TYPE 1 DIABETES HYPOGLYCEMIA PREDICTION BASED ON CONTINUOUS GLUCOSE MONITORING AND HEART RATE

by

STYLIANI TSICHLAKI

BSc. Technological Educational Institute of Crete, 2019

A THESIS

submitted in partial fulfillment of the requirements for the degree

MASTER OF SCIENCE

DEPARTMENT OF ELECTRICAL AND COMPUTER ENGINEERING

SCHOOL OF ENGINEERING

HELLENIC MEDITERRANEAN UNIVERSITY

2021

Approved by:

Major Professor
Professor Manolis Tsiknakis

Abstract

Diabetes is a chronic condition that develops when the human pancreas does not quite contain enough insulin or when the body cannot properly use the insulin, leading to a rise in the blood glucose levels. Specifically, it is a recurrent condition, which includes three different types: Type 1 Diabetes, Type 2 Diabetes and Gestational Diabetes and involves the constant control and self-management of the patient's blood glucose. Improper regulation of blood glucose levels in diabetic patients can lead to severe problems, such as kidney and heart failure, as well as stroke and blindness. Nowadays, the use of continuous glucose monitoring systems allows the collection of blood glucose level information in real time.

Hypoglycemia is a condition that arises when blood glucose levels decrease below 60 mg/dL. This incident can occur due to a variety of causes, such as taking additional doses of insulin, skipping meals, or over-exercising. Mainly, the symptoms of hypoglycemia range from mild dysphoria to more severe conditions, such as strokes, unconsciousness, and potentially permanent brain injury or even death. Hypoglycemia can be simply treated by the patient himself, through an oral intake of glucose, if detected on time. On the other hand, another crucial component of hypoglycemia detection is the changes in the patient’s heart rate. There is evidence that hypoglycemia, electrocardiogram, and heart rate abnormalities are interrelated. Therefore, such abnormal heart rate patterns combined with continuous glucose monitor data could be used as an improved and more reliable method for identifying hypoglycemia in real time or even for predicting such episodes.

In this thesis, we examined the use of biosignals and other measurements provided by a wearable device along with self-assessment parameters, for the development of a hypoglycemia predictive model. We utilized mainstream tools, and the patient was not burdened with additional equipment. Glucose measurements were captured by a clinically certified continuous glucose monitoring sensor, while the predictive model was trained using machine learning techniques. In addition, a diabetes management mobile application was developed and used for the required data collection from the patient, i.e. finger-stick glucose measurements, insulin doses, food and exercise, as well as mood. The mobile application also incorporated an appropriate type 1 diabetes-related questionnaire, which was used to calculate the patients’ diabetes distress. Heart rate

measurements and glucose data were combined in a prediction algorithm that defined hypoglycemia as a blood glucose value below 70 mg/dL.

The results of the hypoglycemia prediction model that was developed revealed, for patient with ID 575, that the 30-minute prediction curve held an RMSE score of 20.25 mg/dL and a MAE score of 13.26 mg/dL. On the other hand, the 60-minute prediction curve had an RMSE and a MAE score of 31.30 and 21.62 mg/dL, respectively. The main finding is that the inaccuracies for each patient gradually rise over time, which is expected since the broader the prediction window, the greater the overall inaccuracy. Finally, we sincerely consider that the proposed model produces useful and applicable outcomes for T1D patients, and we suggest that a 30-minute RMSE of 20.25 mg/dL can provide a basis for avoiding a potentially critical, for the patient's health, hypoglycemic episode.

Table of Contents

List of Figures

List of Tables

Acknowledgements

Firstly, I would like to express my gratitude to Prof. Manolis Tsiknakis for his support and guidance that inspired me, all along this thesis. Our collaboration was a valuable and beneficial experience that I will never forget, and I am grateful for all the knowledge and chances that he offered me.

I would also like to express my sincere gratitude and appreciation to my co-advisor Lefteris Koumakis for his continuous guidance and support, since he shared with me his knowledge on the subject and patiently guided me through every step of this thesis.

Furthermore, I would like to thank the stuff of Biomedical Informatics & eHealth Laboratory (BMI Lab) for their continuous support, emotionally and practically.

Last but not least, a great thank you to my family and close friends, who always believed in me and were there for me through every step of the way.

Dedication

Dedicated to my parents, my siblings, and my beloved grandmother, for always being my greatest supporters.

1 Introduction

Diabetes is a chronic condition that develops when the human pancreas does not quite contain enough insulin or when the body can't properly use the insulin, leading to a rise in blood glucose levels [1]. Normally, after a meal, the body breaks down the food into glucose, which is transported by the blood to the cells of the body. Cells utilize insulin, which is a hormone produced in the pancreas, in order to convert blood glucose to energy [1]. People with diabetes have trouble with this process, which leads to exhaustion and many other severe complications. Late diagnosis and/or poor treatment of diabetes can lead to several severe complications, such as eye impairment, kidney damage, as well as nerve damage [1].

Specifically, there are three types of diabetes. Firstly, there is Type 1 Diabetes (T1D), which results from the prevention of insulin development by the β-cells (beta cells) in the pancreas. These β-cells are located in the pancreas, within groups of cells known as islets, and are responsible for producing insulin, the hormone that regulates blood glucose. This type of diabetes is predominant in children and young adults and requires multiple doses of insulin a day to regulate the blood glucose levels. Secondly, there is Type 2 Diabetes (T2D), which is the most widespread form of diabetes, while it can be developed at any age [2][3]. This type of diabetes typically begins with insulin resistance, which gradually leads to a lack of pancreatic capacity to produce adequate insulin for the food intake [2]. Thirdly, the last type of diabetes is Gestational Diabetes (GD), which can be developed only during pregnancy.

Diabetes is not known to be treated, but early diagnosis of this condition, accompanied by effective treatment, a balanced diet, and regular physical exercise can help control blood glucose levels and decrease the risk of complications. The main purpose for diabetic patients, as well as physicians, is to monitor and sustain the blood glucose levels within the normal range of 70 mg/dL - 120 mg/dL, while also keeping the number of hypoglycemia cases to a minimum [4][5].

1.1 Type 1 Diabetes (T1D)

T1D used to be referred to as “juvenile diabetes”, since it is mostly diagnosed in children and teenagers[1], even though it can also commence in adulthood. T1D is an autoimmune disease

[1] Source: https://en.wikipedia.org/wiki/Type_1_diabetes

that causes the pancreas to generate very little, if any, insulin [6]. Insulin is a hormone that helps to regulate normal glucose concentrations in the bloodstream and is essential for cells, in order for them to use blood glucose for energy [6]. Prior to treatment, this minimized insulin production causes elevated blood glucose levels in the patient's body.

Healthcare professionals seem uncertain of what exactly causes T1D, while genes are thought to be involved in this process. Researchers are investigating any possible triggers for the disease, such as the patient's diet or a virus that the patient might had caught [7]. It can affect people of all races and ethnic groups, while there is a greater risk of potentially inheriting the disease when there is a family history. Furthermore, healthcare professionals do acknowledge that T1D patients have malfunctions in their immune system, which is responsible for the protection of the body against germs. Specifically, this malfunction damages β-cells that exist in the patient's pancreas, which are responsible for the production of the insulin hormone [6]. Insulin enables glucose to infiltrate patient's cells and be converted into energy, however, the body of T1D patients does not produce insulin [6], which leads to glucose accumulation in the patient's bloodstream leading to severe health issues over time. Overall, the primary reason for the appearance of T1D is thought to be an autoimmune destruction of the pancreas' insulin-producing β-cells. The amount of glucose or glycated hemoglobin (HbA1c) in the blood is used to diagnose diabetes. Specifically, the existence of autoantibodies is what distinguishes T1D from T2D, while there is no established method of T1D prevention. Insulin treatment is needed for survival, through insulin injections beneath the skin or via an insulin pump.

1.1.1 Symptomatology

The typical symptomatology usually appears in a short period of time (weeks) [8][9] and usually includes most of the signs mentioned in Table 1.1. While T1D progresses gradually, as the insulin output declines, understanding its symptoms is important, since a delayed diagnosis can have severe implications. Overall, blood glucose can reach menacing high levels when insulin production is outpaced. Patient's symptomatology can suddenly appear, as well as be misdiagnosed as other diseases. This autoimmune disease has no clear cause, although it is presumed to be caused by an interplay between genetics and environmental factors [9][10]. Several of the T1D symptoms are similar to T2D symptomatology, making it difficult to determine which type of diabetes the patient has developed. However, it is critical to understand the distinctions and

determine what is causing the patient's symptoms so that the patient can receive the appropriate treatment.

Table 1.1. Diabetic symptomatology

Typical signs of diabetes [9]
– Excessive urination
– Increased appetite
– Increased thirst
– Sudden rapid and unexplained weight-loss
– Blurred vision
– Frequent skin, oral and/or genital contaminations
– Fatigue
– Emotions of irritation or frustration
– Slow healing of wounds

1.1.2 Diagnosis and Treatment

This disease can sometimes appear as a flu or dysphoria at first, therefore clinicians need to be alerted to the early warning signs of a potential T1D diagnosis and recommend further testing for the patient. Once there is a suspicion of T1D existence, a fasting blood-glucose test is often prescribed [7]. This is a small-sample blood test that is usually done in the morning following a night of fasting. Fasting allows physicians to see how the body regulates blood glucose levels without the influence of food. On the other hand, there is the oral glucose test, which is an alternative for people who have fasted and had an initial blood test, to drink a sweet beverage and then have their blood glucose checked over the course of two hours. This displays the baseline glucose without any outside influences and then tests how the body reacts to sugar consumption. A random glucose test is another method for checking T1D. This test essentially measures a patient's current blood glucose level, regardless of when or what they have consumed. Lastly, there is the HbA1c (glycated hemoglobin) test, which determines the average blood glucose level for the approximate last three months and is thought to be the most extensive method.

The initiation of symptomatic diabetes does not necessarily occur simultaneously. People with T1D may experience a period of asymptomatic behavior. The asymptomatic period usually lasts a few months to a year after diagnosis, as a patient's existing β-cells begin to act normally

and produce enough insulin for blood-glucose control with the aid of some injected insulin. Eventually, the bulk of the pancreas' insulin-producing β-cells quit functioning, and diabetes symptoms revive. During the prementioned period, no matter how strong A1C or blood-glucose tests are, the disease is still present and killing β-cells. During this point, clinicians will use low-dose insulin therapies to help maintain blood-glucose control, even though the remaining healthy cells would eventually die, necessitating an increase in insulin dosage. Overall, T1D's endocrine system activity, during the asymptomatic period is reasonably predictable, but each case differs slightly. The importance of paying careful attention to the body's response to insulin therapy, along with routine blood glucose monitoring, is critical to achieve an effective management.

The treatment process of T1D patients is carried out by a combination of insulins and the collaboration with their healthcare professional, in order to determine the appropriate insulin treatment for their needs. Insulin may be administered using syringes, pens, pumps, or recent artificial pancreas technologies. Although, the administration, frequency, and form of insulin delivery differ by case and injections can be required numerous times throughout the day. It is possible for patients to develop prominent insulin side effects like injection site reactions, which involve redness, soreness, or inflammation around the injection site, while low potassium levels and risk of hypoglycemia are also possible. Although these side effects appear concerning, many people who are under these insulin treatments do not encounter any significant side effects[2]. Another critical aspect, in T1D treatment, involves supervision and lifestyle changes. Blood glucose levels should be checked on a regular basis, through traditional blood glucose meters and continuous glucose monitors (CGMs). Monitoring alerts an individual when insulin is required to treat high blood glucose, as well as carbohydrates are required to treat low blood glucose. Furthermore, the assessment of the correct insulin-to-carb ratio, by a professional, is necessary. This ratio represents the amount of insulin required to regulate the consumption of a certain amount of caloric intake, while it aids in maintaining healthy blood glucose levels after food consumption. In addition, a well-balanced diet is important for diabetic health. People with T1D benefit from a well-balanced diet that includes foods from all four food classes, with an emphasis on limiting empty carbs. It is important to eat healthily and exercise on a regular basis. Maintaining a healthy weight and ensuring adequate food intake help to reduce the impact of diabetic wear on the body.

[2] Source: https://www.jdrf.org/t1d-resources/about/treatment/

Finally, it is important for people with T1D to consult with a team of healthcare professionals on a regular basis to better control diabetes and prevent its possible effects on the patient's body.

1.2 Hypoglycemia and Hyperglycemia

T1D is a chronic disease where the patient's body is not able to produce enough insulin to regulate the blood glucose levels. This condition is treated by injecting artificial insulin into the body few times a day to maintain the body's blood glucose levels within the desired range. Nevertheless, this treatment comes with some side effects, specifically called hypoglycemia and hyperglycemia.

Hypoglycemia is a condition that arises when the body's blood glucose levels drop to sudden lows, specifically below 60 mg/dL. This incident can occur due to a variety of causes, such as taking insulin at a wrong time or injecting more than the required insulin dose, not consuming enough food, skipping meals, or even because of over-exercising without adequate insulin modification [6][9][7]. Hypoglycemia is a result of day-to-day activities and are spontaneous and therefore cannot be detected in advance. The medical professionals rely on daily blood glucose levels and a patient's day to day habits to treat the patient. Mainly, the symptoms of hypoglycemia range from mild dysphoria to more severe conditions, such as strokes, unconsciousness, and potentially permanent brain injury or even death. Although hyperglycemia is associated with long-term consequences in diabetic patients, hypoglycemia is a constant hazard. On the other hand, it can be simply treated by the patient himself/herself, through an oral intake of glucose. In moderate to extreme hypoglycemia, autonomic α-cell (alpha) inputs are more critical to the glucagon stimulation process [11]. Generally, α-cells are endocrine cells found in the pancreatic islets, such as β-cells. These cells synthesize and release the peptide hormone glucagon that is responsible for the increasement in blood glucose levels, whereas β-cells generate and release the insulin hormone [12].

Recrudescent hypoglycemia can cause metabolic changes in the glucose detection regions of the human brain, as well as shift the threshold for compensatory activation of the sympathetic nervous system to reduce the glucose concentration. The prementioned state is referred to as hypoglycemic unawareness [13][14]. Possible sequent hypoglycemia episodes prevent the transmission of anti-regulatory messages to the islets and adrenal cortex, which explains the lack of glucagon and epinephrine release [14]. This glucagon and epinephrine release usually promotes

the liberation of glucose from the liver, saving the diabetic from severe hypoglycemia, coma and even death. In the quest for a cellular cause of hypoglycemic unawareness, several theories have been proposed, but no consensus has been reached. The main theories are outlined in Table 1.2 [13][15][16].

Table 1.2. Hypoglycemic unfamiliarity mechanisms

Glycogen supercompensation	Increased stores of glycogen in astrocytes may contribute to supplemental glycosyl units for metabolism, neutralizing the central nervous system's perception of hypoglycemia.
Enhanced glucose metabolism	Modified glucose transport and increased metabolic efficiency in recurrent hypoglycemia can relieve oxidative stress that could trigger the sympathetic response.
Alternative fuel hypothesis	Reduced dependence on glucose, astrocyte lactate supplementation, or ketones can satisfy metabolic demands while reducing brain stress.

On the other hand, hyperglycemia events occur when less insulin than needed is injected, causing blood glucose levels to rise above the target range (>180 mg/dL). In the first year after diagnosis, postprandial glucagon secretion levels can increase up to 37%, while c-peptide levels (indicative of islet-derived insulin) can decrease by up to 45% [17]. Insulin output continues to decrease as the immune system follows the gradual destruction of beta-cells, and islet-derived insulin will be replaced by exogenous insulin therapy for the foreseeable future [17]. At the same time, there is an observable α-cell hypertrophy and hyperplasia, resulting in an oversized α-cell mass and along with the failure of β-cell insulin secretion, it clarifies the rise in glucagon levels that leads to a hyperglycemic event [18]. The primary theory for the cause of post-marketing hyperglycemia indicates that exogenous insulin therapy is inadequate to replace the lost

intracranial signaling in α-cells that was previously regulated by insulin-derived pulsed cell secretion [19][20]. Therefore, intensive insulin therapy seeks to replicate the natural insulin secretion profiles through exogenous insulin infusions [21].

1.3 Blood Glucose Self-Monitoring

Predominantly, blood glucose self-monitoring requires a blood sample to be collected on many instances throughout the day (Figure 1.1). Nowadays, the use of CGM systems allows the collection of blood glucose level information in real time [1][22]. CGMs monitor the glucose concentration in the interstitial fluid, and not in the bloodstream, thus their measurements typically remain behind the capillary blood glucose levels by 8 to 10 minutes [22]. Therefore, there must be calibration through finger-stick glucose meter several times a day [2][22].

Figure 1.1 Blood glucose self-monitoring through finger-stick blood sample

1.3.1 Continuous Glucose Monitoring Systems

Patients with T1D need to perform regular glucose measurements during their day-to-day life. This is currently done through two invasive methods: a) by using a blood glucose meter or b) through a CGM. A glucose meter is a device used to manually measure the patient's blood glucose levels. On the other hand, CGM is an automated device designed to measure glucose in interstitial tissue throughout the day. CGMs offer a method for monitoring glucose levels throughout the day and night, by taking glucose measurements at regular intervals, and translating readings into

dynamic data, generating glucose direction and rate of change. CGM requires three basic parts: a) a sensor, b) a transmitter and c) a smartphone application, monitor and/or pump.

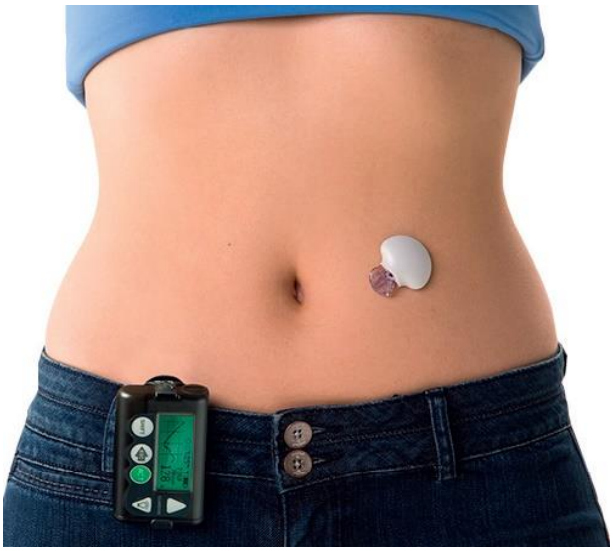


Figure 1.2 Continuous glucose monitoring system (Ipro2, Medtronic) [23]

In CGM systems, measurements are made by a subcutaneously implanted sensor containing glucose-oxidase. Specifically, the sensor is placed directly on the skin (Figure 1.2) and a catheter is implanted under the skin to capture the concentration of glucose present in interstitial fluids[3]. Furthermore, the sensor measures electrical current in relation to the interstitial glucose concentration, while this value is used as a proxy for actual blood glucose concentration. Then, the measured value is stored on device or is wirelessly transmitted to a monitor, through a transmitter which is placed on top of the sensor.

The monitor (or the smartphone application, receiver and/or insulin pump) displays real-time glucose number, trend, and history, while the most current CGMs offer specific smartphone applications for viewing data. CGMs are used to have a finer grain representation of the patient's glucose level and can also be used along with an insulin pump to evaluate the adequacy of the insulin program or to study glucose levels overnight. Some CGM devices can also send the glucose value to an insulin pump, including a growing number that can automate insulin delivery accordingly. However, CGM needs to be calibrated by using a standard glucose meter several times per day.

[3] Source: https://en.wikipedia.org/wiki/Continuous_glucose_monitor

This type of monitoring system has been found to help users to actively manage high and low blood glucose levels and in addition gives insights into the effects that one's meal, exercise, mood or even illness can have on the blood glucose levels [24]. Table 1.3 presents three well-known companies that offer CGM technologies and some of their key features are compared. Pricing varies based on the insurance coverage of the patient and can be provided by the company upon communication. Overall, the evolution of CGM technologies during the last decade has enabled the collection of multi-parametric data (medical, activity, lifestyle and diet) from diabetic patients [25].

Table 1.3 Continuous Glucose Monitoring (CGM) system kits

	Dexcom G6 [4]	***FreeStyle Libre*** [5]	***Medtronic Guardian Connect*** [6]
Kit	DEXCOM G6 - Starter Kit	FreeStyle Libre Flash Glucose Monitoring - System Starter Kit	Guardian Connect CGM - Complete Subscription
Components	– G6 Transmitter – G6 Sensor x 3 (30 days)	– FreeStyle Libre Sensor x 2 – FreeStyle Libre Reader x 1	– Sensors x 60 (10 sensors delivered every other month) – Transmitter – Option to receive 6 months-worth of i-Port Advance injection ports
FDA Approved For ages	Age 2+	Age 18+	Ages 14-75
Calibration Required?	No, but can calibrate if sensor is off-track	No, and not possible	Yes, 3-4 x daily
Sensor Life	10 days	14 days	6 days
Warmup time (New Sensor)	2 hours	12 hours	2 hours
Transmitter	Lasts 3 months, no recharging	Fresh Transmitter connected to each sensor	Must recharge weekly (New transmitter sent every 12 months)
Display options	– Smart phone	– Handheld scanner	– Smart phone

[4] Source: https://store.ca.dexcom.com/en-CA/dexcom-g6/g6-starter-kit/CASTARTERKITG6.html

[5] Source: https://www.freestylelibre.gr/products.html

[6] Source: https://pharmeddirect.com/uk-en/#

	– Smart watch (via phone BT connection), – Tandem X2 pump – Handheld receiver		– Smart watch (via phone connection)
Hi/Low Alerts	Yes, customizable	None	Yes, customizable, including extended predictive alerts
Live Data Sharing	Yes, high/low alerts and current glucose level/trend	None	Yes, high/low alerts
App/System	– Dexcom G6 app (mobile) – Dexcom STUDIO – Dexcom G6 app (mobile)	– FreeStyle LibreLink app (mobile) – LibreView, the cloud-based diabetes management system – FreeStyle Libre Desktop software	– Sugar.IQ app (mobile) – Guardian™ Connect App (mobile) – CareLink Personal system
Downloading/Data Analysis	– Automatic upload to Clarity software. – Compatible with most midware programs for merging data with other devices (Diasend, Glooko, Tidepool)	– Freestyle Libre software – Tidepool (midware)	– Automatic upload to Carelink Software – Sugar IQ program for analyzing data
Data format	.txt	.pdf	.pdf

1.3.2 Diabetes Management Applications

The usage of health-related mobile applications could further motivate individuals by facilitating and enabling patients in better self-managing of long-term conditions, such as diabetes [26]. In terms of diabetes control, evidence-based diabetes recommendations promote lifestyle management, such as healthy eating and physical activity [4][27]. Patients who regularly participate in their own treatment during clinical checkups are more likely to succeed in controlling their diabetes, through using diabetes management applications with glucose level tracking features and insulin dosage calculators [27].

Diabetes applications concentrate on different diabetes self-management activities such as glycemic control, insulin dosage, diabetes-related psychological support, as well as diet and

physical exercise tracking. The incorporation of data sharing functionality in diabetes management applications could provide additional insight into a patient's glycemic control by enabling health care providers to efficiently identify patterns and advise prescription modifications. The majority of diabetes applications are neither supervised nor approved by appropriate government agencies [28]. Currently, there are no specific clinical recommendations for patients to use concrete diabetes applications, nor there are mandatory or preferable characteristics in terms of the development of these applications [29]. Finally, Table 1.4 presents some widely used diabetes management applications, along with their main features.

