A Glucose-Insulin Mixture Model and Application to Short-Term Hypoglycemia Prediction in the Night Time

Weijie Wang, Shaoping Wang, Xingjian Wang, Di Liu, Yixuan Geng, and Teresa Wu

Abstract*—*Objective: **Insulin-induced hypoglycemia is recognized as a critical problem for diabetic patients, especially at night. To give glucose prediction and advance warning of hypoglycemia of at least 30 minutes, various glucose-insulin models have been proposed. Recognizing the complementary nature of the models, this research proposes a Glucose-Insulin Mixture (GIM) model to predict the glucose values for hypoglycemia detection, by optimally fusing different models with its adjusted parameters to address the inter- and intra-individual variability.** ***Methods:*** **Two types of classic glucose-insulin models, the Ruan model, with single-compartment glucose kinetics, and the Hovorka model, with two-compartment glucose kinetics, are selected as two candidate models. Based on Bayesian inference, GIM is introduced with quantified contributions from the models with the associated parameters. GIM is then applied to predict the glucose values and hypoglycemia events.** ***Results:*** **The proposed model is validated by the nocturnal glucose data collected from 12 participants with type 1 diabetes. The GIM model has promising fitting of RMSE within 0.3465 mmol/L and predicting of RMSE within 0.5571 mmol/L. According to the literature, the hypoglycemia is defined as 3.9 mmol/L, and the GIM model shows good short-term hypoglycemia prediction performance with the data collected within the last hour (accuracy: 95.97%, precision: 91.77%, recall: 95.60%). In addition, the probability of hypoglycemia event in 30 minutes is inferred. Conclusion: GIM, by fusing various glucose-insulin models via Bayesian inference, has the promise to capture glucose dynamics and predict hypoglycemia.** ***Significance:*** **GIM based short-term hypoglycemia prediction has potential clinical utility for timely intervention.**

***Index Terms*—Bayesian inference, glucose-insulin model, model uncertainty, parameter uncertainty.**

Manuscript received February 13, 2020; revised April 24, 2020 and July 8, 2020; accepted August 2, 2020. Date of publication August 10, 2020; date of current version February 19, 2021. *(Corresponding author: Shaoping Wang.)*

Weijie Wang, Di Liu, and Yixuan Geng are with the School of Automation Science and Electrical Engineering, Beihang University.

Shaoping Wang is with the School of Automation Science and Electrical Engineering, Beihang University, Beijing 100191, China, and also with the Beijing Advanced Innovation Center for Big Data-based Precision Medicine, Beihang University, Beijing, China (e-mail: shaopingwang@buaa.edu.cn).

Xingjian Wang is with the School of Automation Science and Electrical Engineering, Beihang University and also with the Beijing Advanced Innovation Center for Big Data-based Precision Medicine, Beihang University.

Teresa Wu is with the School of Computing, Informatics, and Decision Systems Engineering, Arizona State University and College of Medicine.

Digital Object Identifier 10.1109/TBME.2020.3015199

I. Introduction

DIABETES is a metabolic syndrome featuring abnormal fluctuation of blood glucose caused by absolute or relative insulin-secretion deficiency [1]. Currently, exogenous insulin infusion is the main therapy for patients with type 1 diabetes and serious type 2 diabetes to maintain the glycemic level within a normal range. Severe hypoglycemia is an acute complication of insulin therapy that can lead to seizures, coma, and even death [2]. Nocturnal hypoglycemia is especially alarming as the sympathoadrenal response to falling glucose concentration may be blunted, resulting in fewer warning symptoms and threatening the life of the patient [3]. The fact is, 75% of hypoglycemic seizures among children occur during sleep [4]; 71% of youth do not respond to hypoglycemia alarms during the night, and 6% of the deaths from diabetes are due to "dead-in-bed" syndrome [5]. Consequently, reducing the frequency of hypoglycemia, especially nocturnal hypoglycemia, is the primary task of insulin therapy [6], [7]. Hypoglycemia prevention also provides the safety baseline for artificial pancreas (AP) [8], a promising technology that can be used to automate glucose-responsive insulin delivery [9], [10]. The optimal solution for hypoglycemia prevention is to predict it before it occurs.

Various models to track and predict glucose changes have been developed over the last decade [11], [12], [13], including data-driven models and physiological models. Data-driven models are also known as black-box models. The models are based on the signal data such as continuous glucose monitoring (CGM) data, insulin delivery data, and amount of carbohydrate absorption, just to name a few, without the details of the patient's internal metabolic behaviors. Examples of data-driven models include autoregressive (AR) model [14], support vector regression (SVR) model [15], and artificial neural network (ANN) model [16].

Physiological models, focusing on the understanding of insulin and glucose metabolism, have been developed due to their good interpretability. The models generally consist of multiple glucose and related subsystems [17], [18], such as insulin subsystem, carbohydrate absorption subsystem, and other subsystems affecting glucose changes, e.g., β-cells, α-cells, glucagon [19] as well as free fatty acid [20]. The glucose subsystem, a most critical component related to hypoglycemia study, is commonly described by compartment models with different complexities, sample types and timescales [21], [22].

Bergman [23] and Cobelli [24] developed a minimal model, using a single-compartment model to describe the glucose kinetics. Ruan [25] and Magdelaine [26] studied the long-term fitting of actual glucose data in steady state, and provided a long-term single-compartment model to describe the glucose kinetics based on a two-week dataset of type 1 diabetes patients. In [27], [28], [29], a two-compartment model of glucose kinetics was proposed by Hovorka, dividing the glucose compartments into fast vs. slow compartments, by observing the tracers within the bodies of healthy subjects under intravenous glucose tolerance test (IVGTT). In [30] and [31], a two-compartment model of glucose kinetics was developed by Cobelli for in silico simulations.

It is noted that each glucose kinetics model reveals the glycemic mechanism from different aspects, and thus has its own unique advantages to study various physiological states [32]. Yet, research has mainly focused on accurately determining the parameters given one specific model of glucose kinetics to address the variability from patients and their physiological states. The approach presented in this paper, hypothesizes that a model fusion approach, optimally integrating advantages of different models, will improve prediction of glucose changes and hypoglycemia events. The proposed Glucose-Insulin Mixture (GIM) model considers various glycemic models with respect to the related model parameters. Considering the high variability of glucose dynamics, the model dynamics and the parameters are updated with new collected data using Bayesian inference. The trend of the glucose is estimated to derive the probability of hypoglycemia onset.

The rest of this paper is organized as follows. In Section II, two basic glucose-insulin models are introduced as candidate models: the Ruan model and the Hovorka model. The models are reformulated for the night physiological condition. Next, the proposed GIM model is presented, fusing the candidate models via Bayesian inference. In Section III, the experimental information is presented. Section IV presents performance (fitting and prediction accuracy) of various glucose-insulin models based on the clinical data. The conclusion is drawn in Section V.

II. Glucose-Insulin Mixture Model

The goal of the proposed Glucose-Insulin Mixture (GIM) model is to integrate advantages of different models with varied complexities, sample types, and timescales using Bayesian inference to accurately capture the glycemic dynamics for individual patient. In this section, the candidate models, model fusion (the GIM model), the prior information setting, and posterior estimation are discussed.

A. Reformulated Candidate Glucose-Insulin Models

Two glucose-insulin models of interest in this research serve as the candidate models for GIM due to the balance between the mechanisms and the complexity. The first candidate model is the Ruan model [25], describing the glucose kinetics through a single-compartment model, which is designed to fit long-term glucose data. The second model is the Hovorka model [28], describing the glucose kinetics through a two-compartment model, which is designed based on the short-term IVGTT data. Given the objective of this study is to capture the nocturnal glucose dynamics when the patients are under a steady-state condition (i.e., the insulin infusion rate is nonnegative and constant), the focus is on the glucose kinetics of the candidate models. This assumption is also used in [25].

The glucose kinetics of the Ruan model is formulated as:

$$\frac{dG_1(t)}{dt} = -S_i\left(x(t) - x_b\right) - K\left(G(t) - G_b\right) + U_M(t) \quad (1)$$

where $G_1(t)$ is the glucose value (mmol/L), $U_M(t)$ is the gut carbohydrate absorption rate (mmol/L/min) with unit converted to glucose concentration rate of change related by the carbohydrate intake (detailed calculation is provided in Appendix A), $x(t)$ is the concentration of effective insulin (mU/L) determined by the insulin infusion rate $u(t)$ (U/h), the subject's body weight W (kg), and the metabolism clearance rate (MCR) fixed as 0.017 (1/kg/min) [33], S_i, x_b, K and G_b are model parameters, representing the insulin sensitivity (mmol/L/min per mU/L), the basal effective insulin concentration (mU/L), the glucose self-regulation fractional rate (/min) and the basal glucose level (mmol/L) respectively.

