Proceedings of the American Control Conference
Anchorage, AK May 8-10, 2002

Model Predictive Control of Blood Glucose in Type I Diabetics Using Subcutaneous Glucose Measurements

Sandra M. Lynch and B. Wayne Bequette*
Isermann Department of Chemical Engineering
Rensselaer Polytechnic Institute, Troy, NY 12180-3590

ABSTRACT

A constrained model predictive controller is implemented on a simulated Type I diabetic patient. A Kalman Filter is used to estimate the blood glucose concentration based on a subcutaneous glucose measurement. The model predictive controller returns blood glucose to normoglycemic ranges when subjected to a meal disturbance. The settling time is similar to that of a non-diabetic.

1. MOTIVATION

Diabetes Mellitus refers to the condition in which the pancreas produces insufficient insulin to control the blood glucose level in a person. Type I diabetes occurs when the pancreas produces no effective insulin whatsoever, thus leading to *hyperglycemia*, the situation when the blood glucose level rises much higher than 135mg/dL for prolonged periods of time. *Hypoglycemia* refers to the situation when the blood sugar level falls below values of 60mg/dL. Both situations can be deleterious to the individual's health. Hyperglycemia leads to blindness, kidney failure, and other complications on a long-term basis. The effects of hypoglycemia are more critical on a short time basis, leading to loss of consciousness and coma within a few hours if not treated (Guyton, 1996).

Treatment consists of daily injections or continuous infusions of insulin to maintain blood glucose levels between critical values. The Diabetes Control and Complications Trial (DCCT, 1993) established the importance of intensive glycemic control in Type I diabetics for prevention of long-term complications due to hyperglycemia but care must also be taken to prevent hypoglycemia. Thus tight control of blood sugar levels is desirable and is achieved by taking glucose readings 4 times a day, and adjusting insulin dosage to meal intake and exercise activity. An insulin pump is designed to deliver insulin to the patient at a continuous rate, and is preferred over the injection route, as it reduces the risk of overdose and hypoglycemia and more accurately simulates the normal pancreas.

The resting range of blood glucose falls between 70-100mg/dL, and is the target range for a controller regulating blood glucose level. The aim of the controller design then is to curb the hyperglycemic trajectory to as short a time as possible, to eliminate hypoglycemia below 60mg/dL and to return to and maintain normoglycemic levels within 3 hours.

2. BACKGROUND

Insulin therapy has traditionally been divided into two major routes of application: intravenous and subcutaneous. Bellazzi *et al.* (2001) discuss a number of applications involving subcutaneous diabetic therapy, while Parker *et al.* (2001) present a review of intravenous methods of therapy.

The major impediment to closed-loop control of blood glucose has been the development of a reliable sensor that functions for a significant length of time. Glucose sensors under development take measurements from the subcutaneous layer. Intravascular insertion is more accurate but infection at this site is more likely (Armour *et al.*, 1990). The relationship between blood glucose and subcutaneous glucose concentrations have been modeled by many workers by a first-order lag term minus the rate of utilization of glucose by the subcutaneous tissue (Freeland *et al.*, 1999; Schmidtke *et al.*, 1998; Sorenson, 1985).

Parker *et al.* (1999, 2001) designed and implemented several model predictive controllers (MPC) on a simulated 19-state nonlinear model of a diabetic patient. It was assumed that arterial blood glucose measurements were available, and that insulin was delivered intravenously.

Many models have been suggested in literature describing the human-glucose insulin system. Of these the Bergman *et al.* (1981) model presents a minimal model using 3 equations to describe the dynamics of the system as simply as possible. Fisher (1991) uses this model to develop 3 open-loop controllers based on optimization techniques.

In this work the Bergman model is used to develop controllers to regulate the system based on the subcutaneous glucose measurement, since we anticipate that these sensors are most likely to receive FDA approval in the near future.

