MD-Logic Artificial Pancreas System

A pilot study in adults with type 1 diabetes

ERAN ATLAS, MSC[1]
REVITAL NIMRI, MD[1]
SHAHAR MILLER, BSC[1]
ELI A. GRUNBERG, BSC[1]
MOSHE PHILLIP, MD[1,2]

OBJECTIVE — Current state-of-the-art artificial pancreas systems are either based on traditional linear control theory or rely on mathematical models of glucose-insulin dynamics. Blood glucose control using these methods is limited due to the complexity of the biological system. The aim of this study was to describe the principles and clinical performance of the novel MD-Logic Artificial Pancreas (MDLAP) System.

RESEARCH DESIGN AND METHODS — The MDLAP applies fuzzy logic theory to imitate lines of reasoning of diabetes caregivers. It uses a combination of control-to-range and control-to-target strategies to automatically regulate individual glucose levels. Feasibility clinical studies were conducted in seven adults with type 1 diabetes (aged 19–30 years, mean diabetes duration 10 ± 4 years, mean A1C 6.6 ± 0.7%). All underwent 14 full, closed-loop control sessions of 8 h (fasting and meal challenge conditions) and 24 h.

RESULTS — The mean peak postprandial (overall sessions) glucose level was 224 ± 22 mg/dl. Postprandial glucose levels returned to <180 mg/dl within 2.6 ± 0.6 h and remained stable in the normal range for at least 1 h. During 24-h closed-loop control, 73% of the sensor values ranged between 70 and 180 mg/dl, 27% were >180 mg/dl, and none were <70 mg/dl. There were no events of symptomatic hypoglycemia during any of the trials.

CONCLUSIONS — The MDLAP system is a promising tool for individualized glucose control in patients with type 1 diabetes. It is designed to minimize high glucose peaks while preventing hypoglycemia. Further studies are planned in the broad population under daily-life conditions.

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The core of the ideal artificial pancreas system is the control algorithm that automatically modulates insulin delivery (and optionally other hormones) according to measured glucose levels (1). Current state-of-the-art control algorithms for clinical use are based on either traditional linear control theory or crisp mathematical models of glucose-insulin dynamics. The most common ones are the proportional-integral-derivative control (2) and the model predictive control (3–6). However, the nonlinearity, complexity, and uncertainty of the biological system, along with the inherent delay and deviation of the measuring devices, make it difficult to characterize the model and correctly evaluate the physiological behavior of the individual patient (2–4,6). In addition, because the published state-of-the-art control algorithms are not amenable to multiple inputs and multiple outputs, the measured blood glucose level is the only input in most of them, and insulin delivery is the only output.

To deal with these challenges, we developed the novel MD-Logic Artificial Pancreas (MDLAP) System. The MDLAP applies the principles of fuzzy logic theory to imitate the line of reasoning of diabetes caregivers. This reasoning is based on medical knowledge and traditional treatment. By taking the individual subject's treatment management into account, the MDLAP can accurately adjust the control parameters and overcome inter- and intrapatient variability.

Fuzzy logic is the science of reasoning, thinking, and inference that recognizes that not everything is true or false in the real world. In fuzzy logic, the correctness of any statement becomes a matter of degree. The main elements of the fuzzy logic controller are fuzzy sets of multiple inputs and single or multiple outputs, fuzzy rules structured according to the form of IF (input)–THEN (output) and methods of "fuzzification" and "defuzzification" to evaluate the fuzzy rule output based on the input (7,8). Several groups have proposed closed-loop systems using a fuzzy logic controller for the management of diabetes (9–11), but to the best of our knowledge, none has been clinically tested and validated. This article describes the principles underlying the MDLAP system, its components and control strategies, and the results of feasibility clinical trials.

RESEARCH DESIGN AND METHODS

MDLAP system

The MDLAP system is a full 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). To imitate the reasoning of diabetes caregivers, the MDLAP system was designed using traditional treatment principles.

