Journal of Diabetes Science and Technology
Volume 4, Issue 5, September 2010

ORIGINAL ARTICLES

Hypoglycemia Prevention via Pump Attenuation and Red-Yellow-Green "Traffic" Lights Using Continuous Glucose Monitoring and Insulin Pump Data

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Abstract

Background:

Hypoglycemia has been identified as a primary barrier to optimal management of diabetes. This observation, in conjunction with the introduction of continuous glucose monitoring (CGM) devices, has set the stage for achieving tight glycemic control with systems that adjust the insulin pump settings based on measured glucose concentrations. Because system safety and system reliability are key considerations, there is a need for algorithms that reduce the risk of hypoglycemia in closed-loop, open-loop, and advisory-mode systems. More specifically, the algorithm presented here is formulated as a component of the independent *safety system module* proposed in the modular *control-to-range* architecture.

Methods:

We developed two algorithms for attenuating insulin pump injections, which we refer to as *Brakes* and *Power Brakes*: Brakes is a pump attenuation function computed using CGM information only, while Power Brakes is an attenuation function in which a metabolic state observer with insulin input is used *in addition to* CGM information to inform the level of pump attenuation. These algorithms modulate the insulin pump delivery so that the insulin injection rate is dramatically reduced when the risk of hypoglycemia is high. Additionally, we combined these algorithms with an alert system that indicates a *level* of hypoglycemic risk to the user.

Results:

We demonstrated the effectiveness of Brakes and Power Brakes in reducing the incidence of hypoglycemia in two simulated scenarios: an elevated basal rate scenario and a scenario in which a bolus is delivered for a meal that is skipped. For these scenarios, the incidence of hypoglycemia using Power Brakes was reduced by 88 and 94%, respectively, where we defined hypoglycemia based on the American Diabetes Association guidelines for defining and reporting as 70 mg/dl. In the elevated basal rate scenario, no rebounds above 180 mg/dl (the desired upper limit of the control-to-range protocol) following hypoglycemia were shown to occur. We demonstrated the way the hypoglycemia alert system can trigger the intake of carbohydrates to reduce the incidence of hypoglycemia by 98%.

continued →

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Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitoring, (T1DM) type 1 diabetes mellitus

Keywords: hypoglycemia, Kalman filter, modeling, risk of hypoglycemia, simulation

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Abstract cont.

Conclusions:

This article offers, for the first time, a method for smoothly reducing insulin delivery rate to prevent hypoglycemia in individuals with type 1 diabetes mellitus based on a mathematically formal assessment of hypoglycemic risk. *In silico*, we demonstrate the way this method can prevent hypoglycemia while avoiding hyperglycemia rebounds that exceed 180 mg/dl. In conjunction with the pump attenuation algorithms, this article also proposes a system for alerting an individual of their hypoglycemic risk that contains three "levels" of alerts in the form of a traffic light. This alert system can be used in an advisory mode setting to alert the user to take action when hypoglycemia is imminent ("red" light) or in a closed-loop setting where initiation of rescue action begins when the red light alert is triggered.

J Diabetes Sci Technol 2010;4(5):1146-1155

Introduction

Hypoglycemia has been identified as a primary barrier to optimal management of diabetes.[1,2] In this article, we present two algorithms for hypoglycemia prevention and detection, one that uses continuous glucose monitoring (CGM) information only and one that uses both CGM and insulin injection information. The algorithms continually assess the risk of hypoglycemia and attenuate the insulin pump delivery rate in accordance with this formal risk assessment. In addition, these algorithms are designed to provide a signal to the user indicating one of three possible "levels" of hypoglycemic risk consistent with the formal risk assessment. This signal is given in the form of a traffic light: green light indicates no risk of hypoglycemia, yellow light indicates that a risk of hypoglycemia is present, and red light indicates imminent hypoglycemia, either initiating automated rescue action from the controller in a closed-loop setting or suggesting the need for rescue action to the user in an advisory mode. We consider the issues of user compliance and time of alarm to be outside the scope of this work. Employing our methods, a "safety supervision" function can be added to different types of blood glucose (BG) management methods, including conventional therapy, open-loop and advisory-mode systems, and closed-loop systems, as in the control-to-range architecture of Kovatchev and colleagues.[3] Under the assumption that other components of the safety module will supervise insulin boluses, the algorithms presented here serve to modify basal insulin rates.

To outline the remainder of this article, we first provide a background of the current methods employed for hypoglycemia detection and prevention. In the Methods section, we present two algorithms for hypoglycemia prevention: Brakes and Power Brakes. In the Results section, we present *in silico* results of pump attenuation methods in two instances of hypoglycemia, elevated basal rate and overbolus scenarios, using the University of Virginia/University of Padova Metabolic Simulator described by Kovatchev and colleagues,[4] which is accepted by the U.S. Food and Drug Administration.

