

Closed-Loop Insulin Delivery Using a Subcutaneous Glucose Sensor and Intra-Peritoneal Insulin Delivery: A Feasibility Study Testing a New Model for the Artificial Pancreas.

Short-running title: Closed-loop intra-peritoneal insulin delivery.

Eric Renard, MD, PHD¹; Jerome Place¹; Martin Cantwell, BSC²;
Hugues Chevassus, Pharm D³; Cesar C. Palerm, PHD².

¹Endocrinology Department, CHU Montpellier & UMR CNRS 5232, University of Montpellier, Montpellier, France;

²Medtronic Diabetes, Northridge, CA, USA;

³INSERM Clinical Investigation Centre 001, CHU Montpellier, Montpellier, France.

Corresponding Author:

Prof. Eric Renard

Email: renard.amtim@wanadoo.fr

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Objective: Attempts to build an artificial pancreas by using subcutaneous (SC) insulin delivery from a portable pump guided by an SC glucose sensor have confronted delays and variability of insulin absorption. We tested closed-loop intra-peritoneal (IP) insulin infusion from an implanted pump driven by an SC glucose sensor via a proportional-integral-derivative (PID) algorithm.

Research design and methods: Two-day closed-loop therapy (except for a 15-minute pre-meal manual bolus) was compared with a one-day control phase with intra-peritoneal open-loop insulin delivery, according to randomized order, in a hospital setting in eight type 1 diabetic patients treated by implanted pumps. Percentage of time spent with blood glucose in the 4.4–6.6 mmol/L range was the primary endpoint.

Results: During the closed-loop phases, the percentage of time spent with blood glucose in the 4.4–6.6 mmol/L range was significantly higher: 39.1 ± 4.5 vs. $27.7 \pm 6.2\%$ (mean \pm SEM, $p=0.05$), and overall dispersion of blood glucose values was reduced between patients. Better closed-loop glucose control came from the time periods excluding the two early postprandial hours with higher % time within 4.4–6.6 mmol/L: 46.3 ± 5.3 vs. 28.6 ± 7.4 ($p=0.025$) and lower mean blood glucose levels: 6.9 ± 0.3 vs. 7.9 ± 0.6 mmol/L ($p=0.036$). Time spent with blood glucose below 3.3 mmol/L was low and similar for both investigational phases.

Conclusions: Our results demonstrate the feasibility of IP insulin delivery for an artificial β -cell and support the need for further study. Moreover, according to a semi-automated mode, the features of the pre-meal bolus in terms of timing and amount warrant further research.

In patients with type 1 diabetes, the near-normal glucose control required to prevent long-term complications (1,2) remains difficult to achieve (3). Indeed, the incidence of hypoglycemia increases when glucose control approaches normal glucose levels (4). For this reason the development of an ‘artificial pancreas’ has been a goal for more than 30 years (5,6)

An artificial β -cell requires three elements: a continuous insulin-delivery device, a continuous glucose monitoring system, and a control algorithm linking insulin delivery to glucose measurements (3,7,8). The recent development of better-performing continuous glucose sensors renewed the potential feasibility of closed-loop insulin delivery (9–11). Short-term initiatives in the clinical-research setting were reported in recent years but showed some limitations (12–14). Identified key limiting factors were, first, delays in the modulation of insulin action related to subcutaneous infusion and, second, time lags in glucose detection due to either the placement of the sensors in the interstitial compartment of subcutaneous tissue or due to the internal structure of implanted intravenous sensors (15). In order to reduce glucose deviations at mealtimes, a hybrid option of closed-loop insulin delivery includes a manual priming bolus (16).

Reported benefits of intra-peritoneal (IP) insulin infusion from implantable pumps include fast insulin action and low basal plasma-insulin levels, resulting in tight glucose control and a low incidence of hypoglycemic events (17). The feasibility of automated closed-loop insulin delivery from implantable pumps has been demonstrated in clinical trials performed with the Long Term Sensor System, which coupled these devices with an intravenous glucose sensor (18).

