DESIGN AND CONTROL OF THE ARTIFICIAL PANCREAS

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Abstract

An artificial pancreas (AP) to treat type 1 diabetes mellitus is currently being designed using the latest control technology. There are many challenges to this undertaking, many due to the fact that this is a biological system, making this device high risk while presenting challenges for sensing and delivery. A controller for this system, zone model predictive control, has been designed to control to a zone, not a set-point, which can result in unnecessary and dangerous overcorrection. The AP design includes a parallel multi-component safety system, the Health Monitoring System (HMS). The components of the HMS focus on specific safety concerns, such as hypoglycemia. In the hypoglycemia prediction component, noisy sensor data are pre-processed and, when imminent hypoglycemia is predicted, notifies the physician.

Insulin delivery vehicles are readily interchangeable in this AP design. Alternative routes, such as the respiratory and intraperitoneal routes, are being explored and incorporated into alternative systems. These routes tend to be faster and safer than the SC route and may be able to improve control. All of these challenges and opportunities are being explored with the goal being an automated AP that can be used in daily life.

Keywords

Artificial Pancreas, insulin delivery, design and control of the artificial pancreas.

Introduction

Diabetes is a chronic disease only controlled by constant vigilance. Chronic elevations, and likely fluctuations, of the blood glucose may result in long term complications (blindness, kidney failure, heart disease, and lower extremity amputations). Conversely, attempts at normalizing glucose concentrations also increases the risk of serious health issues related to hypoglycemia (<70 mg/dL). Despite the use of insulin infusion pumps and programs that promote intensive diabetes management, the average A1c (an indicator of long-term blood glucose control) reported by major diabetes treatment centers remains higher than 8% (Bellazzi, Arcelloni et al. 2003), well above the recommended goal of 6.5-7%. Many factors contribute to this failure: (a) the difficulties in correctly estimating the amount of carbohydrates in a meal; (b) missed meal boluses; and (c) anxiety about anticipated hypoglycemia, resulting in patients giving themselves less insulin, especially overnight.

It has always been difficult to achieve compliance with complicated medical regimens, such as the administration of insulin three or more times a day. As long as diabetes treatment demands constant direct intervention, the vast majority of people with diabetes will not meet treatment goals. An expanding area of research addressing diabetes is working on developing automated closed-loop systems that integrates glucose readings and insulin delivery without the on-going active intervention of the patient.

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The reasons for difficulty in safely achieving optimal glycemic control in patients with type 1 diabetes are many, and could in large part be addressed by beta-cell replacement or a mechanical, automated closed-loop system referred to as an artificial pancreas (AP). Although significant progress has been done regarding beta-cell replacement, a medical solution to diabetes using that approach is currently not widely available. On the other hand, recent advances in subcutaneous (SC) glucose sensors and insulin delivery pumps have made the development of a closed-loop system using these components a feasible solution for the near future.

The long-term goal of this research is to develop an AP that contains a SC continuous glucose monitor (CGM) and an insulin delivery system for type 1 diabetes patients. These two components are connected by the Artificial Pancreas System (APS©) that hosts the control and safety algorithms that use data from the CGM to determine the appropriate insulin delivery (Dassau, Zisser et al. 2008). See Figure 1 for an illustration of the AP components.

Figure 1. Illustration of the Artificial Pancreas device components for clinical testing

The challenges to design such a system are: (a) accuracy of the SC continuous glucose monitor; (b) time lags between the blood glucose concentration and the interstitial SC glucose measurement when the glucose is changing rapidly; (c) delays in the onset of insulin action via the SC route; and (d) prolonged insulin action of 4-6 hours following a subcutaneous injection (Bequette 2005; Harvey, Wang et al. 2010; Cobelli, Renard et al. 2011; Hovorka 2011).

In other words, a SC glucose monitor and a SC insulin delivery system cannot perfectly mimic normal β-cell function. However, initial studies have demonstrated that an automated closed-loop system using SC glucose sensor and SC insulin delivery systems will allow better diabetes control than current manual control methods. In the following sections we will describe several promising technologies for the artificial pancreas (AP) that provides a view on the design and control challenges of the AP and the translation of advance control and system design in the medical field.

