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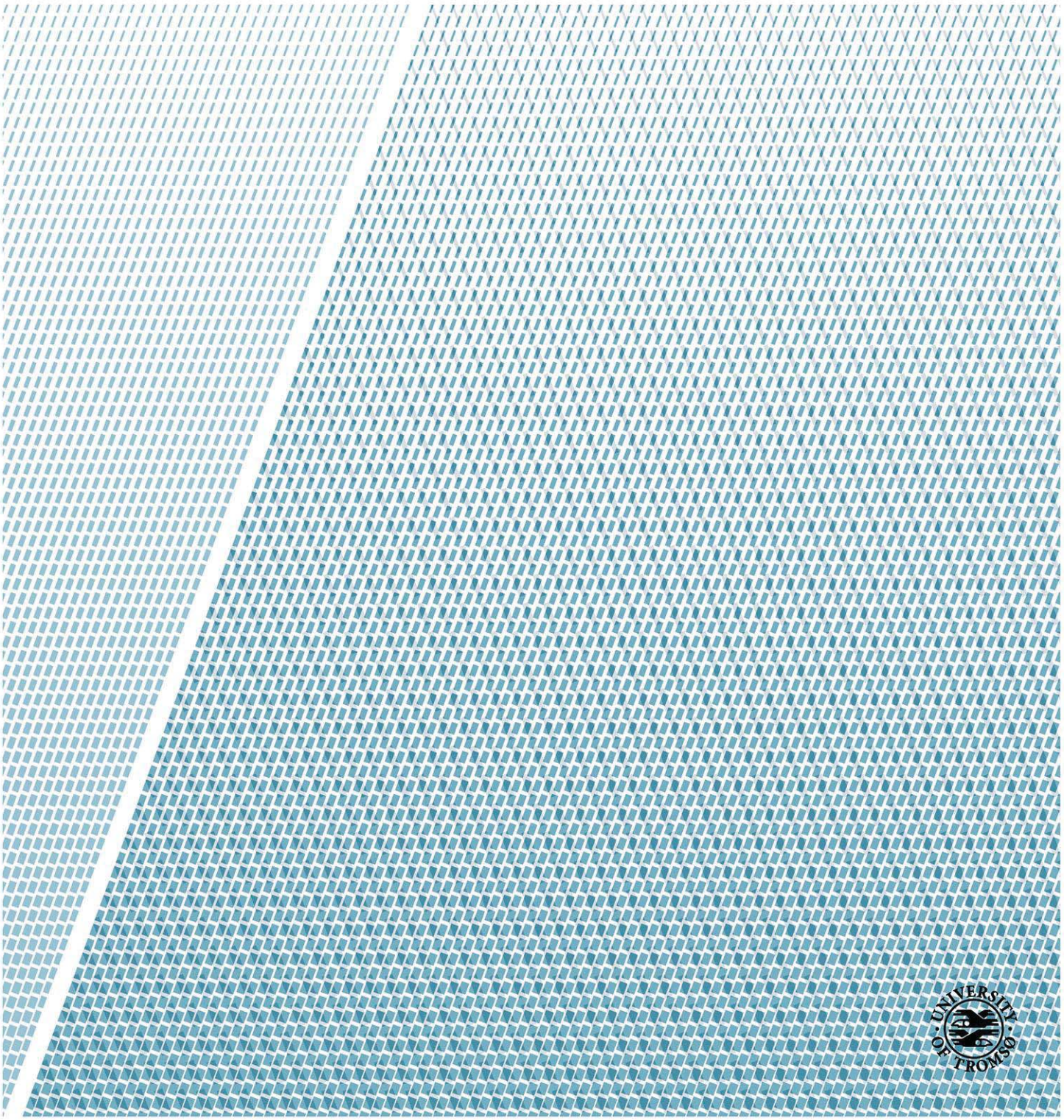
Electronic Disease Surveillance System Based on Inputs from People with Diabetes: An Early Outbreak Detection Mechanism.

Ashenafi Zebene Woldaregay

INF-3997 Master's Thesis in Telemedicine and E-health – May, 2016



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Dedication

TO MY BELOVED

PARENTS

Abstract

Objective: *Generally, the purpose of this thesis project is to develop an effective electronic disease surveillance system, which is capable of detecting a cluster of people with elevated blood glucose (BG) levels within a specific region and timeframe by analyzing diabetes data. Specifically, we mainly focus on developing an early outbreak detection algorithm that can analyze BG data and detect individuals with elevated BG levels (aberrant patterns) using continues BG measurement (CGM) and the mobile-phone based diabetes patients' historical data – the diabetes diary.*

Material: *This thesis project was conducted using data from two individuals with type-1 diabetes. The Dexcom continuous glucose monitoring device (CGM)) was used for the data collection. The collected data were CGM (in 5 minutes' intervals) for a period of one month. We used these datasets to train and validate the developed system. After training and validating the system, for its goodness of fit to the individual BG dynamics, in the non-infection status of the two subjects using normal BG values, we tested our system with artificially simulated datasets, which resemble the individual BG evolution during infections. The simulated datasets were consisted of elevated or high BG values of varies size, duration and shape through a course of time, i.e. a week or more. It was simulated so as to resemble the elevated BG after one is infected, by considering various increments per minutes (ΔBG/ (minutes (t))) and various durations of elevated BG. The system was developed using Matlab version R2015b.*

Method: *We presented a system that is consisted of four modules: the data collection module, the blood glucose prediction, the outbreak detection, and the information dissemination and reporting module. There are two types of early outbreak detection approaches incorporated in the system, a type of statistical control (prediction interval based) algorithm and a moving window based z-score process. The first approach, the prediction interval based algorithm combined a novel mechanism for BG prediction, which is an interval prediction based on a set of autoregressive models and predicts the expected BG intervals for an individual with diabetes. The actual BG value is compared against the predicted intervals, which is generated using auto-regressive (AR) and Autoregressive moving average (ARMA) methods. We evaluated and compared the performance of these methods using the mean square errors (MSE) and root mean square errors (RMSE) functions. The second approach, the moving window based z-score process calculates a running mean and standard deviation based on a specific window size. The running mean and*

standard deviation are used to check the agreement of the current BG reading with the previous trend in the window. The performance of the process was evaluated based on the accuracy of detecting the specific surveillance case definition, i.e. sensitivity, specificity and positive predictive value (PPV).

Result: *Both the prediction interval based algorithm and the moving window based z-score process were tested against the artificially simulated datasets and were capable of detecting statistically significant BG deviation of various sizes and durations. The prediction methods were capable of predicting the single step - ahead BG values with a reasonable accuracy, which were tested against validation datasets (unseen datasets during training). All the methods, autoregressive (AR), autoregressive (AR) with ratio of consecutive data as inputs, and autoregressive moving average (ARMA) have attained minimum root mean square errors (RMSE) for both subjects. However, the second methods predicts well attaining the lowest RMSE for both subjects, which demonstrates the advantage gained through the use of ratio of consecutive data points rather than the raw blood glucose data. Moreover, we accurately monitored the BG fluctuations of both individuals with a significance level of* $\alpha = 0.01$. *However, there were differences in window size and RMSE attained by these subjects for a comparable interval width, where the first subject attained smaller than the second subject. In addition, for comparable detection capability, the size of the moving window used to calculate the z-score for the first subject is less than the second subject. These differences in window size clearly show the effect of personal behavior towards diabetes management on the detection capability, which is mainly due to the significant fluctuations of BG readings as a result of poor personal behavior in managing his/her diabetes.*

Conclusion: *Generally, both of our early outbreak detection approaches have produced optimal detection results and were capable of detecting statistically significant BG deviation of various size and duration. However, considering flexibility, simplicity, computational time, and needs of computational power the moving window based z-score process is better than the prediction interval based algorithm. Moreover, both the approaches are found to be affected by the quality of personal behavior towards diabetes management and this needs to be taken into account during large scale implementations. Besides, these results have clearly shown the effectiveness of the proposed approaches for detecting a cluster of people with similar patterns. Consequently, after validating these approaches on a large scale basis, this promising results will hopefully lead the*

way for the development of the early outbreak detection system (prototype) based on inputs from people with diabetes, which is considered to be the next generation electronic disease surveillance system.

Keywords: *Diabetes Mellitus, Diabetes diary, Blood glucose prediction, Autoregressive models, Moving window z-score, Outbreak detection.*

Preface

Last year I had a course work on Advanced Tele-medicine and eHealth, which gave me deep insights into mobile health (m-health) and diabetes technology. My exposure to these interesting technologies had created an intense interest and motivation to work on diabetes related issues, which came true when I discussed with Prof. Gunnar Hartvigsen that he pointed me out to a couple of projects where I choose to work on electronic disease surveillance system based on inputs from people with diabetes.

New infectious diseases threats to the public health including both naturally occurring and artificially induced bioterrorist attack brought an urgent concern with respect to early outbreak detection. In most cases, when an outbreak is detected, it has been transmitted to a lot of people with in the community. Currently, an early outbreak detection is the major concern of researchers in the area of electronic disease surveillance systems. As part of this task force, the objective of this thesis project is to design and develop an early outbreak detection system based on inputs from people with diabetes. Our approach incorporated a novel mechanism for tracking BG fluctuations on an individual basis. We tested our approach based on real datasets from a small group of type-I diabetes subjects.

First and foremost, I would like to thank the Almighty God, the creator for all he has done and has been doing. Next my warmest and sincere thanks goes to my supervisor Prof. Gunnar Hartvigsen for his close guidance and invaluable support during the ups and downs of this project by providing constructive comments and suggestions and also lending me a lot of books relevant for the work. Besides, I would like to thank my co-supervisors Prof. Eirik Årsand, Dr. Taxiarchis Botsis and Klaske van Vuurden for their invaluable comments and suggestions. Moreover, I would like to thank the diabetes team at the Norwegian Center for E-health Research (previously known as Norwegian Center for Integrated Care and Telemedicine (NST)), for their priceless support during the course of writing and publishing a journal article as part of this thesis work. Furthermore, I would like to thank the Department of Computer science (UiT) for covering all the necessary expenses to present part of my thesis work at SHI2016 conference. Last but not least, I would like to thank the two diabetes testers for their consent to use their data and finally the Norwegian Quota scheme for creating the opportunity to come and study the field I was hoping so long.

I plan to extend the work that have been done in this thesis during my PhD study at the Department of Computer science, University of Tromsø- The Arctic University of Norway, which will be commenced on May 23, 2016.

Ashenafi Zebene Woldaregay,

Tromsø, May 15th, 2016.

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Acronyms

AR……..Autoregressive

ARMA……...Autoregressive Moving Average

BG……..Blood Glucose

CGM……...Continuous Glucose Monitoring

FTA……..Few Touch Application

MSE……Mean Square Error

NST……Norwegian Center for Integrated Care and Tele-medicine

PI…….Prediction Intervals

PMSE……Prediction Mean Square Error

PPV……Positive Predictive Value

POC …….Point Of Care

ROC…….Receiver Operating Characteristic

RMSE…….Root Mean Square Error

Chapter one: Introduction

1.1. Background and Motivation

Major infectious disease threat to the public health are either naturally occurring or artificially induced bioterrorist attack. Infectious diseases have been and also be the burden of any public health authority, which needs well preparedness, proper monitoring and early detection of an outbreak before it spreads. Earlier, disease surveillance systems have been relied on paper based reporting, which have a great impact for its delayed response (Wickramasinghe et al., 2012). However, with the advent of information and communication technology, the availability of electronic based reporting has revolutionized the disease surveillance systems. The availability of such data facilitates early detection and also leaves ample space (time) for further investigation and action to be taken by the responsible body (Wickramasinghe et al., 2012). One of such a kind is syndromic surveillance, which uses data after the incubation period but prior to laboratory or physicians verification such as absenteeism (Weng et al., 2015), chief-complaint data (Wagner et al., 2004), over-the-counter and prescription pharmacy sales (Xiaohui et al., 2004), internet search volumes (Zhou et al., 2013; Zhou et al., 2011) and others. Moreover, various bio-sensors network based disease surveillance systems have been put in place (Chung-Kuo et al., 2005). However, electronic disease surveillance system that detects infectious disease outbreak during incubation period (before the onset of the first symptoms) is not yet developed and is currently under research stage. For example, let us assume that you are working as both epidemiologist and public health official in a large city, where you are the focal person of the city's office for monitoring and controlling of infectious disease outbreaks. It is obvious that your office will be definitely looking for an early outbreak detection system that is capable of detecting any infectious disease outbreak within days after the first person is infected. Let us say on Thursday in a specific part of the city, there were some people infected with respiratory infections such as influenza. According to the current disease surveillance systems, the detection might take some days even more than weeks until the first symptoms are confirmed, which might put some lives in danger. In contrast, let us say that you woke up on Friday morning and ask "the mirror": *How are we today?* ("we" stands for the whole population in the city). "The mirror" then visualizes the health status for the citizens based on daily data from people with diabetes, who are registered in the system. "The mirror" designates the dedicated electronic disease surveillance system based on inputs from people with

diabetes, which is unique for detecting disease outbreaks during the incubation period. The system is capable of analyzing daily data and generating daily information, which is made available for every citizens. For instance, if you are a person with diabetes, you may want to know whether the risk of infections has increased, and if possible, in which areas of the city.

Currently, diabetes is escalating worldwide and according to WHO[1], its global prevalence had reached 8.4% in 2014 and the projection shows that it will become the 7th leading cause of death in 2030. Consequently, as part of the disease management, a lot of diabetes self-management applications including continuous blood glucose monitoring (CGM) and mobile applications have been developed to help individuals to manage their blood glucose, of which almost all of them take the ubiquities nature of mobile as an advantage to base the development of the apps (Arsand et al., 2010; Issom et al., 2015; Quinn et al., 2008; Waki et al., 2014). Moreover, recently mobile diabetes self-management application has shown integration with the electronic health record of patients (Benhamou, 2011; Veinot et al., 2010; Walseth et al., 2005). This integration coupled with the availability of timely data on CGM and mobile apps can further enhances the opportunity of establishing a successful electronic disease surveillance system based on inputs from people with diabetes.

Previous findings indicated that blood glucose levels are elevated due to any exposure to pathogens (Lauritzen et al., 2011). Årsand et al. demonstrated an elevation in Blood glucose levels for both type 1 and type 2 diabetes individuals after being infected by Influenza, Cholera, Plague, Ebola, Anthrax, or SARS viruses (Årsand et al., 2005). Botsis et al. also described the positive correlation between BG elevation and infections in people with type 1 diabetes (Botsis et al., 2007). These findings suggest the potential use of the Blood glucose parameters for the early detection of disease outbreaks in the general population (Botsis et al., 2007). Other physiological parameters (such as body temperature, white blood cell count and blood pressure) are directly associated with the presence of infections in the body (Botsis et al., 2010; Uzedhe et al., 2014). Multiple incidents with abnormal values for the above parameters in the population may indicate the presence of an outbreak (Adam et al., 2007; Lauritzen et al., 2011). We therefore argue that the incorporation of all these parameters into advanced modeling solutions can potentially support the early detection of outbreaks. The objective of this thesis project is to design and develop an electronic disease

[1] http://www.who.int/mediacentre/factsheets/fs312/en/

surveillance system based on inputs from people with diabetes, and that can track the blood glucose values of each individuals separately and detect a cluster of people with statistically significant deviation. The main goal here is to use people with diabetes as a source of information in a disease surveillance system and to effectively detect an infectious disease outbreak during the incubation period. We mainly focused on the development of algorithm that can track BG dynamic and detect any abnormal elevation at an individual level. An interval based blood glucose prediction and a moving window based z-score algorithms are proposed to control and monitor the statistically significant deviation of the blood glucose readings from its most recent trends. The proposed algorithms are developed and tested based on data from two type-one diabetes individuals' and are capable of predicting and detecting statistically significant blood glucose deviations, which shows the effectiveness of the proposed approach.

1.2. Research Problem Statement

1.2.1. Main Problem

To prevent the spread of contagious diseases, early detection is important. Today, when an outbreak is diagnosed, many people may already be infected. Therefore, it is necessary to develop a system that can detect an infectious disease outbreak at a very early stage. We proposed the use of blood glucose as an indicator of infections and to build a mechanism that can effectively track and detect high blood glucose levels at an individual level.

→ *[**P1**] How to design and develop an early outbreak detection system based on blood glucose inputs from people with diabetes?*

In this thesis, we will focus on the important techniques and parameters that can be geared towards an effective early outbreak detection system. Moreover, we give emphasis on modelling of the underlying system architecture for the electronic disease surveillance system based on inputs from people with diabetes.

1.2.1.1. Sub-Problem One

To develop the diseases surveillance system, it is necessary to compute the expected baseline data used for monitoring. Therefore, we need to develop a BG prediction approach to be used in the developed system. Various researchers have tried to develop BG prediction services for several purposes designed for people with diabetes such as hypoglycaemia and hyperglycaemia alerts, serious game development, and others (Agafonov et al., 2015; Daskalaki et al., 2012; Jabali, 2013).

As a result, we need to develop a personal blood glucose prediction model for our defined purpose. The problem we are addressing in this section is:

→ *[**SP1**] What are the important techniques that can be used in developing a successful personal blood glucose prediction model and how to design and develop such a technique that can be accurately used in the electronic disease surveillance system based on inputs from people with diabetes?*

1.2.1.2. Sub-Problem Two

An effective disease outbreak detection systems need to be well designed in terms of its sensitivity, specificity, and positive predicative value (PPV). Therefore, we need to consider and develop a mechanism that can effectively detect any aberrations or statistically significant deviation from the normal blood glucose evolution of an individual with diabetes. As a result, here we study techniques of detecting the individual's consecutive high BG readings from the normal BG readings, which occurred during the presence of infections. Moreover, means of cheeking the degree and severity of the individual's BG deviations and possibly means of producing the required alarm are dealt under this sub-problem:

→ *[**SP2**] How to design and develop an early aberrations detection systems based on the individual's blood glucose data and how to formulate an excellent working threshold for the electronic disease surveillance system considering some constraints or limitations.*

1.3. Objective

1.3.1. General objective

The goal of this thesis project is to design and develop an early outbreak detection algorithm and, therefore to design a system based on the blood glucose inputs from people with diabetes.

1.3.2. Specific objective

- ✓ To design a system architecture for the electronic disease surveillance system based on inputs from people with diabetes.
- ✓ To specify the use case model for the system and its associated requirements specification.
- ✓ To design and develop an early aberration detection algorithm.
- ✓ To develop blood glucose prediction model (Personal blood glucose profile).
- ✓ To develop a prediction interval and a moving window based z-score algorithm.

1.4. Materials, Methods and Scope of system evaluation

This thesis work has been conducted using both Friedman, the tower of achievements in medical informatics (Friedman, 1995) and the Engineering approach described by Denning et al. (Denning et al., 1989). This involves model formulation including defining requirements and specifications, and system development including system design and implementation along with system evaluation techniques including testing of the system for performance (Friedman et al., 2006). The requirements and specifications were defined following Volere's standards (Robertson et al., 2000).

1.4.1. Materials and Methods

1.4.1.1. Datasets

This thesis work was conducted using data from two individuals with type 1 diabetes. The Dexcom CGM and the diabetes diary[2] that have been developed by Norwegian Center for E-health Research (previously known as NST) were used for the data collection. These modules are part of a mobile application designed for diabetes management. The collected data included continuous BG measurements from the Dexcom CGM (in 5 minutes intervals) for a period of one month. We used these datasets to train and validate the developed system for its goodness of fit to the BG dynamics of the two subjects in their non-infection status. We subsequently tested our system with a simulated dataset that included consecutive patterns of high BG values; this resembled the CGM during the infection period. Various increments per minutes ($\frac{\Delta BG}{minutes(t)}$) and various time intervals of elevated BG were considered.

1.4.1.2. Methods

This project work was carried out in three phases, which involves model formulation, model development and system evaluation. The first phase is model formulation, which includes literatures review and system modelling. In addition, discussions with two diabetes experts and other diabetes individuals were held to model the artificially simulated datasets. The second phase is model development, which is divided into research and application development components. We mainly focus on the research component, which involves the development of the mathematical

[2] www.diabetesdagboka.no

models and algorithms in Matlab programming language. However, we thoroughly defined the requirements and specifications of the required application, which its development is not considered in this thesis. The last phase is system evaluation, which includes system testing and evaluation.

The developed system has two compartments, the personal BG profile and the early aberration detection compartment. The first compartment, the personal BG profile involves predication of the individual's BG evolution. For prediction purpose, we have proposed an interval BG prediction mechanism that can predict the step ahead BG values of an individual. Thus, the goal of the prediction interval is to obtain a $100(1-\alpha)\%$ forecast interval single-step-ahead into the future for BG response at a given input level of past BG. These intervals were calculated based on the empirical error distribution (variance) of the recent history of errors (with a specific window size) between the predicted and measured BG values. The developed BG prediction models were a type of linear time series models, which includes Autoregressive (AR) and Autoregressive Moving Average (ARMA). The second compartment, the early aberration detection involves the detection of any cluster of people with elevated BG readings within a specific region and timeframe. This compartment is capable of comparing the measured/observed BG values against the interval predicted by the first compartment. Furthermore, this compartment is capable of calculating the moving window based z-score values as an alternative means of detecting statistically significant BG deviations from its most recent trends.

1.4.2. Scope of system evaluation

According to (Friedman et al., 2006), evaluation of a system in medical informatics is conducted for five major reasons, promotional, scholarly, pragmatic, ethical, and medicolegal purposes. "One or more of these factors should be the driving force for every evaluation study to be carried out; otherwise, the study will lose its value as it has been called a "triple blind study," in which neither evaluators, participants, nor readers of the report can fathom why it was done" (Friedman et al., 2006). Among these deriving factors we considered, the pragmatic purpose, which involves solving the puzzle by justifying which techniques or methods are more effective, or why certain approaches failed. This reason was justified as it has a lot of input in enhancing the clarity regarding the contribution and significance of our approaches. Compartments based evaluation were conducted for the entire system. The first compartment, which is the BG prediction mechanisms were evaluated using mean square error (MSE), and root mean square error (RMSE)

and comparison were carried out based on these parameters. The second compartment, which is the early outbreak detection mechanisms were evaluated based on different criteria such as specificity, sensitivity, and positive predicative value (PPV). In addition to this, the outbreak detection mechanisms were also evaluated based on the capability of the algorithm to detect the individual's consecutive high BG readings from the normal BG readings. Moreover, a Receiver Operating Characteristic (ROC) was used to determine the best operating threshold of the system.

1.5. Significance and Contribution

Early detection of infectious disease outbreaks is the main and important goal of any public health surveillance, as this can provide ample time for controlling and prevention action to be taken by the responsible bodies, i.e. public health authority and hospitals. Today, when an outbreak is diagnosed, many people may already be infected. Therefore, it is necessary to have a system that can detect an epidemic outbreak at a very early stage. Recently, lots of researchers have developed different kind of infectious disease outbreaks detection mechanisms. These mechanisms mainly relied on various kinds of data such as chief-complaint data (Wagner et al., 2004), disease related search volumes in different search engine such as google (Zhou et al., 2013; Zhou et al., 2011), over-the-counter and prescription pharmacy sales (Xiaohui et al., 2004), school absenteeism (Weng et al., 2015), and emergency calls (Adam et al., 2007), and other different physiological indicators including reported symptoms such as body temperature and blood pressure. However, disease outbreak detection mechanisms that focus on the incubation period, before the onset of the first symptoms, have not been developed yet. To our knowledge, an early disease outbreak detection mechanism that rely on BG evolution is a new concept that will provide significant input for the scientific arena, in the broad sense of an early outbreak detection mechanism and blood glucose prediction techniques in particular. We designed and built a system that can detect disease outbreak during the incubation period, before the onset of the first symptoms, which is the novel and unique characteristic of this thesis project. We developed a unique and novel mechanism for monitoring an individual blood glucose fluctuations based on an interval BG prediction. To our knowledge, a BG prediction mechanism that predicts an interval based on the empirical distribution of errors between the predicted and observed BG values is the first of its types. In addition, we introduced and developed the moving window based z-score process for detecting individual's consecutive high BG readings from the normal BG readings. Moreover, this thesis project has also contributed a conference paper and systematic literature reviews. As part of this

thesis project, the author has published a conference paper, journal article and also conducted a comprehensive systematic literature review on the available BG prediction and outbreak detection mechanisms. First of all, in order to assess the available data sources for the implementation of the proposed system, the author has conducted and published a systematic literature review on mobile diabetes self-management apps, which is published in Future Medicine - Diabetes management journal, entitled "A systematic review of mobile applications for people with diabetes published between 2010 and 2015" (Issom et al., 2015). In addition, in order to strengthen and support our approach, the author has also conducted a comprehensive systematic review of literatures on BG predictions and early outbreak detection mechanisms, which is included as part of this thesis report. Moreover, the author has also published part of this thesis work in a conference proceeding, which is entitled "Electronic Disease Surveillance System Based on Inputs from People with Diabetes: An Early Outbreak Detection Mechanism" (Woldaregay et al., 2016), which is presented at Scandinavian health informatics conference (SHI2016, Gothenburg, Sweden).

1.6. Assumptions, Biases and Limitations

The major limitation of this project is the absence of large sample size. We have relied our experiments and simulation based on two type-one individuals, which might affect the generalizability of our results. Moreover, a "holiday effect" is another major limitation of this project. In some circumstances such as during holidays, the recorded BG value may fail to indicate the presence of infection, which is known as the "*Holiday effect*" (Lauritzen et al., 2011). The main cause of the "*Holiday effect*" is the bad eating style of the majority of the population including peoples with diabetes during this period. This may result in an artificial increase in the BG value for the individuals with diabetes. This BG variation might result in generating false alarms, and false outbreak detections. The absence of frequent blood pressure measurements, white blood cell counts and temperature readings from these individuals further aggravates this limitation as it was previously shown (Botsis et al., 2009; Botsis et al., 2010). Considering that body temperature, count of white blood cells and blood pressure can be indicators for the presence or absence of infections in the body, these measurements can be used to compromise the elevated BG values and bypass the generation of false alarm during holidays. However, the data source we are using does not provide such kind of measurements to test and overcome this limitation.

1.7. Organization

The rest of the thesis is organized as follows:

→ ***Chapter 2: Theoretical framework and State of the art:*** *- This chapter describes the basic theoretical concepts and framework of the thesis project. It briefly disuses BG metabolism, diabetes mellitus along with its complications in the presence of infections. In addition, it describes the concept behind BG predictions and early outbreak detection mechanisms. Most importantly, it gives a brief description of the state of the art system that consider in using BG for an early outbreak detection.*

→ ***Chapter 3: Literature Review:*** *- This chapter presents a systematic literature review on BG prediction mechanisms and early outbreak detection mechanisms. It gives an overview of the current available methods for developing the required BG predictions and early outbreak detections mechanisms.*

→ ***Chapter 4: Materials and Method:*** *- This chapter presents the materials and methods used in this thesis project.*

→ ***Chapter 5: Requirements specification:*** *- This chapter describes the necessary requirements and specifications of the electronic disease surveillance system based on inputs from people with diabetes.*

→ ***Chapter 6: Design:*** *- This chapter describes the strategies and techniques used to develop the mathematical models for the BG predictions, interval predictions and early outbreak detection mechanisms.*

→ ***Chapter 7: Implementation and Testing:*** *- This chapter presents the implementations of the models designed in the previous chapter (Chapter 6) and the taste settings and test results of the BG predictions, interval predictions and the early outbreak detection mechanisms.*

→ ***Chapter 8: Discussion:*** *- This chapter discusses the evaluations, comparisons and analysis of the test results and the research findings.*

→ ***Chapter 9: Further works/Recommendations:*** *- This chapter describes research gaps that the author had identified during this thesis project and believes to be considered for future research.*

→ ***Chapter 10: Conclusion:*** *- This chapter concludes the thesis outcomes and findings.*

→ ***References: -*** *This section presents list of references used in this thesis project.*

→ ***Appendix: -*** *This section contains the list of conference paper and journal article published by the author as part of this thesis project.*

Chapter Two: Theoretical framework and State of the Art

2.1. Introduction

This chapter mainly discusses about the theoretical frameworks and concepts, which are basis for developing the dedicated electronic disease surveillance system based on inputs from people with diabetes. Moreover, it describes the state of the art systems that argue to use blood glucose levels as an indicator of infections and for possible outbreak detection purposes. The entire chapter is organized as follows; the first section presents terminologies, preliminaries and definitions that are fundamental for this thesis project. The second section discusses basic concepts concerning blood glucose metabolism, diabetes mellitus, infections and blood glucose levels in diabetes, diabetes management and factors that affect blood glucose values, and prediction approaches. The third section discusses issues related with electronic disease surveillance systems and early outbreak detection. The last section gives an overview of the state of the art system that consider blood glucose levels as an early indicator of infections.

2.2. Terminologies, Preliminaries and Definitions

This section describes basic terminologies, preliminaries and definitions that are fundamental for this thesis project and are also used throughout this thesis project. It also gives the reader a clear insight to pinpoint the basics of our surveillance case definition.

2.2.1. Definitions

Specificity: is defined as "the proportion of true non-events correctly classified as such, the inverse being the false alarm rate" (Drewe et al., 2012).

Sensitivity: refers to "the proportion of actual cases in a population that are detected and notified through the system"(WHO, 2006).

Positive predicative value (PPV): refers to "the proportion of the people, who actually have the disease and correctly classified as such by the disease surveillance system" (WHO, 2006).

Prediction Interval (PI): is the predicted range of values containing upper and lower boundaries.

Simulated dataset: is an artificially simulated BG data containing successive high BG values.

Threshold: is a value that must be exceeded for the individual's BG reading to be regarded as abnormal.

Prediction error: is the difference between observed or measured blood glucose values and predicted blood glucose values within the same prediction horizon.

Prediction horizon: is the number of steps in the future for which prediction is made, is also known as lead time.

2.2.2. Terminologies and mathematical assumptions

Throughout this project, an observed time series, containing n observations, is denoted by $y_1, y_2, y_3 \ldots\ldots\ldots y_n$. Let us say that we want to predict Y_{n+h}, where the integer h is called the lead time (or the prediction horizon) (Chatfield, 1993). The point prediction of Y_{n+h} made conditional on data up to time n for h steps ahead will be denoted by $Y_n(h)$, when regarded as a random variable and by $y_n(h)$, when it is a particular value determined by the observed data. Whenever possible, it is necessary to specify both the horizon (lead time) and the time at which the prediction is made (Chatfield, 1993).

2.2.3. Surveillance case definition

The proposed electronic disease surveillance system is based on inputs from people with diabetes, which is required to capture any statistically significant deviations of individual's blood glucose readings from the CGM-DEXCOM devices (possibly could be used with any other CGMs). Consequently, the surveillance case definition requires consecutive and successive elevated (high) blood glucose readings from a cluster of people within a specific region /area and timeframe. This spatio-temporal nature of the proposed system is believed to exclude individual's elevated blood glucose readings due to other factors, i.e. menstruation cycle, alcohol consumption and others.

2.3. Glucose Metabolism

The human body is consisted of different kinds of metabolic reactions, which is important to maintain the normal physiological states. Blood glucose metabolism is one of such a kind, which controls the proper amount of glucose concentration in the blood (Cescon, 2011). Pancreas is both exocrine and endocrine gland, which is the central point of glucose metabolism. It is consisted of cells known as islet of Langerhans, which contains both the alpha and beta cells. As shown in the Figure 1, when there is external perturbation like intake of food and others, the blood glucose levels raises, which in turn initiates beta cells in pancreas to secrete insulin in the blood. The secreted insulin in turn initiates the uptake of glucose by body cells and conversion of glucose into its stored form glucagon and fat. This results in decreased levels of blood glucose concentration in

bloodstream (Cescon, 2011). Moreover, when there is external perturbation like heavy physical activity or exercises and others, the blood glucose fall from its normal state. This initiates alpha cells in pancreas to secrete glucagon, which causes conversion of glycogen to glucose in liver and muscles. This will increase the proper amount of blood glucose concentration and return it to its normal state (Cescon, 2011).

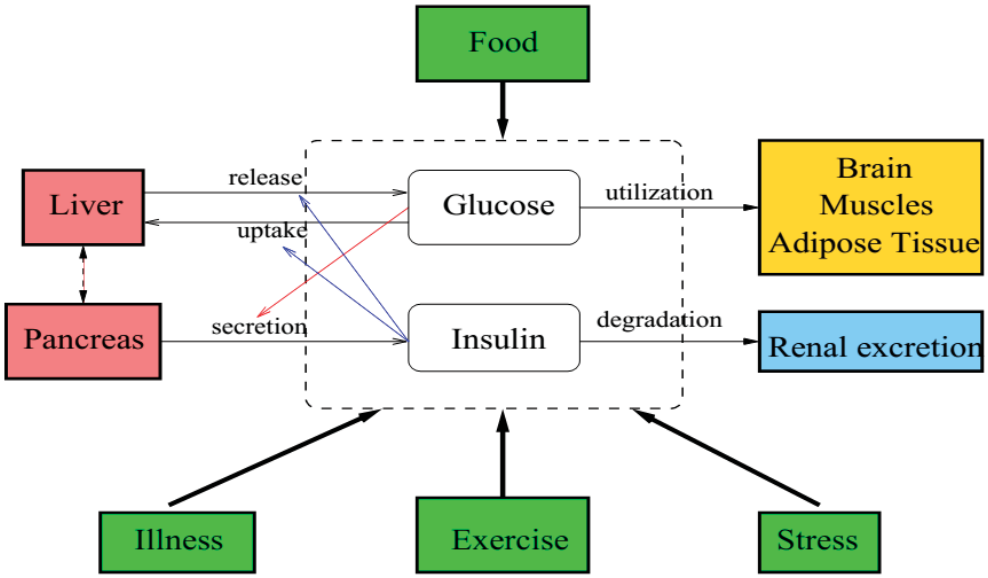


Figure 1: Glucose metabolism.

(Figure 2.1, (Cescon, 2011))

2.4. What is blood glucose level/concentration and the factors that affect it?

Blood glucose level or concentration is the amount of blood glucose that reside in the blood, which is also known as plasma blood glucose level. It can be expressed using either milligram per deci-litters (mg/dl) or milli-mole per liters (mmol/l)[3] (Agafonov et al., 2015). The normal blood glucose levels of an individual are within a narrow range being highest after meal and lowest in the morning. There are different factors that can directly affects the amount of blood glucose concentration, among which amount of injected insulin, amount of physical activity, previous history of blood glucose values and dietary intakes are the prominent ones (Agafonov, 2015; Cescon, 2011). Moreover, blood glucose concentration is also affected by other factors such as

[3] https://en.wikipedia.org/wiki/Blood_sugar

body mass index of the individual, stress level, sleeping time, presence of illness and some other medication, smoking habit, periods (menstruation), alcoholism, allergies, and effect of altitude (Agafonov, 2015; Cescon, 2011; Cescon, 2013). There are other factors, which is not quantified here but still have effect on blood glucose concentration.

2.5. Diabetes

2.5.1. What is diabetes?

Diabetes mellitus is a chronic disease that causes blood glucose metabolic disorder (WHO, 2015a). The person who suffers from diabetes lacks the capability to control the proper amount of glucose in his/her blood, either due to the failure of pancreas beta cells to produce insulin or the failure of the body to use insulin in the right way (Liao et al., 2004; Richesson et al., 2013), which are known to be type I and type II diabetes respectively. Type I diabetes (also known as juvenile-onset or insulin-dependent diabetes) mostly affects children and it is caused by the failure of pancreas to produce little or no insulin (Richesson et al., 2013). Type II diabetes (also known as adult-onset or non–insulin-dependent diabetes) can happen to anyone irrespective of age but it mostly occurs during adulthood and it is due to the failure of the body to use insulin that resides in the blood (Richesson et al., 2013). This kind of complication can arise due to several factors such as lack of exercise, being overweight (Taylor et al., 2015), nutrition and mostly due to inactive personal lifestyle (Liao et al., 2004; Richesson et al., 2013).

2.5.2. How does an infection affect blood glucose level in an individual with diabetes?

During infections, it is a normal activity of the body to produce certain hormones, such as cortisol and adrenaline, as a response for the stress within the body[4]. The action of glucose metabolising hormone, insulin are greatly affected by the work of these hormones. As a result, the body loses control of glucose production that results in a high blood glucose concentrations. Consequently, the high blood glucose concentration causes the white blood cells to be unable to "mop up" bacteria since they can't move around at their usual speed and do not reach the infection site as quick as possible to engulf and kill the bacteria and other pathogens. For non-diabetes person, this might not have any problem since extra insulin is produced to counter back these effects. However, for diabetes persons this is not possible as a result hyperglycemia persists and ketoacidosis can occur.

[4] http://www.livestrong.com/article/375763-how-does-an-infection-increase-blood-sugar-in-diabetes/

Diabetes by itself aggravates susceptibility to various infections. Diabetes patients are believed to be affected more frequently than the non-diabetes peoples (Casqueiro et al., 2012). Generally, the following infections are common for diabetes patients[4], as given in the Table (Casqueiro et al., 2012).

Table 1: Major infections associated with diabetes mellitus.

(Table 1, (Casqueiro et al., 2012))

Respiratory infections	→ Streptococcus pneumoniae → Influenza → H1N1 → Tuberculosis
Urinary tract infections	→ Asymptomatic bacteriuria → Fungal cystitis → Emphysematous cystitis → Bacterial pyelonephritis → Emphysematous cystitis → Perinephric abscess
Gastrointestinal and liver infections	→ *H.pylori* infection → Oral and esophageal candidiasis → Emphysematous cholecystitis → Hepatitis C → Hepatitis B → Enteroviruses
Skin and soft tissue infections	→ Foot infection → Necrotizing fasciitis → Fournier's gangrene
Head and neck infections	→ Invasive external otitis → Rhinocerebral mucormycosis
Other infections	→ Human immunodeficiency virus

2.5.3. Diabetes Management

Diabetes is fatal and can bring a lot of complications, i.e. blindness, kidney failure and even death, if not properly controlled and managed. Therefore, it is necessary to have a proper management, which can reduce the fatality significantly and avoids further complications. This includes controlling diet, recording blood glucose, doing physical exercise and injecting proper amount of insulin when the blood glucose is elevated (Liao et al., 2004; Richesson et al., 2013). Currently, a lot of mobile diabetes self-management application has been developed to help the individuals to manage his/her blood glucose, of which almost all of them take the ubiquities nature of mobile as an advantage to base the development of the apps (Arsand et al., 2010; Issom et al., 2015; Quinn et al., 2008; Waki et al., 2014). Moreover, recently mobile diabetes self-management application has shown integration with the Electronic health record of a patient (Benhamou, 2011; Veinot et al., 2010; Walseth et al., 2005), which is believed to extend the reach of physicians to the patients.

2.6. Prediction approaches

"*Prediction is very difficult, especially if it's about the future*" – Nils Bohr

Prediction is defined as the process of projecting the future based on the past and present data and trends[5]. Generally, prediction can be carried out using either of these prediction approaches, i.e. Structural and Black box approaches (Chatfield, 2000). The first approach, structural, requires an extensive knowledge of the underlying systems dynamics, which in this case requires modeling of the internal blood glucose-insulin dynamics. The second approach, black box , doesn't require an extensive knowledge about the internal systems dynamics, however, it only requires playing with the input and output data from the system to model a satisfactory prediction (Chatfield, 2000). Moreover, depending on the specific purpose at hand, the background knowledge and types of data available, prediction methods can be classified into three distinct categories (Chatfield, 2000). This category includes univariate (which depend only on the past values of a single variable), multivariate (which depends on the past values of two or more variables, called predictor or explanatory variables) and judgmental (Chatfield, 2000). Moreover, the prediction method can be automatic, without requiring human intervention and non-automatic methods. Furthermore, a more useful distinction between methods is that involves fitting an 'optimal' probability model and those

[5]https://en.wikipedia.org/wiki/Forecasting

that do not. There are two ways of achieving the prediction models output stated in the literatures, i.e. point prediction and interval prediction (Chatfield, 2000). Pont prediction is the most used form of prediction in literatures rather than interval prediction, however the latter is more desirable and appropriate even if it is not mostly used approach (Chatfield, 1993). A prediction interval (PI) is defined as an estimate of an (unknown) future value that can be regarded as a random variable at the time the forecast is made (Chatfield, 1993). Prediction interval (PI) is mostly used for assessing and supplementing point prediction with the future uncertainty involved in different parameters. Moreover, it can be used to compare different methods thoroughly and to plan different strategy based on the range of possible values within the interval (Chatfield, 1993).

2.6.1. Blood glucose prediction Models

Blood glucose prediction has a lot of advantage to the patient, physicians and family of the patient in general. Diabetes management involves controlling the blood glucose concentration as close as possible to the normal (euglycemia). In particular, blood glucose concentration prediction can provide the immediate future blood glucose value depending on the previous history of the patient, thereby avoiding any further complication from hypoglycemia and hyperglycemia. According to (Naumova et al., 2012), blood glucose prediction model are divided into two groups, i.e. compartmental (physiological) models and data driven predictive (black box) models. The first group, compartmental (physiological) models involves a deeper understanding of the underlying blood glucose dynamics. This kind of model is highly dependent on the true physiological model selected and are generally a representative of an average subject and may not provide accurate result to an individual scenario (Naumova et al., 2012). The second group, data driven predictive (black box) models are capable of predicting the future blood glucose based on the available information of the previous and present history of the individual patient including amount of insulin, blood glucose concentration, diet and physical activity to mention some. This kind of models require less understanding of the inner glucose-insulin dynamics and are tunable towards an individual. There are three available methods for implementing this kind of models, which include linear extrapolation, time-series and machine learning methods (Naumova et al., 2012). Currently, there a lot of blood glucose prediction algorithms have been put in practice, such as autoregressive model (Daskalaki et al., 2012; Jabali, 2013), causal probabilistic network (CPN) and Bayesian network model (Andreassen et al., 1994; Ståhl, 2012), artificial neural network (Baghdadi et al., 2007; Pappada et al., 2008), Gaussian mixture models (GMM) (Efendic et al.,

2014), support vector regression model (SVR) (Plis et al., 2014), Wiener block-oriented model (Kotz, 2011; Rollins et al., 2011) and others. The data driven predictive (black box) models are the most widely used models for blood glucose prediction and it is also believed to be the future candidate of diabetes management.

