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Handling Quantification Limits in Optimal Design

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LOD vs. LOQ

- Limit of detection (LOD): “lowest quantity of substance that can be distinguished from absence of that substance”
- Limit of quantification (LOQ): “limit at which a difference can be reasonably quantified”
- LOD&LOQ differ between:
  - Analytics
  - Analysis methods
  - Analysts

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Limit of Quantification

- Mostly measurement of concentration
- But also: Bacteria colony counting, Measurement of pain sensitivity etc.

- Mostly lower limit of quantification (LLOQ)
- Similar problems with upper limits

- Here: Concentration & LLOQ

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LOQ in Practice

- How it is handled:
  - Analysis method is characterized & LOQ is determined
  - Data is analyzed
  - Each signal that is < LOQ is reported as BLQ (instead of measured value)

- How it should be handled:
  - Report all data & method characteristics

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Handling BQL

Pharmaceutical Research, Vol. 19, No. 12, December 2002 (© 2002)

Impact of Omission or Replacement of Data below the Limit of Quantification on Parameter Estimates in a Two-Compartment Model

Vincent Duval[1,3] and Mats O. Karlsson[2]

Journal of Pharmacokinetics and Pharmacodynamics, Vol. 28, No. 5, October 2001 (© 2001)

Ways to Fit a PK Model with Some Data Below the Quantification Limit

Stuart L. Beal[1,2]

J Pharmacokinet Pharmacodyn (2008) 35:101–116
DOI 10.1007/s10928-007-9078-9

Impact of censoring data below an arbitrary quantification limit on structural model misspecification

Wonkyung Byon · Courtney V. Fletcher · Richard C. Brundage

J Pharmacokinet Pharmacodyn (2008) 35:401–421
DOI 10.1007/s10928-008-9094-4

Likelihood based approaches to handling data below the quantification limit using NONMEM VI

Jae Eun Ahn · Mats O. Karlsson · Adrian Dunne · Thomas M. Ludden

J Pharmacokinet Pharmacodyn (2011) 38:423–432
DOI 10.1007/s10928-011-9201-9

Impact of low percentage of data below the quantification limit on parameter estimates of pharmacokinetic models

Xu Steven Xu · Adrian Dunne · Holly Kimko · Partha Nandy · An Vermeulen

AAPS Journal, Vol. 11, No. 2, June 2009 (© 2009)
DOI: 10.1208/s12248-009-9112-5

Research Article

Handling Data Below the Limit of Quantification in Mixed Effect Models

Martin Bergstrand[1,2] and Mats O. Karlsson[1]

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Handling BQL (2)

- Many methods:
  - Omit
  - Impute LOQ/2
  - Maximize the likelihood for all the data treating BLQ observation as censored (M3)
  - …

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Likelihood Based Handling (M3)

$$L(\Theta|y_i) = \int_{-\infty}^{\infty} p(y_i|\eta,\Theta)p(\eta|\Theta)d\eta$$

$$p(y_i|\eta,\Theta) = \prod_j p(y_{ij}|\eta,\Theta)$$

$$p(y_{ij}|\eta,\Theta) = (\sigma\sqrt{2\pi})^{-1} e^{\frac{(y_{ij}-f(t_i,\eta,\Theta))}{2\sigma^2}} \quad p(y_{ij}|\eta,\Theta) = \begin{cases} (\sigma\sqrt{2\pi})^{-1} e^{\frac{(y_{ij}-f(t_i,\eta,\Theta))}{2\sigma^2}} & y_{ij} > LOQ \\ \int_{-\infty}^{LOQ} (\sigma\sqrt{2\pi})^{-1} e^{\frac{(x-f(t_i,\eta,\Theta))}{2\sigma^2}} dx & y_{ij} \leq LOQ \end{cases}$$

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Method Comparison

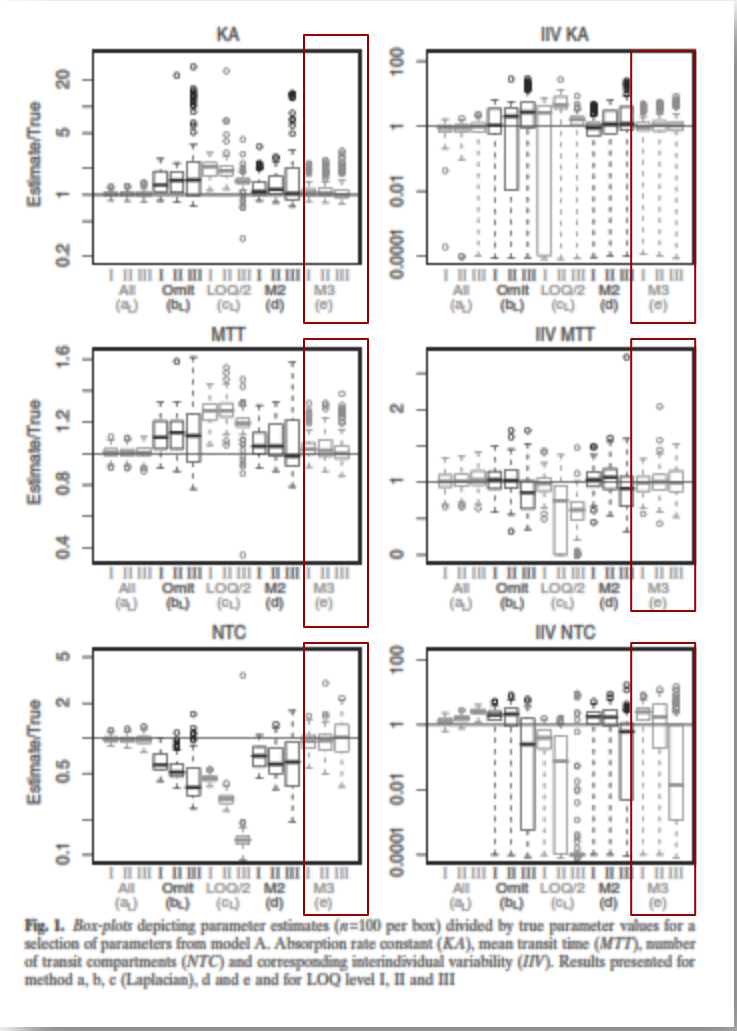

Fig. 1. *Box-plots* depicting parameter estimates (n=100 per box) divided by true parameter values for a selection of parameters from model A. Absorption rate constant (*KA*), mean transit time (*MTT*), number of transit compartments (*NTC*) and corresponding interindividual variability (*IIV*). Results presented for method a, b, c (Laplacian), d and e and for LOQ level I, II and III

