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An Integrated Multivariable Artificial Pancreas Control System

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Abstract

The objective was to develop a closed-loop (CL) artificial pancreas (AP) control system that uses continuous measurements of glucose concentration and physiological variables, integrated with a hypoglycemia early alarm module to regulate glucose concentration and prevent hypoglycemia. Eleven open-loop (OL) and 9 CL experiments were performed. A multivariable adaptive artificial pancreas (MAAP) system was used for the first 6 CL experiments. An integrated multivariable adaptive artificial pancreas (IMAAP) system consisting of MAAP augmented with a hypoglycemia early alarm system was used during the last 3 CL experiments. Glucose values and physical activity information were measured and transferred to the controller every 10 minutes and insulin suggestions were entered to the pump manually. All experiments were designed to be close to real-life conditions. Severe hypoglycemic episodes were seen several times during the OL experiments. With the MAAP system, the occurrence of severe hypoglycemia was decreased significantly ($P < .01$). No hypoglycemia was seen with the IMAAP system. There was also a significant difference ($P < .01$) between OL and CL experiments with regard to percentage of glucose concentration (54% vs 58%) that remained within target range (70-180 mg/dl). Integration of an adaptive control and hypoglycemia early alarm system was able to keep glucose concentration values in target range in patients with type 1 diabetes. Postprandial hypoglycemia and exercise-induced hypoglycemia did not occur when this system was used. Physical activity information improved estimation of the blood glucose concentration and effectiveness of the control system.

Keywords

type 1 diabetes, closed-loop, hypoglycemia, adaptive control

To address pancreatic deficits associated with type 1 diabetes, artificial pancreas (AP) systems have been developed and tested in CL studies. Our CL studies involve the integration of a glucose sensor, an automatic controller that computes the amount of insulin to be infused and an insulin pump and experiments with unannounced meals and exercises over a 32-hour period. Hypoglycemia is a major challenge for the development of AP systems. Many CL studies with various control algorithms have resulted in mild or severe hypoglycemic episodes.[1-4] Mathematical models for the prediction of plasma insulin levels have been incorporated into CL studies for hypoglycemia prevention.[5-9] Hypoglycemia prediction-based pump suspension methods have been noted to decrease the occurrence of hypoglycemia.[10,11] Bihormonal CL studies[7,8,12] using glucagon and insulin have also been proposed for hypoglycemia prevention. Semiautomated hybrid systems[5,8,13-16] have been reported to reduce the increase in postprandial glucose levels and subsequently decrease insulin-induced postprandial hypoglycemia. Though all these reported methods decreased the time spent in hypoglycemia, complete avoidance of hypoglycemia was not achieved, and additional carbohydrate (CHO) supplements were needed for treatment of some of hypoglycemic episodes.

A patient's metabolic and physical activities have significant effects on glucose and insulin dynamics.[9] Energy expenditure (EE) can be used as indicator of physical activity.[17] Physiologic stress such as physical activity can increase the risk of hypoglycemia. Many patients with type 1 diabetes suffer from postexercise hypoglycemia.[18,19] Physiologic stress needs to be considered in the performance of CL studies.[12] Based on the proven relation between stress and galvanic skin response (GSR),[20] GSR can be used as an indicator for stress.[9]

Almost half of hypoglycemic events occur during the overnight period.[21] Since patients are unaware of low

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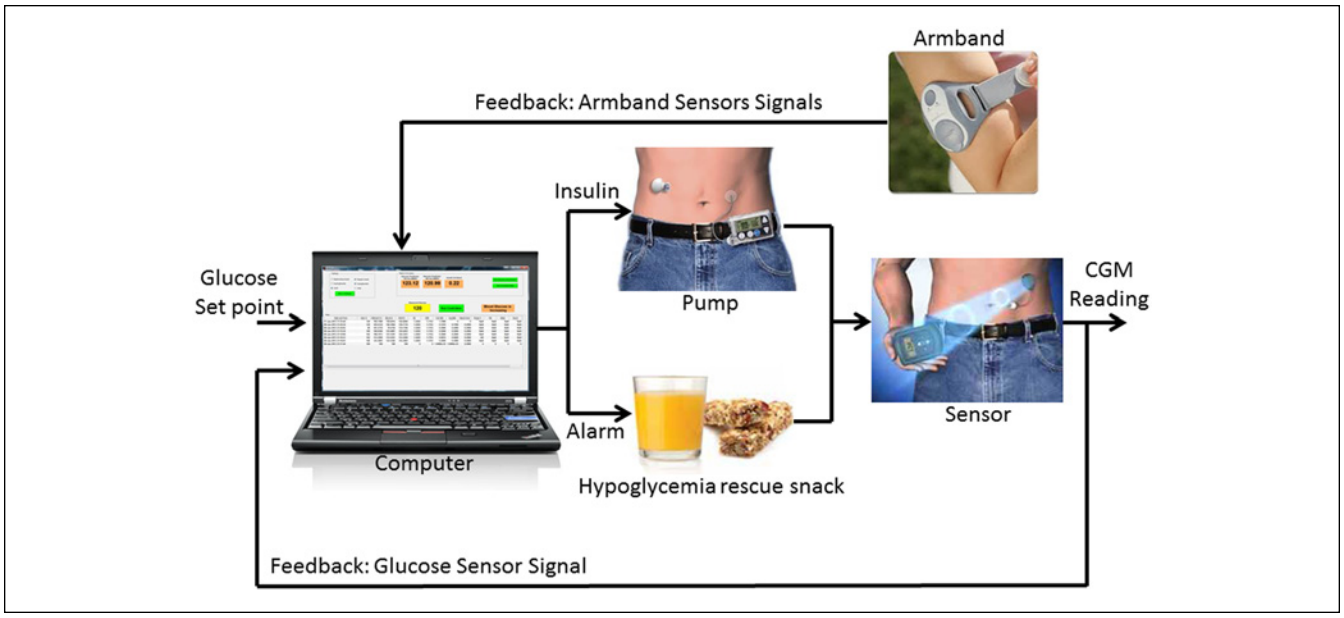

