Control of Blood Glucose Concentration in Type I Diabetic Patients

Abstract— **As the "artificial pancreas" becomes closer to reality, automated insulin delivery based on real-time glucose measurements becomes feasible for people with diabetes. This paper employs a new approach to regulate the blood glucose level of type I diabetic patient under an intensive insulin treatment. The closed-loop control scheme incorporates the design of robust H∞ controller to maintain the normoglycemic average of 80 mg/dl. Due to cost and complexity involved in testing the control algorithms to real patients, studies are done using a Type I diabetic patient model. Controller performance is assessed in terms of its ability to reject the effect of meal disturbance and to overcome the variability in the glucose-insulin dynamics from patient to patient. Computer simulations are used to evaluate the effectiveness of the proposed technique and to show its superiority in controlling hyperglycemia over other existing algorithms.**

***Keywords*—Insulin Delivery rate, Type I diabetes, glucose modeling, control.**

I. INTRODUCTION

HUMAN bodies need to maintain glucose concentration level in a narrow range 70-110 mg/dl. If one's glucose concentration level is significantly out of the normal range, this person is considered to have the plasma glucose problem: Hyperglycemia or hypoglycaemia.

Diabetes mellitus is a disease in glucose-insulin endocrine metabolic system, in which the pancreas either does not release insulin or does not properly use insulin to uptake glucose in the plasma, which is referred as hyperglycemia [1]. The two types of diabetes are Type I and Type II. In this paper the focus is on type I diabetes. In Type I diabetes, the body's immune system destroys pancreatic beta cells, and the patient is totally dependent on an external source of insulin to be infused at an appropriate rate to maintain the blood glucose concentration.

When a normal person is subjected to a glucose meal, the glucose concentration in plasma increases from basal value and so the pancreatic β-cells secrete insulin. The insulin in plasma is hereby increased, and the glucose uptake in muscles, liver, and tissues is raised by the remote insulin in action. This lowers the glucose concentration in plasma, implying the β- cells to secrete less insulin, from which a feedback effect arises [2]. But, in type I diabetic patients whose pancreas does not release insulin, blood glucose level remains in much more than basal value for long period of time. When glucose level remains high for extended periods of time the patient is at risk for neuropathy, nephropathy, blindness, and other long-term vascular complications. However, the result of the Diabetes Control and Complications Trial (DCCT) showed that an intensive insulin therapy can reduce the risk of developing complications [3]. Consequently, an intensive therapy is encouraged for type I diabetic patients prescribed by a continuous subcutaneous insulin infusion pump.

Control strategies of diabetes treatment can be categorized as open loop control, semi closed-loop, and closed-loop control. Current treatment methods utilizing open loop control in which physicians inject a pre determined dose of insulin subcutaneously based on three or four time daily glucose measurements, usually by an invasive method of finger prick. This method not only is painful and inconvenient but also unreliable because of approximation involved in type and the amount of insulin delivered. In semi closed-loop control insulin infusion rate adjust according to intermittent blood glucose readings. This technique is sub-optimal and unable to accomplish the aforementioned normalization and also suffered from long sampling time problem of missing fast or accurate insulin level.

This work deals with the design of controller for the delivery of insulin to the type I diabetic patients. In this contribution, the control problem is reformulated by considering the rate of the blood glucose level.

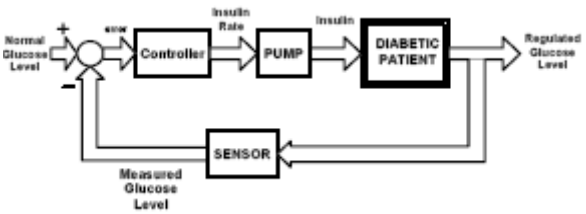

Figure 1. A Closed –loop glucose control system

These are based on the principles of near infrared spectroscopy. Ultimately the objective is to develop a closed-loop glucose control system [7]-[11] consisting of three components: 1) glucose sensor, 2) control algorithm, and 3) mechanical pump (see Fig. 1). In this system, the

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978-1-61284-764-1/11/$26.00 ©2011 IEEE

glucose concentration will be measured by the glucose sensor and based on the measurement, the control algorithm will compute the optimal insulin delivery rate. The mechanical pump will then infuse the computed amount of insulin.

