

A fuzzy logic controller for
intestinal levodopa infusion in
Parkinson's disease

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Abstract

The aim of this work is to evaluate the fuzzy system for different types of patients for levodopa infusion in Parkinson Disease based on simulation experiments using the pharmacokinetic-pharmacodynamic (PKPD) model. Fuzzy system is to control patient's condition by adjusting the value of flow rate, and it must be effective on three types of patients, there are three different types of patients, including sensitive, typical and tolerant patient; the sensitive patients are very sensitive to drug dosage, but the tolerant patients are resistant to drug dose, so it is important for controller to deal with dose increment and decrement to adapt different types of patients, such as sensitive and tolerant patients. Using the fuzzy system, three different types of patients can get useful control for simulating medication treatment, and controller will get good effect for patients, when the initial flow rate of infusion is in the small range of the approximate optimal value for the current patient's type.

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1. Introduction

Parkinson's disease (also known as Parkinson disease or PD) is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills, speech, and other functions [1].

Parkinson's disease is a progressive disorder that affects nerve cells (neurons) in the part of the brain that controls muscle movement. This group of nerve cells (substantia nigra) makes dopamine, a chemical which is important for transmitting signals from one group of brain cells to another to facilitate movement. As dopamine-producing cells are lost, walking, arm movements and facial expressions are affected. By the time Parkinson's disease symptoms appear, 50 to 80 percent or more of these cells have been lost [2].

PD symptoms can include:

- **Tremors** — rhythmic movements or shaking, especially in the hands and particularly when they are at rest
- **Rigid limbs and trunk** — muscle tenseness, stiffness, aching, or weakness
- **Slowness of movement** — difficulty beginning a task, such as washing or dressing
- **Difficulty with walking** — problems with maintaining balance
- **Diminished dexterity and coordination** — changes in handwriting, and a decline in athletic abilities
- **Freezing** — the sudden and brief inability to move

Currently, to treat Parkinson disease, there are fewer types of medications; the most common of this is levodopa/carbidopa. Forty years after its discovery, it remains the most effective medication for Parkinson disease. Duodopa® which is a combination of levodopa/carbidopa is specifically appropriate for patients with advanced stage of Parkinson's disease, where oral treatments are no longer effective and are typically associated with severe motor fluctuations.

1.1. General introduction

Nowadays, the most effective Parkinson's drug is levodopa, which is a natural substance that we all have in our body. Unfortunately, as the disease progresses, the benefit from levodopa may become less stable, with a tendency to wax and wane

("wearing off") and side effects (confusion, delusions and hallucinations, as well as involuntary movements called dyskinesia) [1]. For this situation, it requires medication adjustments, because too low levodopa will make no effect and too high levodopa will cause side effects for PD patient, the situation can be improved with infusion of medicine (levodopa) directly into the intestine (Duodopa® from Solvay Pharmaceuticals) via an adjustable pump.

There is the effect given on a scale from -3 to +3, where -3 represents severe parkinsonism, +3 represents severe dyskinesia, and 0 represent that the PD patients returned to normal state, the medicine pump is typically shut off during the night, the day starts with a initial flow rate supplies medicine, and then it automatically adjust the size of flow rate to improve the status of the PD patient by the value of effect, so the aim of my work is that the flow rate was adjusted so it would appear stable at zero on the effect, but the PD patients have three different type, sensitive patient can return to normal by infusing small dose, and tolerant patient need very large dose, so the problem is how to automatically change flow rate to control different types of patients by a controller in Parkinson Disease based on simulation experiments using the pharmacokinetic-pharmacodynamic(PKPD) model.

A population pharmacokinetic-pharmacodynamic (PKPD) model relating uptake, distribution, elimination and effect of the drug has been estimated from data in clinical studies [3].

1.2. Objective

The first objective is to implement a fuzzy controller to improve patient' symptoms by adjustment of flow rate, according to the rules of flow rate for titration, and the fuzzy controller must be effective on three different types of patients, including sensitive, typical, tolerant patient.

The second objective is to get appropriate control effect by a fuzzy controller in the simulation time, it is required to make the E values of patient reach and steady at target level as soon as possible, where E values present patient' symptoms, target level is zero that presents symptom free for PD patients.

2. Background

The details for PKPD model and three types of PD patients were introduced in this chapter. There are the foundations of the whole work.

2.1. PKPD model

The pharmacokinetic-pharmacodynamic model is named PKPD model [4], which is described by four ordinary differential equations, the following figure (i.e. Figure 1) is the Structural pharmacokinetic- pharmacodynamic model.

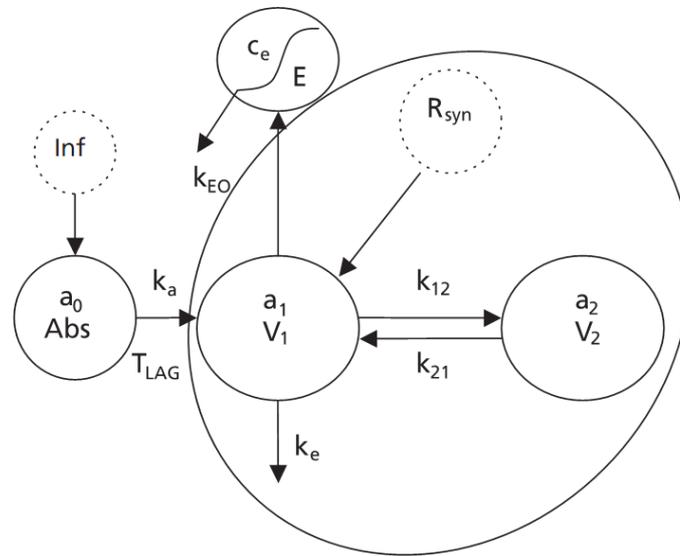


Figure.1. Structural pharmacokinetic- pharmacodynamic model

PKPD model is consisted of four mainly differential equations:

$$\frac{da_0}{dt} = Inf - k_a a_0$$

$$\frac{da_1}{dt} = BIO \cdot k_a a_0 - (k_{12} + k_e) a_1 + k_{21} a_2 + R_{syn}$$

$$\frac{da_2}{dt} = k_{12} a_1 - k_{21} a_2$$

$$\frac{dc_e}{dt} = k_{EO} (a_1 / V_1 - c_e)$$

Where:

Inf	Levodopa infusion (mg/min)
$RSYN$	Endogenous levodopa synthesis rate (mg/min)
a_i	Amount (mg) in compartment i
V_i	Apparent volume (L) in compartment i
k_i	Fractional rate constant (min^{-1})
BIO	Bioavailability (fraction absorbed)
c_e	Effect compartment concentration (mg/L)

The following derived PK parameters were estimated:

$CL = k_e V_1$	Clearance (L/min)
$Q = k_{12} v_1 = k_{21} v_2$	Intercompartmental clearance (L/min)
$TABS = 1 / k_a$	Absorption time constant (min)
$TKEO = 1 / k_{EO}$	Effect time constant (min)

The sigmoid E-max effect model is described by the following equation:

$$E = BASE + \frac{EMAX \cdot c_e^\gamma}{c_e^\gamma + EC50^\gamma}$$

Where:

E	effect (treatment response scale)
γ	sigmoidicity factor
$EC50$	Conc.50% effect

E is a treatment response scale (TRS) between -3 and 3, where -3 represents severe parkinsonism, 3 represents severe dyskinesia, and 0 represent that the PD patients returned to normal, what the controller need to achieve.

