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Research Article

Continuous Drug Infusion for Diabetes Therapy: A Closed-Loop Control System Design

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While a typical way for diabetes therapy is discrete insulin infusion based on long-time interval measurement, in this paper, we design a closed-loop control system for continuous drug infusion to improve the traditional discrete methods and make diabetes therapy automatic in practice. By exploring the accumulative function of drug to insulin, a continuous injection model is proposed. Based on this model, proportional-integral-derivative (PID) and fuzzy logic controllers are designed to tackle a control problem of the resulting highly nonlinear plant. Even with serious disturbance of glucose, such as nutrition absorption at meal time, the proposed scheme can perform well in simulation experiments.

1. INTRODUCTION

Diabetes mellitus is a metabolic disorder in which insulin, a kind of hormone which promotes the uptake of glucose into cells, cannot properly perform its role. Diabetes Mellitus affects more than 100 million individuals throughout the world and this number may be expected to double by 2010 [1, 2]. The healthcare costs are estimated to be over 100 billion dollars annually for the 16 million people who suffer from this debilitating disease and its complications in the US [3]. Based on 2002 death certificate data, diabetes was the sixth-leading listed cause of death in the US [4]. This ranking is based on the 73 249 death certificates in which diabetes was listed as the underlying cause of death. According to death certificate reports, diabetes accounted for a total of 224 092 deaths [4].

For patients with diabetes, especially, type I insulin-dependent diabetes, tight control of glucose level is essential. Regulating blood glucose concentration using insulin infusion pumps is important for these patients, because they have deficiency of insulin production by pancreas that prevents appropriate metabolism of glucose. For many patients under diabetes therapies, insulin injection using needles and syringes under skin is adopted to deliver insulin, so that the functions of the pancreas are replaced with external devices. A typical external insulin pump is an electronic medical device that delivers insulin through a narrow and flexible plastic tubing that ends with a needle inserted just under the skin near the abdomen. The pump releases doses of insulin periodically, at meals or at time when blood glucose is too high based on measured values of glucose sensors.

A patient's glucose concentration may change dynamically depending mostly on his/her physical activities and nutrition, and therefore, the amount of insulin needed varies from time to time. A number of diseases may occur, possibly resulting in life-threatening health conditions if the supply of insulin is not in time or not correctly dosed or fails for some reasons. For example, sustained hyperglycemia (blood glucose exceeding 120 mg/dL) may lead to most of the long-term complications associated with diabetes, such as nephropathy and retinopathy according to the Diabetes Control and Complications Trial (DCCT) Research Group [5]. But to date, a common current method of therapy is a series of 3–5 daily in insulin injections with quantities of insulin based on 4–8 daily invasive glucose measurements. In this sense, infusion of insulin is discretely controlled by users based on the feedback of several blood glucose measurements. It is obvious that such treatment lacks a reliable continuous monitoring,

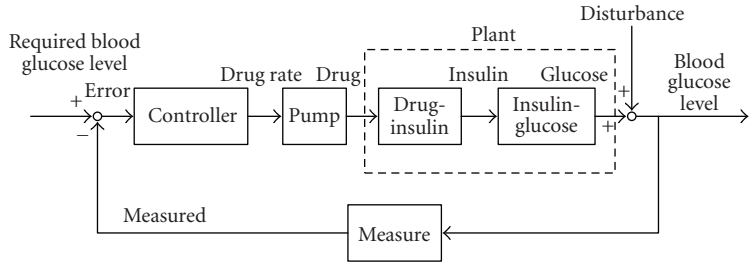

Figure 1: Closed-loop framework of blood glucose concentration control.

which may cause glucose concentration being out of a permitted range because of control delay. This kind of therapy may not prevent glucose fluctuations occurring in many patients. Therefore, designing a continuous closed-loop control system is needed for insulin infusion. The continuous control would be a great improvement in the daily treatment of diabetes, especially, in some cases that medical persons are not presented or the patients have less knowledge about the disease. Such an automatic control will benefit patients and avoid some mistakes during injections and operations.

To implement the continuous closed-loop control, three primary components are needed for such therapy: an implantable glucose sensor, a pump, and a control algorithm. Implantable glucose sensors have been developed to contribute to the interest in feedback-type insulin infusion pumps [6, 7], including needle-type sensors and extracorporal sensors, coupled with iontophoresis [8], microdialysis [9], or microperfusion [10] system. A pump mechanism has been studied extensively and is available. The most important is a control algorithm to design the continuous closed-loop control system, which is the focus of this paper. The detailed implementation of the system is beyond the scope of the paper.

