Predictive Control of Blood Glucose Concentration in Type-I Diabetic Patients in Presence of Unmeasured Disturbances Using Identified Models

Karra Srinivas
Department of Chemical Engineering, Indian Institute of Technology Bombay, India
[*]*Department of Chemical Engineering, Texas Tech University, Lubbock, TX-79415*

Abstract

Control of blood glucose concentration in type-I diabetic patients in presence of meal disturbances has attracted the attention of many researchers in the recent past (Fisher, 1991; Kwok et al., 1992; Gopinath et al., 1995; Parker et al., 1999). The success of the control strategies proposed in the literature depends on the accuracy of the model used in the control frame-work (Parker et al., 1999). In this work, a data based model predictive control algorithm is developed to control the blood glucose concentration in the Type-I diabetic patients in the presence of meal disturbances under patient-model mismatch. A state space model with augmented states representing integrating type of disturbances is developed (Muske and Badgwell, 2002). This augmented state space model is used for the future predictions and then in optimizing the future insulin infusion rate based on the previous blood glucose measurements and previous insulin infusion rates, using a model predictive control (MPC) framework. The states along with the disturbances at each sampling instant are estimated using recursive form of Kalman filter. Appropriate physical and physiological constraints are incorporated in the objective function of MPC to ensure feasible operating regime. Simulation studies are performed on three distinct patient models using Simulink®. The input-output data required for model identification has been obtained from the perturbation studies on patient-1. The mathematical model developed is used in the state estimation based linear model predictive control, which is employed on all three patients. The simulation results revealed that, the proposed control strategy is able to control the blood glucose concentration well within the acceptable limits in the presence of meal disturbances. It was also observed that performance of this strategy, even when large patient-model mismatch along with unmeasured disturbances, is quite encouraging. With the technological advancements in infusion pumps, *in vivo* glucose sensors and microprocessor chips (Wilson and Gifford, 2005) it is possible to incorporate this robust control algorithm to build a portable insulin infusion control system that ensures normoglycemia in type-I diabetic patients.

* current affiliation
e-mail: srinivas.karra@ttu.edu

1. INTRODUCTION

Diabetes mellitus is a metabolic disorder with the inability of the pancreas to secrete sufficient insulin, the most important hormone regulating glucose metabolism. Inadequate secretion of insulin by the diabetic pancreas 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.

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 sub-cutaneous administration of exogenous insulin several times a day (two to four), self-monitoring of blood glucose levels (BGL), and insulin dose adjustment on the basis of the actual measurement, following individualized control tables defined by the physician. As there is not feed-back employed in these open-loop insulin infusion strategies they may result in significantly abnormal BGL for long periods.

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 to reject the sudden spikes of BGL in the patient.

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). Moreover, given the quality of data collected during the patients' self-monitoring, this challenge can be posed as disturbance rejection under unknown external disturbances and plant model mismatch.

This problem has attracted the attention of control community for many years. A significant number of solutions are proposed towards the development of a closed-loop algorithm for insulin infusion (Cobelli and Mari, 1983; Fisher, 1991; Broekhuyse et al., 1981). These approaches have utilized almost exclusively feedback control to maintain normoglycemia, even for the purpose of disturbance rejection. Next generation algorithms used either explicit kinetic models or adaptive time series models for controller synthesis (Salzsieder et. al, 1985, Bellaji et al., 1995; Trajanoski et al., 1998; Kern et al., 1997). Since these conventional algorithms do not allow reaching and maintaining near normal BGL without increasing the frequency of BG measurements or the risk of hyper- or hypoglycemic events, target BGL values are typically higher than desirable. Hence, it is required to predict these events prior to their occurance and take a corrective action.

In this work, model predictive control (MPC) is used for control of blood glucose concentration with insulin to ensure the normoglycemia, under a meal disturbance. MPC

is successfully applied to other biomedical control problems, including blood pressure control (Kwok et al., 1992; Gopinadh et al., 1995) and anesthesia delivery (Wada and Ward, 1995). As MPC class of algorithms can incorporate constraint handling in multi-input multi-output environment they are well suited for drug infusion problems with physical constraints (pumps, sensors) and physiological constraints (human). MPC predicts the future glucose behavior based on the past insulin inputs and past glucose measurements and takes a corrective action for predicted deviation from normal BGL.

The key component of these schemes is model accuracy. Some model based predictive control algorithms reported in the literature (Parker et al., 1999) for insulin infusion control used first principle models with identified parameters. Despite their superior predictions, development of an accurate first principles model is a strenuous task and parameter identification becomes specific to each patient. Another alternative is a data based model, which is easy to identify. Typically, the model used in the model-based controller is developed only once at the beginning of the controller implementation. However, as an unknown disturbance enters the process, the deterministic model predictions become inaccurate. As the dynamics change with time, a large mismatch develops between the model and the process and the model predictions no longer reflect the actual system behavior. Under these conditions the controller performance and its robustness deteriorates and this may even destabilize the control loop. An explicit compensative action is required to eliminate the steady-state offset caused by modeling error and unmeasured disturbances.

In present study, a data based disturbance modeling approach is adopted with constrained state estimation based linear MPC (MPC/SE) control algorithm (Ricker 1990, 1991). 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 modeling. MPC/SE is based on Kalman filter, which explicitly accounts for the effects of the unmeasured disturbances on the current state estimates and, in turn, improves the predicted state estimates over the future horizon. These disturbance and state estimates can be propagated into the future predictions and hence, proper inputs that are to be implemented to reject the external disturbances can be found. Fig. 1 shows the implementation of MPC/SE for insulin infusion control.

