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ORIGINAL ARTICLE

A Composite Model of Glucagon–Glucose Dynamics for *In Silico* Testing of Bihormonal Glucose Controllers

Pau Herrero, Ph.D.,[1] Pantelis Georgiou, Ph.D.,[1] Nick Oliver, M.B.B.S., M.R.C.P.,[2] Monika Reddy, M.B.Ch.B., M.R.C.P.,[2] Desmond Johnston, F.Med.Sci.,[2] and Christofer Toumazou, F.R.S.[1]

Abstract

Background:

The utility of simulation environments in the development of an artificial pancreas for type 1 diabetes mellitus (T1DM) management is well established. The availability of a simulator that incorporates glucagon as a counterregulatory hormone to insulin would allow more efficient design of bihormonal glucose controllers.

Existing models of the glucose regulatory system that incorporates glucagon action are difficult to identify without using tracer data. In this article, we present a novel model of glucagon–glucose dynamics that can be easily identified with standard clinical research data.

Methods:

The minimal model of plasma glucose and insulin kinetics was extended to account for the action of glucagon on net endogenous glucose production by incorporating a new compartment. An existing subcutaneous insulin absorption model was used to account for subcutaneous insulin delivery. The same model of insulin pharmacokinetics was employed to model the pharmacokinetics of subcutaneous glucagon absorption. Finally, we incorporated an existing gastrointestinal absorption model to account for meal intake. Data from a closed-loop artificial pancreas study using a bihormonal controller on T1DM subjects were employed to identify the composite model. To test the validity of the proposed model, a bihormonal controller was designed using the identified model.

Results:

Model parameters were identified with good precision, and an excellent fitting of the model with the experimental data was achieved. The proposed model allowed the design of a bihormonal controller and demonstrated its ability to improve glycemic control over a single-hormone controller.

Conclusions:

A novel composite model, which can be easily identified with standard clinical data, is able to account for the effect of exogenous insulin and glucagon infusion on glucose dynamics. This model represents another step toward the development of a bihormonal artificial pancreas.

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Author Affiliations: [1]Center for Bio-Inspired Technology, Department of Electrical and Electronic Engineering, Institute of Biomedical Engineering, Imperial College London, South Kensington Campus, London, United Kingdom; and [2]Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom

Abbreviations: (IVGTT) intravenous glucose tolerance test, (PD) proportional derivative, (T1DM) type 1 diabetes mellitus

Keywords: artificial pancreas, bihormonal control, glucagon, in silico testing, minimal model

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

Introduction

In silico validation of glucose controllers[1–3] is a valuable tool for the progression of artificial pancreas development for type 1 diabetes mellitus (T1DM) management.[4] Current available simulators[5–7] incorporate only insulin as a regulatory hormone, and do not take account of other regulatory hormones such as glucagon. These simulators are therefore not suitable for designing and testing bihormonal controllers for artificial pancreas design that incorporate both insulin and glucagon.[8–10]

Different attempts have been made to incorporate the glucagon effect in models of the glucose regulatory system. Several complex mathematical models of the endocrine–metabolic system incorporating this have been proposed.[11–13] However, the complexity of these models, with a high number of equations and parameters, makes them difficult to identify and, therefore, impractical for design.

An augmented minimal model was proposed that incorporates the glucagon effect.[14] However, this model is simplistic and is only compared against Sorensen's model,[11] with no validation using clinical data shown. Bequette[15] presented a comprehensive model for glucagon–glucose dynamics. However, details for this model are not available.

In this article, we propose a novel composite model of glucagon–glucose dynamics for *in silico* validation of artificial pancreas bihormonal controllers. This is a modification of the Bergman minimal model[16] by addition of a compartment to account for the pharmacodynamics of glucagon on the net endogenous glucose production, incorporation of an existing insulin absorption model[17] to include the effects of subcutaneous glucagon and insulin delivery on plasma glucagon and insulin concentrations, and, finally, the addition of a gastrointestinal absorption model[17] to account for meal ingestion.

Data from a closed-loop artificial pancreas study using a bihormonal controller on T1DM subjects were employed to identify our composite model.[8]

Finally, an example of utilization of the proposed model is shown through the design and testing of a bihormonal glucose controller.

Methods

The Minimal Model of Glucose Kinetics

The minimal model of plasma glucose and insulin kinetics was developed in the late 1970s by Bergman and coauthors[16] to investigate glucose metabolism *in vivo* in physiological, pathological, and epidemiological studies from a standard intravenous glucose tolerance test (IVGTT). The standard IVGTT consists of injecting glucose over a period of 30–60 s and measuring the resulting plasma glucose and insulin concentrations. To interpret IVGTT data, it is necessary to explicitly describe not only glucose disappearance, but also endogenous production—or at least net endogenous glucose balance—depending on glucose and insulin, since endogenous sources of glucose (liver and kidney) are contributing to the measured plasma glucose concentration. The minimal model does so as shown in **Figure 1**, where $k_{1–6}$ are rate constants characterizing either material fluxes (solid lines) or control actions (dashed lines) and D is an exogenous glucose administration.

