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Insulin dosage optimization based on prediction of postprandial glucose excursions under uncertain parameters and food intake

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ABSTRACT

Considering the difficulty in selecting correct insulin doses and the problem of hyper- and hypoglycemia episodes in type 1 diabetes, dosage-aid systems are very useful for these patients. A model-based approach to this problem must unavoidably consider uncertainty sources such as large intra-patient variability and food intake. In the present study, postprandial glucose is predicted considering this uncertain information using modal interval analysis. This approach calculates a safer prediction of possible hyper- and hypoglycemia episodes induced by insulin therapy for an individual patient's parameters and integrates this information into a dosage-aid system. Predictions of a patient's postprandial glucose at 5-h intervals are used to predict the risk for a given therapy. Then the insulin dose and injection-to-meal time with the lowest risk are calculated. The method has been validated for three different scenarios corresponding to preprandial glucose values of 100, 180 and 250 mg/dl.

1. Introduction

Type 1 diabetes is a metabolic disease characterized by elevated plasma glucose levels corresponding to acute or chronic hyperglycemia, which can lead to long-term micro- and macrovascular complications. This is due to the destruction by cells of the immune system of insulin-producing β-cells in the islets of Langerhans in the pancreas. In the 1990s, the Diabetes Control and Complications Trial (DCCT) [1] showed that any improvement in glucose control as measured by the level of HbA1c leads to a reduction in the risk of chronic complications associated with diabetes. For this reason, euglycemia has been established as the control objective for patients with type 1 diabetes unless contraindications exist. However, a universal, efficient and safe system for normalizing the glucose levels of patients is still lacking.

The intensive insulin therapy required to achieve glucose control objectives is based on injection of basal and bolus insulin to emulate its physiological secretion. The frequency and dose depend on the individual patient owing to variations in weight, physical activity, carbohydrate (CHO) consumption, insulin sensitivity, disease history, etc. Typically, before each meal, the patient measures his preprandial blood glucose level and calculates the adjusted insulin dose in relation to planned CHO intake according to rules prescribed by his physician in his therapy plan. This therapy has a risk of severe hypoglycemia with all its consequences if the dose is too high.

Many systems have been developed to educate and support the patient in the insulin dosage process [2]. The majority

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of these systems are intended for educational purposes [3–7] and only a few decision support systems have been developed [8–12]. Insulin dosage advisory systems have also been incorporated in insulin pumps [13,14], based on proportionality rules that consider insulin/CHO ratio, insulin sensitivity, and insulin remaining from previous injections (insulin on board).

This paper presents a novel method to estimate the dose and injection time relative to meal times required for low-risk intensive insulin therapy. The algorithm is based on interval simulation of an individual patient's glucoregulatory model. The Hovorka model is used as an illustration [15]. Uncertainty in hepatic and peripheral insulin sensitivity and CHO content of the planned meal is considered. As a result, upper and lower envelopes for all possible glucose excursions are predicted and then used to calculate the risk of severe and mild hyper- and hypoglycemia episodes [16]. The dosage-aid system then calculates the optimum insulin dosage and injection-to-meal time with the lowest risk according to the model. The interval simulation is resolved using modal interval analysis (MIA) [17], which permits to avoid, under some conditions, the problem of overestimation of interval computations. MIA has been successfully applied in different fields [18–21].

2. Methodology

Patient-specific bolus insulin optimization unavoidably requires an evaluation of its impact on postprandial glucose, so that sufficiently accurate short-time postprandial glycemia predictions are necessary. The use of dynamic models provides valuable information about postprandial glucose excursions. However, one of the main challenges lies in the large intra-individual patient variability that must be taken into account. There is also an important source of uncertainty in food intake since in real life situations it is not possible to precisely measure the CHO content of a mixed meal. These factors mean that the development of prediction tools able to consider different sources of uncertainty (inputs, parameters, initial state) is required so that a worst-case approach can be addressed in optimization of the insulin dose and injection-to-meal time.

Consider a dynamical model $\boldsymbol{\Sigma}(\mathbf{x}, \mathbf{u}; \mathbf{p}, \mathbf{x}_0)$, where $\mathbf{x}$ is the state vector, $\mathbf{u}$ is the input vector, $\mathbf{p}$ is the parameter vector, and $\mathbf{x}_0$ is the initial state vector. The input vector $\mathbf{u}$ contains the information on the meal, insulin injection and the respective timings. If uncertainty is introduced into model $\boldsymbol{\Sigma}$, considering uncertain parameters, inputs and initial state (these correspond to interval vectors, denoted as $\mathbf{P}$, $\mathbf{U}$ and $\mathbf{X}_0$), an interval extension of the model $\boldsymbol{\Sigma}$ is obtained. Using MIA (see Section 3) upper and lower envelopes for the many possible model responses, i.e., glucose excursions, are calculated taking into account all uncertainty sources, as depicted in Fig. 1.

Given the interval extension of the model, denoted as $\boldsymbol{\Sigma}(\mathbf{X}, \mathbf{U}; \mathbf{P}, \mathbf{X}_0)$, the optimal insulin dose and timing are formulated as the following optimization problem:

$$(t_{im}, d_i) = \text{argmin}_{t_{im}, d_i} J(\boldsymbol{\Sigma}(\mathbf{X}, \mathbf{U}; \mathbf{P}, \mathbf{X}_0)),$$

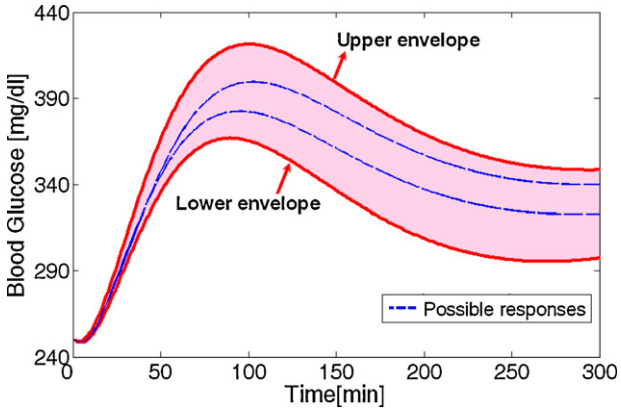

Fig. 1 – Output of an interval dynamic model: upper and lower envelopes of the many possible system responses (shared area).

where d_i is the bolus insulin dose and t_{im} denotes the relative time between insulin injection and meal ingestion (note that in the present approach, this time can be positive or negative, thus implying that the insulin can be injected before the meal starts, typical for high preprandial glucose measurement, or afterwards, characteristic for low preprandial values).

