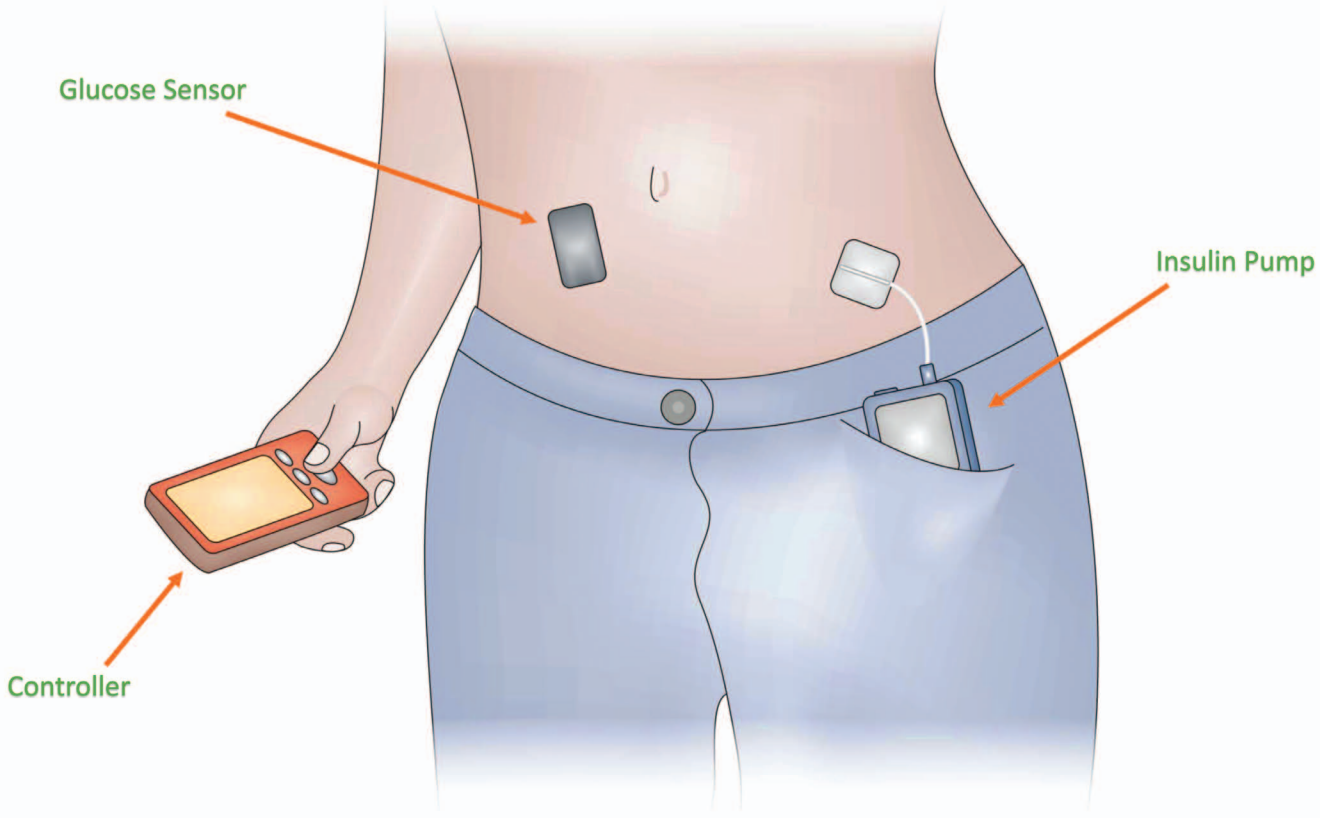
The Artificial Pancreas and Meal Control



AN OVERVIEW OF POSTPRANDIAL GLUCOSE REGULATION IN TYPE 1 DIABETES

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Digital Object Identifier 10.1109/MCS.2017.2766323
Date of publication: 19 January 2018

In healthy individuals, plasma glucose concentration is tightly regulated by the action of the hormones secreted by the endocrine pancreas, principally, insulin and glucagon. Insulin is secreted by the pancreatic beta cells to signal organs to absorb glucose, and glucagon is secreted by the pancreatic alpha cells to signal the liver to produce glucose [1]. In type 1 diabetes (T1D), insulin secretion is lost due to the autoimmune destruction of the beta cells [2]. T1D accounts for 5–15% of the 366 million people with diabetes worldwide [3].

Type 1 diabetes is currently treated with life-long insulin-replacement therapy, implemented using multiple daily injections or continuous subcutaneous (under the skin tissue) insulin infusion via a portable pump. Tight glucose control is critical for health, as a sustained elevation of glucose levels

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Summary

T1D is treated with external insulin to regulate glucose levels. The AP is a closed-loop system that regulates insulin delivery based on glucose sensor readings. MPC is the most common control strategy for an AP because it can easily incorporate meal information, insulin infusion constraints, and the dynamics of insulin absorption. In control systems terminology, the meals are considered as external disturbances that affect glucose levels. Feedback control after meal consumption is challenging because of the fast absorption of meal glucose (fast disturbance dynamics) compared to the slow effect of delivered insulin (slow actuator dynamics), which can result in high glucose levels that lead to long-term macro- and microvascular complications. Combined feedback-feedforward control, where the patients announce all ingested meals (and their size in number of carbohydrates) to the system, achieves better glucose control, which reduces these macro- and microvascular complications. However, when combined feedback-feedforward control adds advanced meal size estimation algorithms to alleviate the need for carbohydrate counting, patients' convenience and quality of life may also increase. When a patient forgets to announce a meal, meal detection algorithms might reduce the risk of severe hyperglycemia. This tutorial reviews numerous aspects related to glucose control following meals with a focus on clinical implications.

(hyperglycemia) leads to long-term complications such as heart disease, blindness, kidney failure, and lower-extremity amputations [4], [5]. How well the patient is able to control glucose is assessed using glycated hemoglobin (HbA1c) levels, a biomarker correlated with the mean blood glucose level over a period of three months. A target of HbA1c below 7.0% is recommended for most patients with T1D [6].

Despite advances in insulin analogs, insulin pumps, and continuous glucose sensors, most patients do not achieve acceptable glucose targets [7], [8]. An Epidemiology of Diabetes Interventions and Complications study reported an average HbA1c of 8.1% in 1349 patients [7]. HbA1c higher than 7.0% is associated with a significant increase in the risk of complications [6]. For instance, an increase of only 10% in HbA1c (for example, 8–8.8%) is associated with a 40% increase in the progression rate of diabetic retinopathy (damage to the retina) [9]. Despite the clinical efforts to control HbA1c levels, only 27% of patients achieve HbA1c levels lower than 7% [10].

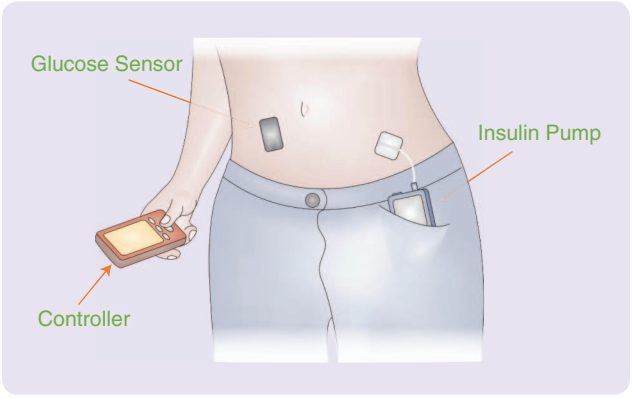

FIGURE 1 An artificial pancreas system. A sensor measures glucose levels and transmits them to a handheld controller, which runs a control algorithm. An insulin pump delivers insulin subcutaneously. The communication is wireless. In another configuration, the algorithm may also reside in the pump. (Courtesy of Macmillan Publishers Ltd. © 2011 [11].)

Advances in continuous glucose sensors have motivated the research towards closed-loop insulin delivery systems, termed the artificial pancreas (AP), to automatically regulate glucose levels in patients with T1D [11]. In the AP, the pump insulin infusion rate is repeatedly altered, based on a control algorithm that relies on continuous glucose sensor readings (Figure 1). Thus, the novelty of this approach resides in the real-time feedback of glucose levels to close the loop and establish hemostasis.

Effective closed-loop glucose control is challenged by inter- and intrapatient variability in insulin sensitivity and insulin absorption, exercise, slow absorption of subcutaneously infused insulin, and meals. Advanced closed-loop systems maintain glucose levels in the target range for 70–75% of the time, and the remaining time spent outside the target range is mostly due to postprandial (postmeal) hyperglycemia [12]. As discussed in "Summary," the purpose of this article is to introduce the specific challenges, models, and control techniques surrounding closed-loop glucose regulation following meal ingestion.

CHALLENGES OF POSTPRANDIAL GLUCOSE CONTROL

Postprandial Glucose Control in Healthy Individuals

In healthy individuals, there is little variation in plasma glucose concentrations, with fasting glucose ranging between 3.9 and 6.1 mmol/L [13] and postprandial glucose not exceeding 10 mmol/L [14]. Postprandial glucose control is ensured by the action of insulin secreted by the pancreas, the inhibition of glucagon secretion, and the resulting metabolic effects on the liver and peripheral tissues.

Plasma glucose concentration typically rises within 10 min following food ingestion [13]. A peak in plasma glucose concentration is observed around 60 min after the start of the meal, and the rate of increase depends on meal composition (such as carbohydrates type and quantity, as well as other nutrients intake) and timing of the meal [13].

Other factors are also known to affect insulin sensitivity and glucose absorption in individuals such as gastric emptying, physical activity, physical or emotional stress, and growth and hormonal fluctuations (such as puberty, pregnancy, menopause, and menstrual cycle) [6]. Plasma glucose concentrations are expected to return to the preprandial (premeal) level within 2–3 h, although carbohydrate and other nutrient absorption can continue for up to 5–6 h postprandial [13].

