Observer Design for a Nonlinear Minimal Model of Glucose Disappearance and Insulin Kinetics

Driss Boutat[1], Mohamed Darouach[2] and Holger Voos[3]

[1]*INSA Centre Val de Loire, Univ. Orléans, PRISME EA 4229, 88 boulevard Lahitolle 18020, Bourges cedex, France*

[2]*CRAN-CNRS, UHP Nancy I, IUT de Longwy 186, rue de Lorraine, 54400 Cosnes-et-Romain, France*

[3]*Université du Luxembourg, Faculté des Sciences, de la Technologie et de la Communication, 6, rue Richard Coudenhove-Kalergi, L-1359, Walferdange, Luxembourg*

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Abstract: This work deals with an observer design for a nonlinear minimal dynamic model of glucose disappearance and insulin kinetics (GD-IK). At first, the model is transformed into a nonlinear observer normal form. Then, using the knowledge of the plasma blood glucose level, we estimate the state variables that are not directly available from the system, i.e. the remote compartment insulin utilization, the plasma insulin deviation and the infusion rate. In addition, we estimate the amount of absorbed glucose by means of the inverse dynamics.

1 INTRODUCTION

Diabetes is a serious disease by which the body's production and use of insulin are impaired, causing an increase of glucose concentration level in the bloodstream. Regulating blood glucose levels as close to normal as possible leads to a substantial decrease in long term complications of diabetes. The most common treatment of diabetes type 1 (where the insulin production of the pancreas is disturbed) is the measurement of the glucose level using suitable measurement devices to regulate this level with an injection of insulin. Advanced solutions are trying to apply automatic feedback control for this process using glucose level sensors and insulin infusion pumps, see e.g. (Chee et al., 2003) for a comprehensive overview of the technological aspects. But all currently available solutions are far from being optimal. One main problem is the fact that not all important variables are known or measurable. Therefore, observers play a very important role in this control task and will also be the main issue of this contribution.

First of all the development of suitable observers as well as control algorithms requires the derivation of a dynamic mathematical model of the system under control, i.e. the complex dynamics of glucose disappearance and insulin kinetics(GD-IK). During the last decades, considerable research has been devoted to the derivation and improvement of such models, and many of them have already been described in the literature ranging from simple expressions to very complex nonlinear mathematical models (Chee et al., 2003). One model which is commonly used in the literature is the so called minimal model. It is a single input-output nonlinear dynamic system with four states: the plasma insulin concentration level $i(t)$, the plasma blood glucose level $g(t)$, a variable $v(t)$ which is proportional to the insulin in the remote compartment and $w(t)$ which represents the infusion rate by means of a pump. The input variable of this minimal GD-IK model is the effect of a pump while the plasma blood glucose level is the output.

Most research which is so far interested in control or observer synthesis using the minimal GD-IK model is based on linearization of this model, see (Percival et al., 2008), (Magni et al., 2007), (Hariri and Wang, 2011), (González and Femat, 2011), (Parker et al., 1999), (Bergman et al., 1979), (L Kovcs, 2007) and references therein. More recent work on the same theme can be found in (Eberle and Ament, 2012) and (Villafaa-Rojas et al., 2013). In this paper however, we will design an observer for the nonlinear minimal GD-IK model without any simplification. Indeed, we will transform this model into a nonlinear observer normal form. The considered model also contains an unknown amount g_M of glucose absorption from the gut which will be estimated by the dynamic inversion method. Furthermore, we distinguish two situations in this work: the case where g_M is known and the case where g_M is considered as an unknown disturbance

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rate. On the one hand, our contribution is based on the works of (Krener and Isidori, 1983), (Respondek and Pogromsky, 2004), (Boutat, 2007), (Boutat and Busawon, 2011), (Boutat et al., 2009) in order to derive a change of coordinates that transforms the minimal GD-IK model into an observer nonlinear normal from. This enables us to design a robust observer. On the other hand, it is based on works of (Kudva et al., 1980), (Yang and Wilde, 1988), (Darouach et al., 1994), (Hui and Zak, 2005), (Bhattacharyya, 1978) to build an observer based on unknown disturbances.

