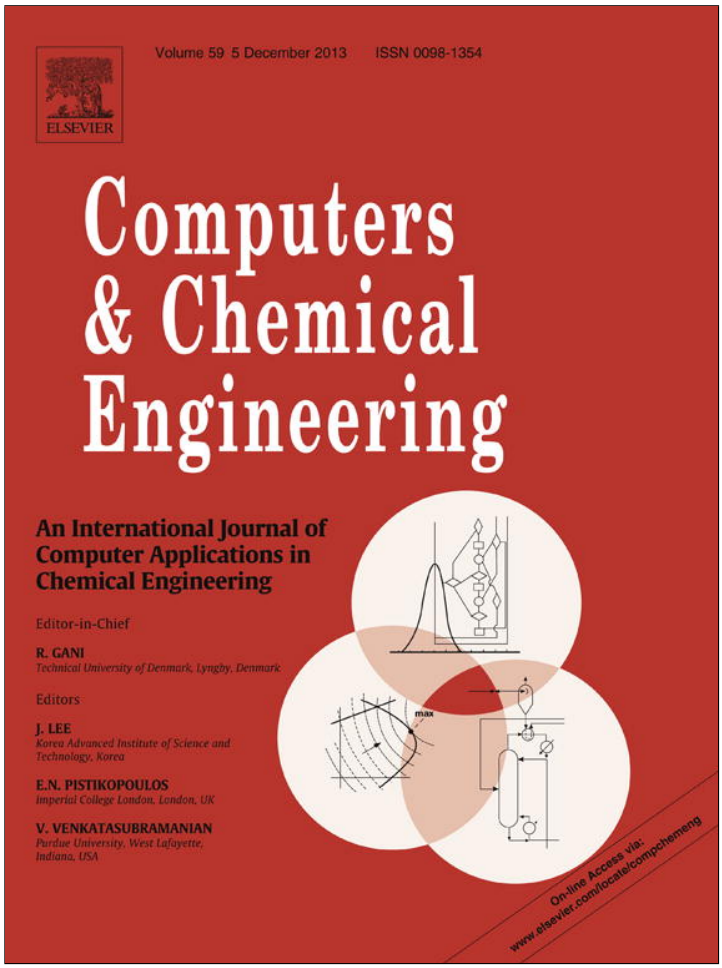

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Extended adaptive predictive controller with robust filter to enhance blood glucose regulation in type I diabetic subjects

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ABSTRACT

In this paper, an improved adaptive predictive control with robust filter is developed to be applied in an artificial pancreas. Several problems inherent to endocrine systems for diabetic persons have to be tackled such as nonlinearities, long time delays or daily variations of parameters. Three Finite Impulse Response models for insulin input and the same for meal intake (perturbations) corresponding to normal, hyper-hypoglycaemia levels to implement three zones control are taken into account. The glycaemia reference trajectory is shaped from a healthy person response. A variable weighting factor in the cost function is included to prevent dangerous glycaemia excursions out of the allowed limits. Additionally, a noisy blood glucose subcutaneous sensor model is used. This control strategy is tested on 30 virtual subjects from the UVa – Padova Simulator. Simultaneous meals and physiological disturbances are taken into account and the main conclusions are drawn from Control Variability Grid Analysis.

1. Introduction

In type I diabetes Mellitus, the body's immune system attacks and destroys beta cells of the pancreas. These cells produce insulin, a hormone that regulates the blood glucose concentration in the body. Whereas insulin lowers the glucose content of the blood (when hyperglycaemia occurs), glucagon (other hormone) frees the glucose in the liver when plasma glucose concentration reaches a hazardous low value (a hypoglycaemic episode can lead a subject to death). The importance of giving an alternative solution through the artificial pancreas seems to be relevant since the prevalence of diabetes for all age-groups worldwide was estimated to be 9.9% in 2030 by the International Diabetes Federation. (2011). The total number of people with diabetes is projected to rise from 366 million in 2011 to 552 million in 2030.

An artificial pancreas is a device that nowadays is being widely studied by scientists worldwide because there are great economical interests in its completion (O'Grady, John, & Winn, 2011). It is composed of a blood glucose sensor, an automatic control algorithm and an insulin pump (Fig. 1). There are several approaches in the application of each of these three elements. For example, glucose sensing could be non-invasive (Campetelli, Zumoffen, & Basualdo, 2011) or minimally invasive and the route for insulin infusion or glucose measure could be either intravenous or subcutaneous. From the control point of view, PID (proportional integral derivative) (Ramprasad, Rangaiah, & Lakshminarayanan, 2004) and MPC (model predictive control) (Campetelli, Zumoffen, Basualdo, & Rigalli, 2010; Hovorka et al., 2004) control laws are among the most well-known methodologies proposed in the literature. However, model-based control strategies have been used with more encouraging outcomes in tighter regulation of blood glucose levels. The knowledge incorporated by the models in these types of controllers is what makes them more appealing.

It is well known that glucose homeostasis of diabetic subjects is affected by many factors. For example, insulin sensitivity can be acutely modified by independent variables such as physical exercise, dietary factors, alcohol intake or harmless drugs. Even psychological conditions like stress can produce daily variations on the glucose regulation capacity of a type I diabetic subject. In this context, model based control algorithms using models with constant coefficients could be inaccurate. Daily variations of the system take away the credibility of model predictions. Up to now, very few researchers addressed this issue. The most remarkable work on this subject is that of Hovorka et al. (2004). They applied a nonlinear model predictive controller that uses a Bayesian parameter estimation to determine time-varying model parameters. El-Khatib, Jiang,

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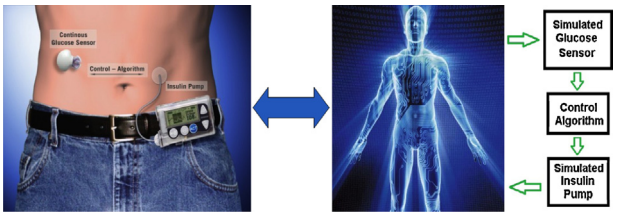


Fig. 1. Artificial pancreas: here the work is done *in silico*. By means of computer simulation a virtual subject, a simulated sensor and insulin pump are commanded by the controller proposed herein so that its performance could be safely tested.

and Damiano (2007) used a Generalized Predictive Control (GPC) algorithm with an ARMAX internal model of the system which is recursively adapted online and in the case of Eren-Oruklu, Cinar, Quinn, and Smith (2009), ARIMAX models were used.

