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Artificial Blood Glucose Control using a DDE Modelling Approach

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Abstract: In this paper we consider the problem of artificial blood glucose control for a type 1 diabetic using delay differential equations to model the glucose metabolism. This model is obtained by considering an adjustment of the minimal model of Bergman. In order to design a controller which can stabilize blood glucose in a safe range, the design of a robust model predictive controller is considered. The various uncertainties and disturbances are introduced through the introduction of perturbed parameters. Finally, the performances of the controller are exemplified on an approved virtual testing platform showing the good properties of the developed controller.

Keywords: robust control, adjoint model, NMPC, time delay system, type 1 diabetes

1. INTRODUCTION

Diabetes is a group of diseases marked by high levels of blood glucose resulting from defects in insulin production, insulin action or both [Control and Prevention, 2011]. For healthy people, glucose is regulated within narrow range *i.e.* in the interval $[60; 120]\text{mg.dL}^{-1}$ [diabetes control and complications trial research group, 1993]. Type 1 diabetes, which represents approximately 5% of the prognosed diabetes, is developed when the immune system has destroyed the pancreatic β cells. These cells are normally responsible for insulin secretion. Because it is the only hormone that can favor glucose storage, a patient which suffers from this disease can not self-regulate its blood glucose. If not treated, this can lead to various complications including heart diseases, blindness, nervous system diseases [Control and Prevention, 2011] ... In order to live a *normal* life, the patients require exogenous insulin which is delivered either by injection or by *continuous* subcutaneous infusion using an insulin pump. An extensive long-term study [diabetes control and complications trial research group, 1993] has demonstrated that intensive diabetes therapy , *i.e.* the cure which consists in regular insulin injection guided by frequent blood glucose monitoring, efficiently reduces the complication of type 1 diabetes.

However, despite the availability of glucose sensors which regularly provide glucose measure, the task of maintaining a safe glycemia still remains a difficult goal to achieve. In fact this is not surprising as, in the every day life, it seems complicated, if not impossible, to control one's insulin injection at such a high rate. That is why there have been considerable interests in developing an *artificial pancreas* [Nicolao et al., 2011], [Patek et al., 2012]. The aim is to use the sensor information to automatically adjust, in real-time, the insulin injection using an adequate control algorithm. To provide a potential solution, many algorithms have already been proposed (see e.g. [Bequette, 2012] for a review of the considered controller and the remaining challenge).

Even if each control approach presents its own advantages, lately, it seems that the model predictive control (MPC) approach is the more promising because of numerous attractive features such as its ability to handle constraints. When using such a controller, a model of the process is needed. It can be chosen to be either a simple transfer function (see e.g. [van Heusden et al., 2012]) or to be expressed using a state space model given by a set of ordinary differential equations (see e.g. the minimal model of Bergman [Bergman et al., 1979], the Dalla Man et al. model [Man et al., 2007] or the Sorensen model [Sorensen, 1985]).

When dealing with glucose control it has often been suggested that this problem is concerned with delays (see e.g. [Keenan et al., 2012]). It is thus quite natural that some models of the glucose metabolism use the delay differential equations (DDE) framework. Once again it is possible to distinguish between models based on transfer function (see e.g. [Abu-Rmileh and Garcia-Gabin, 2012] or [Lee et al., 2013]) and models which use a state space model (see e.g. [Li et al., 2006] or [Palumbo et al., 2011]).

Amongst the above mentioned model, the minimal model of Bergman has often been solicited has a good compromise between accuracy and simplicity (see e.g. [Kirchsteiger and del Re, 2009]). In this work we propose to reformulate this model using a discrete delay in the state in order to suppress the only state of the model which has no physical meaning. The interest of this approach is to obtain a model which is closer to the glucose metabolism and which shares the simple structure of the original model. Then, the problem of artificially controlling the blood

glucose of a type 1 diabetic is addressed by designing a controller which uses this new adjusted model. To do so, it is intended to use a formal extension of a recently designed robust model predictive controller called saddle point MPC [Penet, 2013].