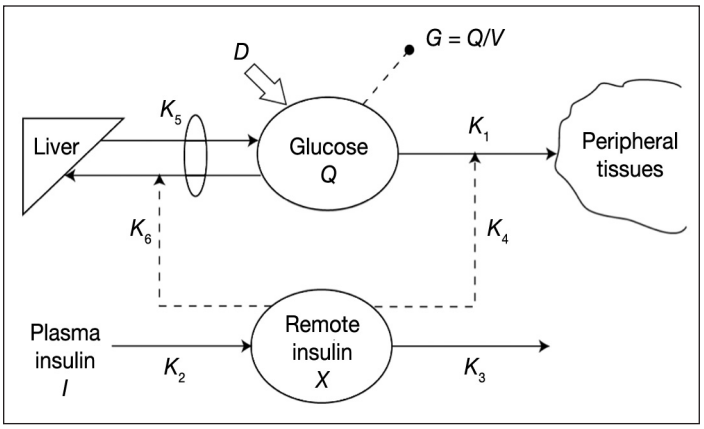

Figure 1. The minimal model of glucose kinetics. $K_{1–6}$ are rate constants characterizing either material fluxes (solid lines) or control actions (dashed lines).

To make the model uniquely identifiable, it needs to be reparameterized as follows:

$$\dot{G}(t) = -[S_G + X(t)]\, G(t) + S_G G_b, \tag{1}$$

$$\dot{X}(t) = -p_2\, X(t) + p_2 S_I\, [I(t) - I_b], \tag{2}$$

where

$$S_G = k_1 + k_5, \tag{3}$$

$$p_2 = k_3, \tag{4}$$

$$S_I = \frac{k_2}{k_3}(k_4 + k_6), \tag{5}$$

and G (mg/dl) is plasma glucose concentration with $G(0) = G_b$, where suffix b denotes basal value; I is plasma insulin concentration with $I(0) = I_b$; X is insulin action on glucose production and disposal, with $X(0) = 0$; S_G (min^{-1}) is fractional (i.e., per unit distribution volume) glucose effectiveness, which measures glucose ability *per se* to promote glucose disposal and inhibit glucose production (min^{-1}); S_I is insulin sensitivity, measuring the ability of insulin to enhance the glucose *per se* stimulation of its disappearance and the glucose *per se* inhibition of endogenous production (min^{-1} per μU/ml); and p_2 is the rate constant describing the dynamics of insulin action (min^{-1}).

The Glucagon-Extended Minimal Model of Glucose Kinetics

Following a similar approach to the one used in the development of the minimal model, an additional compartment was added to account for the pharmacodynamics of exogenous glucagon on net endogenous glucose production. **Figure 2** graphically shows the structure of the proposed glucagon-extended minimal model.

The equations describing the proposed glucagon-extended minimal model are

$$\dot{G}(t) = -[S_G + X(t) - Y(t)]\, G(t) + S_G\, G_b, \tag{6}$$

$$\dot{Y}(t) = -p_3\, Y(t) + p_3\, S_N\, [N(t) - N_b], \tag{7}$$

where

$$p_3 = k_8, \tag{8}$$

$$S_N = \frac{k_7}{k_8}\, k_9, \tag{9}$$

and Y is glucagon action on glucose production, with $Y(0) = 0$; N is plasma glucagon concentration (pg/ml), where suffix b denotes basal value; S_N is glucagon sensitivity, which measures the ability of glucagon to enhance endogenous glucose production by the liver (min^{-1} per pg/ml); and p_3 is the rate constant describing the dynamics of glucagon action (min^{-1}).

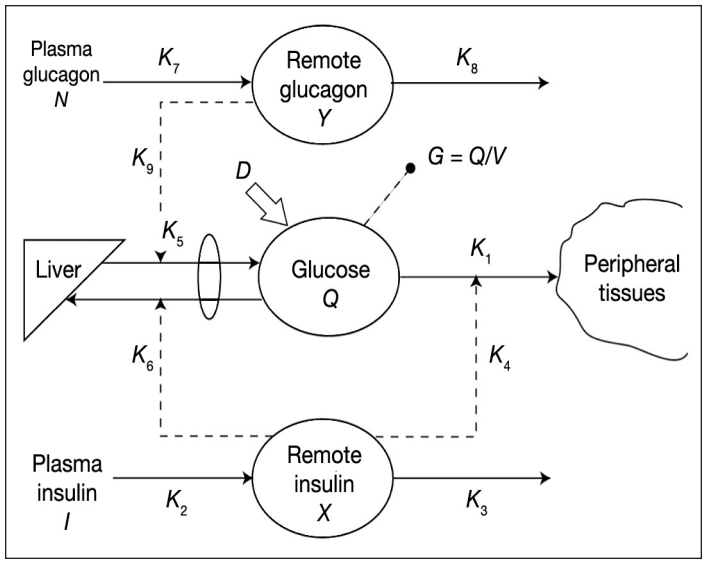

Figure 2. The glucagon-extended minimal model. $K_{1–9}$ are rate constants characterizing either material fluxes (solid lines) or control actions (dashed lines).