Background

Current commercial CGM devices contain an alarm system that alerts the user of hypoglycemia (see References 5 and 6 for a thorough review). The methods designed to generate these alarms come in two general types: low-threshold detection and predictive. Hypoglycemia alarms based on low-threshold detection have a BG concentration such that, when the CGM measurements are at or below this low threshold, an alarm is triggered alerting the user of their risk of hypoglycemia. Some commercial CGM devices also contain predictive alarms. The nature of this type of alarm gives the user the opportunity to administer rescue action so that the hypoglycemic event can be avoided. Rescue action to prevent hypoglycemia may take the form of glucagon infusion[7,8] or fast-acting oral consumption (e.g., glucose tablets).

Other types of alarms for hypoglycemia are based on a combination of glucose threshold and glucose rate of change. In this case, if the CGM device measurements are reading low *and* the rate of decrease in CGM device measurements is high, an alarm is triggered.[9] There has been extensive study of the effectiveness of alarms for the commercial CGM devices.[10–14] Various algorithmic methods for predictive alarms have also been proposed based on linear regression,[15] time series,[16] and optimal estimation theory.[17]

In order to be effective in reducing the incidence of hypoglycemia, alarms must be accompanied by some type of action. Buckingham and associates[18] proposed a hypoglycemia prevention method based on insulin pump shutoff: when the predicted glucose concentration reaches a certain value, the pump halts the delivery of insulin. This method has been tested in a clinical setting[18] and has been shown to reduce the incidence of hypoglycemia while avoiding a glucose rebound effect that can occur when the insulin pump is shut off for a period of 90 minutes. The pump shutoff method proposed regulates insulin delivery to reduce the incidence of hypoglycemia, while another method introduced by Choleau *et al.*[19] demonstrates the effectiveness of a glucose infusion to mimic the appearance of glucose from an intragastric load.

In what follows, we describe a detection method that alerts the user of a "level" of hypoglycemic risk as well as two algorithms for hypoglycemia prevention that work by gradually attenuating insulin delivery.

Methods

Here, we present two algorithms for the attenuation of insulin pump delivery: Brakes and Power Brakes. The similarity between these two algorithms is that they both provide a method for smoothly attenuating the insulin pump delivery rate based on a formal assessment of hypoglycemic risk. The difference comes in the information (CGM only or CGM and insulin) that is used to make this formal risk assessment.

Brakes: Based on Continuous Glucose Monitoring Data

In this subsection, we discuss the implementation of an attenuation of the insulin delivery rate computed using CGM measurements alone. We refer to this method as Brakes.

Attenuation Function

The role of Brakes is to adjust the insulin rate commands to avoid hypoglycemia (refer to **Figure 1** throughout this section). The brake algorithm is designed to smoothly attenuate the insulin delivery rate of the patient at the current time by monitoring the CGM data, assessing a measure of the patient's current *risk* of hypoglycemia, $R(\bar{y}(t))$, and then computing an attenuation factor $\phi_{brakes}(R(\bar{y}(t)))$:

$$\phi_{brakes}(R(\bar{y}(t))) = \frac{1}{1+\Gamma \cdot R(\bar{y}(t))}, \quad (1)$$

where $\bar{y}(t)$ is a measure of the patient's current BG state (described in more detail later), and Γ is a patient-specific "aggressiveness" parameter. The parameter Γ is patient-specific parameter tuned using the University of Virginia/University of Padova Metabolic Simulator. The optimal value of Γ is chosen to avoid hypoglycemia (70 mg/dl) with minimum aggressiveness (based on the American Diabetes Association guidelines for defining and reporting[20]). Following simulation experiments, we conduct a correlation analysis for Γ with a set of known patient-specific biometric parameters that include total daily insulin (*TDI*; U), correction factor (*CF*; mg/dl/U), body weight (kg), and carbohydrate ratio (gCHO/U). Based on this correlation analysis, the per-patient optimal Γ is set according to the following regression formula:

$$\Gamma = e^{-.7672-.0091 \cdot TDI + .0449 \cdot CF}. \quad (2)$$

The attenuation factor $\phi_{brakes}(R(\bar{y}(t)))$ is used to compute the reduced insulin pump rate $J_{actual}(t)$ by