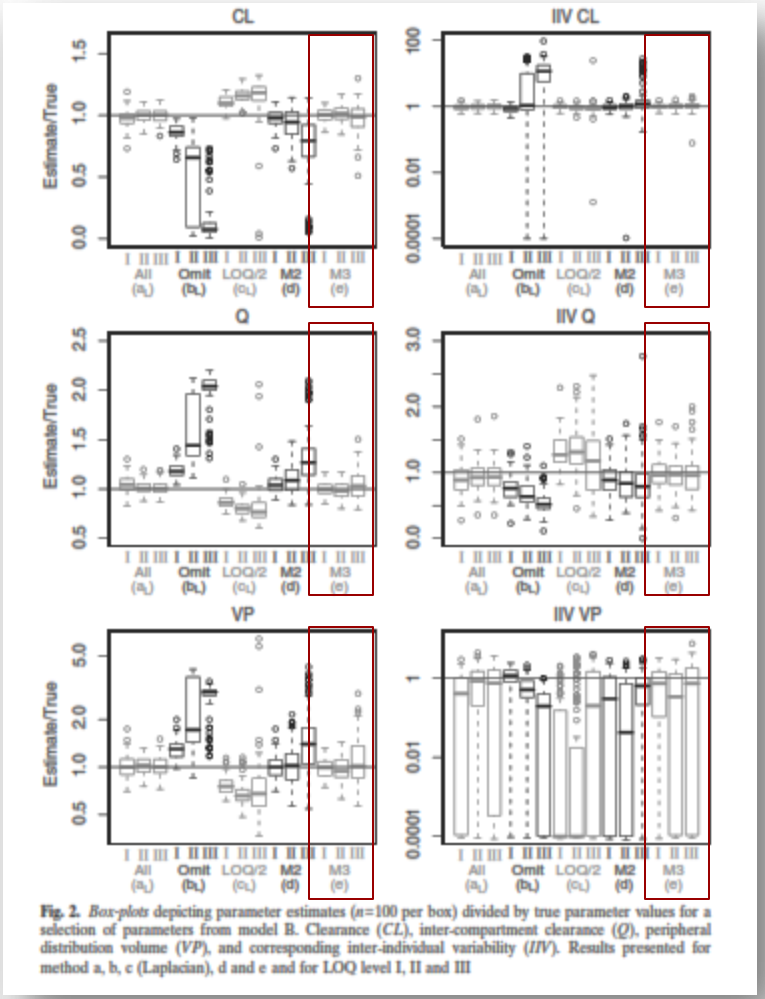

Fig. 2. *Box-plots* depicting parameter estimates (n=100 per box) divided by true parameter values for a selection of parameters from model B. Clearance (*CL*), inter-compartment clearance (*Q*), peripheral distribution volume (*VP*), and corresponding inter-individual variability (*IIV*). Results presented for method a, b, c (Laplacian), d and e and for LOQ level I, II and III

Bergtrand et al., AAPSJ 2009

LOQs When Designing Experiments

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Avoid or don't bother

Avoid

- Maximize non-censored information

Don't bother

- Maximize information ignoring censoring

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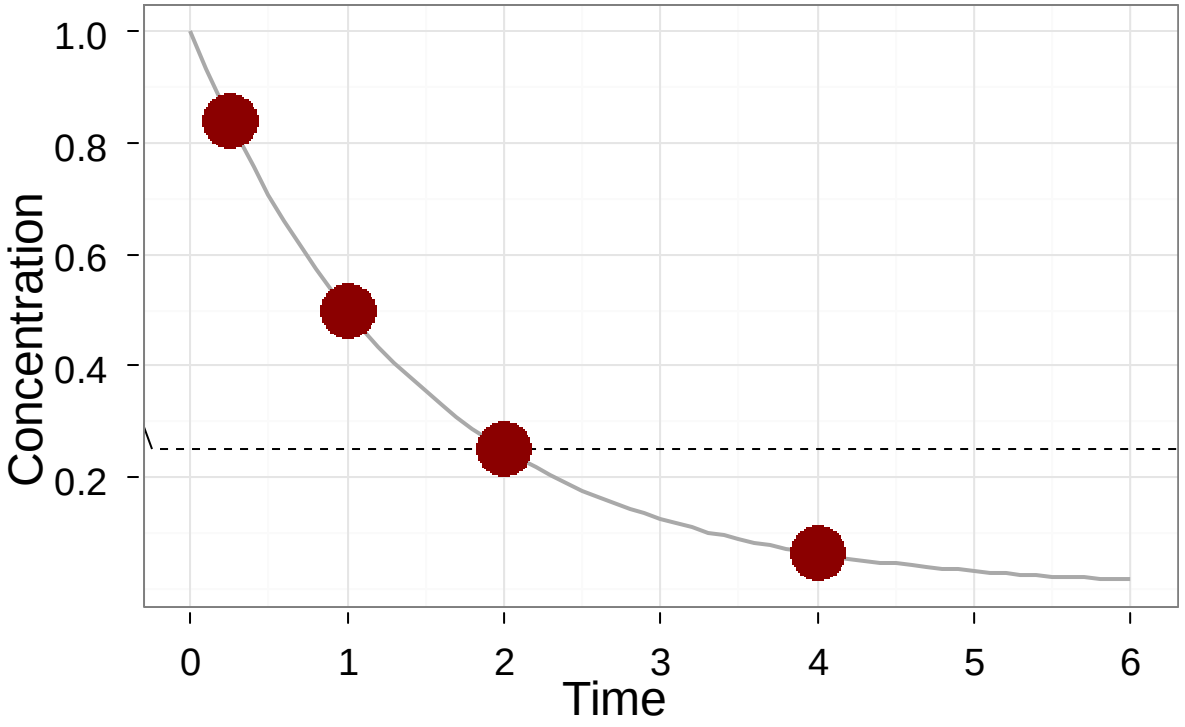
Method D1: Ignore LOQ