Postprandial Glucose Control in Type 1 Diabetes

Postprandial glucose control has a major impact on the risk of long-term complications [15]. Intensive insulin therapy aims for a 2-h postprandial glucose level between 5 and 10 mmol/L in most patients [6]. The main determinant of this postprandial glucose rise is the carbohydrate content of the ingested meal [16], [17]. Therefore, before each instance of food intake, patients need to estimate the carbohydrate content of the meal (carbohydrate counting), and self-administer an insulin bolus (dose) proportional to the carbohydrate content. Carbohydrate counting is a challenging task for patients, with an estimated average error of 20% [18]. Although the meal insulin bolus is based on the amount of carbohydrate, postprandial glucose concentrations are influenced by the type of carbohydrate (glycemic index of the food consumed) [19], [20]. In addition, meals rich in lipids and protein may be absorbed 60% slower than low-fat meals [21], which results in a prolonged postprandial hyperglycemia [22]–[25].

The considerable intra- and interindividual variability in the metabolic effect of subcutaneous insulin infusion in patients with T1D presents further complications [26], [27]. For the same body weight and age, insulin sensitivity can vary by up to sixfold among individuals. Across the daytime, a significant range of insulin sensitivity between meals also exists, with an increasing sensitivity from breakfast to lunch [27]. For the same individual across different days, it is estimated that there is a 31% variability in insulin sensitivity overnight and 17% variability during the day [28].

Adolescence is a period of many changes, including physiological and psychological changes. It is also a difficult period for glucose control, with a low adherence to diabetes self-treatment plan [29]. The National Paediatric Diabetes Audit for England and Wales reported that more than 80% of young people were above the recommended HbA1c level for adolescents (7.5% [30]) [31]. Nonadherence to the standard insulin therapy includes omission [32]–[34] or underestimation [35] of insulin boluses for meals and snacks. Statistics shows that more than 65% of youth using insulin pump therapy miss at least one meal bolus per week [33]. The reasons for insulin bolus omission remain largely unknown, but adolescents are reported to be unaware of missed boluses [33]. It is hypothesized that boluses are simply forgotten. Moreover, several studies have shown a tendency in female adolescents to skip or reduce insulin doses for weight control purposes [36], [37]. These observations suggest that the efficacy and safety of closed-loop control systems relying on patient inputs may be compromised with insulin bolus omissions in youth patients [38], [39]. An AP design minimizing the need for user interaction with the closed-loop controller may especially benefit young diabetes patients.

The major challenge to control postprandial glucose concentrations is the delay in rapid-acting insulin absorption compared with meal-glucose absorption [40], [41]. Subcutaneously injected insulin is absorbed into the blood under the skin, through the capillary membrane. The absorption rate of insulin molecules is related to the molecular size of insulin complexes [42]. Current rapid-acting insulin analogs have an onset (start of effect) between 10 and 15 min, with a peak action between 30 and 90 min [43]. However, after meal consumption, the rate of glucose appearance is much faster than insulin absorption, leading to a rapid increase in postprandial glucose levels. This mismatch between the peak absorption of externally injected insulin and the ingested carbohydrates makes it difficult to ensure tight, closed-loop control of plasma glucose concentrations (see "The Relative Effect of Time-to-Peak of Insulin Action and Time-to-Peak of Meal Absorption") [44].

SYSTEM DYNAMICS FOR POSTPRANDIAL GLUCOSE CONTROL

Plasma glucose concentration is balanced by the rate of glucose entering the blood circulation and the rate of glucose removal from the blood. The glucose entering the blood circulation is a result of the absorption of digested carbohydrate from meals and endogenous glucose production. For T1D, glucose elimination from the blood into skeletal muscle and body fat is driven by external insulin injections. Insulin also decreases the endogenous glucose production, which reduces the rate of glucose entering the blood.

This balancing mechanism is usually described by the interaction of four subsystems (Figure 2). Beginning with the subcutaneous injection of insulin (the system input to regulate plasma glucose concentration), up to the measurement of interstitial glucose concentration (which is the observable variable), the subsystems are the insulin absorption kinetics, plasma glucose kinetics, and interstitial subcutaneous glucose kinetics. The fourth subsystem, glucose meal absorption kinetics, describes the dynamics of glucose appearance from the digested carbohydrates. With this representation, consumed meals are regarded as disturbance signals to the glucoregulatory system of AP users.

Several mathematical models describing the glucoregulatory system of an AP user have been proposed in the literature [40], [45]–[48]. In this section, a representative, control-relevant model based on a compartmental approach is presented.

The Relative Effect of Time-to-Peak of Insulin Action and Time-to-Peak of Meal Absorption

Assuming a first-order glucoregulatory model, the change in glucose concentrations can be represented in the Laplace domain as

$$s\delta Q_g(s) = P_{\text{EGP}}(s) - \frac{S_i}{\tau_i} Q_{i\text{basal}}(s) + U_m(s) - \frac{S_i}{\tau_i} Q_{i\text{bolus}}(s),$$

where Q_g is the glucose mass in the plasma; P_{EGP} is the rate of endogenous glucose production; U_m is the rate of glucose appearance in the plasma due to meal ingestion; $Q_{i\text{basal}}$ and $Q_{i\text{bolus}}$ are the appearance of insulin in the plasma from basal and bolus delivery, respectively; and S_i and τ_i are constants representing the insulin sensitivity and time-to-peak of insulin action, respectively [S1], [S2].

In the postprandial period, the contributions of endogenous glucose production and basal insulin are small in comparison to meal-related glucose appearance and insulin boluses contributions. Therefore, glucose concentrations can be approximated by

$$s\delta Q_g(s) = U_m(s) - \frac{S_i}{\tau_i} Q_{i\text{bolus}}(s).$$

By using a two-compartmental model of subcutaneous insulin delivery and glucose absorption rate, glucose concentrations can be approximated by

$$s\delta Q_g(s) = \frac{K_m}{(1+\tau_m s)^2} Q_{\text{CHO}}(s) - \frac{S_i}{(1+\tau_i s)^2} U_b(s),$$

where $K_m = 10^3 K_{\text{Bio}}/(w\, M_{\text{CHO}})$. K_{Bio} is carbohydrates bioavailability in the meal, w is the patient weight, M_{CHO} is glucose molar mass, Q_{CHO} is the quantity of consumed carbohydrates, and U_b is the insulin bolus. A transformation in the time domain results in

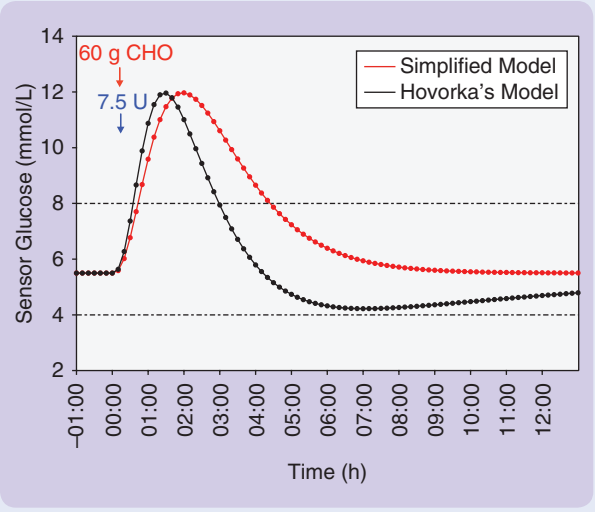

FIGURE S1 A comparison of postprandial glucose peak between Hovorka's model and the proposed simplified model. A virtual patient with weight 70 kg receives his basal insulin to keep the glucose level at 5.5 mmol/L. At time 0, the virtual patient ingests 60 g of carbohydrates and delivers a bolus of 7.5 U of insulin. The two plots superpose Hovorka's model response and the simplified model response. This graph illustrates that, immediately after meal consumption, the simplified model compares well to the complete Hovorka's model. This comparison shows that the simplified model may be used to estimate the maximum peak of glucose after meal ingestion.

Insulin Absorption Kinetics

After subcutaneous delivery, insulin is slowly absorbed following a two-compartment model

$$\begin{bmatrix} \frac{dQ_{i1}(t)}{dt} \\ \frac{dQ_i(t)}{dt} \end{bmatrix} = \begin{bmatrix} -\frac{1}{\tau_i} & 0 \\ \frac{1}{\tau_i} & -\frac{1}{\tau_i} \end{bmatrix} \begin{bmatrix} Q_{i1}(t) \\ Q_i(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} U_i(t),$$

where $Q_{i1}(t)$ and $Q_i(t)$ (units) are the insulin masses in the first and second compartment (the second compartment being the plasma space), $U_i(t)$ (unit/min) is the external insulin infusion rate, and τ_i is the time constant characterizing the peak response time of the insulin absorption, which depends on the insulin analog type. Following an impulse response (such as the administration of an insulin bolus), τ_i equals the time-to-peak of the insulin plasma concentration.

