Application of Soft Computing Method to Parkinson’s Disease Therapy

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ABSTRACT: The paper presents application of the fuzzy logic and neural networks to L-dopa dosing in the Parkinson's disease pharmacotherapy. On the basis of a multi-annual experience base of rules was worked out. Three factors (hypokinesia, rigidity and tremor) or four factors (hypokinesia, rigidity, tremor and postural disorders) were taken as the disease symptoms and a five-degree fuzzy scale was employed. The examinations were conducted on the sample of 51 patients for whom doctor determined L-dopa dose depending on the degree of neurological symptoms. Fuzzy Logic reasoning was considered on the basis of the base of rules that was determined by expert neurologist who generated it automatically. Learning of the neural network was carried out with patients’ data. Verification of the method was carried out by the comparison of doses prescribed by doctor and obtained from the computer program.

KEYWORDS: Parkinson's pharmacotherapy, L-dopa, Fuzzy Logic, Neural Networks

1. INTRODUCTION

Parkinson’s disease is one of the most frequent degenerative diseases of the central nervous system with unknown etiology. The key factor triggering the disease is the lack of dopamine in the strionigral system. The deficit of dopamine is caused by the loss of neurones and their gradual degeneration. As a result of that loss the supply of dopamine to striatum is markedly reduced. In the treatment of Parkinson’s disease the missing amount of dopamine in the central nervous system is supplied. dopamine is administered orally in the form of L-dopa. For nearly 30 years L-dopa has been the most effective medication in treating parkinsonism. However, prolonged taking of L-dopa may result in some side effects. Therefore it is impossible to create an optimal scheme of treatment. In each individual case setting a dose for a particular patient depends on the experience of the physician providing the treatment.

The out-patients’ clinic specialising in degenerative diseases at the Medical Academy of Szczecin has carried out examinations of about 100 patients suffering from Parkinson’s disease. The patients with diagnosed parkinsonism were prescribed L-dopa doses on the basis of the following symptoms: slowing of- movement (hypokinesis), increased muscle tension (rigiditas), tremor, and disorders of the body posture. The above mentioned symptoms of Parkinson’s disease were used for setting up a data base created by expert neurologists.

When the data base was analysed, it turned out that patients with very similar symptoms were administered different doses of medication. This practice was not always compatible with the logical rules of medical treatment as described in the data base.

For this reason, all the patients who undergo the treatment are screened after the first 3 and 6 months in order to measure out the optimal dose of L-dopa. This medical procedure will enable us to create in the future software using fuzzy logic an advisory system for administrating L-dopa to Parkinson’s disease patients.

The first clinical tests proved that this set of algorithms which creates the automatic base of rules is highly effective in medical practice. The data base is meant to help doctors in measuring out the correct and most effective doses of L-dopa in treating Parkinson’s disease patients.

2. FUZZY LOGIC. METHODOLOGY OF DRUG DOSAGE SELECTION IN PARKINSON'S DISEASE

We use two methods of fuzzy logic measuring out doses of :

- of the base of rules that was determined by expert (doctors),
- of the base of rules generated automatically.

2.1. CONSTRUCTION OF THE BASE OF RULES DETERMINED BY EXPERT

On the base of a multi annual experience by expert neurologist was desined three symptoms by the following Parkinson,s disease:

1. Slowing of movements (hypokinesia)
2. Incrised muscule tension(rigidity)
3. Tremor.

The pharmacological treatment should be individually selected, depending on the intensification of the disease symptoms. There is, however, a certain relationship: the less intense symptoms the smaller, in general, dose and vice versa, i.e. more intense symptoms - a greater dose of drug. Nevertheless, there are no fixed schemes in establishing drug doses. Many times, at more intense symptoms, a smaller drug dose has therapeutic effect and vice versa. On the basis of medical experience the indicatory scheme of the L-dopa doses are administered to the patients, depending on the symptoms.

The above symptoms selected based on multi annual experience in curing patients at Clinical of Neurology Pommeranian Medical Academy, were used as a basis for developing a rule base which is shown in Fig. 1 and which has been formulated by the expert -neurologist, Honczarenko (1998).

