In Silico Blood Glucose Control for Type 1 Diabetes with Meal Announcement Using Carbohydrate Intake and Glycemic Index

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Abstract An increasing number of closed-loop blood glucose (BG) control algorithms have been developed in recent years with the 'artificial pancreas' as the ultimate goal, although tight postprandial BG control remains an elusive goal. In this report, the authors propose a novel semi closed-loop BG control algorithm with meal announcement, which involves computation of the optimal continuous subcutaneous insulin infusion for a specific meal 60 min prior to mealtime. It utilizes a mathematical model of glucose-insulin metabolism to predict the impact of carbohydrates on postprandial BG levels based on carbohydrate intake and glycemic index (GI) value. The optimal pre-meal insulin is infused until mealtime, after which the control algorithm switches to model predictive control (MPC) to stabilize postprandial glycemia at the target value of 100 mg/dL (5.55 mmol/L). *In silico* results for four representative foods with GI values spanning a wide range show that in the case of exact patient-model match with precise information of carbohydrate composition and mealtime, postprandial BG levels can be maintained between 86–134 mg/dL (4.78–7.44 mmol/L) and 86–152 mg/dL (4.78–8.44 mmol/L) for 50 g and 100 g of carbohydrates, respectively. With consideration of intra-patient variability and meal-related uncertainties regarding the estimated carbohydrate amount and start of meal consumption, the BG control range is 75–159 mg/dL (4.17–8.83 mmol/L) with no critical hypoglycemic episodes.

Keywords: glycemic index, model predictive control, prandial state, tight blood glucose control, type 1 diabetes.

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1. Introduction

Type 1 diabetes (T1D) is one of several forms of diabetes caused specifically by an abrupt decline in endogenous insulin secretion from pancreatic β -cells, resulting in extremely high blood glucose (BG) levels. To prevent life-threatening complications in the long term, T1D patients must undergo a basal-bolus insulin therapy that requires an accurate estimation of the single-bolus insulin dose based on the total carbohydrate intake at every single meal. Despite continuous development of correction factors to increase the accuracy of estimation of prandial insulin needs [1], T1D patients still not only suffer from postprandial hyper- and/or hypoglycemic episodes-with their respective accompanying symptoms-due to insulin bolus miscalculation, but also are constantly exposed to wide post-meal glycemic excursions that compromise endothelial function and directly impacts microvascular complications [2]. Thus postprandial hyperglycemia has been recently acknowledged to have a more deleterious effect on the overall management of diabetes than fasting BG levels [3].

To reduce the burden of T1D treatment, there has been an increasing number of studies on automatic BG control systems aiming at the development of the 'artificial pancreas' [4]. Proportional-integral-derivative control [5] and model predictive control (MPC) [6] are the most widely utilized algorithms for BG control purposes, with different approaches being constantly proposed,

including fully closed-loop control algorithms with automatic meal detection based on changes in BG levels [7] and semi closed-loop systems with improved postprandial BG control performance at the expense of additional input from the patient for an intended meal (meal announcement) [8]. Others favor a fixed pre-meal bolus of 2 IU [9] or over-bolus [10] along with closed-loop BG control, while a recent intraperitoneal insulin infusion [11] offers an interesting alternative to subcutaneous route due to faster insulin responses. Although these approaches in diurnal BG control have been shown to maintain postprandial BG excursion largely within a specific range, they have not achieved the target maximum peak BG levels below 180 mg/dL (10.0 mmol/L) recommended by the American Diabetes Association (ADA) for prandial BG management in T1D patients [12]. These previous clinical results seem to indicate that tight diurnal BG control might be an unattainable goal, which is arguably attributed to the great plasma glucose appearance from carbohydrate-rich meals, combined with slow insulin absorption kinetics and delayed effect on BG levels of subcutaneous administration by up to several times compared to normal endogenous insulin secretion in nondiabetics.

