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Handling Limit of Quantification Data in Optimal Design

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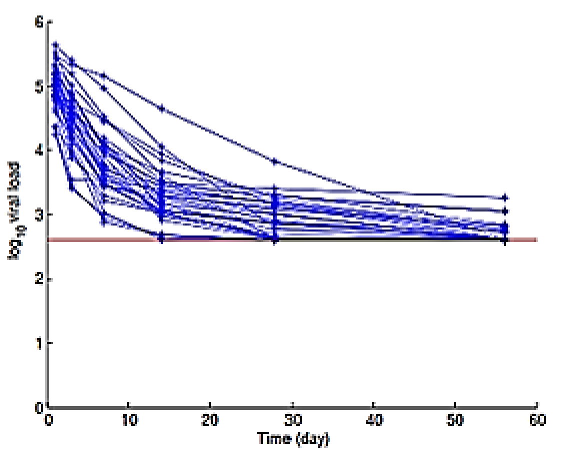
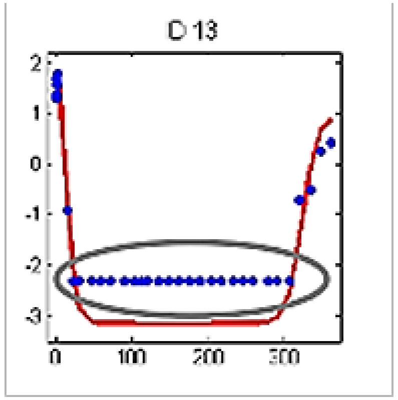
Drug Disease Model Resources
ddmore

Motivating examples

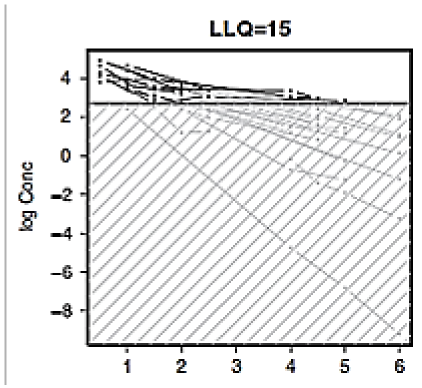
”not well-behaved” data for us!



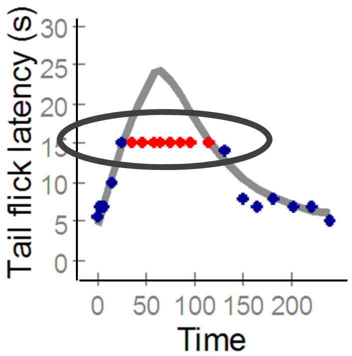
Samson et al., PAGE 2006



Romero et al., PAGE 2011



Yang et al., Pharm. Stat 2010



Sadiq et al., PAGE 2012

Structural model mispecification

Parameters unestimable

Drug clearance
AUC
misinterpreted

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LOQ data in modeling approach

Selected literatures

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) 35:401–421
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

armacokinet 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

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]

aceutical 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]

LOQ data in modeling approach

The "M-methods"

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]