A suitable cost function J, which quantifies the safety of the predicted manifold postprandial glucose excursions, must be considered. So far no gold standard method exists for this purpose. The methods that have been presented include the average daily risk range (ADRR) [22], the mean amplitude of glycemia excursions (MAGE) [23] and lability [24]. However, these methods do not deal with uncertain information.

Furthermore, the cost function J should be easily tunable since the therapeutic goal is patient-specific. An event-based cost function is used for this purpose, taking as input the upper and lower envelopes for glucose excursions and evaluating the risk of suffering different grades of hyper- and hypoglycemia episodes [16] (see Section 4).

To obtain the dose and injection-to-meal time that minimize this cost function, an initial dose, calculated according to rules for the carb factor and correction factor, is taken as the starting point of a two-dimensional grid search (see Section 4.2).

3. Prediction of glycemia face to uncertainty

Simulation of a model with fixed parameters yields trajectories across time of the output variables. When the quantities involved in the simulation take values inside intervals of variation, the set of trajectories determines a manifold bounded by two envelopes (Fig. 1). At each time step of the simulation, the envelopes, i.e., the possible maximum and minimum values of the signal trajectory, have to be determined. This is a range computation problem. The function whose range has to be determined is defined by the interval model of the system and the parameter space is determined by the interval values of the parameters, the input and the initial state.

Simulation of an interval model provides intervals (ranges) that are guaranteed estimates of the envelopes. One way to compute these estimates is by means of interval arithmetic.

Interval arithmetic considers the whole range of possible instances represented by an interval model. The computations of the so-called *natural extension* of a real function is computed by substituting real variables with intervals and real arithmetic operations with corresponding interval operations [25]. An important property is monotonic inclusion: given f a real function and $f_R(X)$ its natural extension to interval X, then $x \in X$ implies $f(x) \in f_R(X)$ i.e., the computed interval will always contain or be equal to the actual range.

As a consequence, the natural extension is very useful for computing the range of a function because it guarantees that the result lies within the computed range. Unfortunately, it does not provide an exact estimate in the general case. This comes from the multi-incidence problem: interval arithmetic considers each instance of a variable in the syntax tree of a function as being independent of each other, leading to an overestimation of the actual range.

In the present study, an interval model was studied using MIA, to compute a tight (sometimes exact) enclosure of the envelope that includes all possible behaviors of the system. Using modal intervals, each interval function to be evaluated is automatically analyzed and put, if possible, in its optimal form (the expression is rewritten in such a way that the exact range is obtained). If optimality cannot be reached, the f^* algorithm [26] is launched. This algorithm uses many optimality and coercion theorems from modal interval theory to compute tight approximations of the range by using branch-and-bound techniques. However, the algorithm is computationally expensive owing to its high complexity.

Prediction of postprandial glycemia involves modeling of subcutaneous insulin absorption, CHO digestion and absorption, insulin pharmacokinetics and pharmacodynamics, and glucose metabolism. In this work, the models presented in [27], for subcutaneous insulin absorption and in [15] for the rest of the components of the model have been combined to represent the glucoregulatory model. In both cases, experimental validation results have been reported in the literature [28,29].

Next, interval simulation of the glucoregulatory model considered is outlined. A change in variables allows computation of the exact range of the trajectories using coercion theorems from MIA. These computations were carried out using the C++ modal interval library IvalDb [30]. Intervals are denoted by capital letter. The model parameters used for the different components of the model (patient 2), are taken from [28] and [15].

3.1. Carbohydrate digestion and absorption interval model

Patients generally do not know the exact amount and composition of their meals and these have to be estimated. It is thus considered that the CHO amount ingested is an interval $D_G = [\underline{D}_G, \overline{D}_G]$. Then the corresponding absorption interval model $U_G(t)$ is:

$$U_G(t) = \frac{t\, D_G\, a_G \exp(-t/t_{max,G})}{t^2_{max,G}}, \tag{1}$$

where a_G is the CHO bioavailability and $t_{max,G}$ is the time-of-maximum appearance of glucose in plasma [15].

3.2. Insulin pharmacokinetics and pharmacodynamics interval model

Insulin pharmacokinetics, either basal or bolus, is considered a first-order process. Plasma insulin concentration, $i(t)$, in Euler discrete form is thus:

$$i(t+1) = i(t)\,(1 - k_e\,\Delta t) + \frac{i_{ex}(t)}{v_i}, \tag{2}$$

where k_e is the fractional elimination rate, v_i is the insulin distribution volume and $i_{ex}(t)$ is the exogenous insulin absorption rate ($i^{bolus}_{ex}(t) + i^{basal}_{ex}(t)$) [27]. No uncertainty is included here since the predominant uncertainty is considered on the insulin pharmacodynamic. In this case, insulin sensitivity parameters in the Hovorka model [28] are considered as intervals $S_{IT} = [\underline{S}_{IT}, \overline{S}_{IT}]$ (distribution/transport), $S_{ID} = [\underline{S}_{ID}, \overline{S}_{ID}]$ (disposal) and $S_{IE} = [\underline{S}_{IE}, \overline{S}_{IE}]$ (endogenous glucose production). The insulin pharmacodynamics model in Euler discrete interval form is thus given by:

$$\begin{aligned} X_1(t+1) &= X_1(t)\ (1 - \Delta t\, k_{a1}) + \Delta t\, S_{IT} k_{a1} i(t) \\ X_2(t+1) &= X_2(t)\ (1 - \Delta t\, k_{a2}) + \Delta t\, S_{ID} k_{a2} i(t) \\ X_3(t+1) &= X_3(t)\ (1 - \Delta t\, k_{a3}) + \Delta t\, S_{IE} k_{a3} i(t) \end{aligned} \tag{3}$$

where X_1 represents the effect of insulin on glucose distribution and transport, X_2 represents the effect on glucose disposal and X_3 the effect on endogenous glucose production; k_{ai}, $i = 1, 2, 3$ are deactivation rate constants. According to MIA, this model is optimal because the insulin sensitivities appear only once in each equation. As a result of the interval computation, the states X_1, X_2, and X_3 are interval states [31].