The plasma insulin concentration (insulinemia) $I_p(t)$ (munits/L) is obtained from $Q_i(t)$ as

$$I_p(t) = \frac{K_i}{\tau_i} Q_i(t),$$

where $K_i = 10^6/(w\, K_{\text{MCR}})$ $(10^{-3}\,\text{min}/L)$ is a gain inversely proportional to the metabolic clearance rate K_{MCR} (mL/kg/min) and the patient weight w (kg) [40]. In the Laplace domain, the plasma insulin concentration $I_p(t)$ (munits/L) is expressed as

$$I_p(s) = \frac{K_i}{(1+\tau_i s)^2} U_i(s).$$

When the insulin is injected as a bolus, the input function $U_i(t)$ takes the form of a Dirac input $U_i(t) = U_{i\text{Bolus}}\,\delta(t)$. This is equivalent to updating the first compartment by the bolus quantity

$$Q_{i1}(0^+) = \lim_{s\to\infty} s \frac{\tau_i}{1+\tau_i s} U_{i\text{Bolus}} = U_{i\text{Bolus}}.$$

Plasma Glucose Kinetics

Bergman's minimal model assumes that plasma glucose concentration $G(t)$ (mmol/L) changes are proportional to both the remote insulin (the delayed insulin effects) $x(t)$ (1/min) and the rate of meal-glucose appearance $U_m(t)$ [49]. The minimal model dynamics are represented as [45]

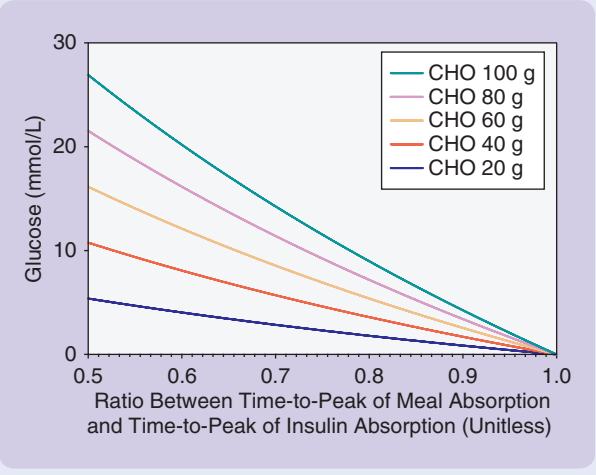

FIGURE S2 A plot of the maximum glucose peak after ingestion of different carbohydrate (CHO) quantities as a function of the ratio between time-to-peak of meal absorption τ_m and time-to-peak of insulin absorption τ_i. This graph shows that, for instance, following a 60-g meal, the maximum peak of glucose is 5.4 mmol/L for a ratio $\alpha = \tau_m/\tau_i = 0.8$. Increasing the ratio to 0.9 (by slowing the meal digestion or providing a faster-acting insulin) may result in decreasing the peak by 46% to 2.5 mmol/L.

$$\delta Q_g(t) = U_b S_i \left(\left(1 + \frac{t}{\tau_i}\right)e^{-\frac{t}{\tau_i}} - 1\right) - Q_{\text{CHO}} K_m \left(\left(1 + \frac{t}{\tau_m}\right)e^{-\frac{t}{\tau_m}} - 1\right).$$

This approximate model compares well to Hovorka's model [S1] (Figure S1) but benefits from allowing analytical analysis. For the postprandial glucose levels to return to the preprandial levels ($\lim_{t\to\infty} \delta Q_g(t) = 0$), a sufficient and necessary condition for the bolus amount is

$$U_b = \frac{Q_{\text{CHO}} K_m}{S_i}.$$

With this matching bolus, the maximum glucose excursion can be calculated as

$$\delta Q_{g_{\max}} = K_m Q_{\text{CHO}} \left(\frac{1}{\alpha} - \alpha - 2\ \ln(\alpha)\right) e^{-\frac{\alpha+1}{\alpha-1}\ln(\alpha)},$$

where $\alpha = \tau_m/\tau_i$ is the ratio between the time-to-peak of meal absorption and time-to-peak of insulin absorption. This equation suggests that the ratio α between the times-to-peak of meal and insulin absorptions determines postprandial glucose excursions. Moreover, the size of the meal (carbohydrate content) modulates this effect.

This result indicates that faster insulins or drugs that slow gastric emptying (for example, pramlintide) would improve glucose control. Figure S2 plots postprandial glucose peaks against the ratio α between the times-to-peak of meal and insulin absorptions for different meal sizes.

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[S2] N. Magdelaine, L. Chaillous, I. Guilhem, J. Y. Poirier, M. Krempf, C. H. Moog, and E. Le Carpentier, "A long-term model of the glucose-insulin dynamics of type 1 diabetes," *IEEE Trans. Biomed. Eng.*, vol. 62, pp. 1546–1552, Jun. 2015.

$$\frac{d}{dt}G(t) = -(p_1 + x(t))G(t) + P_{\text{EGP}} + \frac{1}{V}U_m(t),$$
$$\frac{d}{dt}x(t) = -p_2\ x(t) + p_3\ I_p(t),$$

where $U_m(t)$ (μmol/kg/min) is the rate of glucose appearance from the ingested meal, V (mL/kg) is the glucose distribution volume, P_{EGP} (mmol/L/min) describes the rate of endogenous production of glucose, p_1 (1/min) describes glucose effectiveness (the ability of glucose to promote its own disposal), p_2 (1/min) is a time constant characterizing the delay of the plasma insulin effect on plasma glucose (deactivation rate of insulin effects), and p_3 (1/min^2 per munits/L) describes the activation rate of insulin effects.

A linearized form of Bergman's minimal model may be derived by assuming that the dynamics of remote insulin are faster than glucose dynamics ($x(t)$ arrives at the equilibrium point faster than $G(t)$, $\dot{x}(t) \sim 0$):

$$\frac{d}{dt}G(t) = -p_1 G(t) - \frac{S_i}{\tau_i}Q_i(t) + P_{EGP} + \frac{U_m(t)}{V},$$

where $Q_i(t)$ (units) is the insulin mass in plasma, $S_i \sim G_0 K_i P_3 / P_2$ (mmol/L per units) is a positive insulin sensitivity factor [the amount of glucose level drop (mmol/L) caused by one unit of insulin], and G_0 (mmol/L) is an equilibrium point for glucose concentration. It has been suggested that this linear model (with $p_1 = 0$) may be used to assess long-term glucose dynamics in T1D [50]. The transfer function between the insulin mass in the plasma $Q_i(s)$ and the glucose concentration in the plasma $G(s)$ is expressed as

$$\frac{G(s)}{Q_i(s)} = -\frac{S_i}{\tau_i}\frac{1}{s + p_1}.$$

Interstitial Subcutaneous Glucose Kinetics

The interstitial glucose concentration (where measurements are completed) $G_s(t)$ (mmol/L) is obtained from the plasma glucose concentration $G(t)$ by a simple diffusion model [51]

$$\frac{d}{dt}G_s(t) = k_{\text{sen}}(G(t) - G_s(t)),$$

where k_{sen} (1/min) is the transfer-rate constant.

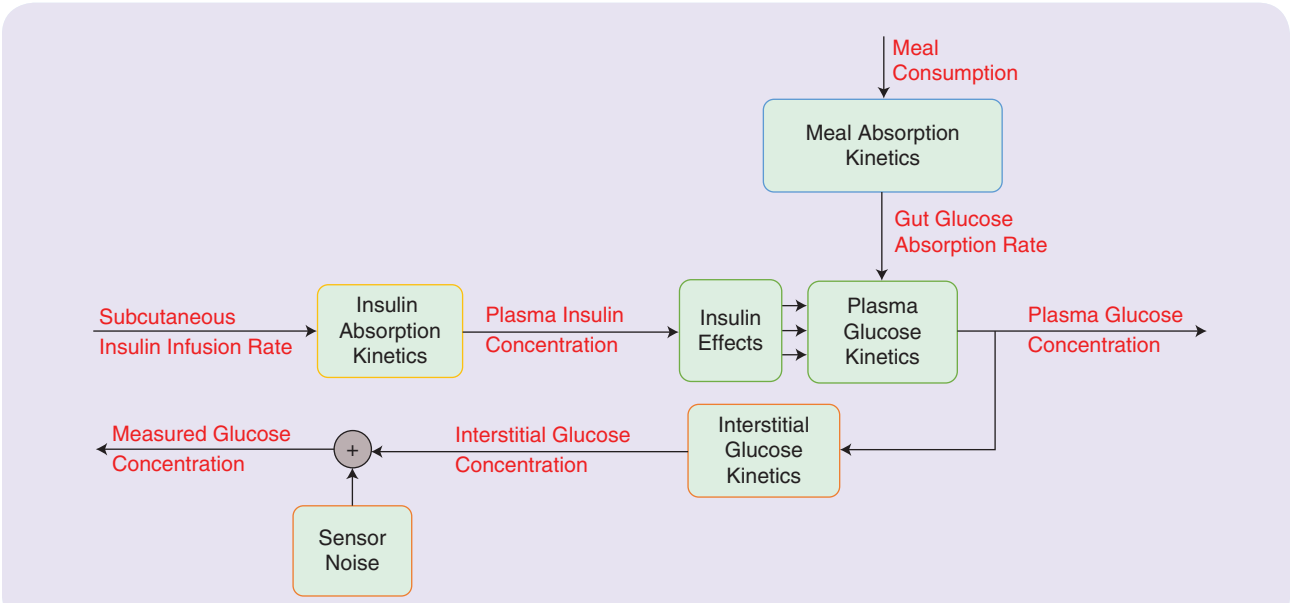

FIGURE 2 A block diagram representing the four subsystems that govern the glucoregulatory system. Insulin is infused subcutaneously and absorbed slowly to the plasma. After a meal consumption, glucose is absorbed from the gut into the plasma. Both insulin absorption and meal-glucose appearance affect plasma glucose levels. The measured interstitial glucose concentration is a delayed and noisy signal, compared to the plasma glucose concentration.

MEAL-RELATED GLUCOSE ABSORPTION DYNAMICS

The identification of the kinetics of glucose appearance after meal ingestion (the disturbance dynamics) may improve the design of the control algorithm for the AP. After food intake, the carbohydrates contained in the chyme (partially digested food in the stomach) are broken into single sugar components in the small intestine. From the small intestine, glucose is integrated into the blood circulation, where it is absorbed by the rest of the organs. The profile of glucose appearance in the circulation can be described using nonparametric functions (estimated experimentally using isotope-tracer techniques [52]), [21], [46] or parametric mathematical models [53]–[55]. In this section, different mathematical models to describe meal-glucose appearance are discussed.

