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A New Animal Model of Insulin-Glucose Dynamics in the Intraperitoneal Space Enhances Closed-Loop Control Performance

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Abstract

Current artificial pancreas systems (AP) operate via subcutaneous (SC) glucose sensing and SC insulin delivery. Due to slow diffusion and transport dynamics across the interstitial space, even the most sophisticated control algorithms in on-body AP systems cannot react fast enough to maintain tight glycemic control under the effect of exogenous glucose disturbances caused by ingesting meals or performing physical activity. Recent efforts made towards the development of an implantable AP have explored the utility of insulin infusion in the intraperitoneal (IP) space: a region within the abdominal cavity where the insulin-glucose kinetics are observed to be much more rapid than the SC space. In this paper, a series of canine experiments are used to determine the dynamic association between IP insulin boluses and plasma glucose levels. Data from these experiments are employed to construct a new mathematical model and to formulate a closed-loop control strategy to be deployed on an implantable AP. The potential of the proposed controller is demonstrated via *in-silico* experiments on an FDA-accepted benchmark cohort: the proposed design significantly outperforms a previous controller designed using artificial data (time in

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Competing Financial Interests

PL is CEO of PhysioLogic Devices, Inc. BS and DC are consultants for PhysioLogic Devices, Inc. Other authors declare no competing financial interests.

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clinically acceptable glucose range: $97.3 \pm 1.5\%$ vs. $90.1 \pm 5.6\%$). Furthermore, the robustness of the proposed closed-loop system to delays and noise in the measurement signal (for example, when glucose is sensed subcutaneously) and deleterious glycemic changes (such as sudden glucose decline due to physical activity) is investigated. The proposed model based on experimental canine data leads to the generation of more effective control algorithms and is a promising step towards fully automated and implantable artificial pancreas systems.

Keywords

Predictive model; proportional-integral-derivative (PID) control; canine model; intraperitoneal cavity; type 1 diabetes; alternative sites

Introduction

Various feedback control strategies in state-of-the-art single-hormone artificial pancreas (AP) systems are deemed clinically safe[1,2] and effectively regulate glucose in people with type 1 diabetes mellitus (T1DM). However, most AP systems developed thus far rely on subcutaneous glucose sensing and subcutaneous insulin delivery (SC-SC), where transport delays in the interstitial fluid renders slow insulin absorption and slow insulin clearance[3]. Furthermore, sluggish kinetics make tight glucose control very difficult[4]. That is, pure feedback control in the SC-SC case can result in sustained high postprandial glucose levels due to delays in insulin absorption, or deleteriously low glucose levels due to slow clearance rates. This necessitates “meal announcement”, where manual boluses are required to compensate for ingested meals, often without improving A1c levels; generally attributed to incorrect estimation of meal sizes[5] or poor knowledge of macronutrient content of meals[6].

A promising alternative site for insulin infusion is the intraperitoneal (IP) cavity. The feasibility of closed-loop control using IP delivery and SC sensing (IP-SC) in an implantable AP was demonstrated in early studies[7,8]: faster insulin clearance in the IP cavity results not only in fewer hypoglycemic (glucose < 70 mg/dL) episodes[9], but markedly improved postprandial glycemic regulation performance[10], compared to SC delivery, even without meal announcement. Furthermore, infusion in the IP cavity more closely approximates the body’s natural insulin distribution, where insulin is maintained at a concentration 3-fold higher in the portal circulation than the peripheral circulation[11,12]. This physiologic balance leads to less hypoglycemia[13] and insulin resistance[14,15] as well as improved glycemic variability compared with iatrogenic peripheral circulation hyperinsulinemia resulting from SC delivery[16]. IP delivery also produces beneficial endocrine effects. For example, prolonged SC delivery adversely affects insulin-like growth factor-1 concentrations; this adversity is not observed in prolonged IP delivery[17,18].

Although the IP-SC space offers clear benefits both from physiological and engineering perspectives, a fully implantable AP residing in the IP cavity should be able to reap the benefits of IP delivery and IP sensing. IP sensing has been shown to be significantly faster than SC sensing[19–21], indicating that controllers designed for the IP-IP space should be more reactive to glycemic disturbances and more aggressive to maintain tight control since

insulin clearance rates are higher: this is especially advantageous for embedded/implantable AP technology where fast speeds and intermittent decision-making enable longer power cycles[22,23].

Methods

Statistical Information

All statistical analyses were performed in MATLAB R2016a using the Statistics and Machine Learning toolbox. All data are reported as means $\pm$ one standard deviation or medians (interquartile ranges) as indicated. Comparison between two groups was performed using a two-tailed criteria Wilcoxon ranked sum test and significance determined at $p < 0.05$ or $p < 0.001$.

Animal Care and Surgical Procedures

Three conscious adult mongrel dogs weighing 22–25 kg were studied. The dogs were fed a 65–75 kcal/kg/day diet of canned meat and chow (28% protein, 49% carbohydrate, and 23% fat). Two weeks prior to the experiment, animals were placed under general anesthesia and a catheter was surgically placed in a femoral artery and a laparotomy was performed for the placement of blood sampling catheters in the hepatic portal vein and hepatic vein[24,25]. In addition, to provide access to the IP space during experiments, a silastic, polytetrafluoroethylene “guide” catheter was placed within the lower right quadrant of the IP space. The free ends of the blood sampling and intraperitoneal access catheters were filled with a heparin/saline solution, knotted, and placed into respective subcutaneous pockets. All surgical incision sites were closed; the dogs were anesthetically recovered and permitted a minimum of 14 recovery days. Prior to study, each dog’s health was confirmed, evidenced by a leukocyte count $< 18,000/\text{mm}^3$, hematocrit $> 35\%$, good appetite, normal stooling, and healthy physical appearance. All procedures were approved by the Vanderbilt University Institutional Animal Care and Use Committee.

