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EPSAC Predictive Control of Blood Glucose Level in Type I Diabetic Patients

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Abstract—**An in-house predictive control algorithm has been implemented to control blood glucose level in type I diabetic patients, by controlling the insulin infusion rate to a mechanical pump. The role of the disturbance filter in model-based predictive control is underlined and its possibility to improve control performance is exploited. For comparison purposes, a classic PID controller has been designed via CAD tools. Controller performance was assessed in terms of its ability to track a normoglycemic setpoint (81mg/dL) from initial states of hypo- and hyperglycemia, as well as in response to a meal disturbance. Unconstrained control gave satisfactory results, within imposed constraints. Both strategies are implemented in discrete manner, thus suitable for future implementation in wearable devices.**

I. Introduction

DIABETES Mellitus is an incurable disease affecting millions of people worldwide. Belgium is one of the leading countries in the astringent fight against the increasing number of diabetic patients so that this *contemporary disease* does not reach its current prediction of 50 million victims in Europe by 2025 [1]. In parallel, scientists are focusing on developing a manifold of new techniques and feasible instrumentation to offer wearable solutions and improve the life of type I diabetic patients. Type I, or insulin-dependent diabetes mellitus (IDDM), is characterized by absent insulin secretion in the pancreas, resulting in plasma glucose concentrations elevated above the *normoglycemic range* (70-120mg/dL) [2].

The treatment methods for insulin-dependent diabetes, subcutaneous insulin injection or continuous infusion of insulin, usually result in frequent variations of glucose concentration in blood. Therefore, a significant effort has been put toward the development of a device to control glycemia [3]–[6] and the methods are continuously improved.

A device of this type would contain three major components: i) a mechanical pump (MP); ii) an in vivo glucose sensor; and iii) a mathematical algorithm (R) to regulate the pump given a sensor measurement (Fig.1). Technological advances allowed a wide variety of programmable and variable-rate infusion pumps to become available [7],[8].

Model-based predictive control (MBPC) algorithms have been recently reported in literature to tackle successfully constraints posed by several biomedical control problems, not only in blood glucose control in diabetic patients [9], [10] but also mean arterial pressure, and cardiac output control during anesthesia [10], [11].

The purpose of this contribution is to present results of an *in-house* extended prediction self adaptive control (EPSAC) algorithm to blood glucose control of IDDM patients, and investigate the effect of a *default* and a *designed* disturbance filter in EPSAC strategy. A comparison between a classical PID controller and EPSAC is made in this report. Correction of hypo- and hyperglycemia states towards normoglycemia is performed and rejection of a meal disturbance is tested. As a *first step,* results are compared and discussed with respect to controller performance and possible improvements.

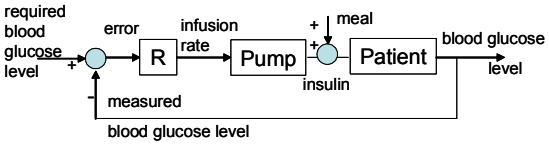

Fig. 1. Schematic overview of a blood glucose control device

II. Patient Model

In [12] it has been concluded that an injected glucose load in normal (glucose tolerant) individuals immediately elevated the glucose concentration in plasma. This initiates the secretion of insulin from the pancreatic ß-cells. The provoked hyperglycemia induces an immediate peak in the insulin concentration in plasma, and the glucose uptake in muscles, liver and adipose tissue is raised by the *remote insulin* action. This lowers the glucose concentration in plasma, affecting the ß-cells to secrete less insulin (biological feedback). By 1 hour the glucose concentration is normalized and in the following 2 hours a moderate undershoot is observed. After 2-3 hours, it is usually found that the perturbed insulin and glucose concentrations have returned to normal.