2.6.2. Time-series Methods

A *time-series* is a set of observations or measurements made sequentially through time. These observations or measurements can be taken on a continuous time or on a discrete time interval. As a result, can be divided as a continuous time series, i.e. Continuous Glucose Measurement (CGM), and a discrete time series. This mainly characterizes the time axis and not about the measured quantity. For example, blood glucose is a continuous quantity, however can be taken as a continuous or discrete time series. There are different kinds of time series in a real world circumstance such as the set of temperature at a particular location on successive days, the amount of measured electricity on a successive months and the amount of blood glucose concentration measured on successive days (Chatfield, 2000). Within the time series context, prediction involves forecasting or estimating the future values, the next (one step) or (two or more steps) of the time series. Recent development in time series based blood glucose prediction shows the potential of the method in predicting an individual blood glucose evolution such as the autoregressive model (Daskalaki et al., 2012; Jabali, 2013).

2.6.2.1. Autoregressive models

An autoregressive model[6] can be defined as the representations of a random time varying process, where the output from the process are designated as a linear combination of past values and unexplained random (stochastic) term. It is a group of time series models, which can be a univariate (involving a single variables) and multi-variate (involving more than two variables) as input and output of the processes. There are various version of an autoregressive approach including AR (involving one output with no input), ARX (involving both output and input), ARMA (involving one output with no input) and ARMAX (involving both output and input) (Jabali, 2013; Stahl et al., 2009). Here only the version of autoregressive models that involves an output without any input are discussed here. Let $\mathcal{Y}_t$ be a time series data with a set of sequence of measurements $\{t$

[6] https://en.wikipedia.org/wiki/Autoregressive_model

=1, 2, 3, 4……n}, where n is the size of the time series. An autoregressive equation of order $\mathcal{P}$ are designated as $\mathcal{AR}(\mathcal{P})$ and given as follows:

$$\mathcal{Y}_t = \mathcal{C} + \sum_{i=1}^{\mathcal{P}} a_i \mathcal{Y}_{t-i} + \mathcal{E}_t \quad \text{.....Eq.1}$$

Where a_i *are* the parameters of the model, $\mathcal{C}$ is a constant, and $\mathcal{E}_t$ is white noise. The maximum lag of the autoregressive equations are defined by the partial autocorrelation since the partial autocorrelation of $\mathcal{AR}(\mathcal{P})$ process is zero after $\mathcal{P}+1$ and beyond this value. Therefore, the maximum order or lag of the $\mathcal{AR}(\mathcal{P})$ process is always equal to the value beyond which the partial autocorrelation vanishes. The parameters or coefficients of an autoregressive $\mathcal{AR}(\mathcal{P})$ process can be computed by using either the ordinary least squares procedure or method of moments (through Yule–Walker equations). A more advanced version of autoregressive is the combination of both autoregressive and moving average component, commonly known as autoregressive moving average (ARMA). It takes the moving average of an error components along with the autoregressive version. An ARMA (p, q) process defines an autoregressive components of order p and a moving average components of order q, as given below:

$$\mathcal{Y}_t = \mathcal{C} + \mathcal{E}_t + \sum_{i=1}^{\mathcal{P}} a_i \mathcal{Y}_{t-i} + \sum_{i=1}^{q} \mathcal{b}_i \mathcal{E}_{t-i} \quad \text{.....Eq.2}$$

Where a_i *are* the parameters of the autoregressive model, $\mathcal{b}_i$ *are* the parameters of the moving average model, $\mathcal{C}$ is a constant, and $\mathcal{E}_t$ is white noise.

2.7. Moving window based z-score process

Standard z-score computation is a widely accepted and used statistical procedure for comparing statistical variables of multiple units. The window based moving z-score process[7] scores are capable of detecting anomalies in a univariate sequential dataset, often a time series. It is a very simple and easily repeatable model that can measure the deviation of each data point in a sequential datasets like a time series. It computes the running mean and standard deviation for a group of successive measurements, where the z-score value of the current measured blood glucose value are computed based on the previous window. This can capture any statistically significant deviations from the mean of the previous successive measurements in terms of its standard deviations. Given a window size of *w*, the moving z-score is defined as the number of standard

[7] https://dato.com/learn/userguide/anomaly_detection/moving_zscore.html

deviations that each observation is found to be away from the mean, where the mean and standard deviation are calculated based on only over the previous *w* measurements. As given in the equation below, the z-score is the ratio of the difference between current observation and the moving mean and the moving standard deviation.

$$\mathcal{Z}(x_i) = \frac{x_i - \bar{x}_i}{\mathcal{SD}_i} \quad \text{.....Eq. 3}$$

Where the moving mean and moving standard deviation are given in the equation below:-

$$\bar{x}_i = \frac{1}{w}\sum_{j=i-w}^{i-1} x_j \quad \text{.....Eq. 4}$$

$$\mathcal{SD}_i = \sqrt{\frac{1}{w}\sum_{j=i-w}^{i-1}(x_i - \bar{x}_i)^2} \quad \text{.....Eq. 5}$$

2.8. Disease surveillance systems

2.8.1. Introduction

Infectious diseases are an abnormality or disorder of the function of the body organs, which is caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi (WHO, 2015b). Infectious diseases are characterized by their capability of passing from an infected person to the normal persons through different transmission media like air, water and physical contact. Infectious diseases are considered to be an outbreak when an excess number of cases occurs than normally expected within a community, geographical area or seasons. An infectious disease outbreak can be epidemics, pandemics or seasonal (WHO, 2015b). It said to be pandemic when it occurs around the globe whereas epidemics involves only a certain city or country. Proper monitoring and early outbreak detection are the most important tasks of any public health surveillances as prevention is always better than cure. In order to accomplish this kind of proper monitoring and early outbreak detection, the use of disease surveillance systems are the ultimate choice, whether it is manual or automatic.

2.8.2. What is disease surveillance system?

The term "surveillance", is consisted of two French words, '*Sur'* which means over and '*veiller'* which means to watch (Choi, 2012). Generally, it can be defined as 'to watch over something'. Consequently, the term disease surveillance can literally be defined as 'to watch over the symptoms and transmission of a disease in a given population and geographical area'. The more

precise and accurate definition of the term disease surveillance can be given as "an active ongoing systematic collection, analysis, interpretation and disseminations of health data for the use of public health purposes" (AMIA, 2002; Choi, 2012). According to this definition, the public health purposes encompasses planning, implementations and evaluation of public health actions (Choi, 2012). This has an added value for taking an effective measures regarding public health actions such as vaccinations, quarantining or isolation and public training that involves creating awareness regarding the outbreak. Moreover, this can be helpful for the government to take the necessary action on policy making and implementations.

2.8.3. Data sources and Timeliness of disease surveillance systems

Various health related data at different point of time (timelines) starting from exposure (pathogens) to the point the person is diagnosed and treated can be used by the surveillance systems, e.g. absenteeism, lab tests, etc. As shown in Figure 2, the timelines of disease evolution begins when the individual is infected by a disease causing organisms (pathogens) and extends up to diagnosis and treatment of the patient (Botsis et al., 2009). During this period, the person who is exposed to a pathogens can be either infected or not. Shortly after infection, incubation and generation of the disease starts and may extend up to the onset of the systems and overlap to the contagious period. An infected person can be contagious even after consultation of their physicians.

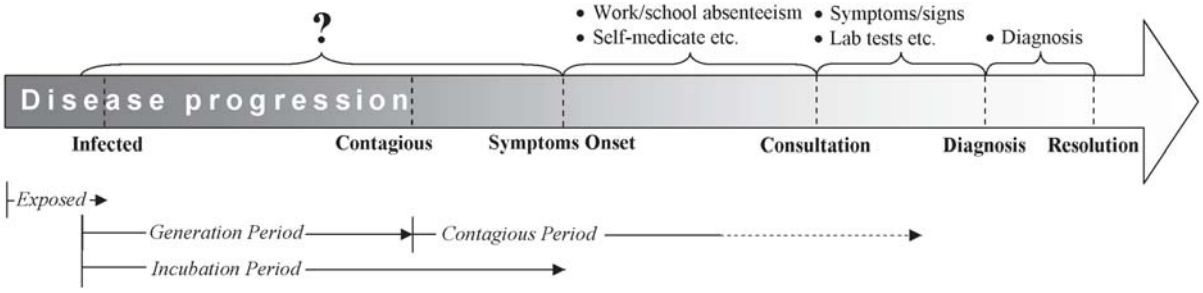


Figure 2: Timelines of disease evolution.

(Figure 1, (Botsis et al., 2009))

Previously, most of the disease surveillance systems are dependent on data that are related to certain symptoms, which are confirmed by the physicians or laboratory technicians. Moreover, it follow paper based reporting systems, which is difficult to analyze and also a time consuming task (Wickramasinghe et al., 2012). This kind of disease surveillance systems have a great limitations since it leave almost no space for the public health authorities or other responsible bodies to take

the necessary actions so as to control the outbreak. As clearly indicated in Figure 3, the response is taken only after having the necessary lab confirmations, which might result in loss of lives before the right action is taken, i.e. vaccinations, quarantining or isolation, treatment and others.

However, the advent of information and communication technology makes the data collection and analysis of disease surveillance systems to be fast and simple. This revolution has paved the way for different types of early disease outbreak detection systems to be developed by various researchers. The main advantage of an early outbreak detection systems is that it leaves a very ample space, as shown in the Figure 4, for monitoring and controlling measures to be taken since it detects the outbreak earlier before it spreads (Wickramasinghe et al., 2012). One of such a kind is syndromic surveillance, which is a kind of an early outbreak detection systems that merely depends on health data that is not yet diagnosed or recorded and confirmed by the physicians.

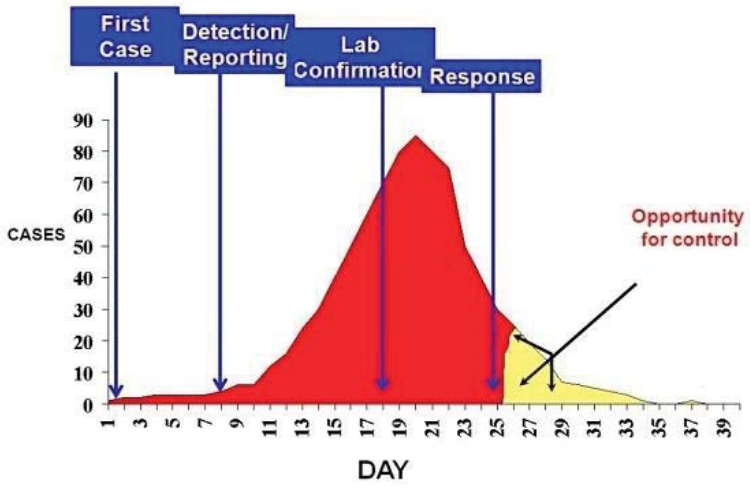


Figure 3: Outbreak Detection and Response - the outcome of a delayed process.

(Figure 2, (Wickramasinghe et al., 2012))

Therefore, the approach behind syndromic surveillance is to collect a symptoms related patterns with in the population for the purpose of disease outbreak detection (Adam et al., 2007). This kinds of disease surveillance systems uses various kinds of data sources such as on the counter pharmacy drug sells, disease related search volumes in different search engine such as google, school absenteeism, emergency calls and others (Adam et al., 2007).

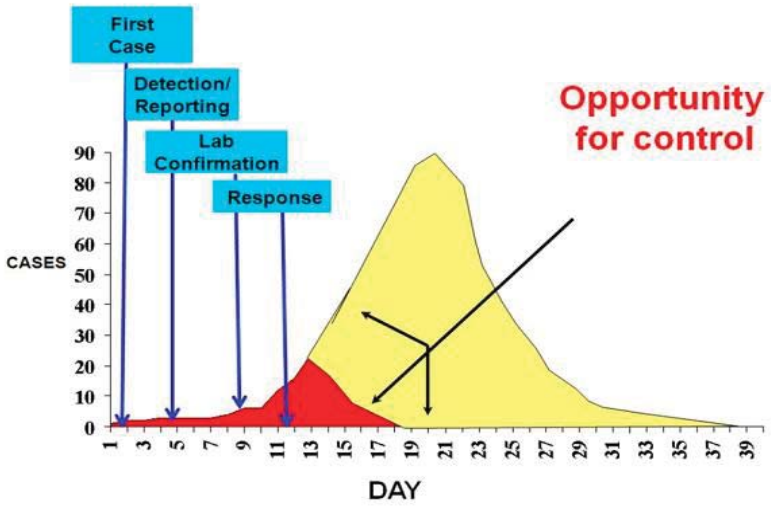


Figure 4: Outbreak Detection and Response - the outcome of a rapid process.

(Figure 4, (Wickramasinghe et al., 2012))

2.8.4. Types of disease surveillance systems

Any system that is intended for surveillance of diseases can be categorized under one of the following classification given by (Arana, 2010). This classification includes a more general systems such as vital records, disease reporting, surveys and more specialized systems such as sentinel surveillance, zoonotic disease surveillance, adverse events, syndromic surveillance, registries and laboratory data (Arana, 2010). Some of these systems are more useful to handle certain diseases than the rest but each systems works better to meet a certain specific needs. For example, vital records is a kind of surveillance systems designed to monitor the death and birth records of the population. However, disease reporting (morbidity data) systems is designed to report certain kinds of disease for the public health authorities that have a potential to be an international risk. Unlike these two, surveys are another kind of surveillance system that are designed to perform some kind of routine survey among the population to monitor chronic diseases and health related problems. In addition, sentinel surveillance is a kind of population based surveillance, which involves only a small group of the population called samples or reporting sites called sentinel to participate in the disease surveillance processes. Zoonotic disease surveillance systems is a bit different from the rest in that it involves detecting infected animals before the disease get transmitted to humans. For example, (Kling et al., 2012) developed a systems called

Computer Assisted Search for Epidemics (CASE), which is computer assistive disease surveillance system tailored for different disease groups including zoonosis. The adverse events surveillance is a kind of surveillance system that is designed to conduct and monitor the occurrences of any adverse reaction such as adverse drug reaction due to the previously taken prescribed drugs. For example, (Tripathy et al., 2015) developed a surveillance system that can detect adverse drug reaction through different data mining techniques. The most recent and advanced disease surveillance system is the syndromic surveillance that relays on using various clinical information that are related to the disease signs and symptoms before any diagnosis is made. This kind of outbreak detection uses different health data sources such as patients' physiological indicators including reported symptoms, amount and types of medication sales, emergency calls and school absenteeism (Adam et al., 2007). The approach behind syndromic surveillance is to collect such patterns with in the population for the purpose of disease outbreak detection. For example, (Zhou et al., 2011) developed a syndromic surveillance systems that relays on Google search trends as a data source for detecting the outbreaks of tuberculosis (TB). Zhou et al. and his groups (Zhou et al., 2011) also formulated a dynamic detection algorithms that can detect and correct the «media effect» to reduce the condition of false alarming.

2.8.5. Disease outbreak detection Algorithms

An effective disease surveillance systems are expected to develop optimal disease outbreak detection mechanisms. A disease outbreak detection algorithms are said to be optimal when it possess reduced false alarm and good detection accuracy with minimum time lag, which is termed as specificity, sensitivity and timeliness. Generally, the approaches (algorithmic models) used to perform detection of disease outbreaks in disease surveillance systems are broadly categorized under three groups: regression methods, time series methods and statistical process control (Guillou et al., 2014). Currently, a lot of outbreak detection algorithms have been put in practice. For example, RODS project used a statistical approach for its outbreak detection mechanisms (Espino JU1, 2004; Wagner et al., 2004). Others types of algorithms such as Bayesian network (Yan et al., 2012; Yigzaw, 2012), Recursive-least-square (RLS) (Yan et al., 2012), Autoregressive Moving Average (ARIMA) (Yan et al., 2013), Hidden Markov Model (HMM) (Zhou et al., 2013), a Decision-Theoretic Model (Wagner et al., 2012) are also investigated and put in practice. A more general anatomy of the temporal aberrancy detection algorithms are briefly shown in Figure 5.

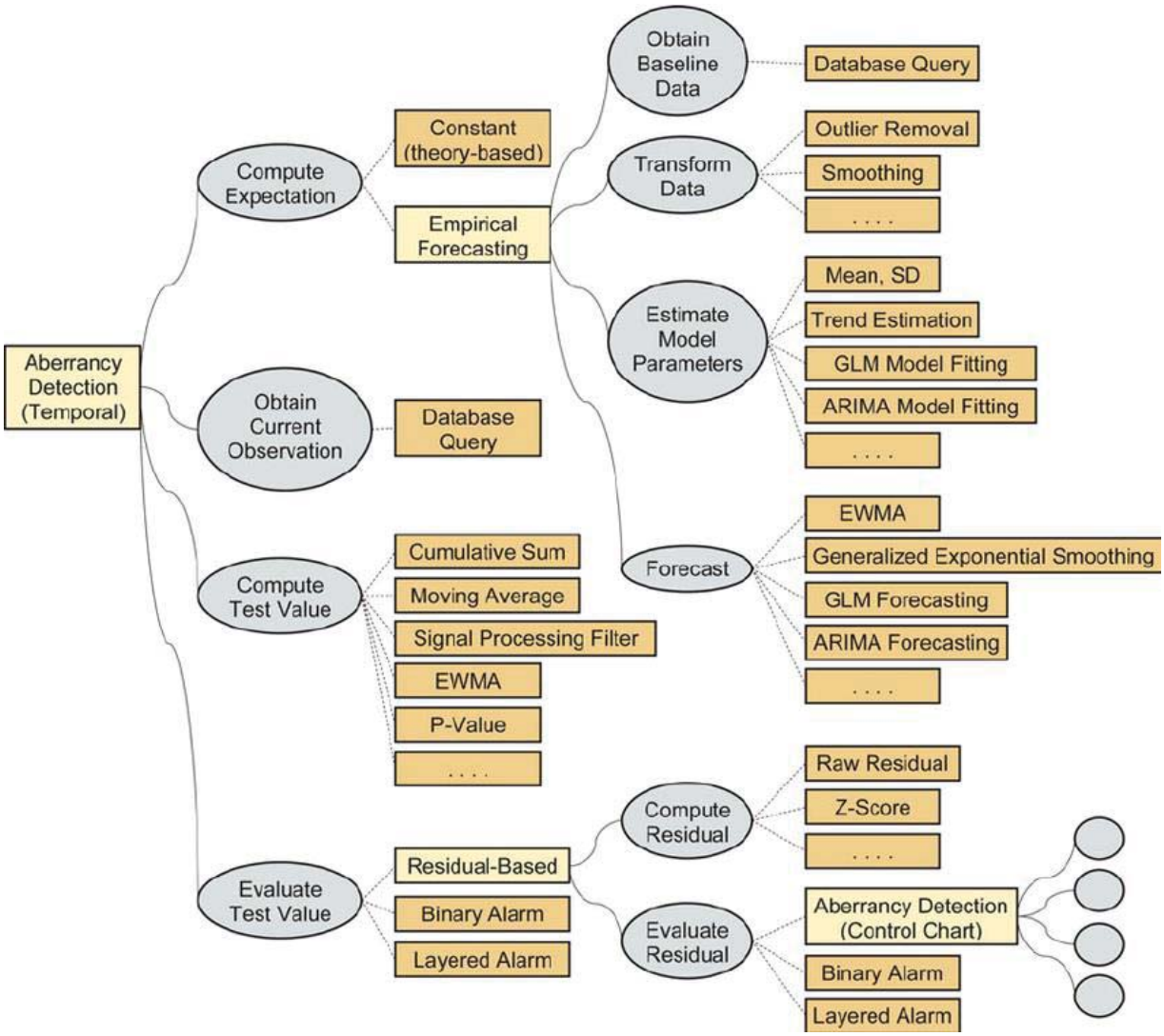


Figure 5: General structure of temporal aberrancy detection algorithms.

(Figure 6, (O'Connor et al., 2009))

2.9. Technical Evaluation Framework of Disease Surveillance Systems

(Drewe et al., 2012; WHO, 2006) defines the technical evaluation framework of any disease surveillance systems including, specificity, sensitivity, positive predictive value (PPV) and timeliness. Accordingly, "Specificity is defined as the proportion of true non-events correctly classified as such, the inverse being the false alarm rate" (Drewe et al., 2012). "Sensitivity in surveillance refers to the proportion of actual cases in a population that are detected and notified through the system"(WHO, 2006). The sensitivity of a disease surveillance systems are described in three levels, i.e. Sensitivity of the surveillance case definition, sensitivity of the detection of

events for public health response and sensitivity of the notification system (WHO, 2006). The first level is sensitivity of the surveillance case definition, "which refers to the ability of the systems case definitions to encompass all the possible cases in the population". The second level is sensitivity of the detection of events for public health response, "which refers the proportion of case detected and reported by the system" (WHO, 2006). The sensitivity here is defined as follows,

$$Sensitivity = \frac{\textbf{persons with the disease detected by the surveillance system}}{\textbf{total number of persons with the disease}} \times 100 \quad \text{.....Eq. 6}$$

The third level is sensitivity of the notification system, "which refers to the proportion of cases meeting the case definition (regardless of the sensitivity of the case definition itself) that are detected and notified as they should be" (WHO, 2006). Moreover, "Timeliness is defined as the Speed between steps in a surveillance system. For outbreak detection, timeliness refers to the time between exposure to the infectious agent and the initiation of interventions to control infection" (Drewe et al., 2012). Positive predicative value (PPV) refers to the "proportion of the people, who actually have the disease and correctly classified as such by the disease surveillance system" (WHO, 2006). It can be considered in three levels, the PPV of the case definition, the PPV of case detection, and the PPV of outbreak detection. The first level, the PPV of the case definition is defined as (WHO, 2006):

$$PPVcd = \frac{\textbf{cases meeting case definition}}{\textbf{total number of actual cases}} \quad \text{.....Eq. 7}$$

The second level, the PPV of case detection is defined as (WHO, 2006):

$$PPVdc = \frac{\textbf{total cases detected (clinically or by laboratory)}}{\textbf{total number of diseased persons}} \times 100 \quad \text{.....Eq. 8}$$

The third level, the PPV of outbreak detection is defined as (WHO, 2006):

$$PPVdo = \frac{\textbf{total alerts confirmed as outbreaks}}{\textbf{total alerts received / detected}} \quad \text{.....Eq. 9}$$

2.10. Related works and State of the art

Recently, the advent of information technology and the availability of different bio-sensors have paved the way for the development of the next generation disease surveillance systems. These technological advancements have enhanced the availability of an electronic form of patients' data

and real time access to patients' health related information. By exploiting these technological advantage, a syndromic surveillance systems have been put in practice already (Chan et al., 2010; Chen et al., 2014; Chung-Kuo et al., 2005; Weng et al., 2015; Yan et al., 2013). However, nowadays, the situation is calling for more enhanced and early outbreak detection systems (during incubation period). Epidemiologists and researchers have been looking for more specific physiological indicators (patient observable parameters) to support early outbreak detection during the incubation period. One of such a kind is the one that is based on blood glucose inputs from people with diabetes. Various researchers have tried to address the use of blood glucose data in the outbreak detection scenarios. For example, (Botsis et al., 2007) has assessed the correlation between blood glucose levels and infection and also proposed a model for detecting infectious diseases in diabetes patients. However, the study didn't develop any methods and only concludes by highlighting the presence of high correlation between the presence of infections and elevated blood glucose values. Moreover, (Lauritzen et al., 2011) highlights the requirements for detecting illness before the onset of the symptoms and illness, and an illness prediction model depending on patient observable parameters. Furthermore, (Liao et al., 2004) has developed a communication platform for diabetes surveillance. The idea is to promote the diabetes patients to measure their blood glucose regularly at home, and the system can provide the remote care persons with complete information about the patients measurement and conditions. Besides, (Årsand et al., 2005) have deeply and briefly described the system architecture, model and requirements of disease surveillance based on patient observable parameter, i.e. blood glucose. The study has addressed the data sampling, data repository, geographical location, and software agent technology, in developing disease surveillance system based on inputs from people with diabetes. In addition, (Botsis et al., 2009) also has assessed the development of electronic disease surveillance systems for detecting infections at the first stage of disease progression (during incubation period). The study has considered patient observable parameters like blood glucose values and count of white blood cells as an indicators. It also describes applying the bottom up approach for detection of an outbreak threat along with conceptual, organizational, architectural and technological issues of the dedicated electronic disease surveillance systems. Moreover, (Botsis et al., 2010) also describes the achievements in developing disease surveillance system based on data from people with diabetes. The study has performed an analysis using the data from two large-scale clinical studies that involved people with type-1 and type-2 diabetes. Moreover, it conducts a feasibility study to

examine the available point of care (POC) technology. The result indicates some interesting facts for further investigation, however the study reported that the available technological solutions have appeared to have significant limitations, mainly in terms of usability.

Chapter Three: Literature Review

An Early Outbreak Detection and Blood glucose prediction mechanisms:- A Systematic review

3.1. Introduction

Recently, a lot of researchers are working towards detecting an infectious disease outbreak as earlier as possible, i.e. during the incubation period using blood glucose value of a diabetes patients (Botsis et al., 2009; Botsis et al., 2010; Lauritzen et al., 2011). These studies have shown a preliminary results on using blood glucose data of peoples with diabetes for detecting disease outbreak. Moreover, (Liao et al., 2004) briefly stated the necessary communication platform for developing a successful diabetes surveillance. However, a system which uses data within the incubation period, such as blood glucose data, is not yet developed and currently, it is a hot research topic. As part of this advancement in disease surveillance, the author is conducting a research on developing an early outbreak detection mechanism that relies on blood glucose inputs from people with diabetes. Therefore, it is the objective of this review to assess, analyze and report the current status of diabetes blood glucose prediction mechanisms and the state of the art in disease surveillance systems, which can be applied and geared towards achieving a successful disease surveillance system based on blood glucose inputs. Moreover, it tries to pinpoint the limitation and challenge imposed by the current methods. Furthermore, it gives recommendation for developing a successful outbreak detection mechanisms based on input from people with diabetes. The entire review are organized as follows: the first section discuss the method used along with the inclusion and exclusion for both blood glucose prediction and outbreak detection mechanisms. The next section discuss the results and the final section concludes the findings with some recommendation of the future systems.

3.2. Method

For the purpose of the study, we conducted a literature search in the following databases. The databases included were Google Scholar, PubMed, Science Direct, MEDLINE, ACM Digital Library, IEEE Xplore, Journal of American Medical Informatics Association (JAMIA), PLOS ONE, and Munin, the proprietary database of the University of Tromsø – The Arctic University of Norway. Peer reviewed journal articles and conference proceedings are considered. For an

effective searching strategy, several combination of string are used during searching. For blood glucose concentration profiles, several combination of the term such as “Blood glucose”, “profile”, “interval forecasting”, “interval”, “prediction”, “forecasting”, “trend prediction”, and “diabetes patient”, were used during searching. However, for the electronic disease surveillance systems, combination of strings such as “Electronic”, “disease”, “surveillance systems”, “syndromic surveillance”, “outbreak detection”, “diabetes patient”, and “mobile phone” were used during searching. First, we identified relevant articles by reviewing the titles, keywords and abstract for a preliminary filter with our selection criteria. We then reviewed full texts for articles that seemed relevant.

3.2.1. Blood Glucose Prediction mechanisms

Inclusion and exclusion criteria

To be included in the study, the articles should possess one or more of the following criteria:

- The model should be at least tested and evaluated
- Evidence based research (i.e. RCT)
- Should be data driven or black box model (based on the patient’s history)

Articles that possess one or more of the following criteria are excluded from the study:

- Published prior to 1995
- Published in other language than English

Data collection

In this review, data collection and extraction from the identified literatures are carried by considering the following parameters of a typical blood glucose prediction systems.

→ *Data types and source:* This describes the source of the data and the type of the data communicated.

→ *Diabetes type:* This describes the type of diabetes patients the study considers. It can be type I (T1) or type II (T2) or both.

→ *Input variables or parameters:* This involves the number and type of the parameter used by the model. This could be diet, exercise, blood glucose concentration, amount of active insulin and others.

→ *Participants:* This describes the Evidence based research (i.e. RCT) nature of the studies. It shows the number of active user participants during the study.

→ *Model:* This describes the kind of model the system implements, which can be compartmental or data driven models.

→ *Algorithm or method:* This describes the type of algorithm or methods implemented by the model.

3.2.2. Early disease outbreak detection systems (Electronic disease surveillance systems)

Inclusion and exclusion criteria

To be included in the study, the articles should possess one or more of the following criteria:

- The surveillance systems should be at least tested and evaluated
- Should be entirely designed for human
- Evidence based research (i.e. RCT)

Articles that possess one or more of the following criteria are excluded from the study:

- Published prior to 2000
- Published in other language than English
- Surveillance designed solely for veterinary medicine and others purposes

Data collection

In this review, data collection and extraction from the identified literatures are carried by considering the following parameters of a typical disease surveillance systems.

→ *Data source:* Signifies the source of the data. It can be EHR or any disease related report used to detect any trends for the disease outbreak detection.

→ *Communication scenario:* This includes the data type and format, means of exchanging data, and any real time monitoring systems.

→ *Algorithms:* For better identification of the disease outbreak, any disease surveillance systems should design and develop a good detection algorithms for the specific data types at hand. Therefore, the types of algorithms implemented on each literature is discussed under this section.

→ *Case reporting:* The purpose of any disease surveillance systems are to detect a disease outbreak and send a notification/report to the public health authorities and other healthcare workers. Therefore, having a good reporting mechanisms is relevant for the success of the systems. In this section the reporting capabilities of each systems will be assessed.

→ *Type:* Any disease surveillance systems can be designed to handle a certain disease types or it can be a group of disease with a certain parameter tuning for each disease case. Therefore, here the types of the disease each surveillance systems handles is discussed under this section.

→ *Periodical updates:* A disease surveillance systems are designed to report as soon as possible if any disease outbreak occurs. This involves a frequently updated data to be used for the analysis of surveillance. Depending on this a disease surveillance systems can be a real-time or periodical. Therefore, the freshness of data and its periodical update will be discussed under this sections.

3.3. Blood Glucose Prediction mechanisms

3.3.1. Result

The search was conducted using the defined strings and refined using the keyword, title and abstract of the relevant articles, which resulted in 60 articles. After properly removing those duplicates resulted in 50 articles, which is screened with our inclusion and exclusion criteria. After screening, 42 articles are left, which are examined in full text. Finally, after full text assessment only 31 articles are included in this study. The details are given in Figure 6 and the brief description of the relevant literatures are given in Table 1.

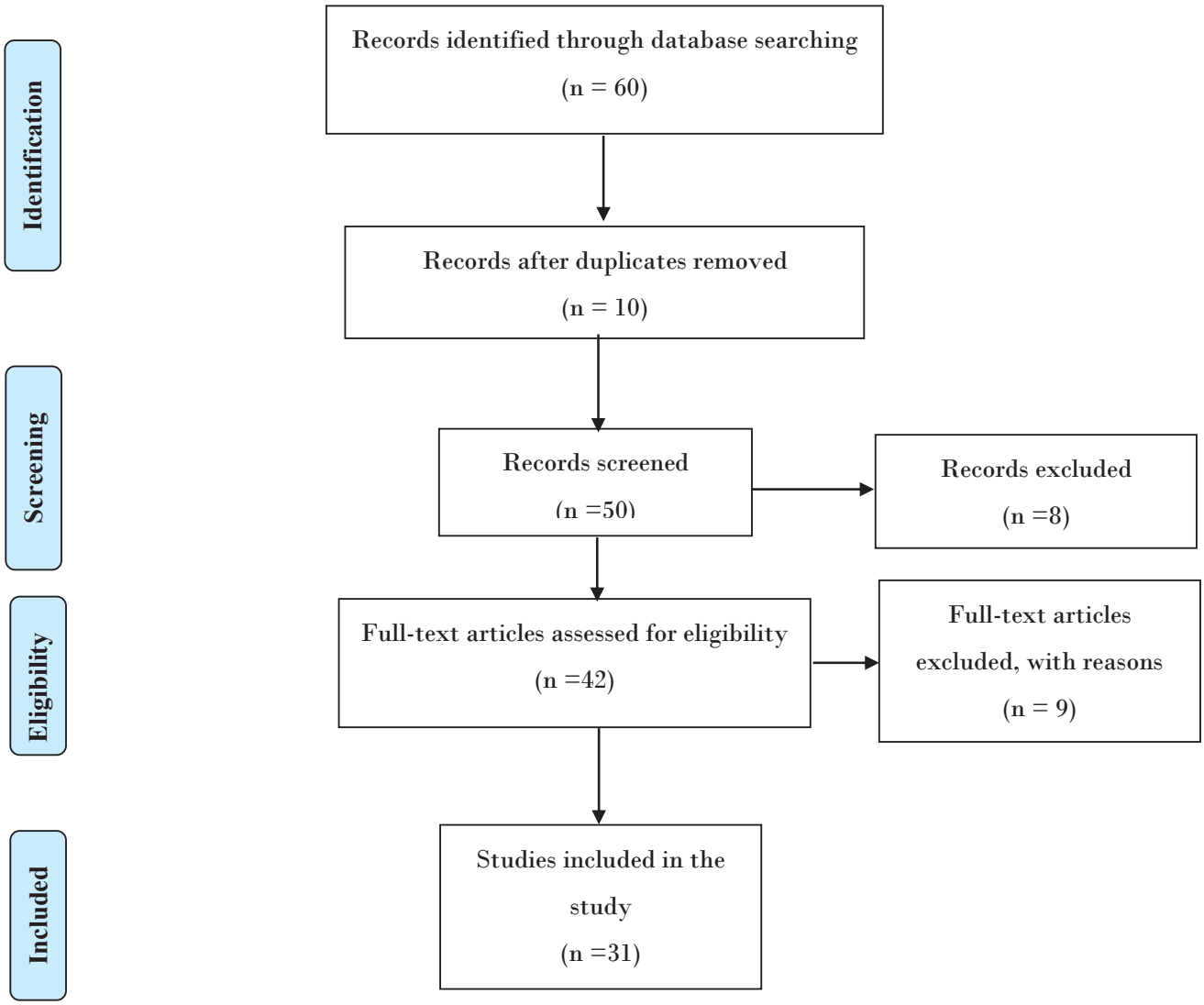


Figure 6: Flow diagram of reviewed literatures in blood glucose prediction.

Table 2: List of literatures

Literature (Study)	Title	Diabetes Type (T1,T2)	Input Variables/parameter (BG, Insulin, exercise, meal)	Participants	Method/Algorithm
(Andreassen et al., 1994)	A probabilistic approach to glucose adjustment: description of metabolic study prediction and insulin dose	T1	Plasma glucose (BG), carbohydrate intake,	12	Causal probabilistic network (CPN) model

	model and pilot evaluation		types, and doses of insulin injected		
(Daskalaki et al., 2012)	Real-time adaptive models for the personalized prediction of glycemic profile in type 1 diabetes patients	T1	Glucose and insulin	30*	Autoregressive (AR), AR model with external insulin input (ARX), and an artificial neural network (ANN)
(Georga et al., 2011)	Glucose Prediction in Type 1 and Type 2 Diabetic Patients Using Data Driven Techniques	T1 & T2	Glucose, Diet, Physical activity and insulin	7	Compartmental models with support vector machines for regression (SVR)
(Jabali, 2013)	Prediction of Patient's Individual Blood Glucose Levels from Home Monitored Readings of Type I Diabetics	T1	Glucose, Diet, Physical activity and insulin	6	Autoregressive exogenous input (ARX) time-series model
(Lauritzen et al., 2011)	Towards a mobile solution for predicting illness in Type 1 Diabetes Mellitus: Development of a prediction model for detecting risk of illness in Type 1 Diabetes prior to symptom onset	T1	Glucose (BG)	-	-
(Liszka-Hackzell, 1999)	Prediction of Blood Glucose Levels in Diabetic Patients Using a Hybrid AI Technique	T1	Glucose, Diet, Physical activity and insulin	1	Hybrid AI technique combining the principal component method, wavelet transform and neural networks
(Pappada et al., 2008)	Development of a Neural Network for Prediction of Glucose Concentration in Type 1 Diabetes Patients	T1	Blood glucose, insulin, carbohydrate, Hypo& hyperglycemic symptoms, lifestyle (activities and events), and emotional states	18	Neural networks
(Pappada et al., 2011)	Neural network-based real-time prediction of glucose in patients with insulin-dependent diabetes	T1	Blood glucose, insulin, carbohydrate, lifestyle (activities and events), and emotional states	10	Neural networks
(Perez-Gandia et al., 2010)	Artificial neural network algorithm for online glucose prediction from continuous glucose monitoring	T1	Blood Glucose	15	Artificial neural network & Autoregressive model (ARM)
(Quchani et al., 2007)	Comparison of MLP and Elman Neural Network for Blood Glucose Level Prediction in Type 1 Diabetics	T1	Glucose, Diet, Physical activity and insulin	10	Multi-Layer Perceptron and Elman neural networks
(Robertson et al., 2011)	Blood Glucose Prediction Using Artificial Neural Networks Trained with the AIDA Diabetes Simulator: A Proof-of-Concept Pilot Study	T1	Blood Glucose	22	A nonlinear auto-regressive neural network with exogenous inputs (NARX)
(Shanthi et al., 2012)	Prediction of blood glucose concentration ahead of time with feature based neural network	T1 & T2	Glucose	20	Neural networks
(Ståhl, 2012)	Diabetes Mellitus Glucose Prediction by Linear and Bayesian Ensemble Modeling	T1	Blood glucose, insulin, carbohydrate, meals	47	Linear and Bayesian Ensemble Models

(Stahl et al., 2009)	Diabetes mellitus modeling and short-term prediction based on blood glucose measurements	T1	Blood glucose, insulin, meals	1	ARMAX, NARMAX
(Baghdadi et al., 2007)	Controlling blood glucose levels in diabetics by neural network predictor	-	Exercise, stress, meal, injected insulin, blood glucose	1	RBF & MLP neural network
(Briegel et al., 2002)	A Nonlinear State Space Model for the Blood Glucose Metabolism of a Diabetic	-	Blood glucose, insulin, meals	-	Artificial neural network, Monte-Carlo generalized EM (expectation maximization) algorithm
(Eskaf et al., 2008)	Predicting blood glucose levels in diabetics using feature extraction and Artificial Neural Networks	T1	Blood glucose, Physical activity, meals	-	Artificial Neural Network, feature extraction procedures
(Tresp et al., 1999)	Neural-network models for the blood glucose metabolism of a diabetic	-	Blood glucose	-	Recurrent neural networks and time series convolution neural networks
(Zainuddin et al., 2009)	A Neural Network Approach in Predicting the Blood Glucose Level for Diabetic Patients	-	Exercise, stress, meal, injected insulin, blood glucose	1	Principal component analysis wavelet and neural network
(Mougiakakou et al., 2006)	Neural network based glucose - insulin metabolism models for children with Type 1 diabetes	T1	Blood glucose, insulin, meals	4	Compartmental Models (CMs) and artificial Neural Networks (NNs)
(Wang et al., 2014)	Personalized State-space Modeling of Glucose Dynamics for Type 1 Diabetes Using Continuously Monitored Glucose, Insulin Dose, and Meal Intake: An Extended Kalman Filter Approach	T1	Blood glucose, insulin, meals	5,30*	Extended Kalman filter (EKF)
(Efendic et al., 2014)	Short-Term Prediction of Blood Glucose Concentration using Interval Probabilistic Models	T1	Blood glucose, insulin, carbohydrate	12	Gaussian Mixture Models (GMM)
(Plis et al., 2014)	A Machine Learning Approach to Predicting Blood Glucose Levels for Diabetes Management	T1	Blood glucose, insulin, carbohydrate	5	Support Vector Regression model
(Rollins et al., 2011)	Forecast Intervals In K-Steps-Ahead Prediction Modeling Under Continuous-Time Monitoring with Application to Blood Glucose Inference	T1	-	20	Static linear regression function in a Wiener block-oriented structure
(Kotz, 2011)	Multiple disturbance modeling and prediction of blood glucose in Type 1 Diabetes Mellitus	T1	Insulin, Physical activity, meals	15	Wiener block-oriented model
(Lu et al., 2010)	The Importance of Different Frequency Bands in Predicting Subcutaneous Glucose Concentration in Type 1 Diabetic Patients	T1	Blood glucose	9	Data-driven autoregressive (AR) models
(Bunescu et al., 2013)	Blood Glucose Level Prediction using	-	Blood glucose, insulin, meal	-	Support Vector Regression

	Physiological Models and Support Vector Regression				Model, ARIMA
(Hemmingsen et al., 2009)	Prediction and Control of Blood Glucose in T1DM Patients	T1	Blood glucose, insulin, meal	-	Autoregressive exogenous input (ARX) and Autoregressive moving average exogenous input (ARMAX)
(Reifman et al., 2007)	Predictive Monitoring for Improved Management of Glucose Levels	T1	Blood glucose, insulin, meal	9	Data-driven autoregressive (AR) models
(Cescon, 2013)	Modeling and Prediction in Diabetes Physiology	T1	Blood glucose, insulin, meal, exercise	-	ARX-, ARMAX- and subspace-based prediction
(Cescon, 2011)	Linear Modeling and Prediction in Diabetes Physiology	T1	-	9	Autoregressive moving average with exogenous inputs (ARMAX) models and state-space models

3.3.2. Analysis and Evaluation

Diabetes is a chronic disease, which needs proper managements of one's blood glucose to prevent further complication from an abnormal state called hypoglycemia and hyperglycemia. Proper management of the disease involves controlling the diet, injecting proper amount of insulin, measuring blood glucose about seven times a day as a standard and performing physical activities. Besides, having an effective decision support systems, which can predict the immediate future values of blood glucose has a great impact on maintaining the wellbeing of the patients. Currently, a lot of researches have done on predicting blood glucose values of the diabetes patients' for various purpose, such as helping the individual and the healthcare givers for a better decision making ability. The literature review done on blood glucose prediction shows that almost greater part of the study have developed a prediction models for type I diabetic patients. This might be due to the availability of frequent blood glucose measurements throughout the day. Moreover, equivalently most of the studies have relied on continuous blood glucose measurement devices (CGM), which has a great impact for a successful prediction within various horizons. Moreover, these studies have shown an evidence based research (RCT), with a significant amount of participants. Depending on the availability, different researchers have used various kinds of inputs like blood glucose, insulin, physical activity, diet and others. As shown in the Figure 7, around 17% of the studies have used blood glucose, insulin, physical activity and diet. Majority of the studies, 37% have relied on blood glucose, insulin and diet. Moreover, around 20% of the studies

have used blood glucose features only. Furthermore, 13% of the studies have used more than the four keystone of diabetes including stress level, medication and others.

