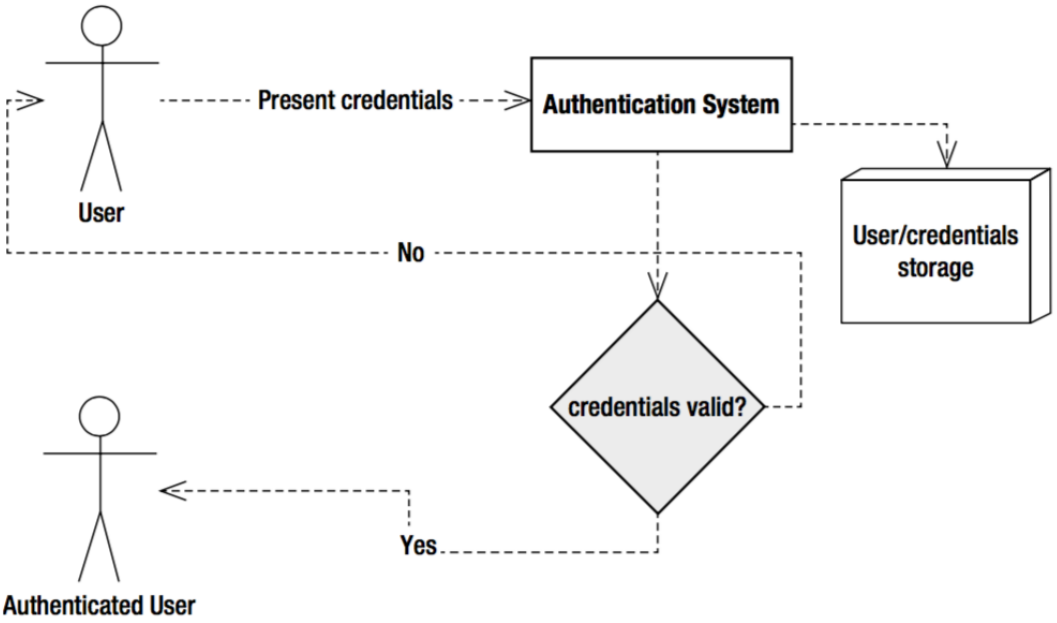
The system was first tested on a cloud platform-as-a-service (PaaS) Heroku (Salesforce, CA). Thereafter, the system switched to the University of Sheffield cloud computing service.

6.3.4 Security

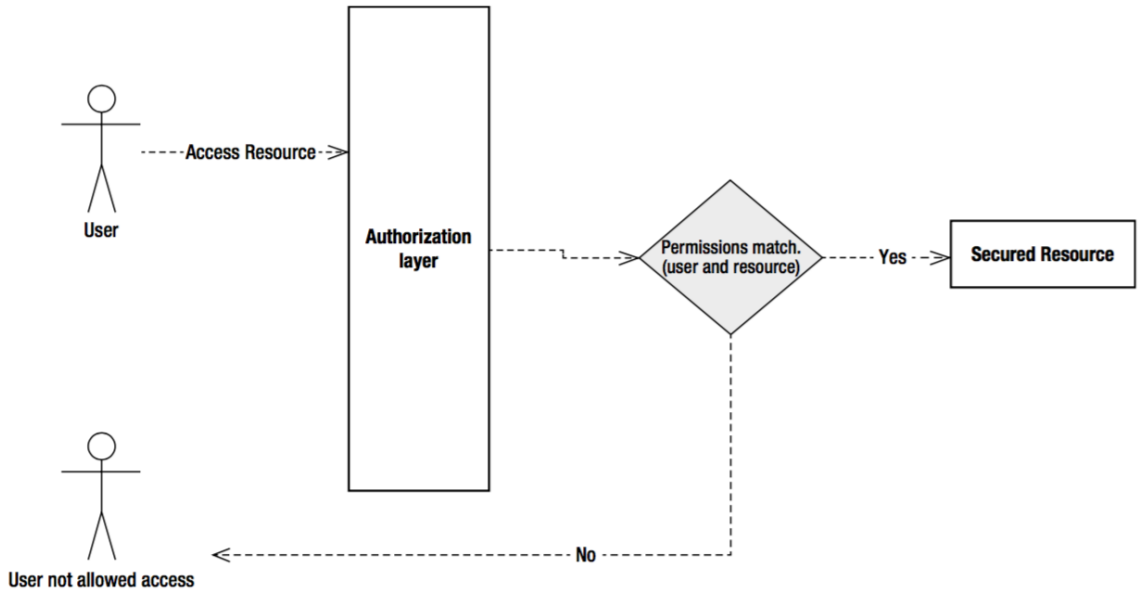
The security of the system is of high importance. Since the application is accessible through the Internet, it opens up the possibility of threats. The system ensures the authorised access by performing authentication and authorisation. The authentication looks for the registered user access, and the authorisation enforces role-based access to the resources (Figure 6.6).

Furthermore, in order to protect users' credential one-way hashing of the password is used, utilising Spring security [263] implementation of BCrypt [264]. In addition, the x.509 mutual authentication is available to the secured computers (i.e. hospital) and front-end devices issued by our system. A self-signed certificate can be downloaded by the authorised user. This is uploaded to the key-chain of the operating system as a trusted source. Therefore, the user can bypass the manual authentication and authorisation by having the certificate installed; the browser requests the certificate as part of the Secure Sockets Layer (SSL) handshake. The user has to request a new certificate after the expiration date. The certificate is generated on the back-end using OpenSSL.

In order to ensure authorised access to the resources, the endpoints are secured. Furthermore, the authorisation has been applied to method invocations. This adds additional security to the business layer. Access to the database is limited to the web username and password which has limited capabilities on the administrative operations. Consequently, auditing is



(a) Authentication



(b) Authorisation

Fig. 6.6 The authentication and authorisation process in Glucollector utilising Spring security

persisted on accessing any resources. Furthermore, the entire system has been protected behind a firewall, and the cloud service provider's backup operation.

6.4 Discussion

The Glucollector was developed using an agile development model through rapid cycles of feedback. This feedback enabled the amendment and introduction of many features with the involvement of various stakeholder over time. Initially, a survey was conducted to assess the usage of technology, especially internet usage of the users, which showed a promising attitude. This survey was taken by the attendees of the clinic and on a voluntary basis that may have resulted in responses from a more technically literate cohort. However, as reported by the Office of National Statistics in the UK, people who use the internet for services have been increasing over time [265]. Therefore, there is a trend for the general population to become more in-tune with the use of the Internet for services and likely more digitally adept.

The rapid advancement in technology and upfront fixed clinical study designs risk the relevance and translation of the technology-related clinical research. Trials take about 5.5 years to finish [257]. Therefore, researchers need alternative designs that can accommodate change and evolve with the up to date technological ecosystem [38, 50]. The R3 [50] study proposed to reduce the length of these studies. But the lifelong chronic conditions such as diabetes require prolonged clinical trials to establish sufficient evidence based on follow-ups and collected data analyses. We modified the agile development life-cycles to enable a responsive design to changes and demands of the technology ecosystem during the study. The incubation periods of the development cycles provided feedback to ensure the quality and safety of the platform. Piloting exposed the design to a larger number of users. These verification processes resulted in a finely tuned working software with new sets of features released to the users in rapid cycles. Also, considering the pace of technology and relevance of the research helped to improve recruitment and retention of the participants.

Agile iterative design and small deliverables help to identify problems and resolve them in the early and manageable stages of the development. However, the benefits of the iterative

agile development can be limited by the requirements of having to meet the standards and regulations when combining the agile with a plan based models (e.g. Agile V-model). To address this issue, we used additional sprint backlogs in different stages of the development to evaluate the needs of standards and regulations, supporting the arguments advanced in the TIR45:2012 report to implement agile throughout.

The focus of the medical device manufacturers is on agility for a better product management and compliance. This is counterintuitive to the essence of the agile methodology; the agile manifest states the user experience of the product has a higher value than the processes.

The manufacturers usually consult the higher senior healthcare staff instead of the intended users of the device. This is a passive role for the users while senior staff represent a more active role. Therefore, the financial motives of the manufacturers seem to have caused a confusion between customers and users [46]. This inadvertently resulted in expecting the users to fit the device rather than the device to fit the needs and wants of the users [48]. This limits the uptake of the technology and is reflected in the current state of type 1 diabetes care.

As this chapter is set up in a research study, and it aims to find new technological approaches for people with diabetes, thus its components and features were unknown at the start and technology is also ever changing. Therefore, agile can be a suitable option as it strives to deliver requirements and promotes change. However, a few considerations need to be made. Risk and safety assessments need to occur continuously especially for new features arising along the research, whether by stakeholders or availability of new technologies. As of the nature of agile for rapid cycles, it may require establishing a structure that fits the team for better collaboration and success in achieving the goals of the design. Continuous contribution of different stakeholders is the essence of successful development that agile promotes. Therefore, there is a need for ensuring their involvement from the start with timely feedback opportunities. This was demonstrated in our development that at times the feedback was provided within a day for some introduced features. However, there also needs to be insight into these rapid requests or changes. One can be caught in scope creep (or requirement creep) as agile welcomes change. A critical assessment for prioritising changes or their dismissal therefore is necessary.

Our research and the use of agile enabled a meaningful participation of the stakeholders. The subject of the study is a chronic disease with the involvement of a wider range of stakeholders (i.e. patients, doctors, nurses, psychologist, behavioural psychologist) which guaranteed the continuous exposure of the designed system for rapid feedback. This was also partly possible due to a higher number of participant patients. However, other researchers who may not have access to users during their development for a sufficiently continuous period (e.g. not a chronic disease, or limited access to other stakeholders) might not be able to benefit from the agility to the same extent. Therefore, some adaptation of agile with traditional models may be needed.

In conclusion, the early involvement of various stakeholders has helped with feedback on user interfaces and various functions through rapid cycles of agile in the development process. This in turn enabled presentation to the users of the system, in particular patients, at the core of the design. This patient centric design may help improved engagement of the patients with their condition, which can assist in maintaining the obtained benefit over time. The developments in this chapter produced various functionalities and were evaluated by the three volunteer groups of patients and clinicians, including the DAFNEplus pilot trial group. These are detailed in the next chapter.

Chapter 7

Glucollector: Functional utility for sustained behaviour change

In 2017, the European patent office registered 13,090 patents in the medical technology sector, claiming the first place with respect to other sectors. One area is telemedicine in type 1 diabetes which focuses on providing applications, tools, and analytics to help with complex daily self-management of blood glucose levels. Commercial companies and researchers have been adopting various technological advancements to support the T1D population. However, the approaches of commercial companies and medical researchers have been different. On the one hand, commercial companies operate in a fast-paced open free market economy driven by advancement in technology. On the other hand, medical researchers work in a slower-paced academic environment relying on established peer review or evidence from randomised controlled trials [38]. This has resulted in commercial companies' products being designed for a broad consumer population and often lacking focus on proven clinical benefits and end-user needs, if not resulting in potential harm [38, 98, 266]. Consequently, there are many issues and impediments to usability and ultimately adoption of technology in T1D care.

The lag and non-adaptive technology-related research coupled with the lack of user-centred system design by commercial companies, have created a gap in an evidence-based system that can fulfil the needs of patients and clinicians for healthcare technologies in

diabetes. This chapter details the features developed using the agile development cycles established in the previous chapter. These cycles enabled design of a patient centric Glucollector system. The Glucollector is evaluated in the DAFNEplus pilot trial to determine its efficacy in contributing to improved diabetes management and behavioural intervention.

7.1 Telemedicine

Telemedicine can be defined as the use of telecommunications to support health care [267]. It comprises transmission and analysis of data for continued monitoring of patients and intervention if needed. It can increase the interaction between the patient and health-care team to improve outcomes and reduces care cost. For effective performance, a telemedicine system requires the following components:

- Accurate data collection in digital format
- Electronic medical record and data transmission
- Data analysis
- Communication tools for effective interaction
- Intelligence in automatic decision support based on the data.
- Population-based solution for health care (i.e. tailored treatment plans)

In a telemedicine system, the transmitted data is analysed and presented to the health-care team and the patient. Then, a personalised treatment plan is recommended. The patient has access to the data and feedback using a computer, smart phones or hand-held devices.

In diabetes, telemedicine is an automated support tool to help patients and clinicians to make objective, informed and accurate decisions based on the data and the presented analyses. The data that can be used in such system are [268–271]:

- Blood glucose levels

- Haemoglobin A1c (HbA1c)
- Carbohydrates intake
- Exercise patterns
- Medications
- Hospital visits (i.e. emergency room, hospitalisation, etc)
- Retinal screening test

The impact of telemedicine can be studied in a variety of aspects to infer enhancement in the care provided to patients. From the informational perspective, the impact is providing a better information quality that replaces handwritten records, which are error-prone, possibly incomplete, and accidentally forgotten at home at the time of health care professional (HCP) clinic visits. Its clinical impact includes communication improvement between patients and the health-care team, resulting in potentially more frequent remote follow-ups, exchange of information and instructions. The behavioural impact is improving patient education and self-care by increasing the support provided through the health-care provider's evaluation of the change in treatment and applying more frequent adjustments. The structural impact is saving the patient's time by providing personalised information and fewer clinic visits. However, these might lead to a higher workload on the clinician side due to more monitoring and adjustments [272].

Also, the advancement in cloud services, data management, and computing power permits a more advanced data analysis. Hence, the decision support tools can analyse the data and recommend prompt predetermined responses intelligently. Mutually, an applied behavioural analysis aids with positive reinforcements from the generated responses. In turn, this should contribute to altering the behaviour of the patient and encouraging achievement towards the intended targets [267].

