Journal of Diabetes Science and Technology
Volume 6, Issue 6, November 2012
© Diabetes Technology Society

ORIGINAL ARTICLE

Improving the Computational Effort of Set-Inversion-Based Prandial Insulin Delivery for Its Integration in Insulin Pumps

Fabian León-Vargas, M.Sc.,[1] Remei Calm, Ph.D.,[1] Jorge Bondia, Ph.D.,[2] and Josep Vehí, Ph.D.[1]

Abstract

Objective:

Set-inversion-based prandial insulin delivery is a new model-based bolus advisor for postprandial glucose control in type 1 diabetes mellitus (T1DM). It automatically coordinates the values of basal–bolus insulin to be infused during the postprandial period so as to achieve some predefined control objectives. However, the method requires an excessive computation time to compute the solution set of feasible insulin profiles, which impedes its integration into an insulin pump. In this work, a new algorithm is presented, which reduces computation time significantly and enables the integration of this new bolus advisor into current processing features of smart insulin pumps.

Methods:

A new strategy was implemented that focused on finding the combined basal–bolus solution of interest rather than an extensive search of the feasible set of solutions. Analysis of interval simulations, inclusion of physiological assumptions, and search domain contractions were used. Data from six real patients with T1DM were used to compare the performance between the optimized and the conventional computations.

Results:

In all cases, the optimized version yielded the basal–bolus combination recommended by the conventional method and in only 0.032% of the computation time. Simulations show that the mean number of iterations for the optimized computation requires approximately 3.59 s at 20 MHz processing power, in line with current features of smart pumps.

Conclusions:

A computationally efficient method for basal–bolus coordination in postprandial glucose control has been presented and tested. The results indicate that an embedded algorithm within smart insulin pumps is now feasible. Nonetheless, we acknowledge that a clinical trial will be needed in order to justify this claim.

J Diabetes Sci Technol 2012;6(6):1420-1428

Author Affiliations: [1]Institute of Informatics and Applications, University of Girona, Girona, Spain; and [2]Institut Universitari d'Automàtica i Informàtica Industrial, Universitat Politècnica de València, Valencia, Spain

Abbreviations: (PPBD) postprandial basal duration, (SIB) set inversion based, (T1DM) type 1 diabetes mellitus

Keywords: bolus advisor, embedded algorithm, optimized computation, smart insulin pump

Corresponding Author: Fabian León-Vargas, M.Sc., Campus de Montilivi, Edifici P-IV, Girona, Spain; email address *fabianmauricio.leon@udg.edu*

Introduction

Intensive insulin therapy is composed of basal insulin, which controls blood glucose overnight and between meals, and bolus insulin to correct high glucose concentrations after meals or snacks.[1] Because of their ability to generate different insulin infusion profiles, insulin pumps improve glycemic control compared with multiple daily injections.[2,3] Standard, extended, and combination boluses are currently embedded into commercial insulin pumps as part of automatic bolus calculators or bolus advisors that deal with different meal compositions or other circumstances such as stress, exercise, and foods that vary in glycemic index or in fat and protein content.[4,5] However, their use is still heuristic based on the experience of both physicians and patients and does not offer complete solutions to the main concerns of type 1 diabetes mellitus (T1DM) patients, only partially meeting the International Diabetes Federation guidelines. Major problems in postprandial control today refer to insulin dynamics: too slow to start and lasts too long for most meals. This undesired imbalance, usually present in poorly controlled T1DM patients, leads to short-term hyperglycemia and late-term hypoglycemia episodes.[6]

Some strategies based on continuous glucose monitoring, as proposed by Wang and coauthors,[7] vary the basal insulin delivery depending on the glucos e trend and some heuristic assumptions. As an alternative prandial insulin delivery method, a set-inversion-based (SIB) algorithm based on mathematically guaranteed techniques (interval analysis) was presented previously.[8,9] The algorithm calculates the optimal prandial basal–bolus combination from a pre-prandial glucose measurement and a patient's prediction model that may account for intrapatient variability. The SIB algorithm revealed the need for a temporal basal decrement at mealtime combined with an equivalent increase in the meal bolus (a generalization of the super-bolus concept introduced by Walsh and Roberts[6]) for good postprandial performance when the carbohydrate content was high, such as in meals that contain grams of carbohydrate equal to or greater than the person's weight (kg). The SIB concept also allows for a decrease in a meal bolus combined with an equivalent increase in basal delivery. These approaches can improve glycemic outcomes with less computational effort by the wearer for higher carbohydrate intakes, low or high glycemic meals, or brunches. Compared with traditional bolus administration mode, one of the major advantages of this new approach is that it allows the patient be more aggressive and flexible with prandial insulin doses without increasing the risk for late-term hypoglycemia.

