# A Decision Support System for Parkinson Disease Management: Expert Models for Suggesting Medication Change

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# A Decision Support System for Parkinson's Disease Management: Models for Suggesting Medication Change

Parkinson's disease (PD) is a degenerative disorder of the central nervous system, which requires a long-term, interdisciplinary disease management. The EU Horizon 2020 project PD_manager (http://www.parkinson-manager.eu/) is aimed at developing a decision support system for PD management. As part of this task, we have developed decision-support models that identify situations in which the disease has progressed to the point which requires a change of medical therapy. The input data includes motor symptoms, non-motor symptoms and epidemiologic data. The models were developed in collaboration with medical experts, using a qualitative multi-criteria method DEX. In this paper, we describe the process and results of model development, and assess the quality of models in terms of classification accuracy, transparency, correctness, and completeness.

Keywords: Parkinson' disease; disease management; medication change; decision support system; expert modelling; multi-criteria model; method DEX

## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by early prominent death of dopaminergic neurons in the brain (Kalia and Lang, 2015). This leads to classical parkinsonian motor symptoms, such as rest tremor, rigidity, bradykinesia, gait and postural disturbances. Besides these motor symptoms, a variety of non-motor symptoms has been described (Martinez-Martin, et al., 2011): olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue. PD has a slow but progressive worsening of symptoms, which severely impair the quality of life. Oral drug therapy can only alleviate the symptoms in the early and middle stages of the disease.

In order to support the patient's independence and best possible quality of life (Den Oudsten, et al., 2007), a complex, long-term and multidisciplinary disease management is required, which includes neurological, psychological, occupational,

nutritional and rehabilitation therapies. However, it is still difficult for the clinicians to manage PD patients, because of the wide variability of symptoms between patients and also in the same patient at different times.

PD_manager (2015–2018) is an EU Horizon 2020 project aimed at developing and evaluating an m-Health platform for PD management (Gatsios, et al., 2015). Based on motor and non-motor data collected from a patient using unobtrusive devices, such as a smartphone, sensor insole and wristband, the system is aimed at providing personalized suggestions for an optimal PD management plan. The suggestions will be made by a decision support system (DSS) and will be calibrated by the treating neurologist (Tsiouris, et al., 2017).

An important task of the PD_manager DSS is related to the change of medication. When the disease progresses and new symptoms emerge, it is essential to perpetually assess the patient's situation and identify the need for changing the medication plan. In this case, the DSS should issue a warning to the responsible physician and provide reasons for it. We approached this task by developing decision models that suggest whether or not to change the patient's medication. The suggestion is made using the data that is available in the PD_manager DSS for each individual patient, i.e., data about motor and non-motor symptoms, and epidemiological data.

In preliminary studies (Bohanec, et al., 2017), we attempted to use the *data mining* approach (Witten, et al., 2011): to develop models, such as decision trees, automatically from data about past decisions. Unfortunately, the results were unsatisfactory; the produced models generally achieved low classification accuracies on test data and had other deficiencies, such as incompleteness or inconsistency.

In order to obtain better models, it was deemed necessary to try a different approach, *expert modelling*: asking medical experts to formulate their rules for

medication change, based on their medical expertise and experience. The approach was facilitated by a number of medical experts collaborating in the PD_manager project.

This paper is aimed at describing the process and results of expert modelling in PD_manager. In the following, we first formulate the addressed problem and describe the main methodological steps of the study. Then, the produced models are presented in terms of their structure and examples of decision rules, and the quality of models is assessed. The paper is concluded by a summary of achievements and contributions.

## Problem Formulation

The problem addressed in this study was to develop a decision-support model for suggesting medication change to physicians: based on the data about an individual patient, the aim is to identify situations in which the current medication therapy is not effective and has to be changed. This should be carried out using the data that is available in the PD_manager DSS for each individual patient (Tsiouris, et al., 2017):

- *Motor symptoms*: bradykinesia, tremor, gait, dyskinesia, and on/off fluctuations.
- *Non-motor symptoms*: daytime sleepiness, cognitive disorder, impulsivity, depression, hallucinations.
- *Epidemiologic data*: patient's age, employment status, disease duration, and whether or not the patient is living alone.

In addition to suggesting the change to the physician, the model has to provide evidence (justification, explanation) to support the suggestion. The model is also expected to have a number of properties; it has to be:

- *Robust and complete*: working on all possible inputs, including missing data.

