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A Review on different controllers used for Blood Glucose regulation system

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Abstract: Maintaining the glucose concentration in normoglycemic range in Type I diabetic patients is challenging. In this study H∞ control is applied for the insulin delivery to prevent the hyperglycaemic levels in a type I diabetic patient. A nonlinear model is linearized around nominal condition and reduced for control synthesis. H∞ controller was compared with the two other types of controller and performances shows evaluatory results.

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Keywords PID control, Robust control, glucose-insulin modeling.

Introduction

The diabetes mellitus is a group of metabolic diseases characterized by a high blood glucose concentration (hyperglycemia) resulting from defects in insulin secretion, insulin action, or both phenomena. This complication has largely exceeded its growth expectative, and its impact in the worldwide health-care problem has raised the interest of the scientific community to provide control algorithms that can be implemented for the real-time patient treatment [5,1]. In a type 1 diabetes mellitus (TIDM) patient, the pancreas is not able of producing the insulin at all. This problem can produce short- and long-term illnesses (diabetes coma, nephropathy, retinopathy, and other tissue damage) due to the variations in the blood glucose level (BGL). As a matter of fact, long-term complications of diabetes include, among others, peripheral neuropathy with risk of amputation [10]. As a result, the BGL has to be monitored externally to maintain it regulated by applying insulin infusions in a regular scheme.

Meanwhile, in a healthy patient, the insulin released by the pancreas maintains the basal blood glucose concentration around euglycemic (normoglycemic) levels 70–120 mg/dl. Hence, the pancreas provides a basal rate of≈22 mU/min [10],[3], and it increases this amount during meal intakes (postprandial peak), in order to process the glucose absorbed from the gut. Consequently, in the absence of insulin, the blood glucose level for a TIDM patient can decrease or increase above euglycemic levels (hypoglycemia and hyperglycemia, respectively) for long periods of time. In fact, the TIDM patient requires external insulin for survival. However, the Diabetes Control and Complications Trial (DCCT)[6] showed that an intensive insulin therapy can reduce the incidence of long-term illnesses. Therefore, an intensive therapy is encouraged for TIDM patients prescribed either by a continuous-infusion pump (CIP), or a multiple daily injection regimen (MDIR). On the other hand, it was also noticed in [6] that a possible side effect of an

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intensive therapy is the propensity to hypoglycemic scenarios in the patient. With this consideration, if an intensive therapy is followed by the patient, the prescribed insulin treatment must be carefully studied by the physician, and it should be constantly updated according with the results achieved.

A wearable artificial pancreas, consisting in a feedback control system regulating insulin delivery according to real time glycaemic changes, is not yet available because of many difficulties, part of them related to the development of efficient and reliable control algorithms. In fact, to cope with the large variability of response from patient to patient and the complexity of physiological regulation, while avoiding hyperglycemia and hyperinsulinization, is a challenge from at least thirty years. The present availability of short acting insulin and subcutaneous insulin pumps plus the advanced studies in the field of subcutaneous glucose monitoring open now the possibility of a new generation of algorithms for artificial wearable pancreas. Simulation is almost a necessity at the state of the art in this field: it can reduce expensive experimental activities in the first phase of control systems development and can give comparison facilities.

Improved contro1 of blood glucose is possible if the patient is removed from the control loop, so there exists a need for a closed-loop insulin infusion pump.

An infusion pump would contain three major components: (i) a glucose sensor, (ii) an algorithm to calculate insulin infusion based on the sensor measurement, and (iii) the pump mechanism. Currently, there exist pumps which can deliver insulin at varying rates [2]. Ongoing research on sensor technology shows that in vivo glucose sensors could soon be realizable [3]. Hence, research is needed toward a more efficient insulin pump control algorithm. This paper explores the use of H infinity controller for regulation of blood glucose in the diabetic patient.

Diabetic Model And Uncertainty Description

A nonlinear pharmacokinetic/pharmacodynamic compartmental model of the diabetic patient has been constructed previously [17][14][15][10].The meal disturbance model of [13]was included in the model of [14], who reported all the model equations and parameters in detail with 19 state equations and 47 parameters. The diabetic patient model had two inputs- insulin delivery and meal disturbance and one measured output namely blood glucose concentration. Insulin delivery rate, represented as deviation from its 22.3mU/min nominal delivery was the manipulated variable. The meal disturbance had a nominal value of 0 mg/min. The measured variable represented the deviation in blood glucose concentration from 81.1mg/dl.

