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SYMPOSIUM

In Silico Simulation of Long-Term Type 1 Diabetes Glycemic Control Treatment Outcomes

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Abstract

Objectives:
The goals of this study were to develop (1) a safe and effective protocol for the clinical control of type 1 diabetes using conventional self-monitoring blood glucose (SMBG) measurements and multiple daily injections with insulin analogues, and (2) an *in silico* simulation tool of type 1 diabetes to predict long-term glycemic control outcomes of clinical interventions.

Methods:
The virtual patient method was used to develop a simulation tool for type 1 diabetes using data from a type 1 diabetes patient cohort ($n = 40$). The tool was used to test the adaptive protocol (AC) and a conventional intensive insulin therapy (CC) against results from a representative control cohort. Optimal and suboptimal basal insulin replacements were evaluated as a function of SMBG frequency in conjunction with the (AC and CC) prandial control protocols.

Results:
In long-term glycemic control, the AC protocol significantly decreased hemoglobin A1c in conditions of suboptimal basal insulin replacement for SMBG frequencies ≥6/day, and reduced the occurrence of mild and severe hypoglycemia by 86–100% over controls, over all SMBG frequencies in conditions of optimal basal insulin.

continued →

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Abbreviations: (AACE) American Association of Clinical Endocrinologists, (AC) adaptive control, (ADA) American Diabetes Association, (CC) conventional control, (CGM) continuous glucose measurement, (CIR) carbohydrate-to-insulin ratio, (CSII) continuous subcutaneous insulin infusion, (DCCT) Diabetes Control and Complications Trial, (FPG) fasting plasma glucose, (IIT) intensive insulin therapy, (ISF) insulin sensitivity factor, (MBG) mean blood glucose concentration, (MDI) multiple daily injection, (MI) monomeric insulin, (SMBG) self-monitoring blood glucose

Keywords: blood glucose, compartmental models, decision support, diabetes, hyperglycemia, insulin, simulation, subcutaneous injection

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Abstract cont.

Conclusions:
A simulation tool to predict long-term glycemic control outcomes from clinical interventions has been developed to test a novel, adaptive control protocol for type 1 diabetes. The protocol is effective *and* safe compared to conventional intensive insulin therapy and controls. As fear of hypoglycemia is a large psychological barrier to glycemic control, the AC protocol may represent the next evolution of intensive insulin therapy to deliver increased glycemic control with increased safety. Further clinical or experimental validation is needed to fully prove the concept.

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Introduction

The control of type 1 diabetes is a widely studied and experimented research field. Previously published control methods are diverse, using different routes of insulin administration and glucose measurement. Since the 1970s, the closed loop artificial endocrine pancreas has been heralded as the solution (as reviewed in Bequette[1]). While no commercial product currently exists, the systems in current clinical use that are likely to constitute the components of an extracorporeal artificial pancreas are the continuous subcutaneous insulin infusion (CSII) pump and a continuous glucose measurement (CGM) device. Advanced control algorithms and methods to "close the loop" have also been widely studied (as reviewed elsewhere[2–4]), despite early and ongoing limitations in sensors and pumps. Currently, the use of open-loop CGM and/or CSII has resulted, in at best, a modest *clinical* advantage over conventional methods of insulin administration or multiple daily injection (MDI) (as reviewed elsewhere[5,6]). Additionally, these systems are only used by a small proportion of type 1 diabetes patients because of high upfront costs, costs of consumables, complexity, and the extensive health care infrastructure and support required. The prevalence of CSII use is as low as 2% of the type 1 diabetes population in the United Kingdom and up to 15–20% elsewhere and in the United States.[7]

Hence, there is a more practical and urgent need to address the large majority of the type 1 diabetes population using conventional glucose measurement, i.e., self-monitoring blood glucose (SMBG), and insulin administration, i.e., MDI methods, and for whom current conventional and/or intensive therapies are failing to deliver recommended levels of glycemic control.[8] In the United States, over 50% of diagnosed diabetics aged 20–64 are deemed "out of control.[9]" The higher accuracy of bedside capillary blood glucose meters[10,11] and the latest insulin analogues for MDI therapy,[12] coupled with better control methods, have the potential to provide better care to the majority of outpatient or ambulatory type 1 diabetics than currently observed. Such techniques must necessarily be simple to implement to ensure broad clinical uptake by the diabetes population.

Previously, a system model of the type 1 insulin–glucose regulatory system and its identification on a virtual patient cohort has been performed.[13] This study reports on the development of a simple and practical adaptive method for the control of type 1 diabetes and subsequent *in silico* simulation on a virtual patient cohort using the system model developed previously.

Glucose Measurement, Insulin Type, and Meals

The control protocols developed and tested in this study aim to treat the broad type 1 diabetes population using conventional techniques, e.g., SMBG and MDI therapy. Hence, the control protocols may only receive discrete glucose data at sparse intervals characteristic of SMBG. Measurement frequencies of 2, 4, 6, 8, and 10/day are simulated in this study.

The AIDA on-line[2] virtual cohort was treated with a range of short-acting, older intermediate/long-acting, or biphasic insulin.[14] In this study, only rapid-acting monomeric insulin (MI) analogues and the basal insulin analogue glargine are used. Insulin analogues have a more physiological and less variable pharmacokinetic profile than traditional insulin preparations[15] and allow

more faithful basal-bolus insulin replacement.[16] Clinically, reduced hypoglycemia and glycosylated hemoglobin A1c have been associated with insulin glargine and MI.[17–19] MI injected at the start of meals reduced postprandial glucose excursions compared to regular human insulin injected 30 minutes prior.[19] In addition, only one daily insulin glargine injection is required for basal insulin replacement.[20] These are the key clinical reasons why insulin analogues are chosen. While suboptimal glycemic control is as much a symptom of poorly adapted treatment strategy[21] as insulin type, it is logical to begin with the least compromised insulin preparations. The insulin model used in this study is capable of modeling the pharmacokinetic profiles of both MI analogues and insulin glargine.[22,23]

The meal carbohydrate content is assumed known to the patient through carbohydrate counting.[24–26] While the technique is only approximate and can be prone to inaccuracy,[27] it remains the key clinical strategy recommended to estimate the glycemic effect of meals for the purpose of adjusting insulin dosage.[8]

Control Methodology

In this study, two prandial insulin treatment protocols, a conventional control protocol (CC) and the adaptive control (AC) protocol developed in this study, are simulated *in silico*. The controls protocol is an unpublished protocol used to treat the AIDA on-line[2] cohort and is not the AIDA[2] insulin dosage advisor.[28] The controls group results are *calculated* from AIDA on-line[2] patient data (the same data used to generate the virtual patient profiles for this *in silico* study). Hence, *in silico* simulation is not required for the controls group.

AIDA on-line[2] data are a simulation of the patient steady-state response to fixed, daily insulin and dietary stimuli. To make the results of this study comparable, simulations were performed over a period of 3 days with the same, fixed insulin and dietary stimuli. Plasma glucose, insulin, and meal R_a profiles from the third day were considered steady state (AIDA assumes data from the second day are steady state[28]) and were taken as the final result.

For each tested protocol, SMBG frequencies of 2, 4, 6, 8, and 10/day were tested. In addition, a basal insulin titration regimen is used with both protocols to observe the outcome of optimal basal insulin replacement using insulin glargine compared to controls. The target blood glucose was 5 mmol/liter, and a maximum bolus dose of 15 units was assumed for both protocols.