Omission
- *Discard BQL data*

Substitution
- *By zero*
- *By LOQ/2*

Likelihood-based
- *Maximum likelihood treating BQL data as censored*

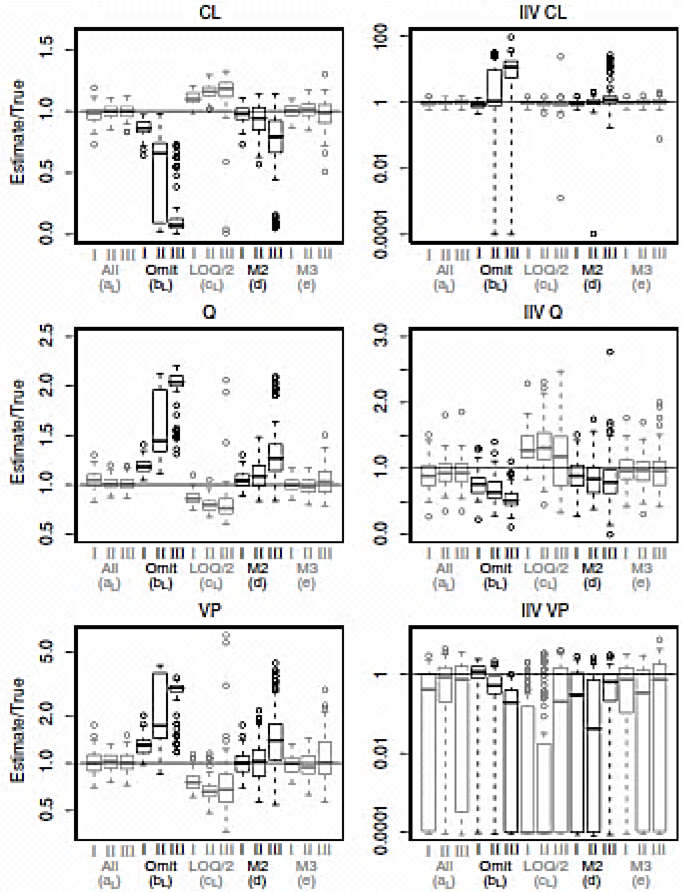

Fig. 2. *Box-plots* depicting parameter estimates (n=100 per box) divided by true parameter values for a selection of parameters from model B. Clearance (CL), inter-compartment clearance (Q), peripheral distribution volume (VP), and corresponding inter-individual variability (IIV). Results presented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

Bergstrand et al., AAPSJ 2009

LOQ data in modeling approach

The “M-methods”

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

Stuart L. Beal[1,2]

Less Bias!

Likelihood-based → ***M3 method***

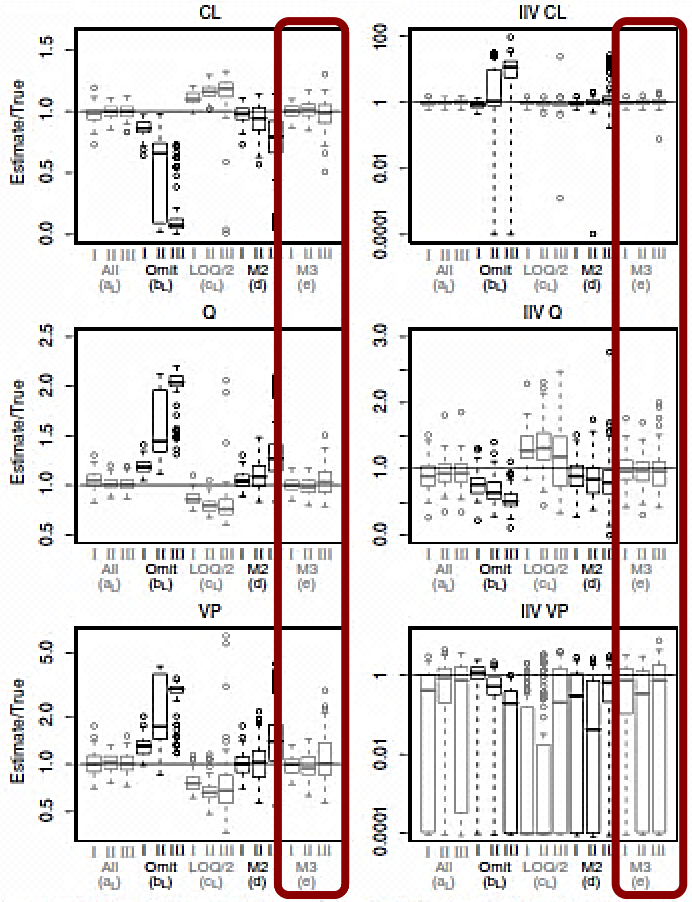


Fig. 2. *Box-plots* depicting parameter estimates ($n=100$ per box) divided by true parameter values for a selection of parameters from model B. Clearance (*CL*), inter-compartment clearance (*Q*), peripheral distribution volume (*VP*), and corresponding inter-individual variability (*IIV*). Results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