- *Consistent*: free of logical errors and obeying the principle of dominance: the more severe the symptoms, the more imperative the change of medication.
- *Transparent and comprehensible*: easy to understand what is inside the model and how it works;
- *Accurate and valid*: providing "right" suggestions for given situations, which are in accordance with clinical guidelines and medical practice.

There are two possible types of suggestions: (1) a *yes/no* (or *change/no_change*) suggestion, which only identifies the need for medication change, but leaves the decision of how to change the therapy to the physician, and (2) a suggestion of *how* to change the medication, for instance, to replace some medicament with another or change the dosage of the current medicament. Both types of suggestions were addressed in PD_manager (Bohanec, et al., 2017). Due to space limitations, the presentation in this paper is restricted only to the first, *yes/no*, type of models.

## Methodology

The model development task was carried out in four main steps: (1) problem analysis, (2) data mining, (3) expert modelling, and (4) assessment of models.

### *Problem analysis*

Problem analysis was aimed at understanding the decision problem and studying the relevant literature. The most important bibliographic items, which were to the largest possible extent incorporated in the expert models, were: EFNS Guidelines (Ferreira, et al., 2013), MDS (2017) evidence based medicine publications, and treatment guidelines in the form of a decision tree (Olanow, et al., 2001).

***Data mining***

In this stage, we attempted to develop models by data mining. For this purpose, we used PPMI, a database provided by the Parkinson's Progression Markers Initiative (PPMI, 2011; www.ppmi-info.org/data), which contains an extensive collection of data sets describing different aspects of PD patients' daily living. For the purpose of this study, we created a subset of PPMI that contained 12 attributes that are available in the PD_manager DSS: 5 motor symptoms, 5 non-motor symptoms and 2 epidemiological data items. Overall, the data set contains 1027 data records, which correspond to 1027 visits of 362 patients. The class attribute, which has the values *yes* and *no*, indicates whether or not medication has been changed after the corresponding patient's visit. The distribution of the class is 654 *no*'s and 373 *yes*'es. Thus, the majority class is *no* and its relative frequency is 654/1027 = 0.6368 = 63.68%.

As already indicated, the results of this stage were not satisfactory. However, the PPMI data was used in the next stages to test the classification accuracy of expert-developed models. A good model is expected to outperform the *a-priori* accuracy of 63.68%, which would have been achieved by blindly saying *no* at each patient's visit.

***Expert Modelling***

The main resource for expert modelling is expert knowledge. In this approach, decision-support models are developed in collaboration between the expert and the decision analyst, taking into account clinical guidelines and medical practice. The work proceeds in the form of a question-answer dialogue, led by the analyst, aimed at identifying the important indicators and decision rules used, implicitly or explicitly, by the expert when making decisions. This process is usually supported by some suitable software.

The collective part of expert modelling in PD_manager took place in two workshops, organised in Venice, Italy (October 10–12, 2016) and Ioannina, Greece

(January 20–21, 2017). The core team consisted of six medical experts (three neurologists, two physiatrists, one psychologist) and two decision analysts. This team was occasionally supported by other members of the PD_manager project, who are specialists in data mining, information technologies and biotechnology. All these members appear as co-authors of this paper.

The expert modelling approach was based on the method DEX (Bohanec, et al., 2013). DEX is a qualitative multi-criteria modelling method. DEX models have a hierarchical structure, which represents a decomposition of some decision problem into smaller, less complex sub-problems. The hierarchy is formulated in terms of attributes and decision rules. All attributes are *discrete* (qualitative), and each attribute has an associated *value scale* that consists of words, such as {*low, medium, high*}. Optionally, scales are preferentially ordered. Attributes in DEX form a *hierarchical structure*, i.e., a directed acyclic graph or, most often, a tree. Aggregation is defined in terms of *decision rules*, grouped in decision tables. Decision rules, while being formulated, are checked for *completeness* and *consistency*. All elements of a DEX model are acquired *interactively* from experts, i.e., no data mining is involved.

The development of DEX models was supported by the free software DEXi (http://kt.ijs.si/MarkoBohanec/dexi.html). DEXi provides methods for acquiring expert knowledge, maintaining the consistency and completeness of models, and carrying out exploratory analysis of decision alternatives and their consequences.

### *Assessment of models*

In the final stage, all the produced models were assessed in terms of completeness, consistency, "medical" and logical correctness, classification accuracy (measured on the PPMI data subset), and in comparison with experts' opinion.