Hence, the main contribution of this work is the use of online adaptation of the model parameters. However, due to the nonlinear nature of the daily dynamic variations suffered by the diabetic subject, the use of three internal nominal models is proposed. Three Finite Impulse Response (FIR) models for predictions are used. They are switched according to the subject's glycaemia levels as starting point for doing the adaptation. Good results using FIR models for diabetic subjects were reported by Ståhl, Johansson, and Renard (2010). These models are implemented in the context of the Adaptive Predictive Control with Robust Filter (APCWRF) approach (Zumoffen & Basualdo, 2012). The novelty is the use of the information given by three FIR models of the perturbation depending on the level of glucose content in blood as meal announcement. The reference trajectory adopted is based on the dynamic response of a healthy person model with the same meal intake. Additionally, a variable weighting factor is included in the control algorithm to prevent the glycaemia excursions outside the healthy range. This set of improvements allowed us to consider several typical issues for diabetes care, leading to better predictions of the internal models and driving to more accuracy in the insulin dosage calculations. Several experiments are performed with data from 30 subjects and the obtained results are rigorously compared through Control Variability Grid Analysis (CVGA) (Magni et al., 2008).

2. The simulation platform

The mathematical model used in this work to synthesize and test the controller is the one developed by (Dalla Man, Rizza, & Cobelli, 2007; Kovatchev, Breton, Cobelli, & Dalla Man, 2008) (UVa/Padova Simulator). It considers the human endocrine system of normal, prediabetic, type II and I diabetic subjects. Because it is one of the only ones that has been validated against clinical and experimental data, the type I diabetic subject version has been approved by the Food and Drugs Administration (FDA) as a substitute to animal trials in the pre-clinical testing of closed-loop control algorithms Kovatchev, Breton, Dalla Man, and Cobelli (2009). This model allows simulating the dynamic effect of exogenous glucose and insulin dosage under different specific tests and it is summarized in the following subsections.

2.1. Glucose intestinal absorption

It is modeled by a recently developed three-compartment model:

$$\dot{Q}_{sto1}(t) = -k_{gri}Q_{sto1}(t) + d(t) \tag{1}$$

$$\dot{Q}_{sto2}(t) = -k_{empt}(t, Q_{sto}(t))Q_{sto2}(t) \ldots + k_{gri}Q_{sto1}(t) \tag{2}$$

$$\dot{Q}_{gut}(t) = -k_{abs} + k_{empt}(t, Q_{sto}(t))Q_{sto2}(t) \tag{3}$$

$$Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t) \tag{4}$$

$$Ra(t) = fk_{abs}Q_{gut}(t)/BW \tag{5}$$

where Q_{sto} (mg) is the amount of glucose in the stomach (solid, Q_{sto1}, and liquid phase, Q_{sto2}), Q_{gut} (mg) is the glucose mass in the intestine, k_{gri} is the rate of grinding, k_{abs} is the rate constant of intestinal absorption, f is the fraction of intestinal absorption which actually appears in plasma, $d(t)$ (mg/min) is the amount of ingested glucose, BW (kg) is the body weight, Ra (mg/kg/min) is the glucose rate of appearance in plasma and k_{empt} is the rate constant of gastric emptying which is a time-varying nonlinear function of Q_{sto}:

$$k_{empt}(t, Q_{sto}(t)) = k_{max} + \frac{k_{max} - k_{min}}{2}[A(t)]; \tag{6}$$

where

$$A(t) = \tanh[\alpha(Q_{sto}(t) - bD(t))] \ldots - \tanh[\beta(Q_{sto}(t) - dD(t))] \tag{7}$$

$$\alpha = \frac{5}{2D(t)(1-b)} \tag{8}$$

$$\beta = \frac{5}{2D(t)d} \tag{9}$$

$$D(t) = \int_{t_i}^{t_f} (t)\,dt \tag{10}$$

where α and β are rate constants of gastric emptying, t_i and t_f, respectively, start time and end time of the last meal, b, d, k_{max} and k_{min} model parameters.

2.2. Glucose subsystem

A two-compartment model is used to describe glucose kinetics:

$$\dot{G}_p(t) = EGP(t) + Ra(t) - U_{ii}(t) \ldots - E(t) - k_1G_p(t) + k_2G_t(t); \tag{11}$$

$$\dot{G}_t(t) = k_1G_p(t) - U_{id}(t) - k_2G_t(t) \tag{12}$$

$$G(t) = \frac{G_p(t)}{V_G} \tag{13}$$

with $G_p(0) = G_{pb}$, $G_t(0) = G_{tb}$, $G(0) = G_b$. Here G_p and G_t (mg/kg) are glucose masses in plasma and rapidly-equilibrating tissues, and in slowly-equilibrating tissues, respectively, G (mg/dl) is plasma glucose concentration, suffix b denotes basal state. EGP is endogenous glucose production, Ra is glucose rate of appearance in plasma, E is renal excretion, U_{ii} and U_{id} are insulin-independent and dependent glucose utilizations, respectively (mg/kg/min), V_G is the distribution volume of glucose (dl/kg), and k_1 and k_2 (min^{-1}) are rate parameters.

2.3. Glucose renal excretion

Renal excretion represents the glucose flow which is eliminated by the kidney, when glycaemia exceeds a certain threshold k_{e2}:

$$E(t) = \max(0, k_{e1}(G_p(t) - k_{e2})); \tag{14}$$

The parameter k_{e1} (1/min) represents renal glomerular filtration rate.

