A Semi Parametric Method for the Estimation of End of Treatment Effect

Mohamed Gewily, Yersultan Mirasbekov, Gustaf J. Wellhagen, Mats O. Karlsson

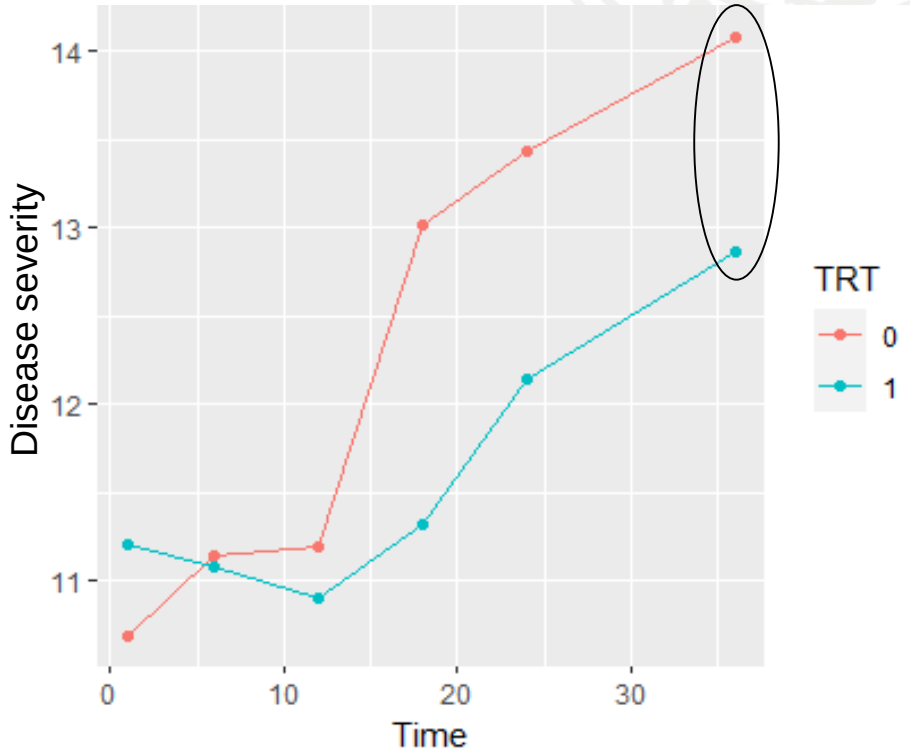
Pharmacometrics group, Department of Pharmacy, Uppsala University, Sweden

31st PAGE meeting

28th of June 2023

Treatment effects in Randomized Clinical Trials

- Definition: a statistically significant change in clinical outcome that is attributable to treatment compared to reference
- Typically assessed at end of treatment
- Methods used in this project:
  - Mixed models for repeated measures (MMRM)
  - Nonlinear mixed effects models (NLMEM)



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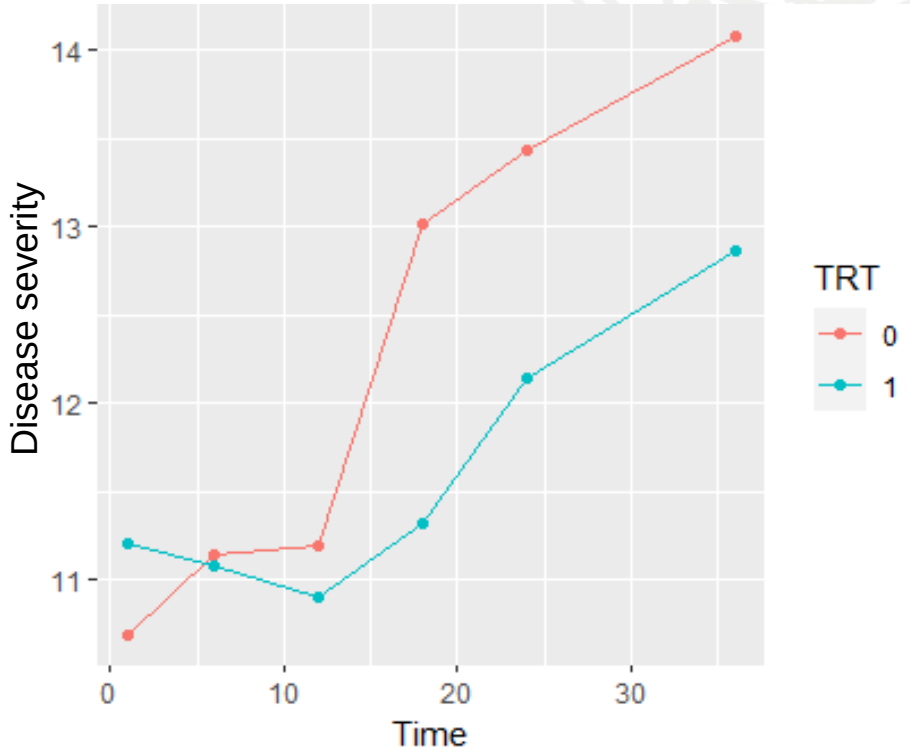
Application to longitudinal data

-Mixed Models for Repeated Measures (MMRM)

- model the mean and standard deviation of observations at each categorical time
- gold standard to handle dropouts

- Non Linear Mixed Effects Models (NLMEM)

- flexible progression equations
- less parameters



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Pros and cons of both methods

Estimation of end of treatment effect:

- MMRM:

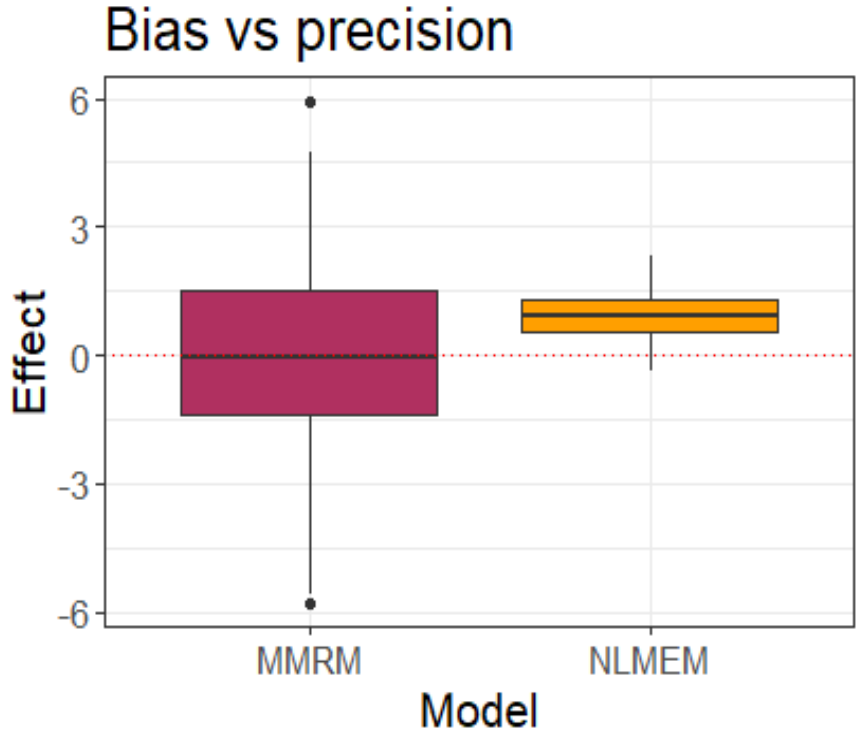
estimate the difference in means between the study arms at the last time point

  - mostly unbiased
  - not very precise

- NLMEM:

can be made to estimate the difference in means between study arms at the last time point

  - subject to misspecification bias
  - can inflate type I error
  - mostly more precise



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Objectives

- Investigate the combination of both MMRM and NLMEM for the estimation of end of treatment effect
- Investigate the impact on treatment effect estimation accuracy

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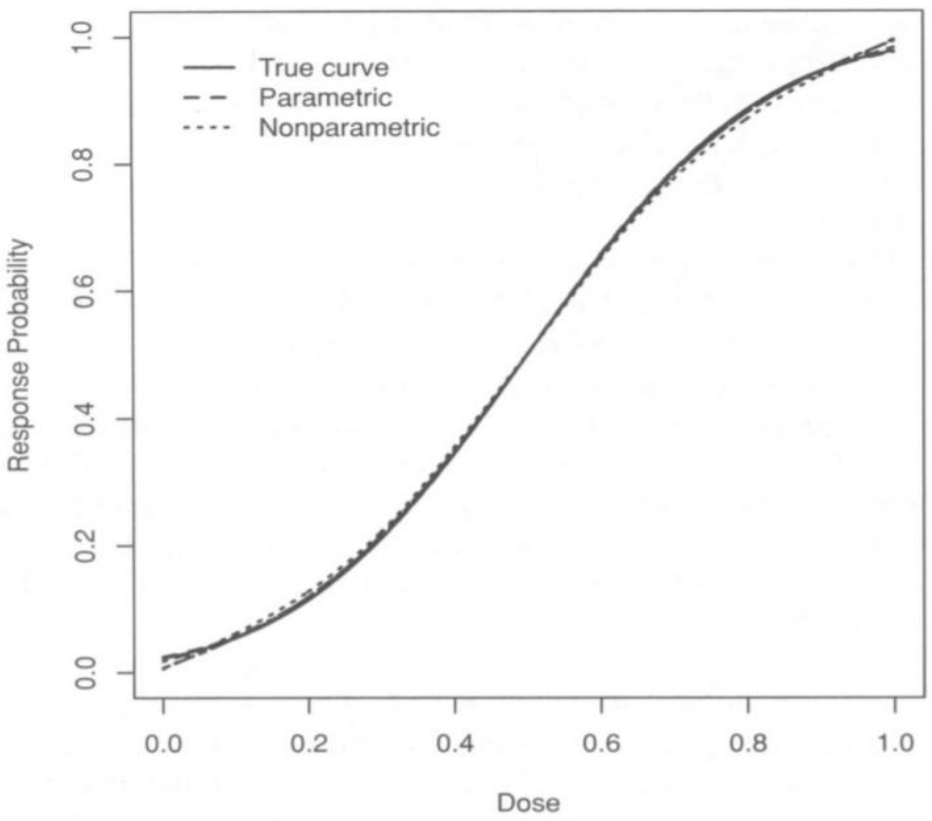
Yuan and Yin article



- Semi parametric estimation of dose response curve (model averaging)
  - Unbiased non-parametric
  - More precise parametric
- Assume non-parametric estimate was unbiased
- Bootstrapping to measure error relative to initial non-parametric estimate
- A semi parametric estimator (π):

  - Use Mean Squared Error (MSE) to estimate the best weights

- $Semi\ parametric = \pi \times parametric + (1 - \pi) \times nonparametric$

Yuan et al.Biometrics. 2011 Dec;67(4):1543–54.

