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ORIGINAL ARTICLE

Dynamic Insulin on Board: Incorporation of Circadian Insulin Sensitivity Variation

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Abstract

Background:

Insulin-on-board (IOB) estimation is used in modern insulin therapy with continuous subcutaneous insulin infusion (CSII) as well as different automatic glucose-regulating strategies (i.e., artificial pancreas products) to prevent insulin stacking that may lead to hypoglycemia. However, most of the IOB calculations are static IOB (sIOB): they are based only on approximated insulin decay and do not take into account diurnal changes in insulin sensitivity.

Methods:

A dynamic IOB (dIOB) that takes into account diurnal insulin sensitivity variation is suggested in this work and used to adjust the sIOB estimations. The dIOB function is used to correct the dosage of insulin boluses in light of this circadian variation.

Results:

Basal–bolus as applied by pump users and model predictive control therapy with and without dIOB were evaluated using the University of Virginia/Padova metabolic simulator. Three protocols with four meals of 1 g carbohydrate/kg body weight were evaluated: a nominal scenario and two robustness scenarios, one in which insulin sensitivity was 15% greater than estimated and the other where the lunch is 30% less than announced. In the nominal and robustness scenarios, respectively, the dIOB led to 6% and 24% and 40% less hypoglycemia episodes than approaches without IOB. The new approach was also compared with the sIOB to evaluate the improvements with respect to the previous approach.

Conclusions:

Improved glucose regulation was demonstrated using the dIOB where circadian insulin sensitivity is used to adjust IOB estimation. Use of diurnal variations of insulin sensitivity appears to promote effective and safe insulin therapy using CSII or artificial pancreas. Clinical trials are warranted to determine whether nocturnal hypoglycemia can be reduced using the dIOB approach.

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Abbreviations: (BB) basal–bolus, (BG) blood glucose, (BW) body weight, (CL) closed loop, (CR) carbohydrate ratio, (CSII) continuous subcutaneous insulin infusion, (CVGA) control-variability grid analysis, (dIOB) dynamic insulin on board, (IOB) insulin on board, (MPC) model predictive control, (sIOB) static insulin on board, (T1DM) type 1 diabetes mellitus

Keywords: artificial pancreas, circadian rhythm, continuous subcutaneous insulin infusion, diabetes, insulin on board, insulin sensitivity

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Introduction

People with type 1 diabetes mellitus (T1DM) need exogenous insulin delivery provided by either multiple daily injections or continuous subcutaneous insulin infusion (CSII) with an insulin pump in order to avoid hyperglycemia [blood glucose (BG) > 180 mg/dl], which is associated with an array of long-term complications. Intensive treatment with insulin injections to maintain near-normal glycemia (BG 70–180 mg/dl) markedly reduces the risk of chronic complications.[1] However, hypoglycemia (BG < 60 mg/dl) can cause severe acute dangers, so the goal for people with T1DM is to control BG within a tight range.

Controlling BG within a narrow range is made more difficult by the fact that both glycemia and insulin action are influenced by many external factors, including physical activity, meals, and temperature changes.[2,3] Circadian rhythms affect insulin sensitivity but, by contrast, are relatively consistent from day to day and within populations.[4] For example, the glucose tolerance of people without diabetes tends to be optimal in the morning and decline during the day, whereas people with T1DM typically require more insulin per gram of carbohydrate at breakfast compared with other meals, due to morning increases in insulin resistance.[5–11] Considerable evidence indicates that a transient decrease in insulin sensitivity is also one of the causes of the so-called dawn phenomenon, a transient increase in insulin requirements that may occur between 5:00 AM and 8:00 AM in people with T1DM.[12–14] Failure to meet the increased early morning insulin requirements can lead to hyperglycemia, which, in turn, can make breakfast-time glycemic control even more difficult.[12–17]

Bolus calculators are standard features of CSII pumps and make insulin-dosing calculations easier and more accurate for pump users by taking into account aspects such as the current BG concentration, target BG concentration, amount of carbohydrate to be consumed, insulin-to-carbohydrate ratio (CR), and—of greatest interest in this discussion—an approximation of the insulin decay curve. The insulin decay curve is used to estimate the amount of insulin remaining in the body from previous insulin boluses, or insulin on board (IOB). Pump users can select the duration of decay from within a range of roughly 2 to 8 h, depending on the bolus calculator; an educated selection of the appropriate duration is needed in order to enable accurate IOB calculation and thus accurate mealtime and correction boluses.[18]

Modern insulin pumps utilize approximations of the insulin action curve that are effectively static, with IOB calculations varying only on the basis of the current glucose concentration. However, the characteristics of glucose regulation vary across by more than 30% the 24 h cycle,[19] as noted earlier.

We describe a technique whereby diurnal insulin sensitivity is superimposed on the static insulin on board (sIOB) to personalize it. Each two-dimensional curve of insulin absorption previously presented[18] has been transformed into a three-dimensional curve, adding the time of the day as another dimension. The result enables a dynamic insulin on board (dIOB) calculation that depends on the time of the day. To evaluate this new approach, two control strategies were explored: a basal–bolus (BB) therapy and the model predictive control (MPC) strategy presented by Patek and coauthors.[20]

Methods

A generic sensitivity variation curve that describes diurnal changes in insulin sensitivity for a population of adult T1DM subjects was defined on the basis of published work.[5–7,9,17,21,22] The evening insulin sensitivity was defined as the nominal value, because insulin sensitivity seems to be fairly stable and close to its daily mean value in the evening. With respect to the evening value, insulin sensitivity variation factors were defined for several other key times of day as reported in **Table 1**. Next a continuous curve was obtained via an interpolation of these main points using a piecewise cubic Hermite interpolating polynomial. Based on this estimated sensitivity curve and a time-shift to account for insulin pharmacokinetic and pharmacodynamic delays, a 24 h IOB penalty curve was obtained. Each time t on the penalty curve is assigned a penalty factor that represents insulin sensitivity at time $t + \Delta$, where $t + \Delta$ is the time of peak effect of any insulin injected at time t. As an example, for insulin doses that have peak effect in the evening, the IOB

Table 1.
Circadian Insulin Sensitivity Variation Obtained via an Elaboration of Published Results Obtained in Clinical Studies of the Dawn Phenomenon[5–7,9,17,21,22]

Time interval (start time)	Description	Insulin sensitivity variation factor
0:00	Insulin sensitivity peaks at +40% with respect to nominal and then falls for the next 8 h	1.4
2:00	Insulin sensitivity reaches -20% with respect to nominal and continues to decline abruptly	0.8
3:00	Insulin sensitivity reaches -40% with respect to nominal and thereafter declines more gradually	0.6
8:00	60% more insulin is required at breakfast time;[9] insulin sensitivity increases for the next 7 h	0.4
11:30	Insulin sensitivity smoothly returns toward the nominal value	0.8
15:00	Insulin sensitivity plateaus at the nominal value for 7 h	1
23:00	Insulin sensitivity starts from the nominal at 22:00 and reaches +20% after 1 h	1.2

penalty factor is equal to 1. A penalty factor less than 1 means that the subject is more resistant to insulin than usual, and so the amount of insulin still active in his body (i.e., IOB) will be considered lower than in the nominal case. If the penalty factor is greater than 1, the subject is more sensitive to insulin action than in the nominal case, and so IOB will be considered higher. Both the sensitivity estimation curve and the IOB penalty curve are displayed in **Figure 1**.

We note that the penalty factor could vary on the basis of other events or factors that influence insulin absorption and/or insulin sensitivity, such as physical activity, stress, or sickness. Such factors could be flagged directly by the user or potentially even inferred from sensor input. Thus, this model of IOB calculation can be adapted and enhanced to account for more complex conditions in the future. Although this curve could also be tailored based on specific information made available on the patient's physiology; the proposed approach considers the case when this information is not available. Clinical studies such as that by Hinshaw and coauthors[4] could provide data helpful to develop an individualization procedure for this method.

