ENHANCED IMC FOR GLUCOSE CONTROL IN TYPE I DIABETIC PATIENTS

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Abstract: Maintaining the glucose concentration in normoglycemic range in Type I diabetic patients is challenging. In this study, the Enhanced Internal Model Controller (EIMC) is developed for a diabetic, due to its simple structure, better disturbance attenuation and uncertainty reduction capabilities. A first order plus time delay (FOTD) model approximation of nominal patient model is used for developing the EIMC. The controller performance is assessed based on its ability to track normoglycemic set point (81.1 mg/dl) in response to a 50 g meal disturbance. In the nominal case, the controller maintains the glucose concentration within ± 6.5 mg/dl of set point. The robustness of the controller is studied by application to a fairly "diverse" group of "patients", and compared with that of IMC controller.

Keywords: Blood glucose control, Glycaemia control, Enhanced IMC, Robust control

1. INTRODUCTION

Diabetes mellitus is a major chronic disease affecting millions of people worldwide, Type I or insulin-dependent diabetes mellitus (IDDM) is characterized by the insufficient secretion of insulin from the β-cells of pancreas, resulting in glucose concentrations elevated beyond the normoglycemic range (70-100 mg/dl) (Ashcroft and Ashcroft, 1992). The prevalence of sustained hyperglycaemia (arterial glucose concentration > 120 mg/dl) is the reason for long-term complications associated with diabetes such as nephropathy and retinopathy. The current treatment methods of insulin therapy are largely “open loop” in nature. Intuitively, it can be said that “closed loop” control approaches can result in good glycaemia control over extended periods of time. Such a strategy would involve three major components – a mechanical pump, *in-vivo* glucose sensor and a mathematical algorithm to regulate the pump and set appropriate insulin dosage based on a sensor measurement. These aspects have been active areas of research in the diabetes literature. Present work focuses on the automatic control aspects of blood glucose regulation.

Early modelling studies of the diabetic condition (Bolie, 1961; Ackerman et al., 1965) established a precedent for mathematical analysis of insulin-glucose interactions. Later studies utilized the more complicated nonlinear models such as Bergman’s “Minimal Model” (Bergman et al., 1981) and incorporated physiological system knowledge in the model structure (Cobelli and Mari, 1983; Sorensen, 1985). Various model based optimal control algorithms have been developed utilizing these models in either an explicit or implicit fashion (Sorensen, 1985; Ollerton, 1989; Fischer 1991; Parker et al., 1999). In the synthesis of these controllers, however, the inherent uncertainty in the model has not been properly addressed. Such control strategies could lead to significant performance degradation, in the presence of inevitable patient-model mismatch.

Significant inter- and intra-patient variability has been documented in literature (Bremer and Gough, 1999; Pucket and Lightfoot, 1995; Simon et al., 1987; Steil et al., 1994), resulting in the controller to be retuned for each patient. The control algorithm employed in the insulin delivery device must be able to compensate for the uncertainty that exists between the internal model and the actual patient. This clearly motivates the synthesis of a controller that can handle the model-patient mismatch. Parker et al. (2000) used the H_∞ framework to explicitly treat the model uncertainty. They employed a detailed and fairly complex physiological patient model (19 state nonlinear dynamic model) because it allows uncertainty characterization on particular tissues or effects that are responsible for the insulin or glucose variability. This detailed model is used in this study too but the focus is on an Enhanced Internal Model Controller (EIMC) scheme of Zhu et al. (1995). owing to its simple structure and better uncertainty and disturbance attenuation. Despite these attractive features, EIMC has not been applied for blood glucose control so far. Its robustness to typical inter- and intra-patient variability will be demonstrated.