$$J_{actual}(t) = \phi_{brakes}(R(\bar{y}(t)))J_{command}(t), \quad (3)$$

where $J_{command}(t)$ is the rate of insulin injection (U/h) that the pump would administer without Brakes, and $J_{actual}(t)$ is the attenuated insulin delivery rate (U/h). In this case, where the risk is computed using CGM information alone, the formula for the risk function is as follows:

$$R(\bar{y}(t)) = \begin{cases} 10\left[.918642\left(ln(\bar{y}(t))^{1.29286} - 7.57332\right)\right]^2 & \text{if } 20 < \bar{y}(t) < 120 \text{ and } \frac{d\bar{y}}{dt} < 0 \\ 100 & \text{if } \bar{y}(t) \le 20 \\ 0 & \text{otherwise} \end{cases} \quad (4)$$

where $\bar{y}(t)$ is a 15 min nonweighted moving average of the CGM device measurements, that is, $\bar{y}(t) = \frac{1}{15}\sum_{i=0}^{14} CGM(t-i)$, where $CGM(t)$ is defined as

the CGM device measurement at time t, $\frac{d\bar{y}}{dt}$ is the rate of change in CGM assessed over a 15 min moving average window, and this condition on $R(\bar{y}(t))$ is set so as to avoid the potential for hyperglycemia rebound. The form of $R(\bar{y}(t))$ for $\bar{y}(t) \in (20,120)$ is adopted from the BG symmetrization function and the low blood glucose index introduced by Kovatchev and colleagues,[21] where a transformation of the BG to a "risk scale" is introduced. **Figure 2** provides a representative subject example of the attenuation factor $\phi_{brakes}(R(\bar{y}(t)))$ applied to the insulin delivery rate to prevent hypoglycemia.

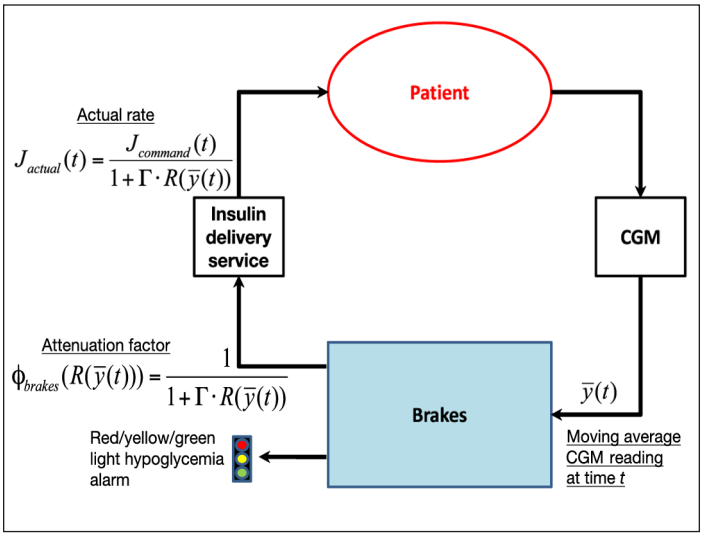

Figure 1. Schematic of Brakes.

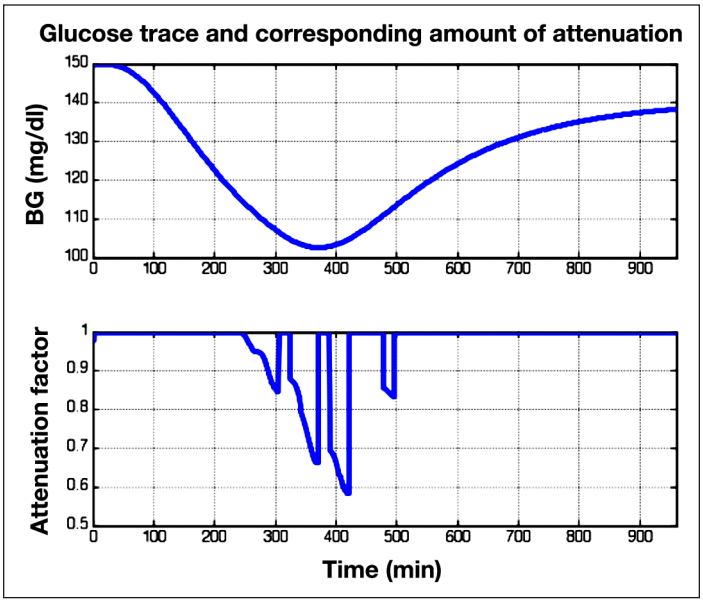

Figure 2. Attenuation factor derived from the Brakes algorithm shown with the corresponding BG trace for a representative subject with a noisy CGM input signal.

