REPUBLIC OF TURKEY
YILDIZ TECHNICAL UNIVERSITY
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AUTOMATED INSULIN PUMP DESIGN BASED ON PROBABILISTIC PREDICTION ALGORITHM

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MSc. THESIS
DEPARTMENT OF ELECTRONICS AND COMMUNICATIONS ENGINEERING
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A thesis submitted by Hatice Vildan DÜDÜKÇÜ in partial fulfillment of the requirements for the degree of **MASTER OF SCIENCE** is approved by the committee on 21.12.2017 in Department of Electronics and Communications Engineering, Electronics Program.

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Hatice Vildan DÜDÜKÇÜ

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LIST OF SYMBOLS

nm	nanometer
μm	micrometer
μ	mean
σ^2	variance

LIST OF ABBREVIATIONS

CGMS	Continuous Glucose Monitoring System
CHO	Carbohydrate
CSII	Continuous Subcutaneous Insulin Infusion
GPIO	General Purpose Input Output
ISF	Insulin Sensitivity Factor
NIR	Near-Infrared Region
SC	Subcutaneous
T1DM	Type 1 Diabetes Mellitus

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ABSTRACT

AUTOMATED INSULIN PUMP DESIGN BASED ON PROBABILISTIC PREDICTION ALGORITHM

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Department of Electronics and Communications Engineering

MSc. Thesis

Adviser: Prof. Dr. Tülay YILDIRIM

Insulin is a hormone secreted by the pancreas that regulates blood sugar in the body. Diabetes mellitus, also known as diabetes, occurs when the pancreas can not produce sufficient insulin for the body. Diabetes is a chronic disease and patients at advanced stages need to inject insulin externally at certain doses during the day. Artificial pancreas designs are aimed to measure these glucose levels and to control these levels by applying insulin to the required amount. Nowadays the systems consist of continuous glucose monitoring systems and automated insulin pumps. In this thesis, an automated insulin pump system is designed. In the system implemented, insulin injection is made to the patient at certain intervals during the day and records of injections made are kept. Thus, the patient's insulin intake is automatically monitored and patient follow-up is facilitated.

The intelligent insulin pump realized is able to make injections by predicting and calculating insulin doses solely with the meal information given by the patient using a probabilistic prediction algorithm. In this system there is no need for patient to make blood glucose measurements for the bolus doses. Depending on the predicted and calculated insulin doses, insulin injection with the pump will be performed. In addition to this bolus dose, an injection of the basal insulin dose will also be performed during the day periodically according to the weight information of the patient.

Key words: Diabetes mellitus, artificial pancreas, automated insulin pump

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ÖZET

OLASILIKSAL TAHMİN ALGORİTMASI TABANLI OTOMATİK İNSULİN POMPASI TASARIMI

Hatice Vildan DÜDÜKÇÜ

Elektronik ve Haberleşme Mühendisliği Anabilim Dalı

Yüksek Lisans Tezi

Tez Danışmanı: Prof. Dr. Tülay YILDIRIM

İnsülin, pankreas tarafından salgılanan ve vücuttaki kan şekerinin dengelenmesini sağlayan bir hormondur. Pankreas tarafından vücut için yeterli insülin üretilemediği durumda şeker hastalığı olarak da bilinen diabetes mellitus ortaya çıkar. Diyabet, kronik bir hastalıktır ve ileri aşamalarında hastaların gün içerisinde belirli dozlarda dışarıdan insülin enjeksiyonu yapmaları gerekir. Yapay pankreas tasarımlarında, kandaki glikoz seviyelerinin ölçülmesi ve gerekli miktarda insülin uygulanması ile bu seviyelerin kontrolünün sağlanması amaçlanmaktadır. Günümüzde sistemler sürekli glikoz takip sistemleri ile insülin pompalarının birlikte çalıştırılması şeklinde olmaktadır. Bu tezde de otomatik bir insülin pompası sistemi tasarlanmıştır. Gerçekleştirilen sistemde hastaya gün içerisinde belirli zamanlarda insülin enjeksiyonu yapılmakta ve yapılan enjeksiyonların kayıtları tutulmaktadır. Böylece hastanın insülin alımları otomatik olarak denetlenmiş ve hasta takibi kolaylaştırılmış olur.

Gerçekleştirilen akıllı insülin pompası, sadece hastanın girdiği öğün bilgileri ile bir olasılıksal tahmin algoritması kullanarak gerekli insülin dozunu tahmin etmekte ve hesaplayarak enjeksiyon yapabilmektedir. Bu sistemde kişinin bolus doz hesaplaması için kan şekeri ölçümü yapmasına gerek yoktur. Tahmin edilen ve hesaplanan insülin dozuna göre pompa ile insülin enjeksiyonu gerçekleştirilmektedir. Bu bolus doza ek olarak gün içerisinde hastanın kilo bilgisi kullanılarak belirli aralıklarla bazal doz enjeksiyonları da yapılmaktadır.

Anahtar Kelimeler: Diabetes mellitus, yapay pankreas, otomatik insülin pompası

CHAPTER 1

INTRODUCTION

1.1 Literature Review

The first insulin pumps, working with the principle of making insulin injections to the patients with diabetes automatically have been developed in the 1970s. Nowadays, these pumps have developed and some models can calculate basal insulin as well as automatic bolus insulin doses [1]. In this thesis, an intelligent insulin pump that performs bolus insulin dose calculation and injection according to the patient's blood sugar and carbohydrate intakes at certain intervals during the day has been designed.

The automation of blood glucose control in diabetics is a long-standing issue. In 1974, an artificial pancreas system was proposed for this process [2], [3]. This system fulfills the tasks of the pancreas by making continuous glucose measurements and insulin injections to the body at required times. In 1978, an insulin pump with electronically controlled piezoelectric valves was designed for insulin injections [4]. In the first designed pumps, the required insulin doses were calculated by the patient and the pumps made insulin injections intermittently during the day. Recent works have focused on adjusting the rate and amount of insulin injections and integrating them with continuous glucose monitoring systems [5]. In addition, studies have been carried out to optimize systems with studies on basal and bolus insulin dose calculations for automatic insulin pumps [6]. Also some studies, pumps for the regulation of blood sugar have been designed with a system closer to the functioning of the body endocrine system by injecting glucagon as well as insulin [7], [8].

The insulin pumps designed in the literature generally require the information of bolus dose or blood sugar and carbohydrate intake from the patients for insulin injections.

According to the information entered by the patient, bolus injections are made intermittently during the day, in addition to the preset amount of basal injections.

1.2 Objective of the Thesis

The main objective of this thesis is to design a user friendly automated insulin pump based on probabilistic prediction algorithms which can replace the manual insulin injections and glucometer measurements of a diabetic patient.

The number of diabetic patients is increasing day by day and these patients need to inject insulin at certain intervals throughout the day. The application and follow-up of these injections is challenging for the patient. Also patients need to measure their blood glucose levels before each meal with glucometers. This thesis is aimed to facilitate the daily life of patients by making predictions of insulin dosages, automatic calculations and injections of insulin with an automated insulin pump. The pump also aims to track the blood sugar levels and the treatment history of the patient by keeping a record of each injection made, thus it can also help for future treatment plans.

1.3 Hypothesis

In this study an insulin pump prototype has been developed for the use of diabetic patients. The automated pump can take the place of manual daily insulin injections applied by the patients. This work is unique in terms of predicting insulin dosages based on probabilistic approaches, having an easy interface that can be used by patients and keeping records of the patient's past injection and meal intakes.

When the designed automated insulin pump is integrated with future non-invasive glucose measurement systems, it can operate similarly to the artificial pancreas and work fully automatic, therefore the dependence on patient input will be minimal.

