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## ► To cite this version:

Pierre-Emmanuel Poulet, Bruno Jedynak, Stanley Durrleman. Learning treatment effect in neurodegenerative diseases with a Bayesian mixed-effect model. 43rd Annual Conference of the International Society for Clinical Biostatistics (ISCB), Aug 2022, Newcastle upon Tyne, United Kingdom. hal-03766119

**HAL Id: hal-03766119**

**<https://inria.hal.science/hal-03766119>**

Submitted on 31 Aug 2022

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# Learning treatment effect in neurodegenerative diseases with a Bayesian mixed-effect model

Pierre-Emmanuel Poulet<sup>1</sup>, Bruno Jedynak<sup>2</sup>, Stanley Durrleman<sup>1</sup>

✉ pierre-emmanuel.poulet@inria.fr  <https://gitlab.com/icm-institute/aramislab/leaspy>

1. Aramis project Team, Inria, Paris Brain Institute, Sorbonne Université, INSERM, CNRS 2. Portland State University

## ➤ Introduction

Disease progression models have successfully been used with longitudinal data in the field of neurodegenerative diseases. In particular mixed-effect models recover the natural history of the disease at a population level but are also able to uncover individual heterogeneity. However these models usually have a hard time coping with the addition of a treatment. A treatment can be purely symptomatic or disease-modifying. We propose a method to learn the first kind of treatment effect and apply it to dopaminergic treatment in Parkinson, which is known to be symptomatic. The goal is to be able to predict how a patient is likely to answer to treatment at a certain point in time. Our method uses a Bayesian mixed-effect model as baseline and learns the treatment effect as an additive effect to the model output.