Conventional Control

The CC protocol is based on a published intensive insulin therapy (IIT).[28–31] The protocol administers a bolus at the start of the meal, $t_{meal,i}$ (where $t_{meal,i}$ is the time of the ith meal). One glucose measurement at the start of the meal, $\overline{G}^{i}_{meal}$, is required to calculate the bolus size. The CC protocol is not adaptive as it uses fixed, suboptimal patient-specific parameters determined from original AIDA on-line[2] patient data. Referring to **Figure 1**, the carbohydrate-to-insulin ratio (CIR) was determined for each patient using the 450 rule (37 out of the 40 patients in the cohort are treated with regular insulin).[30] The CIR can also be calculated using **Equation (1)**:

$$\text{CIR [g of carb per U regular insulin]} = \frac{450}{\text{Total Daily Insulin Dose}} \quad (1)$$

Referring to **Figure 2**, an insulin sensitivity factor (ISF) is similarly determined for each patient using the 1500 rule for regular insulin.[31] The ISF can also be calculated using **Equation (2)**:

$$\text{ISF [mmol/liter per U regular insulin]} = \frac{1500}{18 \times \text{Total Daily Insulin Dose}} \quad (2)$$

Using the patient CIR and ISF parameters, the CC protocol then calculates the ith prandial insulin dose using **Equation (3)** assuming that the ith meal carbohydrate count is known from carbohydrate counting.

$$\text{Prandial dose}_i\,[\text{U}] = \min(\text{Maximum bolus dose}, \text{Meal dose}_i + \text{Correction dose}_i) \quad (3)$$

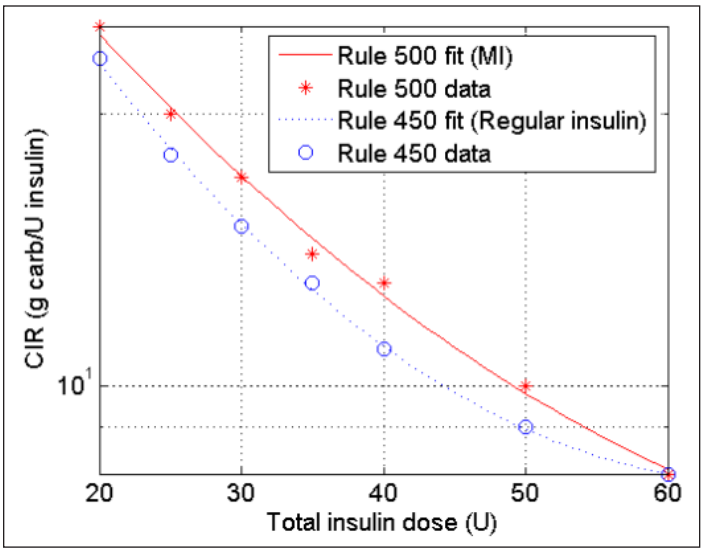

Figure 1. The CIR ratio is determined for each patient using the 450 rule for regular insulin (37 out of the 40 patients in the cohort are treated with regular insulin with the rest on biphasic insulin). Data reproduced from BD Diabetes Learning Centre.[29]

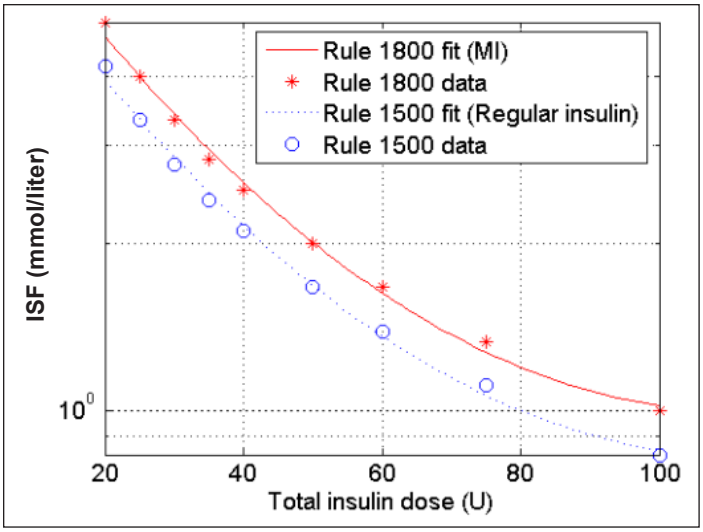

Figure 2. The ISF is determined for each patient using the 1500 rule for regular insulin. Data reproduced from Walsh and Roberts.[30]

where

$$\text{Meal dose}_i\ [\text{U}] = \left(\frac{\text{Meal carbohydrate count}_i}{\text{CIR}}\right)$$

$$\text{Correction dose}_i[\text{U}] = \left(\frac{\overline{G}^i_{meal} - \text{Target blood glucose}}{\text{ISF}}\right)$$

Adaptive Control

The AC protocol utilizes an adaptive method to determine the prandial insulin dose. The protocol comprises a twin bolus regimen per meal, with a conservative initial bolus, and an aggressive second bolus to accurately restore glycemia to basal. The second bolus is administered 90 minutes after the start of the meal and hence the first bolus. The first bolus is dosed according to the CC protocol. As such, two glucose measurements are required per meal, $\overline{G}^i_{meal,1}$ and $\overline{G}^i_{meal,2}$ before each bolus, at $t_{meal,i}$, and $t_{meal,i} + 90$ (where $t_{meal,i}$ is the time of the ith meal).

This time interval between boluses of 90 minutes is not arbitrary. In normal individuals, plasma glucose is restored to premeal basal levels in approximately 120 minutes[32] for a normal meal (~1 g glucose/kg body weight) and up to 360 minutes[33] for a very large meal (~4.5 g glucose/kg body weight). The 90-minute time interval chosen ensures minimal postprandial hyperglycemic exposure. In addition, the time to peak plasma concentration after MI injection ranges from 30 to 70 minutes,[34] which ensures that the second bolus is administered only *after* the plasma insulin concentration from the first bolus has peaked and approximately 30 minutes to the peak pharmacodynamic effect of the first bolus.[35] Hence, the 90-minute time interval is a compromise, injecting the second bolus as late as needed for the first bolus to reach its pharmacodynamic peak for safety, while ensuring that the plasma insulin concentration does not wane, but is maintained and increased as necessary with the second bolus as a correction to minimize the postprandial glycemic excursion.

