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ORIGINAL ARTICLE

A Bio-Inspired Glucose Controller Based on Pancreatic β-Cell Physiology

Pau Herrero, Ph.D.,[1] Pantelis Georgiou, Ph.D.,[1] Nick Oliver, M.B.B.S., MRCP,[1,2] Desmond G Johnston, FMedSci[1,3] and Christofer Toumazou, Ph.D.[1]

Abstract

Introduction:

Control algorithms for closed-loop insulin delivery in type 1 diabetes have been mainly based on control engineering or artificial intelligence techniques. These, however, are not based on the physiology of the pancreas but seek to implement engineering solutions to biology. Developments in mathematical models of the β-cell physiology of the pancreas have described the glucose-induced insulin release from pancreatic β cells at a molecular level. This has facilitated development of a new class of bio-inspired glucose control algorithms that replicate the functionality of the biological pancreas. However, technologies for sensing glucose levels and delivering insulin use the subcutaneous route, which is nonphysiological and introduces some challenges. In this article, a novel glucose controller is presented as part of a bio-inspired artificial pancreas.

Methods:

A mathematical model of β-cell physiology was used as the core of the proposed controller. In order to deal with delays and lack of accuracy introduced by the subcutaneous route, insulin feedback and a gain scheduling strategy were employed. A United States Food and Drug Administration-accepted type 1 diabetes mellitus virtual population was used to validate the presented controller.

Results:

Premeal and postmeal mean ± standard deviation blood glucose levels for the adult and adolescent populations were well within the target range set for the controller [(70, 180) mg/dl], with a percent time in range of 92.8 ± 7.3% for the adults and 83.5 ± 14% for the adolescents.

Conclusions:

This article shows for the first time very good glucose control in a virtual population with type 1 diabetes mellitus using a controller based on a subcellular β-cell model.

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Author Affiliations: [1]Center for Bio-Inspired Technology, Institute of Biomedical Engineering, Imperial College London, London, United Kingdom; [2]Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; and [3]Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom.

Abbreviations: (ASIC) application-specific integrated circuit, (AUC) area under the curve, (BG) blood glucose, (BGRI) blood glucose risk index, (CGM) continuous glucose monitor, (CHO) carbohydrate, (CSII) continuous subcutaneous insulin infusion, (CVGA) control-variability grid analysis, (FDA) Food and Drug Administration, (HBGI) high blood glucose risk index, (IV) intravenous, (LBGI) low blood glucose risk index, (MPC) model predictive control, (PID) proportional-integral-derivative, (RRP) readily releasable pool, (SC) subcutaneous, (SD) standard deviation, (T1DM) type 1 diabetes mellitus

Keywords: artificial pancreas, bio-inspired technology, closed-loop, diabetes management, glycemic control

Corresponding Author: Pau Herrero, Ph.D., Center for Bio-Inspired Technology, Institute of Biomedical Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, United Kingdom; email address *pherrero@imperial.ac.uk*

Introduction

Automatic Blood Glucose Control

In type 1 diabetes mellitus (T1DM) management, an automatic closed-loop system[1] provides the potential to improve hemoglobin A1c while avoiding hypoglycemia. It requires continuous glucose measurement,[2] a control device,[3] and a pump for insulin delivery.[4] Closed-loop control algorithms used in the context of an artificial pancreas have been mainly based on classical control engineering techniques and dominated by proportional-integral-derivative (PID) control[5] and model predictive control (MPC).[6,7] Other approaches, based on empirical knowledge, have also been proposed through the use of artificial intelligence techniques.[8,9]

Bio-Inspired Approach to Blood Glucose Control

Bio-inspired approaches for solving medical problems have been motivated by the belief that evolved physiology is capable of conducting specific function in biology efficiently using nonoptimal resources.[10] Replicating the functionality of the human body can lead to a system with greater physiological function, which may be able to deliver a superior therapeutic approach. Bio-inspired technologies for artificial organs have already been successfully implemented in different medical areas including cochlear implants,[11] which model the way the basilar membrane of the cochlea behaves and therefore can restore hearing; retinal implants,[12] which model the local processing that occurs in the neuronal circuits of the retina to derive extremely fast and low-power image restoration; and vestibular implants,[13] which replicate the inertial measurements of the human body to restore balance. Therefore, there may be some benefit to considering a control strategy for controlling blood glucose (BG) that is based on the biological function of the pancreas.

The idea of using a bio-inspired approach for BG control is motivated by the biphasic nature of insulin secretion from the β cells in the pancreas, which depends on the type and magnitude of the glucose stimulus.[14,15] Both animal and human studies indicate that the first-phase insulin response to intravenous glucose has beneficial effects on the regulation of glucose metabolism. In particular, the first-phase has a profound and long-term inhibitory effect on hepatic glucose production. Likewise, the early insulin response to ingested glucose is an important determinant of prandial glucose tolerance. **Figure 1** shows an example of a simulated biphasic insulin release in response to a step in glucose levels.

