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Control of Glucose Concentration in Type 1 Diabetes Mellitus with Discrete-delayed Measurements

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Abstract: In this work, the problem of controlling the glucose concentration in Type 1 Diabetes Mellitus (T1DM) patients is addressed, with discrete-delayed measurements of peripheral glucose concentration. First, from a constructive control framework and observability ideas, an output-feedback (OF) controller with continuous measurements is designed, which is regarded as a control case with vanishing sampling-delay period. Then, on the basis of a suitable discrete model and feedforward-feedback control considerations, a discrete OF controller is derived, which: (i) has linear components and reduced model-dependency, and (ii) recovers the behavior of its continuous measurements counterpart. The proposed approach is tested through numerical simulations on a T1DM patient under nominal, hyperglycaemic, and hypoglycaemic scenarios.

Keywords: Type 1 Diabetes Mellitus, constructive control, feedback control, discrete measurements.

1. INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is a metabolic disease caused by the auto-immune destruction of pancreatic β-cells, which are responsible of insulin releasing. The direct effect is a blood glucose concentration larger than 120 mg/dL (hyperglycaemia) after meal ingestion; if this high concentration is held for long periods, severe consequences 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 automatic insulin delivery systems (artificial pancreas) as alternative for the T1DM therapy, the 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: (i) several control algorithms have been employed, including fuzzy logic-based (Campos-Delgado *et al.*, 2006), model predictive, *MPC* (Parker *et al.*, 1999), H_∞ (Ruiz-Velázquez *et al.*, 2004) and classical PID (Ramprasad *et al.*, 2004) linear controllers, as well as nonlinear control designs (Hovorka *et al.*, 2004), and (ii) due to their robustness, the preceding approaches have potential implementation in clinical trials; however, the schemes have been based on model-dependent systems, and this feature signifies complexity and reliability drawbacks for medical practitioners. Moreover, given the inherent delay of glucose measurements, either from invasive techniques (like blood glucose monitoring in a clinical setting) or minimally-invasive methods (like interstitial glucose monitoring in long-term uses), the related controllers should include measurement-delay compensation on their designs. Specifically, due to its inherent time-ahead prediction capability, the MPC approach seems to be a suitable design technique to handle discrete-delayed measurements (Parker *et al.*, 1999; Hovorka *et al.*, 2004). Nevertheless, this technique also bears the aforementioned disadvantages of complexity and reliability.

Summarizing, the preceding studies have established the feasibility of implementing automatic control schemes, and provide valuable insight on the nature of the control problem. However, due to the complexity and model dependency features, the glucose regulation in T1DM requires further research, with emphasis on simplicity, low model dependency, and capability to handle measurements-delay. In this work, the problem of controlling the glucose concentration in T1DM patients on the basis of discrete-delayed glucose measurements is addressed, within a constructive control approach. In particular, we are interested in: (i) designing a measurement-driven controller with linearity and reduced model-dependency features for practical implementation, (ii) drawing a systematic construction and a direct tuning procedure, and (iii) addressing the delayed-measurements problem. The proposed approach is tested *in silico* on a T1DM patient under nominal, hyperglycaemic, and hypoglycaemic scenarios.

2. CONTROL PROBLEM

2.1 Glucose-insulin-glucagon System

In order to technically state our glucose 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 nondiabetic and type

1 diabetic subjects. In the model, 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, and the whole 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)

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

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

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

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

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

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

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

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

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)

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

$$\dot{m}^I_{Hgp} = (m^{I\infty}_{Hgp} - m^I_{Hgp})/\tau_I, \quad \dot{m}^I_{Hgu} = (m^{I\infty}_{Hgu} - m^I_{Hgu})/\tau_I \quad (1c.3,4)$$

The states (**x**) are: (a) the glucose concentrations in vascular (g_{Bv}) and interstitial (g_{Bi}) brain tissues, heart and lungs (g_H), guts (g_G), liver (g_L), and kidney (g_K), as well as in peripheral (skeletal muscle and adipose tissue) vascular (g_{Pv}) and interstitial (g_{Pi}) spaces; (b) the insulin concentrations in 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; and (c) 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 (g_{Pi}) in the peripheral interstitial space, as in previous control studies (Ruiz-Velázquez *et al*., 2004). The *measured output* (y) is the glucose concentration (g_{Pi}) in the peripheral interstitial space; the measurement is sampled at discrete times, and its value is available after one sampling time ($\Delta = t_k - t_{k-1}$), when the next measurement is taken, and so on. 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}) and 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 modelled by the respective nonlinear function (Sorensen, 1985).

