MODELING AND CONTROL OF THE BEHAVIOR OF GLUCOSE SENSING DEVICES

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Abstract:

Hydrogels made of glucose oxidase-containing graft copolymers of dimethyl aminoethyl methacrylate and ethylene glycol, or glucose oxidase-containing P(DMAEM-g-EG) copolymers, have been shown to deliver insulin upon exposure to glucose. The glucose oxidase reacts with glucose to form gluconic acid. The production of gluconic acid decreases the pH, which results in the swelling of the hydrogel complex. Once the mesh size has increased, insulin is released from the complex. Previous work has shown that P(DMAEM-g-EG) hydrogels have exhibited pH sensitive swelling and deswelling. Current work focuses on the design of novel hydrogels that allow for insulin release in diabetic patients that is similar to that of healthy, non-diabetic patients. To evaluate the effectiveness of proposed hydrogels, dynamic models of glucose and insulin are being developed for both healthy patients and diabetic patients in order to compare the dynamic responses of the hydrogels to those of a healthy pancreas. In healthy patients, the models show how insulin and glucose dynamics are dependent on each other throughout the body, while in diabetics the hydrogel complex dynamics are included as the primary insulin source. Understanding glucose and insulin dynamics is necessary in order develop control strategies for hydrogels used in glucose regulation.

Introduction:

The main objective of this research was to contribute to the medical field by providing new therapeutic methods and improved devices for insulin delivery in diabetic patients. With the new therapies developed we should be able to:

(i) determine when exactly should insulin be delivered to the patient; and

(ii) avoid unnecessary and premature insulin delivery.

A major goal and contribution of this research were the design and development of glucose-responsive, gel-based devices for insulin delivery that can be used over a prolonged period of time. These systems are known as self-regulated drug delivery systems. A significant distinction of our research is the reliance on robust control theory to establish performance objectives for the proposed hydrogel device, as well as optimal control theory to guide the selection of optimal parameter values for the synthesis of the gel.

We have developed a series of novel self-regulated, glucose- and pH-sensitive gels for insulin delivery. We have experimented already with novel hydrogels in which the swelling ratio and the resulting mesh size change reversibly as a function of environmental parameters such as pH or temperature. These reversible changes allow for the release of drugs or the permeation of solutes depending on surrounding environmental conditions. Poly(methacrylic acid) (PMAA) exhibits interpolymer complexation with poly(ethylene glycol) (PEG) as the protons of the carboxylic acid groups on PMAA form

hydrogen bonds with the ether groups on the PEG chain. This complexation forms only at pH low enough to insure substantial protonation of the carboxylic acid groups.

Complexation of free chains of PMAA with PEG in solution has been studied· We have also shown that poly(dimethyl aminoethyl methacrylate) and poly(ethylene glycol) exhibit the same type of hydrogen bonding, except that the pH dependence is such that the systems decomplex at low pH and complex at high pH values.

Summary of Proposed Models

We developed models describing the dynamics of glucose and insulin in both healthy and diabetic patients. The models were developed by representing the body as a system consisting of several compartments. Glucose and insulin dynamics were determined by deriving mass balance equations for each individual compartment.

Although compartmental models have been used in the past to describe insulin and glucose dynamics, we believe that ours is a novel contribution to the field in four ways. First, we incorporate an accurate model of a meal disturbance into both models, we incorporate an accurate model of the effects of exercise on glucose levels into both models, we attempt to characterize both interpatient and intrapatient uncertainty among model parameters such as the basal values of insulin and glucose in each compartment and we incorporate insulin release dynamics from the hydrogel systems into the diabetic patient model. The model is used to determine the structure of the hydrogel system having insulin release dynamics that most resembles the dynamics of the pancreas. In addition to the use of hydrogels, we also use the models to design effective glucose control algorithms for implantable, self-regulating insulin pumps.

Results

We focused on studying the effects of linearization and feedback control on existing models, most notably the model created by Bergman et al (1) and modified by Furler et al (2).

$$\frac{dG}{dt} = -P_1(G - G_b) - XG + D(t) \tag{1}$$

$$\frac{dX}{dt} = -P_2X + P_3(I - I_b) \tag{2}$$

$$\frac{dI}{dt} = -nI + \frac{U(t)}{V1} \tag{3}$$

In Furler's modification, G is the glucose concentration (mmol/L), X is proportional to the concentration in a remote compartment (min^{-1}), and I is the insulin concentration (mU/L). P_1, P_2, P_3, and n are model parameters. V_1 is taken as the blood volume (12 L). G_b and I_b are the basal glucose and insulin values in the patients (4.5 mmol/L and 15 mU/L, respectively). Finally, D and U are glucose and insulin source terms, in units of mmol/Lmin and mU/min, respectively. In the model, glucose concentrations below 3 mmol/L indicate hypoglycemia, and concentrations above 8 mmol/L signify hyperglycemia. The goal of glucose control was to prevent the glucose concentration from reaching either of these glycemic states. The model was linearized

using a Taylor series expansion using the steady state as the reference point, the resulting linear system is given by Eqs (4)-(6):

$$\frac{dG}{dt} = -P_1(G - G_b) - XG_b + D(t) \tag{4}$$

$$\frac{dX}{dt} = -P_2X + P_3(I - I_b) \tag{5}$$

$$\frac{dI}{dt} = -n(I - I_b) + \frac{U(t) - Uss}{V1} \tag{6}$$

In order to linearize the model at steady state conditions, the steady state conditions must be known or assumed. For the linearization, it was assumed that G and I are at their basal values, i.e., 4.5 mmol/L and 15 mU/L, respectively, at steady state. From Eq. (3), it is easily seen that the steady state insulin input, U_{ss}, must be the quantity nI_bV_1, which is determined to be (50/3) mU/min. It is also clear from the second equation in the model that when $I = I_b$ at steady state, X becomes zero at steady state as well. Finally, the corresponding steady state value of D necessary to achieve the steady state glucose value ($G=G_b$) is zero. Discrepancies between the models were investigated by changing the initial conditions and by varying the insulin flow rate. As Figure 1 shows, varying the insulin flow rate results in visible discrepancies between the nonlinear and linearized models.