2. THE MATHEMATICAL MODEL

A nonlinear pharmacokinetic/pharmacodynamic compartmental model of the diabetic patient has been constructed previously (Guyton et al., 1978; Sorensen, 1985; Parker, 1999), and is detailed in Parker et al. (2000). A few typographical errors in the differential

equations provided there are corrected and listed in the appendix of this article. The meal disturbance model of Lehmann and Deutsch (1992) was included in the model of Parker et al. (2000). The specific operating conditions for the diabetic patient model used in testing the robust controller algorithms are described in Parker (1999). The diabetic patient model had two inputs and one measured output. Insulin delivery rate, represented as deviation from its 22.3 mU/min nominal delivery rate, was the manipulated variable (represented as $\overline{u}$). The meal disturbance had a nominal value of 0 mg/min (absorption into the blood stream), and its signal was denoted as $\overline{m}_d$. The measured variable $\overline{Y}$ represented the deviation in blood glucose concentration from the nominal value of 81.1 mg/dl. All these three variables were scaled as mentioned in Parker et al. (2000).

$$m_d = \frac{1}{360}\overline{m}_d,\ u = \frac{1}{33.125}\overline{u},\ Y = \frac{1}{20}\overline{Y} \qquad (1)$$

Here, the disturbance scaling was determined by its maximum value, and the output scaling by maximum allowable deviation in glucose concentration. Note that the measured value, Y is (blood) plasma glucose concentration, obtained by multiplying the arterial glucose concentration (3rd state in the model of Parker et al., 2000) by a correcting factor of 0.925.

The EIMC controller synthesis requires a linear model of the system to be controlled. A 19th order linear model was obtained by linearizing the nonlinear model of the diabetic around the nominal plasma glucose concentration of 81.1 mg/dl. Subsequently, the 19th order model was reduced to a 3rd order model using "balanced realization" technique. The patient model was also subjected to ±5% step change in the manipulated variable (i.e. insulin) and the resulting step response was used to identify a first order plus time delay (FOTD) model using the method of Sundaresan and Krishnaswamy (1977). From the step responses of the above-mentioned models (Fig 1), it appears that a better fit of the patient dynamics is obtained with the FOTD model.

3. UNCERTAINTY DESCRIPTION

Uncertainty due to the differences between an actual patient and the 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 (Parker et al., 1998). In the patient model, glucose metabolism is mathematically described by threshold functions with the following structure

$$\Gamma_e = E_r\{A_r - B_r \tanh[C_r(x_i + D_r)]\} \qquad (2)$$

The subscript *i* in equation (2) 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

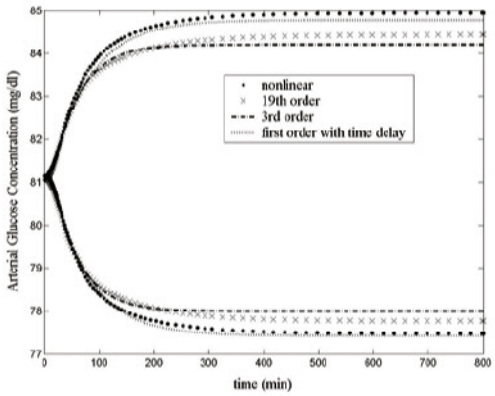

Fig. 1. Response of nonlinear (dot), 19th order linear (cross), 3rd order linear (dash-dot), first order with time delay (dotted) models to ±5% step changes in insulin from the nominal 22.3 mU/min.

glucose uptake (EIPGU). Inter- or intra-patient uncertainty could be classified physiologically as either receptor (D_r parameter) or post-receptor (E_r parameter) defect, and this was modelled mathematically by adjusting the inflection point of the hyperbolic tangent function or the maximum value of Γ_e respectively. Differences in insulin clearance (metabolism) between patients also exist, and could be modelled as deviations in the fraction of clearance from a given compartment such as the fraction of hepatic clearance (FHIC) or the fraction of peripheral insulin clearance (FPIC). This uncertainty formulation essentially focused on the liver (variability in five parameters) and the peripheral (muscle/fat) tissues (variability in three parameters) as these were considered to be more relevant to the control study (Parker et al., 2000).

In the absence of physical data from which to identify ranges for parametric variations, Parker et al. (2000) assumed ±40% parametric variability in each parameter represented 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 were tested at three levels (nominal, low and high) yielding a total of ${}^8C_3 \times 3^3 = 1512$ "patients". Patients with similar values for all the eight parameters were removed and this resulted in a set of 577 unique patients. These patients are assumed to capture all the inter- and intra-patient variability among Type I diabetics. Each of these patients was subjected to a 50 g meal disturbance at t = 0 under closed-loop to test the robustness and disturbance attenuating capabilities of the controller designed.

