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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.

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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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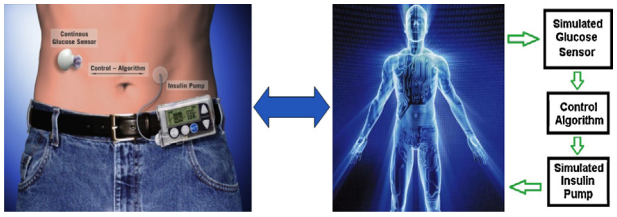

Fig. 1. Artificial pancreas: here the work is done *in silico*. By means of computer simulation a virtual subject, a simulated sensor and insulin pump are commanded by the controller proposed herein so that its performance could be safely tested.

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.

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