Optimal H^∞ Insulin Injection Control for Blood Glucose Regulation in Diabetic Patients

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***Abstract*—The theory of H^∞ optimal control has the feature of minimizing the worst-case gain of an unknown disturbance input. When appropriately modified, the theory can be used to design a "switching" controller that can be applied to insulin injection for blood glucose (BG) regulation. The "switching" controller is defined by a collection of basic insulin rates and a rule that switches the insulin rates from one value to another. The rule employed an estimation of BG from noisy measurements, and the subsequent optimization of a performance index that involves the solution of a "jump" Riccati differential equation and a discrete-time dynamic programming equation. With an appropriate patient model, simulation studies have shown that the controller could correct BG deviation using clinically acceptable insulin delivery rates.**

***Index Terms*—Dynamic programming, H-infinity control, hybrid dynamical systems, insulin infusion, jump Riccati differential equation, optimal control.**

I. Introduction

THE PROBLEM of closed-loop blood glucose (BG) level regulation has been a subject of investigation for decades, with studies conducted both in the mathematical (see, e.g., [1]–[3], etc) and empirical framework (see, e.g., [4]).

While the empirical framework involved clinical experience and knowledge, mathematical framework used mathematical models (that describe the intrinsic glucose regulation performed by the endocrine pancreas) to devise appropriate schemes for the regulation of BG. Of particular interest is the theory of H^∞ control, which has a distinctive feature of minimizing the worst-case gain for an arbitrary unknown disturbance. H^∞ control approach has proved to be a very powerful robust control design technique in modern control engineering (see, e.g., [5] and [6]). The problem of clinical BG control fits into the H^∞ control framework because the glucose-insulin dynamics of the patient can be considered as a continuous-time system with unknown disturbance input (e.g., meal). However, standard linear H^∞ control theory is not applicable, because of the constraints generally found in the clinical environment. Particular to BG regulation via the intravenous insulin infusion route, clinical practice only infused insulin from a bounded set of rates, in fixed step size within the range, and at set intervals. To address the constraints, the results and ideas of [7], [8] were applied to extend the H^∞ control theory to the nonlinear case of switched output feedback controllers.

In this paper, the design of an optimal H^∞ insulin injection "switching" controller is described. The controller is defined by a collection of given insulin infusion rates which are called basic control vectors, and the control strategy is a rule for switching from one basic control vector to another. The goal of the control is to achieve a level of performance defined by an integral performance index similar to the requirement in standard H^∞ control theory (see,, e.g., [5], [6], and [8]). The switching rule is computed by solving a Riccati equation of the game type, and a discrete dynamic programming equation. Since dynamic programming equations and H^∞ type Riccati equations are well known in modern H^∞ control theory, this paper shows that the H^∞ control theory, when suitably modified, provides an effective framework for regulating BG in diabetic patients.

II. Methodology

A. Optimal H^∞ Switching Control

Let $T > 0$ be the BG sampling interval, and N and m be given integers such that insulin delivery is adjusted every mT over the interval $[0, NmT]$. Consider the time-varying linear continuous-time system with discrete measured output defined on the time interval $[0, NmT]$

$$\begin{aligned}\dot{x}(t) &= A(t)x(t) + B_1(t)\xi(t) + B_2(t)u(t);\\ z_c(t) &= K_c(t)x(t); \quad t \neq iT\\ z_d(iT) &= K_d(iT)x(iT), \quad i = 0, 1, 2, \ldots\\ y(iT) &= C_i x(iT) + v_i, \quad i = 0, 1, 2, \ldots \end{aligned} \tag{1}$$

where $x(t) \in \mathbf{R}^n$ is the *state*, $\xi(t) \in \mathbf{R}^p$ is the *external glucose disturbance input*, $u(t) \in \mathbf{R}^h$ is the *insulin infusion rate* (i.e., *control input*), $z_c(t) \in \mathbf{R}^q$ is the *continuous controlled output*, $z_d(iT) \in \mathbf{R}^q$ is the *discrete controlled output*, $y(iT) \in \mathbf{R}^l$ is the *sensor BG measurement output*, $v_i \in \mathbf{R}^l$ is the *sensor noise*, $A(\cdot), B_1(\cdot), B_2(\cdot)$, and $K_c(\cdot)$ are bounded piecewise continuous matrix functions, and C_i and $K_d(\cdot)$ are matrix sequences.

Let the control inputs be

$$u(t) \in \{U_0, U_1, U_2, \ldots, U_k\} \quad \forall\, t \tag{2}$$

where $U_0 = 0, U_1, U_2, \ldots, U_k$ are insulin infusion rates that are called *basic control vectors*. Consider the following class of output feedback controllers.

