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# Modeling the progression of Parkinson's Disease : comparison of subjects with and without Sleep Disorders

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## Introduction

Patients with idiopathic Parkinson's Disease (iPD) may have very different patterns of progression, corresponding to distinct disease subtypes. Here, we describe quantitatively the overall pattern of progression in subgroups of PD by using a Bayesian non-linear mixed effect model that describes the continuous progression of biomarkers at both population and individual level. This approach allows to model variability in progression patterns and disease stage between patients. We analyzed two subgroups of patients, with (iPD-RBD+) and without sleep disorders (iPD-RBD-), that are known to present different patterns of progression [1]. We compared the two groups by extracting the ordering of abnormalities that occurred over the disease course, and by studying their disease onset and speed of progression.

## Methods

### Data

We used the Idiopathic PD patients of the PPMI Dataset. We considered eight biomarkers to describe the disease progression. First four clinical scores, the MDS-UPDRS part III, MoCA, SCOPA-AUT and REM Questionnaire, measuring respectively motor, cognitive, autonomy and sleep dysfunctions. Second, we included four measures from DatScan imaging, the Striatal Binding Ratios (SBR) of left and right side of both Putamen and Caudate. From the 362 idiopathic PD patients of the PPMI dataset, we excluded patients that had less than two visits of the biomarkers to obtain 343 patients. Patients that reached a REM Questionnaire score of 6 over 13 at least once over the course of the study were labeled as iPD-RBD+ (192 patients), the others as iPD-RBD (151 patients).

### Modeling

We used a multivariate non-linear Bayesian mixed-effect model, introduced in [2] and extended in [3], to estimate the longitudinal progression of clinical and imaging scores. We estimated both population and individual parameters of patients, to obtain the average and individual trajectories, respectively. Sub-group trajectories were obtained by averaging individual parameters over the patient sub-groups. Then, to assess the robustness of our method, accounting for both sampling bias and stochastic variations in the estimation algorithm, we performed a patient-wise repeated cross validation (10x5 folds) on our dataset.

### Progression of patients with and without RBD

With the methodology described above, we obtained 50 sub-population average trajectories for each group (iPD-RBD- and iPD-RBD+), shown in Figure 1. To build a hierarchy of arrival of abnormalities of PD biomarkers that may progress at very different speeds and occur at different ages, we introduced abnormality thresholds. For each biomarker independently, thresholds were computed from the data as the optimal cut-off for a balanced logistic regression between PD patients and controls at baseline. We then computed the times of intersection between the averaged trajectories of the sub-groups and these abnormal thresholds to assess an abnormality timing density for each modality. Densities are shown as boxplots in Figure 1.

## Results and Discussion

The ordering of abnormalities between modalities in the two groups was the same, at the exception of sleep since it discriminated our two groups (Figure 1). The first abnormality was observed in the putamen, followed by MDS-UPDRS part III then, caudate, scopa and finally MoCA. Note that MDS-UPDRS abnormality occurred early, as even few points of MDS-UPDRS label patients as PD in our logistic regression. Thus, we could also consider the age at disease onset, mainly based on motor scores, to represent a more advanced stage of motor

abnormality. Noticeably, the distance to PD average age at diagnosis differed between the two subgroups. In RBD- patients, autonomic dysfunction occurred shortly after conversion to PD, whereas in RBD+, the SCOPA-AUT was already abnormal up to 3.4 years before conversion. To a lesser extent, MoCA abnormalities occurred earlier in iPD-RBD+ than in iPD-RBD-. Finally, considering only the individual parameters estimated by the model, we found that RBD+ were affected in average 3.32 years earlier than RBD-, and progressed 26% faster in average.