Theoretically, according to a population PKPD, every PD patient has same characteristic parameters but with different values. Therefore, it can find optimal flow rate of each type patient by simulation [4, 5], as long as its corresponding parameters are known. So it can get data case about the different value of characteristic parameters and its corresponding optimal FR from the existing online simulator.

2.2. Three types of PD patient

For PKPD model, the input is flow rate of infusion dose, the output is effect of PD patient treatment, Effect measurements are described by a treatment response scale (TRS). As mentioned above, -3 stands for most severe PD symptoms, while +3 means severe side effect, zero mean symptom free [3], different flow rate can make E stable at different value, the goal of the optimal of this simulation was keep effect on E stable at target zero. There has four mainly differential equations with the same characteristic parameter for all type of patients, and different type of PD patients can be distinguished by using the different value of characteristic parameters.

PD patients are treated by Duodopa with a pump device. The controlled model is PKPD model that can be built based on corresponding characteristic parameters and differential equations by s-function, and then change the value of characteristic parameters to vary the type of PD patient.

From the online simulator [4,5], an typical characteristic parameters of the patient with the optimal flow rate for typical patient can be obtained, so the Figure 2 show the curve of E value when the optimal flow rate for typical patient is 1 mg/min.

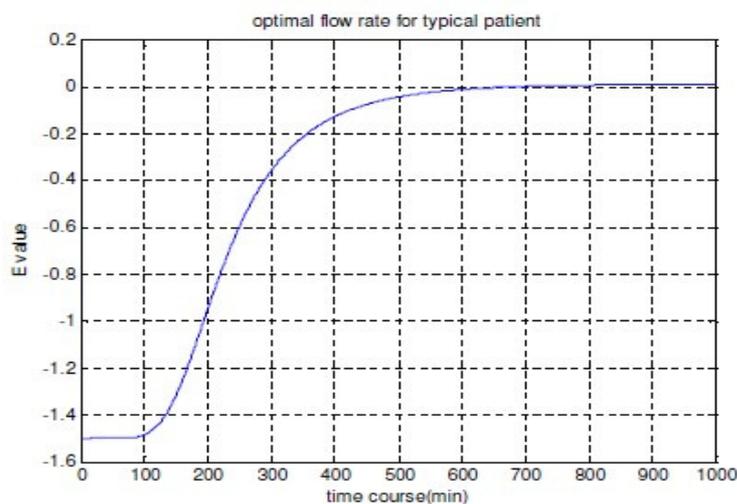


Figure.2. E values when flow rate =1 mg/min for a typical patient

In the same way, the sensitive and tolerant characteristic parameters of the patient with the optimal flow rate also can be obtained from the online simulator, hence, the optimal flow rate for sensitive patient is 0.33mg/min, and the optimal flow rate for tolerant patient is 8 mg/min.

3. Fuzzy controller design

The overall design of system is as follow [5]:

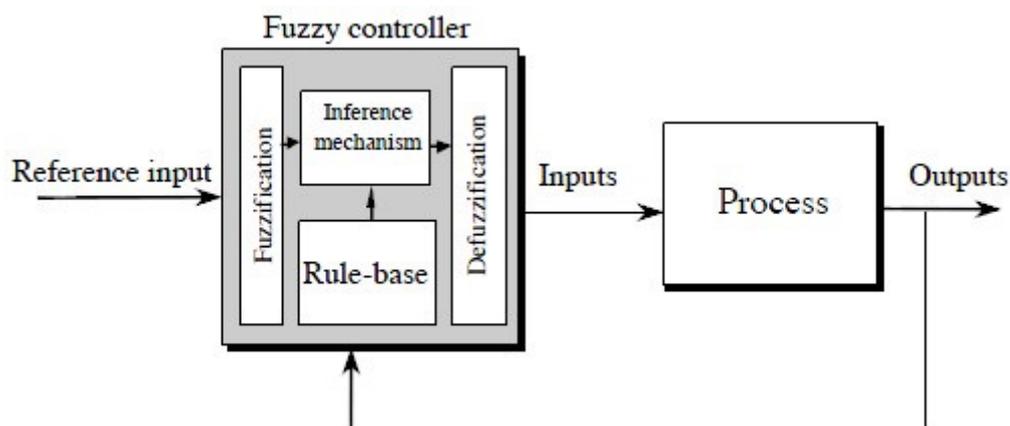


Figure.3. Fuzzy controller architecture

The fuzzy controller has four main components:

- Fuzzification is to take the inputs and determine the degree to which they belong to each of the appropriate fuzzy sets via membership functions.
- The “rule-base” saves the knowledge based on a set of rules, of how best to control the system.
- The inference mechanism estimates which rules should be used at the current time and then decides what the input to the controlled model should be.
- Defuzzification converts the conclusions reached by the inference mechanism into the inputs to the controlled model.

3.1 The algorithm for membership function

According to fuzzy set theory the choice of the shape and width is subjective, but a few rules of thumb apply [9]:

- A term set should be sufficiently wide to allow for noise in the measurement.
- A certain amount of overlap is desirable; otherwise the controller may run into poorly defined states, where it does not return a well defined output.

Here, the triangular membership function was chosen as membership function of flow rate, this function is nothing more than a collection of three points forming a triangle, the algorithm has shown as follows:

$$f(x; a, b, c) = \begin{cases} 0, & x \leq a \\ \frac{x-a}{b-a}, & a \leq x \leq b \\ \frac{c-x}{c-b}, & b \leq x \leq c \\ 0, & c \leq x \end{cases}$$

The triangular membership function was decided by parameter a, b and c. Parameters a and c are the two feet of triangle, parameter b is located in the top of the membership function curves.

Then Gaussian membership function was chosen as membership function of Effect and target E, it is popular methods for specifying fuzzy sets, because the curve has the advantage of being smooth and nonzero at all points, it was decided by parameter σ and c, the algorithm has shown as follows:

$$f(x; \sigma, c) = e^{-\frac{(x-c)^2}{2\sigma^2}}$$

For the output of my fuzzy system, the Sugeno output membership function was used, because the outputs of fuzzy system in my thesis are required to be linear or constant. That is, the output from each rule is a moving singleton, and the defuzzified output is the weighted average of the contributions from each rule, the algorithm has shown as follows:

$$FinalOutput = \frac{\sum_{i=1}^n w_i p_i}{\sum_{i=1}^n w_i}$$

where N is the number of rules, p_i is the output of rule i.

$$p = ax + by + cz + d$$

x, y and z represent input flow rate, Effect and target E, respectively; meanwhile, a, b and c is the coefficient corresponding to inputs, d is a constant as the increment corresponding to inputs. In this paper, the output of FIS is newFR, what is only relevant to input flow rate, so the output $p=x + d$, x is flow rate, d is a constant such as 0.1, 0.3, 0.4 and -0.2.

The firing strength of the rule w_i :

$$w_i = \text{AndMethod}(f_1(x), f_2(y), f_3(z))$$

where $f_{1,2,3}(\cdot)$ are the membership functions for flow rate, Effect and target E.

3.2 Fuzzy inference system based on titration rule

Fuzzy inference is the process of formulating the mapping from a given input to an output using fuzzy logic, there are two types of fuzzy inference systems: Mamdani-type and Sugeno-type, the first two parts of the fuzzy inference process, fuzzifying the inputs and applying the fuzzy operator, are exactly the same. The main difference between Mamdani and Sugeno is that the Sugeno output membership functions are either linear or constant [5]. In my thesis, the output need to be either linear or constant, so Sugeno-type is implemented.

