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ADAPTIVE CONTROL STRATEGY FOR GLUCOSE REGULATION USING RECURSIVE LINEAR MODELS

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Abstract: Using frequently sampled blood glucose measurements (at 5 min intervals), low-order recursive linear time series models have been developed for the prediction of future blood glucose concentrations. Such predicted glucose values are then integrated with model based control algorithms, such as GPC and LQC, for adjusting the required insulin infusion rates with an automated insulin pump. Since the models are derived from patients' own glucose data, the proposed algorithm can dynamically adapt to inter- and intra-subject variability.

Keywords: recursive identification, adaptive control, ARMA parameter estimation

1. INTRODUCTION

Diabetes is a disease characterized by degradation of insulin secretion, leading to insufficient regulation of blood glucose in the body. For patients with type 1 diabetes, this impairment is total which makes patients completely dependent on exogenous insulin. The current therapy for insulin dependent subjects includes 3 to 5 daily insulin injections or insulin infusion by a manual pump, with the insulin dose tuned according to 3 to 7 daily blood glucose measurements, diet and physical activity conditions. The Diabetes Control and Complication Trial study (DCCT 1993) has shown that keeping the blood glucose levels within tight control minimizes the progression of diabetes related complications. However, due to the open loop nature of the current therapy and unexpected daily life disturbances (e.g. change in diet, exercise, stress or illness), patients frequently encounter large variations in blood glucose concentration which may lead to hypo/hyperglycemic episodes. To avoid such large fluctuations, patients are generally forced to follow a strict diet and a very rigid lifestyle. Therefore, a novel therapy that gives the patient a freedom in daily life is of great importance. Such therapy may be possible by totally closing the loop (with no-need of patient intervention) with an automated artificial pancreas, consisting of a continuous blood glucose measuring device, an insulin infusion pump and a control algorithm. In this paper, we focus on the last component of such a device and propose a control algorithm based on adaptive control concept which makes use of a linear model developed from a patient's own glucose data.

Modeling glucose-insulin dynamics has been a flourishing research area (Cobelli *et al.* 1982, Sorensen 1985, Hovorka *et al.* 2002). By prediction of future blood glucose values, the primary objective of such models is to mimic the natu-

ral feedback between glucose and insulin in the body. Due to the nonlinear nature of glucose-insulin dynamics and lack of extensive real patient data, proposed physiological models are generally nonlinear with too many parameters to be identified and are representative of only an average subject under specific conditions. Most of the works in literature proposing model-based control strategies for closing the loop, make use of such physiological models for future blood glucose predictions (Parker *et al.* 1999, Lynch and Bequette 2001, Hovorka *et al.* 2004). However, for the development of an automated artificial pancreas, a more realistic description that takes into account the intra- and inter-subject variability is required. Taking this requirement as the primary objective, simple linear models derived from patient's own frequently sampled blood glucose data are developed for future blood glucose prediction, in the first part of this research. The proposed strategy for model identification is based on glucose time series analysis, and for the disturbance rejection (e.g. effect of meal or exercise) it is incorporated with a change detection method.

Finally, we focus on the development of a control strategy for the case of subcutaneous measurement of glucose and intraperitoneal administration of insulin. Model based control strategy where the model is adaptively identified from the frequently sampled patient blood glucose data, is proposed. The results are demonstrated using two well known control algorithms: generalized predictive control (GPC), and linear quadratic Gaussian control (LQGC).

2. METHODS

2.1 The Model for Blood Glucose Prediction

Glucose prediction for disturbance free conditions is described first. Then a model identification algorithm with a disturbance rejection strategy is proposed.

