Nonlinear Control of Glucose Concentration in Type-1 Diabetes Mellitus

P. González and R. Femat*
Instituto Potosino de Investigación Científica y Tecnológica A.C., División de Matemáticas Aplicadas
Camino a la Presa de San José 2055, Lomas 4a. sección, 78216, San Luis Potosí, SLP, MÉXICO
*Corresponding author: rfemat@ipicyt.edu.mx
Phone: +52 (444) 834 2000, Fax: +52 (444) 834 2010

***Abstract*— In this work, a nonlinear passive controller to regulate the glucose concentration in Type-1 Diabetes Mellitus (T1DM) patients is presented; the controller computes the peripheral insulin delivery rate using measurements of peripheral glucose concentrations. First, the state-feedback problem is addressed with a constructive control framework via passivation by backstepping, yielding the attainable closed-loop behavior, or in other words, the recovery target for the output-feedback (OF) design. Then, on the basis of observability considerations, an OF controller with reduced modeling requirements is derived, which includes a state estimator to compensate modeling errors and meal disturbances. The proposed nonlinear OF controller has a systematic construction and a simple tuning scheme, and is tested through numerical simulations on a T1DM patient under nominal, hyperglycemic, and hypoglycemic scenarios.**

Keywords: Type-1 Diabetes Mellitus, constructive control, geometric control, feedback control.

I. Introduction

Type-1 Diabetes Mellitus (T1DM) is a metabolic disease caused by the auto-immune destruction of pancreatic β-cells, resulting in an insufficient release of insulin into the blood stream. The direct effect of T1DM is a blood glucose concentration larger than 120 mg/dL (hyperglycemia) after meal ingesta; if this glucose concentration is held at hyperglycemic level for long periods of time, severe consequences (atherosclerosis and retinopathy, among others) are presented. For the preceding reasons, external daily insulin injections have become the most accessible and popular treatment of T1DM, on the basis of glucose concentration measurements.

Motivated by the need of developing (i) suitable technology for insulin infusion and glucose monitoring, and (ii) automatic insulin delivery systems (artificial pancreas), the T1DM glucose control problem has been the subject of theoretical, simulation and clinical studies. The state of the art can be seen elsewhere (Hovorka, 2005; Chee and Fernando, 2007), and here it suffices to mention that, regarding control algorithms, several linear approaches have been proposed, including fuzzy logic-based (Campos-Delgado *et al.*, 2006), model predictive (Parker *et al.*, 1999), H_∞ (Ruiz-Velázquez *et al.*, 2004) and classical PID (Ramprasad *et al.*, 2004) control designs, with potential implementation in clinical trials due to their robustness features. However, given the highly-nonlinear behavior of carbohydrates metabolism (Sorensen, 1985), and the health condition variability in patients (such as the counter-regulatory hepatic responses), linear controllers overlook important physiological phenomena (for instance, the effect of lactate on the periphery glucose uptake in exercise scenarios) and the controllers can lose dynamical information from patients.

These observations rise the issue that motivates the present work: the design of a nonlinear controller that, on the basis of mass balances and glucose measurements, computes the insulin amount to keep the glucose concentration within normal levels (80 – 120 mg/dL) in T1DM patients. Methodologically speaking, we are interested in deriving a control scheme with: (i) a design that exploits the nature of carbohydrate metabolism but without including it into the control function, and (ii) robustness and simplicity features for practical implementation.

In this work the problem is addressed via passivation by backstepping. First, the state-feedback (SF) problem is studied, establishing that the problem is solvable with a non-passive controller underlain by a relative degree (RD) equal to 2. To remove this high-RD obstacle for robustness, a backstepping procedure (Sepulchre *et al.*, 1997) is employed to draw a nonlinear passive SF controller whose response constitutes the attainable closed-loop behavior for the output-feedback (OF) design. Then, on the basis of observability considerations, a robust OF controller is designed, and includes a state estimator to compensate modeling errors and unknown load-like (meal) disturbances. The resulting OF controller has reduced modeling requirements, a systematic construction and a simple tuning scheme, and is tested through numerical simulations on a T1DM patient under nominal, hyperglycemic, and hypoglycemic scenarios.

II. Control Problem

In order to technically state our T1DM control problem, let us consider the physiological model proposed by Sorensen (1985), which describes the time evolution of the glucose, insulin and glucagon concentrations for non

diabetic and T1DM subjects. For modeling purposes, the human body is divided into compartments (brain, heart and lungs, liver, gut, kidney, and periphery) where mass balances are performed for glucose and insulin components, whereas the whole human body is regarded as a single compartment for the glucagon balance; physiologic compartments are connected via blood flows. From the preceding considerations, along with physiological and pharmacokinetic-pharmacodynamic arguments, the glucose-insulin-glucagon dynamics are described by the following nonlinear ordinary differential equations:

Glucose subsystem (1a)

$$\dot{g}_{Bv} = (q^g_B/V^g_{Bv})(g_H - g_{Bv}) - (V_{Bi}/V^g_{Bv}t_B)(g_{Bv} - g_{Bi}) \quad (1a.1)$$

$$\dot{g}_{Bi} = (1/t_B)(g_{Bv} - g_{Bi}) - r_{Bgu}/V_{Bi} \quad (1a.2)$$

$$\dot{g}_H = (1/V^g_H)(q^g_B g_{Bv} + q^g_L g_L + q^g_K g_K + q^g_P g_{Pv} - q^g_H g_H - r_{RBgu}) \quad (1a.3)$$

$$\dot{g}_G = (q^g_G/V^g_G)(g_H - g_G) + (r_{meal} - r_{Ggu})/V^g_G, \qquad d = r_{meal} \quad (1a.4)$$

$$\dot{g}_L = (1/V^g_L)(q^g_A g_H + q^g_G g_G - q^g_L g_L + r_{Hgp} - r_{Hgu}) \quad (1a.5)$$

$$\dot{g}_K = (q^g_K/V^g_K)(g_H - g_K) - r_{Kge}/V^g_K \quad (1a.6)$$

$$\dot{g}_{Pv} = (q^g_P/V^g_{Pv})(g_H - g_{Pv}) - (V_{Pi}/V^g_{Pv}t^g_P)(g_{Pv} - g_{Pi}), \quad y_{Pv} = g_{Pv} \quad (1a.7)$$

$$\dot{g}_{Pi} = (1/t^g_P)(g_{Pv} - g_{Pi}) - r_{Pgu}/V_{Pi}, \qquad z = y_{Pi} = g_{Pi} \quad (1a.8)$$

Insulin subsystem (1b)

$$\dot{I}_B = (q^I_B/V^I_B)(I_H - I_B) \quad (1b.1)$$

$$\dot{I}_H = (1/V^I_H)(q^I_B I_B + q^I_L I_L + q^I_K I_K + q^I_P I_{Pv} - q^I_H I_H) \quad (1b.2)$$

$$\dot{I}_G = (q^I_G/V^I_G)(I_H - I_G) \quad (1b.3)$$

$$\dot{I}_L = (1/V^I_L)(q^I_A I_H + q^I_G I_G - q^I_L I_L + r_{PIr} - r_{LIc}) \quad (1b.4)$$

$$\dot{I}_K = (q^I_K/V^I_K)(I_H - I_K) - r_{KIc}/V^I_K \quad (1b.5)$$

$$\dot{I}_{Pv} = (q^I_P/V^I_{Pv})(I_H - I_{Pv}) - (V^I_{Pi}/V^I_{Pv}t^I_P)(I_{Pv} - I_{Pi}) \quad (1b.6)$$

$$\dot{I}_{Pi} = (1/t^I_P)(I_{Pv} - I_{Pi}) + (w_i - r_{PIc})/V^I_{Pi}, \qquad u = w_i \quad (1b.7)$$

Glucagon and auxiliary states subsystem (1c)

$$\dot{\Gamma} = (1/V^\Gamma)(r_{P\Gamma r} - r_{P\Gamma c}) \quad (1c.1)$$

$$\dot{f}_2 = [(m^{\Gamma 0}_{Hgp} - 1)/2 - f_2]/\tau_\Gamma \quad (1c.2)$$

$$\dot{m}^I_{Hgp} = (m^{I\infty}_{Hgp} - m^I_{Hgp})/\tau_I \quad (1c.3)$$

$$\dot{m}^I_{Hgu} = (m^{I\infty}_{Hgu} - m^I_{Hgu})/\tau_I \quad (1c.4)$$

The states (**x**) are: (a) glucose concentrations in the vascular (g_{Bv}) and interstitial (g_{Bi}) brain tissues, heart and lungs (g_H), guts (g_G), liver (g_L), kidney (g_K), and peripheral (skeletal muscle and adipose tissue) vascular (g_{Pv}) and interstitial (g_{Pi}) spaces; (b) insulin concentrations in the brain (I_B), heart and lungs (I_H), guts (I_G), liver (I_L), kidney (I_K), and peripheral vascular (I_{Pv}) and interstitial (I_{Pi}) spaces; as well as glucagon (Γ) and metabolic auxiliary states (f_2, m^I_{Hgp}, and m^I_{Hgu}). The *exogenous input* (d) is the carbohydrates absorption rate (r_{meal}). The *regulated output* (z) is the glucose concentration in the peripheral interstitial space (g_{Pi}). The *measured outputs* (**y**) are: the glucose concentrations in the peripheral vascular (y_{Pv}) and interstitial (y_{Pi}) spaces, meaning that the control scheme will be driven by subcutaneous glucose measurements. The *control input* (u) is the interstitial insulin delivery rate (w_i), or in other words, a subcutaneous insulin supply is assumed.

