A Robust Receding Horizon Control Approach to Artificial Glucose Control for Type 1 Diabetes

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Abstract: The problem of controlling the blood glucose value of a patient suffering from type 1 diabetes is considered. The proposed strategy consists in designing a robust nonlinear model predictive controller based on a minimal nonlinear model. The various uncertainties and disturbances are introduced through the use of a variational model. The control problem is then expressed as a constrained game type minimax optimization problem. The choice of a final cost which ensures good stability properties are detailed. The performances of the controller are exemplified on a virtual testing platform showing its good properties.

Keywords: robust control, adjoint model, NMPC, type 1 diabetes

1. INTRODUCTION

Insulin is a hormone that favors the storage of sugar from blood to liver or muscles. Thus, combined with the action of other hormones, a tight blood glucose control is possible. Type 1 diabetes is an autoimmune disease which leads to the destruction of the pancreas cells responsible for insulin secretion. As it is the only hormone which can lower the blood glucose rate, diabetes has for immediate consequence the impossibility for the body to self-regulate its blood sugar level. This can lead to severe complications whether in the case of high blood glucose or low blood glucose.

So far, the best cure to this disease consists in regular self-injection of insulin. The adequate dose is determined using a measure of the current blood glucose value and others *a priori* knowledge (e.g. future meal consumption or expected exercise). This treatment is relatively simple and theoretically sufficient to ensure nearly normal life conditions. The problem is that, practically, it is quite difficult to master the process in every circumstances as it can be difficult to quantify the effect of some phenomena (e.g. a metabolic disorder due to a sudden stress).

In order to improve and ease the cure, many devices have been designed. They range from the continuous glucose sensors, which regularly provide blood glucose value, to the insulin pumps, which enable to inject small quantity of insulin. Currently the research focus on designing a control algorithm which can combine these two devices to design what is often called an *artificial pancreas*.

Many control strategies have been proposed [B.W.Bequette, 2012], such as PID controllers [M.A.Jaradat and Y.Sardahi, 2012, X.Gao and Y.Wang, 2012], controllers which make use of fuzzy logic or/and neural techniques [B.S.Leon et al., 2012, K.Zarkogianni et al., 2011], run-to-run algorithms [C.Owens et al., 2006, D.U.Campos-Delgado et al., 2008], sliding mode controllers [A.Abu-Rmileh et al., 2010, W.Garcia-Gabin et al., 2008] or model predictive control (MPC) controllers [A.Abu-Rmileh and W.Garcia-Gabin, 2010, F.J.DoyleIII, 2012, L.Magni et al., 2011, van Heusden et al., 2012]. Lately, the MPC approach has been favored because of numerous attractive features, such as its ease to deal with constraints or to give the possibility to anticipate on known disturbances. Furthermore, it is useful to overcome physiological delays due to the use of the subcutaneous route for both the injection of insulin and the glucose measurement [R.Hovorka, 2006].

This paper considers the design of a nonlinear sampled data saddle point MPC controller which will explicitly consider the potentially bad model and the intra patient variability, *i.e.* the various internal change in the patient due to the various situation that can arise in a normal everyday life. The classical cure is split into two components. One aims at stabilizing the blood glucose value in a safe range (basal component), the other aims at rejecting the major disturbances due to a meal consumption (bolus component). In this work, we focus on the basal part. The idea is to adapt it in real time to cope with unexpected event or to recover from bad boluses computation. This is opposed to run-to-run algorithms which use sparse measures and make some post-processing to compute a new basal.

This paper is organized as follows. In section 2 the retained model is presented and the control model is derived. In section 3, the design of the controller is exposed. In section 4, a special point on the final cost, which enables one

to ensure the stability of the controller, is stressed. In section 5, numerical results based on simulation on virtual patients are presented in order to show the performances and the robustness of the designed controller. The paper is concluded in section 6.