Our approach to optimize closed-loop glucose control includes the use of closer-to-physiologic IP insulin delivery, subcutaneous glucose sensing and a proportional-integral-

derivative (PID) algorithm with a manual pre-meal bolus, resulting in a hybrid PID (HyPID) system. The objective of the study reported in this paper was to test the feasibility of such an approach. We investigated patients in the same controlled hospital setting while testing the HyPID system and when following their usual self-management. This marks a difference with the previously reported closed-loop trials, which considered home-use periods for comparison to in-clinic closed-loop studies (13,16).

RESEARCH DESIGN AND METHODS

Patients. Eight patients with type 1 diabetes mellitus, treated by an implanted pump using IP delivery (model MMT-2007D, Medtronic Diabetes, Northridge, CA, USA) and infusing U-400 regular insulin (Insuplant[®], Sanofi-Aventis, Paris, France) for at least 3 months, were enrolled. Inclusion criteria: 18–70 years of age; insulin delivery within 15% of expected accuracy for the 60 days preceding the trial; plasma anti-insulin antibody level below 30% according to a radioimmunoassay of free and total anti-insulin antibody using a technique adapted from that of Palmer (19); written informed consent; and health insurance coverage by the French Social Security System. Exclusion criteria: pregnancy; breast feeding; plasma creatinine > 150 $\mu\text{mol/L}$; serum ALAT and ASAT above twice the superior limit of the normal range; total blood hemoglobin < 12 g/dL; any cardiovascular event during the last six months; any evolutive ischemic or proliferative diabetic retinopathy on eye fundus examination for the previous year; and any known or suspected allergy to glucose sensor components.

The study protocol was approved by the regional ethical committee ‘Comité de Protection des Personnes Sud Méditerranée IV’, Montpellier, France, on September 11, 2007. The study was authorized by AFSSAPS (‘Agence Française de Sécurité Sanitaire des

Produits de Santé') on November 29, 2007 and registered under the reference number: 2007-A00696-47 (www.afssaps.sante.fr).

Study Protocol. Subjects were admitted for a total of 86 hours, divided into a preparation phase (14 hours), a control (open-loop) phase (24 hours) and a closed-loop phase (48 hours). The order of the control and closed-loop phases was randomized.

At admission (day 1, 18:00), two subcutaneous glucose sensors (Medtronic Diabetes, Northridge, CA, USA), similar to those used in Medtronic's CGMS[®]/Guardian RT[®] systems, were inserted in the abdominal area and were calibrated against a capillary blood glucose (CBG) value two hours after insertion, and then every four hours. The second sensor was used as a backup in case the first sensor failed to track glucose. At 20:00, patients were instructed to program their insulin bolus for dinner and to remain fasting until the following morning. On day 2, twenty minutes before the 8:00 experiment start, an intravenous catheter was placed in an antecubital vein for frequent blood sampling. Blood samples were then drawn (for later blood glucose and plasma insulin measurements) every 20 min at the start of each meal for a period of two hours (8:00-10:00, 13:00-15:00, 19:00-21:00, considered as 'early postprandial periods'): breakfast including 40 g CHO, lunch and dinner both including 70g CHO, every hour from 8:00 to 22:00 except for early postprandial periods and every two hours from 22:00 to 8:00 (considered as 'non-postprandial periods').

During the 24-hour control phase, the patients were instructed to monitor their diabetes by seven CBG tests performed before, and 2 hours after, each meal and at bedtime, and to program their pump according to the self-monitoring data. Sensor glucose data were monitored in real time and patient blinded.

During the 48-hour closed-loop phase, the pump's insulin infusion rate was automatically modulated according to the

algorithm. Sensor glucose data and insulin-delivery rate were monitored in real time and patient blinded. Fifteen minutes before meals, a manually programmed insulin bolus, consisting of 30% of the amount the patient would have programmed according to pre-meal blood glucose levels and meal CHO content, was delivered.