Figure 1. Integrated multivariable adaptive artificial pancreas control system.

glucose levels when asleep, an AP system must be able to detect sleep and recommend less aggressive insulin dosing for sleep periods to prevent hypoglycemia. Obviously, some patients may still require high insulin amounts based on the types of food that have been consumed. Thus insulin suggestions should not be based on only night period information, but rather based on an optimization that takes into account glucose values, sleep information, day time, future glucose predictions and other information from patients (such as body weight or insulin sensitivity).

Hypoglycemia early alarm (HEA) systems are needed to provide enough time in advance of predicted hypoglycemia to take preventive measures. Various early alarm techniques[22-28] have illustrated that HEA systems could feasibly allow the avoidance of most hypoglycemia.

For patients with type 1 diabetes, we developed a multivariable AP system that uses physiological signals (EE and GSR) and sleep information to regulate blood glucose,[29] and we developed an HEA system that can predict hypoglycemic episodes 25 minutes before they occur.[26]

In this study, we integrated the HEA system with the AP controller to create a system that uses multivariable techniques to warn the need for glycemic control to avoid hypoglycemia even during exercise or sleep. The IMAAP system developed is adaptive and does not require any information from the user such as meal announcements, preprandial insulin bolus, exercise announcement, or sleep mode setting during CL studies.

Materials and Methods

System Components

Figure 1 shows the block diagram of the IMAAP control system. Glucose concentrations of patients are read via a continuous glucose monitor (CGM) and transferred to the controller. Simultaneously, the physiological signals are measured via a sport activity armband and sent to the controller. The controller calculates the appropriate insulin response based on the glucose value, physiological signals, and set point. In response, an insulin infusion rate is suggested for entry into the insulin pump and/or an early alarm warns patients to consume CHO.

SenseWear Pro3 Armband

The SenseWear Pro3 armband (BodyMedia, Inc, Pittsburgh, PA) was used as a portable device that can measure physical activity and provide EE information.[30] The armband is a light, wireless body monitor that is easy to wear continuously. The armband is worn on the dominant upper arm over the triceps muscle. The device uses a heat flux sensor, GSR sensor, skin temperature sensor, near-body temperature sensor, and a 2 axis-accelerometer for computation of EE (Figure 2). Multiple sensors in the armband distinguish among various activities such as walking, running, biking, resting, and sleeping.[30]

CGM and Pump

Two Guardian® REAL-time CGM (Medtronics, Northridge, CA) were used simultaneously to collect the glucose concentration information during the CL experiments. Twelve subjects wore the iPro® CGM (Medtronics, Northridge, CA) and 3 subjects wore the Guardian® REAL-time CGM during the OL experiments. The Guardian® REAL-time CGM system measures glucose concentration in the interstitial tissue and digitally displays the glucose concentration every 5 minutes. During the experiments readings from only 1 of the CGM devices was used for calculation of insulin amounts.

Figure 2. BodyMedia SenseWear Armband.[30]

The second CGM was used in case the former one had "lost sensor" or "low signals" error.

Controller and Hypoglycemia Early Alarm

The control system is based on generalized predictive control (GPC). GPC is a receding-horizon method that depends on predicting the output of a system over several steps into the future. GPC uses assumed future control actions and selects their values to minimize an objective function. The objective function includes terms that represent the deviation of future glucose concentration trajectories from reference values and penalties associated with large control actions (insulin infusions).[31,32] GPC can automatically adapt in response to changes in the dynamics of the system by updating the model used in GPC recursively with each new measurement. Glucose dynamics in patients with type 1 diabetes have high intra- and intersubject variability; thus, GPC is considered a powerful method for blood glucose regulation with an AP.