CHAPTER 2

DIABETES MELLITUS

Definition of diabetes mellitus, invasive and non-invasive methods of measuring blood glucose, devices such as insulin pumps and artificial pancreas are explained in this chapter.

2.1 Diabetes Mellitus

Diabetes Mellitus or shortly diabetes, is a disease that occurs when insulin hormone cannot be produced or used in sufficient quantities by the human body. Diabetes causes the glucose level in the blood to be constantly high. This high glucose levels (hyperglycemia) causes permanent damage to the body and life-threatening conditions for the patients.

Insulin is a hormone produced by the pancreas and providing glucose passage to the body cells from the bloodstream. When insulin cannot be produced in the body Type 1 diabetes occurs. If the body produce but cannot use insulin adequately then Type 2 diabetes occurs. Type 1 diabetic patients need to inject insulin at regular intervals throughout the day. Patients with Type 2 diabetes can manage with medications in early stages or injections of insulin in advanced stages.

Today more than 400 million people are trying to live with diabetes. Balancing blood sugar is of great importance for these patients because they may suffer permanent damage to tissues and organs such as the blood vessels, kidneys or eyes if they do not take precautions for high glucose levels. In addition, these patients are at constant risk of infection. Because of these reasons, technological advances such as artificial pancreas, non-invasive glucose measurement, automatic insulin pump, etc. about glucose measurement or insulin injection can help these people live with diabetes [9].

2.2 Blood Glucose Measurement

Diabetics need to make measurements at certain intervals throughout the day to regulate and track the glucose levels in their blood. These glucose measurements are made by the patients themself with a glucometer. To make the measurement with the glucometer, the patient's finger should be punctured with the help of a needle and the blood should be dropped on a test strip. Then, measurement is made on this blood by electrochemical means. A glucometer and a test strip can be seen in Figure 2.1 and 2.2.

Figure 2.1 Glucometer [10]

Figure 2.2 Glucometer Test Strips [11]

Glucometers can use amperometric or colorimetric methods to determine the amount of electrons that are released as a result of the chemical reaction in the test strip. In amperometric methods, the test strip used to measure blood sugar contains an enzyme called glucose oxidase. When blood is dropped on this test strip, the glucose molecules in the blood enters into a chemical reaction with the enzyme and releases electrons. The amount of free electrons released by this reaction is directly proportional to the amount of glucose in the reaction, so that it is possible to have information about the blood sugar by determining the number of electrons generated as a result of the reaction [12]. The number of free electrons can be found by measuring the current flowing through the blood on the test strip. The second method that is used by glucometers, colorimetric method, uses color reflectance principle to determine the amount of glucose on the strip [13]. Amperometric method is a more commonly used method in glucometers because of its ease of implementation.

2.3 Non-Invasive Blood Glucose Measurement

Blood glucose measurement is done by taking some blood from the finger and testing this blood. But this method is an invasive method which can result in infections and also a painful process that patients have to do multiple times during the day. Because of these reasons, there has been ongoing researches on a non-invasive solution for measuring blood glucose for years [14].

There are some methods for non-invasive glucose measurement that has been tried in studies. And some of this methods are able to predict the glucose to some extent, however none of these methods have achieved the expected accuracy, therefore they can't be used on patients because wrong measurements can be lethal for diabetes.

Near-infrared spectroscopy, most commonly used method for non-invasive glucose measurement, uses near-infrared (NIR) region (700 nm to 2500 nm) of the electromagnetic spectrum and measures the glucose in blood by using reflection [15], transmission [16] or spectral analysis [17]. Penetration of light in this region is more other wavelengths. But the biggest disadvantage of this method is that the obtained information can easily be affected from other factors and molecules in blood, so it also needs individual calibration [18].

Mid-infrared spectrum which uses 2.5 to 25 μm wavelength region of the electromagnetic spectrum is another possible method for glucose measurement. However in mid-infrared region light cannot travel very deep into tissue, therefore mid-infrared is not very effective for measuring glucose in blood [18].

Another spectroscopic method Raman spectroscopy, uses inelastic scattering of photons of an excited source which is called Raman scattering [19]. Raman spectroscopy is considered an efficient way of glucose measurement but the detection of scattering is very difficult so it is not suitable for everyday patient use.

Photo-acoustic effect, the acoustic wave propagation of optical wave applied materials is another method tried for blood glucose measurement. The molecules in a substance emit heat when an optical wave is applied. This leads to thermoelastic expansion and formation of acoustic wave. When the wavelengths that glucose can absorb are used, glucose measurement can be done by measuring the photoacoustic waves [20].

Optical polarimetry is another method used for non-invasive glucose measurement. Optical polarimetry measures the rotation and amplitude changes that happens in linear polarized light as it travels through molecules. But the glucose amount in blood is very low, therefore the rotation and amplitude changes are very low and very difficult to measure. Also, the molecules with the similar structure as glucose can have the same effect on the light, therefore the rate of error with this method is very high [21].

Millimeter waves are electromagnetic waves with wavelengths between 1 and 10 mm in the extremely high frequency range. There are studies of measuring glucose in blood with millimeter waves and they are based on the assumption that the complex permittivity of blood is in relation with the amount of glucose in blood [22].

Another method studied for non-invasive measurement of blood glucose is impedance sensors. This method measures the impedance with consideration that the dielectric properties of blood change with the molecules present, including glucose. The impedance measured with these sensors varies depending on the shape and the properties of blood, skin and tissues [23]. Each person's body impedance is different so, individual calibrations must be performed with this method. Also body impedance changes with parameters like body temperature, blood pressure and pulse rate [24].

There are a lot of methods tried for non-invasive glucose measurements in studies. But until now, there has been no product accepted on the market using any of these methods due to various reasons such as difficulty in measuring with sufficient precision or difficulty in using.

The general advantages and disadvantages of non-invasive glucose measurements methods mentioned are summarized below with the help of Table 2.1.

Table 2.1 Non-invasive measurement methods [14]

Method	Advantages	Disadvantages
NIR	Low cost, easy to design.	Insufficient accuracy.
Raman spectroscopy	Precise measurement. Adverse effect of water is reduced.	High cost, special detector required.
Photoacoustic spectroscopy	Precise measurement. Extended applicable wavelength range.	Easily affected by environmental variables.
Optical Polarimetry	Measurement made from the aqueous humor, less molecules to cause errors.	Difficult to measure, unmeasurable over skin.
Millimeter waves	Isolated measurement by focusing on important frequencies for glucose.	Easily affected by environmental variables.
Impedance measurement	Low cost, easy to design.	Easily affected by environmental variables.

2.4 Artificial Pancreas

Insulin is a hormone that allows the glucose in the blood to enter the cells and used there. It is produced by the β cells in the pancreas. In cases where insulin can not be produced by the β cells in the body, glucose can not pass through to the cells and blood sugar increases. In these cases, type 1 diabetes mellitus (T1DM) occurs. People with type 1 diabetes need to constantly monitor their blood sugar levels and inject insulin from outside daily to regulate their blood glucose levels.

In the treatment of T1DM, patients need to undergo daily insulin injections or continuous subcutaneous (SC) insulin infusion (CSII) by insulin pumps. In order to determine the insulin injection doses, it is necessary to monitor the blood glucose levels by measuring blood sugar with glucometer at intervals or using Continuous Glucose Monitoring Systems (CGMS).

Artificial pancreas designs, which are considered to be the ideal treatment for diabetic patients are systems containing many different components such as communication, modeling, control algorithms, learning, meal detection and safety algorithms [25]. Today, the closest system to the artificial pancreas is using CGMS and insulin pumps together to measure and control the insulin levels simultaneously.

