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Diabetes Millitus Control Exogenous Insulin Infusion: A Review

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Abstract- **Diabetes Millitus Control remains popular from the past years to explore for more investigations. Exogenous Insulin infusion is explored in the study for further analysis. Administration of Insulin delivery has been discussed for type-1 patients. These are some control challenges faced when Artificial Pancreas is developed. Different linear and non-linear schemes have also been discussed for Diabetes. PID Controller has been applied to control TIDM. Simulink Models has been explained and plotted. It's a control loop strategy which makes Artificial Pancreas reality.**

Index Terms-- **Diabetes, PID Controller, Exogenous Insulin infusion, TIDM.**

I. INTRODUCTION

Diabetes mellitus is a metabolic disease illustrated by high levels of blood glucose leading to chronic hyperglycemia either due to defect in insulin secretion or insulin action or both. Insulin is a hormone produced by specialized type of cells of the pancreas known as beta cells, which is necessary to exploit glucose as a source of energy from digested food. Chronic hyperglycemia is related to further complications such as microvascular and macrovascular damage leading to kidney disease, neuropathy, amputations, cardiac disease, stroke and retinopathy. Hence, diabetes includes a wide range of heterogeneous diseases [1].

Diabetes mellitus is the most common disorder of endocrine system and it has been classified in to two major types based on the presumed etiology; type 1 and type 2. Type 1 diabetes also known as insulin dependent diabetes mellitus (IDDM) or juvenile onset, the body is not capable of producing insulin and insulin inoculations are required on daily basis. Whereas, type 2 diabetes or maturity onset also known as non-insulin dependent diabetes mellitus (NIDDM) is characterized by defect in insulin secretion and insulin resistance. High levels of blood glucose are managed with reduced food intake, improved physical activity and ultimately oral medications or insulin [2]. Type 1 diabetes is further classified into two subgroups; immune mediated and idiopathic by American Diabetes Association in 2007.

Former accounts for the 5-10% and is autoimmune whereas later form of type-1 diabetes has no known etiologies and patients suffering from this type have permanent insulinopenia and are prone to ketoacidosis without any proof of autoimmunity. Morbidity and mortality rate of diabetes mellitus has increased throughout the world. Diabetes has influenced 246 million people worldwide and, of these, approximately 22 million adults and 0.4 million children have type-1 diabetes [3]. Type-1 diabetes is primarily characterized as an autoimmune disease resulting in damage of insulin-producing β-cells in the pancreas by T- cells (CD4+ and CD8+) and macrophages penetrating the islets. Both genetic as well as environmental factors yet unclear trigger the autoimmune responses against β-cells and destroy them, thus proliferating the disease [4].

The criteria of diagnosis for T1DM are the same for adults, children and young people i.e. fasting glycemia >126 mg/dl (>7.0 mmol/L) or postprandial glycemia > 200 mg/dl (>11.1 mmol/L). Other symptoms include polyuria, polydipsia, weight loss and polyphagia and blurry vision. Impaired growth and vulnerability to infections also increases. Clinical manifestations of diabetes differ from non-emergency appearances to severe dehydration, tremor and diabetic ketoacidosis [5].

Since, patients with type 1 diabetes have lost the ability to produce insulin hence such individuals depend on entirely externally administered insulin and it's the only treatment. However, daily dose of insulin required by the patient varies and depends on various factors including age, gender, daily exercise and physique. But an average daily dose is about 1 unit of insulin per kg weight per day [3].

Although, patients suffering from type-1 diabetes are dependent on regular dose of insulin either multiple injections daily or pump therapy but procedures and insulin administration to manage and control the disease varies as per the age. In neonatal diabetes insulin is initially administered through intravenous route with dose of 0.02 - 0.05 U/kg/hour, to be prolonged if possible before subcutaneous. In toddlers, it's difficult to manage the dose due to unpredictable energy consumption. School age children present stable age as they are following schematic daily routine. In adults, the need of insulin increases due to puberty. Behavior also presents a problem in adults influencing in a negative way hence affecting disease management. It is also present an inclination to disobedience and involving into activities like

smoking, alcohol and drugs as well as rebellious to insulin injection [6].