Table 1.4 Overview of the main features of diabetes management mobile applications

Application	***Main Features***	***Data Records***
MySugr *(https://www.mysugr.com/en/)*	▪ Personalized logging screen ▪ Clear blood glucose graphs ▪ Private data safe backup (encrypted user information) ▪ Smart search of patterns ▪ Estimated HBA1c ▪ Insulin dose estimation	▪ Time of the day ▪ Blood glucose ▪ Carbohydrates ▪ Insulin intake (food consumption) ▪ Insulin intake (blood glucose correction) ▪ Activity ▪ Type of food consumed ▪ A1c
Diabetes:M *(https://www.diabetes-m.com/)*	▪ Clean logbook ▪ Food database (portion and quantity selection) ▪ Caloric intake counting and insulin dose calculator ▪ Detailed graph of blood glucose tests, boluses, basal insulin, activity chart and more ▪ Analytical charts and diagrams of the collected data ▪ Various reports, log entries and charts for sharing with diabetes specialists for review ▪ Data import/export from other diabetes management systems ▪ Reminder system	▪ Date and time ▪ Blood glucose ▪ Carbohydrates ▪ Fast-acting insulin type and units ▪ Long-acting insulin type and units ▪ Medications ▪ Reminders ▪ Blood pressure ▪ Physical activity ▪ Weight ▪ Ketones

Contour *(https://www.contournextone.com/)*	▪ SmartLIGHT target range indicator immediately identifies if blood glucose readings are above, below or within target range, giving patients instant feedback ▪ Second-chance sampling allows patients up to 60 seconds to reapply more blood which may help prevent wasted strips while still demonstrating a high degree of accuracy ▪ Seamlessly connect via Bluetooth technology	▪ Date and time ▪ Blood glucose ▪ Food intake ▪ Carbohydrates ▪ Activity (duration and intensity) ▪ Fast/Long-acting insulin intake ▪ Notes
One Drop *(https://onedrop.today/)*	▪ Blood glucose patterns ▪ Medication schedule ▪ Meal planning ▪ Exercise routine ▪ Automated decision support (food and activity suggestions based on future blood glucose estimations) ▪ Report sharing	▪ Weight ▪ Blood pressure ▪ Activity ▪ Food intake ▪ Medication ▪ A1c ▪ Blood glucose

1.3.2.1 MySugr

The mySugr mobile application was released in 2012 and is available in 14 different languages, in over 60 countries around the world [30]. This application is intended to assist diabetic patients with diabetes self-management, primarily in the areas of healthy eating, exercise, health tracking, medication, risk mitigation and possible problem resolution. Through mySugr, it is feasible to automatically transfer glucose data to mySugar from a CGM device or a finger-stick glucose meter, via Bluetooth. Additionally, it can be synchronized with devices through a cloud-based service, while the insulin records can be submitted manually by the user. This application can also contain information about the patient's meals and nutrients, physical activity, as well as medication. The initial user registration and data collection steps are presented in Figure 1.3. All the application data can be accessed and downloaded in different types of file formats, such as comma-separated values (CSV), Excel spreadsheet (XLS), or portable document format (PDF). These data can provide patients and clinicians with an accurate care summary that includes extensive detailed records and patient's glycemic patterns (Figure 1.4). Another feature of mySugr is the instant access to certified diabetes educators (CDE), when required. CDEs recognize and track patients at risk, aided by algorithms that detect problematic glucose patterns, and

communicate with them through the application, with individual glycemic-related advice. Lastly, more algorithms are used in the application, in order to identify personalized patterns and to identify patient's weak points that are in need of optimization.

Figure 1.3 MySugr App - Initial User Registration and Information Collection Steps

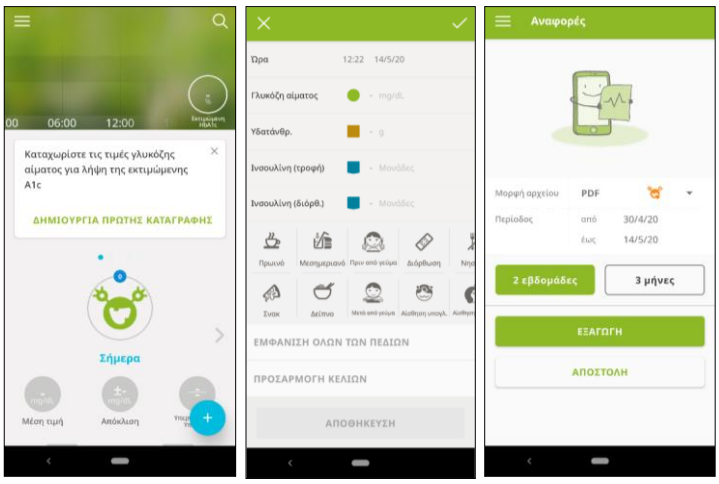


Figure 1.4 MySugr App - Homepage, User's New Entries and Blood Glucose Reports

1.3.2.2 Diabetes:M

Diabetes:M refers to a smartphone application designed for people with diabetes or pre-diabetes to help them monitor and treat their condition [31]. Its aim is towards reducing the risks of complications, by significantly improving the patient's self-monitoring and self-management skills, as well as providing the patient and the medical professionals with a tool that aids in making fast and educated therapy decisions. This application involves a Logbook screen, where the patients can enter their glucose readings, insulin injections, caloric intake and also monitor their weight, ketones, HbA1c, cholesterol levels, blood pressure, pulse, and physical activity. In addition, it includes a Bolus Advisor panel that allows patients to measure their insulin units for a meal based on carbohydrate, fat, and protein intake, as well as select items and foods from a categorized list (Figure 1.5). Furthermore, there is the possibility of personalized notifications about when the patient should consume more carbohydrates or whether he/she should postpone his/her meal, due to high blood glucose levels. Another feature of this application is the insulin dosage calculator, where patients can record their blood glucose level and the calculator can estimate the appropriate insulin dose for their needs. Diabetes:M can display all the available blood glucose entries in a timeline graph, while it includes several charts to aid data presentation in a variety of ways. Lastly, it offers the generation of comprehensive reports, available in PDF, hyper-text markup language (HTML), and XLS formats, for distribution with patient's clinicians.

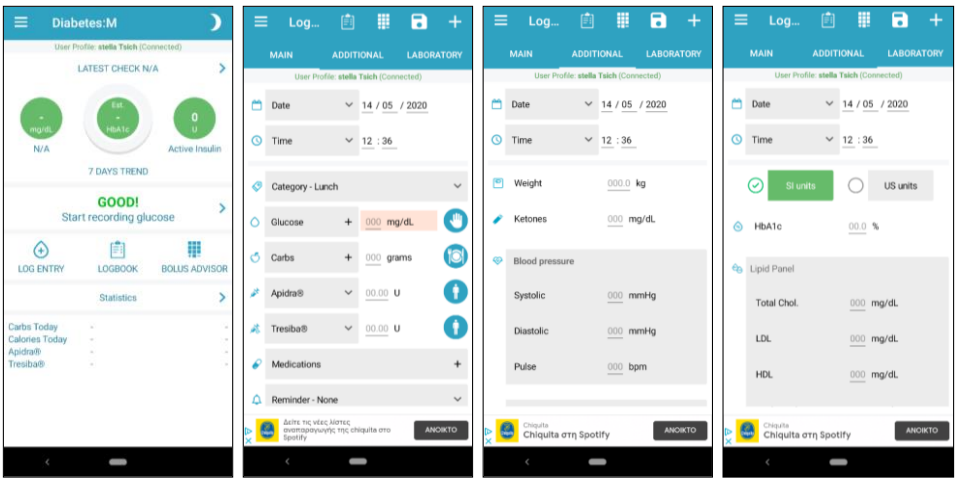


Figure 1.5 Diabetes:M App - Homepage and User Log Entries

1.3.2.3 Contour

Contour is a cloud-enabled mobile application, which has the ability to sync with the Contour Next One glucose meter[7] through Bluetooth Low Energy (BLE) wireless technology for blood glucose monitoring. Individuals with insulin and non-insulin treated diabetes, as well as their caregivers, can use the Contour application to save, view and share glucose meter's readings. Other associated health indicators that may be gathered and shown on a mobile device in a printed report and graphical format for patients, are also available, in order to help with diabetes management. The Contour One system, which is consisted of a Contour Next One glucose meter and the Contour mobile application, employs color to indicate whether a blood glucose is either in or out of the recommended range (Figure 1.6). Specifically, the blood glucose reading button in the application is colored and when a reading is taken with the glucose meter, the test strip port shows a colored indicator. Green represents values that are within target, orange represents values that are above target, and red represents values that are below target. Additionally, patients can record events such as nutrition, activity, and medicine, as well as add images, notes, or voice recordings to further contextualize their results (Figure 1.7). Seamlessly acquired blood glucose measurements are utilized to generate unique patterns and trends, allowing patients to observe how their daily activities affect their blood glucose readings. Finally, data from the application can be exported as a simple logbook referred to as the "Blood Sugar Diary", or as a raw data report in CSV format.

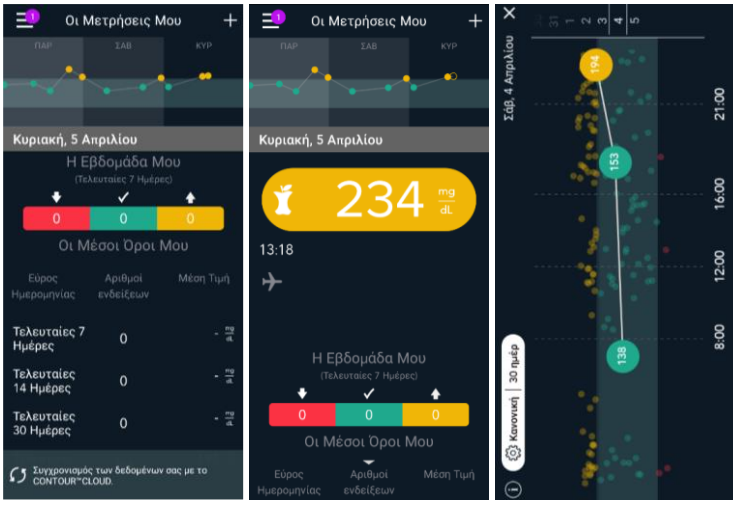


Figure 1.6 Contour App - Homepage and Presentation of User's Log Entries

[7] Source: https://www.contournextone.com/

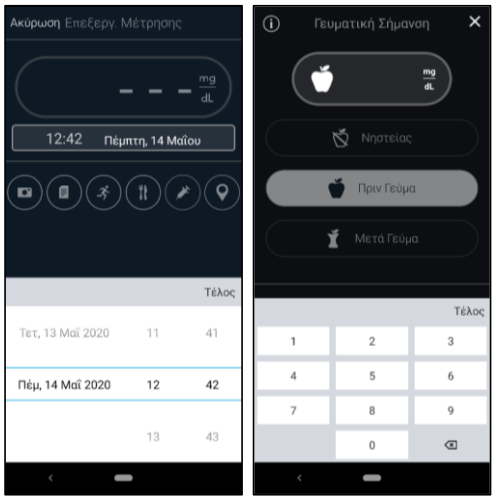


Figure 1.7 Contour App - User Blood Glucose Log Entry

1.3.2.4 One Drop

One Drop is a diabetes management mobile application for diabetic patients to register a range of daily information, such as their blood glucose measurements, food, activity, and insulin dosages, as seen in Figure 1.8. Moreover, patients can anonymously share that information with a community of users, and the application can also provide them with actionable insights based on their data. The One Drop application allows patients to easily save and manage their diabetic information, examine trends, and share their overall health state with a healthcare team. One Drop users can also upload and review their records, including measurements, such as glucose, insulin, caloric intake, and weight (Figure 1.9). It is also possible to link One Drop application with the One Drop glucose meter, and the data from the glucose meter can automatically sync with the application anytime the two devices are in range and the glucose meter is switched on. Finally, the application displays long-term trends and daily blood glucose averages, while comprehensive reports are available for exportation in PDF and CSV formats.

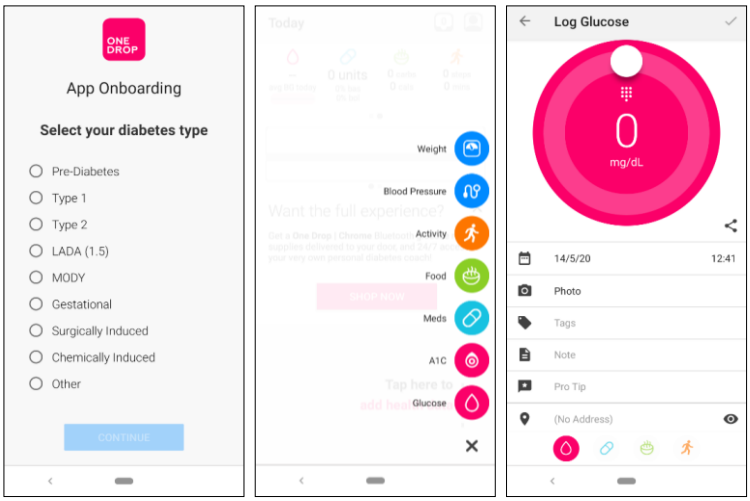


Figure 1.8 One Drop App - User Registration and User Blood Glucose Log Entry

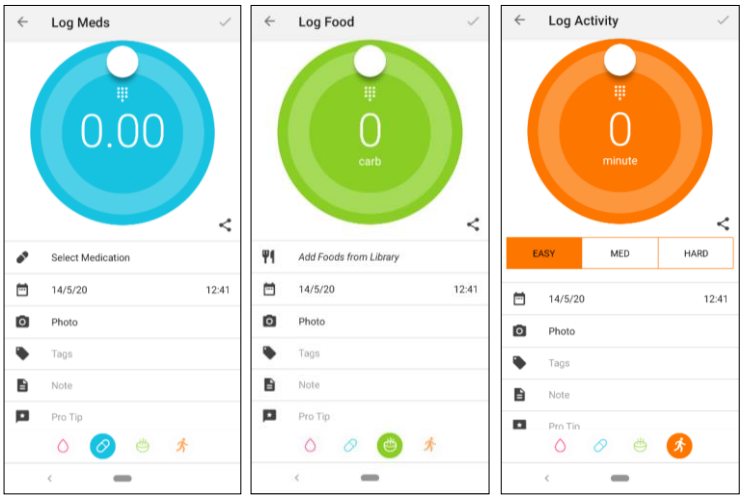


Figure 1.9 Entry One Drop App - User Medication, Food and Activity Log Entry

1.4 Heart Rate

Heart rate, often known as pulse, refers to the heart beats every minute, and it is a useful prognostic indicator of the heart's condition. The average heart rate can differ from individual to individual, while the parameters for evaluation include the rhythm, volume, amplitude, and rate of growth of the heartbeat [32]. The usual adult heartbeat ranges between 60-100 beats/minute, while above and below these points it is characterized as tachycardia and bradycardia, respectively [32]. Variations in the pace and regularity of the heartbeats can occur over time and could possibly indicate a heart disease or another physiological/pathological condition that might need to be detected and resolved.

Inadequate blood glucose levels that approach the hypoglycemic state can result in a faster and more noticeable heartbeat (palpitations). Hypoglycemia can induce hemodynamic alterations, such as an increase in the cardiac output and the peripheral systolic blood pressure, a decrease in the blood pressure and a decreased peripheral vascular resistance [33]. Specifically, hypoglycemic events lengthen the cardiac repolarization, which is the mechanism by which the heart gets ready for synchronized contraction throughout the diastole phase of the cardiac cycle, and in which irregularities in other situations might raise the likelihood of heart arrhythmia (irregular heartbeats) [33][34].

1.4.1 Heart Rate Variability (HRV)

HRV is defined as the *variation* in the *time* interval *between consecutive heartbeats* in milliseconds and is primarily reliant on the extrinsic heart rate [35]. These time intervals between heartbeats are known as RR intervals and are measured in milliseconds (ms). RMSSD stands for the root mean square of successive differences between normal heartbeats and the initial calculation process of it involves the measurement of each successive time difference between heartbeats [36]. These measurements are then squared, and the outcome is averaged before calculating the square root of the sum [36].

Several different approaches can be used to assess variations in heart rate, while the simplest approach is through time domain measurements [35][36]. These approaches can define the heart rate at any moment in time, as well as the intervals between the successive QRS complexes [37]. Each QRS complex is recognized in a continuous electrocardiographic (ECG) record, and the normal-to-normal (NN) intervals or the momentary heart rate is computed (Figure 1.10). The mean NN interval, mean heart rate, difference between longest and shortest NN intervals, the difference between night and day heart rates, etc. are some examples of simple time domain variables that can be measured. Since numerous commercial devices now allow automated HRV monitoring, it is considered a very useful tool for both research and clinical monitoring of patients. However, the importance and interpretation of the many distinct HRV measurements are more complicated than is often recognized, and there is a risk of inaccurate findings and unwarranted extrapolation [35][36].

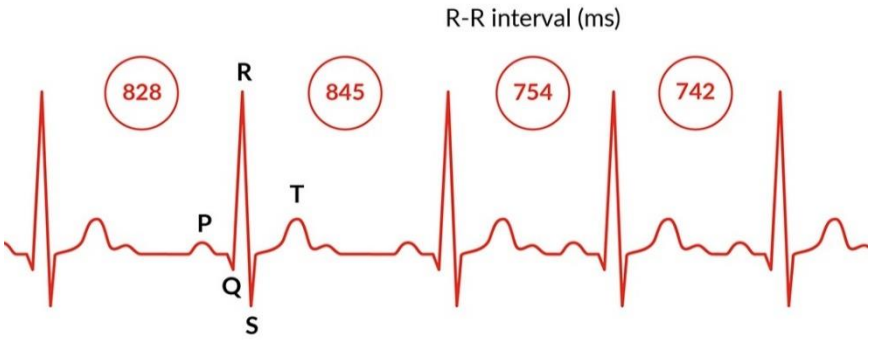


Figure 1.10 An ECG graph displaying a sequence of QRS complexes, where RR intervals fluctuate naturally from beat to beat, and HRV is expressed through an analysis of this variation

A reduced HRV measurement usually occurs when the heart begins to beat quicker and implies a kind of negative overall stress. The constant stimulation of the sympathetic nervous system is a typical cause of a lower measurement [38]. Normally, HRV is higher during calming activities, when the parasympathetic nervous system takes over and while the heart is beating slowly. On the other hand, a high HRV measurement is not always a positive indicator, because HRV can also be caused by pathological conditions. When there are cardiac conduction disorders, which increase HRV measurements, then it is highly associated with an increased risk of mortality, especially among the elderly. In this case, an analysis of the morphology of an ECG can indicate whether the elevated HRV readings are caused by health disorders.

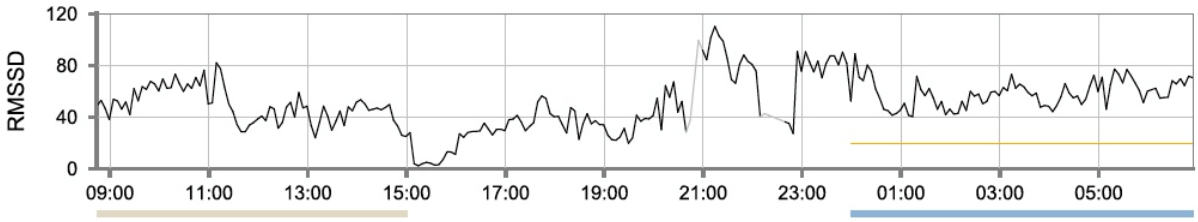


Figure 1.11 An HRV graph (RMSSD in ms) demonstrates how HRV reduces during exercise/stress and increases during sleep/meditation

In autonomic diabetic neuropathy defined by changes in tiny nerve fibers, a decrease in time domain parameters of HRV appears to not only have a poor predictive value, but also to anticipate the clinical manifestation of autonomic neuropathy. Diabetic patients can be distinguished from healthy controls by a decrease in HRV [39]. Furthermore, there is evidence that hypoglycemia, ECG, and heart rate abnormalities are interrelated. HRV is thought to demonstrate

the heart's ability to adjust to changing situations by identifying and reacting rapidly to unexpected stimuli, while HRV analysis can be used to determine the general health of the heart and the state of the autonomic nervous system (ANS), which is responsible for the control of the cardiac activity [35]. Specifically, HRV is found to be linked to hypoglycemia due to the stimulation of the sympathetic nervous system and is among the observable signs for the early detection of hypoglycemia [40]. Therefore, HRV patterns combined with CGM data could be used as an improved and more reliable technique to identify hypoglycemia in real time and even predict such episodes.

1.5 Hypoglycemia Prediction

The primary goal of diabetes management is to rectify hyperglycemia while preventing hypoglycemia, particularly in T1D and T2D insulin-depended patients. The concern of hypoglycemia is a barrier to a successful hyperglycemic control, since it encourages insulin underdosing. Methods to reduce hypoglycemia occurrences include instruction and counseling to increase hypoglycemia recognition in time, as well as the development of predictive technological approaches that could reduce the occurrences of hypoglycemia. These predictive technologies would be particularly beneficial to patients with decreased hypoglycemia consciousness. Furthermore, considering that hypoglycemia is linked to changes in vitals, an ECG and/or heart rate continuous monitoring could be utilized in the process of identifying hypoglycemia.

In this thesis, we will investigate the use of biosignals and other measurements, provided by a wearable device, e.g. heart rate, daily HRV and SpO2, temperature, exercise, steps, and sleep quality, in combination with parameters provided by the user herself/himself, e.g. meals during the day, insulin type and dose, and psychoemotional status, captured through a user-filled questionnaire, for the development of a hypoglycemia prediction model. The blood glucose readings are collected using a clinically approved CGM sensor, and the prediction model is developed using Machine Learning (ML) techniques. In addition, we explore the combination of heart rate data obtained from a smartwatch, that enables continuous heart rate monitoring, with CGM data obtained from T1D patients. Eventually, heart rate readings and CGM data will be integrated into a hypoglycemia prediction algorithm that will define the hypoglycemic state as a blood glucose value < 70 mg/dL. This combination of parameters is meant to be utilized as an improved and more reliable technique/tool for detecting hypoglycemic episodes in the early stages.

Finally, a diabetes management mobile app will be created as a future supporting tool for the patient to collect data, such as finger-stick glucose readings, insulin dosages, meals and exercise, and mood. The mobile app will also include a relevant questionnaire produced by the Behavioral Diabetes Institute[8], which is used to calculate the diabetes distress of the patient. Diabetes distress is a state of unpleasant emotions caused by diabetes and the difficulty of constant self-management over the patient's lifetime. It is linked to poor diabetes self-management, a higher HbA1c, and a negative mental state, while it is frequently confused with depression. Diabetes distress is rather prevalent and it is critical that each session with the healthcare professional provides the ability for the patients to express their emotions regarding their daily life with the disease [41].

[8] Source: https://behavioraldiabetes.org/

2 Systematic Literature Review

Diabetes is a recurrent condition that involves constant control and self-management of the patient's blood glucose. Improper regulation of blood glucose levels in diabetic patients can lead to severe problems, such as kidney and heart failure, as well as stroke and blindness. On the other hand, through the appropriate care of diabetes a patient can live a prosperous life. Nevertheless, a stricter glycemic control can raise the likelihood of developing hypoglycemia, a rapid decrease in blood glucose levels that may lead to coma and potentially death, if proper care is not taken immediately.

The concern of hypoglycemia is a barrier to a successful hyperglycemic control since it encourages insulin underdoing. Methods to reduce hypoglycemia occurrences include instruction and counseling to increase hypoglycemia recognition in time, as well as the development of predictive technological approaches that could reduce the occurrences of hypoglycemia. Blood glucose self-monitoring requires a blood sample to be collected on many occasions throughout the day. Nowadays, the use of CGM systems allows the collection of blood glucose level information in real time.

Artificial intelligence algorithms have been widely used to predict diabetes or as diagnostic tools especially for type 2 diabetes [42]. Unlike glucose prediction, hypoglycemia prediction has received limited research attention. ML models have been used to predict the near future of blood glucose levels and inform patients to take appropriate actions in advance in order to avoid a hypo or hyperglycemic episode [43]. An accurate predictor could improve the quality of life of diabetic patients.

This section presents a review on emerging detection methods and approaches for the identification and prevention of hypoglycemia episodes. Specifically, we investigate the methods used or invented to improve blood glucose monitoring and increase its effectiveness, in order to estimate future glucose levels, which could contribute to the prediction process of future episodes of hypoglycemia. Lastly, we discuss prediction approaches aimed at the early identification and prevention of nocturnal hypoglycemia episodes, which could lead to “dead-in-bed” syndrome, if not identified early. These approaches are categorized, as mentioned above, while their proposed techniques are being discussed.