In compact notation, model (1) is given by

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, d, u), \qquad \mathbf{x}(0) = \mathbf{x_0}; \qquad y = \mathbf{C_y x}, \qquad z = \mathbf{C_z x} \quad (2)$$

$$\mathbf{x} = (g_{Bv}, g_{Bi}, ..., g_{Pi}, I_B, I_H, ..., I_{Pi}, \Gamma, f_2, m^I_{Hgp}, m^I_{Hgu})'$$

$$d = r_{meal}, \quad y(t_k) = g_{Pi}(t_{k-1}), \quad \Delta = t_k - t_{k-1}, \qquad u = w_i, \qquad z = g_{Pi}$$

Our problem consists in: (i) designing a measurement-driven controller ($u = w_i$) with linearity and reduced model-dependency features, (ii) addressing the problem of handling of low sampling rates and long delays, and (iii) drawing a tuning procedure that includes the sampling-delay period (Δ).

3. CONTROL WITH CONTINUOUS MEASUREMENTS

In this section, the control problem with continuous glucose measurements is addressed. The objectives are: (i) the setting of a point of departure for the case with discrete-delayed measurements, and (ii) the determination of the recovery target for the discrete-delayed measurements controller, as the sampling-delay period vanishes.

3.1 Nonlinear State-feedback Control

Let us re-write the peripheral glucose (g_{Pi})-insulin(I_{Pi}) subsystem (1a.8, 1b.7) with the following modification: the insulin state (I_{Pi}) will be replaced by the state "v" that represents the rate of change of the glucose concentration,

$$v := \dot{g}_{Pi} \; [= f^g_{Pi}(g_{Pi}, I_{Pi}, g_{Pv})] \quad (3)$$

This coordinate change can be performed because f^g_{Pi} is I-monotonic $[(\partial f^g_{Pi}/\partial I_{Pi}) < 0]$ (Sorensen, 1985), and physiologically speaking, this inequality is met because the peripheral glucose uptake rate (r_{Pgu}) increases with the insulin concentration. Thus, the peripheral glucose (g_{Pi})-insulin(I_{Pi}) subsystem (1a.8, 1b.7) can be expressed into the phase canonical form (4) associated to a standard mechanical formulation (Slotine and Li, 1991; Sepulchre *et al.*, 1997):

$$\dot{g}_{Pi} = v, \qquad y = g_{Pi} \quad (4a)$$

$$\dot{v} = -\kappa_v(g_{Pi}, I_{Pi})\, v - \kappa_g(g_{Pi}, I_{Pi})\, g_{Pi} - \alpha(g_{Pi}, I_{Pi})\, w_i + \theta(g_{Pi}, I_{Pi}, g_{Pv}, g_H) \quad (4b)$$

$\kappa_v = l_g(g_{Pi}, I_{Pi}) + l_l(I_{Pi}) > 0, \quad \kappa_g = l_g(g_{Pi}, I_{Pi})\, l_l(I_{Pi}) > 0$
$\theta = (1/V_{Pi})(\partial r_{Pgu}/\partial I_{Pi})\, l_I\, I_{Pi} - (1/V_{Pi})(\partial r_{Pgu}/\partial I_{Pi})\, (1/t_P^I)\, I_{Pv}$
$+ (1/t_P^g)\, f_{Pv}^g + l_I\, f_{Pi}^g + \kappa_g\, g_{Pi}, \qquad I_{Pi} = f_{Pi}^{g\,-1}(g_{Pi}, v, g_{Pv})$

where

$$l_g(g_{Pi}, I_{Pi}) = 1/t_P^g + (1/V_{Pi})(\partial r_{Pgu}/\partial g_{Pi}) > 0 \tag{4c}$$

$$l_l(I_{Pi}) = 1/t_P^I + (1/V_{Pi}^I)(\partial r_{PIc}/\partial I_{Pi}) > 0 \tag{4d}$$

$$\alpha(g_{Pi}, I_{Pi}) = (1/V_{Pi})(1/V_{Pi}^I)(\partial r_{Pgu}/\partial I_{Pi}) \tag{4e}$$

