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SYMPOSIUM

Identification of Intraday Metabolic Profiles during Closed-Loop Glucose Control in Individuals with Type 1 Diabetes

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Abstract

Background:

Algorithms for closed-loop insulin delivery can be designed and tuned empirically; however, a metabolic model that is predictive of clinical study results can potentially accelerate the process.

Methods:

Using data from a previously conducted closed-loop insulin delivery study, existing models of meal carbohydrate appearance, insulin pharmacokinetics, and the effect on glucose metabolism were identified for each of the 10 subjects studied. Insulin's effects to increase glucose uptake and decrease endogenous glucose production were described by the Bergman minimal model, and compartmental models were used to describe the pharmacokinetics of subcutaneous insulin absorption and glucose appearance following meals. The composite model, comprised of only five equations and eight parameters, was identified with and without intraday variance in insulin sensitivity (S_I), glucose effectiveness at zero insulin (*GEZI*), and endogenous glucose production (*EGP*) at zero insulin.

Results:

Substantial intraday variation in S_I, *GEZI* and *EGP* was observed in 7 of 10 subjects (root mean square error in model fit greater than 25 mg/dl with fixed parameters and nadir and/or peak glucose levels differing more than 25 mg/dl from model predictions). With intraday variation in these three parameters, plasma glucose and insulin were well fit by the model (R^2 = 0.933 ± 0.00971 [mean ± standard error of the mean] ranging from 0.879–0.974 for glucose; R^2 = 0.879 ± 0.0151, range 0.819–0.972 for insulin). Once subject parameters were identified, the original study could be reconstructed using only the initial glucose value and basal insulin rate at the time closed loop was initiated together with meal carbohydrate information (glucose, R^2 = 0.900 ± 0.015; insulin delivery, R^2 = 0.640 ± 0.034; and insulin concentration, R^2 = 0.717 ± 0.041).

Conclusion:

Metabolic models used in developing and comparing closed-loop insulin delivery algorithms will need to explicitly describe intraday variation in metabolic parameters, but the model itself need not be comprised by a large number of compartments or differential equations.

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Abbreviations: (CGM) continuous glucose monitoring, (MAD) mean absolute difference, (MVP) Medtronic Virtual Patient, (PD) pharmacodynamic, (PID) proportional integral derivative, (PK) pharmacokinetic, (SC) subcutaneous, (SSE) sum square error

Keywords: algorithm, artificial pancreas, automated, closed loop, diabetes, insulin delivery, mathematical model

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Introduction

Open-loop glucose control using either continuous subcutaneous (SC) insulin infusion or multiple insulin injections, with or without continuous glucose monitoring (CGM), results in less-than-optimal glucose control in many individuals with diabetes mellitus.[1] Changing physiological conditions during the day or between days together with an inability of individuals to accurately estimate carbohydrate intake can result in undesired glucose excursions that might be avoided with a closed-loop system. However, limitations exist in designing closed-loop algorithms based on clinical studies alone. Clinical studies take substantial resources to perform, limiting the number of subjects that can be enrolled and the total time each subject is studied. Changing controller design based purely on empirical results may require numerous clinical iterations before satisfactory results are obtained, and closed-loop studies performed with no *a priori* knowledge of the controller's expected behavior may introduce unnecessary risk to the patient. A mathematical model of glucose metabolism can potentially accelerate the process, provided the model can predict results from changes in controller design or tuning. Numerous models exist in the literature for simulating glucose profiles,[2] but the models do not typically describe intraday or interday variance in the patient metabolic profile. Most models have not been identified specifically using data from individuals with type 1 diabetes.[3]

One approach to modeling is to "clone" subjects previously studied under closed-loop insulin delivery. This approach has been used previously to evaluate control algorithm for intravenous insulin delivery in the intensive care unit.[4] Obtaining model parameters from closed-loop data acquired over a 24 h period can potentially allow intraday variance to be quantified. Closed-loop data are ideally suited for identifying parameters in that frequent blood samples are available for measuring plasma glucose and insulin levels, insulin delivery rates vary substantially through the day (persistent excitation), and meal carbohydrate intake can be accurately determined by trained dieticians. Subjects identified from closed-loop data should allow model simulations to be performed, evaluating new control strategies and the results compared with the original clinical results. Ideally, the results from such simulations would be validated in new clinical studies on either the same subjects or on subjects independent from those used to identify the model. The initial step requires model parameters to be identified on a fixed number of subjects, and this is the focus of the present study.

Methods

Patient Characteristics and Data

Data from a previous closed-loop study conducted in 10 adults with type 1 diabetes mellitus were used to identify a composite metabolic model. Details of the study have been published;[5] however, in brief, 10 subjects were studied (8 females, 2 males, mean [± standard deviation] aged 42.5 ± 11.5 years, duration of diabetes 18.0 ± 13.5 years) under closed-loop control for approximately 28 h. Blood samples were taken approximately every 20 min for measurement of plasma insulin and glucose. A proportional-integral-derivative (PID) model of the β cell[6] was used with the Medtronic MiniMed SC glucose sensor and insulin pump to effect closed-loop control on a minute-to-minute sample interval. The content and the amount of ingested carbohydrates was determined and logged by a trained dietician at the time of the study. Breakfast, lunch, dinner, and a late-night snack were given on day 1 followed by breakfast on day 2. Carbohydrate consumed at times other than scheduled meals were in response to blood glucose < 60 mg/dl or hypoglycemic symptoms, with juice denoted by †.

