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Determination of the drug dose by fuzzy expert system in treatment of chronic intestine inflammation

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Abstract In this study, chronic intestine illness symptoms such as sedimentation and prostate specific antigen are used for the design of fuzzy expert system to determine the drug (salazopyrine) dose. Suitable drug dose for patients is obtained by using data of ten patients. The results of some patients are compared with the doses recommended to them by the physician. As a result, it has been seen that proposed system is helped to shorten the treatment duration and minimize or remove the negative effects of determination of drug dose for helping physicians.

Keywords Chronic intestine inflammation · Fuzzy expert system · Dose of drug · Salazopyrine

Introduction

Advances in the area of soft computing have resulted in the development of a variety of intelligent systems. The use of computers has highly increased, especially, in the field of medicine such as diagnosis and treatment of illnesses and patient pursuit. Due to the fact that these fields, in which the computers are used, have very high complexity and uncertainty, the use of intelligent systems such as fuzzy logic, artificial neural network and genetic algorithms have been developed. Artificial Intelligence techniques offer the possibility to design such a system that allows building intelligent models for both predicting patients' response in treatment process and determining an adequate drug dose.

Determination of the amount of the drug dose depends on various items such as age, weight, sex, disease history of patients, blood sedimentation and etc. And there is no formulation for determining drug dose according to these items. In many fields of medicine from kidney diseases to diagnosis of cancer, from asthma to determination of dose of medicine, fuzzy logic based approaches have been developed and used.

Recently, the inputs of 200 dialysis patients have been used to develop a fuzzy rule based automation system that determines the dose of the medicine those patients use and the results have been promising. This fuzzy logic-controlled system helps the physician to decide fast and efficiently about the dose of the medicine to be given to the patient considering all the factors. By means of this system medical errors are minimized, possible complications are prevented. What is more the reliability of this method has been proved and accepted in statistical researches (Gawedal et al. 2003, 2007).

Many patients who suffer from the same illness are given different doses of the same medicine due to many factors. Especially, to determine the dose of the medicine to be given to the patients who need a long term medical treatment, some criterions are taken into consideration such as the patient's age, weight, sex and past diseases etc. and these criterions can be used to design fuzzy logic based systems. In such designed systems, when the results are taken and evaluated, the reliability of the fuzzy rule-based system which is designed to determine the dose of medicine is found out to

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be very high. Especially, in cases where there is no formulation about the dose of medicine and there is high complexity and uncertainty, this system can be safely used in relation to the improvement and characteristics of the illness and the criterions mentioned above (Bellazzi and Siviero 1994).

The ability of fuzzy to adapt the parameters of a pharmacokinetic and pharmacodynamic model-based controller for the delivery of the muscle relaxant pancuronium was investigated (Kern et al. 1997). The system uses the model to control the rate of drug delivery and uses feedback from a sensor which measures muscle relaxation level to adapt the model using fuzzy logic (Kern et al. 1997; Kilic et al. 2004).

Fuzzy logic regulation of nicardipine infusion for hypertension control during anesthesia was presented in (Oshita et al. 1994), where it was noted that automated blood pressure controller, which were made possible with fuzzy logic control rules is satisfactory and safe methods of administering nicardipine.

Some studies are devoted to use of artificial neural networks to predict drug dissolution profiles (Per et al. 2000) and to develop adaptive versions of linear, nonlinear and time-dependant models to test data sets collected from hemodialysis patients receiving anti-coagulant heparin during treatment (Lada et al. 1999).

In view of the fact that many of input data sets of medicine parameters are not crisp, we propose that a form of fuzzy logic needs to be adopted. This will help to create a reasoned approach to determine a drug dose that will permit regulatory bodies to set appropriate standards for drugs (new and perhaps old) and assists drug manufacturers in developing a reasoned approach in product development.

Generally, in medical treatments, physicians determine the dose of medicine for a child according to his weight and for an adult according to the prospectus. However, the dose of the medicine to be used by each patient has to be determined regarding to the patient's properties such as background, age, sex, weight and permanent illnesses. Due to the reasons like stressful working conditions and psychological barriers etc. sometimes the physicians cannot give sound decisions which result in the use of wrong doses. Besides because of medicine firms are manufactured drugs in standard grams, often the patients need another dose of drug. For example, a patient needs 367 mg dose of a drug, but this drug is produced in form of packets with 500 mg. Since some drugs are very expensive and big doses are not economical for many patients and there is a need to decrease its dose. By aid of fuzzy approach in many situations, it is possible to predict exact dose of drug.

