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Self-Tuning Controller for Regulation of Glucose Levels in Patients with Type 1 Diabetes

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Abstract—**Closing the loop with a fully automated artificial pancreas will definitely improve the life of patients with type 1 diabetes. An adaptive control strategy is proposed in order to dynamically respond to unpredicted glucose fluctuations due to internal or external perturbations. The adaptability of the controller is further assured with models derived from continuous glucose measuring device data collected from the patient. The implicit self-tuning tracker is used to keep the glucose concentrations within normoglycemic range, while the controller parameters are directly tuned at each step based on patient specific time-series models. Closed-loop results are demonstrated on a simulated patient assuming intravenous measurement of glucose and subcutaneous infusion of rapid-acting insulin.**

I. Introduction

Type 1 diabetes is characterized with degradation of insulin releasing cells in the pancreas, which consequently leads to the failure of blood glucose regulation in the body. Therefore, patients with type 1 diabetes are totally dependent on exogenous insulin. The current intensive insulin therapy includes 3-5 daily insulin injections or insulin infusion with a manually controlled pump, and 3-7 daily fingerstick blood glucose measurements. Due to the open loop nature of the current therapy and changing daily life conditions (e.g. diet, exercise, stress or illness), it is a difficult task for many patients to decide on the required insulin amount/rate and correct timing of injection or bolus insulin infusion. Closing the loop with a fully automated device will definitely improve the life of the patients. Such fully automated artificial pancreas will basically consist of three components: a continuous blood glucose measuring device, an automated insulin infusion pump, and a control algorithm. In this paper, we focus on the last component of the artificial pancreas, the control algorithm.

In the literature, model-based control strategies have been previously proposed for closing the loop for patients with type 1 diabetes (see e.g. [1]-[3]). Physiological glucose-insulin dynamics models that are only representative of an average patient have been utilized for prediction of future glucose concentrations in these studies. However, for the development of an automated artificial pancreas, a more realistic description that takes into account the intra- and inter-subject variability of glucose-insulin dynamics is required. In this research, we focus on intra-/inter-subject variability by developing patient specific models using subject's own continuous glucose monitoring (CGM) data which is the major novelty of our work. The linear model is recursively updated at each sampling time and is also integrated with a change detection strategy for a faster response to abrupt changes in glucose levels.

With the recent developments in CGM technologies, it is believed that CGM will play a primary role in intensive insulin therapy in the near-future and ultimately in the development of a fully automated artificial pancreas. CGM devices provide real-time frequently measured glucose data [4]-[6]. Techniques have been proposed for analysis of the CGM discrete time-series data [7]-[9]. In this research, we propose an adaptive self-tuning control algorithm that uses linear discrete time-series models derived form patient's own glucose data for tuning the controller parameters. We have previously developed indirect (explicit) adaptive control algorithms for blood glucose regulation using CGM device data [9]. In this paper, we focus on a direct (implicit) control strategy, the self-tuning tracker.

In summary, the implicit self-tuning regulator developed by Astrom and Wittenmark [10] is extended to a self-tuning tracker [11] where the reference trajectory is a time-varying function depending on the current glucose measurement. In order to provide fast response in presence of disturbances, the self-tuning tracker is further incorporated with a change detection method. Closed-loop results are demonstrated on a virtual patient assuming intravenous measurement of glucose and subcutaneous administration of rapid-acting insulin.

II. The Closed-Loop Strategy

Adaptive control strategies try to compensate for variations in process dynamics or disturbances by adapting the controller parameters to changing conditions. The

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glucose-insulin dynamics show great variability from subject to subject. Metabolic changes that are caused by stress, illness or changes in insulin sensitivity might also lead to variation in glucose-insulin dynamics within the same subject. Furthermore, patients with type 1 diabetes are subjected to external disturbances like meal consumption or physical activity on a daily basis. Due to unpredictable fluctuations of glucose-insulin dynamics and external disturbances causing large perturbations, we believe that adaptive control is the most appropriate strategy for closing the loop of such a complex system.