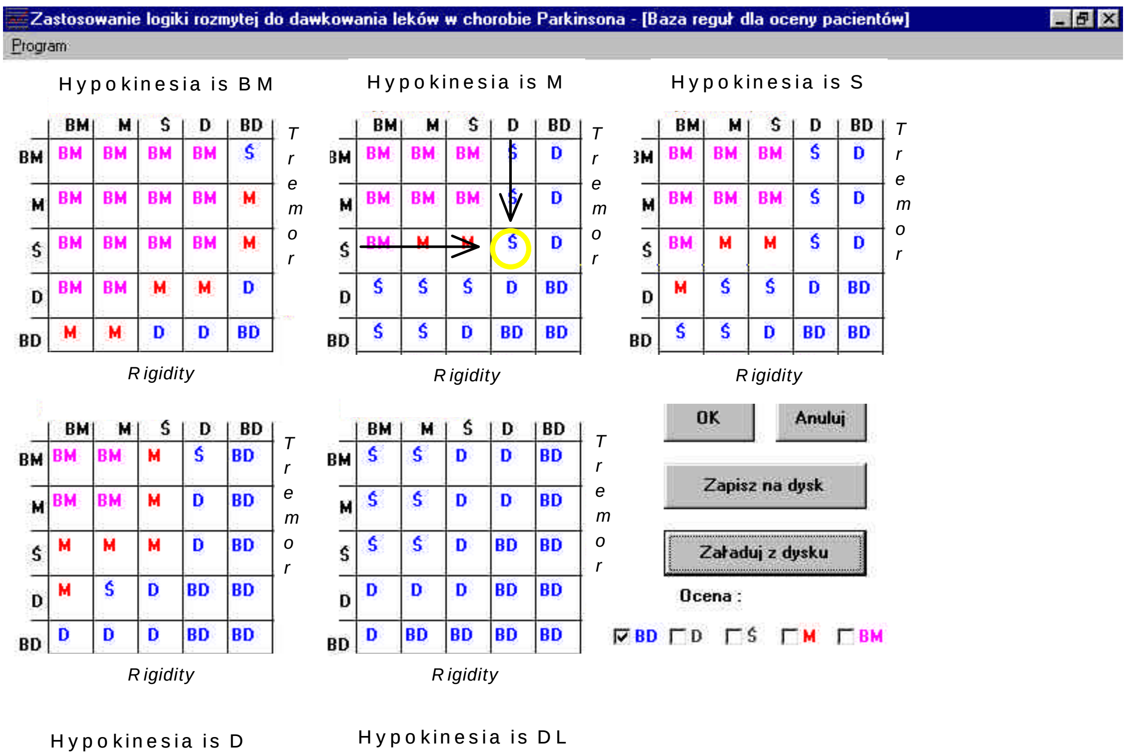

Figure 1: Rule base - a screen display view. Symptoms: BM-very faint, M-faint, Œ-distinct, D-acute,DL-very acute.

This system was built on the basis of the computer program DataEngine which is used for modeling of Fuzzy-Logic systems.

2.2. CONSTRUCTION OF THE BASE OF RULES GENERATED AUTOMATICALLY

During construction of FLC controller there are two main problems the determination of linguistic values and the assigning to the membership functions and to formulation of the base of rules of the fuzzy reasoning control Kiendl (1989), Krabs (1995). In the case of control of the base using expert neurologist knowledge is a difficult task. It is difficult to define linguistic rules. When the data base was analysed, it turned out that patients with very similar symptoms were administered different doses of medication.
Automatically generated decisive rules base can be used by the system to fuzzy FLC reasoning in the self-learning mode of the machining system. In the case of appearance of conflicting production orders FLC system ranks them in the function of time and determines detailed work schedule [6].
Algorithm of designing of the linguistic rule base on the basis of numerical data is based on the Fuzzy-Rosa method Kiendl (1989). It considers such elements as searching linguistic space, generalization of the set of conditions of rules, method of reduction of rules and analysis and automatic assessment of generated rules. Algorithm of automatic generation of the set of linguistic rules on the basis of learning data is presented in fig. 2. Learning data necessary for the generation of rules consists of relations sets of the form:

$$[\, x_1(i) \,,\, x_2(i) \,,\, \ldots\, x_n(i) \,;\, d\,(i)\,] \qquad i = 1\,,\,2\,,\,\ldots \qquad .(1)$$

where $x_1(i)$, $x_2(i)$, ... $x_n(i)$ are input data, d(i) given value of output variable.

