SELF-TUNING CONTROL FOR DIABETES VIA INSULIN THERAPY

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ABSTRACT

A continuously insulin provision to diabetic patients through an open loop and closed loop insulin delivery systems which are based on a Self-Tuning Generalized Predictive Controller (STGPC) has been achieved. The controller succeeded in mimicing the time course of natural plasma insulin in normal subjects. A linear stochastic fourth order model, which simulates a type-I diabetic subject was used. The sampling period was chosen sufficiently large to suit such a slow system. The controller has been tested successfully against the measurement noise and sever load disturbances. The results obtained suggest the application of the proposed controller in controlling type-I diabetes.

1.INTRODUCTION

There are two principal methods that have been used to improve blood glucose control in diabetic individuals [1]. One method is to transplant insulin secreting beta cells. The main problem with this method of diabetic therapy is the rejection of the cells by immunologic reactions of the diabetic patient. A second method is through the use of electromechanical insulin delivery devices.

In this paper two types of electromechanical insulin delivery devices were used [2]. One of them is the open loop electromechanical insulin delivery device in which insulin is infused according to preprogrammed schemes, that is, independent of the actual glucose concentration. The second is the glucose controlled insulin delivery device in which insulin is infused on the basis of continuous measurements of blood glucose.

A fourth order mathematical model of the diabetic subject described recently by Ficher et al. and Salzsieder et al. [3,4] is employed, in which it assumed that the lake of glucose-controlled insulin provision is the only essential difference between the diabetic and nondiabetic states. A self-tuning generalized predictive controller has been proposed to control the diabetic state.

2. MATHEMATICAL MODEL

The fourth order mathematical model of the glucoregulatory system is described by the following first order differential equations [3,4]:-

$$\dot{X}G(t) = UG(t) - b'_3\, ZG(t) + G_{exg}$$

$$\dot{U}\,G(t) = -\,k_0\, UG(t) - b'_1\, b'_3\, [YG(t) - ZG(t)] + b'_1\,(b'_o - G_{exg})$$

$$\dot{Y}G = -k_1\, YG(t) + a'_1(XG(t) - Xw) + a'_2\, \dot{X}G(t) + I_{exg}$$

$$\dot{Z}G(t) = -\,k_2\, ZG(t) + k_2\, YG(t)$$

In fact, this system is a multi-input multi-output (MIMO) system with G_{exg}, I_{exg} and b'_0 acting 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. The model related to this system's structure can take the compact matrix form:-

$$\left.\begin{aligned} \dot{S} &= A\,S + B\,V \\ M &= S \end{aligned}\right\} \qquad (1)$$

where S is state vector, M is the output vector and V is the input vector given by

$$S = [XG(t) \quad UG(t) \quad YG(t) \quad ZG(t)]^T \text{ and}$$

$$V = [G_{exg} \quad I_{exg} \quad b'_0]^T$$

(please see the definition of each variable in the list of symbols at the end of the paper).

The mathematical model of the uncontrolled metabolic system (diabetic state) has the same last structure but with the control constants $a'_1 = 0$ and $a'_2 = 0$.

The digital version of the diabetic state model with a sampling time T_s seconds was calculated using MATLAB Package [5]. The parameters of these input/output discrete transfer functions at different sampling times (25, 60, 120 and 240 seconds) are calculated. The diabetic model was analyzed at these sampling intervals. It is noticed that, in all these intervals the diabetic model was characterized by a single pole at the unit circle and the other three poles lie inside the unit circle. Now, we compare between these intervals according to the relative positions of these stable poles from the +1 point of the unit circle.

From Figure (1) we conclude that the sampling time $T_s=25$ seconds is probably too fast for this application. This is because the dominant poles are close to the +1 point in the Z-plane. The sampling interval of $T_s=1$ minute and $T_s=2$ minutes show a slight improvement in the position of these three poles. A sampling interval of 4 minutes is considered to be suitable for this application.

