An Example of Determination of Medicine Dose in the Treatment by Fuzzy Method

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Abstract: *Often unwanted results are occurred in situations such as long drug treatment durations, for the treatments at which the drug doses are important and for the cases where observation of results of drug interactivity on the blood are required. As a result of wrong decision having done by the physicians, low or high dose drug treatment may result in longer treatment time and complications may occur.*

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 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 minimize or remove the negative effects of determination of drug dose for helping physicians.

Keywords: *Chronic Intestine Inflammation, Fuzzy Expert System, Dose of Drug*

INTRODUCTION

The standard of life has increased due to the introduction of computer technology into almost every field in our daily lives. The use of computers has highly increased, especially, in the field of medicine; in fields 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 algorithm has been developed.

Determination of the amount of the drug dose depends on various items such as old, 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 amount 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 doctor to give fast and efficient decisions 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 [1].

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 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 [2].

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 [12]. 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 [12, 13].

In view of the fact that input data sets of medicine parameters that 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, doctors 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 doctors cannot give sound decisions which result in the use of wrong doses.

In this study, a fuzzy expert system is designed to determine the dose of a salazopyrin medicine used in the treatment of chronic intestinal infection - in relation to two criterions, though it can be determined in relation to many criterions.

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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) through which the values in 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 [3, 4, 5].

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 an expert [6, 7].

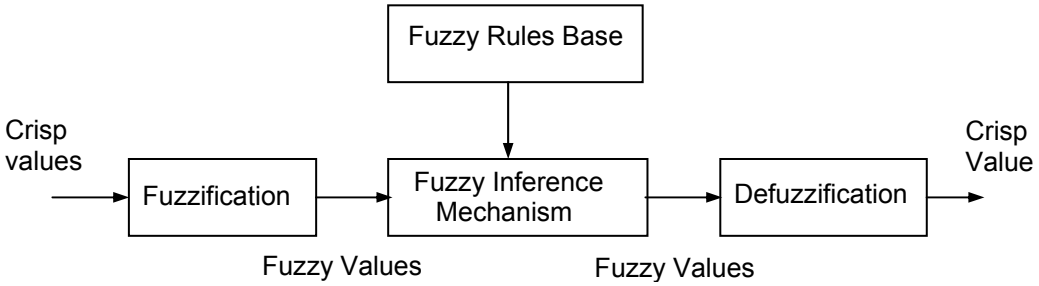

Figure 1 Fuzzy Expert System with Fuzzification and Defuzzyfication [6]

As it is seen in Figure 1, in Fuzzy expert System model the input and output values of the system are crisp values. By fuzzification these 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 using rule-base are send to the defuzzification unit, and from the this unit the final crisp values are obtained as output [8].

MATERIAL AND METHOD

As materials, the data collected from the 10 patients from Selcuk University Campus Medical Care Centre, Matlab Fuzzy Logic Toolbox software, 120 GB Hdd 64

MB Screencard memory and a PC with P4 1.9 GHz processor and 512 MB memory are used.

"If-then" rules lie in the basis of Fuzzy Expert System. For example, it is appropriate reckon the below rule for the symptoms of a patient's chronic intestinal infection and for the dose of medicine for treatment as the rule of Fuzzy system:

"If the Prostate Specific Antigen (PSA) is positive and the sedimentation (SD) is higher, then increase the dose of salazopyrin". 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 in relation to the patient's sex, weight, Prostate Specific Antigen, 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 of target and data base are determined and they are fuzzyfied or clarified [6, 7, 8].

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 an expert [6, 7, 8, 9].

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 doctors are educated about those medicines. The doctors are also instructed in the usage of the newly produced drugs.

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 doctor tells the patient the daily dose of medicine she/he has to take. But, this is not always the exact dose an intelligent software can be very useful with the help of an experienced expert doctor's knowledge. So, in order to help the doctor to determine the exact dose of salazopyrin to be given to a patient of chronic intestinal infection a sample, a FES is developed [10].

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

Input parameters : PSA: Low, medium and high,
: SD: Slow medium and fast.
Output parameters : SL: Little, medium, much and much more.

The doses of salazopyrin (SL) to be given to a patient considering the Prostate Specific Antigen (PSA) and Sedimentation (SD) from the symptoms of chronic intestinal infection are shown linguistically in Table 1.