This paper is organized as follows. In section 2 the retained model is presented and the control model is derived using a variational formulation of the control problem. In section 3, the design of the controller is exposed from a formal point of view. A special point on the numerical aspect is addressed. In section 4, numerical results based on simulations using a testing platform approved by the Food and Drug Administration are presented in order to show the performances and the robustness of the designed controller. The paper is concluded in section 5.

2. A DDE MODELING OF THE GLUCOSE-INSULIN METABOLISM

2.1 Model of the glucose metabolism

To consider the problem of artificial blood glucose control, it is desired to use a model of the glucose metabolism. Because of its good balance between accuracy and simplicity, the minimal model of Bergman [Bergman et al., 1981] has often been envisaged as a good candidate. This model has been built so that all the states represent quantities or concentrations except one. The latter has been introduced to model the fact that it is not insulin that ensures glucose storage but that it only initiates a sequence of action leading to glucose storage.

From a control point of view, it may be advantageous to consider an adjusted model which only use states having a physical meaning. By doing so, it is aimed at obtaining a model which is closer to the real glucose metabolism (in the sense that, in the human body, all is a concentration or a quantity). As we are not really interested in modeling the biological phenomenon which lead to glucose storage but rather in considering the delay in the insulin action, we have envisaged a model which uses delay differential equations.

Also, since a subcutaneous way of action seems more viable (see e.g. [Renard, 2008]), a diffusion process has to be modeled. Indeed, the insulin is injected under the skin but it only becomes active when it reaches the blood stream. So, if it is aimed at good control performances, it is important to consider this phenomenon. Practically, this implies that the problem of artificial blood glucose control is potentially concerned by delays in regards to the use of the subcutaneous route for the insulin injection [Hovorka, 2006]. However, it is not clear whether this diffusion is at the origin of a delay in the control sense or whether it is more at the origin of some kind of filtering. That is why, according to [Fisher, 1991], a simple first order filter has been introduced.

Finally, this leads to consider the following model of the glucose metabolism

$$\begin{aligned}
&\frac{dG}{dt} = -PG - k_0 GI(t-\tau) + D + R_a,\\
&\frac{dI}{dt} = -k_f I + b_f U,\\
&\frac{dU}{dt} = -k_s U + g,\\
&(G,I,U)(t_0+s) = (G_0,I_0,U_0)(s) \text{for all } s \in [-\tau,0],
\end{aligned} \tag{1}$$

where G is the blood glucose, I stands for the blood insulin and U is the insulin *in the skin*. The control input g stands for the injected insulin and the rate of appearance R_a stands for a glucose input, e.g. due to the digestion of a consumed meal. The parameters P, k_0, D, k_f, b_f and k_s are given positive. The discrete delay τ is assumed to be given positive and constant. The initial condition (G_0, I_0, U_0) is a function of $C([-\tau,0],\mathbb{R}^{+3})$.

In the next part, we will reformulate the previously obtained model in order to solve the problem of artificial blood glucose control by considering the design of a robust controller.

2.2 Formulation of the control model

The objective of this paper is to use the previously presented model of the glucose metabolism to tackle the problem of artificial blood glucose control. More precisely, it is desired to formulate the original control problem as the problem of tracking a known and given nominal model. The latter can either stands for a trajectory or a steady state of the system. To do so, in this section, we are interested in formulating the robust control problem using a variational formulation.

The *nominal model* corresponds to (1) where the initial condition (G_0, I_0, U_0), all the model parameters and the inputs g and R_a are assumed to be perfectly known. The state trajectory generated by this nominal model is called *nominal trajectory*.