However, a critical drawback of the SIB algorithm is that it has to compute the complete space (paving) of possible solutions in the basal–bolus space.[9,10] This procedure is highly time consuming and infeasible in practice.

The aim of this work is to optimize the computation time of this SIB algorithm by developing a strategy to compute one single solution of interest in the basal–bolus space. A methodology based on the analysis of interval simulations, physiological assumptions, and search domain contraction was developed to enable integration of this bolus advisor into smart insulin pumps.

Set-Inversion-Based Prandial Insulin Delivery

Set-inversion-based prandial insulin delivery is a control strategy designed to meet a set of constraints through a recursive search among combinations of three components, namely, the bolus dose, the postprandial basal dose, and the time for basal-to-baseline restoration [the postprandial basal duration (PPBD)].[9]

Its functionality is as follows. Given an interval vector (or box) of inputs X, comprising the elements of bolus dose, basal dose, and PPBD, the SIB algorithm determines whether (1) the full range of therapies contained in X meet the constraints, (2) none of them meet the constraints, or (3) some of them meet the constraints. For the third case, the corresponding input box is partitioned, and the resulting boxes are reevaluated in an iterative way by the algorithm until getting a box that meets the constraints.[9]

At each step in the algorithm, a glucose–insulin model is used to predict the postprandial glycemia corresponding to the therapies contained in X, using interval simulation techniques.[11] Revert and coauthors[9] use modal interval analysis for this purpose. After comparing the predicted postprandial glycemia with the constraint set, a three-dimensional plot of boxes meeting these constraints is obtained (see **Figure 1A**). A two-dimensional basal–bolus projection (see **Figure 1B**) is then useful for showing basal–bolus combinations that will lead to a good performance for a particular patient and meal.

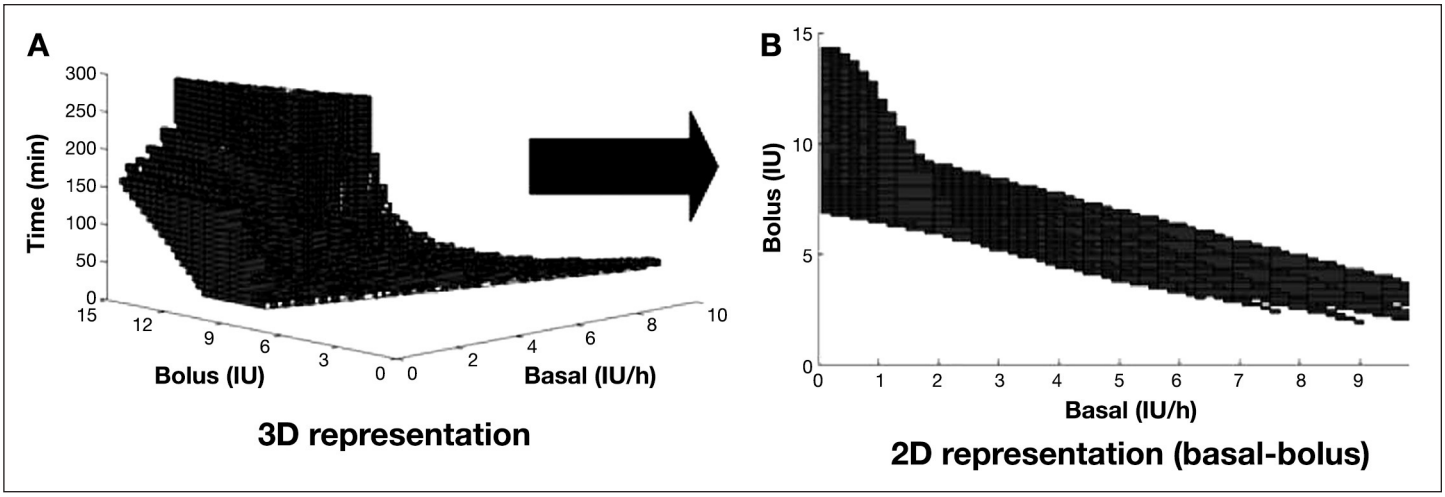

Figure 1. Plot representing a **(A)** three-dimensional (basal dose, bolus dose, and PPBD) feasible set with **(B)** its corresponding basal–bolus two-dimensional projection. Reprinted with permission from *Journal of Diabetes Science and Technology*.[10]

It should be noted that, even when meeting all constraints, the postprandial behavior associated with each possible basal–bolus combination inside the paving of solutions is different. This is the reason for using *in silico* testing:[10] to find the most appropriate basal–bolus combination from among all those possible to obtain the best postprandial performance.