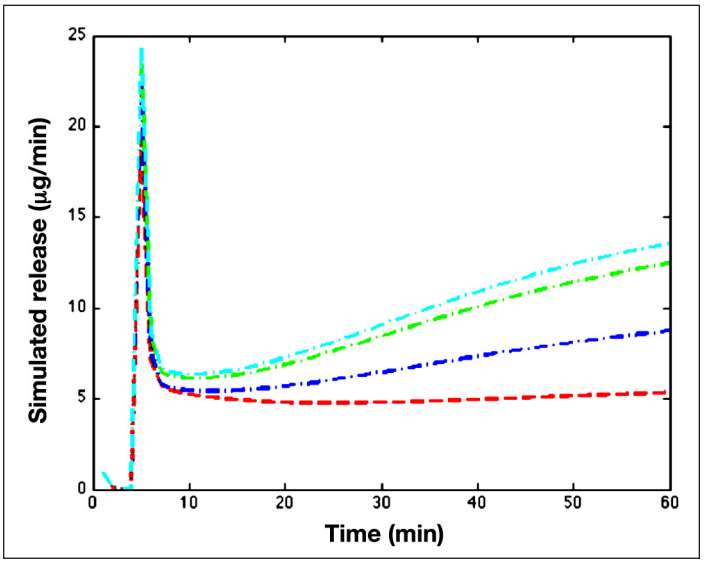

Figure 1. Simulated biphasic insulin release in response to a step in glucose levels at t = 5 min from G = 0 mg/dl to 150 mg/dl (red curve), G = 200 mg/dl (blue curve), G = 300 mg/dl (green curve), and G = 400 mg/dl (cyan curve).

The presence of the sharp first phase due to rapidly changing glucose concentration (i.e., derivative effect) followed by a second phase represented by sustained insulin release is demonstrated.

Therefore, replicating β-cell behavior in response to a glucose stimulus is postulated to be an appropriate approach to controlling BG concentration in T1DM subjects. However, available technologies for continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) use the subcutaneous (SC) route, which, despite the clear advantage of being minimally invasive, are far from being physiological and consequently, nonoptimal. The SC route introduces some extra difficulties to glucose control in the form of time delays in the glucose sensing and insulin action, measurement errors, and higher variability.[16,17] Nevertheless, these technologies are continuously improving, creating an optimistic future for the closed-loop insulin delivery system.

The idea of using a bio-inspired approach for BG control was first postulated by Steil and colleagues.[18] In this work, a minimal model of insulin secretion, proposed earlier by Breda and colleagues,[19] was used for BG control. This simple model represents the insulin secretion by decomposing it into a static rate of secretion, which

basically depends on the plasma glucose concentration, and a dynamic secretion rate (second phase), which depends on the rate of change of plasma glucose concentration (first phase). Steil and colleagues[18] compared the minimal model of insulin secretion with a PID controller, the behavior of which also exhibits biphasic response, and concluded that both were able to fit experimental data. However, the insulin secretion model was less stable than the PID controller under closed-loop conditions due to the simplification of the bio-inspired model. Work by our group[20] proposed the use of a model of the electrical activity of β cells for closed-loop glucose control, showing for the first time how this could be implemented using a semiconductor application-specific integrated circuit (ASIC) to form a silicon β cell. This was a first attempt at a true bionic pancreas but it still lacked detail in the model of insulin release.

Development of mathematical models of β-cell physiology,[21–24] which are able to describe the glucose-induced insulin release at a molecular level, have opened the door to a new class of bio-inspired glucose control algorithms. In this article, a novel glucose controller based on a more complete model of the β cell is presented and validated using the adult and adolescent T1DM virtual populations accepted by the United States Food and Drug Administration (FDA) as a substitute for animal trials.[25]

Methods

After a detailed study of existing glucose-stimulated pancreatic insulin secretion models, the model proposed by Pedersen and colleagues[24] was selected. Minimal models such as the ones proposed in Hovorka and colleagues,[26] Toffolo and colleagues,[27] Cretti and colleagues,[28] Mari and colleagues,[29] and Breda and colleagues[19] are not able to represent some of the experimental data, probably because of their excessively simplistic structure. On the other hand, more sophisticated models such as the ones proposed by Pederson and colleagues,[21] Bertuzzi and colleagues,[22] and Chen and colleagues[23] can be difficult to implement because of their high number of parameters and equations. The selected model is able to represent most of the experimental data, including the biphasic response of insulin secretion, the staircase modulation of insulin secretion, the potentiation effect of glucose, and the kiss-and-run effect of insulin secretion granules.[30] Furthermore, its relative simplicity makes it convenient for practical implementation. Despite this, the Pedersen model is still an incomplete description. Other known characteristics of the β cell not included in this model are as follows:[15] the β cell tends to oscillate or release insulin in discrete pulses; the β-cell's sensitivity to glucose may be altered depending on free fatty-acid levels; prior to meals, the β cell is stimulated to secrete insulin by neural signals, and during the meal, it is stimulated by gut hormones; and finally, β-cell secretion may be inhibited by the prevailing concentration of insulin in plasma.