Control Strategies for the AP

The AP is a high risk device, and must have a robust and safe control system. This is made more difficult by the fact that it is being applied to a biological system, and redundant sensors are not available. Thus, the safety system must rely on the same sensor as the controller.

Algorithms designed to control a system, biological or otherwise, often are designed using a mathematical model of the system. These models can be simple linear models to complex sets of non-linear PDEs (Hovorka, Canonico et al. 2004; Dalla Man, Raimondo et al. 2007; Dalla Man, Rizza et al. 2007; Farmer, Edgar et al. 2008). When designing these controllers, a balance must be made between of ease of design and implementation and quality and performance.

The controller at the heart of the AP has been designed using various strategies, from the simple proportional-integral-derivative (PID) control approach (Steil, Panteleon et al. 2004; Castle, Engle et al. 2010), to the complex approach of fuzzy-logic, which aims to imitate the decision-making of an expert, in this case the physician (Atlas, Nimri et al. 2010). In recent years, the most widely used approach has become model predictive control (MPC), first published by Parker et al. (Parker, Doyle III et al. 1996; Parker, Doyle III et al. 1999) for the management of glucose concentrations in subjects with type 1 diabetes. See Figure 2 for a block diagram of the MPC strategy.

Figure 2. Block diagram for the MPC strategy for type 1 diabetes.
In the MPC formulation, an explicit model of glucose-insulin dynamics can be incorporated. The MPC strategy is to make prediction using the internal model and compare these with the actual output (glucose concentration) and calculate a set of manipulated inputs, in this case insulin. Several human clinical trials using MPC with encouraging results were published by different groups in the recent years, (Dassau, Zisser et al. 2010; Hovorka, Allen et al. 2010; Kovatchev, Cobelli et al. 2010; Elleri, Allen et al. 2011; Hovorka, Kumareswaran et al. 2011; Zisser, Dassau et al. 2011) and others are ongoing. See Figure 3 for an example of a recent trial. The results of the clinical trials are quite encouraging: as demonstrated in Figure 3, glucose concentrations remains for most of the time in the (80 – 180 mg/dL) range with minor time in the hyperglycemia range in the postprandial part of the trial. As observed, if an intrinsic feed-forwarded insulin bolus is given (the first two meals) glucose control is superior to the unannounced case. However, such action requires manual intervention from the user. An overaggressive control action in an attempt to avoid postprandial hyperglycemia may result with hypoglycemia that may be life-threatening to the subject. Hence, control design needs to be conservative and may err toward minimizing control action to prevent low glucose concentration.

Safety and advanced control design

Early MPC control design (MPC, PID,) were designed as a setpoint regulation problem. However, normal glucose physiology does not have a setpoint and glucose may fluctuate between 70 – 140 mg/dL in the postprandial period and between 70 – 99 mg/dL in fasting conditions. Hence, clinically inspired control design will aim to stabilize glucose concentration in a zone rather than a virtual setpoint. The controller, Zone Model Predictive Control (zone-MPC), is designed such that few control moves are made when the sensor is in the region of normoglycemia to lessen the effect of noise. An extension of the zone-MPC controller called multi-zone-MPC has also been designed, in which four zones have been incorporated into the design (Grosman, Dassau et al. 2011). A multi-zone approach provides additional degrees of freedom to improve glucose regulation by allowing more aggressive control action in the tight glycemic range. The safety system, Health Monitoring System (HMS), is executed in parallel to allow the controller to operate independently.

Controller: zone-MPC

The role of zone-MPC in the AP is to maintain BG in a predefined range, increasing or decreasing insulin delivery accordingly, when the CGM measurement or predictions violate the boundaries of the zone. At the heart of the controller is a predictive model that is used to approximate insulin-to-glucose dynamics in the subject. The model describes the dynamic relationship between $G$ and $u$ based on a set of a priori-identified model constants contained in the vector $\beta$. Given a set of glucose and insulin infusion data, the model can be used to predict the future glucose values, $G_p$, given a proposed set of future insulin infusion amounts, $u_p$. In general, this is expressed as:

$$G_p = f(G, u, u_p, \beta)$$  \hspace{1cm} (1)

where $G$ is a vector of recent CGM values, $u$ is a vector of previous insulin infusion amounts, $u_p$ is a vector of proposed near-future insulin infusion amounts, $\beta$ is a vector of the constant model parameters, and $G_p$ is the vector of predicted near future CGM values that will result from $u_p$.