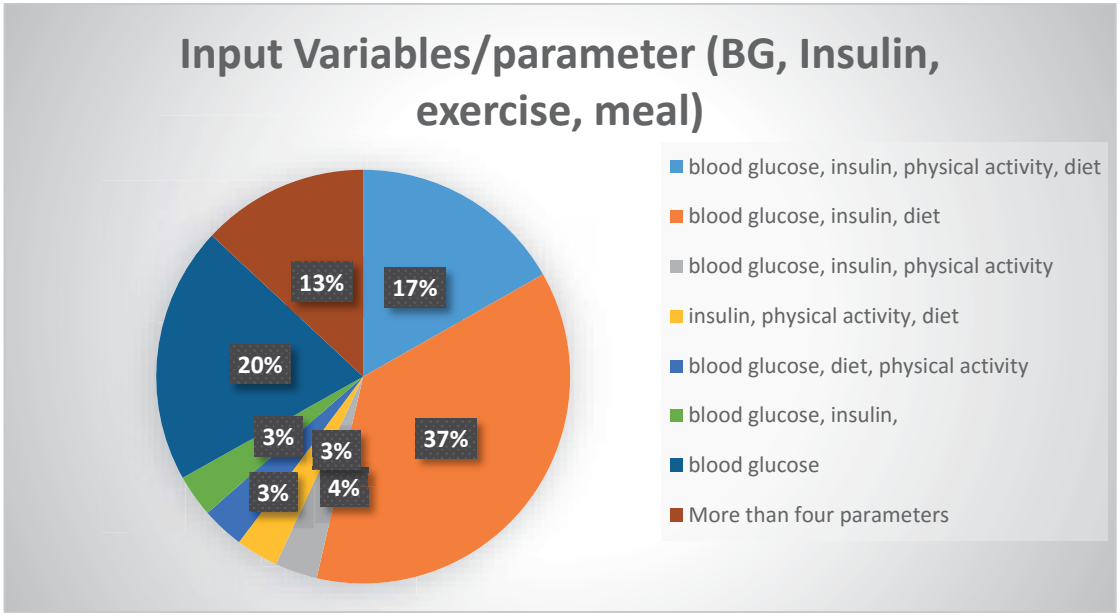


Figure 7: Types of input parameters used by the algorithm in literatures.

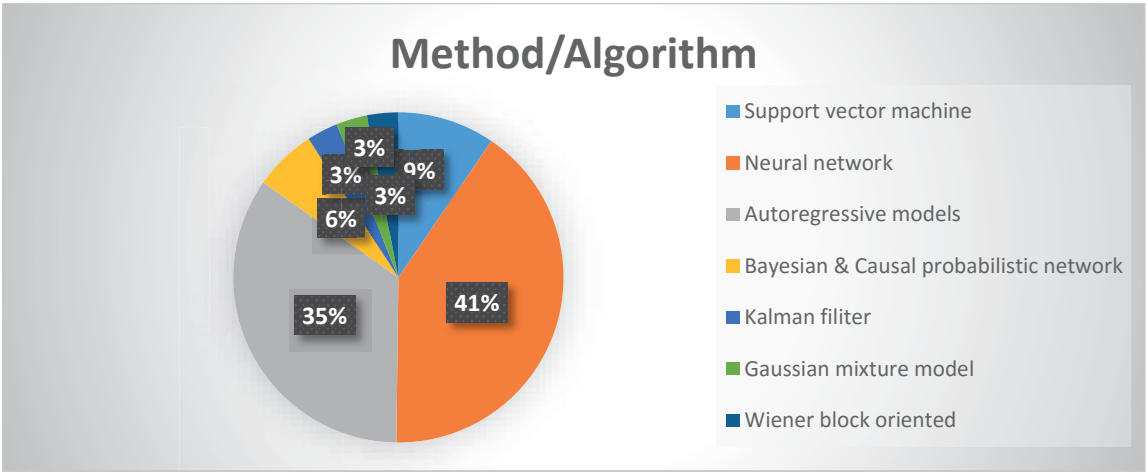


Figure 8: Types of algorithm used in the literatures.

Currently, there are a lot of available models for implementing blood glucose prediction, including neural network, autoregressive, support vector machines and others. As shown in the Figure 8, neural network ranked first and used by almost 41% of the studies. Autoregressive models are ranked second and used by 35% of the studies. Support vector machines are ranked third and accounts 9% of most used algorithms. Bayesian and causal probabilistic network are ranked fourth

and used by 6% of the studies. Finally, Kalman filter, Gaussian mixture model and Weiner block oriented models equally ranked fifth and accounts 3% of most used algorithms.

3.4. Disease Surveillance Systems

3.4.1. Result

The search was conducted using the defined strings and refined using the keyword, title and abstract of the relevant articles, which resulted in 346 articles. After properly removing those duplicates resulted in 305 articles, which is screened with our inclusion and exclusion criteria. After screening 89 articles are left, which are examined in full text. Finally, after full text assessment only 38 articles are included in this study. The details are given in Figure 9 and the whole description of the data collected from the relevant literatures are given in Table 2 and 3.

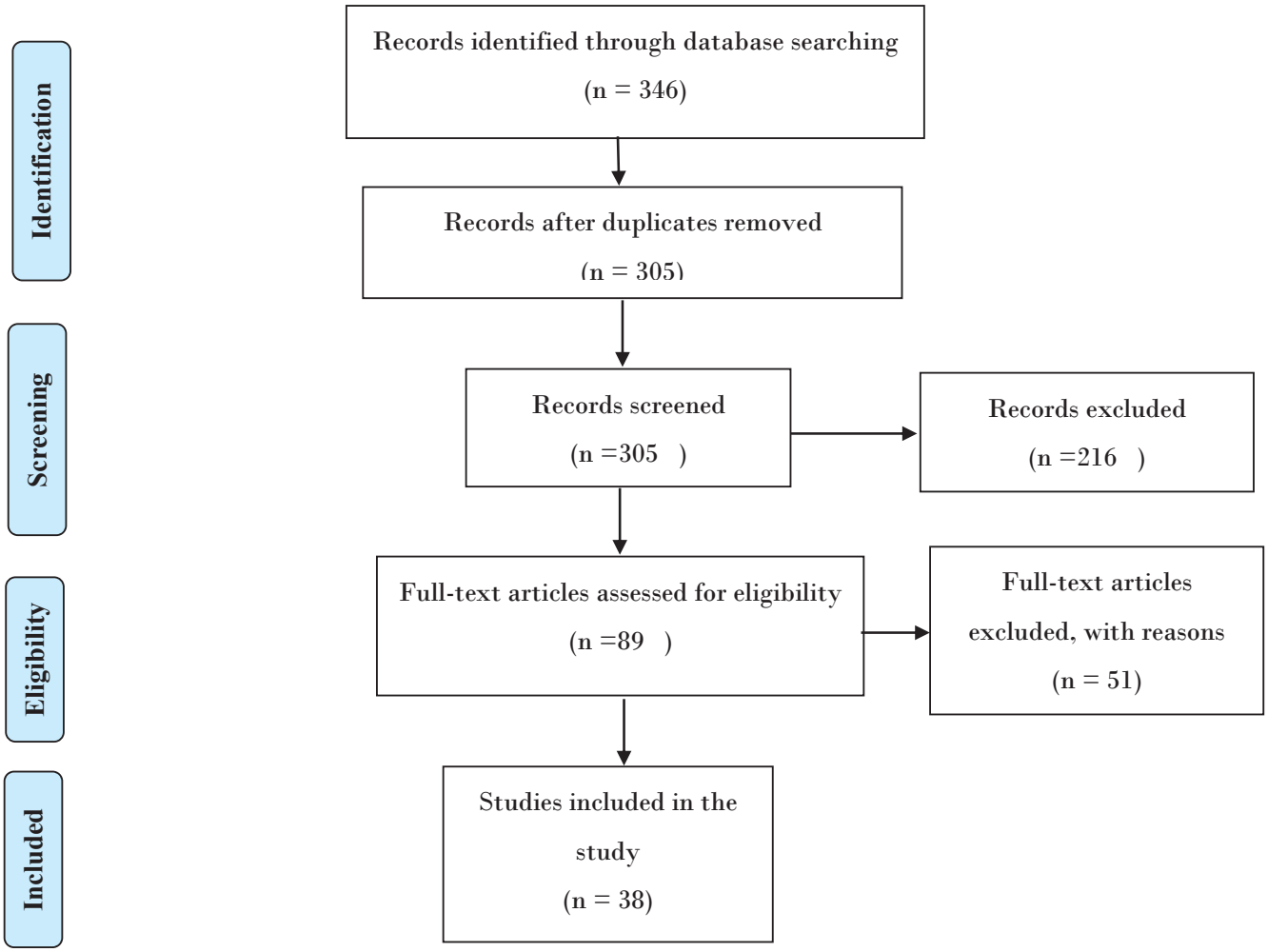


Figure 9: Flow diagram of reviewed literatures in disease surveillance systems.

Table 3: List of literatures

No.	Literature (Study)	Title	System	Type
1	(Kling et al., 2012)	Two Years of Computer Supported Outbreak Detection in Sweden: the User 's Perspective	Computer Assisted Search for Epidemics (CASE)	Communicable Disease Control
2	(Zhou et al., 2011)	Tuberculosis Surveillance by Analyzing Google Trends	Syndromic surveillance using Google trends	Tuberculosis (TB)
3	(Tripathy et al., 2015)	Detection of Adverse Drug Events through Data Mining Techniques	Pharmacovigilance	Adverse Drug Reaction (ADR)
4	(Zhou et al., 2013)	Monitoring Epidemic Alert Levels by Analyzing Internet Search Volume	Syndromic surveillance using Google trends	Epidemic outbreaks
5	(Zhou et al., 2005)	A Real-Time Continuous Cardiac Arrhythmias Detection System: RECAD	RECAD	Cardiac arrhythmia
6	(Zheng et al., 2014)	Epidemic Surveillance Using an Electronic Medical Record : An Empiric Approach to Performance Improvement	Epidemic Surveillance Using an Electronic Medical Record	Acute respiratory infections (ARI)
7	(Yu-Sheng et al., 2010)	Development of a Hospital-Acquired Infection Surveillance Information System by Using Service-Oriented Architecture Technology	hospital-acquired infections surveillance information system (BASIS)	Hospital-acquired infections
8	(Chu et al., 2011)	UPHSM: Ubiquitous Personal Health Surveillance and Management System via WSN Agent on Open Source Smartphone	Ubiquitous surveillance	Chronic diseases
9	(Liao et al., 2004)	A Communication Platform for Diabetes Surveillance	Diabetes Monitoring	Diabetes
10	(Yigzaw, 2012)	Snow Integrated Communicable Disease Prediction Service	Snow Integrated System	Communicable Disease
11	(Yang et al., 2011)	A nationwide web-based automated system for outbreak early detection and rapid response in China	China Infectious Disease Automated-alert and Response System (CIDARS)	Infectious diseases
12	(Yan et al., 2012)	Establishing a web-based integrated surveillance system for early detection of infectious disease epidemic in rural China: a field experimental study	Integrated surveillance system (ISS) (W. Yan et al., 2013) :- Combination of syndromic surveillance and existing case report surveillance	Infectious disease epidemic
13	(Xiaohui et al., 2004)	A bio intelligence system for identifying potential disease outbreaks	Syndromic surveillance using Over-the-Counter Pharmaceutical Sales Data	"Gastrointestinal Diseases and Respiratory Illnesses"
14	(Wong et al., 2007)	Temporal Air Quality Monitoring Using Surveillance Camera	Air Quality Monitoring	Respiratory Illnesses such as heart disease, asthma, stroke, bronchitis
15	(Weng et al., 2015)	Early Detection for Cases of Enterovirus- and Influenza-Like Illness through a Newly Established School-Based Syndromic Surveillance System in Taipei	School-based Infectious Disease Syndromic Surveillance System (SIDSSS)	Most common pediatric infectious diseases such as enterovirus-like illness (EVI) and influenza-like illness (ILI)

16	(Wagner et al., 2004)	Syndrome and Outbreak Detection Using Chief-Complaint Data —Experience of the Real-Time Outbreak and Disease Surveillance Project	Real-Time Outbreak and Disease Surveillance (RODS)	Respiratory and other illness
17	(Wickramasinghe et al., 2012)	Nivārana: System design and implementation focused on rapid response to epidemics	Communicable disease surveillance and analysis system	Communicable disease
18	(Sugawara et al., 2012)	Real-time prescription surveillance and its application to monitoring seasonal influenza activity in Japan	Prescription surveillance	Influenza
19	(Spencer et al., 2011)	The detection of spatially localized outbreaks in campylobacteriosis notification data	-	Campylobacteriosis
20	(Chan et al., 2010)	Probabilistic daily ILI syndromic surveillance with a spatio-temporal Bayesian hierarchical model	Syndromic surveillance	influenza
21	(Chen et al., 2014)	Flu Gone Viral: Syndromic Surveillance of Flu on Twitter Using Temporal Topic Models	Syndromic surveillance	Flu
22	(Chung-Kuo et al., 2005)	An application of sensor networks for syndromic surveillance	Syndromic surveillance	
23	(Cooper et al., 2005)	Can syndromic surveillance data detect local outbreaks of communicable disease? A model using a historical cryptosporidiosis outbreak	Syndromic surveillance	diarrhea
24	(Crubezy et al., 2005)	Ontology-centered syndromic surveillance for bioterrorism	BioSTORM	Trauma, Cardiovascular, Respiratory
25	(Espino JU1, 2004)	The RODS Open Source Project: Removing a Barrier to Syndromic Surveillance	RODS/Syndromic surveillance	Respiratory, flu, diarrhea and skin rashes
26	(Eysenbach, 2006)	Infodemiology: Tracking Flu-Related Searches on the Web for Syndromic Surveillance	Infodemiology: Syndromic surveillance	flu
27	(G.Y. Hong, 2011)	Ubiquitous Healthcare for Environmentally Linked Disease Syndromic Surveillance	Syndromic surveillance	chronic disease (asthma)
28	(Gesteland et al., 2003)	Automated syndromic surveillance for the 2002 Winter Olympics	Syndromic surveillance	Constitutional, respiratory, encephalitic, rash, hemorrhagic, gastrointestinal, and botulinic.
29	(Heffernan et al., 2004)	Syndromic surveillance in public health practice, New York City	Syndromic surveillance	multiple categories such as respiratory, diarrhea, asthma
30	(Hulth et al., 2009)	Web queries as a source for syndromic surveillance	Syndromic surveillance	influenza and influenza-like illness
31	(Lombardo et al., 2004)	ESSENCE II and the framework for evaluating syndromic surveillance systems	Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCEII)	Community-Based Epidemics
32	(Ong et al., 2013)	Syndromic surveillance for health information system failures: a feasibility study	Syndromic surveillance	
33	(Perry & Van Allen, 2005)	Causal Reasoning Engine: An Explanation-Based Approach to Syndromic Surveillance	Syndromic surveillance	multiple non-mutually exclusive diseases
34	(Reis & Mandl, 2003)	Time series modeling for syndromic surveillance	Syndromic surveillance	for overall visits and for respiratory-related visits

35	(van den Wijngaard et al., 2010)	Syndromic surveillance for local outbreaks of lower-respiratory infections: would it work?	Syndromic surveillance	lower respiratory infection
36	(Weng et al., 2015)	Early detection for cases of enterovirus- and influenza-like illness through a newly established school-based syndromic surveillance system in Taipei, January 2010 ~ August 2011	School-based Infectious Disease Syndromic Surveillance System (SIDSSS)	"Enterovirus-like illness (EVI) and Influenza-like illness (ILI)"
37	(Yan et al., 2013)	ISS--an electronic syndromic surveillance system for infectious disease in rural China	ISS	infectious disease
38	(Wagner et al., 2012)	A Decision-Theoretic Model of Disease Surveillance and Control and a Prototype Implementation for the Disease Influenza	SEIR	influenza

Table 4: Features of literatures continued from table 2.

No.	Algorithm	Data format	Data source	Mood of Communication	Periodical updates	Case reporting
1	SaTScan Poisson,SaTScan Space, Time Permutation, Outbreak, simple threshold algorithm		Swedish registry of notifiable diseases (SmiNet)	Email	Daily analysis	The outbreak signal is sent by an email to the epidemiologist(s) in charge of the surveillance of the pathogen in question.
2	A dynamic system in the form of the nonstationary Kalman filter		CDC reported TB and Google search engine"	_	Weekly (Real time service)	Estimated number of TB cases are reported in colored graphical maps
3	Proportionality Reporting Ratio (PRR) and Chi-square function		US FDA database of past patient records, both safe and ADR cases	_	_ /(Real time service)	Accepts the doctor's prescription as an input and provide recommendation on adverse drug events
4	Continuous density HMM		CDC morbidity and Google search volume (hepatitis) data	_	Weekly (Real time service)	Estimated number of hepatitis cases are reported
5	The AWES integrates an ECG diagnostic chip (optional) and is able to offer the capability of the real-time ECG diagnosis.		The ambulatory wireless ECG sensor (AWES) capture 4 leads ECG signals sampled at 500Hz in real-time"	SMS/ Email	Real time service	When a cardiac abnormal event is detected, an alarm message will be sent to the cardiologists to examine the cardiac abnormal events and respond with the shortest latencies
6	Eight previously characterized ARI case detection algorithms (CDA)		Anonymized and de-identified Historical EMR data (Veterans Integrated Service Technology Architecture (VistA) repository)	_	Daily analysis	Early aberration reporting system'' (EARS)
7	Discriminant analysis and Standard threshold	XML and WSDL	Distributed EMR systems		Real time service	Provide more complete infection information based on the CDC's guideline

8	The sensory data value will be compared with whether it is running beyond a preset threshold within a preset period or not.		Bio-monitoring sensor, wireless sensor network (WSN	SMS	Real time service	SMS (short message) with concise information including GPS coordinates will be sent to physicians and relative to help user immediately to receive proper treatment as soon as possible
9	Measured values are compared with the threshold (criteria)		Biological monitor module including Glucose meter and Pressure monitor are used to record from diabetic patients	E-Mail, Fax, phone SMS	Real time service	If the measured values are beyond the criteria, an Alarm will be sent to care persons.
10	Bayesian Model	CSV	Aggregated laboratory confirmed cases from the SNOW system on weekly and monthly period		Weekly	Various information regarding different disease predictions and ranking of algorithms
11	Fixed-threshold detection method (FDM) Temporal detection method (TDM) Spatial detection method (SDM)		Electronic National Notifiable Infectious Diseases Reporting Information System (NIDRIS)		Real-time and daily	Automatically send signals on mobile phones by the SMS system
12	Moving Average (MA), Exponentially Weighted Moving Aver-age (EWMA), Cumulative Sums (CUSUM), Recursive-Least-Square (RLS) Method, Shewhart Chart (P Chart), Small Area Regression and Testing (SMART), Bayesian spatial scan statistics, Space-time Scan Statistics and What is Strange About Recent Event (WSARE)		Patients' major symptoms from health clinics, pharmaceutical sales from pharmacies and absenteeism information from primary school		Daily and user specified	The system send e-mail and/or SMS alerts automatically
13	Rule-Based Alerting		OTC pharmaceutical sales		Daily and Weekly	Specific alerting and the spatial and temporal characteristics of the outbreaks are reported by the embedded Internet GIS application
14	threshold		Still images captured by camera		Real-time	Alerting systems
15	Chi-square tests and the Pearson correlation coefficients and T-tests		Data collected from all school nurses or class teachers based on syndrome reports rather than absenteeism		weekly	A real-time text message alert through short message service (SMS) is immediately sent to the public health professionals for further epidemiologic investigations
16	Mostly Bayesian classifier and others	Health Level 7 (HL7)	Chief complaint data (the patient's reason for visit) was collected from different hospitals		Real-time	Alerting systems
17	Automatically detect the suspicious situations based on the count and disease density for a given geographical area		Weekly Return of Communicable Diseases forms electronically		weekly	Alerting the relevant public health officials via SMS and Email

18	Counting the number of anti-influenza drug prescribed by different physicians		Electronic records related to prescription drugs purchase data		daily	sharing the information related to influenza activity through the Internet with the participating pharmacies and public health authorities
19	Bayesian hierarchical model and spatial scan statistic		The national notifiable diseases database, EpiSurv of New Zealand and simulated data containing outbreaks		weekly	displays Spatial distribution of the sporadic risk at the mesh block level on the map
20	Bayesian posterior probability		The numbers of daily emergency room ILI visits at five community hospitals in Taipei City during 2006–2008		daily	The proposed algorithm recommends an alert for action if the posterior Probability is larger than 70%.
21	Temporal topic model (HFSTM) for inferring hidden biological states for users, and an EMbased learning algorithm (HFSTM-FIT) for modeling the hidden epidemiological state of a user		User tweets		Real time service	flu-trend prediction
22	Bayesian analysis	HL7	Data from 11 hospitals in five health systems. The system copies the data to an Indiana State Department of Health server each night and is reviewed daily.	GUI	daily	The results are displayed on the GIS to demonstrate the spatial distribution of diseases
23	Control chart method & Confidence interval method		Data were obtained from a cryptosporidiosis outbreak that occurred during the spring of 1997 in North London and Hertfordshire		daily	When the proportion n of diarrhea calls (simulated plus outbreak calls) exceeded the upper 99.5% control chart limit or upper 99.5% confidence interval this was termed an ‘exceedance’
24	Poisson Aberrancy Calculator		ER Chief Complaint, School Absenteeism		daily	Temporal and spatial distribution of the diseases
25	Bayesian classifier, recursively least squared algorithm	HL7/ICD-9 codes	Absenteeism data, sales of over the-counter healthcare products, and chief complaints	GUI	Real time service	User interfaces that can display syndromic data as time-series graphs, and work with a geographic information system (GIS) to view the data spatially
26	Pearson correlation coefficients		Internet data for flu-related searches		weekly	Alarm based on correlations and significance level
27			indoor air quality		Real time service	Upon detection of any abnormality, the system can also trigger an alert for immediate medical attention to be provided.

28	Recursive least square (RLS) adaptive filter (RLS, a dynamic autoregressive linear model), Naı¨ve Bayes Complaint Coder (CoCo)	HL7	Chief complaints data (encounter data were collected from 19 urgent care centers and nine emergency departments owned and operated by IHC and from the University of Utah Hospital's emergency department and the Polyclinic located in the Olympic Village.)	Email and SMS	Four hour interval	The signal alarm notifications for the primary detection algorithm—RLS—were broadcast to system administrators, investigators, and public health officials through e-mail, alphanumeric paging, and short messaging service, where they can login and observe the time series and spatial distribution on the map.
29	one-dimensional temporal scan statistic	fixed-column or delimited ASCII text	Chief complaint data	Email	daily	A report consisting of graphs and a brief summary is distributed
30	partial least squares regression		Search logs submitted to a Swedish medical web site for two influenza seasons			Alerting systems
31	Early Aberration Reporting System, Exponentially weighted moving average and Scan statistics	Health Level 7 (HL7)	Ambulatory records generated for Tricare, the military's health-care system, chief-complaint records, school absenteeism data, over-the-counter (OTC) and prescription medication sales, civilian ambulatory visits,	Multiple formats (i.e. alert pager, email, etc.)	daily	A map portal displays geographic distribution of raw data and clusters formed by scan statistics.
32	Shewhart statistical control process charts		Hospital electronic health record system (laboratory information system)		daily	Alerting systems
33	Bayesian network	HIPAA Electronic Data Interchange	Synthetic data generated by an advanced data generator		Real time service	alerts the health officials if any diseases are having an unusually high posterior probability
34	trimmed-mean seasonal models, autoregressive integrated moving average (ARIMA) residuals		A decade of historical data at a major metropolitan academic, tertiary care pediatric emergency department and with simulated outbreaks		daily	Alerting systems
35	space-time permutation scan statistic	ICD-9-CM	Hospitalization data were collected from the Dutch National Medical Register		weekly	Alerting systems
36	spatio-temporal analysis	ICD-9-CM	Data from the Emergency Department-based Syndromic Surveillance System (ED-SSS) and the Longitudinal Health Insurance Database 2005 (LHID2005)	SMS	Real time service	Surface plot of weekly time series as a gradient interpolated between adjacent weeks and district data points.

37	Temporal analysis (Shewhart Chart (P Chart), Moving Average (MA), Exponentially Weighted Moving Average (EWMA), Cumulative Sums (CUSUM)), spatial analysis (Recursive Least Square (RLS) Method, Small Area Regression and Testing (SMART), Bayesian spatial scan statistics), and spatial-temporal analysis (Space-time Scan Statistics and What is Strange About Recent Event (WSARE)).	Excel files	Main symptoms of patients who present at health facilities, medication sales from retail pharmacies and primary school absenteeism	Email and SMS	daily	When an alert is triggered, the system will automatically send e-mail notifications to subscribed communication groups.
38	A Decision-Theoretic Model	Excel	Electronic health record		daily	Visualizing the spread on a map

3.4.2. Analysis and Evaluation

During disease outbreak, early detection meant saving many lives from the incidence. Therefore, any successful disease surveillance should have a detection algorithm that is capable of detecting the outbreak within a short time after the beginning of the outbreak or incidence. This can be quoted with an excellent timeliness, specificity and sensitivity of the detection systems. To this end, various researchers have developed and implemented different outbreak detection mechanisms including Bayesian, regression, moving average, threshold and others as shown in the Figure 10. According to the result, spatio-temporal scan statistics and other models ranked first and accounts 37% of the most used outbreak detection algorithm. Bayesian model ranked second and accounts 15% of most used algorithm. Both the variety of the moving average and threshold mechanisms accounts 9% and ranked third most used detection algorithms. Moreover, both Chi-square and Pearson correlation coefficient and regression models accounts 8% and ranked the fourth most used detection algorithms. Recursive least square is another detection mechanisms, which accounts 6% and ranked fifth. Furthermore, the use of control chart and confidence interval accounts 4% and ranked sixth. Besides, hidden Markov model (HMM) and Kalman filter ranked seventh equally and accounts 2% of the most used detection algorithms.

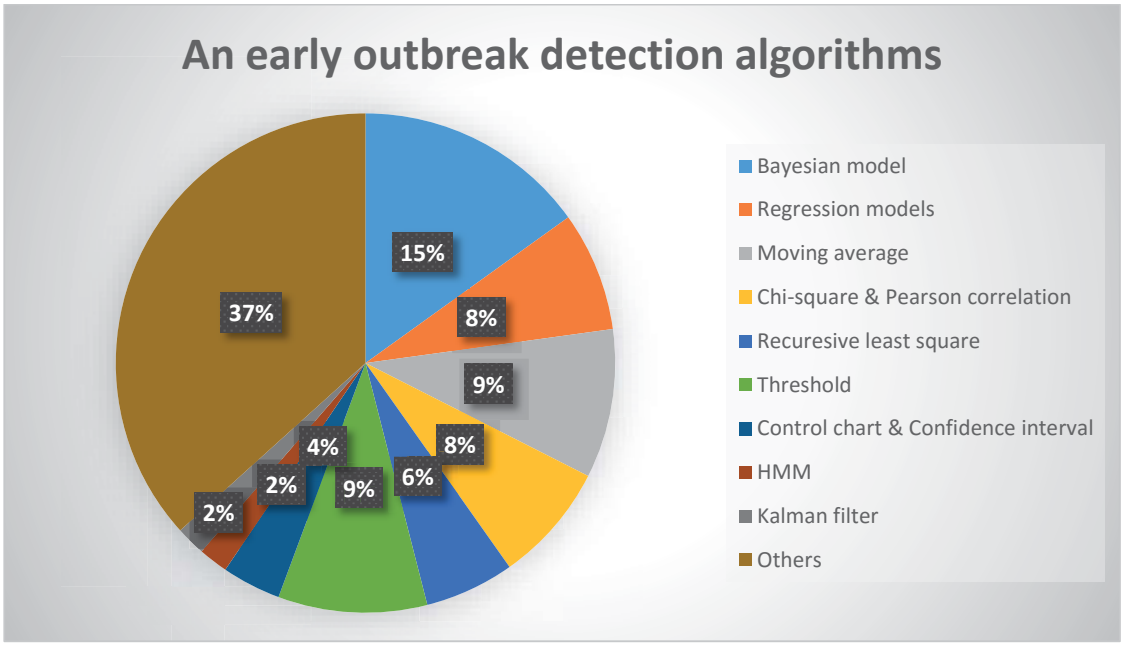


Figure 10: Types of an early outbreak detection algorithm used in the literatures.

After detection of the outbreak, means of disseminating the necessary information for the concerned body is also crucial for the success of the disease surveillance system under consideration. There are a lot of mechanisms for information dissemination including email, SMS, phone, fax and others as shown in the Figure 11. Email is the most used form of communication (39%) followed by SMS (33%). Moreover, Fax accounts 6% followed by Phone calls, which accounts 5%.

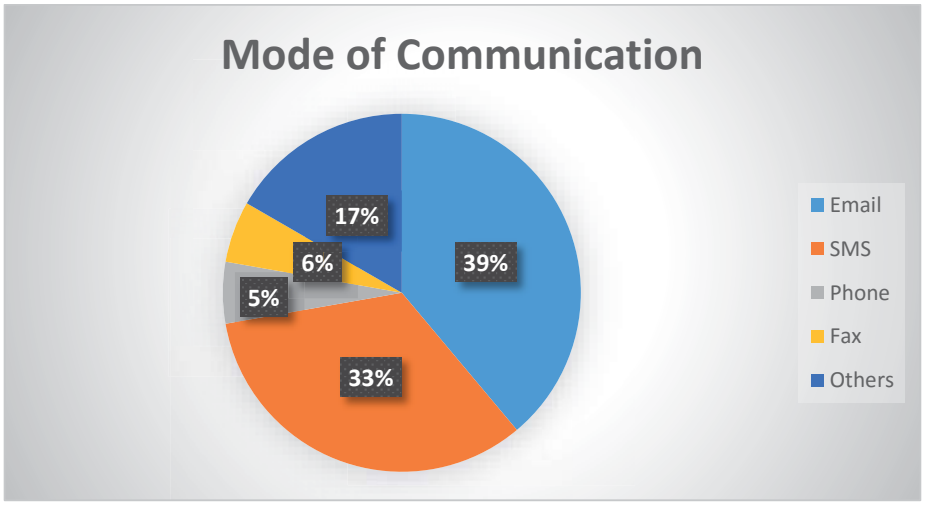


Figure 11: Mode of communication used by the disease surveillance systems.

3.5. Summary

As demonstrated above, both blood glucose prediction mechanisms and early outbreak detection techniques have seen advancements. Different researchers have tried different data driven mechanisms for successful prediction of blood glucose values within various prediction horizon and reported a success. Among them, artificial neural network and autoregressive models are the most practiced form of blood glucose prediction. Due to its simplicity and computational efficiency, an autoregressive models will be implemented in this thesis project. Moreover, researchers have tried different outbreak detection mechanisms, where each mechanisms have its own pro and cons. One outbreak detection techniques might be efficient with a specific disease surveillance systems, however it might be inefficient for the other kind. Therefore, choosing the right outbreak detection techniques depend on the kind of data used, the purpose of the surveillance and the kind of the surveillance implemented. As a result, even if it is least practiced in literatures, control chart, confidence interval and threshold will be explored and implemented in this thesis project. Furthermore, information dissemination are a crucial part of building a successful disease surveillance systems. Therefore, the most practiced form of information dissemination such as email and SMS are considered in this project.

3.6. Conclusion

Major public health treats are either naturally occurring or an artificially induced bioterrorists attack. Either way, it is necessary to detect the outbreak as early as possible to save lives. With the advent of information technology, the transition from paper based reporting into electronic form has revolutionized the disease surveillance systems. One of such a kind is the syndromic surveillance system, which uses data prior to diagnosis but after incubation period including absenteeism, internet search volume, over the counter pharmacy sells and others. However, a system which uses data within the incubation period is not yet developed and currently, it is a hot research topic. Among these early outbreak detection, which uses data within the incubation period, the one that depends on blood glucose inputs from people with diabetes and other physiological parameters from different health sensor networks are considered to be the next generation disease surveillance system. Moreover, the availability of successful blood glucose prediction models and outbreak detection mechanisms coupled with the availability of different physiological monitoring sensors such as heart activity (electrocardiogram (ECG)), muscle

activity (electromyography (EMG)), brain activity (electroencephalography (EEG)), blood pressure and continuous blood glucose sensor, white blood cells count, body temperature, breathing or respiration sensor can enhance the feasibility of the model in the near future. Furthermore, the inclusion of the available physiological parameters from other chronic patients such as COPD might result in an excellent detection accuracy of the developed system. Therefore, we foresee the use of health sensor networks comprising these physiological parameters will solve the early disease outbreak detection puzzle of the public health surveillance in the near future.

Chapter Four: Materials and methods

4.1. Introduction

This thesis project is concerned with developing an early aberration detection mechanism that rely on recorded blood glucose value, amount of insulin, diet and physical activity, and particularly continues blood glucose (CGM) data are used in this thesis project. This project has a couple of major components, research and application development components. The research component involves developing the underlying mathematical model, which is used to implement the system and is consisted of two consecutive phases, blood glucose prediction phase and outbreak detection phase. The first phase includes prediction of the step-ahead BG values using previously record CGM data. It also calculates the confidence interval of the predicted values, where the future measurement is most likely expected to lie within. The second phase is outbreak detection, where the actual BG values are compared with the predicted BG intervals. Additionally, it also involves calculating the z-score of the actual BG readings data with a moving window based z-score computation. The deviation is detected, when the current actual BG reading is found outside of the predicted intervals or when the current actual BG reading has a z-score value with a statistically significant deviation from a group of previous recordings. The total number of people (cluster), assumed to be in a specified region and timeframe is compared with the stated thresholds. If the number of people in the cluster is found to be above the pre-specified threshold, an alarm will be sent to the responsible body, such as public health authority or hospitals. Apart from the research component, the application development component tries to answer the necessary requirements specification for developing and implementing the prototype software system. This includes specifying the system requirements and developing the use case diagram along with the Unified Modelling Language (UML). However, the development of the software application itself is not considered in this project.

4.2. Research Paradigm and Tools

This thesis project has been conducted using both Friedman, the tower of achievements in medical informatics (Friedman, 1995) and an Engineering approach described by Denning et al. (Denning et al., 1989). This involves model formulation including defining requirement and specification, and system development including system design and implementation along with system

evaluation techniques including testing of the system for performance (Friedman et al., 2006). The requirement and specification are defined following Volere's standards (Robertson et al., 2000).

4.3. Materials

In order to develop and test the system, a combination of software and hardware have been used. The system has been entirely developed based on two components, research component and application development component. The research component (development of BG prediction, interval calculation and outbreak detection) were developed based on Matlab programming language. The application development component involves specifying the system requirements and developing the use case diagram along with the Unified Modelling Language (UML), which is done based on a trial version of the Enterprise Architect v.10.0, SPARX Systems©[8].

Table 5: Software and Hardware used in the thesis

Software	Hardware
Microsoft Window 10	Toshiba Laptop (Intel Core i3 2500s, 4Gb RAM)
Matlab R2015b	
Enterprise Architect v.10.0, SPARX Systems	

4.4. Data Collection and Experimental Methods

4.4.1. Literature review & Related Work

A comprehensive review of literatures and related works have been conducted, so as to formulate the functional and non-functional requirements of the system and also to formulate the mathematical models that are used for blood glucose prediction and outbreak detection mechanism. Moreover, a systematic review of literatures was conducted in order to grasp the current trend, advancements and state of the art in blood glucose predictions and outbreak detection mechanisms (see Table 1 and 2).

[8]Enterprise Architect website:- http://www.sparxsystems.com/products/ea/trial.html

4.4.2. Meetings with Diabetes patients and Diabetes expert

Several meeting with diabetes patients, who have long standing experience in diabetes management technologies and experts at Norwegian center for eHealth research (previously known as NST), have been held. The meeting was arranged so as to formulate the simulated blood glucose deviations to resemble as close as possible to the real infections, such as respiratory infections, which is used in testing of the developed system.

4.4.3. Testing

The system was tested for detecting statistically significant deviations of BG reading that are associated with the presence of infections. Testing the system has been takes place in two partitions, where the first partition involves blood glucose prediction in which the system was trained and validated with unseen data. The second partition is the outbreak detection, which was tested with the simulated dataset. The performance was also analyzed in terms of its sensitivity, specificity, and positive predictive value. Moreover, the system was assessed in terms of its usefulness, acceptability, and generalizability.

4.4.4. Data sources

The quality of data used in developing early outbreak detection systems are crucial for the success of the system, which is measured in terms of its representativeness and, completeness. This thesis project was conducted using data collected from two type-I diabetes subjects/testers, from small group of people with diabetes. All these necessary data were collected from Dexcom - continues blood glucose monitoring (CGM) device, which records blood glucose data at every five minutes. The collected data were one month long, which were vertically divided into training and validation datasets. The training datasets were entirely used to train the developed system, whereas the trained system was validated using validation datasets (unseen during training). Additionally, these two subjects' data were modified with artificially simulated blood glucose deviations of different size, shape and durations to be used in testing the performance of the developed early outbreak detection mechanism.

4.5. Critics of the method used

As a first remark, the author believes that the availability of limited diabetes subjects' data has a major limitation to further test and validate the system. The developed system might be more explored with a wide range of possibilities if more data were available. The second remark is on

the availability of a real individual's BG data that is recorded with the presence of infection. This has a great effect on testing of the developed system for the defined surveillance case definition under real settings. Moreover, the presence of such kind of measurements have a great impact on making the developed system representative of the whole surveillance case definitions. Unfortunately, these kind of data were not considered here, since there were not such kind of measurement available during data collection.

The prediction of blood glucose values was developed based on autoregressive model, using Autoregressive (AR), and Autoregressive Moving Average (ARMA) methods. This model was chosen, because this model relies on more recent values to predict the feature values, which is most important for our project, which is helpful to follow the persons' cyclical habit within a day, week or more. Besides, during selection of the procedure more emphasis was given on the simplicity and repeatability of the models. In addition, it has a simple and well-defined procedure for calculating interval of the forecasts. Apart from this, interval prediction was chosen over point prediction so as to compromise for the uncertainty involved with other unexplained BG variations.

4.6. System Evaluation

The developed system has been evaluated based on available gold standard methods in literatures. The first partition, blood glucose prediction methods have been tested and evaluated using mean square errors (MSE) and root mean square errors (RMSE) functions. In addition, the performance of the outbreak detection mechanism is evaluated based on the accuracy of detecting the defined surveillance case definition (an individual's consecutive high BG readings). Moreover, the optimal working threshold is determined using sensitivity, specificity, positive predicative value, which is based on the tradeoff between threshold values and the false-positive rate.

4.7. Summary

The following sets of methods were used in this thesis work:

→ Syestem Design (the Tower of achievements in Medical Informatics & an Engineering approach)

- State requirements;
- State specifications;
- Design and implement the system;
- Test the system.

→ Data Collection

- Literature review
- Meetings with diabetes patients and diabetes experts
- Disccusion with other experts and collegues
- Datasets collection

→ Evaluation (Quantitative methods)

- Glucose prediction (MSE and RMSE)
- Outbreak Detection (Sensitivity, Specificity, and positive predicative value (PPV))

Chapter Five: Requirements specification

5.1. Introduction

In this chapter, an overall description of the requirements and specifications for the electronic disease surveillance based on inputs from people with diabetes are given. During development, main emphasis was given for developing the underline mathematical models for the early outbreak detection mechanisms, i.e. blood glucose prediction models and outbreak detection methods. However, we also gave emphasis for formulating a framework for developing the required system, without giving a due consideration on the development of the required software application (due to time constraint). First, the description of the system is given in relation to various assumptions taken, the presence of any dependences within the system, and the potential users of the system. Next, the main reason behind selecting the method used for specifying the necessary requirements and the sources of the requirements used are described. Afterwards, the specification of both the functional and non-functional requirements of the entire system are given. Finally, a summary at the end of the chapter gives a concluding remark.

5.2. System Description

The electronic disease surveillance system based on inputs from people with diabetes is a system that:

- → Enables monitoring of infectious disease, such as respiratory infection and others, within the diabetes population and the community in general.
- → Enables prediction of BG values for the individuals.
- → Gives a clear indication of the presence or absence of a detected outbreak in a way that can facilitate investigation and decision making.

This early outbreak detection system uses data already being collected by the individuals with diabetes as part of his/her daily management of the disease. Currently, there are a lot of diabetes self-managements devices/apps on the markets, i.e. continuous blood glucose monitoring (CGM) – Dexcom products and few touch application (FTA) - the diabetes diary of Norwegian center for eHealth research (previously known as NST).

5.2.1. Constraints

The developed system had the following constraints:

→ The outbreak detection system shall use aggregated measurements of daily blood glucose, amount of insulin injections, dietary, and physical activities.

→ Privacy/confidentiality: The outbreak detection system shall use users/actors consent for the data access policy.

5.2.2. Stakeholder (Users)

The developed system has a multi-dimensional uses and purposes, though the main users of the developed system are assumed to be:

→ Public health officials and various hospitals (Healthcare).

→ Individual Healthcare professionals (General Practitioner (GP), physician, Laboratory technicians, Pharmacist).

→ Individual diabetes patient and family or relatives.

5.2.3. Interoperability & Communication

The system is designed so as to use a common data exporting standards such as CSV file. The daily data from the user device are aggregated and imported to the system. A highly secured communication channels are used to implement the data exchange between the user mobile devices, i.e. Dexcom, and the developed system. Moreover, an intermediator between the data source and the developed system are considered. The purpose of the intermediator is to perform some kind of deidentification on the individual's data to remove major identifiers and to preserve the confidentiality.

