Automated Glucose Control: A Review

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ABSTRACT

Automated blood glucose control for diabetes mellitus is a highly desired pursuit of researchers around the globe. Advancement in sensing and control capabilities has paced the development of closed-loop control systems for insulin-dependent diabetes. Traditional treatment methods and recent approaches using automated control systems are reviewed in this article. Invasive and non-invasive glucose-sensing methods along with insulin therapy are presented in detail. Control algorithms are studied and evaluated based on their ability to keep blood glucose levels in euglycemic range by regulating the amounts of insulin bolus. The article highlights the advantages of using an automated control system over the traditional control strategies for insulin-dependent diabetes.

KEYWORDS

Closed-Loop, Control System, Diabetes, Glucose Level, Hypo-Hyper Glycaemia, Insulin, Neural Networks, Sensors

INTRODUCTION

Diabetes is a metabolic condition where people are unable to regulate their blood glucose levels according to their needs. In T1D body is unable to produce insulin due to the destruction of insulin secreting beta cells. These cells are destroyed by the autoimmune response because of reasons unknown to us. In case of T2D body produces less amounts of insulin because of insulin resistance, where there is less glucose uptake by the cells. A strict glycemic control is very important to carry out our daily activities and also to reduce risk of developing life threatening complications (Bertachi, 2018). High fluctuations (hyper and hypoglycemic events) of glucose levels for a longer duration often lead to development of micro and macro vascular diseases (Damji, 2021). According to research study carried out in U.K (Stratton, 2000), there is 37% decrease in risk of developing micro vascular disease with just 1% reduction in HbA1c and hence 21% decrease in risk of death related to diabetes. It is often recommended that a person should visit to a general practitioner within 3-months for glycemic control. Although with modern technological advancements, we have more sophisticated glucose monitoring tools and better bolus calculating systems, the less optimal traditional insulin delivery mechanism remains common in people living with diabetes. This is because glucose levels inside the bloodstream are influenced by so many factors including insulin absorption rate, physical activities of varied intensities, sleep amount and pattern, food intake, etc. Research is going on to develop an automated glucose control system that have minimal human intervention possible and it seems that with the effort of researchers globally, artificial pancreas would soon be commercially

DOI: 10.4018/IJEHMC.20211101.0a12

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available. In this article, modern day glucose sensing and insulin delivery mechanisms are discussed. Review of the work that has been done towards development of automated glucose control system is presented; challenges that every automated glucose control strategy should consider while designing the solution; and finally the comparison of different *in-silico* methods used to maintain euglycemia are provided in results section.

METHODS OF GLUCOSE MONITORING AND CONTROL

In the next section, we will discuss about the methods of obtaining glycemic information.

Glucose Monitoring Technologies

Although we do not have any cure for diabetes until now, but we have improved significantly in management and control of the disease through improved glucose monitoring and appropriate medications. Continuous glucose monitoring (CGM) is done through the sensors and they can be categorized into two groups. Invasive and non/minimally invasive blood glucose sensors. Most of the invasive methods widely used today are based on Clark's concept. He was an American biochemist Leland C. Clark who invented the first oxygen based electrode, called "Clark electrode". Clark used glucose and glucose oxidase, to remove oxygen by reducing it to H_2O_2 .

Glucose oxidase serves as a catalyst to convert glucose to gluconolactone. A current is generated from the reduction-oxidation reactions which is measured through electrochemistry (Oliver et al., 2009; Phillips and James, 2004). Finally the measured voltage is translated into glucose scale by a process called calibration.

Self-Monitoring of Blood Glucose

Glucose monitoring for people which are insulin dependent or taking anti diabetic drugs is very crucial to avoid the hypoglycemic events. To obtain an optimal control it is important to know how blood glucose levels are fluctuating during the entire day. Physicians normally check glucose level during fasting and two hour after meals (post prandial). It is observed that certain patients whose fasting levels were under normal range fail to achieve HbA1c (Glycated hemoglobin) below 7%, an index related to the mean blood glucose level over the last 3 months. It may happen because of unnoticed blood sugar exertions in other post meals during the day. So for better control of the disease we need to have a patient record for the entire day.

