BLOOD GLUCOSE CONTROL OF TYPE-I DIABETIC SUBJECTS

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ABSTRACT

A Self-Tuning Generalized Predictive Controller (STGPC) was used to control type-I diabetic subjects. A nonlinear model has been employed, in which renal excretion was taken into account if the blood glucose concentration exceeds the renal threshold level. A large enough sample period was selected to suit the basic slow dynamic feature of the glucoregulatory system. Two types of external mechanical devices, open loop and closed loop types, were used as insulin delivery systems. The effect of the measurement noise and load disturbances are taken into consideration. A variable forgetting factor was used to insure good tracking of system parameters. The results show that the proposed controller is robust against measurement noise, load disturbances and time variation of system parameters.

Keywords: Self-Tuning Control, Predictive Control, glucoregulatory System, diabetic.

1. INTRODUCTION

Insulin is the main anabolic hormone of the body. In the absence of adequate insulin, body tissues are broken down and some of their products are converted into blood sugar, such excess sugar is lost via the urine, and thus improperly metabolized, while excess fat released from peripheral adipose tissue contribute to acetone formation in the liver until life-threatening keto-acidosis prevails [1]. Unfortunately, insulin replacement by a single injection a day under the skin fails to simulate the normal release of insulin in normal subject [1]. In this paper a continuous insulin provision to diabetic patients through open loop and closed loop insulin delivery systems and based on a STGPC has been achieved. The results show that the controller succeeded in simulating the pancreas action of normal subjects. A nonlinear fourth order model recently proposed by Salzsieder et al. [2] has been used in which the renal excretion has been taken into consideration if the blood glucose concentration exceeds the renal threshold level.

2. MATHEMATICAL MODEL

The nonlinear mathematical model of the glucoregulatory system is described by the following first order differential equations [2,3]:

$$\dot{X}G(t) = -r(t) + s(t) - w(t) - v(t) - f(t) - b_3\, ZG(t) + G_{exg}$$

$$\dot{r}(t) = k_3\, b_4\, (XG - Xr) - k_3\, r(t) \qquad (r=0 \quad \text{if } XG < Xr)$$

$$\dot{s}(t) = b_0\, k_0 - k_0\, s(t) - b_2\, b_3\, ZG(t)$$

$$f(t) = b_1\, G_{exg} - k_0\, f(t) + b_5\, G_{exg} \qquad (b_5 = 0 \text{ if } (XG < Xr \text{ and } YG=0)$$

$$\dot{v}(t) = b_0\, b_1 - k_0\, v(t)$$

$$\dot{w}(t) = b_1\, b_3\, YG(t) - k_0\, w$$

$$YG(t) = -k_1\, YG(t) + a_1\, (XG(t) - Xw) + a2\, XG(t) + I_{exg}$$

$$ZG(t) = -k2\, ZG(t) + k2\, YG(t)$$

and

$$UG(t) = s - v - w - f$$

where G_{exg}, I_{exg} and b_0 act as system inputs and the outputs are the four state variables defined by the blood glucose concentration XG(t), endogenous glucose balance UG(t), plasma insulin concentration YG(t), and peripheral insulin dependent glucose utilization ZG(t), respectively. And $\dot{r}$ is a partial balance which is only applied if the upper range of linearity is surpassed (please see the end of the paper for the undefined symbols).

The mathematical model of the uncontrolled metabolic system (diabetic state) has the same last

structure but with the control constants $a_1=0$ and $a_2=0$.

A sampling interval of 4 minutes is considered to be suitable for this application [4].

3. GENERALIZED PREDICTIVE CONTROL STRATEGY

The GPC assumes a Controlled Auto Regressive and Integrated Moving-Average (CARIMA) model:-

$$A(z^{-1})\, y(t)=B(z^{-1})\, u(t-k-1)+C(z^{-1})\, \xi(t)/\Delta \qquad (2)$$

$$, t=0, T_s, 2T_s, \ldots$$

where y(t) and u(t-k-1) are the output (blood glucose concentration) and the input (Infusion Rate of Insulin) respectively.