Medtronic Virtual Patient model formulation

Metabolic models describing the pharmacokinetic (PK) pharmacodynamic (PD) response of SC insulin, glucose appearance following meals (*Ra*), and the effect of insulin to lower blood glucose were used. For the PK/PD response, an identifiable realization of the three-compartment model originally studied by Insel and colleagues[7] was used to describe plasma insulin concentration (*Ip*) in response to SC insulin delivery [*ID*; **Equations (1)–(3)**]. Insulin effect (I_{EFF}) was coupled with the Bergman minimal model[8] [**Equations (3)** and **(4)**, with **Equation (3)** overlapping the Sherwin model] and a two-compartment model of glucose appearance following a meal (R_A) was chosen [**Equation (5)**] based on the work by Hovorka and associates.[4,9,10] Together, the five model equations form the basis of the Medtronic Virtual Patient (MVP) simulator used for educating and training individuals with type 1 diabetes:[11]

$$\frac{dI_{SC}(t)}{dt} = -\frac{1}{\tau_1}\cdot I_{SC}(t) + \frac{1}{\tau_1}\frac{ID(t)}{C_I} \qquad (1)$$

$$\frac{dI_P(t)}{dt} = -\frac{1}{\tau_2}\cdot I_P(t) + \frac{1}{\tau_2}\cdot I_{SC}(t) \quad (2)$$

$$\frac{dI_{EFF}(t)}{dt} = -p_2\cdot I_{EFF}(t) + p_2\cdot S_I\cdot I_P(t) \quad (3)$$

$$\frac{dG(t)}{dt} = -\left(GEZI + I_{EFF}\right)\cdot G(t) + EGP + R_A(t) \quad (4)$$

$$R_A(t) = \frac{C_H(t)}{V_G\cdot \tau_m{}^2}\cdot t\cdot e^{-\frac{t}{\tau_m}} \quad (5)$$

The MVP model has eight identifiable parameters: τ_1 and τ_2 are time constants associated with insulin movement between the SC delivery site and plasma (time constants relate to the more familiar concept of a single process half-time $T_{1/2}$ by a factor 0.693); C_I is insulin clearance (ml/min); $1/p_2$ characterizes the delay in insulin action following an increase in plasma insulin; S_I denotes insulin sensitivity; *GEZI* characterizes the effect of glucose *per se* to increase glucose uptake into cells and lower endogenous glucose production at zero insulin;[12] *EGP* is the endogenous glucose production rate that would be estimated at zero insulin; and V_G is related to the distribution volume in which glucose equilibrates. In the meal **Equation (5)**, C_H is the amount of carbohydrate consumed at different times of the day and τ_m defines the peak time of absorption.

Two modifications to the model were tested. First, the two-compartment PK model [**Equations (1)** and **(2)**] was compared with a three-compartment model:

$$\frac{dI_{SC}(t)}{dt} = -\frac{1}{\tau_1}\cdot I_{SC}(t) + \frac{1}{\tau_1}\frac{ID(t)}{C_I} \quad (6)$$

$$\frac{dI_2(t)}{dt} = -\frac{1}{\tau_2}\cdot I_2(t) + \frac{1}{\tau_2}\cdot I_{SC}(t) \quad (7)$$

$$\frac{dI_P(t)}{dt} = -\frac{1}{\tau_3}\cdot I_P(t) + \frac{1}{\tau_3}\cdot I_2(t) \quad (8)$$

Second, the two-compartment meal model with equal time constants [**Equation (5)**] was compared with a similar two-compartment model with unequal time constants τ_{M1} and τ_{M2}:

$$R_A(t) = \cdot\frac{C_H(t)}{V_G\cdot\left(\tau_{m1}-\tau_{m2}\right)}\left[e^{-\frac{t}{\tau_{m1}}} - e^{-\frac{t}{\tau_m}}\right] \quad (9)$$

Comparisons were performed with sequential F tests[13] with $p < .05$ considered significant.

Parameter Estimation

Equations (1)–(3) and **(5)** were transformed to a discrete form using Z transforms.[14] The bilinear equation describing insulin's effect on glucose [**Equation (4)**] has no exact Z transform and was transformed to the discrete 1 min sample interval using a first forward difference derivative approximation. Parameter identification and model simulations were performed using MATLAB version 6.5 (Mathworks Inc., Natick, MA) together with a custom graphical user interface designed with LabView 6.1 (National Instruments, Austin, TX). Marquardt–Levenberg and Nelder–Mead nonlinear least squares fitting algorithms were used to minimize the sum squared error between the model and measured plasma insulin and glucose concentrations. For **Equations (1)** and **(2)**, which have interchangeable time constants, the larger time constant was assigned to τ_1 and the smaller time constant was assigned to τ_2. Subject data were fit individually, with individual fits averaged. Identification and model validation was performed in four steps:

Step 1: The known insulin delivery rates were used to estimate parameters of the insulin PK model. Parameters τ_1, τ_2, and C_I were identified in each of the 10 subjects by minimizing the sum square error (SSE) between the model predicted plasma insulin concentration (*Ip*) and the measured concentration. Insulin delivery, which was composed of a series of discrete boluses in the original study[5] (each bolus being an integer multiple of 0.1 U), was obtained from pump downloads.[5] Sum square error for the two-compartment PK model was then compared with SSE for the three-compartment model [**Equations (6)–(8)**] with improvement in fit evaluated using the sequential F test.[13]