Uncertainties exist due to the inevitable patient-model mismatch; the uncertainties between the actual patient and the nominal patient model could be translated to variations in the model parameters. The glucose and insulin dynamics were found to be most sensitive to variations in the metabolic parameters. In the patient model, glucose metabolism is mathematically described by threshold functions with the following structure:

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

Where subscript i in equation (1) is the state vector element involved in the metabolic effect and the e subscript denotes specific effects within the model: the effect of glucose on hepatic glucose production (EGHGP), the effect of glucose on hepatic glucose uptake (EGHGU) or the effect of insulin on peripheral glucose uptake (EIPGU). The parameters $A_{\Gamma_e}, B_{\Gamma_e}$ and C_{Γ_e} are constants whose values are given by the threshold function behavior. Inter Differences in insulin clearance between patients also exist, and could be modeled as deviations in the fraction of clearance by a given compartment such as the fraction of hepatic clearance (FHIC) or the fraction of insulin clearance (FPIC). This uncertainty formulation essentially focused on the liver and the peripheral (muscle/fat) tissues. In the absence of physical data from which to identify ranges for parametric variations, [14] assumed ± 40% variability in each parameter to represent a broad range of potential patients. The exception was FHIC, which was limited to ± 20% to guarantee non-negative glucose concentrations. From these

eight parameters sets of three parameters were chosen. Each of these three parameters was tested at three levels (nominal, low and high) yielding a total of 1512 patients. Patients with identical values for all the eight parameters were removed and this resulted in a set of 577 unique patients.

The synthesis of H∞ controller requires a linear model of the system to be controlled. A 19th order linear model was obtained by linearizing the nonlinear model of the nominal diabetic around the nominal plasma glucose concentration around 81.1 mg/dl. Subsequently, the 19th order linear model was reduced to a third order model using the balanced realization technique [7].This third order model was used in the controller synthesis.

Results and discussions

Validation of reference model.

The overall response of the twenty two healthy subjects which is used as reference model is depicted in Figure 1.

The GTC (Glucose Tolerance Curve)'s permit to see that the BG response to a meal in a healthy subject behaves like a second-order system. Therefore the transfer function for reference model is validated

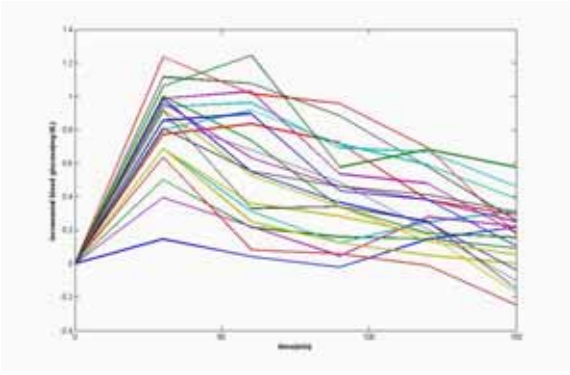

Figure 1. Overall response of all the six subjects.

from mean of twenty two healthy subjects' data. The P_{ref} has the following representation [16]

$$P_{ref} = \frac{K\omega_n^{\,2}}{s^2 + 2\xi\omega_n s + \omega_n^{\,2}} \quad (2)$$

Where K=3900, $\xi = 0.7$, $\omega_n = 0.03$; Therefore the impulse response of P_{ref} resembles the curve shown in Figure 2.

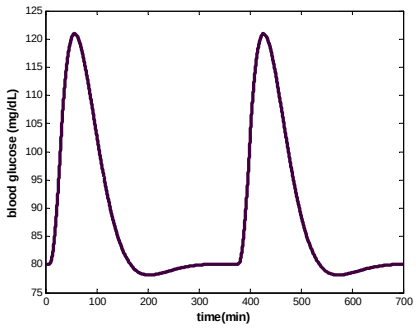

Figure 2: Output of reference model

H∞ controller synthesis

The H∞ control framework is well suited for glucose regulation, due to the ability to tune the controller for robustness to uncertainty while mathematically guaranteeing a certain degree of performance. In this case, it is important for a closed-loop controller to tolerate patient variability and dynamic uncertainty while rapidly rejecting meal disturbances and tracking the constant glucose reference.

A theoretical derivation of the H∞ controller synthesis method is beyond the scope of this work. For an overview of state-space H∞ theory, the reader is referred to [6] the references therein.

There are many complex influences between glucose and insulin concentration for any person, normal or diabetic. However, the steady state blood glucose level in the body is finally determined by how much insulin is present. In order to lower blood glucose level in the blood, insulin needs to be injected [4]. Hence, the controller defines the insulin infusion rate U(t), based on the measured glucose level. For the problem formulation let us consider the feedback system can be described in LFT form (Fig. 3), where G and K are real rational and proper transfer functions. The transfer matrix G is called generalized plant,

$$G(s)=\begin{bmatrix} A & B_1 & B_2 \\ C_1 & D_{11} & D_{12} \\ C_2 & D_{21} & D_{22} \end{bmatrix}=\begin{bmatrix} G_{11} & G_{12} \\ G_{21} & G_{22} \end{bmatrix} \quad (3)$$

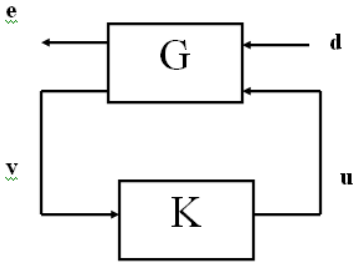

Figure 3. H∞ synthesis problem.