2. CONTROL MODEL OF TYPE 1 DIABETES MELLITUS

2.1 Model of glucose metabolism

Glucose metabolism is a nonlinear process, subject to various perturbations (e.g. practice of an exercise, meal consumptions, ...) which makes it really difficult to model. That is why, to derive a model, many assumptions have to be done. The most common are to neglect the effect of all hormones but insulin, see e.g. the model of [R.N.Bergman et al., 1979], [R.Hovorka et al., 2004] or [Man et al., 2007]. The control objective is to design a sampled-data saddle point MPC controller based on a model identified for each patient. Due to computation burden and identification difficulties, it is desirable to retain the simplest model. In addition, we believe that the nonlinear and time continuous aspects of the glucose metabolism are of prime importance. This leads us to work with a modified version of the minimal model of Bergman [R.N.Bergman et al., 1979]:

$$\begin{aligned}
&\frac{dG}{dt} = -P_1(G - G_b) - XG + d(t),\\
&\frac{dX}{dt} = -P_2X + P_3(I - I_b),\\
&\frac{dI}{dt} = -k_fI + b_fU_1,\\
&\frac{dU_1}{dt} = -k_sU_1 + u(t),\\
&(G, X, I, U_1)(t = t_0) = (G^{(0)}, X^{(0)}, I^{(0)}, U_1^{(0)}),
\end{aligned} \tag{1}$$

where $P_1, P_2, P_3, k_f, b_f, k_s, G_b$ and I_b are positive model parameters, $d(t)$ is a glucose flow input due to a meal consumption and $u(t)$ is the insulin flow input. The state (G, X, I, U_1) respectively stands for the blood glucose, a description of how insulin fixes itself on adequate receptors, the blood insulin and the insulin in the *skin*. The state U_1 has been added to take into account that a subcutaneous mode of action seems more viable [E.Renard, 2008]. For positive model parameters and for bounded inputs, the state remains bounded.

2.2 Formulation of the variational model

The various uncertainties on the system are introduced through time varying parameters. The aim of the controller becomes to regulate the perturbed system around a trajectory generated by a perfectly known nominal model. This leads to express the control problem as a variational control problem.

In the sequel, the *nominal model* corresponds to (1) where all the parameters are assumed to be perfectly known. The trajectory generated by the nominal model for a given initial condition $(G^{(0)}, X^{(0)}, I^{(0)}, U_1^{(0)})$, a given glucose flow profile $d(t)$ and a given insulin flow $u(t)$ is called *nominal trajectory*.

The aim of the controller is to compute a "good" control input such that the system tracks the nominal trajectory despite various disturbances. To obtain the variational problem, we begin to write the nominal model when disturbed both in states and parameters. This leads to the following disturbed system:

$$\begin{aligned}
&\frac{d(x_1 + G)}{dt} = -(\bar{p}_1 + P_1)(x_1 + G - G_b)\\
&\qquad - (x_2 + X)(x_1 + G) + (d(t) + \tilde{d}(t)),\\
&\frac{d(x_2 + X)}{dt} = -(\bar{p}_2 + P_2)(x_2 + X)\\
&\qquad + (\bar{p}_3 + P_3)(x_3 + I - I_b),\\
&\frac{d(x_3 + I)}{dt} = -(\bar{k}_f + k_f)(x_3 + I) + (\bar{b}_f + b_f)(x_4 + U_1),\\
&\frac{d(x_4 + U_1)}{dt} = -(\bar{k}_s + k_s)(x_4 + U_1) + (f + u(t) + \tilde{u}(t)),\\
&(G + x_1, X + x_2, I + x_3, U_1 + x_4)(t = t_0) =\\
&\qquad (G^{(0)}, X^{(0)}, I^{(0)}, U_1^{(0)}) + \chi^{(0)}.
\end{aligned} \tag{2}$$

where $\chi^{(0)} = (\chi^{(1,0)}, \chi^{(2,0)}, \chi^{(3,0)}, \chi^{(4,0)})$. The parameters G_b and I_b correspond to an assumed known and given equilibrium state of the patient and so are not disturbed.