Table 1 The linguistic expressions for the doses of salazopyrine (SL) [10]

		PSA		
		Low	Medium	High
SD	Slow	little	Little	much
	Medium	medium	Medium	much
	Fast	medium	Much	much more

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

$$\mu_{(x)_{LOW}} = \begin{cases} (4-x)/4; & 0 \le x \le 4 \\ 0; & others \end{cases}$$

$$\mu_{(x)_{MEDIUM}} = \begin{Bmatrix} (x/4); & 0 \le x \le 4 \\ (8-x)/4; & 4 < x \le 8 \\ 0; & others \end{Bmatrix} \qquad (1)$$

$$\mu_{(x)_{HIGH}} = \begin{Bmatrix} 0; & x < 4 \\ (x-4)/4; & 4 < x \le 8 \\ 1; & x \ge 8 \end{Bmatrix}$$

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

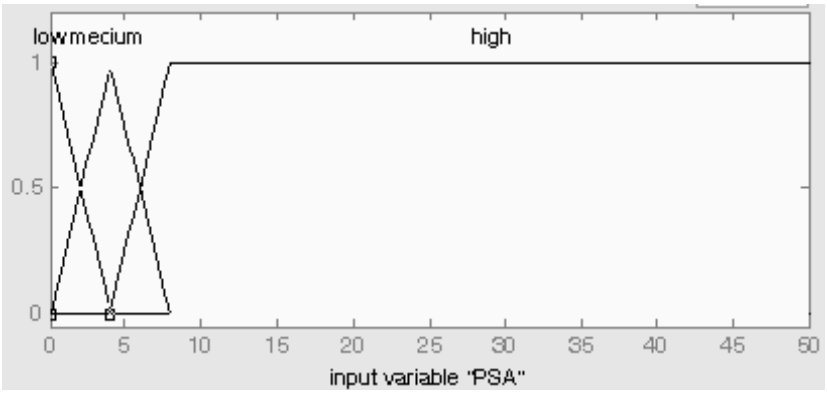

Figure 2 Membership graphics for three fuzzy values of PSA

The fuzzy sets for PSA are formed according to the formulas (1):

$$\mu_{Low}(PSA) = \{1/0 + 0{,}75/1 + 0{,}50/2 + 0{,}25/3 + 0/4\}$$

$$\mu_{Medium}(PSA) = \{0/0 + 0{,}25/1 + 0{,}5/2 + 0{,}75/3 + 1/4 + 0{,}75/5 + 0{,}50/6 + 0{,}25/7 + 0/8\}$$

$$\mu_{High}(PSA) = \{0/0 + \ldots + 0/4 + 0{,}25/5 + 0{,}50/6 + 0{,}75/7 + 1/8 + \ldots + 1/50\}$$

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

$$\mu_{(y)_{SLOW}} = \begin{Bmatrix} (45-y)/45; & 0 \le y \le 45 \\ 0; & others \end{Bmatrix}$$

$$\mu_{(y)_{MEDIUM}} = \begin{Bmatrix} (y/45); & 0 \le y < 45 \\ (90-y)/45; & 45 \le y \le 90 \\ 0; & others \end{Bmatrix} \qquad (2)$$

$$\mu_{(y)_{FAST}} = \begin{Bmatrix} (y-45)/45; & 45 \le y \le 90 \\ 0; & others \end{Bmatrix}$$

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

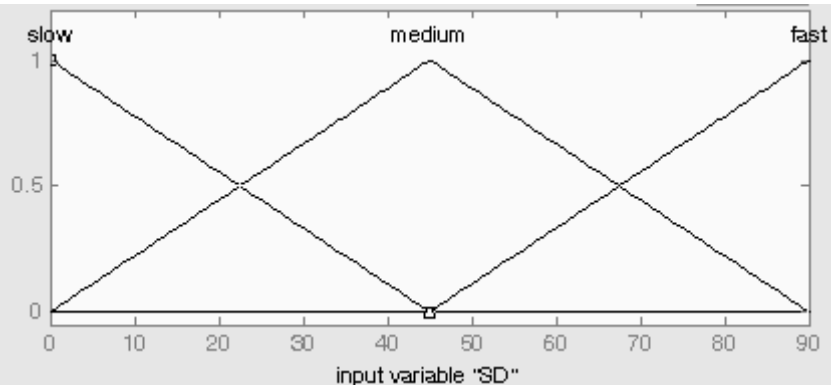

Figure 3 Membership graphics for three fuzzy values of SD

The fuzzy sets for SD are formed according to the formulas (2):