Subcellular Model of Insulin Secretion

The selected model includes mobilization of secretory granules from a reserve pool to the cell periphery, where they attach to the plasma membrane (i.e., docking). The granules can mature further (i.e., priming), thus entering the readily releasable pool (RRP). Calcium influx triggers membrane fusion and subsequent insulin release. The possibility of so-called kiss-and-run exocytosis is included, where the fusion pore reseals before the granule cargo is released. The glucose-dependent increase in the number of cells showing a calcium signal[31] is included by distinguishing between readily releasable granules in silent and active cells. Therefore, the RRP is heterogeneous in the sense that only granules residing in cells with a threshold for calcium activity below the ambient glucose concentration are allowed to fuse. An overview of the model is given in **Figure 2**.

The insulin secretion rate is expressed as

$$SR(t) = mF(t) + SR_b, \quad (1)$$

where SR_b is the basal insulin secretion (not shown in **Figure 2**), m is the rate constant of insulin release, and F is the size of the fused pool. More details about the

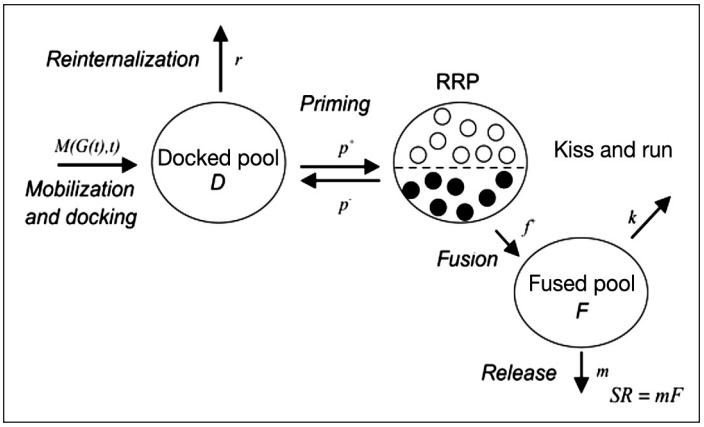

Figure 2. Schematic representation of the mechanistic model of insulin secretion from pancreatic β cells.[24] The readily releasable pool (RRP) has been divided into readily releasable granules located in silent cells with no calcium influx, exocytosis, or release (circles) and readily releasable granules located in triggered cells (dots).

employed model of insulin secretion can be found in **Appendix 1** and in the original publication[24] from which the parameter values used in the simulations were taken.

Intravenous Control

As an initial proof-of-concept for the proposed bio-inspired approach, the selected glucose-stimulated pancreatic insulin secretion model was used to control the 10-adult population of the commercial version of the T1DM simulator[25] using the intravenous (IV) route for glucose sensing and insulin delivery.

In order to deal with interpatient insulin sensitivity variability in the simulator, a tunable gain (K) was added to the dynamic term of **Equation 1**, replacing the constant gain m. Furthermore, as the model does not include the inhibition of the insulin secretion below basal glucose levels as well as the contraregulatory effect of the hormone glucagon, a variable gain (K_b) was added, multiplying the basal insulin secretion term in order to simulate such effect. Hence, the IV controller output (U_{iv}) is described as

$$U_{iv}(t) = \mathrm{K} \cdot F(t) + K_b \cdot SR_b, \quad (2)$$

where K_b is a variable gain that is calculated as

$$K_b = \min\left(1, \frac{G - G_{lim}}{G_{sp} - G_{lim}}\right) \quad (3)$$

where G_{sp} is the glucose setpoint (e.g., 90 mg/dl) and G_{lim} is the threshold to start the inhibition (e.g., 80 mg/dl).

To test the validity of the IV controller, a meal containing 75 g of carbohydrates was used. First, the basal insulin infusion rate was manually adjusted for each subject to keep the basal glucose levels close to 90 mg/dl. Then, the gain K was individually tuned to keep the 10 subjects inside the range [70, 200] mg/dl. **Figure 3** shows an example of IV control corresponding to adult #001.

Despite IV control being optimal from a control perspective, it is not a viable solution for an ambulatory artificial pancreas. The presented IV controller was thus tested *in silico* using the SC route for glucose sensing and insulin delivery but performance was not satisfactory. The main reason for this lack of performance was insulin overdosing caused by time delays and noise introduced by the SC route. For this reason, additional strategies were required.

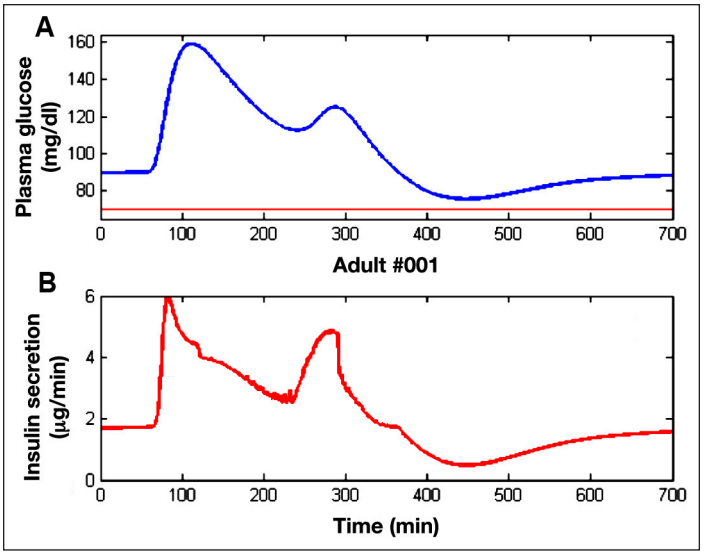

Figure 3. Example of IV control corresponding to adult #001. **(A)** Plasma glucose concentration corresponding to a meal containing 75 g of carbohydrates. Horizontal red line corresponds to the hypoglycemic threshold. **(B)** Insulin delivery proposed by the controller.

