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SYMPOSIUM

A Novel Adaptive Basal Therapy Based on the Value and Rate of Change of Blood Glucose

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Abstract

Background:
Modern insulin pump therapy for type 1 diabetes mellitus offers the freedom to program several basal profiles that may accommodate diurnal variability in insulin sensitivity and activity level. However, these basal profiles do not change even if a pending hypoglycemic or hyperglycemic event is foreseen. New insulin pumps could receive a direct feed of glucose values from a continuous glucose monitoring (CGM) system and could enable dynamic basal adaptation to improve glycemic control.

Method:
The proposed method is a two-step procedure. After the design of an initial basal profile, an adaptation of the basal rate is suggested as a gain multiplier based on the current CGM glucose value and its rate of change (ROC). Taking the glucose value and its ROC as axes, a two-dimensional plane is divided into a nine-zone mosaic, where each zone is given a predefined basal multiplier; for example, a basal multiplier of zero indicates a recommendation to shut off the pump.

Results:
The proposed therapy was evaluated on 20 *in silico* subjects (ten adults and ten adolescents) in the Food and Drug Administration-approved UVa/Padova simulator. Compared with conventional basal therapy, the proposed basal adjustment improved the percentage of glucose levels that stayed in the range of 60–180 mg/dl for all 20 subjects. In addition, the adaptive basal therapy reduced the average blood glucose index values.

Conclusions:
The proposed therapy provides the flexibility to account for insulin sensitivity variations that may result from stress and/or physical activities. Because of its simplicity, the proposed method could be embedded in a chip in a future artificial pancreatic β cell or used in a "smart" insulin pump.

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Abbreviations: (BG) blood glucose, (BGI) blood glucose index, (CGM) continuous glucose monitoring, (FDA) Food and Drug Administration, (ROC) rate of change, (TDD) total daily dose, (T1DM) type 1 diabetes mellitus

Keywords: adaptive basal therapy, artificial pancreatic β cell, glucose prediction, type 1 diabetes mellitus, UVa/Padova simulator

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Introduction

In conventional insulin pump therapy for type 1 diabetes mellitus (T1DM), basal insulin is administered to keep glycemia in the normal range for fasting conditions and bolus insulin is administered to correct for hyperglycemia and to compensate for the influence of meals. Generally, the bolus insulin calculation is based on the subject's insulin-to-carbohydrate ratio, correction factor, and insulin on board.[1,2] There are several steps to determine the basal insulin rate.[3,4] The first step is to determine the total daily dose (TDD):

$$TDD = K \times W, \quad (1)$$

where W is the subject's mass and K is a subject-specific constant. If the units of W are in kilograms, the range of K is typically 0.5 to 2.0 U/kg. The basal insulin requirement is approximately 50% of TDD, so the basic basal rate (U/h) should be

$$B = 0.5 \times TDD/24. \quad (2)$$

Insulin sensitivity changes throughout the day due to circadian variation of hormone levels. During a single 24 h cycle, basal insulin requirements are relatively high during the early morning, decreasing during the daytime, and further declining in the middle of the night. Relative a nominal basal rate from 10:00 AM to midnight, the basal rate would be 50% less between midnight and 4:00 AM and 50% more in the early morning between 4:00 AM and 10:00 AM. **Figure 1** shows insulin delivery with basal–bolus therapy; a 24 h period is divided into three segments corresponding to the main trends in insulin sensitivity. The transition times are flexible and could be subject dependent.

In conventional basal therapy, the basal rate is fixed in each segment. Since 2005, continuous glucose monitoring (CGM) technology has improved significantly, and the reliable duration of *in vivo* sensors continue to increase.[5,6] Frequent CGM measurements provide the possibility of predicting hypoglycemic and hyperglycemic events and suggesting corrective actions.

Using a linear prediction scheme, the glycemia can be predicted as a function of the current glucose concentration and its rate of change (ROC). Furthermore, a new basal rate is suggested using the predicted glucose concentration: if a hyperglycemic event is predicted, the basal rate could be increased, and if a hypoglycemia event is predicted, the basal rate could be decreased. Therefore, an adaptive basal therapy based on the glucose value and its ROC is suggested in this paper. Taking glucose and its ROC as the axes, a two-dimensional plane is divided into nine zones and a corresponding basal multiplier is associated with each zone. For example, a zero multiplier indicates a recommendation to suspend insulin delivery, and a multiplier of two corresponds to doubling the basal rate.

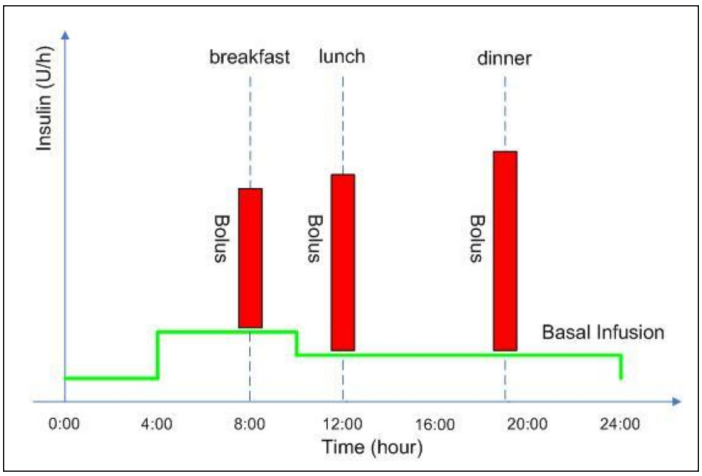

Figure 1. Schematic illustration of basal–bolus therapy. The green line denotes the basal insulin rate during the day, and the three red bars denote boluses for breakfast, lunch, and dinner, respectively.