Bounds on open-loop responses of patient models to step change in insulin (from the value required to maintain the output at 81.1 mg/dl) to 0 mU/min, are shown in Fig 2. These responses are very similar to those reported in Parker (1999), confirming the validity of patient models employed in this study. They also show the broad range of patient dynamics. Note that the glucose profiles shown in Fig. 2 are for ±50% variation in parameters where as only ±40% variation in parameters is considered to test controller robustness.

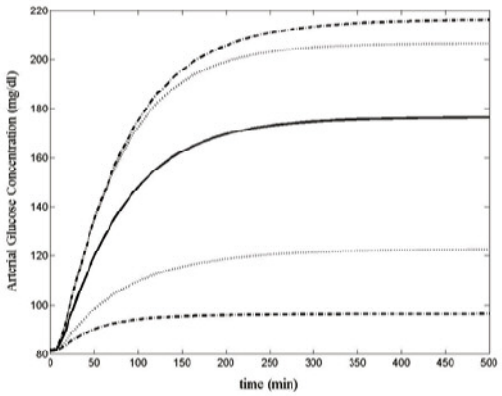

Fig. 2. Response of some patient models to the step change in insulin to 0 mU/min: solid - nominal patient model; dashed - response bounds for ± 50% variations in EGHGP-E_Γ; dash-dot - response bounds for the simultaneous ± 50% variations in EGHGP-E_Γ and EIPGU-D_Γ.

4. SYNTHESIS OF THE EIMC

The conventional IMC structure is shown in Fig 3, where G_p is the plant to be controlled, G_m is a model of the plant, and 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. The IMC controller design involves two steps

Step1: The process model $G_m(s)$ is factorized as

$$G_m(s) = G_m^+(s)\, G_m^-(s) \tag{3}$$

where G_m^+ (s) contains any time delays and right-half plane zeros. It is specified so that its steady-state gain is 1. And, $G_m^-(s)$ contains the remaining invertible dynamics of $G_m(s)$.

Step 2: The IMC controller is specified as

$$C(s) = \frac{1}{G_m^-(s)} f(s) \tag{4}$$

where f (s) is a low-pass filter with steady-state gain of 1. This filter typically has the form

$$f(s) = \frac{1}{(\lambda s + 1)^r} \tag{5}$$

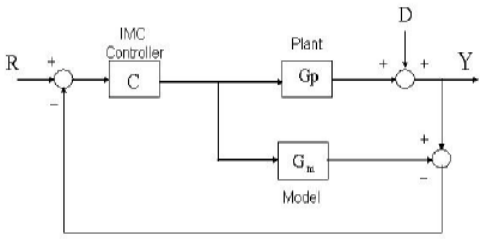

Fig. 3. Conventional IMC system

where λ is the tuning parameter to be selected by the control engineer so as to meet the robustness and performance requirements of the control system. The parameter 'r' is a positive integer that is selected so that either C(s) is a proper transfer function or the order of its numerator exceeds the order of the denominator by 1, if ideal derivative action is allowed.

From Fig 3, the closed loop servo transfer function G^R and the closed loop disturbance transfer function G^D of the conventional IMC system can be derived as follows.

$$G^R = [I + (C^{-1} - G_m)\, G_P^{-1}]^{-1} \tag{6}$$

$$G^D = [I + G_P (C^{-1} - G_m)^{-1}]^{-1} \tag{7}$$

The EIMC structure (Zhu et al., 1995) is shown in Fig 4. It can be seen that an additional path is appended to the IMC system within the plant-model parallel structure. Here, in addition to the IMC controller, C_1 (same as C in Fig. 3), C_2 is the 'complementary' IMC compensator and K is pure gain. By inserting this additional path into the original IMC system, a complementary control signal generated from the plant-model error is injected into the output of the original IMC controller. This leads to the EIMC structure whose performance was shown to be superior to IMC in the presence of modelling errors (Zhu et al., 1995).