The hepatic glucose production (r_{Hgp}), hepatic glucose uptake (r_{Hgu}), renal glucose excretion (r_{Kge}), peripheral glucose uptake (r_{Pgu}), hepatic insulin consumption (r_{LIc}), renal insulin consumption (r_{KIc}), peripheral insulin consumption (r_{PIc}), and glucagon release ($r_{P\Gamma r}$) and consumption ($r_{P\Gamma c}$) rates are set by the nonlinear functions (Sorensen, 1985):

$$r_{Hgp} = \gamma_{Hgp}(g_L, \Gamma, f_2, m^I_{Hgp}), \qquad r_{Hgu} = \gamma_{Hgu}(g_L, m^I_{Hgu}) \quad (2a, b)$$

$$r_{Kge} = \gamma_{Kge}(g_K), \qquad r_{Pgu} = \gamma_{Pgu}(g_{Pi}, I_{Pi}) \quad (2c, d)$$

$$r_{LIc} = \gamma_{LIc}(I_H, I_G), \qquad r_{KIc} = \gamma_{KIc}(I_K) \quad (2e, f)$$

$$r_{PIc} = \gamma_{PIc}(I_{Pi}), \quad r_{P\Gamma c} = \gamma_{P\Gamma c}(\Gamma), \quad r_{P\Gamma r} = \gamma_{P\Gamma r}(g_H, I_H) \quad (2g, h, i)$$

In compact notation, the glucose-insulin-glucagon model (1, 2) is given by

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, d, u), \quad \mathbf{x}(0) = \mathbf{x_o}; \quad \mathbf{y} = \mathbf{C_y x}, \quad z = \mathbf{C_z x} \quad (3)$$

where

$$\mathbf{x} = (g_{Bv}, g_{Bi}, g_H, g_G, g_L, g_K, g_{Pv}, g_{Pi}, I_B, I_H, I_G, I_L, I_K, I_{Pv}, I_{Pi}, \Gamma, f_2, m^I_{Hgp}, m^I_{Hgu})'$$

$$d = r_{meal}, \qquad y = (y_{Pv}, y_{Pi}), \qquad u = w_i, \qquad z = g_{Pi}$$

In a nondiabetic subject, the basal blood glucose concentration is about 80-100 mg/dL; after a meal, this concentration increases for a period of 2 hours, with a peak at 120-140 mg/dL. Thus, our problem consists in designing a robust nonlinear controller that, driven by the measurements (y and d), tracks the glucose concentration at euglycemic levels such that the regulated output motion z(t) resembles the one of a nondiabetic subject. For applicability purposes, the control design must exploit the nonlinear nature of carbohydrate metabolism and minimize the model dependency.

III. State-Feedback Control

In this section the nonlinear SF control problem is addressed under the assumption that the states and exact model are known and available for control. The purpose is the identification of the attainable closed-loop behavior, or equivalently, the recovery target of the proposed OF controller.

III.1 Backstepping procedure

Following the nonlinear approach employed in a previous T1DM control study (Hernández-Ordóñez, 2003), the direct application of the standard geometric control method (Isidori, 1995) leads to the conclusion that the control problem is solvable with RD equal to 2, provided that the zero-dynamics (presented in the next subsection) are stable, and that the following invertibility condition is met:

$$\partial\gamma_{Pgu}/\partial I_{Pi} > 0 \qquad (4)$$

From a constructive control viewpoint (Sepulchre *et al.*, 1997), control schemes with RD's equal or higher than 2 might present wasteful responses and nonrobust behavior. According to the abovementioned constructive control theory, a control scheme is robust if it is underlain by a passive structure, meaning RD's equal to 1 and stable zero-dynamics.

In order to compensate the high RD obstacle for robustness, let us apply a backstepping procedure in the following form: regard the insulin concentration in the peripheral interstitial compartment as a virtual control ($I_{Pi} = I^*_{Pi}$) to decompose the second-order RD insulin delivery rate (w_i)-to-peripheral glucose (g_{Pi}) path into the series interconnection of two first-order RD paths: the insulin delivery rate (w_i)-to-peripheral insulin (I_{Pi}) path, and the peripheral insulin (I_{Pi})-to-peripheral glucose (g_{Pi}) path.

III.2 State-feedback controller

Recall (1a.8), regard its state I_{Pi} as a primary or virtual control I^*_{Pi}, enforce the primary closed-loop LNPA (linear, noninteractive, pole assignable) tracking dynamics

$$\dot{g}_{Pi} = \dot{\bar{g}}_{Pi} - k_g(g_{Pi} - \bar{g}_{Pi})$$

and solve (1a.8) for I^*_{Pi} to obtain the *primary SF controller*:

$$I^*_{Pi} = (f^g_{Pi})^{-1}[g_{Pv}, g_{Pi}, \dot{\bar{g}}_{Pi}-k_g(g_{Pi}-\bar{g}_{Pi})] := \gamma^*_i(g_{Pv},g_{Pi},\bar{g}_{Pi},\dot{\bar{g}}_{Pi},k_g) \quad (5a)$$

meaning that I^*_{Pi} is the insulin time-varying setpoint, and its time derivative is given by

$$\dot{I}^*_{Pi} = (\partial\gamma^*_i/\partial g_{Pv})(f^g_{Pv}) + (\partial\gamma^*_i/\partial g_{Pi})(f^g_{Pi}) + (\partial\gamma^*_i/\partial\bar{g}_{Pi})\dot{\bar{g}}_{Pi} + (\partial\gamma^*_i/\partial\dot{\bar{g}}_{Pi})\ddot{\bar{g}}_{Pi} \qquad (5b)$$

