ORIGINAL ARTICLE

Use of a “Fuzzy Logic” Controller in a Closed-Loop Artificial Pancreas

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Abstract

Background: Most current model-based approaches to closed-loop artificial pancreas systems rely on mathematical equations describing the human glucoregulatory system; however, incorporating the various physiological parameters (e.g., illness, stress) into these models has been problematic. We evaluated a fully automated “fuzzy logic” (FL) closed-loop insulin dosing controller that does not require differential equations of the glucoregulatory system and allows clinicians to personalize dosing aggressiveness to meet individual patient requirements.

Subjects and Methods: This pilot study evaluated the FL controller in the setting of bed rest in a very controlled environment. Two carbohydrate-controlled meals were given (30 g at 8 a.m. and 60 g at 2 p.m. without meal announcement or premeal bolus). The primary end point of the study was avoidance of hypoglycemia, defined at <60 mg/dL. Multiple end points related to the frequency and severity of hyperglycemia and hypoglycemia were also assessed.

Results: Of the 12 subjects we recruited, 10 were enrolled, and seven completed the study. Two of the enrolled subjects were discontinued because of hypoglycemia; the other was discontinued because of sensor failure. Seven of the 10 subjects who completed the study had average blood glucose values of 165 mg/dL and were within a specified target blood glucose range (70–200 mg/dL) for 76% of the 24-h study period.

Conclusions: Our findings suggest that the FL controller provides a viable alternative to model-based controllers as a component of a closed-loop insulin delivery system. Furthermore, our FL controller allows clinicians to easily specify the level of glucose control based on each patient’s clinical needs.

Introduction

THE JUVENILE DIABETES RESEARCH FOUNDATION launched the Artificial Pancreas Project in 2006 to hasten the development of a commercially available “closed-loop” system, utilizing continuous subcutaneous insulin infusion linked with continuous glucose monitoring (CGM) in order to mimic the physiologic function of the pancreas in individuals with type 1 diabetes. It is believed that such a system would facilitate safer, simpler, and more effective diabetes management, leading to improved clinical outcomes. Early proof-of-concept studies of automated closed-loop insulin delivery systems have shown that glycemic control can be achieved through use of this technology.^{1,2}

Significant advances have been made in continuous subcutaneous insulin infusion and CGM technologies, in both performance and interface; however, the clinical utility of automated closed-loop systems has been limited by inaccuracies in glucose sensing and delays in absorption of insulin from the subcutaneous tissue.³ Although these obstacles

are being gradually addressed, a key challenge to moving closed-loop insulin delivery forward is developing “controller” algorithms that can accurately calculate and administer insulin dosages in response to current and anticipated fluctuations in glucose levels. Developers are currently working on various approaches to address these issues.^{4–6}

Most current approaches to closed-loop systems, such as proportional-integral-derivative control^{3,7,8} and model predictive control^{9,10} technologies, rely on mathematical equations describing the human glucoregulatory system for interpretation of glucose data and subsequent calculation and administration of insulin. However, incorporating the various and varying physiological parameters (e.g., illness, stress) into these models has been problematic.

In collaboration with researchers at the University of California Santa Barbara (Santa Barbara, CA) and the Sansum Diabetes Research Institute (Santa Barbara), we refined a closed-loop controller that applies “fuzzy logic” (FL) to the glucose data to calculate and deliver appropriate amounts of insulin. Unlike proportional-integral-derivative and

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model predictive control artificial pancreas controllers, which calculate insulin doses based on mathematical equations describing the glucoregulatory system, FL controllers only depend on glucose management parameters, which were predetermined by an expert diabetes clinician and codified for use in the controller.^{11,12}

We conducted a small pilot study to determine the safety of the FL controller in a research setting, encompassing diurnal variations of glucose secondary to hormonal changes and a small- and a medium-sized meal.

Research Design and Methods

In this pilot study, we evaluated the safety and efficacy of an experimental, automated closed-loop insulin delivery system relevant to reducing the occurrence and/or duration of hypoglycemia without significant hyperglycemia during a 24-h period. The goal of the study was to demonstrate that the controller functions as expected without any unexpected safety concerns.