We have developed an adaptive identification and control algorithm for glucose concentration regulation in patients with type 1 diabetes. Linear and low order models are used for predictions of glucose. They do not require high computational power. Model parameters are updated with every new measurement to track variations in the dynamics of glucose concentrations. Additional constraints are added to the model identification method to prevent physiological extremes. Physiological signals such as EE, GSR, and sleep are sent to the controller to prevent postexercise and sleep-induced hypoglycemia. Insulin on board (IOB) prediction models are used in the controller to prevent hyperinsulinemia. The maximum amount of insulin allowed by the controller is defined as a function of the patient's body weight, IOB, predicted glucose concentration, and the desired glucose concentration (set point or reference). The body weight of the patient is the only information provided to the controller to change its maximum allowed insulin amount based on changes in glucose dynamics. Mathematical details of the model identification and controller design are reported elsewhere.[29,33]

We developed the HEA system based on a multivariable time-series model as well. Time-series models are used for glucose predictions and generation of HEAs. Since the HEA system is based on multiple variables, it can modify the alarm thresholds itself based on exercise or sleep mode. Furthermore, the stability, IOB, and physiologic constraints prevent the HEA system from making unrealistic glucose predictions. Using the past information of patients, the HEA system updates itself and can predict hypoglycemic episodes on average 25 minutes in advance of a potential hypoglycemia. Details of the alarm system have been reported elsewhere.[26]

The IMAAP system recommends insulin infusion rates for high glucose values and triggers hypoglycemia warnings when low glucose values are predicted. Sleep or exercise conditions are assessed prior to deciding on the final insulin infusion rate. An early alarm is triggered and treatment with a 15 g CHO snack is suggested. However, the subject does not have to eat the snack if a meal was consumed within the last 30 minutes as the amount of CHO ingested during the meal should be sufficient to prevent hypoglycemia. Once the snack is eaten, a flag is lifted in the algorithm to prevent a sustained alarms and requests for consumption of additional snacks to prevent snack-induced hyperglycemia. When the predicted glucose concentrations are above the thresholds, the flag is lifted and the system is prepared to give a new early alarm when future hypoglycemia episodes are predicted.

Hypoglycemia, Hyperglycemia, and Target Range

For all experiments, the severe hypoglycemia threshold was defined as 55 mg/dl (3.05 mmol/L). The target range

Table 1. Demographic Information of the Subjects.

Experiments	Duration of diabetes (years)	A1C (%)	Gender (M/F)	Age (years)	BMI
Open loop	13.6	7.43	6/5	25	25.1
Closed loop	10	7.5	9/0	18.3	22

All reported values are means (except gender).

for glucose concentration was defined as 70-180 mg/dl (3.89-9.99 mmol/L). Glucose values higher than 250 mg/dl (13.88 mmol/L) were considered as severe hyperglycemia. The first aim of the integrated system was to maintain glucose levels above the hypoglycemia limit (55 mg/dl) while also keeping them inside the target range.

Open-loop Study

Potential subjects were recruited through institutional review board–approved advertisements and were scheduled to meet with the study research team at the University of Illinois at Chicago–College of Nursing. Eligible subjects included adults (ages 18-35 years) with type 1 diabetes. The armband was placed on the patient's arm as described previously and subjects were instructed to wear the armband over the next 7 days. The CGM sensor was inserted in the stomach and worn for a total of 6 days. The CGM sensor insertion site was changed by the research team 72 hours following insertion. The subjects returned the CGM and armband and the devices were downloaded on the final visit. OL studies were outpatient experiments under free-living conditions and all subjects used continuous subcutaneous insulin pump therapy. Demographic details of subjects are provided in Table 1.

Closed-loop Study

Subjects were recruited from the University of Chicago Medical Center, Kovler Diabetes Center and were scheduled for a visit at the University of Chicago General Clinical Research Center. Subjects selected were young adults (aged 18-35 years) with type 1 diabetes. All subjects used continuous subcutaneous insulin pump therapy and were healthy and physically active. Demographic details of subjects are provided in Table 1. Each visit was approximately 70 hours long. The first day was used for sensor placement and calibration. The subject's own insulin type and pump were used during the experiments. Subjects were provided a total of 8 meals and snacks during the 2-day CL experiment. Armband and CGM data were collected continuously every 10 minutes. CGM readings were entered into a computer, and the armband signals were read wirelessly. The insulin infusion rates were computed every 10 minutes by the controller and reviewed by a medical expert each time a new infusion rate was computed. Upon approval, the computed insulin infusion rates were entered manually into the subject's insulin pump. None of the suggested insulin infusion rates were overwritten by the medical expert.

Every 2 hours and before meals, the blood glucose concentration (BGC) was measured using a portable blood glucose meter or YSI 2300 STAT glucose analyzer (YSI, Inc, Yellow Springs, OH). If there was a significant difference (relative difference > 25%) between the CGM reading and the glucose meter measurements, and the CGM glucose readings were not changing rapidly, the meter BGC value was entered into the CGM devices for calibration. Additional snacks were provided whenever requested by subjects. The types of foods were selected based on subject's usual requirements in terms of creating normal life conditions.