The glucose value is derived as:

$$G_1(t) = G_b - \frac{S_i(1000u(t)/60/MCR/W - x_b) - U_M(t)}{K} + Ce^{-Kt} \quad (2)$$

where C is the constant. Let $\boldsymbol{\theta}_1 = [G_b, S_i, x_b, K]$, where the parameters are nonnegative and variable due to the physiological condition and glucose variability. Specific details on derivation and calculation of constant C are are provided in Appendix B.

The glucose kinetics of the Hovorka model is expressed as:

$$\begin{aligned}\frac{dQ_1(t)}{dt} &= -F_{01} - x_1(t)Q_1(t) + k_{12}Q_2(t) + U_G(t) \\ &\quad + EGP_0[1 - x_3(t)] \\ \frac{dQ_2(t)}{dt} &= x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t)\end{aligned} \quad (3)$$

where $Q_1(t)$ and $Q_2(t)$ represent the masses of glucose in the accessible and non-accessible compartments (mmol/kg). $Q_1(t)$ is related to the glucose distribution volume V_G, which is fixed as 0.16 (L/kg) [29], and glucose value G_2 (mmol/L), i.e., $G_2(t) = \frac{Q_1(t)}{V_G}$. $U_G(t)$ represents the gut absorption rate (mmol/kg/min) (see Appendix A for detailed calculation). k_{12} is the transfer rate parameter from the non-accessible to the accessible compartment (/min). F_{01} is non-insulin-dependent glucose flux (mmol/kg/min). EGP_0 is endogenous glucose production (EGP) extrapolated to zero insulin concentrate (mmol/kg/min). $x_1(t)$, $x_2(t)$, and $x_3(t)$ represent the (remote) effects of insulin on glucose distribution/transport (mU/min), glucose disposal (mU/min), and EGP (mU/min) respectively, and are related to the insulin delivery rate value $u(t)$ (U/h), the subject's body weight W (kg), and the generalized insulin sensitivity of glucose transmission k_1 (kg/mU), consumption k_2 (kg/mU) and EGP k_3 (min kg/mU).

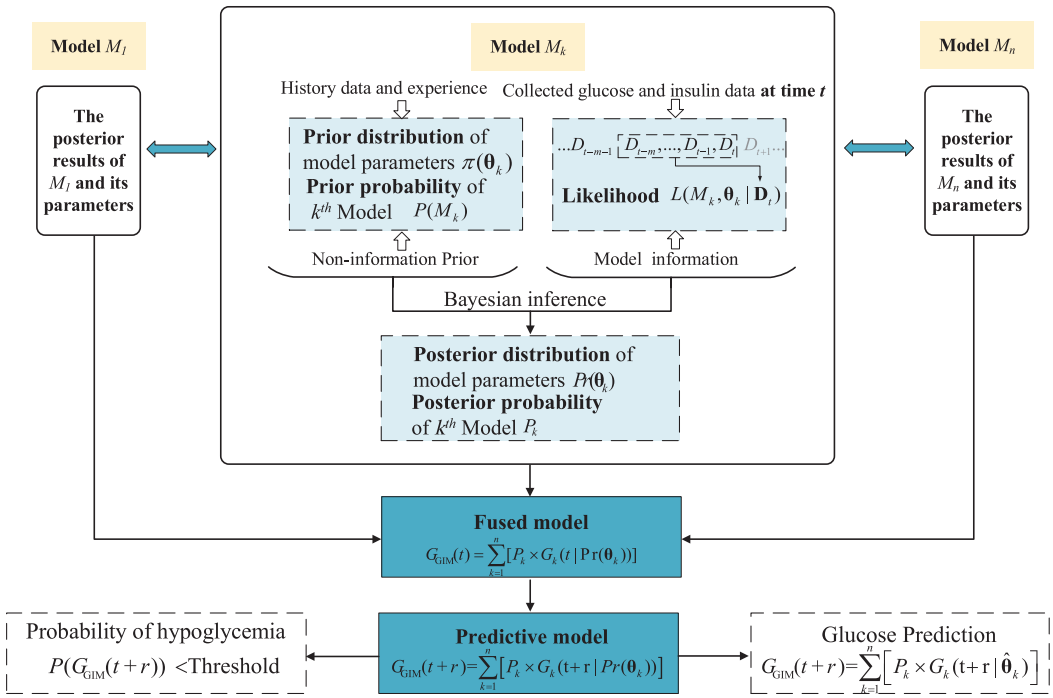

Fig. 1. The overall structure of fusing various glucose models with variable parameters.

For the Hovorka model, the glucose value is derived as:

$$G_2(t) = \frac{C_1\exp\left\{\frac{t}{2}[H_1(t)-H_2(t)]\right\}+C_2\exp\left\{\frac{t}{2}[H_1(t)+H_2(t)]\right\}-H_3(t)}{V_G} \tag{4}$$

where

$$\begin{cases} H_1(t) = -k_{12} - k_1\frac{1000u(t)}{60W} - k_2\frac{1000u(t)}{60W} \\ H_2(t) = \sqrt{k_{12}^2+\frac{2000k_{12}u(t)}{60W}(k_1+k_2)+(k_1-k_2)^2\left(\frac{1000u(t)}{60W}\right)^2} \\ H_3(t) = \frac{\left[F_{01}-EGP_0\left(1-\frac{1000u(t)k_3}{60W}\right)-U_G(t)\right]}{k_1k_2\left(\frac{1000u(t)}{60W}\right)^2} \end{cases}$$

where $G_2(t)$ is the glucose value (mmol/L) at time t, C_1 and C_2 are constants related to the initial glucose value. Similar to the Ruan model, $\boldsymbol{\theta}_2 = [k_{12}, k_1, k_2, k_3, EGP_0, F_{01}]$ where all of the parameters are nonnegative and variable. More details about the derivation and calculation of C_1 and C_2 are presented in Appendix C.

Given the candidate models above, the construction of Glucose-Insulin Mixture (GIM) model is discussed in the next section.

B. Glucose-Insulin Mixture Model

1) GIM: *Integrating Model Fusion Dynamics and Parameter Uncertainty*

A GIM model is proposed by fusing various glucose models with variable parameters. The overall structure is shown in Fig. 1. The GIM model is obtained based on the posterior probabilities of models and distributions of underlying parameters, which are calculated by Bayesian inference. The prior information is obtained from history data and experience, and the likelihood function is obtained from model information and updated data. The prediction of glucose value and hypoglycemia at a future time point (e.g., the next r min) is calculated based on posterior information.

The main concept of GIM is that the glucose value is considered as a stochastic value, which is subject to the joint distribution of posterior probability of models and posterior distribution of the underlying parameters.

To analyze the model uncertainty, the selection consistency is introduced as discussed in [34] and [35]. Let $\boldsymbol{M} = [M_1, M_2, M_3 \ldots M_n]$, where M_k is the k^{th} glucose-insulin model describing the glucose dynamics. The model set is assumed to be complete, that is, each model M_k has a probability $P(M_k)$ of being the 'true model,' and the sum of the models' probability is 1, [36] and [37], i.e., $\sum_{k=1}^{n} P(M_k) = 1$. The probability $P(M_k)$ is an indicator of the contribution from each candidate model to GIM. The probability is updated dynamically with the updated data through Bayesian inference.

For the k^{th} glucose-insulin model M_k, based on the Bayesian framework, the joint posterior probability $P(M_k, \boldsymbol{\theta}_k|D_T)$ is estimated as:

$$P(M_k,\boldsymbol{\theta}_k|D_T) = \frac{L(M_k,\boldsymbol{\theta}_k|D_T)P(\boldsymbol{\theta}_k)P(M_k)}{\sum_{k=1}^{n}\int L(M_k,\boldsymbol{\theta}_k|D_T)P(\boldsymbol{\theta}_k)P(M_k)d\boldsymbol{\theta}_k} \tag{5}$$

where $P(\boldsymbol{\theta}_k)$ is the prior probability of the parameter vector $\boldsymbol{\theta}_k$, $L(M_k, \boldsymbol{\theta}_k|D_T)$ is the likelihood function of M_k, and D_T

denotes the glucose, insulin, and carbohydrate intake data collected during the time window T. The likelihood function which is related to the model function, parameters, and collected data, is defined as:

$$L(M_k, \boldsymbol{\theta}_k|D_T) = \prod_i^m P(D_{Ti}|M_k, \boldsymbol{\theta}_k) \tag{6}$$

where m is the size of sampled data during the time window T and D_{Ti} is the i^{th} element of collected data series D_T.