For safety purposes, CBG tests were also performed every hour from 8:00 to 22:00 and every two hours from 22:00 to 8:00. Additionally, each time the sensor glucose value decreased below 4.4 mmol/L (80 mg/dL) or increased above 13.2 mmol/L (240 mg/dL) and when patients reported symptoms of suspected hypoglycemia, a CBG test was performed. It should be noted that procedures responding to hypoglycemia and sustained hyperglycemia were also followed during the control phase, although at home the subject might not have such close monitoring.

System Considerations. The closed-loop system is made up of three components: a subcutaneous glucose sensor, the insulin-delivery algorithm (running on a laptop computer), and the IP insulin-infusion pump. The laptop receives sensor data using a radio-frequency protocol and sends commands to the pump using the Bluetooth protocol. A modified Personal Pump Communicator (PPC), set up to receive commands from a Bluetooth adapter, was employed instead of the PPC used by the patient. The pump was then set to the minimum-allowed basal infusion rate of 0.2 U/h, with the algorithm delivering discrete 0.2 U boluses as calculated based on real-time sensor glucose measurements.

The mathematical algorithm used to calculate the insulin-delivery rate is based on a model of the β -cell's multiphasic insulin response (20). The first version of this algorithm is described in (13). The version used in this study further incorporates the effect of insulin-inhibiting insulin secretion (i.e.,

insulin feedback) (21). The equations describing the model are:

$$u(n) = P(n) + I(n) + D(n) - \gamma I_p(n)$$

$$P(n) = K_p (G_S(n) - \bar{G}_T)$$

$$I(n) = I(n-1) + \frac{K_p}{\tau_I} (G_S(n) - \bar{G}_T)$$

$$D(n) = K_p \tau_D \bar{G}_{SD}(n)$$

$$I_p(n) = (\alpha_1 + \alpha_2) I_p(n-1) - \alpha_1 \alpha_2 I_p(n-2) + \frac{(1-\alpha_1)(1-\alpha_2)}{K_d} I_B(n-2),$$

where $u(n)$ is the insulin-infusion rate calculated at time step n (which is every 1 minute), and the notation $(n-1)$ denotes the previous time step. The algorithm is tuned with the parameters $K_p, \tau_I, \tau_D, \gamma$, and with $\alpha_1, \alpha_2, K_{cl}$ corresponding to the intra-peritoneal insulin-absorption kinetics. The term γI_p corresponds to the inhibition by plasma-insulin concentration on the delivery of insulin. Since the pump can only deliver insulin as single 0.2 U boluses, the amount actually delivered by the pump (I_B) is used when calculating the estimated plasma-insulin concentration. The tuning parameters are individualized for each subject as a function of their total daily-insulin dose. The target glucose level used for the algorithm was 100 mg/dl (5.5 mmol/L).

Laboratory measurements. Plasma glucose concentrations were measured by hexokinase assay (Olympus SA, Rungis, France). CBG measurements were performed using OneTouch Ultra[®] meters and strips (LifeScan Inc., Milpitas, CA, USA). Plasma insulin was measured by a specific insulin assay (bi-insulin immunoradiometric assay, Schering CIS Bio International, Gif sur Yvette, France).

Assessment of Glucose Control. The primary endpoint is the percent time spent with blood glucose in the 4.4–6.6 mmol/L range. All the analyses are done using the lab blood glucose measurements unless otherwise noted.

Secondary endpoints include: the same index for the early postprandial periods and for the non-postprandial periods; mean blood glucose for the overall experiment, for the early postprandial and non-postprandial periods; and percent time spent with blood glucose below 3.3 mmol/L and above 10 mmol/L.

