Journal of Diabetes Science and Technology
Volume 3, Issue 5, September 2009

SYMPOSIUM

Closed-Loop Artificial Pancreas Using Subcutaneous Glucose Sensing and Insulin Delivery and a Model Predictive Control Algorithm: The Virginia Experience

William L. Clarke, M.D.,[1] Stacey Anderson, M.D.,[2] Marc Breton, Ph.D.,[3] Stephen Patek, Ph.D.,[4] Laurissa Kashmer, M.D.,[1] and Boris Kovatchev, Ph.D.[3]

Abstract

Background:

Recent progress in the development of clinically accurate continuous glucose monitors (CGMs), automated continuous insulin infusion pumps, and control algorithms for calculating insulin doses from CGM data have enabled the development of prototypes of subcutaneous closed-loop systems for controlling blood glucose (BG) levels in type 1 diabetes. The use of a new personalized model predictive control (MPC) algorithm to determine insulin doses to achieve and maintain BG levels between 70 and 140 mg/dl overnight and to control postprandial BG levels is presented.

Methods:

Eight adults with type 1 diabetes were studied twice, once using their personal open-loop systems to control BG overnight and for 4 h following a standardized meal and once using a closed-loop system that utilizes the MPC algorithm to control BG overnight and for 4 h following a standardized meal. Average BG levels, percentage of time within BG target of 70–140 mg/dl, number of hypoglycemia episodes, and postprandial BG excursions during both study periods were compared.

Results:

With closed-loop control, once BG levels achieved the target range (70–140 mg/dl), they remained within that range throughout the night in seven of the eight subjects. One subject developed a BG level of 65 mg/dl, which was signaled by the CGM trend analysis, and the MPC algorithm directed the discontinuance of the insulin infusion. The number of overnight hypoglycemic events was significantly reduced ($p = .011$) with closed-loop control. Postprandial BG excursions were similar during closed-loop and open-loop control

continued →

Author Affiliations: [1]Division of Pediatric Endocrinology, Department of Pediatrics, University of Virginia Health Sciences Center, Charlottesville, Virginia; [2]Department of Internal Medicine, University of Virginia, Charlottesville, Virginia; [3]Diabetes Technology Program, University of Virginia, Charlottesville, Virginia; and [4]Department of Systems and Information Engineering, University of Virginia, Charlottesville, Virginia

Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitor, (FDA) Food and Drug Administration, (MPC) model predictive control, (PID) proportional integrative derivative

Keywords: artificial pancreas, closed-loop control, continuous glucose monitoring, model predictive control algorithms

Corresponding Author: William L. Clarke, M.D., Box 800386, Department of Pediatrics, University of Virginia Health Sciences Center, Charlottesville, VA 22908; email address wlc@virginia.edu

Abstract cont.

Conclusion:

Model predictive closed-loop control of BG levels can be achieved overnight and following a standardized breakfast meal. This "artificial pancreas" controls BG levels as effectively as patient-directed open-loop control following a morning meal but is significantly superior to open-loop control in preventing overnight hypoglycemia.

J Diabetes Sci Technol 2009;3(5):1031-1038

Introduction

Closed-loop "artificial pancreas" control of blood glucose (BG) in type 1 diabetes is neither a new nor a novel concept. Indeed, an artificial pancreas (Biostator™) was developed in the early 1970s, approved by the Food and Drug Administration (FDA), and marketed by Miles Labs (Elkhart, IN) for the management of hospitalized patients with insulin-dependent diabetes.[1,2] The device, however, was cumbersome in size, about that of a console television set, and in application. Blood was withdrawn continuously through an intravenous double-lumen catheter for measurement of glucose using a silver-platinum electrode and then discarded. Insulin and/or glucose was administered through a separate intravenous line every minute based on calculations using a set of algorithms that included average BG each minute and the rise or fall of BG over the previous 5 min. Although the Biostator worked well in the hands of trained researchers, the unreliability of the glucose sensor, the need for continuous venous blood withdrawal, and the need to deliver insulin intravenously limited its clinical usefulness for controlling BG in patients for more than a few hours. Recent progress in the development of clinically accurate continuous glucose monitors (CGMs), automated portable continuous insulin infusion pumps (open-loop systems), and control algorithms for calculating insulin dose based on continuous BG determinations has enabled researchers to explore the development of more practical and portable subcutaneous closed-loop control of BG.[3]