The study was conducted at the clinical research center at the Benaroya Research Institute (Seattle, WA) and in accordance with the Declaration of Helsinki and good clinical practice guidelines.¹³ The study protocol was approved by the Benaroya Research Institute Institutional Review Board, and all subjects provided written informed consent.

Dose safety system

The Dose Safety (Seattle) FL controller is a fully automated, closed-loop system (i.e., insulin is administered according to the glucose readings in a fully automated manner without information on the size or time of meals or premeal “priming” boluses.). The system comprises the FL controller (Dose Safety), a single OmniPod[®] insulin pump (Insulet, Bedford, MA), and two Dexcom[®] (San Diego, CA) SEVEN[®] PLUS CGM sensors. The FL controller has two components: the FL Dosing component and the Dosing Personalization component.

To imitate the reasoning of diabetes clinicians, the FL Dosing component was developed using the traditional FL system development process in collaboration with diabetes clinical experts. The physicians’ clinical expertise is codified in terms of “dosing rules,” where each rule addresses a different glucose circumstance. Each circumstance, or state, is specified by three terms: glucose level (mg/dL), glucose slope or rate (mg/dL/min), and glucose acceleration (mg/dL/min/min), with is the rate of change of the slope. To minimize the number of rules, the glucose term is restricted to five ranges, in which the letters correspond to actual numerical ranges: L (low, <80 mg/dL), N (normal, 80–120 mg/dL), H (high, 120–180 mg/dL), VH (very high, 180–250 mg/dL), and VVH (very, very high, >250 mg/dL). The declared goal of the rules matrix design is to keep the glucose levels stable within the 80–120 mg/dL range.

The controller is fully automated; the current glucose level is determined by the sensor and is transmitted directly to the computer, which calculates the insulin dose and automatically actuates the insulin pump to administer the dose. In the event of CGM data interruption, the controller automatically withholds insulin until a steady, validated stream of data is sensed.

To ensure controller robustness, the span of the three input terms is designed to cover all possible dosing situations that a person with diabetes would normally encounter. The dosing rules matrix design identifies special glucose dynamics indicative of events that require special treatment, such as meals. As a result, it adjusts the dosing accordingly. Figure 1 shows the complete FL design for FL controller version 1.5. For example, when glucose is normal (N), the rate is zero (Z), and the acceleration is positive (P), the dose is 0.10 units of insulin. All of the dosing rules are based on a 5-min glucose sample time. The controller is designed to maintain fully automated closed-loop control during fasting and postprandial periods.

	BG Rate	VN			N			Z			P			VP		
	BG Acceleration	N	Z	P	N	Z	P	N	Z	P	N	Z	P	N	Z	P
BG Level	VVH	0.00	0.00	0.00	0.10	0.15	0.80	0.10	0.15	0.80	0.15	0.30	1.40	0.20	0.50	2.00
	VH	0.00	0.00	0.00	0.05	0.10	0.25	0.10	0.15	0.30	0.10	0.25	1.20	0.15	0.40	1.90
	H	0.00	0.00	0.00	0.00	0.05	0.10	0.05	0.10	0.25	0.10	0.15	1.00	0.10	0.35	1.80
	N	0.00	0.00	0.00	0.00	0.00	0.05	0.00	0.05	0.10	0.05	0.10	0.45	0.05	0.10	0.60
	L	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.05	0.00	0.00	0.05	0.05	0.05	0.10

FIG. 1. Insulin dosage calculation schemata (version 1.5). The fuzzy logic controller uses current glucose level, rate of change, and acceleration to calculate insulin dosage. This example shows that when the glucose level is normal (N) (red circle), the rate is zero (Z) (blue circle), and the acceleration is positive (P) (green circle), the dose is 0.10 units of insulin (black circle). All of the dosing rules are based on a 5-min glucose sample time. BG, blood glucose; H, high; L, low; N, negative (for rate and acceleration); VH, very high; VN, very negative; VVH, very, very high.