A typical adaptive control mechanism (Fig.1) consists of a parameter estimator and a control law. At each sampling step, variations in plant dynamics are monitored by online estimation of the process transfer function parameters. These parameters are then used in the controller design for calculation of the appropriate control action. In general, the controller tries to adapt in response to disturbances or changes in the system itself. In our case, the plant is represented by patient's glucose dynamics where the controller decides on the required insulin infusion rate to keep glucose levels within normoglycemic range. Specifically, we propose a control mechanism that incorporates a recursive least square (RLS) estimator with an implicit self-tuning tracker.

Physiological glucose-insulin dynamics models that are available in the literature [12]-[14] can be used to express the process transfer function for the closed-loop algorithm. These models are generally nonlinear and are representative of only an average subject under specific conditions. In this paper, the proposed closed-loop strategy does not require the use of such physiological models. Instead, we assume that glucose-insulin interactions can be described as a linear discrete time-series model that is developed from patient's glucose measurements from a CGM device. Linear models would be less accurate than nonlinear models for describing variations of a nonlinear system in a wide range of conditions. However, the frequent sampling and recursive identification of the model which is also interfaced with a change detection method will compensate for their simplicity.

The current glucose concentration can be expressed by an autoregressive moving average model with exogenous inputs (ARMAX) as a function of past glucose and insulin observations

$$\begin{aligned} y(t) = {} & a_1 y(t-1) + a_2 y(t-2) + ... + a_n y(t-n) + \\ & b_1 u(t-d-1) + ... + b_m u(t-d-m) + \\ & e(t) + c_1 e(t-1) + ... + c_n e(t-n) \end{aligned} \tag{1}$$

where y and u are the deviations of the process output (glucose concentration) and the control variable (insulin infusion rate) from their set point values, respectively. {e(t)} is a sequence of independent and identically distributed zero-mean Gaussian variables. a_i, b_i and c_i are unknown and time-varying model parameters, and d is the delay term in control action. Using the backward shift operator q^{-1} (e.g. $q^{-k} y(t) = y(t-k)$), (1) can be expressed as:

$$A(q^{-1}) y(t) = q^{-d} B(q^{-1}) u(t) + C(q^{-1}) e(t). \tag{2}$$

The polynomials A, B, and C are defined by

$$\begin{aligned} A(q^{-1}) &= 1 - \sum_{i=1}^{n} a_i q^{-i} \\ B(q^{-1}) &= \sum_{i=1}^{m} b_i q^{-i} \\ C(q^{-1}) &= 1 + \sum_{i=1}^{n} c_i q^{-i}. \end{aligned} \tag{3}$$

It is desired that the control action $u(t)$ minimizes the variance of process output from its set point value. Therefore, the optimal control law is calculated from the minimization of the design criterion

$$V = E y^2(t) \tag{4}$$

as [10]

$$u(t) = -\frac{q^{-d} G(q^{-1})}{B(q^{-1}) F(q^{-1})} y(t) \tag{5}$$

where the F and G are polynomials determined from [10]

$$q^{-d} C(q^{-1}) = A(q^{-1}) F(q^{-1}) + G(q^{-1}). \tag{6}$$

The control algorithm described by (2)-(6) is known as minimum variance control. At each step, after the estimation of model parameters (2), one has to solve for (6) in order to calculate the control law (5).

Astrom and Wittenmark [10] have reparameterized the process function (2) so that it can be expressed in terms of regulator parameters directly. This eliminates the design computations (e.g. (6)) and consequently simplifies the algorithm substantially.