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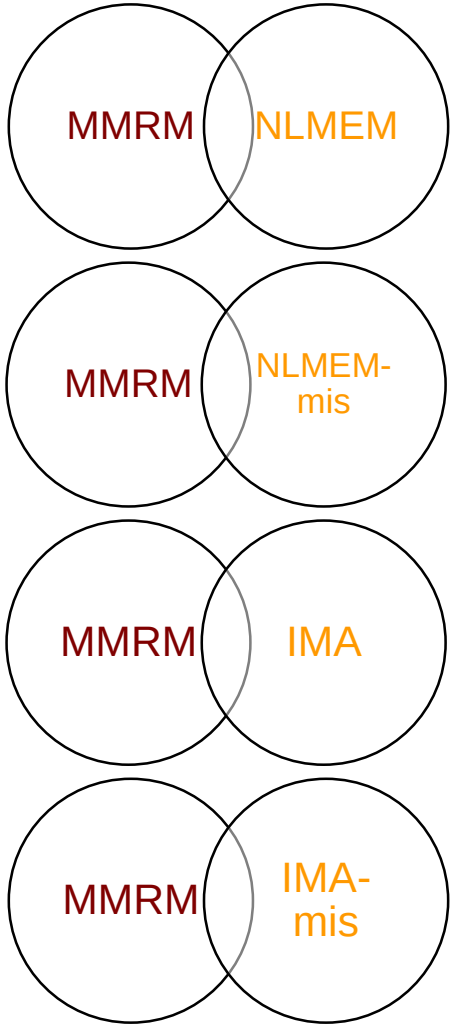
Models

1. MMRM with unconstrained residual error correlation structure
   - Parameters: Mean at each time point
   - Unconstrained residual error variance matrix
2. NLMEM
   - NLMEM
   - NLMEM-mis, slope misspecification
3. IMA (Individual model averaging)
   - IMA
   - IMA-mis, slope misspecification

Averaging across these pairs



Chasseloup et al. AAPS J. 2021 May 3;23(3):63.

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Data

Disease	Parkinson's disease	Alzheimer's disease	Diabetic neuropathy
Score	MDS-UPDRS	ADAS-Cog	Likert pain
TRT	Placebo	Natural progression	Placebo
No. individuals	85	153	114
No. observations	510	918	798
No. visits	6	6	7

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Our workflow

• Repeat 100 times

Progression DATA

- MDS-UPDRS
- ADAS-Cog
- Likert

Random TRT allocation

- 1:1 parallel design

ID	TRT
1	1
2	0
3	1

Fit the Models

- MMRM
- NLMEM
- NLMEM-mis
- IMA
- IMA-mis

600 Bootstraps

- Calculate **π**

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The Semi-Parametric Approach (SPA)

$$TE_{SPA} = \uparrow \pi \times TE^*_{NLMEM} + (1 - \pi) \times TE^*_{MMRM}$$

$$\uparrow \pi = \frac{\uparrow MSE(TE_{MMRM}) - covb(TE_{MMRM}, TE_{NLMEM})}{MSE(TE_{MMRM}) + \downarrow MSE(TE_{NLMEM}) - 2 \times covb(TE_{MMRM}, TE_{NLMEM})}$$

covb accounts for error correlation

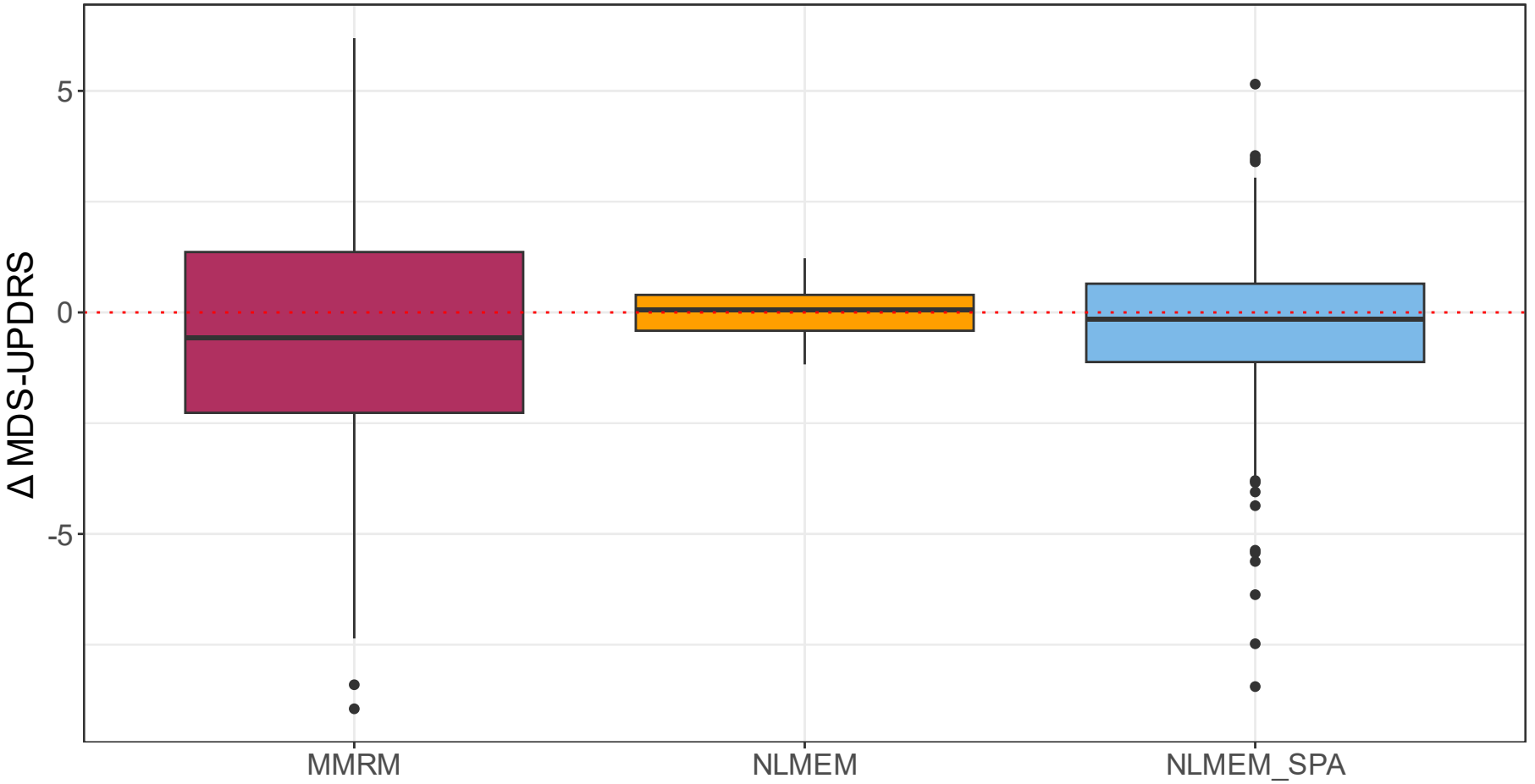
$$MSE(TE_{method}) = \frac{1}{B} \times \sum_{b=1}^{B} \left[\left(TE^{(b)}_{method} - TE^*_{MMRM} \right)^2 \right]$$