Self-Monitoring of blood Glucose (SMBG) refers to the invasive method of glucose monitoring, where a measurements are taken at discrete times from capillary blood by finger pricking. This is very painful but a widely used method of blood glucose monitoring. Figure 1 shows the SMBG with glucometer, sample strip and a lancet finger pricking device. Physicians help patients to use the readings from SMBG's to correct the abnormalities out of the predefined range by adjusting their insulin bolus, amount of exercise, carbohydrate intake etc. The number of samples taken during the day varies from individual to individual. For people who are insulin dependent it is recommended to monitor their glucose levels at least four times a day, including fasting, before meals and before sleeping. For non-insulin dependent individuals, SMBG data should be taken during changes in their physical activity or at times of increased stress.

Latest generation of glucose monitors has the capability to connect to a smartphone and provide the real-time data. For example iBGstar TM glucometer can be connected to an iPhone to record all the information a diabetic patient needs (Shelly and Ferreri, 2012). Measurements provided by

Figure 1. SMBG glucose monitor

these devices are accurate enough to monitor the glucose levels inside the blood stream at a particular moment.

Continuous Glucose Monitoring

Glucose monitors such as SMBG's are limited by the number of samples (5-6 samples) taken during the entire day. Even though they provide the overall understanding of glucose dynamics but they fail to capture the complex details. Continuous glucose monitors (CGM) emerged during year 2000. They are minimally invasive and measure the glucose levels in a continuous manner. SMBG's measure the glucose levels directly from the blood sample while as CGM measures it from the interstitial fluid under the skin, it's because of this reason these devices need calibration three to four times a day. A CGM device (Figure 2) is combination of a sensor which is implanted under the skin and a transmitter which communicates with a remote device used to display and store the data received from the transmitter. A micro-needle sensor used commonly in CGM's, is an enzyme based sensor in which a needle is covered by a glucose permeable membrane. Current generated by the reaction at the electrode is captured by an ammeter, which is then turned into a glucose scale through calibration. Various commercially available CGM devices are.

1. Dexcom G5®, Food and Drug Administration (FDA) approved mobile enabled CGM System.
2. Abbott FreeStyle® Libre System, approved by U.S Food and Drug Administration, provides real time glucose result and eight hour historical trend.
3. Guardian™ CGM from Medtronic, is a smart system that give us alert 10 to 60 minutes before we fall low or high on blood glucose levels.
4. MINIMED™ 670 also from Medtronic is a CGM system with an insulin pump.

Figure 2. CGM equipment

There are different opinions regarding the use of SMBG and CGM technologies. Research conducted by Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF CGM) suggest that use of implantable sensors helped in improving glycemic control but it could not address the problem of type 1 diabetic children and young adults significantly. They monitored 322 diabetic patients with different age groups, all of the patients were insulin dependent with HbA1c > 7%. Patients from different age groups were randomly selected and distributed in two groups. One group was using the traditional capillary blood and a glucose meter and the other group was put on continuous glucose monitoring using sensors. The experimental results of the study revealed that HbA1c factor improved in adults greater than 24 years of age but showed no significant improvement in young patients. Similarly use of sensors below 25 years age group decreased over time. However study could not reveal why these adolescents and children could not benefit from this technology.

Non-Invasive Glucose Monitoring

Graphine Wrist-band Sensors

It is a see through wrist band that measures the blood glucose level of an individual with diabetes and it has also the ability to supply a drug (metformin), if needed, in smaller quantity. In order to infer the blood glucose level of a patient, the wrist band senses so many different things like the temperature, mechanical strain, chemical composition of sweat etc. A sensor in wrist band shares the data wirelessly with a mobile device. It has an array of micro needles that are used to supply the drug in quantities suggested by an algorithm running on a mobile device. During the experiments conducted on animals it was revealed that the band normalized the blood sugar in a controlled environment.

Transdermal Sensors

It is also a watch like sensor (GlucoWatch), which is worn on a wrist. This non-invasive CGM was approved in 2001 by the United States FDA. This device employs a method called reverse iontophoresis.

GlucoWatch measures the blood glucose of a patient by applying a small current through iontophoretic electrode, current passes through the hydrogel applied to the skin and extracts the interstitial fluid from the skin. The concentration of glucose in the fluid drawn from skin is significantly low as compared to its concentration in interstitial fluid. This procedure often leads to problems like skin irritation, repeated calibrations, difficult operation etc. Due to all of these disadvantages this product was withdrawn from the market in 2008.