The function set $\{l_g, l_l\}$ corresponds to the time-varying eigenvalues of the peripheral glucose-insulin dynamics (1a.8, 1b.7). It should be noted that system (4) requires the detailed glucose-insulin-glucagon model (1), implying that an estimator-based controller derived from (4) will be highly model-dependent. As a step to simplify the control model and reduce the model dependency, let us re-express (4) in the following form

$$\dot g_{Pi} = v, \qquad \dot v = -\,c_v\, v - c_g\, g_{Pi} - a\, w_i + b_v \tag{5a,b}$$
$$b_v = \beta_v(g_{Pi}, v, g_{Pv}, g_H, w_i) \tag{5c}$$

$$c_v = \kappa_v(g_{Pi}^b, I_{Pi}^b), \qquad c_g = \kappa_g(g_{Pi}^b, I_{Pi}^b), \qquad a = \alpha(g_{Pi}^b, I_{Pi}^b) \tag{6a}$$
$$\beta_v(g_{Pi}, v, g_{Pv}, g_H, w_i) = \theta[g_{Pi}, I_{Pi} = f_{Pi}^{g\,-1}(g_{Pi}, v, g_{Pv}), g_{Pv}, g_H]$$
$$+ c_v\, v + c_g\, g_{Pi} + [\alpha(g_{Pi}^b, I_{Pi}^b) - a]\, w_i \tag{6b}$$

The constants $\{a, c_v, c_g\}$ are steady-state (i. e., basal state) approximations of the functions $\{\alpha, \kappa_v, \kappa_g\}$, g_{Pi}^b and I_{Pi}^b are the basal values of the peripheral glucose and insulin, and b_v is regarded as a nonlinear disturbance load generated by the nonlinear map β_v. System (5) is an exact representation of the peripheral glucose-insulin subsystem (1a.8, 1b.7). In deviation form, (5) is expressed as follows:

$$\dot{\tilde g}_{Pi} = \tilde v, \qquad \dot{\tilde v} = -\,c_v\, \tilde v - c_g\, \tilde g_{Pi} + \tilde \upsilon \tag{7a,b}$$
$$\tilde g_{Pi} = g_{Pi} - \bar g_{Pi}, \quad \tilde v = v - \bar v, \qquad \tilde \upsilon = \upsilon - \bar \upsilon$$
$$\upsilon = -\,a\, w_i + b_v, \qquad \bar \upsilon = \dot{\bar v} + c_v\, \bar v + c_g\, \bar g_{Pi}$$

In a mass-damper-spring system analogy, $\tilde g_{Pi}$ is the position deviation and $\tilde \upsilon$ is the force acting upon mass. Accordingly (Slotine and Li, 1991), introduce the corresponding (kinetic plus potential) energy (8a), enforce its negative dissipation rate (8b),

$$V_{SF} = (c_g\, \tilde g_{Pi}^2 + \tilde v^2)/2 > 0 \tag{8a}$$

$$\dot V_{SF} = -\,(c_v + k_v)\, \tilde v^2 < 0, \qquad k_v > 0 \tag{8b}$$

and obtain the *nonlinear state-feedback (SF) controller*:

$$w_i = [b_v - (\dot{\bar v} + c_v\, \bar v + c_g\, \bar g_{Pi}) + k_v(v - \bar v)]/a \tag{9a}$$
$$b_v = \beta_v(g_{Pi}, v, g_{Pv}, g_H, w_i) \tag{9b}$$

Observe that the implementation of the preceding controller still needs the detailed glucose-insulin-glucagon system, via the nonlinear map β_v.