- Description:
  - TE – treatment effect
  - TE* – treatment effect before bootstrapping
  - MSE – mean squared error
  - B – number of bootstraps
  - Covb- covariance_bias
  - π- NLMEM weight

Type I error

- Type I error assessed across 100 trials:
  - the frequency of which models detect a treatment effect that is significantly different from 0 is counted as an error

Treatment effect estimate, Parkinson's disease



Abbreviation	Meaning
MMRM	Mixed Models for Repeated Measures
NLMEM	Nonlinear Mixed Effects Model
_mis	Misspecified
IMA	Individual Model Averaging
SPA	Semi Parametric Approach

Label	Measurement
Bias	Mean - true effect (0)
Precision	Standard deviation
Accuracy	Mean Squared Error (bias + precision)

Mean Δ:	-0.687	-0.007	-0.483
SD Δ:	3.050	0.562	2.272

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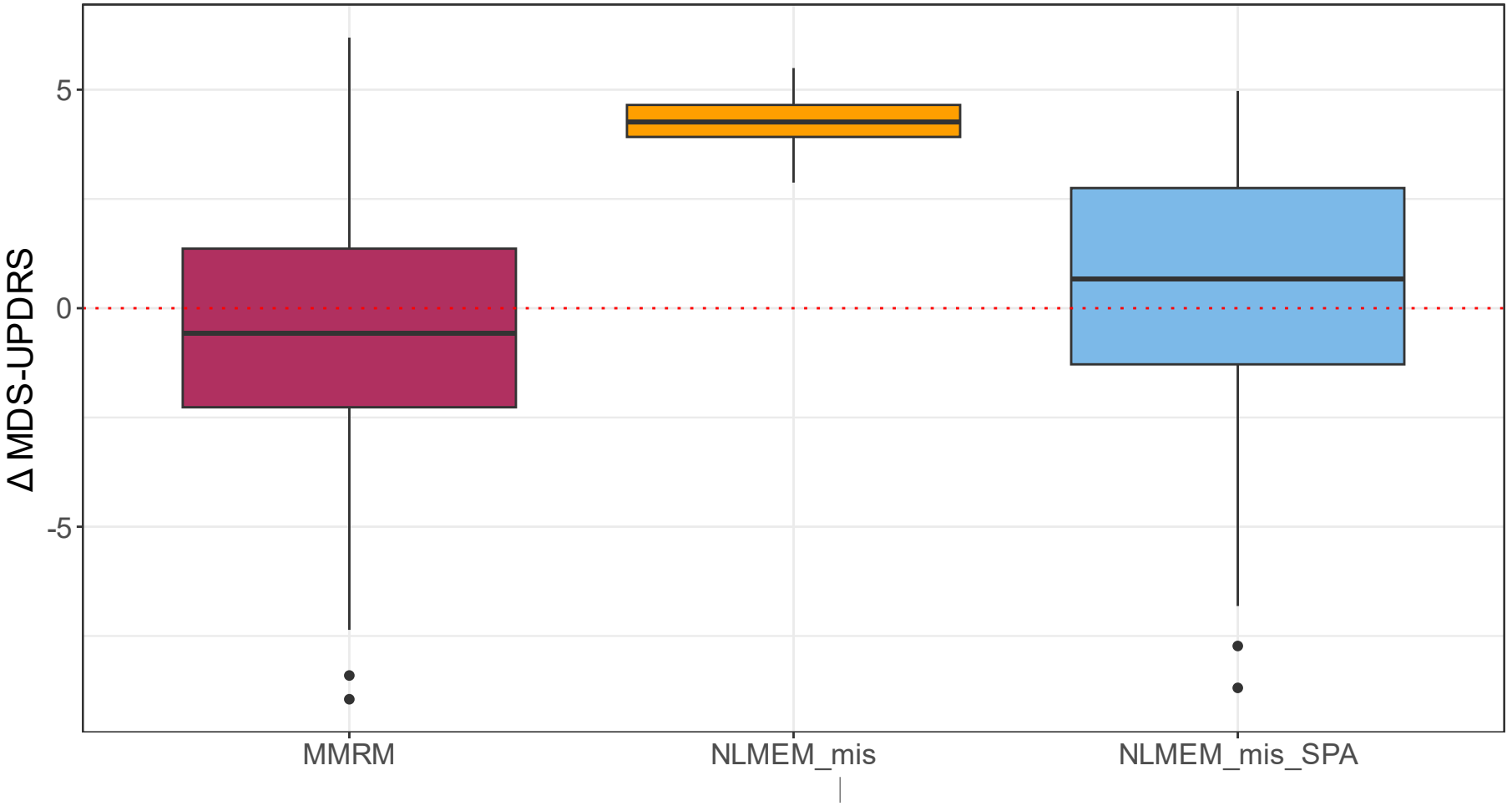
Treatment effect estimate, Parkinson's disease



