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PREDICTIVE CONTROL OF BLOOD GLUCOSE CONCENTRATION IN TYPE-I DIABETIC PATIENTS USING LINEAR INPUT-OUTPUT MODELS

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Abstract: Intra- and inter-patient variability poses a challenging task to control blood glucose concentration in diabetic patients. A data based model predictive control with state and disturbance estimation has been developed to control the blood glucose concentration in the type-I diabetic patients in the presence of meal disturbances under patient-model mismatch. Simulation studies were performed on three distinct patient models generated as a result of sensitivity analysis, which revealed that the proposed control strategy is able to control the blood glucose concentration well within the acceptable limits and also able to compensate for the slow parametric drifts.

Keywords: IDDM, state & disturbance estimation based model predictive control.

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder with the inability of the pancreas to secrete sufficient insulin, the most important hormone regulating glucose metabolism, results in poor maintenance of normoglycemia (defined as blood glucose 70–100 mg/dL) with elevated blood glucose concentrations. Chronic hyperglycemia (arterial blood glucose >120 mg/dL) causes damage to the eyes, kidneys, nerves, heart and blood vessels (Alberti and Zimmet, 1998). Particularly, type-I DM, known also as insulin dependent diabetes mellitus (IDDM), defines a group of patients that need exogenous insulin in order to prevent hyperglycemia. Conventional therapy of IDDM out-patients involves subcutaneous administration of exogenous insulin several times a day (two to four). With the developments in programmable extra corporeal and implantable insulin pumps as well as implantable non-invasive glucose concentration sensors, it has become practical to develop a closed-loop insulin infusion device. The problem of IDDM management is very complex, due to the great inter- and intra-individual variability of patients' response, and to the variety of factors that may determine fluctuations in the glucose metabolism (from diet to physical exercise, from stress to the insulin injection site). This challenge can be posed as disturbance rejection under unknown external disturbances and plant model mismatch. Initial approaches have utilized direct feedback control. Next generation algorithms used either explicit kinetic models or adaptive time series models for controller synthesis. Since these conventional algorithms do not allow reaching and maintaining near normal BGL without increasing the frequency of BG measurements, the risk of hyper- or hypoglycemic events is typically higher than desirable. Next generation insulin infusion control employed model predictive control to predict these events prior to their occurrence and take a corrective action. The models used typically require either patient-specific parameters that are not generically available, and/or knowledge of glucose or exercise inputs that may not be known *a priori*. Some researchers modelled insulin infusion dynamics with fuzzy logic and/or neural network. Developing such models and incorporating them into the control algorithm demands a greater computational effort compared to any linear control algorithm. Even in such cases, if proper correction is not made for plant-model mismatch due to external disturbances, control system may become unstable. Hence, in case of inter and intra-patient variations due the inherent uncertainty in the influential parameters affecting the glucose and insulin metabolism, plant-model mismatch is to be explicitly addressed to synthesize a robust control algorithm for insulin infusion.

In present study, an input-output data based disturbance modelling approach is adopted with constrained disturbance and state estimation based linear MPC (MPC/DSE) control algorithm (Ricker, 1990). If the characteristics of the unmeasured disturbances that are expected to disturb the process are known, one can estimate the disturbances along with the states. This relaxes the stringent requirement of efficient process modelling. In MPC/DSE optimal disturbance and state estimates are propagated into the future predictions and hence, proper input moves that are to be implemented to reject the external disturbances can be found. Since IDDM management involves several general issues that are common to a variety of intelligent monitoring tasks, it is believed that the methodology proposed could be applicable to other monitoring problems.

2. PATIENT MODEL UNCERTAINTY

In this work diabetic patient model used for patient simulations is taken from Parker *et al*(1999). This pharmacokinetic - pharmacodynamic compartmental model of the human glucose-insulin system was initially developed by Guyton et al (1978) and Sorensen (1985), and then modified by Parket *et al.*(1999) to include meal and exercise disturbances. This model has 19 state equations and 47 physiological parameters. Utilizing compartmental modelling techniques, the diabetic patient model is represented schematically in Fig. 1. In this model human body is divided into six compartments (brain, heart/lungs, gut, liver, kidney, and periphery).