Referring to **Equation (4)**, the AC protocol is adaptive by optimizing the patient-specific model parameter S_I to glucose measurement data. Accurately identifying the current patient condition in S_I allows safer administration of the aggressive insulin bolus. Referring to **Equation (5)**, $G(t)$ for the identification of S_I is interpolated linearly from the glucose measurements $\overline{G}^i_{meal,1}$ and $\overline{G}^i_{meal,2}$. For the ith meal, the identified patient $\overline{S}_{I,i}$ value between the measurements at $t_{meal,i}$ and $t_{meal,i} + 90$ is used to predict the glycemic response of the patient in the period $\geq t_{meal,i} + 90$ to some prediction end point, t_{pred} [refer to **Equation (6)**].

$$\int_{t_{meal,i}}^{t_{meal,i}+90} \dot{G}(t)\,dt = \int_{t_{meal,i}}^{t_{meal,i}+90} \left[EGP_{0-G} - p_G G(t) - \overline{S}_{I,i} G(t)Q(t) - RGC(t) - CNS + P(t)\right] dt$$

$$G(t_{meal,i}) - G(t_{meal,i}+90) = \int_{t_{meal,i}}^{t_{meal,i}+90} \left[EGP_{0-G} - RGC(t) - CNS + P(t)\right] dt - p_G \int_{t_{meal,i}}^{t_{meal,i}+90} G(t)\,dt - \overline{S}_{I,i} \int_{t_{meal,i}}^{t_{meal,i}+90} G(t)Q(t)\,dt$$

$$\overline{S}_{I,i} \int_{t_{meal,i}}^{t_{meal,i}+90} G(t)Q(t)\,dt = \int_{t_{meal,i}}^{t_{meal,i}+90} \left[EGP_{0-G} - RGC(t) - CNS + P(t)\right] dt - p_G \int_{t_{meal,i}}^{t_{meal,i}+90} G(t)\,dt - \left[G(t_{meal,i}) - G(t_{meal,i}+90)\right]$$

Substituting the measurements, $\overline{G}^i_{meal,1}$ and $\overline{G}^i_{meal,2}$

$$\overline{S}_{I,i} \int_{t_{meal,i}}^{t_{meal,i}+90} G(t)Q(t)\,dt = \int_{t_{meal,i}}^{t_{meal,i}+90} \left[EGP_{0-G} - RGC(t) - CNS + P(t)\right] dt - p_G \int_{t_{meal,i}}^{t_{meal,i}+90} G(t)\,dt - \left(\overline{G}^i_{meal,1} - \overline{G}^i_{meal,2}\right) \quad (4)$$

$$G\left(t_{meal,i} \leq t \leq t_{meal,i}+90\right) = G\left(t_{meal,i}\right) + \left[G\left(t_{meal,i}+90\right) - G\left(t_{meal,i}\right)\right]\left(\frac{t - t_{meal,i}}{90}\right) = \overline{G}^i_{meal,1} + \left(\overline{G}^i_{meal,2} - \overline{G}^i_{meal,1}\right)\left(\frac{t - t_{meal,i}}{90}\right) \quad (5)$$

Then, assuming S_I is constant over the prediction horizon,

$$S_{I,pred}\left(t_{meal,i} + 90 \leq t \leq t_{pred}\right) = \overline{S}_{I,i} \quad (6)$$

Once the patient $\overline{S}_{I,i}$ value is known, the second bolus dose is determined iteratively. From **Equation (6)**, a predicted glycemic response is generated using $S_{I,pred} = \overline{S}_{I,i}$, up to a prediction horizon of 2 hours ($t_{pred} = t_{meal,i} + 90 + 120$). The objective of the iteration is to achieve the 5-mmol/liter target blood glucose level from the predicted

glycemic response within the 2-hour prediction horizon. If $\overline{G}^{i}_{meal,2} \leq$ target blood glucose level of 5 mmol/liter or if the iteration results in a zero dose (the predicted glucose response *without* an administered second bolus achieves the target blood glucose level within the prediction horizon), then no second bolus is administered. If the iteration results in a dose exceeding the 15-unit maximum bolus dose, then the full 15 units is administered. In all iterations, using the models means that all incoming glucose and insulin from prior MI and insulin glargine doses can be accounted for accurately in determining the correction bolus.

Basal Insulin Titration Regimen

To optimize basal insulin replacement, a protocol based on the forced-titration regimens of Fritsche *et al.*[36] and Riddle *et al.*[37] was used (see **Table 1**). Unlike other basal dosing schemes,[38,39] this regimen has been shown to be clinically effective in a treat-to-target trial.[37] The protocol by Fritsche and colleagues[36] does not specify a dose decrement if hypoglycemia occurs, but the similar Riddle *et al.*[37] protocol specifies a small dose decrement of 2–4 U/day if the fasting plasma glucose (FPG) is below 3.0 mmol/liter. Hence, referring to **Table 1**, the protocol decreases the basal dose by 2 U/day if FPG <3 mmol/liter and by 4 U/day if FPG <2 mmol/liter.

Table 1.
Basal Insulin Dosing Regimen[a] Used to Optimize the Single, Daily Insulin Glargine Dose Based on the Forced-Titration Regimens of Fritsche *et al.*[35] and Riddle *et al.*[36]

Fasting plasma glucose (mmol/liter)	Initial dose equivalent to 80% of total basal dose	
	Increment in glargine dose (U/day)	Decrement in glargine dose (U/day)
≥10.0	8	
≥7.8 and <10.0	6	
≥6.7 and <7.8	4	
≥5.6 and <6.7	2	
≥3.0 and <5.6		
≥2.0 and <3.0		2
<2		4

[a] This regimen incorporates a dose decrement if hypoglycemia occurs, which the Riddle *et al.*[36] protocol does not specify explicitly. Unlike Riddle *et al.*,[36] the initial basal dose is chosen to be 80% of the total basal dose from AIDA on-line[2] cohort data, which is recommended for patients changing over to insulin glargine from other basal insulin types.[39]

As in Riddle and colleagues,[37] the FPG is assumed to be the prebreakfast blood glucose level and is closest to the American Diabetes Association (ADA) definition of FPG of "no caloric intake for at least 8 hours.[8]" The single daily insulin glargine dose is injected at the last meal of the day instead of bedtime as in Riddle *et al.*,[37] as it does not require assumptions about bedtimes and is unlikely to affect the titration scheme. Unlike Riddle *et al.*,[37] the initial basal dose is chosen to be 80% of the total basal dose from original patient data, which is recommended for patients changing over to insulin glargine from other basal insulin types.[40] The Riddle *et al.*[37] initial basal dose of 10 units is recommended only for insulin-naive patients and is less suitable for this study.[40] The maximum insulin glargine dose is limited to 80 units (hence 80 U/day), even though doses up to 100 units can be prescribed clinically.[40] In the case of suboptimal basal insulin replacement, basal insulin therapy from the controls cohort (AIDA on-line[2] patient data) is used.

Location of SMBG Measurements

Self-monitoring blood glucose frequencies of 2, 4, 6, 8, and 10/day were examined. For both CC and AC protocols, the first SMBG measurement is always located at the start of breakfast (the approximate FPG) to titrate the basal insulin dose according to the Fritsche *et al.*[36] protocol (see later). For the CC protocol, each subsequent SMBG measurement is located at the start of the meal in descending order of meal size. As the AC protocol requires two SMBG measurements per meal, the second SMBG measurement is always 90 minutes after breakfast. Each subsequent *pair* of SMBG measurements is located at the start and 90 minutes after the start of the meal in descending order of meal size. Thus, additional pairs of measurements occur at lunch/dinner followed by between-meal snacks. Hence, for an equivalent SMBG frequency, the CC protocol covers double the number of meals.

Hemoglobin A1c Calculation

Glycosylated hemoglobin is one of two clinical assessment techniques for glycemic control recommended by the ADA.[8] The test assesses glycemic control over the preceding 2–3 months.[41] Like AIDA,[28] the control simulations in this study are for steady-state glucose and insulin stimuli. The resulting steady-state glycemic response can then be used to calculate an indicative and approximate hemoglobin A1c value,[41] *if* the control is assumed to be relatively constant over a 2- to 3-month period. From Rohlfing and colleagues,[42] hemoglobin A1c can be defined as a linear function of mean plasma glucose only. Referring to **Figure 3** of data reproduced from Rohlfing *et al.*,[42] a

hemoglobin A1c regression equation, can be estimated as

$$\text{Hemoglobin A1c} = 0.5\ \text{MBG} + 2.25 \quad (7)$$

where MBG is mean blood glucose concentration (mmol/liter).

