Minimizing levodopa infusion titration period for Parkinson's disease, using simulated data.

Ilias Thomas[1,*], Moudud Alam[1], Marina Senek[2], Dag Nyholm[2] and Jerker Westin[1]

[1]Dalarna University, Sweden, [2]Uppsala University Hospital, Sweden,
*Presenter of this poster, e-mail: ith@du.se

Aim

The aim is to reduce the number of dose titration days, using a optimization algorithm that individualizes pharmacokinetics-pharmacodynamics (PKPD) models, when initiating levodopa-carbidopa intestinal infusion.

Models and Methods

Individual model fitting

Mathematical optimization was used to fit individual PKPD models. The PKPD model calculated an effect, given a dose. The effect was reported in a 7 point scale, ranging from bradykinesia at lower values to dyskinesia at higher values of the scale. Certain parameter values of the PKPD model were fixed to population mean values whereas others were altered (decided upon sensitivity analysis) in order to minimize a distance function. **The altered parameter values together with the fixed parameters described the individual model.** The input to the distance function were the observations from the dose titration days. Multiple algorithms were applied to the minimization process and showed similar performance. An example of a fitted model can be seen in figure 1.

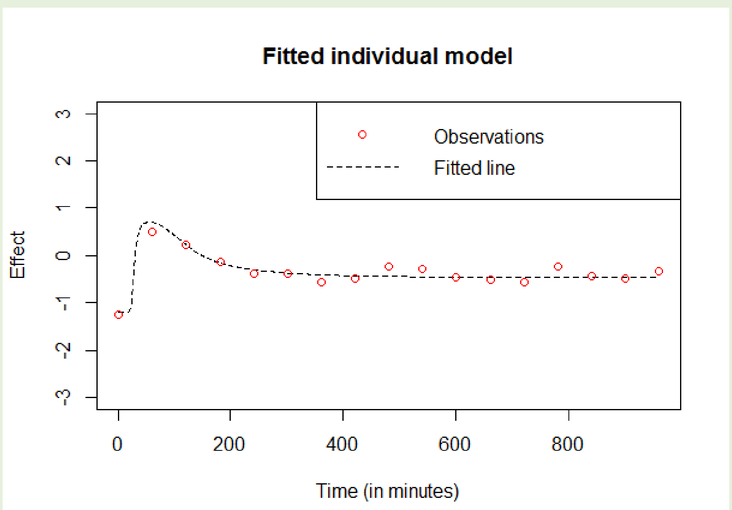

Figure 1: Individual model fitting for one patient from the simulated dataset. Only one day of observations are used in the model fitting process. The model is fitted using the Nelder-Mead algorithm.

Dosing optimization algorithm

An optimization algorithm derived the optimal dosing regiment for each fitted model. **The algorithm simulated the optimal maintenance dose in terms of mg/h and the optimal morning dose for the patient**. Simulations were carried out in a 16 hour interval and **optimal regiments were defined as the ones that maximize the "on-state" of patients.** This was achieved by minimizing the time where the patient was either over medicated or under medicated when receiving the morning dose. The maintenance dose stabilized the patient at "on-state" throughout the day.

Applying the algorithms to the Simulated dataset

Simulated dataset

A dataset of 100 patients was generated based on the population parameters of the PKPD model. **For all patients, a baseline morning dose and maintenance dose was simulated on the first day.** For the ones that appropriate individual models could not be fitted on day 1, an increased or decreased dose was given on day 2 (based on the first day's observations), and so on until day 3. **More titration days were deemed unnecessary, because of the performance of the method**. For all simulated titration days, only one observation per hour was considered and used for the computations.

Results

For each patient the simulated optimal dose regimen was obtained using the known individual parameters. Running the optimization and simulation procedures, dosing suggestions were calculated for each patient through their individual fitted models. The suggestions were then compared to the optimal regimen to check for agreement with a 5% error tolerance. The maintenance dose prediction has better performance (the majority of the observations are when the patient is "stable") and **two days of titration is enough to approximate the optimal maintenance dose** in 96% of the cases.

	Morning Dose	Maintenance Dose
Day I	46%	55%
Day II	74%	96%
Day III	85%	99%

Table 1: Accuracy of morning and maintenance dose predictions, with a 5% error tolerance, compared with the simulated optimal doses, presented as the percentage of patients with the correctly predicted dose for each day of observation.

Three days of dose titration provides enough information to fit individual models, that yield dosing suggestions very similar to the optimal ones for the morning dose. A great improvement can be noted between day 1 and 2. Correlation between optimal morning dose and suggested morning dose is shown in table 2.

	Correlation	Relative Error
Day I	0.89	11%
Day II	0.94	5%
Day III	0.95	5%

Table 2: Correlation between the optimal morning dose and the suggested morning dose when using different number of days in the model fitting algorithm. On the right column the prediction error is shown.