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II. BLOOD GLUCOSE CONTROL PROBLEM

Since the 80's, from the paper by [4, 5] several models have been proposed to reproduce the glucose-insulin dynamics. The proposed models include: i) glucagons effects and threshold functions representing metabolic processes [6], ii) nonlinear terms for pharmacokinetic-pharmacodynamic effects [7] and iii) physiologic equations toward compartmental representations [8]. More recently exercise effects have been included [9]. A physiological-based compartmental model has the advantage that the simulations can yield insight into the physiological parameters [10]. Such a model offers a powerful tool for generating predictions and clinical decision support in diabetes care. [11],[12]. Here, a physiological-based compartmental model is used to design and test the tracking control. The control problem is formulated such that the healthy behavior of the blood glucose level is tracked by the glucose level of the TIDM patient from peripheral glucose measurements against disturbances by meals. The control input is the insulin delivery rate. Once the blood glucose level has been controlled, the control output should hold constant. In this sense, the insulin rate from the robust controller can mimic the insulin release by pancreas. In fact, a healthy pancreas is able to release the insulin at time varying rate when the glucose level increases by meal and when the glucose level is stationary, the rate of the insulin release remains constant. The controller should be robust against parametric uncertainties. First approach is to design the feedback control via H∞ theory. The nonlinear system is approached by a linear model around basal conditions. The resulting controller is tested on the nonlinear physiological model. For the control formulation, the meal is simulated as a load disturbance by carbohydrate.

Doing mathematical modeling of physical systems is not an easy job because of the components involved in the system. Also the physical behavior may change due to transitions between two metabolic states. Physiological control of a non- diabetic human being is taken care of by the pancreas that functions normally. For diabetic patient, glucose is controlled through insulin delivery, which involves feedback methods.

A .Glucose: insulin modelling

A variety of methods have been there in the literature to model the glucose- insulin dynamics. The most primitive one was reported by [4]. This was a low order system. Some little more complex models had been reported, which includes glucagon effects and threshold functions that represent metabolic processes [13],[5]. Sorensen (1985) departed from experimental results to formulate and validate metabolic processes of the model on the whole organ and tissue level. It was concluded that model is nonlinear. Each compartment is divided into two sub compartments where mass balances were derived.. In this sense, the glucose-insulin model is nonlinear and has following subsystems: glucose, insulin and glucagon. This nonlinear model was used for control purposes by [14]. This process is based on the compartmental technique. One of the features of this technique is that the model design based on an understanding of the physiology; also, these models offer a powerful tool for generating predictions and clinical decision support in diabetes care [12, 15]. Hence this model was chosen in this work to simulate the glucose insulin dynamics and test the different controllers to validate the model and also compare the performance of the controllers.

B. Patient Model Uncertainty

In this work diabetic model used for patient simulations is taken from Parker et al [16]. This pharmacokinetic-pharmacodynamic compartmental model of the human glucose-insulin system was initially developed by Guyton et al [17] and Sorensen [5], and then modified by Parker et al. [16] to include meal and exercise disturbances. This model has 19 state equations and 47 physiological parameters. In this model human body is divided into six compartments (brain, heart/lungs, gut, liver, kidney, and periphery). Individual compartment models are obtained by performing mass balance around tissues important to glucose or insulin metabolism. Sub-compartments (namely, capillary and tissue), such as those in the brain and periphery, were included where significant transport resistance (e.g., time delay) exists. The periphery represents the combined effects of muscle and adipose tissue while stomach and intestine effects are lumped into the gut compartment. This model was constructed to represent a sedentary 70-kg male diabetic patient. Controlled output for this system is the arterial glucose concentration, which is regulated by the manipulated variable, insulin infusion rate. A disturbance variable, glucose uptake from the gut compartment is added to the model to simulate the diabetic patient ingesting a meal. The mathematical representation of the meal sub model is described in Lehmann and Deutsch [18].

Due to the inevitable patient-model mismatch there exists some uncertainties; these uncertainties between the actual patient and the normal patient model could be translated to variations in the model parameters which represent glucose or insulin metabolism. The glucose and insulin dynamics were found to be most sensitive to variations in the metabolic parameters of the liver and the periphery. 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 A, B, C, D *and* E are constants.

C. Validation of Reference Model

Glucose curve during a quasi continuous sampling Oral Glucose Tolerance Test (OGTT) can be considered as a complex system composed by a set of linear, under damped, second order subsystems. The overall system output is considered as a multifunction composed by the algebraic sum of each individual subsystem output, where each subsystem is excited by a unit impulse, $\delta(t)$, that represents the only exogenous glucose load, or an endogenous excitation.

For the blood glucose level is used like a reference, the transfer function P_{ref} is validated from the glucose tolerance curves (GTC's) of twenty two healthy subjects. The GTC's were obtained in the classical method, at t=0 the blood glucose level is measured and the subjects drank, a solution of 75 g of dextrose dissolved in 300ml of water (glucose load) and later, blood samples for blood glucose concentration determinations were obtained using a $\Delta t = 30$ min sample interval, at least during 150 min.