Hereto, $P(M_k, \boldsymbol{\theta}_k|D_T)$ is calculated, and the posterior probability of M_k is calculated as:

$$P_k = \int P(M_k, \boldsymbol{\theta}_k|D_T)d\boldsymbol{\theta}_k \tag{7}$$

In the remainder of the paper, the posterior probability P_k is used as a quantifying indicator of the model uncertainty.

The posterior probability of parameter $\boldsymbol{\theta}_k$ in model k is calculated as

$$P(\boldsymbol{\theta}_k|M_k, D_T) = \frac{P(M_k, \boldsymbol{\theta}_k|D_T)}{P_k} \tag{8}$$

As for the k^{th} glucose-insulin model, the mean of the parametric posterior distribution is taken as the point estimate. The parameter $\boldsymbol{\theta}_k$ is estimated as

$$\hat{\boldsymbol{\theta}}_k \propto \int P(\boldsymbol{\theta}_k|M_k, D_T)\boldsymbol{\theta}_k d\boldsymbol{\theta}_k \tag{9}$$

The model probability and the parameters are estimated based on the updated data. Based on the k^{th} glucose-insulin model G_k, the fused glycemic dynamics is calculated as:

$$G(t) = \sum_{k=1}^{n} [P_k \times G_k(t|\hat{\boldsymbol{\theta}}_k)] \tag{10}$$

The GIM model adjusts the probabilities of models and underlying parameters adaptively, with new data continuously being assimilated. In this study, the length of the time window T is a set value. That is, the size of data D_T is fixed, i.e., the old data are replaced with new sampled data. With the new data, D_T is updated in real-time, and the fusing process discussed above is repeated. The GIM model is updated based on the new estimation of parameters and model probability.

Now, based on the updated probabilities of models and parameters at time t, it is possible to (i) predict the glucose concentration at a future time, and (ii) predict the probability of hypoglycemia in a future period.

Specifically, the glucose concentration G at time $t + r$ can be predicted as:

$$G(t + r) = \sum_{k=1}^{n} [P_k \times G_k(t + r|\hat{\boldsymbol{\theta}}_k)] \tag{11}$$

If the point estimation of glucose concentration is lower than the hypoglycemic threshold (e.g., 3.9 mmol/L [7]), it is reasonable to consider that the risk of hypoglycemia may be considerable. Here, the risk of hypoglycemia is estimated and indicated with a probability, by comparing the predicted distribution interval of glucose value with a pre-set threshold. The probability of glucose value is dependent on the joint posterior probability related to the candidate models and corresponding parameters, as:

$$P(G(t + r)|D_T) = \sum_{k=1}^{n} [P_k \times P(G_k(t + r, \boldsymbol{\theta}_k|D_T))] \tag{12}$$

The probability of hypoglycemia in the next r min is calculated as $\mathrm{P}(G(t + r) < G_{hypo}|D_T)$, where G_{hypo} is the hypoglycemia threshold. Traditionally, the hypoglycemia threshold is generally set as 3.9 mmol/L [7].

In this study, we set the Ruan model as M_1 and the Hovorka model as M_2. The likelihood functions for the models are:

$$L(M_1, \boldsymbol{\theta}_1|D_T) = \prod_i^m [P(M_1) \times P(D_{Ti}|G_b, S_i, x_b, K)]$$

$$L(M_2, \boldsymbol{\theta}_2|D_T) = \prod_i^m [P(M_2) \times P(D_{Ti}|k_{12}, k_1, k_2, k_3, EGP_0, F_{01})] \tag{13}$$

2) Prior Information for Bayesian Inference: In GIM model, the preference of each candidate model is not known as a prior. For simplicity, it is assumed that the prior probability of each model is the same, that is, $P(M_k) = 1/\mathrm{n}$. The prior

Algorithm 1: Monte Carlo Simulation for Glucose Data Fitting and Hypoglycemia Prediction.

1: Initialize N, G_{hypo}, $hypo = 0$
2: **for** $i = 1 : N$ **do**
3: Sample θ_i from the posterior distribution of model parameter
4: Sample P_{1i}, P_{2i} from the posterior probabilities of M_1 and M_2
5: **end for**
6: **if** predicting glucose value **then**
7: $\hat{\theta} = \sum_i^N \theta_i/N$
8: $\hat{P}_1 = \sum_i^N P_{1i}/N$
9: $\hat{P}_2 = \sum_i^N P_{2i}/N$
10: Calculate $G(t + r)$ by:
$G(t + r) = \hat{P}_1\{\hat{G}_b - \frac{\hat{S}_i(1000u(t)/60MRC/W - \hat{x}_b)}{\hat{K}} + Ce^{-\hat{K}(t+r)}\} + \hat{P}_2\frac{C_1 e^{\frac{t+r}{2}(\hat{H}_1 - \hat{H}_2)} + C_2 e^{\frac{t+r}{2}(\hat{H}_1 + \hat{H}_2)} - \hat{H}_3(t+r)}{V_G}$
11: **end if**
12: **if** hypoglycemia prediction **then**
13: **for** $i = 1 : N$ **do**
14: Based on P_{1i}, P_{2i} and θ_i, calculate $G_i(t + r)$ by:
$G_i(t + r) = P_{1i}\{G_{bi} - \frac{S_{ii}(1000u(t)/60MRC/W - x_{bi})}{K_i} + C_i e^{-K_i(t+r)}\} + P_{2i}\frac{C_{1i} e^{\frac{t+r}{2}(H_{1i} - H_{2i})} + C_{2i} e^{\frac{t+r}{2}(H_{1i} + H_{2i})} - H_{3i}(t+r)}{V_G}$
15: **if** $G_i(t_{pre}) < G_{hypo}$ **then**
16: $hypo = hypo + 1$
17: **end if**
18: **end for**
19: Estimate the hypoglycemia probability by $P_{hypo} = hypo/N$
20: **end if**

TABLE I
DETAIL OF PRIOR INFORMATION OF PARAMETERS

	Parameter	Meaning	Value	Variance
Ruan model	K	Glucose self-regulation fractional rate	0.01 min^{-1} [25]	1 $(\text{min}^{-1})^2$
	S_i	Insulin sensitivity	0.04 mol/min/U [25]	0.1 $(\text{mol/min/U})^2$
	x_b	Basal insulin concentration	10 mU/L [25]	0.1 $(\text{mU/L})^2$
	G_b	Basal glucose level	8 mmol/L [25]	1 $(\text{mmol/L})^2$
Hovorka model	F_{01}	Non-insulin-dependent glucose flux	0.0097 mmol/kg/min [28]	0.01 $(\text{mmol/kg/min})^2$
	K_1	Generalized insulin sensitivity of transport	0.3092 kg/mU [28]	0.01 $(\text{kg/mU})^2$
	K_2	Generalized insulin sensitivity of disposal	0.0495 kg/mU [28]	0.01 $(\text{kg/mU})^2$
	K_3	Generalized insulin sensitivity of EGP	3.1401 min kg/mU [28]	0.1 $(\text{min kg/mU})^2$
	K_{12}	Transfer rate	0.066 min^{-1} [28]	0.1 $(\text{min}^{-1})^2$
	EGP_0	EGP extrapolated to zero insulin concentration	0.0161 mmol/kg/min [28]	0.001 $(\text{mmol/kg/min})^2$

distributions of the parameters are determined according to historical information (Table I).

Due to the inherent positivity of physiological parameters, each parameter $\theta \in \boldsymbol{\theta}$ is assumed to be independent and subject to a log-normal distribution with corresponding hyper-parameter μ_θ and σ_θ, i.e., $\theta \sim f_{LN}(\mu_\theta, \sigma_\theta^2)$ (as adopted by [22], [25] and [28]). According to the properties of the log-normal distribution and the prior information, the hyper-parameters μ_θ and σ_θ of log-normal distribution are calculated as:

$$\mu_\theta = \ln\left(\mathrm{E}\left(\theta\right)\right) - \frac{1}{2}\ln\left[1 + \frac{\mathrm{var}\left(\theta\right)}{\mathrm{E}\left(\theta\right)^2}\right]$$
$$\sigma_\theta^2 = \ln\left[1 + \frac{\mathrm{var}\left(\theta\right)}{\mathrm{E}\left(\theta\right)^2}\right] \tag{14}$$

where $\mathrm{E}(\theta)$ and $\mathrm{var}(\theta)$ represent the expectation and the variance of parameter θ respectively.