## DEX Models for Medication Change

The model development process went through two distinctive stages, closely related to two workshops that took place in October 2016 in Venice, Italy, which involved medical experts from the San Camillo Hospital, and in January 2017 in Ioannina, Greece, with the University of Ioannina team. Several DEX models were developed in this way; the models developed during the first workshop are collectively called the "Venice models" and named Model A, B, C, and D, while the model developed in Ioannina is called the "Ioannina model" and named Model I.

| Attribute | Scale |
|---|---|
| **MedicationChange** | **change**; maybe; ***no_change*** |
| ├**Motor** | **problematic**; maybe; ***normal*** |
| ├─bradykinesia | **problematic**; ***normal*** |
| ├─tremor | **problematic**; ***normal*** |
| ├─gait | **problematic**; ***normal*** |
| ├─dyskinesia | **severe**; **problematic**; ***normal*** |
| ├─on/off fluctuations | **problematic**; ***normal*** |
| └***Epidemiologic*** | **active**; ***passive*** |
| ├**Non-Motor** | **problematic**; maybe; ***normal*** |
| ├─daytime sleep. | **problematic**; ***normal*** |
| ├─cog.disorder | **problematic**; ***normal*** |
| ├─impulsivity | **problematic**; ***normal*** |
| ├─depression | **problematic**; ***normal*** |
| ├─hallucinations | **problematic**; ***normal*** |
| └***Epidemiologic*** | **active**; ***passive*** |
| └***Epidemiologic*** | **active**; ***passive*** |
| **Epidemiologic** | **active**; ***passive*** |
| ├─age | **younger**; ***older*** |
| ├─employment | **employed**; ***unemployed*** |
| ├─living alone | **yes**; ***no*** |
| └─disease duration | **short**; ***long*** |

| Attribute | Scale |
|---|---|
| **MedicationChange** | **change**; maybe; ***no_change*** |
| ├─activity | **high**; ***low*** |
| ├**Motor Response Complications** | **severe**; moderate; ***mild*** |
| ├─offs duration | **severe**; moderate; ***mild*** |
| ├─dyskinesia intensity | **severe**; moderate; ***mild*** |
| └─dyskinesia duration | **severe**; moderate; ***mild*** |
| ├**Symptoms** | **severe**; moderate; ***mild*** |
| ├─bradykinesia | **severe**; moderate; ***mild*** |
| ├**Overall Gait** | **severe**; moderate; ***mild*** |
| ├─freezing of gait | **severe**; moderate; ***mild*** |
| └─gait | **severe**; moderate; ***mild*** |
| └**Tremor** | **severe**; moderate; ***mild*** |
| ├─tremor at rest | **severe**; moderate; ***mild*** |
| └─tremor of hands | **severe**; moderate; ***mild*** |
| └**Non-Motor Symptoms** | **severe**; moderate; ***mild*** |
| ├─hallucinations | **severe**; moderate; ***mild*** |
| ├─BIS-11 | **severe**; moderate; ***mild*** |
| ├─mood | **severe**; moderate; ***mild*** |
| ├─cognition | **severe**; moderate; ***mild*** |
| └─NMSS | **severe**; moderate; ***mild*** |

Figure 1: Structure and value scales of Venice models (left) and Ioannina model (right)

Table 1: An example of decision rules: Model B, Motor symptoms

| | bradykinesia | tremor | gait | dyskinesia | on/off fluctuations | Epidemiologic | Motor |
|---|---|---|---|---|---|---|---|
| 1 | **problematic** | **problematic** | * | * | * | * | **problematic** |
| 2 | **problematic** | * | * | <=**problematic** | * | * | **problematic** |
| 3 | **problematic** | * | * | * | **problematic** | * | **problematic** |
| 4 | **problematic** | * | * | * | * | **active** | **problematic** |
| 5 | * | **problematic** | * | <=**problematic** | * | * | **problematic** |
| 6 | * | **problematic** | * | * | **problematic** | * | **problematic** |
| 7 | * | **problematic** | * | * | * | **active** | **problematic** |
| 8 | * | * | **problematic** | * | * | * | **problematic** |
| 9 | * | * | * | **severe** | * | * | **problematic** |
| 10 | * | * | * | * | **problematic** | **active** | **problematic** |
| 11 | **problematic** | ***normal*** | ***normal*** | ***normal*** | ***normal*** | ***passive*** | maybe |
| 12 | ***normal*** | **problematic** | ***normal*** | ***normal*** | ***normal*** | ***passive*** | maybe |
| 13 | ***normal*** | ***normal*** | ***normal*** | **problematic** | * | ***passive*** | maybe |
| 14 | ***normal*** | ***normal*** | ***normal*** | >=**problematic** | **problematic** | ***passive*** | maybe |
| 15 | ***normal*** | ***normal*** | ***normal*** | **problematic** | ***normal*** | * | maybe |
| 16 | ***normal*** | ***normal*** | ***normal*** | ***normal*** | ***normal*** | * | ***normal*** |