$$\mu_{Slow}(SD) = \{1/0 + 0.89/5 + 0.78/10 + .. + 0.22/35 + 0.11/40 + 0/45\}$$

$$\mu_{Medium}(SD) = \{0/0 + 0.3/15 + 0.7/30 + 1/45 + 0.7/60 + 0.3/75 + 1/90\}$$

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

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

$$\mu_{(z)_{LITTLE}} = \begin{cases} 1; & z \le 200 \\ (600 - z)/400; & 200 < z \le 600 \\ 0; & others \end{cases}$$

$$\mu_{(z)_{MEDIUM}} = \begin{cases} (z - 200)/400; & 200 \le z \le 600 \\ (1000 - z)/400; & 600 < z \le 1000 \\ 0; & others \end{cases}$$

(3)

$$\mu_{(z)_{MUCH}} = \begin{cases} (z - 600)/400; & 600 \le z \le 1000 \\ (1400 - z)/400; & 1000 < z \le 1400 \\ 0; & others \end{cases}$$

$$\mu_{(z)_{MUCH\_MORE}} = \begin{cases} (z - 1000)/400; & 1000 \le z \le 1400 \\ 1; & 1400 < z \\ 0; & others \end{cases}$$

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

The fuzzy sets for SL are formed according to the formulas (3):

$$\mu_{Little}(SL) = \{1/0 + 1/200 + 0.8/300 + 0{,}5/400 + 0{,}3/500 + 0/600\}$$

$$\mu_{Medium}(SL) = \{0/200 + 0{,}25/300 + 0{,}5/400 + 1/600 + 0{,}5/800 + 0{,}5/9000 + 0/1000\}$$
$$\mu_{Much}(SL) = \{0/600 + 0{,}25/700 + 0{,}5/800 + 1/1000 + 0{,}5/1200 + 0{,}25/1300 + 0/1400\}$$
$$\mu_{Much\_more}(SL) = \{0/1000 + 0{,}25/1100 + 0{,}5/1200 + 0{,}75/1300 + 1/1400 + 1/1500\}$$

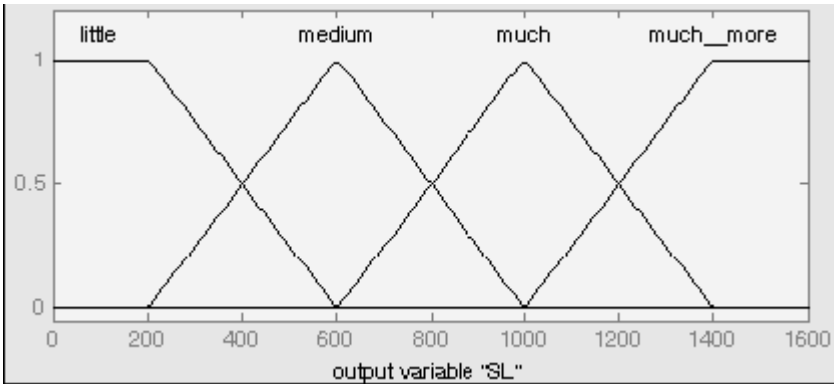

Figure 4 Membership graphics for four fuzzy values of SL

The general structure of the FES developed is shown in Figure 5 [10].