3) Markov Chain Monte Carlo for Posterior Estimation: The posterior distribution of models' probabilities, (7), and underlying parameters, (9), is high-dimensional and difficult to calculate. In this study, the Markov Chain Monte Carlo (MCMC) is used to approximate the posterior distribution [38]. The basic idea of the MCMC method is to construct a Markov chain with the stationary distribution being considered as the posterior distribution. The Monte Carlo integration is performed based on Monte Carlo samples until the Markov chain reaches a stationary distribution. In this research, the Metropolis-Hastings algorithm is adopted, as a well-studied algorithm to construct the Markov chain transfer nucleus [38]. The commercial software OpenBUGS [39] is used for implementation. For convergence analysis, two Markov chains are constructed with different initial values. For the first chain, the initial values are set as the mean values listed in Table I. For the second chain, the initial values are generated by sampling from the set prior distribution. For convergence criteria, the Gelman-Rubin ratio is used, and the two Markov chains are considered to have converged when the ratio is less than 1.2 [39].

The Monte Carlo simulation is designed to calculate the glucose changes and predict the hypoglycemia (see Algorithm 1). In Algorithm 1, N is the size of the Monte Carlo samples and r is the prediction horizon. The posterior distributions of model probability and parameters at time t are obtained from MCMC, where $\theta \in \boldsymbol{\theta}$ denotes any of the parameters, including $G_b, S_i, x_b, K, k_{12}, k_1, k_2, k_3, EGP_0$, and F_{01}.

III. DATA

This study was approved by the Institutional Review Boards, and all the participants signed informed consent forms prior to participation. The study was based on the group of 12 participants with type 1 diabetes (see Table II for details). The insulin and glucose data of each participant were monitored over seven days. All the participants used insulin pumps for insulin Lispro infusion. Participants did not take any drugs other than exogenous insulin infusion.

During the experiment, all the participants lived in a typical free-living and self-monitoring environment. The information on habits, carbohydrate intake, and sleep during the experiment was recorded by the physicians. All the participants maintained routine schedules and fell asleep before 11:00 PM. The glucose data were sampled every 15 minutes by the glucose sensor, FreeStyle Navigator II CGM system (Abbott Diabetes Care). The time series and doses of insulin infusion were recorded by the insulin pump.

Since the primary focus of the study was on the overnight conditions, in which the insulin was infused at the basal rate, the data was collected between 00:00 AM and 5:00 AM on a daily basis and subsequently analyzed. The data collected on each participant in one night consisted of a data set containing 21 pairs of glucose and insulin values. In total, 292 hypoglycemic data points (lower than 3.9 mmol/L) and 45 nocturnal hypoglycemic events were observed across 84 (7×12) monitored nights.

IV. EXPERIMENTS

The proposed GIM model (M_{GIM}) is compared against four models in terms of fitting and predicting performances. The four models are: the Ruan model (M_{RP}), the Hovorka model (M_{HP}), both considering the uncertainty of parameters, and the Ruan model (M_{R}) and the Hovorka model (M_{H}), both with fixed parameters (provided in [25] and [28]).

A. Fitting Performance Evaluation

The root-mean-square error (RMSE) is used to quantitatively assess the fitting accuracy. The data for each night were used to estimate the probabilities of models and parametric distributions. Specifically, the length of the time window T was set as 5 hours, and the size m of data for identification was set to 21 in this part. The identified model was used to fit the data.

TABLE II
DETAILS OF PARTICIPANTS AND COLLECTED DATA

Participants ID	1	2	3	4	5	6
Gender	F	F	M	F	M	F
Age (year)	25	32	18	23	26	22
Weight (kg)	56	60	70	44	57	50
Insulin resistance	No	No	Yes	No	No	No
Duration of diabetes (year)	14	20	10	8	10	8
HbA1c (%)	6.1	5.2	6.3	6.8	6.6	6.2
Insulin analogue	Lispro	Lispro	Lispro	Lispro	Lispro	Lispro
The number of collected data	147 (7 nights)	147 (7 nights)	147 (7 nights)	147 (7 nights)	147 (7 nights)	147 (7 nights)
The number of CGM values with hypoglycemia (events)	28 (5 times)	4 (1 time)	11 (2 times)	50 (8 times)	13 (3 times)	5 (1 time)
Participants ID	7	8	9	10	11	12
Gender	F	F	M	M	M	F
Age (year)	31	37	26	29	17	21
Weight (kg)	80	75	60	52	58	53
Insulin resistance	Yes	No	No	No	No	No
Duration of diabetes (year)	14	23	13	14	1	1
HbA1c (%)	7	6.1	6.5	6.8	10.9	6.7
Insulin analogue	Lispro	Lispro	Lispro	Lispro	Lispro	Lispro
The number of collected data	147 (7 nights)	147 (7 nights)	147 (7 nights)	147 (7 nights)	147 (7 nights)	147 (7 nights)
The number of CGM values with hypoglycemia (events)	23 (4 times)	27 (3 times)	18 (4 times)	51 (5 times)	5 (2 times)	57 (7 times)

The two Markov chains were trained each with 1,100,000 samples, in which the first 1,000,000 samples were discarded as training chains. The remaining 100,000 samples were used for further analysis. The Gelman-Rubin ratios of all parameters were within the interval of (1, 1.2). An illustrative example showing the probability of models and the distribution of model parameters for one night is given in Fig. 2.

All the posterior distributions of estimated parameters were within the reasonable ranges, as discussed in [25] and [28]. This indicates that the parameter estimation of the GIM model based on the Bayesian method is reasonable.

As for the models mentioned above, their fitting abilities with glucose variability are also of interest. To intuitively indicate the ability of different models to fit CGM data in various glycemic states, as in literature [40], four-night data were selected, with different initial glucose values: hyperglycemia (12 mmol/L), high normal (7.3 mmol/L), low normal (4.3 mmol/L), and hypoglycemia (3.1 mmol/L). The fitting results are shown in Fig. 3. It can be observed that the fitting results of M_{GIM}, M_{Rp}, and M_{Hp} significantly outperform those of M_{R} and M_{H}, supporting the need for personalized parameter estimation.

Next, the focus is the quantitative assessment of M_{GIM}, M_{Rp}, and M_{Hp} only. The participant-level RMSEs for overnight data are listed in Table III, together with mean and standard deviation (SD). It can be observed that, across all participants, M_{GIM} has the best performance in fitting the glucose dynamics, as indicated by the smallest RMSE of 0.3465 mmol/L. Compared with M_{Rp} and M_{Hp}, the performance of M_{GIM} is improved by 12.92% and 26.23%.

Based on the comparison using RMSEs, it can be concluded that the GIM model, which considers model uncertainty, is successful in fitting glucose changes.

B. Prediction Performance Evaluation

Since predicting glucose 30 minutes in advance is considered to be effective at helping to avoid hypoglycemia [7], the glucose predictive abilities of M_{GIM}, M_{Rp} and M_{Hp} are studied over the 30 minutes period. Future glucose value can be predicted based on the data sampled by a time window. It should be noted that for different window lengths, T, the volumes of valid training data are different which may significantly impact the accuracy. The prediction performances with different window lengths T (30 min, 60 min, 90 min, 120 min, 150 min, and 180 min) are evaluated. The hypoglycemia prediction abilities of the three models are assessed based on the accuracy rate (AR), precision rate (PR), false-positive rate (FPR), and the recall rate (RR).

The prediction performance is evaluated by comparing the predicted glucose value with the CGM value. The predictive abilities for different window lengths are measured by RMSE (mean, 95% level of confidence), and the results are shown in the Fig. 4.

The results show that M_{GIM} has consistently the smallest RMSEs across all conditions, indicating the potential of M_{GIM} for accurate and robust prediction of glucose changes. This also indicates the need of incorporating model uncertainty into the prediction. The smallest RMSEs occur for 60 min window length. In this case, the mean RMSEs of M_{GIM}, M_{Rp} and

