Published in final edited form as:
Comput Methods Programs Biomed. 2013 February ; 109(2): 220–225. doi:10.1016/j.cmpb.2011.12.016.

Historical Data Enhances Safety Supervision System Performance in T1DM Insulin Therapy Risk Management★

Colleen Hughes-Karvetski[a], **Stephen D. Patek**[a], **Marc D. Breton**[b], and **Boris P. Kovatchev**[a,b]
[a]Systems and Information Engineering, University of Virginia

[b]Psychiatry and Neurobehavioral Sciences, University of Virginia

Abstract

Safety measures to prevent or mitigate hypoglycemia are an important component of open loop, closed loop, and advisory mode insulin therapy control settings in type 1 diabetes. In recent work, we introduce a method for the automatic, gradual attenuation of the insulin pump delivery rate when a risk of hypoglycemia is detected, a method that we refer to as *brakes*. In the methods presented here, we demonstrate the use of historical glucose measurement data to inform and enhance the ability of the brakes to prevent hypoglycemia in real-time. The updated *brakes* are based on a patient-specific, time-varying model that reflects the typical trajectory of glycemic fluctuations throughout the day. Historical heightened risk of hypoglycemia throughout the day prompts an increase in the aggressiveness of insulin attenuation as compared to the original *brakes* that are based on real-time data alone. Through the use of available real-time data supplemented with historical glucose information to assess hypoglycemic risk, we are able to better anticipate and prevent hypoglycemia.

Keywords

diabetes; artificial pancreas; behavioral profiles; safety; alarms; continuous glucose monitoring; pump attenuation

1 Introduction

Hypoglycemia has been identified as the limiting factor in the optimal management of type 1 and type 2 diabetes [1]. In healthy human subjects, insulin secretion decreases and glucagon and epinepherine (counterregulatory hormones) secretion increases so that hypoglycemia can be avoided. In type 1 diabetes (T1DM), where insulin secretion is nearly if not totally absent, insulin must be delivered exogenously to maintain normoglycemia. Hypoglycemia in diabetes is most commonly the result of the combination of overinsulinization or an increased sensitivity to insulin and a weakened or absent counter-regulatory response to low blood glucose (BG) levels that is characteristic of patients with type 1 diabetes. To further complicate the situation in type 1 diabetes, hypoglycemia-

★This work was sponsored in part by the the NIH NIDDK Grant R01 DK 085623, the National Library of Medicine (Award Number T15LM009462), and National Science Foundation grant CNS-0931633. This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Library of Medicine or the National Institutes of Health.

associated autonomic failure (HAAF) assumes that glucose counterregulation is further impaired given recent hypoglycemic events.

Recent advancements in T1DM treatment technology offer the opportunity to inform the insulin pump delivery rate with glucose measurement feedback from a continuous glucose monitor (CGM) that provides subcutaneous glucose concentration data every 5–10 minutes. The present work proposes a method for prevention of hypoglycemia through an algorithm that automatically attenuates the insulin pump delivery rate. The novelty of the algorithm is that it is informed not only with real-time glucose measurement *and* insulin delivery data, but with historical information that allows us to assess hypoglycemic risk attributed to routine events that affect glycemic fluctuation in a temporal and patient-specific way.

2 Background

Models that provide information regarding the metabolic state of the patient serve as useful tools in the design of insulin delivery strategies for treatment of T1DM. For patients with T1DM, transient increases (e.g. dawn phenomenon) or decreases (e.g. exercise, see [2]) in insulin requirements are required to respond to the decrease or increase in sensitivity to insulin in an effort to maintain normoglycemia. Most metabolic models are not equipped to *anticipate* behavioral events or even some routine metabolic processes that may influence the glycemic state of the patient or the trajectory of the patient's glycemic state in the near future. Arguably, even the most routine of daily behaviors, meals, challenge models to generate accurate estimates and predictions of the patient's metabolic state even with certainty regarding timing and size of upcoming meals.

Insulin dosing control algorithms account for time-varying, patient-specific changes in insulin requirements using Bayesian parameter estimation methods that identify model parameters in real-time [3], by forecasting likely changes in insulin sensitivity parameters in the next 1–3 hours using an integration-based parameter identification method [4], or using run-to-run control methods to adjust the basal insulin infusion rate [5]. Other work incorporates dawn phenomenon or diurnal cycles in simulation in an effort to build and evaluate insulin dosing strategies that can account for routine metabolic events [6]. The insulin delivery strategies for patients with T1DM undergoing an exercise regimen include preventing accelerated insulin absorption, mimicking insulin secretion during exercise, supplying additional carbohydrates during exercise, and providing patients with diabetes education [7].