The only manipulated variable is $u_p$; manipulation of this variable allows optimization of the balance between $u_p$ and $G_p$. This optimization problem, that minimizes a cost function, is the basis of the control law; the control law maps process knowledge and previous data into optimal insulin infusion amounts. The cost function in the zone-MPC is composed of two terms representing the deviation of proposed CGM values from a desired glycemic zone, and the deviation of proposed insulin infusion amounts from the basal insulin infusion profile. Mathematically, the optimization problem is formulated in the following manner:

$$\min_{u_{MPC}} J_{zone-MPC}(u_{MPC}) = \sum [G_{true}^{zone}]^2 + R \sum (u_{MPC} - u_b)^2$$  \hspace{1cm} (2)

subject to the model dynamics of Eq. (1), with $u_{MPC} = u_p$. 
In Eq. (2), \( u_b \) is the patient’s basal insulin infusion profile. \( R \) is a tuning factor that both accounts for the different units of the two terms and weighs their relative contributions. The vector \( u_{\text{MPC}} \) contains the set of proposed near-future insulin infusion amounts. It is the manipulated variable because it is adjusted in order to find the minimum in \( J_{\text{MPC}} \). \( G_{p}^{\text{zone}} \) is a variable quantifying the deviation of a model-predicted CGM values \( G_p \) outside a specified glycemic zone, and is determined by making the following comparisons:

\[
G_{p}^{\text{zone}} = \begin{cases} 
0 & \text{if } G_{ZL} \leq G_{p} \leq G_{ZH} \\
G_{p} - G_{ZH} & \text{if } G_{p} > G_{ZH} \\
G_{ZL} - G_{p} & \text{if } G_{p} < G_{ZL}
\end{cases}
\]

(3)

where the glycemic zone is defined by the upper limit \( G_{ZH} \) and the lower limit \( G_{ZL} \). Thus, if all the predicted glucose values are within the zone, then every element of \( G_{p}^{\text{zone}} \) is equal to 0, and consequently \( J_{\text{MPC}} \) is minimized with \( u_{\text{MPC}} = u_b \) for that time of day, i.e., the algorithm defaults to the patient’s current basal insulin infusion rate. On the other hand, if any of the predicted glucose values are outside of the zone, then \( G_{p}^{\text{zone}} > 0 \) and thus the first term in Equation 2 contributes to the cost function. In this case, the near-future proposed insulin infusion amounts \( u_{\text{MPC}} \) will deviate from the basal, \( u_b \), in order to prevent out-of-zone deviation in \( G_{p}^{\text{zone}} \) from happening, which will also contribute to the cost function. Then, a quantitative balance is found in the optimization, based on the weighting factor \( R \). At each control cycle, only the first element of \( u_{\text{MPC}} \) is delivered as an insulin dose to the patient through the insulin pump. The process is then repeated when a new CGM reading becomes available. For technical details, see (Grosman, Dassau et al. 2010).

Controller: multi-zone-MPC

Multi-zone-MPC is an extension of zone-MPC in which the number of control zones have been increased to four, allowing for safer and more efficient control (Grosman, Dassau et al. 2011). The blood glucose concentration was be divided into four zones: zone 1, hyperglycemia, \( BG > 180 \text{ mg/dL} \); zone 2, near normal glycemia, \( 140 < BG < 180 \text{ mg/dL} \); zone 3, normoglycemia, \( 80 < BG < 140 \text{ mg/dL} \), and zone 4, danger of imminent hypoglycemia, \( BG < 80 \text{ mg/dL} \), chosen by reference to medical expertise (Nathan et al., 2008 and Moghissi et al., 2009). These zones are included into the cost function used in the multi-zone-MPC that is described by the following equation:

\[
J(\mathbf{u}) = \sum_{k=1}^{P} \mathbb{E} \left[ \sum_{i=0}^{M-1} \| I_{D,k} \| R_{k} \right] + \sum_{k=0}^{M-1} \| I_{D,k} \| R_{k}
\]

\[\text{s.t.}\]
\[\tilde{G}_{k1} = \left\{ \tilde{G}_{k1}, I_{D,k} \right\} \forall k = 1, P\]
\[I_{\text{min}} \leq I_{D,k} \leq I_{\text{max}} \forall k = 1, M\]