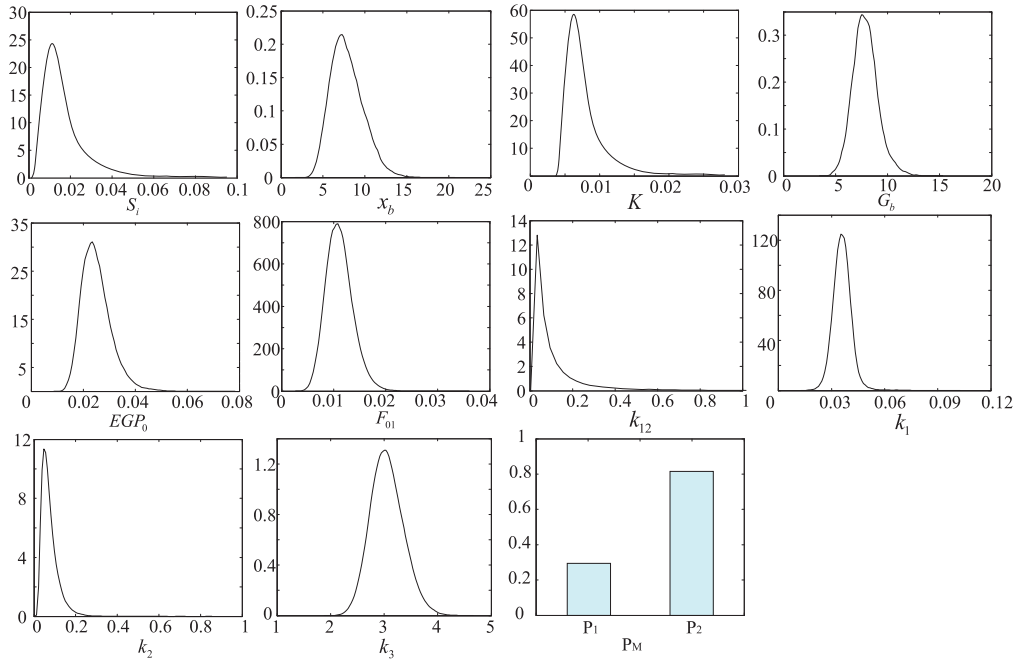

Fig. 2. An example of the posterior kernel density distributions of models and corresponding parameters, where $[S_i, x_b, K, G_b]$ denotes the parameters in M_1, $[EGP_0, F_{01}, k_{12}, k_1, k_2, k_3]$ denotes the parameters in M_2, and P_M shows the probabilities of M_1 and M_2.

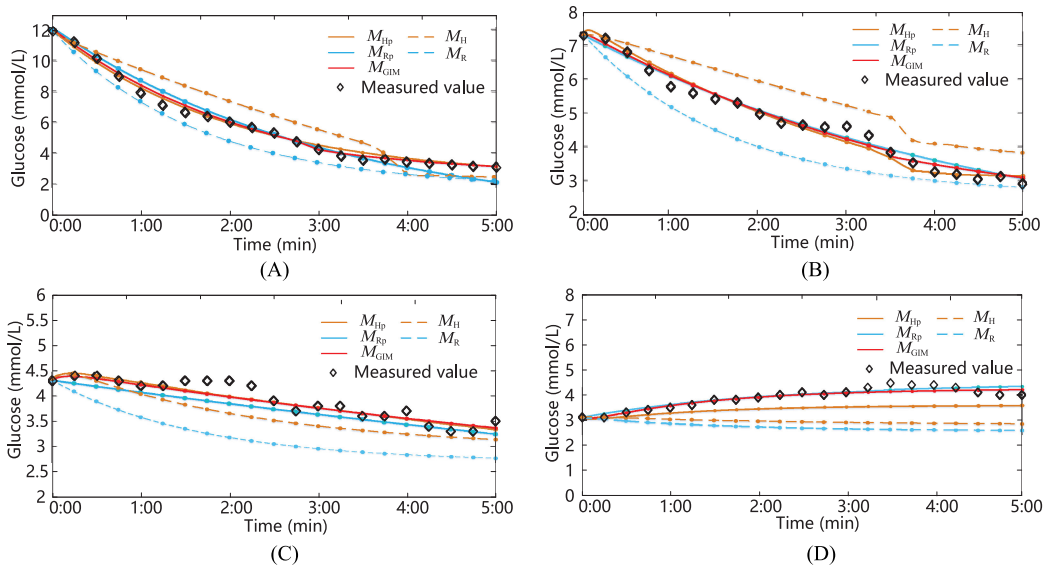

Fig. 3. Examples of fitting comparison for four-night data among the five models (M_{GIM}, M_{Rp}, M_{Hp}, M_{R}, and M_{H}) with initial glucose values: (A) hyperglycemia, 12 mmol/L, (B) high normal, 7.3 mmol/L, (C) low normal, 4.3 mmol/L, and (D) hypoglycemia, 3.1 mmol/L.

M_{Hp} are 0.5571 (mmol/L), 0.8922 (mmol/L), 0.9081 (mmol/L) respectively. As window length decreases to 30 min, it can be observed that RMSEs increase for all the models. This may be due to the fact that when D_T is limited, the information contained in the data is insufficient for good estimation. It is also interesting to observe that all the models have higher RMSE values when window length is longer than 60 min, which may be attributed to the glucose variability. Generally speaking, the longer the window length is, the more data are used to estimate the model probability and its parameters. However, as the model probability and its parameters are deemed as time-invariant during the time window, when T increases, the sensitivity of models to dynamic characteristics decreases. One observation is that M_{GIM} is relatively less sensitive to the change in window length. Thus it is more robust.

Based on the best performance, the experimental results for window length of $T = 60$ min are considered in further discussion. The estimation results of parameters for all subjects are shown in Fig. 5. It is observed that the estimations of the parameters change within certain ranges, which are similar to

TABLE III
THE FITTING RMSES OF CGM DATA OBTAINED BY M_{GIM}, M_{Rp}, AND M_{Hp} FOR ALL PARTICIPANTS

Participants ID	1	2	3	4	5	6	7
The RMSE of M_{GIM}	0.2695	0.2914	0.2543	0.4598	0.2236	0.3687	0.3854
(mmol/L)	±0.0195	±0.0657	±0.0451	±0.1537	±0.5692	±0.0636	±0.1095
The RMSE of M_{Rp}	0.3328	0.3406	0.3598	0.4636	0.2483	0.3951	0.4614
(mmol/L)	±0.0595	±0.0853	±0.0758	±0.1529	±0.5807	±0.1137	±0.2998
The RMSE of M_{Hp}	0.3980	0.6101	0.3334	0.3285	0.5284	0.5284	0.3894
(mmol/L)	±0.1324	±0.4814	±0.0660	±0.9131	±0.3186	±0.3186	±0.8243
Participants ID	8	9	10	11	12	Mean	Improvement
The RMSE of M_{GIM}	0.4876	0.3349	0.3504	0.3526	0.3802	0.3465	
(mmol/L)	±0.2272	±0.0987	±0.0628	±0.0553	±0.1079	±0.1315	
The RMSE of M_{Rp}	0.6501	0.3775	0.3611	0.3966	0.3885	0.3979	12.92%
(mmol/L)	±0.4434	±0.0980	±0.0673	±0.1106	±0.1260	±0.1844	
The RMSE of M_{Hp}	0.4277	0.5224	0.5757	0.4976	0.4974	0.4697	26.23%
(mmol/L)	±0.7892	±0.3642	±0.0510	±0.0867	±0.1418	±0.3739	

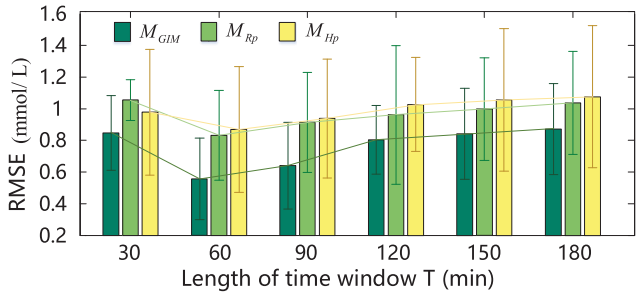

Fig. 4. The prediction RMSEs of M_{GIM}, M_{Rp} and M_{Hp} for window lengths of 30 min, 60 min, 90 min, 120 min, 150 min, and 180 min.

TABLE IV
PERFORMANCES OF MODELS FOR HYPOGLYCEMIA PREDICTION (BASED ON PREDICTED GLUCOSE VALUE)*

Model	AR	PR	FPR	RR
M_{Rp}	93.04% ±2.51%	84.58% ±7.43%	15.42% ±7.43%	94.16% ±4.18%
M_{Hp}	87.16% ±9.16%	89.61% ±8.48%	10.39% ±8.48%	89.52% ±8.42%
M_{GIM}	95.97% ±3.81%	91.77% ±5.41%	8.23% ±5.41%	95.6% ±3.83%

*The hypoglycemia threshold is set as 3.9 mmol/L [7].

those in reference [25] and [28]. Taking advantage of prior distribution information, the parameters can be estimated based only on the last one hour data (5 sample points). It took 162 seconds to update and predict a glucose value (Intel(R) Core i9-9900 K 2-Core 3.60 GHz processor).

