Linear time-varying Luenberger observer applied to diabetes

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ABSTRACT

We present a linear time-varying Luenberger observer (LTVLO) using compartmental models to estimate the unmeasurable states in patients with type 1 diabetes. The LTVLO proposed is based on the linearization in an operation point of the virtual patient (VP), where a linear time-varying system is obtained. LTVLO gains are obtained by selection of the asymptotic eigenvalues where the observability matrix is assured. The estimation of the unmeasurable variables is done using Ackermann’s methodology. Additionally, it is shown the Lyapunov approach to prove the stability of the time-varying proposal. In order to evaluate the proposed methodology, we designed three experiments: A) VP obtained with the Bergman minimal model; B) VP obtained with the compartmental model presented by Hovorka in 2004; and C) real patients data set. For experiments A) and B), it is applied a meal plan to the VP, where the dynamic response of each state model is compared to the response of each variable of the time-varying observer. Once the observer is evaluated in experiment B), the proposal is applied to experiment C) with data extracted from real patients and the unmeasurable state space variables are obtained with the LTVLO. LTVLO methodology has the feature of being updated each instant of time to estimate the states under a known structure. The results are obtained using simulation with MATLAB and SIMULINK. The LTVLO estimates the unmeasurable states from in silico patients with high accuracy by means of the update of Luenberger gains at each iteration. The accuracy of the estimated state space variables is validated through fit parameter.

1 INTRODUCTION

Diabetes is a chronic disease characterized by high levels of blood glucose (hyperglycemia). Type 1 diabetes mellitus (T1DM) occurs when the pancreas does not produce insulin due to an immune system response that destroys the β cells, which are responsible to produce insulin, that is the key hormone of carbohydrate metabolism. β cells response in a healthy person is characterized by reducing or increasing insulin secretion to match low or high blood glucose concentrations Pørksen (2002). An hyperglycemic condition leads to serious damage on many of the body’s systems in a medium-term time, especially in nerves and blood vessels, developing retinopathy and nephropathy among others. Since 1920 insulin therapy has evolved bringing the ability to mimic the average physiological profile of insulin secretion with the aim of trying to regulate glucose levels Grunberger (2013).

T1DM is controlled by therapies based on the administration of exogenous insulin following multiple insulin injections (MDI) Control et al. (1993). Nowadays, the use of insulin pumps makes the treatment less invasive, reducing pain associated MDI and can improve patient lifestyle Jeandidier et al. (2008). The alternative treatment with insulin pumps is based on continuous subcutaneous insulin infusion (CSII) systems Linkeschova et al. (2002). When exogenous insulin is administered in excess appears hypoglycaemia events (low blood glucose levels), which is very dangerous to human body in short-term time.

Patients have to decide the insulin bolus to be administered before each carbohydrate intake (CHO).
To fit this prandial bolus to the meal is a complex task, mainly due to the variability in insulin effects and the presence of CHOs with different absorption rates. People with T1DM may try to reduce the insulin doses to avoid hypoglycaemia, but increasing the hyperglycaemia risk. The development of an artificial pancreas (AP) is a field of intensive research to optimize patients' CSII therapy reducing the associated risks and to avoid the patient dependence of his illness using closed loop algorithms.

An AP integrates three components: an insulin pump, a subcutaneous continuous glucose monitoring (CGM) system and a control algorithm connected by wireless communication. The current challenges of the scientific community working on building the AP are: develop more reliable CGM sensors, create faster-acting insulin, administrate the glucagon hormone to recover from hypoglycaemia and designing control algorithms. The control algorithms should be capable of: dealing with physiological inter patient and intra patient variability and working stable way against delays in subcutaneous glucose measurement and insulin action. Mathematical modeling is a powerful tool that allows describing the behaviour of a dynamic system. Mathematical models emerge as an option to save resources at the time of testing, allowing simulations that could be dangerous to perform with the system described by the model. The availability of mathematical models to deal with a specific disease does not guarantee the success of a control algorithm on the treatment of such disease.

Different disturbances are taken into account by mathematical models describing T1DM: some disturbances are the endogenous glucose production in the liver, renal excretion, insulin-independent glucose utilization (brain and central nervous system) and the bioavailability of the ingested CHOs. Other disturbance is physical activity practicing but, still it is not considered on the mathematical models; another disturbances such as stress situations are not modeled as parametric variation.

On the other hand, it is known that in the design of control algorithms, it is necessary the complete knowledge of the plant (the T1DM patient in this particular case) variables, which means that all state space variables are measurable; but in reality this is not possible. Independently of the model chosen for the control algorithm design, it is only possible to measure the subcutaneous glucose concentration considered as the output variable and to know the model input, that is, the insulin dose amount. The main alternative to approach this problem is the use of linear and non-linear observers. Such is the case of the Luenberger observer applied to linear and non-linear systems, Heydari and Demetriou (2015), Wu et al. (2012), Chen et al. (2015). Other observers are using sliding modes Liu (2014), Mincarelli et al. (2015), Zhang et al. (2015), Chen and Chowdhury (2010), Xia et al. (2015). The ones applied to artificial pancreas Palumbo et al. (2012, 2013), Kovács et al. (2007), Palumbo et al. (2014), among others. The strategies that use these observers result in obtaining constant gains, which in a general way, constitutes a good alternative in order to estimate the unmeasurable variables.

In this paper we propose to extend the theory of Luenberger observers for time-invariant systems, to time-varying systems. These time-varying systems result from the linearization of two T1DM nonlinear models. This type of Luenberger linear time-varying observer should be capable of estimating the unmeasurable variables with a structure of known models. The observer should be robust to deal with parametric variability in T1DM patients that will change within the day and also from day to day, due to lifestyle changes and metabolic performance. The main disturbance to take into account is a meal, composed mainly of CHOs, which is usually used to stimulate the dynamic system of a T1DM patient.

We design a Luenberger linear time-varying observer to the field of the AP using Bergman and Hovorka (2004) compartmental models. The observer is used to estimate unmeasurable variables from patients with T1DM. The computation of the time-varying Luenberger gains is obtained by the correct selection of the asymptotic eigenvalues to assure convergence of the unmeasurable variables and Lyapunov stability proof is done. Different experiments are used to evaluate the methodology, using VP, and data extracted from insulin and glucose variables obtained from real patients. In order to validate the methodology, statistical analysis is done.

This paper is organized as follows: in section 2 the main theoretical information regarding the T1DM models used in this work is explained, as well as the state space observers; in section 3, the proposed methodologies for the time-varying formulation and the experiments design are described; in section 4 the results of the present work are shown; some discussion is presented in section 5 and finally, conclusions are expressed in section 6.
2 STATE OF ART

T1DM patients can be described physiologically through mathematical models, whose output and input are the glucose concentration and the insulin infusion, respectively. In this work a time variant state space observer is designed for two mathematical models commonly used to describe T1DM patients.