Study Design

Animals were fasted overnight prior to each experiment. On the morning of the study, the free ends of the intraperitoneal access catheter and the blood sampling catheters were exteriorized from their subcutaneous pocket under local anesthesia (2% lidocaine). The dogs were placed in a Pavlov harness for the remainder of each experiment. Three protocols were employed and each experiment consisted of a 30 min somatostatin equilibration period, a 30 min glucose loading period, an intraperitoneal insulin bolus, and a 150-minute glucose and insulin sampling period; see Figure 1.

Somatostatin (Bachem Americas, Torrance, CA) was infused intravenously at $0.8 \mu\text{g}/\text{kg}/\text{min}$ to inhibit endogenous insulin and glucagon secretion, approximating the insulin-deficient state of type 1 diabetes. Somatostatin rapidly[26,27] and potently[28] inhibits insulin production such that virtually all insulin in the plasma and interstitium was of exogenous origin by the time the bolus was given at 0 min[29]. During the 30 min glucose loading period, an intravenous infusion of 20% dextrose was used to raise the arterial plasma glucose concentration from a basal concentration of approximately 115 mg/dL up to 200 mg/dL

(protocol 1, n=4 experiments), 300 mg/dL (protocol 2, n=2 experiments), or no glucose was infused, allowing plasma glucose to fall to 90 mg/dL (protocol 3, n=2 experiments); we observe this to be the steady-state glucose level at euglycemia for the dogs.

Near the end of the 30 min glucose loading period, a sterile, 18-gauge nylon catheter (Access Technologies, Stokie, IL) was primed with surfactant-stabilized, recombinant human insulin (U-400, Thermalin Diabetes, Cleveland, OH) *ex-vivo*, then advanced through the exteriorized intraperitoneal access catheter such that the tip of the catheter extended 5 cm past the end of the guide catheter and into the intraperitoneal space. Simultaneously, at the end of the 30 min glucose infusion period, an IP insulin bolus was given using a 25 or 50 μ L Hamilton syringe. In protocol 1, one dog was studied four times and received IP insulin boluses of 0.075, 0.15, 0.3, and 0.6 U/kg when arterial plasma glucose was $\approx$ 200 mg/dL. A second and third dog were studied twice, receiving 0.15 and 0.45 U/kg IP insulin doses in protocol 2 from an initial glucose level of approximately 300 mg/dL, and 0 and 0.075 U/kg in protocol 3 from an initial glucose level of 90 mg/dL. Surfactant-stabilized, U-400 concentrated insulin was tested in this study because of its favorable properties for use in an implantable insulin pump. The surfactant decreases the likelihood of fibrillation that could lead to pump occlusion and the increased concentration allows for more time between insulin refills.

Following each study, the free ends of the catheters were placed into new subcutaneous pockets under general anesthesia for use in subsequent studies. All studies were conducted at least one week apart.

Development of Control-Relevant Insulin-Glucose Models

Widely tested decision-making algorithms in AP research such as model predictive control and PID control require a mathematical model that captures the dynamics between insulin infusion and the corresponding glucose response. Prior investigations[30–32] have yielded ‘control-relevant’ models for SC-SC, IP-SC, and IP-IP dynamics based on computer-simulated impulse response tests and approximations using the UVA/Padova metabolic simulator[33]. Here, we utilize experimental glucose data obtained from dogs lacking the ability to secrete insulin via somatostatin inhibition to mimic the insulin deficient state of type 1 diabetes and enable formulation of control-relevant models for IP-IP dynamics.

We construct a transfer function having a structure identical to prior insulin-glucose transfer function models that have performed well in clinical studies. Our transfer function model has the form

$$H(z^{-1}) = \frac{Y(z^{-1})}{U(z^{-1})} = \frac{Kz^{-1}}{\prod_{j=1}^3 (1 - p_j z^{-1})} z^{-L},$$

where z^{-1} is a shift operator having a sampling time of 5 min, Y denotes the blood glucose deviation from the basal glucose in mg/dL, U is the insulin infusion rate in U/5 min, $L \in \mathbb{N}$ (the set of natural numbers) denotes an actuation lag in minutes, representing the diffusion lag exhibited by insulin at the site of infusion, K is a gain parameter, and $p_{1,2,3}$ are the poles

of the transfer function model. The model fitting procedure comprises of optimizing five parameters: namely, K , p_1 , p_2 , p_3 , and L .

Since data is collected aperiodically during the experiments (every 5 min between $t = 0$ min and $t = 30$ min, more sparsely thereafter), we begin by interpolating the data every 5 min from $t = 0$ min to the time of experiment completion, $t = 150$ min. We use a piecewise Hermite polynomial interpolation scheme to leverage its shape-preserving properties[34] during interpolation: that is, Hermite polynomials do not introduce unnecessary undulations to the underlying data to maintain continuous second-derivatives, unlike various other schemes like cubic splines. Constructing local linear models with respect to basal glucose magnitudes and basal insulin rates enable personalization of the model, since basal insulin rates differ widely within mammalian populations. Basal glucose is determined to be 89 mg/dL based on median values of steady-state measurements (protocol 3), and the corresponding basal insulin delivery rate is fixed at 0.36 U/hr.

Note that the protocols 1–3 in the experiments performed correspond to impulse response tests in the system identification nomenclature. Therefore, one can use normalized nonlinear least squares to compute the model parameters. This is done in MATLAB R2016a via the *tfest* function, using the interpolated data $Y_{0:5:150}$ with multiple values of $L \in \{0,1,2,3\}$.