The input is delayed by a time delay k, Δ is the differencing operator $(1 - z^{-1})$, $\xi(t)$ is a sample of a stationary independent Gaussian noise with zero mean and A, B and C are polynomials in the backward shift operator z, i.e.

$$A(z^{-1}) = 1 + a_1 z^{-1} + a_2 z^{-2} + \ldots$$
$$B(z^{-1}) = b_o + b_1 z^{-1} + \ldots$$
$$C(z^{-1}) = 1 + c_1 z^{-1} + c_2 z^{-2} + \ldots$$

Let $T(z^{-1})$ be an observer polynomial, used to improve both the robustness and the disturbance response of GPC.

Define:

$$y'(t) = (\Delta/T)\, y(t), \quad u'(t) = (\Delta/T)\, u(t).$$

so that the resulting overall model becomes:

$$A(z^{-1})\, y'(t)=B(z^{-1})\, u'(t-k-1)+\xi(t),\ t=0, T_s, 2T_s, \ldots$$

The signals u'(t) and y'(t) are filtered by bandpass transfer functions, so that both high-frequency noise and dc levels are removed.

3.1 RLS with Variable Forgetting Factor

The estimation procedure for the system parameters is the well known Recursive Least Squares (RLS) algorithm [5]. The non-linear model of the glucoregulatory system is characterized by a random changes of the system parameters if the blood glucose concentration exceeds a certain threshold level (renal threshold Xr). This means we are in a need for an estimator which can track the system parameters under these conditions. RLS estimator with variable forgetting factor is found to be reasonable for this situation. This idea is due to Fortescue et al. [6] and relies on a time varying forgetting factor $\rho(t)$ which is automatically set so that $\rho(t) \rightarrow 1$ when the prediction error (the difference between the actual output and the estimated output) is small and r(t) is set to a small value ($\rho(t) < 1$) if the prediction error is large; that is to place greater emphasis on the recent samples and allow the estimator to go towards the correct values of the system parameters at this operating point. However, an additional mechanism to insure that the covariance matrix $P_o(t)$ remains bounded has to be imposed, otherwise even with a variable forgetting factor the covariance matrix can grow exponentially. For the variable forgetting factor algorithm, we follow the following steps:

$$\hat{\theta}(t) = \hat{\theta}(t-1) + K(t)\,(y'(t)-X(t)\,\hat{\theta}(t-1))$$
$$\rho(t) = 1 - \epsilon^2(t)/[1 + X^T(t)\, P(t-1)\, X(t)]$$

where

$$\epsilon(t) = y'(t) - X^T(t)\,\hat{\theta}(t-1)$$
$$K(t) = P(t-1)\, X(t)/\,[1 + X^T(t)\, P(t-1)\, X(t)]$$
$$V(t) = P(t-1) - K(t)\, X^T(t)\, P(t-1)$$

$\hat{\theta}$ is the estimated parameters vector and P(t) is the covariance matrix.

An upper bound (L) on P(t-1) is ensured by updating as follows:

$$P(t) = V(t)/\rho(t) \text{ if trace } (V(t)/\rho(t)) \leq L$$

else

$$P(t) = V(t) \qquad \text{i.e. } \rho(t) = 1.$$

where X(t) and $\theta(t)$ are the measurement vector and the parameter vector respectively:

$$X(t)=[-y'(t-1),\ -y'(t-4),\ u'(t-k-1),\ \ldots,\ u'(t-k-4)]$$

$$\hat{\theta} = [a_1\ a_2\ a_3\ a_4,\ b_o\ b_1\ b_2\ b_3]$$

where k is a pure delay samples.

3.1- *The Long- Range predictor*

The GPC is a long-range predictive controller [7,8]. From the above model GPC predicts future outputs, given currently available input/output data [y(t-i), u(t-i-1); $i \leq 0$] and depending on increments in present and future controls [$\Delta u(t+j)$, $j \geq 0$]. one important aspect of GPC is that after a future time instant, called the control horizon Nu, these increments are taken to be zero: [$\Delta u(t+j) = 0, j \geq Nu$].

