

Assessment of the predictive performance of DeepNLME for a typical population pharmacokinetics: a simulation study and a case study with data from a first-in-human study of DS-8500

 Daiichi-Sankyo

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Objectives

A deep nonlinear mixed effects model (DeepNLME) is a novel approach that includes small neural networks (NNs) in the function of population parameters and/or the ordinary differential equations, allowing to benefit partially from a completely data-driven approach in the framework of pharmacometrics even with less understanding of underlying mechanisms. Since this is an emerging methodology, the predictive performance is still unclear.

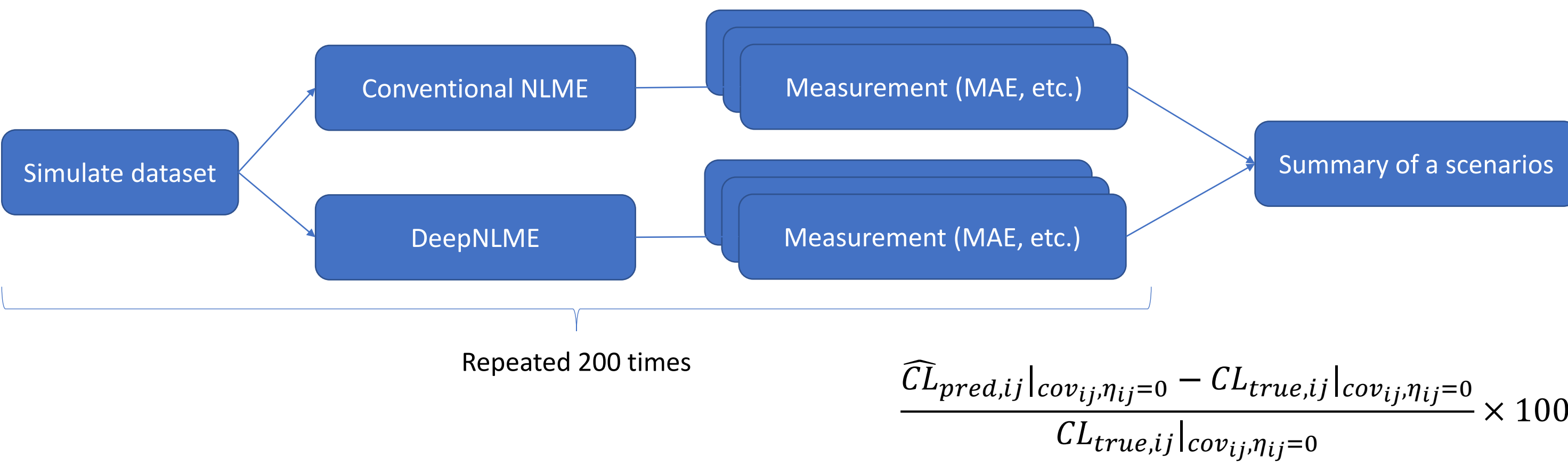
The present work investigated the performance of DeepNLME in a typical population pharmacokinetics using both simulated data and an actual dataset from a first-in-human study of DS-8500. The experiments with simulated data and the actual dataset focused on covariate modeling and dynamics identification, respectively.

Methods

Simulated data:

A one-compartment model with 1st-order absorption and elimination was used in the simulations. The setting and the workflow are summarized in **Table 1** and **Figure 1**, respectively. The scenario 2 was used to assess the sensitivity to hyperparameters such as the number of iteration during the estimation step. A code fragment to define a NN is shown in **Figure 2**.