In [8], we introduce an algorithm referred to as *brakes* that works by automatically attenuating the insulin delivery rate when a risk of hypoglycemia is detected based on CGM measurement and insulin delivery information. The algorithm uses an estimate and projection of the BG concentration obtained through a metabolic state observer. The observer is used to formally assess *risk* of hypoglycemia based on a symmetrization of the BG scale as described in [9]. In the present work, we propose a method for employing historical CGM data to inform an assessment of hypoglycemic risk in real-time that can be employed to enhance the *brakes* algorithm. This work utilizes historical information to assess hypoglycemic risk allowing us to *anticipate* routine behavioral events, like exercise or consistent overdelivery of insulin, that affect glycemic fluctuation in a temporal and patient-specific way.

3 Methods

3.1 Blood Glucose Estimate Based on Real-Time Data

The *real-time* data sources that we consider are:

1. blood glucose estimates obtained through the use of a continuous glucose monitor (CGM) and
2. insulin delivery data obtained from the insulin pump

Using glucose sensor measurements and insulin information at time t, we assume a time-invariant, linear model of glucose insulin kinetics and employ a Kalman filtering methodology to estimate the BG concentration of the patient (state space model parameters are described in [8]). Real-time data to estimate the BG level of the patient is employed in conjunction with historical glucose measurement information to better predict impending hypoglycemia risk.

3.2 Blood Glucose State Trajectory Based on CGM Historical Data Collection

The collection and retrospective analysis of CGM data to modify open loop insulin therapy parameters is considered an important clinical application for CGM devices [10]. Various effective algorithms exist for predicting the BG concentration in real-time using CGM data, including methods based on statistical linear prediction [11], time series [12], and Kalman filter state estimation [13]. Predictive algorithms are typically used to generate hypoglycemia alarms [14], or to inform control algorithms (see [15] for a review). The novelty of the algorithm introduced here is that it employs *insulin information* as a critical component in estimating the BG level with the primary goal being to inform safety algorithms that take automatic action to prevent or mitigate the severity of a hypoglycemic event. In addition, the algorithm anticipates the potential for hypoglycemic risk based on patient's routine behavioral events, targeting the historical impact that these events have on glycemic fluctuation.

Collected CGM data serves as our historical data source. The choice to collect historical output data (subcutaneous glucose measurements) rather than historical input data (meals, insulin, exercise) is motivated by the fact that output data allows us to focus on modeling a patient's reaction to a behavior rather than modeling the behavior itself. Let us assume that we collect a set of CGM measurements every cycle-minutes k of the day for $k = \{1, 2, \ldots, \text{floor}(1440/\text{cycle})\}$, where the value of "cycle" is chosen to optimize the ability of the algorithm to detect routine fluctuations in the glucose profile that are not attributed to CGM noise. Our goal is to determine the glucose trajectory from stage k to stage (k + floor(30/cycle)) based on the historical CGM data. We define the time-varying linear model:

$$BG_{hist}^{(k+\text{floor}(30/\text{cycle}))} = \beta_{0,k} + \beta_{1,k} \cdot X^k + \varepsilon_k \quad (1)$$

for $k = \{1, 2, \ldots, \text{floor}(1440/\text{cycle})\}$, where X^k represents the CGM value at stage k, $BG_{hist}^{(k+\text{floor}(30/\text{cycle}))}$ represents the CGM value 30 minutes from k, and ε_k represents the error term of the linear model at each stage k where we assume that the error terms are independent and normally distributed. Using collected historical CGM data, we determine $\beta_{0,k}$ and $\beta_{1,k}$ by collecting all pairs ($CGM(k)$, $CGM(k + \text{floor}(30/\text{cycle}))$ and using these pairs to build a linear model at each stage k.