From Fig 4, the closed loop servo transfer function (G_1^R) and the closed loop disturbance transfer function (G_1^D) of the EIMC structure can be derived as follows.

$$G_1^R = [I + (C_1^{-1} - G_m)\, M]^{-1} \tag{8}$$

and

$$G_1^D = (I - G_m C_1)\, [I + (G_p - G_m) C_1 + G_p C_2 K]^{-1} \tag{9}$$

Here,

$$C_1(s) = \frac{1}{G_m^-(s)} f_1(s); \qquad C_2(s) = \frac{1}{G_m^-(s)} f_2(s);$$

$$f_1(s) = \frac{1}{(\lambda_1 s + 1)^{r_1}}, \qquad f_2(s) = \frac{1}{(\lambda_2 s + 1)^{r_2}}$$

and $$M = [G_p (I + C_2 K G_p)^{-1} (I + C_2 K G_m)]^{-1}$$

The disturbance attenuating capability of the EIMC is improved with large K and a smaller λ_2 as the denominator in the equation (9) becomes high. The values of both r_1 and r_2 are 1 in the present study.

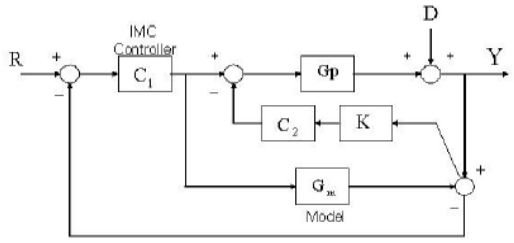

Fig. 4. Enhanced IMC structure

5. RESULTS AND DISCUSSION

Internal Model Controller (IMC) was developed for regulating the glucose level in diabetics. The filter constant, λ of 25 was initially chosen based on robust performance and stability analysis. Then, the IMC performance with various values of λ was tested by subjecting the nominal patient to 50 g meal disturbance (see the results in Fig. 5 for K = 0 and λ = 25). Disturbance rejection of the IMC improved with decrease in λ. Robustness of the IMC was then tested on all 577 patients and the results are summarized in Table 1. Number of patients whose blood glucose concentration was maintained by IMC within normoglycemic range (70-100 mg/dl), is given in the second column. Glucose concentration below 60 mg/dl is the dangerous hypoglycaemic region. Hence, number of patients whose glucose concentration was maintained by the IMC within 60-100 mg/dl, is also presented in Table 1. Also, average IAE and standard deviation of IAE based on all 577 patients are reported in this table. Results in Table 1 show that decreasing λ has increased number of patients whose glucose concentration is maintained between 70-100 mg/dl and 60-100 mg/dl while rejecting 50 g meal disturbance, and also the average IAE and standard deviation of IAE decreased. These and transient responses (not shown here) indicate that decreasing λ has improved the performance of IMC. But the IMC even with λ =2 is not able to maintain the glucose concentration within normoglycemic range in 46% of the patients. This led us to investigate if the EIMC strategy can deliver better disturbance rejection even in the presence of model uncertainty as compared to the conventional IMC.

For EIMC, conservative values of λ_1 = 25 and λ_2 = 20 were selected. The performance of the EIMC for various values of K, in rejecting 50 g meal disturbance acting on the nominal patient at t = 0, is shown in Fig. 5 Overshoot, undershoot and IAE of the closed-loop response are summarized in Table 2. As expected from equation (9), the disturbance attenuating capability of the EIMC improves with increasing K; however, oscillations in the glucose concentration also increase with K. Table 2 shows that increase of K from 0 to 8 reduces overshoot, undershoot and IAE, and increasing K further to 12 increases overshoot, undershoot and IAE indicating possible stability problems at higher K.

Table 1: Performance of IMC with various values of filter constant, for all 577 patients subjected to 50 g meal disturbance at time t = 0.

λ	No. of Patients with Glucose Conc. (mg/dl)		Average IAE for all 577 patients	Standard Deviation of IAE
	70-100	60-100		
25	113	198	318.9	185.9
15	163	294	262.5	170.4
5	250	412	193.5	145.5
2	310	451	169.4	134.7

Note: In this and subsequent tables, IAE values for a simulation time of 800 min for each patient.