The adaptive basal therapy is a two-step method. An initial basal profile is designed by using existing methods. Based on current CGM reading and its ROC, the basal rate is adapted using a gain multiplier. For simplicity and robustness, the basal rate is adjusted every 30 min, so it can be managed automatically or manually.

The simplicity of the proposed approach is advantageous for rapid implementation because it does not require a subject model, unlike some closed-loop control algorithms. As a rule-based methodology, the adaptive basal therapy has some similarities with the fuzzy logic methodology.[7] However, unlike the fuzzy logic methodology, membership functions are not used in the proposed therapy, so the adaptive basal therapy is simpler to implement and easier to understand. The proposed method is evaluated on 20 *in silico* subjects in the Food and Drug Administration (FDA)-approved UVa/Padova simulator.[8] The results indicate that the basal adaptation can improve the control performance for all subjects. Using advisory mode evaluation,[9] the proposed method is further tested on retrospective clinical data from subjects with T1DM.

Adaptive Basal Therapy

Basal Gain Mosaic

According to the Diabetes Control and Complications Trial Research Group,[10] *hyperglycemia* is defined as postprandial blood glucose (BG) concentration greater than 180 mg/dl. The hypoglycemia definition varies according to the research context and the subject's symptoms. In this work, a value of 60 mg/dl is selected as the threshold, and deviations below this value are termed *significant hypoglycemia*. Accordingly, BG concentrations between 60 and 180 mg/dl are considered to be within the *safe range* for T1DM in this paper. The objective of updating the basal rate is to keep glucose concentration within the safe range.

If the BG concentration at step k, $G(k)$, and its ROC, $G'(k)$, are known, the simplest prediction for glucose at step $k + l$, where l denotes the number of prediction steps, is as follows:

$$\hat{G}(k+l) = G(k) + G'(k) \times l \times \Delta t, \quad (3)$$

where Δt is the sample time. Therefore, the current glucose value and its ROC can be used to modify the basal rate to achieve tighter glycemic control. Hence the basal rate can be described as a function of the value and ROC of BG.

The frequency of changes to the basal rate is governed by two factors: (1) convenience to the user and (2) consideration of delayed insulin action. The latter aspect addresses the fact that insulin Lispro achieves peak levels 30 to 90 min after administration.[11] If the frequency of changes to the basal rate is too slow, the improvement will be ineffective. The basal rate will be updated every 30 min to balance these two factors.

The main idea of this work is illustrated in **Figure 2**, which shows the *basal gain mosaic*. The mosaic consists of nine zones (A–I), and five predefined gains are presented for the insulin basal rate multiplier. The key scenarios for choosing the basal gains are as follows:

- Case 1: if BG is in the hypoglycemic range (e.g., BG = 50 mg/dl) or BG is normal with a significant negative ROC (e.g., BG = 100 mg/dl and ROC = -2 mg/[dl·min]), then the basal gain multiplier should be chosen as zero, which indicates a recommendation to suspend insulin delivery, i.e., zone A.
- Case 2: if BG is normal and ROC has a small absolute value, i.e., zone E (e.g., BG = 110 mg/dl and ROC = 0.5 mg/[dl·min]), or BG is a little low but ROC is very positive, i.e., zone B (e.g., BG = 70 mg/dl and ROC = 2 mg/[dl·min]), or BG is a little high but ROC is very negative, i.e., zone I (e.g., BG = 150 mg/dl and ROC = -2 mg/[dl·min]), the basal gain multiplier is recommended to be unity; in other words, the nominal basal rate is used.
- Case 3: if BG is greater than 140 mg/dl with positive ROC (e.g., BG = 150 mg/dl and ROC = 0.5 mg/[dl·min]) or BG is normal with significant positive ROC (e.g., BG = 100 mg/dl and ROC = 2 mg/[dl·min]), a multiplier of two is given to the basal rate in order to compensate for the existing or anticipated hyperglycemia, i.e., zone F.

Two additional basal gain multipliers are introduced as intermediate cases: 0.5 in zones C and H and 1.5 in zones D and G.

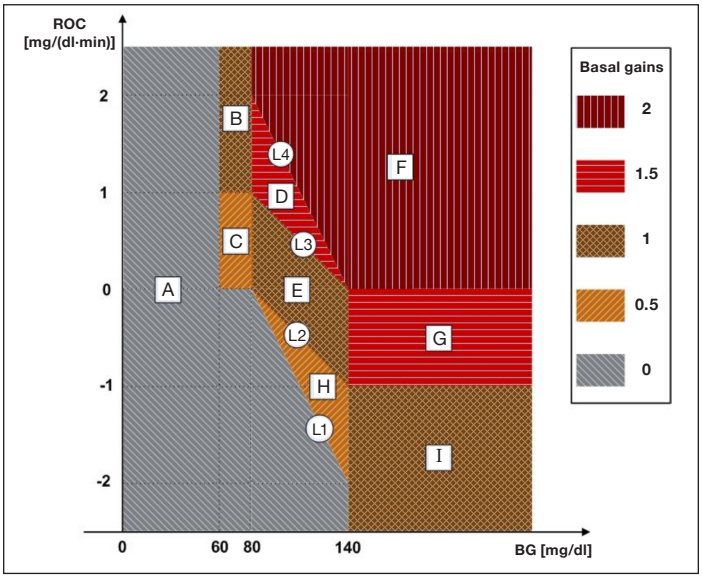

Figure 2. Basal gain mosaic. The two-dimensional plane is divided into nine zones, A–I. The different colors denote five predefined gains for the basal rate: 0, 0.5, 1, 1.5, and 2.