Substituting (6) into (2), a new model structure is expressed

$$\begin{aligned} y(t+d+1) = {} & \alpha_1 y(t) + \alpha_2 y(t-1) + ... \alpha_n y(t-n+1) \\ & + \beta_0 \left[u(t) + \beta_1 u(t-1) + ... + \beta_k u(t-k) \right] \\ & + e(t+d+1) \end{aligned} \tag{7}$$

where $k = m + d - 1$ and the coefficients α_i and β_i are in terms of a_i, b_i and c_i. At each sampling step, the model parameters of (7) can be estimated using weighted recursive least squares (RLS) method:

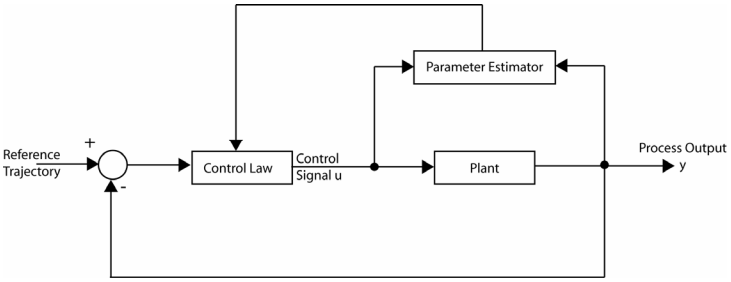

Fig. 1. Block diagram of a typical adaptive control strategy.

$$y(t) = \varphi^T(t)\,\theta(t) + e(t) \tag{8}$$

$$\hat{\theta}(t) = \hat{\theta}(t-1) + K(t)\left\{ y(t) - \varphi^T(t)\,\hat{\theta}(t-1)\right\} \tag{9}$$

$$K(t) = \frac{P(t-1)\,\varphi(t)}{\lambda + \varphi^T(t)\,P(t-1)\,\varphi(t)} \tag{10}$$

$$P(t) = \frac{1}{\lambda}\left[P(t-1) - \frac{P(t-1)\,\varphi(t)\,\varphi^T(t)\,P(t-1)}{\lambda + \varphi^T(t)\,P(t-1)\,\varphi(t)} \right] \tag{11}$$

where the vector of past observations is described by

$$\begin{aligned}\varphi(t) = [&y(t-d-1)\ldots y(t-d-n), u(t-d-1)\ldots \\ &u(t-d-k-1)]\end{aligned} \tag{12}$$

and the estimate of model parameters is given by

$$\hat{\theta}(t) = [\alpha_1(t)\ldots\alpha_2(t), \beta_0(t)\ldots\beta_k(t)]. \tag{13}$$

The terms *K* and *P* denote the estimator gain vector and the matrix proportional to the covariance matrix of the parameter estimates, respectively, and λ is the forgetting factor ($0 < \lambda \le 1$). The forgetting factor puts relative weights on the past observation. For $\lambda = 1$, all the observations are equally weighted (infinite memory). On the other hand, small values of forgetting factor gives more weight on recent observations and less weight on older ones (short memory).

The control law is then obtained to satisfy

$$\varphi^T(t)\,\hat{\theta}(t) = 0 \tag{14}$$

and more explicitly is described by

$$\begin{aligned} u(t) = &\frac{-1}{\beta_0}[\alpha_1 y(t) + \ldots + \alpha_n y(t-n+1) + \\ &\beta_1 u(t-1) + \ldots + \beta_k u(t-k)] \\ = &\frac{-1}{\beta_0}\,\frac{\alpha(q^{-1})}{\beta(q^{-1})}\,y(t). \end{aligned} \tag{15}$$

The adaptive control mechanism expressed by (8)-(15) is known as the implicit self-tuning tracker [11]. Non adaptive version of the self-tuning tracker ($\lambda = 1$) is used if the system parameters are unknown but fixed. Self tuning then is viewed as a mechanism for initial adjustment. An adaptive version of the self-tuning tracker ($\lambda < 1$) can follow the model parameter variations, since an adaptive controller will adapt to changing dynamics. The self-tuning tracker also handles an operating point dependent nonlinearity as a time variant problem [15].