3.2 Linear Output-feedback Control

Due to the instantaneous observability property of system (5) from the measurement ($y = g_{Pi}$) and its time derivatives ($\dot y, \ddot y$), the pair (v, b_v) can be reconstructed by means of a linear reduced-order observer (10a, b) (Stefani *et al.*, 2001). The combination of the observer (10a, b) with the SF controller (9) yields *the linear output-feedback (OF) controller*:

$$\dot\chi_v = -\,(c_v + k_v^o)\, \chi_v + \chi_b + [k_b^o - k_v^o(c_v + k_v^o) - c_g]\, y - a\, w_i, \qquad \hat v = \chi_v + k_v^o\, y \tag{10a}$$

$$\dot\chi_b = -\,k_b^o\, \chi_v - k_v^o\, k_b^o\, y, \qquad \hat b_v = \chi_b + k_b^o\, y \tag{10b}$$

$$w_i = [\hat b_v - (\dot{\bar v} + c_v\, \bar v + c_g\, \bar g_{Pi}) + k_v(\hat v - \bar v)]/a \tag{10c}$$

This linear measurement-driven dynamic controller, with reduced modeling requirements with respect to its state-feedback counterpart (9), constitutes the recovery target for the controller with discrete-delayed measurements (as the sampling-delay period vanishes).

4. CONTROL WITH DISCRETE DELAYED MEASUREMENS

In this section, a linear OF controller is designed on the basis of discrete-delayed glucose measurements and a suitable discrete model, with reduced model-dependency.

4.1 Discrete Model

Although our present control problem with discrete measurements can be addressed with an Euler discretization, the implementation is simplified at the cost of limiting the capability to handle delay. Given the form of the continuous model (5), the model prediction can be enhanced by performing the *analytical integration* of (5) with the enforcement of the step control specification $w_i(t) = w_k\ \forall\ t \in [t_{k-1}, t_k]$. The result is the discrete model:

$$g_k = \kappa_{11}\, g_{k-1} + \kappa_{12}\, v_{k-1} + \beta_1(-\,a\, w_{k-1} + b_{k-1}) \tag{11a}$$
$$v_k = \kappa_{21}\, g_{k-1} + \kappa_{22}\, v_{k-1} + \beta_2(-\,a\, w_{k-1} + b_{k-1}) \tag{11b}$$

$$\kappa_{11} = (\lambda_I e^{-\lambda_g \Delta} - \lambda_g e^{-\lambda_I \Delta})/(\lambda_I - \lambda_g)$$
$$\kappa_{12} = \beta_2 = (e^{-\lambda_g \Delta} - e^{-\lambda_I \Delta})/(\lambda_I - \lambda_g)$$
$$\kappa_{21} = \lambda_I \lambda_g (e^{-\lambda_I \Delta} - e^{-\lambda_g \Delta})/(\lambda_I - \lambda_g)$$
$$\kappa_{22} = (\lambda_I e^{-\lambda_I \Delta} - \lambda_g e^{-\lambda_g \Delta})/(\lambda_I - \lambda_g)$$
$$\beta_1 = [(1 - e^{-\lambda_g \Delta})/\lambda_g - (1 - e^{-\lambda_I \Delta})/\lambda_I]/(\lambda_I - \lambda_g)$$

$$g_k = g_{Pi}(t_k), \quad v_k = v(t_k), \quad w_k = w_i(t_k), \quad b_k = b_v(t_k)$$

In the preceding model, the constants $\{\lambda_g, \lambda_I\}$ are the steady-state values of the functions $\{l_g, l_l\}$ (4c, d), or equivalently, the local eigenvalues of the glucose-insulin dynamics (1a.8, 1b.7). In input-output form, model (11) is expressed as:

$$g_{k+1} - \tau\, g_k + \delta\, g_{k-1} = \upsilon_k \tag{12}$$

$$\upsilon_k = \beta_1(-\,a\, w_k + b_k) + \beta_p(-\,a\, w_{k-1} + b_{k-1})$$

$\tau = \kappa_{11} + \kappa_{22}, \quad \delta = \kappa_{11}\,\kappa_{22} - \kappa_{12}\,\kappa_{21}, \quad \beta_p = \kappa_{12}\beta_2 - \kappa_{22}\beta_1$

"υ_k" is regarded as a new control input at time t_k.