Let $S_j(\cdot)$ be a function which maps from the set of the BG measurements output $\left\{ y(\cdot)|_0^{jmT} \right\}$ to the set of symbols $s_j \in \{1, 2, \ldots, k\}$. Then, for any sequence of such functions

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$\{S_j\}_{j=0}^{N-1}$, we will consider the following dynamic nonlinear output feedback controller:

$$\begin{aligned}&\forall\, j \in \{0,1,\ldots,N-1\} \quad u(t) = U_{s_j}\\ &\forall\, t \in [jmT,(j+1)mT) \quad \text{where } s_j = S_j\left(y(\cdot)|_0^{jmT}\right). \end{aligned} \tag{3}$$

As above, the control strategy is a rule for switching from one basic control vector (2) to another. Such a rule constructs a symbolic sequence $\{s_j\}_{j=0}^{N-1}$ from the output measurement $y(\cdot)$. The sequence $\{s_j\}_{j=0}^{N-1}$ is called a *switching sequence*.

Definition 1: Let $\gamma > 0$ be a given number. If there exists a controller of the form (2) and (3) such that

$$\sup\left\{\frac{\int_0^{NmT}\|z_c(t)\|^2\,dt + \sum_{i=0}^{Nm}\|z_d(iT)\|^2}{\sum_{i=0}^{Nm}\|v_i\|^2 + \int_0^{NmT}\|\xi(t)\|^2\,dt}\right\} \le \gamma^2 \tag{4}$$

where the supremum is taken over all solutions to the closed-loop system (1) and (3) with the initial condition $x(0) = 0$ and arbitrary $\xi(\cdot)$, $v_0, v_1, \ldots, v_{Nm}$, then the output feedback H^∞ control problem with the disturbance attenuation γ is said to have a solution via the controlled switching with the basic control vectors (2).

The problem in (4) is not a standard H^∞ control problem with transient (see, e.g., [9]), but has the following distinctive features:

1) the class of controller under consideration consists of those that take values in a given finite set;
2) the underlying system is continuous-time whereas the measured output data are available only at discrete sampling instants, and the control input is piecewise constant.

Notation 1: Let $g(t)$ be a given matrix or vector function which is right continuous and may be left discontinuous. Then $g(t^{0-})$ denotes the value of $g(t)$ just before t, i.e.,

$$g(t^{0-}) \triangleq \lim_{\varepsilon>0,\varepsilon\to 0} g(t-\varepsilon).$$

Our solution to the above problem involves the following Riccati differential equation which contains jumps in its solution:

$$\begin{aligned}\dot{P}(t) &= A(t)P(t) + P(t)A(t)'\\ &\quad + \frac{1}{\gamma^2}P(t)K_c(t)'K_c(t)P(t)\\ &\quad + B_1(t)B_1(t)', \text{ for } t \ne iT\\ P(iT) &= \left[P((iT)^{0-})^{-1} + C_i{}'C_i\right.\\ &\quad\left. - \frac{1}{\gamma^2}K_d(iT)'K_d(iT)\right]^{-1}, \text{ for } t = iT. \end{aligned} \tag{5}$$

Also, we consider a set of state equations of the form

$$\begin{aligned}\dot{\hat{x}}(t) &= \left[A(t) + \frac{1}{\gamma^2}P(t)K_c(t)'K_c(t)\right]\hat{x}(t)\\ &\quad + B_2(t)u(t), \text{ for } t \ne iT\\ \hat{x}(iT) &= \hat{x}((iT)^{0-}) + P((iT)^{0-})C_i{}'y(iT)\\ &\quad + P((iT)^{0-})\left[\frac{1}{\gamma^2}K_d(iT)'K_d(iT) - C_i{}'C_i\right]\\ &\quad \times \hat{x}((iT)^{0-}), \text{ for } t = iT. \end{aligned} \tag{6}$$

The jump Riccati differential equation being considered in this paper is similar to those in [9], and it behaves like a standard Riccati differential equation between sampling instants. However, at the sampling time, its solutions exhibit finite jumps [9]. The jump state equation also exhibits similar jump behavior. Riccati differential equation of this type have been widely studied in the theory of H^∞ control and there exist reliable methods for obtaining solutions.

Notation 2: Let $M(\cdot)$ be a given function from $\mathbf{R}^n$ to $\mathbf{R}$ and let $x_0 \in \mathbf{R}^n$ be a given vector. Introduce the following cost function:

$$F_j^s(x_0, \hat{M}(\cdot)) \triangleq \sup_{y([jm+1]T),\ldots,([j+1]mT)} \cdot[M \times (\hat{x}([j+1]mT)) + \rho] \tag{7}$$

with

$$\begin{aligned}\rho &= \frac{1}{\gamma^2}\int_{jmT}^{(j+1)mT}\|K_c(t)\hat{x}(t)\|^2\,dt\\ &\quad + \sum_{i=jm+1}^{(j+1)m}\left(\frac{1}{\gamma^2}\|K_d(iT)\hat{x}(iT)\|^2 - \|C_i\hat{x}(iT) - y(iT)\|^2\right)\end{aligned}$$

where the supremum is taken over all solutions to the system (6) with arbitrary inputs $y(\cdot)$, $u(t) \equiv U_s$ and initial condition $\hat{x}(jmT) = \hat{x}_0$. Here $\|\cdot\|$ denotes the standard Euclidean norm.