where \( \tilde{G}_{k1} \) is a binary function that yields the values of the upper bound of the normoglycemia zone (140 mg/dL) when \( \tilde{G}_{k1} > 140 \text{ mg/dL} \), and the values of the lower bound of the normoglycemia zone (80 mg/dL) when \( \tilde{G}_{k1} < 80 \text{ mg/dL} \). \( Q_k \) and \( R_k \) are predicted blood glucose concentration dependent optimization weights as listed in Table 1. \( P \) and \( M \) are the output prediction horizon, and control horizon, respectively.

Table 1. Multi-zone-MPC weights as function of glucose concentration

<table>
<thead>
<tr>
<th>Zone</th>
<th>Glycemia zones</th>
<th>( Q_k ) ( R_k )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>( G_{k1} &gt; 180 \text{ mg/dL} )</td>
<td>2E-4</td>
</tr>
<tr>
<td>2.</td>
<td>( 140 &lt; G_{k1} \leq 180 \text{ mg/dL} )</td>
<td>2</td>
</tr>
<tr>
<td>3.</td>
<td>( 80 &lt; G_{k1} \leq 140 \text{ mg/dL} )</td>
<td>0</td>
</tr>
<tr>
<td>4.</td>
<td>( G_{k1} &lt; 80 \text{ mg/dL} )</td>
<td>2E10</td>
</tr>
</tbody>
</table>

The multi-zone-MPC predicts \( P \) steps in every control sample. \( Q_k \) and \( R_k \) switch values according to the predictions. If \( 80 \leq \tilde{G}_{k1} \leq 140 \text{ mg/dL} \), then \( Q_k \) is set to zero. If \( \tilde{G}_{k1} > 180 \text{ mg/dL} \) for at least a single prediction then \( Q_k \) and \( R_k \) are switched to \( Q_k = 1 \) and \( R_k = 5000 \). Otherwise, \( R_k = 0.5 \) for all prediction and \( Q_k \) switches according to each \( \tilde{G}_{k1} \) value. The switching is based on glycemia predictions in order to prevent future deviation from the quiescent control zone. The deviations above 140 mg/dL are all calculated as a deviation to 140 mg/dL, and all deviations below 80 mg/dL are calculated as a deviation to 80 mg/dL. This introduces a smooth switching out of the quiescent control zone.

Table 1 describes the various glycemic zones and the control weights ratio (\( Q_k \) and \( R_k \)) used for the multi-zone-MPC. In zone 1 (\( \tilde{G}_{k1} > 180 \text{ mg/dL} \)) control actions are constrained to prevent insulin over-dosing. In zone 2 (\( 140 < \tilde{G}_{k1} \leq 180 \text{ mg/dL} \)) most of the control actions are implemented. In zone 3 (\( 80 \leq \tilde{G}_{k1} \leq 140 \text{ mg/dL} \)) the controller is quiescent to deviation in glucose measurements. In zone 4 (\( \tilde{G}_{k1} < 80 \text{ mg/dL} \)) the controller is allowed to respond fast to potential hypoglycemia.

Safety system: HMS

Hypoglycemia is one of the major concerns of individuals using manual intensive insulin therapy as well as the automated AP. The research community has been developing several methods to predict, alert, and prevent pending hypoglycemic events, as described by (Palerm and Bequette 2007; Buckingham, Chase et al. 2010; Dassau, Cameron et al. 2010; Hughes, Patek et al. 2010).

The HMS functions as a process monitoring module that is executed in real time and parallel to any controller. Several components designed for specific safety concerns will comprise the HMS. The principal section is the Low Glucose Predictor (LGP), which serves as an additional...
safeguard in the AP device against risks of hypoglycemia. The zone-MPC algorithm controls the delivery of insulin, while the LGP evaluates the trend of the glucose from a different perspective. The LGP uses a more conservative algorithm to make an independent assessment of the risk of hypoglycemia and add an extra layer of safety to ensure the health of the subject. When LGP indicates that hypoglycemia is imminent, the HMS will generate an audible and visual alert to the investigator and send short and multimedia message services (SMS and MMS) to the physician in charge with a profile of the current trend and prediction for the upcoming 15 minutes.