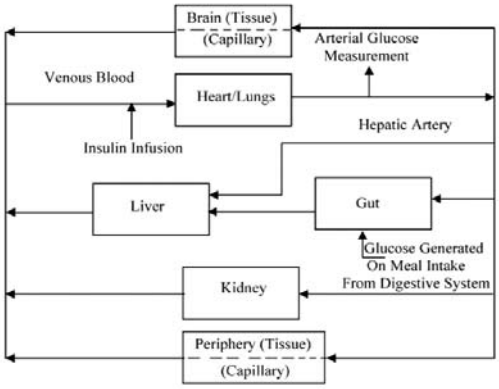

FIGURE 1. Compartmental diagram of the glucose and insulin system in diabetic patient model

Individual compartment models are obtained by performing mass balances around tissues important to glucose or insulin metabolism. Sub-compartments (namely, capillary and tissue), such as those in the brain and periphery, were included where significant transport resistance (e.g., time delay) exists. The periphery represents the combined effects of muscle and adipose tissue while the stomach and intestine effects are lumped into the gut compartment. This model was constructed to represent a sedentary 70-kg male diabetic patient. Controlled output for this system is the arterial glucose concentration, which is regulated by the manipulated variable, insulin infusion rate. A disturbance variable, glucose uptake from the gut compartment, is added to the model to simulate the diabetic patient ingesting a meal. The mathematical representation of the meal sub model is described in Lehmann and Deutsch(1992).

Due to the inevitable patient-model mismatch there exists some uncertainties; these uncertainties between the actual patients and the nominal patient model could be translated to variations in the model parameters which represent glucose or insulin metabolism. The glucose and insulin dynamics were found to be most sensitive to variations in the metabolic parameters of the liver and the periphery. In the patient model, glucose metabolism is mathematically described by threshold functions with the following general structure;

$$\Gamma_e = E_{\Gamma_e}\left\{A_{\Gamma_e} - B_\Gamma \tanh\left[C_{\Gamma_e}\left(x_i + D_{\Gamma_e}\right)\right]\right\} \qquad (1)$$

The subscript is the state vector element involved in the metabolic effect, and subscript *e* denotes specific effects within the model: the effect of glucose on hepatic glucose production (EGHGP), the effect of glucose on hepatic glucose uptake (EGHGU), and the effect of insulin on peripheral glucose uptake (EIPGU). Inter- or intra-patient uncertainty were classified physiologically as either a receptor (D_{Γ_e}) or a post-receptor (E_{Γ_e}) defect; these two parameters were estimated to fit the actual patient data. Differences in insulin clearance (metabolism) between patients also exist and were modelled as deviations in the fraction of clearance (i.e., insulin utilized) by a given compartment, such as the fraction of hepatic clearance (F_{LC}) or the fraction of peripheral insulin clearance (F_{PC}). This uncertainty formulation essentially focuses on the liver (variability in five parameters) and the peripheral (muscle/fat) tissues (variability in three parameters), as these are considered to be more relevant to the control study. Nominal values of the above eight parameters (three sets of D_{Γ_e} and E_{Γ_e}, F_{LC}, and F_{PC}) are listed in Table 1.

Figure 2 shows the steady state blood glucose concentration levels with variation in each sensitive parameter affecting the glucose and insulin metabolism. It can be seen from this figure that post-receptor defect on the effect of either glucose or insulin on the glucose uptake ($E_{\Gamma_{EGHGU}}$ and $E_{\Gamma_{EIPGU}}$) is similar. When these metabolic parameters increase glucose uptake rate increases causing hypoglycemia and when decreases causes hyperglycemia. Where as, the receptor defects with the hepatic and periphery glucose utilization ($D_{\Gamma_{EGHGU}}$ and $D_{\Gamma_{EIPGU}}$) shows a different trend. A small decrease in the nominal value makes the patient dynamics insensitive to further change in these parameters. These are significant only in hypoglycemic conditions. F_{LC}, and F_{PC} bear the similar regulatory effects on the blood glucose concentration. When the fractional clearance is higher the patient dynamics are tend to