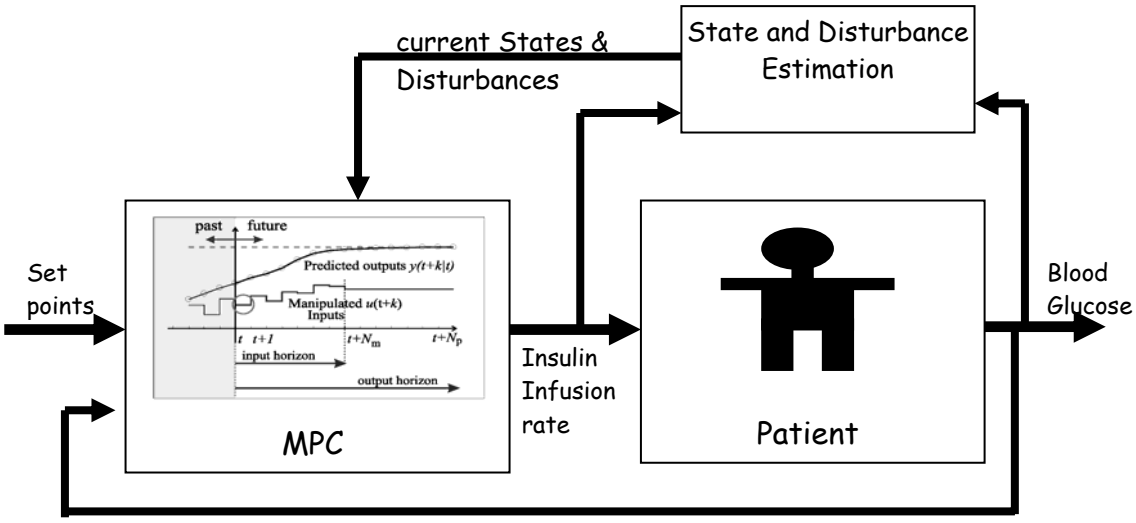

Figure 1: Pictorial representation of MPC/SE strategy for Insulin Infusion control

Since IDDM management involves several general issues that are common to a variety of intelligent monitoring tasks, it is believed that the methodology here proposed could be applicable to other monitoring problems.

3. METHODOLOGY ADOPTED

As discussed earlier, when the MPC is implemented with linear deterministic process model, under constant unmeasured disturbances entering the process, there will be an offset in the setpoint tracking. If the characteristics of the disturbances that are expected to enter the system are known *apriori*, a new model can be formed to obtain better output and disturbance predictions.

The disturbances can be any one of the following types:

- Output disturbances which are entering the process at the output and are additive in nature; these can be modeled as the augmented output states.

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

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

- Purely integrating disturbances; this can be partially attributed to a constant output disturbance and partially to a constant integrating state disturbance.

Table 1 shows the augmented state space models for different kind of disturbances. The augmented process model for disturbance rejection should be both observable and controllable to be fit for usage in control synthesis. Necessary and sufficient conditions for the augmented system to be observable and controllable are presented in Muske and Badgwell (2002).

Table 1: Augmented disturbance Models (Muske and Badgwell, 2002)

OUTPUT DISTURBANCE MODEL	INPUT/STATE DISTURBANCE MODEL
$\begin{bmatrix} x(k+1) \\ p(k+1) \end{bmatrix} = \begin{bmatrix} \Phi & 0 \\ 0 & I \end{bmatrix} \begin{bmatrix} x(k) \\ p(k) \end{bmatrix} + \begin{bmatrix} \Gamma \\ 0 \end{bmatrix} u(k)$ $y(k) = \begin{bmatrix} C & \Gamma_p \end{bmatrix} \begin{bmatrix} x(k) \\ p(k) \end{bmatrix}$ Γ_p bears the effect of augmented disturbance state on output. Usually, $\Gamma_p = I$ *p(k)* is the output disturbance and can be chosen as innovation	$\begin{bmatrix} x(k+1) \\ d(k+1) \end{bmatrix} = \begin{bmatrix} \Phi & \Gamma_d \\ 0 & I \end{bmatrix} \begin{bmatrix} x(k) \\ d(k) \end{bmatrix} + \begin{bmatrix} \Gamma \\ 0 \end{bmatrix} u(k)$ $y(k) = \begin{bmatrix} C & 0 \end{bmatrix} \begin{bmatrix} x(k) \\ d(k) \end{bmatrix}$ Γ_d bears the effect of disturbance on the input states. Usually, $\Gamma_d = \Gamma$ *d(k)* is the input disturbance
COMBINED DISTURBANCE MODEL	**INTEGRATING DISTURBANCE MODEL**
$\begin{bmatrix} x(k+1) \\ d(k+1) \\ p(k+1) \end{bmatrix} = \begin{bmatrix} \Phi & \Gamma_d & 0 \\ 0 & I & 0 \\ 0 & 0 & I \end{bmatrix} \begin{bmatrix} x(k) \\ d(k) \\ p(k) \end{bmatrix} + \begin{bmatrix} \Gamma \\ 0 \\ 0 \end{bmatrix} u(t)$ $y(t) = \begin{bmatrix} C & 0 & \Gamma_p \end{bmatrix} \begin{bmatrix} x(k) \\ d(k) \\ p(k) \end{bmatrix}$ Γ_p *and* Γ_d are output and state disturbance transfer functions.	$\begin{bmatrix} x(k+1) \\ p(k+1) \end{bmatrix} = \begin{bmatrix} \Phi & \Gamma_d \\ 0 & I \end{bmatrix} \begin{bmatrix} x(k) \\ p(k) \end{bmatrix} + \begin{bmatrix} \Gamma \\ 0 \end{bmatrix} u(k)$ $y(k) = \begin{bmatrix} C & \Gamma_p \end{bmatrix} \begin{bmatrix} x(k) \\ p(k) \end{bmatrix}$ Γ_p *and* Γ_d are output and state disturbance transfer functions. *p(k)* is an integrating disturbance

At every sampling instant the process states and disturbance states are estimated using a recursive form of Kalman filter. The state estimator for augmented states is given by

$$\begin{aligned} \tilde{x}(k-1\,|\,k) &= \tilde{\Phi}\tilde{x}(k-1\,|\,k-1) + \tilde{\Gamma}u(k-1) \\ \tilde{x}(k\,|\,k) &= \tilde{x}(k-1\,|\,k) + K\left[\, y(k) - \tilde{C}\tilde{x}(k/k-1)\right] \end{aligned} \tag{1}$$

These equations refer to state prediction and state correction steps. K is the Kalman gain which is updated in recursive fashion.