Low-Order Linear Models for the Rigid Lifestyle Case: The intensive insulin therapy, in a way restricts patients to follow a rigid lifestyle. Patients are constrained to eat at specific time and specific amount of food, and to avoid unexpected physical activity or stress conditions. In literature, the proposed physiological models describing glucose-insulin dynamics are capable to illustrate such disturbance free conditions. However, even for the strict lifestyle case, the main restriction of these nonlinear models is the increased number of parameters to be identified, which makes it difficult to isolate the effect of inter-individual variations. To overcome this limitation, we propose development of linear models from patients' own glucose data in the form of time series. The considered models include; Autoregressive (AR), Autoregressive Moving Average (ARMA) and Subspace State Space Models:

$$AR: \quad A(q^{-1}) \cdot y_k = e_k \tag{1}$$

$$ARMA: \quad A(q^{-1}) \cdot y_k = C(q^{-1}) \cdot e_k \tag{2}$$

$$State\ Space: \quad \begin{aligned} x_{k+1} &= A \cdot x_k + w_k \\ y_k &= C \cdot xk + v_k \end{aligned} \tag{3}$$

Here y_k denotes the output variable of interest at time instant k, which corresponds to blood glucose measurement, and x_k is the process state vector. The e_k and w_k are the process noise, and v_k is the measurement noise. And all are assumed to be zero mean white noise. (q^{-1}) is the back shift operator, where the polynomials $A(q^{-1})$ and $C(q^{-1})$ are represented by: $A(q^{-1}) = 1 + a_1 \cdot q^{-1} + \ldots + a_{n_A} \cdot q^{-n_A}$, and $C(q^{-1}) = 1 + c_1 \cdot q^{-1} + \ldots + c_{n_C} \cdot q^{-n_C}$.

Only low-order models and with time-invariant parameters are considered. The idea of using such simple linear models is to test whether the near future glucose values can be predicted using only the previous glucose readings regardless of the meal, and insulin administration, or physiological conditions of the subject. In the results section, it will be shown that models with order of 3 are satisfactory to capture the 24-hour glucose dynamics.

Recursive Linear Models for the Unexpected Disturbance Case: Different from the previous section, here we focus on strategies that provide the subject with freedom in his/her daily life. Daily life disturbances, such as change in the diet, illness, stress, physical activity conditions may occur unexpectedly and instantaneously. In such situations, time-invariant models will not work well enough. The proposed modelling strategy is the Recursive Least Square (RLS) method with a forgetting factor, λ:

$$y_k = \varphi_k^T \cdot \theta_k + e_k \tag{4}$$

$$\widehat{\theta_k} = \widehat{\theta_{k-1}} + K_k \left\{ y_k - \varphi_k^T \cdot \widehat{\theta_{k-1}} \right\} \tag{5}$$

$$K_k = \frac{P_{k-1} \cdot \varphi_k}{\lambda + \varphi_k^T \cdot P_{k-1} \cdot \varphi_k} \tag{6}$$

$$P_k = \frac{1}{\lambda} \cdot \left[P_{k-1} - \frac{P_{k-1} \cdot \varphi_k \cdot \varphi_k^T \cdot P_{k-1}}{\lambda + \varphi_k^T \cdot P_{k-1} \cdot \varphi_k} \right] \tag{7}$$

where y_k is the output of interest, φ_k describes the vector of past observations at k^{th} time step, and θ_k corresponds to vector of model parameters while the $\widehat{\theta_k}$ is its estimate. The terms K_k and P_k stand for smoothing parameter and estimate of error variance, respectively. At each sampling time, the linear model is updated based on the blood glucose measurements, meantime the forgetting factor puts relative weights on the past

data sequence and makes the more recent data predominant in model parameter estimation.

Additionally, in order to capture drastic changes and to provide a quicker respond to such changes, the proposed RLS algorithm is interfaced with a change detection method. When change in model parameters is detected, to ensure quicker convergence to new parameter values, the forgetting factor is decreased to a smaller value. This way, the past observations are rapidly excluded, and the model is derived from the more recent and fresh data only. The proposed change detection method can be described by null and alternate hypotheses given as:

$$\begin{aligned} H_0: &\quad E(\widehat{\theta_k}) = \widehat{\theta_0} \quad for\ N < k < N + N_W \\ H_1: &\quad E(\widehat{\theta_k}) \neq \widehat{\theta_0} \quad for\ N < k < N + N_W \end{aligned} \tag{8}$$

where $E(\widehat{\theta_k})$ denotes the expected value of the parameter estimate at time instant k. $\widehat{\theta_0}$ is the vector of unbiased parameter estimates computed by RLS algorithm using the data till time instant N. N_W is the window size for change detection persistency check. When a persistent change within the window size is detected, the λ is reduced to a smaller value and $\widehat{\theta_0}$ is replaced with its new estimate.