Lehmann and Deutsch Meal-Glucose Model

Gastric emptying $G_{\text{emp}}(t)$ (μmol/kg/min) is the rate of expelling the chyme from the stomach to the gut. This process has been described as a piecewise-linear function by Lehmann and Deutsch [54]

$$G_{\text{emp}}(t) = \frac{K_{\text{Bio}} D_m}{T - \frac{T_{\text{des}} + T_{\text{asc}}}{2}} \begin{cases} t/T_{\text{asc}}, & t < T_{\text{asc}} \\ 1, & T_{\text{asc}} \le t \le T - T_{\text{des}} \\ (T-t)/T_{\text{des}}, & T - T_{\text{des}} < t' \\ 0, & T < t \end{cases}$$

where D_m (μmol/kg) represents the total amount of ingested glucose; K_{Bio} is the carbohydrates bioavailability in the meal; and T_{asc}, T_{des}, and T (min) are the durations of ascending and descending rates and the total duration of gastric emptying, respectively.

Following the gastric emptying from the stomach to the gut, the glucose mass in the gut can be obtained as [46], [53], [54]

$$\frac{d}{dt} Q_m(t) = -\frac{1}{\tau_m} Q_m(t) + G_{\text{emp}}(t),$$

where $Q_m(t)$ (μmol/kg) is the glucose mass in the gut compartment and τ_m (min) is a time constant characterizing the appearance of glucose in the blood circulation from the gut. Moreover, the glucose gut absorption rate in the plasma $U_m(t)$ (μmol/kg/min) is expressed as

$$U_m(t) = \frac{1}{\tau_m} Q_m(t).$$

This model was validated on a set of 24 subjects [56] and used in simulation and control algorithms [57], [58].

Two-Compartmental Model for Meal-Related Glucose Appearance

Meal-glucose absorption from the stomach to the gut and then to the blood circulation may be described by a two-compartment model, with identical fractional transfer rates [55]. Such models have been popular in T1D patient control and simulation [50], [51], [59], [60]

$$\begin{bmatrix} \frac{dQ_{m_1}(t)}{dt} \\ \frac{dQ_m(t)}{dt} \end{bmatrix} = \begin{bmatrix} -\frac{1}{\tau_m} & 0 \\ \frac{1}{\tau_m} & -\frac{1}{\tau_m} \end{bmatrix} \begin{bmatrix} Q_{m_1}(t) \\ Q_m(t) \end{bmatrix} + \begin{bmatrix} K_{\text{Bio}} \\ 0 \end{bmatrix} D_m(t),$$

where $D_m(t)$ (μmol/kg/min) is the rate of glucose ingestion, Q_{m_1} and Q_m (μmol/kg) are the glucose masses in

first and second gut compartments, and τ_m (min) is the time to peak of the appearance of glucose from the gut following an impulse input (instantaneous meal). In the Laplace domain, the glucose mass $Q_m(t)$ (μmol/kg) is expressed as

$$Q_m(s) = \frac{K_{\text{Bio}}\,\tau_m}{(1+\tau_m s)^2} D_m(s).$$

In general, meals are assumed to be ingested instantly. In this case, $D_m(t)$ is a Dirac impulse occurring at mealtime whose area is given by $D_m = 10^6 Q_{\text{CHO}}/(w\,M_{\text{CHO}})$, where Q_{CHO} (g) is the quantity of carbohydrates ingested, $M_{\text{CHO}} = 180.156$ (g/mol) is the molar mass of glucose, and w (kg) is the patient weight. Using the initial value theorem, the quantity of glucose in the first compartment following the meal is obtained as

$$Q_{m_1}(0^+) = \lim_{s\to\infty} s\frac{K_{\text{Bio}}\,\tau_m}{1+\tau_m s} D_m = K_{\text{Bio}} D_m.$$

Three-Compartmental Model with Nonlinear Gastric Emptying Rate

In addition to having a single compartment describing meal-glucose appearance from the gut, this model represents the gastric emptying from the stomach by a two-compartment, biphasic process of solid and liquid phase [46]

$$\begin{cases} \frac{d}{dt}Q_{\text{sto1}}(t) = -K_{gri}Q_{\text{sto1}}(t) + K_{\text{Bio}}D_m(t) \\ \frac{d}{dt}Q_{\text{sto2}}(t) = -K_{\text{emp}}(Q_{sto})Q_{\text{sto2}}(t) + K_{gri}Q_{\text{sto1}}(t), \\ \frac{d}{dt}Q_m(t) = -\frac{1}{\tau_m}Q_m(t) + K_{\text{emp}}(Q_{\text{sto}})\,Q_{\text{sto2}}(t) \end{cases}$$

where Q_{sto1} and Q_{sto2} (μmol/kg) are the amounts of glucose in the stomach (solid and liquid phase, respectively), $Q_{\text{sto}} = Q_{\text{sto1}} + Q_{\text{sto2}}$ is the total amount of glucose in the stomach, K_{gri} (1/min) is the rate of chyme grinding in the stomach, and $K_{\text{emp}}(Q_{\text{sto}})$ (1/min) is the rate of gastric emptying that depends on the amount of glucose in the stomach (Q_{sto}) in a nonlinear fashion

$$K_{\text{emp}}(Q_{\text{sto}}) = k_{\min} + \frac{k_{\max}-k_{\min}}{2}\{\tanh(\alpha(Q_{\text{sto}} - a\,Q_{\text{stoFull}})) - \tanh(\beta(Q_{\text{sto}} - b\,Q_{\text{stoFull}})) + 2\},$$

where $k_{\max}$ and $k_{\min}$ are the maximum and minimum rates of gastric emptying; Q_{stoFull} is the total amount of ingested glucose that makes the stomach full; and α, β, a, and b are tuning parameters.

This rate is maximal (equals $k_{\max}$) when the stomach is close to empty ($Q_{\text{sto}} \sim 0$) or when the glucose quantity in the stomach is maximal (Q_{stoFull}). Otherwise, this rate decreases to the minimal value $k_{\min}$. This model is used in a U.S. Food and Drug Administration-accepted T1D patient simulator [46], [61].

Two-Compartmental Model with Double Time-To-Peak of Meal-Glucose Absorption

Since different foods have different absorption profiles depending on their content (protein and fat) and complexity (glycemic index), a model has been proposed [62] that allows double peaks in the meal-glucose absorption profile. High glycemic index food produces a fast increase in the plasma glucose with a high peak, whereas low glycemic index food produces a slow and sustained increase of glucose concentration (which may continue beyond 8 h) [21]. This model uses the same two-compartmental model described above and assumes that ingested meals $D_m(t)$ are Dirac delta functions

$$\begin{aligned} D_m(t) &= \frac{10^6 Q_{CHO}}{w\,M_{CHO}}\delta(t), \\ U_{m_1}(t) &= p_m \frac{K_{bio}\,D_m}{\tau_m}\frac{t}{\tau_m}e^{-\frac{t}{\tau_m}}, \\ U_{m_2}(t) &= \begin{cases} (1-p_m)\frac{K_{bio}\,D_m}{\tau_m}\,\frac{t-d}{\tau_m}\,e^{-\frac{t-d}{\tau_m}}, & t > d, \\ 0, \quad \text{otherwise} \end{cases} \end{aligned}$$

where U_{m_1} and U_{m_2} (μmol/kg/min) are the rate of glucose appearances from the first and second absorption channels, d (min) is a delay associated with the second absorption channel, and p_m is the portion of carbohydrate absorbed through the first channel. The total rate of glucose absorption is then expressed as the sum of the glucose appearing from the two channels

$$U_m(t) = U_{m_1}(t) + U_{m_2}(t).$$

CONTROLLER CONFIGURATIONS FOR POSTPRANDIAL GLUCOSE CONTROL

Closed-loop glucose controllers provide insulin delivery (control actions) based on glucose sensor values. Meal consumption induces an increase of plasma glucose concentrations (the controlled quantity) moving the insulin-glucose system from its steady state. Meals are considered external disturbances to the glucoregulatory system for an AP user. However, the information about the meal carbohydrates may be observed by the patient and provided to the main controller. The fact that meals are measured disturbances presents three possible configurations for controlling postprandial glucose concentrations: 1) no meal information is provided to the controller (feedback only), 2) complete meal information is provided to the controller (feedforward-feedback), or 3) only partial meal information is provided to the controller (partial feedforward-feedback) (Figure 3).

Feedback-Only Control

Automated closed-loop control aims to relieve the patient from the burden of carbohydrate counting. Early AP studies attempted to control postprandial glucose concentrations by relying solely on glucose sensor readings (disturbance rejection by feedback control) [63], [64]. However, feedback-only

