INSULIN DEPENDENT DIABETES MELLITUS CONTROL

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Abstract — This work considers the problem of automatically controlling the glucose level in Insulin Dependent Diabetes Mellitus (IDDM) patients. The objective is to include several important and practical issues in the design: model uncertainty, time variations, nonlinearities, measurement noise, actuator delay and saturation, and real-time implementation. These are fundamental issues to be solved in a device implementing this control. A simulator of the well known Sorensen 19-th state model has been built. It has been found that this compartmental model although nonlinear, is almost linear Time Invariant (LTI) in practice. To this end, a robust \( H_\infty \) controller is designed and tested against the simulator in order to check all the previous practical issues.

Keywords — Diabetes control, robust control, \( H_\infty \) control.

I. INTRODUCTION

Under normal conditions, blood glucose concentration should be in the interval of [60,120] mg/dL (DCCT, 1993). The body regulates this concentration by means of glucagon and insulin, both pancreatic endocrine hormones secreted from \( \alpha \) and \( \beta \) cells respectively. The absence of insulin released by the pancreas is called Insulin dependent Diabetes Mellitus (IDDM) and produces a higher glucose level in the blood (hyperglycaemia). The consequences of this fact can be atherosclerosis, retinopathy, etc. The excess of insulin on the other hand, may produce a lower value of glucose (hypoglycaemia) which may produce diabetic coma or even death. Meals and exercise tend respectively to increase and decrease blood glucose levels. It is very important to maintain glucose levels between the previously mentioned bounds. Therefore, diabetic patients need external injections of insulin according to their actual conditions in order to regulate their glucose level. This is particularly painful in children with IDDM which may need several insulin shots a day, plus regular glucose measurements which may involve finger picks. Instead, type II diabetes is generally produced in the long term and has to do with patient’s aging, which may not even need external insulin provision.

Glucose-Insulin dynamics has been extensively studied. A few models based upon ordinary differential equations (ODE) can be used, for simulation or control system design purposes (Makroglou et al., 2006). As controller design is concerned, solutions are frequently based upon either Bergman’s 3rd. order model (Fisher, 1991; Cocha et al., 2009; Makroglou et al., 2006), or Sorensen’s 19th. order model (Sorensen, 1985). Both models are nonlinear and suitable for design purposes.

The control system design for this process has been approached in different ways using both models (see Kovács et al., 2009; Chee and Fernando, 2007; Bondia et al., 2010; for a survey). Solutions go from semiclosed-loop solutions (Fisher, 1991) and simplified PID control to heuristic fuzzy-logic procedures or parametric-programming (Dua et al., 2006). The aforementioned models, present significant sources of uncertainty that are worth considering systematically. Robust Control Theory (Ruiz-Velázquez et al., 2004; Parker et al., 2000) has been applied to this problem, centered on the uncertainty issue. Also a Linear Parameter Varying (LPV) model has been derived in Kovács and Kulcsár (2007) based on Sorensen’s model and again an \( H_\infty \) LTI controller has been designed for it in Kovács et al. (2008, 2011). In addition, due to the nature of the dynamics in both standard models, nonlinear control design methods have also been applied (Cocha et al., 2009; Kovács et al., 2008) but with no clear robustness guarantees. In previous works by one of the authors of this paper (Sánchez Peña and Ghersin, 2010; Sánchez Peña et al., 2011) both, LPV and Unfalsified control (UC) where tested for this problem. Based on the latter, attention should be paid to all of the following issues:

- Model uncertainty.
- Time-varying and/or nonlinear phenomena.
- Time delays, actuator saturation, measurement noise.
- Real-time implementation.

In several works, these items have been considered separately or simultaneously (Parker et al., 2000; Dua et al., 2006; Kovatchev et al., 2009; Ruiz-Velázquez et al., 2004; Kovács et al., 2011; Willimska et al., 2010). In Sánchez Peña et al. (2011), they have all been considered simultaneously over the simplified Bergman’s 3rd. order model (Makroglou et al., 2006; Fisher, 1991). The objective of the present work is to continue the one in Sánchez Peña et al. (2011), but based on Sorensen’s 19th order model. This last model is not only more elaborated than the first one, but also was created with a different objective. The purpose of Bergman’s model was to generate minimal mathematical dynamics capable of explaining variations in individual response to a single input (IVGTT: Intravenous Glucose Tolerance Test). On the other hand, Sorensen intended to develop a generalized physiologic model yielding predictions of mean normal response over a wide variety of inputs (Sorensen, 1985). In order to take into account the practical issues listed above, a model simulator has been constructed and the following observation has been
made: the model can be considered LTI for all practical purposes. Hence, a robust \( \mathcal{H}_\infty \) controller has been designed and tested. As a byproduct, several errors in most of the Sorenson’s model literature have been found.