Power Brakes: Based on Continuous Glucose Monitoring and Insulin Pump Data

In this subsection, we introduce an algorithm that is informed with the history of past insulin delivery rates that allows us to attenuate insulin pump delivery rate *in anticipation* of hypoglycemia by accounting for the insulin that has been injected. We refer to this as Power Brakes, as the use of both insulin information and prediction increase our ability to prevent hypoglycemia through pump attenuation. (Please refer to **Figure 3** throughout this section.) Here, we present a Kalman filtering technique to account for CGM signal noise.

Metabolic State Observer Design

The model from which our metabolic state observer is derived is the compartmental "minimal model" of Bergman and colleagues,[22] with extensions that account for subcutaneous oral glucose sensing and actuation. The coefficients of the model reflect population average glucose–insulin dynamics with a 1-minute sample time. The discretized, linearized implementation of this model in state space form is

$$x(k+1) = Ax(k) + Bu(k) + G\omega(k), \qquad (5)$$

where $x(k)$ is the state of the system k at the the sample time, $u(k) = J_{actual}(k) - J_{basal}$ (in mU/min) is the insulin input signal at stage k (held constant between samples)—where $J_{actual}(k)$ (in mU/min) is the current rate of insulin infusion and J_{basal} (in mU/min) is the *minimum* value over the patient's basal rate profile—and $\omega(k) = meal(k) - meal_{ref}$ (in mg/min) is the ingested glucose disturbance signal at stage k, where $meal(k)$ (in mg/min) is the rate of ingested

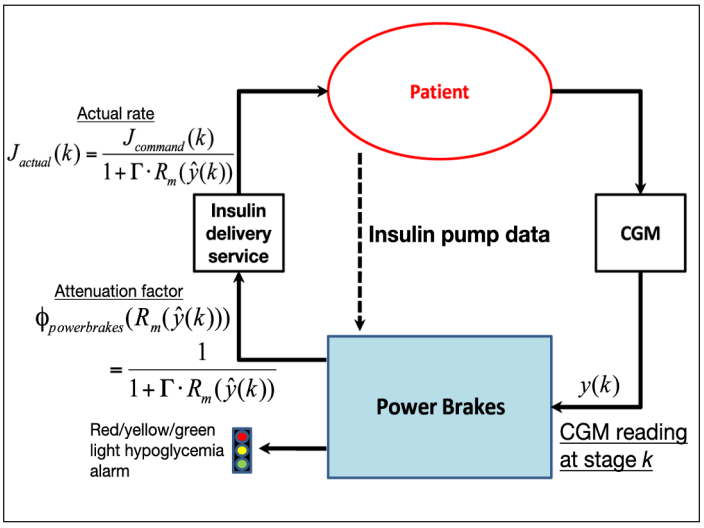

Figure 3. Schematic of Power Brakes.

glucose at stage k and $meal_{ref}$ (in mg/min) is the reference meal input value. Matrices A, B and G are derived from a linearized, discretized form of the model, with model parameters chosen to be representative of an average adult patient with type 1 diabetes mellitus (T1DM). Matrix parameters are provided in the **Appendix**.

The state observer is based on a steady state Kalman filter. Since only CGM device measurements are available at each 1-minute sample period, it is necessary to compute estimates $\hat{x}(k)$ of $x(k)$ based on the knowledge of infused insulin rate $u(k)$ and measurements $y(k)$, where

$$y(k) = CGM(k) - G_{ref}, \tag{6}$$

where $CGM(k)$ is the readout of the continuous glucose monitor at stage k and G_{ref} is a reference glucose value, set here at 112.5 mg/dl. We model the measurement signal as

$$y(k) = Cx(k) + v(k), \tag{7}$$

where $v(k)$ (mg/dl) represents the CGM signal noise and is added to the state variable representing plasma glucose. The matrix C is given by

$$C^T = [1 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0]. \tag{8}$$

The metabolic state observer is derived from the state space model, which generates $x(k)$ and the measurements $y(k)$ as a Kalman filter, treating the meal disturbance process $\omega(k)$ and the noise process $v(k)$ as zero-mean, white Gaussian processes with covariances $R_s = 1$ (mg/min) and $Q_s = 5e-4$ (mg/dl), respectively. These covariance parameters are time and state invariant.