Additionally, we incorporate as part of our historical model the probability of hypoglycemia based on collected data. Let $p_{hypo}(k)$ for $k = \{1, 2, \ldots, (\text{floor}(1440/\text{cycle}))\}$ be the probability of hypoglycemia at each time step, defined by

$$p_{hypo}(k) = \frac{|CGM(k) < 70|}{|CGM(k)|} \quad (2)$$

where $CGM(k)$ represents a historical CGM measurement collected at stage k (in accordance with ADA guidelines, any sensor value less than 70 mg/dl is considered a hypoglycemia [16]). $p_{hypo}(k)$ is used in the adjustment of the brake algorithm activation threshold, as described in the following section. Together, the probability of hypoglycemia and the model of BG trajectory encode historical information regarding the extent of and the trajectory for decreasing BG.

3.3 Reconciling Real-Time State Estimation and History-Based CGM Trajectory for Hypoglycemia Risk Assessment

Let $BG_{risk}(t)$ be the input to the brakes algorithm detailed in [8], so that the risk of hypoglycemia at time t, $R(BG_{risk}(t))$, is given by

$$R(BG_{risk}(t))=\begin{cases} 10[\gamma_\theta(ln(BG_{risk}(t))^{\alpha_\theta}-\beta_\theta)]^2 & \text{if } 20<BG_{risk}(t)<\theta \text{ and } \frac{dBG_{risk}(t)}{dt}<0 \\ 100 & \text{if } BG_{risk}(t)\leq 20 \\ 0 & \text{otherwise} \end{cases} \quad (3)$$

where the assessment of hypoglycemic *risk* is based on the BG symmetrization function and the low blood glucose index (LBGI) introduced by Kovatchev and colleagues [9]. The input to the function is the estimate of BG (mg/dl), the output is a measure of hypoglycemic risk between 0 (no risk) and 100 (high risk). Parameters γ_θ, α_θ, and β_θ are determined based on the brake activation threshold value θ (mg/dl) and are computed from equations described in [9]. The condition on the slope of BG, $\frac{dBG_{risk}(t)}{dt}<0$, is employed to ensure that the attenuation of the insulin delivery rate is released during recovery from hypoglycemia to reduce the potential for hyperglycemic rebound. The amount of attenuation of the insulin pump delivery rate, $\varphi(R(BG_{risk}(t)))$, is computed as

$$\varphi(R(BG_{risk}(t)))=\frac{1}{1+\Gamma\cdot R(BG_{risk}(t))} \quad (4)$$

where Γ is a patient-specific aggressiveness parameter determined based on the patient's biometric parameters total daily insulin (U) and correction factor (mg/dl/U). The modified insulin delivery rate, $J_{actual}(t)$ (U/hr) is given by

$$J_{actual}=\varphi(R(BG_{risk}(t)))J_{command}(t) \quad (5)$$

where $J_{command}(t)$ (U/hr) represents the insulin delivery rate that the pump was scheduled to deliver; in open loop insulin therapy, this is described by the basal rate pattern of the patient.

In its original implementation, $BG_{risk}(t)=\widehat{BG}(t+\tau|t)$ for τ = 15 minutes, where $\widehat{BG}(t|t)$ is the BG estimate obtained from the state observer given CGM and insulin delivery information up to time t (as described in [8]) and $\widehat{BG}(t+\tau|t)$ is the linear extrapolation obtained using the linear model of glucose-insulin kinetics with model inputs, insulin and CGM, held constant over the τ-minute prediction horizon. The brake activation threshold θ is fixed at 120 mg/dl, with parameters γ_θ, α_θ, and β_θ computed accordingly.

In the proposed implementation, historical data informs the BG input so that $BG_{risk}(t)$ is defined by

$$BG_{risk}(t)=\beta_{0,k^*}+\beta_{1,k^*}\cdot\widehat{BG}(t|t) \quad (6)$$

where $\widehat{BG}(t|t)$ represents our best current estimate of the BG level based on CGM and insulin information and k^* such that $(k\cdot \text{cycle} - t)$ for $k\in\{1, 2, \ldots, \text{floor}(1440/\text{cycle})\}$ is minimized and nonnegative. The value of θ in the historically-informed brakes implementation varies depending on p_{hypo} and is given by

$$\theta=\begin{cases} 140 & \text{if } p_{hypo}(k^*+\tau^*_{hypo})>p_{thresh} \\ 120 & \text{otherwise} \end{cases} \quad (7)$$

where τ^*_{hypo} minutes and p_{thresh} are parameters tuned to optimize the use of historical hypoglycemia probability data. Parameters γ_θ, α_θ, and β_θ are set accordingly. Figure 1 shows a schematic of the brakes algorithm, informed now by historical glucose data.