The controller synthesis for the suboptimal H∞ case is formulated as follows: given $\gamma > 0$ to find an internally stabilizable controller $K(s)$, if there is any, such that. Thus $\|T_{zw}\| < \gamma$ .Thus, T_{zw} is the closed-loop transfer matrix from d to e:

$$T_{zw} = F_l(G,K) = G_{11} + G_{12}K(I - G_{22}K)^{-1}G_{21} \quad (4)$$

In order to find the controller, if exists, $G(s)$ should satisfy the following conditions:

1) (A_1) (A, B_2) is stabilizable and (C_2, A) is detectable.

2) $(A_2)\begin{bmatrix} A - j\omega I & B_2 \\ C_1 & D_{12} \end{bmatrix}$ has column rank for all ω.

3) $(A_3)\begin{bmatrix} A - j\omega I & B_1 \\ C_2 & D_{21} \end{bmatrix}$ has full row rank for all ω

Assumption 1 simply states that the linearized reduced order system must satisfy the controllability and observability criterion for linear systems based on the insulin delivery rate manipulated variable and arterial insulin concentration measurement. The second assumption guarantees a synthesized

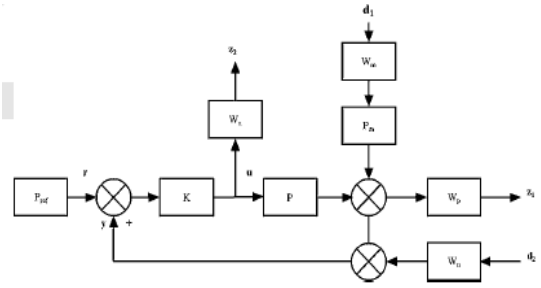

Figure 4: Standard feedback configuration with weights

H_∞ controller is proper, and therefore realizable .The final assumption is a mathematical technicality to ensure that the techniques in [4]. The system of two Riccati equations is solved through the $\gamma -$ iteration technique utilizing the hinfsyn command in the $\mu -$ Tools toolbox of MATLAB, which produces a nonunique suboptimal controller. Here, as it was mentioned above, the insulin delivered to patient $i(t)$ (mU/min) is given by

$$i(t) = u(t) + 22 \quad (5)$$

Where $u(t)$ is the insulin portion calculated by the controller.

Following figure shows the simulation of the BG response of a TIDM patient under a meal, at t=0 min and at t=370 min. The controller used for this simulation is resulted by H∞ approach. The meal contains 100 g of glucose. The maximum difference between the BG reference and the glucose level of the diabetic patient is 15.6 mg/dL.

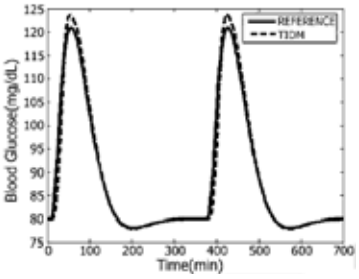

Figure 5. BG response for the TIDM patient under feedback control

Robust controller design

Uncertainty in the frequency domain manifested through parameter variations in the 19th order model, was then measured with respect to the reduced (nominal) model of the diabetic patient over the frequency range of interest. This was represented as relative uncertainty

$$U_{rel}(\omega) = \left| \frac{P_p(\omega) - P(\omega)}{P(\omega)} \right| \tag{6}$$

Where P is the nominal model, while P_p represents the perturbed model. The most sensitive parameter set was therefore identified by summing the relative uncertainty in the frequency range of interest for each perturbation, and summing over the parameter set. The parameter set which displayed the most significant effect on glucose and insulin dynamics was EIPGU (Effect of insulin on peripheral Glucose uptake) (D_Γ) in the range of ± 40% from the nominal value of -5.82113[14].EGHGU (Effect of Glucose on Hepatic Glucose Uptake)(D_Γ) in the range of ± 40% from the nominal value of -1.48[14].FHIC (Fraction of Hepatic Insulin clearance) (F_{LC}) varies in the range of ±20% from 0.4.[14]

The block diagram in Figure 6 contains the modified block feedback scheme when parameter variations are included into the model; which are incorporated in the form of weighted transfer functions.