Statistical Analysis. Results are expressed as arithmetic mean \pm standard error of the mean (SEM), or standard deviation (SD) when specified, and 95% confidence intervals of differences (95% CI). Means were compared using the Wilcoxon signed rank test. The level of significance was set at $p < 0.05$. Calculations and statistical analysis were performed using SYSTAT[®] 10 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients. Eight patients were enrolled: gender: 7 male, 1 female; age: 59.8 \pm 8.7 years; body mass index (BMI): 26.4 \pm 3.4 kg/m²; diabetes duration: 31.7 \pm 15.1 years; treatment duration by implanted pump: 8.5 \pm 7.4 years; HbA_{1c}: 6.8 \pm 1.0%; daily insulin requirement: 0.60 \pm 0.21 units \cdot kg⁻¹ \cdot day⁻¹. All these data are presented as mean \pm SD.

Sensor Accuracy. Mean and median relative absolute differences (\pm SD) between paired sensor and lab blood glucose values were 15.9 \pm 3.8% and 13.9 \pm 2.9%, respectively, which are consistent with previous reports (16).

Insulin Delivery and Algorithm Assessment. The correlation coefficient (R^2) between the measured and algorithm-estimated plasma-insulin levels was 0.730 \pm 0.067. Data for each patient are shown in Figure 1. In general, while the magnitude of the estimated levels is higher than that of the measured levels, the kinetics observed are well described by the model. The observed difference in the slope of the estimates versus the predictions may be due to specific aspects of intra-peritoneal insulin infusion.

Glucose Control during Control and Closed-Loop Periods. The distribution of blood glucose values and the mean blood glucose and plasma insulin levels are presented in Table 1.

A significantly higher percentage of time was spent between 4.4 and 6.6 mmol/L during closed-loop vs. control phases: $39.1 \pm 4.5\%$ vs. $27.7 \pm 6.2\%$ ($p=0.05$), although mean blood glucose shows no significant difference. No carry-over phenomenon is detected.

Tighter control was obtained for closed-loop phases in non-postprandial periods, where both mean blood glucose level and percentage of time spent with blood glucose between 4.4 and 6.6 mmol/L are significantly better. In contrast, early postprandial glucose control was similar during closed-loop and control periods. Of note, plasma insulin levels were significantly higher in non-postprandial periods but significantly lower in early postprandial periods during closed-loop phases.

When focusing on the night-time period between 22:00 and 8:00, mean blood glucose levels and percent-time spent between 4.4 and 6.6 mmol/L were similar (Figure 2, Panel A). Only a trend to better control was observed from 22:00 to 2:00 during closed-loop phases (6.2 ± 0.4 vs. 7.9 ± 0.9 mmol/L, $p=0.069$). Data analysis in early postprandial periods shows similar glucose peak levels and time-to-glucose peak (Figure 2, panel B). However, for closed-loop phases, plasma-insulin peak levels were significantly lower: 29.7 ± 2.9 vs. 51.5 ± 8.4 mIU/L ($p=0.017$) and time-to-plasma insulin peak was longer: 79.9 ± 7.2 vs. 38.3 ± 7.2 min ($p=0.012$). These differences were observed similarly with all three main meals (data not shown).

Figure 3 indicates the higher mean frequency of blood glucose between 4.4 and 6.6 mmol/L during closed-loop phases. It also shows a tighter inter-patient distribution of glucose values in these phases.

In terms of safety, thirteen glucose deviations below 4.4 mmol/L were detected by the patients through suggestive symptoms and/or identified early by the glucose sensors during closed-loop phases, and three were detected during control phases. All events occurred in non-postprandial periods. Of note, following oral glucose administration (10 g on average), a trend for earlier correction of blood glucose was observed during closed-loop phases: 82.67 ± 0.81 vs. 70.33 ± 0.19 mg/dL after 20 min.

CONCLUSIONS

Our study demonstrates the feasibility of closed-loop insulin delivery by means of implanted insulin pumps using the IP route and driven by subcutaneous glucose sensors and a PID algorithm. Interestingly, time spent in near-normal glucose range is increased in comparison with open-loop use of this insulin therapy based on self-monitoring data and patient initiative in the same environmental conditions.