The observer itself can be expressed recursively (as a dynamic process) as

$$\begin{aligned} \hat{x}(k \mid k-1) &= A\hat{x}(k-1 \mid k-1) + Bu(k-1) \\ \hat{x}(k \mid k) &= \hat{x}(k \mid k-1) + L_f(y(k) - C\hat{x}(k \mid k-1)), \end{aligned} \tag{9}$$

where $\hat{x}(k|k-1)$ refers to the best estimate of using data $x(k)$ collected up to stage $k-1$ and $\hat{x}(k|k)$ refers to the best estimate of $x(k)$ given information up to stage k. The filter gain matrix is defined by

$$L_f = AP_fC^T(CP_fC^T + R_S)^{-1}, \tag{10}$$

where the matrix P_f is the unique stabilizing solution to the algebraic Riccati equation:

$$A^TPA - A^TPG(G^TPG + R_S)^{-1}G^TPA + Q_S = P. \tag{11}$$

(In our implementation, this step is performed in Matlab using the command "*kalman*.") We point out that, even though meals $\omega(k)$ and sensor noise $v(k)$ are not zero-mean, white Gaussian processes in reality, the resulting Kalman filter is still a stable observer.

We compute an estimate of the (projected) BG concentration at stage k by

$$\hat{y}(k) = C\hat{x}_\tau(k), \tag{12}$$

where C is defined in **Equation (8)**, τ represents an amount of time (in minutes), and

$$\hat{x}_\tau(k) = A^\tau \cdot \hat{x}(k) + A_\tau B \cdot u(k) + A_\tau G \cdot w(k), \tag{13}$$

where A^τ is the A matrix of the state space model raised to the τ^{th} power and

$$A_\tau = \begin{cases} 0 & \text{if } \tau = 0 \\ \sum_{s=0}^{\tau-1} A^s & \text{if } \tau > 0 \end{cases} \tag{14}$$

We note that the insulin input signal and the meal signal are held at their operating point values of J_{basal} and $meal_{ref}$, respectively, over the prediction horizon τ. In computing $\hat{y}(k)$, τ is a parameter that must be specified; $\tau = 0$ corresponds to assessing risk based on the best estimate of BG given all the data received up to stage k, while $\tau > 0$ corresponds to an assessment of the future risk of hypoglycemia, giving Power Brakes the opportunity to intervene well before the onset of hypoglycemia. We set $\tau = 15$ minutes.

Attenuation Function

An estimate of the BG concentration allows us to assess the risk of hypoglycemia, informed now by our metabolic state observer, R_m:

$$R_m(\hat{y}(k)) = \begin{cases} 10 \cdot \left[.918642 \cdot \left(ln(\hat{y}(k))^{1.29286} - 7.57332 \right) \right]^2 & \text{if } 20 < \hat{y}(k) < 120 \text{ and } \frac{d\hat{y}(k)}{dk} < 0 \\ 100 & \text{if } \hat{y}(k) \le 20 \\ 0 & \text{otherwise.} \end{cases} \tag{15}$$

where $\hat{y}(k)$ is from **Equation (13)** and $\frac{d\hat{y}(k)}{dk}$ is the rate of change in the projected glucose over a 15 min moving average window. Given $R_m(\hat{y}(k))$ we compute the amount of insulin pump attenuation by

$$\phi_{powerbrakes}(R_m(\hat{y}(k))) = \frac{1}{1 + \Gamma R_m(\hat{y}(k))}, \tag{16}$$

where the aggressiveness parameter Γ is as defined in **Equation (2)**.

The attenuation factor $\phi_{powerbrakes}(R_m(\hat{y}(k)))$ is used to compute the reduced pump rate $J_{actual}(k)$ by

$$J_{actual}(k) = \phi_{powerbrakes}(R_m(\hat{y}(k))) \cdot J_{command}(k), \quad (17)$$

where $J_{command}(k)$ is the rate of insulin injection (U/h) that the pump would administer without Power Brakes and $J_{actual}(k)$ is the attenuated insulin delivery rate (U/h).

Hypoglycemia Traffic Lights for Brakes and Power Brakes

This subsection introduces a corresponding traffic light signal designed to alert the user as to their level of hypoglycemic risk. The traffic light works in conjunction with the risk computation as follows, where K_{red} and $K_{red,IOB}$ are BG thresholds used to trigger the transition from the yellow to the red light signal for use in conjunction with Brakes and Power Brakes, respectively. For Brakes, the lights are triggered as follows:

- If $R(\overline{y}(t)) = 0$, the green light is triggered.
- If $R(\overline{y}(t)) > 0$ and $\overline{y}(t) \geq K_{red}$, the yellow light is triggered.
- If $\overline{y}(t) < K_{red}$, the red light is triggered.

The value of K_{red} is chosen as 80 mg/dl. For Power Brakes, the lights are triggered similarly, but our threshold for the trigger is based on a Kalman filter state estimate:

- If $R_m(\hat{y}(k)) = 0$, the green light is triggered
- If $R_m(\hat{y}(k)) > 0$ and $\hat{y}_{shutoff}(k) \geq K_{red,IOB}$, the yellow light is triggered
- If $\hat{y}_{shutoff}(k) < K_{red,IOB}$, the red light is triggered.