3.4 In Silico Study for Model Validation

In this section, we evaluate the use of historical CGM data to improve *brakes* performance through an in silico study. Our historical model is built with the value of "cycle" = 30 minutes; we choose this cycle length to optimize performance and avoid the disruption in the model parameters that may be caused by CGM noise. We assume that insulin pump delivery can be modified on a minute-by-minute basis. The value of τ^*_{hypo} is chosen through simulation tests to optimize brakes performance and is set to $\tau^*_{hypo}=60$ minutes.

We simulate and collect 30 days of historical CGM data, where the data assumes the original brakes algorithm employed in patient's insulin pump delivery settings so that historical data reflects the impact of brake action *without* historical information being employed. Table 1 summarizes the random meal behavior assumptions with meal timing and size drawn from a normal distribution with mean (standard deviation) given in Table 1. Meals, particularly snacks, may be "skipped" if the realized amount of carbohydrates associated with the meal is 0 gCHO. We assume that insulin delivery follows a typical open loop therapy approach with boluses delivered at meal times computed based on the patient's current carbohydrate ratio (gCHO/U) and correction factor (mg/dl/U) with a target BG of 130 mg/dl (with possibility for reverse correction), and the patient's basal rate delivered otherwise.

In addition to this, we simulate an unmodeled random disturbance that is likely to result in hypoglycemia. This disturbance is an increase in the patient's basal rate designed to represent an increase in the patient's sensitivity to insulin, where the *intensity* of the disturbance is represented by the value of the multiplier on the nominal basal rate. The disturbance has probability $\frac{5}{7}$ with random intensity $\mathcal{N}$ (2, .25) and random start time $\mathcal{N}$ (900, 15) minutes with disturbance length $\mathcal{N}$(60, 15) minutes. The disturbance remains constant intensity over the disturbance length, after which the intensity decreases linearly for a period of 12 hours.

After collecting 30 days of simulated historical data for 100 in silico adult subjects, we employ the collected CGM data to construct the time-varying linear models for each adult subject as described by Equation 1. In the next step, we conduct a 1680 minute (28 hour) simulated scenario with the same random meal behavior and unmodeled random disturbance characteristics as described in Table 1, where we apply, for comparison, the brakes algorithm in its original and historically-informed implementations.

4 Results and Discussion

4.1 Representative Subject Results

Each in silico subject has a unique set of pairs ($\beta_{0,k}$, $\beta_{1,k}$) and parameters $p_{hypo}(k)$ for k = {1, 2, …, 48}. These patient-specific model parameters are designed to capture the effect on the glycemic trajectory of various behaviors that occur throughout the day with some regularity. We test the linearity assumption by computing a mean R^2 for the linear model and by testing the hypothesis that the slope of the linear model is different than 0 (p-value reported) for each in silico subject's set of linear models. Results are presented in Table 2. We analyze the independence of errors generated in the linear model fit using the Durbin - Watson (DW) statistic with results (using the command "dwtest" in Matlab) from this analysis indicating a mean DW value over 100 in silico subjects of 2.01 (std. dev. of mean across all subjects .05). The normality of the residual distribution is tested using the Jarque - Bera (JB) test, where the null hypothesis is that the sample of residuals come from a normal distribution with unknown mean and variance, against the alternative that the sample does not come from a normal distribution. Results of the JB test (using the command "jbtest" in Matlab) using an α = .05 to reject the null hypothesis indicate that in a mean of 83.90% (std. dev. of the mean 6.13%) of cases we fail to reject the null hypothesis across the linear models for 100 subjects. These results indicate that the linear model assumption for BG trajectory is reasonable.

For some patients, the increase in basal rate around 3pm does not have a dramatic effect on glycemic fluctuation. For other patients, results show that they are more sensitive to deviations from their nominal insulin sensitivity. It is the latter set of patients for which the historical model proves particularly beneficial. Figure 2 presents the 30 days of collected CGM history for a representative subject.

Figure 3 presents the historical model parameters that result for the same representative subject. We observe that the increase in the activation threshold (corresponding to nonzero p_{hypo}) occurs at around 1290 minutes after midnight (9:30pm) and continues through the end of the day and into the morning hours, during which the change in insulin sensitivity from our unmodeled disturbance results in additional hypoglycemic risk for this subject. A value of 60 minutes for τ^*_{hypo} allows us to anticipate the increased sensitivity by increasing the brake activation threshold *prior* to the hypoglycemia onset.