The MBG is calculated as the arithmetic mean of the 24-hour simulated glycemic profile (1-minute time step). Compared to the hemoglobin A1c regression equation in **Equation (8)** adapted from by AIDA on-line[2],[43] the Rohlfing *et al.*[42] equation is more conservative:

$$\text{Hemoglobin A1c} = 0.6\ \text{MBG} + 2.87 \quad (8)$$

The hemoglobin A1c value calculated with **Equation (7)**, while approximate and only if the control is assumed to persist for 2–3 months, provides a clinically significant performance metric to the results of this study. In particular, the Diabetes Control and Complications Trial (DCCT)[44] and others have shown clinical outcomes as functions of hemoglobin A1c, which is a reliable and accepted metric in large intervention trials.

Summary of Simulations Performed

Four controllers are simulated. These controllers are:

- AC prandial insulin protocol—optimal basal insulin
- AC prandial insulin protocol—suboptimal basal insulin
- CC prandial insulin protocol—optimal basal insulin
- CC prandial insulin protocol—suboptimal basal insulin

For each controller, SMBG frequencies of 2, 4, 6, 8, and 10/day are simulated, giving a total of 20 simulations (five SMBG frequencies simulated *per* controller type). In addition:

- Controls cohort results *are* calculated from AIDA on-line[2] patient data (the same data used to generate the virtual patient profiles for this *in silico* study) and are not the AIDA[2] insulin dosage advisor.[28] No *in silico* simulation is required for the controls group.
- Optimal basal insulin replacement is performed using the Fritsche–Riddle basal insulin forced-titration regimen. For suboptimal basal insulin replacement, the basal insulin therapy from the controls cohort (AIDA on-line[2] patient data) is used.

Hemoglobin A1c distributions are compared using a nonparametric, two-tailed Wilcoxon signed-rank test. An asymptotic significance value of <0.05 is considered statistically significant. All calculations and analyses were performed using SPSS® (SPSS Inc., Chicago, IL).

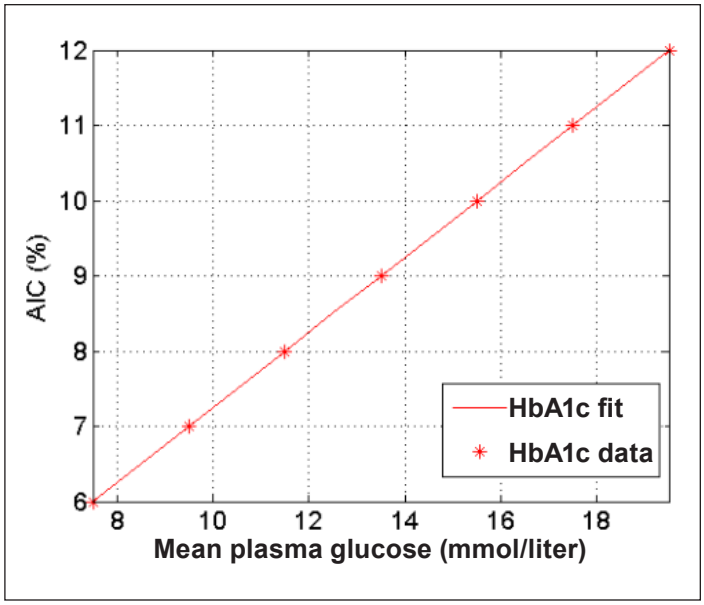

Figure 3. Estimating hemoglobin A1c (HbA1c) from mean plasma glucose with linear regression. Data reproduced from Rohlfing *et al.*[42]

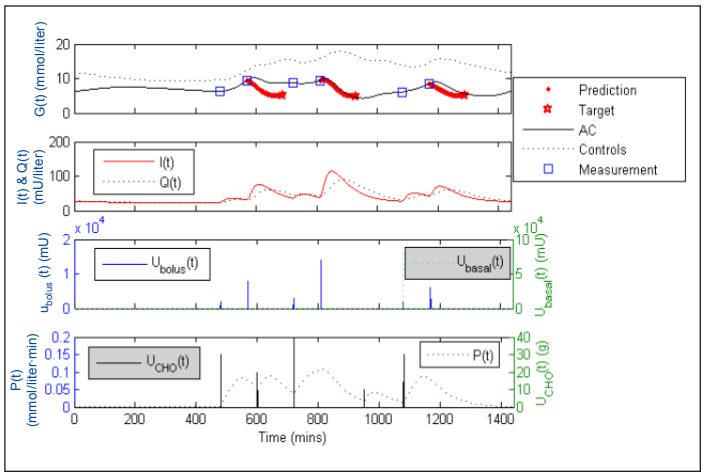

Figure 4. A sample *in silico* simulation of patient 6 under control by the AC protocol with a SMBG frequency of 6/day.

Results and Discussion

Results of the *in silico* control simulation are as follows. A sample simulation is shown in **Figure 4** of patient 6 under control by the AC protocol with a SMBG frequency of 6/day. From this result, a patient-specific hemoglobin A1c can be calculated for this patient and control scheme.

Hemoglobin

Figures 5–8 show the empirical cumulative distribution function of hemoglobin A1c for the AC and CC protocols with the controls group for comparison, with and without optimal basal insulin replacement.

Referring to **Figure 5** and **Table 2**, only 52.5% of the controls group cohort had a hemoglobin A1c <7.0%, whereas 40% had <6.5%. These thresholds are noteworthy as they are the hemoglobin A1c glycemic goals recommended by the ADA[8] and American Association of Clinical Endocrinologists (AACE),[45] respectively. Only 22.5% had a hemoglobin A1c<6%, which is the normal hemoglobin A1c level. The percentage of the controls cohort that meet the ADA recommended glycemic goal of hemoglobin A1c ≤7.0% is in agreement with the figure of 48.9% of the U.S. adult diabetes population being "in control,[9]" which supports the controls group as a realistic representation of the broad diabetes population and its treatment.

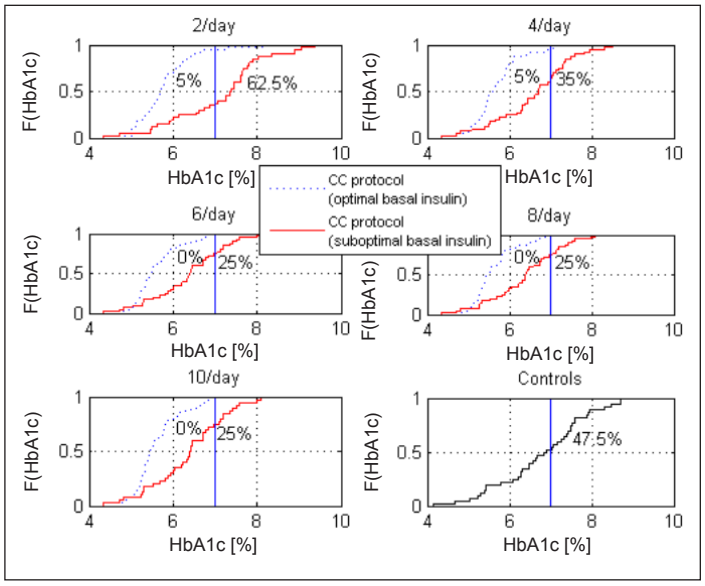

Figure 5. Empirical cumulative distribution function (CDF) of hemoglobin A1c (HbA1c) for the CC protocol with optimal and suboptimal basal insulin replacement compared to the controls group. The ADA-recommended glycemic control level as measured by HbA1c ≤7% is shown with the percentage time spent above the threshold for each case.

