



A comparison between nonlinear mixed effects and naïve pooled data methods in population PK model selection

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BACKGROUND AND OBJECTIVES

BACKGROUND

- Nonlinear mixed-effect (NLME) models are a more appropriate representation of data from multiple subjects than naïve pooled data (NPD) models. However, NPD models may have shorter runtimes and are often more robust. There may exist an advantage to use NPD for model building decisions when NLME models are too run-time intensive or when high robustness is sought.
- Use of NPD models as proxies for NLME models depends on the similarity in the relative goodness-of-fit of contending models.

OBJECTIVES

- This study aims to explore how similar model selection is between NLME and NPD models.

METHODS

REAL DATA

- NLME and NPD were compared for 13 previously developed population pharmacokinetics models based on real data.

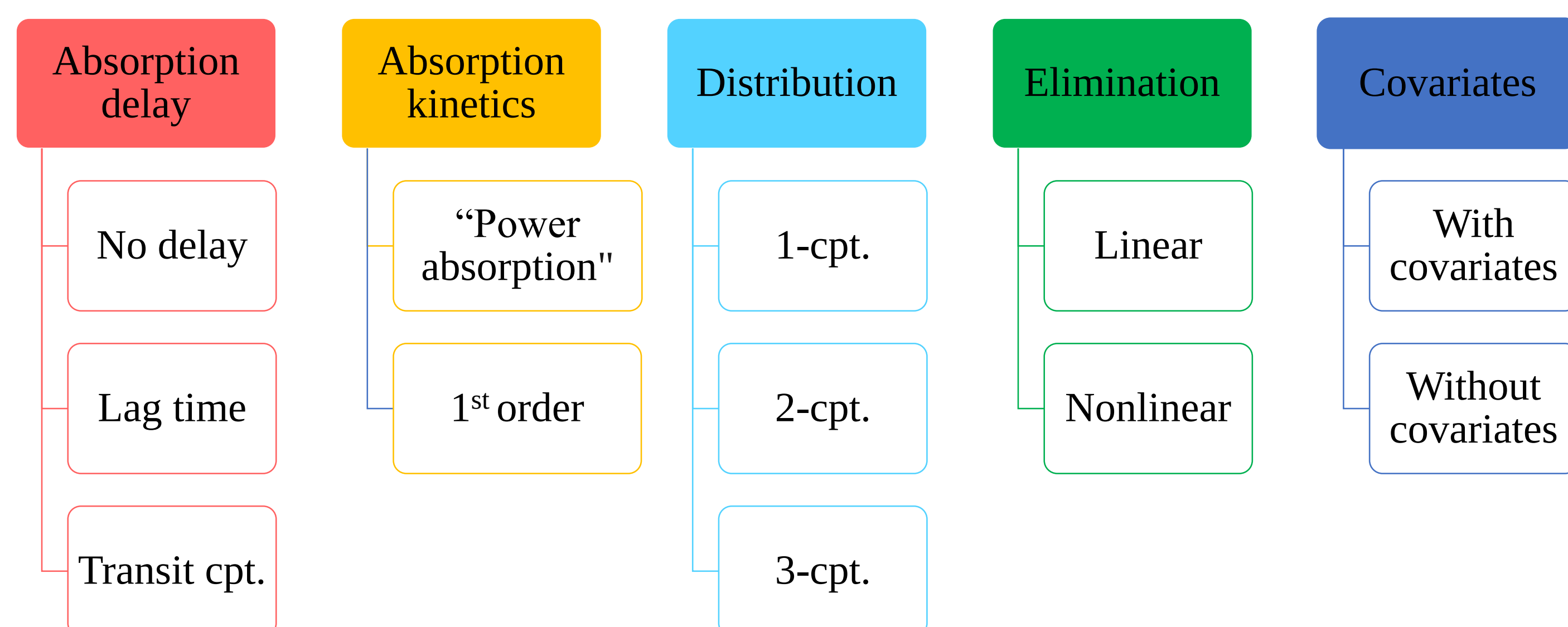
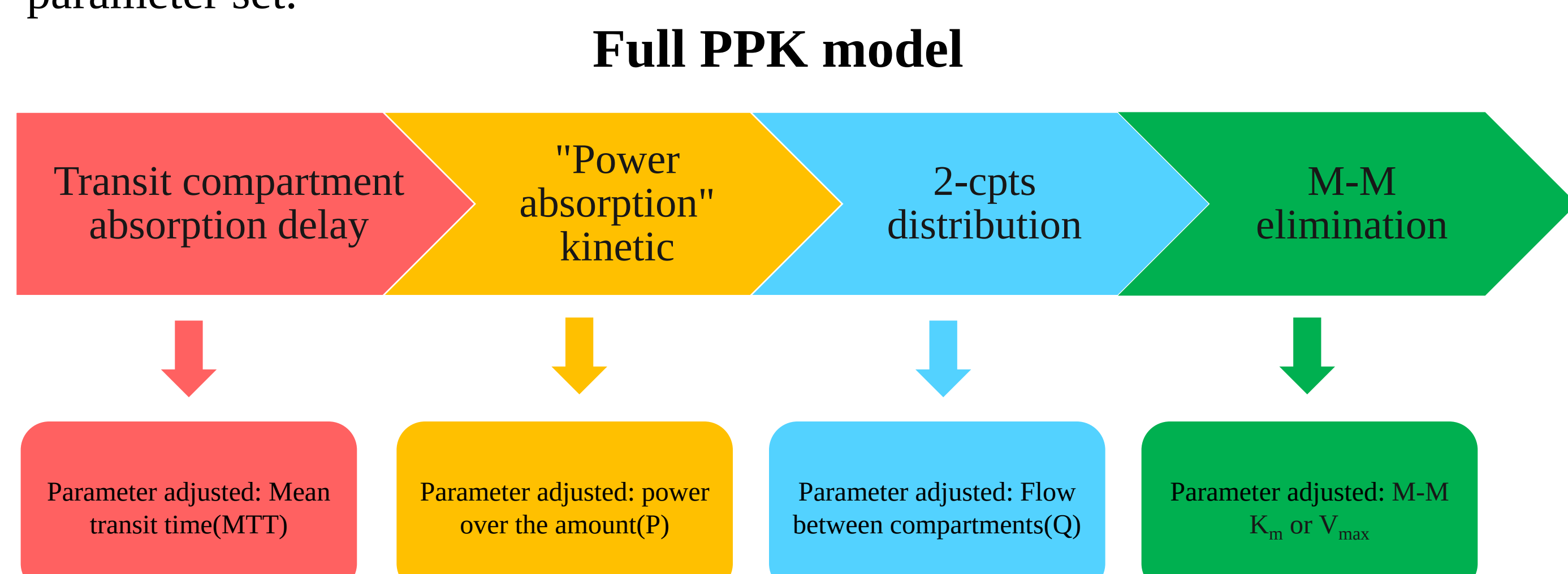