The MDLAP system uses an individual patient's treatment management, which includes the patient's physical characteristics, insulin delivery regimen (insulin basal plan and insulin correction factor), and insulin pharmacodynamic parameters. The treatment management is extracted from prerecorded data, including subcutaneous continuous glucose sensor (CGS) readings, glucometer measurements, insulin treatment, and activity diary, that were recorded during the

From [1]The Jesse Z. and Sara Lea Shafer Institute for Endocrinology and Diabetes, The National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel; and the [2]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
Corresponding author: Moshe Phillip, mosheph@post.tau.ac.il.
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Table 1—*Subject characteristics*

Subject no.	Age (years)	Gender (female/male)	BMI (kg/m^2)	A1C (%)	Disease duration (years)	Means ± SD of blood glucose level (mg/dl)*	IU · kg^{-1} · day^{-1}
1	30	Female	22.9	5.9	19	113 ± 54	0.72
2	23	Male	21.2	7	8	120 ± 35	0.59
3	22	Female	26.5	6.2	8	126 ± 44	0.63
4	25	Female	22.4	5.4	8	151 ± 66	0.72
5	23	Male	20.0	7.1	14	143 ± 48	0.72
6	19	Female	19.5	7.4	5	137 ± 49	1.04
7	25	Female	19.8	7.1	10.5	119 ± 43	1.08

*As measured at home by CGS.

patient's everyday regular therapy at home (i.e., home care).

The system applies a combination of two control strategies: control to range and control to target. The control-to-range strategy is implemented in the control-to-range module (CRM), which aims at bringing the patient's glucose levels into the desired range. The CRM is a fuzzy logic controller that uses treatment rules that were phrased in collaboration with the medical staff. The declared goal of the rules was to keep the glucose levels stable within the 80–120 mg/dl range. The rules use four inputs that are calculated from CGS readings: past and future glucose trend as well as current and future glucose levels. Each rule has two outputs: *1*) change in basal rate and *2*) portion of insulin bolus (in percentage from the patient's basal plan and the calculated bolus, respectively).

The control-to-target module (CTM) aims to bring the patient's glucose to a specific target level. To reach the final dosing recommendation, the CTM takes into consideration the *1*) recommendation of the CRM (in percentage), *2*) the predefined glucose target level, *3*) insulin dosing regimen history, and *4*) safety constraints related to the insulin pharmacodynamics. Since the MDLAP is a full close-loop system, the CTM uses a detector in order to identify special glucose dynamics indicative of a sign of events that require special treatment, such as meals. As a result, it adjusts the dosing accordingly.

Both the patient's treatment management and the performance of the controller are adjustable, making it easier for the system to deal with inter- and intrapatient variability. Detailed descriptions of the system components are provided in the online appendix (available at http://care.diabetesjournals.org/cgi/content/full/dc09-1830/DC1).

Clinical studies

The studies were designed as pilot prospective trials. The study group consisted of seven patients with type 1 diabetes attending the National Center for Childhood Diabetes of Schneider Children's Medical Center of Israel. Inclusion criteria were age >18 years, disease duration of at least 1 year, and treatment with an insulin pump for at least 6 months. Patients with a concomitant disease affecting metabolic control or another medical condition that could compromise their safety during the trial were excluded, as were patients with a known or suspected allergy to the trial products or who had participated in another study of drugs that could affect glucose measurements or glucose management. The study was approved by the institutional ethics committee. All subjects signed an informed consent form.

Prior to the closed-loop sessions, the patients' demographic data, diabetes history, and other significant medical history were recorded, in addition to height, weight, and A1C level (Table 1). The patients wore a CGS (Freestyle Navigator, Abbott Diabetes Care, Alameda, CA; or STS-Seven System, DexCom, San Diego, CA) and recorded their meals and physical activities for 3–5 consecutive days. These data and corresponding insulin doses (downloaded from the insulin pump) were used to formulate the patients' treatment management for application in the MDLAP system.

