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Prediction of glucose excursions under uncertain parameters and food intake in intensive insulin therapy for type 1 diabetes mellitus

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Abstract— Considering the difficulty in the insulin dosage selection and the problem of hyper- and hypoglycaemia episodes in type 1 diabetes, dosage-aid systems appear as tremendously helpful for these patients. A model-based approach to this problem must unavoidably consider uncertainty sources such as the large intra-patient variability and food intake. This work addresses the prediction of glycaemia for a given insulin therapy face to parametric and input uncertainty, by means of modal interval analysis. As result, a band containing all possible glucose excursions suffered by the patient for the given uncertainty is obtained. From it, a safer prediction of possible hyper- and hypoglycaemia episodes can be calculated.

I. INTRODUCTION

Diabetes mellitus is a metabolic disease that is accompanied by elevated plasma glucose levels comprising all forms of acute or chronic hyperglycaemia. This is so due to the lack of insulin secretion by the β-cells in the islets of Langerhans in the pancreas (type 1 diabetes) or a reduction in its efficiency to promote transport of glucose into the cells (type 2 diabetes).

Since the Diabetes Control and Complications Trial [1], euglycaemia has been established as the control objective for patients with type 1 diabetes, except if some contraindication exists. However, there still lacks a universal, efficient and safe system able to normalize the glucose levels of patients. The intensive insulin therapy required to achieve the glucose control objectives, based on the injection of basal and bolus insulin to "emulate" its physiological secretion, has as counter-action an increase in the risk of severe hypoglycaemia with all their consequences.

Although several rules do exist for the calculus of the bolus insulin dose, and even these ones have been lately incorporated for automatic calculus in some insulin pumps, trial-and error adjustments of the therapy must be carried out. Considering the difficulty in the insulin dosage selection and the problem of hyper- and hypoglycaemia episodes, dosage-aid systems appear as tremendously helpful for patients with type 1 diabetes.

Such a system must rely on accurate enough predictions of glycaemia. However, there exists a large intra-individual and inter-individual variability in the patients' behavior. Other important source of uncertainty is the food intake (grams of carbohydrates) since it is difficult to have a precise estimation from a mixed meal.

This makes necessary the development of prediction tools able to consider different sources of uncertainty (input, parameters, initial state). In this work, modal interval analysis has been applied for the plasma glucose prediction face to uncertain food intake and patient parameters such as insulin hepatic and peripheral sensitivity. As result, upper and lower envelopes of all the possible glucose excursions suffered by the patient, as predicted by the model, are obtained. This prediction can be used by patients to evaluate the result of different insulin therapy decisions, and evaluate the risk of hypoglycaemia and hyperglycaemia within the framework of a dosage-aid system.

II. GLUCORREGULATORY MODEL

Simulation of an insulin therapy involves modelling subcutaneous insulin absorption, carbohydrates digestion and absorption, insulin pharmacokinetics and pharmacodynamics (PK/PD), and glucose metabolism. The relationship among these processes is shown in Figure 1.
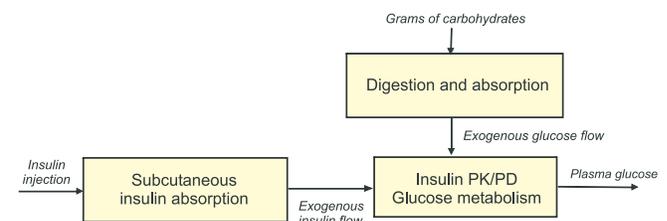
Fig. 1.   Model overview.

In this work, the models presented in [8], for subcutaneous insulin absorption, and [5], for the rest of the components of the model, have been combined to represent the glucorregulatory model. In both cases, experimental validation results have been reported in the literature.