3. GENERALIZED PREDICTIVE CONTROL STRATEGY

For digital controller design, the time-varying dynamics of the glucoregulatory system can be represented by the discrete time relation:

$$A(z^{-1})\, y(t) = B(z^{-1})\, u(t-k-1) + C(z^{-1})\, \xi(t)/\Delta \quad (2)$$
$$,t=0\ ,T_s,\ 2T_s,\ \ldots$$

this is called a Controlled Auto Regressive and Integrated Moving-Average (CARIMA) model [6]:- where y(t) and u(t-k-1) are the output (blood glucose concentration) and the input (Infusion Rate of Insulin IRI) respectively. The input is delayed by a time delay k, Δ is the differencing operator $(1-z^{-1})$, $\xi(t)$ is sample of a stationary independent Gaussian noise wi zero mean, and A, B and C are polynomials in t backward shift operator z^{-1}, i.e.

$$A(z^{-1}) = 1 + a_1 z^{-1} + a_2 z^{-2} + a_3 z^{-3} + a_4 z^{-4},$$

$$B(z^{-1}) = b_0 + b_1 z^{-1} + b_2 z^{-2} + b_2 z^{-3}$$

and

$$C(z^{-1}) = 1 + c_1 z^{-1} + c_2 z^{-2} + c_3 z^{-3} + c_4 z^{-4}$$

Let $T(z^{-1})$ be an observer polynomial, used to impro both the robustness and the disturbance response GPC [6].

Then define

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

so that the resulting overall model becomes (assumi T=C) :

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

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

The estimation procedure for the system paramete is the well known Recursive Least Squares (RL algorithm with the following equations [7]:-

$$\hat{\theta}(t) = \hat{\theta}\ (t-1) + K(t)\ (y(t)-X(t)\ \hat{\theta}(t-1))$$

$$K(t)=P(t-1)\ X^T\ (t)/[\alpha(t)+X(t)\ P(t-1)X^T\ (t)]$$

$$P(t) = [I - K(t)\ X(t)\ ]\ P(t-1)\ /\ \alpha(t)$$

where the vector θ is given by:-

$$\theta^T = [a_1 \quad a_2 \quad a_3 \quad a_4, \quad b_0 \quad b_1 \quad b_2 \quad b_3]$$

X(t) is the measurement vector and is defined as :-

$X(t)= [-y'(t-1),\ldots,-y'(t-4),\ u'(t-k-1),\ldots,u'(t-k-4)]$ and $\alpha(t)$ is an exponential forgetting factor.