Step 2: The measured plasma insulin profile and known meal carbohydrate content was used to identify p_2, GEZI, S_I, EGP, V_G, and τ_m. Plasma insulin concentration was interpolated on a 1 min interval and used as input to Equation (3) and carbohydrate content input to Equation (6). Parameters p_2, *GEZI*, S_I, *EGP*, V_G, and τ_m were then estimated by minimizing the difference between the plasma glucose and model prediction [G; **Equation (4)**]. Minimization was first performed assuming no intraday variation in any parameter and identical time constants for the two-compartment meal model [**Equation (5)**]. Fits were repeated with the meal model in which the two meal time constants were allowed to be different [**Equation (9)**], and improvement in fit was evaluated using the sequential F test.[13]

Step 3: Model fits were evaluated, and if deemed to be inadequate, intraday variation was introduced. Each fit from the procedures in step 2 was assessed for adequacy according to three criteria: (1) root mean square difference 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 with the peak values needing to be within 0.5 h of each other, 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, with the nadirs occurring within 0.5 h of each other. If the fitted profile failed to meet any of these three criteria, the fit was repeated but with S_I, *GEZI*, and *EGP* allowed to vary in three windows. The parameters of windows 1 and 3 were constrained to have equal values such that each parameter could have only two values during a 24 h period (diurnal variation). Start and end times of window 2 were identified by nonlinear least squares with the times chosen to minimize the SSE in all three windows. If the introduction of diurnal variation in any of one the three parameters did not significantly contribute to the improvement of SSE in window 2 (designated by the *F* test[13]), then that parameter was constrained to equal the value in windows 1 and 3 and the remaining parameters allowed to vary.

Step 4: Validation of model simulations. Once metabolic parameters for each subject were identified, the entire closed-loop study was reconstructed using the original control equations together with a previously published model of the SC glucose sensing[15,16] with 10 min (τ_{SEN}) SC interstitial fluid (*ISF*) delay:[15,16]

$$\frac{dG_{ISF}(t)}{dt} = -\frac{1}{\tau_{SEN}} \cdot G_{ISF}(t) + \frac{1}{\tau_{SEN}} \cdot G_P(t) \qquad (10)$$

Digital filters used in the original study to smooth the sensor signal (seven-point finite impulse response filter with 3 cycles/hour cutoff) and estimate the rate of change of glucose (slope of the sensor signal over the previous 15 min) were also included to reproduce as closely as possible all conditions under which the original study[5] was performed (a process sometimes referred to as putting the hardware in the loop[17]). With experimental conditions in place, plasma glucose, insulin delivery, and insulin concentration were simulated using only the glucose concentration and the basal insulin delivery rate at the time closed loop was initiated. The simulated results (10 individual profiles) were then compared to the clinical study data using R^2 and mean absolute difference (MAD).

Statistics were performed either with GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA) or MATLAB version 6.5. Data are reported as mean ± standard error of the mean unless otherwise noted.

Results

Step 1: Plasma insulin concentration was well described by the two-compartment PK insulin model [**Equations (1)** and **(2)**] with average correlation (R^2) equal to 0.879 ± 0.0151 (range 0.819 to 0.972) and MAD 4.20 ± 1.15 μU/ml (**Figure 1B**, with plasma and sensor glucose from the original study shown in **Figure 1A**). Time delays associated with insulin appearance in plasma were estimated to be 70.5 ± 8.8 and 44.6 ± 6.4 min (**Table 1**). Repeating the analysis with the three-compartment PK model [Equations (6)–(8)] resulted in significantly better plasma insulin fits in 2 of the 10 subjects (*F* test; $p < .05$; data not shown).

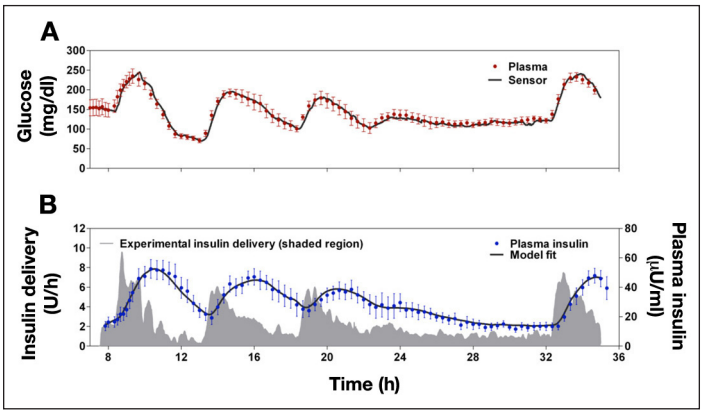

Figure 1. Average profile of all 10 subjects. **(A)** Closed-loop plasma glucose (closed circles ± standard error) and sensor (solid curve; SEM not shown) observed in the adults studied under closed-loop PID insulin delivery.[5] **(B)** Plasma insulin concentrations (closed circles ± standard error) and fitted PK insulin model (solid curve; SEM not shown) using the experimentally obtained insulin delivery profile (shaded area) as input to **Equation (1)**. Profiles were fit individually and then averaged.