3. BERGMAN "MINIMAL MODEL"

The Bergman minimal model consists of 3 differential equations. Fisher (1991) developed the following modified form for a type I diabetic by omitting the insulin secretion term and inserting an insulin infusion term in equation (3).

$$\frac{dG}{dt} = -P_1 G - X(G + G_b) + D(t) \qquad (1)$$

$$\frac{dX}{dt} = -P_2 X + P_3 I \qquad (2)$$

$$\frac{dI}{dt} = -n(I + I_b) + U(t)/V_I \qquad (3)$$

where the states are blood plasma glucose concentration (G, mg/dl) above basal value, a species proportional to insulin in the remote compartment (X, mU/L), and plasma insulin

* bequette@rpi.edu

0-7803-7298-0/02/$17.00 © 2002 AACC

concentration (I, mU/L) above basal value. The inputs are the meal glucose disturbance ($D(t)$, mg/dL/min) and the manipulated insulin infusion rate ($U(t)$, mU/min). The parameter values are

G_b = 81 mg/dL (4.5 mmol/L), basal glucose conc.
I_b = 15 mU/L, basal insulin concentration
V_I=12L
n = 5/54 min^{-1}

Since most glucose measurements are obtained via the subcutaneous layer, the model was augmented with a 4th equation relating subcutaneous glucose concentrations to the blood glucose concentration. Subcutaneous values are then used to estimate and control the blood glucose value. The 4th equation models a first-order lag of 5 minutes between blood glucose concentration and subcutaneous glucose with the tissue rate of utilization (R_{utln}, mg/dL/min) accounting for the steady state difference betweeen the two. This equation is given by:

$$\frac{dG_{sc}}{dt} = \frac{G - G_{sc}}{5} - R_{ut\ln} \qquad (4)$$

where G_{sc} is the glucose concentration in the subcutaneous or peripherous layer (mg/dL).

Meal Disturbance Models

Fisher (1991). The meal disturbance function is:

$$D(t) = A\exp(-0.05t) \qquad (5)$$

where t is in minutes, $D(t)$ is in mg/dL/min.

Lehmann and Deutsch (1992). The rate of glucose absorption via the gut wall is

$$RG_{abs} = K_{gabs}G_{gut} \qquad (6)$$

where RG_{abs} is the rate of glucose absorption via the gut wall (mg/min). G_{gut} is the amount (mg) of glucose in the gut following ingestion of a meal and is defined by the following differential equation:

$$\frac{dG_{gut}}{dt} = RG_{empt} - K_{gabs}G_{gut} \qquad (7)$$

RG_{empt} is the rate of gastric emptying which is described by a trapezoidal function, saturating at V_{max}, the maximal rate of gastric emptying. K_{gabs} is the rate constant for glucose absorption from the gut and is given the value of $1h^{-1}$. Incorporating this oral disturbance into equation (1) gives:

$$D(t) = RG_{abs} / V_I . \qquad (8)$$

4. ESTIMATION-BASED MODEL PREDICTIVE CONTROL

In model predictive control (MPC), the value of the estimated state output (blood glucose) is predicted P sample times into the future, based on model of the process. The objective is to minimize the square of the deviations of the model-predicted output from the desired setpoint trajectory, by adjusting M future control (insulin infusion) moves:

$$J = \sum_{i=1}^{P} (r_{k+i} - \hat{y}_{k+i})^2 + \lambda \sum_{i=1}^{M} \Delta u_{k+i-1}^2 \qquad (9)$$

where J is the objective function, k is the sample time index, λ is the weighting on the manipulated input, Δu is the manipulated input increment, r is the blood glucose setpoint, and $\hat{y}$ is the predicted blood glucose concentration.

The first control move in the sequence is implemented, and at the next step the optimization is repeated.

A clear advantage of MPC is that the control algorithm can explicitly enforce constraints. Physiological constraints are necessary in the diabetic system, encompassing the limits of hyperglycemia/hypoglycemia. The following constraints were imposed.

$$0 \le u \le 100\text{mU/min} \qquad (10)$$

$$60\text{mg/dL} \le \hat{y} \le 180\text{mg/dL} \qquad (11)$$

$$-16.7\text{mU/min} \le \Delta u \le 16.7\text{mU/min} \qquad (12)$$

Limits on u were chosen to maintain insulin concentrations below 100mU/L. The value of Δu was chosen to ensure that changes in delivery rate are within the capabilities of the pump mechanism (Parker *et al.*, 1999).