In recent years, significant efforts have been made in the development of glucose control algorithms. Model-based predictive control (MPC) algorithms have been recently reported in literature to successfully tackle constraints posed by several biomedical control problems, not only in blood glucose concentration control in diabetic patients [11, 12], but also in mean arterial pressure and cardiac output control during anesthesia [12, 13]. Parker et al. proposed a model predictive control for type I diabetic patient blood glucose control and adopted an asymmetric objective unction to address the inherent performance requirement of the physiological problem [14]. However, we believe that the function of drug should be cumulated if continuous injection is applied, and this makes the plant highly nonlinear. Such a characteristic of the plant will weaken the performance of MPC. The authors in [15] considered a considerable amount of uncertainty of the parameters in a mathematical model of blood glucose dynamics and proposed an H∞ controller for robust closed-loop regulation. However, their approach took a simple glucose absorption model from food into account. Some intelligent advance control strategies are applied to the blood glucose control system. A neural-network controller was developed in [16], which suggests an appropriate next-time insulin dose based on short historical discontinuous blood glucose measurements and insulin doses' settings. Using fuzzy logic controllers to regulate blood glucose level also had been proposed in [17, 18]. In [17], fuzzy reasoning method was used to monitor and help to detect hypoglycemia in diabetic patients. In [18], knowledge about patient treatment was incorporated, and inner-loop and outer-loop controllers using a Mamdani-type fuzzy scheme were designed. Other strategies like optimal control with quadratic cost function and artificial systems had been applied to blood glucose control [19, 20]. But these strategies were all discrete control, and the injection only happened at meal time.

In this paper, we present reviewed results of discrete control to blood glucose concentration of type I diabetes. An integral form is proposed to model the time course of plasma insulin concentration along with continuous injection of a typical dose of insulin preparations. Although the resulting plant model is highly nonlinear, PID and Fuzzy logic controllers are carefully framed to tackle the corresponding nonlinear control problem. Simulation experiment results show that with such controllers the real-time blood glucose could be restricted in the permitted bound, and the unexpected concentration fluctuation due to the patients accidental dangerous behaviors could also be dealt with.

The remainder of the paper is organized as follows. In Section 2, a continuous model is proposed to explore the accumulative effect of drug on insulin, which is involved in the design of a closed-loop control system. Both PID controller and fuzzy logic controller are designed, and the performance is evaluated by extensive simulation experiments in Section 3. Section 4 concludes this paper.

2. A CONTINUOUS CLOSED-LOOP MODEL

To describe the complete metabolism process of glucose, three important parameters related to type I diabetes patients are involved: dose of drugs, insulin concentration, and glucose concentration. Therefore, we need two different models to describe the relationships among them. One is the time course function of drug to insulin while the other is the insulin to glucose. The process flow chart can be described in Figure 1. The object of the controller design is to minimize the error, which makes the output track the required blood glucose level. The controller drives the pump to implement continuous insulin infusion. Before the controllers are designed, the plant should be modeled firstly.

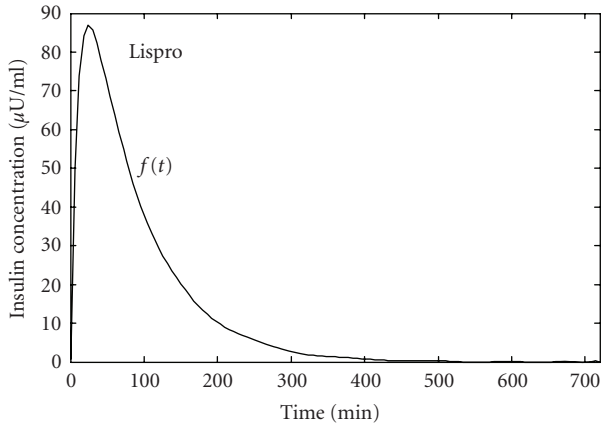

Figure 2: Time course of plasma insulin concentration after a subcutaneous injection (10 U) of Lispro.

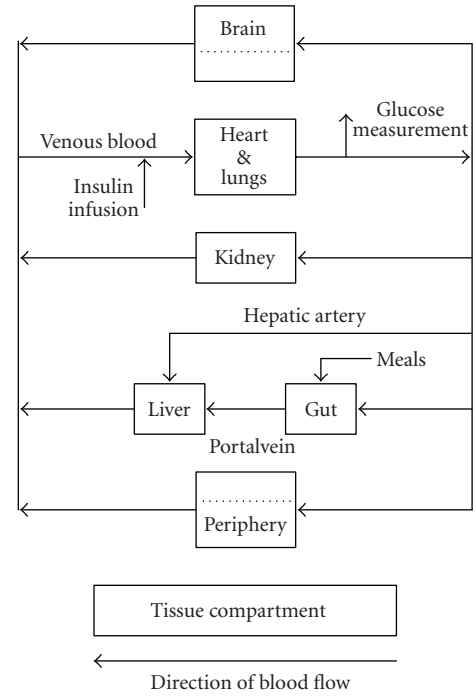

Figure 3: Detailed compartmental model of glucose-insulin interactions.

2.1. A continuous model of drug to insulin

The development of the implantable sensor technology has made it possible for continuous insulin injection. There have been a number of results regarding related topics [21]. Pharmaceutical research has produced various types of insulin to glucose, through their combined injection and subcutaneous injections. The typical insulin preparations with faster dynamics, namely, Lispro and regular insulin, and delayed action, such as neutral protamine hagedorn (NPH), are used to meet the basal insulin requirement. In this paper, it is assumed that only the drug Lispro is used to produce insulin [22], whose plasma insulin concentration is shown in Figure 2 after subcutaneous injection of a typical dose of the Lispro.