This paper is organized as follows. The next section presents the nonlinear minimal GD-IK model and states the problem to be solved. The third section deals with the change of coordinates and describes the observer nonlinear normal form. The fourth section is devoted to the design of two types of observers, a full order observer by assuming that g_M is known and a reduced observer in the case where g_M is unknown.

2 NOTATIONS AND PROBLEM STATEMENT

In this paper the considered nonlinear minimal GD-IK model is a combination of models extracted from papers of (Hariri and Wang, 2011), (Percival et al., 2008):

$$\begin{cases} \dot{g} = -P_1 g(t) - g(t)v(t) + P_1 g_b + g_M(t) \\ \dot{v} = -P_2 v(t) + P_3 i(t) - P_3 i_b \\ \dot{i} = -ni(t) + \gamma(g(t) - h)t \\ y = g(t) \end{cases} \tag{1}$$

where $g(t)$ is the plasma blood glucose level; $i(t)$ is the plasma insulin concentration level; $v(t)$ is the variable which is proportional to the insulin in the remote compartment, g_b is the basal blood glucose level, g_M is the rate of glucose absorption from meal (glucose absorption from the gut) and i_b is the basal insulin level. Parameter P_1 represents glucose effectiveness, P_2 denotes the decreasing level of insulin, P_3 is the rate at which insulin action is increased as the level of insulin deviates from the corresponding baseline, γ is the rate at which insulin is produced, n denotes the fractional insulin clearance and h denotes the pancreatic target glycemia level. As in ((Hariri and Wang, 2011)), we add to the above model the pump dynamics:

$$\dot{w} = \frac{1}{a}(-w(t) + u(t)) \tag{2}$$

where $w(t)$ represents the infusion rate, $u(t)$ the control input and a denotes the time constant of the pump. From now on, this model is rewritten in a general state variable format with four state variables $x_1(t) = g(t),\ x_2(t) = v(t),\ x_3(t) = i(t),\ x_4(t) = w(t)$:

$$\begin{cases} \dot{x}_1 = -P_1 x_1 - x_1 x_2 + P_1 g_b + g_M(t) \\ \dot{x}_2 = -P_2 x_2 + P_3 x_3 - P_3 i_b \\ \dot{x}_3 = -n x_3 + x_4 + \gamma(x_1 - h)t \\ \dot{x}_4 = -\frac{1}{a} x_4 + \frac{1}{a} u \\ y = x_1 \end{cases} \tag{3}$$

This dynamic system can be further expressed in the following compact form:

$$\begin{cases} \dot{x} = f(x) + B_1 u + \nu(t,y) + g_M(t) B_2 \\ y = h(x) \end{cases} \tag{4}$$

where

- $x = (x_1, x_2, x_3, x_4)^T$ is the vector of state variables and $h(x) = x_1$ is the output,
- $f(x) = \begin{pmatrix} -x_1x_2, -P_2x_2 + P_3x_3, -nx_3 + x_4, -\frac{1}{a}x_4 \end{pmatrix}^T$ is the drift vector field
- $B_1 = \begin{pmatrix} 0, 0, 0, \frac{1}{a} \end{pmatrix}^T$ is the control direction,
- $B_2 = \begin{pmatrix} 1, 0, 0, 0 \end{pmatrix}^T$ is the unknown direction,
- $\nu(t,y) = \begin{pmatrix} P_1 g_b - P_1 y, -P_3 i_b, \gamma(y - h)t, 0 \end{pmatrix}^T$ is a direction depending on the output y and time t.