The paper is organized as follows. Some brief background material on Sorenson’s model and the errors found in the literature are pointed out in Section II. The weight selection and controller design is performed in Section III. Simulations illustrating the controller performance over the nonlinear simulator and all practical issues mentioned previously are presented in section IV. Final conclusions are drawn in section V.

II. SORENSEN’S MODEL

Sorenson’s mathematical model is an explanatory physiological mechanism of the glucose metabolism in the human body. It is the model to choose because of its sophistication and predictive capability, given the statistical value of its parameters. In general lines, it divides the body in six compartments: 1) brain, representing the central nervous system; 2) heart and lungs; 3) liver; 4) gut; 5) kidneys and 6) muscular skeleton and adipose tissue (peripheral). In addition, each compartment is composed of three spaces: 1) blood capillary, fed by the arterial blood and evacuated by the venous one; 2) interstitial and 3) intracellular. Nevertheless, as shown in Fig. 1, where the glucose model scheme is represented, the number of spaces can be reduced to two or one, depending on the permeability of the membranes in each compartment.

In Sorenson’s formulation three models participate: glucose, insulin and glucagon. In order to obtain a mathematical representation, a mass balance is performed in each physiological compartment. As a consequence, twelve nonlinear ordinary differential equations are obtained for the glucose (three associated to non dimensional variables) and glucagon dynamics and seven linear ones for the insulin. It is important to note that the linearity in the insulin model is due to the fact that Diabetes type I is considered. This assumption not only induces linearity, but also the decoupling with the other dynamics. Nonlinearity of the glucose and glucagon models arise due to the fact that metabolic rates are suitably represented by hyperbolic tangent functions. Therefore, the sigmoidal nonlinearity commonly observed in biological data correlations, can be depicted (Sorenson, 1985).

The equations for glucose dynamics are:

\[
\begin{align*}
\frac{\dot{G}_h}{G^C_h} &= (G^C_h - G^R_h) \frac{q_h}{v_h} + \frac{G^R_h}{v_h} - \frac{G^C_h}{v_h} \frac{q_h}{v_h} \\
\frac{\dot{G}_p}{G^C_p} &= (G^C_p - G^R_p) \frac{q_p}{v_p} + \frac{G^R_p}{v_p} - \frac{G^C_p}{v_p} \frac{q_p}{v_p} \\
\frac{\dot{G}_h}{G^C_h} &= (G^C_h q_h + G^C_h q_l + G^C_h q_k + G^C_h q_r - G^C_h q_{hi} - \frac{1}{v_h}) \\
\frac{\dot{G}_p}{G^C_p} &= (G^C_p q_p + G^C_p q_l + G^C_p q_k + G^C_p q_r - G^C_p q_{pi} - \frac{1}{v_p})
\end{align*}
\]

Equations for insulin dynamics:

\[
\begin{align*}
\frac{\dot{I}_h}{I^C_h} &= (I^C_h Q_h + I^C_h Q_l + I^C_h Q_k + I^C_h Q_r - \frac{1}{v_h}) \\
\frac{\dot{I}_p}{I^C_p} &= (I^C_p Q_p + I^C_p Q_l + I^C_p Q_k + I^C_p Q_r - \frac{1}{v_p}) \\
\frac{\dot{I}_h}{I^C_h} &= (I^C_h - I^C_h) \frac{q_h}{v_h} + \frac{G^R_h}{v_h} - \frac{G^C_h}{v_h} \\
\frac{\dot{I}_p}{I^C_p} &= (I^C_p - I^C_p) \frac{q_p}{v_p} + \frac{G^R_p}{v_p} - \frac{G^C_p}{v_p}
\end{align*}
\]

and the remaining four equations of Sorenson’s model:

\[
\begin{align*}
\dot{N} &= (\Gamma_{\text{meas}} - N) \frac{F_{\text{BGU}}}{V_N} \\
\dot{A}_{\text{BGR}} &= \frac{1}{25} \left\{ 1.2088 - 1.138 \tanh \left[ 1.6169 \left( \frac{I^C_h}{21.43} - 0.8885 \right) \right] \right\} - A_{\text{BGR}} \\
\dot{A}_{\text{NBR}} &= \frac{1}{65} \left\{ 2.7 \tanh(0.388N) - 1 \right\} - A_{\text{NBR}} \\
\dot{A}_{\text{BGU}} &= \frac{1}{25} \left\{ 0.549 \left( \frac{I^C_h}{21.43} \right) - A_{\text{BGU}} \right\}
\end{align*}
\]
The \( \Gamma \) parameters which appear in the equations are as follow: \( \Gamma_{RU} = 70, \Gamma_{RBCU} = 10, \Gamma_{SU} = 20, \Gamma_{PIR} = 0 \),
\[
\Gamma_{KC} = F_{KC} [ I'_{KC} Q_k + I'_{KC} Q_k + \Gamma_{nu} ]
\]
\[
\Gamma_{HCU} = 20 A_{RBCU} \left[ 5.6648 + 5.6589 \tanh \left( \frac{2.4375 (G^C_{\nu})}{101} - 1.48 \right) \right]
\]
\[
\Gamma_{HGU} = 155 A_{RBCU} [2.7 \tanh(0.388V) - A_{NHGP} ] \times \left( \frac{1.425 - 1.406 \tanh(0.388V)}{0.1699 \left( \frac{G^C_{\nu}}{101} - 0.4969 \right)} \right) \tag{4}
\]
\[
\Gamma_{PGU} = \frac{35G^C_{\nu}}{86.81} \left[ 0.0375 + 0.61623 \tanh \left( \frac{0.33827 (I''_{PGU})}{5.304} - 5.82113 \right) \right] \times \left( \frac{1.3102 - 0.61016 \tanh(0.388V)}{1.0571 \left( \frac{G^C_{\nu}}{15.15} - 0.46981 \right)} \right) \times \left( \frac{2.9285 - 2.095 \tanh(0.388V)}{4.18 \left( \frac{G^C_{\nu}}{91.89} - 0.6191 \right)} \right)
\]
\[
\Gamma_{IC} = \frac{I''_{IC}}{1 - F_{IC} - I''_{IC}} \times \left( \frac{G^C_{\nu}}{91.89} \right)
\]
\[
\Gamma_{KC} = F_{KC} I''_{KC} Q_k \tag{5}
\]
\[
\Gamma_{KE} = \left[ \frac{71I}{1 + \tanh[0.11 \left( G^C_{\nu} - 460 \right)]} \right] \text{if} \ G^C_{\nu} < 460 \text{mg/dl} \tag{6}
\]
\[
\Gamma_{KE} = \left[ \frac{0.872G^C_{\nu} - 330}{1 + \tanh[0.11 \left( G^C_{\nu} - 460 \right)]} \right] \text{if} \ G^C_{\nu} \geq 460 \text{mg/dl}
\]

The indices and the model variable notation in the above equations are the same used in Parker et al. (2000) and Kovács et al. (2011).

**Indices:**
- A: hepatic artery
- B: brain
- BU: brain uptake
- C: capillary space
- G: glucose
- H: heart and lungs
- HGP: hepatic glucose production
- HGU: hepatic glucose uptake
- I: insulin
- IHP: insulin effect on HGP
- IHGU: insulin effect on HGU
- IVI: intravenous insulin infusion
- K: kidney
- KC: kidney clearance
- KE: kidney excretion
- L: liver
- LC: liver clearance
- N: glucagon
- NHGP: glucagon effect on HGP
- P: periphery(muscle/adipose tissue)
- PC: peripheral clearance
- PGU: peripheral glucose uptake
- PIR: pancreatic insulin release
- PNC: pancreatic glucagon clearance
- PNR: pancreatic glucagon release(normalized)
- RBCU: red blood cell uptake
- S: gut (stomach/intestine)
- SIA: insulin absorption into blood stream from subcutaneous depot
- SU: gut uptake
- T: tissue space

**Model variables notations:**
- A: auxiliary equation state (dimensionless)
- B: fractional equation state (I, dimensionless; N, L/min)
- G: glucose concentration (mg/dL)
- I: insulin concentration (mU/L)
- N: glucagon concentration (normalized, dimensionless)
- Q: vascular plasma flow rate (L/min)
- q: vascular blood flow rate (dl/min)
- T: transcapillary diffusion time constant (min)
- V: volume (L)
- v: volume (dl)
- F: metabolic source or sink rate (mg/min or mU/min)