Step 2: Fitting the plasma glucose profile with the equal time constant meal model [**Equation (6)**] and no intraday variation in S_I, *GEZI*, or *EGP* resulted in acceptable fits in only 3 of the 10 subjects (**Figure 2A**). Fits deemed acceptable were not completely free of residuals (**Figure 2A** meal response at hour 13) but passed the criteria that the overall root mean square error be <25 mg/dl (root mean square error = 21.1 mg/dl) and the criteria that the peak postprandial glucose be within 25 mg/dl and all nadir glucose values below 80 mg/dl be predicted by the model to within 15 mg/dl, with the predicted time of peak or nadir being within 0.5 h of the experimentally

Table 1.
Estimated Virtual Patient Model Parameters Based on Known Insulin Delivery Rates and Measured Plasma Insulin Concentrations.

Subject	Body weight (kg)	Total daily insulin (U/day)	C_l (ml/min)	τ_1 (min)	τ_2 (min)	V_G (dl)	p_2 (min^{-1})	Window	Start	End	*EGP* (mg/dl/min)	*GEZI* (min^{-1})	S_I (ml/μU)
1	89	50	2010	49	47	253	$1.06\ 10^{-2}$	1,3			1.33	$2.20\ 10^{-3}$	$8.11\ 10^{-4}$
								2	22:00	4:00	1.4	$3.87\ 10^{-8}$	$4.93\ 10^{-4}$
2	63	43	1281	41	10	261	$1.16\ 10^{-2}$	1,2,3			0.6	$4.38\ 10^{-3}$	$9.64\ 10^{-5}$
3	65	30	909	71	70	199	$2.33\ 10^{-2}$	1,3			1.07	$3.50\ 10^{-3}$	$4.63\ 10^{-4}$
								2	3:00	10:00	0.856	$3.50\ 10^{-3}$	$1.70\ 10^{-4}$
4	116	65	1813	91	70	337	$8.14\ 10^{-3}$	1,3			0.98	$1.64\ 10^{-5}$	$3.77\ 10^{-4}$
								2	18:00	0:00	2.59	$7.58\ 10^{-8}$	$3.77\ 10^{-4}$
5	64	42	1535	46	46	188	$9.63\ 10^{-3}$	1,2,3			0.6	$4.33\ 10^{-3}$	$2.05\ 10^{-4}$
6	51	21	588	68	30	104	$9.15\ 10^{-3}$	1,3			0.603	$1.01\ 10^{-3}$	$4.12\ 10^{-4}$
								2	18:00	4:00	0.603	$3.79\ 10^{-3}$	$9.48\ 10^{-4}$
7	77	40	1806	60	60	263	$1.01\ 10^{-2}$	1,2,3			1.11	$2.30\ 10^{-3}$	$8.16\ 10^{-4}$
8	65	30	540	95	37	137	$1.03\ 10^{-2}$	1,3			1.3	$1.00\ 10^{-8}$	$3.68\ 10^{-4}$
								2	18:00	23:25	0.601	$1.00\ 10^{-8}$	$5.40\ 10^{-4}$
9	100	50	875	131	21	193	$1.03\ 10^{-2}$	1,3			1.27	$6.39\ 10^{-3}$	$2.56\ 10^{-4}$
								2	13:00	22:00	3.45	$6.39\ 10^{-3}$	$6.89\ 10^{-4}$
10	64	34	1309	53	53	204	$1.02\ 10^{-2}$	1,3			0.611	$1.04\ 10^{-3}$	$6.03\ 10^{-4}$
								2	0:00	4:43	0.611	$1.04\ 10^{-3}$	$1.73\ 10^{-3}$

observed time. As described in Methods, the glucose profile was fit using measured plasma insulin profiles (closed circles in **Figure 2B**) rather than model-predicted curves obtained from the insulin PK model identified in step 1 (solid curve in **Figure 2B**) to avoid carrying over any model error associated with the insulin model. For the subject shown, the model underestimated the insulin response to the meal at hour 8 and overestimated the response to the meal at hour 22 (**Figure 2B**, black curve); however, the correlation was reasonable (R^2 = 0.854). Exogenous glucose appearance peaked within 10–34 min of each meal (**Table 2**, subject 7) with the appearance curve shown **Figure 2C**.

Step 3: Seven of the 10 subjects failed to meet one of the three fit criteria and were deemed to have intraday variation in their metabolic profiles. An example subject (**Figure 3**, subject 8) showed good model fits for meals at hours 8 and 13 (peak postprandial meal and model not different by more than 15 mg/dl) but failed to follow the meal at hour 18 (no postprandial peak and a nadir error of 34 mg/dl, failing both criteria 2 and criteria 3). Allowing intraday variation in metabolic parameters