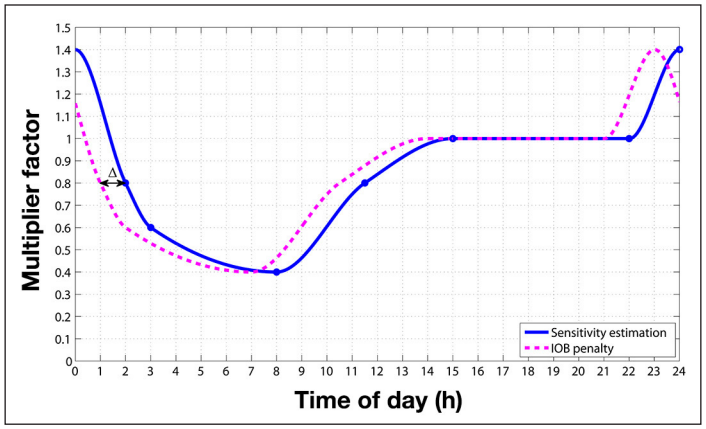

Figure 1. The sensitivity variation curve was defined by fixing main values obtained from the literature[5–7,9,17,21,22] and interpolating them through a piecewise cubic Hermite interpolating polynomial. The penalty curve was obtained by applying an anticipation Δ to the curve to take into account insulin absorption delays.

The sensitivity variation curve is described by the following equation:

$$y(t) = \begin{cases} 0.09130t^3 - 0.33261t^2 + 1.4 & t \in [0,2] \\ 0.0869t^3 - 0.05217t^2 - 0.23478t + 0.8 & t \in [2,3] \\ 0.00007t^3 - 0.00730t^2 - 0.07826t + 0.6 & t \in [8,8] \\ -0.01244t^3 - 0.007619t^2 - 0.07826t + 0.4 & t \in [8,11.5] \\ -0.00078t^3 - 0.00272t^2 - 0.07619t + 0.8 & t \in [11.5,15] \\ 1 & t \in [15,22] \\ 0.0125t^3 - 0.15t^2 - 0.45t + 1 & t \in [22,24] \end{cases} \quad (1)$$

where t is the time of day in hours, $y(t)$ is the sensitivity variation, and the time of day is defined in the square brackets. This equation also describes the penalty curve, which is identical except for the insertion of anticipatory

time-shift Δ. In this work, Δ was set to 1 h in order to take into account delays associated with subcutaneous insulin delivery and insulin pharmacokinetics and pharmacodynamics.[3]

The static decay curves currently used in different bolus calculators can be adapted based on the time-dependent penalty factor described by this function. At any point that a standard decay curve would be consulted to evaluate IOB and inform a dosage decision, an improved IOB curve that accounts for that time of day can be found by multiplying the standard curve by the penalty factor. We perform this operation on the insulin decay curve described by Zisser and coauthors[18] in order to obtain time-variant decay curves for calculating IOB. We refer to such a time-dependent IOB calculation technique as dIOB, and we refer to traditional techniques that use the same curve at all times of day as sIOB. **Figure 2** provides an example of an 8 h IOB curve[18] as it would be modified at three different times of day in a dIOB scheme. As with sIOB curves, these new curves can be used along with recent insulin dosage information in order to compute the amount of IOB. The insulin pump's own internal IOB assessment is never used by the system; instead, the IOB is computed as

$$\mathrm{IOB} = \sum_{i=1}^{96} a(i)u(i), \tag{2}$$

where elements $u(i)$, $i = 1,\ldots, 96$ represent the vector of delivered insulin in the previous 8 h as delivered in 5 min intervals. The element $u(96)$ represents the most recent insulin delivery, $u(i)$ represents insulin delivery $480 - 5i$ min ago, and $u(1)$ represents the oldest insulin, delivered 8 h ago. The vector of coefficients $a(i)$, $i = 1,\ldots, 96$ describes the decay curve discretized in accordance with a 5 min time step of insulin delivery intervals; this curve is the one described by Zisser and coauthors.[18] The $a(i)$ coefficients are chosen from the 8 h IOB curve if the glucose concentration is lower than the low threshold (set to 100 mg/dl), from the 4 h IOB curve if the glucose concentration is higher than the high threshold (set to 140 mg/dl), from an interpolation of the 4 and 6 h IOB curves if the glucose is between the middle and the high threshold (between 120 and 140 mg/dl), and from an interpolation of the 6 and 8 h IOB curves otherwise. The curve selected using this method is used to compute the sIOB, while to compute the dIOB each coefficient $a(i)$ is multiplied by the penalty factor.

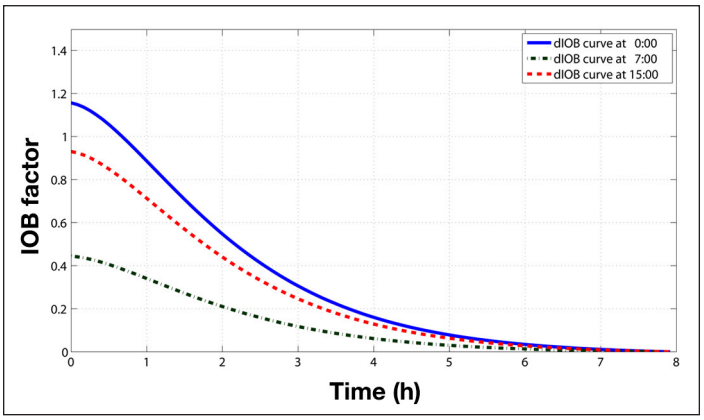

Figure 2. Three examples of the same 8 h insulin absorption curve considered at different times of the day. To account for insulin sensitivity variations, one of the absorption curves defined by Zisser and coauthors[18] was multiplied by penalty factors corresponding to different times of the day. At 3:00 PM, this factor is equal to 1, so the curve is the nominal one. At midnight, the penalty factor is greater because people with T1DM tend to be more sensitive at this time, while at 7:00 AM the penalty is decreased to reflect the lower insulin sensitivity that is typical in the morning.

Once the IOB is statically or dynamically computed, it can be used to define constraints on the maximum allowable insulin dosage, as described in previous work,[20,23] and to evaluate the effect of correction boluses with changes in insulin sensitivity.

Twelve IOB simulated experiments were conducted on 100 *in silico* adult subjects. The 28 h experiments began at 8:00 AM under steady-state conditions and involved four meals of 1 g carbohydrate/kg body weight (BW): at 9:00 AM, 1:00 PM, 7:00 PM, and 7:00 AM on the following day. Experiments were run on the Food and Drug Administration-accepted University of Virginia/Padova metabolic simulator,[23,24] which was modified so that patients' insulin sensitivity changed throughout the day according to the sensitivity variation curve defined in this work. In this engineering approximation based on the simulator, the endogenous glucose production and the insulin-dependent glucose utilization have been changed according to the sensitivity variation curve through parameters k_{p3} and V_{mx} of the glucose–insulin model described by Cobelli and coauthors;[25] these parameters influence the effect of insulin on glucose production and utilization, respectively.

The experiments allowed comparison of glucose control using dIOB, sIOB, or no IOB constraints. These three methods were each implemented and evaluated in two modes of control: closed-loop (CL) control with a linear MPC[20] and patient-directed, manual BB control. It should be noted that BB doses were optimized to account for the circadian insulin sensitivity variations implemented in the simulator; in particular, the CR was optimized to avoid severe hypoglycemia.

The individualization of the aggressiveness of the MPC controller, q, was obtained using BW in kilograms and CR in the regression function described by **Equation (3)**:

$$q = -0.01813 \times \mathrm{BW} - 0.03217 \times \mathrm{CR} \tag{3}$$

Each IOB-constraint/control-method pairing was evaluated under three experimental scenarios. In the nominal scenario, the estimate of insulin sensitivity was correct as well as the ingested meal amounts, while in the first robustness scenario each patient's insulin sensitivity was 15% higher than the estimated value and in the second, the lunch was 30% less than the announced amount.