Light-based (Optical) Sensors

These sensors are based on phenomenon called photoluminescence. A molecule absorbs light of specific wavelength and is excited from ground state to an excited state. While returning back it emits light and releases energy which is lower in intensity than that of the absorbed light. This process is known as fluorescence. Fluorescence based glucose sensors not only provide the glucose measurements but also provide information about the molecular structure and environment etc. There are some other techniques that are based on absorption or scattering of light like Near Infrared Spectroscopy, Occlusion Spectroscopy, Raman Spectroscopy, Photo-acoustic Spectroscopy and Thermal Emission Spectroscopy etc. Development of non-invasive sensors is an active field of research as it represents the preferable choice for the diabetic patients. At present invasive CGM's offer more accuracy, reliability and require limited calibration (Vaddiraju et al., 2010). Glucose monitoring using invasive techniques (SMBG's and CGM's) allows diabetic patients to gather a lot of information about their glucose dynamics. This information is utilized by the physicians to correct insulin demands of the patients and suggest if corrections are needed. A lot of datasets available for use today come from glucose monitoring via SMBG's. These datasets help in research involving long term variations of glucose levels and glucose differences among individuals ("The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus", 1993). With the emergence of CGM's more insightful analysis of glucose variability can be performed. Continuous sensing nature of these devices makes them vital in development of automatic insulin delivery systems (Artificial Pancreas).

Insulin Delivery

With the discovery of Insulin in 1920 diabetes, considered to be a fatal disease turned into an incurable condition. Since then a lot of achievements have been made to improve the life of the people living with this disease. With the development of latest management tools like SMBG's, CGM's and advancements in insulin therapy, there has been a significant improvement in diabetes control. Table 1 shows different types of insulin available today with their peak action and lasting duration. For the optimal glucose control in a diabetic patient's insulin bolus is calculated based on glucose profile provided by the glucose monitors, amount of carbohydrate ingested in meals, insulin basal rate and insulin sensitivity of a patient. Insulin requirement significantly depends upon the maximal activity shown by the SMBG. Based on the readings one must decide on the target ranges of these maximal activity periods. As recommended by the American Diabetes Association (ADA) pre-prandial target range should be 70-130 mg/dl and pre-prandial glucose levels < 70 mg/dl should be termed as hypoglycemia (Glycemic Targets, 2014).

Insulin dosage adjustments are also made based on the circumstances. For example, if glucose measurements taken at specific times are consistently high or low, we raise or lower the insulin dose accordingly. In case of overweight persons there will be a rise or decrease of 4 units and if a person is slim there will be an increment or decrement of 2 units. Table 2 shows the relationship between insulin prescription period of activity and their injection times. Frequency of glucose monitoring for insulin bolus adjustments is also very important to maintain euglycemia. Individuals on basal insulin therapy are required to take measurements in the fasting state and patients on multiple injections are suggested to take measurements before each meal and at bedtime.

Table 1. Types of Insulin

Type of Insulin	Onset	Peak	Duration
Rapid-acting			
Lispro	15-30 min	30-90 min	3-5 hours
Aspart	10-20 min	50-50 min	3-5 hours
Glulisine	20-30 min	30-90 min	1-2.5 hours
Short-acting			
Regular	30 min - 1hour	2-5 hours	5-8 hours
Insulin Pump	30 min - 1hour	1-2 hours	2-3 hours
Intermediate-Acting			
Insulin glargine	1-1.5 hours	No peak time	20-24 hours
Insulin detemir	1-2 hours	6-8 hours	Up to 24hours
Insulin degludec	30-90 min	No peak time	42 hours

However, it is usually observed that testing before each meal become very difficult for these patients so they are advised to take at least two measurements daily, before breakfast and lunch or before lunch and bedtime alternatively. Hypoglycemia is another important factor in determining insulin bolus for a diabetic person. It is a condition where glucose levels fall below 70 mg/dl inside blood stream. There are severe consequences associated with this condition. Hypoglycemia can be mild, moderate to severe depending upon the scale and period for which glucose levels drop less than usual. Mild to moderate hypoglycemic events can lead to anxiety, confusion, and difficulty in speaking, nausea while in severe hypoglycemia a person can go into coma, brain damage and needs immediate assistance etc. Glucose levels can fall because of lifestyle changes or changes in diet, these changes should not be treated as hypoglycemia. For example, if the hypoglycemic condition started to improve within 20 minutes by taking some carbohydrate a patient should not be considered as hypoglycemic and does not need changes in insulin dosage. In contrast if measurements shown by the glucose monitor are consistently low during patient's usual lifestyle routine, then a physician must consider lowering the insulin dose accordingly. If a type 1 diabetic patient has lower HbA1c levels, aggressive insulin therapy often leads to hypoglycemia (Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group, 1997).