5.3. Selection of requirements and specification method

During development of a system, requirements and its associated specification processes are mandatory. Currently, there are a lot of requirements specification methods evolved through time, each with its own pros and cons. One requirements specification method can be effective for some kind of tasks, while it can be ineffective for others. Therefore, a compromise between the nature and type of problem at hand and the available requirements specification methods should be done during method selection. In a project, which needs an iterative approach that brings change at any course of time during development needs a method that can facilitate this kind of task. As a result, the Volere Requirements Process and its associated Specification Template (Robertson et al., 2000) are found to be effective for this project. Therefore, this approach were used for organizing, and documenting of the requirements along with its specifications.

5.4. Source of Requirements

As part of requirements specification for a project, credible sources are mandatory for the success of the project. Functional requirements are the fundamental subject matters of the system; they can be measured by concrete means like data values, decision making logic and algorithms (Robertson et al., 2000). Non-functional requirements are the behavioral properties that the system must have, for example, performance, usability and others (Robertson et al., 2000). The main source of both functional and non-functional requirements were relevant literatures, including the state of the art in blood glucose prediction and disease surveillance systems, which were reviewed in Chapter 3. Moreover, discussion with diabetes patients, diabetes expert and colleagues were used to improve the requirements specification.

5.5. Functional Requirements

This section briefly describes the specification of the functional requirements. Based on the available sources of requirements described above, the specification of requirements for the prototype are briefly described below.

Table 6: Functional Requirement number 1

Requirement #: 1	Event/Use case #: 1
Description: The system shall load data from the individual device's database, i.e. Dexcom CGM device, to the central repository (database).	
Rationale: To make the data accessible to the system.	
Source: Author and Background knowledge from Literatures	
Fit Criterion: The data shall be accessed by the system components.	
Dependencies: None	Conflict: None

Table 7: Functional Requirement number 2

Requirement #: 2	Event/Use case #: 2
Description: The developed system shall make daily monitoring of infectious disease outbreak.	
Rationale: Daily make monitoring of infectious disease outbreak based on the inputs.	
Source: Author	
Fit Criterion: The daily monitoring and the detected outbreak results shall agree with the preset timeframe.	
Dependencies: None	Conflict: None

Table 8: Functional Requirement number 3

Requirement #: 3	Event/Use case #: 3
Description: The developed system shall make a prediction of future BG values.	
Rationale: To follow the individual's BG evolution.	
Source: Background knowledge from Literatures	
Fit Criterion: The prediction shall agree with the actual BG reading.	
Dependencies: 1	Conflict: None

Table 9: Functional Requirement number 4

Requirement #: 4	Event/Use case #: 4
Description: The developed system shall make comparison of the individual's predicted BG values and the measured BG values.	
Rationale: To detect deviation of the individual's BG from the normal.	
Source: Author and Background knowledge from Literatures	
Fit Criterion: The prediction result shall agree with the measured blood glucose.	
Dependencies: 1 and 2	Conflict: None

Table 10: Functional Requirement number 5

Requirement #: 5	Event/Use case #: 5
Description: The developed system shall detect the individual's significant deviation of BG.	
Rationale: Enable to detect the presence of any infectious disease outbreak.	
Source: Author and Background knowledge from Literatures	
Fit Criterion: The system should detect the presence of BG deviation with infected individual.	
Dependencies: 1,2,3, and 4	Conflict: None

Table 11: Functional Requirement number 6

Requirement #: 6	Event/Use case #: 6
Description: The developed system shall send a notification signal to the concerned bodies using SMS.	
Rationale: Enable users to be aware of the infectious disease outbreak.	
Source: Background knowledge from Literatures	
Fit Criterion: The users should receive the notification signal.	
Dependencies: 1,2,3, and 4	Conflict: None

Table 12: Functional Requirement number 7

Requirement #: 7	Event/Use case #: 7
Description: The developed system shall send an Email containing the detected outbreak depicted on a regional map of interest.	
Rationale: Enable users to view the spatio-temporal distribution of the outbreak.	
Source: Background knowledge from Literatures	
Fit Criterion: Users shall receive and view the outbreak patterns.	
Dependencies: 1,2,3 and 4	Conflict: None

Table 13: Functional Requirement number 8

Requirement #: 8	Event/Use case #: 8
Description: The developed system shall store the daily results of monitoring and analysis.	
Rationale: Enable users to view it at any point of time in the future.	
Source: Author	
Fit Criterion: The user can query and search past daily analysis.	
Dependencies: 1,2, 3 and 4	Conflict: None

Table 14: Functional Requirement number 9

Requirement #: 9	Event/Use case #: 9
Description: The product shall allow other systems to access the detected outbreak patterns.	
Rationale: Enable decision support systems to access the patterns.	
Source: Background knowledge from Literatures	
Fit Criterion: Users shall view the spatio-temporal distribution of the detected outbreak patterns.	
Dependencies: 7	Conflict: None

5.6. Use Case

The system boundary are defined along with the interaction between the developed system and different actors (users). Based on the above requirements specification, a use case is developed as shown in the Figure 12. The use case entirely shows the interaction of the actors (users) with the system and also the connection among them and the system component itself. A trial version of the Enterprise Architect v.10.0, SPARX Systems©[9] was used to create the use case diagram given in Figure 12.

[9]Enterprise Architect website http://www.sparxsystems.com/products/ea/trial.html

Use Case#:1 Get the measured blood glucose data

Purpose: Read the daily measured data from the mobile device, i.e. Dexcom CGM, and store it in the system repository.

The procedural events are executed in the following ways:

→ System check calendar for data extraction.

→ System reads the data from the individual's mobile device, i.e. Dexcom CGM device's database.

→ System formats the data.

→ System stores the data.

Use Case#:2 Daily Outbreak Detection

Purpose: Make time triggered detection of outbreak based on daily measurements from the mobile devices, i.e. Dexcom CGM device.

The procedural events are executed in the following ways:

→ System checks the calendar.

→ System compares the current time with the preset time.

→ Execute the detection algorithm if the current and the preset time agree.

Use Case#:3 Blood Glucose prediction

Purpose: The system predicts the individual's blood glucose based on the available information of the history of blood glucose evolution.

The procedural events are executed in the following ways:

→ System checks the calendar.

→ System retrieves stored data from the mobile devices, i.e. Dexcom CGM device's database in to the system database.

→ System makes a prediction based on these data.

→ System calculates prediction interval.

→ System stores the result.

Use Case#:4 Compare the predicted and measured blood glucose

Purpose: The system compares the individual's measured and predicted blood glucose intervals.

The procedural events are executed in the following ways:

→ System retrieves the current predicted and measured blood glucose data.

→ System makes a comparison.

→ System stores the result.

Use Case#:5 Outbreak detection

Purpose: The system counts the number of individuals with statistically significant deviated BG readings and issues outbreak if necessary.

The procedural events are executed in the following ways:

→ System retrieves the individual comparison result.

→ System counts the number of individual with significant deviation.

→ System compares with the preset threshold.

→ System sends a notification signal if necessary and stores the result.

Use Case#:6 Notification signal

Purpose: The system sends a notification signal with SMS indicating the presence of some form of infections.

The procedural events are executed in the following ways:

→ System retrieves address or phone numbers.

→ System prepares the information to be sent.

→ The system send the notification signals for the users.

Use Case#:7 Email

Purpose: The system sends an email containing the spatio-temporal distribution of the detected patterns.

The procedural events are executed in the following ways:

→ System retrieves email address.

→ System prepares and plots the pattern on the map if any outbreak pattern is detected.

→ The system send the information for the users.

Use Case#:9 Store Daily Analysis

Purpose: The system should store the overall analysis and results performed at each day.

The procedural events are executed in the following ways:

→ The system checks for calendar to check the specific date.

→ System aggregates the result and stores it along with the specific date.

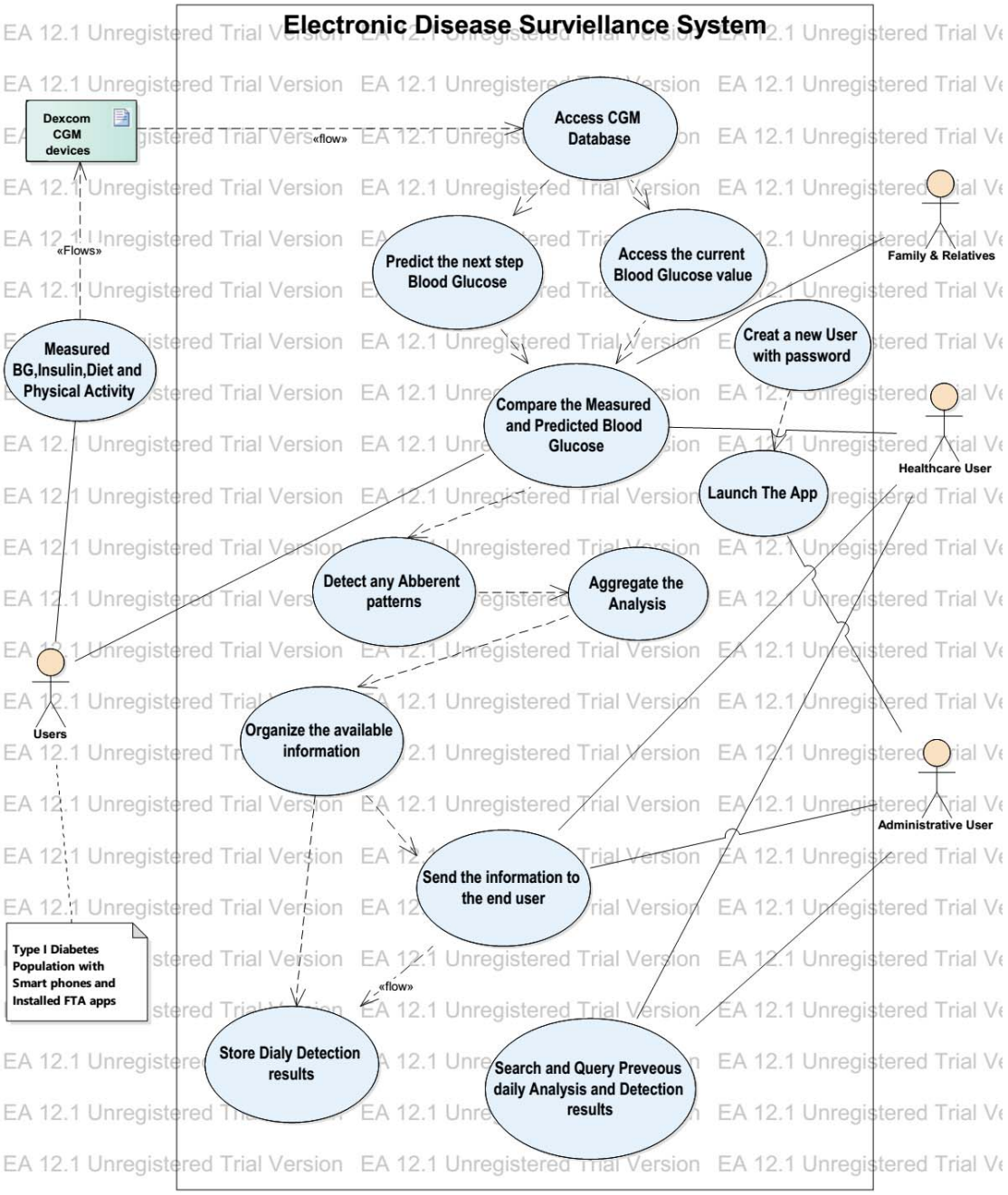


Figure 12: UML Use Case diagram.

Use Case#:8 Query Detected patterns

Purpose: The system should allow other systems to use the detected patterns and the blood glucose prediction results.

The procedural events are executed in the following ways:

→ User enter a query with specified date.

→ System searches the database.

→ System returns the result.

5.7. Non-functional requirements

5.7.1 Scalability

Scalability of a system defines its ability to respond to any future expansion and integration of other functionalities. Therefore, the developed system shall incorporate an ability to include more region under the surveillance system. Moreover, additional subjects and their associated data into the surveillance system.

5.7.2 Extensibility

The developed system shall be easy for extension of components and their functionalities, whenever such a need arises. Moreover, it shall be open for improvements and inclusion of more outbreak detection algorithms and mechanisms.

5.7.3 Usability

The developed system shall provide the required information regarding the detected patterns in a way that is easily understood by its users, as this will provide good opportunity for further investigation and quick decision making.

5.7.4. Security

Health data are private and sensitive when it comes to third party usage, therefore, security is the major concern while working on these data. The users' data are sensitive and shall be protected throughout the entire course of the systems. Therefore, during accessing the data from the user's mobile device, i.e. Dexcom CGM device or FTA app, a mechanism that protects the user's privacy should be implemented. This can be implemented through the users' consent and applying some form of deidentification procedures, where the user vital identifiers such as name, age, sex and others are removed from the data before it is transferred into the system database.

5.7.5. Legality

During transmission of the personal health data, it is necessary to have the consent of the users. This requires to persuade the individual users that their privacy and confidentiality are preserved during the entire course of the system. Therefore, it is necessary to prepare an individual consent form that comply with the international standards on the third party usage of personal health data. Moreover, it is necessary to consider highly secured means of transmitting the user information to the system database.

5.8. Summary

This chapter entirely describes the specification of the functional and non-functional requirements of the system based on Volere's requirements specification template. Most of the requirements were developed mainly from literatures, discussion with diabetes patients, diabetes experts and colleagues. The chapter concludes with the non-functional requirements that should be met by the developed system.

Chapter Six: System Design

6.1. Introduction

The purpose of this project is to design and develop an electronic disease surveillance system based on inputs from people with diabetes. The main idea is to use people with diabetes as the source of information for disease surveillance purpose. The main inputs of the system are the four keystone of diabetes, which include BG values, insulin injection, dietary and physical activity. However, due to limited availability of such data, we base our development on continuous BG readings (CGM) from Dexcom device. The whole aspects of the system are divided into development component and research component. The development component involves the development of the required software application based on the previously given requirements specification (see chapter 5). The research component involves developing the necessary mathematical models and determination of its associated parameters. However, due to time constraint we left the development of the required software application for future research and therefore is not considered in this thesis project. Consequently, this chapter describes the research component, which is the design aspects of the system including the architectural design and its associated components. Moreover, design consideration of the mathematical model along with the proposed solution are presented, including the BG prediction, moving window z-score process and outbreak detection mechanism. The developed system can predict the individual's BG values with a certain confidence interval and asses these predicted and observed BG readings for the presence of any aberrant patterns. Moreover, it also calculates the z-score value of each individual's BG readings based on a moving window and asses these values for the presence of outliers from a recent trend. If there is detection of a cluster of people with any aberrant patterns within a specific region and timeframe, it can send a notification signal for the concerned body or authorities and help to investigate by displaying the cluster on the map of the interest. The entire chapter presents the details of the design consideration under the following sections, data source design, architectural design, design of mathematical models (prediction model, prediction interval, moving window based z-score computation and surveillance).

6.2. Data Source Design

The data used in this project were collected from a small group of type I diabetes individuals, particularly based on two diabetes subjects. The data were taken from continuous blood glucose

monitoring (CGM) – Dexcom devices. The datasets are consisted of continuous blood glucose readings recorded on every five minutes' intervals for a period of one month. To make effective use of the data sets, vertical partition was carried out. The vertical partition involves separating the whole data sets in to two groups, i.e. training and validation data sets. The training datasets were used to compute and determine the autoregressive coefficients, whereas the validation datasets were used to test the validity of the system with unseen data. The BG datasets used for training and validating the developed system are shown in Figure 13. The whole dataset are consisted of 8495 consecutive data points, where the first 4000 (47%) data points were used for training and the rest 4495 (53%) data points were used for validating the model and to construct the prediction intervals.

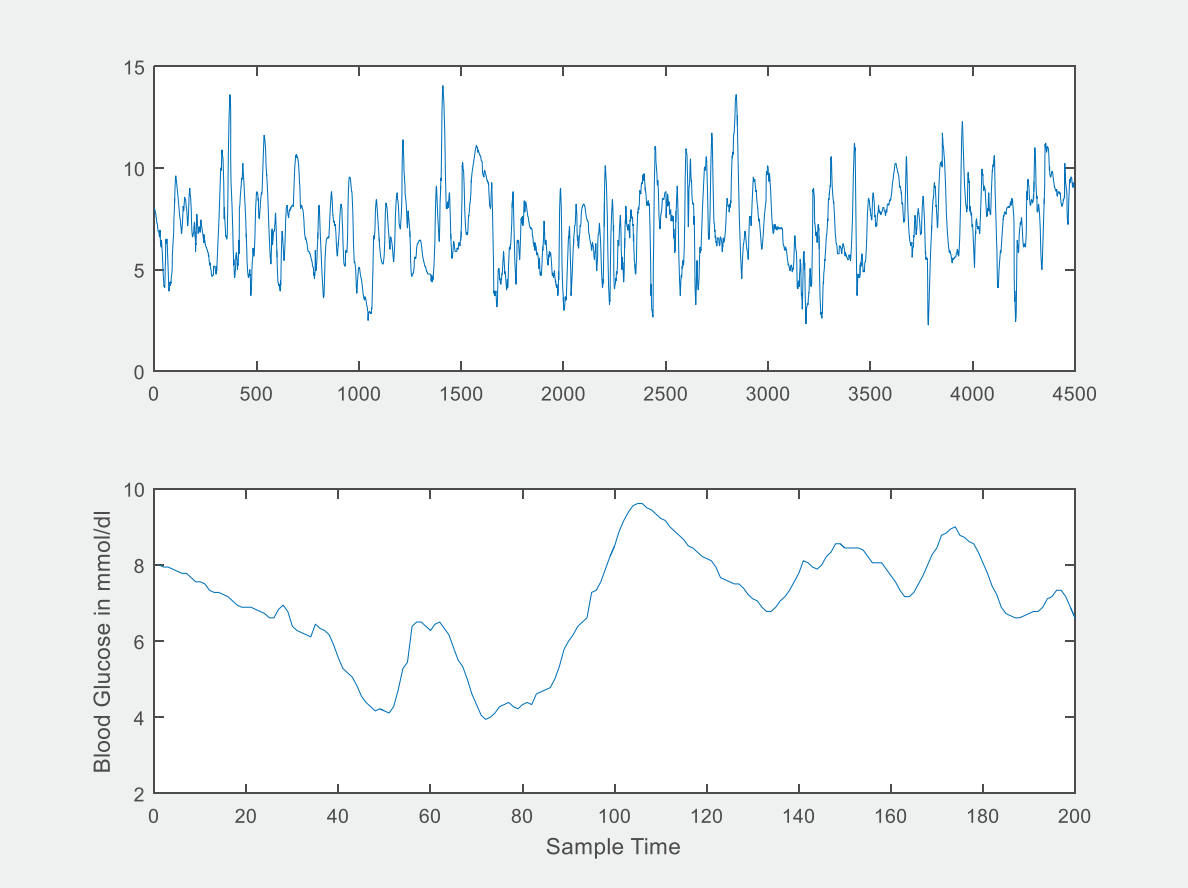


Figure 13: Plot of the entire sets and the first 200 data elements of the continuous blood glucose data of the first subject.

Moreover, an artificially simulated datasets were created and used for testing the performance of the system in detecting any statistically significant deviations of BG values. The simulated datasets are consisted of blood glucose shots/surge of varies size, duration and shape through a course of time, i.e. a day or more. It is simulated so as to resemble the elevated blood glucose evolution of an infected individuals, by considering various increments per minutes ($\frac{\Delta BG}{minutes(t)}$) and various time intervals of elevated BG. The blood glucose shots that resemble the case in response to an infections are simulated. The first simulated datasets as shown in Figure 14, are a type of steady growth, where the individual's blood glucose are shown to raise a maximum of 0.1 mmol/l per minutes and stays high for some consecutive hours, where thereafter shows a steady decays to the normal BG levels.

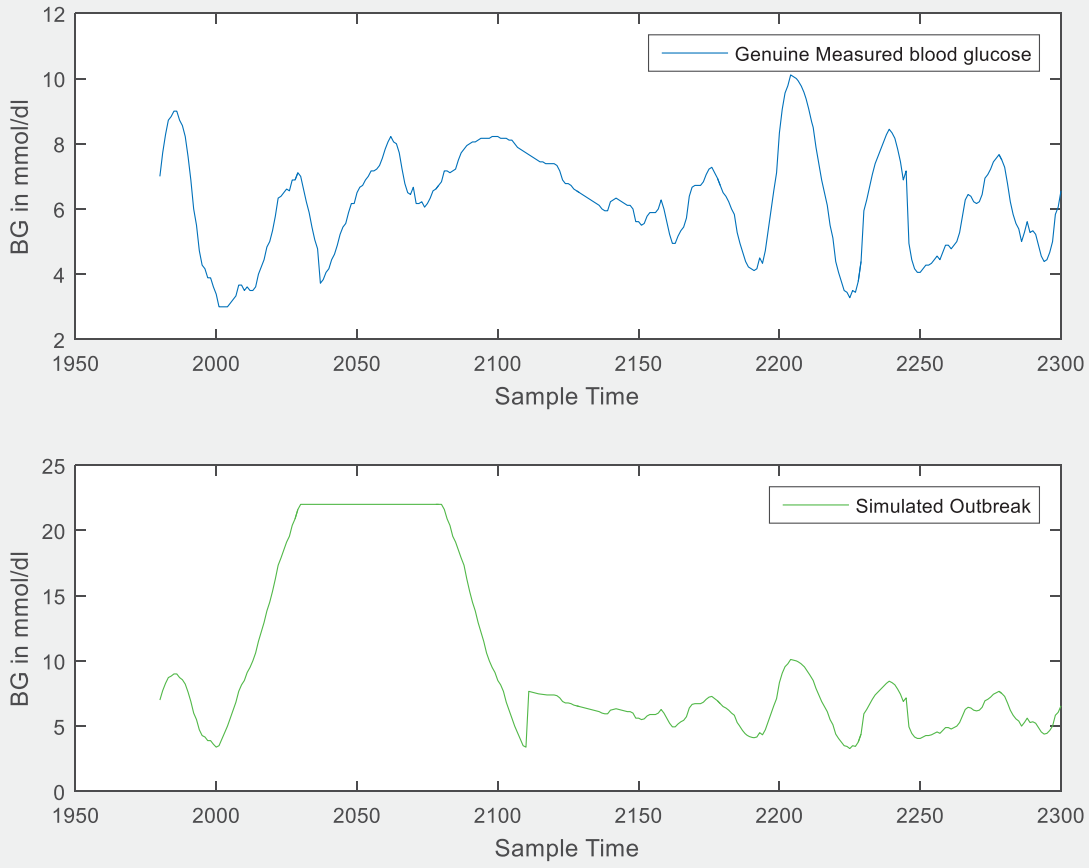


Figure 14: Artificially simulated steady growth of an individual blood glucose values in response to an infections.

The second simulated datasets, shown in Figure 15, are a type of sudden shot, where the individual's blood glucose readings are shown to attain high values out of a sudden and stays there for some consecutive hours, where it shows immediate decays thereafter.

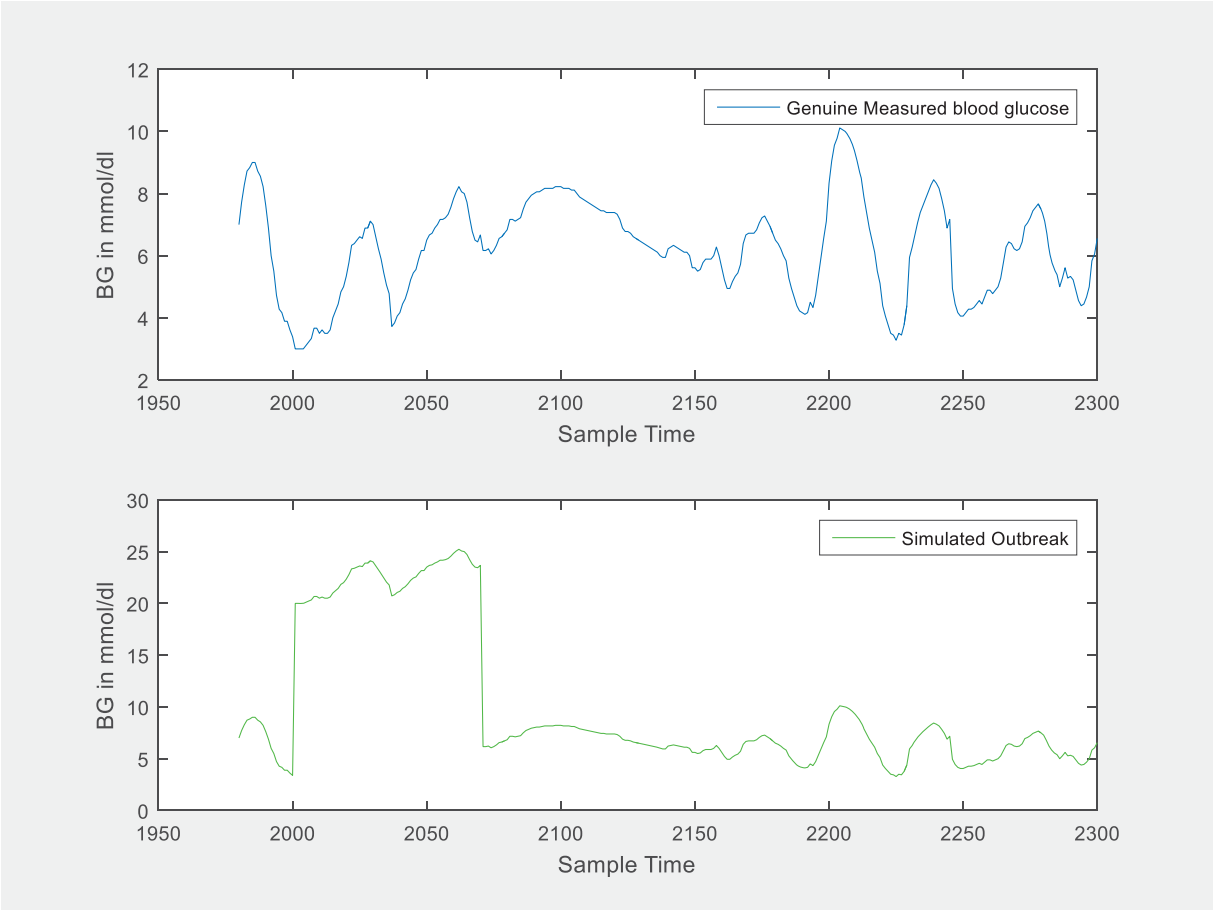


Figure 15: Artificially simulated sudden shots of an individual blood glucose values in response to an infections.

6.3. Architectural Design

System architecture can be centralized, distributed as two-tired or multi-tiered architecture. Though, in this study, we consider a centralized architecture, where the users' data are expected to be submitted to a centralized server, where the execution of aberrancy detection is also expected to be performed. In this approach, the privacy of the patients' data is a concern and therefore, it is necessary to use the patients' consent and to implement some kind of deidentification procedure to protect the data confidentiality of the patients. However, since we are using already extracted data based on the patients' consent, it is not a concern in this work. The developed system is

consisted of various modules: data collection, personalized health model, and analysis, reporting and information dissemination modules, as shown in the Figure 16. This architecture is partially adopted from the work of (Wickramasinghe et al., 2012), known as Nivārana, which is a system design and implementation focused on rapid response to epidemics.

I. ***Data Collection module*:** This module is required to collect data from the diabetes individuals residing in a given region, which is divided into equal cells (see section 6.8). The user's data are collected in a form containing of a user ID, BG values and geographical location (Årsand et al., 2005). The data are stored in its associated database after stamping with their corresponding cell identifier. The size of the data repository will depend on the size of the area the system covers. After proper data acquisition, it is necessary to record the geographical position where each samples were taken. This can facilitate the processing of the data depending up on its geographical location. The geographical location of the patient are determined by using GSM/3G network nodes for adequate positioning, which is described in *Årsand* (Årsand et al., 2005).

II. ***BG profile (Personalized health model)*:** This modules is expected to carry out prediction of blood glucose values depending on a set of input parameters, such as previous BG values, dietary data, amount of physical activity, amount of insulin injection, and others. It involves modelling a personalized health model, which mimic the blood glucose dynamics of the individual diabetes subjects. It keeps track of the individual's blood glucose fluctuations. This model needs to include as much parameters as possible, which affects blood glucose concentration, the like of insulin, physical activity, history of blood glucose value, body mass index, stress level, sleeping time , dietary intake, presence of illness and some other medication, smoking habit, periods (menstruation), alcoholism, allergies, effect of altitude and others.

III. ***Analysis module:*** At the time of computing, the analysis modules will carry out data analysis and outbreak detection. It is consisted of mathematical models such as interval and z-score computation that can compare and detect any statistically significant deviation. Moreover, aggregational analysis is capable of counting the maximum number of events based on three different approach, such as temporal cluster detection, spatial cluster detection, and spatio-temporal cluster detection**.**

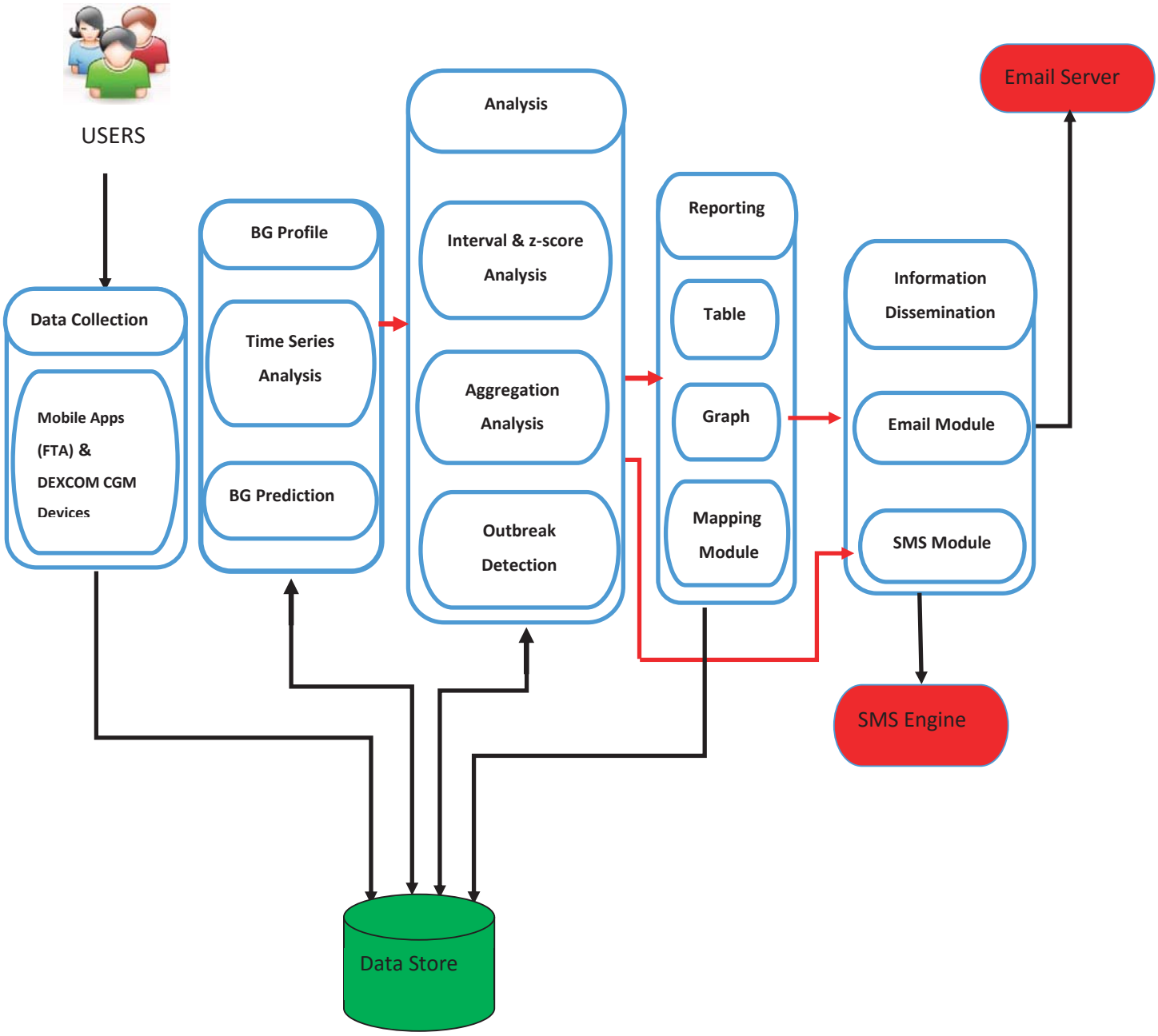


Figure 16: System Architecture of the developed system.

[Adapted from (Wickramasinghe et al., 2012)]

Temporal cluster detection is the process of identifying a maximum number of events within the specified fixed timeframe or most importantly within a fixed and moving time window. However,

spatial cluster detection involves identifying a maximum number of events within a specified fixed region of interest. It is also possible to implement both temporal and spatial cluster detection at the same time to have a spatio-temporal cluster detection**,** which involves identifying a maximum number of events within a fixed and moving time window and also within a fixed region of interest. In this project, spatio-temporal cluster detection are considered.

IV. ***Reporting*****:** if there are any detected patterns of outbreak, the system should organizes the information and make it ready for dissemination to the responsible body. Therefore, in order to meet the principal function of any disease surveillance systems, we need to implement a means of reporting. As a result, the function of this module is to prepare and organize the information about the current disease outbreak, using various means of presenting information, such as tables, graphs and mapping module.

V. ***Information Dissemination*****:** After having packed all the necessary disease outbreak related information, the information dissemination module is responsible for distributing the necessary information to the concerned bodies or authorities. The information dissemination module has two means of disseminating the necessary information, i.e. SMS and Email. For first notification purpose, SMS will be sent and then email containing adequate information regarding the outbreak will also be sent to the responsible persons. The email will contain information such as spatial and temporal distribution of the disease outbreak on a map of the region, the degree of severity and others.

6.4. Method selection

Broadly, the method used in literature for prediction (follow up) of blood glucose trends are grouped into two categories, physiological and black box (data-driven) model (see chapter 2, section 2.4). The former group include formulating mathematical model that simulate the underlying physiology of the glucose – insulin regulatory system. The second group provides data-driven model, which can predict BG concentrations based on only the historical records (information) of existing input-output data. In recent times, black-box model has shown to achieve good prediction with a specific prediction horizon (PH), among which time series approaches are found to be reliable for prediction (Jabali, 2013; Stahl et al., 2009). There are various kinds of such models used in literature, such as structural, state space, neural network, and others (Pappada et al., 2011; Shanthi et al., 2012; Stahl et al., 2009). During method selection, we give emphasis on the trade-off between simplicity and accuracy, stability, and its effectiveness for predicting an

interval. Moreover, the capability of the method to determine the predicted values based on more recent data or history are also considered. Based on the literature review (see chapter 3), a linear time series model, a version of AR model is found to predict well in a limited prediction horizons (Jabali, 2013; Stahl et al., 2009). For example, (Jabali, 2013) have reported the success of Autoregressive Moving Average (ARMA) in predicting of BG levels and also (Stahl et al., 2009) achieves a 99.9% accuracy in a single step prediction horizon with Exogenous input Autoregressive Moving Average (ARMAX) method. Consequently, AR model is considered for developing our model, where we proposes to predict intervals rather than point values. It is obvious that supplementing point predictions with an interval predication is one way of assessing the uncertainty involved with the other diabetes related parameters (Chatfield, 2000). Therefore, the method is implemented so as to predict a certain range of value, prediction interval (PI), using a point prediction value along with the variance of the empirical error distribution between the set of step ahead BG predictions and actual BG readings.

Moreover, a moving window based z-score process is selected since it is capable of detecting deviation that can be quantified in terms of the number of standard deviation from the mean (see chapter 2, section 2.5). Moreover, the moving window version is considered to follow the trend in blood glucose dynamics of the individual's subject using the most recent trends, which is necessary to capture the subject's cyclical habits within a day, week or longer periods.

6.5. Design of Mathematical Models

In this section, the proposed mathematical solutions for the electronic disease surveillance system based on inputs from people with diabetes are given.

6.5.1. Task overview and the proposed Algorithms

The high level block diagram representation of the blood glucose deviation detection algorithm is given in the Figure 17 and 18. The proposed algorithms are of two types, blood glucose prediction and moving window z-score process. The blood glucose prediction based model, as shown in the Figure 17, is consisted of different tasks such as compute expected BG value, obtain current BG measurement, compute test and evaluate test. For instance, the value generated from the compute expected BG value and obtain current BG measurement tasks is used to compute the test value and the final result is evaluated to decide the need of any alarming signal based on the current analysis.

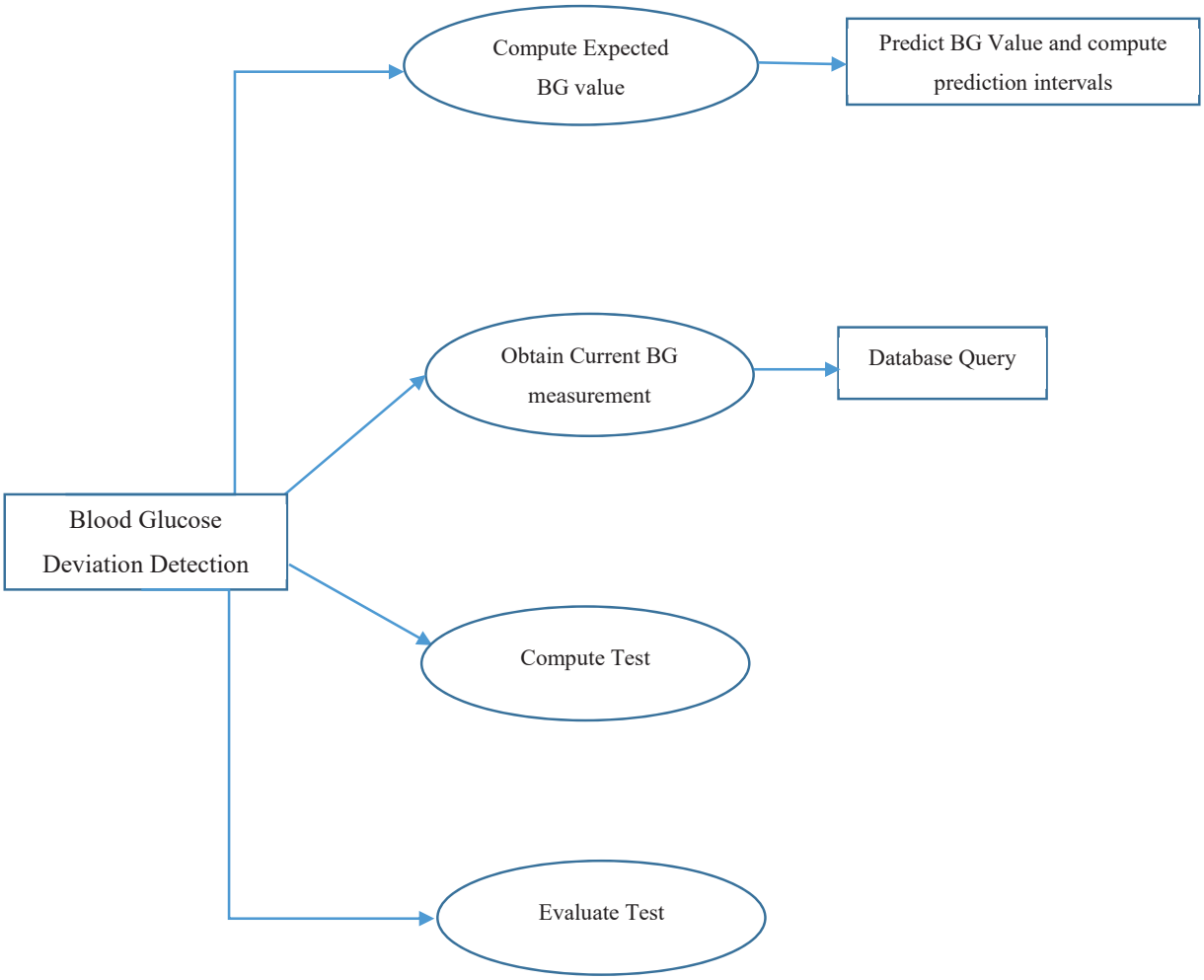


Figure 17: Blood glucose prediction and detection Algorithm.

The moving window z-score model, as shown in the Figure 18, is consisted of different tasks such as Moving window based z-score computation, Obtain Current BG measurement, Compute Z-score values and Evaluate Test. The Moving window based z-score computation is used to compute the running mean and standard deviation of the BG values in the current window, w. Therefore, the mean and standard deviation are used to compute the z-score of the current blood glucose reading. This z-score value will be compared against a preset threshold value, which is determined by analyzing the respective sensitivity vs. threshold and specificity vs. threshold characteristics. The final result is used to decide the need of any alarming signal based on the current analysis.