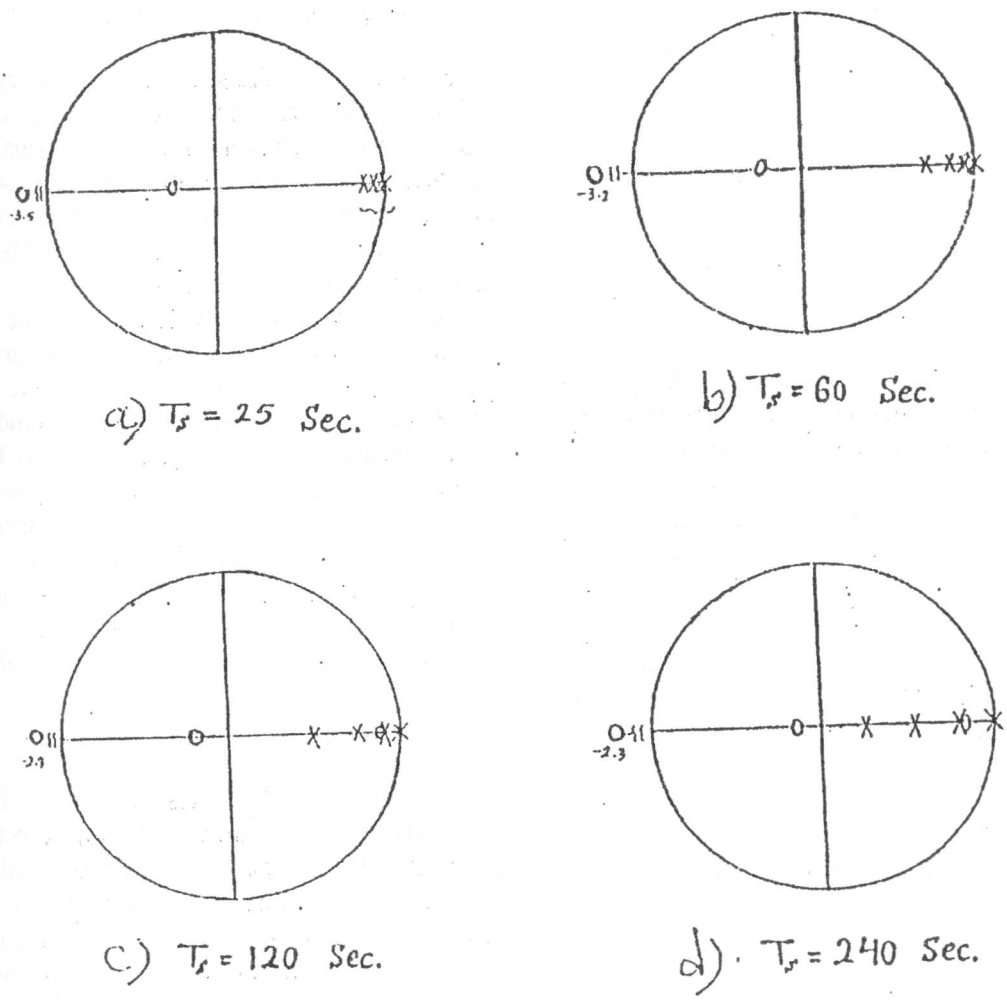

Figure 1. Pole-zero plot for discreet time model of the Glucoregulatory system at various sampling interval.
(0 for zeros, and x for poles).

3.1 The Long-Range predictor

GPC is a long-range predictive controller. 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 [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: [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:

$$\hat{y} = [y(t+N_1), \ldots, y(t+N_2)]^T$$

$$\tilde{u} = [\Delta u(t), \Delta u(t+1), \ldots, \Delta u(t + Nu-1)]^T$$

$$y_f = [y_f(t+1/t), y_f(t+2/t), \ldots, y_f(t+N_2/t)]^T$$

the predictions can be represented by the following equation [6]:

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

$$G = \begin{bmatrix} g_{N1} & 0 & .. & 0 \\ g_{N+1} & g_{N1} & .. & 0 \\ : & : & & \\ g_{N2-1} & g_{N2-2} & .. & g_{N2-Nu} \\ g_{N2} & g_{N2-1} & .. & g_{n2-N-1} \end{bmatrix}$$

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). The suggested future control sequence u(t+j) is chosen by GPC at time t to minimize a cost function
given by:-

$$J_{GPC}(N_1,N_2,N_u,\lambda) = \sum_{j=N_1}^{N_2} e^2(t+j)$$

$$+ \lambda \sum_{j=1}^{N_u} [\Delta u\,(t+j-1)]^2 \qquad (5)$$

where

λ is the control weighting

and the solution giving the minimum cost is then [6]:-

$$\tilde{u}_{opt} = (G^T G + \lambda I)^{-1} G^T (w - y_f) \qquad (6)$$

4. NUMERICAL SIMULATION RESULTS

The default settings of the GPC controller (N_1=delay, N_2=10, N_u=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:-

$\alpha(0) = 0.98$ $\quad$ $P(0) = 100\,I$

4.1 Using Preprogrammed Devices

Figure (2) shows the glucoregulatory system resp under GPC control. The blood glucose concentr XG(t) was reduced from the ubnormal diabetic le the desired normal concentration (100 mg/dl) wi any steady state error and without hypoglyc (undershoot). The other state variables were plott understand all the controller effects on glucose-insulin control system. The insulin infu rate increases during the transient period which c the insulin-controlled peripheral glucose utilizatio (b'_3 ZG(t)) to increase and the net endogenous glu production UG(t) to decrease. And hence, the b glucose concentration starts decreasing until it rea the desired level. At that level the insulin infusio reaches the constant basal rate and the insulin med glucose utilization becomes equal to the net endoge glucose production which insures the good b glucose regulation at the desired level.

4.2 Using Artificial Pancreas

Artificial pancreas, means an external device w is used to inject insulin to the subject on the bas the continuous measurement of blood glucose. H an autoanalyzer must be included in this machi provide the controller with the actual measuremen blood glucose concentration. We first study the delay effect of the autoanalyser. Figure (3), show system response, with the four state variables pl against time to show the net reciprocal effects bet these states. A good regulation of blood glu concentration has been achieved. It is noticed also the machine (Glucose Controlled Insulin Infu system GCII) simulates successfully the pancreas a in normal subjects.