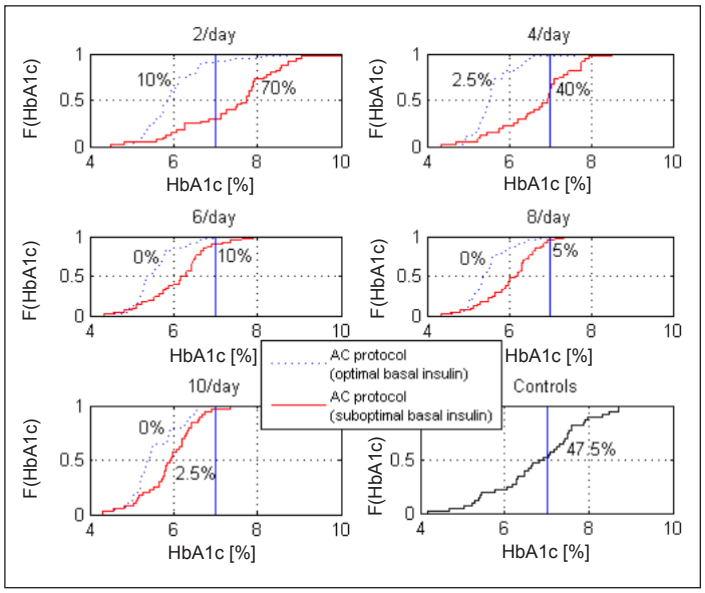

Figure 6. Empirical cumulative distribution function (CDF) of hemoglobin A1c (HbA1c) for the AC protocol with optimal and suboptimal basal insulin replacement compared to the controls group. The ADA-recommended glycemic control level as measured by HbA1c ≤7% is shown with the percentage time spent above the threshold for each case.

Table 2.
Summary of the Cohort Percentage Controlled to ADA[8] and AACE[44] Glycemic Control Recommendations and to Normal Hemoglobin A1c Levels[a]

			Hemoglobin A1c (%)		
			<6.0	<6.5	<7.0
Basal protocol type	Prandial protocol type	SMBG frequency (/day)			
Controls			22.5	40.0	52.5
Controls (suboptimal)	CC	2	22.5	25.0	37.5
		4	25.0	42.5	60.0
		6	32.5	60.0	75.0
		8	32.5	60.0	75.0
		10	32.5	60.0	75.0
	AC	2	15.0	25.0	30.0
		4	22.5	35.0	60.0
		6	37.5	72.5	90.0
		8	42.5	77.5	95.0
		10	57.5	85.0	97.5
Forced-titration regimen (optimal)	CC	2	70.0	90.0	95.0
		4	80.0	92.5	95.0
		6	82.5	90.0	100.0
		8	82.5	90.0	100.0
		10	82.5	90.0	100.0
	AC	2	62.5	77.5	90.0
		4	82.5	95.0	97.5
		6	85.0	92.5	100.0
		8	85.0	95.0	100.0
		10	77.5	92.5	100.0

[a] The percentage of the controls group controlled to ADA-recommended hemoglobin A1c (52.5%) is in excellent agreement with the figure of 48.9% of the U.S. adult diabetes population being "in control.[9]"

Suboptimal Basal Insulin

Compared to controls, both CC and AC protocols with suboptimal basal insulin replacement perform significantly better for SMBG frequencies ≥4/day and ≥6/day respectively. By design, the CC protocol covers twice as many meals as the AC protocol; this advantage is apparent at lower SMBG frequencies. At higher SMBG frequencies, the AC protocol is able to cover most meals in the day with increased accuracy, outperforming the CC protocol significantly for all SMBG frequencies ≥6/day. At a SMBG frequency of 6/day, 90 and 72.5% of the cohort meet ADA and AACE clinical recommendations, respectively, compared to 75 and 60% for the CC protocol.

This result is in agreement with clinical results of long-term control using MI. It has been shown that optimal basal insulin replacement *to* the use of MI is required to achieve maximum benefit.[19,34,46] The pharmacokinetic profile of MI enables truer *bolus* insulin replacement than regular human insulin and, as such, requires a truer *basal* insulin regimen. Basal insulin regimens developed and optimized to regular insulin boluses will be suboptimal with MI boluses. This is evident for both AC and CC protocols with suboptimal basal insulin replacement, which have nonsignificant hemoglobin A1c to controls for SMBG frequencies less than ~3/day.

Optimal Basal Insulin

With optimal basal insulin replacement, glycemic control is enhanced further. For a 6/day SMBG frequency, the AC protocol now results in 100% of the cohort controlled to ADA guidelines, 92.5% to AACE guidelines, and 85% have normal hemoglobin A1c levels. However, the difference between CC and AC protocols with suboptimal basal insulin replacement (**Figure 7**) is much larger than with optimal basal insulin treatment (**Figure 8**). As expected, the AC protocol exceeds the CC protocol for all SMBG frequencies except 2/day. However, only the result from the 8/day SMBG frequency is statistically significant. For AACE and the normal hemoglobin A1c thresholds given a 6/day SMBG frequency, the difference between the two protocols is just 2.5% of the cohort or one patient.

These results indicate that if basal insulin replacement is optimal, both prandial insulin protocols perform adequately. However, if basal insulin replacement is suboptimal and insulin requirements in the postabsorptive period are not met, then the AC protocol compensates, especially at SMBG frequencies ≥6/day where sufficient measurements exist to cover most of the meals in the day. Hemoglobin A1c results are summarized in **Figure 9**.

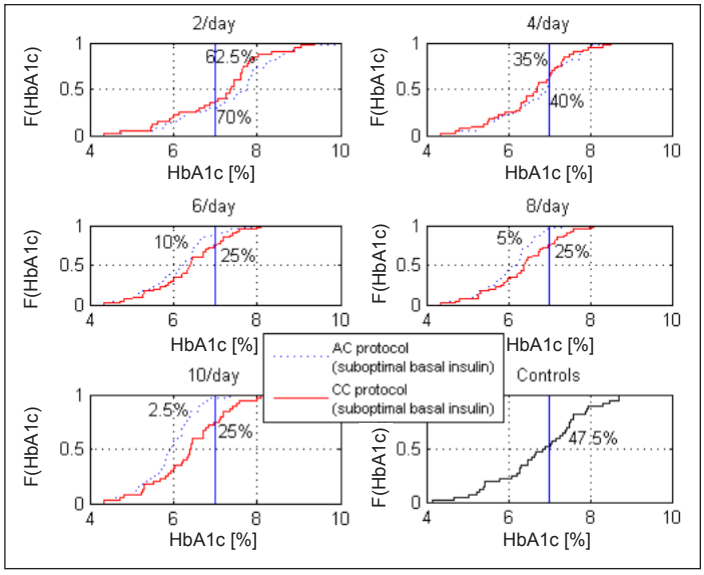

Figure 7. Empirical cumulative distribution function (CDF) of hemoglobin A1c (HbA1c) for both AC and CC protocols with suboptimal basal insulin replacement compared to the controls group. The ADA-recommended glycemic control level as measured by HbA1c ≤7% is shown with the percentage time spent above the threshold for each case.