7.1.1 Current commercial systems

From industry, the manufacturers provide software and systems such as Medtronic's Carelink (Watford, Hertfordshire), or Ascensia's Glucofacts (Basel, Switzerland) for the management and analysis of diabetes data. However, these applications are installed on a PC that only connect to the manufacturers' meters. Clinicians have to operate different applications with different views to access patients' data in the clinic. Standardised views are suggested to offer interoperability among various softwares of manufacturers [43, 44]; Ambulatory Glucose Profile (AGP) graphs are presented as such a solution [45]. The AGP comprises three sections: first is statistical information; the second is a modal day of the blood glucose measurements, and the third is the calendar view of the days of the week. Another solution to interoperability is provided by a few commercial companies. These systems collect the data from different manufacturers' meters and upload for viewing. Therefore, the data from different glucose meters is presented in the same way. Among current popular commercial systems for diabetes is glooko+diasend® (Mountain View, CA). It is an online subscription-based service whereby the user can upload their data from different devices and have the result online to view. This provides interoperability to support different data from different manufacturers. It shows the self monitoring blood glucose (SMBG), continuous glucose monitoring (CGM) and insulin data separately for analysis. Another commercial solution is presented by the non-profit company Tidepool [273, 274]. It provides support for online access to diabetes data. Similar to glooko+diasend, it provides interoperability of the collected data. Unlike glooko+diasend, it combines the SMBG and CGM readings in their visualisation. mySugr (Vienna, Austria) is another popular commercial system for diabetes. mySugr is a mobile application that is available either under free or premium subscription. It relies on manual entry of data (it supports a few Bluetooth glucose meters), and it introduces challenges for patient motivation and engagement. Clinicians do not have access to the patients' data. However, in the premium subscription service, mySugr provides coaching from a certified diabetes educator. It also provides educational material for type 2 diabetes.

The research in this chapter utilises an agile methodology to develop a telemedicine system in type 1 diabetes. This helps to establish a holistic design that values change, patients

and clinicians collaboration and interactions during lengthy periods of clinical studies. A novel patient-centred platform (Glucollector) was designed and evaluated during a two-year multi-centre clinical pilot trial. The Glucollector platform provides tools, visual analytics and data analysis to improve diabetes management and engagement of type 1 diabetes patients and clinicians. Glucollector and its development process provide a proof of concept on how technology oriented diabetes research can be readily translated into practice.

7.2 Research Design and Methods

The Glucollector system was used by the volunteers from The University of Sheffield (UoS), DAFNE graduates from Sheffield Teaching Hospitals (STH), and DAFNEplus pilot trial (details of these cohorts were outlined in the previous chapter). These volunteers provided feedback on the functions of the system in the development process. They also used the system for their diabetes management with the support of their clinical team. Therefore, they helped to evaluate the effect of the technology on their diabetes control.

7.2.1 Evaluation

The clinical outcome and efficacy of the system are measured by the improvement in HbA1c levels. Patients with HbA1c >58 mmol/mol at baseline were considered in the analysis. A longitudinal analysis was carried out to measure the change.

Also, semi-structured interviews were conducted as part DAFNEplus pilot trial by Dr Stephanie Stanton-Fay at University College London. This was to provide patients' impression and detailed views on different components and overall design and usability of the system. The Glucollector facilitated a feedback webpage on the system utilising a questionnaire to provide the needed input from the users during the development process. Also, patients answered the usability questionnaire to assess the systems' acceptability.

7.3 Results

The Glucollector was designed for the diabetes population. Therefore, the goal of the research is to develop functionalities to help reduce the burden on the patients and improve their engagement with the condition while improving access to healthcare professionals through improved decision making and communication tools. Functional architecture of the Glucollector is shown in Figure 7.1. These functions were realised through a thorough understanding of the problem space and extensive development skills. This is to ensure an effective coding that is accurate, efficient, bug free, and to a high degree of standards which can be used in the safety-critical medical field. Interfacing with different modules, testing, and continuous integration for a holistic solution, namely an integrated Glucollector platform and its various functional components. In the next section, the developed functions are detailed.

7.3.1 Glucollector design

The users of the website can be a clinician, patient and front-end ubiquitous. The clinicians have access to the records of the patients for their designated centre. An ordered list of statistical information is provided to assist the clinicians in focusing their attention on cases of interest such as patients with high blood glucose levels of above certain percentages for the past month (Figure 7.2).

Data viewing is available to both patients and clinicians. The users (i.e. patients and clinicians) can view the readings in the form of charts, patterns, and lists. The clinicians can create caseloads to filter the patients into focus groups. Furthermore, the registration of other users is carried out by clinicians and administrators only. Feedback can be sent to the patients based on the assessed data and patterns which creates an alert for the patient to read on the secure messaging tool. Also, a clinician can refer patients to other clinicians for review.

The glucose meters' data are collected automatically using the front-end devices. These devices can sync their data for the patients and clinicians to review. Patients can connect their account to activity tracking devices to further automate collecting data (i.e. exercise, sleeping,

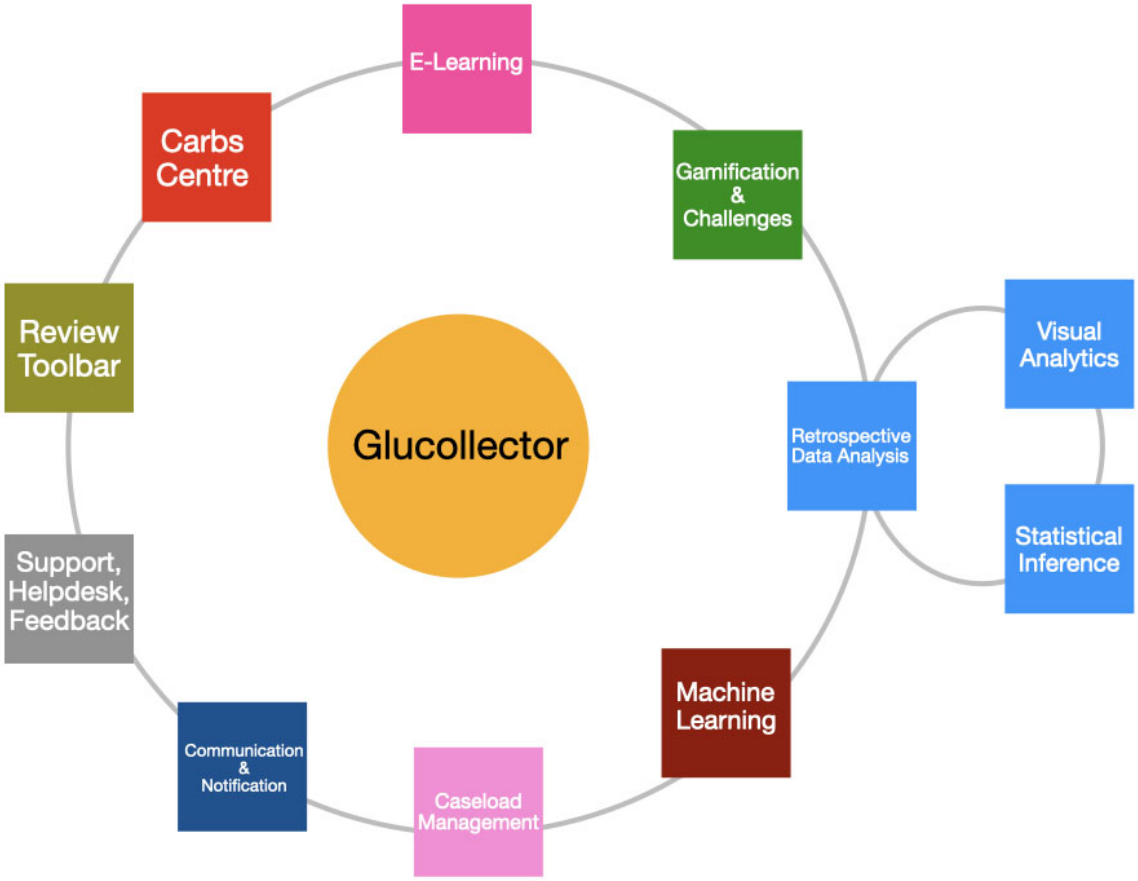


Fig. 7.1 Functional architecture of the Glucollector

DAFNE_EX

Search

Hospital No	User Name	Last Upload Date	7d Hypo %	7d Hyper %	7d Average (mmol/L)	7d #Readings / Day	30d Hypo %	30d Hyper %	30d Average (mmol/L)	30d #Readings / Day	Yellow Flags	Score
TT4444	Severe Illness Example 1	29/09/2017	0.0	85.0	10.1	2.9	0.0	85.0	10.1	0.7		36.05
AA1111	Example 9 Above Range Bgs Across The Day	08/11/2017	0.0	61.1	9.4	2.6	0.0	61.1	9.4	0.6		32.15
TT4444	Minor Illness Example 1	29/09/2017	0.0	62.5	9.7	2.3	0.0	62.5	9.7	0.5		31.50
TT4444	Splitting Basal Insulin Example 1	22/09/2017	0.0	40.0	7.7	2.9	0.0	40.0	7.7	0.7		30.20
TT4444	Overnight Basal Assessment Example 1	22/09/2017	0.0	31.2	7.0	2.3	0.0	31.2	7.0	0.5		28.25
TT4444	Once Daily Basal Assessment Example 1	22/09/2017	0.0	41.7	7.9	1.7	0.0	41.7	7.9	0.4		28.25

Fig. 7.2 Clinician dashboard

Summary

Number of Readings	Average Number of Readings/Day	Average(mmol/L)	Estimated HbA1C(mmol/mol)	%Above Range	%In Range	%Below Range	Variation(SD)	Min(mmol/L)	Max(mmol/L)
54	3.6	10.1	59.0	42.6	55.6	1.9	4.6	3.9	26.2

Fig. 7.3 Statistical summary of the glycaemic control on Glucollector

etc). The transferred data are checked for integrity and duplication. If the patient had a high or low reading, they would be prompted to further comment on their data. This helps the patient and the clinician to look for patterns and improve the patient's awareness. Patients can request a feedback from clinicians or reply to a feedback received. The retrospective analysis of the presented data by the statistical information and/or visual analytics yields a structured analysis for finding patterns and treatment adjustment.

Retrospective data analysis

Informed decision making for a better outcome requires reliable data, timely diagnosis, and interpretation. Hence, statistical information and graphs are utilised to infer hypotheses to help with treatment adjustment in an objective and timely manner.

Statistical Inference A summary of statistical information can provide an overall state of the glycaemic control for the specified period. Figure 7.3 shows the statistical summary on Glucollector (Figure 7.4) . The information is colour coded to provide context to the presented value. Further to this goal, arrows are used to display the trend in which values are following.

The aforementioned statistical information are reported passively on a webpage. To use a more active model, sets of flags are defined utilising rule-based reasoning referred to as Amber flags. The amber flags are processed to produce message notifications to both patients and clinicians depending on the severity of the rule.

The amber flags are divided into two levels. At the first level, the notification is sent to the patient only. The first level amber flags are motivational notifications asking the patient to review their data and visit the E-Learning material to help with their diabetes management.

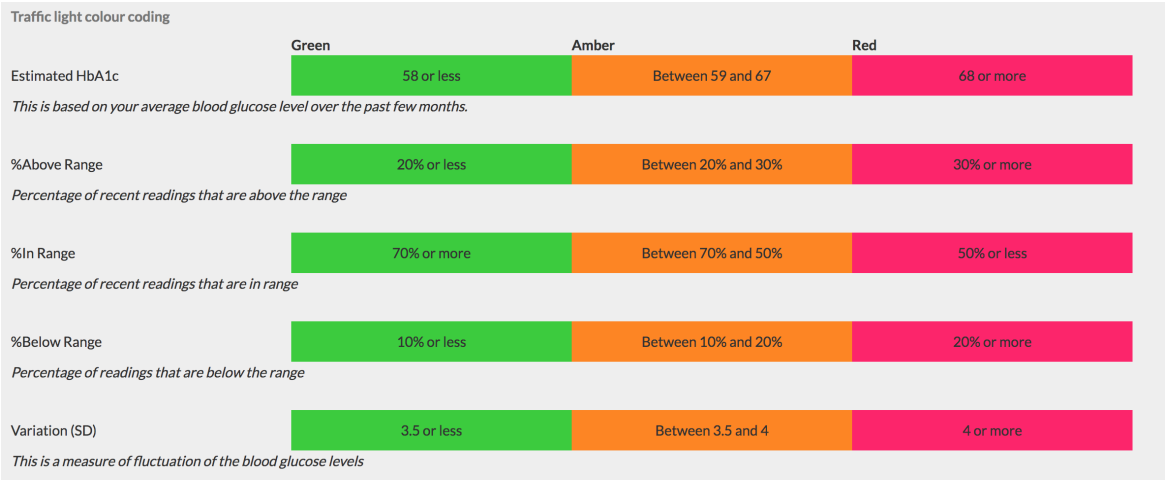


Fig. 7.4 Colour scheme of the summary table

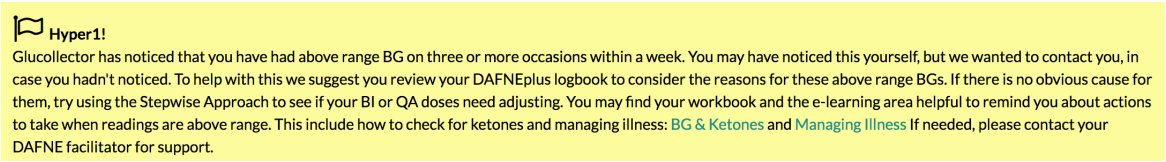


Fig. 7.5 The level one hypo amber flag notification

At the second level, both the patient and clinicians are notified. The second level amber flags indicate a persisting problem which requires an intervention by clinicians. This provides an objective measure driven by data to proactively tackle the shortfalls in the complex diabetes management. The targeted reasons were decided by a group of clinicians, whilst the content was created by the psychologist expert in the behaviour change.