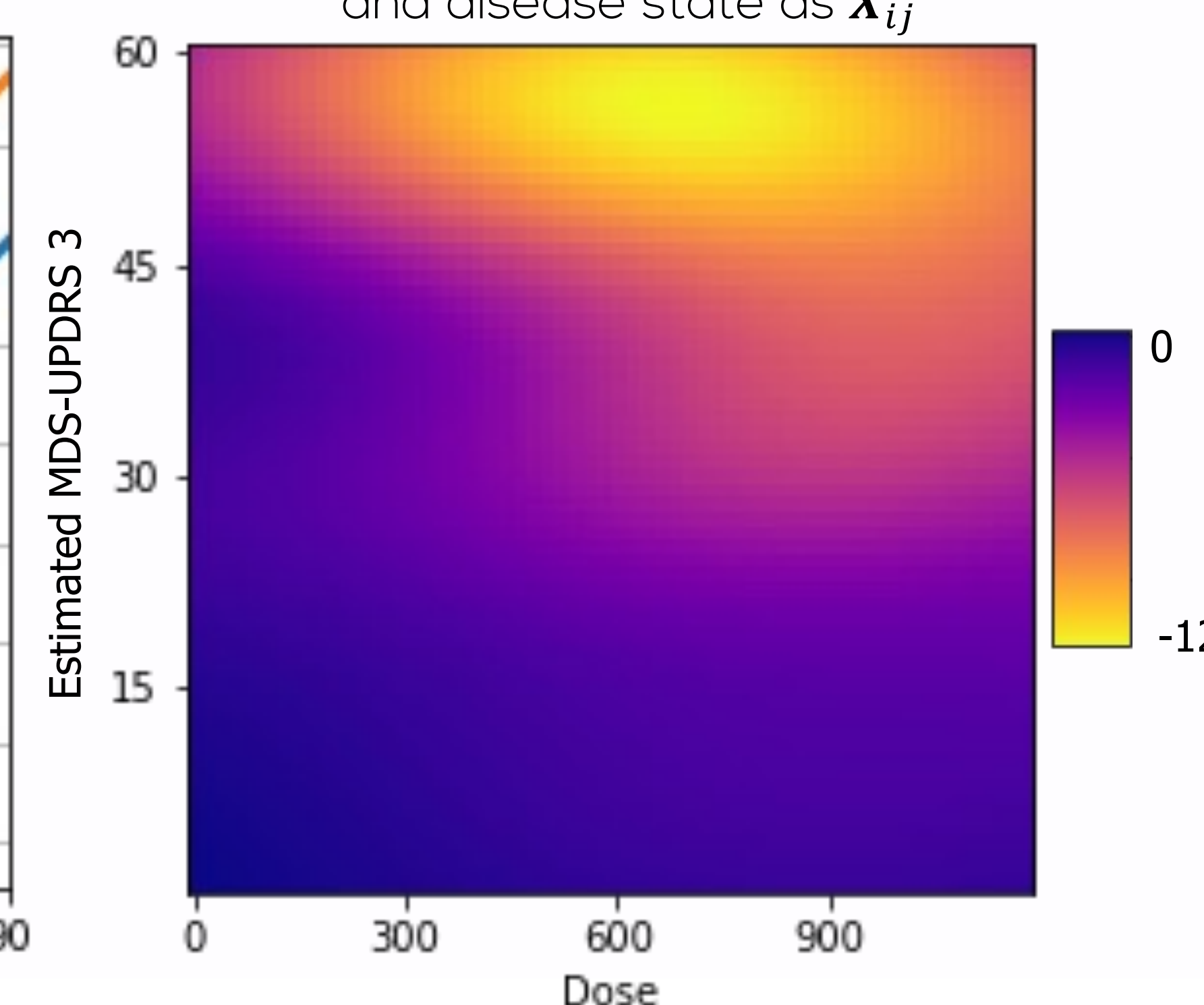