A close analysis of the equations in Sorensen (1985) points out several inconsistencies with respect to the models presented in previous works. For example, in Kovács and Kulcsár (2007), Eqn. (4), variable \( A_{HGU} \) is confused with \( A_{HGP} \); there are no parenthesis in Eq. (3) and there are numerical differences in Eq. (7). Also in Eq. (5) the denominator should read \( T'_{KU}/V'_{KU} \) instead of \( 1/(T'_{KU}/V'_{KU}) \). These last three errors are present also in Parker et al. (2000). In Ruiz-Velázquez et al. (2004), in Eq. (2) instead of \( V'_{IC} \) we find \( V'_{KU} \), which erroneously does not allow the simplification of this equation. Although all of these errors can always be interpreted as misspellings, there is a common error in all these works with respect to Eq. (6). The variable which should be there is \( I''_{KC} \), but \( I''_{KC} \) instead. This error already appears in the original work (Sorensen, 1985) in the section where the whole model is presented (pages 213-222), but the correct variable can be identified through the analysis of page 134 over \( \Gamma_{KC} \), which references Chamberlain and Stimmer (1967). The latter can be also ratified by the programming instructions of the model in page 535 of Sorensen (1985).

**III. CONTROLLER DESIGN**

The model has two inputs \( \Gamma_{meal} \) (meal disturbance) and \( \Gamma_{IVI} \) (insulin infusion) and one output \( G^I_{p} \) (glucose concentration in the interstitial space-peripheral). The linearization is performed by gridding \( \Gamma_{IVI} \) from 0 to 35 mU/min, assuming no disturbance (\( \Gamma_{meal}=0 \) mg/min), which moves the steady state value of \( G^I_{p} \) from 183 to 46 mg/dl respectively. The Bode plots of this grid are represented in Fig. 2. The *normoglycaemic* condition which defines the nominal model is associated to a concentration of \( G^I_{p} = 87 \) mg/dl, produced when the insulin infusion is 22 mU/min. The similarities between the different plots denote their low level of nonlinearity, which allows to represent the nominal system as a LTI model, which can be reduced from 19 to 6 states with no major impact (see Fig. 3). The modeling error is covered by additive uncertainty (\( G-G_{\nu} \)). The difference between all previous curves and the reduced order nominal model is represented in Fig. 4. There, the uncertainty weight \( W_{\Delta}(s) \) covers all additive errors at all frequencies. Note that this model order reduction is based on a balanced and truncated state-space realization of the LTI original model, whose precision is measured in terms of its Hankel singular values. It is a numerical method which
has no connection whatsoever with the reduced nonlinear dynamical model presented in Bergman (2003). The latter has reduced nonlinear dynamics but with a physiological interpretation, as explained in section I.

A brief explanation of the analysis and design methodology follows (see Zhou et al., 1996; Sánchez Peña and Sznaier, 1998). The set
\[ G = G_0 + \Delta W_\Sigma, \quad |\Delta| < 1 \]
known as the additive uncertainty model set, represents the physical phenomena. This dynamical description, instead of a single model, may include nonlinearities, high order unknown phenomena and time delays. Here \( G_0(s) \) is the reduced-order nominal model and \( W_\Sigma(s) \) represents the variation of model uncertainty with frequency. Nominal performance (NP) is defined as the weighted tracking error of the nominal model \( G_0(s) \) measured in terms of its signal energy, for all perturbations \( d \) in a set measured accordingly (see Fig. 5):
\[ |z_1| < \gamma \quad \text{for all} \quad ||d|| < 1 \quad (8) \]
Robust stability (RS) is the (internal) stability\(^1\) of all possible closed loops which combine a single controller \( K(s) \) with all elements of set \( G \). Finally Robust performance (RP) is defined as the validity of condition (8) for all elements of set \( G \). Standard Robust control results guarantee that these conditions are equivalent to:
\[ NP \Leftrightarrow \frac{1}{\gamma} \left[ \begin{array}{c} W_p(s)S(s) \\ W_\Sigma(s)K(s)S(s) \end{array} \right] < 1 \quad (9) \]
\[ RS \Leftrightarrow \frac{1}{\gamma} \left[ W_p(s)K(s)S(s) \right] < 1 \quad (10) \]
\[ RP \Leftrightarrow \frac{1}{\gamma} \mu_\Delta |T_{zd}(j\omega)| < 1 \quad \forall \omega \quad (11) \]
where \( S(s) = (I+G\bar{K})^{-1} \) is the sensitivity function, \( \mu_\Delta(.) \) is the structured singular value, \( T_{zd}(\omega) \) the transfer matrix between \( d \) and \( z = [z_1, z_2]^T \) in Fig. 5 and \( \gamma \) is a scalable variable. A sufficient condition to guarantee \( RP \) is the so-called mixed-sensitivity condition, which can be used for controller design:
\[ \min \gamma \quad \text{such that} \quad \left[ \begin{array}{c} W_p(s)S(s) \\ W_\Sigma(s)K(s)S(s) \end{array} \right] < \gamma \]