During daily life, many conditions like meal consumption, exercise, or stress cause large and sometimes unexpected variations in glucose levels. In order to capture drastic changes in glucose concentrations and to provide a quicker respond to such changes, the RLS algorithm is also integrated with a change detection method. When change in model parameters is detected (physically corresponds to a significant change in glucose levels), 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 alternative hypotheses given as:

$$\begin{aligned} H_0: &\quad E(\hat{\theta}(t)) = \hat{\theta}_0 \quad \textit{for } T < t < T + T_W \\ H_1: &\quad E(\hat{\theta}(t)) \neq \hat{\theta}_0 \quad \textit{for } T < t < T + T_W \end{aligned} \tag{16}$$

where $E(\hat{\theta}(t))$ denotes the expected value of the model parameters estimate at time instant *t*. $\hat{\theta}_0$ is the vector of unbiased parameter estimates computed by RLS algorithm using the data until time instant *T*. T_W is the window size for change detection persistency check. When a persistent change within the window size is detected, the forgetting factor is reduced to a smaller value and $\hat{\theta}_0$ is replaced with its new estimate.

In summary, the algorithm can be described as follows:

Step 1: Start with guesses for orders *n* and *k*, to select a suitable controller structure (15).

Step 2: Using regression model (8) estimate the controller parameters (13) by RLS algorithm (9)-(11).

Step 3: Check for change detection (16). If change is detected reduce the forgetting factor.

Step 4: Compute the appropriate control action by (15).

Step 5: Test for stability and optimality of the structure

using the two theorems of Astrom [10].

Step 6: In case the structure appears to be appropriate based on step 5, implement the control action computed at step 4 and return to step 2 at the next sampling time, otherwise go to step 1 and start with a different guesses for n and k.

Reference Trajectory: Using a constant desired glucose value as a reference trajectory, may result in overestimated insulin infusion rates especially when large and sudden changes in glucose concentrations are experienced (for instance during meal consumption). Overestimated insulin rates may lead to hypoglycemia particularly when subcutaneous administration of insulin is considered due to large time delay associated with its absorption from adipose tissue. Therefore, depending on the current glucose measurement, a time-varying trajectory is preferred, and the self-tuning regulator problem is extended to a self-tuning tracker [11]. Similar to [3], for high glucose levels, a gradually decreasing target trajectory (Fig.2) is selected to avoid overestimated insulin infusion rates. On the other hand, for low glucose levels an exponentially increasing trajectory (Fig.2) is used to make the control action more aggressive and provide faster recovery during hypoglycemia.

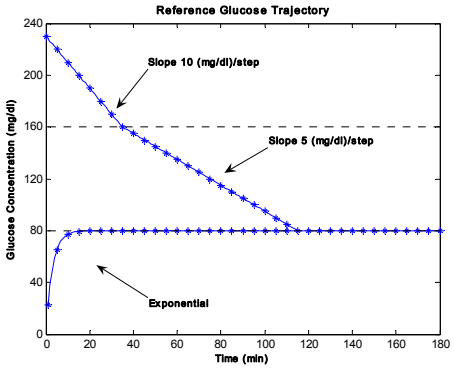

Fig. 2. Time-varying reference trajectory for glucose concentration.

III. RESULTS AND DISSCUSSION

Due to safety considerations, it is always prudent to test the proposed algorithms on virtual environments before implementing them on real-world processes. When the application is dealing with human health, this concern is even more pronounced. Therefore, we investigate the performance of the proposed adaptive closed-loop strategy on a virtual patient with type 1 diabetes that is simulated using GlucoSim [16]. GlucoSim is a web-based educational simulation package for computing the dynamics of glucose-insulin levels in human body. The software utilizes models developed by Puckett [17] for glucose-insulin interactions in the body. It also incorporates the model by Puckett [17] for glucose absorption from the intestine and the model by Hovorka [3] for subcutaneous infusion of rapid-acting insulin.