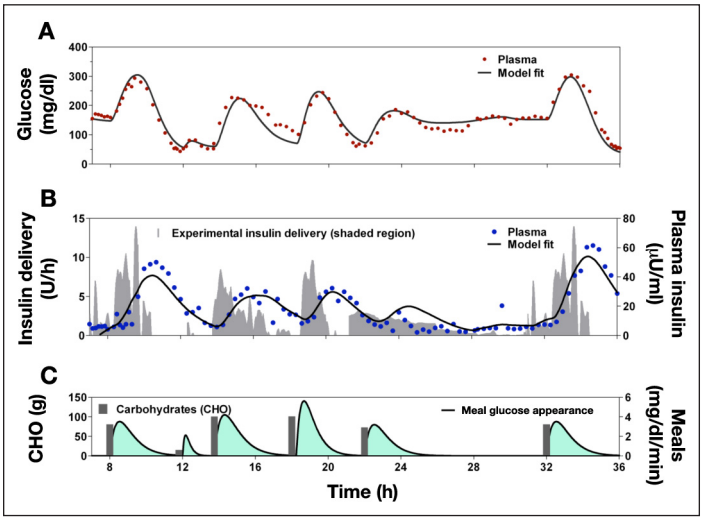

Figure 2. Identification of a subject where no intraday variation was necessary to fit the glucose profile (subject 7). **(A)** Plasma glucose concentration (solid circles) and model fit (solid curve) showing peak postprandial and nadir glucose for glucose below 80 mg/dl within 15 mg/dl and each occurring with 0.5 h of each other. **(B)** Proportional-integral-derivative insulin delivery profile (shaded region) and measured insulin concentration5 (solid circles) with model insulin profile (solid curve). **(C)** Carbohydrates intake (bars, left axis) with model **[Equation (5)]** estimated exogenous glucose appearance (solid curve with shading, right axis).

produced acceptable fits (**Figure 3C**) by increasing S_I and endogenous glucose production decreasing between 18:00 and 23:25 h (**Table 1**). Fit was again based on the measured plasma insulin (**Figure 3E**, closed circles) rather than model fit (**Figure 3E**, solid curve), which showed minor errors in the rise following meals at hours 19 and 31 and an underestimation of peak insulin during breakfast on day 2.

The 10 individual model-predicted glucose profiles, 3 identified without intraday variation like the one shown in **Figure 2** and 7 identified with intraday variation like the one shown in **Figure 3**, fit their respective measured plasma glucose profiles well. Correlation coefficients ranging from 0.879 to 0.974 (R^2 = 0.933 ± 0.00971) with MAD 11.51 ± 2.93 mg/dl (parameters in **Tables 1** and **2**; average of the individual fits shown in **Figure 4A**, solid curve). No significant improvement in fit was obtained when the two meal time constants were allowed to be unequal [equation (9); data not shown]. Peak meal absorption times tended to be fastest at breakfast, with increasingly longer times observed for lunch, dinner, and snack (47 ± 5, 55 ± 6, 74 ± 19, and 78 ± 17 min analysis of variance; **Table 2**), although this did not achieve statistical significance. Supplemental carbohydrate, however, peaked significantly faster (31 ± 10 min; $p < .05$, analysis of variance), with juice typically peaking within 10–15 min (**Table 2**, pure juice indicated by †).

Step 4: The entire study was simulated using only the conditions at the time closed-loop control was initiated and the meal carbohydrate information**.** Coupling the MVP model with a model describing SC glucose sensor delay [Equation (10)] and the PID algorithm used in the original clinical study[5] produced plasma glucose (**Figure 4A** dashed curve; R^2 = 0.900 ± 0.015, ranging from 0.816 to 0.961), insulin delivery (**Figure 4B**; R^2 = 0.640 ± 0.034, range 0.448 to 0.767), and insulin concentration

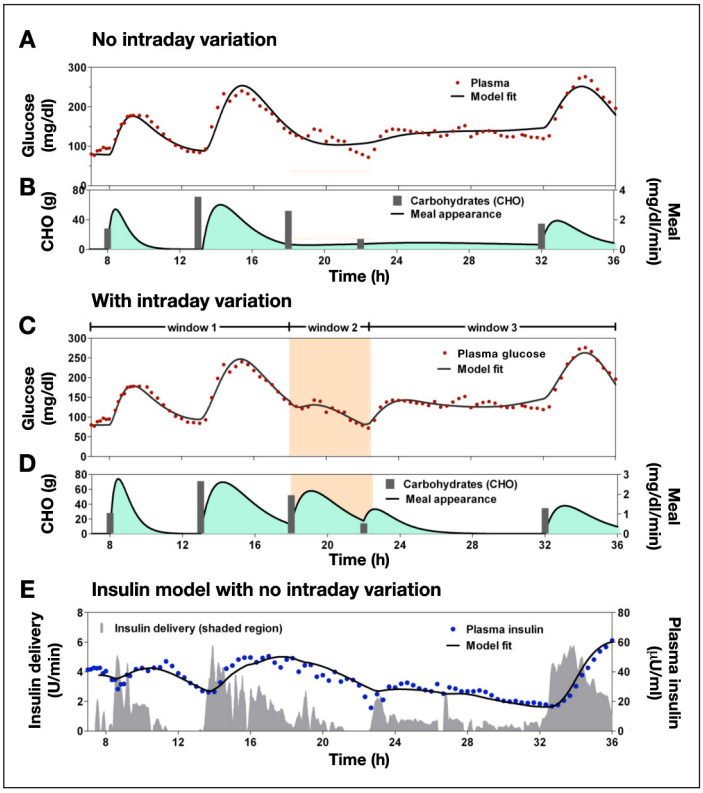

Figure 3. Identification of a subject where intraday variation in model parameters was necessary to adequately fit plasma glucose (subject 8). **(A)** Glucose profile fit without intraday variation. **(B)** Meal glucose appearance identified without intraday variance. **(C)** Glucose profile fit with an increase in insulin sensitivity (S_I) and decrease in endogenous glucose production (*EGP*) during window 2. **(D)** Meal glucose appearance identified with intraday variance. **(E)** Proportional-integral-derivative insulin delivery profile (shaded region) and measured insulin concentration (solid circles) obtained from the original study data[5] together with the fitted plasma insulin profile (solid curve).