A short-acting insulin analog (NovoRapid; Novo Nordisk, Bagsvaerd, Denmark) was used in the clinical trials. The CGS readings were entered (automatically or manually) into the MDLAP system every 5 min, and the system provided an insulin dose recommendation after each entry. The control to range was set at 90–140 mg/dl and the control to target at 110 mg/dl. The clinical trials lasted 8 or 24 h of closed-loop control. Each clinical session was supervised by a diabetologist who had to approve any treatment recommendation before it was automatically or manually delivered by the pump to the patient. Reference blood glucose levels were measured by the YSI 2300 STAT Plus (YSI, Yellow Springs, OH) every 30 min. Carbohydrate was administered when the reference blood glucose level dropped below 70 mg/dl.

8-h closed-loop sessions. The 8-h closed-loop sessions were conducted in the resting state under two conditions: fasting or meal. The subject's insulin pump was replaced by the research insulin pump (OmniPod Insulin Management System; Insulet, Bedford, MA; or MiniMed Paradigm 722 Insulin Pump, Medtronic, Northridge, CA). In the fasting closed-loop condition, subjects arrived to the clinic in the morning (usually 0800 h) after an overnight fast and were instructed to measure their blood glucose when they woke up (usually 0630 h). If the level was <120 mg/dl with no hypoglycemia, they were asked to eat one to two slices of bread. In the closed-loop sessions with meal challenge, patients arrived to the clinic after about an 8-h fast and consumed a mixed meal with a carbohydrate content of 40–60 g.

24-h closed-loop sessions. Two 24-h closed-loop visits were conducted. The two subjects who participated in the 24-h sessions were the first subjects who completed four short sessions (8 h) and were willing to participate in this session. There were no other criteria for choosing subjects for the 24-h session. Subjects arrived at the clinic in the afternoon after a fast of at least 3 h. The subject's insulin pump was replaced with the OmniPod CSII, which includes a commercial Pod and an engineering PDM (Insulet) that can communicate in real time with a per-

Table 2—*Average and range results from 8-h closed-loop sessions*

	Average	Range
Fasting sessions (n = 6, 9 sessions)		
Blood glucose at the beginning of the closed-loop session (mg/dl)	237	178–300
Time to <180 mg/dl from system connection (h)	2.13	0.5–4.43
Time to stable blood glucose levels (h)	4.4	2.3–6.75
Blood glucose level at stabilization (mg/dl)	112	77–155
Meal challenge sessions (n = 2, 3 sessions)		
Blood glucose at the beginning of the closed-loop session (mg/dl)	96	70–138
Peak postprandial blood glucose level (mg/dl)	234	211–251
Time to <180 mg/dl from meal onset (h)	2.56	2.18–3
Time to stable blood glucose levels (h)	3.43	3–4.3
Blood glucose level at stabilization (mg/dl)	102	70–134.5

sonal computer (12). This communication with the insulin pump was conducted using the Artificial Pancreas Software (APS) version 2.5, developed by Dassau et al. (13). Three standard mixed meals were consumed at 1930, 0800, and 1300 h, based on the patient's regular diet. The estimated carbohydrate content for each meal was 17.5–70 g. Each patient slept for 7–8 h at night during the study.

Data analysis of control performances. To examine the control performances of the MDLAP system during the 8-h closed-loop sessions, we focused on two parameters: glucose excursion and degree of stabilization. Glucose excursion is determined by the peak postprandial glucose level and the time from initiation of closed-loop control to return of the glucose level to <180 mg/dl. Stable glucose levels were defined as a change of ±10 mg/dl for a period of at least 30 min. The time from initiation of closed-loop control or mealtime until the stable state was attained, and the average glucose levels at the stable state, were calculated.

