



Individual levodopa dosing suggestions based on a single dose test.

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Aims

- ▶ Construct patient-specific models from a single dose experiment
- ▶ Use the models to make optimized dosing suggestions for oral administration of levodopa.

Models and Methods

Dataset

- ▶ 19 patients with Parkinson's disease participated in a clinical study (Uppsala University Hospital, Sweden, 2015)
- ▶ They were given a **single dose of levodopa-carbidopa, 150% of their normal morning dose.**
- ▶ Three movement disorder specialists rated the patients' condition on a seven-level treatment response scale from very off (-3) to very dyskinetic (+3) in regular time points after the dose. The mean values of the raters' assessments at each point were used as target values for model parameter estimation.

Individual model fitting

- ▶ Mathematical optimization was used to fit individual Pharmacokinetics-Pharmacodynamics (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.** Multiple algorithms were applied to the minimization process and showed similar performance. Fitted models can be seen in figure 1.

Individual model fitting

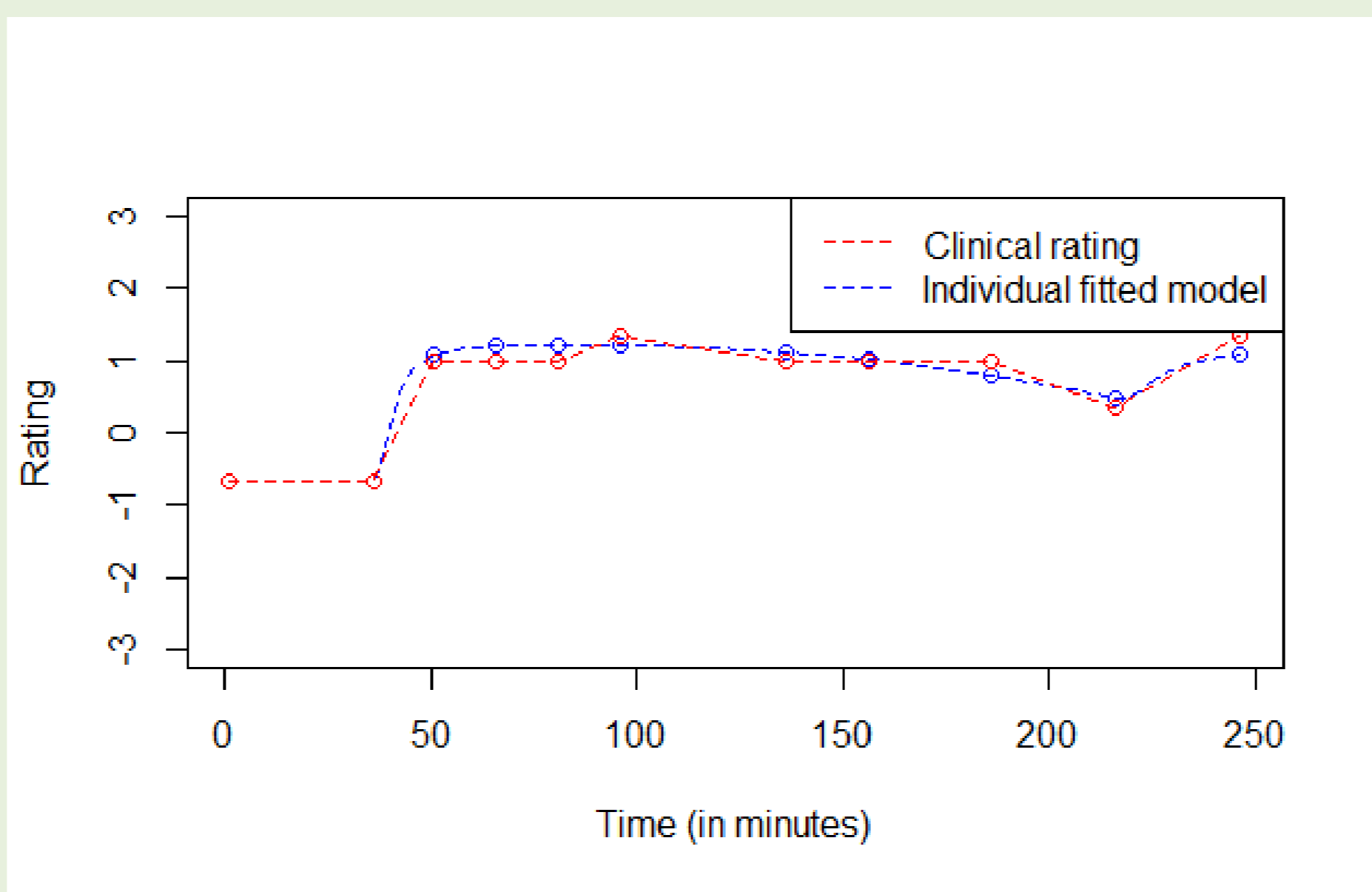
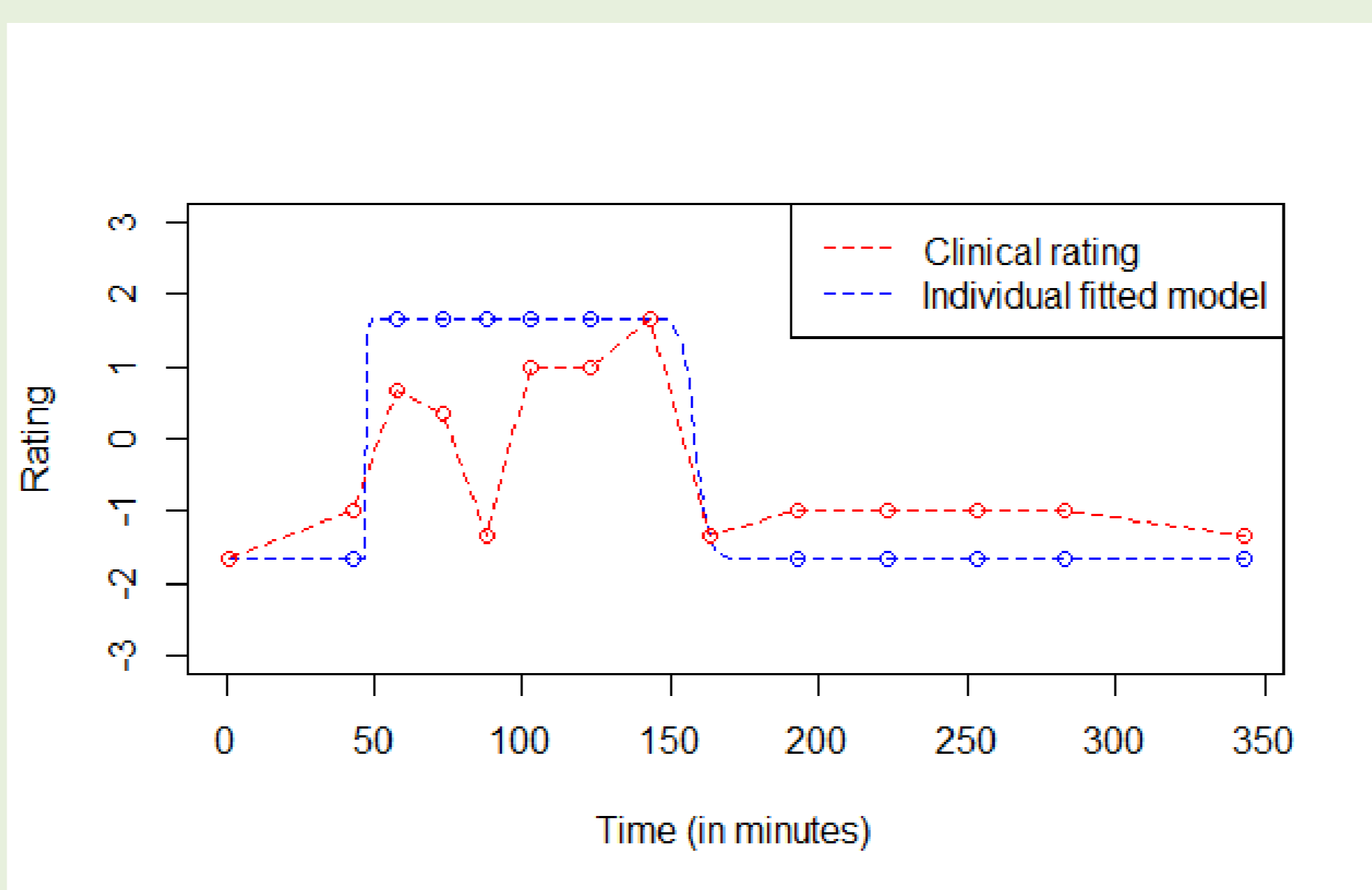
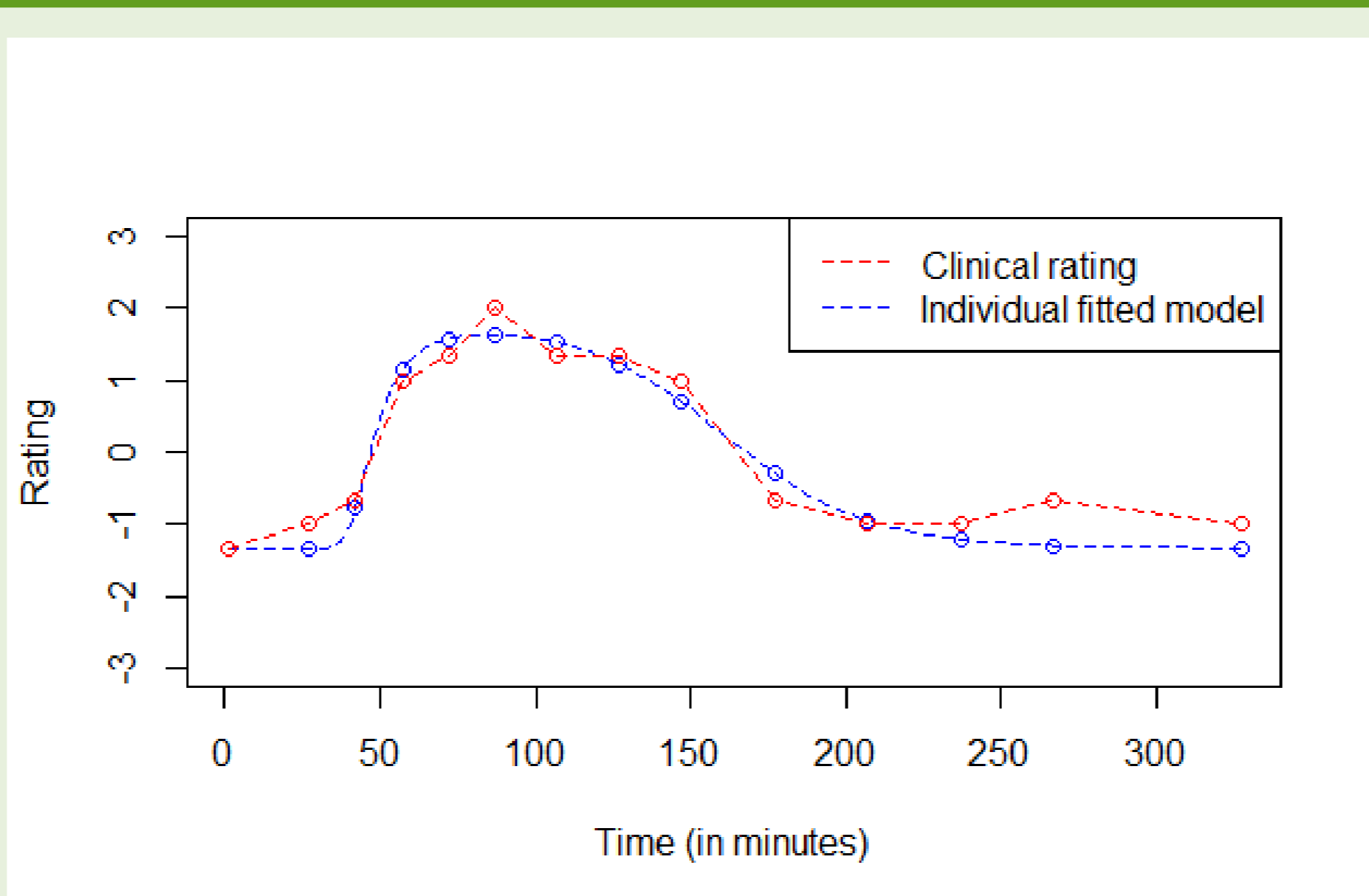