2.1 Search Strategy

A systematic literature search following the PRISMA guidelines [44] was performed. For the research we used “PUBMED”, “Google Scholar”, “IEEE Xplore” and “ACM” digital libraries

to find articles about technologies related to hypoglycemia detection and prevention in T1D patients. After exploring and combining many search terms to ensure having the broadest results, we used the following terms: “hypoglycemia”, “prediction”, “detection”, “continuous glucose monitoring”, “CGM”, “type 1 diabetes”, “T1D”, “HRV”, “heart rate variability”, “machine learning” and “deep learning”.

The search was performed in June 2021 and was restricted to articles from 2005 onward. In parallel, an alert was set to avoid missing articles. References of the selected articles were analyzed to extract other related articles, and a complementary search in Google Scholar was used to find further information when necessary and to complete the review with original works on each subtopic identified. Articles reporting on new glucose sensors, that exhibit a linear detection range wide enough for blood or interstitial measurement, were eligible. For prediction algorithms, the eligible articles had to report methods for glucose prediction and present details on the datasets used, methodology and performance metrics. We included algorithms that predicted glucose values in a defined prediction horizon, as well as those that specifically predicted hypoglycemic events up to a maximum of 24h in the future. To be eligible, a study had to focus on hypoglycemia or include hypoglycemia prediction/detection techniques based on patient data. The patient group had to have T1D, while the trials had to have a control group. We excluded trials that focused on the primary prevention of diabetes, those targeting gestational diabetes, those pertaining to a closed-loop or artificial pancreas system, and those which primarily focus on T2D.

The literature search gave in total 397 results. Complimentary alerts helped to add 3 more articles. 382 records were screened after the removal of 15 duplicates. 348 articles were excluded because they did not meet our eligibility criteria. After reading the full-text of the remaining 34 articles, we included 19 eligible articles. Figure 2.1 presents the PRISMA flow diagram [44], illustrating the search and screening procedure of this review.

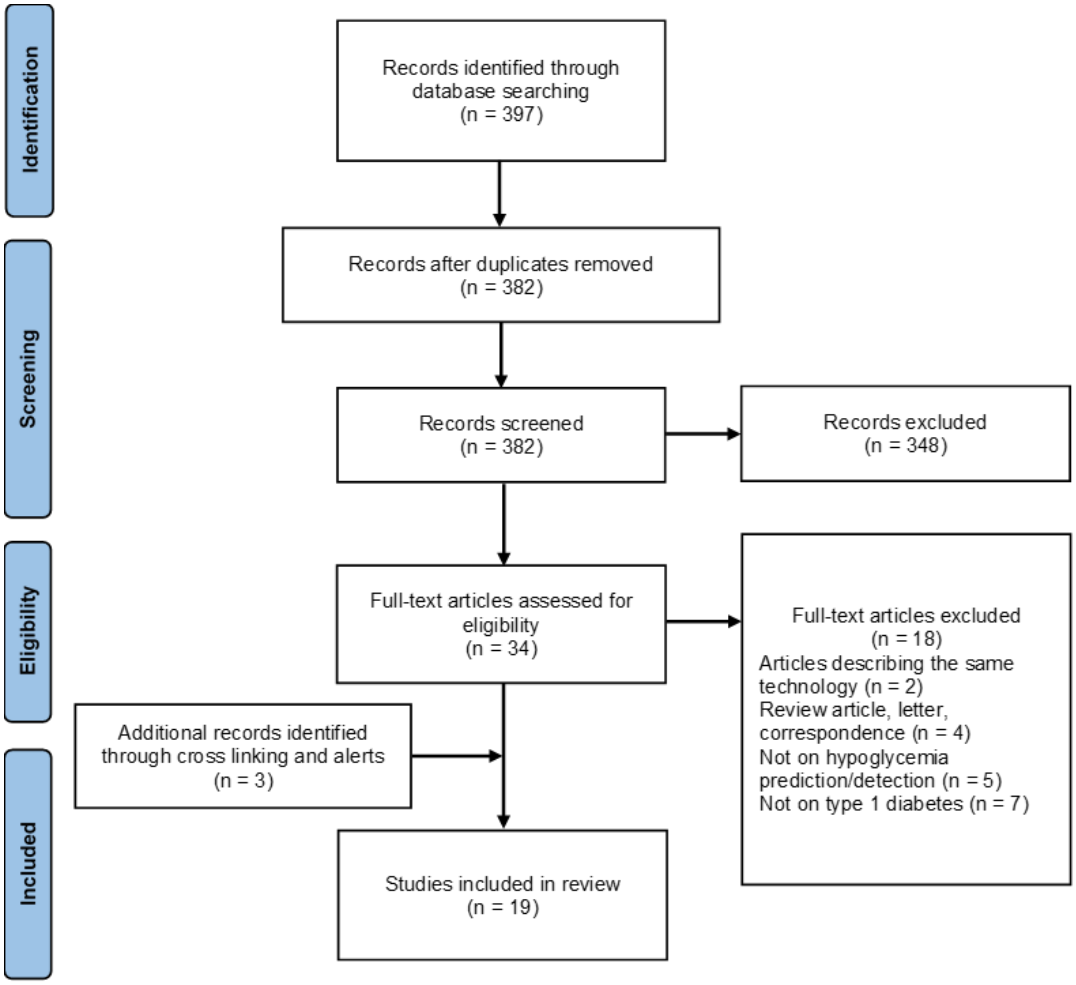


Figure 2.1 The PRISMA flow diagram [44], which presents the search and screening strategy followed in the systematic review

2.2 Hypoglycemia Prediction Algorithms

Prediction algorithms aid toward further enhancing the quality of life of diabetics and their ability to avoid hypoglycemia. They enable patients to intervene early and successfully in the prevention of hypoglycemia episodes. Several of the approaches introduce novel algorithms for predicting hypoglycemia. However, just a few of them have sought to assess their clinical efficacy and advantages in real-life settings. In the presented approaches, several different evaluation metrics were used, such as Relative Error (RE), which refers to the percentage value of the model's prediction error, and Area Under the ROC Curve (AUC-ROC), that is used as a performance evaluation metric for classification tasks. The details about each reviewed study are presented in Table 2.1.

Table 2.1 Summary of the reviewed hypoglycemia prediction approaches

Ref	*Year*	*Dataset*	*Technique*	*Result*
[45]	2017	11 Virtual Adults through UVA-Padova T1D Simulator	K-Nearest Neighbors (KNN)	Accuracy: 83.64 %
[46]	2015	6 Patients from Diabetes Research in Children Network (DirecNet)	Linear Autoregressive (AR) Models of Higher and Lower Orders State Space Model	Relative Error (Higher AR): -7% Relative Error (Lower AR): -24% Relative Error (State Space): -12%
[47]	2013	10 Male T1D Patients	Support Vector Machine (SVM)	Area Under the ROC Curve (AUC-ROC): 0.962 Sample-based Sensitivity: 81% Sample-based Specificity: 93% Event-based Sensitivity: 100%
[48]	2008	Multiparameter Intelligent Monitoring in Intensive Care Database II (MIMIC II)	Classification Tree	Accuracy: 86% Sensitivity: 89.87%
[49]	2020	112 T1D Patients	Logistic Regression (LR) Random Forests (RF)	Sensitivity (LR): 91.85 % Specificity (LR): 96.25% Sensitivity (RF): 94.20% Specificity (RF): 96.67%
[50]	2010	54 T1D Patients	Absolute Predicted Glucose Values Cumulative-Sum (CUSUM) Exponentially Weighted Moving Average (EWMA)	Sensitivity: 89%, 87.5%, 89% Specificity: 67%, 74%, 78%
[51]	2010	40 T1D Patients	Linear Projection Kalman Filtering Hybrid Infinite Impulse Statistical Prediction Numerical Logical Algorithm	Sensitivity: 84%
[52]	2013	19 T1D Patients	Kalman Filtering	Area Under Curve (AUC): Algorithm 1: 71% Algorithm 2: 90% Algorithm 3: 89%

[53]	2013	15 T1D Patients	Support Vector for Regression (SVR)	Sensitivity (30-min horizon): 92% Sensitivity (60-min horizon): 96%
[54]	2018	10 T1D Patients	Support Vector Machine (SVM)	Sensitivity: 78.75% Specificity: 82.15%
[55]	2018	93 T1D Patients	Random Forest Regressor MLP (Neural Networks) Regressor	Mean Absolute Percentage Error (MAPE): Random Forest Regressor: 27.9% MLP Regressor: 29.6%
[56]	2020	1 T1D Patient	Gradient Boosting Decision Tree (GBDT)	Accuracy: 82.7% Sensitivity: 76.7% Specificity: 84.2%
[57]	2016	15 T1D Children	Deep Belief Neural Network (DBN) Restricted Boltzmann Machines (RBM)	Sensitivity: 80% Specificity: 50%
[58]	2021	12 T1D Patients from OhioT1DM Dataset	Deep Neural Networks (DNNs) Long Short-Term Memory (LSTM) Artificial Recurrent Neural Network (RNN)	30-min Prediction Horizon (mg/dL): Root Mean Square Error (RMSE):19.10 Mean Absolute Error (MAE): 13.59 Glucose RMSE (gRMSE): 22.08 60-min Prediction Horizon (mg/dL): Root Mean Square Error (RMSE):32.61 Mean Absolute Error (MAE): 24.25 Glucose RMSE (gRMSE): 38.04
[59]	2020	10 Virtual Adults through UVA-Padova T1D Simulator & 6 T1D Patients from OhioT1DM Dataset	Dilated Recurrent Neural Network (DRNN) Transfer Learning	Root Mean Square Error (RMSE): 20.1 mg/dL
[60]	2019	10 Virtual Adults and 10 Virtual Children through UVA-Padova T1D Simulator	Deep Reinforcement Learning (RL) Double Dilated Recurrent Neural Network (RNN)	Adults: Glucose Time in Target Range (TIR): 93% Children: Glucose Time in Target Range (TIR): 83%
[61]	2020	40 Virtual Adults through AIDA Diabetes Software & 9 T1D Patients D1NAMO Open Dataset	Long Short-Term Memory (LSTM) Recurrent Neural Network (RNN)	Virtual Patients: Root Mean Square Error (RMSE): < 5 mg/dL Real Patients: Root Mean Square Error (RMSE): <10 mg/dL
[62]	2016	1 T1D Patient	Decision Tree	Model validation is in progress, due to the lack of patient data variety
[63]	2014	10 T1D Patients	Forward Selection Linear Logistic Regression	Accuracy: 99% Sensitivity: 79%

In a study by Mordvanyuk et al. [45], authors examined 11 diabetic patient profiles using the UVA-Padova type 1 diabetes simulator. In their method, they presented the use of k-nearest neighbor on patient data, along with details relevant to a sequence of meals, to be able to forecast a possible hypoglycemic/hyperglycemic episode. Their findings indicate that the use of consecutive data can dramatically improve the results of the prediction, especially when estimates determine the type of meal, i.e., breakfast, snack, lunch, etc. Their approach obtained a sensitivity of 88%, when taking into account only carbohydrate intake, fast-acting insulin dose and pre-meal blood glucose.

In terms of blood glucose prediction, the algorithms used in these studies include linear autoregressive (AR) and state space time series models, classification algorithms like the Support Vector Machine (SVM), classification trees, logistic regression (LR) and random forests (RF) [46][47][48][49]. Paul et al. [46] studied the use of generalized autoregressive conditional heteroscedasticity models (GARCH) on CGMS profiles of young T1D children. They aimed to analyze glucose time series and variability, as well as the feasibility of credible blood glucose level prediction. The forecasting capabilities of the GARCH methodology were compared to those of other existing modeling techniques, such as lower and higher order AR models and state space models, where the GARCH method proved to be efficient in recognizing the variability of the glucose profiles and in providing a more credible prediction of short-term future blood glucose levels.

All the research was conducted specifically on T1D patients, who have the greatest need for this kind of prediction algorithm, as they are more complex for algorithms to implement due to their high sensitivity to exogenous factors and their increased blood glucose variability. In an experiment by Jensen et al. [47], they established a pattern classification approach to enhance real-time hypoglycemia identification. They examined data from 10 T1D patients, who suffered 17 insulin-induced hypoglycemic episodes. These episodes were then analyzed to extract characteristics, including the recent insulin intake time and the linear regression of the CGM signal, along with other measures (kurtosis and skewness), at different periods of time. The various combinations of features were employed in an SVM model, and its performance was measured, resulting to the detection of 17/17 hypoglycemic incidents with one false positive and a lead time of 14 minutes.

Another team [48] employed a classification learning technique to forecast hypoglycemic events during a one-hour time span. A classification tree was created with the use of a data mining tool, while the input data consisted of blood glucose measurements and insulin injection frequency. The accuracy and specificity for hypoglycemia prediction of the classification tree was 86% and 89%, respectively.

Dave et al. [49] investigated two different approaches to effectively detect hypoglycemic episodes. These approaches consisted of Logistic Regression (LR) and Random Forests (RF). In their ML-based hypoglycemia detection method, they used data from 112 T1D patients and relied on an extensive feature extraction process to identify any possible glucose patterns. Their final model was developed by considering linear and nonlinear models and combining the collected features. The proposed method correctly forecasted hypoglycemic episodes and achieved high sensitivities close to 95% and 94%, and specificities around 97% and 95%, for prediction horizons of 0-15 and 15-30 minutes.

Clinical studies of such algorithms are projected to rise in the future years, as prediction approaches are integrated into CGM systems and other devices. The advantages for diabetic patients are evident, as they are empowered to make preventative decisions before their blood glucose levels reach critical points. Nevertheless, like with any new equipment, education will be required, in order to avoid the negative side effects of overreactions.

A few studies [50][51] incorporated different algorithms to improve the performance of their models, and take advantage of the unique qualities of each algorithm.

One specific team [50] examined three different time series-based methodologies for hypoglycemia forecasting on a dataset of 54 T1D patients. Their approach involved an exponentially weighted moving-average and a cumulative-sum control chart, as well as the absolute values of the forecasted blood glucose. Each patient was fitted with a Medtronic CGM device, which obtained blood glucose readings every 5 minutes. They merged the CGM's integrated alert with the estimated hypoglycemia alert, through each one of the three prementioned methodologies. They utilized a 30-minute prediction horizon, where the methodologies scored a sensitivity of 89%, 87.5% and 89%, respectively.

Some prediction algorithms used in these studies used linear regressions or Kalman filters, which are computational approaches that use prior data to make short-term predictions and can also be integrated into a monitoring equipment. According to the Diabetes Control and

Complications Trial (DCCT) [64], 55% of the hypoglycemic events occur during sleep, hence some of the studies [51][52] addressed the issue of nocturnal hypoglycemia in T1D and argued that CGM alerts may be ineffective while the patient is sleeping [51][52].

In [51] they tracked 40 patients who wore GlucoWatch CGM during the nighttime and they discovered that 71% of the patients did not react to the alert throughout the night. They proposed that when hypoglycemia is expected, the CGM sensor sends a signal to the pump to cease injecting insulin. In order to anticipate hypoglycemia, they utilized a mathematical model, which employed a system that included specific prediction algorithms. These algorithms were linear projection, Kalman filtering, hybrid infinite impulse, statistical prediction, and numerical logical algorithm. When three algorithms were utilized to prompt the insulin pump suspending, nocturnal hypoglycemia was avoided, with a sensitivity of 60% while by utilizing just two of the algorithms the sensitivity raised to 84% and authors discovered that when the voting threshold increases, the prediction rate drops. The purpose of their study was to create a balanced ratio between nocturnal hypoglycemia forecasting and the probability of false alarms.

Three prediction algorithm variants were examined in a 21-night randomized study, using a Kalman filter-based model [52],. The study comprised 19 adult T1D patients, who were already using the MiniMed Paradigm REAL-Time insulin pump and the Medtronic Sof-sensor blood glucose sensor. Pump suspension events happened on 53% of the intervention nights using the final algorithm. Preliminary effectiveness results indicated that their final algorithm reduced nighttime hypoglycemia by approximetely 50%.

2.3 Algorithmic Inputs, Process, and Outputs

Through the increasing availability of equipment such as CGMs, insulin pumps and physical activity trackers, along with the counting of carbohydrates by diabetics, a wide variety of data can be collected that can be used to predict blood glucose. Depending on the data gathered, their complexities, and the ultimate objective of the algorithm, a variety of methodologies were used in some of the studies, with one or two supplementary data inputs, which were typically the insulin doses, the caloric intake, or even both. The aforementioned input data are conveniently available, since they are usually captured in sensor enhanced pump trials and offer sufficient precision for modelling purposes. These two additional data inputs are processed by physiological models, in many of the evaluated studies [53][54][62][63], in order to derive additional

characteristics to determine the effects and dynamics of insulin action or meals, for a better interpretation by the prediction algorithms.

There is evidence that inclusion of insulin and carbohydrate data in prediction models often increases the performance of the algorithm, even by a very small amount. However, apart from clinical trials, in which patients are deliberately selected based on their compliance with instructions and their ability (e.g., to count carbohydrates), such an input into a real-life environment seems unlikely. Table 2.2 presents the features that were considered and analyzed in each reviewed study.

Table 2.2 Features/Characteristics considered in the reviewed approaches

Author	*CGM readings*	*Glucose meter measurements*	*Insulin dosage*	*BMI*	*Carbohydrates*	*Meals*	*Activity*	*ECG*	*HRV*	*Diabetes duration*	*HbA1c*
[45]	✓		✓		✓	✓					
[46]	✓										
[47]	✓		✓	✓						✓	
[48]		✓	✓								
[49]	✓		✓		✓					✓	✓
[50]	✓	✓									
[51]	✓	✓		✓						✓	✓
[52]	✓										✓
[53]	✓		✓			✓	✓				✓
[54]	✓		✓				✓				
[55]	✓			✓			✓			✓	

[56]	✓								✓		
[57]		✓						✓			
[58]	✓										
[59]	✓		✓			✓					
[60]	✓		✓			✓					
[61]	✓		✓			✓					
[62]						✓	✓	✓			
[63]	✓	✓	✓					✓	✓	✓	✓

In a study by Georga et al. [53], authors utilized data from a recent patient profile to provide their support vector regression (SVR) model for predicting hypoglycemia incidents during sleep, as well as in the daytime, over 30-minute and 60-minute time spans. With a hypoglycemia threshold of 70 mg/dL, the patient profile included glucose readings, meals, insulin dosage and physical activity, along with additional elements to account for recurrent nocturnal hypoglycemia caused by previous hypoglycemia, exercise, and sleep. Their model was developed based on a dataset of 15 T1D patients in an unrestricted environment. Nocturnal hypoglycemia predictions had a sensitivity of 94% and time delays of 5.43 and 4.57 minutes, respectively. When physical activities were not considered, the sensitivity for non-nocturnal events was 92% and 96% for a 30-minute and 60-minute horizon, respectively, with both time delays being under 5 minutes. Nevertheless, when physical activities were considered, the diurnal sensitivity reduced by 8% and 3%, in each time span. In conclusion, they suggest that their method is reliable and both nocturnal and daytime predictions had a high precision, over 90%.

2.3.1 Activity Wearables

Another important factor influencing blood glucose levels is physical exercise. One study examined the usage of physical activity monitors to gather data on heart rate, energy expenditure and the number of steps taken, in order to improve the prediction ability of their model [54]. In particular, the authors investigated the prediction of nocturnal hypoglycemia in T1D adults,

through a FreeStyle Libre CGM device and a physical activity monitor (Fitbit Alta HR; Fitbit). In their 12-week study, 10 T1D adults were examined under free-living conditions at home, while details about the management of T1D, CGM and the physical activity tracker were obtained. Supervised machine-learning algorithms were applied to the data, and prediction models were developed to predict the occurrence of nocturnal hypoglycemia. Authors conclude that more than 70% of the nocturnal hypoglycemia could be prevented using their approach. Specifically, the prediction of the SVM model produced the highest scores, with a sensitivity of 78.75% and a specificity of 82.15%.

Overall, the inclusion of a patient activity signal alerting the algorithm can improve its predictability, which in practice indicates that many widely available systems are accurate enough to be used for this task. The possible issue might be more technical, in terms of merging a variety of models and considering the variability of data formats in each system. Other relevant information, such as stress, medical treatment, and daily events in the patient's life, can be considered as potential inputs, which could be useful in differentiating these prediction models.

In another study, Vahedi et al. [55] investigated the adaption of an ML based model that predicts continuous glucose levels and aims to prevent hypoglycemia, through using physiological and physical exercise data. They used the Medtronic MiniMed 530G insulin delivery device, along with Enlite sensor, to collect 4 months of physiological measures, physical activity, and nutrition data from 93 T1D individuals. Overall, their findings indicated that the model's projected glucose levels were very close to the glucose values as measured with the Enlite sensor.

Another ML model was developed in the context of an ongoing research study by Maritsch et al. [56], whose objective is to identify hypoglycemia by utilizing physiological data collected from a wearable sensor. Specifically, one T1D patient participated in a one-week study, wearing an Empatica E4 smartwatch to collect physiological data and a FreeStyle Libre CGM to gather patient's glucose data. The results reported indicate that physiological data can indeed be used to infer hypoglycemic phases, but frequent false positive results were observed due to the model’s high sensitivity.The authors report that they intent to employ AI-based techniques to make the classification output comprehensible for patients, as well as to incorporate their model into wearables to alert about impending hypoglycemic episodes.

Finally, the ability to connect CGM, insulin pumps and activity trackers to a mobile device can allow for the application of multiple variant algorithms and complex cloud-based estimations. One of the primary aspects in common among many of the prementioned prediction algorithms is that using carbohydrate consumption, insulin dosages and activity tracking data can improve the accuracy over a forecast period. Furthermore, integrating several models could allow for different kinds of hypoglycemia alerts, each one designed for a certain context (activity, sleep, type of meal).

2.3.2 Electrocardiogram-based Hypoglycemia Detection

In recent years, researchers have examined the effect of low blood glucose levels on the electrical activity of the heart. During hypoglycemia, studies revealed a lengthening of the QT interval (the time elapsed between the onset of the Q wave and the conclusion of the T wave), a rise in HRV and alterations in the cardiac repolarization. Thus, monitoring ECG alterations to detect the beginning of hypoglycemia can be a noninvasive method. The emergence of novel ECG wearables permitted the effortless collection of cardiac signals and paved the path for hypoglycemia identification through ECG data and using deep learning techniques.

In a study by San et al. [57], a Deep Belief Network (DBN) was used to build a deep learning system for detecting the initiation of hypoglycemia based on patient's ECG signal. According to the authors, the probability of hypoglycemia in diabetic individuals is most impacted by QT interval prolongation, although an increase in heart rate can also influence the status of the hypoglycemic event. Specifically, their suggested DBN delivers high classification performance with feature transformation. Through the efficiency testing of the system, 15 T1D children participated and were monitored overnight, while their findings revealed that the suggested DBN excelled and produced higher classification performance when compared to other current methods, with a sensitivity and specificity score of 80% and 50%.

Another deep learning framework for predicting blood glucose levels was recently developed and was reported in [58], which utilized edge inference on a microcontroller unit (MCU). The performance of their models was evaluated, based on a clinical dataset acquired from 12 T1D patients and their glucose data from a CGM, as well as through a Long Short-Term Memory (LSTM) artificial recurrent neural network. Such a system could significantly aid in

diabetic care and eventually be used in various diabetes management wearables, such as insulin pumps and CGMs.

Generally, ML and deep learning approaches have demonstrated significant possibilities in terms of data analysis and prediction, while they concentrate on automatically learning behaviors and extracting characteristics from large-scale data. A deep learning model based on a Dilated Recurrent Neural Network (DRNN) that can anticipate future glucose levels for 30 minutes, was reported in [59],. The DRNN model acquired a considerably wider receptive field of neurons when dilation was used, with the goal of capturing long-term relationships, while they also used a transfer learning approach to take advantage of data from various patients.

One specific team [60] suggested a dual-hormone delivery approach for T1D patients using deep reinforcement learning (RL), and based on data from the UVA/Padova simulator [65]. In terms of the hormone delivery strategy, they used double dilated recurrent neural networks, while input data were blood glucose and carbohydrates, and output was the insulin and glucagon distribution. Overall, their findings revealed that deep RL appeared to be helpful in developing customized hormone delivery strategies for patients with T1D.