The Bergman parameters P_1, P_2, and P_3 for a Type I diabetic were obtained using a least squares algorithm to fit the blood glucose and subcutaneous glucose concentrations of the Sorenson (19^{th} state nonlinear model) plant for step changes in input to give:

$P_1 = 0.028735\ min^{-1}$ $P_2 = 0.028344\ min^{-1}$
$P_3 = 5.035\text{x}10^{-5}$mU/L

Values of steady state blood and subcutaneous glucose concentrations (G_b and G_{bsc}) were obtained from the Sorenson steady state data (the 7^{th} and 8^{th} state respectively) to be 81.3 mg/dL, and 77.6 mg/dL.

This model is discretized with a sample time of 5 minutes in the form:

$$x_{k+1} = \Phi x_k + \Gamma u_k + \Gamma_d d_k \qquad (13)$$

$$d_{k+1} = d_k + w_k \qquad (14)$$

$$y_{k+1} = Cx_{k+1} + v_k \qquad (15)$$

The term v_k is the noise on the output measurement, while w_k is the noise on the input disturbance d_k, (glucose meal) to the system, which is then augmented as a state to the 4 state model to give the following state space system:

$$\Phi^a = \begin{pmatrix} 8.67\text{x}10^{-1} & -3.52\text{x}10^{2} & -4.67\text{x}10^{-2} & 0 & 4.67 \\ 0 & 8.68\text{x}10^{-1} & 2.19\text{x}10^{-4} & 0 & 0 \\ 0 & 0 & 6.290\text{x}10^{-1} & 0 & 0 \\ 5.62\text{x}10^{-1} & -1.32\text{x}10^{2} & -1.28\text{x}10^{-2} & 3.39\text{x}10^{-1} & 1.71 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$$\Gamma^a = \begin{pmatrix} -6.90\text{x}10^{-3} & 0 \\ 5.05\text{x}10^{-5} & 0 \\ 3.34\text{x}10^{-1} & 0 \\ -1.46\text{x}10^{-3} & 0 \\ 0 & 1 \end{pmatrix} \qquad C = [0 \quad 0 \quad 0 \quad 1 \quad 0]$$

$$D = [0 \; 0]$$

These state space matrices are then used in the Kalman Filter-based MPC strategy to improve disturbance rejection.

Only the 4th state is measured, so state estimation is used to determine the best estimate of the current state vector, which is used as the initial condition for the future predictions. The Kalman Filter (KF) used is of the following form:

$$\hat{x}^a_{k|k-1} = \Phi^a \hat{x}^a_{k-1|k-1} + \Gamma^a u_{k-1} \qquad (16)$$

$$\hat{x}^a_{k|k} = \hat{x}^a_{k|k-1} + L(y_k - C^a \hat{x}^a_{k|k-1}) \qquad (17)$$

where $\hat{x}_{m|n}$ represents the estimate at time step m, given measurements up to time step n, y_k is the actual measured value with 1% standard deviation in Gaussian distribution sensor noise (v_k), and L is the steady-state Kalman Filter gain. Superscript a indicates that the disturbance is modeled as an additive input and is augmented into the state space matrices as a fifth state. Q/R is used as a tuning parameter, where Q is the variance of noise on the disturbance, and R is the variance of noise on the output measurement, a high Q/R ratio infers that noise on disturbance is high, but the estimate is aggressive, while a low ratio indicates a slower smoother estimate. The actual values used vary from 0.01 – 0.10.

The goals are to reduce the hyperglycemic trajectory to as short a time as possible, to avoid hypoglycemia below 60 mg/dL and to return to and maintain normoglycemic levels within 3 hours.

5. RESULTS

5.1 Perfect Model

The controller's action was demonstrated on the perfect model, with Fisher's disturbance at t = 100 minutes. The controller was tuned to values of P=10, M=1, to achieve the results displayed in Figure 1. Higher values of M cause more aggressive control action resulting in oscillatory behavior. A relatively high prediction horizon is desirable so as to predict a hypoglycemic trend, and curb insulin delivery. However too long a prediction horizon produces sluggish reaction to the rising blood glucose levels. The Kalman Filter also shows excellent tracking of the actual blood glucose, although only the subcutaneous is measured.