Assume predictions are required for a range of future times [$t+N_1$, $t+N_2$] where:

N_1 is the minimum costing horizon and
N_2 is the maximum costing horizon.

and defining the following vectors:

$$\hat{y} = [\hat{y}(t+N_1),..., \hat{y}(t+N_2)]^T$$
$$\tilde{u} = [\Delta u(t), \Delta u(t+1),....,\Delta u(t+Nu-1)]^T$$
$$y_f = [y_f(t+1/t), y_f(t+2/t),..., y_f(t+N2/t)]^T$$

the predictions can be represented by the following equation [7]:

$$\hat{y} = G\tilde{u} + y_f$$

where:

$$G = \begin{bmatrix} g_{N1} & g_{N1-1} & .. & 0 \\ g_{N1+1} & g_{N1} & .. & 0 \\ g_{N2-1} & g_{N2-2} & .. & g_{N2-N} \\ g_{N2} & g_{N2-1} & .. & g_{N2-Nu+1} \end{bmatrix}$$

The elements of G are g_i, being points on the plant's step response, can be computed recursively from the above model, assuming zero noise and a constant unit control input. Also the free response $y_f(t+j)$ can be computed for all j simply by iterating the plant model, assuming $\xi(t+j) = 0$ and that future controls equal the previous control u(t-1).

Consider the vector e composed of predicted future system errors $w(t+j) - \hat{y}(t+j)$, w(t+j) is the set point. The suggested future control sequence u(t+j) is chosen by GPC at time t to minimize a cost function given by:

$$J_{GPC}(N_1,N_2,N2,Nu,\lambda) = \sum_{j=N1}^{N2} e^2(t+j) + \lambda \sum_{j=1}^{Nu} [\Delta u(t+j-1)]^2 \quad (3)$$

where

λ is the control weighting coefficient and the solution giving the minimum cost is then [7]:

$$\tilde{u}_{opt} = (G^T G + \lambda I)^{-1} G^T (w - y_f) \quad (4)$$

4. NUMERICAL SIMULATION RESULTS

The default settings of the GPC controller (N_1=delay, N_2=10, Nu=1, λ =0) were used in both the preprogrammed device and the artificial pancreas results. The following initial values were found to be satisfactory for Self-Tuning Control (STC):

$P(0) = 100\ I$, and $\hat{\theta}(0)=0$ where I is the identity matrix.

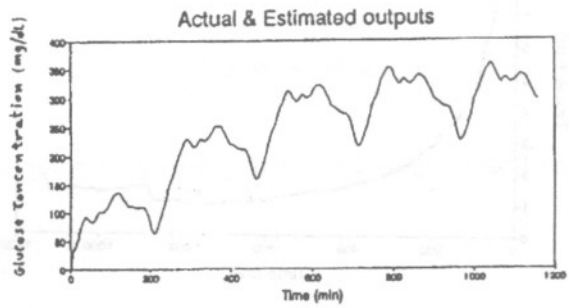

Figure 1. Non-linear model.

Figure (1) shows the actual blood glucose concentration together with the estimated blood glucose concentration, and they are identical. Figure (2) shows the identified "A" and "B" parameters as given by the RLS identifier. The trace of the covariance matrix was plotted in Figure (3) with the upper bound selected to be 5. Finally the variable forgetting factor $\rho(t)$ was plotted against time in Figure (4). As shown in that Figure the value of $\rho(t)$ during the transient period (the first 10 samples of operation) is small and after parameter tuning the prediction error becomes minimum and the value of $\rho(t) \approx 1$ and any increase in the prediction error reduces the value of the forgetting factor and hence increases the trace of the covariance matrix allowing a chance for tracking the system parameters as shown in the figure.

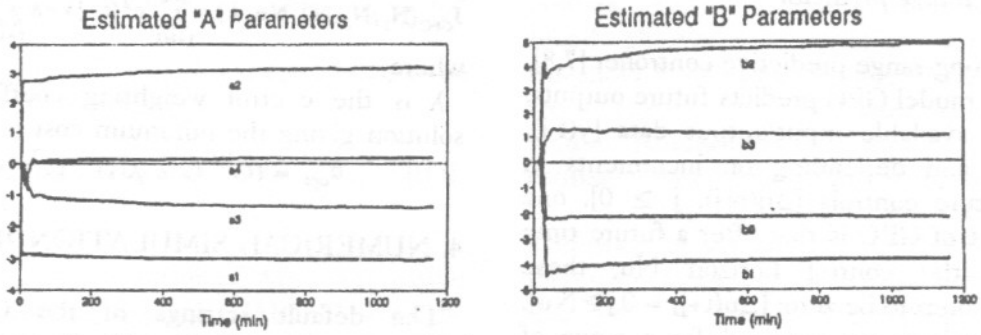

Figure 2. Identified parameters of the non-linear model using RLS variable forgetting factor.