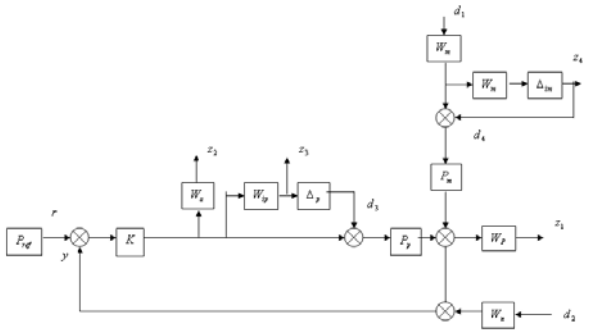

Fig 6. Modified Block diagram of BG regulation including parametric uncertainties

The generalized plant, $G(s)$, has the following representation [12]

$$\begin{bmatrix} z_1 \\ z_2 \\ z_3 \\ z_4 \\ y \end{bmatrix} = G(s) \begin{bmatrix} d_1 \\ d_2 \\ d_3 \\ d_4 \\ u \end{bmatrix} = \begin{bmatrix} W_m G_m W_p & 0 & W_p P & G_m W_p & W_p P \\ 0 & 0 & 0 & 0 & W_u \\ 0 & 0 & 0 & 0 & W_i \\ W_m W_{im} & 0 & 0 & 0 & 0 \\ -W_m G_m & -W_n & -P & G_m & -P \end{bmatrix} \begin{bmatrix} d_1 \\ d_2 \\ d_3 \\ d_4 \\ u \end{bmatrix} \tag{7}$$

The nominal model was given by P and the transfer function of the nominal diabetic patient model is

$$P = \frac{2.132e-005s^4 - 0.0001197s^3 + 0.0002405s^2 - 0.001201s - 9.775e-005}{s^5 + 1.183s^4 + 0.3804s^3 + 0.03953s^2 + 0.001381s + 1.34e-005} \tag{8}$$

Nominal model was perturbed by varying any one of the above mentioned parameters, with the variation of F_{LC} following plant transfer function and controller transfer function can be obtained,

$F_{LC} = 0.48$ the transfer function of the perturbed diabetic patient model is

$$P_p = \frac{1.2e-005s^4 - 8.043e-005s^3 + 0.0001531s^2 - 0.00104s - 8.513e-005}{s^5 + 1.152s^4 + 0.381s^3 + 0.0405s^2 + 0.001432s + 1.401e-005} \tag{9}$$

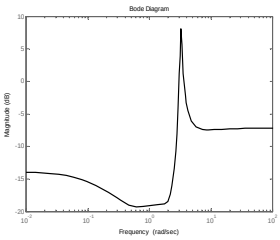

Fig 7: Relative model uncertainty as a function of frequency

Model uncertainty as a function of frequency is as shown in Figure 7 for the variation of parameter. Low uncertainty is seen at low frequency increasing beyond the 100% uncertainty at 5 rad/sec. Modified block diagram of BG (Blood Glucose) regulation including parametric uncertainties is as shown in Fig 8.[16]

Weighting functions W_p, W_m, W_n and W_u represents the performance weight, weight for the meal disturbance, weight for the sensor noise effects and Weight for the control input respectively. G_m corresponds to the meal model and order of this model is fifth [16],

$$G_m = \frac{-0.0008165s^4 + 0.000732s^3 + 0.0001269s^2 + 5.522\times10^{-5}s + 5.839\times10^{-8}}{s^5 + 0.3029s^4 + 0.0369s^3 + 0.001946s^2 + 4.342\times10^{-5}s + 2.753\times10^{-7}} \quad (10)$$

And the weighted transfer functions are: W_p is a first order transfer function, and was chosen such that the frequency content of G_m was captured. Moreover, W_p was selected taking into consideration the frequency content of P_{ref} [16].

$$W_p = \frac{0.8s + 0.01}{s + 0.01} \quad (11)$$

The weight W_m represents the effects of meal model, and permits to induce the maximum carbohydrate content into the meal [16]

$$W_m = \frac{1}{3.5s + 1} \quad (12)$$

The sensor noise effects are weighted by W_n i.e it emulates possible errors generated by the glucose sensor and W_u stands for the weight for the control input [16].

W_{im} and W_{ip} represents the multiplicative uncertainty representation for the input disturbance (meal) and performance weight respectively. P_p represents the perturbed patient model for different uncertainty parameters.

The weights W_{im} and W_{ip} were calculated as the least upper bound on the relative uncertainty of the perturbed plants subjected to the constraint that they were represented using low order transfer functions. These weights were

$$W_{ip} = \frac{s^2 + 0.4s + 0.014}{s^2 + 0.23s + 0.024}$$ and

$$W_{im} = \frac{1.5s^2 + 0.25s + 0.065}{s^2 + 0.55s + 0.015} \quad (13)$$

Now the synthesis problem is to find a controller that minimizes $z = [z_1, z_2, z_3, z_4, y]'$ as small as possible in the H_∞ sense.