2.1 Bergman Model

The Bergman minimal model contains three state space variables that describe the glucose-insulin regulatory system. With the purpose of facilitating the mathematical comprehension on later sections, in this work the Bergman model is taken from [Bergman et al., 1979] and is arranged in state space form as follows:

\[
\begin{align*}
\dot{x}_1 &= -p_1 [x_1 - G_b] - x_2 x_1 + d \\
\dot{x}_2 &= -p_2 x_2 + p_3 [x_3 - I_b] \\
\dot{x}_3 &= -\eta [x_3 - I_b] + u_i
\end{align*}
\]

(1)

where \( x_1 \) renames \( G \) (blood glucose concentration) \((mg/dl)\), \( x_2 \) corresponds to \( X \) (insulin influence on glucose concentration reduction) \((1/min)\), and \( x_3 \) replaces \( I \) (insulin concentration in plasma) \((\mu U/ml)\).

Table 1 describes the parameters and values for three T1DM patients and the information of a healthy person is included. The parameterization was obtained from [Kaveh and Shtessel, 2008] to simulate in silico patients with the Bergman model (1).

Table 1. Bergman model parameter values.

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Patient zero</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>( p_1 )</td>
<td>0.0317</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>( p_2 )</td>
<td>0.0123</td>
<td>0.0112</td>
<td>0.0123</td>
<td>0.0072</td>
<td>0.0142</td>
</tr>
<tr>
<td>( p_3 )</td>
<td>( 8.2 \times 10^{-8} )</td>
<td>( 4.48 \times 10^{-8} )</td>
<td>( 8.2 \times 10^{-8} )</td>
<td>( 3.6 \times 10^{-8} )</td>
<td>( 1.656 \times 10^{-6} )</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>( 6.5 \times 10^{-5} )</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>( \eta )</td>
<td>0.2659</td>
<td>0.2646</td>
<td>0.2659</td>
<td>0.2659</td>
<td>0.2659</td>
</tr>
<tr>
<td>( h )</td>
<td>79.0353</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Observer parameters

For all patients \( G_b = 70mg/dl \) and \( I_b = 7mU/dl \) are the basal glucose and basal insulin respectively.

2.1.1 Generating VP with Bergman minimal model

Berger and Rodbard modeled the course of insulin absorption which is basically responsible for the characteristic form of plasma profiles for different types of insulin and how its kinetic evolves [Berger and Rodbard, 1989]. Below is a mathematical representation of the profile that appears in blood as the initial insulin deposit is diluted after insulin is administered:

\[
u_i = u - \frac{s}{\tau^2} \frac{T_{50} r_2}{r_1} \frac{(e^{-r_1 t} - e^{-r_2 t})}{(T_{50} + \tau)^2},
\]

(2)

where \( u \) is the insulin dose that has been injected as a bolus \((UI)\), which is represented as amplitude of Dirac-delta; \( T_{50} \) is time interval to permit 50% of injected dose to be absorbed; \( s \) is the parameter itself absorption type of insulin used, and \( \tau \) is the time after injection.

Lehmann and Deutsch modeled CHOs absorption via intestinal as \( d \) [Lehmann and Deutsch, 1992], which is considered the main disturbance of Bergman systems, using the following function:

\[
d = u_C(t) \frac{r_1 r_2}{r_2 - r_1} (e^{-r_1 t} - e^{-r_2 t}),
\]

(3)

where \( u_C(t) \) is the amount of ingested carbohydrates \((g \text{ of CHOs})\), \( r_1 \) and \( r_2 \) \((1/min)\) are specific parameters for the type of CHOs that represent a slow rate of assimilation.

The equations (2) and (3) are absorption functions added to Bergman model, which shape the absorption of insulin administered as a bolus and CHOs ingested amount (both depicted as delta signals in simulation), respectively to in silico patients. The absorption functions to generate a VP with the Bergman model use the next parameterization in equations (2)-(3): \( s = 1.7; a = 0.02 \text{ unitless} \) and \( b = 1 \text{ unitless} \) are natural constants of the Lispro insulin [Berger and Rodbard, 1989]: \( r_1 = 0.0170 \text{ 1/min} \) and \( r_2 = 0.173 \text{ 1/min} \).
2.2 Hovorka model

The model was built based on experimental and modeling work, which employed glucose tracers to determine structure and parameter values of glucose kinetics [Hovorka et al. (2002)]. The Hovorka model described in [Hovorka et al. (2004) and Wilinska et al. (2010)] consists of a glucose subsystem (glucose absorption, distribution and disposal), an insulin subsystem (insulin absorption, distribution and disposal), and an insulin action subsystem (insulin action on glucose transport, disposal and endogenous production).

With the aim of using a common nomenclature, the Hovorka model is rewritten in terms of $x_i$ as follows:

$$
\begin{align*}
\dot{x}_1 &= k_d (G(t) - x_1) \\
\dot{x}_2 &= - \left( \int_0^t f_{01} f_{G(t)} + x_4 \right) x_2 + k_{12} x_3 - EGP_0 x_6 + d \\
\dot{x}_3 &= x_4 x_2 - [k_{12} + x_5] x_3 \\
\dot{x}_4 &= - k_{d1} x_4 + k_{b1} x_7 \\
\dot{x}_5 &= - k_{d2} x_5 + k_{b2} x_7 \\
\dot{x}_6 &= - k_{d3} x_6 + k_{b3} x_7 \\
\dot{x}_7 &= \frac{v_t}{t_{max,t}} - k_c x_7 \\
\dot{x}_8 &= \frac{x_8}{t_{max,f}} - \frac{x_8}{t_{max,f}} \\
\dot{x}_9 &= u - \frac{x_9}{t_{max,f}}
\end{align*}
$$

where $x_1$ represents $C$ and is glucose concentration ($\text{mmol/l}$) in the subcutaneous tissue. This submodel of the interstitial glucose kinetics was added from Wilinska et al. (2010). $x_2$ replaces $Q_1$ and represents the mass of glucose in the accessible compartment ($\text{mmol}$); $x_3$ rewrites $Q_2$ that is the non-accessible glucose mass compartment ($\text{mmol}$); $x_4$ corresponds to $X_1$ and is the remote effect of insulin on glucose distribution/transport ($1/\text{min}$); $x_5$ substitutes $X_2$ and is the remote effect of insulin on glucose disposal ($1/\text{min}$); $x_6$ renames $X_3$ that is the remote effect of insulin on endogenous glucose production ($1/\text{min}$); $I$ is changed by $x_7$ and is the plasma insulin concentration ($\text{mU/ml}$); $x_8$ and $x_9$ are interchanged with $S_2$ and $S_1$, respectively, and are two-compartments chain representing absorption of subcutaneously administered short-acting insulin ($\text{mU}$); $G(t) = x_2/V_G$ is the glucose concentration in the plasma ($\text{mmol/l}$); $u$ is the insulin dose ($\text{mU}$). The inner and outer disturbances are expressed as:

$$
d = U_G(t) + EGP_0 - f_R - f_{01}',
$$

where $EGP_0$ represents the endogenous glucose production extrapolated to a 0 concentration ($\text{mmol/min}$) $f_R$ is the renal glucose clearance ($\text{mmol/min}$) above the glucose threshold of 9 $\text{mmol/l}$ represented as:

$$
f_R = \begin{cases} 
0.003(G(t) - 9) V_G & \text{if } G(t) \geq 9 \text{ mmol/l} \\
0 & \text{otherwise}
\end{cases}
$$