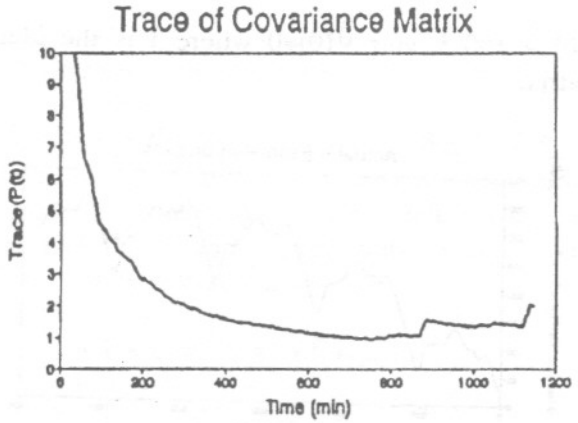

Figure 3.

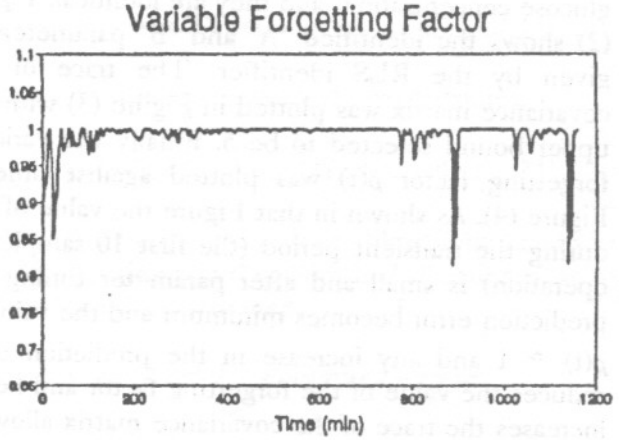

Figure 4.

4.2 GPC Blood Glucose Regulation

4.2.1 *Using Preprogrammed Devices*

Figure (5) shows the system response with the four state variables XG(t), UG(t), b_3 ZG(t) and YG(t) were plotted together with the insulin infusion rate (control signal) required to regulate the blood glucose concentration at the desired normal level. The control signal is shown to have a biphasic action of the pancreas which consists of a fast increase in the insulin infusion rate at the step change instant and then a constant infusion rate corresponding to the constant basal rate of the pancreas secretion when the blood glucose concentration reaches its normal fasting level. It is noticed that there is a difference between the insulin mediated glucose utilization b_3 ZG(t) and the net endogenous glucose production UG(t) after reaching to the desired level. We refer this difference to the loss of blood glucose due to renal excretion which in turn reduces the net endogenous glucose production.

4.2.2 *Using Artificial Pancreas*

Figure (6) shows the system response, with the four state variables plotted against time. A good regulation of blood glucose concentration has been achieved with a very small undershoot.

The GPC controller was tested against the same severe load disturbances used in the linear model application [4]. The controller shows a fast response to these changes in blood glucose concentration which appears in the fast increase of the injected insulin rate over the basal rate and the increase of the insulin controlled glucose utilization and the reduction in the net endogenous glucose production during the existence of that load as shown in Figures (7,8). Note that a negative value for UG(t) means glucose storage instead of glucose production.