The improved glucose control obtained during the closed-loop phases represents a valuable improvement for patients who were already well controlled as indicated by their initial HbA1c levels of $6.8 \pm 1.0\%$, since it was achieved with minimal patient interaction with the system. The assessment of closed-loop effectiveness, measured by percentage of time spent in the tight near-normal glucose range, illustrates the usefulness of sensor- and algorithm-driven insulin infusion. Because hyperglycemic excursions have been associated with oxidative stress (22), and hypoglycemic deviations impair quality of life and can promote hypoglycemia unawareness, leading to the occurrence of severe hypoglycemia (23), an important goal for a closed-loop system is to reduce glucose deviations. Additionally, reduced inter-patient variability of glucose levels also merits notice. This result is valuable in terms of reproducibility and safety of the algorithm.

The main benefit on glucose control during closed-loop phases was observed in time periods excluding the early postprandial (two hour) periods. Improvement of glucose control during these periods appears to be mainly driven by higher plasma insulin levels obtained by algorithm-driven insulin delivery. The trend to a quicker return to pre-meal glucose levels in the late postprandial periods, i.e., more than two hours after meals, can be highlighted. However, in spite of the manual delivery of a pre-meal bolus during closed-loop phases, the early postprandial period remains a challenging situation that also was not solved in previously reported closed-loop experiments (14,15).

Programming a manual bolus before meals did not appear as effective in our study as in a recent trial using continuous subcutaneous insulin infusion (16). Of note, in our experiments, postprandial insulin peaks were lower and later during closed-loop versus control phases. Reproduction of the dynamics of the physiological first phase of insulin secretion would require reaching higher acute plasma-insulin levels corresponding both to the ‘cephalic phase’ of insulin secretion and to the ‘incretin-promoted’ component (24,25). Future clinical trials should evaluate the amount and timing of the manual pre-meal bolus in order to better mimic physiology. From an algorithmic consideration, we can speculate that insulin action resulting from the pre-meal bolus may mask the appearance of glucose, therefore delaying the increase in the insulin-delivery rate by the algorithm.

Blood glucose could be maintained between 3.85 and 10 mmol/L for 85% of the time in a recently reported 24-hour closed-loop trial performed on eight adolescent type 1 diabetic patients in a hospital setting by combining subcutaneous insulin infusion, subcutaneous sensing and a PID algorithm—the two latter elements being very similar to ours, except that insulin feedback was included in our algorithm (16). Glucose control was

maintained in the same range only 58% of the time in the open-loop phase performed in the home environment. Our data show that blood glucose was kept between 4.4 and 10 mmol/L for 76.5% of the time in 48-hour closed-loop phases, which was also significantly better than in the open-loop phases during which glucose was kept in the same range for 63.7% of the time. The evaluation of the open-loop period in the same hospital setting has, however, a stronger value for comparison. The large between-patient variability of glucose control, while performing the closed-loop trial using subcutaneous insulin delivery reported by the authors, may represent a significant difference with our data obtained with intra-peritoneal infusion (16). This difference in terms of blood glucose variability may be partially due to differences between these two routes of insulin delivery, which has already been reported in previous papers assessing implantable insulin pumps (17).

Hypoglycemia is a worrisome situation when performing closed-loop insulin delivery. In our study, hypoglycemic deviations occurred in a limited percentage of time, which was not significantly different from the control phase. This observation argues for the safety of the algorithm used. Moreover, since all hypoglycemic events were either detected by the patients from suggestive symptoms and/or immediately identified by the sensor, we may expect that a low-glucose warning system based on the sensor signal would be sufficient to prevent severe hypoglycemia in patients using the closed-loop algorithm at home.