The Glucagon–Glucose Composite Model

The glucagon secretory response of α cells to low glucose concentrations is impaired in T1DM and long-standing type 2 diabetes mellitus, increasing the risk of severe hypoglycemia, especially in subjects with diabetes treated with insulin.[18] Therefore, subjects with diabetes may require exogenous delivery of glucagon, or glucose, to address hypoglycemia.

The minimal model of plasma glucose and insulin kinetics, in combination with a subcutaneous insulin absorption model and a gastrointestinal absorption model, has already been used to estimate blood glucose levels in T1DM.[19,20] However, this model fails to estimate blood glucose levels when exogenous glucagon is delivered. We propose an extension of the minimal model to account for this effect.

With the aim of building a model of the glucose regulatory system of a subject with T1DM that allows the testing of a bihormonal glucose controller, a gastrointestinal absorption model, a subcutaneous insulin absorption model, and a subcutaneous glucagon absorption model were added to the glucagon-extended minimal model.

Gastrointestinal Absorption Model

The gastrointestinal absorption model presented by Hovorka and coauthors[17] was incorporated to the glucagon-extended minimal model to account for the glucose rate of appearance into the systemic circulation after the ingestion of a meal. The equations representing such a model are

$$\dot{F}(t) = \frac{1}{t_{maxG}}(-F(t) + A_G D_G), \tag{10}$$

$$\dot{R}_{a(t)} = \frac{1}{t_{maxG}}(-R_a(t) + F(t)), \tag{11}$$

where R_a (mg/min/kg) is plasma appearance of glucose, F is glucose appearance in the first compartment, A_G is carbohydrate bioavailability (unitless), and D_G (mg) is the amount of carbohydrates ingested at meal time t_{meal} (min).

The resulting equation representing the glucagon-extended minimal model is expressed by

$$\dot{G}(t) = -[S_G + X(t) - Y(t)]\, G(t) + S_G G_b + \frac{R_a}{V}, \tag{12}$$

where V is the glucose distribution volume (dl/kg).

Subcutaneous Insulin Absorption Model

To estimate plasma insulin concentration I (μU/ml) due to subcutaneous insulin infusion, an existing model of subcutaneous insulin absorption[17] was employed. The equations of such a model are

$$\dot{I}(t) = -k_e\, I(t) + \frac{S_2(t)}{V_I t_{maxI}} \tag{13}$$

$$\dot{S}_1(t) = u(t) - \frac{S_1(t)}{t_{maxI}} \tag{14}$$

$$\dot{S}_2(t) = \frac{S_1(t) - S_2(t)}{t_{maxI}} \tag{15}$$

where, k_e (min) is the first-order decay rate for insulin in plasma, u (μU/kg) is the subcutaneous insulin infusion rate, V_I (ml/kg) is the distribution volume of plasma insulin, t_{maxI} (min) is the time-to-maximum insulin absorption, and S_1 and S_2 are a two-compartment chain representing absorption of subcutaneously administered short-acting analog insulin (e.g., lispro).

Subcutaneous Glucagon Absorption Model

Assuming that the pharmacokinetics of subcutaneous glucagon absorption can be modeled by the same model structure as the one proposed for subcutaneous insulin absorption by Hovorka and coauthors,[17] plasma glucagon concentration N (pg/ml) was estimated as

$$\dot{N}(t) = -k_N N(t) + \frac{Z_2(t)}{V_N t_{maxN}} \tag{16}$$

$$\dot{Z}_1(t) = w(t) + \frac{Z_1(t)}{t_{maxN}} \quad (17)$$

$$\dot{Z}_2 = \frac{Z_1(t) - Z_2(t)}{t_{maxN}} \quad (18)$$

where k_N (min^{-1}) is the first-order decay rate for glucagon in plasma, w (ng/kg) is the subcutaneous glucagon infusion rate, V_N (ml/kg) is the distribution volume of plasma glucagon, t_{maxN} (min) is the time-to-maximum glucagon absorption, and Z_1 and Z_2 are a two-compartment chain representing absorption of subcutaneously administered glucagon.