Methods

According to the results of Revert and coauthors,[10] the basal–bolus combination of interest within the paving of solutions corresponds to the box containing the maximum value for bolus dose, and this was established as the optimization aim in this work.

The input domain corresponds to the standard capabilities found in commercial insulin pumps: 0–40 IU for the bolus dose; 0–10 IU/h for the basal dose; and 0–300 min for the PPBD.

The basal–bolus plane of the input domain was partitioned into a grid of fixed granularity (see **Figure 2**). The optimization method uses a box with basal–bolus components of a predefined size. This size corresponds to the minimum width used in the conventional version of the SIB strategy and covers the range of inaccuracy present in insulin pumps.[12]

The PPBD component was treated as a single-value (real value) throughout the optimization process, and only at the last stage, an upper and lower limit was computed to produce an interval output.

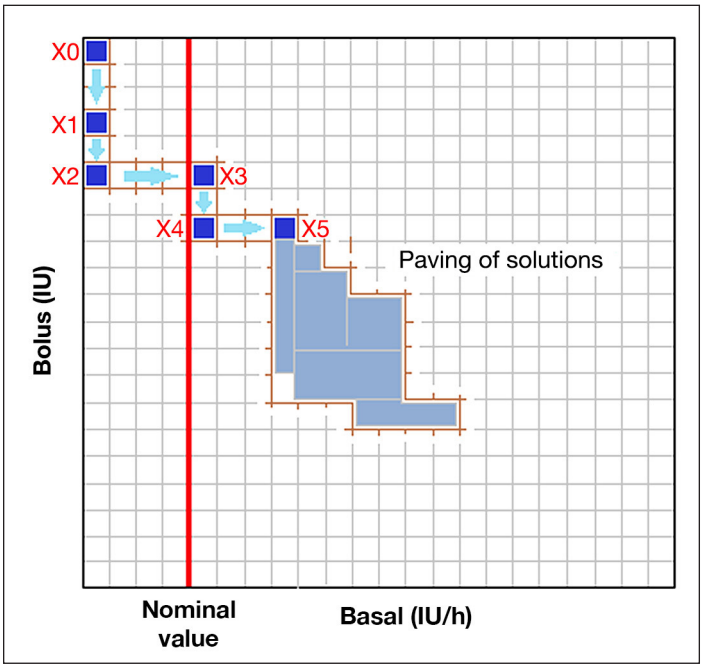

Figure 2. Typical search path used by the optimization algorithm. If the constraints are met by a basal value less than the nominal value, the solution may be found in checkpoints "X1" or "X2"; otherwise, it will be in "X4," "X5," or beyond.

In essence, the optimization algorithm focuses on moving the box across the grid following a pathway to reach the target solution in few steps.

The set of constraints used here correspond to those used by Revert and coauthors: a 2 h postprandial glucose value below 140 mg/dl in a 5 h time horizon and a maximum glucose slope of 10 mg/dl/h starting 4 h after the meal in order to avoid the late-term hyperglycemia;

and a hypoglycemic threshold of 70 mg/dl and a 5 h postprandial glucose value above 90 mg/dl in order to avoid hypoglycemia.

The dynamic relationship between glucose and insulin was included implicitly through a simple physiological assumption: the more insulin delivered, the more that blood glucose is lowered in the patient. Such physiological knowledge is useful for ruling out search areas according to the optimization aim.

Interval simulations,[11] characterized by reflecting the collection of postprandial glucose profiles predicted by the patient model for a set of therapies and/or model uncertainty, were used. The glucose–insulin model used in this optimized SIB strategy was the same as that used in the conventional version. Model identification and validation was carried out from 6-day domiciliary data using a continuous glucose monitor. For 3 days, the patient advanced or delayed bolus infusion with respect to mealtime at lunch, according to an optimal experiment design to maximize sensitivity of identified parameters. Three additional days following the standard treatment were used for model validation. A detailed description about the model and its identification was presented by Laguna and coauthors.[13]

Algorithm Rationale

The optimization task was divided into two main stages: first finding the box containing the maximum bolus value that meets the hypoglycemia and hyperglycemia constraints (including the 5 h glucose above 90 mg/dl) and then verifying the slope constraints.

We describe the optimization procedure using a graphical example as follows. A typical search path in the basal–bolus plane is shown in **Figure 2**. In this figure, the blue squares represent "checkpoint" input boxes at algorithm steps where a certain condition is reached.