Figure 1 Schematic representation of the workflow



Mean absolute error (MAE) was calculated based on the above error; *i* and *j* denote *i*th replicate and *j*th subject, respectively

Table 1 Summary of simulated scenarios

#	Scenario	Example	True covariate submodel	Covariate submodel in conventional approach	# of patients	Note
1	Binary covariate	Sex	CL = CL _{pop} * θ ^{cov}	CL = CL _{pop} * θ ^{cov}	20	Identical results are expected
2	Continuous covariate	Weight	Power model	Power model	50	Comparable results are expected
3	Continuous covariate	eGFR	Hockey-stick model	Power model (wrong model)	50	Realistic setting; DeepNLME is expected to outperform

Figure 2 Example of code for the DeepNLME approach

```
@param begin
  "Clearance (L/h)"
  tvcl ∈ RealDomain(lower = 0)
  "Volume (L)"
  tvvc ∈ RealDomain(lower = 0)
  "MLP for covariate"
  mlp ∈ MLP(1, 4, 4, (1, identity)); reg = nothing
  ""
  - QCL
  - QVc
  ""
  Q ∈ PDiagDomain(2)
  "Exponential RUV"
  R ∈ RealDomain(lower = 0)
end

@pre begin
  mlp_ = only ◦ mlp
  neGFR = eGFR / 90
  popCL = tvcl * mlp_(neGFR)
  CL = popCL * exp(η[1])
  Vc = tvvc * exp(η[2])
  Ke = CL / Vc
end
```

A first-in-human study:

As an actual dataset, PK data from single ascending dose (SAD) and multiple ascending dose (MAD) cohorts in a first-in-human study of DS-8500, a small molecule, were used. The PK data which showed a second peak around 10 hours after dose is presented in **Figure 3**.

The SAD data were used as the training set while the MAD was used as the test set. The training set was given to both the conventional NLME and DeepNLME to estimate parameters including a NN describing absorption rate.

The predictive performance of the conventional NLME and DeepNLME was compared using the test set. Both approaches included a two-compartment model with first-order elimination. The conventional approach employed a simple first-order absorption model for a comparison purpose while DeepNLME embedded a small NN containing three input variables, two hidden layers, and a single output. The input variables were dose level, time after dosing, and a random effect for the neural network. The code fragment is shown in **Figure 4**.

All the analyses were conducted in DeepPumas (v0.5.1) on JuliaHub (v6.1.1).

Figure 3 PK profile of the FIH study data (left, training set; right, test set)