In order to validate the constructed model, we use artificially constructed insulin and glucose data to augment our experimental insulin-glucose data. We generate four data vectors for validation: the mean and median of the protocol 1 data, and the mean of the protocol 2 and 3 data. Our proposed model demonstrates good performance on this validation set: the model validation performance is illustrated in the lowest block in Figure 3.

Tuning the PID controller gains

Although PID controllers typically comprise three design variables, it is challenging to compute these variables systematically for a wide range of systems while maintaining tight yet robust control performance. Classical tuning rules such as Ziegler-Nichols tuning tend to be very aggressive, which could result in controller-induced hypoglycemia. Alternatively, internal model control (IMC) based analytic tuning rules[35] have exhibited good glucose regulation properties[30]. In this paper, we use a digital control variant of the IMC tuning rules to obtain a PID controller in the incremental form

$$u_k = u_{k-1} + \Delta P_k + \Delta I_k + \Delta D_k, \quad (1)$$

$$\Delta P_k = K_p \Delta e_k, \quad \Delta I_k = \frac{K_p T_s}{T_i} \Delta e_k, \quad \Delta D_k = \frac{K_p T_d}{T_s} (\Delta e_k - \Delta e_{k-1}),$$

$$\Delta e_k = e_k - e_{k-1}, \quad e_k = y_k - r_k.$$

Here, u_k is the insulin bolus at time instant k , T_s is the sampling time of the system, y_k is the glucose output, r_k is a set-point to which the glucose is driven, K_p is the proportional gain, and T_i , T_d are integral and derivative time constants, respectively.

Note that the transfer function equivalent in the z -domain for the PID with structure (1) is given by[36]

$$G_{PID}(z^{-1}) = \frac{U(z^{-1})}{E(z^{-1})} = \frac{b_0 + b_1 z^{-1} + b_2 z^{-2}}{1 - z^{-1}}, \quad (2)$$

where $U(z^{-1})$ and $E(z^{-1})$ are the z -transforms of the control action and error signals, respectively, and

$$b_0 = K_p \left(1 + \frac{T_s}{T_i} + \frac{T_d}{T_s} \right), \quad b_1 = -K_p \left(1 + \frac{2T_d}{T_s} \right), \quad b_2 = \frac{K_p T_d}{T_s}. \quad (3)$$

We now propose a method for obtaining the constants b_0 , b_1 and b_2 (and hence the controller gains) using discrete-time IMC and optimization-based transfer function matching. Let G_{IMC} denote the IMC controller and recall that (z^{-1}) is the transfer function representation of the insulin-glucose dynamical model. We begin by factorizing (z^{-1}) into two components: an all-pass component $H_a(z^{-1}) = z^{-3}$ and a minimum-phase component

$$\tilde{H}(z^{-1}) = \frac{1800}{TDI} \frac{K_s K_m}{(1 - 0.61z^{-1})(1 - 0.90z^{-1})^2}.$$

Then we compute

$$G_{IMC}(z^{-1}) = G_q(z^{-1})G_f(z^{-1}), \quad (4)$$

where

$$G_q(z^{-1}) = (z^{-q} \tilde{H}(z^{-1}))^{-1}$$

has a design parameter $q \in \mathbb{N}$ that ensures $G_q(z^{-1})$ has numerator and denominator polynomials of identical degree in z^{-1} , and

$$G_f(z^{-1}) = \frac{1 - \lambda}{1 - \lambda z^{-1}}$$

is a low-pass filter with a tuning parameter $\lambda \in (0,1)$ that enables the user to trade-off set-point tracking ($\lambda \rightarrow 0$) and disturbance rejection ($\lambda \rightarrow 1$). We choose $\lambda = 0.98$ since our

primary concern is rejecting glucose disturbances. From the block diagram representation of IMC-based PID tuning in Supplementary Figure S2, it is clear that

$$\tilde{G}_{PID}(z^{-1}) = \frac{G_{IMC}(z^{-1})}{1 - H(z^{-1})G_{IMC}(z^{-1})}. \quad (5)$$

Substituting equation (4) into equation (5) generally yields transfer functions of order higher than that described in equation (2). While many methods have been proposed in the literature for dealing with specific classes of $H(z^{-1})$ that yields simple forms of $\tilde{G}_{PID}(z^{-1})$, few deal with control-relevant models of order 3.

For this application, we propose an optimization-based procedure to compute b_0 , b_1 , and b_2 by matching the transfer functions G_{PID} and $\tilde{G}_{PID}$. We sample N_s points in the frequency domain within the closed-loop bandwidth $[1.2 \times 10^{-2}, 8.0 \times 10^{-2}]$ rad/min which is where we require equation (2) to resemble equation (5) most closely. This enables us to pose the following optimization problem

$$\arg \min_{b_0, b_1, b_2} \sum_{\ell=1}^{N_s} \left(w_1 \delta_{m_\ell}^2 + w_2 \delta_{p_\ell}^2 \right) \quad (6)$$

subject to:

$$\begin{aligned} \delta_{m_\ell} &= |G_{PID}(\omega_\ell)| - |\tilde{G}_{PID}(\omega_\ell)|, & \delta_{p_\ell} &= \angle G_{PID}(\omega_\ell) - \angle \tilde{G}_{PID}(\omega_\ell), \\ G_{PID}(\omega_\ell) &= G_{PID}(z^{-1})|_{z^{-1} = \exp(-i\omega_\ell T_s)}, & \tilde{G}_{PID}(\omega_\ell) &= \tilde{G}_{PID}(z^{-1})|_{z^{-1} = \exp(-i\omega_\ell T_s)}, \end{aligned}$$

where $i = \sqrt{-1}$. Solving (6) using a Nelder-Mead simplex procedure (MATLAB: *fminsearch*) with $w_1 = 1$ and $w_2 = 0.01$ yields optimal coefficients b_0^* , b_1^* , b_2^* , from which we can obtain K_p , T_i , and T_d by solving the equations (3). The proximity of the two transfer functions in the frequency domain is demonstrated in Supplementary Figure S3. Specifically, we get

$$K_p = -9.18 \times 10^{-5} \times TDI [U/5 \text{ min}], \quad T_i = 76.94 \text{ min}, \quad T_d = 33.38 \text{ min}.$$