Now we are in the position to present the main result of this section. The main result will be given in terms of the existence of suitable solutions to a Riccati equation of the H^∞ filtering type and a dynamic programming equation. If such solutions exist, then it is shown that they can be used to construct a corresponding controller.

Theorem 1: Consider the system (1) and the basic vectors (2). Let $\gamma > 0$ be a given number, and let $F_j^s(\cdot,\cdot)$ be defined by (7). Suppose that the solution $P(\cdot)$ to the jump Riccati (5) with initial condition $P(0) = 0$ is defined and positive definite on the interval $(0, NmT]$, and the dynamic programming equation

$$V_N(\hat{x}_0) = 0; \quad V_j(\hat{x}_0) = \min_{s=0,1,\ldots,k} F_j^s(\hat{x}_0, V_{j+1}(\cdot)) \tag{8}$$

has a solution for $j = 0, 1, \ldots, N-1$ such that $V_0(0) = 0$.

Furthermore, let $s_j(\hat{x}_0)$ be an index[1] such that the minimum in (8) is achieved for $s = s_j(\hat{x}_0)$, and $\hat{x}(\cdot)$ be the solution to the (6) with initial condition $\hat{x}(0) = 0$. Then, the controller described by (2) and (3) associated with the switching sequence $\{s_j\}_{j=0}^{N-1}$ where $s_j \triangleq s_j(\hat{x}(jmT))$ solves the output feedback H^∞ control problem (4) with the disturbance attenuation γ.

The solution to the discrete-time dynamic programming equation, such as (8) above, has been the subject of much research in the field of optimal control theory. Furthermore, many methods of obtaining numerical solutions have been proposed for specific optimal control problems.

Proof: In order to prove this theorem, we will use the following lemma.

Lemma 1: Let $y_0(\cdot)$ and $u_0(\cdot)$ be given vector functions. Suppose that the solution $P(\cdot)$ to the Riccati (5) with initial

[1]In another word, $s_j(\hat{x}_0)$ signifies the index into $u(t)$ (see (2) and (3)) associated with a particular starting point $\hat{x}_0$ that gives a minimum in (8).

condition $P(0) = 0$ is defined and positive definite on the interval $[0, NmT]$. Then, the condition

$$\int_0^{NmT} \left(\frac{1}{\gamma^2} \|z(t)\|^2 - \|\xi(t)\|^2 \right) dt + \sum_{i=0}^{Nm} \frac{1}{\gamma^2} \|z(iT)\|^2 - \sum_{i=0}^{Nm} \|v_i\|^2 \le 0 \quad (9)$$

holds for all solutions to the system (1) with $y(\cdot) = y_0(\cdot)$ and $u(\cdot) = u_0(\cdot)$ if and only if

$$\frac{1}{\gamma^2} \int_0^{NmT} \|K_c(t)\hat{x}(t)\|^2 dt + \sum_{i=0}^{Nm} \frac{1}{\gamma^2} \|K_d(iT)\hat{x}(iT)\|^2 - \sum_{i=0}^{Nm} \|C_i\hat{x}(iT) - y(iT)\|^2 \le 0 \quad (10)$$

for the solution to the (6) with $y(\cdot) = y_0(\cdot)$ and $u(\cdot) = u_0(\cdot)$ and initial condition $\hat{x}(0) = 0$.

a) Proof of Lemma: Given an input-output pair $[u_0(\cdot), y_0(\cdot)]$, if condition (9) holds for all vector functions $x(\cdot)$, $\xi(\cdot)$ and v_i satisfying (1) with $u(\cdot) = u_0(\cdot)$ and such that

$$y_0(iT) = C_i x(iT) + v_i, \quad \forall\, i = 0, 1, \ldots, Nm \quad (11)$$

then, substitution of (11) into (9) implies that (9) holds if and only if

$$J[x_f, \xi(\cdot)] \ge 0 \quad (12)$$

for all $\xi(\cdot) \in \mathbf{L}_2[0, NmT]$, $x_f \in \mathbf{R}^n$ where $J[x_f, \xi(\cdot)]$ is defined by

$$\begin{aligned} J[x_f, \xi(\cdot)] &\triangleq \int_0^{NmT} \left(\|\xi(t)\|^2 - \frac{1}{\gamma^2} \|K_c(t)x(t)\|^2 \right) dt \\ &\quad - \sum_{i=0}^{Nm} \left(\frac{1}{\gamma^2} \|K_d(iT)x(iT)\|^2 - \|(y_0(iT) - C_i x(iT))\|^2 \right) \end{aligned} \quad (13)$$

and $x(\cdot)$ is the solution to system (1) with disturbance input $\xi(\cdot)$ and boundary condition $x(t_N) = x_f$.