On an average the occurrence of mild-moderate hypoglycemia for a type 1 diabetic patient is around 2.7 episodes per week (Choudhary et al., 2010). The occurrence of hypoglycemia that requires immediate assistance is around 1.3 episodes in a year (Pedersen-Bjergaard et al., 2004; Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration, 2007). A trial conducted by JDRF Prolonged Nocturnal Hypoglycemia Is Common during 12 Months of

Table 2. Insulin recommendations

Insulin Preparation	Period of Activity	Time Injected
Regular	Between that meal and next one	Before a meal
NPH Regular	Between lunch and supper	Before breakfast
NPH Regular	Overnight	Before Bedtime
Glargine	24 hours	Any time

Continuous Glucose Monitoring in Children and Adults With Type 1 Diabetes (2010), revealed that despite using glucose monitoring sensors, hypoglycemia occurred in 8.5% of the nights. Usually hypoglycemia remains underestimated and in 60% of hypo-glycemic events it remains undetected (Chico et al., 2003). Once a patient is diagnosed with type 1 diabetes he is immediately put on insulin therapy except for people with latent autoimmune diabetes of the adult, these individuals are put on non-insulin drugs unless they fail. Similarly, patients with type 2 diabetes are also suggested anti diabetic drugs like sulfonylurea supplied in limited quantity initially to avoid hypoglycemia. However, type 2 diabetic people with high HbA1c levels require insulin for maintaining good glycemic control.

Insulin Pumps

Insulin delivery via an insulin pump was introduced in 1970's and are used in diabetes management since then. It is a small device that is worn externally, and can easily fit into a pocket or clipped to a waist belt. Based on the patient's body needs it delivers the rapid acting insulin in appropriate amounts.

Basal Rate

A physician calculates the basal rate for a diabetic individual, which is delivered steadily for 24 hours for the normal functions of the body (excluding food).

Insulin Bolus dose

Increased blood glucose levels due to the carbohydrates consumption are corrected via an additional insulin bolus that can be delivered on-demand. Amount of dosage is again calculated after a proper consultation with a specialist. A complete insulin delivery system consists of an Insulin pump, insulin reservoir, infusion set and infusion set insertion device. An insulin pump consists of a Liquid Crystal Display (LCD) to display the programmable readings, buttons to set your basal/bolus infusion rate, Insulin reservoir compartment. A Reservoir is a plastic container which is inserted into an insulin pump. Normally it can hold about 300mU of insulin and can last up to 3 days. An infusion set comprises of a tube that goes from the reservoir cartridge to the infusion site on patient's body. The cannula is inserted with a small needle which is removed after it is in place. It is also needs to be changed after three days. Insertion device is used to insert the infusion set easily into the patient's body. Insulin pumps offers flexibility of schedule for activity, eating food and insulin injections etc. Due to the delivery of rapid-acting insulin patients can broaden their food preferences, eat when they feel hungry and even skip a meal. Decrease in blood sugar due to various physical activities like playing, gardening etc, can be compensated by adjusting the basal insulin delivery rate. Insulin pumps offer more control as compared to multiple daily injections (Pickup, 2012) and has the potential to reduce blood glucose levels by 84%. It also helps in reducing the long term complications (heart, kidney, eyes and nerve damage) associated with the disease. Glucose sensing technology and advanced insulin pumps has led the researchers to develop closed loop insulin delivery systems (also called artificial pancreas).

CLOSED-LOOP CONTROL IN DIABETES MANAGEMENT

Individuals with diabetes must effectively manage glycaemia to avoid severe complications related to rapidly changing glucose levels. The closed loop control of blood glucose levels might help to reduce many short and long-term complications of type 1 diabetes. Recent advancements in continuous glucose monitoring (Srivastava, 2020) and insulin pumps have facilitated the development of the closed loop insulin delivery systems also called artificial pancreas. Closed-loop control of blood glucose in diabetes is a system combining a glucose sensor, a control algorithm, and an insulin infusion device (Figure 3). A control algorithm is engaged after every 5 to 15 minutes based on the glucose readings provided by the sensor. It continuously works to keep the blood glucose levels in a non-diabetic range. Researchers strongly believe that closed-loop insulin delivery systems have potential to improve the quality of life for people suffering from diabetes.