Data

Data from a closed-loop artificial pancreas study using a bihormonal controller on T1DM subjects were employed.[8] In particular, the data sets corresponding to subjects 117-1, 126-1, and 128-1 were selected. The criterion for selecting these data sets was that no additional carbohydrates to the predefined protocol were provided to prevent hypoglycemia and that sufficient glucagon was administered in order to appreciate its effect on glucose dynamics. The duration of the trial was 26 h, starting at 15:00 h. Venous blood glucose, plasma insulin, and plasma glucagon were measured at intervals of 5, 15, and 10 min, respectively. The corresponding meal protocols (i.e., ingestion time and ingested carbohydrates) and the body weight of the subjects are shown in **Table 1**. More information about the meal protocols and details about the control algorithm can be found from El-Khatib and coauthors.[8]

Parameter Identification

Table 1.
Meal Protocols of the Selected Data Sets and Body Weight of the Corresponding Subjects

Data set	Dinner (18:00 h), g	Breakfast (07:00 h), g	Lunch (12:00 h), g	Body weight, kg
117-1	108	80	80	85
126-1	87	64	64	68.6
128-1	144	107	107	94.8

Identification of the model parameters was performed following a similar methodology to the one proposed by Kanderian and coauthors[6] and summarized in three steps:

Step 1: The known insulin (glucagon) delivery rates were used to estimate parameters of the insulin (glucagon) absorption model [**Equations (13)–(15)** and **Equations (16)–(18)**]. Parameters k_e, t_{maxI}, and V_I (k_N, t_{maxN}, and V_N) were identified in each of the three data sets by minimizing the sum square error between the model-predicted plasma insulin (I_p) [glucagon *(N)*] concentration and the measured concentration. Since basal plasma insulin (I_b) and basal plasma glucagon (N_b) concentrations are *a priori* unknown, they were also identified. It is important to note that both models represent increments with respect to the basal concentrations.

Step 2: Because no independent data of the glucose rate of appearance were available, the glucagon-extended minimal model was simultaneously identified with the gastrointestinal absorption model. To minimize identifiability issues due to the elevated number of parameters to be identified, the following assumptions were made. For the glucagon-extended minimal model, parameters *SG* and *V* were fixed to the mean T1DM population values reported by Krudys and coauthors[21] (i.e., $SG = 0.014$ min^{-1} and $V = 1.7$ dl/kg) since, as reported by Dalla Man and coauthors,[22] the variability of these parameters is low. For the gastrointestinal absorption model, the carbohydrate bioavailability (f) was assumed to be 0.9, because this is a standard value for mixed meals.[22] Basal glucose concentration G_b was set to the bihormonal controller set point (i.e., 100 mg/dl).

Plasma insulin and plasma glucagon concentration were interpolated and used as inputs to **Equations (2)** and **(7)** and carbohydrate content as input to **Equations (10)–(12)**. Parameters p_2, S_I, p_3, S_N, and t_{maxG} were then estimated by minimizing the sum square error between the measured plasma glucose and model prediction [**Equation (12)**].

Minimization was performed considering intraday variation in the parameters (i.e., circadian rhythm). Three different time windows were considered for this purpose, each one containing one of the three ingested meals and sufficient

glucagon administration in order to appreciate its effect on glucose dynamics. In particular, the following windows were selected: 15:00–05:00, 05:00–12:00, and 12:00–18:00.

Step 3. Each fit (i.e., time window) from the procedures in step 2 was assessed for adequacy according to three criteria:

1. root mean square error between the fitted glucose profile and the measured plasma glucose profile was required to be less than 25 mg/dl;

2. peak postprandial glucose and the peak model predicted glucose were required be within 25 mg/dl following each meal ($\Delta G_{peak} < 25$ mg/dl), with the peak values needing to be within 30 min of each other ($\Delta T_{peak} < 30$min); and

3. nadir glucose for excursions of plasma glucose below 80 mg/dl were required to be predicted by the model to within 15 mg/dl ($\Delta G_{nadir} < 15$ mg/dl), with the nadirs occurring within 30 min of each other ($\Delta T_{nadir} < 30$ min).

All models were numerically identified by nonlinear least squares[23] as implemented in *lsqnonlin* optimization routine from the Matlab Optimization Toolbox and numerically integrated using the Matlab *ode45* differential equation solver (2010b, Matworks, Natick, MA).

Results

Subcutaneous Insulin Absorption Model Identification

Table 2 shows the values (i.e., mean ± 1 standard deviation provided by the *lsqnonlin* routine) for the identified subcutaneous insulin absorption model parameters corresponding to the three studied subjects. **Figure 3** graphically shows the fitting of the model with the experimental measurements for subject 117-1.