The performance weight \( W_p(s) \) is selected in order to have a small steady state tracking error to follow the reference, almost like an integrator. The reference is based on the response of an average normal patient to a disturbance of 100 g of glucose at \( t=0 \). This response can be represented as the impulse response of a second order system (Ruiz-Velázquez et al., 2004):
\[ P_{opt}(s) = \frac{K\bar{w}_n^2}{s^2 + 2w_n\bar{\xi} + \bar{\xi}^2} \]
with \( K=3900, \bar{w}_n=0.02 \) and \( \bar{\xi}=0.7 \).

The design is performed via the \( \mathcal{H}_\infty \) optimal control method using Linear Matrix Inequality (LMI) optimization and considering the following performance and uncertainty weights, respectively:
\[ W_p(s) = \frac{0.1667s + 0.05}{s + 0.0025} \]
\[ W_\Sigma(s) = 10^{-4} \frac{0.1976s^3 + 1.779s^2 + 4.743s + 3.953}{s^3 + 0.2125s^2 + 0.0125s + 0.000125} \]
The controller designed has order 10, and is reduced to order 8 also based on a balanced truncated method. The optimal performance/robustness value is \( \gamma=0.9038 \). Robust stability and performance and Nominal performance necessary and sufficient conditions are represented in Fig. 7, based on equations (9)–(11).

\(^1\) Internal stability of a closed loop interconnection is equivalent to the input/output (I/O) stability of all possible I/O transfer functions in the loop.
Concerning the practical limitation of the insulin pumps of 100 mU/min, $W_s$ can also be considered as a weight to bound the control signal. As illustrated in section IV, no further adjustments where necessary in order to limit the insulin injection to the previous bound.

### IV. SIMULATIONS

For the simulations, a meal disturbance which contains 100 g carbohydrate is considered and the gut absorption model presented in Lehmann and Deutsch (1992) is used. This model assumes that gastric emptying is a trapezoidal time limited signal with a maximum of 360 mg/min, which inputs a first order filter $1/(60s+1)$, in order to represent the intestinal absorption. This results in signal $\Gamma_{\text{meal}}$ illustrated by Fig. 6. In addition, noise was included as random errors in the measurement of the glucose concentration, with a band limited value of 5 mg/dl. The time response of the closed-loop system with measurement noise, injected insulin levels bounded by 100 mU/min, the meal disturbance of 100 g of glucose and delays (both in the insulin injection and glucose measurements) due to the subcutaneous–intravenous differences, can be seen in Fig. 8.

The control action (insulin injection) plotted in Fig. 9, shows that there was no saturation of the pump, which tends to a steady state value of 22 mU/min. This is due to the fact that the reference steady state is approximately 87 mg/dl. A fact that was also considered when simulating was that the reference is related to the blood concentration while the output is the interstitial glucose concentration. Therefore, a 5 min. delay was added to the reference in order to assimilate this behavior. This value was taken from the computed delay in these two values in Sorensen’s model.

### V. CONCLUSIONS AND FURTHER RESEARCH

A detailed version of the Sorensen model has been presented, and a few errors have been detailed which appear in the previous literature. The fact that this model can be considered as LTI for practical purposes has been pointed out. As a consequence, a reduced order nominal model has been obtained and its difference with several linearization points has been covered by additive uncertainty. An $H_\infty$ optimal controller has been designed which achieves the robustness and performance analysis. A closed-loop simulation has been presented, considering the existing delays due to the interstitial-intravenous differences and measurement noise. The 8th order controller may be easy to achieve in a future real-time implementation.

This procedure proves useful for the Sorensen average patient, but most probably for large intra- and inter-patient variations, a more elaborated controller-nonlinear and/or time-varying, should be used.

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