Postprandial Blood Glucose Control in Type 1 Diabetes for Carbohydrates with Varying Glycemic Index Foods

Shogo Hashimoto[1], Claudia Cecilia Yamamoto Noguchi[1] and Eiko Furutani[1]

Abstract— **Treatment of type 1 diabetes consists of maintaining postprandial normoglycemia using the correct prandial insulin dose according to food intake. Nonetheless, it is hardly achieved in practice, which results in several diabetes-related complications. In this study we present a feedforward plus feedback blood glucose control system that considers the glycemic index of foods. It consists of a preprandial insulin bolus whose optimal bolus dose and timing are stated as a minimization problem, which is followed by a postprandial closed-loop control based on model predictive control. Simulation results show that, for a representative carbohydrate intake of 50 g, the present control system is able to maintain postprandial glycemia below 140 mg/dL while preventing postprandial hypoglycemia as well.**

I. INTRODUCTION

In the treatment of type 1 diabetes (T1D), overall blood glucose (BG) levels close to normoglycemia is known to decrease eventual life-threatening complications, especially in young patients with long-standing diabetes [1]. Recently, postprandial glycemia has been considered more determinant than fasting BG levels in the management of T1D [2]. It consists of invasive blood glucose measurement and bolus insulin administration previous to every single meal intake in an attempt to maintain a good glycemic control throughout the day. However, bolus insulin assessment tools such as the carbohydrate-counting method [3] provide only an approximate of the optimal insulin dose for a given meal.

To alleviate the burden of continuous BG self-management in these patients, several BG control systems [4] have been developed to date, which are mainly proportion-integrative-derivative control [5] and more recently Model Predictive Control (MPC) [6]. Although these studies have succeeded in avoiding hypoglycemia [7], they are still unable to maintain postprandial normoglycemia.

In our study, we propose a feedforward plus feedback blood glucose control system that consists of a preprandial insulin bolus dose followed by MPC-based postprandial blood glucose control, both of which rely on a previously developed mathematical model of glucose-insulin metabolism in T1D that considers the glycemic impact of carbohydrates according to the amount and absorption properties, including the glycemic index (GI) of foods [8]. The main objective of our study is to minimize postprandial hyperglycemia for varying amounts and types of carbohydrate ingested.

Firstly, the aforementioned mathematical model of glucose-insulin in T1D is introduced in section 2. Our proposed blood glucose control method for postprandial glycemia in T1D patients is detailed in section 3. Computer simulation results are given in section 4 and lastly discussion is added in section 5.

[1]S. Hashimoto, C. C. Yamamoto and E. Furutani are with Department of Electrical Engineering, Kyoto University, Kyoto 615-8510, Japan ccyamamoto at rotary.kuee.kyoto-u.ac.jp

II. MATHEMATICAL MODEL OF GLUCOSE-INSULIN METABOLISM IN T1D FROM CARBOHYDRATE INTAKE

We consider a mathematical model of T1D developed by Yamamoto *et al.* [9], which is divided into three sub-compartments to represent a) carbohydrate digestion/absorption, b) subcutaneous insulin pharmacokinetics and c) glucose-insulin metabolism.

First, carbohydrate digestion and absorption in such model is given as a glucose-equivalent representation of rapidly (RAG) and slowly (SAG) available carbohydrates, according to its breakdown and absorption rate as originally classified by Englyst *et al.* [10]. Such model comprises

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} x_{\mathrm{R}} \\ x_{\mathrm{S}} \end{bmatrix} = \begin{bmatrix} A_{\mathrm{R}} & 0 \\ 0 & A_{\mathrm{S}} \end{bmatrix}\begin{bmatrix} x_{\mathrm{R}} \\ x_{\mathrm{S}} \end{bmatrix} + \begin{bmatrix} B_{\mathrm{R}} \\ B_{\mathrm{S}} \end{bmatrix} G_{\mathrm{food}}(t), \tag{1}$$

$$\frac{\mathrm{d}G_{\mathrm{ext}}(t)}{\mathrm{d}t} = \frac{1}{\tau_{\mathrm{dg}}}[-G_{\mathrm{ext}}(t) + C_{\mathrm{R}}x_{\mathrm{R}}(t) + C_{\mathrm{S}}x_{\mathrm{S}}(t-L)], \tag{2}$$

