A Bayesian Disease progression model of Parkinson Disease combining RWD and natural history data to evaluate a new treatment

Pissoort Antoine | Maud Hennion | Bruno Boulanger (Pharmalex)
Anne Bousseau | Caroline Denot (Brainever)

22 May 2019
Summary of the Methodology

0. Subset PPMI
   - Available database
   - Select relevant historical data

1. Model on PPMI patients
   - Over the whole period (24 Months)
   - Random slope
   - Change from baseline

2. Simulate future studies
   - Based on posterior estimates of 1.
   - 3-12m (history)
   - 15-24m
   - Different scenarios (i.e. treatment effects)

3. Model on simulated patients
   - 3-12m
   - Informative priors based on 1.

4. PPD
   - From posterior estimates of 3.
   - Predict normal trajectory of patients (15-24m)
   - Compare with simulated patients
Summary of the Methodology

0. Subset PPMI
   - Available database
   - Select relevant historical data

1. Model on PPMI patients
   - Over the whole period (24 Months)
   - Random slope
   - Change from baseline

2. Simulate future studies
   - Based on posterior estimates of 1.
   - 3-12m (history)
   - Random slope
   - Different scenarios (i.e. treatment effects)

3. Model on simulated patients
   - 3-12m
   - Informative priors based on 1.

4. PPD
   - From posterior estimates of 3.
   - Predict normal trajectory of patients (15-24m)
   - Compare with simulated patients

© PharmaLex
**Parkinson's Progression Markers Initiative (PPMI)**

- The **Parkinson’s Progression Markers Initiative** (PPMI) is an *observational* clinical study whose purpose is to identify clinical, imaging and biological markers of PD progression for use in clinical trials of disease-modifying therapies.

- Among parameters tracked to define PD progression, focus on the MDS-UPDRS\textsubscript{m} score.

- The endpoint of interest is the *change from baseline* (cfl).

- 1870 patients are enrolled in the PPMI study from about 35 centers.

- Study period is 13 years

— As, the PPMI dataset gives a good representation of the *normal progression* of the disease (no treatment), it will be used to simulate virtual patients of a future study, define informative priors, evaluate operating characteristics of a future study…
The historical Data: a subset of the PPMI dataset

- Based on the inclusion/exclusion criteria defined in the protocol, only a subset of the PPMI database is included for the future analysis.
  - Inform the model only with relevant patients

- For example, based on
  - Category: Parkinson disease cohort, genetic cohort, …
  - Enrollment Age
  - Disease Duration
  - …
  - N = 163 patients are selected in this study

- These patients should be the most similar to those expected in the future application.
Example of patients selected in the database
Summary of the Methodology

0. Subset PPMI
   - Available database
   - Select relevant historical data

1. Model on PPMI patients
   - Over the whole period (24 Months)
   - Random slope
   - Change from baseline
   - Based on posterior estimates of 1.
   - 3-12m (history)
   - 15-24m
   - Different scenarios (i.e. treatment effects)

2. Simulate future studies
   - 3-12m
   - Informative priors based on 1.

3. Model on simulated patients
   - From posterior estimates of 3.
   - Predict normal trajectory of patients (15-24m)
   - Compare with simulated patients

4. PPD
1. Model over 24 months

- Fit a **random slope model** on the selected subset of PPMI:

  \[
  Y = \beta_1 \cdot t + \epsilon, \quad \beta_1 \sim N(\mu_{\beta_1}, S_{\beta_1}^2), \quad \epsilon \sim N(0, S^2),
  \]

  where \(Y\) is the **MDS-UPDRS\(\text{m}\) change from baseline (cfbl)** and \(t = \{3, 6, \ldots, 24\}\) is the month.

- Gibbs sampling (PROC MCMC) to estimate the parameters
- 3 parameters \((\mu_{\beta_1}, S_{\beta_1}^2, S^2)\) → posterior chains:

![Graphs showing random slope model parameters with median, 80% and 99% CI]

© PharmaLex
Summary of the Methodology

0. Subset PPMI
   - Available database
   - Select relevant historical data

1. Model on PPMI patients
   - Over the whole period (24 Months)
   - Random slope
   - Change from baseline

2. Simulate future studies
   - Based on posterior estimates of 1.
   - 3-12m (history)
   - 15-24m
   - Different scenarios (i.e. treatment effects)

3. Model on simulated patients
   - From posterior estimates of 3.
   - Informative priors based on 1.
   - 3-12m
   - Predict normal trajectory of patients (15-24m)
   - Compare with simulated patients

4. PPD
2. Simulate Future Studies Based on the Fitted Model

- Based on parameter posterior chains, simulate **12 patients** from **100 studies**:

<table>
<thead>
<tr>
<th>Treated</th>
<th>( Y = s_1 \cdot t - I_{t&gt;12} \cdot \beta \cdot (1 - \exp[-r \cdot (t - 12)]) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>( Y = (s_1 + I_{t&gt;12} \cdot \gamma) \cdot t - I_{t&gt;12} \cdot \beta \cdot (1 - \exp[-r \cdot (t - 12)]) )</td>
</tr>
</tbody>
</table>

- **Time period (t) of 3 to 24 months:**
  - 3-12 months → Normal evolution of the disease (\~ PPMI)
  - 15-24 months → Introduce treatment and placebo effects