In the presence of volumes of data collected during therapy within some period of time, it is possible to build intelligent models for both predicting patients' response and determining an adequate drug dose, whish allows for achieving desired drug concentration or drug effect (Kilic et al. 2004; Lada et al. 1999). In this study, a fuzzy expert system is designed to determine the dose of a salazopyrine medicine used in the treatment of chronic intestinal infection—in relation to two criterions, though it can be determined in relation to many criterions.

The remainder of this paper is organized as follows: Sect. "Fuzzy expert system" briefly describes fuzzy expert systems. In Sect. "Material and method" we describe our fuzzy expert system, fuzzification, defuzzification processes, fuzzy rule base and inference mechanism. Finally, in Sect. "Discussion and conclusion" we finish with the discussion, conclusions and future work.

Fuzzy expert system

Fuzzy logic (FL) is a mathematical discipline that we use every day and helps us to reach the structure in which we interpret our own behaviors. Its basis is formed by "true" and "false" values and Fuzzy Set Theory (FST) in which the values between—"partially true", "partially false"—are determined.

FST is a theory that aims to express the uncertainties of life such as "warm" and "cool" which are in between "hot" and "cold" mathematically. And behind these values there is an unclear numerical value. Generally, fuzzy expert systems (FES) are systems based on knowledge or rule. That is, in the basis of a FES lie the "if-then" rules (Zadeh 1965; Nguyen et al. 2003; Baykal and Beyan 2004).

After deciding on designing a fuzzy system the first step to follow is to collect the rules of "if-then". These rules are generally collected with the help of a domain expert (Allahverdi 2002, 2007).

As it is seen in Fig. 1, in FES model the input and output values of the system are crisp values. By fuzzification these

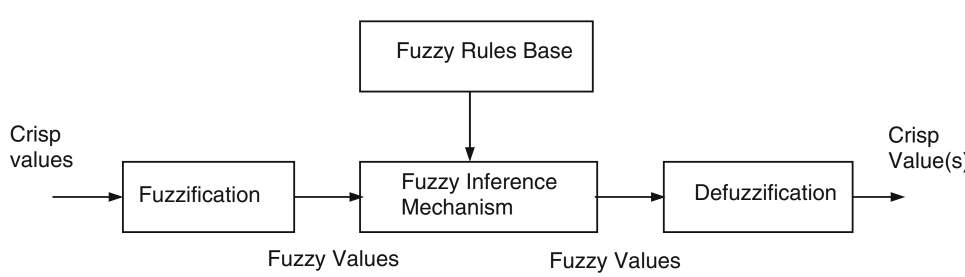

Fig. 1 Fuzzy expert system with fuzzification and defuzzification (Allahverdi 2007)

crisp input values, its fuzzy membership values and degrees are obtained. These obtained fuzzy values are processed in fuzzy inference mechanism. Here, the fuzzy output values which are also obtained by using rule-base are sending to the defuzzification unit, and from this unit the final crisp values are obtained as output (Wang 1997).

Material and method

A lot of drugs are produced by many drug firms for all of the known illnesses. For these drugs, introductory brochures are provided and also the physicians are educated about those medicines. The physicians are also instructed in the usage of the newly produced drugs.

Chronic intestine inflammation is a modern bacteria related lifestyle illnesses, which recently can only be treated by a drastic surgical procedure, if the illness is very severe. Bacterial infections often cause chronic cases that have same clinical characteristics; resisting the host immune defense and cannot be treated efficiently with antibiotics. One needs a determined scientific accomplishment, but also an increase attention from the public. Minimizing and efficient treatment of such infections would also have great significance for the medico-industry. In the case of light chronic intestinal, infection physicians are attempted to treat it by drug salazopyrine and the drug dose is played a great role here.

The dose of medicine to be given to the patient is generally determined according to the prospectus. However, the doses of many medicines show differences due to variables such as age, sex, and the degree of the illness. An expert physician tells the patient the daily dose of medicine she/he has to take. But, because this is not always the exact dose, intelligent software can be very useful with the help of an experienced expert physician's knowledge to determine the exact dose of drugs. So, in order to help the physician to determine the exact dose of salazopyrine to be given to a chronic intestinal infection patient a sample FES is developed (Saritas 2002).