where $G_{\mathrm{food}}(t)$ is the food input of the model for a given meal, $G_{\mathrm{ext}}(t)$ is glucose-equivalent of carbohydrates and Eq. (2) represents gastric emptying delay in T1D, with the corresponding matrices

$$A_{\mathrm{R}} = \begin{bmatrix} 0 & 1 \\ -\dfrac{1}{T_{\mathrm{R}}^2} & -\dfrac{2}{T_{\mathrm{R}}} \end{bmatrix}, \quad A_{\mathrm{S}} = \begin{bmatrix} 0 & 1 \\ -\dfrac{1}{T_{\mathrm{S}}^2} & -\dfrac{2}{T_{\mathrm{S}}} \end{bmatrix},$$

$$B_{\mathrm{R}} = \begin{bmatrix} 0 & \dfrac{k_{\mathrm{R}}}{T_{\mathrm{R}}^2}\mathrm{Glc}^{\mathrm{EQ}} \end{bmatrix}^{\mathrm{T}}, \quad B_{\mathrm{S}} = \begin{bmatrix} 0 & \dfrac{k_{\mathrm{S}}}{T_{\mathrm{S}}^2}\mathrm{Glc}^{\mathrm{EQ}} \end{bmatrix}^{\mathrm{T}},$$

$$C_{\mathrm{R}} = C_{\mathrm{S}} = [1 \quad 0],$$

$$L = 20 \text{ min},$$

$$\mathrm{Glc}^{\mathrm{EQ}} = \frac{50 \text{ g}}{\mathrm{AvCHO}}\left\{1.5\frac{\mathrm{GI}}{100}\ (1-\mathrm{e}^{-k_1\cdot\mathrm{AvCHO}}) + 0.13\ k_2\right\},$$

$$\mathrm{AvCHO} = \int_0^{t_{\mathrm{food}}} G_{\mathrm{food}}(t)\mathrm{d}t.$$

Variables and parameters of the complete model as given in Table I with corresponding values specified elsewhere [9]. Subcutaneous rapid-acting insulin absorption kinetics is

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TABLE I

VARIABLES AND PARAMETERS OF THE T1D MODEL.

$x_R(t)$	State variable for representation of RAG absorption
$x_S(t)$	State variable for representation of SAG absorption
$G_{food}(t)$	Carbohydrate intake input
τ_{dg}	Food-specific gastric emptying delay constant
$G_{ext}(t)$	Carbohydrate absorption as glucose-equivalent
T_R, T_S	Time-constant parameters of RAG and SAG absorption
k_R, k_S	Proportion constants of RAG and SAG amount
Glc^{EQ}	Glucose equivalent of carbohydrate intake
AvCHO	Carbohydrate amount ingested
GI	Glycemic index of foods
k_1, k_2	Constants
$x_1(t)$	Insulin mass at the subcutaneous depot
$x_2(t)$	Subcutaneous compartment proximal to plasma
$I(t)$	Plasma insulin concentration
V_d	Plasma distribution volume
k_{21}	Insulin diffusion parameter
k_a	Insulin transition rate
k_d	Degradation rate constant in subcutaneous tissue
k_e	Degradation rate constant in plasma
$u_s(t)$	Subcutaneous insulin administration (bolus or infusion)
$G(t)$	Blood glucose concentration
V_1	Volume distribution space
p_1	Glucose mass action rate constant
G_b	Basal blood glucose level parameter
$X(t)$	Remote-insulin concentration
p_2	Rate of decrease in tissue glucose uptake ability
p_3	Rate of insulin-dependent tissue glucose uptake ability

based on Shimoda insulin model [11] as

$$\frac{dx_1(t)}{dt} = -k_{21}x_1(t) + u_s(t), \tag{3}$$

$$\frac{dx_2(t)}{dt} = k_{21}x_1(t) - (k_d + k_a)x_2(t), \tag{4}$$

$$\frac{dI(t)}{dt} = \frac{k_a}{V_d}x_2(t) - k_e I(t). \tag{5}$$

Lastly, the glucose-insulin metabolism subsystem is based on the glucose kinetics and remote insulin compartments from Bergman minimal model [12] given by

$$\frac{dG(t)}{dt} = -X(t)G(t) + p_1[G_b - G(t)] + \frac{G_{ext}(t)}{V_1}, \tag{6}$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3I(t). \tag{7}$$