In conclusion, our study demonstrates the feasibility, safety and benefits on glucose control of a new alternative for closed-loop control. The reduced between-patient variability in glucose control is also worth noticing. Although currently limited to a few patients in which subcutaneous insulin delivery was considered as unreliable, implanted devices for IP insulin infusion have

been shown to provide additional benefits in terms of quality of life (17). Further development is needed to improve early postprandial glucose control, requiring pre-meal manual intervention for bolus programming in agreement with previous trials (12,16).

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Figure legends

Figure 1. Correlations between measured (Lab) and algorithm-estimated (Model) plasma insulin levels during the closed-loop phases in each of the eight type 1 diabetic patients investigated by the HyPID system.

Figure 2. Blood glucose levels (mean, 95% CI) during closed-loop (continuous lines) and control (dashed lines) phases in the eight type 1 diabetic patients investigated by the HyPID system. Panel A: from 22:00 to 08:00. Panel B: from one hour before to five hours after meal start.

Figure 3. Cumulative distribution of blood glucose values during closed-loop and control (open-loop) phases in the eight type 1 diabetic patients investigated by the HyPID system. Individual data are presented as thin continuous lines during closed-loop phases and as thin dashed lines during control (open-loop) phases. Thick lines indicate the median cohort distributions of blood glucose values. Vertical red dotted lines denote the glucose range between 4.4 (80) and 6.6 (120) mmol/L (mg/dL).

TABLE 1

Glucose control and plasma insulin levels during closed-loop and control phases in eight type 1 diabetic patients treated by implanted insulin pumps and monitored by a subcutaneous glucose sensor.

Blood glucose (mmol/L)	Whole period				Non-postprandial period				Early postprandial period			
	Control	Closed-loop	95% CI	P	Control	Closed-loop	95% CI	P	Control	Closed-loop	95% CI	P
	7.6 [0.7]	7.4 [0.4]	-1.1 , 0.5	0.401	7.9 [0.6]	6.9 [0.3]	-1.9 , 0.0	0.036	8.6 [0.9]	8.8 [0.5]	-0.9 , 1.4	0.484
Plasma insulin (mIU/L)	20.9 [3.5]	17.7 [2.2]	-7.9 , 1.4	0.161	11.8 [2.0]	15.6 [2.1]	0.9 , 6.7	0.012	30.4 [5.4]	21.8 [2.7]	-16.5 , -0.6	0.050
Time spent (%) with blood glucose (mmol/L)	Control	Closed-loop	95% CI	P	Control	Closed-loop	95% CI	P	Control	Closed-loop	95% CI	P
> 10	21.0 [8.0]	13.6 [3.3]	-19.0 , 4.2	0.263	18.0 [7.3]	9.0 [2.6]	-21.1 , 3.2	0.128	29.9 [11.5]	27.4 [6.8]	-20.2 , 15.2	0.866
> 6.6	57.0 [8.1]	51.0 [4.9]	-16.2 , 4.1	0.161	53.8 [8.4]	42.0 [6.0]	-22.2 , -1.4	0.036	66.5 [11.9]	77.7 [4.2]	-10.7 , 33.0	0.575
≥ 4.4 and ≤ 6.6	27.7 [6.2]	39.1 [4.5]	1.9 , 20.8	0.05	28.6 [7.4]	46.3 [5.3]	4.9 , 30.4	0.025	25.0 [7.0]	17.7 [3.4]	-18.7 , 4.1	0.123
< 4.4	15.3 [4.6]	9.9 [2.7]	-18.2 , 7.6	0.401	17.6 [5.4]	11.7 [3.5]	-21.9 , 10.2	0.779	8.5 [5.5]	4.6 [1.4]	-15.2 , 7.4	0.753
< 3.3	0.6 [0.5]	1.6 [1.2]	-2.3 , 4.3	0.686	0.6 [0.6]	1.8 [1.4]	-2.8 , 5.0	0.593	0.5 [0.5]	1.0 [0.7]	-1.8 , 2.8	0.593

Results are expressed for each period as arithmetic means [standard error of the mean, SEM] and 95% confidence intervals of differences (95% CI)