The divisions for BG and ROC are now described. Continuous glucose monitoring sensors are prone to measurement noise and drift; for example, the numerical errors of the DexCom STS (DexCom, San Diego, CA) sensor are approximately 30%.[12] To improve the robustness of the proposed method in the presence of measurement noise, the hypoglycemia threshold for the BG is chosen as 80 mg/dl. The actual BG for a CGM value of 80 mg/dl might be as low as 56 mg/dl; therefore, CGM readings larger than 80 mg/dl indicate the real BG concentrations are approximately above the hypoglycemia threshold (60 mg/dl). On the other hand,

120 and 180 mg/dl are considered the hyperglycemia thresholds under fasting and postprandial conditions, respectively.[10] Therefore, a moderate value, 140 mg/dl, is chosen as the hyperglycemia threshold in this work.

The division of ROC depends on the current value of BG. If the glucose value is between 80 and 140 mg/dl, the time when the glucose curve will cross the threshold from one zone to another is estimated using **Equation (3)**. The time when the glucose curve crosses the lower threshold is called the *lower cross time*, and the time when the glucose curve crosses the upper threshold is called the *upper cross time*. For example, if BG = 110 mg/dl and ROC = -1 mg/(dl·min), the estimated lower cross time is 30 min. A lower cross time less than 30 min indicates a significant negative ROC. If both the lower cross time and the upper cross time are longer than 60 min, then it is deemed that ROC has small absolute value. The upper cross time less than 30 min indicates a significant positive ROC. Therefore, two lines can be obtained for the lower cross time:

L1: BG + 30 × ROC = 80,

L2: BG + 60 × ROC = 80.

On line L1, the lower cross time is 30 min, and on line L2, the lower cross time is 60 min. Similarly, another two lines are obtained for the upper cross time:

L3: BG + 30 × ROC = 140,

L4: BG + 60 × ROC = 140.

The upper cross times are 30 min on line L3 and 60 min on line L4.

Estimating Rate of Change

To use the basal gain mosaic, the value of the ROC should first be estimated. The simplest way to do this at step k is as follows:

$$G'(k) = \frac{G(k) - G(k-1)}{T}, \tag{4}$$

where $T > 0$ is the sample time and is set to be 5 min in this work, in accordance with the DexCom STS.[12] However, the preceding scheme is very sensitive to measurement noise. To improve the robustness, a three-point (current and two previous samples) backward difference was used to estimate ROC in the literature.[13] Because the basal rate is updated every 30 min and the sample time is 5 min, there are six new samples available for estimation of the ROC; therefore, a weighted average scheme is used in this work. Thus

$$G'(k,\lambda) = \frac{\sum_{i=0}^{4}\lambda^i\left[G(k-i) - G(k-i-1)\right]}{T\sum_{i=0}^{4}\lambda^i}$$

$$= \frac{G(k) - \sum_{i=0}^{3}\lambda^i(1-\lambda)G(k-i-1) - \lambda^4 G(k-5)}{T(1-\lambda^5)/(1-\lambda)}, \tag{5}$$

where $0 \le \lambda < 1$ is the *forgetting factor*.[14] The forgetting factor is used to balance the contributions of current data and historical data. If the forgetting factor is zero, only the current data are used; if the forgetting factor is unity, the current data and historical data are given the same weight. In general, a larger forgetting factor indicates increased robustness to measurement noise but a decrease in accuracy for estimating the real-time ROC. **Equation (5)** reduces to **Equation (4)** if $\lambda = 0$. Hence the estimation of ROC can be considered a function of λ. Furthermore, the prediction of the glucose measurement 30 min later can be expressed as

$$\hat{G}(k+6) = G(k) + 30G'(k,\lambda). \tag{6}$$

This prediction scheme is linear. The optimal λ is defined as

$$\lambda^* = \arg_\lambda \min \sum_{k=1}^{N}\left[\hat{G}(k+6) - G(k+6)\right]^2. \tag{7}$$

Note that λ^* is related to the sensor type and the subject; even for the same sensor and subject, λ^* may vary from day to day. The following results demonstrate that even a fixed, nonoptimal λ can improve the control performance, validating the robustness of the proposed method.

Summary of Adaptive Basal Therapy

The procedure to implement the proposed scheme is summarized in the following algorithm:

Algorithm (flowchart of adaptive basal therapy)

1. Initialization: determine the optimal basal rate using standard methods.
2. Use the available glucose measurement to get λ^* based on **Equation (7)**.
3. Using λ^* and **Equation (5)**, calculate the estimation of ROC every 30 min.
4. Based on BG and its ROC, get the corresponding multiplier from the basal gain mosaic and then get the new basal rate for the next 30 min duration.
5. After 30 min, go to step 3 and repeat.