Figure 4 presents, in the top plot, 3 traces for the same representative subject: the blue trace is the patient's CGM, the red trace is the output value obtained from the historically-informed linear model (the input to the historically-informed brakes), and the green trace represents the BG signal output from the Kalman filter state estimation and prediction procedure (the input to the original brakes algorithm). The corresponding attenuation factor $\varphi(R(BG_{risk}(t)))$ resulting from each corresponding input employed from the top plot is shown in the bottom plot.

A comparison of the traces beginning at 900 minutes indicates that the red trace is able to better anticipate the increased sensitivity to insulin and the resulting lowering of BG than the Kalman filter output shown in green because the red trace is encoded with historical information, resulting in a more aggressive and earlier onset attenuation (seen through the comparison of the red and green traces in the bottom plot of Figure 4). As expected, both the red and green traces improve upon the ability of the CGM (shown in blue) to anticipate the lowering in BG and subsequent attenuation of the insulin delivery rate.

4.2 Population Results

Table 3 presents a collection of the population results for no attenuation, original brakes implementation, and the new historically-informed brakes implementation. Because our goal in the attenuation of insulin delivery rate is prevention of hypoglycemia, our results focus on the ability of the historically-informed brakes algorithm to reduce the incidence of hypoglycemia, particularly when the patient's risk of hypoglycemia is associated with a behavioral disturbance.

For a small increase in the mean BG and % time in the target range, we are able to reduce the incidence of hypoglycemia overall and in particular in our "critical" range from 900 to 1680 minutes by nearly 25% as compared with the original brakes implementation. There is a statistically significant increase in the *minimum* BG over all 100 in silico subjects when the historically informed brakes are employed ($p < .05$). Additionally, we reduce the total number of subjects experiencing hypoglycemia by 10 (from 28 to 18) when the historically-informed brakes are employed.

5 Conclusions

The incorporation of behavioral and metabolic historical information regarding patient behavior in an effort to improve glycemic control is becoming increasingly important as part of the development of personalized insulin delivery control algorithms and insulin delivery safety supervisory systems. In this work, we introduce a method for incorporating historical glucose measurement data into an assessment of a patient's risk of hypoglycemia in real-time. This risk assessment informs the gradual and automatic attenuation of the insulin delivery rate designed to prevent or mitigate hypoglycemia. Results indicate that historical CGM data can improve the performance of the hypo-glycemia prevention method over the use of real-time data alone.

Acknowledgments

Authors would like to acknowledge the insight of Dr. Goufen Yan, University of Virginia Biostatistics Assistant Professor, and the comments provided by UVA Postdoctoral Fellow Sandip Kulkarni.

References

1. Cryer PE. Hypoglycemia: The limiting factor in the management of IDDM. Diabetes. 1994; 43:1378–1389. [PubMed: 7926315]
2. Dalla Man C, Breton MD, Cobelli C. Physical activity into the meal glucose-insulin model of type 1 diabetes: *in-silico* studies. J Diabetes Sci Technol. 2009; 3(1):56–67. [PubMed: 20046650]
3. Hovorka R, Canonico V, Chassin LJ, Haueter U, Massi-Benedetti M, Federici MO, Pieber TR, Schaller HC, Schaupp L, Vering T. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. Physiological Measurement. 2004; 25:905–920. [PubMed: 15382830]
4. Lin J, Lee D, Chase JG, Shaw GM, Le Compte A, Lotz T, Wong J, Lonergan T, Hann CE. Stochastic modelling of insulin sensitivity and adaptive glycemic control for critical care. Computer Methods and Programs in Biomedicine. 2008; 89:141–152. [PubMed: 17544541]
5. Palerm C, Zisser H, Jovanovic L, Doyle FJ III. A run-to-run control strategy to adjust basal insulin infusion rates in type 1 diabetes. J Process Control. 2008; 18:258–265. [PubMed: 18709180]
6. Lehmann ED, Deusch T, Carson ER, Sonksen PH. AIDA: an interactive diabetes advisor. Computer Methods and Programs in Biomedicine. 1994; 41:183–203. [PubMed: 8187465]
7. Kemmer FW. Prevention of hypoglycemia during exercise in type I diabetes. Diabetes Care. 1992; 15:1732–1735. [PubMed: 1468309]
8. Hughes CS, Patek SD, Breton M, Kovatchev BP. Hypoglycemia Prevention via Pump Attenuation and Red-Yellow-Green "Traffic" Lights using CGM and Insulin Pump Data. Journal of Diabetes Science and Technology. 2010; 4:1146–1155. [PubMed: 20920434]