The GPC controller was tested against severe disturbances. A step load disturbance (in the for oral glucose administration or food intake) o amplitude equal to 1 gm/min and a duration o samples was applied to the simulated system. controller shows a fast response to these chang blood glucose concentration which appears in the increase of the injected insulin rate over the basal and the increase of the insulin controlled glu utilization and the reduction in the net endoge glucose production during the existence of that lo

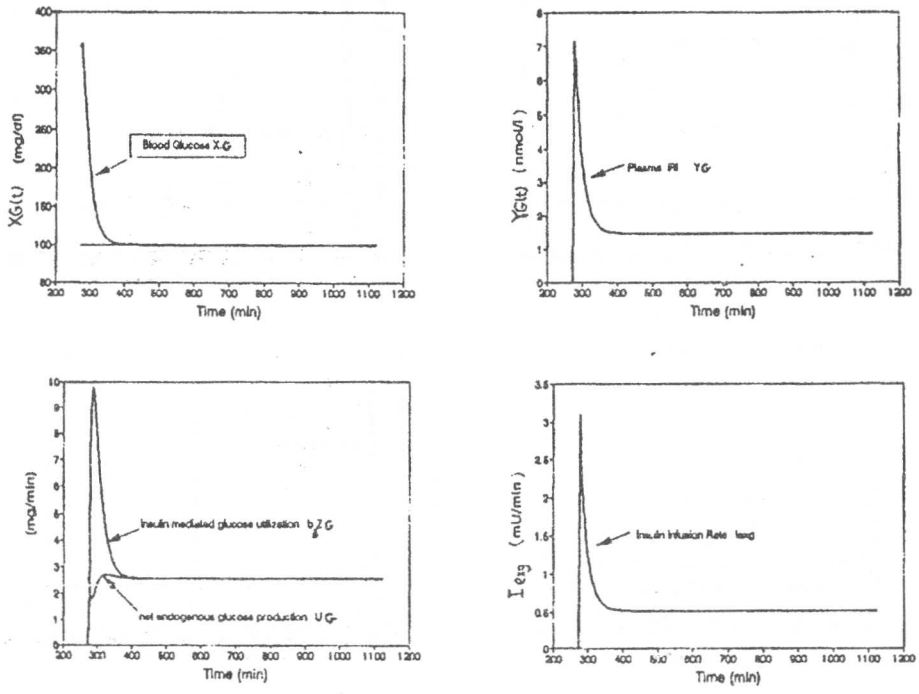

Figure 2. System response under GPC control (default settings, preprogrammed case).