A mathematical representation of glucose and insulin kinetics is necessary before implementing the EPSAC model-based control scheme. Although it suffers from glucose effectiveness overestimation and insulin sensitivity underestimation [13] , the *Bergman minimal model* [14] proved to be suitable for exemplifying this study:

$$\dot{G} = -p_1 G - X(G + G_B) + G_{meal} / V_I \qquad (1a)$$

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$$\dot{X} = -p_2 X + p_3 I \quad (1b)$$

$$\dot{I} = -n(I + I_B) + u(t)/V_I \quad (1c)$$

The plasma insulin at time t, denoted by I(t), fills a remote insulin compartment with a constant rate p_3. The active insulin in the remote compartment accelerates glucose utilization by the peripheral tissues and liver. Consequently, p_3 is referred to as the insulin-dependent increase in glucose uptake ability in tissue. The intra-cellular metabolism of the remote insulin effect is constant and determined by p_2. The dynamic insulin response denoted by X(t) is proportional to the active insulin in the remote compartment and describes the time dependent effect of the insulin on the net glucose disappearance. The plasma glucose concentration G(t) is governed by the balance between the glucose production/uptake by the liver and the utilization of glucose by the peripheral tissues. The glucose uptake in muscles, liver and tissues is assumed to be of constant rate p_1. Basal levels of glucose and insulin are denoted by G_B and I_B respectively. V_I is the insulin distribution volume, n is the fractional disappearance of insulin, and the insulin infusion rate delivered by the pump is denoted as u(t).

Defining the state, input, and output variables as:

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = \begin{bmatrix} G \\ X \\ I \end{bmatrix}; \begin{bmatrix} u_1 \\ u_2 \end{bmatrix} = \begin{bmatrix} U - U_B \\ G_{meal} - 0 \end{bmatrix}; \; y = G \quad (2)$$

one can derive a linear state space model where the first input is manipulated (insulin infusion rate) and the second input represents a meal glucose disturbance:

$$A = \begin{bmatrix} -p_1 & -G_B & 0 \\ 0 & -p_2 & p_3 \\ 0 & 0 & -n \end{bmatrix}; B = \begin{bmatrix} 0 & 1/V_I \\ 0 & 0 \\ 1/V_I & 0 \end{bmatrix}; \quad (3)$$
$$C = [1 \quad 0 \quad 0]; \; D = [0 \quad 0].$$

Diabetic (glucose intolerant) subjects can be modeled by the following set of parameters [15]: G_B=81mg/dL, I_B=15mU/L, U_B=16.667mU/min, V_I=12L, n=5/54min^{-1}, p_1=0min^{-1}, p_2=0.025min^{-1}, p_3=13*10^{-6}mU/min. Assuming the meal glucose G_{Meal} and glucose output in mg/dL the resulting state space model is:

$$A = \begin{bmatrix} 0 & -81 & 0 \\ 0 & -0.025 & 13*10^{-6} \\ 0 & 0 & -5/54 \end{bmatrix}; B = \begin{bmatrix} 0 & 0.463 \\ 0 & 0 \\ 1/12 & 0 \end{bmatrix}; \quad (4)$$
$$C = [18 \quad 0 \quad 0]; \quad D = [0 \quad 0]$$

To avoid that the patient enters hypo- or hyperglycemia state, the glucose level is imposed between $65 \le G + G_B \le 180$ for an insulin infusion rate within $0 \le U + U_B \le 100$. Notice that a negative/positive limit denotes the deviation from the basal value.

III. EPSAC Predictive Control

EPSAC strategy [16],[17] is based on a generic process model:

$$y(t) = x(t) + n(t) \quad (5)$$

The disturbance $n(t)$ includes the effects in the measured output $y(t)$ which do not come from the model input $u(t)$ via the available model. These non-measurable disturbances have a stochastic character with non-zero average value, which can be modelled by a colored noise process:

$$n(t) = \left[C(q^{-1}) / D(q^{-1}) \right] \cdot e(t) \quad (6)$$

with: $e(t)$ - uncorrelated (white) noise with zero mean value; $C(q^{-1})$ and $D(q^{-1})$ - monic polynomials in the backward shift operator q^{-1} of orders n_c and n_d. The filter $C(q^{-1})/D(q^{-1})$ is considered to be a *design filter*. It plays an *important role* in MBPC and will be discussed later in this Section.

A. Prediction Algorithm

The model output $x(t)$ represents the effect of the control input $u(t)$ on the process output $y(t)$ and is also a non-measurable signal, and the relationship between $u(t)$ and $x(t)$ is given by the generic dynamic system model:

$$x(t) = f\left[x(t-1), x(t-2), \cdots, u(t-1), u(t-2), \cdots \right] \quad (7).$$

The fundamental step in MBPC methodology consists in prediction of the process output $y(t+k)$ at time instant t, indicated by $\{ y(t+k \mid t), \; k = 1 \ldots N_2 \}$, over the *prediction horizon* N_2, and based on:

- the measurements available at sampling time instant t: $\{ y(t), y(t-1), \cdots, u(t-1), u(t-2), \cdots \}$;
- The future values of the input signal (postulated at time t): $\{ u(t \mid t), u(t+1 \mid t), \cdots \}$.

