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

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Abstract. A decision support system (DSS) was implemented based on a fuzzy inference system (FIS) to provide assistance in dose alteration of Duodopa infusion in patients with advanced Parkinson’s disease, using data from motor state assessments and dosage. The DSS has a web enabled graphical user interface that presents alerts indicating non-optimal dosage and states, recommendations (typical advice with typical dose) and statistical summary measures. One data set was used for design and tuning of the FIS and another data set was used for evaluating performance compared with actual given dose. Overall goodness-of-fit ($R^2$) was very good (0.97) for stabilized patients in the evaluation data set, and acceptable (0.64) for new (Duodopa untreated) patients in the design data set. User evaluation has not yet been performed.

1. Introduction

Rule-based decision support systems (DSS) have been developed but rarely used in medicine since the 1970s. For dose adjustments, similar technology has been used for diabetes treatment [1]. In neurology, DSS have been developed for diagnosis [2] and epilepsy treatment [3]. Web based decision support systems first appeared around 1995. Fuzzy set theory and fuzzy logic is a highly suitable and applicable basis for developing rule-based systems in medicine and has proven to be a powerful tool for decision-support systems and is also applicable to real-time monitoring of patient data [cf. 4-5]. Fuzzy inference systems (FIS) have been applied for regulating depth of anaesthesia [6], and for recommending regimen changes in diabetes [7]. It appears that very little has yet been done in applying FIS in neurological DSS.

Parkinson is a slowly progressive neurological disease. It affects a small area of cells in the mid-brain, vital for motor function control. Standard treatment at the initial stage of the disease is levodopa/carbidopa in tablet form, aimed at restoring depleted dopamine levels. Medication must be individually tuned, under dosing does not relieve the symptoms and overdosing leads to side effects with uncontrolled movements. The dosing also must be adjusted daily with respect to food intake, exercise and mood. The interval for the correct dose shifts upwards and gets narrower as the disease progresses. In advanced Parkinson, improvement can be achieved with intestinal infusion of a levodopa/carbidopa gel (Duodopa) compared with tablets. [8, 9]
Administering Duodopa is complex and requires special training of clinical staff and patients. For new patients the treatment is tried-out using a nasal tube. Initial pump settings are calculated based on previous tablet dose and are adjusted based on after-dose response (state) during some days in the hospital. Typically, the pump is shut off at night. The day starts with a morning bolus dose to reach steady state and a continuous flow rate is supplied thereafter. In addition it is possible to take extra doses if needed depending on food intake etc. Since Parkinson is a progressive disease, there is a need to follow up on the treatment over time.

A demonstrator of a web-based decision support system for Duodopa was constructed using a rule-based FIS. Generated advices were evaluated vs. actual taken doses in the hospital. The aim of the final system is to help follow up the treatment and assist dose adjustments through dose advice, alerts and summaries.

2. Development process

Development was done according to a linear model with added iterations to define the user interface requirements and tune the FIS.

Analysis: This phase involved acquiring a general understanding of the problem and formalizing the expert knowledge. Interviews and discussions with two domain experts were used to formulate natural language rules based on their current practice.

Design: The overall architecture involved database design, class design, FIS design and user interface design. The system was designed as a 3-tier architecture: front-end was the user interface (web-application), middle-ware was the DSS and the back-end was the database. All business logic, FIS and calculations were implemented in the middle-ware. Object oriented design and programming were used to develop the system.

Construction: For constructing the database, a database script was generated. A business level was created with object oriented programming to generate summaries of alerts, states and doses. In the FIS for calculating new doses, all values of doses and states were treated as fuzzy variables that were described by a fuzzy set. Fuzzy rules based on a domain expert’s experience were implemented here to carry out evaluations and “crisp” values (new advised doses) that came out after firing rules were stored into the database.

Testing: To get minimal mean absolute error compared to actual taken doses for design data the parameters of the membership functions in the fuzzy inference system were manually tuned. One data set was used to develop and tune the FIS and another was used for evaluation. Several iterations of the user interface were done.

3. User requirements

The users of this system will be physicians and nurses (clinical staff) at neurology clinics. Typically the system will be used shortly before or at patient-visits. Specification of user requirements was done by interviewing a few experienced users and letting them evaluate user interface prototypes.

Clinical staff needs summaries of patients’ personal details, dose and state information over test periods that may be a few days long. Mapping between staff and patients, alerts of unusual or unwanted states and dosing, and advice on dose adjustments are examples of required functionality. Non-functional requirements are that summaries should be condensed to a few pages and navigation should be easy. Dose advice should be given as a domain expert would do it and should be explained.

A typical scenario is login; see the list of patients and periods and most recent alerts. Subsequently the user selects a patient and period and can check dose and state statistics and
pointers to possible alerts and suggested dose adjustments. Going further, one can compare different periods graphically and access detailed data via time series plots.

4. Design considerations

Fuzzy rules were chosen for dose adjustments because of their property to easily capture human knowledge. A single rule with one membership function could capture a statement such as; if after-dose state is low, the dose should increase. How much depends on how low the state is, but never more than 20% change. For finding the after-dose states, a crisp mechanism was used. Typically the 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 certain priority order. Since this timing would not impact the dosing decisions, we found no reason to include it in the FIS. Instead this logic was added in the business level. The expert statements about when to produce alerts were not fuzzy and were therefore included in the business logic. Our choice to tune the FIS based on the new patients was that they had many dose changes. It would not be appropriate to evaluate the FIS based on these patients since the rules were designed for follow-up of already stabilized patients.

5. Design and construction

The DSS was built in Java-based three-tier architecture. The user interface was a web application built in Cold Fusion. The middle layer contained the FIS (NRC FuzzyJ Toolkit [10]) and business logic and the back-end contained the RDBMS. This relational database (MySQL) was used for both the decision support system and web application.

Design data were provided by NeoPharma AB, Uppsala, Sweden. Data consisted of dosage and status information from new Duodopa patients and were collected from April, 2002 to October, 2004 for 16 patients, observed between one and six consecutive days. Patient states were defined by clinical examination of motor function of a standardized sequence of motor tasks. Global state was noted on a discrete integer scale from -3 to +3 where negative values represented Parkinson symptoms due to too little medicine and positive values represented side effects due to too much medicine. This scale (TRS) is further described in [9]. Doses were entered in attributes: morning dose, flow rate and extra dose. State and all doses information were entered in 15 minute intervals from 6:00 to 23:00 hours. Infusion was not used at night.

The fuzzy rule-based system consisted of three conceptual components: a rule base that consists of a collection of fuzzy IF–THEN rules (table 1); a database that defines the membership functions (MF) used in the fuzzy rules; and 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. A single-input single-output fuzzy model was extracted from the expert’s knowledge. ‘Negative’, ‘positive’, ‘falling’ and ‘rising’ were linguistic values determined by the fuzzy sets “RightLinearFuzzySet” and “LeftLinearFuzzySet” associated with the fuzzy variable TRS state (or slope of TRS vs. time regression line for flow rate). Increased and decreased were linguistic values determined by the fuzzy sets “SingletonFuzzySet” associated with the fuzzy variable new dose. Manual tuning of membership function parameters was performed to minimize mean absolute difference between advised dose and the next relevant taken dose in the design data set.
Table 1: Rules of the FIS

<table>
<thead>
<tr>
<th>Rule no.</th>
<th>Antecedent</th>
<th>Consequent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After dose State</td>
<td>new Morning Dose (MD)</td>
</tr>
<tr>
<td>1</td>
<td>negative</td>
<td>MD + 20%MD (old dose)</td>
</tr>
<tr>
<td>2</td>
<td>positive</td>
<td>MD - 20%MD (old dose)</td>
</tr>
<tr>
<td></td>
<td>After dose State</td>
<td>new Extra Dose (ED)</td>
</tr>
<tr>
<td>3</td>
<td>negative</td>
<td>ED + 20%ED (old dose)</td>
</tr>
<tr>
<td>4</td>
<td>positive</td>
<td>ED - 20%ED (old dose)</td>
</tr>
<tr>
<td></td>
<td>State (regression slope)</td>
<td>new Flow Rate (FR)</td>
</tr>
<tr>
<td>5</td>
<td>falling</td>
<td>FR + 20%FR (old dose)</td>
</tr>
<tr>
<td>6</td>
<td>rising</td>
<td>FR - 20%FR (old dose)</td>
</tr>
</tbody>
</table>

Logic for finding after-dose states, typical doses and advice and for generating alerts based on expert knowledge was included in the business level.

**After-dose state logic:**

*Morning dose:*
- If patients had not taken any extra doses within one hour after morning dose, then states were considered.
- State was considered for decision making from 45 minutes to 90 minutes after the dose. If found, priority order was 60, 75, 45 and 90 minutes.

*Extra dose:*
- If patients had not taken any other extra doses within two hours after taking an extra dose then states were considered.
- State was considered from 45 minutes to 90 minutes after the dose with same priority as morning dose described above.

*Flow rate:*
- If patients had not taken any extra doses or a morning dose within four hours after last changing flow rate, then state and dose time were scanned.
- If number of states were more than one within 4 hours interval then states and times were considered for calculation of a regression slope used for decision making.

**Typical dose and advice:**

- Median of old dose values or the nearest upper of median dose value for a period was considered the typical dose.
- Median of new dose values related to the typical dose value was considered the typical advice for the typical dose of a period.
Alerts:

Dose alerts
- If extra doses were taken more than three times in a day.
- If flow rate was changed more than three times during a day.
- If total daily dose differed more than (20%) from the previous day

State alerts
- If states were more than 2 or less than -2.
- If regression slopes were more than 0.5 or less than -0.5 TRS units per hour

6. Evaluation

Evaluation data were taken from the DireQt study [9]. This study was a three + three
weeks crossover study of Duodopa vs. conventional anti-Parkinson medications with blinded
assessment of Parkinson symptoms and side effects from video recordings of patients and
using the TRS. Only the days when the patients were on Duodopa were used as evaluation
data. In this case, doses had already been stabilized 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.

Goodness of fit ($R^2$), between advised and taken doses was calculated for all categories
of doses: morning dose, extra dose, flow rate and this was done for both design and evaluation
data sets. Advices of ‘no change’ were excluded from calculations. Overall goodness-of-fit
for the design data set (Duodopa untreated) was 0.64 and for the evaluation data set (Duodopa
stabilized), 0.97. For the design data set the $R^2$ was 0.85 for flow rate but for morning dose
and extra doses it was only 0.28 and 0.30 respectively. For the evaluation data set $R^2$ for the
flow rate and extra dose was 0.87 and 0.91 respectively which showed that the system
behaved much better in case of the evaluation data compared to the design data. There was no
result for morning dose in the evaluation data, since that data came from non-consecutive
days. The worse performance in the new patients can be explained by the fact that the rules
were designed for ongoing patients, usually needing only minor adjustments. The initial
acclimatization period for new patients often requires bigger changes and a more individual
approach by the treating doctor.

7 Future plans

A formal user evaluation e.g. using questionnaires will be the next step. The present
system is an off-line demo of a planned system. 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.
8. References