Based on observation in clinical studies in which insulin bolus given 15 min prior to meal consumption reduced postprandial glycemic excursion [13], the authors previously developed a prandial control algorithm that satisfactorily maintained postprandial BG levels within the recommended clinical range, by combining a pre-meal single insulin bolus with postprandial closed-loop BG control initiated at mealtime [14] to compensate for the rapid and large glycemic increase after a meal. Such BG control algorithm utilizes a novel mathematical model of glucose-insulin metabolism in T1D [15, 16], which uses the amount of carbohydrates as well as the glycemic index (GI) [17] to accurately predict the glucose absorption rate according to the type of

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carbohydrate consumed and the impact on postprandial BG level.

Because of the limited performance of previous BG control algorithms during postprandial state, the present study seeks to determine the degree of attainability of tight prandial BG control in T1D *in silico*. In this way, provided meal announcement information of carbohydrate amount and GI value of the intended meal, the optimal continuous subcutaneous insulin infusion is determined from an insulin optimization problem computed at the initial time, and accordingly infused to the patient until mealtime. Thence, closed-loop MPC control is used for the following 440 min (> 7 hours) post-meal to ensure complete stabilization of BG level at the target value of 100 mg/dL (5.55 mmol/L) for the assessment of the BG control performance for different GI foods, as well as patient and food-related uncertainties.

The present article includes an elaborate description of the prandial BG control algorithm in Section 2, an *in silico* evaluation of BG control performance in Section 3, followed by further discussions of the results in Section 4, and conclusions in Section 5.

2. Method

2.1 Blood Glucose Control Strategy

In the present study, we use discrete-time control systems with sampling period Δt and discrete time step k , where $t = k\Delta t$. Utilizing the mathematical model developed in a previous study (see supplementary material) [15, 16], the novel control algorithm proposed in the present section is detailed as follows. First, let k_{food} be defined as mealtime for the T1D patient, where $k_{\text{food}} = 0$ is the initially intended mealtime. From this, let $k_i (< 0)$ be defined as the initial time of prandial BG control and potential start of preprandial insulin infusion; and let $k_f (> 0)$ be the ending time in prandial BG control at which BG levels are completely stabilized at the target value (**Fig. 1**). The purpose of the present control is to maintain prandial BG levels within those recommended by the ADA (**Table 1**). Provided that $k_{\text{food}} = 0$, the control strategy in the present study is divided into two parts. Initially, optimal prepran-

Fig. 1 Insulin infusion strategy for the prandial BG control algorithm in the present study. (1) At $k = k_i$, optimal prandial insulin infusion from $k = k_i$ to k_f is calculated from meal content information (amount and type of carbohydrate), and infused accordingly from k_i to 0 (mealtime). (2) At $k = 0$, the control algorithm switches to MPC to maintain BG levels at the target value.

Table 1 ADA recommendations for BG management in T1D [12].

Condition	BG levels [mg/dL]
Fasting / premeal	70–130
Peak postprandial	< 180
Premeal / overnight (pregnancy)	60–99
Peak postprandial (pregnancy)	100–129

dial insulin infusion to maintain tight BG control throughout the prandial state from $k = k_i$ to k_f is computed at $k = k_i$, although insulin is effectively infused only from $k = k_i$ to 0 (mealtime). Thereafter, the control algorithm automatically switches to closed-loop BG control utilizing MPC for stabilization and maintenance of BG levels at the target BG value until the final time of $k = k_f$. At mealtime, a single-meal is represented by an impulse signal in the input $G_{\text{food}}(t)$ with specific carbohydrate intake in the input of the T1D patient model given by Eq. (S2) in the supplementary material.

2.2 Prandial Insulin Optimization

At the initial time k_i , the optimal prandial insulin infusion is calculated by the cost function given by

$$J_{\text{opt}} = \sum_{i=0}^{k_f-k_i} Q(E)E^2(k_i + i | k_i) + \sum_{i=k_i}^{k_f} R\Delta u_s^2(i) \quad (1)$$