$f_{01}'$ ($\text{mmol/min}$) as the total non-insulin-dependent glucose flux corrected by the ambient glucose concentration represented as:

$$
f_{01}' = \begin{cases} 
\frac{f_{01}}{G(t)} & \text{if } G(t) \geq 4.5 \text{ mmol/l} \\
\frac{f_{01}}{3.5} & \text{otherwise}
\end{cases}
$$

The Glucose absorption is a fundamental process affecting postprandial glucose excursions. In Hovorka model [4], the gut absorption rate $U_G(t)$ ($\text{mg/min}$) is represented by:

$$
U_G(t) = \frac{D_G A_G \tau}{t_{max,G} e^{\frac{-t}{t_{max,G}}}},
$$

where $t_{max,G}$ is the time-of-maximum appearance rate of glucose in the accessible glucose compartment, $D_G$ is the amount ($\text{mg}$) of CHOs ingested, $A_G$ is carbohydrate bioavailability ($\text{unitless}$).

Table [2] includes the parametric values of six Hovorka patients (VP#1 - VP#6) and a VP#0, whose parameterization is contained around a mean considering a standard deviation of the other six patients [Hovorka et al. (2002)].

The parameters plasma insulin elimination rate $k_c = 0.138(1/\text{min})$, CHOs bioavailability $A_G = 0.8(\text{unitless})$, CHOs absorption max time $t_{max,G} = 40(\text{min})$ and max time of short action insulin absorption $t_{max,l} = 55(\text{min})$ are equal for the six patients and patient zero.
Table 2. Hovorka model parameter values and description.

<table>
<thead>
<tr>
<th>Symbol / units</th>
<th>Description</th>
<th>Value per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>zero* 1 2 3 4 5 6</td>
</tr>
<tr>
<td>$k_{12}$ (1/min)</td>
<td>Transfer rate</td>
<td>0.066 0.0343 0.0871 0.0863 0.0968 0.0390 0.0458</td>
</tr>
<tr>
<td>$k_{d1}$ (1/min)</td>
<td>Deactivation rate</td>
<td>0.006 0.0031 0.0157 0.0029 0.00088 0.0007 0.0017</td>
</tr>
<tr>
<td>$k_{d2}$ (1/min)</td>
<td>Deactivation rate</td>
<td>0.06 0.0752 0.0231 0.0495 0.0302 0.1631 0.0689</td>
</tr>
<tr>
<td>$k_{d3}$ (1/min)</td>
<td>Deactivation rate</td>
<td>0.03 0.0472 0.0143 0.0691 0.0118 0.0114 0.0285</td>
</tr>
<tr>
<td>$V_I$ (l/kg)</td>
<td>Insulin volume distribution</td>
<td>0.12 0.18 0.13 0.22 0.14 0.14 0.13</td>
</tr>
<tr>
<td>$V_G$ (l/kg)</td>
<td>Glucose volume distribution</td>
<td>0.16 0.18 0.13 0.22 0.14 0.14 0.13</td>
</tr>
<tr>
<td>$k_{b1}$ (1/min)</td>
<td>Insulin elimination rate</td>
<td>3.584 2.076 6.932 2.9435 9.471 4.6457 1.0823</td>
</tr>
<tr>
<td>$k_{b2}$ (1/min)</td>
<td>Insulin elimination rate</td>
<td>5.74 1.541 3.327 1.2437 1.7743 2.2875 5.0257</td>
</tr>
<tr>
<td>$k_{b3}$ (1/min)</td>
<td>Insulin elimination rate</td>
<td>1.82 4.3112 1.2797 4.9925 1.062 1.0042 7.695</td>
</tr>
<tr>
<td>$E_{GP_0}$ (mmol/kg/1/min)</td>
<td>EGP extrapolated to 0 insulin concentration</td>
<td>0.0161 0.0148 0.0143 0.0156 0.0213 0.0200 0.0105</td>
</tr>
<tr>
<td>$F_{0i}$ (mmol/kg/1/min)</td>
<td>Glucose flux non insulin dependent</td>
<td>0.0097 0.0121 0.0075 0.0103 0.0119 0.0071 0.0092</td>
</tr>
<tr>
<td>$ICR$ (U/g)</td>
<td>Insulin-CHO ratio</td>
<td>0.1 0.13 0.1 0.12 0.1 0.07 0.12</td>
</tr>
<tr>
<td>$BIR$ (U/hr)</td>
<td>Basal insulin ratio</td>
<td>0.8 0.89 0.95 0.9 1.05 1.2 1.1</td>
</tr>
</tbody>
</table>

* Observer parameters

3 METHODOLOGY

In this section, the proposed method is described in generic terms, where the time-varying observer design and its implementation are presented. Additionally, it is shown the Lyapunov approach in order to prove the stability of the time-varying proposal.

3.1 Linear time-varying Luenberger observer design

In order to introduce the proposed method let us consider a continuous-time nonlinear Single-Input-Single-Output (SISO) disturbed system, which represents the structure of the Hovorka and Bergman compartmental models, as follows:

$$\dot{x} = f(x) + g(x)u + d,$$

$$y = h(x),$$

where $x \in \mathbb{R}^{n \times 1}$ is the state space vector; $u$ is the input signal; $y \in \mathbb{R}^{1 \times n}$ represents the output of the system, with $n$ as the state dimension; $f(x)$ and $g(x)$ constitute smooth vector functions; $d$ represents the vector function of external and internal disturbance; $h(x)$ is a smooth function continuous and differentiable. For both aforementioned models Bergman (1) and Hovorka (4) $u$ is the insulin infusion dose; the output signal in Bergman’s model (1) $y = x_1 = G$ is the plasma glucose concentration and in Hovorka’s model (4) $y = x_1 = C$ is the interstitial glucose concentration measured through CGM sensor. Then, system (9)-(10)
is linearized using the Jacobian of the following form \cite{sidori2000}:

\[
A = \frac{\partial f(x)}{\partial x} \bigg|_{x = \rho}, \quad b = \frac{\partial g(x)}{\partial u} \bigg|_{x = \rho}, \quad c = \frac{\partial h(x)}{\partial x} \bigg|_{x = \rho}.
\] (11)

In order to avoid the loss of information by the linearization process, the operation point \( \rho \) used to evaluate the resulting matrices from the Jacobian, is going to be updated with the new values of state variables at each instant of time \( t \), resulting the following linear time-varying system:

\[
\dot{x} = A(t)x + bu + d,
\] (12)

\[
y = cx.
\] (13)

where \( A(t) \) is the time-varying state matrix containing the dynamic information of linearized state space variables; \( b \) is the input vector, \( u \) is the control signal; \( c \) is the output vector. For this particular application \( d \) is considered as disturbance due to real amount of CHO intake.