Insulin can be administered in several ways from basal-bolus approach to pump therapy depending on factors like age, diet, lifestyle, health, enthusiasm, self-management capability and availability/accessibility. While choosing, insulin type the most important that needs to be considered is the risk of hypoglycemia. Longer acting analogues of insulin (glargine and detemir) are preferred over intermediate-acting human insulin posing reduced risk of hypoglycemia Rapid-acting insulin analogues (lispro, aspart and glulisine) also preferred due greater improvements in HbA1c and with reduced risk of hypoglycemia over regular ones [7, 8]

II. PHYSIOLOGICAL METHOD OF INSULIN DELIVERY

It is important to go through how β-cell responds to glucose system in order to understand how an artificial system should behave [9]. There are two phases "first" and "second" phase responses of β- cell [9]. Significance of first phase insulin secretion. The immediate release of insulin after a meal is known as "First Phase Insulin Release". The first-phase insulin secretions have a major effect in extinguishing hepatic glucose production [10]. As shown in the figure [10]. Small change in the plasma insulin can have a significant effect on hepatic glucose output [10]. Normally , insulin production in an early phase is actually less than the total insulin needed to yield a similar area under the glucose curve [9] [11]. Improving first phase response has been related to glucose tolerance [12]. A person whose system is insulin resistant without the variation in insulin secretion becomes diabetic. While a person's system which maintains the required level of glucose tolerance by adopting the "control gain" is a non-diabetic individual [9].

After the First phase of insulin secretion if the blood sugar is not back at the level 100 mg/dl (5.5 mmol/L) then there is a second phase insulin secretion which brings back the glucose to its normal level. Second phase insulin secretion have major effect on glucose production as well as its utilization [10]. The importance of second phase insulin secretion cannot be ignored as it is necessary to maintain plasma glucose at set point [9].Insulin is not infused until blood glucose level is exceeds 180-200mg / dl . This condition is referred as hyperglycemia [13].The condition of hyperglycemia is found to be common in intensive care unit (ICU) [13]. According to surveys in [14], even a small level of hyperglycemia associated with increased rate of hospital mortality in ICU [14].

Sugar level control with insulin infusion has a risk of hypoglycaemia. Sugar level which is <50 mg/dl is the called hypoglycemia. Hypoglycemia can be diagonosed by Whipple's triad, with three steps. 1) neuroglycemia symptoms, 2) immediate glucose of < 40 mg/dl and 3) symptoms of relief after glucose intake [15].

III. OPEN LOOP ADMINISTRATION OF INSULIN

The requirement of an automated artificial pancreas has been there from 1921, the time insulin was discovered [9]. The production of insulin needs definition in terms of prehepatic insulin as well as portal insulin concentration in order to work as closely as a non-diabetic state [16]. With the increase in the demand of insulin infusion and its mechanism it is recommended to take the dose with almost every meal [17]. One major concern is the timing of insulin delivery [18]. Depending on the type of insulin, rapid-acting insulin should be infused 15 minutes before a meal. Short-acting or regular insulin can be infused 30 minutes before meal. Having food activity straight away after regular insulin can cause hypoglycemia (low sugar level) [18]. Changing the interval between insulin infusion and meal shows remarkable effect in Postprandial Hyperglycemia in insulin dependent patients. Recent studies show that near-normal glucose levels were achieved when patient had their insulin administered 60 minutes before meal [17]. Results infer that adjusting the time and the amount of insulin administered can be helpful in the management of diabetes [17]. As shown in (Fig. 1) delayed insulin infusion before meal can be linked to greater hyperglycemia up to 3 hours after meal [19].