where $E(k_i + i | k_i) = \hat{y}(k_i + i | k_i) - W_R$ is the deviation of the estimated model output $\hat{y}(k_i + i | k_i)$ from the target BG value W_R ; $\hat{y}(k_i + i | k_i)$ is the model-predicted BG value as the output $\hat{y}(k) = G(k\Delta t)$ at $k = k_i + i$ provided the initial condition $\hat{y}(k_i)$ of subcutaneous insulin infusion sequence $u_s(i)$ as given in Eq. (S10); $\Delta u_s(i) = u_s(i) - u_s(i-1)$ is the change in insulin rate; and Q and R are weighting matrices for E and $\Delta u_s(i)$, respectively. In particular, we consider $\Delta u_s(i)$ to be more suitable than $u_s(i)$ in the cost function J_{opt} to provide a smooth continuous variable insulin infusion and eliminate steady-state offset errors. Moreover, as a countermeasure of critical hypoglycemia, we consider a variable weighting matrix Q depending on the BG deviation E , with a larger weight $Q_{\text{LO}} > Q$ for values below the reference BG given as

$$Q(E) = \begin{cases} Q, & E \geq 0 \\ Q_{\text{LO}}, & E < 0 \end{cases} \quad (2)$$

The prandial optimization problem is thus

$$\begin{aligned} &\underset{\{u_s(k)\}}{\text{minimize}} && J_{\text{opt}} \\ &\text{subject to} && 0 \leq u_s(k) \leq U_{\text{pre}}, \quad k < 0 \\ & && 0 \leq u_s(k) \leq U_{\text{post}}, \quad k \geq 0 \end{aligned} \quad (3)$$

where U_{pre} and U_{post} are the maximum preprandial and postprandial insulin infusions, respectively, allowed for patient safety to avoid over-insulinization. Note that although the optimal insulin for $0 \leq k \leq k_f$ is also computed in Eq. (3), only preprandial bolus insulin from k_i to 0 is actually infused to the patient.

2.3 Postprandial BG control algorithm

After the total optimal insulin is computed according to Eq. (3) and effectively infused to the T1D patient until $k = 0$, the control algorithm switches to closed-loop BG control based on an MPC algorithm with cost function given by

$$J_{\text{MPC}}(k) = \sum_{i=N_1}^{N_2} Q(e)e^2(k + i | k) + \sum_{i=0}^{N_u-1} R\Delta u_s^2(k + i) \quad (4)$$

where the weighting matrix $Q(e)$ also follows Eq. (2). N_1 and N_2 define the prediction horizon; N_u is the control horizon; and $e(k + i | k) = \hat{y}(k + i | k) - w(k + i | k)$ is BG deviation of the model prediction from the reference trajectory given by

$$w(k + i | k) = \alpha^i w(k | k) + (1 - \alpha^i) W_R, \quad (5)$$

with convergence rate constant $0 < \alpha < 1$ and reference trajectory span of $i = N_1, \dots, N_2$. In particular, the reference trajectory in Eq. (5) is an exponential curve for smoother approach of BG to-

wards the target BG value W_R , to prevent abrupt variations in BG level throughout the postprandial period.

The MPC optimization problem to solve is thus

$$\begin{aligned} & \underset{\{u_s(k+i)\}}{\text{minimize}} && J_{\text{MPC}}(k) \\ & \text{subject to} && 0 \leq u_s(k+i) \leq U_{\text{post}}, \quad 0 \leq i \leq N_u - 1 \end{aligned} \quad (6)$$

from which the optimal postprandial insulin infusion is iteratively computed by evaluation of $J_{\text{MPC}}(k)$ and respective insulin infusion to the patient at each step from $k = 0$ until the end of the prandial state at $k = k_f$.

