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Asymptotic output tracking in blood glucose control. A case study.

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Abstract—**Glucose is the primary source of energy for the human body. Keeping the blood glucose level between certain thresholds is essential for the proper energy transport. Insulin plays a key role in maintaining the glucose homeostasis. Because of its great importance, many models were published on either to describe the glucose-insulin interaction in case of patients under Intensive Care Unit (ICU), or to model Type 1 Diabetes Mellitus (T1DM). Currently for most of the models linear control concepts are used in order to design an appropriate controller. The aim of the current paper is to investigate applicability of nonlinear control theory providing exact mathematical background in the control problem of glucose-insulin interaction. Both ICU and T1DM cases are analyzed on well-known models with different complexity. Our aim is to hide the nonlinearity of the models by transforming the input signal so that the response of the model would mimic the behavior of a linear system; hence extending the validity of linear controllers. The asymptotic tracking problem needs the value of the state variables; therefore extended Kalman-filter is applied. The capabilities of this approach are examined through classical control algorithms and input data recorded in clinical environment.**

I. Introduction

THE blood glucose level is maintained through a complex endocrine system of the human body, which is responsible among others for energy transport. The normal blood glucose concentration varies in a narrow range (70 - 110 mg/dL). If the human body is unable to control the glucose-insulin interaction diabetes is diagnosed. The consequences of diabetes are mostly long-term; among others increasing the risk of neuropathy, retinopathy and cardiovascular diseases [3]. Due to its frightening increase the World Health Organization (WHO), warns that diabetes could be the "disease of the future" [4].

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From an engineering point of view, the treatment of diabetes mellitus can be represented by an outer control loop, to replace the partially or totally deficient blood glucose control system of the human body. The quest for artificial pancreas can be structured in three different tasks [5]-[6]: continuous glucose sensor for measurements, insulin pump for infusion and control algorithm.

To design an appropriate controller, an adequate model is necessary. In the last few decades different mathematical models of the human blood glucose system appeared. A brief overview can be found in [7]. Nowadays, the most complex models used in T1DM research are [2], [8]-[10].

On the other hand, blood glucose control is also very important in intensive care treatment. Critically ill patients admitted to the ICU often display hyperglycaemia and insulin resistance associated with adverse outcomes, which can result in increased morbidity and mortality [11]. Tight glycaemic control (TGC) can reduce these adverse outcomes [12], as well as reducing economic costs [13]. Hence, TGC using model-based methods has become an active research field [14]. The best known model is the minimal model of Bergman [15]. However, the model's simplicity is a disadvantage. Hence, different models were derived from the minimal model, trying to generalize / extend the validity for the ICU case [1], [16]-[17].

The nonlinearity in each of the above mentioned models, ICU or T1DM represent specific control aspects, but the applied control strategies are usually developed for their linearized (i.e. working point based) versions.

Generalization of this problem can be realized using nonlinear control theory [18]. The current paper investigates this aspect in terms of differential geometric approach. A similar method has been presented in [19], for a 4^{th} order model containing a discrete-delay differential equation. In this paper both ICU and T1DM cases are analyzed on well-known, but different complexity models: the model presented by Lotz et al [1] in case of ICU, and the model presented by Magni et al [2] in case of T1DM.

Our aim is to hide the nonlinearity of the physiological model by transforming the control input provided by a linear controller so that the response of the model would mimic the behavior of a linear system. Hence, the validity of linear controllers can be extended from the neighborhood of a working point to a larger subset of the state-space bounded by specific constraints.

This approach might not increase the performance of the controllers to a great extent, but the reliability of tight glucose control can directly effect the quality of life of a type-1 diabetes or ICU patient. Our goal is a control

algorithm whose stability and performance can be guaranteed and mathematically proven according to adequate medical specifications.

The paper is structured as follows. First, the target of our investigation, the two models (ICU [1] and T1DM [2]) are presented. This is followed by a brief summary of the applied nonlinear control theory methods and aspects of Kalman-filtering. Section IV presents the obtained results, while Section V concludes the paper and formulates further research directions.