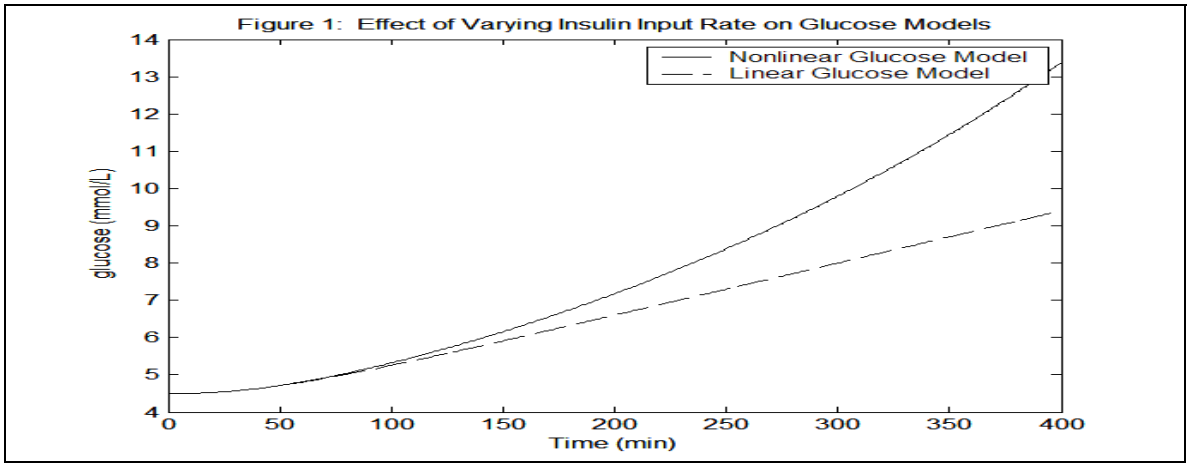

Figure 1: Effect of varying the insulin input concentration on the glucose response for the linear and nonlinear models. U = 10mU/min

Feedback control for both the nonlinear and linearized systems was investigated by implementing a proportional (P), proportional-integral (PI), and proportional-integral-derivative (PID) control schemes on both models when subjected to a meal disturbance.

The results of all three control schemes being implemented on the nonlinear model is given in Figure 2. In all cases, the model was subjected to the meal disturbance. All control schemes exhibit significant overshoot as the meal is initially consumed,

meaning that normoglycemic conditions are not maintained throughout the duration of the meal.

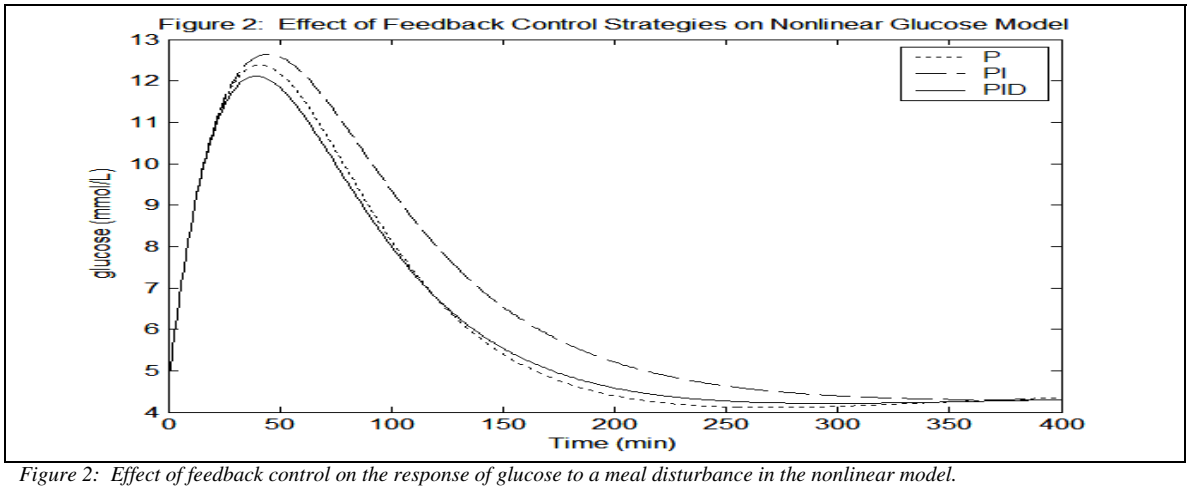

Figure 2: Effect of feedback control on the response of glucose to a meal disturbance in the nonlinear model.

Conclusions

As Figure 1 shows, varying the insulin flow rate results in discrepancies between the linear and nonlinear models. This discrepancy is amplified as the deviation of the flow rate from the basal value increases. Because a successful control system will require insulin release rates that deviate from the basal value, we conclude that it is important that nonlinearities be included in the proposed model. We believe that applying P, PI, or PID control appears to successfully reject the meal disturbance. However, the large overshoot shows that feedback control will not effectively keep the glucose response of either mode within normoglycemic conditions throughout the entirety of the meal.

References

1) Bergman, R. N.; Phillips, L. S.; Cobelli, C. Physiologic Evaluation of Factors Controlling Glucose Tolerance in Man. *J. Clin. Invest*. **1981**, *68*, 1456-1467.
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