In addition, we compared 24-h closed-loop control to the patient's home care. The percentage of glucose readings within, above, and below the range of 70–180 mg/dl was determined. The dataset of home care included sensor readings from the 3-day period prior to the 24-h closed-loop session. Control variability grid analysis (CVGA) (14) served as an auxiliary outcome measure. The CVGA is a graphical representation of the minimum/maximum glucose values over a certain time period. The CVGA is divided into nine rectangular zones that are associated with different qualities of glycemic regulation. For example, accurate control (A zone) means that the minimum glucose level is between 90 and 110 mg/dl and the maximum glucose level is between 110 and 180 mg/dl. Other zones are benign control deviation (lower B, B, and upper B zones), overcorrection of hypoglycemia/hyperglycemia zones (lower C and upper C), failure to deal with hypoglycemia/hyperglycemia zones (lower D and upper D), and erroneous control (E zone). In this analysis, the home care dataset included sensor readings from a period of 9–16 days. CVGA was performed over two time periods: 24 h and overnight (0000–0800 h).

RESULTS — During all of the experiments, our diabetes physicians approved each and every one of the MDLAP system treatment suggestions. Table 2 summarizes the results of the 8-h feasibility clinical studies under fasting and meal challenge conditions. Two sessions were excluded from the analysis due to technical problems with the insulin pump. In the first instance, there was an occlusion in the insulin pump tubing, and in the second, the patient accidentally administrated insulin in addition to the insulin that was administrated by the MDLAP system.

Two 24-h closed-loop sessions were conducted with subjects 1 and 2 (Table 1). During the night, glucose levels ranged between 80 and 160 mg/dl, with a nadir of 93 mg/dl for subject 1 and 80 mg/dl for subject 2. Figure 1*A* shows an example of a 24-h closed-loop session of subject 1. Glucose levels peaked at 260 mg/dl after dinner, 190 mg/dl after breakfast, and 210 mg/dl after lunch. The corresponding values for subject 2 were 221, 211, and 219 mg/dl. Between meals, glucose levels returned to <180 mg/dl within a mean of 2.7 ± 0.8 h for both subjects.

Mean peak postprandial glucose level for overall sessions (8 and 24 h) was 224 ± 22 mg/dl, and glucose level returned to <180 mg/dl at a mean interval of 2.6 ± 0.6 h. Mean time to stabilization was 4 ± 1 h. Performance analysis of the CTM detection algorithm shows that the overall mean detection time was 23 min after meal consumption.

Based on our control performances analysis (see RESEARCH DESIGN AND METHODS), glucose control was found to be better during the MDLAP-regulated 24-h closed-loop sessions than during the prestudy home care. Seventy-three percent of the sensor values measured 70–180 mg/dl during closed-loop control compared with 70.5% over the 3-day home care period prior to the trial day. In addition, none of the sensor readings were <70 mg/dl during closed-loop control compared with 15.3% for home care. However, 27% of the sensor values were >180 mg/dl during closed-loop control compared with 14.2% during home care. On CVGA, the MDLAP maintained benign control over a 24-h perspective, whereas the subjects at home care overcorrected and failed to manage hypoglycemia. During the night as well, the MDLAP system maintained benign or accurate control, whereas home care was characterized by considerable variability. Results of the comparison between the MDLAP performances and home care for subject 1 are presented in Fig. 1*B* and *C*.

No events of hypoglycemia occurred during either the 8-h (overnight) or 24-h closed-loop sessions. An impending hypoglycemic event was detected on two occasions (8-h closed-loop sessions), with glucose levels ranging between 62 and 65 mg/dl for ~10 min. Although the subjects did not experience any symptoms of hypoglycemia, our physician decided to administer 15 g of fast carbohydrate for safety reasons.

CONCLUSIONS — The present feasibility study demonstrated the use of MDLAP to fully close the loop between an external subcutaneous glucose sensor and insulin pump in adults with type 1 diabetes.