TABLE 1. Values of uncertain parameters which determine the patient dynamics

Parameter	Patient-1 (nominal value)	Patient-2	Patient-3
$E_{\Gamma_{EGGP}}$	1.0	1.0	1.0
$D_{\Gamma_{EGGP}}$	-5.82113	-5.82113	-5.82113
$E_{\Gamma_{EGHGU}}$	1.0	1.0	1.0
$D_{\Gamma_{EGHGU}}$	-1.48	-2.072	-1.48
$E_{\Gamma_{EIPGU}}$	1.0	1.0	0.6
$D_{\Gamma_{EIPGU}}$	-0.4969	-0.4969	-0.4969
F_{LC}	0.4	1.0	1.0
F_{PC}	0.15	1.0	1.0

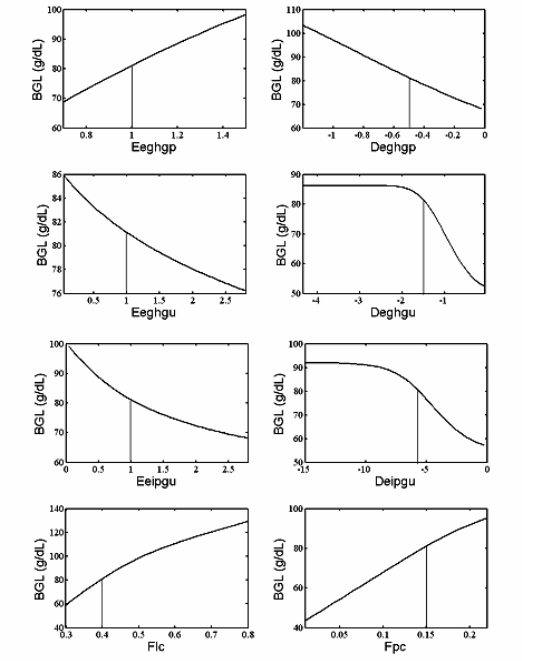

FIGURE 2. Variation in blood glucose concentration with respect to the variation in metabolic parameters.

be hyperglycemic levels and vice versa. In other words, impaired suppression of hepatic glucose production (higher values of F_{LC}) will result in accumulation blood glucose level. These two metabolic parameters are very important in determining the patient dynamics as they cause large variation in the blood glucose concentration (from 40 mg/dL to 130 mg/dL) for similar percent parametric change compared to other parameters, which is evident from the figure.

Three kinds of patient simulations were generated by setting values for uncertain parameters ($D_{\Gamma_{EGHGU}}$, F_{PC} and F_{LC}) so that the sensitivity of the patients to insulin differed significantly; Patient-1 with nominal parameters, Patient-2 with higher sensitivity to insulin infusion, and Patient-3 with relatively insensitive dynamics to insulin infusion. The steady-state insulin infusion rates to keep the blood glucose concentration at 81.1 mg/dL for three patients were 22.3, 15.2 and 22.88 mU/min respectively. The sensitive parameter values of three patients are given in Table 1.

Transient responses to open-loop changes in the insulin infusion rate were simulated in order to characterize the insulin-to-glucose dynamics of three patient models. A unit negative step (-1 mU/min) was introduced in the insulin infusion rate and the corresponding response in the blood glucose concentration for three patients was plotted in Fig. 3a. From the step response curves it is evident that the insulin-glucose metabolism in three patients differs from each other in both steady state and dynamic behavior. Patient-3's glucose metabolism was relatively insensitive to insulin infusion, where are as Patient-2 was highly sensitive. Patient-1 with nominal parameters had the insulin-glucose dynamics in between these two patients.

Transient responses to a meal disturbance were simulated in order to characterize the post-meal glucose concentration dynamics. A 50 g meal disturbance was introduced at 300 min into the patient simulations. The responses of three patients for the similar meal disturbance in open loop (without control action) were plotted in Fig. 3b. It was observed that, the blood glucose levels goes up from 140 to 170 mg/dL. Even though these levels

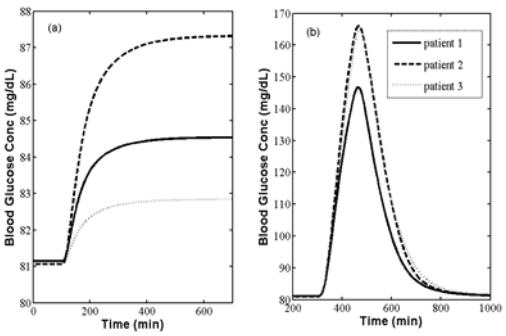

FIGURE 3. (a) Openloop response of three patients for a negative unit step in insulin infusion rate at t=100 min; **(b)** Openloop response of the three patients for similar meal disturbance