4.2 State-feedback Control

In deviation form, the open loop difference equation (12) is

$$\tilde{g}_{k+1} - \tau\,\tilde{g}_k + \delta\,\tilde{g}_{k-1} = \tilde{\upsilon}_k, \quad \tilde{g}_k = g_k - \bar{g}_k, \quad \tilde{\upsilon}_k = \upsilon_k - \bar{\upsilon}_k \quad (13)$$

where, by design, the input "υ_k" has feedforward ($\bar{\upsilon}_k$) and feedback ($\tilde{\upsilon}_k$) components. Assume that the glucose concentration is at its nominal value at time t_k [$g_k = \bar{g}_{Pi}(t_k)$], and obtain the feedforward discrete component from (12):

$$\bar{\upsilon}_k = \bar{g}_{k+1} - \tau\,\bar{g}_k + \delta\,\bar{g}_{k-1} \quad (14)$$

In comparison with the controller driven by continuous measurements (10), a controller with sampled and delayed measurements runs with less information, and therefore, exhibits a more sluggish and degraded performance. This consideration suggests us to impose a second-order closed-loop difference equation in order to enable the possibility of speeding-up the glucose response. Accordingly, recall equation (13) and enforce its two-gain closed-loop output-error version:

$$\tilde{g}_{k+1} - (\tau + k_1)\,\tilde{g}_k + (\delta + k_2)\,\tilde{g}_{k-1} = 0 \quad (15)$$

and thus, the feedback discrete component is given by:

$$\tilde{\upsilon}_k = k_1\,\tilde{g}_k - k_2\,\tilde{g}_{k-1} \quad (16)$$
$$k_1(\Delta, \omega_c, \zeta_c) = -\tau + [\lambda_1(\Delta, \omega_c, \zeta_c) + \lambda_2(\Delta, \omega_c, \zeta_c)]$$
$$k_2(\Delta, \omega_c, \zeta_c) = -\delta + [\lambda_1(\Delta, \omega_c, \zeta_c)\,\lambda_2(\Delta, \omega_c, \zeta_c)]$$
$$\lambda_i(\Delta, \omega_c, \zeta_c) = \exp\{-\Delta\omega_c[\zeta_c \mp (\zeta_c^2 - 1)^{1/2}]\}, \quad i = 1, 2$$

ω_c and ζ_c are, respectively, the control characteristic frequency and damping factor, associated to the mappings of the control design poles from the continuous representation in the LHS of the complex plane to the unit circle (Hernández and Alvarez, 2003). The combination of the control input υ_k (12) and its feedforward (14) and feedback (16) components yields the *discrete SF controller:*

$$w_k = -(\beta_p/\beta_1)\,w_{k-1} + [b_k + (\beta_p/\beta_1)\,b_{k-1}]/a - (\bar{g}_{k+1} - \tau\,\bar{g}_k + \delta\,\bar{g}_{k-1})/(a\,\beta_1) - [k_1(g_k - \bar{g}_k) - k_2(g_{k-1} - \bar{g}_{k-1})]/(a\,\beta_1) \quad (17)$$

In (17): (i) the first term is an integral-like action due to discretization, (ii) the second and third terms represent feedforward action, on the basis of present (b_k) and past (b_{k-1}) load estimates, and (time-varying) glucose reference evolution, and (iii) the last term is a feedback correction driven by present (g_k) and past (g_{k-1}) values of the peripheral glucose concentration.

4.3 Output-feedback Control

Differently from the case with continuous measurements, where the estimation task of the load-state pair b_v-v can be efficiently performed with a reduced-order observer (10a, b), in the discrete measurements case, with less information available, a full-order observer must be designed in order to effectively tackle the one-step-ahead prediction problem. The application of the full-order discrete observer technique (Ogata, 1994) on the discrete model (11) yields the state observer (18a-c), and its combination with the discrete controller (17) yields the *discrete OF controller*:

$$\hat{g}_k = \kappa_{11}\hat{g}_{k-1} + \kappa_{12}\hat{v}_{k-1} + \beta_1(-a\,w_{k-1} + \hat{b}_{k-1}) + k_1^o(\Delta, \omega_o, \zeta_o)[y(t_k) - \hat{g}_{k-1}] \quad (18a)$$