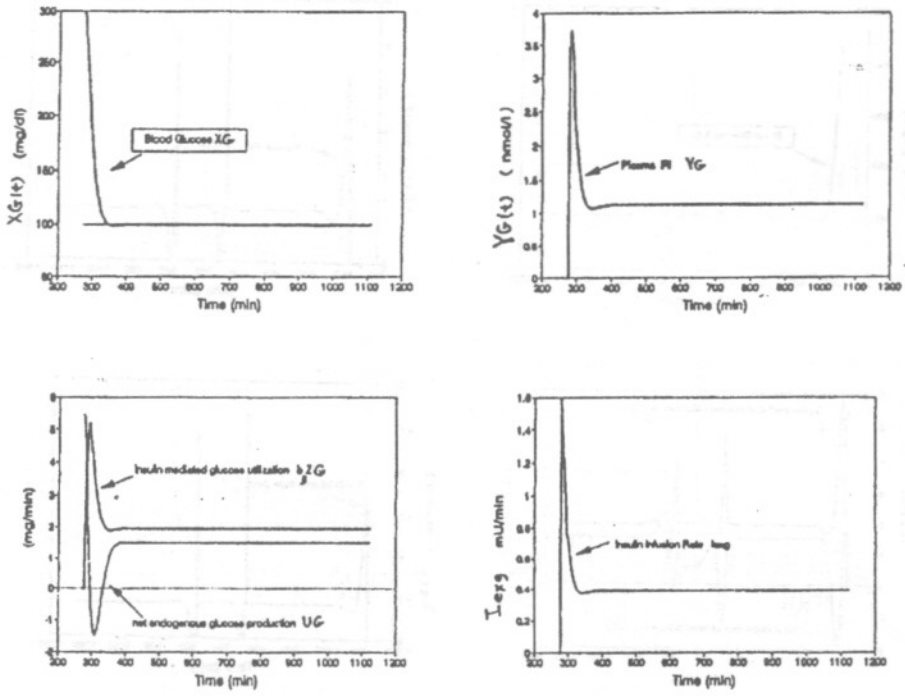

Figure 5. System response under GPC using non linear model (default setting, preprogrammed case).

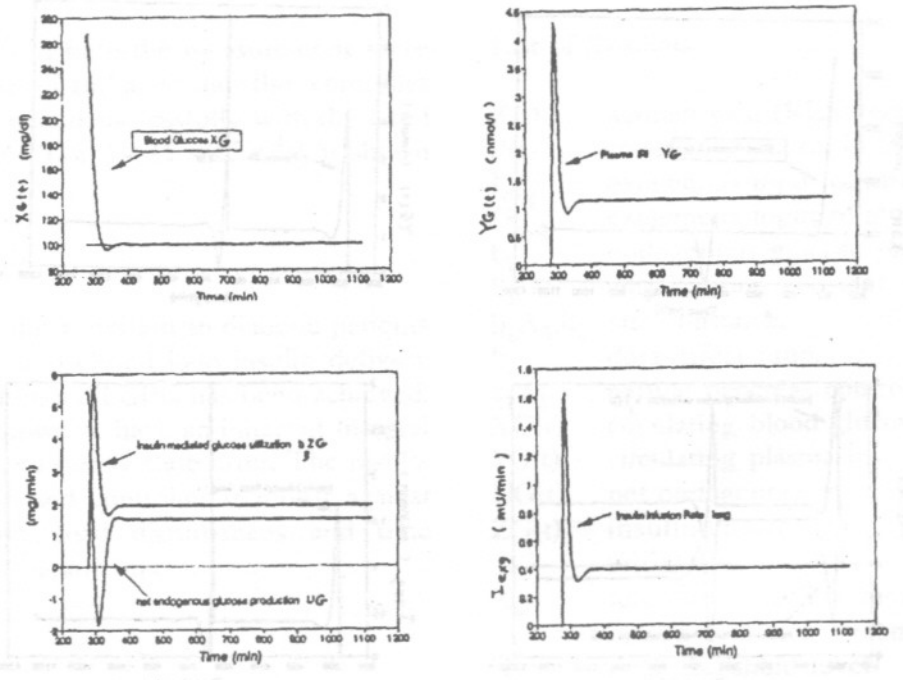

Figure 6. System response under GPC using non linear model (default setting, artificial pancreas case).