Notice that the inputs have been split into two terms. This can be done as a way to parametrize the nominal model, *i.e.* the reference the controller has to track. The variational model is obtained by subtracting the nominal model (1) from the previous disturbed model:

$$\begin{aligned}
&\frac{dx_1}{dt} = -\bar{p}_1(x_1 + G - G_b) - x_1(P_1 + X)\\
&\qquad - x_2G - x_1x_2 + \tilde{d}(t),\\
&\frac{dx_2}{dt} = -\bar{p}_2(x_2 + X) + \bar{p}_3(x_3 + I - I_b)\\
&\qquad - P_2x_2 + P_3x_3,\\
&\frac{dx_3}{dt} = -\bar{k}_f(x_3 + I) + \bar{b}_f(x_4 + U_1) - k_fx_3 + b_fx_4,\\
&\frac{dx_4}{dt} = -\bar{k}_s(x_4 + U_1) - k_sx_4 + f + \tilde{u}(t),\\
&(x_1, x_2, x_3, x_4)(t = t_0) = \chi^{(0)}.
\end{aligned} \tag{3}$$

In the sequel, we note w the vector of disturbances $(\bar{p}_1, \bar{p}_2, \bar{p}_3, \bar{k}_f, \bar{b}_f, \bar{k}_s)^T$ and $\chi^{(i)}$ the value of the initial condition at $t = t_i$. The state value $x(t) = (x_1, x_2, x_3, x_4)(t)$ at time $t \geq t_i$ yielded by the integration of (3), under the control f, disturbances w and initial condition $\chi^{(i)}$ is denoted by $x(\chi^{(i)}, f, w, t_i; t)$.

3. DESIGN OF A NONLINEAR ROBUST RECEDING HORIZON CONTROLLER

3.1 A saddle point model predictive control approach

Due to the numerous uncertainties in glucose metabolism, the objective consists in robustly stabilizing blood glucose in a safe interval ($[70; 140]$mg/dL), reducing high glycemia (over 180mg/dL) and avoiding low glycemia (under 60mg/dL). To reach this objective, we focus on robust receding horizon strategies. Taking benefit from the simple structure of the retained model, we transform robust

stability and performance problem into constrained game-type minimax optimization problem and in turns transform these into unconstrained one following the methodology developed by [A.Belmiloudi, 2008].

The aforementioned algorithm provides, for a given initial condition, a couple of optimal control and disturbances trajectories for a given time horizon $T > 0$. This algorithm is then embedded in a receding horizon framework leading to the classical MPC controller algorithm:

(1) Compute an optimal couple control disturbances $(f_i^*(t), w_i^*(t))$ defined for all $t \in [t_i; t_i + T[$, on the basis of the initial condition $\chi^{(i)}$ available at $t = t_i$,
(2) Apply $u(t)+f_i^*(t)$ in an open loop fashion on $[t_i; t_{i+1}[$,
(3) Obtain a new initial condition $\chi^{(i+1)}$ at $t = t_{i+1}$, go to first step with $i = i + 1$.

It is implicitly assumed that $t_{i+1} - t_i < T$ and that the computation time are negligible with respect to the sampling time $t_{i+1} - t_i$. Notice that the proposed control algorithm does not require a fixed sampling rate. Simply, the saddle point MPC controller yields a continuous time control law (associated to a continuous time disturbance) which is regularly computed, as the solution of a saddle point optimization problem, on the basis of sampled-data.

