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ORIGINAL ARTICLES

Combining Basal–Bolus Insulin Infusion for Tight Postprandial Glucose Control: An *in Silico* Evaluation in Adults, Children, and Adolescents

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Abstract

Background:

Achieving good postprandial glycemic control, without triggering hypoglycemia events, is a challenge of treatment strategies for type 1 diabetes subjects. Continuous subcutaneous insulin infusion, the gold standard of therapy, is based on heuristic adjustments of both basal and prandial insulin. Some tools, such as bolus calculators, are available to aid patients in selecting a meal-related insulin dose. However, they are still based on empiric parameters such as the insulin-to-carbohydrate ratio and on the physicians' and patients' ability to fit bolus mode to meal composition.

Method:

In this article, a nonheuristic method for assessment of prandial insulin administration is presented and evaluated. An algorithm based on set inversion via interval analysis is used to coordinate basal and bolus insulin infusions to deal with postprandial glucose excursions. The evaluation is carried out through an *in silico* study using the 30 virtual patients available in the educational version of the Food and Drug Administration-accepted University of Virginia simulator. Results obtained using the standard bolus strategy and different coordinated basal–bolus solutions provided by the algorithm are compared.

Results:

Coordinated basal–bolus solutions improve postprandial glucose performance in most cases, mainly in terms of reducing hypoglycemia risk, but also increasing the percentage of time in normoglycemia. Moreover, glycemic variability is reduced considerably by using these innovative solutions.

Conclusions:

The algorithm presented here is a robust nonheuristic alternative to deal with postprandial glycemic control. It is shown as a powerful tool that could be integrated in future smart insulin pumps.

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Abbreviations: (3D) three dimensional, (AUC) area under the curve, (CGM) subcutaneous continuous glucose monitoring, (CSII) continuous subcutaneous insulin infusion, (FDA) Food and Drug Administration, (I:C) insulin-to-carbohydrate ratio, (MPC) model predictive control, (OED) optimal experiment design, (PID) proportional-integral-derivative, (SIVIA) set inversion via interval analysis, (T1DM) type 1 diabetes mellitus, (UVa) University of Virginia

Keywords: blood glucose control, insulin pump therapy, interval analysis, set inversion, type 1 diabetes mellitus

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Introduction

The Diabetes Control and Complications Trial[1] and the UK Prospective Diabetes Study[2] first demonstrated that chronic hyperglycemia is responsible for diabetic complications, both in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus. A growing body of evidence has stressed the importance of postprandial hyperglycemia and glycemic variability as possible determinants of diabetes-related complications, as well as increased cardiovascular risk in people with diabetes.[3,4] Indeed, impairment of postprandial control has been shown to be the first alteration of glycemia homeostasis contributing to chronic hyperglycemia,[5] and it is associated with an increase of oxidative stress and accelerated atherosclerosis.[6,7]

The need to optimize postprandial control has prompted the development of insulin analogs with more physiologic pharmacokinetic properties.[8] It has also stimulated research in the field of subcutaneous continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII), with the introduction of different bolus strategies and bolus calculators to counteract meal-related blood glucose excursions and to prevent insulin stacking.[9,10] Tools have been developed to account for differences in meal absorption with respect to nutritional content, including fat and protein counting in the bolus computation (standard, square, or dual wave).[11] However, despite the development of these new tools, optimization of postprandial control is still an empiric process based on the experience of both the physician and the patient.

Control of postprandial glycemia excursions is also a barrier to the development of the artificial pancreas. Certainly, meals are one of the major perturbations to counteract and the main challenge found in current clinical validations of the few existing prototypes of automated glycemia control systems.[12–19] Different approaches have been suggested to deal with meal disturbances in this context, including fully closed-loop systems, semi-closed-loop with meal announcement, and hybrid approaches, using proportional-integral-derivative (PID) controllers[12] or algorithms such as model predictive control (MPC).[13,16–19] Fully closed-loop systems have shown poor performance, with postprandial glucose higher and postmeal nadir glucose lower than desired.[12] The less ambitious semi-closed-loop and hybrid approaches have demonstrated improved efficacy as compared with fully closed-loop systems. However, published clinical trials showed unsatisfactory results in terms of postprandial glucose control,[17–19] failing to demonstrate superiority to open-loop control.[18,19] Indeed, despite the use of meal announcement, the main challenge of current control algorithms is still the avoidance of overcorrection and subsequent hypoglycemia. In an attempt to solve this problem, constraints on residual insulin activity (insulin on board) have been introduced both in PID-[12] and MPC-based[13] systems. Bihormonal closed-loop control, with the inclusion of glucagon as counterregulatory control action, has also been proposed.[20,21] Clinical results still show the incidence of hypoglycemia, although it may be reduced with high-gain glucagon delivery.[20]

Interval techniques[22–25] have shown to be particularly suitable to deal with constraints under uncertainty, and they are applied in a wide range of fields such as robotics, control, computer graphics, economy, global optimization, and fault detection, among others.[24] These techniques were first introduced in the context of postprandial glucose control in insulin pump therapy for T1DM by Bondia and colleagues.[26] The Set Inversion Via Interval Analysis (SIVIA) algorithm[22] was proposed to compute the feasible set of insulin profiles (consisting of an insulin bolus at mealtime and a basal insulin deviation from baseline *during 5 h* postmeal) to fulfill the International Diabetes Federation recommendations on postprandial glycemia[27] according to a patient's mathematical prediction model.

Results of Bondia and colleagues,[26] although obtained in a virtual patient (i.e., *in silico*) suggest that a coordinated action of basal and bolus insulin is required to maintain blood glucose in a physiological range in the postprandial state, outperforming standard bolus. However, some limitations were found in their study:

1. The algorithm considers a basal deviation from baseline at mealtime of arbitrary fixed duration (5 hours).

2. It remains unanswered how a mismatch between a patient's model and actual patient's behavior, as it will be found in any attempt to identify a patient's model, will affect the behavior of the algorithm.

3. There was no formal evaluation of the methodology in a virtual patient population representative of T1DM subjects to support its superior performance versus standard bolus.

In this article, these limitations are addressed, and an innovative, nonheuristic method for the assessment of the most appropriate prandial insulin administration is presented. Indeed, duration of basal deviation is incorporated into the original algorithm proposed by Bondia and colleagues[26] as a new design parameter, leading to a three-dimensional set inversion problem. This allows, for a given meal, the determination of the optimal insulin administration mode: standard, square, and dual-wave boluses currently available in insulin pumps, as well as the new mode of *temporal basal decrement* (currently not available in pumps), which can be considered as a generalization of the concept of *superbolus* introduced by Walsh and Roberts.[28,29] A thorough evaluation of the methodology is performed in a population of virtual T1DM, CSII-treated patients included in the Food and Drug Administration (FDA)-accepted University of Virginia (UVa) simulator,[30] with the consideration of structural mismatch between the patient's model and the model used to describe he virtual patient.