Each subject participated in a 20-minute exercise bout of moderate-to intense intensity (treadmill running) before or after lunch each day. The exercise was performed based on a target heart rate and upper limit exercise tolerance of the subjects. However, each subject was free to stop the exercise at any time. The subjects walked on a treadmill using a ramped protocol where the speed (miles per hour [mph]) and the incline (%) of the treadmill were gradually increased until the exercise session ended. Overall, the subjects exercised at 85 ± 8.3% (mean and standard deviation) of their age-predicted maximum heart rate of 220-age (range, 70-97%).[34]

Clinical experiments were designed to mimic real life as much as possible. Any additional snacks were provided when requested by the subjects. The exercise protocols changed if subjects were not satisfied. During the experiments, subjects were free to shower, watch TV, play computer games, walk in the hospital corridors, and rest.

Statistical Analysis

Results are expressed as arithmetic means ± standard deviation (SD), minimum-maximum values, and percentage of time spent in severe hypoglycemic (< 55 mg/dl), mild hypoglycemic (55-70 mg/dl), target (70-180 mg/dl), mild hyperglycemic (180-250 mg/dl), and severe hyperglycemic (>250 mg/dl) ranges. Comparisons between groups were performed using 2-tailed hypothesis z test for which the level of significance was set at .01.

Results

Overall 20 experiments were performed. Patients used their own insulin calculation methods during 11 OL experiments. The MAAP system was applied to the first 6 CL experiments

Table 2. Comparison of Open-loop and Closed-loop Experiments.

Experiment	<55	55-70	70-180	180-250	>250	Mean ± SD	Min-Max	Hypoglycemia
OL experiments								
1	0	0.1	40.1	42.7	17.2	198 ± 59.2	68-389	Mild
2	11.4	6.2	53.5	10.1	18.9	158 ± 98.5	40-400	Severe
3	3.7	2.6	32.3	16.9	44.5	228 ± 105.9	40-400	Severe
4	11.7	4.6	53	15.2	15.5	154 ± 94.4	40-400	Severe
5	0.1	0.3	75.4	23.0	1.2	143 ± 47.4	54-256	Severe
6	6.9	5	37.4	21.3	29.4	191 ± 99.7	40-400	Severe
7	0	0	40.1	33.5	26.3	209 ± 69.5	70-397	None
8	2.1	3.7	60.7	27.8	5.8	155 ± 59.9	45-368	Severe
9	15	10.4	58	9.3	7.3	122 ± 73.4	40-400	Severe
10	0.6	3.7	65.1	17.2	13.4	156 ± 77.1	44-400	Severe
11	4.5	3.2	60	24.8	7.5	153 ± 66.1	40-367	Severe
MAAP experiments								
1	0	0	62.6	24.3	13	178 ± 47.3	75-253	None
2	0	0.9	53	36.1	10	170 ± 59.7	66-290	Mild
3	0	0	54.5	38	7.5	177 ± 47.6	90-300	None
4	0	1.5	64	24	10.5	162 ± 54.9	64-290	Mild
5	0	0	60.8	27.5	11.7	169 ± 57.5	71-304	None
6	0	7	67.3	11.3	14.5	153 ± 72.8	59-348	Mild
IMAAP experiments								
1	0	0	66	29	5	164 ± 54.5	73-375	None
2	0	0	32.1	38.6	29.3	210 ± 68.2	80-349	None
3	0	0	60	24	16	176 ± 66.5	72-345	None

IMAAP, integrated multivariable adaptive artificial pancreas; MAAP, multivariable adaptive artificial pancreas. Mean, standard deviation, minimum, and maximum values are shown in mg/dl. Glucose intervals are shown in percentage of time (columns 2-6).

and the IMAAP system was used during the last 3 CL experiments. Table 2 summarizes the results of all OL and CL experiments. Most of the subjects had severe hypoglycemic episodes during the OL experiments. Those subjects had to consume additional snacks for rescuing glucose levels. No severe hypoglycemic episodes were seen during the CL experiments with MAAP approach. However some mild hypoglycemic episodes were seen when MAAP system was used. Mild hypoglycemia was decreased significantly ($P < .01$) compared to OL experiments with the MAAP system. During the last 3 experiments, complete hypoglycemia prevention was obtained with the proposed IMAAP algorithm. There were 9 subjects faced with severe hypoglycemic events in 11 OL experiments versus 0 in 9 CL experiments ($P < .01$). Glucose values stayed within target range 54%, 62% and 53% of the time during OL and with MAAP and IMAAP systems during CL experiments respectively. Taking account all the CL experiments, 58% of the time the glucose concentration stayed within target range.

The first CL experiment with the IMAAP system began at 08:15 hours (Figure 3) with a confirmatory YSI measurement. The subject ate breakfast, which included 65 g CHO at 08:20 hours. The typical glucose peak was not seen after the breakfast. This is most probably due to the correction bolus (not shown on the Figure 3) that was infused by the subject before CL started because of high glucose levels around 07:30 hours. The CGM and insulin pump devices were calibrated based on the YSI value at 10:10 hours (CGM: 153 mg/dl, YSI: 238 mg/dl). The subject had 144 grams of CHO at lunch around 11:30 hours. Based on the protocol, the subject was supposed to have high-intensity treadmill exercise after lunch. But the subject preferred to have a fast walking exercise (E* in Figure 3). Thus, 30 minutes of walking was performed. Once the exercise started, EE measurements informed the controller about the exercise, which subsequently suggested less aggressive insulin dosing to prevent postexercise hypoglycemia. The HEA system triggered a low glucose prediction alarm at 15:45 hours, and 2 glasses of orange juices (30 g CHO) were consumed by the subject. At dinner at 18:05 hours 75 g CHO was provided.