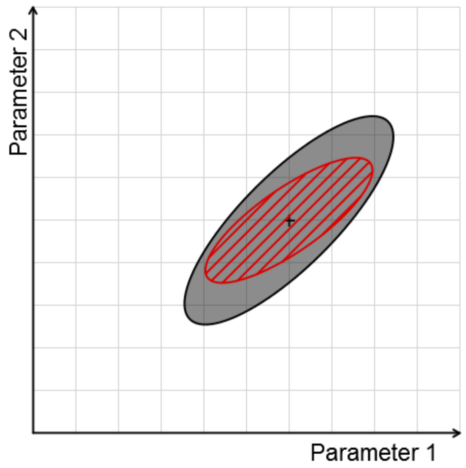
Bergstrand et al., AAPSJ 2009

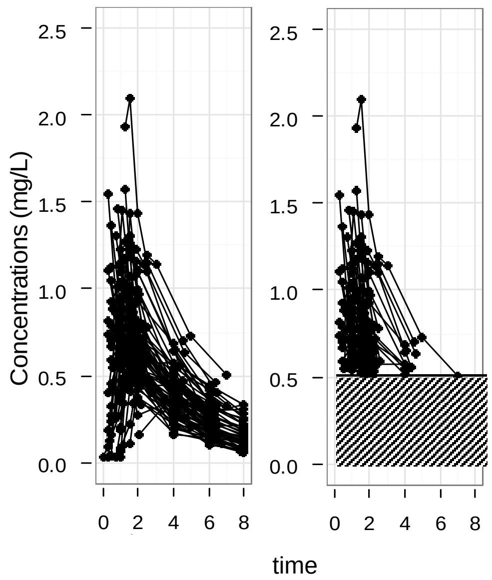
Designing a Trial design

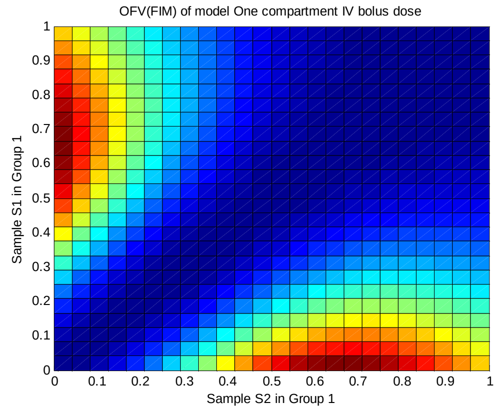
Optimal Design (OD) theory and Aim

Cramer-Rao inequality → **Prior knowledge of LOQ** → **Most INFORMATIVE design**

$$\mathrm{Var}(\hat{\theta}) \geq \mathrm{FIM}^{-1}$$







Aim:

Design optimization to prevent loss of information from LOQ constraints

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LOQ data in Trial design

3 common approaches

Don't bother

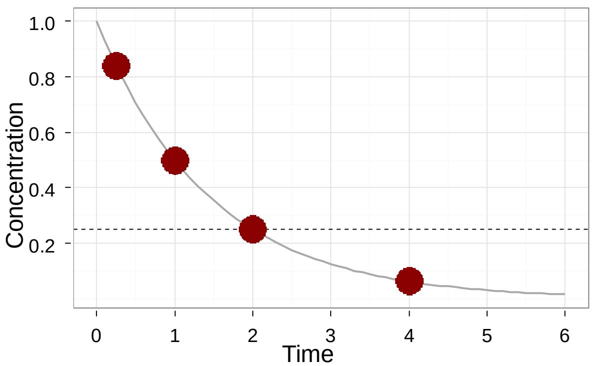
Maximize information ignoring censoring

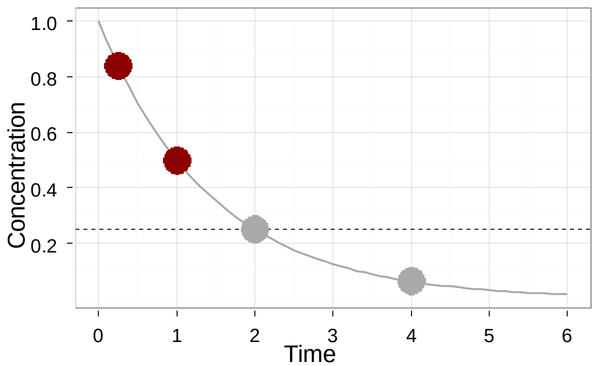
Avoid

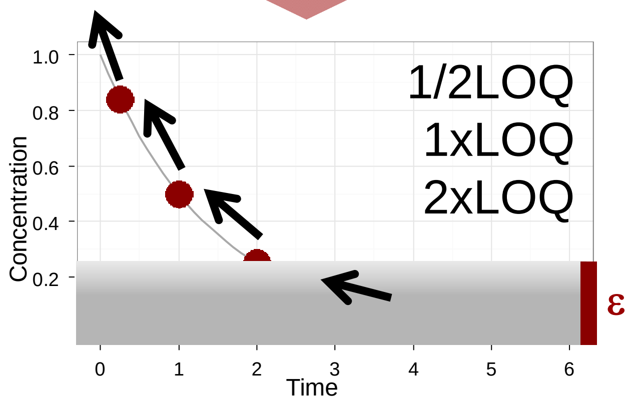
Maximize non-censored information

Penalize

Add an extra additive error







Method D1

Ignore LOQ

Method D2

PRED<LOQ

Method D4

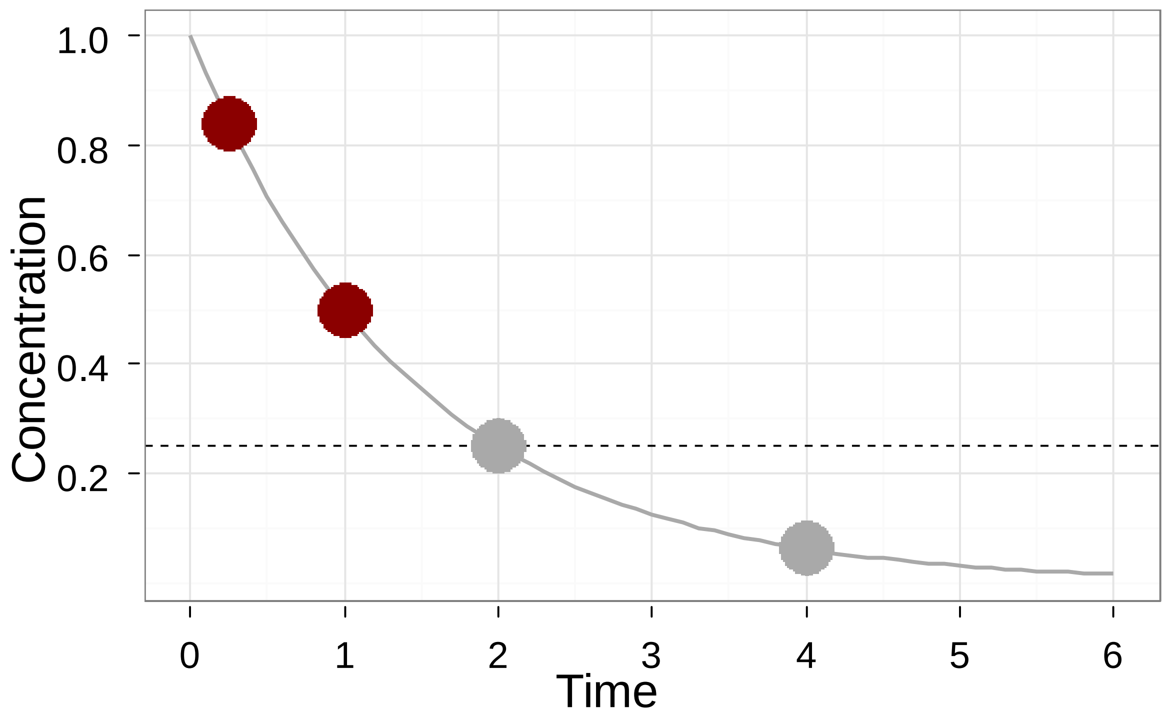
PRED + ε

not handling ULOQ!