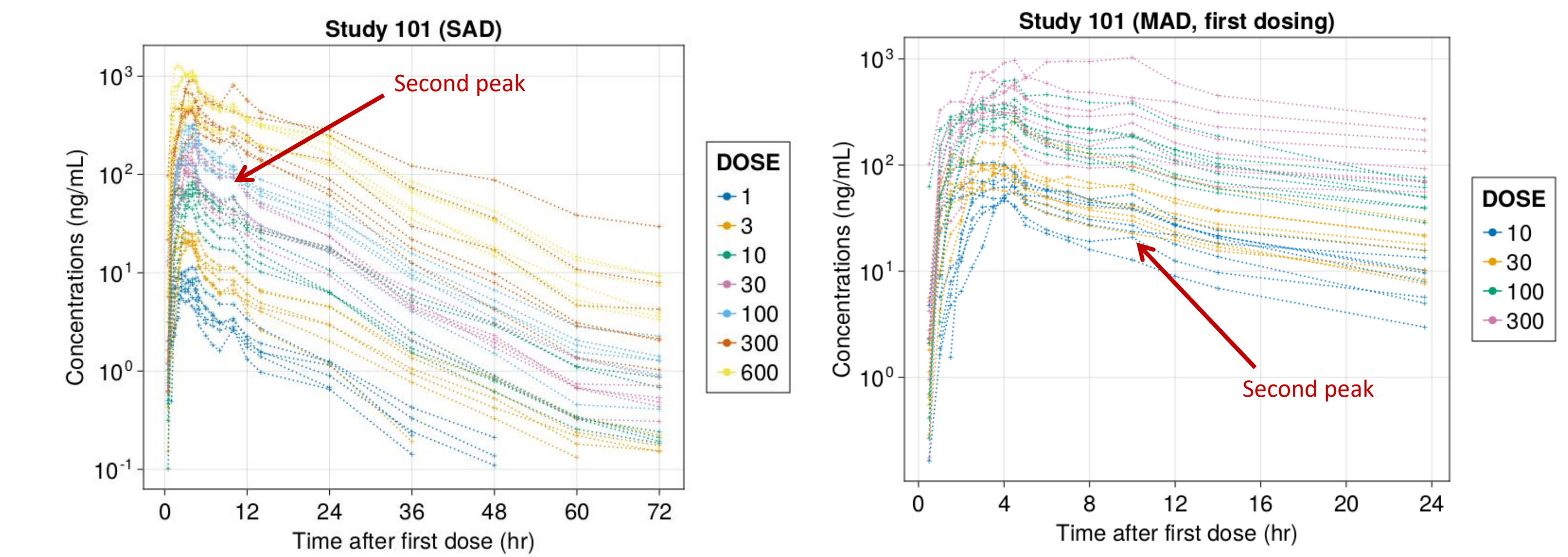


Figure 4 Example of code for the DeepNLME approach

```
"NN for absorption rate"
nn ∈ MLPDomain(3, 4, 4, (1, identity)); reg = L2(0.1)

@physics begin
  Depot' = -abs(nn(sdose, t, η_nn))*Depot
  Central' = abs(nn(sdose, t, η_nn))*Depot - (CL/Vc)*Central - (Q/Vc)*Central + (Q/Vp)*Peripheral
  Peripheral' = (Q/Vc)*Central - (Q/Vp)*Peripheral
end
```

Results

Simulated data:

Scenario 1 (a binary covariate like sex) showed exactly the same results from the conventional NLME and DeepNLME, which was as expected because no room for flexibility was available under this scenario (**Figure 5**).

In scenario 2 (a continuous covariate like weight), the conventional NLME performed slightly better than DeepNLME. This was also as expected because the conventional NLME was given the true model of power function (**Figure 6**).

In scenario 3, on the other hand, DeepNLME outperformed over the conventional NLME, suggesting the potential advantage of DeepNLME because the true function is always unknown in an actual drug development setting (**Figure 7**).

The DeepNLME approach was shown to be sensitive to the number of iterations during the estimation step, suggesting early stopping or other techniques such as regularization is helpful to maximize the performance by avoiding overfitting to the dataset (**Figure 8**).

Figure 5 One example of simulated dataset (left, individual CL by the covariate; middle, PK profile by the covariate); comparison of the bias (trial-level estimation error) in the estimated covariate effect between the conventional and DeepNLME approaches from 200 replicates (right)