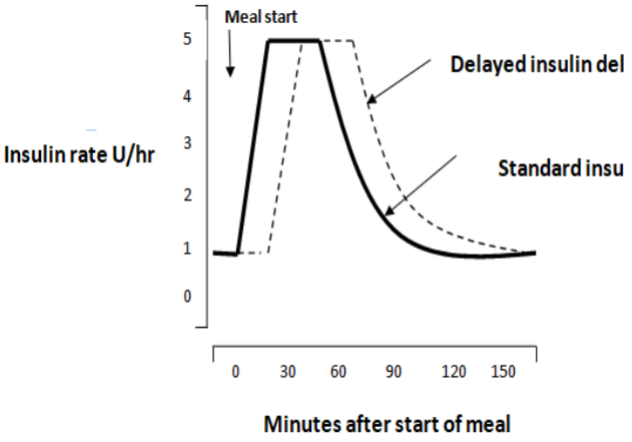

FIGURE 1. Comparison of delayed and standard insulin delivery with meal.

Injection technique is most common and early cure of a diabetic patient. Dosage is different for different individual. People with type 1 diabetes mellitus do not produce enough insulin to meet the glucose level of a normal person so they need external insulin. Most of the type 2 patients do not require external insulin. Timing of the injection depends on the glucose level and various other factors [18]. Injection site is important. Insulin can be injected into subcutaneous tissue of the upper arm and the anterior aspect of thighs and buttocks [18].

Inhaled insulin has been proven way more effective and reliable in Type 1 and Type 2 diabetes. Infusion of regular insulin through lungs by inhalation has shown insulin absorption and lowering of blood glucose [20]. As shown in(Figure 2), the maximum insulin concentration is more rapid in case of inhaled insulin as compared to SC injection [21] .

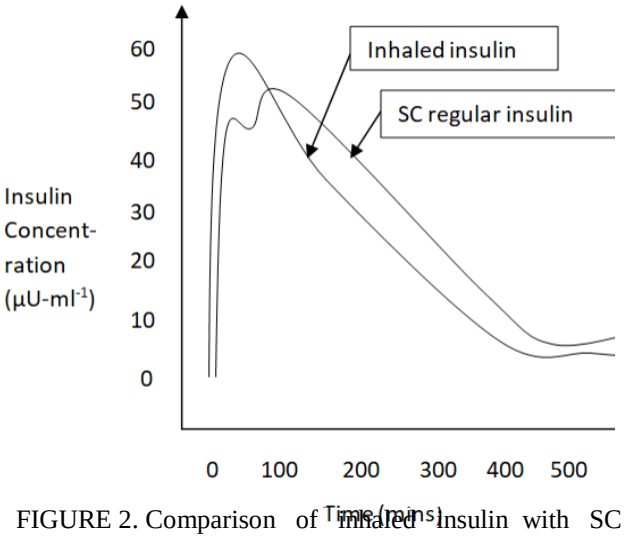

FIGURE 2. Comparison of inhaled insulin with SC injection.

It deals with the absorption and distribution process of insulin. Insulin gets absorbed into the directly into the stream [22]. Rate of absorption depends on the type of insulin , volume of injection, rate of flow. It has been observed that absorption s decreased with the increased in the ntration and the volume. Studies shows that d insulin is absorbed faster [23]. Insulin is uted with the help of circulating antibodies, e if they are present insulin is distributed as the plasma and other compartments [22]. This section deals with effect of insulin on the body. It is basically called the euglycaemic clamp study [24]. Glucose Infusion Rate (GIR) is used to represent pharmacodynamics of insulin [24].

IV. CLOSED LOOP ADMINISTRATION OF INSULIN

Current Treatment methods like SC injections and continuous delivery of insulin can result frequents glucose level variations due to their open- loop nature [25]. In order to keep a stable basal glycemia with continuous insulin infusion we require a feedback system [26] . The main aim of the feedback system is to maintain a set point which is predefined. Variable transfer functions like proportional integral or derivative terms are used to implement a feedback system [26]. Diabetes Control and Complications Trial (DCCT) published in 1993 showed how important it is to tight control the blood glucose [21]. The trial showed that there is an increased risk of hypoglycemia by combining the result of SC injections and insulin pumps [21]. A person with Type 1 diabetes has always in a long term risk related with hyperglycemia and short term risks of hypoglycemia, so they need to have a tight blood glucose control . Type-2 diabetic patients need an insulin treatment when oral antidiabetic agent and changing life style do not provide glucose control [25]. An artificial pancreas [Fig. 2] (Closed Loop) requires; Continuous Glucose Monitor (CGM) or Glucose sensor, An insulin pump. A control device that receives CGM and uses algorithm to convey signal to insulin pump [26].

