Static Output Feedback $\mathcal{H}_\infty$ Control for a Fractional-order Glucose-insulin System

Ibrahima N’Doye*, Holger Voos, Mohamed Darouach, and Jochen G. Schneider

Abstract: This paper presents the $\mathcal{H}_\infty$ static output feedback control of nonlinear fractional-order systems. Based on the extended bounded real lemma, the $\mathcal{H}_\infty$ control is formulated and sufficient conditions are derived in terms of linear matrix inequalities (LMIs) formulation by using the fractional Lyapunov direct method where the fractional-order $\alpha$ belongs to $0 < \alpha < 1$. The control approach is finally applied to the regulation of the glucose level in diabetes type 1 treatment. Therefore, it is attempted to incorporate fractional-order into the mathematical minimal model of glucose-insulin system dynamics and it is still an interesting challenge to show, how the order of a fractional differential system affects the dynamics of the system in the presence of meal disturbance. Numerical simulations are carried out to illustrate our proposed results and show that the nonlinear fractional-order glucose-insulin systems are, at least, as stable as their integer-order counterpart in the presence of exogenous glucose infusion or meal disturbance.

Keywords: Diabetes control, fractional calculus, fractional-order model, $\mathcal{H}_\infty$ control, linear matrix inequality (LMI), Lyapunov fractional, minimal model of glucose-insulin, static output feedback.

1. INTRODUCTION

Fractional calculus is a generalization of classical differentiation and integration to arbitrary (non-integer) order. In recent years fractional calculus has gained significant attention as one of the topics that can be applied to a variety of fields in engineering [1]. Especially in control engineering, this trend coming from applied mathematics has led to the new field of fractional-order control. Many studies and researches in controls have concentrated on using fractional calculus for modeling systems or designing controllers. The fractional-order differential equations are, at least, as

Manuscript received April 18, 2013; revised November 14, 2013, January 8, 2014, and July 31, 2014; accepted September 21, 2014. Recommended by Associate Editor Guang-Hong Yang under the direction of Editor Poo-Gyeon Park.

This present work is supported by the National Research Fund, Luxembourg and the European Commission (FP7-COFUND).

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In this contribution the focus is on the interaction between blood glucose and insulin in the human body as a biological process. Diabetes is a long-term disease during which the body’s production and use of insulin are impaired, causing glucose concentration level to increase in the bloodstream. The blood glucose dynamics can be described using a generalized minimal model structure for the intravenously infused insulin-blood glucose dynamics, which can represent a wide variety of diabetic patients [18]. Diabetes represents a major threat to public health with alarmingly rising trends of incidence and severity in recent years, and numerous detrimental consequences for public health. The most common treatment of diabetes Type 1 (patients with defects in insulin production) is the measurement of the glucose level using suitable measurement devices and to regulate this level with an infusion of insulin. Advanced solutions are trying to apply continuous automatic feedback control for this process using glucose level sensors and insulin infusion pumps. Unfortunately, all currently available solutions are far from being optimal.

One mathematical model that describes the glucose insulin dynamics with a small number of parameters can be found in [19-21]. It is a model containing two separate parts: one describing the glucose kinetics and one describing the insulin kinetics. This model with incorporated fractional-order derivatives will be described and analyzed in this paper.

Several methods have been previously employed to design the feedback controller for insulin delivery. These include classical linear control design ideas such as PID and pole placement designs, linear quadratic regulator control, etc. [22,23], where a linearized model of the system is used for the feedback control design. Nonlinear control design ideas such as model predictive control [24,25] and higher order sliding mode control [21] have also been proposed in the literature. Recently, an intelligent online feedback-treatment strategy has been presented for the control of blood glucose levels in diabetic patients using single network adaptive critic neural networks [26]. A novel idea is to apply fractional-order calculus also in the modeling and control of the insulin-blood glucose interaction, see (i.e., [27,28,29]). The additional parameters of the differential orders on one hand give more flexibility to the designer to adapt the model in a better way to the real system dynamics, on the other hand it requires advanced optimization techniques to arrive at the best choice of the variables. In our knowledge, the recent work [27] is the first one presenting in used framework the robust $\mathcal{H}_\infty$ control for the fractional-order glucose-insulin system.