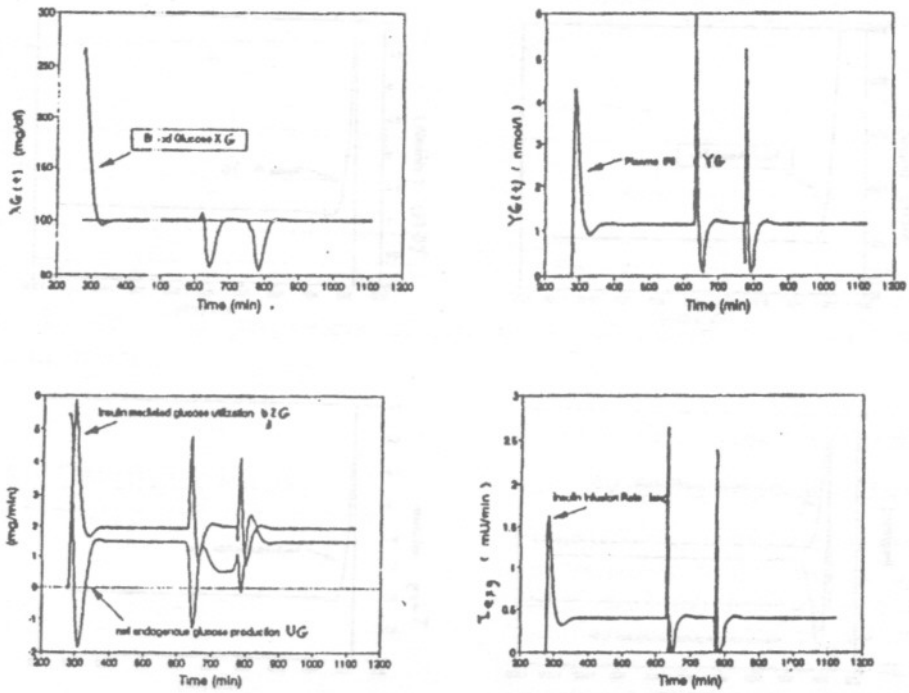

Figure 7. Limited step load disturbance effect (GPC, default settings, non-linear model.

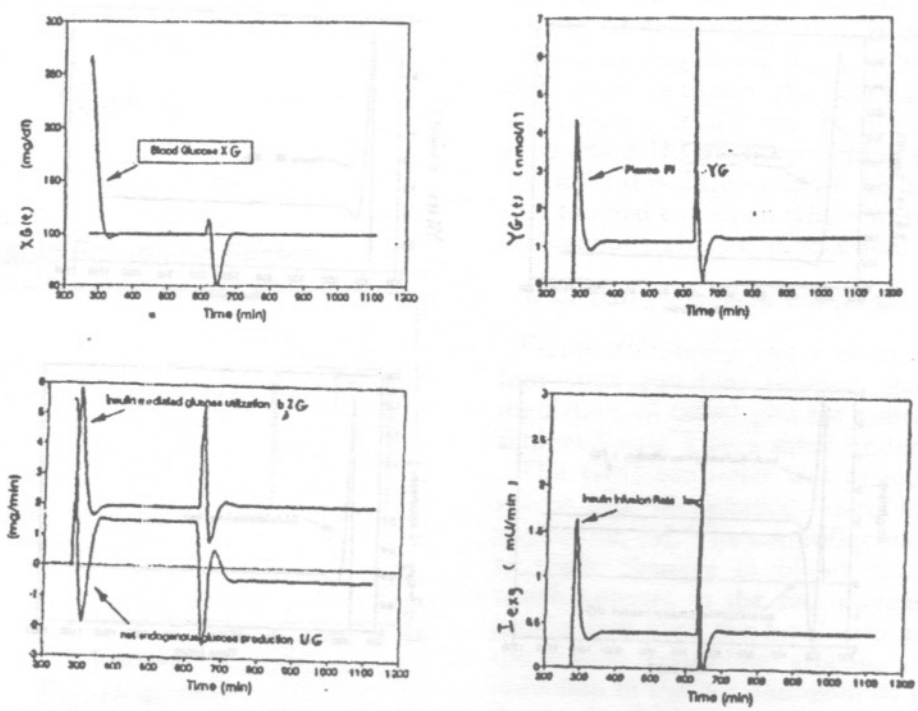

Figure 8. Step load disturbance effect (GPC, default settings, non-linear model).