2.4. Endogenous glucose production

EGP comes from the liver, where a glucose reserve exists (glycogen). EGP is inhibited by high levels of glucose and insulin:

$$EGP(t) = \max(0, EGP_b - k_{p2}(G_p(t)\ldots - G_{pb}) - k_{p3}(I_d(t) - I_b)); \quad (15)$$

where k_{p2} and k_{p3} are model parameters and I_d (pmol/l) is a delayed insulin signal, coming from the following dynamic system:

$$\dot{I}_1(t) = k_i I(t) - k_i I_1(t) \quad (16)$$

$$\dot{I}_d(t) = k_i I_1(t) - k_i I_d(t) \quad (17)$$

where I (pmol/l) is plasma insulin concentration or insulinemia and k_i (1/min) is a model parameter.

2.5. Glucose utilization

Glucose utilization is made up of two components: the insulin-independent one U_{ii}, which represents the glucose uptake by the brain and erythrocytes, and the insulin-dependent component U_{id}, which depends non-linearly on glucose in the tissues:

$$U_{id}(t) = V_m(X(t))\frac{G_t(t)}{K_m + G_t(t)}; \quad (18)$$

where V_m (1/min) is a linear function of interstitial fluid insulin X (pmol/l)

$$V_m(X(t)) = V_{m0} + V_{mx}X(t); \quad (19)$$

which depends from insulinemia in the following way:

$$\dot{X}(t) = p_{2u}(I(t) - Ib) - p_{2u}X(t); \quad (20)$$

where K_m, V_{m0}, V_{mx} are model parameters and I_b (pmol/l) is the basal insulin level. Parameters p_{2U} (rate of insulin action on peripheral glucose utilization) and V_{mx} (disposal of insulin sensitivity), will be used in Section 6 to simulate physiological disturbances related to insulin sensitivity.

2.6. Insulin subsystem

Insulin enters the bloodstream and is degraded in the liver and in the periphery:

$$\dot{I}_p(t) = m_1 I_l(t) - (m_2 + m_4)I_p(t) + s(t) \quad (21)$$

$$\dot{I}_l(t) = m_2 I_p(t) - (m_1 + m_3)I_l(t) + S(t) \quad (22)$$

$$I(t) = I_p(t)/V_I \quad (23)$$

where V_I (l/kg) is the distribution volume of insulin and m_1, m_2, m_3, m_4 (1/min) are model parameters. The model has exogenous insulin flow s, coming from the subcutaneous compartments (from a subcutaneous insulin pump), and enters directly to plasma. In the case of a subject that do not receive exogenous insulin, i.e. a normal subject or a type II diabetic, $s = 0$. S is the pancreatic insulin secretion (pmol/kg/min) which is zero in the case of a type I diabetic subject.

2.7. Subcutaneous insulin subsystem

The subcutaneous insulin subsystem is modeled here with two compartments, S_1 and S_2 (pmol/kg), which represent, respectively, polymeric and monomeric insulin in the subcutaneous tissue:

$$\dot{S}_1(t) = -(k_{a1} + k_d)S_1(t) + u(t) \quad (24)$$

$$\dot{S}_2(t) = k_d S_1(t) - k_{a2}S_2(t) \quad (25)$$

$$s(t) = k_{a1}S_1(t) + k_{a2}S_2(t) \quad (26)$$

Table 1
Zones definition: the models of the system and the perturbation are identified using small steps as inputs in the insulin infusion and the meal intake respectively. There are two models in each zone: one for the insulin system and the other for the perturbation effects.

Zone	Glycaemia range [mg/dl]	Nominal model basal [mg/dl]	Health state
1	$G_M(t) < 84$	$i = 1$: 70	Hypoglycaemia
2	$84 \le G_M(t) \le 140$	$i = 2$: 95	Normal (desirable)
3	$G_M(t) > 140$	$i = 3$: 151.3	Hyperglycaemia

where $u(t)$ (pmol/kg/min) represents injected insulin flow, k_d is called degradation constant, k_{a1} and k_{a2} are absorption constants.

2.8. Subcutaneous glucose subsystem

The delay of the sensor was modeled with a system of first order:

$$\dot{G_M}(t) = k_{sc}G(t) - k_{sc}G_M(t); \quad (27)$$

where G_M is the subcutaneously measured glucose concentration.

3. Improved APC for diabetes care

Model Predictive Controllers need future process responses to be specified a priori. According to Grosman, Dassau, Zisser, Jovanoviè, and Doyle (2010), there are four ways of achieving this goal: fixed set-point, zone, reference trajectory and funnel. For the problem of diabetes, a fixed set-point is not as realistic as a specified zone. A normal subject is supposed to have higher or lower glycaemia depending on the situation. Therefore a zone control would be a more suitable solution in this case study. The followed approach in this work uses a combination of two of the aforementioned strategies: a reference trajectory of a healthy subject and a zone defined by upper and lower bounds.

The main control structure used here involves a commutation between a linear time-varying robustness filter (RF) in the feedback path of the control loop and an adaptive predictive controller (APC). The decision of which of both modes has to work is based on specific indicators (z_N and s_1) that will be explained later. They are closely related to the state of the subject which is checked every sampling time. For further details as the convergence and stability of the control system the reader should see Zumoffen and Basualdo (2012).

According to the specific characteristics of the diabetes problem, it was necessary to introduce some important modifications to the original algorithm cited above. The controller uses an FIR model for the predictions which is adapted on-line. Because of the non-linearity and variability of our system, three internal models are used in different operating points instead of one: hypoglycaemic state (70 mg/dl), normal state (95 mg/dl) and hyperglycaemic state (151.3 mg/dl) (Table 1).