Enforce the secondary closed-loop LNPA tracking dynamics for the peripheral insulin concentration

$$\dot{I}_{Pi} = \dot{I}^*_{Pi} - k_i(I_{Pi} - I^*_{Pi})$$

and solve (1b.7) for w_i to obtain the *secondary SF controller*:

$$w_i = V^I_{Pi}[\dot{I}^*_{Pi} - k_i(I_{Pi} - I^*_{Pi}) - (1/t^I_P)(I_{Pv} - I_{Pi})] + \gamma_{PIc}(I_{Pi}) := \gamma_i(g_{Pv}, g_{Pi}, \bar{g}_{Pi}, \dot{\bar{g}}_{Pi}) \qquad (5c)$$

The application of the preceding *cascade SF controller* (5) to the glucose-insulin-glucagon system (1) with the restriction $g_{Pi} = \bar{g}_{Pi}$, yields the *zero-dynamics*:

$$\dot{\mathbf{x}}_\mathbf{I} = \mathbf{f_I}(\mathbf{x_I}, \bar{g}_{Pi}, d, I^*_{Pi}), \qquad \mathbf{x_I}(0) = \mathbf{x_{Io}} \qquad (6)$$

$$\mathbf{x_I} = (g_{Bv},g_{Bi},g_H,g_G,g_L,g_K,g_{Pv},I_B,I_H,I_G,I_L,I_K,I_{Pv},\Gamma,f_2,m^I_{Hgp},m^I_{Hgu})'$$

$$I^*_{Pi} = \gamma^*_i(g_{Pv}, \bar{g}_{Pi}, \dot{\bar{g}}_{Pi})$$

III.3 Solvability conditions

The SF control problem is solvable due to the fulfillment of the following conditions:

i) The glucose-insulin-glucagon system has RD = 2 because there is a univocal correspondence between the peripheral glucose uptake rate (r_{Pgu}) and the peripheral insulin concentration (I_{Pi}). In other words, the glucose uptake rate increases (4) with the insulin concentration, and this is a condition that is physiologically met.

ii) The zero-dynamics (6) has a unique steady-state $\bar{\mathbf{x}}_\mathbf{I}$ which is asymptotically stable. It has been previously shown (Quiroz and Femat, 2007) that the state motions $\mathbf{x}(t)$ of the glucose-insulin-glucagon system are stable in a practical sense: the state motions $\mathbf{x}(t)$ remain arbitrarily close to the nominal one by making the parameter perturbations sufficiently small, yielding a unique steady-state. In our case, since the reference glucose evolution $\bar{g}_{Pi}$ is designed such that it resembles a healthy-person glucose evolution, the stability (in a practical sense) of zero dynamics (6) is a consequence of the state motion stability in nondiabetic subjects.

It must be pointed out that, even though the SF controller (5) has a simple cascade structure, an estimator-based implementation of the preceding controller would require the detailed glucose-insulin-glucagon system (1) as well as metabolic rates (2), and this means a strong model-dependency drawback for applicability. This consideration motivates the control model simplification to be developed in the next section.

IV. Output-Feedback Control

In order to reduce the model dependency of the control scheme, let us re-express the peripheral glucose concentrations dynamics (1a.7, 8) in the following form

$$\dot{y}_{Pv} = a_{Pv}\, y_{Pv} + b_{Pv}, \qquad y_{Pv} = g_{Pv} \qquad (7a)$$

$$\dot{y}_{Pi} = (1/t^g_P)(y_{Pv} - y_{Pi}) - r_{Pgu}/V_{Pi}, \qquad y_{Pi} = g_{Pi} \qquad (7b)$$

where

$$a_{Pv} = -\,[\hat{q}^g_P/\hat{V}^g_{Pv} + \hat{V}_{Pi}/(\hat{V}^g_{Pv}\hat{t}^g_P)] \qquad (8a)$$

$$b_{Pv} = (q^g_P/V^g_{Pv})\, g_H + (V_{Pi}/V^g_{Pv}t^g_P)\, g_{Pi} \qquad (8b)$$

a_{Pv} is an approximation of hemodynamic parameters, and b_{Pv} is regarded as a "synthetic" load disturbance. Thus, given the available measurements and their time derivatives (y_{Pv}, y_{Pi}, $\dot{y}_{Pv}$, $\dot{y}_{Pi}$), the algebraic solution of the system (7) for the pair (b_{Pv}, r_{Pgu}) is

$$b_{Pv} = \dot{y}_{Pv} - a_{Pv}\, y_{Pv}, \qquad r_{Pgu} = V_{Pi}\,[(1/t^g_P)(y_{Pv} - y_{Pi}) - \dot{y}_{Pi}] \qquad (9)$$