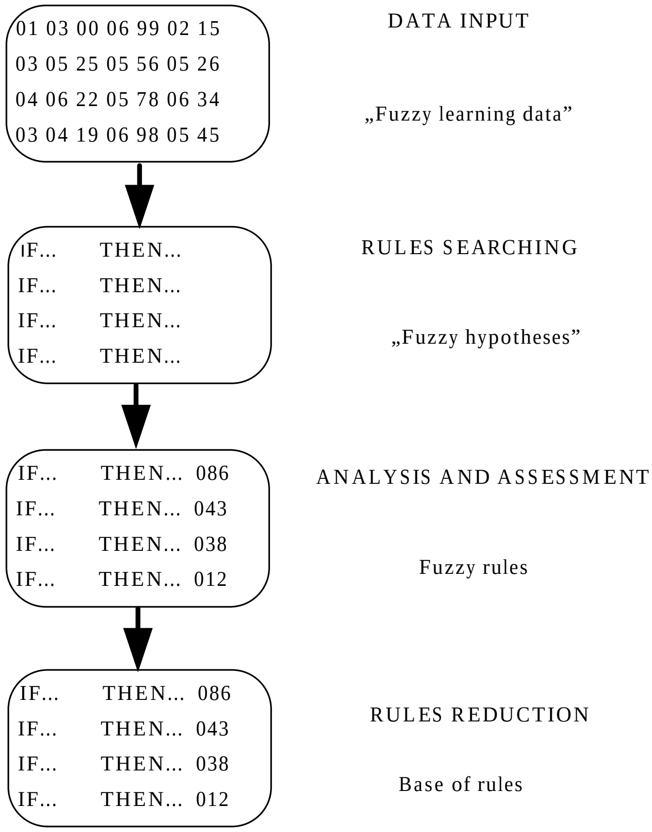

Figure 2: Algorithm of automatic generation of the set of linguistic rules.

Construction of the base of fuzzy rules was conducted for a system for which set of learning data was obtained from the experts. Following input linguistic data was defined for the above mentione three or four symptoms.
Using generated linguistic decisive rules a system of fuzzy reasoning was built. It allows assesing the importance of the particular production orders. This system was built on the basis of a computer program Data Engine which is used for modeling of Fuzzy-Logic systems. Series of sample numerical experiments, that verified of the correctness of the membership function, selection of fuzzy system, into account reasoning was conducted. View of the computer screen during conducted examinations is shown in fig. 3.

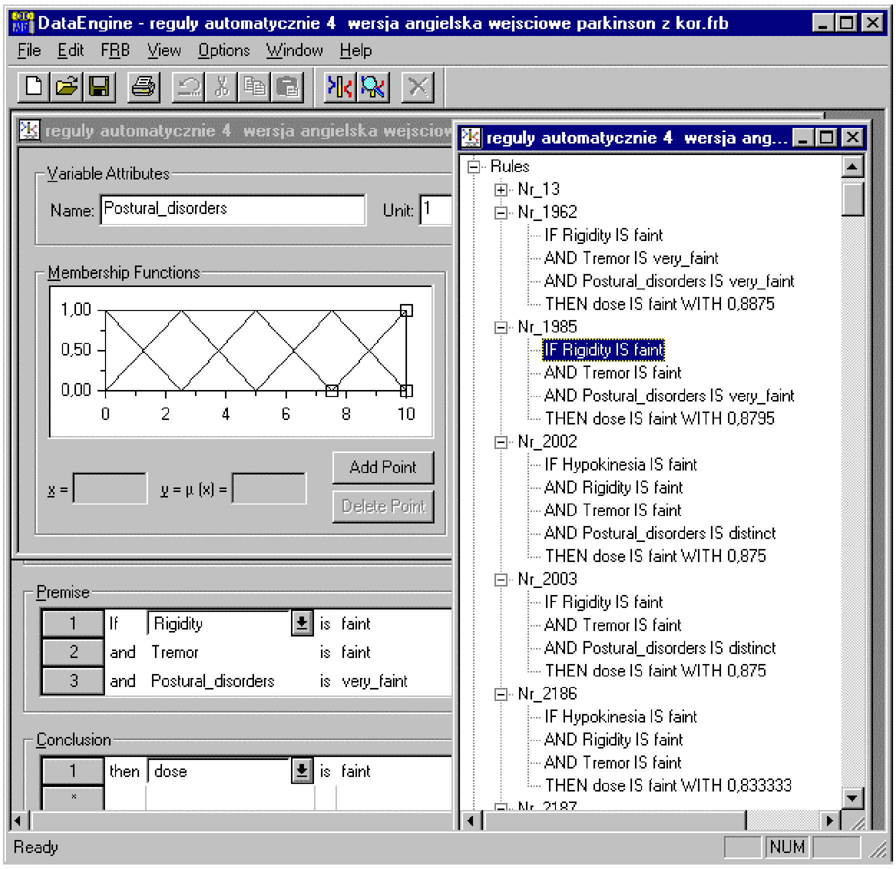

Figure 3: Fuzzy reasoning system, which controls determining of drug doses.