The LGP has three major sections: a pre-processing section to get the CGM data ready for prediction; a core algorithm section to calculate the rate of change, make predictions, and determine if hypoglycemia is imminent; and an alarm mode section to prepare the audible and visual alerts (see Figure 4).

The pre-processing section is used to filter the CGM data and prepare them for accurate prediction. This is a necessary step because CGM may include noisy data points such as missed data points, and shifts due to calibration. These issues are all addressed in the pre-processing section, detailed below.

The first component of the pre-processing section is shift detection. In order to make a better and more accurate prediction, shifts introduced to the system, such as calibrations, must be detected so that the shift does not produce a non-physiologic rate of change estimate. A shift in the signal is detected when the change in the raw signal is large (>4mg/dL/min, considered to be non-physiologic (Dunn, Eastman et al. 2004)) and then the next point continues roughly the same trend as before the shift, but with an offset. When a shift is detected, the points after the shift can be considered more accurate, and the same offset can be applied to the points before the shift to reflect the true trend.

Due to electrical noise and interference, CGM data are often noisy; therefore filtering the data using physiologically-based parameters is used to ensure that data reflect accurately the glucose value. The algorithm filters the data using a noise-spike filter to reduce the impact of noise spikes, written as follows:

\[
G_{F,NS}(k) = \begin{cases} 
G_{n}(k) & \text{if } |G_{n}(k) - G_{F}(k-1)| \leq \Delta G \\
G_{F}(k-1) - \Delta G & \text{if } (G_{F}(k-1) - G_{n}(k)) > \Delta G \\
G_{F}(k-1) + \Delta G & \text{if } (G_{n}(k) - G_{F}(k-1)) > \Delta G 
\end{cases} 
\]  

(5)

where \( k \) is the sampling instant, \( G_{F}(k-1) \) is the previous filtered value, \( G_{F,NS}(k) \) is the filtered value resulting from the noise-spike filter, \( G_{n}(k-1) \) is the measurement, and \( \Delta G \) is the maximum allowable step change (Seborg, Edgar et al. 2011). The data are then passed through a low pass filter to damp high frequency fluctuations from electrical noise, written as follows:

\[
G_{F}(k) = \frac{\Delta t}{\tau_{F} + \Delta t} G_{F,NS}(k) + \left(1 - \frac{\Delta t}{\tau_{F} + \Delta t}\right) G_{F}(k-1) 
\]  

(6)

where \( G_{F} \) is the filtered value, \( \Delta t \) is the sampling time, and \( \tau_{F} \) is the filter time constant (Seborg, Edgar et al. 2011). The filter is the second component of this section.

The last component of the pre-processing section is interpolation, in which recent data gaps are interpolated so that the most recent data can be used for prediction.

The objective is to ensure that the HMS will make an accurate prediction despite a missing data point. When a point is missing, its value will be extrapolated to allow a prediction to be made at that point in time. The algorithm then extrapolates gaps of up to 20 minutes linearly. This is

Figure 4. Overview of HMS algorithm

The LGP has three major sections: a pre-processing section to get the CGM data ready for prediction; a core
extremely important when the trend is negative and nearing the hypoglycemia threshold.

The next section in the LGP is the core algorithm, in which the rate of change is calculated to make a prediction and issue an alarm if hypoglycemia is imminent (in the next 15 minutes).

The rate of change is calculated and the trajectory is projected through the hypoglycemia threshold, \( TH \), to decide if hypoglycemia will occur within the prediction horizon, \( PH \), based on findings and clinical evaluation from Buckingham et al. (2010) and Dassau et al. (2010). The rate of change calculation is performed using the first derivative of the Lagrange interpolation polynomial as follows:

\[
G_r'(j) = \frac{t(j)-t(j-1)}{(t(j-2)-t(j-1))(t(j-2)-t(j))}G_r(j-2) + \frac{t(j)-t(j-2)}{(t(j-1)-t(j-2))(t(j-1)-t(j))}G_r(j-1) + \frac{2t(j)-t(j-2)-t(j-1)}{(t(j)-t(j-1))(t(j)-t(j-2))}G_r(j)
\]

where \( j=k-A+1:k \) (Harvey, Dassau et al. 2011).