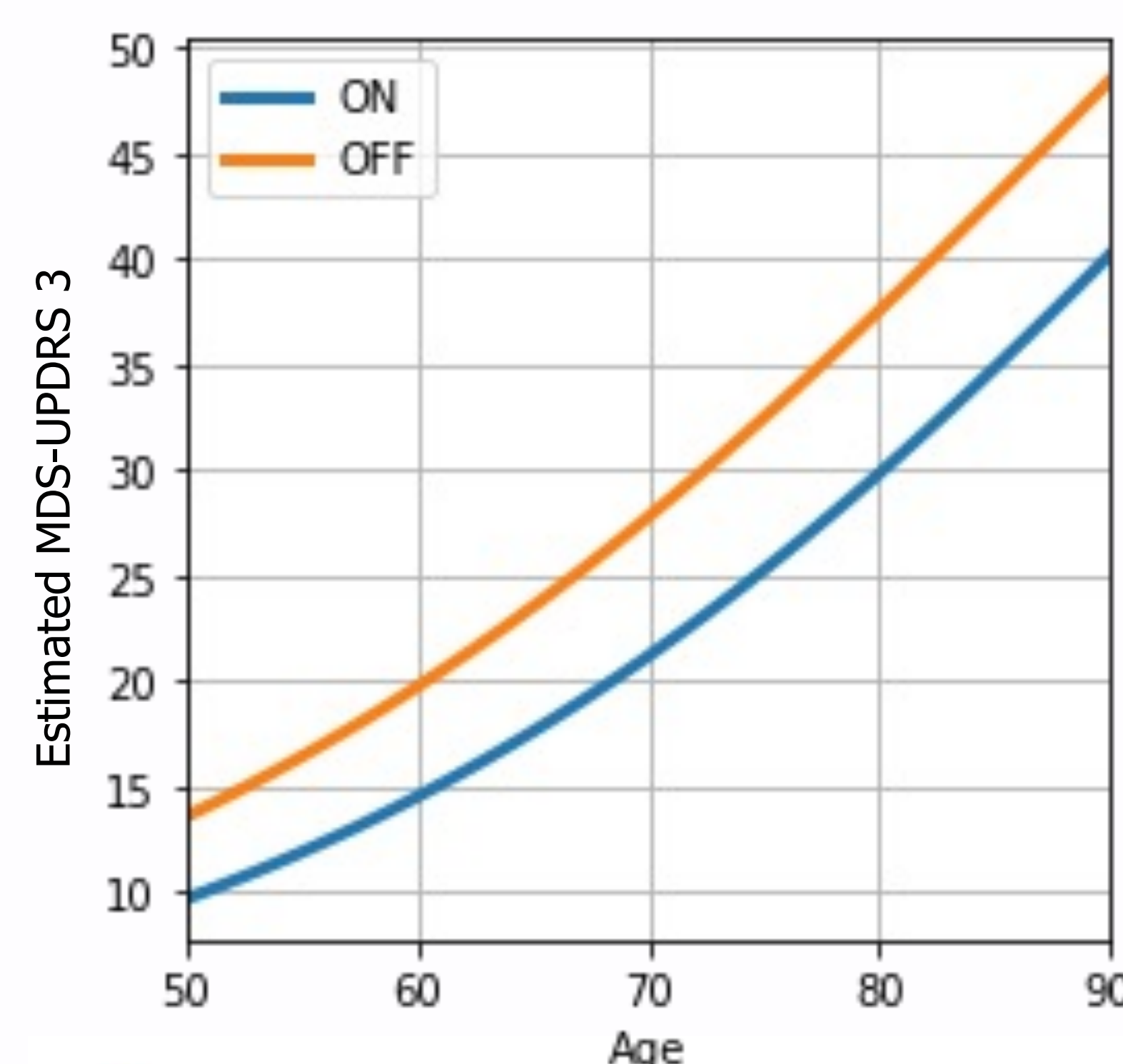
## ➤ Method

