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

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Abstract: This paper presents the $\mathscr{H}_\infty$ static output feedback control of nonlinear fractional-order systems. Based on the extended bounded real lemma, the $\mathscr{H}_\infty$ 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 α 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, $\mathscr{H}_\infty$ 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 stable as their integer order counterpart [2]. Furthermore the relation between memory and fractional mathematics has to be pointed out.

Recently many mathematicians and applied researchers have tried to model real processes using the fractional-order differential equations [3]. Thus, as mentioned in [4], there is no field that has remained untouched by fractional derivatives. Fractional calculus has attracted increasing interests and there has been a rapid growth in the number of applications where fractional calculus has been used [3]. Fractional-order systems have been studied by many authors in engineering science from an application point of view (see [1-3] and references therein). Many systems can be described with the help of fractional derivatives : electromagnetic systems [5,6], dielectric polarization [7], viscoelastic systems [8,9], chaos synchronization and secure communication [10,11].

Besides technical applications, fractional calculus has proved advantageous to model certain processes in biology, it has been deduced for example that the membranes of cells of biological organism have fractional-order electrical conductance [12] and thus they are classified as non-integer order models. Also, it has been shown that modeling the behavior of brainstem vestibule-oculumotor neurons by fractional-order differential equations has more advantages than classical integer-order modeling [13]. Actually, more and more investigators begin to study the qualitative properties and numerical solutions of fractional-order biological models [14-17]. The main reason is that fractional-order equations are naturally related to systems with memory which exists in most biological systems. In addition they are closely related to fractals which are also abundant in biological systems.

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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 $\mathscr{H}_\infty$ 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 $\mathscr{H}_\infty$ 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 $\mathscr{H}_\infty$ 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 α 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 $\|A\| = \sqrt{\lambda_{\max}(A^T A)}$ are the Euclidean vector norm and the spectral matrix norm, respectively, where $\lambda_{\max}(A^T A)$ is the maximal eigenvalue of the symmetric matrix $A^T A$. M^T is the transpose of M and D^α represents initialized α^{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]

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

the Caputo derivative given by [30],

$$ {}^{C}D^{\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{\dfrac{\mathrm{d}^n f(\tau)}{\mathrm{d}t^n}}{(t-\tau)^{\alpha-n+1}} \mathrm{d}\tau, \quad n-1<\alpha<n \tag{2} $$

and the Grünwald-Letnikov derivative with fractional order α defined as

$$ {}^{G}D^{\alpha} f(t) = \lim_{t\to 0} h^{-\alpha} \sum_{j=0}^{\left[\frac{t-\alpha}{n}\right]} (-1)^j \binom{\alpha}{j} f(t-jh) \tag{3} $$

with $n \in \mathbb{N}$ and $\alpha \in \mathbb{R}^+$, $[\bullet]$ means the integer part, $f(t)$ is an arbitrary integrable function. $\Gamma(\bullet)$ is the

Gamma function and is defined by the integral

$$\Gamma(z)=\int_0^\infty e^{-t}t^{z-1}\mathrm{d}t.$$

${}^{R}D^{\alpha}$, ${}^{C}D^{\alpha}$ 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 $\mathscr{D}^{\alpha}$ is used to denote both the Caputo and Riemann-Liouville fractional derivative of order α. In the rest of this paper, the notation D^{α} 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]

$${}^{R}D^{\alpha}f(t)={}^{C}D^{\alpha}f(t)+\sum_{k=0}^{n}\frac{t^{k-\alpha}}{\Gamma(k-\alpha+1)}f^{(k)}(0), \quad n-1<\alpha<n, \tag{4}$$

$${}^{R}D^{\alpha}\left[f(t)-\sum_{k=0}^{n}f^{(k)}(0)\frac{t^{k}}{k!}\right]={}^{C}D^{\alpha}f(t), \quad n-1<\alpha<n. \tag{5}$$

Let us consider the Riemann-Liouville fractional derivative of order α, then we have

$${}^{R}D^{\alpha}(a)=\frac{at^{-\alpha}}{\Gamma(1-\alpha)}, \tag{6}$$

where α is a positive constant.

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 α^{th} derivative at the points kh (see also [32,33,35]) is given by

$${}_{(k-L_m/h)}D_{kh}^{\alpha}f(t)\approx h^{-\alpha}\sum_{j=0}^{k}(-1)^{j}\binom{\alpha}{j}f(t_k-j), \tag{7}$$

where L_m is the memory length, $t_k=kh$, 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

$$c_0^{(\alpha)}=1,\quad c_j^{(\alpha)}=\left(1-\frac{1+\alpha}{j}\right)c_{j-1}^{(\alpha)}. \tag{8}$$

Numerical solution of the fractional differential equation

$$D_t^{\alpha}y(t)=f(y(t),t), \tag{9}$$

can be expressed as [33]

$$y(t_k)=f(y(t_k),t_k)h^{\alpha}-\sum_{j=1}^{k}c_j^{(\alpha)}f(t_k-j). \tag{10}$$

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

$$\mathscr{D}^{\alpha}x(t)=f(t,x)\qquad 0<\alpha<1, \tag{11}$$

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-$\mathscr{K}$ functions $\beta_i(i=1,2,3)$ satisfying

$$\beta_1(\|x\|)\le V(t,x)\le\beta_2(\|x\|), \tag{12}$$

$$\mathscr{D}^{\alpha}V(t,x)\le-\beta_3(\|x\|). \tag{13}$$

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

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

$$X^{T}Y+Y^{T}X\le\varepsilon X^{T}X+\varepsilon^{-1}Y^{T}Y. \tag{14}$$

3. $\mathscr{H}_\infty$ 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:

$$\begin{cases}{}^{C}D^{\alpha}x(t)=Ax(t)+f(x(t))+Bu(t)+Dd(t),\\ y(t)=Cx(t),\end{cases}\quad 0<\alpha<1, \tag{15}$$

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

$$\lim_{\|x\|\to 0}\frac{\|f(x(t))\|}{\|x(t)\|}=0. \tag{16}$$

We describe the class of admissible disturbance inputs as follows:

$$\mathscr{D}=\left\{d(t):\int_0^\infty d^T(t)d(t)\le\beta^2\right\}, \tag{17}$$

where $\beta>0$ represents the level of the disturbance.

The $\mathscr{H}_\infty$ norm can be interpreted in time domain as the largest energy among output signals resulting from all inputs of unit energy. In [38-40] the norm $\mathscr{H}_\infty$ definition is given for linear fractional-order systems and consequently, the physical interpretation of the $\mathscr{H}_\infty$ norm is the same for fractional-order systems as for integer-order systems, in frequency and time domains. In this paper, the $\mathscr{H}_\infty$ 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 $\mathscr{H}_\infty$ 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 infractional-order systems, and a set of design parameters satisfying the LMI constrains parameterizes all the admissible fractional-order $\mathscr{H}_\infty$ control.

Consider system (15) and a given set of admissible disturbance signals $\mathscr{D}$. To minimize the effects of the disturbance, we consider the $\mathscr{H}_\infty$ norm of $x(t)$ with respect to $d(t)$ which is given by the following definition

Definition 1: The $\mathscr{H}_\infty$ norm is given by

$$\eta=\sup_{\|d(t)\|\neq 0}\frac{\|x(t)\|_2^2}{\|d(t)\|_2^2}, \tag{18}$$

where $\eta>0$ is a positive number.

The goal in this section is to design an $\mathscr{H}_\infty$ static output feedback to stabilize asymptotically the nonlinear fractional-order system with unknown time-varying disturbance.

The asymptotical $\mathscr{H}_\infty$ 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

$$u(t)=-Ky(t), \tag{19}$$

where $0<\alpha<1$ is asymptotically stable for $d(t)=0$ and $\|x(t)\|_2<\eta\|d(t)\|_2$ for $d(t)\neq 0$, if there exist matrices $P=P^T>0$, W, M, N and two positive scalars ε_1 and ρ such that the following linear matrix inequality (LMI) is satisfied

$$\begin{bmatrix}\Xi & PD & P\\ D^TP & -\eta^2 I & 0\\ P & 0 & -\varepsilon_1^{-1}I\end{bmatrix}<0, \tag{20}$$

$$\begin{bmatrix}\rho I_n & MC-CW\\ * & \rho I_n\end{bmatrix}>0,$$

$$W>0,$$

where

$$\Xi=AW+WA^T+BNC-C^TN^TB^T+(\varepsilon_1\lambda^2+1)I+\mu W,$$

$W=P^{-1}$ and μ 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

$$\begin{cases}\begin{bmatrix}AW+WA^T+BNC-C^TN^TB^T+I & P\\ P & -\varepsilon_1^{-1}I\end{bmatrix}<0,\\ MC=CW,\\ W>0,\end{cases} \tag{21}$$

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

$${}^CD^\alpha x(t)=(A-BKC)x(t)+f(x(t))+Dd(t),\qquad 0<\alpha<1. \tag{22}$$

Consider the following Lyapunov function candidate

$$V(t)=x^T(t)Px(t). \tag{23}$$

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

$${}^CD^\alpha V(t)={}^RD^\alpha\left(x^T(t)Px(t)-\left[\sum_{k=0}^{n}(x^T(t)Px(t))^{(k)}(0)\frac{t^k}{k!}\right]\right) \tag{24}$$

or equivalently

$$\begin{aligned}{}^CD^\alpha V(t)&=({}^RD^\alpha x(t))^TPx(t)+x^T(t)P({}^RD^\alpha x(t))\\&\quad+P\sum_{k=1}^{\infty}\frac{\Gamma(1+\alpha)}{\Gamma(1+k)\Gamma(1-k+\alpha)}\,{}^RD^kx(t)\,{}^RD^{\alpha-k}x(t)\\&\quad-{}^RD^\alpha(x^T(0)Px(0)).\end{aligned} \tag{25}$$

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

$$\begin{aligned}{}^CD^\alpha V(t)&=({}^RD^\alpha x(t))^TPx(t)+x^T(t)P({}^RD^\alpha x(t))\\&\quad+P\sum_{k=1}^{\infty}\frac{\Gamma(1+\alpha)}{\Gamma(1+k)\Gamma(1-k+\alpha)}\,{}^RD^kx(t)\,{}^RD^{\alpha-k}x(t)\\&\quad-\frac{t^{-\alpha}P}{\Gamma(1-\alpha)}(x^T(0)x(0)).\end{aligned} \tag{26}$$

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

$$\begin{aligned} {}^{C}D^{\alpha}V(t) &= ({}^{C}D^{\alpha}x(t))^{T}Px(t) + x^{T}(t)P({}^{C}D^{\alpha}x(t)) \\ &\quad - \frac{t^{-\alpha}P}{\Gamma(1-\alpha)}\left\|x(0)\right\|^{2} + P\Upsilon_{x}(t), \end{aligned} \tag{27}$$

where

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

and we can consider the following boundedness condition

$$\Upsilon_{x}(t) \le \mu\left\|x(t)\right\|^{2}, \tag{29}$$

where μ is a positive constant scalar.

Since $\frac{t^{-\alpha}\|P\|}{\Gamma(1-\alpha)}\left\|x(0)\right\|^{2} \ge 0$ and substituting (22) into (27), one can easily conclude that

$$\begin{aligned} {}^{C}D^{\alpha}V(t) &\le x^{T}(t)((A\text{–}BKC)^{T}P + P(A-BKC))x(t) \\ &\quad + x^{T}(t)P\delta(t) + \delta^{T}(t)Px(t) + x^{T}(t)PDd(t) \\ &\quad + (Dd(t))^{T}Px(t) + P\Upsilon_{x}(t), \end{aligned} \tag{30}$$

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

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

$$\begin{aligned} &x^{T}(t)P\delta(t) + \delta^{T}(t)Px(t) \\ &\quad \le \varepsilon_{1}\delta^{T}(t)\delta(t) + \varepsilon_{1}^{-1}x^{T}(t)PPx(t). \end{aligned} \tag{31}$$

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

$$\left\|f(x(t))\right\| \le \lambda\left\|x(t)\right\| \quad \text{as} \quad \left\|x(t)\right\| \le \lambda_{0}. \tag{32}$$

It follows from (32) that

$$\delta^{T}(t)\delta(t) \le \lambda^{2}\left\|x(t)\right\|^{2} = \lambda^{2}x^{T}(t)x(t). \tag{33}$$

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

$$\begin{aligned} {}^{C}D^{\alpha}V(t) &\le x^{T}(t)\Big[(A-BKC)^{T}P + P(A-BKC) \\ &\quad + \varepsilon_{1}^{-1}PP + \varepsilon_{1}\lambda^{2} + \mu P\Big]x(t) \\ &\quad + x^{T}(t)PDd(t) + (Dd(t))^{T}Px(t). \end{aligned} \tag{34}$$

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

$${}^{C}D^{\alpha}V + x^{T}x - \eta^{2}d^{T}d < 0. \tag{35}$$

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

$$\begin{aligned} \Omega &= (A-BKC)^{T}P + P(A-BKC) \\ &\quad + \varepsilon_{1}^{-1}PP + (\varepsilon_{1}\lambda^{2}+1)I + \mu P. \end{aligned}$$

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

$$\begin{cases} \begin{bmatrix} \Xi & PD & P \\ D^{T}P & -\eta^{2}I & 0 \\ P & 0 & -\varepsilon_{1}^{-1}I \end{bmatrix} < 0, \\ MC = CW, \\ W > 0, \end{cases} \tag{37}$$

where

$$\Xi = AW + WA^{T} + BNC - C^{T}N^{T}B^{T} + (\varepsilon_{1}\lambda^{2}+1)I + \mu W,$$

$W = P^{-1}$ 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 difficulty since $MC = CW$. We can transform $MC = CW$ into the following LMI optimization problem

$$\text{Minimize } \rho \text{ such that : } \begin{bmatrix} \rho I_{n} & MC-CW \\ * & \rho I_{n} \end{bmatrix} > 0, \tag{38}$$

where ρ is a positive scalar. In order to make MC approximating CW with satisfactory precision, a sufficiently small positive scalar ρ 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 $\mathscr{H}_\infty$ 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

$$\begin{cases} \dot{G}(t) = -p_{1}[G(t)-G_{b}] - Z(t)G(t) + d(t), \\ \dot{Z}(t) = -p_{2}Z(t) + p_{3}[I(t)-I_{b}], \\ \dot{I}(t) = -n[I(t)-I_{b}] + \gamma[G(t)-h]^{+}t, \end{cases} \tag{39}$$

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_b 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 therate 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 $((\mu U/ml)^{-1}min^{-2})$. The term p_1G_b 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 $d(t)$ 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 number of 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 (x_1), 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

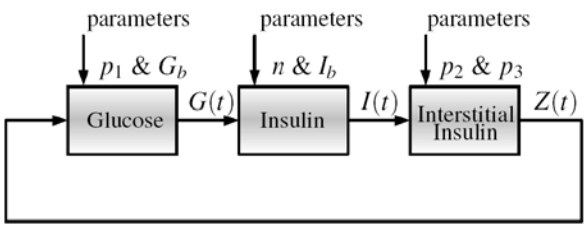

Fig. 1. Closed loop model of Bergman without unknown input $d(t)$.

$$\begin{cases} {}^{C}D^{\alpha}x_1(t) = -p_1[x_1(t)-G_b] - x_1(t)x_2(t) + d(t), \\ {}^{C}D^{\alpha}x_2(t) = -p_2x_2(t) + p_3[x_3(t)-I_b], \qquad 0<\alpha<1, \\ {}^{C}D^{\alpha}x_3(t) = -n[x_3(t)-I_b] + u(t), \end{cases} \tag{40}$$

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

$$y(t) = [1 \quad 0 \quad 0]\,x(t). \tag{41}$$

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:

$$\begin{cases} x_1(t_k) = [-p_1(x_1(t_{k-1})-G_b) - x_1(t_{k-1})x_2(t_{k-1}) \\ \qquad +d(t_{k-1})]h^{\alpha_1} - \sum_{j=1}^{k} c_j^{(\alpha_1)} x_1(t_k - j), \\ x_2(t_k) = [-p_2x_2(t_{k-1}) + p_3(x_3(t_{k-1})-I_b)]h^{\alpha_2} \\ \qquad -\sum_{j=1}^{k} c_j^{(\alpha_2)} x_2(t_k - j), \\ x_3(t_k) = [-n(x_3(t_{k-1})-I_b) + u(t_{k-1})]h^{\alpha_3} \\ \qquad -\sum_{j=1}^{k} c_j^{(\alpha_3)} x_3(t_k - j), \end{cases} \tag{42}$$

with T_s as the simulation time $N = [T_s/h]$, the index of the discrete time steps is $k = 1,2,\cdots,N$ 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

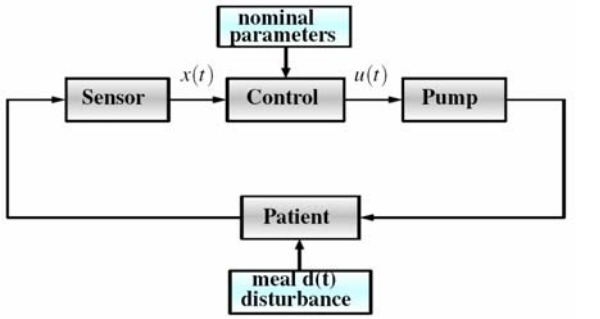

Fig. 2. Schematic of diabetic control system with nominal parameters and meal disturbance.

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

$$\begin{cases} {}^{C}D^{\alpha}x(t) = Ax(t) + f(x(t)) + Bu(t) + Dd(t), \\ y(t) = Cx(t), \end{cases} \quad 0 < \alpha < 1,$$

with the following matrices

$$x(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix}, \quad A = \begin{bmatrix} p_1 & 0 & 0 \\ 0 & -p_2 & p_3 \\ 0 & 0 & -n \end{bmatrix},$$

$$B = [0 \quad 0 \quad 1]^T, \quad f(x(t)) = [-x_1(t)x_2(t) \quad 0 \quad 0]^T,$$

$$D = [1 \quad 0 \quad 0]^T \quad \text{and} \quad C = [1 \quad 0 \quad 0].$$

The basal value of glucose G_b and insulin I_b concentrations in plasma are assumed as 80 mg/dl and 10 $\mu U/ml$, 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 $\beta = 10$ mg/dl, $\omega = \frac{2\pi}{T}$ and $T = 6$ h. Using the following diabetic patient parameters [50]

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

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:

$$N = 0.74, \quad M = 2.75, \quad \eta = 0.7 \quad \mu = 0.2,$$
$$\lambda = 0.14, \quad \rho = 0.11 \quad \text{and} \quad \varepsilon_1 = 0.36.$$

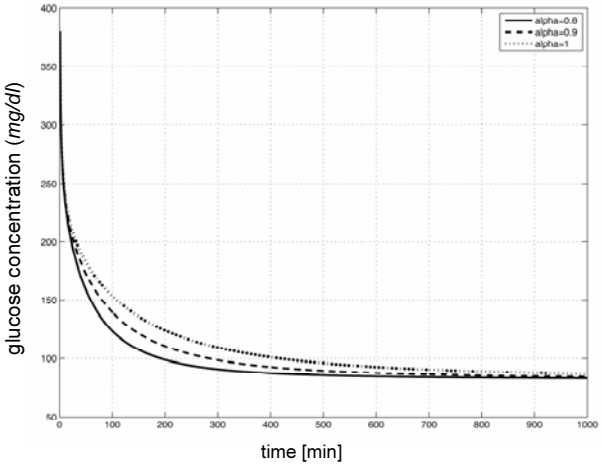

Fig. 3. State response of the glucose concentration with $\alpha = 0.8$, $\alpha = 0.9$ and $\alpha = 1$.

Finally, the stabilizing output feedback gain matrix is derived as

$$K = -NM^{-1} = -0.2691.$$

Then, the simulated behavior of the closed-loop nonlinear fractional-order glucose-insulin system (15) is shown in Fig. 3 which shows that it is asymptotically stable and the $\mathscr{H}_\infty$ norm of the transfer from x and d inclosed-loop is satisfied. It can be clearly seen that the glucose concentration comes down to the basal value $G_b = 80$ mg/dl after injecting an amount of 380 mg/dl of glucose inside a diabetic patient. Fig. 3 shows that the level of the glucose concentration inside diabetic patient decreases and reaches the basal value $G_b = 80$ mg/dl after 400 minutes with the fractional-order derivative from the time the glucose concentration was injected. In contrast it becomes obvious that this regulation lasts more than 800 minutes with the integer-order derivative, which leads the conclusion that the nonlinear fractional-order glucose-insulin systems are as stable as their integer-order counterpart. The result is ideal and effective, the glucose value is stabilized at the basal value during about

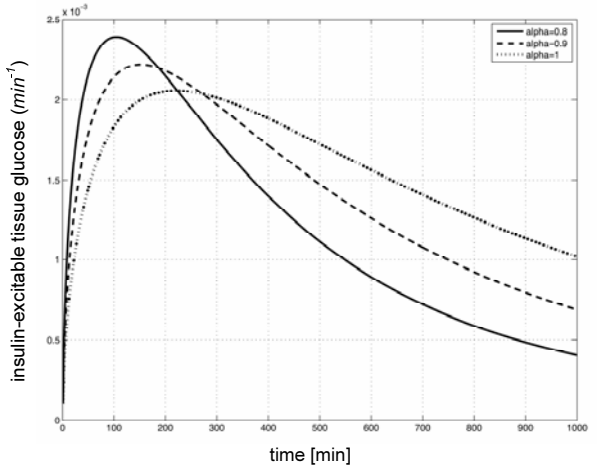

Fig. 4. State response of the insulin-excitable tissue glucose with $\alpha = 0.8$, $\alpha = 0.9$ and $\alpha = 1$.

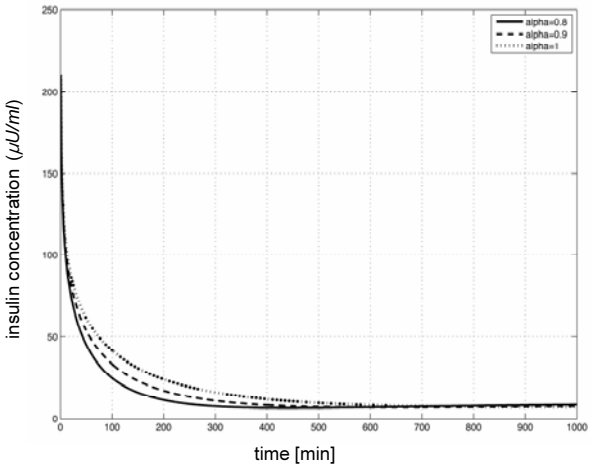

Fig. 5. State response of the insulin concentration with $\alpha = 0.8$, $\alpha = 0.9$ and $\alpha = 1$.

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 $\mathscr{H}_\infty$ 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 α 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 $\mathscr{H}_\infty$ 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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