3. DRUG DOSES DETERMINING WITH RBF-NEURAL NETWORK LEARNED WITH ERROR-RESIDUUM METHOD

Neural networks are learned with measurements of the modeled plant. In this case the plant or rather taking up decision process is a doctor prescribing drug doses basing on the patient observation and on evaluation of the decease symptoms x_1-hypokinesia (slowing of movements), x_2 -hypertonia (rigidity), x_3 -tremor, x_4 -posture distortions. Learning data included the symptoms evaluation of 70 patients and the doctor decision-drug dose. The RBF-neurons had activation functions expressed by formula (2).

$$y = exp[\sum_{i=1}^{4} \left| x_i - m_i \right| / d_i] \tag{2}$$

The network structure and the self-organizing/self-tuning learning method was elaborated by Piegat (1999). The network consists of a base model M_O and of a number of additional ones referred to as error residua models E_{OM}-E_{kM}, (fig.4). Each of parallel branches of the network contains one 4-inputs modificated RBF-neuron with the activation function (2) with 12 tuned parameters m_i,d_i ,l_i , i = 1 - 4 .In the first step only base neuron is tuned. If the base model is after the tuning not sufficiently accurate then its error e_O is calculated and in the next step only this error is modeled and only with one neuron E_{OM} .If the network consisting of the base neuron M_O and of the error neuron E_{OM} is insufficient then the error of the error e_o is calculated and modeled with (only one) third neuron E_{1M} .Introducing next neurons modeling successive error residua increases the network accuracy to a satisfactory level. The learning method forms itself the network structure which depends on the required accuracy and on the mapping surface complication (non-linearity) of the modeled system. Learning of the network according to the error residua method gave few models of the doctor decision process ,each of them with different neurons number and different accuracy. Increasing neuron number an „ideal" network with zero-modeling error could be achieved. However, such „ideal" network would model all noised measurements and its generalized properties would be very small.

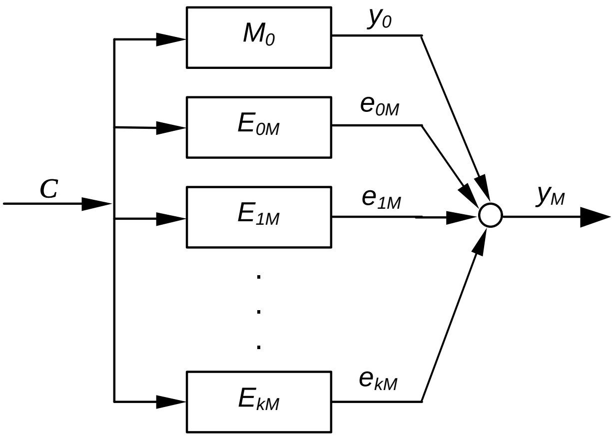

Figure 4: General structure of the neural network -the base model M_O and error residua ones E_{iM}.

As can be seen on Fig. 5 the neurological symptoms increase is accompanied with a nonlinear drag dose rise, which is particularly strong at the biggest symptoms. The decision surface has no rapid „valleys" or „mountains" what means that the neural model smoothly and stepwise increases the dose as the symptoms increase and at similar symptoms „prescribes" similar doses. The model doesn't change the doses as violently as the doctor (in many cases) did. This „quiet and balanced" drug ordering by the neural network is undoubtedly its great advantage in comparison with a doctor and agrees with investigations results on human decision processes in undisturbed conditions published by Zimmermann (1994).

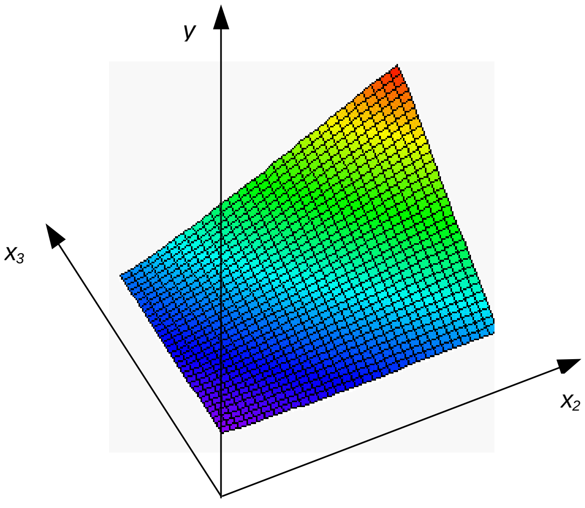

Figure 5: 3-dimensional projection of the doctor decision surface ordering drug doses at Parkinson's-disease.