The Venice models share the same structure (Figure 1, left), which was agreed among the contributing physicians. The output attribute *MedicationChange* can, in addition to the obvious *change* and *no_change* values, additionally take the third, intermediate

value *maybe*; this value does not mean indecision, but indicates a situation that requires a more deep and thoughtful analysis of the patient's symptoms, for instance, conducting further medical or psychological tests. The Venice models are composed of three subtrees of criteria, representing indications for medication change based on *Motor* and *Non-Motor* symptoms, and *Epidemiologic* data. The majority of attributes in the Venice models are binary, taking two values: *normal* and *problematic*. The latter represents the state of the corresponding symptom that is troublesome for the patient and may require a change of medication. The Ioannina model (Figure 1, right) has the same output attribute and similar input attributes, but the latter are structured differently and predominantly use a three-value scale *severe*, *moderate*, and *mild*.

In addition to attributes and scales, DEX models contain decision rules. In Venice, the contributing physicians were using the same attribute structure, but defining their own decision rules. This gave four different models, called A, B, C, and D. In Ioannina, a single Model I was produced by a single neurologist.

To illustrate the concept of decision rules, **Error! Reference source not found.** shows an example from Model B: a decision table that determines the overall severity of *Motor* symptoms based on the severity of five motor symptoms (*bradykinesia*, *tremor*, *gait*, *dyskinesia*, and *on/off fluctuation*). Additionally, *Epidemiologic* data is considered as an assessment of whether the patient is *active* or *passive* (physically or at work). The rules in Table 1, as all the other rules in the models, were acquired in a dialogue with the physician and decision analyst, using the DEXi software. The rules are shown in a compact form, using the symbols '*', which represents any value of the corresponding attribute, and '<=', which means 'worse than or equal'.

**Assessment of the models**

*Completeness and consistency*. All the models are, by design, guaranteed to be complete and consistent. The completeness means that the models contain rules that cover all the possible combinations of input values. There are no "holes" or unspecified parts in the model. The consistency refers to the fact that the models obey the principle of dominance, which holds in the PD medication change domain: the more severe the symptoms, the more imperative the change of medication.

*Transparency and comprehensibility*. The models contain decision rules that represent normative medical knowledge in a consistent way. The rules were formulated and verified by medical experts; they can be easily inspected, reviewed and changed if necessary.

*Accuracy and validity*. These criteria refer to the ability of the models to provide "right" suggestions for given inputs, which should be in accordance with medical guidelines and physicians' expertise. We assessed them in two different ways: by measuring the accuracy of models on the PPMI data subset, and by comparing models' and physicians' decisions on a sample of use-cases (Table 2).

Table 2: Classification accuracy of DEX models [%], assessed on the PPMI data and in comparison with experts

| **Assessed on** | **Model A** | **Model B** | **Model C** | **Model I** |
|---|---|---|---|---|
| *PPMI data* | 46.28 | 37.00 | 36.32 | 52.50 |
| *Experts' answers* | 77.22 | 85.28 | N/A | 78.19 |

The classification accuracy, measured on the PPMI data, was generally quite low and was in all cases below the *a-priori* accuracy of 63.68%. The best accuracy was achieved by Model I. These measurements reconfirmed our experience with the PPMI data, with which we were unable to produce *any kind* of model that would outperform the *a-priori* accuracy. There are many possible reasons for that (Bohanec, et al., 2017), from a high variability and inconsistency of decisions captured in the PPMI, to the fundamental

difference between *normative* knowledge, which is captured in DEX models, and *descriptive*, real-life performance, which is reflected in the PPMI. For the PD_manager DSS, which is aimed at identifying situations that require medical response rather than giving instructions of how to react, the normative aspect seems more relevant.