"If-then" fuzzy rules lie in the basis of FES. For example, it is appropriate to reckon the rule in the following paragraph as the rule of fuzzy system for the symptoms of a patient's chronic and for the dose of medicine for treatment:

"If the Prostate Specific Antigen (PSA) is positive and the sedimentation (SD) is higher, then increase the dose of salazopyrine". Here, linguistic values such as positive, high, low or medium positive are used and these linguistic values have appropriate membership values, because the dose of medicine changes with respect to the patient's sex, weight, PSA, sedimentation etc.

Fuzzy theory is used to apply a linguistic controlling strategy dependent on human knowledge in FES and especially in Automatic Control System. While designing fuzzy control systems the fuzzy rules are determined and inputs and outputs of the system are fuzzyfied and then output is clarified (Allahverdi 2002, 2007; Wang 1997).

After deciding on designing a fuzzy system the first step to follow is to produce the rules of "if-then". These rules are generally collected with the help of an expert (Allahverdi 2002, 2007; Ross 1995; Wang 1997).

FES is developed by means of the knowledge provided by physician M. Argindogan from S.U. Campus Medical Care Centre and a modern drug guide. In order to make fuzzification the linguistic expressions below are used.

Input parameters:

PSA: Low, medium and high,
SD: Slow, medium and fast.

Output parameter:

SL: Little, medium, much and much more.

The doses of salazopyrine (SL) (Ommaty 2007) to be given to a patient considering the Prostate Specific Antigen (PSA) and Sedimentation (SD) speed from the symptoms of chronic intestinal infection are shown in linguistic form in Table 1.

For PSA value (let x), that is varied from 0 to for example 50 and more the fuzzy expressions will be as:

$$\mu_{\text{Low}}(x) = \left\{ \begin{array}{ll} \dfrac{4-x}{4}; & 0 \le x \le 4 \\ 0; & \text{others} \end{array} \right\} \tag{1}$$

$$\mu_{\text{Medium}}(x) = \left\{ \begin{array}{ll} \dfrac{4}{x}; & 0 \le x < 4 \\ \dfrac{8-x}{4}; & 4 \le x \le 8 \\ 0; & \text{others} \end{array} \right\} \tag{2}$$

$$\mu_{\text{High}}(x) = \left\{ \begin{array}{ll} 0; & x < 4 \\ \dfrac{x-4}{4}; & 4 \le x \le 8 \\ 1; & 8 \le x \end{array} \right\} \tag{3}$$

Table 1 The linguistic expressions for the doses of salazopyrine (SL) (Saritas 2002)

SD	PSA		
	Low	Medium	High
Slow	Little	Little	Much
Medium	Medium	Medium	Much
Fast	Medium	Much	Much more

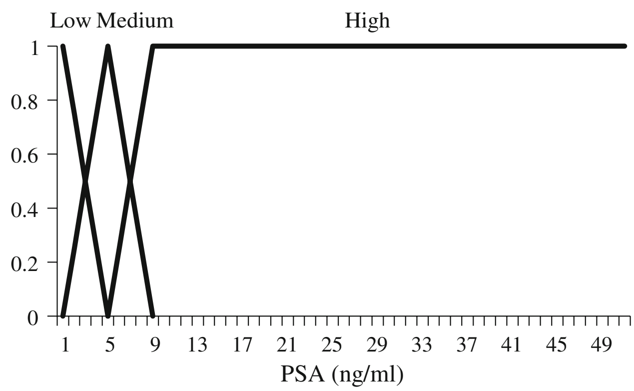

Fig. 2 Membership graphics for three fuzzy values of PSA

Membership graphics for three fuzzy value of PSA are shown in Fig. 2.

The fuzzy sets for PSA are formed according to the formulas (1, 2 and 3):

$$\mu_{\text{Low}}(\text{PSA}) = \{1/0 + 0.75/1 + 0.50/2 + 0.25/3 + 0/4\}$$

$$\mu_{\text{Medium}}(\text{PSA}) = \left\{ \begin{array}{l} 0/0 + 0.25/1 + 0.5/2 + 0.75/3 + 1/4 \\ +0.75/5 + 0.5/6 + 0.25/7 + 0/8 \end{array} \right\}$$

$$\mu_{\text{High}}(\text{PSA}) = \left\{ \begin{array}{l} 0/0 + \cdots + 0/4 + 0.25/5 + 0.50/6 \\ +0.75/7 + 1/8 + \cdots + 1/50 \end{array} \right\}$$

For SD value (let y), that is varied from 0 to for example 90 and more the fuzzy expressions will be as:

$$\mu_{\text{Slow}}(y) = \left\{ \begin{array}{ll} \dfrac{45-y}{45}; & 0 \le y \le 45 \\ 0; & \text{others} \end{array} \right\} \tag{4}$$

$$\mu_{\text{Medium}}(y) = \left\{ \begin{array}{ll} \dfrac{y}{45}; & 0 \le y < 45 \\ \dfrac{90-y}{45}; & 45 \le y \le 90 \\ 0; & \text{others} \end{array} \right\} \tag{5}$$

$$\mu_{\text{Fast}}(y) = \left\{ \begin{array}{ll} \dfrac{y-45}{45}; & 45 \le y \le 90 \\ 0; & \text{others} \end{array} \right\} \tag{6}$$

Membership graphics for three fuzzy values of SD speed are shown in Fig. 3.

The fuzzy sets for SD are formed according to the formulas (4, 5 and 6):

$$\mu_{\text{Slow}}(\text{SD}) = \left\{ \begin{array}{l} 1/0 + 0.89/5 + 0.78/10 + \cdots + 0.22/35 \\ +0.11/40 + 0/45 \end{array} \right\}$$

$$\mu_{\text{Medium}}(\text{SD}) = \left\{ \begin{array}{l} 0/0 + 0.3/15 + 0.7/30 + 1/45 \\ +0.7/60 + 0.3/75 + 1/90 \end{array} \right\}$$

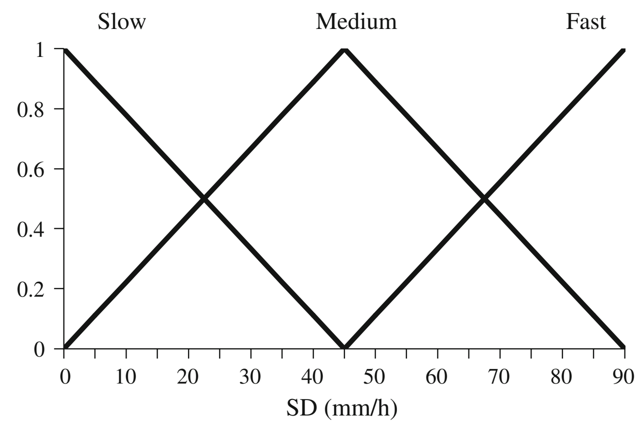

Fig. 3 Membership graphics for fuzzy values of SD

$$\mu_{\text{Fast}}(\text{SD}) = \{0/45 + 0.3/60 + 0.7/75 + 1/90\}$$

For SL value (let z) that is varied from 0 to for example 1600 and more the fuzzy expressions will be as:

$$\mu_{\text{Little}}(z) = \left\{ \begin{array}{ll} 1; & z \le 200 \\ \dfrac{600-z}{400}; & 200 < z \le 600 \\ 0; & \text{others} \end{array} \right\} \tag{7}$$

$$\mu_{\text{Medium}}(z) = \left\{ \begin{array}{ll} \dfrac{z-200}{400}; & 200 \le z \le 600 \\ \dfrac{1000-z}{400}; & 600 < z \le 1000 \\ 0; & \text{others} \end{array} \right\} \tag{8}$$

$$\mu_{\text{Much}}(z) = \left\{ \begin{array}{ll} \dfrac{z-600}{400}; & 600 \le z \le 1000 \\ \dfrac{1400-z}{400}; & 1000 < z \le 1400 \\ 0; & \text{others} \end{array} \right\} \tag{9}$$

$$\mu_{\text{Much more}}(z) = \left\{ \begin{array}{ll} \dfrac{z-1000}{400}; & 1000 \le z \le 1400 \\ 1; & 1400 < z \\ 0; & \text{others} \end{array} \right\} \tag{10}$$

Membership graphics for four fuzzy value of SL are shown in Fig. 4.

The fuzzy sets for SL are formed according to the formulas (7, 8, 9 and 10):

$$\mu_{\text{Little}}(\text{SL}) = \left\{ \begin{array}{l} 1/0 + 1/200 + 0.8/300 + 0.5/400 \\ +0.3/500 + 0/600 \end{array} \right\}$$

$$\mu_{\text{Medium}}(\text{SL}) = \left\{ \begin{array}{l} 0/200 + 0.25/300 + 0.5/400 \\ +1/600 + 0.5/800 + 0.5/9000 \\ +0/1000 \end{array} \right\}$$

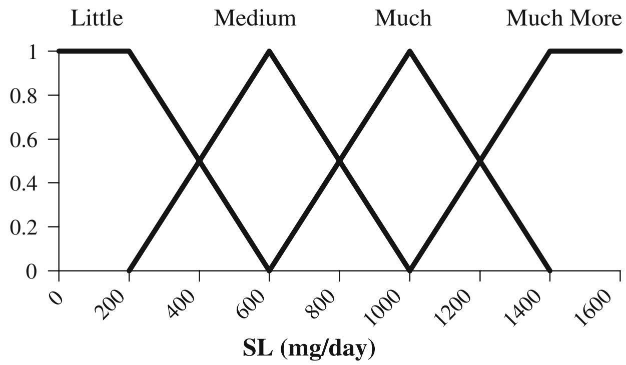

Fig. 4 Membership graphics for fuzzy values of SL

$$\mu_{\text{Much}}(\text{SL}) = \left\{ \begin{array}{l} 0/600 + 0.25/700 + 0.5/800 \\ +1/1000 + 0.5/1200 + 0.25/1300 \\ +0/1400 \end{array} \right\}$$

$$\mu_{\text{Much more}}(\text{SL}) = \left\{ \begin{array}{l} 0/1000 + 0.25/1100 \\ +0.5/1200 + 0.75/1300 \\ +1/1400 + 1/1500 \end{array} \right\}$$

The general structure of the developed FES is shown in Fig. 5 (Saritas 2002).

According to Table 1 nine fuzzy rules, some of which are given below, are formed and for each rule the validity value is found out (Saritas 2002).

Rule 1: If PSA is low and SD is slow then SL is little.
Rule 2: If PSA is low and SD is medium then SL is medium.
…
Rule 8: If PSA is high and SD is medium then SL is much.
Rule 9: If PSA is high and SD is fast then SL is much more.

As the output mechanism Mamdani approach is used. The validity degrees **(α)** for each rule according to Mamdani max-min rule are shown with the formulas below.

$$\alpha_1 = \min(\text{Low}(x), \text{Slow}(y))$$
$$\alpha_2 = \min(\text{Low}(x), \text{Medium}(y))$$
$$\ldots$$
$$\alpha_8 = \min(\text{High}(x), \text{Medium}(y))$$
$$\alpha_9 = \min(\text{High}(x), \text{Fast}(y))$$

The maximum of the validity degrees of the triggered rules are calculated with the formulas below.

$$\alpha_{1,2\ldots n} = \max(\alpha_1, \alpha_2, \ldots \alpha_n)$$

In the defuzzification process, the exact expression is obtained with "centroid" method according to a validity degree.

The output value (daily dose of salazopyrine is found as 661 mg) with respect to the input values (PSA is 3 ng/ml and Sedimentation is 50 mm/h) obtained from the designed FES is shown as an example in Fig. 6, whereas the physician will possible recommend to the patient daily two tablets where each of them would be 500 mg (see also Table 2).

As materials, the data collected from the 10 patients from Selçuk University Campus Medical Care Centre, Matlab Fuzzy Logic Toolbox software and P4 3.0 GHz PC (Properties of PC: 120 GB-7200 rpm HDD and 1024 MB memory) are used.

Discussion and conclusion

Determination of the dose of medicine is complex and uncertain process because many variables such as the patient's age, sex, weight, height, the degree of the illness, the amount of medicine in blood are all considered for the treatment. Developed FES, even in the case of inadequate data, gives valid or almost valid results.

In this study, FES is designed to help the expert physicians to determine the dose of medicine to be given to the patients of chronic intestinal infection. Results showed that proposed FES can be used to determine the dose of medicine, which is a complex and uncertain issue, and can get good results.

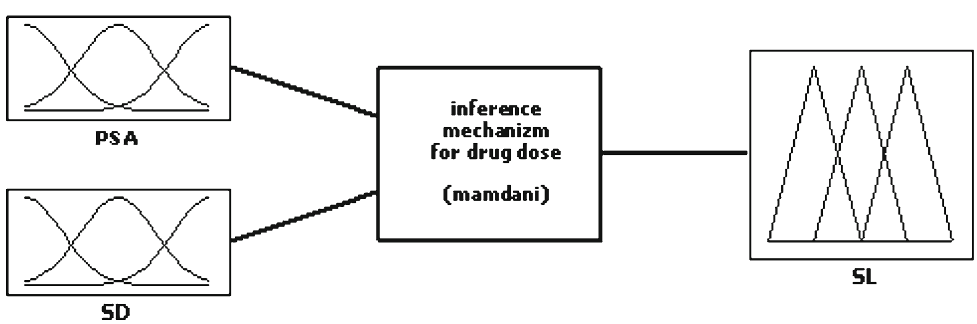

Fig. 5 The general structure of the FES developed

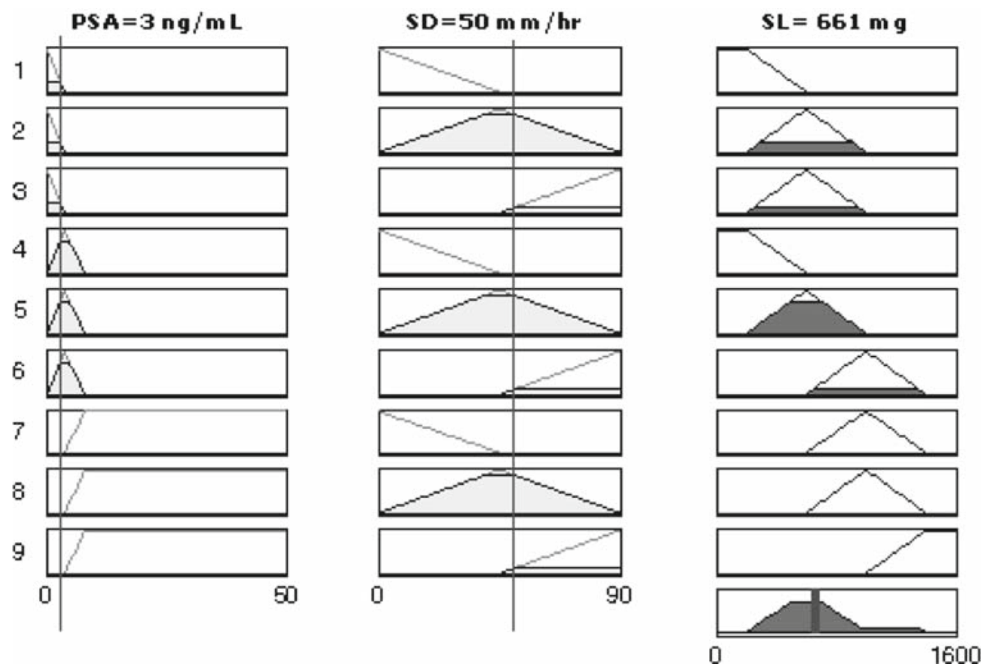

Fig. 6 The SL dose obtained according to the obtained PSA and SD

Table 2 The SL doses obtained with the data given by the expert physician (Saritas 2002)

Patient	Input variables		Output variable (SL mg)	
	PSA (ng/ml)	SD (mm/h)	Daily dose recommended by the physician	Daily dose obtained from FES
1	0,4	10	500 (1 × 1)	334
2*	1	20	500 (1 × 1)	427
3	2	25	500 (1 × 1)	461
4*	2	70	1000 (2 × 1)	800
5	3	50	1000 (2 × 1)	661
6*	5	50	1000 (2 × 1)	755
7*	7	80	1500 (3 × 1)	1120
8*	8	25	1500 (3 × 1)	1000
9	8	75	1500 (3 × 1)	1220
10	15	90	1500 (3 × 1)	1390

Note: (3 × 1) etc. is daily tablet of drug

This FES can be taken as a sample to develop new FESs for the treatment of other illnesses.

As shown in the Table 2, 10 patients with chronic intestinal infection are chosen randomly to test the developed method. We must note that to find the patients with the light chronic intestinal illness is very difficult. We classified these patients into two groups. The first group (five patients which are denoted by *) have received daily dose of SL, recommended by the physician and the second group (another five patients) have received daily dose of SL, obtained from our FES. In result of this treatment the first group recoveries were very slow and took about a year. But the second group of patients which have been received the daily dose recommended by FES, recovery duration were shorted to almost 3 months.