Figure 1: Individual model fitting for a number of individuals with PD. A single dose experiment is used in the model fitting process. The model is fitted using the Nelder-Mead algorithm.

Simulation algorithm

- ▶ An optimization algorithm derived the optimal dosing regimen for each fitted model.
- ▶ **The algorithm simulated the optimal morning bolus dose and optimal normal doses in terms of mg/dose.** Simulations were carried out in a 16 hour interval.
- ▶ **Optimized dosing for the algorithm was defined as the dosing routine that minimizes motor fluctuations and maximizes the "on" time throughout the day, and was restricted to a maximum number of doses.**

Results

Preliminary results show the ability of the optimization routines to identify individual dose-response curves and fit individual models.

Results

- ▶ The simulation algorithm makes optimized individualized dosing suggestions according to the models. The suggestions are similar to the real-life dosing regimens of the patients in terms of total dosing per day (Pearson's correlation 0.84, p-value 0.07), but still changes are proposed.
- ▶ In Figures 2 and 3 results from the application of the proposed method are shown.

Time interval	Normal dose	Morning dose
90 minutes	119	162
100 minutes	129	174
110 minutes	138	189
120 minutes	159	208
130 minutes	182	229
140 minutes	208	173
150 minutes	239	176
160 minutes	0	0
170 minutes	0	0

Figure 2: Example of simulated optimal doses for the different intervals. The values at large intervals are set to 0 because optimized doses cannot be derived.