2.5 Insulin Pump

Insulin pumps are devices that continuously inject insulin into the body subcutaneously throughout the day. These pumps make insulin injections daily by performing two different basal and bolus doses calculations. Basal insulin is patient specific and is calculated according to the patient's physiological state. Bolus insulin dose is done to reduce the elevated blood sugar levels and balance the amount of carbohydrates taken at meals. The injections made from insulin pumps are done in small doses and over a long period of time to minimize the sudden fluctuations in blood sugar levels.

Although some insulin pumps can communicate directly with CGMSs and can work without the patient's input, it is now generally expected for the patient to enter dose information based on blood sugar level and carbohydrate intake during the meals. Following this input, the pump can deliver the necessary insulin to patient in a controlled manner. An insulin pump with CGMS is shown in Figure 2.3.

Figure 2.3 Insulin pump with continuous glucose measurement system [26]

The use of insulin pumps reduce the risk of hyperglycemia by ensuring that the patient's blood sugar levels throughout the day are balanced. Pumps use also minimize blood glucose imbalances during night and between meals as the insulin is slowly taken in small doses. As a result, the life of the patient becomes easier and the quality of life increases [1].

CHAPTER 3

INSULIN PUMP SOFTWARE

The intended use of insulin pumps is to bring the relative glucose level to normal ranges. For this purpose, two types of insulin injections are made from the pumps, basal and bolus doses. Basal insulin is given in small doses at regular intervals to compensate the overall blood sugar level during the day. Bolus insulin is used to lower blood sugar levels, which rise due amount of carbohydrates taken in meals.

The automated insulin pump designed for this study makes multiple basal and bolus insulin injections daily. The basal insulin injection doses are calculated using only the weight information of patient saved in the pump as shown in Figure 3.1.

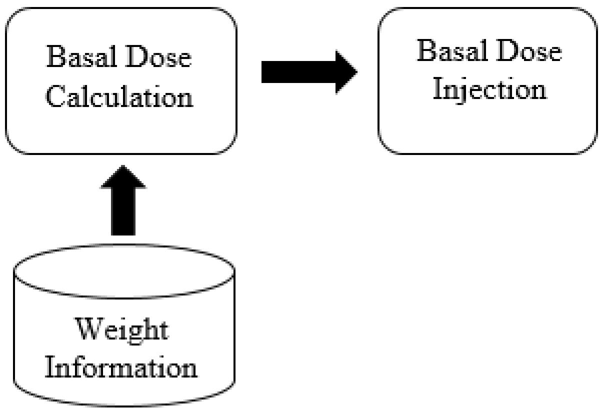

Figure 3.1 Basal dose injection

Bolus dose injections made with the pump are calculated using prediction algorithms and some basic equations explained in this chapter. The bolus dose calculation block diagram can be seen in Figure 3.2.

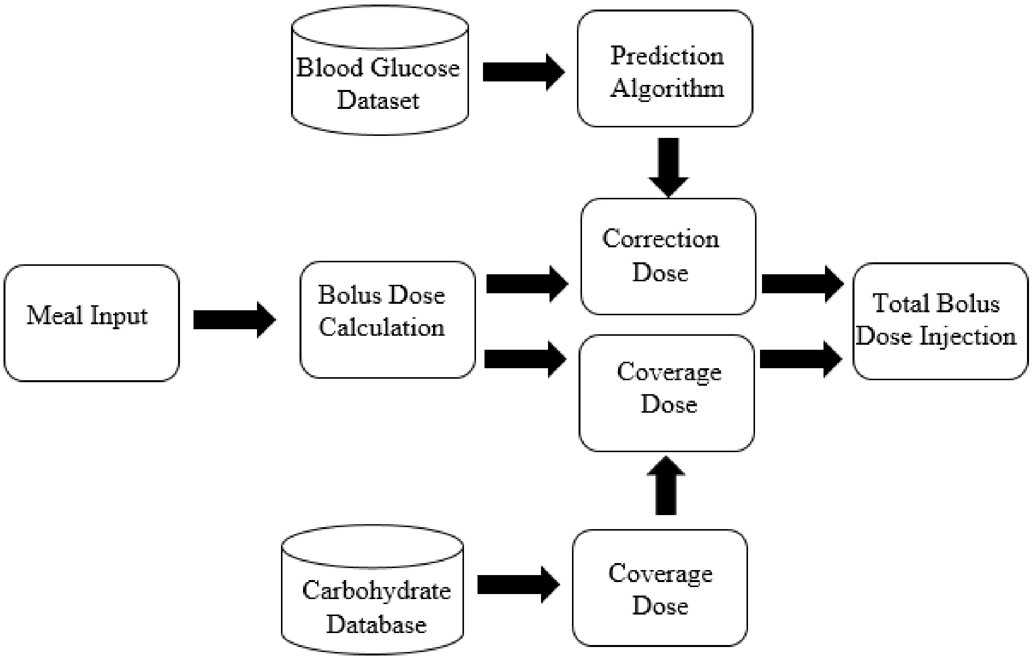

Figure 3.2 Bolus dose injection

3.1 Basal Insulin Dose Calculation

Basal insulin is intended to balance the level of insulin between meals and during night time by injecting insulin slowly and at certain intervals throughout the day. Basal insulin program takes previously saved patient weight data, then uses this data to calculate the total basal injection for that day. Calculation of these doses can be obtained by the following formulas [27].

$$Total\ basal\ dose = \frac{0.55\ x\ Total\ weight}{2} \tag{3.1}$$

$$Basal\ dose\ per\ injection = \frac{Total\ basal\ dose}{4} \tag{3.2}$$

The amount of basal dose to be performed within a day is calculated using the patient's weight. Here, the patient's weight information is withdrawn from the previously saved file and the total basal dose is calculated. Basal insulin injections is administered to the patient four times a day. The amount required for each injection is calculated as one fourth of the total basal dose.

3.2 Bolus Insulin Dose Calculation

Bolus insulin is used to lower blood sugar, which is raised by carbohydrates taken in the meals. To calculate this dose, firstly the blood sugar before meal is measured and the correction dose is given according to the glucose level. Calculation of this correction dose is done as follows [27].

$$Correction\ dose = \frac{Current\ blood\ glucose - Target\ blood\ glucose}{ISF} \quad (3.3)$$

The Insulin Sensitivity Factor (ISF) used in this equation indicates the rate of reduction of the relative glucose level for a unit insulin and it is patient specific. Calculation of this value was made with the Rule of 1800 given in equation (3.4) [27].

$$Insulin\ sensitivity\ factor\ = \frac{1800}{0.55\ X\ Total\ weight} \quad (3.4)$$

Carbohydrate (CHO) coverage dose should be given in addition to correction dose for total bolus insulin. Calculation of this dose is given in equation (3.5) [27].

$$Carbohydrate\ coverage\ dose = \frac{Total\ grams\ of\ CHO\ in\ the\ meal}{carbohydate\ coverage\ ratio} \quad (3.5)$$

$$Carbohydrate\ coverage\ ratio = \frac{500}{0.55\ X\ Total\ weight} \quad (3.6)$$

The designed insulin pump uses probabilistic methods to calculate the correction dose to prevent the patient from doing measurements with a glucometer before every meal. Also a database and an interface was created for carbohydrate coverage dose to facilitate the patient's use of the pump. In this pump after patient’s meal input, the pump calculates CHO for the meal and saves the data to a table. Then the program calculates correction dose from this table using a prediction algorithm. It also calculates the carbohydrate coverage dose from the CHO intake for the specific meal. After calculating total bolus dose the pump makes necessary injections. The bolus insulin dose calculation program flow chart is shown in Figure 3.3.