In this work, we consider the following problem: How can we find a change of coordinates $z = \phi(x)$ in order to transform (3) into a nonlinear observer normal form, i.e.

$$\begin{cases} \dot{z} = A_O z + \beta(y,t) + \overline{B}_1 u + \alpha(y) g_M(t) \\ \overline{y} = C_O z = z_4 \end{cases} \tag{5}$$

where $A_O = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix}$, $C_O = \begin{pmatrix} 0 & 0 & 0 & 1 \end{pmatrix}$, and the new output $\overline{y} = \varphi(y)$ is a diffeomorphism of the output y. In addition, this nonlinear observer normal form enables us to deal with the following problems: (i) Design an observer-based feedback if $g_M(t)$ is known or if $g_M(t) = 0$ and (ii) Design an observer-based feedback by the concept of inversion dynamics if $g_M(t)$ is unknown.

3 NONLINEAR OBSERVER NORMAL FORM OF GD-IK

3.1 Transformation Algorithm

There are several sophisticated geometrical algorithms that enable us to transform the dynamic system (4) into a nonlinear observer normal form (5), see

(Krener and Isidori, 1983), (Respondek and Pogromsky, 2004), (Boutat, 2007), (Boutat and Busawon, 2011). In this paper, thanks to the special form of the proposed system, we can establish an algorithm based on matrix calculus. At the same time, we provide an algorithm to compute change of coordinates. For this purpose, let us consider a single input-output dynamic system with the following form:

$$\begin{cases} \dot{x} = Ax + \mu(y,t,u,s(t)) \\ y = Cx \end{cases} \tag{6}$$

with the vector of state variables $x \in \mathbb{R}^n$, the output $y \in \mathbb{R}$ and the function $\mu(y,t,u,s(t))$ which does not depend on the unmeasured state. We assume that the pair (C,A) is observable. Thus, the matrix

$$O = \begin{pmatrix} C \\ CA \\ \dots \\ CA^{n-1} \end{pmatrix}$$

is of full rank n. Let $p(s) = s^n + a_{n-1}s^{n-1} + a_{n-2}s^{n-2} + \dots + a_1 s + a_0$ be the characteristic polynomial of the matrix A. We recall that the Cayley-Hamilton theorem states that $p(A) = 0$. Then the following result holds.

Theorem 1. *The following linear change of coordinates*

$$\begin{array}{l} z_n = Cx \\ z_{n-i} = CA^i x + \sum_{k=1}^{i} a_{n-k} CA^{i-k} x \ \ for \ \ i = 1:n-1 \end{array} \tag{7}$$

transforms the dynamic system (6) into the following observer normal form:

$$\begin{cases} \dot{z} = A_O z + \overline{\mu}(y,t,u,v(t)) \\ y = C_O z = z_n \end{cases} \tag{8}$$

where the pair (C_O, A_O) is in Brunovsky canonical form and $\overline{\mu}$ is defined by its components as follows

$$\begin{array}{l} \overline{\mu}_n = C\mu - a_{n-1} y \\ \overline{\mu}_{n-i} = CA^i \mu + \sum_{k=1}^{i} a_{n-k} CA^{i-k} \mu - a_{n-i-1} y \\ for \ \ i = 1:n-1 \end{array} \tag{9}$$

Proof. We proceed by successive derivation of the change of coordinates given in (7). Then, we obtain:

$$\begin{aligned} \dot{z}_n &= CAx + C\mu = z_{n-1} - a_{n-1}y + C\mu \\ \dot{z}_{n-i} &= z_{n-i-1} - a_{n-i-1}y + CA^i\mu + \\ &\quad + \sum_{k=1}^{i} a_{n-k} CA^{i-k} \mu \qquad (10) \\ &\quad \text{for } \ i = 1:n-2 \qquad (11) \\ \dot{z}_1 &= -a_0 y + CA^{n-1}\mu + \sum_{k=1}^{n-1} a_{n-k} CA^{n-1-k} \mu \end{aligned}$$

where the last equation is obtained by using the Cayley-Hamilton theorem. □

3.2 Application to the GD-IK

In this subsection, we will apply the results obtained in the previous section to the GD-IK model. Let us consider the nonlinear dynamic system (3). We start by transforming it first into the form (6). For this we use the concept of diffeomorphism on the output (see (Respondek and Pogromsky, 2004) ,(Boutat, 2007), (Boutat and Busawon, 2011), (Boutat et al., 2009)). In our case we define the new output $\overline{y} = -\ln(y)$. Hence, if we consider the new variable $\xi = -\ln(x_1)$, then the dynamic system (3) is rewritten as follows:

$$\begin{cases} \dot{\xi} = x_2 + P_1 - P_1 e^{\overline{y}} g_b - e^{\overline{y}} g_M \\ \dot{x}_2 = -P_2 x_2 + P_3 x_3 - P_3 i_b \\ \dot{x}_3 = -n x_3 + x_4 + \gamma(e^{-\overline{y}} - h)t \\ \dot{x}_4 = -\frac{1}{a} x_4 + \frac{1}{a} u \\ \overline{y} = \xi = -\ln y \end{cases} \tag{12}$$

With the definition of the matrix

$$A = \begin{pmatrix} 0 & 1 & 0 & 0 \\ 0 & -P_2 & P_3 & 0 \\ 0 & 0 & -n & 1 \\ 0 & 0 & 0 & -\frac{1}{a} \end{pmatrix}$$

and the vector $C = \begin{pmatrix} 1 & 0 & 0 & 0 \end{pmatrix}$, the dynamic system given in (12) can be written in the desired form given in (6):

$$\begin{aligned} \dot{X} &= AX + B_1 u + B_2(y) g_M + \beta(y,t) \\ \overline{y} &= CX = \xi \end{aligned}$$

with $X = (\xi, x_2, x_3, x_4)^T$ and $\mu = B_1 u + B_2(\overline{y}) g_M + \beta(\overline{y}, t)$.

As the pair (C,A) is observable, we can use Theorem 1. The characteristic polynomial of A is given by $s^4 + \left(n + P_2 + \frac{1}{a}\right) s^3 + \left(\frac{1}{a}(n + P_2) + nP_2\right) s^2 + \frac{1}{a} n P_2 s$, then the change of coordinates can be given by th following expression:

$$\begin{array}{l} z_1 = \frac{1}{a} P_3 x_3 + \frac{n}{a} x_2 + P_3 x_4 - \frac{1}{a} n P_2 \ln x_1 \\ z_2 = P_3 x_3 + \left(n + \frac{1}{a}\right) x_2 - \left(\frac{1}{a}(n + P_2) + nP_2\right) \ln x_1 \\ z_3 = x_2 + \left(n + P_2 + \frac{1}{a}\right) \ln x_1 \\ z_4 = -\ln x_1 = \xi \end{array}$$

Therefore, we obtain the nonlinear observer normal form (6) for the nonlinear dynamic system (3) as follows:

$$\begin{cases} \dot{z} = A_O z + \beta(y,t) + \overline{B}_1 u + \alpha(y) g_M(t) \\ \overline{y} = C_O z = z_4 \end{cases} \tag{13}$$

where

- $\beta(\overline{y},t) = \begin{pmatrix} \beta_1, \beta_2, \beta_3, \beta_4 \end{pmatrix}^T$ with $\beta_1 = \left(\frac{1}{a}\left(e^{-\overline{y}} - h\right) t\gamma P_3 - \frac{1}{a} n P_3 i_b\right) + \frac{1}{a} n P_2 P_1 + \frac{P_1}{\overline{y}} \frac{1}{a} n P_2 g_b$, $\beta_2 = \frac{1}{a} n P_2 \ln x_1 +$

$P_3\gamma(e^{-\bar{y}} - h)t - \left(n+\frac{1}{a}\right)P_3 i_b + \left(\frac{1}{a}(n+P_2)+nP_2\right)P_1 + \frac{P_1}{\bar{y}}\left(\frac{1}{a}(n+P_2) + nP_2\right)g_b$,
$\beta_3 = -\left(\frac{1}{a}(n+P_2)+nP_2\right)\bar{y} - P_3 i_b + \left(n+P_2+\frac{1}{a}\right)P_1 + \frac{P_1}{\bar{y}}(n + P_2 + \frac{1}{a})g_b$,
$\beta_4 = -\left(n+P_2+\frac{1}{a}\right)\bar{y} + P_1 + \frac{P_1}{\bar{y}} g_b$