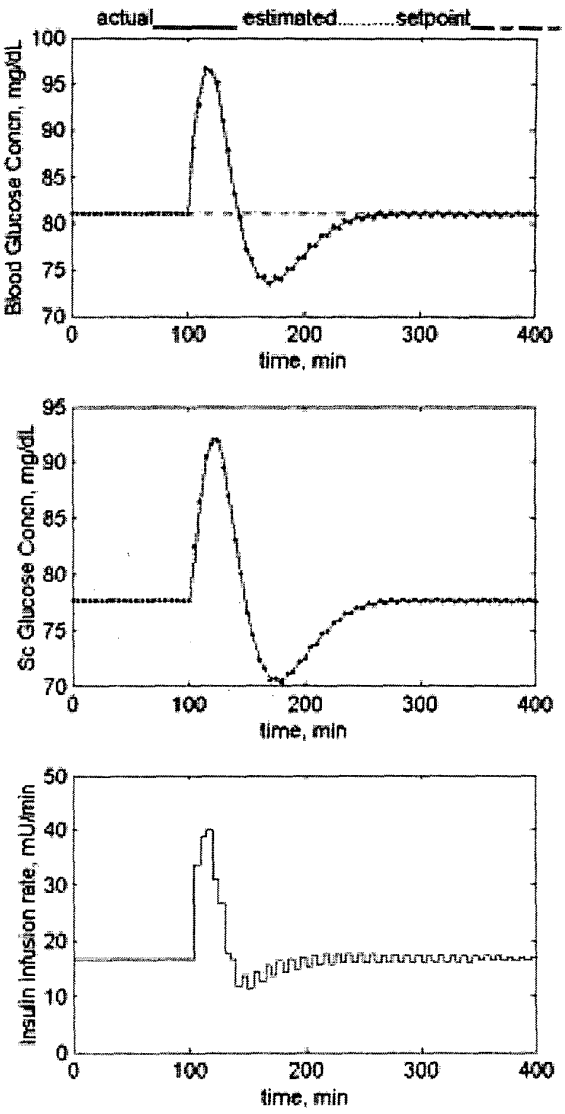

Fig 1. Action of MPC controller based on perfect model as plant

Plant-Model Mismatch

In order to simulate a Type I diabetic patient, use of a higher order model is desirable to more accurately describe the interactions and responses of the glucose-insulin mechanisms of the body. The Sorenson (1985) model, used here to simulate the patient, consists of 22 states describing glucose, insulin and glucagon concentrations in various regions of the body, with three of the equations representing a fully functioning pancreas. For the Type I Diabetic simulation, the three pancreatic equations are removed, and a term representing intravenous insulin infusion is introduced. The model used by the estimator/controller remains the low-order model used previously. It should be noted that Parker *et al.* (1999, 2000, 2001) have also used the Sorenson model to represent a Type 1 diabetic.

In Fig 2, Fisher's meal disturbance is implemented at t = 100 minutes, and the resulting trajectory with the response of the MPC strategy plotted. It is demonstrated that the MPC ably handles the 50g meal disturbance, with blood

glucose rising to 95mg/dL maximum within half an hour, decreasing to 75mg/dL minimum and thus is kept safely within normoglycemic ranges. The blood glucose concentration then returns to setpoint levels within 3 hours in time for the next meal. The Kalman Filter estimate of the blood glucose matches the true value closely, deviating slightly during the rise in blood glucose after the 50g meal disturbance. Q/R tuning parameter was adjusted to a value of 0.01 to obtain the desired response, P and M the prediction and control horizons, were tuned to values of 10 and 1 respectively.

The subcutaneous measurement is also displayed in Fig. 2b, and shows quite good correlation with the blood glucose measurement trajectory displayed above. The maximum insulin infusion rate reaches just above 40 mU/min. The response to the Lehmann meal disturbance at t=100 minutes is shown in Fig. 3. Tuning parameters used were Q/R ratio=0.11, P=5, M=1. The maximum levels are similar to Fisher's disturbance, but the glucose levels approach 65mg/dL. This however does not reach the hypoglycemic value of 60 mg/dL. The trajectory of the subcutaneous measurement continues to show good correlation with the blood glucose values, as with the previous form of the disturbance.