As shown in Figure 3, around 21:00 and 24:00 hours, there were discrepancies in CGM readings; thus, the YSI values were used in the controller for 1 sampling time (10 minutes) to bring glucose values into the target range. After glucose levels reached the target range, the subject had his usual snack around 22:40 hours. At 01:45, 04:32, and 06:30 hours, the HEA triggered alarms, and juice (37 g CHO) was provided each time. The EE and GSR information was lost for the first few hours of the experiment in the database because of technical problems (during battery replacement) even though these signals were used during the complete closed-loop period.

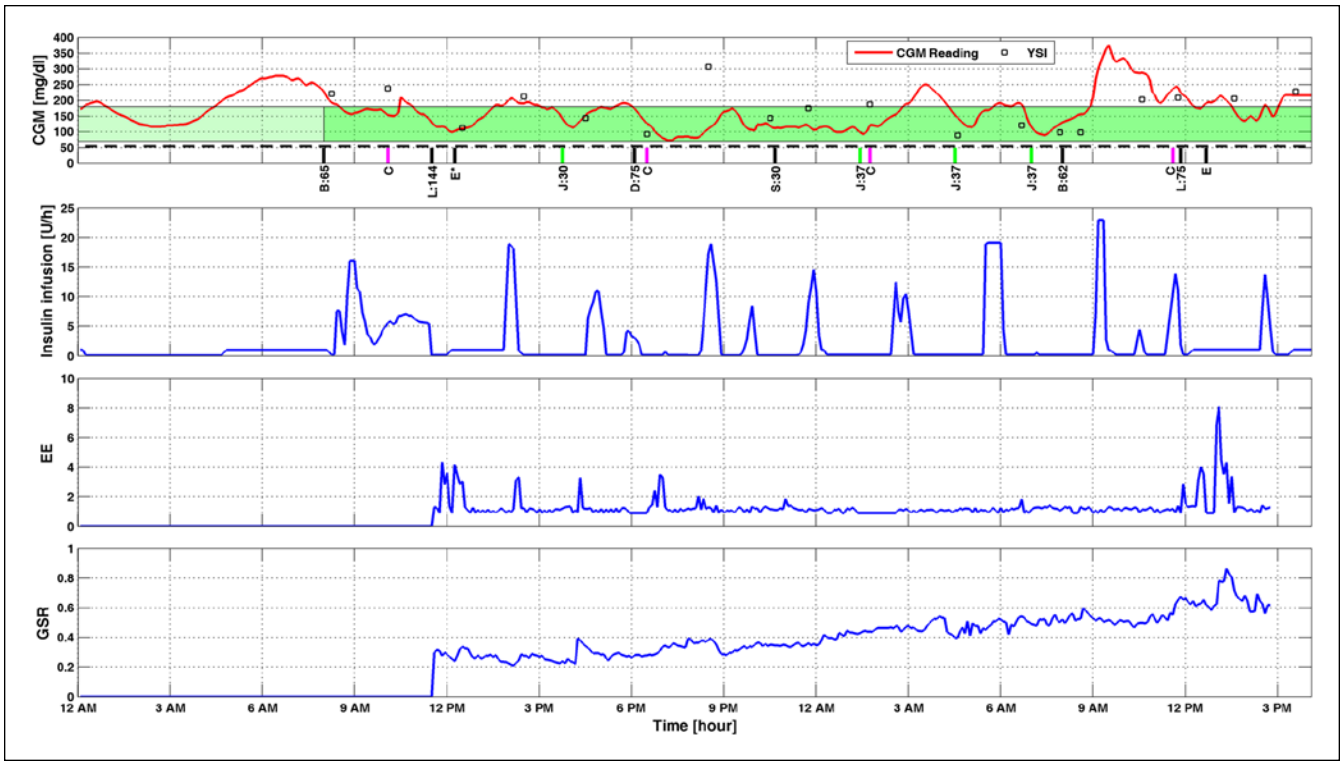

Figure 3. Glucose concentration from continuous glucose monitor (CGM), infused insulin rate (Ins), energy expenditure (EE), and galvanic skin response (GSR) of Experiment 1. The green band indicates the target range of blood glucose concentration. The darker green section indicates the closed-loop duration. The black dashed line shows hypoglycemia threshold. Vertical bars: black, regular meal, snack, or exercise; green, hypoglycemia early alarm–based meal, snack, or juice; magenta, calibration. B, breakfast; L, lunch; D, dinner; S, snack; E, exercise; C, calibration; J, orange juice.

