Modeling Day-to-Day Variability of Glucose–Insulin Regulation Over 12-Week Home Use of Closed-Loop Insulin Delivery

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***Abstract*—Parameters of physiological models of glucose–insulin regulation in type 1 diabetes have previously been estimated using data collected over short periods of time and lack the quantification of day-to-day variability. We developed a new hierarchical model to relate subcutaneous insulin delivery and carbohydrate intake to continuous glucose monitoring over 12 weeks while describing day-to-day variability. Sensor glucose data sampled every 10-min, insulin aspart delivery and meal intake were analyzed from eight adults with type 1 diabetes (male/female 5/3, age 39.9 ± 9.5 years, BMI 25.4 ± 4.4 kg/ m^2, HbA1c 8.4 ± 0.6%) who underwent a 12-week home study of closed-loop insulin delivery. A compartment model comprised of five linear differential equations; model parameters were estimated using the Markov chain Monte Carlo approach within a hierarchical Bayesian model framework. Physiologically, plausible *a posteriori* distributions of model parameters including insulin sensitivity, time-to-peak insulin action, time-to-peak gut absorption, and carbohydrate bioavailability, and good model fit were observed. Day-to-day variability of model parameters was estimated in the range of 38–79% for insulin sensitivity and 27–48% for time-to-peak of insulin action. In conclusion, a linear Bayesian hierarchical approach is feasible to describe a 12-week glucose–insulin relationship using conventional clinical data. The model may facilitate *in silico* testing to aid the development of closed-loop insulin delivery systems.**

***Index Terms*—Artificial pancreas, bayesian parameter estimation, hierarchical model, simulation, type 1 diabetes (T1D).**

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I. Introduction

TYPE 1 diabetes (T1D) is characterized by autoimmune destruction of the pancreatic β-cells secreting insulin in health and leads to a lifelong dependency on exogenous insulin to prevent the development of ketoacidosis, coma, and death [1]–[3]. Maintaining glycemic level within the near-normal target range by applying individualized insulin dosing regimens is a key factor in reducing the risk of long-term and acute diabetes micro- and macrovascular complications and delaying the progression of the disease. As glucose excursions in T1D are affected by numerous factors including diet, exercise, stress with considerable day-to-day and between-subject variability, achieving and maintaining glycemic target on a daily basis is challenging despite guidance by experienced healthcare professionals.

Closed-loop glucose control referred to as "the artificial pancreas" is an emerging technology that offers automated, glucose responsive insulin delivery. The extracorporeal device comprises a continuous glucose monitoring (CGM) system, an insulin pump and a control algorithm, which directs insulin delivery by the insulin pump based on real-time CGM values. The artificial pancreas has recently been evaluated in longer term home studies in children and adults with T1D demonstrating improved glycemic control and a reduced hypoglycemia risk compared to conventional sensor-augmented pump therapy [4]–[6].

The safety and efficacy of the control algorithm and system-level performance requires rigorous assessments. Testing via computer simulations may accelerate the development and saves resources compared to clinical testing [7]. An *in silico* simulation environment for T1D encompasses as a key feature a mathematical model of glucose–insulin regulation in T1D [7]–[9]. Numerous gluco-regulatory models of varying complexity have been proposed [10]–[14]. However, existing models are commonly limited by the fact that glucose excursions are modeled over relatively short periods of time, from several hours up to two days, and lack the ability to describe evidence-based day-to-day variability. As closed-loop insulin delivery systems have entered the stage of long-term home trials [15], a simulation model that produces realistic multiday glycemic excursions is highly desirable to describe day-to-day variability of responses to insulin, meals, and other relevant factors.

Here, we present a model of glucose-insulin regulation developed with the aim to fulfill such requirements. Major motivation

was the availability of a unique dataset comprising continuously measured sensor glucose, meals, and insulin data over 12 weeks. The data were collected in adults with T1D who used 24/7 closed-loop insulin delivery for 12 weeks in free-living home settings [4]. The multiday datasets allowed us to impose a hierarchical model structure to capture day-to-day variability. Individual physiological parameters were estimated using a full Bayesian approach adopting the Markov chain Monte Carlo (MCMC) technique. Having identified model parameters and to demonstrate the model's ability to predict glucose excursions, we carried out computer simulations of an unrelated clinical trial to support model validity [16].