LOQ data in Trial design

Alternative strategies

- *D1: Ignore*
- ***D2: Omit PRED<LOQ***
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation & FIM scaling*
- *D6: Integration & FIM scaling*
- *D7: Laplace*



LOQ data in Trial design

Alternative strategies

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
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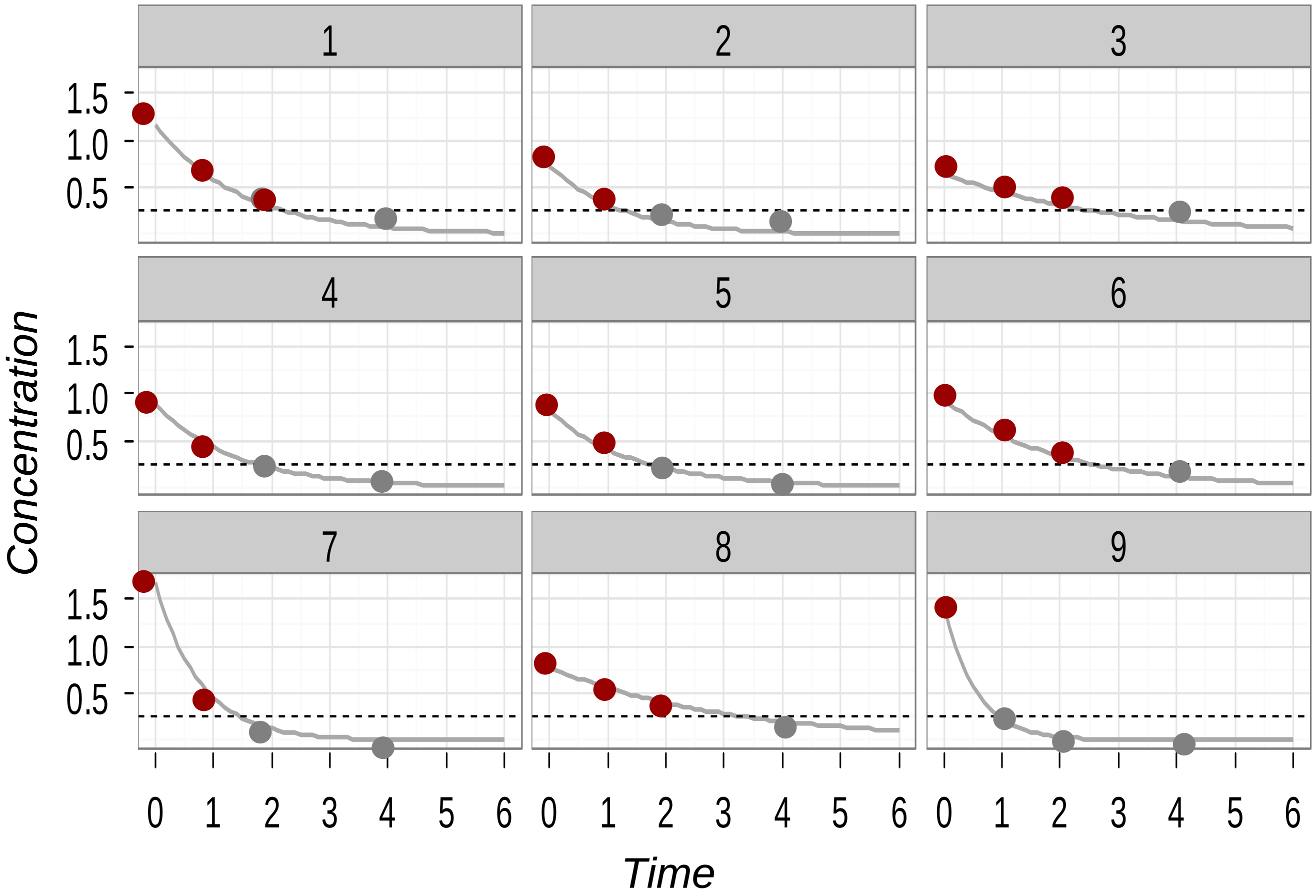