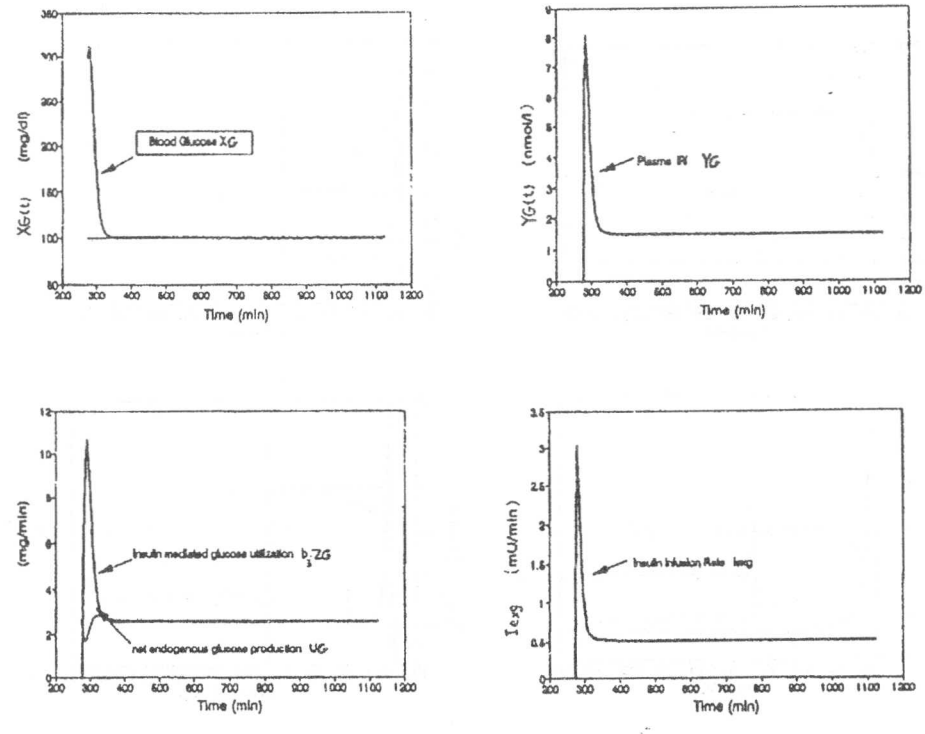

Figure 3. System response using artificial pancreas (GPC, default settings).

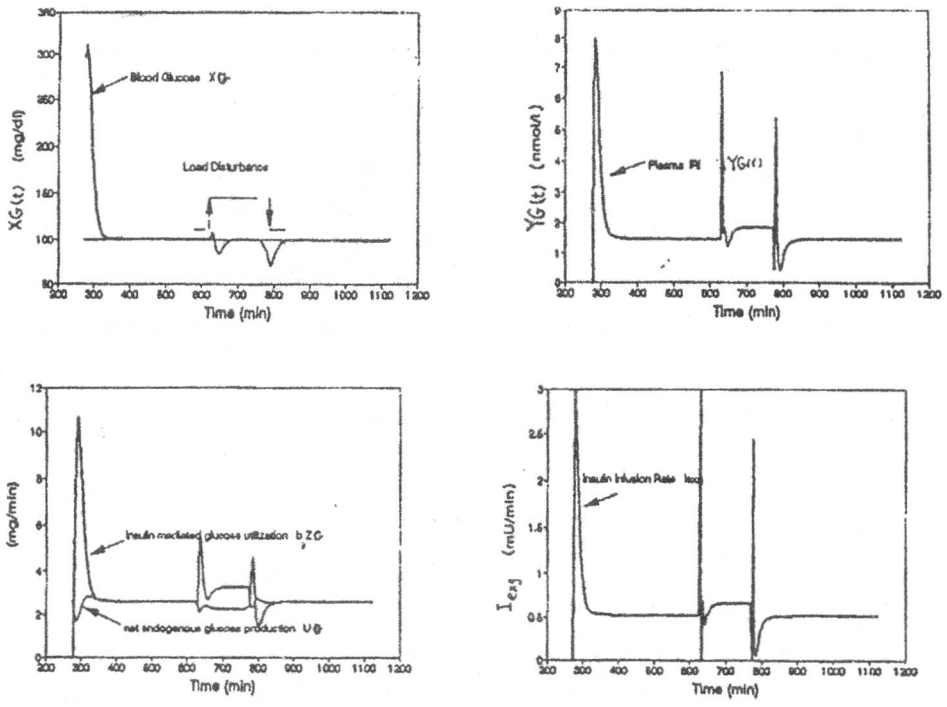

Figure 4. Limited step load disturbance effect (GPC, default settings).