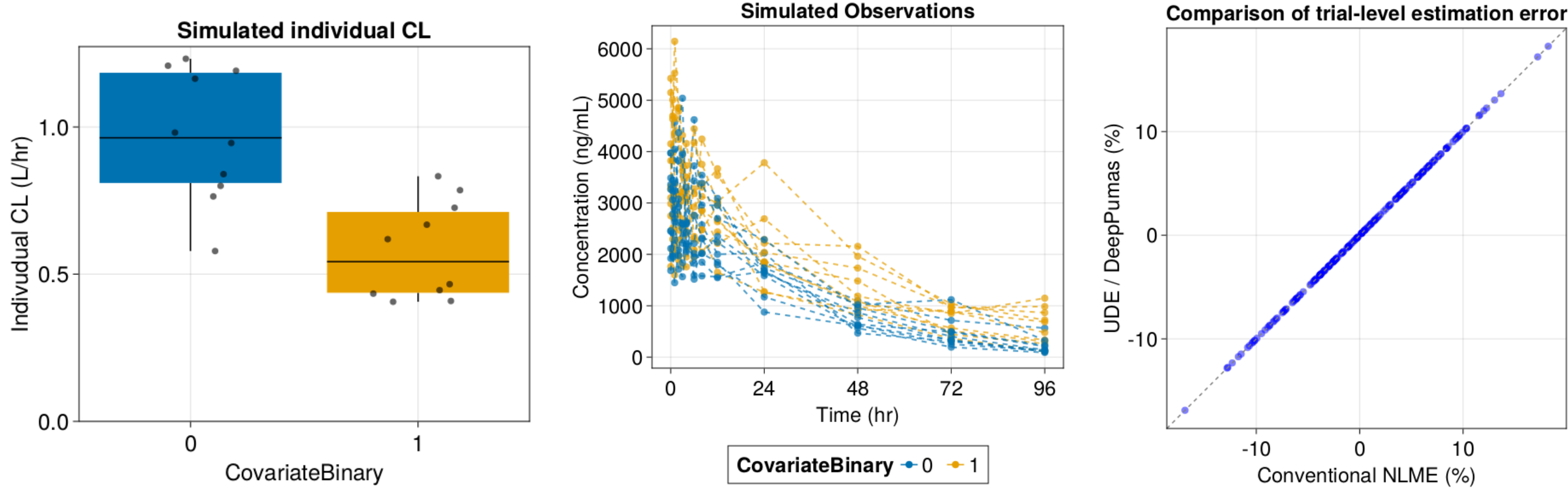


Figure 6 One example of simulated dataset (left, individual CL and the covariate; middle, PK profile); comparison of the predictive performance between the conventional and DeepNLME approaches from 200 replicates (right)

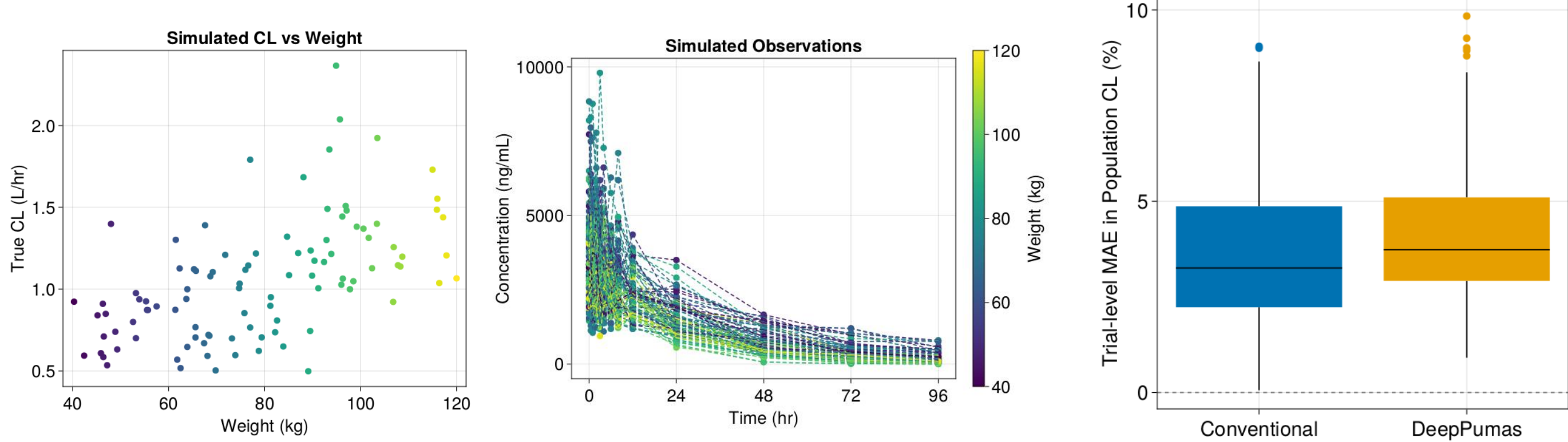


Figure 7 One example of simulated dataset (left, individual CL and the covariate; middle, PK profile); comparison of the predictive performance between the conventional and DeepNLME approaches from 200 replicates (right)