In step 2, λ^* is determined by solving the optimization problem in **Equation (7)**; λ^* is fixed at 0.5 in this work for simplicity.

In Silico Evaluation

The proposed therapy was tested on 10 adult subjects, adults 1–10, and ten adolescent subjects, adolescents 1–10, in the FDA-approved UVa/Padova diabetes simulator. Because a virtual CGM sensor was included in the UVa/Padova simulator to approximate the real measurement noise, there are two sets of values for glucose: CGM readings and BG concentrations. Only CGM reading is available for control design, while the BG value is used to evaluate the designed controller in this work. All these subjects followed a protocol of three meals: 40 g of carbohydrates at 7:00 AM, 75 g at noon, and 60 g at 6:00 PM. A matching insulin bolus and an optimal basal rate were provided in the simulator for each *in silico* subject; this therapy is called the *fixed basal therapy*, where the bolus is based on perfect meal size estimation and the basal is optimized for each *in silico* subject. If the same bolus is dosed and the basal rate is updated based on the basal gain mosaic, this therapy is called the *adaptive basal therapy*. The control performances for fixed and adaptive basal therapies are compared in this section.

Optimal Forgetting Factor

The fixed basal therapy was implemented on each subject for one day, and the CGM data were used to calculate the optimal forgetting factor for each subject based on **Equation (7)**. The optimization problem in **Equation (7)** was solved with the command "fminbnd" in MATLAB® (The MathWorks Inc., Natick, MA). The optimal forgetting factors for 20 subjects are given in **Table 1**. The best way to use the adaptive basal therapy is to find the optimal forgetting factor for the corresponding subject. However, to simplify the design procedure and validate the robustness of the proposed scheme, a median value of $\lambda = 0.5$ is used for all subjects.

From **Table 1**, the optimal forgetting factor for adolescent 4 is 0.51, and that for adult 1 is 0. The prediction results for these subjects are given in **Figure 3** for performance evaluation. For instance, the prediction for 60 min is based on the CGM values from 0 to 30 min. It is evident that the prediction is not good even though the optimal forgetting factor is used. There are two possible reasons for the bad performance:

- Due to measurement noise, the CGM value is far from the BG value.
- The linear prediction scheme is too simple to describe the actual glucose trend.

The control results as shown demonstrate that the adaptive basal improved the control performance even though a simple prediction scheme was utilized.

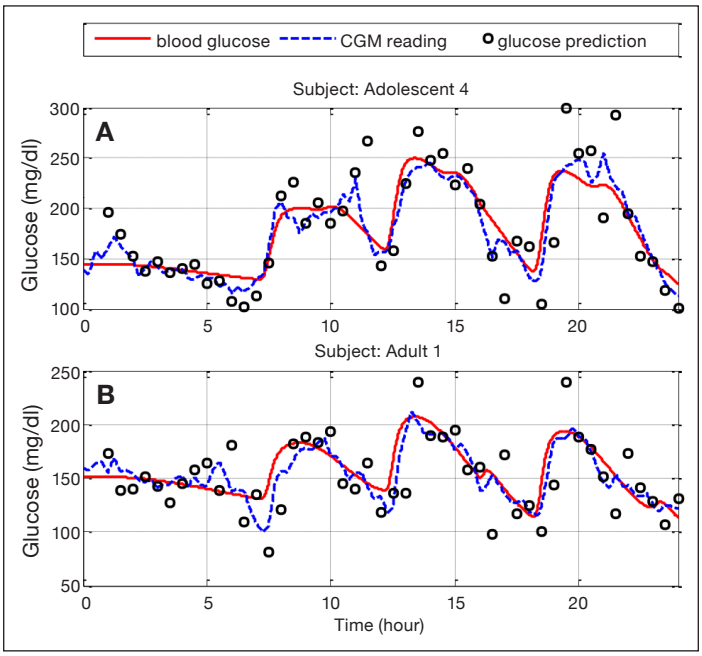

Figure 3. Glucose prediction results. The solid curve is the BG concentration. The dashed curve is the CGM reading. The circle denotes the prediction (every 30 min) of glucose based on CGM for **A** adolescent 4 and **B** adult 1. Both subjects consumed fived meals, of which the size and timing are 45, 70, 5, 80, and 5 g and 7:00 AM, 12:00 PM, 4:00 PM, 6:00 PM, and 11:00 PM, respectively.

Table 1.
Optimal Forgetting Factors for Different Subjects

Adults	1	2	3	4	5	6	7	8	9	10	Mean	Standard deviation
λ^*	0.00	0.64	0.61	0.78	0.63	0.79	0.35	0.60	0.78	0.62	0.58	0.24
Adolescents	1	2	3	4	5	6	7	8	9	10	Mean	Standard deviation
λ^*	0.00	0.49	0.29	0.51	0.40	0.51	0.43	0.00	0.65	0.00	0.33	0.24

In Silico Evaluation

The control performances under fixed and adaptive basal therapies are compared in **Table 2**. In terms of time percentage within the safe range, the adaptive basal therapy improved the control performance in 90% of the cases for adults and in 100% of the cases for adolescents. The average percentages in the safe range for all adults are 86.7% under the fixed basal therapy and 95.1% under the adaptive basal therapy. Correspondingly, the percentages for adolescents are 63.6% and 76.1%, respectively. In both age groups, the adaptive basal improved the control performance.