- $\overline{B}_1 = \left(\frac{P_3}{a}, 0, 0, 0 \right)^T$
- $\alpha(\bar{y}) = \frac{1}{\bar{y}}\left(\frac{1}{a}nP_2, \frac{1}{a}(n+P_2)+nP_2, n+P_2+\frac{1}{a}, 1 \right)^T$

4 OBSERVER DESIGN

In this section we will present two types of observers. The first one assumes that g_M is known and the second one assumes that g_M is unknown. In the last case we will design an observer to estimate both the state and g_M. First, it should be noted that (13) is controllable.

4.1 Full Order Observer

In the first case, we consider (13) and we define the following observer-based feedback:

$$\dot{\hat{z}} = A_O\hat{z} + \beta(y,t) + \overline{B}_1 u + \alpha(y)g_M + K(\hat{\bar{y}} - \bar{y}). \quad (14)$$

If we set the observation error $e = \hat{z} - z$, we can obtain that its dynamics is linear and given by $\dot{e} = (A_O + KC_O)e$.As the pair (C_O, A_O) is observable we can find a gain K such that $A_O + KC_O$ is asymptotically stable.
We provide also an observer-based feedback with $u = K\hat{z}$ such that the output $g(t)$, the glucose level, reaches the glucose basal level $(99mg/dl)$, see also Fig. 1. The estimations of the states as well as the actual values obtained in the simulation are given in Fig. 2 - Fig. 4, respectively. The parameters and initial states used in the simulations are: $P_1 = 0$ $P_2 = 0.81/100$, $P_3 = 4.01/1e6$ $n = 0.23$, $a = 2$, $gb = 99$, $ib = 8$, $\gamma = 2.4/1000$, $h = 93$, $x_1(0) = 337$, $x_2(0) = 0$, $x_3(0) = 192$, $x_4(0) = 2$. These parameters and initial states are the same as in (Hariri and Wang, 2011).

4.2 Observer for Unknown Input

In the second case we assume that g_M is an unknown input and we will design an observer to estimate both the state and g_M. If we consider g_M as an unknown input, we can follow (Kudva et al., 1980), (Yang and Wilde, 1988), (Darouach et al., 1994), (Hui and Zak, 2005), (Bhattacharyya, 1978) which leads to a decomposition of the state of the observer normal form (13) into two parts, namely the unmeasurable and the

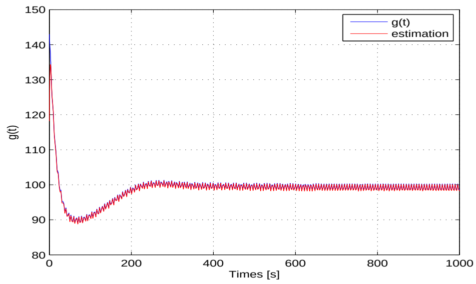

Figure 1: Evolution of $g(t)$.

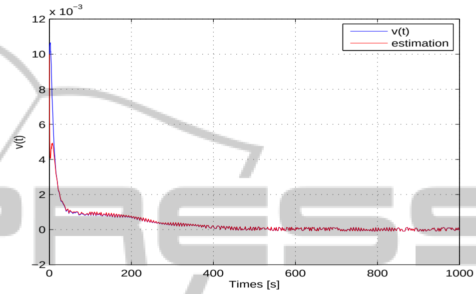

Figure 2: Evolution of $v(t)$.

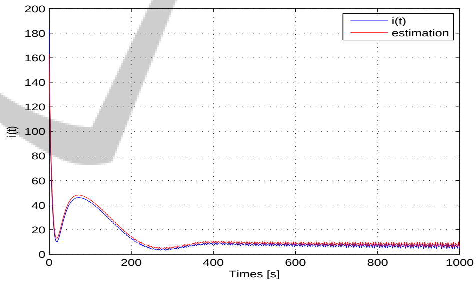

Figure 3: Evolution of $i(t)$.