The conventional Luenberger observer has been a popular approach to state estimation for linear dynamical systems. In the well known linear Luenberger observer, the output of the system (subcutaneous glucose measurement) is compared with the estimated output by the observer (estimated glucose). With the estimated state vector \( \hat{x} \), then is calculated the output estimation error \( (e = y - \hat{c}x) \) passing through an \( n \times 1 \) constant gain vector \( l \) is used as correcting term, in order to estimate the state \( x \) of system \( (12)-(13) \) \cite{chen1995}. If the gain \( l \) is properly designed, the difference will drive the estimate state to the actual state. Such estimator is called an asymptotic estimator and is described by the following equation:

\[
\dot{\hat{x}} = A\hat{x} + bu + d_1 + l(y - c\hat{x})
\] (14)

where \( \hat{x} = [\hat{x}_1 \ \hat{x}_2 \ \cdots \ \hat{x}_n]^\top \) is the estimated state vector, and \( l \in \mathbb{R}^{n \times 1} \) represents the Luenberger gain vector, \( d_1 \) is the meal absorption used in the observer. The idea of this observer is to compute the constant gain vector \( l \) such that all eigenvalues of matrix \( \left[A - lc\right] \) from equation (14), can be set arbitrarily in the left-half of the complex plane using Ackermann’s methodology. This can be done if and only if the pair \( (A, c) \) of system \( (12)-(13) \) is observable \cite{ackermann1972}.

In the present paper, the linear Luenberger observer theory for time-invariant systems is extended for linear time-varying Luenberger observer. These time-varying systems result from the linearization of two T1DM nonlinear models (Bergman and Hovorka) treated in this work.

In order to estimate the dynamic of nonlinear system \( (9)-(10) \) including the available information about external and internal disturbances \( d \), we propose to extend the linear time-invariant theory from equation (14) designing a time-varying Luenberger observer for a system with the form \( (12)-(13) \), as:

\[
\dot{\hat{x}} = A(t)\hat{x} + bu + d_1 + l(t)(y - c\hat{x}),
\] (15)

where \( A(t) \) is the linear time-varying state matrix, \( b \) is the input vector, \( d_1 \) are the general disturbances used in the observer, \( l(t) \) is the Luenberger’s time-varying gain vector, which includes the time-varying feature of the present proposal, and \( (y - c\hat{x}) \) is the estimation error computed as the difference between measurable output \( y \) and estimated output \( c\hat{x} \).

The procedure to obtain the time-varying formulation consists of two stages, which are explained in the flow diagram presented in Figure 1. In this diagram, the block enclosed by short dashed line corresponds to **Stage I**, where it is tested the observability condition; this stage is executed only one time at beginning of the process. The block enclosed by long dashed line corresponds to **Stage II**, where it is obtained the estimation of state space variables, this stage is executed as infinite loop. These stages are detailed as follows:

**Stage I.** It is proved the observability property of system \( (12) \) at instant time \( t_0 \):

a) The system \( (9)-(10) \) is linearized around an operation point \( \rho \), through Jacobian at time \( t_0 \). The operation point \( \rho \) is selected when output \( y = x_1 = 90 \text{ mg/dl} \) and are extracted the other state variables values to evaluate \( (11) \).
b) It is proved the observability condition in $t_0$ of system \((12)-(13)\): the $n$-dimensional pair \((A(t), c)\) is observable at $t_0$ if there exists a finite interval of time $t_1 > t_0$ such that:

$$\operatorname{rank} \begin{bmatrix} N_0(t_1) \\ N_1(t_1) \\ \vdots \\ N_{n-1}(t_1) \end{bmatrix} = n ,$$

\(163\)

where

$$N_{q+1}(t) = N_q(t)A(t) + \frac{d}{dt}N_q(t), \quad q = 0, 1, \ldots, n-1 ,$$

\(17\)

with

$$N_0(t) = c .$$

\(18\)

Thus, if condition \((16)\) holds, then the SISO system \((12)-(13)\) is observable at time $t_0$. This means that for any unknown initial state $x_0$, there exists a finite $t_1 > t_0$ such that it is possible to determine the initial state $x_0$ with the knowledge of the input $u$ (insulin) and the output $y$ (glucose). Otherwise system \((12)-(13)\) is said to be unobservable at time $t_0$ \(\text{Chen (1995)}\).

c) The desired observer eigenvalues $\lambda_1, \lambda_2, \ldots, \lambda_n$ are selected to be located to the left of the eigenvalues of matrix $A$ at $t = 0$, in the left-half of the complex plane. With this, the negative eigenvalues regulate the exponential rate of decay of estimation error and it is guaranteed the asymptotic convergence of the time-varying observer at instant time $t_1 > t_0$. Noticed that the desired eigenvalues can be set in the real axis or complex conjugate.

**Stage II.** To compute the time-varying Luenberger gains vector, in order to estimate the unmeasurable state space variables:

---

**Figure 1.** Luenberger time-varying state space estimator.
a) The matrix $A$ obtained from process (11) becomes time-varying $A(t)$ on Stage II, as it was described before; this is evaluating the matrix $A$ at each instant of time with the current values of $a(t)$.

b) The desired characteristic polynomial is obtained through the desired observer eigenvalues as follows:
\[
\phi(s) = (s - \lambda_1)(s - \lambda_2) \cdots (s - \lambda_n) = s^n + \alpha_1 s^{n-1} + \cdots + \alpha_{n-1} s + \alpha_n,
\]
where $\lambda_1, \lambda_2, \ldots, \lambda_n$ represents the desired observer eigenvalues, and $\alpha_1, \alpha_2, \ldots, \alpha_n$ are used for compute $\phi(A(t))$ as follows:
\[
\phi(A(t)) = A^n(t) + \alpha_1 A^{n-1}(t) + \cdots + \alpha_{n-1} A(t) + \alpha_n I,
\]
where $I$ is the $n \times n$ identity matrix.

c) Once the observability condition is fulfilled at instant of time $t > t_0$ with condition (16), it is necessary to compute the time-varying observability matrix at $t > t_0$. The compute of time-varying observability matrix is done at each instant of time as follows:
\[
O(t) = \begin{bmatrix}
c & cA(t) & \cdots & cA^{n-1}(t)
\end{bmatrix}.
\]

For the particular cases treated in this work, it is assumed that observability matrix (21) is invertible at each instant of time.

d) The required $I(t)$ Luenberger gains vector in (15) is determined by Ackermann’s methodology, which is extended to time-varying case as:
\[
I(t) = \phi(A(t)) O(t)^{-1} \begin{bmatrix} 0 \\ \vdots \\ 0 \\ 1 \end{bmatrix}.
\]

e) The $I(t)$ Luenberger time-varying gains are used as correcting term in order to update the estimated state variables $\hat{x}$ at instant time $t$, where the estimation error $(y - \hat{x})$ converges to 0.

f) The estimated state space variables $\hat{x}$ are employed to update the time-varying terms $(a_1(t), a_2(t), \ldots, a_n(t))$ in matrix $A(t)$ on the next iteration.

g) Finally, the estimated state space variables are available.