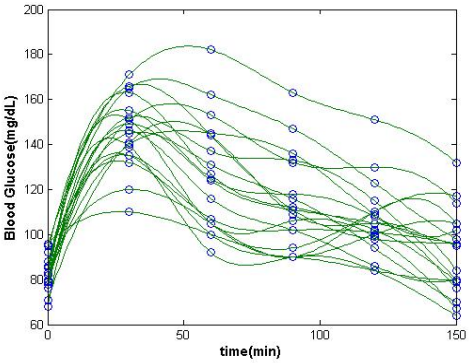

Figure 2. Overall Glucose Tolerance Curves of twenty two healthy subjects

The data's of healthy subjects can be analyzed as follows first by determining the values of mean and standard deviations the plot shown in Fig 3 can be obtained.

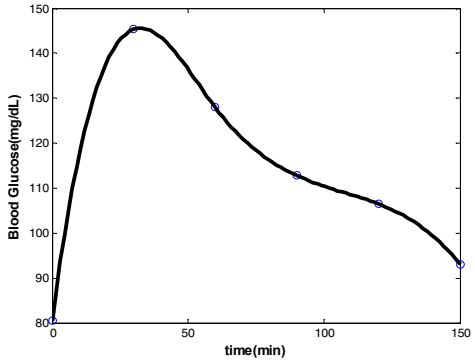

Figure 3. Mean Glucose Tolerance Curve of healthy subject

The Glucose Tolerance Curve shown in the Fig 3 is used like a "nominal" BG level in the BG problem for a TIDM patient. Thus the transfer function validated from Fig. 2 like the response of the BG level to a meal when the pancreas has the capability to deliver insulin. 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. In this contribution, it is proposed that the overall system can be considered as composed by a set of finite number of linear, under-damped, second order subsystems of the same type, where the excitation to each subsystem is a unit impulse. On these conditions, each subsystem time output at the shifted time t_s is defined as [19]

$$g(t) = [G]_0 + C_p e^{-\alpha t}\sin(\omega t) \tag{2}$$

The Laplace transform of $g(t)$ is

$$H(s) = \frac{C_p.\omega}{(S+\alpha)^2 + \omega^2} \tag{3}$$

Hence:

$$H(S) = \frac{C_p.\omega}{S^2 + 2.\alpha.S + \alpha^2 + \omega^2} = \frac{C_p.\omega}{S^2 + 2.\alpha.S + \omega_n^2} \tag{4}$$

Where the parameters in the above equation (2) are $[G]_0$=fasting blood glucose concentration (mg/dL); C_p is amplitude of the function (mg/dL); α=damping factor ($\min^{-1}$); ω=angular frequency (rad/min); t=time (min) and $\omega_n = (\alpha^2 + \omega^2)^{1/2}$=natural frequency (rad/min).

The transfer function for reference model is given by [20]

$$P_{ref} = \frac{\tilde{K}\omega_n^{\,2}}{s^2 + 2\xi\omega_n s + \omega_n^{\,2}} \tag{5}$$

Where $\tilde{K}$ is gain, ω_n is natural frequency and ξ is damping factor.
So from equations (3) and (4), the parameters for healthy patient model can be calculated by using the equations shown below

$$\tilde{K} = C_p.\omega/\omega_n^{\,2}$$

$$\xi = \alpha/\omega_n$$

$$\omega_n = (\alpha^2 + \omega^2)^{1/2} \tag{6}$$

It is important to mention that the selection of parameters in Eq (5) is not unique since there are several combinations for, $\widetilde{K}$, ξ and ω_n that could represent the behavior of curves in Fig. 2. And after selecting the parameters for the mean blood glucose response of all the twenty two healthy subjects and by plotting, the response shown in Fig 4 is obtained and is used as reference model.

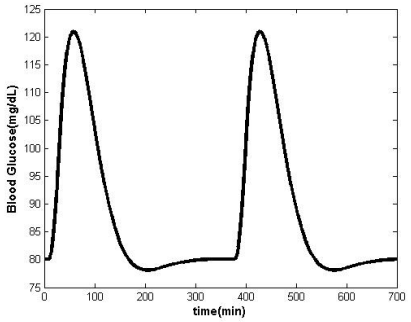

Figure 4. Output of reference model

III. ROBUST CONTROL DESIGN IN TIDM

The block diagram in Fig 5 contains the modified block feedback scheme when parameter variations are included into the model; which are incorporated in the form of weighted transfer functions.