9. Kovatchev B, Cox D, Gonder-Frederick L, Clarke W. Symmetrization of the blood glucose measurement scale and it's applications. Diabetes Care. 1997; 20:1655–1658. [PubMed: 9353603]

10. Hirsch IB, Armstrong D, Bergenstal RM, Buckingham B, Childs BP, Clarke WL, Peters A, Wolpert H. Clinical Application of Emerging Sensor Technologies in Diabetes Management: Consensus Guidelines for Continuous Glucose Monitoring (CGM). Diabetes Technology and Therapeutics. 2008; 10:232–246. [PubMed: 18699743]

11. Cameron F, Niemeyer G, Gundy-Burlet K, Buckingham B. Statistical hypoglycemia prediction. J Diabetes Sci Technol. 2008; 2:612–621. [PubMed: 19885237]

12. Sparacino G, Zanderigo F, Corazza S, Maran A, Facchinetti A, Cobelli C. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. IEEE Trans Biomed Eng. 2007; 54:931–937. [PubMed: 17518291]

13. Palerm C, Willis JP, Desemone J, Bequette BW. Hypoglycemia prediction and detection using optimal estimation. Diabetes Technol Ther. 2005; 7:3–14. [PubMed: 15738700]

14. Choleau C, Dokladal P, Klein JC, Ward KW, Wilson GS, Reach G. Prevention of hypoglycemia using risk assessment with a continuous glucose monitoring system. Diabetes. 2002; 51:3262–3273.

15. Bequette BW. A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. Diabetes Technology and Theraputics. 2005; 7:28–47.