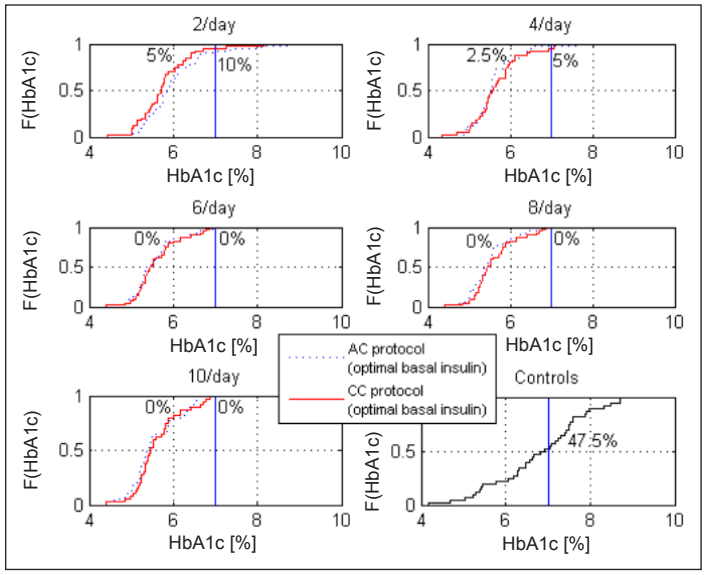

Figure 8. Empirical cumulative distribution function (CDF) of HbA1c for both AC and CC protocols with optimal basal insulin replacement compared to the controls group. The ADA-recommended glycemic control level as measured by HbA1c ≤7% is shown with the percentage time spent above the threshold for each case.

Hypoglycemia

The hypoglycemic level of 3.9 mmol/liter defined by the ADA is adopted in this study[47] as the mild hypoglycemic threshold. The glucose level used to define severe hypoglycemia is assumed to be 3 mmol/liter. Cognitive function is impaired from ~3 mmol/liter,[48,49]

which matches the definition of the ADA for severe hypoglycemia as "an event requiring assistance of another person to actively administer [resuscitative actions].[47]" While these definitions are used globally in this study, it is acknowledged that the hypoglycemic level and response are complex and patient specific.[50]

Conventional Control Protocol

Referring to **Figures 10–13**, the total time spent by the cohort in mild ($t_{hypo,mild}$) and severe hypoglycemia ($t_{hypo,sev}$) is shown as a percentage. For the controls group, $t_{hypo,mild}$ is 7.7%. From **Figure 10** for the CC protocol with suboptimal basal insulin replacement, $t_{hypo,mild}$ is relatively constant over all SMBG frequencies at 4.2–4.9%. For the CC protocol with optimal basal insulin replacement, $t_{hypo,mild}$ decreases with increasing SMBG frequency, with the highest $t_{hypo,mild}$ of 8.5% occurring for a SMBG frequency of 2/day. This figure exceeds the controls group (7.7%) and the suboptimal basal insulin CC protocol (4.3%). At a SMBG frequency of 4/day, $t_{hypo,mild}$ is 6.5% compared to 4.5% for the suboptimal basal insulin CC protocol. At a SMBG frequency of 6/day, $t_{hypo,mild}$ is comparable to the suboptimal basal insulin CC protocol (4.5% compared to 4.2%), dropping further to 2.9% compared to 4.9% for the suboptimal basal insulin CC protocol at a SMBG frequency of 10/day.

Similarly, $t_{hypo,sev}$ is relatively constant at ~1.8% for the CC protocol with suboptimal basal insulin replacement. Like $t_{hypo,mild}$, $t_{hypo,sev}$ under the CC protocol with optimal basal insulin replacement is maximum at 1.2% for a SMBG frequency of 2/day and decreases to 0.6% for a SMBG frequency of 10/day. For the controls group, $t_{hypo,sev}$ is 3.5%.

In summary, across all SMBG frequencies, $t_{hypo,sev}$ under the optimal basal insulin CC protocol is reduced by 66–83% over controls and by 33–67% over the suboptimal basal insulin CC protocol. However, $t_{hypo,mild}$ is increased at least until a SMBG frequency of 4/day and is decreased for all SMBG frequencies >6/day. Under the CC protocol and with a low SMBG frequency, e.g., 2–4/day, the prandial glycemic excursion, especially for the last meal of the day, is usually not completely restored to basal.

This failure to reach a basal level overnight is important because it affects the prebreakfast glucose measurement used for the titration of the basal insulin dose, resulting in an aggressive dose increase and increased mild hypoglycemia. Fortunately, this problem does not result in increased severe hypoglycemia; in fact, optimal basal insulin replacement with insulin glargine results in lower

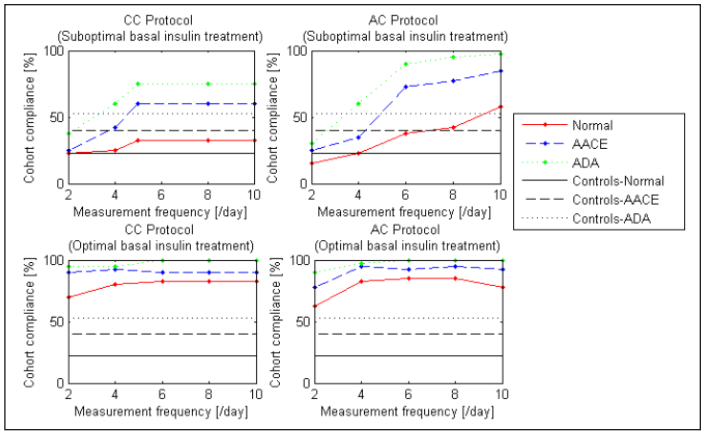

Figure 9. The cohort percentage controlled to clinically relevant hemoglobin A1c (HbA1c) levels (as recommended by the ADA[8] and AACE[45]) as compared to the controls group. The normal HbA1c level of 6.0% is shown for comparison.

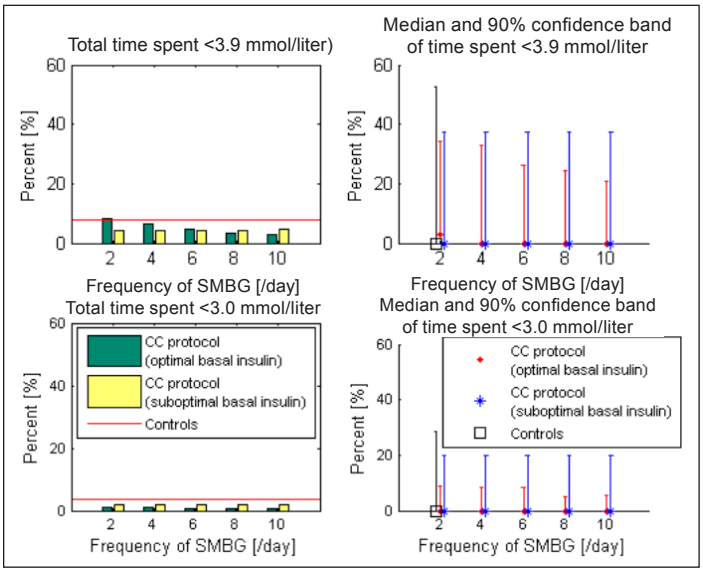

Figure 10. Total time spent by the cohort, and the cohort median and 90% confidence band for the time spent in mild and severe hypoglycemia under the CC protocol in conditions of optimal and suboptimal basal insulin replacement.

occurrences of severe hypoglycemia across all SMBG frequencies. With SMBG frequencies of 6/day or more, occurrences of both mild *and* severe hypoglycemia are reduced over controls and the suboptimal basal insulin CC protocol.