$$\hat{v}_k = \kappa_{21}\hat{g}_{k-1} + \kappa_{22}\hat{v}_{k-1} + \beta_2(-a\,w_{k-1} + \hat{b}_{k-1}) + k_2^o(\Delta, \omega_o, \zeta_o)[y(t_k) - \hat{g}_{k-1}] \quad (18b)$$

$$\hat{b}_k = \hat{b}_{k-1} + k_3^o(\Delta, \omega_o, \zeta_o)[y(t_k) - \hat{g}_{k-1}], \quad y(t_k) = g_{k-1} \quad (18c)$$

$$w_k = -(\beta_p/\beta_1)\,w_{k-1} + [\hat{b}_k + (\beta_p/\beta_1)\,\hat{b}_{k-1}]/a - (\bar{g}_{k+1} - \tau\,\bar{g}_k + \delta\,\bar{g}_{k-1})/(a\,\beta_1) - [k_1(\hat{g}_k - \bar{g}_k) - k_2(\hat{g}_{k-1} - \bar{g}_{k-1})]/(a\,\beta_1) \quad (18d)$$

where the observer gains (k_1^o, k_2^o, k_3^o) are set according to a root locus-based pole pattern (Hernández and Alvarez, 2003), and ω_o and ζ_o are, respectively, the observer characteristic frequency and damping factor. Structurally speaking, the OF controller (18) amounts to an interlaced estimator-control design, with a second-order SF controller and a third-order observer, and in principle, the analytic solution-based discrete model (11) provides a prediction capability than an Euler-based design.

4.4 Implementation and Tuning

Modelling requirements. The OF controller (18) only needs the approximated static constants *a* (6a) and (λ_g, λ_l), or in other words, steady-state (local) approximations of the eigenvalues corresponding to the peripheral glucose-insulin dynamics (1a.8, 1b.7). These modelling requirements are fewer than the ones of previous control studies with glucose measurements (Hovorka *et al.*, 2004; Magni *et al*., 2007; Lee *et al*., 2009).

Stability Considerations and Tuning. The rigorous assessment of the closed-loop stability goes beyond the scope of the present work, and here it suffices to mention that the application of Small Gain Theorem-based tools (Isidori, 1999; González and Alvarez, 2005) in conjunction with the stability assessment of estimators with sampled-delayed measurements (Hernández and Alvarez, 2003) leads to the result that closed-loop stability can be attained by: (i) setting the observer gain (ω_o) within an interval (ω_o^-, ω_o^+), whose size increases (or decreases) as the sampling-delay period (Δ) decreases (or grows), and (ii) setting the control frequency (ω_c) sufficiently smaller than ω_o. The associated tuning guidelines are the following:

1. Set the observer characteristic time ($\tau_o = 1/\omega_o$) about two times greater than the sampling-delay period: $\tau_o = 2\Delta$. Thus, the observer frequency (ω_o) is about: $\omega_o = 1/(2\Delta)$. Set the controller frequency (ω_c) two times slower than the observer frequency: $\omega_c = \omega_o/2$.
2. Choose the damping factors greater than one, say $(\zeta_o, \zeta_c) \in (1, 3]$, to preclude the amplification of the high-frequency unmodeled dynamics (López and Alvarez, 2004).
3. Increase the observer frequency up to its ultimate value ω_o^u, where the response becomes oscillatory, and backoff until a satisfactory response is attained, say at $\omega_o \leq 2\ \omega_o^u$.
4. If necessary, adjust the damping factors (ζ_o, ζ_c) and/or controller frequency (ω_c).

In this manner, the OF controller (18) is tuned according to prescribed root locus-based pole patterns (inside the unit circle), with the damping factors (ζ_o, ζ_c) and the characteristic frequencies (ω_o, ω_c) as adjustable parameters.