Figure 3. Insulin delivery system

The current generations of Closed-loop systems are not completely automated and they require lot of user involvement. Once in-silico simulations are carried out, the system needs to be tested in clinical trials under proper medical supervision before it becomes available to masses. The first commercial closed-loop system, MiniMed® Paradigm® Veo™ consists of a glucose sensor and an insulin pump. It suspends its activity for two hours once it senses low glucose readings. More advanced versions of closed-loop system could be used to treat nocturnal hypoglycemia, and later on they can handle complex user activities and meal uncertainties. At present, a patient manually has to adjust his daily diet and exercise routines based on the recommendations of a medical consultant. Closed-loop systems for diabetes control offer clinical benefits and helps in development and evaluation of such systems in a more controlled environment. In the section below we list some of the benefits of using closed-loop control over the traditional glucose regulation using multiple daily injections.

Clinical Trials

In any research facility or a hospital clinical studies are carried out to evaluate the efficiency and safety of closed-loop control of the disease. Initially the study is conducted for a shorter durations of time maybe for less than a day. These studies are important for many reasons (a) in testing the robustness of a system in a controlled environment; (b) evaluation of combined strategies used with closed-loop systems (e.g. different physical activities, meal variations etc); (c) evaluating single hormone (insulin) and multiple hormone (insulin and glucagon) delivery systems; (d) adjusting and improving the bolus calculation of control algorithm.

Algorithm Simulation

Clinical evaluation of patients is a costly, time consuming and less controlled process. Before testing the closed-loop control on live patients, simulation of the whole system is carried out on a computer. This computer simulation allows researchers to test the extreme cases which normally are impossible to test during the clinical study. Testing the whole system in extreme cases is significant because the hardware like sensors, pumps, etc, are prone to failures and malfunctioning in certain scenarios. Once the simulation studies are carried out the system then undergoes for clinical trials. This is an iterative process where the improvements in the control algorithm are made from the data obtained during the clinical trials. Once there is significant improvement in the closed-loop system it can be sent for approvals.

Regulatory Approvals

Closed-loop systems associated with the human health are considered to be high risk devices in most of the countries like USA, Canada and India. In United Stated, approval from Federal Drug

Administration (FDA) is needed before these systems are used for in-patient studies. In India; Central Drugs Standard Control Organization (CDSCO) is the regulatory authority for pharmaceutical and medical devices.

Short And Long-Term Home Studies

Once the system undergoes simulation and clinical studies, it now needs to be tested in homes where there is less controlled environment. Testing in real life environment is important because of the unpredictable and varied conditions. These conditions reflect the environment where the system is finally implemented. These studies help in (a) testing the closed-loop system in maintaining nocturnal glycaemia in presence of a medical professional; (b) simulating the complex daily activities (walking, running, playing, etc) at home to test the robustness of the closed-loop control. Long term studies will help in understanding merits/demerits of closed-loop control when compared to traditional diabetes treatment methods.

CHALLENGES FACED IN DESIGN OF CONTROL ALGORITHMS

Glucose regulation via closed-loop control system involves different equipment's that collectively work towards optimal glucose control. In this section, some of the potential problems that may hinder the performance of bolus calculating algorithm along with possible solutions are presented.

Insulin Pumps

Insulin pumps like any other hardware equipment are prone to faults and failures. There could be problems like clogging of insulin tubes, motor shut down due to a fault or pump leakage due to cracking or breaks. The control algorithm should be designed to recognize these faults and make the user aware by indicating the failure in the hardware. Usually insulin pumps are inserted in the abdomen because of high absorption rate in that area as compared to other body parts. The algorithm has to deal with challenges involving pumps replacement like irregular insulin absorption¹ due to the repeated injections in the same area which leads to hypertrophy (or tissue building). Site selection and rotation is significant to avoid tissue hardening and providing predictable insulin absorption rates. The change in absorption rates due to site rotation often leads to changes in the insulin bolus calculations. To accommodate for these changes antiseptic medicines are used to avoid infections or tissue building in those areas of insertions and by choosing the appropriate sites of insertions with predictable absorption rates.