II. MODELS

A. The considered ICU model

The clinically validated model of [1] is basically a generalization of the Bergman minimal model [15]. It better captures insulin losses to the liver and kidneys, and saturation dynamics through the use of Michaelis-Menten functions. The parameters of the model have been identified to a wide range of patients. Below, we summarize the model equations. Numerical values can be found in [1].

$$\dot{G}(t) = -p_G G(t) - S_I\left(G(t)+G_E\right)\frac{Q(t)}{1+\alpha_G Q(t)} + EGP + \frac{P(t)}{V_G} \quad (1/a)$$

$$\dot{Q}(t) = -n_C Q(t) + \frac{n_I}{V_Q}\left(I(t)-Q(t)\right) \quad (1/b)$$

$$\dot{I}(t) = -n_K I(t) - \frac{n_L I(t)}{1+\alpha_I I(t)} - \frac{n_I}{V_P}\left(I(t)-Q(t)\right) + \left(1-x_L\right)\frac{u_{en}}{V_P} + \frac{u_{ex}(t)}{V_P} \quad (1/c)$$

The states of the system are:

- G is the deviation of plasma glucose concentration (mmol/L) from equilibrium level (G_E);
- I represent the concentration of plasma insulin resulting from external input (mU/L);
- Q is the concentration of insulin bounded to interstitial sites (mU/L);

Regarding the inputs of the system, P represents the glucose input through enteral feeding (mmol/min), while u_{ex} is the intravenously administered external insulin (mU/min).

Other notations appeared represent parameters: p_G is the endogenous glucose clearance (min^{-1}); S_I is the insulin sensitivity (L/mU/min); α_G is the insulin dependent glucose clearance/insulin effect (L/mU); EGP is the endogenous glucose production (mmol/min); V_G, V_Q and V_P are the glucose distribution volume, interstitial fluid volume and the plasma volume with fast exchanging tissues (L); x_L represents the fraction of hepatic extraction (-); n_K, n_L are the kidney and liver clearance rates of insulin from plasma (min^{-1}); n_I is the diffusion constant of insulin between compartments (L/min); n_C is the cellular insulin clearance rate from interstitium (min^{-1}); α_I is the plasma insulin disappearance rate (L/mU); u_{en} is the constant endogenous insulin production (mU/min).

B. The considered T1DM model

The T1DM model of [2] represents an in-silico glucose metabolism model with compartments to describe subcutaneous insulin delivery and subcutaneous continuous glucose monitoring, as well as an intestinal glucose absorption model integrated into its structure. The model has a modular build, but in this paper it will be presented as a single system. Numerical values can be found in [2], [8].

The system has 10 state variables:

- G_M – subcutaneous glucose concentration (mg/dL);
- G_p – glucose in plasma and rapidly equilibrating tissues (mg/kg);
- G_t – glucose in slowly equilibrating tissues (mg/kg);
- X – insulin in interstitial fluid (pmol/L);
- I_d, I_1 – state variables for delayed insulin signal (pmol/L);
- I_p – insulin mass in plasma (pmol/kg);
- I_l – insulin mass in liver (pmol/kg);
- S_2 – monomeric insulin in the subcutaneous tissue (pmol/kg);
- S_1 – polymeric insulin in the subcutaneous tissue (pmol/kg).

The inputs of the system are the u injected insulin flow (pmol/min) and Ra the glucose rate of appearance in plasma (mg/min).

The parameters of the model are the followings: V_G is the distribution volume of glucose (dL/kg); U_{ii} is the insulin-independent glucose utilization (mg/kg/min); k_1, k_2 are rate parameters of the glucose subsystem (min^{-1}); k_{e1} represents renal glomerular filtration rate (min^{-1}); k_{e2} renal threshold (mg/kg); V_i is the insulin distribution volume (L/kg); m_1, m_2, m_3, m_4 are rate parameters of the insulin subsystem (min^{-1}); BW is the body weight (kg); k_{p1} is the extrapolated endogenous glucose production at zero glucose and insulin (mg/kg/min); k_{p2} is the liver glucose effectiveness (min^{-1}); k_{p3} is the indicator of effect of a delayed insulin signal (mg·L/kg/min/pmol); k_i is the model parameter of delayed insulin signal (min^{-1}); I_b is the basal level of plasma insulin concentration (pmol/L); p_{2U} is the rate constant of insulin action (min^{-1}); K_{m0}, K_{mx}, V_{m0} and V_{mx} are model parameters for insulin-dependent glucose utilization (-); k_d is degradation constant (-); k_{a1}, k_{a2} are absorption constants (-); $k_{s.c.}$ is rate constant for the subcutaneous glucose compartment (-).