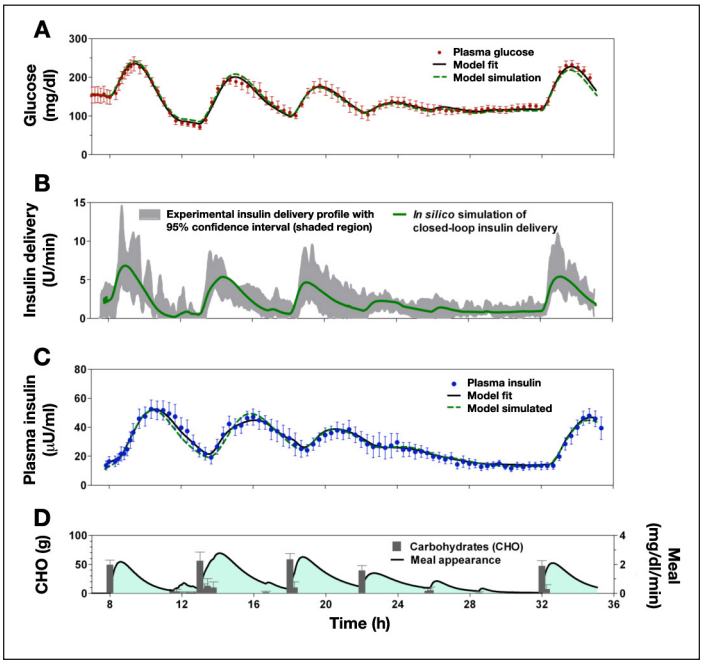

Figure 4. Average fit (solid curve) and simulated (dashed curve) profiles of all 10 subjects. Profiles were fit and simulated individually and then averaged. **(A)** Plasma glucose (circles ± standard error), model fit (solid curve; standard error bars not shown) using measured plasma insulin concentrations, and closed-loop model simulation (dashed curve; standard error bars not shown) results. **(B)** Insulin delivery obtained from the original closed-loop study[5] with shaded area indicating the 95% confidence interval for the mean, together with the simulated profile (solid curve; standard error bars not shown) using the MVP model [**Equations (1)–(5)**] and PID algorithm. **(C)** Plasma insulin (circles ± standard error) obtained in the original study with model fit using the measured insulin delivery (solid curve; standard error not shown) and simulated values using only the initial conditions at the time closed loop was started (dashed curve; standard error not shown).

(**Figure 4C**, dashed curve; R^2 = 0.717 ± 0.041, range 0.558 to 0.880) responses nearly identical to those of the original study despite no knowledge of experimental data other than the glucose concentration and basal insulin rate at the time closed loop was initiated and the amount of carbohydrates consumed at each meal. Mean absolute difference for the simulated profiles was 16.2 ± 1.6 mg/dl, 1.04 ± 0.148 U/h, and 6.973 ± 0.435 μU/ml for glucose, insulin delivery, and insulin concentration, respectively, with the simulated profiles virtually overlaying the profiles obtained using the known insulin delivery rates and measured plasma insulin concentrations (**Figure 4**, dashed and solid curves).

Table 2.
Carbohydrate Consumed in the Proportional-Integral-Derivative Closed-Loop Study[5] Used in Identifying the Virtual Patient Model[a]

Subject		Breakfast			Lunch		Dinner	Snack		Breakfast	
1	Time	8:00	11:30		13:15		18:00	22:00		32:00	
	Carbohydrates (g)	72	36		131		51	70		72	
	τ_M (min)	47	21		52		24	60		39	
2	Time	8:00			13:00		18:00			32:00	
	Carbohydrates (g)	8			140		18			20	
	τ_M (min)	107			84		231			12	
3	Time	8:00	11:40	12:40	13:15		18:00	22:00		32:00	
	Carbohydrates (g)	55	36	15	84		90	44		54	
	τ_M (min)	60	107	82††	79		76	131		66	
4	Time	8:00	12:30		13:00	16:45	18:00	22:00	25:45	32:00	
	Carbohydrates (g)	68	15†		129	20†	98	27	43	100	
	τ_M (min)	45	16		30	14	65	144	45	103	
5	Time	8:00	12:00		13:00		18:00	22:00		32:00	
	Carbohydrates (g)	49	5†		51		56	70		49	
	τ_M (min)	39	10		37		35	68		30	
6	Time	8:00			13:00		18:00	22:00		32:00	
	Carbohydrates (g)	20			54		63	48		24	
	τ_M (min)	27			62		68	150		27	
7	Time	8:00	11:48		13:45		18:00	22:00		32:00	36:12
	Carbohydrates (g)	81	15†		102		101	73		81	15†
	τ_M (min)	32	10		34		25	32		32	10
8	Time	8:00			13:00		18:00	22:00		32:00	
	Carbohydrates (g)	28			71		52	14		35	
	τ_M (min)	27			73		72	47		66	
9	Time	8:00			13:00		18:00	22.00		32:15	
	Carbohydrates (g)	76			37		101	54		76	
	τ_M (min)	46			46		58	38		51	
10	Time	8:00	11:45		13:00		18:00	25:48	28:30	32:00	
	Carbohydrates (g)	40	14†		80		61	56	14†	40	
	τ_M (min)	31	16		57		83	31	10	44	

[a] Breakfast, lunch, and dinner were scheduled at 8:00, 13:00, 18:00, and 22:00 (actual times given in table) expressed as the elapsed time from midnight of day 1 of the study period. Carbohydrate consumed at times other than scheduled meals were in response to blood glucose < 60 mg/dl or hypoglycemic symptoms, with juice denoted by † (†† excluded for analysis, as juice and meal could not be resolved as separate components). Subject 2 requested not to consume carbohydrates for most meals (followed Atkins low carbohydrate diet).