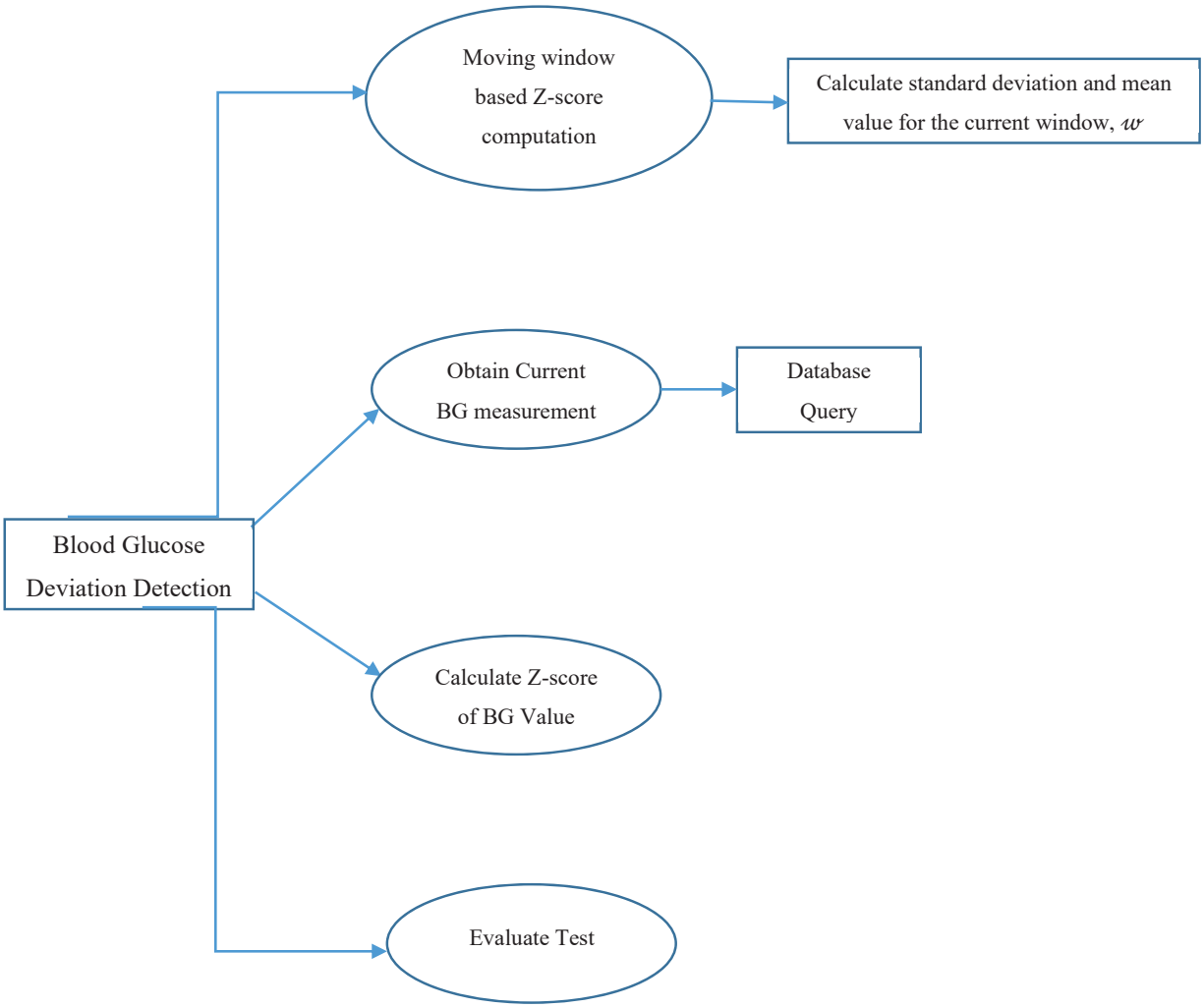


Figure 18: Moving window based z-score process and the detection Algorithm.

6.5.2. Blood glucose prediction based model

The first model, the blood glucose prediction model, is based on an interval prediction mechanism that can compute confidence intervals based on the point prediction and the empirical distribution of errors between the set of predicted and observed BG values, as shown in the Figure 19. The detailed design of the mathematical model, the prediction model and the prediction interval, are given under the model building section.

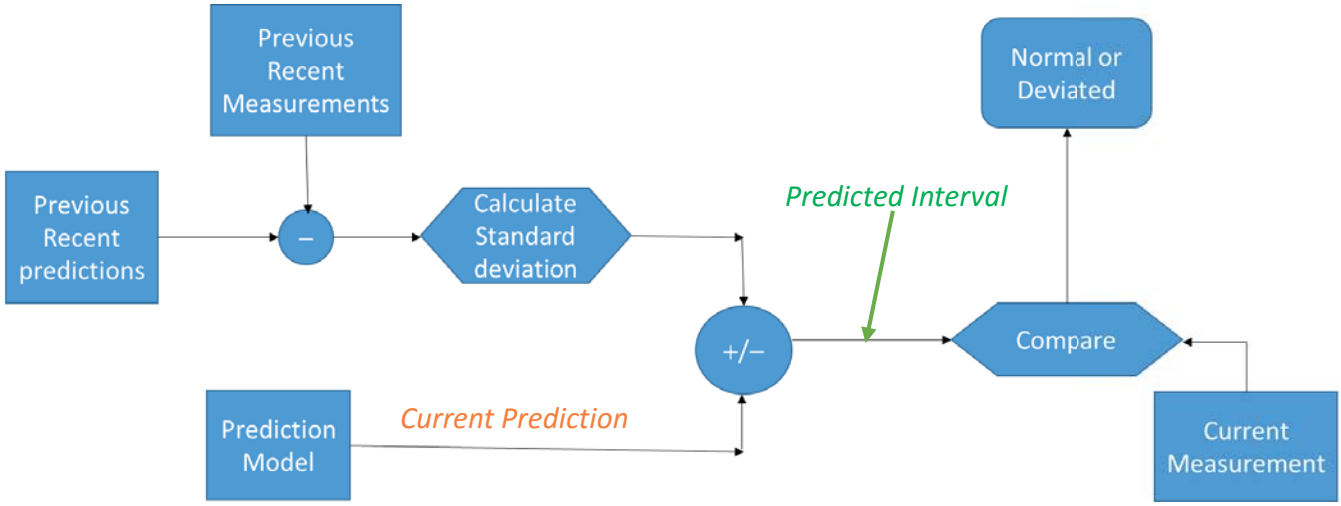


Figure 19: The prediction interval based model.

6.5.2.1 Model Building

The BG prediction model is the mathematical representation of the glucose-insulin dynamics related to an individual subject. It serves to describe the BG evolution of an individual by modeling the systematic variation and the unexplained variation (or 'error' component). The systematic variation can facilitate computation of good point predictions, while the unexplained variation will help to compute prediction intervals (Chatfield, 1993). As shown in Figure 20, the logic of the developed system is to use the systematic variation of the most recent BG records so as to predict the future blood glucose values. Moreover, the unexplained variation (or 'error' component) are exploited by computing the empirical distributions of errors between the set of actual and predicted BG values, which is used to construct a prediction intervals. To solve this logic with time-series approach, it is necessary to take BG values as a time series random variable. Let $\mathcal{X}, \mathcal{Y}$ be random time series variables as described below:

$$\text{let } \mathcal{X} \text{ be the set of measured or observed blood glucose values}$$

$$\text{let } \mathcal{Y} \text{ be the set of predicted blood glucose values}$$

$$\mathcal{X} = \{x_1, x_2, x_3, x_4, x_5, x_6 \dots \dots \dots \dots \dots . x_n\}$$

$$\therefore \mathcal{Y}_n(h) = \mathcal{F}(\mathcal{X}) \quad \text{.....Eq. 10}$$

where $\mathcal{F}(\mathcal{X})$ is the prediction model that takes the random variable input (blood glucose readings) to make prediction of the future blood glucose values.

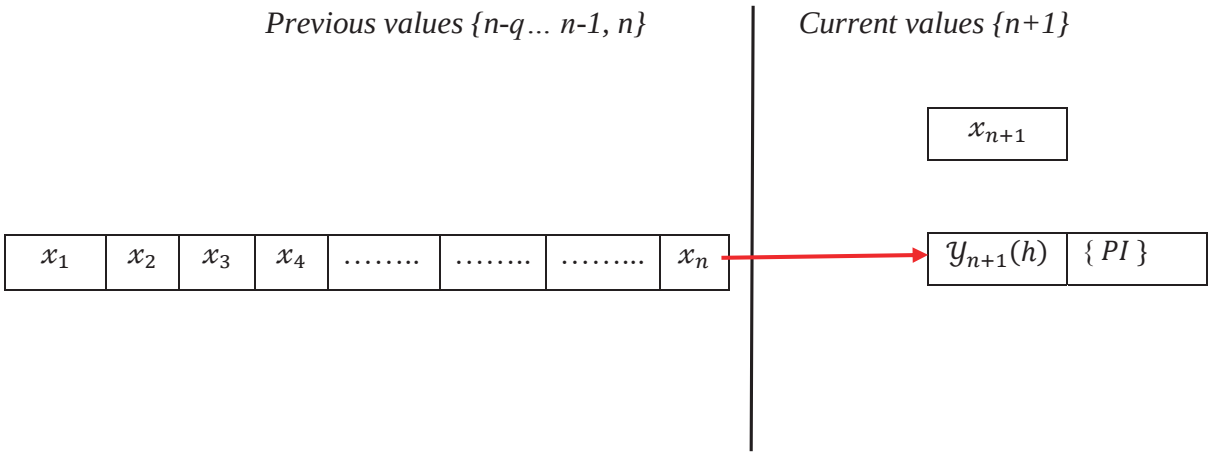


Figure 20: State of the developed model.

The prediction error is the difference between the observed or measured blood glucose values and the predicted blood glucose values with in the same prediction horizon, as given in the equation below:

$$e_n(h) = y_n(h) - X_{n+h} \quad \text{.....Eq. 11}$$

The prediction errors are mostly dependent on the specified prediction horizon considered during computations. Therefore, it is necessary to compute the empirical distribution of error $e_n(h)$ for each prediction horizon considered.

6.5.2.2. The Prediction model

The prediction model is based on two version of Autoregressive (AR) models, Autoregressive (AR) and Autoregressive Moving Average (ARMA) (see chapter 2, section 2.5.2.1). The kind of prediction is an interval based with a certain confidence of seeing the future values in the predicted range, where the interval are calculated based on the recent empirical distribution of errors between the actual value and the predicted value. The type of model considered here is goodness-of-fit to past data.

- Autoregressive using Yule Walker Algorithm

The autoregressive equation (see chapter 2, section 2.5.2.1) used in this scenario has the following form:

$$y(n+1) = \mathcal{A}(q)y(n) \quad \text{.....Eq. 12}$$

$$a_n y_n = a_{n-1}y_{n-1} + a_{n-2}y_{n-2} + a_{n-3}y_{n-3} + a_{n-4}y_{n-4} \dots\dots\dots\dots$$

Where a_n are the autoregressive coefficients and y_n are the blood glucose values at time *n*.

- Autoregressive using Ratio of consecutive data points

Here an autoregressive equation that can capture the trends based on the ratio of consecutive readings are proposed. It uses the rate of change of the ratio between two consecutive data points to estimate and predict the future blood glucose values.

The autoregressive equation used in this scenario has the following form:

$$a_n \frac{y_n}{y_n - 1} = a_{n-1} \frac{y_{n-1}}{y_{n-2}} + a_{n-2} \frac{y_{n-2}}{y_{n-3}} + a_{n-3} \frac{y_{n-3}}{y_{n-4}} + a_{n-4} \frac{y_{n-4}}{y_{n-5}} \dots\dots\dots\dots$$

Where a_n are the autoregressive coefficients and y_n are the blood glucose values at time *n*. Therefore, the next step blood glucose value are computed as follows.

$$a_n y_n = y_{n-1} * (a_{n-1} \frac{y_{n-1}}{y_{n-2}} + a_{n-2} \frac{y_{n-2}}{y_{n-3}} + a_{n-3} \frac{y_{n-3}}{y_{n-4}} + a_{n-4} \frac{y_{n-4}}{y_{n-5}} \dots\dots\dots\dots) \quad \text{.....Eq. 13}$$

- Autoregressive Moving Average using Yule Walker Algorithm

The autoregressive equation (see chapter 2, section 2.5.2.1) used in this scenario has the following form:

$$\mathcal{A}(q)y(n) = \mathcal{C}(q)e(n) \quad \text{.....Eq. 14}$$

$$a_n y_n = a_{n-1} y_{n-1} + a_{n-2} y_{n-2} + a_{n-3} y_{n-3} + a_{n-4} y_{n-4} \dots + \mathcal{E}_n + b_{n-1} \mathcal{E}_{n-1} + b_{n-2} \mathcal{E}_{n-2} + \dots$$

Where a_n is autoregressive coefficients, b_n is moving average coefficients and y_n is the blood glucose values at time *n* and $\mathcal{E}_n$ are normally distributed Gaussian noise with zero mean and standard deviation σ.

6.5.2.3. Model order selection

One of the necessary and important step in developing autoregressive model is identification and selection of an appropriate model order. A system identification toolbox along with the partial autocorrelation function (PACF) was used to identify the optimal model order. For example, as shown in Figure 21, the values of the partial autocorrelation sequence that reside outside the 95% confidence bounds occur at lags 1, 2, 3,4 and 5. This indicates that the correct model order for the AR process is 6, where beyond this point there is no correlation between terms.

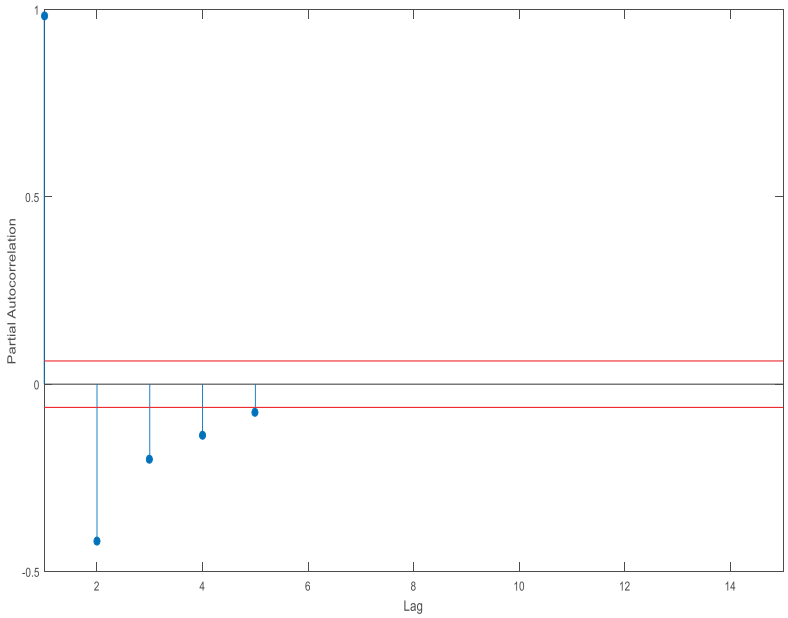


Figure 21: Partial autocorrelation function (PACF).

6.5.2.3. Prediction interval

The prediction intervals are computed for a certain level of significance α based on the empirical distribution of error between the measured and predicted values. $(a\ 100(1-\alpha)\%\ P.I\ for\ X_{n+k})$ is given by assuming an unbiased prediction with PMSE as defined with Eq.15.

$$E[e_n(k)^2]\ = Var[e_n(k)]\ and\ the\ prediction\ errors\ are\ normal$$

$$\therefore \tilde{y}(n) = y(n) \pm z_{\frac{\alpha}{2}} \sqrt{Var[e_k(n)]} \quad \text{.....Eq. 15}$$

Where $y(n)$ is the point prediction obtained from the prediction models and $\tilde{y}(n)$ is the final predicted interval to be used in the electronic disease surveillance systems. Generally, there are two ways of computing $Var[e_h(n)]$ and the required prediction intervals, known as Model based PI (Theoretical PMSE Formula) and empirically based PI (Chatfield, 1993). The former PMSE (Prediction Mean Square Error) based computing requires to have put an assumption that the fitted model is optimal. However, the latter empirically based computing generally require fewer (or even no) assumptions about the underlying model, since the variance of the error are calculated

from the distribution of the errors from past data and have much promise, and are starting to be used (Chatfield, 1993). Therefore, we use empirically based PI to compute our prediction intervals. The simplest type of procedure involves applying forecasting method to past data, finding the within-sample 'forecast' errors (i.e., the residuals) at 1, 2, 3 ... steps ahead for forecasts made from all available time origins in the period of fit, and then finding the variance of these errors at each lead time. Let $S_{e,h}$ denote the standard deviation of the *h*-steps-ahead errors. Then an approximate empirical *100 (1 −α) % P.I.* for Y_{n+h} is given by $\widehat{y_n}(h) \pm z\alpha_{/2} S_{e,h}$. Generally, we consider both the within and out of sample 'forecast' errors as a base of calculating our prediction intervals.

6.5.3 Moving window based z-score process

The second model, the moving window based z-score process compute the z-score values using the current blood glucose reading and the mean and standard deviation computed from previously recorded blood glucose data in a certain window size w, where the running mean and standard deviation are calculated for the data in the window (see chapter 2, section 2.5).

6.6. Outbreak detection mechanism (Surveillance)

Generally, the approach (algorithmic model) used to perform detection of disease outbreak in a disease surveillance systems is broadly categorized under three groups: regression methods, time series methods and statistical process control (Guillou et al., 2014). An outbreak detection mechanism that resembles the statistical process control and the time series method are developed using the interval prediction and the moving window z-score model respectively.

6.6.1. Prediction Interval based

The proposed solution is like a control chart/statistical process control algorithm, where the controls are determined by the intervals predicted from the individual's records of blood glucose readings defined by the AR models given above. From the equation of the interval prediction given above, the upper and lower limit can be defined as follows:

$$\begin{cases} Upper\ Control\ Limit\ (UCL) = \widehat{y_n}(h) + z\alpha_{/2} S_{e,h} \\ Lower\ Control\ Limit\ (LCL) = \widehat{y_n}(h) - z\alpha_{/2} S_{e,h} \end{cases} \quad \text{.....Eq. 16}$$

where $\widehat{y_n}(h)$ is the one step prediction of BG value and $S_{e,h}$ are standard deviation of errors

Logic: The immediate future actual BG reading/measurement is expected to lie within these limit, which is calculated from the immediate past history. The details are given in the figure below,

$$LCL \leq Y_{n+h} \leq UCL, \quad \text{.....Eq. 17}$$

$$where\ Y_{n+h}\ is\ the\ newly\ measured\ BG\ value.$$

As can be seen from the Figure 22, the actual blood glucose values can be effectively monitored and controlled by these upper and lower control limits.

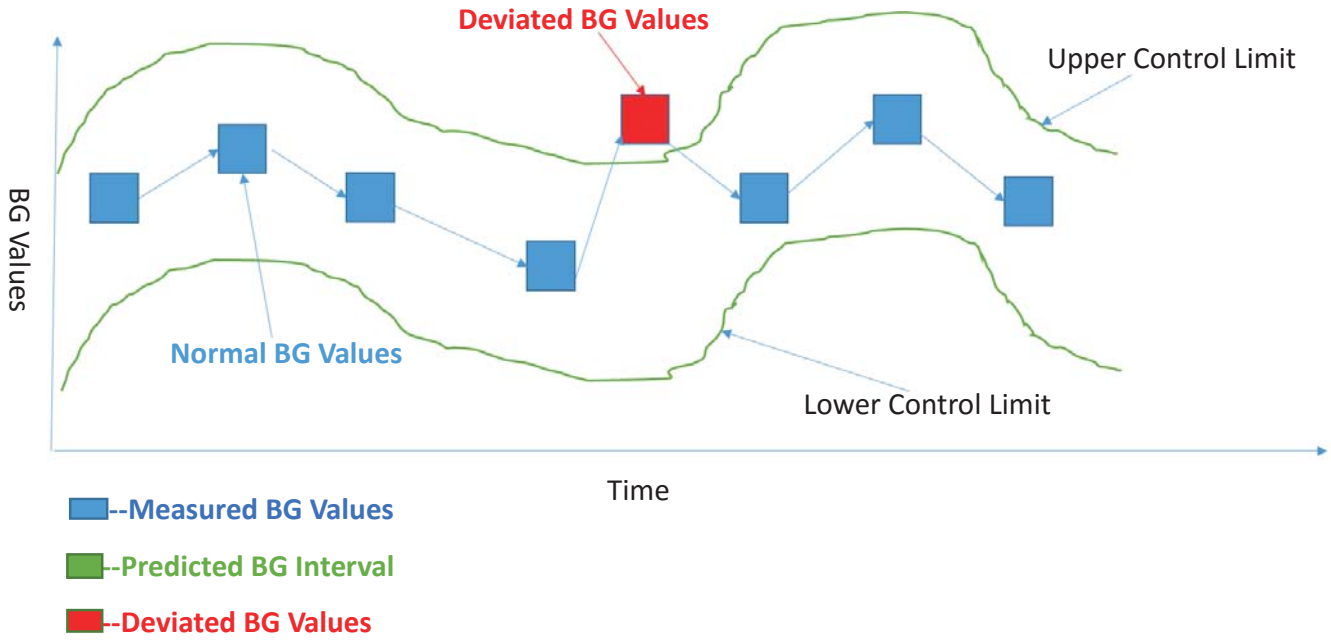


Figure 22: Proposed solution for the detection algorithm of the disease surveillance (blood glucose prediction based).

6.6.2. Moving window z-score process based

The proposed solution is like a time series based outbreak detection algorithm, where the detection of aberrant patterns are determined by a specific threshold values. The threshold is defined by the number of standard deviations from the mean value. For example, as shown in Figure 23, to detect a pattern of anomalies or outliers in the presented data a threshold value of three standard deviations are sufficient. Therefore, by setting a window dependent threshold value one can effectively and efficiently detect the aberrant patterns for an individual's blood glucose readings. However, setting the threshold values require a compromise between accuracy and timeliness; setting high threshold might ignore true positive values and using low threshold might allow false positive cases to be considered.

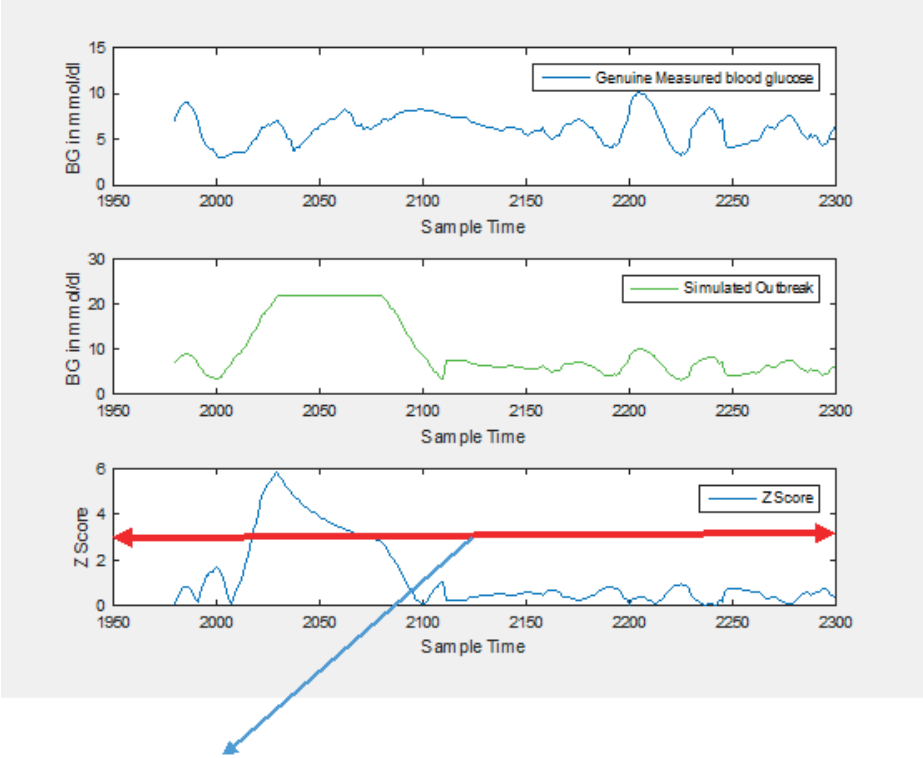


Figure 23: Proposed solution for the detection algorithm of the disease surveillance (moving z-score based).

6.7. Performance metrics

Performance metrics are important for evaluating the system, which should be based on widely accepted scientific standards and methods. The performance of the developed system is evaluated based on the metrics defined in this section. Since our solution is consisted of two components, i.e. prediction and outbreak detection, therefore, a separate evaluation metrics are used for each of the components. The first component is the prediction mechanism, which is evaluated based on the Root Mean Square Error[10] (RMSE) and Mean Square Error[11] (MSE) functions as defined in the equation below:

[10] https://www.kaggle.com/wiki/RootMeanSquaredError

[11] https://en.wikipedia.org/wiki/Mean_squared_error

$$MSE = \frac{1}{n}\sum_{i=1}^{n}\left(Y_i - \tilde{Y}_i\right)^2, \quad \text{.....Eq. 18}$$

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(Y_i - \tilde{Y}_i\right)^2}, \quad \text{.....Eq. 19}$$

where Y_i and $\tilde{Y}_i$ are the actual and predicted BG values respectively

However, the second component, the outbreak detection mechanism is evaluated based on different performance evaluation criteria. The developed solutions for the outbreak detection mechanism are of two types, interval prediction based and the moving window z-score process based algorithm. The first approach, the interval prediction based algorithm is evaluated based on the accuracy of capturing deviated BG readings using the predicted upper and lower control limits. However, the second approach, the moving window based z-score process is evaluated based on specificity, sensitivity, positive predictive value (PPV) (see chapter 2, section 2.8) (Drewe et al., 2012; WHO, 2006). In this project, due to the absence of large sample size so as to simulate an artificial outbreak scenario, specificity, sensitivity, and PPV of the surveillance case definition are used to evaluate the system and also used to determine the best operating threshold of the system.

6.8. Geographical location of the diabetes subjects

It is important to locate the geographical location of diabetes subjects' so as to estimate the accurate number of cluster with an elevated blood glucose value (surveillance case definition). Therefore, the region of interest is partitioned into different small equal cells as shown in Figure 24, where the accurate location of the users are determined with GPS/GSM mobile network's address. The user is first placed into one of the cells based on the address input at the time of submitting the necessary data, as shown in the Figure 24. This is a kind of dynamic mechanisms, where the user's location is resolved by the time of data submission and also it puts the mobility of the users into consideration. As a result, the number of subjects in each cells that meets the surveillance case definition (elevated blood glucose value) can easily be computed and tested for the presence of any cluster above the specified threshold (expected number of people meeting the surveillance case definition). For example, let us say that C1 can encompass some part of the city as just the other do. Any users, who reside in C1 during the time of data submission are resolved to be C1. However, any user might move to a different cell, say C14, next time when he/she submits the data, which then is resolved to be C14.

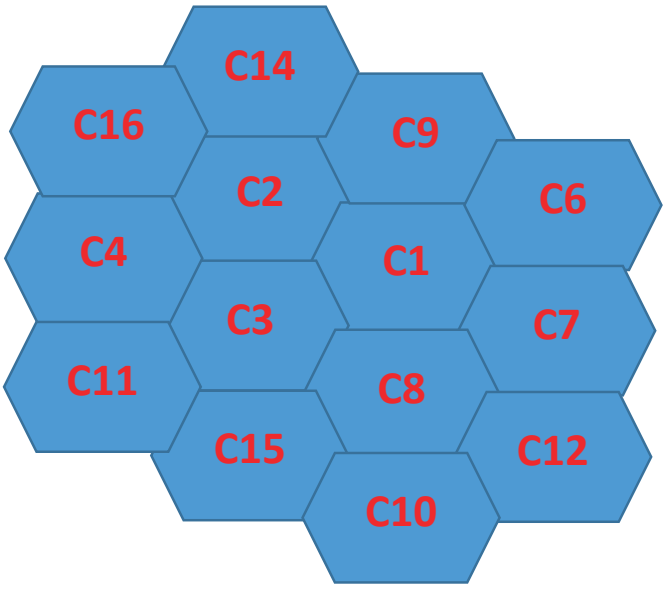


Figure 24: Partitioning the entire region of the map into equal cells.

6.8.1. Outbreak Detection Matrix

In order to detect subjects meeting the surveillance case definition (elevated BG values) at the same sampling time, a mechanism that can make the process simple and easy is necessary. Therefore, an outbreak detection matrix is proposed so that at each sampling time the individual's status is updated on its allocated slot on the outbreak detection matrix. Each row from the corresponding detection matrix is designated to indicate the status of an individual. Let Z be MxN detection matrix, where M is the sequence of sampling time and N represents the status of each individuals as shown in the matrix below:

$$Sample\ sequence/time \begin{vmatrix} \mathcal{S}_1 & \mathcal{S}_2 & \mathcal{S}_3 & \mathcal{S}_4 & \mathcal{S}_5 & \mathcal{S}_6 \\ 0 & 1 & 0 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 0 & 1 \\ 1 & 1 & 1 & 1 & 1 & 1 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & 1 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 & 0 \end{vmatrix}$$

For example, from the above outbreak detection matrix all subjects have elevated blood glucose values at the sampling time of 3. This is computed as

$$f(t) = \mathcal{S}_1@\mathcal{S}_2@\mathcal{S}_3@\mathcal{S}_4@\mathcal{S}_5@\mathcal{S}_6, \ldots\ldots\ldots\ldots\ldots\ldots Eq.\ 20$$

where @ is a summation (addition) function. Therefore, $f(t)$ is always compared to a pre-set threshold value for that particular cells.

6.9. Timeliness and Accuracy

The accuracy and timeliness of the outbreak detection mechanism are the two most important variable that needs careful investigation for building a successful disease surveillance system. Early detection and accurate detection are a complimentary issue in disease surveillance systems. According to our surveillance case definition, accurate detection requires series of elevated blood glucose readings before issuing an alarm, whereas early detection (timeliness) requires the use of the individual's first elevated BG reading without further waiting for more conformation. Relying on the individual's first elevated BG reading might affect the accuracy of the detected pattern. In order to solve this complimentary issue, it is necessary to make a compromise and to develop a mechanism that is capable producing an acceptable solution. For example, as shown in Figure 25, the outbreak detection system is expected to detect a high number of people within a single cell to operate only with the individual's first elevated BG reading. However, relying on the individual's previous consecutive elevated blood glucose readings for conforming outbreak can reduce the number of expected people within a cell to a small value as this might guarantee the presence of some form of infection.

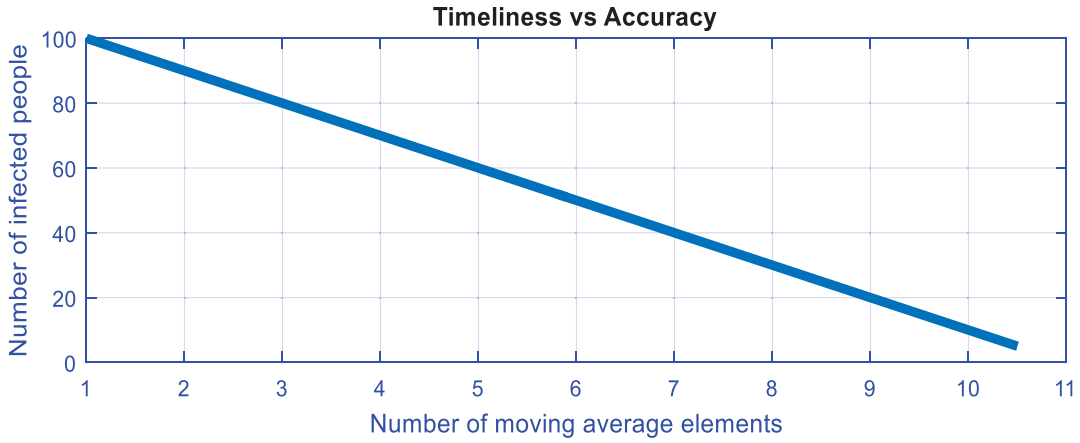


Figure 25: Timeliness vs. Accuracy.

Chapter Seven: Implementation and Testing

7.1. Introduction

This chapter gives brief descriptions of the implementations for the electronic disease surveillance system based on inputs from people with diabetes. The entire descriptions are given based on the system design given in the previous chapter. The first section gives brief description of software, programming languages and technologies used to implement the system. After presenting the implementation techniques, afterwards brief description of test settings and testing results are presented.

7.2. System Implementation

7.2.1. Software and Programming Languages

The system was developed using MATLAB version R2015b software. MATLAB[12], also known as MATrix LABoratory, is a high-performance language mainly used for technical computing. The interesting concept of Matlab is that one can express the problem and the solution in familiar mathematical notation, mainly used for algorithm development, modelling, simulation, data analysis, exploration, and visualization and others. Matlab eases simulation through its comprehensive toolboxes that support different kinds of purposes. One of such a kind is the Econometrics toolbox, which is capable of simulating various prediction models including the autoregressive (AR) models. The availability of these toolboxes along with the author's experience with this software were the reason for choosing this language platform. From the Econometric toolboxes, various types of Autoregressive model were used to implement prediction of the individual's blood glucose dynamics.

7.2.2. Data sources

The developed system was implemented and tested based on two types of datasets, genuine (observed) and artificially simulated datasets. The first datasets, shown in Figure 13, the genuine (observed) datasets were used to train and validate the system for fitting the dynamics of the individual's blood glucose evolution. The whole dataset consisted of 8495 consecutive data points (recorded BG values), where the first 4000 (47%) data points were used for training and the rest 4495 (53%) data points were used for validating the model and to construct the prediction intervals.

[12] http://se.mathworks.com/products/matlab/

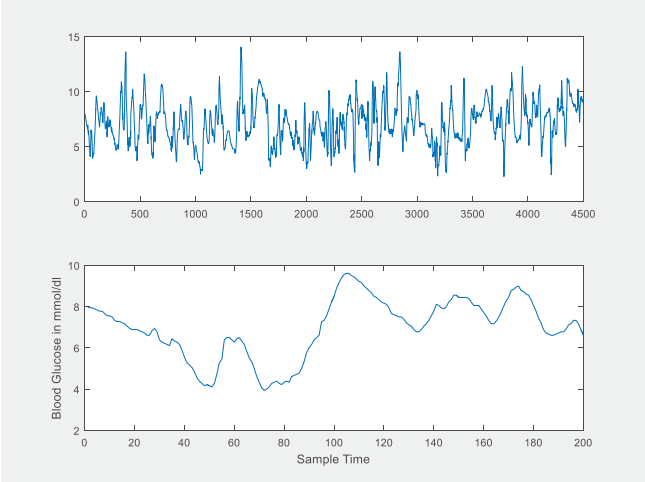


Figure 26: Plot of the entire sets and the first 200 data elements of the continuous blood glucose data of the first subject.

The second datasets, the artificially simulated datasets were used for testing the performance of the system in detecting any statistically significant deviations of blood glucose values from the recent observed trend. The simulated datasets as shown in Figure 14 & 15 (see the previous chapter), are a type of steady growth and sudden shot and simulated to resemble blood glucose evolution during the presence of infections.

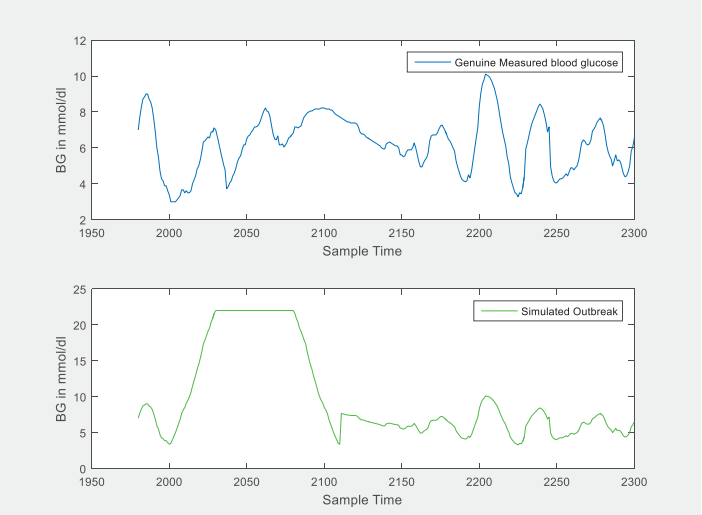


Figure 27: Artificially simulated steady growth of an individual blood glucose values in response to an infections.

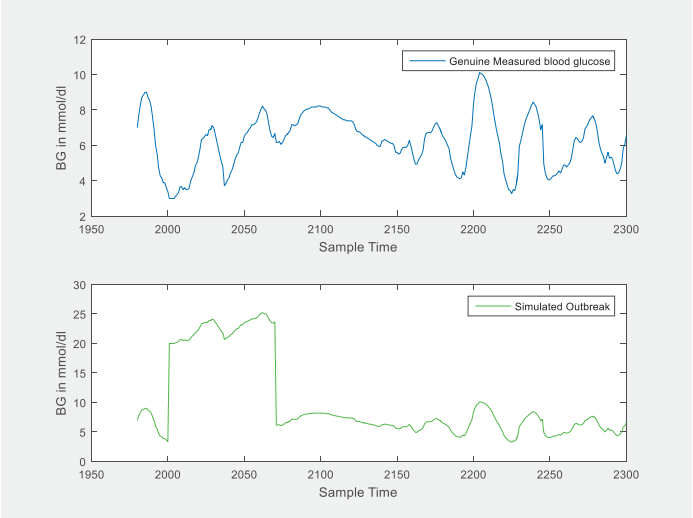


Figure 28: Artificially simulated sudden shots of an individual blood glucose values in response to an infections.

7.2.3. Auto-regression model

An Auto-regression model generally tries to relate and specify the output variable by a linear relationship of its previous values and a certain unexplained variation, known as a random disturbance signal. We developed an Auto-regression models, which predicts the single step ahead blood glucose evolution of an individuals. Both an Autoregressive (AR) and Autoregressive Moving Average (ARMA) were explored.

7.2.3.1. Autoregressive (AR)

Autoregressive (AR) is a single output with no inputs function, which uses the previous consecutive blood glucose readings to predict the next value in the sequence. The autoregressive coefficients were determined using the training datasets and the model were used to predict the unseen validation datasets. For example, the following Matlab command was used to determine the autoregressive coefficients. Ayrule is an autoregressive function, which uses a Yule-Walker algorithm to compute the respective coefficients.

Coeff = aryule (data, p);

The above command returns Coeff, which is AR model with computed coefficients to be used for prediction. The aryule () function takes input parameters, data and p. The first input parameter is data, which is a matrix vector containing consecutive blood glucose readings. The second input is p, which is a user specified model order, where its optimal value is determined by using the partial

autocorrelation function. The prediction of the future blood glucose values in the time series sequence is computed using Coeff, which is evaluated by the above ayrule function.

7.2.3.2. Autoregressive Moving Average (ARMA)

This technique predicts the future blood glucose evolutions based on a moving average autoregressive model (ARMA). It uses an autoregressive coefficients and moving average of the error terms to predict the blood glucose evolution of an individuals. Both the autoregressive coefficients and the moving average terms are calculated based on Yule-Walker algorithm using the training data set. The model is validated with the unseen validation datasets, where it is tested to predict the unseen datasets. For example, the following Matlab command was used to determine the autoregressive coefficients and moving average terms:

Model = armax (data, [p, q], 'approach', 'yw');

The above command returns Model, which is an ARMA model with computed AR and MA coefficients to be used in prediction. The armax () function takes input parameters, data, p, q, and approach. The first input parameter, data is a matrix vector consisted of consecutive blood glucose readings. Both p and q are the order of autoregressive coefficients and moving average terms. The optimal values of these model order are determined using Matlab system identification toolbox-polynomial approximation. The third input parameter 'approach', specifies user selected algorithm for computing the required coefficients. In this case, 'yw' indicates that the Yule-Walker algorithm was used for computing the coefficients. The prediction of the future blood glucose values in the time series sequence is computed using Model, which is evaluated by the above armax function.

7.2.4. Prediction Interval

The prediction interval is computed by using the empirical distribution of errors between the recent blood glucose readings and predictions. The interval based prediction algorithm were implemented using Matlab following these procedures:

I. Define the window size w, let $w = n - 1\ data\ points, 1 < w < n$
II. Collect the first $n - 1\ BG\ data\ points, \{X_1, X_2, X_3 \dots \dots \dots X_n\}$
III. Make prediction for these data points from the prediction model (*predicted*)
IV. Calculate the difference (errors) between the predicted and these data points

Error = X - *predicted*

V. Calculate standard deviation of these error for the window size.

$$SD_{i=1,n} = \sqrt{\frac{\sum_{i=1}^{n-1}(\text{Error}_i)^2}{n}}$$

VI. Obtain the current X_{n+1} BG reading and current BG prediction (*nextValue)*

VII. Calculate the prediction interval using the current prediction and the standard deviations of errors.

UCL (Upper Control Limit) = *nextValue* + $z\alpha_{/2}$ × ($SD_{i=1,n}$);

LCL (Lower Control Limit) = *nextValue* - $z\alpha_{/2}$ × ($SD_{i=1,n}$);

Where α the level of significance, and all the models were tested for $\alpha = 0.01, 0.05\ and\ 0.1$.

VIII. Check the current measurement (X_{n+1}) is inside the predicted interval?

- If yes continue to the next step (IX)
- If not use/take $X_{n+1} = \frac{X_{n+1}+X_n}{2}$ and continue to the next step (IX)

IX. Shift the window w one step forward $2 < w < n + 1$

X. Repeat from step III up to VI for the whole datasets

7.2.5. Moving Window based z-Score

The z-score value of each BG data points are calculated based on a moving window, w. The following algorithm was implemented on Matlab.

I. Define the window size w, let $w = n - 1\ data\ points, 1 < w < n$

II. Collect the first $n - 1\ data\ points, \{X_1, X_2, X_3 \dots \dots \dots X_n\}$

III. Calculate the mean $\overline{X_{\iota=1,n}}$ and standard deviation $SD_{i=1,n}$ for these data points.

$$\overline{X_{\iota=1,n}} = \frac{1}{n}\sum_{i=1}^{n-1} X_i\ ,\ SD_{i=1,n} = \sqrt{\frac{\sum_{i=1}^{n-1}(X_i - \overline{X_{\iota=1,n}})^2}{n}}$$

IV. Obtain the current X_{n+1} blood glucose reading

V. Calculate the standard z-score of X_{n+1} using $\overline{X_{\iota=1,n}}$ and $SD_{i=1,n}$

$$(z - score)_{n+1} = \frac{X_{n+1} - \overline{X_{\iota=1,n}}}{SD_{i=1,n}}$$

VI. Shift the window w one step forward $2 < w < n + 1$

VII. Repeat from step III up to VI

VIII. Set a specific threshold.

7.3. System Testing and Results

The electronic disease surveillance system based on people with diabetes was developed based on Matlab programming environment. From the four modules of our system architecture, we developed and carried out the simulations for the core part, blood glucose prediction module, outbreak detection module. Consequently the blood glucose prediction (point and interval) module, outbreak detection (interval comparison and moving window based z-score) module were tested and evaluated. Three approaches for predicting an individual's blood glucose evolution have been developed and tested. This module was tested for predicting the validation datasets (unseen datasets during learning) for both type-I diabetes subjects, as a point and interval prediction. The outbreak detection module was also tested for detecting the abnormal deviation of blood glucose values, from the simulated dataset, using the predicted interval and the moving window based z-score computation.