Results and Discussion

To illustrate the utility of IOB-related constraints, results of CL and BB control without such constraints are presented in **Figure 3** using control-variability grid analysis (CVGA).[26] As expected, CL control minimizes hypoglycemia and provides superior control relative to BB therapy in the nominal scenario, but both methods are too aggressive when patients' insulin sensitivity is underestimated.

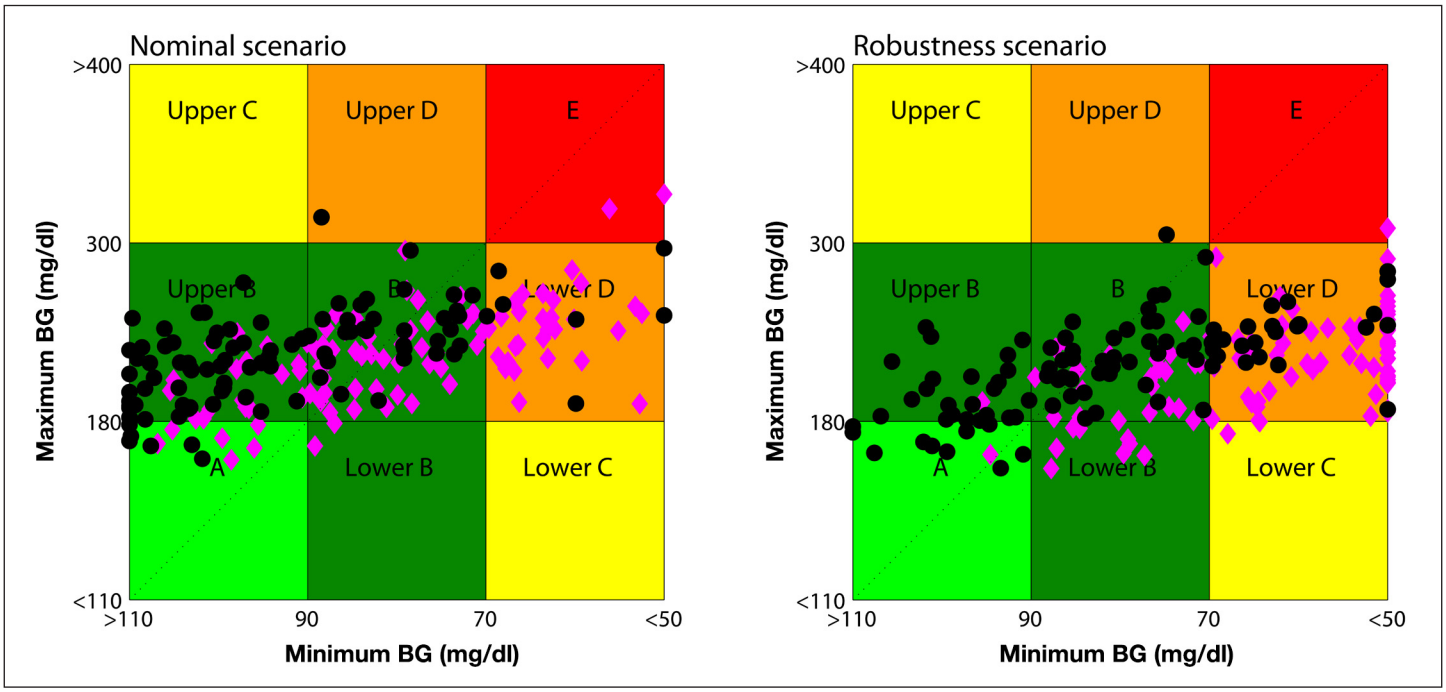

Figure 3. Results of BB therapy (magenta diamonds) and CL control[20] (black circles), each without constraints related to IOB, in the nominal (left) and robustness (right) scenarios. In the nominal scenario, both control modalities perform fairly well, and CL causes fewer patients to experience hypoglycemia <70 mg/dl compared with BB (7 versus 30). However, in the robustness scenario, both CL and BB are too aggressive, as seen by the high prevalence of patients with hypoglycemia (25 for CL, 66 for BB). This example suggests a need for additional insulin dosage constraints, which could be based on IOB. The distribution of subjects among CVGA zones was as follows in the nominal scenario with BB (6 in zone A, 64 in zone B, 0 in zone C, 28 in zone D, 2 in zone E) and with CL (6 in zone A, 86 in zone B, 0 in zone C, 8 in zone D, 0 in zone E) and in the robustness scenario with BB (1 in zone A, 33 in zone B, 2 in zone C, 63 in zone D, 1 in zone E) and with CL (10 in zone A, 65 in zone B, 0 in zone C, 25 in zone D, 0 in zone E).

Adding IOB constraints improves hypoglycemia prevention as measured by percentage of time in hypoglycemia (<60 mg/dl), number of patients with at least one BG result below 70 mg/dl, and number of patients with at least one BG result below 60 mg/dl. However, IOB constraints also lead to higher mean BG and reduce percentage of time in the target range (70–180 mg/dl) and tight target range (80–140 mg/dl). This general result is seen for both sIOB and dIOB, regardless of control method or experimental scenario (**Table 2**), though we focus on the dIOB results due to its novelty. Considering the mean values from both BB and CL simulations, dIOB resulted in less time in target compared with the non-IOB-constrained approach: the differences were 16.30% in the nominal scenario and 9.08% and 13.63% in the two robustness scenarios. Counterbalancing the reduction of time in target range, dIOB successfully minimized time spent in hypoglycemia (<60 mg/dl) from 0.23% to 0% in the nominal scenario, from 3.08% to 0.10% in the first robustness scenario, and from 0.40% to 0% in the second robustness scenario.

Table 2.
Statistical Indexes Resulting from the Simulation Performed with the Engineering Approximation Based on the University of Virginia/Padova Metabolic Simulator[8]

Index	Therapy	% time in target (70–180 mg/dl)	% time in tight target (80–140 mg/dl)	% time in hypoglycemia (<60 mg/dl)	% time in hyperglycemia (>180 mg/dl)	Mean BG (mg/dl)	Standard deviation of BG (intrasubject; mg/dl)	Maximum BG (mg/dl)	Minimum BG (mg/dl)	# of patients BG < 70 mg/dl	# of patients BG < 60 mg/dl
Nominal scenario	BB	87.13[a]	59.78[a]	0.29[b]	11.14[a]	132.34[a]	34.94[a]	220.08[a]	80.03[a]	30	8
	BB + sIOB	62.73[a]	21.95[a]	0	37.22[a]	171.29[a]	26.83	233.60[b]	127.56[a]	2	0
	BB + dIOB	67.35	23.19	0	32.60	167.95	26.14	230.65	124.20	2	0
	CL	88.71[a]	53.30[a]	0.16	10.85[a]	140.23[a]	29.64[a]	220.00[a]	93.19[a]	7	4
	CL + sIOB	67.35[a]	21.88[a]	0	32.60[a]	168.04[a]	27.62[a]	232.34[a]	121.28[c]	1	0
	CL + dIOB	75.90	24.13	0	24.05	161.81	25.30	227.81	119.78	1	0
Robustness scenario	BB	82.73[a]	58.96[a]	5.45[a]	6.87[a]	115.69[a]	36.89[a]	212.83[a]	60.68[a]	66	44
	BB + sIOB	69.29[a]	28.83[a]	0.09	30.42[a]	162.65[a]	28.37	227.54	115.52	5	2
	BB + dIOB	73.96	31.01	0.09	25.74	159.07	28.05	225.92	111.14	5	2
	CL	90.64[a]	59.12[a]	0.70[c]	7.49[a]	131.47[a]	30.60[a]	213.36[a]	81.42[a]	24	7
	CL + sIOB	73.07[a]	28.07[a]	0.11	26.76[a]	161.30[a]	28.22[a]	226.05[a]	111.61[a]	2	1
	CL + dIOB	81.25	31.00	0.11	18.57	154.89	25.83	222.57	109.94	2	1
Second robustness scenario	BB	85.64[a]	57.44[a]	0.61[b]	10.13[a]	126.90[a]	37.56[a]	220.08[a]	71.73[a]	46	11
	BB + sIOB	64.87[a]	26.13[a]	0	35.11[a]	167.17[a]	30.60[b]	233.97[b]	111.08[a]	1	0
	BB + dIOB	69.69	27.52	0	30.28	163.68	29.83	231.26	109.29	1	0
	CL	88.73[a]	54.03[a]	0.19	10.47[a]	137.19[a]	32.09[a]	219.99[a]	83.01[a]	10	3
	CL + sIOB	68.91[a]	26.35[a]	0	31.07[a]	164.45[a]	30.72[a]	232.27[a]	108.76[c]	1	0
	CL + dIOB	77.42	28.38	0	22.57	158.24	28.12	228.21	107.63	1	0

[a] p value < .001.
[b] p value < .01.
[c] p value < .05.