We assume that the virtual subject's blood glucose concentration is monitored with a CGM device that provides intravenous glucose readings at 5 minute intervals. Based on the intravenous glucose data, the corresponding insulin infusion rate is administered subcutaneously, also at every 5 min. 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. In addition, constraints are imposed due technical restrictions on the limits of insulin infusion rate $0\ mU/\min \le u(t) \le 67\ mU/\min$, and on maximum change of insulin infusion rate $\Delta u(t)_{\max} = u_{\max}/3$. The initial guess for control structure with $n = 3$, and $k = 16$ is selected based on physiological insight about the action of subcutaneously administered insulin. It is assumed that insulin will enter the depot after 5 min (a delay of 1 step, $d = 1$) of its administration, and will have a dominant effect on glucose regulation for around 80 min (order of 16 for k).

Blood glucose regulation in response to a single meal with carbohydrate content of 40 g, consumed 45 min after the connection of the automated pump is demonstrated in Fig. 3. Results are for 70 kg male virtual patient. The forgetting factor is reduced from 0.4 to 0.005 when a change in model parameters (13) is detected. Maximum glucose concentration (146 mg/dl) is observed at 2.5hr. Glucose concentrations fall back to normoglycemic range (70-120 mg/dl) about 2.5-3 hours after the meal consumption and settle down to approximately 75-80 mg/dl. Note that, this value is consistent with the desired 80 mg/dl for fasting conditions (Fig. 2). A slight hypoglycemia (57 mg/dl of glucose concentration) is detected at around 6hr which is recovered within 1-1.5 hours.

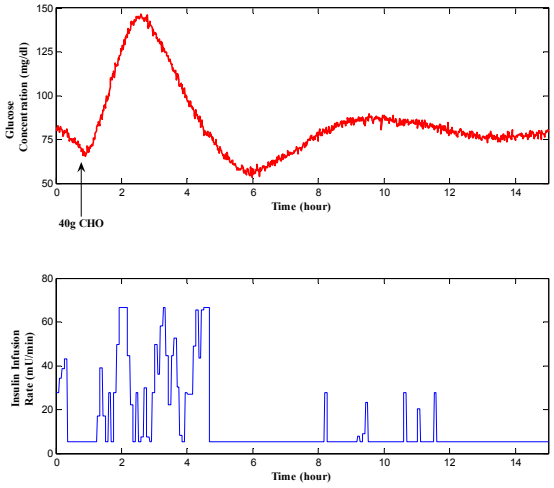

Fig. 3. Blood glucose regulation in response to single meal at 45 min. Control action with change detection strategy incorporated to the self-tuning tracker. In case of change detection the forgetting factor is reduced from 0.4 to 0.005.

Reducing the maximum change of insulin infusion rate (e.g. $\Delta u(t)_{\max} = u_{\max}/5$), reduces the aggressiveness of the control action and smoothes the insulin infusion rates. However, less aggressive control action leads to slower reduction of insulin infusion rates from high values (extended time periods for insulin rates to decrease) which

results in pronounced hypoglycemic glucose levels (results not shown) when combined with the slow absorption of subcutaneously administered insulin. On the other hand, increasing the maximum change of insulin infusion rate makes the control action more aggressive (rapid saturations), which results in more fluctuating glucose concentrations. Furthermore, increasing the delay in control action leads to more sluggish controller response.

Removing the constraints on the input and the maximum rate of change ($\Delta u(t)_{\max}$), leads to high (above 200 mU/min) and impulse-like control actions at meal time which cause glucose concentrations to fall below 40 mg/dl within 1-2 hours after meal and recovery from hypoglycemia can not be achieved during the 15 hour period. When, only the constraint on input ($0\ mU/\min \le u(t) \le 67\ mU/\min$) is removed, the trend of control action is similar to the one of Fig.3, however maximum insulin infusion rates of 110-115 mU/min (compare with 67 mU/min) are observed which lead to two hypoglycemic episodes (34 mg/dl at 4hr and 40 mg/dl at 11hr) that are recovered within 1-2 hours.