Proper disturbance modeling coupled with optimal MPC tuning ensures perfect disturbance rejection and an offset-free response. In MPC implementation, at each sampling instant, the controller input is taken as the first element of an open-loop optimal input sequence that is computed by driving the model predicted outputs as closely as possible to a desired future trajectory. At each sampling time, the system states are estimated and a new open-loop optimization is carried out.

The process model in discrete state space form is given by,

$$x(k+1) = \widetilde{\Phi}x(t) + \widetilde{\Gamma}u(t)$$
$$y(t) = \widetilde{C}x(t) \quad (2)$$

where, $x \in R^r$, $u \in R^m$ and $y \in R^n$ represent State, Manipulated and Controlled variable vectors, respectively. State-space representation of MPC is given by Lee et al. (1994).

As in a typical MPC formulation, at each sampling instant, an **open loop state observer** is used for predicting future behavior of the plant over a finite future time horizon of length p (*prediction horizon*) starting from current time instant k. We are free to choose only q (*control horizon*) future manipulated input moves. A standard estimator for state space form models is given by,

(1)

$$\hat{Y}(k) = S_x\hat{x}(k/k-1) + S_u U_f(k) + S_d\hat{d}(k) \quad (3)$$

where

$$U_f(k) = \begin{bmatrix} u(k/k)^T & u(k+1/k)^T & \dots & u(k+q-1/k)^T \end{bmatrix}^T \quad (4)$$

$$\hat{Y}(k) = \begin{bmatrix} \hat{y}(k+1/k)^T & \hat{y}(k+2/k)^T & \dots & \hat{y}(k+p/k)^T \end{bmatrix}^T \quad (5)$$

$$\hat{d}(k) = y(k) - C\hat{x}(k/k-1) \quad (6)$$

$U_f(k)$ is future input vector, $\hat{Y}(k)$ is future output predictions. The S_x, S_u *and* S_d matrices are given by,

$$S_x = \begin{bmatrix} \widetilde{C}\widetilde{\Phi} \\ \widetilde{C}\widetilde{\Phi}^2 \\ \dots \\ \widetilde{C}\widetilde{\Phi}^p \end{bmatrix} \quad S_d = \begin{bmatrix} I \\ I \\ \dots \\ I \end{bmatrix} \text{ and } \quad S_u = \begin{bmatrix} \widetilde{C}\widetilde{\Gamma} & 0 & 0 & \dots & 0 \\ \widetilde{C}\widetilde{\Phi}\widetilde{\Gamma} & \widetilde{C}\widetilde{\Gamma} & 0 & \dots & 0 \\ \dots & \dots & \dots & \dots & 0 \\ \widetilde{C}\widetilde{\Phi}^{q-1}\widetilde{\Gamma} & \widetilde{C}\widetilde{\Phi}^{q-2}\widetilde{\Gamma} & \dots & \dots & \widetilde{C}\widetilde{\Gamma} \\ \widetilde{C}\widetilde{\Phi}^{q}\widetilde{\Gamma} & \widetilde{C}\widetilde{\Phi}^{q-1}\widetilde{\Gamma} & \dots & \dots & \widetilde{C}(\widetilde{\Phi}+I)\widetilde{\Gamma} \\ \dots & \dots & \dots & \dots & \dots \\ \widetilde{C}\widetilde{\Phi}^{p-1}\widetilde{\Gamma} & \widetilde{C}\widetilde{\Phi}^{p-2}\widetilde{\Gamma} & \dots & \dots & \widetilde{C}(\widetilde{\Phi}^{p-q}+\dots+I)\widetilde{\Gamma} \end{bmatrix} \quad (7)$$

A **future set-point trajectory**

$$R(k) = \begin{bmatrix} y_r(k+1/k)^T & y_r(k+2/k)^T & \dots & y_r(k+p/k)^T \end{bmatrix}^T \quad (8)$$

is generated at instant k as follows

$$x_r(k+j+1/k) = \Phi_r x_r(k+k/k) + \Gamma_r r(k)$$
$$y_r(k+j+1/k) = C_r x_r(k+j+1/k) \quad (9)$$

for $j = 0,1,....p-1$

The MPC problem at the sampling instant k is formulated as a constrained optimization problem as follows $\min_{U_f(k)} E(k)^T W_E E(k) + \Delta U_f(k)^T W_U \Delta U_f(k)$ (10)

subjected to the following constraints

$$
\begin{aligned}
Y^L \le \hat{Y}(k) \le Y^H \\
U^L \le U_f(k) \le U^H \\
\Delta U^L \le \Delta U_f(k) \le \Delta U^H
\end{aligned} \tag{11}
$$

where, the prediction error *E(k)* at instant *k* is given as, $E(k) = R(k) - \hat{Y}(k)$. W_E and W_U represent error weighting and input move weighting matrices, respectively, and are defined as

$$
\begin{aligned}
W_E &= diag[w_e \quad w_e \quad \ldots \quad w_e] \\
W_U &= diag[w_u \quad w_u \quad \ldots \quad w_u]
\end{aligned} \tag{12}
$$

$\Delta U_f(k)$ can be written as

$$
\Delta U_f(k) = \begin{bmatrix} u(k/k) - u(k-1) \\ u(k+1/k) - u(k/k) \\ \ldots \\ u(k+q-1/k) - u(k+q-2/k) \end{bmatrix} = \Lambda U_f(k) - \Lambda_0 u(k-1) = \begin{bmatrix} I & 0 & 0 & 0 \\ -I & I & 0 & 0 \\ \ldots & \ldots & \ldots & \ldots \\ 0 & \ldots & -I & I \end{bmatrix} U_f(k) - \begin{bmatrix} I \\ 0 \\ \ldots \\ 0 \end{bmatrix} u(k-1) \tag{13}
$$