In this paper, we attempt to model the insulin-blood glucose interaction dynamics using a fractional-order system. Our presentation is based on the glucose-insulin systems for control design which are presented by [21,26], the $\mathcal{H}_\infty$ control is well suited for glucose regulation, due to the ability to tune the controller for robustness in the face of model uncertainties while mathematically guaranteeing a certain degree of performance. In this case, it is important for a closed-loop controller to tolerate patient variability and dynamic uncertainty while rapidly rejecting meal disturbances and tracking the constant glucose reference.

This paper is organized as follows. In Section 2, we provide some preliminary definitions on the fractional derivative and the stability results of the fractional-order systems. Sufficient conditions for the $\mathcal{H}_\infty$ static output feedback control of nonlinear fractional-order systems are derived in terms of linear matrix inequalities (LMIs) formulation by using the fractional Lyapunov direct method where the fractional-order $\alpha$ belongs to $0 < \alpha < 1$ in Section 3. In Section 4, the mathematical modeling aspects to show the dynamics of the glucose-insulin regulatory system of the human body are presented and some necessary definitions and notations are proposed. A fractional-order model of glucose-insulin dynamics is deduced and the new system is described as a set of fractional differential equations. Finally, numerical simulations are presented to illustrate our proposed results.

Notations: $\|x\| = \sqrt{x^T x}$ and $\|A\| = \sqrt{\lambda_{\text{max}}(A^T A)}$ are the Euclidean vector norm and the spectral matrix norm, respectively, where $\lambda_{\text{max}}(A^T A)$ is the maximal eigenvalue of the symmetric matrix $A^T A$. $M^t$ is the transpose of $M$ and $D^n$ represents initialized $\alpha^\text{th}$ order differ integration.

2. PRELIMINARY DEFINITIONS

In this section, we first give the definition of fractional-order fractional-order differentiation. There are several forms of definitions of fractional derivatives, such as the Riemann-Liouville fractional derivative, Caputo’s fractional derivative, the Grünwald-Letnikov fractional derivative, and so on.

2.1. Fractional derivative

Fractional-order differentiation is the generalization of the integer-order ones. Formulations of noninteger-order derivatives fall into three main classes: the Riemann-Liouville derivative defined as [2]

$$^R D^n \alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dr^n} \int_0^t (t-\tau)^{\alpha-n+1} f(\tau) \, d\tau, \quad n-1 < \alpha < n,$$

(1)

the Caputo derivative given by [30],

$$^C D^n \alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{d^n f(\tau)}{dr^n} \, d\tau, \quad n-1 < \alpha < n$$

(2)

and the Grünwald-Letnikov derivative with fractional order $\alpha$ defined as

$$^G D^n \alpha f(t) = \lim_{h \to 0} h^{-\alpha} \sum_{j=0}^{[\frac{1-n}{\alpha}]} (-1)^j \binom{\alpha}{j} f(t-jh)$$

(3)

with $n \in \mathbb{N}$ and $\alpha \in \mathbb{R}^+$, $[\cdot]$ means the integer part, $f(t)$ is an arbitrary integrable function. $\Gamma(\cdot)$ is the
Gamma function and is defined by the integral
\[ \Gamma(z) = \int_0^{\infty} e^{-t} t^{z-1} \, dt. \]

\( ^R D^\alpha \), \( ^C D^\alpha \) and \( ^G D^\alpha \) are Riemann-Liouville, Caputo and Grünwald-Letnikov fractional derivatives, respectively. The physical interpretation of the fractional derivatives and the solution of fractional differential equations are given in [30]. In this paper, the symbol \( \mathcal{D}^\alpha \) is used to denote both the Caputo and Riemann-Liouville fractional derivative of order \( \alpha \). In the rest of this paper, the notation \( D^\alpha \) is chosen as the Caputo fractional derivative operator \( ^C D^\alpha \).