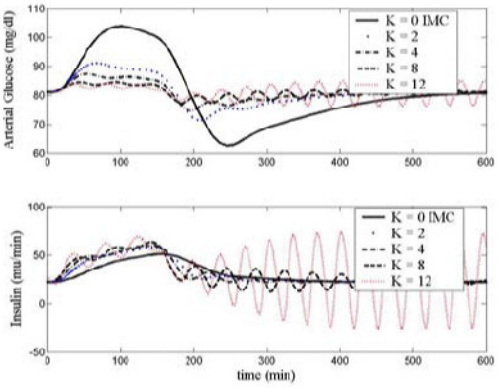

Fig. 5. Disturbance rejection of the EIMC with λ_1 = 25 and λ_2 = 20 for various values of K: nominal patient model subjected to 50 g meal disturbance.

Table 2. Effect of K on rejecting the 50 g meal disturbance by the EIMC: nominal patient model.

K	Overshoot (mg/dl)	Undershoot (mg/dl)	IAE
0	22.77	18.38	272.6
2	9.99	9.63	111.5
4	6.33	6.49	69.4
8	3.54	3.85	42.4
12	3.99	4.90	94.6

From the results in Fig. 5 and Table 2, K = 4 is considered to be most suitable in the EIMC in order to obtain good performance and robustness, and will be used in the subsequent simulations. The effect of λ_1 and λ_2 on the performance of the EIMC was tested while keeping K = 4. As before, 577 patients were subjected to 50 g meal disturbance and the results are summarized in Table 3. Reducing λ_1 and λ_2 does not provide much improvement in performance, and the marginal increase in the average IAE and standard deviation of IAE is due to oscillations in the response at lower λ_1 and λ_2. The parameters K = 4, λ_1 = 20 and λ_2 = 20 will be used in the EIMC for subsequent simulations. For these parameter values, only 75 patients (13%) have entered the dangerous hypoglycaemic region (i.e., glucose concentration < 60 mg/dl). In all these 75 patients, one parameter, namely, FPIC is at 0.21 (a +40% variation from nominal). This number is comparable to 72 patients mentioned by Parker et al. (2000) when H_∞ controller was employed.

Table 3: Effect of λ_1 and λ_2 on EIMC (with K = 4) performance for all 577 patients, when each of them is subjected to a 50 g meal disturbance.

λ_1	λ_2	No. of Patients with Glucose Conc. (mg/dl)		Average IAE for all 577 patients	Std. Dev. of IAE
		70-100	60-100		
25	20	461	502	102	95.6
20	20	462	502	93.2	89.2
20	15	473	505	95.3	119

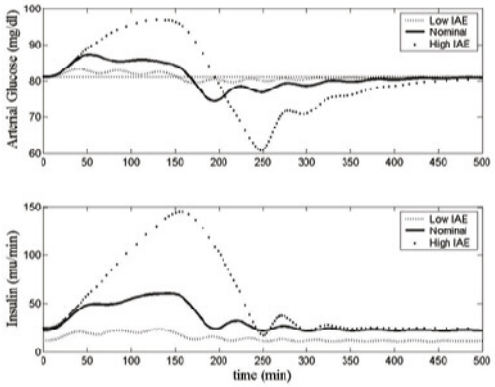

Fig. 6. Transient response of the EIMC for two perturbed patients (giving the lowest and highest IAE) and the nominal case, in attenuating 50 g meal disturbance at time t = 0.

Performance of the EIMC on two perturbed patients and nominal patient are depicted in Fig 6. The two perturbed patients considered are those having the lowest and highest IAE value among the 502 patients whose glucose concentration was controlled within 60-100 mg/dl. The parameters of the patient with the lowest IAE are EGHGU-D_Γ=-0.88; FHIC=0.32; FPIC =0.09, while those of the patient with the highest IAE are EIPGU-E_Γ= 1.4; EGHGU-E_Γ=1.4; FPIC=0.21. Rest of the parameters are at their nominal values for both cases. Responses of about 250 perturbed patients with parameters different from those of the nominal patient, when subjected to 50 g meal disturbance, are similar, and one of these responses is shown in Fig 7. The transients in Figs. 6 and 7 have just a few oscillations and are acceptable.

