Longitudinal Parkinson's Disease Progression Model using Item-Response-Theory Utilized to Predict Treatment Effect of Levodopa

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Background

- Parkinson's disease (PD) ranks among the most common late-life neurodegenerative diseases affecting 2% of people over 60 years of age.
- Disease progression is measured primarily using a single, 6-part composite Unified Parkinson Disease Rating Scale (UPDRS)[1] consisting of 4 sub-categories (sub-scores) under Part I, 13 under Part II, 27 under Part III and 11 under Part IV
- Part I (Mentation, Behavior and Mood), Part II (Activities of Daily Living), Part III (Motor Examination), Part IV (Complications of therapy), Part V (Hoehn and Yahr (H&Y) Staging), Part VI (Schwab and England ADL scale)
- A limitation to the UPDRS scale is the inter-rater variability, especially for each of the subscale scores. This added variability affects the diagnosis and estimation of the progression of PD as well as differentiating between early and late disease stages.

Objective

- To evaluate and understand the natural history of early and long-term disease progression in Parkinson's Disease (PD) by applying Item-Response-Theory (IRT) to analyze the longitudinal change of item-level data from the UPDRS collected during NINDS trials.
- To predict the effect of Levodopa treatment of the longitudinal change of item-level data from the UPDRS using IRT.

Methods

1. Data and Subjects

- UPDRS data from 44 different sub-scores (Part I, Part II, Part III) obtained from the following NINDS trials were utilized:

Datasets for Natural Disease Progression Model Development

- DATATOP- 24 month study on 800 early untreated patients, H&Y stage <= 3
- ELLDOPA- 15 month study on 360 subjects in early, mild PD, not requiring symptomatic medications, H&Y <= 2.5
- PRESTO- 6 month study on 450 subjects with idiopathic PD who are experiencing motor fluctuations on levodopa therapy, H&Y Stages <= 4
- QE2 – 16 month study on 80 early PD patients not requiring treatment with levodopa or any other antiparkinsonian medication, H&Y Stage< = 3
- RAPID-20-24 weeks study on 300 PD patients with motor fluctuations on chronic LD/CD therapy, H&Y Stage <= 5

Dataset for Placebo Effect and Drug Effect Model Development

- ELLDOPA - Dataset with Placebo + Levodopa

  Dose of Levodopa – Low (50mg), Medium (100mg), High (200mg)

  No dose modifications in the subjects under study

- IRT model[2] was developed in R 3.2.3 to predict patient specific latent scores using R package "mirt".
- Longitudinal Bayesian framework with random intercept was developed using "brms" package in R 3.2.3.
- Logistic regression model was established using the "nnet" package from the CRAN directory.
- Visual Predictive Check (VPC) plots were used to evaluate the developed model using R 3.2.3.

Model Adaptation Workflow

- Tree diagrams obtained from bootstrap algorithm[3], to provide a hierarchical structure to hypothesize the interlink between individual sub-scores of the UPDRS composite scale and to identify key drivers of sub-scales informing the overall diseases progression (Figure 1).