16. A. D. A Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005; 28:1245–1249. [PubMed: 15855602]

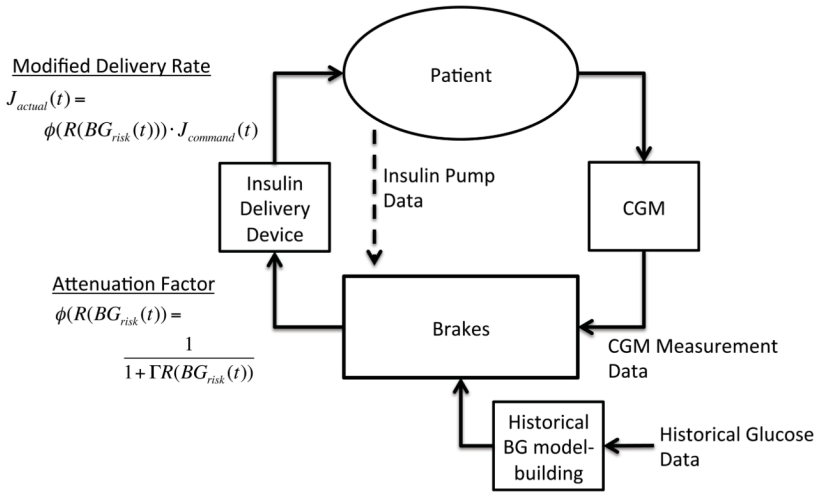

Fig. 1.
Schematic of the Historically-Informed Brakes

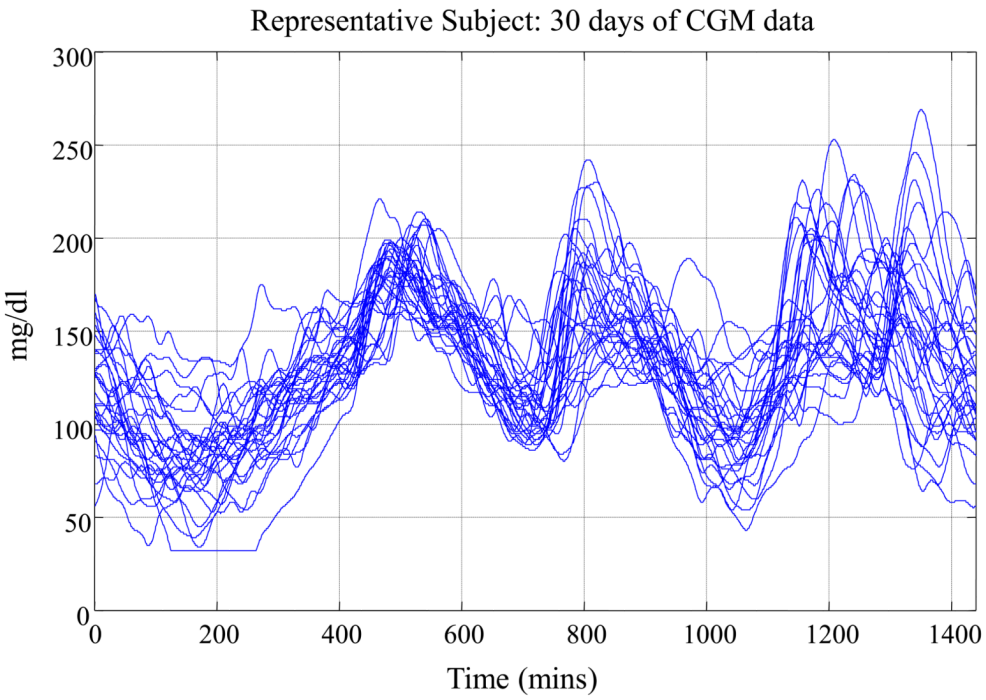

Fig. 2.
Representative Subject Collected CGM Historical Data

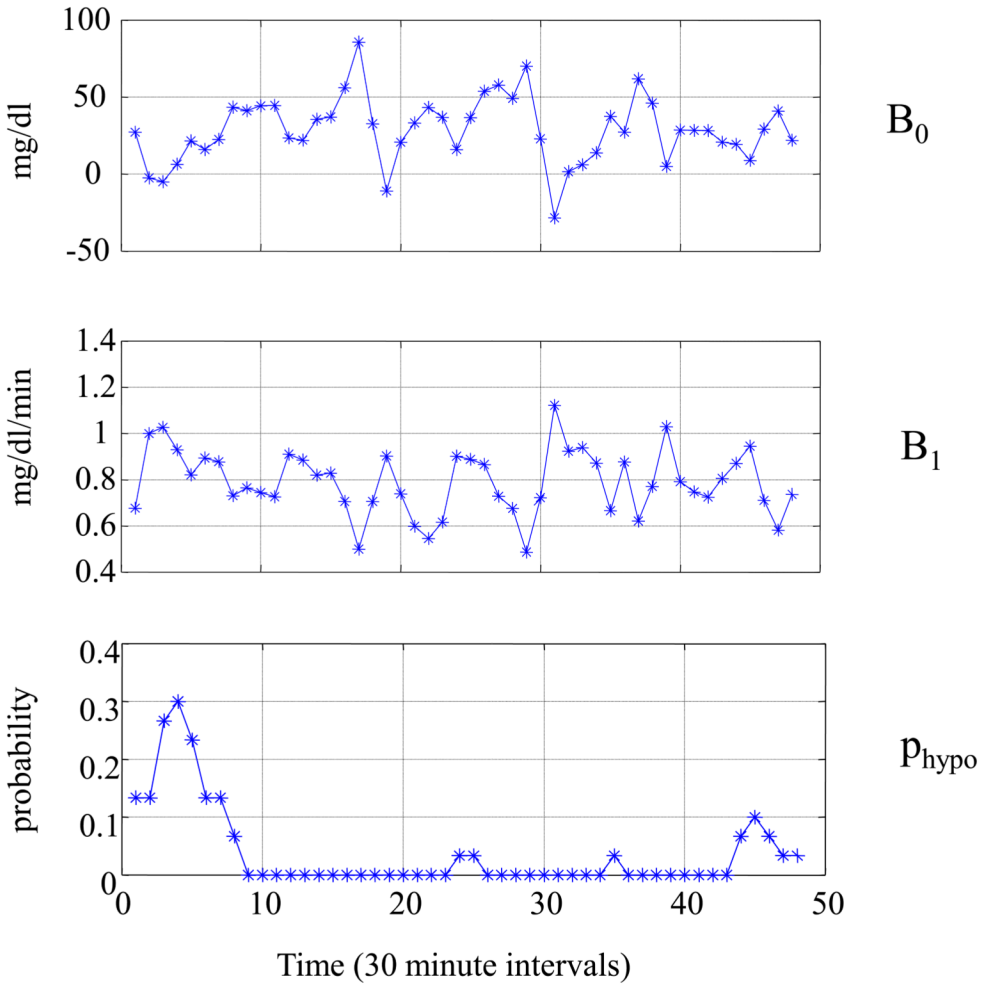

Fig. 3.
Representative Subject Historical Model Parameters; Top: β_0, Middle: β_1, Bottom: p_{hypo}