The ideal closed-loop system will control BG levels within a set target range 24 h a day, preventing postprandial hyperglycemia and exercise-induced hypoglycemia. Initial trials of a closed-loop system using proportional integrative derivative (PID) algorithms to control meal-related hyperglycemia produced significant hypoglycemia 2–3 h post meals, which required rescue glucose administration.[4] Indeed, the PID algorithms are similar to the original Biostator algorithms, and the Biostator closed-loop system included a glucose reservoir that was used to prevent postmeal insulin-induced hypoglycemia.[1] Attempts to reduce the occurrence of postprandial hypoglycemia associated with PID algorithm BG control include a "hybrid" system in which basal insulin is raised prior to the beginning of a meal to prevent or reduce the marked increase in insulin infusion signaled by the rapid rise in BG postprandially.[5] Although this modification reduces postmeal hypoglycemia, it also requires the patient to alert the system prior to the start of a meal. Thus, as implied by the adjective "hybrid," this is not a totally artificial pancreas, but a combination of closed-loop and open-loop BG control. A second problem with PID algorithms is the difficulty in preventing hypoglycemia associated with inaccurate dosing or overdosing of insulin. Recent reports suggest that predictive alarm algorithms, which signal the suspension of insulin delivery by the insulin pump, can markedly reduce the occurrence of moderate hypoglycemia.[6] Such suspension may last for several hours and, in subjects carefully monitored on a hospital clinical research unit, has not been associated with marked rebound hyperglycemia. Whether suspending insulin delivery will be a practical method for reducing the occurrence of overnight hypoglycemia remains to be demonstrated.

The shortcomings associated with PID insulin infusion algorithms have stimulated the design and testing of different control algorithms that are not reactive to BG alone, but utilize physiologic models of glucose metabolism to simulate insulin requirements to maintain BG levels within a target range while preventing postprandial hyperglycemia as well as overnight hypoglycemia.[7–9] Model predictive control (MPC) algorithms can predict glucose dynamics, reduce or eliminate the inherent time delays between interstitial glucose monitoring and

subcutaneous insulin infusion, and incorporate meal or hypoglycemia detection methods. In addition, MPC can be patient-personalized, i.e. have the ability to learn specifics of patients. In addition, models have the ability to learn specifics of patients' daily routines (e.g., usual timing and content of meals and usual exercise timing, duration, and intensity) in order to optimize insulin delivery. Finally, models can be tested *in silico* using computerized simulations.[10] Such simulations have recently been accepted by the FDA as substitutes for more laborious and time-consuming animal studies.[11] This article describes the initial experience of our research group in using MPC algorithms to control BG levels overnight and following a morning meal.

Methods

Subjects

Eight adults with type 1 diabetes aged 27 to 51 years, with an average diabetes duration 3 to 26 years, all of whom were using continuous subcutaneous insulin infusion pumps to control their BG levels, were recruited for this study, which was approved by the University of Virginia Institutional Review Board. Each subject signed a written consent form prior to undergoing a screening evaluation. The screening evaluation included a physical examination, routine blood chemistries, hemoglobin, hematocrit, insulin antibody determination, and an EKG. Subjects were excluded if they had a history of a cerebrovascular event, had symptomatic coronary artery disease, were pregnant or anemic, used medication (other than insulin) that could affect glucose metabolism, or were using a device such as a pacemaker, which might pose an electromagnetic issue and/or radiofrequency interference with CGM data transmission.