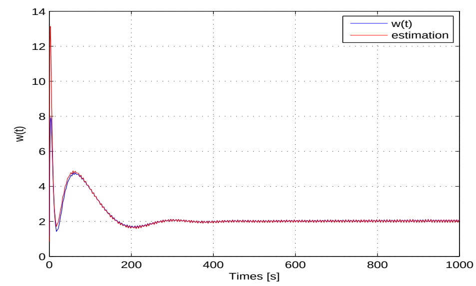

Figure 4: Evolution of $w(t)$.

measurable part: $z = (I - MC)z + MCz = q + My$, where

$$M = \frac{1}{C_O\alpha}\alpha = \left(\frac{1}{a}nP_2, \frac{1}{a}(n+P_2)+nP_2, n+P_2+\frac{1}{a}, 1 \right)^T$$

is a constant matrix even if α is not constant. Therefore we have the following projector:

$$\tilde{\Pi} = I - MC = \begin{pmatrix} 1 & 0 & 0 & -\frac{1}{a}nP_2 \\ 0 & 1 & 0 & -\left(\frac{1}{a}(n+P_2)+nP_2\right) \\ 0 & 0 & 1 & -\left(n+P_2+\frac{1}{a}\right) \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Now, we consider the dynamics of the unknown part q. Thanks to the fact that $\tilde{\Pi}\alpha = 0$, we obtain $\dot{q} = \tilde{\Pi}\left(A_O q - My + \overline{B}_1 u + \beta(y,t)\right)$. An observer for this last dynamic system is derived as follows:

$$\begin{aligned} \dot{\hat{q}} &= \tilde{\Pi}\left(A_O\hat{q} - My + \overline{B}_1 u + \beta(y,t)\right) - \\ &\quad -\tilde{\Pi}\left(LC_O(\hat{q}-q)\right) \qquad (15) \\ \hat{z} &= \hat{q} + My \qquad (16) \end{aligned}$$

Therefore, the dynamics of the error $e_q = \hat{q} - q$ is given by $\dot{e}_q = \tilde{\Pi}(A_O - LC_O)e$. In order to write the projector $\tilde{\Pi}$ in the canonical form, we proceed as in the algorithms described in (Kudva et al., 1980), (Yang and Wilde, 1988), (Darouach et al., 1994), (Hui and Zak, 2005), (Bhattacharyya, 1978), and we consider the change of coordinates given by the following matrix:

$$Q = \begin{pmatrix} 1 & 0 & 0 & \frac{1}{a}nP_2 \\ 0 & 1 & 0 & nP_2 + \frac{1}{a}(n+P_2) \\ 0 & 0 & 1 & n+P_2+\frac{1}{a} \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

In these new coordinates the projector $\tilde{\Pi} = I - MC$ becomes:

$$\Pi = Q^{-1}\tilde{\Pi}Q = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and the matrix A_O is decomposed into four blocs:

$$\tilde{A}_O = Q^{-1}A_O Q = \begin{pmatrix} \widetilde{A}_{1,1} & \widetilde{A}_{1,2} \\ \widetilde{A}_{2,1} & \widetilde{A}_{2,2} \end{pmatrix}$$

where $\widetilde{A}_{1,1} = \begin{pmatrix} 0 & 0 & -\frac{1}{a}nP_2 \\ 1 & 0 & -\frac{1}{a}(n+P_2) - nP_2 \\ 0 & 1 & -P_2 - \frac{1}{a} - n \end{pmatrix}$