Figure 1. The structural components of the models and related optional components. It should be noted that in the "power absorption" model the absorption kinetics differential equation was: $\frac{dA}{dt} = -k_a \cdot A^P$, where A is the amount in absorption compartment; k_a is rate constant; P which ranged from 0 to 1 is the parameter to adjust the characteristic of absorption kinetics; the "nonlinear" in the elimination component represented the Michaelis-Menten (M-M) elimination model governed by Michaelis-Menten equation which contains V_{max} and K_m .

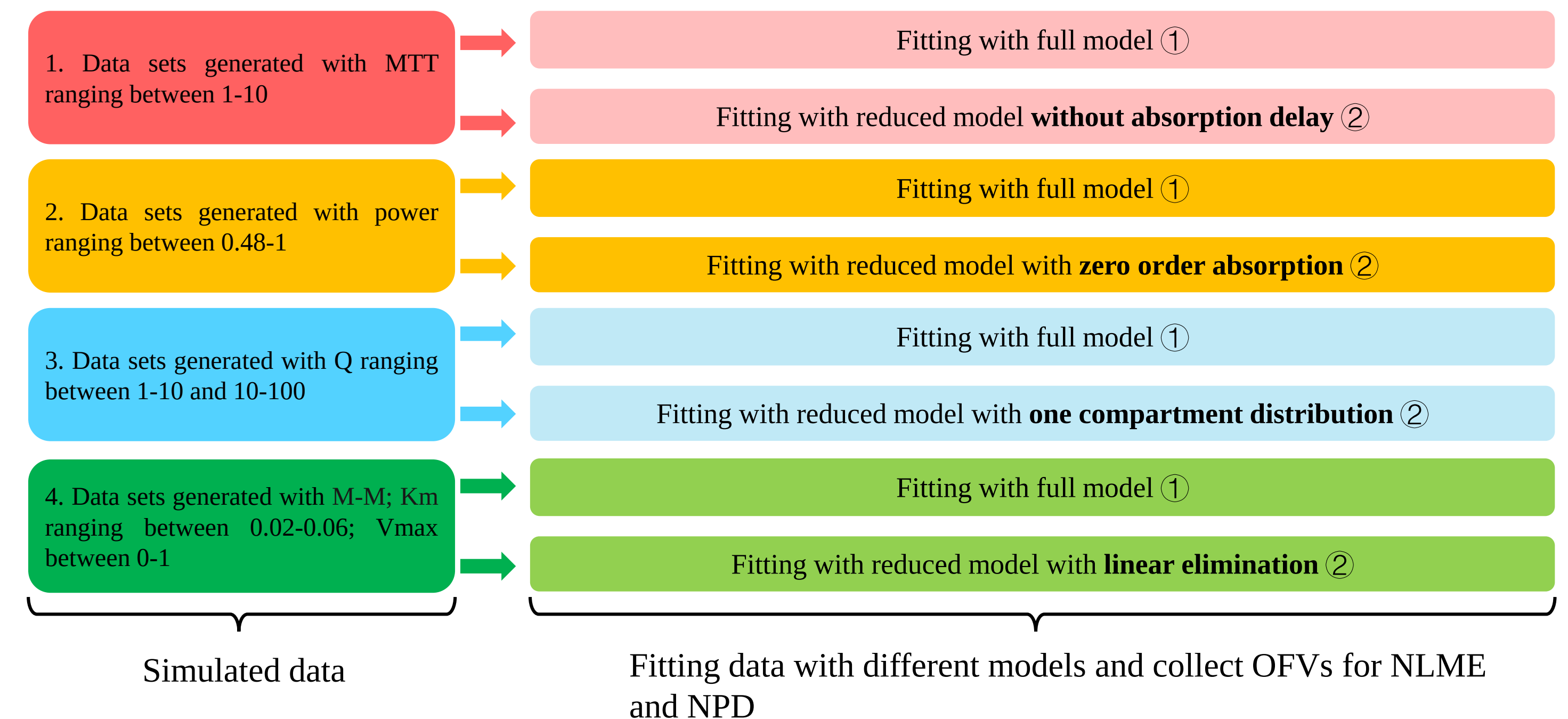
- For the 13 original models, 56 test models were generated, by iteratively changing one of the components with different options (Fig. 1). The test models and original models were fit to the corresponding real data using both NLME and NPD methods, followed by a calculation of the difference of objective function value (OFV) of NLME and NPD separately. Model selection was then performed using the likelihood ratio test (5% significance level).

SIMULATIONS

- To explore if both methods are able to identify the "true" model, as well as to expand the model types coverage, simulation was introduced. A full PPK model was employed to simulate data with different PK characteristics.
- A uniform distribution was simulated for each of the parameters which stand for each structural component and relative rich data sets were generated for each parameter set.



- full model ① and relevant reduced models ② were fit to the simulated data using both NLME and NPD.
- Δ OFVs were collected between the full and reduced models