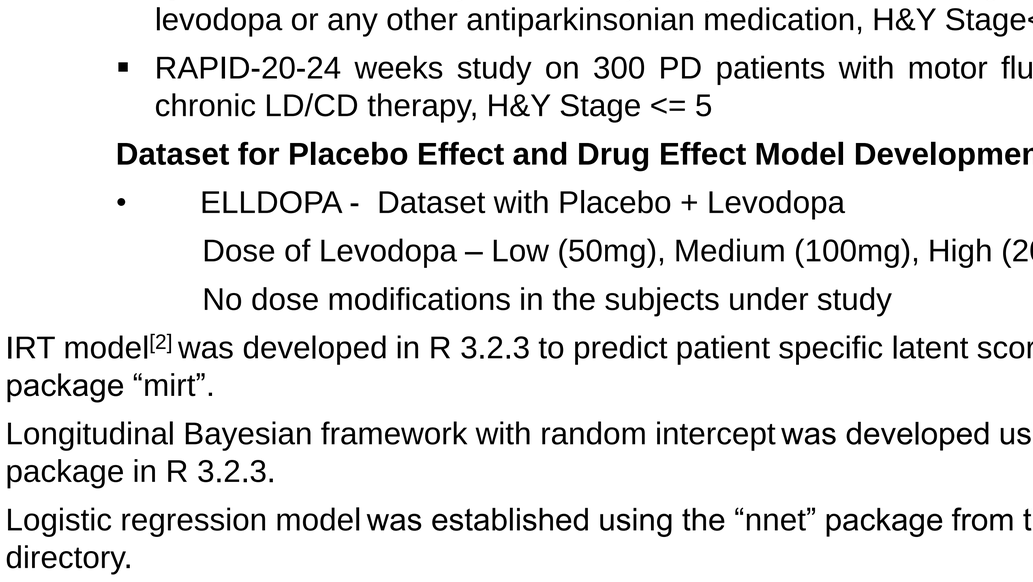


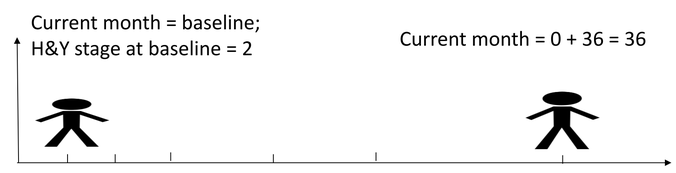
Figure 1: The figure shows the tree diagram outlining the hierarchy of the sub-scores obtained using bootstrap algorithm. For every cluster, the diagram lists bp and au value. bp shows the probability of the particular cluster to appear in the bootstrapping algorithm with 1000 simulations. au is a modified form of bootstrap probability, which shows the p-value for 95% CI, if bootstrapping algorithm is repeated with varying sample sizes.

Bootstrap → Create Dendograms to obtain Hierarchy in sub-scores → **Hand Movements (rt hand) (HM) and Rapid/Alter Movement (rt hand) (RAM)** Most influential in predicting sub-scores higher in hierarchy

Methods

3. Development of Algorithm for longitudinal PD Simulation Model

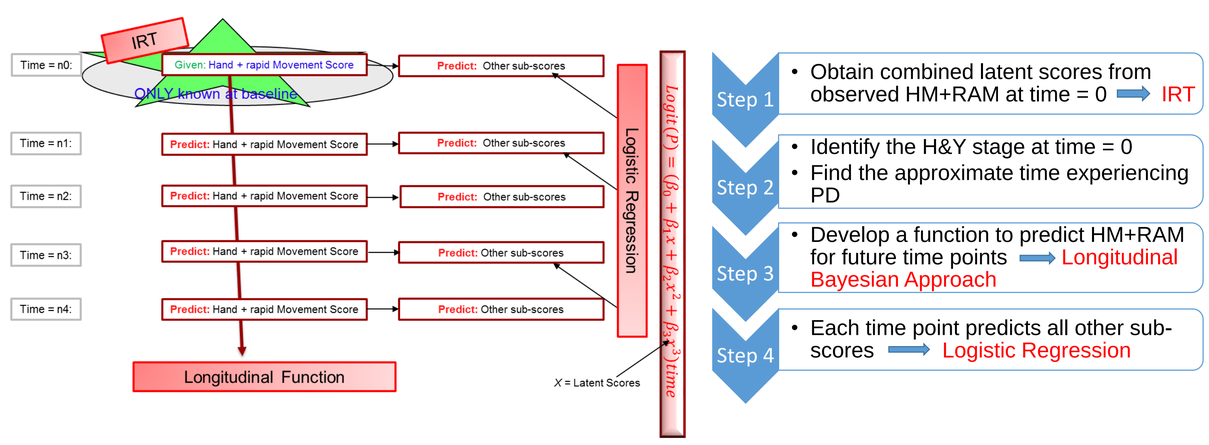
Place subjects in HY Timeline



Transition to H&Y Stage	Duration (months)
1-1.5	10
1.5-2	26
2.5-3	30
3-3.5	41
3.5-4	59
4-4.5	13

Figure 2: The chart (left) shows an approximate time of transition between different H&Y stages. This chart have been obtained from the literature[5,6]. The figure (right) shows the method to approximately calculate the time or duration, the subject spend as PD patient before entering the study. If the H&Y stage at baseline is 2, from the chart, we know that the subject is in 26th month in PD timeline.

Model Development Overview



Results

1. Development of longitudinal natural progression model of Hand and Rapid Movement

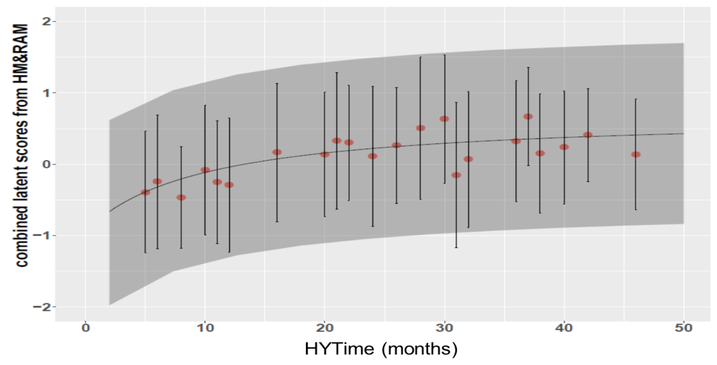


Figure 3: The figure shows the longitudinal progression of natural disease progression model. The model development of the natural disease progression model uses data from all five datasets in NINDS trial used in the model development. The red dots represent the mean and the vertical bars represent the standard deviation of the observed data. The black line represent the model evaluated mean prediction whereas the grey shaded region represent the 90%PI.