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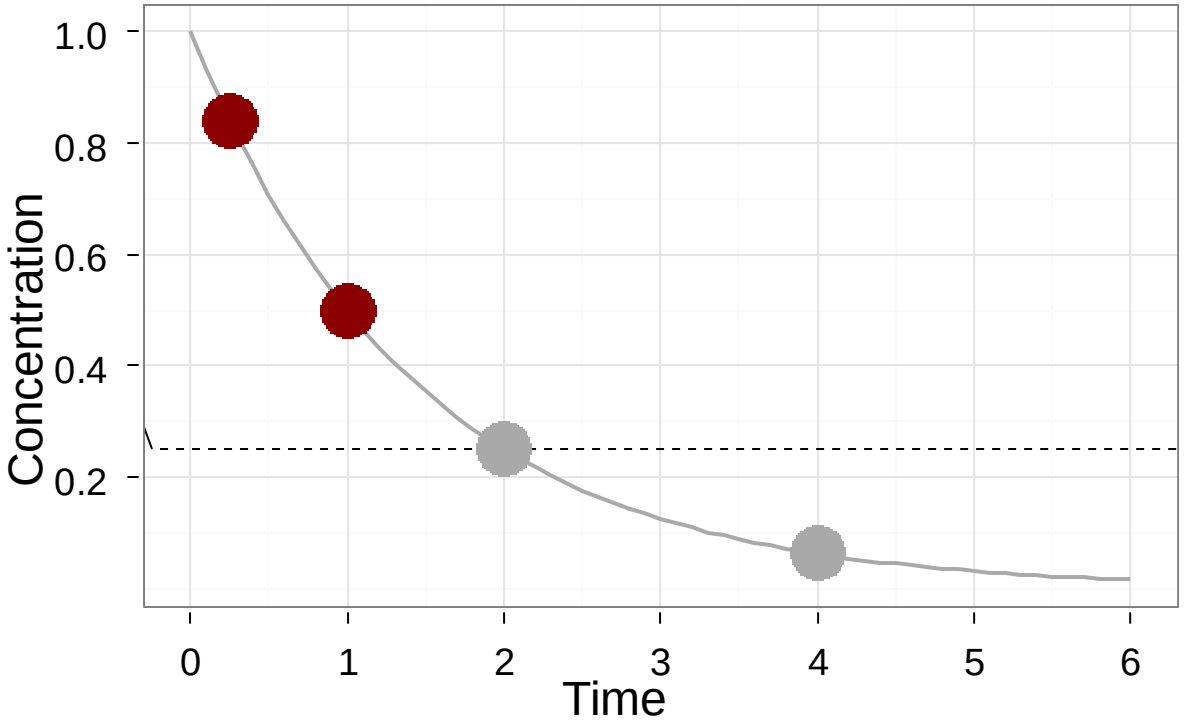
Method D2: PRED<LOQ → I=0



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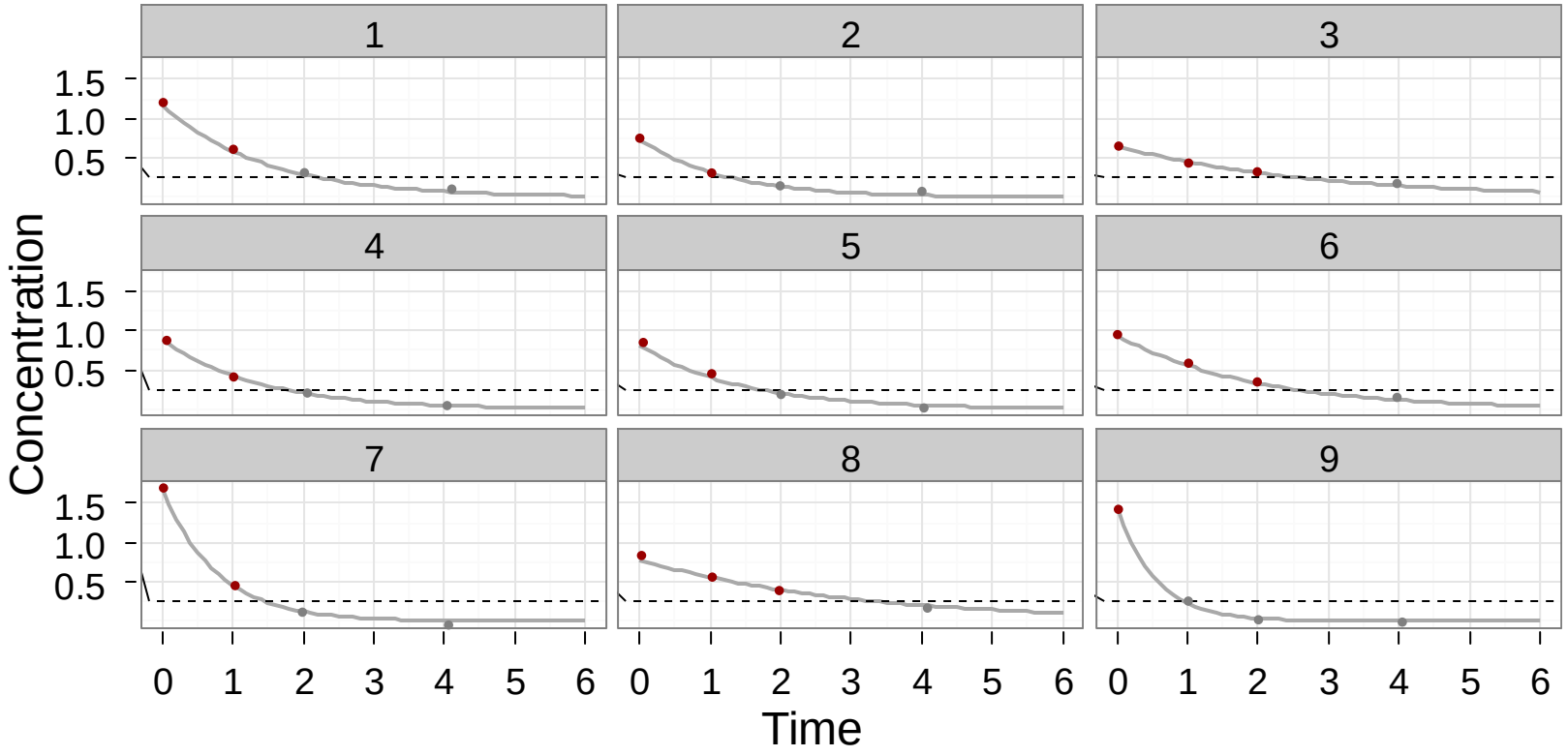
Method D3: IPRED<LOQ → I=0