Using the generic process model (5), the predicted values of the output are:

$$y(t+k \mid t) = x(t+k \mid t) + n(t+k \mid t) \quad (8)$$

Prediction of $x(t+k|t)$ and of $n(t+k|t)$ can be done respectively by recursion of the process model (7) and by using filtering techniques on the noise model (6) [17].

B. Control Algorithm

In EPSAC for linear models, the future response is then considered as being the cumulative result of two effects:

$$y(t+k\,|\,t) = y_{\text{base}}(t+k\,|\,t) + y_{\text{optimize}}(t+k\,|\,t) \qquad (9)$$

The two contributions have the following origins:

$\boxed{y_{\text{base}}(t+k\,|\,t)}$:

- effect of past control $\{u(t\text{-}1),\ u(t\text{-}2),\ \ldots\}$ (initial conditions at time t);
- effect of a *base* future control scenario, called $u_{\text{base}}(t+k\,|\,t),\ \ k \geq 0$, which is defined *a priori* [17]; for linear systems the choice is irrelevant, a simple choice being $\{u_{\text{base}}(t+k\,|\,t) \equiv 0,\ \ k \geq 0\}$;
- effect of future (predicted) disturbances $n(t+k|t)$.

The component $y_{\text{base}}(t+k\,|\,t)$ can be easily obtained using (6)(7)(8) taking $u_{base}(t+k\,|\,t)$ as the model input for (7).

$\boxed{y_{\text{optimize}}(t+k\,|\,t)}$:

- effect of the *optimizing* future control actions $\{\delta u(t\,|\,t),\ \delta u(t+1\,|\,t),\ \ldots\ \delta u(t+N_u-1\,|\,t)\}$ with $\delta u(t+k\,|\,t) = u(t+k\,|\,t) - u_{\text{base}}(t+k\,|\,t)$.

Refer to Fig. 2 for the concepts of *base* and *optimizing* controls. Notice that $u(t+k|t)$ is constrained to be constant from $k=N_u$ on (and this is realized by *selecting* $u_{\text{base}}(t+k|t)$ constant from $k=N_u$ on and by *imposing* that $\delta u(t+k|t)$ should be constant from $k=N_u$ on). The *design* parameter N_u is called the *control horizon* (a well-known concept in MBPC-literature).

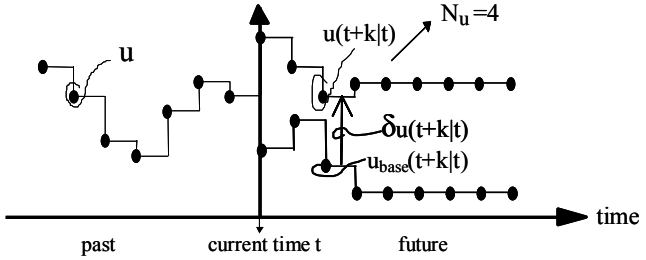

Fig. 2. The EPSAC concept of *base/optimizing* controls

From Fig. 2 it is obvious that the component $y_{\text{optimize}}(t+k\,|\,t)$ is the cumulative effect of a series of *impulse* inputs and a *step* input:

- an *impulse* with amplitude $\delta u(t\,|\,t)$ occurring at time t, resulting in a contribution $h_k \delta u(t\,|\,t)$ to the process output at time $t+k$ (k sampling periods later);
- an *impulse* with amplitude $\delta u(t+1\,|\,t)$ occurring at time t+1, resulting in a contribution $h_{k-1}\delta u(t+1\,|\,t)$ to the predicted process output at time $t+k$ (k-1 sampling periods later);
- etc;
- finally a *step* $\delta u(t+N_u-1\,|\,t)$ at time $t+N_u-1$, resulting in a contribution $g_{k-N_u+1}\delta u(t+N_u-1\,|\,t)$ to the predicted process output at time $t+k$.

