

# Evaluation of Parameter Estimation when Fitting a Mixture Model with Covariate Effects using NONMEM®

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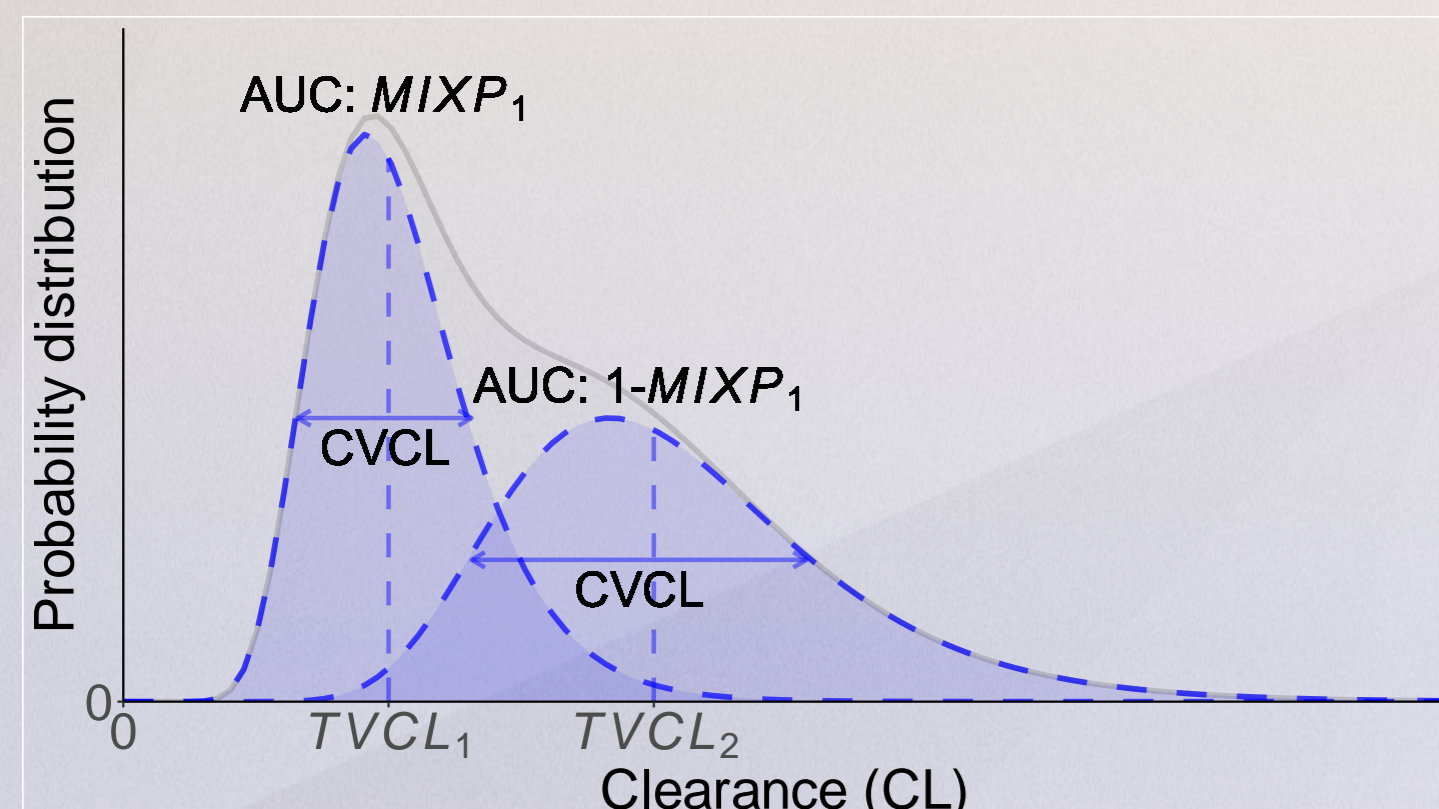
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## INTRODUCTION

### Background and insights

- Mixture model in NONMEM
  - Presumes a mixture of distinct behaviors in a study population
  - Potential use: describe two subpopulations with distinct typical values of clearance



Parameter estimation in the presence of covariate effects has not been evaluated yet!