We formulate $\hat{y}_{shutoff}(k)$ in the same way as $\hat{y}(k)$ in **Equation (13)**, except that we hold the insulin input signal $J_{actual}(k)$ at 0 over the prediction horizon τ so as to trigger the red light when it is predicted that no amount of pump attenuation will allow hypoglycemia to be avoided. The value of $K_{red,IOB}$ is chosen as 77.5 mg/dl.

For implementation, this signal would appear on the CGM device display in conjunction with an alert sound or vibration. This threshold is designed to allow the user the time to administer rescue carbohydrates *prior* to the onset of hypoglycemia to mitigate or avoid the event. During recovery from a hypoglycemic event, the red light remains "on" until at least 80% of the past 30 CGM measurements are above 90 mg/dl.

Results

In this section, we present a series of results that demonstrate the ability of both Brakes and Power Brakes to lower the incidence of hypoglycemia. We also present results demonstrating the performance of the red light alarm in detecting hypoglycemia. Experiments are run on the (FDA-accepted) University of Virginia/University of Padova Metabolic Simulator at the University of Virginia with the noise model developed by Breton and Kovatchev.[23] We present two scenarios designed to cause hypoglycemia if no action is taken:

1. Some T1DM patients experience highly variable insulin sensitivity (e.g., after physical activity). For such patients, it happens that his/her basal rate of insulin delivery, which is tuned to achieve fasting euglycemia under normal circumstances, is suddenly too high, putting the patient at risk of hypoglycemia. This change in the effectiveness of insulin has been observed following exercise.[24] We simulate this increased sensitivity to insulin by delivering two times the normal basal rate of the subject, where this increase in basal level can be used to simulate the increase in insulin sensitivity following exercise.[25] All 100 adult *in silico* subjects are initialized at glucose concentrations of 150 mg/dl and are subjected to a basal insulin delivery rate that is two times what would be required to achieve their respective fasting glucose concentration of 112.5 mg/dl. **Figure 4** shows the results of this scenario in the case when (a) no action is taken, (b) Brakes are applied, (c) Power Brakes are applied.

2. Patients often administer premeal insulin boluses in anticipation of the meal they are about to consume. In unusual circumstances, the patient may forget (or otherwise be unable) to eat the anticipated meal. This scenario puts the patient at severe risk of hypoglycemia. We simulate this by administering a premeal bolus for a meal that is missed. The amount of this premeal bolus is designed such that the subject will drop to a BG concentration of 50 mg/dl (from an initial value of 150 mg/dl) if the meal is not taken (we note that the size of this "missed meal" will vary from patient to patient, depending on their sensitivity to insulin). We can also think of this scenario as a case in which a patient administers a bolus that is too

large to correct for a positive deviation from a target glucose concentration. The patient may intend to take a bolus in order to return to a glucose concentration of 90 mg/dl, but instead the bolus taken is incorrectly computed to reach a target of 50 mg/dl. **Figure 5** shows the results of this scenario in the case when (a) no action is taken, (b) Brakes are applied, and (c) Power Brakes are applied. **Figure 6** shows the way in which the red light alarm can be triggered to deliver rescue carbohydrates. In this case, 16 g of rescue carbohydrates are delivered at the time that the red light is triggered.

In the case of both the elevated basal rate and the missed meal scenario, our results indicate the ability of both Brakes and Power Brakes to reduce the incidence of hypoglycemia (when compared to the case where no action is taken). In scenario 1, Brakes works well to gradually attenuate the insulin delivery rate in reaction to a gradual decrease in BG when insulin information is not available. In scenario 2, Power Brakes, using the insulin injection information, is aware that the large bolus delivered in anticipation of a meal will lead to decreasing BG concentrations. This is reflected in the projected estimate of the BG state obtained from our model of glucose–insulin kinetics and metabolic state observer. Power Brakes acts aggressively in scenario 2 by considering the *projected* effect of the insulin on board. Another key benefit of Power Brakes is its performance during a recovery from a low BG excursion: as soon as *predicted* BG rate of change is positive, the attenuation effect is released.

In the case of scenario 1, where the basal rate is elevated to two times basal, we experience no rebound glucose concentrations above 180 mg/dl following the pump attenuation for both Brakes and Power Brakes (where, following the recovery from low BG, the basal rate is returned to a normal basal rate) over 12 hours of total simulation time. In scenario 2, where our pump attenuation algorithm responds to an overbolus of insulin, rebounds above 180 mg/dl occur in less than 3% of subjects.