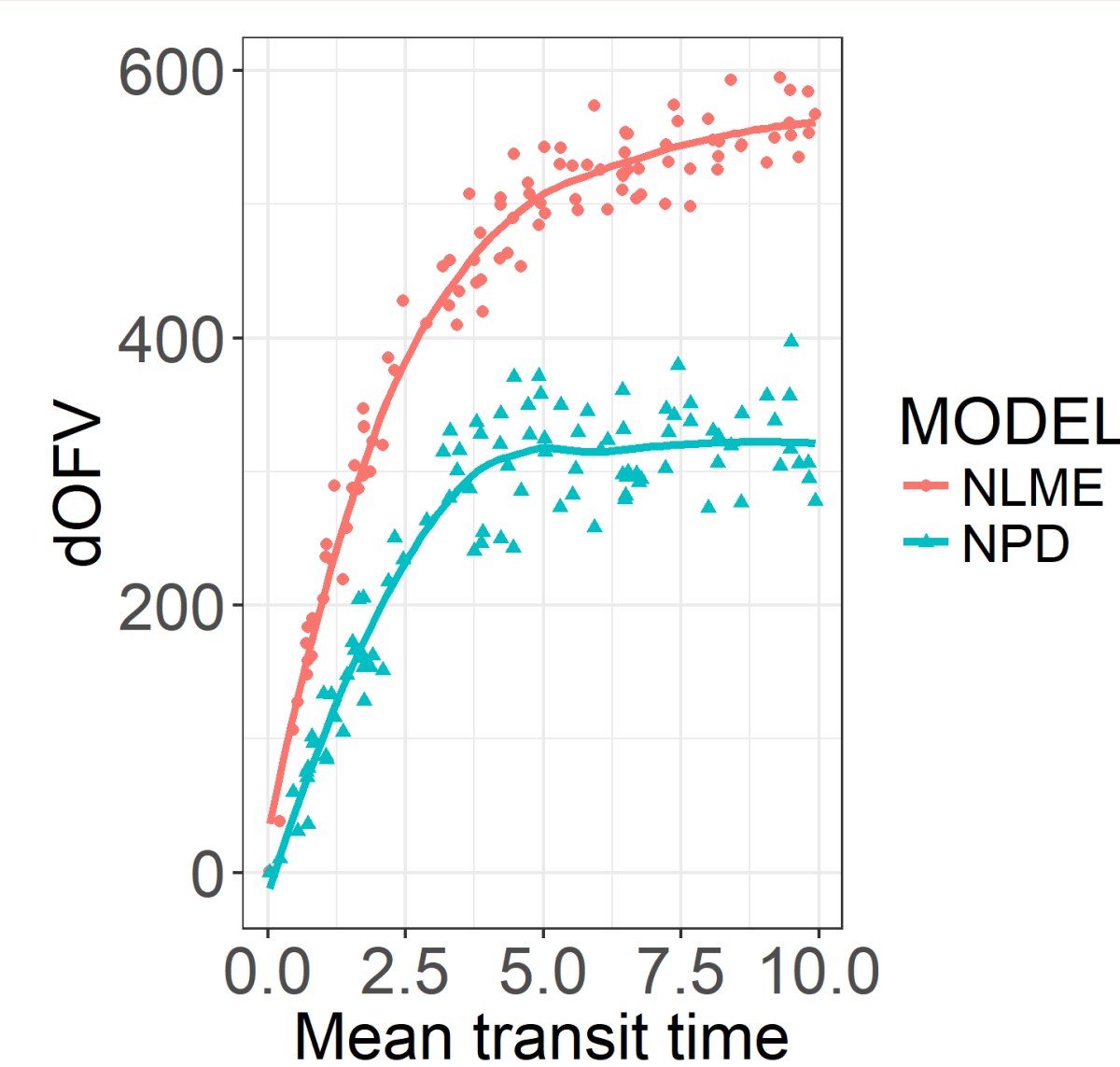
RESULTS

REAL DATA

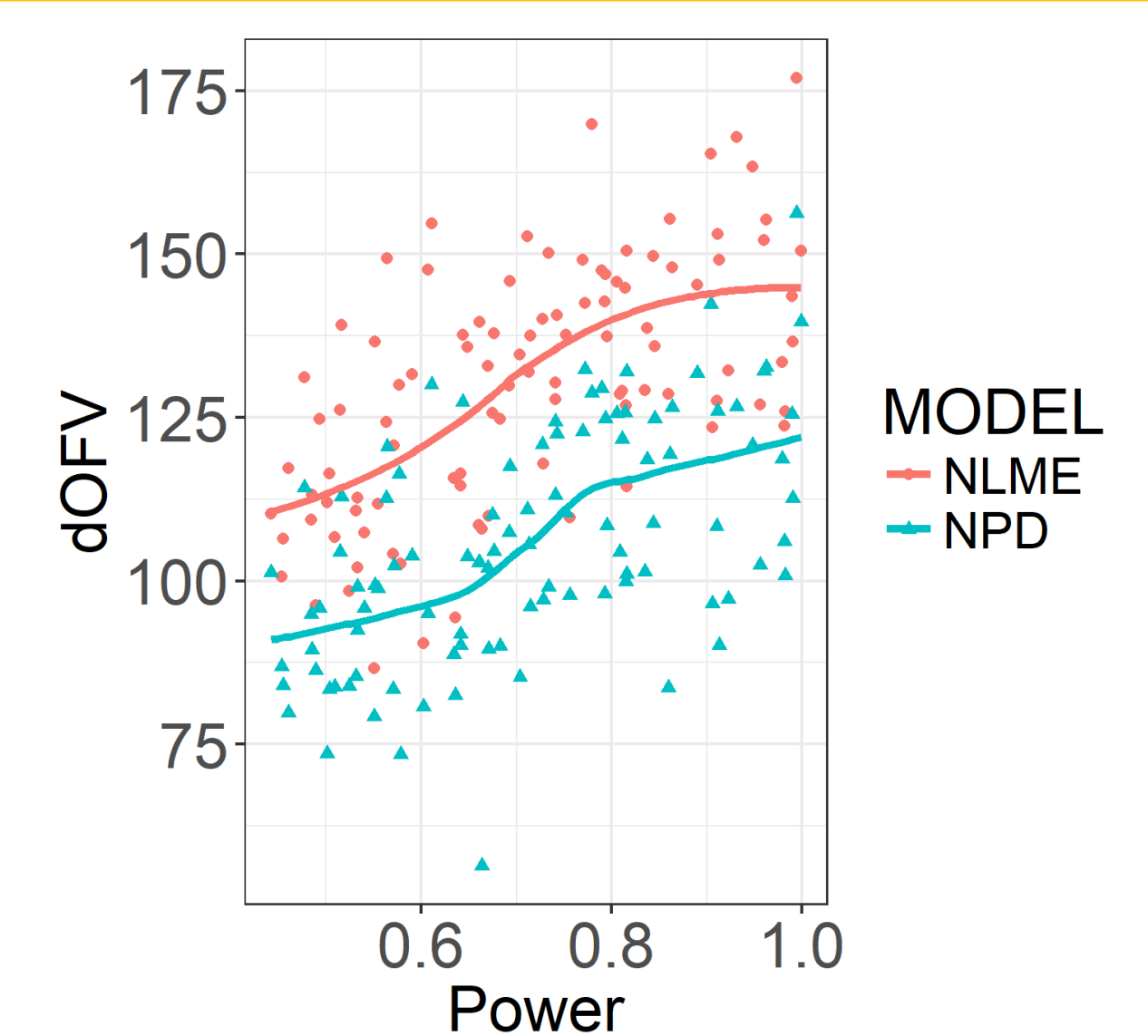
- NLME and NPD selected the same model 48 times out 56.
- Of the 8 situations where NPD and NLME selected different models, NPD always selected the simpler model and the difference concerned distribution aspects in 5 cases and elimination in 3 cases.