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Bias	Mean - true effect (0)
Precision	Standard deviation
Accuracy	Mean Squared Error (bias + precision)

Mean Δ:	-0.687	4.527	0.344
SD Δ:	3.050	0.546	3.070

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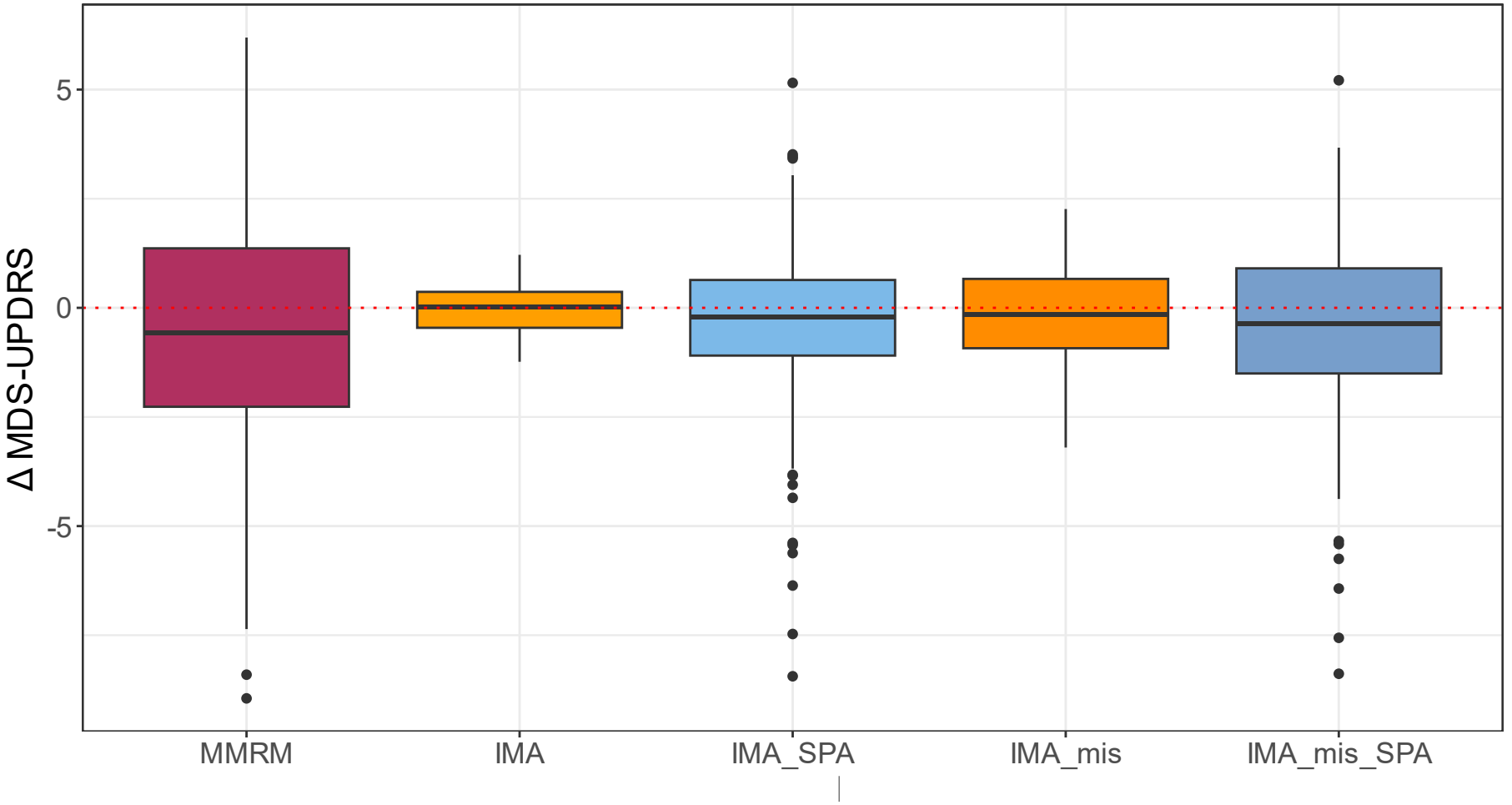
Treatment effect estimate, Parkinson's disease