The above formulation can be transformed into QP as follows:

$$
\min_{U_f(k)} \frac{1}{2} U_f(k)^T H U_f(k) + F^T U_f(k) \tag{14}
$$

$$
\text{subjected to } AU_f(k) \le b
$$

where,

$$
\begin{aligned}
H &= 2(S_u^T W_E S_u + \Lambda^T W_U \Lambda) \\
F &= -2\left[\left(R(k) - S_x \hat{x}(k/k-1) - S_d \hat{d}(k)\right)^T W_E S_u + (\Lambda_0 u_{k-1})^T W_U \Lambda\right]
\end{aligned} \tag{15}
$$

$$
A = \begin{bmatrix} I_{qm} \\ -I_{qm} \\ \Lambda \\ -\Lambda \\ S_u \\ -S_u \end{bmatrix} \quad \text{and} \quad b = \begin{bmatrix} U^H \\ -U^L \\ \Delta U^H + \Lambda_0 u_{k-1} \\ -\Delta U^L - \Lambda_0 u_{k-1} \\ -S_x \hat{x}(k/k-1) - S_d \hat{d}(k) + Y^H \\ S_x \hat{x}(k/k-1) + S_d \hat{d}(k) - Y^L \end{bmatrix} \tag{16}
$$

The controller is implemented in a moving horizon framework. Thus, after solving the optimization problem, only the first move $u_{opt}(k|k)$ is implemented on the patient, and optimization problem is reformulated at the next sampling instant based on the updated information from the patient. The algorithm is given in Figure 2.

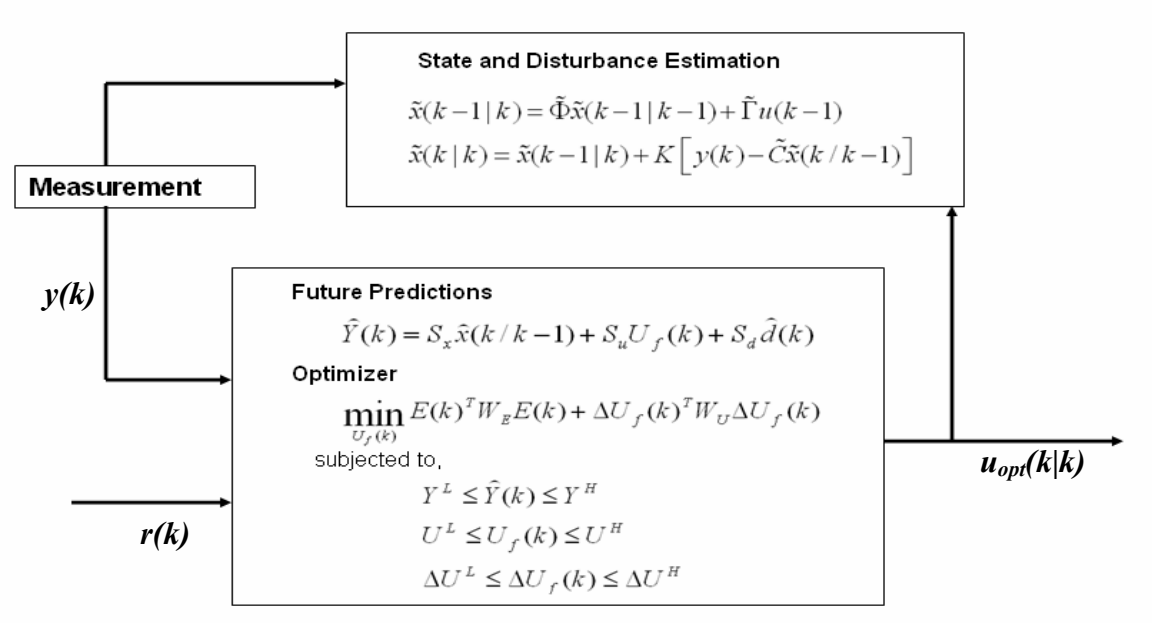

Figure 2: Block diagram of MPC/SE algorithm

3. RESULTS AND DISCUSSIONS

The objective of this work is to design a robust model based control for effective disturbance rejection under plant model mismatch. Three kinds of patient models whose response is distinct from each other are considered for performing simulation studies. The steady-state information for three patients is given in Table 2.

Table 2: Steady state behavior of three test patient simulations

Patient	Steady-state Insulin Infusion rate (mU/min)	Steady-state Blood Glucose concentration (mg/dl)
1	22.3	81.141
2	15.205	81.0635
3	22.88	81.1

The simulation studies are carried out using Simulink® model and Matlab® routines. A meal disturbance was introduced at 1000 min into the patient simulations. The responses of three patients for the similar meal disturbance in open loop (without control action) are plotted in Fig.3. It was observed that, the blood glucose levels increased up to 140 to 170 mg/dl. Even though these levels reduced to normal eventually, the time period for which they are above the normoglycemia threshold was significant. This has to be considered seriously, as the prolonged hypo- or hyperglycemic excursion deteriorates the metabolism rates.