Discussion

Results from the present study demonstrate that a low-order PK/PD insulin model can be combined with a low-order model describing glucose appearance following meals and a single compartment model of glucose distribution to yield an identifiable composite model capable of reproducing clinical closed-loop study results. The composite model, composed of only five equations with eight identifiable parameters, reproduced approximately 90% of the observed dynamics in glucose concentration *per se* (**Figure 4**; insulin delivery and insulin concentration reconstructed with model equations). Although none of the submodels used in the MVP model are new, the present study is the first to combine them into a single model and identify parameters from data in subjects with type 1 diabetes and identify changes in parameters over a 24 h period. We believe—as do many others[3]—that understanding how the parameters change during the day will be an important consideration when developing new closed-loop insulin delivery algorithms.

Although results in the present study establish the MVP model[11] as an identifiable model capable of reproducing prior closed-loop study results,[5] they do not fully validate the model as a *simulation* tool. Using the model as a simulation tool will require model validation against clinical results obtained independent from those used during model development and identification. For example, the clinical study results in which the PID algorithm was modified to include a meal bolus[18] should be reasonably reproducible with only minor differences being attributed to the difference between adult[5] and pediatric[18] patient populations. Further validation would be to optimize control parameters for patients previously identified under closed loop and demonstrate in a subsequent clinical study, on the same subjects, that the optimization improves control performance.

Components of the MVP model [**Equations (1)–(5)**] have all been taken from existing literature—with the insulin PK/PD model first advocated by Sherwin and colleagues[19] in 1974, the Bergman minimal model dominating clinical assessment of insulin sensitivity since 1979,[20] and the meal model taken almost verbatim from work by Hovorka and associates.[9] Nonetheless, many higher-order models exist to describe in greater detail metabolic fluxes specific to different tissues and to separate out subtle differences in the time course of insulin's effect to increase glucose uptake and decrease endogenous glucose production. The complete model proposed by Hovorka and coworkers,[9,10] from which the meal subcomponent used here [**Equation (5)**] was taken, uses higher-order model components for both glucose and insulin, as does the model proposed by Kovatchev and colleagues[21] and approved by the Food and Drug Administration for preclinical testing of control algorithms. Noteworthy is that many different metabolic models exist, including, but not limited to, the model originally proposed by Sorenson[22] in 1985, the Karlsburg *Diabetes* Management System developed in Karlsburg to aid in optimizing open-loop insulin therapy,[23–25] the Internet AIDA simulator developed by Lehmann and associates[26,27] as an educational tool, and models that have been developed by Chase and coworkers[28,29] and Van Herpe and colleagues[30,31] for aid in developing critical care insulin delivery algorithms. Virtually all the models are higher order than the MVP model; however, in most cases, they do not explicitly address intraday or interday variance of model parameters. Variation in these parameters creates a requirement for different basal insulin rates throughout the day and potentially between days. The change in insulin requirement is important for closed-loop simulation studies insofar as different classes of controllers exist that can be shown to correct for a change in control output absent any change in the variable being controlled[32] (e.g., compensate for decrease in insulin sensitivity with an increase in insulin delivery not driven by any change in fasting glucose,[2] which should remain at target).

The existence of so many different models raises the question of whether model comparisons of different control algorithms depends on the choice of model or, more importantly, whether model-derived preclinical safety analysis depends on the choice of model. It is possible that all the different models—seven if one were to just consider those referenced in this article[4,11,21,24,27,28,30]—will produce results sufficiently similar to generate substantially the same conclusions. If this is true, an argument could be made for using the simplest model. More likely, however, is that the differences among models are sufficient to generate different conclusions regarding both the type of controller that should be implemented and how safe it is. If the latter is true, the importance of validating model-based conclusions with clinical studies where the safety of the subject is ensured by monitoring the patient *per se* will become increasingly important.

Generally, the use of higher-order model terms, or more equations, should improve the ability to describe differences in the time course of insulin action in different tissues (e.g., liver, muscle, and fat); however, the use of

high-order terms increases the number of parameters to be identified. In some cases, the models may require the addition of multiple glucose tracers,[33–35] and in other cases, certain model configurations may produce states that are *near* unobservable.[32] Many advocates of metabolic modeling[3] argue that these models should be reserved for simulation purposes only, with lower-order models acceptable for use in a control algorithm *per se*. However, if the "simulation" and "control" models differ, understanding the relationship between the two may still be important. Open-loop predictions obtained with the two models should be expected to have a correlation less than 1, as $R^2 = 1$ would mean the higher-order terms contribute nothing to the dynamic response. However, the two models should also be expected to have a sufficiently high correlation to effect improvements in model-based control algorithms. It is not clear what the threshold correlation needs to be to affect improvements in control or to what extend the unexplained variance ($1 - R^2$) should be attributed to inconsistencies in model order versus inconsistencies in model parameters. Differences in how the unexplained variance is attributed can substantially impact closed-loop stability analysis (a full discussion of the relationship between model order and closed-loop stability requires root-locos analysis[32] and is beyond the scope of this article).