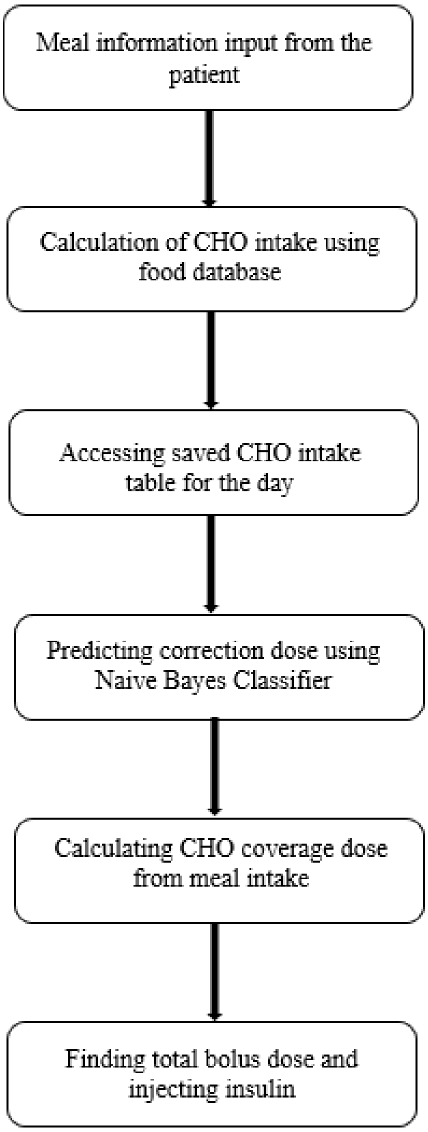

Figure 3.3 Flow chart of bolus insulin injection program

3.2.1 Probabilistic Methods

The insulin pump designed in this thesis uses Naive Bayes Classifier and Gaussian distribution to predict correction doses as part of the bolus insulin dose calculations.

3.2.1.1 Naive Bayes Classifier

Naive Bayes Classifier is a probabilistic approach used in classification problems. In the Naive Bayes approach the features are assumed to be independent from each other. Naive Bayes Classifier computes the probabilities using Bayes Theorem given in equation (3.7).

$$P\ (A \mid B) = \frac{P\ (B \mid A) P\ (A)}{P(B)} \tag{3.7}$$

Bayes Theorem calculates the probability of event A when event B occurs by multiplying the probability of event B when event A occurs with the probability of event A, then dividing the result by probability of event B. Since probability of event B is constant for all classes, to decide the probability of variable x belonging to class Si equations (3.8) and (3.9) can be used.

$$P\ (x \mid S_i) = \prod_{k=1}^{L} P\ (x_k \mid S_i) \tag{3.8}$$

$$P(S_i) \prod_{k=1}^{L} P\ (x_k \mid S_i) > \ P(S_j) \prod_{k=1}^{L} P\ (x_k \mid S_j) \tag{3.9}$$

Variable x belongs to the class that gives the maximum value of equation (3.8) [28].

3.2.1.2 Gaussian Distribution

Gaussian distribution is a continuous probability distribution also called as the normal distribution. Values for this distribution can be found with parameters $\theta = (\mu,\sigma^2)$. The probability density function can be defined with only these two parameters, mean and variance. With these two parameters the continuous gaussian density function of variable x can be found using equation (3.10) [28].

$$P_\theta(x) = \frac{1}{\sigma\sqrt{2\pi}} \exp(-\frac{(x-\mu)^2}{2\sigma^2}) \tag{3.10}$$

3.2.2 Blood Glucose Dataset

Automated insulin pump uses a prediction algorithm to calculate correction part of the bolus insulin dose. In this prediction algorithm classification is made using a previously created blood glucose dataset. This dataset is created using AIDA, an online simulator program of glucose-insulin interaction for diabetics.

3.2.2.1 AIDA Simulator

AIDA is a computer program that enables simulation of blood glucose profile with a glucose-insulin interaction model for insulin-dependent diabetic patients. When AIDA is run, the user can see the effects of different treatment types, insulin doses and dietary changes on the daily blood sugar levels for the virtual diabetic patient by selecting the patient's disease status, individual characteristics, body weight and main metabolic indices [29].

AIDA simulator uses a model that reflects the physiology of insulin action, carbohydrate absorption and blood glucose levels. The simulator's predictions generates a 24 hour simulation of blood glucose profiles for hypothetical patients. AIDA comes with previously prepared 40 patient case scenarios. In addition to this patient simulations the users can add further case scenario. AIDA can also identify some basic problems in the case scenario data. Therefore it can make a list of suggestions to correct these problems [30].

When using the AIDA simulator a patient case must be selected and then the user can enter the meal and insulin injection information for the duration of the day. After the program is run, the simulator gives the output file of 24 hour blood glucose levels.

3.2.2.2 Creating a Blood Glucose Level Dataset

The insulin pump designed obtains the correction dose information from the patient's meal inputs, rather than the patient's knowledge of blood glucose levels. For this estimation a dataset was created using AIDA simulator program.

The dataset used in this pump is created with AIDA simulator using a hyperglycemia patient profile. For 10 different patient weights, five different daily simulations are made for a 6 meal diet with 3 main meals and 3 snacks, in which the patient received four doses of basal insulin per day. During these five-day simulations, the amounts of carbohydrates received at the meals were changed. The patient has 6 meals on the first day, skips the breakfast on the second day, delays the lunch for the third day, skips the snacks on the fourth day, and excessively eats at one of the meals during the last day. The result of each simulation is saved as 24-hour blood glucose level data. 24 hours of data for 5 days and for 10 different weights makes the dataset size 1200x16. There is 16 columns for each row and this columns keeps the information about time, carbohydrate intakes for the meals, basal insulin injections, patient weight and blood glucose levels. The dataset example for a patient’s 24 hours of blood glucose levels and insulin dosages can be seen in Figure 3.4. The correction doses for the dataset are calculated using equation (3.3) and insulin dose data are classes appointed for these doses.

ID	Time	Breakfast	Snack 1	Lunch	Snack 2	Dinner	Snack3	Basal 1	Basal 2	Basal 3	Basal 4	Weight	Glucose Level	Correction Dose	Injection Dose
11	5	0	0	0	0	0	0	0	0	0	0	70	139,042	0,407287222	0
11	6	0	0	0	0	0	0	0	0	0	0	70	144,25	0,518680556	0
11	7	20	0	0	0	0	0	5	0	0	0	70	152,628	0,697876667	0
11	8	20	0	0	0	0	0	5	0	0	0	70	185,813	1,407666944	1
11	9	20	0	0	0	0	0	5	0	0	0	70	226,825	2,284868056	2
11	10	20	20	0	0	0	0	5	0	0	0	70	212,493	1,9783225	1
11	11	20	20	0	0	0	0	5	0	0	0	70	212,216	1,972397778	1
11	12	20	20	30	0	0	0	5	4	0	0	70	233,882	2,435809444	2
11	13	20	20	30	0	0	0	5	4	0	0	70	238,811	2,541235278	2
11	14	20	20	30	10	0	0	5	4	0	0	70	275,159	3,318678611	3
11	15	20	20	30	10	0	0	5	4	0	0	70	273,876	3,291236667	3
11	16	20	20	30	10	0	0	5	4	0	0	70	246,18	2,69885	2
11	17	20	20	30	10	30	0	5	4	4	0	70	209,665	1,917834722	1
11	18	20	20	30	10	30	0	5	4	4	0	70	208,495	1,892809722	1
11	19	20	20	30	10	30	0	5	4	4	0	70	251,901	2,821215833	2
11	20	20	20	30	10	30	0	5	4	4	0	70	238,222	2,528637222	2
11	21	20	20	30	10	30	0	5	4	4	0	70	204,82	1,814205556	1
11	22	20	20	30	10	30	10	5	4	4	5	70	180,248	1,288637778	1
11	23	20	20	30	10	30	10	5	4	4	5	70	187,197	1,437269167	1
11	24	20	20	30	10	30	10	5	4	4	5	70	187,113	1,4354725	1
11	1	20	20	30	10	30	10	5	4	4	5	70	169,84	1,066022222	1
11	2	20	20	30	10	30	10	5	4	4	5	70	154,609	0,740248056	0
11	3	20	20	30	10	30	10	5	4	4	5	70	143,563	0,503986389	0
11	4	20	20	30	10	30	10	5	4	4	5	70	138,445	0,394518056	0

Figure 3.4 Dataset example for 24 hours of a patient

3.2.3 Correction Dose Prediction

Automated insulin pump in this thesis uses the blood glucose level dataset and Naive Bayes Classifier for correction dose prediction to prevent the patient from doing invasive blood glucose measurements.