The controller transfer function for this variation is as shown below,

$$K = \frac{0.4985s^6 - 3.234e004s^5 - 4.299e004s^4 - 1.9e004s^3 - 216s^2 - 92.47s - 1.152}{s^6 + 13.39s^5 + 62.05s^4 + 118.3s^3 + 124.9s^2 + 31.41s + 0.009412} \quad 14)$$

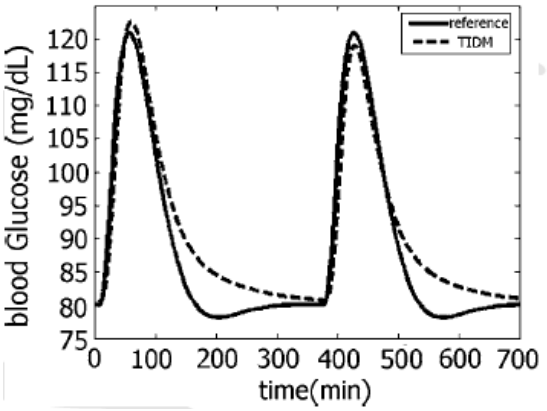

Figure 8. BG response with uncertainty parameter Flc=0.48

Figure 8 shows the Blood Glucose response with uncertainty parameter Flc=0.48, which shows the exact tracking of the TIDM patient signal with reference signal. The simulation represents the worst case on the parametric variations. Since minimum BG level is higher than 70 mg/dL, hypoglycaemia effects cannot be presented in the closed-loop.

Figure 9 also shows the Blood Glucose response of TIDM patient by considering other uncertainty parameter.

Comparison with the PID controller

Available tuning methods for PID controllers are often based on a first-order plus dead time (FOPDT) model of the system to be controlled. The nominal patient model was subjected to a ±5% step change in the manipulated variable (i.e insulin), and the resulting step response for a positive step change was used to identify an FOPDT model using the method of Sundaresan and Krishnaswamy [15].The step responses of the nominal patient model and FOPDT

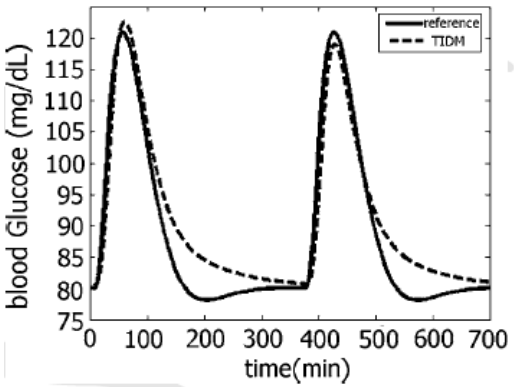

Figure 9. BG response by adding parametric uncertainties.

model are shown in Fig 10. The optimal FOPDT model for diabetic patient model is given by

$$\widetilde{G} = \frac{-7.31e^{-20.32s}}{73.14s+1} \qquad (15)$$

The FOPDT model with gain =-7.31 (mg/dL), time constant=73.14 min, and the dead time= 20.32 min is then employed to find the tuning parameters K_P, K_I and K_D using different tuning methods.

In this study, PID controllers designed by IAE minimization (for disturbance rejection) tuning, Cohen-Coon tuning, and the recently developed Shen tuning and DMC- based method are used for blood glucose regulation in diabetics.

The FOPDT model was obtained by approximating the step response of the nominal diabetic patient. The parameters K_P, K_I and K_D of the PID controller using the aforementioned four methods are reported as follows.

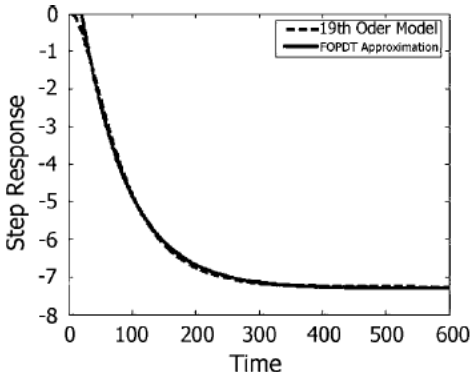

Figure 10. Step response of 19th order Model and its FOPDT approximation

Table 1, Performances of PID controllers tuned by four methods on the nominal patient case in attenuating 50-g meal disturbance

Tuning	K_p	K_I	K_D	Overshoot(mg/dL)	Undershoot(mg/dL)
IAE minimization	-1.23	-0.055	-6.034	20.32	10.1
Cohen-Coon	-1.35	-0.046	-6.076	20	6.54
DMC based	-0.84	-0.007	-6.724	4	0.001
Shen	-3.87	-0.08	-36.5	4	0.01

The relations employed in the four methods are reported as follows: [14]

Relations for the four methods of PID controller tuning used in this study are based on assuming the process model of

$$G(s) = \frac{Ke^{-\theta s}}{\tau s+1}. \qquad (16)$$

Where K is gain, θ is dead time and τ is time constant.