### 3.2 Linear time-varying Luenberger observer implementation

The observer goal is to estimate asymptotically the unmeasurable state space variables $\hat{x}$, through the knowledge of the output $y$ (subcutaneous glucose measurement) and the input $u$ (insulin). In this subsection, it is treated the observer implementation for Bergman (1) and Hovorka (4) T1DM models. This implementation is the procedure explained in Stages I and II presented in subsection 3.1. For this, let us define the estimation error as follows:
\[
e = x - \hat{x},
\]
and its dynamics is described as:
\[
\dot{e} = \hat{x} - \hat{x}.
\]
Then, substituting equations (12) and (15) into (24), yields:
\[
\dot{e} = A(t)x + bu + d - A(t)\dot{x} - bu - d_1 - l(t)(y - c(\dot{x}))
\]
\[
= [A(t) - l(t)c]x + x - \dot{x} + (d - d_1).
\]
Thus
\[
\dot{e} = [A(t) - l(t)c]e + (d - d_1).
\]

**Assumption 1**: The linearized system obtained in (12)-(13) is observable at each instant time \( t > t_0 \).

**Assumption 2**: The time-varying observability matrix (21) at instant time \( t > t_0 \) is nonsingular.

The elements of matrix \( A(t) \) that are time-varying correspond to the values, which are time-updated from estimated states in each instant \( t > t_0 \) by the asymptotic Luenberger observer.

**Assumption 3**: The matrices \( A(t) \) and \( \theta(t) \) are Hurwitz at each instant of simulation time. Then, the time-varying observability matrix (21) at instant time \( t > t_0 \) is nonsingular and it is possible to compute the time-varying \( l(t) \) Luenberger gains, which are obtained in each instant \( t > t_0 \) using the Ackermann’s methodology shown in (22).

**Theorem 1** For system (12)-(13), the time-varying Luenberger observer (13) obtained from the Ackermann’s methodology (22), ensures that the estimation error (23) is semi globally uniformly ultimately bounded (SGUUB).

The proof of Theorem 1 is presented in A.

Next, the desired observer eigenvalues are adjusted to be located in the left-half of complex plane.

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**Theorem 1** For system (12)-(13), the time-varying Luenberger observer (13) obtained from the Ackermann’s methodology (22), ensures that the estimation error (23) is semi globally uniformly ultimately bounded (SGUUB).

The proof of Theorem 1 is presented in A.

Now, it is going to be implemented the procedure to design a LTVLO. For the case of nonlinear Bergman model (1) with the form (9)-(10), it is applied the linearization procedure (11). In this procedure, the resulting matrix \( A(t) \) and vector \( c \) are:
\[
A(t) = \begin{bmatrix} a_1(t) & a_2(t) & 0 \\ 0 & -p_2 & p_3 \\ 0 & 0 & -\eta \end{bmatrix}, \quad c = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix},
\]
where \( a_1(t) = -\dot{x}_2, a_2(t) = -\dot{x}_1 \) and the parameters are described in Table 1. Note that the time-varying values \( a_1(t) \) and \( a_2(t) \) in (27) involve the estimated variables \( \dot{x}_1 \) and \( \dot{x}_2 \), which updates their values for the next iteration. These estimated variables give the feature of linear time-varying to the present proposal. As it was explained before, vector \( c \) is time-invariant due to the output \( y = x_1 = G \) of system (1), which constitutes the plasma glucose concentration. Once the linearized procedure is done, it is proved the observability condition (16) at instant time \( t_0 \) of the pair \( (A(t), c) \) (27) as:
\[
\text{rank} \begin{bmatrix} 1 & a_2(t) & a_3^2(t) + p_2 a_2(t) + p_3 [b - a_3(t)] \\ 0 & a_1(t) & [a_2(t) - p_1 - p_2] - p_1 G_b \\ 0 & 0 & -p_3 a_1(t) \end{bmatrix}^T = 3.
\]
(28)

where \( a_3(t) = \dot{x}_3 \). The evaluation of (28) is only done in \( t_0 \) to prove the observability condition of the pair \( (A(t), c) \). As the diagonal of matrix (28) depends on \( a_1(t) \) (say \( \dot{x}_1 \)), and as \( \dot{x}_1 \neq 0 \) due to system (1) the glucose can not be null, so the eigenvalues are chosen to avoid this variable \( \dot{x}_1 \) no crosses by zero during the transitory period. As there not exists zero crosses by \( a_1(t) \), the condition (16) in matrix (28) is achieved (rank of matrix (28) = 3). Therefore, the linearized system with the form (12)-(13) obtained from system (1) with the pair \( (A(t), c) \) (27) is observable at time \( t_0 \).

Next, the desired observer eigenvalues are adjusted to be located in the left-half of complex plane.

In general way, it is recommendable that these eigenvalues are located to the left of the eigenvalues of matrix \( A(t) \) at \( t_0 \). This results a good practice in order to assure faster convergence of the observer and to consider the system response is dominated by the observer eigenvalues.

With the desired observer eigenvalues chosen as: \( \lambda_1 = -2.659, \lambda_2 = -0.126 \) and \( \lambda_3 = -0.12 \), it is obtained the characteristic polynomial of the form (19). The matrix \( \phi(A(t)) \) of the form (20) is computed each instant of time, in such manner as the time-varying observability matrix (21) is:
\[
\theta(t) = \begin{bmatrix} 1 & 0 & 0 \\ a_2(t) & a_1(t) & 0 \\ a_3^2(t) & a_1(t) [a_2(t) - p_2] & p_3 a_1(t) \end{bmatrix}.
\]
(29)
Then, it is computed the time-varying Luenberger gain vector $I(t)$ as:

$$I(t) = \left[ -\frac{2.905 + \eta - p_2 - a_1(t)}{2.905\eta - 2.905p_2 - 2\eta - p_2 + \eta^2 + 0.6692} \right].$$

The designed LTVLO for Bergman model with the form (1) is:

$$\dot{x}_1 = -\dot{x}_1 + d(t) + l_1(t)(y - \dot{x}_1)$$
$$\dot{x}_2 = -p_2\dot{x}_2 + p_3\dot{x}_3 + p_4\dot{b} + l_2(t)(y - \dot{x}_1)$$
$$\dot{x}_3 = -\eta\dot{x}_3 + \eta\dot{b} + u + l_3(t)(y - \dot{x}_1)$$

where the parameters $p_2$, $p_3$, $\eta$ and $l_0$ corresponds to the mean of the parameters of three patients shown in Table[1] with all the elements of formulation (15) are estimated the unmeasurable state variables $x$ for T1DM Bergman model (1).

The same procedure explained for the Bergman model (1) is applied to the Hovorka model (4) (Stages I and II of subsection 3.1). For simplicity, the description of this procedure applied to the Hovorka model is not shown. The asymptotic Luenberger observer is initialized around $\pm 10\%$ of initial values of VP. This is due to biological conditions of VP which allows faster convergence.

### 3.3 Experiments design

In this subsection, the experiments design explanation is done for each T1DM model described in this work. We proposed three experiments: A) VP modeled with Bergman model (1) and LTVLO with the same structure, B) VP modeled with Hovorka model (4) and LTVLO with the same structure, and C) data come from real patients and observer is with Hovorka model structure proposed in experiment B.