Function $f(t,d)$ is defined to describe the time course of plasma insulin concentration after a subcutaneous injection d dose of Lispro. It is assumed that there is a linear relationship as in (1) when d is not so large:

$$f(t, c*d) = c*f(t,d). \tag{1}$$

When $d = 10$ U, we can get the function $f(t)$ with the curve described in Figure 2. Because of the continuous injection, the effects on insulin concentration each time should be cumulated. Therefore, the integral form is used as follows to calculate the insulin concentration:

$$I(t) = \int_{t-360}^{t} \frac{d(\tau)*f(t-\tau)}{10} d\tau, \tag{2}$$

where $d(t)$ is defined as the dose of drug injected at time t. The duration from time point of injection of Lispro to invalidation equals 360 minutes, and its effect should be taken into account and calculated in active term of Lispro. This is the most distinct characteristic of continuous control of blood glucose. In the previous works [18, 23], the interval of injection is long enough and the effects will not be overlapped, so that there is no accumulative result on insulin concentration.

Taking the accumulative effect into consideration, (2) stands for a new time course model for plasma insulin concentration after a subcutaneous injection (10 U) of Lispro in continuous closed-loop control for diabetes therapy. Although such accumulative effect has been neglected in, for instance, the traditional three meal-time discrete control methods, it is crucial for our continuous control. The tradeoff is that the nonlinearity of this model makes the control strategy hard to realize.

2.2. Model of insulin to glucose

The relationship between insulin and glucose has been well investigated in recent years [23–25]. There are mainly two different proposed models: Sorensen model and minimal model.

Sorensen model: as a physiologically based compartmental model of glucose and insulin dynamics, Sorensen model [23, 24] is a six compartment model, as shown in Figure 3, where the compartments are physiological representations of brain, heart and lungs, liver, gut, and kidney peripheral tissue.

As a physiologically based compartmental model, Sorensen model is described vividly. Furthermore, it also represents glucagon to complete the glucose-insulin system model. However, it is difficult to get the parameters since parameters of 6 compartments for different patients are different.

Minimal model: as a typical minimal model, Bergman model [24, 25] is widely used in the blood glucose-level control. It offers a good benchmark for testing the relationship

Table 1: Insulin-glucose model parameters.

Parameters	Value
p_1	$0.0337\ \text{min}^{-1}$
p_2	$0.0209\ \text{min}^{-1}$
p_3	$0.00000751\ \text{min}^{-2}(\mu\text{U/mL})^{-1}$
n	$0.214\ \text{min}^{-1}$
T	5 min
G_b	0.811 mg/mL
M	0.012 mg/mL/min
$\overline{G}$	0.81 mg/mL
$\overline{X}$	$0.0054\ \mu$U/mL

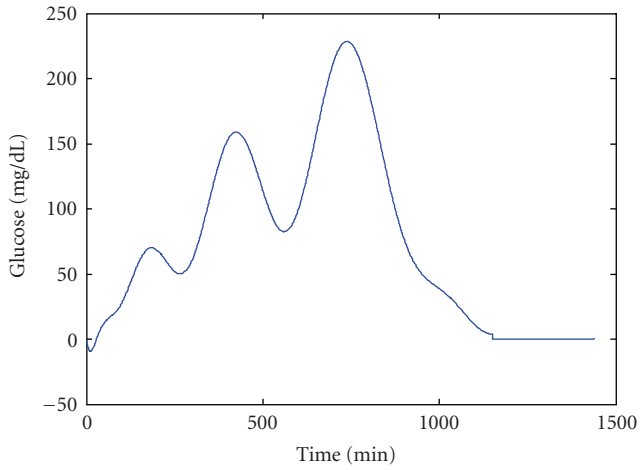

Figure 4: The meal disturbance of blood glucose.

between insulin and glucose. The model can be depicted as follows:

$$\begin{aligned}\dot{G}(t) &= -[p_1 + X(t)]G(t) + p_1 G_b + m(t),\\ \dot{X}(t) &= -p_2 X(t) + p_3 I(t),\\ \dot{I}(t) &= \tau \cdot u(t) - n \cdot I(t),\end{aligned} \tag{3}$$

where $G(t)$ is the concentration of glucose, $I(t)$ is the concentration of insulin, $X(t)$ is the dynamic insulin response, G_b is the basal level of glucose, and $m(t)$ is the rate of exogenous glucose infusion; p_1, p_2, p_3, τ, and n are parameters defined in Table 1.

In order to simplify the nonlinearity, the idea of linearity of Bergman model is proposed in [26]:

$$\begin{aligned}\dot{G}(t) &= -[p_1 + \overline{X}(t)]G(t) - \overline{G} \cdot X(t) + \overline{G} \cdot \overline{X} + p_1 G_b + m(t),\\ \dot{X}(t) &= -p_2 X(t) + p_3 I(t),\\ \dot{I}(t) &= \tau \cdot u(t) - n \cdot I(t),\end{aligned} \tag{4}$$

where $\overline{G}$ and $\overline{X}$ are the average values of $G(t)$ and $X(t)$, which are defined in Table 1.

The above parameters in Bergman model can be obtained easily [26, 27]. The Bergman model ignores the effects of glucagon, which is not important in this paper.