### Aims of study

- Identify factors associated with estimation biases of covariate effects and other parameters
- Quantify any association

## METHODOLOGY

### Simulation scheme

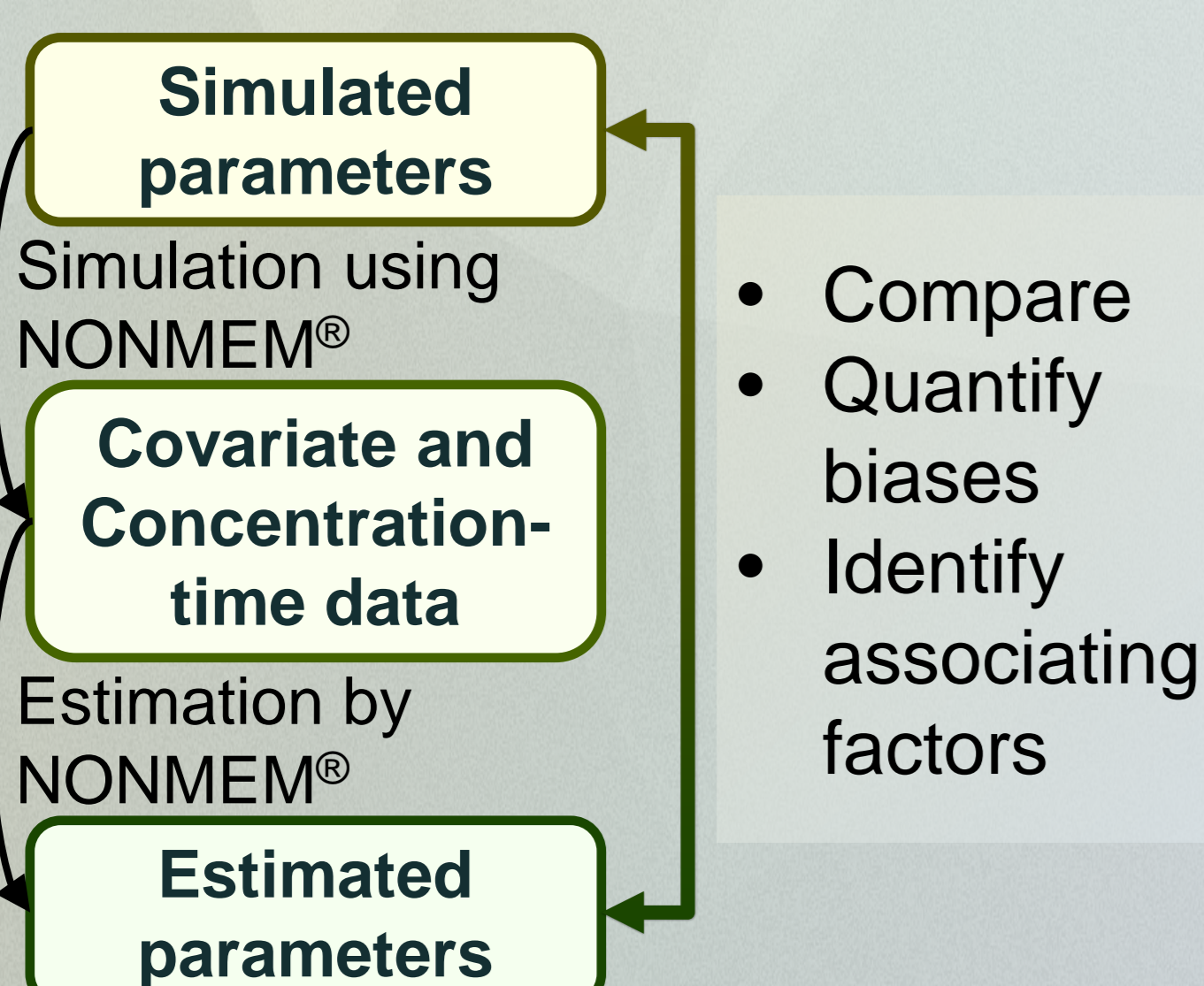
| Param       | Range 1     | Range 2       | Range 3      |
|-------------|-------------|---------------|--------------|
| $n$         | [20, 50]    | [50, 100]     | [100, 300]   |
| $TVCL_1$    | [1, 3.7]    | [3.7, 6.3]    | [6.3, 9]     |
| $rCL$       | [1, 2]      | [2, 3]        | [3, 4]       |
| $CVCL$      | [0.1, 0.23] | [0.23, 0.37]  | [0.37, 0.5]  |
| $MIXP_1$    | [0.05, 0.3] | [0.35, 0.65]  | [0.65, 0.95] |
| $TVV_D$     | [50, 367]   | [367, 683]    | [683, 1000]  |
| $TVk_a$     | [0.1, 0.37] | [0.37, 0.63]  | [0.63, 0.9]  |
| $\sigma$    | [0.1, 0.17] | [0.17, 0.23]  | [0.23, 0.3]  |
| $COV_{eff}$ | $\leq rCL$  | $\approx rCL$ | $\geq rCL$   |
| $\gamma$    | -0.85       | 0             | 0.85         |