3.2 Robust control and adjoint model

If we note (f_i^*, w_i^*) the optimal solution of the control problem for an initial condition $\chi^{(i)} \in \mathbb{R}^{n_x}$ and a terminal constraint Ω, then the optimal couple solution is defined as a solution of the following saddle point optimization problem:

$$\begin{aligned}(f_i^*, w_i^*) &= \arg \inf_{f\in U_{ad}} \sup_{w\in W_{ad}} J^{t_i}(f, w)\\ &= \arg \sup_{w\in W_{ad}} \inf_{u\in U_{ad}} J^{t_i}(f, w),\\ &s.t.\ (3) \text{ with } x(t_i) = \chi^{(i)} \text{ in a given set},\\ &x(\chi^{(i)}, f, w, t_i; t_i + T) \in \Omega,\end{aligned} \tag{4}$$

where Ω is a robust positive control invariant set (see e.g. [F.Blanchini, 1999] for a definition), U_{ad} is the set of admissible control and W_{ad} is the set of admissible disturbances. These sets are assumed to be given non-empty, closed, convex and bounded subspace of $L^2(I)$ where I is an interval of length T. The cost function J^{t_i} is defined as follows:

$$\begin{aligned}J^{t_i}(f, w) &= E(x(\chi^{(i)}, f, w, t_i; t_i + T) - x_{obj}(t_i + T))\\ &+ \int_{t_i}^{t_i+T} F(x(\chi^{(i)}, f, w, t_i; s) - x_{obj}(s), f, w)ds,\end{aligned} \tag{5}$$

where $x_{obj} = (x_{obj,1}, x_{obj,2}, x_{obj,3}, x_{obj,4})$ is the prognostic trajectory and the final cost E is a positive scalar.

For simplicity reason the stage cost $F(x, f, w)$ is quadratic:

$$F(x, f, w) = \|x\|_R^2 + \|f\|_\alpha^2 - \|w\|_Q^2, \tag{6}$$

where the notation $\|x\|_R^2$ stands for $x^T Rx$. The matrices R, α and Q are symmetric positive-definite.

Notice that the solution $(f_i^*, w_i^*) \in U_{ad} \times W_{ad}$ of the optimization problem (4) verifies the following property:

$$J^{t_i}(f_i^*, w) \le J^{t_i}(f_i^*, w_i^*) \le J^{t_i}(f, w_i^*), \tag{7}$$

To obtain the appropriate optimality system (necessary conditions), which corresponds to the identification of the gradient of J^{t_i} that is necessary to develop a numerical scheme in order to solve the saddle point problem, we introduce the adjoint system as follows:

$$\begin{aligned}-\frac{d\tilde{x}_1}{dt} &= -(P_1 + \bar{p_1} + X + x_2)\tilde{x}_1\\ &\quad + 2\sum_{i=1}^{4} R_{1i}(x_i - x_{obj,i}),\\ -\frac{d\tilde{x}_2}{dt} &= -(G + x_1)\tilde{x}_1 - (P_2 + \bar{p}_2)\tilde{x}_2\\ &\quad + 2\sum_{i=1}^{4} R_{2i}(x_i - x_{obj,i}),\\ -\frac{d\tilde{x}_3}{dt} &= (P_3 + \bar{p}_3)\tilde{x}_2 - (k_f + \bar{k}_f)\tilde{x}_3\\ &\quad + 2\sum_{i=1}^{4} R_{3i}(x_i - x_{obj,i}),\\ -\frac{d\tilde{x}_4}{dt} &= (b_f + \bar{b}_f)\tilde{x}_3 - (k_s + \bar{k}_s)\tilde{x}_4\\ &\quad + 2\sum_{i=1}^{4} R_{4i}(x_i - x_{obj,i}),\\ \tilde{x}(T) &= \nabla E(x(\chi^{(i)}, f, w, t_i; t_i + T) - x_{obj}(t_i + T)),\end{aligned} \tag{8}$$

where ∇ is the gradient operator.

