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Asymptotic tracking and disturbance rejection of the blood glucose regulation system

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ABSTRACT

Type 1 diabetes patients need external insulin to maintain blood glucose within a narrow range from 65 to 108 mg/dl (3.6 to 6.0 mmol/l). A mathematical model for the blood glucose regulation is required for integrating a glucose monitoring system into insulin pump technology to form a closed-loop insulin delivery system on the feedback of the blood glucose, the so-called "artificial pancreas". The objective of this paper is to treat the exogenous glucose from food as a glucose disturbance and then develop a closed-loop feedback and feedforward control system for the blood glucose regulation system subject to the exogenous glucose disturbance. For this, a mathematical model for the glucose disturbance is proposed on the basis of experimental data, and then incorporated into an existing blood glucose regulation model. Because all the eigenvalues of the disturbance model have zero real parts, the center manifold theory is used to establish blood glucose regulator equations. We then use their solutions to synthesize a required feedback and feedforward controller to reject the disturbance and asymptotically track a constant glucose reference of 90 mg/dl. Since the regulator equations are nonlinear partial differential equations and usually impossible to solve analytically, a linear approximation solution is obtained. Our numerical simulations show that, under the linear approximate feedback and feedforward controller, the blood glucose asymptotically tracks its desired level of 90 mg/dl approximately.

1. Introduction

Because the pancreas of type 1 diabetes patients does not produce insulin, which is required for glucose uptake and endogenous glucose mobilization, they have high blood glucose levels and need external insulin to assist glucose uptake and utilization. External insulin needs to be infused at an appropriate rate to maintain blood glucose within the narrow range from 65 to 108 mg/dl (3.6 to 6.0 mmol/l).

Mathematical models for the blood glucose regulation system are required for integrating a glucose monitoring system into insulin pump technology to form a closed-loop insulin delivery system, the so-called "artificial pancreas" (see Hovorka [13], Panteleon et al. [28], Steil et al. [32]). To make this artificial pancreas as close as possible to the natural pancreas, many mathematical models for the regulation system have been proposed since the pioneering work of Albisser et al. [2,3] and Clemens et al. [11], including the linear model of Ackerman et al. [1] and various compartmental minimal models proposed by Bergman et al. [5–7], Bertoldo et al. [9], Li et al. [18], Liu et al. [19,20,22], Man et al. [23–25], Sturis et al. [34], and Toffolo et al. [35,36].

The objective of this paper is to treat the exogenous glucose from food as a glucose disturbance and then develop a closed-loop feedback and feedforward control system for the blood glucose regulation system subject to the exogenous glucose disturbance. For this, a mathematical model for the glucose disturbance will be proposed on the basis of experimental data, and then incorporated into the blood glucose regulation model proposed by Liu et al. [19]. Because all the eigenvalues of the disturbance model have zero real parts, we will use the center manifold theory to establish blood glucose regulator equations, and then use the solutions of the regulator equations to synthesize required feedback and feedforward controllers to reject the disturbance and asymptotically track either a constant glucose reference of 90 mg/dl or a time-dependent reference $r(t)$ around 90 mg/dl. Since the regulator equations are nonlinear partial differential equations and usually impossible to solve analytically, a linear approximation solution is obtained. Our numerical simulations show that, under the linear approximate feedback and feedforward controller, the blood glucose asymptotically tracks its desired level of 90 mg/dl approximately.

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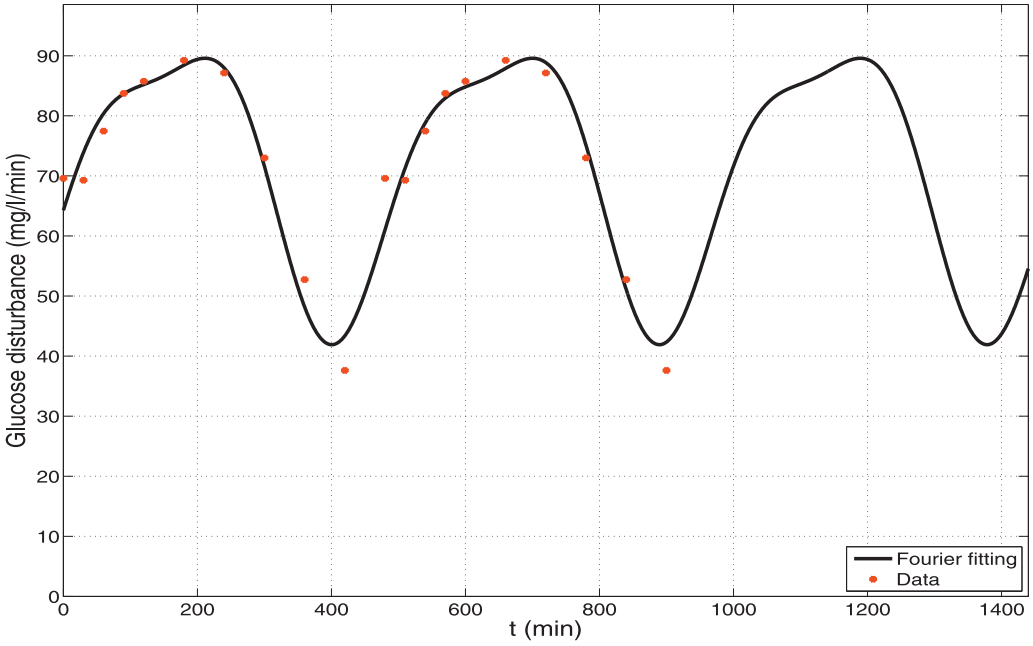

Fig. 1. Experimental exogenous glucose input data of Korach-André et al. [16] and Fourier polynomial fitting.