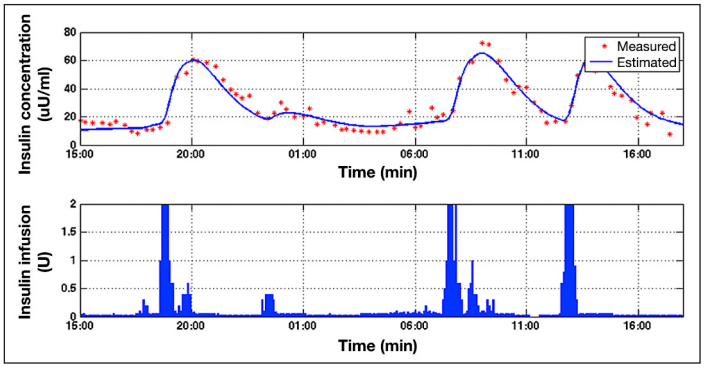

Figure 3. Fitting of the subcutaneous insulin absorption model to the experimental measurements corresponding to subject 117-1. (Upper) Measured mean plasma insulin concentration (red dots) and estimated plasma insulin concentration (solid blue line). (Lower) Insulin infusion (blue bars).

Subcutaneous Glucagon Absorption Model Identification

Table 3 shows the values for the identified subcutaneous glucagon absorption model parameters corresponding to the three studied subjects. **Figure 4** graphically shows the fitting of the model with the experimental measurements for subject 117-1. It is important to note that data from hour 16:00 onward were discarded because of a suspicion of glucagon pump failure.

Table 2.
Subcutaneous Insulin Absorption Model Estimated Parameters (Mean ± 1 Standard Deviation), Coefficient of Determination (R^2), and Root Mean Square Error

Parameter	117-1	126-1	128-1
K_e (min^{-1})	0.196 ± 0.127	0.171 ± 0.126	0.217 ± 0.161
V_I (ml/kg)	21.10 ± 9.39	17.33 ± 8.38	25.17 ± 13.03
t_{maxI} (min)	54.36 ± 1.43	57.63 ± 1.65	58.03 ± 1.31
I_b (μU/ml)	11.01 ± 0.45	19.76 ± 0.80	10.03 ± 0.25
R^2 (%)	93.3	91.1	83.1
Root mean square error (μU/ml)	4.5	7.1	4.7

Table 3.
Subcutaneous Glucagon Absorption Model Estimated Parameters (Mean ± 1 Standard Deviation), Coefficient of Determination (R^2), and Root Mean Square Error

Parameter	117-1	126-1	128-1
K_N (min^{-1})	0.62 ± 0.38	0.383 ± 0.130	0.735 ± 0.438
V_N (ml/kg)	16.06 ± 8.83	29.20 ± 8.07	23.46 ± 12.47
t_{maxN} (min)	32.46 ± 0.56	15.76 ± 0.40	20.59 ± 0.45
N_b (pg/ml)	46.30 ± 0.60	48.13 ± 0.60	59.23 ± 0.33
R^2 (%)	93	88	91
Root mean square error (pg/ml)	15.2	18.3	10.6

Glucagon-Extended Minimal Model and Gastrointestinal Absorption Model Identification

Table 4 provides, for each one of the time windows, the values for the identified parameters of the glucagon-extended minimal model coupled to the gastrointestinal absorption model, corresponding to the three studied subjects. **Table 5** provides the results for the metrics to assess for adequacy of the data fitting (see Parameter Identification under Methods). **Figure 5** shows, for each one of the time windows, the fitting model with the glucose experimental data corresponding to subject 117-1.

In Silico Testing of a Bihormonal Glucose Controller

To test the usability of the proposed glucagon–glucose composite model, a bihormonal glucose controller that consists of a validated bioinspired controller, based on

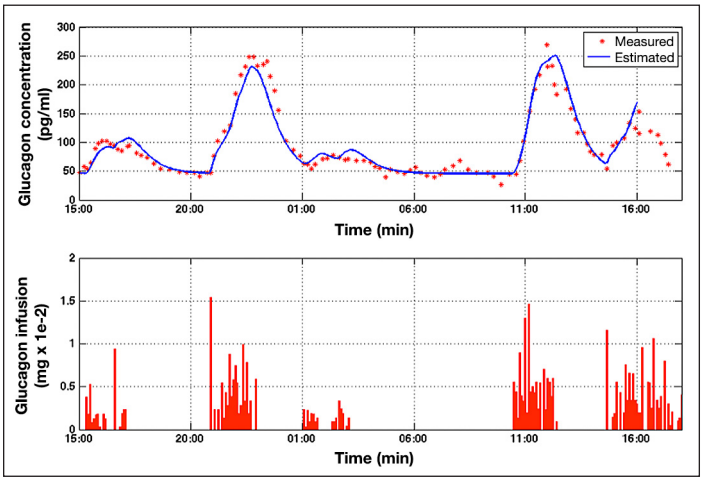

Figure 4. Fitting of the subcutaneous glucagon absorption model to the experimental measurements corresponding to subject 117-1. (Upper) Measured mean plasma glucagon concentration (red dots) and estimated plasma glucagon concentration (solid blue line). (Lower) Glucagon infusion (red bars).

