

A fuzzy rule-based decision support system for Duodopa treatment in Parkinson

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Background and aims

Fluctuating response to oral levodopa treatment in advanced Parkinson's disease is partly explained by irregular gastric emptying. In advanced stages, improvement can be achieved with intestinal infusion of a levodopa/carbidopa gel (Duodopa[®]) compared with tablets [1]. Administering this treatment is complex and requires special training of clinical staff and patients. The day starts with a morning bolus dose and a continuous flow rate is supplied thereafter. In addition it is possible to take extra doses if needed depending on e.g. food intake, physical activity and mood. Some patients can adjust their dosage well to their needs without assistance, whereas others may experience problems. Since Parkinson is a progressive disease, there is a need to follow-up the treatment over time.

Fuzzy sets and fuzzy inference systems (FIS) are highly suitable for representation and processing of inexact medical entities in decision-support systems (DSS) in a variety of application areas [2]. A demonstrator of a web-based decision support system for Duodopa was constructed. Dose advice was generated based on after-dose patient state using a rule-based FIS. The aim of the FIS was to propose individual dose adjustments in stabilised patients in a similar manner as domain experts. In the demonstrator system, patient state was assessed by clinical scores of patients performing motor tests and patient state and dosage data were added manually to the database. In a future system, patient state will be recorded in a hand computer with built in mobile communication via a combination of diary assessments and motor tests on the screen. Pump data will be wireless-transferred to the hand unit and dose and state data will be uploaded to a central database (Figure 1). The aim is to help doctors and nurses to follow-up the treatment and assist in dose adjustments through dose advice, alerts and summaries on patient state and dosage.



Figure 1. Vision for the decision support system (DSS). Arrows represent main data or information flow (images reproduced with permission from Solvay Pharmaceuticals GmbH).

Design considerations

Dose advice was generated based on after-dose patient state and proposed calculated doses were validated vs. actual given doses in the hospital. Fuzzy rules were chosen because of their property to easily capture human knowledge. For instance, a single rule with one membership function could capture a statement such as: "If patient state is 'off' one hour after the morning dose then the dose should be increased. How much increase depends on how much 'off' the state is, but we never change more than 20% at a time". If we had chosen 'crisp' rules, the expert would have been forced to specify detailed actions in different intervals of the patient state scale. The number of rules would increase and there would be more parameters to tune. For finding the after-dose patient states, a crisp (non-fuzzy) mechanism was used. Typically the patient state should be assessed 60 minutes after the dose. However, for practical reasons sometimes state was assessed at other times and should be considered for decision-making between 45 to 90 minutes after the dose in a priority order.

Knowledge elicitation

Specification of user requirements was done by interviewing two caregivers experienced in the treatment and letting them evaluate user interface prototypes. Expert knowledge was assembled through interviewing the two expert users about their current practice. The expert knowledge was formalised as natural language rules based on their practice for Duodopa dose adjustments. An example rule was given in the section on design considerations and the final rules as implemented in the FIS are presented in Table 1. The logic for finding after-dose state is defined in Table 2.

Table 1.

Rules of the FIS. MD= Morning dose, ED=Extra dose, FR=Flow rate. State is a fuzzy variable representing after-dose patient state, 'negative' is a fuzzy set with full truth when the patient state is very off and 'positive' is a fuzzy set with full truth when the patient state is very dyskinetic. 'Positive' and 'negative' are linear functions symmetric around State = 0 and will output equal truth there, and therefore New dose will be the same as taken dose if State = 0. New dose is a fuzzy variable representing the output dose. 'Increased' and 'decreased' are constants defined as the current dose + 20% and the current dose -20%, respectively. Slope is a fuzzy variable representing the linear regression coefficient of patient state vs. time, 'falling' and 'rising' are fuzzy sets with full truth if the slope of the regression line is large negative and large positive, respectively.

Rule no.	Antecedent	Consequent
1	If State is 'negative'	New MD is 'increased'
2	If State is 'positive'	New MD is 'decreased'
3	If State is 'negative'	New ED is 'increased'
4	If State is 'positive'	New ED is 'decreased'
5	If State is 'falling'	New FR is 'increased'
6	If State is 'rising'	New FR is 'decreased'

Table 2. Logic for finding after-dose state

Dose type	Logic
Morning Dose	If patients had not taken any extra doses within one hour after the morning bolus dose, then states were considered.
Extra Dose	If patients had not taken any other extra doses within two hours after taking an extra dose then states were considered.
Flow rate	If patients had not taken any extra doses or a morning bolus dose within four hours after last changing flow rate, then state and dose time were considered.

References

- Nyholm D, Nilsson Remahl AI, Dizdar N, Constantinescu R, Holmberg B, Jansson R, Aquilonius SM, Askmark H. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005 Jan 25; 64(2): 216-23.
- Boegli K, Adlassnig K-P, Hayashi Y, Rothenfluh T, Leitich H. Knowledge acquisition in the fuzzy knowledge representation framework of a medical consultation system. *Artif Intell Med.* 2004 Jan;30(1): 1-26.