**Property 1:** It is well known that Caputo’s definition of a fractional derivative is a modification of the Riemann-Liouville definition and has the advantage of dealing with initial value problems in a proper way. Between the two definitions (Riemann-Liouville and Caputo fractional derivative), there are the following relations [2,31]

\[ ^R D^\alpha f(t) = ^C D^\alpha f(t) + \sum_{k=0}^{n} \frac{t^{\alpha-k}}{\Gamma(k-\alpha+1)} f^{(k)}(0), \quad n-1<\alpha<n, \]

\[ ^R D^\alpha \left[ f(t) - \sum_{k=0}^{n} \frac{f^{(k)}(0)}{k!} t^k \right] = ^C D^\alpha f(t), \quad n-1<\alpha<n. \]

Let us consider the Riemann-Liouville fractional derivative of order \( \alpha \), then we have

\[ ^R D^\alpha (a) = \frac{a^{\alpha} - a}{\Gamma(1-\alpha)}, \quad \alpha > 0, \]

where \( \alpha \) is a positive constant. \( \square \)

2.2. Numerical solution of fractional differential equations

For numerical simulation of the fractional-order systems, we can use the Grünwald-Letnikov method [32,33] based on the Adams-Bashforth-Moulton type predictor-corrector scheme [34]. The method is suitable for Caputo’s derivative because it just requires the initial conditions and has a clear physical meaning for unknown functions. The relation for the explicit numerical approximation of the \( D^\alpha \) derivative at the points \( kh \) (see also [32,33,35]) is given by

\[ (k-L_m)D^\alpha_{kh} f(t) \approx h^\alpha \sum_{j=0}^{k} (-1)^j \binom{\alpha}{j} f(t_k - j), \]

where \( L_m \) is the memory length, \( t_i = kh \), \( h \) is the time step of the calculation and \( (-1)^j \binom{\alpha}{j} \) are binomial coefficients \( c_{j}^{(\alpha)} \) (\( j = 0, 1, \cdots \)) which can be computed as

\[ c_{j}^{(\alpha)} = 1, \quad c_{j}^{(\alpha)} = \left( 1 - \frac{1+\alpha}{j} \right) c_{j-1}^{(\alpha)}. \]

Numerical solution of the fractional differential equation

\[ D^\alpha y(t) = f(y(t),t), \]

can be expressed as [33]

\[ y(t_k) = f(y(t_k),t_k)h^\alpha \sum_{j=1}^{k} c_{j}^{(\alpha)} f(t_k - j). \]

Equation (10) is nonlinear with respect to finding \( y(t_k) \) and can be solved using any suitable method for such equations.

2.3. Stability of nonlinear fractional-order systems

**Lemma 1** [36]: Let \( x = 0 \) be an equilibrium point for the nonautonomous fractional-order system

\[ \mathcal{D}^\alpha x(t) = f(t, x) \quad 0 < \alpha < 1, \]

where \( f(t, x) \) is piecewise continuous in \( t \) and locally Lipschitz in \( x \). Assume that there exists a Lyapunov function \( V(t, x(t)) \) and class-\( \mathcal{K} \) functions \( \beta_i \) (\( i = 1, 2, 3 \)) satisfying

\[ \beta_i \left( ||x|| \right) \leq V(t, x) \leq \beta_3 \left( ||x|| \right), \quad \beta_2 \left( ||x|| \right) \leq \beta_3 \left( ||x|| \right), \]

Then the nonlinear fractional-order system (11) is asymptotically stable. \( \square \)

To proof the results in the Section 3, we need the following lemma.

**Lemma 2** [37]: Let \( X \) and \( Y \) be real vectors of the same dimension. Then, for any scalar \( \varepsilon > 0 \), the following inequality holds

\[ X^T Y + Y^T X \leq \varepsilon X^T X + \varepsilon^{-1} Y^T Y. \]

\( \square \)