To perform the above flags, the patient needs to have access to the system and be able to upload data. Hence, any sign of a problem in engaging with the system such as no login, no upload, or no communication would trigger an engagement amber flag that would notify the engineers and clinicians to investigate further.

Considering the above explanation, the following rules are used to trigger a flag:

- Uploading amber flag is defined as:
  - This flag is only processed if there was a website login in the previous 70 days .
  - No meter upload being attempted in 8 days is to be flagged (UPLOAD1).
  - The flag will not result in a message if another message was issued last week.
  - If 28 days since the previous uploading message issued and flag occurs issue level 2 message (UPLOAD2).
- Hypo amber flag is defined as:
  - Blood glucose (BG) reading <3.1 mmol/L counts as a qualifying hypo-event
  - Repeated qualifying hypo-events within 2 hours only count once
  - 3 or more hypo-events over the previous 7 days is to be flagged (HYPO1).
  - The flag will not result in a message if another message was issued last week
  - The hypo-events are processed as if leading by one day over hyper events to ensure hypo events have priority.
  - If 7 days since the previous hypo message, and the flag occurs again, issue level 2 message (HYPO2).

- Hyper amber flag is defined as:
  - BG >14.9 counts as a qualifying hyper-event unless the measurement is within 3 hours after carbohydrate data record.
  - Repeated qualifying hyper-events within 2 hours only count once.
  - 3 or more hyper-events over the previous 7 days is to be flagged (HYPER1).
  - The flag will not result in a message if another message issued in last week.
  - If 7 days since the previous hyper message, and the flag occurs again, issue level 2 message (HYPER2).
- Engagement amber flag is defined as:
  - Engagement stars calculated over 28 days from the last upload if upload within the last 7 days.
  - Each star is calculated over the 28 day period as 4+ upload over 28 days, 16+ days of three+ carbs a day, 16+ days of three+ quick acting insulin a day, 16+ days of 4+ BG a day, and 16+ days of basal insulin records.
  - A adjustment period of up to 7 days is applied since date of last upload.
  - This flag is only processed if there was a website login in the previous 70 days.
  - Two or fewer engagement stars over the previous 28 days is to be flagged (ENGAGE1)
  - The flag will not result in a message if another message issued in last week
  - If 14 days since the previous engagement message and the flag occurs again, issue a level 2 message (ENGAGE2).

visual analytics The graphical unit creates the visualisation of the available data. This is designed to be easy to navigate and provide simple to understand visuals for both patients and clinicians. These visuals provide inferences to help with pattern finding and data interpretation.

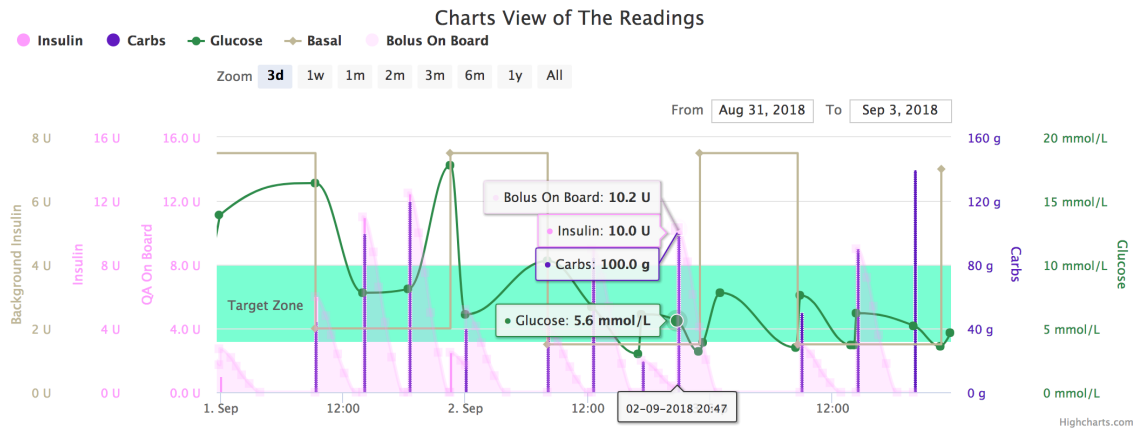
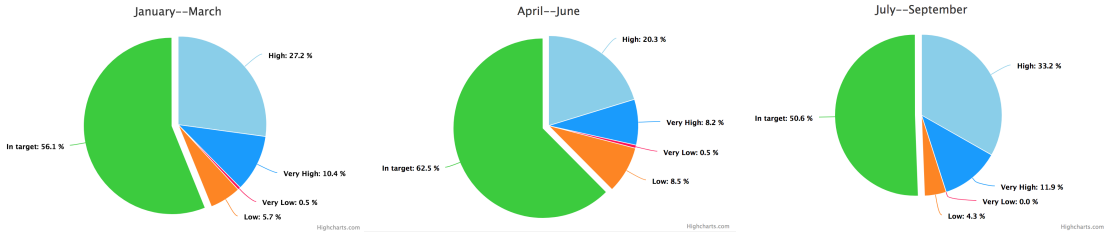


Fig. 7.6 Full chart

Figure 7.6 shows the time series data of a typical type 1 diabetes patient in the Full chart of Glucollector. The SMBG readings are interpolated using a cubic spline for increased readability. Bolus doses are used to calculate the bolus on board and provide a visual reference to its effect on the glucose levels. Carbohydrate intake and basal injections are added to improve the context of the data.

The Full chart (Figure 7.6) includes a lot of information and many conclusions can be deduced based on the graph. Therefore, before arriving at this level of details, a structured approach can be followed utilising summaries and diagnostic graphs to construct sets of hypotheses that can then be investigated using the full chart. In the following, we explore different graphs by taking the presented data of a user to demonstrate a use-case.

Long-term summaries provide an overall progression of glycaemic control over longer periods. The 3-month percentages of hypo, hyper and in-target BG readings are represented in the pie chart of quarterly summaries. The 3-months period relates to HbA1c through the average age of red blood cells. Hence, quarterly summaries can represent a similar period in glycaemic control terms. In the case shown in 7.7, one can deduce that there is a need to reduce the hypoglycaemic and hyperglycaemic episodes, particularly the very high BG ranges. Looking at Figures 7.7a and 7.7b, there seems to be a reduction in hyperglycaemic events and an increase in the in-target and hypoglycaemic results. This pattern is usually observed when attempting to improve glycaemic control. However, the effect is not continued



(a) Jan to Mar (b) Apr to Jun (c) Jul to Sep

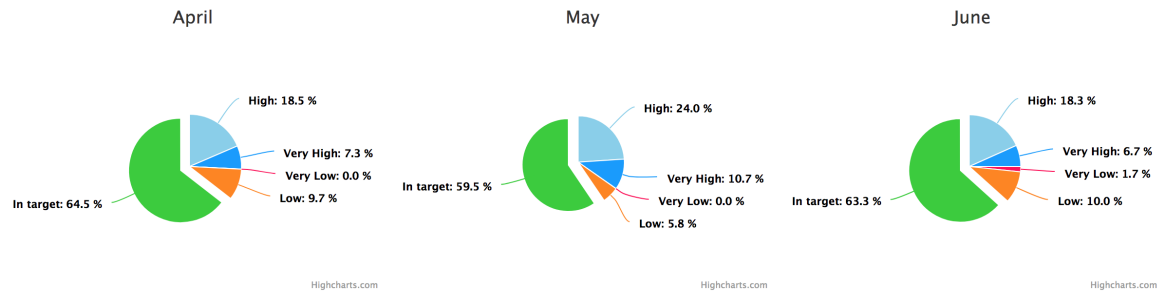
Fig. 7.7 Quarterly summary of the glycaemic control measured in percentage of blood glucose below, above and in range.

over to the months of July to September (figure 7.7c). Therefore, we can target this period to find an explanation for the change in the trend.

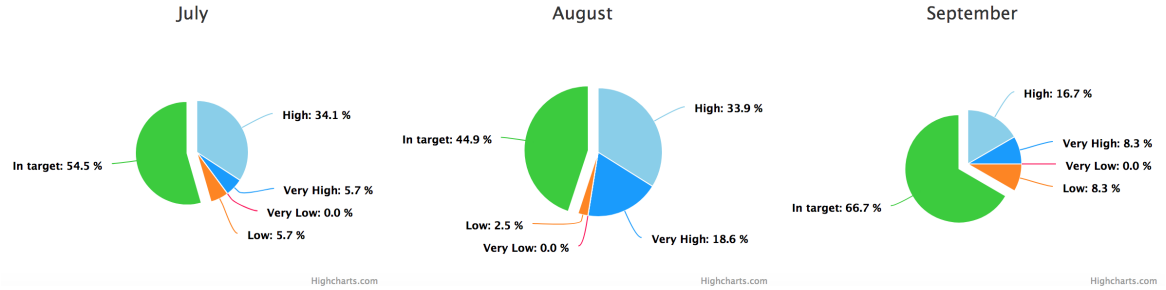
The quarterly summary is useful to relate the glycaemic control to HbA1c progression. However, this is a high-level view of the data. More detailed long-term summaries can provide more insights. Figure 7.8 shows a month-to-month breakdown of the glycaemic control. It can be seen that the patient is almost consistent with a larger in-target piece of the pie chart, and smaller pieces of hypos and hypers during the presented six months, except the month of August. As noticed previously in the quarterly summary of Jul to Sep, there is an unusual increase in the percentages of out-of-range BG readings. The monthly summary shows that August has skewed the result which can be investigated further. This provides more insight into the data and directs the analysis objectively in a timely manner.

A more granular look at these data is possible through the weekly summary. Noticing the weekly summary, Figure 7.9, that indeed the month of August has been a difficult month for the patient. However, recovery of the control is observable as the month has progressed (larger pieces of green from week 32 to week 35). These show how the patient has worked through their diabetes control over time.

Continuing with the analysis of the data through graphs, we can notice that although the patient has gained some control, the percentages of hyperglycemia remain high. Further levels of detail can be provided utilising short-term summaries that can help to unfold a better view for diagnosis. Looking at different periods of the day can be a good starting point. Therefore, the weekly average of the results segmented based on the time-blocks of the bolus

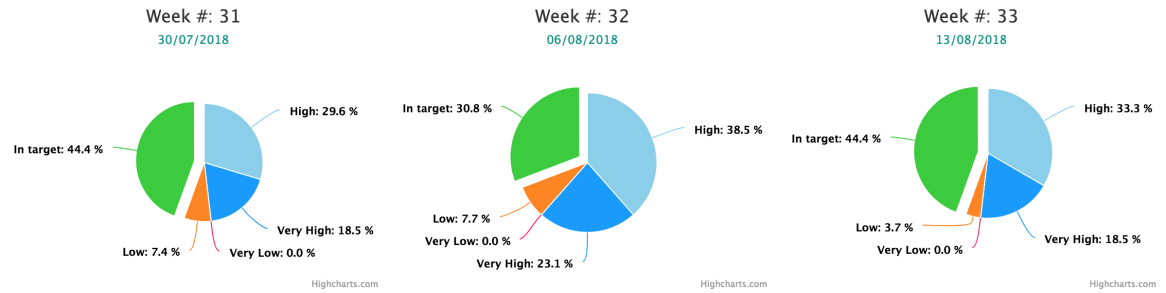


(a) Apr to Jun

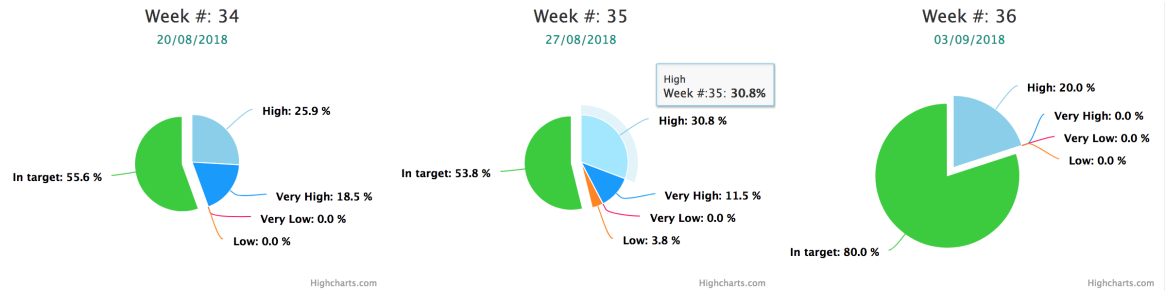


(b) Jul to Sep

Fig. 7.8 Monthly summary of the glycaemic control measured in percentage of blood glucose below, above and in range.