Subcutaneous Control

Available technologies for continuous glucose sensing and insulin delivery mainly use the SC route, the main problem of which is the time delays introduced on glucose sensing (up to 15 min) and insulin action (15–20 min). Furthermore, the variability of these delays can be high and the accuracy of available SC continuous glucose sensors is far from being optimal, with mean absolute differences of up to 20%,[2] especially in hypoglycemia, the critical state to avoid.

The aim of this work is to develop an SC closed-loop glucose controller based on the selected model of glucose-stimulated pancreatic insulin secretion, which is able to cope with the drawbacks introduced by the SC route.

Insulin Feedback

The main problem with delays in glucose sensing and insulin delivery is excess insulin overdosing and the consequent risk of hypoglycemia, in particular postprandially.

One solution to this problem is to incorporate an insulin feedback term as proposed by Steil and colleagues.[5] From a physiological point of view, this term can be seen as the inhibition of insulin secretion induced by the prevailing concentration of elevated plasma insulin levels. Mathematically speaking, this term reduces the β-cell model insulin delivery by an amount proportional to an estimate of the plasma insulin level (i.e., insulin-on-

board). Hence, the SC controller output (U_{sc}) is described as

$$U_{sc}(t) = K \cdot F(t) + SR_b - K_y I(t) \quad (4)$$

where $I(t)$ is an estimate of the plasma insulin concentration (relative to the basal conditions) and K_y is a tuning gain. In order to simulate the insulin absorption pharmacodynamics and estimate the plasma insulin concentration, the insulin absorption model proposed by Hovorka and colleagues[6] was employed. The parameters of this model were fixed to mean population values proposed by the same author. Note that the variable gain (K_b) multiplying the basal insulin secretion term is not included anymore in the SC controller equation.

Gain Scheduling

One of the main challenges when controlling glucose levels in T1DM subjects is the glucose excursion after the ingestion of a meal. Due to the delays mentioned earlier, the controller needs to be more aggressive at the beginning of the glucose excursion in order to minimize postprandial hyperglycemia. On the other hand, during late postprandial or fasting conditions, the controller needs to be less aggressive to minimize the risk of insulin stacking. Furthermore, the effect of the sensor noise at low glucose levels is more critical than at high levels (>180 mg/dl); hence, the controller has to be more, or less, conservative depending on the operation region.

For this reason, instead of a single gain (K), three different gains (K_p, K_h, and K_f) were considered: K_p is used just for a certain period of time (T_p) after the ingestion of a meal; K_h is used at all other times when the glucose concentration is above a threshold (180 mg/dl); and K_f is used otherwise. Note that snacks (i.e., <20 g of carbohydrates) are not considered as proper meals and the gains K_f or K_h are used.

$$\begin{gathered} \text{if } t > T_{meal} \text{ and } t < T_{meal} + T_p \; K = K_p \\ \text{else if } G(t) > 180 \text{ mg/dl } K = K_h \\ \text{else } K = K_f \end{gathered} \quad (5)$$

Note that in order to apply the gain scheduling strategy described earlier, meal announcement or meal detection[32] is required.

Hypoglycemia Prevention

In order to prevent and minimize hypoglycemia, a safety mechanism is used on top of the glucose controller that suppresses or reduces insulin delivery when low glucose values are predicted.[33] This mechanism consists of forecasting the glucose concentration (e.g., 20 minutes ahead) and stopping or reducing insulin delivery [$U_{sc}(t)$] if glucose levels fall below a predefined threshold. Although more sophisticated algorithms for glucose forecasting exist,[33] a simple in-house linear one has been proposed for the current version of the safety mechanism and for short-term prediction horizons (e.g., 20 minutes). The safety mechanism is defined as

$$\begin{gathered} \text{if } G(t) + S \cdot H < 70 \text{ mg/dl} \Rightarrow U_{sc}(t) = 0, \\ \text{else if } G(t) + S \cdot H < 90 \text{ mg/dl} \Rightarrow U_{sc}(t) = 0.5U_{sc}(t), \end{gathered} \quad (6)$$

where $G(t)$ is the current glucose value, H is the forecasting horizon, and S is the glucose rate-of-change calculated as the slope of a linear regression using previous n samples.

Figure 4 shows the block diagram of the presented bio-inspired glucose controller and **Figure 5** show an example of insulin delivery by the bio-inspired glucose controller. Notice that a partial bolus calculator block is included to account for whether a partial insulin bolus is administered manually or automatically.[34]

Control Tuning

In order to achieve optimal control for each one of the T1DM subjects, the controller needs to be individually tuned. First of all, basal insulin requirements for the studied subject are required to optimize glycemia. However, the controller is able to tackle possible mismatches on the basal insulin profile as well as possible perturbations such as exercise.