By using the Fréchet derivatives of the operator solution $(f, w) \longrightarrow x(\chi^{(i)}, f, w, t_i; .)$ and of the cost functional J^{t_i} we can deduce (according to the adjoint problem (8)) the following expression of the gradient of J^{t_i}:

$$\frac{\partial J^{t_i}}{\partial f}(f, w) = \tilde{x}_4 + 2\alpha f,$$

$$\frac{\partial J^{t_i}}{\partial w}(f, w) = \begin{pmatrix} -\tilde{x}_1(x_1 - G - G_b) - 2\sum_{i=1}^{6} Q_{1i}w_i \\ -\tilde{x}_2(x_2 + X) - 2\sum_{i=1}^{6} Q_{2i}w_i \\ \tilde{x}_2(x_3 - I - I_b) - 2\sum_{i=1}^{6} Q_{3i}w_i \\ -\tilde{x}_3(x_3 + I) - 2\sum_{i=1}^{6} Q_{4i}w_i \\ \tilde{x}_3(x_4 + U_1) - 2\sum_{i=1}^{6} Q_{5i}w_i \\ -\tilde{x}_4(x_4 + U_1) - 2\sum_{i=1}^{6} Q_{6i}w_i \end{pmatrix},$$

where x is the solution of (3) with initial condition $\chi^{(i)}$ under the influence of the couple control disturbances (f, w) and $\tilde{x}$ is the solution of (8).

In the unconstrained case it is possible to verify that the saddle point (f_i^*, w_i^*) is such that $\frac{\partial J^{(i)}}{\partial f}(f_i^*, w_i^*) = 0$ and $\frac{\partial J^{(i)}}{\partial w}(f_i^*, w_i^*) = 0$. For more details, particularly concerning the constrained case, see e.g. [A.Belmiloudi, 2008].

Notice that to reduce the computation time it is interesting to use a hot start defined by:

$$\tilde{f}_{i+1}(t) = \begin{cases} f_i^*(t), & \forall t \in [t_{i+1}, t_i + T[, \\ f_E(x(t)), & \forall t \in [t_i + T, t_{i+1} + T], \end{cases}$$

and

$$\tilde{w}_{i+1}(t) = \begin{cases} w_i^*(t), & \forall t \in [t_{i+1}, t_i + T[, \\ w(t) \in W_{ad}, & \forall t \in [t_i + T, t_{i+1} + T], \end{cases}$$

which uses the fact that if the system has behaved as predicted then the new optimal solution should be *near* to the previous optimal solution. The function f_E will be defined in section 4.

Given our control objectives and the considered biological system, in the sequel we choose $x_{obj}(t) = 0 \ \forall t$.

4. THE FINAL COST

One of the key issue with MPC controller is the stability property of the closed-loop. To ensure good properties of the controller, one of the classical method consists in adding a final cost and a terminal set constraint in the optimization problem, see e.g. [H.Chen and F.Allgoewer, 1998]. They are often computed by using a local polytopic linear differential inclusion (PLDI) description of the full nonlinear dynamics. This formulation is often used because it permits to use the linear matrix inequality (LMI) framework.

As for nonlinear MPC, it is proved in [M.Penet et al., 2013] that by adding a final cost and a terminal set constraint in the optimization problem, the closed-loop is stable. More precisely, it is shown that if the stage cost F is quadratic and if for all $x \in \Omega$ and for all $w \in W_{ad}$ the final cost $E : \mathbb{R}^{n_x} \to \mathbb{R}^+$ satisfies the following inequalities:

$$\begin{aligned} &a_E(\|x\|) \leq E(x) \leq b_E(\|x\|), \\ &\nabla E(x).\mathcal{G}(x, f_E(x), w) + F(x, f_E(x), w) \leq 0, \end{aligned} \tag{9}$$

where Ω is a robust positive control invariant set via the feedback control f_E, a_E and b_E are $\mathcal{K}^\infty$ functions and the model dynamics is given as follows:

$$\begin{aligned} \frac{dx}{dt} &= \mathcal{G}(x, f, w), \\ x(t_i) &= \chi^{(i)}. \end{aligned}$$

Then the state trajectory is input-to-state practically stable at each sampling instant.