Now consider the following minimization problem:

$$\min_{\xi(\cdot) \in \mathbf{L}_2[0,NmT]} J[x_f, \xi(\cdot)] \quad (14)$$

where the minimum is taken over all $x(\cdot)$ and $\xi(\cdot)$ connected by system (1) with the boundary condition $x(NmT) = x_f$. This problem is a linear quadratic optimal tracking problem in which the system operates in reverse time.

To convert the above tracking problem into a tracking problem of the standard form, first define $x_1(t)$ to be the solution to the state equations

$$\dot{x}_1(t) = A(t)x_1(t) + B_2(t)u_0(t); \quad x_1(0) = 0. \quad (15)$$

Now let $\tilde{x}(t) \triangleq x(t) - x_1(t)$. Then, it follows from (1) and (15) that $\tilde{x}(t)$ satisfies the state equations

$$\dot{\tilde{x}}(t) = A(t)\tilde{x}(t) + B_1(t)\xi(t) \quad (16)$$

where $\tilde{x}(0) = x(0)$. Furthermore, the cost function (13) can be rewritten as

$$\begin{aligned} J[x_f, \xi(\cdot)] &= \tilde{J}[\tilde{x}_f, \xi(\cdot)] \\ &= \int_0^{NmT} \left(\|\xi(t)\|^2 - \frac{1}{\gamma^2} \|K_c(t)[\tilde{x}(t) + x_1(t)]\|^2 \right) dt \\ &\quad - \sum_{i=0}^{Nm} \frac{1}{\gamma^2} \|K_d[\tilde{x}(iT) + x_1(iT)]\|^2 \\ &\quad + \sum_{i=0}^{Nm} \|y_0(iT) - C_i [\tilde{x}(iT) + x_1(iT)]\|^2 \end{aligned} \quad (17)$$

where $\tilde{x}(t_N) = \tilde{x}_f = x_f - x_1(t_N)$. Equations (16) and (17) now define a tracking problem of the standard form where $y_0(\cdot)$ and $x_1(\cdot)$ are all treated as reference inputs.

The solution to this tracking problem is well known in the literature (e.g., see [10, Section 6.3]). If the jump Riccati equation (5) has a positive-definite solution defined in $[0, NmT]$ with initial condition $P(0) = 0$, then the minimum in $\tilde{J}[\tilde{x}_f, \xi(\cdot)]$ will be achieved for any x_0 and $y_0(\cdot)$. Furthermore, by making use of the result from [11] which dealt with the problem of estimating the state of a linear dynamic system using noise-corrupted observations, we can eliminate the term $\xi(t)$ in (17) to arrive at

$$\begin{aligned} &\min_{\xi(\cdot) \in \mathbf{L}_2[0,NmT]} \tilde{J}[\tilde{x}_f, \xi(\cdot)] \\ &= (\tilde{x}_f - \hat{x}_1(NmT))' P(NmT)^{-1} (\tilde{x}_f - \hat{x}_1(NmT)) \\ &\quad - \left[\frac{1}{\gamma^2} \int_0^{NmT} \|K_c[x_1(t) + \hat{x}_1(t)]\|^2 dt + \sum_{i=0}^{Nm} \frac{1}{\gamma^2} \|K_d[x_1(iT) + \hat{x}_1(iT)]\|^2 - \sum_{i=0}^{Nm} \|C_i[x_1(iT) + \hat{x}_1(iT)] - y(iT)\|^2 \right] \end{aligned} \quad (18)$$

where $\hat{x}_1(\cdot)$ is the solution to state equations

$$\begin{aligned} \dot{\hat{x}}_1(t) &= \left[A(t) + \frac{1}{\gamma^2} P(t) K_c(t)' K_c(t) \right] \times [x_1(t) + \hat{x}_1(t)] - A(t)x_1(t), \text{ for } t \ne iT \\ \hat{x}(iT) &= \hat{x}((iT)^{0-}) + P((iT)^{0-}) C_i' y(iT) + P((iT)^{0-}) \left[\frac{1}{\gamma^2} K_d(iT)' K_d(iT) - C_i' C_i \right] \times \hat{x}((iT)^{0-}), \\ &\text{for } t = iT \end{aligned}$$

with initial condition $\hat{x}_1(t_0) = x_0$. By letting $\hat{x}(\cdot) \triangleq x_1(\cdot) + \hat{x}_1(\cdot)$ and using the fact that $\tilde{x}_f = x_f - x_1(NmT)$, (18) can be rewritten as