In the present study, evidence supporting a higher-order PK insulin model was found in only 2 of 10 subjects. Using the lower-order two-compartment model produced fits with R^2 ranging from 0.819 to 0.972, suggesting little room for improvement given that some of the variance can be attributed to errors in blood sample times, error in the insulin assay, or errors associated with removing small air bubbles trapped in the insulin syringe. It is possible that the present study lacked statistical power to identify the higher-order terms. If this is the case, testing the PK/PD model order using conditions in which the glucose concentration does not change[36,37] may offer a more powerful method to detect high-order PK/PD terms. Generally, metabolic models should fit and/or predict not only the data they were identified on, but other experimental conditions such as clamps specifically designed to elucidate insulin PK/PD profiles,[36–38] different meal responses,[39–41] and interruptions of insulin delivery.[42] A more detailed modeling analysis of these types of studies may provide further insight into the need for higher-order PK/PD model terms.

Although high-order model terms were not required to fit the closed-loop data evaluated here, changes in the parameters during the course of the day were required in 7 of 10 subjects. None of the changes related to the insulin model *per se* but were rather associated with the minimal model (parameters *GEZI*, S_I, and *EGP*). The criteria used to determine the need to change parameters was not overly strict: overall mean error less than 25 mg/dl, model-estimated peak postprandial glucose within 25 mg/dl of measured peak values with times within 0.5 h of each other, and nadir values for glucose excursions below 80 mg/dl to be predicted within 15 mg/dl with time of nadir within 0.5 h. The 0.5 h window was chosen based on the limited availability of blood glucose samples (~20 min) and to allow 10–20 min for subjects to consume meals. The criteria were empirically chosen to not be so stringent that every profile would be rejected and thus bias the results in favor of intraday variance, but to still be sufficiently stringent to reject a model fit that did not reproduce occurrences of hypoglycemia and hyperglycemia. Intraday variance was structured such that parameters could only assume one of two values in a 24 h period and only allowed for the three parameters (*GEZI*, S_I, and *EGP*) for which evidence already exists in the literature for intraday variation.[43–46]

Although variation in model parameters was structured to capture putative diurnal changes in insulin requirement,[43–46] the timing of the identified window was surprising in some subjects. For example, the ~18 to 22 h window in **Figure 3D** would not normally be thought of as coinciding with a diurnal change in insulin sensitivity. The window identified was in response to a lower-than-expected postprandial glucose excursion given the amount of carbohydrate ingested and the amount of insulin on board at the time of the meal. For the example, plasma glucose concentration actually fell below premeal levels after the meal was consumed, and the profile could only be fit by decreasing *EGP* and increasing S_I. It is possible that an acceptable fit may have been obtained by changing the bioavailability of the carbohydrate (A_G in Reference 9), but this was not tested here. We have previously observed similar behavior in a canine closed-loop modeling study[47] and speculated that glucose extraction by the gut may be insulin sensitive. Ideally, a closed-loop controller should be able to handle either scenario, with an acute increase in gut extraction being the easier control problem, as it is equivalent to eating a smaller meal.

In the present study, the number of patients identified is too small ($N = 10$) to provide a sufficient range of parameters, and the conditions under which the model was shown to reproduce clinical data are too limited, to allow the model to be applied as the sole means of

comparing different algorithms or assessing preclinical safety. As more closed-loop studies are conducted, the virtual population can of course be increased, but a more immediate approach would be to expand the range of parameters identified here by increasing or decreasing the value of any one parameter and re-identifying the remaining parameters in the presence of realistic measurement noise (~3% for glucose and 7% for insulin). This should allow the range of parameters to be expanded while ensuring each new parametric configuration produces a realistic subject. Having an identifiable model may also allow published studies to be used in identifying new parametric configurations. For example, changes in parameters that might occur in response to a high-fat meal such as pizza[39,40] can be identified, or widely varying meal absorption profiles in the presence of carbohydrate from different sources[41] can be identified. Probably the most promising source of new virtual subjects may reside in the ability to identify the MVP model from open-loop pump and CGM data, for which large databases exist. The low-order submodels chosen as a basis for the MVP model, and the inclusion of intraday variance in insulin requirement, make the MVP model ideally suited for identifying parameters in subjects with different basal rates during the day or documented changes in fasting glucose between days despite the same basal rate.

Conclusion

Metabolic models are widely believed to be able to accelerate the design of closed-loop insulin delivery algorithms. We conclude that such models will need to explicitly describe intraday variation in metabolic parameters but that the model itself need not be comprised of a large number of compartments or differential equations. In the present study, a model comprised of only five equations was identified for 10 subjects using previously acquired closed-loop glucose and insulin profiles. Insulin delivery, insulin concentration, and plasma glucose dynamics were well predicted by the model ($R^2 > 0.9$ for glucose), but intraday variation in insulin sensitivity, endogenous glucose production, and glucose effectiveness was required to accurately predict the high and low glucose values in 7 of the 10 subjects. Adding intraday variation increased the total number of parameters to be identified from 8 to 11 plus the added the meal time constants, but identification was still achieved using data readily obtained from a closed-loop study.

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