Model Predictive Control Algorithm

The basics of the MPC algorithm used in this study have been published previously.[10] Lineal unconstrained MPC was selected following *in silico* testing of two algorithms: linear quadratic Gaussian approach[12] and MPC.[10]

The two algorithms were tested extensively *in silico* using a computer simulator built on an *in silico* model of the human metabolic system, with specific application to testing insulin treatment strategies in diabetes. The mathematical basis for this *in silico* model is provided in a published meal model of glucose–insulin dynamics, which encompasses several metabolic subsystems, including the gastrointestinal tract, renal function, and hepatic glucose production.[13,14] This simulation environment includes the *in silico* images of 300 different simulated "subjects" in three age groups: 100 adults, 100 adolescents, and 100 children. In addition, the simulator emulates the characteristics of three CGM devices [Freestyle Navigator™ (Abbott Diabetes Care, Alameda, CA), Guardian RT™ (Medtronic, Northridge, CA), and DexCom™ STS™, 7-day sensor (DexCom, San Diego, CA)] and two insulin pumps [OmniPod Insulin Management System™ (Insulet Corp., Bedford, MA) and Deltec Cozmo® (Smiths Medical MD, Inc., St. Paul, MN)]. With this technology, any meal and insulin delivery scenario can be pilot tested very efficiently *in silico* prior to its clinical application.[11]

A three-parameter log linear regression using weight (kg), average total daily insulin dose, and BG correction factor measured during admission 1 was used to develop an individually "prescribed" MPC algorithm for the closed-loop study.

Procedure

Subjects were studied on two separate occasions 2 to 4 weeks apart. Each subject was admitted to the General Clinical Research Center in the early afternoon and was discharged the following afternoon. Two days prior to each admission, two Freestyle Navigator CGMs were inserted to ensure stabilization of the sensors and assessment of their accuracy prior to the study. During each study, only one CGM was designated as the primary sensor. The primary sensor was selected based on which of the two sensors' glucose curve most closely matched the self-monitoring of BG data obtained by the subject during the preadmission period. The two admissions were identical with the exception that, during admission 1, subjects used their personal continuous insulin infusion pump to control their basal infusion rates and their meal-related boluses according to their usual routines and their self-monitoring of BG data. Subjects were blinded to their CGM data during admission 1. The evening meal was selected by the subjects from three choices (salmon, pasta, or beef; carbohydrate content 45–95 g) and was repeated during admission 2. During admission 2, the subjects' insulin pump was exchanged for an Omni Pod insulin pump, and closed-loop control of BG was initiated 3 h postdinner and continued overnight and for 4 h after the morning meal. Rapid-acting Humalog (Eli Lilly Co., Indianapolis, IN) was used in all studies. The MPC began data collection prior to dinner to allow the algorithm to collect CGM and insulin data needed to initialize the closed-loop procedure to begin later. Each breakfast was a standardized mixed meal of Ensure Plus (Abbott Nutrition) containing 50 g of carbohydrates, 11 g of

fat, and 13 g of protein and was consumed at 0800 h. Model predictive control was continued for an additional 4 h until the conclusion of the study at 1200 h.

Continuous glucose monitor data were automatically transmitted each minute to a laptop computer that calculated the insulin dose to be infused every 15 min to achieve and maintain BG levels within a target range of 70–140 mg/dl. To maximize patient safety, the FDA required a physician to review and approve each insulin dose prior to manually instructing the insulin pump to begin infusing. Thus fully automated closed-loop MPC did not occur. Reference BG (YSI analyzer) was determined every 30 min unless hypoglycemia occurred, at which time sampling frequency was increased to every 15 min. Rapid-acting carbohydrate was given when the reference BG was below 70 mg/dl, regardless of CGM readings. Continuous glucose monitor low-BG alarms were suspended to allow the subjects to sleep uninterrupted since a physician was present to monitor BG levels throughout the entire procedure.

Two statistical comparisons were made contrasting open- and closed-loop control; a paired *t*-test was used to compare the percentage of time within the target range, and a Wilcoxon nonparametric test was used to compare the frequency of hypoglycemic episodes. Reference BG data were used for these comparisons.

Results

Subject characteristics are shown in **Table 1**. As can been seen, there was much heterogeneity in age, diabetes duration, average total daily insulin dose, average carb ratio, and level of glucose control as indexed by hemoglobin A1c.