In order to investigate the effect of the change detection strategy (16), glucose regulation by the self-tuning tracker with no-change detection method (skip *Step 3*) is demonstrated in Fig.4 (both constraints are imposed). The results are for a constant forgetting factor of value 0.4 and the same case scenario as in Fig.3. Exclusion of change detection strategy results in glucose concentrations below 45 mg/dl (severe hypoglycemia), and cycling fluctuations in glucose levels after the meal. Additionally, insulin infusion rate shows rapid and prolonged saturation to its maximum limit for glucose concentrations above 90 mg/dl (observe the saturation in insulin infusion rate after 8 hours).

In summary, the incorporation of the change detection strategy to the self-tuning tracker generates superior glucose regulation by preventing hypoglycemia and rapid saturation of the control action.

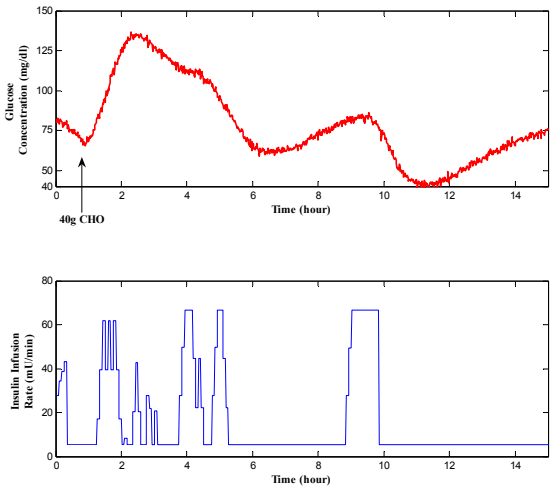

Fig. 4. Blood glucose regulation in response to single meal at 45 min. Control action with no-change detection strategy in the self-tuning tracker.

A more realistic meal disturbance scenario is the multiple meals case, where the meal schedule for the day is as: Breakfast at 8:45 AM with 35 g of carbohydrate (CHO) consumption, lunch at 1:30 PM with 60 gr of CHO, and dinner at 6:30 PM with 50 gr CHO. Figure 5 illustrates blood glucose regulation for the multiple meal disturbance case with the change detection strategy interfaced to the implicit self-tuning tracker.

The only nadir that can be remarked as slight hypoglycemia occurs just before 12am corresponding to 58.55 mg/dl of glucose concentration (Fig.5). There are no blood glucose concentrations below 45 mg/dl (severe hypoglycemia). Maximum glucose levels are observed at 158.1, 163.5 and 205.1 mg/dl following breakfast, lunch and dinner respectively. The control action is more sluggish at the start (lower insulin infusion rates before 11pm and slower normalization of glucose during breakfast compared to other meals), and becomes more active or aggressive as more data become available to capture the glucose-insulin dynamics. The automated artificial pancreas demonstrated in Fig. 5, is able to prevent hypoglycemia and bring the glucose levels back to normal range within 3 hours after meals.

Finally, we compare the results of the direct self-tuning regulator with another controller strategy previously developed by our research group. The extensive description of the control strategy can be found in [9]. In summary, it consists of a recursive least squares estimation of a patient specific ARMAX model incorporated with a change detection method and explicitly computed control law (e.g. linear-quadratic-control, LQC and generalized-predictive-control, GPC). In this paper, the LQC law is considered only. Figure 6 displays the glucose regulation with this indirect adaptive control algorithm.