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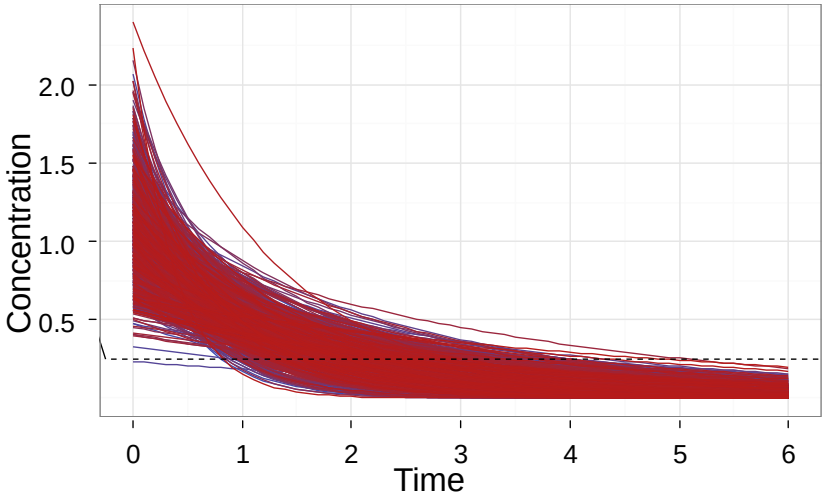
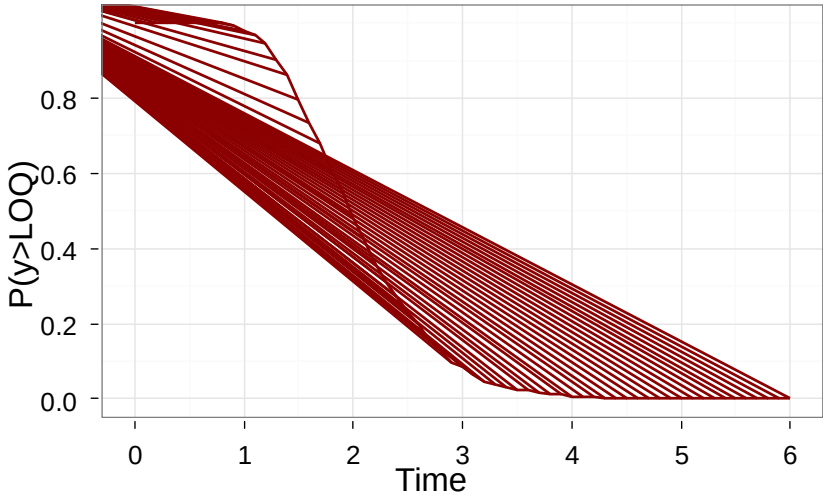
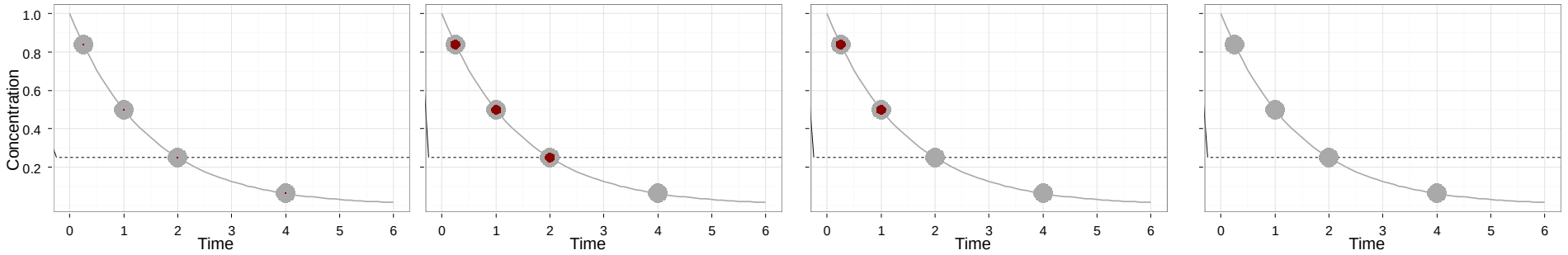
Method D4: Simulation & Scaling







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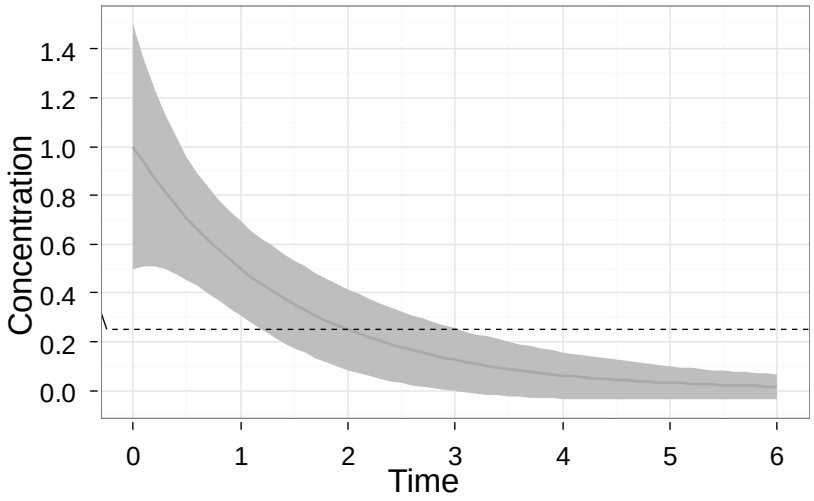
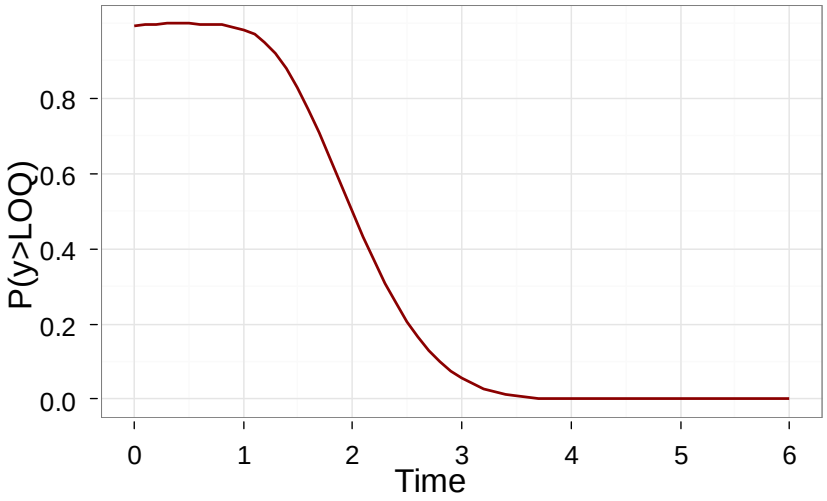
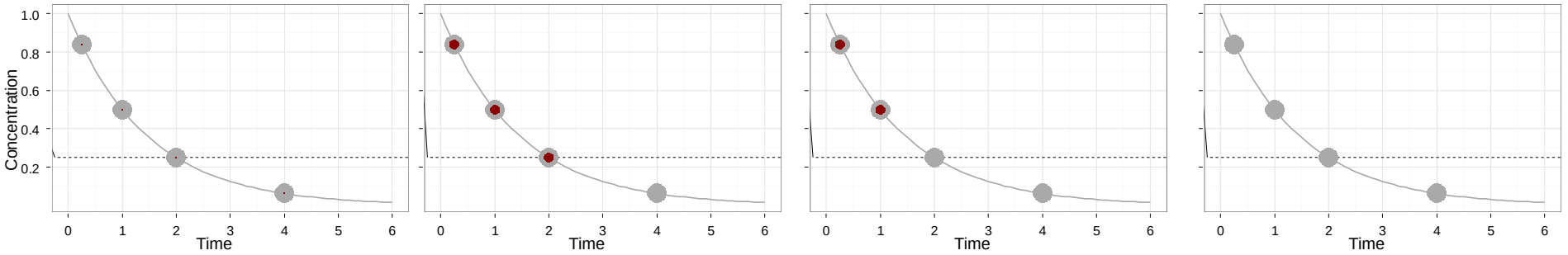
Method D5: FO Approx. & Scaling