$rCL = TVCL_2 / TVCL_1$ ;  $n$  is the Sample size;  $COV_{eff}$  represents the covariate effect size relative to the ratio of  $TVCL$  between the two subgroups;  $\gamma$  is the skewness of the covariate distribution. Note that  $CVV_D$  and  $CVk_a$  are fixed at 0.2.

### Simulation of datasets

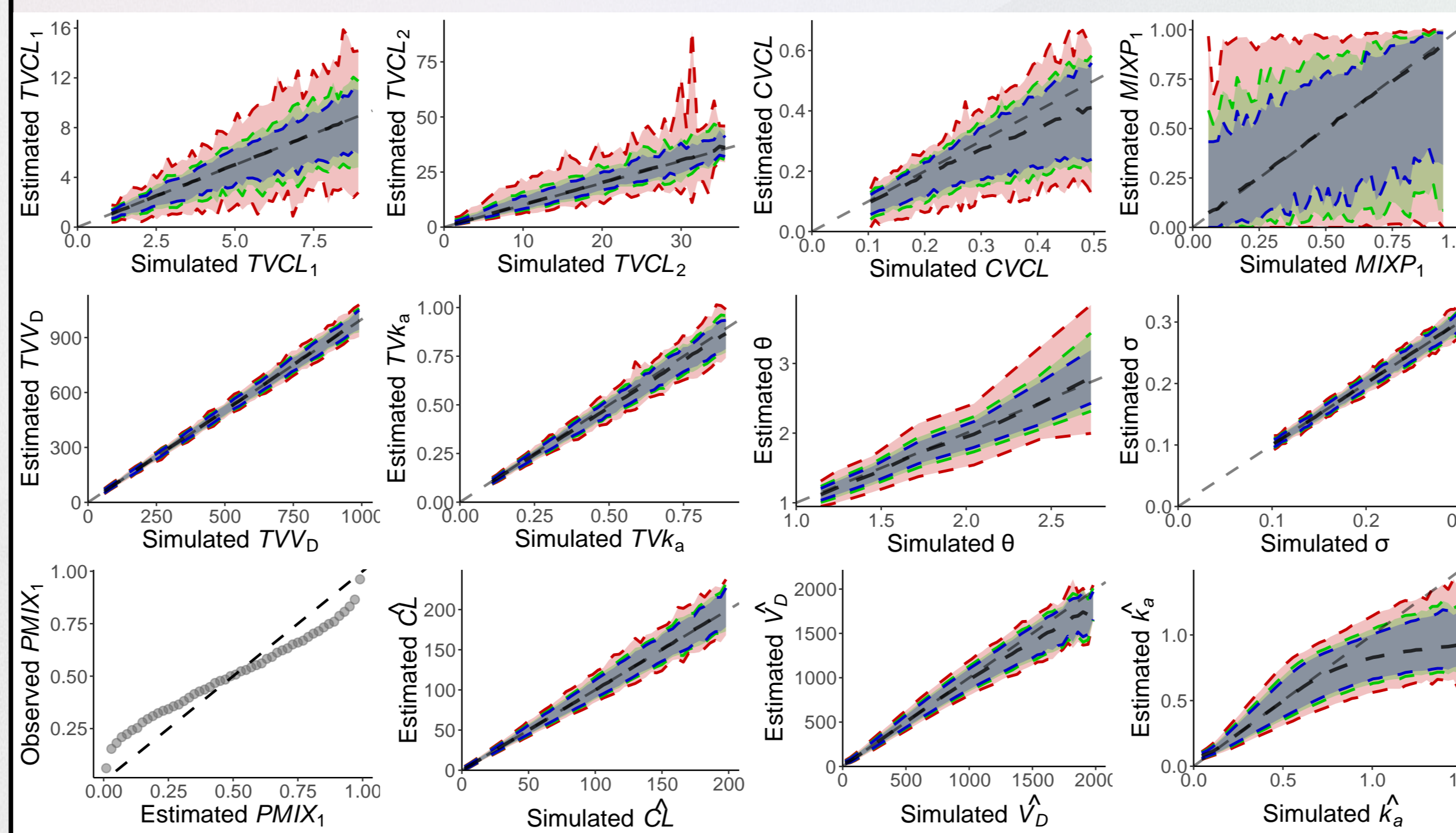
- PK model – One-compartment model with first-order absorption (ADVAN2 TRANS2)
- Block-sampling was performed based on the above simulation scheme
  - Total number of datasets =  $3^{10} = 59,049$
- 12 samples per subject