III. POSTPRANDIAL BLOOD GLUCOSE CONTROL ALGORITHM

A. Insulin Administration Strategy

For the design of a postprandial BG control system, we consider the insulin infusion strategy shown in Fig. 1. Food intake is set at $t = 0$, from which we first consider a preprandial insulin bolus administered at t_{bolus}, *i.e.,* an instant somewhere between -30 and 0 min depending on carbohydrate amount and composition. Subsequently, we include a postprandial closed-loop BG control to maintain late-postprandial normoglycemia using MPC algorithm [13] based on the mathematical model of T1D introduced in the previous section. Target glycemic values (see Table II) follow clinical recommendations for postprandial glycemia specifically for T1D patients [14].

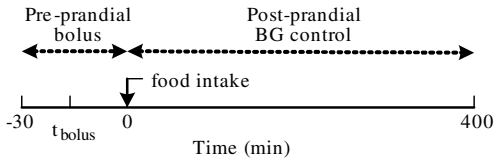

Fig. 1. Diagram of the prandial insulin administration strategy in our study. Considering food intake at instant $t = 0$, it includes a preprandial insulin bolus at t_{bolus} between -30 min and 0 min, followed by MPC-based postprandial blood glucose control.

B. Determination of Preprandial Insulin Bolus (Feedforward Control)

The optimal insulin bolus dose is food-specific and determined from an optimization problem whose objective function is given as

$$J = \int_{t_{begin}}^{t_{end}} \left\{ e^2(t) + Q_c u_s^2(t) \right\} dt \tag{8}$$

where $e(t) = G(t) - 100$ mg/dL indicates the difference between the current and target BG levels, u_s is subcutaneous insulin administration and Q_c is the weighting matrix.

The optimal insulin bolus U_b administered at t_{bolus} is obtained by minimizing Eq. (8) while considering that

- By definition, insulin bolus is administered as a single dose at

$$u_s(t) = \begin{cases} U_b, & t = t_{bolus} \\ 0, & \text{otherwise} \end{cases} \tag{9}$$

  where bolus timing can be effective from $t = -30$ min (30 min prior to food intake) to $t = 0$.
- End time is set to $t_{end} = 240$ min in Eq. (8) as an approximation of the total lasting hypoglycemic effect after a subcutaneous insulin bolus dose.
- Insulin infusion is given at a one-minute interval.
- Only positive insulin bolus doses are allowed.

Furthermore, we assume that normal BG levels are maintained by means of basal insulin infusion until the start of the prandial control period ($t = -30$ min), as well as absence of insulin-on-board, *i.e.,* remaining active insulin from a previous bolus dose.

The minimization problem is stated as

$$\begin{aligned} \underset{U_b,\ t_{bolus}}{\text{minimize}} \quad & J \\ \text{subject to} \quad & U_b \geq 0, \\ & \text{Eq. (9)}. \end{aligned} \tag{10}$$

TABLE II

POSTPRANDIAL BG REQUIREMENTS IN OUR CONTROL SYSTEM [14].

Target blood glucose level	100 mg/dL
Acceptable late postprandial BG range	80–130 mg/dL
Maximum postprandial glycemia	170 mg/dL
Minimum postprandial glycemia	70 mg/dL

TABLE III

OPTIMAL PREPRANDIAL INSULIN BOLUS TIMING t_{BOLUS} AND DOSE U_{B}

Food	GI	t_{bolus} (min)	U_{b} (IU)
Instant potato	83	−30	9.59
White bread	71	−30	8.33
Spaghetti	41	−1	5.32
Pearled barley	25	−1	3.59

By solving the above problem considering that $Q_c = 450$ mg^2 min^2 dL^{-2} IU^{-2}, we obtain the optimal insulin dose U_{b} and timing t_{bolus} for four representative carbohydrate-rich staple foods with different GI values across the range, as shown in Table III.