The set-point trajectory of the controller considered in this work is the blood glucose evolution of a healthy subject and when the diabetic subject's blood glucose is in the hyper-hypoglycaemic (hazardous) range, a higher weight (α) is applied to the tracking error between the desired trajectory and the predicted system output. The controller is also improved with the information given by 3 FIR models for the perturbation as Meal Announcement (60 minutes in advance). Finally, to prevent hypoglycaemic episodes a pump shut-off algorithm is used (Lee, Buckingham, Wilson, & Bequette, 2009). See the overall structure in Fig. 2. There, both the type I diabetic subject whose blood glucose is desired to be controlled and the model of the healthy subject whose blood glucose is used as reference trajectory are shown. It can be seen that the

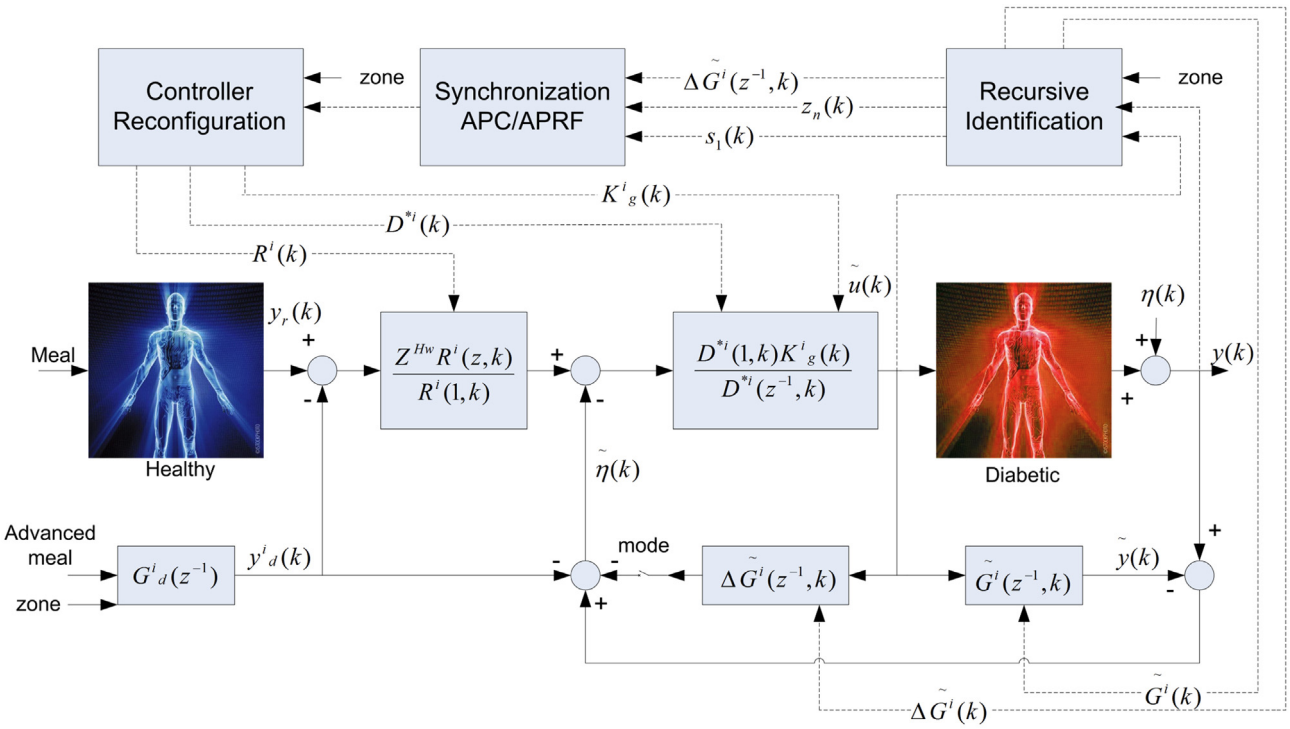


Fig. 2. Improved adaptive predictive control with robustness filter structure.

supra-index i represents the different models 1, 2 or 3 that are chosen according to the level of glucose in blood. Also important to notice is the fact that the meal announcement is given to the perturbation model 60 minutes in advance.

3.1. Adaptive predictive approach

Consider a single input, single output system with linearizable dynamic for every operation point in the working region. Therefore the predictive controller structure can be obtained by minimizing the energy criterion in Eq. (28) applied at every step k.

$$J(k) = \sum_{j=H_w}^{H_p} \alpha_j^2 e^2(k+j) + \sum_{j=0}^{H_u-1} \beta_j^2 \hat{u}^2(k+j) \tag{28}$$

where α_j is a weighting coefficient of $e(k)$ (the tracking error between a desired trajectory $y_r(k)$ and the predicted system output $\hat{y}(k)$ evaluated on the so-called prediction horizon $[H_w, H_p]$ via model), $y(k)$ corresponds to the past values of the system output and $\hat{u}(k)$ is the control action; being $\hat{u}(k)$ the calculated future control action over the so-called control horizon $[0, H_u - 1]$. Eq. (28) can consider the restrictions on $y(k)$ and $\hat{u}(k)$. The future output trajectory is originally calculated by means of an FIR model ($\hat{g}(j)$, $j = 1, \ldots, N$) of the system. The optimal control sequence $\hat{u}(k)$ can be easily deduced for the unconstrained case by searching for the global minimum of $J(k)$ with respect to $\hat{u}(k)$ over H_u.

The variation law of the weight α_j is illustrated in Fig. 4. Whenever the blood glucose concentration exceeds the healthy range (Fig. 3, the value of α_j reaches its maximum. Otherwise, it varies linearly depending on the concentration of glucose and is centered half way from the lower to the upper bound.

As the functional of Eq. (28) is quadratic, the minimum can be analytically calculated as a linear optimization problem without restrictions, so the energy criterion can be expressed as:

$$J(k) = \mathbf{e}^T(k)\mathbf{A}^2\mathbf{e}(k) + \hat{\mathbf{u}}^T(k)\mathbf{B}^2\hat{\mathbf{u}}(k) \tag{29}$$

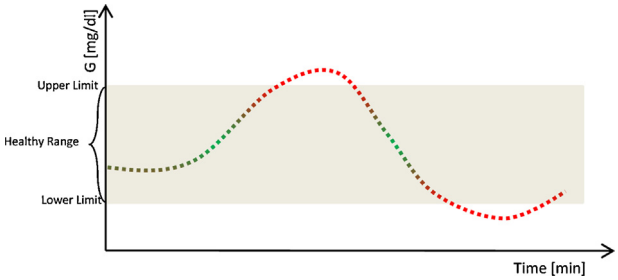


Fig. 3. Illustration of zone APCWRF as applied herein.