Table 4.
Estimated Parameters (Mean ± 1 Standard Deviation) of the Glucagon-Extended Minimal Model Coupled to the Gastrointestinal Absorption

Subject	Parameter	15:00–05:00	05:00–12:00	12:00–18:00
117-1	S_I (min^{-1} per μU/ml)	$7.73e^{-4}$ ± $1.22e^{-5}$	$8.55e^{-4}$ ± $8.85e^{-5}$	$6.82e^{-4}$ ± $7.96e^{-6}$
	p_2 (min^{-1})	0.012 ± 0.001	0.0039 ± 0.001	0.021 ± 0.001
	S_N (min^{-1} per pg/ml)	$1.38e^{-4}$ ± $2.70e^{-6}$	$1.96e^{-4}$ ± $1.41e^{-5}$	$8.10e^{-5}$ ± $2.27e^{-6}$
	p_3 (min^{-1})	0.017 ± 0.001	0.016 ± 0.002	0.139 ± 0.024
	t_{maxG} (min)	69.6 ± 0.1	59.9 ± 0.1	59.9 ± 0.6
126-1	S_I (min^{-1} per μU/ml)	$2.26e^{-4}$ ± $4.76e^{-6}$	$1.06e^{-3}$ ± $2.46e^{-4}$	$1.16e^{-3}$ ± $8.47e^{-5}$
	p_2 (min^{-1})	0.057 ± 0.006	0.002 ± 0.001	0.002 ± 0.001
	S_N (min^{-1} per pg/ml)	$8.96e^{-5}$ ± $2.31e^{-4}$	$1.45e^{-4}$ ± $6.53e^{-6}$	$1.25e^{-4}$ ± $1.61e^{-6}$
	p_3 (min^{-1})	0.022 ± 0.001	0.164 ± 0.002	0.210 ± 0.034
	t_{maxG} (min)	57.9 ± 0.7	55.4 ± 1.1	89.8 ± 0.8
128-1	S_I (min^{-1} per μU/ml)	$6.40e^{-4}$ ± $3.67e^{-5}$	$5.13e^{-4}$ ± $3.43e^{-4}$	$7.20e^{-4}$ ± $4.56e^{-5}$
	p_2 (min^{-1})	0.0048 ± 0.0003	0.0037 ± 0.0039	0.0077 ± 0.0008
	S_N (min^{-1} per pg/ml)	$1.19e^{-4}$ ± $8.11e^{-6}$	$1.98e^{-5}$ ± $6.01e^{-6}$	$1.20e^{-4}$ ± $7.25e^{-6}$
	p_3 (min^{-1})	0.0108 ± 0.0009	0.074 ± 0.016	0.251 ± 0.098
	t_{maxG} (min)	102.7 ± 1.9	88.5 ± 0.1	78.0 ± 3.3

Table 5.
Results for the Metrics to Assess for Adequacy of the Data Fitting to the Glucagon-Extended Minimal Model Coupled to the Gastrointestinal Absorption

Subject	Metric	15:00–05:00	05:00–12:00	12:00–18:00
117-1	ΔG_{peak} (mg/dl)	8.3	5.8	4.7
	ΔT_{peak} (min)	1	26	4
	ΔG_{nadir} (mg/dl)	8.1	5.3	2.2
	ΔT_{nadir} (min)	23	12	0
	R^2 (%)	93	97	97
	Root mean square error (mg/dl)	10.5	8.5	9.2
126-1	ΔG_{peak} (mg/dl)	14.2	25.6	11.3
	ΔT_{peak} (min)	19	6	9
	ΔG_{nadir} (mg/dl)	10.1	0	3.9
	ΔT_{nadir} (min)	7	0	11
	R^2 (%)	96	95	97
	Root mean square error (mg/dl)	9.7	13.6	8.2
128-1	ΔG_{peak} (mg/dl)	7.2	5.7	2.6
	ΔT_{peak} (min)	1	15	13
	ΔG_{nadir} (mg/dl)	6.7	6	0.4
	ΔT_{nadir} (min)	2	0	0
	R^2 (%)	93	86	90
	Root mean square error (mg/dl)	11.6	12.6	10.7