In **Tables 1 and 2**, we present the sensitivity, false red light alarm, and time to hypoglycemia event statistics for our alarm system in the case of (1) elevated basal rate and (2) overbolus scenarios. For each scenario, we consider the red light alarm designed for both Brakes and Power Brakes, as described in Methods.

Results from **Tables 1 and 2** indicate the ability of the red light alarm to provide an alert that can be used to

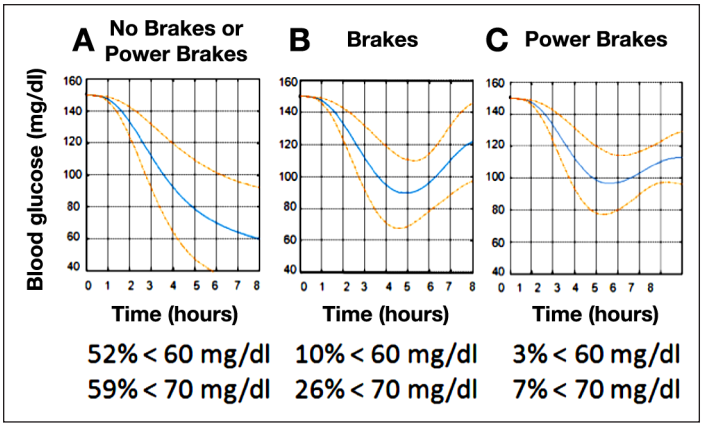

Figure 4. Elevated basal rate scenario. The plots show the mean BG trace (blue) for 100 subjects and ±1 standard deviation (orange).

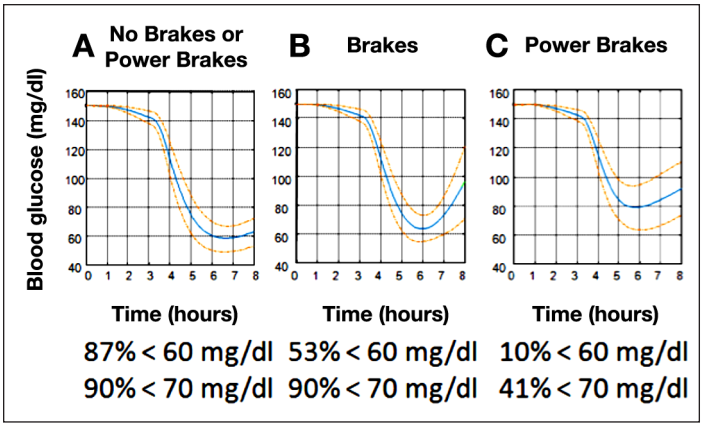

Figure 5. Missed meal (or over-bolus) scenario. Plots show the mean BG trace (blue) for 100 subjects and ±1 standard deviation (orange).

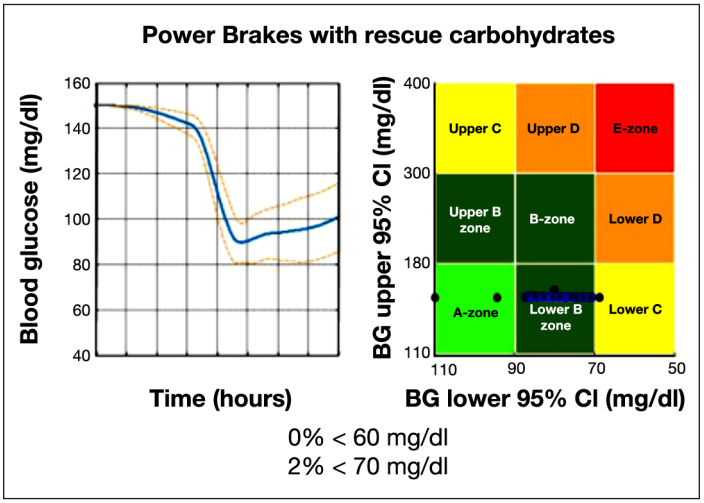

Figure 6. Missed meal (or overbolus) scenario. Power Brakes is employed to attenuate insulin delivery rate, and the red light alarm triggers the automated administration of 15 g rescue carbohydrates. The left plot shows the mean BG trace (blue) for 100 subjects and ±1 standard deviation (orange). The right plot shows the control variability grid analysis[26] for each of 100 subjects. CI, confidence interval.