### Study procedure



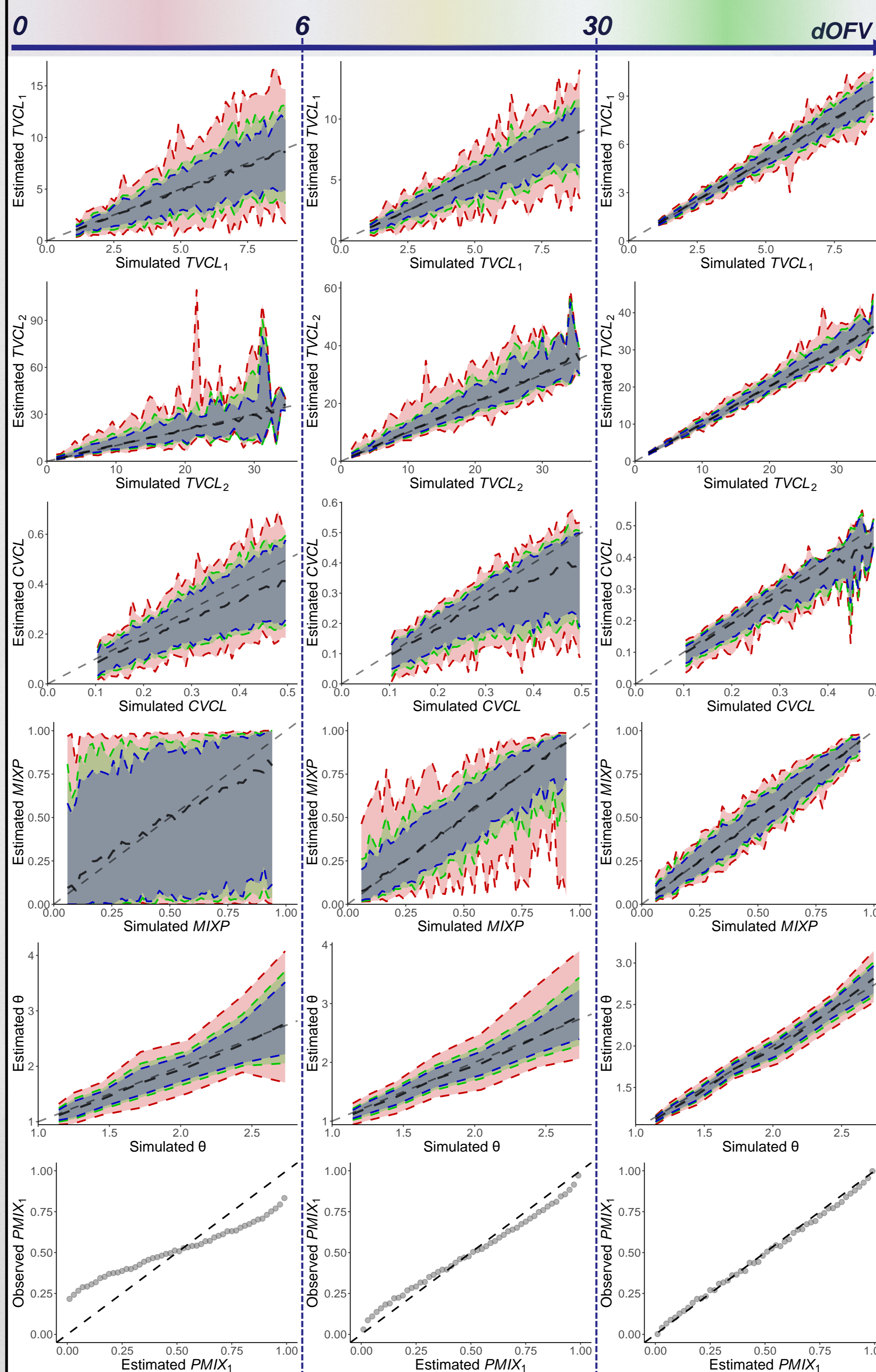
## RESULTS

### Plotting estimated vs simulated parameters (unstratified)



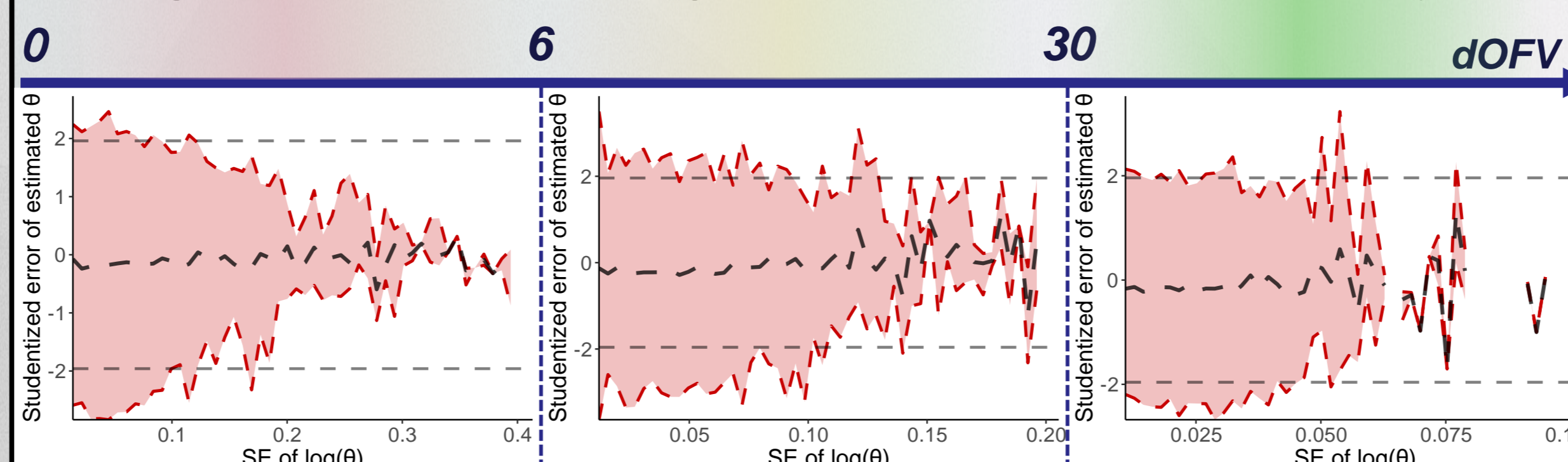
Red: 99% CI; Green: 95% CI; Blue: 90% CI; dashed lines: median or identity  
 $\theta$ : Covariate effect parameter (base of exponential covariate model)  
 $\bar{CL}$ ,  $\bar{V}_D$  and  $\bar{k}_a$ : individual  $CL$ ,  $V_D$  and  $k_a$ , respectively  
 $PMIX_1$  denotes the individual probability of belonging to subgroup 1  
 Observed  $PMIX_1$  is the simulated proportion of subgroup 1 binned by estimated  $PMIX_1$

### Plotting estimated vs simulated parameters (stratified by dOFV)



$dOFV$  denotes the change in minimum objective function value after removing the mixture component (i.e. fixing  $MIXP_1 = 1$  and  $TVCL_2 = TVCL_1$  during parameter estimation)

### Plotting error of estimates of $\theta$ against SE of estimated $\theta$ (stratified by dOFV)



The black dashed line represents the median. The shaded region in red represents the 95% CI of the data. Ideally, the shaded regions should resemble the areas enclosed by the grey dashed lines which represent the 95% CI of a standard normal distribution.