To formulate the control problem, we begin to write the nominal model when disturbed both in states and parameters. This leads to the following disturbed model

$$\begin{aligned}
&\frac{d(x_1+G)}{dt} = -(\overline{p}+P)(x_1+G) + (D+\overline{d}) + (R_a+r_a),\\
&\quad -(\overline{k}_0+k_0)(x_1+G)(x_2(t-\tau)+I(t-\tau))\\
&\frac{d(x_2+I)}{dt} = -(\overline{k}_f+k_f)(x_2+I) + (\overline{b}_f+b_f)(x_3+U),\\
&\frac{d(x_3+U)}{dt} = -(\overline{k}_s+k_s)U + (g+f),\\
&(x_1+G, x_2+I, x_3+U)(t_0+s)\\
&\quad = \xi_0(s) + (G_0,I_0,U_0)(s)\ \forall s \in [-\tau,0],
\end{aligned} \tag{2}$$

where $\xi_0 \in \mathcal{C}([-\tau,0],\mathbb{R}^3)$. The control input f is a disturbance of the control input g. It has been introduced in order to reject the state disturbances $(x_i)_{i\in 1,2,3}$ despite the parameters disturbances $\overline{p}$, $\overline{d}$, $\overline{k}_0$, $\overline{k}_f$, $\overline{b}_f$ and $\overline{k}_s$ and the disturbance of the rate of appearance r_a. In the sequel we denote $w = \begin{pmatrix}\overline{p} & \overline{d} & \overline{k}_0 & \overline{k}_f & \overline{b}_f & \overline{k}_s & r_a\end{pmatrix}^T$ the vector of parameter disturbances.

Remark 1. *It has to be noticed that the discrete delay τ is assumed to be perfectly known.*

Finally, let us subtract the nominal model (1) from the previous disturbed model. This leads to the following control model

$$\begin{aligned}
&\frac{dx_1}{dt} = -\overline{p}(x_1+G) - \overline{k}_0(x_1+G)(x_2(t-\tau)+I(t-\tau)) + \overline{d} \\
&\quad -(P+k_0 I(t-\tau))x_1 - k_0 G x_2(t-\tau) - k_0 x_1 x_2(t-\tau) + r_a, \\
&\frac{dx_2}{dt} = -\overline{k}_f(x_2+I) + \overline{b}_f(x_3+U) - k_f x_2 + b_f x_3, \\
&\frac{dx_3}{dt} = -\overline{k}_s(x_3+U) - k_s x_3 + f, \\
&(x_1,x_2,x_3)(t_0+s) = \xi_0(s)\ \forall s \in [-\tau, 0].
\end{aligned} \tag{3}$$

The next part will be interested in formally presenting a robust MPC algorithm to consider the problem of stabilizing (3) toward the origin.

3. DESIGN OF A NONLINEAR ROBUST RECEDING HORIZON CONTROLLER

3.1 General points

In order to track a given nominal model, it is desired to control a perturbed model toward the origin. To do so, it is intended to use a recently developed saddle point MPC (SPMPC) controller. It has been proved that this controller can be used to robustly stabilized systems described by ordinary differential equation (ODE) in a sampled-data framework [Penet, 2013]. In this part we consider a formal presentation to tackle the problem of controlling systems described by delay differential equation (DDE). The control input is calculated according to the following definition.

Definition 1 (SPMPC)**.** *The saddle point model predictive control (SPMPC) consists, for a given sampling rate δ, robust control positive invariant set $\Omega_a^{f_E}$ and prediction horizon $T > \delta$, in calculating $f(t) = f_i^*(t)$ for $t \in [t_i; t_{i+1}[$ where f_i^* is computed with respect to the initial condition $x_i \in C([-\tau,0],\mathbb{R}^{n_x})$ at $t = t_i$ and the optimal disturbances w_i^*, as the optimal solution of:*