Adaptive Control Protocol

Referring to **Figure 11** for the AC protocol with suboptimal basal insulin replacement, $t_{hypo,mild}$ is relatively constant over all SMBG frequencies at 4.2–4.4%. For the AC protocol with optimal basal insulin replacement, $t_{hypo,mild}$ decreases with increasing SMBG frequency with the highest $t_{hypo,mild}$ of 3.1 and 3.2% occurring for SMBG

frequencies of 2/day and 4/day, respectively. This figure is 60% less than the controls group (7.7%) and 28% less than the suboptimal basal insulin CC protocol (4.4%). At a SMBG frequency of 8/day, $t_{hypo,mild}$ reaches a nadir of 0.7% before increasing to 1.3% for a SMBG frequency of 10/day.

Similarly, $t_{hypo,sev}$ is relatively constant at ~1.8% for the AC protocol with suboptimal basal insulin replacement. Like $t_{hypo,mild}$, $t_{hypo,sev}$ under the AC protocol with optimal basal insulin replacement is maximum at 0.6% for SMBG frequencies of 2/day and 4/day but decreases to 0% for SMBG frequencies ≥6/day.

In summary, across all SMBG frequencies, $t_{hypo,sev}$ under the AC protocol with optimal basal insulin replacement is reduced by 86–100% over controls and by 72-100% over the AC protocol with suboptimal basal insulin replacement. Across all SMBG frequencies, $t_{hypo,mild}$ under the AC protocol with optimal basal insulin replacement is reduced by 58–91% over controls and 27–84% over the AC protocol with suboptimal basal insulin replacement. Prandial glycemic excursions are restored more completely to basal under the AC protocol even with a low SMBG frequency. This results in a more accurate prebreakfast glucose measurement for basal insulin titration on the forced-titration regimen with lower resultant mild and severe hypoglycemia.

Summary of Hypoglycemia Results

Referring to **Figure 13** for optimal basal insulin replacement, the AC protocol outperforms the CC protocol in hypoglycemia occurrence over all SMBG frequencies. Given suboptimal basal insulin replacement, occurrence of hypoglycemia both mild and severe is similar between the two protocols (see **Figure 12**). The results of this comparison are similar to that of hemoglobin A1c, whereby the advantage of the AC protocol is most apparent in conditions of poor basal insulin replacement.

Contrary to the DCCT,[44] hypoglycemia did not increase from controls under the conventional IIT (CC protocol) in this study. In both cases of suboptimal and optimal basal insulin replacement, severe hypoglycemia was reduced for all SMBG frequencies compared to controls. This result is in excellent agreement with the study by Sämann *et al.*[21] where implementation of a flexible IIT protocol improved glycemic control without an increased risk of severe hypoglycemia. The protocol in the Sämann *et al.*[21] study consisted of a structured inpatient training course, implemented into routine care with continuous quality assurance on a national level. Hence, it is reasonable to

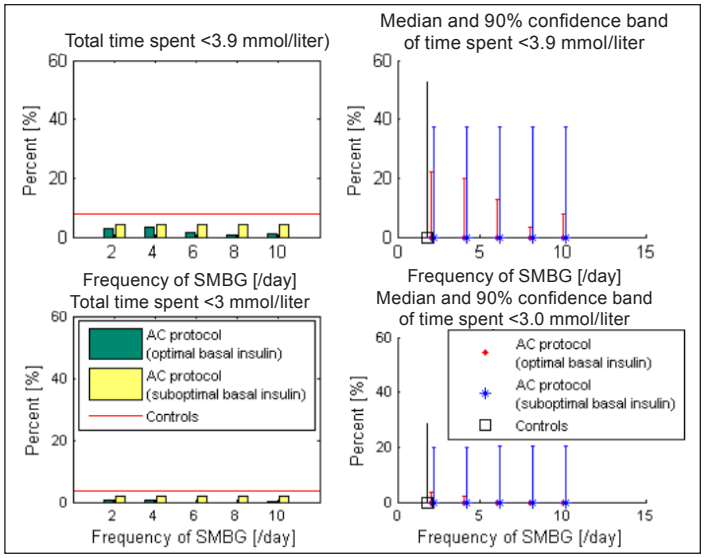

Figure 11. Total time spent by the cohort, and the cohort median and 90% confidence band for the time spent in mild and severe hypoglycemia under the AC protocol in conditions of optimal and suboptimal basal insulin replacement.

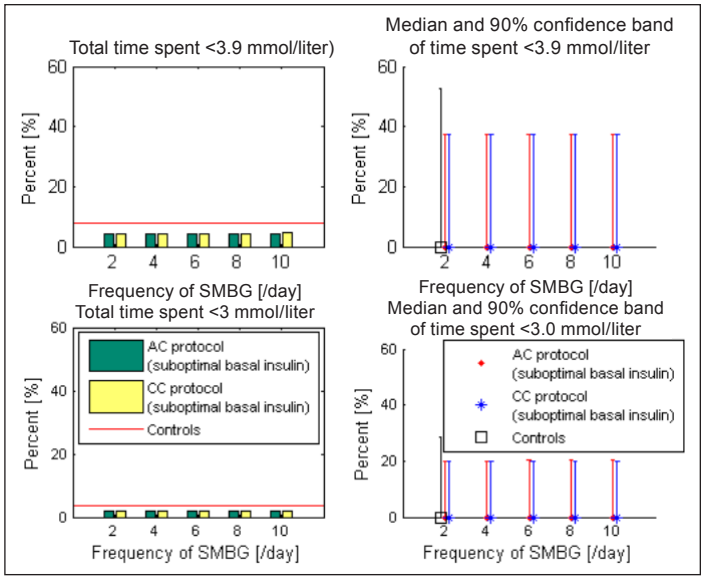

Figure 12. Total time spent by the cohort, and the cohort median and 90% confidence band for the time spent in mild and severe hypoglycemia under AC and CC protocols and suboptimal basal insulin replacement.

assume high patient protocol adherence and that the conditions in this study are similar to that inherent of the *in silico* simulation, which assumes full patient adherence.

Self-Monitoring Blood Glucose Frequency

The frequency of SMBG has been known to affect glycemic control, as reviewed elsewhere.[51] For type 1 diabetes, the ADA[8] and AACE[45] both recommend a

SMBG frequency ≥3/day, and in a study by Monnier and colleagues,[52] five- to eight-point daily glucose monitoring is recommended. Davidson *et al.*[53] modeled hemoglobin A1c and SMBG with **Equation (9)**:

$$\text{Hemoglobin A1c} = 5.99 + \frac{5.32}{(\text{tests per day} + 1.39)} \quad (9)$$

Referring to **Figure 14**, data from Davidson and colleagues[53] were reproduced with the *median* cohort hemoglobin A1c of this study for the various protocols and basal insulin replacement regimens.