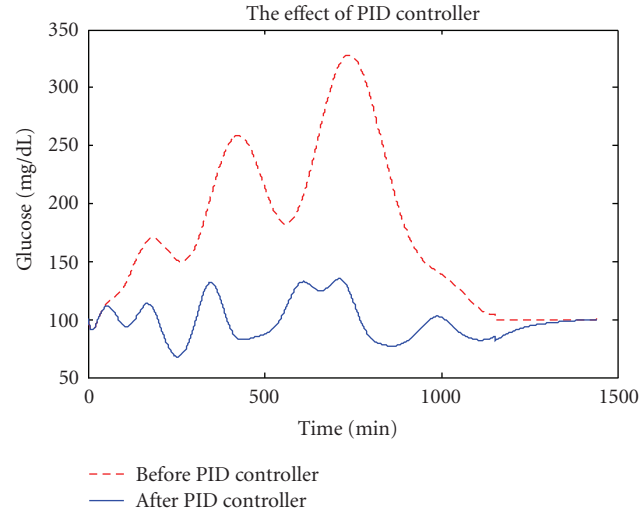

Figure 5: The output of system with PID controller.

3. CONTROLLER DESIGN AND SIMULATION EXPERIMENTS

Before the controller design, we would like to parameterize the whole plant model as follows. The function $f(t)$ is approached by a high-order binomial. For the model of insulin to glucose, by applying Laplace transform for (4), the transfer function from insulin to glucose is presented with the parameters shown in Table 1. The simulations are carried out in Matlab Simulink, and the data are collected by "*scope*" in sink:

$$G(s) = \frac{-0.00003}{s^3 + 0.274s^2 + 0.013656s + 0.00018}. \tag{5}$$

The main disturbance caused by three meals can be depicted as a curve shown in Figure 4 [23]. Under the disturbance, we want to design a controller to meet the requirements of normal person's glucose concentration of about 60–100 mg/dL before the meal and less than 140 mg/dL after meal. As the meal disturbance is much higher than normal glucose concentration level, it demands a controller with good performance of disturbance rejection.

Considering the possible unmodeled nonlinearities, two control strategies are introduced to design corresponding controllers, that is, the PID controller and fuzzy logic controller.

3.1. PID controller design for continuous closed-loop control system

The standard PID controller could be stated as

$$\text{PID} = \frac{K_c * (1 + s/T_i) * (T_d * s + 1)}{T_d * s/A_d + 1}, \tag{6}$$

where $K_c = P$, $T_i = I$, $T_d = D$, and $A_d = 10$.

For this PID controller, there are three important parameters: P, I, and D, where P is a proportional feedback in which the stronger it is, the more powerful the feedback is;

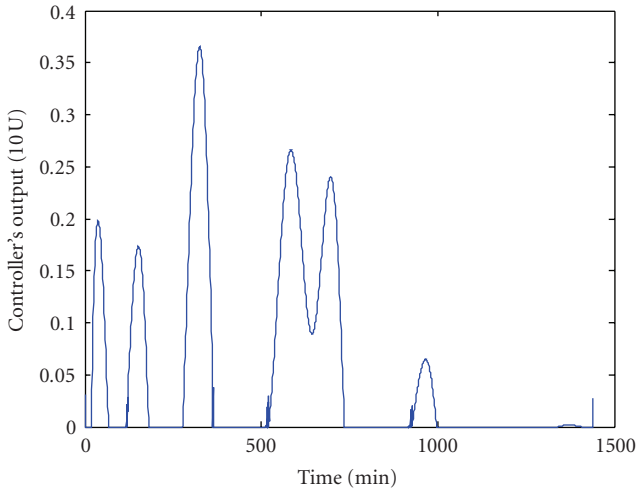

Figure 6: The corresponding output of PID controller.

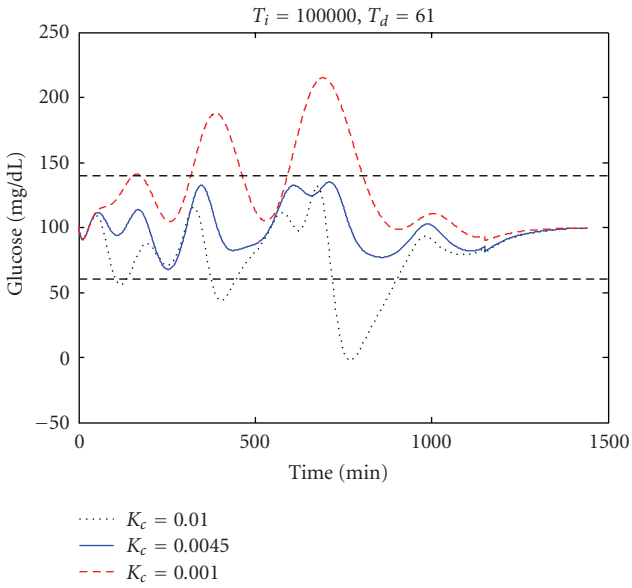

Figure 7: The effect of parameters of K_c in PID controller.