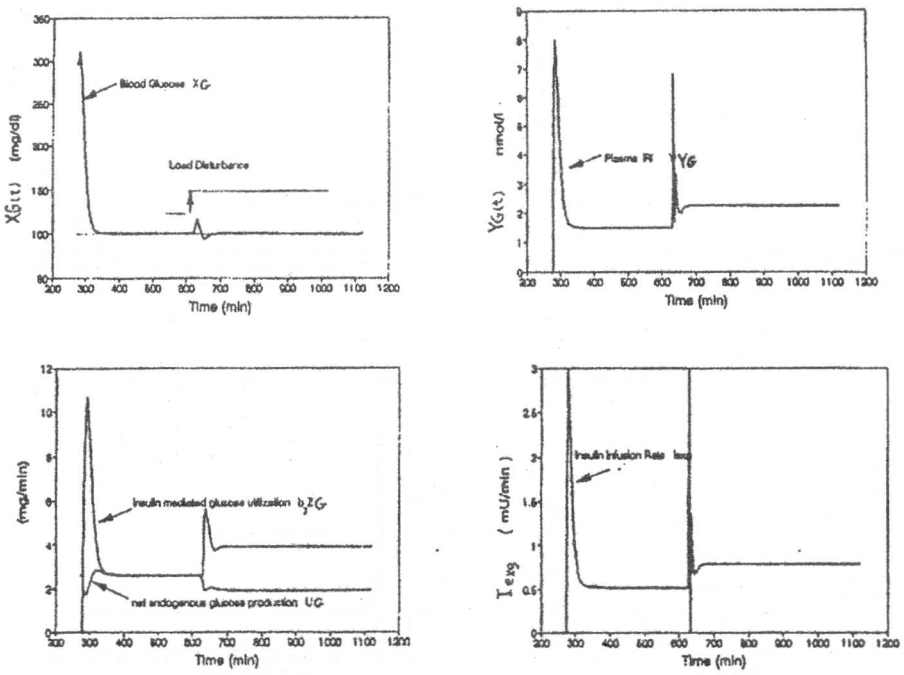

Figure 5. Step load disturbance effect (GPC, default settings).

After the removal of the load disturbance the insulin infusion rate returned again to its basal rate and the insulin mediated glucose utilization b_3 ZG(t) became equal to the net endogenous glucose production UG(t) as shown in Figure (4). Figure (5) shows the effect of another type of load disturbance. A step load disturbance of an amplitude equal to 2 gm/minute was applied to the simulated system and continued to the end of the experiment. The results show that the GPC controller can cancel the undesired effects caused by these load disturbances and maintain the blood glucose concentration at the normal level.

Finally, the effect of the measurement noise on the controller behavior has been tested successfully using the fixed polynomial observer $T(z^{-1})$. Figure (6), shows the blood glucose response, insulin mediated glucose utilization, net endogenous glucose production, plasma and the insulin infusion rate Iexg when $T(z^{-1}) = C(z^{-1})$. A considerable reduction in the variance of the control signal with good blood glucose regulation is the result of data filtering. The effect of both the measurement noise and the step load disturbance on the system responses with T=C is shown in Figure (7). The actual and estimated outputs using the RLS estimator with data filtering were plotted together in Figure (8). Both outputs are nearly identical which indicates that the estimated model represents completely the glucoregulatory system dynamics. The four A parameters and the four B parameters -as identified by the RLS- were plotted in Figure (9).