On the second day, the protocol-based high-intensity treadmill exercise was performed after lunch. Overall, during the CL study, CGM values stayed inside the target range 66% of the time, between 180 and 250 mg/dl 29% of the time, and above 250 mg/dl 5% of the time. No hypoglycemia occurred. Whenever the hypoglycemia limit was approached based on HEA predictions, CHO was provided and glucose levels rose.

Figure 4 shows the results of the second experiment with the IMAAP algorithm. The CL study started at 07:50 hours. After a confirmatory YSI measurement, the subject had a breakfast containing 65 g CHO at 08:15 hours. Calibration of devices was performed with YSI value at 1010 (CGM: 193 mg/dl, YSI: 250 mg/dl). The pump infusion site was changed at 11:40 hours because it seemed that the insulin pump was not working properly at the current insertion site. Seventy-five grams of CHO at lunch was provided at 11:45 hours, and high-intensity treadmill exercise was performed after lunch. After the exercise started, the controller suggested less aggressive insulin dosing to prevent hypoglycemia. After the likelihood for postexercise hypoglycemia lessened (around 30-45 minutes), the controller adapted itself to suggest more aggressive insulin dosing because glucose values were still above the target range. The HEA system gave an alarm about the potential hypoglycemia episode at 15:45 hours, and a complex CHO snack (peanut butter cookies) was provided. Another early alarm was triggered before dinner, and 15 grams of potato chips were provided. Regular snacks, device calibration, and HEA-based additional snacks were provided during the night. CGM readings stayed above the target range most of the CL period. Only 32% of readings were observed to be within the target range, yet no hypoglycemic episodes were seen during the experiment. A snack in the form of complex CHO was provided to avoid potential hypoglycemic episodes, unlike the first experiments where simple CHO was given. The glucose concentration values stayed above the target range.

The results of the last experiment with the IMAAP system are shown in Figure 5. The first day of CL study started at 08:10 hours, and breakfast with 71 grams CHO content was provided. The postprandial increase of glucose was countered by insulin infusions suggested by the controller. An alarm was triggered by HEA at 12:50 hours, and lunch was provided. After 30 minutes fast walking exercise (E* in Figure 5) after lunch, another alarm was given, and snacks were provided. At the time of the planned dinner, the HEA predicted hypoglycemia, but no additional snack was provided because dinner was due.

