CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

World Health Organization (WHO), has estimated that more than 371 million people are affected by diabetes all over the world, and this number is expected to increase up to 438 million, in the year 2030. Diabetes mellitus, is a disease of disordered glucose metabolism due to the defects in insulin secretion or insulin action. This has become a major health topic to be attended to. There has been much hype in the research and development of Continuous Glucose Monitoring (CGM) market and in the ever increasing base of diabetes patients. This chapter discusses the need for such work along with the aim and objectives of current research work.

1.2 NEED FOR RESEARCH

Diabetes is one of the pandemic diseases and causes 4 million deaths per year and ranks fifth by causing specific mortality in the most high-income countries. Hence it is undoubtedly one of the most challenging health problems of the 21’st century (IDF, 2011). The Indian Council of Medical Research (ICMR) estimated that the country already had around 65.1 million diabetes patients. Along with the increasing numbers of affected, the total costs towards medicare and treatment increases dramatically. Diabetes health care constitutes 11.6% of the total health care expenditure of the world (Zhang et al 2010).
One should maintain the glucose concentration in blood, within the normal range (70 – 120 mg/dL or 3.6 – 6.9 mmol/L). Lower glucose levels (< 50mg/dL) are said to be hypoglycemia, which is characterized by excessive thirst, sweating, seizures and coma. Higher glucose levels (> 200 mg/DL) are known as hyperglycemia, which leads to long term vascular complications, diabetic retinopathy, neuropathy, and nephropathy.

![Blood Glucose Profile of a Diabetic Person](image)

**Figure 1.1 Blood glucose variations of a person with Diabetes (Age: 54 years)**

Figure 1.1 represents the dynamics of glucose concentration in 5 hours, in the blood of a person with diabetes. The horizontal lines in the plot represent the lower and upper bounds of normoglycemia. The arrowheads indicate the timing at which the respective amount of carbohydrate food was consumed by the subject.

The human body’s glucose levels are in constant flux, and any abnormal high or low level can yield extremely negative repercussions for patients, including fainting and blindness apart from heading to amputation.
Monitoring of blood glucose is inevitable for diabetes control. Monitoring has been shown to be efficacious in reducing the acute and chronic complications, and thereby to improve the quality of the life of affected people.

The prediction of hypo / hyperglycemia is clinically an important task in the management of diabetes. Hyperglycemia has a chronic effect on the health of diabetic patients whereas hypoglycemia has immediate dangerous effects such as, seizure and coma. It has to be predicted therefore well in advance, and preventive measures should be taken. Likewise, hyperglycemia should also be inferred earlier to avoid the micro and macrovascular complications. It is established that, hypoglycemia is prevalent among 70 to 80% of people with Diabetes mellitus. The Juvenile Diabetes Research Foundation (JDRF) accomplished a study to characterize the amount of nocturnal hypoglycemia (JDRF 2004). The analysis included 36,467 nights with greater than four hours of CGM reading from 167 subjects. The results were in such a way that, hypoglycemia occurred during 8.5% of nights with duration of hypoglycemia to be greater than or equal to 2 hours (Beck 2010). Another problem with hypoglycemia is night time death, also called as Dead in Bed Syndrome. An estimated 6% of deaths among young adults have been attributed to hypoglycemia (Sovik & Thordarson 1999). Hypoglycemia-associated autonomic failure was observed in both type I and type II diabetes and works have been carried out to contemplate the impact of hyperglycemia in cardiovascular diseases, oxidative stress and autonomic system failure (Dagogo-Jack et al 1993, Beckett 2010, Krinsley 2003).

Predictive monitoring is mandatory for the success of the Artificial Pancreas Project (APP) promoted by JDRF (APP 2006, JDRF 2006), United States of America (USA). Further research is being carried out by various groups around the world, to circumvent the drawbacks associated with the predictive monitoring systems.
1.3 MANAGEMENT OF DIABETES

Diabetes has evolved as an alarming threat to public health. Diabetes mellitus is a chronic disease, due to the failure of pancreatic beta cells in secreting sufficient insulin. Insulin is the hormone necessary to regulate the glucose in blood and for inducing the uptake of glucose by the body cells from the blood stream. The glucose concentration in blood fluctuates, in response to the assimilation of food, hormonal cycles or behavioral factors. The daily management of diabetes can be done by regular monitoring of Blood Glucose (BG), and proper drug administration. The Diabetes Control and Complications Trial (DCCT), has stated that, strict glycemic control significantly reduces the short term and long term complications of diabetes (Nathan et al 2005).