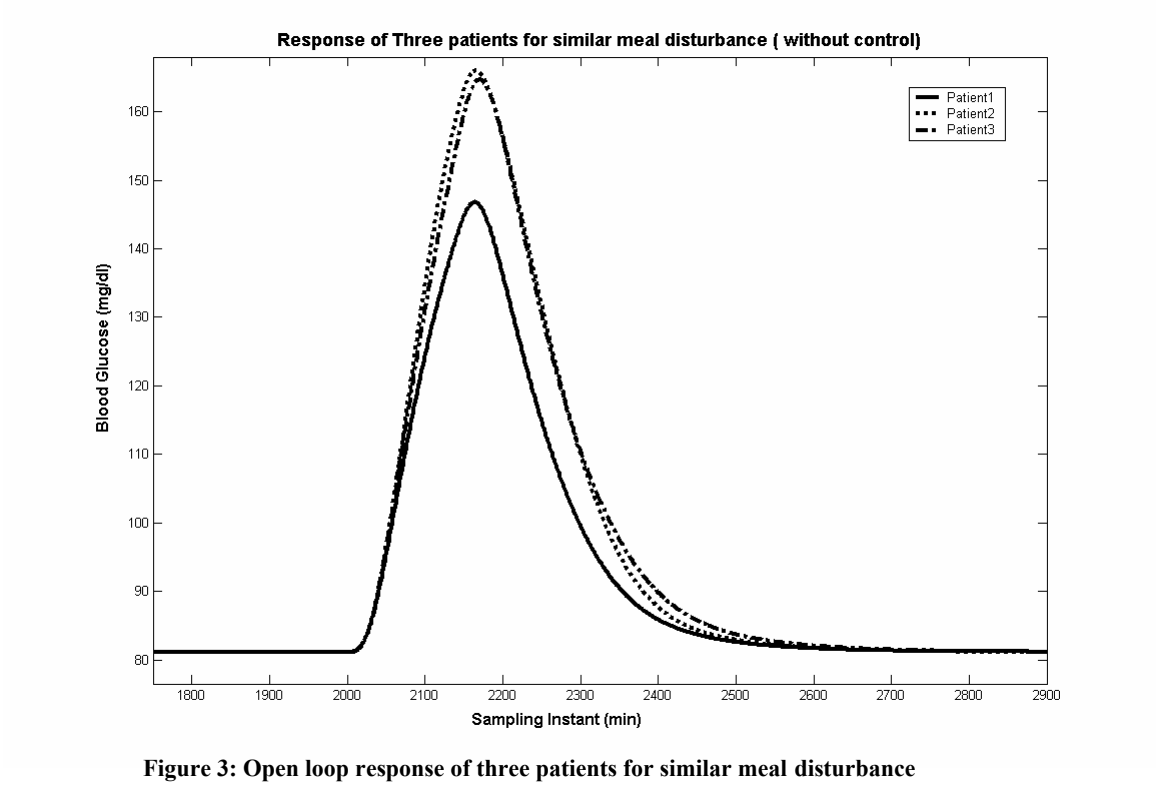

Figure 3: Open loop response of three patients for similar meal disturbance

3.1 Mathematical Modeling:

Patient-1 was used for perturbation studies and subsequent model generation. The choice of sampling time was made keeping view of system dynamics and constraints on the sensor sampling rates. As the approximate settling time was 85 min to capture the faster dynamics the sample time must be less than 17 min (20%). Lower bound on the sampling time was derived from the ability of BGL sensor. Researchers in the sensor field have reported the ability to sample glucose every 1 min utilizing a commercially available electrochemical biosensor (Wilson and Gifford, 2005). Latest literature discusses the work on some sensors which are reported to measure the blood glucose concentrations at a rate 15 sec, which are yet to be commercialized. In this work a sampling time of 1 min was chosen.

A pseudo random binary sequence (PRBS) input signal in insulin infusion rate is introduced at time t=1000min to t=2000min. The PRBS signal was generated using ***idinput*** routine in matlab. The switching time was chosen to be equal to 10 sampling instants, which was appropriate to study the fast rate dynamics of the patient. The obtained input (insulin infusion rate) and output (blood glucose concentration) data is plotted in Fig.4.

A third order state-space model was built using the ***ident*** toolbox in Matlab® using prediction error method. A prediction accuracy of 89.01% was obtained using this

model. The step response and impulse responses for model simulations were in good agreement with the actual patient-1 simulations.

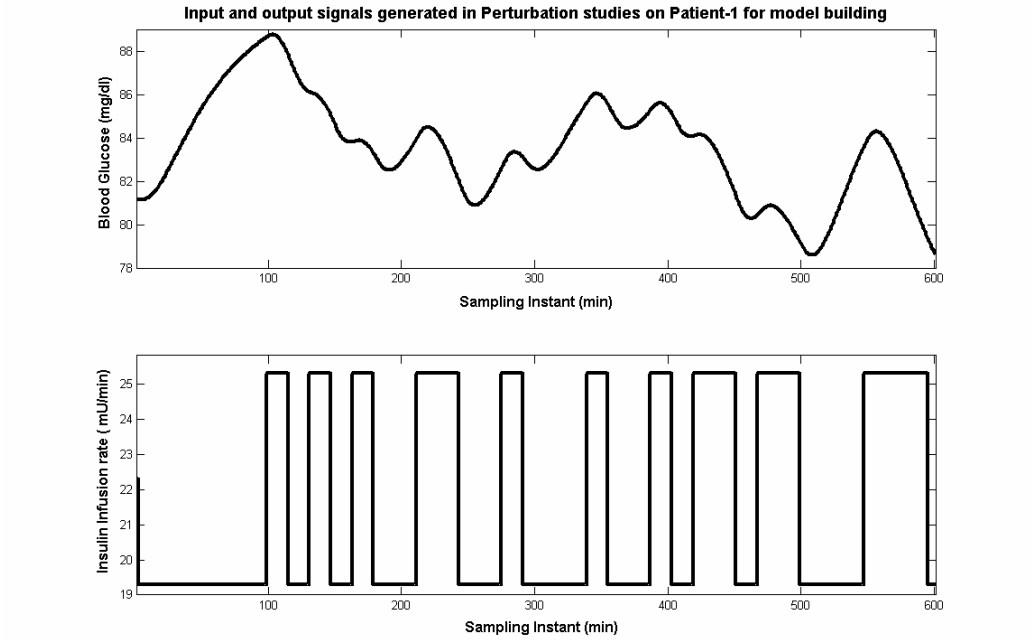

Figure 4: Input - output data generated using perturbations studies on patient-1 for model building

The developed 3rd order state-space model is given by,

$$x(t+1)=\begin{bmatrix} 1.0186 & -0.083982 & 0.0038902 \\ 0.028795 & 0.98165 & -0.076631 \\ -0.0078752 & 0.19558 & 0.76488 \end{bmatrix}x(t)+\begin{bmatrix} -2.1466e-06 \\ 3.9958e-05 \\ -0.001936 \end{bmatrix}u(t) \qquad (17)$$

$$y(t)=\begin{bmatrix}56.291 & -0.99586 & 0.029398\end{bmatrix}x(t)$$

$$and, x(0)=\begin{bmatrix}-0.042213 & -0.0099637 & -0.01299\end{bmatrix}^T$$

The disturbance was assumed to enter as both additive and state/input form. As evident from the open-loop disturbance responses plotted in Fig.3, an integrating disturbance produced a prolonged deviation in the output from the steady state. As discussed earlier, 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

$$\begin{bmatrix} x(k+1) \\ p(k+1) \end{bmatrix}=\begin{bmatrix} \Phi & \Gamma_d \\ 0 & I \end{bmatrix}\begin{bmatrix} x(k) \\ p(k) \end{bmatrix}+\begin{bmatrix} \Gamma \\ 0 \end{bmatrix}u(k) \qquad (18)$$

