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(54) **Title**: MODEL-BASED PERSONALIZATION SCHEME OF AN ARTIFICIAL PANCREAS FOR TYPE I DIABETES APPLICATIONS

(57) **Abstract**: An internal model-based proportional-integral-derivative (IMC-PID) controller with an insulin feedback (IFB) scheme personalized based on a priori subject characteristics and comprising a lower order control-relevant model to obtain PID controller parameters through an IMC based approach for artificial pancreas (AP) applications.

Model-Based Personalization Scheme of an Artificial Pancreas for Type I Diabetes Applications

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INTRODUCTION

[002] Nearly 16,000 new cases of Type 1 diabetes mellitus are diagnosed annually among people younger than 20 years of age in the United States alone [1]. Without treatment, these individuals suffer effects of unnaturally high blood glucose concentrations (called "hyperglycemia", defined as having a blood glucose concentration greater than 180mg/dl [2]), leading to diabetic ketoacidosis and long-term complications such as cardiovascular disease, kidney failure, blindness, and death [3]. Manual administration of exogenous insulin to treat T1DM requires multiple exacting calculations of blood glucose concentrations and carbohydrate ingestion daily, as even a slight overdose may cause immediate life-threatening consequences of low blood glucose concentrations (called "hypoglycemia" and generally defined as having a blood glucose concentration lower than 70mg/dl [2]), including trembling, weakness, difficulty speaking, convulsion, unconsciousness, and death [3]. Due to these and other complications, the average life expectancy of individuals with type 1 diabetes continues to lag at least a decade behind that of the overall population [4].

[003] The key component in a successful artificial pancreas (AP) system designed to help these people is the control algorithm that can automatically direct the delivery of insulin with or without a pre meal bolus. A closed-loop system combines a subcutaneous continuous glucose monitor (CGM) and continuous subcutaneous insulin injections (CSII) pump to deliver insulin.

[004] There are two main approaches for control design of AP: (a) proportional-integral-derivative (PID) controllers [5-7], and (b) model predictive control (MPC) controllers [8-10]. There are other approaches that are also being evaluated, such as fuzzy logic [11] and artificial neural networks [12]. The use of an internal model-based PID controller (IMC-PID) for AP systems is disclosed here. IMC based approach for tuning PID controllers have an advantage in that it only requires a single tuning parameter to modify controller performance [13].

Among different control-relevant models that have been made available in varying complexities, a discrete third order model with ***a priori*** subject information proposed by Van Heusden ***et al.*** [14] can be used to design a controller based on linear models. A subject's basal insulin injection characteristic is incorporated in addition to the total daily insulin (TDI) clinical parameter used by Van Heusden ***et al.*** to further attune the controller action in cases of model and patient mismatch.

[005] The disclosed controller also incorporates an insulin feedback scheme (IFB) which accelerates the apparent insulin pharmacokinetic profile. PID controllers that incorporate this scheme can exhibit improved performance, as shown in both model simulations [15] and a clinical trial [16].

[006] Below are described (i) the control challenges for glucose regulations in subjects with T1DM, (ii) the development of the IMC-PID controller, incorporation of the additional personalization factor, and adoption of the IFB, (iii) implementation of variations of this controller in in silico trials, and (iv) a discussion of the results.

SUMMARY OF THE INVENTION

[007] The key component in a successful artificial pancreas system designed to maintain the blood glucose concentrations of people with type I diabetes mellitus within the euglycemic zone (80-140mg/dl) is the control algorithm, which automatically directs the delivery of insulin to be administered to a subject with type 1 diabetes. The controller must meet a variety of challenges, such as the inherent long time delays between subcutaneous sensing, subcutaneous pump action, and the body's insulin-blood glucose dynamics, among others. The performance of any algorithm is limited by the development of a reliable model from which to base the controller design - controllers based on irrelevant models may not deal with the particular control challenges inherent in the artificial pancreas applications successfully, inducing hypoglycemic risk within the subjects. The invention combines an internal model control based design of a proportional-integral-derivative controller with individual gain personalization based on each subject's clinical characteristics. The invention uses a discrete model with a priori subject information; in particular embodiments the personalized controller is based on a lower order model, such as a 3^{rd} order model, but 1^{st}, 2^{nd}, 4^{th}, 5^{th} or other lower order model may be used, and preferred lower dimensional models are 5^{th} order or lower. The subject's basal insulin is incorporated into the lower order model to further personalize the controller's aggressiveness and take into account the wide variations in insulin sensitivity throughout the population. This personalization allows the controller to

be appropriately aggressive in cases where the subject is insensitive to insulin and requires a large basal amount to maintain euglycemia, while preventing hypoglycemic risk by bringing down the controller's aggressiveness in cases where the subject requires a low basal amount to maintain normal blood glucose levels.

[008] In one aspect the invention provides an internal model-based proportional-integral-derivative (IMC-PID) controller with an insulin feedback (IFB) scheme personalized based on a priori subject characteristics and comprising a lower order control-relevant model to obtain PID controller parameters through an IMC based approach adapted for artificial pancreas (AP) applications.

[009] In another aspect the invention provides an internal model-based proportional-integral-derivative (IMC-PID) controller adapted for an artificial pancreas (AP) system which controller requires only a single tuning parameter to modify controller performance and comprises a discrete lower order model with ***a priori*** subject information as design criteria, wherein a subject's basal insulin injection characteristic is incorporated, in addition to the total daily insulin (TDI) clinical parameter to further attune the controller's action in cases of model and patient mismatch, and an insulin feedback scheme (IFB), which accelerates the apparent insulin pharmacokinetic profile.