Self Monitoring of Blood Glucose (SMBG), is a method of measuring the BG levels with blood glucometers. A sample of capillary blood obtained from the fingertip, is placed over the test strip, and is inserted in the meter. The glucose in the blood reacts with glucose oxidase in the strip, resulting in the production of hydrogen peroxide, and free electrons which are proportional to the glucose concentration in blood (Newman & Turner 2005). This flow of free electrons, i.e., the current is then converted to digital values, and displayed on the glucometers. The problem with this conventional measurement is the pain and the inconvenience associated with lancing, and finger bleeding. Furthermore, the tests have to be performed 4-6 times a day. Moreover, this method is not effective in tracking BG variability throughout the daytime. The SMBG provides only a snapshot of BG concentration. Most of the diabetes patients are unable, either to track changes in the level of glucose, or to take adequate steps to control its level under check.
The state-of-art CGMSs represent a significant advancement in BG monitoring, because they offer real-time information about the current BG levels. The CGMS is an ingenious device, which constantly displays the current levels of glucose and reproduces the information every five minutes. The CGMS also provides information about the magnitude, direction, duration, frequency and causes of fluctuations in BG levels (Klonoff 2005, Skyler 2009). Continuous monitoring, thus, enables to study the variation in glucose levels because of insulin, exercise, food and other factors. This additional information is quite handy, for administering correct insulin dosage, food intake, and control of hyperglycemia. The occurrence of hypoglycemia during nights can also be identified and rectified by the CGMS. This device can also alert the patient by sounding an alarm during hypo/hyperglycemia and thus becoming an important tool in diabetes management.

1.4 MOTIVATION AND CRUX OF THE RESEARCH WORK

If a person’s glycemic state was predicted in time slots earlier, and if he were alerted for any impending hypo/hyperglycemia levels, he could take preventive measures to avoid further complications. Therefore, forecasting of glucose levels is extremely essential. The accuracy of prediction is affected by the presence of various noise components in the CGM sensor data and in the lack of adaptive, personalized real time tuning methods in the prediction algorithms. Despite the wide range of work that has been done in predictive monitoring by various research groups such as Pappada et al (2008), Cobelli et al (2009), Fachinetti et al (2010b) and Perez-Gandia et al (2010), many challenges are still there in denoising of errors in CGM signal, the uncertainties which lead to inter patient and intra patient variability which affects the accuracy in prediction of the concentration of plasma glucose.
The goal of this research is the prediction of near future glucose levels in blood plasma with CGM data, for those people affected by Diabetes mellitus. It is done through adaptive and customized prediction models with Artificial Intelligence (AI) techniques. The objectives of research work are as follows.

1. To apply HFT with State Space (SS) modeling of BG dynamics and sensor gain deviation with Auto Regressive processes and applying it for the Extended Kalman Filter (EKF) algorithm which is used for training the Neural Network (NN) in denoising the CGM sensor data thereby improving the quality of CGM signal.
2. To compare the performance of the Hybrid Filtering Technique (HFT) with the Moving Average (MA) and Kalman Filter.
3. To incorporate the BG variability features with a moving window for training a NN for the prediction of BG.
4. To apply an Adaptive Neuro Fuzzy Inference System (ANFIS) model with minimum input features and custom error propagation with differential evolution and use that model for the prediction of BG.
5. To compare the performance of the above said models for the prediction of BG with different data sets (scenarios) and to analyze the accuracy of prediction models.