These relations provide values of K_c, τ_I and τ_D that can be employed to calculate, K_P, K_I and K_D in PID controller equation, from $K_P = K_C$, $K_I = \frac{K_C}{\tau_I}$ and $K_D = K_C\tau_D$.

The relations for IAE minimization tuning for disturbance inputs are

$$K_C = \frac{a_1}{K}\left(\frac{\theta}{\tau}\right)^{b_1} \quad \tau_I = \frac{\tau}{a_2}\left(\frac{\theta}{\tau}\right)^{b_2} \quad \tau_D = a_3\tau\left(\frac{\theta}{\tau}\right)^{b_3}$$

where $a_1 = 1.435,\ a_2 = 0.878$, $a_3 = 0.482$ $b_1 = -0.921$, $b_2 = 0.749$ and $b_3 = 1.137$.

The relations for Cohen- Coon tuning are

$$K_C = \left(\frac{\tau}{K\theta}\right)\left(\frac{4}{3}+\frac{\theta}{4\tau}\right),\ \tau_I = \overline{\tau}_I\tau,\ _{\tau_D=\overline{\tau}_D\tau},\ L = \frac{\theta}{\tau}$$

$$K_C(L) = \frac{6.84}{1+2.33L^{0.7}+7.82L^{3.5}} + 0.64$$

$$\overline{\tau}_I = \begin{cases} 0.95+2.58L+3.57L^2 \; for 0 < L \le 0.29 \\ 2.15-0.76L+0.33L^2 \; for 0.29 < L < 4 \end{cases}$$

$\overline{\tau}_D$

$$\begin{cases} 0.29\left(\frac{L}{1+L}\right) + 3.94\left(\frac{L}{1+L}\right)^2 - 4.65\left(\frac{L}{1+L}\right)^{2.8} & for\, 0 < L \le 1.9 \\ 0.87L - 0.49L^2 + 0.09L^{2.8} \end{cases}$$

Finally, the Shen tuning formula the tuning equations for disturbance rejection are given by

$\alpha = K\frac{\theta}{\tau}$ and $T = \frac{\theta}{\theta+\tau}$ where αK_C, $\frac{\tau_I}{\theta}$ and τ_D/θ are given by empirical formulations of the form $\exp(a_0 + a_1 T + a_2 T^2)$ and the coefficients, $a_0 - a_2$ are given by Table 2 [4].

Table2: Coefficients for the Shen tuning formula

	a_0	a_1	a_2
αK_c	2.94	-11.63	11.15
τ_i/θ	1.88	-3.63	8.86
τ_D/θ	-0.25	-0.06	-1.99

The performances of the PID s in rejecting, according to the four tuning methods, a 50 g meal taken by a nominal patient are depicted in Figures 11-14.

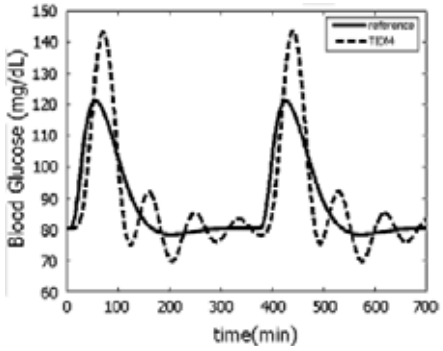

Figure 11: Performance of IAE based tuned PID controller

From the performance of IAE minimization it is observed that there is a overshoot of around 25 mg/dL and undershoot of 12mg/dL.

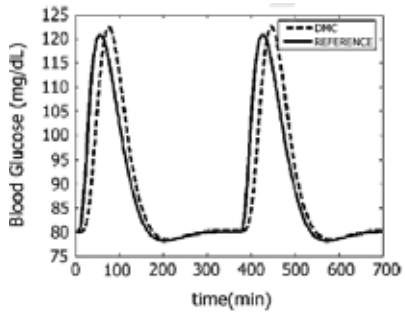

Figure 12: Performance of DMC based tuned PID controller

This leads to corresponding hyperglycaemia and hypoglycaemic effects.Performances of DMC based tuned controller indicates the presence of overshoot of 2 mg/dL .

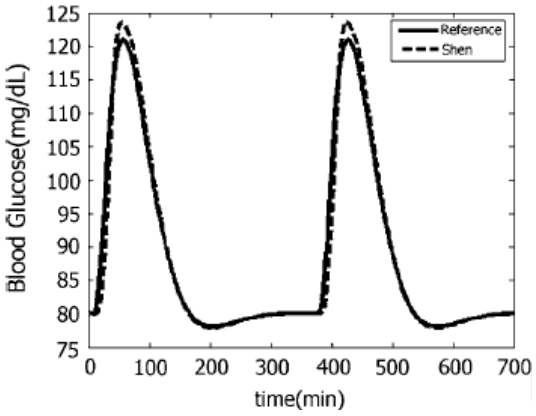

Figure 13: Performance of Shen based tuned PID controller

Performances of Shen tuned controller indicates the presence of overshoot of 3 mg/dL .