Subcutaneous insulin absorption.   Given and insulin therapy, *i.e.* a set of basal and bolus insulin doses and injection times, this model calculates how the injected insulin appears in blood (exogenous insulin flow). The model in [8] has been selected since it comprehends long- and intermediate-acting insulin preparations, used as basal insulin, as well as rapidly- and short-acting (regular) insulin, used as bolus insulin. The reader is referred to [8] for a

detailed description of this model. As result, the exogenous insulin flow, $I_{\mathrm{ex}}(t) = I_{\mathrm{ex}}^{\mathrm{bolus}}(t) + I_{\mathrm{ex}}^{\mathrm{basal}}(t)$ is obtained.

Carbohydrates digestion and absorption. This model describes the carbohydrates catabolism to monosaccharide (mostly glucose) taking place during meal digestion, as well as intestinal absorption. The model considered here is that described in [5], where the glucose absorption rate U_G is represented by

$$U_{\mathrm{G}}(t) = \frac{D_G A_G t \exp(-t/t_{\max,G})}{t_{\max,G}^2} \tag{1}$$

being D_G the amount of carbohydrates ingested, A_G is carbohydrate bioavailability and $t_{\max,G}$ is the time-of-maximum appearance of glucose in plasma.

Insulin PK/PD and glucose metabolism. Insulin pharmacokinetics, either basal or bolus, is considered of first-order. Plasma insulin concentration, $I(t)$, is thus described as

$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = \frac{I_{\mathrm{ex}}(t)}{V_I} - k_e I(t) \tag{2}$$

where $I_{\mathrm{ex}}(t)$ is the exogenous insulin absorption rate above-described, k_e is the fractional elimination rate and V_I is the insulin distribution volume.

Plasma insulin concentration is considered to affect on glucose transport from plasma to the tissues, hepatic glucose production and peripheral glucose disposal [5]. These actions are modelled as first-order processes:

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -k_{a1}x_1(t) + k_{b1}I(t)$$
$$\frac{\mathrm{d}x_2}{\mathrm{d}t} = -k_{a2}x_2(t) + k_{b2}I(t)$$
$$\frac{\mathrm{d}x_3}{\mathrm{d}t} = -k_{a3}x_3(t) + k_{b3}I(t) \tag{3}$$

where x_1 represents the effects of insulin on glucose distribution/transport, x_2 represents the effect on glucose disposal and x_3 the effect on endogenous glucose production; k_{ai}, $i = 1, \ldots, 3$ are deactivation rate constants and k_{bi}, $i = 1, \ldots, 3$ activation rate constants. It will be considered here an alternative parameterization where $\frac{k_{b1}}{k_{a1}} = S_{IT}$, $\frac{k_{b2}}{k_{a2}} = S_{ID}$ and $\frac{k_{b3}}{k_{a3}} = S_{IE}$.

Finally, glucose metabolism is represented as the two-compartment system [5]

$$\frac{\mathrm{d}Q_1(t)}{\mathrm{d}t} = -F_{01}^c(t) - x_1(t)Q_1(t) + k_{12}Q_2(t) -$$
$$- F_R(t) + U_{\mathrm{G}}(t) + \mathrm{EGP}_0(1 - x_3(t))$$
$$\frac{\mathrm{d}Q_2(t)}{\mathrm{d}t} = x_1(t)Q_1(t) - (k_{12} + x_2(t))Q_2(t)$$
$$G(t) = \frac{Q_1(t)}{V_G}$$

where Q_1 and Q_2 represent the masses of glucose in the accessible and non-accessible compartments, k_{12} represents the transfer rate constant from the non-accessible to the accessible compartment, V_G represent the distribution volume of the accessible compartment, G is the glucose concentration and EGP_0 represents endogenous glucose production

extrapolated to the zero insulin concentration. F_{01}^c is the total non-insulin-dependent glucose disposal, and F_R is the renal glucose clearance above the glucose threshold of 9 mmolL^{-1}. Contrary to [5], these ones are modelled by the functions:

$$F_{01}^c(t) = \frac{f_{01}}{9}(G(t) - 4.5 - \sqrt{(G(t) - 4.5)^2}\,) + f_{01}$$
$$F_R(t) = \frac{0.003V_G}{2}(G(t) - 9 + \sqrt{(G(t) - 9)^2}\,)$$

Table I lists the model parameters used for the different components of the model, taken from [4], [5], patient n=2.