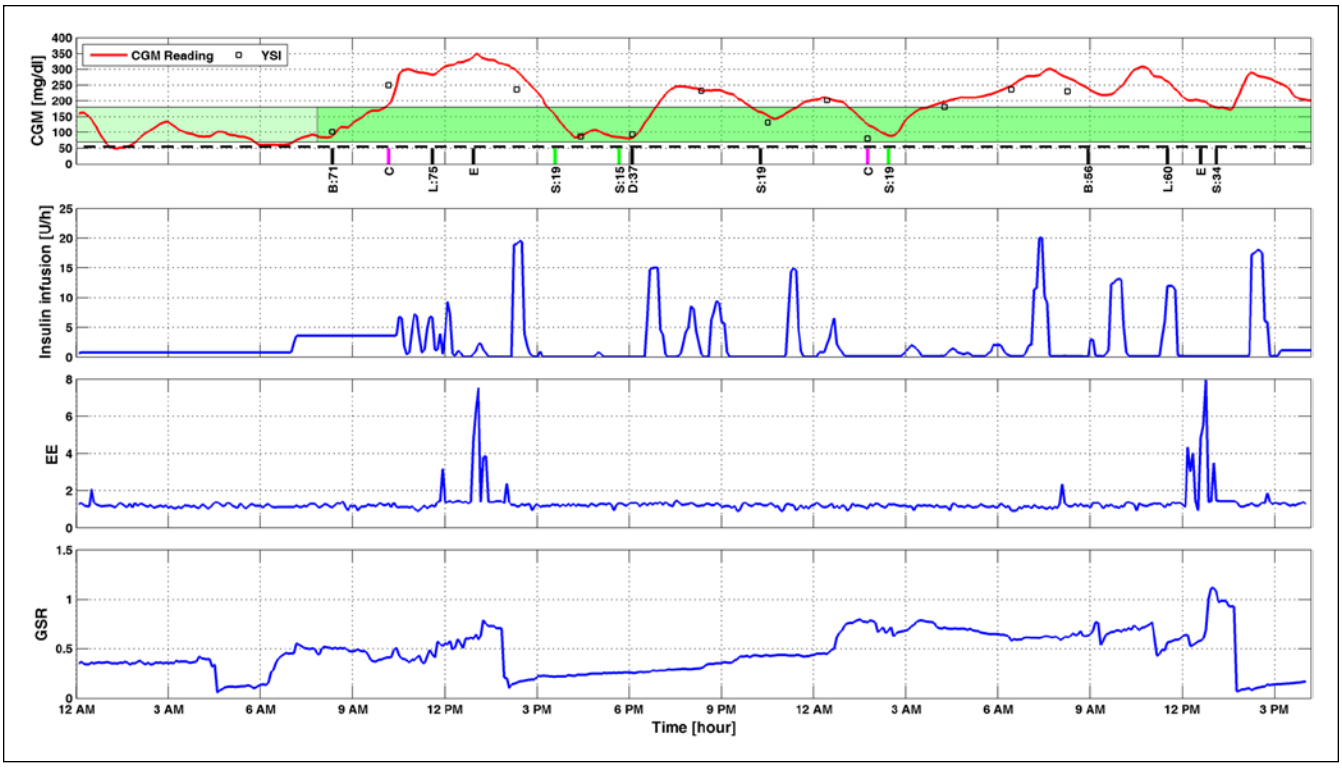

Figure 4. Glucose concentration from continuous glucose monitor (CGM), infused insulin rate (Ins), energy expenditure (EE), and galvanic skin response (GSR) of Experiment 2. The green band indicates the target range of blood glucose concentration. The darker green section indicates the closed-loop duration. The black dashed line shows hypoglycemia threshold. Vertical bars: black, regular meal, snack, or exercise; green, hypoglycemia early alarm–based meal, snack, or juice; magenta, calibration. B, breakfast; L, lunch; D, dinner; S, snack; E, exercise; C, calibration.

During the night period, since there was a slow and almost linear increase in glucose readings, the controller suggested very small amounts of insulin to be infused. On the second day, high-intensity treadmill exercise was performed after lunch. The controller suggested less aggressive insulin dosing during the exercise, though the level of glucose was increasing. During 60% of the CL study, the CGM readings values stayed inside the target range, and no hypoglycemia was seen.

Discussion of Results

A multivariable AP control system that integrated an HEA was tested as a possible system that could prevent hyperglycemia after meals yet alarm to alert for predicted hypoglycemia after exercise and during sleep. Clinical experiments showed that this system alarmed when hypoglycemia was predicted so that preventive action could be taken.

The HEA and control system used in these experiments are completely adaptive. Since the HEA system is tailored to the patient by using the patient's past glucose information with stability, IOB and physiological constraints, it has advantages over the linear trend based alarm systems that are available in some of CGM devices. The accuracy problem of CGM devices is still under consideration and an alarm system that is based on only the linear trends of CGM readings may not be sufficient. Our HEA system uses sleep, stress or physical activity information as well to predict glucose values.

In the first experiment with the IMAAP system (Figure 3), orange juice was provided for hypoglycemia prevention when an alarm was triggered. However, results showed that large amounts (30-37 g CHO) of orange juice (insisted upon by the subject, not recommended by team) caused too drastic increases in glucose level, and lower amounts would be sufficient to avoid hypoglycemia as typically instructed for treatment of low blood glucose levels. In the second experiment (Figure 4), instead of juice, complex CHOs were offered to avoid hypoglycemia. However, complex CHOs were seen to have very slow and long-lasting effects on glucose levels. This slow and long-lasting effect caused glucose values to stay above the target range for an extended period of time. We found that complex CHOs were not good candidates as rescue food for hypoglycemia prevention. During the third experiment (Figure 5), orange juice (15 g CHO) was seen to be sufficient to avoid hypoglycemia and not cause a large postprandial increase in glucose values.