Sensor Disturbances

All control systems are affected by some disturbance/noise. In the closed-loop insulin delivery systems disturbance can be generated by sensor placed under the skin. To deal with disturbances optical estimation methods (BW, 2005) can be used to perform sensor recalibration. The subcutaneous sensor uses an enzyme to measure the blood glucose of the patient. Any change in the insertion site also changes the flow of enzyme which is proportional to the glucose at the insertion site. Glucose variability due to changing sites leads to sensor disturbances. These disturbances are often corrected by sensor recalibrations. Sensor readings are also affected by the infections at the insertion site. Any response by the immune system to these infections changes the subcutaneous chemistry resulting in false sensor readings. These readings are also influenced by the long term sensor insertion at the same site due to hypertrophy.

Meal And Other Disturbances

In a closed-loop diabetes control meal detection is a big challenge. Meals can be of varied size and carbohydrate content. Most of the algorithms work on nominal meal methods where the size and time

is manually fed into the system but the chances of hypoglycemia increases if the meal size is smaller than calculated or if it is not consumed entirely (Klonoff, 2007). Modeling and understanding the nature of these disturbances can be very challenging. Other disturbances that can affect the blood glucose levels may be lack of proper sleep, intense physical activity, disease, stress etc. Deutsch and Lehman proposed a model to accommodate for meal disturbances. It is based on consumption of all the carbohydrate content from stomach and its absorption into the bloodstream from small intestine.

Insulin

Diabetes management is dependent on insulin therapy. In closed-loop control, insulin is delivered via an insulin pump. Insulin accumulation under the skin often leads to hypoglycemia. Delayed subcutaneous insulin absorption poses a challenge for control algorithms. Even with rapid acting insulin with peak value only after 15 minutes of injection prolonged absorption can lead to complications. Insulin sensitivity is another concern for algorithm efficiency. Sensitivity varies among individuals over time and is also known to vary due to stress, health, time of the day etc (Hanaire, 2006). It also varies among diabetic patients with different age groups (Bhonsle, 2020). Subcutaneous insulin stacking can be prevented by incorporating the insulin bolus on board feature (considering the previous bolus and the remaining insulin on board) into the control algorithm. By changing the insertion sites we can deal with the problems associated with the insulin pumps. Similarly, by providing the predictable sensor rotation, noise from sensor can be greatly reduced and for minimizing the meal disturbance we can use different models, which are created to predict the approximated carbohydrate content inside the meal. Control algorithms must be optimized to accommodate the challenges associated with subcutaneous insulin accumulation as suggested by the clinical studies. There is also a need to have extra-fast acting insulin as the current generations of controllers are less robust in responding to meal disturbances and subcutaneous insulin absorption rate.

REVIEW OF CLOSED-LOOP CONTROL ALGORITHMS IN DIABETES MANAGEMENT

In last few decades both the sensing capability and computational power of machines have advanced (Jeelani, 2020) and this advancement has led to the development of closed-loop insulin delivery systems possible. Researchers are considering closed-loop control as more effective and advanced mechanism for the control of disease (diabetes). In literature many control algorithms have been proposed for the closed-loop control of insulin delivery (Clarke WL, 2009; BW, 2005). El-Khatib FH, (2010) developed a closed-loop control system that uses continuous glucose measurements and a pump which can deliver both insulin and glucagon. A computer algorithm decides the amount of insulin or glucagon to be delivered based on the blood glucose measurements of a patient. The 27 hour experiment was conducted with 11 subjects who were given announced carbohydrate meals. In six subjects, the closed loop system achieved a mean BG concentration of 140 mg/dl and there were no instances of treatment requiring hypoglycemia.

Kovatchev B, (2009) proposed a control to range algorithm which is composed of two modules, Range correction module and Safety supervisor module. Both of these modules interact with each other and monitor the hyper and hypo glycemic events. Once the glucose levels fluctuate above or below the predefined range Safety supervisor module regulated the insulin delivery rate in order to keep the glucose levels within normal limits for a longer duration of time. Artificial Pancreas Group from the University of Cambridge developed a model predictive control based algorithm together with multiple parameter estimation algorithm (Mazor et al., 1998). These models based on varied human physiology run in parallel to calculate the glucose production inside the blood stream, carbohydrate and insulin absorption profiles. Two parameters are updated using Kalman filters (a) blood glucose disturbance used for correcting errors in model based predictions and (b) carbohydrate estimates of the ingested food. Hyper and hypoglycemic events are forecasted by the predictive algorithm using

the prediction horizon of 2.5 hours. Recently, a study was conducted where MPC based algorithm developed by Artificial Pancreas Group was compared to open loop traditional insulin pump therapy. Closed-loop control was used in 19 children and adolescents with type 1 diabetes (Hovorka et al., 2010) to treat nocturnal hypoglycemia. It was revealed that there was 20% increase in nocturnal euglycemic range (3.9 to 8.0 mmol/L) by the closed-loop insulin delivery system and the risk of hypoglycemia (< 3.9 mmol/L) also reduced to half. The algorithm also revealed similar promising results when tested with pregnant women and adults with type-1 diabetes (Hovorka et al., 2011; Murphy et al., 2011).