3. \( \mathcal{H}_\infty \) STATIC OUTPUT FEEDBACK CONTROL OF NONLINEAR FRACTIONAL-ORDER SYSTEM

In this section, sufficient conditions for the asymptotical stabilization of the nonlinear fractional-order system are derived in terms of linear matrix inequalities (LMIs) formulation by using the fractional Lyapunov direct method. Consider the following fractional-order system in state variable format:

\[ \{ ^C D^\alpha x(t) = Ax(t) + f(x(t)) + Bu(t) + Dd(t), \quad 0 < \alpha < 1, \]

where \( x(t) \in \mathbb{R}^n \) is the state vector of the system, \( y(t) \in \mathbb{R}^p \) is the measured output, \( u(t) \in \mathbb{R}^m \) is a measurable control input and \( d(t) \in \mathbb{R}^q \) is the input disturbance. \( A, B, C \) and \( D \) are known constant real matrices with appropriate dimensions and \( f(x(t)) \) is a bounded and measurable function with \( f(0) = 0 \) and satisfies the Lipschitz conditions for nonlinear functions.

**Assumption 1**: The nonlinearity \( f(x(t)) \) verifies the following condition
disturbance, we consider the respect to disturbance signals. In this paper, the \( H_\infty \) norm is given for linear fractional-order systems and consequently, the physical interpretation of the \( H_\infty \) norm is the same for fractional-order systems as for integer-order systems, in frequency and time domains. In this paper, the \( H_\infty \) control for nonlinear fractional-order systems is developed based on the extended bounded real lemma of integer-order systems and the results presented in [38-40]. The fractional-order \( H_\infty \) control synthesis and Lyapunov stability conditions are formulated by a linear matrix inequality (LMI). It is shown that the numerical methods to solve convex optimization problems are feasible in fractional-order systems, and a set of design parameters satisfying the LMI constrains parameterizes all the admissible fractional-order \( H_\infty \) control.

Consider system (15) and a given set of admissible disturbance inputs \( D \). To minimize the effects of the disturbance, we consider the \( H_\infty \) norm of \( x(t) \) with respect to \( d(t) \) which is given by the following definition

**Definition 1:** The \( H_\infty \) norm is given by

\[
\eta = \sup_{\|d(t)\| \leq \beta} \frac{\|x(t)\|}{\|d(t)\|},
\]

where \( \beta > 0 \) represents the level of the disturbance.

The goal in this section is to design an \( H_\infty \) static output feedback to stabilize asymptotically the nonlinear fractional-order system with unknown time-varying disturbance. The asymptotical \( H_\infty \) static output feedback stability of system (15) is given by the following theorem.

**Theorem 1:** Under assumption 1, the nonlinear fractional-order system (15) controlled by the following linear output feedback

\[
u(t) = -KY(t),
\]

where \( 0 < \alpha < 1 \) is asymptotically stable for \( d(t) = 0 \) and \( \|x(t)\| < \eta \|d(t)\| \) for \( d(t) \neq 0 \), if there exist matrices \( P = P^T > 0 \), \( \hat{W}, M, N \) and two positive scalars \( \epsilon_1 \) and \( \rho \) such that the following linear matrix inequality (LMI) is satisfied

\[
\begin{bmatrix}
\Sigma & PD & P \\
D^TP & -\eta^2I & 0 \\
P & 0 & -\epsilon_1^{-1}I
\end{bmatrix} < 0,
\]

where \( \Sigma = AW + WAT + BNC - C^TN^TB^T + (\epsilon_1 \lambda^2 + 1)I + \mu W, \)

\( W = P^{-1} \) and \( \mu \) is a positive constant scalar given in (29). Moreover, the stabilizing output feedback gain matrix is given by

\[
K = -NM^{-1}.
\]

**Proof 1:** First, we can see that if the LMI (20) is satisfied, we obtain the following LMI by using the Schur complement

\[
\begin{bmatrix}
AW + WAT + BNC - C^TN^TB^T + I & P \\
P & -\epsilon_1^{-1}I
\end{bmatrix} < 0,
\]

and the output feedback law (19) leads to asymptotical stabilization for \( d(t) = 0 \).

Now, let \( d(t) \neq 0 \) and using the linear output feedback control law (19), the nonlinear fractional-order system can be written as

\[
C^Dz(t) = (A - BKC)x(t) + f(x(t)) + Dd(t),
\]

\( 0 < \alpha < 1 \).