For my thesis, the controller can adjust the size of flow rate by adjustment rules to vary E value of PD patient, so that it keep effect on E stable at target zero, what mean that the patients have return to normal. Meanwhile, it is important for the next estimation to obtain current E value of the patient, because the controller require the current value of flow rate and E to judge if the new flow rate need to be increased, decreased or remain unchanged. So the fuzzy controller should be three input and single output, three inputs are the flow rate, E value and target E, and the output is new flow rate value.

The rule of flow rate for titration is described as follow [7]:

(1) The rough adjustment for flow rate:

- If the flow rate is less than 6ml/h and effect of PD patient is less than zero, then it needs to increase by 0.3ml/h.
- If the flow rate is less than 6ml/h and effect of PD patient is more than zero, then it needs to decrease by 0.2ml/h.
- If the flow rate is more than 6ml/h and effect of PD patient is less than zero, then it needs to increase by 0.4ml/h.
- If the flow rate is more than 6ml/h and effect of PD patient is more than zero, then it needs to decrease by 0.2ml/h.

(2) The fine-tuning for flow rate:

If effect before the moment is less than zero, and then it increases 0.3ml/h or 0.4ml/h according to rough adjustment above, but effect will become more than zero, so it seem that it require more accurate adjustment to keep effect on E stable at target zero. Hence, it needs to be decreased by 0.2ml/h first, and then just increase by 0.1ml/h for fine-tuning.

(3) Control period

As to adjustment style, it needs to be controlled every four hours, that is, the flow rate will vary the value every two hundred and forty minutes, and during the four hours, the flow rate will keep no change. Because the patient cans not immediately obtain effective response when the flow rate was increased or decreased, there need some time to take effect in patients' body.

3.2.1 Fuzzy inference system design

The first step for the establishment of fuzzy controller is fuzzify inputs, because the input is always a crisp numerical value limited to the universe of discourse of the input variable. So it needs to map fuzz flow rate, E and target E value to the appropriate membership functions, and then obtain membership value, respectively.

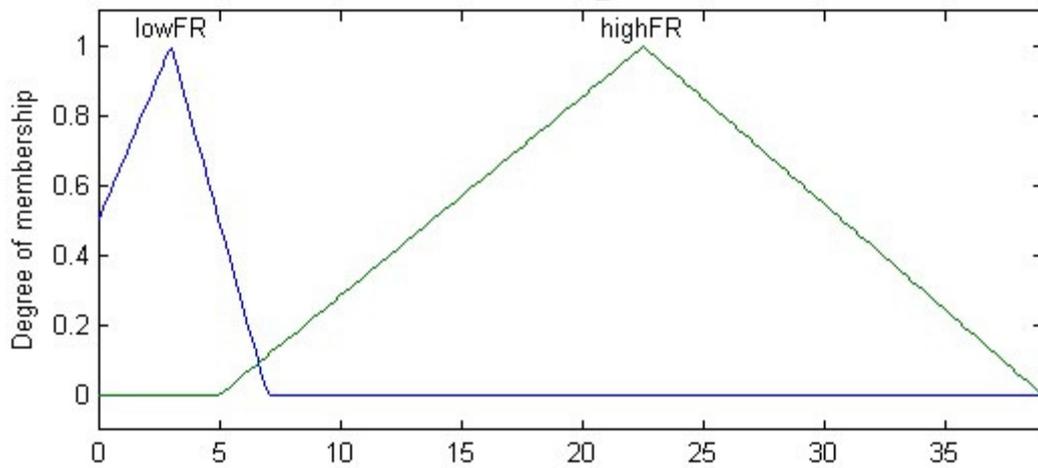


Figure.4. Membership function of input flow rate for titration

Figure 4 show the MF of input flow rate, and the universe of discourse for flow rate is the range $[0\ 39]$, it represents max flow rate is 39ml/h. Because the max flow rate is 13mg/min in the PKPD model, that is, the dose can be took in when max flow rate is no more than 13mg/min, there exists a conversion unit that is 20mg/ml, so 13mg/min is equal to 39ml/h. Moreover, there are two memberships for flow rate, the universe of discourse for lowFR is the range $[-3\ 7]$, and highFR is the range $[5\ 39]$, when the value of flow rate is less than 6 ml/h, which belong to area of lowFR, it will compute the membership value by lowFR, and vice versa.

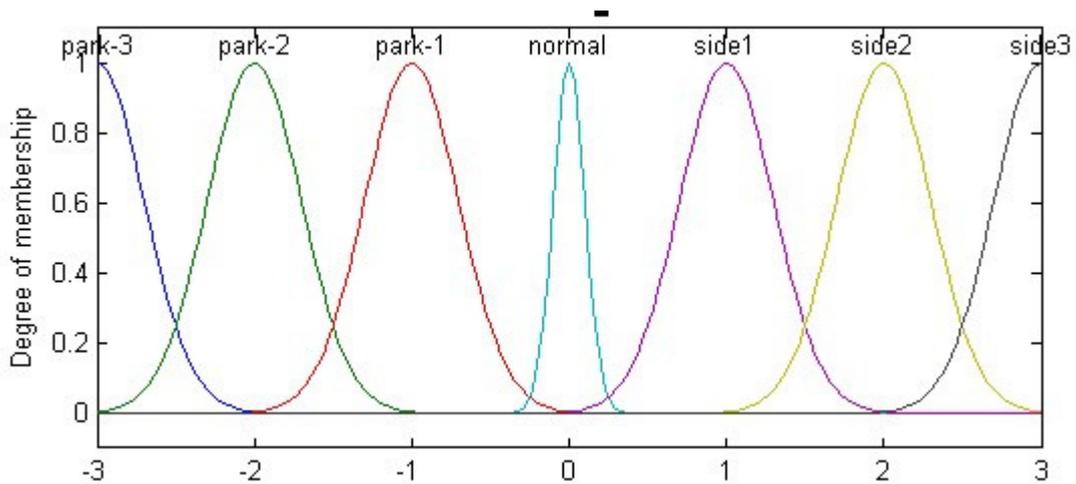


Figure.5. Membership function of input Effect for titration

The picture above (i.e. Figure 5) is MF for effect of PD patients, and it is the same as input target E, there both have the same memberships and linguistic value. For these membership functions, normal represent symptom free for PD patient, that is, the patients have no parkinsonism and side effect response at the moment; park-1, park-2 and park-3 represent slight, moderate, and severe parkinsonism; furthermore, side1,side2 and side3 represent slight, moderate, and severe side effect for PD patient.

The second step is to take the membership value and apply them to the antecedents of the fuzzy rules. Because my fuzzy rule have three inputs, that is, there have three antecedents, so the fuzzy operator of And method is used to obtain truth value that presents the result of input flow rate, Effect and target E estimation for every rule, then the truth value will be applied to the consequent output.

The final step is to obtain the defuzzified output that is the weighted average of the contributions from each rules, the relatively weighted value is mentioned truth value of each rule.

The table below (i.e. Table 1) is the titration rule for flow rate.

Table.1. The fuzzy rule for titration

Flow rate	Effect	Target E	newFR
lowFR	park-1	normal	add0.1
highFR	park-1	normal	add0.1
lowFR	park-2	normal	add0.3
lowFR	park-3	normal	add0.3
highFR	park-2	normal	add0.4
highFR	park-3	normal	add0.4
none	side1	normal	sub0.2
none	side2	normal	sub0.2
none	side3	normal	sub0.2

From the table, fuzzy inference system vary the value of flow rate to improve patients' condition by judging Effect of patient and the flow rate at the moment, there have the two operations of rough adjustment and fine-tuning:

- Rough adjustment: if Effect is positive, the output will be subtracted by 0.2ml/h in despite of how much is the value of the current flow rate; while Effect was in park-2 or park-3, it will be increased by 0.3ml/h or 0.4ml/h, according to the value of the current flow rate.
- Fine-tuning: when Effect is in park-1, which represent that the patient is in mild condition, that is, it must give smaller flow rate than before, therefore, here newFR is increased by 0.1ml/h for fine-tuning.