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Method D6: Discrete/Continuous LL

$$I(\Theta) = -E\left(\frac{\partial^2}{\partial\theta^2} log L(\Theta|y_i)|\Theta\right)$$

Numeric Differentiation

Monte Carlo Integration

$$L(\Theta|y_i) = \int_{-\infty}^{\infty} p(y_i|\eta,\Theta)p(\eta|\Theta)d\eta$$

Laplace Integral Approximation

$$p(y_i|\eta,\Theta) = \prod_j p(y_{ij}|\eta,\Theta)$$

$$p(y_{ij}|\eta,\Theta) = \begin{cases} (\sigma\sqrt{2\pi})^{-1} e^{\frac{(y_{ij}-f(t_i,\eta,\Theta))}{2\sigma^2}} & y_{ij} > LOQ \\ \int_{-\infty}^{LOQ} (\sigma\sqrt{2\pi})^{-1} e^{\frac{(x-f(t_i,\eta,\Theta))}{2\sigma^2}} dx & y_{ij} \leq LOQ \end{cases}$$

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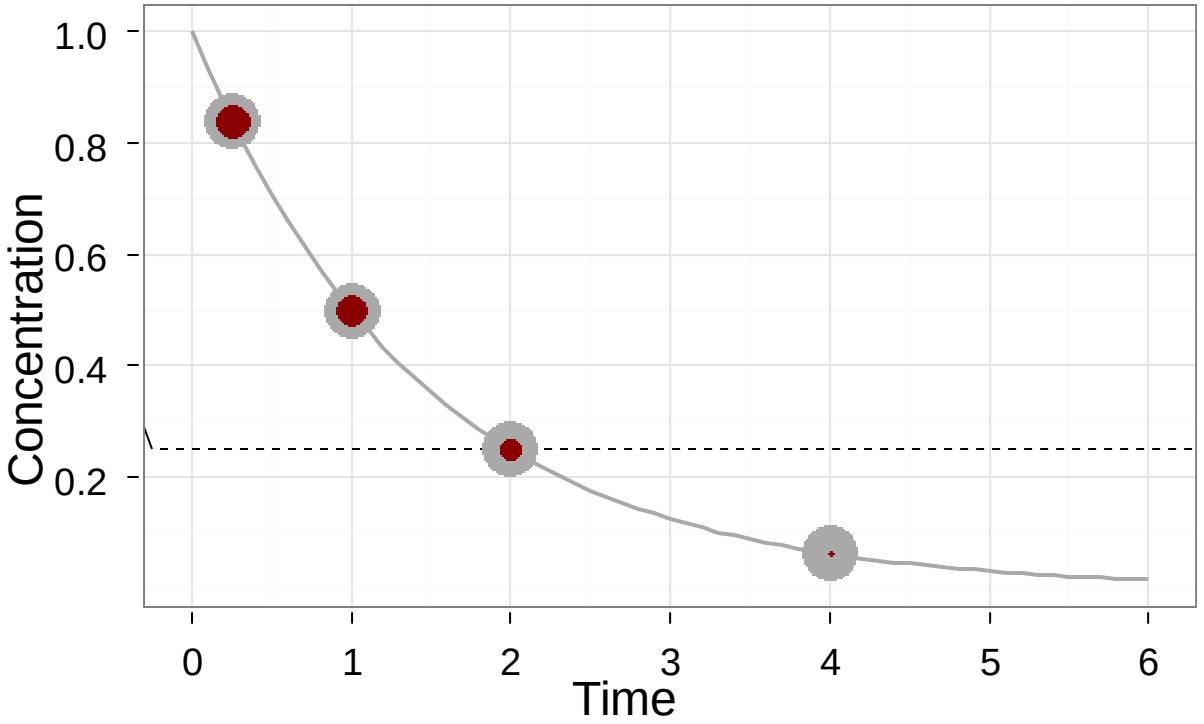
Method D6: Discrete/Continuous LL



Expected vs. Observed Parameter Precision

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Methods

1. Implement D1-D6 in PopED
2. Calculate expected parameter precision
3. Calculate empirical parameter precision
    1. Simulate 1000 datasets for each LOQ
    2. Re-estimate population parameters using M3 method (NM 7.2, Laplace estimation with interaction)

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Evaluation Model 1

Model

$$y_{ij} = \frac{D}{V_i} e^{-\frac{CL_i}{V_i} t_j} (1 + \varepsilon_{ij})$$

$$V_i = \theta_2 e^{\eta_{2i}} \qquad \eta_{xi} \sim N(0, \omega_x^2)$$

$$CL_i = \theta_1 e^{\eta_{1i}} \qquad \varepsilon_{ij} \sim N(0, \sigma^2)$$

Parameter	Value
θ_1	0.693
θ_2	1
ω_x^2	0.09
σ^2	0.005

Design Variables

Variable	Value
D (Dose)	1
Number of Individuals	50
Sampling Times	[0.25, 1, 2, 4]

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LOQ settings

LOQ	Observations <LOQ
0	0 %
0.0625	22 %
0.0884	27 %
0.125	33 %
0.1768	40 %
0.25	48 %