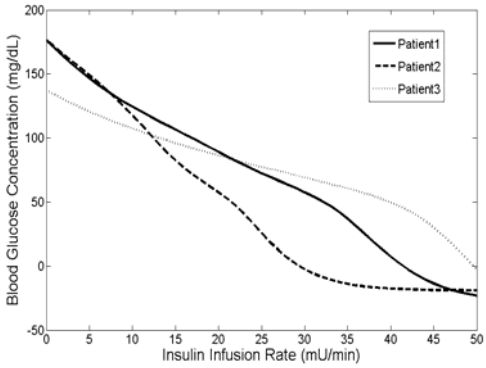

FIGURE 4. Steady state input-output mapping for the three patient models with different insulin sensitivity used in the study

reduced to normal, eventually, the time period for which they were above the normoglycemia threshold was significant. This had to be considered seriously, as the prolonged hypo- or hyperglycemic excursion deteriorates the metabolism rates. From the response of three patients to similar disturbances, it can be seen that the disturbance model (meal to glucose dynamics) also differs from one patient to another. Figure 4 shows the steady-state mapping of blood glucose concentration and insulin infusion rate for the three patients. It can be seen that not only the dynamics of three patients are different but also there exist a significant difference in the steady-state behavior of the patients. From Fig. 4, it is also evident that, they possess highly nonlinear insulin-glucose dynamics.

3. DISTURBANCE AND STATE ESTIMATION BASED MPC

3.1 Disturbance modeling and estimation.

A model predictive control formulation based on the initially identified process model can pose practical difficulties in the presence of mismatch between the plant behavior and the model predictions. Over a period of time the behavior of the plant changes due to the shift in operating conditions or changes in the disturbance characteristics. As a natural consequence, there will be a large discrepancy in the model predictions. Under such situations achieving an offset free control is an impossible task. Some times this plant-model mismatch may destabilize the control loop. Compensation for model mismatch and unmeasured disturbances can be achieved by augmenting additional disturbance states in the state space model, which introduces an integral action in the control implementation. If the characteristics of the disturbances that are expected to enter the system are known *a priori*, a new model can be formed by augmenting the process model with the disturbance model (Muske and Badgwell, 2002). This augmentation facilitates in better predictions for future output and disturbances in MPC formulation. The disturbances can be classified as;

(i) Output disturbances which enter the process at the output and are additive in nature; these can be modeled as the augmented output states.

(ii) Input disturbances which enter the process at input and bear some functionality on them before

TABLE 2. State augmentation for disturbance modeling for various kinds of disturbances

Output disturbance	Input disturbance
$\begin{bmatrix} x(k+1) \\ p(k+1) \end{bmatrix} = \begin{bmatrix} \Phi & 0 \\ 0 & I \end{bmatrix} \begin{bmatrix} x(k) \\ p(k) \end{bmatrix} + \begin{bmatrix} \Gamma \\ 0 \end{bmatrix} u(k) + \begin{bmatrix} w(k) \\ 0 \end{bmatrix}$ $y(k) = \begin{bmatrix} C & \Gamma_p \end{bmatrix} \begin{bmatrix} x(k) \\ p(k) \end{bmatrix} + v(k)$	$\begin{bmatrix} x(k+1) \\ d(k+1) \end{bmatrix} = \begin{bmatrix} \Phi & \Gamma_d \\ 0 & I \end{bmatrix} \begin{bmatrix} x(k) \\ d(k) \end{bmatrix} + \begin{bmatrix} \Gamma \\ 0 \end{bmatrix} u(k) + \begin{bmatrix} w(k) \\ 0 \end{bmatrix}$ $y(k) = \begin{bmatrix} C & 0 \end{bmatrix} \begin{bmatrix} x(k) \\ d(k) \end{bmatrix} + v(k)$
Combined disturbance	**Integrating disturbance**
$\begin{bmatrix} x(k+1) \\ p(k+1) \\ d(k+1) \end{bmatrix} = \begin{bmatrix} \Phi & \Gamma_d & 0 \\ 0 & I & 0 \\ 0 & 0 & I \end{bmatrix} \begin{bmatrix} x(k) \\ p(k) \\ d(k) \end{bmatrix} + \begin{bmatrix} \Gamma \\ 0 \\ 0 \end{bmatrix} u(k) + \begin{bmatrix} w(k) \\ 0 \\ 0 \end{bmatrix}$ $y(k) = \begin{bmatrix} C & 0 & \Gamma_p \end{bmatrix} \begin{bmatrix} x(k) \\ d(k) \\ p(k) \end{bmatrix} + v(k)$	$\begin{bmatrix} x(k+1) \\ i(k+1) \end{bmatrix} = \begin{bmatrix} \Phi & \Gamma_d \\ 0 & I \end{bmatrix} \begin{bmatrix} x(k) \\ i(k) \end{bmatrix} + \begin{bmatrix} \Gamma \\ 0 \end{bmatrix} u(k) + \begin{bmatrix} w(k) \\ 0 \end{bmatrix}$ $y(k) = \begin{bmatrix} C & \Gamma_p \end{bmatrix} \begin{bmatrix} x(k) \\ i(k) \end{bmatrix} + v(k)$