[010] In another aspect the invention provides a controller for an artificial pancreas (AP) system adapted to maintain blood glucose concentrations of people with type I diabetes mellitus within the euglycemic zone (80-140mg/dl) comprising a control algorithm, and which automatically directs the delivery of insulin to be administered to a subject with type 1 diabetes, comprising an internal model control (IMC) based design of a proportional-integral-derivative (PID) controller with individual gain personalization based on each subject's clinical characteristics, using a lower order discrete model with ***a priori*** subject information, wherein the subject's basal insulin is incorporated into the lower order model to further personalize the controller's aggressiveness and take into account variations in insulin sensitivity, wherein the personalization allows the controller to be aggressive in cases where the subject is insensitive to insulin and requires a large basal amount to maintain euglycemia, while preventing hypoglycemic risk by reducing the controller's aggressiveness in cases where the subject requires a low basal amount to maintain normal blood glucose levels.

[011] The invention also provides corresponding algorithms for programming the subject controllers to effectively implement the disclosed control steps.

[012] The invention also provides an artificial pancreas system or subsystem comprising a subject controller, which may comprise for example, the controller and a pump.

[013] The invention also provides a model-based personalization scheme of an artificial pancreas (AP) for Type I diabetes applications comprising a control algorithm which controls a subject controller.

[014] The invention also provides a method comprising directing insulin delivery using a subject controller, and optionally delivering the insulin.

[015] The invention includes controllers, algorithms and insulin directing systems essentially as described herein, and includes all combinations of the recited particular embodiments. All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[016] Figure 1. Comparison of different personalization schemes without noise.

[017] Figure 2. Comparison of various τ_c settings with noise.

[018] Figure 3. Comparison of the best PID controller with noise and the optimal basal bolus scheme.

DESCRIPTION OF PARTICULAR EMBODIMENTS OF THE INVENTION

[019] **Control Specifications**

[020] Controllers are assessed as a part of an AP system that utilizes noise-free and noise-included blood glucose measurements and continuous subcutaneous insulin injections. The system is incorporated as a part of a ten subject study using the Food and Drug Administration (FDA) accepted University of Virginia and Padova (UVA/Padova) metabolic simulator [17]. The control sampling period are set to 5 minutes. An unannounced meal is used to challenge the system without prior insulin bolus (feedforward action) to counteract the meal. The control system is evaluated by its performance in

1) minimizing the postprandial blood glucose concentration peak;

2) maximizing the time the subject's blood glucose concentration remains within the euglycemic zone (approximately 80-140mg/dl) [18]; and

3) minimizing the time the subject's blood glucose concentration spends below the target zone (approximately 70-180mg/dl) [18].

[021] A controller that is implemented in this manner must meet a variety of challenges. The use of subcutaneous monitoring, while unobtrusive compared to intravenous measurements, adds a measurement delay of approximately 12 minutes [19]. The use of subcutaneous insulin pumps also adds an additional actuation delay of up to one hour before the injected insulin affects glucose concentration [20]. Insulin cannot be delivered in negative values. Consequently, avoidance of excess insulin delivery is imperative.

[022] **Model-based Subject Specific Control Algorithm Development**

[023] Development of a model that is used for control purposes must be optimized for different objectives than the traditional goal of modeling – that is, rather than focusing on deriving an accurate prediction of future glucose values, the model should rather be designed with the specific control goal in mind [14]. In our previous work, we proposed a discrete 3rd order control- relevant model M_r defined as

[024]
$$M_r(q) = \frac{Kq^{-3}}{(1-0.98q^{-1})(1-0.965q^{-1})^3} \quad (1)$$

[025] where q^{-1} is the backward shift operator as described in [14], the units of insulin is expressed as (pmol/min), and blood glucose concentration is expressed as (mg/dl). For further details on the development of this model, the reader is referred to [14].

[026] K can be personalized using ***a priori*** subject parameters as

[027]
$$K = K_i c SF_b \quad (2)$$

[028] where K_i is an individualized gain based on the correction factor calculated as

[029]
$$K_i = K_x/TDI \quad (3)$$

$$1600 \leq K_x \leq 2400 \quad (4)$$

[030] using the range of rules for calculating correction factor as shown in [18]. TDI represents the subject's total daily insulin requirement, an easily available clinical parameter for any subject with a history of type 1 diabetes. c is a factor to maintain consistency in units as

[031]
$$c = \frac{1}{\frac{1U}{6.64h} * \frac{6000pm}{1U} * \frac{1h}{60min}} \quad (5)$$

[032] with the average clearance time for 99% of 1U of Humalog insulin analog to leave the system represented as 6.64h (1h half time in an average adult [21]) and conversion for 1U of insulin applied as 6000pm as per the standard clinical definition. SF_b is a scaling factor

based on the actual value of the subject's basal profile, another easily available clinical parameter, versus what is recommended as the standard starting basal quantity calculated from their TDI prior to further adjustments, as follows

[033] $SF_b = b_{calc}/(b)$ (6)

[034] $b_{calc}\ (U/h) = (K_y TDI)/24$ (7)

[035] $0.4 \leq K_y \leq 0.6$ (8)

[036] Here, b is the subject's actual nominal basal in U/h, and b_{calc} is the recommended calculation for a subject with T1DM's initial basal rate prior to fine-tuning, with the factor in the formula for the calculation varying between 0.4 and 0.6 depending on the subject's fitness, age, and other characteristics. Basal insulin profile of a subject with T1DM is a standard part of the subject's daily injection regimen, and is designed to maintain the subject at euglycemia absent meal disturbances [18]. Thus, this unitless scaling factor can attenuate the control signal based on how much more or less insulin the subject actually requires to maintain open-loop glucose concentration compared to the standard as calculated by the subject TDI, thus providing a measure of insulin sensitivity greater or less than standard.

[037] The discrete model as shown in (1) can be transformed to continuous domain using a bilinear transform approximation as The discrete model as shown in (1) can be transformed to continuous domain using a bilinear transform approximation as

[038] $$q = e^{sT_s} \sim \frac{1+s\frac{T_s}{2}}{1-s\frac{T_s}{2}} \quad (9)$$

[039] where T_s is the sampling time of the discretized model at 5 minutes. The result of this discretization gives $M_{r1}(s)$ a

[040] $$M_{r1}(s) = \frac{Ke^{-15s}(-2s+1)^2}{(247s+1)(140s+1)^2}. \quad (10)$$

[041] (8) can be converted into a second order plus time delay model through Skogestad's half rule [22]. This results in a second order plus time delay model of the form

[042] $$\tilde{G}(s) = \frac{Ke^{-\theta s}}{(\tau_1 s+1)(\tau_2 s+1)} \quad (11)$$

[043] From the original model (8), one can find the new θ, τ_1 and τ_2 as

[044] $$\theta = \frac{180}{2} + 15 + 3 \cdot 2 + \frac{5}{2} = 93.5 \quad (12)$$

[045] $$\tau_1 = 247 \quad (13)$$

[046] $$\tau_2 = 140 \div \frac{140}{2} = 210 \quad (14)$$

[047] These calculations give the final model as

[048] $$M_{T2}(s) = \frac{Ke^{-93.5s}}{(247s+1)(210s+1)^2} \quad (15)$$

[049] Given a reasonably accurate dynamic model of the process, a method of controller design based on the process model is an approach that holds many advantages. The IMC method allows for model uncertainty and gives the user the capability to modify the tradeoffs of increased robustness versus better performance from tuning just one parameter.

[050] The second order plus time delay model from (15) can be factored with a first order Taylor series approximation of the time delay as

[051] $$M_{T2}(s) = M_{T2+}(s)M_{T2-}(s) \quad (16)$$

[052] $$M_{T2+}(s) = 1 - \theta s \quad (17)$$

[053] $$M_{T2-}(s) = \frac{K}{(\tau_1 s+1)(\tau_2 s+1)} \quad (18)$$

[054] The IMC method for PID controller tuning relations calls for a low pass filter with a gain of 1 and a tuning parameter τ_c, leading to the calculations of the three PID controller parameters K_c, τ_I and τ_D as [23]

[055] $$K_c K = \frac{\tau_1+\tau_2}{\tau_c+\theta} \quad (19)$$

[056] $$\tau_I = \tau_1 + \tau_2 \quad (20)$$

[057] $$\tau_D = \frac{\tau_1\tau_2}{\tau_1+\tau_2} \quad (21)$$

[058] Consequently, the PID controller settings can be simplified as

[059] $$K_{c1f} = -\frac{458}{\tau_c+93.5} \frac{1}{\frac{K_X}{TDI} \frac{1}{\frac{1}{6.64}\times 6000\times\frac{1}{60}} \frac{\frac{K_Y\times TDI}{24}}{b}}$$

[060] $$= -\frac{298}{(\tau_c+93.5)K_X K_Y} b \quad (22)$$

[061] $$\tau_I = 458 \quad (23)$$

[062] $$\tau_D = 113 \quad (24)$$

[063] with the choice of either of each rule's extremes to be determined and the specific value of τ_c (min) left as a tuning parameter. As a result of the additional personalization based on the subject's basal profile, the numerical value of the subject TDI is canceled from the controller, leaving the final form of the gain to only include the subject's current basal levels as their target (the units are still maintained).

[064] The control signal as a result of the application of these parameters in the standard parallel form of the PID controller is added on the subject's basal to signal the final suggested insulin delivery ID_{PID} to the insulin pump. This insulin signal can then be further attenuated by the use of IFB [15], which takes into account the amount of insulin previously delivered, accelerating the apparent insulin pharmacokinetics as

[065] $$\hat{I}_p(n) = K_0 ID(n-1) + K_1 \hat{I}_p(n-1) - K_2 \hat{I}_p(n-2) \quad (25)$$

[066] $$ID(n) = (1+\gamma) ID_{PID}(n) - \gamma \hat{I}_p(n-1) \quad (26)$$

[067] Here, n denotes the most recent time value, $ID(n)$ is the final insulin delivery profile, and $I_p(n)$ is a real time estimate of insulin concentration. K_1, K_2, and γ are constants each reported as 1.966308, 0.966584, and 0.5, with K_0 given as

[068] $$K_0 = 1 - K_1 + K_2. \quad (27)$$

[069] For more details on the development of this IFB scheme, the reader is directed to [15] and [16].

[070] **Results**

[071] The performance of the designed PID controller is tested ***in silico*** within the FDA accepted UVA/Padova metabolic simulator [17]. The simulator contains ten subject models with various time-invariant clinical characteristics that have a large intersubject variability. The simulator also has the capability of providing an optimal bolus injection when given the meal size for each subject based on the subject's basal rate and insulin to carbohydrate ratio (I:C), a clinical parameter that signifies how many grams of carbohydrates are compensated for that specific patient for a unit of insulin.

[072] Optimal regulation, in the context of the disclosed AP, is defined providing the perfect basal rate for each subject that would, given no disturbances, maintain blood glucose concentration at the 110mg/dl target (average of the euglycemic zone). Further, a perfect bolus should also be provided at the beginning of each meal that does not over or under-compensate for the glucose content of the meal, thus both avoiding late postprandial hypoglycemia and minimizing hyperglycemia prior to returning to the target. On the other hand, the minimum amount of regulation would feasibly still provide the same basal rate but

eschew meal disturbance rejection, and thus will be prone to long episodes of hyperglycemia. The performance of each controller is measured using a medically inspired metric that takes into account the three objectives outlined in the control specifications, scored in a linearly scaled approach with the perfect basal-only control scheme serving as the baseline ("0") and the perfect basal-bolus scheme serving as the top performer ("1"). The specific metrics are

1) peak postprandial blood glucose concentrations

2) percent of total time the subject's blood glucose concentration within the euglycemic zone of 80-140mg/dl;

3) percent of total time the subject's blood glucose concentration spent within the clinically safe non hyper- and hypoglycemic blood glucose zone of 70-180 mg/dl [18]; and

4) percent of total time the subject's blood glucose concentration spent within the hyperglycemic zone of greater than 180mg/dl.

[073] In addition to these metrics, any controller that causes a subject to experience hypoglycemia b virtue of blood glucose concentrations below 70mg/dl is discarded.

[074] The controller is turned on after an initialization period of 20 minutes from the beginning of the simulation. A 50g meal is given at 7 hours after the beginning of the simulation. Each subject's blood glucose profile is recorded for 24 hours after the meal disturbance, with total simulation duration of 31 hours. The controller is activated every 5 minutes, and actual insulin delivery is discretized to the nearest 0.05U to simulate the limits on current generation subcutaneous insulin pumps [24].

[075] The 1600 and 2400 rules for the correction factor portion of the gain, and the choice between 0.4 and 0.6 rules for the basal scaling factor portion of the gain, are first tested [18].

[076] All tested control schemes and their respective ID to be used in the remaining portion of the results are shown in Table I. τ_c was fixed at 180 minutes (3 hours). 2400 correction factor rule and 0.4 basal calculation factor is mathematically identical to 1600 and 0.6. Non-personalized versions of the gain based on [14] with and without insulin feedback are also presented for comparison. The average responses of relevant controller variations in Fig. 1 and the scaled performance scores for each controller variation in Table II show that settings of 1600 and 0.4 give the highest scaled scores.

[077] Using these settings, the value for τ_c is varied as the only tuning parameter from 60 to 300 minutes, in 60 minute intervals. As can be seen in the scaled performance scores in Table II, a τ_c of 120 minutes gives the best response among the tested settings while still avoiding any instances of hypoglycemia. The controller setting with τ_c of 1h was discarded due to the presence of hypoglycemia.

[078] After the optimal IMC PID controller is found through this method under noise-free conditions, the controller is then detuned accordingly within noisy conditions to test for robustness. τ_c is varied from 2 to 6 hours in 30 minute intervals. τ_c settings of 4 hours or less induced hypoglycemia. Fig. 2 shows the average glucose and insulin profiles of controllers that does not express hypoglycemia under noisy conditions. As can be in the Fig. 2 and the scaled performance scores in Table II, τ_c setting of 4.5h achieves the closest performance to the optimal basal-bolus profile while still avoiding hypoglycemia, with an average postprandial (post meal) peak of 183mg/dl and over 95 percent of time spent within the safe zone of 70mg/dl to 180mg/dl within 24 hours of the meal disturbance. Fig. 3 shows the average, minimum, and maximum values for each step for this setting and is compared with the optimal basal-bolus control scheme. As can be seen in the figure, while the disclosed controller has a slightly higher prandial peak, it still maintains all subject glucose profiles within the target zone for an extreme majority of the simulations and avoids any instances of hypoglycemia.

[079] Discussion

[080] This disclosure demonstrates the value of an IMC-based design method with a personalization scheme to calculate PID controller parameters and combine it with IFB for AP applications. Under the stated simulation conditions, the subject controller with subject specific personalization of the controller's aggressiveness and inclusion of IFB give good control results based on a set of metrics designed to quantify each controller's adherence to medically inspired objectives. Selection of correct personalization methods and an optimal τc value gives a resulting average subject glucose profile that can closely match the optimal basal-bolus scheme, while avoiding hypoglycemia for all 10 tested subjects.

[081] A 3rd order control-relevant model was used to obtain PID controller parameters through an IMC based approach for AP applications. The resulting PID controller with accompanying IFB scheme was personalized based on a priori subject characteristics and tested on ten simulated subjects under the UVA/Padova metabolic simulator. Optimal controller settings were determined through a set of controller performance metrics, and the PID controller based on the resulting choice in personalization rule parameters and τc was able to achieve comparable performance to the optimal basal-bolus scheme. The average post prandial peak was maintained below 185mg/dl, and 97% of the combined total simulation time for all subjects was maintained within the target safe blood glucose zone of 70-180mg/dl with 80% of the time remaining within the euglycemic zone of 80-140mg/dl – all without inducing instances of hypoglycemia. The controller can achieve this performance without a

time-consuming model identification step, and thus will have greater utility in practical applications.

[082] Figures

[083] Figure 1. Comparison of different personalization schemes without noise. Average blood glucose profiles and insulin delivery for 10 ***in silico*** subjects simulated in the UVA/Padova metabolic simulator to a 50g meal disturbance applied to the IMC PID controller as described in the text, with setpoint at 110mg/dl, τ_c at 3h, and various combinations of personalization rule settings as in table I. Solid continuous line represents controller 1 (optimal basal-bolus scheme), thin continuous line represents controller 2 (optimal basal scheme), thick dashed line represents controller 3 (1600 correction factor and 0.4 basal factor), thin dashed line represents controller 4 (1600 correction factor and 0.6 basal factor), thick dash dotted line represents controller 5 (2400 correction factor and 0.6 basal factor), thin dash dotted line represents controller 10 (PID without personalization but with insulin feedback), and thick dotted line represents controller 11 (PID without personalization and without insulin feedback).

[084] Figure 2. Comparison of various τ_c settings with noise. Average blood glucose profiles and insulin delivery for 10 ***in silico*** subjects simulated in the UVA/Padova metabolic simulator to a 50g meal disturbance applied to the IMC PID controller as described in the text, with setpoint at 110mg/dl, correction factor rule chosen as 1600, basal calculation factor chosen as 0.4, and τ_c varied from 2h to 6h in 30 minute intervals. Controller with τ_c of 4h or less were discarded due to presence of hypoglycemia. Solid continuous line represents controller 1 (optimal basal-bolus scheme), thin continuous line represents controller 2 (optimal basal scheme), thick dashed line represents controller 17 (τ_c of 4.5h), thin dashed line represents controller 18 (τ_c of 5h), and thick dash dotted line represents controller 19 (τ_c of 5.5h) and thin dash dotted line represents controller 20 (τ_c of 6h).

[085] Figure 3. Comparison of the best PID controller with noise and the optimal basal bolus scheme. Average, minimum, and maximum blood glucose profiles and average insulin delivery for 10 ***in silico*** subjects simulated in the UVA/Padova metabolic simulator to a 50g meal disturbance applied to the IMC PID controller as described in the text, with setpoint at 110mg/dl, correction factor rule chosen as 1600, basal calculation factor chosen as 0.4, and τ_c chosen as 4.5h. Dashed lines represent the controller's average, minimum, and maximum values at each time point and controller insulin delivery profiles. Solid lines represent the same characteristics of the basal bolus scheme.

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TABLE I. CONTROLLER VARIATIONS TESTED

Controller ID	Controller Variant	τ_c (min)	Personalization Rule Variations	
			Correction Factor Rule	Basal Calculation Factor
1	Optimal Basal-Bolus	-	-	-
2	Optimal Basal	-	-	-
3	IMC-PID w/feedback	180	1600	0.4
4	IMC-PID w/feedback	180	1600 (2400 equivalent)	0.6 (0.4 equivalent)
5	IMC-PID w/feedback	180	2400	0.4
6	IMC-PID w/feedback	60	1600	0.4
7	IMC-PID w/feedback	120	1600	0.4
8	IMC-PID w/feedback	240	1600	0.4
9	IMC-PID w/feedback	300	1600	0.4
10	IMC-PID w/feedback	180	-	-
11	IMC PID w/o feedback	180	-	-
12	IMC-PID w/feedback, noise	120	1600	0.4
13	IMC-PID w/feedback, noise	150	1600	0.4
14	IMC-PID w/feedback, noise	180	1600	0.4
15	IMC-PID w/feedback, noise	210	1600	0.4
16	IMC-PID w/feedback, noise	240	1600	0.4
17	IMC-PID w/feedback, noise	270	1600	0.4
18	IMC-PID w/feedback, noise	300	1600	0.4
19	IMC-PID w/feedback, noise	330	1600	0.4
20	IMC-PID w/feedback, noise	360	1600	0.4

Table II. Averaged Performance Metrics and Scaled Metric Values for each Controller with Optimal Balal-Bolus and Optimal Basal Control Schemes as Baseline Performances

Controller ID	% Time in Hypoglycemia, <70mg/dl	Peak Blood Glucose [mg/dl]	% above 70-180mg/dl	% within 70-180mg/dl	% within 80-140mg/dl	Scaled Peak Blood Glucose	Scaled % above 70-180mg/dl	Scaled % within 70-180mg/dl	Scaled % within 80-140mg/dl
1	0 (0)	209 (25.2)	13.8 (7.2)	86.2 (7.2)	65.8 (9.1)	0.00	0.00	0.00	0.00
2	0 (0)	162 (14.4)	0.11 (0.3)	99.9 (0.3)	85.6 (8.9)	1.00	1.00	1.00	1.00
3	0 (0)	174 (18.3)	1.64 (2.6)	98.4 (2.6)	83.7 (10.8)	0.74	0.89	0.89	0.90
4	0 (0)	181 (19.7)	3.63 (5.2)	96.4 (5.2)	82.1 (8.8)	0.60	0.74	0.74	0.82
5	0 (0)	187 (21.2)	4.62 (6.0)	95.4 (6.0)	79.1 (9.7)	0.46	0.67	0.67	0.67
6	0.70 (2.2)	167 (16.4)	1.42 (1.4)	99 (2.4)	86 (9.7)	0.90	0.90	0.91	1.03
7	0 (0)	170 (17.6)	0.83 (1.9)	99.2 (1.9)	85.2 (11)	0.82	0.95	0.95	0.98
8	0 (0)	177 (18.9)	2.55 (3.5)	97.5 (3.5)	82.8 (9.9)	0.67	0.82	0.82	0.86
9	0 (0)	180 (19.5)	3.36 (4.7)	96.6 (4.7)	82.4 (8.7)	0.61	0.76	0.76	0.84
10	0 (0)	202 (22.8)	9.95 (6.5)	80.1 (6.5)	71.1 (11.7)	0.15	0.28	0.45	0.27
11	0 (0)	207 (23.6)	11.32 (6.8)	88.7 (6.8)	68.8 (12.3)	0.05	0.18	0.18	0.15
12	1.34 (2.9)	179 (19.3)	1.69 (2.4)	97.0 (4.4)	80.7 (11.4)	0.64	0.88	0.79	0.75
13	0.68 (2.1)	180 (19.4)	1.96 (2.8)	97.4 (3.6)	81.2 (12.0)	0.62	0.86	0.81	0.78
14	0.48 (1.5)	181 (19.4)	2.34 (3.5)	97.2 (3.8)	80.9 (11.7)	0.60	0.84	0.80	0.76
15	0.35 (1.1)	182 (19.5)	2.63 (4.1)	97.0 (4.2)	80.5 (11.5)	0.58	0.81	0.79	0.74
16	0.09 (0.3)	183 (19.6)	3.20 (4.6)	96.7 (4.6)	80.2 (11.0)	0.56	0.77	0.77	0.73
17	0 (0)	183 (19.6)	3.52 (5.1)	96.5 (5.1)	79.9 (10.3)	0.54	0.75	0.75	0.72
18	0 (0)	184 (19.9)	3.74 (5.3)	96.3 (5.3)	80.1 (9.0)	0.52	0.73	0.73	0.72
19	0 (0)	185 (20.1)	3.87 (5.4)	96.1 (5.4)	79.7 (9.1)	0.50	0.72	0.72	0.70
20	0 (0)	186 (20.3)	4.09 (5.5)	95.9 (5.5)	79.4 (9.3)	0.48	0.71	0.71	0.69

WHAT IS CLAIMED IS:

1. An internal model-based proportional-integral-derivative (IMC-PID) controller with an insulin feedback (IFB) scheme personalized based on a priori subject characteristics and comprising a control-relevant model to obtain PID controller parameters through an IMC based approach configured for artificial pancreas (AP) applications.

2. An internal model-based proportional-integral-derivative (IMC-PID) controller adapted for an artificial pancreas (AP) system which controller requires only a single tuning parameter to modify controller performance and comprises a discrete control-relevant model with ***a priori*** subject information as design criteria, wherein a subject's basal insulin injection characteristic is incorporated, in addition to the total daily insulin (TDI) clinical parameter to further attune the controller's action in cases of model and patient mismatch, and an insulin feedback scheme (IFB), which accelerates the apparent insulin pharmacokinetic profile.

3. A controller for an artificial pancreas (AP) system adapted to maintain blood glucose concentrations of people with type I diabetes mellitus within the euglycemic zone (80-140mg/dl) comprising a control algorithm, and which automatically directs the delivery of insulin to be administered to a subject with type 1 diabetes, comprising an internal model control (IMC) based design of a proportional-integral-derivative (PID) controller with individual gain personalization based on each subject's clinical characteristics, using a control-relevant discrete model with ***a priori*** subject information, wherein the subject's basal insulin is incorporated into the lower order model to further personalize the controller's aggressiveness and take into account variations in insulin sensitivity, wherein the personalization allows the controller to be aggressive in cases where the subject is insensitive to insulin and requires a large basal amount to maintain euglycemia, while preventing hypoglycemic risk by reducing the controller's aggressiveness in cases where the subject requires a low basal amount to maintain normal blood glucose levels.

4. A controller of claim 1, 2 or 3 where in the model is lower order, wherein the model is 1^{st}-5^{th} dimensional.

5. An artificial pancreas system or subsystem comprising a controller of claim 1, 2, 3 or 4.

6. A model-based personalization scheme of an artificial pancreas (AP) for Type I diabetes applications comprising a control algorithm which directs the controller of claim 1, 2, 3 or 4.

7. A method comprising directing insulin delivery using the controller of claim 1, 2, 3 or 4.

8. The method of claim 7 further comprising delivering the insulin to the person.

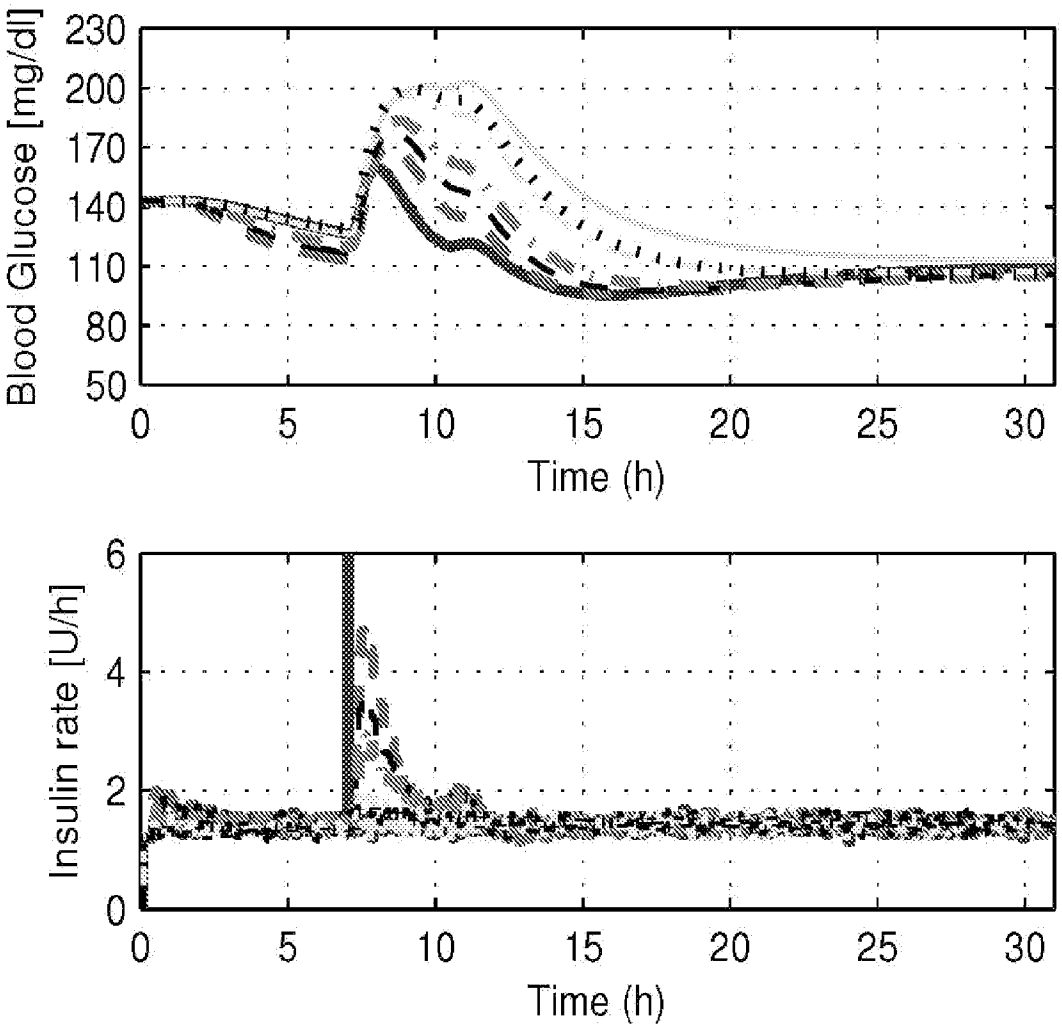
Blood Glucose [mg/dl]
230
200
170
140
110
80
50
0
5
10
15
20
25
30
Time (h)
Insulin rate [U/h]
6
4
2
0
0
5
10
15
20
25
30
Time (h)

Fig. 1

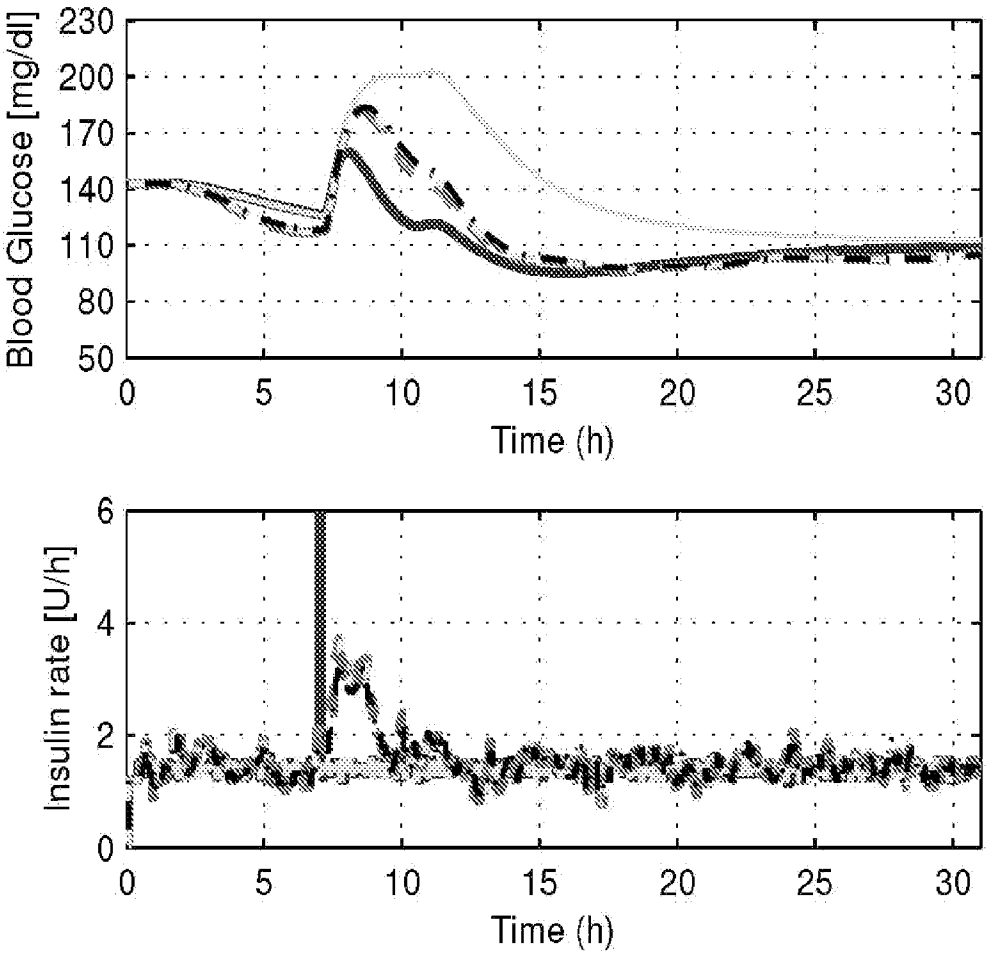
Blood Glucose [mg/dl]
230
200
170
140
110
80
50
0
5
10
15
20
25
30
Time (h)
Insulin rate [U/h]
6
4
2
0
0
5
10
15
20
25
30
Time (h)

Fig. 2

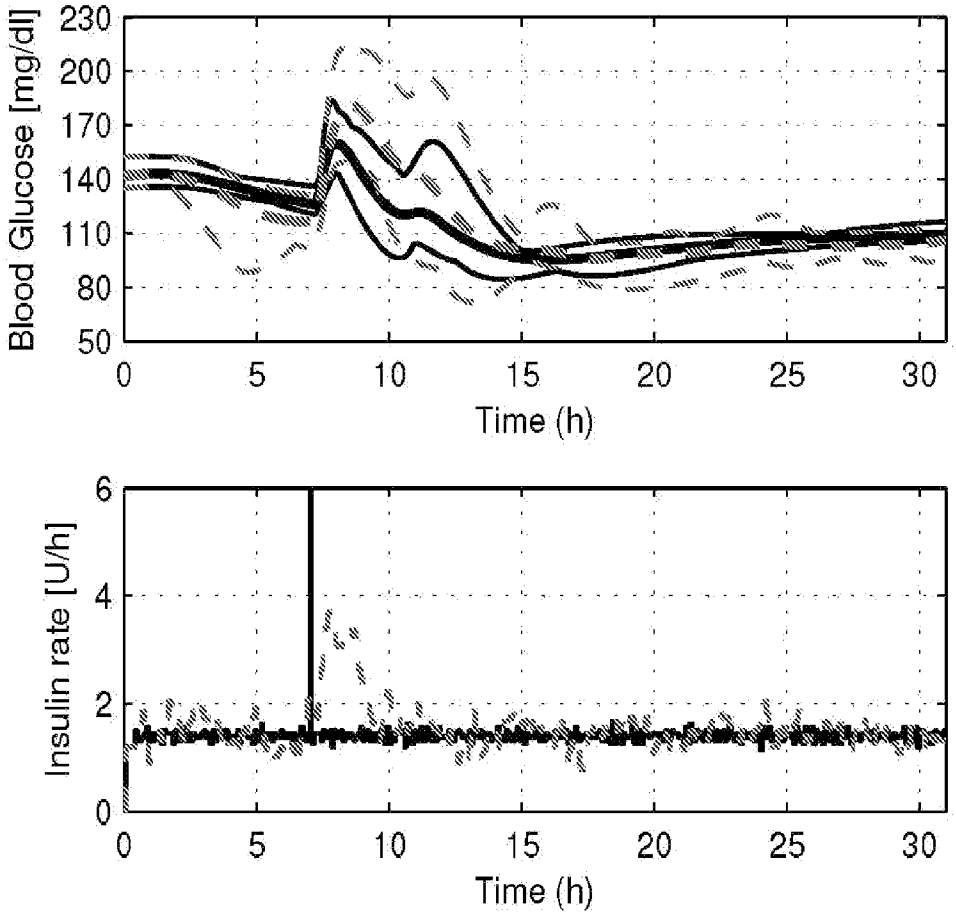
Blood Glucose [mg/dl]
230
200
170
140
110
80
50
0
5
10
15
20
25
30
Time (h)
Insulin rate [U/h]
6
4
2
0
0
5
10
15
20
25
30
Time (h)

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/077363

A. CLASSIFICATION OF SUBJECT MATTER

A61F 2/02(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F 2/02; A61B 5/0476; A61B 5/1468; A61F 2/04; A61M 5/168

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: artificial pancreas, diabete,proportional-integral-derivative, PID, control algorithm, subject, patient, priori, information, characteristic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	van HEUSDEN, K. et al., 'Control-Relevant Models for Glucose Control Using A Priori Patient Characteristics', IEEE Trans Bio Eng, Vol. 59, pp. 1839-1849, July 2012 See abstract; pages 1840, 1843; figure 4.	1
A		2-4
Y	US 2010-0228110 A1 (TSOUKALIS, A.) 9 September 2010 See abstract; claim 8-12; figures 1a/b.	1
A		2-4
A	US 2004-0034295 A1 (SALGANICOFF, M.) 19 February 2004 See abstract; claim 7; paragraphs [0035], [0038], [0041]; figure 1A.	1-4
A	US 2011-0208156 A1 (DOYLE, III, F. J. et al.) 25 August 2011 See abstract; claim 1; paragraphs [0052]-[0056]; figure 10.	1-4
A	US 2012-0095359 A1 (NGUYEN, H. T.) 19 April 2012 See abstract; claims 1, 18, 21; paragraphs [0054]-[0056]; figure 4.	1-4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 April 2014 (02.04.2014)	**03 April 2014 (03.04.2014)**

Name and mailing address of the ISA/KR
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Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701,
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Han, Inho
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/077363

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 8
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 8 is unclear, beacause it refers to multiple dependent claims which do not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 5-7
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/077363

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010-0228110 A1	09/09/2010	EP 2228004 A1	15/09/2010
		EP 2228004 B1	18/09/2013
		GR 1007310 B	10/06/2011
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		WO 02-27659 A3	27/06/2002
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		EP 2521483 A1	14/11/2012
		JP 2013-519451 A	30/05/2013
		WO 2011-100624 A1	18/08/2011
US 2012-0095359 A1	19/04/2012	EP 2421439 A1	29/02/2012
		EP 2421439 A4	23/10/2013
		WO 2010-121301 A1	28/10/2010