Furthermore, fewer subjects experienced any hypoglycemia with the dIOB approach: from an average of 6 subjects to 0 in the nominal case and from an average of 26 to 2 (**Figure 4**) and an average of 7 to 0 in the robustness scenarios.

Dynamic IOB performed slightly better than sIOB with regard to percentage of time in target (6.59% and 6.43% and 6.67% more time with respect to sIOB in the nominal case and in the robustness cases, respectively; average of BB

and CL control), percentage of time in tight target (1.75% more time than sIOB for the nominal case and 2.55% and 1.71% more time for the robustness cases), and percentage of time in hyperglycemia above 180 mg/dl (6.59% less time respect to sIOB for the nominal case and 6.44% and 6.66% less time for the robustness case). An iterative process can improve the performance and avoid hypoglycemia.

Figure 4 shows how BB therapy with dIOB reduced the prevalence of hypoglycemia phenomena, relative to BB therapy without IOB constraints. The hypoglycemia reductions are particularly evident if insulin sensitivity is underestimated, as in the robustness scenario (**Figure 4**, right).

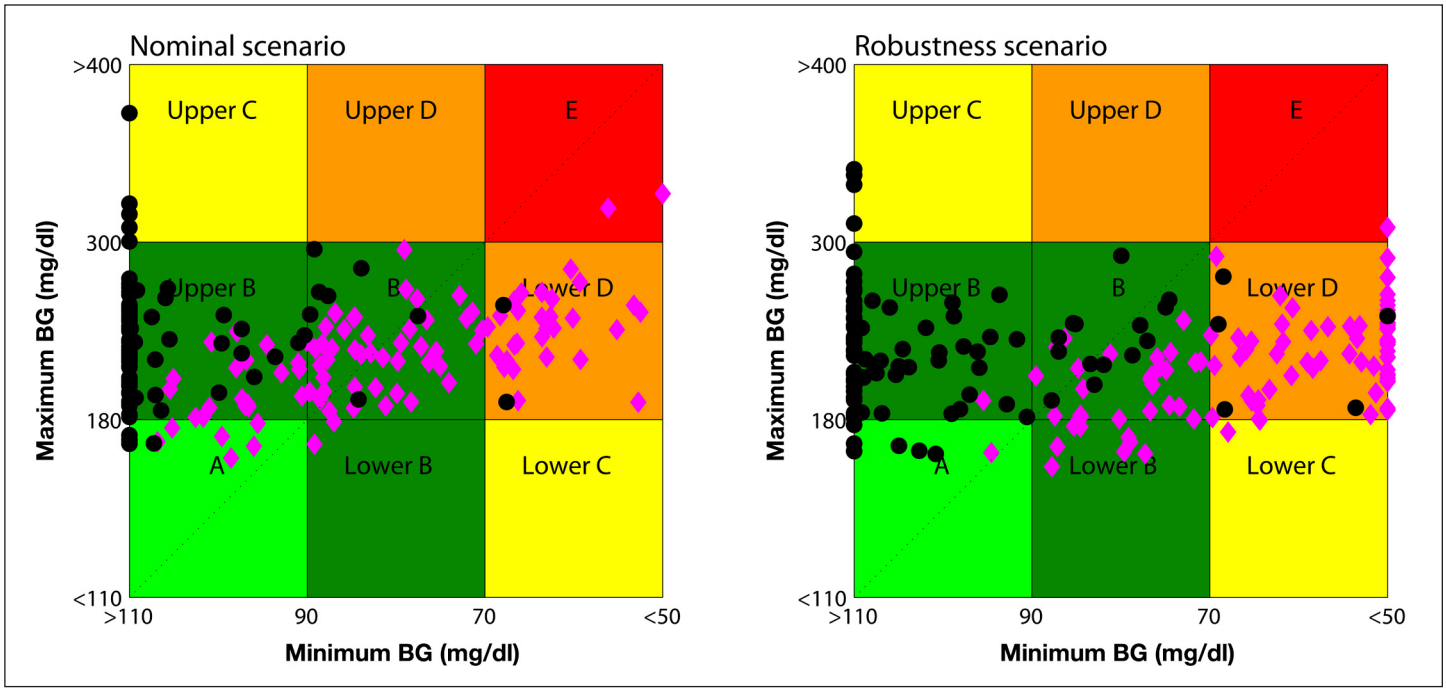

Figure 4. Results for BB therapy with dIOB constraints (black circles) and with no IOB constraints (magenta diamonds) in the nominal (left) and robustness (right) scenarios. The number of subjects with minimum glucose <70 mg/dl was notably lower with dIOB than without IOB, in both the nominal scenario (2 versus 30) and the robustness scenario (5 versus 66). The distribution of subjects among CVGA zones was as follows in the nominal scenario with dIOB (5 in zone A, 88 in zone B, 5 in zone C, 2 in zone D, 0 in zone E) and with no IOB constraints (6 in zone A, 64 in zone B, 0 in zone C, 28 in zone D, 2 in zone E) and in the robustness scenario with dIOB (6 in zone A, 85 in zone B, 4 in zone C, 5 in zone D, 0 in zone E) and with no IOB constraints (1 in zone A, 33 in zone B, 2 in zone C, 5 in zone D, 0 in zone E).

In comparison with BB therapy that uses sIOB, BB with dIOB led to better BG control (lower mean and smaller standard deviation) during the night and in the following morning. These benefits are not evident from CVGA, which represents only the glucose extremes, so instead we compare dIOB and sIOB results with time-profile plots (**Figures 5A** and **5B**). **Figures 5C** and **5D** show the differences in insulin delivery relative to non-IOB-constrained BB therapy. To avoid nocturnal hypoglycemia, both IOB approaches reduce the basal insulin before midnight. However, in the middle of the night, both approaches restore a basal rate similar to the unconstrained rate in order to improve glycemic control during breakfast. Similar conclusions can be drawn when the various IOB constraints are tested in CL control; **Figure 6** compares dIOB with no IOB, and **Figure 7** compares dIOB with sIOB. In **Figures 8–11**, the time profiles of two significant subjects are shown: the first is particularly sensitive to insulin (**Figures 8** and **9**), while the second subject is more typical (**Figures 10** and **11**).

Compared with the average subject, the sensitive subject has 13% higher BW, 45% lower daily basal insulin dose, and 43% higher CR. The particular discrepancy of CR from the average value can lead to a control that is too aggressive (e.g., q value that is too high in CL control). This aggressiveness increases the risk of mealtime insulin overdose, which cannot be compensated through subsequent control actions.