they show up in the controlled variable; these can be modeled as ramping output disturbances (Morari and Lee, 1991) or an augmented input or disturbance state (Davison and Smith, 1971).

(iii) Combined state and output disturbances; these can be modeled as a combination of both output and input disturbances

(iv) Purely integrating disturbances; these can be partially attributed to a constant output disturbance and partially to a constant integrating state disturbance (Muske and Badgwell, 2002).

Let the process model in discrete state space form be given by,

$$\begin{aligned} x(k+1) &= \Phi x(k) + \Gamma u(k) + w(k) \\ y(k) &= Cx(k) + v(k) \end{aligned} \tag{2}$$

where $x \in R^r$, $u \in R^m$ and $y \in R^n$ represent state, manipulated and controlled variable vectors, respectively. This model can be augmented with additional states to account for the disturbances entering the plant. The augmented process models for various kinds of disturbances are shown in the Table 2. In these models p, d and i represent the output, input, and integrating disturbance states, respectively; Γ_d and Γ_p are the output and input disturbance transfer functions, respectively. The necessary and sufficient conditions for the augmented model to be observable and controllable are given by Muske and Badgwell (2002). The key idea of generating the augmented state space model is to quantify the disturbances and correcting the states based on the plant-model mismatch. The process and disturbance states are not directly accessible and must be estimated. The quality of these estimates has important bearings on the overall performance of a model predictive controller. Thus comes a need of an optimal state estimator. Kalman filter is the most established tool for state estimation. A discrete form of recursive Kalman filter is employed to estimate the current states in this work. In its simple form, the augmented model can be written as,

$$\begin{aligned} x_a(k+1) &= \Phi_a x_a(k) + \Gamma_a u(k) + w_a(k) \\ y(k) &= C_a x_a(k) + v(k) \end{aligned} \tag{3}$$

w_a and v are the process and measurement noises, respectively. They are assumed to be independent white noise sequences with covariance of Q and R (constant in most applications), respectively. At every sampling instant it is implemented in two steps as given below;

Time update

$$\begin{aligned} \hat{x}_a(k)^- &= \Phi_a \hat{x}_a(k-1) + \Gamma_a u(k-1) \\ P(k)^- &= \Phi_a P(k-1) \Phi_a{}^T + Q \end{aligned} \tag{4}$$

Measurement update

$$\begin{aligned} K(k) &= P(k)^- C_a{}^T \left[C_a P(k)^- C_a{}^T + R \right]^{-1} \\ \hat{x}_a(k) &= \hat{x}_a(k)^- + K(k) \left[y(k) - C_a \hat{x}_a(k)^- \right] \\ P(k) &= \left[I - K(k) C_a \right] P(k)^- \end{aligned} \tag{5}$$

This optimal estimate of current states is used in the MPC algorithm for future output predictions.

3.2 Predictive Control Implementation.

An online constrained optimization is carried out at every sampling instant to choose the control action. This aims at minimizing certain performance criterion over a finite future time horizon, where the future behavior is computed according to the model of the plant. The predictive control implementation involves following steps;

(i) Optimal current state and disturbance estimation is carried out using the Kalman filter.

