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Artificial Pancreas Systems: An Integrated Multivariable Adaptive Approach

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Abstract: An artificial pancreas (AP) system with a hypoglycemia early alarm system and adaptive control system based on multivariable recursive time series models is developed. The inputs of the model include glucose concentration (GC) and physiological signals that provide information about the physical activities and stress of the patient. The stability of the recursive time-series models is guaranteed by a constrained optimization method. Generalized predictive control (GPC) is used to regulate GC. Experiments in a clinical setting illustrate the performance of the AP and compare it to open-loop regulation by the patient. Results show that the AP can regulate GC successfully and prevent hypoglycemia in spite of exercise.

Keywords: Type 1 Diabetes, Artificial Pancreas, Adaptive Control, Hypoglycemia Alarm, Integrated Systems

1. INTRODUCTION

Artificial pancreas systems enable automatic control of blood glucose concentrations (GC) of patients with Type 1 Diabetes (T1D) by providing substitute endocrine functionality of a healthy pancreas. Patients with T1D administer 3-5 insulin injections (usually pre-meal) per day or use a manual insulin pump to keep their GC in normal range (70-180 mg/dl). The success of maintaining GC in normal range by manual injection therapies has been limited. Changing life style conditions such as stress, illness, or physical activity are some factors that affect the performance of manual regulation. Diabetes can cause long-term complications such as cardiovascular diseases, kidney failure, retinopathy, neuropathy, and problems with wound healing. Diabetes has been reported as the seventh leading cause of death in the United States, and the total cost of diagnosed diabetes has been estimated to be $245 billion in 2012 (American Diabetes Association, 2013). Better regulation of GC will reduce the morbidity caused by diabetes and its complications, and medical expenditures.

Use of proportional-integral-derivative (PID) controllers for implementing an artificial pancreas showed the advantages of closed-loop control (Bequette, 2005) but the mean GC remained similar in open-loop and PID closed-loop control which also caused hypoglycemia 2-3 hours post meals (Steil et al., 2006). Model-based control strategies provided better performance by handling delays in GC measurement and insulin delivery and constraints on input and output signals. Model-predictive controllers (MPC) used in vivo (Bruttomesso et al., 2009; Clarke et al., 2009; Breton et al., 2012) needed modification of model parameters for different patients in these studies. Meal information (time and amount) was provided as known disturbances. Adaptive control strategies based on generalized predictive control (GPC) were also proposed (Turksoy et al., 2013a; El-Khatib et al., 2010). Recursive least square (RLS) parameter estimation was used to identify unknown parameters of time-series models in (Turksoy et al., 2013a; El-Khatib et al., 2010) without providing any information about meals. Glucagon was used as a second manipulated variable with a proportional-derivative controller to prevent hypoglycemia events (El-Khatib et al., 2010).

Recursive time-series models are a powerful tool for describing the dynamics of GC (Turksoy et al., 2013a; El-Khatib et al., 2010) and for glucose prediction and hypoglycemia alarm systems (Turksoy et al., 2013b; Eren-Oruklu et al., 2012; Sparacino et al., 2007). Any unconstrained identification method may give unstable models because of process and measurement noise even when the process is known to be stable. Systems such as GC are sensitive to disturbances such as meals and physical activities. Thus it is possible to identify unstable models describing GC dynamics with regular identification methods (RLS, extended least square (ELS) method, and subspace identification), compromising controller or hypoglycemia alarm system performance by using predictions from an unstable model.

Fear of hypoglycemia is a major concern of patients in using AP systems. Many closed-loop studies with various

control algorithms have resulted in mild or severe hypoglycemic episodes (Steil et al., 2006; Schaller et al., 2006; Bruttomesso et al., 2009; Clarke et al., 2009). Mathematical models for the prediction of plasma insulin levels have been incorporated into closed-loop studies for hypoglycemia prevention (Steil et al., 2011; Ruiz et al., 2012; El-Khatib et al., 2010; Turksoy et al., 2013a). Hypoglycemia prediction-based pump suspension methods have been noted to decrease the occurrence of hypoglycemia (Buckingham et al., 2009; Elleri et al., 2010). Bihormonal closed-loop studies (El-Khatib et al., 2010; Ward et al., 2011) using glucagon and insulin have also been proposed for hypoglycemia prevention. Semi-automated hybrid systems (Steil et al., 2011; Weinzimer et al., 2008; Elleri et al., 2013; Breton et al., 2012) have been reported to reduce the increase in postprandial glucose levels and subsequently decrease insulin-induced postprandial hypoglycemia. Although the reported methods decreased the time spent in hypoglycemia, complete avoidance of hypoglycemia was not achieved, and additional carbohydrate (CHO) supplements were needed for treatment of some of hypoglycemic episodes.