The cumulative effect of all impulses and the step is:

$$\begin{aligned} y_{\text{optimize}}(t+k\,|\,t) = {} & h_k\,\delta u\,(t\,|\,t) + h_{k-1}\delta u\,(t+1\,|\,t) + \\ & + \ldots + g_{k-N_u+1}\,\delta u\,(t+N_u-1\,|\,t) \end{aligned} \qquad (10)$$

The parameters $g_1, g_2, \ldots g_k, \ldots g_{N_2}$ are the coefficients of the *unit step response* of the system, i.e. the response of the system for a stepwise change of the input (with amplitude 1). The parameters $h_1, h_2, \ldots h_k, \ldots h_{N_2}$ are the coefficients of the *unit impulse response* of the system and can be easily calculated from the step response coefficients and vice versa: $h_k = g_k - g_{k-1}$ (and $h_0 = h_{-1} = \ldots = g_0 = g_{-1} = \ldots \equiv 0$).

Using (9) and (10), the ***key EPSAC-MBPC equation***:

$$\mathbf{Y} = \bar{\mathbf{Y}} + \mathbf{G}\mathbf{U} \qquad (11)$$

is obtained, where:

$$\begin{aligned} \mathbf{Y} &= \left[y(t+N_1\,|\,t) \cdots y(t+N_2\,|\,t)\right]^T \\ \bar{\mathbf{Y}} &= \left[y_{\text{base}}(t+N_1\,|\,t) \cdots y_{\text{base}}(t+N_2\,|\,t)\right]^T \\ \mathbf{U} &= \left[\delta u(t\,|\,t) \cdots \delta u(t+N_u-1\,|\,t)\right]^T \\ \mathbf{G} &= \begin{bmatrix} h_{N_1} & h_{N_1-1} & h_{N_1-2} & \ldots & g_{N_1-N_u+1} \\ h_{N_1+1} & h_{N_1} & h_{N_1-1} & \ldots & \ldots \\ \ldots & \ldots & \ldots & \ldots & \ldots \\ \ldots & \ldots & \ldots & \ldots & \ldots \\ h_{N_2} & h_{N_2-1} & h_{N_2-2} & \ldots & g_{N_2-N_u+1} \end{bmatrix} \end{aligned} \qquad (12)$$

The controller output is then the result of minimizing the cost function:

$$V(\mathbf{U}) = \sum_{k=N_1}^{N_2} [r(t+k\,|\,t) - y(t+k\,|\,t)]^2 \qquad (13)$$

with $r(t+k\,|\,t)$ the desired *reference trajectory* and the *horizons* N_1, N_2 being design parameters.

It is now straightforward to derive the solution. The cost function (13) is a quadratic form in **U,** having the following structure using the matrix notation from (12) and with **R** defined similarly to **Y**:

$$V(\mathbf{U}) = [\mathbf{R} - \bar{\mathbf{Y}} - \mathbf{G}\mathbf{U}]^{-1}[\mathbf{R} - \bar{\mathbf{Y}} - \mathbf{G}\mathbf{U}] \qquad (14)$$

which leads after minimization w.r.t. **U** to the optimal solution:

$$\mathbf{U}^* = [\mathbf{G}^T\mathbf{G}]^{-1}\mathbf{G}^T(\mathbf{R} - \bar{\mathbf{Y}}) \qquad (15)$$

The matrix $\mathbf{G^TG}$ which has to be inverted has dimension N_u x N_u. For the default case N_u=1, this results in a simple *scalar* control law. Only the first element $\delta u(t/t)$ in $\mathbf{U}^*$ is required in order to compute the actual control input applied to the process:

$$u(t) = u_{base}(t \mid t) + \delta u(t \mid t) = u_{base}(t \mid t) + \mathbf{U}^*(1) \qquad (16)$$

At the next sampling instant t+1, the whole procedure is repeated taking into account the new measurement information $y(t+1)$. This is called the principle of *receding horizon control*, another well-known MBPC-concept.

C. Disturbance Filter Design

The disturbance $n(t)$ includes all effects in the measured output $y(t)$ which do not come from the model output $x(t)$ (effects of process disturbances, effects of un-modeled process inputs, measurement noise, model errors, etc). The net effect of all these unknown disturbances has a stochastic character with non-zero average value and can be modeled by a colored noise process as in (6) where the filter C/D is the *disturbance model*. In the MBPC approach this filter is considered as a *design filter* and can be used - in order to improve the quality of the control performance - to *supply* information to the controller about the type of disturbances that can be expected.