The significance of this work is the introduction of the exogenous glucose disturbance model. It is because of the introduction of the disturbance model that the center manifold theory can be used to establish the blood glucose regulator equations, which are a key to synthesizing feedback and feedforward controllers.

2. Glucose disturbance model

The glucose disturbance could be periodic with a period of 24 h. In order to build up such a glucose disturbance model with a biological sense, experimental exogenous glucose input data are needed. Because we could not find such data over a time interval of 24 h, we use Korach–André et al.'s data over a time interval of 8 h [16]. Thus the period of the disturbance model we are building up below is 8 h. However, this drawback does not hamper the use of our model mathematically as all the theories we are developing below still hold after the period of 8 h is changed to the period of 24 h, or even to any other period.

The data are converted into the glucose input rate (mg/l/min) by multiplying the data by 70 (kg) and dividing it by 6 (l) because the blood volume of a person with the weight of 70 (kg) is about 6 (l). In order to fit the data by a Fourier polynomial, the data are replicated over another period of 8 h. As shown in Fig. 1, the data can be well fitted by the Fourier polynomial

$$G_{in} = \bar{G}_{in} + \alpha_1 \sin(\omega t) + \beta_1 \cos(\omega t) + \alpha_2 \sin(2\omega t) + \beta_2 \cos(2\omega t), \tag{1}$$

where $\bar{G}_{in} = 71.21$ mg/l/min, $\alpha_1 = 17.91$ mg/l/min, $\beta_1 = -13.41$ mg/l/min, $\alpha_2 = 5.387$ mg/l/min, $\beta_2 = 4.004$ mg/l/min, and $\omega = \pi/240$ /min.

To maintain the blood glucose at a normal level of about 90 mg/dl, a basal exogenous glucose input $\bar{g}_{in}$ of about 18 mg/l/min is required [19,40]. Setting $\alpha_0 = \bar{G}_{in} - \bar{g}_{in} = 71.21 - 18 = 53.21$ mg/l/min, $\bar{G}_{in}$ is decomposed into $\bar{G}_{in} = \bar{g}_{in} + \alpha_0$ and then

$$G_{in} = \bar{g}_{in} + \alpha_0 + \alpha_1 \sin(\omega t) + \beta_1 \cos(\omega t) + \alpha_2 \sin(2\omega t) + \beta_2 \cos(2\omega t).$$

The part

$$G_d = \alpha_0 + \alpha_1 \sin(\omega t) + \beta_1 \cos(\omega t) + \alpha_2 \sin(2\omega t) + \beta_2 \cos(2\omega t) \tag{2}$$

can be treated as an exogenous glucose disturbance. The disturbance vector

$$\mathbf{g}_d = \begin{bmatrix} 1 \\ \sin(\omega t) \\ \cos(\omega t) \\ \sin(2\omega t) \\ \cos(2\omega t) \end{bmatrix} \tag{3}$$

can be generated by the exosystem

$$\frac{d\mathbf{v}}{dt} = \mathbf{A}_d \mathbf{v}, \quad \mathbf{v}(0) = \mathbf{g}_{d0}, \tag{4}$$

where

$$\mathbf{A}_d = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \omega & 0 & 0 \\ 0 & -\omega & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 2\omega \\ 0 & 0 & 0 & -2\omega & 0 \end{bmatrix}, \quad \mathbf{g}_{d0} = \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 1 \end{bmatrix}.$$

3. Mathematical model of the glucose regulation subject to disturbance

The blood glucose regulation system is briefly sketched in Fig. 2 [19,20]. Glucose is produced from food and liver, and utilized by brain and nerve cells (insulin-independent) via the glucose transporter 3 (GLUT3) and by tissue cells such as muscle, kidney, and fat cells (insulin-dependent) via the glucose transporter 4 (GLUT4). Glucose is transported into and out of liver cells by the concentration-driven GLUT2, which is insulin-independent. In response to low blood glucose levels (< 80 mg/dl), the α cells of the pancreas produce the hormone glucagon. The glucagon initiates a series of activations of kinases, and finally leads to the activation of the glycogen phosphorylase, which catalyzes the breakdown of glycogen into glucose. In addition, the series of activations of kinases also result in the inhibition of glycogen synthase and then stop the conversion of glucose to glycogen. In response to high blood glucose levels (> 120 mg/dl), the β cells of the pancreas secrete insulin, which triggers a series of reactions to activate glycogen synthase to catalyze the conversion of glucose into glycogen. Insulin also initiates a series of activations of kinases in tissue cells to lead to the redistribution of the glucose transporter 4 (GLUT4)