#### 3.3.1 Experiments definition

The implementation as models as observers is done in the continuous time domain, using numerical integration with fixed step-size $= 1s$, and with Runge Kutta solver. In order to obtain the results, Matlab$^TM$ and Simulink$^TM$ are used. The time simulation is 48 hours, taking for the analysis 24hrs, which starts from 00:00hrs of the second day and ends at 23:59hrs the same day. The meal plan was identical for all VP. The plan was composed of: breakfast at 7:30hrs, 40g of CHO; snack at 11:00hrs, 15g of CHO; lunch at 13:00hrs, 90g of CHO; dinner at 19:00hrs, 80g of CHO; and snack at 23:00hrs, 15g of CHOs Anguita et al. (2003). The prandial bolus was fitted to each patient with his insulin CHO ratio and the snacks do not have insulin boluses. In order to demonstrate the observer convergence ability estimating the state variables, three different experiments are proposed, which are described as follows:

1. **Bergman in silico** involves three VP. The LTVLO is designed with Bergman model structure (1) and parameterized with a mean of three VP shown in Table[1]. First, the LTVLO methodology is applied to Bergman model because it is simpler to understand. The observer is tested to estimate the variables of the three different patients.

2. **Hovorka in silico** imply six VP. Then, the approach of time-varying observer is extended to a more complex system, as it is the Hovorka model (4). The observer is parameterized with values of patient zero from Table[2].

3. **Estimation of the inner variables from real patients.** Data were obtained from a clinical study Capel et al. (2014) about a glucose control algorithm in real T1DM patients, where along the day it is only known continuous glucose measurements, insulin doses and amount of ingested CHO, and with this information the Luenberger time-varying observer estimates the corresponding Hovorka variables. Each patient was equipped with a CGM device (Paradigm$^\text{®}$ REAL-Time; Medtronic, Minneapolis, MN) and an insulin pump Animas$^\text{®}$ 2020 (Animas Corp., West Chester, PA). The measurement period and infusion period was 5 minutes. The LTVLO remains the same as designed in experiment B with Hovorka model structure and parameterized with values of patient zero in Table[2].
3.3.2 Experiments evaluation
The graphs of results exhibit a qualitative performance of LTVLO. However, it is necessary to employ a quantitative parameter. In this sense, the parameter fit of estimated variables to model variables offer a quantitative reliability of estimation capacities of Finan et al. (2006), the designed Luenberger observer. The fit parameter expressed in percentage is calculated for every state as in [32]

$$fit = \sqrt{1 - \frac{\sum_{t=1}^{N} |x(t) - \hat{x}(t)|^2}{\sum_{t=1}^{N} |x(t) - \bar{x}|^2}} \times 100\% \tag{32}$$

where N is the amount of iterations that the simulation executes, x(t) are the state space variables of the model and $\hat{x}(t)$ are the corresponding estimated variables.

4 RESULTS
In this section, it is shown the performance of the LTVLO. For simplicity, only 24 hours of simulation are presented, where in results figures, the initial time of simulation corresponds to 00:00 hrs of second day, and the triangles that appear in those Figure, constitute the moment in which the intake is acquired by the patient according to the meal plan.

4.1 Experiment A: Estimating Bergman variables
The proposed methodology is applied to design an observer to Bergman model [1], which is parameterized by a mean of the model parameters (patient zero). The LTVLO is tested with VP generated by the three patients parameter described Kaveh and Shieles (2008).

Figure 2 shows the three states of VP#1, estimated states, and their corresponding time-varying gains when the intake plan is applied. Each observer variable estimates asymptotically its corresponding model variable in approximately 100s of simulation, tracking them for the rest of simulation. The states X (x2), insulin influence and f (x3), plasma insulin, are increased due to insulin dose applied at 7:15hrs. When the VP#1 is having breakfast at 7:30 hrs, the state G (x1) plasma glucose, is increased due to CHO intake. The gains $l_1(t)$, $l_2(t)$ and $l_3(t)$ change suddenly when the model variables present high rate of change.

![Figure 2. VP#1 states from Bergman model, states estimated from LTVLO and their respective time-varying gains: a) comparative of plasma glucose $x_1$ vs. $\hat{x}_1$; b) gain $l_1(t)$ relative to $\hat{x}_1$; c) comparative of insulin influence $x_2$ vs. $\hat{x}_2$; d) gain $l_2(t)$ relative to $\hat{x}_2$; e) comparative of plasma insulin $x_3$ vs. $\hat{x}_3$; f) gain $l_3(t)$ relative to $\hat{x}_3$.](image)

Table 3 shows the reliability percentage on estimated variables by the LTVLO; having over 94% of confidence on the three observed variables. These results represent an accurate estimation of the non-measurable variables.
### 4.2 Experiment B: Estimating Hovorka variables

The proposed methodology is applied to develop an observer to Hovorka model (4), which is parameterized with the patient zero (mean of six patient parameters included in Hovorka et al. (2002)). The LTVLO is tested with the other six VP generated from the parameters in Hovorka et al. (2002).

Figure 3 shows three state variables ($x_1$, $x_3$ and $x_7$) of the Hovorka model, in particular to VP#6, the behaviour of the observer states estimated, and their corresponding time-varying gains, when the intake plan is applied. The states $x_3$, non-accessible glucose ($Q_2$) and $x_7$, plasma insulin ($I$), are increased due to insulin dose applied at 7:15 hrs. When the VP#6 is breakfasting at 7:30 hrs, the state $x_1$ subcutaneous glucose (C), is increased due to CHOs intake. The gains $l_1(t)$, $l_3(t)$ and $l_7(t)$ change suddenly when the model variables present high rate of change. Even when the states observer variables ($x_3$ and $x_7$) do not match accurately the state model variables ($Q_2$ and $I$), qualitatively have similar profile as their corresponding model variable. This is due to different parametrization of VP#6 and the LTVLO. In Table 4 it is shown the reliability percentage on estimated variables by the Luenberger time-varying observer to Hovorka model.

![Figure 3](image-url)

**Figure 3.** VP#6 states from Hovorka model, states estimated from Luenberger time-varying observer and their respective time-varying gains: a) comparative of CGM sensor $x_1$ vs. $\hat{x}_1$; b) gain $l_1(t)$ relative to $\hat{x}_1$; c) comparative of non-accessible glucose $x_3$ vs. $\hat{x}_3$; d) gain $l_3(t)$ relative to $\hat{x}_3$; e) comparative of plasma insulin $x_7$ vs. $\hat{x}_7$; f) gain $l_7(t)$ relative to $\hat{x}_7$.