Operationally, at time t , the current values for glucose rate and acceleration are updated using CGM values for t , $t-1$, and $t-2$. The standard Mamdani¹⁴ FL defuzzification process uses the FL design components to transform the updated glucose level, rate, and acceleration (three related inputs that are known as a 3-tuple) into internal parameters, which results in an updated insulin dose at time t . The dose is then multiplied by the personalization factor (PF) scale factor, which is calculated in the Dosing Personalization component. The scale factor is the product of the PF multiplier and each subject's total daily dose (TDD) (Table 1). A PF of "0" yields the most aggressive glycemic control (i.e., greatest dosing scale factor), whereas a PF of "10" yields the least aggressive control (i.e., least dosing scale factor). The PF scale factor remains fixed during operation. The robustness of the FL controller combined with the flexibility of the PF scale factor makes it easier for the system to deal with inter- and inpatient variability. The controller is operated by a Windows XP laptop running version 2.9 of the UCSB/SDRI APS software. A more detailed description of the controller is provided in Supplementary Data (available online at www.liebertonline.com/dia).

Subjects

The study recruited 12 subjects with type 1 diabetes through the Benaroya Research Institute Diabetes Clinical Research Program Registry. Subjects were screened for eligibility on the day prior to the study day. Inclusion criteria were as follows: diagnosed with type 1 diabetes for >1 year; age ≥ 18 –45 years; >3 months of insulin pump use; <9.0% hemoglobin A1c; and willing and able to give informed consent. Subjects were excluded if they had a preexisting medical condition of concern to the investigators, were taking medications that affect blood glucose other than insulin, abused alcohol or illicit drugs, were pregnant or breast feeding, or were unable to comply with the protocol.

Procedures

One day prior to the study, investigators obtained informed consent from eligible subjects and downloaded subjects' current insulin pump to assess their total daily basal insulin dosages. Two blinded sensors were placed on subjects' abdominal area to allow ample time for warm-up and calibration. One sensor served as the primary sensor, and the second was designated as the "back-up" sensor.

Subjects returned to the clinic the following day at 5 p.m., and an intravenous line was started. At 6 p.m. subjects ate an unrestricted meal, taking 75% of their usual insulin dose to elevate glucose levels for subsequent correction by the con-

troller. At 8 p.m. subjects' current pumps were removed, and the OmniPod insulin pump, governed by the FL controller, was attached and initialized. Subjects were started at PF-4. If, during the course of the study, two subjects become hypoglycemic at the PF-4 setting, the PF will be changed to a less aggressive setting (e.g., PF-5), per protocol. Also per protocol, if no subjects experienced hypoglycemia, the PF would have been changed to the more aggressive PF-3. The starting PF determination was based on results from in silico testing, using the UVA in silico simulator, a computer-based diabetes simulation tool developed by the University of Virginia (Charlottesville, VA) and accepted by the Food and Drug Administration.¹⁵

For the remainder of the study, the FL controller governed insulin dosing, which was based solely on the three previous readings from the primary glucose sensor. Venous blood samples were drawn every 15 min to allow for comparison against the Yellow Springs Instrument (YSI) (Yellow Springs, OH) reference. If the variance between the primary sensor and YSI reading was >20% for two consecutive readings, the back-up sensor was designated as the primary sensor. If the reference readings were <80 mg/dL, the YSI testing frequency was increased to every 5 min. Hypoglycemia, defined as a blood glucose level of <60 mg/dL, was treated with 15 g of carbohydrate (CHO) orally every 10 min until the YSI blood glucose was over 70 mg/dL. Intravenous dextrose was available, and a software engineer and physician were present at the bedside at all times. The next day, subjects were given a meal at 8 a.m. (30 g of CHO) and 2 p.m. (60 g of CHO). The study was concluded at 8 p.m.