To evaluate the risk level of glucose concentration, indices from the literature[15] are employed. For a given glucose concentration value G in units of mg/dl, these risk indices are defined as

$$U(G) \triangleq 1.509 \times \left\{ \left[\log(G) \right]^{1.084} - 5.381 \right\}$$

$$HR \triangleq \begin{cases} 0, & \text{if } G < 112.5 \text{mg/dl} \\ 10 \times U(G)^2, & \text{else} \end{cases}, \quad (8)$$

$$LR \triangleq \begin{cases} 0, & \text{if } G > 112.5 \text{mg/dl} \\ 10 \times U(G)^2, & \text{else} \end{cases}$$

Table 2.
Control Performance Comparison between Fixed and Adaptive Basal Therapies for 20 Subjects [a]

Subjects		Fixed basal therapy				Adaptive basal therapy			
		Hypo-percent	Safe percent	Hyper-percent	BGI	Hypo-percent	Safe percent	Hyper-percent	BGI
Adults	1	0.0%	90.1%	9.9%	3.7	0.0%	100%	0.0%	1.5
	2	24.2%	75.8%	0.0%	7.7	4.4%	95.6%	0.0%	2.6
	3	0.0%	81.0%	19.0%	4.0	0.0%	93.1%	6.9%	2.6
	4	0.0%	100%	0.0%	1.4	0.1%	100%	0.0%	1.8
	5	0.0%	88.0%	12.0%	3.2	0.0%	93.6%	6.4%	2.2
	6	0.0%	85.5%	14.5%	4.7	0.0%	100%	0.0%	1.5
	7	0.0%	96.5%	3.5%	1.4	0.0%	100%	0.0%	1.1
	8	2.7%	97.3%	0.0%	2.8	0.0%	100%	0.0%	1.2
	9	0.0%	100%	0.0%	0.7	0.0%	100%	0.0%	1.1
	10	0.0%	94.4%	5.6%	2.4	0.0%	100%	0.0%	1.3
	Mean	2.69%	90.9%	6.5%	3.2	0.5%	98.2%	1.3%	1.7
	Standard deviation	0.076	0.082	0.070	2.03	0.014	0.029	0.028	0.59
Adolescents	1	0.0%	93.7%	6.3%	1.6	0.0%	94.9%	5.1%	1.1
	2	0.0%	75.0%	25.0%	5.4	0.0%	91.5%	8.5%	2.7
	3	0.0%	86.2%	13.8%	3.0	0.0%	88.1%	11.9%	2.4
	4	0.0%	55.6%	44.4%	7.5	0.0%	86.8%	13.2%	4.0
	5	0.0%	78.9%	21.1%	5.0	0.0%	93.0%	7.0%	2.2
	6	0.0%	51.8%	48.2%	9.5	0.0%	71.2%	28.8%	5.5
	7	0.0%	60.8%	39.2%	7.6	0.0%	72.5%	27.5%	4.6
	8	0.0%	73.4%	26.6%	5.0	0.0%	78.4%	21.6%	4.0
	9	0.0%	51.7%	48.3%	8.8	0.0%	92.6%	7.4%	3.3
	10	0.0%	70.8%	29.2%	5.6	0.0%	75.6%	24.4%	4.1
	Mean	0.0%	69.8%	30.2%	5.9	0.0%	84.5%	15.5%	3.4
	Standard deviation	0	0.145	0.145	2.49	0	0.091	0.091	1.30

[a] Hypo-percent, hyper-percent, and safe percent denote the percentages of time at which glucose level is below 60 mg/dl, above 180 mg/dl, and within the range of 60–180 mg/dl, respectively.

where *HR* is the *high blood glucose index* (BGI) and *LR* is the *low BGI*, respectively. Furthermore, *HR* + *LR* is defined as the BGI. Low BGI suggests minor risk of hyperglycemia and hypoglycemia. Given multiple CGM readings, the value of BGI is computed as the means of all BGI. In terms of a smaller BGI, the adaptive basal therapy improved the control performance in 90% of the cases for adults and in 100% of the cases for adolescents. The average BGI values for adults were 3.2 under the fixed basal therapy and 1.7 under the adaptive basal therapy; these values for adolescents were 5.9 and 3.4, respectively. These indices validate that the adaptive basal scheme improved glucose control. Furthermore, the differences between these results are statistically significant with p values less than 0.05.[16] The p values for the time percentage in the safe range and BGI in the adult subjects were 0.0160 and 0.0361. Similarly, the p values in adolescent subjects were 0.0145 and 0.0112.

The glucose levels of adult 2 under both therapies are shown in **Figure 4A**, and the basal gain is displayed in **Figure 4B**. **Figure 4** illustrates how the proposed scheme avoided hypoglycemia. Control results for adolescent 9 are given in **Figure 5** to show how hyperglycemia was avoided.

Magni and coworkers[17] introduced a tool for evaluating the quality of closed-loop glucose control on a group of subjects, termed as control-variability grid analysis. The control-variability grid analysis results for 20 subjects under adaptive and fixed basal therapies are compared in **Figure 6**. Compared to the fixed basal therapy, the adaptive basal therapy increases the percentage in A zone and decreases the percentage in C zone, which indicates better performance.