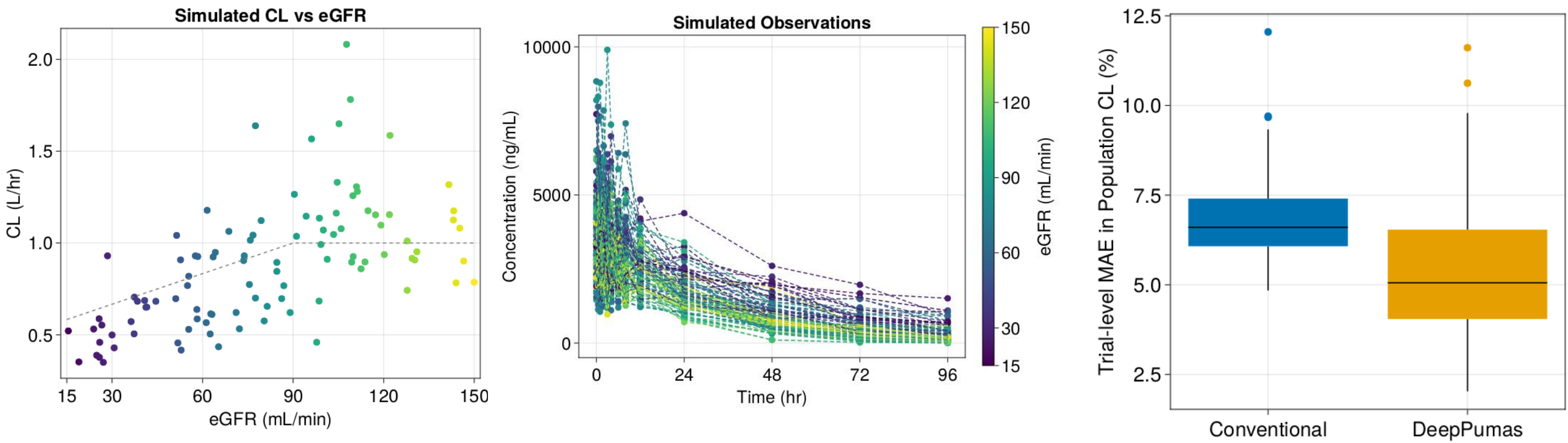
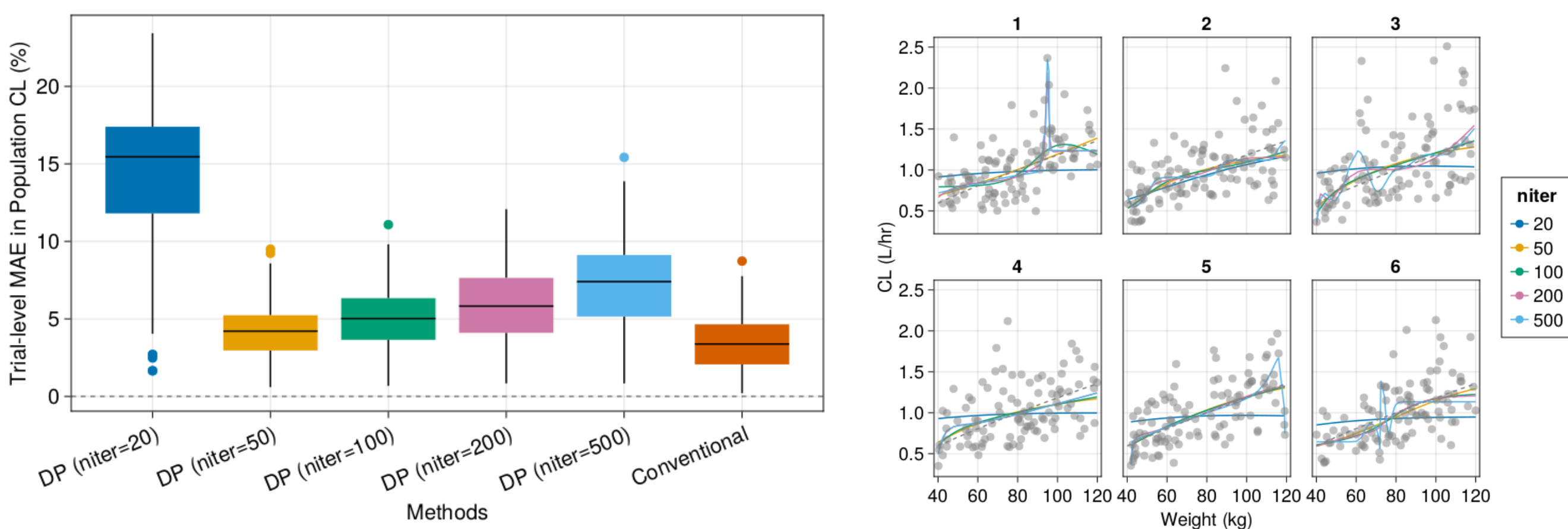