Description of Closed-Loop Glucose Control

Continuous glucose monitoring data, reference BG levels (every 30 min), and insulin infused (every 15 min) for each of the eight subjects are shown graphically in **Figure 1**. The data prior to the start of closed-loop control are presented to show that, in most subjects (2–4 and 6–8), BG was falling postprandially at the start of closed-loop control. Subjects 1, 2, 5, and 6 began closed-loop control with BG levels between 70 and 140 mg/dl and continued with BG levels within this range overnight. Subjects 4 and 8 reached that target range within an hour of the initiation of closed-loop control, and no subject had a BG reading above 160 mg/dl overnight after achieving the target range. Although there were several instances where the Navigator CGM reading was at or below 70 mg/dl (subjects 2 and 6), at no time was the reading below 65 mg/dl. The low CGM reading in subject 2 was not accompanied by a reference BG reading in the hypoglycemic range and was presumed to be the result of a temporary movement artifact (rolling over on the sensor and disturbing its transmission to the receiver). This type of "dropout" artifact also occurred overnight in subject 4, but in that subject, the CGM reading did fall to a hypoglycemic level. Only one reference BG determination was below 70 mg/dl (subject 7), and that reading was detected by trend CGM readings and signaled the discontinuance of insulin infusion. Serious hypoglycemia did not occur during the overnight period.

Insulin was infused, as shown, every 15 min at doses calculated to attain and maintain BG levels within the target range. In most subjects, the amount of insulin infused was very small. In two instances (subjects 3 and 8), the physician operator decided to override or cancel the controller's recommended insulin infusion. In subject 3,

Table 1.
Subject Characteristics

Subject	Gender	Age (years)	Duration (years)	Body mass index	Average total daily insulin dose	U/kg/day	Hemoglobin A1c
1	Female	51	21	25.7	40.5	0.58	7.3
2	Female	36	25	33	30.3	0.34	7.9
3	Female	30	10	28.2	46.15	0.66	6.6
4	Female	26	3	24.5	29.6	0.44	5.3
5	Female	33	26	20.7	29.7	0.54	6.7[a]
6	Male	48	4	22.2	26.36	0.40	5.7
7	Male	46	22	28.2	73.85	0.67	8.1[a]
8	Female	27	18	25.3	69.5	0.99	8.0

[a]Self-report.