In another deep learning-based hybrid model, reported in [61], authors attempt to imitate the metabolic behavior of physiological blood glucose techniques, based on both virtual and actual patient data. Furthermore, they simulated a set of differential equations for insulin and carbohydrate intake through a LSTM recurrent neural network. Results demonstrated that their model performs better for virtual patients, due to the intricacy of the insulin and carbohydrate intake dependence in blood glucose levels, which is restricted to a specific cluster of parameters.

In a non-invasive approach by Ranvier et al. [62] aiming to detect hypoglycemic events based on the continuous collection of sensed data from an off-the-shelf sensor belt, they base their method on two distinct models. The first one leverages a physiological consequence of hypoglycemia, namely an alteration of the user ECG's features. They additionally use the accelerometer and breathing sensor of the belt to infer the energy expenditure of the T1D patient, correlated with the food intake to estimate the blood glucose level. Then, they combined these two models to improve the accuracy of their prediction.

Cichosz et al. [63] proposed a novel algorithm for hypoglycemia prediction, where they obtained data from 10 T1D patients, who were observed during insulin-induced hypoglycemia, while the collected blood glucose samples were used as a reference. Their equipment involved the

calculation of ECG, through lead II, and a Minimed Guardian RT CGM, which generated a reading every 5 min. The extracted HRV patterns were incorporated into a mathematical prediction algorithm, along with the CGM data. Cichosz et al. [63] treated the early prediction as a pattern recognition problem based on a fixed hypoglycemia level (3.9 mmol/L). Thus, measuring blood glucose from each patient was used as a reference to categorize each 5-minute reading into 2 groups, normal blood glucose (Cn) or hypoglycemia (Chy). Features obtained from HRV and CGM, prior to each blood glucose measurement, were used to assess if that point in time was below the hypoglycemic threshold of 3.9 mmol/L. As a result, a total of 903 samples were evaluated using their proposed algorithm with a sensitivity of 79% and an accuracy of 99%. The algorithm was able to predict 16/16 hypoglycemic events with no false positives and had a lead time of 22 minutes relatively to the CGM device.

These studies indicate that ECG could be utilized in a free-living environment to assist patients in detecting hypoglycemic episodes. Upgraded equipment and optimized algorithms could make certain methods more precise and simpler to deploy in practice. Although T1D patients might not be the first to benefit from these technological approaches, other non-diabetic patients suffering from hypoglycemic episodes arising from other conditions, such as endocrine, hepatic, or cardiac disorders, etc. could be positively impacted by these ECG-based algorithms.

2.4 Open issues and outcomes

In the context of diabetic hypoglycemia risk management, several hypoglycemia/blood glucose level prediction approaches were assessed in this review. Each of these approaches included different techniques and tools that were used for the blood glucose level prediction. In general, hypoglycemia prediction algorithms can offer a valuable alternative to T1D patients, in order to prevent possible episodes, since there are many patients that suffer from asymptomatic hypoglycemic episodes.

Several of the approaches reviewed have already been incorporated in commercially available systems, i.e. the approach proposed by Bertachi et al. [54] using a FreeStyle Libre CGM device and a Fitbit Alta HR physical activity monitor, and have been shown to effectively decrease hypoglycemic episodes. A common key aspect in several of the evaluated studies is that the inclusion of carbohydrate consumption data, insulin dosages, and/or exercise data can enhance the accuracy of the algorithm, in the context of a defined (medium or long term) forecast horizon.

Furthermore, integrating various models could allow for several stages of hypoglycemia alerts, each of which could be tailored for a unique scenario, such as a post-meal, post-activity, or during sleep prediction [66].

It is evident that CGM can improve the glucose control in diabetes [67] and can provide real time data for the creation of predictive models. The challenge is to use mainstream noninvasive sensors such as wristbands and smartwatches in order to build reliable predictive models for hypo- and hyper- glycemia. Clinical studies of such algorithms are projected to rise in the future, as prediction approaches are integrated into CGM systems and other devices. Furthermore, the evolution of deep learning algorithms that are trained using streaming data already provide promising results for glycose prediction [59]. The advantages for diabetic patients are evident, as they are empowered to make preventative decisions before their blood glucose levels reach critical points [68]. Nevertheless, like with any new equipment, education will be required, in order to avoid the negative side effects of overreactions.

Among the most encouraging techniques is the use of ECG in the process of detecting hypoglycemia. Several ECG products seem to be available nowadays and are often used to treat people suffering from cardiac conditions [69]. As a result, there is the anticipation that sensor companies will be able to add new functionality, such as hypoglycemia detection, soon. The main motivation for such predictive models is that CGM products have a limited lifespan and consumable expenses may make them unaffordable for life-long tracking.

Nevertheless, there can be significant variations in accuracy when predicting blood glucose. It highly depends on the type of diabetes, the patient's lifestyle [70], as well as on the existence of any other chronic disease. Some of the underlying mechanisms, such as age, gender, intestinal microbiota, psychological factors, and genetic traits, may also contribute to variations in the outcomes [71].

In this systematic review we included a wide range of hypoglycemia prediction algorithms and systems, some of which utilized specific medical and/or activity devices. Our research was conducted specifically on T1D patients, who have the greatest need for this kind of prediction algorithm, as they are more complex due to their high sensitivity to exogenous factors and their increased blood glucose variability. The main outcome of our review is that the evolution of ML and DL algorithms already provide promising results for glycose prediction. The

advantages for diabetic patients are evident, as they are empowered to make preventative decisions before their blood glucose levels reach critical points.

Many studies indicate that ECG could be utilized in a free-living environment to assist patients in detecting hypoglycemic episodes. Upgraded equipment and optimized algorithms could make certain methods more precise and simpler to deploy in practice. Although T1D patients might not be the first to benefit from these technological approaches, non-diabetic patients suffering from hypoglycemic episodes arising from other conditions, such as endocrine, hepatic, or cardiac disorders, etc. could be positively impacted from ECG-based algorithms.

Nevertheless, these approaches cannot be recommended to patients on their own, they must be supported by a comprehensive plan, to be effective for supporting medical care. Specifically, prior to deploying the right equipment or technology to aid a diabetic patient, education and medication management are required to decrease the probability of developing hypoglycemia.

3 Methodological Approaches for the Development of Blood Glucose Prediction Models

Generally, ML is an aspect of the rapidly rising discipline of data science and concentrates on the use of structured data and algorithms to emulate the human learning process, while progressively enhancing its accuracy [72]. Algorithms are trained to generate classifications/predictions using statistical approaches, revealing valuable information in data mining initiatives. This information is then utilized to drive decision-making in applications and enterprises, with the goal of influencing important key performance indicators [72]. Through learning and extracting patterns in data, ML enables intelligent systems to develop pertinent models, while these models can establish mappings from the input data interpretation to the rendition of the output data [73]. The performance of traditional machine learning techniques, such as logistic regression, k-nearest neighbors [74], and support vector regression [75], is largely dependent on the data rendition. Predominantly, the information contained in the data rendition (the features) are constructed using previous knowledge and statistical features (such as mean, standard deviation, variance, etc.) [76], principal component analysis (PCA) [77], or linear discriminant analysis [78].

3.1 Computational Models for Blood Glucose Prediction

There are numerous computational models that can be utilized to forecast blood glucose levels in patients with T1D. Several of the most prominent computational models for blood glucose prediction are described in this section [22][59][73][75][79].

3.1.1 Autoregressive Model

Autoregressive models, in general, work on the assumption that previous values have an impact on the current values. Therefore, an autoregressive model is a regression model that predicts the future value based on its own prior values. For instance, we could utilize the last three blood glucose measurements to forecast the glucose concentration in a period of 60 minutes [80] through the use of a weighted sum formula (1), as following:

$$y_{60} = a \cdot x_{-30} + b \cdot x_{-15} + c \cdot x_0 \quad (1)$$

In the above formula, y_t represents the forecasted blood glucose and x_t represents the previous blood glucose measurement, each at time t. The best parameters for a, b and c can be identified, through error reduction among the current and the forecasted blood glucose values for all the accessible points of data. The number of past values, used as an input to the autoregressive model, is a crucial decision, while training the model. In general, the most recent known value is strongly correlated with the value that must be forecasted, and this interdependence declines as values are pushed further back in time. This process indicates that the performance advantages decrease, the more past values are provided as supplementary input.

3.1.2 Support Vector Regression

Support Vector Regression (SVR) is based on the same premise as Support Vector Machines (SVM), but it is used to solve regression problems. In general, SVM is a classification model that uses the maximum potential margin between the support vectors and a hyperplane (Figure 3.1), in order to separate two classes.

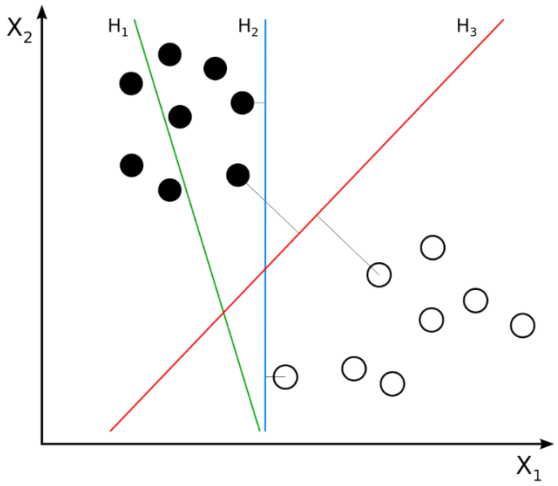


Figure 3.1 In the graphic[9], H2 and H3 are two acceptable linear separations between the two classes. H1 is not a good separation; it classifies 5 instances of the black class as white. H3 is the optimal separation because the margin between the line and the two classes is maximum.

[9] Source: https://nl.wikipedia.org/wiki/Support_vector_machine#

While SVR is similar to SVM, it is a regression algorithm, therefore it can be used to for continuous values rather than classification. This regression algorithm allows for the determination of how much error is permissible in the model and proceeds to fit the data with an appropriate hyperplane or line (depends on the dimensions).

In order to handle data that is not inherently linearly separable, a kernel function can be employed to transform the data into polar coordinates. In that way, data is linearly separable in the form of polar coordinates (Figure 3.2).

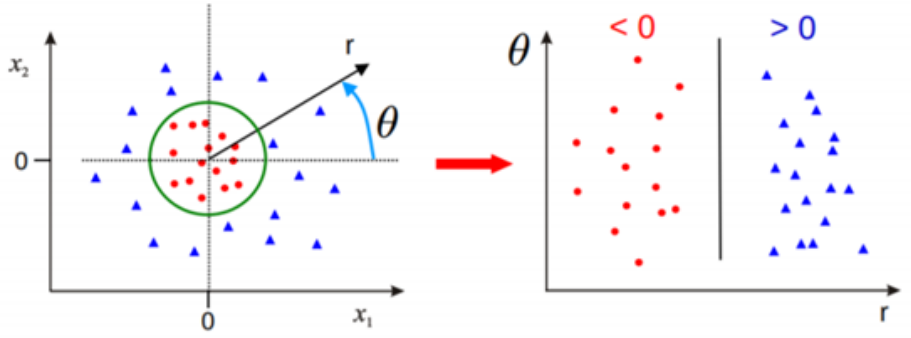


Figure 3.2 Transformation of non-linearly separable data into polar coordinates[10]

The same concept applies to the operation of SVR, with the main difference being that it generates a real number, rather than a binary classification. In addition, a kernel function is employed and the data instead of being linearly separable, is converted into linearly predictable [81][82] (Figure 3.3).

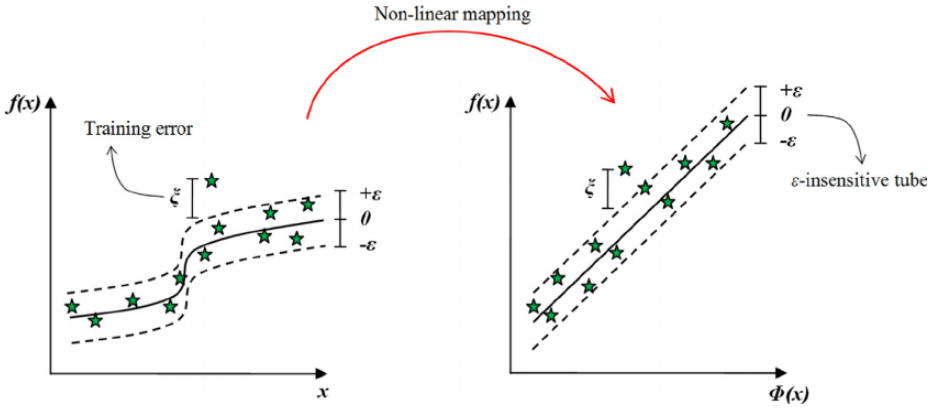


Figure 3.3 Data is linearly predictable through the use of a kernel function [82]

[10] Source: https://www.ic.unicamp.br/~rocha/teaching/2011s2/mc906/aulas/lect3.pdf

Then, the cost is minimized through the following formula:

$$\frac{1}{2}\|w\|^2 + C\sum_{i=1}^{N}\xi_i \qquad (2)$$

In the above equation (2), w represents the linear function's weights and ξ represents the distance between the error margin and the points outside of it $[-\in, +\in]$[11]. Furthermore, there is a hyperparameter that defines how much weight will be from the algorithm on the cost minimization and it is represented with C.

3.1.3 Artificial Neural Networks

An Artificial Neural Network (ANN) is a computational model that is approximately based on how neurons operate in biological brain functioning. When neuron dendrites send signals to the neuron and these signals meet a specific threshold, then a signal fires through the neuron's axon, branching into dendrites of several neurons (Figure 3.4). Generally, neurons can learn by adjusting the weight they assign to other neurons' various inputs.

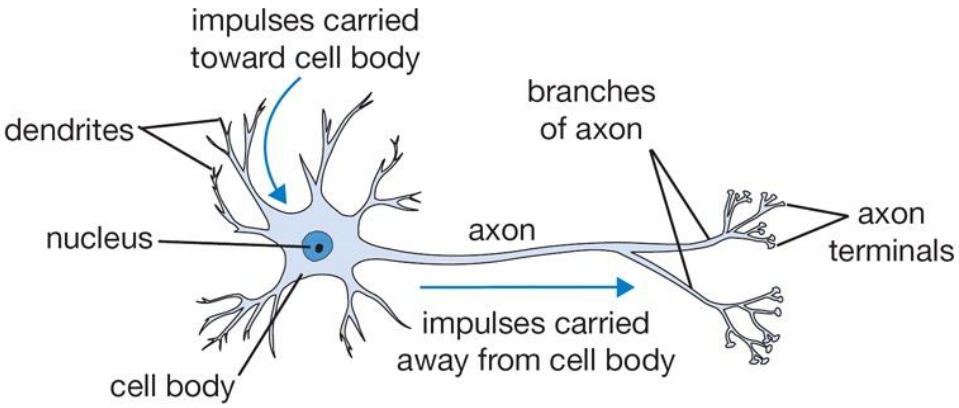


Figure 3.4 An approximate illustration of a biological neuron

In the mathematical model, there are the inputs of each artificial neuron and their weights, added with the bias. Then, there is the application of a non-linearity (or activation) function, which is applied to this value, and is equivalent to a predetermined threshold for the neuron

[11] Source: https://www.saedsayad.com/support_vector_machine_reg.htm

firing (Figure 3.5). Overall, optimizing these weights and biases for each neuron is what training an artificial neural network implies.

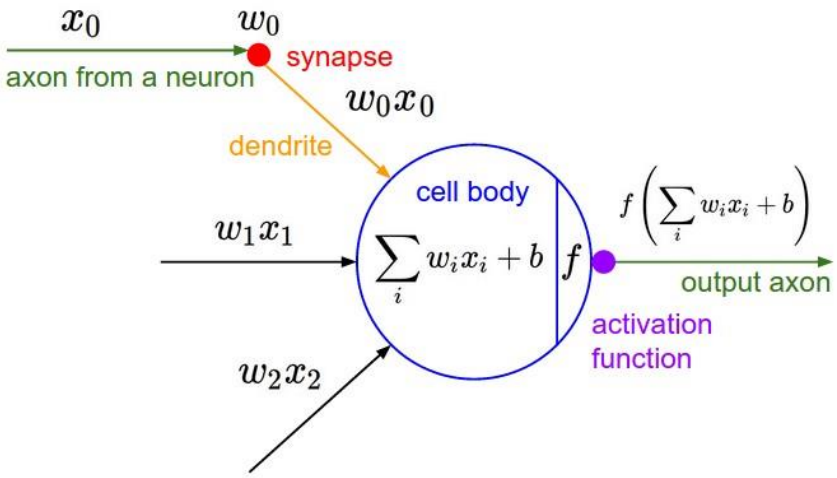


Figure 3.5 The mathematical model of a neuron

3.1.3.1 Regression Neural Network

A neural network is commonly represented as a graph (Figure 3.6), with each node indicating a neuron and the interactions between neurons expressing the weights. In Figure 3.6, there is a graph representation of a regular neural network. The fully-connected layer is the most pervasive layer type in these types of neural networks, with neurons in adjacent layers being fully pairwise associated, while neurons within a single layer do not share any type of connectivity.

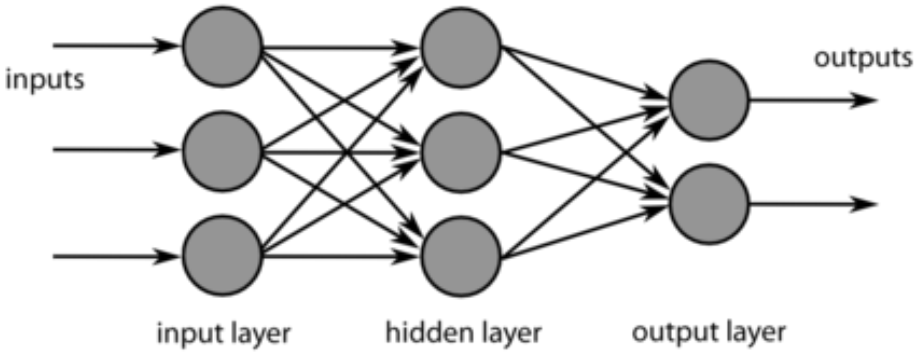


Figure 3.6 Graph of a 2-layer neural network, one hidden layer of 3 neurons and one output layer with 2 neurons, and three inputs[12]

[12] Source: https://www.wikiwand.com/simple/Deep_learning

Since neural networks are adaptable, they can be utilized for classification, as well as regression. In general, regression facilitates the correlation between a dependent and an independent variable (or more than one). In order for the regression model to perform successfully, the regression equation needs to fairly match the data, while this is a rare case for most of the regression models. Despite neural networks being complicated and computationally costly, they can dynamically select the optimal form of regression, and if that is insufficient, supplementary hidden layers can be included to enhance the prediction. Nowadays, neural networks are being studied extensively in the field of diabetes management [73]. Nevertheless, in the literature, neural networks are typically developed with fewer than three layers, limiting their learning potential due to the complexity of the model [73].

A specific output can be derived through feeding input data into the neural network, from the left side to the right side, which can be evaluated and contrasted to the expected output through a cost function, such as Mean Squared Error (MSE). MSE is the sum of the squared discrepancies between the prediction and the true value, while the result is a single number that represents the cost. The mathematical formula of MSE is presented as following:

$$MSE = \frac{1}{N}\sum_{i=1}^{N}(x_i - \hat{x}_i)^2 \qquad (3)$$

In the above equation, N is the number of data points, while x_i denotes the true value of data point i. In addition, $\frac{1}{N}\sum_{i=1}^{N}$ is the mean and $\hat{x}_i$ is the predicted value of data point i. The evaluation of this cost derivative is performed considering the weights and biases of the model, in order to determine the way that these parameters should change to reduce the cost. Model improvements can be accomplished, through continuously feeding series of data into the network and adjusting the weights and biases, depending on the estimated derivatives. Overfitting is a typical issue with neural networks, which indicates that the network has become overly acclimated to the noise in the training data, and as a result, it will not perform well on new data. Weight regularization is one technique to overcome this problem that involves assigning a cost to the weight parameters, prompting the network to maintain lower weights.

3.1.3.2 Recurrent Neural Network

A further concern with regular ANNs is that they are unsuitable for use in sequential data. For example, assuming the goal is to use neural networks to predict the upcoming word in a phrase, this process would require knowledge of the previous words. In this case, the previous five words in the phrase can be fed to the network as input and observe whether the network can predict the next word. Nevertheless, it is likely that more information from several past phrases might be needed to figure out the following word. A recurrent neural network (RNN) architecture to tackle this problem. In the structure of the RNN presented in Figure 3.7, the neurons in the hidden layer can obtain further input from their prior state, which is also linked by weights. These weights are learnt by backward propagation of errors (supervised learning algorithm). In this manner, knowledge about previous inputs can be retained, while feeding data into the neural network for one time-step.

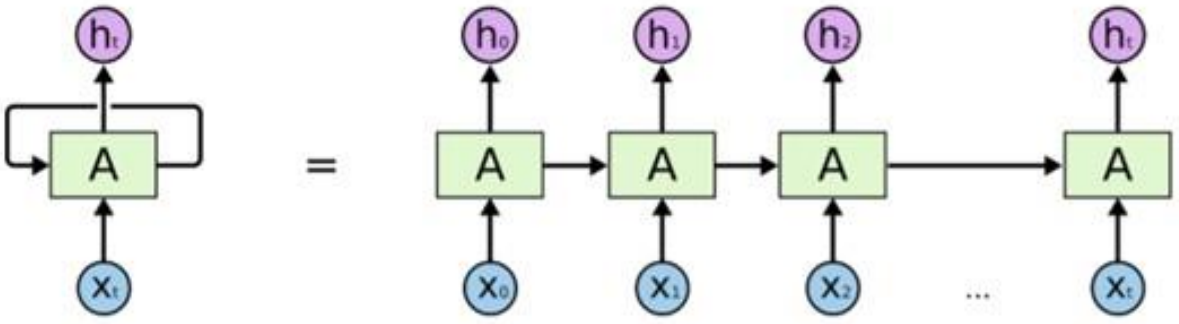


Figure 3.7 The structure of an RNN is displayed as several copies of the network, in which every copy is passing a message to the following[13]

The vanishing gradient problem is a frequent issue with RNNs, which can make the learning of large data sequences difficult. The cost function's gradient is computed in the RNN, based on a previous input, and it holds information utilized in the RNN weights update (). As the computing takes place on inputs from many time-steps ago, the gradient vanishes and the weight updates are minimized, implying that no actual learning occurs. This difficulty of long-term dependencies learning is due to the large number of calculation steps between a preceding input and the output.

[13] Source: https://towardsdatascience.com/introduction-to-recurrent-neural-network-27202c3945f3

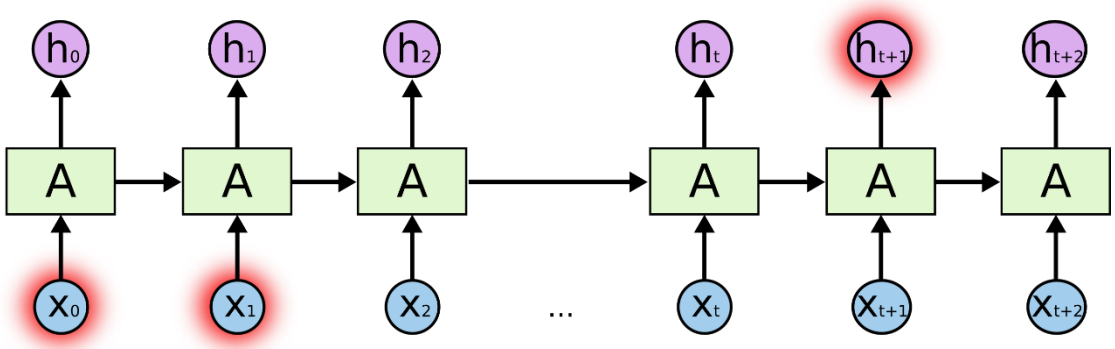


Figure 3.8 The problem of vanishing gradients in RNNs[14]

3.1.3.2.1 Long Short-Term Memory (LSTM) Network

To address the prementioned problem of vanishing gradients and improve the learning of long-term dependencies in RNNs, Hochreiter et al. [83] presented an artificial recurrent network architecture called Long Short-Term Memory (LSTM).