(a) Weeks 31 to 33



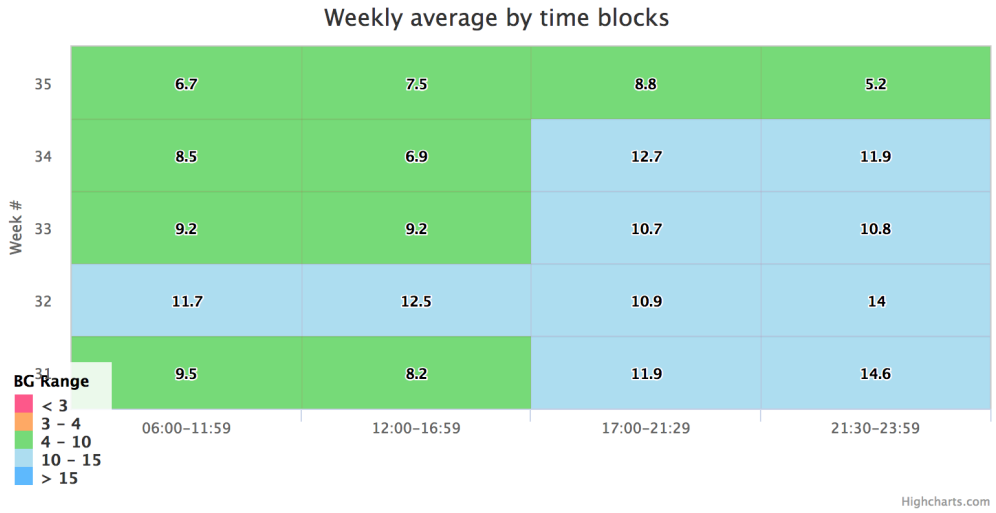
(b) Weeks 34 to 36

Fig. 7.9 Weekly summary of the glycaemic control measured in percentage of blood glucose below, above and in range.

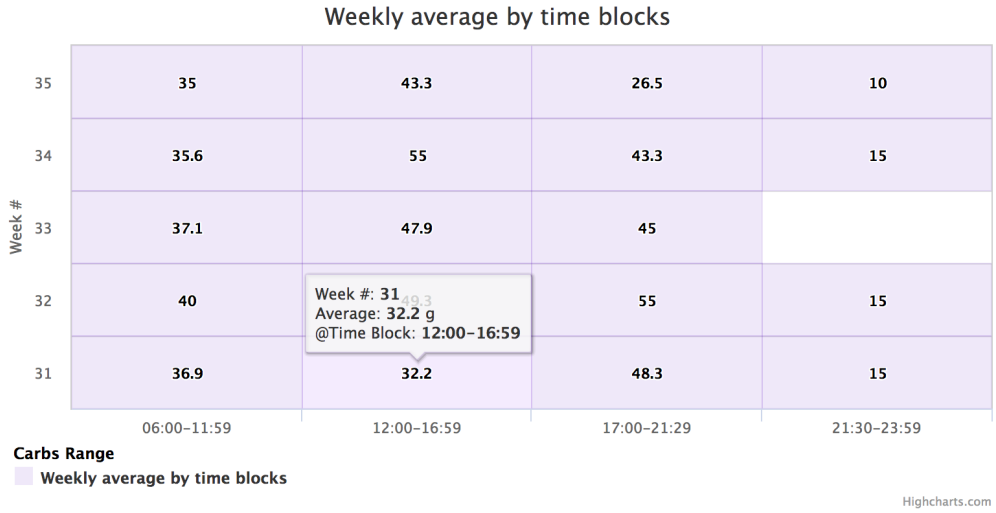
advisor can help to identify possible daily patterns. As shown in Figure 7.10a, the glycaemic control in time-blocks 17:00-21:29 and 21:30-23:59 is out-of-range. Figure 7.10b shows a relatively consistent carbohydrate intake. Figure 7.10c shows proportionate insulin injections to carbs. It can be noticed an increase in carbs intake is reflected in the relative increase in insulin doses. Since the patient on average does not show a high variability in carbs intake and insulin injections over different weeks, it can be suggested that the high BG levels are a result of incorrect sensitivity factor and/or carbs ratio.

Summary graphs and statistics are valuable tools to infer long-term control and guide to a possible short-term hypothesis for diagnosis. However, there are other ways to help with the diagnosis process and hypothesis investigation through visual analytics. These graphs are more targeted in purpose and clearer instruction for navigation of hypotheses can be advised.

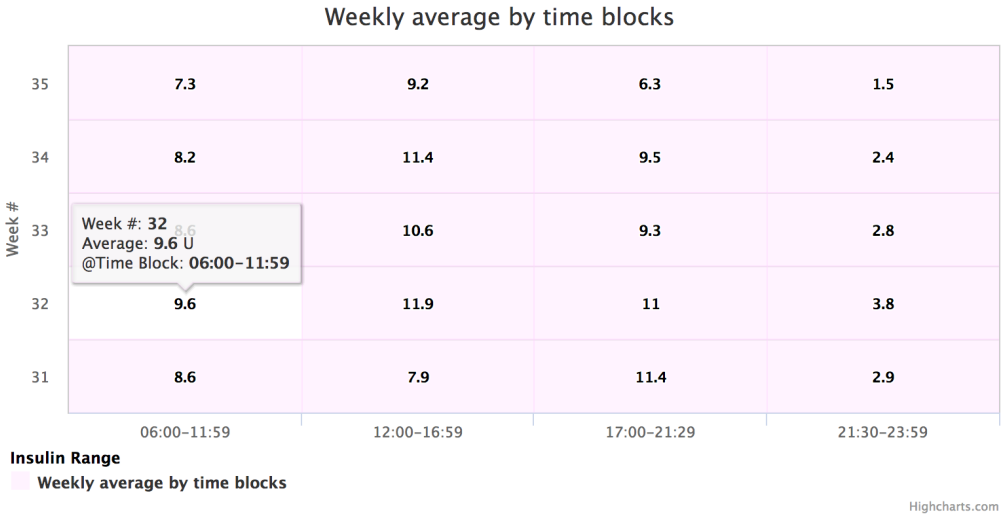
Figure 7.11 shows the Dot plot. Each dot on the graph represents how the previous BG compares with the next BG taken. This then gives an indication of how the dose calculation has worked. The chart is divided into nine regions. The aim to get as many dots in the green regions (2 (BG goes from hypo to in range), 5 (BG starts and stays in-range - the ideal) and 8 (BG goes from above range to in range)). Frequent dots in region 9 indicates BG starts above range and stays above range. This could indicate that the bolus advisor settings requires adjustments (i.e. Timeblocks or insulin sensitivity factor (ISF)) or consistently underestimating carbs. Region 7, dots here indicate above range BG are followed by hypos. Frequent dots in this region is an indication of overcorrection (incorrect ISF or not following advice on the meter and adding extra corrective). Region 1, hypo and stay hypo. This can be because of the retests. If it is not a retest, frequent dots can be an indication of frequent asymptomatic hypoglycemia or under treating hypos. Region 3 is an indication of a hypo resulting in a consequent above range BG; possibly indicating over-treatment of hypo. Region 4, an in range BG resulted in hypo; an indication of over-estimating carbs, physical activity, or high-fat meals. If this is happening during one particular time block, this could indicate the quick acting (QA) ratio or background insulin (BI) dose needs reviewing. Region 6, an in range BG resulted in an above range BG; an indication of under-estimating carbs or



(a) Blood glucose



(b) Carbohydrates



(c) Bolus (QA) insulin

Fig. 7.10 Weekly average based on the time-blocks of the bolus advisor.

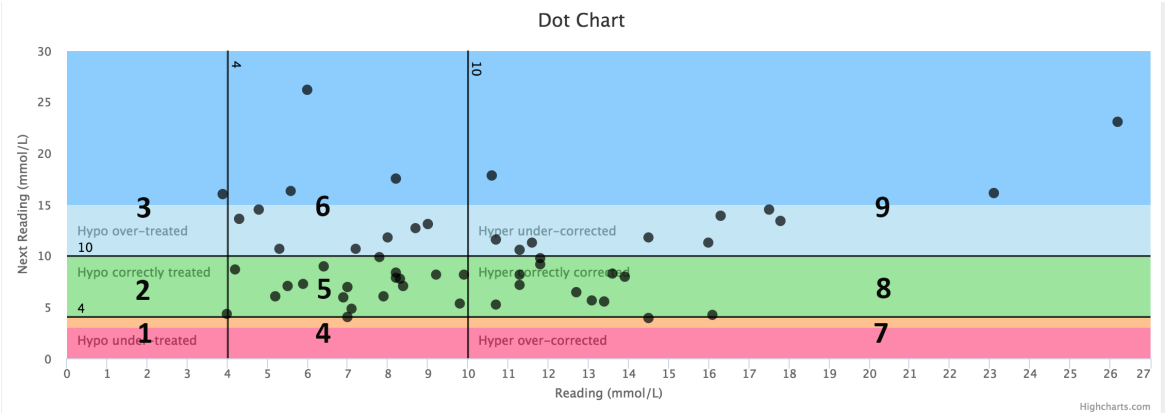


Fig. 7.11 Dot chart

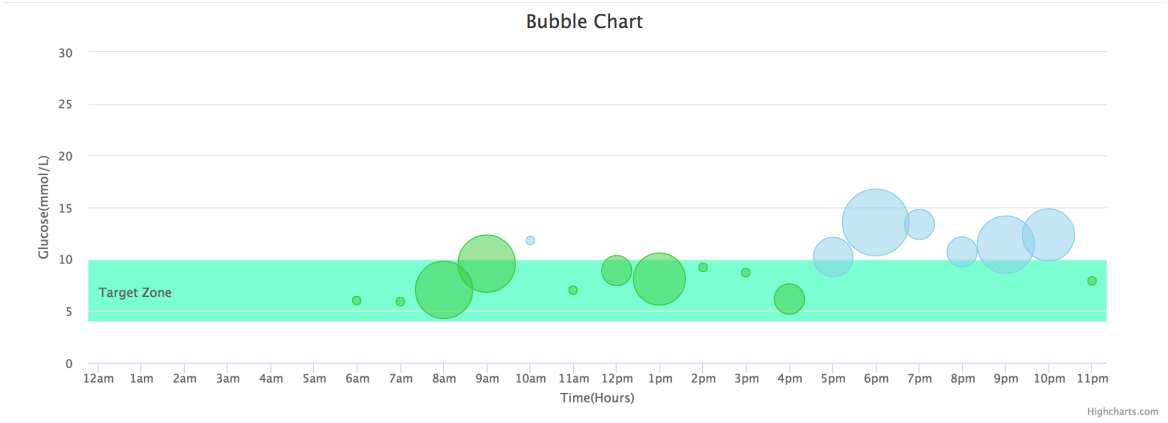
high-fat meals. If this is happening during one particular time block, this could indicate the QA ratio or BI dose needs reviewing; or testing too quickly post-prandially.

For this particular patient, regions 9 and 6 include many dots. This is an indication of high readings resulted from the incorrect management of the previous glucose reading. Therefore, the previously presented hypotheses for regions 9 and 6 holds. However, there are many readings in the green regions of the dot plots. Hence, further investigation into which hours of the day result in the high readings is required.

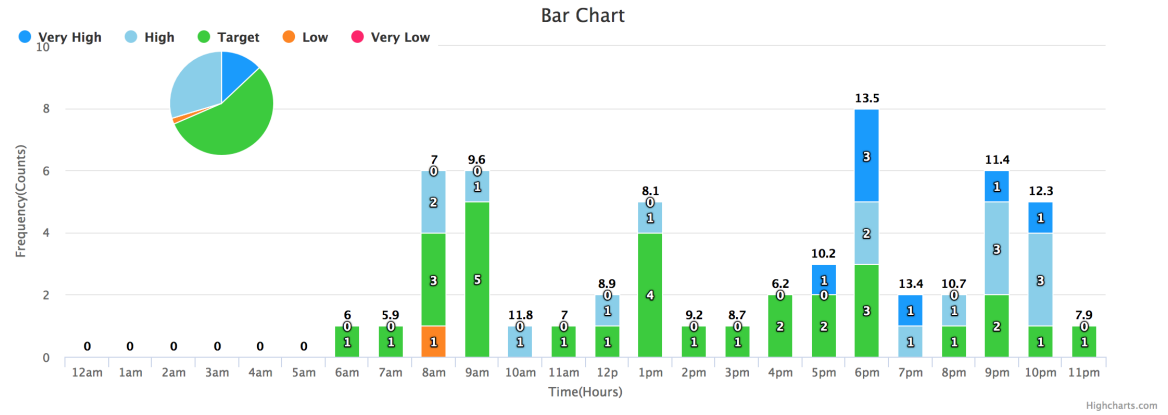
The Bubble chart of the BG readings can pinpoint the targeted hours. As shown in the figure 7.12a, the evening hours (> 4pm) are on average above the range. A more detailed view is shown in the bar chart figure 7.12b. The bar chart provides details on how the average bubble chart is deduced and can confirm the higher ranges of BG in the evening. Also, it can be seen that a higher percentage of readings are above range in the evening (Figure 7.12c). The percentage bar chart helps to view the result in terms of percentages of readings occurring in each hour.

Next is to investigate the presence of such patterns in the days of the week. The day by day bubble chart (Figure 7.13) shows that the pattern is recurrent; more blue bubbles in the afternoon period.

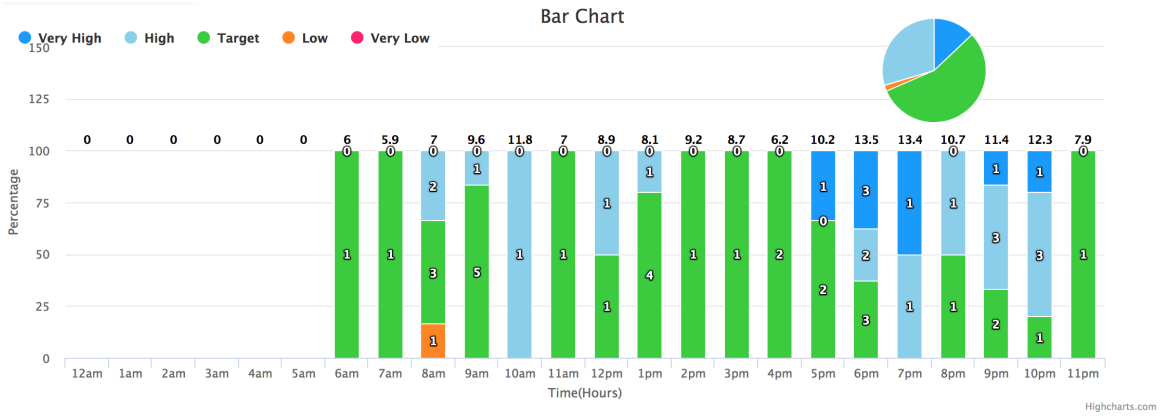
These graphs provide more detail on the glycaemic patterns of the patient and confirmed the hypothesis of requiring a possible change in the sensitivity factor and/or carbohydrate ratio.