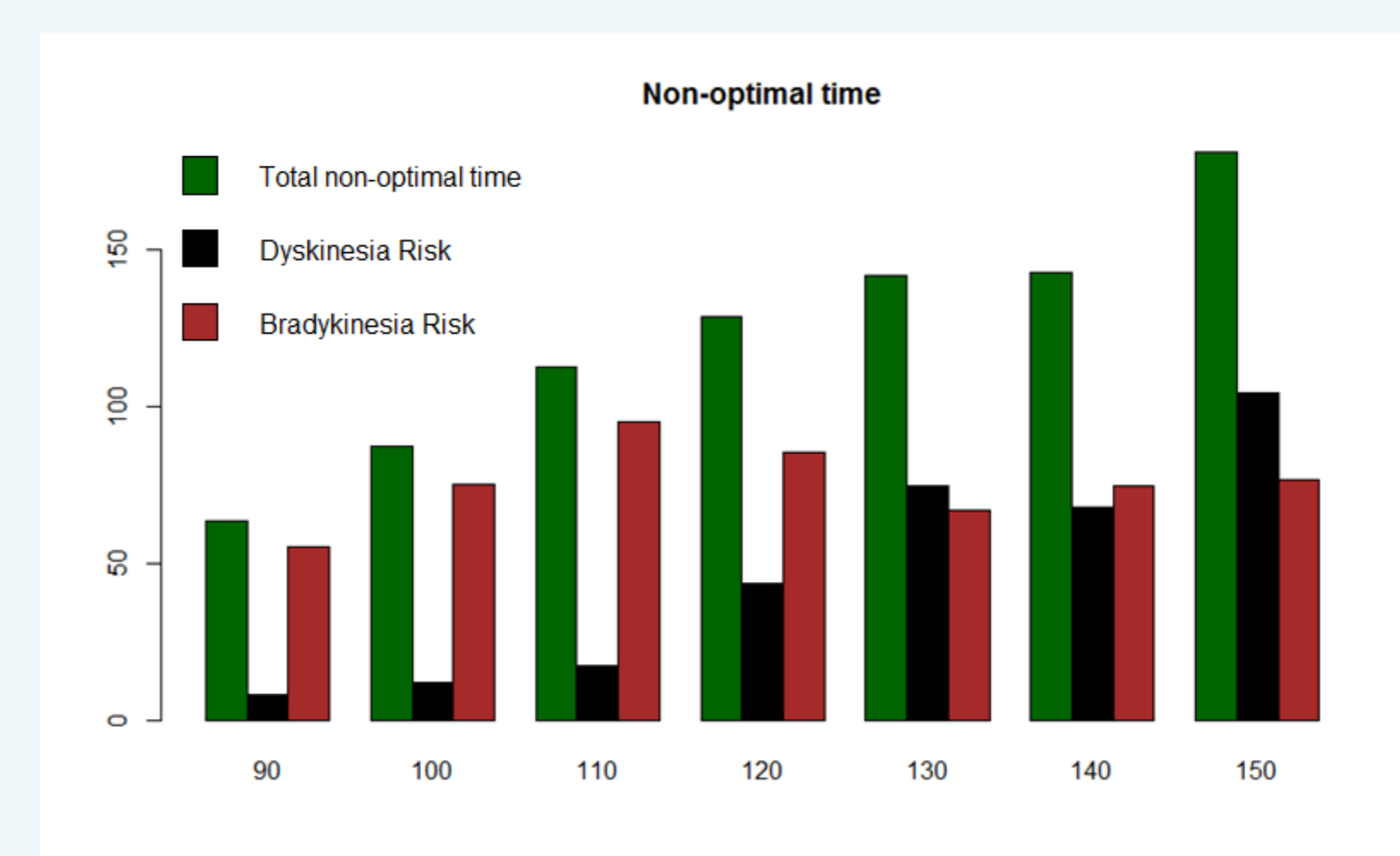


Figure 3: Visualization of the results from figure 2. For each interval a corresponding barplot is created that gives information about the risk of being overmedicated or undermedicated. On the x-axis the different dosing intervals are shown and on the y-axis the total time an individual would spend on a non-optimal state for a day is plotted.

Conclusions

- ▶ As Parkinson's disease progresses the levodopa response duration gradually changes. Our findings suggest that the response to a single dose of levodopa provides enough information to propose individualized dosing regimens that may reduce motor fluctuations.
- ▶ Evaluation of single-dose response profiles could be automated using objective motor performance measurements with accelerometry, and may in combination with individualized dose-response simulations be used to aid patient and physician in dose regimen optimization when patients start to develop motor fluctuations.