The basic architecture of an LSTM network extends the conventional sequential RNN by adding three gates to the hidden layer: a) the input gate, b) the forget gate and c) the output gate, as presented in Figure 3.9. They are essentially just additional weight parameters that the network utilizes to decide what information to discard and what to preserve. Specifically, these gates regulate what information is accepted in the input gate, what information is discarded based on low importance (forget gate), and what information is allowed to influence the output at the current time-step (output gate).

[14] Source: https://towardsdatascience.com/introduction-to-recurrent-neural-network-27202c3945f3

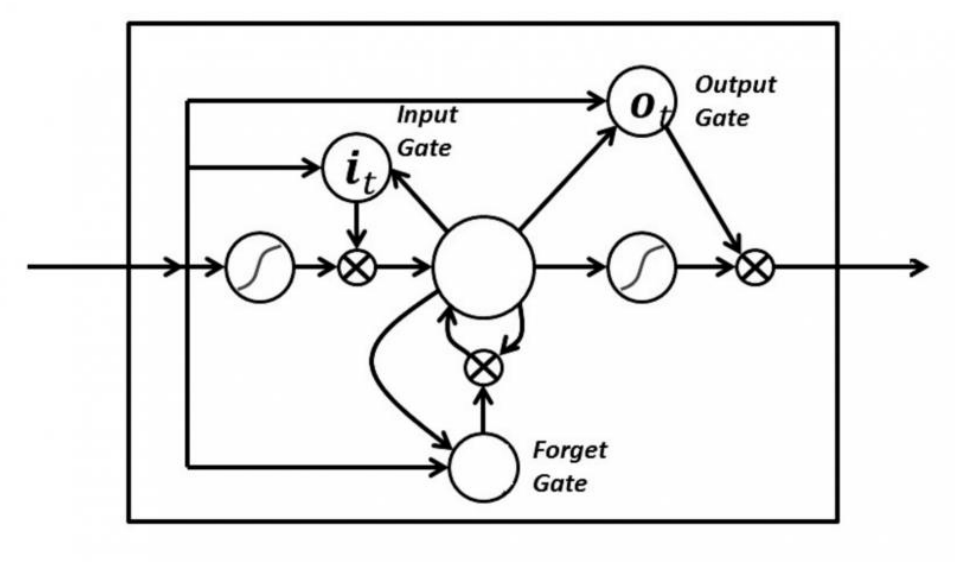


Figure 3.9 LSTM network architecture with the three additional gates (input, forget and output)[15]

In summary, LSTM is a type of recurrent network that can learn long-term dependencies. In comparison to RNNs, an LSTM has the privilege of being able to retain information stored in the memory for a longer time period. The learning process occurs through LSTM cells, as they have memory that can preserve past time-step data. In addition, this type of recurrent network is an appropriate solution for the classification, analysis, and prediction processes for time-series with uncertain time lags. Finally, through LSTMs learning process, models can be trained with hundreds of time-step series, which an RNN typically has difficulty coping with.

[15] Source: https://builtin.com/data-science/recurrent-neural-networks-and-lstm

4 Implementation

In this thesis, we developed a deep learning strategy for hypoglycemia prediction in T1D patients, based on a multi-layer convolutional recurrent neural network (CRNN) architecture established and reported in [73]. Furthermore, a supporting T1D management mobile application, named “T1D Diary”, was also developed as a future patient data collection method and diabetes management system, which is presented in chapter 4.2.

Multi-step predictions, a regression model using blood glucose level data for each patient every 5 minutes, and the incorporation of other training data like basal insulin, bolus insulin, and heart rate are all part of our proposed hypoglycemia prediction model. The use of a CRNN architecture (Figure 4.1) serves two purposes. First, convolutional layers perform as filters, learning to recognize and forecast the features of interest in an automatic way. They are also effective for evaluating time series that do not require a lot of signal processing. Second, recurrent neural networks (RNNs) are widely known for their ability to learn long-term correlations among various values [60]. For example, the neural network needs to be able to detect a relationship between the current insulin ingestion and a shift in glucose levels in the near term. The objective of this thesis is to forecast blood glucose levels in T1D patients and highlight the possible hypoglycemic incidents, in order to avoid them, as well as other possibly severe health consequences that could occur as a result of these events. Thus, we present an approach that is able to forecast hypoglycemic incidents in T1D patients, while MAE and RMSE metrics were used for the evaluation and accuracy measurement of the model.

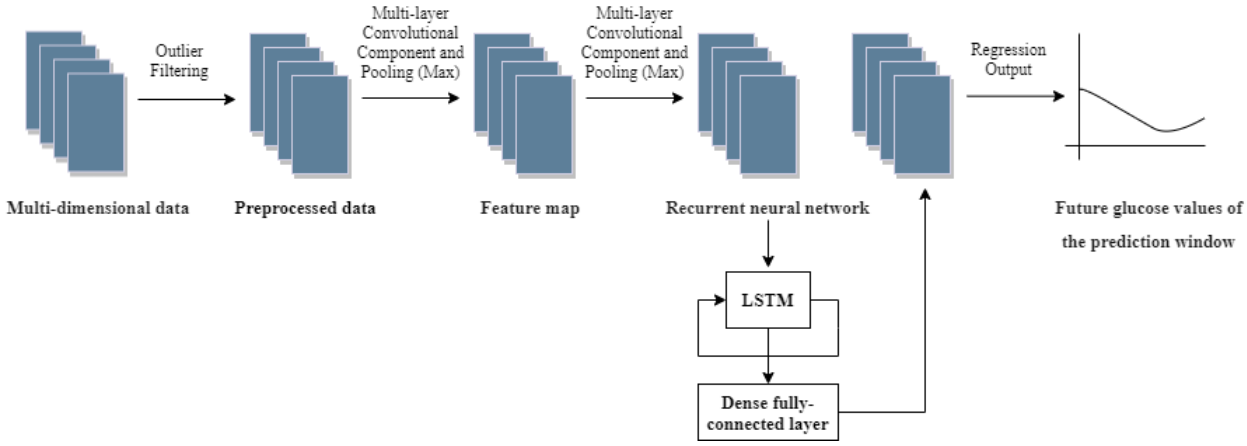


Figure 4.1 Convolutional Recurrent Neural Network (CRNN) architecture

4.1 Dataset Description

For the purpose of this thesis a dataset was used, namely, OhioT1DM (2018) [84]. The OhioT1DM dataset contains data from 6 T1D patients with the following identification numbers (IDs): 559, 563, 570, 575, 588, and 591, who were monitored for 8 weeks. All of the data patients were between the ages of 40-60 years old and there were two males and four females in the group. Throughout the parse of the 8-week period, all of them wore a CGM and an insulin pump. Specifically, they used Medtronic 530G insulin pumps and Medtronic Enlite CGM sensors. They also contributed physiological data through the Basis Peak physical activity monitor, as well as blood glucose, insulin, and other life event data via a tailored smartphone application.

OhioT1DM dataset consists of 5-minute aggregations of CGM blood glucose levels, basal and bolus insulin units, meal's caloric intake, exercise, sleep, work, stress, and illness. Furthermore, it contains physiological data from various physical activity trackers, such as heart rate every 5-minutes, galvanic skin response (GSR), skin (thermal homeostasis) and air temperature, as well as step count. The prementioned data were all formed into extensible markup language (XML) files, divided into testing and training data for each patient's data, resulting to two files for each participant (12 in total).

The training and testing examples for each participant are presented in Table 4.1. Since OhioT1DM data are obtained from various devices and some of the data are manually reported by patients, they tend to be unsynchronized, while in the data collected from the CGM blood glucose sensor and the Basis Peak activity tracker there are cases of missing data. Every XML file in OhioT1DM dataset contains specific data fields [84], presented in Table 4.2.

Table 4.1 OhioT1DM test and training examples for each patient

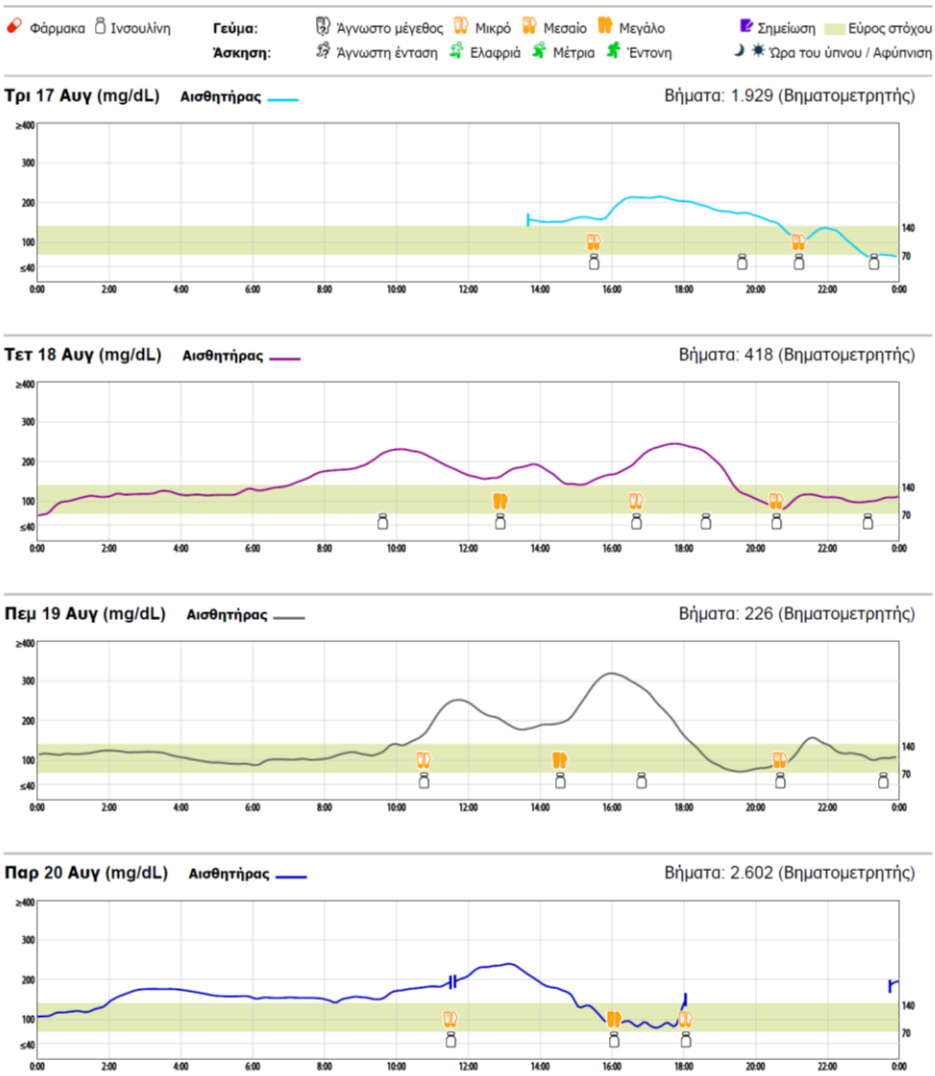
Patient ID	***Testing Examples***	***Training Examples***
559	2514	10796
563	2570	12124
570	2745	10982
575	2590	11866
588	2791	12640
591	2760	10847

Table 4.2 Data fields contained in the OhioT1DM dataset

Field	*Description*
patient	The patient's identification number and their insulin brand.
glucose level	Blood glucose data from CGM, taken every 5 minutes.
fingerstick	Blood glucose measurements collected by the individual through finger-sticks.
basal	The basal rate at which basal insulin is administered on a continual basis, and starts when the period of time is defined, while it continues until another basal rate is specified.
temp basal	A temporary basal insulin rate that takes precedence over the patient's regular rate.
bolus	Type of insulin that is administered to patients, usually before a meal or when the patient's glucose levels are too high.
meal	The patient's carbohydrate estimation for the meal, as well as the meal's self-reported timing.
sleep	The patient's subjective rating of sleep quality and times: 1 for poor, 2 for fair, and 3 for good.
work	Times of getting to and from work, as stated by the employee. On a scale of 1 to 10, with 10 being the most physically active, intensity is the patient's subjective rating of physical activity.
stressors	Self-reported stress periods.
hypo event	Time of the hypoglycemic episode.
illness	Time of self-reported illness.
exercise	Self-reported workout time and duration in minutes. On a scale of 1 to 10, with 10 being the most physically active, intensity is the patient's subjective rating of physical activity.
basis heartrate	5-minute heart rate measurements.
basis gsr	5-minute galvanic skin response measurements.
basis skin temperature	5-minute measurements of skin temperature in degrees Fahrenheit.
basis air temperature	The air temperature accumulated in degrees Fahrenheit, every 5 minutes.
basis steps	The total number of steps tallied every 5 minutes.

basis sleep	The times that Basis Peak fitness band reported that the individual was sleeping, as well as its sleep quality estimate.

Furthermore, we extended the aforementioned dataset, by including an additional T1D patient's data (blood glucose level, bolus and basal insulin and heart rate) collected over a one-week period under free-living conditions. For the collection of the patient data, we used Medtronic Minimed Envision Pro blinded CGM system and a physical activity monitor, Fitbit Sense, tracking the patient's heart rate.



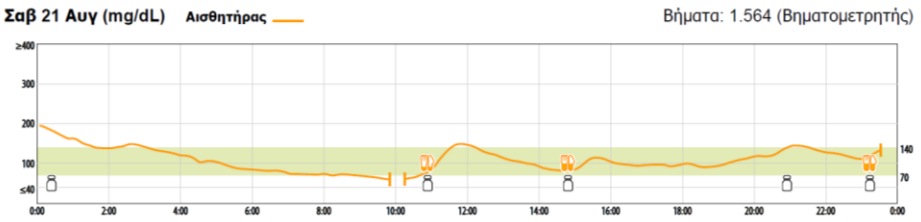


Figure 4.2 Medtronic Envision Pro blinded CGM system patient data

The CGM system included an Envision glucose sensor, an Envision recorder, and a one-press serter, used in the course of the data collection week. Through this blinded CGM evaluation, the patient self-reported periodic finger-sticks, as well as insulin units (basal and bolus) and meal information (Figure 4.2). The heart rate data were measured throughout the data collection week, and a daily report was available at the end of it, along with weekly heart rate variability (HRV) and resting heart rate (RHR) averages, as seen in Figure 4.3 and Figure 4.4.

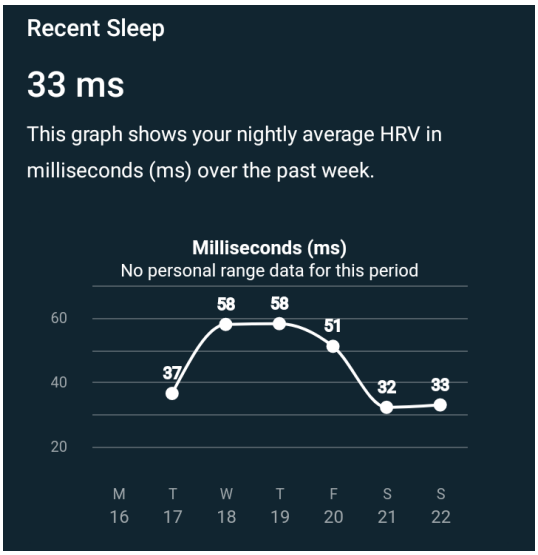


Figure 4.3 Average weekly HRV (ms) of the additional patient

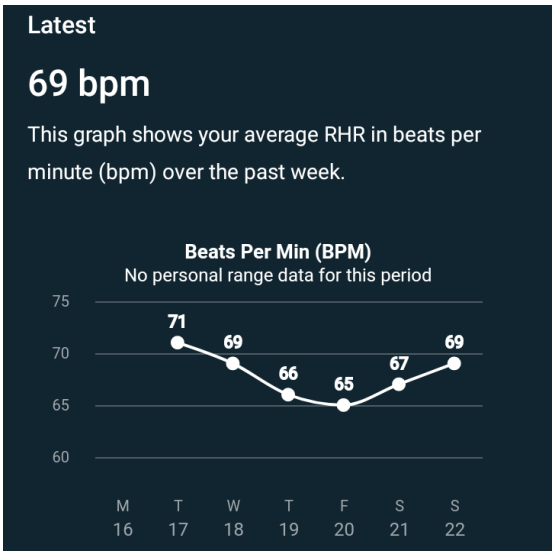


Figure 4.4 Average weekly RHR (bpm) of the additional patient

The previously mentioned data were reported by the patient through Medtronic's Envision Pro mobile application and the Fitbit mobile application. Specifically, the data acquired from Envision Pro mobile application involved the time and day of the event, 5-minute aggregations of CGM blood glucose measurements, step count from the CGM device, basal and bolus insulin information (time of the day and units), self-monitoring glucose levels, as well as meal's carbohydrate count (g) (Figure 4.5). In this way, the T1D patient kept track of every action

throughout the day, even though the CGM system that was used was blinded and didn't offer her/his blood glucose information. The specific blinded CGM system was particularly chosen, in order to assure that we will have a clear view of the patient's hypoglycemic events, without any distractions. On the other hand, Fitbit mobile application provided real-time heart rate data, as well as resting heart rate, blood oxygen saturation (SpO2) and daily averages of HRV. Specifically, the heart rate data acquired from Fitbit were then combined with Medtronic's CGM readings into 5-minute aggregations, based on the time and date of the events, in order to follow the data structure of the OhioT1DM dataset.

Ημερομηνία και ώρα	Συμβάν	Λεπτομέρειες συμβάντος	
Τρίτη 17 Αύγουστος 2021			Βήματα: 1.929 (Βηματομετρητής)
15:31:28		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 11,0 μονάδες
		Γεύμα	Μεσαίο γεύμα, 15 γραμ.
19:38:20		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 5,0 μονάδες, υψηλό σάκχαρο στο αίμα
21:13:42		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 7,0 μονάδες
		Γεύμα	Μεσαίο γεύμα, 10 γραμ.
23:18:14		Ινσουλίνη	Ινσουλίνη μακράς δράσης, 14,0 μονάδες
Τετάρτη 18 Αύγουστος 2021			Βήματα: 418 (Βηματομετρητής)
9:38:42		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 5,0 μονάδες, υψηλό σάκχαρο στο αίμα
12:54:42		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 10,0 μονάδες
		Γεύμα	Μεγάλο γεύμα, 20 γραμ.
16:42:40		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 4,0 μονάδες
		Γεύμα	Μικρό γεύμα, 10 γραμ.
18:37:03		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 4,0 μονάδες, υψηλό σάκχαρο στο αίμα
20:35:42		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 7,0 μονάδες
		Γεύμα	Μεσαίο γεύμα, 15 γραμ.
23:08:41		Ινσουλίνη	Ινσουλίνη μακράς δράσης, 14,0 μονάδες
Πέμπτη 19 Αύγουστος 2021			Βήματα: 226 (Βηματομετρητής)
10:47:14		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 5,0 μονάδες
		Γεύμα	Μικρό γεύμα, 15 γραμ.
14:34:37		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 12,0 μονάδες
		Γεύμα	Μεγάλο γεύμα, 45 γραμ.
16:50:39		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 5,0 μονάδες, υψηλό σάκχαρο στο αίμα
20:42:21		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 7,0 μονάδες
		Γεύμα	Μεσαίο γεύμα, 15 γραμ.
23:34:09		Ινσουλίνη	Ινσουλίνη μακράς δράσης, 14,0 μονάδες
Παρασκευή 20 Αύγουστος 2021			Βήματα: 2.602 (Βηματομετρητής)
11:31:36		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 6,0 μονάδες
		Γεύμα	Μικρό γεύμα, 15 γραμ.
16:04:03		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 12,0 μονάδες
		Γεύμα	Μεγάλο γεύμα, 40 γραμ.
18:04:06		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 4,0 μονάδες
		Γεύμα	Μικρό γεύμα, 10 γραμ.
Σάββατο 21 Αύγουστος 2021			Βήματα: 1.564 (Βηματομετρητής)
0:24:46		Ινσουλίνη	Ινσουλίνη μακράς δράσης, 14,0 μονάδες
10:54:00		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 7,0 μονάδες
		Γεύμα	Μικρό γεύμα, 20 γραμ.
14:49:54		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 7,0 μονάδες
		Γεύμα	Μεσαίο γεύμα, 20 γραμ.
20:55:45		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 4,0 μονάδες, υψηλό σάκχαρο στο αίμα
23:14:02		Ινσουλίνη	Ινσουλίνη βραχείας/ταχείας δράσης, 8,0 μονάδες
		Γεύμα	Μεσαίο γεύμα, 20 γραμ.

Figure 4.5 Self-reported patient data in Envision Pro mobile application

Final patient data added to the pre-existing OhioT1DM dataset included the following fields: the patient's 5-minute CGM blood glucose readings, basal insulin doses, insulin bolus doses, and heart rate measurements every 5 minutes (paired with the time and date of the CGM reading).

4.2 T1D Management Mobile Application

Nowadays, smartphone technologies are fast evolving, particularly in terms of connection, information processing, architecture, functionality, and networking. At the same time, diabetes monitoring and treatment technologies are also quickly expanding, and can interact with relevant applications. Diabetes, and especially T1D, is highly suitable for smartphone-based assistance due to the difficulties associated with the overall disease management [85]. As a result, various diabetes management applications strive to deliver patient data parameters, such as carbohydrate consumption, exercise, blood glucose monitoring, which can be evaluated and utilized by the application for patient decision guidance.

A supporting T1D management mobile application, named "T1D Diary", was also developed in this thesis as a future patient data collection method and diabetes management system. In this mobile application the user can keep records of T1D-related parameters including finger-stick glucose measurements, basal and bolus insulin doses, carbohydrates count, exercise, and mood. Self-monitoring blood glucose measurements are registered in mg/dL units, insulin doses are recorded in units/mL and caloric intake is calculated in carbohydrate grams (g).

The aforementioned smartphone application was built using React Native[16] and Firebase Realtime database[17]. React Native is based on the React framework and provides an open-source mobile application framework that enables cross-platform development, as well as native platform capabilities[18]. On the other hand, the Firebase Realtime Database is a cloud-based database that stores data in JSON format. In addition, the database instance is synchronized in real-time across all the connected clients and is updated with the most recent data. With every user data submission, the collected data and the questionnaire responses are all forwarded to the personalized space in

[16] Source: https://reactnative.dev/

[17] Source: https://firebase.google.com/docs/database

[18] Source: https://github.com/facebook/react-native

the Firebase Realtime database. Data are stored based on their type, and the date and time of submission, as seen in Figure 4.6.

Figure 4.6 T1D Diary - Realtime Database structure

In terms of the user interface (UI), "T1D Diary" is easy to access, understand and use. The main functionalities and components of the application are maintained in a simple form to avoid adding unnecessary complexity that could detract from the user experience (UX). Specifically, the developed mobile application includes several navigation, notification, and database communication components (Figure 4.7), such as the home screen, the login and the sign-up screen, and more. Figure 4.8 presents the main menu items of the application, which are the patient profile, the patient records (glucose and insulin, activity/exercise, carbohydrates) and a T1D-related questionnaire.