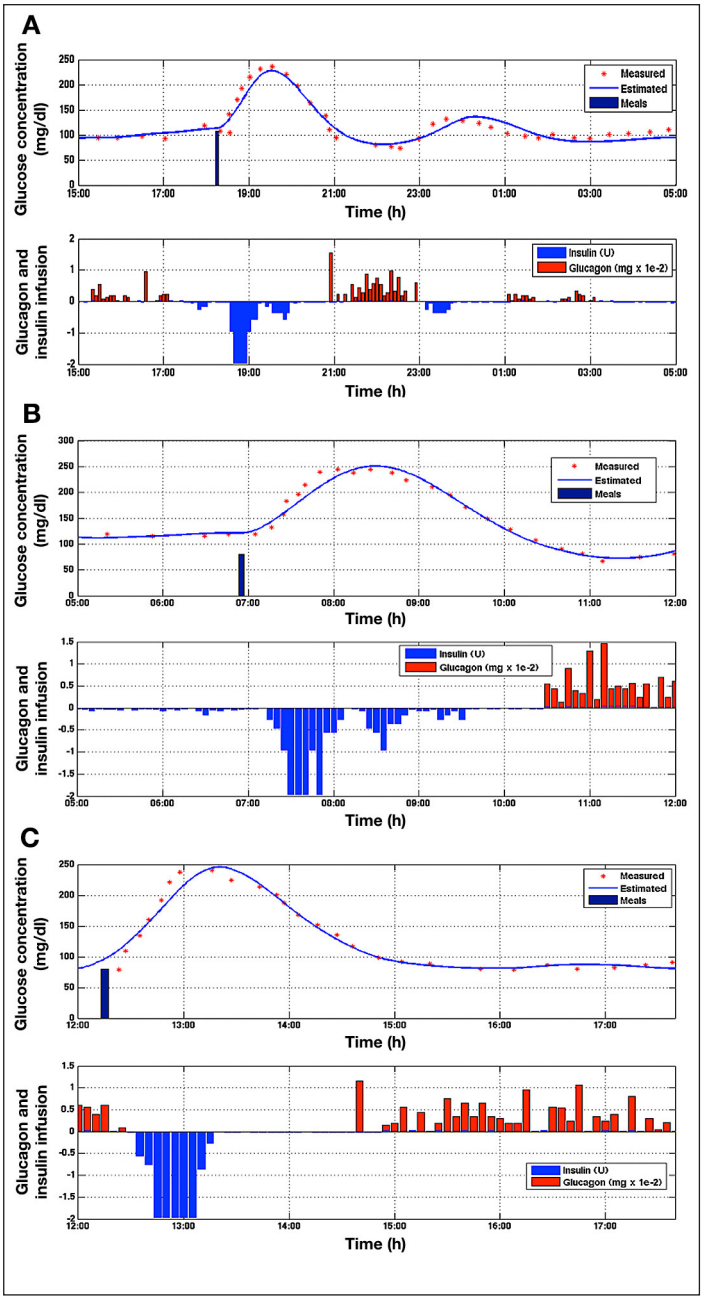

Figure 5. Fitting of the glucagon-extended minimal model coupled to the gastrointestinal absorption to the experimental measurements corresponding to subject 117-1 for each one of the time windows. **(A)** Time window 15:00–05:00. **(B)** Time window 05:00–12:00. **(C)** Time window 12:00–18:00. (Upper **A–C**) Measured mean plasma glucose concentration (red dots), estimated plasma glucose concentration (solid blue line) and meal (black bar). (Lower **A–C**) Glucagon infusion (positive red bars) and insulin infusion (negative blue bars).

beta-cell physiology, for insulin delivery[3] combined with a proportional-derivative (PD) controller for glucagon delivery[8] was employed. The bioinspired controller can be described by the equation

$$u = K \cdot F(t, G, G_{sp}) + SR_b - K_y \cdot I, \qquad (19)$$

where u is insulin delivery, F is insulin secretion calculated with the beta-cell model presented by Pedersen and coauthors,[24] G is glucose concentration (forecasted 15 min ahead), G_{sp} is the glucose set point, SR_b is basal insulin delivery, K_p and K_y are tuning parameters, and I is the plasma insulin estimation calculated using **Equations (13)–(15)**.

The PD controller with glucagon feedback is described by the equation

$$if\ G < G_{sp} w = K_p \cdot \max(0,(GN_{sp} - G)) + K_d(-dG) - K_Z N, \text{ else } w = 0, \qquad (20)$$

where w is glucagon delivery; K_p, K_d, and K_Z are tuning parameters; G is glucose concentration (forecasted 15 min ahead); GN_{sp} is the glucagon controller glucose set point; dG is the glucose rate of change (i.e., derivative); and N is the plasma glucagon estimation calculated using **Equations (16)–(18)**.

The same scenario used to identify the parameters of the glucagon–glucose composite model was employed to test the proposed bihormonal controller. It is important to note the parameters of the model change along the scenario.

First, the bioinspired controller was tested alone and specifically tuned (i.e., K = 3; K_y = 15) to induce hypoglycemia (see **Figure 6**). Then, for the same tuning of the bioinspired controller, the PD controller was tuned (i.e., K_p = 0.002, K_d = 0.02, and K_Z = 30) to prevent hypoglycemia (see **Figure 7**). Glucose set points for the bioinspired controller and for the PD controller was set to G_{sp} = 120 mg/dl and GN_{sp} = 90 mg/dl.