$$\begin{aligned}\min_{\xi(\cdot)\in\mathbf{L}_2[0,NmT]} & J[x_f,\xi(\cdot)] \\ &= (x_f - \hat{x}(NmT))' P(NmT)^{-1}(x_f - \hat{x}(NmT)) \\ &\quad - \left[\frac{1}{\gamma^2}\int_0^{NmT} \|K_c\hat{x}(t)\|^2 \, dt + \sum_{i=0}^{Nm} \frac{1}{\gamma^2}\|K_d(iT)\hat{x}(iT)\|^2 \right. \\ &\qquad \left. - \sum_{i=0}^{Nm} \|C_i\hat{x}(iT) - y(iT)\|^2 \right] \qquad (19)\end{aligned}$$

where $\hat{x}(\cdot)$ is the solution to state (6) with initial condition $\hat{x}(0) = 0$. From this we can conclude that condition (9) with a given input-output pair $[u_0(\cdot), y_0(\cdot)]$ is equivalent to the inequality (10). This completes the proof of the lemma.

b) Proof of Theorem 1: From the dynamic programming optimality principle (see, e.g., [12]), (8) implies that for the controller associated with the switching sequence $\{s_j\}_{j=0}^{N-1}$ in the statement of the theorem, we have

$$\begin{aligned}&\left[\frac{1}{\gamma^2}\int_0^{NmT} \|K_c\hat{x}(t)\|^2 \, dt + \sum_{i=0}^{Nm} \frac{1}{\gamma^2}\|K_d(iT)\hat{x}(iT)\|^2 \right. \\ &\quad \left. - \sum_{i=0}^{Nm} \|C_i\hat{x}(iT) - y(iT)\|^2 \right] \\ &\quad \le V_0(\hat{x}(0)) = V_0(0) = 0 \qquad (20)\end{aligned}$$

for the solution to the (6) with the initial condition $\hat{x}(0) = 0$ and $u(\cdot)$ and $y(\cdot)$ connected by the corresponding controller. According to Lemma 1, the condition (20) implies that the inequality (9) holds for the closed-loop system with the initial condition $x(0) = 0$. Finally, (9) is equivalent to (4). This completes the proof of the theorem. ■

B. Implementation

Let the glucose-insulin dynamics of a patient be described by

$$\begin{aligned}\dot{G}(t) &= -[p_1 + X(t)]\, G(t) + p_1 G_b + m(t) \\ \dot{X}(t) &= -p_2 X(t) + p_3 I(t) \\ \dot{I}(t) &= \tau \cdot u(t) - n \cdot I(t) \qquad (21)\end{aligned}$$

where $G(t)[\text{mg/dl}]$ is the BG concentration at time $t[\text{min}]$; $I(t)[\mu\text{U/ml}]$ is the blood insulin concentration from the basal value; $m(t)[\text{mg/dl per min}]$ is the rate of exogenous glucose infusion; $\tau \cdot u(t)[\mu\text{U/ml per min}]$ is the rate of exogenous insulin infusion per unit blood volume; and p_1, p_2, p_3, n, and G_b are described in [13]–[15].

The model (21) is a modified Minimal Model, where the endogenous insulin secretion in the original (nonlinear) Minimal Model [13] has been removed, and replaced by the term $\tau \cdot u(t)$ (see [14]). The conversion factor τ allowed $u(t)$ to be described in terms of U/h (rather than $\mu\text{U/ml per min}$), and in consistency with clinical convention of insulin delivery rate prescription.

The nonlinear model (21) can be linearized and used in the design of the optimal H^∞ "switching" controller described in Section II-A. Using the steps in [16], the linearized model is

$$\begin{aligned}\dot{G}(t) &= -\left[p_1 + \bar{X}\right] G(t) - \bar{G} \cdot X(t) \\ &\quad + \bar{G}\cdot\bar{X} + p_1 G_b + m(t) \\ \dot{X}(t) &= -p_2 X(t) + p_3 I(t) \\ \dot{I}(t) &= \tau \cdot u(t) - n \cdot I(t) \qquad (22)\end{aligned}$$

where $\bar{G}$ and $\bar{X}$ are the nominal values of $G(t)$ and $X(t)$ around a chosen operating condition at time t, respectively. It can be shown that for model (22) to be equivalent to model (21) requires $\bar{G} = G(t)$ and $\bar{X} = X(t)$.

A rearrangement of (22) gives

$$\begin{aligned}\begin{bmatrix}\dot{G}(t)\\ \dot{X}(t)\\ \dot{I}(t)\end{bmatrix} &= \begin{bmatrix} -\left(p_1 + \bar{X}\right) & -\bar{G} & 0 \\ 0 & -p_2 & p_3 \\ 0 & 0 & -n\end{bmatrix}\begin{bmatrix}G(t)\\ X(t)\\ I(t)\end{bmatrix} \\ &\quad + \begin{bmatrix}1\\0\\0\end{bmatrix} m(t) + \begin{bmatrix}0\\0\\ \tau\end{bmatrix} u(t) + \begin{bmatrix}\bar{G}\cdot\bar{X} + p_1 G_b \\ 0 \\ 0\end{bmatrix} \qquad (23)\end{aligned}$$

which identifies with the functions $A(\cdot)$, $B_1(\cdot)$, $\xi(\cdot)$, and $B_2(\cdot)$ in the continuous-time system of (1). With these functions now defined, the "switching" controller can be designed, and used to calculate an insulin rate at each insulin prescription instance, in the following steps:

1) Generate the sequences of the "jump" Riccati equation $P(\cdot)$ of (5) over the control horizon.
2) Generate the sequences of the "jump" state estimator $\hat{x}(\cdot)$ of (6) for all possible $u(t)$, and sequences of $y(iT)$ based on all possible sequences of $\xi(t)$ that are likely to occur during the controller's operation.
3) Using the cost function (7) and the dynamic programming (8), calculate the minimum cost associated with the trajectories taken by $\hat{x}(\cdot)$ for each initial condition $\hat{x}_0 \in \hat{X}_0(jmT)$, $\forall\, j = 0, 1, \ldots, N-1$, beginning with $j = N-1$.
4) At the end of the dynamic programming process, the optimal path would be found, and the associated insulin rate to be prescribed would be obtained.

C. Simulation

1) Comparison With MPCSE: The performance of the "switching" controller was compared to a Model Predictive Controller with State Estimation (MPCSE) (see [3], [17]). The internal model structure was

$$\begin{aligned}\hat{x}(k+1) &= \Phi\hat{x}(k) + \Gamma u(k) + \kappa\left[y(k) - C\hat{x}(k)\right] \\ \hat{y}(k) &= C\hat{x}(k)\end{aligned}$$

(as in [3]) where the Kalman filter gain κ was computed with

$$\begin{aligned}\kappa(i) &= \Phi P_m(i) C^T \left(C P_m(i) C^T + R_2\right)^{-1} \\ P_m(i+1) &= \Phi P_m(i)\Phi^T + R_1 - \kappa(i) C P_m(i)\Phi^T.\end{aligned}$$

The functions Φ and Γ are the discrete counterparts of $A(\cdot)$ and $B(\cdot)$ in (23), converted using the MPC toolbox in Matlab®

TABLE I
PARAMETERS USED FOR THE CONTROLLER IN THE SIMULATION

p_1	$= 0$	min^{-1}	γ	$= 1 \times 10^5$
p_2	$= 0.025$	min^{-1}	$B_1(t)$	$= [\ 0.16 \quad 0 \quad 0\ ]'$
p_3	$= 13 \times 10^{-6}$	$min^{-2}\,(\mu U/ml)^{-1}$	C_i	$= [\ 1 \quad 0 \quad 0\ ]$
n	$= 0.09$	min^{-1}		
$\bar{G}$	variable (see text)	mg/dl	$K_c(t)$	$= K_d(iT) = [\ 1 \quad 0 \quad 0\ ]'$
$\bar{X}$	variable	min^{-1}	U_S	$= \Delta u(k) \in \{0, 0.5, 1, 1.5, 2, 2.5, 3\}\ U/hr$
N	$= 1$			
m	$= 12$		$\xi(t)\vert_{t_a}^{t_b}$	$\in \{0, 5, 10\}\ g/hr$
T	$= 5$	min	$[t_a,\, t_b)$	$\approx 1\,hr$

R13 (Mathworks, Inc). The Kalman filter was tuned with $R_1 = 0.001 \times eye(3,3)$, $R_2 = 136$, and $P_m(0) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}$.

A quadratic objective of the form

$$\min_{\triangle u(k), \triangle u(k+1)} \left\{ \sum_{l=1}^{p} \left\| \Gamma_y \left(y(k+l|k) - r(k+l) \right) \right\|^2 + \sum_{l=1}^{m} \left\| \Gamma_u \left(\Delta u(k+l-1) \right) \right\|^2 \right\} \quad (24)$$

was used with sampling time $T_s = 5\ \mathrm{min}$, $m = 2$, $p = 8$, $\Gamma_y = 1$, $\Gamma_u = 8$, $\Delta u(k+l-1) = 0\ \forall\, l \geq 3$, and $r(k+l) = 0\ \forall\, l \geq 0$ (see [18]). To allow more insulin moves, we set $\Delta u(k) \in \{0, 0.5, 1, 1.5, 2, 2.5, 3\}$ U/h but only the first calculated insulin move for $\Delta u(k)$ was implemented. As in [17], we set $y(k+i) = y(k|k-1)\ \forall\, i \geq 0$.

D. Controllers Simulation

Simulation studies involving both the "switching" controller and MPCSE controller were performed using a "virtual patient", which was a nonlinear pharmacokinetic/pharmacodynamic compartmental model of Type I diabetic patient (Sorensen's model). The model's parameters were set the same as those used in [19] and [20], and with the endogenous insulin secretion set to zero. Due to our familiarity with the Intensive Care Unit (ICU) setting, we compared both controllers in terms of their responses to a common ICU clinical situation where a patient has a high BG on admission, and later required external glucose infusion $m(t)$ as part of routine clinical treatment. The external glucose was infused directly into the patient's body through the venous line.