2.4 Clinically relevant control parameters

Parameter settings of the present control algorithm take into consideration clinical requirements for BG control application. Due to the rapid BG fluctuation from meal-derived glucose appearance, we consider $\Delta t = 1$ min adequate as commonly used in clinical studies [7, 18]. Start of preprandial insulin infusion is set at $k_i = -60$ to provide sufficient margin for the computation of the optimal preprandial insulin infusion and $k_f = 440$ to guarantee complete stabilization of late postprandial BG levels. Target BG level is set at $W_R = 100$ mg/dL (5.55 mmol/L) according to the ADA clinical recommendations. To prevent insulin overdosing, maximum preprandial insulin infusion rate is set at $U_{\text{pre}} = 2$ IU/min considering that the insulin bolus required (including differences in insulin-to-carbohydrate ratio) for a regular meal ranges from 3.7 to 10.9 IU [19], whereas maximum postprandial insulin infusion rate is set at $U_{\text{post}} = 0.05$ IU/min, which although considerably above basal profiles [20], is considered adequate since it includes not only basal insulin needs but also residual prandial insulin needs, especially for foods with low GI. Tuning parameters for the prandial control algorithm are $Q = 1$, $Q_{\text{LO}} = 10$, $R = 111$, $N_1 = 40$ steps, $N_2 = 130$ steps, $N_u = 1$, and $\alpha = 0.995$, such that the control algorithm satisfies the ADA clinical recommendations for prandial BG management (Table 1). In particular, the values of N_1 and N_2 are set to include the maximum hypoglycemic effect of insulin, which occurs between 1–2 hours after infusion, and the unitary value in N_u for increased robustness in the control system against errors [21].

2.5 Simulation

In order to assess the effectiveness of the proposed prandial BG control algorithm, we perform BG control simulations in MATLAB® for varying amounts of carbohydrate-rich foods with a wide range of GI (values in parenthesis); instant potato (83), white bread (71), spaghetti (41) and pearled barley (25). First, for the nominal case, the BG control algorithm is assessed for carbohydrate loads of 50 g and 100 g with exact model-patient match and mealtime in the T1D patient model at $k_{\text{food}} = 0$. Second, intra-patient variability due to continuous subcutaneous same-tissue utilization [22] and differences in reproducibility of the GI value of a meal [23] are also considered, incorporating $\pm 20\%$ variation in insulin-dependent glucose uptake (*i.e.*, insulin sensitivity), parameter p_3 of the T1D patient model, and GI value of the food as given in Eqs. (1) and (14) in the supplementary material. Lastly, food-related uncertainties commonly found in real-life scenarios include misestimation of carbohydrate intake of ± 10 g (20%) from the nominal amount of 50 g and deviation in mealtime ($k_{\text{food}} = \pm 15$ min) in the continuous-time T1D patient model, considering that the assumed mealtime in the controller remains

fixed at 0. Initial parameter values for all simulations are set at fasting state with basal insulin infusion to maintain BG levels at 100 mg/dL. In particular, the function 'fmincon' is utilized exclusively for computation of the cost function in Eq. (3).

3. Results

Results of the three aforementioned cases examined in the simulation study are presented in the following subsections.

3.1 Nominal case

We assess the performance of the present BG control algorithm for 50 g of the aforementioned carbohydrate-rich foods with GI values as shown in Fig. 2. The optimal preprandial bolus and postprandial basal insulin infusions are shown separately in Figs. 3 and 4. In particular, Fig. 3 shows that the optimal preprandial bolus insulin follows a hill-shaped infusion pattern with

Fig. 2 Prandial BG control response for a meal with carbohydrate content of 50 g and varying GI (value in parenthesis); instant potato (83), white bread (71), spaghetti (41) and pearled barley (25), consumed at $k_{\text{food}} = 0$.

Fig. 3 Optimal preprandial subcutaneous insulin infusion from $k = -60$ min to 0 for a nominal meal containing 50 g of carbohydrate-rich food (GI value in parenthesis); instant potato (83), white bread (71), spaghetti (41), and pearled barley (25).

Fig. 4 Closed-loop MPC postprandial subcutaneous insulin infusion from $k = 0$ to 440 for a nominal meal of 50 g of carbohydrate-rich food (GI value in parenthesis): (Top) instant potato (83) and white bread (71); (Bottom) spaghetti (41), and pearled barley (25).

large differences in peak bolus insulin infusion and timing among the representative carbohydrate-rich foods. Note that only the optimal preprandial insulin from k_i to 0 is infused to the T1D patient, although the optimization in Eq. (1) computes the total prandial insulin requirement from k_i through k_f . For exact comparison, the range in BG excursion for each type of food is also given in **Table 2**. There are definite differences in BG control response between high and low GI foods. BG is maintained close to ideal values for foods with lower GI values, whereas postprandial glycemia is observed with peaks within the ADA recommended value for foods with higher GI values. Additionally, we examine the response of the prandial BG control algorithm for a larger carbohydrate load of 100 g, and the prandial BG control ranges are shown in **Table 2**. For each food, BG levels are also maintained within similar values as those for a 50-g load with the same GI value, with equally similar insulin infusion pattern depending on the GI value.