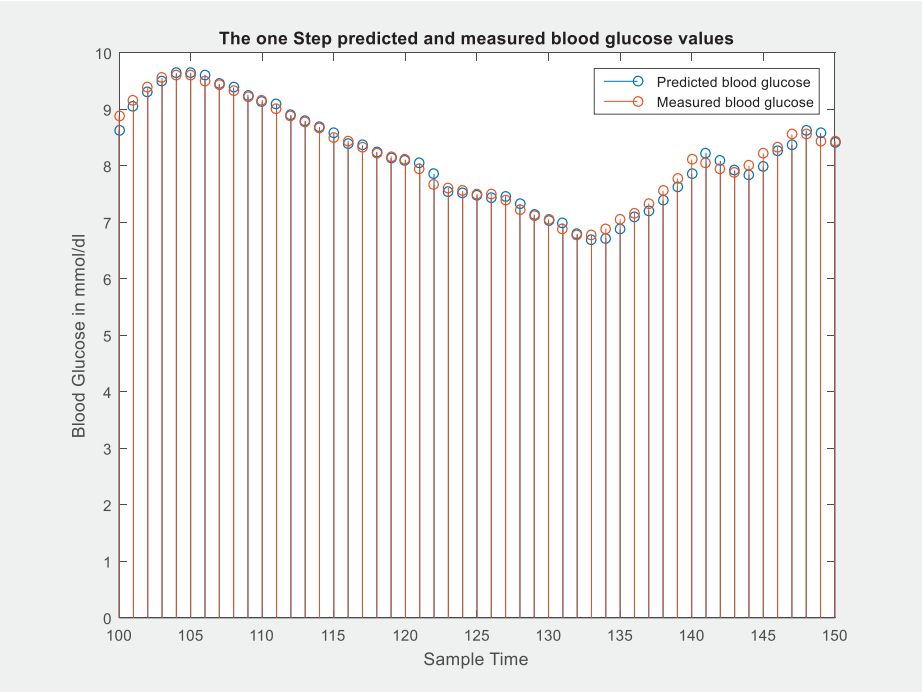
7.3.1. Blood glucose prediction: Point and Interval prediction

For all of the prediction approaches, the performance of the individual approach was evaluated and compared for different model order. The chosen optimal model for the individual approach is then used for predicting the validation datasets. Moreover, the prediction interval was computed and compared for various values of window size and level of significance. The chosen optimal window size and level of significance are used to construct the intervals for that individual approach. Furthermore, during interval calculation, we tested our assumption that the error distribution should follow a normal distribution. The result suggest that the error distribution follows a shifted version of a normal distribution, which is reasonably enough for calculating the prediction intervals.

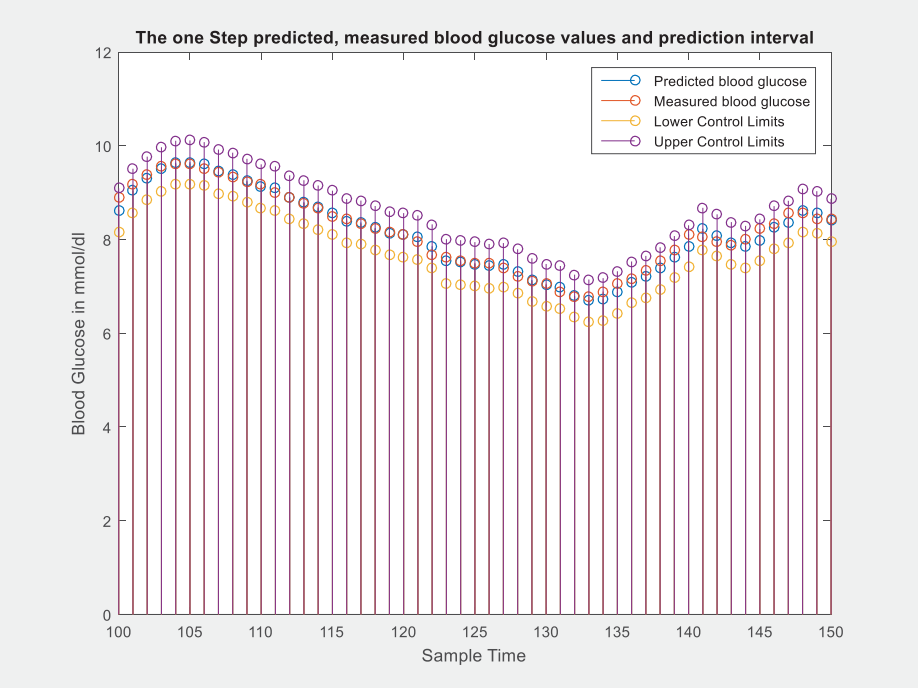
7.3.1.1. Autoregressive (AR)

This approach was designed and developed using the raw blood glucose data without any data preprocessing. For the first subject, an autoregressive model of order five (p = 5) was found to be the optimal for the point BG prediction and fitted best with a mean square error (MSE) of 0.0466 and a root mean square error (RMSE) of 0.2159. The autoregressive polynomial approximation of this subject takes the form: $AR(z) = 1.2611z^{-1} - 0.1296z^{-2} - 0.0423z^{-3} - 0.0497z^{-4} - 0.0430z^{-5}$. The prediction interval was found to be optimal with a window size of $w = 100$ and a statistically significance level of $\alpha = 0.01$. The second subject also attains its optimal order for

point BG prediction at p = 5 with a mean square error (MSE) of 0.0942 and a root mean square error (RMSE) of 0.3068. The autoregressive polynomial approximation of the second subject takes the form: $\mathrm{AR(z)} = 1.2328z^{-1} - 0.1239z^{-2} - 0.0258z^{-3} - 0.0562z^{-4} - 0.0281z^{-5}$. The prediction interval was found to have a reasonable size with a window size of $w = 200$ and a statistically significance level of $\alpha = 0.01$. The point and interval prediction of both subjects are given in the Figure 29 & 30 below.

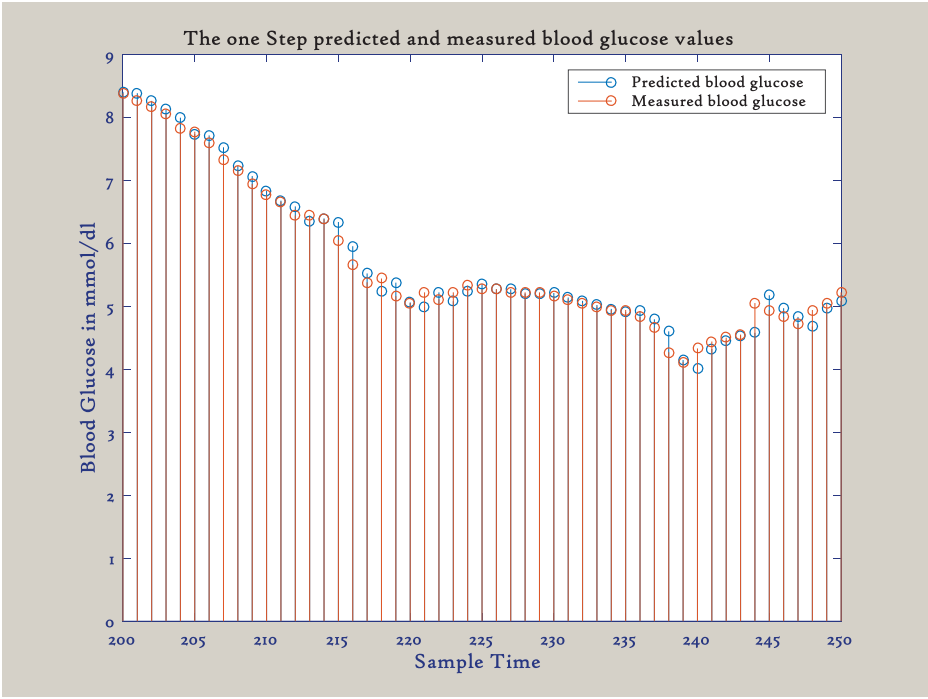


a)

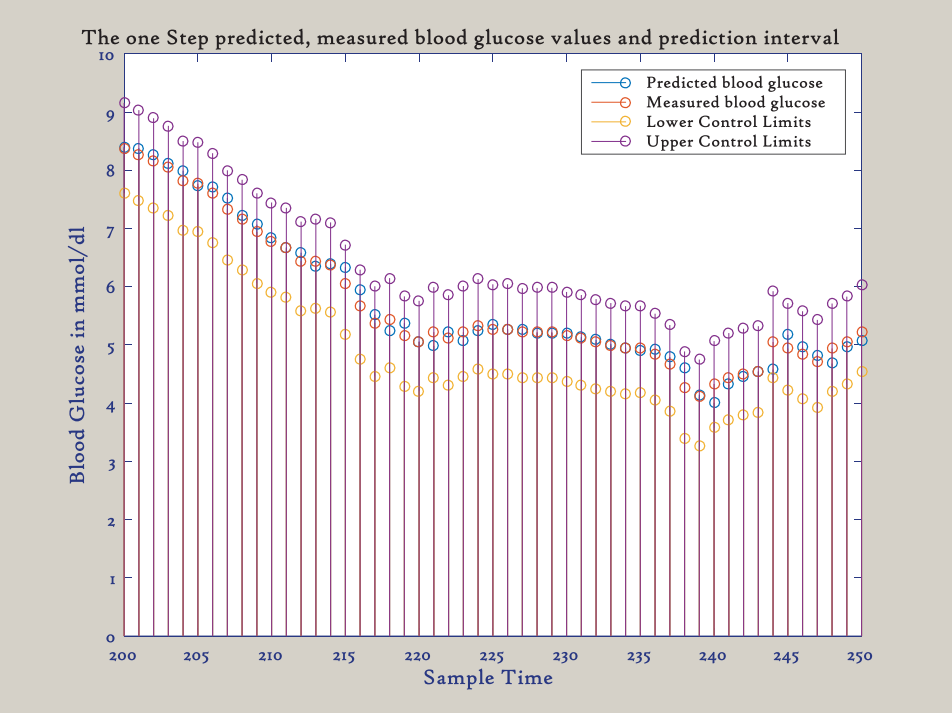


b)

Figure 29: Subject one- point and interval prediction using autoregressive (AR) model. a) Point prediction and b) Interval prediction.



a)



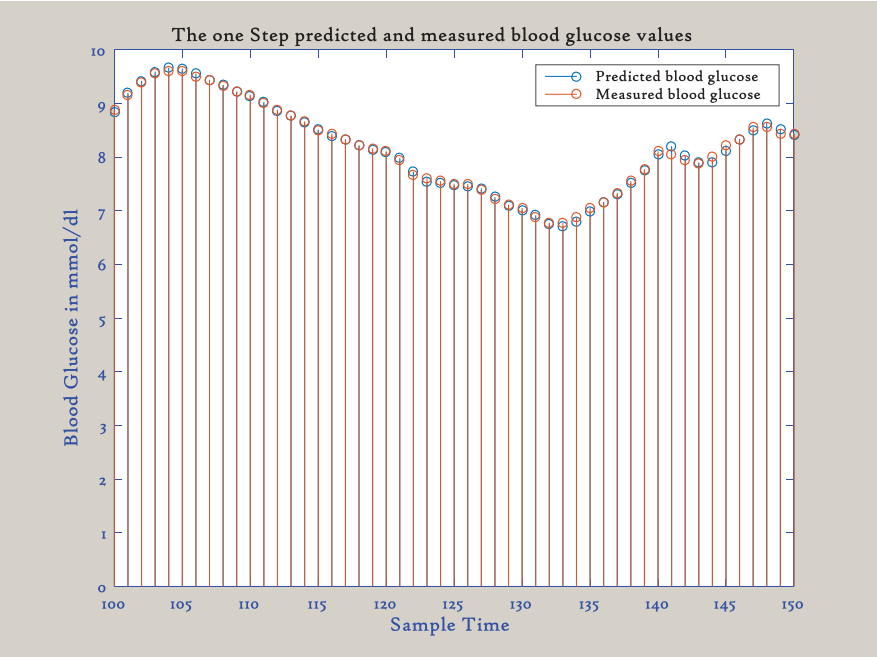
b)

Figure 30: Subject two- point and interval prediction using autoregressive (AR) model. a) Point prediction and b) Interval prediction.

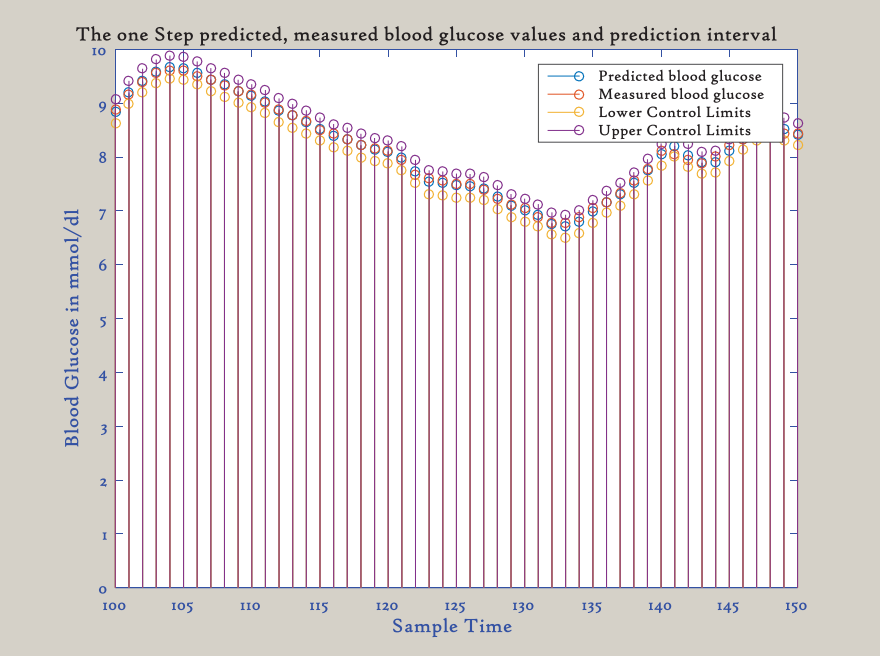
7.3.1.2. Autoregressive (AR) with Ratio inputs

This model was designed and developed after applying some data preprocessing techniques on the raw blood glucose data. Ratio of the consecutive blood glucose data points were computed and used for training and testing. For the first subject, an autoregressive model of order p = 4 was found to be the optimal order for the point BG prediction and fitted best with a mean square error (MSE) of 0.0102 and a root mean square error (RMSE) of 0.1010. The autoregressive polynomial approximation of this subject takes the following form: $AR(z) = 0.5477z^{-1} - 0.2530z^{-2} - 0.1176z^{-3} - 0.0805z^{-4}$. The prediction interval was computed using an optimal window size of $w = 100$ and a statistically significance level of $\alpha = 0.01$. The second subject also attains its optimal order for point BG prediction at p = 4 with a mean square error (MSE) of 0.0115 and a root mean square error (RMSE) of 0.1074. The autoregressive polynomial approximation of the second subject takes the following form: $\mathrm{AR(z)} = 0.6446z^{-1} - 0.1698z^{-2} - 0.1270z^{-3} - 0.0579z^{-4}$. The prediction interval was found to have a reasonable size with a window size of $w =$

200 and a statistically significance level of $\alpha = 0.01$. The point and interval prediction of both subjects are given in the Figure 31 & 32 below.

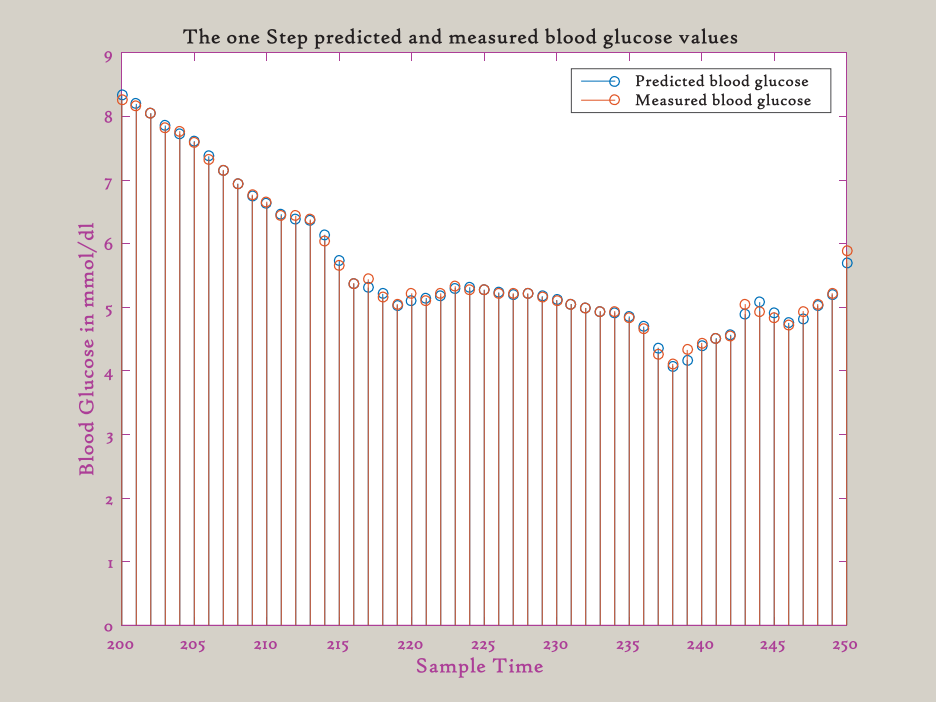


a)

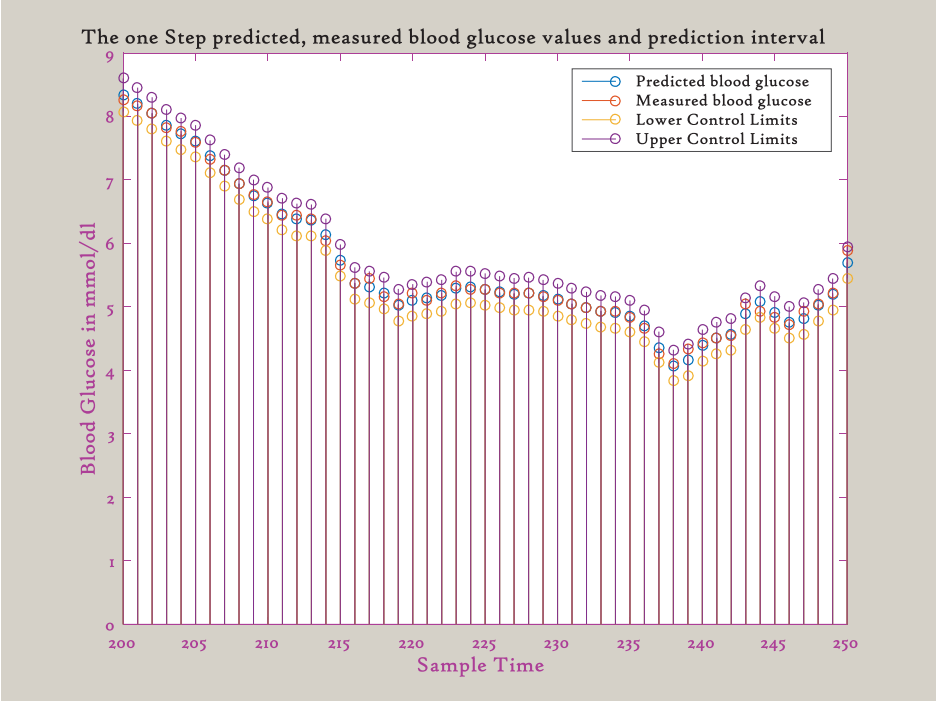


b)

Figure 31: Subject one- point and interval prediction using autoregressive (AR) model with ratio inputs. a) Point prediction and b) Interval prediction.



a)

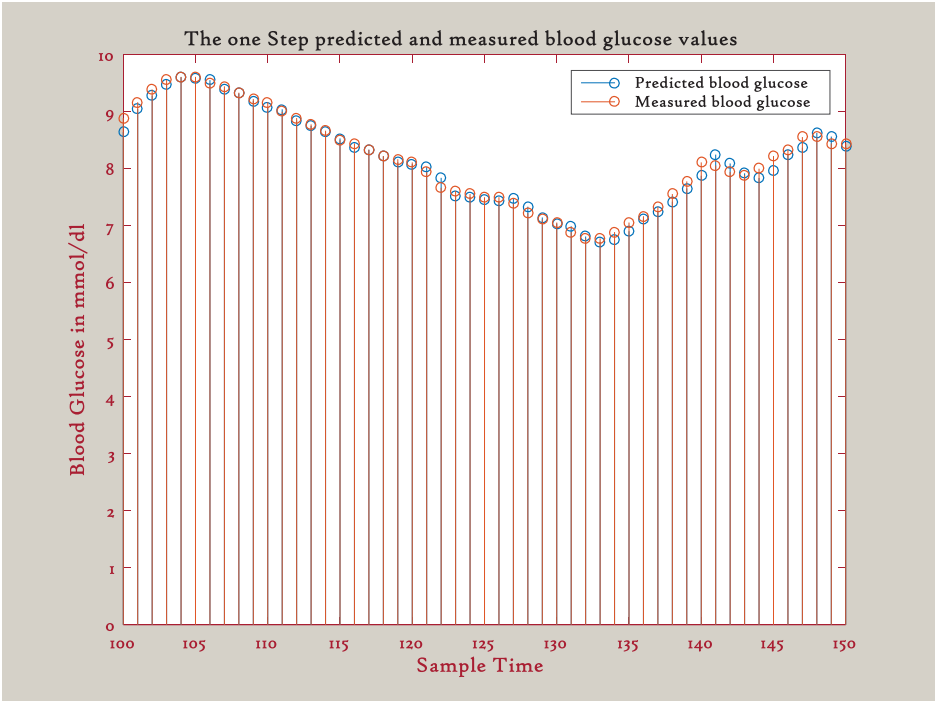


b)

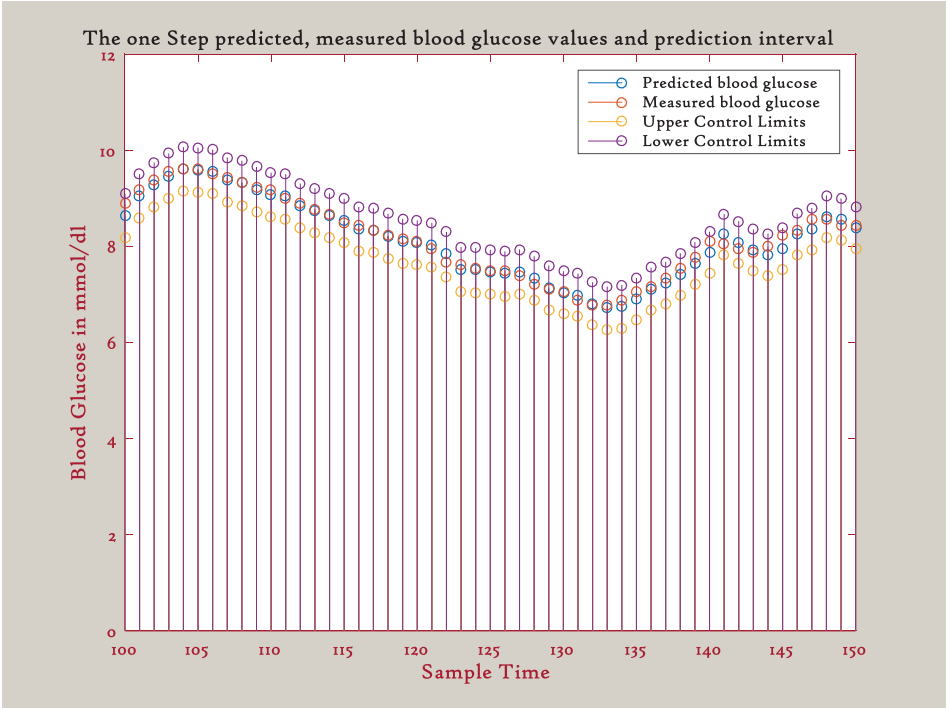
Figure 32: Subject two- point and interval prediction using autoregressive (AR) model with ratio inputs. a) Point prediction and b) Interval prediction.

7.3.1.3. Autoregressive Moving Average (ARMA)

This approach is different from the above models in that it incorporates a moving average component for the error terms. It was developed without considering any preprocessing of the blood glucose data. The approach was also evaluated and compared for different model order (autoregressive and moving average coefficients) along with the window size. For the first subject, the autoregressive moving average was found to be optimal with an autoregressive order of 6 and a moving average order of 2. It generates accurate enough prediction with a mean square error (MSE) of 0.0447 and a root mean square error (RMSE) of 0.2114. The discrete-time ARMA model $\mathrm{A(z)y(n)} = \mathrm{C(z)e(n)}$ of this subject takes the following polynomial approximation form with $\mathrm{A(z)} = 1 - 1.318\,\mathrm{z}^{-1} + 0.2129\mathrm{z}^{-2} + 0.02436\mathrm{z}^{-3} + 0.03331\mathrm{z}^{-4} + 0.1295\mathrm{z}^{-5} - 0.04759\mathrm{z}^{-6}$ and $\mathrm{C(z)} = 1 - 1.042\mathrm{z}^{-1} + 0.04253\mathrm{z}^{-2}$. The prediction interval was found to be effective with a reasonable width with a window size of $w = 100$ and a statistically significance level of $\alpha = 0.01$. The second subject also attains its optimal prediction with an autoregressive order of 6 and a moving average order of 2 with a mean square error (MSE) of 0.0850 and a root mean square error (RMSE) of 0.2915. The discrete-time ARMA model for this subject follows the following polynomial approximation: $\mathrm{A(z)} = 1 - 0.3934\,\mathrm{z}^{-1} - 1.084\mathrm{z}^{-2} + 0.3003\mathrm{z}^{-3} + 0.09445\mathrm{z}^{-4} + 0.09712\mathrm{z}^{-5} + 0.008629\mathrm{z}^{-6}$ and $\mathrm{C(z)} = 1 - 0.001844\mathrm{z}^{-1} + -0.9945\mathrm{z}^{-2}$. For this individual, the prediction interval was found to be effective with a reasonable width with a window size of $w = 200$ and a statistically significance level of $\alpha = 0.01$. The point and interval prediction of both subjects are given in the Figure 33 & 34 below.

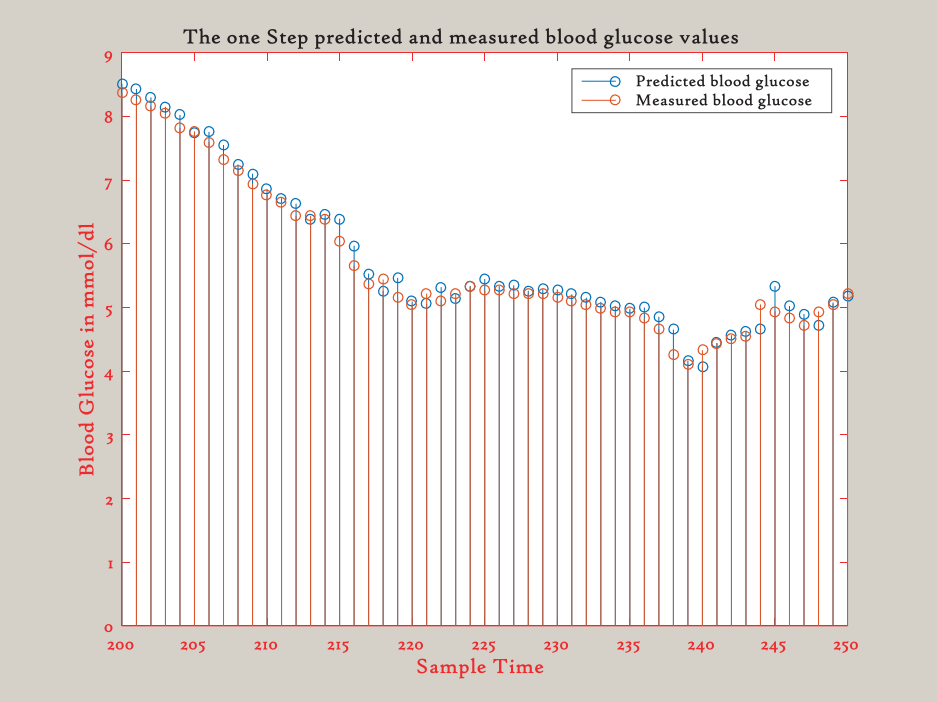


a)

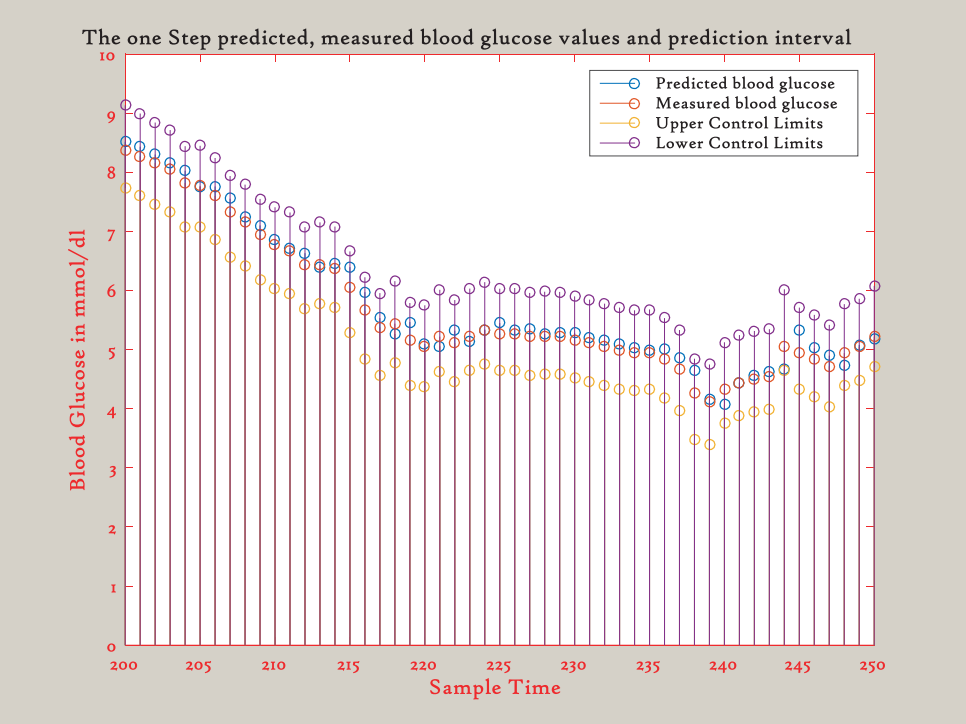


b)

Figure 33: Subject one- point and interval prediction using autoregressive moving average (ARMA) model. a) Point prediction and b) Interval prediction.



a)



b)

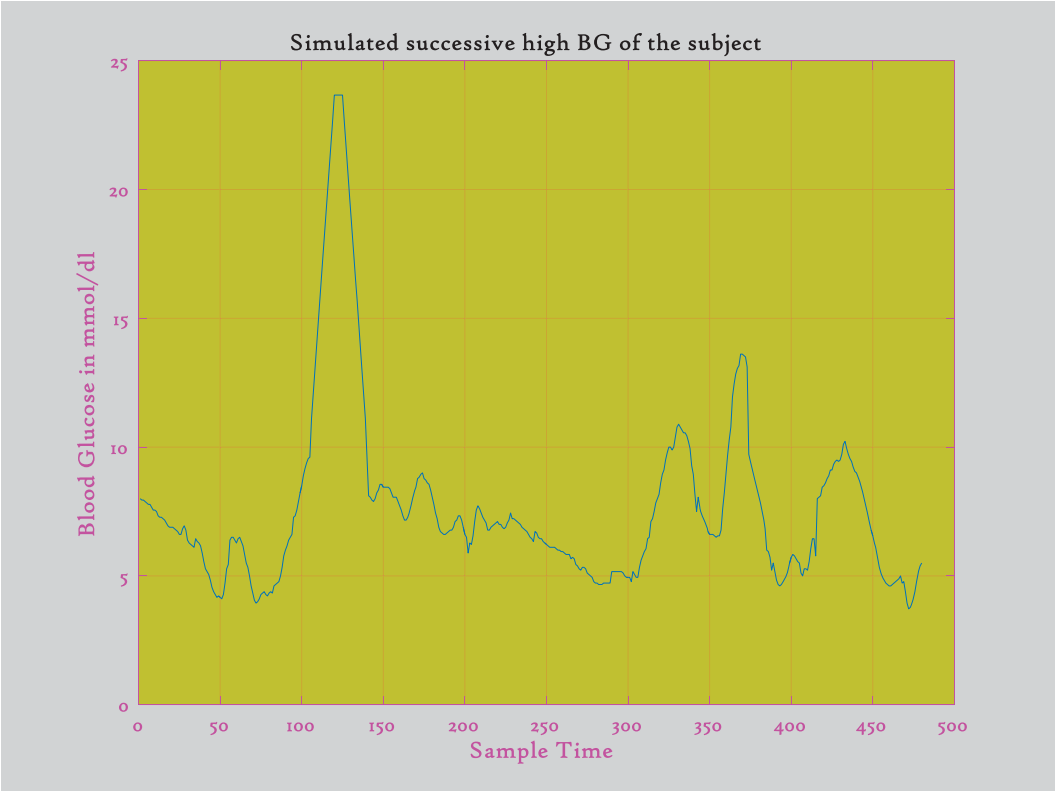
Figure 34: Subject two- point and interval prediction using autoregressive moving average (ARMA) model. a) Point prediction and b) Interval prediction.

7.3.2. Outbreak detection/Surveillance

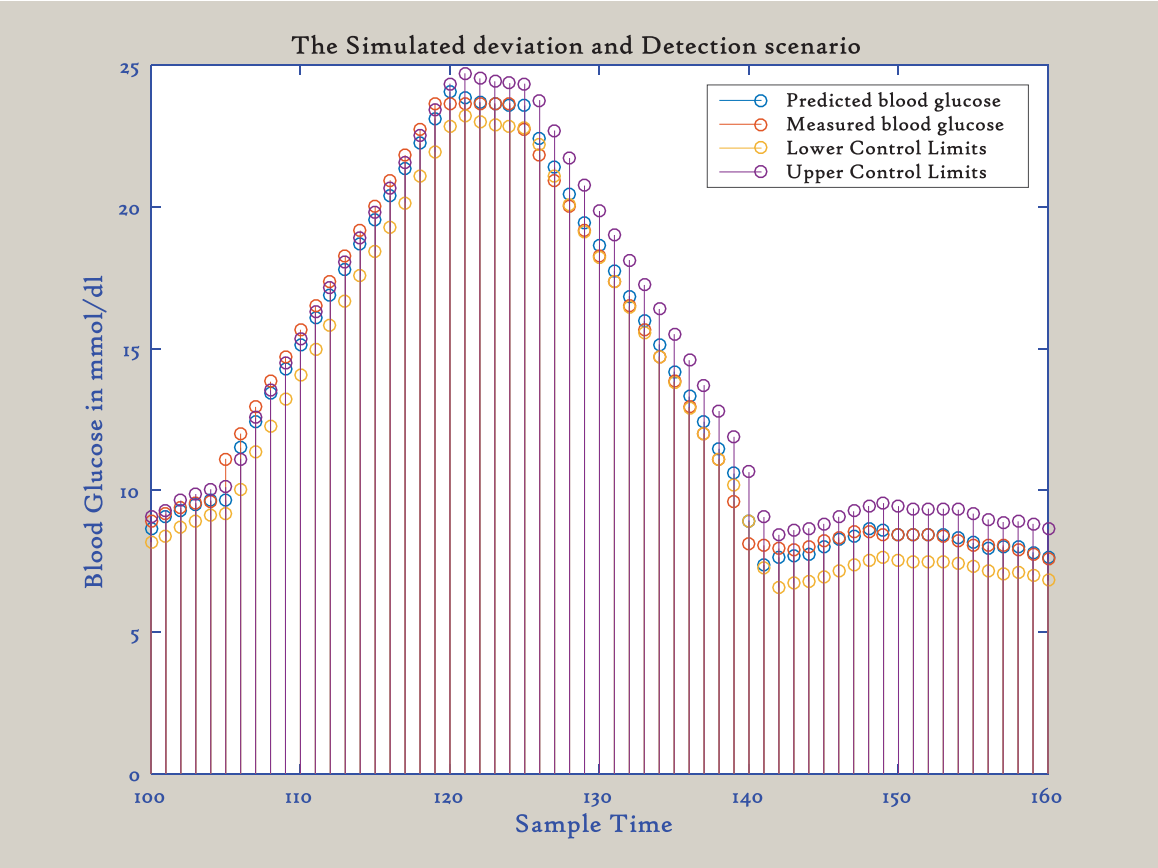
The developed outbreak detection algorithms are a type of statistical control and a moving window based z-score process. The former involves blood glucose point and interval prediction for computing the outbreak detection while the later involves the computation of z-score values for each BG readings based on a moving window and comparison of each score with a pre-specified threshold value.

7.3.2.1. Prediction interval based

The developed prediction interval based blood glucose deviation detection algorithm is tested with the artificially simulated datasets (consecutive high blood glucose values), as shown in the Figure 35 a; these resemble the individual's blood glucose readings with the presence of infections. The developed algorithm successfully detected the deviated blood glucose readings as shown in the Figure 35 b. As clearly shown, the algorithm is highly sensitive to the slope, and clearly captures the rise and fall of the individual's blood glucose readings, which is the requirements for initiating the required alarm signal.



a)

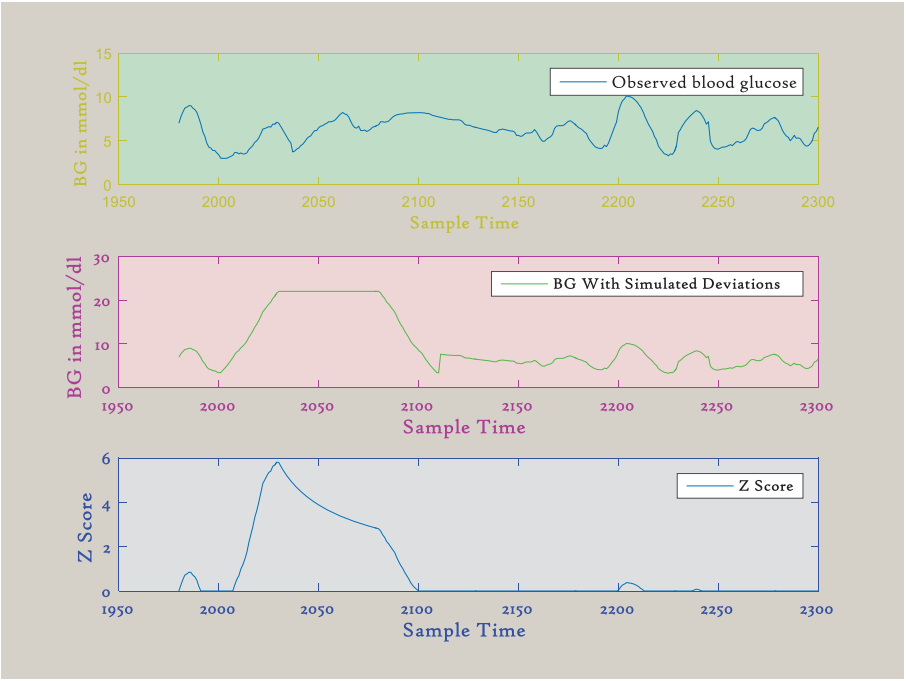


b)

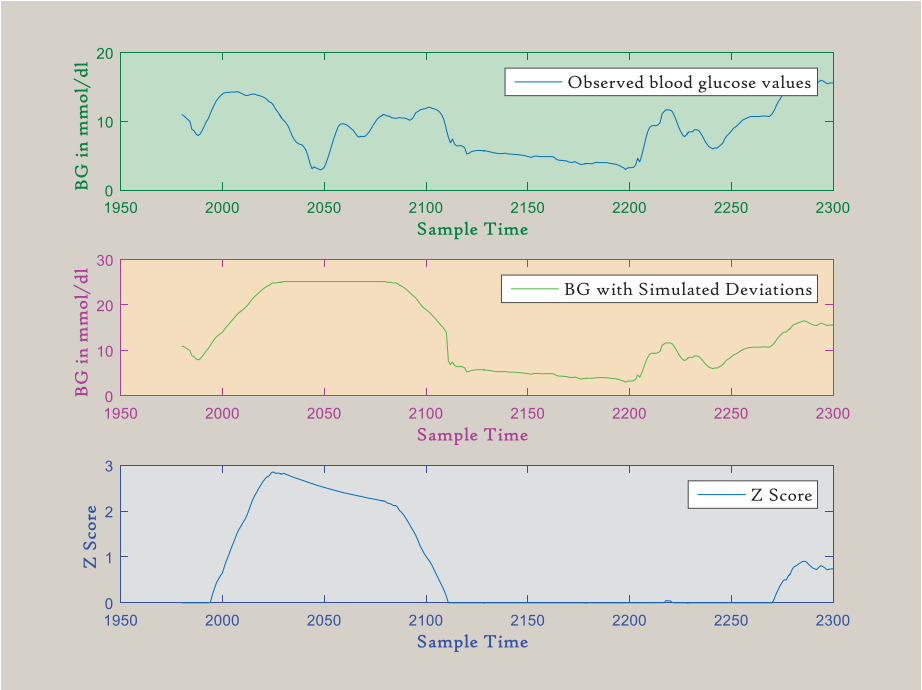
Figure 35: The statistical control type algorithm. a) The artificially simulated blood glucose readings used for testing the algorithm. b) The detection capabilities of the developed statistical control algorithm on the testing data.

7.3.2.2. Moving window z-score based

The developed moving window based z-score process was also tested against the simulated dataset. The algorithm was capable of successfully detecting the consecutive high blood glucose reading of both subjects as shown in the Figure 36a & b. The algorithm is found to be highly affected by the variability of the blood glucose readings and needs to be tuned towards the individuals with the optimal window size. For example, as shown in the Figure 36a & b, the variability of the blood glucose readings involved in the first subject is minimal (only a window size of n = 600) as compared to the second subject (a window size of n = 800).



a)



b)

Figure 36: The moving window based z-score process. a) The observed blood glucose, simulated dataset, and the detection accuracy for the first subject. b) The observed blood glucose, simulated dataset, and the detection accuracy for the second subject.