meaning that the pair (b_{Pv}, r_{Pgu}) is instantaneously observable, or equivalently, in virtue of the invertibility condition (4), the peripheral insulin (I_{Pi}) and the load disturbance (b_{Pv}) can be quickly reconstructed via a state observer, say a Luenberger-type PI-geometric estimator (López and Alvarez, 2004). The direct application of this technique yields the next state estimator:

$$\dot{\hat{g}}_{Pv} = a_{Pv}\,\hat{g}_{Pv} + \hat{b}_{Pv} + 2\,\zeta_{Pv}\omega_{Pv}\,(y_{Pv} - \hat{g}_{Pv})$$

$$\dot{\hat{b}}_{Pv} = (-\,2\,a_{Pv}\,\zeta_{Pv}\omega_{Pv} + \omega_{Pv}^2)\,(y_{Pv} - \hat{g}_{Pv})$$

$$\dot{\hat{g}}_{Pi} = (1/t^g_P)(\hat{g}_{Pv} - \hat{g}_{Pi}) - \gamma_{Pgu}(\hat{g}_{Pi}, \hat{I}_{Pi})/V_{Pi} + 2\,\zeta_{Pi}\omega_{Pi}\,(y_{Pi} - \hat{g}_{Pi})$$

$$\dot{\hat{I}}_{Pi} = (1/t^I_P)(\hat{I}_{Pv} - \hat{I}_{Pi}) + [w_i - \gamma_{PIc}(\hat{I}_{Pi})]/V^I_{Pi}$$
$$+\,2\,\zeta_{Pv}\omega_{Pv}\kappa_1\,(y_{Pv} - \hat{g}_{Pv}) + (2\,\zeta_{Pi}\omega_{Pi}\kappa_2 + \omega_{Pi}^2\kappa_3)(y_{Pi} - \hat{g}_{Pi})$$

$$\dot{\hat{\mathbf{x}}}_\mathbf{i} = \mathbf{f_i}(\hat{\mathbf{x}}_\mathbf{i}, \hat{I}_{Pi}), \qquad \mathbf{x_i} = (I_B, I_H, I_G, I_L, I_K, I_{Pv})'$$

where $\{\omega_{Pv}, \omega_{Pi}\}$ [or $\{\zeta_{Pv}, \zeta_{Pi}\}$] is the set of the observer characteristic frequencies (or damping factors), and $\{\kappa_1, \kappa_2, \kappa_3\}$ is a set of nonlinear observer gains

$$\kappa_1 = -\,(1/t^g_P)/(\partial f^g_{Pi}/\partial I_{Pi}), \qquad \kappa_2 = -\,(\partial f^g_{Pi}/\partial g_{Pi})/(\partial f^g_{Pi}/\partial I_{Pi})$$

$$\kappa_3 = 1/(\partial f^g_{Pi}/\partial I_{Pi})$$

The combination of the preceding state estimator with the SF control yields the *output-feedback* (OF) *controller*:

Glucose estimator (10a)

$$\dot{\hat{g}}_{Pv} = a_{Pv}\,\hat{g}_{Pv} + \hat{b}_{Pv} + 2\,\zeta_{Pv}\omega_{Pv}\,(y_{Pv} - \hat{g}_{Pv})$$

$$\dot{\hat{b}}_{Pv} = (-\,2\,a_{Pv}\,\zeta_{Pv}\omega_{Pv} + \omega_{Pv}^2)\,(y_{Pv} - \hat{g}_{Pv})$$

$$\dot{\hat{g}}_{Pi} = (1/t^g_P)(\hat{g}_{Pv} - \hat{g}_{Pi}) - \gamma_{Pgu}(\hat{g}_{Pi}, \hat{I}_{Pi})/V_{Pi} + 2\,\zeta_{Pi}\omega_{Pi}\,(y_{Pi} - \hat{g}_{Pi})$$

Insulin estimator (10b)

$$\dot{\hat{I}}_{Pi} = (1/t^I_P)(\hat{I}_{Pv} - \hat{I}_{Pi}) + [w_i - \gamma_{PIc}(\hat{I}_{Pi})]/V^I_{Pi}$$
$$+\,2\,\zeta_{Pv}\omega_{Pv}\kappa_1\,(y_{Pv} - \hat{g}_{Pv}) + (2\,\zeta_{Pi}\omega_{Pi}\kappa_2 + \omega_{Pi}^2\kappa_3)(y_{Pi} - \hat{g}_{Pi})$$

$$\dot{\hat{\mathbf{x}}}_\mathbf{i} = \mathbf{f_i}(\hat{\mathbf{x}}_\mathbf{i}, \hat{I}_{Pi})$$

Set point filter (10c)

$$\dot{\hat{I}}^*_{Pi} = \hat{\Diamond}^*_i + 2\,\zeta^*_i\omega^*_i(I^*_{Pi} - \hat{I}^*_{Pi}), \qquad \dot{\hat{\Diamond}}^*_i = (\omega^*_i)^2(I^*_{Pi} - \hat{I}^*_{Pi})$$