To further evaluate the robustness of the proposed algorithm, we consider a practical scenario where meal size was poorly estimated by the subject. This will result with either over- or under-size insulin bolus. Both the adult average subject and the adolescent average subject in the UVa/Padova simulator were compared under fixed and adaptive basal therapies, respectively. As shown in **Table 3**, the adaptive basal therapy is superior to the fixed basal one in all cases.

Clinical Advisory Mode Evaluation

After the simulation study and before implementation of the proposed method in clinic, it is desirable to evaluate the algorithm on retrospective clinical data. Hence advisory mode evaluation, or advisory mode control,[9,18]

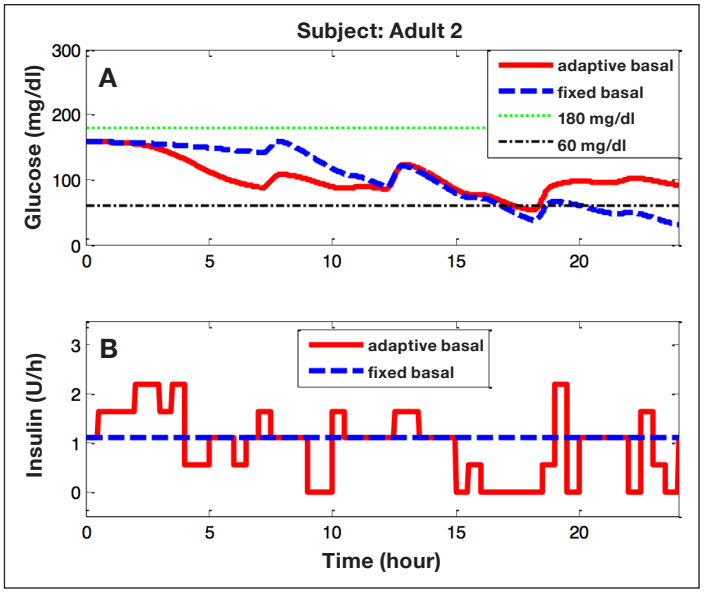

Figure 4. Control results for adult 2, where a comparison of glucose response under two therapies is presented in **A** and a comparison of basal insulin is in **B**. As can be seen, adaptive basal therapy successfully prevented severe hypoglycemia.

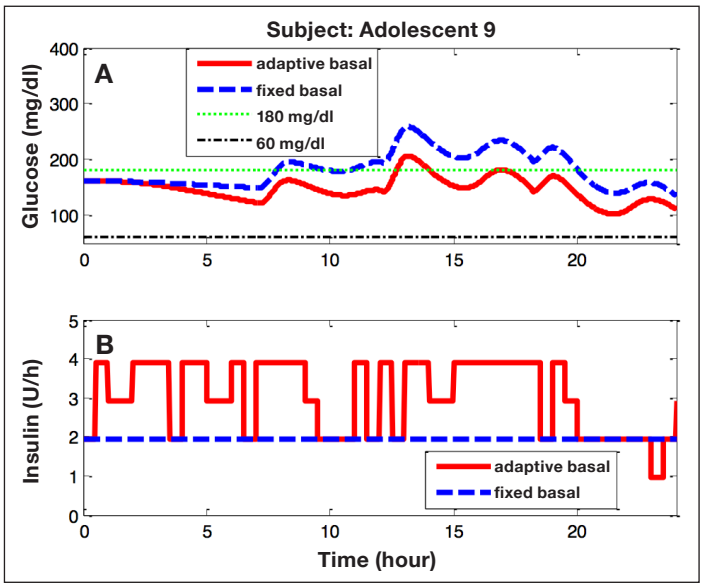

Figure 5. Control results for adolescent 9, where a comparison of glucose response under two therapies is presented in **A** and a comparison of basal insulin is in **B**. As can be seen, adaptive basal therapy successfully prevented most hyperglycemia.

is used to ascertain whether the adaptive basal scheme makes reasonable suggestions for basal gains.

The block diagrams of the adaptive basal therapy and the advisory mode control are presented in **Figure 7**. Unlike in adaptive basal therapy, in the advisory mode control, the components in the dashed frame are