In this study, the focus is on the 30-min hypoglycemia prediction, namely, the goal is to predict if the glucose value will be lower than the hypoglycemic threshold in the next 30 min ($r = 30$ min). In the context, when the CGM measurement value is lower than 3.9 mmol/L, it is considered that the hypoglycemic event occurs. At time t, let $G(t+r)$ be the predicted glucose value at time $t+r$, and $CGM(t+r)$ be the CGM value at time $t+r$. Then, definitions of true-positive (TP) event, true-negative (TN) event, false-positive (FP) event, and false-negative (FN) event are given as follows:

TP: $G(t+r) < 3.9$ mmol/L, while $CGM(t+r) < 3.9$ mmol

TN: $G(t+r) \geq 3.9$ mmol/L, while $CGM(t+r) \geq 3.9$ mmol

FP: $G(t+r) < 3.9$ mmol/L, while $CGM(t+r) \geq 3.9$ mmol

FN: $G(t+r) \geq 3.9$ mmol/L, while $CGM(t+r) < 3.9$ mmol

With TP, TN, FP, and FN having been identified, four metrics: accuracy rate (AR), precision rate (PR), false-positive rate (FPR), and recall rate (RR) are derived as:

$$AR = \frac{N_{TP} + N_{TN}}{N_{TP} + N_{TN} + N_{FP} + N_{FN}}$$
$$PR = \frac{N_{TP}}{N_{TP} + N_{FP}}$$
$$FPR = \frac{N_{FP}}{N_{TP} + N_{FP}}$$
$$RR = \frac{N_{TP}}{N_{TP} + N_{FN}} \quad (15)$$

Table IV shows the prediction performances of M_{Rp}, M_{Hp}, and M_{GIM}, together with mean and standard deviation (SD).It can be observed that for the prediction of hypoglycemia event, M_{GIM} has the best prediction performance with AR 95.97%, PR 91.77%, FPR 8.23%, and RR 95.6%, indicating the advantages of model fusion approach.

The proposed GIM method is further compared with five methods from the literature on glucose prediction performance with 30-min prediction horizon (Table V). The RMSEs of the five methods are 1.03 mmol/L [41], 1.13 mmol/L [42], 0.92 mmol/L [43], 1.04 mmol/L [44] and 0.42 mmol/L [45]. The RMSE of M_{GIM} is 0.5304 mmol/L. While the proposed GIM method shows higher error compared to [45], it is worth noting that the five comparison methods require more than 200 data points for preliminary training to achieve reported accuracy,

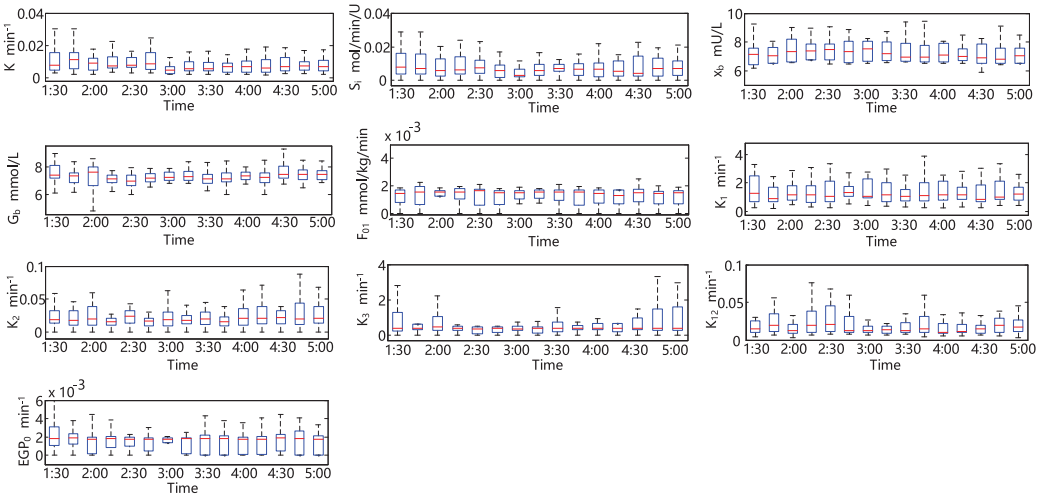

Fig. 5. The estimation results of parameters for all subjects during the experiment ($T = 60$ min).

TABLE V
COMPARATIVE RESULTS WITH OTHER METHODS IN THE LITERATURES (30-min PREDICTION HORIZON)

Study	Method	Input	Results
Turksoy et al. [41] (2013)	ARMAX model	CGM Data Insulin on board Energy expenditure Galvanic skin response	RMSE=1.03 mmol/L
Wang et al. [42] (2014)	Time-varying state-space model with Extended Kalman Filter	CGM data Insulin on board Carbohydrate absorption	RMSE=1.13 mmol/L
Zecchin et al. [43] (2014)	Jump Neural Network model	CGM data Carbohydrate absorption	RMSE=0.92 mmol/L
Georga et al. [44] (2018)	Nonlinear regression model with Kernel Adaptive Filters	CGM data Insulin on board Carbohydrate absorption Energy expenditure	RMSE=1.04 mmol/L
Jaouher et al. [45] (2018)	Back propagation Neural Network model	CGM Data	RMSE=0.42 mmol/L
The proposed model	GIM model	CGM data Insulin on board Carbohydrate absorption	RMSE=0.5304 mmol/L

All the RMSE values are converted units (1 mmol/L = 18 mg/dL).

whereas the proposed algorithm requires only 5 samples within the last hour. It should be mentioned that most of the nocturnal data were not affected by carbohydrate intake and the participants' bodies remained in stable states, which makes it easier to capture dynamic tendency of glucose. It can be concluded that GIM method has advantage when only limited glucose data are available.

C. Potential Clinical Utility for Intervention

One outcome from GIM model is a hypoglycemia probability which can be taken as a risk indicator of hypoglycemia 30 min in advance. This risk indicator is not an objective and measurable value, but rather a belief of the risk calculated by the model. This has the potential in the clinical practices for an effective intervention strategy.

Here, for illustrative purposes, the probability threshold is set as 50%, i.e., when the predicted probability exceeds 50%, it is believed that hypoglycemia will occur after 30 min. The predictive performances of M_{GIM}, M_{Rp}, and M_{Hp} are summarized in Table VI.

It can be observed that the proposed GIM has the best performances on AR, PR, FPR, and RR. It should be noted that this performance heavily depends on the selection of the probability threshold. When the threshold was set larger than 90%, as a particularly conservative warning threshold, all models

TABLE VI
PERFORMANCES OF MODELS FOR HYPOGLYCEMIA PREDICTION (BASED ON ESTIMATED HYPOGLYCEMIA PROBABILITY)*

Model	AR	PR	FPR	RR
M_{Rp}	76.03% ±5.64%	81.45% ±9.34%	18.65% ±9.34%	76.52% ±7.15%
M_{Hp}	82.40% ±8.20%	85.97% ±9.09%	14.03% ±9.09%	81.85% ±10.25%
M_{GIM}	90.77% ±4.37%	89.39% ±7.26%	10.61% ±7.26%	90.88% ±5.52%

*The hypoglycemia threshold is set as 3.9 mmol/L [7].

had higher false positive rates. To improve the performance of the algorithm, the comparison of probability threshold and sensitivity analysis will be conducted in the future studies.

It is also proved that the proposed fused model has an advantage in predicting the hypoglycemia with fewer data. In the proposed model, the length of time window is only 60 min, which is much shorter than required in previously published studies. The promising results can be attributed to the Bayesian approach, which can incorporate the prior information of parameters into the analysis process. In this study, all the prior information of the 10 parameters comes from prior publications, [8] and [9], giving relatively strong prior distributions with tight variances. In addition, it is recognized that the parameters may vary given each individual difference. In future, the authors intend to explore determination of prior parameter distribution using the clinical data directly.

At this stage, the proposed model is more suitable to predict hypoglycemia at night when hypoglycemia is likely to occur and present threat to the patient. In the case of large insulin bolus injections, the applicability of the proposed model remains to be improved and verified.

V. CONCLUSION

Considering the complementary nature of various glucose-insulin models, a model fusion approach based on Bayesian inference is proposed to estimate contribution of different models along with associated model parameters. The proposed approach is termed Glucose-Insulin Mixture (GIM) model. Based on the GIM model, change in glucose level can be described and predicted, and probabilistic hypoglycemia predictions can be estimated. Since the posterior probabilities of models and distributions of parameters are calculated through a fast MCMC method, GIM can capture the glycemic variability in real-time. In addition, the prediction relies only on the data sampled within the last hour (5 sample points), including CGM data, insulin delivery data, and amount of carbohydrate absorption, making it easier for clinical application. While promising, the proposed model in its current stage is more suitable for predicting hypoglycemia at night especially after falling asleep. In the case of high-dose carbohydrate intake and insulin bolus injections, the applicability of the proposed model remains to be verified. Authors intend to use larger clinical data sets to analyze the sensitivity of the model to different hypoglycemia probability thresholds.