5. APPLICATION EXAMPLE

The proposed OF controller (18) was evaluated *in silico* under typical scenarios, with a 70-kg T1DM patient under a carbohydrate intake of 50 g. Without losing generality, the reference glucose evolution ($\bar{g}_{Pi}$) is described by the next peak function:

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

where $\{A_{Pi}, t_p, w\} = \{40, 70, 30\}$ is a constant parameters set such that $\bar{g}_{Pi}(t)$ resembles the glucose response of a healthy subject after a carbohydrate intake. The parameter values for system (1) are reported by Sorensen (1985), and the carbohydrate absorption rate model (r_{meal}, exogenous input) was taken from Lehmann and Deutsch (1992). The controller was tested under nominal, hyperglycaemic and hypoglycaemic scenarios; for the purpose at hand, the hepatic glucose production rate function (r_{Hgp}) is given by the nonlinear function:

$$r_{Hgp}(g_L, \Gamma, f_2, m_{Hgp}^I) = m_{Hgp}^I\, \mu_{Hgp}^{\Gamma}(\Gamma, f_2)\, \mu_{Hgp}^{g}(g_L)\, r_{Hgp}^*$$
$$\mu_{Hgp}^{g}(g_L) = a_{Hgp}^g - b_{Hgp}^g \tanh\{c_{Hgp}^g\, [(g_L/101) - d_{Hgp}^g]\}$$

where the constants $\{a_{Hgp}^g, c_{Hgp}^g\}$ are two of the most sensitive parameters (Quiroz and Femat, 2007) such that hyperglycaemic and hypoglycaemic scenarios can be emulated.

The controller was tested with two different sampling-delay periods: (i) $\Delta = 1$ min, to evaluate the recovery target towards the continuous measurements case (10), and (ii) $\Delta = 6$ min, with the understanding that this situation represents a typical case in the light of the common measurements delay (from 50 seconds to 5 minutes; Chee and Fernando, 2007). Following the tuning guides of Section 4, the control and observer parameters were set as follows:

Δ (min)	ζ_o	ω_o (min^{-1})	ζ_c	ω_c (min^{-1})
1	1.2	1.5	1.8	0.2
6	4	0.5	0.71	0.15

In Figure 1, three closed-loop responses are shown with: (i) the OF controller with continuous glucose measurements (10), (ii) the proposed OF controller (18) with discrete-delayed glucose measurements and $\Delta = 1$ min, and (iii) the proposed OF controller with discrete-delayed measurements and $\Delta = 6$ min. As it can be seen, the discrete controller with small sampling-delay period ($\Delta = 1$ min) recovers the behavior of the controller with continuous measurements; the control input response (insulin delivery, w_i) is smooth and away from saturation, and the glucose reference evolution ($\bar{g}_{Pi}$) is adequately tracked with deviations due to the estimation errors dynamics. On the other hand, the discrete controller with typical measurements delay ($\Delta = 6$ min) also yields a glucose evolution that remains close to the reference evolution, without destabilization of the closed-loop system; the resulting behavior is similar (or improved) to the ones obtained with previous control schemes (Hovorka *et al.*, 2004; Magni *et al.*, 2007; Lee *et al.*, 2009). In other words, the proposed control scheme can perform the same task with less modeling requirements and more robustness with respect to model uncertainty.