We modify the nominal PID controller structure described in equation (1) in order to provide immunity against adverse effects occurring in practice such as derivative kick (sharp jump in control actions caused by changing glucose targets) or integral windup (large control actions

due to accumulation of non-zero tracking error). Specifically, we implement the derivative gain as

$$\Delta D_k = \frac{\beta T_d}{T_s + \beta T_d} \Delta D_{k-1} + K_p \frac{T_d}{T_s + \beta T_d} (\Delta e_k - \Delta e_{k-1}),$$

where $\beta = 0.1$ is a recommended derivative filter gain[37], and the integral windup is implemented using a forgetting factor $0 < \alpha \ll 1$, where

$$\Delta I_k = K_p \exp(-\alpha) \left| e_k \right| \frac{T_s}{T_i},$$

which ensures the integral term remains small in spite of high tracking error (such as after a glycemic disturbance), but rises during small magnitude but sustained error signals, thereby resulting in faster set-point tracking; we choose $\alpha = 0.04$.

Fitting the Plasma Insulin Kinetics and Insulin Feedback Component

High quantities of insulin in the blood inhibits insulin production in a healthy β -cell. To replicate this physiological phenomenon, authors have proposed using models to predict plasma insulin content, and exploit these predictions to inform control actions[4,38]. This is expressed as an insulin feedback (IFB) term that reduces the magnitude of the control obtained from the PID equation (1). That is,

$$U_k = (1 + \gamma)u_k - \gamma I_{P,k}, \quad (7)$$

where U_k is the insulin actually infused into the patient in U/hr, $I_{P,k}$ is the plasma insulin concentration predicted at time k in $\mu\text{U/mL}$, and γ is a positive scalar selected to express the degree to which the current insulin bolus is suppressed by plasma insulin. The scalar γ must be selected to ensure that U_k is equal to the basal insulin infusion rate when the system is in steady-state.

In order to construct a model for the plasma insulin estimate, we employ the following continuous-time bi-exponential impulse response structure[4]:

$$I_P(t) = \frac{U(t)}{K_{IFB}(\tau_4 - \tau_3)} \left(e^{-\frac{t}{\tau_4}} - e^{-\frac{t}{\tau_3}} \right), \quad (8)$$

where τ_3 and τ_4 are time constants in minutes. We interpolate the experimental data to obtain a richer dataset with 5 min sampling time using Hermite polynomials, and employ a nonlinear least squares cost function (MATLAB: *lsqcurvefit*) to fit the model and validate on data constructed as in the insulin-glucose fitting procedure.

Results

Development of closed-loop intraperitoneal artificial pancreas system

In this paper, canine data is obtained by using an impulse response test in open-loop. That is, different magnitudes of insulin are bolused into the IP cavity and changes in glucose and plasma insulin concentrations are recorded. Based on these measurements, we employ model fitting techniques to formulate a control-relevant discrete-time linear mathematical model of insulin effects and glycemic responses for an implantable AP. We also construct personalized dynamical models for human subjects, based on total daily intake (TDI) of insulin, as reported in the literature[10,30,32]. Although this dynamical model can be employed to design a wide range of control algorithms (such as model-based predictive controllers used in AP research), we formulate a proportional-integral-derivative (PID) controller operating in the IP space, using a novel optimization-based transfer function matching method. The main reason for selecting PID controllers for the implantable AP is because the time delays have smaller magnitude in the IP space, and dynamics are faster. Therefore, PID control performs similarly to computationally complex algorithms requiring higher memory capacity and execution times such as MPC, as reported in prior *in-silico* simulation studies[30]. We also model the plasma insulin concentration based on experimental data in order to derive estimates of plasma insulin based on insulin dosing history (see Methods). This model is exploited to derive an insulin feedback (IFB) term[38] for the IP system. The performance of our proposed PID controller with IFB is tested on the UVA/Padova metabolic simulator modified to reflect IP-IP[30] and IP-SC[31] behavior. A schematic illustrating the different phases of this work and the complete proposed implantable AP system residing in the IP space is provided in Figure 2.

A new intraperitoneal insulin-glucose dynamical model

The discrete-time transfer function model

$$\bar{H}(z^{-1}) = \frac{-8.10z^{-3}}{(1 - 0.61z^{-1})(1 - 0.90z^{-1})^2} \quad (9)$$

is found to provide the best fit based on the following goodness-of-fit metric[32]:

$$J_{\text{fit}} = 100 \times \frac{1 - |\hat{Y}_{0:5:150} - Y_{0:5:150}|}{|Y_{0:5:150} - \mathbb{E}(Y_{0:5:150})|},$$

where $\hat{Y}$ denotes model predictions with the same input sequence as Y , and $\mathbb{E}(Y_{0:5:150})$ represents the average of the interpolated training data sequence (more details are provided in the Methods section). The experimental data with corresponding model responses and goodness-of-fit metrics J_{fit} is provided in Figure 3.