3.3. Glucose subsystem interval model

The interval output for the CHO digestion and absorption subsystem, U_G, as well as the interval states computed for the insulin subsystem, X_i, $i = 1, 2, 3$, are interval inputs of the glucose subsystem. Thus, even if no uncertainty for the glucose subsystem is considered, it becomes an interval model and interval methods should be used to compute its evolution.

Glucose metabolism is represented in [15] as a two-compartment system for which Q_1 and Q_2 represent the glucose mass in accessible and non-accessible compartments and G is the glucose concentration. State equations for Q_1 and Q_2 must be rewritten to obtain optimality and compute the exact range using MIA. The state variables $Q_1(t)$ and $Q_2(t)$ are not monotonic with respect to all their multi-incident variables. Therefore, a new state variable $S(t) = Q_1(t) + Q_2(t)$ is defined with the objective of obtaining monotonicity with respect to the multi-incident variables.

Applying the theorem of coercion to optimality [20] and taking into account the definition of a dual operator as

$Dual([\underline{a}, \overline{a}]) = [\overline{a}, \underline{a}]$, rational computation for the algorithm of the model is:

$$\begin{aligned} Q_1(t+1) &= (1 - \Delta t\,(k_{12} + X_1(t)))\,Q_1(t) - \Delta t\,(Dual(F^c_{01}(t)) \\ &\quad + Dual(F_R(t))) + \Delta t\,k_{12}S(t) + \Delta t\,B(t) \\ S(t+1) &= \Delta t\,Dual(X_2(t))\,Q_1(t) - \Delta t\,(Dual(F^c_{01}(t)) \\ &\quad + Dual(F_R(t))) + (1 - \Delta t\,X_2(t))\,S(t) + \Delta t\,B(t) \\ G(t) &= \frac{Q_1(t)}{v_G} \end{aligned} \tag{4}$$

with:

$$B(t) = U_G(t) + EGP_0\,(1 - X_3(t)), \tag{5}$$

where k_{12} represents the transfer rate constant from the non-accessible to the accessible compartment, $F^c_{01}(t)$ is the total non-insulin-dependent glucose disposal, $F_R(t)$ is the renal glucose clearance above the glucose threshold of 9 mmol L^{-1}, v_G represents the distribution volume of the accessible compartment and EGP_0 is the endogenous glucose production extrapolated to zero insulin concentration. The time step Δt is defined so that:

$$\Delta t < \min\left(\frac{1}{k_{12} + X_1(t) + FC(t)}, \frac{1}{k_{12} + X_2(t)}\right), \tag{6}$$

where:

$$FC(t) = \begin{cases} \dfrac{f_{01}}{4.5v_G} & \text{if} \quad Q_1(t) < 4.5v_G \\ 0 & \text{if} \quad 4.5 \le Q_1(t) \le 9 \\ 0.003 & \text{if} \quad Q_1(t) \ge 9v_G \end{cases}.$$

This condition is necessary to obtain monotonicity in the model variables and achieve optimality. The functions $F^c_{01}(t)$ and $F_R(t)$ are monotonically increasing with respect to the state variable $Q_1(t)$. Therefore, they can be computed as a function of the interval bounds:

$$F^c_{01}(t) = [\underline{F^c_{01}(t)}, \overline{F^c_{01}(t)}] \quad F_R(t) = [\underline{F_R(t)}, \overline{F_R(t)}],$$

where:

$$\underline{F^c_{01}(t)} = \begin{cases} \dfrac{f_{01}\,\underline{Q_1(t)}}{4.5v_G} & \text{if } \underline{Q_1(t)} < 4.5v_G \\ f_{01} & \text{if } \underline{Q_1(t)} \ge 4.5v_G \end{cases}$$

$$\overline{F^c_{01}(t)} = \begin{cases} \dfrac{f_{01}\,\overline{Q_1(t)}}{4.5v_G} & \text{if } \overline{Q_1(t)} < 4.5v_G \\ f_{01} & \text{if } \overline{Q_1(t)} \ge 4.5v_G \end{cases}$$

and:

$$\underline{F_R(t)} = \begin{cases} 0 & \text{if } \underline{Q_1(t)} < 9v_G \\ 0.003\;\underline{Q_1(t)} - 0.027\,v_G & \text{if } \underline{Q_1(t)} \ge 9v_G \end{cases}$$

$$\overline{F_R(t)} = \begin{cases} 0 & \text{if } \overline{Q_1(t)} < 9v_G \\ 0.003\,\overline{Q_1(t)} - 0.027\,v_G & \text{if } \overline{Q_1(t)} \ge 9v_G. \end{cases}$$

3.4. Initial states

To run an interval simulation of the whole system, the initial states and inputs must be given. Since not all of the states are measurable (in fact, only preprandial glucose measurements will be available), the initial state must be estimated. This is carried out by simulating the past history of the patient in terms of insulin injections and meals. Owing to uncertainty, the initial state will correspond to an interval vector, except for the measured glucose value.

In the present study we assumed that the patient follows the same regime every day. A history of 3 days was considered to obtain the intervals for non-measurable states.

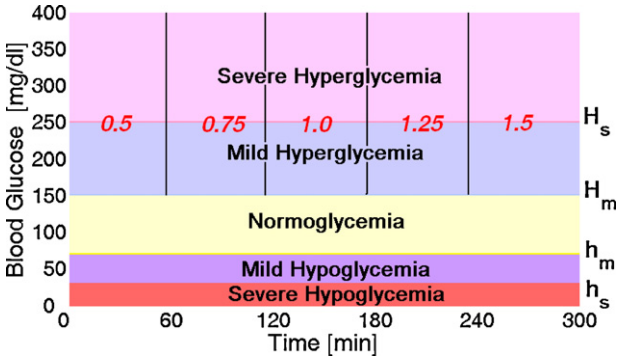

Fig. 2 – Grid for glucose ranges and hyperglycemia time weights (cursive numbers) used for risk index computation.