Figure 1

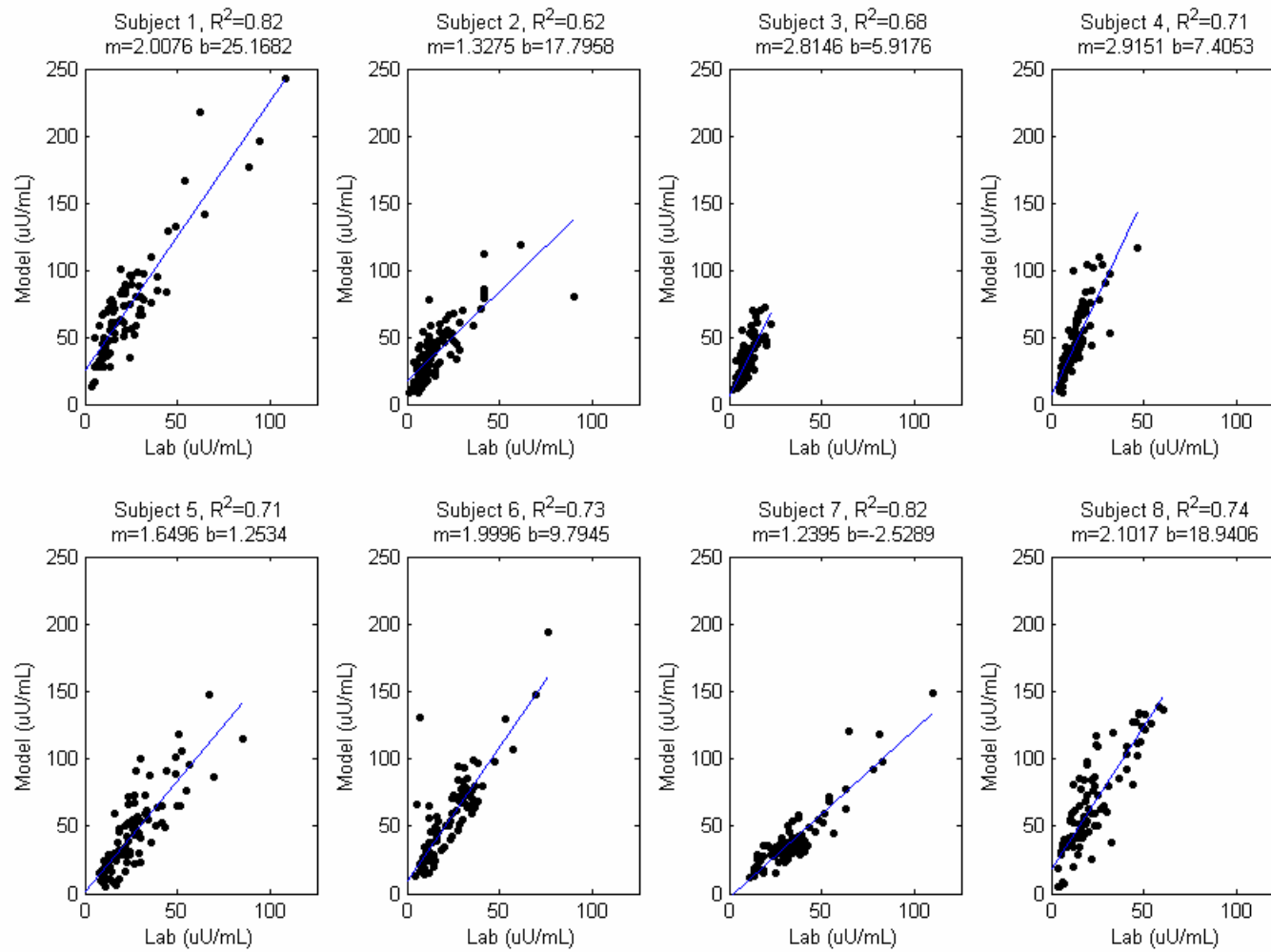


