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Development of a fully automated closed loop artificial pancreas control system with dual pump delivery of insulin and glucagon

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Abstract—**Patients with diabetes have difficulty controlling their blood sugar and suffer from acute effects of hypoglycemia and long-term effects of hyperglycemia, which include disease of the eyes, kidneys and nerves/feet. In this paper, we describe a new system that is used to automatically control blood sugar in people with diabetes through the fully automated measurement of blood glucose levels and the delivery of insulin and glucagon via the subcutaneous route. When a patient's blood sugar goes too high, insulin is given to the patient to bring his/her blood sugar back to a normal level. To prevent a patient's blood sugar from going too low, the patient is given a hormone called glucagon which raises the patient's blood sugar. While other groups have described methods for automatically delivering insulin and glucagon, many of these systems still require human interaction to enter the venous blood sugar levels into the control system. This paper describes the development of a fully automated closed-loop dual sensor bi-hormonal artificial pancreas system that does not require human interaction. The system described in this paper is comprised of two sensors for measuring glucose, two pumps for independent delivery of insulin and glucagon, and a laptop computer running a custom software application that controls the sensor acquisition and insulin and glucagon delivery based on the glucose values recorded. Two control algorithms are designed into the software: (1) an algorithm that delivers insulin and glucagon according to their proportional and derivative errors and proportional and derivative gains and (2) an adaptive algorithm that adjusts the gain factors based on the patient's current insulin sensitivity as determined using a mathematical model. Results from this work may ultimately lead to development of a portable, easy to use, artificial pancreas device that can enable far better glycemic control in patients with diabetes.**

I. INTRODUCTION

PATIENTS suffering from diabetes cannot maintain their blood sugar at a constant normal level. The blood sugar of a patient with type 1 diabetes can go too low - a condition called hypoglycemia. Hypoglycemia, if left untreated can lead to feelings of discomfort, seizures, and in rare cases brain damage or death. Patients with type 1 and type 2 diabetes can also suffer from excessively high blood sugar – a condition called hyperglycemia. Exposure to hyperglycemia over many years can cause neuropathy, retinopathy, and damage to other tissue and organs. Current methods of maintaining euglycemia in patients with diabetes involves periodic monitoring of blood sugar using off-the-shelf blood glucose monitoring sensors and then subsequent delivery of insulin via either multiple needle injections throughout the day or alternatively through the use of an insulin pump. Insulin injections enable the patient to reduce his/her blood sugar levels when they are too high. If a patient finds that their blood sugar levels are too low, they typically eat carbohydrates to bring their levels back up again. While regular monitoring and subsequent infusion of insulin into the body has proven to be effective at improving patients' ability to control their blood sugar [1], maintenance of a stable blood sugar requires constant monitoring of a variety of factors including current blood sugar, meal times, amount of carbohydrate consumed, amount of physical activity and an individual's own variable sensitivity to insulin. It is difficult and time consuming for a patient with diabetes to continuously monitor their blood sugar and accurately determine the amount of insulin that they need to dose themselves. Furthermore, episodes of hypoglycemia can occur without the patient realizing it, such as at nighttime while the patient is asleep. Other groups have described a manually-controlled artificial pancreas system used to maintain constant blood sugar levels in patients with diabetes [2; 3; 4]; in these systems blood sugar levels were entered by hand into the control system and the control system then determined the amount of insulin and glucagon to dose to the patient. In this paper, we describe a fully automated artificial pancreas whereby continuous acquisition of multiple sensor values and delivery of insulin and glucagon are done without human interaction.

The concept of a closed-loop artificial pancreas was first described by Kadish in 1964 [5]. Since then there have been other groups that have made significant contributions to artificial pancreas technology [6; 7; 8]. Several groups have discussed various methods for implementing a closed-loop artificial pancreas using model predictive control systems [9; 10; 11; 12; 13] and others using neural network-based control methods [14; 15]. Albisser et al. [16; 17] described how proportional and derivative parameters could be used to control insulin and glucagon based on sensed glucose. Ward et al. also have described the use of proportional and derivative parameters to develop a novel method of insulin

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delivery using an algorithm called the fading memory proportional-derivative method or FMPD [18] which was designed to deliver insulin based on the normal physiology of the β-cells. The current paper discusses implementation of the FMPD algorithm to control both insulin and glucagon based on sensed glucose readings. The FMPD algorithm is extended in this paper to include an adaptive control mechanism based on a modification of Hovorka's model of glucose and insulin absorption [12] that accounts for a patient with diabetes ongoing change in insulin sensitivity.