Since the model is derived from a patient's own glucose data and since in response to changes or disturbances, the model is updated recursively with a forgetting factor and a change detection algorithm, the proposed algorithm can dynamically adapt to inter- and intra-subject variability.

2.2 The Control Strategy

The proposed control algorithm is based on adaptive control concept which makes use of a linear model developed from patients own glucose data, figure 1. At each step with the new coming glucose measurement, the model parameters are updated, and the estimation of future time course of blood glucose is performed, using the RLS method described. Then the necessary insulin infusion rate that minimizes the deviation of the predicted glucose values from a set point trajectory is determined using a model-based control law. For the demonstration of the effectiveness of the proposed algorithm, GPC and LQC methods are selected for the computation of the control action.

Generalized Predictive Control (GPC) Strategy: Differently from equations 1-3, the time series model should also include an input (insulin infusion rate) term, for the close-loop conditions. Based on GPC, the glucose dynamics in response to insulin infusion is described by an autoregressive integrated moving-average model (ARIMAX) in the form of:

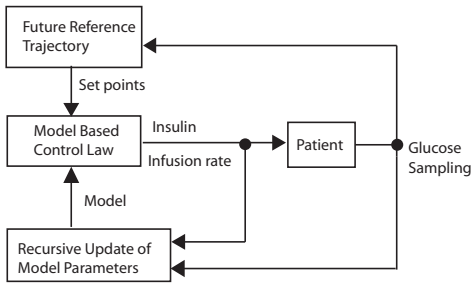

Fig. 1. Block diagram of the control strategy

$$A(q^{-1}) \cdot y_k = B(q^{-1}) \cdot u_{k-d} + \frac{C(q^{-1})}{\Delta} \cdot e_k \tag{9}$$

where y_k, e_k, $A(q^{-1})$, and $C(q^{-1})$ have the same definition as in equation 1 or 2. Similarly, polynomial B is given by $B(q^{-1}) = b_0 + b_1 \cdot q^{-1} + \ldots + b_{n_B} \cdot q^{-n_B}$. The term u_{k-d} represents the insulin infusion rate with d units of delay in action, and Δ is the difference operator, $(1 - q^{-1})$.

Using the ARIMAX model, the j-step ahead prediction of blood glucose concentration ($\widehat{y}(k+j|k)$) is computed as a function of past glucose measurements, and past and future control actions (insulin infusion rates). For detailed description of the formulations please refer to (Bitmead *et al.* 1990). The optimum control law is given by minimization of the following quadratic function:

$$\begin{aligned} J(Ny, Nu) = \sum_{j=1}^{Ny} q \cdot [\widehat{y}(k+j|k) - y_{ref}(k+j)]^2 \\ + \sum_{j=1}^{Nu} r \cdot [\Delta u(k+j-1)]^2 \end{aligned} \tag{10}$$

where $y_{ref}(k+j)$ is the desired reference trajectory for the output (glucose concentration). Ny is output prediction horizon and Nu is the control horizon with $\Delta u(k+Nu) = \Delta u(k+Nu+1) = \ldots = 0$. q and r are the weights on output and input terms respectively. Due to the technical restrictions of insulin pumps and safety limitations, constraints on control action are added. The ultimate control law is found by solution of the following quadratic programming (QP) problem:

$$\begin{aligned} \underset{\Delta u}{min} \quad & J(Ny, Nu) \\ s.t.\ & u_{min} \leq u(k+j) \leq u_{max} \\ & \Delta u(k) \leq \Delta_{max} \end{aligned} \tag{11}$$

The limits on infusion rate due the technical restrictions are $0\ mU/min \leq u(t) \leq 67\ mU/min$, and to avoid infusion of an excessive amount of insulin at a time: $\Delta_{max} = u_{max}/3$. Note that, even tough the QP problem gives control action for Nu step ahead, only the first one is implemented and the procedure is repeated at each sampling step.