Because of utilization of glucose in the subcutaneous tissue, the subcutaneous glucose concentration falls 2-3 mg/dl below that of the blood glucose value. However the general rise and fall of the blood glucose trajectory is matched quite closely by a corresponding pattern in the subcutaneous trajectory. Since both trajectories are kept out of the critical bounds, subcutaneous measurements are thus adequate for controlling blood glucose. On the lower bound approaching hypoglycemia, a downward trend in subcutaneous measurements would be anticipated by the MPC strategy and corrected before the blood glucose trajectory reaches the hypoglycemic bound. On the upper bound, where the blood glucose would perhaps reach the hyperglycemic bound first, the time element is not as critical, as long as normoglycemia can be resumed in a couple of hours. Thus the use of subcutaneous measurements has proven effective in controlling blood glucose level in this simulation study.

6.CONCLUSIONS and FUTURE WORK

These simulations of a Type I Diabetic indicate that blood glucose levels can be adequately controlled using state estimation based on saturation measurements and Model Prediction Control. Performance would be improved by use of a dynamic Kalman Filter, and our current effort involves subcutaneous rather than intravenous insulin delivery, as well as the use of infrequent blood glucose measurements to update the Kalman Filter estimates. The Sorenson model does not realistically capture the extremes of the blood glucose deviations, especially into hyperglycemia, in periods of food consumption, or during nocturnal periods. Future studies will include a more realistic simulation of a Type I Diabetic patient.

ACKNOWLEDGMENTS

Brian Aufderheide contributed to the model development.

REFERENCES

Armour, J., Lucisano B., McKean B., and Gough, D.,"Application of chronic intravascular blood glucose sensor in dogs," *Diabetes* 39, 1519-1526 (1990).

Bellazzi, R., Nucci, G.,and Cobelli, C., "The Subcutaneous Route to Insulin-Dependent Diabetes Therapy,", *IEEE Eng. Med. Biol. Mag.,* 20(1), 54-64 (2001).

Bergman, R.N., Philips, L.S., and Cobelli, C., "Physiological evaluation of factors controlling glucose tolerance in man," *J.Clin.Invest.* 68, 1456-1467 (1981).

Diabetes Control and Complications Research Group:, "The effect of intensive treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus." *N. Engl. J. Med.* 329, 977-986 (1993).

Fisher, M.E., "A semi-closed loop algorithm for the control of Blood-glucose levels in Diabetics," *IEEE.Trans. Biomed. Eng.,* 38, 57-61 (1991).

Freeland, A.C., and Bonnecaze, R.T., "Inference of Blood Glucose Concentrations from Subcutaneous glucose concentrations: Applications to Glucose Biosensors," *Ann. BioMed. Eng.,* 27, 525-537, (1999).

Guyton, C.A., Textbook *of Medical Physiology,* 9th ed., WB Saunders, (1996).

Lehmann, E.D., and Deutsch, T., "A Physiological Model of Glucose-Insulin Interaction in Type I Diabetes Mellitus," *J. Biomed. Eng.*, 14, 235-242 (1992)

Parker, R.S., Doyle, F.J. III, and Peppas, N.A.., "A model based algorithm for blood glucose control in Type Idiabetic patients," *IEEE. Trans. Biomed. Eng.* 46, 48-57, (1999).

Parker, R.S., Gatzke, E.P., and Doyle, F.J. III, "Advanced Model Predictive Control (MPC) for Type I diabetic patient blood glucose control," *Proc. Am. Contr. Conf.* 3483-3487 (2000).

Parker R.S., Doyle, F.J. III, and Peppas, N.A. "The Intravenous Route to Blood Glucose Control." *IEEE Eng. Med. Biol. Mag.,* 20(1), 65-73 (2001).

Schmidtke, D.W., Freeland, A.C., Heller, A., and Bonnecaze, R.T., "Measurement and Modeling of the transient difference between blood and subcutaneous glucose concentrations in the rat following injection of insulin." *Proc Natl. Acad. Sci. USA,* 95, 294-299 (1998).

Sorenson, J.T., "A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes". Ph.D. thesis Dept. Chem. Eng. Massachusetts Institute of Technology, Cambridge, (1985).