For the impulse response tests in protocols 1 and 2, high model fits are achieved, ranging from 81% and 94%. The fits for protocol 3 are notably lower, with one fit being highly

negative, in spite of the trend being suitably captured by the model (1) (see Supplementary Figure S1 for a zoomed-in view of this fit). This is explained as follows: for both experiments in protocol 3, the insulin infused is small (in one case it is zero), thus, the glucose variation is not large. Thus, small measurement errors result in highly oscillatory signals around a slowly-varying glucose signal: this noisy variability cannot be captured by a linear model, resulting in (seemingly) poor fits for this protocol. We compare the response and kinetics of our proposed model, as described in equation (9), with other transfer function models previously described in the literature: for SC-SC dynamics[32], and IP-IP dynamics[10,20].

Specifically, we compare the impulse response and frequency responses in Figure 4. As expected from the faster poles of our proposed model (0.61 vs. 0.75 in the previous model[30]), the peak glucose deviation occurs around 1 hr in an impulse response test, as compared to the much slower peak time of 5 hr for the SC-SC model. Although the time to peak is similar with our model and the IP-IP model proposed earlier[30], the time needed to return to steady-state for the glucose is much faster in our model, reflecting a faster clearance rate of insulin than that expected in the earlier model. Despite this disparity, the frequency characteristics of our model aligns closely to those described in the literature[30,31], especially around the estimated closed-loop bandwidth of 1.2×10^{-2} rad/min and 8.0×10^{-2} rad/min, reported in those studies (see shaded area in Figure 4).

Model personalization for human testing

In order to personalize this model structure to individuals within a human population, we propose the following patient-specific model

$$H(z^{-1}) = \frac{1800}{TDI} \frac{K_s K_m z^{-3}}{(1 - 0.61z^{-1})(1 - 0.90z^{-1})^2}, \quad (10)$$

where K_s is a unit-less safety factor that compensates for model mismatch, the scalar

$$K_m = -60(1 - p_1)(1 - p_2)(1 - p_3) \text{mg/dL/hr}$$

is a constant for compensating the steady-state gain contributed by the poles of the transfer function, and TDI is the total daily insulin intake for the individual in question; this is the factor that enables personalization, along with the poles. The '1800' factor arises from an empirical rule relating fall in blood glucose to insulin dose[39]. Hereafter, we will use the individualized model (10) to design personalized PID controllers for testing *in-silico*.

A new insulin feedback model in the IP space

Based on the plasma insulin data collected from the animal study, we obtain the following statistics: $K_{IFB} = 0.98 \pm 0.42$ L/min, $\tau_3 = 34.51 \pm 12.88$ min, and $\tau_4 = 14.87 \pm 4.88$ min for the plasma insulin prediction model described in equation (8) (see Methods). These values

closely resemble those reported in the literature[40,41], specifically 34.60 ± 5.90 min, 17.40 ± 4.70 min for the time constants τ_3 and τ_4 , and 1L/min for the gain K_{IFB} .

The model fits with corresponding fit [%] is provided in Figure 5. The fit of the validation data ranged between 49.2% and 92.1%. The plasma insulin model

$$\frac{I_P(s)}{U(s)} = \frac{1}{K_{IFB}} \frac{1}{(\tau_3 s + 1)(\tau_4 s + 1)} \quad (11)$$

is formulated with the average values obtained above, that is, $\tau_3 = 34.51$ min, $\tau_4 = 14.87$ min, and $K_{IFB} = 0.98$ L/min. For discrete-time implementation with a 5 min sampling time, the plasma insulin estimate at time k is given by

$$I_{P,k} = 1.58I_{P,k-1} - 0.62I_{P,k-2} + 0.02U_{k-1} + 0.18U_{k-2}$$

which informs the controller through the equation (7).

Clinical scenarios and challenges

We report results of simulation studies on the 10 subject cohort of the US FDA-accepted UVA/Padova simulator[33]. Clinical scenarios for both nominal and robust analysis are illustrated in Figure 6. In the nominal scenario, three large (90g CHO) meals are provided at widely spaced intervals to test set-point tracking of the proposed controller. In the robustness test scenario, five meals in total are consumed within 43 hours of closed-loop control. A 70 g meal of carbohydrates is given at 4 PM, after 4 hours of closed-loop initiation. A snack is provided at 7 PM containing 40 g CHO. At 1 AM, the safety of the closed-loop system is assessed by testing the controller's reaction to an undetected insulin bolus (representing manual overbolusing, latent exercise effects, or heightened insulin sensitivity due to illness). The next morning, a 70 g CHO breakfast is consumed at 8 AM, followed by a 70 g CHO lunch at noon, and a dinner of 70 g CHO at 7 PM. Meals in both scenarios are completely unannounced, that is, the controller is responsible for autonomously recommending appropriate insulin doses.

Comparison with design using earlier model

We compare our proposed PID controller to a prior design where the control-relevant model was formulated using simulated data[10,30,31]. The improvement of control performance in the IP space over the SC space is verified in these studies, both *in-silico*, and clinically. Herein, we show that our proposed PID outperforms these algorithms due to a complete redesign of the controller using the new dynamical models.

The simulation results of the comparative study is provided in Figure 7, with corresponding glucose metrics reported in Table 1. From Figure 7[A], we observe that the glucose trajectory with the proposed controller (green) is considerably tighter within the safe glycemic zone of 70–180 mg/dL compared to the corresponding glucose trajectory (black, dashed) based on the earlier model. As observed in Figure 7[B], our proposed controller is

more aggressive than the prior design, which is justified because the impulse response based on experimental data demonstrates higher insulin sensitivity and faster insulin clearance than the older model (see Figure 4).