Compared to the direct self-tuning tracker (Fig. 5), the LQC-based control strategy provides less aggressive insulin infusion rates and therefore slightly higher glucose

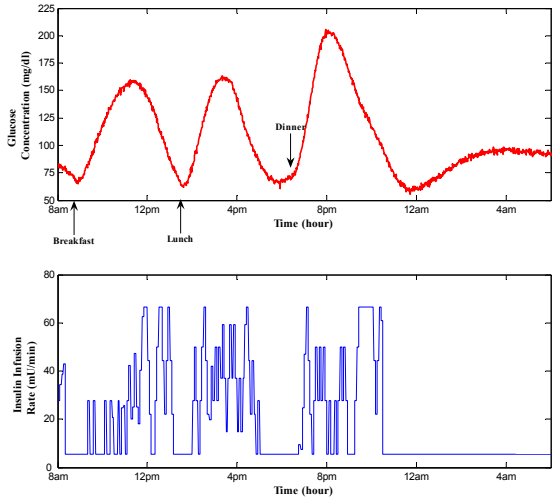

Fig. 5. Blood glucose regulation in response to multiple meals. Control action with change detection strategy incorporated to the self-tuning tracker. In case of change detection the forgetting factor is reduced from 0.4 to 0.005.

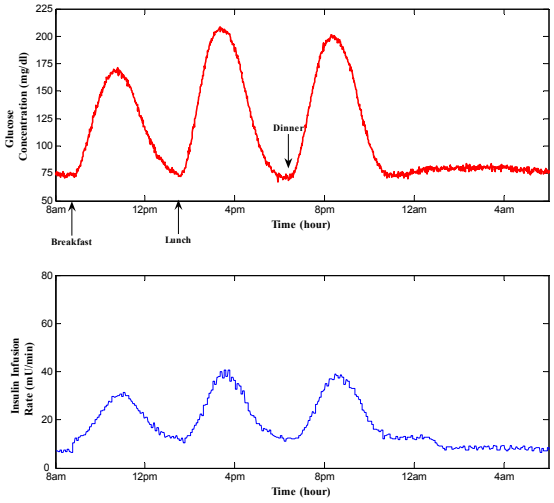

Fig. 6. Blood glucose regulation in response to multiple meals. Control action with previously published [9] indirect control strategy.

concentrations. Minimum glucose concentration is observed around 6pm with 67.2 mg/dl, and maximum glucose values following breakfast, lunch, and dinner are 167.5, 206.8, and 201.1 mg/dl respectively.

The control action provided by LQC strategy more closely mimics the physiological insulin release from a healthy pancreas. Instead of going up-and-down, like the control action of the implicit self-tuner (Fig.5), a healthy pancreas will release insulin at a rate proportional to the meal size that will closely follow the variation in glucose levels (notice the similarity in the trends of glucose concentrations and insulin infusion rates in Fig.6). However, even with the more aggressive control action, the direct self-tuning tracker provides glucose regulation that is not significantly different from the LQC strategy (compare Fig.5 to Fig.6) and is able to keep the blood glucose concentrations within normoglycemic range avoiding hypoglycemia.

The self-tuning tracker simplifies the 2-step process (model identification followed by controller design and tuning) of an indirect control strategy (e.g. LQC) to a 1-step process by directly integrating the changes in the model to the control law. The simplicity of the control algorithm and the good glucose regulation provided, make the real-life implementation (in terms of hardware development) of the self-tuning tracker superior compared to the more computationally demanding indirect model-based control methods that require the solution of a quadratic optimization problem at each step.

IV. CONCLUSION

An implicit adaptive control algorithm for closed-loop insulin infusion has been proposed. Specifically, the self-tuning tracker is selected for the control law where controller parameters are updated directly form the process coefficients. The computational simplicity of the direct control strategy makes it superior in terms of hardware development compared to explicit control methods. The reliability of the algorithm has been tested for subcutaneous administration of insulin. The algorithm provides glucose concentrations within normoglycemic limits, and gives promising results for closing the loop for patients with type 1 diabetes with a fully automated artificial pancreas. Real-life implementation of the algorithm should also address safety issues like pump and sensor failure.

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