When measured in comparison with physicians on selected use cases, the performance of the models turned out to be much better. A questionnaire was prepared, containing 15 use-cases that were designed to cover as many as possible different (and difficult) situations that occur in practice. The response was obtained from 27 medical experts: 15 from Greece, 7 from Italy, 1 from the UK, and 1 from Slovenia. Comparing the models with the experts' suggestions, the models A, B and I achieved relative accuracies as shown in the third row of Table 2. Even though the numbers are not directly comparable with the ones measured on the PPMI, they are much higher and indicate a good match (about 80%) between the models' and physicians' answers.

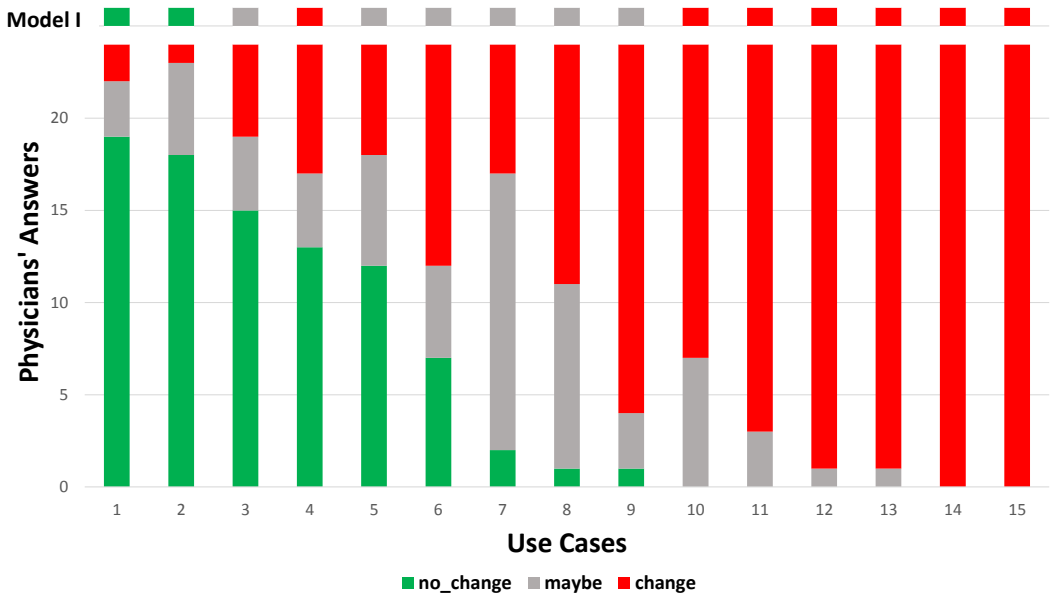


Figure 2: Comparing suggestions of Model I and 27 physicians on 15 use cases

The matching is illustrated by Figure 2: Comparing suggestions of Model I and 27 physicians on 15 use cases. Model I correctly identifies both simple (green, shown on

the left) and difficult cases (red, on the right). In the middle, Model I tends to suggest "*maybe*" in the cases in which there is no obvious consensus between the physicians.

## Conclusion

In the framework of the PD_manager project, we constructed a variety of medication change models using expert modelling and the method DEX. The approach turned out to be feasible: a group consisting of decision analysts and medical experts was able to formulate medication change models in terms of hierarchical structure of qualitative attributes, and the experts were able to define all the necessary decision rules in a fairly comfortable and efficient way. The resulting models are all guaranteed to contain consistent decision rules that cover the whole space of input attributes' values, i.e., any combination of motor and non-motor symptoms, and any epidemiologic characterization of a patient.

The models have a number of other qualities: they contain decision rules that represent normative medical knowledge in a consistent way. The rules were formulated and verified by medical experts, the models are transparent and can be thus inspected, reviewed and changed if necessary. In terms of accuracy, the models' did not perform well on the PPMI data, but they resembled very well decisions made by physicians on a sample of hypothetical use-cases. We believe that the constructed models are sufficiently good and thus fit for the purpose of making "second-opinion" suggestions to medical users of the PD_manager DSS.

In the following work, the Models A, B and I will be implemented in the PD_manager DSS. A clinical trial of the DSS will be carried out in 2018, including the tracing of the models' performance and their comparison with actual decisions.

**Acknowledgment**

This work is supported by the PD_manager project, funded within the EU Framework Programme for Research and Innovation (Horizon 2020), under grant number 643706. The authors wish to thank 27 physicians contributing to the use-case analysis. Some of the data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (http://www.ppmi-info.org/data).

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