The controller parameters to be tuned are: gains K_f, K_h, and K_p; period T_p for which post-prandial gain (K_p) is valid; insulin feedback gain (K_y); number of samples used for linear regression (n); and forecasting horizon (H). Also tunable is glucose setpoint (G_{sp}). After several *in silico* tests with the T1DM simulator, it was observed that most of these parameters have small intersubject variability and can be fixed without significantly affecting the performance. The only parameter that needs to be individually tuned is the gain K_p, since the gains K_f and

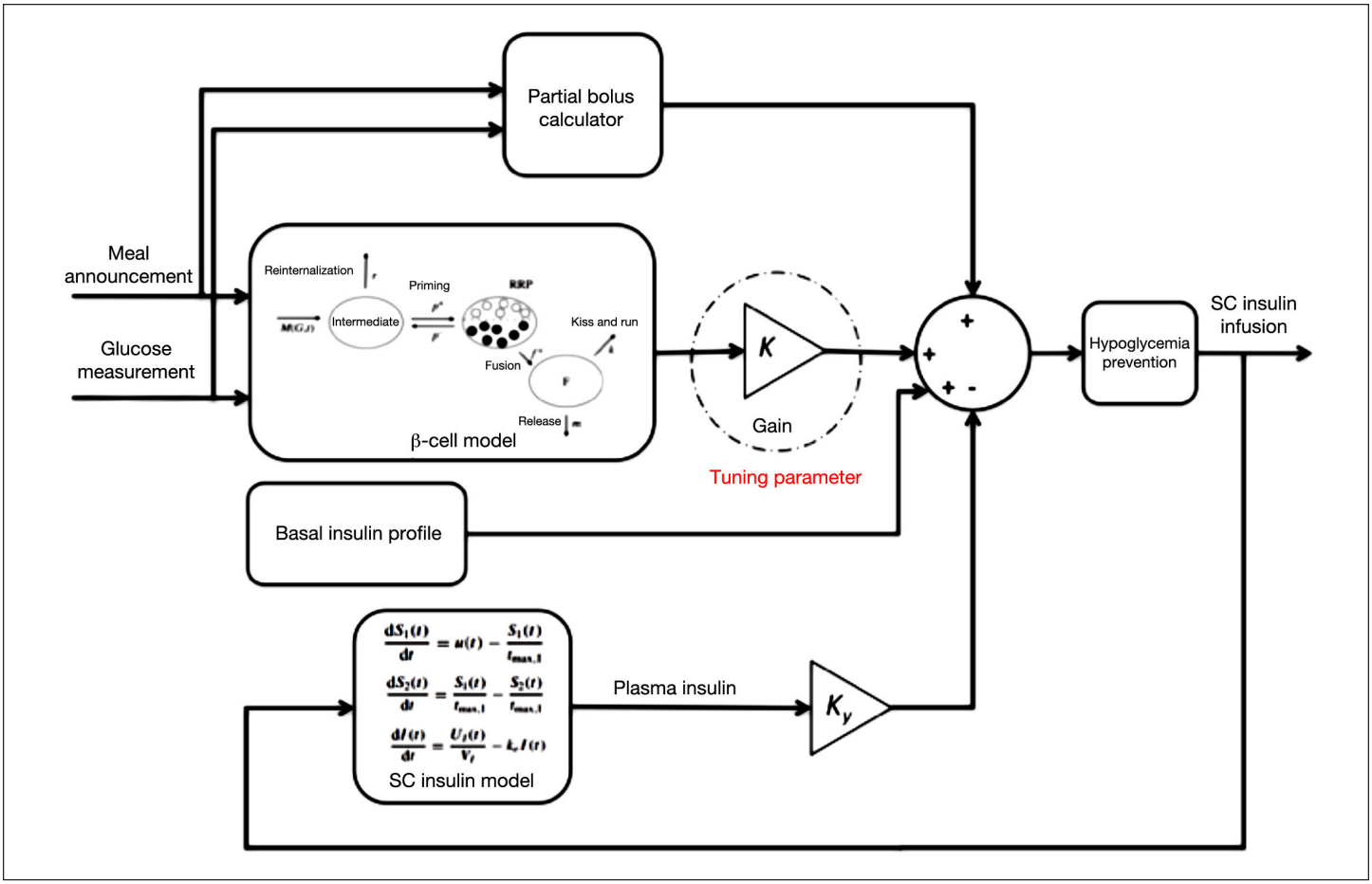

Figure 4. Block diagram of the presented bio-inspired glucose controller.