- Observations :  $y_{ij}^{ON} \in [0, 1]^n$  of patient  $i$  at time  $t_{ij}$  after taking drug (ON state),  $y_{ij}^{OFF}$  when treatment effect wears off (OFF state)
- Disease course mapping (DCM) model : a Bayesian mixed-effect model predicts natural progression of the disease
- $y_{ij}^{OFF} = \gamma(t_{ij}; \theta, z_i) + \varepsilon_{ij}$
- Population parameters  $\theta$  and individual parameters  $z_i$  are estimated with a MCMC SAEM.
- Treatment effect is the difference between OFF state and ON state:  $y_{ij}^{OFF} - y_{ij}^{ON} \approx \gamma(t_{ij}; \theta, z_i) - y_{ij}^{ON} = \Delta_{ij}$
- Treatment model:  $\Delta_{ij} = f(X_{ij}; \psi)$  with time-dependent variables  $X_{ij}$
- We compare several models for  $f$  with different variables  $X_{ij}$ :

1) A linear model (LME) with dose and disease state as  $X_{ij}$

2) A mixed-effect model learning  $y_{ij}^{ON}$  and  $y_{ij}^{OFF}$  jointly (DCM)

3) A kernel regression using radial basis functions with dose and disease state as  $X_{ij}$

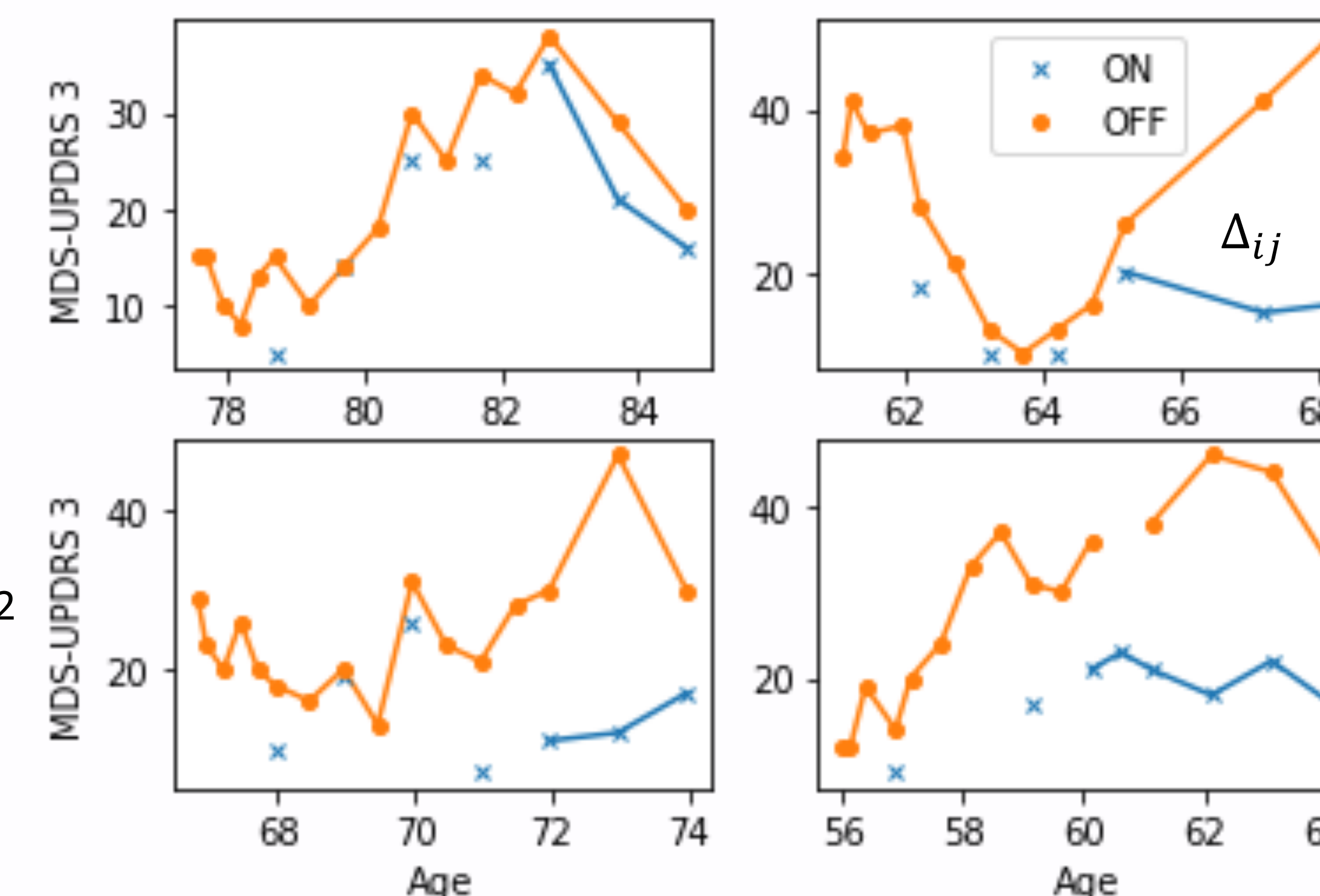


## ➤ Data (from PPMI\*)

Outcome : Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 (motor examination). Treatment dose is computed as Levodopa (dopaminergic drug) equivalent daily dose (LEDD).

# Patients	# Visits/patient	Mean age	Follow-up (years)
900	8.8±5.6	64.6±10.0	4.0±2.8
State	# observations	MDS-UPDRS 3	Dose (LEDD mg)
ON	2285	21.3±12.0	565±904
OFF	7519	25.5±12.4	-