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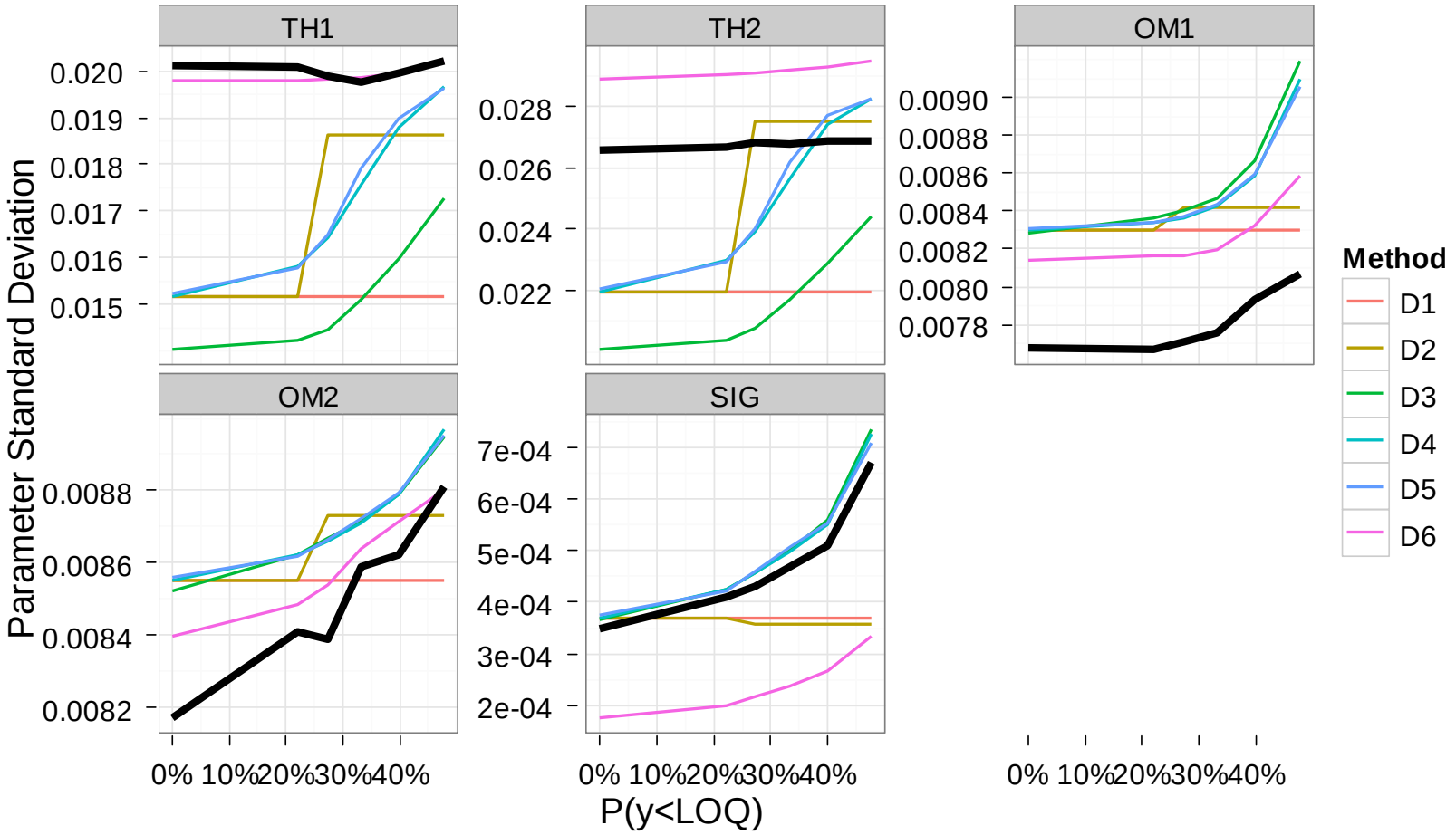
Expected vs. Observed Precision



RUNTIMES

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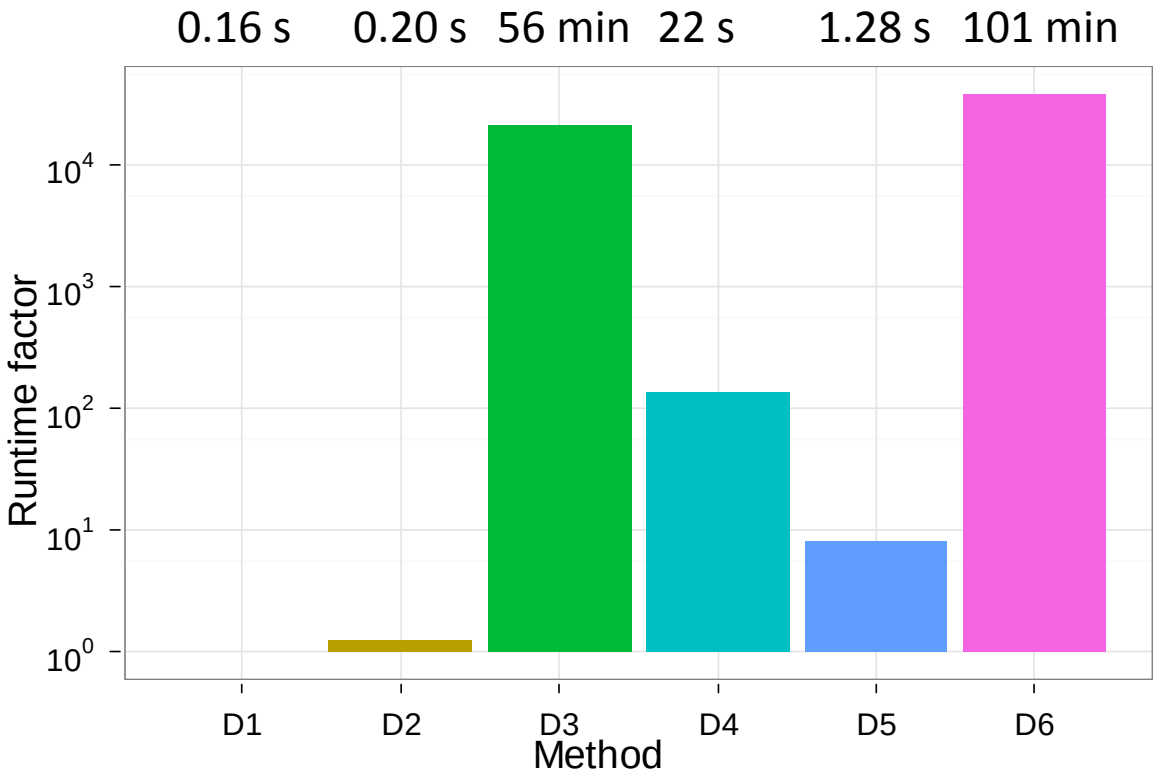
Runtimes

- Time to obtain expected parameter precision for 1 design relative to D1



D1 – Ignore LOQ
D2 – PRED<LOQ → I=0
D3 – IPRED<LOQ → I=0
D4 – Simulation & Scaling
D5 – FO Approx. & Scaling
D6 – Discrete/Continuous LL

DESIGN OPTIMIZATION

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Methods

1. Optimize sampling times using methods D1, D2, D4, D5 for different LOQs
2. Evaluate design performance of each design in a simulation study
    1. Simulate 200 datasets
    2. Re-estimate population parameters using M3 method (NM 7.2, Laplace estimation with interaction)