Cascade controller (10d)

$$I^*_{Pi} = \gamma^*_i(\hat{g}_{Pv}, \hat{g}_{Pi}, \bar{g}_{Pi}, \dot{\bar{g}}_{Pi}, k_g)$$

$$w_i = V^I_{Pi}[\hat{\Diamond}^*_i - k_i(\hat{I}_{Pi} - I^*_{Pi}) - (1/t^I_P)(\hat{I}_{Pv} - \hat{I}_{Pi})] + \gamma_{PIc}(\hat{I}_{Pi})$$

Structurally speaking, the controller has the following components: (i) a glucose concentrations observer (10a), with a reconstructible load term (b_{Pv}) that accounts for disturbance and plant/model parameters mismatch for the glucose subsystem (1a); (ii) an insulin estimator (10b) to infer the peripheral interstitial insulin concentration (I_{Pi}) on the basis of glucose measurements; (iii) a cascade controller (10d) with feedforward and feedback elements, and (iv) a linear filter (10c) which provides the set point derivative estimate $\hat{\Diamond}^*_i$ of I^*_{Pi}, and that has been introduced to circumvent the (cumbersome) analytic calculation, via equation (5b).

Modeling requirements. As mentioned, a direct implementation of the SF controller (5) with a state observer (say an Extended Kalman Filter, a Luenberger observer or a PI-geometric type estimator), would yield a dynamic controller with a strong model dependency on the overall glucose-insulin-glucagon system (1) and the metabolic rates (2). This is so because the control law (5a) requires the peripheral (vascular) glucose concentration state (g_{Pv}), which in turn needs the on-line integration of the heart glucose concentration (g_H) [see (1a.7) and (1a.3)], and thus, the integration of the ODE's for all glucose states (1a), and glucagon and auxiliary states (1c). Here, in our proposed OF controller (10), the estimated load $\hat{b}_{Pv}$, which is reconstructed via the peripheral glucose measurements (y_{Pv}, y_{Pi}), replaces the heart glucose concentration state (g_H), and thus, the glucose states (g_{Bv}, g_{Bi}, g_G, g_L, g_K), glucagon (Γ) and auxiliary states (f_2, m^I_{Hgp}, and m^I_{Hgu}) are not needed. Summarizing, the modeling requirements of our dynamic control scheme (10) are only: an approximated hemodynamic constant a_{Pv} (8a), the peripheral glucose uptake rate function (γ_{Pgu}) and three insulin metabolic functions (2e-g), and these requirements are rather few in the light of the capability of the controller to handle the nonlinear nature of the original glucose-insulin-glucagon system (1).

Convergence and tuning. The formal consideration of the closed-loop stability issue goes beyond the scope of the present work, and here it suffices to mention that the application of the Small Gain Theorem (Isidori, 1995;

González and Alvarez, 2005) to the system (1) in closed-loop mode with the OF controller (10) leads to the following results: The observer gain (ω) should be tuned by considering the peripheral glucose eigenvalue λ^g_{Pv} as preliminary value (and then retune ω), and the primary (k_i) and secondary (k_g) control gains should be set sufficiently separated ($k_g < k_i$) and slower than the observer gain (ω):

$$\lambda^g_{Pv} = -[(q^g_P/V^g_{Pv}) + (V_{Pi}/V^g_{Pv}t^g_P)], \qquad k_g < k_i < \omega$$

This tuning should yield a closed-loop stable system (1) with the following features: (i) a non-wasteful control input w_i (in the light of the cascade structure with RD's = 1), and (ii) a glucose concentration (g_{Pi}) which is asymptotically tracked according to linear error dynamics and convergence rate fixed by the designer.

V. Application Example

To evaluate the proposed OF controller (10) under typical scenarios, let us consider (through numerical simulations) a 70-kg T1DM patient, under a carbohydrate intake of 50 g. The reference glucose evolution ($\bar{g}_{Pi}$) is given by the next peak function:

$$\bar{g}_{Pi}(t) = \bar{g}^b_{Pi} + A_{Pi}\, e^{1-\tau(t)-e^{-\tau(t)}}, \qquad \tau(t) = (t - t_p)/w$$

where $\bar{g}^b_{Pi}$ is the basal value of the peripheral interstitial glucose concentration, and $\{A_{Pi}, t_p, w\} = \{40, 70, 30\}$ is a constant parameters set such that $\bar{g}_{Pi}(t)$ resembles the glucose evolution of a healthy subject. The parameter values for system (1) are reported by Sorensen (1985), and the carbohydrate absorption model (exogenous input, $d = r_{meal}$) was taken from Lehmann and Deutsch (1992). The controller was tested under nominal, hyperglycemic and hypoglycemic scenarios. For the purpose at hand, the hepatic glucose production rate function (γ_{Hgp}) is given by the nonlinear function:

$$\gamma_{Hgp}(g_L, \Gamma, f_2, m^I_{Hgp}) = m^I_{Hgp}\, \mu^\Gamma_{Hgp}(\Gamma, f_2)\, \mu^g_{Hgp}(g_L)\, r^*_{Hgp}$$

$$\mu^g_{Hgp}(g_L) = a^g_{Hgp} - b^g_{Hgp} \tanh\{c^g_{Hgp}\,[(g_L/101) - d^g_{Hgp}]\}$$

where the constants $\{a^g_{Hgp}, c^g_{Hgp}\}$ are two of the most sensitive parameters (Quiroz and Femat, 2007) such that hyperglycemic and hypoglycemic scenarios can be emulated.