4. Bolus insulin dose and injection-to-meal time optimization

The method developed to estimate the dose and injection-to-meal time needed to obtain the next desired therapeutic goal is based on a risk index (or cost function) that quantifies hyper- and hypoglycemia episodes of the glucose prediction provided by a dynamical model with uncertainties [16]. The risk index is computed for a two-dimensional grid of bolus insulin and injection-to-meal time, selecting the solution that generates lower risks of hyper- and hypoglycemia. Other useful information can be extracted from this analysis, such as the dose that allows greater injection time flexibility.

Next, the cost function and optimization strategy is presented.

4.1. Risk index

The cost function consists of a risk index obtained from three different metrics:

1. Glucose ranges corresponding to severe (H_s) and mild (H_m) hyperglycemia and to severe (h_s) and mild (h_m) hypoglycemia are those depicted in Fig. 2 with thresholds $h_s = 36$, $h_m = 70$, $H_m = 150$, and $H_s = 250$ mg/dl.
2. A weighting function $\gamma(t)$ is defined for the time occurrence of hyperglycemia (mild and severe). Major relevancy is given to zones far from meal time to take into account long-term hyperglycemia (see Fig. 2).

$$\gamma(t) = \begin{cases} 0.5 & 0 \le t < 60 \\ 0.75 & 60 \le t < 120 \\ 1 & 120 \le t < 180 \\ 1.25 & 180 \le t < 240 \\ 1.5 & 240 \le t < 300 \end{cases}.$$

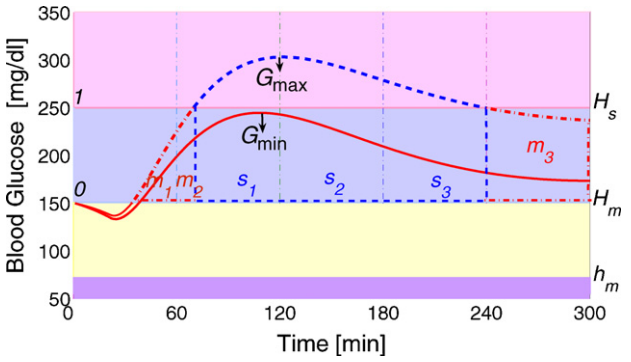

Fig. 3 – Example of risk index computation.

3. Weights are defined to quantify the relative importance of mild and severe hypo- and hyperglycemia events (α_{hs}, α_{hm}, α_{Hm}, and α_{Hs}). They are adjusted using a quadratic function in the following way: $\alpha_{hs}\alpha_{hm}=1$; for mild hyperglycemia, $\alpha_{Hm}=1/16$; and for severe hyperglycemia, $\alpha_{Hs}=1/4$. These values, obtained heuristically from clinical judgement, could be modified by the physician according to patient's specific needs.

Now let $G_{max}(t)$ and $G_{min}(t)$ be the upper and lower envelopes of the predicted manifold glucose trajectories. The risk of severe and mild hyperglycemia and severe and mild hypoglycemia are respectively defined as:

$$\begin{aligned}
J_{Hs} &= \frac{\int_{T_{Hs}} \gamma(t)\,(G_{\max}(t)-H_m)\,dt}{H_s-H_m} && T_{Hs}=\{t/G_{\max}(t)\geq H_s\}\\
J_{Hm} &= \frac{\int_{T_{Hm}} \gamma(t)\,(G_{\max}(t)-H_m)\,dt}{H_s-H_m} && T_{Hm}=\{t/H_m\leq G_{\max}(t)<H_s\}\\
J_{hs} &= \frac{\int_{T_{hs}} (h_m-G_{\min}(t))\,dt}{h_m-h_s} && T_{hs}=\{t/G_{\min}(t)\leq h_s\}\\
J_{hm} &= \frac{\int_{T_{hm}} (h_m-G_{\min}(t))\,dt}{h_m-h_s} && T_{hm}=\{t/h_s<G_{\min}(t)\leq h_m\}
\end{aligned} \tag{7}$$

where H_s, H_m, h_s and h_m are the threshold values described above and $\gamma(t)$ is the weighting assigned to the time of occurrence of hyperglycemia.

The risk index is finally calculated as the weighted sum:

$$J:=\alpha_{Hs}J_{Hs}+\alpha_{Hm}J_{Hm}+\alpha_{hs}J_{hs}+\alpha_{hm}J_{hm}. \tag{8}$$

An example of the risk index calculation for a predicted manifold response with its upper and lower envelopes is depicted in Fig. 3. The areas m_i, s_i, $i=1,\ldots,3$ correspond to the area under the curve for normalized glucose for the different episodes and time weight. The components of the risk index corresponding to hyperglycemia are then calculated as: $J_{Hm}=0.5\,m_1+0.75\,m_2+1.5\,m_3$ and $J_{Hs}=0.75\,s_1+1\,s_2+1.25\,s_3$. The same procedure is used to obtain J_{hm} and J_{hs}, but in this case without time weights. Finally, Eq. (8) is applied to obtain the final risk index.

Table 1 – Initial meal time (IM) for regular insulin according with preprandial glucose.

Blood glucose (mg/dl)	IM (min)
<70	0
70–140	30
140–180	45
>180	60

The risk index was validated for different scenarios considering variation in preprandial glucose, food intake, insulin dose and meal time [16].

4.2. *Grid search method*

To calculate the optimum insulin dose and injection-to-meal time, a two-dimensional grid search can be carried out since the input space is discrete. The typical resolution of an insulin pen is 0.5 IU and 0, 15, 30, 45, 60 min are taken for injection-to-meal time.