By capturing both between-subject and day-to-day variability of physiological parameters, the presented model could be implemented in an *in silico* testing environment to aid the development of closed-loop insulin delivery systems.

II. Methods

The proposed model comprises five compartments and is used to fit CGM data collected in a 12-week long clinical study [4]. A hierarchical Bayesian framework is utilized for parameter estimation.

A. Glucose–Insulin Model

The glucose–insulin model comprises three submodels describing insulin absorption and action, meal absorption dynamics, and glucose dynamics. The model uses subcutaneous insulin delivery and carbohydrate intake as model input and CGM as model output.

1) Insulin Absorption and Action: The insulin absorption action submodel is described by a set of equations:

$$\frac{dx_1(t)}{dt} = -\frac{1}{t_{\max,IA}}x_1(t) + \frac{u_I(t)}{60} \quad (1)$$

$$\frac{dx_2(t)}{dt} = \frac{1}{t_{\max,IA}}(x_1(t) - x_2(t)) \quad (2)$$

$$X(t) = \frac{1000 \times x_2(t)}{t_{\max,IA}\mathrm{MCR}_I W} \quad (3)$$

where $x_1\,(t)$ and $x_2\,(t)$ represent the amount of effective insulin in the first and second insulin absorption compartment, respectively (U); $u_I\,(t)$ represents exogenous delivery rate of insulin aspart (U/h) at time t (immediate insulin bolus is modeled as a short burst insulin infusion); $t_{\max,\mathrm{IA}}$ is the time-to-maximum of effective insulin concentration (min); $X\,(t)$ is the concentration of effective insulin (mU/l); W is the subject's body weight (kg); and MCR_I is the metabolic clearance rate of effective insulin fixed at 0.017 (l/kg/min) as reported in [17].

2) Meal Absorption Dynamics: The meal absorption is represented by two compartments and described by the following equations:

$$\frac{da_1(t)}{dt} = -\frac{1}{t_{\max,G}}a_1(t) + \delta_{t_j}(t)u_G(t_j) \quad (4)$$

$$\frac{da_2(t)}{dt} = \frac{1}{t_{\max,G}}(a_1(t) - a_2(t)) \quad (5)$$

$$U_M(t) = \frac{5.556 \cdot A_G a_2(t)}{t_{\max,G}V_G W} \quad (6)$$

where $a_1\,(t)$ and $a_2\,(t)$ represent carbohydrate amount in the first and second meal absorption compartment, respectively (g); $u_G\,(t_j)$ represents the carbohydrate amount eaten at time t_j (g); $t_{\max,\mathrm{G}}$ is the time-of-maximum appearance rate of glucose (min); A_G is the fractional bioavailability (unitless); V_G is the plasma glucose pool size fixed at 0.16 (l/kg) as reported in [12]; $U_M\,(t)$ is the gut carbohydrate absorption rate with unit converted to glucose concentration rate of change (mmol/l/min).

3) Glucose Dynamics: The kinetics of the continuously monitored glucose concentration is represented by a single compartment:

$$\frac{dG(t)}{dt} = -S_I(X(t) - X_b) + U_M(t) - K(G(t) - G_b) \quad (7)$$

where $G\,(t)$ is the blood glucose concentration (mmol/l); S_I is the insulin sensitivity (mmol/l/min per mU/l); X_b represents the basal effective insulin concentration at which glucose level would be maintained constant (mU/l); G_b is the basal glucose level (mmol/l) and K the glucose self-regulation fractional rate (/min) which has an effect of self-regulating the glucose level towards G_b.

It is assumed that the insulin-dependent glucose utilization does not depend on plasma glucose concentration. This assumption is also used by Magdelaine *et al.* in their recent modeling work [11].

B. Closed-Form Solution

The linearity of the system of ordinary differential equations (1)–(7) allows a closed-form solution to be obtained substantially speeding up inference. The description of the solution is presented in online supplementary material (OSM) Appendix A. The solution is coded into the parameter estimation software, accelerating the estimation process when the Bayesian inference and MCMC methods are utilized (see Section II-D).