(a) Blood glucose



(b) Bar chart



(c) Percentage bar chart

Fig. 7.12 Hourly distribution of BG readings

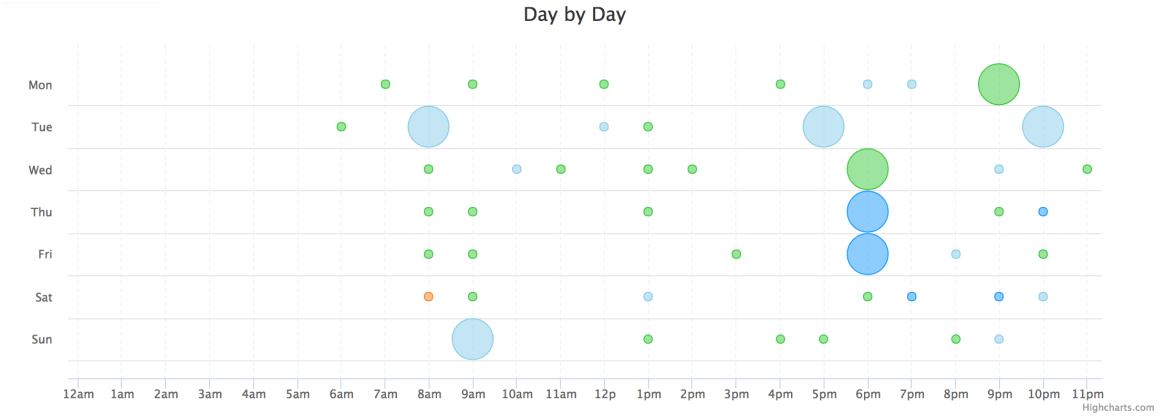
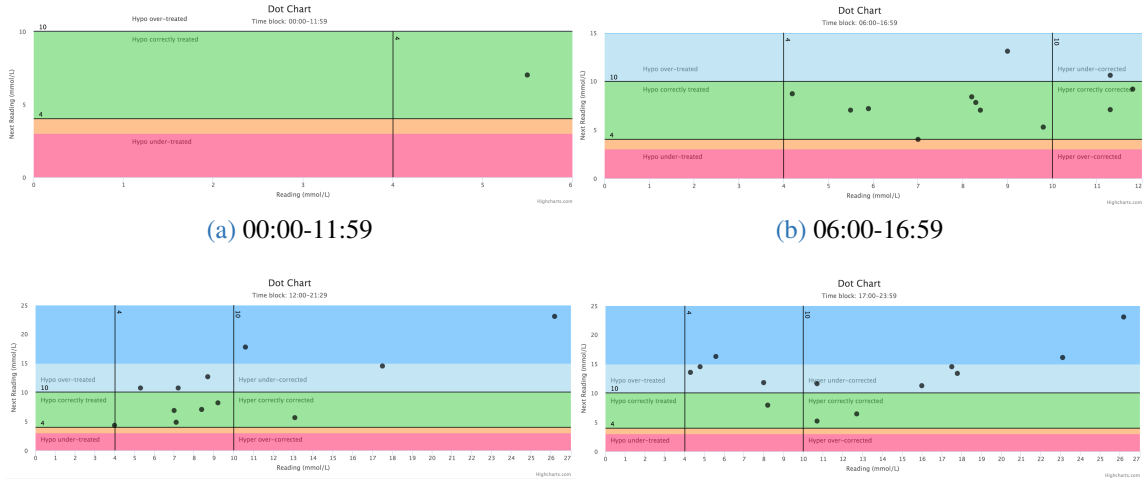


Fig. 7.13 Day by day bubble chart

By referring to the dot chart of the time-blocks, we can investigate the time-blocks requiring amendment. As shown in figure 7.14, the transitions of time-blocks 12:00-16:59→17:00-21:29 and 17:00-21:29 →21:30-23:59 present a high percentage of dots in the regions 9 and 6. Although there are few dots in those regions in the time-block transition between 06:00-11:59 to 12:00-16:59, the majority of the dots are in the green region. Therefore, the focus for review of bolus calculator settings is on the time-blocks 12:00-16:59 and 17:00-21:29. At this stage, a look back at the full chart might help to investigate the bolus on board effect on the patient's glucose levels to aid with adjustments of either correction or carbs ratios.

For the hypoglycemic episodes, one might be interested to see the adherence to the retest procedure. Figure 7.15 shows the time passed after a hypoglycemic reading and the next test. In the presented graph, except for two occasions, the patient has carried out a retest within 30 minutes or less.

For CGM users, the aforementioned structured review is applicable. We can look at a CGM user to demonstrate a possible pathway to diagnosis. Figure 7.16 shows the percentage bar chart of a CGM user. The percentage bar chart is particularly useful for CGM since the sampling rate is constant. A look on the graph shows a high percentage (>25%) of low glucose readings between the hours of 7 pm to 9 pm.



(a) 00:00-11:59 (b) 06:00-16:59

(c) 12:00-21:29 (d) 17:00-23:59

Fig. 7.14 Dot charts of the combined two consecutive time-block readings

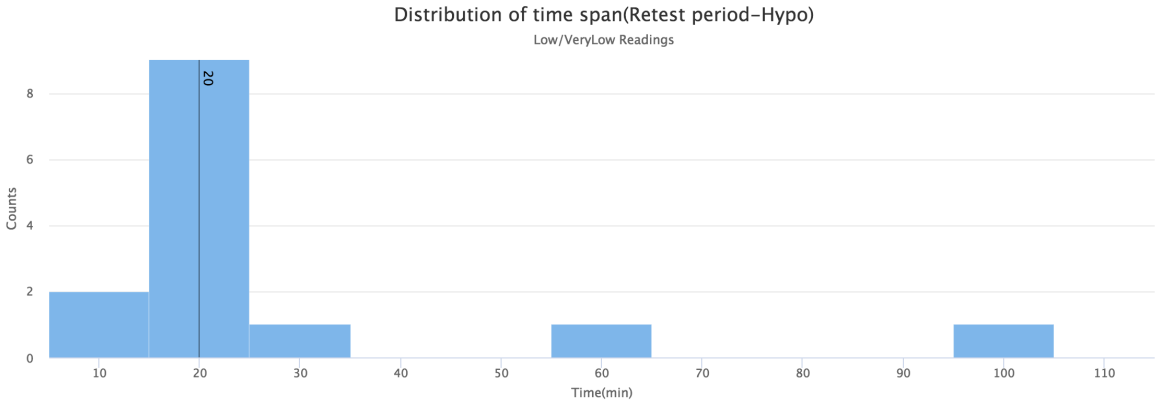


Fig. 7.15 Time in minutes to perform a retest after a hypo reading

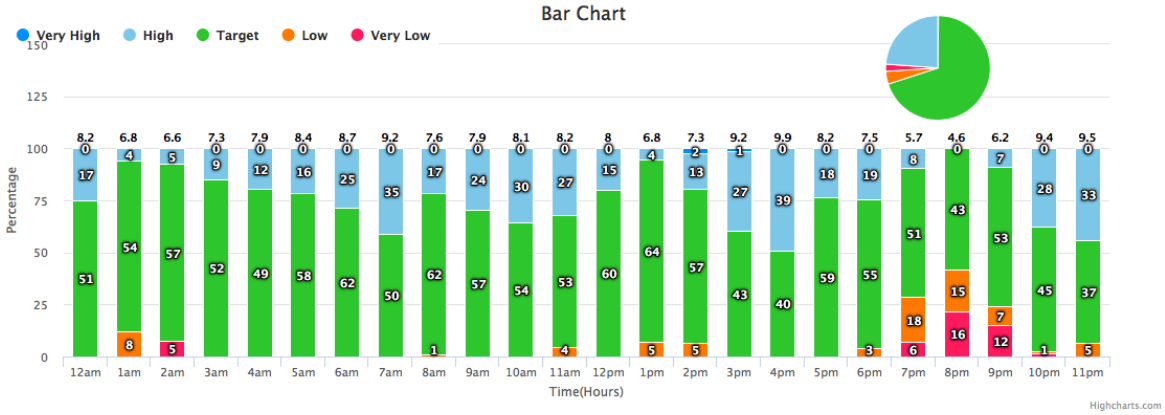


Fig. 7.16 Percentage bar chart for a CGM user

We can investigate the pattern for the hypoglycemia around those hours by looking at the overlaid daily charts for the duration of a month categorised on a weekly basis. Figure 7.17 shows the graph divides the data based on the day of the week. Each particular day is overlaid with the same weekday of the past three weeks. Each colour and shape on the graph represent blood glucose readings of a certain day. Looking at the graphs, we can see that there is a pattern of low glucose levels at around 8 pm on every day of the week in the past month. This indicates a possibility of incorrect time-settings and/or ratios for that particular hour or perhaps lifestyle related such as post-work alcohol that is not considered when administering insulin. Also, notice except the Mondays and Saturdays, the hypo treatment has resulted in hypers at later hours, a sign that the patient is over-treating. Further investigation can be sought by looking at the same graphs of SMBG-case presented previously.

This retrospective analysis requires reliable data and engagement from patients. Therefore, the gamification and challenges are utilised to encourage users in engagement and adherence.

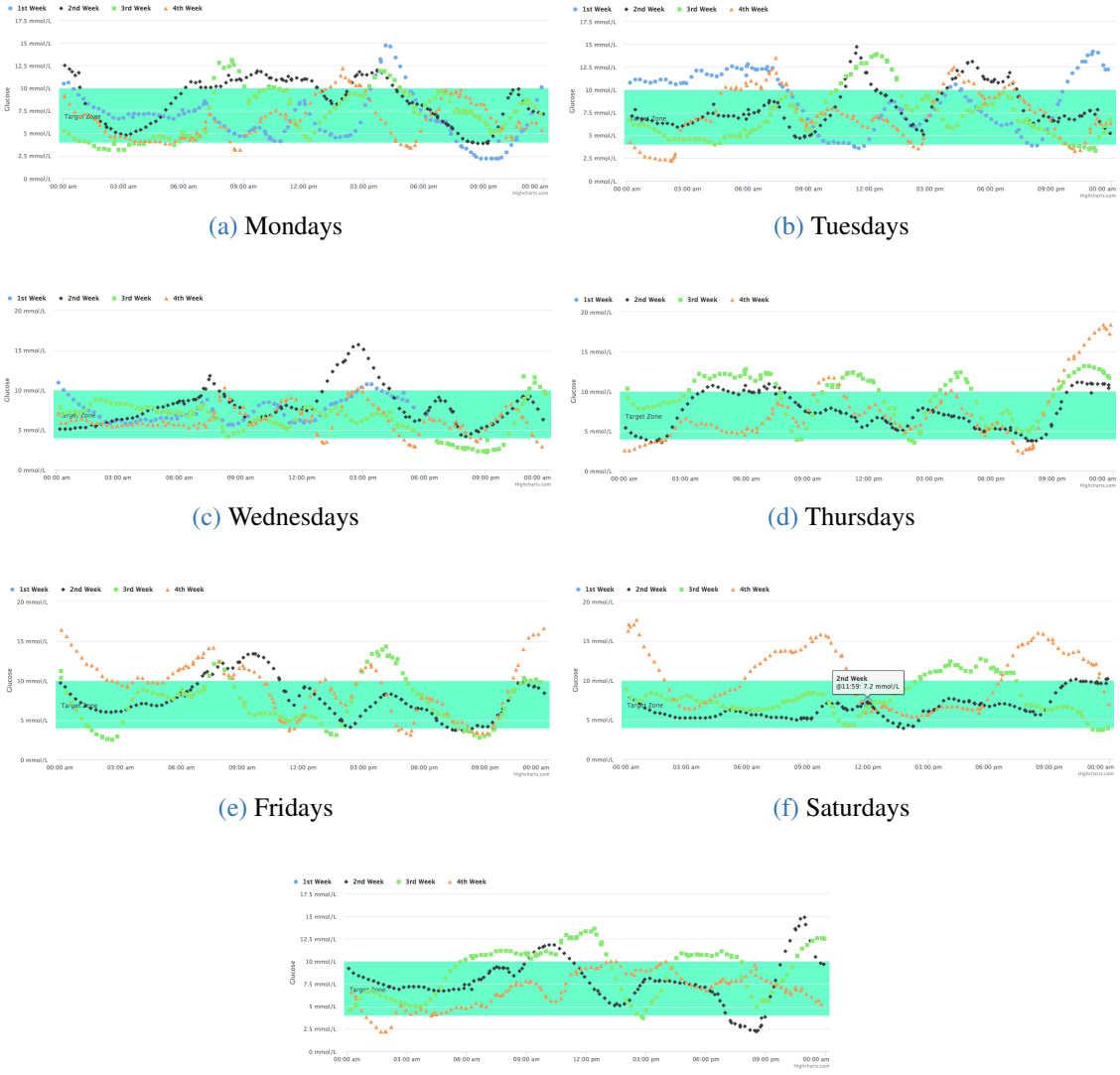
7.3.2 Gamification and challenges

Recommendations of the National Institute of Health and Care Excellence (NICE) and American Diabetes Association (ADA) on SMBG frequency, preprandial BG targets, and achieving a better HbA1c level (<58 mmol/mol) embody the three main factors of engagement, glycaemic control and the golden goal for efficient diabetes management. In line with these recommendations and concepts, gamification and challenges are set for patients to achieve and acquire the corresponding rewards.