For the Naive Bayes approach features of the blood glucose dataset are assumed to be independent from each other. Insulin pump uses equation (3.11) for time feature of 16 featured database. For the other features of the dataset, Gaussian density function is used in the Bayes Theorem since the assignment of numeric values to certain class ranges will result in loss of precision. Therefore the equation (3.12) is used for meal, basal insulin injections and weight features of the dataset.

$$P\ (x \mid S_i) = \prod_{k=1}^{L} P\ (x_k \mid S_i) \tag{3.11}$$

$$P_\theta(x) = \frac{1}{\sigma\sqrt{2\pi}}\ \exp(-\frac{(x-\mu)^2}{2\sigma^2}) \tag{3.12}$$

Insulin dose prediction algorithm works by taking the time information from the patient. After time information is given, the program calculates the probabilities of given time variable to belonging each of the insulin dose classes. Then it finds the class by finding the maximum probability.

Every time a meal or insulin basal injection information is given to the database it is also recorded to a table of 24 hours. This table is then used in the prediction program by taking the row of dosage calculation time. Then the class this dosage time belongs can be found using Naive Bayes Classification algorithm.

The accuracy of the algorithm is shown using Clarke Error Grid Analysis. This analysis is a method to show the clinical significance of differences between the predicted glucose values and reference glucose measurement values. There are five zones in this diagram. Zone A is clinically accurate, B is benign error, C is overcorrection, D is dangerous failure and E is serious errors zone. In this method zones A and B shows the clinically acceptable results, C,D and E zones shows dangerous results [18].

3.2.4 Carbohydrate Food Database

When calculating doses of bolus insulin for diabetic patients, the correction dose should be supplemented with the CHO coverage dose, according to the amount of carbohydrates taken during the meal. Therefore while high blood glucose is reduced, carbohydrates taken during meals are prevented from raising the blood glucose levels again. Thus glucose levels are kept in balance for a longer time.

Diabetes patients calculate the amount of carbohydrates in the food they consume during meals and calculate a coverage dose using the equations (3.5) and (3.6). For this insulin pump design a food database was created and the patient only needs to enter the food they consumed. Then a program calculates the right carbohydrate amounts from this information.

Grams of carbohydrates in foods are calculated using a food database. To create this database, a food-carbohydrate list for diabetic patients was used [31]. From this list 10 different food was selected and added to the database. This database contains the grams of carbohydrate per portion for each food. For the CHO coverage dose calculation, the patients must first enter the name of the food, then the amount of the portion they consumed for the meal to the program.

3.2.5 Carbohydrate Coverage Dose Calculation

The designed insulin pump requires the patient to enter the data of the food he consumes in the meal for the CHO correction dose calculation prior to bolus insulin injection. This way, the grams of carbohydrates the meal contains can be obtained using the CHO information saved in the database. The total amount of carbohydrate is found by entering how many portions the patient has eaten from the food. The input interface is given in Figure 3.5.

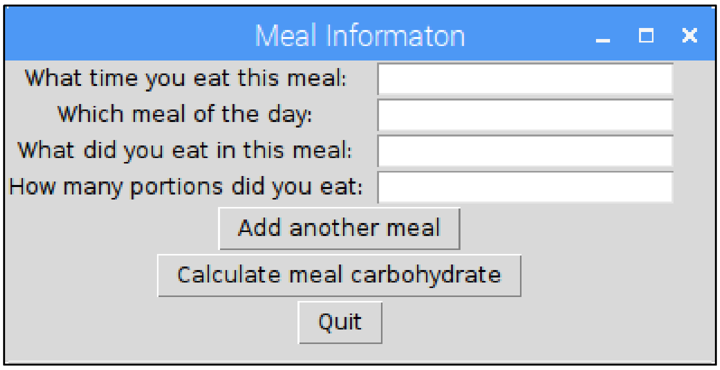

Figure 3.5 Meal input interface for bolus dose calculation

When the CHO calculation program is run, the program first takes the food name and portion data. Then the database is searched by the food name and the CHO grams contained in the food per portion is accessed from this database. After finding the CHO amount contained in one portion the program then calculates the amount of carbohydrate for the meal using portion data input given by the patient.

Patient has the option to enter more than one food for every meal. In this case the program calculates the total CHO amount for the meal by adding the CHO amounts found for each food. After calculating total amount of carbohydrate intake for the meal, the program then uses equations (3.5) and (3.6) to calculate the CHO correction dose for this meal.

3.3 Basal Dose Injection

Automated insulin pump injects basal insulin doses periodically throughout the day to balance the glucose levels between meals and during night time. The designed insulin pump makes automated injections four times daily. At scheduled times during the day a basal insulin injection program is run by the controller. This program takes the weight information saved in a file and makes necessary calculations to find basal dosage for one injection. After calculating the basal dose the microcontroller gives the output to inject necessary amount of insulin. After every basal injection the pump saves the date, time and dose information to a database for patient records. Then informs patient with window given in Figure 3.6.

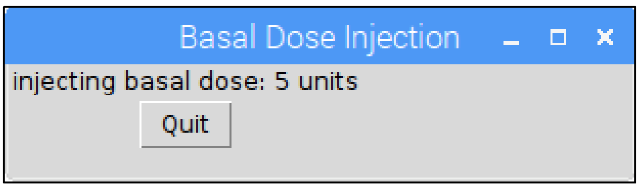

Figure 3.6 Basal insulin injection notification

3.4 Bolus Dose Injection

Automated insulin pump injects bolus insulin doses at meal times to balance the increased glucose levels after carbohydrate intakes. Bolus injection program works after the patient's prompt. When the wants to make the injection the program first takes the meal information with the window given in Figure 3.7. Then it calls another program to predict the blood glucose level of the patient using daily meal intake and injections table. This prediction uses Naive Bayes Classifier to predict the correction insulin dose for the given time of the day. After calculating correction dose, the program then makes the CHO coverage dose calculations with the given meal input data. After calculating both the correction and CHO coverage doses total bolus dose then can be found by equation (3.13).