$$\begin{aligned}
&(f_i^*, w_i^*) = \arg \inf_{f\in U} \sup_{w\in W} J^{t_i}(f,w) = \arg \sup_{w\in W} \inf_{f\in U} J^{t_i}(f,w), \\
&\qquad s.t.\ z \in \Omega_a^{f_E}.
\end{aligned} \tag{4}$$

with

$$\begin{aligned}
z : [-\tau, 0] &\to \mathbb{R}^{n_x} \\
t &\to x(x_i, f, w, t_i; t_i + T + t),
\end{aligned} \tag{5}$$

where $x(x_i, f, w, t_i; t)$ stands for the state value at time t with respect to the initial condition x_i and the inputs (f, w). The cost function $J^{t_i}(f,w)$ is defined as:

$$J^{t_i}(f,w) = E(z) + \int_{t_i}^{t_i+T} F(x(x_i,f,w,t_i;s),f,w)ds, \tag{6}$$

The final cost $E : C([-\tau,0],\mathbb{R}^{n_x}) \to \mathbb{R}^+$ and the stage cost $F : \mathbb{R}^{n_x} \times \mathbb{R}^{n_g} \times \mathbb{R}^{n_w} \to \mathbb{R}$ are given.

In the ODE case, the stability results were obtained by choosing a suitable final cost and an adequate terminal state constraint. Based on the remark that it is sufficient to adjust the tools used for the usual NMPC to design a stable NMPC controller for time delay system (see e.g. [Esfanjani and Nikravesh, 2011] or [Reble and Allgöwer, 2010]), it is conjectured that by choosing an adequate final cost and terminal state constraint, it is possible to design a SPMPC controller which can robustly stabilize systems described by delay differential equations in a sampled-data framework. The aim of this paper is then to test this hypothesis by considering the problem of artificial blood glucose control when using the DDE model (3).

Inspired from the results presented in [Reble and Allgöwer, 2012], the final cost E is chosen to be a Krasovskii functional and the terminal state constraint $\Omega_a^{f_E}$ is defined by using Razumikhin argument (for more details on Krasovskii and Razumikhin functional see e.g.[Gu et al., 2002]). The idea behind these results is to introduce a final cost and a terminal state constraint which share the same meaning as for the usual ordinary differential case. Namely, the final cost is a local Lyapunov function and the terminal state constraint is a robust control positive invariant set under a feedback controller f_E (see e.g. [Blanchini, 1999] for a definition).

More precisely, the final cost $E : C([-\tau,0],\mathbb{R}^{n_x}) \to \mathbb{R}^+$, the terminal state constraint $\Omega_a^{f_E}$ and the feedback controller $f_E : C([-\tau,0],\mathbb{R}^{n_x}) \to \mathbb{R}^{n_g}$ are chosen *a priori* as follows

$$\begin{aligned}
&f_E(y) = K_0 y(0) + K_1 y(-\tau), \\
&E(y) = y(0)^T S_1 y(0) + \int_{-\tau}^{0} y(s)^T S_2 y(s) ds, \\
&\Omega_a^{f_E} = \{y \in C([-\tau,0],\mathbb{R}^{n_x}) / \max_{\theta\in[-\tau;0]} y(\theta)^T P_0 y(\theta) \le a\},
\end{aligned} \tag{7}$$

where $K_0 \in \mathbb{R}^{n_x,n_g}$ and $K_1 \in \mathbb{R}^{n_x,n_g}$. The matrices $S_1 \in \mathbb{R}^{n_x,n_x}$, $S_2 \in \mathbb{R}^{n_x,n_x}$ and $P_0 \in \mathbb{R}^{n_x,n_x}$ are symmetric definite positive.

These various elements can be computed using linear matrix inequalities and a local linear differential embedding of the system dynamic. First, for a given structure of the final cost E, the final controller f_E is computed by designing a controller which can robustly stabilize the differential inclusion. Then, the terminal state constraint $\Omega_a^{f_E}$ is computed by searching for a Lyapunov function of the closed-loop. More details on how these elements can be computed when using a SPMPC controller in order to consider the control of (3) can be found in [Penet, 2013].