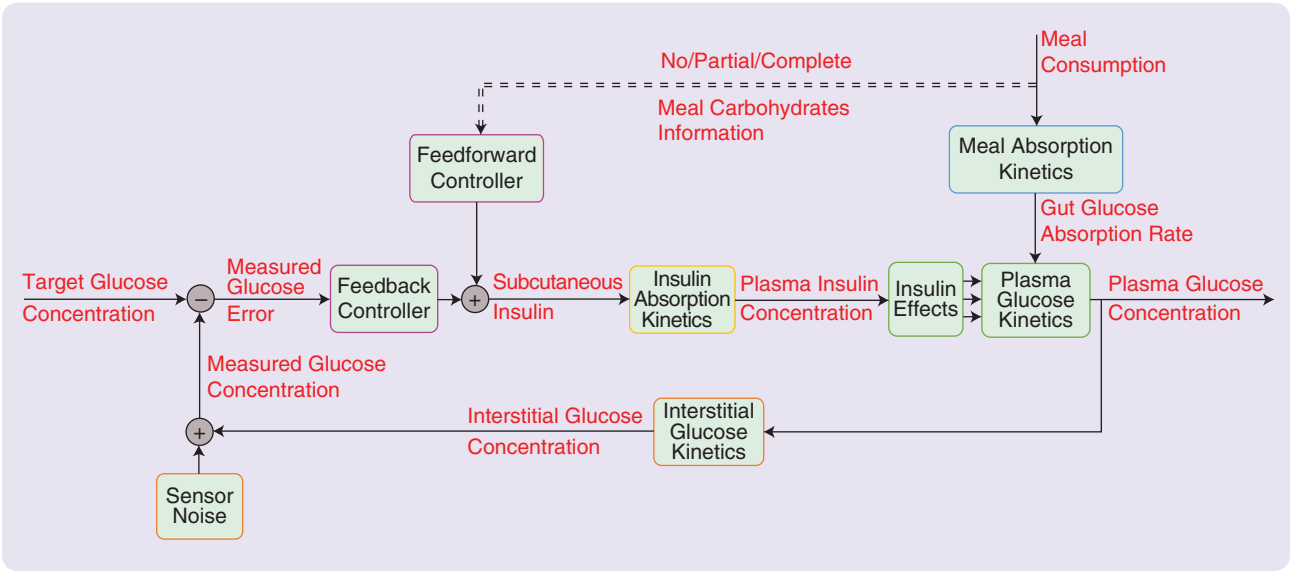

FIGURE 3 A block diagram representing control design strategies for the artificial pancreas. The feedback-only controller uses the offset between the measured glucose concentration and the target glucose to generate the subcutaneous insulin command, while ignoring any information about the consumed meal (disturbance). The feedforward-feedback controller requires complete information about the consumed meal (carbohydrate counting). This information is given to the controller to compute an insulin bolus to achieve tight postprandial glucose control. Partial feedforward-feedback only requires qualitative information about the consumed meal (for example, only the size of the meal is provided) to deliver the meal-accompanying insulin bolus.

control of postprandial glucose concentrations suffers from two major hindrances:

- Early postprandial hyperglycemia due to 1) the rate of meal-glucose appearance in the blood (the disturbance dynamics), which is faster than the absorption of subcutaneously infused insulin (the actuator dynamics), and 2) the delay in glucose sensing in the interstitial fluid (around 15 min [65], [66]). Even though a feedback controller is capable of taking corrective actions, no insulin dosing is effectively made until a deviation is observed in the controlled variable, which makes the control sluggish because of the slow dynamics of infused insulin.
- Late postprandial hypoglycemia (undesirable low glucose levels) due to the fast increase in postprandial glucose. The closed-loop system needs to react aggressively by infusing a significant amount of insulin in the 2 h after the meal ingestion, to prevent glucose concentrations from further increasing. However, due to the slow absorption of insulin delivery, this insulin continues to be absorbed and act beyond meal absorption, which may lead to late postprandial hypoglycemia. (insulin stacking [63]).

Early postprandial hyperglycemia and late postprandial hypoglycemia are interconnected. Delivering insulin aggressively to prevent early postprandial hyperglycemia increases the risk of late postprandial hypoglycemia [63]. Conversely, delivering insulin in a conservative manner in the early postprandial period to reduce the risk of late postprandial hypoglycemia results in early hyperglycemia. This tradeoff is caused by the fact that insulin-only AP systems are positive systems where the input (insulin) and the systems states can only attain positive values [44]. This tradeoff between hyperglycemia and hypoglycemia is the major barrier to adequately control postprandial glucose concentrations using a closed-loop system without feedforward control. Because hypoglycemia is a more critical issue, feedback-only control systems typically focus on eliminating hypoglycemia at the expense of hyperglycemia.

The early feedback-only algorithms tested in clinical trials showed sustained hyperglycemic levels after meal consumption and some episodes of induced postprandial hypoglycemia [64], [67]. The postprandial hypoglycemia was mainly triggered by the insulin-stacking effect caused by either not considering the delay in subcutaneous insulin delivery [64] or inaccurate modeling of the insulin subcutaneous kinetics (mainly, the time-to-peak of insulin [67]). A recent pilot, noncontrolled, inpatient clinical trial of a feedback-only algorithm based on multiple-model predictive control (MPC) was conducted with more promising results [68]. However, further clinical trials are warranted for this approach.

Different approaches can be investigated to improve feedback-only postprandial glucose control. First, glucagon may be infused in the late postprandial period (in a closed-loop manner) to reduce hyperglycemia while safely avoiding hypoglycemia [69]. However, feedback-only, dual-hormone systems require delivering excessive amounts of glucagon to counteract high, late-postprandial, plasma insulin concentrations [67], [70]. Second, a better control of

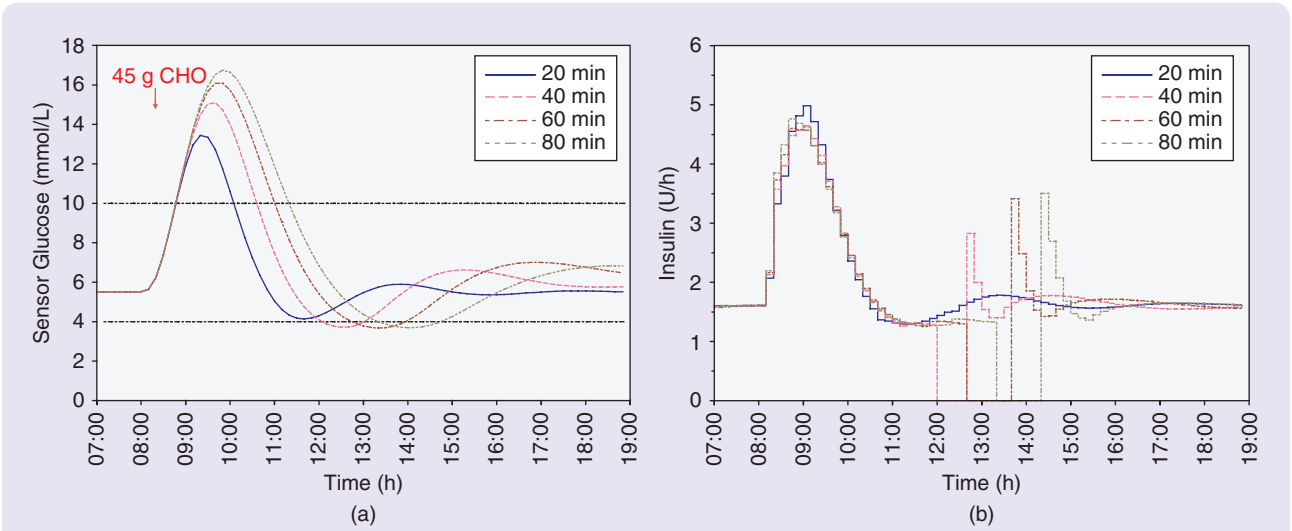

FIGURE 4 A simulation of postprandial glucose with feedback-only control using hypothetical insulin analogs with varying insulin time-to-peak plasma concentrations τ_i. Four 12-h experiments with varying τ_i values were conducted on a virtual patient [62] given a breakfast meal at 8 a.m. with a 45-g carbohydrate content and no insulin bolus. The control algorithm used in all experiments is a model predictive controller. The controller's aggressiveness was fixed for each τ_i value with an objective of simultaneously avoiding hypoglycemia and minimizing postprandial glucose levels. The meal information was not provided to the controller in all experiments. Postprandial glucose responses in (a) demonstrate that closed-loop systems using insulin analogs with low τ_i values achieve better postprandial control and less hyperglycemia. Faster insulin analogs have the potential to remove the burden of carbohydrate counting, while achieving acceptable glucose control. In (b), the controller's insulin infusions are plotted for each τ_i experiment.

postprandial glucose concentrations may be achievable with faster insulin analogs than the ones currently on the market (Figure 4). Third, other hormone analogs, such as Pramlintide and GLP-1, may be used to delay gastric emptying [71], [72] (that is, alter disturbance dynamics) to achieve better postprandial glycemic control by a feedback-only approach.

Feedforward-Feedback Control

A feedforward controller is constructed to profit from anticipated or measured disturbances to control the process. When the disturbance dynamics are available and accurate, the feedforward control takes corrective action based on the disturbance before it affects the process. Ideally, feedforward would perfectly compensate the measured disturbance dynamics [73].

With current therapy, patients with T1D calculate their meal insulin bolus as the carbohydrate content of the meals, multiplied by the insulin-to-carbohydrate ratio [a ratio in (g/unit) that specifies how many grams of carbohydrates are covered by one unit of insulin, which is typically different for breakfast, lunch, and dinner] [74]. Meal boluses are then adjusted based on 1) the preprandial glucose concentrations (additional correction bolus in case of preprandial hyperglycemia) and 2) previously infused insulin (insulin-on-board is subtracted from the correction bolus) [75]. Moreover, the timing of meal boluses may be adjusted for specific meals (for example, boluses are often delivered 15 min prior to high glycemic index meals) [76]. The most common feedforward-feedback control configuration of AP systems (referred to as hybrid systems) adopts a similar approach. The patient calculates the carbohydrate content of the meal and provides this information to the AP prior to meal ingestion. The AP then computes the insulin bolus based on 1) the carbohydrate content, 2) preprandial glucose concentrations, and 3) insulin-on-board.