3.2.2 System simulation design

The overall framework of system simulation is as follow (i.e. Figure 6):

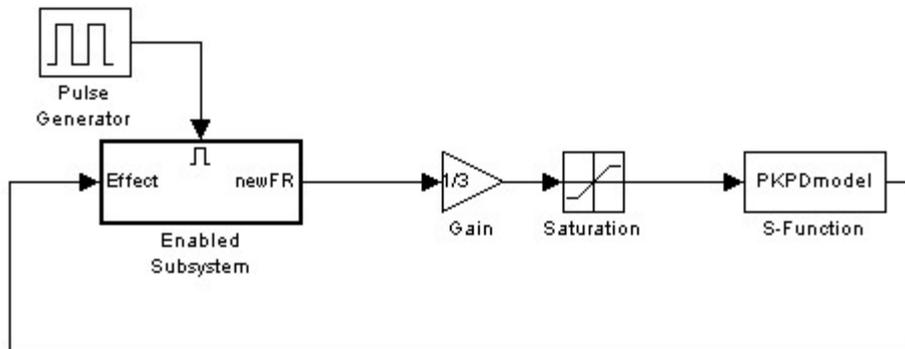


Figure.6. system simulation structure

From the framework above (i.e. Figure 6), PKPD model is required to build by s-function, and then it is controlled through enable subsystem, which is constructed by fuzzy logic controller (FLC). Moreover, the enable control signal is generated by a Pulse Generator block that is used to set control time, in this paper, it need to enable FLC every 240 minutes, so interval time of this block is set to 240 minutes; Saturation block is used to limit flow rate, so that the flow rate in the model is no more than 13mg/min; the purpose of Gain block is change the unit between ml/h and mg/min, because there exist the relationship that a constant is 20mg/ml, and the unit in the FLC is ml/h, so the unit of the output of enable subsystem which is labeled by newFR is ml/h, but for the PKPD model, the flow rate just accept mg/min for patient, so it must be transformed into mg/min via divided by 3.

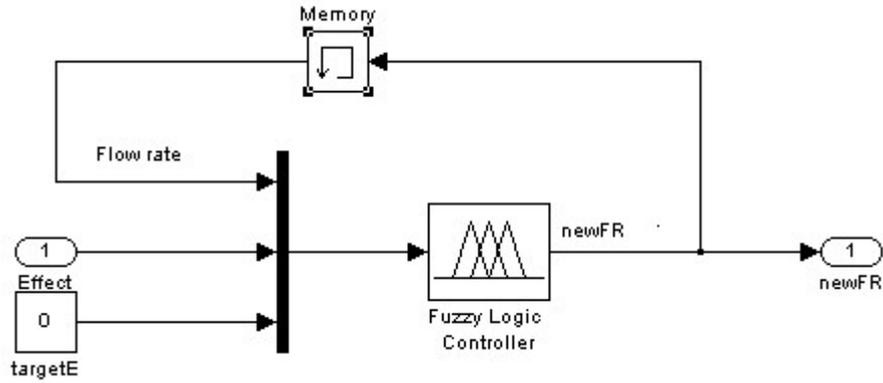


Figure.7.The structure in the enable subsystem

The figure above (i.e. Figure 7) show the detailed structure of enable subsystem, firstly, Fuzzy Logic Controller block should be connected with fuzzy inference system based on titration rule, which was build in the previous section, and then Memory block is used to set initial value of flow rate. For example, the PKPD model is the model of typical patients, and the initial FR for typical patient is 1 mg/min, therefore, so memory block is required to set into 3ml/h (3ml/h=1mg/min).

For the simulation configuration, in my system, simulation time is 1000 minutes, it represents one day for PD patients; fixed-step mode was applied to simulation, and the size is 0.1, simultaneously the fourth-order Runge-Kutta method was chose as a solver, it is one member of Runge-Kutta methods that are an important family of implicit and explicit iterative methods for the approximation of solutions of ordinary differential equations [10].

4. Result and analysis

4.1 The result of flow rate for titration

As for the patients, there are no medicines in the body before infusion of dose, and different types of patient was chose by manually replacing patient type. When initial flow rate is set to 3ml/h (i.e.1mg/min), which is the optimal FR for the typical patients, and the type of PKPD model is the typical patient, then the effect of fuzzy

controller for the patient is shown by the figure below (i.e. Figure 8). In the figure, horizontal axis is the simulation time, vertical axis simultaneously stand for the value of Flow rate and E value for the patient, so the blue solid line and purple dotted line represent the flow rate curve and Effect curve for the patient, respectively. As it is shown, the control effect is good for the typical patient when initial FR is the optimal FR corresponding to typical patient, and also have control effect when initial FR is in the range of the approximate optimal value, because the value of flow rate will be changed every 240 minutes if the Effect of PD patient is not zero at the moment, that is, when the controller check the Effect of patient, if the Effect is more than zero or less than zero, the flow rate must be changed according to titration rule.

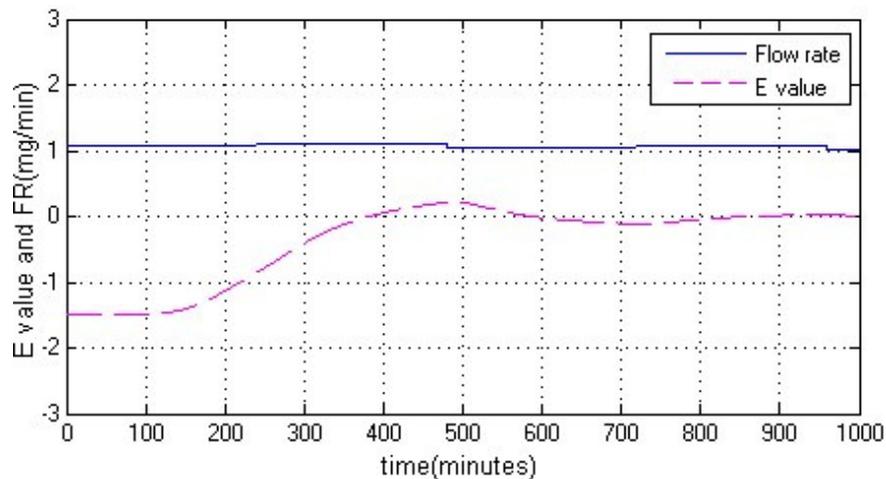


Figure.8. FR and E values when flow rate = 1mg/min for typical patient.

The following two pictures (i.e. Figure 9 and 10) show the results of fuzzy controller for tolerant and sensitive patient when initial flow rate is 24ml/h (i.e.8mg/min) and 1ml/h (i.e.0.33mg/min), which is the optimal FR for the tolerant and sensitive patient, it show the fact that the fuzzy controller has good control effect for tolerant patient and not bad effect for sensitive patient when initial FR is the optimal FR for the current type of patient.