(ii) At every sampling instant, the augmented state space model is used for the openloop predictions of the controlled variable over a finite future time horizon of length, p(*prediction horizon*) starting from the current time instant, k. Let the degrees of freedom for future manipulated input moves be q(*control horizon*). Assuming that the expectation of the future innovations is zero, future output trajectory can be estimated by propagating the current states into future horizon as,

$$\begin{aligned} &\hat{x}_a(k+i \mid k) = \Phi_a \hat{x}_a(k+i-1 \mid k) + \Gamma_a u(k+j-1 \mid k) \\ &\hat{y}(k+i-1 \mid k) = C_a \hat{x}_a(k+i-1 \mid k) \\ &\text{for } i = 1,\ldots,p;\ j = \begin{cases} i & \text{if } i \le q \\ q & \text{if } i > p \end{cases} \end{aligned} \tag{6}$$

where $\hat{x}_a(k+i \mid k)$ is the state estimate at $(k+i)^{\text{th}}$ instant given the information till k^{th} instant.

(iii) A filtered future setpoint trajectory is generated using a reference system of the form

$$\begin{aligned} x_r(k+i \mid k) &= \Phi_r x_r(k+i-1 \mid k) + \Gamma_r \left[r(k) - y(k) \right] \\ y_r(k+i \mid k) &= C_r x_r(k+i \mid k) + y(k) \\ &\text{for } i = 1,\ldots,\ p \end{aligned} \tag{7}$$

with initial condition $x_r(k \mid k) = 0$ and unit steady state gain. Here, $r(k) \in R^n$ is the setpoint vector and the coefficient matrices of the reference system are tuning parameters.[28]

(iv) The future manipulated input moves $u(k+j \mid k)$ *for* $j = 1,\ldots,q$ are determined by minimization of an objective function (performance criteria) defined as

$$\underset{u(k+j|k), j=1,\ldots q}{Min} \quad \sum_{i=1}^{p} e_f(k+i|k)^T W_e e_f(k+i|k) + \sum_{j=1}^{q} \Delta u(k+j|k)^T W_u \Delta u(k+j|k)$$

subject to the following constraints,

$$\begin{aligned} &y^L \le \hat{y}(k+i|k) \le y^H, \quad i = 1,\ldots p \\ &u^L \le u(k+j|k) \le u^H \ \text{ and } \Delta u^L \le \Delta u(k+j|k) \le \Delta u^H, \quad j = 1,\ldots q \end{aligned} \tag{8}$$

where the tracking error $e_f(k+i|k)$, is defined as the difference between $y_r(k+i|k)$ and $\hat{y}(k+i|k)$. W_e and W_u are the positive definite weighting matrices on tracking error and input rate, respectively. Thus, after solving the optimization problem, only the first move is implemented on the plant and the optimization problem is reformulated at the next sampling instant based on the updated information from the plant.

4. RESULTS AND DISCUSSIONS

The objective of this work is to design a robust model based control for effective disturbance rejection under patient model mismatch. Simulation studies were carried out using Simulink® model and Matlab® routines.

4.1 MPC relevant model identification

Patient-1 was used for perturbation studies and the resultant input-output data was used for nominal MPC relevant model generation. The choice of sampling time (1 min) was made keeping view of the system dynamics (settling time is 85 min) and constraints on the sensor sampling rates. A pseudo random binary sequence (PRBS generated using *idinput* routine in Matlab® with amplitude of ±3 mg/dL and a switching time of 10 min to extract fast rate dynamics) input signal in insulin infusion rate is introduced for 600 min. The data encompassing first 400 min was used for model building and rest is used for validation. Different linear state space models were developed using the *ident* toolbox in Matlab®, and a third order state space model was selected for control implementation, which had small R^2-value compared to others. The developed 3rd order state-space model is given by,

$$x(t+1)=\begin{bmatrix}1.018 & -0.0839 & 0.00389\\ 0.0287 & 0.98165 & -0.07663\\ -0.00787 & 0.19558 & 0.76488\end{bmatrix}x(t)+\begin{bmatrix}-2.14e-06\\ 3.99e-05\\ -0.0193\end{bmatrix}u(t)$$
$$y(t)=\begin{bmatrix}56.291 & -0.995 & 0.0293\end{bmatrix}x(t) \quad (9)$$
$$and, x(0)=\begin{bmatrix}-0.0422 & -0.00996 & -0.0129\end{bmatrix}^T$$