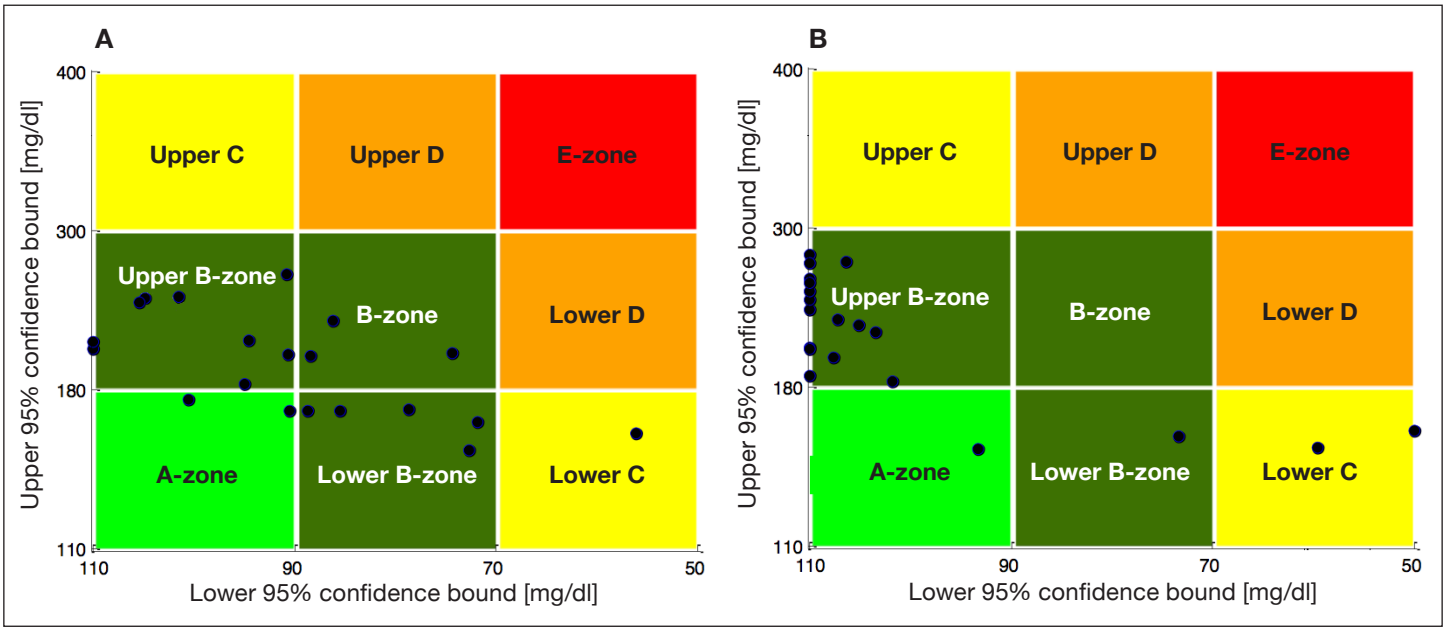

Figure 6. Control-variability grid analysis results for 20 subjects: **A** adaptive basal therapy, with 10% in zone A, 85% in zone B, and 5% in zone C and **B** fixed basal therapy, with 5% in zone A, 85% in zone B, and 10% in zone C.

Table 3.
Robustness of the Proposed Algorithm to Mismatched Boluses [a]

Bolus mode	Adult average subject				Adolescent average subject			
	Fixed basal		Adaptive basal		Fixed basal		Adaptive basal	
	Safe Percent	BGI	Safe Percent	BGI	Safe Percent	BGI	Safe Percent	BGI
Accurate estimated	93.3%	2.4	100%	1.6	65.2%	6.3	75.9%	3.9
Underestimated	77.2%	5.1	96.5%	2.2	51.6%	9.7	65.9%	5.6
Overestimated	98.2%	2.0	98.7%	1.6	76.8%	4.0	84.7%	3.0

[a] For the underestimated case, the real bolus is 0.5 time the accurate one; for the overestimated case, the real bolus is 1.5 time the accurate one. Safe percent denotes the percentages of time at which the glucose level is within the range of 60–180 mg/dl.

not implemented. The real-time CGM measurement information is replaced by the historical clinical data.

Data were collected from two adult subjects with T1DM wearing continuous glucose sensors (DexCom STS, San Diego CA). Five-minute glucose sampling produced 288 measurements per day. The CGM readings in 24 and 12 h periods for two subjects, respectively, were used to evaluate the adaptive basal therapy. Subject 1 is an 83 kg, 173.5 cm male, and subject 2 is a 58 kg, 173 cm male.

The advisory mode evaluation results for subject 1 are shown in **Figure 8**. Control actions in terms of basal gain change start before hypoglycemic and hyperglycemic events occur in most cases. For example, the suggested basal insulin increases at 3:00 PM in advance of a hyperglycemic event. Hyperglycemia can be avoided or at least mitigated using the adaptive basal therapy. Similarly, the advisory mode evaluation results for subject 2 are shown in **Figure 9**. From 7:15 AM, the glucose level decreased. To avoid hypoglycemia, a meal was consumed at 8:04 AM. For the adaptive basal case, the basal insulin was suspended after 7:15 AM; therefore, the need for a correction meal may have been avoided. For both subjects, the total basal insulin amount for each algorithm is similar. Therefore, the proposed therapy could improve closed-loop performance by changing the distribution, not the amount, of basal insulin.

Summary

The simulation study showed that CGM-based basal adaptation can improve control performance of basal therapy. The advisory mode evaluation study with actual