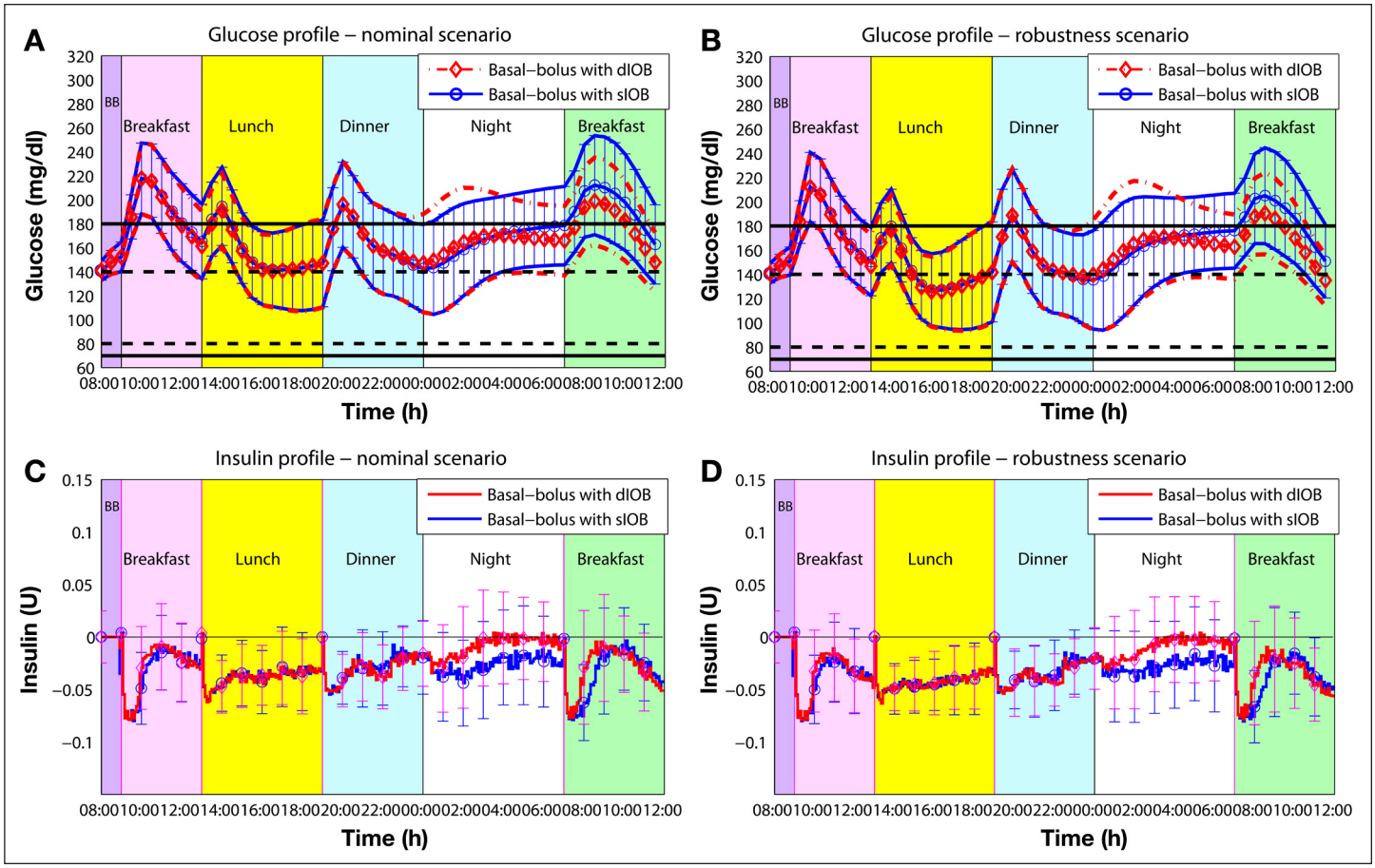

Figure 5. Mean (plus or minus standard deviation) glucose profiles for BB therapy with sIOB (blue) and dIOB (red) in the **(A)** nominal and **(B)** robustness scenarios. **(C, D)** The corresponding insulin injection profiles for each scenario, with dosage expressed as the mean (plus or minus standard deviation) of the difference relative to IOB-unconstrained BB therapy.

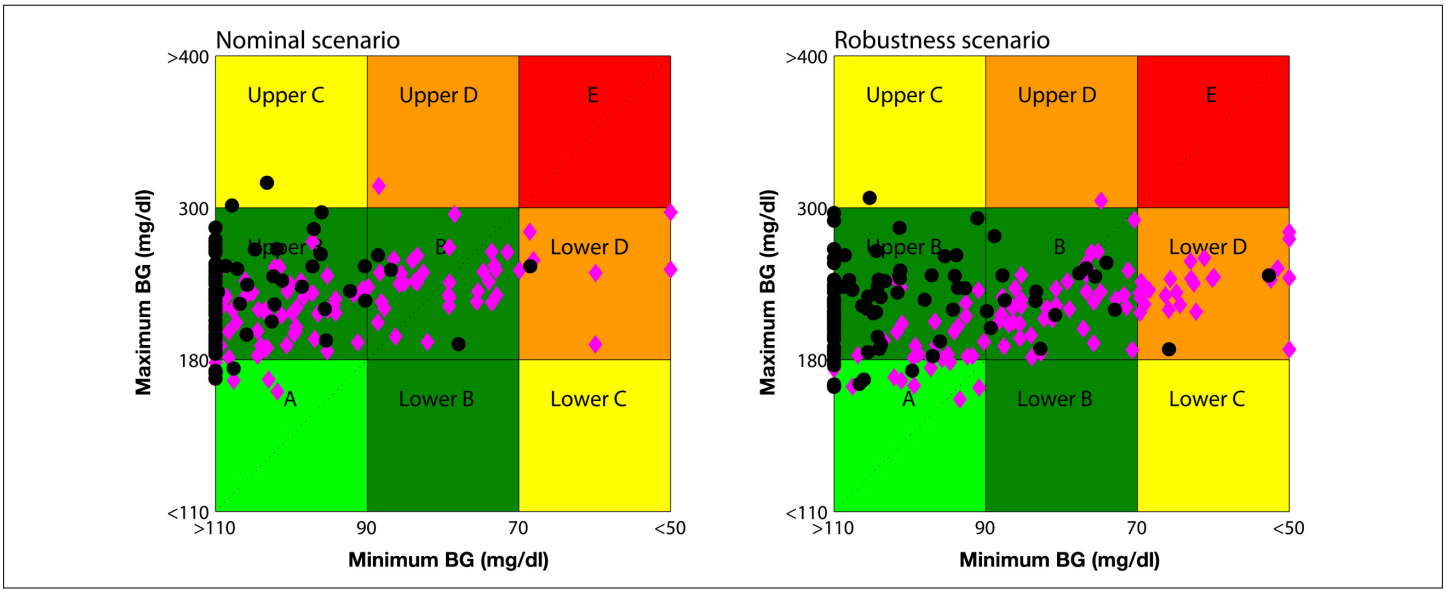

Figure 6. Results for CL control with dIOB constraints (black circles) and with no IOB constraints (magenta diamonds) in the nominal (left) and robustness (right) scenario. As part of the CL strategy's safety layer to account for intersubject variability, dIOB constraints were seen to decrease the prevalence of hypoglycemia, with a moderate increase in maximum BG. The distribution of subjects among CVGA zones was as follows in the nominal scenario with dIOB (5 in zone A, 92 in zone B, 2 in zone C, 1 in zone D, 0 in zone E) and with no IOB constraint (6 in zone A, 86 in zone B, 0 in zone C, 8 in zone D, 0 in zone E) and in the robustness scenario with dIOB (7 in zone A, 90 in zone B, 1 in zone C, 2 in zone D, 0 in zone E) and with no IOB constraint (10 in zone A, 65 in zone B, 0 in zone C, 25 in zone D, 0 in zone E).