Clinical measures

The primary end point of our study was avoidance of hypoglycemia (blood glucose level <60 mg/dL). The secondary measurements (as recommended by the Juvenile Diabetes Research Foundation at the time of the study) for the entire 24-h period included the following: average, lowest, and highest blood glucose level; time spent at target (70–200 mg/dL), below target (<70 mg/dL), and above target (>200 mg/dL); number of hypoglycemic (<60 mg/dL) and hyperglycemic (>300 mg/dL) events; Low Blood Glucose Index and High Blood Glucose Index; area above the curve <70 mg/dL; and area under the curve >200 mg/dL. Post hoc analyses were also conducted using glycemic target ranges of 70–180 mg/dL and >180 mg/dL.

We evaluated these measures by individual subject for the entire 24-h period and in four 6-h subsets of the entire study period as follows: correction of hyperglycemia from 8 p.m. to 2 a.m.; fasting and diurnal variation from 2 a.m. to 8 a.m.; small meal glycemic control (30 g of CHO) from 8 a.m. to 2

TABLE 1. EXAMPLE OF PERSONALIZATION FACTOR SCALE FACTOR MULTIPLIER VALUES

	PF-0	PF-1	PF-2	PF-3	PF-4	PF-5	PF-6	PF-7	PF-8	PF-9	PF-10
PF multiplier values	0.032	0.029	0.026	0.023	0.020	0.017	0.014	0.011	0.008	0.005	0.002
Insulin dose	1.74	1.58	1.41	1.25	1.08	0.92	0.75	0.59	0.42	0.26	0.09
Percentage doses relative to the PF-5 dose	190%	172%	154%	136%	118%	100%	82%	64%	46%	28%	10%

This example shows calculations of the insulin dosages and percentages associated with each personalization factor (PF) when the fuzzy logic dose equals 1.0 unit of insulin and the total daily dose equals 55 units of insulin per day. The PF-5 dose values are in bold type for comparison.

p.m.; and moderate meal glycemic control (60 g of CHO) from 2 p.m. to 8 p.m.

Statistical analysis

Descriptive statistics are reported in our analyses of clinical measurements. Missing or incomplete data were not imputed. Glycemic calculated end points were not calculated or reported for those subjects with early discontinuation or rescue. We used standard statistical techniques using Mathworks® (Natick, MA) tools and Microsoft® (Redmond, WA) Excel.

Results

Of the 12 subjects who were recruited, 10 participated in the study: five men and five women. The two remaining subjects did not meet inclusion criteria because of elevated hemoglobin A1c levels (>9%). The mean age of participants was 23.6 years (range, 18–35 years), the mean hemoglobin A1c level was 7.7% (range, 6.4–8.6%), and the mean duration of diabetes was 8.7 years (range, 2–12 years). The relevant clinical characteristics of the study participants are presented in Table 2.

Seven of the 10 subjects completed the 24-h study with no incidents of hypoglycemia (<60 mg/dL). Among the non-completers, two were discontinued because of hypoglycemia (subjects #01 and #04). Because two subjects experienced hypoglycemia at the PF-4 setting, we used the PF-5 setting for all subsequent subjects (#5–#10) per our protocol, which provided a less aggressive dosing output. The third subject (#10) was discontinued because both sensor receivers failed to display glucose readings simultaneously approximately 18 h into the study. During the study, sensors were switched back and fourth three times with patient #07, four times with patient #12, and once with patient #03. The remaining patients used the same sensor throughout the study.

Primary and secondary end points

Table 3 presents findings for each of the metrics assessed, overall and for the four time parts. Measurements for each subject are included in Supplementary Data. Figure 2 presents an example of glucose change over the 24-h period. Glucose tracings for all patients are included in Supplementary Data.

Causes of hypoglycemia in discontinued subjects

In our analysis of the two subjects who were discontinued because of hypoglycemia, it was determined that the TDD calculated for subject #01 was overestimated given the CHO restriction of the study: 90 g over the 24-h study period versus the subject's usual 400 g/day as indicated in his 14-day insulin pump download. In response, we revised our controller initialization scheme for all subsequent subjects, defining TDD as the total daily basal insulin obtained from the pump download plus the units of bolus insulin the subject would normally take for 90 g of CHO. Furthermore, review of sensor downloaded data from subject #04 revealed that her blood glucose had been <60 mg/dL for >6 h during the night prior to study initiation, suggesting that the subject's basal insulin dosage was inappropriately high.