In the next part we are interested in the numerical aspect which arises when it comes to solve the constrained saddle point problem (4).

3.2 Some words on the resolution

To solve the control problem given by (4), we have to consider the solution of a constrained saddle point optimization problem. To meet this objective, we propose a method which has been inspired by the augmented Lagrangian technique (see e.g. Nocedal and Wright [1999]). The idea is to substitute the original constrained saddle point problem by a sequence of unconstrained saddle point problem whose solution tends to the solution of the constrained problem. To do so, instead of optimizing the cost function J^{t_i}, we optimize a modified functional which is given as a sum between the original cost function and a penalty function

$$\mathcal{L}_A^{t_i,\mu}(f,\tilde{w}) = J^{t_i}(f,w) + \Psi^\mu(c(x(t_i+T)),\lambda_\Omega), \tag{8}$$

where

$$c(x(t_i+T)) = a - \max_{\theta\in[-\tau,0]} x(t_i+T+\theta)^T P_0 x(t_i+T+\theta), \tag{9}$$

with $x(t_i+T+\theta) = x(x_i,f,w,t_i;t_i+T+\theta)$. The penalty function Ψ^μ is given by

$$(z,\lambda) \to \Psi^\mu(z,\lambda) = \begin{cases} -\lambda z + \frac{1}{2\mu} z^2 & \text{if } z - \mu\lambda \le 0 \\ -\frac{\mu}{2}\lambda^2 & \text{if } z - \mu\lambda \ge 0 \end{cases}, \tag{10}$$

where $(z, \lambda) \in \mathbb{R}^2$. The vector of augmented disturbances $\tilde{w}$ is defined by $\tilde{w} = \left(w^T \ \lambda_\Omega\right)^T$.

The saddle point $(f_i^{*,\mu}, \tilde{w}_i^{*,\mu})$ of the unconstrained functional is characterized as follows (see e.g. [Belmiloudi, 2008]), for all $f \in U$ and for all $\tilde{w} \in \tilde{W}$ we have

$$\begin{aligned} &\int_{t_i}^{t_i+T} \left(\frac{\partial \mathcal{L}_A^{t_i,\mu}}{\partial f}(f_i^{*,\mu}, \tilde{w}_i^{*,\mu})^T (f - f_i^{*,\mu}) \right) ds \geq 0, \\ &\int_{t_i}^{t_i+T} \left(\frac{\partial \mathcal{L}_A^{t_i,\mu}}{\partial \tilde{w}}(f_i^{*,\mu}, \tilde{w}_i^{*,\mu})^T (\tilde{w} - \tilde{w}_i^{*,\mu}) \right) ds \leq 0. \end{aligned} \tag{11}$$

This means that to determine whether we have found the saddle point of the game, we need to evaluate the gradient of the functional (8). To do so we use adjoint model technique. Let us assume that the stage cost F is chosen quadratic

$$F(x, f, w) = x^T R x + f^T \alpha f - w^T Q w, \tag{12}$$

where the matrices R, Q and α are chosen symmetric definite positive.

If we choose a final cost and a terminal state constraint according to (7) then, associated to the primal problem (3), the adjoint model is given by