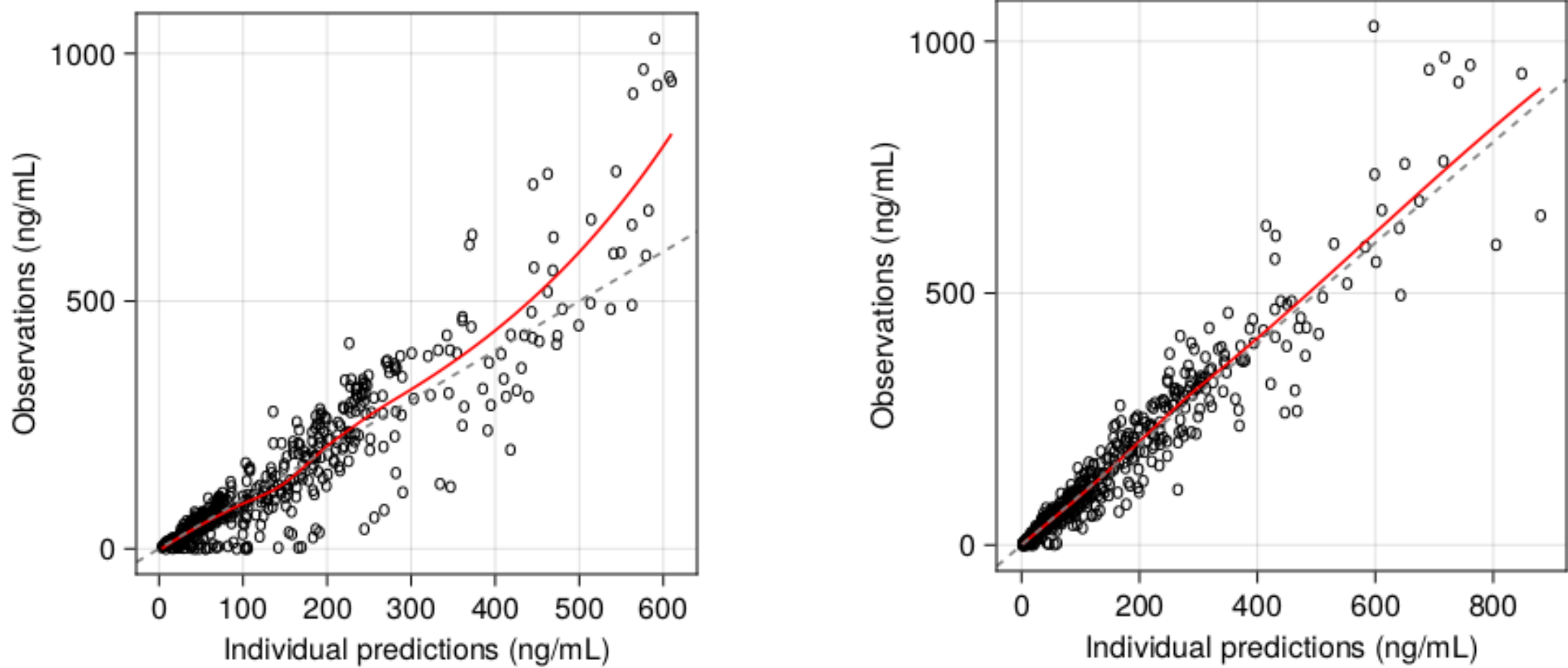
Figure 8 Comparison of the predictive performance under scenario 2 by the number of iterations (niter) during estimation process (left); Six replicates showing how DeepNLME estimated the relationship of covariates (right)



The first-in-human study:

DeepNLME predicted the unseen PK data from the test set better than the conventional NLME, with little systematic deviations in the standard goodness-of-fit plots (**Figure 9**).

Figure 9 Goodness of fit plots using test set (left, conventional; right, DeepNLME)



Conclusions

The present work showed the potential advantages of the novel modeling approach, DeepNLME. Further assessment is necessary as this work just compared the performance under limited conditions.

Conflict of Interest

The first and presenting author, Masato Fukae, is an employee of Daiichi Sankyo Co., Ltd.