TABLE I

PARAMETERS OF THE GLUCORREGULATORY MODEL

Symbol	Quantity	Value	Unit
A_G	Carbohydrate (CHO) bioavailability	0.8	unitless
$t_{\max,G}$	Time-to-maximum of CHO absorption	40	min
V_I	Insulin distribution volum	0.12	L/Kg
k_e	Insulin elimination from plasma	0.138	1/min
k_{a1}	Deactivation rate	0.0157 (12)*	1/min
k_{a2}	Deactivation rate	0.0231 (27)	1/min
k_{a3}	Deactivation rate	0.0143 (6)	1/min
S_{IT}	Insulin sensitivity of distribution/transport	18.7×10^{-4} (11)	min^{-1} per mUL^{-1}
S_{ID}	Insulin sensitivity of disposal	6.1×10^{-4} (8)	min^{-1} per mUL^{-1}
S_{IE}	Insulin sensitivity of EGP	379×10^{-4} (2)	mUL^{-1}
k_{12}	Transfer rate	0.0871 (8)	1/min
f_{01}	Non-insulin-dependent glucose flux	0.0075 (2)	mmol /(kg min)
V_G	Glucose distribution volume	0.13 (1)	L/kg
EGP_0	EGP extrapoled to zero insulin concentration	0.0143 (2)	mmol /(kg min)

*Accuracy of a parameter estimate expressed as a fractional standard deviation (%).

III. INTERVAL SIMULATION

The simulation of a model with particular real values of the parameters, starting from any initial state, 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 determine a plane band bounded by two envelopes. At each time step of the simulation, the envelopes, i.e. the possible maximum and minimum values of the variable, 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. The simulation of an interval model provides intervals (ranges) which can be estimates of the envelopes. A way to compute these estimates is by means of interval arithmetic.

Interval arithmetic [7], [6] considers the whole range of possible instances represented by an interval model. The

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computations of the natural extension of a real function is done by substituting real numbers by intervals and real operations by their interval extensions. 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 $f(x) \in f_R(X)$.

In consequence, the natural extension is very useful to compute the range of a function because it guarantees on the result. Unfortunately, it does not provide the exact estimate in a 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 this paper, the interval model is studied using Modal Interval Analysis (MIA) [2], allowing to compute a tight (sometimes exact) enclosure of the envelope that includes all the 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 a such a way that the exact range is obtained). Then, the Modal Interval Library IvalDB computes the exact range. In case optimality cannot be reached, the f^* algorithm [3] is launched. This algorithm takes benefit of many optimality and coercion theorems from Modal Interval Theory to compute tight approximations of the range by using branch-and-bound techniques.

A. Carbohydrates digestion and absorption

The glucose absorption model presents uncertainties because the patients generally do not know the exact amount and composition of their meals, which they have to estimate. In addition, the absorption time depends on the patient and the composition of the meal, and therefore it is also an approximation.

It will be thus considered that $D_G = [\underline{D}_G, \overline{D}_G]$, $A_G = [\underline{A}_G, \overline{A}_G]$ and $t_{\max,G} = [\underline{t}_{\max,G}, \overline{t}_{\max,G}]$ in (1). Then, the corresponding absorption interval model is

$$
\begin{aligned}
[\underline{U}_G(t), \overline{U}_G(t)] &= \\
&= \frac{t * [\underline{D}_G, \overline{D}_G] * [\underline{A}_G, \overline{A}_G] * \exp(-t/[\underline{t}_{\max,G}, \overline{t}_{\max,G}])}{[\underline{t}_{\max,G}, \overline{t}_{\max,G}]^2}
\end{aligned}
$$

where $*$ denotes the interval product and $\exp(\cdot)$ and $(\cdot)^2$ are the interval counterparts of the corresponding real functions. As in this equation, $t_{\max,G}$ appears twice (it is multi-incident) and (1) do not verify the monotonicity conditions to obtain an optimal computation by means of optimality theorems of MIA, an optimal computation of the range of the glucose absorption rate, $[\underline{U}_G(t), \overline{U}_G(t)]$, is not possible. Then, the f^* algorithm must be used to obtain tight upper and lower envelopes of U_G.