$$y(k)=\begin{bmatrix} C & \Gamma_p \end{bmatrix}\begin{bmatrix} x(k) \\ p(k) \end{bmatrix}$$

where, $\Gamma_p = I$, $\Gamma_d = \beta \times \Gamma$ and β is chosen to be $2.5x10^3$, which is a tuning parameter. Here one (= number of outputs) state is augmented so as to ensure the observability and controllability of the augmented model. The augmented model is given by,

$$
\begin{aligned}
x(t+1) &= \begin{bmatrix} 1.0186 & -0.0840 & 0.0039 & 0.0054 \\ 0.0288 & 0.9816 & -0.0766 & -0.0999 \\ -0.0079 & 0.1956 & 0.7649 & 4.8401 \\ 0 & 0 & 0 & 1 \end{bmatrix} x(t) + \begin{bmatrix} -2.1466e-06 \\ 3.9958e-05 \\ -0.001936 \\ 0 \end{bmatrix} u(t) \\
y(t) &= \begin{bmatrix} 56.291 & -0.99586 & 0.029398 & 1 \end{bmatrix} x(t) \\
and, x(0) &= \begin{bmatrix} -0.042213 & -0.0099637 & -0.01299 & 0 \end{bmatrix}^T
\end{aligned}
\tag{19}
$$

Observability matrix for this augmented system was found to be a full rank matrix and hence the augmented system was observable. The controllability matrix was of rank *3*. The difference in rank of controllability matrix and the rank of Φ gave the number of uncontrolled states. As the rank of Φ was 4, the number of uncontrolled states was *1*, which is evidently the disturbance entering into the process. And other states which directly influence the output were controllable; hence, the process was controllable.

3.2 Control Implementation:

Three controllers are studied for their performance for disturbance rejection.

- Linear Model Predictive Controller (using actual process model and without output constraints)
- State Estimation based MPC with augmented process model (without output constraints)
- State Estimation based MPC with augmented process model with output constraints

For all these controllers the common control parameters used are given by,

Weight on error in MPC objective function, $w_e = 2$
Weight on input-rate in MPC objective function, $w_u = 0.6$
Prediction horizon, $p = 400$
Control horizon, $q = 1$
Bounds on Input (Insulin Infusion rate) = [0 and 250] mU/min
Input-Rate bounds = [-10 and 10] mU/min

For State Estimation based MPC, the Kalman filter parameters are given by,

Output covariance, $R = 0.1$
State covariance matrix, $Q = 0.4\, I_{4x4}$

For the third controller the Output (Blood glucose concentration) bounds are given as [Y_s-6 and Y_s +8] mg/dl, where Y_s is the steady-state Blood glucose concentration when there is no disturbance.

The performance of the Linear Model Predictive Controller without output constraints using actual process model ws plotted in the Fig.5. These controller parameters were first tuned for patient-1 and then detuned to get optimal performance in

all the three patients. The control parameters were reported earlier. 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 higher than the allowable range (70-100 mg/dl). This controller was to be rejected.

To account for the disturbance that entered the process and effectively rejecting it by taking appropriate action, a proper disturbance model and an observer were essential. A State Estimation based MPC (MPC/SE) was implemented to serve this purpose. The response with MPC/SE in three patients is plotted in the Fig.6. It was observed that the controller showed tremendous improvement in disturbance rejection in the case of patient-1 and patient-2. But, patient-3 displayed hypo- and hyperglycemic excursion of blood glucose.

Later, to increase the sensitivity of MPC/SE algorithm output constraints were introduced in 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 in normal condition. Hence, they were not designed to be stringent. The response of MPC/SE with output constraints was found to be satisfactory for all the patients and shown in Fig.7. This was achieved with a maximum insulin infusion rate of 245 mU/min. It was reported that the maximum insulin excretion rate in a healthy human being is 100 mU/min, and it is impossible to remove insulin once it has been delivered to the patient. This problem can be solved by using multi-point injection and following homogenization strategies (Ellison et al., 2002) which reduces the risk of exposure of higher amounts of insulin as a pulse.

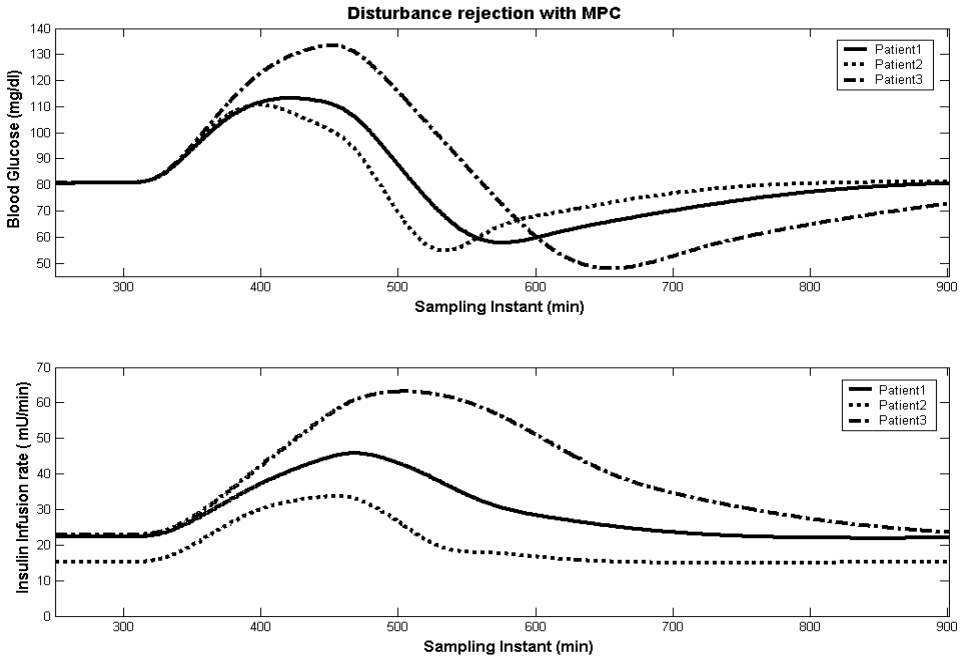

Figure 5: Disturbance rejection with Linear Model Predictive Control for three patients for a similar kind of meal disturbance