SIMULATION

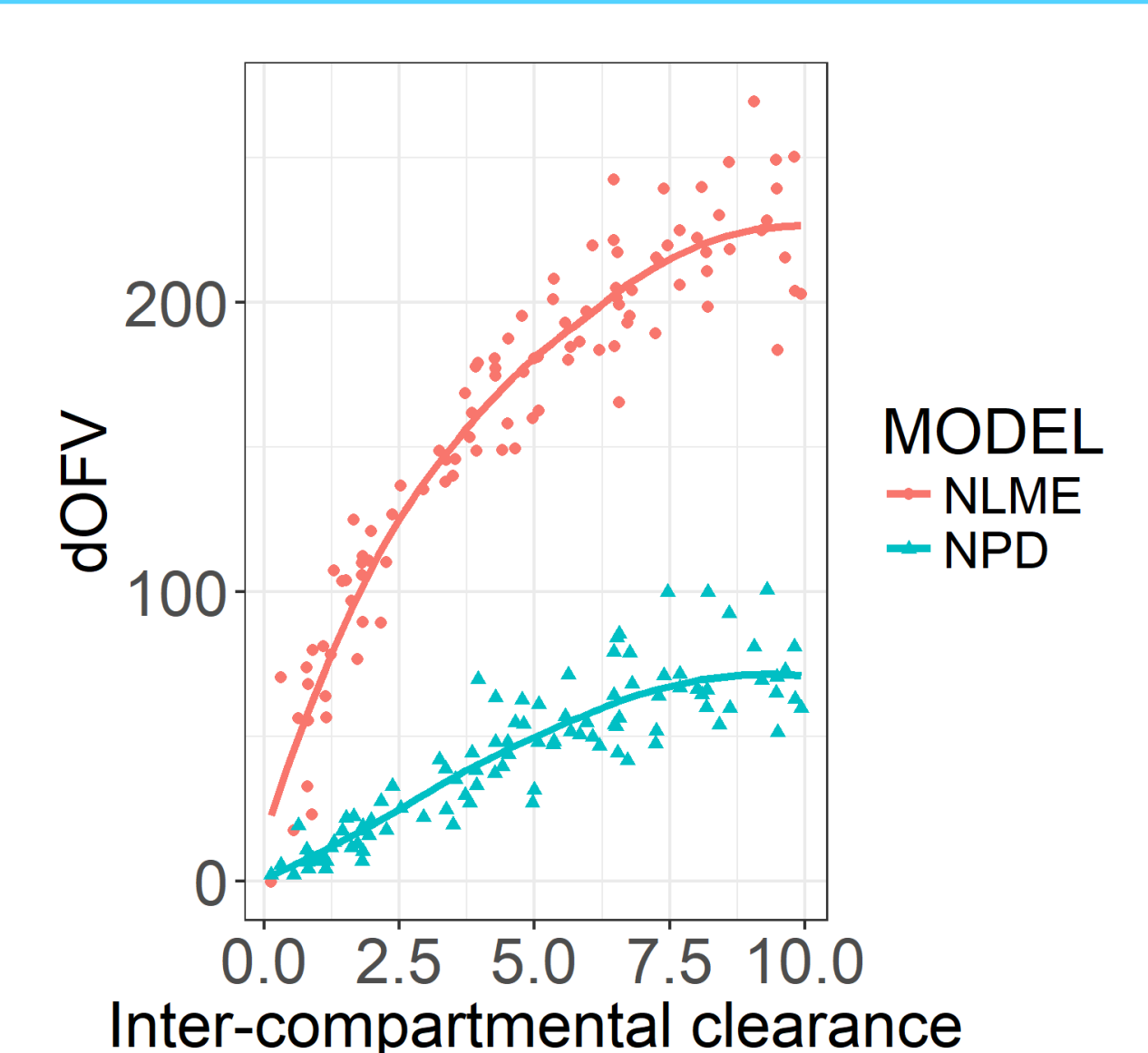
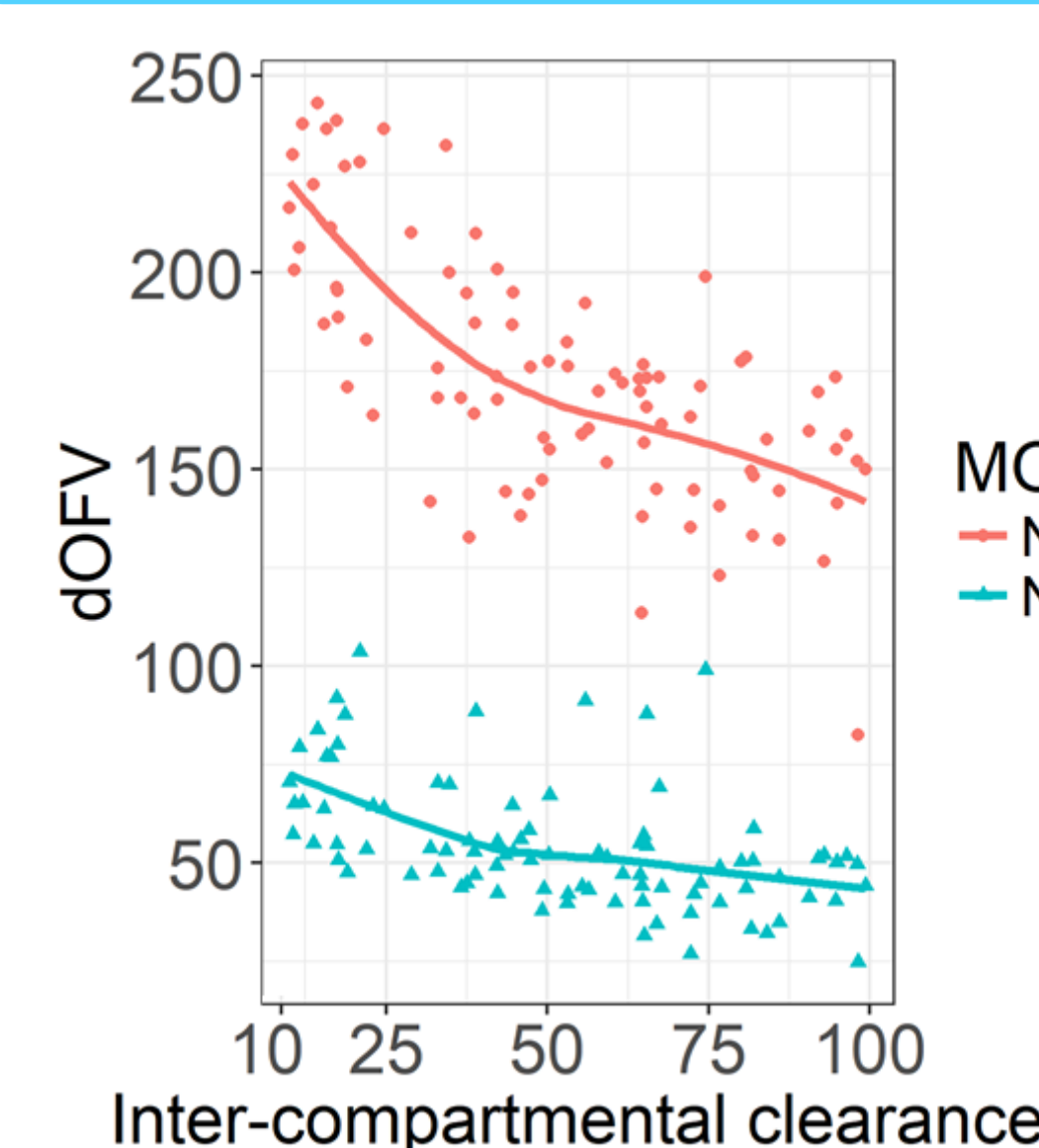
1. Δ OFV between transit model and no delay model.