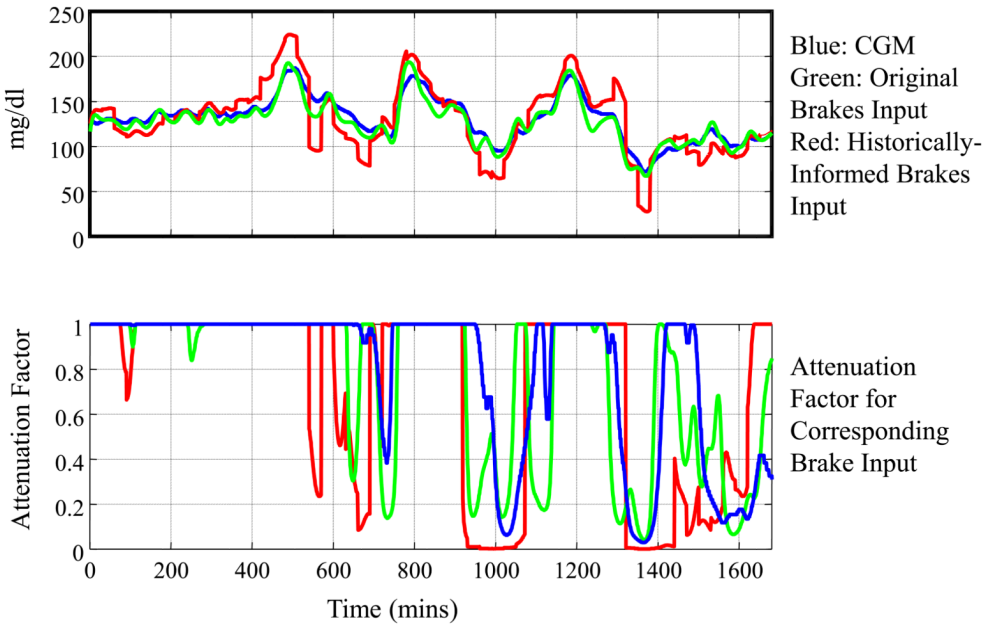

Fig. 4.

Top: Blue: CGM, Green: BG_{risk} from Original Brakes Implementation, Red: BG_{risk} from Historically-Informed Model; Bottom: Corresponding Attenuation Factor $\varphi(R(BG_{risk}(t)))$

Table 1

Behavioral Assumptions for Historical Data Collection

Behavioral Profile	Meal 1	Meal 2	Snack 1	Meal 3	Snack 2
Expected meal size (g CHO)	60	70	20	85	35
Std. dev. of meal size (min.)	15	30	5	20	10
Earliest mealtime (min.)	400	600	1020	1080	1260
Most likely mealtime (min)	420	720	1050	1140	1320
Latest mealtime (min)	600	900	1080	1260	1440
Std. dev. of mealtime	30	20	15	90	40

Comput Methods Programs Biomed. Author manuscript; available in PMC 2014 February 01.

Table 2

Statistics for Linear Model Assumption in Historical In Silico CGM Data

Statistic (mean, std)	
R^2	.60 (.09)
p-value	.05 (.06)
Prop. of p-value below .05	.98 (.02)

Table 3

In Silico Population Results: median (IQR, [90% CI])

Results	No Brakes	Original Brakes	New Brakes
% time in target	73.7(22.0,[61.8,100])	99.9(6.9,[87.9,100])	100(6.5, [88.1,100])
Mean BG (mg/dl)	107.8(14.1,[94.6,120.7])	127.2(6.3,[121.8,133.2])	128.8(7.7,[121.8,137.3])
Minimum BG (mg/dl)	40.3(38.6,[7.7,76.2])	78.5(18.2,[58.4,94.9])	80.3(16.2,[62.2,94.0])
# of subjects experiencing hypo	84	28	18
Severity of hypo event (mg/dl)	33.3 (30.8,[6.2,60.3])	61.0 (9.1,[46.5,67.9])	61.2(12.3,[49.3,68.1])
Time spent in hypo (min)	408.0(350.5,[0,624.5])	0(18.5,[0,75])	0(0,[0,63])