Consider the following Lyapunov function candidate

\[
V(t) = x^T(t)Px(t).
\]

Using property 1, the fractional-order Caputo derivative of (23) is given by

\[
C^DzV(t) = R^Dz\left(x^T(t)Px(t) - \sum_{k=0}^{n_2}(x^T(t)Px(t))^{(k)}(0)\frac{t^k}{k!}\right)
\]

or equivalently

\[
C^DzV(t) = \left(R^Dz x(t)^T P x(t) + x^T(t)P R^Dz x(t)\right) + P \sum_{k=1}^{\infty} \frac{\Gamma(1+\alpha)}{\Gamma(1+k)\Gamma(1-\alpha+k)} R^Dz x(t)^{R^Dx^{\alpha-k}} x(t)
\]

Using (6), equation (25) can be modified as follows:

\[
C^DzV(t) = \left(R^Dz x(t)^T P x(t) + x^T(t)P R^Dz x(t)\right) + P \sum_{k=1}^{\infty} \frac{\Gamma(1+\alpha)}{\Gamma(1+k)\Gamma(1-\alpha+k)} R^Dz x(t)^{R^Dx^{\alpha-k}} x(t)
\]

For notational convenience of the results formulation, we
replace the Riemann-Liouville fractional derivative (26) by the Caputo fractional derivative. Then, (26) can be written as

\[ C D^\alpha V(t) = (C D^\alpha x(t))^T P x(t) + x^T(t) P (C D^\alpha x(t)) \]

\[ - \frac{\Gamma(\alpha)}{\Gamma(1-\alpha)} \|x(0)\|^2 + P Y_s(t), \]  \( \tag{27} \)

where

\[ Y_s(t) = \sum_{k=1}^{\infty} \frac{\Gamma(1+\alpha)}{\Gamma(1+k+\alpha)} C D^\alpha x(t) C D^{\alpha-k} x(t), \]  \( \tag{28} \)

and we can consider the following boundedness condition

\[ Y_s(t) \leq \mu \|x(t)\|^2, \]  \( \tag{29} \)

where \( \mu \) is a positive constant scalar.

Since \( \frac{\Gamma(\alpha)}{\Gamma(1-\alpha)} \|x(0)\|^2 \geq 0 \) and substituting (22) into (27), one can easily conclude that

\[ C D^\alpha V(t) \leq x^T(t)((A-BKC)^T P + P(A-BKC))x(t) \]

\[ + x^T(t) P \delta(t) + \delta^T(t) P x(t) + x^T(t) P D d(t) \]

\[ + (D d(t))^T P x(t) + P Y_s(t), \]  \( \tag{30} \)

where \( \delta(t) = f(x(t)) \).

By using the relation (14), we obtain the following inequality

\[ x^T(t) P \delta(t) + \delta^T(t) P x(t) \]

\[ \leq \rho \delta^T(t) \delta(t) + \rho \|x(t)\|^2 \]  \( \tag{31} \)

Based on the properties of \( \lim_{\|x(t)\| \to 0} \frac{\|f(x(t))\|}{\|x(t)\|} = 0 \) in assumption 1 there exists a constant \( \lambda \geq 0 \) such that

\[ \|f(x(t))\| \leq \lambda \|x(t)\| \]  \( \tag{32} \)

It follows from (32) that

\[ \delta^T(t) \delta(t) \leq \lambda^2 \|x(t)\|^2 = \lambda^2 x^T(t)x(t). \]  \( \tag{33} \)

Then, using condition (29) we obtain the following inequality

\[ C D^\alpha V(t) \leq x^T(t) \left[ (A-BKC)^T P + P(A-BKC) + \epsilon_1^{-1} P + \epsilon_1 \lambda^2 + \mu P \right] x(t) \]

\[ + x^T(t) P D d(t) + (D d(t))^T P x(t). \]  \( \tag{34} \)

Considering the \( \mathcal{H}_\infty \) condition in (18), we have

\[ C D^\alpha V(t) = x^T(t)^2 - \eta^2 \|d(t)\|^2 < 0. \]  \( \tag{35} \)