Methods

Virtual Population

The UVa simulator was accepted by the FDA in January 2008 as a substitute for animal trials for the preclinical testing of control strategies in artificial pancreas studies in T1DM patients. The educational version used here includes a total of 30 virtual patients (10 adults, 10 adolescents, and 10 children) based on data of real individuals.

Table 1 shows the demographic, anthropometric, and metabolic parameters of the 30 patients. Nominal basal is taken as the basal infusion normalizing glucose around 100 mg/dl, and the insulin-to-carbohydrate ratio (I:C) is estimated through simulations trying to obtain a 2 h glucose concentration below 140 mg/dl.

Main Algorithm: Three-Dimensional (3D) Set-Inversion-Based Prandial Insulin Delivery

The algorithm presented by Bondia and colleagues[26] is extended here to a parameterization of prandial insulin infusion consisting of:

1. bolus dose at mealtime (IU),
2. basal rate at mealtime (IU/h), and
3. time of restoration of basal rate to baseline (min).

The SIVIA algorithm is applied to get, given a patient's model characterizing postprandial behavior up to 5 h, the feasible set of insulin infusion according to the aforementioned parameterization fulfilling the following constraints:

1. *The IDF guidelines for postmeal control*: nonhypoglycemia (plasma glucose >70 mg/dl) and 2 h postprandial glucose value below 140 mg/dl in a 5 h time horizon.

2. *Terminal constraints*: 5 h postprandial glucose value above 90 mg/dl and a maximum glucose slope of 0.05 mg/dl/min starting 4 h after the meal (i.e., conditions of glycemic stability).

Terminal constraints are included here to minimize both the risk of hypoglycemia after the first 5 h and late undesirable glucose rebounds. It must be considered that these are constraints applied to the model prediction, which is not considered reliable enough after a few hours after the meal. They were tuned so as to get a good blood glucose response in spite of model prediction discrepancies.

Table 1.
Demographic, Anthropometric, and Metabolic Parameters of the 30 *in Silico* Subjects Available in the Educational Version of the University of Virginia Simulator

Adults				
	Age	Weight (kg)	Nominal basal (IU/h)	I:C (g/IU)
Mean	51.6	86.07	1.685	9.92
Standard deviation	16	15.79	0.25	6.33
Adolescents				
	Age	Weight (kg)	Nominal basal (IU/h)	I:C (g/IU)
Mean	16.5	47.7	1.17	9.65
Standard deviation	1.75	7.89	0.24	6.09
Children				
	Age	Weight (kg)	Nominal basal (IU/h)	I:C (g/IU)
Mean	9.4	35.865	0.502	21.11
Standard deviation	1.56	5.96	0.07	13.76

As a result, the SIVIA algorithm produces an inner subpaving consisting of a 3D volume made up of a collection of hyperrectangles, as shown in **Figure 1** (left). A point inside this volume represents an insulin infusion profile, as defined by the selected parameterization, fulfilling the above constraints according to the patient's model.

Interpretation of the resulting feasible set is eased by the consideration of the 2D projection onto the basal–bolus dimensions (**Figure 1**, right). This projected set contains all the basal–bolus combinations at mealtime so there exists a time of restoration of basal to baseline in the (0,5) h interval fulfilling the constraints. The projected basal–bolus space can be divided into regions corresponding to different bolus administration modes present in current insulin pumps, plus a new one coined here as *temporal basal decrement*:

1. a "standard bolus" corresponds to an insulin infusion profile with nominal basal at mealtime,
2. a "square bolus" corresponds to an insulin infusion profile with no bolus and basal rate at mealtime above baseline,
3. a "dual-wave bolus" corresponds to an insulin infusion profile with basal rate at mealtime above baseline and nonzero bolus, and
4. a "temporal basal decrement bolus" corresponds to an insulin infusion profile with basal rate at mealtime below baseline.

This is illustrated in **Figure 2**, where basal and bolus axes have been normalized with respect to nominal basal and nominal bolus for the given meal (computed from the patient's I:C), respectively. Point (1,1) corresponds thus to the standard therapy.

This is especially important since it allows the automatic selection of the best administration mode. For a given meal, the projected set reveals which bolus administration modes are feasible. As the carbohydrate content of the meal increases, fewer options are available, until no solution exists (**Figure 3**). In this case, either the patient reduces the meal intake or constraints must be relaxed.

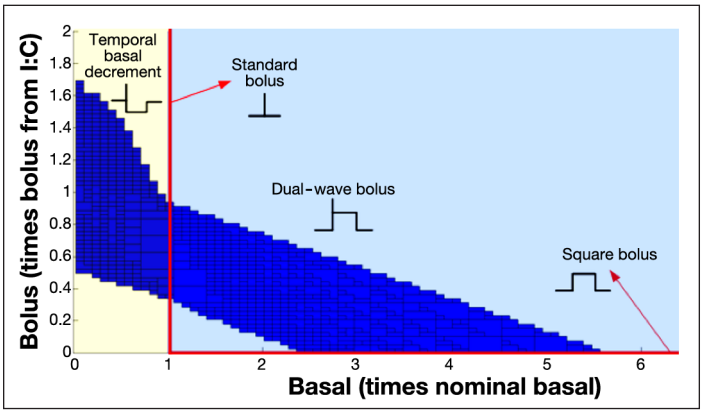

Figure 2. Plot that illustrates all possible bolus administration modes. The figure is normalized with respect to the patient's nominal basal and standard bolus from its I:C. Therapies with higher basal infusion than nominal correspond to the dual-wave and square bolus administration modes already implemented in insulin pumps. A decrement in the postprandial basal infusion results in the innovative temporal basal decrement mode. Therapies with nominal basal correspond to the standard bolus mode.