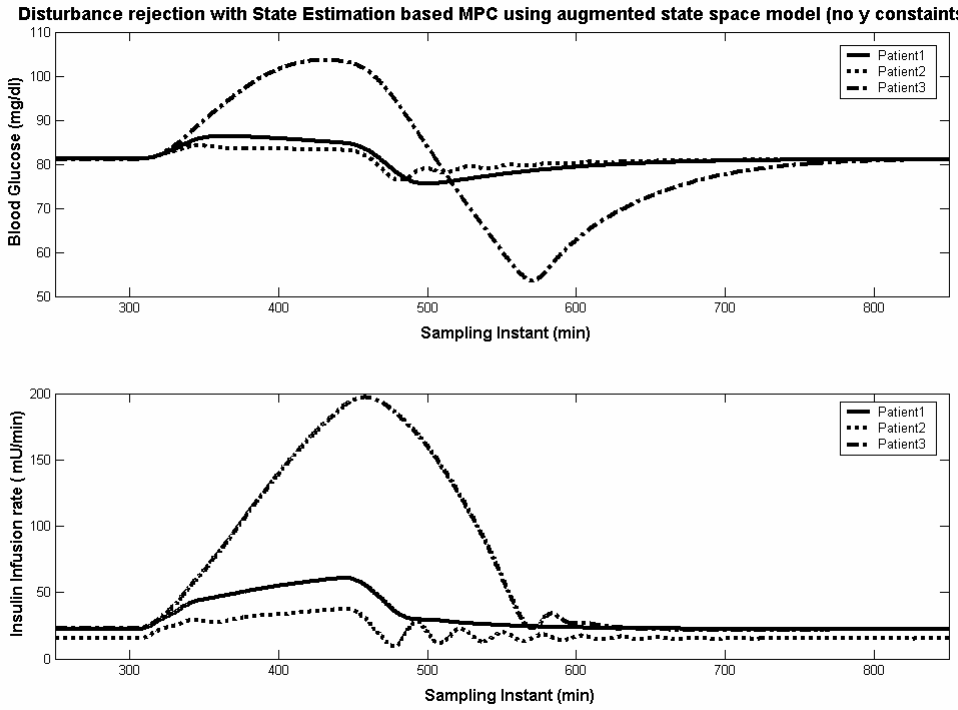

Figure 6: Disturbance rejection with State Estimation based Linear Model Predictive Control using augmented state space model (without output constraints) for three patients for a similar kind of meal disturbance

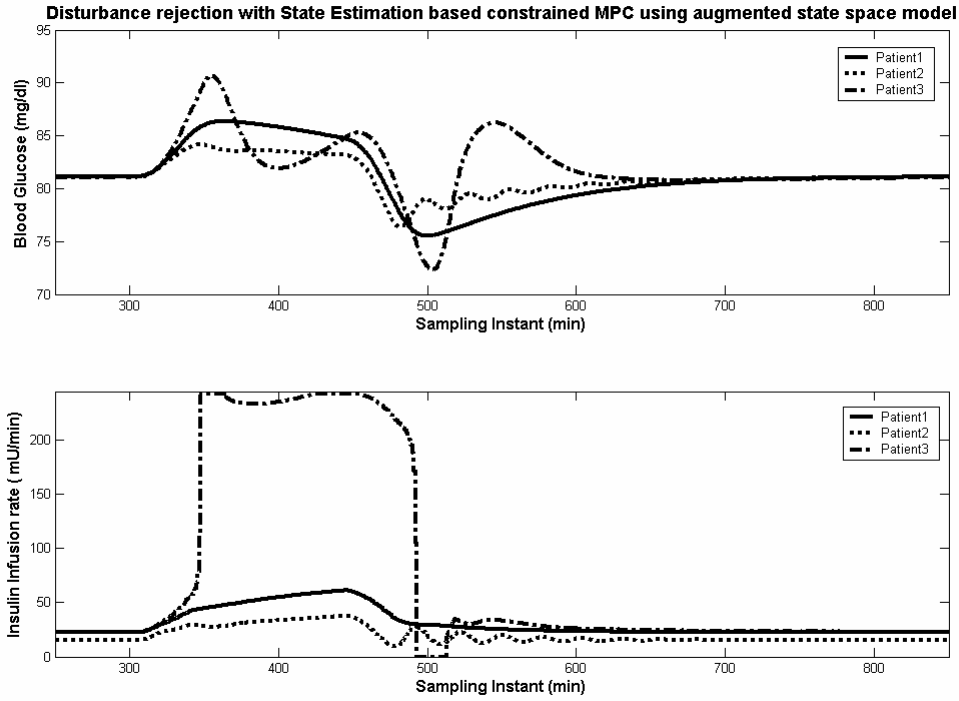

Figure 7: Disturbance rejection with State Estimation based Constrained Linear Model Predictive Control with augmented state space model for three patients for a similar kind of meal disturbance

Finally, the performances of the three controllers are tabulated in Table 3. As these controllers were tuned in an iterative fashion these parameters may not be optimal. But, it is evident from the table that constrained MPC/SE with proper disturbance modeling efficiently rejects the disturbance.

Table 3: Comparison of performance of different control algorithms for insulin infusion control

	LMPC			MPC/SE			MPC/SE with output constraints		
	Patient1	Patient2	Patient3	Patient1	Patient2	Patient3	Patient1	Patient2	Patient3
Settling time (min)	610	460	710	310	260	435	310	260	280
Overshoot (mg/dl)	113.2	110.5	133.5	86.3	84.1	103.5	86.3	84.1	90.5
Undershoot (mg/dl)	57.8	54.8	47.9	75.5	76.5	53.6	75.5	76.5	72.4
Sum of Squares of Error ($x 10^3$)	166.38	122.3	444.21	4.5245	1.4903	94.274	4.525	1.4903	5.59

5. CONCLUSIONS AND FUTURE WORK

Model-based predictive control of insulin infusion system requires a compensation mechanism for mismatch in patient behavior and model predictions given external disturbances such as meal or exercise. Disturbance modeling by additional augmented disturbance states as integrating process will essentially serve this purpose. A MPC/SE algorithm with augmented state space model was used for insulin infusion control. Physical and physiological constraints were incorporated in the control design. It was observed that, even under huge process-model mismatch with an integrating type of disturbance (meal disturbance) entering the system, constrained MPC/SE with augmented state space model gave promising control ensuring perfect normoglycemia. In addition to efficient disturbance rejection, the digital nature of this control algorithm enables potential implementation onto to a microprocessor chip, which makes it possible to design portable insulin infusion systems mounted on the patient.