Using inequalities (34), (35) and the fractional direct Lyapunov method in lemma 1, the sufficient condition can be written as

\[ \begin{bmatrix} x \\ d \end{bmatrix}^T \begin{bmatrix} \Omega & PD \\ D^T P & -\eta^2 I \end{bmatrix} \begin{bmatrix} x \\ d \end{bmatrix} < 0, \]  \( \tag{36} \)

where

\[ \Omega = (A-BKC)^T P + P(A-BKC) + \epsilon_1^{-1} P + \epsilon_1 \lambda^2 + \mu P. \]

Let matrices \( W, M \) and \( N \) be the solutions of the “W-problem” formulated in Theorem 1 of [41], then we obtain the following LMI by using Schur complements

\[ \begin{bmatrix} \Xi & PD & P \\ D^T P & -\eta^2 I & 0 \end{bmatrix} < 0, \]

\[ \begin{bmatrix} P & 0 & -\epsilon_1 I \\ W & CW, \end{bmatrix} \]

\[ W > 0, \]  \( \tag{37} \)

where

\[ \Xi = AW + WA^T + BNC - C^T N^T B^T + (\epsilon_1 \lambda^2 + 1)I + \mu W, \]

\[ W = P^{-1} \] and the stabilizing output feedback gain matrix is given by

\[ K = -NM^{-1}. \]

The inequality (37) can be solved by using the LMI toolbox in Matlab, but here the solution is more difficult since \( MC = CW \). We can transform \( MC = CW \) into the following LMI optimization problem

Minimize \( \rho \) such that:

\[ \begin{bmatrix} \rho I_n & MC-CW \end{bmatrix} > 0, \]  \( \tag{38} \)

where \( \rho \) is a positive scalar. In order to make \( MC \) approximating \( CW \) with satisfactory precision, a sufficiently small positive scalar \( \rho \) should be selected in advance to meet (38).

Substituting (38) into (37), one can conclude that the nonlinear fractional-order dynamics (15) is minimized by the \( \mathcal{H}_\infty \) norm (18). This ends the proof.

4. FRACTIONAL-ORDER MINIMAL MODEL FOR GLUCOSE-INSULIN INTERACTION

Bergman’s model or the so-called minimal model is composed of two parts: the first part describes the plasma glucose concentration considering the dynamics of glucose uptake and independent of the circulating insulin. It is treating the insulin plasma concentration as a known forcing function [22]. Minimal models must be parsimonious and describe the key components of the system functionality. Thus, a sound modeling methodology must be used to select a valid model, i.e., a well-founded and useful model which fulfills the purpose for which it was formulated [42-46]. The minimal model applied here is given by

\[ \begin{cases} \dot{G}(t) = -p_1(G(t) - G_c) - Z(t)G(t) + d(t), \\ \dot{Z}(t) = -p_2 Z(t) + p_3 [I(t) - I_c], \\ \dot{I}(t) = -n[I(t) - I_c] + \gamma[G(t) - h]^\gamma t, \end{cases} \]  \( \tag{39} \)
where \( t = 0 \) shows the time glucose enters blood, \( G(t) \) is the glucose concentration in the blood plasma in \((mg dl)\), \( Z(t) \) is the insulin effect on the net glucose disappearance or the auxiliary function representing insulin-excitable tissue glucose uptake activity, proportional to insulin concentration in a ‘distant’ compartment in \((1/min)\). \( G_0 \) is the basal pre-injection level of glucose in \((mg dl)\).