A starting estimate based on currently used heuristic rules is first calculated, constituting the center of the exploratory grid. The initial insulin dose, denoted as (II), is calculated using the carb factor and correction factor rules based on the patient's total daily dose (TDD) and the factor associated. To determine the carb factor, how many grams of CHO will be covered by one unit of insulin are used the "500 Rule" for rapid-acting insulin and "450 Rule" for short-acting insulin [32]. The "1500 Rule" for regular short-acting insulin and "2000 Rule" for rapid-acting insulin are used to determine the correction factor, which estimates how far blood glucose is likely to drop per unit of insulin [33].

Using the planned CHO intake, the carb factor and correction factor, the meal bolus is calculated as:

$$II=\frac{CHO}{\text{carb factor}}+\frac{GC-G_{obj}}{\text{correction factor}}, \tag{9}$$

where G_{obj} is the glucose objective defined to regulate blood glucose around normal levels and GC is the preprandial glucose measurement. The minimum objective is 70 mg/dl (G_{objmin}) and the maximum is 150 mg/dl (G_{objmax}).

In accordance with preprandial glucose, the injection-to-meal time (IM) [34] is defined as shown in Table 1.

Once the initial estimation is calculated, the exploratory grid is defined as the cartesian product $(II-n\Delta I,\ldots,II,\ldots,II+n\Delta I)\times\left(0,60\frac{1}{k},\ldots,60\frac{k-1}{k},60\right)$, where $n,k\in\mathbb{N}^+$ and ΔI denote the granularity considered for the insulin dose. The values $\Delta I=0.5$, $n=6$ and $k=4$ are considered here. The element of the grid with the lowest risk index is finally chosen.

5. Results

To demonstrate the feasibility of the proposed methodology, a virtual patient with nominal parameters is considered. For this patient, the following daily situation is evaluated:

- Meal ingestion: 60 g of CHO with 5% uncertainty.
- Insulin injection: regular insulin.
- Insulin sensitivity parameters: S_{IT} with 11% variation, S_{ID} with 8% variation and S_{IE} with 2% variation according to the standard deviation presented in [28].

Table 2 – Risk index in scenario i, it is classified as: low risk (<10), intermediate risk (10–60), high risk (60–120) and very high risk (>120).

Bolus (IU)	Meal (min)	Severe hypoglycemia index	Mild hypoglycemia index	Severe hyperglycemia index	Mild hyperglycemia index	Total index
6.0	30	0.00	0.00	0.00	2.10	2.10
6.5	45	0.00	2.31	0.00	1.12	3.43
5.0	30	0.00	0.00	0.00	5.36	5.36
4.5	30	0.00	0.00	0.00	7.25	7.25
7.0	45	0.00	8.79	0.00	0.54	9.34
5.0	0	0.00	0.00	7.21	3.86	11.07
7.0	60	0.00	17.30	0.00	0.45	17.75
4.0	45	0.00	0.00	23.92	5.39	29.31
6.5	0	0.00	36.50	0.00	2.28	38.78
3.5	15	0.00	0.00	43.57	4.40	47.97
8.0	45	0.00	51.03	0.00	0.02	51.05
3.5	45	0.00	0.00	64.50	0.97	65.47
3.0	60	0.00	1.06	77.19	0.84	79.09
3.0	15	0.00	0.00	82.58	0.54	83.12
7.5	0	31.40	62.22	0.00	1.55	95.17
2.0	60	0.00	0.00	105.78	0.57	106.35
2.0	0	0.00	0.00	116.27	0.30	116.57
8.0	0	91.10	32.76	0.00	1.29	125.15

Three scenarios are considered corresponding to preprandial glucose levels: (i) 100 mg/dl (initial normoglycemia), (ii) 180 mg/dl (initial mild hyperglycemia) and (iii) 250 mg/dl (initial severe hyperglycemia).

The algorithm was initialized using the insulin bolus calculated with Eq. (9) and with the injection-to-meal time (Table 1) as described in Section 4.2. The search grid is built with step size of 0.5 IU and 15 min. The maximum grid size is ±3 IU from the starting point for the insulin dose and 0–60 min for the injection-to-meal time. A total of 65 grid points were examined. An example of the risk index calculation, in this case for scenario i, is shown in Table 2, which summarizes the results for low risk (index < 10), intermediate risk (index between 10 and 60), high risk (index between 60 and 120) and very high risk (index > 120). The initialization value obtained with the heuristic rules is an insulin dose of 5 IU injected 30 min before eating, which has a risk index of 5.36. The minimum risk index for hyper- and hypoglycemia episodes is 2.10, corresponding to an insulin dose of 6 IU 0.5 h before eating.

Fig. 4(a), (c), and (e) shows a two-dimensional grid with the risk index evaluation for each scenario. The area demarcated by the rectangle corresponds to the four lowest values of the risk index. Fig. 4(b), (d), and (f) shows the influence of meal time with respect to the bolus insulin dose. For scenario i the lowest risk index values occur between 5.5 and 6.0 IU for the insulin dose and between 15 and 30 min for the injection-to-meal time, with a risk index < 3.60 (see Fig. 4(a)). For scenario ii the risk index is <3.42 between 7.0 and 7.5 IU for the insulin dose and between 45 and 60 min for the injection-to-meal time (see Fig. 4(c)). Finally, for scenario iii, the area demarcated is the same than that for scenario ii but the risk index is <6.20 (see Fig. 4(e)). Table 3 shows a comparison of the initial estimate versus optimal insulin performance, as calculated by the proposed methodology.

Fig. 5 shows the optimum bolus dose and injection-to-meal time resulting from the algorithm for the three scenarios considered (preprandial glucose levels of 100, 180 and 250 mg/dl). The envelopes for possible glucose excursions for optimal therapy are shown and compared with the initial estimation using heuristic rules.