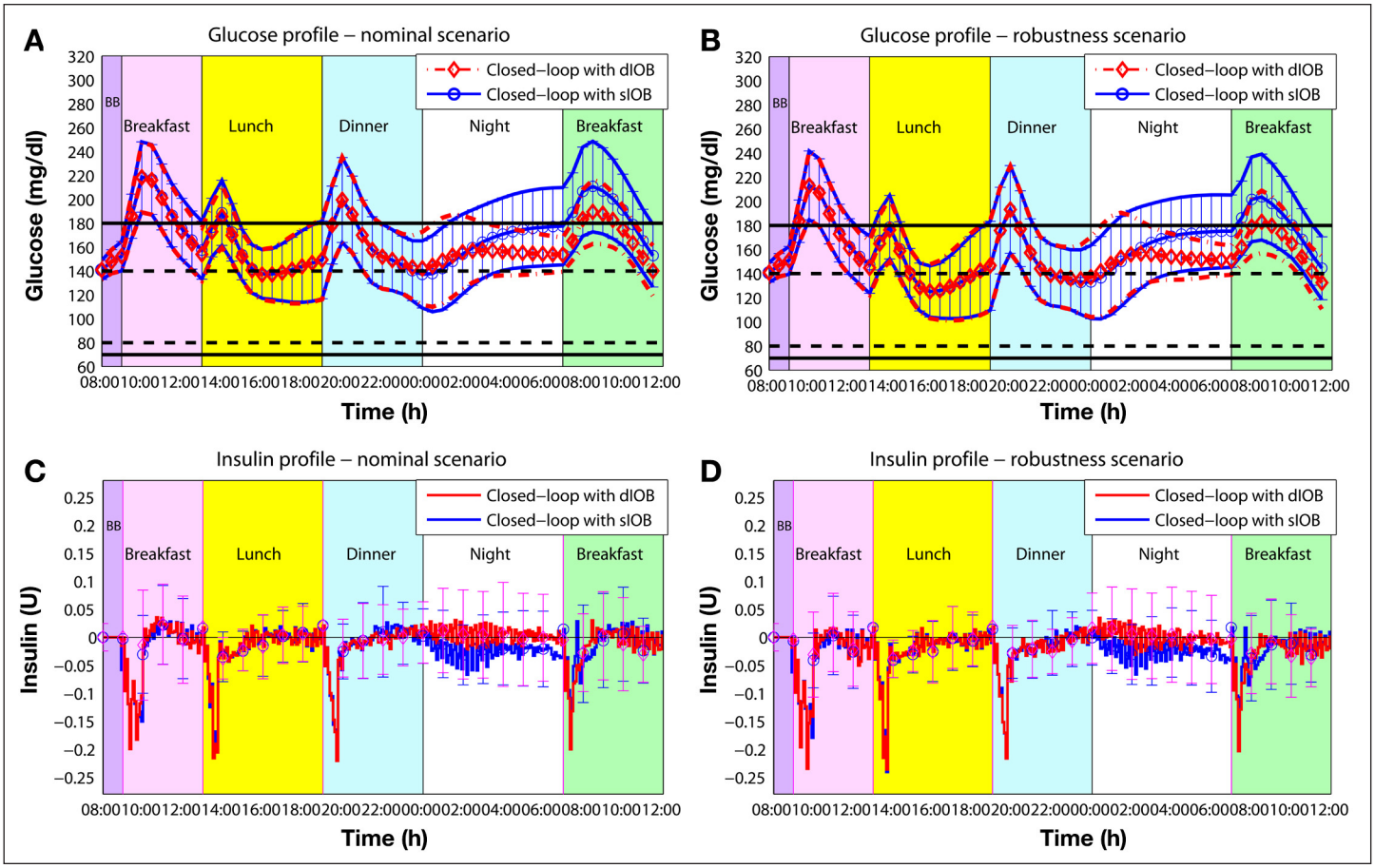

Figure 7. Mean (plus or minus standard deviation) of BG for CL control with the sIOB (blue) and dIOB (red) approaches in the **(A)** nominal and **(B)** robustness scenarios. **(C, D)** The corresponding insulin profiles for each scenario, with dosage expressed as the mean (plus or minus standard deviation) of the difference relative to IOB-unconstrained CL control. The advantages of dIOB compared with sIOB can be clearly noted at night and during the next morning.

Figures 8 and **9** show the glucose–insulin profiles of the extremely sensitive *in silico* subject using BB therapy and CL therapy, respectively. Each figure's panels A and B show the improvements obtained using the dIOB approach over the unconstrained therapy in the nominal and robustness scenarios, respectively, as evidenced by fewer hypoglycemic episodes. No significant improvement is achieved by applying the dIOB constraints in place of the sIOB.

Despite the improvements that the subject may have experienced owing to use of IOB constraints, some hypoglycemia phenomena still occurred after dinner with the nominal scenario (**Figures 8C** and **9C**) and after lunch and dinner with the robustness scenario (**Figures 8D** and **9D**). A possible explanation of this behavior is that a constant CR was used in the meal bolus calculation, whereas insulin sensitivity is a time-variant characteristic. This effect is emphasized in the robustness scenario.

The more-typical patient experienced reductions in hypoglycemia using the dIOB approach compared with the non-IOB-constrained BB therapy in the nominal (**Figure 10A**) and robustness (**Figure 10B**) scenarios. When compared with the sIOB approach, the use of dIOB constraints improves glucose control during the night and in the morning in both the nominal (**Figure 10C**) and robustness (**Figure 10D**) scenarios.

With the nominal scenario (**Figures 10A** and **10C**), the unconstrained BB therapy had good performance, and the introduction of dIOB or sIOB constraints led to an overall increase in the glucose concentration. But when insulin sensitivity is underestimated in the robustness scenarios (**Figures 10B** and **10D**), the introduction of IOB constraints markedly reduces the rate of hypoglycemia.