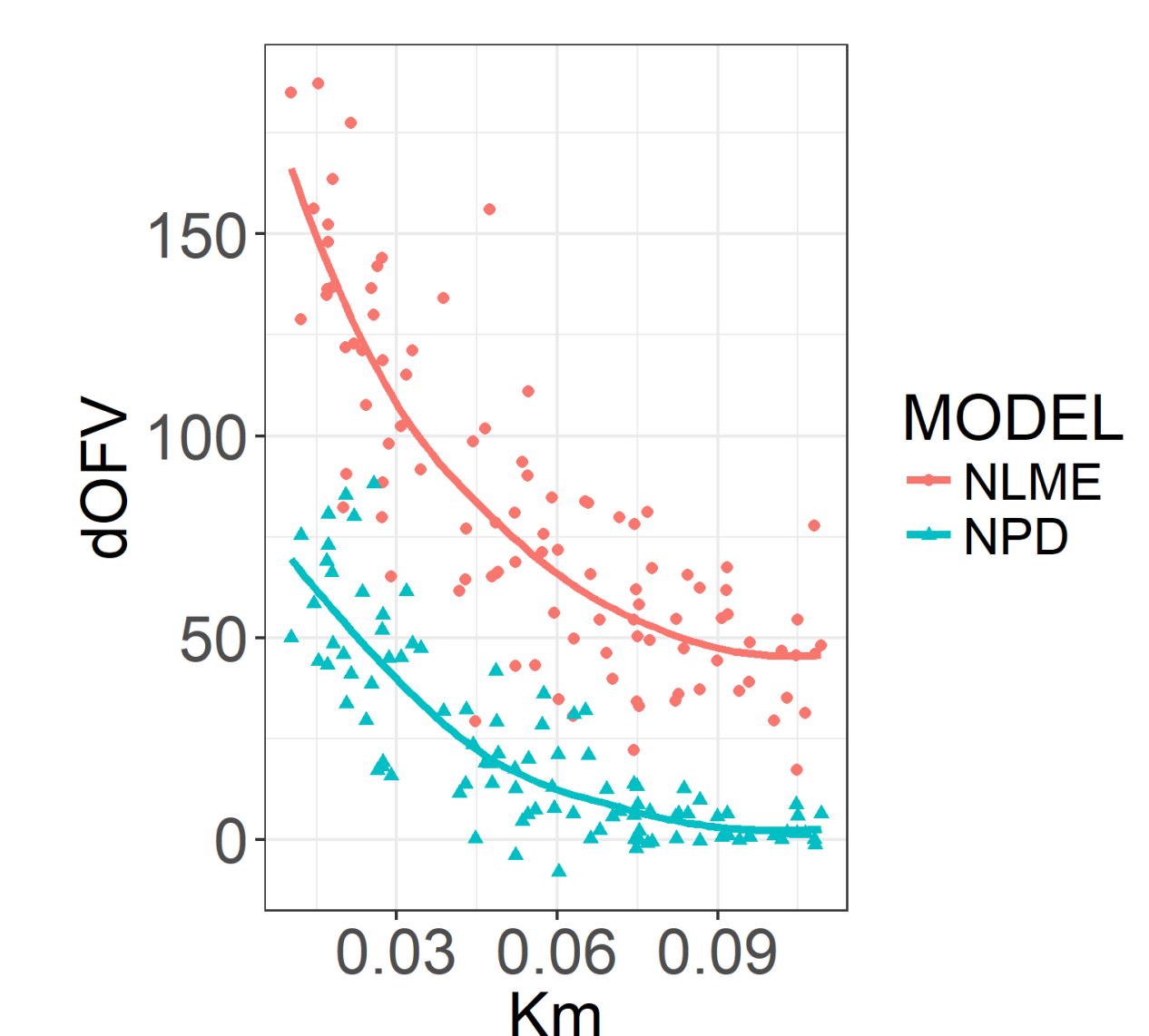
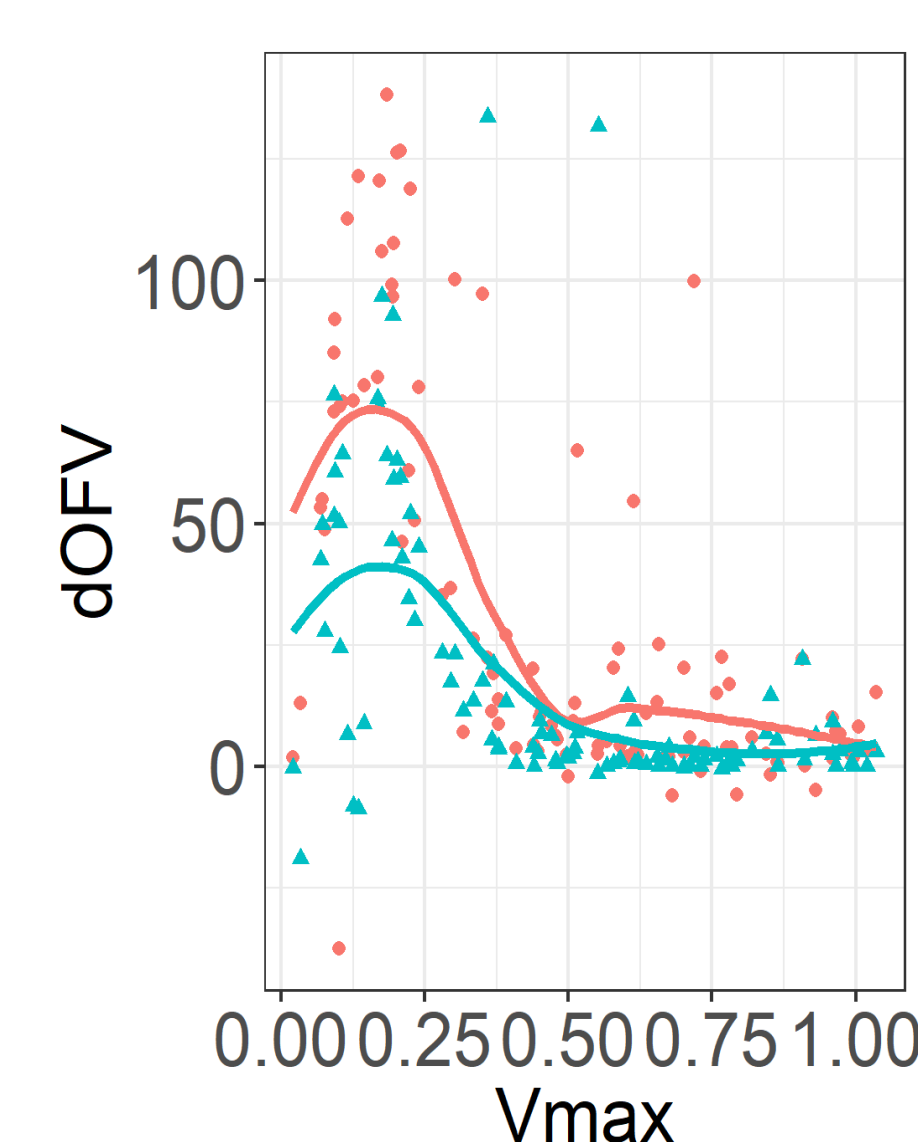
2. Δ OFV between the "power absorption" and zero order absorption model



3. Δ OFV between 1 and 2 compartment models



4. Δ OFV between M-M elimination model and linear elimination model.



CONCLUSION

- NPD is less powerful in model selection compared to NLME and tends to give simpler model selection. More complex models should be considered with NLME model selection when starting from a final model based on NPD analysis.