Mean Δ:	-0.687	-0.045	-0.505	-0.225	-0.553
SD Δ:	3.050	0.563	2.260	1.147	2.376

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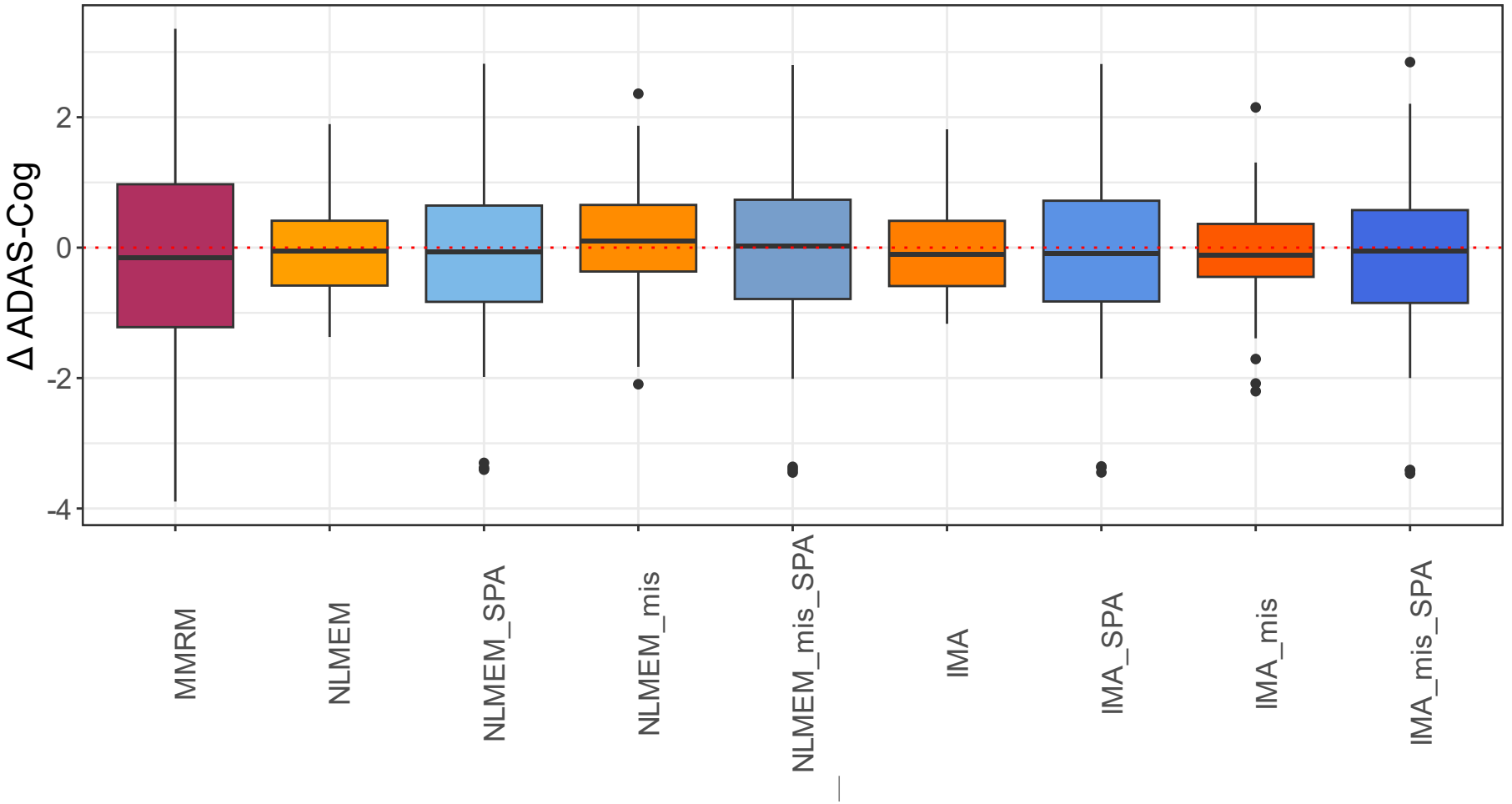
Treatment effect estimate, Alzheimer's disease



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Label	Measurement
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Precision	Standard deviation
Accuracy	Mean Squared Error (bias + precision)

Mean Δ:	-0.169	-0.059	-0.090	0.125	-0.015	-0.041	-0.095	-0.069	-0.101
SD Δ:	1.518	0.686	1.169	0.790	1.201	0.625	1.161	0.745	1.174