A *basic choice* for the disturbance model might be:

$$C(q^{-1}) / D(q^{-1}) = 1/1 - q^{-1} \qquad (17)$$

resulting in a disturbance signal $n(t)$ with *non-zero* average value. In this case the MBPC-controller will *intrinsically* take action to remove steady-state errors, similar to the effect of the integrator in a PID-type controller. Notice that (17) is the *default* disturbance model (EPSACdd) that is usually applied in practice.

Generally, the disturbance signal $n(t)$ can be reconstructed using the generic model (5), by *measuring* the process output y and *calculating* the model output x with the system model (7). As $n(t)$ has usually the character of a correlated (colored) random signal, a useful and simple approach is then to calculate its power spectra density using a spectral analysis software. This allows then to detect around which frequency the main disturbance energy is situated. Once the main frequency is known, a more *intelligent design* of the filter C/D can be made so that it has a band-pass characteristic around this frequency (EPSACid). Some guidelines on designing an effective disturbance filter are detailed in [18].

IV. Classical PID Controller Design

Controller design is based on the CAD (Computer Aided Design) methodology, requiring an available dynamic model of the system.

The CAD-software based on *Frequency Response techniques (FR-tool)* has been used. This *in-house* developed methodology is based on specifications such as: robustness, settling time, overshoot, and is a very interactive and visual design tool. The principle is the following: *play* with the PID-zeros to reshape the Nichols curve, so that it fits into the requirements of the given specifications. Notice that it is necessary to provide a dynamic model of the system.

The PID design procedure consists of playing with the 2 PID-zeros in the transfer function $K(s-z_1)(s-z_2)/s$, so that the controller proportional gain K is as large as possible, to reduce the settling time (Ts<120min), but still satisfying the required specification for overshoot (OS<30%) and a relatively high robustness (Ro>0.65 on a scale 0…1). The 2 zeros are located at $z_{1,2}$= -0.02 and the gain is K=-0.5, as depicted in Fig. 3.

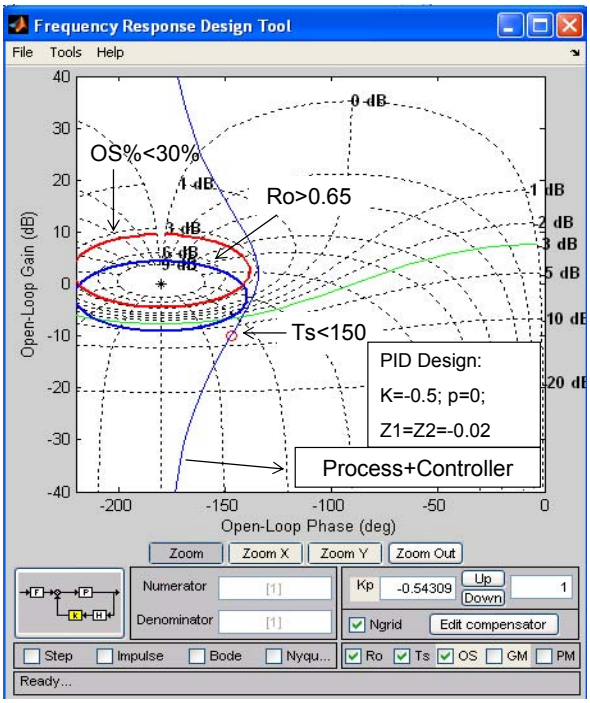

Fig. 3. Sample figure from CAD frequency response toolbox for PID design

Further on, the PID parameters are used in a *discrete-time control scheme*, with a software implemented controller:

$$u(t) = u(t-1) + c_0 e(t) + c_1 e(t-1) + c_2 e(t-2) \qquad (18)$$

with the error: $$e(t) = w(t) - y(t) \qquad (19).$$

Denoting the shift-operator: $q^{-1}e(t) = e(t-1)$ results in:

$$u(t) = \frac{C(q^{-1})}{1-q^{-1}} e(t) = \frac{c_0 + c_1 q^{-1} + c_2 q^{-2}}{1-q^{-1}} e(t) \qquad (20)$$

and the control loop is depicted below. The sampling period of the controller was T_s=*3min* [19].