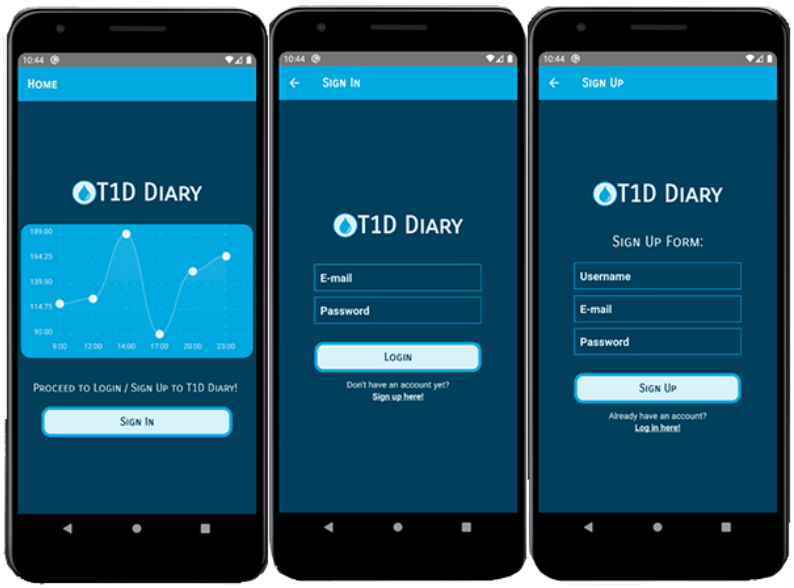


Figure 4.7 T1D Diary Components

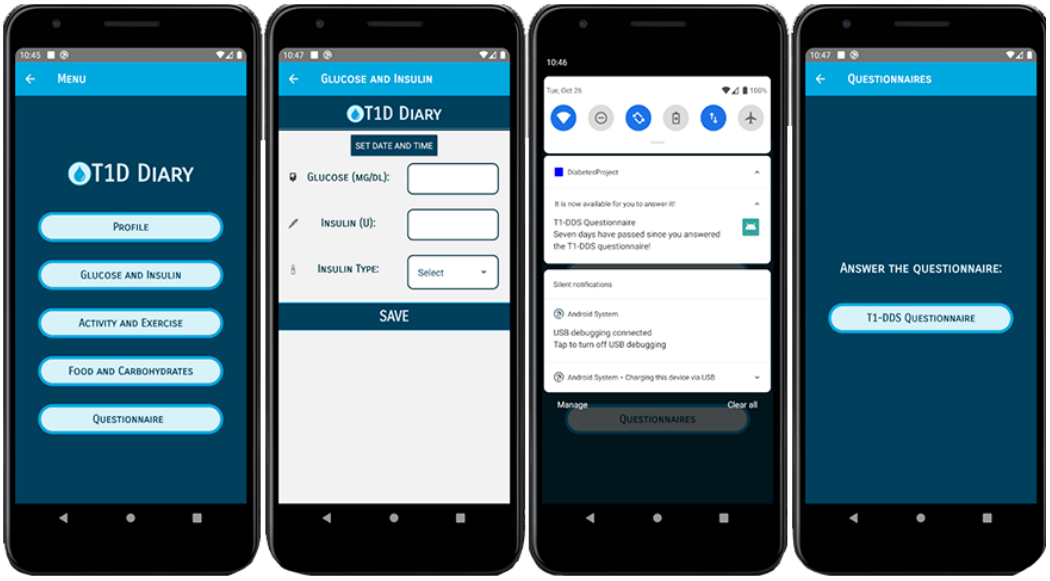


Figure 4.8 T1D Diary menu items and notifications

"T1D Diary" incorporates an appropriate T1D-related questionnaire, which was used to calculate the patients' diabetes distress once a week (Figure 4.9 and Figure 4.10). The particular questionnaire was extracted from Behavioral Diabetes Institute (BDI)[19] and measures Diabetes Distress Scales for adults with T1D (T1-DDS). T1-DDS is a clinical tool and useful outcome

[19] Source: https://behavioraldiabetes.org/

measure for studies, that was published in 2015. This self-report scale involves 28 questions concerning seven distress dimensions. Particularly, these dimensions are powerlessness, management distress, hypoglycemia-related distress, negative social attitudes, eating distress, physician distress, and friends/family distress [41]. It was first published in 2015 and has swiftly gained popularity as a clinical tool for initiating talks with T1D patients as well as a key outcome measure in upcoming studies. In addition, a reminder is established for the application to notify the patient that the questionnaire is available.

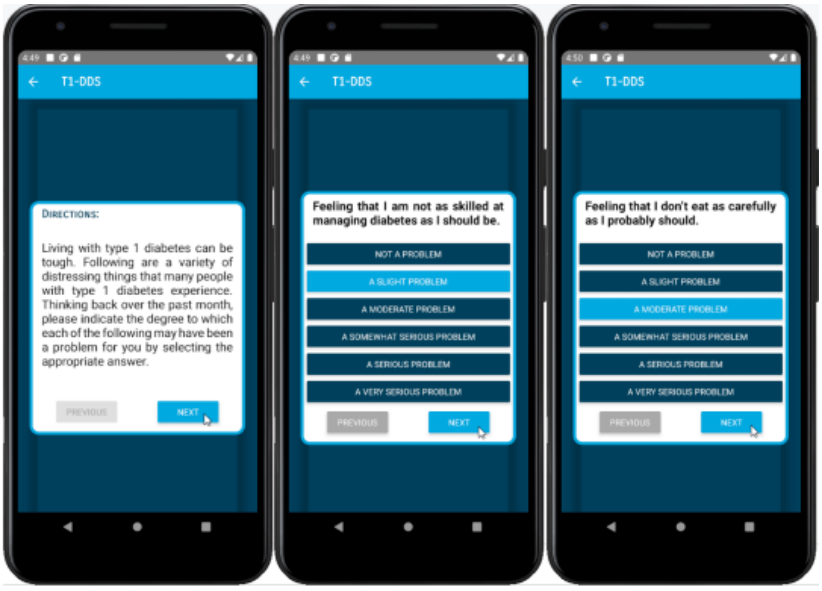


Figure 4.9 A sample of the questions contained in the T1-DDS questionnaire[20] concerning the patient's level of distress (1)

[20] Source: https://behavioraldiabetes.org/scales-and-measures/#1448434304201-ce67e63c-8e90

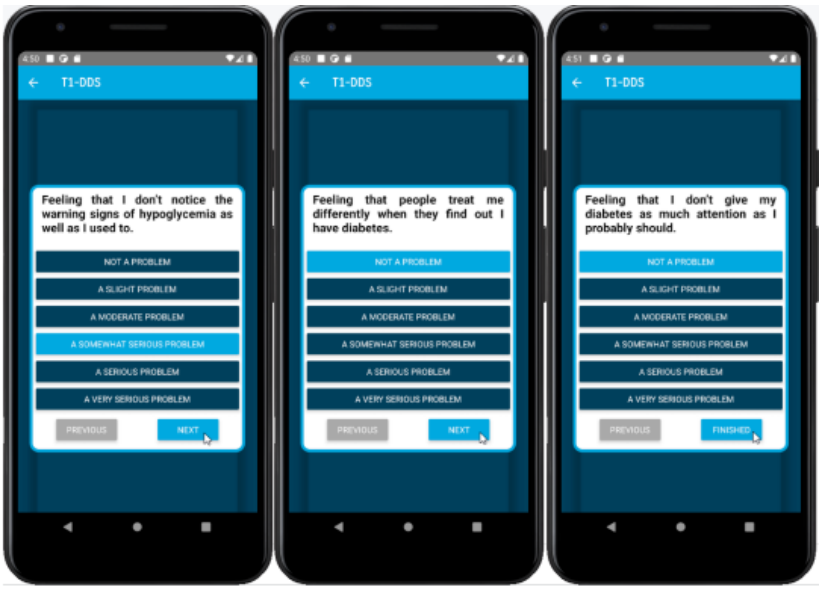


Figure 4.10 A sample of the questions contained in the T1-DDS questionnaire[21] concerning the patient's level of distress (2)

4.3 Hypoglycemia Prediction Model

4.3.1 Data Importation and Preprocessing

Importing data entails importing, integrating, and aligning values from several sources throughout the same time frame. Patient glucose levels, basal and bolus insulin, and heart rate were chosen as features. These features must all have sampling values carried over at the same moment during the preprocessing step. This necessitates the employment of subsampling or oversampling techniques, as well as the definition of imputing methods as a consequence. To resample the time series at a frequency of 5 minutes, linear interpolation is employed on the blood glucose levels in the training dataset. Due to their relatively deficient nature, the insulin (basal and bolus) and heart rate features might be substituted with null values, when this is necessary. A summary of the series of preprocessing steps followed at this stage is presented in Table 4.3.

Table 4.3 A summary of the steps followed in the preprocessing stage

	Preprocessing Steps
i.	Save the timestamps indexes where the blood glucose levels are available.

[21] Source: https://behavioraldiabetes.org/scales-and-measures/#1448434304201-ce67e63c-8e90

ii. Resample the features' timeseries to a 1-second delta time.

iii. Use the most recent available data, to fill the missing data in advance.

iv. Use 0 to fill in the remaining missing data.

v. Resample the features to a 5-second time delta.

vi. In a window comprising the preceding 2-hours' worth of data values, we use a 1D Gaussian smoothing filter with a smoothing degree of $std = 1$ (standard deviation) on every feature.

The stored timestamps from the first preprocessing step (i) are then used to obtain the outcomes at the same points in time. The missing data are imputed using linear interpolation during the training phase and this increases the number of data points on which the model may be trained. Nevertheless, linear interpolation is not suitable for large gaps in missing data, and it is not utilized during testing since it could result in a data peek. As a result, future data would contaminate the forecasts. Equation (4) is used to calculate the target values for the CRNN model.

$$x_{t+L} = b_{t+L} - b_t, for\ L = 1,2, \dots ,12 \quad (4)$$

In the above equation, b_t is the blood glucose level at time t, and L is the lag value in time-steps for the horizon. Furthermore, x is the label to predict (the differentiated blood glucose value).

The proposed model does not forecast the blood glucose level directly, but it calculates the difference from the previous established value. For example, if the current blood glucose level is 95 mg/dL and in the following 30-minutes the blood glucose level drops at 65 mg/dL, then the label for a 30-minute forecast horizon at the current time would be -30 mg/dL. The following equation (5) yields the forecasted blood glucose level:

$$\hat{b}_{t+L} = b_t + \hat{x}_{t+L}, for\ L = 1,2, \dots ,12 \quad (5)$$

In the above equation b_t is the blood glucose value at time t and $\hat{b}_{t+L}$ is the forecasted blood glucose level at time $t + L$. In addition, x is the label to predict, L is the lag value in time-steps and $\hat{x}_{t+L}$ is the predicted blood glucose level difference at time t with lag L.

4.3.2 Implementation of the CRNN Prediction Model

4.3.2.1 Training, testing, and tuning on selected features

After preprocessing, the multi-dimensional timeseries observed at successive time points (blood glucose, basal and bolus insulin, and heart rate data) are supplied to the CRNN for training.

The proposed CRNN model is trained end-to-end (E2E)[22] and consists of two basic layers. The first layer is a multilayer convolutional neural network that uses convolution and pooling to extract data features. The second one, is an RNN layer including LSTM cells and fully linked layers. A 1D Gaussian kernel filter is employed in the convolutional layer to accomplish temporal convolution, while pooling layers are used to reduce the set of features. Considering that LSTMs perform well in predicting timeseries with extensive temporal dependencies, a variation of it is used, and the fully linked layers produce a regression output as the end result.

The CRNN model is implemented using the open-source software package TensorFlow[23]. TensorFlow is an open-source end-to-end machine learning platform that has a broad and versatile set of tools, libraries, and community resources that allow state-of-the-art advances in machine learning and a quick deployment of machine learning applications. The CRNN only outputs the values $\hat{x}t + L$, which is essential to keep in mind. The model can provide predictions for each 5-minutes forecast horizon up to 1 hour (5, 10, 15, 20, ..., 55, 60-minutes). This ability may provide useful information to T1D patients, allowing them to better manage their blood glucose levels. The implemented CRNN's architecture is represented in Figure 4.11.

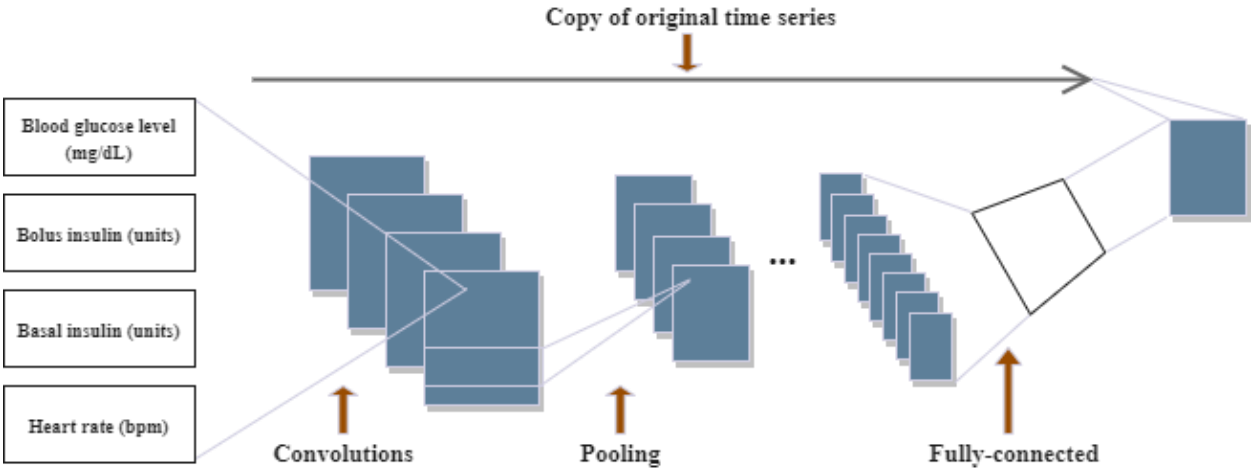


Figure 4.11 A multi-layer CRNN composed of convolutional layers, pooling layers, an RNN network and a dense neural network based on [73]

[22] Source: http://proceedings.mlr.press/v77/glasmachers17a/glasmachers17a.pdf

[23] https://www.tensorflow.org/

The preprocessing output contains the four main patient data: i) blood glucose data from CGM, ii) heart rate from physical activity monitors, and iii) manually registered basal and bolus insulin doses and time of injection. The algorithm's input is a timeseries of signals from these data, which is given to the CNN to identify and retrieve relational features. The CNN is comprised of three convolutional layers, with the feature map acquired from the preceding convolutional layer downsampled using max pooling (signal sampling at a lower rate). The pooling layers' objective is to progressively decrease the spatial dimension, while only including the highest values in the pooling window. In order to reduce the size of the representation and the computation, it is a typical move to insert a pooling layer in between subsequent convolutional layers, which can also act as a shield against overfitting.

Backpropagation (BP) and the stochastic gradient descent method (SGD) are used to train the CNN during the training stage. Generally, BP calculates the loss function's gradient with respect to the network's weights, whereas SGD is an iterative approach for optimizing an objective function with sufficient smoothness attributes. In this case, the initiatory weights of the CNN are randomly selected. Then, the final convolutional layer feeds directly into the following component, which is the recurrent layer.

An RNN layer is used to represent the relationships over time, while a dense neural network is employed as the final layer for the regression of the intended target. The CNN output is fed into the RNN, as multi-dimensional timeseries data that represent the concatenation of the initial signals' features. Then, the RNN's output is a 30-minute/60-minute prediction of the patient's blood glucose level, whereas hidden states are inherited and updated continually within the RNN component. Considering that every individual glucose reaction is distinctive, then a single-population approach does not appear to be appropriate. Therefore, one model is trained for every patient. The detailed architecture of the model is presented in Table 4.4.

Table 4.4 CRNN model architecture

Neural Network Layers	***Output Shape (batch_size, downsampled_steps, features)***
Conv1D	(batch_size, 24, 8)
MaxPooling1D	(batch_size, 12, 8)
Conv1D	(batch_size, 12,16)
MaxPooling1D	(batch_size, 6, 16)

Conv1D	(batch_size, 6, 32)
MaxPooling1D	(batch_size, 3, 32)
LSTM	(batch_size, 64)
Dense	(batch_size, 256)
Dense	(batch_size, 32)
Dense	(batch_size, 12)

A Root Mean Square Propagation (RMSProp) optimizer is used to pretrain the model over 1000 epochs, with a 1024 batch size. In neural network training, RMSprop is a gradient-based optimization strategy, which normally keeps a moving average of gradient squares and divides gradient by the root of that average [86]. This normalization equalizes the step size (momentum), lowering it for high gradients to prevent exploding and raising it for minor gradients to avoid disappearing. The RMSprop's update rule is described by the following equation[24]:

$$
\begin{aligned}
v_{dw} &= \beta \cdot v_{dw} + (1-\beta) \cdot dw^2 \\
v_{db} &= \beta \cdot v_{dw} + (1-\beta) \cdot db^2 \\
W &= W - a \cdot \frac{dw}{\sqrt{v_{dw}} + \varepsilon} \\
b &= b - \alpha \cdot \frac{db}{\sqrt{v_{db}} + \varepsilon}
\end{aligned}
\tag{6}
$$

When the model does not progress after three epochs, the learning rate is set to 0.001 and then reduced by a factor of 0.1. Generally, the training is more efficient and accurate with a lower learning rate, but optimization can take a long time since the steps towards the loss function's minimum are very small. To regularize the model, early stopping is utilized in a similar way with a 50 epochs patience. Subsequently, the weights of the last model with the least validation loss are rehabilitated. The pretrained model is loaded and trained like the pretraining step for each patient's data in the final dataset (containing OhioT1DM dataset and one supplementary patient data). The main difference is that the learning rate is decreased with a 15 epochs patience and each patient's model is saved separately.

[24] Source: https://medium.com/analytics-vidhya/a-complete-guide-to-adam-and-rmsprop-optimizer-75f4502d83be

4.3.3 Model Evaluation

Root Mean Squared Error (RMSE) and Mean Absolute Error (MAE) are commonly used for evaluation, in order to assess the difference between predicted values and actual values. RMSE is a quadratic evaluation method that determines the error's average size [87][88]. The difference between the predicted and the analogous true values are squared and then averaged over the sample, and then, the average's square root is calculated. Because the errors are squared before being averaged, the RMSE gives large emphasis to errors with great significance. As a result, the RMSE scoring rule is mostly appropriate when significant errors are not desired. On the other hand, MAE is a linear scoring rule that assesses the mean magnitude of errors in a group of predictions, without taking into consideration their direction, while it assesses the precision of continuous data [87][88]. Specifically, the average of the square of the difference between the true and forecasted data values is used in the MAE calculation process, and it is a suitable method to evaluate the performance of a model [87].

MAE and RMSE can be combined to assess the error variation in a series of predictions. RMSE scores are typically greater than or equal to MAE, while when they are equal then all the errors have the same magnitude. Otherwise, the larger the difference between the two scores, the larger the variance in the errors in the sample. In general, the lower the scores, the more efficient the model.

Specifically, when it comes to T1D hypoglycemia prediction, the main benefit for a patient is the ability to make decisions at any moment, based on the forecast of future values, perhaps avoiding hypoglycemic occurrences while using the least intrusive means possible. In our model's evaluation process, RMSE and MAE scores were calculated for all of the patients using the following equations [87][88]:

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(\hat{x}_i - x_i)^2} \tag{7}$$

$$MAE = \frac{1}{n}\sum_{i=1}^{n}|\hat{x}_i - x_i| \tag{8}$$

Where $\hat{x}_i$ are the predicted variable values, x_i refers to the observations (true values) and n is the number of the observations/rows.

4.3.4 Results

From the evaluation process of our model, we notice that the smaller the prediction window is, such as 5-minutes and 15-minutes, the closer the prediction curves come to the actual blood glucose level values and to the identification of most of the hypoglycemic episodes.

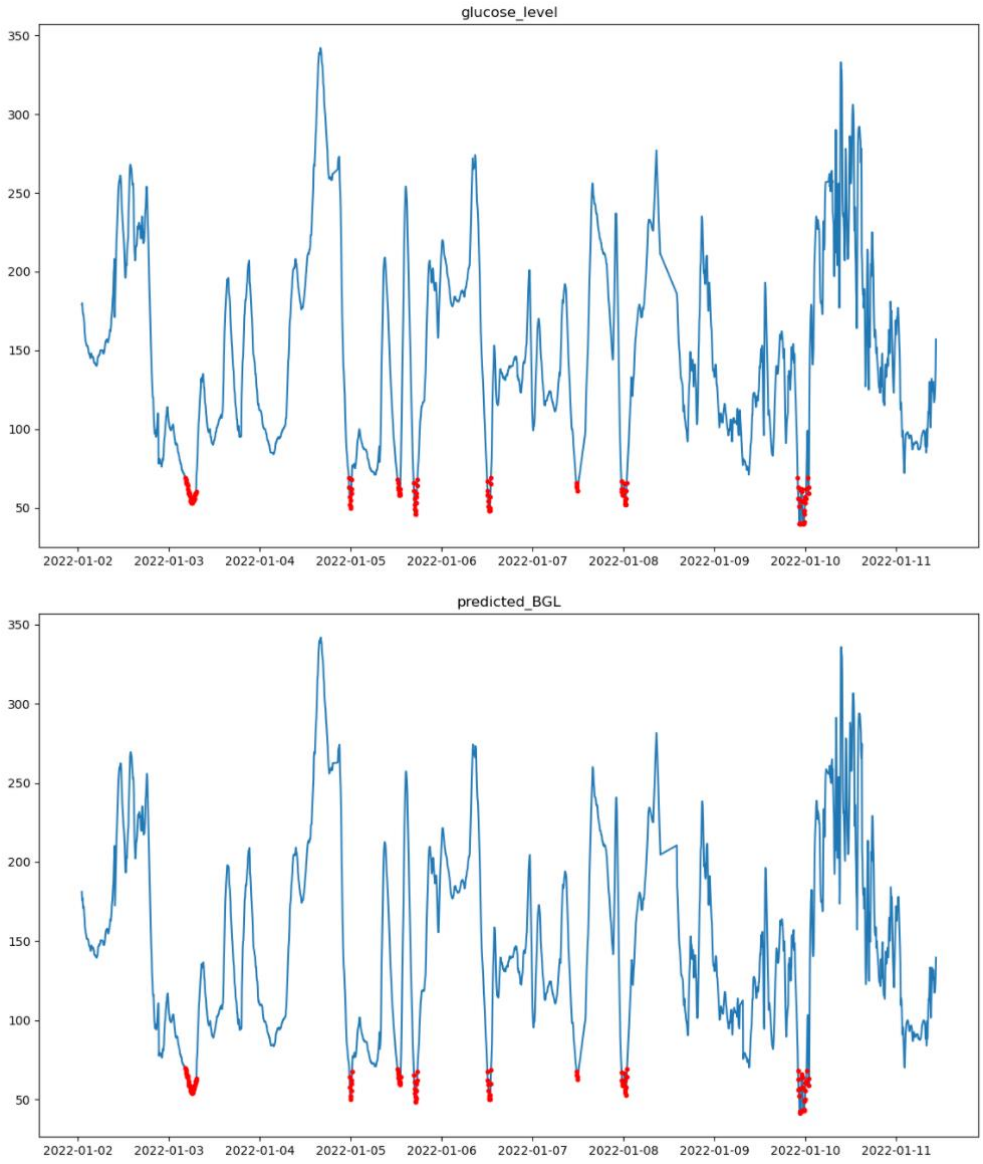


Figure 4.12 Actual and 5-minute predicted hypoglycemic events noted in red (Patient 575)

For example, for patient 575, we observe that the 5-minute prediction window leads to the detection of most of the hypoglycemic episodes (<70 mg / dL incidents marked with red dots), as seen in in Figure 4.12. In this case, there are small differences in the predicted blood glucose values compared to the actual blood glucose values (Table 4.5).

Table 4.5 Comparison of actual and 5-minute predicted hypoglycemia values over a 2-hours period (Patient 575)

Time	***Actual blood glucose***	***Predicted blood glucose***
04:30	67	67.67033
04:35	66	66.64014
04:40	65	65.65437
04:45	65	64.66782
04:50	65	64.75912
04:55	64	64.9151
05:00	62	64.02937
05:05	60	62.05135
05:10	59	59.99266
05:15	59	58.9657
05:20	59	59.10684
05:25	58	59.36786
05:30	58	58.62356
05:35	57	58.9336
05:40	55	58.21251
05:45	54	56.31018
05:50	54	55.39118
05:55	53	55.57805
06:00	53	54.73113
06:05	54	54.88534
06:10	53	56.12573
06:15	54	55.24182
06:20	56	56.37534
06:25	55	58.58047
06:30	55	57.64726

In addition, in Figure 4.13 where the 15-minute prediction is presented for patient 575, we note that many of the actual hypoglycemic episodes were detected and predicted, but with a lower accuracy than the 5-minute prediction. The comparison between the actual and the 15-minute predicted blood glucose values is presented in Table 4.6.