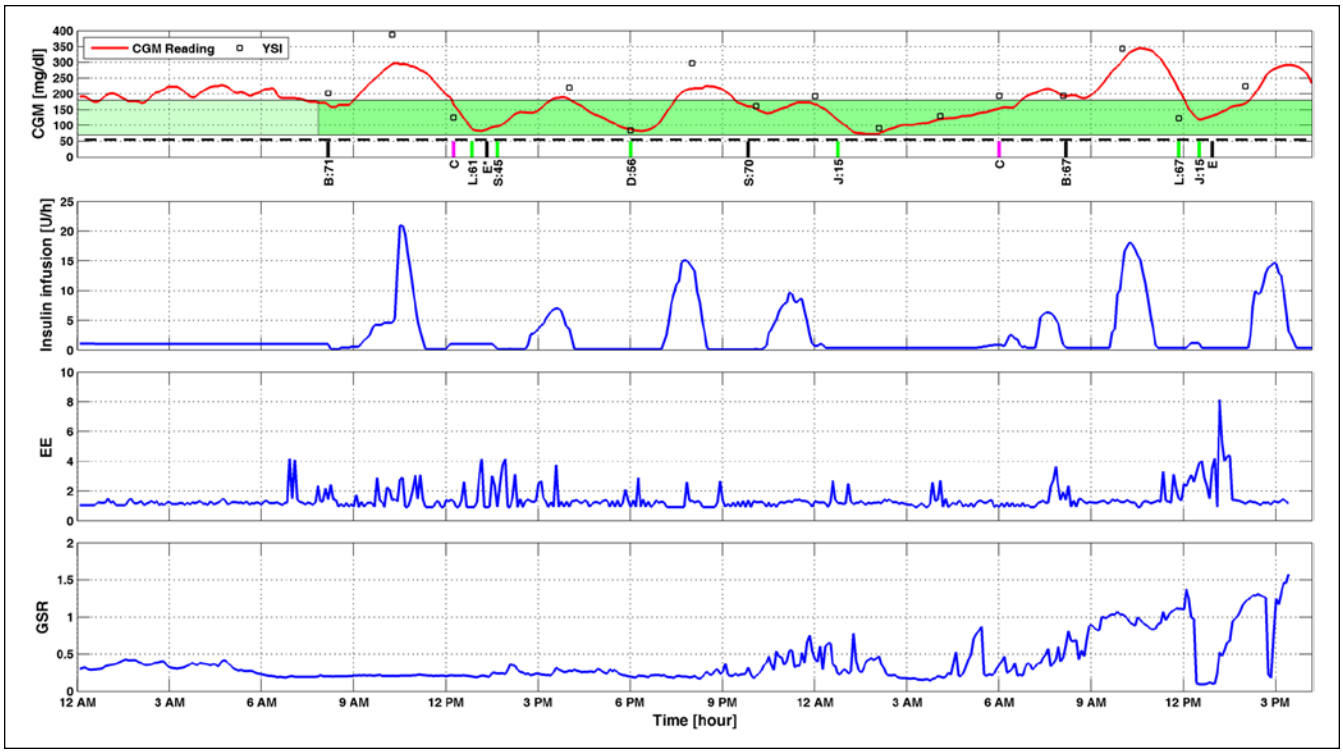

Figure 5. Glucose concentration from continuous glucose monitor (CGM), infused insulin rate (Ins), energy expenditure (EE), and galvanic skin response (GSR) of Experiment 3. The green band indicates the target range of blood glucose concentration. The darker green section indicates the closed-loop duration. The black dashed line shows hypoglycemia threshold. Vertical bars: black, regular meal, snack, or exercise; green, hypoglycemia early alarm–based meal, snack, or juice; magenta, calibration. B, breakfast; L, lunch; D, dinner; S, snack; E, exercise; C, calibration; J, orange juice.

Stress is another factor that caused high glucose levels in the second experiment. In Figure 4, GSR values are seen to be high compared to the other 2 experiments. High GSR values indicate high stress levels. Physical or psychological stress decreases the insulin sensitivity of patients with type 1 diabetes,[35] necessitating higher amounts of insulin to achieve normoglycemia. A higher glucose profile was obtained in this experiment. This information can be confirmed with the last 3-6 hours periods of the first and third experiments as well as experiments with MAAP system (results are not shown), where again GSR values and glucose values are high due to low insulin sensitivity. High stress levels may cause the controller to over dosing of insulin as well. For example, if glucose levels stay above the target range after infusing enough insulin (Figure 4, 11:00-12:00 hours), the controller may overreact by recommending additional insulin such as in Figure 4 around 14:30 hours. This high insulin suggestion might be the cause of the 2 early alarms between 15:00 and 18:00 hours. If this high insulin infusion were given as soon as stress was detected, neither the glucose levels would have stayed above the threshold nor HEA system would have triggered the alarms. The IMAAP system will be modified in future experiments to be more aggressive when stress is detected. Safeguards will also be added to prevent hypoglycemia by overdosing of insulin to compensate for lower insulin sensitivity. Confirmation of stress will be sought by monitoring the trends in other variables from the armband along with high GSR values.

All clinical experiments in the CRC were designed to be close to regular daily life as much as possible. We did not impose any standardization on meal times or amounts to test the performance of the system under real-life conditions. The system requires fewer manual data entries from patients than other reported AP technologies. It does not require any meal or exercise information to be entered. Only the patient's body weight and age group is needed before closed-loop control is started. The IMAAP system provides a good opportunity for patients with type 1 diabetes not to be continuously reminded of their disease by eliminating announcements.

Though promising results were obtained, the study had some limitations. First, the number of clinical experiments with the IMAAP system was not large enough, and more clinical experiments are needed for better statistical analysis. For optimal operation of the proposed IMAAP system (or any AP), the accuracy of the devices used is crucial. Inaccuracies of CGM sensors may have contributed to hyperglycemia during our CL experiments at some points.

Conclusions

An integrated HEA and AP control system was able to keep glucose concentration values in target range, reduce hypoglycemia in patients with type 1 diabetes, and generate early warnings when hypoglycemia was predicted. Postprandial hyperglycemia and postexercise and sleep-induced hypoglycemia did not occur when the integrated system was used. Future experiments will factor into the algorithm a stronger element for stress as a contributor to decreasing insulin sensitivity, and thus decrease time spent in mild hyperglycemia.

Abbreviations

AP, artificial pancreas; BGC, blood glucose concentration; CGM, continuous glucose monitor; CHO, carbohydrate; CL, closed loop; EE, energy expenditure; GPC, generalized predictive control; GSR, galvanic skin response; HEA, hypoglycemia early alarm; IMAAP, integrated multivariable adaptive artificial pancreas; IOB, insulin on board; MAAP, multivariable adaptive artificial pancreas; OL, open loop; SD, standard deviation.

Declaration of Conflicting Interests

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