Using Fuzzy logic to Adjust Plasma Concentration Based on a Two-compartment Pharmacokinetic Model

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Keywords: fuzzy logic; fuzzy controller; pharmacokinetic model; parameter adaption

Abstract. In this paper, a closed-loop control system was developed using fuzzy logic to adapt the parameters of a pharmacokinetic (PK) model. The system is based on a two-compartment PK model with first-order rate process of oral administration. The fuzzy logic adaptation scheme uses the error and the change in error as the input variables. The output variable of the fuzzy controller is the scaling factor to adjust the PK parameter. The fuzzy controller adjusted the real situation concentration to the reference value derived from the parameters of population mean data according to the established rule-base. The simulation results show that the controller provides good performance to adjust the concentration with the reference values.

Introduction

The clinical judgment of disease involves several levels of uncertainty and imprecision [1]. This is because unlike some professions, whose calculations results are based on yes/no or present/absent, very little is clearly black and white in clinical medicine [2]. Besides, due to the existing variability in person a single disease may show quite differently with different patients. The appropriate description of disease entities is linguistic terms which are also imprecise and vague [1].

Fuzzy logic which was first introduced by Zadeh in 1965 is more suitable than the traditional logical systems to model and deal with the inherent variability and uncertainty [3]. It provides an effective means of capturing the approximate, inexact nature of the real world [3]. Although it has been well-established for nearly half a century the application on fuzzy logic in medicine gained momentum till the last two decades [2]. Fuzzy logic which can map linguistic conditions into quantitative relationships provides an alternative adaptation method for model parameters [4]. It can incorporate rules related clinical variations to adaption of specific model parameters [4].

In this paper, we use the fuzzy logic to design a controller to adapt the parameters of a two-compartment pharmacokinetic model with first-order rate process. The simulation results show that the controller provides good performance to adjust the concentration with the reference values.

Method

A closed-loop system shown in Fig. 1 was developed to provide appropriate plasma drug concentration. The system is based on a two-compartment pharmacokinetic (PK) model with first-order rate process of oral administration for the simulation.

The structure of a fuzzy controller is shown in Fig. 2. It consists of four main parts, a fuzzification interface, an inference engine, a rule-base and a defuzzification interface [3]. A fuzzification interface can convert crisp input value into fuzzy inputs. Firstly it performs a scale mapping that transfers the range of input variables into corresponding universes of discourse using (1) as described in the following manner;

$$IN = \left\langle k_{in} \cdot \left(in - \frac{in_H + in_L}{2} \right) \right\rangle \qquad (1)$$

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where < > represents the rounding operation; *in* is the continuous input value; in_H, in_L are the maximum and minimum values of the input variable; k_{in} is the scaling factor given as bellow;

$$k_{in} = \frac{2 * n}{in_H - in_L} \quad (2)$$

where *n* is the maximum value of the universes of discourse of the input variable. Then it converts the input data into linguistic values by determining their degree of membership to the fuzzy sets defined for the variables.

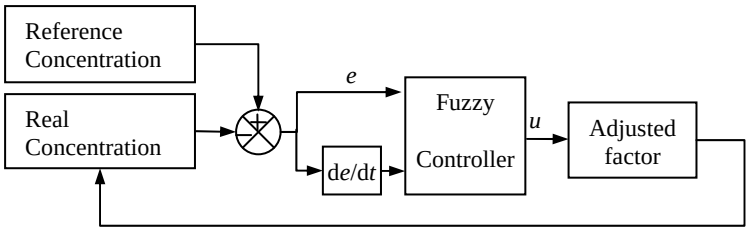

Figure 1. Block diagram of the overall closed-loop system

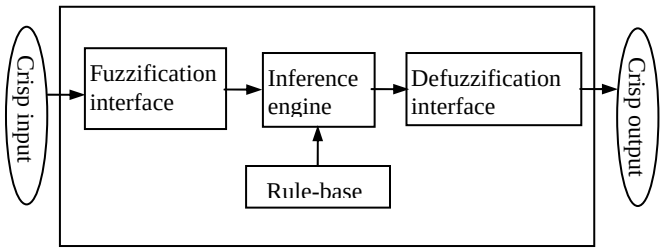

Figure 2. The structure of a fuzzy controller

The rule-base contains the definitions for the fuzzy sets, as well as the relationships between input variables and the output of the system in the form of IN-THEN rules. For the controller of two input variables E, EC and one output variable U the rule can be described as

R_i: IF E is A_i AND EC is B_i THEN U is C_i

where A_i, B_i, and C_i are the linguistic values of the linguistic variables E, EC and U respectively. All of these rules can be defined as a matrix and used to generate a fuzzy relationship matrix.

The inference engine is the kernel of a fuzzy controller. It uses the fuzzy relationship contained in the rule-base and the transformed input values to control or predict the output of the system. The defuzzification interface first converts the values of the generated fuzzy output into corresponding universes of discourse and then transforms into a crisp value calculated by (4)

$$out = k_{out} \cdot OUT + \frac{out_H + out_L}{2} \quad (4)$$

where *OUT* is the fuzzy output value; out_H, out_L are the maximum and minimum values of the output variable; k_{out} is the scaling factor given as bellow;

$$k_{out} = \frac{out_H - out_L}{2 * m} \quad (5)$$

where *m* is the maximum value of the universes of discourse of the output variable.

Results

We have developed a closed-loop control system which is able to adjust the central compartment plasma drug concentration to the expected value. All the simulations were performed by using MATLAB software. The population mean data taken from the literature [6] was used as starting values of each parameter, i.e. k_a=2.6 h^{-1}, k_{12}=0.126 h^{-1}, k_{21}=0.062 h^{-1}, *CL*=75L· h^{-1}, V_c=961L.