$$\begin{aligned} -\frac{d\tilde{x}_1}{dt} &= -\left(P + \overline{p} + (k_0 + \overline{k_0})(x_2(t-\tau) + I(t-\tau))\right)\tilde{x}_1 \\ &\quad + \sum_{k=1}^{3} \left(R_{(1,k)} + S_{2,(1,k)} \mathbb{1}_{\mathcal{I}}(t)\right) x_k, \\ -\frac{d\tilde{x}_2}{dt} &= -(k_f + \overline{k}_f)\tilde{x}_2 \\ &\quad - (k_0 + \overline{k}_0(t+\tau))(x_1(t+\tau) + G(t+\tau))\tilde{x}_1(t+\tau)\mathbb{1}_{\mathcal{J}}(t) \\ &\quad + \sum_{k=1}^{3} \left(R_{(2,k)} + S_{2,(1,k)} \mathbb{1}_{\mathcal{I}}(t)\right) x_k, \\ -\frac{d\tilde{x}_3}{dt} &= -(k_s + \overline{k}_s)\tilde{x}_3 + (b_f + \overline{b}_f)\tilde{x}_2 \\ &\quad + \sum_{i=k}^{3} \left(R_{(3,k)} + S_{2,(1,k)} \mathbb{1}_{\mathcal{I}}(t)\right) x_k, \\ \tilde{x}(t_i + T) &= 2S_1 x(t_i + T) + \nabla_x \left(\Psi^\mu(c(x(t_i + T)), \lambda_\Omega)\right), \end{aligned} \tag{13}$$

where $\mathcal{I} = [t_i + T - \tau, t_i + T]$ and $\mathcal{J} = [t_i, t_i + T - \tau]$. The notation $\mathbb{1}_{\mathcal{I}}(t)$ denotes the indicator function.

Remark 2. *It is worth noticing that the adjoint problem is well-defined. Indeed the previous differential equations are characterized by a terminal condition. Thus the differential problem has to be solved in a backward fashion. For $t \notin \mathcal{J}$ the adjoint model is given by a simple ODE and so the corresponding problem is well defined. When $t \in \mathcal{J}$, the value of $\tilde{x}_1(t+\tau)$ for $t \in [t_i + T - 2\tau, t_i + T - \tau]$ is given by the solution of the previous ODE and so we can solve the corresponding DDE.*

Then, assuming that the matrix Q is diagonal, the following expression of the gradient of $\mathcal{L}_A^{t_i,\mu}$ is deduced

$$\frac{\partial \mathcal{L}_A^{t_i,\mu}}{\partial f}(f, \tilde{w}) = \tilde{x}_3 + \alpha f,$$

$$\frac{\partial \mathcal{L}_A^{t_i,\mu}}{\partial \tilde{w}}(f, \tilde{w}) = \begin{pmatrix} -\tilde{x}_1(x_1 + G) - Q_{(1,1)}\overline{p} \\ \tilde{x}_1 - Q_{(2,2)}\overline{d} \\ \tilde{x}_1 - Q_{(3,3)}\overline{r}_a \\ -\tilde{x}_1(x_1 + G)(x_2(t-\tau) + I(t-\tau)) \\ -Q_{(4,4)}\overline{k}_0 \\ -\tilde{x}_2(x_2 + I) - Q_{(5,5)}\overline{k}_f \\ \tilde{x}_2(x_3 + U) - Q_{(6,6)}\overline{b}_f \\ -\tilde{x}_3(x_3 + U) - Q_{(7,7)}\overline{k}_s \\ \dfrac{\partial \Psi^\mu}{\partial \lambda}(c(x(t_i + T)), \lambda_\Omega) \end{pmatrix}, \tag{14}$$

where x is the solution of (3) with initial condition ξ_0 under the influence of the couple control disturbances (f, w) and $\tilde{x}$ is the solution of (13) according to x.

Using these expressions it becomes possible to find the saddle point $(f_i^{*,\mu}, \tilde{w}_i^{*,\mu})$ of the unconstrained optimization problem characterized by (8). Then, by reducing the value of the parameter μ and starting from the optimal solution $(f_i^{*,\mu}, \tilde{w}_i^{*,\mu})$ obtained for the previous larger value of μ, it becomes possible to find iteratively the solution of the original constrained problem (4).