The model used internally by both the "switching" and MPCSE controllers was (23) with the last term set to zero (i.e., $\bar{G} \cdot \bar{X} + p_1 G_b = 0$) for simplicity.

Both controllers were given noisy BG readings, $G_{noisy}(t)$, which was generated by first adding Gaussian noise of amplitude $[-3, 3]\ \mathrm{mmol/l}$ to $G(t)$ every 10 sec, and then taking an average every 5 min. Both controllers were only started 1 h into the simulation, and thereafter programmed to calculate an insulin rate every 30 min, in line with the action time of the insulin used in the ICU environment. During the time, $\bar{G}$ was also updated to $G_{noisy}(t)$. Simulations were conducted using Matlab® R13 (Mathworks, Inc), and the parameters chosen for the controller are summarized in Table I.

The value of the parameter γ was chosen to satisfy (10), while $B_1(t)$ was tuned to give a desirable simulation output. Both glucose and insulin infusion rates per unit blood volume (i.e., $m(t)$ and $\tau \cdot u(t)$ respectively) were calculated assuming the plasma space is 5% of body weight.

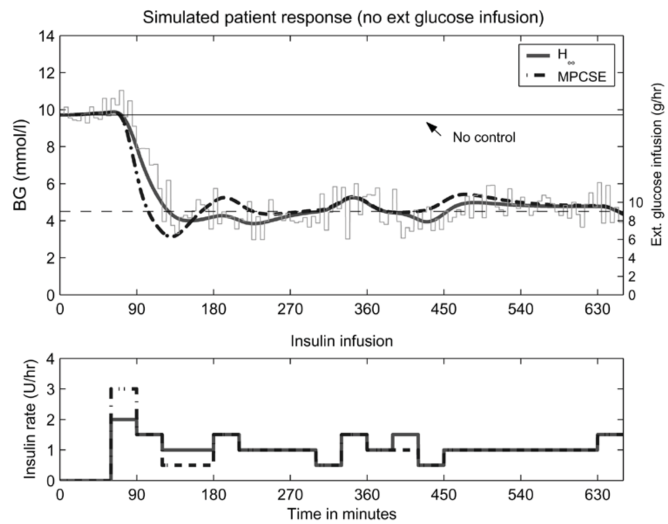

Fig. 1. Both controllers managed to normalize and keep BG near the target level of 81 mg/dl ($\approx 4.5\ \mathrm{mmol/l}$). The black solid line shows the BG excursion under no control.

III. RESULTS AND DISCUSSION

Given that a patient's glucose-insulin dynamics can be represented mathematically, both the MPCSE and the H^{∞} "switching" controllers made use of this mathematical model to calculate an insulin infusion rate that would result in BG being normalized in an optimal fashion. For MPCSE, the BG normalization process is optimized in the sense of minimizing the performance index [see (24)] which considered both the BG and the use of insulin. For the H^{∞} "switching" controller, BG is normalized in the sense of minimizing a performance index that takes into account the worst-case scenario of the external glucose infusion and the finite set of insulin rates [see (7)].

In the simulation, both the "switching" controller and the MPCSE controller (with the chosen parameters) normalized the BG in an unchallenged environment, with the BG settling near the target level of 4.5 mmol/l (Fig. 1). Similarly, when external glucose infusion was given, both controllers were able to keep the BG around the target level (Fig. 2) despite relying on noise-corrupted BG values as inputs. However, when the noise-corrupted BG values were delayed by 30 min (before being used by the controllers), the BG managed by MPCSE controller began to show larger oscillations (Fig. 3), when compared to the BG

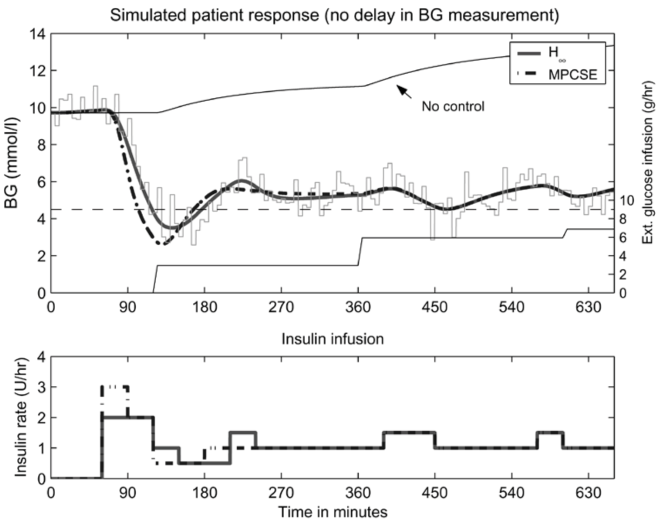

Fig. 2. When challenged with external glucose infusion, both the "switching" controller and MPCSE controller managed to keep the BG near the target level of 81 mg/dl ($\approx 4.5\ \mathrm{mmol/l}$). Both controllers were started at $t = 60\ \mathrm{min}$, and both used BG samples that were corrupted with noise (not shown on MPCSE for clarity).