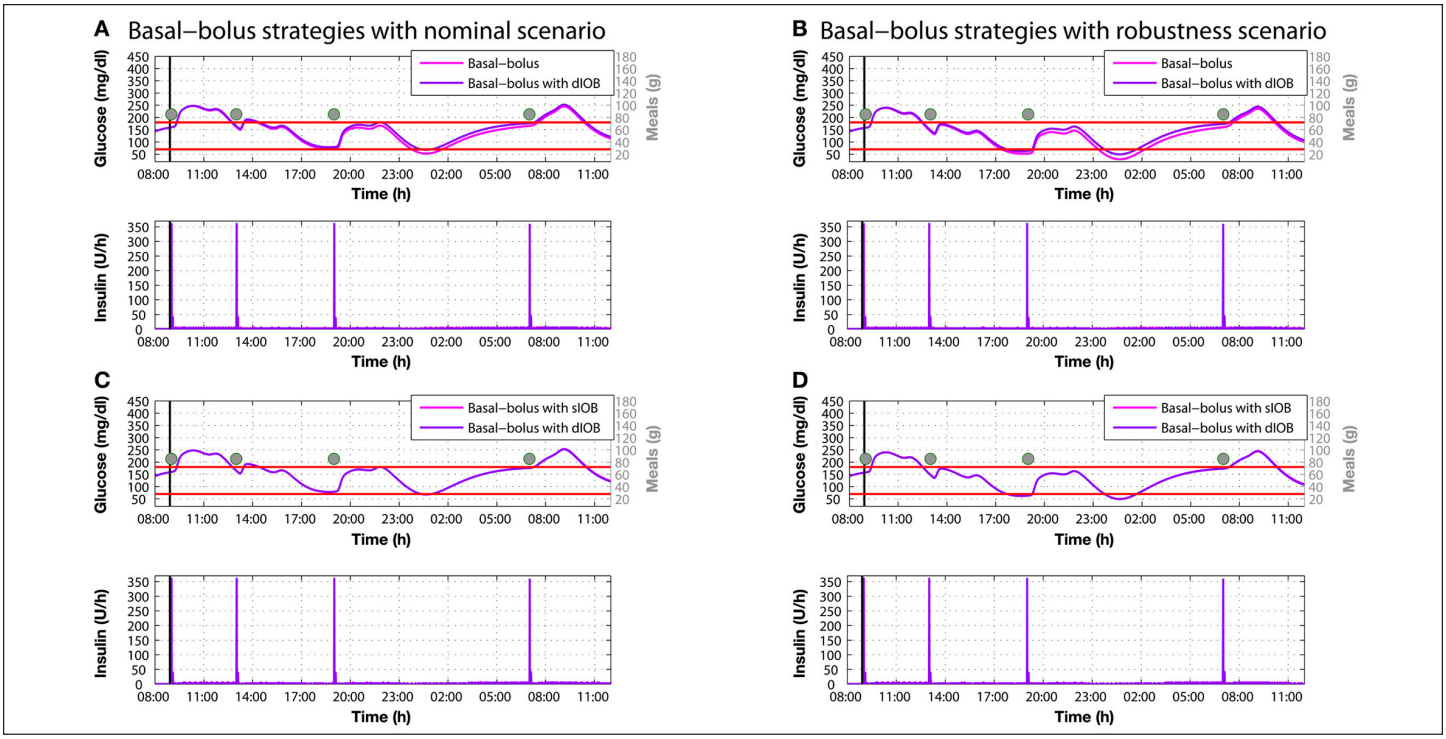

Figure 8. Glucose and insulin profiles of an extremely insulin-sensitive *in silico* subject during BB therapy experiments. **(A, B)** The improvements obtained using the dIOB approach relative to no IOB constraint in the nominal and the robustness scenarios, respectively: hypoglycemia was notably reduced. The dIOB and sIOB constraints were effectively equivalent to each other in both the **(C)** nominal and the **(D)** robustness scenarios. With each IOB constraint, some hypoglycemia still occurred after dinner in the **(C)** nominal scenario and after both lunch and dinner in the **(D)** robustness scenario: a time-variant CR could be necessary for this subject.

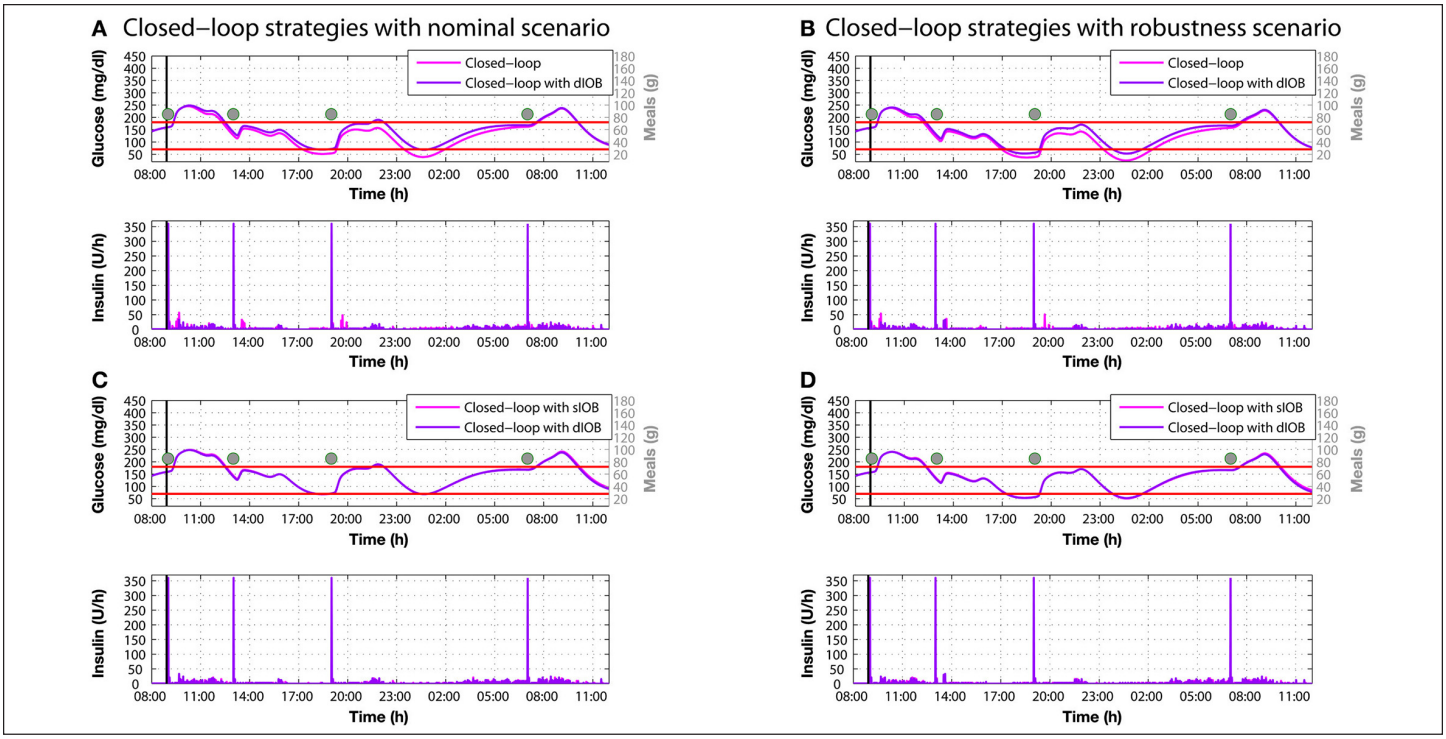

Figure 9. Glucose and insulin profiles of an extremely insulin-sensitive *in silico* subject during CL therapy experiments. **(A, B)** The improvements obtained using the dIOB approach relative to no IOB constraint in the nominal and the robustness scenarios, respectively: hypoglycemia was notably reduced. The dIOB and sIOB constraints were effectively equivalent to each other both in the **(C)** nominal scenario and in the robustness scenario. With each IOB constraint, some hypoglycemia still occurred after lunch and dinner with the **(D)** robustness scenario: a time-variant CR could be necessary for this subject.