Parameter \( p_1 \) is the insulin-independent constant rate of glucose uptake in muscles and liver in \((1/min)\), \( p_2 \) is the rate for decrease in tissue glucose uptake ability in \((1/min)\), \( p_3 \) is the insulin-dependent increase in glucose uptake ability in tissue per unit of insulin concentration above the basal level in \(((\mu U/ml)^{-1} \text{min}^{-2})\). The term \( p_2 G_0 \) accounts for the body’s natural tendency to move toward basal glucose levels. \( I(t) \) is the insulin concentration in plasma at time \( t \) in \((\mu U/ml)\). The sign ‘+’ shows the positive reflection to glucose intake, i.e., when \([G(t) - h] > 0\) the term \( \gamma[G(t) - h] \) in equation (39) acts as an internal regulatory function that formulates the insulin secretion in the body, which does not exist in diabetic patients [22] (and therefore assumed to be not present in simulations carried out with diabetic patients). \( I_b \) is the basal pre-injection level of insulin in \((\mu U/ml)\), \( n \) is the first order decay rate for insulin in blood in \((1/min)\) and \( a(t) \) is the exogenous glucose infusion rate after meal (glucose rate disturbance). ‘U’ indicates insulin strength. The plasma glucose concentration compartment \( G(t) \), the plasma insulin concentration compartment \( I(t) \) and the interstitial insulin compartment \( Z(t) \) build a closed-loop system as shown in Fig. 1.

A wide range of models has been used to describe the insulin-glucose regulatory system dynamics in the body. Bergman’s generalized minimal model [21,26,46] is a commonly referenced model in the literature and approximates the dynamic response of a diabetic patient’s blood glucose concentration to the insulin injection using nonlinear ordinary differential equations. The Bergman minimal model is a nonlinear compartmental model and contains the fewest parameters that describe the glucose-insulin regulatory system with sufficient accuracy [47]. Based on the nonlinear ordinary differential equations for control design [21,26], we consider a fractional-order model which monitors the temporal dynamics of the blood glucose concentration at time \( t \), the auxiliary function representing insulin-excitable tissue glucose uptake activity, proportional to insulin concentration in a ‘distant’ compartment \( x_2 \) and the blood insulin concentration at time \( t \) \((x_3)\). While practical problems require the definition of fractional derivatives with physically interpretable initial conditions, as mentioned in [48], we have to consider the fact that the initialization problem of fractional-order systems remains an open question. In this paper, we consider that the new system is described by the following Caputo fractional-order differential equations

\[
\begin{align*}
C D^\alpha x_1(t) & = -p_1[x_1(t) - G_0] - x_1(t)x_2(t) + d(t), \\
C D^\alpha x_2(t) & = -p_2x_2(t) + p_3[x_1(t) - I_b], \quad 0 < \alpha < 1, \\
C D^\alpha x_3(t) & = -n(x_3(t) - I_b) + u(t),
\end{align*}
\]  

(40)

where \( u(t) \) defines the insulin injection rate and replaces the normal insulin regulation of the body [21,26], which acts as the control variable. Since the normal insulin regulatory system does not exist in the body of diabetic patients, this glucose absorption is considered as a disturbance for the system dynamics presented in (40) and \( d(t) \) shows the rate at which glucose is absorbed by the blood from the intestine, following food intake. The glucose concentration in blood is considered as the output \( y(t) \), where

\[
y(t) = [1 \quad 0 \quad 0] x(t).
\]  

(41)

Similar to the integer-order glucose-insulin system [26, 44], system (40) also has the equilibrium values

\[
[x_1 \quad x_2 \quad x_3]^T = [G_b \quad 0 \quad I_b]^T.
\]

A numerical solution of the fractional-order glucose-insulin system (40) is given as follows:

\[
\begin{align*}
x_1(t_k) & = [p_1(x_1(t_{k-1}) - G_0) x_1(t_{k-1}) x_2(t_{k-1}) ] + d(t_{k-1}) \gamma^{\alpha_1} \sum_{j=1}^{N} c_j^{(\alpha_1)} x_1(t_{k-j}), \\
x_2(t_k) & = [-p_2 x_2(t_{k-1}) + p_3 (x_1(t_{k-1}) - I_b) ] \gamma^{\alpha_2} - \sum_{j=1}^{N} c_j^{(\alpha_2)} x_2(t_{k-j}), \\
x_3(t_k) & = -n(x_3(t_{k-1}) - I_b) + u(t_{k-1}) \gamma^{\alpha_3} - \sum_{j=1}^{N} c_j^{(\alpha_3)} x_3(t_{k-j}),
\end{align*}
\]  

(42)

with \( T_i \) as the simulation time \( N = [T_i/h] \) the index of the discrete time steps is \( k = 1, 2, \ldots, N \) and \((x_1(0), x_2(0), x_3(0))\) are the initial conditions. The binomial coefficients \( c_j^{(\alpha_i)} \), \( \forall i \) are calculated according to relation (8).