For a linear, time-invariant glucose model, the feedforward controller may be designed to cancel the effect of the disturbance $D_m(s)$, such that the overall transfer function between the plasma glucose concentration $Q_g(s)$ and the meal disturbance is null [77]. With an insulin input $U_i(s) = C_{ff}(s)\, D_m(s)$, where $C_{ff}(s)$ is the feedforward controller transfer function, the transfer function yields

$$\frac{G(s)}{D_m(s)} = G_g(s)\left(C_{ff}(s)\frac{-S_i}{(1+\tau_i s)^2} + \frac{1}{V}\frac{K_{\text{Bio}}}{(1+\tau_m s)^2}\right) = 0,$$

$$C_{ff}(s) = \frac{K_{\text{Bio}}}{S_i\, V}\frac{(1+\tau_i s)^2}{(1+\tau_m s)^2},$$

where S_i is the insulin sensitivity as defined before, K_{Bio} is the carbohydrates bioavailability, V is a volume distribution, τ_i and τ_m are time constant characterizing the delay of insulin and meal effects to plasma glucose concentrations, and $G_g(s)$ is the transfer function from plasma insulin concentration to plasma glucose concentration ($G_g(s) = 1/(s+p_1)$ for the model presented in the section "System Dynamics for Postprandial Glucose Control"). Because of the input constraints (insulin infusion rate cannot be negative) and

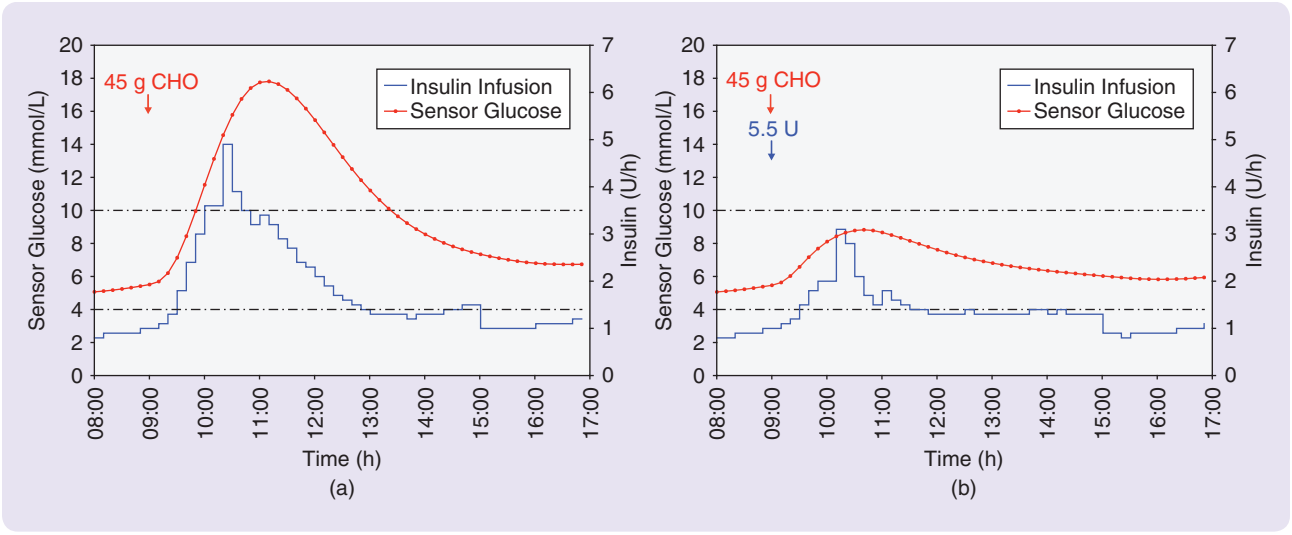

FIGURE 5 A simulation of postprandial glucose control with feedback-only with respect to feedforward-feedback control. To demonstrate and compare the performance of both control strategies, two simple in silico experiments are conducted on a virtual patient [62] given a breakfast meal at 9 a.m. with a 45-g carbohydrate content. A model predictive controller was used in both experiments. In the feedback-only control experiment (a), the meal information was not provided to the controller. In the feedforward-feedback control experiment (b), a bolus was calculated according to the patient's meal insulin-to-carbohydrate ratio. Although postprandial hypoglycemia was avoided in both experiments, the increase in glucose level is much higher with the feedback-only controller, leading to hyperglycemia. With current insulin analogs, feedforward-feedback controllers are more effective in maintaining tighter glucose control.

the slow dynamics of the insulin absorption (τ_i), this controller cannot be realized. Analysis of this straightforward, model-based controller was conducted for different meal sizes and shapes, but it has not been assessed clinically [78]. In practice, the feedforward controller is reduced to a simple gain multiplicator, a similar strategy to the open-loop insulin-to-carbohydrate ratio. An illustration of feedback-only performance compared to feedforward-feedback is presented in Figure 5.

Recent clinical trials assessing a closed-loop glucose controller based on the feedforward-feedback design have shown good results increasing the time in normoglycemia after meal consumption, compared to conventional therapy [79]–[83]. Despite its success, the need for an estimate of the disturbance, which means patients must not forget to announce the meal to the AP and to accurately count the carbohydrate contents of the meal, remains a limitation of this strategy.

Partial Feedforward-Feedback Control

The partial feedforward-feedback strategy is based on keeping the meal bolus advantage while relieving the burden of carbohydrate counting. Instead of inputting the exact amount of carbohydrates contained in the meal, an indication of meal size is provided. This strategy offers two advantages. First, the control algorithm is informed that a meal will be eaten soon, which may trigger a change in controller aggressiveness to better handle the expected fast increase in glucose concentration. Second, the quantity of the soon-to-be-ingested carbohydrates may be estimated. Using learning algorithms or by applying empirical standards, a partial insulin bolus may be computed and provided by the control algorithm [84].

The most common approach is to provide a qualitative indication of the size of the ingested meal (such as regular or large) to compute an insulin bolus. Both a three- and four-scale meal size have been clinically investigated [85], [86]. The amount of the partial insulin bolus may be computed based on patient body weight [87] or the insulin-to-carbohydrate ratio [85], [88]. This design has shown comparable results with the complete feedforward-feedback approaches and better results compared to feedback-only approaches [64], [84], [85], [87].

Carbohydrate counting is prone to human errors, and this uncertainty does not give the full-feedforward strategy a significant advantage over the partial feedforward one. However, partial feedforward approaches still bear the risk of a patient misjudging the meal size or forgetting to announce it.

POSTPRANDIAL GLUCOSE CONTROL

The MPC and proportional-integral-derivative (PID) controllers are the two most common controllers tested in randomized controlled trials [89], and their comparative merits have been debated in the literature [90], [91]. In this section, MPC (adaptive and nonadaptive) and PID controllers for postprandial glucose control are discussed. A large body of literature based on simulation studies also exists but is out of the scope of this article. Controllers tested in simulations only include H∞-controllers [92], sliding-mode controllers [93], neural network controllers [94],

linear parameter-varying controllers [95], [96], and robust controllers [97].

Meal Control with PID

PID controllers were among the first algorithms to be tested for the closed-loop control of plasma glucose concentrations [100]. The insulin command U_i is computed from the error in glucose concentration between the measured and reference glucose concentration $e_G(t)$ as

$$U_i(t) = U_{i0}(t) + K_P\, e_G(t) + K_I \int e_G(t)dt + K_D\, \frac{de_G(t)}{dt},$$

where $U_{i0}(t)$ is the basal inulin (insulin needs for maintaining glucose equilibrium under fasting conditions) rate specific to the individual, $e_G(t)$ is the error between the measured and reference glucose concentration; and K_p,K_D, and K_i are the PID gains.

In response to a carbohydrate meal disturbance, most of the control action and aggressiveness comes from the proportional gain K_P. The derivative gain K_D reacts to fast postprandial glucose increase and reduces postprandial hypoglycemia by adding damping to the glucose response. The integral gain K_i is needed to ensure that the target glucose is achieved in steady state [63], [101].

Because of the excessively slow dynamics of the insulin command, simple PID controllers have often induced insulin stacking, which increases the risk of hypoglycemia. Negative insulin feedback, based on an estimation of plasma insulin concentration $I_p(t)$, has been proposed to reduce the aggressiveness of the controller when insulin-on-board is high, thus reducing postprandial hypoglycemia periods [102]. Clinical studies have shown the merit of such an approach on hypoglycemia risk. However, an overall increase in the mean glucose, especially postprandial, was observed [103], [104]

$$U_i(t) = U_{i0}(t) + (1-\gamma) \times \left(K_P\, e_G(t) + K_I \int e_G(t)dt + K_D\, \frac{de_G(t)}{dt}\right) - \gamma I_p(t),$$

where γ is a tuned constant, typically equal to 0.5.

MEAL CONTROL WITH MODEL PREDICTIVE CONTROL

MPC is a widely used approach to control plasma glucose concentrations [89]. This controller provides the control action minimizing an objective function, constrained to a model describing the process evolution. The minimization of the objective function ensures the tracking of desired glucose concentrations expressed as a setpoint or zone [105], [106]. Other constraints on the control action (insulin delivery rate), which express physical limitations and reflect required performance (mainly avoiding hypoglycemia) [107], are usually added to the minimization problem. Finally, the use of a process model permits the incorporation of disturbance modeling and patient-specific parameters, which is particularly effective for postprandial glucose control [90].