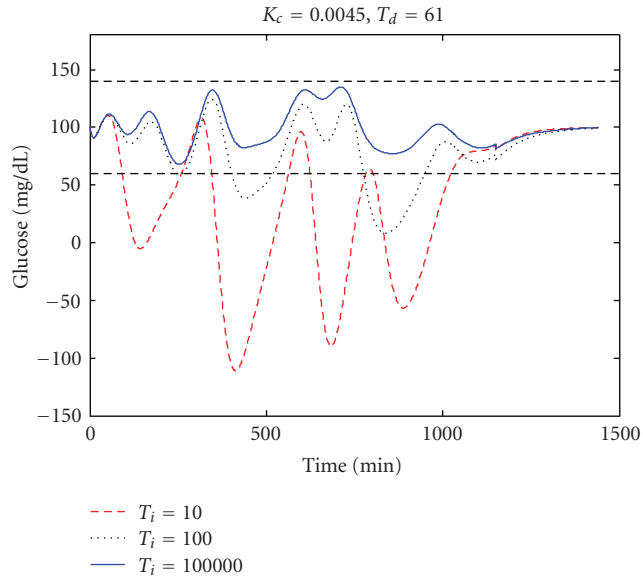

Figure 8: The effect of parameter of T_i in PID controller.

I is an integral role feedback, which benefits the steady performance but does not contribute to the dynamic performance of the system; and D is a differential role of feedback. Appropriate differential role of the plot can improve dynamic performance significantly.

The parameters are adjusted and chosen based on the results in [28]. Figure 5 depicts the control effects with P = .0045, I = 10000, and D = 61. Obviously, the effect of PID controller meets output requirements that the concentration of blood glucose is between 60 mg/dL and 140 mg/dL while the output of the controller is shown in Figure 6 which is very small.

We have also done a lot of experiments to explore the control effects of tuning the controller parameters K_c, T_i, and T_d, as well as the sample time. Some of them are analyzed as follows. Figure 7 shows the effect caused by changing the proportional parameters of K_c. When K_c = 0.001, it is reasonable that the glucose (dash line) is much higher than expected since K_c is so small that the injected drug is deficient. On the contrary, when K_c = 0.01, which is stronger than expected, too much drug is injected which leads to the fluctuations of glucose (dotted line). Furthermore, the concentration of glucose is also lower (about 60 mg/dL) than floor level of the expected bound. By a large scale simulation, it is found that when K_c = 0.0045, the glucose (solid line) meets the required range better.

With given K_c = 0.0045, the effect of the integral parameter T_i in PID controller is illustrated in Figure 8. When T_i = 100000, which means that there is almost no integral effect, the output (solid line) meets the demands well. When T_i = 100, which enriches the integral effect a little, the controller considers the effect in a long duration, for example, from beginning to current time point, the effect of more doses of drug is taken into account for type I diabetes patients, and the output (dotted line) of blood glucose concentration is lower than the required. When T_i = 10, which means the integral effect has been quite large, the output of blood glucose concentration (dash line) is much worse and far lower than expected floor limitation.

Figure 9 shows the effect of parameter of T_d under given K_c and T_i. When T_d = 30, which means the differential effect is weak, the controller considers the rate of glucose little, the hysteresis is too strong, which makes the system react too late, and the output (dash line) cannot meet the requirement and goes beyond the upbound sporadically. When T_d = 61, the output (solid line) performs better within the expected bound than during a period of 24 hours. When T_d = 100, differential role is enhanced, the controller considers the rate of glucose change, and the output of controller is too strong, so that the fluctuations of glucose (dotted line) are more serious.

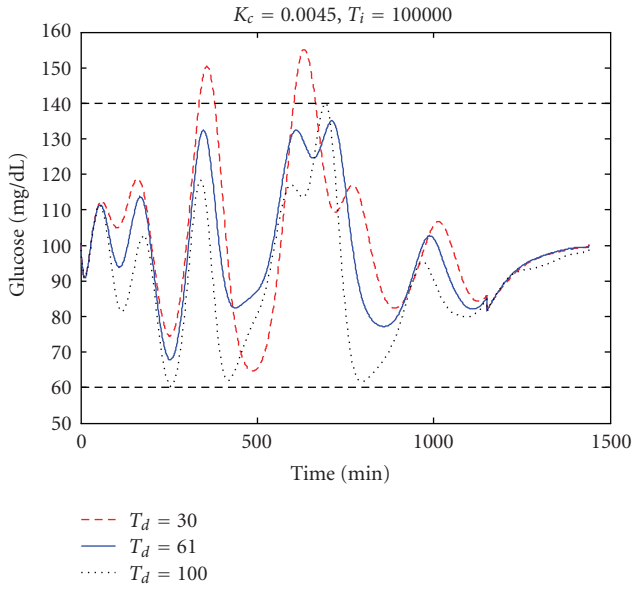

Figure 9: The effect of parameter of T_d in PID controller.