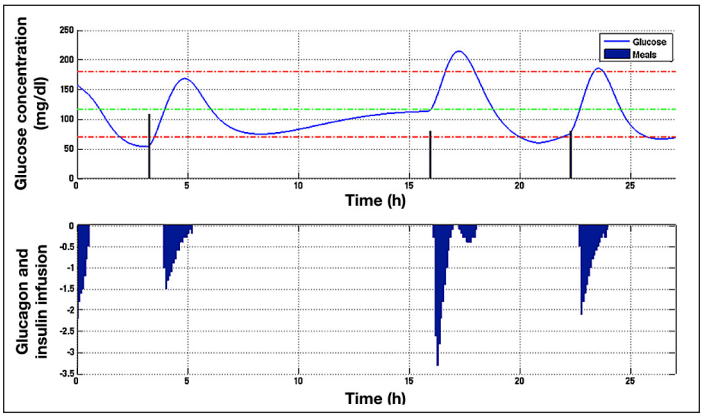

Figure 6. (Upper) Glucose concentration trace (blue solid line) resulting from tuning the insulin bioinspired controller to induce hypoglycemia. **(Lower)** Delivered insulin by the bioinspired controller.

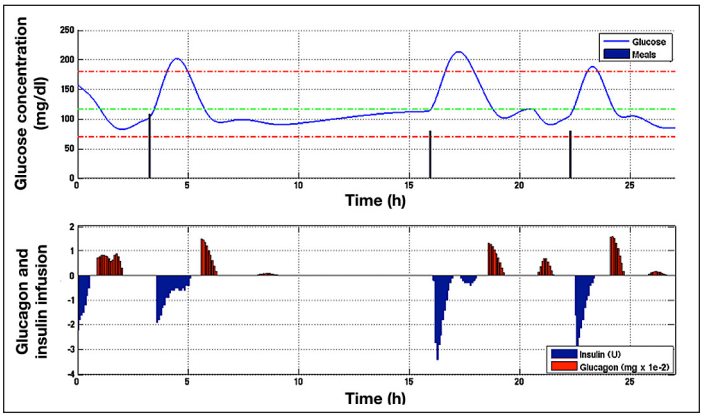

Figure 7. (Upper) Glucose concentration trace (blue solid line) resulting from the bihormonal control. **(Lower)** Delivered insulin (negative blue bars) and glucagon (positive red bars) by the bihormonal controller.

Discussion

Although only three sets of data were used, the quality of the results suggests that they could be replicated with other similar experiment data. This work is currently taking place with the purpose of building a cohort of virtual subjects with T1DM to be incorporated within a simulation environment.

It has to be noted that, although a good fitting of the model with the experimental data was achieved and the model parameters were identified with good precision, the employed data were not created for this purpose. Therefore, the results of the performed parameter identifications may not be optimal. In order to capture the complete dynamics of the system to facilitate parameter identification, specifically designed clinical trials should incorporate the delivery of insulin and glucagon separately and the delivery of both hormones simultaneously. It should be noted that the identification of the presented model could be done more accurately through tracer studies. However, the realization of tracer studies is out of the scope of this work.

Subcutaneous glucagon pharmacokinetics are known to be simpler than that of insulin because multimers of glucagon are not thought to be present in the subcutaneous interstitial space.[25,26] Therefore, the insulin pharmacokinetic model employed to represent subcutaneous glucagon pharmacokinetics may be unduly complex but sufficient for its purpose.

Although a bihormonal controller was successfully tested on the proposed composite model, one may argue that the use of glucagon can increase the risk of overinsulinization, which is known to be unsuitable for subjects with T1DM, and the instability of the system. One easy way to avoid this problem is by introducing constraints on both insulin and glucagon delivery. By doing so, we guarantee that only safe amounts of both hormones are delivered.

To make the proposed model more realistic, several improvements could be made. First of all, a model of the dynamics of glucose diffusion between plasma glucose and interstitial fluid glucose and a model of the subcutaneous continuous glucose monitoring sensor could be incorporated.[27] Then, a cohort of virtual subjects with T1DM and a library of different mixed meals could be included in order to represent intersubject and intraday variability. This work is currently taking place in our group.

Conclusions

A novel glucagon–glucose composite model, which accounts for the effect of exogenous insulin and glucagon infusion on glucose dynamics, was successfully identified using data extracted from a published bihormonal artificial pancreas study. In addition, the proposed subcutaneous glucagon absorption model succeeded in accurately estimating experimental plasma glucose concentrations.

The usability of the glucagon–glucose composite model was tested by means of the realization of an *in silico* trial using a bihormonal glucose controller developed by our group. The obtained results proved the ability of the bihormonal controller to avoid hypoglycemia when the insulin delivery controller was tuned too aggressively. We have shown that our new model can aid the design of bihormonal glucose controllers, which represents an incremental step toward the realization of an artificial pancreas.

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