3.2 Intra-individual variability

Simulation results considering intra-individual variation of parameter $p_3 \pm 20\%$ and $GI \pm 20\%$ in the patient model for a high GI food (instant potato) are shown in **Fig. 5**. The results indicate that BG levels can be effectively maintained within the ADA recommended values. Slower meal-derived glucose appearance from low GI foods contributes to less pronounced BG excursions directly proportional to the GI value of the food (**Table 2**).

3.3 Food-related uncertainties

Simulation results of food-related uncertainties in mealtime and carbohydrate estimation for a high GI food (instant potato) are shown in **Fig. 6**, and the BG control ranges for the four representative foods are given in **Table 2**. Even though postprandial glycemic excursion is maintained below 160 mg/dL (8.89 mmol/L) in all cases, there is a risk of borderline hypoglycemia with BG level reaching 75 mg/dL (4.17 mmol/L) between 20–30 min due to delayed mealtime, and 79 mg/dL (4.39 mmol/L) between 190–220 min caused by early mealtime combined with a 10-g un-

Table 2 Ranges of prandial BG excursion using the present control algorithm for nominal intake of 50 g and 100 g, with intra-individual variability (p_3 and GI value), and with meal-related uncertainties in carbohydrate intake and mealtime.

Simulation case	GI	BG range [mg/dL]
50 g (nominal)	83	86–134
	71	91–114
	41	96–102
	25	97–101
100 g (nominal)	83	86–152
	71	92–126
	41	96–104
	25	97–101
$p_3 \pm 20\%$ 50 g	83	81–157
	71	82–135
	41	89–112
	25	92–108
$GI \pm 20\%$ 50 g	83	86–158
	71	87–132
	41	93–108
	25	97–103
$k_{\text{food}} = -15$ min 50 g ± 10 g	83	79–159
	71	81–139
	41	93–114
	25	98–104
$k_{\text{food}} = +15$ min 50 g ± 10 g	83	75–148
	71	82–122
	41	92–106
	25	94–103

Fig. 5 Simulation of prandial BG control for 50 g of instant potato (high GI) consumed at $k_{\text{food}} = 0$ with intra-individual variability in glucose effectiveness ($p_3 \pm 20\%$) and $GI \pm 20\%$.

derestimation of carbohydrate intake.

4. Discussion

This study presents an *in silico* evaluation of a semi closed-loop BG control algorithm for prandial state with prior meal announcement, which consists of preprandial insulin bolus infusion com-

Fig. 6 Simulation of prandial BG control for instant potato (high GI) considering mealtime deviation of $k_{\text{food}} = -15$ min (advance) or $k_{\text{food}} = +15$ min (delay) in combination with carbohydrate miscalculation of ± 10 g from the intended nominal intake of 50 g.

puted 60 min prior to the intended mealtime, followed by postprandial closed-loop control to maintain BG levels at the target value of 100 mg/dL as recommended by the ADA. Compared to our previous work [14] which was limited to an instantaneous single-bolus administered at a specific instant between $k_i = -30$ and 0 (*i.e.*, single-bolus administration at a specific instant between 30 min prior to mealtime and 0 min), the present study considers continuous variable insulin infusion instead and the potential of starting insulin infusion from $k_i = -60$ in order to obtain the optimal preprandial bolus dose and timing for each specific type of food. This study also extends the time span in the cost function to include the total prandial state from k_i to k_f . Moreover, the mathematical model utilized is an enhanced version of the model employed in our previous study [14]. It includes the maximum rate of glucose appearance from carbohydrates [16] to provide a more accurate model-based prediction of postprandial BG excursion in the present study. For a more thorough assessment of the performance of the BG control algorithm, we not only consider the nominal case as in our previous study [14] but also examine variability in subcutaneous insulin absorption as well as uncertainties in food amount and mealtime in the T1D patient model. Considering that daytime hypoglycemia (BG levels below 60 mg/dL) in T1D patients has a negative impact on the quality of life and health care cost even for mild episodes [24], the above improvements are necessary to prevent the risk of late postprandial hypoglycemia due to the remnant hypoglycemic effect of insulin several hours after large preprandial bolus doses. In addition, computation of maximum doses for preprandial and postprandial insulin infusions ($U_{\text{pre}} = 2$ IU/min and $U_{\text{post}} = 0.05$ IU/min) are necessary for safety reasons. In particular, U_{post} is noticeably above the maximum basal insulin infusion in closed-loop clinical trials [25]. Yet, this dose is considered necessary since slow digestion and absorption of low GI foods require greater insulin infusion rates than the basal rate for as long as 200 min post-meal. Note that the utilization of U_{pre} and U_{post} does not affect noticeably the performance of the control algorithm for any of the simulations cases examined in this study.