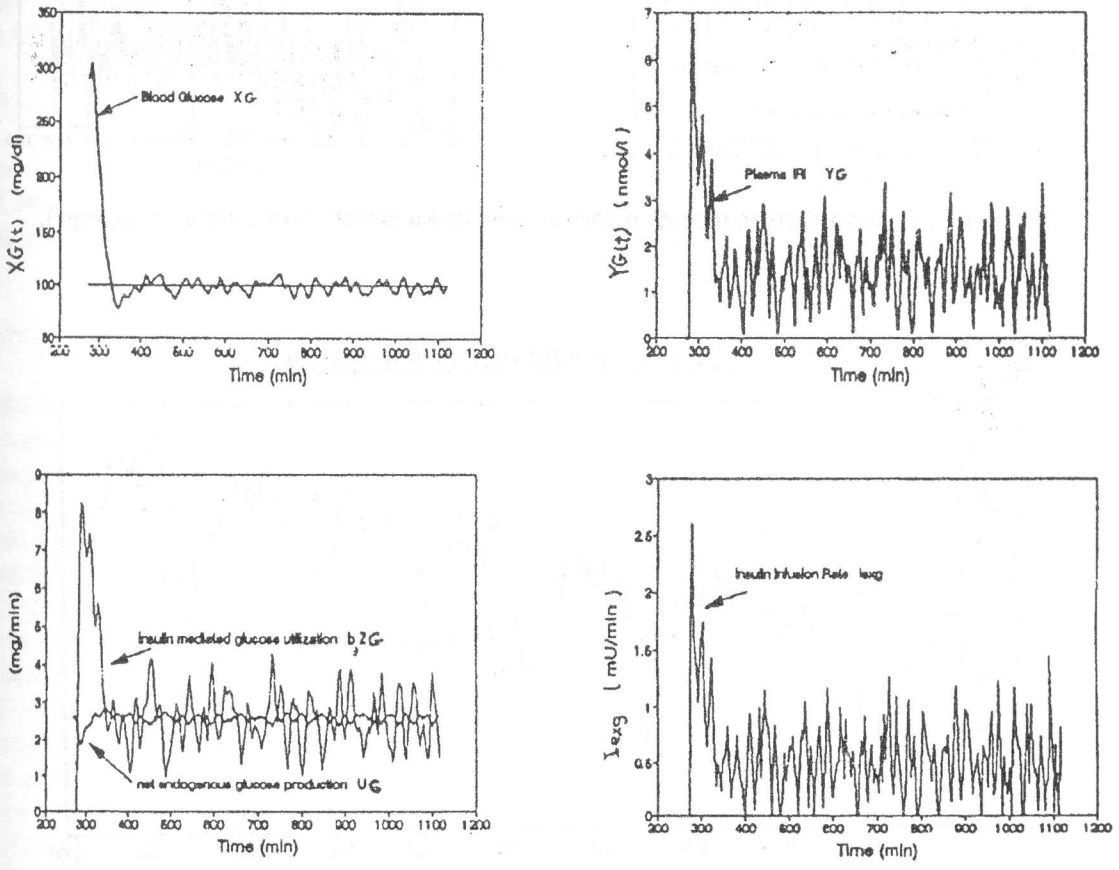

Figure 6. Measurement noise effect with T = C (GPC, default settings).