The generalized plant, $G(s)$, has the following representation [20]

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

Where weighted transfer functions are the same described in

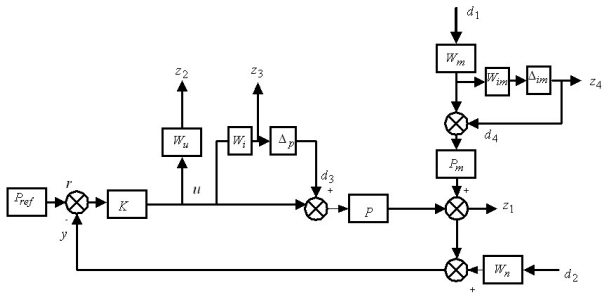

Figure 5. Block diagram for the BG control including parametric uncertainties

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

$$W_i\Delta = \left| \frac{P_p - P}{P} \right| \tag{8}$$

Where $W_i\Delta$ is the relative uncertainty, 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 perturbed models from this parameter set were selected to represent the frequency-domain uncertainty expected in the diabetic patient population. Different patient models could be obtained by varying all the three parameters randomly from their nominal values. This resulted in various possible perturbed plant models. And the weighting function W_i could be determined by finding the maximum value of relative uncertainty values at each frequency.

Fig 6 shows the upper bound of this relative uncertainty as a function of frequency. This bound was created by taking the maximum uncertainty magnitude of the perturbed patient models at each frequency. Here the uncertainty exhibited a local minimum around the bandwidth frequency of 0.2 rad/sec, then a relative uncertainty increases with increasing frequency to an asymptote around 10 rad/sec.

The reasoning to incorporate parameter variations in the diabetic and meal model raises from the fact that the resulting controller must keep its performance with respect to changes in the metabolism of the diabetic. Thus in regard to weight W_{im}, the digestion process can be assumed different when metabolic changes are present.

The weights W_{im} and W_i 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.

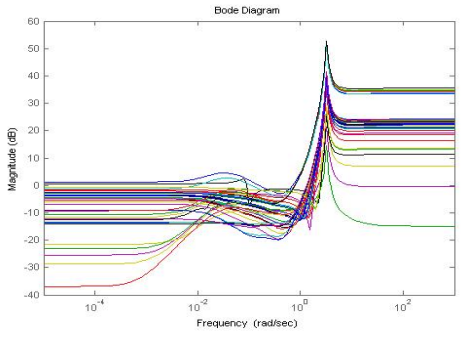

Figure 6. Relative model uncertainty of set of perturbed model as a function of frequency

Fig. 7 shows the upper bound of relative uncertainty as a function of frequency and the weighting function W_i can be calculated from this upper bound. The transfer function W_i was identified considering the maximum in the frequency response of the set of multiplicative perturbations on the nominal plant P.

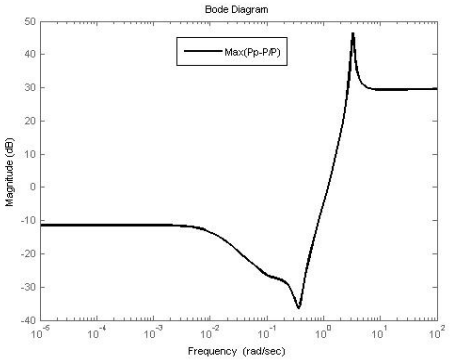

Figure 7. Upper bound of Relative model uncertainty as a function of frequency.

A. Robust stability

The closed-loop system achieves robust stability if the closed-loop system is internally stable for all possible plant models $P_p = F_U(P,\Delta)$. In the present case this means that the system remain stable for the variation of $EIPGU(D_\Gamma)$ and $EGHGU(D_\Gamma)$ in the range of ±40% from the nominal values such as -5.82118 and -1.48 respectively, and the parameter F_{LC} in the range of ±20% from the nominal value of 0.4

$$3.4592 \le EIPGU(D_\Gamma) \le 8.148,\ 0.888 \le EGHGU(D_\Gamma) \le 2.072,\ 0.36 \le FHIC(F_{LC}) \le 0.48$$

B. Robust performance

In addition to the robust stability, the closed-loop system, for all $P_p = F_U(P,\Delta)$ must satisfy the performance criterion

$$\left\| \begin{bmatrix} W_P(I+P_pK)^{-1} \\ W_uK(I+P_pK)^{-1} \end{bmatrix} \right\|_\infty < 1 \qquad (9)$$

Also, it is desirable that the complexity of the controller is acceptable, i.e it is of sufficiently low order.

IV. CONCLUSION

Diabetes management is one of the important issues in the human regulatory systems, which is discussed in recent years. In this work, a closed loop control system based on H∞ control theory has been proposed. It is important to mention that the control algorithm is essence model-free. The proposed controller can successfully tolerate patient variability and dynamic uncertainty while rapidly rejecting meal disturbances and tracking the constant glucose reference. Robustness was tested over a group of patients with model parameters varying considerably from the averaged model. Employed control technique reported in this paper is expected to simplify insulin automatic injection mechanism and increase the quality of life, and life expectancy of diabetic patients.

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