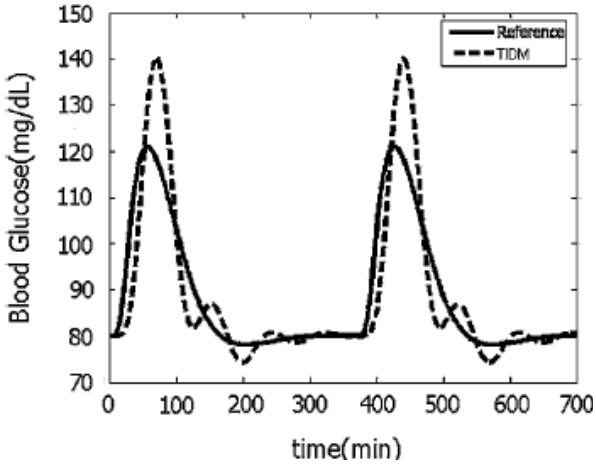

Figure 14: Performance of Cohen Coon based tuned PID controller

But from the performance of Cohen-Coon tuning one can observe that an approximately 20 mg/dL of overshoot and 5mg/ dL of undershoot.

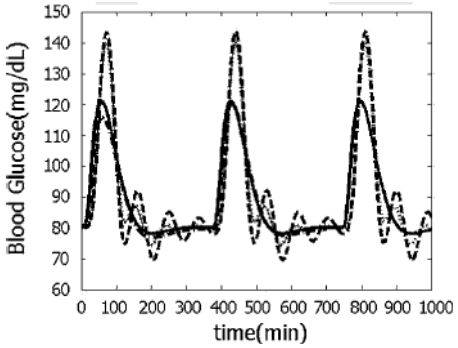

Figure 15: Overall Performances of PID controllers tuned by four methods on the nominal patient model in rejecting a 50-g meal disturbance at time t=0 min.

From the overall response it is evident that the performance of the PID controller with the Shen and DMC method of tuning is better than the perform ances of the controllers designed by the other two methods in terms of the lowest and highest glucose concentrations observed in the rejection of the meal disturbance.

Performance of IMC Controller:

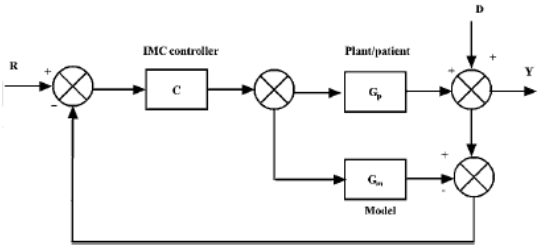

Figure 16: Conventional IMC controller

The conventional IMC structure is shown in Fig 16, where G_P is the plant/patient to be controlled. G_m is a model of the plant/patient, C is the IMC controller, R is the reference input to the control system, Y is the system output and D is the equivalent external disturbance.

Based on the FOPDT approximation of the nominal diabetic model, IMC controller was developed for the regulation of glucose level in diabetics. The optimal FOPDT model for diabetic patient model is given in equation (15) and the IMC controller is designed by the standard design approach given in [18]. The various parameters such as, K_C , Γ_I and Γ_D can be evaluated by using following formulae.

$$K_c = \frac{2\tau + \tau_d}{2(\lambda + \tau_d)}, \quad \tau_I = \tau + (\tau/2) \quad \text{and}$$

$$\tau_D = \frac{\tau\tau_d}{2\tau + \tau_d} \qquad (17)$$

From the above mentioned FOPDT model the different parameters are $\theta = 20.32, K = -7.31, and \tau = 73.14$. Figure 17 shows the response of IMC controller for nominal patient to 50 g meal disturbance. From the response it is evident that the controller response does not exactly track the reference input.