The system we describe includes a method for glucose sensor redundancy; the system includes two glucose sensors rather than one to reduce the error caused by sensor drift, latency effects, and calibration errors. Advantages of a two-sensor design have been previously reported [19].

II. PROCEDURES

The artificial pancreas system constructed is shown in Figure 1 below. The system consists of a custom software application called Artificial Pancreas Control (APC) written in C# which wirelessly acquires subcutaneous interstitial glucose readings from two off-the-shelf glucose sensors (Dexcom Inc.), and controls two off-the-shelf pumps (Insulet Corporation). One of the pumps is filled with insulin and the other is filled with glucagon.

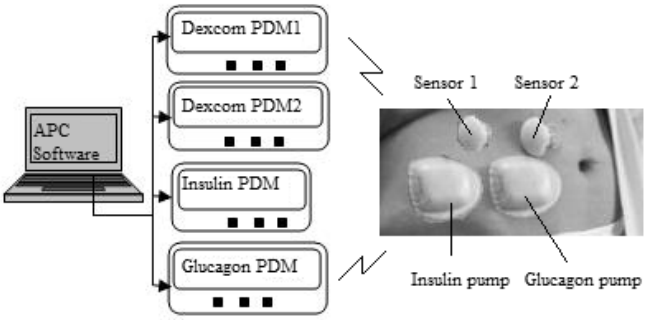

Figure 1: System diagram of dual-sensor bi-hormonal artificial pancreas system.

The APC software determines how much insulin and glucagon must be delivered to a patient based on the glucose sensor readings recorded as well as various events that are input into the software including meal events, oral / IV carbohydrate boluses, and sensor calibrations.

Insulin infusion rates (IIR) and glucagon infusion rates (GIR) are determined using the FMPD control algorithm [16]. The FMPD algorithm is extended in this paper to include an adaptive component that adjusts a patients' total daily insulin requirement (TDR) based on real-time simulations from a physiologic model of insulin and glucose metabolism described in Hovorka et al. [12] This new algorithm is called Adaptive Proportional Derivative (APD). Figure 2 outlines the FMPD algorithm and the shaded block shows how the model is extended to incorporate APD.

A. Fading Memory Proportional Derivative (FMPD)

Steil et al. [20] describe how the pancreatic β-cell response to glucose is biphasic; specifically, there is an initial increase in insulin release by the cell followed by a slower release of insulin that persists during the course of the hyperglycemic event. The FMPD algorithm models this biphasic quality by utilizing current information in addition to a fading history of previous information to estimate the amount of insulin and glucagon that should be dosed. The β-cell is responsible for maintaining blood glucose at a set target level (G_T). If blood sugar (G) at time t deviates from this target level, there is a proportional error called PE(t).

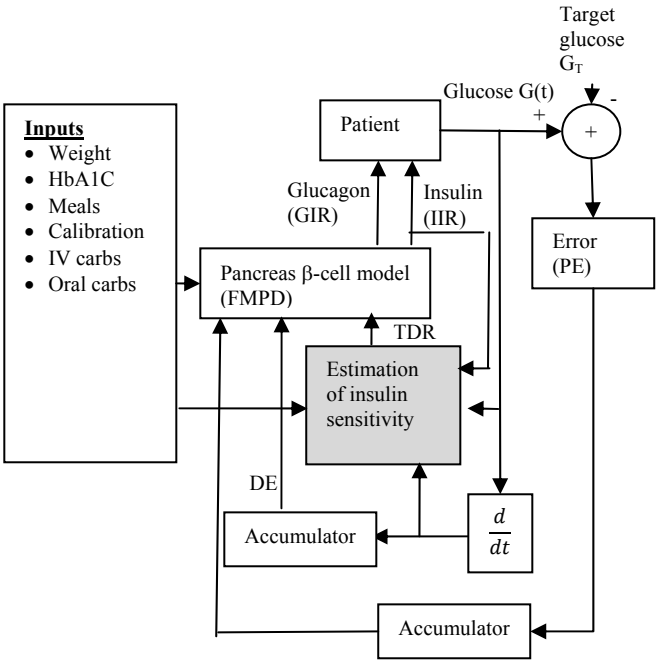

Figure 2: FMPD model for delivering insulin and glucagon based on periodic glucose sensor inputs and other event inputs including meal and oral carbohydrate consumption. The adaptive component of the model (shaded box) adjusts the total daily insulin requirement (TDR) based on the patient's estimated insulin sensitivity.