Discussion

Preliminary data from our study suggest that use of a FL controller as a component of a closed-loop system can provide a safe method for automating the regulation of blood glucose in sedentary subjects in clinical research settings, using only the subject's total daily insulin and CGM data, and that it is comparable to other current closed-loop insulin delivery controllers that use proportional-integral-derivative control^{3,4} and model predictive control^{5–7} technologies.

Because our FL-based controller responds to changes in glucose, it can address many of the physiologic changes (e.g., illness, stress, menstrual cycle, exercise, varying meal content, frequent insulin sensitivity variations) that patients experience in their daily diabetes management. The FL controller also has the advantage of offering defined levels of glycemic control (PF), which clinicians can specify to individualize patient care, using their own clinical judgment and expertise. Moreover, as first described by the Yale group,¹⁶ insulin absorption with continuous subcutaneous insulin infusion is not stable over time; the longer the infusion set is in place, the faster the absorption. With FL, these changes in pharmacokinetics and pharmacodynamics will not matter because the algorithm will automatically correct for this. The controller used in this study currently does not track insulin on board; this function will be included in subsequent versions.

TABLE 2. RELEVANT CLINICAL CHARACTERISTICS OF STUDY PARTICIPANTS

Subject number	Age (years)	Gender	BMI (kg/m ²)	Correction factor (U:mg/dL)	CHO ratio (U:CHOg)	HbA1c (%)	Diabetes duration (years)	TDD (U/day)	TDD per FL controller (U/day) ^a
01	18	Male	21.1	70	8	8.6	11	NA ^b	73.1 [§]
02	23	Male	29.0	25	8	8.0	6	32.8	44.0
03	24	Female	21.3	50	8	6.7	10	17.6	28.8
04	28	Female	34.5	30	10	8.3	11	28.5	37.5
05	20	Male	24.4	50	10	8.3	12	33.9	42.9
06	19	Female	24.5	50	8	8.2	7	21.9	33.1
07	35	Male	25.0	50	15	6.4	9	19.4	25.4
08	22	Male	30.4	25	8	7.6	10	32.1	43.3
09	27	Female	27.1	50	15	6.8	9	21.1	27.1
10	30	Female	26.7	70	30	7.8	2	20.0	23.0
Mean (SD) average	24.6 (5.4)	50% male	26.4 (4.1)	47.0 (16.2)	12.0 (6.9)	7.7 (0.8)	8.7 (3.0)	25.3 (6.5)	33.9 (8.3)

^aTotal daily insulin controller = (total basal insulin + 90 g of carbohydrate [CHO]/CHO ratio).

^bNot available (NA). Total daily insulin was used for subject #01.

BMI, body mass index; FL, fuzzy logic; HbA1c, hemoglobin A1c; TDD, total daily dose.

TABLE 3. GLYCEMIC EFFECTS OF THE FUZZY LOGIC SYSTEM ACROSS ALL PARTS OF THE DAY FOR ALL SEVEN SUBJECTS COMPLETING THE STUDY