An integrated AP with a hypoglycemia early alarm (HEA) system and GPC based control system is reported in this paper. Both systems rely on multivariable recursive time series models developed by extending RLS methods with a constrained optimization method that guarantees model stability. Modifications are made to classical GPC. Physiological signals collected from a sports armband are used to improve the prediction of GC (Eren-Oruklu et al., 2012) and to indicate exercise or sleep to the controller for computing the appropriate insulin infusion rate. Section 2 describes system identification. The HEA system and the GPC system are introduced in Sections 3 and 4. The results comparing the open-loop and closed loop insulin regulation of one subject in a clinical study is presented in Section 5. Discussion and conclusions are given in Sections 6 and 7.

2. SYSTEM IDENTIFICTION

2.1 Recursive Time-Series Models

Recursive time-series models can describe the time-varying dynamics of blood GC (BGC) by adapting the model with every new measurement. An autoregressive moving average model with exogenous inputs (ARMAX) is used to describe BGC dynamics. ARMAX models can easily be extended to multi-input-multi-output systems. An ARMAX model is:

$$A(q^{-1})y(k) = B_i(q^{-1})u_i(k-1-d_i) + C(q^{-1})\epsilon(k) \quad (1)$$

where $y(k)$ is the observation (system output) at time k, $u_i(k-1)$ the i^{th} input, $\epsilon(k)$ white noise, d_i the delay term for input i.

$$A(q^{-1}) = 1 + a_1q^{-1} + a_2q^{-2} + ... + a_{n_A}q^{-n_A} \quad (2)$$

$$B_i(q^{-1}) = b_{0_i} + b_{1_i}q^{-1} + b_{2_i}q^{-2} + ... + b_{n_{B_i}}q^{-n_{B_i}} \quad (3)$$

$$C(q^{-1}) = 1 + c_1q^{-1} + c_2q^{-2} + ... + c_{n_C}q^{-n_C} \quad (4)$$

where q^{-1} is the backward shift operator, and n_A, n_{B_i}, n_C are model orders to be determined from data. Writing the ARMAX model in linear regression form:

$$\hat{y}(k) = \phi(k)^T\hat{\theta}(k) \quad (5)$$

$$\begin{aligned}\phi(k) = [&-y(k-1) \cdots -y(k-n_A) \;\; u_1(k-1-d_1), \\ &\cdots u_1(k-n_{B_1}-d_1) \cdots u_m(k-1-d_m), \\ &\cdots u_m(k-n_{B_m}-d_m) \;\; e(k-1) \cdots e(k-n_C)]^T\end{aligned} \quad (6)$$

$$\begin{aligned}\hat{\theta}(k) = [&a_1 \;\; \cdots \;\; a_{n_A} \;\; b_{0_1} \;\; \cdots \; b_{n_{B_1}} \\ &\cdots \qquad b_{0_m} \;\; \cdots \; b_{nB_m} \;\; c_1 \;\; \cdots \;\; c_{n_C}]^T\end{aligned} \quad (7)$$

where $\phi(k)$ and $\hat{\theta}(k)$ are the vectors of past observations and model parameters, respectively. The white noise term in Eq (6) is replaced with model error $e(k)$ since the former is an unknown signal:

$$e(k) = y(k) - \hat{y}(k) = y(k) - \phi(k)^T\hat{\theta}(k) \quad (8)$$

The coefficients in Eqs (1)-(4) are recomputed with every new measurement and the model is used until the next measurement.