Different implementations of MPC exist, depending on the choice of the model and the objective function [57], [59], [105], [108], [109]. Since the glucoregulatory system may be regarded as an interaction of four subsystems, the following describes the state-space dynamics:

$$\frac{d}{dt}X(t) = \begin{bmatrix} A_g & A_{gq} & 0_{12} & 0_{12} \\ 0_{21} & A_q & A_{iq} & A_{mq} \\ 0_{21} & 0_{22} & A_i & 0_{22} \\ 0_{21} & 0_{22} & 0_{22} & A_m \end{bmatrix} X(t) + \begin{bmatrix} 0_{11} \\ 0_{21} \\ B_i \\ 0_{21} \end{bmatrix} U_i(t) + \begin{bmatrix} 0_{11} \\ 0_{21} \\ 0_{21} \\ B_m \end{bmatrix} D_m(t),$$

where U_i is the control action (insulin injection rate), D_m is the disturbance (ingested meal), 0_{nm} is a zero matrix of size $n \times m$, and B_i, B_m A_g, A_{qg}, A_q, A_{iq}, A_{mq}, A_i, and A_m denote matrices characterizing the process dynamics. Those matrices are deduced from a linear model, derived from the glucoregulatory system of an AP user that was previously presented, and a two-compartmental model of meal-glucose absorption as

$$X(t) = [G_s(t)\ \ G(t)\ \ P_{\mathrm{EGP}}(t)\ \ Q_i(t)\ \ Q_{i_1}(t)\ \ Q_m(t) Q_{m_1}(t)]^T,$$

$$A_g = [-k_{\mathrm{sen}}],\ A_{qg} = [k_{\mathrm{sen}}],\ A_q = \begin{bmatrix} -p_1 & 1 \\ 0 & 0 \end{bmatrix},\ A_{iq} = \begin{bmatrix} -\frac{S_i}{\tau_i} & 0 \\ 0 & 0 \end{bmatrix},$$

$$A_{mq} = \begin{bmatrix} \frac{1}{V\tau_m} & 0 \\ 0 & 0 \end{bmatrix},\ A_i = \begin{bmatrix} -\frac{1}{\tau_i} & \frac{1}{\tau_i} \\ 0 & -\frac{1}{\tau_i} \end{bmatrix},\ A_m = \begin{bmatrix} -\frac{1}{\tau_m} & \frac{1}{\tau_m} \\ 0 & -\frac{1}{\tau_m} \end{bmatrix},$$

$$B_i = \begin{bmatrix} 0 \\ 1 \end{bmatrix}, \text{ and } B_m = \begin{bmatrix} 0 \\ K_{\mathrm{Bio}} \end{bmatrix}.$$

The controlled quantity $Y(t)$ (plasma glucose concentration) and the measured quantity $Z(t)$ (interstitial glucose concentration) are obtained from $X(t)$ by $Y(t) = C\,X(t)$ and $Z(t) = C_Z\,X(t)$, where $C = [0\ 1\ 0\ 0\ 0\ 0\ 0]$ and $C_Z = [1\ 0\ 0\ 0\ 0\ 0\ 0]$.

The objective function penalizes the deviation of model-predicted, plasma glucose concentration $Y(t)$ from the targeted plasma glucose concentration $Y_r(t)$ (with emphasis on the terminal time to ensure stability [110]), and the incremental insulin dose $\delta U_i(t) = U_i(t) - U_{i0}(t)$

$$J_t(\delta U_i(t)) = \sum_{K=0}^{T-1} \left(\Gamma_y \left\| \frac{Y(t+k) - Y_r(t+k)}{Y_r(t+k)} \right\|^2 + \Gamma_u \left\| \frac{\delta U_i(t+k)}{U_{i0}(t+k)} \right\|^2 \right) + \Gamma_y^T \left\| \frac{Y(t+T) - Y_r(t+T)}{Y_r(t+T)} \right\|^2,$$

where t is the current discrete time Γ_y, Γ_y^T and Γ_u are unitless weighting parameters, and T is the time horizon (4–5 h). The optimization problem is solved, subject to the model dynamics, the insulin delivery rate limit $U_{i\mathrm{Limit}}$, and the limit on the incremental insulin delivery $\delta U_{i\mathrm{Limit}}$

$$X(t+1) = A^d\, X(t) + B_i^{*d}\, U_i(t) + B_m^{*d}\, D_m(t),$$
$$Y(t) = C\, X(t),$$
$$0 \le U_i(t+k) \le U_{i\text{Limit}}, \quad \text{for } k = 0 \ldots T-1,$$
$$|\delta U_i(t+k)| \le \delta U_{i\text{Limit}}, \quad \text{for } k = 0 \ldots T-1,$$

where A^d, B_i^{*d}, and B_m^{*d} are obtained by discretizing the system dynamics above. At the end of each optimization cycle, only the first control action $\delta U_i(t)$ is inputted to the process.

Variants of the objective function may penalize asymmetrically positive and negative variations of the plasma glucose from the reference value to emphasize postprandial hypoglycemia protection [107]. Other forms of the cost function penalize the incremental insulin command based on the real-time estimate of insulin-on-board, to avoid insulin stacking [67], [111]. In the MPC setup, an accurate model is necessary to ensure optimal dosing; underestimating insulin time-to-peak value can lead to late hypoglycemia because model inaccuracy can lead to insulin overdosing [67].

At every control cycle (5–10 min), when meal information is available, the meal input is provided to the controller in the form of a Dirac delta, depending on the carbohydrate content D_m (μmol/kg). This addition is equivalent to adding D_m to the first meal compartment $Q_{m_1}(t)$

$$Q_{m_1}(t) = Q_{m_1}(t) + K_{Bio} D_{m_{\text{Bolus}}}.$$

Similarly, when a mealtime insulin bolus $U_{i\text{Bolus}}$ (units) is delivered to the patient (in a feedforward manner), this information is added as a Dirac delta input to $U_i(t)$. This action is equivalent to increasing the first subcutaneous insulin compartment $Q_{i_1}(t)$

$$Q_{i_1}(t) = Q_{i_1}(t) + U_{i\text{Bolus}}.$$

The new updated state (with meal and bolus information) is used as the initial condition for the MPC optimization problem. By doing so, the controller will consider future glucose and insulin appearances from the meal and bolus, respectively.

The MPC algorithm requires the availability of an internal state of the process $X(t)$. This internal state may be estimated by incorporating glucose measurement $\tilde{Z}(t)$. The state vector is updated using a state estimation technique, such as Kalman filtering, before the next optimization problem is solved. Assume a process noise $W(t)$ of zero-mean, multivariate Gaussian type with covariance matrix $Q(t)$, and a measurement noise $V(t)$, a zero-mean Gaussian white noise with covariance $R(t)$. The state-space equations can be rewritten as

$$X(t) = A^d\, X(t-1) + B_i^{*d}\, U_i(t-1) + B_m^{*d}\, D_m(t-1) + W(t),$$
$$Z(t) = C_z X(t) + V(t).$$

The corrected state estimation is obtained from

$$X(t \mid t-1) = A^d\, X(t-1 \mid t-1) + B_i^{*d}\, U_i(t-1) + B_m^{*d}\, D_m(t-1),$$
$$X(t \mid t) = X(t-1 \mid t-1) + K(t)\,(\tilde{Z}(t) - Z(t \mid t-1)),$$

where $X(t \mid t-1)$ is the state prediction based on the model, $X(t-1 \mid t-1)$ is the state of the system in the previous instant, $Z(t \mid t-1)$ is the predicted measurement, and $K(t)$ is the Kalman gain. The Kalman gain depends on the choice of $Q(t)$ and $R(t)$, and can be computed using the standard Kalman filtering equations [112]

$$P(t \mid t-1) = A\, P(t-1 \mid t-1)\, A^{\top} + Q(t),$$
$$K(t) = P(t \mid t-1)\, C_Z^T\, (C_Z\, P(t \mid t-1)\, C_Z^T + R(t))^{-1},$$

where $P(t \mid t-1)$ is the predicted covariance matrix based on the model, and $P(t-1 \mid t-1)$ is the covariance matrix from the previous instant. The estimated covariance matrix $P(t \mid t)$ provides an indication of the accuracy of the state estimate. It is obtained from the previous cycle by

$$P(t \mid t) = P(t \mid t-1) - K(t)\, C_Z\, P(t \mid t-1).$$

When a patient ingests a meal, the diagonal elements corresponding to the meal absorption states in the covariance matrix $Q(t)$ (column 4, row 4 in the state-space dynamics above) may be increased to indicate uncertainty in the carbohydrate content of the meal. This allows the Kalman filter to improve the estimate of the carbohydrate content using future glucose measurements. Similarly, the process noise characteristics $Q(t)$ may be adjusted in the postprandial period to emphasize uncertainty in the meal absorption profile.

Adaptive Control Applications for Postprandial Glucose

Efficient postprandial glucose control may be improved by the knowledge of meal absorption dynamics (how the disturbance affects the model) and insulin sensitivity (how the controller actions reject the disturbances). Meals may be absorbed in different patterns, depending on their content and complexity (food glycemic index, fat, and protein) [76]. Conversely, T1D patients display a high variability on insulin sensitivity among patients [26], [113], [114]. An adaptive controller may be capable of considering these variabilities and providing better performances globally [115].

Interacting multiple model (IMM) filters were used as an indirect adaptive strategy to account for meal and insulin variabilities [116], [117]. This strategy estimates the filter state using several competing models, running in parallel with different parameters (different rates of subcutaneous insulin absorption τ_i and carbohydrate absorption profile τ_m). At each instant, every model is assigned a probability, and the filter state is estimated by mixing the model states based on their models' corresponding probabilities. Mathematically, IMM is characterized by the followings three steps:

Efficient postprandial glucose control may be improved by the knowledge of meal absorption dynamics (how the disturbance affects the model) and insulin sensitivity (how the controller actions reject the disturbances).

» The interaction step: The state vector $X_{0j}(k-1 \mid k-1)$ characterizing the model j is mixed with the state vectors of each model $X_i(k-1 \mid k-1)$ (i is the index of the model)

$$X_{0j}(k-1 \mid k-1) = \frac{1}{\sum_i p_{ji}\mu_i(k-1)} \times \sum_i p_{ij}\, X_i(k-1 \mid k-1)\mu_i(k-1),$$

where $\mu_i(k-1)$ is the probability of model i matching the true patient dynamics, and $(p_{ij})_{ij}$ is a Markov transition probability matrix that indicates the probability of the model i transiting to model j.

» The filtering step: For each model, the glucose measurement is incorporated into the state with the use of a filtering technique (such as Kalman filter). This provides a filtered state $X_j(k \mid k)$ for each model. At the same time, the mixing probability is updated for each model as

$$\mu_j(k) = \frac{1}{c}\Lambda_j(k) \sum_i p_{ji}\mu_i(k-1),$$

where $\Lambda_j(k)$ is a likelihood function that characterizes the effort provided by the filter to improve (innovate) the predicted state vector based on the used model [117], and c is a normalizing factor.