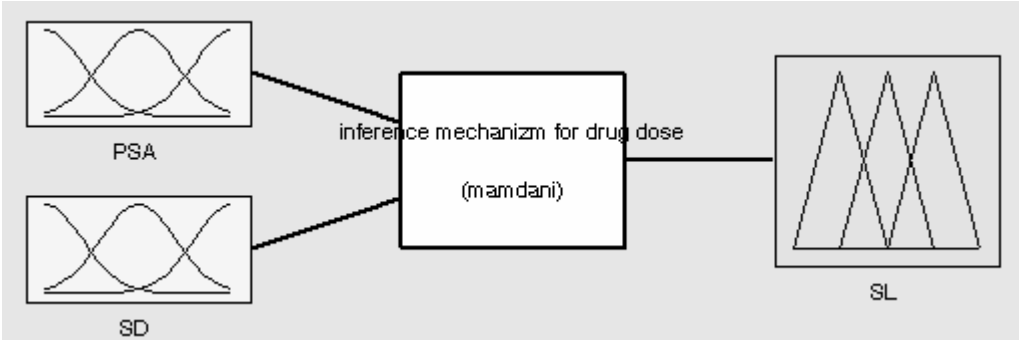

Figure 5 The general structure of the FES developed

According to Table 1 nine Fuzzy rules, some which are given below, are formed and for each rule the validity value is found out [10].

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.

α_1= min (low(x), slow(y))
α_2= min (low(x), medium(y))
…
α_8= min (high(x), medium(y))
α_9= min (high(x), 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 the exact expression is obtained with “centroid” method according to validity degree.

The output value according to the input values obtained from the designed FES is shown as an example in Figure 6.

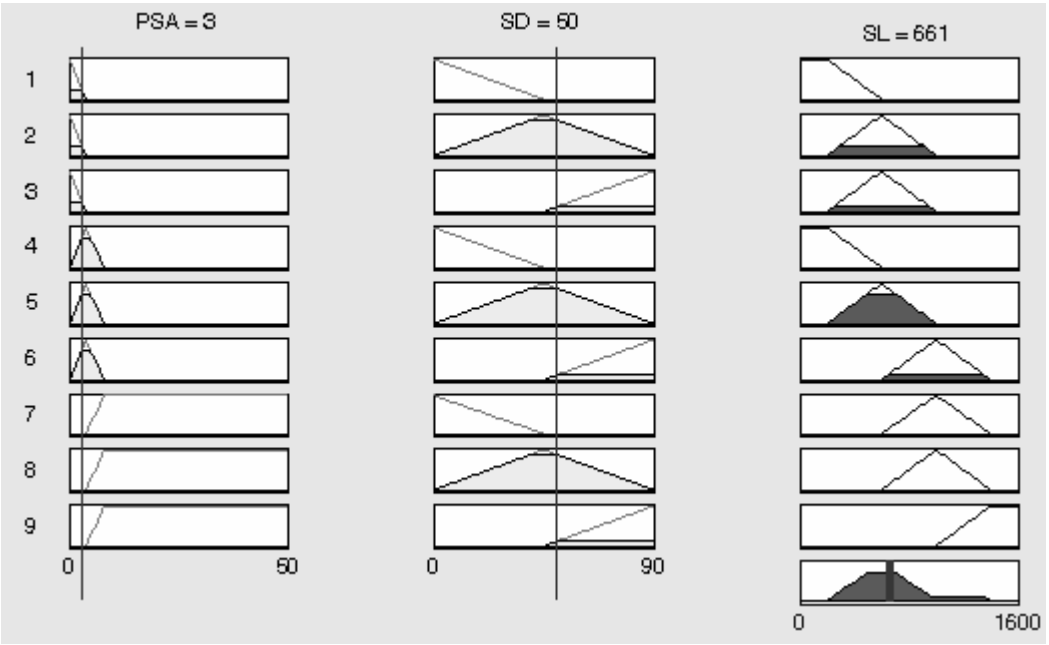

Figure 6 The SL dose obtained according to the obtained PSA and SD.

CONCLUSION

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

In this study, FES is designed to help the expert doctors to determine the dose of medicine to be given to the patients of chronic intestinal infection. Results showed that Fuzzy Expert Systems can be used to determine the dose of medicine, which is a complex and uncertain issue, and can get good results. This FES can be taken as a sample to develop new FES’s 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 chronic intestinal illness are very difficult. We classified these patients into two groups. The first group (5 patients which are denoted by *) have received daily dose of SL, recommended by the doctor and the second group (another 5 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 three months.

As seen in the graphs in Figures 7, 8 and 9, it is verified that FES can be used to determine the daily dose of medicine to be taken more acurately in ragarding to PSA and SD. This system prevents the patients from taking the wrong dose, thus,

help them to recover quicker and be exposed to minimum side effects. This system also prevents waste of medicine.

Table 2 The SL doses obtained with the data given by the expert doctor [10].

Patient	Input Variables		Output Variable (SL mg)	
	PSA (ng/ml)	SD (ms)	Daily dose recommended by the doctor	Daily dose obtained from FES
1	0,4	10	500 (1x1)	334
2*	1	20	500 (1x1)	427
3	2	25	500 (1x1)	461
4*	2	70	1000 (2x1)	800
5	3	50	1000 (2x1)	661
6*	5	50	1000 (2x1)	755
7*	7	80	1500 (3x1)	1120
8*	8	25	1500 (3x1)	1000
9	8	75	1500(3x1)	1220
10	15	90	1500 (3x1)	1390

As a result, it is seen that FES's 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.

What is more, since the results are obtained by entering the patient data into the FES input parameters without giving any harm to the patient and evaluated by the experienced expert doctors, they can be used to instruct medicine students in a fast fast and reliable way with minimum cost.

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

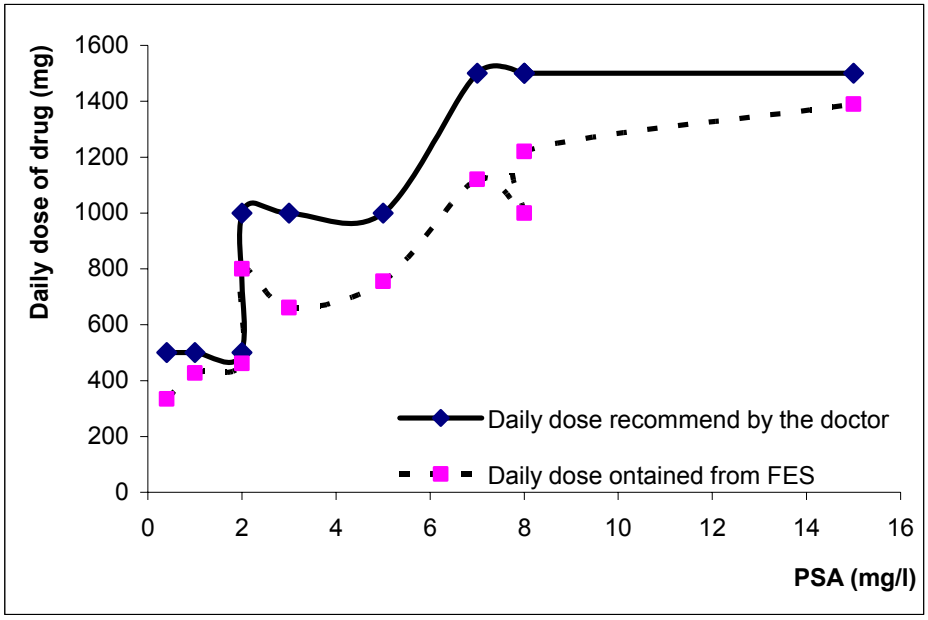

Figure 7 the dose of medicine recommended by the doctor and obtained from FES regarding to PSA