4. RESULTS DISCUSSION AND EVALUATION

Using methods presented in chapters 2 and 3 of the paper 4 calculation series for 51 disease examples were carried out. On fig.6 are presented results (determined L-dopa doses) for the various methods used. In tab.1 is shown a matrix of correlation coefficients between the considered results. Generally, a good agreement of the results achieved can be stated, for the correlation coefficients are not smaller than 0,75.

The greatest differences occur in these cases, in which the L-dopa dose prescribed by the neurologist deviates considerably of the dose calculated with introduced or automatically generated inference rules. Differences between doses ordered by the neurologist and doses calculated by investigated methods mean from mathematical point of view certain „chaos", caused first of all by non-uniqueness of data (doses) determined by the doctor. This data nonuniqueness considerably hinders modelling with Fuzzy Logic methods and learning of neural networks. Application of the presented methods in practice requires further intensive investigations mainly of clinical character.

Table 1: Correlation matrix

	Doctor	Rules automat 4 Symptoms	Neural net 4 Symptoms	Rules expert 3 Symptoms	Rules automat 3 Symptoms
Doctor	**1,00**	**0,79**	**0,75**	**0,76**	**0,84**
Rules automat 4 Symptoms	0,79	1,00	0,89	0,85	0,87
Neural net 4 Symptoms	0,75	0,89	1,00	0,92	0,79
Rules expert 3 Symptoms	0,76	0,85	0,92	1,00	0,81
Rules automat 3 Symptoms	0,84	0,87	0,79	0,81	1,00

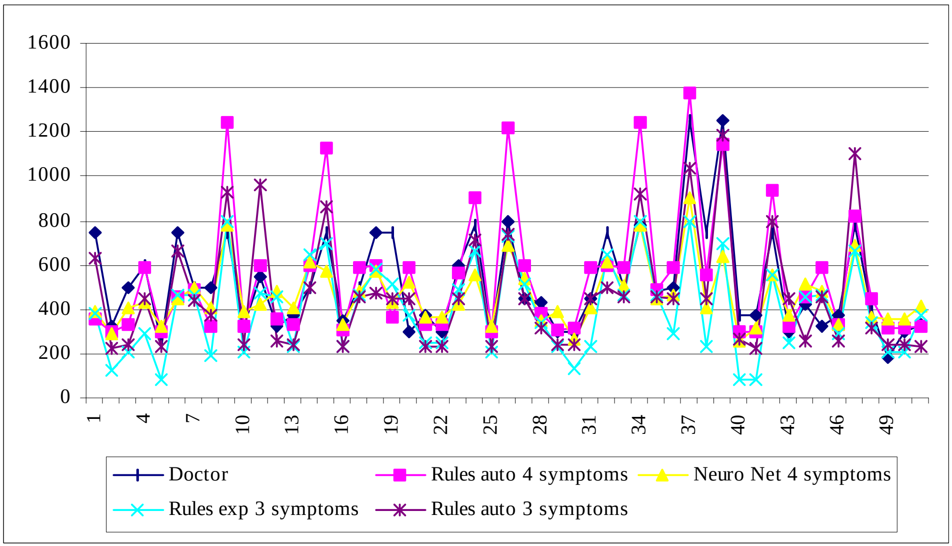

Figure 6: L-dopa doses for 51 patients prescribed by a doctor and by the 4 investigated soft computing methods

5. CONCLUSION

Farmacotherapy of the Parkinson's disease is a difficult task, for the drug ordering should take into consideration many significant factors. The results achieved by the authors can be considered as encouraging ones. They allow the conclusion that both the inference based on fuzzy logic methods and application of neural networks can in the farmacotherapy facilitate the drug dose determining and support the doctor decision process.
The authors are of the opinion, that offer of a computer program determining proper L-dopa doses would be right step to modernity, all the more so as one doesn't meet at present informations about similar offer proposed to doctors. However, such offers can be met in others knowledge branches e.g. in techniques, where firms have at their disposal programs enabling determining optimal parameters of produced elements or sets.

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