---

**Table 3.** fit (%) of LTVLO to Bergman model.

<table>
<thead>
<tr>
<th>Variable renamed</th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$x_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP#1</td>
<td>99.35</td>
<td>92.77</td>
<td>58.68</td>
</tr>
<tr>
<td>VP#2</td>
<td>99.99</td>
<td>92.97</td>
<td>97.03</td>
</tr>
<tr>
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<td>99.90</td>
<td>79.45</td>
<td>95.43</td>
</tr>
<tr>
<td>VP#4</td>
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<td>94.46</td>
<td>31.27</td>
</tr>
<tr>
<td>VP#5</td>
<td>98.94</td>
<td>99.65</td>
<td>90.20</td>
</tr>
<tr>
<td>VP#6</td>
<td>99.96</td>
<td>96.55</td>
<td>88.88</td>
</tr>
</tbody>
</table>

---

**Table 4.** fit (%) of LTVLO to Hovorka model.

<table>
<thead>
<tr>
<th>Variable renamed</th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$x_3$</th>
<th>$x_4$</th>
<th>$x_5$</th>
<th>$x_6$</th>
<th>$x_7$</th>
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<tbody>
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<td>58.68</td>
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<td>94.07</td>
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<td>100</td>
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<tr>
<td>VP#4</td>
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<td>94.66</td>
<td>98.19</td>
<td>61.45</td>
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<td>99.99</td>
<td>100</td>
</tr>
<tr>
<td>VP#5</td>
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</tr>
<tr>
<td>VP#6</td>
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<td>88.88</td>
<td>99.14</td>
<td>95.52</td>
<td>99.22</td>
<td>55.07</td>
<td>99.98</td>
<td>100</td>
</tr>
</tbody>
</table>

The fit of the estimation variables $x_1$, $x_3$ and $x_7$ for the six patients is between the values of 31.27%...
and 100%. This is explained because these variables are directly influenced by known information, glucose, insulin, and CHO absorption via gut. Variable $x_3$ for VP#3 is 79.45%, which can be due to the parametrization of the LTVLO. As it can be seen in Figure 3(c), the estimation is not as accurate as it seems to be. Nevertheless, its corresponding fit value for patient six, is acceptable (88.88%). In general, fit values between 50% and 90% can be associated to the extremely sensitive metric of fit parameter to differentiate between means of estimated variables and model variables. The fit value for variable $x_3$ for patient 4 (31.27%) corresponds to a poor estimation of this variable.

### 4.3 Experiment C: Estimating real T1DM patients unmeasurable variables

The LTVLO is employed to estimate the corresponding Hovorka model state variables from real patient data, for simplicity are showing results only for a set of patient data. Figure 4(a) displays the estimation of variable $x_1$ by its corresponding time-varying observer variable, the glucose measured with the sensor having a fit= 99.61%; b) shows the corresponding gain evolution. c) and e) correspond to unmeasurable variables of non-accessible glucose compartment and plasma insulin, respectively. Frame d) is the gain adjustment for the non-accessible glucose compartment and f) is the shape depicting the evolution at each iteration of Luenberger gain for the plasma insulin. The CHO intake of this particular real patient is depicted with black triangles, corresponding to 20g at 7:00hrs, 60g at 10:00hrs, 80g at 15:15hrs and 80g at 21hrs.

![Figure 4](https://doi.org/10.7287/peerj.preprints.3341v1)

**Figure 4.** Estimation of the inner variables from real patients, states estimated from Luenberger time-varying observer and their respective time-varying gains: a) comparative of subcutaneous glucose $x_1$ vs. $\hat{x}_1$; b) gain $l_1(t)$ relative to $x_1$; c) non-accessible glucose estimation $\hat{x}_3$; d) gain $l_3(t)$ relative to $x_3$; e) plasma insulin estimation $\hat{x}_7$; f) gain $l_7(t)$ relative to $x_7$.

### 5 DISCUSSION

The LTVLO provides helpful information about unavailable variables to measurement in real-time to use it as base of a control law design in a future work. We have used the Luenberger methodology to build a T1DM observer, although it exists other methods as sliding modes observers or artificial neural networks, because Luenberger methodology is easy to understand and allows to select the desired dynamic of the estimated variables.

Even when linear time-varying systems results a challenge to guarantee the observability condition, we guarantee such condition in each instant of time. Although, to the particular cases treated in this work, the observability condition depends on the parameter values, which define the VP dynamics and are determined by the author of the model. These parametric values characterized the model dynamic used to design the observer, but we could explore others parameters to guarantee the observability; e.g. setting the VP parameters on the observer according to real patient behaviour classifying them by their insulin sensibility.
The location of desired observer eigenvalues $\lambda_n$ to the left of eigenvalues of matrix $A(t)$ at $t_0$, results in a good practice assuring faster convergence of the observer and to consider the system response is dominated by the observer eigenvalues. The best location of the eigenvalues, is out of the scope of this paper.

The equilibrium point $\rho$ is chosen from a basal patients period ($y = 90\, \text{mg/dl}$); with the aim of having the desired dynamic on the patient when this one is not disturbed and the linearization of the model is made concerning an stable operating point.

We have chosen the fit parameter to evaluate the performance of the observer. This is because it is a percentage measurement defined independent from the variable scale versus the mean square error.

In experiment A) the fit parameter indicates a high precision estimation mainly due to simplicity of the Bergman model. There is only one variable between the interaction of the output variable (blood glucose) and the variable that contains the input (insulin infusion), which facilitates the calculation of the Luenberger gains. The plasma glucose $G(x_1)$ is estimated with 100%, and the plasma insulin $I(x_3)$ above 94%.

In experiment B) the variables $C(x_1)$, $Q_2(x_3)$ and $I(x_7)$ were chosen in order to reduce the employee space demonstrating how the LTVLO reduce the estimation error for the measurable variable and it is able to estimate the unmeasurable variables with the established parametrization. Luenberger gains show variation due to high rate of updating made at each simulation instant; this complicates the Luenberger gains calculus because when the observer reduces at minimum the estimation error of the measurable variable (subcutaneous glucose), the gains keep varying upon a mean.

As can be seen on Table 4 the fit parameter for patient 4 of variable $Q_2(x_3)$, the value 31.27%, quantitatively is indicating that the observer is little reliable because is not estimating well its corresponding variable. Nevertheless, qualitatively is seen that estimated variables by the observer, are conditioned to the parametrization of LTVLO. This parametrization causes the existence of differences between VP variables profiles and the estimated variables.

The reliability in estimated variables by LTVLO to Hovorka VP in $C(x_1)$ is above 98% but in state $I(x_7)$ is over 55% due to the observer always proposed a high value of $\hat{x}_7$. This result can be good when is pretended to design a control law because the excess of insulin can conditioned the control behaviour to do it less sensible and therefore avoiding the hypoglycaemic events. Information provided from Table 4, it can be seen that state variable $x_2$ would be used as main variable to feedback a control law, because is the plasma glucose the desired variable to control.

Table 5 summarizes the minimum values of the fit parameter shown in Tables 3 and 4. The minimum values of the variables are grouped by their physiological relation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bergman LTVLO performance (From Table 3)</th>
<th>Hovorka LTVLO performance (From Table 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>fit (%)</td>
<td>Patient</td>
</tr>
<tr>
<td>Glucose</td>
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<tr>
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<tr>
<td>x_3</td>
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</table>

As can be seen in Table 5 values of glucose compartments for Bergman and Hovorka present high accuracy. The intermediate insulin effects compartments and plasma insulin compartment are the inaccuracy fit results of the LTVLO, due to the observer always adjusted a high value to these variables.
Hovorka LTVLO results insulin compartments and glucose compartments have the better fit performance because these state variables are directly connected with available information.