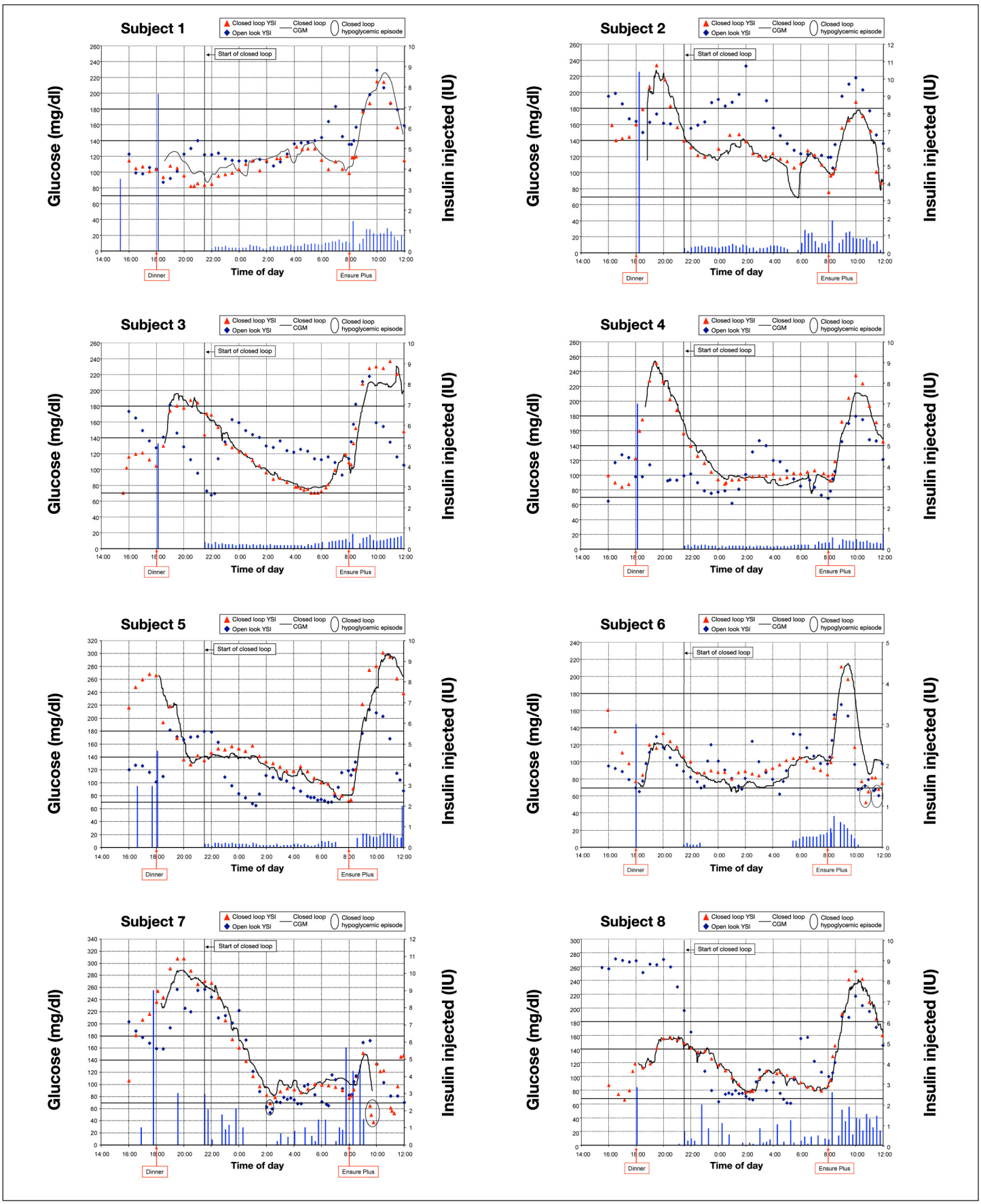

Figure 1. Continuous glucose monitoring data, reference BG levels, and insulin injected for the eight subjects.

the CGM readings were in the upper 70 mg/dl range, but the reference BG was 71 mg/dl. The controller using CGM readings suggested an insulin dose that might have precipitated hypoglycemia. In subject 8, a small insulin bolus was cancelled at 0215 h because there had been a 21 mg/dl drop in CGM readings over the previous hour and the current reading was 79 mg/dl. In both cases, the omission of insulin was not followed by significant hyperglycemia.

Postmeal hyperglycemia (BG > 180 mg/dl) occurred in almost every subject (subjects 1–6 and 8) with reference BG levels above 210 mg/dl 1–3 h after the meal. In three of the subjects (subjects 1, 2, and 6), BG was lowered into the target range of 70–140 mg/dl by the end of the study (4 h). In two others (subjects 4 and 8), BG was reduced to below 180 mg/dl by that time. The postprandial BG rose the highest (300 mg/dl) in subject 5 and did not return to the target range by the end of the study. In subject 6, BG rose more rapidly than in the others, peaking at 210 mg/dl in just 1 h. However, this rapid rise signaled an insulin infusion that led to postprandial hypoglycemia (BG of 55 mg/dl) 3 h postprandially. This subject had required almost no insulin overnight to maintain BG within the target range. Subject 7 had the smallest postprandial rise (BG of 145 mg/dl) at 1.25 h postprandially and then experienced an episode of hypoglycemia within 30 min (BG of 40 mg/dl) that prompted discontinuing closed-loop control. The subsequent episode of hypoglycemia shown 3 h postprandially occurred when the subject decided to reattach his insulin pump and give himself an insulin bolus.