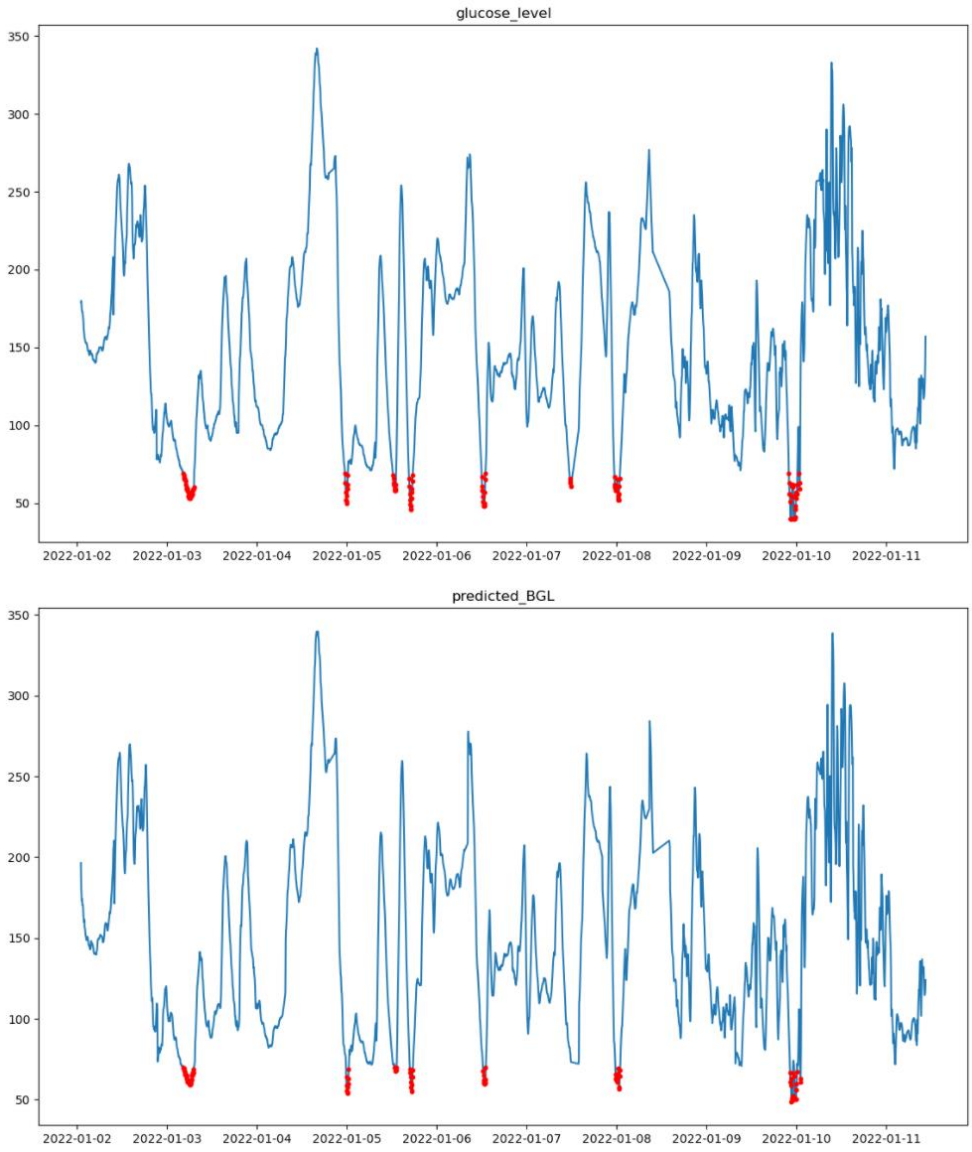


Figure 4.13 Actual and 15-minute predicted hypoglycemic events noted in red (Patient 575)

Table 4.6 Comparison of actual and 15-minute predicted hypoglycemia values over a 2-hours period (Patient 575)

Time	*Actual blood glucose*	*Predicted blood glucose*
04:30	67	70.56069
04:35	66	69.55949
04:40	65	68.69939
04:45	65	67.83501
04:50	65	67.18814
04:55	64	66.73238
05:00	62	67.18218
05:05	60	67.37998
05:10	59	66.30801
05:15	59	64.30154
05:20	59	62.74737
05:25	58	62.47922
05:30	58	63.18813
05:35	57	64.05988
05:40	55	63.87657
05:45	54	64.20983
05:50	54	63.50606
05:55	53	62.07985
06:00	53	61.55693
06:05	54	62.02432
06:10	53	61.65446
06:15	54	61.95936
06:20	56	63.32908
06:25	55	62.89374
06:30	55	64.07625

Regarding the blood glucose curves, we can see that there are not many deviations between the curves presented in the following plots (Figure 4.14 and Figure 4.15), where we compare the actual blood glucose level and the predicted blood glucose level at each time-step. In this case also, the prediction of 5-minutes outperforms the 15-minute prediction in accuracy.

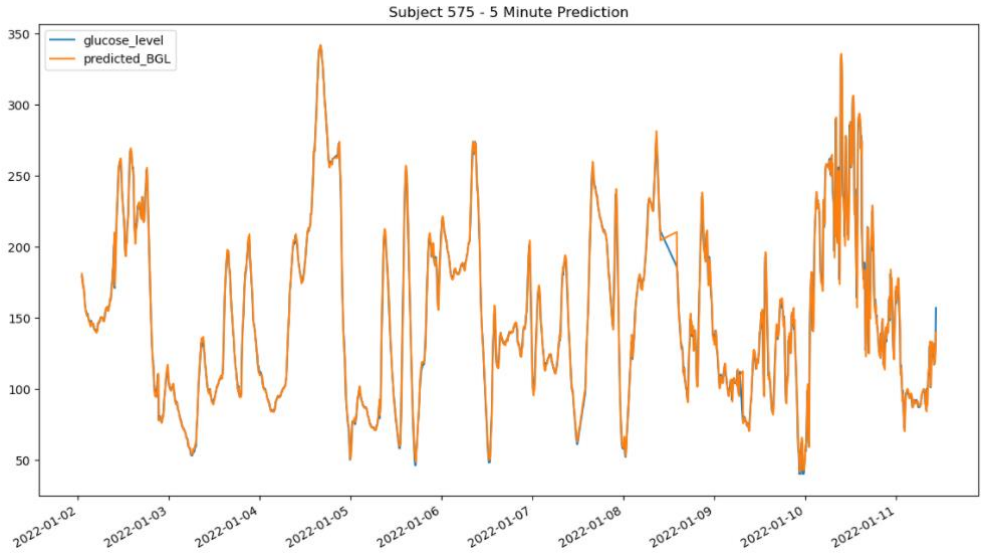


Figure 4.14 Actual and 5-minute predicted blood glucose levels (Patient 575)

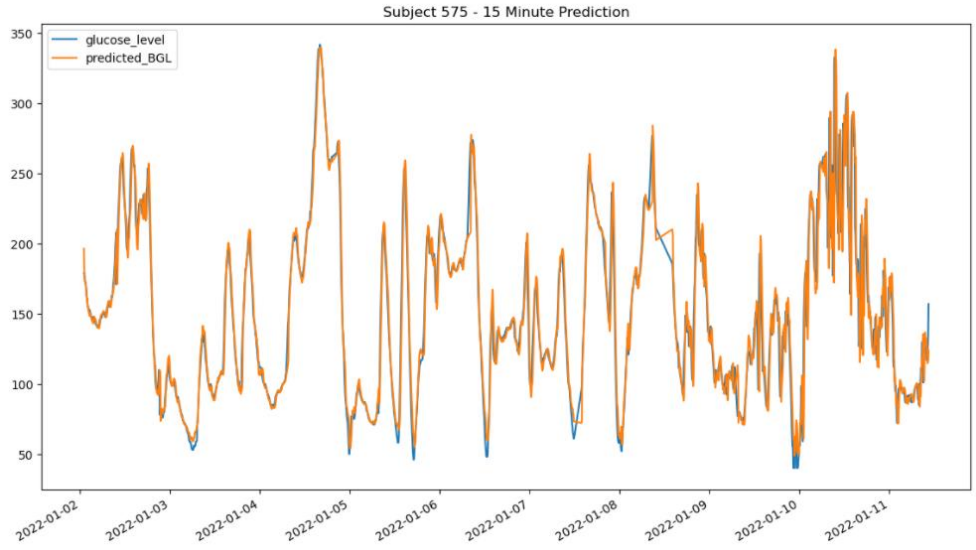


Figure 4.15 Actual and 15-minute predicted blood glucose levels (Patient 575)

Consequently, we conclude that the smaller the prediction window, the more the actual and predicted values agree with each other. Specifically, the 5-minute and 15-minute predictions scored an RMSE of 6.37 with a MAE of 3.47 mg/dL, and an RMSE of 14.48 with a MAE of 8.50 mg/dL, respectively (Table 4.7). On the other hand, as we proceed to larger prediction windows, we notice that the deviations between the curves of the actual and the prediction values become more frequent and noticeable.

Table 4.7 RMSE and MAE (Patient 575)

Prediction Minutes	***RMSE Score***	***MAE Score***
5	6.373965	3.478169
10	11.12169	6.282281
15	14.48338	8.506673
20	16.89985	10.34936
25	18.98019	12.17489
30	20.25772	13.26722
35	21.65472	14.44646
40	22.80271	15.39568
45	25.36908	17.39454
50	27.07653	18.5508
55	29.23947	20.12504
60	31.30821	21.62753

Moving forward we will focus on the 30-minute and 60-minute predictions of the CRNN model, since the ultimate goal would be to predict hypoglycemia events as soon as they can be predicted. The earlier the prediction, the sooner the T1D patient will be able to act on the hypoglycemic episode and avoid a potentially more severe condition, such as a stroke, unconsciousness, a permanent brain injury or death. As seen in the following figures for patient 575 (Figure 4.16 and Figure 4.17), the detection rate of hypoglycemic events decreases as the prediction window expands.

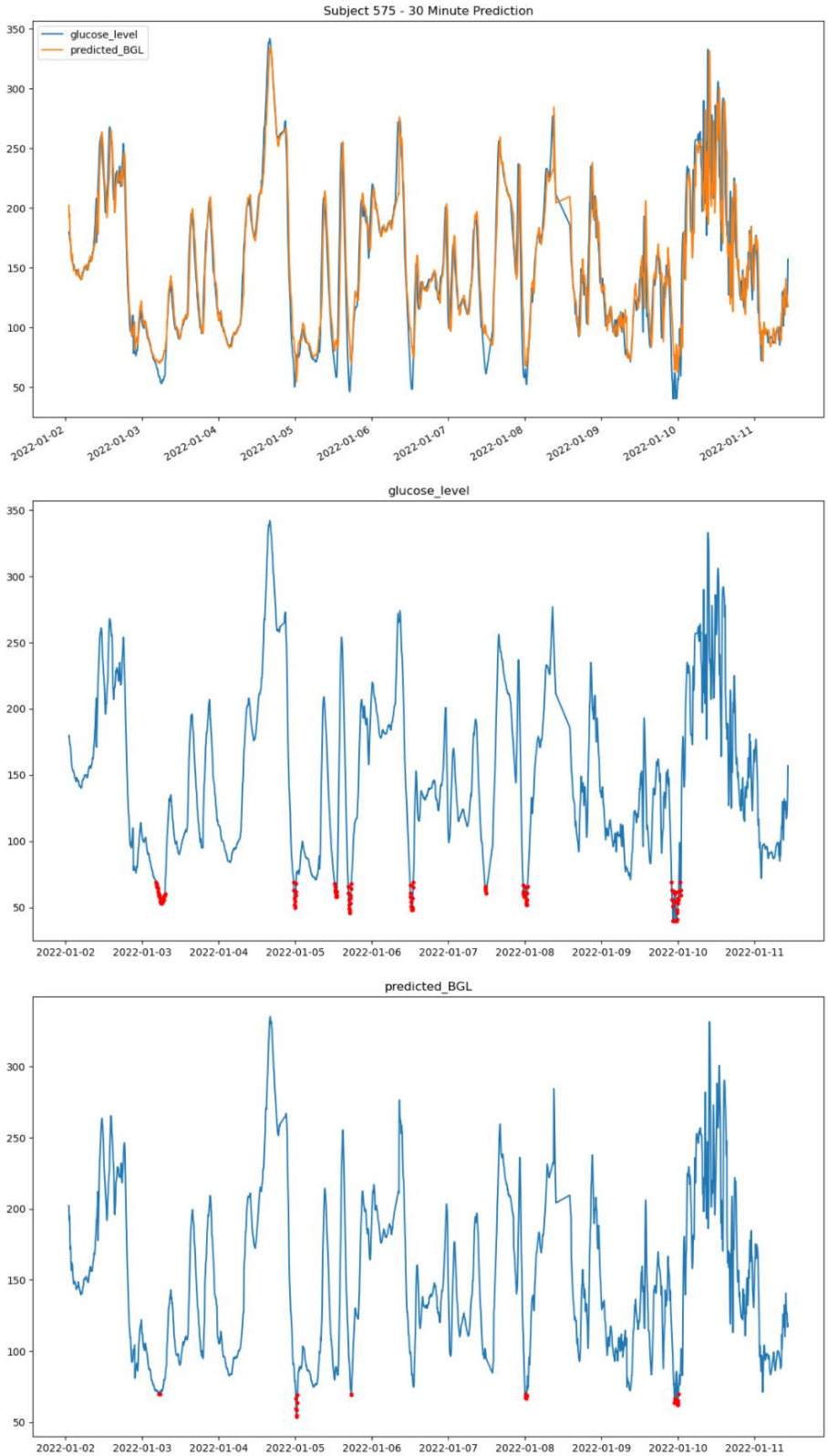


Figure 4.16 Actual and 30-minute predicted blood glucose levels, and hypoglycemic events noted in red (Patient 575)

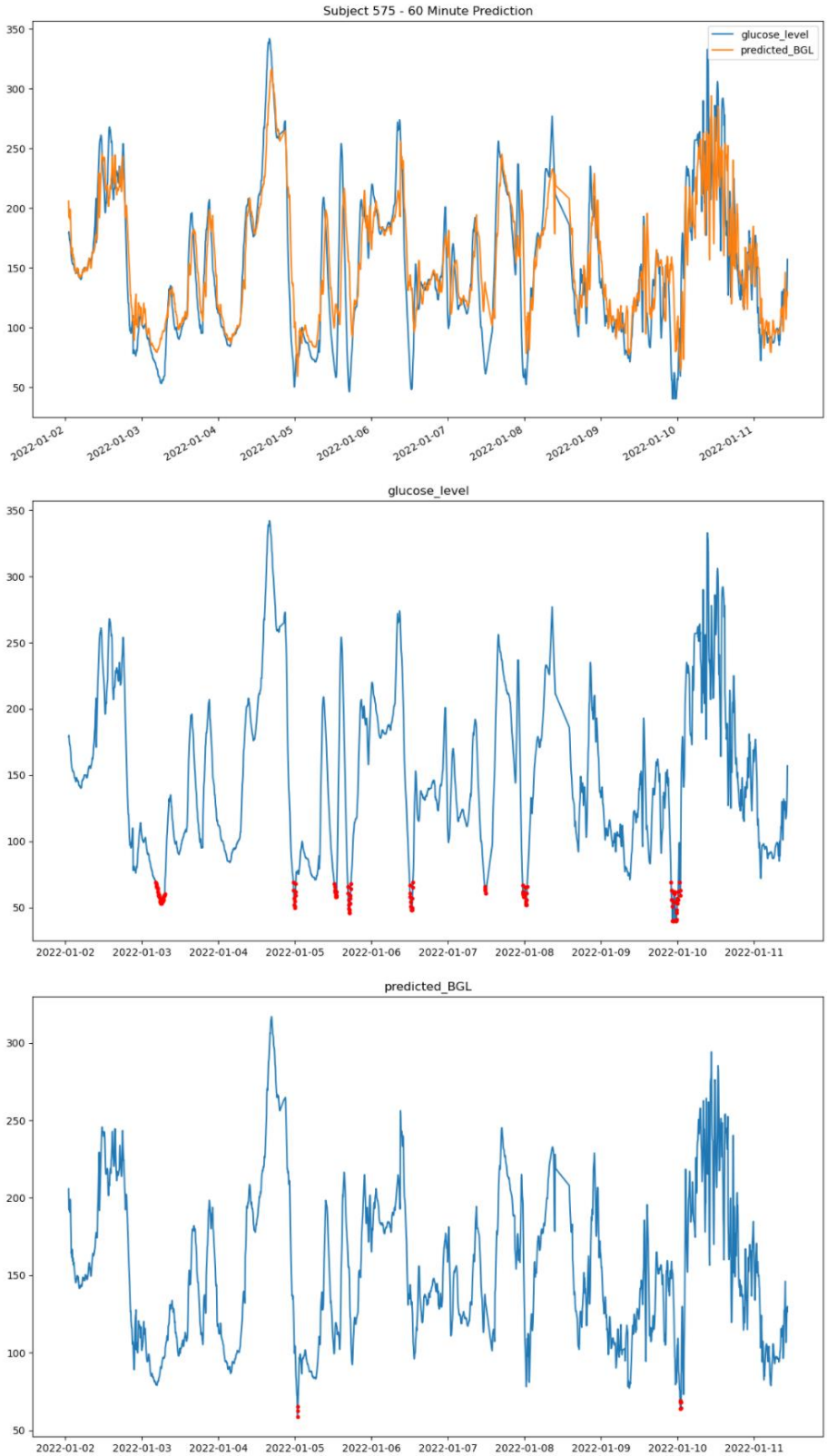


Figure 4.17 Actual and 60-minute predicted blood glucose levels, and hypoglycemic events noted in red (Patient 575)

The main finding is that the inaccuracies for each patient gradually rise over time. As previously stated, it is expected that the broader the prediction window, the greater the overall inaccuracy. An analysis of all the patients was also undertaken, where it is noteworthy that the 30-minute curve follows the 60-minute prediction curve (Figure 4.18 and Figure 4.19). In particular, patient 575 has a 30-minute curve with RMSE = 20.25 and MAE = 13.26 mg/dL, and a 60-minute prediction curve with RMSE = 31.30 and MAE = 21.62 mg/dL. Overall, we sincerely consider that the proposed model produces useful and applicable outcomes for T1D patients, following the notion that hypoglycemic events occur with blood glucose below 70 mg/dL, based on [89][90]. Finally, we suggest that a 30-minute RMSE of 20.25 mg/dL can provide a basis from which actions could be taken to avert possible severe hypoglycemia, based on patient data and the model's outcomes.

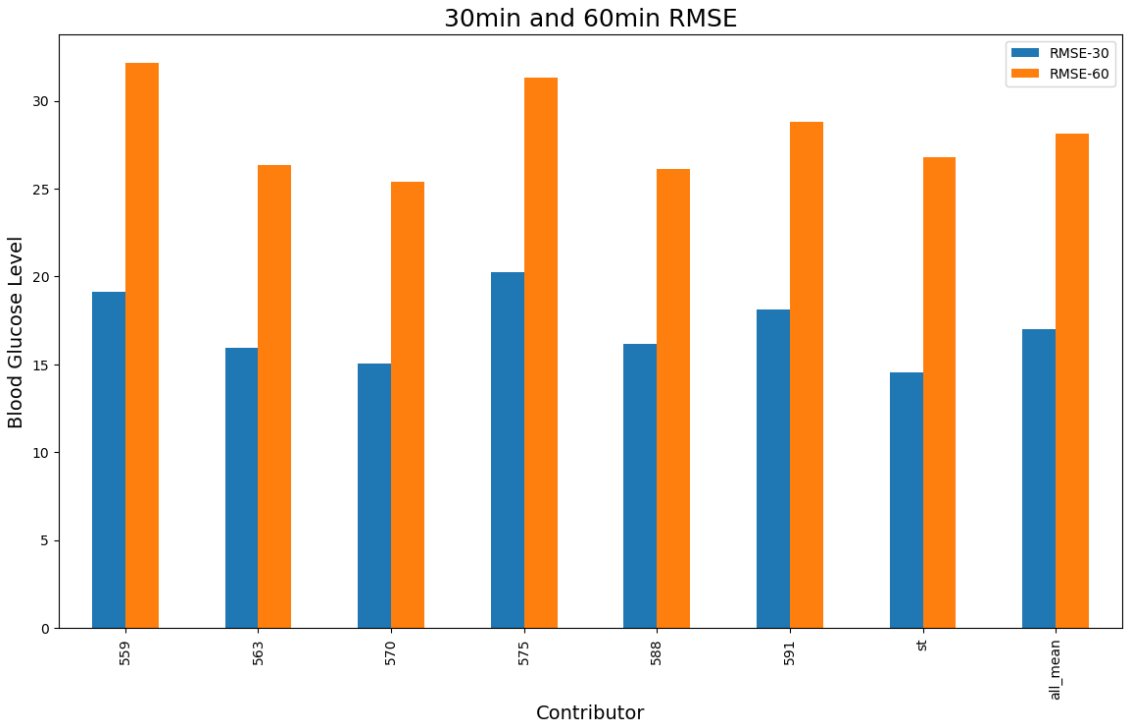


Figure 4.18 RMSE scores of 30-minute and 60-minute predictions of all the patients (individually and the mean of the total)

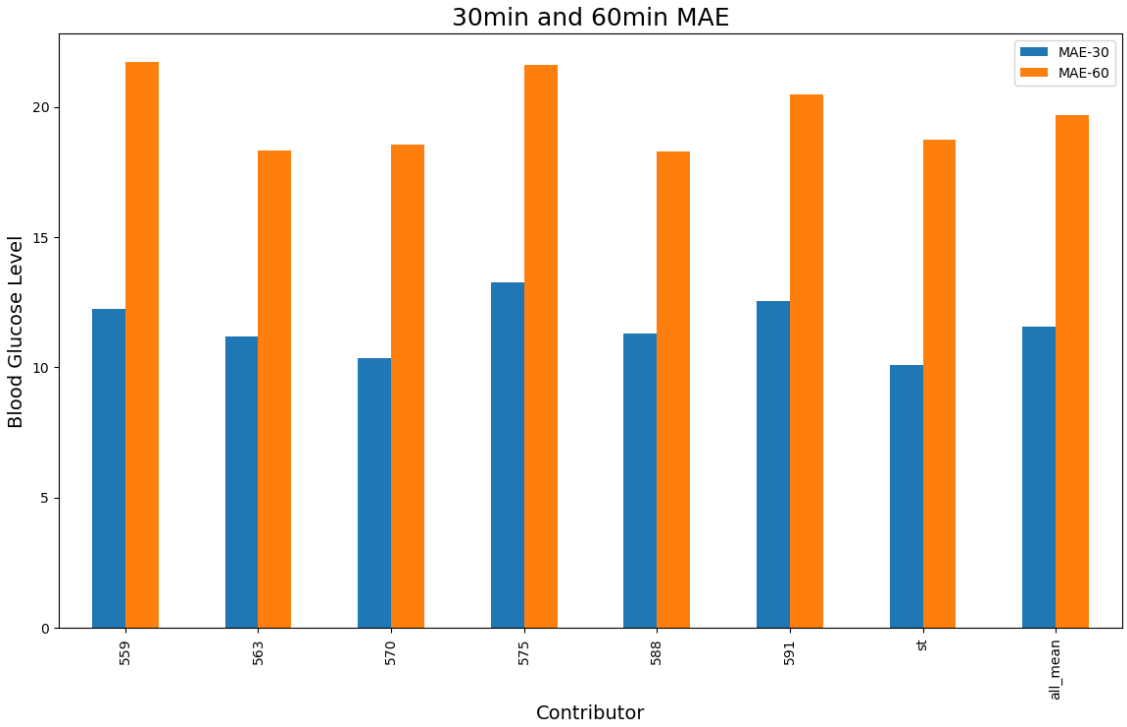


Figure 4.19 MAE scores of 30-minute and 60-minute predictions of all the patients (individually and the mean of the total)

Despite the fact that the CRNN has reached a substantial prediction accuracy, it still faces some concerns. For example, as we extend the prediction window, the performance in predicting hypoglycemia decreases significantly faster. This situation can occur based on the exclusion of other features that can also affect the patient's blood glucose levels, such as exercise, meal carbohydrate count and emotional state based on physiological models. Therefore, in order to achieve a better model performance, a future inclusion of the prementioned relevant parameters that affect blood glucose levels could possibly be incorporated into the proposed approach.