To our knowledge, the present study demonstrates for the

first time the feasibility of tight prandial BG control in patients with T1D even beyond ADA recommendations, although at the expense of starting prandial insulin infusion approximately 50 min before meal, which is arguably not a practical value for the operation of an artificial pancreas system in everyday conditions. Furthermore, the post-meal glycemic excursions in the simulation results, which are proportional to the GI values of the foods, are identical to those observed in nondiabetics for similar GI values [26]. This finding indicates that the BG control results obtained in the present study are comparable to the ideal response in healthy subjects. Nevertheless, the apparent inability of the present control algorithm to obtain a completely flat BG response for high GI foods—as represented by instant potato—compared to medium and low GI foods actually demonstrates the extent at which tight BG control is feasible under ideal conditions. Moreover, the insulin infusion patterns for nominal carbohydrate intakes of 50 g and 100 g indicate that the GI of the food is more relevant than the total intake in determining the infusion pattern, whereas carbohydrate intake only impacts the preprandial insulin dosage. This is consistent with reports from recent clinical studies that emphasize the difficulty in determining an appropriate bolus infusion pattern for a specific meal [27] despite the availability of insulin pump technologies with several bolus infusion patterns. It is also interesting that despite all the foods having an identical carbohydrate content of 50 g, the start of preprandial insulin infusion and the total bolus required differ proportionally to the GI value (Fig. 3), which supports prior clinical studies [28] suggesting that the current insulin bolus estimation from carbohydrate intake alone should be extended to include the GI value.

Assessment of the present control algorithm beyond the nominal case includes patient-model mismatch (individual variability) and food-related uncertainties. In particular, since parameters of the mathematical model of glucose-insulin metabolism in T1D are assumed to have a good fit for a representative patient, only intra-patient variability is considered as a source of model mismatch. Simulation results not only show that the control algorithm effectively maintains BG levels within the ADA recommended clinical values, but also that spontaneous patient variability regarding insulin sensitivity and glycemic impact of the food, as well as food-related uncertainties in both amount and timing can be managed within a BG peak below 160 mg/dL (8.89 mmol/L) and a nadir of 75 mg/dL (4.16 mmol/L) in all cases. Although the duration of meal consumption—and consequently impact on BG levels—in the T1D patient model might vary among individuals, the mathematical model previously developed (supplementary material) has been validated by clinical studies in which patients explicitly consumed the meal within 10 min. Hence, differences in postprandial BG excursion due to the meal consumption time are considered to be less relevant than intra-individual variability and food-related uncertainties examined in the present study for assessing the performance of the BG control algorithm.