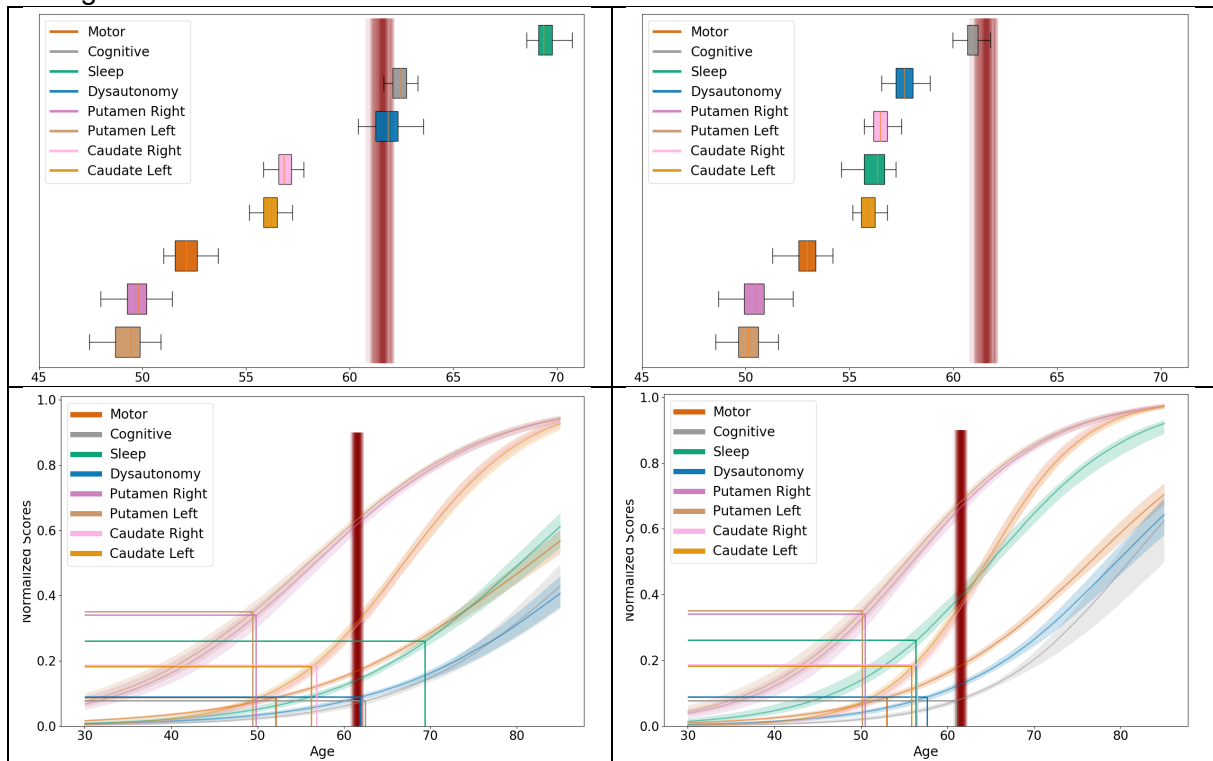


Figure 1 : Progression of iPD-RBD is shown on the left plots, and iPD-RBD+ on the right. In each plot, average ages of conversion to PD for each split is shown in dark red.

On the bottom, cross validated (10x5 folds) average scenario of progression for the 2 subgroups, relative to age. Lowest and highest points of the filled area represent quantiles at 5% and 95% of the biomarker's progression. Note the major difference for the REM Questionnaire, in green, as this biomarker was used as a criteria to split our subgroup. Thresholds of abnormalities for each score are represented as horizontal lines.

On the top, boxplot of cross validated (10x5 folds) times of intersection with threshold of abnormalities for each considered biomarker.

## Conclusions

Using a longitudinal model, we were able to compare two sub-populations of a longitudinal cohort in several ways: progression speed, age at onset and ordering of abnormalities. iPD-RBD+ were affected 3.32 years earlier and progressed 26% faster. They also presented autonomic dysfunction up to 4 years before PD onset whereas these symptoms occurred around PD onset in iPD-RBD- patients. These results stand as a proof of concept for longitudinal group comparison methodology, which could be applied to other types of diseases. Furthermore, this first subgroup analysis lay the foundations of a more precise subtyping of patterns of progression in PD.

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