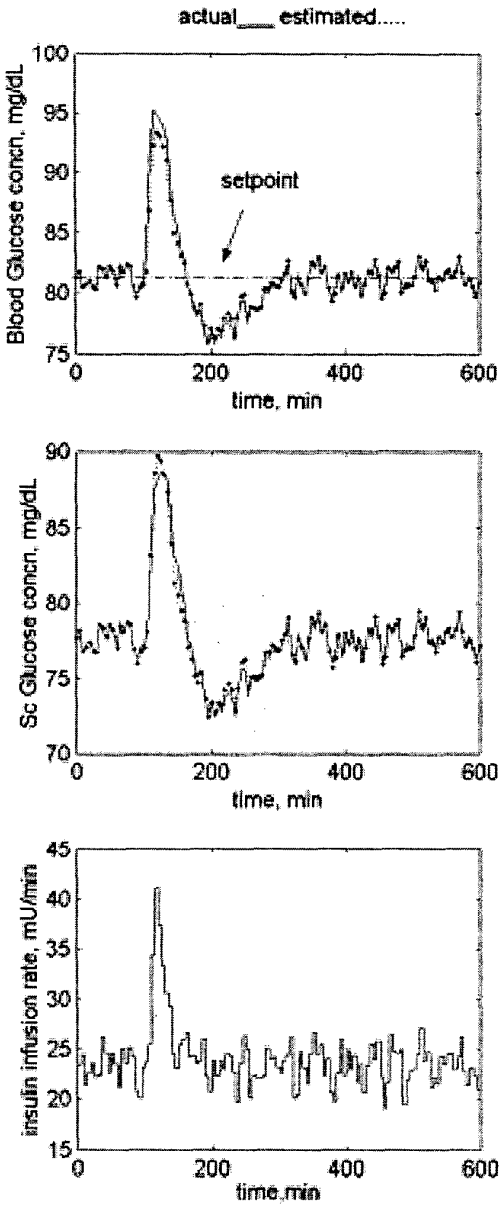

Fig 2. Action of MPC on Sorenson plant to reject Fisher model of 50 g meal disturbance at t=100 mins.

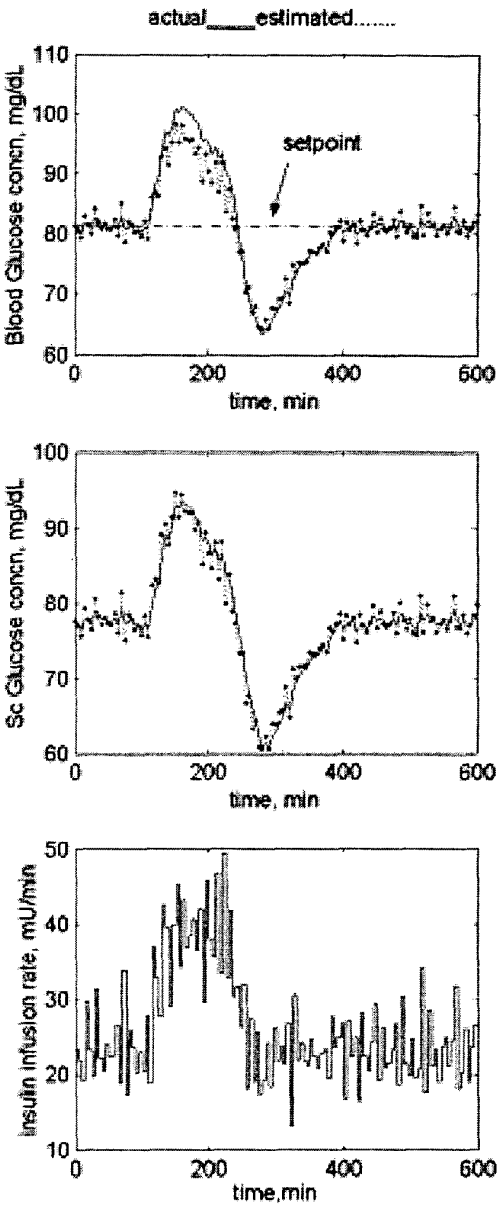

Fig 3. Action of MPC on Sorenson plant to reject Lehmann model of 50g meal disturbance at t=100 mins.