The MDLAP incorporates the fuzzy logic theory as applied to the patient's medical and diabetes history and treatment profile. The MDLAP applies tradi-

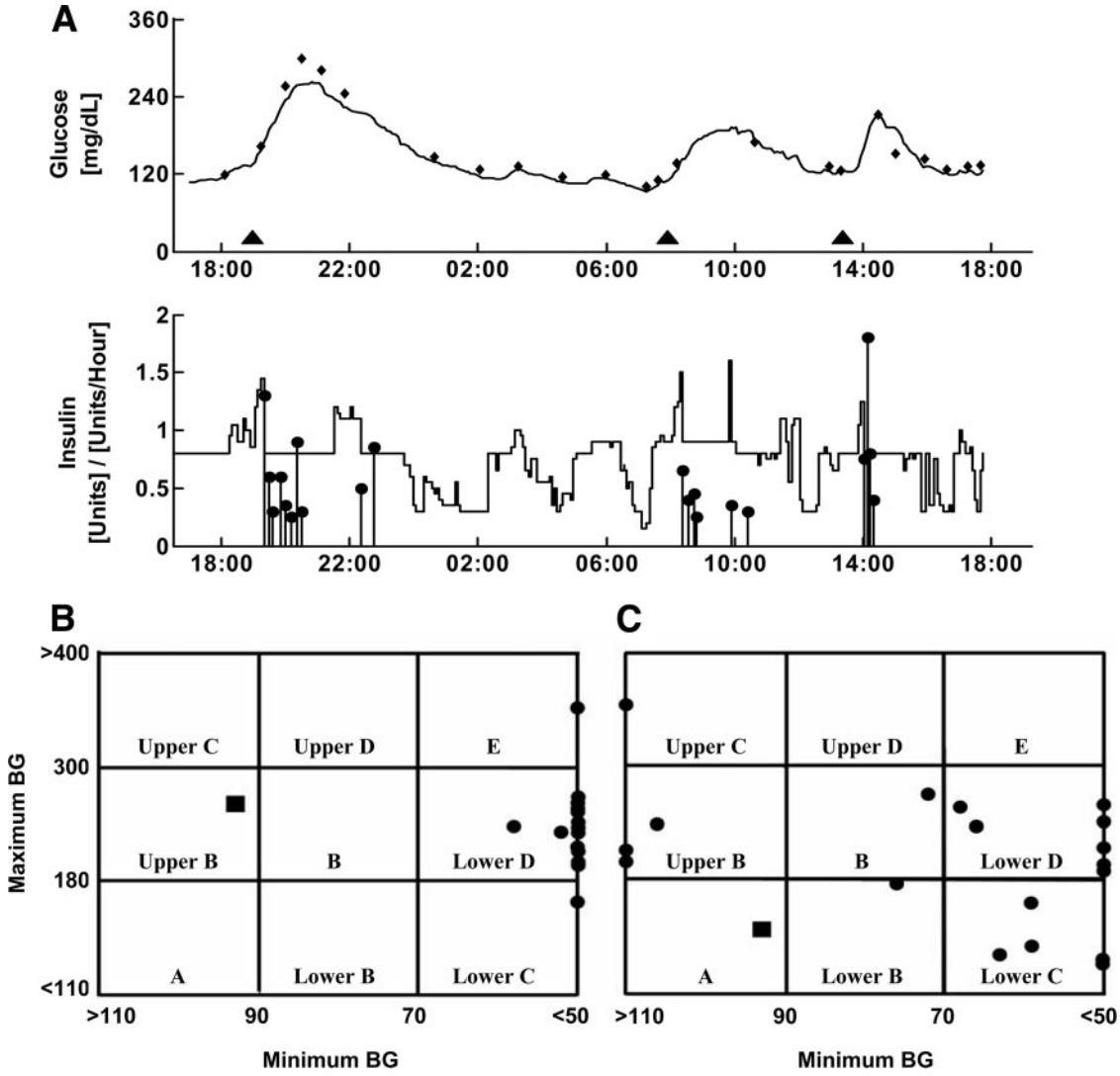

Figure 1—*Example of 24-h closed-loop session results conducted with subject 1.* A: *Glucose trace and the insulin treatment during the 24-h closed-loop trial with subject 1. The* top graph *shows the CGS readings (black line), reference YSI measurements (♦), and the meal times (▲). The* bottom graph *shows the insulin treatment delivered by the MDLAP (horizontal line = basal rate, vertical lines with ● = insulin boluses).* B: *Control variability grid analysis over a time period of 24 h for subject 1.* C: *Control variability grid analysis overnight (0000–0800 h) for subject 1. The nine zones of the CVGA are associated with different qualities of glycemic regulation: A, accurate control; lower B, benign deviations into hypoglycemia; B, benign control deviations; upper B, benign deviations into hyperglycemia; lower C, overcorrection of hypoglycemia; upper C, overcorrection of hyperglycemia; lower D, failure to deal with hypoglycemia; upper D, failure to deal with hyperglycemia; and E, erroneous control. In both figures, the circles represent the minimum/maximum glucose level taken from the relevant time period glucose readings during home care and the rectangles indicate the levels during the MDLAP-regulated closed-loop session. BG, blood glucose.*

tional treatment principles as well as combined control-to-range and control-to-target strategies in order to achieve the clinical goals of glucose control. To the best of our knowledge, this is the first time that clinical diabetes treatment logic has been transformed into an automatic closed-loop system and tested in human subjects.

In our pilot studies, the time needed for stabilization of glucose levels within the desired range after meal consumptions for overall sessions was somewhat extended, as expected. It is noteworthy that full closed-loop systems have an inherent deficiency for managing postmeal glucose excursion relative to the traditional home care. While the patient is required to inject bolus insulin before each meal in traditional home care, the closed-loop system depends on the detection of changes in blood glucose levels to recognize a meal event and, therefore, an inhabitant delay in insulin delivery is mandatory. To keep postprandial levels closer to the normal range, the closed-loop system needs to include an effective meal detection algorithm as well as a control strategy dedicated to treat meals. We believe that a fuzzy