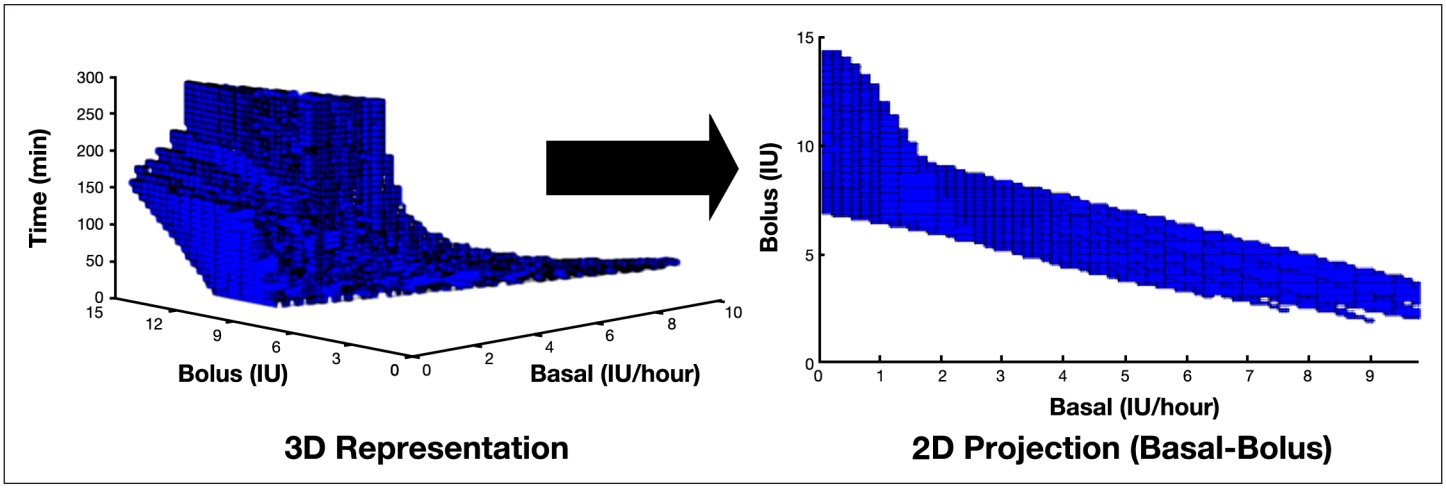

Figure 1. Three-dimensional feasible set of insulin infusions and its corresponding 2D projection onto the basal–bolus dimensions.

Once the projected feasible set is computed and an administration mode is selected, a basal–bolus combination in the corresponding subset must be chosen. This can be done in several ways, and different approaches will be considered here:

1. *Centroid solution*: The basal–bolus combination is chosen as the geometric centroid of the corresponding subset. This alternative leads to a conservative solution where the glucose response remains as far as possible from the constraints. Although this solution does not optimize the glucose profile, it is the most robust solution against mismatches between patients' model and actual patients.

2. *Maximal-bolus solution*: The basal–bolus combination is chosen by applying the highest possible bolus to optimize the 2 h postprandial glucose concentration. This solution follows a similar philosophy to the typical physicians' approach for selecting the appropriate I:C for each patient. The difference here is

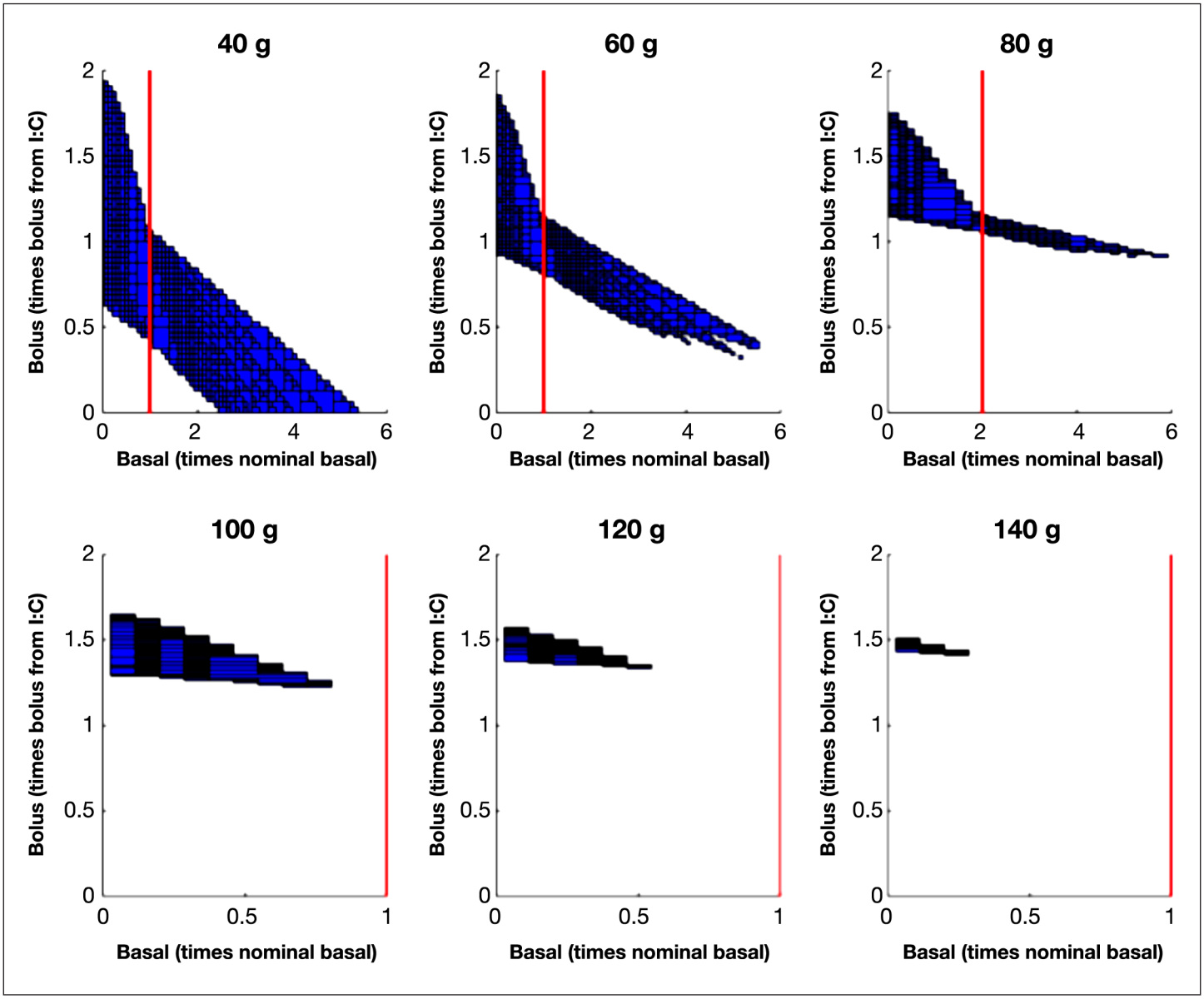

Figure 3. Plot that shows the evolution of the 2D basal–bolus projection feasible sets for a particular example and different carbohydrate content meals. For 40 g, any administration mode will lead to a good postprandial control according to the defined constraints. For 60 and 80 g, a square bolus is not feasible. For values greater than 100 g, *only* a temporal basal decrement bolus will lead to a good postprandial control. As the carbohydrate content of the meal increases, the projected feasible set shrinks, reducing the possible bolus administration modes. The vertical red line represents the standard bolus strategy, with basal equal to its baseline value.

that the coordinated basal–bolus action will allow an optimal 2 h postprandial glucose control, while avoiding hypoglycemia.