Following the tuning guides presented in section IV, the observer and control gains were set as follows:

$$\omega = \omega_{Pv} = \omega_{Pi} = \omega^*_i = 1\ \text{min}^{-1}, \qquad \zeta_{Pv} = \zeta_{Pi} = \zeta^*_i = 0.71$$
$$k_i = 1/5\ \text{min}^{-1}, \qquad k_g = 1/10\ \text{min}^{-1}$$

In Figure 1, two closed-loop responses are shown with: (i) the SF control (5) with full-model dependency, and (ii) the OF control (10) with reduced modeling requirements.

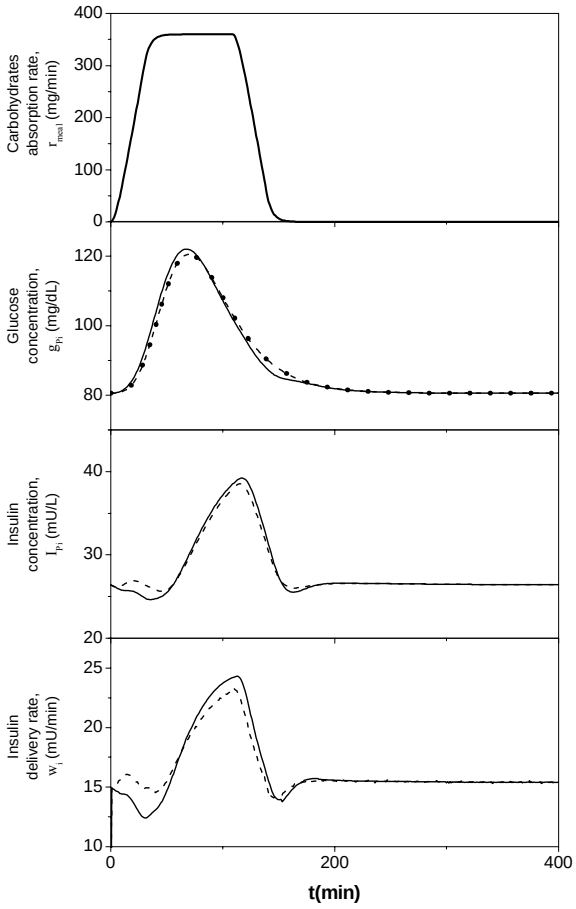

Figure 1. Closed-loop responses with SF (- - -) and OF (—) controllers, and reference glucose evolution $\bar{g}_{Pi}(t)$ (• • • •).

Figure 1 shows that: (i) as expected from the theoretical developments (7-9), the OF controller (10), with fewer modeling requirements, basically recovers the behavior of the exact model-based SF counterpart (5), and with a control input (insulin delivery, w_i) that is smooth (non wasteful) and away from saturation, and (ii) the glucose reference evolution ($\bar{g}_{Pi}$) is adequately tracked, with slight deviations in the output-feedback case due to estimation errors dynamics.

In Figure 2, two closed-loop responses are shown with: (i) the OF control under a hyperglycemic situation, by introducing a 50 % error in the constant a^g_{Hgp} (nominal value: 1.425) in model (1), and (ii) the OF control under a hypoglycemic situation, by introducing a 50 % error in the constant c^g_{Hgp} (nominal value: 0.6199) in model (1). For comparison purposes, the response with the OF control and nominal model is also presented. As it can be seen in the figure: (i) glucose concentration is acceptably tracked, and (ii) in hyperglycemia situation, the insulin delivery rate (and insulin concentration) increases, whereas the controller behaves the other way around in hypoglycemia.