Comparison of Open-Loop and Closed-Loop Glucose Control

Table 2 shows a comparison of BG levels attained during open-loop (patient directed) and closed-loop (controller directed) overnight and postprandial periods. The BG range across all subjects during open-loop control was 54–254 mg/dl and 38–304 mg/dl during closed-loop control. The extremes of the excursions were due to subject 7 (**Figure 1**). As can be seen, there were no differences in average overnight, minimum low BG, maximum high BG, or percentage of time spent within the target range (70–140 mg/dl). There was a trend, however, toward a greater average percentage of time that BG was between 70–180 mg/dl overnight ($p = .051$) with closed-loop control, and there were significantly fewer episodes instances of overnight hypoglycemia during closed-loop control ($p = .011$).

Table 2 also shows no differences in average postprandial (4 h after breakfast), minimum, and maximum BG between open- and closed-loop control. In addition, the average amount of time within the target BG range did not differ, and the occurrence of hypoglycemia was similar. Thus closed-loop MPC resulted in meal-related glucose excursions similar to patient-directed open-loop BG control but with significantly fewer episodes of overnight hypoglycemia.

Discussion

These pilot studies demonstrate that subcutaneous closed-loop MPC of BG levels in adults with type 1 diabetes can be achieved overnight and following a breakfast meal. Model predictive control was at least as effective as patient-directed open-loop control in

Table 2.
Continuous Glucose Monitoring Overnight and Postbreakfast during Open- and Closed-Loop Control

	Open loop	Closed loop	*p*
Average overnight BG (mg/dl)	113.16	111.89	.903
Average minimum overnight BG (mg/dl)	75.00	81.69	.505
Average maximum overnight BG (mg/dl)	186.38	161.38	.286
Average percentage of time overnight YSI (70–140 mg/dl))	68.98	84.95	.121
Average percentage of time overnight YSI (70–180 mg/dl)	81.69	96.94	.052
Average number of overnight hypoglycemic episodes	1.63	0.13	.007
Average postbreakfast BG (mg/dl)	140.78	146.94	.682
Average postbreakfast minimum BG (mg/dl)	90.81	77.06	.270
Average postbreakfast maximum BG (mg/dl)	201.81	224.13	.243
Average percentage postbreakfast BG (70–140 mg/dl)	34.12	32.28	.843
Average percentage postbreakfast BG (70–180 mg/dl))	66.29	54.60	.281
Average number of postbreakfast hypoglycemic episodes	0.50	0.50	1.000

managing meal-associated rises in BG level and was superior to open-loop control in preventing overnight hypoglycemia.

As expected in pilot studies, several problems were encountered. The first problem related to sensor dropout of BG readings. At times, subjects inadvertently positioned themselves such that pressure on the sensor or lying directly on top of the sensor interfered with signal transmission. These dropouts are observed with all the currently approved CGM sensors and may be rectified in future CGM products. In addition, future versions of the controller may be modified in such a way as to account for temporary suspensions in signal transmission. In the studies presented here, this loss of sensitivity was restored in each case, and because the insulin was being infused every 15 min, not more than one bolus was omitted. In no case did this interruption result in hyperglycemia. During potential home use, hypoglycemia alarms would sound when the signal was lost, and patients would be awakened to investigate the phenomena and restore transmission.

A second problem related to the higher-than-desired rise in postprandial BG and the two instances of postmeal hypoglycemia. The study meal selected included 50 g of carbohydrates given in liquid form. Such a meal might be expected to result in a higher BG level than a meal of similar content that contained solids. As can be seen in **Figure 1**, during closed-loop control, insulin was infused in multiple doses rather than in a single premeal bolus as would be customary with open-loop control. A more aggressive prandial insulin algorithm might be called for but could increase the occurrence of postprandial hypoglycemia. Personalized "model" control permits the system to learn from the behaviors of the subject. Thus it is possible for MPC to initiate an increase in insulin infusion prior to the consumption of a meal if that meal is occurring at a set time each day and if that meal includes similar carbohydrate content and form. The advantage of this system's modeling is the reduction of postprandial hyperglycemia and a decrease in glycemic variability.