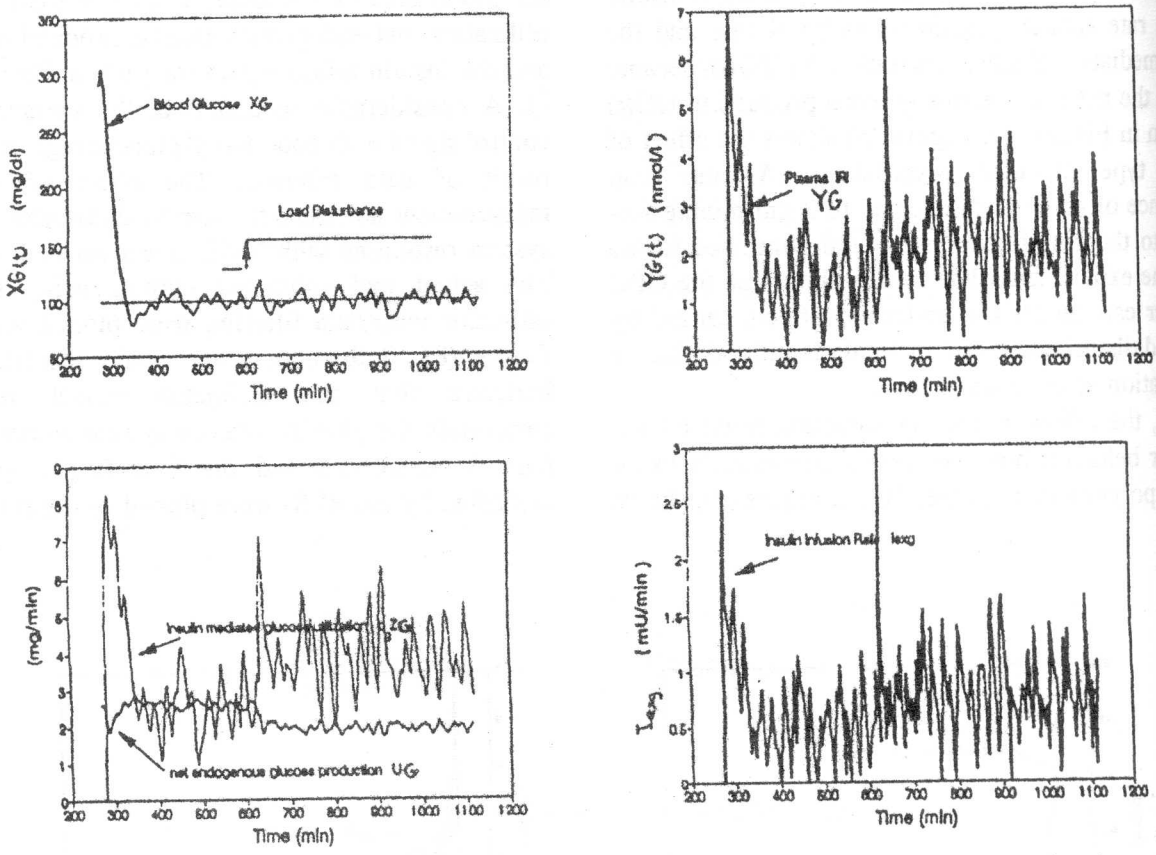

Figure 7. Step load disturbance & measurement noise effect (GPC, default settings).

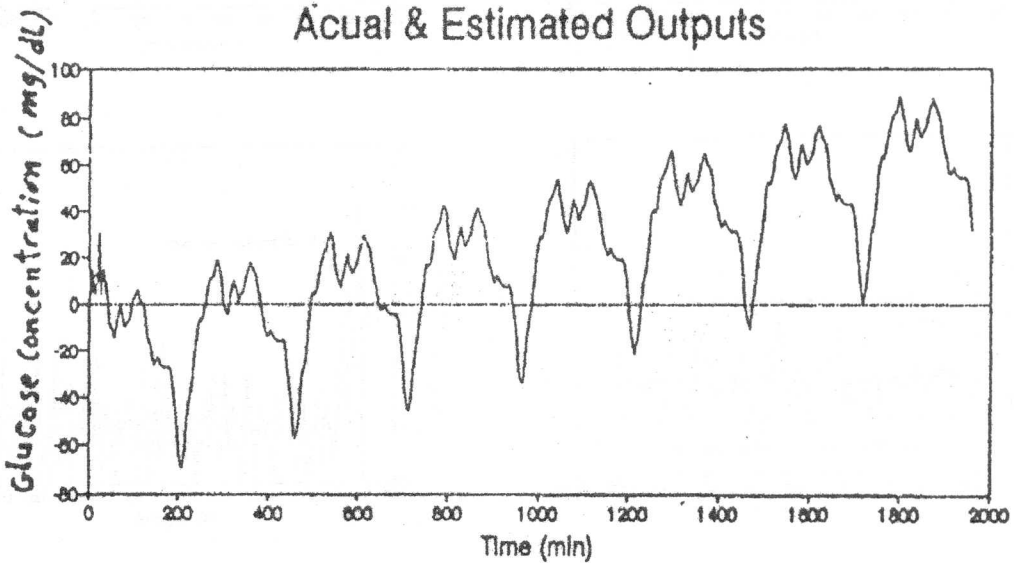

Figure 8. Fourth order model.

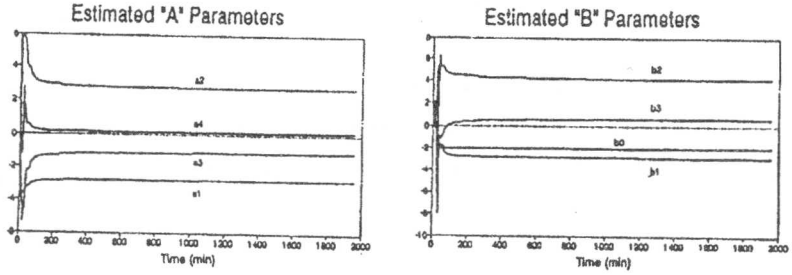

Figure 9.. Estimated system parameters using RLS.

5. CONCLUSIONS

An open loop and closed loop electromechanical devices were used successfully for the regulation of blood glucose in the diabetic subjects, based on a fourth order model. A STGPC was used as the control algorithm needed to inject proper rates of external insulin. The results show that, in the presence of parameter variations and disturbances due to food intake and/or measurement noise, the control scheme works with high efficiency.

ACKNOWLEDGEMENT

The author would like to thank Dr. Hosham Dabbous (Faculty of Medicine, Ein Shams University) for his consultation in medical sides concerning the research subject.

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

MEASUREMENT UNITS

mU/min	milli Unit per minute (The measurement unit for IRI)
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)

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