Linear Quadratic Control (LQC) Strategy: Based on optimal control theory, LQC gives the control law as

$$u_k = -K \cdot \widehat{x_k} \tag{12}$$

which minimizes the quadratic cost function

$$J = \sum_{k=0}^{\infty} \left(x_k^T \cdot Q \cdot x_k + u_k^T \cdot R \cdot u_k \right)$$
$$s.t.\ x_{k+1} = A \cdot x_k + B \cdot u_k \tag{13}$$
$$y_k = C \cdot x_k + D \cdot u_k$$

over infinite prediction horizon subject to the process state space model. $\widehat{x_k}$ is the optimal (Kalman) estimate of the process states.

Since the LQC requires the model in a state space representation, the time series model from the proposed RLS algorithm is converted to a minimum realization of state space model at each step. Additionally, at each step, the constraints on control action are checked.

Reference Trajectory: At each step, depending on the current glucose measurement, a time-varying trajectory is selected. The objective is to avoid any sudden decrease in blood glucose concentration that can be caused by high insulin infusion rates, and to have a faster response during hypoglycemic conditions. Therefore, similar to (Hovorka *et al.* 2004), for high glucose levels, a gradually decreasing target trajectory is selected, while for low glucose levels an exponentially increasing trajectory is used to make the control action more aggressive.

3. RESULTS AND DISCUSSION

Computational studies are conducted to assess the effectiveness of the proposed linear recursive algorithm for prediction of future blood glucose concentrations. Then, the reliability of such models is tested in closed loop using model based control strategies described in the previous section.

3.1 Blood Glucose Prediction with Recursive Models

The results of the proposed algorithms for glucose prediction are validated on two sources of data: (1) real subject blood glucose concentration data collected at high frequency (5 minute intervals); (2) simulation data on blood glucose concentration of a virtual subject with type 1 diabetes.

The real patient data consists of frequently sampled blood glucose measurements of healthy, glucose intolerant and type 2 diabetic subjects. During data acquisition, patients were hospitalized and subjected to a predefined, fixed diet and disturbance free conditions. Subject's blood glucose concentration was monitored with a continuous glucose monitoring system (CGMS System $Gold^{TM}$, Medtronic MiniMed, Northridge, CA) over a period of 48 hour at 5 min intervals.

Time-invariant models described by equations 1-3 are developed using the first half of the data, while the second half is used for model validation. The MATLAB System Identification Toolbox is used for model development. The order of models is determined based on Akaike's Information Criterion (AIC), a statistical model fit measure. For all subject groups, results show AR model of order three ($n_A = 3$), ARMA model of order (3,1) ($n_A = 3$, and $n_C = 1$) and state space model of order two to be satisfactory. Figure 2 demonstrates the prediction capabilities of these models for a subject with type 2 diabetes.

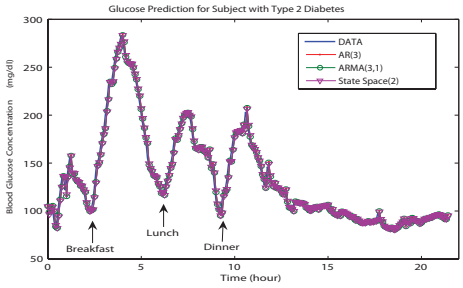

Fig. 2. Prediction of blood glucose for a subject with type 2 diabetes

The prediction performance of each model is evaluated based on Sum of Squares of Prediction Error (SSPE), defined by:

$$SSPE = \sqrt{\frac{\sum (y - \widehat{y})^2}{\sum y^2}} \cdot 100 \tag{14}$$

where y is the vector of blood glucose measurements and $\widehat{y}$ represents the vector of predicted glucose values. For the comparison of the prediction performances of the models, table 1 provides the $SSPE$ values together with the model parameter values for the same subject with type 2 diabetes.