Among all of the parameters of the PK model, the central volume of distribution V_c is mainly of influence on the concentration. Firstly, to determine the rules for adaptation of the distribution volume the concentration-time characteristics varying with the parameter V_c were simulated.

Graphical representations are shown in Fig. 3. It can be observed that peak plasma concentration decreases as V_c increases. With the smaller V_c the concentration declines faster within 10 hours.

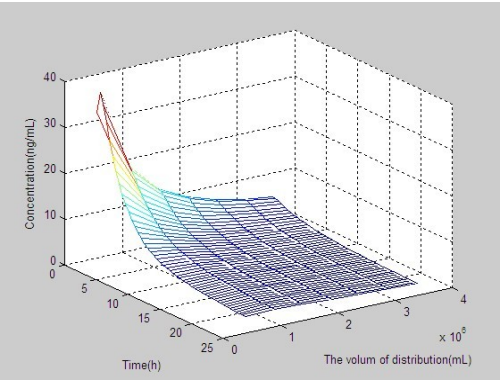

Figure 3. Plasma drug concentration (*z*-axis) as a function of time (*x*-axis) and V_c (*y*-axis).

Based on the characteristic results, a fuzzy logic adaptation scheme was devised to determine how to adapt the parameter. The controller has two antecedents (inputs) E, EC, i.e., the error (discrepancy between the reference concentration and the simulated patient concentration) and change in error (current error minus previous error) and one consequent U which is a scaling factor for the parameter V_c. The linguistic values of the two input variables are defined as NB, NS, ZO, PS, PB which represent negative big, negative small, zero, positive small, positive big respectively. The linguistic values of the output variables are defined as VS, S, O, B, VB which represent very small, small, ok, big, very big respectively. The universes of discourse of both the input and output variables are defined as {-4, -3, -2, -1, 0, 1, 2, 3, 4}. The membership function of each linguistic variable is shown in Fig. 4. According to the simulation result, the rule-base was established using twenty-five rules. These rules also can be represented in a table given in Table 1.Based on the rule-base the relationship between the antecedent and consequent can be represented using a three-dimensional control surface shown in Fig 5.

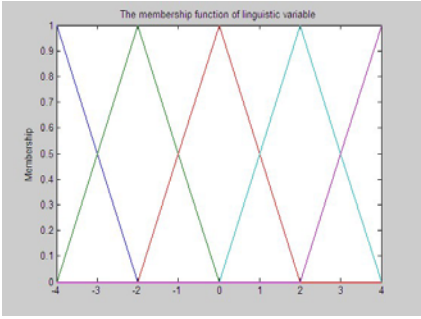

Figure 4. The membership function of the input and output linguistic variables error, change in error and scaling factor

Table 1 Fuzzy rules between input variables E, EC and output variable U

U		EC				
		NB	NS	ZO	PS	PB
E	NB	VB	VB	VB	B	OK
	NS	VB	VB	B	OK	OK
	ZO	VB	B	OK	S	VS
	PS	OK	OK	S	VS	VS
	PB	OK	S	VS	VS	VS

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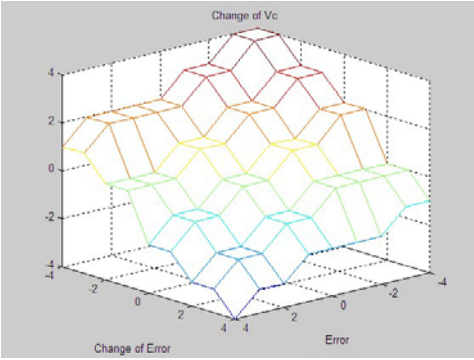

Figure 5. Control surface of the fuzzy controller

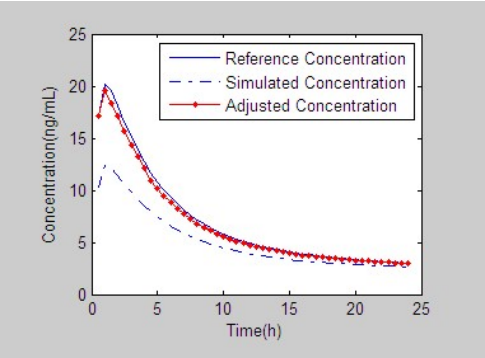

Figure 6. The simulation results of the reference concentration, simulated patient concentration and the adjusted concentration

The controller was tested by varying the parameter of distribution volume to simulate a patient with V_c 50% greater than the average value. The simulation results are given in Fig. 6. It shows the reference concentration derived from the parameters of population mean data, the simulated patient concentration and the adjusted concentration using the fuzzy controller. From the figure it can be seen that the controller performed well to adjust the simulated concentration nearly match with the reference values.

Conclusion

A fuzzy logic method for adapting the parameters of a two-compartment PK model with first-order rate process of oral administration in a closed-loop control system has been shown. This method uses fuzzy relationship between the input variables and the output variable to determine the scaling factor. The simulation results show that the fuzzy controller provides good performance to adjust the concentration with the reference values. The fuzzy logic theory which is a qualitative computational approach can be considered as a suitable formalism to deal with the imprecision intrinsic existed in many biomedical problems. Further implementation along with expansion to investigate drug effect based on the pharmacodynamic model can be undertaken in the future.

Acknowledgment

This work was supported by the Natural Science Foundation of China (No. 61261007).

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