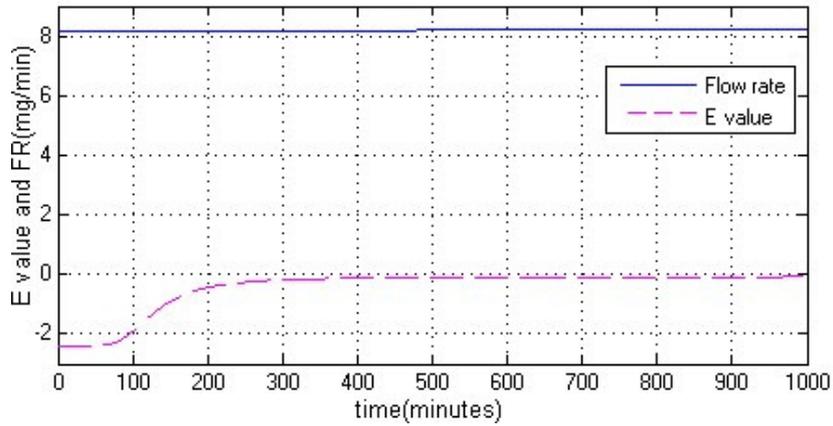


Figure.9. FR and E values when flow rate = 8 mg/min for tolerant patient.

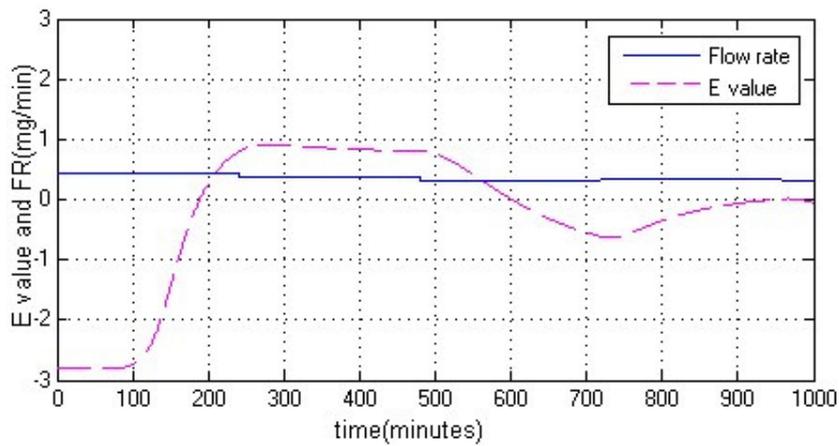


Figure.10. FR and E values when flow rate = 0.33mg/min for sensitive patient

For the sensitive patients, they are very sensitive to dose, and need small FR to make E at zero, but the opposite is for tolerant patient, they are very resistant to dose, that is, the FR that they require is far more than sensitive and typical patient. So the compromise of increment and decrement rules of adjusting flow rate for different types of patient should be achieved, and this goal has been achieved by the current rule.

However, when initial FR is zero, the fuzzy controller can not get desirable control effect for any type of patient, because they need very large doses to make the Effect of patient return to normal, especially for the tolerant patients. But the current increment of flow rate for titration is not large, so it can not obtain control effect in the simulation time, if initial FR is far less than target level that is required to make

E at zero for the current patient, the three figure blew (i.e. Figure 11, 12 and 13) show the control result when initial FR is too small for three types of patients.

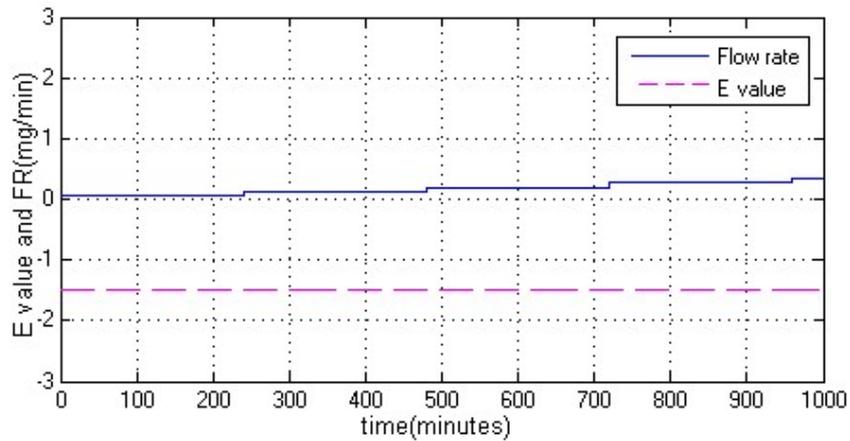


Figure.11. FR and E values when flow rate = 0mg/min for typical patient.

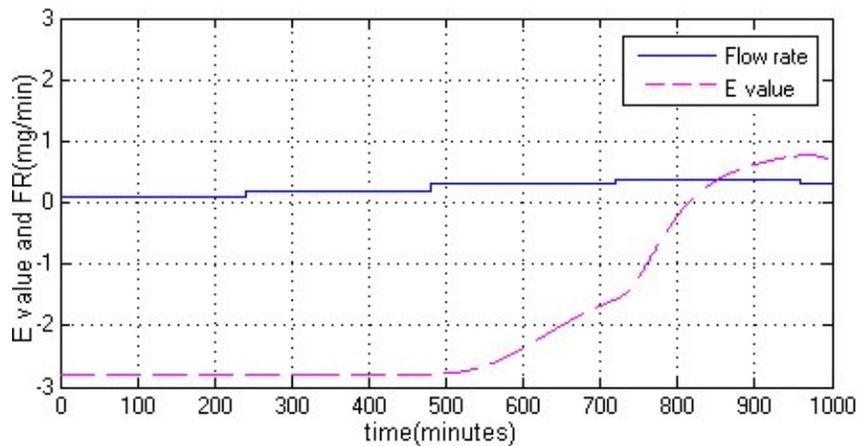


Figure.12. FR and E values when flow rate = 0mg/min for sensitive patient.

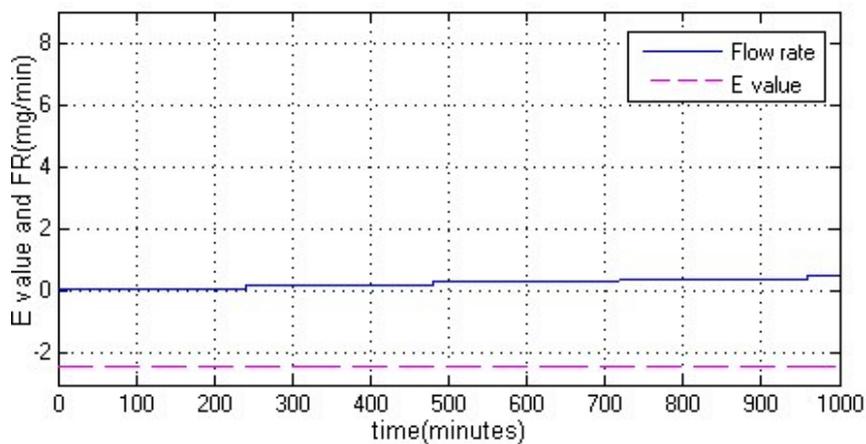


Figure.13. FR and E values when flow rate = 0mg/min for tolerant patient.

From the result above (i.e. Figure 11, 12 and 13), the value of flow rate has been increasing all the time according to the rules when initial FR is zero, but cumulative amount of FR is not enough to take effect for typical and tolerant patient in the 1000 minutes, simultaneously the result show the fact that the dose for sensitive patient are far less than typical and tolerant patient.

4.2 Improvement of FIS based on my own rule

4.2.1 FIS design

Because the FIS above cans not obtain desirable effect when initial FR is zero, I try to achieve the goal by changing fuzzy rules, the detailed description is as follow.