Engagement

We have defined a five-star score for patient's engagement. The engagement stars are shown on the dashboard of the patient upon logging in. These are awarded for adherence to SMBG frequency and record keeping as follows:

- A star for four glucose readings a day
- A star for three carbs readings a day



(a) Mondays

(b) Tuesdays

(c) Wednesdays

(d) Thursdays

(e) Fridays

(f) Saturdays

(g) Sundays

Fig. 7.17 Overlaid daily charts of the past month of a CGM user

Fig. 7.18 Dashboard challenges and awards

- A star for three QA doses recorded a day
- A star for recording background insulin
- A star for uploading on a weekly basis

Glycaemic control

Glycaemic control is an important factor in improving HbA1c and quality of life for patients. Based on DAFNE, measurement of BG levels at the three main meals of the day and before bed is recommended. A clock is awarded for the in-target readings of these measurements.

Golden goal

Ultimately, the improvement in HbA1c is the golden goal of diabetes management. Therefore, a golden star is awarded if the patient achieves levels below 58 mmol/mol, whilst having <10% of readings in the hypo range.

Carbs challenge

For many patients estimating carbohydrates accurately is a challenging task. This requires practice and memorisation. To help improve these skills, carbs challenge is set for patients to undertake and receive points for guessing the carbs content correctly. The game begins by hiding the face of four cards of foods. Then, the patient is faced with the choice of choosing a card to be revealed. The patient guesses the amount of carbs in the presented food. If the guess was within one gram of the correct amount they receive 10 points; if within 5 grams, 5

points; otherwise no point is awarded. If any points were awarded, the user gets a chance to have another go on the remaining three cards; this time the points are doubled since the patient is on a streak. However, if no points were awarded, the chosen cards' correct amount is revealed and the card is put back for a reshuffle. Now, the user can choose again from the shuffled four cards. At this time, the user has seen one of the cards and knows the correct answer. If they get lucky and choose the first card again they have a higher chance of scoring 10 points. Each round, two cards can be drawn. After each round, the remaining two cards are revealed to the users so they can have a look and be reminded of their carbs content.

7.3.3 Carbs centre

The Carbs centre on Glucollector was designed to reflect patients' effort on accurate carbs counting and record keeping. Patients can find accurate carbs information on a variety of foods using the carbs centre. They can create meals that they have consumed and attach the content to a carbs record on the logbook. This process is automated to reduce the burden of record keeping. The patient provides the date and the content of the meal; Glucollector finds the corresponding carbs reading to attach the content to it. The patient can create favourite lists and have access to recent records of their food logs to speed up the process. This is all in an attempt to encourage patients to provide more context easily and accurately with minimum effort. Further to this goal, a reviewing toolbar was added to semi-automate the review process for patients.

7.3.4 The review toolbar

The review toolbar attempts to intelligently collect context from patients for the review process. Utilising rule-based reasoning, it includes Hypo and Bolus-adherence case collection. The rules and reasons were developed with consultation of the clinical team at STH.

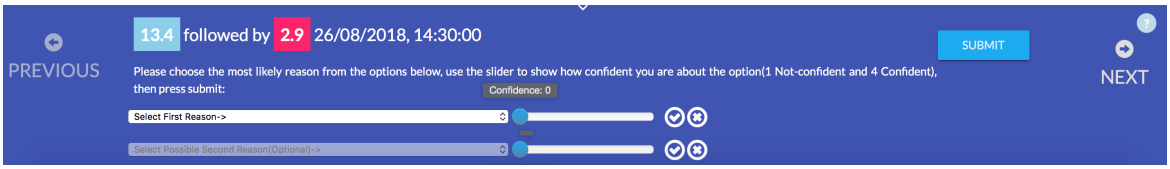


Fig. 7.19 Hypo collector toolbar

Hypo case collector

The hypo case collector is a tool to navigate the relevant hypoglycemic episodes. It provides the patient sets of possible reasons for the occurrence of the hypo episodes. Then, the patient can add the appropriate reason and their confidence level in the provided answer.

TABLE 7.1
HYPO CASE COLLECTOR REASON FOR PATIENTS TO CHOOSE THE MOST RELEVANT ONE

	Hypo Reasons
1	Over-estimated carbs
2	Did not eat all of the meal
3	Unplanned physical activity
4	Prolonged physical activity, but insulin not reduced enough
5	Alcohol
6	Insulin to carb ratio (QA ratio) for the meal beforehand set too high
7	Background insulin too high
8	Forgot to over-ride the advice for mealtime QA insulin following earlier hypo
9	High fat meal so carb absorbed slower than expected
10	QA correction lowered glucose too much, insulin sensitivity setting needs changing
11	Injected QA as opposed to background insulin by mistake, or vice-versa
12	Specify others

The rules to identify a hypo case of interest were devised by the medical supervisory team. These included:

- Any results below 4 mmol/L is a hypo candidate.
- Hypo results within 30 minutes are counted as an episode (Avoiding retest events).
- Similarly, for CGM, half an hour average of the hypo results are counted as an episode.
- An inquiry for review occurs on each episode.

- Previous non-hypo results should be presented to investigate possible links (e.g. over treatment of hyper).

Bolus case collector

The bolus case collector is a tool to navigate the bolus records with discrepancies to the recommended doses. The Glucollector has a bolus calculator that retrospectively looks at the data and uses rule-based reasoning to flag the relevant bolus records to ask patients for a possible reason for non-adherence to the settings and recommended doses. The implemented bolus calculator is based on the published work that is also utilised in Accu-Chek Expert meter.

TABLE 7.2
BOLUS REASONS

	Bolus Reasons	
	Higher dose	Lower dose
1	Decreased physical activity	Increased physical activity (and did not use exercise setting)
2	High fat meal	Drinking alcohol
3	Meter keeps advising too little quick acting insulin, but unsure how to change the settings	Recent hypo so being cautious
4	Other(specify)	Meter keeps advising too much quick acting insulin causing hypos, but unsure how to change the settings
5		Other(specify)

The rules to identify the non-adherence to advised bolus are as follows:

- Acquire the most recent bolus advisor setting from the meter, in particular, time-blocks, insulin sensitivity factor (ISF), insulin to carbs ratio (ICR) and active time for the insulin.
- Each injection of insulin must at least be followed by either Carbs or blood glucose reading; or both.
- Determine using historical injections whether the user is on 0.5 or 1 unit of insulin increment.
- If 0.5 unit increment, any discrepancy higher than 0.5 unit is flagged.

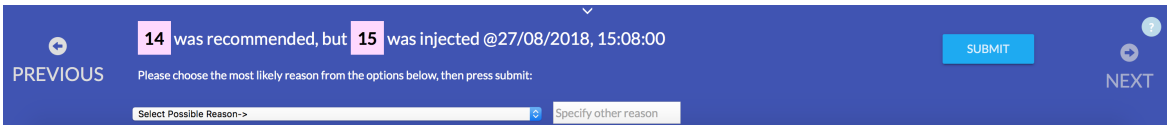


Fig. 7.20 Bolus collector toolbar

- If 1 unit increment, any discrepancy higher than 1 unit is flagged.

7.3.5 e-Learning

The e-Learning modules were based on the DAFNE curriculum and included carb counting, SMBG adherence, hypo treatments, exercise and illness management. Modules on insulin dose adjustment, technology use and relapse prevention were also included. Lifestyle topics such as alcohol, eating out, healthy living and travel were supported as well. Each module includes static information and dynamic interactive features to promote engagement. The modules are available for patients to explore on a self-paced pathway. They can also be recommended to the patient either by clinicians or the system in a data-driven fashion utilising the amber flag features. As patients progress with each module, they receive a score on their progress. Additionally, the patient can receive scores on the quizzes throughout the e-Learning modules. These are designed to motivate and support participants to sustain self-management behaviours in everyday life.

7.3.6 Evaluations

The UoS volunteers cohort were asked to fill in a usability questionnaire and comment on their experience of using the system. The usability survey showed a high satisfaction (Figure 7.22). An overall usability score of 81.8.

The variety of views were emphasised by the users: *"I like the variety of way of presenting the data."*. And others expressed preferences on graphs: *"The range of ways that data is presented across the Glucollector system is excellent - the hourly glucose "bubble chart" is particularly useful."*

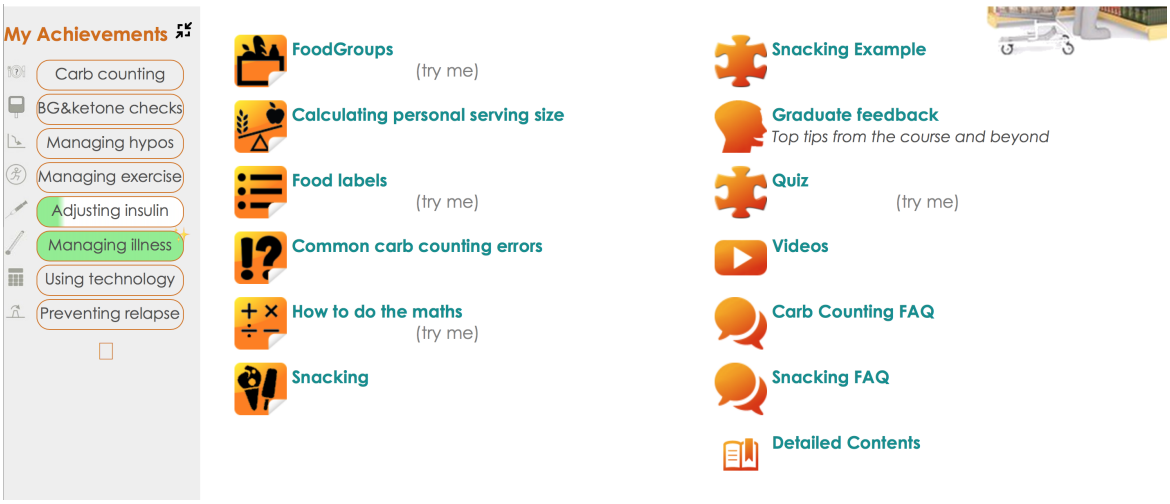


Fig. 7.21 e-Learning modules and structure

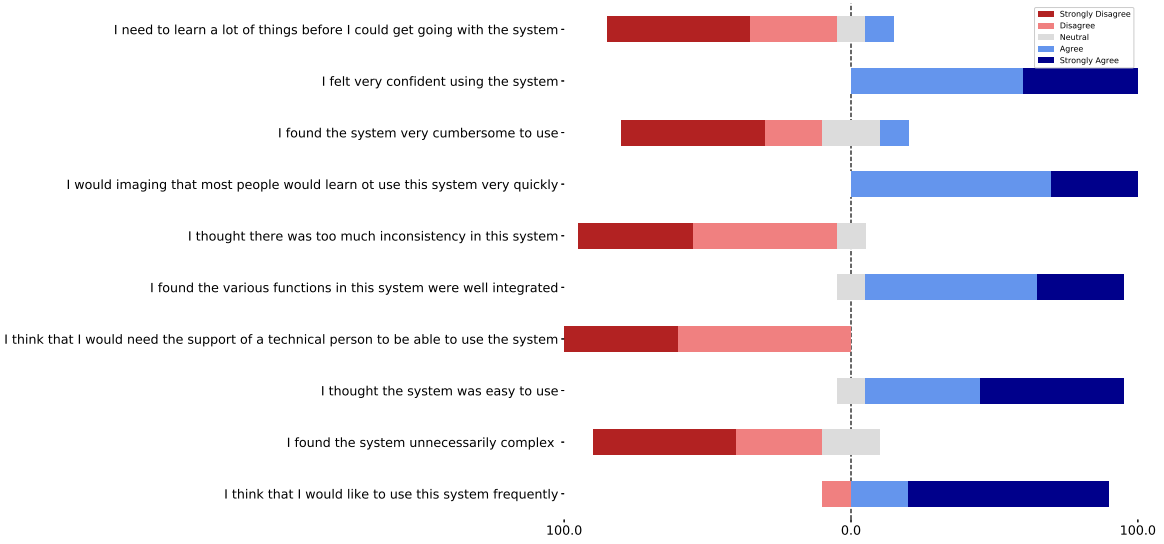


Fig. 7.22 Usability questionnaire answers of UoS volunteers cohort.

They also commented on their experience compared to previous care: *" I normally don't keep a diary so normally only download my meter every 4-6 months at clinic, so it's good to be able to see it at home."*

Half of the UoS volunteers continued to use the system past their two-week period. An ethics amendment to support their continuation was submitted and approved allowing individual participants to continue using the system.

The first wave of semi-structured interviews were carried out with DAFNEplus groups after 6 months from the start of the pilot trials. The patients expressed the availability of the service and ease of access and use as an uptake of utilising technology in their diabetes management; stating: *"Being able to access it via tablet makes reviewing data easy and convenient"*

In terms of aesthetic appeal and views patients expressed their opinion as *"It's fun to look at"*. Appreciation of the variety of views, charts and summaries were looked as useful and engaging.