Table 1.
Red Light Alarm Statistics for Scenario 1

Scenario 1	Brake red light	Power Brake red light
% detected (prior to event)	80.77	94.23
% false alarm	15.38	6.77
Minimum BG for false alarms (mg/dl)	76.17	74.63
Time to event (min)	16.49	17.16

Table 2.
Red Light Alarm Statistics for Scenario 2

Scenario 2	Brake red light	Power Brake red light
% detected (prior to event)	83.52	93.41
% false alarm	6.59	3.30
Minimum BG for false alarms (mg/dl)	75.52	77.23
Time to event (min)	10.19	28.51

trigger rescue carbohydrates. We note that the percentage of hypoglycemic episodes detected represents only the percentage of episodes detected prior to the onset of hypoglycemia. Events that trigger the red light alarm at any time following the onset of hypoglycemia are not considered "detected" events, as we assume that the purpose of the red light alarm is to alert the control system (or the user) so that action can be taken to prevent or mitigate the event. Time to event statistics indicate that Power Brakes, because of its ability to account for insulin on board, provides a longer time, on average, between the red light alarm and the hypoglycemic event.

Discussion

In **Figure 6**, we demonstrate the way in which hypoglycemia can be prevented when the red light alarm triggers action through the delivery of rescue carbohydrates. This ability of Power Brakes to anticipate imminent hypoglycemia allows adequate time for taking preventative action, which avoids the hypoglycemic episode in 98% of cases. In this case of a closed-loop control system, the delivery of rescue action in the form of glucagon can be envisioned as an automated process. In an advisory mode, the red light trigger will prompt an alarm to the user, advising that rescue action be taken. While the issue of user compliance and alarm time of day is deemed outside the scope of the work presented here, we envision the simulation of user delay and/or the probability of user compliance in future work.

The simulation experiments presented here offer insight into the use of Brakes and Power Brakes for *in vivo* patients in open-loop, advisory-mode, and closed-loop settings. In an advisory-mode setting, communication with the user through the red light alarm gives the user an opportunity to react to increasing hypoglycemic risk. In a future closed-loop setting, the gradual attenuation of the insulin pump delivery rate and the administration of rescue in the form of an automated glucose infusion offer the potential to prevent hypoglycemic events.

Conclusions

We describe two methods to attenuate insulin levels gradually to avoid the risk of hypoglycemia. While Brakes can compute pump attenuation without requiring access to insulin history, Power Brakes uses insulin pump feedback to increase accuracy of the hypoglycemia risk assessment. The pump attenuation method for hypoglycemia prevention presented here is contrasted with pump shutoff methods, as it does not suffer the complexity of deciding (1) exactly when to shut off and (2) exactly when to resume operation, with both decisions being significantly hampered by CGM device noise/errors. Smooth attenuation of the insulin pump delivery rate based on risk allows us to conveniently handle the case when glucose is dropping but is not yet at a dangerously low level. Spurious errors in the CGM device signal can only become spurious errors in the degree of attenuation since there is never a point in time where a "crisp" attenuation decision has to be made.

Additionally, we present an alert system that communicates with the user to indicate a level of hypoglycemic risk. Results indicate the power of the red light alert to trigger action in the form of rescue carbohydrates to prevent a hypoglycemic event.

Funding:

This work was supported by grants from the Juvenile Diabetes Research Foundation Artificial Pancreas Project, National Library of Medicine Training (T15LM009462), and National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK 51562).

Disclaimer:

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Appendix

Matrix model parameters/model equations for the state space model presented in **Equation (5)**:

$$A = \begin{bmatrix} .9913 & -102.7 & -1.50\times10^{-8} & -2.89\times10^{-6} & -4.1\times10^{-4} & 0 & 2.01\times10^{-6} & 4.30\times10^{-5} \\ 0 & .839 & 5.23\times10^{-10} & 7.44\times10^{-8} & 6.84\times10^{-6} & 0 & 0 & 0 \\ 0 & 0 & .9798 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & .0200 & .9798 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1.9\times10^{-4} & .0180 & .7882 & 0 & 0 & 0 \\ .0865 & -4.667 & -2.73\times10^{-10} & -6.59\times10^{-8} & -1.26\times10^{-5} & .9131 & 6.00\times10^{-8} & 1.90\times10^{-6} \\ 0 & 0 & 0 & 0 & 0 & 0 & .9083 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & .09115 & .9891 \end{bmatrix}$$

$$B^T = \begin{bmatrix} -3.05\times10^{-9} & 1.34\times10^{-10} & .9900 & .0100 & 6.50\times10^{-5} & -4.61\times10^{-11} & 0 & 0 \end{bmatrix}$$

$$G^T = \begin{bmatrix} 6.76\times10^{-7} & 0 & 0 & 0 & 0 & 1.52\times10^{-8} & .9534 & 0.0464 \end{bmatrix}$$