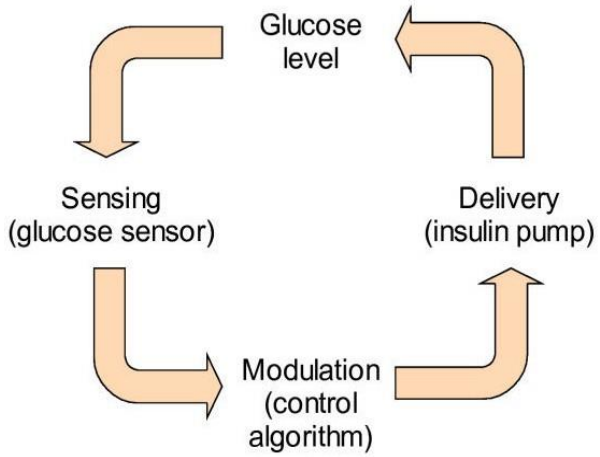

FIGURE 3 Example of Closed Loop Insulin Delivery System [29].

Different algorithms have been introduced so far but two of the most common are: Proportional integral control PID- regulates insulin by noticing variations from target glucose and Model Predictive Control MPC- regulates insulin by minimizing the difference of forecasted and target GL.

V. CONTROLLER CHALLENGES

Following are the different control challenges which need to be considered for artificial Pancreas:

- When there is closed loop system insulin is delivered when there is glucose deviation only without the information about meal size and timing.

- Hypoglycemia condition is also risky as it can cause coma, seizures and mental illness. Also hyperglycemia is not good as it causes cardiovascular disease and other chronic diseases. So these conditions must be considered.
- Different treatments have different requirements. Sometimes rapid and sometimes slow insulin delivery is required. Exercise can also create the hypoglycemia condition so all of these things are important to consider.
- When creating a rapid insulin delivery control algorithm mostly the maximum blood glucose lowering effect occur after up to 90–120 min. When designing control algorithm this time lag should be considered.

Sometimes there occurs noise in sensor measurements so different estimation techniques should be used for compensating this noise. In this paper glucose insulin system model is described. This is a simple model with few parameters. Another controller named design of Fuzzy and PID controller is described. The model is designed using Mamdani type Fuzzy structure. It has two input variables and one output variable. The inputs are error and rate of it and output is rate of insulin infusion.

PID Controller

A new device CMOS (complementary metal oxide semiconductor microprocessor) is presented which works on wakeup cycle each 2.86ms.CMOS operational amplifier and dc driver provides voltage to motor from 0 to 7.5 volt in 29.41 mV [1]. Feedback loop is used having three parts. (1) Blood glucose monitors (2) Control system (3) Insulin pump. The input of the control system is output of glucose sensor and output of the control system is the input to insulin pump. According to glucose concentration the control system instruct the insulin pump on how much insulin to be injected.

An expert PID controller is designed to regulate blood glucose level. It has clinical sliding table technique. Sliding table contains insulin concentration rates. PI controller is mostly used controller. PI stands for proportional integral. P and I controller are implemented for individual purpose. There are many methods to tune PI controller one of those is trial and error method. In this method the gains of proportional and integral were adjusted randomly to enhance the performance of insulin delivery system. Controller designers improved the steady and transient performance of PI controller by introducing fuzzy theory.

VI. LINEAR AND NON-LINEAR INSULIN INFUSION CONTROL SCHEMES

Self-Tuning Control. A self-tuning controller is basically a nonlinear control scheme which was made to implement on a micro-controller unit [21]. This scheme was checked using computer simulation and it was found that glycemia control is insensitive to changing patient behavior; also insulin concentration it produced was more physiological. Discrete-time model is assumed for the controlled system to implement a self-tuning controller. Self-Tuning uses estimator, coefficients are estimated by least-square method, it compares the true output of the model one and controlled system; so that estimation is sensitive to slow changes in patient response.