6. Discussion

The metrics proposed in this paper (see Fig. 2) were established according to the clinical relevance of each hyper- and hypoglycemia episode. Therefore, these metrics can be modified by the physician according to a patient's medical history. The relevance of these metrics can be appreciated clearly in the results shown in Table 2. Very high risk index values occur when the insulin bolus-mealtime pair produces severe hypoglycemia for a long time and/or mild or severe hyperglycemia (index of 125.15 in Table 2). There is also a high risk when the combinations result in the highest blood glucose levels for a long time and/or mild hypoglycemia (index values of 65.47–116.57). When severe and mild hyperglycemia and/or mild hypoglycemia episodes occur during simulation, an intermediate risk index value is generated (index values of 11.07–51.05). The lowest risk index values (<10) all present mild hyperglycemia episodes and a few present mild hypoglycemia (lasting for <20 min and with values close to euglycemia). Hyperglycemia episodes occurring within 2 h after ingestion generated a low level of risk. By contrast, hyperglycemia at long times after food intake generated the highest risk index values.

The previous results are also shown in Fig. 4(a). In this case, the combinations of bolus insulin and injection-to-meal time that produce less episodes of hyper- and hypoglycemia are in the center of the grid. The greatest risks are present at the borders, corresponding to excess or insufficient insulin. This greatest risk with respect to insulin dose is also evident in Fig. 4(c) and (e), but in these cases the corresponding injection-to-meal time is longer owing to the preprandial glucose levels. Fig. 4(b), (d), and (f) shows the influence of meal time with respect to the insulin dose. In Fig. 4(b) the dose that generates the lowest index is greatly influenced by the meal time. This

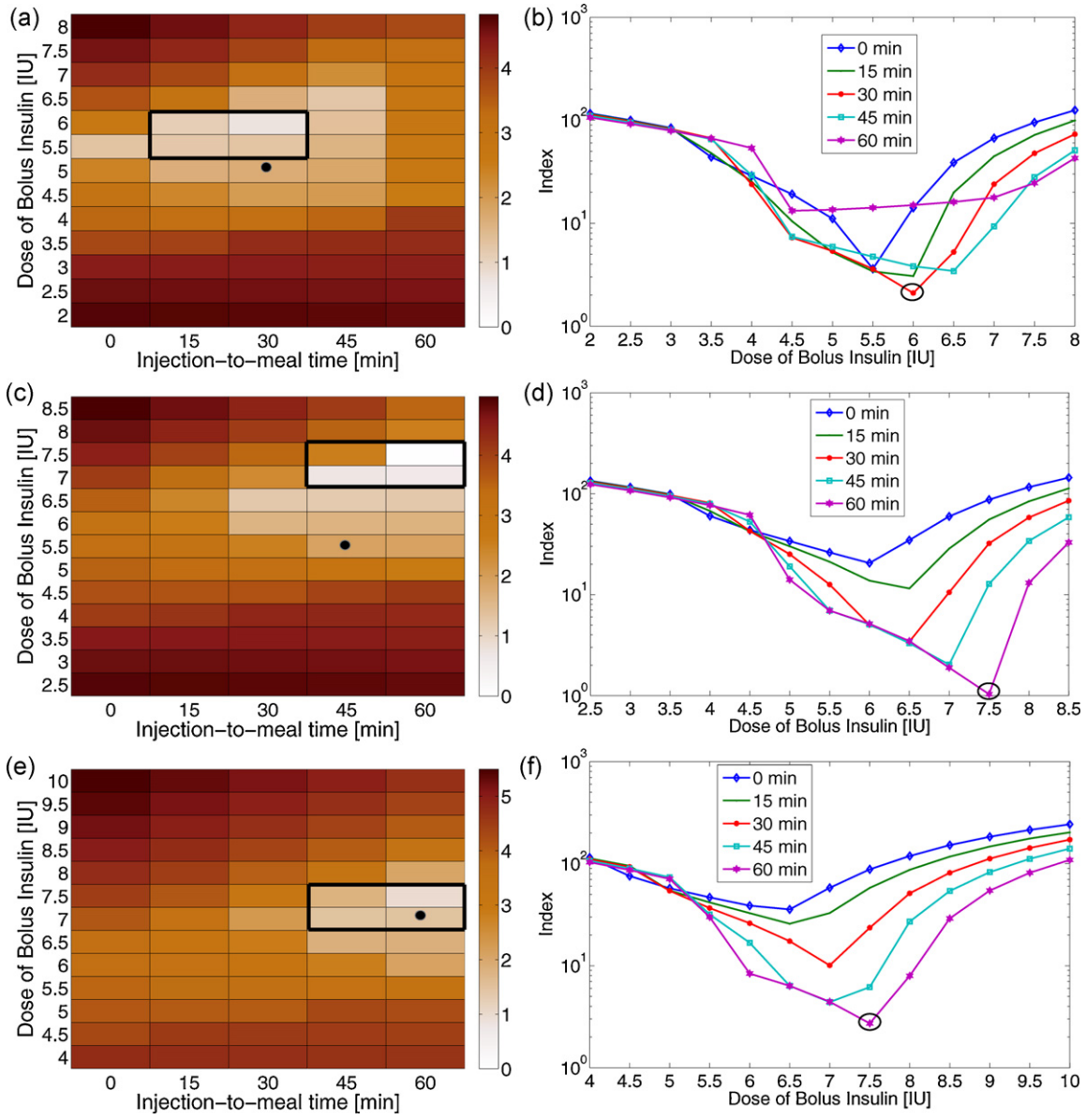

Fig. 4 – Grid-based optimization for scenarios i (a), ii (c) and iii (e). The points correspond to currently used heuristic rules. Relationship between insulin bolus and injection-to-meal time, with the optimal risk index indicated by a circle for scenarios i (b), ii (d) and iii (f). The risk index is represented on a logarithmic scale.

means that selection of 6 IU may be too risky if the patient does not follow exactly the recommended meal time. For this reason, a safer bolus insulin dose would be 5.5 IU, which is less dependent on meal time. For scenarios ii (see Fig. 4(d)) and iii (see Fig. 4(f)) the risk is directly related to the injection-to-meal time.

Comparison of insulin therapy based on heuristic rules and optimization of the risk index reveals that the latter yields glucose profiles closer to euglycemia, as observed in Fig. 5. With regard to initial versus optimal mealtimes, the minimum risk index of scenario i was obtained for injection 0.5 h before eating. However, the optimization suggests

Table 3 – Comparison of risk index (RI) for initial estimate (II) versus optimal insulin performance for each scenario.