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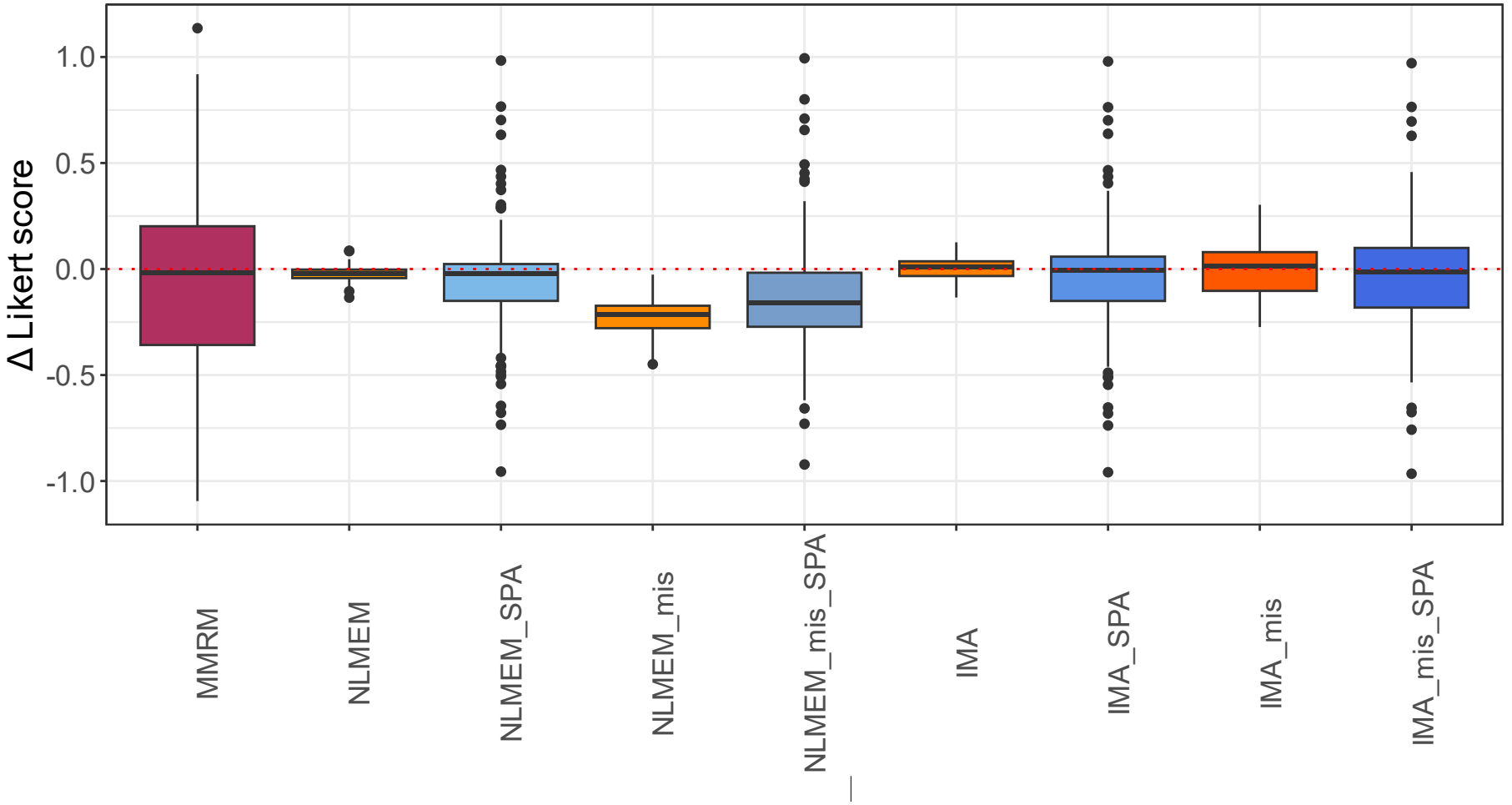
Treatment effect estimate, Diabetic neuropathy



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NLMEM	Nonlinear Mixed Effects Model
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IMA	Individual Model Averaging
SPA	Semi Parametric Approach

Label	Measurement
Bias	Mean - true effect (0)
Precision	Standard deviation
Accuracy	Mean Squared Error (bias + precision)

Mean Δ:	-0.043	-0.022	-0.040	-0.224	-0.108	0.004	-0.031	-0.007	-0.040
SD Δ:	0.438	0.035	0.298	0.082	0.313	0.050	0.301	0.119	0.307

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MSE of the Semi-Parametric Approach (SPA)

Methods:	MSE		
	Parkinson's disease	Alzheimer's disease	Diabetic neuropathy
MMRM	9.72	2.32	0.19
NLMEM SPA	5.34	1.36	0.09
misNLMEM SPA	9.51	1.43	0.10
IMA SPA	5.33	1.35	0.09
IMA_mis SPA	5.89	1.37	0.09