5. SIMULATIONS RESULTS

A realistic strategy is to have the controller design based on nominal parameters. It can guarantee sufficient robustness for inaccuracies in the model parameters and retain its generality for a large number of patients (see Fig. 2). Herein, \( u(t) \) defines the insulin injection rate and

![Fig. 1. Closed loop model of Bergman without unknown input \( d(t) \).](image)
replaces the normal insulin regulation of the body while
the vector of the state variables \( x(t) \) represents: the blood glucose concentration at time \( t \), the blood insulin concentration at time \( t \) and the insulin-excitable tissue glucose uptake activity. Finally, \( d(t) \) represents the meal disturbance.

The nonlinear fractional-order glucose-insulin model (40) with the parameter values of a diabetic patient can be rewritten as

\[
\begin{align*}
C D^\alpha x(t) &= Ax(t) + f(x(t)) + Bu(t) + Dd(t), \quad 0 < \alpha < 1, \\
y(t) &= Cx(t),
\end{align*}
\]

with the following matrices

\[
x(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix}, \quad A = \begin{bmatrix} p_1 & 0 & 0 \\ 0 & -p_2 & p_3 \\ 0 & 0 & -n \end{bmatrix}, \quad B = [0 \ 0 \ 1]^T, \quad f(x(t)) = [-x_1(t)x_2(t) \ 0 \ 0]^T, \quad D = [1 \ 0 \ 0]^T \text{ and } C = [1 \ 0 \ 0].
\]

The basal value of glucose \( G_b \) and insulin \( I_b \) concentrations in plasma are assumed as 80 mg/dl and 10 μU/ml, respectively, and the initial values are \((380, 0.0001, 210)\).

The disturbance can be modeled by a sinusoidal term (periodic effect) of the form \( \beta \sin(\omega t) \) with specified amplitude and frequency. These terms represent circadian rhythms [18,49] (endocrine cycles) with period 6h and amplitude around 10 mg/dl. This disturbance is given by the following equation

\[
d(t) = \beta \sin(\omega t),
\]

where \( \beta = 10 \text{ mg/dl}, \quad \omega = \frac{2\pi}{T} \quad \text{and} \quad T = 6 \text{ h}. \) Using the following diabetic patient parameters [50]

\[
p_1 = 0.001, \quad p_2 = 0.23, \quad p_3 = 6.3 \times 10^{-4} \quad \text{and} \quad n = 0.16,
\]

and the Matlab LMI toolbox, we find that the linear matrix inequality (20) in Theorem 1 is feasible. A feasible solution of (20) is obtained as follows:

\[
N = 0.74, \quad M = 2.75, \quad \eta = 0.7, \quad \mu = 0.2, \quad \lambda = 0.14, \quad \rho = 0.11 \quad \text{and} \quad \varepsilon_1 = 0.36.
\]
two hours. Figs. 4 and 5 show the trajectories of the insulin concentration and the insulin excitable tissue glucose uptake activity, respectively.

6. CONCLUSION

In this paper, we have proposed a fractional-order glucose-insulin model as a generalization of an integer-order model. An \( \mathcal{H}_\infty \) static output feedback control has been considered for the problem. Sufficient conditions for the asymptotical stabilization of a nonlinear fractional-order glucose-insulin systems has been derived in terms of linear matrix inequalities (LMIs) formulation by using the fractional Lyapunov direct method where the fractional-order \( \alpha \) belongs to \( 0 < \alpha < 1 \). Numerical simulations show that the nonlinear fractional-order glucose-insulin systems are as stable as their integer-order counterpart. Future research direction concerns the development of robust \( \mathcal{H}_\infty \) control and fractional-order model predictive control in a population of simulated "type 1 diabetic patients" that could take advantage of the knowledge of the nonlinear dynamics described by the large-scale in silico model.

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