As evident from the open-loop disturbance responses plotted in Fig. 3b, an integrating disturbance produced a prolonged deviation in the output from the steady state. It was assumed that prediction error can be attributed partially to a constant output disturbance and partially to a constant integrating state disturbance. The corresponding augmented model used in control synthesis is given by

$$\begin{bmatrix}x(k+1)\\ p(k+1)\end{bmatrix}=\begin{bmatrix}\Phi & \Gamma_d\\ 0 & I\end{bmatrix}\begin{bmatrix}x(k)\\ p(k)\end{bmatrix}+\begin{bmatrix}\Gamma\\ 0\end{bmatrix}u(k) \quad (10)$$
$$y(k)=\begin{bmatrix}C & \Gamma_p\end{bmatrix}\begin{bmatrix}x(k)\\ p(k)\end{bmatrix}$$

where, $\Gamma_p = I$, $\Gamma_d = \beta \times \Gamma$ and β is chosen to be $2.5x10^3$, which is a tuning parameter. The resulted augmented model is given by,

$$x(t+1)=\begin{bmatrix}1.018 & -0.0839 & 0.0039 & 0.0054\\ 0.028 & 0.9816 & -0.076 & -0.099\\ -0.007 & 0.1956 & 0.7649 & 4.8401\\ 0 & 0 & 0 & 1\end{bmatrix}x(t)+\begin{bmatrix}-2.14e-06\\ 3.99e-05\\ -0.00193\\ 0\end{bmatrix}u(t)$$
$$y(t)=\begin{bmatrix}56.291 & -0.995 & 0.0293 & 1\end{bmatrix}x(t) \quad (11)$$
$$and, x(0)=\begin{bmatrix}-0.0422 & -0.00996 & -0.0129 & 0\end{bmatrix}^T$$

4.2 Control Implementation.

Two controllers are studied for their performance for disturbance rejection.

- Linear Model Predictive Controller (LMPC) using nominal process model and without output constraints
- Disturbance and state estimation based MPC

For these two controllers the tuning parameters are tabulated in Table 3.

The performance of the linear MPC without output constraints using actual process model is shown in Fig. 5. These controller parameters were first tuned for patient-1 and then detuned to get optimal performance in all the three patients. It was observed that LMPC's performance for disturbance rejection was unacceptable. In all cases, both positive and negative offsets in the Blood glucose concentrations were outside the allowable range (70-100 mg/dL). This controller should be rejected. To account for the disturbance that entered the process and for effective rejection of the disturbance by taking appropriate control action, a proper disturbance model and an observer were essential. A MPC/DSE was implemented to serve this purpose. Later, to

TABLE 3. Controller parameters for LMPC and MPC/DSE

Parameter	Linear MPC	MPC/DSE
Weight on error (w_e)	2	2
Weight on input rate (w_u)	0.6	0.6
Prediction horizon (p)	400	400
Control horizon (q)	1	1
Bounds on input (insulin infusion rate in mU/min)	[0 and 250]	[0 and 250]
Input-rate bounds (mU/min)	[-10 and 10]	[-10 and 10]
Output bounds (mg/dL)	...	[Ys-6 and Ys+8]
Output covariance, R	...	0.1
State covariance matrix, Q	...	$0.4I_{4\times4}$

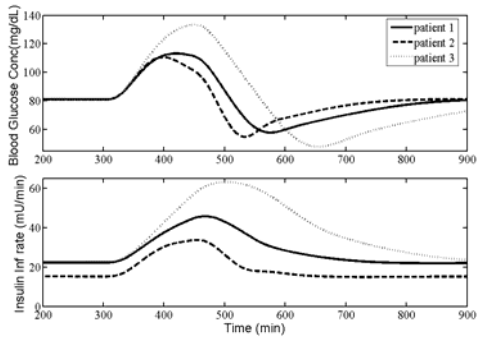

FIGURE 5. Disturbance rejection with Linear Model Predictive Control for three patients for a similar kind of meal disturbance