B. Insulin pharmacokinetics and pharmacodynamics

The insulin pharmacokinetics model (2) is easy to compute as the only parameter that can be considered as interval is k_e. In this case, the computations of $I(t)$ are straightforward

using IvalDB. Insulin pharmacodynamics (3) is a more complex interval model, as uncertainty is in many parameters.

In case only insulin sensitivity parameters are considered as intervals, $S_{IT} = [\underline{S}_{IT}, \overline{S}_{IT}]$, $S_{ID} = [\underline{S}_{ID}, \overline{S}_{ID}]$ and $S_{IE} = [\underline{S}_{IE}, \overline{S}_{IE}]$, then the discrete interval model

$$
\begin{aligned}
X_1(t+1) &= X_1(t) * (1 - t * k_{a1}) + t * S_{IT} * k_{a1} * I(t) \\
X_2(t+1) &= X_2(t) * (1 - t * k_{a2}) + t * S_{ID} * k_{a2} * I(t) \\
X_3(t+1) &= X_3(t) * (1 - t * k_{a3}) + t * S_{IE} * k_{a3} * I(t)
\end{aligned}
$$

is optimal because the insulin sensibilities appear only once in each equation. As result of the interval computation, the states X_1, X_2, and X_3 will be interval states.

In case uncertainty is also considered in the deactivation parameters, $K_{ai} = [\underline{k}_{ai}, \overline{k}_{ai}]$, $i = 1, \ldots, 3$, the interval model (3) is not optimal. Upper and lower bound for X_i are obtained using the f^* algorithm.

C. Glucose subsystem.

The output of the carbohydrates digestion and absorption subsystem, U_G, as well as the computed states from the insulin subsystem, X_i, will be interval arguments of the glucose subsystem. So, even in the case uncertainty in the parameters of the glucose subsystem is not considered, it becomes an interval model and interval methods should be used to compute its evolution.

Additional parameters of the glucose system that have been considered as intervals are EGP_0, f_{01}, and k_{12}. In the general case, it is not possible to get exact computations and the f^* algorithm should be always used. Exact computations are obtained for Q_2 using IvalDB, while f^* algorithm is needed to compute Q_1

$$
\begin{aligned}
Q_1(t+1) &= -F_{01}^c(t) * t + Q_1(t) * (1 - t * X_1(t)) + \\
&\quad + t * (k_{12} * Q_2(t) - F_R(t) + U_G(t) + \\
&\quad + \text{EGP}_0 * (1 - X_3(t))) \\
Q_2(t+1) &= Q_2(t) * (1 - t * (k_{12} + X_2(t))) + \\
&\quad + t * X_1(t) * Q_1(t) \\
G(t) &= \frac{Q_1(t)}{V_G}
\end{aligned}
$$

D. Initial states.

To run the interval simulation of the whole system, initial states and inputs should be given. In this work, three days has been simulated for the given therapy. Starting from a real initial state, it will be considered that at the beginning of the third day the interval values of the states do represent the set of possible initial states the patient may have.

IV. RESULTS

To show the feasibility of the interval approach, a virtual patient with nominal parameters as described in previous sections has been considered. For this patient, the following typical one day routine has been implemented:

- Food intake: 50 gr CHO at 6:40; 17 gr CHO at 10:00; 137 gr CHO at 12:20 and 100 gr CHO at 19:30

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- Basal dosage (Protaphane$^{©}$): 8IU at 6:20 and 7 IU at 19:10
- Bolus (Actrapid$^{©}$): 5IU at 6:20; 9IU at 12:15 and 6 IU at 19:20

Different scenarios have been considered:
- Scenario 1: 10% variation in the carbohydrates digestion and absorption model parameters (D_G, A_G and $t_{\max,G}$).
- Scenario 2:
  - 2a) 10% variation in the insulin PK/PD parameters (S_{ID} and S_{IE});
  - 2b) Scenario 2a with 20% variation in the insulin PK/PD parameters;
  - 2c) Scenario 2a with 8IU instead of 9IU at 12:15.
- Scenario 3: 10% variation in both, carbohydrates digestion and absorption model parameters and insulin PK/PD parameters.