"It is good to have so many views to choose from and see the data presented in different ways, e.g it's nice that they've done that to just- if it was just one format, it would seem a bit say linear"

Colour coding of the charts and data were significantly viewed as helpful and informative. *"Colour coding makes it easier to spot patterns"*

Since the coloured graphs made spotting progress and patterns easier, the prospect of being a motivational reinforcement was expressed:

"it just gives you the motivation to carry on doing what you're doing I think, cause if you see lots of stuff in the green you sort of feel a bit good about yourself"

Also, the statistical summary was presented as informative and motivating; stating their experience:

"I saw the 45[mmol/mol HbA1c level] and that- that's inspired me to think: oh, you know...., cause it said 45 ..... that might be good when I go next to the hospital"

Data driven flags and reminders were found to be sensible and positively viewed to contribute towards their engagement. *"It's good that reminders come according to the date of the last upload, rather than on the same day every week. It is more personalised based on when they last uploaded data, if it did it every Monday, I think it'd drive me a bit nuts, cause like: well hold on. I h- I only uploaded it yesterday"*

Tools to communicate with the clinicians through the messaging system on the Glucollector was favoured: *"Like the facilitator contact bit"*

However, some of the participants mentioned their preference for paper rather than the screen: *"I find it a lot easier cause you don't have to go onto the website, and you don't have to- the paper diary's just there isn't it."* A couple of participant mentioned that they preferred the diary because *"they could write down notes in it, e.g. to explain readings or to record correction doses."*

We considered this feedback and amended the commenting process and improved the feature by auto selecting the possible areas of interest in the data based on hypo or hyper episodes. Also patients suggested:

"An algorithm/function to help people take into account intensity and duration of physical activity, types of carbohydrate eaten and insulin on-board (and the weather) to inform insulin dose calculations"

This feedback contributed towards the improvement of graphs and inclusion of various data i.e. insulin on board to provide more context. Also, to provide further information on bolus calculation the bolus case collector was added to provide data driven review of bolus administration by patients to facilitate reflective look on the boluses and later changes in the glucose levels accordingly.

The second wave of the semi-structured interviews were carried out to provide further feedback on the changes and new features on the system. This wave of interviews were with different groups of people from the first wave.

They described their first impression of the system by stating: *" I wanted to use it."* and the accessibility was expressed as: *"Having access to the stuff online and the meter probably for me was more helpful than sessions about, you know, [clinical content]"* ; especially the ease of use was found helpful. *"The most useful thing [about the course] is the Glucollector thing, because you can do stuff on the fly and it's recorded forever."*

Few patients expressed the value of change in the care model: *"That's [the website is] the most useful thing I got out of it, I think. It's just being able to go and review it and have that data there indefinitely and be able to use it. That's the most useful thing for me."*

The practicality of use and the need for such system further outlined by stating: *"When I get up, I can't remember a thing. But when you can refer to the website, it's in there in purple, green, orange and whatever other colours they are on that chart. For me, that website is invaluable I think."*

The comprehensiveness of the system was considered useful since it provided the bases for diabetes management. *"It's so useful because. . . ,.... it covers everything from the carbs, and can tell*

you how much carbs there are in the food you're eating right through to how much insulin you've injected, then also your sugars. It covers all the bases and that to me is really useful."

The variety of views were also emphasised in this group as well. And others emphasised the statistical information: *I like that the banner across the top. You know, it gives you, like, your percentages and things... I think it's really good. "*

Patients felt encouraged for a habit of trying to setup times to review their data: *"If I do sort of make a point to review it [data] once a week, then I will sort of notice the trends. That's the most useful bit."*

For patients finding patterns were easier to spot: *"Without that website, the graph and it showing it in the... colours... I wouldn't have been aware of the pattern that was developing. ... The colours and everything that are used, it just makes everything stand out."*

Specifically, patients consumed the diagnostic graphs well when they have realised the information presented can aid with spotting behavioural traits. *"That one that shows you when you've over treated and under treated. Like, before looking at that, I didn't know what that showed and I don't really understand it. But when they went through it, when they've been through it on the course, so I understand it now. So, yes, good."*

Some found the trends can be tracked easier on the system: *"With the data, like, this new meter, I can get real-time trends... So, I can be reflective of the meter, whereas I couldn't really be reflective before, because I was just based off my readings, like, you know, within the past day. ...it's much easier to see it in a graph format, or the bubble chart type thing, rather than just plain numbers."*

And how these trends can impact their behaviour were put forward as: *"So, being able to see the trends....the pie charts and stuff, having green for when you're in range and when [you've] got a percentage in range, when you're on target, it's positive, you know, it's a bit of a positive reinforcement.... this is a really good way to get constant reinforcement that what you're doing is the right thing."*

In addition to motivational impact, the access to data and variety of presentations can be structural for patients:

"It's really good ...because it gives you a goal ... to get your sugar levels ...controlled and being able to add comments etc ... you can see visually ...where your blood sugars are rising ... and being able to see at a glance ... a better picture of your readings .... And having ... your long term blood

reading up there as well is really useful because it's all together and it gives a better picture of how your control is. ...it's all in one place."

The Carbs centre was introduced for these wave of patients. They expressed the feature to be a helpful tool. *"The carb counting really helped and now I can go on this computer and put your foods in and it does it for you, you keep it as your favourites which is a big help I keep referring back to that. When I'm having the same foods say as what I had probably week or two week ago, I just bring that up and it tells me straight away how many carbs it is. So that was very helpful."*

Especially, the availability of reliable source and its adaptability on calculating the carbs content. *I use the Glucollector [for carb-counting] because I put the DAFNE booklet somewhere and I cannot find it and also... there's just more information on the Glucollector one and there's more results and there's different... portion sizes and also you can put in the weight of what you have and it does the calculation for you. Like that's incredibly useful."*

The gamification and challenges were viewed as interesting features. *[The quizzes are] good, it's a good way of finding out how far you are out on some things, you're guessing the carbs,... it's interesting. "*

The system generally promoted the motivation to be engaged more as patients' experience stated: *"This is the most I've gone with active testing all the time. ...I think it's because I get a direct benefit from it, and I can see the data straight away, as soon as I upload it."*

And it can setup a possible positive habit for review and treatment adjustments outside the clinics by the patient.

"What it was [about the course], was really how they were able to explain the website because that's the thing that [is most useful]... Now that the Mondays are finished and we're on our own as it were, we can continue to look at that website and all the patterns that will emerge. And we'll get to see the patterns that are emerging through that particular website."

However, patients feedback on the the carbs centre provided insight for possible improvement stating: *"[When] you've made all your meal plans, instead of putting dates as you go along, [would like to] be able to highlight one and then ... put a date in when you had it, then you had that meal and change your carbs on it and save it."*

And adaptability for mobile phones was requested: *"When you look at it on your telephone especially. You don't see the whole screen, you know, it's not populated in the same way as it is on a PC."*

Further data collection and integration with the third parties was suggested. *"If [the site] could... because it pulls through Fitbit data, maybe it could pull through MyFitnessPal data... what I'm actually eating. "*

Clinical feedback

Throughout the study, patients contacted the team through the messaging system of Glucollector if they found the matter to be of clinical importance (i.e. data review, clinical questions, prescription requests, test result discussions and request for advises). These messages were directed to the clinicians. Overall, there was more than 700 messages exchanged among the users; this is equivalent of 8 messages per user for the intended period of the study. If equated to yearly appointments, this would be of two appointments per patient .

Longitudinal analysis

For the clinical outcome measure, a longitudinal analysis of the HbA1c changes of Glucollector patients was carried out to investigate the improvement. Since the data are correlated by the subject and time, generalised estimating equation (GEE) longitudinal regression analysis was carried out. The results are as follows:

The DAFNEplus pilot trial patients on average improved by $\sim 0.42 mmol/mol$ per month ($p<0.05$); which is about $5 mmol/mol$ for a 12-month period. The retention rate was 75%; five of the users stopped using the system, one encountered health complications and the rest did not finish the DAFNE course or did not attend the follow ups. About 70% continued using the system after the intended study period.

The analysis of each month average change was carried out by stratification of the months. As the study proceeded, each month in comparison to the baseline had resulted in improvement in HbA1c (Figure 7.23). This shows that the HbA1c was constantly improving in varying amounts throughout the study.

Also, the improvement was investigated for the effect of centres using multilevel modelling. The result shows no significant effect by the centre. Hence, the improvement observed is similar in the three participating centres.

Also, DAFNE graduates on average improved by $\sim 0.41 mmol/mol$ per month($p<0.05$), corresponding to average improvement of $\sim 4.9 mmol/mol$ for 12 months. Figure 7.24 shows the average

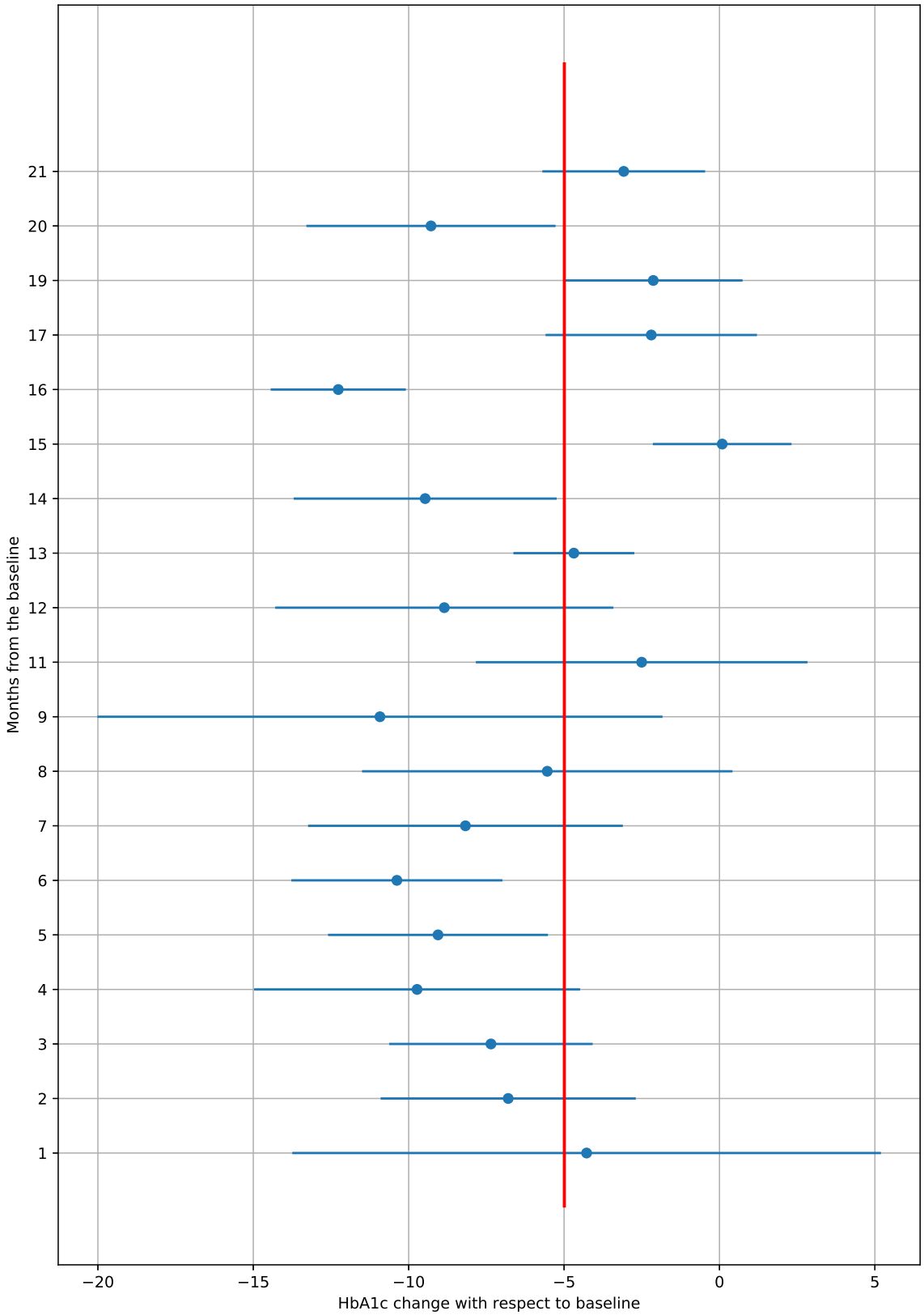


Fig. 7.23 Monthly change in HbA1c of DAFNEplus cohort with reference to the baseline with confidence interval of each estimated point. The red line shows the yearly average change

change of HbA1c levels per month with reference to the baseline. The retention rate was 84%; one patient discontinued due to an unrelated complication at the start of the study, and another moved from Sheffield to another city. The rest of the participants have continued using the system after the intended study period.

In addition to the clinical outcome of improved HbA1c levels, the success of the users' experience and views were key in the assessment of the clinical pilot trial. It was mentioned in the checkpoint report to National Institute of Health Research (NIHR):

*"**Success in support and technology piloted with at least one DAFNEplus course – Met;** We have exceeded expectations in this area of work. All eight DAFNEplus cohorts in the pilot study (N=54 participants) have been given access to the technology and structured follow-up support as part of the intervention. The technology had already been tested and refined by taking into account the views / experiences of 45 participants in the pre-pilot work."*

7.4 Discussion

The Glucollector is an interactive and individualised internet-based platform developed to motivate and support behavioural change in type 1 diabetes patients to improve self-management skills and sustain this improvement over time. The E-Learning modules and components of the Glucollector were designed on DAFNE principles to provide a holistic framework integrating both education and data analytics within one system. The various presentations of the information, review toolsets, and amber flags provided a tailored experience according to individuals' glycaemic patterns. The data-driven interactive tools created and reminded patients about the context and time-specific action plan to prevent relapse and promote self-management. As of usability and user satisfaction, half of the UoS volunteers continued to use the system past their two-week study period. Also, more than 80% and 70% of DAFNE graduates and DAFNEplus cohorts continued using the system past the intended period, respectively. This is a pointer towards answering a healthcare need.