Previous studies employing bi-hormonal closed-loop BG control systems with both insulin and glucagon infusions [29, 30] utilize the latter to prevent postprandial hypoglycemia, although such approach is known to increase both the complexity of the control system and burden to the patient due to the requirement of additional glucagon infusion. Compared to this, the control algorithm proposed in the present study considers the glycemic im-

pect of different types of carbohydrates—as represented by their GI values—for more accurate BG prediction and early insulin infusion as a countermeasure against the well-known delay in subcutaneous absorption. As a result of this ‘proactive’ approach, the maintenance of BG levels above 75 mg/dL (**Table 2**) suggests that an additional algorithm for glucagon infusion might not be necessary for successful diurnal BG control. It should be noted, though, that even with such prediction capabilities, the present control algorithm does not consider insulin-on-board, *i.e.*, residual insulin active for as long as 4–5 hours in the case of rapid-acting insulin, and thus entails a risk of postprandial hypoglycemia in the case of successive meals with few hours in-between. Although the cost function includes a penalty term Q_{LO} to reduce the risk of hypoglycemia, we believe that the BG impact from successive meals and the overlapped effect of the respective prandial insulin infusions might require more meticulous consideration of the control algorithm law, as well as the case of unplanned additional food or nibbling through a longer time span as in typical real-life scenarios. Nevertheless, due to the satisfactory *in silico* results achieved in the present study, further clinical implementation might be eventually considered, which would provide more strict evaluations of hypoglycemic risk for patient safety and methods to curtail the time of preprandial insulin infusion for practical reasons.

5. Conclusion

In the present study, the feasibility of a BG control algorithm that maintains tight BG control during prandial state even beyond ADA recommendations was demonstrated *in silico*. The total carbohydrate intake and GI value of the food are used in the computation of the optimal prandial insulin infusion under an ideal setting. Tight postprandial BG control is achieved by insulin infusion from 60 min prior to the intended mealtime in combination with closed-loop postprandial BG control based on MPC. Simulation results of the control algorithm proposed in this study show satisfactory performance not only for nominal carbohydrate loads of 50 g and 100 g but also with considerations of intra-individual variability and uncertainties in actual carbohydrate intake and mealtime.

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Conflict of Interest

The authors declare no conflicts of interest regarding this manuscript, nor do they have any relationship with companies or commercial organizations based on the definition of Japanese Society of Medical and Biological Engineering.

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Supplementary Material

Mathematical Model of glucose-insulin metabolism

We have proposed a mathematical model of glucose-insulin metabolism in T1D [15,16], which represents a) carbohydrate digestion and absorption, b) subcutaneous insulin pharmacodynamics and c) glucose-insulin metabolism. In particular, carbohydrate digestion and absorption (**Fig. S1**) consider carbohydrate intake and the GI value to derive the glucose-equivalent amount (GR), and further divided into rapidly (RAG) and slowly (SAG) available glucose according to the Englyst method.

Table S1 lists the variables and parameters of the mathematic model. the main model equations are given by

Fig. S1 Diagram of carbohydrate digestion and absorption as glucose-equivalent (GR) amount from carbohydrate intake and GI value, which is further divided into rapidly and slowly available glucose (RAG and SAG). Physiological considerations of maximum absorption rate of meal-derived glucose appearance Ra_{max} and delay in gastric emptying (first order delay) are also included.

Table S1 Variables and parameters of the mathematical model of glucose-insulin metabolism from carbohydrates in T1D used in the present study.

$x_R(t)$	State variable for RAG absorption
$x_S(t)$	State variable for SAG absorption
$G_{food}(t)$	Carbohydrate intake input
τ_{dg}	Gastric emptying delay constant
$G_{ext}(t)$	Carbohydrate as glucose-equivalent
T_R, T_S	Parameters of RAG and SAG absorption
k_R, k_S	Constants of RAG and SAG proportion
GR	Glucose equivalent of carbohydrate intake
AvCHO	Carbohydrate amount ingested
GI	Glycemic index of foods
k_1, k_2	Glucose relative constants
$\bar{G}_{EQ}(t)$	Glucose-equivalent considering Ra_{max}
Ra_{max}	Maximum rate of glucose appearance
$x_1(t)$	Insulin mass at the subcutaneous depot
$x_2(t)$	Subcutaneous absorption compartment
$I(t)$	Plasma insulin concentration
V_d	Plasma distribution volume
k_{21}	Insulin diffusion parameter
k_a	Insulin transition rate
k_d	Degradation rate constant
k_e	Degradation rate constant in plasma
$u_s(t)$	Subcutaneous insulin administration
$G(t)$	Blood glucose concentration
V_1	Volume distribution space
p_1	Glucose mass action rate constant
G_b	Basal blood glucose level
$X(t)$	Remote-insulin concentration
p_2	Rate of decrease in glucose uptake ability
p_3	Rate of insulin-dependent glucose uptake ability