Figures 2 to 4 show upper and lower bands of the plasma gluc
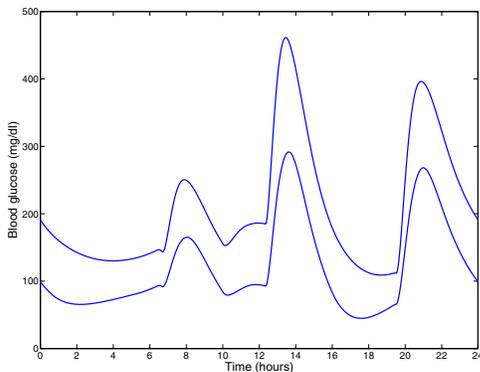
Fig. 2. Envelopes obtained for 10% variation in D_G, A_G and $t_{\max,G}$.
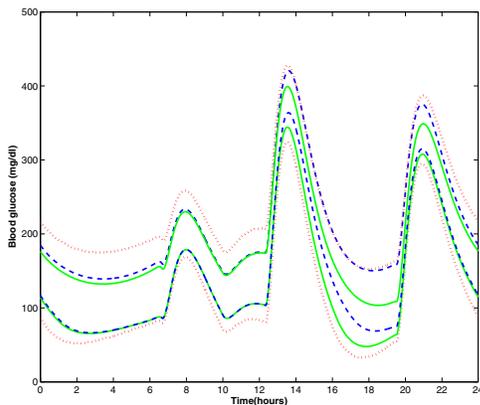
Fig. 3. Envelopes obtained for Scenarios 2a (solid line); 2b (dotted line) and 2c (dashed line).

As it may be observed, consideration of uncertainty reveals the chance of suffering a severe hypoglycemia around 5 p.m. as well as two hyperglycaemias around 2 p.m. and 9 p.m. Hypoglycaemia risk can be reduced significantly by decreasing in 1 IU the bolus dose at 12:15 without affecting too much the hyperglycaemias.

V. CONCLUSIONS AND FUTURE WORKS

Modal interval analysis has successfully been applied to the prediction of glucose excursions in patients with type 1
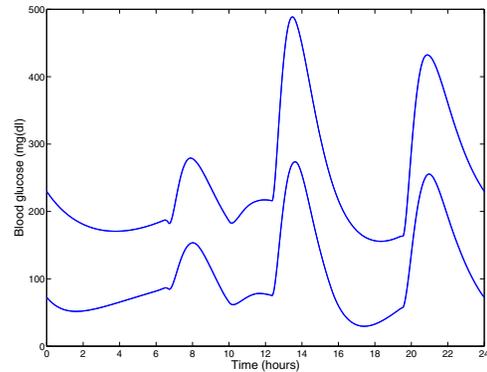
Fig. 4. Envelopes obtained for 10% variation in D_G, A_G, $t_{\max,G}$, S_{ID} and S_{IE}.

diabetes face to uncertain information. Uncertain parameters such as hepatic and peripheral insulin sensitivities as well as food intake have been considered for the prediction of the effects of a given insulin therapy on glycaemia. As result, a band containing all possible glucose excursions suffered by the patient for the given uncertainty is obtained.

By considering intra-patient variability and uncertainty in the food intake, a safer prediction of possible hyper- and hypoglycaemia episodes induced by the tested insulin therapy can be calculated, leading to a reduction in the number of false-negatives.

Currently, the methods here developed are being integrated in a model-based decision-aid system for the suggestion of bolus insulin doses and injection time which minimize the risk of postprandial hyper- and hypoglycaemia in patients with type 1 diabetes.

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