Patient samples



## ➤ Results

### Performance (R<sup>2</sup>):

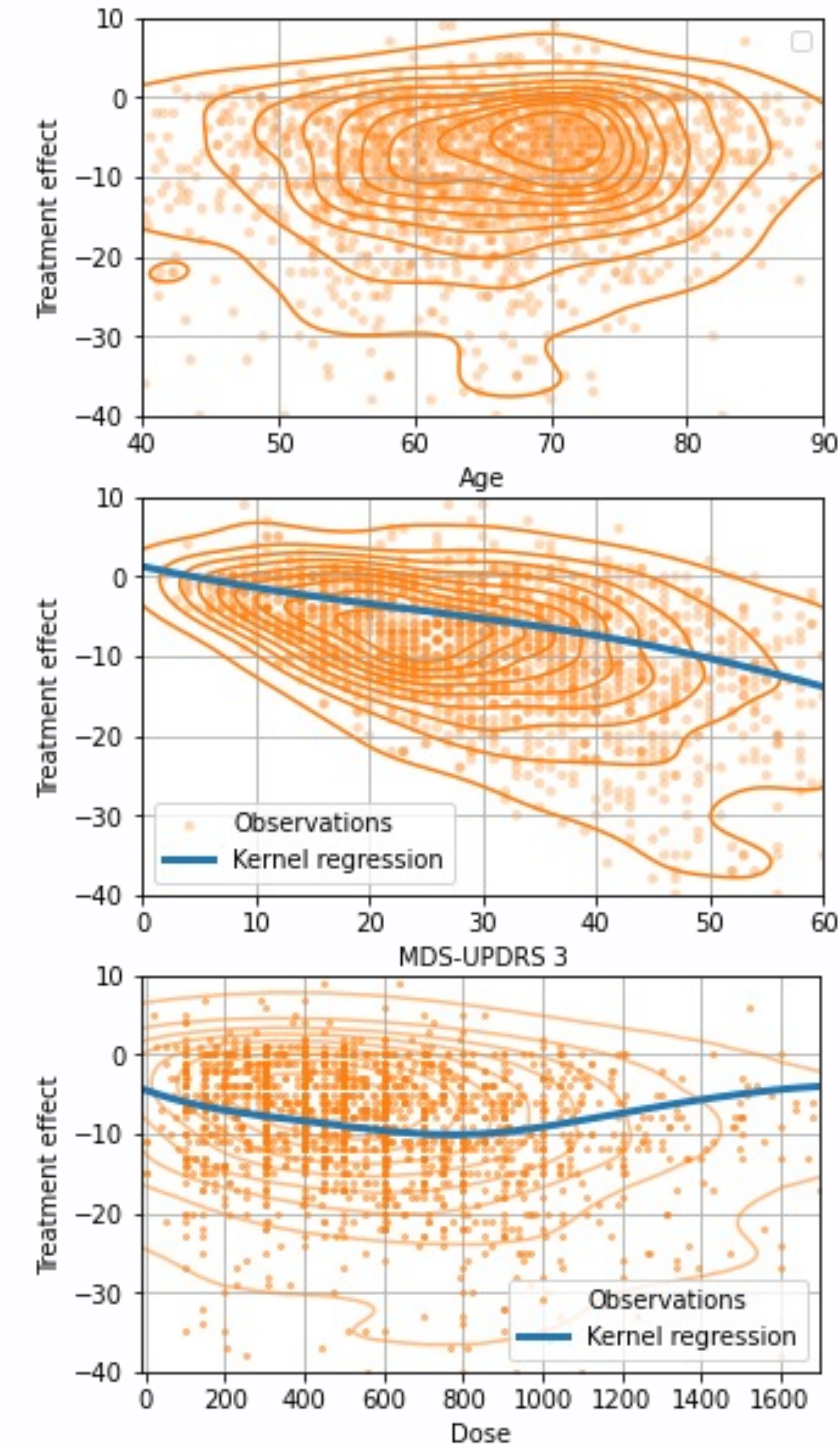
- LME: 0.13
- Joint DCM model: 0.11
- Kernel regression: 0.47

### Results:

- Values are low due to inherent noise in the data
- Kernel regression performs better, suggesting that the relationship between treatment effect and the selected variables is non-linear

### Analysis of variables:

- Selection of variables was made by fitting several models and selecting the best BIC
- There is no clear relation between age and treatment effect, thus age was not selected
- Other covariates were not selected either (imaging and biologic fluid biomarkers, other cognitive scores)
- For the remaining selected variables : there seems to be a linear link between treatment effect and current disease state (measured by MDS-UPDRS 3)
- For the dose we have a sweet spot to maximize the effect; taking too much or too few dopaminergic drug is less efficient (note that there is a bias due to the doctors adjusting the dose for the patient at each visit)
- Interaction of dose and current disease state was captured by the kernel regression (cf plot on the left)



## ➤ Conclusions

Our results show that treatment effect in the case of Parkinson can be partially explained by the disease stage and the dose. We proposed a generic method to model symptomatic treatment. The potential applications of our model include determining the optimal dose when a new patient starts the treatment and testing which covariates influence treatment effect.