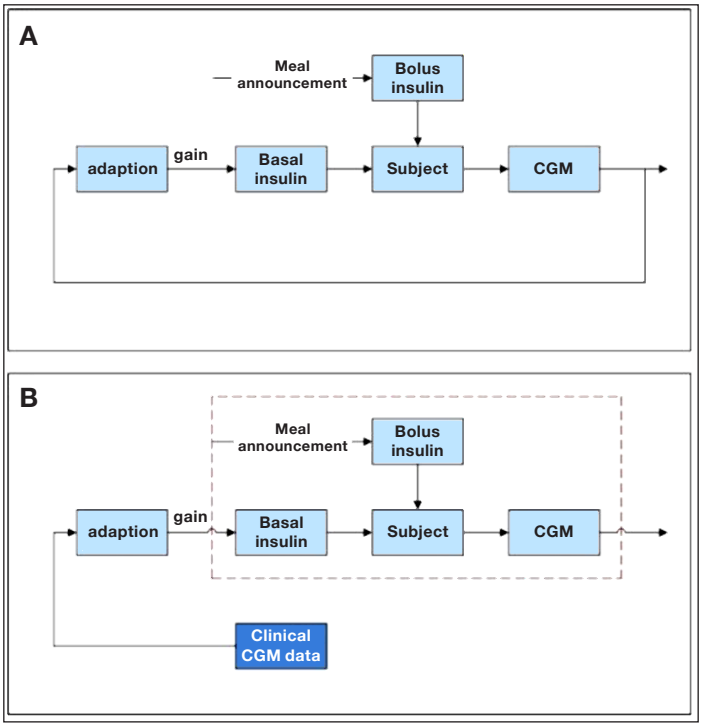

Figure 7. Block diagram of adaptive basal therapy and advisory mode control: **A** adaptive basal therapy and **B** advisory mode control. The components in the dashed frame are not used in the advisory mode control.

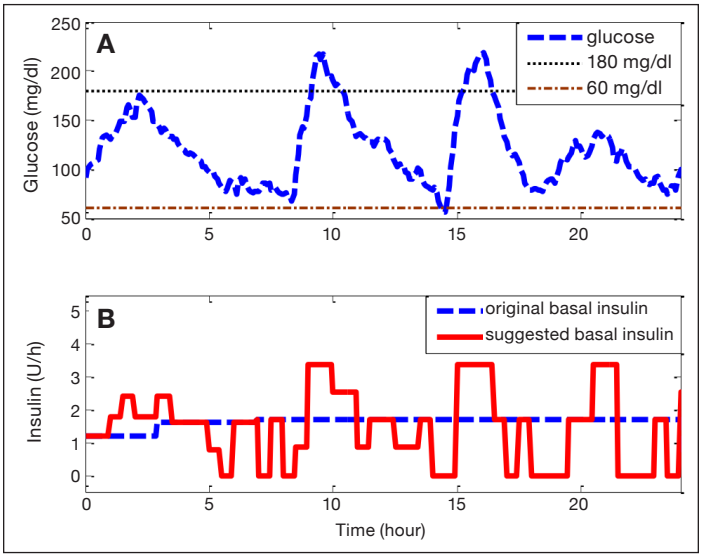

Figure 8. Advisory mode evaluation results for subject 1: **A** CGM values and hyper- and hypoglycemic thresholds and **B** original basal insulin and suggested basal insulin. The total original basal insulin is 39.4 U, and the total suggested basal insulin is 34.6 U. The following meals and matching boluses were given: at 10:12 AM, a meal with 61 g carbohydrates and 10.9 U of bolus insulin were consumed; at 1:02 PM, a meal with 60 g carbohydrates was consumed without bolus; at 3:42 PM, 10 U of bolus was injected; and at 10:21 PM, a meal with 60 g carbohydrates and 6.8 U of bolus were consumed.

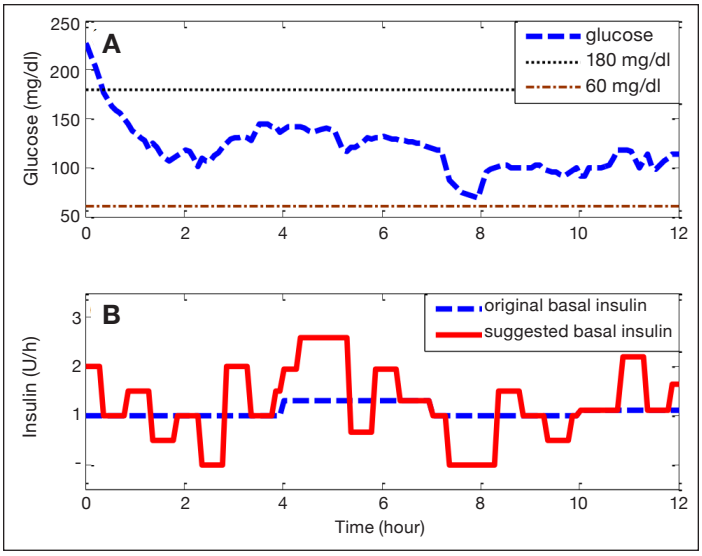

Figure 9. Advisory mode evaluation results for subject 2: **A** CGM values and hyperglycemic and hypoglycemic thresholds and **B** original and suggested insulin delivery rates. The total original basal insulin is 13.2 U, and the total suggested basal insulin is 14.8 U. At 8:04 AM, a breakfast with 52.5 g carbohydrates was consumed and no bolus was injected.

clinical data also showed the feasibility of the proposed method. The adaptive scheme provides the flexibility to account for insulin sensitivity variations due to stress and physical activities.

Because of its simplicity, the adaptive basal therapy could be implemented on microchip in future algorithm-driven insulin pumps. The basal gain mosaic could be used as a guideline for patients and physicians to adjust basal rate. In future studies, this method will be validated *in vivo* for both "normal" days and days with abnormal insulin sensitivities due to stress and/or exercise.

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