5 Conclusion and Future Work

In this thesis, we presented a hypoglycemia prediction model focused on patients with T1D. The main reason for distinguishing T1D from the general population with diabetes mellitus was that this autoimmune disease is very common at young ages up to 40 years old and cannot be avoided if a predisposition exists. Even though diabetes mellitus is just as serious as T1D and has the same number of potential complications if left untreated, T1D, which is more common in children and adolescents, requires a tighter control and attention from both the patients and their families.

For that purpose, a CRNN approach was presented, which has the benefit of obtaining only four distinct signals (CGM blood glucose, basal insulin, bolus insulin and heart rate) and requiring minimal signal processing. This small number of signals required for the blood glucose prediction process, makes the model more patient-friendly, as it does not require the simultaneous use of various devices (medical or non-medical) to record multiple different types of data. The evaluation process was carried out on various data providers, through using RMSE and MAE performance measures. Despite the complexity of glucose prediction, the findings demonstrate low error rates that could potentially be deemed for real-life application. Specifically, we evaluated the outputted blood glucose values of the model based on the actual blood glucose values provided by the T1D patients. The 5-minute prediction horizon held substantial performance outcomes, with an RMSE of 6.37 mg/dL and a MAE of 3.47 mg/dL (patient 575). Thus, a 5-minute prediction is not adequate for the hypoglycemic prevention from the patient since the needed glucose intake may not act in this period of time [91]. The 15-minute prediction could be a more efficient timeline for the glucose intake acting, with an RMSE of 14.48 mg/dL and a MAE of 8.50 mg/dL (patient 575). On the other hand, it depends on how each patient's body will react to the glucose intake to prevent the hypoglycemic episode [89][90]. In this case, we suggest that the 30-minute prediction window with an RMSE curve of 20.25 mg/dL and a MAE of 13.26 mg/dL, which was extracted from the evaluation of patient 575, is sufficient enough and could provide a foundation for the avoidance of possible severe hypoglycemic episodes in the average population of T1D patients. Despite the fact that CRNN has reached high prediction performance, it still faces significant provocations. As we mentioned in chapter 4.3.4, as the prediction window lengthens, the performance in predicting hypoglycemia decreases significantly faster. This could be associated with an additional fast-

acting calorie intake or an intense exercise occurrence. Therefore, these occurrences may need to be considered over longer prediction windows, in order to enhance the model's performance.

A simple T1D management mobile application was also developed as a part of this thesis, in order to serve as a future patient data collection method and diabetes management system. In a future version of this smartphone application, it could potentially be updated to analyze additional patient-related data and cater to more features, such as medical contact, daily well-being advice, mood assessments, etc.

Nevertheless, many research paths are yet to be pursued, such as testing extra factors that could affect the patient’s blood glucose levels. These factors could refer to stress levels and mood, or to other coexisting pathological conditions. Another future consideration could be the use of signal processing techniques to obtain various characteristics from the already provided signals and design domain-specific imputation techniques. These imputation techniques could be related to the carbohydrate absorption or to the basal/bolus insulin effect, over time.

6 References

[1] D. Rodbard, “Continuous Glucose Monitoring : A Review of Recent Studies Demonstrating Improved Glycemic Outcomes,” vol. 19, pp. 25–37, 2017.

[2] S. L. Cichosz, J. Frystyk, L. Tarnow, and J. Fleischer, “Combining information of autonomic odulation and CGM measurements nables prediction and improves etection of spontaneous hypoglycemic vents,” *J. Diabetes Sci. Technol.*, vol. 9, no. 1, pp. 132–137, 2015.

[3] A. Bertachi, L. Biagi, I. Contreras, N. Luo, and J. Vehí, “Prediction of blood glucose levels and nocturnal hypoglycemia using physiological models and artificial neural networks,” *CEUR Workshop Proc.*, vol. 2148, pp. 85–90, 2018.

[4] M. Care, “Standards of medical care in diabetes-2009,” *Diabet. Retin.*, pp. 1–36, 2010.

[5] B. W. Bode, “Clinical utility of the continuous glucose monitoring system,” *Diabetes Technol. Ther.*, vol. 2, no. SUPPL. 1, 2000.

[6] NIDDK, “Your Guide to Diebetes: Type 1 and Type 2,” 2014.

[7] Z. Wang, Z. Xie, Q. Lu, C. Chang, and Z. Zhou, “Beyond Genetics: What Causes Type 1 Diabetes,” *Clin. Rev. Allergy Immunol.*, vol. 52, no. 2, pp. 273–286, 2017.

[8] Y. Oikawa and A. Shimada, “Type 1 diabetes,” *Nihon Rinsho.*, vol. 73, no. 12, pp. 1997–2002, 2015.

[9] J. L. Chiang, M. S. Kirkman, L. M. B. Laffel, and A. L. Peters, “Type 1 diabetes through the life span: A position statement of the American Diabetes Association,” *Diabetes Care*, vol. 37, no. 7, pp. 2034–2054, 2014.

[10] P. Elfström, J. Sundström, and J. F. Ludvigsson, “Systematic review with meta-analysis: Associations between coeliac disease and type 1 diabetes,” *Aliment. Pharmacol. Ther.*, vol. 40, no. 10, pp. 1123–1132, 2014.

[11] S. Banarer, V. P. McGregor, and P. E. Cryer, “Intraislet hyperinsulinemia prevents the glucagon response to hypoglycemia despite an intact autonomic response,” *Diabetes*, vol. 51, no. 4, pp. 958–965, 2002.

[12] T. Moede, I. B. Leibiger, and P. O. Berggren, “Alpha cell regulation of beta cell function,” *Diabetologia*, vol. 63, no. 10, pp. 2064–2075, 2020.

[13] N. Tesfaye and E. R. Seaquist, “Neuroendocrine responses to hypoglycemia,” *Ann. N. Y.*

Acad. Sci., vol. 1212, pp. 12–28, 2010.

[14] N. R. Gosmanov, E. Szoke, Z. Israelian, T. Smith, P. E. Cryer, and J. E. Gerich, "Role of the decrement in intraislet insulin for the glucagon response to hypoglycemia in humans," *Diabetes Care*, vol. 28, no. 5, pp. 1124–1131, 2005.

[15] C. M. Reno, M. Litvin, A. L. Clark, and S. J. Fisher, "Defective Counterregulation and Hypoglycemia Unawareness in Diabetes. Mechanisms and Emerging Treatments.," *Endocrinol. Metab. Clin. North Am.*, vol. 42, no. 1, pp. 15–38, 2013.

[16] I. Martín-Timón, "Mechanisms of hypoglycemia unawareness and implications in diabetic patients," *World J. Diabetes*, vol. 6, no. 7, p. 912, 2015.

[17] R. J. Brown, N. Slnaii, and K. I. Rother, "Too much glucagon, too little insulin: Time course of pancreatic islet dysfunction in new-onset type 1 diabetes," *Diabetes Care*, vol. 31, no. 7, pp. 1403–1404, 2008.

[18] G. L. C. Yosten, "Alpha cell dysfunction in type 1 diabetes," *Peptides*, vol. 100, no. October 2017, pp. 54–60, 2018.

[19] J. J. Meier, L. L. Kjems, J. D. Veldhuis, P. Lefèbvre, and P. C. Butler, "Postprandial suppression of glucagon secretion depends on intact pulsatile insulin secretion: Further evidence for the intraislet insulin hypothesis," *Diabetes*, vol. 55, no. 4, pp. 1051–1056, 2006.

[20] B. A. Cooperberg and P. E. Cryer, "B-Cell-Mediated Signaling Predominates Over Direct A-Cell Signaling in the Regulation of Glucagon Secretion in Humans," *Diabetes Care*, vol. 32, no. 12, pp. 2275–2280, 2009.

[21] G. Paolisso *et al.*, "Pulsatile insulin delivery is more efficient than continuous infusion in modulating islet cell function in normal subjects and patients with type 1 diabetes," *J. Clin. Endocrinol. Metab.*, vol. 66, no. 6, pp. 1220–1226, 1988.

[22] M. Frandes, B. Timar, R. Timar, and D. Lungeanu, "Chaotic time series prediction for glucose dynamics in type 1 diabetes mellitus using regime-switching models," *Sci. Rep.*, vol. 7, no. 1, pp. 1–10, 2017.

[23] G. Cappon, G. Acciaroli, M. Vettoretti, A. Facchinetti, and G. Sparacino, "Wearable continuous glucose monitoring sensors: A revolution in diabetes treatment," *Electron.*, vol. 6, no. 3, pp. 1–16, 2017.

[24] D. Rodbard, "Continuous glucose monitoring: A review of recent studies demonstrating

improved glycemic outcomes," *Diabetes Technol. Ther.*, vol. 19, pp. S25–S37, 2017.

[25] S. R. Colberg, R. J. Sigal, B. Fernhall, J. G. Regensteiner, and B. J. Blissmer, "Exercise and type 2 diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint position statement," *Diabetes Care*, vol. 33, no. 12, 2010.

[26] G. Jimenez, E. Lum, and J. Car, "Examining diabetes management apps recommended from a Google search: Content analysis," *JMIR mHealth uHealth*, vol. 7, no. 1, 2019.

[27] I. Clinical and G. Team, "NICE. Internal Clinical Guidelines Team. Type 2 diabetes in adults. Type 2 diabetes in adults: management. Clinical Guideline Update (NG28). Methods, evidence and recommendations. December 2015," no. December, 2015.

[28] L. McAndrew, S. H. Schneider, E. Burns, and H. Leventhal, "Does patient blood glucose monitoring improve diabetes control?: A systematic review of the literature," *Diabetes Educ.*, vol. 33, no. 6, pp. 991–1011, 2007.

[29] C. Hou, B. Carter, J. Hewitt, T. Francisa, and S. Mayor, "Do mobile phone applications improve glycemic control (HbA<>1c<>) in the self-management of diabetes? A systematic review, meta-analysis, and GRADE of 14 randomized trials," *Diabetes Care*, vol. 39, no. 11, pp. 2089–2095, 2016.

[30] F. Debong, H. Mayer, and J. Kober, "Real-World Assessments of mySugr Mobile Health App," *Diabetes Technol. Ther.*, vol. 21, no. S2, pp. S2-35-S2-40, 2019.

[31] G. F. Mainoti, N. Isabirye, and L. Cilliers, "Trust attributes of mobile applications for improved self-management of diabetes in South Africa," *SA J. Inf. Manag.*, vol. 21, no. 1, pp. 1–7, 2019.

[32] R. Avram *et al.*, "Real-world heart rate norms in the Health eHeart study," *npj Digit. Med.*, vol. 2, no. 1, 2019.

[33] B. M. Frier, G. Schernthaner, and S. R. Heller, "Hypoglycemia and cardiovascular risks," *Diabetes Care*, vol. 34, no. SUPPL. 2, 2011.

[34] S. Chopra and A. Kewal, "Does hypoglycemia cause cardiovascular events?," *Indian J. Endocrinol. Metab.*, vol. 16, no. 1, p. 102, 2012.

[35] U. R. Acharya, K. P. Joseph, N. Kannathal, C. M. Lim, and J. S. Suri, "Heart rate variability: A review," *Med. Biol. Eng. Comput.*, vol. 44, no. 12, pp. 1031–1051, 2006.

[36] F. Shaffer and J. P. Ginsberg, "An Overview of Heart Rate Variability Metrics and Norms," *Front. Public Heal.*, vol. 5, no. September, pp. 1–17, 2017.

[37] D. E. Becker, “Fundamentals of electrocardiography interpretation.,” *Anesth. Prog.*, vol. 53, no. 2, pp. 53–64, 2006.

[38] M. Jaiswal *et al.*, “Association between impaired cardiovascular autonomic function and hypoglycemia in patients with type 1 diabetes,” *Diabetes Care*, vol. 37, no. 9, pp. 2616–2621, 2014.

[39] De Souza, N. M., L. C. M. Vanderlei, and D. M. Garner, “Risk evaluation of diabetes mellitus by relation of chaotic globals to HRV,” *Complexity*, vol. 16, no. 4, pp. 10–21, 2014.

[40] S. L. Cichosz, M. M. Henriksen, L. Tarnow, B. Thorsteinsson, U. Pedersen-Bjergaard, and J. Fleischer, “Validation of an Algorithm for Predicting Hypoglycemia From Continuous Glucose Measurements and Heart Rate Variability Data,” *J. Diabetes Sci. Technol.*, vol. 13, no. 6, pp. 1178–1179, 2019.

[41] B. D. Institute, “T1- -DDS,” pp. 16–18.

[42] I. Kavakiotis, O. Tsave, A. Salifoglou, N. Maglaveras, I. Vlahavas, and I. Chouvarda, “Machine Learning and Data Mining Methods in Diabetes Research,” *Comput. Struct. Biotechnol. J.*, vol. 15, pp. 104–116, 2017.

[43] S. M. Pappada, B. D. Cameron, and P. M. Rosman, “Development of a neural network for prediction of glucose concentration in type 1 diabetes patients,” *J. Diabetes Sci. Technol.*, vol. 2, no. 5, pp. 792–801, 2008.

[44] M. J. Page *et al.*, “The PRISMA 2020 statement: An updated guideline for reporting systematic reviews,” *Int. J. Surg.*, vol. 88, pp. 1–10, 2021.

[45] N. Mordvanyuk, F. Torrent-Fontbona, and B. López, “Prediction of glucose level conditions from sequential data,” *Front. Artif. Intell. Appl.*, vol. 300, pp. 227–232, 2017.

[46] S. Paul and M. Samanta, “Predicting Upcoming Glucose Levels in Patients with Type 1 Diabetes Using a Generalized Autoregressive Conditional Heteroscedasticity Modelling Approach,” *Int. J. Stat. Med. Res.*, vol. 4, no. 2, pp. 188–198, 2015.

[47] M. H. Jensen, T. F. Christensen, L. Tarnow, E. Seto, M. Dencker Johansen, and O. K. Hejlesen, “Real-time hypoglycemia detection from continuous glucose monitoring data of subjects with type 1 diabetes,” *Diabetes Technol. Ther.*, vol. 15, no. 7, pp. 538–543, 2013.

[48] Y. Zhang, “Predicting occurrences of acute hypoglycemia during insulin therapy in the intensive care unit,” *Proc. 30th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS’08 - "Personalized Healthc. through Technol.*, pp. 3297–3300, 2008.

[49] D. Dave, D. J. DeSalvo, B. Haridas, S. McKay, and A. Shenoy, “Feature-Based Machine Learning Model for Real-Time Hypoglycemia Prediction,” *J. Diabetes Sci. Technol.*, 2020.

[50] M. Eren-Oruklu, A. Cinar, and L. Quinn, “Hypoglycemia prediction with subject-specific recursive time-series models,” *J. Diabetes Sci. Technol.*, vol. 4, no. 1, pp. 25–33, 2010.

[51] H. P. Chase, B. A. Buckingham, E. Dassau, E. Cobry, P. Clinton, and K. Caswell, “Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension,” *Diabetes Care*, vol. 33, no. 5, pp. 1013–1017, 2010.

[52] B. A. Buckingham, F. Cameron, P. Calhoun, D. M. Maahs, D. M. Wilson, and H. P. Chase, “Outpatient safety assessment of an in-home predictive low-glucose suspend system with type 1 diabetes subjects at elevated risk of nocturnal hypoglycemia,” *Diabetes Technol. Ther.*, vol. 15, no. 8, pp. 622–627, 2013.

[53] E. I. Georga, V. C. Protopappas, D. Ardigò, D. Polyzos, and D. I. Fotiadis, “A glucose model based on support vector regression for the prediction of hypoglycemic events under free-living conditions,” *Diabetes Technol. Ther.*, vol. 15, no. 8, pp. 634–643, 2013.

[54] A. Bertachi, C. Viñals, L. Biagi, I. Contreras, J. Vehí, and I. Conget, “Prediction of nocturnal hypoglycemia in adults with type 1 diabetes under multiple daily injections using continuous glucose monitoring and physical activity monitor,” *Sensors (Switzerland)*, vol. 20, no. 6, pp. 1–11, 2020.

[55] M. R. Vahedi *et al.*, “Predicting glucose levels in patients with type1 diabetes based on physiological and activity data,” *Proc. 8th ACM MobiHoc 2018 Work. Pervasive Wirel. Healthc. Work. MobileHealth 2018*, pp. 1–5, 2018.

[56] M. Maritsch *et al.*, “Towards wearable-based hypoglycemia detection and warning in diabetes,” *Conf. Hum. Factors Comput. Syst. - Proc.*, 2020.

[57] P. P. San, S. H. Ling, and H. T. Nguyen, “Deep learning framework for detection of hypoglycemic episodes in children with type 1 diabetes,” *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS*, vol. 2016-Octob, no. Cd, pp. 3503–3506, 2016.

[58] L. Kuang, T. Zhu, K. Li, J. Zeng, P. Herrero, and P. Georgiou, “Blood Glucose Prediction in Type 1 Diabetes Using Deep Learning on the Edge,” pp. 1–5, 2021.

[59] T. Zhu, K. Li, J. Chen, P. Herrero, and P. Georgiou, “Dilated Recurrent Neural Networks for Glucose Forecasting in Type 1 Diabetes,” *J. Healthc. Informatics Res.*, vol. 4, no. 3, pp. 308–324, 2020.

[60] K. Li, T. Zhu, and P. Georgiou, “A Dual-Hormone Closed-Loop Delivery System for Type 1 Diabetes Using Deep Reinforcement Learning,” no. December, 2019.

[61] M. Munoz-Organero, “Deep physiological model for blood glucose prediction in T1DM patients,” *Sensors (Switzerland)*, vol. 20, no. 14, pp. 1–17, 2020.

[62] J. E. Ranvier, F. Dubosson, J. P. Calbimonte, and K. Aberer, “Detection of hypoglycemic events through wearable sensors,” *CEUR Workshop Proc.*, vol. 1588, pp. 21–26, 2016.

[63] S. L. Cichosz, J. Frystyk, O. K. Hejlesen, L. Tarnow, and J. Fleischer, “A novel algorithm for prediction and detection of hypoglycemia based on continuous glucose monitoring and heart rate variability in patients with type 1 diabetes,” *J. Diabetes Sci. Technol.*, vol. 8, no. 4, pp. 731–737, 2014.

[64] D. M. Nathan, S. Genuth, J. Lachin, P. Cleary, O. Crofford, and M. Davis, “DCCT reseach trial,” *N. Engl. J. Med.*, vol. 329, no. 14, pp. 977–986, 1993.

[65] C. Dalla Man, F. Micheletto, D. Lv, M. Breton, B. Kovatchev, and C. Cobelli, “The UVA/PADOVA type 1 diabetes simulator: New features,” *J. Diabetes Sci. Technol.*, vol. 8, no. 1, pp. 26–34, 2014.

[66] D. Dave *et al.*, “Improved low-glucose predictive alerts based on sustained hypoglycemia: Model development and validation study,” *JMIR Diabetes*, vol. 6, no. 2, pp. 1–11, 2021.

[67] N. Poolsup, N. Suksomboon, and A. M. Kyaw, “Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes,” *Diabetol. Metab. Syndr.*, 2013.

[68] K. M. Miller *et al.*, “Evidence of a strong association between frequency of self-monitoringof blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants,” *Diabetes Care*, 2013.

[69] M. A. Serhani, H. T. El Kassabi, H. Ismail, and A. N. Navaz, “ECG monitoring systems: Review, architecture, processes, and key challenges,” *Sensors (Switzerland)*. 2020.

[70] M. Y. Johansen *et al.*, “Effect of an intensive lifestyle intervention on glycemic control in patients with type 2 diabetes: A randomized clinical trial,” *JAMA - J. Am. Med. Assoc.*, 2017.

[71] P. E. Cryer, S. N. Davis, and H. Shamoon, “Hypoglycemia in Diabetes,” 2003.

[72] M. Thorström, “Applying machine learning to key performance indicators,” pp. 1–64, 2017.

[73] K. Li, J. Daniels, C. Liu, P. Herrero, and P. Georgiou, “Convolutional Recurrent Neural

Networks for Glucose Prediction," *IEEE J. Biomed. Heal. Informatics*, vol. 24, no. 2, pp. 603–613, 2020.

[74] Asha Gowda Karegowda, M.A. Jayaram, and A.S. Manjunath, "Cascading k-means clustering and k-nearest neighbor classifier for categorization of diabetic patients," *Int. J. Eng. Adv. Technol.*, vol. 1, no. 3, pp. 147–151, 2012.

[75] E. I. Georga *et al.*, "Multivariate prediction of subcutaneous glucose concentration in type 1 diabetes patients based on support vector regression," *IEEE J. Biomed. Heal. Informatics*, vol. 17, no. 1, pp. 71–81, 2013.

[76] K. Yan and D. Zhang, "Blood glucose prediction by breath analysis system with feature selection and model fusion," *2014 36th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBC 2014*, pp. 6406–6409, 2014.

[77] H. Abdi and L. J. Williams, "Principal component analysis," *Wiley Interdiscip. Rev. Comput. Stat.*, vol. 2, no. 4, pp. 433–459, 2010.

[78] K. Polat, S. Güneş, and A. Arslan, "A cascade learning system for classification of diabetes disease: Generalized Discriminant Analysis and Least Square Support Vector Machine," *Expert Syst. Appl.*, vol. 34, no. 1, pp. 482–487, 2008.

[79] K. Zarkogianni *et al.*, "Comparative assessment of glucose prediction models for patients with type 1 diabetes mellitus applying sensors for glucose and physical activity monitoring," *Med. Biol. Eng. Comput.*, vol. 53, no. 12, pp. 1333–1343, 2015.

[80] J. Reifman, S. Rajaraman, A. Gribok, and W. K. Ward, "Predictive monitoring for improved management of glucose levels," *J. Diabetes Sci. Technol.*, vol. 1, no. 4, pp. 478–486, 2007.

[81] M. T. Sattari, R. Mirabbasi, R. S. Sushab, and J. Abraham, "Prediction of Groundwater Level in Ardebil Plain Using Support Vector Regression and M5 Tree Model," *Groundwater*, vol. 56, no. 4, pp. 636–646, 2018.

[82] S. Mahdevari, K. Shahriar, S. Yagiz, and M. Akbarpour Shirazi, "A support vector regression model for predicting tunnel boring machine penetration rates," *Int. J. Rock Mech. Min. Sci.*, vol. 72, no. December, pp. 214–229, 2014.

[83] S. Hochreiter and J. Schmidhuber, "Long Short-Term Memory," *Neural Comput.*, vol. 9, no. 8, pp. 1735–1780, 1997.

[84] C. Marling and R. Bunescu, "The OhioT1DM dataset for blood glucose level prediction," *CEUR Workshop Proc.*, vol. 2148, pp. 60–63, 2018.

[85] S. Veazie *et al.*, “Rapid Evidence Review of Mobile Applications for Self-management of Diabetes,” *J. Gen. Intern. Med.*, vol. 33, no. 7, pp. 1167–1176, 2018.

[86] T. Kurbiel and S. Khaleghian, “Training of Deep Neural Networks based on Distance Measures using RMSProp,” pp. 1–6, 2017.

[87] W. Wang and Y. Lu, “Analysis of the Mean Absolute Error (MAE) and the Root Mean Square Error (RMSE) in Assessing Rounding Model,” *IOP Conf. Ser. Mater. Sci. Eng.*, vol. 324, no. 1, 2018.

[88] S. P. Neill and M. R. Hashemi, *Ocean Modelling for Resource Characterization*. 2018.

[89] S. Scott, P. Kempf, L. Bally, and C. Stettler, “Carbohydrate intake in the context of exercise in people with type 1 diabetes,” *Nutrients*, vol. 11, no. 12, pp. 1–21, 2019.

[90] P. E. Cryer, “Hypoglycemia in type 1 diabetes mellitus,” *Endocrinol. Metab. Clin. North Am.*, vol. 39, no. 3, pp. 641–654, 2010.

[91] A. B. Evert, “Treatment of mild hypoglycemia,” *Diabetes Spectr.*, vol. 27, no. 1, pp. 58–62, 2014.