The alarm mode will be activated if hypoglycemia is predicted or if the current measurement is below the hypoglycemia threshold (70 mg/dL) and the rate of change is negative \( (G'_r(k)<-0.1 \text{ mg/dL/min}) \). However, if the current measurement is above 110 mg/dL, alarm mode is not activated, because the proximity of the hypoglycemia threshold is too small. In addition, if the rate of change is below -3 mg/dL/min, which is considered non-physiological below this value.

The visual and audible alarm that appears on the AP device clearly indicates that the individual with type 1 diabetes should eat approximately 16 grams of carbohydrates. The user may select the “ignore” button of the HMAS warning. In that case, at the next cycle, i.e. 5 minutes later, if the prediction is that glucose concentration is predicted to be \( <70 \text{ mg/dL} \) or is \( <70 \text{ mg/dL} \), then a new alarm will sound and appear.

The user may select the “accept” button and treat with carbohydrates as recommended. The system will continue to perform a new analysis of the glucose prediction based on the new data point in the background, but it will not activate any warning for the following 30 minutes. The alert system will be blocked. This time is to allow the effect of ingesting carbohydrates to take place. After 30 minutes, if the calculation continues to predict that the glucose is \( <70 \text{ mg/dL} \) in the next 15 minutes or is actually \( <70 \text{ mg/dL} \), then a new visual and audible alarm will be raised and a new text message will be sent.

In silico testing

Comparison of multi-zone-MPC and zone-MPC was conducted on 100 in silico adult subjects following a one meal scenario of 75 g of CHO given at 8pm using the Food and Drug Administration (FDA)-accepted UVA/Padova metabolic simulator (Kovatchev, Breton et al. 2009). Control was enabled after two hours of open-loop response. As can be seen in Figure 6, multi-zone-MPC (a) outperforms the zone-MPC (b) with extended time in the near normal glucose range without any severe hypoglycemic events.

Magni et al. (2008) introduced the control variability grid analysis (CVGA) for measuring the quality of closed-loop glucose control on a group of subjects. The nine categories in the CVGA grid represent different levels of control as follows: accurate control (A-zone); benign deviation into hypoglycemia (Lower B-zone); benign deviation into the hyperglycemia range (Upper B-zone); benign control (B-zone); overcorrection of hyperglycemia (Lower C-zone); overcorrection of hypoglycemia (Upper C-zone); failure to mange hypoglycemia (Lower D-zone); failure to mange hyperglycemia (Upper D-zone) and erroneous control (E-zone). It is a method for visualization of the extreme glucose excursions caused by a control algorithm in a group of subjects, with each subject presented by one data point for any given observation period. A numeric assessment of the overall level of

Figure 5. Example SMS text and MMS CGM graph.

If at least 30 minutes have elapsed since the last warning, the alarm mode will issue an audible and visual alarm on the AP device HMI and send a text message to the user or attending physician. The secondary alert via text messages uses the SMS and MMS technology. The SMS sends the text only message while the MMS sends an attached chart showing the trending of recent glucose values and the predicted values for the next 15 minutes (see Figure 5). Although only smart phones can receive a chart, the text message can be received by any cell phone. The SMS and MMS are redundant to the active alarm in the AP device.

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glucose regulation in the population is given by the summary outcome of the CVGA.

Figure 6. Population response of the zone-MPC (a), multi-zone-MPC (b), and the histogram of the population glucose distribution (c).

Figure 7 depicts the CVGA for the multi-zone-MPC and the Zone-MPC. As can be seen the multi-zone-MPC significantly reduces the risk of hypoglycemia and at the same time lowers the hyperglycemia levels. It should be noted that the majority of the results as presented in Figure 2 are in the B zone that represent benign control which is extremely encouraging for a 75 g unannounced meal challenge. The superiority of the multi-zone-MPC approach is demonstrated by the minimization of severe hypo- and hyper-glycemia with some of the more complex in silico subjects.

The combination of zone-MPC and HMS were also evaluated in silico using the UVa/Padova 100 subject metabolic simulator. The protocol included 3 unannounced meals (2 large meals and a snack) and an overnight period. An example of a subject that did have an HMS alert and treatment of 16g of carbohydrates is in Figure 8. The HMS alert was invoked only 5 times for the entire cohort. For all 100 subjects, 0% of time was spent below 70mg/dL, and 81% of time was spent between 70-180mg/dL, considered the safe zone.