As seen in the graphs in Figs. 7 and 8 it is verified that developed FES can be used to determine the daily dose of medicine to be taken more accurately regarding to PSA and SD. In many cases, the dose of the medicine recommended by developed FES is lower than dose of physician suggestion. So, this system prevents the patients from taking the wrong dose, thus, help them to recover quicker and be exposed to minimum side effects. In the chronic intestinal infection disease treatment patient's accepting of salazopyrine takes a long time that's why this system prevents wasting of medicine.

As a result, it is seen that generally FESs can be used and applied in complex and uncertain fields such as the treatment of illnesses; determining the exact dose of medicine and evaluation of clinic and laboratory data.

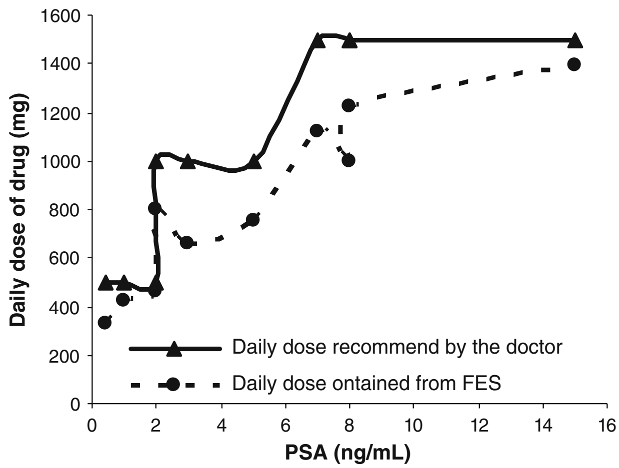

Fig. 7 The dose of medicine recommended by the physician and obtained from FES regarding to PSA

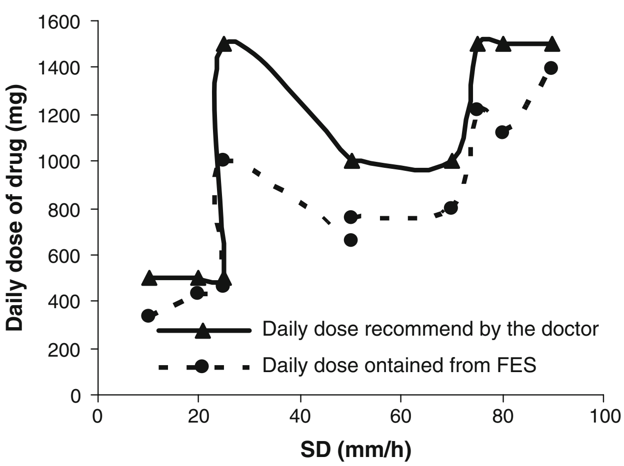

Fig. 8 Daily dose of medicine recommended by the physician and obtained from FES regarding to SD

What is more, since the results are obtained by entering the patient data into the developed FES without giving any harm to the patient and are evaluated by the experienced physicians, they can be used to instruct medicine students in a fast and reliable way with minimum cost. Drug dose related to both SD and PSA can be seen in Fig. 9.

In similar systems to be developed in the future, if the number of input parameters and linguistic variables are increased, better results can be obtained.

This study also gives an idea how to determine dose of drug produced by medicine firms. Generally, because of economical reasons, the firms like to produce drugs with high efficiency. In reality, this study shows that producing of various doses of drugs is more efficient for the patients.

Moreover, drug doses given to the patient in the intensive care, is very important. For this reason this study has ability to be used in the different diseases for determination of the drug dose, and better results could be obtained in the treatment.

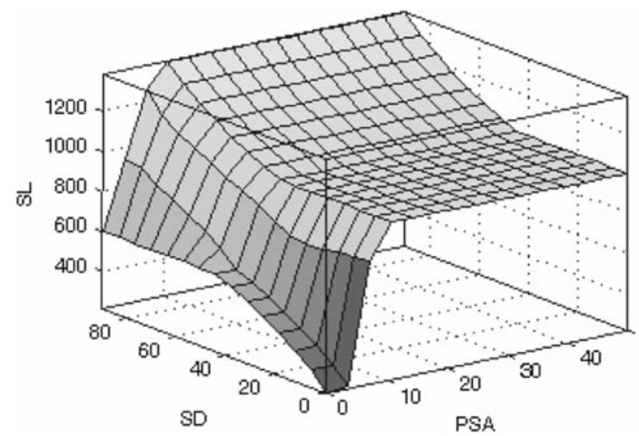

Fig. 9 The change in the dose of medicine regarding to PSA and SD

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