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Evaluation Model 2

Model

$$\frac{dA_{1i}}{dt} = -\frac{CL_{1i}}{V_{1i}}A_{1i} - \frac{CL_{2i}}{V_{1i}}A_{1i} + \frac{CL_{2i}}{V_{2i}}A_{2i}$$

$$\frac{dA_{2i}}{dt} = \frac{CL_{2i}}{V_{1i}}A_{1i} - \frac{CL_{2i}}{V_{2i}}A_{2i} \quad C(t) = \frac{A_{1i}(t)}{V_{1i}}$$

$$CL_{1i} = \theta_1 e^{\eta_{1i}} \qquad \eta_{xi} \sim N(0, \omega_x^2)$$
$$CL_{2i} = \theta_3 e^{\eta_{3i}} \qquad \varepsilon_{ij} \sim N(0, \sigma^2)$$
$$V_{1i} = \theta_2 e^{\eta_{2i}}$$
$$V_{2i} = \theta_4 e^{\eta_{4i}}$$

Parameter	Value
θ_1	10
θ_2	100
θ_3	100
θ_4	80
ω_x^2	0.09
σ^2	0.01

Design Variables

Variable	Value
D (Dose)	25
Number of Individuals	50
Sampling Times	[0 0.25 1 12 24]

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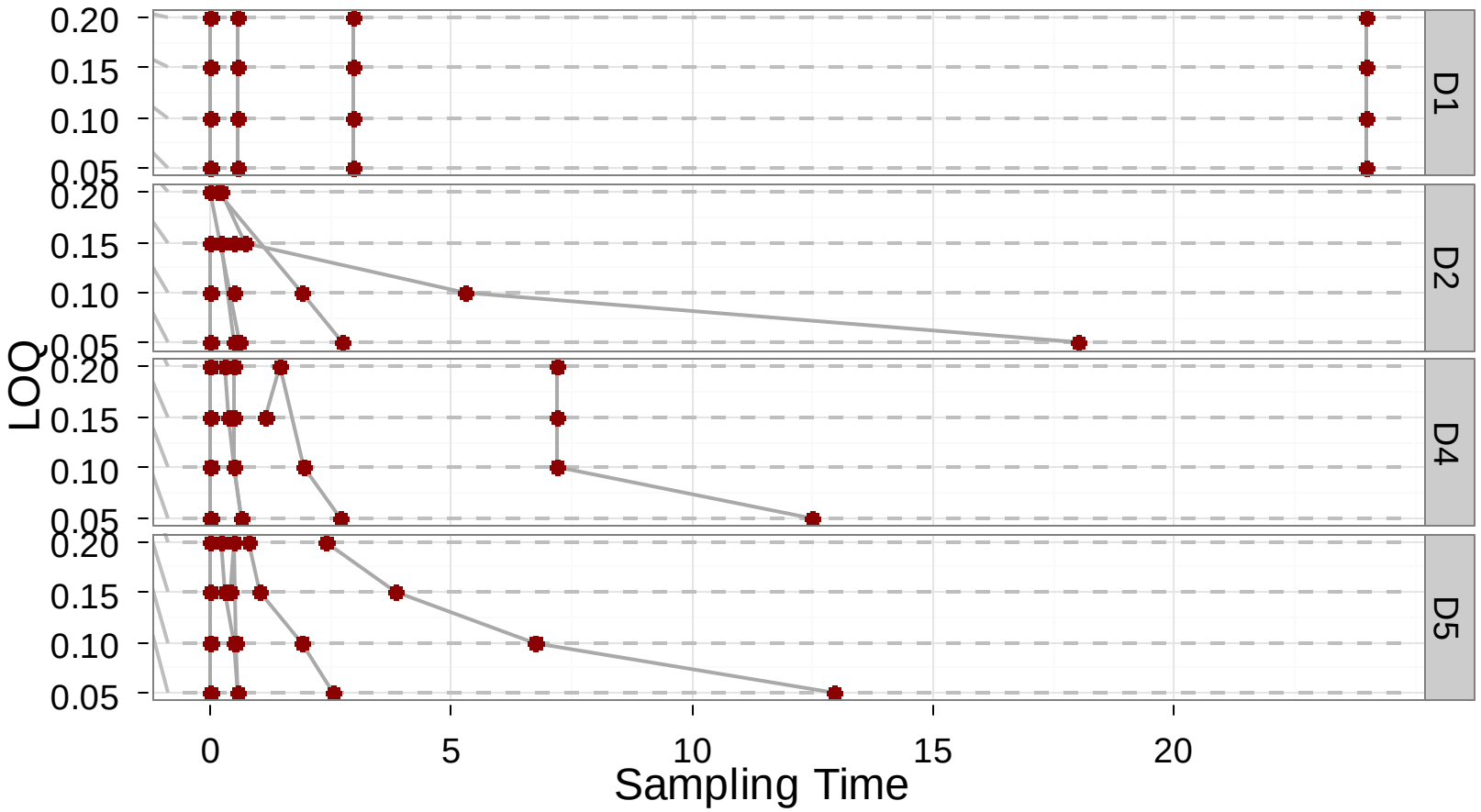
Optimal Designs



D1 – Ignore LOQ | D2 – PRED<LOQ → I=0 | D4 – Simulation & Scaling | D5 – FO Approx. & Scaling