2.2 State Space Representation of RLS

Recursive least square (RLS) parameter estimation is used to identify the unknowns in Eq (7). When the disturbance acting on the system is non-stationary, RLS may estimate coefficients that are outside the stability region. A constrained RLS method must be used to guarantee model stability. To apply the stability constraints to RLS, the time series model is written in state space form.

$$\begin{aligned}X(k) &= \tilde{A}X(k-1) + \tilde{B}\tilde{u}(k-1) + \tilde{K}e(k) \\ y(k) &= \tilde{C}X(k-1) + \tilde{D}\tilde{u}(k-1) + e(k)\end{aligned} \quad (9)$$

with the state matrix $\tilde{A}$

$$\tilde{A} = \begin{bmatrix} -[a_1 \cdots a_{n_A}] & [b_{1_1} \cdots b_{B_1}] & \cdots & [b_{1_m} \cdots b_{B_m}] & [c_1 \cdots c_{n_C}] \\ I_{p\times p} \;\; 0_{p\times 1} & 0_{p\times r_1} \;\; 0_{p\times 1} & \cdots & 0_{p\times r_m} \;\; 0_{p\times 1} & 0_{p\times s} \;\; 0_{p\times 1} \\ 0_{1\times p} \;\; 0 & 0_{1\times r1} \;\; 0 & \cdots & 0_{1\times r_m} \;\; 0 & 0_{1\times s} \;\; 0 \\ 0_{r_1\times p} \;\; 0_{r_1\times 1} & I_{r_1\times r_1} \;\; 0_{r_1\times 1} & \cdots & 0_{r_1\times r_m} \;\; 0_{r_1\times 1} & 0_{r_1\times s} \;\; 0_{r_1\times 1} \\ \vdots \;\; \vdots & \vdots \;\; \vdots & \cdots & \vdots \;\; \vdots & \vdots \;\; \vdots \\ 0_{1\times p} \;\; 0 & 0_{1\times r1} \;\; 0 & \cdots & 0_{1\times r_m} \;\; 0 & 0_{1\times s} \;\; 0 \\ 0_{r_m\times p} \;\; 0_{r_m\times 1} & 0_{r_m\times r_1} \;\; 0_{r_m\times 1} & \cdots & I_{r_m\times r_m} \;\; 0_{r_m\times 1} & 0_{r_m\times s} \;\; 0_{r_m\times 1} \\ 0_{s\times p} \;\; 0_{s\times 1} & 0_{s\times r_1} \;\; 0_{s\times 1} & \cdots & 0_{s\times r_m} \;\; 0_{s\times 1} & I_{s\times s} \;\; 0_{s\times 1} \end{bmatrix} \quad (10)$$

where $p = n_A - 1$, $r_i = n_{B_i} - 2$ (for $i = 1, \cdots, m$) and $s = n_C - 1$

$$X(k-1) = \begin{bmatrix} \begin{bmatrix} y(k-1) \\ y(k-2) \\ \vdots \\ y(k-n_A) \end{bmatrix} \\ \begin{bmatrix} u_1(k-1-1) \\ u_1(k-1-2) \\ \vdots \\ u_1(k-1-n_{B_1}) \end{bmatrix} \\ \vdots \\ \begin{bmatrix} u_m(k-1-1) \\ u_m(k-1-2) \\ \vdots \\ u_m(k-1-n_{B_m}) \end{bmatrix} \\ \begin{bmatrix} e(k-1) \\ e(k-2) \\ \vdots \\ e(k-n_C) \end{bmatrix} \end{bmatrix} \quad \tilde{B} = \begin{bmatrix} b_{0_1} & \cdots & b_{0_m} \\ 0 \;\; 0_{1\times(m-2)} & & 0 \\ \vdots & \vdots & \vdots \\ 0 \;\; 0_{1\times(m-2)} & & 0 \\ 1 \;\; 0_{1\times(m-2)} & & 0 \\ 0 \;\; 0_{1\times(m-2)} & & 0 \\ \vdots & \vdots & \vdots \\ 0 \;\; 0_{1\times(m-2)} & & 0 \\ \vdots & \vdots & \vdots \\ 0 \;\; 0_{1\times(m-2)} & & 1 \\ 0 \;\; 0_{1\times(m-2)} & & 0 \\ \vdots & \vdots & \vdots \\ 0 \;\; 0_{1\times(m-2)} & & 0 \\ 0 \;\; 0_{1\times(m-2)} & & 0 \\ 0 \;\; 0_{1\times(m-2)} & & 0 \\ \vdots & \vdots & \vdots \\ 0 \;\; 0_{1\times(m-2)} & & 0 \end{bmatrix} \quad (11)$$

$$\tilde{D} = [\, b_{0_1} \;\cdots\; b_{0_m} \,] \;\; \tilde{u}\,(k-1) = \begin{bmatrix} u_1(k-1) \\ \vdots \\ u_m(k-1) \end{bmatrix} \quad (12)$$