Moreover, in order to further validate the moving window based z-score process, it was tested for an abrupt change (maximum rise within a single interval) within the blood glucose readings. This was conducted using data from the first subject as an illustration. As clearly seen in the Figure 37, the algorithm was capable of successfully detecting the elevated blood glucose readings. Due to major fluctuations in the z-score values, as shown in the Figure 37, forward difference of the z-score values is used to generate an impulse function as a result of the elevation in blood glucose values, which can be used for initiating the required alarm. All these results demonstrate the success of our approach.

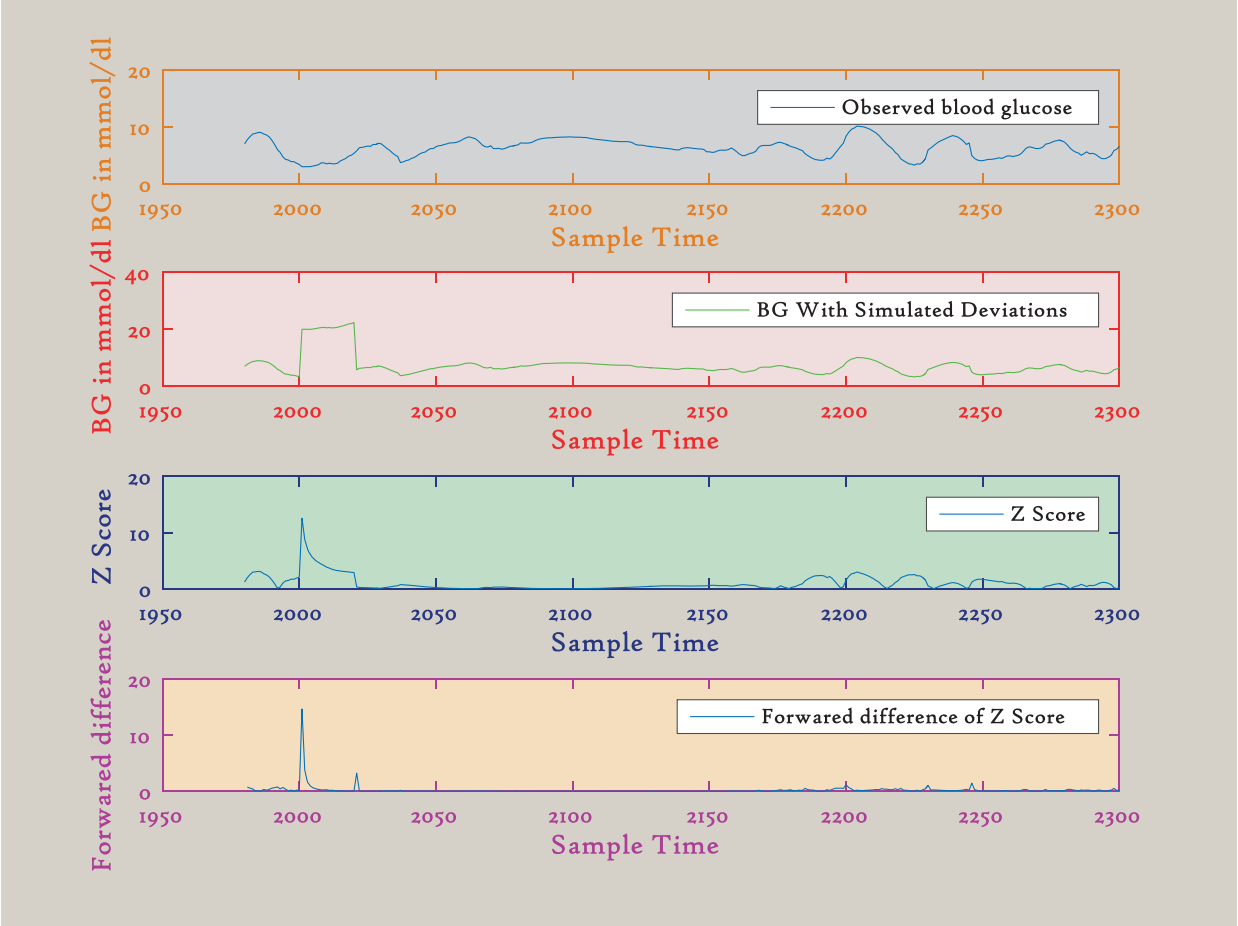
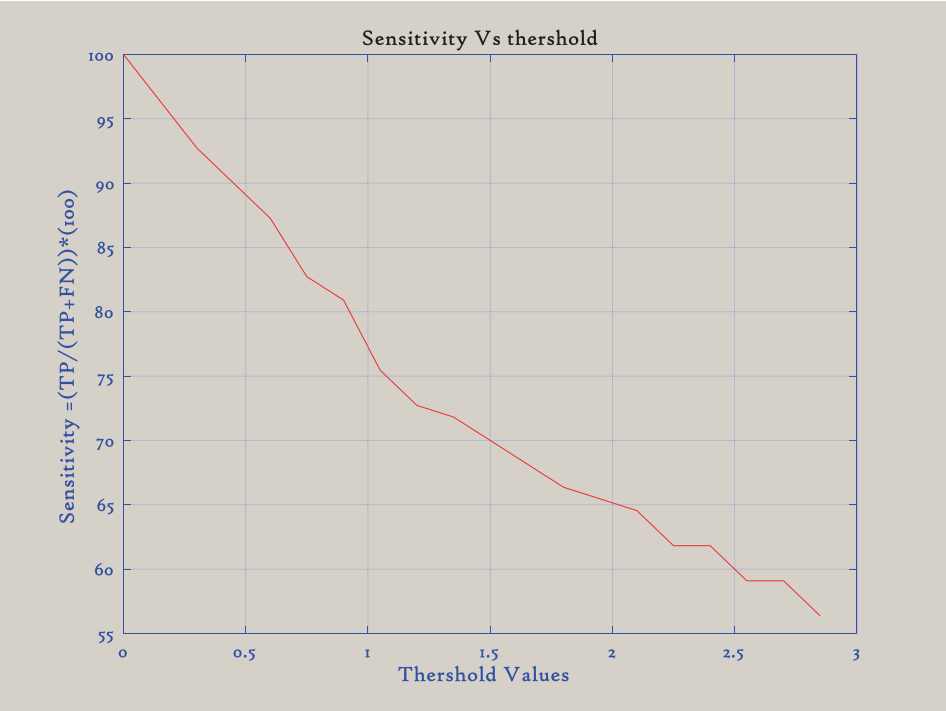
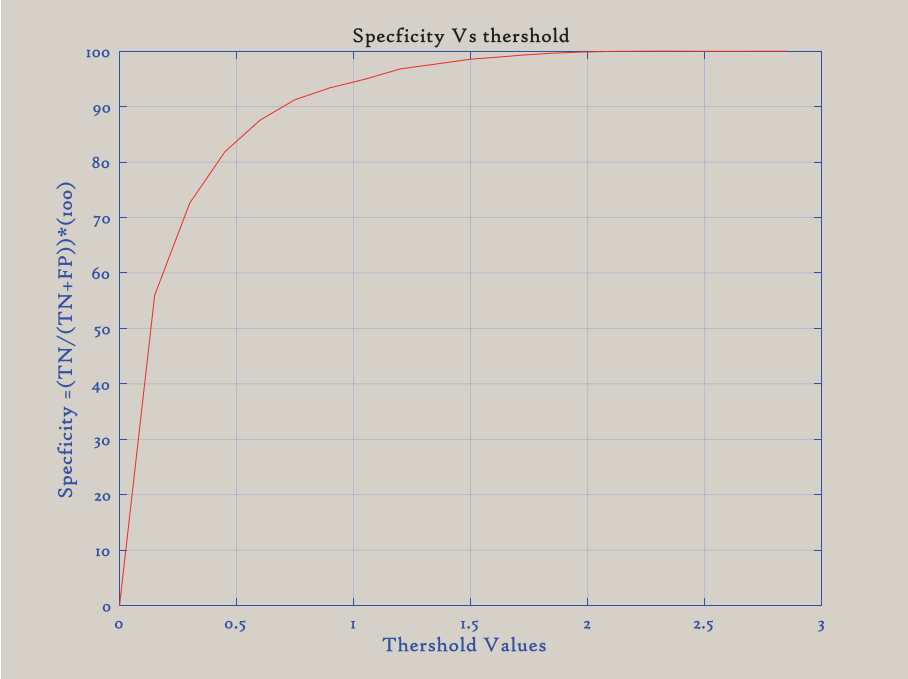


Figure 37: Simulated based on the data from the first subject. The observed blood glucose, simulated dataset, and the detection accuracy of the moving window z-score with respect to an abrupt change (maximum rise within a single interval) in blood glucose values

Besides, in order to meet the defined surveillance case definition (capturing successive elevated or high blood glucose readings) with the moving window based z-score process, it is necessary to determine the optimal working value of the threshold to initiate the required alarm. This can be achieved by computing and plotting the sensitivity (Probability of being test positive when the blood glucose is higher than normal), specificity (Probability of being test negative when the blood glucose is in a normal amount) and positive predicative values (tells us how many blood glucose readings tested to be deviated are actually deviated) against various threshold values. The optimal threshold value is selected in a way to improve the capability of the system for detecting and differentiating outliers (deviated blood glucose readings) from the normal blood glucose readings and at the same time discarding small and short duration blood glucose increments so as to suppress unwanted and false alarm. For example, as shown in the Figure 38a & b, a threshold value of 1.5 has discarded all the normal blood glucose readings (regarded as a True Negative) and however, rejects some of the elevated blood glucose readings (regarded as True Positive). Therefore, during selection of the working threshold, it is necessary to make a compromise between the presences of some false alarm and the rejection of some actually deviated blood glucose readings.



a)



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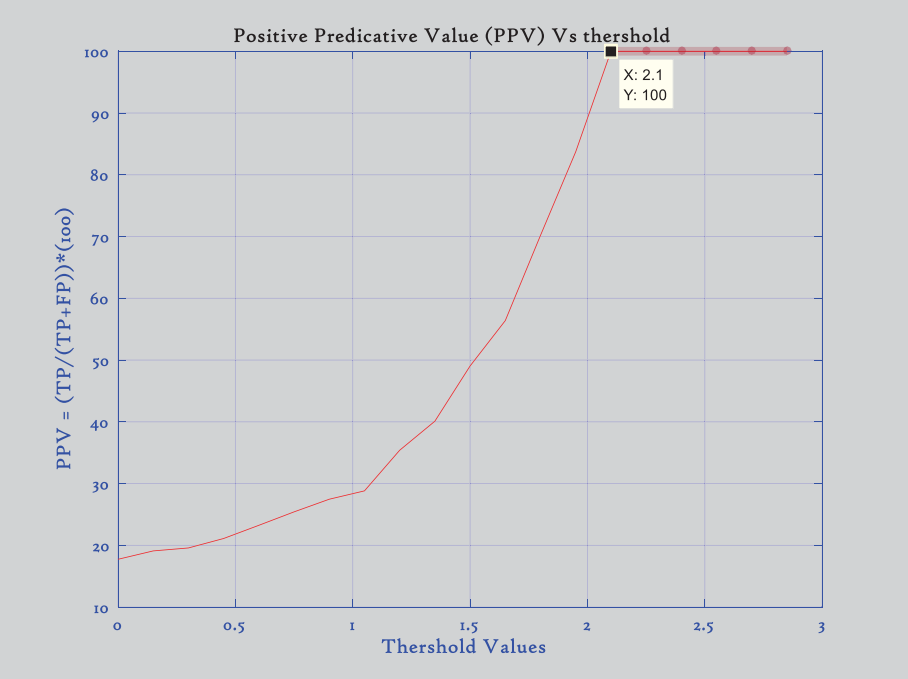

c)

Figure 38: Parameters associated with the moving window based z-score process. a) Sensitivity vs. threshold. b) Specificity vs. threshold. c) Positive predicative values vs. threshold.

Chapter Eight: Discussion

8.1. Introduction

Early detection of disease outbreaks is the central goal of any public health surveillances, to afford ample time for controlling and prevention action to be taken by the responsible bodies, i.e. public health authorities and hospitals. Currently, a large number of disease surveillances and control algorithms are industrialized and deployed for detecting potential disease outbreaks. Practically, all of these systems have benefited from the advancements in information technology. They make use of electronically available data that are generated before diagnosis and laboratory or physician verification, such as chief-complaint data (Wagner et al., 2004), disease related search volumes in different search engine such as google (Zhou et al., 2013; Zhou et al., 2011), over-the-counter and prescription pharmacy sales (Xiaohui et al., 2004), school absenteeism (Weng et al., 2015), and emergency calls (Adam et al., 2007), and other different reported symptoms. Nevertheless, disease outbreak detection systems that focus on the incubation period, before the onset of the first symptoms, have not been developed yet. Besides, the common denominator of the existing approaches are that they mainly target the general population giving less consideration to those groups, who are referred here as Sensitive Population Groups - SPGs, such as people suffering from COPD (Chronic Obstructive Pulmonary Disease) or diabetes, who may be at heightened risk even in non-outbreak settings (Botsis et al., 2007) and can easily spread an infection under certain circumstances (Baker et al., 2006). To fill these research gaps, this thesis project proposes and argues the use of blood glucose data as an indicator for the presence of infections. Recently, researchers have demonstrated the presence of positive correlation between elevated blood glucose levels (for both type 1 and type 2 diabetes individuals) and an infections (due to Influenza, Cholera, Plague, Ebola, Anthrax, or SARS viruses) (Årsand et al., 2005; Botsis et al., 2007; Lauritzen et al., 2011). Therefore, it is the objective of this thesis to design and develop an early outbreak detection algorithm based on inputs from diabetes individuals, and that can track the blood glucose values of each individuals separately and detect a cluster of people with statistically significant deviation. The main goal here is to use people with diabetes as a source of information in a disease surveillance system and to effectively detect infectious disease outbreaks during the incubation period.

8.2. Experimental Analysis and Results

8.2.1. System Architecture

In this section, we will discuss the solution put forward for the defined main problem [P1[13]]. The developed system architecture is a centralized system, where the data from individual diabetes users are submitted to a central repository (database), see Figure 16. It is consisted of four modules, data collection module, blood glucose prediction module, outbreak analysis module and information dissemination and reporting module. The individual diabetes user data are consisted of the four keystones (blood glucose, dietary, physical activity and insulin injection) along with the geographical location and the time stamp, the time at which the data are recorded. The geographical location is determined on a dynamic (late) binding bases, where the address of the user is resolved at the time of data submission using the GSM network. The dynamic binding concept is implemented by dividing the entire region under surveillance into equal cells stamped with their unique cell identifiers. The cellular address of the individual user is resolved during data submission by comparing the unique cellular identifiers with the address received from the GSM network, without the need of static address, thereby allowing user mobility. Besides, blood glucose prediction module tracks the individual blood glucose fluctuations (evolutions) and computes the baseline data for surveillance purpose. The output from the prediction module is input to the outbreak detection module, where the current blood glucose reading is compared with the baseline generated by the blood glucose prediction module. Depending on the outbreak detection result, presence of a cluster of people with statistically significant blood glucose deviation, the information dissemination and reporting module deliver the outbreak information for the concerned bodies (i.e. public health authority, physicians and family and relatives) via SMS and email. The SMS is used as a first remainder concerning the current outbreak and email is used to provide adequate information, such as the degree of severity and the spatio-temporal plot of the detected cluster of people (affected region) on a map of interest.

[13] Main Problem Definition (See problem definition, Chapter one)

8.2.2. Blood glucose prediction

This section discusses the solution put forward and results achieved for the defined sub-problem one, [SP1[14]]. The personal blood glucose profiling involves forecasting the expected (probable) blood glucose values of an individual based on various parameters referred to as the keystones of diabetes, i.e. blood glucose, dietary, insulin injection, physical activities and others. The central purpose of profiling is to compute the expected (probable) blood glucose values based on the recent history. It is a vital component of the disease surveillance system, which enables the system to track the individual blood glucose evolution. Practically due to the limited availability of the necessary data, we developed a univariate (one variable) prediction algorithm that depends only on continuous blood glucose monitoring (CGM) data. The prediction model uses an autoregressive model for predicting the single step blood glucose value of the individual. These models are tuneable towards the individual's blood glucose dynamics with its polynomial orders. This model was selected for a number of reasons, due to its capability of predicting the future based on the most recent data, and its simplicity and its well defined procedure for computing prediction intervals. The former is important to capture the habit of the individual based on a daily or weekly basis. Three version of autoregressive model were developed, i.e., Autoregressive (AR), Autoregressive (AR) with Ratio inputs and Autoregressive Moving Average (ARMA). These models were trained and validated based on data from two type-one diabetes subjects, where during validation the trained model were tested with unseen datasets. The first model, Autoregressive (AR) achieves optimal prediction for both subjects with model order of $p = 5$ and capable of predicting the single step blood glucose values with RMSE of 0.2159 and RMSE of 0.3068 for the first and the second subjects respectively. The second model, Autoregressive (AR) with Ratio inputs was found to be optimal for both subjects with model order of $p = 4$ and predicts the single step blood glucose values with RMSE of 0.1010 and RMSE of 0.1074 for the first and the second subjects respectively. The third model, Autoregressive Moving Average (ARMA) also was found to be optimal with an autoregressive order of 6 and a moving average order of 2. It generated accurate enough prediction with a RMSE of 0.2114 and RMSE of 0.2915 for the first and the second subjects respectively. Among these models, the second model predicts well as compared with the other models attaining the minimum RMSE for both subjects, which

[14] Sub Problem one (See problem definition, Chapter one)

demonstrates the advantage of using ratio of successive data points for training rather than the raw blood glucose data. The RMSE attained by the second subject in all these models are higher than the first subject, which is mainly due to the significant fluctuations of blood glucose readings as a result of the personal behavior in managing his/her diabetes.

8.2.3. Prediction interval

This section presents the solution and results achieved from our approach, which combines the individual's BG prediction with the proposed early outbreak detection mechanism as defined in both sub-problem one and two, [**SP1 & SP2**]. The main purpose of the prediction interval is to compute the baseline for controlling and detecting blood glucose deviations at an individual level and generally at population levels. The prediction interval is computed based on the most recent measurements, which is helpful for evaluating the current status of the individual relying on the most recent status. The empirical distributions of error between the previous recent measurements and predictions are used to construct the prediction intervals. Prediction intervals were computed for all of the prediction models, stated above, with an experimentally determined significance level α and window size w. All these models are capable of producing an optimal prediction intervals for both subjects with a significance level of $\alpha = 0.01$. Nevertheless, produced reasonable interval size with a window size of $w = 100\ and\ 200$ for the first and the second subjects. The reason behind this window size is due to the significant fluctuations of blood glucose readings as a result of the personal behavior in managing his/her diabetes.

8.2.4. Outbreak detection/Surveillance

In this section, we will discuss the thesis solutions and results achieved for the early outbreak detection mechanism as defined in sub-problem two, [**SP2**[15]]. Outbreak detection mechanism plays the central role in any disease surveillance systems. To have a better detection efficiency, the system should have an optimal detection algorithm that can and accurately detect the defined surveillance case, i.e. consecutive high blood glucose readings. We developed two outbreak detection algorithms, type of statistical control and moving window based z-score process. The former involves blood glucose point and interval prediction for detection whereas the later involves the computation of z-score values based on a moving window along with a specified threshold

[15] Sub Problem Two (See problem definition, Chapter one)

value. The first mechanism, prediction interval based is capable of detecting consecutive high blood glucose readings (see Figure 35a & b), which was tested on simulated deviations of such kind (BG values simulated to resemble the pattern during infections). It is more efficient in detecting the slope (from the beginning up to the end of successive increments or decrements), where the blood glucose evolution shows more variability. However, it shows shortcoming in detecting peak blood glucose values with zero slope, where there is no variability between successive readings. This is due to the absence of other supporting parameters such as insulin injection, dietary and physical activity in calculating the prediction intervals, which were not considered in our approach due to absence of these data. The second mechanism, moving window based z-score process is also capable of detecting the individual blood glucose deviations (see Figure 36a & b). However, the detection accuracy of this algorithm is highly affected by the variability of the blood glucose readings and needs to be tuned towards the individuals by properly selecting the optimal window size. As shown in the Figure 36a & b, the variability of the blood glucose readings involved in the first subject is minimal (only a window size of n = 600) as compared to the second subject (a window size of n = 800). The working threshold value of the z-score is determined by computing Sensitivity vs Threshold and Specificity vs Threshold (see Figure 38a & b). During selection of the optimal working threshold, a compromise between immediate detection of the case (with small consecutive deviations) and the generation of false alarm rate should be considered. Generally, as compared to the first approach, the moving z-score process is simple and can be easily adapted to the individual blood glucose dynamics.

8.3. Assumptions, Biases and Limitations

This early outbreak detection system is a near real time system that is developed based on an assumption that the user updates his/her status by measuring and recording the CGM data. Additionally, the patients' data is very personal and sensitive, therefore some form of privacy preserving mechanisms such as secured data transmission medium, data deidentification and the consent of the patients' are required. On the other hand, sample size was the major limitation of this project. We based our experiments and simulation on two individuals with type 1 diabetes, and more data is needed to further validate our approach. Besides, the "holiday effect" has not been considered in this study. The "*Holiday effect*" is the bad eating style of the majority of the population including people with diabetes in the holiday season (Lauritzen et al., 2011) and usually leads to high blood glucose values. In such cases our system may generate false alarms, especially

given the absence of frequent measurements for other supporting parameters, such as the white blood cell counts and temperature readings from these individuals (Botsis et al., 2009; Botsis et al., 2010). Considering the fact that body temperature, count of white blood cells and blood pressure can be an indicator for the presence or absence of infection with in the body, these measurement can be used to compromise the elevated BG value so as to bypass the generation of false alarm during holidays. Currently, there are a lot of sensors on the market, which can be used for a variety of health monitoring purposes (Chu et al., 2011), such as heart activity (electrocardiogram (ECG)), muscle activity (electromyography (EMG)), brain activity (electroencephalography (EEG)), blood pressure and glucose sensor, breathing or respiration sensor. However, the data source we are using, currently doesn't provide such kind of measurements.

8.4. System evaluation and characterization

In this section, we discussed some of the intended features and attributes of the developed disease surveillance system. These main points are used to characterize and evaluate our system as compared to other disease surveillance systems available in literatures (see Chapter 3).

8.4.1. Acceptability of the system or components

Acceptability refers to the willingness of the people and different organizations to participate or use the developed system. The main participants of the developed system are people with diabetes, who are required to sign an informed consent form prior to entry into the system. The form is developed so as to motivate the individual by incorporating all those elements required by the International Conference on Harmonization (ICH), the Good Clinical Practice (GCP), and also adhere to the ethical principles that have their origin in the Declaration of Helsinki of the World Medical Association (2000). The developed system could be used in evaluating the infection "threats" for not only other diabetes individuals in a region but also to the general population in the same area. The system is intended to be used by public health authorities, hospitals and physicians. The developed system is not used for any clinical decision support practices; such as treatment, advice for the individual patients, and others.

8.4.2. Privacy or Confidentiality

Health related data are very sensitive and needs to be confidential; the privacy of the patients should be protected. The intended disease surveillance system is based on a secure communication

channel dedicated for this purposes. The participants are expected to sign a consent form, which is developed based on the current most practiced international and national regulation, to participate in the developed system. In order to guarantee the participants privacy, an intermediate system that can arbitrate between the sending and receiving end is considered. The purpose of the intermediator is to process and remove the most significant personal identifiers, such as name (commonly known as deidentification procedure). Therefore, the intended system can receive the deidentified data and possibly without any privacy problems.

8.4.3. Compliance with Standards

Compliance with standards means the extent to which a system makes use of standards for data representation, message format, code sets, and case definitions. The intended system is developed based on a common data representation format (such as CSV), since the system is entirely dependent on data transferred from mobile diabetes self-management apps (such as the Few Touch Application (FTA)) and continuous glucose monitoring devices (CGM). A dedicated messaging server is considered that can manage the messages from the individual device, which is sent either manually or automatically. The messaging server is intended to have multiple features; send/receive on multiple channels simultaneously, scripting support, to enhance processing of incoming multipart messages, traffic limitation option and others.

8.4.4. Support for outbreak characterization

The main purpose of building a disease surveillance system is not only detecting cases and outbreaks but also the characterization of the outbreak for a better public health response. We proposed and developed a system that can identify set of affected individuals, the geographic scope on a spatio-temporal bases (map of a region) and severity of the cases. However, our system is not capable of characterizing and recommending a single biological agent as the source of the outbreak. The developed system is intended to deliver the outbreak information so as to facilitate the investigation on the specific areas reported.

8.4.5. Time latencies

Time latencies refer to the time delay between the generations of data by the user and is received by the system for processing. Moreover, it signifies the time gap between the generation of outbreak reports by the system and the time it takes the user for further processing. The developed system is expected to receive the BG update as soon as the user recorded via electronic transfer of

data over a secure communication medium. Besides, in order to avoid delays at the receiving end, the system uses SMS as a first notification purposes.

Chapter Nine: Further works/Recommendations

The electronic disease surveillance system based on inputs from people with diabetes is a system that can track the blood glucose evolution of an individuals and capable of detecting a cluster of people with elevated blood glucose in a specific region within a pre-defined timeframe. In the course of this project, the author identified areas, which needs further research. Therefore, any enhancements in two or more of the following issues can be considered as potential improvements:

→ Blood glucose prediction is the heart of the developed disease surveillance system. Due to the limited availability of the necessary data, we developed a univariate prediction algorithm that depends only on continuous blood glucose monitoring (CGM) data. However, in order to improve and achieve a better and accurate prediction result, it is necessary to develop a multi-variate prediction algorithm by incorporating more input parameters such as insulin, dietary and physical activity for both the point and interval prediction of the blood glucose dynamics.

→ The blood glucose prediction can be carried out using either of these prediction approaches, i.e. Structural and Black box approaches. The first approach, structural, requires an extensive knowledge of the underlying systems dynamics, which in this case requires modeling of the internal blood glucose-insulin dynamics. The second approach, black box, doesn't require an extensive knowledge about the internal systems dynamics, however, it only requires playing with the input and output data from the system to model a satisfactory prediction. In this project, we carried out the blood glucose prediction based on the black box approach, specifically using the autoregressive models. Therefore, it is necessary to research other approaches including both the Structural and Black box (other than the autoregressive models used in this thesis project) for any performance improvement.

→ The "*Holiday effect*" is the bad eating style of the majority of the population including people with diabetes in the holiday season and usually leads to high blood glucose values. In such cases our system may generate false alarms, especially given the absence of frequent measurements for other supporting parameters, such as the white blood cell counts and temperature readings from these individuals. Therefore, it is necessary to consider means of alleviating this problem. Moreover, the use of large sample size should considered to solve any validation problems associated with the defined approaches.

→ The main task of the developed disease surveillance system is to provide an adequate information regarding the current infectious outbreak. As a result, the system should provide the outbreak information in a simple and an easy way to understand. Therefore, it is necessary to consider designing and implementing a proper user interface (GUI) or application. The developed application should have an interface to allow the user to view the spatiotemporally plotted outbreak information on the map of interest, degree of severity and others.

→ The developed system is capable of following the individual blood glucose evolution. Sometimes one can achieve a good management of his/her blood glucose values within a certain days of the week and fail to do on the next time. Therefore, it is necessary to consider a mechanisms that can make analysis of the recent management practice and give feedback as how he/her is doing now as compared to the recent practice. The feedback information should be delivered to the individuals, physicians and family about recent behavioral changes based on the available historical data.

→ The performance of the developed system is highly dependent on the strict behavior of the individual in managing his/her blood glucose values and built on the assumption of good self-management practice. However, having a poor self-management practice can potentially affect the false alarm rate. As a result, it is necessary to discard these individuals from the system. However, it is much needed to look in detail about these kind of people and research a mechanisms that can possibly consider them in the developed system without affecting the false alarm rate.

→ The developed system is kind of a system, which provide disease outbreak information in a more general format (only notifies the presence of a disease outbreak) without specifying and giving a clue about the possible type of pathogens involved. Therefore, it is necessary to look into the possible disease outbreak characterization mechanism. The research should consider the length of the incubation period for each distinct pathogens and make possible associations between patterns of blood glucose evolution with the presence of infections and its causative agent.

Chapter Ten: Conclusion

Major public health treats are either naturally occurring or artificially induced bioterrorists attack. In any case, it is essential to detect the disease outbreaks as early as possible (before it spreads) to save peoples' life. With the advent of information technology, the transition from paper based into electronic reporting has revolutionized the disease surveillance systems. The most up-to-date advancement due to this transition is the syndromic surveillance systems, which use health related data prior to diagnosis (after the onset of the first symptoms) but after incubation period including absenteeism, internet search volume, over the counter pharmacy drug sells and others. However, a system which uses health related data during incubation period is not yet developed and currently, it is a hot research topic. As part of this advancements in disease surveillance, we proposed the use of inputs from people with diabetes and to detect infectious disease outbreaks during the incubation period. The main idea here is to use people with diabetes as source of information by taking the advantage of blood glucose elevation with the presence of infections. The developed system is expected to detect a cluster of people with elevated blood glucose readings within a specified region and pre-defined timeframe. For example, assume that you are working as both epidemiologist and public health official in a large city, where you are the focal person of the city's office for monitoring and controlling of infectious disease outbreaks. It is obvious that your office will be definitely looking for an early outbreak detection system that can detect any infectious disease outbreak within days after the first person is infected. Let us say on a certain day of the week, there were some peoples infected with respiratory infections such as influenza in a specific part of the city. Moreover, among those infected individuals, let us say ten of them are diabetes individuals with elevated BG readings due to the influenza infection. The individual's elevated BG readings are the result of the influenza infection and appeared before the onset of any symptoms (during the incubation period), even the infected diabetes individuals have no clue about his/her infection status. Therefore, our proposed system is capable of detecting the elevated BG of those ten individuals and sends the necessary alarm for the public health authority, which includes the specific area of the city where the outbreak is detected, the number of infected diabetes individuals and the degree of severity. The proposed system is unique from the rest of the disease surveillance system in that it is capable of detecting the situations within days of its onset (during the incubation period).

We designed and developed a system that can perform the proposed task, detect disease outbreak during the incubation period, by identifying the consecutive high blood glucose readings at an individual and population levels. We present a system consisted of four modules, data collection, blood glucose prediction, outbreak detection, and information dissemination and reporting module. We developed novel approaches for detecting consecutive high blood glucose readings at an individual and population levels. Our approaches are of two types, a type of statistical control algorithm and a moving window z-score process. These approaches are developed based on two type-one diabetes subjects, and the data were collected from continuous glucose monitoring (CGM) device for a period of one month. Moreover, both of these approaches were tested against a simulated blood glucose values (containing consecutive high blood glucose values), which resembles the BG readings of an individual's with the presence of infections.

The first approach, a type of statistical control algorithm, is based on an interval prediction mechanism, where the controls are determined by the predicted intervals. The prediction models are a type of autoregressive model, i.e., Autoregressive (AR), Autoregressive (AR) with Ratio inputs and Autoregressive Moving Average (ARMA). These methods were trained and validated (during validation the trained model was tested with unseen datasets) and were capable of predicting the single-step ahead blood glucose evolution of both subjects with better accuracy. Besides, these methods have also generated optimal prediction intervals for both subjects with a significance level of $\alpha = 0.01$ and, window size of $w = 100$ and $w = 200$ for the first and the second subject respectively. These results indicate that lack of strict behavior in diabetes self-management has a direct effect on the construction of the prediction intervals and one needs to carefully select the optimal window size for the individuals. During testing with the simulated datasets, this approach has performed well in detecting deviated BG values, which shows the effectiveness of our approach. It is more efficient in detecting the slope (from the beginning up to the end of successive increments or decrements), where the BG evolution shows more variability. However, it shows shortcoming in detecting peak BG values with zero slope, where there is no variability between successive readings. This is due to the absence of other supporting parameters such as insulin injection, dietary and physical activity in calculating the prediction intervals, which were not considered in this thesis project due to the limited availability of these data from our subjects. The second approach, the moving window based z-score process involves the computation of z-score values based on a moving window. This approach has also performed well

in detecting deviated BG readings, which shows the effectiveness of our approach. However, the detection accuracy of this algorithm is highly affected by the variability of the individual's BG readings and needs to be tuned towards the individual's BG dynamics by properly selecting the optimal window size.

Generally, both of our early outbreak detection approaches have produced optimal detection results and were capable of detecting statistically significant BG deviation of various size and duration. Both of these approaches are found to be affected by the quality of personal behavior towards diabetes self-management and this needs to be taken into account during large scale implementations. However, considering flexibility, simplicity, computational time, and needs of computational power, the moving window based z-score process is found to be better than the prediction interval based algorithm. Apart from this, these results have clearly shown the effectiveness of the proposed approaches for detecting a cluster of people with similar patterns. Consequently, after validating these approaches on a large scale basis, this promising results will hopefully lead the way for the development of the early outbreak detection system (prototype) based on inputs from people with diabetes, which is considered to be the next generation electronic disease surveillance system.

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Appendix

Appendix A

Journal Article……"Mobile applications for people with diabetes published between 2010 and 2015: A Systematic Review".

SYSTEMATIC REVIEW

Diabetes Management

Mobile applications for people with diabetes published between 2010 and 2015

David-Zacharie Issom[‡,1], Ashenafi Zebene Woldaregay[‡,2], Taridzo Chomutare[2], Meghan Bradway[2], Eirik Årsand[2] & Gunnar Hartvigsen[*,2,3]

Practice points

- Although the related studies are well documented, they mainly focus on clinically relevant features and very little on those that affect a user's perception.
- This review highlights novel criteria like the perception of an app by users, the popularity and ranking given by users, press releases and the presence in social media.
- In order to identify the relevant studies matching our criteria, we searched in the major literature databases, in web search engines and in the vendors' online app stores.
- We found 26 relevant studies in the literature and 53 publicly available systems and apps. The results have shown a relatively high number of well-designed systems with a comprehensive set of features and a good average scoring by reviewers. Few have been recommended by medical specialists but the majority have been tested by patients. Outside of app stores, an app's presence in social media and the press is generally scarce.
- We observed that an increasing number of publicly available systems are integrated with cloud-based solutions and offer interoperability with smartwatches or Bluetooth blood glucose meters. Few systems have obtained any kind of certification or clearance, and we noticed that the certified systems have a higher number of users and a better ranking.
- We suggest that future systems comply with certification authorities and the development be evidence-based, in order to reach a higher level of popularity among users and aim for medical specialists' recommendations.

The use of mobile diabetes self-management applications (apps) is rising. However, current reviews mainly focus on clinically relevant features, and very little on those that affect a user's perception. This review highlights recent developments of these systems, coupled with user perceptions, public presence and availability. After including novel review criteria, we found that most apps have a comprehensive range of features and received good scores from public reviewers. However, the visibility of apps in social media or press is scarce, and few

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systems are recommended by medical specialists. While we noticed that certified systems are more desired, very few obtained certification or regulatory approval. We foresee that these criteria will be influential in user perceptions and ultimate success of future systems.

KEYWORDS
• diabetes mellitus • lifestyle
• mHealth • mobile apps
• self-management

Diabetes is escalating globally and, according to the WHO [1], affects more than 347 million people. While predictions say that the number of cases will double by 2030, the burden can be reduced through prevention and early diagnosis as well as through proper control of the four keystones of self-management: blood glucose and insulin levels as well as physical activity and diet [2]. The rapid advancement and wide spread use of pervasive technologies such as smartphones have paved the way for development of systems potentially helpful in diabetes self-management. The use of mobile apps to support an individual's self-management has been strongly suggested to improve their quality of life [3].

Recently, many reviews have been published regarding mobile diabetes self-management systems [4–8]. Chomutare *et al.* [9] reviewed the salient features of mobile applications for diabetes care, in comparison with clinical recommendations for diabetes self-management. El-Gayar *et al.* [4] reviewed the functional and nonfunctional requirements of applications that were developed between January 1995 and August 2012 together with related issues necessary for large-scale adoption of such interventions. Arnhold *et al.* [6] used experts to evaluate the usability of diabetes applications, and their appropriateness for use by an elderly population. Others include results of surveys or questionnaires that are intended to provide an understanding of users' perceptions. However, because of the structure and formality of these survey proceedings, designed to answer-specific research questions, there is limited consideration of unbiased or unsolicited responses. In effect, reviews conducted by clinical research are unbalanced, giving more weight to the medical use of these tools instead of the core of sustainable and effective use: the users' perceptions of a tool's usability and relevance to their specific needs. Indeed, patients decide what tool stays or goes in the commercial markets.

The concept of usability is a major determinant of a tool or product's sustainability. This is subsequently one of the largest concerns of individuals and health professionals alike regarding the use of mobile apps for diabetes self-management. Because these diabetes self-management tools have a larger presence in the commercial environment than within the medical environment, users' perceptions are shared just as they would be with any other consumer product: openly and honestly through social media and other public sources. In order to best assess their impact and potential, research reviews should take advantage of the candid and unbiased reviews of actual users in addition to targeted surveys through traditional research methods.

The objective of this review is to present a novel approach and an updated review of the most recent self-management solutions found in the literature and in the publicly available markets. Our approach emphasizes an app's appearance in public and social media in order to gain a greater understanding of user needs and an app's adherence to user demands. Our goal is not to predict an app success, but to investigate what apps offer and what patients are asking for. This could show where apps are falling short and in which ways they should be further developed. We also considered the incorporation of recent cloud-based services, emerging wearable devices and fitness apps to illustrate new developments. We describe each app's features according to the four keystones and symptom areas critical to diabetes outcomes [10,11], and to other criteria such as user-friendliness, interoperability, quality controls, popularity in social media and in the vendor online stores, and availability of the systems in terms of languages and platforms. Ultimately, we aimed to use these parameters to determine any correlation between certain app characteristics and its popularity or success among users.

Methods

The coauthors have extensive research experience with mobile applications and have a multidisciplinary background ranging from healthcare and business, to health informatics, statistics, computer science and electrical engineering. Search criteria, categories of assessment and finally the structure of our results are a combination of input from these coauthors and their experience in their fields as they pertain to mobile diabetes self-management systems.

We reviewed a variety of systems such as mobile applications, standalone systems and

prototypes, including systems that are classified as medical devices. We conducted our search between March and April 2015 using Google search engine, frequently referenced journal databases and the online app stores of the most commonly used platforms. We decided to separate search methods and their results by their origin to illustrate the differences in information available between research and publicly disseminated reviews, to further demonstrate the added value of data derived from social media. If a system appeared in more than one source, the results were combined to consider a comprehensive set of information about that system in our review, such as inclusion of available languages and the evidence-based background. Based on available data and our novel set of criteria, we performed evaluation and scoring on each of the selected apps, which is described under each search method type.

• Selection criteria & search strategy for scientific publications

In order to be included in the review, the scientific publications had to exhibit the following characteristics:

- Patient-operated mobile self-help system (e.g., smartphone app, smartwatch app, etc.)
- Support at least one of the self-management tasks (i.e., blood glucose, insulin, physical activity, diet)
- Include an evaluation or description of the system or the app written in English.

Publications excluded from the review were either designed to be exclusively used by healthcare professionals or were published prior January 2010. This 'cut-off date' was based upon the probability of outdated technology. The databases included were Google Scholar, PubMed, ScienceDirect, MEDLINE, ACM Digital Library, IEEE Xplore, DBLP Computer Science Bibliography, *Diabetes Management Journal*, Web of Science, Cinahl, *PLoS ONE*, Cochrane and Munin, the proprietary database of the University of Tromsø– The Arctic University of Norway. Searches were performed on peer-reviewed journals and journal publications of conference proceedings. The terms used were 'diabetes,' 'mobile,' 'smartphone,' 'system,' 'phone,' 'app,' 'application,' 'self-management' and 'self-help.' Logical operators 'AND' and 'OR' were used to combine the terms in multiple ways. First, we identified relevant articles by reviewing the titles, keywords and abstract for a preliminary filter with our selection criteria. We then reviewed full texts for articles that seemed relevant.

• Selection criteria & search strategy for publicly available systems

We searched for information regarding publicly available mobile diabetes systems on Google search engine, blogs and patient association websites. Publicly available systems are available on major vendor app stores, including Google Play Store as well as app stores specific to various mobile phone platforms including Blackberry App World, Apple iTunes, Nokia Ovi Store and Windows Phone Store. We used the terms 'diabetes' AND 'mobile' OR 'app' OR 'self-management' on the search engines and webpages, but only used the unique term 'Diabetes' on the app stores. We included systems that were attached to insulin pumps directly, which we separately classified as standalone 'Proprietary' mobile systems. Inclusion criteria for the publicly available systems are defined as follows:

- Mobile apps and systems that have a user interface in English
- Mobile apps and systems that are publicly available for free or for purchase
- Mobile apps and systems that provide at least the function for self-monitoring of blood glucose (SMBG)
- Mobile apps and systems that had a rating of more than three stars.

We excluded the mobile apps and systems that could only be considered as educational or informational tools, meaning those that did not provide any direct functionality for the self-management of diabetes-related issues.

• Selecting studies & apps for inclusion

From the search completed in the literature databases, one coauthor (AZ Woldaregay) vetted the initial hits to assess their relevance to our inclusion criteria by evaluating the titles, the keywords and the abstracts. Next, the two primary-authors (AZ Woldaregay and D-Z Issom) independently evaluated the full text of the selected studies. The inter-rater agreement was measured using the Cohen's Kappa test, and disagreements were resolved through discussion.