The beneficial effects of this redesign is seen clearly from the clinical metrics presented in subplots [C] and [D] in Figure 7. The proposed PID results in significantly higher time in the 70–180 mg/dL range ($97.3 \pm 1.5\%$ vs. $90.1 \pm 5.6\%$; $p < 0.001$) and lower time above 180 mg/dL ($2.7 \pm 1.5\%$ vs. $9.8 \pm 5.6\%$; $p < 0.001$). It is also important to note that our proposed PID greatly outperforms the prior design in terms of time in the tight range of 80–120 mg/dL ($73.0 \pm 5.9\%$ vs. $54.8 \pm 8.7\%$; $p < 0.001$). Additional glucose metrics are provided in Table 1 (second and third columns, blue shading): we note that the proposed PID not only improves time in range, but the median blood glucose (averaged over 10 subjects) in spite of large unannounced meals is kept around 110 mg/dL with a very small standard deviation, unlike the prior controller (110.4 ± 0.6 mg/dL vs. 117.5 ± 4.9 mg/dL; $p < 0.001$). Another positive consequence of such improved control performance is that the maximum blood glucose level is curtailed (196.4 ± 9.8 mg/dL vs. 221.0 ± 12.1 mg/dL; $p < 0.001$).

Robustness against real life events such as unannounced physical activity

Herein, we demonstrate that our proposed controller is capable of handling unannounced meal challenges, sudden glucose declivity due to unannounced physical exercise, along with measurement noise and model mismatch. To this end, we re-simulate the closed-loop system using an SC sensor in the UVA/Padova metabolic simulator. Results from this evaluation are provided in Figure 8, with corresponding insulin-glucose values reported in the 3rd to 5th columns (pink shading) of Table 1.

It is clear from Figure 8 that the presence of sensing lags and susceptibility to measurement noise produces a conservative control action (red dotted line) trajectory compared to the IP-IP case (green line). Hence, the time in the 70–180 mg/dL range is reduced ($98.7 \pm 1.0\%$ to $98.1 \pm 1.0\%$; $p = 0.91$) and the time in severe hypoglycemia (< 54 mg/dL) is slightly increased ($0.1 \pm 0.3\%$ to $0.5 \pm 0.7\%$; $p = 0.11$) with the glucose minimum falling by ≈ 11 mg/dL (67.2 ± 13.1 mg/dL to 56.4 ± 13.0 mg/dL; $p = 0.85$), although these differences are statistically indistinguishable. Both the time above 180 mg/dL ($0.6 \pm 0.6\%$ to $0.7 \pm 0.6\%$; $p = 0.76$), and the maximum glucose level (186.9 ± 9.7 mg/dL to 173.8 ± 8.1 mg/dL; $p = 0.79$) are similar for this cohort. As demonstrated in the nominal scenario, the proposed PID takes advantage of the fast clearance rate of insulin in the IP cavity and exhibits markedly improved control performance compared to the PID designed using an earlier IP-IP model (black, dashed line). Remarkable improvements are demonstrated in the tight 80–120 mg/dL range ($76.6 \pm 4.6\%$ to $59.9 \pm 6.4\%$; $p < 0.001$) with the redesign, as is the time spent > 180 mg/dL ($0.6 \pm 0.6\%$ to $3.0 \pm 2.3\%$; $p < 0.001$).

Controller evaluation using clinical study data

Ten adults (7 male, 3 female) with T1DM participated in a non-randomized, non-blinded sequential AP study[‡] using subcutaneous glucose sensing via Dexcom Seven Plus sensors

[‡]Registered at [ClinicalTrials.gov](https://clinicaltrials.gov) under NCT01555788

(Dexcom, San Diego, USA) and zone MPC modified[31] for IP delivery via the Diaport system (Second Generation, Roche Diagnostics, Mannheim, Germany). The clinical protocol included three unannounced meals with 70, 40 and 70 g carbohydrate, respectively. Herein, we study the behavior of our proposed PID controller on real patient data obtained from this clinical study. Although this test does not leverage feedback since the glucose values are used exactly as obtained in the clinical study, one can ascertain whether the controller performs expectedly, or whether the controller exhibits anomalous characteristics when faced with real sensor noise and glucose variability.

The median and interquartile range of BG for 10 subjects is shown in the top plot of Figure 9. The lower plot compares the control actions of the clinical controller zone MPC (red, dashed line) and our proposed PID controller (green, continuous line). A Wilcoxon rank sum test reveals that the two control trajectories are not statistically significant ($p = 0.28$), which is reflected by the similarity of the two control trajectories. Disparity between the two controllers can be observed at (i) around the meal disturbances, where the interquartile ranges imply that our controller is more aggressive than the clinical controller; (ii) around 8AM that our proposed controller is more sensitive to glucose excursions than the clinical controller; there is a 60 min delay before the zone MPC reacts to the glucose increase; and (iii) prolonged suspension after a meal compensating bolus. The speed of IP sensing and the faster poles of the new model enables the quick response of the controller.

Discussion

This work is a first attempt to model insulin-glucose dynamics in the mammalian IP space and subsequently design a closed-loop control system for a fully autonomous, implantable AP using experimental data obtained from insulin impulse response tests on diabetic dogs. The canine model has been previously utilized to study insulin-glucose kinetics[42,43] and successfully evaluate closed-loop PID control algorithms with subcutaneous insulin delivery[44]. Prior experiments have shown that these kinetics closely resemble human glucose metabolism[45], insulin responsiveness, and absorption profiles in the IP space[46,47]. Additionally, the animal's size and anatomical characteristics permit the placement of blood sampling catheters necessary for assessing the pharmacokinetics and pharmacodynamics *in-vivo*.