- **Note:** Different scenarios should be compared
  - Sensitivity analysis
2. Simulate 12 new patients (100 studies)

\[ Y = s_1 \cdot t + I_{t>12} \cdot \gamma \cdot t - I_{t>12} \cdot \beta \cdot (1 - \exp[-r \cdot (t - 12)]) \]

- Fix the parameters:
  - \( s_1 = 0.331 \) → Slope before treatment
    Value given by the model on PPMI data
  - \( \gamma = 0.1 \) → Difference placebo to treatment
  - \( \beta = 5.2 \approx \) growth range
  - \( r = 0.4 \approx \) growth rate

- Open question: What placebo effect?
- Need to consider several scenarios
Check the simulations on 3-12 months
Summary of the Methodology

0. Subset PPMI
   - Available database
   - Select relevant historical data

1. Model on PPMI patients
   - Over the whole period (24 Months)
   - Random slope
   - Change from baseline

2. Simulate future studies
   - Based on posterior estimates of 1.
   - 3-12m (history)
   - 15-24m
   → Different scenarios (i.e. treatment effects)

3. Model on simulated patients
   - 3-12m
   - Informative priors based on 1.
   - From posterior estimates of 3.
   - Predict normal trajectory of patients (15-24m)
   - Compare with simulated patients

4. PPD
Model only the **first part** of the simulated data
Model only the first part of the simulated data: by study

\[ Y_i = \beta_{1i} \cdot t + \epsilon_i, \quad \beta_{1i} \sim N(\mu_{\beta_{1i}}, S_{\beta_{1i}}), \quad \epsilon_i \sim N(0, S_i^2) \]

Study \( i = 1, 2, \ldots, 100 \)

... Up to study nr 100
Informative priors: Method of Moments

Fit a new model (also random slope) on the simulated patients over the first 12 months
→ Use the PPMI data model’s posterior chains to inform this new model

If $X \sim \text{Inverse Gamma}(\alpha, \beta)$,

- $E(X) = \frac{\beta}{\alpha-1}$, $V(X) = \frac{\beta^2}{(\alpha-1)^2(\alpha-2)}$

Estimate $E(X)$ with $\hat{\mu}$ and $V(X)$ with $\hat{\sigma}^2$ of the corresponding chain of the PPMI data model.

Solve the system of 2 equations and find the $\alpha$ and $\beta$ to use in the prior.

- $\hat{\alpha} = \frac{\hat{\mu}^2}{\hat{\sigma}^2} + 2$
- $\hat{\beta} = \hat{\mu} \cdot \left( \frac{\hat{\mu}^2}{\hat{\sigma}^2} + 1 \right)$

→ To use in the $IG$ prior of $S^2$ and $S^2_{\beta_1}$

For $\mu_{\beta_1}$, simply take the empirical mean and sd of $\mu_{\beta_1}$ of the 1st model in the normal prior.

$Y = \beta_1 \cdot t + \epsilon$, $\beta_1 \sim N(\mu_{\beta_1}, S^2_{\beta_1})$, $\epsilon \sim N(0, S^2)$
Summary of the Methodology

0. Subset PPMI
   - Available database
   - Select relevant historical data

1. Model on PPMI patients
   - Over the whole period (24 Months)
   - Random slope
   - Change from baseline

2. Simulate future studies
   - Based on posterior estimates of 1.
   - 3-12m (history)
   - 15-24m
   - Different scenarios (i.e. treatment effects)

3. Model on simulated patients
   - 3-12m
   - Informative priors based on 1.

4. PPD
   - From posterior estimates of 3.
   - Predict normal trajectory of patients (15-24m)
   - Compare with simulated patients

© PharmaLex
Illustrate with 3 patients in one study: Treated vs Placebo

- Normal evolution of the disease
  - PPD by patient (\(\forall t\)) as if disease evolves normally
  - Compare to simulations (with treatment): the dots

\[
Y = \beta_1 \cdot t + \epsilon, \quad \beta_1 \sim N(\mu_{\beta_1}, S_{\beta_1}^2), \quad \epsilon \sim N(0, S^2)
\]
Compare simulated patients with their PPD: illustration with some studies
Other illustrations: predictive intervals
Results
The different scenarios to show treatment effect

- **Power:** treatment 100% and placebo “significantly” different
- **Controlling type 1 error:** treatment 0% and placebo should be similar
Probability of a simulated patient to be below its Predictive Distribution

Dashed vertical lines represent the medians over the studies for each timepoint.
Probability of a simulated patient to be below its Predictive Distribution (2)

Dashed vertical lines represent the medians over the studies.
Results with 90 + 30 patients
The different scenarios
Probability of a simulated patient to be below its Predictive Distribution

Dashed vertical lines represent the medians over the studies for each timepoint
Probability of a simulated patient to be below its Predictive Distribution (2)

Dashed vertical lines represent the medians over the studies

(Consider more than 100 studies to obtain smoother densities)
Conclusion

- A complete framework is set up and can be used in similar applications 
  - E.g. Charcot disease

- Bayesian analysis provides meaningful metrics to inform the scientist.

- The variability observed in such measurements (UPDRS) is very high.
- As a result, treatment effect is hard to discriminate from placebo effect.

- It is easier to discriminate between placebo and treated patients if the sample size increases.