The amount of insulin delivered is dependent on this proportional error. Proportional error is the difference between the patient's sensed glucose and the target glucose. If the sensed glucose is larger than the target glucose level, then the insulin infusion rate increases. The model of the biphasic nature of the proportional error is implemented by maintaining a 90 minute history of the proportional error and performing a weighted average using an exponential multiplier. This weighted average term is called the proportional error average and is defined in Equation 1. The terms K and z terms are the proportional gain coefficient and decay coefficient, respectively [18].

Equation 1
$$PE_{Avg}^{IIR} = K_{PE}^{IIR}\left(\frac{\sum_{t=0}^{18} PE(t)e^{-z_{pe}^{iir}t}}{19}\right)$$

The amount of insulin delivered is also dependent on how quickly the patient's glucose level is changing. If the patient's glucose is increasing rapidly, then the insulin infusion rate also increases. Likewise if the patient's glucose is decreasing rapidly, the insulin infusion rate decreases further. The rate at which the glucose is changing is called the derivative error (DE) and is calculated using a least squares regression over the prior 10 minutes of sensor

data. As with the proportional error, the biphasic nature of the β-cell is incorporated into DE by accumulating 90 minutes of data and applying a weighted average such that the more recent DE values affect the infusion rate more significantly. The equation for DE_{Avg} is defined below.

Equation 2 $$DE_{Avg}^{IIR} = K_{DE}^{IIR}\left(\frac{\sum_{t=0}^{18} 60DE(t)e^{-Z_{DE}^{iir}t}}{19}\right)$$

Finally, the amount of insulin delivered is dependent upon the patient's adjusted total daily insulin requirement (TDR_{Adj}), which is their physician-prescribed TDR adjusted by their HbA1C as defined below.

Equation 3 $$TDR_{Adj} = TDR(0.0667HbA1C + 0.5331)$$

Lastly, the total insulin infusion rate includes a basal insulin infusion component. The basal rate is defined as being a constant value when the patient's glucose is greater than or equal to the target glucose. If the blood glucose is less than 60% of the target glucose, then the basal insulin rate is turned off. If glucose is less than the target, but greater than 60% of the target, then the basal rate decreases linearly according to Equation 4.

Equation 4

$$BR(t) = \begin{cases} \frac{TDR_{Adj}K_B}{24}, & G_T \le G(t) \\ \left(\frac{TDR_{Adj}K_B}{24}\right)\left[\left(\frac{2.5*G(t)}{G_T}\right) - 1.5\right], & 0.6G_T \le G(t) < G_T \\ 0, & G(t) < 0.6G_T \end{cases}$$

The total insulin infusion rate is a sum of PE_{Avg}, DE_{Avg}, and BR shown in Equation 5.

Equation 5 $$IIR = PE_{Avg}^{IIR} + DE_{Avg}^{IIR} + BR$$

Delivery of glucagon is also dependent on the proportional error and the derivative error. There are several important differences between how glucagon infusion rate (GIR) is calculated in comparison with IIR by the FMPD algorithm. First, FMPD allows for a different target glucose level for glucagon than for insulin. This enables the glucagon infusion to be independent of the insulin infusion. Second, the glucagon proportional error is only dependent on the 4 most recent glucose readings (15 minutes) and the derivative error average is only dependent on the 3 most recent derivate error calculations (10 minutes). This is because the effect of glucagon on the body is more rapid than insulin, so only the most recent glucose history is pertinent. Third, no basal component exists for the glucagon infusion rate. Finally, the average PE and DE for glucagon is adjusted by the patient's weight (W). GIR is summarized below.

Equation 6 $$PE_{Avg}^{GIR} = K_{PE}^{GIR}\left(\frac{\sum_{t=0}^{3} W(PE_{GIR})e^{-Z_{PE}^{GIR}t}}{4}\right)$$

Equation 7 $$DE_{Avg}^{GIR} = K_{DE}^{GIR}\left(\frac{\sum_{t=0}^{2} W(DE)e^{-Z_{DE}^{iir}t}}{3}\right)$$

Equation 8 $$GIR = PE_{Avg}^{GIR} + DE_{Avg}^{GIR}$$

B. Physiologic model for changing insulin sensitivity

The FMPD control algorithm described above can be extended to adjust for each patient's changing insulin sensitivity. Insulin sensitivity can vary based on factors including fatigue, stress, exercise, and other events. The new algorithm is called the Adaptive Proportional Derivative algorithm (APD), and it is briefly described here; a future paper will describe it in more detail.

The extension of FMPD to include adaptive control over the insulin sensitivity is shown as the shaded box in Figure 2. The total daily insulin requirement (TDR) as used in the FMPD algorithm does not need to be a fixed input parameter, but rather can change dynamically. TDR is a function of insulin sensitivity, and it directly influences the calculation of the basal insulin rate (Equation 3 and 4). Therefore, we can capture dynamic changes to a patient's insulin sensitivity by adjusting TDR.