Scenario	Initial estimate			Optimal estimate		
	II (IU)	IM (min)	RI	d_i (IU)	t_{im} (min)	RI
i	5.0	30	5.36	6.0	30	2.10
ii	5.5	45	6.95	7.5	60	1.03
iii	7.0	60	4.44	7.5	60	2.72

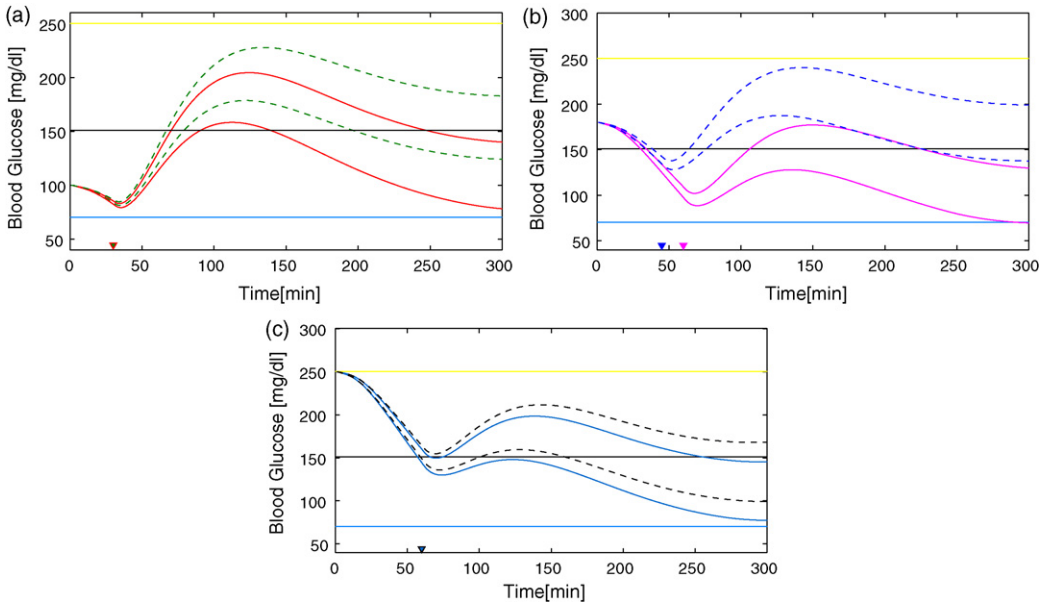

Fig. 5 – Blood glucose response over 5 h for scenarios i (a), ii (b) and iii (c). Triangles indicate the start time for meals. The solid line indicates blood glucose for the correct bolus dose of insulin (minimal index) and the dotted line is the blood glucose response for an initial insulin bolus and a meal.

a higher bolus insulin dose, which reduces the risk index by 61% (Fig. 5(a)). To reduce the risk for scenario ii, it is necessary to increase the injection-to-meal time and bolus insulin dose compared to those obtained with heuristic rules. This yields a reduction of 85% in mild hyperglycemia risk. Finally, for scenario iii the optimum bolus dose is 7.5 IU injected 1 h before eating (Fig. 5(c)). This yields a reduction of 39% in the risk of mild hyperglycemia given by the initial estimation.

7. Conclusions

MIA was successfully applied to the prediction of glucose excursions in patients with type 1 diabetes in the light of uncertain information. By considering intra-patient variability and uncertainty in food intake, safer prediction of possible hyper- and hypoglycemia episodes induced by insulin therapy can be calculated, leading to a reduction in the number of false-negatives. This interval simulation is integrated in a system for evaluating bolus insulin doses and injection times, which minimizes the risk of postprandial hyper- and hypoglycemia in patients with type 1 diabetes.

In each scenario evaluated, the bolus insulin and injection time computed for the insulin dosage led to a reduction of the risk index compared to that obtained using heuristic rules.

To apply the methodology presented here in a patient-specific scenario, it is necessary to adjust the model for individual patients. The model parameters would be estimated from measurements taken by a continuous glucose monitor over several days. The system presented is modular and can be used with other glucoregulatory models, as well as in a feed-forward action for closed-loop glucose control.

The resulting optimum bolus dose is apparently consistent with clinical judgment; however, formal clinical validation is required. The authors are currently working on clinical validation of this decision support system.

Conflict of interest statement

None declared.

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REFERENCES

[1] The Diabetes Control and Complications Trial Research Group, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, N. Engl. J. Med. 329 (14) (1993) 977–986.
[2] E.D. Lehmann, T. Deutsch, Application of computers in diabetes care—review II-Computers for decision support and education, Med. Inform. 20 (4) (1995) 303–329.
[3] B.U. Agar, M. Eren, A. Cinar, Glucosim: educational software for virtual experiments with patients with type 1 diabetes, Proc. IEEE Eng. Med. Biol. Soc. 1 (2005) 845–848.
[4] J. Hedbrant, S. Nordfeldt, J. Ludvigsson, The Särimner diabetes simulator—a look in the rear view mirror, Diabetes Technol. Ther. 9 (1) (2007) 10–16.
[5] O.K. Hejlesen, S. Plougmann, D.A. Cavan, Diasnet—an internet tool for communication and education in diabetes, Stud. Health Technol. Inform. 77 (2000) 563–567.