$\widetilde{A}_{2,1} = \begin{pmatrix} 0 & 0 & 0 \end{pmatrix}$ $\widetilde{A}_{1,2} =$

$$\begin{pmatrix} -\frac{1}{a}nP_2\left(n+P_2+\frac{1}{a}\right) \\ \frac{1}{a}nP_2 + \frac{1}{a}\left(n+P_2+\frac{1}{a}\right)(-n-P_2-anP_2) \\ nP_2 + \frac{1}{a}(n+P_2) + \frac{1}{a}\left(n+P_2+\frac{1}{a}\right)(-an-aP_2-1) \end{pmatrix}$$

$\widetilde{A}_{2,2} = 0$, $\widetilde{C} = CQ = \left(\widetilde{C}_1, \widetilde{C}_2\right)$ with $\widetilde{C}_1 = \begin{pmatrix} 0 & 0 & 0 \end{pmatrix}$ and $\widetilde{C}_2 = 1$. The following result is widely established in (Kudva et al., 1980), (Yang and Wilde, 1988), (Darouach et al., 1994), (Hui and Zak, 2005), (Bhattacharyya, 1978):

Theorem 2. *As $rank(C_O\alpha) = rank(\alpha)$ and the pair $(\widetilde{A}_{1,1}, \widetilde{C}_1)$ is detectable (because $\widetilde{A}_{1,1}$ is asymptotically stable for all initial condition $q(0) = Pz(0)$), (15) is an asymptotic observer.*

Remark 3. *The observer normal for (14) becomes under the change of coordinates $\tilde{z} = Qz$ as follows:*

$$\dot{\tilde{z}} = \tilde{A}_O\tilde{z} + \tilde{\beta}(y,t) + \overline{B}_1 u + \tilde{\alpha}(y)G_M \qquad (17)$$

where $\overline{B}_1$ has not changed, $\tilde{\alpha} = Q^{-1}\alpha = (0,0,0,\frac{1}{y})^T$, and $\tilde{\beta} = Q^{-1}\beta = \beta + \beta_4 Q^{-1}(0,0,0,1)^T - (0,0,0,\beta_4)^T$.

Now, we are ready to compute the inverse dynamics of the observer normal form (13). For this, let us denote $z_r = (\tilde{z_1}, \tilde{z_2}, \tilde{z_3})^T$, $\tilde{\beta}_r = (\tilde{\beta_1}, \tilde{\beta_2}, \tilde{\beta_3})^T$, and $\overline{B}_{1,r} = (\overline{B}_{1,1}, 0, 0)^T$, then the inverse dynamics is as follows:

$$\begin{cases} \dot{z}_r = \tilde{A}_{1,1} + \overline{B}_{1,r}u + \tilde{\beta}_r(y,t) \\ g_M = e^{-\overline{y}}(\dot{\overline{y}} - \beta_4) \end{cases} \qquad (18)$$

Using the same parameters and initial states given in the previous subsection, an estimation of the unknown g_M is performed. The results of this simulation are depicted in Fig. 5.

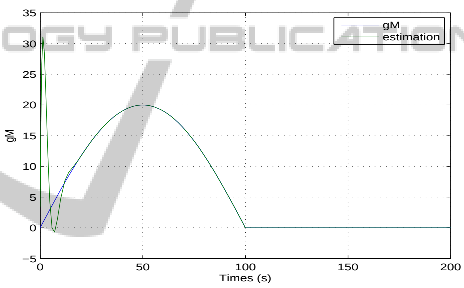

Figure 5: Estimation by inverse dynamics of g_M.

Remark 4. *The existing papers dealing with the observer of the GD-IK model given by the nonlinear dynamic system (3), only estimated the glucose level $g(t)$. However, in this work we estimate also $i(t)$ and $\nu(t)$. Moreover, we estimate by inverse dynamics g_M which has not been addressed anywhere yet.*

5 CONCLUSIONS

To the best of our knowledge this paper is the first one which has dealt with observer an design for the minimal model GD-IK using the nonlinear observer form concept. Moreover, it has applied the inverse dynamics of the GD-IK model in the case where the amount of glucose absorption is unknown or considered as a meal disturbance input. First simulation results have underlined the correctness and applicability of this novel approach. Furthermore, this observer can be used to design a controller to regulate the glucose level.

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