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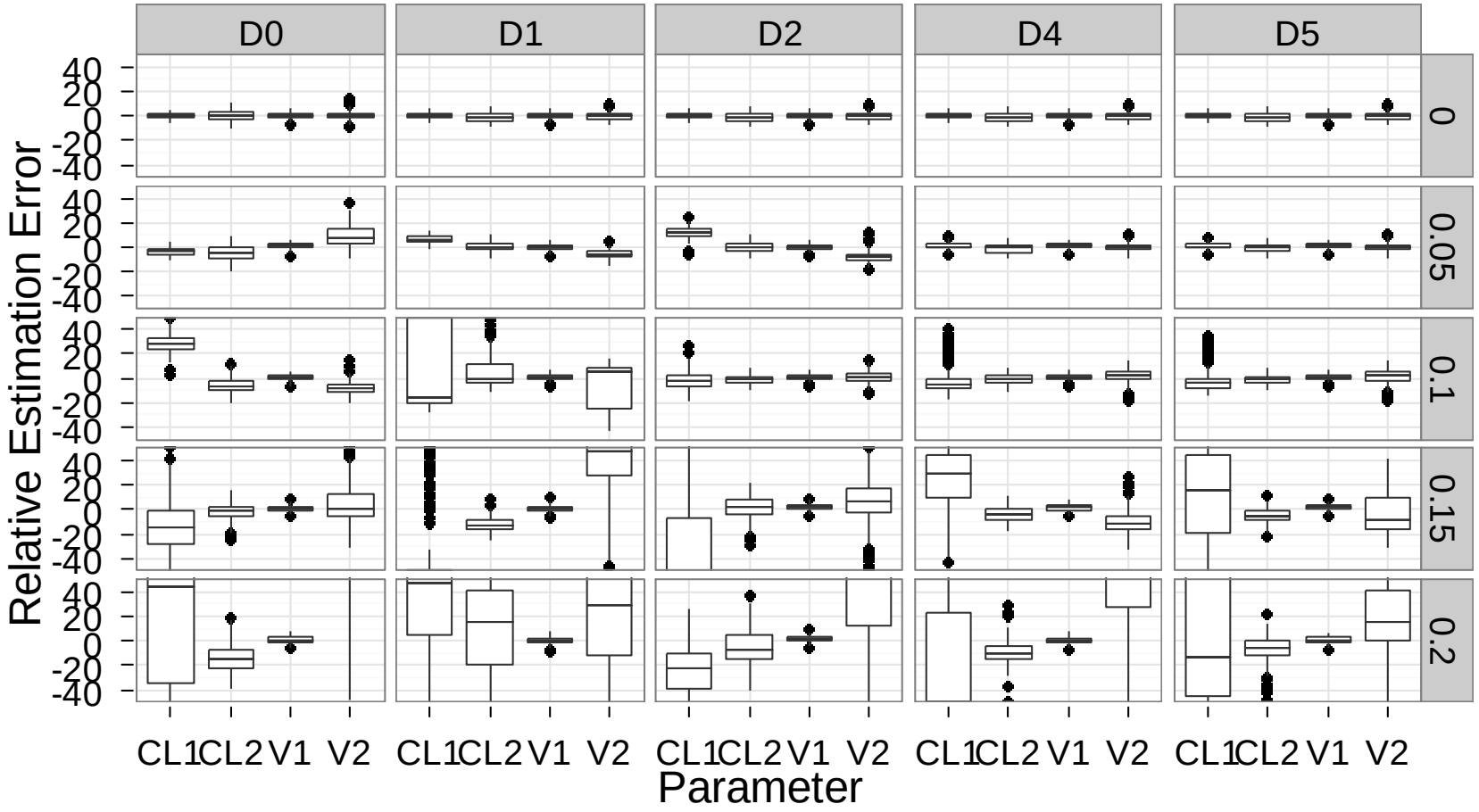
REE Fixed Effects



D1 – Ignore LOQ | D2 – PRED<LOQ → I=0 | D4 – Simulation & Scaling | D5 – FO Approx. & Scaling

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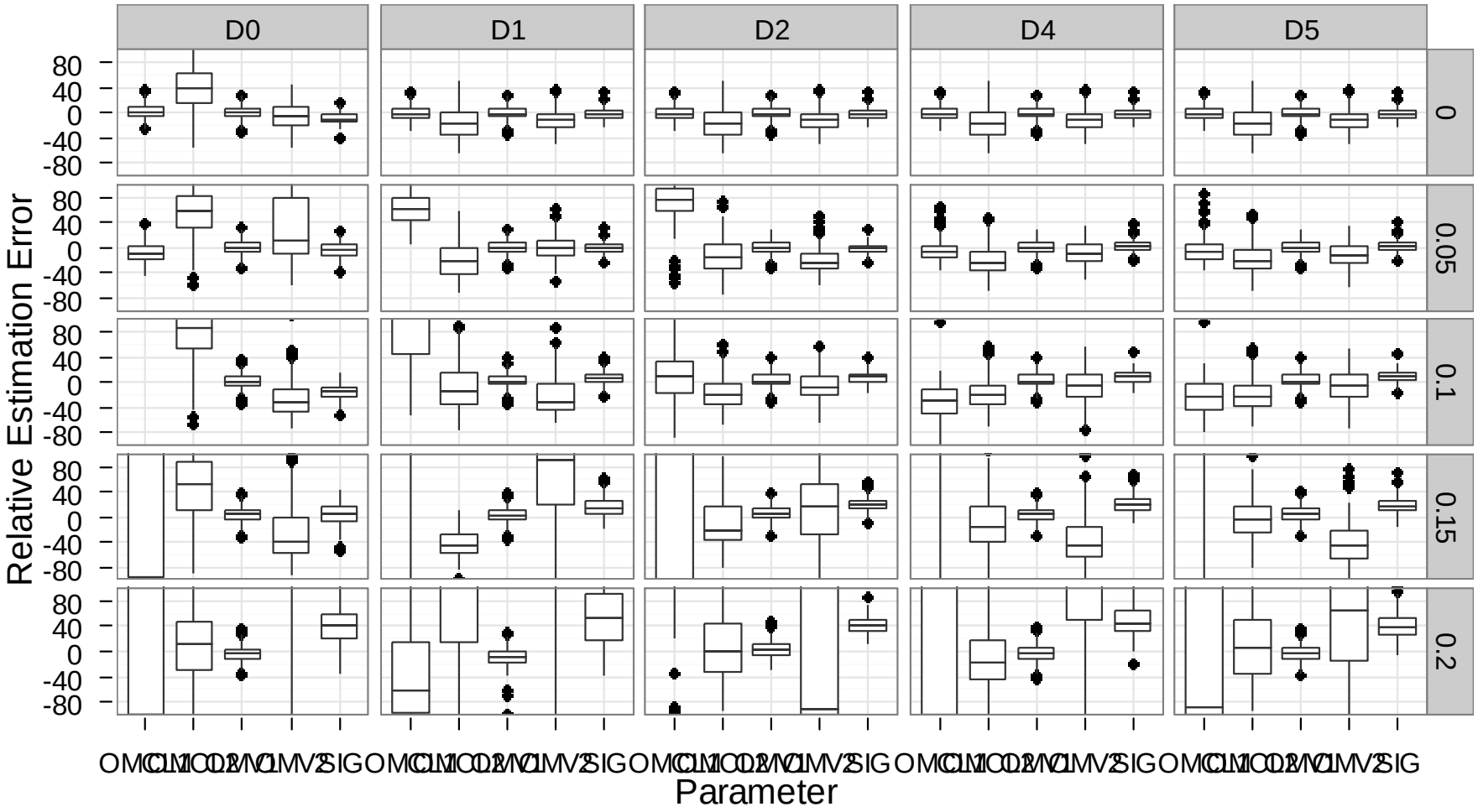
REE Random Effects



D1 – Ignore LOQ | D2 – PRED<LOQ → I=0 | D4 – Simulation & Scaling | D5 – FO Approx. & Scaling

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Summary

- Precision prediction:
  - Only method D6 accurately described the loss in information for increasing LOQ levels
  - All other methods (except D1) are to pessimistic (actual information is higher than predicted)
- Optimization:
  - Runtime renders D6 impractical for optimization
  - Designs obtained with methods D4 & D5 perform better than D1 (ignoring LOQ)

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Recommendations

- If expected number of observations < LOQ is small → use D1
- If expected number of observations < LOQ is big → use D4 or D5
- Use D6 to obtain accurate predictions for parameter precision