YSI end points	All time periods (8 p.m.–8 p.m.)	Hyperglycemia correction (8 p.m.–2 a.m.)	Diurnal variation (2 a.m.–8 a.m.)	Small meal (8 a.m.–2 p.m.)	Moderate meal (2 p.m.–8 p.m.)
BG (mg/dL)					
Average	165.1	159.7	129.7	174.9	195.2
Lowest	68.0	82.00	68.0	88.0	88.0
Highest	342.0	342.0	215.0	255.0	266.0
Time (%) BG was					
<70 mg/dL	0.1%	0.0%	0.6%	0.0%	0.0%
70–180 mg/dL	65.0%	69.6%	95.8%	61.9%	32.7%
70–200 mg/dL	76.3%	79.8%	97.6%	72.6%	55.4%
>200 mg/dL	23.5%	20.2%	1.8%	27.4%	44.6%
Hypoglycemia events (BG < 60 mg/dL)	0.0	0.0	0.0	0.0	0.0
Hyperglycemia events (BG > 300 mg/dL)	0.1	0.1	0.0	0.0	0.0
LBGI	0.2	0.2	0.6	0.0	0.0
HBGI	7.1	6.5	2.2	8.0	11.3
AAC < 70 mg/dL·min	4.3	0.0	4.3	0.0	0.0
AUC > 200 mg/dL·min	11,817.3	4,236.4	122.1	2,941.6	4,517.1
Overnight end points [time (%) BG was]	Midnight–7:30 a.m.		Midnight–8:00 a.m.		9:30 p.m.–8:00 a.m.
<70 mg/dL	0.0%		0.4%		0.3%
70–144 mg/dL	62.4%		62.1%		58.8%
70–180 mg/dL	91.9%		92.0%		84.4%
>180 mg/dL	8.1%		7.6%		15.3%
>200 mg/dL	6.2%		5.8%		10.0%
Meal end points [time (%) BG was]	4 h (30 g/60 g)		5 h (30 g/60 g)		6 h (30 g/60 g)
<70 mg/dL	0%/0%		0%/0%		0%/0%
70–140 mg/dL	17%/10%		19%/9%		22%/8%
70–180 mg/dL	64%/16%		61%/19%		63%/30%
>180 mg/dL	36%/84%		39%/81%		37%/70%

Data are mean values for each study period.

AAC, area above the curve; AUC, area under the curve; BG, blood glucose; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index; YSI, Yellow Springs Instrument blood glucose analyzer.

Atlas et al.¹⁷ also used FL technology in the control-to-range pre-processor module of their MD-Logic Artificial Pancreas (MDLAP) controller. Use of this design was recently shown to be effective in reducing nocturnal hypoglycemia and improving glycemic control in young patients at a diabetes camp.¹⁸ The MDLAP system and our FL controller are similar in several ways. Both use a Mamdani-type FL con-

troller having glucose and rate input membership functions, a rules matrix developed with medical experts, and an insulin bolus output membership function. Unlike the MDLAP system, which provides an insulin delivery regimen for both the basal plan and an insulin correction factor, our controller produces a single mini-bolus of insulin. Additionally, our controller's FL dosing is based solely on the current glucose

FIG. 2. Example of patient continuous glucose monitoring tracing. BG, blood glucose.

value, its rate, and its acceleration, whereas the MDLAP control-to-range inputs include current blood sugar and rate, as well as predictions for both. The dose produced by our FL system is multiplied by a scale factor constant that is a function of the physician-selected PF and the subject's total daily insulin. The control-to-range module in the MDLAP system identifies special glucose dynamics indicative of events that require special treatment, such as meals. As a result, the control-to-range basal and bolus dosing suggestions are refined. The insulin-on-board capability prevents overdosing. A comparison of the Dose Safety and Atlas MDLAP controllers is presented in Supplementary Data.

A key weakness of our study was the small number of subjects, which limits the generalizability of our findings. Also, our study was conducted with subjects under a limited number of controlled conditions (e.g., subjects were at bed rest, only two meals in which the CHO content was strictly defined). Additional studies are needed to evaluate the system in real-life situations and within the parameters of a greater variety of clinical conditions (e.g., exercise, stress, meals with varying CHO content).

Although our "proof-of-concept" study was designed to assess the feasibility and safety of an early-stage experimental controller, our findings suggest that use of a FL controller offers a viable alternative to proportional-integral-derivative and model predictive control controllers. Moreover, our FL controller allows clinicians to easily select levels of glycemic control that address the specific needs of each patient.

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Author Disclosure Statement

R.K., D.M., and R.M. are principals in Dose Safety Inc., Seattle, WA. I.B.H., J.B., S.S., and C.B. declare no competing financial interests exist.

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