Sliding Mode Control (SMC). The advantages of sliding mode control is ultimate accuracy, insensitive to internal and external disturbances, robustness and convergence in finite time that are important characteristics of sliding mode control which are suitable choice for the control algorithms related to human body because it is important to get extreme precision [22]. Also the robustness against the parameter variation is better in SMC to that of PID. Sliding mode control is basically simple and robust procedure to synthesize controllers for both the linear and non-linear processes. The design problem of SMC consists of defining the switching logic and parameters tuning of each controller structure. The first step in SMC is to define a surface s(t), along which the process can slide to its desired final value. The sliding surface breaks the phase plane into regions where the switching function s(t) has different signs. The structure of the controller is intentionally altered as its state crosses the surface in accordance with a prescribed control law [23]. It was designed for T1DM.

Adaptive Control. It is a control method used by a controller which must adapt to a controlled system with varying parameters and which are uncertain initially. For adaptive modeling, *"Minimal Model of Bergman* [24]*"* is commonly used due to its simplicity. Most of the T1DM models are designed via model of Bergman. The model designed with it can be extended for the T2DM. The model has two inputs: glucose rate and the subcutaneously injected insulin flow; at the same time this input is the control input as well. The output of the model is plasma glucose level. The model has three state variables, which are connected to the blood plasm, these are: the blood glucose concentration, insulin-excitable tissue glucose uptake activity and the blood insulin concentration. The controller reacts promptly to large and rapid variations in insulin action [25].

Another Adaptive method used is Robust Fixed Point Transformation (RFPT) [24]. The RFPT method is an alternative for the model reduction techniques. Only the response of the system to the control signal is observed. Deformed input is used to calculate this signal to approximate the model for already defined "desired system response". "Purely kinematic terms" are used to determine the desired response without using any information on the system's dynamics. For the adaption of RFPT method route for control signal is elaborated which determines control actions and parameters. The control parameters can be set without any optimization. Controller is efficient to control blood glucose level very close to basal value for patient.

Model Predictive Control (MPC). Mostly work done in MPC is for the glucose control in T1DM. Flexibility to individually specify the critical parameters such as body weight, total insulin dose and control specifications are considered [36]. The feed forward ability of MPC that acts in anticipation of the future fluctuations due to disturbances is enhanced when considering a reference meal plan of specific size and time that is always given to the patient. Thus, the system is ready to provide the optimal insulin infusion to compensate for a small in size reference meal, in order to overcome the effect of long [26]

H∞ Control. When using LTI models H∞ is practical controller synthesis approach. There is an effective tradeoff between the strength of control action and the tracking error when considering low order robust controller characterized by H∞. This tradeoff is known as the mixed-sensitivity problem and the optimal solution in terms of the lowest gain between the input disturbance and the output errors is achieved by this optimal control procedure. The glucose-insulin response obtained by simulations shows that it got stabilized in a reasonable time interval [17]

State-Dependent Riccati Equation (SDRE). This technique is used to design blood glucose regulator for T1DM patients. There is a tracking problem defined so that blood glucose concentration tracks exponential decreasing desired trajectories. Hypoglycemia and hyperglycemic problems are limited by time- varying desired trajectory. Effects of uncertainties like meals and exercise have been investigated for ten different patients. Important advantages of this treatment are that for T1DM patients there are no hypoglycemia conditions and it has robustness against parametric uncertainties in glucose insulin system [38].

Proportional Integral Derivative (PID). It has three parts P,I and D. P is for proportional , I is for Integral and D is for Derivative. It may vary with requirements e.g. It may be P, PI , PD and PID. It calculates the error between set point and measured value.

Fuzzy Logic Control. The feedback FLC model is made. It is Mamdani-type fuzzy architecture which has two input and one output method. It is configured with PID.

VII. CONCLUSION

This review article discusses about Diabetes Millitus Control. Exogenous Insulin infusion term is briefly added. Administration of Insulin delivery has been discussed for type-1 patients. These are some control challenges faced when Artificial Pancreas is developed. Different linear and non-linear schemes have also been discussed for Diabetes. PID Controller has been applied to control TIDM. Simulink Models has been explained and plotted. It's a control loop strategy which makes Artificial Pancreas reality.

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