The Davidson *et al.*[53] curve follows closely the suboptimal basal insulin CC protocol. This result supports the validity of the *in silico* simulation, which produces a similar hemoglobin A1c simulating a conventional IIT under suboptimal basal insulin replacement. With SMBG frequency >4/day, the suboptimal basal insulin AC protocol reduces the median hemoglobin A1c over the CC protocol under the same basal insulin replacement. Both protocols with optimal basal insulin replacement result in a normal median hemoglobin A1c even at a low SMBG frequency of 2/day, although the AC protocol results in marginally lower hemoglobin A1c for all SMBG frequencies ≥6/day. This result also implies that clinically, poor glycemic control is mainly a result of suboptimal basal insulin replacement. As shown previously, basal insulin replacement has the single, most significant effect on hemoglobin A1c, much more so than the difference between AC and CC prandial insulin protocols.

The forced-titration regimen of basal insulin dosing has been found to be safe only if sufficient SMBG and, consequently, prandial control are applied in order for the assumed FPG value to be accurate. The basal insulin forced-titration regimen relies on a single, prebreakfast FPG value, and if a patient is poorly controlled prandially, the assumed FPG value is likely to be influenced by the postprandial excursion from the previous night. From this study, this minimum SMBG frequency was approximately ~6/day for a conventional IIT (CC protocol). With the AC protocol, the SMBG frequency does not present a safety issue, regardless of basal insulin replacement.

Referring to **Table 2**, the suboptimal basal insulin CC protocol (a conventional IIT) and a SMBG frequency of 4/day result in 60% of the cohort controlled to ADA guidelines and 25% to normal hemoglobin A1c levels. With six- or eight-point daily glucose monitoring, these figures are 75.0 and 32.5%, respectively. Hence, control with the minimum ADA-recommended SMBG frequency, or even the Monnier *et al.*[52] daily eight-point measurements, is unsatisfactory if the protocol implemented is a conventional IIT with suboptimal basal insulin replacement. From this study, glycemic control with the suboptimal basal insulin CC protocol saturates at a SMBG frequency of 6/day with 75% of the cohort meeting ADA guidelines. Hence, a SMBG frequency of 6/day should be the minimum for a conventional IIT with a suboptimal basal insulin regimen.

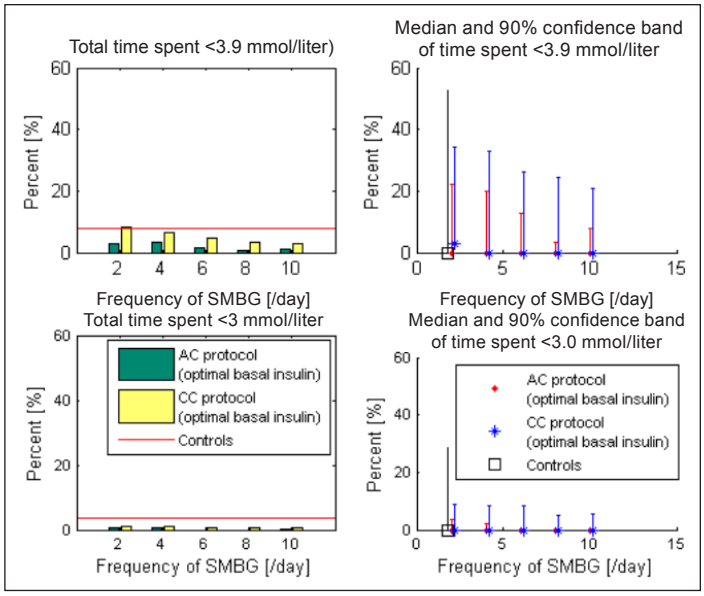

Figure 13. Total time spent by the cohort, and the cohort median and 90% confidence band for the time spent in mild and severe hypoglycemia under AC and CC protocols and optimal basal insulin replacement.

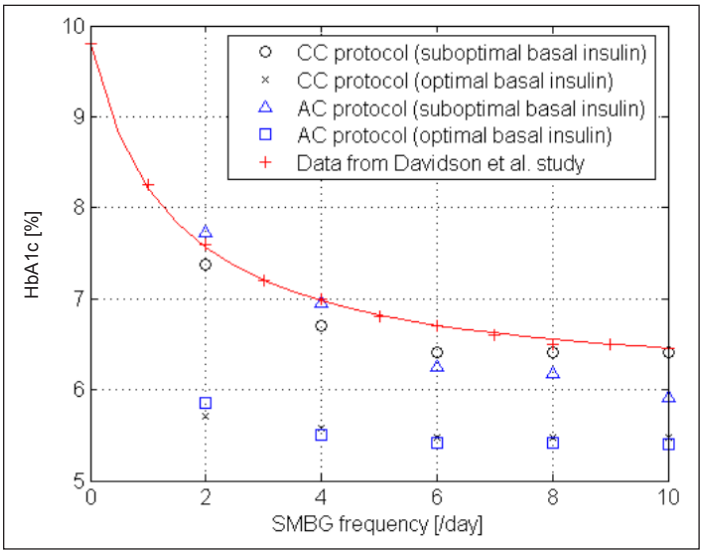

Figure 14. Predicted hemoglobin A1c (HbA1c) data from Davidson *et al.*[53] and the *median* cohort HbA1c of this study vs SMBG frequency. The Davidson *et al.*[53] curve follows approximately the suboptimal basal insulin CC protocol.

With optimal basal insulin replacement, the adaptive AC protocol with a SMBG frequency of 4/day results in 97.5% of the cohort controlled to ADA guidelines and 82.5% to normal hemoglobin A1c levels. In addition, mild hypoglycemia is reduced by 27% and severe hypoglycemia by 50% in comparison to the suboptimal basal insulin CC protocol. With optimal basal insulin replacement, the CC protocol produces similarly excellent glycemic control, but mild hypoglycemia is increased 103% compared to the AC protocol. Fear of hypoglycemia is frequently cited for deliberate insulin underdosing, both prandial and basal.[36,54] Hence, the adaptability of the AC protocol may represent the next evolution of IIT to deliver increased glycemic control with increased safety.

Conclusions

An *in silico* simulation tool has been presented that utilizes an extended model of glucose kinetics and the novel application of a subcutaneous insulin pharmacokinetic model. The virtual patient cohort and its default control protocol (data of which are used for *in silico* simulation) can be considered a good representation of the broad diabetes population. The simulation tool is used to develop a robust, adaptive protocol for prandial insulin dosing.

In virtual trial simulations, the adaptive protocol has been shown to decrease hemoglobin A1c significantly in conditions of suboptimal basal insulin replacement for SMBG frequencies ≥6/day and to reduce the occurrence of mild and severe hypoglycemia by 86–100% over controls over all SMBG frequencies in conditions of optimal basal insulin. When a conventional IIT is employed in conditions of suboptimal basal insulin, the increase in cohort compliance to clinical control guidelines saturates at a SMBG frequency of 6/day. In addition, under conventional IIT, the basal insulin forced-titration regimen requires a minimum SMBG frequency of 6/day to safely titrate the basal dose without increased hypoglycemia. The overaggressive basal dose titration with a conventional IIT at lower SMBG frequencies is likely to be caused by uncorrected postprandial hyperglycemia from the previous night, resulting in an erroneous assumed FPG used for dose titration.

With a SMBG frequency of 4/day and optimal basal insulin replacement, 97.5% of the cohort can be controlled to ADA clinical guidelines using the adaptive protocol, a result similar to a conventional IIT but which has 103% more mild hypoglycemia. As fear of hypoglycemia is a large psychological barrier to glycemic control, the AC protocol may represent the next evolution of IIT that can deliver increased glycemic control with increased safety. Further clinical or experimental validation is needed to fully prove the concept.

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