An artificial pancreas system capable of leveraging the rapid sensing and actuation dynamics in the intraperitoneal cavity shows potential in paving the way towards completely automated glucose management for type 1 diabetics. A step is taken in this direction in the current work, where experimental data in the IP space is collected using canines, a species with insulin-glucose kinetics with close resemblance to humans[45,48,49]. This data is utilized to formulate a controlrelevant model that reflect these faster dynamics and can be used seamlessly in PID or model predictive controllers for AP research. The model is then compared to a prior model used in clinical studies via simulations and personalized for different people based on their total daily insulin intake. A PID controller designed using optimization-based transfer function matching (instead of empirical tuning rules) is subsequently constructed and tested on a challenging scenario with unannounced meals, sensor noise, and model mismatch.

Our proposed closed-loop system operating in the IP space has several important advantages. First, it reflects the faster insulin clearance kinetics that is expected in the IP cavity[11] compared to the earlier model[30] that is based on simulated data. This, in turn, enables the PID controller to recommend more aggressive control strategies without producing sustained controller-induced hypoglycemia. This is especially important in vulnerable cohorts such as youth and adolescents with type 1 diabetes, where glucose variability is much higher than in adults, and maintaining tight glucose control (especially hypoglycemia prevention) is very challenging[50]. Second, the proposed control architecture possesses very low complexity; indeed, the computational bottleneck lies in the computation of a simple controller update equation (10) that involves a few simple arithmetical operations. This simplicity of execution implies that our control architecture is amenable to implementation on resource-limited platforms such as implantable AP systems of the future. Third, the newly proposed controller tuning framework allows the user to design the controller gains using higher-order models of insulin-glucose dynamics. Generally, lower order models are used for controller design[2,30], which involves removal of higher-order poles and, therefore, loss of dynamical information. The improved quality of the control can be attributed to the method of controller design: unlike the method of approximating higher-order transfer functions by lower-order ones described in previous designs, we preserve the full dynamical intricacies exhibited by the higher-order transfer function and try to replicate the frequency response behavior in a bandwidth of interest. This leads to lesser degrees of approximation, and as evident by the simulation study, tighter closed-loop control.

Several challenges associated with fully-implantable intraperitoneal insulin delivery systems warrant consideration, including risk of infection[51], insulin under-delivery related to insulin aggregation, and intraperitoneal catheter obstruction[52]. As experience with implantable intraperitoneal insulin delivery has accumulated, however, the risk of these complications has decreased considerably[53–56]. Further development is likely needed to miniaturize the pump device, maximize battery life, and extend the amount of time needed between insulin refill procedures before such systems are broadly accepted.

Despite extensive development over the past decade, fully-automatic closed-loop insulin delivery systems have yet to demonstrate comparable postprandial glycemic control compared with closed loop systems that employ meal announcement strategies. The favorable pharmacokinetic-pharmacodynamic profile associated with intraperitoneal insulin delivery provides a practical approach for fully closed-loop systems to normalize postprandial hyperglycemia, a prominent contributor to overall hyperglycemia[57] and cardiovascular complications[58] in T1DM. Moreover, a key limitation of current therapy is the necessity of insulin delivery into subcutaneous tissue. This approach requires higher levels of insulin in the peripheral circulation to provide the liver with an adequate amount of insulin to prevent excessive hepatic glucose production and hyperglycemia. Concurrently, a narrow therapeutic balance must be achieved where the higher insulin concentrations in the peripheral circulation do not lead to excessive muscle glucose uptake and hypoglycemia. By contrast, intraperitoneal insulin delivery would be expected to restore the physiologic insulin distribution between the hepatic portal and peripheral circulations. Due to portal insulin absorption and first-pass hepatic insulin extraction, control of hepatic glucose production would not require the price of over-insulinization at muscle. Thus, when compared with

subcutaneous closed loop systems, the intraperitoneal approach would operate on a flatter portion of the dose-response curve relating insulin dose to change in blood glucose. This factor that would mitigate the early postprandial hyperglycemia[59] and late postprandial hypoglycemia[60] associated with fully automated closed-loop systems presently, paving the way towards eliminating the burden of meal and exercise announcement and thereby improving quality of care and quality of life in people with T1DM.

Some limitations of the current work are discussed next. First, the sample size of the population studied in this work is small, and therefore, our modeling scheme (though generic from an algorithm perspective), is susceptible to the variance of the parameter estimation scheme. Additionally, population-level parameters with confidence intervals are difficult to analyze and obtain. Future work will involve increasing the cohort size in order to get higher-confidence estimates of the parameters as the development of IP dynamical models continue to progress. Second, the model-based controller that is formulated in this paper is tested on data off-line, where the controller cannot elicit a glucose feedback response, indicating that more involved testing of the algorithm is required to validate the control formalism in clinical settings. This being said, the current formulation shows definite potential in improving the quality of care in people with T1DM that are resistant to SC strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- State-of-the-art control algorithms delivering insulin subcutaneously (SC) to treat type 1 diabetes mellitus (T1DM) are susceptible to slow diffusion and lag dynamics
- Alternative insulin delivery sites such as the intraperitoneal cavity have demonstrated benefits in prior simulation studies
- Here, a transfer function model of insulin-glucose dynamics in the IP space is constructed from data obtained by performing experiments on dogs exhibiting dynamics similar to humans with T1DM
- The new transfer function is leveraged to design a PID controller with insulin feedback to prevent controller-induced hypoglycemia
- Experiments supported physiological knowledge that insulin clearance rates in the IP space are faster than SC space, and closed-loop numerical simulations illustrate potential of IP delivery in next-generation artificial pancreas (AP) systems

Figure 1 - Schematic representation of experimental protocols. [SRIF: somatostatin equilibration period. IV: intravenous. IP: intraperitoneal.]