A big advantage of the model is the integrated, three-compartment intestinal glucose absorption model, which describes glucose transit through the stomach and intestine to the plasma in case of enteral feeding. Detailed description of this system can be found in [8].

Although the glucose absorption model is used in the simulations to acquire glucose absorption profile, it is not regarded as part of the model. The glucose rate of appearance (Ra) is either considered as disturbance or a known time-varying parameter.

III. METHODS

A. Exact linearization via feedback

The concept of exact linearization of a nonlinear system via nonlinear state feedback control was introduced in [18]. Consider a SISO nonlinear system in the form:

$$\begin{aligned} \dot{x}(t) &= f(x(t)) + g_i(x(t))u(t) \\ y(t) &= h(x(t)) \end{aligned} \tag{2}$$

where f and g are smooth R^n-valued mappings and h is a smooth real-valued mapping defined on an open set $U \subset R^n$. For system (2) the concepts of relative degree analysis, exact linearization and asymptotic output tracking can be considered according to [18]. Let us choose a prescribed reference linear system of the form:

$$\begin{aligned} \dot{\varsigma} &= A \cdot \varsigma + B \cdot w \\ y_R &= C \cdot \varsigma \end{aligned} \tag{3}$$

Then, the following control law can be used for asymptotic tracking of the output of the reference system with the original (3) nonlinear system:

$$\begin{aligned} u(t) = \frac{1}{L_g L_f^{r-1} h(z(t))} \Bigg(& - L_f^r h(z(t)) - \sum_{i=0}^{r-1} \left(a_i \cdot L_f^i h(z(t)) \right) + \\ & + b_r \cdot CA^{r-1} B w(t) + C \sum_{j=0}^{r} \left(b_r \cdot A^j \right) \varsigma(t) \Bigg) \end{aligned} \tag{4}$$

where a_i and b_i ($i=0...r$) are the parameters of the tracking dynamics.

Both exact linearization and asymptotic output tracking need the values of the state variables. However, in practice the only measured quantity is either the intravenous or subcutaneous glucose concentration. The sensors used in these measurements usually have relatively high noise and a sampling time of 3-5 minutes, therefore a Kalman-filter is needed to provide adequate state-estimation. In our case, the algorithm presented in [20] was used.

IV. RESULTS

A. Asymptotic tracking of the ICU model

The relative degree of the ICU model is maximal, therefore the coordinate transformation for both exact linearization and asymptotic output tracking are unequivocally determined, and the system has no zero dynamics. The system has a single output (G), and only the external insulin input (u_{ex}) can be controlled, therefore the system can be considered as a SISO system. The other input (P) can be regarded as disturbance, but its value is known. Considering the connections between each compartment the system can be divided into a subsystem described by differential equations (1/b) and (1/c) with Q as its output, and a second one described by a single differential equation (1/a). Hence, determining control law for exact linearization or asymptotic output tracking separately is possible. Real advantage of this approach is when working with more complex models [8]-[10].