Proportional-integral-derivative algorithm developed by Medtronic (world known medical device maker and therapies) has been tested and used in clinical research (Weinzimer et al., 2008; Steil et al., 2006). The algorithm showed the promising results, but it failed to maintain total euglycemia at night in the subjects under study (Weinzimer et al., 2008). The algorithm was then modified and feed-back loop was added to prevent the nocturnal hypoglycemic events (< 3.3 mmol/L) due to insulin overdosing (Steil et al., 2011). The new algorithm for closed-loop insulin delivery was tested to treat nocturnal hypoglycemia in children with diabetes (Grady et al., 2012).

In a multinational research study conducted in Padova, Montpellier and Virginia by the International Artificial Pancreas (iAP) study group, an MPC based insulin delivery algorithm was tested on 20 subjects with T1D [34]. In the study it was revealed that by using closed-loop control there was increase in the time for which blood glucose concentrations remained in euglycemic range (3.9 to 7.8 mmol/L) as compared to the traditional insulin pump therapy (78% vs. 64%). There were some hypoglycemic events during the closed-loop control although the frequency of occurrence was still lower than the conventional methods of treatment (in 20 nights, 5 vs 23 events). The study was conducted in a well controlled manner with no random design adopted and sometimes on the recommendations of a medical professional, algorithm's predictions were altered. The MPC based algorithm has been recently extended to other clinical studies as well (Breton et al., 2012). Researchers also used fuzzy systems in regulating the glycemic control (Klir, 2000). A closed loop fuzzy system was tested in 7 T1D subjects within a well-controlled environment (Atlas et al., 2010). These systems were successful in avoiding the hypoglycemic events and also provided promising overall results. All the studies we mentioned above were based on insulin to regulate the blood glucose levels.

Researches have recently proposed dual hormone closed-loop systems comprising of both glucagon and insulin to regulate the blood glucose levels in T1D patients (El-Khatib et al., 2010; Castle et al., 2010). Subcutaneous insulin and glucagon delivery in two recent studies have shown good results in subjects with T1D. El-Khatib et al., (2010) developed a dual hormone closed-loop delivery system, where no hypoglycemic events were reported in eleven T1D subjects for a period of 27 hours. Two separate controllers with no interaction among themselves were used for both the hormones. Insulin delivery was regulated by generalized predictive algorithm whereas PID controller regulated glucagon delivery. Few hypoglycemic events due to excessive insulin delivery by the dosing algorithm was still experienced in both the systems which were treated with oral carbohydrate consumption. It was revealed that glucagon in fusion at regular intervals shows better performance as compared to continuous glucagon infusion. However, the dual hormone closed-loop delivery used venous glucose samples (El-Khatib et al., 2010; Castle et al., 2010) or multiple sensors (Castle et al., 2010) to calculate the dosage requirement; they lack the ability to use single CGM system for providing the sampling information. The closed-loop system developed by El-Khatib et al. has been tested in other studies as well (Russell et al., 2012).

Researchers also have developed few simulators for testing the closed-loop control of insulin delivery systems (Kovatchev et al., 2009; Wilinska et al., 2010; Kanderian et al., 2009). (Kovatchev et al., 2009) developed a synthetic dataset of 300 T1D patients. Based on this dataset they proposed a complex model of glucose regulation where the model parameters (covariance matrix, mean etc) were estimated from the glucose dynamics of healthy individuals. To represent the T1D patients they altered the multivariate parameter distributions where random samples from this distributions represent individual subjects. (Wilinska et al., 2010) also simulated 18 virtual T1D subjects in a