Next, the EIMC controller is tested on a patient whose parameters are different from the 577 patients considered in this study. This case is specified as the worst-case performance of the continuous-time H_∞ controller, including uncertainty weighting and parametric uncertainty in Parker et al., (2000). Disturbance rejection by the H_∞ controller for this case was shown in Figure 9 of Parker et al. (2000). The response by the EIMC for this patient model, illustrated in Fig 8, is better than that by the H_∞ controller.

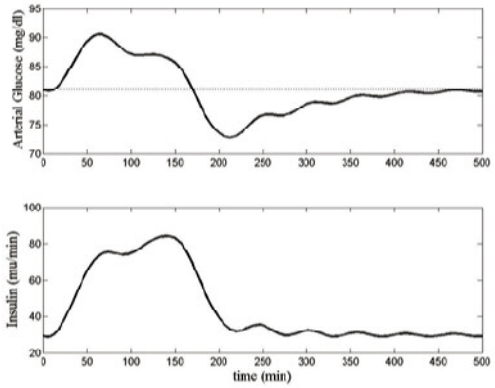

Fig. 7. Performance of EIMC on a perturbed patient model with parameters EGHGP-E_Γ = 1.4, EIPGU-D_Γ = -8.15, EGHGP-D_Γ = -0.6957. The remaining five parameters are at their nominal values.

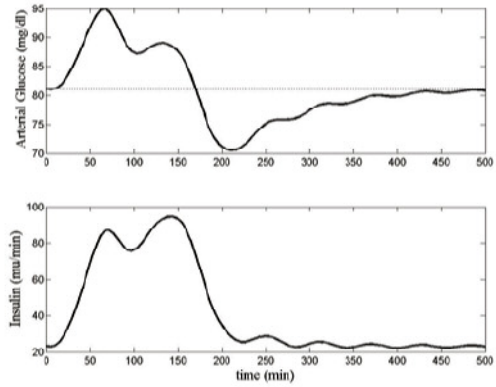

Fig. 8. Performance of EIMC on a perturbed patient model with parameters: EIPGU-D_Γ = -8.15, EGHGU-D_Γ = -2.072, FHIC = 0.36. The remaining five parameters are at their nominal values.

6. CONCLUSIONS

The EIMC structure utilizes a simple FOTD model and is shown to provide a very good regulation of blood glucose concentration of diabetics. It is able to maintain the glucose concentration above the dangerous hypoglycaemic range (< 60 mg/dl) in 87% of 577 patient models tested. For these patients, average IAE and standard deviation of IAE are reduced by nearly half by the EIMC scheme compared to the IMC structure. Further, the performance of the former is comparable to that of H_∞ controller. Thus, the EIMC is very attractive for glycaemia control owing to its simple structure and design as well as good robustness.

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APPENDIX

Equations A13, A20, A25 and A29 in Parker et al. (2000), corrected for typographical errors, are listed below. The parameter $F_{KC} = 0.3$ is missing in Table A1 of Parker et al. (2000). All these were confirmed by Parker (2002).

$$\dot{A}_{IHGP} = \frac{1}{25}[1.2088 - 1.138 (\tanh(1.669 (\frac{I_L^C}{21.43} - 0.8885))) - A_{IHGP}] \quad \text{(A13)}$$

$$\dot{I}_H^C = (I_B^C Q_B + I_L^C Q_L + I_K^C Q_K + I_P^C Q_P - I_H^C Q_H + \Gamma_{IVI}) \frac{1}{V_H^C} \quad \text{(A20)}$$

$$\dot{I}_P^T = (I_P^C - I_P^T) \frac{1}{T_P^I} + \frac{\Gamma_{SIA} - \Gamma_{PC}}{V_P^T} \quad \text{(A25)}$$

$$\Gamma_{PC} = \frac{I_P^T}{\frac{1-F_{PC}}{F_{PC}} \frac{1}{Q_P} - \frac{T_P^I}{V_P^T}} \quad \text{(A29)}$$