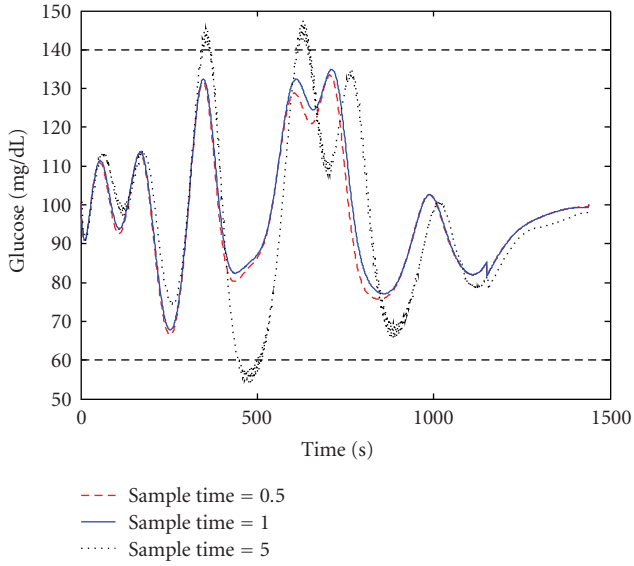

Figure 10: The effect of parameter of sample time in PID controller under the best parameters of controller like in Figure 5.

The effect of parameter of sample time in PID controller is also analyzed in Figure 10 under the best parameters of controller like in Figure 5. When the sample time equals to 5 minutes, the data cannot describe the system characteristics properly and in time, and the output (dotted line) also has fewer errors. When the sample time equals to 0.5 (dash line) and time equals to 1 (solid line), the result is much better. A higher sample rate makes the data approach much closer to real system, but if there is a wireless monitoring station for patients of diabetes, the data of glucose concnetration of patines should be transmitted to the central station, and there exists a tradeoff between wireless communication cost and the performance of control system [29].

Table 2: Rules for fuzzy logic controller.

Rate	Glucose			
	Overlow	Good	High	Overhigh
Overlow	Zero	Zero	Zero	Zero
Low	Zero	Zero	Zero	Little
High	Zero	Norm	Most	Most
Highest	Zero	Norm	Most	Most

3.2. Fuzzy logic controller

Fuzzy logic control is also an advanced process control, which imitates the logic of human thought, and much less rigid than the calculations computers generally perform [30]. There are three steps for the process of a fuzzy logic algorithm: fuzzification, rules, and defuzzification.

(1) *Fuzzification:* the input of a controller is an exact number, for example, the concentration of glucose is 100 mg/dL. What the fuzzification does is to fuzzify the concentration such as low concentration, high concentration, and proper concentration. Every exact number has the weight of all these low, high, and proper concentrations.
(2) *Rules:* After defining the fuzzy concept of input, we should make rules to decide what the output should be: more drug, a little drug, or no drug. For example, we define the following rule: if the concentration of glucose is high and the rate of glucose is rising, then the drug should be more.
(3) *Defuzzification:* After the rule, we get the output of fuzzy concept, for example, more of 0.8 and little of 0.2. But the output which is the object model's input must be an exact number that needs to be defuzzified. By defuzzification, the output gets an exact number.

In this paper, it is assumed that there are two different inputs of the concentration of glucose and the change rate of concentration, and one output of the dose of drug. "overlow," "good," "high," and "overhigh" are defined for the concentration. The rate is "overlow," "low," "high," and "highest." The dose of drug is defined as "zero," "little," "norm," "more," and "most." Ten rules are defined such as

(1) if (rate is overlow) then (dosage is zero);
(2) if (concentration is overhigh) and (rate is low) then (dosage is little);
(3) if (concentration is overhigh) and (rate is highest) then (dosage is most).

For rule 1, when the rate is overlow, the injection dose should be chosen as zero. If we still inject some drug, the concentration will decrease so fast that it may reach below 60 mg/dL. Therefore, we choose rule 1. For rule 2, when the concentration is overhigh and rate is low, the little dose is chosen. If the rate is low, we do not need more drug, while if the concentration is overhigh, we need drug to avoid the

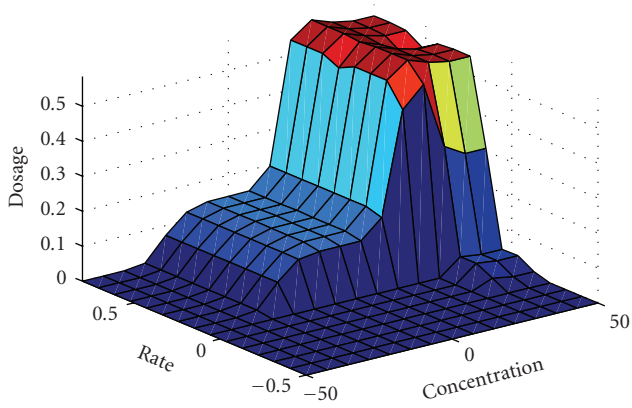

Figure 11: The surface viewer of fuzzy logic controller.

concentration staying high for too long. Therefore, we choose little for this situation. For rule 3, when the concentration is overhigh and the rate is high, the dose will be given with the most quantity, since we need more insulin to decrease the concentration.

The ten rules also can be described in detail in Table 2.

We can then get the surface viewer which depicts the relationship between the input and the output in Figure 11.

After discussing the fuzzy logic controller, we can see the effect in Figure 12. As illustrated in this figure, the concentration of blood glucose is too high (may ≥ 300 mg/dL) for the diabetes patients without any control strategies. When the strategies of continuous control are applied to the closed-loop system, the output value of PID is bounded at about 66–135 mg/dL while the output of fuzzy logic control is about 71–128 mg/dL. It is shown that fuzzy logic controller is similar to, but gets a little better performance than, PID.