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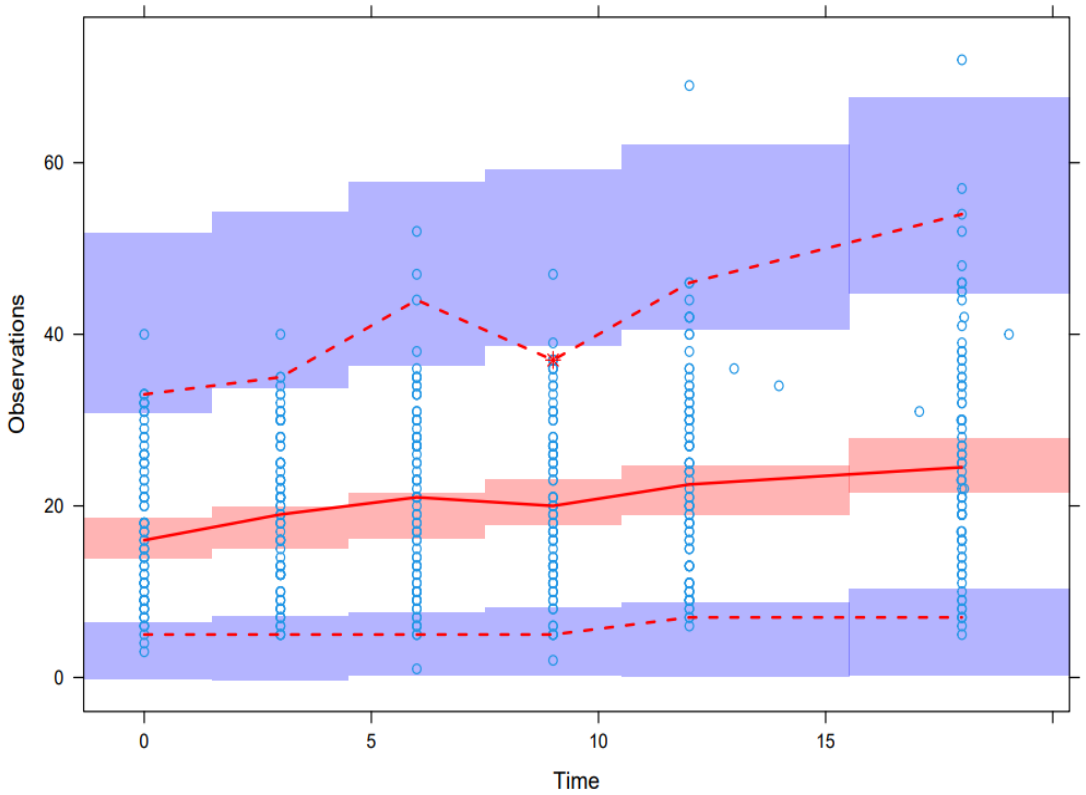
Type I error

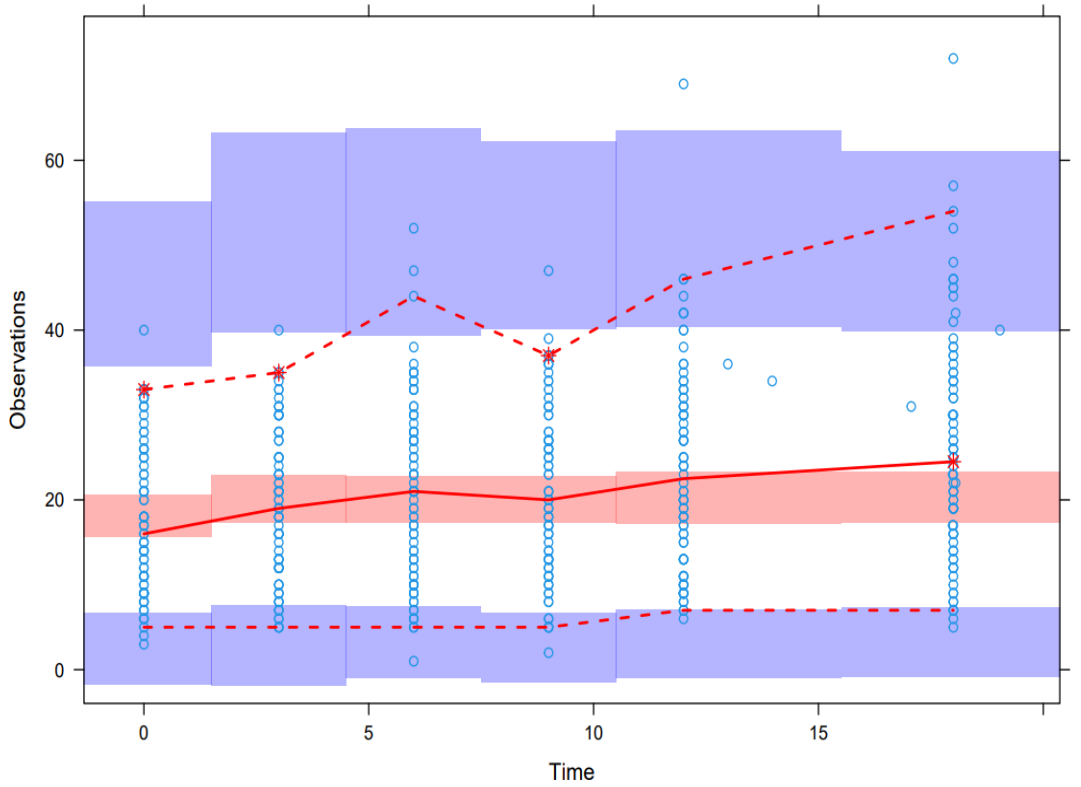
Methods:	Type I error (%)		
	Parkinson's disease	Alzheimer's disease	Diabetic neuropathy
MMRM	7	4	6
NLMEM	0	12	3
NLMEM SPA	2	4	4
misNLMEM	100	5	53
misNLMEM SPA	14	3	18
IMA	0	3	4
IMA SPA	2	2	4
IMA_mis	2	3	4
IMA_mis SPA	2	3	4

An example of model fit

Slope misspecification

NLMEM → NLMEM-mis





Visual predictive checks: Parkinson's disease

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Conclusions

- SPA had better treatment effect estimation accuracy compared to MMRM
- SPA resulted in more controlled type I error compared to NLMEM
- IMA was unbiased in all scenarios, and had better treatment effect accuracy compared to MMRM
- SPA is a compromise between MMRM and NLMEM/IMA and is sensitive to the properties of those components
- SPA is a tool that lies on a continuum of methods that can be used to estimate treatment effect

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Acknowledgements

- Pharmacometrics group
- PK/PD group
- Apotekarsocieteten
- Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX)