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STATE FEEDBACK CONTROL OF THE GLUCOSE-INSULIN SYSTEM

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Abstract

The paper investigates the problem of tracking a desired level of plasma glucose concentration. The model for the glucose-insulin system considered here, and recently published, belongs to the class of single-distributed delay models. The control law is obtained according to the feedback linearization theory. Both the cases of hyperglycemic and hypoglycemic patients have been considered. Simulations support theoretical results and show the physical reliability of the approach proposed.

Key words: Mathematical modeling, feedback linearization, nonlinear systems.

1. Introduction

The design of glucose/insulin infusion devices able to control plasma glucose concentration is of great importance when attempting to reduce the diabetic complications in selected clinical situations. From an applicative point of view, different therapeutic schemes can be considered, according to the accuracy of the glucose-insulin model adopted and to the technology available in actuating the scheme selected. Glucose control strategies are mainly actuated by subcutaneous or intravenous injections or infusions. The former consist of subcutaneous insulin injections, three or four times a day, with the dose adjusted on the basis of capillary plasma glucose concentration measurements: it has a wide field of application, especially in type 1 diabetes, because, thanks to its superior management and safety, the dose is administered by the patients themselves (see [1] and references therein). However, only open loop or semiclosed loop control strategies can be used, mainly due to the problem of modeling accurately the absorption from the subcutaneous depot in the plasma circulation (see [1] for a critical review of subcutaneous absorption models).

On the other hand, a closed loop control design, based on intravenous glucose/insulin administration, provides a wider range of possible strategies and ensures a rapid delivery with negligible delays (see [11] and references therein for a survey of the intravenous route to plasma glucose control). Naturally, the more accurate is the model of the glucose-insulin kinetics, the more appropriate and effective can the control law be. The modeling of the glucose-insulin system is an appealing and challenging topic in biomathematics: many different models have been presented in the last decades, mostly referring to the well-known experimental framework of the *Intra Venous Glucose Tolerance Test* (IVGTT), where a bolus of glucose is administered intravenously and glucose and insulin concentrations are frequently sampled (see e.g. the ODEs of the Minimal Model [2], [12], or the more recent integro-differential equations models of [3], [9]). An interesting survey on a very wide class of most significative models available in literature and the software tools related to them can be found in [8]. The main role of these models is to evaluate glucose and insulin sensitivity in clinical patients [2], [12].

In this paper a closed loop approach is investigated in order to track a desired level of basal glycemia, by means of intravenous administration of either glucose or insulin. Taking into account the family of distributed-delay models recently developed in [9], a nonlinear ordinary differential system is achieved, whose components evolve on a suitably defined extended state space. The key-role is played by the *feedback linearization* of the system [7]. Differently from other control laws based on the linear *approximation* of the nonlinear model around the equilibrium point (e.g. [4, 5]), the proposed approach provides the *exact* linearization of the system (no approximations have been considered), by suitably designing the control law. Tracking is, then, achieved for the linearized system. Both the needs of increasing and decreasing the level of glycemia to the target have been considered.

Simulation results support the efficacy of the theoretical developments and show the physical reliability of the approach proposed.

2. The glucose-insulin model

The glucose-insulin model here considered belongs to the family of single-distributed delay models [9], and is reported below; the names of the parameters have been maintained as in [9].

$$\begin{aligned} \frac{dG}{dt} &= -b_1 G(t) - b_4 G(t) I(t) + b_7, \\ \frac{dI}{dt} &= -b_2 I(t) + b_6 \int_0^{+\infty} \omega(s) G(t-s) ds; \end{aligned} \tag{2.1}$$

b_1 is the insulin-independent glucose disappearance rate, b_4 is the insulin dependent glucose disappearance rate per (μU/ml) of plasma insulin concentration, b_7 is the constant increase in plasma glucose concentration due to constant baseline liver glucose release, b_2 is the first-order insulin disappearance rate, b_6 is the second-phase insulin release rate per (mg/dl) of average plasma glucose concentration per unit time.

The kernel $\omega(s)$ in the insulin dynamics characterizes the choice of the model and is such that:

$$\int_0^{+\infty} \omega(s) ds = 1, \qquad \int_0^{+\infty} s\omega(s) ds = T < +\infty. \tag{2.2}$$

T represents the average time delay.

It has been proven in [9] that all the models provide unique, positive bounded solutions and admit a unique locally asymptotically stable equilibrium point, given by the basal glycemia and insulinemia, (G_b, I_b). We can then consider equilibrium concentrations and write:

$$b_1 G_b + b_4 G_b I_b = b_7, \qquad b_2 I_b = b_6 G_b. \tag{2.3}$$

Global asymptotical stability is ensured if the average time delay T is sufficiently small, [9].

According to standard identification procedures, mainly based on the IVGTT, basal values of glucose and insulin concentrations are acquired as measurements so that equations (2.3) are used to reduce the total amount of the parameters to be identified (e.g. b_7 and b_6 are computed from b_1, b_2, b_4, identified, and G_b, I_b, measured). The standard identification task is performed by injecting intravenously a glucose bolus and acquiring plasma glucose and insulin concentrations at frequent times for a period of about three hours. This means, by setting $t = t_0$ the injection time, that the initial conditions for the IVGTT are:

$$\begin{aligned} &G(t) \equiv G_b, \quad t \in (-\infty, t_0), && I(t) \equiv I_b, \quad t \in (-\infty, t_0), \\ &G(t_0) = G_b + b_0, && I(t_0) = I_b + b_3 b_0, \end{aligned} \tag{2.4}$$

where b_0 is the theoretical increase in plasma concentration over the basal glycemia after the bolus injection and b_3 is the first-phase insulin concentration increase per (mg/dl) increase in the glycemia, due to the injected bolus. b_0 and b_3 are further parameters to be identified.

As it has been done in [9], also in this paper $\omega(s)$ has been chosen as:

$$\omega(s) = \gamma^2 s e^{-\gamma s}, \qquad \gamma > 0, \tag{2.5}$$

so that, the integral in the insulin kinetics is written as:

$$\int_0^{+\infty} \omega(s) G(t-s) ds = \int_0^{+\infty} \gamma^2 s e^{-\gamma s} G(t-s) ds = \int_{-\infty}^{t} \gamma^2 (t-\tau) e^{-\gamma(t-\tau)} G(\tau) d\tau. \tag{2.6}$$

By setting the following positions:

$$\begin{aligned} x_1(t) &= G(t), & x_3(t) &= \int_{-\infty}^{t} \gamma^2 (t-\tau) e^{-\gamma(t-\tau)} G(\tau) d\tau \\ x_2(t) &= I(t), & x_4(t) &= \int_{-\infty}^{t} e^{-\gamma(t-\tau)} G(\tau) d\tau \end{aligned} \tag{2.7}$$

due to the *linear chain trick* [6], the glucose-insulin system (2.1) evolves according to a 4-dimensional ordinary differential system:

$$\begin{aligned} \frac{dx_1}{dt} &= -b_1 x_1(t) - b_4 x_1(t) x_2(t) + b_7, \\ \frac{dx_2}{dt} &= -b_2 x_2(t) + b_6 x_3(t), \\ \frac{dx_3}{dt} &= -\gamma x_3(t) + \gamma^2 x_4(t), \\ \frac{dx_4}{dt} &= x_1(t) - \gamma x_4. \end{aligned} \tag{2.8}$$

According to (2.4), the initial conditions for (2.8) in an IVGTT occurring at time $t = t_0$ become:

$$x_1(t_0) = G_b + b_0, \qquad x_2(t_0) = I_b + b_3 b_0, \qquad x_3(t_0) = G_b, \qquad x_4(t_0) = G_b/\gamma. \tag{2.9}$$

3. Glucose control: the case of hyperglycemic patients

The aim to decrease the level of plasma glucose concentration in a diabetic patient is of primary importance, in order to reduce or delay the long-term complications associated with sustained hyperglycemia. In such a framework, especially in type 1 diabetes, the control law needs to be a suitably defined insulin infusion, named $u_i(t)$, occurring in the insulin dynamics which is, then, modified as follows:

$$\frac{dx_2}{dt} = -b_2 x_2(t) + b_6 x_3(t) + u_i(t). \tag{3.1}$$

By taking into account (3.1), system (2.8) will be referred to as:

$$\frac{dx}{dt} = f\big(x(t)\big) + g_i\big(x(t)\big) u_i(t) \qquad \text{with} \qquad f(x) = \begin{pmatrix} -b_1 x_1 - b_4 x_1 x_2 + b_7 \\ -b_2 x_2 + b_6 x_3 \\ -\gamma x_3 + \gamma^2 x_4 \\ x_1 - \gamma x_4 \end{pmatrix} \tag{3.2}$$

and $g_i(x) = (0 \;\; 1 \;\; 0 \;\; 0)^T$. Consider the output function as the glucose measurements:

$$y(t) = h\big(x(t)\big) = x_1, \tag{3.3}$$

according to which, system (3.2) endowed with the output (3.3) has relative degree 2 [7]:

$$L_{g_i} h = \frac{dh}{dx} \cdot g_i = 0, \qquad L_{g_i} L_f h = \frac{dL_f h}{dx} \cdot g_i = -b_4 x_1 \neq 0, \qquad \forall x_1 > 0. \tag{3.4}$$

Note that the relative degree is global in the domain of x, whose components are strictly positive. Despite of a non-full relative degree, it is possible to design a state feedback control law, which linearizes the system equations w.r.t. the following change of coordinates:

$$z = T(x) = \begin{pmatrix} h(x) \\ L_f h(x) \\ x_3 \\ x_4 \end{pmatrix} = \begin{pmatrix} x_1 \\ -b_1 x_1 - b_4 x_1 x_2 + b_7 \\ x_3 \\ x_4 \end{pmatrix}, \tag{3.5}$$

with

$$T^{-1}(z) = \begin{pmatrix} z_1 \\ \dfrac{b_7 - b_1 z_1 - z_2}{b_4 z_1} \\ z_3 \\ z_4 \end{pmatrix}. \tag{3.6}$$

According to (3.5), system (2.8) becomes, in the new coordinates:

$$\begin{aligned} \frac{dz_1}{dt} &= z_2(t), \\ \frac{dz_2}{dt} &= \varphi_i\big(T^{-1}(z)\big) - b_4 z_1(t) u_i(t), \\ \frac{dz_3}{dt} &= -\gamma z_3(t) + \gamma^2 z_4(t), \\ \frac{dz_4}{dt} &= z_1(t) - \gamma z_4(t), \end{aligned} \tag{3.7}$$

with:

$$\varphi_i(x) = L_f^2 h(x) = (b_1 + b_4 x_2)(b_1 x_1 + b_4 x_1 x_2 - b_7) + b_2 b_4 x_1 x_2 - b_4 b_6 x_1 x_3. \tag{3.8}$$

The linearizing feedback is, then, given by:

$$u_i(t) = u_i\big(x(t)\big) = \frac{1}{L_{g_i} L_f h\big(x(t)\big)} \Big(- \varphi_i\big(x(t)\big) + v_i(t) \Big) = \frac{\varphi_i\big(x(t)\big) - v_i(t)}{b_4 x_1(t)}, \tag{3.9}$$

with $v_i(t)$ an exogenous input to be assigned in order to achieve the desired tracking. According to (3.9) the equations (3.7) are linearized as:

$$\begin{aligned} &\frac{dz}{dt} = A_i z(t) + B_i v_i(t), \\ &y(t) = C z(t), \end{aligned} \qquad \text{with} \qquad \begin{aligned} A_i &= \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & -\gamma & \gamma^2 \\ 1 & 0 & 0 & -\gamma \end{bmatrix}, \quad B_i = \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \\ C &= \begin{bmatrix} 1 & 0 & 0 & 0 \end{bmatrix}. \end{aligned} \tag{3.10}$$

The input v_i is chosen in order to stabilize the linearized closed loop and to assign the desired glucose level:

$$v_i(t) = F_i z(t) + K_i. \tag{3.11}$$

Notice that the pair (A_i, B_i) is controllable, which means that, for any chosen set of values $\Lambda = \{\lambda_1, \lambda_2, \lambda_3, \lambda_4\}$, there exists a suitably defined matrix $F_i = [f_{i,1} \;\; f_{i,2} \;\; f_{i,3} \;\; f_{i,4}]$ such that the spectrum of $A_i + B_i F_i$ is equal to Λ. The scalar gain K_i is designed in order to achieve

the desired basal glucose level $G_d = \lim_{t\mapsto+\infty} y(t)$, so that, by naming $W_i(s)$ the input/output transfer function of (3.10):

$$G_d = \lim_{s\mapsto 0} W_i(s) = \lim_{s\mapsto 0} C(sI - A_i - B_iF_i)^{-1}B_iK_i = -\frac{\gamma K_i}{(f_{i,1} + f_{i,3})\gamma + f_{i,4}}, \tag{3.12}$$

from which:

$$K_i = -\frac{G_d\big((f_{i,1} + f_{i,3})\gamma + f_{i,4}\big)}{\gamma}. \tag{3.13}$$

The scheme of the control law is reported in Fig.3.1.

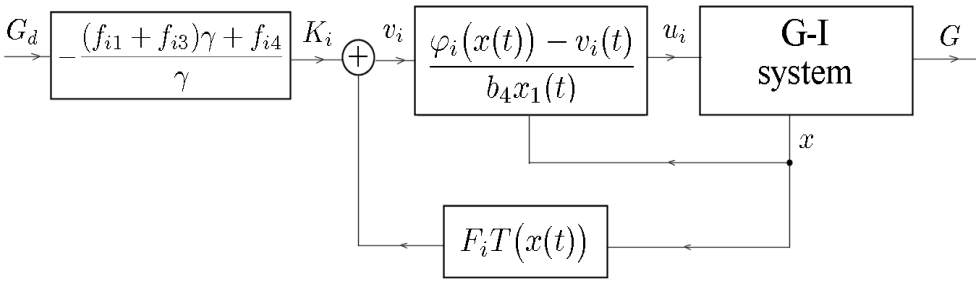

Fig.3.1 - Glucose control scheme: the hyperglycemic case.

Remark 3.1. By assigning the desired target glycemia, also the target insulinemia changes. In this case:

$$\lim_{t\mapsto+\infty} z_2(t) = 0 \quad \Rightarrow \quad \lim_{t\mapsto+\infty} I(t) = \lim_{t\mapsto+\infty} \frac{b_7 - b_1 z_1(t) - z_2(t)}{b_4 z_1(t)} = \frac{b_7 - b_1 G_d}{b_4 G_d}. \tag{3.14}$$

•

Remark 3.2. It has to be stressed that in a feasible framework the feedback law $u_i(t)$ can neither assume negative values, nor can produce negative sub-oscillations for the glucose/insulin evolutions. The first drawback is readily overcome by assuming to switch off the feedback when the input approaches the zero-level; nevertheless, even by adding such an input constrain, sub-oscillations can still appear. Moreover, as far as the plasma glucose concentration is concerned, sub-oscillations under 50mg/dl may produce permanent side effects, if occurring for too long a period. Preliminary simulations have, then, the task to determine the closed loop eigenvalues so as to prevent oscillations, besides converging to the desired glucose level. •

4. Glucose control: the case of hypoglycemic patients

Consider the case of a basal level of plasma glucose concentration lower than the one desired to be tracked. A control law based on a glucose infusion is required in this case. By naming this control $u_g(t)$, the glucose dynamics is modified as follows:

$$\frac{dx_1}{dt} = -b_1 x_1(t) - b_4 x_1(t) x_2(t) + b_7 + u_g(t). \tag{4.1}$$

By taking into account (4.1), system (2.8) will be referred to as:

$$\frac{dx}{dt} = f\big(x(t)\big) + g_g\big(x(t)\big) u_g(t) \quad \text{with} \quad f(x) \quad \text{as in (3.2)} \quad \text{and} \quad g_g(x) = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}. \tag{4.2}$$

According to the output function (3.3), system (4.2) has relative degree 1:

$$L_{g_g} h = \frac{dh}{dx} \cdot g_g = 1 \neq 0. \tag{4.3}$$

Also in this case the relative degree is global in the domain of x. Nevertheless, the state feedback linearization can be obtained without a change of coordinates: the linearizing control law is readily given by

$$u_g(t) = -\varphi_g\big(x(t)\big) + v_g(t), \quad \text{with} \quad \varphi_g(x) = L_f h(x) = -b_1 x_1 - b_4 x_1 x_2 + b_7, \tag{4.4}$$

and $v_g(t)$ an exogenous input to be assigned in order to achieve the desired tracking. According to (4.4) the glucose-insulin system (2.8) is linearized as:

$$\begin{aligned} &\frac{dx}{dt} = A_g x(t) + B_g v_g(t), \\ &y(t) = C x(t), \end{aligned} \quad \text{with} \quad A_g = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -b_2 & b_6 & 0 \\ 0 & 0 & -\gamma & \gamma^2 \\ 1 & 0 & 0 & -\gamma \end{bmatrix}, \quad B_g = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} 1 & 0 & 0 & 0 \end{bmatrix}. \tag{4.5}$$

Also in this case, the input v_g is chosen in order to stabilize the linearized closed loop and to assign the desired glucose level:

$$v_g(t) = F_g x(t) + K_g; \tag{4.6}$$

the pair (A_g, B_g) is controllable which means that, for any chosen set of values $\Lambda = \{\lambda_1, \lambda_2, \lambda_3, \lambda_4\}$, there exists a suitably defined matrix $F_g = [f_{g,1} \quad f_{g,2} \quad f_{g,3} \quad f_{g,4}]$ such that the spectrum of $A_g + B_g F_g$ is equal to Λ. The scalar gain K_g is designed in order to achieve the desired basal glucose level $G_d = \lim_{t \mapsto +\infty} y(t)$, so that:

$$G_d = \lim_{s \mapsto 0} C(sI - A_g - B_g F_g)^{-1} B_g K_g = -\frac{\gamma b_2 K_g}{(f_{g,1} b_2 + f_{g,2} b_6 + f_{g,3} b_2)\gamma + f_{g,4} b_2}, \tag{4.7}$$

from which:

$$K_g = -\frac{G_d\big((f_{g,1} b_2 + f_{g,2} b_6 + f_{g,3} b_2)\gamma + f_{g,4} b_2\big)}{\gamma b_2}. \tag{4.8}$$

The scheme of the control law is reported in Fig.2.

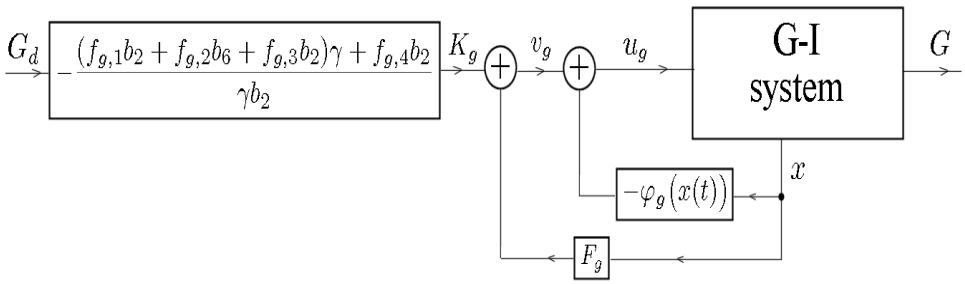

Fig.4.1 - Glucose control scheme: the hypoglycemic case.

Remark 4.1. By assigning the desired target glycemia, also the target insulinemia changes. In this case:

$$\lim_{t\mapsto+\infty} I(t) = \lim_{t\mapsto+\infty} x_2(t) = \frac{b_6 G_d}{b_2}. \tag{4.9}$$

•

Remark 4.2. Considerations written in Remark 3.2 can be repeated also for the hypoglycemic case. •

5. Numerical simulations

In the following, simulations are proposed referring to a pair of hyperglycemic patients and to a healthy subject. In all cases, the control law starts at the initial time, set to zero, and the simulation goes on for 2 hours. The first case is that of a type 2 diabetic patient, whose parameters are below reported.

$$\begin{aligned} &G_b = 150\text{mg/dl}, && I_b = 40\mu\text{U/ml} \\ &b_1 = 0.018063\text{min}^{-1} && b_2 = 0.041342\text{min}^{-1} \\ &b_4 = 1.484 \cdot 10^{-4}(\mu\text{U/ml})^{-1}\text{min}^{-1} && b_6 = 0.011(\mu\text{U/ml})(\text{mg/dl})^{-1}\text{min}^{-1} \\ &b_7 = 3.6(\text{mg/dl})\text{min}^{-1} && \gamma = 0.1022\text{min}^{-1} \end{aligned} \tag{5.1}$$

The desired target level of plasma glucose concentration is set to $G_d = 80$mg/dl. All eigenvalues of the closed loop dynamics are chosen equal to -0.1. The evolution of glucose and insulin concentrations is reported in fig. 5.1.

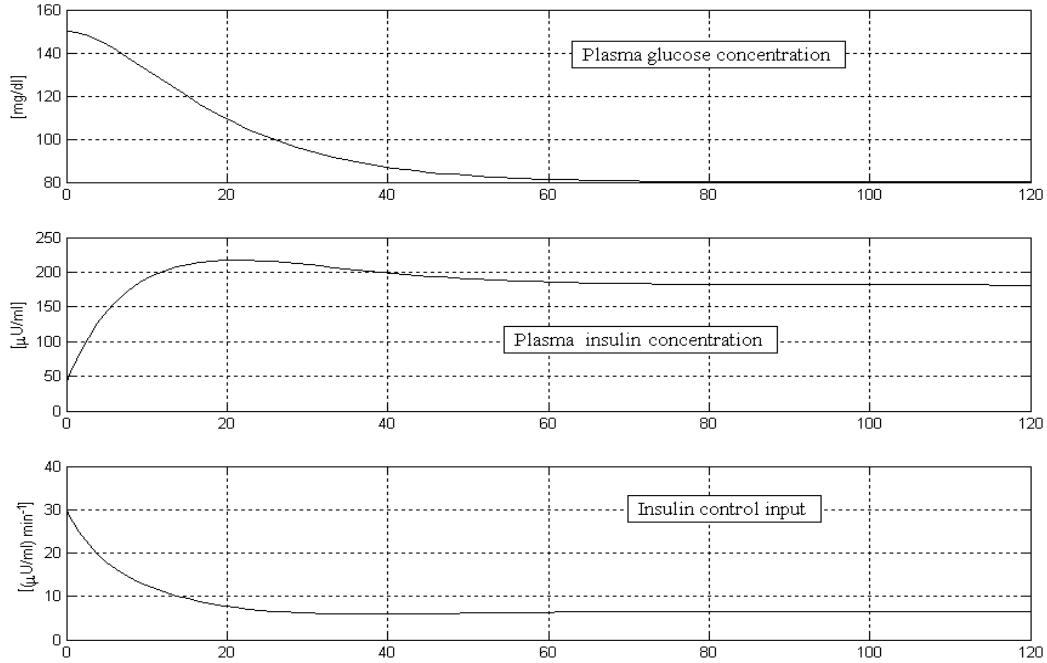

Fig.5.1 - Glucose/insulin evolution for a type 2 diabetic patient: $\lambda = -0.1$.

In this case the tracking of the desired target of glycemia is performed in less than an hour.

Below, physical parameters are reported for a type 1 diabetic patient.

$$\begin{aligned} &G_b = 180\text{mg/dl}, && I_b = 3\mu\text{U/ml} \\ &b_1 = 0.018063\text{min}^{-1} && b_2 = 0.041342\text{min}^{-1} \\ &b_4 = 6.457 \cdot 10^{-4}(\mu\text{U/ml})^{-1}\text{min}^{-1} && b_6 = 6.890 \cdot 10^{-4}(\mu\text{U/ml})(\text{mg/dl})^{-1}\text{min}^{-1} \\ &b_7 = 3.6(\text{mg/dl})\text{min}^{-1} && \gamma = 0.1022\text{min}^{-1} \end{aligned} \tag{5.2}$$

Also in this case, the desired target level of plasma glucose concentration is set to $G_d = 80$mg/dl and the eigenvalues of the closed loop dynamics are chosen equal to -0.1. The evolution of the plasma glucose and insulin concentrations is reported in fig. 5.2.

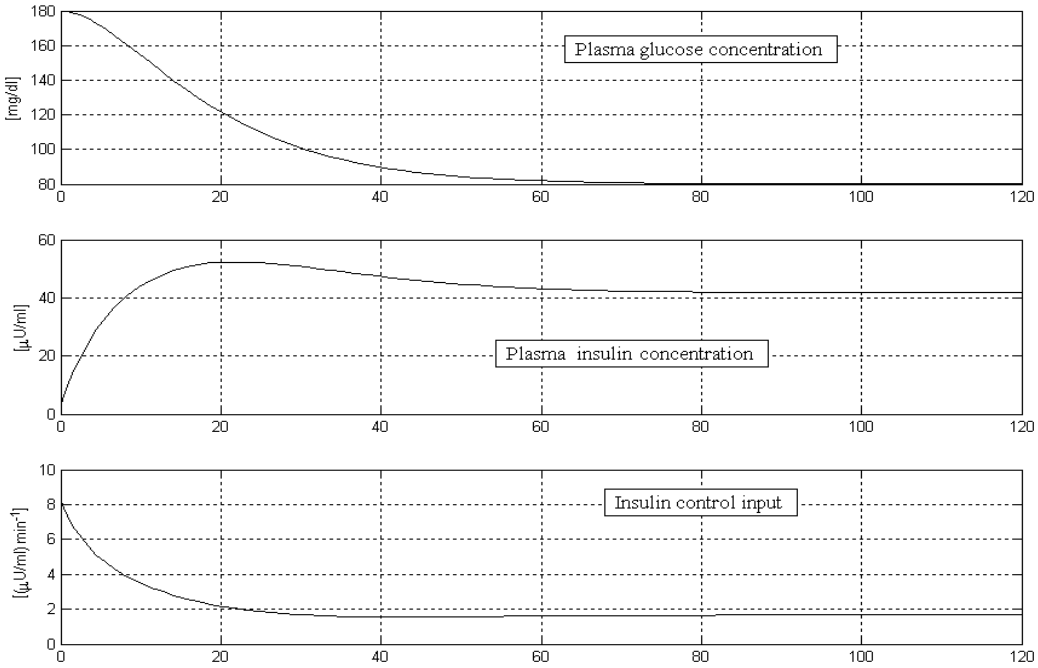

Fig.5.2 - Glucose/insulin evolution for a type 1 diabetic patient: $\lambda = -0.1$.

In order to test the effectiveness of the theoretical results when attempting to increase the desired glucose concentration, the following case has been considered (corresponding, for instance, to the establishment of a *clamped* hyperglycemic state in a normal subject). The parameters below reported refer to a healthy subject, whose basal glycemia has to be increased from 79mg/dl to 120mg/dl.

$$\begin{aligned} &G_b = 79\text{mg/dl}, && I_b = 62.5\mu\text{U/ml} \\ &b_1 = 0.018063\text{min}^{-1} && b_2 = 0.041342\text{min}^{-1} \\ &b_4 = 1\cdot 10^{-5}(\mu\text{U/ml})^{-1}\text{min}^{-1} && b_6 = 0.032707(\mu\text{U/ml})(\text{mg/dl})^{-1}\text{min}^{-1} \\ &b_7 = 1.4763(\text{mg/dl})\text{min}^{-1} && \gamma = 0.1022\text{min}^{-1} \end{aligned} \tag{5.3}$$

In fig. 5.3 simulations are reported, with the eigenvalues of the closed loop system chosen equal to -0.08.

Finally, taking into account the same healthy subject, a comparison between the natural response of the organism and the response under supplemental regulation (3.9) is reported in fig.5.4, when an intravenous glucose bolus is injected at time $t_0 = 10$min. According to (2.4), parameters b_0 and b_3 are set to $b_0 = 159.74$mg/dl and $b_3 = 2.827(\mu\text{U/ml})(\text{mg/dl})^{-1}$. Eigenvalues are chosen equal to -0.1. It is apparent that the proposed regulator provides a faster convergence to the target level without oscillations. It should be noted that the theoretical model chosen does not seem to reproduce well the secondary-phase insulin secretion *hump*, often seen in IVGTT's. This limitation leads naturally to the exploration of further models for the glucose-insulin system.

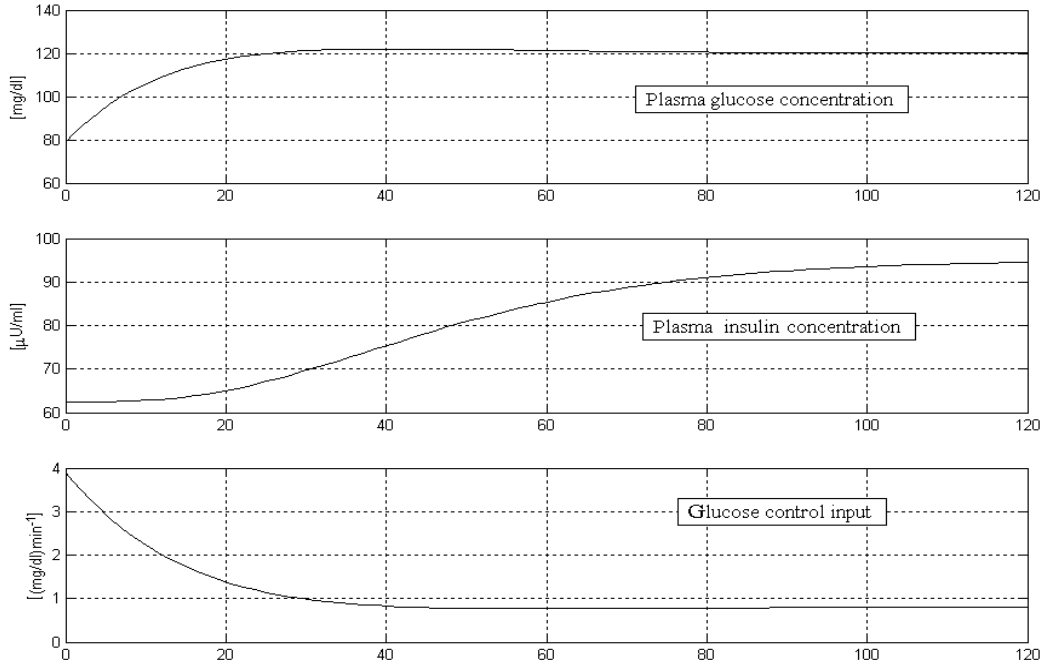

Fig.5.3 - Glucose/insulin evolution for a healthy subject: $\lambda = -0.08$.

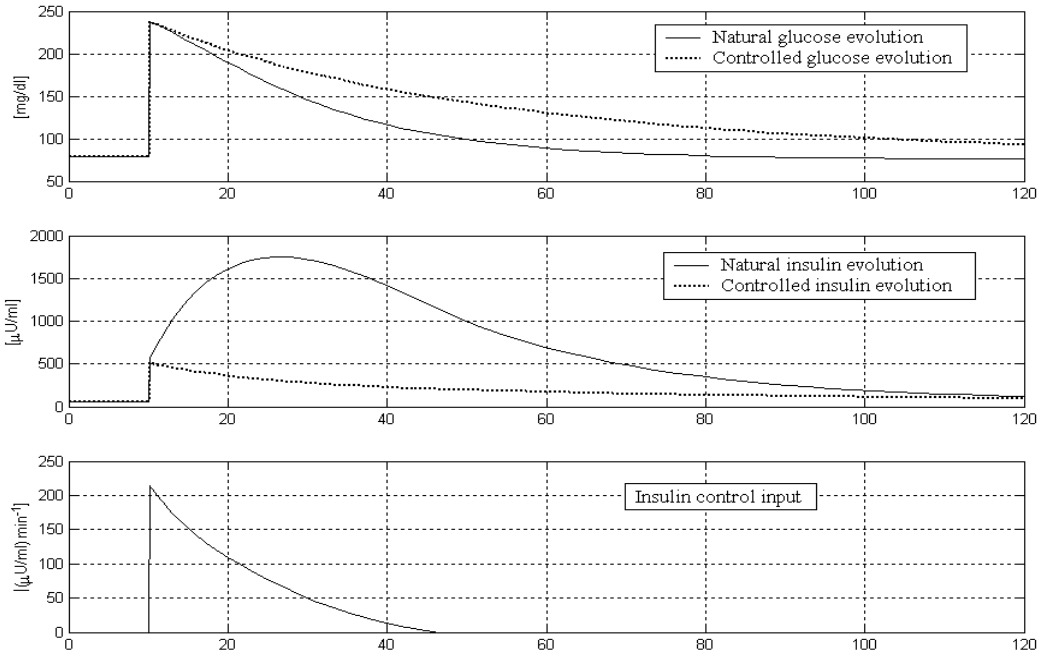

Fig.5.4 - Glucose/insulin evolution after an IVGTT for a healthy subject: $\lambda = -0.1$.

6. Conclusions

The tracking to a desired level of glycemia has been investigated according to intravenous therapy acting on a recently published single-distributed delay model of the glucose-insulin system. The control law design is based on the state feedback linearization theory and provides feasible glucose/insulin infusions, according to the simulations considered. The regulators proposed in the present work require the complete knowledge of the state of the system, which means complete glucose and insulin measurements. Nevertheless, according to the state-space methodology adopted, it may be possible to obtain essentially the same performance following an observer-based regulator approach, which only uses glucose measurements. This is work in progress by the same authors.

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