As for the output of fuzzy logic controller that is corresponding to the dose of drug, it can be found in Figure 13 that the dose of drug is less than 10 U and can be injected automatically from time to time.

3.3. The effect of unexpected disturbance

Unexpected disturbance may happen, for example, a patient might eat an apple in nonmeal time, and this should be considered but obviously is difficult to deal with by using the traditional discrete time methods. Taking this into account, simulation experiments, shown in Figures 14-15, are presented to test the robustness of the two control strategies. In Figure 14, we put the unexpected disturbance at the vale point of concentration of glucose. Both the PID controller and fuzzy logic controller perform better when the amplitude of the unexpected disturbance is not too large. But when the amplitude reaches around 30 mg/dL, the output of closed-loop system will be out of the expected bound, especially, when the amplitude is lower than 60 mg/dL.

It should also be observed that if the unexpected disturbance occurs at a local peak concentration of glucose, the output becomes worse, especially, for the fuzzy logic controller. It is quite reasonable that the larger the amplitude of the disturbance becomes, the worse the result is obtained, as

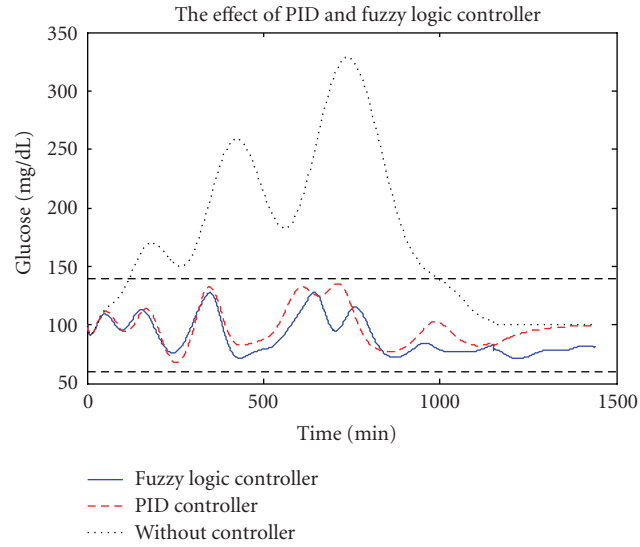

Figure 12: The system output of glucose concentration under PID and fuzzy logic controller.

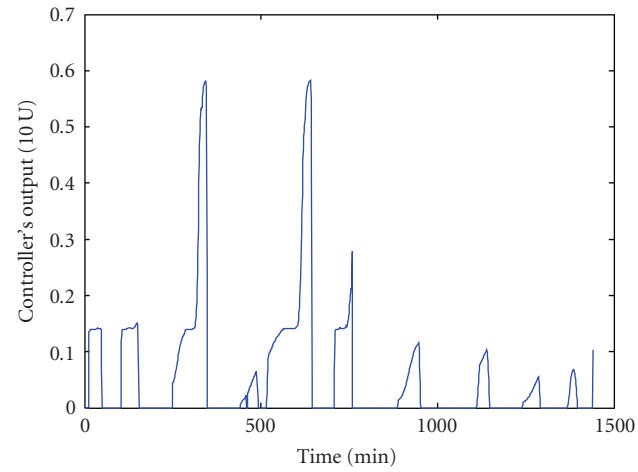

Figure 13: The controller output under fuzzy logic controller.

shown in Figure 15. Therefore, we suggest that the patients can get a little food when the concentration of glucose is at the point of vale, while it is dangerous to eat any more food when the concentration is the peak point.

Above all, the robustness of the two control strategies is quite desirable for the system with small unexpected disturbance. While the unexpected disturbance happens at the vale point of the concentration of glucose for both two strategies, the confined amplitude is about 30 mg/dL which meets the required concentration of glucose, that is, between 60 mg/dL and 140 mg/dL, as shown in Figure 14. On the other hand, the confined amplitude would decrease to about 15 mg/dL for the PID controller and 3.7 mg/dL for the fuzzy logic controller while the disturbance happens at the peak point of the concentration of glucose, as shown in Figure 15. Therefore, the robustness of PID controller seems a little better than fuzzy logic controller. In other words, the PID and Fuzzy