The fit values between 90% and 100% constitute a very accurate estimation, which means that the estimation error \( e \approx 0 \). A fit value between 50% and 90% means that the correlation error between the model variable and estimated variable is increased in some periods. The fit value between 1% and 50% means that the coincidence between the model variable and estimated variable occurs during small periods and majority of the time keeps differences between them. A fit value of 0% means that the estimated variable does not match its corresponding variable, but the LTVLO is providing helpful information biased by its parametrization.

In experiment C) the unmeasurable variables are estimated under a well-known model structure, although the measurement by the CGM is noisy. The model structure matches the output variable (subcutaneous glucose) and input variable (insulin dose) with the data available from real patients. With the Hovorka model structure on the LTVLO, it is possible to incorporate information about the main disturbances (CHOs intake) available with the patients data. The chosen variables \( C, \ Q_1 \) and \( I \) graphed for this experiment demonstrate how the LTVLO reduce the estimation error for the measurable variable and it is able to estimate the unmeasurable variables.

However, we do not know the CGM sensor accuracy. The measured variable by a CGM is objective because comes from a sensor. Both meal and doses are recorded by the patients and sometimes they forget to write down some data. The LTVLO in front of a CGM sensor calibration or loss of information becomes oscillating or unstable. For this reason the LTVLO needs to be strengthened against those adversities to be applied in a real scenario with T1DM patients.

6 CONCLUSION

This paper proposes a Luenberger time-varying observer applied to Bergman and Hovorka T1DM models. The observer has the feature of being updated each instant of time in order to estimate the states under a known structure, and only with the knowledge of the insulin dose, the CGM information and the intake of CHOs. Lyapunov stability proof stablishes the operation boundedness of the time-varying proposal. The time-varying formulation is used to estimate unmeasurable states in real patients. The results obtained in the designed experiments validate the applicability of the proposed observer. Additionally, a time-varying observer used to estimate the unmeasurable variables with a well-known structure, opens a possibility to apply a control law (employed in other areas with success) in order to improve the design and development of the ambulatory artificial pancreas.

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A PROOF OF THEOREM 1

Proof: Let \( e = 0 \) be an equilibrium point asymptotically stable for the Luenberger time-varying system [15] represented in the error dynamic [26]. Lyapunov’s candidate function positive definite is described in terms of the error as:

\[
V(e,t) = e^\top P(t)e,
\]

where \( P(t) \) is continuously differentiable, bounded and positive definite symetric matrix [Khalil and Grizzle [1996]]. The derivative of Lyapunov candidate function is computed as:

\[
\dot{V}(e,t) = e^\top P(t)\dot{e} + e^\top \dot{P}(t)e + e^\top P(t)e,
\]

where \( \dot{P}(t) \) must be negative definite to guarantee that function [34] is negative definite. Using the Riccati’s function as:

\[
\dot{P}(t) = -P(t)\Lambda(t) - \Lambda(t)^\top P(t) - Q(t),
\]
for $\dot{P}(t) = 0$ and $A(t) = [A(t) - L(t)]e$ from (26), $Q(t)$ must be continuous, positive definite and symmetric. Then, it is computed the matrix $P(t)$ such that fulfill the aforementioned characteristics. Now replacing (26) and (35) into (34), yields:

$$\dot{V}(e,t) = -e^T Q(t) e + (d - d_1),$$

which is negative definite with $|e^T Q(t) e| \geq |d - d_1|$, showing that the LTVLO (15) in the error dynamics (26) is an asymptotically stable estimator. The derivative of $V(e,t)$ along the trajectories of (26) is given by:

$$\dot{V}(e,t) = \frac{\partial V}{\partial t} + \frac{\partial V}{\partial e} f(e,t) + \frac{\partial V}{\partial e} g(e,t),$$

where $f(e,t)$ are the state space functions in the error dynamic and $g(e,t)$ are the functions related to the disturbances. Then, applying the derivative along the trajectories (37), it is obtained:

$$\dot{V}(e,t) = -||e||^2 + 2l(t) e_1^2 \varphi_f + 2(d - d_1) e_1 \varphi_e,$$

where $\varphi_f$ and $\varphi_e$ correspond to the coefficients of second and third terms of equation (37), respectively. Suppose $l(t) \leq \frac{c - 1}{2K}$, where $0 \leq \zeta \leq 1 \forall |e| \leq K$, and using the inequality $(d - d_1) \leq \delta$, where $\delta$ is the maximum value of $(d - d_1)$ and $\varphi_e e_1 \leq ||e|| |\varphi_e|$, yields:

$$\dot{V}(e,t) \leq -\zeta ||e||^2 + 2\delta |\varphi_e| ||e||^2,$$

where $\zeta \leq (1 - 2l(t)K^2) \forall |e| \leq K$, with $K$ as the upper bound on $|e_1|$. Suppose that:

$$\theta \leq \frac{2\delta |\varphi_e|}{\zeta ||e||^2}.\quad (40)$$

Then

$$\dot{V}(e,t) \leq -(1 - \theta)\zeta ||e||^2,$$

where $0 \leq \theta \leq 1$. From (40), it is established that:

$$||e||^2 \leq \mu = \frac{2\delta |\varphi_e|}{\zeta \theta}.\quad (42)$$

In order to estimate the bound $K$, let $\Omega_c = \{e \in \mathbb{R}^n \mid V(e,t) \leq c\}$. For any positive constant $c$, the set $\Omega_c$ is closed and bounded. The boundary of $\Omega_c$ is the Lyapunov surface $V(e,t)$. The largest value of $|e_1|$ on the surface $V(e,t) = c$, can be determined by differentiating the surface equation partially with respect to $e_q$, where $q = 2, \ldots, n$ (for Bergman Model $n = 3$ and for Hovorka model $n = 9$), as:

$$\frac{\partial V}{\partial e_q} = 0.$$\quad (43)

By simple calculations to evaluate the Lyapunov candidate function with the partial derivatives, concludes that:

$$V(e,t) \bigg|_{\frac{\partial V}{\partial e_q} = 0} = \Upsilon(e_1,t).\quad (44)$$

Then, the largest value of $e_q^2$ on the Lyapunov surface is $\zeta$. Therefore, all points inside $\Omega_c$ satisfy the bound $|e_1| \leq K$, where $K^2 = \zeta$.

Thus, if $l(t) \leq \frac{c - 1}{2K}$ and $\delta$ is so small that $\mu^2 \mu_{\text{max}}(P(t)) < c$, then $B_{\mu} \subset \Omega_c$ and all trajectories starting inside $\Omega_c$ remain for all future time in $\Omega_c$. Therefore, the solutions of the disturbed system are uniformly ultimately bounded by:

$$B = \mu \sqrt{\frac{\lambda_{\text{max}}(P(t))}{\lambda_{\text{min}}(P(t))}}.\quad (45)$$

It is important to mention that $l(t)$ and $(d - d_1)$ are treated differently as two disturbance terms, since the first term vanishes at the origin, while the second one does not.
REFERENCES