Table 3. Plasma Parameters of Patient

Parameter	Glucose (mg/dl)	Insulin (mU/min)
Mean	132.771	12.767
SD	36.284	3.823
Minimum	52	5.49
Maximum	260	26.15

controlled environment. They used maximum likelihood approach for model parameter estimations with the prior data distributions calculated from glucose tracer data (Hovorka et al., 2002) and posterior parameter distribution vectors identified from glucose measurements of the 18 simulated virtual subjects (Hovorka et al., 2004). Team of researchers from Medtronic (Kanderian et al., 2009) developed a simulation environment based on Bergman's minimal model (Bergman et al., 1979). They used the second-order differential equations to represent meal and insulin kinetics. Ten T1D subjects who volunteered for clinical trials underwent closed-loop experiments and model parameters were obtained by fitting the glucose data. Using non-linear regression, estimations were made and least squared error minimizations were used when a mismatch between real data and model estimations were observed.

Artificial neural networks (ANN) are widely applied in problems of non-linear nature, researchers have used ANN in diabetes control. Work presented in (Pappada SM, 2011; Facchinetti A, 2011; Robertson G, 2011) used ANN for making non-linear glucose predictions and in some studies these networks are used in feedback control algorithms (Robertson G, 2011; De Leiva-Hidalgo A, 2011; S., 2011). Authors (Mougiakakou SG, 2005) in their study presented a system comprising of neural network and compartmental model (CM). CM provides an estimation of insulin bolus and also takes absorption delay into consideration. Neural network predicts the glucose levels based on the estimations provided by the CM and the values provided by the CGM. These studies suggest that using artificial neural networks it is possible to obtain a robust non-linear model for a diabetic person based on his/her clinical profile.

CLOSED-LOOP CONTROLLER EXPERIMENTAL RESULTS

In-silico trials of studies presented in (Grosman B, 2010; Ata S, 2017; Bhat Owais, 2019) was carried out and the techniques were evaluated in terms of RMS error and percentage of values spent in euglycemic range. Figure (4) presents the performance a control systems presented in (Bhat Owais, 2019). Data used in these simulations is a publicly available dataset² containing data from 70 patients collected over several weeks to months. It should be noted that the data is collected after the predefined dietary schedule, where fixed amount and times were assigned to breakfast (08:00), lunch (12:00), dinner (18:00), and bedtime (22:00). Table 3 shows the mean glucose levels, standard deviation, minimum and maximum values of insulin bolus and measured plasma glucose levels of a

Table 4. Performance comparison of different techniques

Control System	Average RMSE (%)	Average 70-180 (%)
Zone-MPC	8.75	89.71
PID-Controller	11.58	85.69
NN Controller	5.84	92.62

Figure 4. Controller performance, (a) Glucose Level maintained, (b) Insulin bolus calculated.

(a)

(b)

single patient. The experimental results reveal (Table 4) that the closed loop controllers adjusted well to meal and glucose disturbances. They also prove to be robust in maintaining the glucose levels in normal acceptable range. Based on the *in-silico* results we can say that intelligent artificial pancreas could soon be a reality and are suitable enough to replace the less efficient traditional methods of diabetes control.

CONCLUSION

Diabetes management using modern tools and technology is becoming preferable choice for people with diabetes. Modern day sensors provide health profile of a person including blood glucose measurements at reduced cost and effort. Sophisticated insulin pumps provide more flexibility than the traditional multiple daily injections. Bolus estimations using a control algorithm along with sensor based insulin delivery has shown greater advantage over traditional open-loop diabetes management techniques. The *in-silico* studies suggest that closed-loop diabetes control system achieves lower HbA1c levels and was able to reduce hypoglycemic events as well. Despite all of these advantages, more effort is needed to make the technology accessible and affordable to greater population.

Recent technological advancements are further accelerating the development of fully automated artificial pancreas system. To provide for an optimal glucose control while engaging in different daily activities, eating the food one wants, handle stressful situation with reduced complications is an ultimate goal of these smart control systems. Developing such a system is still a big challenge and needs experimentation in different conditions and with diverse diabetic population. To develop fully automated diabetes control system experimentation needs to be conducted with dual hormone (glucagon) system that will help reducing more dangerous hypoglycemic events. Researchers are seeing a simpler and safer artificial pancreas system as an optimal solution to diabetes management.

ACKNOWLEDGMENT

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ENDNOTES

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- ² AIM '94 (1994). Diabetes Data Set [online]. Website <https://archive.ics.uci.edu/ml/datasets/Diabetes> [accessed 23 August 2019]

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