Then, the control law can be obtained by means of $\partial J/\partial u = 0$ and considering that only the first component of the optimal future control actions vector will be applied $\hat{\mathbf{u}}(k)$ in this sampling time.

As it can be observed from Eq. (29) this structure is suitable for the design of APC by making an on line adaptation of the linear FIR models. Using, for example, recursive least-squares identification

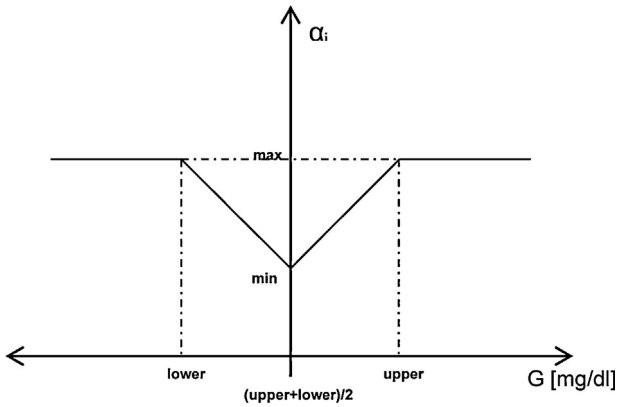


Fig. 4. The variation range of α_j.

with forgetting factor and UD factorization a suitable APC algorithm can be developed (Jordán, Basualdo, & Zumoffen, 2006).

3.2. Adaptive predictive robust filter approach

In the case of a process-model mismatch $\Delta G^i = G - \hat{G}^i \neq 0$ (where $i = 1$, 2 or 3 depending on the active model), the parallel compensation structure provides a direct way to achieve robustness of the closed loop by including a filter in the feedback path. The basic idea consists of making a correction of the predictions given by 3 nominal FIR models $G_0^i(z^{-1})$ by means of an adaptive modification. Consider that:

$$\hat{G}^i(z^{-1}, k) = \hat{\Delta G}^i(z^{-1}, k) + G_0^i(z^{-1}), \tag{30}$$

where

$$\hat{\Delta G}^i(z^{-1}, k) = \hat{\Delta g}^i(1, k)z^{-1} + \ldots + \hat{\Delta g}^i(N, k)z^{-N} \tag{31}$$

The 3 nominal FIR models $G_0^i(z^{-1})$ are available by an off-line identification procedure, their coefficients are $g_0^i(j) = [h^i(j) - h^i(j-1)]/\Delta u(k)$ and $h^i(k)$ are the endocrine system responses to step changes in the control signal $u(k)$. These nominal models generate stable controllers ($D_0^i(z^{-1})$, $R_0^i(z)$, K_g^i). Hence, rewriting the FIR model prediction as:

$$\hat{y}(k) = \sum_{j=1}^{N} \hat{\Delta} g^i(j)u(k-j) + \sum_{j=1}^{N} g_0^i(j)u(k-j) \ldots + y_d^i(k) + cgl^i + \eta(k); \tag{32}$$

(cgl is the state of the blood glucose concentration) if it is represented as a linear regression, the same structure as the APC case can be found with the same regressor $\boldsymbol{\psi}(k)$ (Jordán et al., 2006). The values of $y_d^i(k)$ were computed off-line by means of 3 nominal FIR models for the perturbation given by different meal intakes which were 60 minutes anticipated.

Then, by applying any recursive algorithm for identification purposes again, the models can be updated on-line to be used for the robust filter $\hat{\Delta G}^i(z^{-1})$. Under these conditions the static compensation are:

$$K_g^i(k) = \frac{1}{(\hat{\Delta G}^i(1, k) + G_0^i(1))} \tag{33}$$

This control strategy is initially based on stable nominal controllers, obtained from the nominal stable FIR models $G_0^i(z^{-1})$ identified off-line. Taking into account Eqs. (32)–(33) and recursive identification the control structure shown at Fig. 2 can be implemented. The final control law is:

$$\hat{U}(z) = \frac{D^{*i}(1)K_g^i}{D^{*i}(z^{-1})}\left[z^{H_w}\frac{R^i(z)}{R^i(1)}(y_r(z) - y_d^i(z)) \ldots - y(z) + \hat{y}(z) + y_d^i(z)\right]; \tag{34}$$

In accordance to Eq. (34), both the reference trajectory y_r and the meal announcement in advance signals y_d^i must be known *a priori*, at least $(H_p - H_w)$ samples into the future from the current sample.

The asymptotic performance of the adaptive control system is, in general, better than that obtained by a robust filter system, mainly if the particular tuning coefficients allow the adaptive control to guarantee asymptotic steady state stability. Therefore, if sudden dynamic changes affect significantly the closed loop response behavior, they may be much more efficiently damped down by a robust-filter system. Additionally, an asymptotic stable and good performance behavior is achievable without extra tuning parameters. It must be noted that a suitable synchronization of both approaches is useful in order to share the advantages of both modes (Jordán et al., 2006).

3.3. Adaptive predictive control with robust filter

In order to improve the performance a proper synchronization between both, the adaptive predictive control and the adaptive robust filter approaches, has to be done. It is carried out by means of an appropriate indicator function (*mode*) that enables the commutation between both algorithms automatically. It is well known that adaptive control systems may suffer from long-term instability when the manipulated variable $u(k)$ is not rich enough in order to ensure a good persistent excited regressor $\boldsymbol{\psi}(k)$ in the space $\Re^N$. In order to supervise if this condition is done, the use of proper indicators is recommended in case it would be necessary to stop the estimation at any time. For instance, the eigenvalues evolution of $P(k) = U_*(k)D_*(k)U_*^T(k)$ or $D_*(k)$ is found suitable to detect a future degradation of the estimates $\hat{\theta}(k)$; where $P(k)$ is the prediction error covariance matrix. Another useful indicator is the real variable (Jordán et al., 2006):

$$z_N = \frac{\lambda}{\lambda + \psi^T(k)U_*(k-1)D_*(k-1)U_*^T(k-1)\psi(k)} \tag{35}$$

where $0 \leq z_N \leq 1$, indicating a well excited system when it is close to 0, and a poorly excited one when it is next to 1. In addition the second indicator defined as it is shown in Eq. (36) is very useful (Jordán et al., 2006):

$$s_1(k) = \begin{array}{ll} 0.7s_1(k-1) + 0.3z_N^2(k), & (a) \\ 0.99s_1(k-1) + 0.01z_N^2(k), & (b) \end{array} \tag{36}$$

The condition (a) is valid if $s_1(k-1) \leq 0.8z_N(k)$ and (b) otherwise. Finally a set of equations is available for screening if the excitation quality was good enough for deciding to update or not the vector of parameters. In addition, a supervision of the control loop stability in adaptive predictive control mode must be done. It can be made by analyzing the roots of the polynomial $D^*(z^{-1}, k)$ at each sampling time. Thus, a complete set of conditions for developing the synchronization rule is given.