Visual comparison of correlation and accuracy using different number of days in the analysis

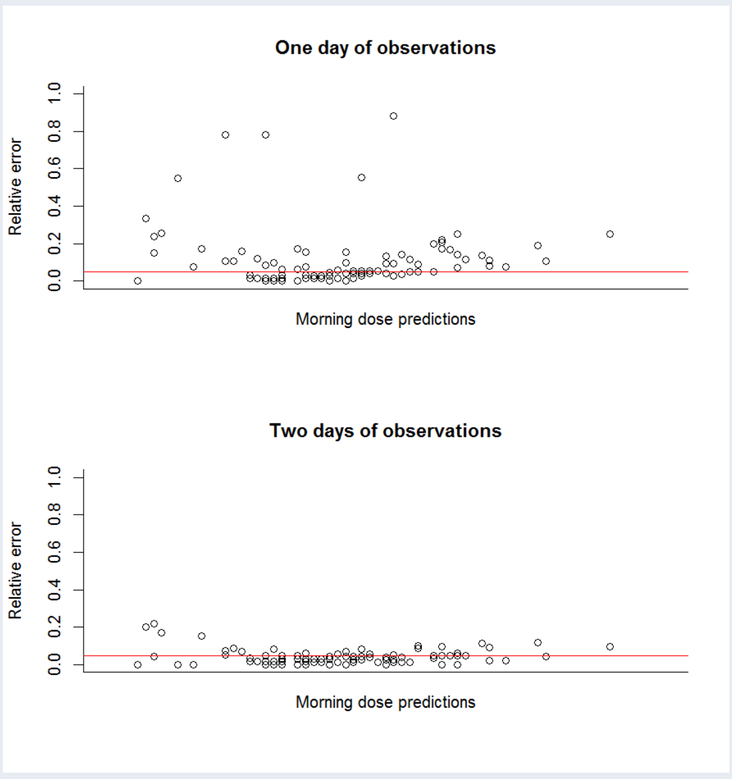

Figure 2: Relative errors when predicting the optimal morning dose, using one or two titration days in the model fitting process. A great improvement can be noted when comparing prediction after one day versus two days of observations. The red line shows the 5% error tolerance level.

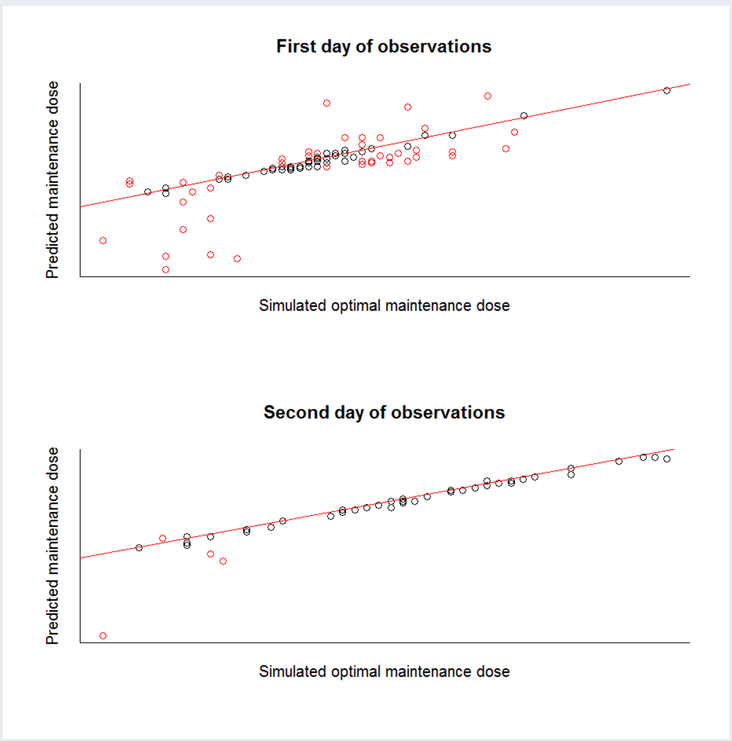

Figure 3: Results when predicting the optimal maintenance dose, using only two titration days in the model fitting process. 96% of the patients have correct rate prediction after the second day. In the top plot all 100 patients predictions vs. optimal dose are shown. In red colour are the predictions that did not fall withing the acceptable prediction interval, of 5% error tolerance. These observations from the first day are shown in the bottom plot. The red lines go through the origin to demonstrate the agreement.

Conclusions

- **Two dose-titration days**, with one observation per hour, **are sufficient to approximate the optimal morning and maintenance dose** for the vast majority of the cases. This is shorter compared with previous results from clinical trials, where the mean dose-titration duration was reported to be 7.6 and 7.1 days (Lew et al. 2015[1])
- Adding more observations after the patient receives the morning dose (an observation every 15-20 minutes for the first 2 hours),would further **improve the performance of the method** when predicting the morning dose.

Reference:

[1]Lew MF, Slevin JT, Krüger R, et al. Initiation and dose optimization for levodopa-carbidopa intestinal gel: Insights from phase 3 clinical trials. Parkinsonism Relat Disord. 2015;21:742–748.