From figure 2 and from $SSPE$ values in table 1, it is clear that none of the models overweighs the others, and all three show promising results for capturing the future glucose dynamics based on past glucose data. Models of healthy and glucose intolerant subjects show similar results.

Although, the results from real patient data are very encouraging, it can be debated that the model derived from first day data is very good in prediction of glucose levels for the second day, partly because of the disturbance free conditions (hospitalized and predefined diet conditions). Therefore, for the case of variable daily life, the prediction performance of the proposed RLS models will be analyzed.

Due to the lack of real patient data under the conditions of total freedom in daily life, the results

Table 1. Model parameters for subject with type 2 diabetes

Model	Model Parameters				SSPE
	a1 (or A)	a2 (or C)	a3	c1	
AR(3)	1.367	-0.521	0.153	-	3.792
ARMA(3,1)	1.290	-0.414	0.117	0.086	3.784
State Space(2)	$\begin{bmatrix} 0.994 & 0.004 \\ -0.005 & 0.106 \end{bmatrix}$	$\begin{bmatrix} -124.091 \\ -1.215 \end{bmatrix}$	-	-	3.870

are demonstrated using simulated glucose data. A web-based educational simulation package for glucose-insulin levels in human body, GlucoSim, is used for data acquisition. The variability in daily life is captured with a 4 day scenario of changes in the diet. The 4 day scenario for simulation includes predefined meal content and timing on day 1, 50% increased carbohydrate intake at lunch on day 2, 1 hour late lunch on day 3, and both 50% increased carbohydrate intake and 1 hour late lunch on day 4. The simulated patient is a 154 lb male with type 1 diabetes taking 3 daily meal-related regular insulin injections with an early morning basal insulin administration. The meal schedule for day 1 is as following: Breakfast at 8:30 AM with 40 gr of carbohydrate (CHO) consumption, snack at 11:00 AM with 10 gr of CHO, lunch at 1:30 PM with 50 gr of CHO, snack at 5:30 PM with 10 gr of CHO, dinner at 7:30 PM with 70 gr CHO, and snack at 10:30 PM with 25 gr of CHO. The insulin regimen is: 5 U of insulin administered before breakfast, 5 U before lunch, and 10 U before dinner.

To depict the sensor noise of a possible glucose monitoring device, Gaussian noise with a standard deviation of 4.5 mg/dl is added to the data provided by GlucoSim. Figure 3 illustrates the prediction capability of the proposed algorithm, for $ARMA(2,1)$ model and with $N_W = 5$ (25 min), $\lambda = 0.5$ and reduced to 0.005 in the case of change detection.

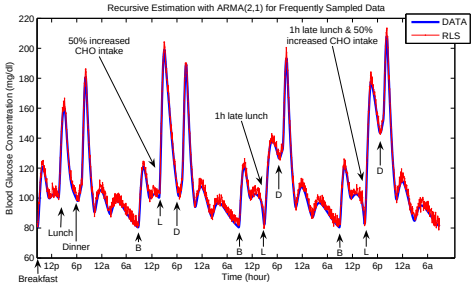

Fig. 3. Glucose prediction results with RLS from frequently sampled data

To investigate the effect of sampling interval on prediction performance, the data with 15 min interval is acquired from GlucoSim for the same case scenario. The results in figure 4 with $N_W = 2$ (30 min) are very encouraging, which demonstrate that even for the infrequent sampling case the proposed RLS algorithm can adapt and respond to daily life disturbances easily.