In Fig. 5 a representative flow chart of how the synchronization algorithm works is shown. The binary variable *mode* indicates which control algorithm must be executed. For each step time, the *mode* variable is analyzed, *mode* = 0 indicates that the APC approach has been executed in the previous step time. Before going on with this approach the stability of the controller $D^*(z^{-1}, k)$ is evaluated. If it is stable, then the excitation degree is checked through the condition $z_N(k) < s_1(k)$ and if it is true the APC approach is run again in the next sampling time and the controller matrices are updated. On the other hand, if the polynomial $D^*(z^{-1}, k)$ is unstable or the excitation degree is not enough, the APC algorithm is switched off and the RF approach begins to work with *mode* = 1 indicating this situation. The RF algorithm runs during a specific period (N samples) before returning to the APC approach and update the controller matrices. The recursive estimation of the complete FIR model is avoided in case of poor excitation degree, under this condition the RF is switched on. In the adaptive predictive with RF method a nominal stable controller is used together with the nominal FIR model (both computed off-line). In this case, the recursive estimation of the model residuals is always made without considering the excitation degree, since slight modifications around the nominal FIR model are performed. In Fig. 2 the block diagram corresponding to the APCWRF can be seen. The interconnection of the two methods is carried out by the synchronization structure shown at Fig. 5.

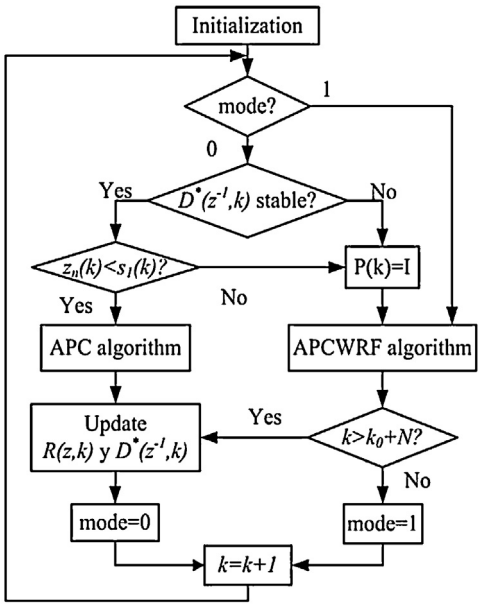


Fig. 5. APCWRF synchronization algorithm.

The commutation to the RF approach gives better robustness characteristics specially when sudden changes occur (faults, important blood glucose concentration modifications, large disturbance magnitudes, etc). Meanwhile, the APC approach is mainly suitable under small dynamic changes and normal operation conditions. When the APCWRF algorithm commutes from the RF to APC the controller matrices are updated (R and D*) and the stability is checked. The need for running the RF during N iterations (the same as the FIR model order) is performed so that the regressor vector could be entirely updated. Therefore, it is guaranteed that the complete FIR model is updated.

3.4. Reference trajectory

For the reference trajectory of the controller $y_r(k)$, the blood glucose evolution of a normal subject for the same meal intake was used. To do so, a simulated normal subject using the model described in Section 2 was submitted to the *in silico* Preclinical Trial that will be explained in Section 4. The evolution of this subject was recorded and then given to the control algorithm as reference trajectory.

3.5. Pump shut-off for hypoglycaemia

To prevent hypoglycaemic episodes a shutting-off algorithm is applied to the insulin infusion pump (Lee et al., 2009). In this case the implementation can be written as:

if $\Delta G_M(t) < 0$ & $G_M(t) < 93$ mg/dl

then $u = 0$ mU/h

where $\Delta G_M(t)$ is the first order derivative and $G_M(t)$ is the subcutaneously measured glucose concentration. Whenever the glucose concentration is below 93 mg/dL with a negative rate of change, the insulin pump is turned off.

4. The *in silico* preclinical trial

The performance of the controller was tested on a 1-day virtual protocol (Patek et al., 2009). First of all, the type I diabetic subject received an insulin infusion so that his basal blood glucose reached the basal blood glucose of the normal subject (95 mg/dl). Then, the subject is submitted to the following perturbations (example for an adult):

1. Subject's blood glucose steady at 95 mg/dl at 18:00 Day 1.
2. Control loop is closed at 21:00 Day 1.
3. At 7:30 Day 2, the subject has breakfast lasting about 2 min with a carbohydrate (CHO) content of 50 g.
4. At approximately noon (12:00) Day 2, the subject takes a lunch meal containing 65 g CHO. Meal duration is 15 min.
5. At 18:00 Day 2, the subject takes a dinner meal containing 80 g CHO. Meal duration is 15 min.

This scenario changes for adolescents and children just in the amount of CHO they eat (adolescents: 40/50/65 g; children: 25/30/40 g).