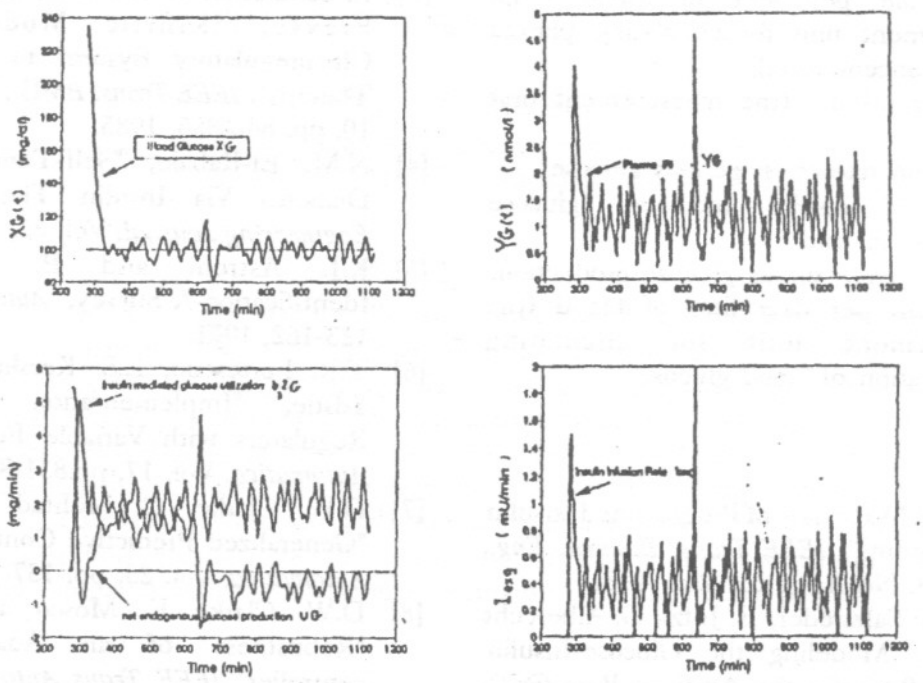

Figure 9. Load disturbance & measurement noise effect $T=(1-0.7\ z^{-1})^2$ (GPC, default settings, non-linear model.

Finally, the effect of both the measurement noise and the step load disturbance on the controller behavior has been tested successfully with the fixed polynomial observer $T(z^{-1}) = (1 - 0.7\ z^{-1})$} as shown in Figure (9).

5. CONCLUSIONS

A continuous insulin provision to diabetic patients through open loop and closed loop insulin delivery systems and based on a STGPC has been achieved. The controller is shown to have an inherent integral action to achieve zero steady state error. The results show that the proposed controller is robust against measurement noise, load disturbances and time variation of system parameters.

Aknowledgememt

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List of Symbols

$K(t)$	kalman gain (RLS gain vector).
$P(t)$	coveriance matrix in RLS.
I_{exg}	exogenous input of insulin.
G_{exg}	exogenous input of glucose.
b_0	endogenous glucose provision.
b_1	amplification constant.
b_2,k_1,k_2	rate constants.
b_3	dose-effect ratio.
a_1,a_2	natural pancreas control parameters.
$XG(t)$	circulating blood glucose concentration.
$YG(t)$	circulating plasma insulin concentration.
$UG(t)$	net endogenous glucose balance.
$ZG(t)$	insulin-controlled peripheral glucose utilization.
X_w	reference value at which glucose-controlled insulin provision becomes zero
X_r	renal threshold level.

Measurement Units

mU/min milli Unit per minute (The measurement

nmol/l nano mole per liter of blood (The measurement unit for circulating plasma insulin concentration).

gm/min gram per minute (the measurement unit for:
1) infusion rate of exogenous glucose
2) rate of insulin mediated glucose utilization, and
3) rate of endogenous glucose production.

mg/dl milli gram per deci liter of blood (the measurement unit for circulating concentration of blood glucose

REFERENCE

[1] W.J. Spencer, "A Review of Programmed Insulin Delivery Systems", *IEEE Trans. Biomed. Eng.*, Vol. BME-28, No. 3, pp.237-251, 1981.

[2] U. Fischer E. Salzsieder, E. Jutzi, G. Alberecht E.J. Freyse, "Modeling the Glucose-Insulin System as a Basis for the Artificial Beta Cell", *Biomed. Biochim. Acta*, Vol. 43, No. 5, pp. 597-605, 1984.

[3] E. Salzsieder, G. Albrecht, U. Fischer and E.J. Freyse, "Kinrtic Modeling of the Glucoregulatory System to Improve Insulin Therapy", *IEEE Trans. BM*E., Vol. BME-32, No. 10, pp. 846-855, 1985.

[4] N.M. El-Rabaie, "Self-Tuning Control For Diabetes Via Insulin Therapy", *Alexandria Engineering Journal*, Vol. 33, No. 2, April 1994.

[5] K.J. Astrom and P. Eykhoff,"System Identification-A Survey," *Automatica*, Vol. 7, pp. 123-162, 1971.

[6] T.R. Fortescue, L.S. Kershenbaum and B.E. Ydstie, "Implementation of Self-Tuning Regulators with Variable Forgetting Factors", *Automatica*, Vol. 17, pp.831-835,1981.

[7] D.W. Clarke, C. Mohtadi and P.S. Tuffs, "Generalized Predictive Control, Part I and II", *Automatica*, Vol. 23, pp. 137-160, 1987.

[8] D.W. Clarke E. Mosco and R. Scattolini, "Robustness of an Adaptive predictive controller" *IEEE Trans Automatic Control*, vol. 39, No. 5, pp. 1052-10555, May, 1994.