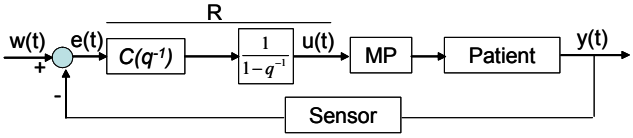

Fig. 4. PID control loop scheme (R denotes the regulator from Fig.1)

V. Performance Evaluation

A. Hypoglycemia and Hyperglycemia Correction

If insulin is applied in excess, the blood glucose level goes below normal (<65mg/dL) causing *hypoglycemia*. *On a short term*, hypoglycemia can induce fainting, muscle convulsions,

deeper state of consciousness-loss such as coma. On the other hand, if insulin is supplied insufficiently, the blood glucose level elevates above the normoglycemia values (>120mg/dL) causing *hyperglycemia*. Most of *the long-term complications* associated with diabetes, such as nephropathy (a kidney disease) and retinopathy (diseased condition of the eye-retina, esp. non-inflammatory) result from *sustained* hyperglycemia [10], thus an immediate return to the normoglycemic values is important.

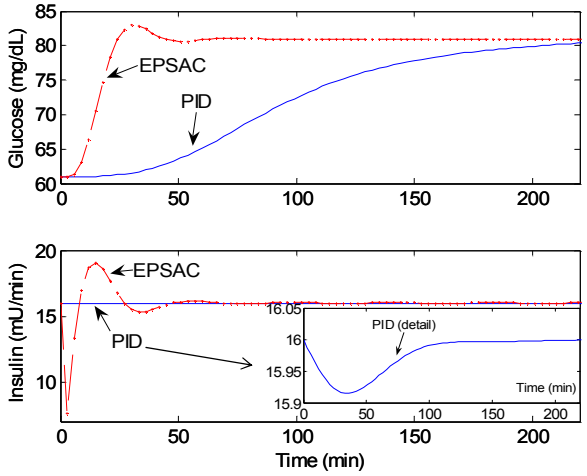

Fig. 5. Correction of a hypoglycemic state

The controllers are tested from the performance standpoint for correcting a state of hypo- and hyperglycemia, respectively. Correcting a state of hypoglycemia implies bringing the glucose level in the blood as soon as possible from the hypoglycemic value (<65mg/dL) to the basal value (81mg/dL). Respectively, correcting hyperglycemia implies bringing the glucose level in blood from the hyperglycemic value (>120mg/dL; in this case 180mg/dL).

Fig.5 and Fig.6 depict the PID and EPSAC controller (N_u=1, N_1=1, N_2=5) performance by means of input (insulin infusion rate) and output (glucose concentration) variables for hypo- and hyperglycemia state corrections, respectively. Control is evaluated in the absence of exogenous glucose infusion (zero meal disturbance).

B. Glucose Level Control Following a Meal Disturbance

In this test the effect of infusing (exogenous) glucose is examined and controllers are compared. It is expected that the extra information given in the disturbance filter of the EPSACid strategy leads to improved results compared to EPSACdd.

It has been reported that a realistic meal glucose disturbance is around 0.3g glucose per kg bodyweight [12]. In this paper, a 23g glucose infusion disturbance has been considered. In the oral glucose tests, the glucose does not enter directly the blood stream and is more realistic to consider a lag in the gut of about 20 minutes. This information is then provided to the disturbance filter:

$$C(q^{-1})/D(q^{-1}) = 1/\left[(1-q^{-1})(1-0.9q^{-1})\right] \qquad (21)$$

and the corresponding results (EPSACid) are in Fig.7.