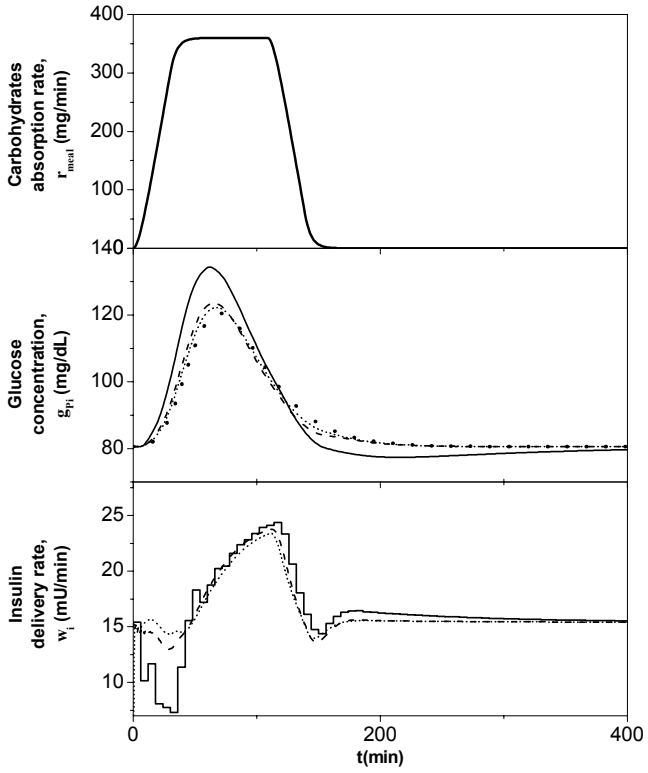

Figure 1. Closed-loop responses with OF controllers, with continuous measurements (11) (····), and discrete-delayed measurements (19) with $\Delta = 1$ min (- - -) and $\Delta = 6$ min (—), and reference evolution $\bar{g}_{Pi}(t)$ (• • • •).

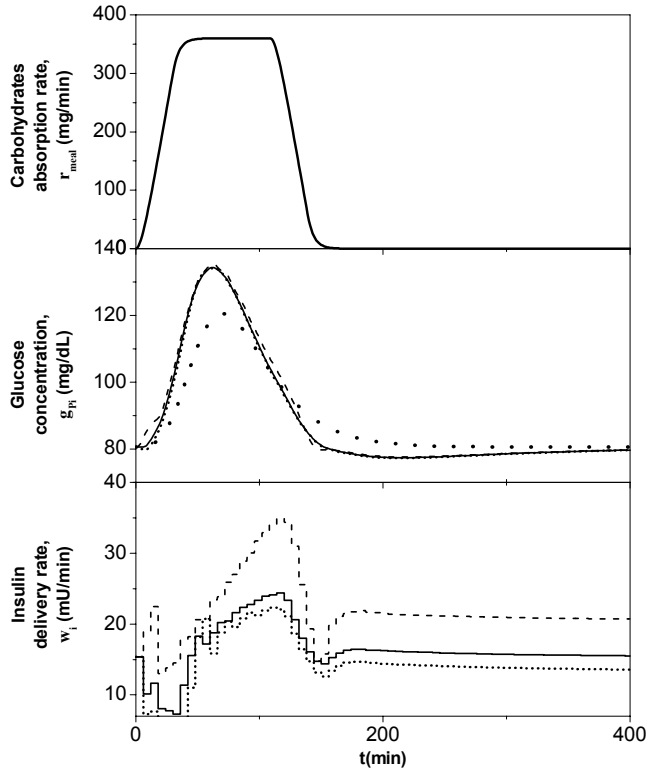

Figure 2. Closed-loop responses with OF controller (19) with discrete-delayed measurements (Δ = 6 min), under nominal (—), hyperglycaemic (- - -) and hypoglycaemic (····) scenarios, and reference evolution $\bar{g}_{Pi}(t)$ (• • •).

In Figure 2, closed-loop responses are shown with the proposed discrete OF controller (Δ = 6 min): (i) under a hyperglycaemic situation, by introducing a 50 % error in the constant a^{g}_{Hgp} (nominal value: 1.425) in model (1), and (ii) under a hypoglycaemic situation, by introducing a 50 % error in the constant c^{g}_{Hgp} (nominal value: 0.6199) in model (1). Figure 2 shows that: (i) the glucose tracking task is acceptably executed, without controller degradation, and (ii) in hyperglycaemic (or hypoglycaemic) situation, the insulin delivery rate increases (or decreases). Summarizing, due to the reduced-model dependency of the proposed controller and its prediction capability, health-conditions variability can be adequately handled despite significant the measurement delay.

6. CONCLUSIONS

The control of glucose concentration in T1DM patients with discrete-delayed measurements of peripheral glucose concentration has been addressed within a constructive control framework, with emphasis on the attainment of applicability-oriented features (linearity and reduced-model dependency). The controller was designed by combining passivity, discrete model realization, and observability considerations. The proposed control technique has a systematic construction and simple tuning guides, and its implementation in a T1DM patient *in silico* showed that the controller yields: (i) closed-loop stable behavior, (ii) a glucose response that resembles the one of a healthy (nondiabetic) person, with less modelling requirements than previous control schemes, and (iii) a performance that is not significantly affected by typical parameter uncertainty, despite the measurement delay.

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