Figure 8. Example of subject with an HMS alert and hypoglycemia treatment.

The CVGA of with all 100 subjects is in Figure 9. Note that only 13% of the subjects are in the B-zone, representing benign control, while 87% are in the A-zone, signifying good control.
Alternative design for the Artificial Pancreas

One of the foremost challenges for the AP is actuation delay due to slow pharmacokinetic (PK) characteristics of the SC delivery route (PK peak at 50 min and residence time of 6-8 h). As a result of this delay, an AP based on the SC route cannot respond quickly enough to an unannounced meal and cannot blunt postprandial glucose excursions.

Two alternative insulin delivery routes, intraperitoneal (IP) and Technosphere® Insulin (TI) (see Figure 10) showed faster PK characteristics that can improve the design of future AP systems. The novel design of the AP using these fast acting alternative routes may enhance BG regulation by reducing actuation delays, especially during meal time. This section describes the design of alternative APs utilizing the respiratory or IP insulin delivery routes to improve BG regulation.

Respiratory route using TI

The semi-automated AP with TI combines the SC and TI insulin delivery methods to replicate the normal physiological insulin secretion at meal time. Rapid acting TI captures the first and cephalic phase and a Continuous Subcutaneous Insulin Infusion (CSII) pump that is controlled by zone-MPC delivers the basal and any supplemental meal-related insulin. It should be noted that the TI insulin in this example is an unmeasured disturbance to the control algorithm and, as such, the system was designed to work with or without TI.

To evaluate the performance of the semi-automated AP with TI, a protocol of a single large unannounced meal (100 g carbohydrate) after an overnight period was used on the UVa/Padova metabolic simulator, and the result was compared to the fully automated closed-loop AP using the SC route (with zone-MPC). Average BG, CGM, and insulin delivery plots are given in Figure 11 to show differences in the controller action with and without the input of TI insulin (Semi-automated and Closed-Loop, respectively).

The closed-loop AP based on the SC route successfully managed BG within normoglycemia (70 – 180 mg/dL) during the overnight period. However, the average BG went up to 280 mg/dL after the meal (black dashed line) and stayed in the hyperglycemia (BG > 180 mg/dL) region until 1 pm due to the actuation delay of SC insulin and 7-15 min lag in the CGM (McGarraugh 2009).

In contrast, the semi-automated AP with TI, effectively blunted the BG rise (BG peak = 203 mg/dL) and significantly decreased the duration in the hyperglycemia region (1.9 h). Additionally, the CSII delivered considerably less insulin in the postprandial period (~5 h after the meal) in the semi-automated AP with TI compared to the fully closed-loop AP via the SC
route, which decreases the risk of postprandial hypoglycemia.

**IP route**

An alternative AP design based on IP delivery was also developed based on zone-MPC with an IP PK/PD model. The closed-loop AP using the IP route (see Figure 12), the controller effectively blunts the BG peak (228 mg/dL), and the average duration in the hyperglycemia region decreased to 1.5 h. Also, due to the fast clearance rate of IP insulin, the controller can be more aggressive (e.g. bolus-like action at meal time) without the risk of hypoglycemia compare to the SC based AP (see Figure 12, black dashed line).

![Figure 12. Population result of fully automated closed-loop AP based on intraperitoneal vs. SC insulin.](image)

**Conclusions**

The zone-MPC controller has been designed to control BG to a normoglycemia zone. This dampens the effect noise and non-physiologic sensor fluctuations on controller action, resulting in smoother and safer control. The inclusion of HMS, a parallel safety system, allows for adverse events to be monitored independently. Using LGP, one component of HMS, hypoglycemia can be predicted and prevented by informing the physician to administer rescue carbohydrates using redundant means, both a pop-up on the AP device and SMS/MMS message via telemedicine.

A prominent challenge in the design of the AP is the delays in insulin delivery and absorption using the SC route. This may be alleviated by utilizing alternative insulin delivery routes with faster PK. As presented above, both the semi-automated AP with TI and the closed-loop AP using the IP route showed superior performance over the current closed-loop AP using the SC route without imposing hypoglycemia risk.

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**References**