C. Postprandial MPC-based Blood Glucose Control (Feedback Control)

At $t = 0$, we initiate a BG control algorithm based on the model of T1D presented in the previous section and MPC algorithm with cost function

$$\hat{J} = \sum_{i=N_{\text{b}}}^{N_{\text{b}}+N_{\text{p}}-1} \hat{e}^2(k+i) + \sum_{i=1}^{N_{\text{m}}} \left\{ Q_2 u_{\text{s}}^2(k+i) + R_2 \Delta u_{\text{s}}^2(k+i) \right\} \tag{11}$$

where k is current sampling time, $\hat{e}$ is the difference between the predicted BG value and reference trajectory, u_{s} and Δu_{s} are the manipulated variable (subcutaneous insulin infusion) and its rate change, respectively. MPC parameters are sampling period $\Delta t = 1$ min, $N_{\text{b}} = 36$ with a prediction horizon of $N_{\text{p}} = 100$ steps, control horizon $N_{\text{m}} = 1$, a first-order reference trajectory with $\alpha = 0.9$ (with a maximum slope of -0.8 mg/dL/min) for positive and $\alpha = 0.95$ for negative error in a single step; and weighting matrices in Eq. (11) are set to $Q_2 = 555$ mg^2 min^2 dL^{-2} IU^{-2} and $R_2 = 2220$ mg^2 min^4 dL^{-2} IU^{-2}.

IV. SIMULATION

In this section we present simulation results of the feedforward-feedback blood glucose control system for postprandial state in the present study.

A. Simulation Settings

Parameter settings of the glucose-insulin model of T1D follow original specifications in [9] while initial simulation settings are $x_1(-30) = 0.248$ IU, $x_2(-30) = 0.504$ IU, $I(-30) = 22.4$ IU L^{-1}, $X(-30) = 2.80 \times 10^{-3}$ min^{-1} and $G(-30) = 100$ mg/dL.

B. Simulation Results

We first simulate the effect of the optimal preprandial insulin bolus alone according to the solution of the optimal insulin timing and dose for each type of GI food as given in Table III. As shown in Fig. 2, the postprandial BG excursion for instant potato (—), white bread (- -), spaghetti (-·-·) and pearled barley (···) all reach postprandial normoglycemia after 2 hours, which confirms the adequacy of the food-specific dose U_{b} from the preprandial insulin bolus optimization problem. Nonetheless, as the effect of the bolus insulin diminishes, BG levels increase due to hepatic glucose production. By including postprandial MPC, late-postprandial normoglycemia is maintained in the target BG levels independently of the type of food, as shown in Fig. 3.

Moreover, we include some specific cases such as deviations in food intake time, carbohydrate amount and GI value, which are likely to occur in an everyday setting. In addition to this, we also consider inter-individual variability by changing parameters of insulin sensitivity and endogenous glucose balance in our model of T1D. Under the aforementioned circumstances, the control method developed in our study is still able to control postprandial glycemia satisfactorily except for instant potato (very high GI value) where postprandial BG levels briefly fall to 66 mg/dL at $t = 180$ min approximately.

V. DISCUSSION

We propose a BG control system with the specific purpose of minimizing postprandial glycemia in T1D patients considering the impact of carbohydrates with different GI foods. Such system comprises a preprandial rapid-acting insulin bolus whose dose and bolusing time are the result of an optimization problem given in Eq. (10), followed by MPC-based feedback control to maintain normoglycemia for late postprandial state.

To the best of our knowledge, no previous research on BG control has been able to maintain postprandial normoglycemia in T1D patients, particularly during early postprandial state. The preprandial insulin bolus concept in our study is based on a study by Luijf *et al.* [17], who suggest that a preprandial insulin bolus 15 min prior to meal intake significantly lowers postprandial glycemia in T1D. In our study, however, instead of a fixed time we consider it to be dependent on the type of carbohydrate ingested, as expressed as a whole by its GI. In this way, the most appropriate insulin bolus dose and timing varies widely depending on the specific food, as shown in Table III. Regarding the maximum allowed preprandial timing, we consider as much as -30 min despite explicit indications of prandial administration to avoid hypoglycemia [16], which suggests that further modifications to the current guideline might be done for the

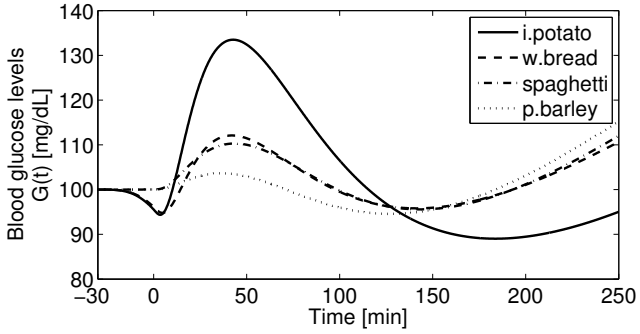

Fig. 2. Simulation of postprandial glucose excursion in T1D after preprandial bolus insulin only, with bolus dose and timing as indicated in Table III.