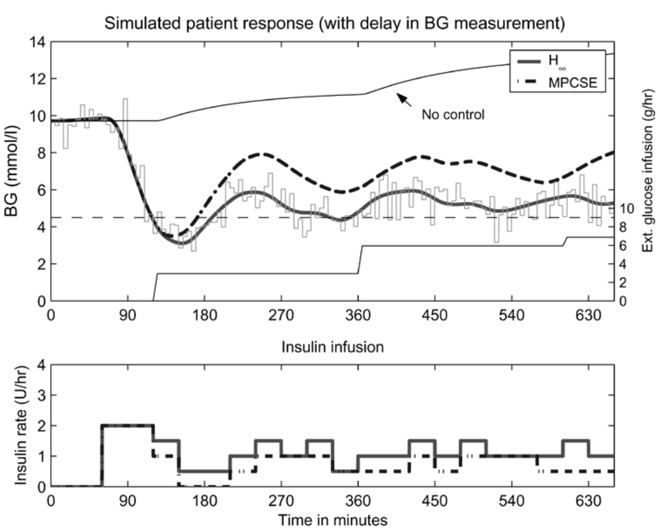

Fig. 3. A delay in the arrival of BG samples to the MPCSE controller caused a larger oscillation in BG above the target level of 81 mg/dl ($\approx 4.5\ \mathrm{mmol/l}$) compared to the BG regulated by the "switching" controller. Both controllers were started at $t = 60\ \mathrm{min}$, and both used BG samples that were corrupted with noise as well as delayed by 30 min (not shown on MPCSE for clarity).

regulated by the "switching" controller. This result suggested the applicability of the "switching" controller in BG regulation where BG measurement could be delayed by as much as 30 min. The parameters $\Gamma_u = 8$ and $B_1(t) = [0.16 \quad 0 \quad 0]'$ for MPCSE controller were the same across all the figures. The target level[2] of 81 mg/dl ($\approx 4.5\ \mathrm{mmol/l}$) was chosen with reference to the recommended BG range defined in [21].

By using a different model for the controller design (to those of simulation), a model-mismatch was introduced. In the simulation, the impact of model-mismatch was minimized by bringing closer the behavior of both models through parameters adjustment (and adjusting for the sensitivity of both models to the externally infused insulin). Attention needs to be paid to the issue of model-mismatch when designing the "switching" controller for different settings, due to the optimal tracking nature of the algorithm [see (19)].

Despite the performance of the H^∞ "switching" controller seen in Figs. 2 and 3, it came at the expense of involved procedures required prior to its deployment. The tuning of the parameter $B_1(t)$ and the compensation for model-mismatch are by far an *ad hoc* (and time-intensive) process. Also, the lead time to the deployment of the controller depends on the time required to complete the calculations of all the possible paths taken by $\hat{x}(\cdot)$ under all possible patterns of $\xi(t)$ and $u(t)$. This amounts to $[(n+1)(k+1)]^N$ trajectories, where $n+1$ is the number of levels which the external glucose infusion can take, and $k+1$ is the number of insulin rates chosen.

The difference between the control algorithm discussed in this paper to those of [19] and [20] is the context in which it is applied. The "switching" controller was designed for ICU settings where insulin rates were chosen from a finite set, and infused intravenously at set intervals using a bedside medical infusion pumps (e.g., IMED® Gemini PC-1 from Alaris Medical System, San Diego, CA), as opposed to continuous insulin infusion as described in [19] and [20].

Although the "switching" controller could be extended to the case where subcutaneous insulin injection is preferred, the dynamics of subcutaneous route (e.g., delay in insulin activity) needs to be taken into consideration, and this requires corresponding adjustment to the internal model and the controller parameters. Techniques to overcome the aforementioned complex procedures (and adjustments) would be desirable before an investigation of the "switching" controller in real-life clinical study could take place.

IV. Conclusion

H^∞ optimal control theory was modified and applied to insulin injection BG regulation, where an optimal H^∞ "switching" controller was designed and used to minimize the BG deviations from the target levels in the sense of worst-case gain, under simulation and in the presence of noisy BG measurements. Simulation result showed that with an appropriate patient model, the "switching" controller can regulate BG using clinically acceptable insulin delivery rates.

[2]To allow a nonzero target BG to be set in the "switching" controller, an extra term $(81 - \hat{x}(NmT)) \cdot P(NmT) \cdot (81 - \hat{x}(NmT))$ was added to the result of V_{N-1} in (8).

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