5. List of experiments

Different experiments were conducted as follows:

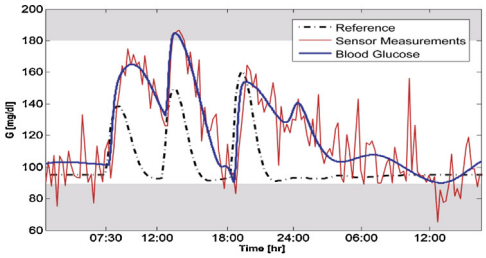
1. Experiment I: Adaptive Predictive Control with a step-like changing of α_j.
2. Experiment II: Adaptive Predictive Control with a linear changing of α_j with Meal Announcement in advance.
3. Experiment III: Adaptive Predictive Control with a linear changing of α_j without Meal Announcement.
4. Experiment IV: Adaptive Predictive Control with a linear changing of α_j with a delayed Meal Announcement.
5. Experiment V: Adaptive Predictive Control with a linear changing of α_j with Meal Announcement in advance adjusted with only two parameters: the maximum of α_j and the permitted rate of change of the pump.

6. Results

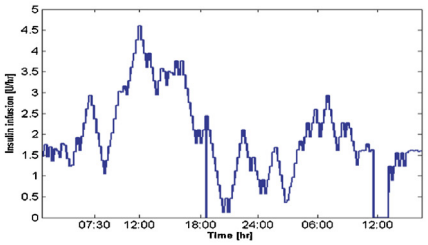
In this section, the performance of the system presented will be tested mainly using the Control Variability Grid Analysis, (Magni et al., 2008). It is a graphical representation of min/max glucose values in a population of subjects either real or virtual. The CVGA provides a simultaneous assessment of the quality of glycaemic regulation in all subjects. As such, it has the potential to play an important role in the tuning of closed-loop glucose control algorithms and also in the comparison of their performances. So, it is a method for visualization of the extreme glucose excursions caused by a control algorithm in a group of subjects, with each subject represented by one data point for any given observation period. The testing scenario is the *in-silico* preclinical trial of Section 4 on all the type I diabetic subjects from the UVa/Padova Simulator of Section 2.

Everything was implemented in Matlab R2012b, version 8.0.0.783, under a Windows 7 64 bits interface on an Intel Core i7-3770 CPU 3.40 GHz. The integration method was a variable-step ode45 Dormand-Prince and the elapsed time for each simulation was 8.747449 seconds.

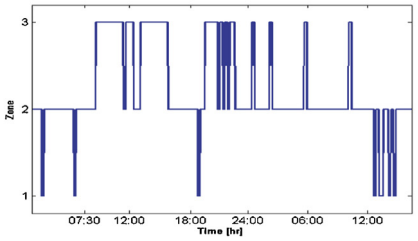
Fig. 6 shows the performance and the evolution of some variables of the control strategy applied in an Adult subject from the simulator submitted to Experiment II (Section 5). It is worth mentioning that this adult experiences a reduction in insulin sensitivity by 10 % at 18:00 h(Eren-Oruklu et al., 2009). This has been done by modifying parameters V_{mx} and p_{2u} from the simulator (Eqs. (19) and (20)). Both parameters were chosen because they are related to the insulin sensitivity of the patient. In Fig. 6(a) the blood glucose concentration of the adult type I diabetic subject using the artificial pancreas can be seen. The erratic signal is the erroneous



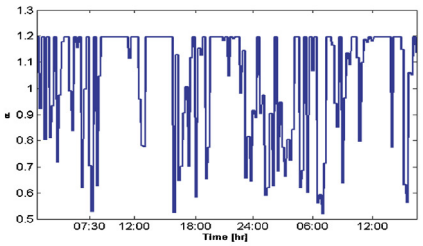
(a) Blood glucose concentration evolution



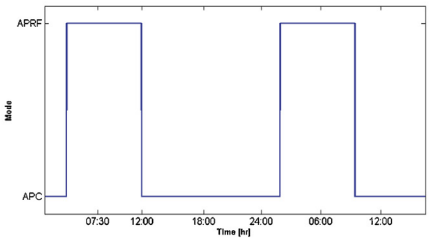
(b) Insulin infusion to the diabetic subject as a function of time.



(c) Models changing during the trial using the proposed controller.



(d) Variation of α_j during the trial.



(e) Controlling mode selection.

Fig. 6. Controller performance for the adult diabetic subject ♯1. (a) Blood glucose concentration evolution. (b) Insulin infusion to the diabetic subject as a function of time. (c) Models changing during the trial using the proposed controller. (d) Variation of α_j during the trial. (e) Controlling mode selection.

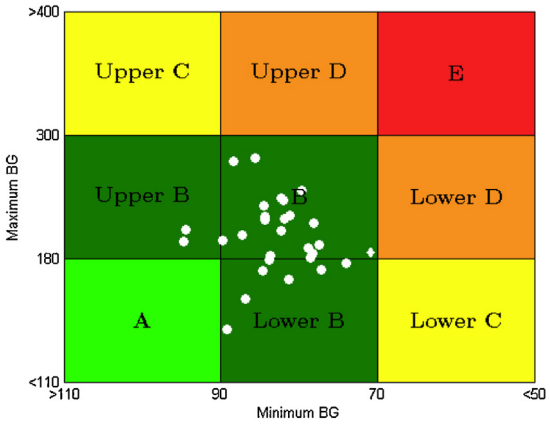


Fig. 7. CVGA for Experiment I.

information given by the sensor to the controller. A non-white Gaussian noise representative of commercially available blood glucose monitoring systems was added to the subcutaneous signal as in Breton and Kovatchev (2008). The white zone would be the healthiest one, like the A zone of the CVGA (Fig. 7). The corresponding insulin infusion is in Fig. 6(b). Note that in two occasions the pump shut-off algorithm has been activated. In this case, the algorithm has used the three models during the trial depending on the blood glucose level (Fig. 6(c)). The variation of α_j during the trial can be seen in Fig. 6(d). In the case proposed here, the upper bound when hyperglycaemia should be avoided is fixed in 140 mg/dl, and the lower bound is 94 mg/dl (risk of hypoglycaemia). The last, Fig. 6(e), shows the selected control mode based on the synchronization algorithm of Fig. 5.