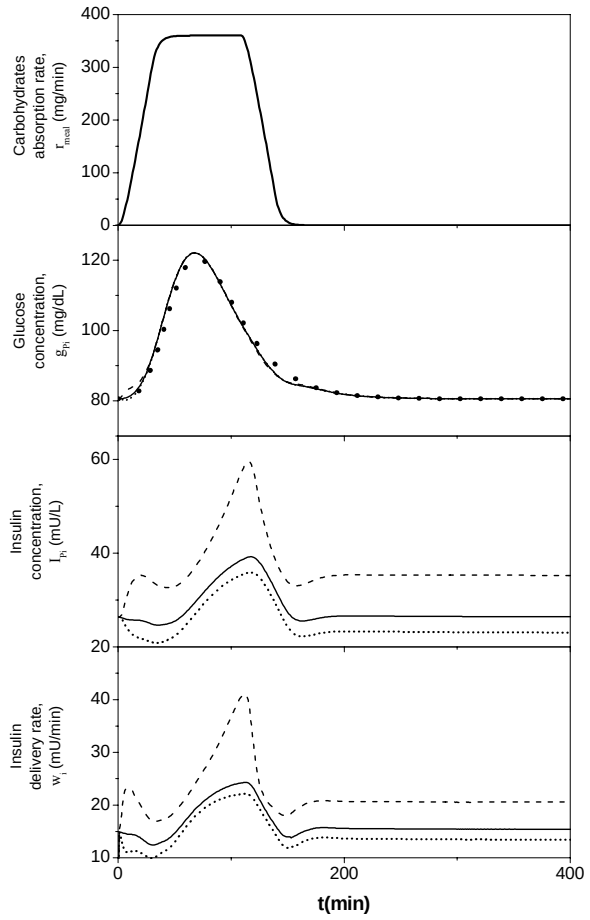

Figure 2. Closed-loop responses with OF controller, under nominal (—), hyperglycemic (- - -) and hypoglycemic (····) scenarios, and reference glucose evolution $\bar{g}_{Pi}(t)$ (• • • •).

VI. Conclusions

A nonlinear constructive approach has been presented for the control of glucose concentration in Type 1 Diabetes Mellitus patients with glucose measurements. The result is a robust output-feedback controller that, on the basis of peripheral glucose measurements and mass balances, computes the insulin amount to track a prescribed glucose evolution. The OF controller recovers the behavior of an exact model-based state-feedback passive (cascade) controller. The key robustness-oriented step of the control design was performed by means of a backstepping procedure, employing the peripheral insulin concentration as virtual (primary) control input; the recovery property was accomplished via a state estimator to compensate the effect of modeling errors and unknown disturbances. The tracking of glucose concentration in a T1DM patient was considered as application example, such that the closed-loop glucose evolution resembles the one of a healthy (nondiabetic) person. The results show that: (i) the glucose reference evolution is acceptably tracked; (ii) as expected, the measurement-driven controller behaves like its more model-dependent state-feedback counterpart, and (iii) the control performance is not significantly affected by typical parameter uncertainty. Further studies on the attainment of linearity are underway.

VII. Acknowledgements

The authors gratefully acknowledge the postdoctoral scholarship from the Mexican National Council for Research and Technology (CONACyT) for P. González. This work was partially supported by CONACyT under grant number 48307-R.

References

Campos-Delgado, D.U., M. Hernández-Ordóñez, R. Femat and A. Gordillo-Moscoso (2006). Fuzzy-based controller for glucose regulation in Type-1 diabetic patients by subcutaneous route. IEEE Transactions on Biomed. Eng. 53, 2201-2210.

Chee, F. and T. Fernando (2007). Closed-Loop Control of Blood Glucose, Springer-Verlag, NY.

González, P. and J. Alvarez (2005). Combined proportional/integral-inventory control of solution homopolymerization reactors. Ind. Eng. Chem. Res., 44, 7147-7163.

Hernández-Ordóñez, M. (2003). Control Geométrico SISO para Regulación de Glucosa en Sangre Humana en Diabéticos del Tipo I, M. Sc. Thesis (in Spanish), Universidad Autónoma de San Luis Potosí, México.

Hovorka, R (2005). Continuous glucose monitoring and closed-loop systems, Diabet. Med., 23, 1-12.

Isidori, A. (1995). Nonlinear Control Systems (3rd ed.). McGraw-Hill, Springer-Verlag, New York.

Lehmann, E.D and T. Deutsch (1992). A physiological model of glucose-insulin interaction in type 1diabetes mellitus, J. Biomed. Eng. 14, 235-242.

López, T. and J. Alvarez (2004). On the effect of the estimation structure in the functioning of a nonlinear copolymer reactor estimator, J. Proc. Cont. 2004, 14, 99-109.

Parker, R.S, F.J. Doyle III, and N.A. Peppas (1999). A model-based algorithm for blood glucose control in Type I diabetic patients. IEEE Transactions on Biomed. Eng. 46, 148-157.

Quiroz, G. and R. Femat (2007). On hyperglycemic glucose basal levels in type 1 Diabetes Mellitus from dynamic analysis, Math. Biosci., 210, 554-575.

Ramprasad, Y., G. P. Rangaiah, and S. Lakshminarayanan (2004). Robust PID controller for blood glucose regulation in Type I Diabetics, Ind. Eng. Chem. Res., 43, 8257-8268.

Ruiz-Velázquez, E., R. Femat, and D. U. Campos-Delgado (2004). Blood glucose control for type I diabetes mellitus: A robust tracking H_∞ problem, Control Eng. Practice, 12, 1179-1195.

Sepulchre, R., M. Jankovic and P. Kokotovic (1997). Constructive Nonlinear Control, Springer-Verlag, NY.

Sorensen, J. T. (1985). A Physiologic Model of Glucose Metabolism in Man and its Use to Design and Assess Improved Insulin Therapies for Diabetes, Ph.D. dissertation, Mass. Inst. Technol., Cambridge, MA.