Because we are seeking a solution with a maximum bolus value, the starting point (initial box) "X0" always corresponded to the maximum bolus dose possible and the minimum basal dose according to insulin pump capabilities. At this point, the hypoglycemia condition was always obtained because of the extreme bolus value (see **Figure 3**).

To achieve a nonhypoglycemia condition, i.e., to reach checkpoint box "X1," a bolus decrement is required. In this procedure, the basal component was fixed at the minimum (0 IU/h) and the PPBD component to the maximum (300 min) (i.e., the minimum basal infusion, because the nominal basal dose > 0 IU/h) to perform a domain-space contraction in the bolus component (see **Figure 2**) until the hypoglycemia constraint was met.

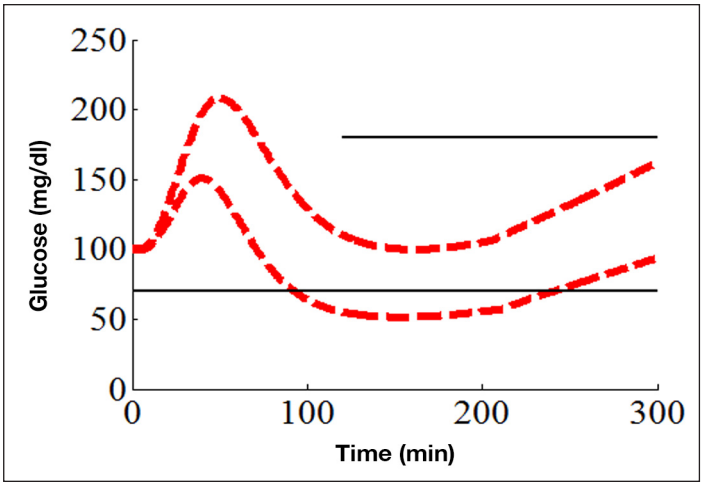

Figure 3. Typical glucose response when using the maximum bolus limit. The hypoglycemia constraint is always violated at the initial box "X0."

After reaching "X1," the hyperglycemia constraint is checked. If it is met, the algorithm verified that the slope constraints are met. If not, a change in PPBD can be conducted.

When the box is below the nominal basal dose, a longer PPBD implies a smaller basal infusion. Conversely, when the box is above the nominal basal dose, a longer PPBD implies a larger basal infusion. **Figure 4** shows this behavior.

Two parameters, tHyper and tHypo, were used to discover if a PPBD variation could help meet the hyperglycemia constraint. When the box is below the nominal basal tHyper corresponds to the maximum time at which the hyperglycemia condition is no longer true, and tHypo corresponds to the minimum time at which the hypoglycemia condition is no longer true (see **Figure 4**, case A). In case the box is above the nominal basal, tHyper corresponds to the minimum time at which the hyperglycemia condition is no longer true and tHypo corresponds to the maximum time at which the hypoglycemia condition is no longer true (see **Figure 4**, case B). Hence hypoglycemia and hyperglycemia constraints will be met simultaneously if

(1) tHyper ≥ PPBD ≥ tHypo for below nominal basal boxes or

(2) tHyper ≤ PPBD ≤ tHypo for above nominal-basal boxes.

Therefore, if condition (1) is not valid for the box "X1," it is still possible to modify the bolus value to affect the dynamics of tHyper and tHypo.

The next checkpoint box, "X2," is the bolus value when tHyper or tHypo is zero. If tHyper is zero for "X2," (1) is not fulfilled and a basal/bolus dose is not found. On the other hand, if tHypo is zero for "X2," (1) is fulfilled, and therefore it is a solution. Typical dynamics for tHyper and tHypo in reaching "X2" are shown graphically in **Figure 5**. Such dynamics are quite different. The trends can be explained based on the bolus reduction effect, whose action is mainly reflected on the hypoglycemia rather than the hyperglycemia condition. This behavior can also be treated as a "slopes" problem. When a bolus reduction occurs, tHypo starts with a slope "*s*0" and tHyper with a slope "*s*1." Both trends finalize with the same slope "*sf*" when reaching "X2" (see **Figure 5**). Therefore, (1) will or will not be fulfilled for "X2" according to the distance between tHyper and tHypo for box "X1."

It is worth mentioning that basal value may be increased according to the patient needs, but there is a limit on how far the basal dose may be decreased in order to increase the bolus dose sufficiently to cover large carbohydrate meals. Up to this checkpoint, the most likely situation where no solution would be found will be for large carbohydrate intakes and foods with high glycemic index.

If, when reaching "X2," (1) is not fulfilled, a further decrement in the bolus value will not be useful unless a new checkpoint with a different basal value is considered.

As (1) is not fulfilled for "X2," no value below the nominal basal will be part of the solution. Indirectly, all basal insulin values between the minimum and the nominal have been applied through the previous PPBD variation. Therefore, the next checkpoint box "X3" corresponds to the same bolus, but using the nominal basal value. Here, PPBD is again set at 300 min.

However, a value equal to the nominal basal implies a new and lower bolus value to meet the hypoglycemia constraint. This procedure corresponds to checkpoint box "X4."

In later checkpoints (e.g., "X4" and "X5"), iterative changes in bolus insulin to meet the hypoglycemia constraint followed by changes in basal insulin to meet the hyperglycemia constraint are performed until both constraints are met simultaneously. In this process, some changes in PPBD will be performed.

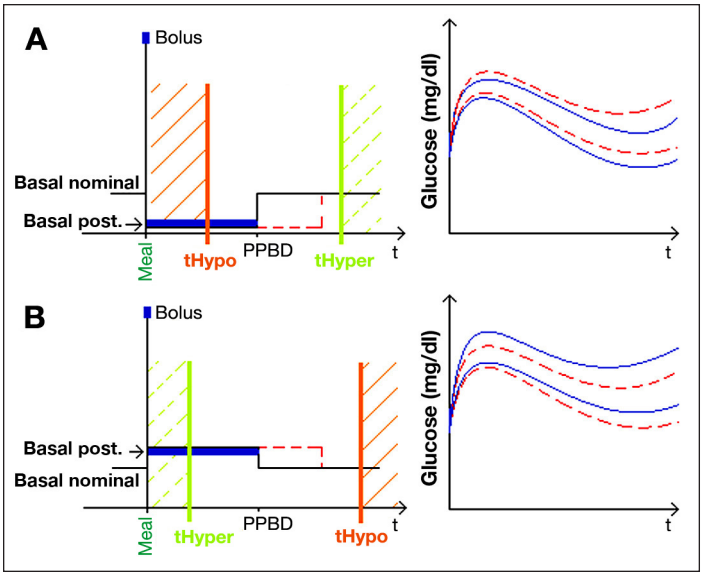

Figure 4. Insulin profiles (left) and their corresponding glucose responses (right) for two cases. **(A)** When a box is below the nominal basal, a shorter PPBD value produces a lower glucose response (blue solid curve) than a longer PPBD value (red dashed curve). **(B)** When a box is above the nominal basal, those PPBD values imply the opposite action. The dashed green lines area and the solid orange lines area indicates the values of PPBD at which hyperglycemia or hypoglycemia conditions are obtained, respectively.

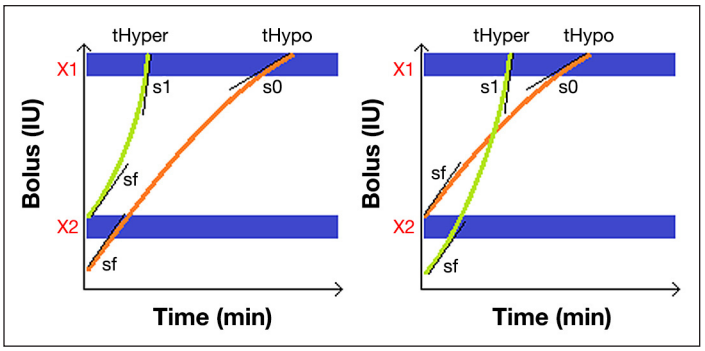

Figure 5. tHyper and tHypo dynamics observed in a bolus–PPBD plane. For some cases, no bolus reduction will achieve tHyper ≥ tHypo **(left)**; for other cases, it can be achieved **(right)**.

After the hypoglycemia and hyperglycemia constraints are met, PPBD should be changed to meet the slope constraints depending on the current basal value and on which slope was violated (upper or lower).

If this action is insufficient, with the slope violated being the lower slope, the algorithm will finish with no solution and a new process will need to be started using constraints more relaxed. However, if the upper slope is violated, a final option for improving the insulin action is to reduce the bolus component in an iterative way while the basal component is maximized.

The flowchart of the optimized version of the SIB strategy is summarized in **Figure 6**.

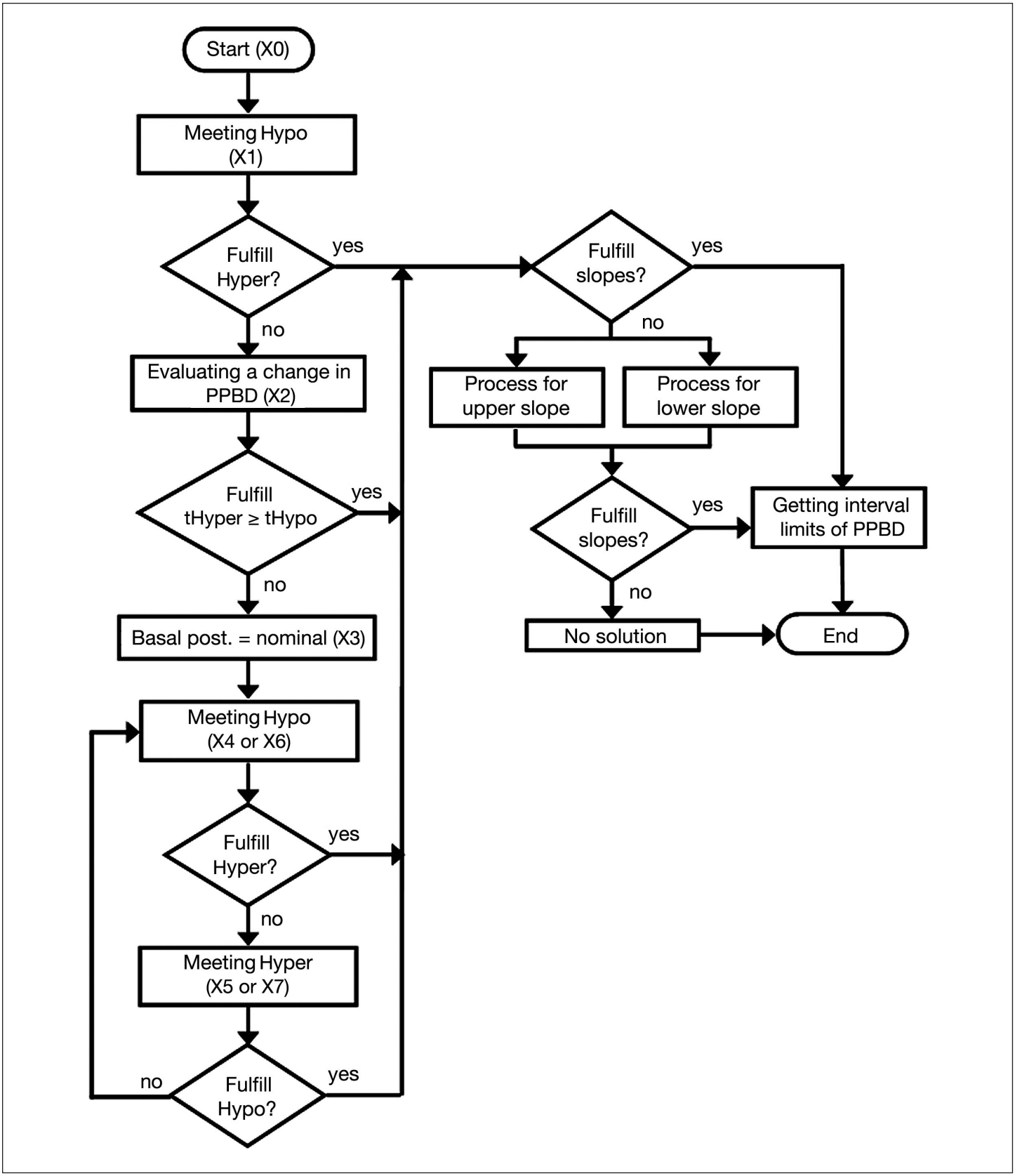

Figure 6. Flowchart of the optimized version of the SIB strategy. Hypo, hypoglycemia constraint; Hyper, hyperglycemia constraint; PPBD, postprandial basal duration.

Results

To compare the optimization performance, responses of a conventional processing method obtained for six real patients with T1DM was used. The optimized version reused the patient model of the conventional version. Continuous glucose monitoring data were used to obtain the respective patient model. Demographic characteristics of the subjects were as follows: six subjects (three males), age 41.8 ± 7.3 years, diabetes duration 20 ± 10 years, hemoglobin A1c 8.0% ± 0.6%, and body weight 68.7 ± 10 kg.

The comparison was carried out on a workstation Dell Precision T3500, Intel® Xeon Processor of 2.67 GHz and RAM memory of 4096 MB.

Results are presented in **Table 1**. As comparison metrics, the number of iterations and the total computation time was used (see **Table 1**). Iteration counting was based on how many interval simulations were performed during the corresponding algorithm steps.

Regarding the final solutions given by each algorithm, once the solution box is found, the insulin to be infused corresponds to the middle point of each component range (center of the box). The results show that the recommended basal/bolus doses found with this faster SIB method showed only minor differences from those of the conventional SIB strategy, as can be seen in **Table 2**.

LabVIEW software was used to estimate the computation time of the optimized SIB strategy when it is running at a very low processing rate. The results show that the mean of iterations for the optimized strategy requires approximately 3.59 s at 20 MHz processing. According to the Medical Solutions Guide,[14] a similar processing power is used in current smart insulin pumps.

Discussion

Parameter values of the patient model were set using data obtained from an ongoing clinical study about the performance of the SIB strategy in real patients. An optimization algorithm was implemented to compare its solutions with those of the standard SIB strategy. We found that the optimization algorithm obtains similar solutions to the conventional strategy, but in 0.032% of the time. However, it must be said that the baseline for the comparison time was the complete space of solutions of the conventional strategy. The new algorithm does not require the computation of such a global grid; therefore, a much lower computation time was expected.

Table 1.
Performance Comparison between the Standard and Optimized Set-Inversion-Based Strategy[a]

Patient	Iterations for standard strategy	Time (s) standard strategy	Iterations for optimized strategy	Time (s) optimized strategy
01- 1	277675	3098.38	30	0.406
01- 2	364653	4127.28	25	0.328
01- 3	333043	3266.38	34	0.468
01- 4	55735	540.04	67	0.889
02- 1	155781	1556.45	123	1.623
02- 2	277279	2833.72	69	0.936
02- 3	112321	1150.76	93	1.154
02- 4	587443	5946.55	168	2.153
03- 1	151707	1486.5	25	0.343
03- 2	711113	7133.46	24	0.328
04- 1	119139	1187.17	34	0.452
04- 2	274975	2735.84	33	0.452
04- 3	125455	1242.06	37	0.514
04- 4	240843	2384.65	62	0.842
05- 1	58335	601.87	46	0.593
05- 2	72971	745.05	96	1.217
05- 3	36977	379.51	44	0.577
05- 4	32263	368.36	75	0.967
06- 1	332203	3330.83	88	1.124
06- 2	992627	9929.81	90	1.154
06- 3	38929	384.01	90	1.108
06- 4	81337	831.82	73	0.952
Mean	246945.6	2617.7	64.8	0.844

[a] For each patient, several tests were conducted using different meal sizes.

Table 2.
Statistical Comparison of the Difference between Solutions Obtained from Optimized Strategy and the Conventional Set-Inversion-Based Strategy

Error	Basal comparison	Bolus comparison	PPBD comparison
Mean absolute error ± standard deviation	0.05 ± 0.06 IU/h	0.17 ± 0.14 IU	12.3 ± 8.8 min
90th percentile	0.12 IU/h	0.43 IU	20.56 min
Median	0.028 IU/h	0.13 IU	8.87 min

In order to put method into context, the accuracy and efficiency of the optimized version was compared against a Monte Carlo approach. A standard Monte Carlo test was developed with 1% and 5% of all possible combinations of basal, bolus, and PPBD at random. The best solution in each test was selected to calculate the mean absolute

error with respect to the solution obtained using conventional SIB strategy (see **Table 3**). An important difference in accuracy was obtained compared with the one achieved by the optimized version (see **Table 2**). Moreover, as the total number of boxes is 320,000, 1% and 5% of Monte Carlo correspond to 3200 and 16,000 simulations, respectively. This means 50 and 250 times the number of simulations required by the optimized version of SIB strategy.

The inclusion of physiological knowledge in the optimization algorithm enables development of efficient search strategies to replace methods based on extensive search algorithms, where each possible combination is tested, whatever its physiological effects.

We acknowledge that this computing optimization is an *ad hoc* approach designed for our insulin therapy. It must be pointed out that embedding this algorithm into an insulin pump may require modifications of the bolus-on-board computation as currently done. Although a temporal basal decrement at mealtime does not contribute to bolus on board, basal increments above baseline may be considered as combo boluses. In this case, the basal excess should compute as bolus on board.

It is worth noting that temporal basal decrements are related to super boluses as introduced by Walsh and Roberts[6]. However, in our case, no constraints on total insulin administered exist. The algorithm automatically computes the required bolus dose and basal decrement (and for how long) to fulfill constraints on postprandial glucose based on the amount of carbohydrate intake and the prediction of the patient's behavior (considering intrapatient variability). Thus the algorithm may present an increment of total insulin dose if a patient changes his eating. Carbohydrate counting is used as input to the model, but not for a direct computation of the bolus size. An additional advantage of the method is that carbohydrate estimation error, as commonly done by the patients, can be naturally considered by the method as intervals in the meal intake.

As a limitation, the method relies on a mathematical model including meal absorption. Current models of carbohydrate digestion and absorption are limited due to the clinical data used for its development and may be representative of only a particular type of meal. Although variability in glucose absorption can be included in our methodology, more research is needed for the characterization of absorption profiles for different groups of meals.

Table 3.
Mean Absolute Error Using the Best Solution of the Monte Carlo Technique for 1% and 5% of All Possible with Respect to the Solution of the Conventional Set-Inversion-Based Strategy

Monte Carlo test	Basal comparison	Bolus comparison	PPBD comparison
Mean absolute error ± standard deviation for 1%	0.31 ± 0.3 IU/h	1.03 ± 0.6 IU	53.08 ± 46.3 min
Mean absolute error ± standard deviation for 5%	0.15 ± 0.14 IU/h	0.33 ± 0.25 IU	27.23 ± 30 min

In conclusion, a computationally efficient method for finding the maximum bolus–insulin solution using a SIB strategy has been presented and tested. The results indicate that an embedded version within smart insulin pumps is now feasible. Clinical studies are needed for a validation of the clinical efficiency of the method.

Funding:

This work was partially supported by the Spanish Ministry of Science and Innovation through Grant DPI-2010-20764-C02 and by the Autonomous Government of Catalonia through Grant SGR 523. Fabian León-Vargas acknowledges the FI grants of Generalitat de Catalunya.

References:

1. Shetty G, Wolpert H. Insulin pump use in adults with type 1 diabetes--practical issues. Diabetes Technol Ther. 2010;12 Suppl 1:S11–6.
2. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. BMJ. 2002;324(7339):705.
3. Bell DS, Ovalle F. Improved glycemic control with use of continuous subcutaneous insulin infusion compared with multiple insulin injection therapy. Endocr Pract. 2000;6(5):357–60.
4. Chase HP, Saib SZ, MacKenzie T, Hansen MM, Garg SK. Postprandial glucose excursions following four methods of bolus insulin administration in subjects with type 1 diabetes. Diabet Med. 2002;19(4):317–21.
5. Zisser H, Wagner R, Pleus S, Haug C, Jendrike N, Parkin C, Schweitzer M, Freckmann G. Clinical performance of three bolus calculators in subjects with type 1 diabetes mellitus: a head-to-head-to-head comparison. Diabetes Technol Ther. 2010;12(12):955–61.
6. Walsh J, Roberts R. Pumping insulin: everything you need for success with a smart insulin pump. 4th ed. San Diego: Torrey Pines Press; 2006.
7. Wang Y, Percival MW, Dassau E, Zisser HC, Jovanovic L, Doyle FJ 3rd. A novel adaptive basal therapy based on the value and rate of change of blood glucose. J Diabetes Sci Technol. 2009;3(5):1099–108.

8. Bondia J, Dassau E, Zisser H, Calm R, Vehí J, Jovanovič L, Doyle FJ 3rd. Coordinated basal-bolus infusion for tighter postprandial glucose control in insulin pump therapy. J Diabetes Sci Technol. 2009;3(1):89–97.
9. Revert A, Calm R, Vehi J, Bondia J. Calculation of the best basal-bolus combination for postprandial glucose control in insulin pump therapy. IEEE Trans Biomed Eng. 2011;58(2):274–81.
10. Revert A, Rossetti P, Calm R, Vehí J, Bondia J. Combining basal-bolus insulin infusion for tight postprandial glucose control: an in silico evaluation in adults, children, and adolescents. J Diabetes Sci Technol. 2010;4(6):1424–37.
11. Calm R, García-Jaramillo M, Bondia J, Sainz MA, Vehí J. Comparison of interval and monte carlo simulation for the prediction of postprandial glucose under uncertainty in type 1 diabetes mellitus. Comput Methods Programs Biomed. 2011;104(3):325–32.
12. Zisser HC, Bevier W, Dassau E, Jovanovic L. Siphon effects on continuous subcutaneous insulin infusion pump delivery performance. J Diabetes Sci Technol. 2010;4(1):98–103.
13. Laguna AJ, Rossetti P, Ampudia-Blasco FJ, Vehí J, Bondia J. Optimal design for individual model identification based on ambulatory continuous glucose monitoring in patients with type 1 diabetes. UKACC International Conference on CONTROL 2010, Coventry, UK, 2010.
14. Maxim Integrated. Medical solutions guide. *www.maxim-ic.com/Medical*. Accessed June 26, 2011.