Figure 2 - Schematic diagram of the closed-loop intraperitoneal artificial pancreas system. The catheter is used for IP sensing to enable IP-IP control, whereas the Dexcom sensor is used for SC sensing for IP-SC control. [MedRadio: medical radio communication unit; SPP: serial port profile].

Figure 3 -

Experimental data (red circles) of glucose obtained from the IP cavity, and corresponding insulin-glucose dynamical model fits (black dashed lines). Data obtained in Protocol 1–3 is used for fitting the model, and artificially constructed data is used for validation. Fit [%] are provided above each plot to demonstrate goodness-of-fit. A zoom-in of Protocol 3 left subplot is given in the supplementary material.

Figure 4 -

Comparison of impulse responses and frequency responses of different dynamical models. Impulse responses depict the glucose response to a unit impulse bolus of insulin (left), and frequency domain characteristics (right, above: magnitude and below: phase) are illustrated via Bode plots. Comparison is made amongst the proposed IP-IP model (continuous black line) versus prior models for SC-SC (dash-dot blue line) and IP-IP (dashed red line) dynamics.

Figure 5 -

Experimental data (red circles) and corresponding insulin-glucose dynamical model fits (black dashed lines). Data obtained in Protocol 1–3 is used for fitting the model. Fit [%] are provided above each plot to demonstrate goodness-of-fit.

Figure 6 -

Scenario for testing the performance of the proposed AP with unannounced meals. (Top) Nominal scenario with 90g meals and prolonged gap after last meal to assess regulation performance. (Bottom) Robustness analysis with undetected insulin input representing exercise effects.

Figure 7 -

Closed-loop performance of the proposed PID controller (green) with model obtained from animal studies versus prior (red, dashed) PID design for the IP-IP system[30]. [A] Median glucose trajectories with shaded interquartile ranges (in mg/dL) with unannounced 90g CHO meals (inverted cyan triangles). Set point is at 110 mg/dL. [B] Corresponding median insulin delivery in U/5 min. [C] Comparison of the percent time in safe (70–180 mg/dL) glycemic zone (green: proposed PID, red: PID in[30]). [D] Comparison of the percent time in hyperglycemia (>180 mg/dL).

Figure 8 -

Closed-loop robustness analysis of the proposed IP-IP controller (green) vs. the proposed IP-SC controller with subcutaneous sensing (red), and the IP-IP PID controller (black) designed by Huyett et al 24. [A] Median glucose trajectories in mg/dL with unannounced meals (inverted cyan triangles) and effect of exercise input (red triangle). Set point is at 110 mg/dL. [B] Corresponding median insulin delivery in U/5 min. [C] Comparison of the percent time in hypoglycemia (< 70 mg/dL). [D] Comparison of the percent time in glycemic safe zone (within 70–180 mg/dL). [E] Comparison of the percent time in hyperglycemia (>180 mg/dL).

Figure 9 -

Implementation of the proposed PID controller on clinical data obtained in a previous clinical study[10]. (Top) Median and interquartile glucose ranges for 10 subjects. (Bottom) Median and IQR insulin comparison between our proposed PID controller (green) and the clinical Zone MPC controller used in the study (red). The meal protocol for these traces is not repeated in this work.

Table 1 -

Glucose metrics for nominal and robustness performance comparison of proposed PID, a PID designed using an earlier model, and our proposed PID with model mismatch due to SC sensing (IP-SC).

Clinical Metrics	Nominal Performance		Robustness Analysis		
Controller Type	Proposed PID	Earlier PID	Proposed PID	Proposed PID	Earlier PID
Insulin/Glucose	IP/IP	IP/IP	IP/IP	IP/SC	IP/IP
BG < 54 mg/dL [%]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.29	0.53 ± 0.71	0.13 ± 0.40
BG < 70 mg/dL [%]	0.00 ± 0.00	0.00 ± 0.00	0.69 ± 0.62	1.25 ± 1.02	0.67 ± 0.64
BG in 70 – 180 mg/dL [%]	97.29 ± 1.48	90.13 ± 5.63 (♠)	98.71 ± 0.97	98.07 ± 0.96	96.33 ± 2.29 (♦)
BG in 80 – 120 mg/dL [%]	73.05 ± 5.93	54.82 ± 8.66 (♠)	76.60 ± 4.64	67.27 ± 4.76 (♦)	59.85 ± 6.37 (♦ ♦)
BG > 180 mg/dL [%]	2.71 ± 1.48	9.87 ± 5.63 (♠)	0.60 ± 0.61	0.67 ± 0.66	3.00 ± 2.34 (♦ ♦)
Median BG [mg/dL]	110.37 ± 0.55	117.45 ± 4.90 (♠)	110.01 ± 0.32	110.58 ± 1.26	113.44 ± 3.57 (♦ ♦)
Minimum BG [mg/dL]	92.21 ± 6.10	104.71 ± 3.16 (♠)	67.17 ± 13.08	56.43 ± 12.98	68.74 ± 15.81
Maximum BG [mg/dL]	196.38 ± 9.87	221.01 ± 12.05 (♠)	186.87 ± 9.68	187.23 ± 12.61	208.83 ± 13.62 (♦)

Note: Statistical significance is computed against the proposed PID (IP-IP) controller for nominal and robustness analysis using a Wilcoxon rank sum test. The symbol ♠ implies p-values < 0.05, respectively; comparison is between the proposed PID and the PID in [24] for the nominal case. The symbols ♦ and ♦ ♦ imply p-values < 0.05 and < 0.001, respectively; comparison is between the proposed PID, and both PID controllers in the last two columns of the table for the robustness case.