For various reviewing tools on Glucollector, rule-based reasoning was devised using clinical knowledge combined with knowledge from historical data to determine a solution plan. This has enabled us to identify reasons where patients can potentially benefit by reinforcement of learning through contextual review of the data. The rule-based reasoning in general has limitations since it relies mainly on the knowledge of the expert and engineered data. Therefore, the rules are required

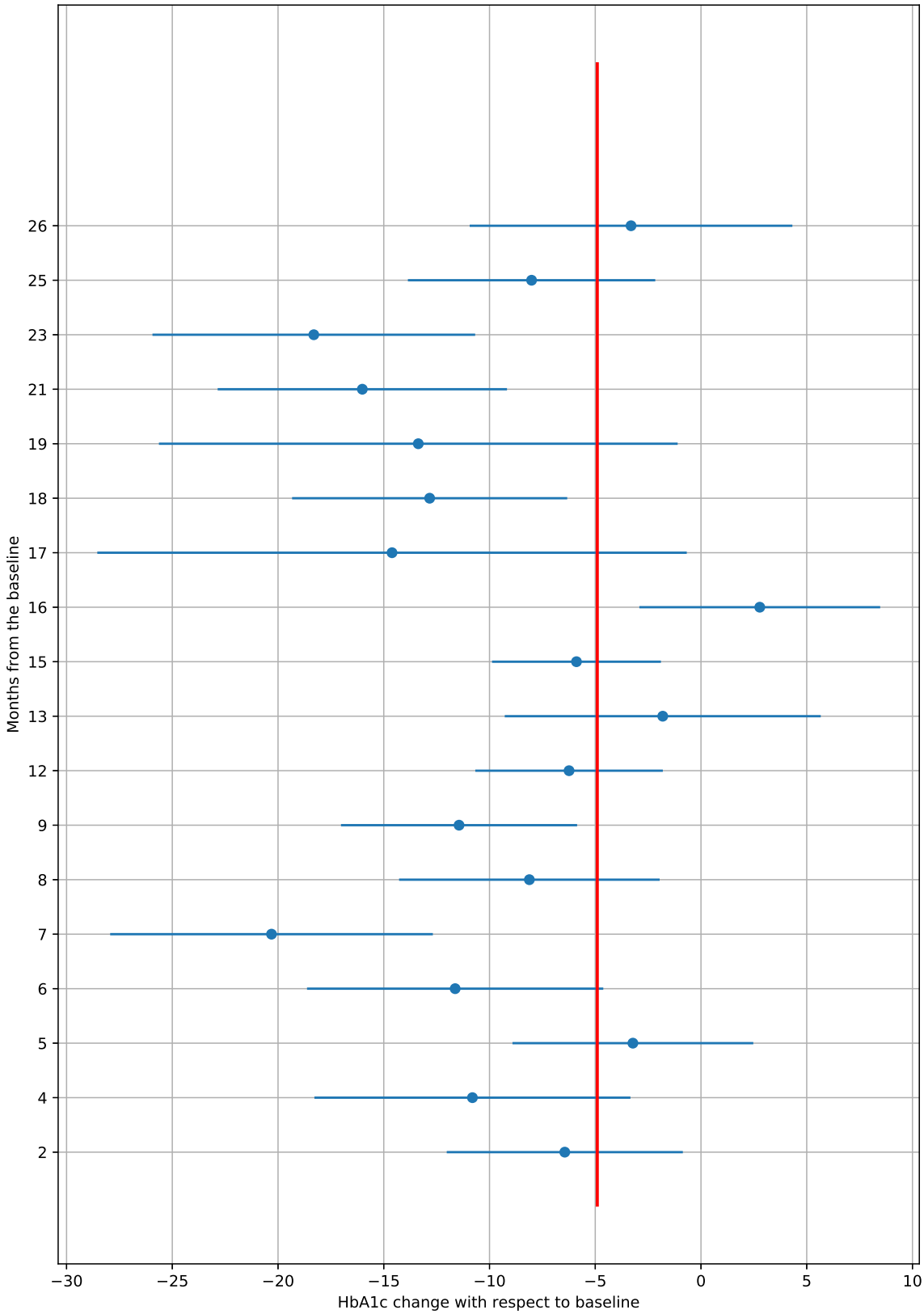


Fig. 7.24 Monthly change in HbA1c of DAFNE graduate cohort with reference to the baseline with confidence interval of each estimated point. The red line shows the yearly average change

to be updated continuously. Also, in certain situations, it can arise that few of the rules are met and therefore, not a single solution can be advised. Hence, it may be difficult to codify all the solutions of a complex problem using rule-based reasoning.

The remote access to data and various components and tools of the Glucollector helped to shift the culture of reactive response to patients' needs to a proactive model whereby clinicians can spot issues earlier and faster. This change in clinical workflow can be difficult for clinicians [275, 276]. In our study, clinicians' involvement in the development process and patients satisfaction enhanced clinicians acceptability of the change in the workflow. This has the potential to improve the communication and engagement between patients and clinicians which has been shown to improve primary and secondary outcomes of the diabetes targets.

The software provided by glucose meter manufacturers is mostly not used by patients [277]. In the clinics, dealing with different software complicates and delays the review process [44]. To resolve this issue, a unified view, such as ambulatory glucose profile, is proposed. However, this is a complicated graph based on statistical concepts such as the median, inter-quartile and decile ranges that are tailored to the clinicians and harder to be understood by patients. This limits patients' visual analysis of data for interpreting patterns. Consequently, it hinders the effective communication of the findings in the review appointments with the clinicians. The experience of the Glucollector users showed a preference for the variety of data presentation, colour coding of data and easy-to-understand information. Furthermore, there are benefits in presenting a summary of the data in different detail levels in time. In each level, hypotheses can be investigated further by referring to a more detailed period. As we have noticed, patients can have periods of malfeasance but these graphs can outline the patient's effort and be a positive reinforcement. Also, patients and clinicians can review the data in a structured fashion utilising the developed graphs.

Another solution is provided by companies such as glooko+diasend; since these are subscription-based services and 90% of the diabetes population is type 2, their product does not fit the needs of a type 1 diabetes patient and healthcare model. To fill this gap, Tidepool was developed for type 1 diabetes. However, their design is not far apart from glooko+diasend in that it provides a service for data management and storage. Hence, a generality in design is noticed that cannot fit the specific needs of type 1 diabetes. Tidepool claims their design is generic enough that can be adapted for type 2 diabetes, asthma or congestive heart failure data. To our knowledge, this software lacks established evidence of being patient-centric and effective.

The DAFNEplus multi-centre clinical pilot trial study resulted in a significant improvement of HbA1c among patients of the three participating centres. Additionally, the DAFNE graduate cohort who were not attending the DAFNE course acted as the control group and have shown similar improvements in the HbA1c levels. Hence, the results conclude that the use of Glucollector is associated with significant improvement in HbA1c levels.

Involving multiple centres in the study offered the prospect of designing a more comprehensive and applicable telehealth platform. The breadth of features and design considerations provide the opportunity to employ the platform at other clinical centres in the UK. This has the potential to reduce cost, training time; and to improve the interchangeability of data, and maintenance of high-quality care across centres.

In conclusion, telemedicine is perceived as a means to empower patients by providing tools and support outside the clinical setup with the potential to reduces complications, risks and costs. The Glucollector is a novel intervention system for type 1 diabetes to provide tools—for constructive and prompt interventions and objective inferences—to aid with the analysis and expedite the process. The Glucollector was designed based on DAFNE for a common framework and effective communication of the adjustments in insulin regimen. It included communication tools to improve the link between clinicians and patients. This is reinforced by the data-driven review toolbar and E-Learning modules. From patients' feedback, these features enhance the user experience and likely contribute to improving clinical outcome. These results are further evaluated in an upcoming randomised control trial utilising the Glucollector platform.

Chapter 8

Conclusion

This thesis produced solutions in chronic disease management of adults/adolescents with type 1 diabetes to promote self-care and clinical support. Pivotal to the solutions are the statistical analysis and machine learning techniques used to implement translational engineering solutions. Therefore, the results can be adopted in the current healthcare frameworks and practices. Moreover, the developed management system (the Glucollector) provided a comprehensive type 1 diabetes management platform and was evaluated in the DAFNEplus clinical pilot trial. The Glucollector system is at the time of writing this thesis being deployed in a major randomised clinical trial (RCT).

The presented work in this thesis tackled the identified major aspects of type 1 diabetes management as follows:

- **Guidelines and recommendations:** By providing suggestions on glycaemic targets to enhance engagement and reduce the treatment exhaustion and anxiety experienced by type 1 diabetes patients.

- **Clinical outcome measures:** By improving HbA1c prediction for a quicker and continuous feedback on patients' glycaemic control.

- **Proximal technology:** By automating the contributing elements in employing technologies such as bolus calculators in glucose meters and pumps. These are to improve accuracy, context and cut down the burden on patients and clinicians.

- **Distal technology:** By developing a holistic diabetes management platform that provides inferences, tools, and support through iterative processes including the end-users for better design.
- **Clinical pilot trial:** By evaluating and enhancing the developed technologies to support the DAFNEplus clinical pilot trial.

8.1 Summary

Chapter 3 produced a novel dataset to enable a retrospective analysis of adherence of patients to the recommended guidelines. The analysis defined novel recommendations of adherence and target-measures for type 1 diabetes patients. The study has noted that the aim of the further blood glucose (BG) measurements should be intertwined with skill development to improve the actions taken in response to hyperglycaemia and hypoglycaemia, which are often sub-optimal, and more problematic the poorer the glycaemic control. The day-to-day demands of type 1 diabetes treatment adjustments require a significant effort that can cause anxiety and treatment exhaustion. The novel mid-term targets of proportion in-range can provide feedback on diabetes management and help reduce its burden whilst promoting adherence. We recommend National Institute of Health and Care Excellence (NICE) to consider these proportions in-range in its guidelines. These proportions lend more context to the BG data measured by patients every day while HbA1c is not well understood and is limited by its measurement being performed in 3-6 monthly clinic visits. We see a great value in obtaining the SMBG data of patients for researchers. Hence, we advocate building a system where the anonymous SMBG data of diabetes patients could be reported alongside the compiled diabetes data submitted in the national diabetes audit.

In chapter 4, the developed models show that glycaemic patterns can predict the long-term diabetes measure of glycaemic control, HbA1c. The models were designed utilising the dataset from patients in the real-life clinical setup instead of experimental conditions. This culminated in developing practical models conforming to the realistic expectation of the generated diabetes data. The presented work shows the high glycation index (HGI) as a risk measure can be used for prediction of HbA1c. This is an innovative use of the HGI that can help to identify the high-risk patients in association to the HbA1c levels. Deep learning provided the means to analyse the incomplete raw SMBG data of patients utilising the non-linear activation functions and convolutions of various filters. This resulted

in a novel model predicting the HbA1c based on the most recent findings in artificial intelligence (AI) concepts. The presented work further confirms the results of chapter 3 in that the glycaemic patterns can be a measure for the outcome of patients' diabetes management. This provides a frequent availability of a more accurate estimated HbA1c measure that can enhance treatment adjustment and decision making by patients and clinicians.

In chapter 5 diurnal patterns of type 1 diabetes time-series data were identified utilising the clustering of SMBG measurement patterns. This provided a novel solution to automate adjusting the time-block settings in the bolus advisors of pumps, glucose meters, and mobile applications. Also, it provides the possibility of tracking changes in diurnal patterns. The identified diurnal patterns provide further clues and context to the data that can be utilised to drive the clinician-patient conversation to specific actions to influence glycaemic control. The result of the proposed method was compared to clinician-suggested time-blocks using a Turing test whereby the experts were blind to the source of the generated recommendations. We believe the evaluation method utilised in the study should be the standard for any developed work related to the bolus advisors. Reported works on the developed bolus advisors have tended to be based on simulators/in-silico experiments; the testing of the efficacy of these advisors with patients rely on the degree of their glycaemic control and acceptance of the recommended bolus. Such methodology lacks context and cannot be used to support an evidence-based approach to adoption.

Chapter 6 presented a novel patient-centred telehealth platform for diabetes management. The platform was developed utilising agile methodology to improve human-factor engineering in the design. Additionally, the iterative process of the agile methodology helped with the pace and relevance of the findings of the study in the context of the rapidly shifting technology landscape. The components of the platform such as statistical information, visual analytics, e-Learning modules, gamification of the platform, and the introduction of challenges are associated with the improvement in HbA1c levels of the patients. The participants expressed their satisfaction with the system in the semi-structured interviews. The high acceptability and improvement of primary outcomes resulted in the high retention rate. Findings in diabetes self-management require long-term monitoring based on evidence in clinical pilots and trials. Therefore, we recommend that agile methodology be used in technology-related diabetes management solutions to keep up with the shift in technology while implicitly involving the end-users in the design, development and testing processes.

8.2 Possible Extensions

- Adaptation of the Glucollector in populations such as Gestational Diabetes, children with type 1 diabetes, and type 2 diabetes
- Continouos glucose monitoring (CGM) and Flash glucose monitoring (FGM) RCT in a continuous and diagnostic fashion
- Further refinement of the HbA1c prediction using Recurrent Neural Network to provide the consideration of time, utilising their memory units.
- Developing a review toolbar to provide automated decision support tools for diagnostic purposes and recommendations for treatment adjustments (at least initially through health care proffesionals (HCP))
- Automatically calculate the optimal insulin to carbs ratio (ICR) and insulin sensitivity factor (ISF) for each identified time-block

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