$$f(HYTime) = (\theta_i^{stability} + \eta_{stability}) + \left(\theta_i^{shape} \Big/ (\theta_i^{asymptote} + HYTime)\right)$$

2. Development of longitudinal drug effect model for Hand and Rapid Movement

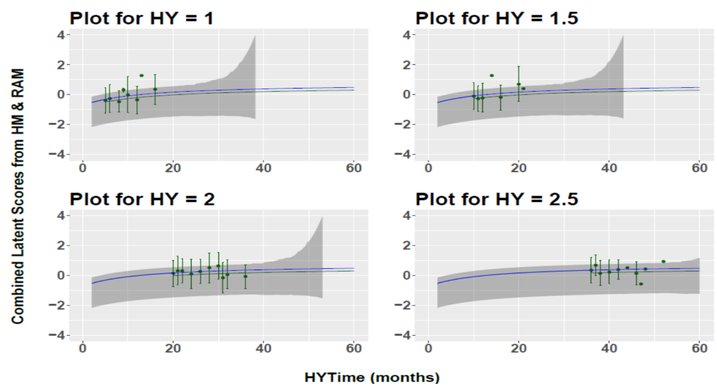


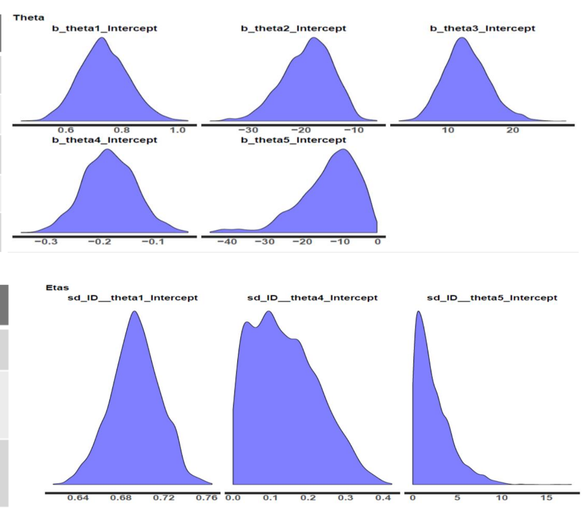
Figure 4: The figure shows the longitudinal progression of drug effect model. The model development of the drug effect model, only uses data from Elldopa study in NINDS trial. The green dots represent the mean whereas the vertical bars represent the standard deviation of the observed placebo data. The solid green line represent the mean prediction from the drug effect model where the grey shaded region represent the 90%PI. The blue line represent the prediction from the natural disease progression model. The plots were stratified by H&Y stage.

$$f(time) = D_i(HYTime) = (\theta_i^{stability} + \eta_{stability}) + \left(\theta_i^{shape} \Big/ (\theta_i^{asymptote} + HYTime)\right) + (\theta_i^{Shift_{drug}} + \eta_{Shift_{Drug}})(1 - \exp(r_{placebo_{Drug}} * study_{time}))$$

3. Estimated model parameters and its distribution

Fixed Effect Parameters	Estimate	95%CI of estimate
$\theta_i^{stability}$	0.74	(0.57,0.92)
θ_i^{shape}	-18.74	(-28.68,-10.78)
$\theta_i^{asymptote}$	12.81	(6.7, 20.14)
$\theta_i^{Shift_{Drug}}$	-0.18	(-0.28, -0.08)
$r_{Drug_{Onset}}$	-12.89	(-32.35, -2.01)

Random Effect Parameters	Estimate	95%CI of estimate
$Sd(\eta_{stability})$	0.69	(0.65,0.74)
$Sd(\eta_{Drug_{Shify}})$	0.14	(0,01, 0.33)
$Sd(\eta_{Drug_{Shify}})$	2.32	(0.08,7.64)



Conclusion

- The model identified "Hand Movement" (HM) and "Rapid/Alter Movement" (RAM) as the most influential and sensitive sub-scores within the UPDRS
- The simulator needs only information of HM & RAM at baseline and the Hoehn & Yahr stage of the subject at baseline to predict disease progression in PD subjects and to predict the overall change and severity for all 44 sub-scores of UPDRS including motor and non-motor functions
- Well defined placebo effect was not observed in the dataset
- Drug effect was clearly identified by the parameter estimates
- The simulator can be utilized for clinical trial simulations

REFERENCES

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