It is important to point out the marked reduction in overnight hypoglycemia observed in this small pilot sample. In particular, subject 5 experienced two hypoglycemia episodes during open-loop control and no episodes during closed-loop control. Subject 6 had three overnight hypoglycemic episodes during open-loop control and no overnight episodes with closed-loop control. Subject 7 had four low BG episodes with open-loop control and one with closed-loop control, and subject 8 had four episodes with open-loop control and none with the closed-loop. Thus, for these four individuals, closed-loop control resulted in significant improvements in overnight safety. This is the first study to report a reduction in nocturnal hypoglycemic episodes using closed-loop control.

In conclusion, this pilot study of MPC of BG levels is an important example of how *in silico* modeling and testing of human metabolism can be used to develop uniquely personalized methods for reducing morbidity associated with diabetes. Simulation studies substantially reduced the time to clinical trials by eliminating the need for animal trials and also aided in the establishment of the relationship between biometric characteristics of subjects and the aggressiveness of the control algorithm. This allowed for personalizing the controller for each subject. Further studies using *in silico* computer simulations of different scenarios associated with daily behaviors, i.e., exercise, variable mealtimes and contents, and physiologic and psychological stress, are planned as essential steps in the development of a totally artificial pancreas.

Funding:

This work was supported in part by National Institutes of Health GrantS RO1 DK 51562 and M01 RR 00847 and by the Juvenile Diabetes Research Foundation Artificial Pancreas Consortium.

References:

1. Santiago JV, Clemens AH, Clarke WL, Kipnis DM. Closed-loop and open-loop devices for blood glucose control in normal and diabetic subjects. Diabetes. 1979;28(1):71–84.
2. Clemens AH, Chang PH, Myers RW. The development of Biostator, a glucose controlled insulin infusion system (GCIIS). Horm Metab Res. 1977;Suppl 7:23–33.
3. Clarke WL, Kovatchev B. The artificial pancreas: how close are we to closing the loop? Pediatr Endocrinol Rev. 2007;4(4):314–6.
4. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes. 2006;55(12):3344–50.
5. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care. 2008;31(5):934–9.
6. Buckingham B, Cobry E, Clinton P, Gage V, Caswell K, Kunselman E, Cameron F, Chase HP. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. Diabetes Tech Ther. 2009;11(2):93–97.

7. Dua P, Doyle FJ III, Pistikopoulos EN. Model-based blood glucose control for type 1 diabetes via parametric programming. IEEE Trans Biomed Eng. 2005;53(8):1478–91.

8. Hovorka R, Canonico V, Chassin LJ, Haueter U, Massi-Benedetti M, Orsini Federici M, Pieber TR, Schaller HC, Schaupp L, Vering T, Wilinska ME. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. Physiol Meas. 2004;25(4):905–20.

9. Dassau E, Bequette BW, Buckingham BA, Doyle FJ III. Detection of a meal using continuous glucose monitoring: implications for an artificial beta-cell. Diabetes Care. 2008;31(2):295–300.

10. Magni L, Raimondo DM, Bossi L, Dalla Man C, De Nicolao G, Kovatchev B, Cobelli C. Model predictive control of type 1 diabetes: an in silico trial. J Diabetes Sci Technol. 2007;1(6):804–12.

11. Kovatchev BP, Breton M, Dalla Man C, Cobelli C. *In silico* preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. J Diabetes Sci Technol. 2009;3(1):44–55.

12. Patek SD, Breton MD, Chen Y, Solomon C, Kovatchev B. Linear quadratic Gaussian-based closed-loop control of type 1 diabetes. J Diabetes Sci Technol. 2007;1(6):834–41.

13. Dalla Man C, Rizza RA, Cobelli C. Meal simulation model of the glucose–insulin system. IEEE Trans Biomed Eng. 2007;54(10):1740–9.

14. Dalla Man C, Raimondo DM, Rizza RA, Cobelli C. GIM, simulation software of meal glucose–insulin model. J Diabetes Sci Technol. 2007;1(3):323–30.