Remark 3. *One interest of this approach is that the considered numerical scheme has the same complexity as for the ODE case. Indeed, to control a system modeled by DDE in a sampled-data framework, we just have to consider the integration of a primal and a dual problem. Then, according to the resulting state trajectories, we obtain an expression of the gradient of the criterion that has to be optimized. Finally, using any gradient based algorithm, we can solve the robust control problem.*

4. NUMERICAL RESULTS

Before further proceeding with simulations, let us recall that the classical cure of a type 1 diabetic can be split into two parts: the basal term which consists in the constant injection of small quantity of insulin and whose objective is to stabilize blood glucose in a safe interval (usually set to $[70, 140]\text{mg.dL}^{-1}$) and the bolus part which consists in injecting important quantity of insulin in a short lapse of time to counter sudden blood glucose increase, e.g. due the consumption of a meal. For control purpose we will only be interested in controlling the basal component of the cure (see e.g. [diabetes control and complications trial research group, 1993]).

4.1 Simulation setting

In order to test the interest of the proposed approach, simulation has been realized on a virtual testing platform (Uva/Padova T1DM metabolic simulator the distributed version [Kovatchev et al., 2009]). The numerical simulation consists in a day with three meals according to the following scenario

- $t = 0h$ The initial blood glucose is set at 100mg.dl^{-1}. The observer is switched on.
- $t = 2h$ The controller is switched on.
- $t = 7h$ The patient eats a meal of 25g.
- $t = 12h$ The patient eats a meal of 70g.
- $t = 20h$ The patient eats a meal of 80g.
- $t = 35h$ The simulation is ended.

Adult	% $G \in [70;140]$		$\min G$ mg.dL^{-1}		$\max G$ mg.dL^{-1}	
	Std	SPMPC	Std	SPMPC	Std	SPMPC
1	70	83	60	83	160	163
2	89	92	87	80	148	144
3	99	96	83	85	141	149
4	93	91	75	80	178	187
5	96	94	81	84	146	149
6	80	77	84	87	174	186
7	100	93	77	81	134	153
8	81	100	60	82	127	134
9	69	71	70	73	187	183
10	80	80	86	84	176	179

Table 1. Simulation results using the UVA/ Padova testing platform, injection of 75% of the optimal bolus

Adult	% $G \in [70;140]$		$\min G$ mg.dL^{-1}		$\max G$ mg.dL^{-1}	
	Std	SPMPC	Std	SPMPC	Std	SPMPC
1	61	93	39	77	147	155
2	86	100	66	76	125	131
3	92	100	61	80	117	134
4	76	95	65	78	155	170
5	72	100	57	82	121	130
6	70	94	58	86	132	155
7	76	100	63	76	108	126
8	45	100	38	79	114	129
9	67	85	27	70	159	164
10	75	91	59	77	151	158

Table 2. Simulation results using the UVA/ Padova testing platform, injection of 125% of the optimal bolus

It is assumed that each meals are regulated via injection of 75% or 125% of the optimal bolus (according to the insulin to carbohydrate ratio determined by the physician). The information concerning the real meal size and the bolus are provided when the corresponding event occurs.

The stage cost F is chosen quadratic (12) with

$$R = \text{diag}\left(\frac{1}{G_{eq}^2}, \frac{1}{I_{eq}^2}, 0\right), \ \alpha = \frac{1}{u_{eq}^2},$$
$$Q = \text{diag}\left(\frac{1}{(P+10^{-10})^2}, \frac{1}{D^2}, \frac{1}{k_0^2}, \frac{1}{k_f^2}, \frac{1}{b_f^2}, \frac{1}{k_s^2}\right), \quad (15)$$

where $I_{eq} = \dfrac{D - PG_{eq}}{k_0 G_{eq}}$ and $u_{eq} = \dfrac{k_s k_f}{b_f} I_{eq}$.

The simulation concerns all the adults of the trial version of the testing platform. The delay τ is identified for each patient. The parameters of the model have been identified with an assumed accuracy of $\pm 30\%$ using optimal control techniques. The prediction horizon, in minutes, has been set to $\max(300, 5\tau)$. To consider the asymmetric control objective, the supplementary (soft) state constraint $G \geq 80\text{mg.dL}^{-1}$ has been added in the optimization problem. The control objective is to robustly stabilize the blood glucose at $G_{eq} = 100\text{mg.dL}^{-1}$. Thus the nominal model is defined as the steady state corresponding to a blood glucose value of $G = G_{eq}$. Also this implies that the meal information is fully given in the variationnal model. The observer is an adjusted EKF filter for DDE [Raff and Allgöwer, 2006].

To assess the controller performances, we introduce the following metrics: % $G \in [70;140]$ the percentage of time spent in the interval $[70;140]\text{mg.dL}^{-1}$, $\min G$ the minimal value of blood glucose and $\max G$ the maximal value of blood glucose. All metrics are computed when the loop is closed. To show the interest of dynamically adjusting the basal, the simulation are also undergone when using the standard cure (Std), *i.e.* the basal value is kept constant equal to u_{eq}.

4.2 Simulation results

The simulation results for all adults for a bolus corresponding to 75% of the optimal bolus and 125% of the optimal bolus can be seen on table 1 and 2 respectively. The glucose trajectory and the corresponding control input for adult 9 can be seen on fig.1.

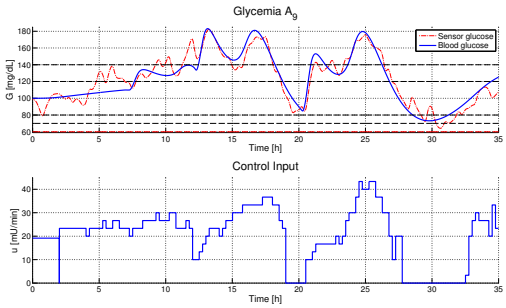

Fig. 1. Simulation for adult 9, injection of 75% of the optimal bolus

It can be seen that for all adults, and for all kind of bolus, when using our SPMPC controller, no hypoglycemia events occur and the time spent in hyperglycemia state is small enough such that it does not lead to heavy trauma. Furthermore, the percentage of time spent in the target is relatively good. Also, the control behavior is safe in the sense that the control actions consist in small variations of the insulin dose. This is in agreement with the retained control objective which is to design a control law able to handle the basal part of the cure. Also when comparing our controller with the standard cure, the interest of dynamically adjusting the basal can be clearly seen. Especially when we consider the results given by table 2 where for the standard cure 6 adults have been subject to at least one hypoglycemia event whereas for the SPMPC controller none have to be deplored.

5. CONCLUSION

The problem of blood glucose control is a challenging problem which gathers many control difficulties. To tackle this problem we have considered a new model of the glucose metabolism which uses delay differential equations. This model has been obtained by considering a modified version of the minimal model of Bergman. Then the control problem has been considered by designing a robust model predictive controller which considers the full nonlinear model. A special point on the numerical issue has been stressed. It has been shown how a constrained saddle point problem can be solved by considering an augmented Lagrangian technique. The interest of this approach is that the numerical scheme shares the same numerical complexity as for the ODE case. Finally, simulation on a FDA approved testing platform have shown the interest

of the retained approach. For all adults, the blood glucose is regulated in a safe interval and low blood glucose are avoided even in case the bolus is over estimated.

For further works, in regards to the positive results obtained in this paper and in order to obtain a better characterization of the control performances, it is worth considering the theoretical aspect of the extension of the SPMPC controller to control time delay systems. From a more practical point of view it can be interesting to design an algorithm which can be used to control the remaining part of the classical cure (*i.e.* the bolus part of the cure) and to consider the identification problem of a reliable model when using clinically realistic experimental data. Also, because the testing platform is still far to accurately model a type 1 diabetic, if it is desired to have a more rigorous proof that the considered algorithm can bring a potential solution, a practical validation thanks to clinical studies is required.

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