Data sets

One data set (16 new patients) was provided by NeoPharma AB, Uppsala, Sweden. Data consisted of dosage and patient state information from new Duodopa patients receiving initial dose adjustments and were collected from April, 2002 to October, 2004 for patients at different Nordic clinics observed between one and six consecutive days. The first day's data was removed from this data set since it was not representative for the situation the system was designed to operate in. Another data set (18 stabilised patients) was taken from the DireQt study [1]. This study was a crossover study of Duodopa vs. conventional anti-Parkinson medications performed in five Swedish clinics. Data from two non-consecutive days when the patients were on Duodopa were used. In this case, doses had already been stabilised at the time of data collection. Dosage of Duodopa was tailored to each patient's need based on the practice we tried to capture in our DSS. Both data sets were separately used for tuning the FIS and the pooled data was used for validation.

Patient states were defined by clinical assessment of motor function on a treatment response scale (TRS) between -3 and 3, where -3 represents severe parkinsonism and 3 represents severe dyskinesia. Details of this procedure are described in [1].

Design and tuning

The fuzzy rule-based system module consists of three components: (i) a rule base with a collection of fuzzy IF-THEN rules (Table 1); (ii) a database that defines the membership functions used in the fuzzy rules; and (iii) a reasoning mechanism that combines these rules into a mapping routine from the inputs to the outputs of the system to derive an output conclusion. To minimise mean absolute error of calculated advised doses compared to actual given doses, the parameters of the membership functions in the FIS were manually tuned. The resulting tuned membership function parameters were the same regardless if the tuning was performed based on the new patients' or ongoing patients' data sets. The median or the nearest existing dose above the median of taken doses for a period was considered the typical dose. The median of the advised doses related to that typical dose was then considered the typical advice for the typical dose of a period.

Validation of the FIS module

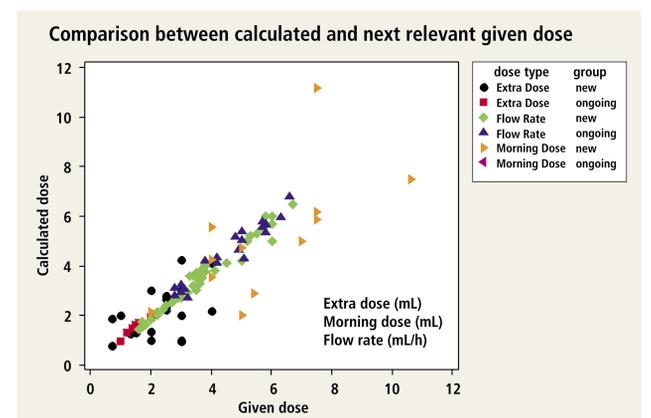
Proposed calculated doses were validated vs. actual given doses in the hospital. Goodness of fit (R^2), mean error and mean absolute error between advised and next given doses were calculated for all types of doses: morning dose, extra dose, flow rate, for the validation data set. Advice of 'no change' by the system was excluded from calculations. About one third of all generated advice was 'no change'. Instances when the given dose was changed and the system generated no advice were included in calculations. Results are shown in Table 3 and Figure 2. The system was successful with calculated flow rates but it was less successful with morning doses and extra doses. With the ongoing patients, requiring only minor adjustments it was successful even for these dose types. The low R^2 for the extra dose can be explained by the process for titrating doses in new patients, which is quite different from the adjustments in stabilised patients: Typically low flow rates are used in the beginning and repeated extra doses are used to reach state TRS = 0 and thereafter the flow rate is adjusted.

Table 3. Validation results

Dose type	Mean difference	Mean absolute difference	R^2	Number of doses
Flow rate (mL/hr)	-0.12	0.24	0.96	60
Morning dose (mL)	-0.73	1.66	0.45	12
Extra dose (mL)	-0.12	0.38	0.43	41
Total	-0.18	0.44	0.82	113

Figure 2.

Plot of calculated doses vs. given doses for each of the three dose types



Usage

A typical scenario of the use of the future DSS after login is that the user watches a list of patients with notation of test periods and recent alerts. Subsequently the user selects a patient and period of interest, and can then check dose and state statistics and pointers to possible alerts and suggested dose adjustments of typical taken doses. Based on this information the treating physician decides if adjustments should be made. A necessary condition for the DSS advice is that the treatment goal should be a state of TRS = 0. In some cases, patients prefer and physicians accept that patients are kept slightly overmedicated to reduce the number of occasions with painful symptoms in negative states. On the other hand, other patients are experiencing intolerable side effects in states greater than 0 and are therefore kept a bit undermedicated. In both these situations, the advice from the DSS will not be valid. A sample dose advice from the system is shown in Figure 3.

Figure 3.

Example of dose advice as presented by the DSS demonstrator.

Summary advice for morning dose			
Summary for patient: SB, id: 11			
Period: Baseline (2003-11-18 to 2003-11-20) <<< Back			
Number of days: 3			
Decision based on: 2 instances of high after-dose patient state.			
Taken dose	Patient state	Typical advice	New dose
Typical value 4.0 ml	high	decrease (8.6 %)	3.7 ml