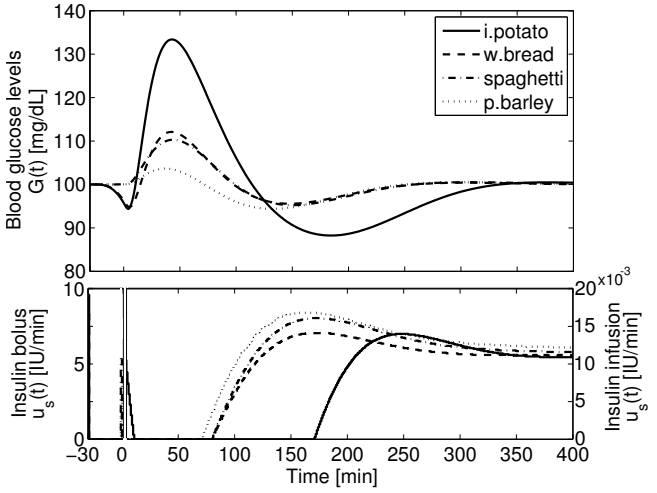

Fig. 3. Simulation of postprandial glucose excursion in T1D after preprandial bolus insulin as indicated in Table III, and the addition of closed-loop postprandial MPC.

sake of an improved treatment of T1D.

The mathematical model of T1D utilized in the present study plays a determinant role since it includes the effect of varying GI foods and their impact on BG levels. Regarding feedforward control, our system is able to reduce postprandial hyperglycemia in the case of instant potato (high GI) from 240 mg/dL for $t_{\text{bolus}} = 0$ [9], to 135 mg/dL for $t_{\text{bolus}} = -30$ min in the current study with no risk of hypoglycemia whatsoever. By relaxing the timing constraint for preprandial bolusing, we found that for instant potato and white bread in particular, the optimal bolusing times are in fact $t_{\text{bolus}} = -50$ min and -37 min, respectively. Nevertheless, the preprandial bolusing time constraint of -30 min in our study is considered for patient safety reasons to prevent hypoglycemia and thus we do not consider the aforementioned preprandial bolus time values sensible for eventual clinical tests. During feedback control, the utilization of MPC for the late-postprandial state guarantees that BG levels are maintained in the target range as the effect of the prandial insulin bolus dose fades away. The compensating effect of MPC is clearly seen by comparison of Figs. 2 and 3. Such feedback control is possible because of the accurate model of subcutaneous insulin dynamics utilized and the ability of the prediction algorithm to foresee the diminishing effect of preprandial insulin, the effect of different types of carbohydrates and the hypoglycemic effect of postprandial insulin infusion altogether. Additionally, small fluctuations in food intake, timing or model parameters have shown negligible impact on the closed-loop control system.

A few limitations in our study include the response of the control system to much greater amounts of carbohydrates especially for particularly high GI foods, as is common in the western diet. We consider $t_{\text{begin}} = -30$ min (prior to food intake) as adequate in the preprandial optimization problem in order to avoid a potential hypoglycemic episode, as Fig. 2 shows some glycemic reduction at $t = 0$ before the high GI food impacts BG levels. Thus, knowing that a larger intake and/or even higher GI foods cause a greater postprandial hyperglycemia and thus requires a longer preprandial bolus time, we should also be aware of possible preprandial hypoglycemia in case we consider increasing the maximum preprandial bolus timing beyond $t_{\text{begin}} = -30$ min. In fact, one of the limits of our proposed control system to suppress postprandial hyperglycemia is determined by the ability to avoid preprandial hypoglycemia, which is essentially determined by the pharmacokinetics of rapid-acting insulin formulations.

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