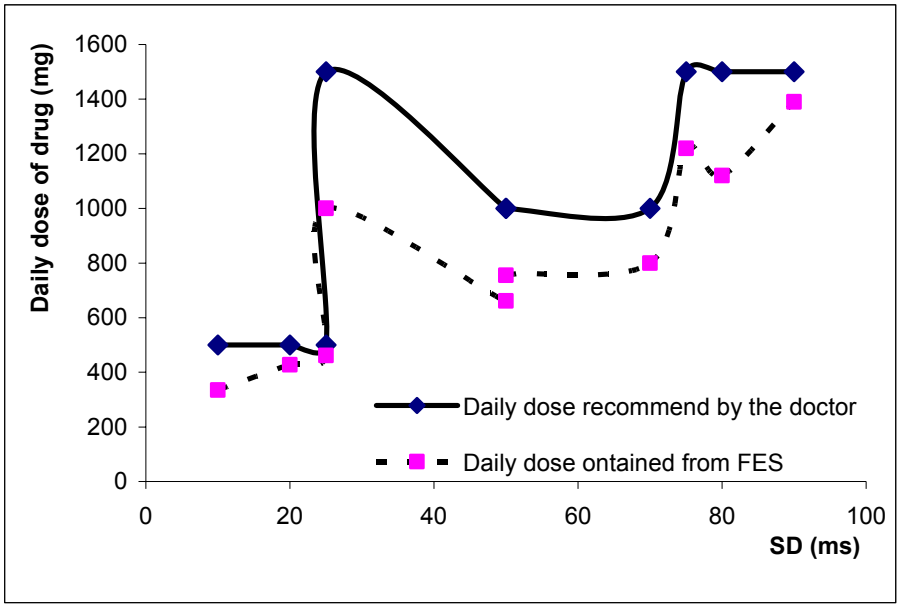

Figure 8 Daily dose of medicine recommended by the doctor and obtained from FES regarding to SD

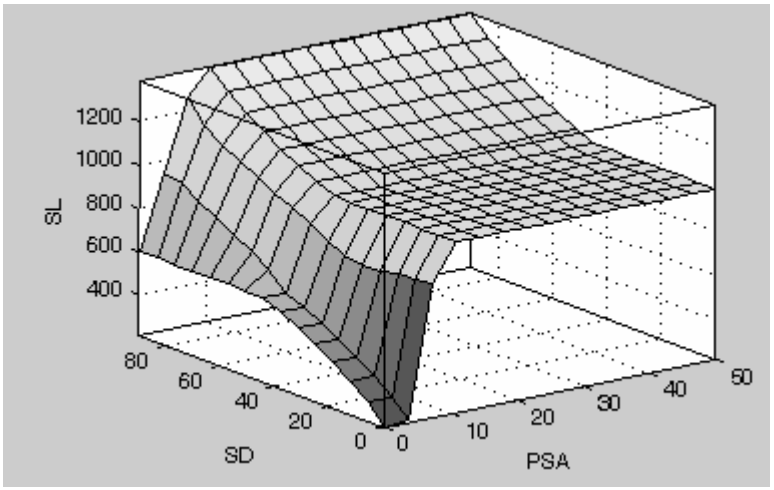

Figure 9 The change in the dose of medicine regarding to PSA and SD

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 have ability to be used in the different diseases for determination of the drug dose, and more results could be obtained in the treatment.

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REFERENCES

[1] Adam E. Gawedal, Alfred A. Jacobs, Michael E. Brierl, Fuzzy Rule-based Approach to Automatic Drug Dosing in Renal Failure, The IEEE International Conference on Fuzzy Systems, 2003.

[2] R Bellazzi and C Siviero, Predictive Fuzzy Controllers for Drug Delivery, Universita di Pavia, Italy, "Intelligent Systems Engineering", 5-9 September 1994.

[3] Geocities, http://www.geocities.com/memoada/arastirma/flc/, 25 Nisan 2003.

[4] Zadeh LA., Fuzzy Sets, Information and Control, 3: pp.338-353, 1965.

[5] BUMAT, Bulanık mantık ve bulanık sistemler, www.bumat.itu.edu.tr/ dokuman_BULANIK_KUMELER.doc, Haziran 2003.

[6] Allahverdi N., Bulanık mantık ve sistemler. http://farabi.selcuk.edu.tr/ egitim/bulanik/index.html, Haziran 30, 2005.

[7] Allahverdi N., Uzman Sistemler, Bir Yapay Zeka Uygulamasi, Atlas Yayınevi, Istanbul, 248 s., 2002.

[8] Wang L., A course in fuzzy systems and control. Pearson Education POD, 1st Education (January 1997), 424 p., 1997.

[9] Ross, T.J., Fuzzy logic with engineering applications, McGraw-Hill, 1995.

[10] Saritas I., Fuzzy Control in Medicine Field, Master thesis, Selçuk University, Konya, 2002.

[11] Vademecum, Istanbul, 1999.

[12] Kern S.E., Johnson J.O., Westenskow D.R., Fuzzy logic for model adaptation of a pharmacokinetic-based closed loop delivery system for pancuronium, Artificial Intelligence in Medicine, Volume 11, Number 1, September, pp 9-31, 1997.

[13] Kilic K., Sproule B.A., Türksen I.B., Naranjo C.A., Pharmacokinetic application of fuzzy structure identification and reasoning, Inf. Sci., 162 (2): pp.121-137, 2004.

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