The next figures illustrate how the controller reacted against the different scenarios proposed in Section 5. The first experiment was done using a step-like change in the value of α_j. So, it switches between the upper bound and the lower bound which were determined for each subject. Seeing the CVGA from Fig. 7, it can be concluded that the overall performance of the controller is fairly good. Every subject distributed among zone A and B means that the glycaemic excursions they underwent were acceptable for an artificial pancreas of these characteristics. If we compare this result to that of Fig. 8, a marked improvement can be seen. The use of a linearly varying value of α_j has let many subjects be in zone A which is the safest one. Experiments III and IV, show what would happen if the subject forgets to announce a meal in advance. See that in both Figs. 9 and 10, many subjects reached dangerous zones, meaning that their glycaemia was either too low or too high. From

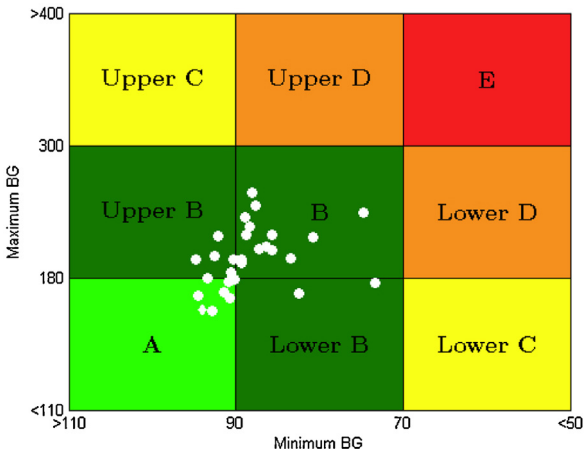


Fig. 8. CVGA for Experiment II.

Table 2
APCWRF Parameters Adjustment for Experiment V

Variable	H_w[samp]	H_p[samp]	H_u[samp]	T_s[min]	**B**	λ	Upper [mg/dl]	Lower [mg/dl]	Min
Value	1	4	1	15	**1.5**	0.9836	140	94	1

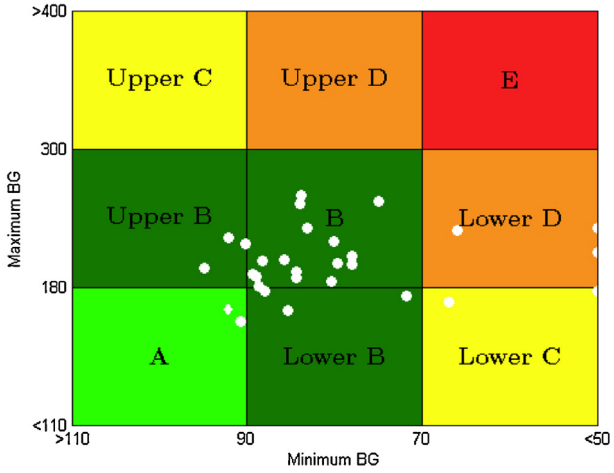


Fig. 9. CVGA for Experiment III.

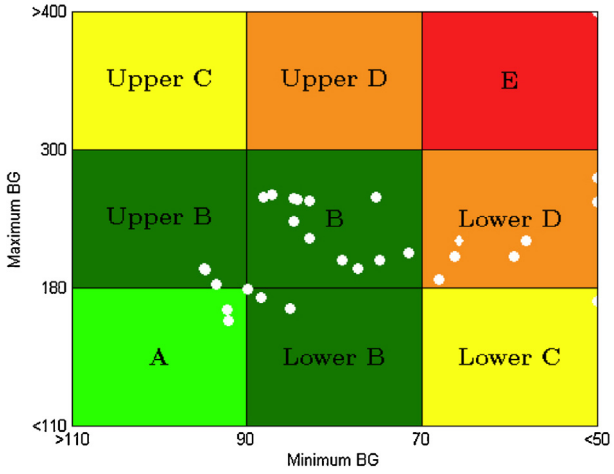


Fig. 10. CVGA for Experiment IV.

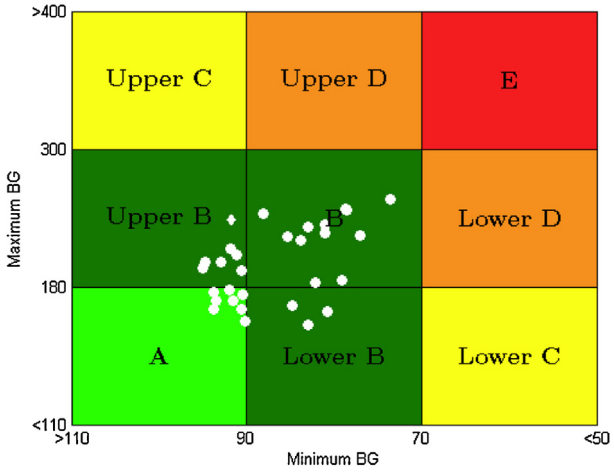


Fig. 11. CVGA for Experiment V.

both cases, evidently, the worst scenario is when the subject use a delayed meal announcement.

Finally, experiment IV was intended to facilitate the tuning of the controller to new subjects. For this purpose, the mean of all the parameters were calculated. In Table 2, they can be seen. Leaving these parameters fixed, every subject were re-adjusted by changing the maximum value of α_j and the rate of change of the insulin infusion from the pump alone. This resulted in a quite good performance of the controller for all the subjects as shown in Fig. 11.

7. Conclusions

In accordance with the good results shown, it can be concluded that the improved APCWRF, thinking specifically on the diabetic subject requirements, can be considered as a good alternative for the Artificial Pancreas. It could take into account the main difficulties inherent to the system nonlinearities, long-term and daily variations, risks of hyper and hypoglycaemic events, etc. In addition, the reference trajectory proposed of a healthy person, was helpful as a guide to tune the controller to achieve an acceptable glycaemia dynamic behaviour. These results were obtained thanks to the inclusion of a perturbation model acting as meal announcement. It is remarkable the importance of the subject remembering to announce meals correctly. This is evident from the results obtained with Experiments III and IV. From Experiment V it can be concluded that an easy to tune controller was presented and validated with the database of 30 subjects. Even though the results from this experiment did not overcome the ones from Experiment II, the simplicity reached when requiring only two parameters to adjust the control algorithm to a new subject made it worthwhile.

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