Within the APD algorithm, the initial TDR is estimated using the patient's first glucose reading and the patient's basal insulin rate at the start of the experiment. The Hovorka insulin sensitivity model is used to estimate glucose using each of the possible sensitivity composites ranging from 10% to 200% of baseline sensitivity factors. A least squares regression is done to determine which sensitivity yields a glucose estimate closest to the patient's current glucose reading. After the initialization, TDR is updated once every 30 minutes. The updated TDR is calculated using the previous 90 minutes of sensor readings, insulin boluses, and meal events. Insulin sensitivity composites of between 10% and 200% are input into the insulin sensitivity model and used to predict glucose levels. A least squares regression is again performed to determine which sensitivity component yields the predicted glucose pattern that is closest to the actual glucose pattern during that time. The sensitivity is then converted to TDR, which is input into the FMPD algorithm.

We have done testing adjusting insulin sensitivity in patients with type 1 diabetes through the administration of steroids to verify that the model of insulin sensitivity is valid and detects the fall in sensitivity. Results are beyond the scope of this paper; a future publication will discuss further.

III. Results

Preliminary results shown in Figure 3 demonstrate how the adaptive control algorithm performs in an actual patient with diabetes. Results show that the system delivers insulin when the patient's glucose is high and delivers glucagon when the patient's glucose drops rapidly. The system also responds to meal events, adjusting the amount of insulin and glucagon based on the meal consumed and the amount of carbohydrate within the meal.

Notice in Figure 3 that the patient's blood glucose is initially high. After breakfast, their blood sugar rises even higher. Insulin is automatically delivered to the patient's body and the patient's blood glucose is brought down to a euglycemic level. As the patient's blood glucose continues to drop below the target blood sugar level, glucagon is delivered to increase the blood sugar. The patient's blood

sugar is eventually brought into a range that is clinically acceptable.

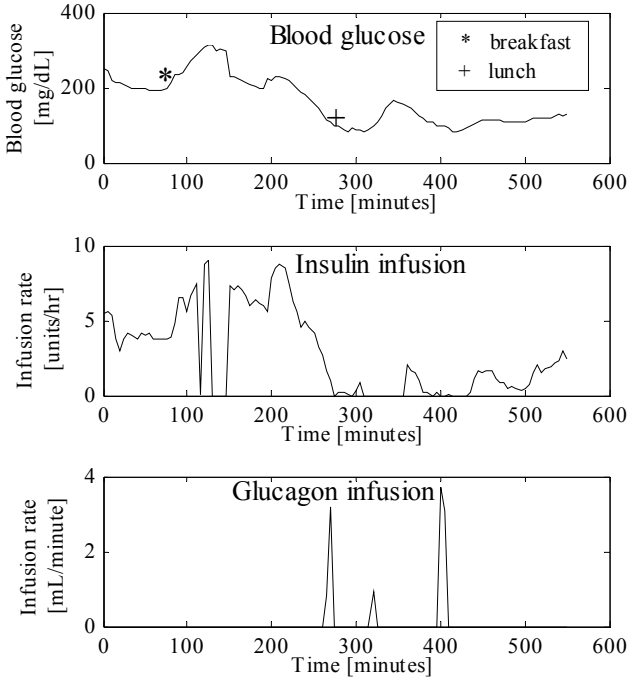

Figure 3: Diabetic patient's blood glucose during automated delivery of insulin and glucagon using the APD control algorithm.

IV. Discussion

We have described a fully automated artificial pancreas control system that acquires glucose from two sensors while delivering insulin and glucagon to a patient's body without human interaction. The advantages of bi-hormonal delivery are evident in Figure 3 which shows how a hypoglycemic episode is avoided through the delivery of glucagon at minute 280 as the patient's blood sugar is falling rapidly. Likewise, hyperglycemic events are minimized by the delivery of insulin at the beginning of the experiment and also at other times when the patient's blood sugar begins to rise above euglycemia such as minute 200 and minute 350. Sensor drift issues are minimized through the use of two sensors within the system to estimate the patient's blood sugar. The most accurate sensor at the time of calibration is used within the control algorithm and a sensor which has drifted will not be used. In this experiment, sensor 1 was selected as the most accurate and sensor 2 readings were discarded. Future plans include using the system within a clinical study of human subjects with diabetes in inpatient and then outpatient environments. Other plans involve miniaturizing the system so that it can be easily carried and used within a patient's home.

V. Acknowledgements

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