For this fuzzy inference system, the structure is very similar to the FIS above that was mentioned in the previous section, the flow rate, Effect and target E are also the input, and newFR is the output of fuzzy system, and the unit of FIS is also ml/h, it just change titration rule into my own rule, but the rules are based on the fact that it has known the optimal flow rate for the current patient's type. In this paper, it can obtain the data from the online simulator [4, 5].

My own rule also have two operations of rough adjustment and fine-tuning, firstly, the optimal FR for each type of patients must be known, from the online simulator, I can get the data that the optimal FR is 1ml/h, 3ml/h and 24ml/h, corresponding to sensitive patient, typical patient and tolerant patient, respectively. Secondly, the range of FR needs to be divided into different areas, which represent the areas of fine-tuning and rough adjustment.

The entire process is to make the value of rough range change into the value of fine-tuning range first, and then do fine-tuning in the optimal FR range (the fine-tuning range is the optimal FR range). For example, when initial FR is 0ml/h for the different types of patients, firstly, it change 0ml/h into 1ml/h, then do fine-tuning for the range of 1ml/h, if there is no obvious effect for the patient,

immediately jump into 3ml/h, then it needs some time to see the Effect of patient by fine-tuning, if there is also not effective, so it should jump into 24ml/h, then do fine-tuning.

The figure below (i.e. Figure 14) shows the different the areas of fine-tuning and rough adjustment in the membership function. VernierFR-1, vernierFR-2 and vernierFR-3 present the optimal FR range for 1ml/h, 3ml/h and 24ml/h, which is considered as the fine-tuning range, others are the rough adjustment range.

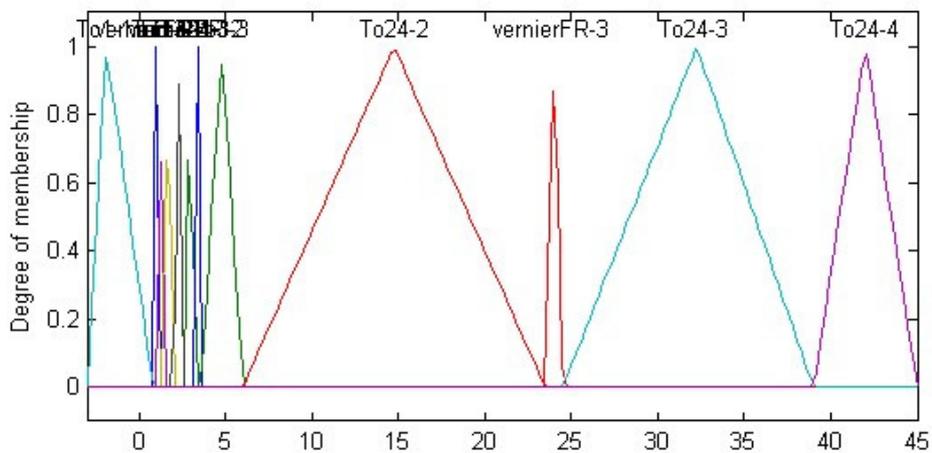


Figure.14. Membership function of input flow rate for my own rule

For these membership functions below (i.e. Figure 15), normal is present symptom free for PD patient; park-1, park-2 and park-3 present slight, moderate, and severe parkinsonism; furthermore, side1,side2 and side3 present slight, moderate, and severe side effect for PD patient.

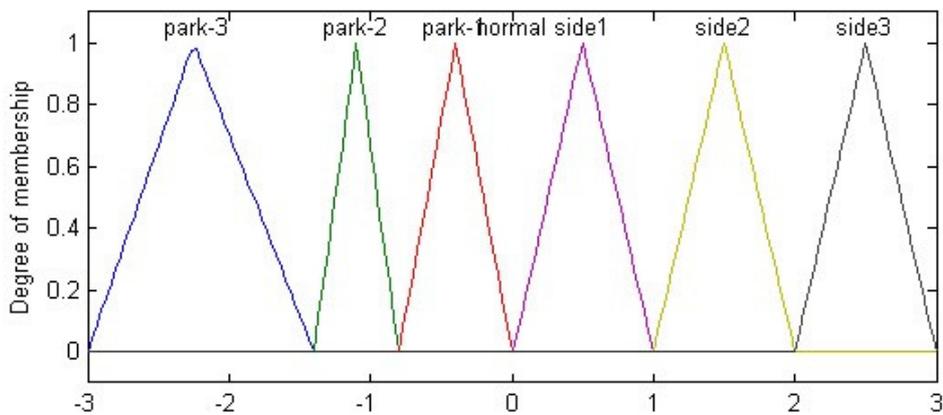


Figure.15. Membership function of input Effect for my own rule

In my rules, control period is ten minutes, that is, the flow rate will vary the value every ten minutes, because it need to be adjusted many times to get control effect when initial FR is zero for tolerant patient. Corresponding to increase the number of FR adjustment, it reduce the increment of FR for each adjustment, the table below (i.e. Table 2) is the rule for flow rate:

Table.2.The fuzzy rule for my own rule

Flow rate	Effect	Target E	newFR
vernierFR-1	side3	normal	sub0.008
vernierFR-1	side2	normal	sub0.008
vernierFR-1	side1	normal	sub0.008
vernierFR-1	normal	normal	add0
vernierFR-1	park-1	normal	add0.002
vernierFR-1	park-2	normal	add0.004
vernierFR-1	park-3	normal	add0.006
vernierFR-2	side3	normal	sub0.008
vernierFR-2	side2	normal	sub0.008
vernierFR-2	side1	normal	sub0.008
vernierFR-2	normal	normal	add0
vernierFR-2	park-1	normal	add0.002
vernierFR-2	park-2	normal	add0.004
vernierFR-2	park-3	normal	add0.006
vernierFR-3	side3	normal	sub0.008
vernierFR-3	side2	normal	sub0.008
vernierFR-3	side1	normal	sub0.008
vernierFR-3	normal	normal	add0
vernierFR-3	park-1	normal	add0.002
vernierFR-3	park-2	normal	add0.004
vernierFR-3	park-3	normal	add0.006
To1-1	park-3	normal	To1
To3-1	park-3	normal	To3
To3-1	park-2	normal	add0.004
To1-2	park-3	normal	To1
To3-2	park-3	normal	To3
To24-1	park-3	normal	To24

To3-3	park-3	normal	To3
To24-2	park-3	normal	To24
To24-3	park-3	normal	To24
To24-4	park-3	normal	To24

4.2.2 The result for my own rule

There are no medicines in the body before infusion of dose for the patient, the results from the figures below (i.e. Figure 16 and 17) has shown desirable control effect for any type of patient by controller when initial FR is zero. In the figure, horizontal axis is the simulation time, vertical axis simultaneously stand for the value of Flow rate and E value for the patient, so the blue solid line and purple dotted line represent the flow rate curve and Effect curve for the patient, respectively. And the FR will be changed every ten minutes, because the increment value of FR for fine-tuning is so small that the fine-tuning curve of FR is not very obvious change in the figure.