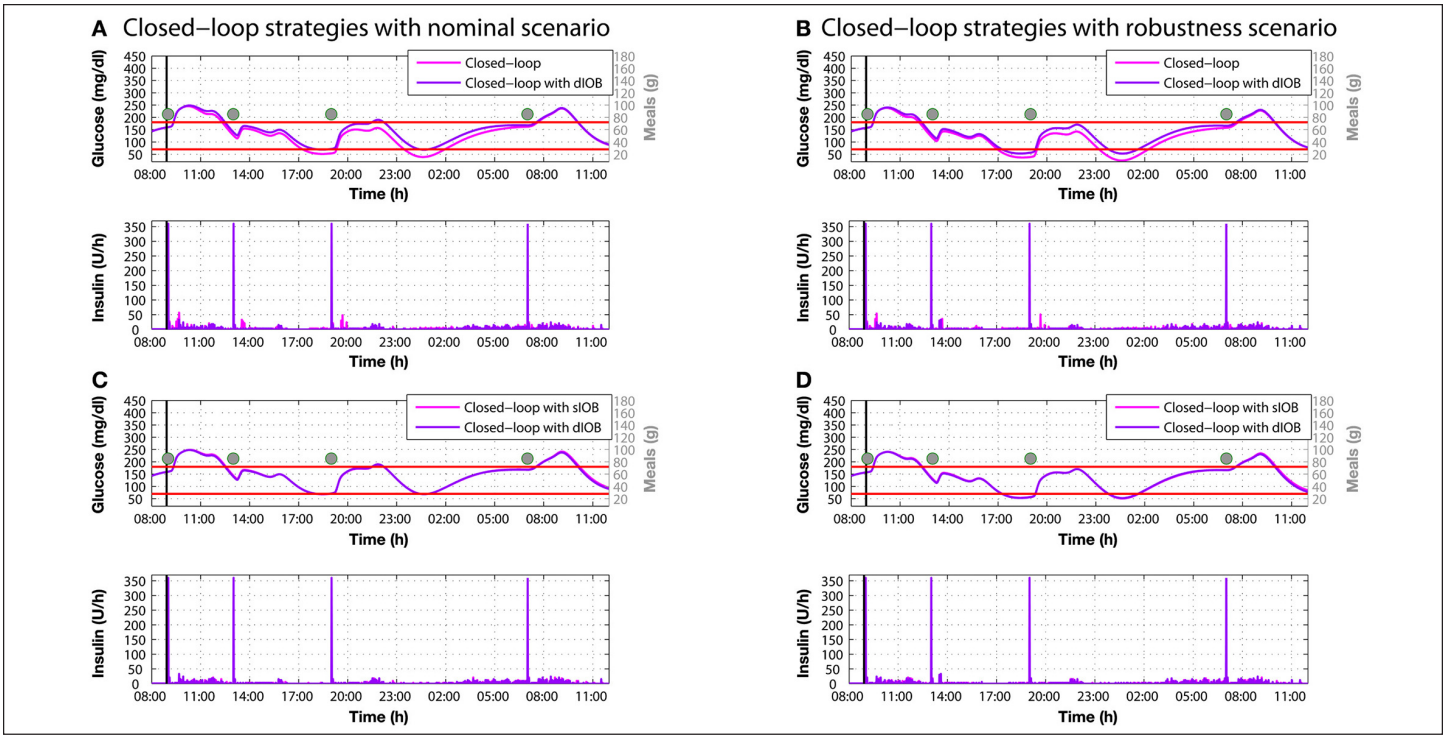

Figure 10. Glucose and insulin profiles of a typical *in silico* subject during BB therapy experiments. **(A, B)** The improvements obtained using the dIOB approach relative to no IOB constraint in the nominal and the robustness scenarios, respectively. **(C, D)** The use of dIOB constraints conferred better glucose control than sIOB constraints during the night and the next morning in the **(C)** nominal and **(D)** robustness scenarios. **(A, C)** In the nominal scenario, the BB therapy had good performance, and the introduction of dIOB or sIOB constraints led to an increase in the glucose concentration. **(B, D)** In the robustness scenario, the introduction of these constraints is critical to avoid hypoglycemia phenomena as a result of erroneous estimation of insulin sensitivity.

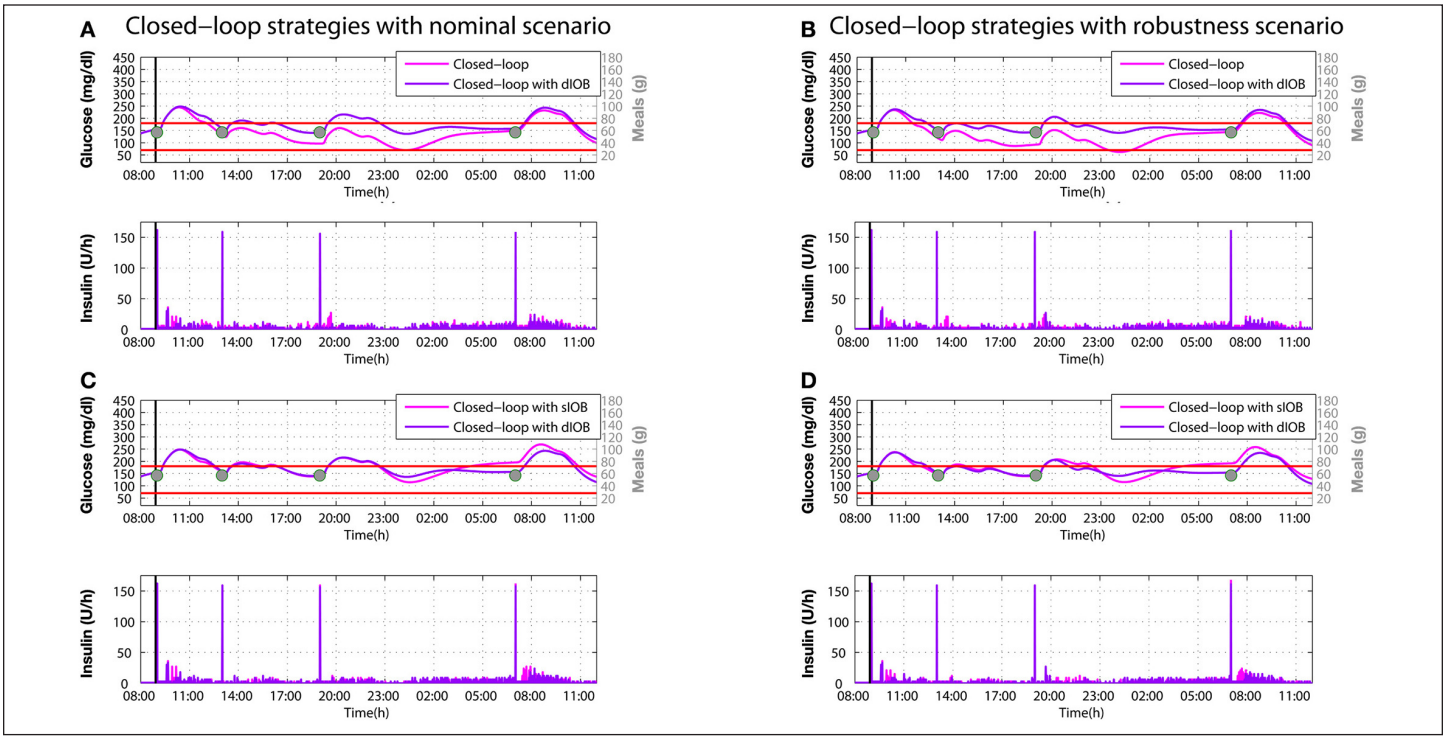

Figure 11. Glucose and insulin profiles of a typical *in silico* subject during CL therapy experiments. **(A, B)** The improvements obtained using the dIOB approach compared to no IOB constraint in the nominal and the robustness scenarios, respectively. **(C, D)** The use of dIOB constraints improved the glucose control compared to sIOB constraints during the night and in the morning in the **(C)** nominal and **(D)** robustness scenarios. **(A, C)** In the nominal scenario, the IOB-unconstrained CL therapy had good performance, and the introduction of dIOB or sIOB constraints led to an increase in the glucose concentration. **(B, D)** With the robustness scenario, the introduction of these constraints is critical to avoid hypoglycemic events stemming from the underestimate of insulin sensitivity.

The same conclusion can be drawn from the results with CL therapy. **Figure 11** shows the comparison of CL control with dIOB to CL with no IOB constraints in the nominal (**Figure 11A**) and robustness (**Figure 11B**) scenarios. Compared with sIOB constraints, dIOB constraints improved glucose control in particular during the night and in the next morning in both the nominal (**Figure 11C**) and robustness (**Figure 11D**) scenarios.

In the nominal scenario, CL control performed well without IOB constraints, and the introduction of dIOB or sIOB constraints increased the overall glucose concentration (**Figure 11A** and **11C**). The dIOB approach proved to be only marginally useful for reducing hypoglycemia in the nominal case, but it is the key factor for hypoglycemia prevention in the robustness scenario (**Figure 11B** and **11D**). As a result, dIOB could play a key role in daily insulin management.

Conclusions

The presented dIOB approach is based on a generic insulin sensitivity variation profile; it showed benefits in terms of hypoglycemia phenomena prevention compared with insulin delivery without IOB constraints. As expected, this improvement came at the expense of higher mean glucose and less time in target than without IOB constraints. However, dIOB kept the mean value within the target range and decreased the intrasubject glucose standard deviation.

Relative to sIOB, dIOB conferred slight improvements with regard to percentage of time in target, tight target, and hyperglycemia and maximum BG. As shown in **Figures 5A**, **5B**, **7A**, and **7B**, nocturnal glucose regulation was better with dIOB than with sIOB in terms of both mean and intrasubject variability.

In sum, the dIOB approach enabled better hypoglycemia prevention relative to insulin delivery without IOB constraints, and it enabled better night and morning glucose regulation compared with the sIOB approach. We believe that this method can be tailored for the single patient and extended to account for changes in insulin pharmacokinetics due to exercise, glycemic extremes, stress, illness, and other factors.

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