APPENDIX

A. Calculation of Carbohydrate Assumption

The meal absorption subsystem of Ruan model is used to describe carbohydrate consuming [25]. That is

$$\begin{aligned}\frac{\mathrm{d}a_1(t)}{\mathrm{d}t} &= -\frac{a_1(t)}{t_m} + \delta_{tj}(t)u_G(t_j)\\ \frac{\mathrm{d}a_2(t)}{\mathrm{d}t} &= \frac{a_1(t)-a_2(t)}{t_m}\\ U_M(t) &= \frac{5.556A_Ga_2(t)}{t_mV_GW}\end{aligned} \tag{16}$$

where $a_1(t)$ and $a_2(t)$ represent carbohydrate amount (g) in the first and second meal absorption compartment respectively, $u_G(t_j)$ represents the carbohydrate amount (g) eaten at time t_j, t_m is the time-of-maximum appearance rate of glucose (min), A_G is the fractional bioavailability (unitless), $U_M(t)$ is the gut carbohydrate absorption rate with unit converted to glucose concentration rate of change (mmol/l/min).

Reformulate the above ordinary differential equations as explicit expressions:

$$U_M(t) = \frac{5.556A_Gu_G(t_j)te^{-t/t_m}}{t_m^2V_GW} \tag{17}$$

In this study, the parameters of the meal absorption model are fixed to constant, i.e., $A_G = 0.8$, $t_m = 55$ (min) [25].

In the Hovorka model, $U_G(t)$ can be calculated as:

$$U_G(t) = \frac{5.556A_Gu_G(t_j)te^{-t/t_m}}{t_m^2W} \tag{18}$$

B. Derivation and Solution of Candidate Model From Ruan Model

The glucose subsystem of Ruan model is described as (1). In the literature [25], the insulin absorption subsystem is described as:

$$\begin{aligned}\frac{\mathrm{d}x_{\mathrm{R}1}(t)}{\mathrm{d}t} &= -\frac{x_{\mathrm{R}1}(t)}{t_I} + \frac{u(t)}{60}\\ \frac{\mathrm{d}x_{\mathrm{R}2}(t)}{\mathrm{d}t} &= \frac{x_{\mathrm{R}1}(t)-x_{\mathrm{R}2}(t)}{t_I}\\ x(t) &= \frac{1000x_{\mathrm{R}2}(t)}{t_I\times MCR\times W}\end{aligned} \tag{19}$$

where $x_{\mathrm{R}1}(t)$ and $x_{\mathrm{R}2}(t)$ represent the amount (U) of effective insulin in the first and second insulin absorption compartment respectively, $u(t)$ represents exogenous delivery rate of insulin (U/h), t_I 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 is the metabolic clearance rate of effective insulin fixed at 0.017 (L/kg/min).

The patient is assumed to have a steady state of insulin infusion rate, i.e., $x(t) = \frac{1000u(t)}{60\times 0.017\times W}$. The simplified Ruan model

is derived as (2), in which the constant C involved in the explicit expression from ordinary differential equation, calculated as:

$$C = -G^1 - G_{\mathrm{b}} + \frac{S_i}{K}\left(\frac{1000u_0}{1.02 \times W} - x_b\right) - \frac{U_{M0}}{K} \tag{20}$$

where the G^1 is the first glucose value (mmol/L) of measured data in series D_T given time window T, u_0 and U_{M0} are mean values of insulin infusion rate and the gut carbohydrate absorption rate during time window T. C is determined by the model parameters and the initial values of the calculated data. As predicting glucose value based on Markov Chain Monte Carlo (MCMC) algorithm, there would be the same amount of C values with respect to the N Monte Carlo samples.

C. Derivation and Solution of Candidate Model From Hovorka Model

The glucose subsystem of Hovorka model is described as (3). In the literature [28], the insulin subsystem is expressed as:

$$\begin{aligned} \frac{\mathrm{d}\, S_1(t)}{\mathrm{d}\, t} &= -\frac{S_1(t)}{t_I} + u_H(t) \\ \frac{\mathrm{d}\, S_2(t)}{\mathrm{d}\, t} &= \frac{S_1(t) - S_2(t)}{t_I} \end{aligned} \tag{21}$$

where $S_1(t)$ and $S_2(t)$ are two-compartment chains representing absorption of subcutaneously administered short-acting (e.g., Lispro) insulin (mU/kg), $u_H(t)$ represents administration of insulin (mU/kg/min), converted by insulin delivery rate of $u(t)$ (U/h), $u_H(t) = \frac{1000u(t)}{60\,W}$, t_I is the time-to-maximum insulin absorption (min). The insulin absorption rate (appearance of insulin in plasma) is obtained as $U_I(t) = \frac{S_2(t)}{t_I}$.

The plasma insulin concentration $I(t)$ is described as

$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = \frac{U_I(t)}{V_I} - k_e I(t) \tag{22}$$

where k_e is the fractional elimination rate (/min), and V_I is the distribution volume (L/kg).

The insulin action subsystem is described as three actions of insulin on glucose kinetics:

$$\begin{aligned} \frac{\mathrm{d}x_1(t)}{\mathrm{d}t} &= -k_{a1}x_1(t) + k_{b1}I(t) \\ \frac{\mathrm{d}x_2(t)}{\mathrm{d}t} &= -k_{a2}x_2(t) + k_{b2}I(t) \\ \frac{\mathrm{d}x_3(t)}{\mathrm{d}t} &= -k_{a3}x_3(t) + k_{b3}I(t) \end{aligned} \tag{23}$$

where k_{ai}, $i = 1, 2, 3$, represent deactivation rate constants, and k_{bi}, $i = 1, 2, 3$, represent activation rate constants.

In our study, we focus on the nocturnal glucose dynamics in which the patient is assumed that has the steady state of insulin infusion rate. For the $x_1(t)$, $x_2(t)$, and $x_3(t)$, $x_i(t)$ is expressed as $x_i(t) = k_i u(t)$, $i = 1, 2, 3$, where $k_i = \frac{k_{bi}}{k_{ai}k_e V_I}$. Only the k_i need to be estimated, rather than other parametersk_{ai}, k_{bi}, k_e, and V_I. Specifically, k_1, k_2, and k_3 are generalized insulin sensitivity of glucose transmission (kg/mU), consumption (kg/mU) and EGP (min kg/mU) respectively. The simplified Hovorka model is derived as (4), in which where the constants C_1 and C_2 related to the initial glucose value, calculated as

$$\begin{aligned} C_1 &= \frac{0.16G^2 + H_3 - (0.16G^2 + H_3)e^{[H_1+H_2]\frac{T_0}{2}}}{e^{[H_1-H_2]\frac{T_0}{2}} - e^{[H_1+H_2]\frac{T_0}{2}}} \\ C_2 &= 0.16G^1 + H_3 - C_1 \end{aligned} \tag{24}$$

where G^1 and G^2 are the first and the second glucose value (mmol/L) of measured data in series D_T given time window T, T_0 is the sampling period, H_1, H_2, and H_3 are calculated by (4) as the insulin infusion rate and the gut carbohydrate absorption rate are the mean values of them during time window T. Similar to the Ruan model, C_1 and C_2 are determined by the model parameters and the initial values of the calculated data. As predicting glucose value based on Markov Chain Monte Carlo (MCMC) algorithm, there would be the same amount of C_1 and C_2 values with respect to the N Monte Carlo samples.

Acknowledgment

The authors acknowledge funding support from Beijing Advanced Innovation Center for Big Data-based Precision Medicine. Authors thank Prof. Mileta Tomovic, Old Dominion University, for his contribution to the language of this paper. Authors also recognize efforts and support by Department of Endocrinology, Xuanwu Hospital Capital Medical University, China, and Department of Endocrinology, The First People's Hospital of Yangquan City, China for recruitment of subjects and collection of physiological data.