### Estimation error (unstratified)

| Param       | Median | 95% range        |
|-------------|--------|------------------|
| $TVCL_1$    | +0.2%  | (-45.3%, +33.5%) |
| $TVCL_2$    | +2.0%  | (-24.1%, +55.8%) |
| $CVCL$      | -2.2%  | (-18.8%, +5.8%)  |
| $MIXP_1$    | -0.2%  | (-47.5%, +35.2%) |
| $TVV_D$     | +0.4%  | (-5.7%, +6.9%)   |
| $TVk_a$     | -2.5%  | (-12.7%, +7.9%)  |
| $\theta$    | -0.5%  | (-12.8%, +11.7%) |
| $\sigma$    | +0.03% | (-1.3%, +1.4%)   |
| $PMIX_1$    | <0.001 | (-2.17, +2.65)   |
| $\bar{CL}$  | +1.3%  | (-18.8%, +43.4%) |
| $\bar{V}_D$ | -0.2%  | (-15.1%, +18.8%) |
| $\bar{k}_a$ | -2.7%  | (-31.6%, +33.9%) |

Estimation errors are expressed in absolute values for  $CVCL$ ,  $MIXP_1$  and  $\sigma$ , and expressed in relative values for the other parameters.  $PMIX_1$  is expressed as deviance residuals.

### Estimation error (stratified by dOFV)

| Param    | dOFV   | Median | 95% range        |
|----------|--------|--------|------------------|
| $TVCL_1$ | (0,6)  | -3.4%  | (-56.5%, +46.5%) |
|          | (6,30) | +0.4%  | (-39.4%, +31.0%) |
|          | (30,∞) | +1.4%  | (-11.7%, +14.4%) |
| $TVCL_2$ | (0,6)  | +3.7%  | (-31.8%, +79.9%) |
|          | (6,30) | +2.4%  | (-18.3%, +45.7%) |
|          | (30,∞) | +1.2%  | (-8.4%, +13.9%)  |
| $CVCL$   | (0,6)  | -4.2%  | (-20.4, +8.8%)   |
|          | (6,30) | -2.8%  | (-20.0%, +4.2%)  |
|          | (30,∞) | -0.9%  | (-7.0%, +2.3%)   |
| $MIXP_1$ | (0,6)  | -1.6%  | (-62.8%, +50.6%) |
|          | (6,30) | +0.3%  | (-21.2%, +19.8%) |
|          | (30,∞) | -0.1%  | (-10.0%, +10.1%) |
| $\theta$ | (0,6)  | -0.6%  | (-14.8%, +14.4%) |
|          | (6,30) | -0.7%  | (-13.2%, +12.4%) |
|          | (30,∞) | -0.3%  | (-6.0%, +4.9%)   |
| $PMIX_1$ | (0,6)  | <0.001 | (-2.79, +3.56)   |
|          | (6,30) | <0.001 | (-1.90, +1.95)   |
|          | (30,∞) | <0.001 | (-0.89, +0.89)   |

### Studentized error VS SE for $\theta$

| Param    | dOFV   | 95% range      |
|----------|--------|----------------|
| $\theta$ | (0,6)  | (-2.73, +2.16) |
|          | (6,30) | (-3.10, +2.52) |
|          | (30,∞) | (-2.58, +2.10) |

## MAJOR FINDINGS

- Accuracy of parameter estimations improves drastically with increasing  $dOFV$
- Underestimation of  $TVCL_1$  is more severe than overestimation; the contrary is true for  $TVCL_2$
- $CVCL$  is more often underestimated than overestimated, particularly when  $CVCL$  is large
- Estimation for  $MIXP$  is highly volatile
- Probability of belonging to the classified subgroup is generally overestimated
- Population parameters not involved in the mixture model generally do not show trend of systematic biases and also produce accurate estimates
- Trends of systematic biases cannot be observed in the estimation of covariate effect size
- Estimated SE of covariate effects cannot well describe the distributions of the errors of the estimates