Figure 4 shows the two strategies used in this work for the case of temporal basal decrement bolus administration mode. This will be the case discussed in this article because of its innovative nature.

After the selection of the desired basal–bolus combination, the time of restoration of basal to baseline is selected from the third dimension in the 3D feasible set, which corresponds to an interval of feasible times of restoration. The mid-value is considered here.

Summarizing, after identification of the patient's model characterizing postprandial behavior up to 5 hours, the algorithm consists of the following steps:

1. Computation of the feasible set of prandial insulin infusions in the 3D space (bolus insulin at mealtime, basal rate at mealtime, time of basal restoration).
   A. If it is empty, relax constraints and go to 1.
   B. If it is not empty, go to 2.
2. Projection onto the two-dimensional space (bolus insulin, basal rate at mealtime).
3. Selection of the desired administration mode among the feasible ones in the two-dimensional projection.
4. Selection of a bolus insulin and basal rate at mealtime among the selected subset.
5. Selection of a feasible time of basal restoration, according to the selection in 4, from the three-dimensional feasible set.

Constraints relaxation is only applied to the hyperglycemia constraint. It is relaxed in steps of 20 mg/dl until a solution exists, up to a glucose value of 300 mg/dl. If this value is reached, it is concluded that the patient is impossible to control for that specific meal.

Patient's Model Identification

The algorithm requires obtaining an individual model for each of the patients, characterizing their postprandial glucose behavior. The UVa simulator uses the Cobelli model[31,32] as a mathematical description of T1DM patients. In order to force a mismatch between patient's model and the virtual patient behavior, the Hovorka model,[33,34] structurally different, is used as the patient's model. Its parameters are identified from 4-day virtual patient's data for a period of 5 h after a meal, following an optimal experiment design (OED).[35,36] The setup parameters considered in the OED are the ingested amount of carbohydrates, the bolus insulin dose, and the time instant of bolus insulin infusion. Constraints are added to avoid glucose concentrations below 70 mg/dl or above 300 mg/dl. The experiment can be carried out in ambulatory conditions.

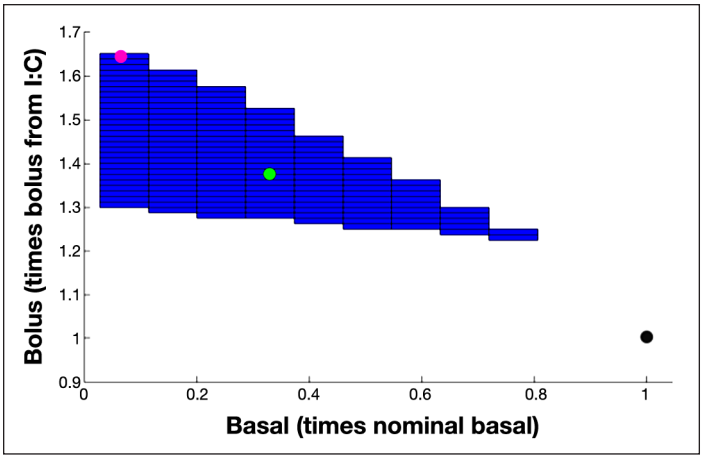

Figure 4. The two different basal–bolus combination approaches compared with the standard solution. The green point represents the centroid basal–bolus combination, whereas the pink point represents the maximal-bolus solution. The grey point represents the standard bolus strategy with basal equal to its baseline value and the bolus given by the I:C. In this particular example, standard therapy is out of the set of feasible solutions.

The use of a model that is structurally different than the model used in the UVa simulator is justified by the unavoidable discrepancies that always exist between the real behavior of a patient and the response of its model. Choosing a different model for identification than the one used in the simulator allows evaluating the robustness of the algorithm with respect to model and patient mismatch.

Algorithm Evaluation

Once an individual patient model is obtained for each of the 30 virtual patients available, the feasible sets are computed for meals in the range of 40–140 g of carbohydrates and initial normoglycemia. In this study,

temporal basal decrement is selected among the feasible bolus administration modes. Indeed, for some situations, it is the only feasible solution[26] (see **Figures 3** and **4**).

Efficiency of postprandial glucose control for both the centroid and the maximal-bolus solution from the temporal basal decrement feasible set is measured and compared with the standard bolus. A 7 h postprandial horizon is considered to evaluate the risk of late hypoglycemia and hyperglycemia. Different indicators are used for this comparison:

1. The area under the curve (AUC) of glucose concentration above 140 mg/dl and below 70 mg/dl is calculated using the trapezoidal rule[37] in the 0–2, 0–5, and 0–7 h postprandial periods for the whole 40–140 g range of carbohydrates.

2. The percentage of time spent in normoglycemia (70 mg/dl < glucose < 140 mg/dl), as well as the percentage of time spent in hypoglycemia (glucose <70 mg/dl) are also calculated.

3. The blood glucose standard deviation within the 0–5 and 0–7 h time intervals ($SD_{ws\ h}$)[38] is calculated as a measure of the glycemic variability associated with each prandial insulin administration strategy.

Total and bolus insulin dose are also reported to allow for correct interpretation of the aforementioned indicators. The AUC_{0-2h}, AUC_{0-5h}, and the AUC_{0-7h}, as well as the insulin dose, are normalized with respect to the respective values obtained using the standard bolus.

All data are subjected to repeated-measures analysis of variance with Huynh–Feldt adjustment for nonsphericity.[39] The analysis of variance model includes only the test condition (standard bolus, centroid, and maximal-bolus temporal basal decrement), as within-subjects factor, and *post hoc* comparisons (Tukey test) are carried out to pinpoint specific differences on significant interaction terms.

As a visual and qualitative indicator, the mean glucose response using the three different bolus strategies is plotted for the adults, adolescents, and children.

Results

Tables 2, **3**, and **4** show the mean AUC of the three groups of patients (adults, adolescents, and children, respectively) following meals with different carbohydrate content. A comparison among the percentages of time in normoglycemia and hypoglycemia for each of the solutions is also provided along with the amount of prandial bolus insulin and total insulin dose in the 7 h postprandial period. One virtual child (child number 8, weighing 23.73 kg) was eliminated from the study because the feasible set of prandial insulin infusions was empty for meals higher than 60 g, even relaxing constraints.

As a whole, results demonstrate the feasibility and effectiveness of the proposed algorithm-based insulin administration. It performed generally better than the traditional bolus in all of the considered time horizons. In particular, both centroid and maximal-bolus temporal basal decrement solutions were associated with significantly less hypoglycemic exposure in all groups of patients (**Tables 2**, **3**, and **4**). This was associated with a lower (or at least not different) overall exposure to undesired glycemic levels (both hyperglycemia and hypoglycemia), as indicated by the AUC values and the percentage of time spent in the normoglycemic range (the latter did not approach statistical significance only in children).

Total insulin dose was generally lower with the algorithm-based administration as compared with the standard therapy, and this was mainly attributable to a reduction in the basal insulin dose. In the adult population, total insulin dose was lower with the algorithm-based administration, but the difference was statistically significant only for the centroid solution (**Table 2**). Indeed, bolus increase with the maximal-bolus solution is compensated with reduction of basal insulin in the following hours. The increase in the bolus insulin dose was not seen in the adolescent and children populations in most of the tested meals. This fact may be explained by the high incidence of hypoglycemia in those groups as compared with the adult population.

Table 5 represents the glycemic variability during the 5 and 7 h postprandial period for the centroid, maximal-bolus, and standard solution, showing significant improvement with temporal basal decrement solutions in all the considered meals.

In **Figures 5**, **6**, and **7**, the mean glucose response of the adults, adolescents, and children is shown for different carbohydrate content meals.

Discussion and Conclusions

This study was carried out to test an algorithm based on set inversion (SIVIA) for prandial insulin administration. Results demonstrate the feasibility, efficacy, and robustness of this approach. To the best of our knowledge, this is the first study describing and evaluating a nonheuristic approach for the control of postprandial glucose excursions. Algorithm-based bolus insulin administration is associated with lower hypoglycemic risk and less glycemic variability, as compared with standard strategy, in both the 5 h and the 7 h postprandial horizons.

Table 2.
Mean Different Indicator Values for the 10 Adults in the University of Virginia Simulator.

		Adults							
		AUC 2 h	AUC 5 h	AUC 7 h	% of time Normo 7 h	% of time Hypo 5 h	% of time Hypo 7 h	Bolus	Total IU 7 h
40 g	Standard	1	1	1	92.28	0.83	6.34	1	1
	Centroid	0.57	0.53	0.15	97.91	0	0	0.88	0.88[a]
	Maximal-bolus	0.08	0.08	0.02	99.55	0	0	1.54[a,b]	0.92[a]
	p value	0.409	0.148	0.06	0.06	0.135	0.135	<0.001	<0.001
60 g	Standard	1	1	1	81.59	2.83	9.90	1	1
	Centroid	0.91	0.78	0.39	91.57[a]	0	0.71	1.01	0.89[a]
	Maximal-bolus	0.62[a]	0.53[a]	0.28[a]	93.99[a]	0	0.93	1.38[a,b]	0.93[b]
	p value	0.034	0.034	0.006	0.011	0.135	0.368	<0.001	0.007
80 g	Standard	1	1	1	71.30	3.53	11.80	1	1
	Centroid	1.02	0.98	0.60	82.94[a]	0	0.59	0.97	0.88[a]
	Maximal-bolus	0.73[a,b]	0.66[a,b]	0.41[a]	87.60[a,b]	0	1.07	1.26[a,b]	0.92[b]
	p value	0.002	0.002	<0.001	<0.001	0.135	0.204	0.001	0.007
100 g	Standard	1	1	1	61.04	3.87	14.56	1	1
	Centroid	0.96	0.91	0.63	76.41[a]	0	1.47[a]	0.99	0.87[a]
	Maximal-bolus	0.80[a,b]	0.73[a,b]	0.50[a]	80.00[a,b]	0.33	1.35[a]	1.17[a,b]	0.90
	p value	0.007	0.007	<0.001	<0.001	0.368	0.043	0.001	0.002
120 g	Standard	1	1	1	54.47	3.97	16.77	1	1
	Centroid	1.05	1.03	0.78[a]	63.59[a]	0	4.75[a]	0.94	0.85[a]
	Maximal-bolus	0.88	0.82	0.62[a]	69.24[a]	0	5.04[a]	1.10[a,b]	0.88
	p value	0.184	0.111	<0.001	0.002	0.135	0.005	0.039	0.002
140 g	Standard	1	1	1	49.24	4.13	17.53	1	1
	Centroid	1.09	1.09	0.86	54.89	0[a]	4.92[a]	0.92	0.83[a]
	Maximal-bolus	0.96	0.91	0.73[a]	60.97	0[a]	6.08[a]	1.02	0.85
	p value	0.249	0.180	0.004	0.056	0.05	<0.001	0.061	0.006

[a] $p < .05$ versus standard bolus
[b] $p < .05$ versus centroid

Results indicate that, when looking for tight postprandial glucose control, a parallel reduction in basal insulin dose is required to limit late postabsorptive hypoglycemia, especially for meals with higher carbohydrate content.

A strength of the proposed method is its robustness. The use of a model significantly different than the virtual patient for the identification of the patient's postprandial behavior shows the feasibility of the method in spite of imperfect glucose predictions due, for instance, to intrapatient variability. Robustness of the solution could be further increased, if needed, with explicit consideration of intrapatient variability (as interval quantities in model parameters) in the computation of the feasible solution

Table 3.
Mean Different Indicator Values for the 10 Adolescents in the University of Virginia Simulator

		Adolescents							
		AUC 2 h	AUC 5 h	AUC 7 h	% of time Normo 7 h	% of time Hypo 5 h	% of time Hypo 7 h	Bolus	Total IU 7 h
40 g	Standard	1	1	1	63.7	10.97	27.43	1	1
	Centroid	1.38	0.91	0.43[a]	87.17[a]	0	1.42[a]	0.89	0.82
	Maximal-bolus	1.25	0.83	0.47[a]	84.94[a]	2.10	5.84	1.18[b]	0.88
	p value	0.163	0.18	0.01	0.01	0.066	0.011	0.027	0.273
60 g	Standard	1	1	1	56.22	11.63	28.38	1	1
	Centroid	1.33	1.13	0.64[a]	74.06[a]	0[a]	5.11[a]	0.85	0.81[a]
	Maximal-bolus	1.14	0.93	0.59[a]	68.41[a]	2.50[a]	13.92[a]	1.07	0.86
	p value	0.106	0.054	<0.001	0.012	0.016	0.011	0.184	0.049
80 g	Standard	1	1	1	48.15	12.33	29.81	1	1
	Centroid	1.23	1.13	0.75[a]	58.50	0[a]	13.06[a]	0.85	0.80
	Maximal-bolus	1.13	1.03	0.72[a]	58.08	2.13[a]	16.82[a]	0.99[a,b]	0.84
	p value	0.138	0.205	<0.001	0.236	0.01	0.023	0.045	0.061
100 g	Standard	1	1	1	40.36	12.37	29.90	1	1
	Centroid	1.22	1.22	0.89	49.74[a]	1.30[a]	16.27[a]	0.81[a]	0.77
	Maximal-bolus	1.14	1.13	0.85[a]	49.22[a]	2.70[a]	19.24	0.92[b]	0.81
	p value	0.111	0.082	0.017	0.023	0.002	0.006	0.045	0.061
120 g	Standard	1	1	1	36.13	12.03	29.19	1	1
	Centroid	1.21	1.25	0.98	44.20[a]	1.40[a]	16.39[a]	0.78[a]	0.75
	Maximal-bolus	1.15	1.19	0.94	48.79[a]	1.97[a]	15.11[a]	0.87[b]	0.78
	p value	0.096	0.061	0.067	0.002	0.004	0.023	0.045	0.273
140 g	Standard	1	1	1	49.24	4.13	17.53	1	1
	Centroid	1.09	1.09	0.86	54.89	0[a]	4.92[a]	0.92	0.83[a]
	Maximal-bolus	0.96	0.91	0.73[a]	60.97	0[a]	6.08[a]	1.02	0.85
	p value	0.249	0.180	0.004	0.056	0.05	<0.001	0.061	0.006

[a] $p < .05$ versus standard bolus
[b] $p < .05$ versus centroid

set with SIVIA (that would yield smaller feasible sets and thus more constrained solutions). This is a unique feature of the presented algorithm. Another one is the possibility of determining, in a nonheuristic way, the feasible insulin administration modes for a given meal, which could be included in smarter insulin pumps in the future.

The main limitation of this study is that its results may not apply to the real diabetes patient population in daily life. Adult virtual patients are built on data from real patients' response to a specific (and nonphysiologic) mixed meal,[40] not necessarily representative of the postprandial response to a meal of different composition. Extrapolation of results from virtual adolescents and children to the real population should be done even more cautiously. Indeed, to the best of our knowledge, no published data are available on traced mixed meal postprandial response of nonadult people with diabetes. Data published so far for young people have been

Table 4.
Mean Different Indicator Values for Nine Children Analyzed from Those Available in the University of Virginia Simulator

		Children							
		AUC 2 h	AUC 5 h	AUC 7 h	% of time Normo 7 h	% of time Hypo 5 h	% of time Hypo 7 h	Bolus	Total IU 7 h
40 g	Standard	1	1	1	66.77	10.26	22.75	1	1
	Centroid	1.64	1.95	1.33	69.52	0.00[a]	0.00[a]	1.33	0.78[a]
	Maximal-bolus	1.41	1.46	1.04	71.47	0.00[a]	0.00[a]	1.04	0.80[a]
	p value	0.278	0.129	0.642	0.923	0.041	0.003	0.06	<0.001
60 g	Standard	1	1	1	61.12	11.96	24.49	1	1
	Centroid	1.36	1.27	0.87	73.24	0.00[a]	3.93[a]	0.87	0.78[a]
	Maximal-bolus	1.29	1.27	0.90	72.34	0.00[a]	4.70[a]	0.90	0.80[a]
	p value	0.278	0.129	0.642	0.251	0.007	0.006	0.092	<0.001
80 g	Standard	1	1	1	51.31	14.04	30.48	1	1
	Centroid	1.34[a]	1.36	1.00	61.52	0.04[a]	6.91[a]	1.00	0.77[a]
	Maximal-bolus	1.27	1.27	0.95	64.71	0.30[a]	7.31[a]	0.95[b]	0.78[a]
	p value	0.031	0.154	0.187	0.164	0.002	<0.001	0.019	<0.001
100 g	Standard	1	1	1	46.95	11.74	30.40	1	1
	Centroid	1.33[a,c]	1.41[a,c]	1.08	54.50	0.67[a]	7.47[a]	1.08[a]	0.75[a]
	Maximal-bolus	1.27	1.33	1.04	56.85	0.85[a]	7.86[a]	1.04[b]	0.77[a]
	p value	<0.001	<0.001	0.328	0.278	0.048	0.001	0.004	<0.001
120 g	Standard	1	1	1	40.83	10.74	30.19	1	1
	Centroid	1.29[a]	1.41[a]	1.13	47.43	0.37[a]	7.44[a]	1.13[a]	0.74[a]
	Maximal-bolus	1.26	1.37	1.11	48.19	0.44[a]	7.73[a]	1.11[b]	0.76[a]
	p value	0.006	<0.001	0.209	0.406	0.031	0.001	0.019	<0.001

[a] $p < .05$ versus standard bolus
[b] $p < .05$ versus centroid
[c] $p < .05$ versus maximal-bolus

obtained from oral glucose tolerance test studies,[41] but results are certainly not equivalent to a mixed meal.

Another limitation of the study is that choosing one point from the algorithm-generated feasible set of basal–bolus combinations is still an empiric process. However, data from ongoing clinical studies conducted by our research team may help to develop the most appropriate strategies for basal–bolus selection, leading to optimized algorithms for its implementation in future smart insulin pumps.

Finally, identification of the patient model will definitely require specific protocols to be followed by the patient

Table 5.
Glycemic Variability over the Course of Five and Seven Hours

		Adults		Adolescents		Children	
		Standard deviation 5 h	Standard deviation 7 h	Standard deviation 5 h	Standard deviation 7 h	Standard deviation 5 h	Standard deviation 7 h
40 g	Standard	13.48	15.91	24.90	28.20	27.19	27.99
	Centroid	9.30[a]	9.72[a]	17.80[a]	20.13[a]	18.69[a]	19.53[a]
	Maximal-bolus	11.59	11.12[a]	20.69[a]	21.71	19.17[a]	19.95[a]
	p value	0.009	<0.001	0.002	<0.001	<0.001	<0.001
60 g	Standard	19.77	23.18	33.89	39.63	29.35	40.05
	Centroid	14.68[a]	15.81[a]	27.53[a]	31.71[a]	28.74	30.22[a]
	Maximal-bolus	16.92	16.93[b]	29.15[a]	32.03[a]	29.35	30.22[a]
	p value	0.002	<0.001	<0.001	<0.001	0.154	<0.001
80 g	Standard	25.79	29.85	42.00	49.86	48.05	51.55
	Centroid	20.22[a]	22.07[a]	36.47[a]	42.51[a]	39.63[a]	41.88[a]
	Maximal-bolus	21.96[a]	22.37[a]	37.14[a]	42.13[a]	39.42[a]	40.96[a]
	p value	0.002	<0.001	0.006	<0.001	<0.001	<0.001
100 g	Standard	31.67	35.96	50.23	59.78	57.05	61.99
	Centroid	25.84[a]	27.82[a]	45.03[a]	52.99[a]	50.57[a]	54.45[a]
	Maximal-bolus	27.00[a]	27.70[a]	45.16[a]	52.30[a]	50.11[a]	53.09[a]
	p value	0.001	<0.001	0.006	<0.001	0.01	0.005
120 g	Standard	37.36	42.02	57.87	68.97	65.83	71.72
	Centroid	31.00[a]	33.95[a]	53.35[a]	63.37[a]	60.27	65.20
	Maximal-bolus	31.78[a]	33.32[a]	52.57[a]	61.91[a]	60.04	64.18
	p value	<0.001	<0.001	<0.001	<0.001	0.067	0.328
140 g	Standard	42.37	47.66				
	Centroid	35.82[a]	39.33[a]				
	Maximal-bolus	36.30[a]	38.72[a]				
	p value	<0.001	<0.001				

[a] $p < .05$ versus standard bolus
[b] $p < .05$ versus centroid

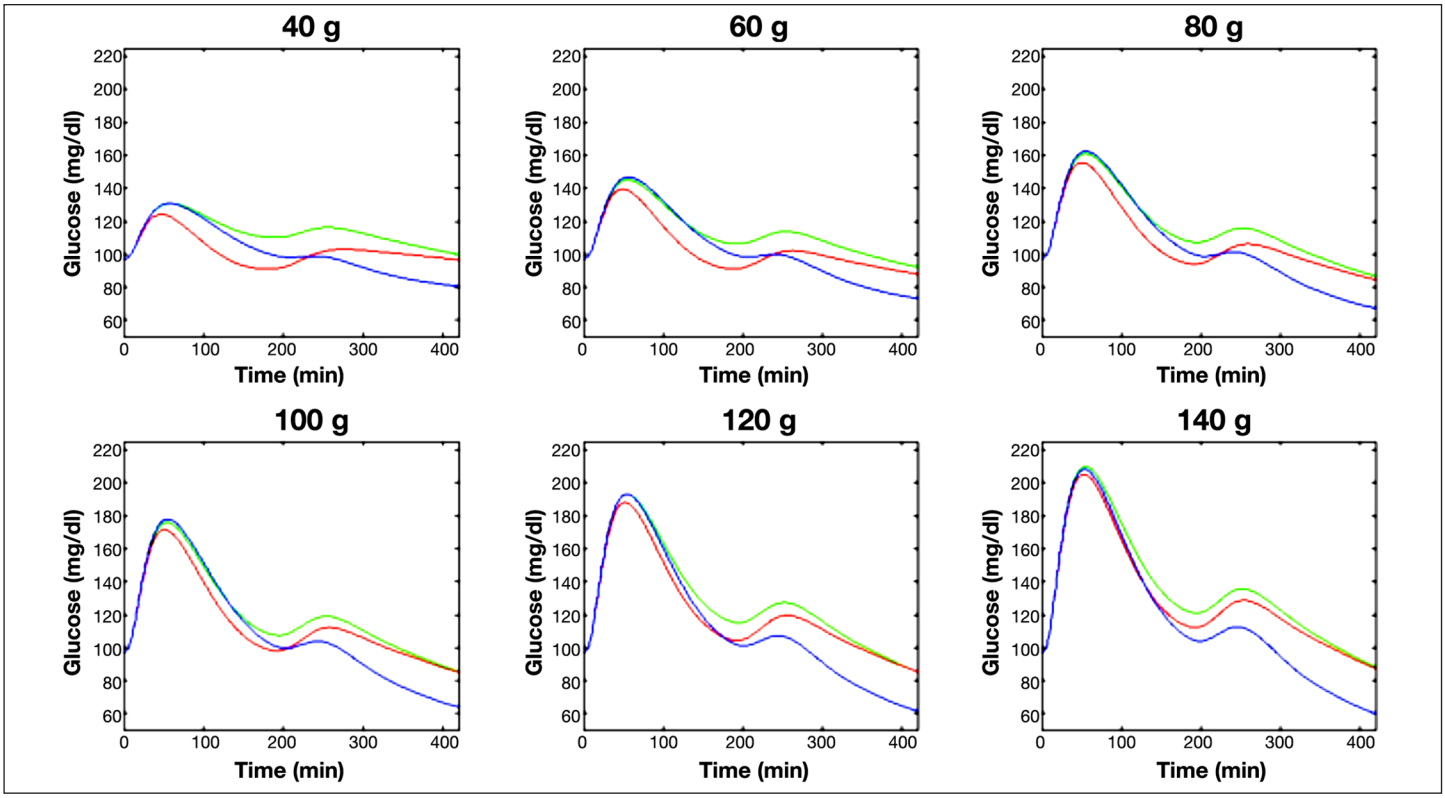

Figure 5. Mean glucose response of the 10 adults in the UVa simulator. The blue line represents the response applying the standard bolus, whereas the green and the red line correspond to the centroid and maximal-bolus solution, respectively. These latter solutions produce a flatter profile than the one observed with the standard bolus, avoiding late hypoglycemia. In addition, the peak in the glucose profile remains similar or even lower.

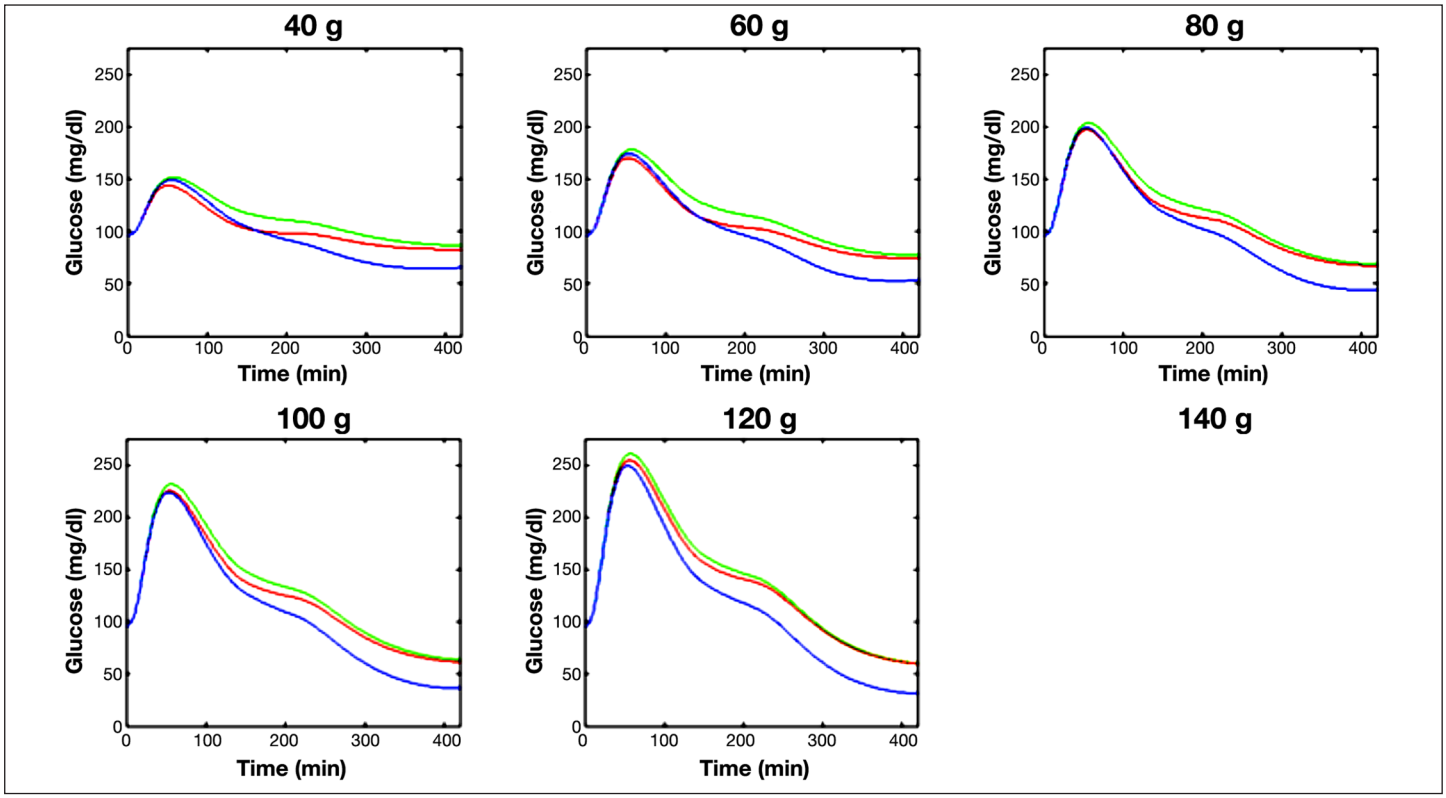

Figure 6. Mean glucose response of the 10 adolescents in the UVa simulator. The blue line represents the response applying the standard bolus, whereas the green and the red line correspond to the centroid and maximal-bolus solution, respectively. These latter solutions produce a flatter glucose profile than the one observed with the standard bolus, avoiding late hypoglycemia. The peak in the glucose profile using any of the solutions is similar.

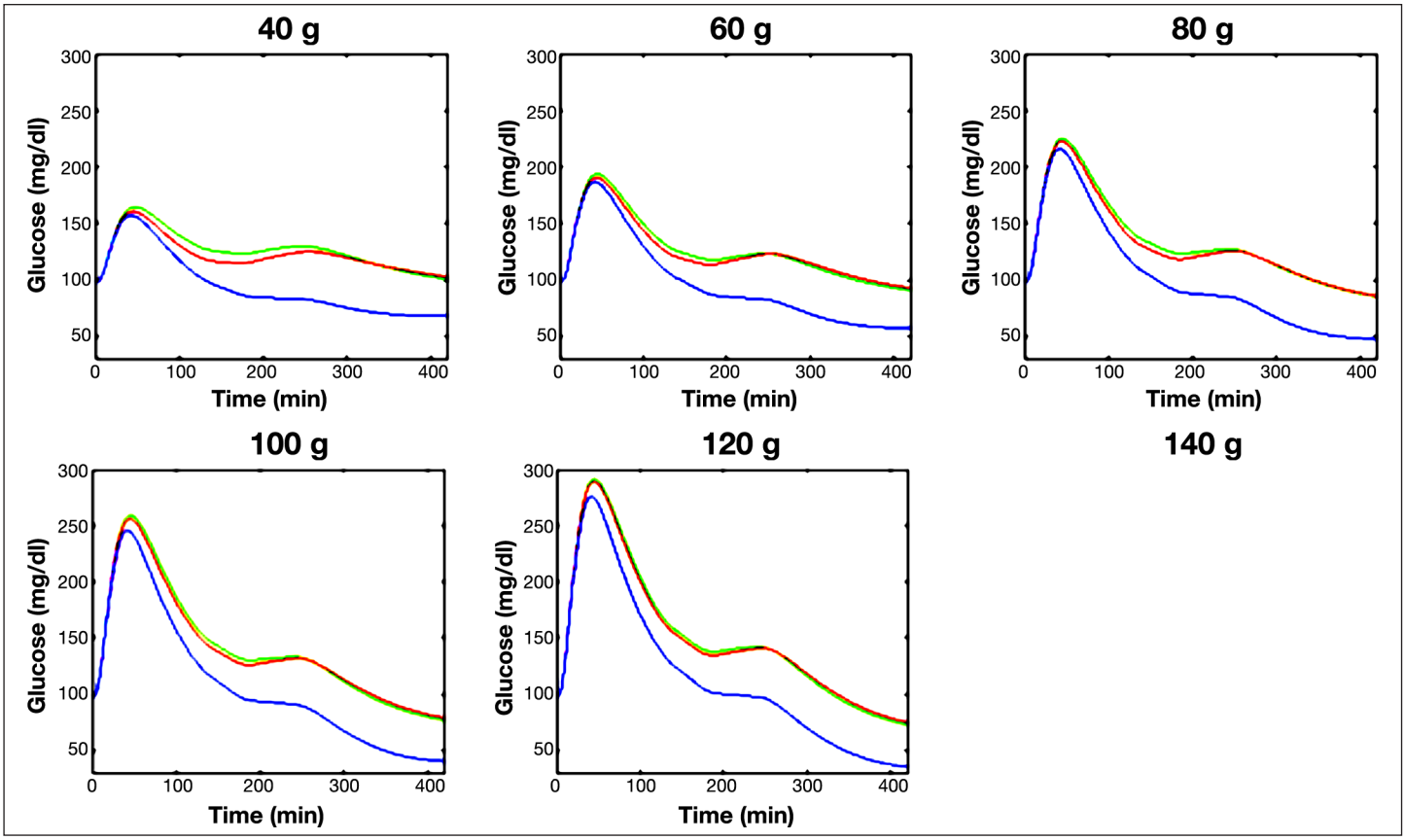

Figure 7. Mean glucose response of nine children analyzed from those available in the UVa simulator. The blue line represents the response applying the standard bolus, whereas the green and the red line correspond to the centroid and maximal-bolus solution, respectively. These latter solutions, although producing a slightly higher peak in the glucose profile than the standard bolus, achieve a flatter glucose profile, avoiding the severe late hypoglycemia.

during several days to avoid nonidentifiability issues. This can be inconvenient for the patient. This problem also arises in the context of closed-loop glucose control.

In conclusion, despite its limitations, this is a proof-of-concept study that may prelude the development of new robust nonempiric (CGM-based) tools, aiding patients and physicians to attain a better metabolic control.

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