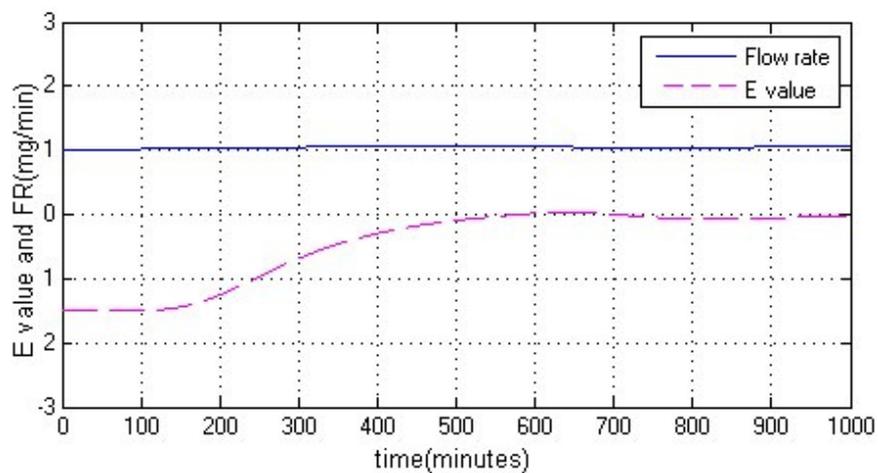


Figure.16. initial FR = 1mg/min (optimal) for typical patient in my own rule

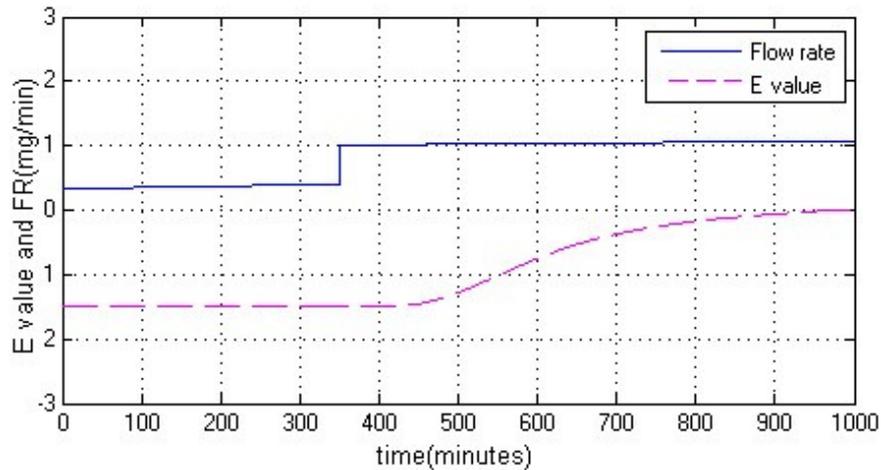


Figure.17. initial FR = 0 mg/min for typical patient in my own rule

From the two figures above (i.e. Figure 16 and 17), with the optimal flow rate, the Effect will reach the target zero quickly and stable at zero, and the result also show that the patient need more time and more adjustment make Effect of patient at zero when initial FR is zero, compared with the optimal value.

The result for sensitive and tolerant patient is similar to typical patient, that is, if initial value is zero, the patient need more dose to return to normal states, it means the adjustment of FR must be increased.

5. Conclusion

With the existing pharmacokinetic-pharmacodynamic model for the patients, the fuzzy inference system based on titration rule was finished to achieve the useful and powerful control effect for patient condition. It simulates Parkinson disease treatment by automatically infused dose, and might help PD patient' symptom eased.

For three types of patients, each types of patient need different doses and flow rate to make the Effect value reach and stable at target E level as soon as possible, so there have a controller that it is effective on three types of patients at the same time. In this fuzzy controller, it cans automatically adjust the FR by checking the current body status of the patient according to titration rule, and also can obtain good control effect when the initial FR is in the range of the approximated optimal FR for corresponding to patient type.

However, if initial FR is too small for the current patient, such as zero, then the symptom of patient will be under control by this fuzzy controller after simulation time over, so increment rule of flow rate for the titration is not enough to increase large dose infusion in limited time.

As for this situation, I try to improve the performance of fuzzy controller by changing into my own rules, and it is effective on three types of patients, too. Though the new FIS can get appropriate effect when initial FR is both zero and the optimal FR, but it is not good compared with titration rule, because of the limited condition that the optimal FR for each type of patient must be known.

6. Discussion

In my thesis, a fuzzy controller was design based on titration rule to improve the state of the patients by changed flow rate of infusion dose, but for the patients, there have three different types, different types of patients require different flow rate of infusion and doses of drugs to improve the symptom, so the goal of the controller also is effective on three different types of patients.

For the PKPD model of patients, the FR and dose for typical patient is fit for majority of the patients, which is not too much or little for patient; but there also have some special patients, the sensitive patients are very sensitive to the doses of drug, it can reach target level by the change of small FR; just the opposite, the tolerant patients are very resistant for infusion doses of drug, the FR and dose that they need are far more than other patient type. For the situation, when initial FR is appropriated, the titration rule of controller has achieved the aim about the appropriate increment and decrement of flow rate, and simultaneously they are effective on three types.

As for the result of titration rule, the symptoms of patients can be under control by fuzzy controller when initial FR is appropriate value for the current patient, because the controller only has the rules of flow rate for titration, which look more like fine-tuning in the range of appropriate FR, therefore, when initial FR is too small for the patient, it is far from enough to improve the symptoms of Parkinson's patients by the controller in the limited time.

Finally, I try to mend performance of the controller by adding rules, but the result is not good, although the goal has been achieved, which is effective on three types of patients when initial FR is too small for the patient, there have a serious shortcoming that the optimal FR for each type of patients must be known. So the new rules are not very good for improvement of controller, only for reference.

7. Future work

In this study, a fuzzy controller was accomplished to improve the state of PD patients by adjusted flow rate of drug infusion, but it will become invalid when initial FR is too small for the current patient, so this problem should be solved in the future work.

There are good ideas to append the rules for morning dose and extra dose to improve the performance of the controller, the appropriate morning dose can speed up patient return to normal state as soon as possible. Simultaneously, when initial FR is too small for the current patient, extra doses can be taken on top of the set flow rate, in order to keep the state of symptom free. I think if the gap is too large between initial FR and the appropriate FR for the current patient, the rules for extra doses can reduce this gap so that PD patient can quickly return to normal state.

However, the ideas that it has mentioned above just for reference, the realization for the idea must be considered in detail.

Reference

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Appendix A: Three type of patients (S-Function)

The typical patients:

```
function [sys,x0,str,ts] = typical(t,x,u,flag)

V1=11;
V2=27;
Q=0.58;
TABS=27.9;
TKEO=22;
BIO=0.971;
Rsyn=0.01;
BASE=-1.5;
EMAX=3.1;
EC50=2.0;
GAMMA=11;
CL=0.52;

switch flag,

    case 0,
        [sys,x0,str,ts]=mdlInitializeSizes();

    case 1,
        sys=mdlDerivatives(t,x,u,TABS,Q,V1,V2,TKEO,CL,BIO,Rsyn);

    case 3,
        sys=mdlOutputs(t,x,u,BASE,EMAX,GAMMA,EC50);

    case { 2, 4, 9 },
        sys = [];

    otherwise
        DAStudio.error('Simulink:blocks:unhandledFlag', num2str(flag));

end

function [sys,x0,str,ts]=mdlInitializeSizes()

sizes = simsizes;
sizes.NumContStates = 4;
sizes.NumDiscStates = 0;
```

```

sizes.NumOutputs    = 1;
sizes.NumInputs     = 1;
sizes.DirFeedthrough = 1;
sizes.NumSampleTimes = 1;

```

```

sys = simsizes(sizes);
x0 = zeros(4,1);
str = [];
ts = [0 0];

```

```

function sys=mdlDerivatives(t,x,u,TABS,Q,V1,V2,TKEO,CL,BIO,Rsyn)

```

```

ka=1/TABS;
k12=Q/V1;
k21=Q/V2;
kEO=1/TKEO;
ke=CL/V1;

```

```

sys(1)=u-ka*x(1);
sys(2)=BIO*ka*x(1)-(k12+ke)*x(2)+k21*x(3)+Rsyn;
sys(3)=k12*x(2)-k21*x(3);
sys(4)=kEO*(x(2)/V1-x(4));

```

```

function sys=mdlOutputs(t,x,u,BASE,EMAX,GAMMA,EC50)

```

```

sys =BASE+(EMAX*(x(4)^GAMMA))/((x(4)^GAMMA)+EC50^GAMMA);

```

The sensitive and tolerant patients are similar to typical patient, just change the value of characteristic parameter, they are shown as follow:

Characteristic parameter for the sensitive patients:

```

V1=12;
V2=31;
Q=1.1;
TABS=24;
TKEO=22;
BIO=0.971;
Rsyn=0.00795;
BASE=-2.8;
EMAX=4.1;
EC50=0.65;
GAMMA=11;

```

CL=0.47;

Characteristic parameter for the tolerant patients:

V1=5;

V2=34;

Q=1.6;

TABS=7;

TKEO=22;

BIO=0.971;

Rsyn=0.00433;

BASE=-2.4;

EMAX=3.1;

EC50=7.3;

GAMMA=11;

CL=0.99;

Appendix B: Code for FIS based on titration rule

```
[System]
Name='titration'
Type='sugeno'
Version=2.0
NumInputs=3
NumOutputs=1
NumRules=9
AndMethod='min'
OrMethod='max'
ImpMethod='prod'
AggMethod='sum'
DefuzzMethod='wtaver'

[Input1]
Name='FR'
Range=[0 39]
NumMFs=2
MF1='lowFR':'trimf',[-3 3 7]
MF2='highFR':'trimf',[5 22.5 39]

[Input2]
Name='effect'
Range=[-3 3]
NumMFs=7
MF1='park-3':'gausmf',[0.3 -3]
MF2='park-2':'gausmf',[0.3 -2]
MF3='park-1':'gausmf',[0.3 -1]
MF4='normal':'gausmf',[0.1 0]
MF5='side1':'gausmf',[0.3 1]
MF6='side2':'gausmf',[0.3 2]
MF7='side3':'gausmf',[0.3 3]

[Input3]
Name='targetEffect'
Range=[-3 3]
NumMFs=7
MF1='park-3':'gausmf',[0.3 -3]
MF2='park-2':'gausmf',[0.3 -2]
MF3='park-1':'gausmf',[0.3 -1]
MF4='normal':'gausmf',[0.1 0]
```

```
MF5='side1': 'gausmf', [0.3 1]
MF6='side2': 'gausmf', [0.3 2]
MF7='side3': 'gausmf', [0.3 3]
```

```
[Output1]
```

```
Name='newFR'
```

```
Range=[0 1]
```

```
NumMFs=4
```

```
MF1='add0.1': 'linear', [1 0 0 0.1]
```

```
MF2='add0.3': 'linear', [1 0 0 0.3]
```

```
MF3='add0.4': 'linear', [1 0 0 0.4]
```

```
MF4='sub0.2': 'linear', [1 0 0 -0.2]
```

```
[Rules]
```

```
1 3 4, 1 (1) : 1
```

```
2 3 4, 1 (1) : 1
```

```
1 2 4, 2 (1) : 1
```

```
1 1 4, 2 (1) : 1
```

```
2 2 4, 3 (1) : 1
```

```
2 1 4, 3 (1) : 1
```

```
0 5 4, 4 (1) : 1
```

```
0 6 4, 4 (1) : 1
```

```
0 7 4, 4 (1) : 1
```

Appendix C: Code for FIS based on my own rule

```
[System]
Name='newFRtuning'
Type='sugeno'
Version=2.0
NumInputs=3
NumOutputs=1
NumRules=31
AndMethod='min'
OrMethod='max'
ImpMethod='prod'
AggMethod='sum'
DefuzzMethod='wtaver'

[Input1]
Name='FR'
Range=[-3 45]
NumMFs=12
MF1='vernierFR-1':'trimf',[0.801 1 1.199]
MF2='vernierFR-2':'trimf',[2.601 3 3.229]
MF3='vernierFR-3':'trimf',[23.501 24 24.499]
MF4='To1-1':'trimf',[-3 -1.9 0.801]
MF5='To3-1':'trimf',[1.199 1.25 1.299]
MF6='To1-2':'trimf',[1.299 1.65 2.001]
MF7='To3-2':'trimf',[2.001 2.3 2.601]
MF8='To24-1':'trimf',[3.229 3.4 3.599]
MF9='To3-3':'trimf',[3.599 4.8 6.001]
MF10='To24-2':'trimf',[6.001 14.75 23.501]
MF11='To24-3':'trimf',[24.499 32.25 39.001]
MF12='To24-4':'trimf',[39.001 42 45]

[Input2]
Name='effect'
Range=[-3 3]
NumMFs=7
MF1='park-3':'trimf',[-3 -2.25 -1.4]
MF2='park-2':'trimf',[-1.4 -1.1 -0.8]
MF3='park-1':'trimf',[-0.8 -0.4 0]
MF4='normal':'trimf',[0 0.005 0.01]
MF5='side1':'trimf',[0.01 0.5 1]
MF6='side2':'trimf',[1 1.5 2]
```

MF7='side3': 'trimf', [2 2.5 3]

[Input3]

Name='targetEffect'

Range=[-3 3]

NumMFs=7

MF1='park-3': 'gausmf', [-0.3 -3]

MF2='park-2': 'gausmf', [-0.3 -2]

MF3='park-1': 'gausmf', [-0.3 -1]

MF4='normal': 'gausmf', [0.1 0]

MF5='side1': 'gausmf', [0.3 1]

MF6='side2': 'gausmf', [0.3 2]

MF7='side3': 'gausmf', [0.3 3]

[Output1]

Name='newFR'

Range=[0 39]

NumMFs=8

MF1='add0.002': 'linear', [1 0 0 0.002]

MF2='add0.004': 'linear', [1 0 0 0.004]

MF3='add0.006': 'linear', [1 0 0 0.006]

MF4='sub0.008': 'linear', [1 0 0 -0.008]

MF5='To1': 'linear', [0 0 0 1]

MF6='To3': 'linear', [0 0 0 3]

MF7='To24': 'linear', [0 0 0 24]

MF8='add0': 'linear', [1 0 0 0]

[Rules]

1 7 4, 4 (1) : 1

1 6 4, 4 (1) : 1

1 5 4, 4 (1) : 1

1 4 4, 8 (1) : 1

1 3 4, 1 (1) : 1

1 2 4, 2 (1) : 1

1 1 4, 3 (1) : 1

2 7 4, 4 (1) : 1

2 6 4, 4 (1) : 1

2 5 4, 4 (1) : 1

2 4 4, 8 (1) : 1

2 3 4, 1 (1) : 1

2 2 4, 2 (1) : 1

2 1 4, 3 (1) : 1

3 7 4, 4 (1) : 1

3 6 4, 4 (1) : 1
3 5 4, 4 (1) : 1
3 4 4, 8 (1) : 1
3 3 4, 1 (1) : 1
3 2 4, 2 (1) : 1
3 1 4, 3 (1) : 1
4 1 4, 5 (1) : 1
5 1 4, 6 (1) : 1
5 2 4, 2 (1) : 1
6 1 4, 5 (1) : 1
7 1 4, 6 (1) : 1
8 1 4, 7 (1) : 1
9 1 4, 6 (1) : 1
10 1 4, 7 (1) : 1
11 1 4, 7 (1) : 1
12 1 4, 7 (1) : 1