In each stage, the performance of the prediction model has been compared with its related recent counterpart in the literature. Knowing that CGM sensor data do have errors, when the rate of change is high, our first module has dealt with the development of an HFT for denoising of errors and to improve the quality of CGM sensor data. The possible noise distributions were analyzed and the filter was designed to remove any non physiological variation in the incoming data. The performance of HFT was compared with the existing (MA) filter and Kalman Filter. In the second module of work, the
prediction of glucose levels has been tried out with three methods. The first approach was smoothening of data with Tikhonov regularization and forecasting with ARIMA process. The second method comprised of the utilization of an Artificial Neural Network (ANN), which has been developed according to the extracted features and variable learning rate, and custom made activation functions at hidden and output layers. The third approach was with customized ANFIS which has been developed with a first order Sugeno Fuzzy model and trained with features of input signal to predict the future values. Input selection procedure and customized error back propagation have been employed.

The proposed methods were developed with MATLAB (R2010a) and tested with three different data sets. The prediction approaches were tested initially with simulated diabetes data and then with real data sets. The simulated data were obtained from Glucosim, a web based Diabetes educator (Glucosim, 2006). The second data set was gleaned up with glucose control project of University of California San Diego (UCSD, 2008). The third data set is the Continuous Glucose Monitoring Sensor data obtained from Rollins et al (2010).

For real-time evaluation of proposed methods, data have been collected in two ways. Self Monitoring Blood Glucose (SMBG) values from 100 subjects for five, 24 hour days. The SMBG values were acquired once in every three hours, with One Touch Ultra® glucometer. Then the discrete values were smoothened to acquire a continuous time course using cubic splines. The second real time data set was from the users (10 subjects) of Medtronic CGMS® (Medtronic Minimed, Inc., Minneapolis, CA). The anthropological parameters of the diabetic subjects such as age, weight, glycosylated haemoglobin (HbA1C), insulin dosages and duration of disease were chosen, so as to obtain different types of CGM profiles. Patients chosen were of different age groups and categories, and confined to the region of
Tamil Nadu, South India. The data set is in turn classified into Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D), male and female patients, gestational diabetes, diabetes with hypertension and diabetes with sports activity.
The prediction strategies were applied and tested with Prediction Horizons (PHs) in 30 and 60 minutes. Root Mean Square Error (RMSE) and time lag were considered as the performance metrics. The results show that, the prediction with ANFIS is the optimized method, producing more accurate predictions even in the 60 minutes PH. The flow of research work has amply been demonstrated through a graphical workflow in Figure 1.2. The details have been elaborated in the chapter on research methodology.

1.5 ORGANIZATION OF THESIS

Chapter 1 gives the introduction and need for research in the prediction of near future glucose values. Chapter 2 provides the background information needed for research along with a review of literature in denoising of CGM sensor errors and prediction strategies with CGM time series data.
Chapter 3 gives the details of the research methodology. Chapter 4 elaborates the details of data collection used for study and for experimental purpose. The current research comprises of 4 parts viz, denoising of CGM sensor data with HFT, prediction of BG with time series ARIMA model, Feature based Neural Network (FNN) and customized ANFIS. Chapter 5 discusses the HFT and its performance in denoising the CGM sensor data. The traditional time series prediction approach with ARIMA has been presented in chapter 6. Prediction of BG with AI, i.e., with a feature based neural network has been described in Chapter 7. The details of the customized ANFIS model for prediction are given in Chapter 8. The results and discussion of all the methods have been given in Chapter 9. Conclusion and scope of the prospective work are enumerated in Chapter 10.

1.6 SUMMARY

CGM devices provide the feedback from food and therapeutic decisions. Still, there remains a need for better predictive alarms for the impending hypoglycemia. Hyperglycemia is prevalent in critical illness and it increases the risk of further complications and mortality. This proposed research work analyses the feasibility of employing AI techniques for the prediction of glucose concentration in blood plasma. All the proposed methods for the prediction of glucose concentration in blood plasma, were tested with PHs in 30 and 60 minutes and performance analysis was carried out with the above mentioned data sets.

The issues in CGM sensor data have to be analyzed at first so as to find out the solution. A review of denoising technique and prediction methodologies with respect to CGM sensor data, are discussed in detail in the following Chapter.