Figure 2

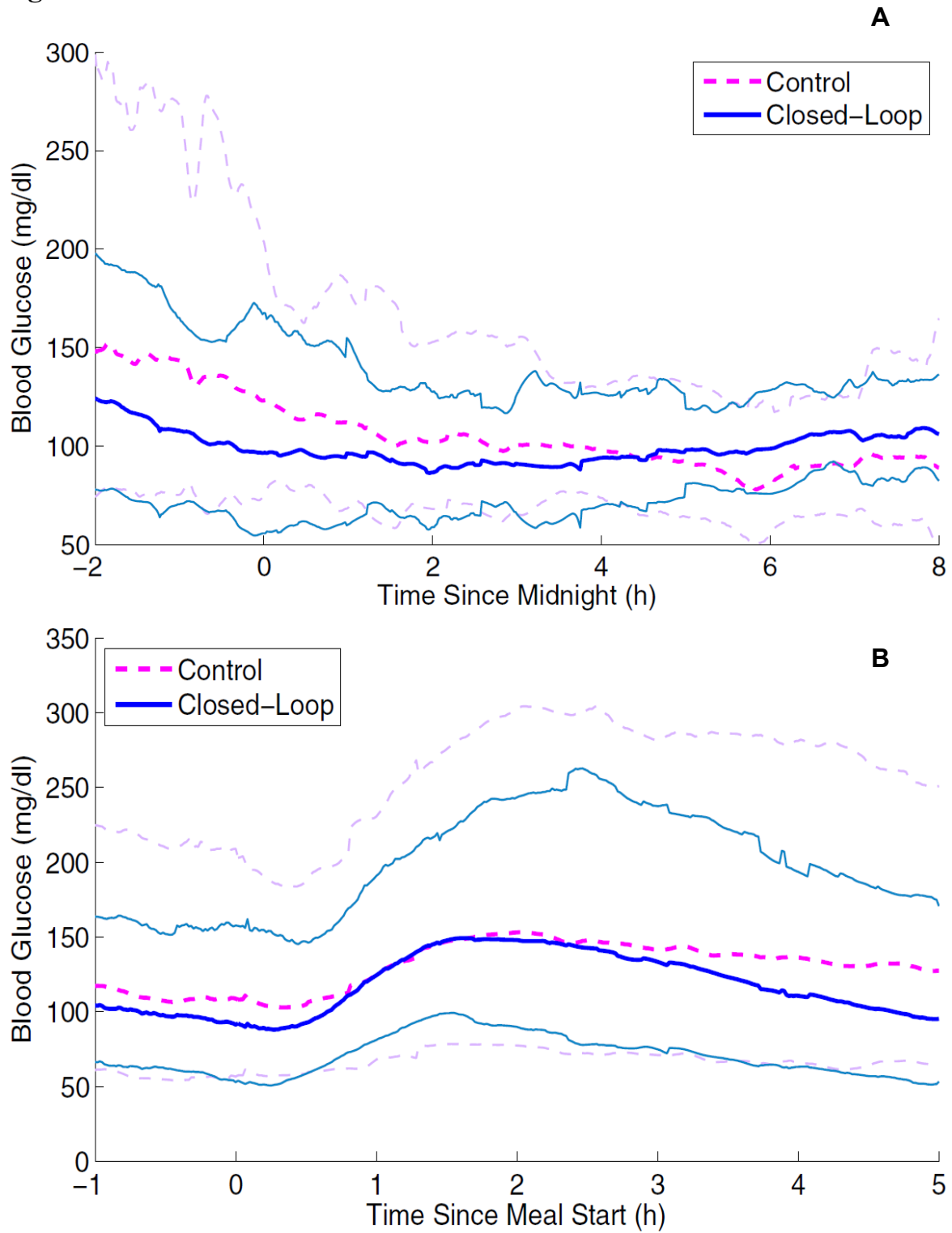


Figure 3