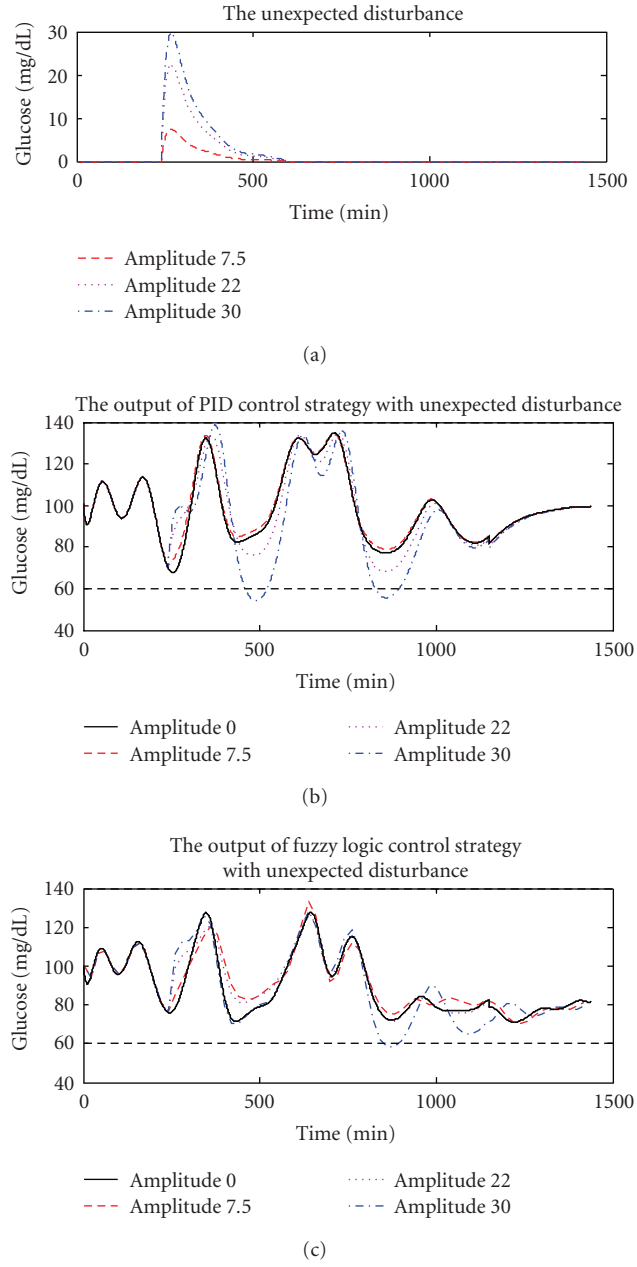

Figure 14: The robustness test while the unexpected disturbance occurs at the vale point of the concentration of glucose.

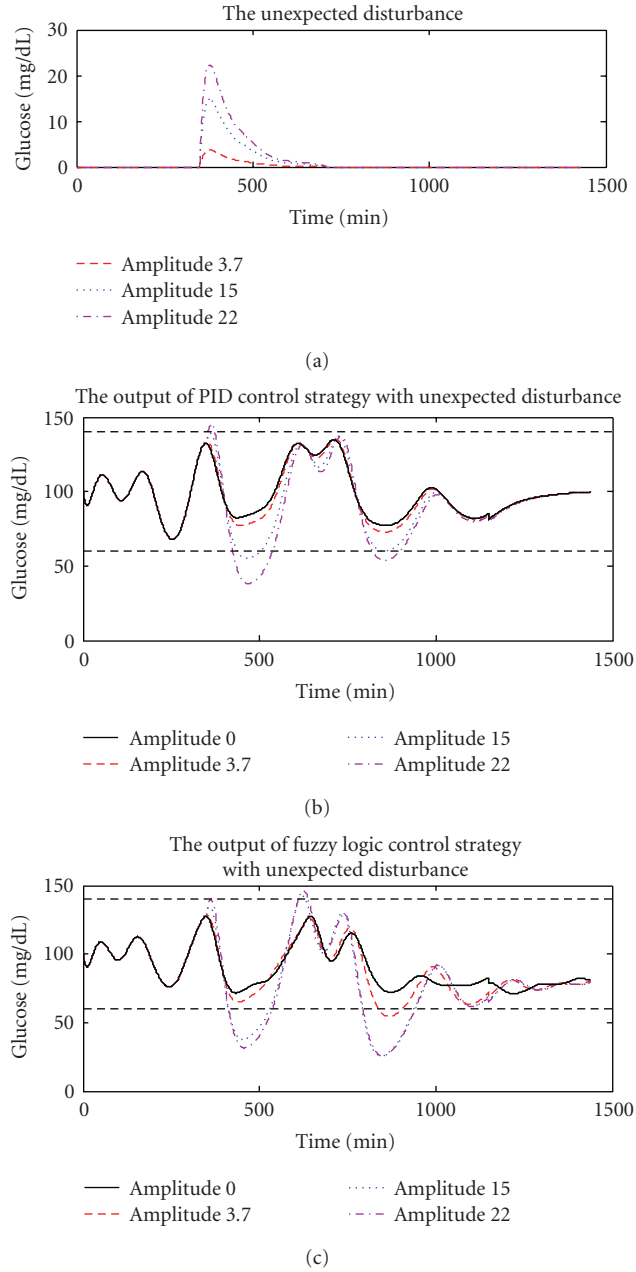

Figure 15: The robustness test while the unexpected disturbance occurs at the peak point of the concentration of glucose.

logic controllers have their advantages for different kinds of patients, and the PID controller is more appropriate for those who often take some saccharated food unexpectedly, while the fuzzy is a better one for those taking food on schedule.

4. CONCLUSIONS

In this paper, the problem of continuous drug infusion for diabetes therapy was considered. Firstly, a continuous drug-insulin model for closed-loop control system was proposed, exploring the accumulative effects from drug to insulin. Then based on the classical Bergman model depicting the relation between insulin and glucose, a general plant model is presented. In order to deal with the resulting nonlinear control problem, two different control strategies, PID controller and Fuzzy logic controller, are presented and well analyzed. Based on our simulation experiments, both strategies meet the expected objective, that is, maintaining the blood glucose in the permitted bound.

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