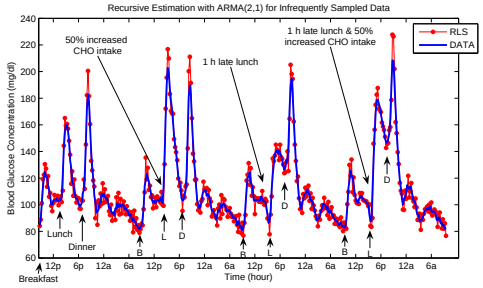

Fig. 4. Glucose prediction results with RLS from infrequently sampled data

3.2 Closed Loop Performance

The performance of the proposed adaptive control algorithm is demonstrated on a simulated patient with type 1 diabetes. Based on the intravenous glucose measurements coming from GlucoSim every 5 min, the corresponding insulin infusion rate of regular insulin is administered intraperitoneally, also at every 5 min. However, the future continuous glucose monitoring devices may prefer the subcutaneous route. Hence, a delay of 25 min is introduced to the data from GlucoSim for the subcutaneous depiction of intravenous glucose concentration, 5-10 min technical delay due to the dead space of the sensor plus 10-15 min delay due to glucose transport from plasma to interstitial fluid (Hovorka 2005).

The ARIMAX model with $n_A = 1$, $n_B = 14$, $n_C = 1$, and $d = 1$ is selected based on physiological insight about the action of intraperitoneally administered regular insulin. It is assumed that insulin will enter the circulation after 5 min (a delay of 1 step) of its administration, and will have a dominant effect on glucose regulation for around 70 min (order of 14 for $B(q^{-1})$). Keeping the model structure constant, its parameters are updated at each step which gives the adaptive nature of the algorithm.

Due to the delay between the subcutaneous and intravenous glucose concentrations, the control action near normoglycemic conditions requires a more careful consideration. For glucose measurements below 100 mg/dl, this is achieved with the use of an exponential trajectory and with an

increase (3 times) in the weight of output term in the minimization problem, which puts further effort on trajectory tracking.

Figures 5 and 6 show the control action of GPC strategy with Ny=36 and Nu=15, and the resultant 48 hour time course of glucose, where day 1 and day 2 corresponds to day 1 and day 4 scenarios of figure 3 or 4. The results for the LQC strategy are demonstrated in these figures as well.

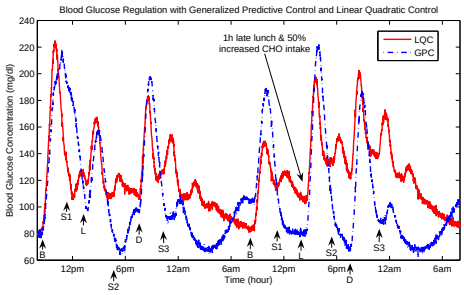

Fig. 5. Blood glucose regulation with GPC and LQC strategies

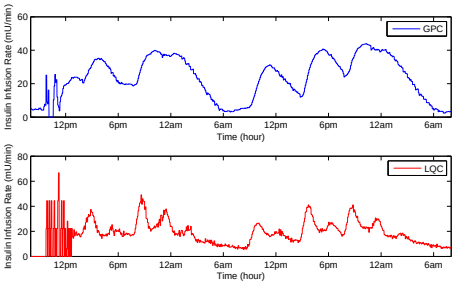

Fig. 6. Control actions for GPC and LQC strategies

From insulin infusion plots, a transition period is clearly seen, where the control action is aggressive at the start and gradually smooths as more data became available to capture the glucose dynamics. Note that the transition is not repeated the next morning when going from a long fasting state to a sudden feeding state, demonstrating the adaptive capabilities of the proposed RLS strategy. The control action by GPC is more sluggish (figure 6) resulting in sustained higher insulin infusion rates and consequently lower glucose concentrations than the LQC. This can be explained with the constrained QP (equation 11) problem that may result in suboptimal solution for some cases, while the optimal solution is guarantied in LQC with the infinite horizon. Both control studies manage to bring glucose levels back to normal after a meal disturbance, showing the reliability of the proposed RLS strategy for blood glucose prediction.

4. CONCLUSIONS AND FUTURE WORK

An adaptive control algorithm for closed-loop insulin infusion has been proposed. The novelty of the work is the use of the proposed RLS strategy with a forgetting factor and change detection method, for the model development using patient's own glucose data, which makes the model dynamically to adapt to changing external conditions, or physiological inter- and intra-subject variability. The reliability of the algorithm has been tested with model based control methods. An interesting future project will be testing the algorithm for the subcutaneous route of insulin.

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