In this part, it is intended to compute an adequate final cost using a local PLDI embedding.

Before further proceeding, notice that $(x, w, f) = (0, 0, 0)$ is an equilibrium point of the system (3). This implies that a local linear differential inclusion (LDI) representation of this latter is possible [S.Boyd, 1994].

The only nonlinearity of the nominal model (1) comes from the state product XG. That is why it seems interesting to use x_1 as a parameter to build the LDI representation. However, this is clearly not enough as (3) shows supplementary coupling between the state x and the parameter disturbances w. In order to simplify the problem, we suppress this coupling by enlarging the initial space of admissible disturbances and considering the product parameter disturbances/ state as simple additive disturbances. This possible because for bounded input the state is bounded.

Let us introduce $\tilde{W}_{ad} \supset W_{ad}$ such that for all $w \in \tilde{W}_{ad}$, it is possible to rewrite system (3) as:

$$\frac{dx}{dt} = A(x_1)x + B_1(x_1)w + B_2 f, \tag{10}$$

where

$$A(x_1) = \begin{pmatrix} -(P_1 + X) & -(G + x_1) & 0 & 0 \\ 0 & -P_2 & P_3 & 0 \\ 0 & 0 & -k_f & b_f \\ 0 & 0 & 0 & -k_s \end{pmatrix}, B_2 = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \end{pmatrix},$$

$$B_1(x_1) = \begin{pmatrix} -(x_1 + G - G_b) & 0 & 0 & 0 & 0 & 0 \\ 0 & -X & I - I_b & 0 & 0 & 0 \\ 0 & 0 & 0 & -I & U_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & -U_1 \end{pmatrix}.$$

For bounded control input, the state remains bounded. So, there exists two constants $\underline{x}_1$ and $\bar{x}_1$ such that $-\infty < \underline{x}_1 < \bar{x}_1 < +\infty$ and if $\chi_1^{(i)} \in [\underline{x}_1; \bar{x}_1]$ then for all $t \geq t_i$ we have $x_1(\chi^{(i)}, f, w, t_i; t) \in [\underline{x}_1; \bar{x}_1]$. Using (10), it is deduced that, locally, (3) is equivalent to the following PLDI:

$$\frac{dx}{dt} = \sum_{i=1}^{4} \beta_i(t) \left(A_i x + B_{1,i} w + B_2 f \right). \tag{11}$$

where $A_1 = A_2 = A(\underline{x}_1)$, $A_3 = A_4 = A(\bar{x}_1)$, $B_{1,1} = B_{1,3} = B_1(\underline{x}_1)$, $B_{1,2} = B_{1,4} = B_1(\bar{x}_1)$, for all $i \in \{1, \ldots, 4\}$ and for all $t \geq t_i$ $\beta_i(t) \geq 0$ and $\sum_{i=1}^4 \beta_i(t) = 1$.

If we write the second inequality on the final cost (9) for system (11) with the retained stage cost F (6), we obtain the following inequality :

$$\begin{aligned} \sum_{i=1}^{4} \beta_i(t) (\nabla E(x)^T &\left(A_i x + B_{1,i} w + B_2 f_E \right) \\ &+ \|x\|_R^2 + \|f_E\|_\alpha^2 - \|w\|_Q^2) \leq 0. \end{aligned} \tag{12}$$