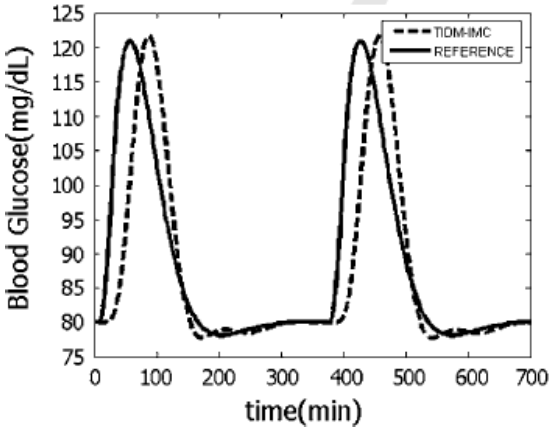

Figure17: Performance of IMC controller

Conclusion

Currently, the clinical application of the blood glucose control is mostly using open-loop method. But these methods suffer from main disadvantage that frequent glucose concentration variations due to the open loop nature. Hence it is advisable to design closed-loop controller for blood glucose regulation. The closed-loop method is a new direction and it can control human blood glucose ideally. At present, using of appropriate control algorithm to regulate blood glucose becoming a new direction for the treatment of diabetics. Apart from the controller, there are some technical problems. The first is the glucose sensor, because closed-loop control needs an accurate blood glucose signal. How to measure the blood glucose concentration stably and reliably is an important problem. The second is the biological compatible problem. Both the mechanical pump and the blood glucose sensor are necessary to consider the compatibility of the human body. Now the closed-loop control method has been mentioned more and more, but it has not applied widely [9]. To obtain excellent control methods of blood glucose level, we should make great efforts on it.

References

[1] Bellazi R. Nucci G, Cobelli G.(2001). The subcutaneous route to insulin-dependent diabetes therapy. IEEE Eng Med Biol,20: 54-64.

[2] Bergman, R., Phillips, L., and cabal, C.(1981). Physiologic evaluation of factors controlling glucose tolerance in man. J. Clinic Investigation, 68, 1456-1467.

[3] Bode BW .(2004). Medical management of Type I diabetes , 4th edn. American diabetes Association, Alexandria, Virginia.

[4] Campos-Delgado DU, Femat R, ruiz-velaquez E,et al.(2003).Knowledge-based controllers for blood glucose regulation in type I diabetic patients by subcutaneous route. In : proceedings of the International Symposium on Intelligent control, Houston., 3-5 October.

[5] Carson ER, deutsch T.(1992). A spectrum of approaches for controlling diabetes. IEEE Control Syst Mag 12(6): 25-31.

[6] Donald R. Coughanowr , " Process Systems Analysis and Control ", second edition MGH International Editions Chemical Engineering Series1991.

[7] Doyle,J.C.,Glover,K.,Khargonekar,P.P.,andFracisB. A.(1989).State space solutions tostandard H^2 and H^∞ control problems. IEEE Trans. On Automatic Control,34,831-847.

[8] - DCCT- The Diabetes Control and Complications Trial Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl F med, 329: 977-86.

[9] Erzen,F.C., Birol,G., and Cinar.A.(2000), Simulation studies on the dynamics of diabetes mellitus. Proc. IEEE Int. Symp. Bio-Informatics and Biomedical Eng.232-235.

[10]Guyton, J.R., Foster, R.O., Soeldner, J.S., Tan, M.H., Kahn, C.B., Koenz,L.and Gleason, R.E.,1978, A model of glucose-insulin homeostasis in man that incorporates the heterogeneous fast pool theory of pancreatic insulin release, Diabetes, 27: 1027.

[11]Kennedy F.P (1987) Recent developments in insulin delivery techniques: current status and future potential, Drugs,vol.42,pp.123-137,.

[12]Lehmann E.D., and Deutsch,T.(1998). Compartmental models for glycaemic prediction and decision-support in clinical diabetes care: promise and reality. Computer Methods and programs in Biomedicine, 56, 193-204.

[13]Lehmann, E.D., and Deutsch, T. (1992). A physiological model of glucose-insulin interaction in type I diabetes mellitus. J. of Biomedical Engineering, 14,235-242.

[14]Parker ,R.S., Doyle III,F.J., and Peppas,N.A ."Robust H∞ glucose control in diabetes using a physiological model." A.I.Ch.E.Journal, 46(12),2537-2549. .(2000).

[15]Parker ,R.S., Doyle III,F.J., and Peppas ,N.A.(1999)."A model based algorithm for blood glucose control in type I diabetes patients." IEEE Transactions on BiomedicalEngineering ,46(2),148-157.

[16]Ruiz-Velaquez,E., Femat,R. Campos-delgado,D.U .(2003). A robust approach to control blood glucose level: Diabetes Mellitus Type I . Proceedings of the fourth IFAC symposium on robust control design (IFAC-ROCOND)25-27 June, Milan, decision-support in clinical diabetes care: promise and reality. Computer Methods and programs in Biomedicine, 56, 193-204.

[17]Sorensen J .T (1985)" A physiologic model of glucose metabolism in man and its use to design and access improved insulin therapies for diabetes," Ph.D.Thesis,deptchem.Eng.,MassachusettsInst.Tecnol.(MIT).Cambridge

[18]Sundaresan, K.R., and Krishnaswamy P.R. Estimation of time delay, time constant parameters in time, frequency and Laplace domains. Can. J. Chem. Eng. 1977, 56,257.

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