$$Total\ bolus\ dose = Correction\ dose + CHO\ coverage\ dose \tag{3.13}$$

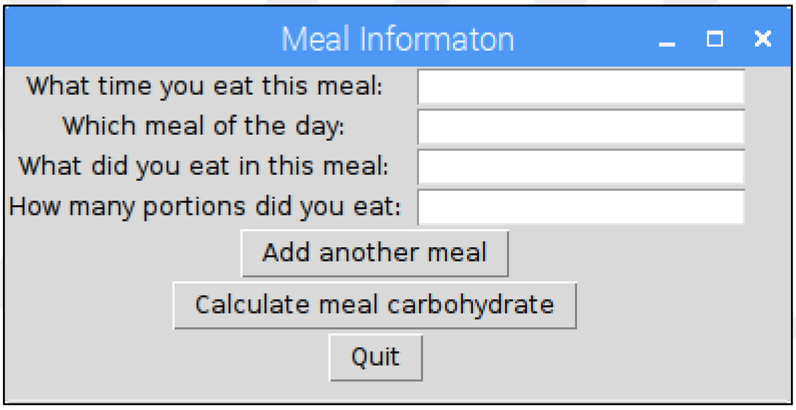

Figure 3.7 Meal information input interface for bolus insulin injection

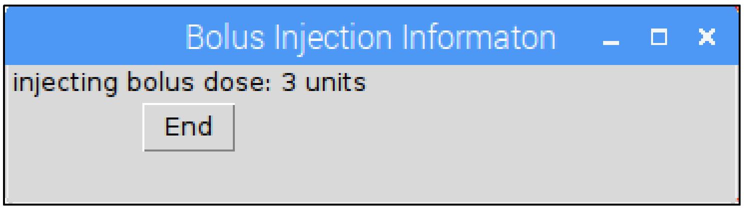

Figure 3.8 Bolus dose injection notification

After total bolus dose calculation the output for the necessary amount of insulin injection is given by the microcontroller. Then patient is informed as seen in Figure 3.8. After every bolus injection the pump saves the date, time, meal intake and dose information to a database for patient records.

3.5 Patient Records

The designed automated insulin pump stores patient's past injection and meal data to keep track of patient's treatment history. Therefore it can be helpful for future treatment plans and patient monitoring.

After every injections the date, time and dose information is recorded to a database along with the injection type. In addition to these data for bolus doses the carbohydrate intakes for the meals are also recorded. This way the patient can access the injections records.

Access to patient's records can be done by entering a desired date with an interface seen in Figure 3.9. After the date information is given the program searches the records database for the injections made in this date and gives the results. The results for a andom query can be seen in Figure 3.10.

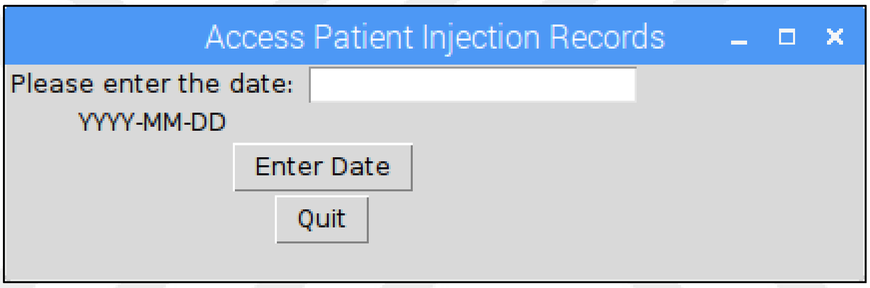

Figure 3.9 Interface for accessing patient's records

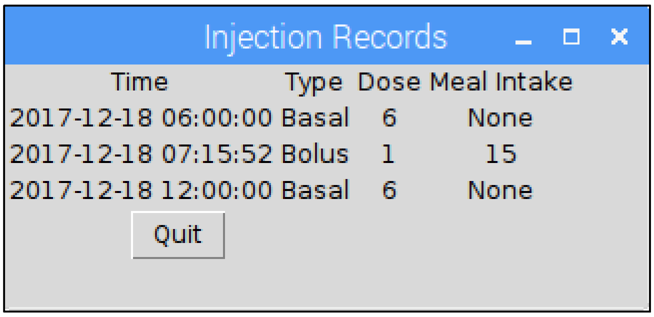

Figure 3.10 Patient records query output

CHAPTER 4

INSULIN PUMP HARDWARE

Automated insulin pump designed in this thesis uses a Raspberry Pi microcontroller to calculate insulin doses and control the injections. Injections are made by a 3D printed pump working with a stepper motor driven by a motor driver circuit. The block diagram of the system is shown in Figure 4.1.

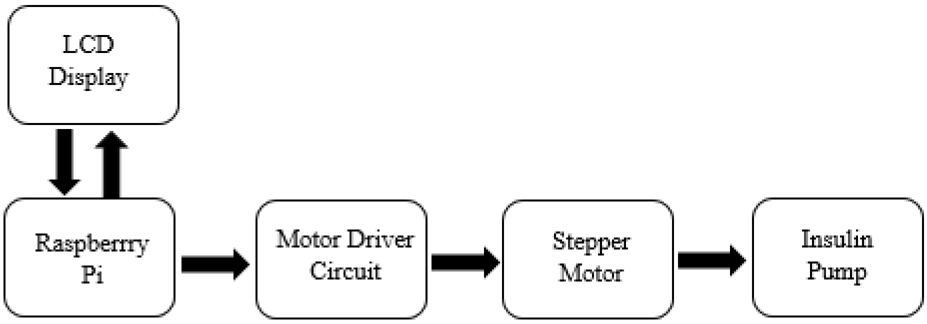

Figure 4.1 Insulin pump hardware

4.1 Raspberry Pi

Raspberry Pi 3 Model B has been chosen to control the system while the smart insulin pump designed in this thesis is realized. Since Raspberry is a microcontroller with its own operating system, it can run multiple programs on it. Besides, it can control the stepper motor which provides pump injection by providing 3.3V output with GPIO pins located on it [32]. In Figure 4.2 a Raspberry Pi 3 Model B microcontroller can be seen.

Figure 4.2 Raspberry Pi 3 Model B [32]

4.2 Motor Driver Circuit

A stepper motor is used for the insulin syringe to inject the insulin in the pump. This stepper motor is controlled at the output of the Raspberry Pi by a connection with motor driver circuit, ULN2003A.

ULN2003A is a Darlington array for high voltage, high current use [33]. The circuits with motor loads need high current that can damage microcontrollers. Therefore Darlington arrays are used in these circuits to prevent any damage to components. The microcontroller pins control the motor via four input pins of the ULN2003A when the corresponding four output pins are connected to the stepper motor. The motor driver circuit and Raspberry Pi 3 connections are shown in Figure 4.3.

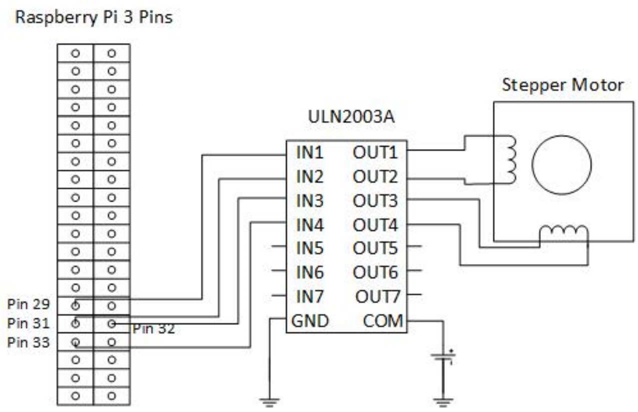

Figure 4.3 Motor driver circuit

4.3 Pump Design

The pump of the design is controlled by a stepper motor. The stepper motor is connected to a lead screw which moves a tiny traveling nut that pushes the syringe plunger. The connectors and syringe holders are 3D printed parts of the pump. The printed and assembled pump part of the system is shown in Figure 4.4.