$$GR = 1.5 \frac{GI}{100} (1 - e^{-k_1 \cdot AvCHO}) + 0.13k_2 \quad (S1)$$

$$AvCHO = \int_0^{t_{food}} G_{food}(t) dt \quad (S2)$$

$$\frac{d}{dt} \begin{bmatrix} x_R \\ x_S \end{bmatrix} = \begin{bmatrix} A_R & 0 \\ 0 & A_S \end{bmatrix} \begin{bmatrix} x_R \\ x_S \end{bmatrix} + \begin{bmatrix} B_R \\ B_S \end{bmatrix} G_{\text{food}}(t) \quad (\text{S3})$$

where $G_{\text{food}}(t)$ is the meal input signal of the model, t_{food} is the total food ingestion period, and further matrix representation of RAG and SAG absorption is given by

$$A_R = \begin{bmatrix} 0 & 1 \\ -\frac{1}{T_R^2} & -\frac{2}{T_R} \end{bmatrix}, \quad A_S = \begin{bmatrix} 0 & 1 \\ -\frac{1}{T_S^2} & -\frac{2}{T_S} \end{bmatrix} \quad (\text{S4})$$

$$B_R = \begin{bmatrix} 0 & \frac{k_R}{T_R^2} \text{GR} \end{bmatrix}^T, \quad B_S = \begin{bmatrix} 0 & \frac{k_S}{T_S^2} \text{GR} \end{bmatrix}^T \quad (\text{S5})$$

$$G_{\text{RAG}}(t) = C_R x_R(t) \quad (\text{S6})$$

$$G_{\text{SAG}}(t) = C_S x_S(t - \tau_{\text{SAG}}) \quad (\text{S7})$$

$G_{\text{RAG}}(t)$ and $G_{\text{SAG}}(t)$ represent RAG and SAG absorption, respectively, with $C_R = C_S = [1 \ 0]$, and $\tau_{\text{SAG}} = 20$ min for delay of SAG absorption by definition. Maximum rate of meal-derived exogenous glucose appearance ($R_{\text{a}_{\text{max}}}$) followed by food-specific delay in gastric emptying [$G_{\text{ext}}(t)$] are also considered as

$$\bar{G}_{\text{EQ}}(t) = \begin{cases} G_{\text{RAG}}(t), & t < t_1 \\ R_{\text{a}_{\text{max}}}, & t_1 \leq t \leq t_2 \\ G_{\text{RAG}}(t - t_3) + G_{\text{SAG}}(t), & t > t_2 \end{cases} \quad (\text{S8})$$

$$\frac{dG_{\text{ext}}(t)}{dt} = \frac{1}{\tau_{\text{dg}}} (-G_{\text{ext}}(t) + \bar{G}_{\text{EQ}}(t)) \quad (\text{S9})$$

with time parameters t_1 , t_2 and t_3 being specific to the amount and GI value of the food.

Subcutaneous rapid-acting insulin absorption kinetics from Shimoda et al. [5] is given by

$$\frac{dx_1(t)}{dt} = -k_{21}x_1(t) + u_s(t) \quad (\text{S10})$$

$$\frac{dx_2(t)}{dt} = k_{21}x_1(t) - (k_d + k_a)x_2(t) \quad (\text{S11})$$

$$\frac{dI(t)}{dt} = \frac{k_a}{V_d}x_2(t) - k_e I(t) \quad (\text{S12})$$

Lastly, the glucose-insulin metabolism subsystem from Bergman minimal model [6] comprises

$$\frac{dG(t)}{dt} = -X(t)G(t) + p_1(G_b - G(t)) + \frac{G_{\text{ext}}(t)}{V_1} \quad (\text{S13})$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3I(t) \quad (\text{S14})$$

Parameter values of a representative patient with T1D, as well as carbohydrate absorption parameters for four representative staple foods are further detailed elsewhere [15,16].

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