[6] E.D. Lehmann, T. Deutsch, Aida: an automated insulin dosage advisor, Proc. Annu. Symp. Comput. Appl. Med. Care (1992) 818–819.
[7] M. Levy, P. Ferrand, V. Chirat, Sesam-diabete, an expert system for insulin-requiring diabetic patient education, Comput. Biomed. Res. 22 (5) (1989) 442–453.
[8] D.U Campos-Delgado, R. Femat, E. Ruiz-Velazquez, A. Gordillo-Moscoso, Knowledge-based controllers for blood glucose regulation in type 1 diabetic patients by subcutaneous route, IEEE Int. Symp. Intel. Contr. (2003) 592–597.
[9] C.B. Cook, J.P. Mcmichael, R. Lieberman, L.J. Mann, E.C. King, K.M. New, P.S. Vaughn, V.G. Dunbar, J.M. Caudle, The intelligent dosing system: application for insulin therapy and diabetes management, Diabetes Technol. Ther. 7 (1) (2005) 58–71.
[10] O.K. Hejlesen, S. Andreassen, R. Hovorka, D.A. Cavan, Dias: the diabetes advisory system: an outline of the system and the evaluation results obtained so far, Comput. Methods Programs Biomed. 54 (1997) 49–58.
[11] M.E. Hernando, E.J. Gomez, F. del Pozo, R. Corcoy, Diabnet: a qualitative model-based advisory system for therapy planning in gestational diabetes, Med. Inform. 21 (4) (1996) 359–374.
[12] S.G. Mougiakakou, K.S. Nikita, A neural network approach for insulin regime and dose adjustment in type 1 diabetes, Diabetes Technol. Ther. 2 (3) (2000) 381–389.
[13] D. Takahashi, Y. Xiao, F. Hu, M. Lewis, A survey of insulin-dependent diabetes. Part I. Therapies and devices, Int. J. Telemed. Appl. (2008).
[14] H. Zisser, L. Robinson, W. Bevier, E. Dassau, C. Ellingsen, F.J. Doyle III, L. Jovanovic, Bolus calculator: a review of four "smart"; insulin pumps, Diabetes Technol. Ther. 10 (6) (2008) 441–444.
[15] R. Hovorka, V. Canonico, L.J. Chassin, U. Haueter, M. Massi-Benedetti, M. Orsini Federici, T.R. Pieber, H.C. Schaller, L. Schaupp, T. Vering, M.E. Wilinska, Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes, Physiol. Meas. 25 (4) (2004) 905–920.
[16] M. García-Jaramillo, R. Calm, J. Bondia, C. Tarín, Josep Vehí, Computing the risk of postprandial hypo- and hyperglycemia in type 1 diabetes mellitus considering intrapatient variability and other sources of uncertainty, J. Diabetes Sci. Technol. 3 (4) (2009) 895–902.
[17] E. Gardeñes, M.A. Sainz, L. Jorba, R. Calm, R. Estela, H. Mielgo, A. Trepat, Modal intervals, Reliable Comput. 7 (2) (2001) 77–111.
[18] G. Calderón-Espinoza, J. Armengol, J. Vehí, E.R. Gelso, Dynamic diagnosis based on interval analytical redundancy relations and signs of the symptoms, AI Commun. 20 (2007) 39–47.
[19] M.A. Sainz, J. Armengol, J. Vehí, Fault diagnosis of the three tanks system using the modal interval analysis, J. Process Control 12 (2) (2002) 325–330.
[20] M.A. Sainz, P. Herrero, J. Armengol, J. Vehí, Continuous minimax optimization using modal intervals, J. Math. Anal. Appl. 339 (2008) 18–30.
[21] SIGLA X Group, Modal intervals. Basic tutorial, applications of interval analysis to systems and control, in: Proc. MISC'99, University of Girona, Spain, 1999, pp. 157–227.
[22] B.P. Kovatchev, E. Otto, D. Cox, L. Gonder-Frederick, W. Clarke, Evaluation of a new measure of blood glucose variability in diabetes, Diabetes Care 29 (11) (2006) 2433–2438.
[23] F.J. Service, G.D. Molnar, J.W. Rosevear, E. Ackerman, L.C. Gatewood, W.F. Taylor, Mean amplitude of glycemic excursions, a measure of diabetic instability, Diabetes 19 (9) (1970) 644–655.
[24] D Bruttomesso, D. Crazzolara, A. Maran, S. Costa, A. Dal Pos, M. Girelli, G. Lepore, M. Aragona, E. Iori, U. Valentini, S. Del Prato, A. Tiengo, A. Buhr, R. Trevisan, A. Baritussio, In type 1 diabetic patients with good glycaemic control, blood glucose variability is lower during continuous subcutaneous insulin infusion than during multiple daily injections with insulin glargine, Diabet. Med. 25 (3) (2008) 326–332.
[25] R.E. Moore, Interval Analysis, Prentice-Hall, 1966.
[26] P. Herrero, M.A. Sainz, J. Vehí, L. Jaulin, Quantified set inversion algorithm with applications to control, Reliable Comput. 11 (5) (2005) 369–382.
[27] C. Tarín, E. Teufel, J. Picó, J. Bondia, H.J. Pfleiderer, Comprehensive pharmacokinetic model of insulin glargine and other insulin formulations, IEEE Trans. Biomed. Eng. 52 (2005) 1994–2005.
[28] R. Hovorka, F. Shojaee-Moradie, P.V. Carroll, L.J. Chassin, I.J. Gowrie, N.C. Jackson, R.S. Tudor, A.M. Umpleby, R.H. Jones, Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT, Am. J. Physiol. Endocrinol. Metab. 282 (5) (2002) 992–1007.
[29] E Teufel, C. Tarín, J. Picó, J. Bondia, G. Freckmann, H.J. Pfleiderer, Parameter identification of the endogenous glucose metabolism model for diabetes mellitus i patients, in: Proc. Int. Wissenschaftliches Kolloquium, 2004.
[30] P. Herrero, Quantified real constraint solving using modal intervals with applications to control, Ph.D. Thesis, Ecole Doctorale d'Angers, 2006.
[31] R. Calm, M. García-Jaramillo, J. Vehí, J. Bondia, C. Tarín, W. García-Gabín, Prediction of glucose excursions under uncertain parameters and food intake in intensive insulin therapy for type 1 diabetes mellitus, Proc. IEEE Eng. Med. Biol. Soc. (2007) 1770–1773.
[32] J. Walsh, R. Roberts, The Pocket Pancreas: Your Diabetes Guide for Improved Blood Sugars, Diabetes Services Inc., 1994, pp. 11–12.
[33] J. Walsh, R. Roberts, T. Bailey, C.B. Varma, Using Insulin Everything you Need for Success with Insulin, 1st ed., Torrey Pines Press, San Diego, 2003.
[34] R. Hanas, Type 1 Diabetes in Children Adolescents and Young Adults, 2nd ed., Class Publishing, London, 2004, p. 75.