References

[1] M. A. Atkinson *et al.*, "Type 1 diabetes," *The Lancet*, vol. 383, no. 9911, pp. 69–82, 2014.
[2] C. Greenhill, "Nocturnal hypoglycemia is frequent in patients with type 1 diabetes mellitus," *Nature Rev. Endocrinol.*, vol. 6, no. 6, pp. 299–300, 2010.
[3] T. Veneman *et al.*, "Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia," *Diabetes*, vol. 42, no. 9, pp. 1233–1237, 1993.
[4] E. Davis *et al.*, "Hypoglycemia: Incidence and clinical predictors in a large population-based sample of children and adolescents with iddm," *Diabetes Care*, vol. 20, no. 1, pp. 22–25, 1997.
[5] O. Sovih and H. Thordarson, "Dead-in-bed syndrome in young diabetic patients," *Diabetes Care*, vol. 22, pp. B40–B42, 1999.
[6] P. Choudhary *et al.*, "Insulin pump therapy with automated insulin suspension in response to hypoglycemia: Reduction in nocturnal hypoglycemia in those at greatest risk," *Diabetes Care*, vol. 34, no. 9, pp. 2023–2025, 2011.
[7] B. Buckingham *et al.*, "Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension," *Diabetes Care*, vol. 33, no. 5, pp. 1013–1017, 2010.
[8] R. Hovorka, "Closed-loop insulin delivery: From bench to clinical practice," *Nature Rev. Endocrinol.*, vol. 7, no. 7, pp. 385–395, 2011.
[9] B. P. Kovatchev *et al.*, "Feasibility of outpatient fully integrated closed-loop control: First studies of wearable artificial pancreas," *Diabetes Care*, vol. 36, no. 7, pp. 1851–1858, 2013.
[10] T. Battelino *et al.*, "Closed loop insulin delivery in diabetes," *Best Pract. Res. Clin. Endocrinol. Metabolism*, vol. 29, no. 3, pp. 315–325, 2015.
[11] A. Boutayeb and A. Chetouani, "A critical review of mathematical models and data used in diabetology," *Biomed. Eng. Online*, vol. 5, no. 1, pp. 43–52, 2006.
[12] S. Oviedo *et al.*, "A review of personalized blood glucose prediction strategies for t1dm patients," *Int. J. Numer. Methods in Biomed. Eng.*, vol. 33, no. 6, pp. 2833–2867, 2017.

[13] M. Gadaleta *et al.*, "Prediction of adverse glycemic events from continuous glucose monitoring signal," *IEEE J. Biomed. Health Inform.*, vol. 23, no. 2, pp. 650–659, Mar. 2018.
[14] A. Gani *et al.*, "Predicting subcutaneous glucose concentration in humans: Data-driven glucose modeling," *IEEE Trans. Biomed. Eng.*, vol. 56, no. 2, pp. 246–254, Feb. 2008.
[15] E. I. Georga *et al.*, "Multivariate prediction of subcutaneous glucose concentration in type 1 diabetes patients based on support vector regression," *IEEE J. Biomed. Health Inform.*, vol. 17, no. 1, pp. 71–81, 2012.
[16] C. Zecchin *et al.*, "Neural network incorporating meal information improves accuracy of short-time prediction of glucose concentration," *IEEE Trans. Biomed. Eng.*, vol. 59, no. 6, pp. 1550–1560, 2012.
[17] C. Cobelli *et al.*, "Diabetes: Models, signals, and control," *IEEE Rev. Biomed. Eng.*, vol. 2, pp. 54–96, 2009.
[18] S. Rathee *et al.*, "ODE models for the management of diabetes: A review," *Int. J. Diabetes in Developing Countries*, vol. 37, no. 1, pp. 4–15, 2017.
[19] W. Boutayeb *et al.*, "The interaction between glucose, insulin, β-cells, α-cells and glucagon: Mathematical model," *Diabetes and Metabolism*, vol. 42, no. 4, pp. 296–302, 2016.
[20] W. Boutayeb, "A mathematical model on glucose homeostasis in type 1 diabetes," *Basic and Clin. Pharmacol. Toxicol.*, vol. 124, no. S3, pp. 251–258, 2019.
[21] C. Cobelli *et al.*, "Advancing our understanding of the glucose system via modeling: A perspective," *IEEE Trans. Biomed. Eng.*, vol. 61, no. 5, pp. 1577–1592, 2014.
[22] K. Lunze *et al.*, "Blood glucose control algorithms for type 1 diabetic patients: A methodological review," *Biomed. Signal Process. Control*, vol. 8, no. 2, pp. 107–119, 2013.
[23] R. N. Bergman, "Toward physiological understanding of glucose tolerance: minimal-model approach," *Diabetes*, vol. 38, no. 12, pp. 1512–1527, 1989.
[24] A. Caumo and C. Cobelli, "Hepatic glucose production during the labeled IVGTT: Estimation by deconvolution with a new minimal model," *Amer. J. Physiol.-Endocrinol. Metabolism*, vol. 264, no. 5, pp. E829–E841, 1993.
[25] Y. Ruan *et al.*, "Modeling dayto-day variability of glucoseinsulin regulation over 12-week home use of closed-loop insulin delivery," *IEEE Trans. Biomed. Eng.*, vol. 64, no. 6, pp. 1412–1419, 2017.
[26] M. A. Atkinson *et al.*, "A long-term model of the glucoseinsulin dynamics of type 1 diabetes," *IEEE Trans. Biomed. Eng.*, vol. 62, no. 6, pp. 1546–1552, 2015.
[27] R. Hovorka, "Continuous glucose monitoring and closed-loop systems," *Diabetic Med.*, vol. 23, no. 1, pp. 1–12, 2006.
[28] R. Hovorka *et al.*, "Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes," *Physiol. Meas.*, vol. 25, no. 4, pp. 905–920, 2004.
[29] R. Hovorka *et al.*, "Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT," *Am. J. Physiol. Endocrinol. Metabolism*, vol. 5, no. 282, pp. E992–E1007, 2002.
[30] G. Toffolo and C. Cobelli, "The hot IVGTT two-compartment minimal model: An improved version," *Amer. J. Physiol. Endocrinol. Metabolism*, vol. 284, no. 2, pp. E317–E321, 2003.
[31] C. D. Man *et al.*, "The uva/padova type 1 diabetes simulator: New features," *J. Diabetes Sci. Technol.*, vol. 8, no. 1, pp. 26–34, 2014.
[32] D. J. Albers *et al.*, "Personalized glucose forecasting for type 2 diabetes using data assimilation," *PLoS Comput. Biol.*, vol. 13, no. 4, pp. 1–38, 2017.
[33] A. Haidar *et al.*, "Pharmacokinetics of insulin aspart in pump-treated subjects with type 1 diabetes: Reproducibility and effect of age, weight, and duration of diabetes," *Diabetes Care*, vol. 36, no. 10, pp. e173–e174, 2013.
[34] N. T. Longford, "Model selection and efficiency: Is 'which model...?' the right question?" *J. Roy. Stat. Soc. Ser. A (Statist. Soc.)*, vol. 168, no. 3, pp. 469–472, 2005.
[35] Z. Ma *et al.*, "Reliability estimation from two types of accelerated testing data considering measurement error," *Reliab. Eng. Syst. Saf.*, vol. 193, 2019.
[36] X. Zhengxiang *et al.*, "Bayesian probabilistic flood forecasting model based on adaptive metropolis-MCMC algorithm," *J. Hydraul. Eng.*, vol. 38, no. 12, pp. 1500–1506, 2007.
[37] D. Liu *et al.*, "Bayesian model averaging based reliability analysis method for monotonic degradation dataset based on inverse Gaussian process and gamma process," *Reliab. Eng. Syst. Saf.*, vol. 180, pp. 25–38, 2018.
[38] C. Andrieu *et al.*, "An introduction to mcmc for machine learning," *Mach. Learn.*, vol. 50, nos. 1–2, pp. 5–43, 2003.
[39] D. Lunn *et al.*, "The bugs project: Evolution, critique and future directions," *Stat. Med.*, vol. 28, no. 25, pp. 3049–3067, 2009.
[40] L. O. Avila *et al.*, "Robust insulin estimation under glycemic variability using Bayesian filtering and Gaussian process models," *Biomed. Signal Process. Control*, vol. 42, pp. 63–72, 2018.
[41] K. Turksoy *et al.*, "Hypoglycemia early alarm systems based on multivariable models," *Ind. Eng. Chem. Res.*, vol. 52, no. 35, pp. 12329–12336, 2013.
[42] Q. Wang *et al.*, "Personalized state-space modeling of glucose dynamics for type 1 diabetes using continuously monitored glucose, insulin dose, and meal intake: An extended kalman filter approach," *J. Diabetes Sci. Technol.*, vol. 8, no. 2, pp. 331–345, 2014.
[43] C. Zecchin *et al.*, "Jump neural network for online short-time prediction of blood glucose from continuous monitoring sensors and meal information," *Comput. Methods Programs in Biomed.*, vol. 113, no. 1, pp. 144–152, 2014.
[44] E. I. Georga *et al.*, "Short-term prediction of glucose in type 1 diabetes using kernel adaptive filters," *Med. Biol. Eng. Comput.*, vol. 57, no. 1, pp. 27–46, 2019.
[45] J. B. Ali *et al.*, "Continuous blood glucose level prediction of type 1 diabetes based on artificial neural network," *Biocybernetics Biomed. Eng.*, vol. 38, no. 4, pp. 828–840, 2018.