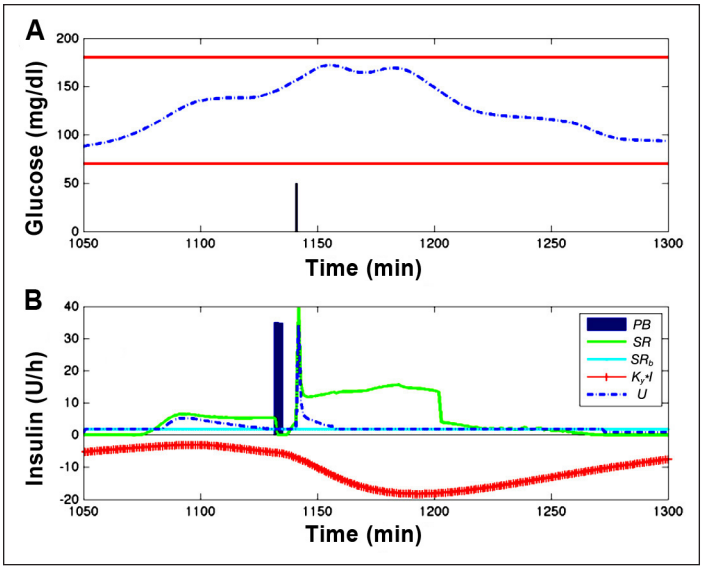

Figure 5. Example of insulin delivery by the SC bio-inspired glucose controller. **(A)** Subcutaneous glucose measurements (dashed blue line); hyper- and hypoglycemia thresholds (red horizontal lines) and meal (bars). **(B)** premeal partial bolus (*PB*, blue bar); β-cell model insulin secretion (*SR*, solid green line); basal insulin (SR_b, solid cyan line); insulin feedback (K_y**I*, crossed red line), and delivered insulin (*U*, blue dashed line).

K_h can be set to be proportional to K_p. **Table 1** shows the employed fixed values used for the control of the T1DM simulator population.

For evident safety reasons, it is not possible to tune parameter K_p during an *in vivo* study; hence, an off-line autotuning methodology was implemented for this purpose. This methodology requires open-loop historical

Table 1.
Tuning Parameters Used for the Simulations

Parameter	Value
K_y	15
T_p	60 min
K_h	$0.5K_p$
K_f	$0.2K_p$
n	30 min
H	20 min
G_{sp}	100 mg/dl

data from the studied subject (i.e., meal information, continuous glucose monitor, and insulin pump data) corresponding to a good glucose control scenario and similar conditions with respect to the planned closed-loop test (i.e., similar meals, time of the day, exercise, etc). The autotuning methodology consists of an optimization algorithm that adjusts the K_p gain such that for the given glucose profile, the controller delivers the same amount of insulin that was administered during the open-loop scenario.

To obtain the required open-loop data for tuning the controller, the metabolic test function from the T1DM simulator was employed. The employed scenario consisted of a 24-h scenario with a single meal of 60 g of carbohydrates ingested 3 h after the beginning of the scenario. The basal insulin rate (SR_b) was adjusted to achieve a basal glucose concentration close to the glucose setpoint (i.e., 100 mg/dl). This was achieved by using the metabolic test function provided by the T1DM simulator under fasting conditions. Note that in a real scenario, this basal insulin rate could correspond to the basal insulin profile that is programmed in an insulin pump, which could be fine-tuned, using existing CGM data and pump data, to the correct basal rates at initiation and this will be within tolerance.

Furthermore, the proposed controller, although not a classic closed-loop control algorithm, behaves in a similar way to others (i.e., PID controller)[35] and consequently can manage changes in basal insulin requirement. This ability is partially due to the so-called potentiation effect,[30] i.e., the fact that after a prolonged glucose stimulus, the pancreas is hypersensitive to further stimulation (see **Figure 1**), which could be seen as the integral component of a PID controller.[35]

Finally, the insulin-to-carbohydrate ratio was adjusted in order to achieve a postprandial inverse response (i.e., undershoot) close to 80 mg/dl. The resulting glucose profile was then used to tune the controller. The *fmincon* function from the MATLAB Optimization Toolbox™ (2010b, The MathWorks, Natick, MA) was used to find the gain (K_p) that minimizes the following cost function:

$$J = \int_0^T U_{sc}(t)dt - \left(SR_b T + \frac{CHO}{ICR} \right), \qquad (7)$$

where T is the duration of the scenario (i.e., 24 h), CHO is the amount of ingested carbohydrates (i.e., 60 g), and ICR is the calculated insulin-to-carbohydrate ration.

In Silico *Validation*

The commercial version of the T1DM simulator (30 subjects) was initially used to design and tune the presented bio-inspired controller. Then, the controller was tested by the Epsilon Group (University of Virginia, VA) using the 100 adults and 100 adolescents of the FDA-accepted population for the same simulator. The controller was tested according to a scenario published earlier.[36] Simulation testing was performed for each population with the prescribed meal/snack profiles given over 43 h (including a 7 h warm-up period) with simulation beginning at 5:00 p.m. and continuing until 12:00 p.m. on the second day. The Abbott Navigator® CGM sensor (Abbott Park, Illinois) and the Smiths Medical Deltec Cozmo® insulin pump (St. Paul, MN) were selected to carry out the simulations. The BG target range used for analysis was 70–180 mg/dl.

The safety and efficacy measures were as follows[37] [presented as mean ± standard deviations (SD)]: the primary outcome was mean BG (mg/dl); secondary outcomes were percentage of time in extreme hypoglycemia (BG < 50 mg/dl); percentage of time and incidence below range (any BG < 70 mg/dl); percentage of time within the 70–180 mg/dl target range; percentage of time above range in hyperglycemia (BG > 180 mg/dl); percentage of time in extreme hyperglycemia (BG > 300 mg/dl); postprandial area under the curve (AUC) per grams of carbohydrates (CHO); low blood glucose risk index (LBGI); high blood glucose risk index (HBGI); blood glucose risk index (BGRI). Finally, the control-variability grid analysis (CVGA) graphs[38] were used.

Results

Table 2 shows a summary of the corresponding safety and efficacy measures. **Figure 6** and **Figure 7** show the CVGA graphs for both the adult and adolescent FDA-accepted simulation populations.

The overall, premeal and postmeal mean ± SD BG levels for the adult and adolescent populations were well within the target range set for the controller, with a percentage of time in range of 92.8 ± 7.3% for the adults and 83.5 ± 14% for the adolescents.

Adult subjects did not experience a single episode of extreme hypoglycemia, with 6% experiencing BG < 70 mg/dl for a mean of 0.4%. The adolescent population also experienced minimal extreme hypoglycemia (2.0% of subjects for 0.1% of time) but slightly more hypoglycemia <70 mg/dl (21% of subjects for 1.7% of time). The CVGA

Table 2.
Safety and Efficacy Measures for the FDA-Accepted Simulation Population with the Bio-Inspired Controller

BG analysis target range 70–180 mg/dl	FDA-accepted adults			FDA-accepted adolescents		
	Mean	SD	Median	Mean	SD	Median
Mean BG	125	12	121	133	17	131
Mean premeal BG	111	11	109	113	12	111
Mean postmeal BG	155	22	152	174	29	169
% Time <50	0.00	0.00	0.00	0.09	0.74	0.00
% Time <70	0.44	2.25	0.00	1.74	4.93	0.00
% Time in range	92.82	7.32	94.2	83.53	13.98	86.4
% Time >180	6.74	6.95	5.25	14.73	11.95	11.74
% Time >300	0.09	0.52	0.00	0.87	2.32	0.00
Postprandial AUC / g CHO	0.64	0.07	0.63	0.70	0.10	0.68
LBGI	0.46	0.41	0.38	0.77	0.81	0.58
HBGI	1.77	1.37	1.34	3.32	2.53	2.55
BGRI	2.23	1.32	1.82	4.08	2.77	3.57
SD of BG rate of change	0.75	0.25	0.70	1.05	0.39	1.03

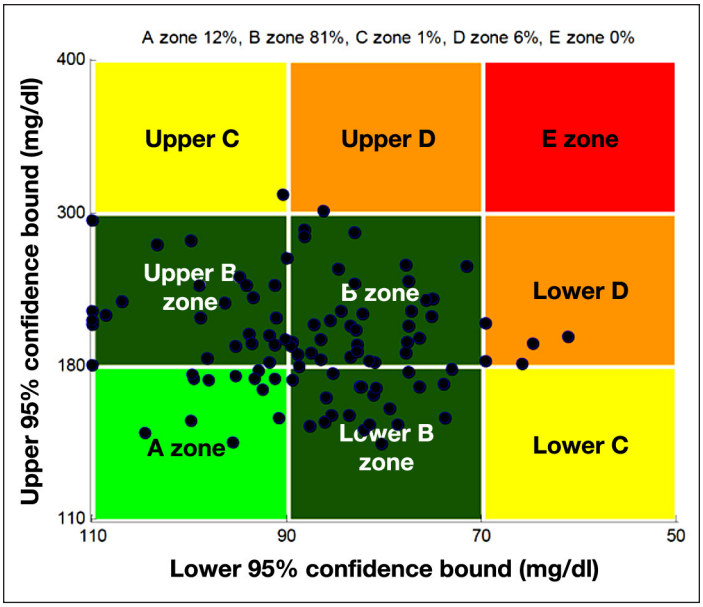

Figure 6. CVGA graph for the FDA-accepted adult population.

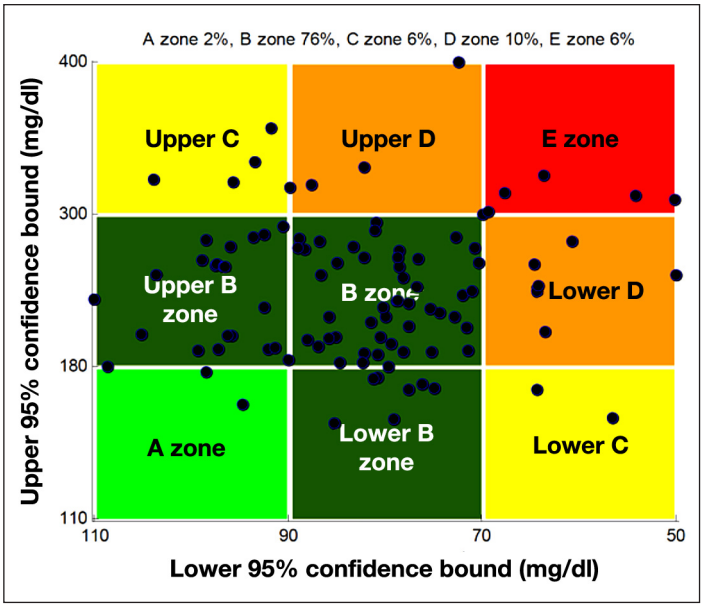

Figure 7. CVGA graph for the FDA-accepted adolescent population.

graphs showed 67.0 ± 17% of time in zones A + B, which is good for the adolescent population, with 1.3 ± 3.1% in failure zones D + E.

Adult population data documenting hyperglycemia (BG > 180 mg/dl and BG > 300 mg/dl) showed a low rate of hyperglycemia with 6.7 ± 7.0% for BG > 180 mg/dl and < 0.1 ± 0.5% of extreme hyperglycemia, resulting in an HBGI risk of 1.8 ±1.6. Adolescent subjects had a mean 14.73 ± 12% of time in hyperglycemia >180 mg/dl, with 3.3 ± 2.5 HBGI risk.

The total risk index was found to be low at 2.2 ± 1.3 for the adults, and while higher for the adolescents (4.1 ± 2.8), was also low overall. These data demonstrate that the bio-inspired controller was able to avoid hypoglycemia in most subjects with minimal hyperglycemia risk with meal announcement alone.

Discussion

The presented bio-inspired glucose controller has been shown to be a valid approach for an ambulatory artificial pancreas using the available technologies for glucose sensing and insulin delivery.

The presented bio-inspired controller only requires the meal to be announced by the user, something that can be done easily by just pressing a button. In the case of a meal not being announced, the controller will react less aggressively, something that will translate into less optimal control (i.e., hyperglycemia) but will not expose the user to a higher risk of hypoglycemia. Note that for a fully automated system, a meal-detection algorithm[30] could be employed. However, the utilization of such an algorithm would introduce an additional time delay and the consequent risk of false positives.

While the obtained results are good from a clinical point of view, they are still suboptimal in some cases, in part, due to the limitations of the available technologies (i.e., CGM and CSII). Nevertheless, the constant improvement of continuous glucose sensors as well as the development of faster insulin analogs provide hope for improvement.

The employed T1DM simulator covers a wide range of scenarios in a T1DM population. However, it still has some limitations. For instance, it is not able to represent the insulin sensitivity variations during the day and does not incorporate the effect of exercise on insulin requirements. For this reason, clinical trials are planned to validate the controller in a real population of T1DM subjects under different environmental conditions.

Conclusion

In this article, a novel bio-inspired glucose controller based on a model of the β-cell physiology is presented. Technologies for sensing glucose levels and delivering insulin use the subcutaneous route, which make the use of β-cell physiology models not straightforward, requiring additional strategies to make the approach viable.

The developed controller performed very well in the simulations with very good glucose control, with limited hypoglycemia and minimum hyperglycemia.

The presented controller has already been embedded in a portable prototype of an artificial pancreas, which includes the electronic instrumentation to interface with a continuous glucose sensor. Furthermore, the prototype has been successfully tested in a hardware-in-the-loop platform including the T1DM simulator. Finally, clinical trials with T1DM subjects are planned to validate the bio-inspired glucose controller together with the whole artificial pancreas architecture.

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Appendix 1

Mobilization is assumed to depend on glucose concentration (G) but with a delay τ, as proposed by Grodsky:[31]

$$\frac{dM(t)}{dt} = \frac{M_\infty(G) - M(t)}{\tau} \tag{8}$$

The docked pool develops according to the mass-balance equation

$$\frac{dD(t)}{dt} = M(G,t) - rD(t) - p^+D(t) + p^- \int_0^\infty h(g,t)dg \tag{9}$$

where M is the mobilization flux and r is the rate of reinternalization. The last two terms describe priming and depriming of granules, respectively.

The RRP is described by a time-varying density function $h(g,t)$, indicating the amount of insulin in the RRP in β cells with a threshold between g and $g + dg$. Granules are primed with rate p^+ and are assumed to lose the capacity of rapid exocytosis with rate p^-. Moreover, if the granule is in a triggered β cell, i.e., a cell with a threshold below the glucose concentration, it will fuse with rate f^+. This leads to the equation

$$\frac{\partial h(g,t)}{\partial t} = p^+D(t) - p^-h(g,t) - f^+h(g,t)\theta(G - g) \tag{10}$$

Here, $\theta(G - g)$ is the Heaviside unit step function, which is 1 for $G > g$ and zero otherwise, indicating that fusion occurs only when the threshold is reached. The priming flux p^+D distributes among cells according to the fraction of cells with threshold g described by the time-independent function $\varphi(g)$. Thus, priming is assumed to occur with the same rate in all cells but the fraction of cells with the corresponding threshold is taken into account.

The secretion rate can be expressed as

$$SR(t) = m \cdot F(t) + SR_b \tag{11}$$

where SR_b is basal insulin secretion, m is the rate constant of release, and F is the size of the fused pool, which follows

$$\frac{dF(t)}{dt} = f^+ \cdot \int_0^\infty h(g,t) \cdot dg - [k + m] \cdot F(t) \tag{12}$$

where f^+ is the rate constant of fusion and k is the kiss-and-run rate. The integral represents the amount of insulin in the RRP in cells with a threshold below G.