logic controller is most suitable for coping with the latter need, since it is modular and allows aggregation of different and independent treatment modes (e.g., it can incorporate a separate module that treats fasting periods and another one that treats meals). Another advantage of the fuzzy logic controller over the currently tested controllers is its ability to intuitively implement different types of outputs on the same control platform (e.g., insulin and glucagon).

There were no events of symptomatic hypoglycemia during our feasibility clinical trials. Moreover, glucose levels were maintained in the near-normal range (80–160 mg/dl) at night. There was a short incident of impending asymptomatic hypoglycemia in two of the 14 closed-loop sessions. It is important to mention that the MDLAP made treatment suggestions, which were judged as appropriate and approved by the diabetes physician in charge.

The main objective of this study was to evaluate the feasibility of the MDLAP to provide good glucose control under the conditions that were studied. Since it is a seven-patient pilot study, there is no control group. The performances of the system were evaluated using objective and appropriate parameters. Patients with well-controlled type 1 diabetes were selected to participate in this study since they were usually compliant with the study demands and, therefore, were more suitable for a feasibility study and also since we wanted to compare the capabilities of the system to the patients' self-regulated control at home. We used the percentage of glucose readings in different ranges as well as CVGA to provide the reader with qualitative comparisons between the MDLAP's glucose control and the patient's home glucose control. The close-loop sessions were conducted in conditions that were very different to those in the subject's home, precluding a statistical analysis between the two settings.

In conclusion, the MDLAP system is a promising tool for individualized glucose control of patients with type 1 diabetes, with the ultimate aim of minimizing high glucose peaks while preventing hypoglycemia. The MDLAP is a potential tool to overcome threatening nocturnal hypoglycemia. The MDLAP system allows the incorporation of a learning algorithm for automatic analysis of control performances against intrapatient variances in the glucose/insulin dynamics, with adjustments of the control parameters accordingly for further improvement of its performance. Further studies in larger populations under ordinary daily life conditions are needed.

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