Theoretically any feedback controller $f_E(x)$ which is such that a set Ω is robust control invariant under this controller is admissible. For control purpose, we have retained a quasi-infinite control strategy [H.Chen and F.Allgoewer, 1998]. This implies that we are not interested in finding efficient controller but rather in finding a simple one. That is why we will look for a linear state feedback $f_E(x) = Kx$. The main advantage is that it becomes possible to search for a quadratic final cost , *i.e.* $E(x) = x^T S x$ where S is symmetric, definite, positive. The main disadvantage is that the terminal set is possibly small. Using the retained form of f_E and E, the inequality (12) is rewritten as follows:

$$\begin{aligned} \sum_{i=1}^{4} \beta_i(t) [2x^T S &\left((A_i + B_2 K)x + B_{1,i} w \right) \\ &+ x^T R x + \alpha x^T K^T K x - w^T Q w] \leq 0. \end{aligned} \tag{13}$$

Inequality (13) has to hold everywhere on the PLDI so in particular at each vertex. So for $i \in \{1, \ldots, 4\}$ we have to solve in S and K the following inequalities:

$$\begin{aligned} &2x^T S \left((A_i + B_2 K)x + B_{1,i} w \right) \\ &+ x^T \left(R + \alpha K^T K \right) x - w^T Q w \leq 0. \end{aligned}$$

And so, using matrix notation, we have:

$$\begin{pmatrix} x \\ w \end{pmatrix}^T \Big[\begin{pmatrix} 2S(A_i + B_2K) & SB_{1,i} \\ * & -Q \end{pmatrix} + \begin{pmatrix} R + K^T \alpha K & 0 \\ 0 & 0 \end{pmatrix} \Big] \begin{pmatrix} x \\ w \end{pmatrix} \leq 0.$$

Notice that we have:

$$\begin{pmatrix} -(R + K^T \alpha K) & 0 \\ 0 & 0 \end{pmatrix} = \begin{pmatrix} R^{\frac{1}{2}} & K^T \alpha^{\frac{1}{2}} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} -I_{n_x} & 0 \\ 0 & -I_{n_u} \end{pmatrix} \begin{pmatrix} R^{\frac{1}{2}} & 0 \\ \alpha^{\frac{1}{2}} K & 0 \end{pmatrix},$$

where I_n stands for the n-dimensional identity matrix. The exponent $\frac{1}{2}$ indicates that we consider the square root of the corresponding matrix (well defined because we consider positive definite matrices).

By introducing the notation $\bar{S} = S^{-1}$ and $Y = K\bar{S}$ and using the Schur complement, it is deduced that the solution of an inequality on a vertex is given by the solution in $\bar{S}$ and Y to the following LMI:

$$D_i = \begin{pmatrix} M(\bar{S}, Y) & B_{1,i} & \bar{S}R^{\frac{1}{2}} & Y^T \alpha^{\frac{1}{2}} \\ * & -Q & 0 & 0 \\ * & * & -I_{n_x} & 0 \\ * & * & * & -I_{n_u} \end{pmatrix} \leq 0.$$

where $M(\bar{S}, Y) = A_i\bar{S} + \bar{S}A_i^T + B_2Y + Y^TB_2^T$.

And so, using classical tools, e.g. the LMI lab of Matlab [Gahinet et al., 1995], it is possible to solve the final cost problem by solving the following LMI (in S and K):

$$\begin{pmatrix} D_1 & 0 & 0 & 0 \\ 0 & D_2 & 0 & 0 \\ 0 & 0 & D_3 & 0 \\ 0 & 0 & 0 & D_4 \end{pmatrix} \leq 0.$$

The supplementary constraints on the state and control input are considered using the same methodology as in [W.-H.Chen et al., 2001].

5. *IN SILICO* VALIDATION

The proposed approach is tested thanks to numerical simulation on a virtual patient testing platform (Uva/Padova T1DM metabolic simulator the distributed version [B.P.Kovatchev et al., 2009]). The simulation concerns all the 10 adults of the trial version. It is assumed that for each patient the model has been identified (using Matlab toolbox). The disturbances on the parameters are assumed to belong to an interval of $\pm 10\%$ around the nominal value of the corresponding parameter. As the measure only provides the glucose value, an Unscented Kalman Filter is used to estimate the state (see e.g. [J.Dunik et al., 2012]). The sampling time on the input is set to 5 min and on the output is set to 15min.