» The combination step: The state vector that best describes the patient model is a combination of all the state vectors weighted by their respective mixing probabilities

$$X(k \mid k) = \sum_i X_i(k \mid k)\ \mu_i(k).$$

This filter has been developed [118] and evaluated in a three-month clinical trial [81].

The adaptive generalized predictive controller strategy has also been proposed and evaluated in a series of clinical trials [84], [86], [87]. Another similar adaptive predictive controller is proposed and tested in feasibility clinical experiments [109], [119], [120]. In these controllers, the process takes the generic form of an autoregressive moving average model with exogenous inputs, which is a function of past plasma glucose values, insulin observations, and an exogenous input (representing other process noise and disturbances) [121], [122]. For the glucoregulatory system, this model is represented as

$$Y(t) = \sum_{k=1}^{n}\alpha_k Y(t-k) + \sum_{k=0}^{m}\beta_k U_i(t-d-k) + \sum_{k=0}^{p}\gamma_k W(t-k),$$

where α_k, β_k, and γ_k are system parameters (with $\gamma_0 = 1$); d is the insulin delay action; $Y(t)$ is the history of plasma glucose concentrations; $U_i(t)$ is the history of insulin infusion rates; and $W(t)$ is the sequence of independent, zero-mean Gaussian variables. The model parameters are estimated using the recursive least squares method [123], by introducing the following model regressor form

$$Y(t) = \psi^T(t)\theta(t) + W(t),$$

where the regressor is $\psi(t) = [Y(t-1)\ldots Y(t-n)\ U_i(t-d)\ \ldots U_i(t-d-m)\ W(t-1)\ldots W(t-p)]^T$, and the parameter vector is $\theta(t) = [\alpha_1 \ldots \alpha_n\ \beta_0 \ldots \beta_m\ \gamma_1 \ldots \gamma_p]^T$. The estimated parameter vector $\hat{\theta}(t)$ is computed recursively by

$$\hat{\theta}(t) = \hat{\theta}(t-1) + \frac{P(t-1)\psi(t)}{\lambda + \psi^T(t)P(t-1)\psi(t)} \times (Y(t) - \psi^T(t)\hat{\theta}(t-1)),$$

$$P(t) = \frac{1}{\lambda}\left(P(t-1) - \frac{P(t-1)\psi(t)\psi^T(t)P(t-1)}{\lambda + \psi^T(t)P(t-1)\psi(t)}\right),$$

where $P(t)$ is a covariance matrix of the parameter vector, and λ is the forgetting factor. The online parameter vector estimation is combined with a generalized predictive control (GPC) algorithm (indirect adaptive control strategy) [124].

OTHER PERSPECTIVES FOR POSTPRANDIAL GLUCOSE CONTROL

Besides closed-loop algorithms, other techniques were proposed to control postprandial glucose concentrations.

Meal Detection and Meal Size Estimation

Meal detection and a meal size estimation algorithm may potentially improve the performance of the closed-loop controller at mealtime. In the case of a feedforward-based design, this algorithm may be used to detect an unannounced or underestimated meal, as commonly experienced by adolescents [32]–[35]. For feedback-only design, meal detection adds a means to adjust internal gains for tighter postprandial glycemic control. Several groups have developed algorithms for meal detection and meal size estimation [125]–[127]. These algorithms may be divided into data-driven and data-model-driven algorithms.

Early meal detection algorithms only used real-time glucose measurements to detect abrupt changes, interpreted as

meal responses. The first and second derivatives of the glucose signal may be estimated either by numerically filtering data or a white-noise-driven Kalman filter [127], [128]. Using those values, heuristic rules have been proposed to detect unannounced meals [129] within 30–60 min after meal ingestion. A finite impulse response filter may be used to estimate the meal size by deconvoluting glucose measurements [129]. This strategy is prone to measurement error and patient variability. Yet, a voting scheme combining different meal detection algorithms may be utilized to increase its robustness and reduce the risk of false positives [127].

The second category uses both a predefined meal digestion model and filtered glucose measurement for meal evaluation. A meal detection method based on a multiple probabilistic model of meals has been developed and tested in inpatient clinical trials with multiple, large, unannounced meals [68], [130]. This algorithm increases the probability of a meal by matching the glucose profile with possible shapes of glucose excursion after meal consumption [131]. Recent approaches consider meal detection as a fault detection problem in a statistical signal processing framework [132], [133]. The null hypothesis is that a "meal is consumed but not announced," which is evaluated by either a parameter-invariant approach [133] or by testing the optimality of the Kalman filter (the innovation sequence is not a white noise) [132]. This hypothesis testing approach showed a high success rate and small false alarm rate compared to other approaches; however, it is only tested on simulation [132]. The unscented Kalman filtering technique (a powerful tool for state estimation of nonlinear systems [134]) has also been recently used to estimate the rate of ingested glucose $\widehat{D_m}(t)$ as part of an augmented state [135]

$$X^*(t) = \begin{bmatrix} X(t) \\ \widehat{D_m}(t) \end{bmatrix}.$$

Machine Learning Algorithms for Postprandial Glucose Control

The increase in plasma glucose concentrations after a meal is highly variable between individuals and can vary within the same individual consuming the same meal at different times. Understanding the various factors contributing to this observed inter- and intravariability in dietary responses is desirable in algorithms that aim to predict accurate postprandial glucose responses. Machine learning approaches promise to provide improved, individualized predictions.

A comprehensive database of postprandial studies, called DISRUPT, was produced to provide insights into the physiological factors that influence postprandial glucose responses [136]. The database includes postprandial measurements of insulin and glucose, in addition to subject attributes of age, gender, genotype, menopausal status, body mass index, blood pressure, and a fasting biochemical profile for recorded glucose. The database allows for the analysis of the postprandial glucose responses using conventional statistical techniques to facilitate the development of accurate predictive algorithms.

A prediction algorithm based on machine learning methods was developed to predict postprandial glucose readings of elderly patients [137]. A learning component used data to relate patient meals with observed glucose readings before and after meal consumption. The prediction model of the machine learning algorithm relied on linear regression methods. Although the algorithm's prediction error value was lower than 20% in 73% of all tests performed on healthy subjects, additional tests in diabetes patients are necessary to assess the prediction performance of the system under greater variability.

Algorithms predicting postprandial glucose concentrations need to model the effect of different kinds of foods on glucose concentrations. Rice and potatoes, for example, produce high responses on average, compared to the low responses produced by dark chocolate [138]. In addition to modeling this meal variability and composition, algorithms need to include physiological information to provide improved, personalized predictions. A machine learning algorithm has been proposed to integrate blood parameters, dietary habits, anthropometric measurements, physical activity, and gut microbiota to accurately predict the postprandial glucose concentrations [139]. The algorithm was trained in a cohort of 800 individuals with type 2 diabetes by using leave-one-out cross validation and validated against an independent cohort of 100 volunteers. By analyzing real-life, complex meals that were consumed at different times during the day and in varying proximity to previous meals, physical activity, and sleep, the algorithm integrated the multidimensional clinical and microbiome patient data to accurately predict the personalized postprandial glucose responses using stochastic gradient boosting regression. Moreover, the algorithm was used to construct personalized dietary interventions that induced lower postprandial glucose concentrations.

Machine learning algorithms adopting data-driven approaches to infer the major factors that are predictive of postprandial glucose may outperform current model-based predictions [140]. Big data strategies may be important to model the complex individual response patterns of diabetes patients, and support personalized diets into the clinical decision-making scheme to improve glucose control.

FUTURE WORK

With current insulin analogs (Aspart, Lyspro, and Glulisine), AP systems cannot prevent postprandial hyperglycemia, whether feedforward or feedback control configuration is used. Postprandial hyperglycemia is the main reason why patients using an AP still spend approximately 8 h per day (on average) in hyperglycemia [12]. More advanced controllers alone will unlikely resolve this issue, but the

A feedback-only approach based on the interstitial glucose measurement is a challenging task, mainly because of the long delays in insulin absorption.

combination of noninsulin drugs and advanced controllers might.

Pramlintide is a hormone that delays gastric emptying (modifying the disturbance dynamics). It can be codelivered with insulin in a closed-loop manner (multi-input control) to better control glucose concentrations. Pramlintide was studied when delivered at mealtime (in an open-loop manner) in addition to insulin-alone, closed-loop delivery [72], [141]–[143] but has not been assessed when delivered in a closed-loop manner. SGLT2i is a class of medications that increases the kidney filtering rate of high glucose concentrations (modifying systems dynamics) and may be combined with advanced controllers to develop efficient feedback-only controllers that remove the burden of carbohydrate counting from the patients. Combining SGLT2i with closed-loop systems remains an uncharted territory. Other noninsulin drugs than pramlintide and SGLT2i also exist [144].

During long-term use of the AP, patients' insulin needs will change with time (over weeks or months). A suboptimal insulin-to-carbohydrate ratio is equivalent to misestimating the carbohydrate content of the ingested meals, and may degrade glucose control, although this might affect closed-loop systems less than open-loop therapy [145], [146]. Filtering algorithms that estimate optimized insulin-to-carbohydrate ratios (using data over several days) during closed-loop operation would likely improve glucose control. Limited work has been done in this area [87], [147].

CONCLUSION

The AP is a closed-loop system for glucose regulation intended for T1D. Meal consumption is a major disturbance of the glucoregulatory system. A feedback-only approach based on the interstitial glucose measurement is a challenging task, mainly because of the long delays in insulin absorption. Combining the feedback controller with minimal feedforward disturbance information is an approach that presents tradeoffs between patient convenience and controller efficiency on postprandial regulation.

Model predictive controllers represent the forefront of current research. Incorporating meal information, bolus information, input constraints, and model dynamics allow for bypassing the slow absorption of insulin to prevent postprandial late hypoglycemia. Meal detection may mitigate the risks of insulin bolus omission, while learning algorithms may optimize the prediction capabilities of the AP.

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