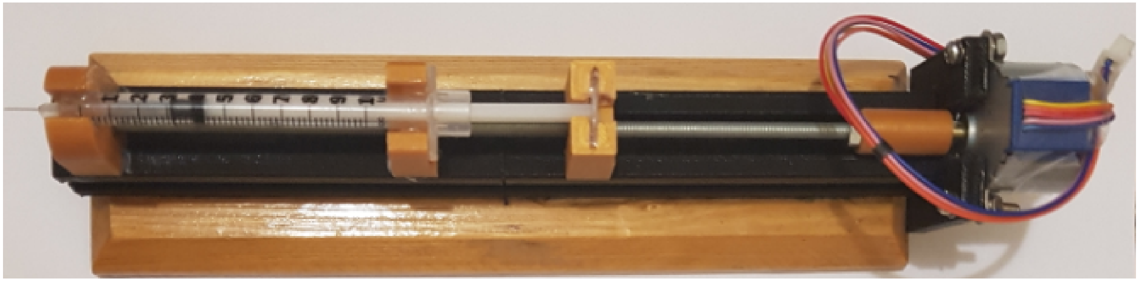

Figure 4.4 Pump mechanism

The stepper motor turns when the injection programs in the Raspberry Pi 3 activate the GPIO pins accordingly. Four pins need to be activated in a specific order for the stepper motor's motion. The number of steps needed for the necessary injection is decided by the microcontroller Raspberry Pi which is connected to the pump through a driver circuit.

The pump injects insulin when the stepper motor is working and the step count of this motor is controlled by Raspberry Pi. The overall system is shown in Figure 4.5.

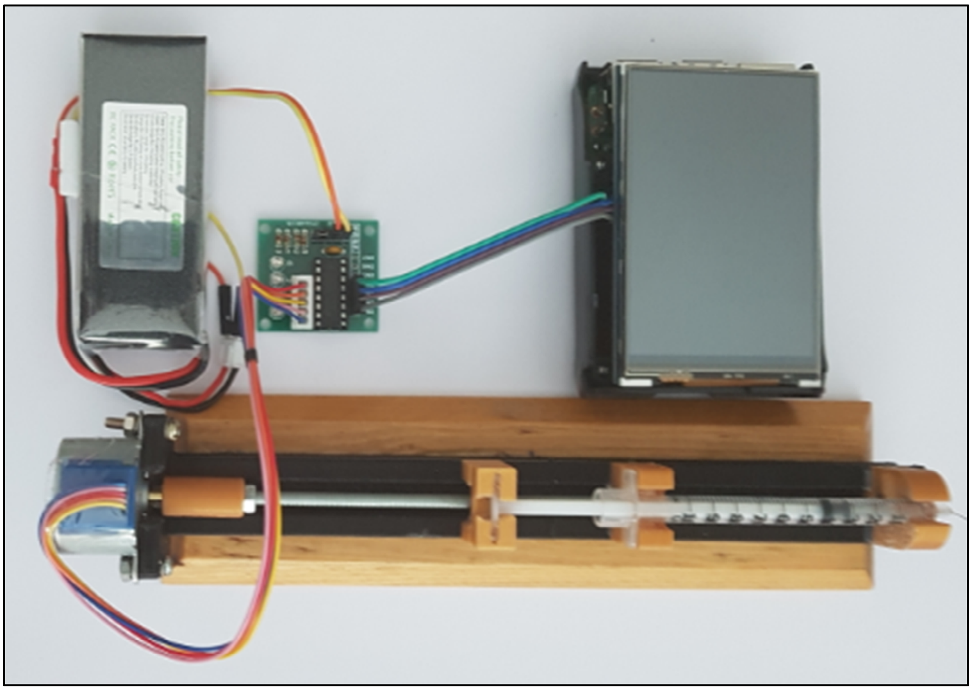

Figure 4.5 Automated insulin pump

CHAPTER 5

RESULTS AND DISCUSSION

In this thesis an automated insulin pump prototype has been realized for the use of patients with diabetes mellitus. The pump developed makes insulin injections intermittently throughout the day for basal insulin doses without any input from the patient. In addition to these basal doses this insulin pump also takes meal information from the patient and uses this input to calculate bolus insulin doses without any blood glucose level information. Therefore there is no need for invasive blood glucose measurement in the designed system. This pump also keeps records of the insulin injections made, thus it can be helpful for future treatment plans and patient monitoring.

The insulin pump designed can take the place of manual daily insulin injections applied by the patients themself. This work is unique in terms of predicting the bolus dose solely from meal inputs. The automated pump uses a prediction algorithm based on Naive Bayes Classifier. It also has an interface that can be used by patients easily and keeps records of the patient's past injection and meal intake information and provides access to these records.

The accuracy of the prediction algorithm used in the pump is shown with Clarke Error Grid Analysis. This analysis classifies the results according to the difference between predicted and reference glucose values. Zones A and B in the plot shows the clinically acceptable results, where A is clinically accurate and B is benign errors zone. The designed prediction algorithm with Naive Bayes Classifier has 97.5% of the results in clinically acceptable zones with 59.3% in clinically accurate A zone when two thirds of the dataset is used for training and the rest is used for testing. The results for Clarke Error Grid is shown in Figure 5.1.

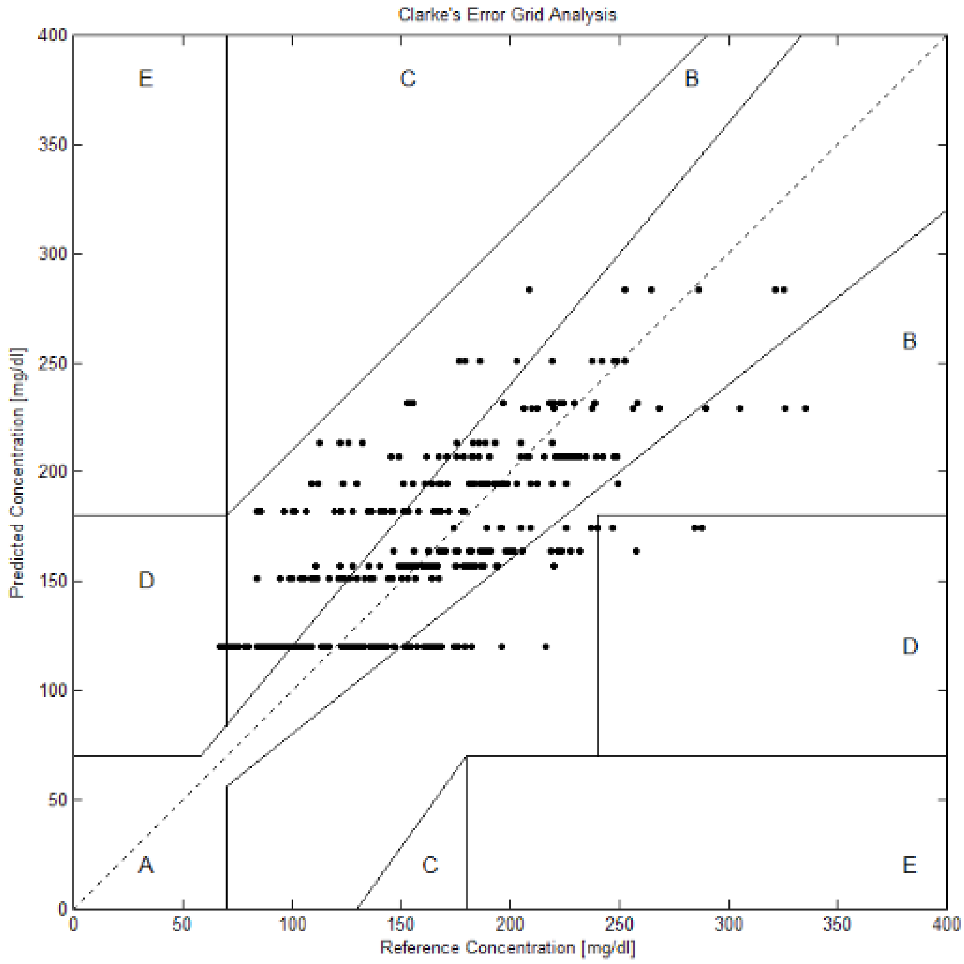

Figure 5.1 Clarke Error Grid Analysis of the prediction algorithm

Insulin pump in this thesis is realized by using Raspberry Pi microcontroller and stepper motor. The motor is controlled by the microcontroller and a motor driver circuit and the pump works by a syringe mechanism pushed forward with the help of the motor.