The numerical simulation aimed at testing the designed controller for a day with three meals. The glucose flow input is computed thanks to a second order model whose parameters are identical for all adults. These informations (meal carbohydrate (CHO) quantity and injected bolus) are provided to the observer and the controller at the instant the events occur (no anticipatory behavior). The considered scenario is:

- At $t = t_0$ the observer is switched on,

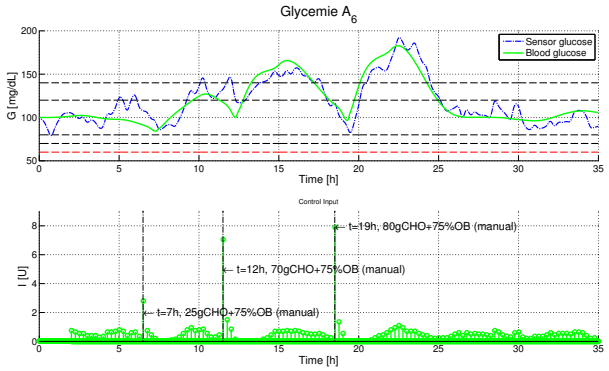

Fig. 1. Simulation results for Adult 6

Adult	% $G \in [70; 140]$	$\min G$ mg.dL^{-1}	$\max G$ mg.dL^{-1}
1	100	71	140
2	84	91	164
3	85	88	203
4	90	78	169
5	87	97	154
6	77	84	183
7	97	80	146
8	100	80	123
9	78	67	169
10	79	88	165

Table 1. Synthesis of numerical simulation

- At $t = t_0 + 2$h the controller is switched on,
- At $t = t_0 + 7$h the patient eats a meal of $25g$CHO,
- At $t = t_0 + 12$h the patient eats a meal of $70g$CHO,
- At $t = t_0 + 19$h the patient eats a meal of $80g$CHO,
- At $t = t_0 + 35$h the simulation is ended.

All meals are assumed to be self-regulated by the patient with a bolus of 75% the optimal dose. The controller objective is set to the equilibrium point corresponding to a blood glucose of 100mg/dL (*i.e.* in (2) $\tilde{d}$ and $\tilde{u}$ respectively stands for the complete glucose flow and injected bolus). In order to consider that for a given patient it is quite difficult to tune the controller parameters, all simulation have been undergone with the same tuning. To consider the non symetric objective (*i.e.* hypoglycemia are more dangerous), the soft constraint $x_1 \geq x_{1,min}$ has been added in the optimization problem (4).

The table 1 summarizes the simulation results for all adults. The envisaged scenario favors a safety aspect. Indeed, by assuming that the bolus is underestimated, the hypoglycemia risk is reduced. However, such a strategy implies an increasing risk of hyperglycemia. Furthermore, the controller has not been optimized for each patient in order to be closed to realistic cases. Nevertheless, the control algorithm safely and robustly stabilizes the patient blood glucose. It can be seen on fig.1, that even for patient 6, whose percentage in the target zone is the lowest, the controlled behavior is satisfactory (at least from a medical point of view). Despite the noise in measure, his glycemia is stabilized.

6. CONCLUSION

Blood glucose control is an extremely challenging problem as it accumulates many difficulties. The proposed control strategy consists in applying a robust controller in a

receding horizon fashion. It has been developed using a modified version of the minimal model of Bergman. The main interest is that stability and robustness aspects have been studied with the full nonlinear model and the various constraints on control input have been explicitly handled. The controller has then be tested on a virtual patient simulator approved by the FDA.

The future development of this research consist in assessing the controller performances in clinical study. Furthermore the numerical simulation have shown that a *good* digestion model is necessary if it is desired to smartly reject their effects (e.g. by considering a time varying target). It is also interesting to consider an algorithm to automatically and safely optimize the controller performances for a given patient.

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