

Automated control of an adaptive bi-hormonal, dual-sensor artificial pancreas and evaluation during inpatient studies

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Abstract— Automated control of blood glucose in patients with type 1 diabetes has not yet been fully implemented. The aim of this study was to design and clinically evaluate a system that integrates a control algorithm with off-the-shelf subcutaneous sensors and pumps to automate the delivery of the hormones glucagon and insulin in response to continuous glucose sensor measurements. The automated component of the system runs an adaptive proportional derivative control algorithm which determines hormone delivery rates based on the sensed glucose measurements and the meal announcements by the patient. We provide details about the system design and the control algorithm, which incorporates both a fading memory proportional derivative controller (FMPD) and an adaptive system for estimating changing sensitivity to insulin based on a glucoregulatory model of insulin action. For an inpatient study carried out in eight subjects using Dexcom SEVEN PLUS sensors, pre-study HbA1c averaged 7.6, which translates to an estimated average glucose of 171 mg/dL. In contrast, during use of the automated system, after initial stabilization, glucose averaged 145 mg/dL and subjects were kept within the euglycemic range (between 70 and 180 mg/dL) for 73.1% of the time, indicating improved glycemic control. A further study on five additional subjects in which we used a newer and more reliable glucose sensor (Dexcom G4 PLATINUM) and made improvements to the insulin and glucagon pump communication system resulted in elimination of hypoglycemic events. For this G4 study, the system was able to maintain subjects' glucose levels within the near-euglycemic range for 71.6% of the study duration and the mean venous glucose level was 151 mg/dL.

Index Terms— glucose sensor, artificial pancreas, bihormonal insulin delivery, glucagon delivery

I. INTRODUCTION

There has been significant progress made in recent years in developing technology for the automated delivery of hormones to people with type 1 diabetes. Ever since the

concept of automated control of glucose was first proposed [1, 2] there has been a steady evolution of methods for implementing the artificial pancreas. An overview of this progress is provided in [3, 4] which begins by describing how the artificial pancreas resulted from the simultaneous development of continuous glucose monitoring techniques [5-7] along with automated insulin delivery technologies.

The Biostator [8, 9], based on the work of Albisser et al. [1,2] was the first commercial implementation of the artificial pancreas controller. The Biostator used an average blood glucose reading taken continuously and the delivery of insulin was based on this average glucose reading along with the change in blood glucose over a prior five-minute window. The Biostator delivered insulin intravenously and blood was withdrawn intravenously for external glucose measurement. There have been many challenges to intravenous insulin delivery and glucose measurement and most current approaches to closed loop glucose control, including the one described in this paper, use the subcutaneous route.

A proportional controller [1] was the first algorithm used to control the delivery of insulin based on glucose sensor readings. This proportional controller used the difference between a target glucose level and the sensed glucose measurement to calculate the insulin delivery amount. A derivative component was introduced [2] which incorporated the change in measured glucose over time to calculate the insulin infusion amount. Steil and others have incorporated an integral component in the controller that utilizes a history of proportional values to improve the performance of maintaining glucose homeostasis [10-12]. These three components (proportional, integrative, and derivative) form the basis of many PID-based artificial pancreas delivery controllers. The one described in this paper also contains elements of these three components.

An alternative to PID controllers is model predictive control (MPC). MPC has been applied towards automated blood glucose control as reported by numerous groups using simulated data [13-16] and also within clinical studies [17-19]. MPC based approaches to glucose control use a mathematical model of the body's metabolism of insulin and glucose to project future glucose levels of the patient. The control variable (insulin delivery) is then adjusted by solving an optimization problem that is designed to achieve euglycemia. The design of the cost equation that is minimized is therefore

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of critical importance in MPC approaches to glucose control. The control algorithm that we describe in this paper also uses a physiologic model of insulin and glucose metabolism; however, we use the model to estimate the subject's varying insulin sensitivity and then modify parameters within a PID controller based on this varying sensitivity. The unique aspect of our controller is that we use a PID-like controller in concert with a gluco-regulatory mathematical model that adjusts for changing insulin sensitivity to control blood sugar levels in patients. Comparisons between MPC approaches and our algorithm will be discussed.

Other groups have reported alternative methods for closed loop control of blood glucose including those using fuzzy logic, artificial neural networks, and those which use mathematical models of β -cells to control delivery of hormones [20-26].

Vigorous treatment of type 1 diabetes increases the frequency of hypoglycemia [27]. In the setting of the artificial pancreas, attempts have been made to algorithmically predict when a patient is approaching hypoglycemia, leading to discontinuation of insulin delivery [28]. However, subcutaneously-delivered insulin has a delayed absorption, so this approach is not always successful, even with currently available fast-acting insulin analogs [29]. Our group [30], as well as groups from Boston University (USA) and McGill University (Canada) [31-34], have addressed the issue of avoiding hypoglycemic events by incorporating a second pump that delivers glucagon in response to impending or overt hypoglycemia. Glucagon is the natural secretory product of pancreatic alpha cells in mammals and is normally released in response to hypoglycemia. Our algorithm adapts to changes in insulin sensitivity, which can occur during stress or exercise.

While we have previously reported on certain aspects of our controller [35-37], we have not yet presented the entire algorithm and automated control hardware and software system. In this paper, we describe the details of the controller, the value of each parameter in the model, and describe how the parameters were tuned using two types of simulators. We discuss how we integrate a control algorithm with an adaptive expert system and a physiologic gluco-regulatory model to enable automated bi-hormonal drug delivery (insulin and glucagon) for the purpose of maintaining glucose homeostasis within the near euglycemic range. The only part of the system that is not fully closed loop is the element in which the patient must enter a rough estimate of carbohydrate consumption to the system.

II. SYSTEM DESIGN

The closed loop system that we are presenting here consists of two off-the-shelf wire-based continuous glucose sensors (SEVEN PLUS and G4 PLATINUM, Dexcom Inc.), two off-the-shelf micro-delivery pumps (Omnipod, Insulet Corporation), and custom controller software running on a palm top tablet computer (Viliv, Yuckyung). Software was developed in C#.NET. Each sensor interfaces with its own receiver and each pump is controlled by its own personal diabetes manager (PDM, Insulet) through separate wireless

channels. The controller software communicates with the sensor receivers and the pump PDMs across a USB interface. The receivers and PDMs communicate wirelessly with the sensors and pumps, respectively. A custom battery pack was used to power all of the system components during the data acquisition process. Our algorithm relies on redundant sensor measurements to help mitigate the risk of sensor drop-outs and drift. The SEVEN PLUS sensors are not capable of interfacing with more than one computing device, and so when the CGM was used, we used a virtual operating system on the Viliv tablet such that one sensor communicated with the primary operating system, while the back-up sensor communicated with the virtual operating system. We used VMWare Workstation (VMWare, Palo Alto, CA) to enable the virtual operating system and used custom software to automatically acquire the sensors between the two operating systems. Fig. 1 shows a diagram of the system.

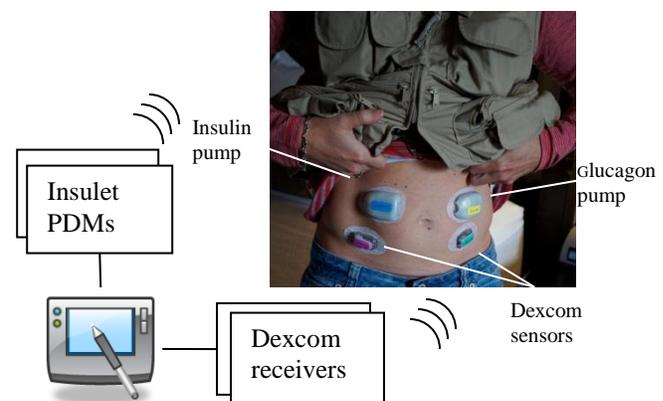


Fig. 1. System diagram of artificial pancreas hardware components. Receivers and mobile computing devices are held in the vest.

The system is capable of delivering both a pre-meal insulin bolus and automated insulin or glucagon infusion. The pre-meal insulin bolus is calculated based on the patient's indicated carbohydrate intake, estimated to the nearest 20 g. The patient enters this carbohydrate amount into the control software and the controller then calculates a suggested insulin bolus amount. The patient then acknowledges this amount of pre-meal insulin and the bolus is given. The bolus is then given with the expectation that the patient will consume the meal at that time. We believe that the pharmacodynamic properties of subcutaneously-delivered insulin are too long to enable a fully-automated system without meal announcements. While automated meal detection algorithms have been proposed [38,39], they may not be able to detect the meal soon enough to optimize post-prandial glycemic control.

A. Overview of control algorithm

The artificial pancreas control (APC) algorithm used to regulate glucose consists of (1) a fading memory proportional derivative (FMPD) controller, and (2) an adaptive expert system that modifies the insulin delivery rates by changing the FMPD gain factors [36]. The adaptive system is based on the physiologic model of glucose-insulin regulation developed by Hovorka [40] and reported by El Youssef et al [35]. The

system takes into account the subject's HbA1c, weight, total daily insulin requirement (TDR), as well as current and prior glucose sensor readings, announced meals, rescue carbohydrate deliveries, sensor calibration history, and calculated insulin sensitivity values. The system makes executive decisions based on the proportional and derivative errors (and their histories or 'fading memories') using a target glucose. A general concept of this control system is shown in Fig. 2.

The system of automated insulin and glucagon administration is specifically designed to minimize the risk of the two drugs opposing one another, which would otherwise increase the risk for system instability. For example, as discussed below in further detail, when glucagon is given to treat impending hypoglycemia, the insulin delivery gain settings are temporarily reduced in order to avoid triggering insulin delivery as a result of the glucagon-induced rise in glucose. Although the system is bihormonal in nature, it is important to emphasize that it does not require administration of glucagon, which is only delivered for rescue purposes.

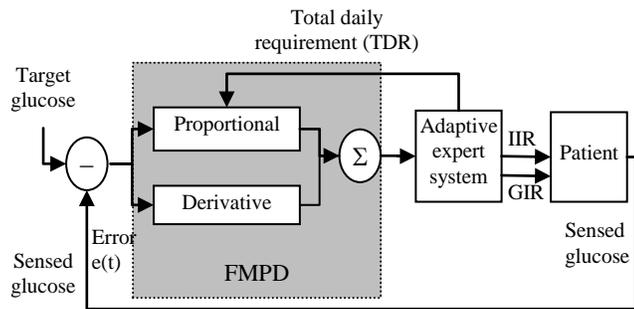


Fig. 2. APC algorithm that consists of the FMPD control algorithm that is updated by an adaptive expert system.

1) Fading memory proportional derivative (FMPD) control algorithm

The FMPD controller consists of a proportional error term (PE), a derivative error term (DE), and a basal rate term (BR). The FMPD controller has separate parameters for controlling insulin infusion rate (IIR) as compared with glucagon infusion rate (GIR). In this paper, the superscript for mathematical terms includes reference to the type of hormone being infused, IIR or GIR.

The proportional error at time t ($PE(t)$) is the difference between a target glucose level (G_T) and a sensed glucose level (G). A superscript indicates whether PE is related to IIR (PE^{IIR}) or GIR (PE^{GIR}). The insulin and glucagon control algorithms use different target glucose levels. These target values (115 mg/dL for insulin and 95 mg/dL for glucagon) have been shown to perform well in humans as we have demonstrated [36]. The insulin delivery target is more conservative at night to reduce the risk of nocturnal hypoglycemia. The target values are summarized in Table 1.

An exponentially weighted sum of PE terms is averaged over the prior 90 minutes such that the most recent PE terms receive the largest weighting while those from 90 minutes

prior are least relevant. The weighting value at a time t is adjusted by the proportional error time constant z_{PE}^{IIR} as shown in Equation 1. Likewise, the entire average proportional error is scaled by the PE gain constant K_{PE}^{IIR} . Note that the weighted PE values are only summed every 5 minutes such that a total of 19 prior $PE(t)$ readings are included. The reason for this rule is that the sensed glucose measurements only arrive once every 5 minutes from the Dexcom sensors. The term k is a 5-minute increment index such that when $k=3$, for example, the $PE(t-5k)$ term is from 15 minutes prior to the current time.

$$\text{Equation 1: } PE_{Avg}^{IIR}(t) = K_{PE}^{IIR} \times \left(\frac{\sum_{k=0}^{18} PE(t-5k) \times (e^{-z_{PE}^{IIR} \times 5k})}{19} \right)$$

The derivative error term (DE) is defined as the slope or the change in sensed glucose over the prior 10 minutes. If the subject's glucose is changing very rapidly, the IIR will be adjusted more significantly because the DE term will be larger. It is important to use a short time period over which to estimate DE so as to more accurately capture the change in glucose at a given point in time. A linear least-squares regression was done on the prior 10-minute data record to calculate this slope DE term. As was carried out with the PE average, the DE terms are also averaged over the prior 90 minutes using a weighted average that is dependent on the DE gain constant (K_{DE}^{IIR}) and the DE time constant (z_{DE}^{IIR}). Using a weighted average of DE over 90 minutes minimizes the influence of sensor noise on the IIR calculation (Equation 2). The selection of the gain and time constants were derived empirically as previously described [36]. Model parameters were derived within rats. For use within humans, the model parameters were tuned using the UVa-Padova simulator [41-42] and separately using a simulator based on the glucoregulatory model described by Hovorka et al. [40] implemented using Visual Basic for Applications within Microsoft Excel (Microsoft Inc., Redmond, WA).

Equation 2:

$$DE_{Avg}^{IIR}(t) = K_{DE}^{IIR} \times \left(\frac{\sum_{k=0}^{18} 60 \times DE(t-5k) \times (e^{-z_{DE}^{IIR} \times 5k})}{19} \right)$$

The subject's initial TDR is obtained from an interview of the patient. Due to the fact that TDR is underestimated in patients with poorly-controlled diabetes, this TDR value is adjusted using the patient's HbA1c according to Equation 3. An HbA1C of 7% is chosen as a target for the initial TDR adjustment based on ADA recommendations [43]. If the subject's TDR is above 7%, the TDR will be increased by 10% for every 1.5% increase in HbA1C. This relationship is given in Equation 3 whereby the constants 0.0667 and 0.5331 were selected to enable this relationship between the subject's clinical TDR, their TDR_{Adj} and the HbA1C.

Equation 3:

$$TDR_{Adj} = \begin{cases} TDR, & TDR \leq 7\% \\ TDR \times (0.0667 \times HbA1C + 0.5331), & TDR > 7\% \end{cases}$$

TDR_{Adj} is then used to calculate the basal rate of insulin delivery which depends on the patient's sensed glucose relative to their target glucose level. If the sensed glucose is below 60% of the target, then the basal rate is zero. If the sensed glucose is between 60% of the target and the target, then the basal rate is linearly proportional to the TDR_{Adj} and the basal multiplier (K_B) according to Equation 4. And finally, if the sensed glucose is greater than or equal to the target, then the basal rate is a fixed value corresponding to the TDR_{Adj} and the basal multiplier. The basal multiplier was selected by running simulations using the UVa-Padova simulator [41,42].

Equation 4:

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

The insulin infusion rate at time t is then a sum of the weighted average PE, weighted average DE, and basal rate terms according to Equation 5.

Equation 5: $IIR(t) = PE_{Avg}^{IIR}(t) + DE_{Avg}^{IIR}(t) + BR(t)$

Insulin on board at time t ($IOB(t)$) is a weighted sum of all past insulin boluses (B) over the past 9 hours as defined by Equation 6. If $IOB(t)$ exceeds 20% of TDR_{adj} , then IIR gets set to 0 as shown in Fig. 3. The decay constant of IOB was selected based on data presented by Holmes et al [29].

Equation 6:

$$IOB(t) = \sum_{k=0}^{18} B(t-5k) + \sum_{k=19}^{108} B(t-5k) e^{-z_{IOB}(t-5k)}$$

The glucagon infusion rate (GIR) is calculated in a manner similar to that of the insulin infusion rate. GIR is calculated using a PE term and a DE term, however, the target glucose is independent of the insulin target glucose. This independence enables the GIR control parameters to be adjusted without influencing the control of insulin. Unlike the IIR calculation, the GIR calculation does not include a basal delivery rate. Furthermore, the history over which the weighted average is taken for the proportional error is smaller (15 minutes) as compared with 90 minutes for insulin. This is because glucagon acts faster than insulin within the body.

Equation 7:

$$PE_{Avg}^{GIR}(t) = K_{PE}^{GIR} \times \left(\frac{\sum_{k=0}^3 W \times (PE^{GIR}(t-5k)) \times (e^{-z_{PE}^{GIR} \times 5k})}{4} \right)$$

Note that the glucagon PE average is dependent on the patient's weight (W), the glucagon PE, the glucagon decay time constant z_{PE}^{GIR} and the PE gain constant (K_{PE}^{GIR}).

Equation 8:

$$DE_{Avg}^{GIR} = K_{DE}^{GIR} \times \left(\frac{\sum_{k=0}^2 W \times DE(t-5k) \times (e^{-z_{DE}^{GIR} \times 5k})}{3} \right)$$

Finally, the GIR is the sum of the average PE_{Avg}^{GIR} and DE_{Avg}^{GIR} terms. There is no basal rate term for calculating GIR .

Equation 9: $GIR(t) = PE_{Avg}^{GIR}(t) + DE_{Avg}^{GIR}(t)$

2. Adaptive expert system (AES)

The adaptive expert system (AES) consists of two sub-system components, (1) a decision tree based on the FMPD output along with patient-specific information, and (2) an adaptive physiologic model that calculates the patient's insulin sensitivity once every 30 minutes and feeds this information back to the FMPD algorithm in the form of the TDR. Each of these is further discussed below.

B. Decision tree

During the use of the system, the patient and the clinician have the ability to enter various events including meals, oral rescue carbohydrates, intravenous (IV) carbohydrates, and sensor calibrations. The inclusion of IV carbohydrates is applicable only to studies done in an inpatient setting. Intravenous carbohydrates were given if the patient's glucose dropped below 50 mg/dL. The IIR and GIR values calculated by the FMPD algorithm are adjusted according to these events using the decision trees shown in Figs. 3 and 4, respectively. As an example of the rationale for these special circumstances is the following: As glucose rises quickly after a glucagon dose or after oral rescue carbohydrates, it would be inappropriate for the rising slope to trigger the derivative element of IIR . If IIR were not reduced during these circumstances, one could see instability in the system during which IIR and GIR both escalate to compensate for each other's independent effects.

The IIR is adjusted according to four events: (1) the maximum glucagon over a 50-minute period has been exceeded, (2) an oral rescue carbohydrate has been given in the past 15 minutes for treatment of hypoglycemia, (3) an IV carbohydrate has been given in the past 20 minutes for treatment of hypoglycemia, or (4), the maximum IOB has been exceeded.

The IIR is reduced to 25% of its FMPD calculated value (IIR_{FMPD}) if the amount of glucagon delivered within a 50-minute period (GG_{Limit}) has exceeded a maximum value or if an oral rescue carbohydrate load has been given within 15 minutes for treatment of hypoglycemia. If either of these conditions arises, then the IIR is reduced to 25% of IIR_{FMPD} for 40 minutes. The 40-minute turn-down period was selected because it represents the half-life of maximum insulin action [29]. The 25% reduction in IIR was chosen based on clinical standards of care [43] and was verified in-silico using the UVa-Padova simulator [41,42]. Intravenous carbohydrate delivery or the condition whereby IOB has exceeded 20% of TDR results in a complete turn-off of insulin infusion.

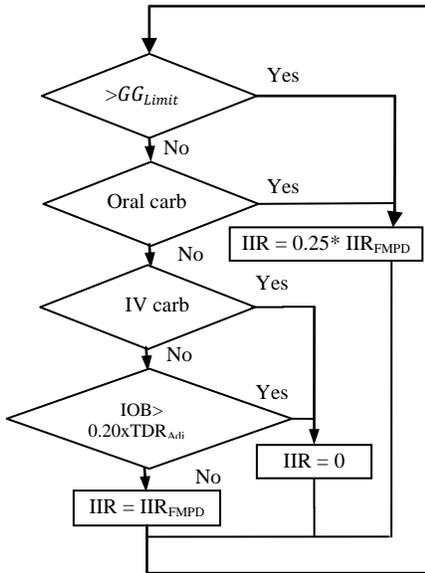


Fig. 3. Insulin infusion rate (IIR) decision tree.

The GIR calculated by the FMPD algorithm (GIR_{FMPD}) is adjusted using a decision tree as shown in Fig. 4. The maximum glucagon that may be delivered by the system within a 50-minute period is termed GG_{Limit} . GG_{Limit} is defined according to Equation 10.

Equation 10:

$$GG_{Limit} = \begin{cases} GG_{conc} W \left(GG_{LMin} + \frac{IOB}{TDR_{Adj}} (GG_{LMax} - GG_{LMin}) \right), & IOB < TDR_{Adj} \times 0.2 \\ GG_{conc} W (GG_{LMax}), & IOB \geq TDR_{Adj} \times 0.2 \end{cases}$$

Notice that the maximum glucagon delivered within a 50-minute period is dependent on the glucagon concentration (GG_{conc}), the patient’s weight (W), and the ratio of the IOB and the TDR_{Adj} for that patient. If the patient’s IOB is less than 20% of the TDR_{Adj} , then the GG_{Limit} is proportional to the ratio of IOB/TDR_{Adj} within the range of that subject’s minimum and maximum limit glucagon delivery amount (GG_{LMax} and GG_{LMin}) which are dependent on the subject’s weight (W). If the IOB is greater than 20% of the patient’s TDR_{Adj} , then GG_{Limit} is set equal to the limit of the maximum glucagon delivery amount.

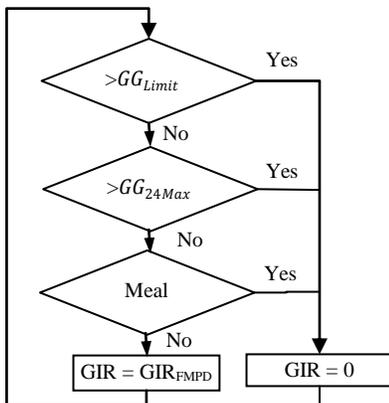


Fig. 4. Glucagon infusion rate (GIR) decision tree.

The glucagon decision tree in Fig. 4 is based on three conditions: (1) has the maximum 50-minute glucagon as

defined by Equation 10 been exceeded, (2) has the maximum glucagon delivery over 24-hours been exceeded, and (3) has a meal occurred within the last 20 minutes. If any of these conditions occur, the GIR is set to 0. Otherwise, the GIR is set according to the FMPD algorithm.

C. Adaptive physiologic model

We have incorporated a glucoregulatory model for estimating insulin sensitivity based on the one described by Hovorka et al. [40]. The Hovorka model describes a 3-compartment model including a glucose compartment, insulin absorption compartment, and insulin action compartments which feed back to the glucose compartment. This model can be used to estimate the patient’s insulin sensitivity based on their current and prior sensed glucose readings, meal events, and insulin bolus amounts. The insulin sensitivity is estimated every 30 minutes using the approach described further below and in Fig. 5.

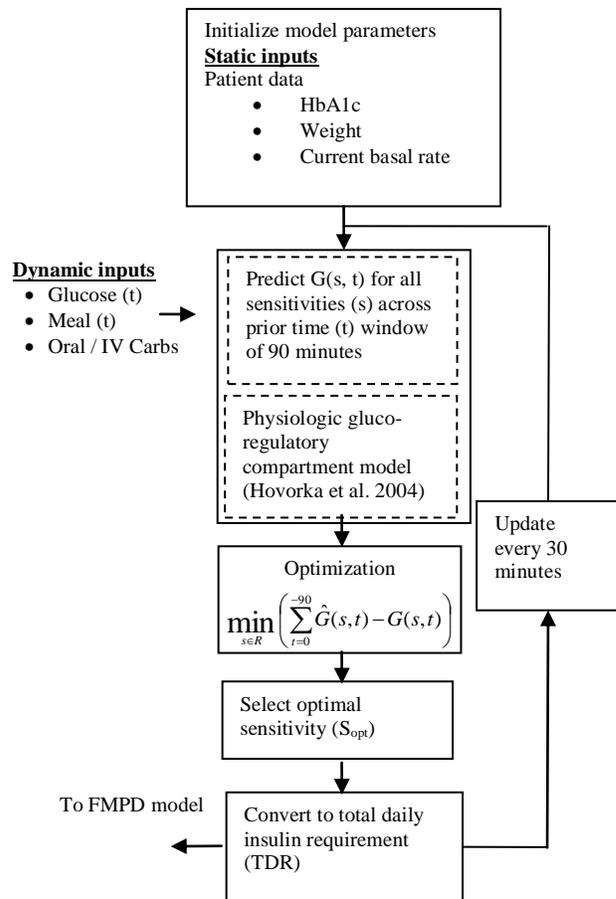


Fig. 5. Adaptive algorithm for adjusting patient’s insulin sensitivity based on a physiologic gluco-regulatory model [35].

The newly estimated insulin sensitivity is related to TDR using Equations 11 and 12 and also further explained below. Because TDR influences both glucagon and insulin delivery (Equation 4 and Equation 10, respectively), the control algorithm adapts the delivery of hormones based on a patient’s changing insulin sensitivity. Details of the Hovorka model and how we have used it to adjust insulin sensitivity are included in the appendix of El Youssef et al. [35]. Fig. 5 provides a summary of how it was used in this study.

Notice in Fig. 5 that every 30 minutes, the TDR is updated based on the subject’s updated insulin sensitivity. The patient’s insulin sensitivity is estimated by using the patient’s prior 90 minutes of sensed glucose along with meal data, oral rescue / IV carbohydrates, and insulin boluses delivered during that time and comparing the sensed glucose with glucose values predicted by a glucoregulatory model [40]. One of the parameters in the glucoregulatory model is an insulin sensitivity composite coefficient (S_c). When determining the patient’s insulin sensitivity, we select a fraction of the sensitivity composite coefficient that can range from 0.1 to 2.0 of the original setting. The final fraction is selected based on a least squares fit of the patient’s prior 90 minutes of sensed glucose data with respect to the model-predicted glucose values. The sensitivity composite is selected which yields the closest match of the model-predicted glucose with the prior 90 minutes worth of sensed glucose data using a mean-squared-error criteria.

The sensitivity composite coefficient and the sensitivity composite exponent were chosen by modeling the relationship between TDR and insulin sensitivity using the glucoregulatory model [40]. The glucose target of 115 was selected and for each insulin sensitivity composite (S_c), which is a percentage of the model sensitivity, was varied between 10 and 200%; the insulin infusion (mU/kg/minute) that maintained glucose at the target was plotted relative to the sensitivity composite. This relationship is a nonlinear inverse function and a power regression was fit with an R^2 of 0.9995 (see Fig. 6) to determine the sensitivity exponent value (S_e).

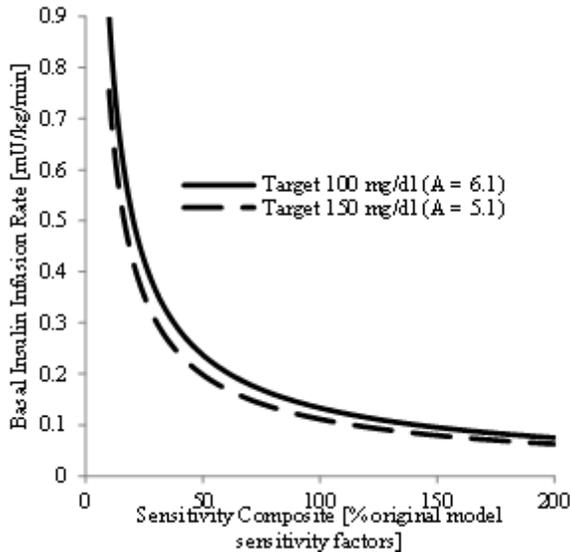


Fig. 6. Relationship between IIR and insulin sensitivity composite. For lower sensitivity to insulin, IIR is higher, and it changes based on different target glucose levels as shown. These curves were determined by Equation 11 empirically using simulation runs.

Equation 11: $BR_{target} = (S_c)^{S_e}$

We can convert the basal rate determined in Equation 11 to a TDR by adjusting for the subject’s weight and by multiplying the basal rate in Equation 11 by the total number of minutes in a day (1440). Dividing by a factor of 1000 converts the units from mU to μ U. We multiply the basal rate by a factor of 2 because we assume that the basal rate delivered by a patient is

typically about 1/2 of their TDR. Equation 12 summarizes the relationship between the target basal rate and the TDR.

Equation 12: $TDR = \frac{BR_{target} \times 2 \times W \times 1440}{1000}$

The rate at which the TDR was allowed to change was limited to avoid representing a non-physiologic swing in insulin sensitivity. This limitation in the rate at which TDR could change was controlled by the TDR up-governor and down-governor. The values of 6% and 12% for the up and down governors, respectively, were selected empirically running simulations of data within the glucoregulatory model [40] implemented within Excel using Visual Basic for Applications. The more stringent limit on the TDR up-governor is to avoid hypoglycemia resulting from an inappropriate increase in TDR, such as that may occur with a glucose sensor that is over-estimating blood glucose. The insulin sensitivity influences the basal rate using Equation 12, and influences the PE and DE using Equation 13.

Equation 13: $K_{PE}^{IIR} = K_{PE}^{IIR} \times K_{Adj} \times TDR$
 $K_{DE}^{IIR} = K_{DE}^{IIR} \times K_{Adj} \times TDR$

The adjustment factor (K_{Adj}) was selected to ensure that as TDR is adapted with a patient’s changing insulin sensitivity, it only influences the gain factor by a limited amount. This adjustment factor is set according to Equation 14.

Equation 14: $K_{Adj} = (\ln(TDR) \times 0.0072932) - 0.0076795$

A. Model parameters summary

The model parameters for the control algorithm are shown in Table 1.

TABLE 1
APC Model Parameters

Parameter	Description	Value
K_{PE}^{IIR}	Insulin PE gain constant	0.08
K_{DE}^{IIR}	Insulin DE gain constant	0.45
Z_{PE}^{IIR}	Insulin PE decay constant	0.03
Z_{DE}^{IIR}	Insulin DE decay constant	0.18
K_B	Basal rate multiplier	0.4
I_p	Percent pre-meal insulin	60%
K_{pe}^{GIR}	Glucagon PE gain constant	-2.7
K_{DE}^{GIR}	Glucagon DE gain constant	-0.6
Z_{PE}^{GIR}	Glucagon PE decay constant	0.3
Z_{DE}^{GIR}	Glucagon DE decay constant	0.4
IOB/TDR	Max IOB/TDR ratio	0.20
GG_{LMax}	Maximum glucagon limit in 50 min [μg/kg]	2
GG_{LMin}	Minimum glucagon limit in 50 min [μg/kg]	0.4
G_{DT}^{IIR}	Day target glucose level for insulin [mg/dL]	115
G_{NT}^{IIR}	Night target glucose level for insulin [mg/dL]	140
G_{DT}^{GIR}	Day target glucose level for glucagon [mg/dL]	95
G_{NT}^{GIR}	Night target glucose level for glucagon [mg/dL]	95
GG_{ref}	Glucagon refractory period [min]	50

The values shown in Table 1 were initially chosen based on a study done on diabetic rats as described [36]. Notice that the PE gain constant is significantly smaller than the DE gain constant. Given the delayed action of subcutaneous insulin, the change in glucose is more relevant than the absolute error. Also note that the decay constant for the PE is smaller than the

decay constant for the DE. The inverse of this decay constant represents the half-life of the insulin infusion caused by a change in glucose. The basal gain constant is set to 0.4, which translates to 40% of the subject's TDR. In a typical clinical scenario, between 40-60% of TDR is used as basal infusion for type 1 subjects who use insulin pumps.

The model parameters for the adaptive algorithm are given in Table 2 and were chosen by running simulations to determine how the adaptive algorithm responds to dynamic events such as meals as well as rapid increases and decreases in glucose.

TABLE 2

Adaptive Model Parameters		
Parameter	Description	Value
TDR _{ug}	Up governor	6%
TDR _{dg}	Down governor	12%
Se	Sensitivity composite exponent	-0.83
Sc	Sensitivity composite coefficient	5.3

III. METHODS

Subjects were recruited from clinics at Legacy Health and Oregon Health and Science University (OHSU). Subjects were required to have type 1 diabetes for at least one year, to be age 21-65 years old, and to be currently using an insulin pump. Women of childbearing age were required to have a negative urine pregnancy test prior to participation. Patients with prior history of cardiovascular, cerebrovascular, kidney, or liver disease or any other uncontrolled chronic medical conditions were excluded. Other exclusion criteria included oral or parenteral corticosteroid use, adrenal insufficiency, seizure disorder, immunosuppressant use, visual or physical impairments that impede the use of a continuous glucose monitoring (CGM) device, insulin or glucagon allergies, hypoglycemia unawareness, serum insulin antibody level ≥ 100 μ Units/ml, C peptide level ≥ 0.5 mg/ml, or insulin resistance requiring more than 200 units of insulin per day.

The research protocol was approved by the Legacy and OHSU Institutional Review Boards, and all subjects provided written informed consent. Permission to carry out these

studies was granted by the U.S. Food and Drug Administration (IDE #G120009). A total of 13 closed loop studies were performed. The mean age of the subjects was 39.5 ± 10.9 years, mean duration of diabetes was 22.5 ± 12.4 years, HbA1c was 7.7 ± 0.6 %, TDR was 50.1 ± 11.2 u/day and weight was 82.7 ± 18.5 kg.

Subjects ($n = 13$) participated in a 28 hour sensor-augmented automated glycemic control experiment. Subjects were fitted with two subcutaneous sensors (DexcomTM SEVEN[®] PLUS CGM or Dexcom G4 PLATINUM) systems the day prior to their study visit. During this period subjects were trained by study personnel on how to use and calibrate the CGM system as well as instructed not to eat (unless necessary for treatment of hypoglycemia) after midnight prior to the study. During this 8-hour pre-study period, subjects performed calibration using a OneTouch Ultra 2 blood glucose meter. Upon arrival, subjects were admitted and an IV catheter was placed. Venous blood glucose (VBG) was sampled every hour during the day (07:00 h–23:00 h) and every two hours at night (if one sensor failed, the nocturnal frequency of venous blood glucose draws increased to every hour). In addition, extra safety blood glucose draws occurred at night (23:00 h–07:00 h) when the insulin infusion rate (IIR) was ≥ 0.4 units/kg per hour averaged over 30 minutes and the IIR rate of rise obtained over 30 minutes was also ≥ 0.4 units/kg per hour. When average sensed glucose reached ≤ 85 mg/dL, VBG was measured every 20 minutes until the reading went above 85 mg/dL. At any point when VBG was ≤ 70 mg/dL the frequency of blood draws increased to every 10 minutes until VBG increased above 70 mg/dL.

An insulin infusion pump (OmniPod, Insulet Corp) was filled with aspart insulin (NovoLog, Novo Nordisk) and a second OmniPod was filled with glucagon (GlucaGen, Novo Nordisk), reconstituted with sterile water to 1 mg/ml. A new pod with fresh glucagon solution was prepared and inserted into the subject every 8 hours.

During each inpatient experiment, the CGM telemetrically streamed sensed glucose data every 5 minutes to a handheld tablet computer (Viliv, Yuckyung) running the control

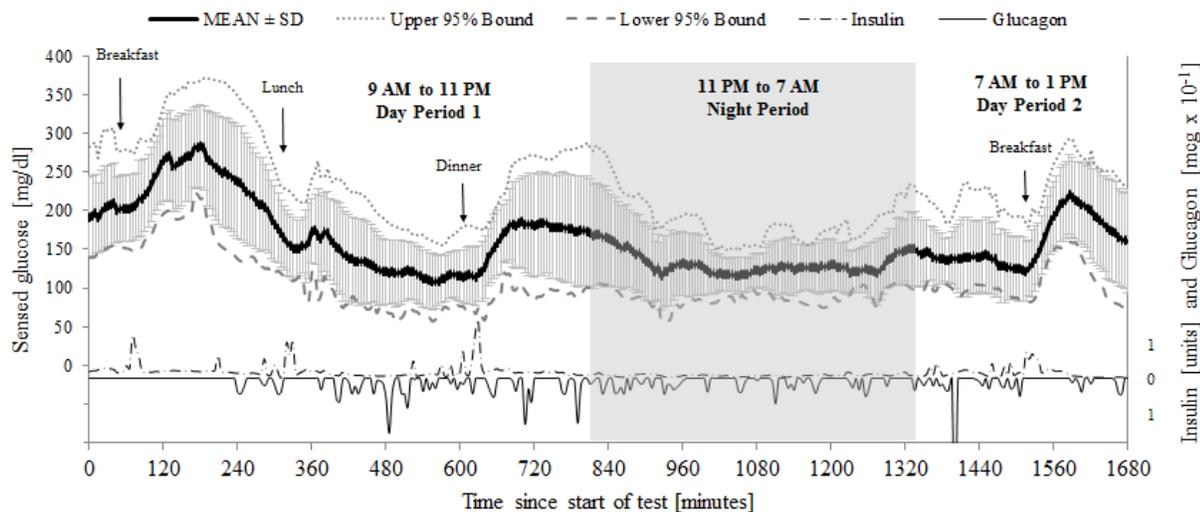


Fig. 8. Results showing glucose control over entire study duration for all subjects in both the 7+ and G4 studies. Mean and upper/lower bounds are shown. Notice that control was best during the night. Meals occurred at 60, 300, 600, and 1500 minutes from the experiment start time. Glucose levels were higher during the first 5 hours of the study because the subjects arrived at the study in hyperglycemia. Furthermore, the APC algorithm system parameters need time to initialize. In the remainder of results presented in this paper, we exclude the first five hours of data. Average insulin and glucagon are plotted on second y-axis with the insulin delivery shown going up and the glucagon delivery shown going down.

algorithm described above. The algorithm used the average of the two sensor values to compute insulin and glucagon infusion rates and automatically call for the insulin or glucagon delivery at the calculated rates by the OmniPod pumps which delivered the hormones subcutaneously. The CGM sensors were calibrated at time zero and every 6 hours for the duration of the 28 hour study. Sensor recalibration occurred if accuracy became suboptimal, defined as when the absolute relative difference (ARD) met or exceeded 35% for glucose ≥ 75 mg/dL or when the absolute difference exceeded 30 mg/dL for glucose < 75 mg/dL. In addition sensor calibration occurred when the system determined that the two sensors differed by more than 60%.

During the experiment each subject was given four meals: breakfast, lunch, and dinner on Day 1, and breakfast on Day 2. Meals were self-selected by the subject from the hospital menu. By design, the precise carbohydrate content for meals was not entered into the controller. Instead, subjects were asked to estimate the carbohydrate content to the nearest 20 grams, and this value was entered into the APC which determined an appropriate insulin pre-meal bolus based upon 60% of the subject's standard insulin-to-carbohydrate ratio for their current TDR. The insulin bolus command was then sent wirelessly to the insulin pump for delivery.

1) Phase 1 and phase 2 of inpatient study

Results are presented from two separate phases of the study. The control algorithm used was the same in both studies. In the first phase, we used the Dexcom SEVEN PLUS sensors. In the second phase, we moved to the more accurate and reliable Dexcom G4 PLATINUM once it was made available. We also made improvements in the communication protocol with the OmniPods. Results from these two phases are summarized separately and individual results are designated with either a 7+ or G4 designator in the results tables below.

Glucose values during both studies were well controlled, however control was better for the G4 study. A plot showing a grand mean and standard deviation of all data plotted during the both 7+ and G4 studies is shown in Fig. 8.

IV. RESULTS

For the 7+ study, the study went to completion for 7 out of the 8 subjects. The one subject who did not complete the study was stopped after 20 hours due to failure of the palmtop tablet computer to hold a charge. For the Dexcom G4 study, it went to completion in 5 out of 5 subjects.

The mean blood glucose value across all subjects in both inpatient studies was 153 mg/dL. It should be noted that most subjects were quite hyperglycemic upon entry into the study (mean entry glucose, 199 mg/dL). Therefore, a more appropriate glycemic control metric may be calculated by excluding the first 5 hours to discount the effect of insulin delivered prior to automated control. Results obtained with such an exclusion criteria are as follows: mean glucose: 147.4 mg/dL; mean daytime glucose: 160.1; mean nocturnal glucose, 11 PM to 7 AM: 139.2.

A control variability grid is shown in Figure 9. The A region is considered accurate control, lower B is benign deviations into hypoglycemia, B is benign control deviations,

upper B is benign deviations into hyperglycemia, lower C is overcorrection of hypoglycemia, upper C is overcorrection of hyperglycemia, lower D is failure to deal with hypoglycemia, upper D is failure to deal with hyperglycemia, and E represents failed control or errors [44].

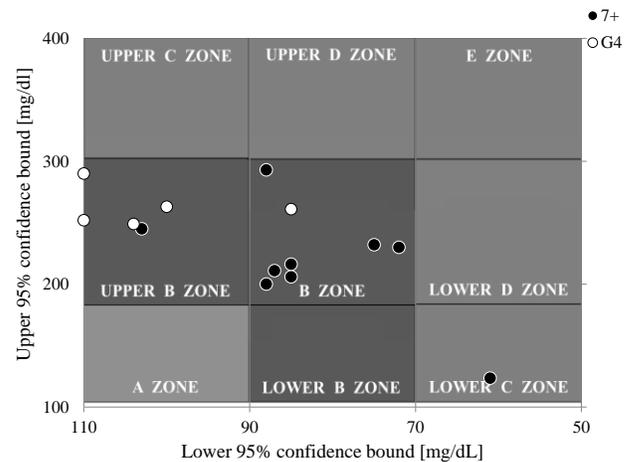


Fig. 9. Control variability grid. Each dot on the graph represents results from a single trial. The horizontal axes represent the minimum glucose level above which 95% of the subject's venous glucose values were measured during the study. The vertical axis is the maximum glucose below which 95% of the subject's values were measured during the study. The white circles are from the study done using the Dexcom G4 sensors which have been found to be more accurate and reliable than the Dexcom 7+ sensors (black circles). Control was significantly better when using the G4 sensors.

Results show that the subjects evaluated during the G4 study were better controlled than during the 7+ study, with results from the G4 study all falling within the B or upper B regions. There were no values in the E region for either of the studies. One of the reasons why the results were better for the G4 study than the 7+ study had to do with improvements we made with communication between the tablet computer and the sensors and the Omnipod PDMs for the G4 study. There were times in the 7+ study when communication failed between the sensors or the glucagon pump during hypoglycemic events which prevented the system from responding with glucagon dosing in a timely manner.

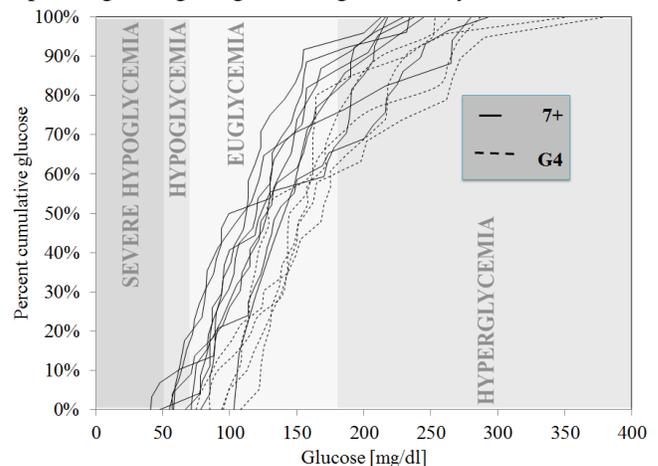


Fig. 10. Cumulative glucose graph. Each line represents the entire closed loop trial for a single subject with the data plotted to show the percent of time spent in each glucose range, severe hypoglycemia (< 60 mg/dl), hypoglycemia, (60-70 mg/dl), euglycemia (70-180 mg/dl), hyperglycemia (>180 mg/dl).

A cumulative glucose plot is shown in Fig. 10. As depicted there were instances of hyperglycemia, and to a much lower degree hypoglycemia, with the values predominantly in the euglycemic range. While Figure 10 may appear to indicate that there was a change in algorithm tuning between 7+ and G4, this was not the case. The algorithm did not change between 7+ and G4 studies. What changed between the two was the accuracy and reliability of the sensors in G4 relative to 7+. By ensuring that glucose sensor data was reliably transmitted and was accurate, the overall performance and control of the system improved.

A primary feature of our closed loop system is that we use glucagon to avoid hypoglycemic events. Fig. 11 shows that when we switched to the G4 sensors and improved communication between the tablet computer and the PDM hardware, there were no occurrences of hypoglycemia, and the mean absolute relative error was significantly less than during the 7+ study.

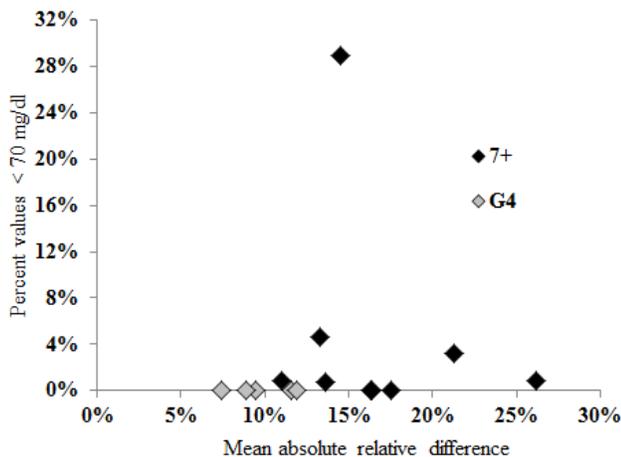


Fig. 11. Closed loop studies done using the G4 sensors yielded significantly lower error and also zero incidence of hypoglycemia (values less than 70 mg/dl) compared with the studies done using the older 7+ sensors. The one outlier study which showed 28% of values < 70mg/dl was a subject whose glucagon pump was not functioning properly. This subject’s study ended early because of the pump failure, thereby creating a high percentage of values less than 70 mg/dL

1) Meal analysis

A critical component of an AP control system is the ability to handle meal events. In this study, subjects were asked to estimate the amount of carbohydrates in a meal announcement that they then input into the APC system, which simulates a real-life situation whereby subjects must estimate their carbohydrate intake. On average, the subjects underestimated the amount of carbohydrates in their meal as shown in Table 3.

TABLE 3
Estimated vs. actual carbohydrate intake in grams

	Breakfast Day 1	Lunch Day 1	Dinner Day 1	Breakfast Day 2
Mean estimated	62.5	65.0	65.7	54.3
Mean actual	73	72	93	69

The post meal increment in blood glucose (average of 1 and 2 hour post meal minus pre-meal value) for the entire study

duration was 12 mg/dL; however, this value is misleadingly optimistic because glucose was unstable during the first 5 hours of the study and markedly declined after the second meal as the automated system called for substantial doses of insulin. This is apparent in Fig. 12 which shows that glucose levels decreased after lunch on the first day, as the patient’s glucose levels were still being brought down by the control system. The post-meal glucose levels increased as expected for the dinner and breakfast. If one excludes the first two meals (first breakfast and lunch), the mean increment was 30 mg/dL. This degree of glycemic control falls within a range that virtually always is associated with avoidance of long term complications in persons with type 1 diabetes [43].

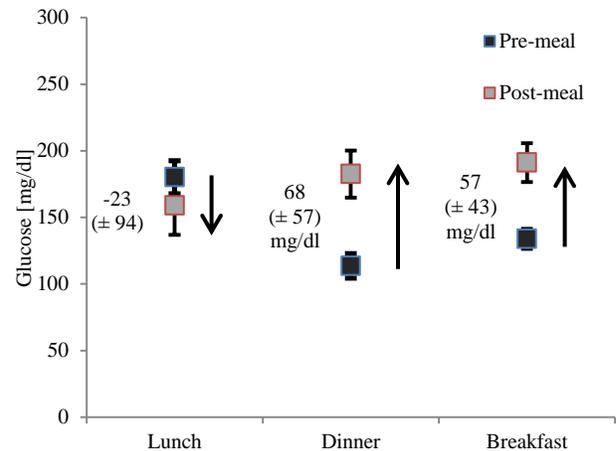


Fig. 12. Glucose excursions two hours after a meal. Notice that the glucose increased (up arrow) after both dinner and breakfast, but decreased (down arrow) after lunch. The reason that glucose dropped after lunch is because the subjects arrived hyperglycemic, and the system had not yet had time to bring their glucose levels into the euglycemic range prior to lunch.

When the 60 minute period after each glucagon dose was analyzed, the glucagon was successful in keeping sensed glucose above 70 mg/dL in 86% of cases; above 60 mg/dL in 91% of cases, and above 50 mg/dL in 100% of cases.

Rescue carbohydrate was given for blood glucose values of less than 60 mg/dL. For the 7+ study, the mean number of rescue carbohydrate doses was 0.9 per study (median, 0.5). Four out of the 8 subjects in the 7+ study required rescue carbohydrates. All oral rescue carbohydrates were given during the day. Three IV carbohydrates were given during the 7+ phase of the study. Two of these were given during the day (subject 301-B and 313), and one was given in the middle of the night (subject 313). The reasons these rescue carbohydrates were required have to do with mis-estimations of carbohydrate intake combined with problems with the glucagon pump telemetry. For example, when subject 313 had lunch, he estimated his carbohydrate intake to be 100 g, but his actual carbohydrate intake was 57. This caused a significant over-delivery of insulin which caused a subsequent hypoglycemic event. Subsequently, there was a failure of the glucagon pump to deliver, which then led to an IV carbohydrate intervention. There were no oral or IV carbohydrates delivered for the G4 study as shown in Table 4. Also provided in Table 4 is the low blood glucose index for each subject tested and the total insulin and glucagon

delivered for each subject. Results for each subject are presented to show intersubject variability in Table 5.

TABLE 4

Summary of delivery metrics during closed loop control

Subject	Study	Oral Carb [count / amount]	IV carb [count / amount]	LBGI	Ins given [units]	Glcn given [mcg]
301 – B	7+	0 / 0	1 / 5 g	4.65	64.90	436
307	7+	2 / 40 g	0 / 0	7.83	66.75	673
308	7+	0 / 0	0 / 0	3.06	76.25	752
309	7+	0 / 0	0 / 0	2.87	89.45	363
313	7+	1 / 26 g	2 / 45 g	15.67	83.90	635
314	7+	2 / 40 g	0 / 0	6.50	48.40	560
315	7+	0 / 0	0 / 0	0.18	30.90	57
316	7+	0 / 0	0 / 0	1.58	62.70	453
Mean all 7+		0.6 / 13.3	0.4 / 0.6	5.29	59.90	453
500	G4	0 / 0	0 / 0	0.56	32.90	44
504	G4	0 / 0	0 / 0	1.84	51.10	185
505	G4	0 / 0	0 / 0	0.84	62.10	421
506	G4	0 / 0	0 / 0	2.51	105.50	259
506	G4	0 / 0	0 / 0	0.06	74.80	68
Mean all G4		0 / 0	0 / 0	1.31	65.3	195

TABLE 5

Results of glucose control across all subjects

Subject	Study	Mean VBG [mg/dL]	StdDev [mg/dL]	% <70 mg/dL	% >70 <=180 mg/dL	% >180 mg/dL
301 – B	7+	133.5	36.7	0.8%	83.5%	15.7%
307	7+	137.6	40.9	0.8%	86.0%	13.2%
308	7+	139.3	40.0	0.0%	84.3%	15.7%
309	7+	153.0	49.8	0.8%	57.1%	42.1%
313	7+	167.6	65.8	4.6%	55.7%	40.9%
314	7+	147.4	50.3	3.2%	61.4%	34.6%
315	7+	158.4	54.0	0.0%	64.7%	35.3%
316	7+	125.6	31.9	0.0%	92.1%	7.9%
Mean all 7+		145.3	46.2	1.3%	73.1%	25.7%
500	G4	147.4	54.2	0.0%	78.3%	21.7%
504	G4	125.6	42.6	0.0%	74.8%	25.2%
505	G4	125.6	36.3	0.0%	83.2%	16.8%
506	G4	173.0	62.3	0.0%	60.6%	39.4%
506	G4	181.8	69.1	0.0%	60.9%	39.1%
Mean all G4		150.7	52.9	0.0%	71.6%	28.4%

Telemetry problems with the sensors were common. Due largely to signal strength issues, the Dexcom SEVEN PLUS sensors were off-line on average 17.3% of the time. The pumps were somewhat more reliable; overall, the insulin and glucagon pumps delivered their prescribed doses 93% of the time. The Viliv tablet computer was sometimes unreliable (several failure modes). The G4 sensors were significantly more accurate than the 7+ sensors as summarized in Table 6.

TABLE 6

Clarke Error Grid showing sensor accuracy of Dexcom 7+ vs. G4 sensors for inpatient study (average between two sensors)

Sensor	A	B	C	D	E
7+	72.6%	25.2%	0%	2.2%	0%
G4	90.1%	9.9%	0%	0%	0%

V. DISCUSSION AND CONCLUSIONS

The closed loop control system presented here performed well during the inpatient study, particularly after meals and during the evening time.

A. Comparison with other AP control systems

There have been many closed loop clinical trials and an especially large number of them over the past several years.

Results from these trials generally demonstrate that closed loop control can lead to glucose levels ranging within the normal glycemic range of 70-180 mg/dL approximately 70% of the time. For example, the dual-hormone closed loop system described in Russell et al. [31] was able to achieve mean plasma glucose of 158 mg/dL with 68% of the glucose values within the range of 70-180 mg/dL. At nighttime, their control was at 123 mg/dL with 93% within the euglycemic range. Another bihormonal closed loop system described in Haidar et al. [34], showed how the use of glucagon could nearly eliminate hypoglycemia while maintaining euglycemia for 70.7% of the time compared with standard open-loop control (57.3%). However the Haidar et al. system is not automated and the bolus amounts of glucagon and insulin were suggestions made by the algorithm with the actual amounts given by a clinician rather than automatically. The system described in Breton et al. [17] was not bihormonal and only supplied insulin to the patient. The Breton et al. system maintained overall glucose levels on average at 120 mg/dL and nighttime values at 110 mg/dL. The Breton et al. system maintained glucose control within the normal glycemic range of 70-180 mg/dL for an impressive 90.1% of the time. However, there were also reports of hypoglycemia (1.1 episodes per patient) in the Breton et al. study. For a single-hormone system the only means for preventing hypoglycemia is to predict when a hypoglycemic event is forthcoming, and then to turn off the insulin delivery. Our system takes advantage of a secondary pump that can help to prevent hypoglycemia through the delivery of glucagon when a hypoglycemic event is pending. During our inpatient study, the average venous blood glucose across subjects was 145.3 for the 7+ study and 150.7 for the G4 study. For our system, we were able to maintain subjects' glucose levels within the near-normal glycemic range for 72.5% of the study duration as measured by taking the percentage of venous blood glucose draws that measured below 70 mg/dL relative to the total venous blood glucose draws normalized with respect to time across both studies. Importantly, for the G4 study, none of the subjects had a hypoglycemic event. We attribute this prevention of hypoglycemia to the use of the bihormonal system whereby glucagon leads to rapid glycogenolysis as the patient's glucose begins to drop and approach the target glucose. In contrast, in single-hormone systems such as the one described by Breton and colleagues, 32% of their subjects experienced a hypoglycemic event. When we include both the 7+ and the G4 data, our subjects experienced hypoglycemia (sensed glucose <70 mg/dL) for 1.5% of the time. Comparisons between our results and other studies is summarized in Table 7. We acknowledge that the G4 study included only 5 subjects, which is likely too few subjects to conclude that control was significantly improved between the G4 vs. the 7+ study.

B. Summary, technical challenges and future directions

To avoid complications caused by long-term exposure to hyperglycemia, the American Diabetes Association recommends HbA1c levels to be below 7% [43], which translates to a glucose level of 154 mg/dL. While the automated system described here achieved this goal, the results from this study also highlighted several technical issues

that must be overcome to make the artificial endocrine pancreas a reality.

TABLE 7
Comparison of AP control systems

System	Summary of results
OHSU, this paper	Mean glucose level of 147 when using either the 7+ or G4 sensors. Euglycemia for 72.5% of the study duration. Zero hypoglycemic events for subjects wearing the G4 sensors. For subjects wearing either G4 or 7+ sensors, subjects spent 1.5% of time in hypoglycemia range (sensed glucose < 70 mg/dL).
Russell et al. 2012 [30]	Mean glucose level of 158 mg/dL. Euglycemia for 68% of the study duration. Eight hypoglycemia events during 576 hours of closed loop control (0.7% of total time).
Haidar et al. 2013 [33]	Mean glucose level of 140 mg/dL. Maintained glucose levels within near euglycemia for 70.7% of the time. One subject out of 15 had at least one hypoglycemia event (2) during closed loop control. Note that this study was not fully automated so there were no connectivity issues to overcome. A doctor delivered the hormones based on the algorithm's recommendation.
Breton et al. 2012 [16]	Mean glucose levels of 120 mg/dL. Maintained glucose within euglycemic range for 90.1% of the study duration. High percentage of hypoglycemic events (1.1 episodes per patient).

While the bihormonal system can help to prevent hypoglycemia, there are disadvantages to using glucagon. The primary disadvantage is that current formulations of glucagon are not stable beyond 8 hours. This is why patients in our study had to change their glucagon pods every 8 hours. In the future, we plan to use new formulations of glucagon, currently under clinical trials testing, which are stable for multiple days. An additional disadvantage is that excessive glucagon delivery to a patient may lead to liver glycogen depletion. If liver glycogen depletion occurs, the patient's glucose will not increase and hypoglycemia could result. Furthermore, excessive glucagon administration can lead to side effects including hyperglycemia and nausea. Our control algorithm limits glucagon delivery amounts as described in Equation 10 and Figure 4. None of our subjects experienced side effects of glucagon over-exposure and a study using non-invasive imaging to estimate hepatic glycogen is underway to address the question of potential glycogen depletion resulting from repeated SC doses of glucagon. An additional limitation of our AP system is that it requires the patient to provide an estimate of carbohydrate intake into the system during meals. If a patient enters an incorrect amount, the algorithm will potentially deliver an incorrect amount of hormone in response. Several groups have proposed methods for accounting for inaccurate estimates of carbohydrates by the patient [14,45] and in the future, we will consider improving our algorithm to handle inaccurate meal estimates. While some other groups' AP algorithms do not require a meal announcement, we feel that it is necessary for the patient to estimate his carbohydrates so that insulin can be delivered immediately to overcome the slow action of currently-available insulin preparations.

Wireless telemetry for communicating with the sensors and the pumps was a problem during the study. Fortunately, our system utilized two sensors which enabled continued automation when one sensor was missing. The purpose of having two sensors is primarily to help overcome the problems

associated with sensor inaccuracy, for example when signal averaging was used by Castle et al. [44]. Averaging cannot be carried out when a sensor value does not arrive because of telemetry problems. In future studies, we will continue to use the next generation Dexcom sensors (G4 PLATINUM) which we have already found to have a more reliable wireless interface. The reliability and accuracy of the G4 sensors has made it unlikely that we will need to use 2 sensors in the future. Because of the difference in performance between the 7+ and G4 studies (trend toward less hypoglycemia with the latter), it is natural to assume that the system is sensitive to sensor inaccuracies and / or missing sensor data. Like all closed loop control systems, the system performance is dependent on accurate sensor readings. We attempted to mitigate sensor inaccuracy by using two sensors. In the future, we plan to use a single G4 sensor which is both more reliable and more accurate than the earlier Dexcom models.

The wireless interface for the pumps performed poorly for the Insulet iDex. Our set-up required that both the Dexcom receivers and the Insulet PDM be hard-wired to a USB port, making disconnection during regular activities of daily living a common problem. In the future we will be migrating to a fully wireless system that will have the mobile phone communicating directly with the sensors and the pumps without requiring the sensor receiver or the pump PDM to enable communication.

We conclude that the bihormonal APC algorithm presented here functioned well when the hardware was functional, especially in preventing hypoglycemia. We therefore expect the system to perform well in an outpatient study once the hardware inter-connections are made to be more robust.

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