Induction of an Adaptive Neuro-Fuzzy Inference System for investigating fluctuations in Parkinson's disease

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Abstract. This paper presents a methodology to formulate natural language rules for an adaptive neuro-fuzzy system based on discovered knowledge, supported by prior knowledge and statistical modeling. These rules could be improved using statistical methods and neural nets. This gives clinicians a valuable tool to explore the importance of different variables and their relations in a disease and could aid treatment selection. A prototype using the proposed methodology has been used to induce an Adaptive Neuro Fuzzy Inference Model that has been used to "discover" relationships between fluctuation, treatment and disease severity in Parkinson. Preliminary results from this project are promising and show that Neuro-fuzzy techniques in combination with statistical methods may offer medical research and medical applications a useful combination of methods.

1 Introduction

A fuzzy rule-based system consists of if-then statements and uses a human interpretable language. Rules can be formulated with linguistic expressions. However, a limitation of fuzzy models is the difficulty to quantify the fuzzy linguistic terms. There is a potential gain in combining the advantages of fuzzy systems in terms of transparency with the advantages of artificial neural networks which provide a learning ability. Neuro-fuzzy [1] is such a combination of artificial neural network and fuzzy systems which appears to be a powerful tool, being both readable and able to learn at the same time. Adaptive Neuro Fuzzy Inference System (ANFIS) [1] is functionally equivalent to a Sugeno type fuzzy inference system. ANFIS is able to learn from data by using the gradient descent algorithm.

In the initial stage of Parkinson's disease (PD), patients are treated with 'artificial dopamine' (levodopa) in tablet form but long-term use of levodopa causes motor fluctuations [2]. It is important to model factors for fluctuations in advanced PD to offer an improved treatment strategy.

It has been shown that motor fluctuations in advanced PD are at least partially related to variations in blood levodopa concentrations [3] Motor fluctuation probably also is related to disease duration, disease severity, and doses of oral levodopa [4].

We defined a methodology to discover knowledge from data sets and formulated rules to build a neuro-fuzzy system, which was applied in predicting fluctuations based on other

disease related variables. The methodology described here, generally follows the following steps:

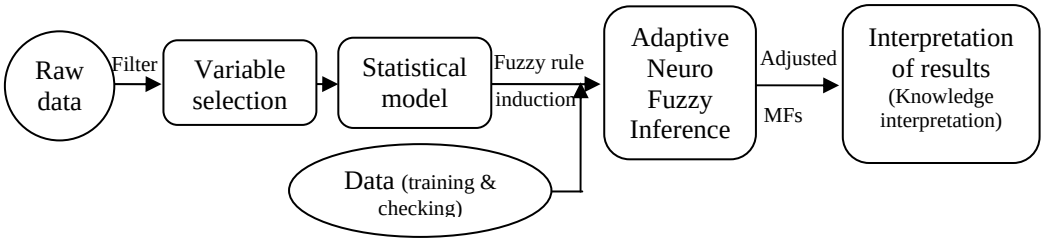

Figure 1: *Overview of the proposed method to generate/induce an ANFIS system*

The methodology was applied to fluctuation in advanced PD in two different clinical studies. Data were provided by NeoPharma AB, Sweden which included all the 12 patients from study 1 [5] and 18 patients (all that fulfilled the study requirements according to the protocol) from study 2 [6]. Motor performance was rated by blinded investigators from -3 (severe Parkinsonism) to +3 (severe dyskinesia) on a discrete integer global treatment response scale (TRS) based on video recordings on different tasks. We used fluctuations in Parkinson's disease in our case study, but the method and approach also has some general qualities and may be applicable to other symptoms in other diseases.

2 Methodology

i) Data filtering: Data were in raw format. For data cleaning and examining simple descriptive features of the attributes MS ACCESS was used and only attributes that possibly could be related to fluctuations were extracted using SQL quires. Now datasets for study 1 and study 2 contained 15 and 10 attributes respectively.

ii) Variable selection: The dependent variable **fluctuation** was defined as the standard deviation of ratings on TRS. Preliminary fit (Y X) analysis was done to select explanatory variables. fit (Y X) analysis provides methods for examining the relationship between a response (dependent) variable and a set of explanatory (independent) variables. Now both datasets contained attributes within the range of p values $0.05<=P<0.60$ for supplying knowledge to the model. Datasets for study 1 contained 4 and study 2 contained 5 attributes. Variables were taken in their standard normalized form with zero mean and standard deviation one. A forward-selection technique was applied to the considered variables after the fit analysis to select the significant explanatory variables.

iii) Statistical method: The dependent variable fluctuation was independently and normally distributed. Quantile-quantile (Q-Q) plot was used to check the normality, so design data (study 2) were modeled as a general linear model (GLM) [7]. SAS (Statistical Analysis System) system for windows V8.0 was used for this.

Model: $fluctuation = \alpha + \beta_1 * treat + \beta_2 * severity + \beta_3 * treat * severity + \varepsilon$ ----- (1)

Where, α = intersection, β_1 = estimate of treament1 (oral) or treatment2 (infusion). β_2 = estimate of severity (sum2-daily activities), ε = Random error. β_3 = estimate of the interaction

between severity (sum2-daily activities) and treatment. The customary measure of effect size in a GLM is the squared multiple correlations denoted as R^2.

iv) ANFIS model: *Formulate rules:* Findings from the statistical method was taken into account for formulating rules in fuzzy models which makes it more understandable (Table 1). Statistical model gives the statistically significant variables that were influencing the fluctuation and also gave the knowledge which variable was affecting more than the other. From this discovered knowledge rules were defined manually and the range of linguistic values (*high*, *medium*, *low)* were defined (by using histogram and observing the threshold values) from the variables. MatLab 7 Fuzzy Logic Toolbox was used for ANFIS.

ANFIS (Adaptive Neuro-fuzzy) design: Initial parameters of the membership functions were chosen by looking at the training data (study 2). **severity** and **treatment** were two linguistic input variables and fluctuation was the output linguistic variable. *low* and *high* were the linguistic values for the fuzzy variables **severity**. *oral* and *infusion* were the linguistic values for the linguistic variable **treatment**. For **fluctuation** linguistic values were *low, medium high* and *veryHigh*. All values were standard normalized with zero mean and standard deviation one. Gaussian membership functions (MFs) were used for **severity** and **treatment** and constant (fuzzy singletons) MFs for **fluctuation** values. Study data 1(validation data) was used for validation and early stopping.

Training ANFIS using early stopping: Back propagation training was used in training data to estimate parameters of the MFs. Training error in validation data decreased up to a certain point in the training and then it increased. This increase represented the point of model over fitting. Based on that minimum point, the number of training epochs was set to 40.

v) Interpretation of results: During training the membership functions were tuned in order to get the minimum error. After training, parameters of membership functions of fuzzy values were changed and the knowledge that we have got from this movement of membership function is described.

3 Results

Statistical model

Calculated goodness-of-fit/R^2 was 0.48. ANOVA table (Type III test) shows that **treatment** and **severity** (standardized value of severity-daily activities) have p value 0.0001 and 0.0125 respectively and were statistically significant. For the interaction term **severity*****treatment**, the p value (0.1708) suggested that, although not so strong, there was indicative evidence against the null hypothesis.

Estimate of **treatment** from the GLM tells us that if all other conditions remain same, on average, in *oral* **fluctuation** become 1.146 standard deviations higher than that of *infusion* and an increase of one standard deviation in the independent variable **severity** predicted an increase of 0.1585 standard deviations in the dependent variable, **fluctuation**. The interaction term between **treatment** and **severity** tells that **severity** effects differently under different treatments. From the estimates found that when *oral* was given, one standard deviation

severity increase will increase 0.3562 (on an average) standard deviation of fluctuations over and above that experience when treated by *infusion*.

From the above statistical results that in *oral* **fluctuation** becomes higher and also *high* value of **fluctuation** associated with the higher value of **severity**. So when patients are taking *oral* medicine and at the same time **severity** is higher then the **fluctuation** becomes *very high*. In case of *infusion* and *low* **severity** it shows the opposite i.e. *low* **fluctuation**. Also the interaction term between **severity** and **treatment** support that with *oral* and *low* **severity** value **fluctuation** is *high* and, in case of *infusion* and *high* value of **severity fluctuation** is *medium*. Thus using these statistical results deduce the rules shown in Table 1:

Rule based on results from statistical model:	
If **t** is *oral* and **s** is *high* then **f** is *veryHigh*	If **t** is *infusion* and **s** is *high* then **f** is *medium*
If **t** is *oral* and **s** is *low* then **f** is *high*	If **t** is *infusion* and **s** is *low* then **f** is *low*
Where, t= treatment s= severity and f= fluctuation	

Table 1: *Fuzzy rule in readable form generated from statistical model*

ANFIS model

After training, the universe of discourse for **severity** remained unchanged but parameters of membership functions of fuzzy values *low* and *high* were changed (Figure 2). For *low* value centre was moved to the less negative direction and spreading increased and for *high* the spreading was decreased and centre moved to more positive direction. For **fluctuation** the fuzzy value *low* shifted more to the negative direction, *medium*, *high* and *veryHigh* values were decreased after tuning but still remained positive. For training data Goodness-of-fit or R^2 for the untrained FIS was 0.49. After 40 epochs training using the same data, R^2 was 0.52.

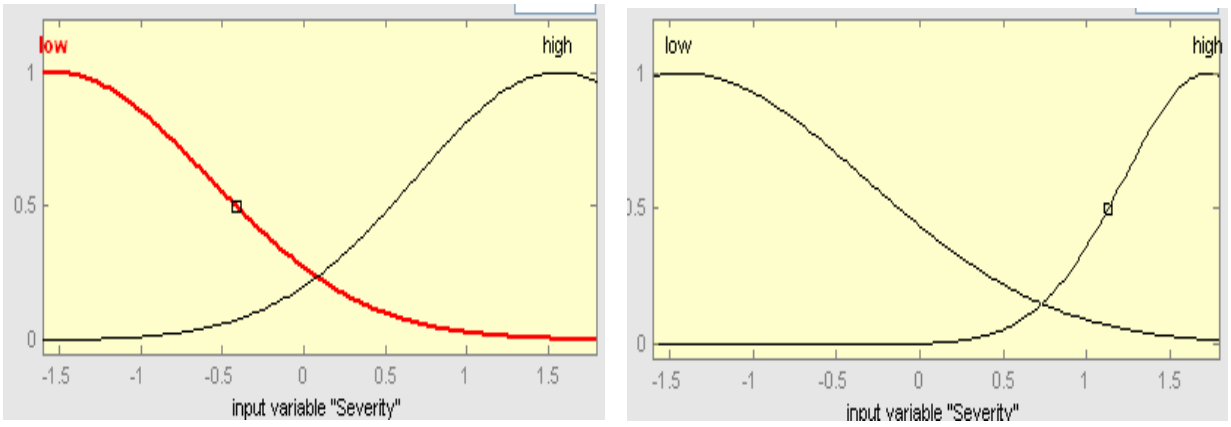

Figure 2: *Membership functions of severity before (left) and after (right) training*

4 Conclusions

A methodology is described here for induction of a neuro-fuzzy system to model fluctuations in Parkinson's disease. The method contains a number of statistical steps to extract knowledge from data and formulate natural language rules for an ANFIS and train it to achieve deeper knowledge through the trained positions of MFs such as *high* and *low*. Results showed that treatment and disease severity influenced fluctuations in both studies and treatment was the most important variable. In the ANFIS model, these two variables could explain 52% of the fluctuations after training. Rules (Table 1) from the ANFIS model and the movement of the MFs after training give an interpretable knowledge about the system.The proposed methodology allows for inclusion of other variables that based on prior knowledge should have an effect. Such variables were however not included in our model example. In future, the methodology can be applied with the other data sets to check the performance. It might be an interesting method for small datasets, e.g. for rare diseases or where the data collection is difficult.

5 References

[1] Jang J.S.R, Sun C.T. and Mizutani E. (1997), Neuro-fuzzy and Soft Computing. A computional approach to learning and machine intelligence. Prentice Hall, NJ. 1997

[2] Rinne UK. (1983) Problems associated with long/term levodopa treatment of Parkinson's disease. Acta Neurol Scand 1983; 95

[3] Bredberg E, Tedroff J, Aquilonius S-M, Paalzow L: (1995) Pharmacokinetics and effects of levodopa in advanced Parkinson's disease. Eur J Clin Pharmacol 1995

[4] Tanner CM, Kinori I, Goetz CG, Carvey PM, Klawans HL.(1985) Age at onset and clinical outcome in idiopathic Parkinson's disease [abstract]. Neurology 1985; 35 [Suppl 1]: 276

[5] Nyholm D, Askmark H, Gomes-Trolin C, Knutson T, Lennernas H, Nystrom C, Aquilonius SM. Optimizing levodopa pharmacokinetics: (2003) intestinal infusion versus oral sustained-release tablets. Clin Neuropharmacol 2003;

[6] Nyholm D, Nilsson Remahl AI, Dizdar N, Constantinescu R, Holmberg B, Jansson R, Aquilonius SM, Askmark H. (2005) Duodenal levodopa infusion monotherapy vs. oral polypharmacy in advanced Parkinson disease. Neuorology 2005 Jan 25; 64(2): 216-23.

[7] http://www.statsoft.com/textbook/stglm.html, © Copyright StatSoft, Inc., 1984-2003. Last referred on January 2006