Future work is directed towards zone control of the blood glucose concentration to further reduce the control effort. In MPC objective function instead of having a single setpoint, a zone is to be defined and the setpoint is also made as an optimization variable (along with input moves) which is to be constrained in the zone. This modification is expected to give drastic reduction in insulin consumption, but still giving the desired performance.

REFERENCES

Broekhuyse H. M., Nelson J. D., Zinman B., and Albisser A. M. (1981), Comparison of algorithms for the closed-loop control of blood glucose using the artificial beta cell, *IEEE Transactions in Biomedical Engineering,* vol. BME-28, pp. 678–687.

Cobelli C. and Mari A. (1983), Validation of mathematical models of complex endocrine-metabolic systems. A case study on a model of glucose regulation, *Medical and Biological Engineering Computation.,* vol. 21, pp. 390–399.

Davison E.J., Smith H.W. (1971), Pole assignment in linear time-invariant multivariable systems with constant disturbances, *Automatica*, 7, 489–498.

Fisher M. E. (1991), A semiclosed-loop algorithm for the control of blood glucose levels in diabetics, *IEEE Transactions in Biomedical Engineering,* vol. 38, pp. 57–61.

Feldman, B., Brazg, R., Schwartz, S., Weinstein, R. (2003), A continuous glucose sensor based on wired enzyme technology—results from a 3-day trial in patients with Type I diabetes. *Diabetes Technology Ther.* 5, 769–779.

Gopinath R., Bequette B. W., Roy R. J., Kaufman H., and Yu C. (1995), Issues in the design of a multirate model-based controller for a nonlinear drug infusion system, *Biotechnoogy Progress,* vol. 11, pp. 318–332.

Gross, T.M. (2000), Efficacy and reliability of the continuous glucose monitoring system. *Diabetes Technology Ther*. 2, S19–S26.

Kennedy F. P. (1991), Recent developments in insulin delivery techniques, current status, and future potential, *Drugs,* vol. 42, pp. 213–227.

Kwok K. Y., Shah S. L., Clanachan A. S., and Finegan B. A. (1992), Evaluation of a long-range adaptive predictive controller for computerized drug delivery systems, in *Proc. IFAC Adaptive Signals in Control and Signal Processing Conference* pp. 317–322.

Lee, J.H., Morari, M., and Garcia, C.E. (1994), State-space interpretation of Model Predictive Control, *Automatica* 30(4), 707-717.

Mastrototaro, J.J. (2000), The MiniMed continuous glucose monitoring system. *Diabetes Technology Ther*. 2, S13–S18.

Meyerhoff C., Bischof F., Sternberg F., Zier H., and Pfeiffer E. F. (1992), On line continuous monitoring of subcutaneous tissue glucose in men by combining portable glucosensor with microdialysis, *Diabetologia,* vol. 35, pp. 1087–1092.

Morari M., Lee J.H. (1991), Model predictive control: the good, the bad, and the ugly, in: Arkun Y., Ray W.H. (Eds.), Chemical Process Control—CPC IV, *Fourth International Conference on Chemical Process Control*, Elsevier, Amsterdam, pp. 419–444.

Muske K.R., Badgwell T.A. (2002), Disturbance modeling for offset-free linear model predictive control *Journal of Process Control* , 12, pp. 617–632

Parker R.S., Doyle F.J., and Peppas N.A. (1999), A Model-Based Algorithm for Blood Glucose Control in Type I Diabetic Patients, *IEEE Transactions in Biomedical Engineering*, 46, 2, 148-157.

Preidel W., Saeger S., I. Von Lucadou, and Lager W. (1991), An electrocatalytic glucose sensor for in-vivo application, *Biomedical Instrumentation Technology,* vol. 25, pp. 215–219.

Qin S.J., Badgwell T.A. (1997), An overview of industrial model predictive control technology, in: Kantor J.C., Garcy C.E., Carnahan B. (Eds.), *Fifth International Conference on Chemical Process Control*, AIChE Symposium Series, Vol. 93, No. 316, pp. 232–256.

Rao C.V., Wright S.J., Rawlings J.B. (1998), Application of interior point methods to model predictive control, *Journal of Optimization Theory Applications*, 99, 723–757.

Salzsieder E., Albrecht G., Fischer U., and Freyse E.-J. (1985), Kinetic modeling of the glucoregulatory system to improve insulin therapy, *IEEE Transactions in Biomedical Engineering,* vol. BME-32, pp. 846–855.

Selam J.L. and Charles M. A.(1990), Devices for insulin administration, *Diabetes Care,* vol. 13, pp. 955–979.

Taylor, C., Kenausis, G., Katakis, I., Heller, A. (1995), Wiring of glucose oxidase with a hydrogel made with polyvinyl imidazole coplexed with [(Os-4,4'-dimethoxy-2,2'-bipyridine)Cl]$^{+/2+}$. *Journal of Electroanalytical Chemistry* 396, 511–515.

Wada D. R. and Ward D. S. (1995), "Open loop control of multiple drug effects in anesthesia," *IEEE Transactions in Biomedical Engineering,* vol. 42, pp. 666–677.

Wilson. G.S., Gifford R. (2005), Biosensors for real-time in vivo measurements, *Biosensors and Bioelectronics*, in press, vol. 20(12) , pp. 2388-2403.

Ellison John M, Janet M. Stegmann, Sandra L. Colner, Ragui H. Michael, Manoj K. Sharma, Kenneth R. Ervin, and David L. Horwitz (2002), Rapid Changes in Postprandial Blood Glucose Produce Concentration Differences at Finger, Forearm, and Thigh Sampling Sites, *Diabetes Care* 25:961-964, 2002.