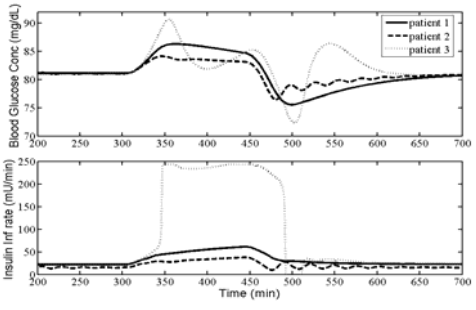

FIGURE 6. Disturbance rejection with Disturbance and State Estimation based Constrained Linear Model Predictive Control for three patients for a similar kind of meal disturbance

increase the sensitivity of MPC/DSE algorithm, output constraints were introduced in the optimization problem of MPC. This resulted in an aggressive insulin addition, when the open loop observer predicted the blood glucose concentrations outside the given output limits. These constraints were carefully chosen, in such a way that they did not affect the feasibility of the optimum solution under normal condition. It was observed that the controller showed tremendous improvement in disturbance rejection in all three patients as shown in Fig. 6. The strict maintenance of normoglycemia was achieved with MPC/DSE in all three patients even though there exists a large patient-model mismatch. The performances of the two controllers are tabulated in Table 4. It can be seen that for each patient, the performance of the MPC/DSE was superior, with 100-fold reduction in sum of squares of tracking error (SSE) compared to linear MPC. As these controllers were tuned in an iterative fashion these parameters may not be optimal. But, it is evident from the table that the constrained MPC/DSE with proper disturbance modeling efficiently rejects the disturbance.

In addition to parameter mismatch, the MPC/DSE controller was able to compensate for slow parameter drifts. Parametric drift is a common phenomenon in patients, which is generally governed by the gradually altering metabolism due to pathological effects. To reflect these conditions, a gradual change was introduced in the fraction of hepatic glucose clearance (F_{LC}) from 0.4 to 0.7 over a period of seven days as given by the following equation,

$$F_{LC} = 0.4 + 0.3\,e^{-t/3000} \qquad (12)$$

The patient was assumed to consume two 50g meals per day. The corresponding regulatory response with MPC/DSE is shown in Fig. 7. As the hepatic glucose clearance becomes worse, the demand for insulin infusion is expected to increase which was met by MPC/DSE as seen from Fig. 7. The augmented disturbance state estimate encompassed slow parametric drifts along with the external meal disturbances and hence showed excellent regulatory control performance.

CONCLUSIONS

Model-based predictive control of insulin infusion system requires a compensation mechanism for patient-model mismatch under external disturbances such as meal or exercise. In such conditions disturbance modelling by additional augmented disturbance states essentially served the purpose of rejecting disturbances under plant-model mismatch. It was observed that, even under huge process-model mismatch with an integrating type of disturbance (meal disturbance) entering the system, constrained MPC/DSE gave promising control ensuring perfect normoglycemia. Slow parametric drifts representing the pathological effect on the patient metabolism towards glucose was also efficiently handled with MPC/DSE. The digital nature of this control algorithm enables potential implementation onto a microprocessor chip to design portable insulin infusion systems mounted on the patient.

TABLE 4. Comparison of performance of MPC and MPC/DSE algorithms for insulin infusion

Performance Metric	Linear MPC			MPC/DSE		
	Patient-1	Patient-2	Patient-3	Patient-1	Patient-2	Patient-3
90% of Settling time (min)	427.0	322.0	497.0	217.0	182.0	196.0
Overshoot (mg/dL)	32.1	29.4	52.4	5.2	3.0	9.4
Undershoot (mg/dL)	23.3	26.3	33.2	5.6	4.6	8.7
SSE (x 1e3)	166.4	122.3	444.2	4.5	1.5	5.5

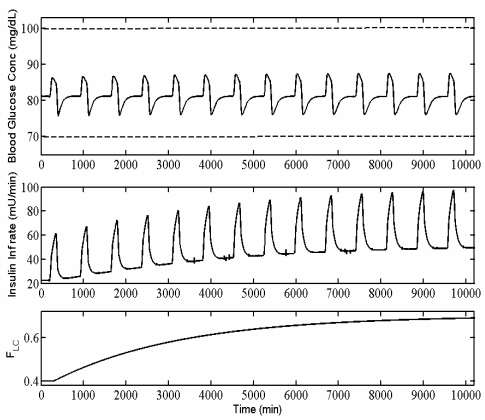

FIGURE 7. Regulatory control of blood glucose concentration with MPCDSE for 7 days on a patient whose hepatic glucose clearance is becoming worse (F_{LC} gradually increasing from 0.4 to 0.7) on twice a day meal (50 gm glucose each) basis.

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