The first subsystem is transformed into a series of integrators through exact linearization. The local coordinate transformation determined by the Lie-derivates is a local diffeomorphism regardless of the state variables.

$$\begin{aligned} z_1 &= \Phi_1(x) = x_2 \\ z_2 &= \Phi_2(x) = -n_c x_2 + \frac{n_I}{V_Q}(x_3 - x_2) \end{aligned} \tag{5}$$

$$\left| \frac{\partial \Phi}{\partial x} \right| = \left| \begin{matrix} 1 & 0 \\ -\left(n_c + \frac{n_I}{V_Q} \right) & \frac{n_I}{V_Q} \end{matrix} \right| = \frac{n_I}{V_Q} \tag{6}$$

The control law is applicable as long as $-\alpha_I^{-1} \neq x_3$, which is always satisfied as x_3 represents a concentration. The second control law of the controller does not realize exact linearization, but asymptotic output tracking, working with the following nonlinear system:

$$\begin{aligned} \dot{x}_1(t) &= -p_G x_1(t) - S_I(x_1(t) + G_E) \frac{x_2(t)}{1 + \alpha_G x_2(t)} + EGP + \frac{P(t)}{V_G} \\ \dot{x}_2(t) &= x_3(t) \\ \dot{x}_3(t) &= u(t) \end{aligned} \tag{7}$$

The local coordinate-transformation for this system is a local diffeomorphism as long as:

$$\left| \frac{\partial \Phi(x)}{\partial x} \right| = \left(- \frac{S_I(x_1 + G_E)}{(1 + \alpha_G x_2(t))^2} \right)^2 \neq 0 \tag{8}$$

The properties of the second control loop are determined in a way that the nonlinear system would track the output of its own steady-state linearization with appropriately fast error dynamics.

To provide the values of state variables for the control laws, an extended Kalman-filter algorithm has been used. The discrete-time nonlinear model has been created with fourth-order Runge–Kutta method.

The output signal was measured with 5 minute sampling time. The performance of the Kalman-filter is presented in Fig. 1.

The output of the nonlinear system with and without using the presented control laws is compared with the series of linear systems determined for the tracking error and the linear system that needs to be followed in Fig. 2.

For the steady-state linearization of model (1) a classical PID controller was implemented to show the advantages of the applied methodology even in case of a low level controller (Fig. 3). It can be seen that quality parameters (settling time and overshoot) gave better results in case of asymptotic tracking then in case of the nonlinear model. The structure of the controller was first determined in continuous time domain, and then transformed into a discrete-time:

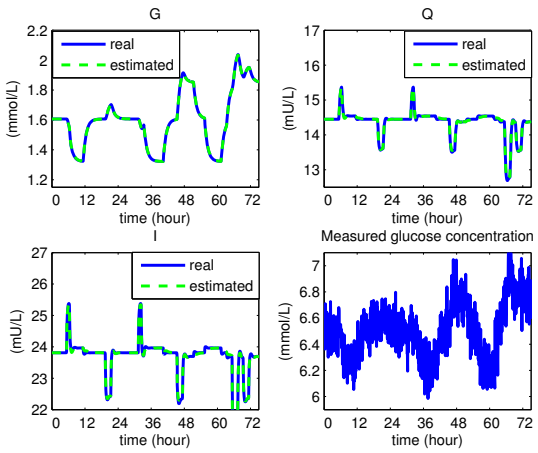

Figure 1. The real and estimated values of state variables acquired from the simulated output samples with added Gaussian measurement noise.

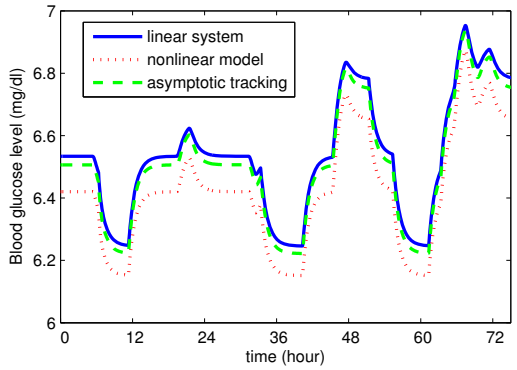

Figure 2. Comparison of the steady-state linearization of the ICU model with the output resulting from asymptotic output tracking and with the output of the original model.

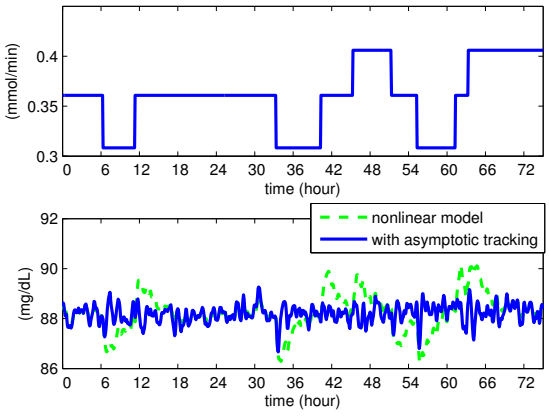

Figure 3. Glucose absorption profile used in the simulations (top) and the performance of a PID controller with and without asymptotic output tracking (bottom).

$$W_{PID}(s) = A_p \frac{(T_I s+1)}{T_I s} \frac{(T_D s+1)}{\left(\frac{T_D}{n}s+1\right)} \tag{9}$$

$$D_{PID}(z) = \left(1-z^{-1}\right) Z\left\{L^{-1}\{W_{PID}(s)\}\right\} \tag{10}$$

B. Asymptotic output tracking of a T1DM model

The model presented in [2] is not easy to be handled with methods based on differential geometry, because it has a relatively high number of state variables and it has a relative degree that is almost the half of that value. Moreover, some modifications need to be done in order to have smooth mappings in the system. Considering the connections between each compartment the system can be divided into three subsystems.

The first subsystem has 4 states, with injected insulin flow as input, and I_p as output. It is basically linear with a relative degree of 2.

$$\begin{aligned}
\dot{x}_1(t) &= -(m_2+m_4)x_1(t) + m_1 x_2(t) + k_{a2}x_3(t) + k_{a1}x_4(t) \\
\dot{x}_2(t) &= m_2 x_1(t) - (m_1+m_3)x_2(t) \\
\dot{x}_3(t) &= -k_{a2}x_3(t) + k_d x_4(t) \\
\dot{x}_4(t) &= -(k_{a1}+k_d)x_4(t) + \frac{u(t)}{BW}
\end{aligned} \tag{11}$$

The second subsystem has 5 states, with I_p as input, and G_p as output. Its relative degree is 3.

$$\begin{aligned}
\dot{x}_1(t) &= -k_1 x_1(t) + k_2 x_2(t) - k_{e1}\frac{(x_1(t)-k_{e2})}{1+\exp(M_1(k_{e2}-x_1(t)))} - \\
&- U_{ii} + \frac{Ra(t)}{BW} + \frac{\left(k_{p1}-k_{p2}x_1(t)-k_{p3}x_4(t)\right)}{1+\exp\left(M_2\left(k_{p2}x_1(t)+k_{p3}x_4(t)-k_{p1}\right)\right)} \\
\dot{x}_2(t) &= k_1 x_1(t) - k_2 x_2(t) - \frac{V_{mx}x_2(t)x_3(t)}{K_m + x_2(t)} - \frac{V_{m0}x_2(t)}{K_m + x_2(t)} \\
\dot{x}_3(t) &= -p_{2U}x_3 - p_{2U}I_b + \frac{p_{2U}}{V_i}I_p(t) \\
\dot{x}_4(t) &= -k_i x_4(t) + k_i x_5(t) \\
\dot{x}_5(t) &= -k_i x_5(t) + \frac{k_i}{V_i}I_p(t)
\end{aligned} \tag{12}$$

The last subsystem is a first order linear system with G_p as input and G_M as output.

$$\dot{G}_M(t) = -k_{s.c.}G_M(t) + \frac{k_{s.c.}}{V_G}G_p(t) \tag{13}$$

The three subsystems are noted on Fig. 4 with $\tilde{f}_1$, $\tilde{f}_2$ and $\tilde{f}_3$ respectively.

We can perform exact linearization on the first subsystem using the following local coordinate transformation:

$$\Phi(x) = \begin{pmatrix} x_1 \\ -(m_2+m_4)x_1 + m_1 x_2 + k_{a2}x_3 + k_{a1}x_4 \\ -k_{a2}x_3 + k_d x_4 \\ -(k_{a1}+k_d)x_4 \end{pmatrix} \tag{14}$$

$\Phi(x)$ is a local diffeomorphism in all points of the whole state-space, since:

$$\left|\frac{\partial \Phi}{\partial x}\right| = m_1(k_{a2}(k_{a1}+k_d)) \tag{15}$$

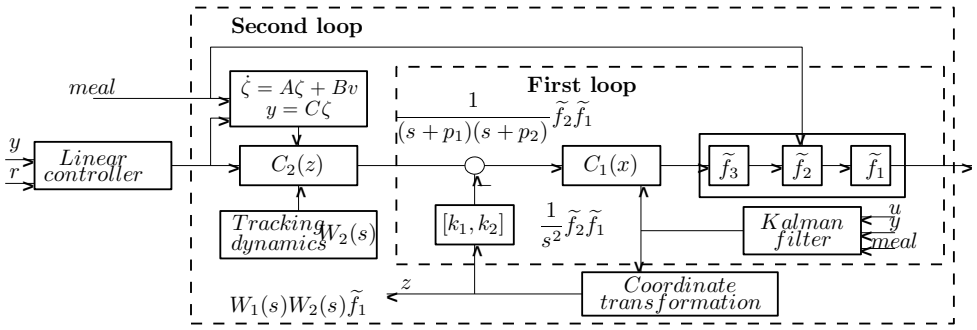

Figure 4. Structure of the tracking controller for the T1DM model [2].

The zero dynamics of the system are uniformly asymptotically stable in Ljapunov-sense (16).

$$\dot{z}_3 = -k_{a2}z_3 + k_d z_4 + \frac{k_d}{BW}u$$
$$\dot{z}_4 = -(k_{a1} + k_d)z_4 - \frac{(k_{a1} + k_d)}{BW}u \quad (16)$$

After applying the proper control law, it is essential to transform the resulting series of integrators into an asymptotically stable system with poles p_1 and p_2 guaranteeing that the zero dynamics of the next subsystem will be asymptotically stable as well:

$$\dot{z}_1 = z_2$$
$$\dot{z}_2 = -p_1 p_2 z_1 - (p_1 + p_2)z_2 + u \quad (17)$$

Consequently, the structure of the current control problem can be delimited in two loops: the first responsible for the exact linearization via feedback and Kalman-filtering, while the second for the asymptotic output tracking. The structure of the complete controller is presented in Fig. 4.

In the second loop, the asymptotic output tracking will be realized on the series of (17) and the second subsystem.

The relative degree of this system is 5; therefore, two 5th order linear systems are needed: Let $W_1(s)$ be a reference system (3) for the output tracking and $W_2(s)$ the tracking dynamics. Due to the subsystems' nonlinearities, the coordinate transformation and the control law have limited applicability with several inequality-constrains to be taken into consideration, and singular points to be avoided.

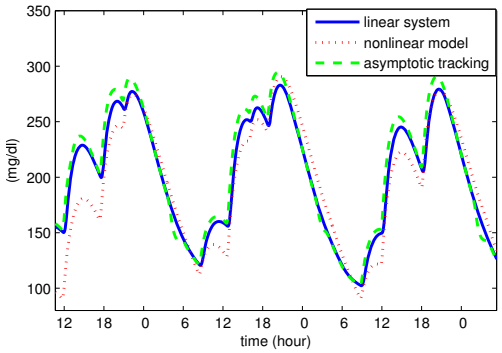

Figure 5. Comparison of the steady-state linearization of model (2) with asymptotic output tracking and with the deviation of the output for the original model from its basal value (250 mg/dL).

Since the steady-state linearization of the series of the first two subsystems results in a 9th order linear system, only one extra pole should be added to complete W_1(s) and W_2(s). In Fig. 4 $C_1(z)$ represents the state-feedback for exact linearization of the first subsystem, while $C_2(z)$ represents the control law (4).

The difference between the steady-state linear system, the model, and the model combined with the control law introduced above is shown in Fig. 5. Although the asymptotic output tracking response converges to the linearized model, slight deviations occur when there is a sudden change in the meal absorption input. This is caused by the fact that the relative degree of the model for the absorbed glucose input (Ra) is less than the relative degree for the injected insulin input. We should also mention that for the original system the deviation of the output from its basal value (250 mg/dL) is displayed.

For the state estimation the extended Kalman-filter was used similarly to the ICU case. The sensor model is similar to the one presented in [21]. The sampling time was 5 minutes. The performance of the Kalman-filter is displayed on Fig. 6. It can be seen that the output is well filtered even with a relatively big measurement noise.

For the steady-state linearization of the model a classical PID controller was implemented to show the advantages of the applied methodology. The structure of the controller was first determined in continuous time domain, and then transformed into discrete-time with the same 5 minute sampling frequency that was used in the sensor model:

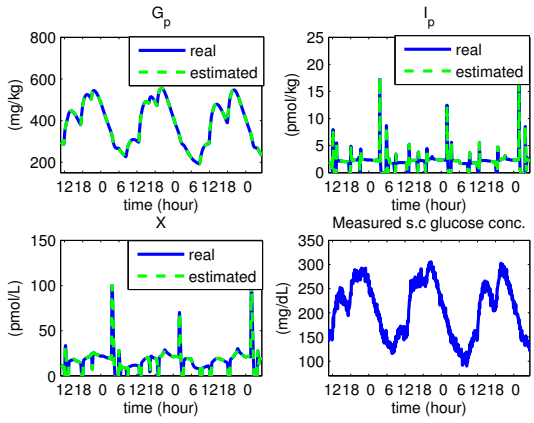

Figure 6. The real and estimated values of three state variables (G_p, I_p and X) acquired from the simulated output samples with added Gaussian measurement noise (bottom right).

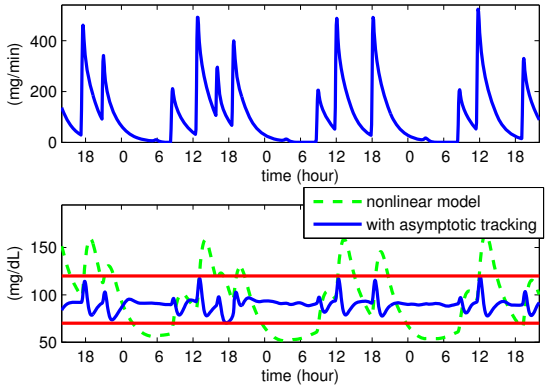

Figure 7. Glucose absorption profile used in the simulations (top) and the performance of a PID controller with and without asymptotic output tracking (bottom).

$$W_{PID}(s) = A_p \frac{(T_I s + 1)}{T_I s} \frac{\left(T_D^2 s^2 + 2\xi T_D s + 1\right)}{\left(\frac{T_D^2}{n^2} s^2 + 2\frac{T_D}{n} s + 1\right)} \tag{18}$$

$$D_{PID}(z) = \left(1 - z^{-1}\right) Z\left\{L^{-1}\left\{W_{PID}(s)\right\}\right\} \tag{19}$$

The performance of the controller on the model has been compared with the case when the control law for asymptotic tracking is used (Fig. 7). In this case, the glucose rate of appearance (R_a) is considered as a known time-varying parameter. It can be seen that the designed nonlinear approach is able to keep the glucose level inside the defined 80-120 mg/dL interval. For T1DM case simulations a clinically recorded feeding profile has been used (Fig. 7.), regarding 1 week's real data of a 17 year old boy.

V. Conclusion

The aim of the current paper was to apply asymptotic tracking for the nonlinear models [1]-[2]. We managed to hide the nonlinearity of the physiological model by transforming the control input provided by a linear controller so that the response of the model would mimic the behavior of a linear system. In addition, a Kalman-filter extended for nonlinear systems was designed to estimate the values of the state variables.

Simulation results concluded that the methods presented could extend the validity of linear controllers. However, several practical issues should be considered in the future, like: state estimation particularities; limited sensor capabilities; meal detection and estimation. Identification and the effect of parameter variability among patients are not investigated in this paper, and represent future tasks as well.

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