• Data categorization & data collection

Categories, upon which we extracted relevant app information, were based on previous research a literature reviews and further elaborated upon via iterative brainstorming among the coauthors. The agreed upon categories are as follows:

- Diabetes-related features: Diabetes self-management functionalities such as the tracking of physical activity, dietary habits, insulin doses and/or blood glucose measurements, among others. We used the following scoring mechanism to assess depth of the features:
- 0 was assigned if no chart, statistics or trends were available.
- 1 was assigned if the system or app was able to show trends, charts, lists or statistics.
- 2 if the system had more advanced graphs or statistics such as averages, deviations, distributions.
- Popularity and presence in social media: Popularity is also characterized by user feedback and comments, the number of installations, the number of ratings by reviewers and the score they gave as well as a system or app's presence on social media characterized by the number of likes on Facebook, the number of re-tweets and the number of Press releases.
- Availability: The platforms available, their cost and the languages in which a system or app can be used.
- Interoperability and 'shareability': Interoperability is defined by the ability for a system to communicate with other systems for data input or for data export. A main feature associated with this criterion is data export, which enables the app or system's ability to share data, thus taking into account the openness to other systems. We identified the information related to the format of data export, the compatibility with third-party apps, cloud-based solutions for the backup of data, the ability to transfer data to an electronic health record, compatibility with blood glucose meters or with other wearable devices such as smartwatches. We also considered the concept of 'shareability,' which describes the possibility for an app or system to mutually share information, for instance, on social media like Facebook or Twitter and also through other apps. It includes the ability of a system to be used by more than one user through, for instance, several accounts.
- User friendliness: This is defined by one main criterion; the type of data input, which can be manual or automatic. We did not assess the User Interface (UI) design or the quality of presentation.
- Quality assurance and regulatory oversight: This criterion identifies systems that are CE marked, FDA cleared or HIPAA compliant. A CE marking means that the system has been verified and complies with the safety and health standards defined in the European Union. The FDA clearance means that the use of the system or app for clinical treatment or prevention of the diabetes has been approved. A HIPAA compliant product follows the American law on the protection of personal healthcare information. This is also characterized by the level of maintenance of a system or app, including information regarding last update.
- Research based*:* This category identifies if the development of the system or app is driven by evidence-based research and if patients or clinicians have evaluated the system or app. For instance randomized clinical trials, or validation or evaluation tests done by individuals or groups other than the developer.

Results

• Search results for literature systems & apps

The literature review search retrieved a total of 287 papers (Google Scholar, n = 140, ACM n = 23, PubMed n = 51, IEEE Xplore n = 15, Medline (PMC) n = 36 and Munin n = 22). After removing duplicates, there were 272 records remaining. As illustrated in **Figure 1**, screening, which was based on our inclusion and exclusion criteria, eliminated 196 papers, leaving 76 relevant papers (Google Scholar n = 29, ACM n = 3, PubMed n = 21, IEEE Xplore n = 13, Medline n = 5 and finally Munin n = 5).

The inter-rater agreement, calculated using the Cohen Kappa test, was 0.595. According to Landis and Koch [12], this score is considered as a moderate agreement. Finally, 26 articles were accepted by consensus, and the study characteristics are shown in **Table 1**. Most of the studies 77% (20/26) were about design of the application or usability evaluations, and only 23% (6/26) were clinical trials or pilots assessing health outcomes.

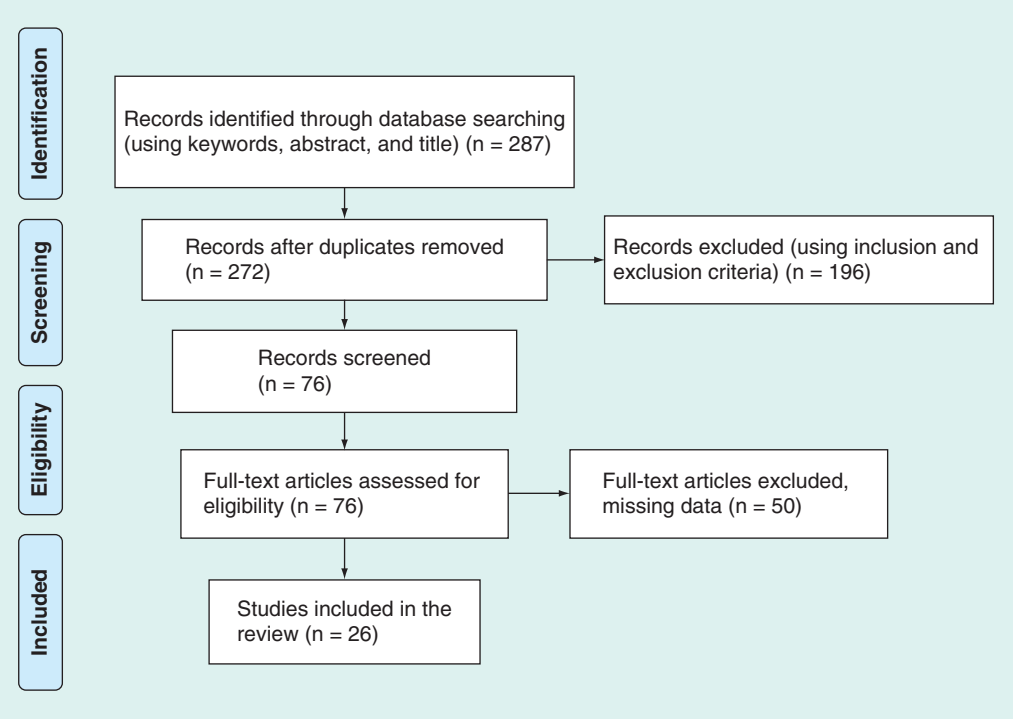

Figure 1. Flow chart of reviewed articles.

Two studies had a specific focus on children with Type 1 diabetes, and the follow-up period for clinical studies was 6 months or less. We present the literature-extracted studies and publicly available systems in two different tables, because most of the literature systems are prototypes, not publicly available for patients. We identified three applications used in the studies, which were also available on public vendor markets.

• Search results for publicly available systems & apps

The search for systems and apps occurred in April 2015 (Google Play store n = 261 apps, Apple iTunes n = 4000 apps, Windows Phone n = 240 apps, Blackberry App World n = 66 apps and the conference proceedings search n = 5 apps and systems). Searches in blogs, websites and patients associations' websites retrieved 81 apps and systems. After screening with the inclusion criteria, comparing the papers' abstracts, full texts, apps descriptions, testing the apps and discussing with the coauthors, 53 eligible apps remained, as illustrated in **Figure 2**.

Evaluation of the systems & apps

• Diabetes-related features

From the 26 relevant studies, 46% (12/26) have functionalities that support all four keystones of diabetes self-management, 16% (4/26) support at least two of the four keystones. We found that systems only supporting SMBG without another keystone accounted for 23% (6/26). The systems support nutrition 65% (17/26), exercise 62% (16/26) and medication management needs 58% (15/26).

The majority of the relevant studies extracted from the literature, 57% (15/26), provided statistics to the users. We gave one point to 30% (8/26) of the studies and the maximum two points to 27% (7/26) of the studies, based on our grading scheme for advanced graphs or statistical features.

From the 53 publicly available systems, 72% (38/53) have features that support the four keystones. Of these apps, 85% (45/53) allowed the user to manage their medication, while 77% (41/53) have a physical activity functionality and 85% (41/53) have a nutrition management feature.

We gave at least one point to most of the charts offered by the publicly available systems based on presence of basic statistics or trends. However, a few 28% (15/53) of the systems offered more advanced graphs or statistics.

• Interoperability aspects of the systems

Of the 26 relevant literature studies, only 8% (2/26) described their data export and import

Table 1. Included studies from the literature, sorted by year of study.

Study	Participants	Follow-up (months)	Diabetes/age	Type of study (design, usability, clinical study)	Year	Public market	Ref.
Quinn *et al.* (2015)	7	1	Type 2, elderly	Clinical study	2015	Yes	[13]
Årsand *et al.* (2015)	6	N/A	Type 1	Design, usability	2015	Yes	[14,15]
Padman *et al.* (2013)	8	2	Type 1, children	Clinical study, usability	2014	–	[16]
Bin-Sabbar (2013)	-	-	N/A	Design, usability	2014	–	[17]
Waki *et al.* (2014)	5	3	Type 2, adults	Clinical study	2014	–	[18]
Dohr *et al.* (2012)	-	-	Type 2	Usability	2014	–	[19]
Mougiakakou *et al.* (2010)	12	1/3	Type 1	Design	2014	–	[20]
Gittens *et al.* (2014)	45	N/A	N/A	Usability	2014	–	[21]
Tsui *et al.* (2014)	60	6	Type 1, Type 2, adults	Clinical study	2014	–	[10]
Le *et al.* (2011)	5	1/6	N/A, adults	Design, usability	2013	–	[22]
Takenga *et al.* (2014)	40	2	Type 2, adults	Clinical study	2013	–	[23]
Villarreal *et al.* (2014)	20	N/A	N/A, adults	Design	2013	–	[24]
Stroulia *et al.* (2013)	-	-	-	Design	2013	–	[25]
Tsai *et al.* (2012)	5	2	Type 1, adults	Clinical study, design	2012	–	[3]
Cai *et al.* (2012)	-	-	-	Design	2012	–	[26]
Batool *et al.* (2014)	276	N/A	N/A	Design	2012	–	[27]
Cafazzo *et al.* (2012)	20	3	Type 1, children	Usability	2012	Yes	[28]
Gislason *et al.* (2012)	N/A	N/A	N/A	Design	2012	–	[29]
Alhazbi and Alkhateeb (2012)	-	-	-	Design	2012	–	[30]
Pandey *et al.* (2012)	5	1/2	Type 1, Type 2	Usability	2012	–	[31]
Lee (2011)	27	N/A	Type 2	Design, usability	2011	–	[32]
Kim and Seo (2014)	N/A	N/A	N/A	Design, usability	2011	–	[33]
Rollo *et al.* (2011)	10	1/10	Type 2, adults	Design, usability	2011	–	[34]
Harris *et al.* (2010)	14	N/A	Type 1, Type 2, adults	Usability	2010	–	[35]
Curran *et al.* (2010)	6	1/2	N/A	Design	2010	–	[36]
Valdez *et al.* (2010)	22	N/A	Adults	Design, usability	2010	–	[37]

mechanisms. Harris *et al.* [35] describe the use of Extensive Mark-up Language (XML) and Årsand *et al.* [14] describe the use of CSV, XLS, PDF or a formatted e-mail for the export of data. Approximately 35% (9/26) used a Bluetooth interface for wireless data input from blood glucose meters. In terms of standards-based data interchange, only one study 4% (1/26), Takenga *et al.* [23], implemented the Health Level Seven International (HL7), Web Services Description Language (WSDL), Clinical Document Architecture (CDA) and XML standards. Cafazzo *et al.* [28] integrated their system with a cloud-based electronic health record (TELUS) powered by Microsoft's HealthVault, and Årsand *et al.* [14] integrated their system with Pebble smartwatch, RunKeeper fitness app and also with Bluetooth blood glucose meters. In contrast, 54% (14/26) did not use any kind of wireless data transfer standard.

The majority of the publicly available systems offer some form of data export 81% (43/53). However, few offer a raw data format for export like CSV 23% (12/53) or XLS 34% (18/53). The most common form was via e-mail 45% (24/53). Of the less common data export options were iTunes (n = 1), Twitter (n = 1), web platform (n = 5), desktop (n = 1) or plain text (n = 3).

In publicly available systems, we found that many apps offered a wide variety of interoperability options, but less than half 34% (18/53) offered any kind of support for other systems or devices. The apps were compatible with cloud-based services offered by Apple Health Kit, Microsoft HealthVault, Google Fit, Google Drive, OneDrive or Dropbox. Two of the smartphone-based apps (NST's Diabetes Diary and Diabetes:M) and one standalone system (Dexcom G4) include a user interface designed for smartwatches like Android Wear, Apple Watch or Pebble.

• Availability of the systems

Based on extracted information from the literature studies, **Figure 3** (left) shows the distribution of available platforms. As shown, many of the systems have been exclusively developed on Android 42% (11/26). However, not all specify the platform of development 19% (10/53). Complete results are displayed in **Supplementary Data 1**.

The publicly available systems show a different distribution. Most of the systems are available on Android 51% (27/53) and/or iOS 53% (28/53), with some available on multiple platforms. As shown in **Figure 3** (right), the less common platforms included Blackberry. We found only three standalone systems: one Blackberry app, one app on Nokia Ovi Store and one for Amazon Kindle. More details on the platform availability are in **Supplementary Data 2**. We found that most publicly available apps were free 81% (43/53), and 30% (16/53) of the apps were available in an additional language other than English.

• User-friendliness

In the 26 studies from the literature, 54% (14/26) support both automatic and manual data input, while 42% (11/26) support only manual entry and 4% (1/26) support only automatic only data entry. Among the publicly available systems and apps, the majority 89% (47/53) offered manual data input, while 38% (20/53) offered automatic and 25% (13/53) offered both.

• Quality assurance & evidence-based research

Of the literature studies, 46% (12/26) performed some form of evaluation. Interviews and questionnaires, mainly for clinicians, were used in 35% (9/26) of the studies, while 23% (6/26) assessed clinical outcomes. Regarding the publicly available systems, 8% (4/53) were FDA approved, 4% (2/53) were HIPAA approved and 6% (3/53) were CE approved. Most 89% (47/53) of the systems found in the publicly available places have not been evaluated by patients through questionnaires, usability or acceptance studies.

• Social media presence

Of the systems found in the literature, we found that only the system by Årsand *et al.* [14] had an appearance on Facebook (502 likes) and the app made by Cafazzo *et al.* [28] on Twitter (78 times).

28% (15/53) of the publicly available apps have been reviewed by more than 400 users. 64% (34/53) of the apps have a score of at least four stars. 84% (21/26) of the Android apps have a score above four stars in the Google Play Store, while 70% (18/26) of the iOS store have a score above four stars. We observed that the apps on Android have the highest scores, while iOS and multiplatform apps are the most popular on social networks (see **Supplementary Data 2**).

Most of the apps found in the literature did not have any press releases 96% (23/26). We also found that 68% of the papers are neither widely cited nor viewed/downloaded in social

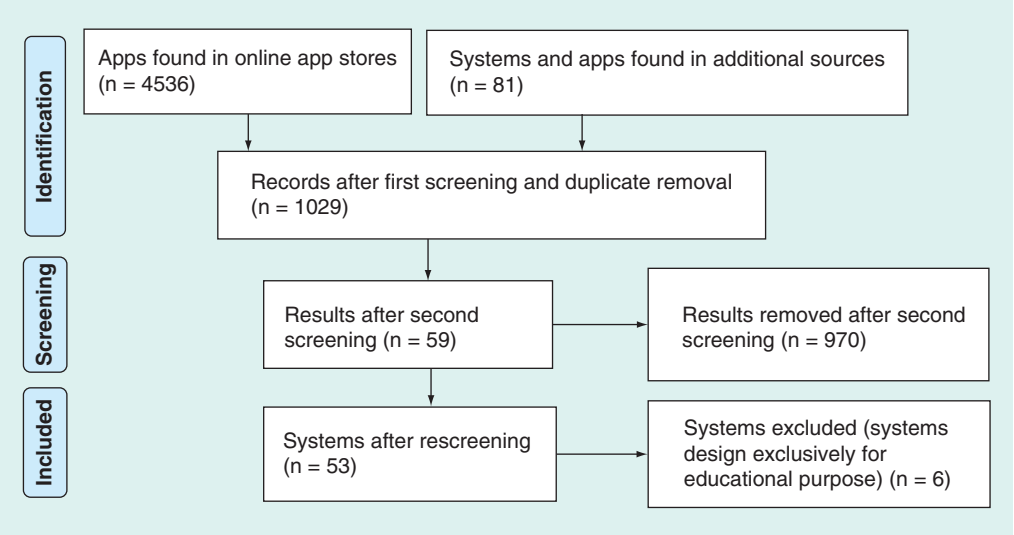

Figure 2. Flow chart of the publicly available systems.

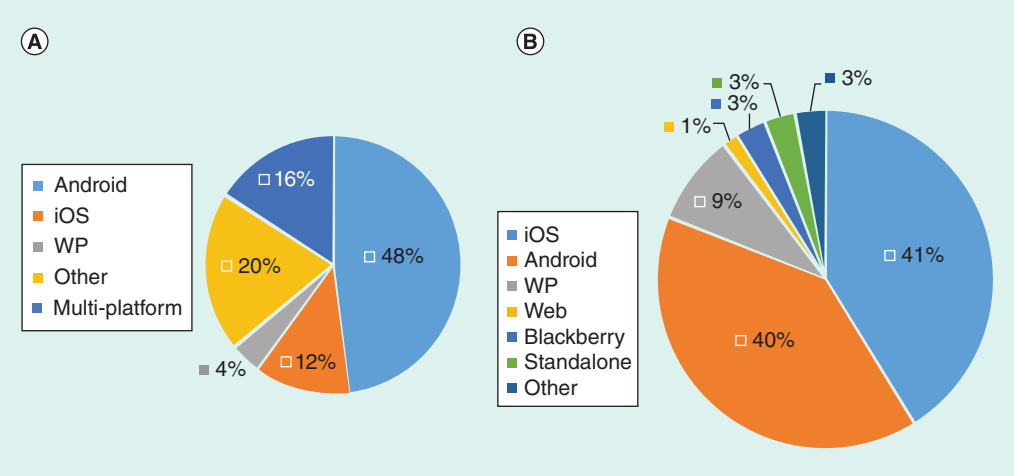

Figure 3. Platforms for literature-extracted studies (left) and publicly available systems (right).

media such as ResearchGate or Facebook, while 88% did not have any social media presence. Twitter and Facebook are equally represented and press releases are the most popular way of communicating about the apps. We noted that only the Google Play store provides information regarding number of current installs. The mean score of the apps that have not been updated since January 2014 is 3.8 stars and that of more recently updated apps is 4.2 stars.

Discussion

From these results, we were able to make additional inferences about apps than were not evident through research and literature-based studies alone. While clinical research provides essential information regarding relevance to the medical realm, by including such novel sources as social media and public reviews, we introduce a number of features of the apps, and characteristics surrounding the apps themselves, that influence an app's relevance to users' needs, in other words, the context in which they are used.

An important finding is the absence of most of the literature-extracted studies in social media or press releases, limiting the possibilities of evaluating the users' perception of literature papers and limiting it to the clinicians' perception and approval. Overall, the most popular methods of dissemination were via press release on tech blogs or public information from companies and communications through popular science articles. And, while we expected much more information from Twitter and Facebook sharing, consistent with their prevalent use, most apps are not shared or discussed on social networks. However, of those that were present, we found that the most commented on or 'liked' apps on social media tended to have a comprehensive set of features. This supports previous accounts by Quinn *et al.* [13,38–39], who reported that patients' self-efficacy could be improved by using apps that incorporate a comprehensive set of features.

It is difficult to demonstrate it, but compliance with standards and the use of gamification concepts seem to result in more comprehensive and well-received apps. Additionally, despite the fact that more evidence is need, clinical approvals and regulatory authorities compliance might ensure that an app is harmless. Moreover, patients who use only few of the publicly available apps such as MySugr Diabetes Logbook, NST Diabetes Diary, WellDoc BueStar Diabetes or BANT are founded on evidence-based research [14,28,40]. Such systems are often validated by randomized clinical trials that help to convince medical experts to recommend the apps to patients. Furthermore, based on examples we found, like BlueStar and mySugr, an app may be used and recommended more likely if it is integrated within the healthcare sector or showed a compliance with evidence-based practice and certifications authorities like the US FDA or CE.

Following with more granular details of an app's context, we observed that timing of release and the presence of more recent updates directly corresponded with the number of 'likes', comments or similar displays of attention during that time. We also found that iOS and multiplatform apps receive the most 'likes' within social network sites. However, there was no clear influence

of the price on an app's download trends or positive feedback from users. Moreover, nonfree apps have a mean score of 4.3/5 stars within app stores. This suggests users are willing to pay for apps of good quality.

Unexpectedly, we observed that an app's presence in social media was not necessarily dependent upon the level of usability. Some apps we judged to be less user-friendly had a strong social media presence. This finding seemed rather counter-intuitive because we expected apps with inferior design elements to have less social media visibility. This suggests that social media presence must be considered in the context of other metrics such as number of installs, ratings by users and recommendations by fellow patients or medical specialists.

We selected our ten 'favorite' apps (see **Table 2**) based on the design elements discussed in this study.

• Risk of bias & other limitations

Selected literature studies mostly focused on design and usability, and only a few assessed clinical outcomes. In spite of more than a decade with mobile applications, we have not seen many credible clinical trials. The studies that assessed clinical outcomes were poorly designed, with very short follow-up periods, and many had just a handful of participants, yet they made extraordinary claims. This poor evidence may partially explain why we have not seen many mobile application recommendations from clinicians or clinical guidelines.

In terms of search for publicly available systems, some online markets have restrictions on selected applications. There are applications with region restrictions that could not be found by normal search in the Norwegian Google Play market. This may have limited our reach, but it is unlikely that this limitation significantly affects our overall findings as we were able to contact developers directly for information for most apps in our review. Additionally, we omitted apps that did not include SMBG, putting the focus on the patients with the biggest self-monitoring needs.

The exclusion of the apps that have been ranked under three stars add bias in the calculation of the average rankings and should be taken into account. Furthermore, we do not know who is rating the apps, adding another risk of bias.

Conclusion & future perspective

An EU-funded report [41] found that, among individuals with diabetes, the most important

Table 2. Top ten most user-friendly diabetes self-management apps in rank order.

	Developer	Product	Platforms	Highlights
1	mySugr GmbH	Diabetes Logbook	iOS, Android, Web Browser	Growing list of compatible Blood Glucose Monitoring (BGM), compatible with Apple Health Kit, automatic data entry, large possibilities of data export, GUI full of gamification items, evidence-based, standard compliant and FDA, CE marking, praised by communities and the press, notable popularity and generally supported in social media. doi:10.1177/1460458214537511
2	WellDoc, Inc	BlueStar Diabetes	iOS	Comprehensive features, FDA cleared, the UI gives an immediate feedback on the automatic glucose data entries. It is supported by evidence-based research, and is highly recommended by doctors but must be prescribed. doi:10.1089/dia.2014.0341
3	NST	Diabetes Diary	iOS, Android	Effective and simple UI, very good interoperability, CE marking pending, based on research, evidence-based, RCT, automatic data entry. doi:10.1089/dia.2014.0276
4	MyNetDiary	Diabetes Tracker	iOS	Attractive design, full platform compatibility, follows best practices, praised in social media, regularly updated
5	Nicholas Martin	Diamedic	iOS	Follows best practices, sleek and simple UI, regular updates
6	FridayForward	Diabetes Diary	iOS	Large data export possibilities, very pleasant UI, charts and functions
7	MedHelp	Sugar Sense	iOS, Android	Many compatible devices, clear UI, lack of data export
8	Coheso	Track3	iOS	Sufficient level of interoperability, low level of maintenance
9	Taconic System	Healthsome G	iOS	Excellent possibilities of data export, large set of health data tracked, dated UI that can be difficult to read
10	Sanofi-Aventis	iBGStar Diabetes Manager	iOS	Pluggable BGM compatibility, simple UI but lack of updates and additional information

aspects of a diabetes app are the trustworthiness and accuracy of data or information. These are concepts which are tested throughout traditional research methods for health authority approval. Design approaches that take into account compliance with standards such as HIPAA, FDA clearing and CE marking, seem to enhance the quality of the apps and increase the chances of success among the users. Although research-based apps help build quality evidence for informing related clinical guidelines, they were not necessarily the determining factor of success among real-time users. Herein lies the potential for expanded review methods.

This review highlights areas which may contribute to sustainable use by patients, therefore, what will influence the greatest positive impact, and which much be considered by medical and commercial researchers. We have demonstrated that social media can be a positive tool for raising awareness of high-quality products. As more common trends suggest, we predict that in order to remain relevant and maintain the interest of users, developers must constantly attend to user comments, fix issues and update systems according to state of the art APIs available on the platforms. An outdated system that, for instance, does not offer any possibility for automatic data export or entry can become obsolete or undesirable the long-term and, thus, not relevant to patients and current users. Furthermore, although the number of user comments can be overwhelming, the feedback loop fosters attractive designs that are sensitive to user needs.

Our approach is a pilot study in itself of what is available and what should be included in the review of patient-empowering and patient-operated tools for disease self-management. Future trends that we expect to make a great impact on the medical realm as well as an individual patient's life include the observed growing trend in the use of wearable devices. From our results, we can predict that patient's will welcome the ease of use, ever presence and possibilities that this next generation of mobile and personalized health will offer. Therefore, we expect to see more concerted efforts toward the development of systems that are compatible with several devices and platform standards, like Apple Health Kit, Microsoft HealthVault or Google Fit. We foresee that greater interoperability by integrating platform standards [42] will be a valuable feature for future developments [43]. This ability facilitates the integration of more advanced features and could allow for the use of data for clinical decision support systems. Previous studies have reported that such features can lead to better long-term use, a greater interest, higher user ratings, higher number of users and, overall, better acceptance level among users [44].

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at www.futuremedicine.com/doi/full/10.2217/dmt.15.40

Acknowledgements

Special thanks to the Diabetes Group at the Norwegian Centre for Integrated Care and Telemedicine for their very close support, their useful feedback and advices.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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Appendix B

Conference Article ……." Electronic Disease Surveillance System Based on Inputs from People with Diabetes: An Early Outbreak Detection Mechanism"

Electronic Disease Surveillance System Based on Inputs from People with Diabetes: An Early Outbreak Detection Mechanism

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Abstract

Pandemics or epidemics are serious concerns for any public health authority and mandate for proper monitoring and early detection strategies. In this study, we focus on people with diabetes and propose the use of continuous blood glucose, insulin, and dietary data, to develop an algorithm for the early detection of infections during the incubation period (i.e. before the onset of the first symptoms).

We present a system that consists of three modules: the blood glucose prediction, the outbreak detection, and the information dissemination and reporting module. The novel approach incorporated in the system is an interval prediction mechanism that is based on a set of autoregressive models and predicts the blood glucose values for an individual with diabetes. The actual blood glucose value is compared against the predicted interval, which is generated using autoregressive (AR) and Autoregressive moving average (ARMA) methods. The system was trained and validated based on continuous blood glucose measurements (CGM) from two individuals with type 1 diabetes. The single step point prediction was found to be accurate with a Root Mean Square Error (RMSE) of 0.2121 mmol/l. Moreover, we accurately monitored the blood glucose fluctuations for an individual with a significance level of α =0.01. The model was also tested against an artificially simulated dataset, which resembles blood glucose evolution of an infected individual with diabetes, and successfully detected statistically significant deviations from the normal blood glucose values. Our prototype system is still under development and has not been fully tested yet. Our initial findings though are promising and we plan to further test and validate our approach.

***Keywords**:*

Diabetes Mellitus, Continuous blood glucose measurement, Self-management system, Blood glucose prediction, Outbreak detection, Electronic disease surveillance.

Introduction

Most of the existing self-management applications for people with diabetes include modules for continuous monitoring of the blood glucose measurements (CGM) to assist individuals in better controlling their blood glucose (BG) levels. Mobile devices and smart phones offer considerable advantages towards the development of sophisticated apps [2, 9, 11, 14]. Recently, mobile self-management applications for people with diabetes have been integrated with Electronic Health Records [4, 13, 15]. If this integration is coupled with timely CGM data from people having diabetes, it can further enhance the establishment of efficient and effective disease surveillance systems.

Previous findings indicated that BG levels are elevated due to any exposure to pathogens [10]. Årsand et al. demonstrated an elevation in BG levels for both type 1 and type 2 diabetes individuals after the infection by Influenza, Cholera, Plague, Ebola, Anthrax, or SARS viruses [3]. Botsis et al. also described the positive correlation between BG elevation and infections in people with type 1 diabetes [7]. These findings suggest the potential use of the BG parameter for the early detection of disease outbreaks in the general population [3, 7]. Other parameters (such as body temperature, white blood cell count and blood pressure) are directly associated with the presence of infections in the body [6, 12]. Multiple incidents with abnormal values for the above parameters in the population may indicate the presence of an outbreak [1, 10]. We therefore argue that the incorporation of all these parameters into advanced modeling solutions can potentially support the early detection of outbreaks. The objective of our research is the development of a reliable electronic disease surveillance system for the analysis of diabetes data at both the individual and the population level. In this paper, we describe our initial exploration and our first-hand results.

Materials and Methods

Datasets

This research was conducted using data from two individuals with type 1 diabetes. The Dexcom CGM and the diabetes diary[1] that have been developed by Norwegian Center for E-health Research (previously known as NST) were used for the data collection. These modules are part of a mobile applica-

tion designed for diabetes management. The collected data included continuous BG measurements from the Dexcom CGM (in 5 minutes intervals) for one month and BG, insulin, diet and physical activity data from the diabetes diary for one year[1]. We used these datasets to train and validate the developed system for its goodness of fit to the BG dynamics of the two subjects in their non-infection status. We subsequently tested our system with a simulated dataset that included consecutive patterns of high BG values; this resembled the CGM during the infection period. Various increments per minutes ($\frac{\Delta BG}{minutes(t)}$) and various time intervals of elevated BG were considered.

Methods

The system can predict the BG values with a confidence interval and assess this prediction against the actual BG values. It can further analyze the measured and predicted BG values for the presence of any aberrant pattern. If there is a detection of any abnormality, the system will generate and send a notification signal to the concerned bodies or authorities and support the investigation by displaying this on the map of the interest. The system consists of a BG prediction module, an outbreak detection module, and an information dissemination and reporting module.

Blood glucose prediction module

This module includes a personalized health model that monitors the BG fluctuations of the individual with diabetes. It predicts the single step BG value using the previous BG, insulin, diet and physical activity records. This module also calculates the confidence interval of the predicted values based on the recent empirical distribution of errors between the actual value and the predicted value. The prediction module utilizes a black box approach using an autoregressive model that incorporates Autoregressive (AR), Autoregressive with Exogenous input (ARX), Autoregressive Moving Average (ARMA), and Autoregressive Moving Average with Exogenous input (ARMAX) methods. Autoregressive models were selected because they rely on the most recent information to forecast the future values. In our approach, it is very important to follow the persons' cyclical habit on a weekly or longer-period basis. The model simplicity and reproducibility were the factors that were considered in our selection. The well-defined procedure for calculating the intervals of the forecasts is definitely important as well. We evaluated and compared the performance of these models using the Root Mean Square Error (RMSE) function.

Outbreak detection module

The outbreak detection module is necessary for comparing the actual BG values with the predicted intervals. This module is built on mathematical models that can compare and detect any statistically significant deviations between the measured and the predicted BG values. This outbreak detection mechanism evaluates whether the actual BG values are outside of the predicted interval for the individual. Moreover, moving window z-score are used for better detection accuracy. The purpose of this moving window z-score is the detection of any significant deviations (anomalies in the data) based on the moving mean and standard deviation. Given a window size w, the mean and standard deviations are used to check the agreement of the actual BG measurement with the previous trend in w. This module also performs an aggregation analysis, which counts the maximum number of events on a spatio-temporal basis. In other words, it detects a disease outbreak in both space and time using a specified threshold that is defined based on the region it covers (space) and occurrence of statistically deviated BG values (time) for a number of individuals. If the number of people in the cluster exceeds the threshold, an alarm will be sent to public health authorities or hospitals. The performance of this module is evaluated based on the accuracy of detecting the cluster in a timely manner. A Receiver Operating Characteristic (ROC) curve is used to determine the best operating threshold of the system.

Information dissemination and reporting module

A principal function of the disease surveillance system is the generation of reports containing information about the detected disease outbreak. The related information is presented in tables, graphs and maps. The corresponding module submits the reports to the authorities and other interested parties via SMS and Email. Initially, an SMS is sent followed by an email to the responsible persons with the adequate information regarding the outbreak. The email contains information about the spatial and temporal distribution of the disease outbreak on a map of the region, the degree of severity and other critical data.

Design and Implementation

Prediction Model and Interval Prediction

The prediction of the BG values is based on an Autoregressive model including autoregressive with Yule Walker Algorithm, Autoregression using ratio of consecutive data points and Autoregressive Moving Average using Yule Walker Algorithm.

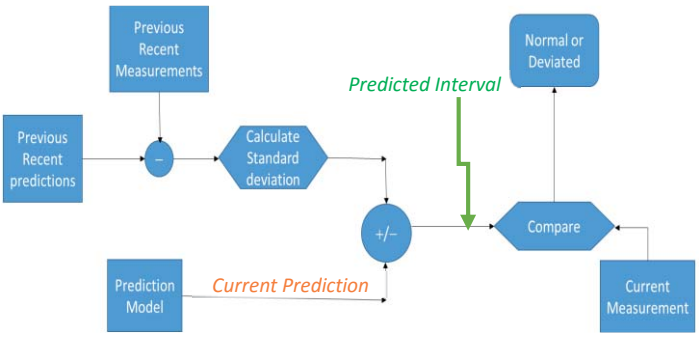

Figure 1: The Proposed Algorithm

Based on the point prediction and the empirical error distribution between the measured and the predicted value, a prediction interval is calculated with a certain confidence interval (1-α)*100%, where α is the level of significance [8].

[1] www.diabetesdagboka.no

As shown in Figure 1, the proposed algorithm computes the predicted intervals based on the previous recent predictions and measurements along with the current point predictions. The empirical distributions of errors between the previous predictions and measurements are the basis for the current interval prediction. This is clearly shown in Figure 1, where the predicted intervals are compared with the current measurements.

The system was developed in MATLAB version R2015b. A system identification toolbox along with the partial autocorrelation function (PACF) was used to identify the optimal model order. The autoregressive (AR) and autoregressive moving average (ARMA) were developed based on the CGMs that are shown in the Figure 2.

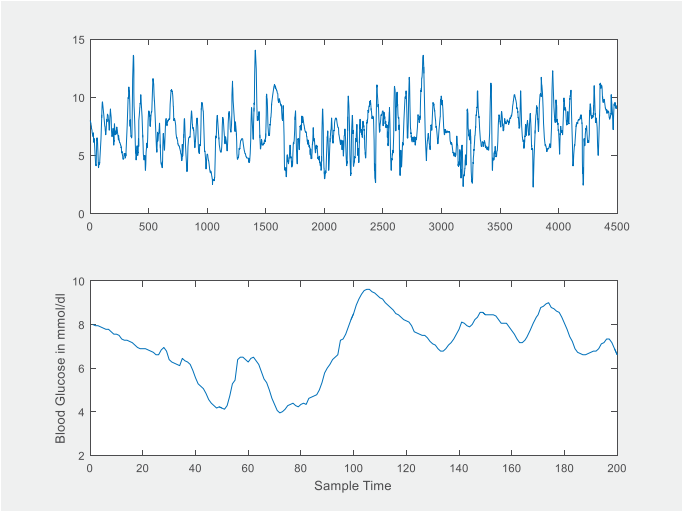

Figure 2: Plot of the entire sets and the first 200 data elements of the continuous blood glucose data.

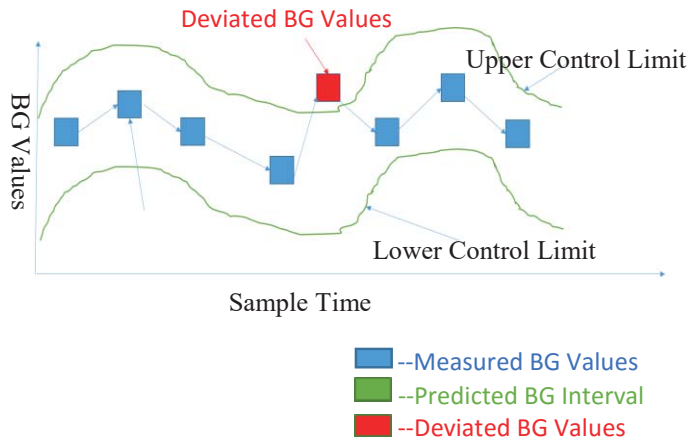

Figure 3: The proposed solution for the detection of the blood glucose deviation for an individual patient.

Outbreak Detection/Surveillance

The proposed solution is similar to a control chart/statistical process control algorithm, where the controls are determined by the intervals predicted from the individual blood concentration profiles defined by the AR models. As shown in Figure 3, the next BG value can be effectively controlled by the predicted upper and lower control limits with a reasonable accuracy. Moreover, as described in the above section (see outbreak detection module), the output results from the moving window z-score and the output results from the predicted intervals mechanism are augmented for better accuracy.

Results

We used the autoregressive models to predict the BG values using CGMs in 5-minute intervals. Autoregressive model using Yule-Walker algorithm, autoregressive model using ratio of the consecutive data points and autoregressive moving average with Yule-Walker algorithm were implemented and tested for 8495 data points. The RMSEs were calculated for 4495 testing data points. The first model, a fifth order autoregressive (AR), efficiently predicted the single step BG values with a RMSE equal to 0.9727 *mmol/l*. The second model, a fifth order autoregressive, is also capable of predicting the single step BG values. The prediction produced interesting results with a RMSE equal to 0.3413 *mmol/l*. Furthermore, the third model, an autoregressive moving average with a third order autoregressive terms and a second order moving average terms, is also capable of predicting the single step BG values. The prediction generated promising results with a RMSE equal to 0.2121 *mmol/l*. The prediction interval calculated from these models was constructed with a significance level of $\alpha = 0.01$, which means that one is 99% confident that the future values fall within the predicted intervals. Both the first and the second models produced intervals with reasonable sizes. However, the third model had a shortcoming in producing a good prediction interval, which is too narrow.

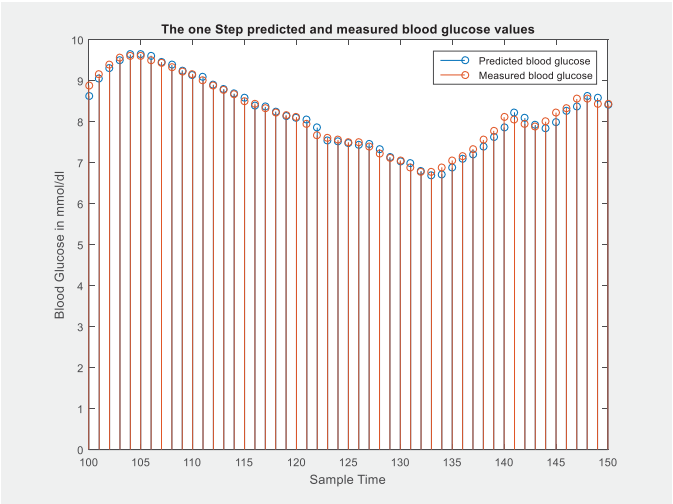

Figure 4: The predicted and measured blood glucose.

The point prediction and its interval prediction for the single diabetes subject are given in the Figure 4 and 5. These results were generated from the first model, the Autoregressive model using Yule-Walker algorithm.

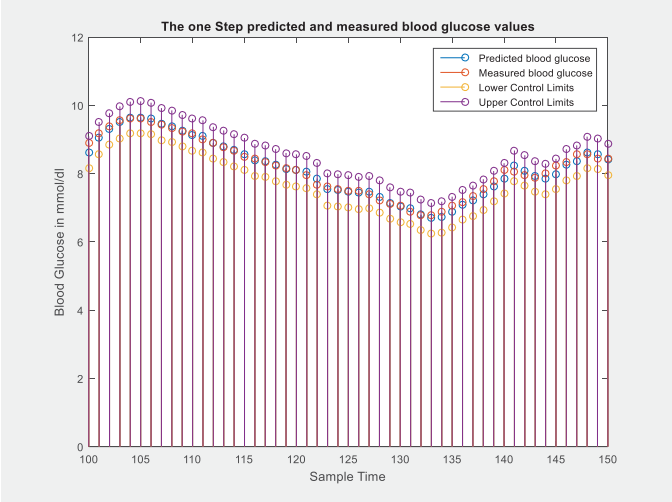

Figure 5: The predicted interval, predicted and measured blood glucose.

The moving window z-score process is also capable of detecting high BG values based on trends for various periods and rates of growth. For example, as shown in Figure 6, it can detect BG values over a long period of time. Therefore, an outlier can be detected by setting threshold values of three and more standard deviations from the mean value.

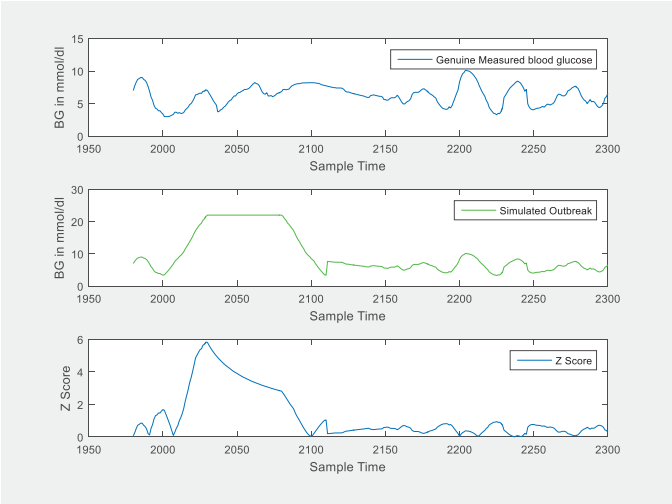

Figure 6: Measured blood glucose, simulated outbreak and the moving window z-score.

Assumptions, Biases and Limitations

The major limitation of this project is the sample size. We based our experiments and simulation on two individuals with type 1 diabetes, and more data is needed to further validate our approach. Moreover, the "holiday effect" has not been considered in this study. The "*Holiday effect*" is the bad eating style of people with diabetes in the holiday season [10] and usually leads to high BG values. In such cases our system may generate false alarms, especially given the absence of frequent measurements for other supporting parameters, such as the white blood cell counts and temperature readings from these individuals [5, 6].

Conclusion

With the advent of information technology, the transition from paper- into electronic-based reporting has revolutionized the disease surveillance systems. Our system should be grouped under the syndromic surveillance systems that also use certain data (absenteeism, Internet search volume, over the counter pharmacy sells and so forth) prior to the confirmation of infections through diagnosis. However, this information is generated after the onset of the first symptoms and syndromic surveillance systems that focus on the incubation period have not been developed yet. This is the novel and unique characteristic of our work. Our system incorporates a BG prediction mechanism that can both predict the BG values for an individual and efficiently detect an infection during the incubation period. Even though we have not fully tested and evaluated our approach, we believe that our initial findings are very promising to support our next steps. The systematic evaluation and validation of our system is among our future plans. We also hope to pave the way for the next generation disease surveillance systems.

Acknowledgements

The project is part of the Electronic Disease Surveillance Monitoring Network (EDMON), led by the University of Tromsø – The Arctic University of Norway and the Norwegian Centre for eHealth Research, University Hospital of North Norway.

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