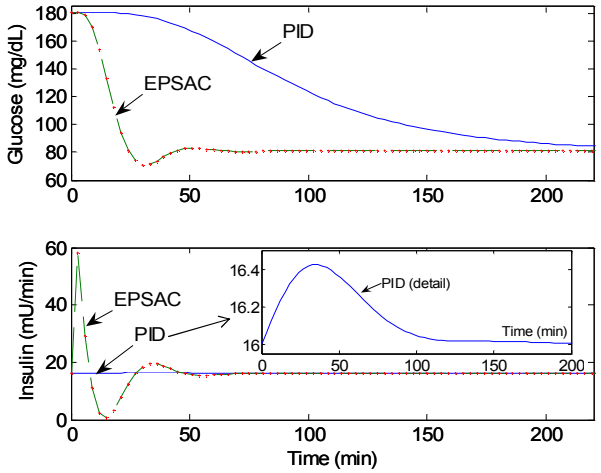

Fig. 6. Correction of a hyperglycemic state

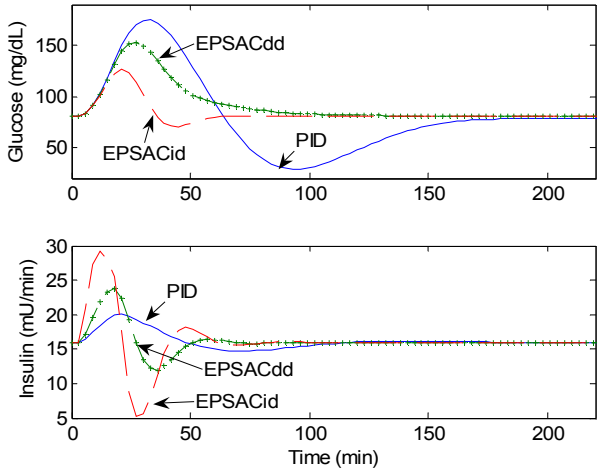

Fig. 7. Correction after an exogenous glucose infusion

C. Discussion

The benefit of using predictive control instead of classical control algorithm is the estimation of future glucose behavior based on the past insulin inputs. By definition, the predictive controller takes action for a *predicted* hypo- or hyperglycemic state of the patient before it occurs, while a classical feedback controller reacts afterwards. In the present contribution, constrained EPSAC control has not been applied, although the design of N_u, N_1 and N_2 parameters had been made such that it fulfills the requested constraints.

Mixing types of insulin is expected to diminish controller performance, since it is desirable that the results are obtained fast (thus a fast-active insulin type is applied). For hypo- and hyperglycemia state correction, the designed PID controller performed smoothly, converging to the setpoint value in approximately 3 hours. Notice that the design of the PID

controller based on the specifications does not necessarily give optimal controller parameters. The EPSAC controller performed better from the settling time standpoint (approx. 1 hour), but it applies a more aggressive control. For disturbance rejection, as expected from theory of disturbance filter design, the EPSACid had the best performance. This improved result is due to the fact that the controller *knows* about the type of disturbance it can expect and takes the *appropriate* control action. The settling times for both EPSAC are similar, around 1.5 hours, and they outperform the PID controller (3 hours).

An important aspect is the comparison between control efforts of the controllers in the disturbance rejection test. For the PID, the control effort range is within 5mU/min, while the EPSAC controller requires more energy. Notice that the maximum control effort range for EPSACdd is about (24-16)mU/min, while for EPSACid is about (29-16)mU/min; respectively 9.5% and 15.5% (considering (100-16)mU/min as 100% and relating to basal values in Section II). The remarkable observation is that the output of the EPSACid is significantly better than the one of EPSACdd, requiring only a 6% increase in its control effort. This observation *enhances the importance of the role of disturbance filter* in EPSAC-MPC methodology.

VI. Conclusion

As a starting point, the results presented in this paper comprise the application of the *in-house* EPSAC algorithm to blood glucose control in IDDM patients. Although constrained control has not been yet applied, useful results within imposed constraints have been obtained. A common advantage of the PID and EPSAC-MBPC strategies stands in their discrete nature, suitable for DSP implementation in recent circuit technology.

The nonlinear EPSAC applied on *a generalized (nonlinear) patient model* is an undergoing research. Therefore, inter- and intra-patient variability is subject to further investigation, in robustness tests. Using a designed disturbance filter, the un-modeled effects, modeling errors and other disturbances are expected to be well tackled in this EPSAC-MBPC control strategy. Moreover, if used in constrained control, the predictive algorithms provide optimal results in coping with the imposed constraints on input-output variables.

Clinical trials are the final aim of this research, whereas a modified Biostator (an device that monitors blood glucose and gives incrementally insulin to mimic normal insulin secretion) is considered to be used on subjects. Since studies employing fast acting insulin and the subcutaneous delivery routes with a PID controller reported good results [19], some further investigation is required for PID parameter tuning via the FR-tool toolbox.

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