C. Experimental Data

Conventionally collected clinical data including sensor glucose, insulin aspart delivery, and meal intake were analyzed. The data were collected from eight adults with T1D (male/female 5/3, age 39.9 ± 9.5 years, BMI 25.4 ± 4.4 kg/ m^2, HbA1c 8.4 ± 0.6%) who underwent a 12-week study of closed-loop insulin delivery in free-living home settings [4].

The study protocol was approved by local ethics committee. All participants signed informed consent and the study was conducted in accordance with the Declaration of Helsinki.

During closed loop, the sensor glucose were sampled every 10 min by FreeStyle Navigator II CGM system (Abbott Diabetes Care); basal insulin infusion rates on the study pump (Dana R Diabecare, Sooil) were automatically adjusted every 12 min using a model-predictive-control algorithm [18] and real-time continuous glucose sensor levels; participants additionally administered prandial insulin using the standard pump bolus calculator, which also recorded the carbohydrate content for each bolused meal as estimated by the subject.

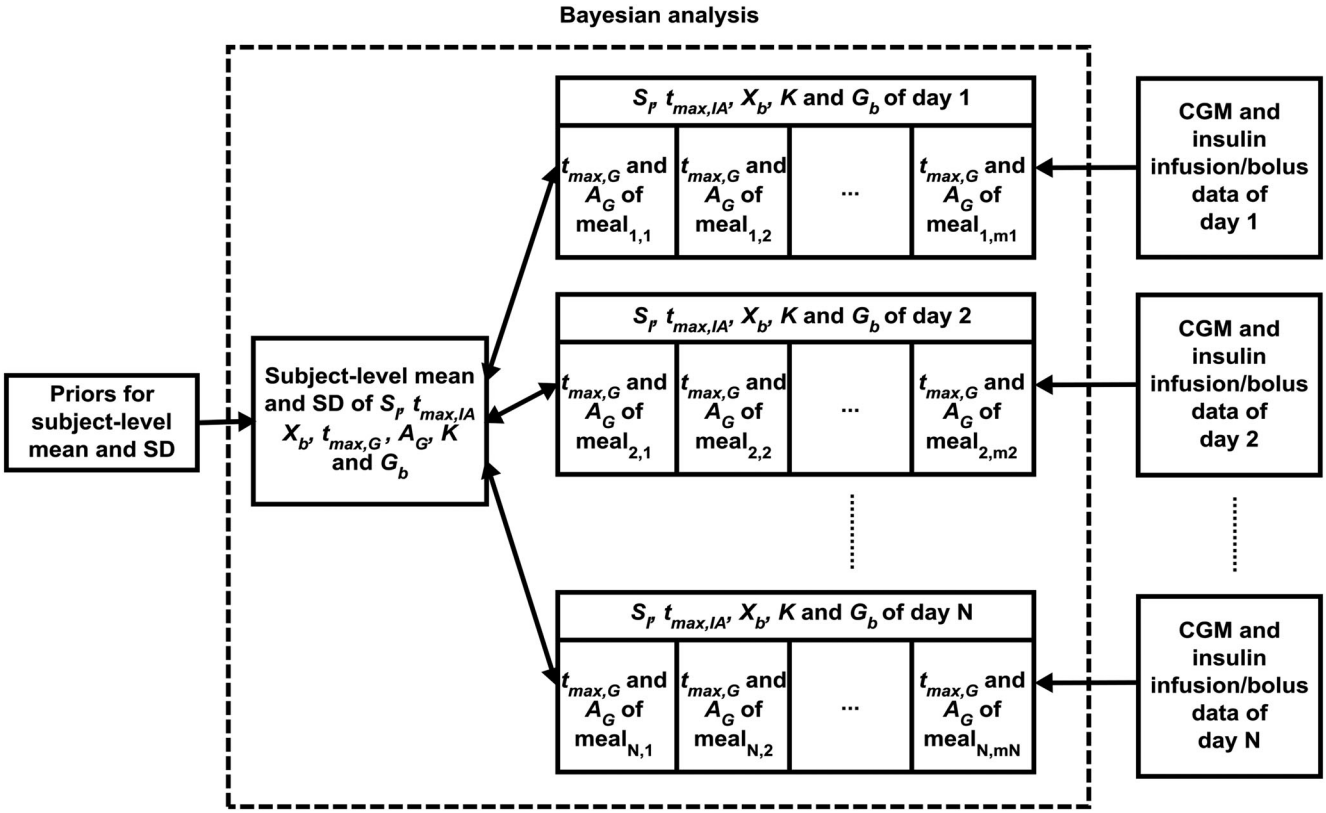

Fig. 1. Bayesian hierarchical analysis of the glucose–insulin regulation. Estimates of the day-level parameters S_I, $t_{\max,\mathrm{IA}}$, X_b, $t_{\max,\mathrm{G}}$, A_G, K, and G_b were made in parallel with the subject-level mean and SD in one subject over N days. The advantage of Bayesian estimation is the possibility of "information flow" between days since the day-level estimates rely on the observed glucose–insulin data of that day, and also on the subject-level distribution, which in turn is derived totality of individual day data.

Data of individual days with amount of sensor glucose readings less than 85 out of 144 reads per day (<60%) were considered incomplete and excluded from the present analysis.

D. Parameter Estimation

For each subject, model parameters were estimated using the MCMC approach within a hierarchical Bayesian framework.

1) Bayesian Hierarchical Analysis: A multiday dataset with up to 84 days per subject was used by the Bayesian hierarchical approach, which incorporated vague prior information at the subject level to estimate the model parameters. For each subject, estimates of the day-level parameters S_I, $t_{\max,\mathrm{IA}}$, X_b, $t_{\max,\mathrm{G}}$, A_G, K, and G_b (one set of parameters per day; during the day parameters were assumed time invariant) were made in parallel with the subject-level mean and the coefficient of variation (CV) of day-to-day variability. Qualified day-level clinical data (see Section II-C) collected from closed-loop insulin delivery were utilized. A schematic representation of the Bayesian hierarchical framework is shown in Fig. 1. A more detailed description of the Bayesian hierarchical approach is provided in OSM Appendix C.

2) Prior Density Functions: The Bayesian analysis utilizes prior distribution of model parameters. In principle, reliable prior knowledge for some of the parameters allows relatively strong prior distributions with tight variances to be applied. Generally, noninformative vague prior distributions are adopted for parameters of interest to allow clinical data to determine the posterior distributions [19]. In the present analysis, vague but proper prior information with a large variance was assigned to model parameters (OSM Appendix B).

3) Implementation Details: The parameter estimation was carried out using the Bayesian framework (OSM Appendix C). Following the model specification and assignment of prior distributions to unknown parameters, Bayesian statistical inference was applied to obtain posterior distributions of parameters. The WinBUGS software [20] using MCMC techniques [21] and Metropolis–Hasting algorithm [22] was utilized to draw samples from the target posterior distributions of unknown parameters. The WinBUGS extension "WBDev" [23], [24] was used to implement the closed-form solution of the glucose–insulin regulation model into the statistical model. For the purposes of parameter estimation, the errors associated with the CGM measurements were assumed to be non-correlated normally distributed with zero mean and a CV of 10%.

For each parameter, a single Markov chain was analyzed with 4000 samples (with thinning of 200—equivalent to 800 000 iterations in total), from which the first 2000 samples were discarded as burn-in chains and the remaining 2000 samples were used for further analysis. The calculations were performed on a Microsoft Windows Server version 6.1. For each subject's

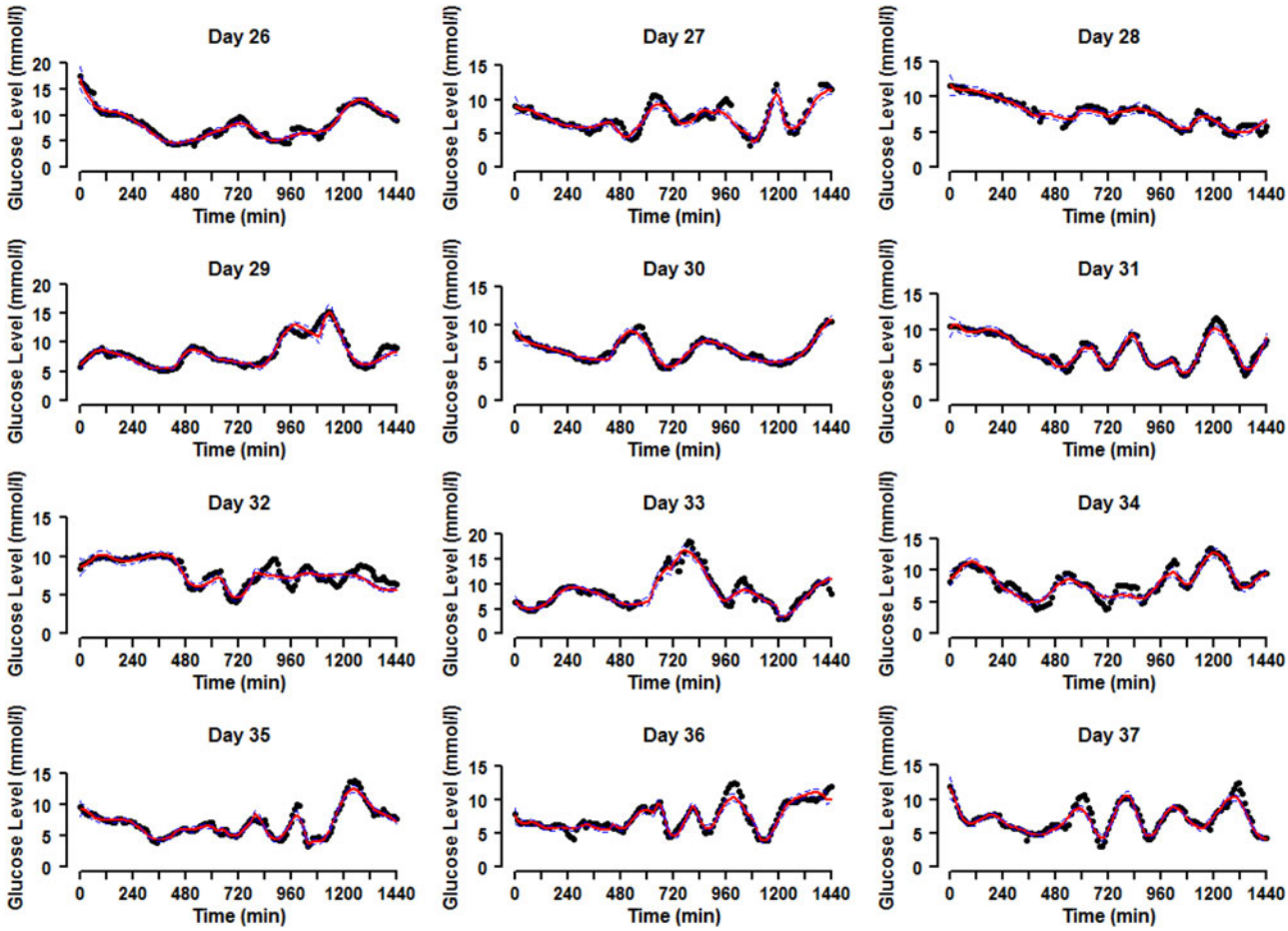

Fig. 2. Model fit of CGM data in a sample subject Cam03 (Day 26–Day 37 are shown). The black circles are CGM measurements, the red solid lines represent the median of model fit, and the blue dashed lines represent 95% credible intervals of model fit.

dataset, the generation of the chains with 4000 samples took approximately 70 h.

Further details of the Bayesian approach can be found in OSM Appendix C.

III. Results

A. Sample Fit

A sample model fit to 12 days of CGM measurements is shown in Fig. 2, indicating the ability of the model to fit the data.

B. Assessment of Model Fit

Good unbiased model fit was obtained for all eight datasets as demonstrated by the plot of weighted residuals associated with CGM measurements, see Fig. 3.

C. Parameter Estimates

Posterior realizations of subject-level and day-level parameters demonstrated physiological plausibility. Parameter estimates of the subject-level mean and CV, and population mean $\pm$ SD are reported in Table I. The estimated $t_{\max,\mathrm{IA}}$ for insulin aspart at 78 min lies within the reported range of 30–90 min [25]. The insulin sensitivity index S_I was estimated at 0.005 mmol/l/min per mU/l, which is in accordance with published literature reporting 0.0005/min per mU/l if at a glucose concentration of 10 mmol/l [26]. The basal effective insulin concentration X_b was estimated at 12.9 mU/l, which, in steady-states conditions (when $X(t) = X_b$, $G(t) = G_b$, and $x_1(t) = x_2(t) = x_{\mathrm{ss}}$), represents "a constant insulin infusion rate x_{ss} of 0.017U/h/kg [or 1.2 U/h at 70-kg body weight as calculated from (3)] that maintains constant glucose level. The CVs represent day-to-day variability of the model parameters which were estimated in the range of 38–79% for insulin sensitivity and 27–48% for time-to-peak insulin action. Boxplots representing the variability of individual day-level estimates of S_I, $t_{\max,\mathrm{IA}}$, and X_b are shown in Fig. S1, OSM Appendix D.

D. Simulation of 2-h Insulin Pump Suspension

For the purpose of model validation, we performed an *in silico* simulation of an independent clinical trial during which the insulin pump basal infusion was suspended for 2 h followed by insulin infusion at 1 U/h for another 2 h over 99 nights in 17 people with T1D [16]. We simulated glycemic changes during and after the 2-h pump suspension using the proposed glucose–insulin model and adopting 96 estimated day-level pa-

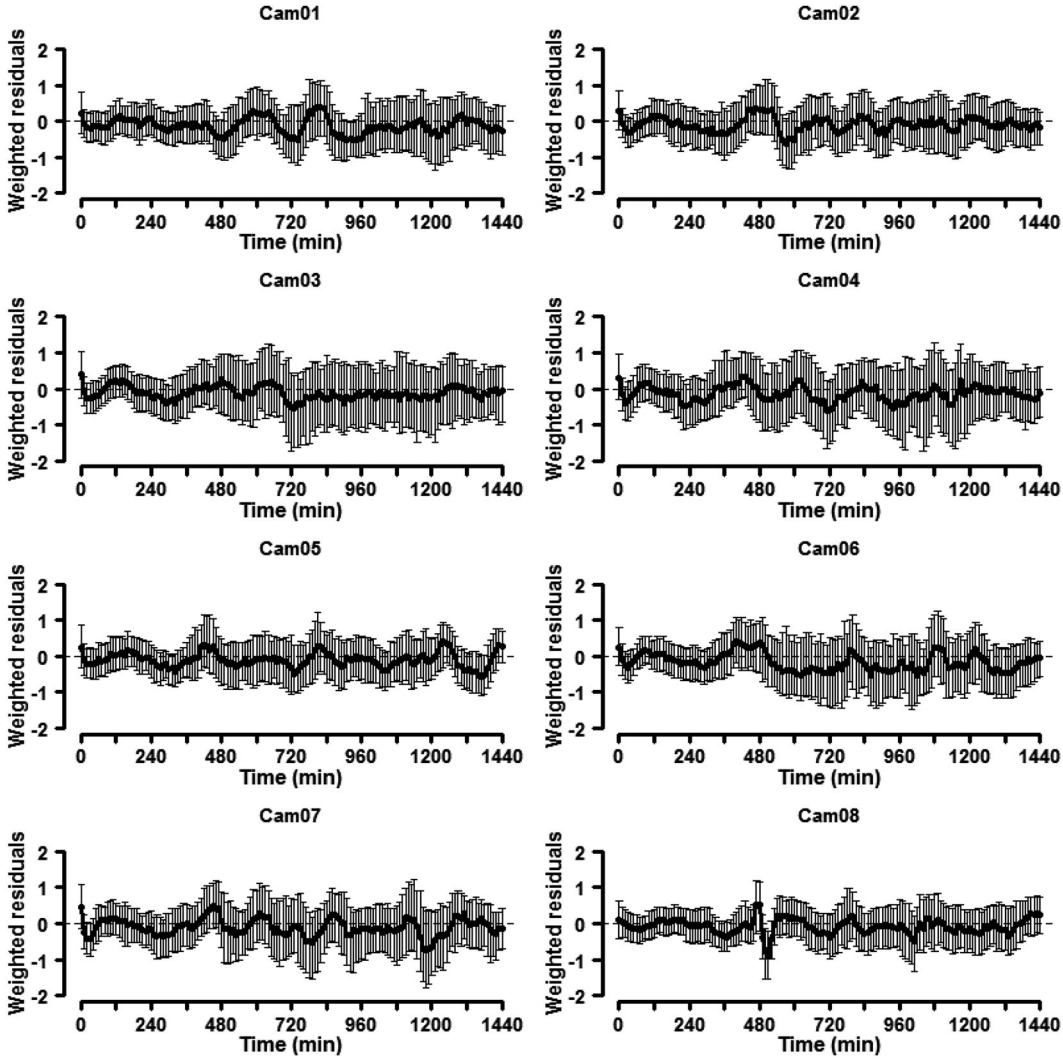

Fig. 3. Weighted residuals (difference between model-predicted and measured CGM values divided by the measurement error) [median (IQR)].

TABLE I
ESTIMATES OF SUBJECT-LEVEL AND POPULATION-LEVEL MODEL PARAMETERS

	Parameter						
Subject	$t_{max,IA}$ (min)	SI(mmol/ l/ min per mU/ l)	X_b (mU/ l)	$t_{max,G}$ (min)	A_G (unitless)	K(/ min)	G_b (mmol/ l)
Cam01	93	0.0055	8.5	59	0.88	0.0040	6.5
	(43)	(69)	(55)	(41)	(64)	(43)	(32)
Cam02	75	0.0052	10.8	40	0.85	0.0041	7.7
	(48)	(50)	(35)	(65)	(69)	(40)	(27)
Cam03	72	0.0063	12.2	39	0.72	0.0046	7.2
	(44)	(73)	(28)	(68)	(69)	(50)	(27)
Cam04	70	0.0044	11.7	40	0.68	0.0046	6.8
	(43)	(69)	(32)	(68)	(85)	(70)	(26)
Cam05	74	0.0065	11.0	64	1.11	0.0033	6.2
	(35)	(38)	(26)	(37)	(39)	(11)	(30)
Cam06	104	0.0037	16.2	47	0.64	0.0037	6.8
	(47)	(79)	(30)	(56)	(97)	(32)	(32)
Cam07	68	0.0035	17.1	38	0.85	0.0035	5.5
	(42)	(58)	(25)	(66)	(57)	(28)	(29)
Cam08	71	0.0049	16.0	53	0.96	0.0033	6.3
	(27)	(49)	(27)	(50)	(50)	(13)	(29)
Population	78±13	0.0050±0.0011	12.9±3.1	48±10	0.84±0.16	0.0039±0.0005	6.6±0.7
	(41±7)	(60±14)	(32±10)	(56±12)	(66±18)	(36±19)	(29±3)

Subject-level mean (CV) over days and population parameter values (population CV) mean ± SD are reported.

rameter sets randomly chosen from the eight tested participants (12 day-level parameter sets from each subject).

The comparison between the simulated and published clinical results shown in Fig. S2, OSM Appendix E, demonstrates comparable changes in glucose concentration at 2 h (end of the 2-h-insulin suspension) and at 4 h (2 h after resumption of insulin delivery) including the between-subject and between-night variability.

IV. Discussion

To our knowledge, the presented insulin–glucose regulation model is the first to describe frequently measured sensor glucose data in adults with T1D over a prolonged period of up to 84 days. We investigated a Bayesian hierarchical modeling approach to estimate subject-level and within-subject day-to-day model parameters including insulin sensitivity, time-to-peak insulin action, time-to-peak gut absorption, and carbohydrate bioavailability. The model quantified between-day variability of the key physiological parameters. The proposed mathematical model comprises five linear differential equations and is of moderate complexity with an aim to capture essential features of glucose–insulin dynamics and, at the same time, guarantee applicability to the rich datasets. The results obtained from eight study participants' datasets not only show the physiological plausibility of estimated model parameters (see Table I) and good model fit (see Figs. 2 and 3), but also the model's ability to reproduce published clinical results (OSM Fig. S1).

Previous studies successfully demonstrated applications of the Bayesian hierarchical framework in various biomedicine- or physiology-related dynamic systems [26]–[31] including the well-known "minimal model" describing the glucose–insulin kinetics [26], [28]. Important advantages of using the Bayesian hierarchical approach is that it allows each subset to "borrow strength" from the likelihood contributions of other subsets via their joint influence on the estimate of the unknown "joint distribution" of parameters, especially under missing data scenarios. The multiday datasets utilized in the present analyses enabled us to implement the hierarchical structure facilitating the information flow between days and thus increasing the credibility of the estimated day-level and subject-level parameters.

Our model of glucose–insulin regulation consists of five compartments and three submodels. The insulin effect is described by a two-compartment model, simplified from previously used three compartment [12], [14] to avoid identifiability issues due to the lack of plasma insulin concentration measurements. The meal absorption dynamics is represented by a two compartment model similar to one used in a previously published simulation model [7]. As no information pertaining to the meal contents was provided which may prompt different meal absorption patterns [32], when fitting the data, each consumed meal was assumed to have its own time-to-peak of maximum absorption $t_{\max,\mathrm{G}}$ and bioavailability A_G. The glucose dynamics is described by a single compartment with insulin-dependent glucose utilization assumed as linear, assumption also recently adopted by Magdelaine *et al.* [11]. In addition, a glucose self-regulation parameter K was incorporated into the model which allowed the glucose level to be driven toward a basal state G_b. This self-regulation effect may represent renal clearance of glucose at high glucose concentration [33] or counter-regulatory hormone effect at low glycaemia [34], an important but omitted component in previously published models.

The reported results support the use of the model in *in silico* testing of glucose controllers. For each virtual subject, with identified day-level parameter set, the presented model enables simulations of long-term study reflecting the day-to-day variability in the individual physiology. A clear benefit of using the current model in the simulation environment is that due to its linearity, the insulin effects on the glucose concentrations can be separated out from the full analytical solution. Thus, simulations can be performed fast by separating the meal effect and re-evaluating glycemic changes stimulated by different insulin dosing schemes advised by different glucose controllers.

The main strength of the present study is its novelty in characterizing day-to-day variability of physiological parameters through the use of a large dataset collected over 84 days. Identification of the presented model only requires standard clinical data (CGM levels, insulin dose and amount of carbohydrate contents) to be collected without the need of glucose tracer or plasma insulin concentration data, which are utilized by more complex models [12], [13]. The long-term model proposed by Magdelaine *et al.* [11] used the same type of clinical data but only described CGM readings for two days and assumed identical parameter values between-days. Another advantage of adopting the proposed model is the availability of the closed-form solution speeding up the parameter estimation process especially when using the Bayesian inference and MCMC methods.

However, as with all modeling efforts, there are limitations. The relatively simple model structure does not currently take into account diurnal variations. In an attempt to capture diurnal variations in the model parameters and potential influences resulting from other factors, such as physical activities and stress levels, we tested the integration of an autoregressive model into the residual errors in our preliminary analyses (data not shown). However, parameter estimation became notably (three to five times) protracted and posterior model identifiability issues became apparent. Computational speed and memory considerations prevented us from including subject-level domain as another layer in our hierarchical analysis. Having such a layer might have led to increased accuracy of population parameter estimates and could be implemented through a two-stage approach as described recently [35]. Nonetheless, these limitations do not diminish the major achievements of our modeling approach.

V. Conclusion

In conclusion, the present study demonstrates the feasibility of a new model to represent 12-week glucose-insulin interactions within a Bayesian hierarchical framework. The day-to-day variability of physiological parameters was assessed quantitatively. The model could be implemented in an *in silico* testing environment to simulate realistic data-informed long-term closed-loop insulin delivery trials and to aid the development of closed-loop systems for home use. Further investigations are warranted.

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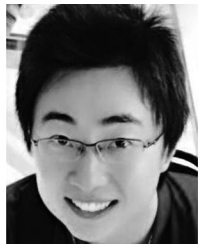

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