For future studies, with other prediction algorithms the ratio of clinically accurate zone can be increased. Also if the designed insulin pump is integrated with the non-invasive glucose measurement systems it can operate similarly to the artificial pancreas therefore the dependency on patient input will be minimal.

REFERENCES

[1] Mcadams, B. and Rizvi, A., (2016). "An Overview of Insulin Pumps and Glucose Sensors for the Generalist", Journal of Clinical Medicine, 5(1), 5.

[2] Albisser, A.M., Leibel, B.S. and Ewart, T.G., (1974). "Clinical Control of Diabetes by the Artificial Pancreas", Diabetes, 23(5):397-404.

[3] Albisser, A.M., Leibel, B.S., Ewart, T.G., Davidovac, Z., Botz, C.K. and Zingg, W., (1974). "An artificial endocrine pancreas", Diabetes, 23(5):389–396.

[4] Spencer, W.J., Corbett, W.T., Dominguez, L.R. and Shafer B.D., (1978). "An Electronically Controlled Piezoelectric Insulin Pump and Valves", IEEE Transactions on Sonics and Ultrasonics, 25(3): 153-56.

[5] Dikondwar, S.R., (2011). "Design and development of insulin delivery system prototype", 2011 IEEE 3rd International Conference on Communication Software and Networks.

[6] Revert, A., Calm, R., Vehi, J. and Bondia, J., (2011). "Calculation of the Best Basal–Bolus Combination for Postprandial Glucose Control in Insulin Pump Therapy". IEEE Transactions on Biomedical Engineering, 58(2):274-281.

[7] Jacobs, P.G., Youssef, J.E., Castle, J.R., Engle, J.M., Branigan, D.L., Johnson, P., Massoud, R., Kamath, A. and Ward W.K., (2011). "Development of a fully automated closed loop artificial pancreas control system with dual pump delivery of insulin and glucagon". 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society.

[8] Jacobs, P.G., Youssef, J.E., Castle, J., Bakhtiani, P., Branigan, D., Breen, M., Bauer, D., Preiser, N., Leonard, G., Stonex, T. and Ward, W.K., (2014). "Automated Control of an Adaptive Bihormonal, Dual-Sensor Artificial Pancreas and Evaluation During Inpatient Studies". IEEE Transactions on Biomedical Engineering, 61(10):2569-2581.

[9] International Diabetes Federation (2015) IDF Diabetes, (7th ed.), International Diabetes Federation, Brussels, Belgium. [Online]. Available from: www.diabetesatlas.org, [Accessed 2 Feb. 2017].

[10] Contour Next, Contour Next Meter, www.contournext.com, 11 December 2017.

[11] Contour Next, Contour Next Test Strips, www.contournext.com, 11 December 2017.

[12] Anoop, A. E., Mohan, N. M. and Guruvayurappan, K., (2014). “Simulation of a multi-strip blood glucometer”. TENCON 2014 - 2014 IEEE Region 10 Conference.

[13] Dalvi, N., (2013). Glucose Meter Reference Design, (1st ed.), Microchip Technology Inc., [Online]. Available from: www.microchip.com, [Accessed 20 Oct. 2017].

[14] Dudukcu, H.V. and Yildirim, T., (2017). “Noninvasive Glucose Measurement for Diabetes Mellitus Patients”. Current Trends in Biomedical Engineering and Biosciences, 2(3):555586.

[15] Lawand, K., Parihar, M. and Patil S.N., (2015). “Design and development of infrared LED based non invasive blood glucometer”. India Conference (INDICON), India.

[16] Hotmartua, R., Pangestu, P.W., Zakaria, H. and Irawan, Y.S., (2015). “Noninvasive Blood Glucose Detection Using Near Infrared Sensor”. International Conference on Electrical Engineering and Informatics, Indonesia.

[17] Malin, S.F., Ruchti, T.L., Blank, T.B., Thennadil, S.N. and Monfre, S.L., (1999). “Noninvasive Prediction of Glucose by Near-Infrared Diffuse Reflectance Spectroscopy”. Clinical Chemistry, 45(9): 1651-1658.

[18] Smith, J.L., (2015). The Pursuit of Noninvasive Glucose: “Hunting the Deceitful Turkey”. (4th ed.), John L. Smith.

[19] Vilaboy, M.J., Ergin, A., Tchouassi, A., Greed, R. and Thomas, G.A., (2003). “Optical measurement of glucose concentrations using Raman spectroscopy.” Northeast Bioengineering Conference, USA.

[20] Pai, P.P., Sanki, P.K., De, A. and Banerjee, S., (2015). “NIR Photoacoustic Spectroscopy for Non-Invasive Glucose Measurement”. Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Italy.

[21] Malik, B.H. and Cote, G.L., (2010). “Real-time, closed-loop dual-wavelength optical polarimetry for glucose monitoring”. Journal of Biomedical Optics, 15(1): 017002.

[22] Nikawa, Y. and Michiyama, T., (2006). “Non-Invasive Measurement of Blood-Sugar Level by Reflection of Millimeter-Waves”. Asia-Pacific Microwave Conference, Japan.

[23] Gelao, G., Marani, R., Carriero, V. and Perri, A.G., (2012). “Design of a dielectric spectroscopy sensor for continuous and non-invasive blood glucose monitoring”. International Journal of Advances in Engineering & Technology 3(2): 55-64.

[24] Sharma, N.K. and Singh, S., (2012). “Designing a non invasive blood glucose measurement sensor”. International Conference on Industrial and Information Systems (ICIIS), India.

[25] Harvey, R.A., Wang, Y., Grosman, B., Percival, M.W., Bevier, W., Finan, D.A., Zisser, H., Seborg, D.E., Jovanovic, L., Doyle, F.J.III. and Dassau, E., (2010). “Quest for the Artificial Pancreas”, IEEE Engineering in Medicine and Biology Magazine, 29(2): 53-62.

[36] Medtronic, Continuous Glucose Monitoring, www.medtronicdiabetes.com, 11 December 2017.

[27] Diabetes Education Online, Calculating Insulin Dose, www.dtc.ucsf.edu, 21 October 2017.

[28] Shai, S.S. and Shai, B.D., (2014). Understanding Machine Learning: From Theory to Algorithms. (1st ed.), Cambridge University Press.

[29] Lehmann, E.D., Tarin, C., Bondia, J., Teufel, E. and Deutsch, T., (2011). “Development of AIDA v4.3b Diabetes Simulator: Technical Upgrade to Support Incorporation of Lispro, Aspart, and Glargine Insulin Analogues”. Journal of Electrical and Computer Engineering, 2011: 427196

[30] AIDA Online Free Web-Based Educational Diabetes Simulator, Welcome to AIDA, www.2aida.net, 11 December 2017.

[31] Michigan Medicine, Diabetes: Carbohydrate Food List, www.med.umich.edu, 11 December 2017.

[32] Raspberry Pi, Raspberry Pi 3 Model B, www.raspberrypi.org, 21 Ekim 2017.

[33] STMicroelectronics, “Seven Darlington Array”, ULN200xA-ULN200xD1 datasheet, Rev. 6, 2007.

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