LOQ data in Trial design

Alternative strategies

- *D1: Ignore*
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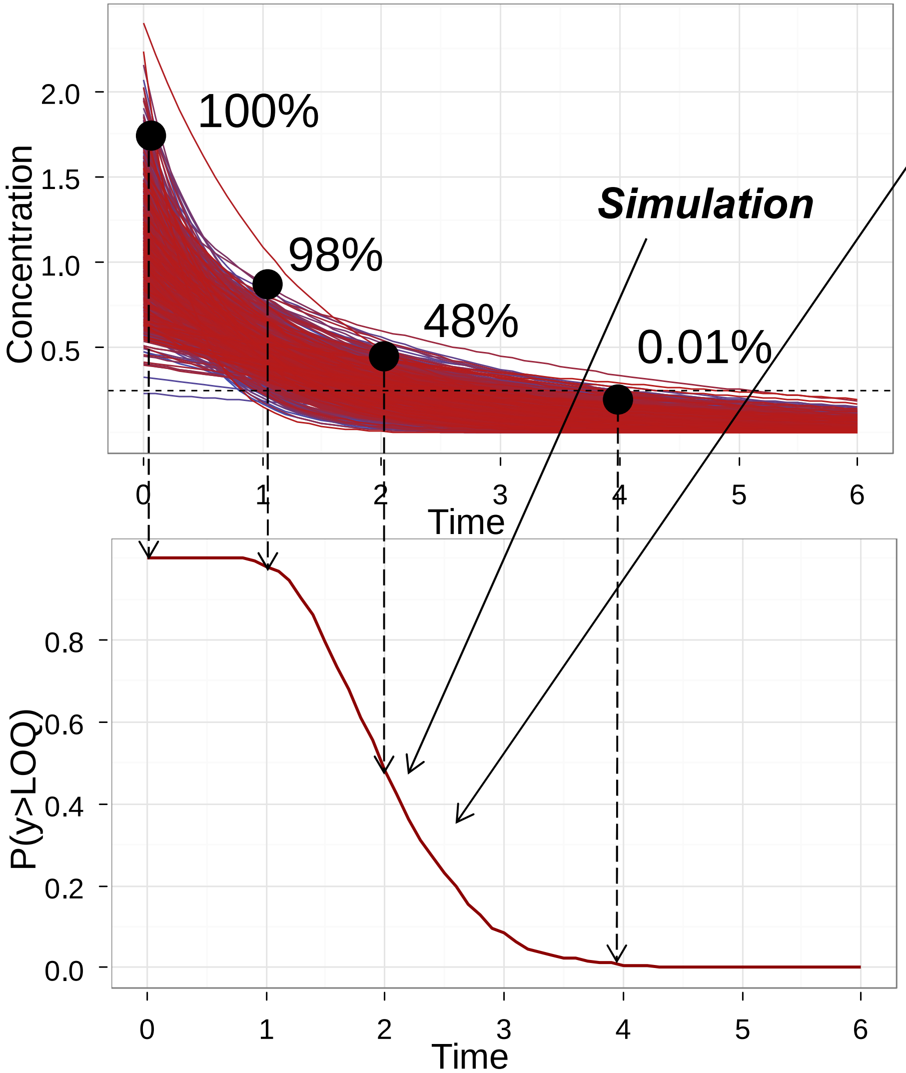


Count the different combinations

<u>Designs</u>

4 sampling times

0.008%

3 sampling times

e.g. ***1101***

20%

e.g. ***1110***

56%

2 sampling times

7%

1 sampling time

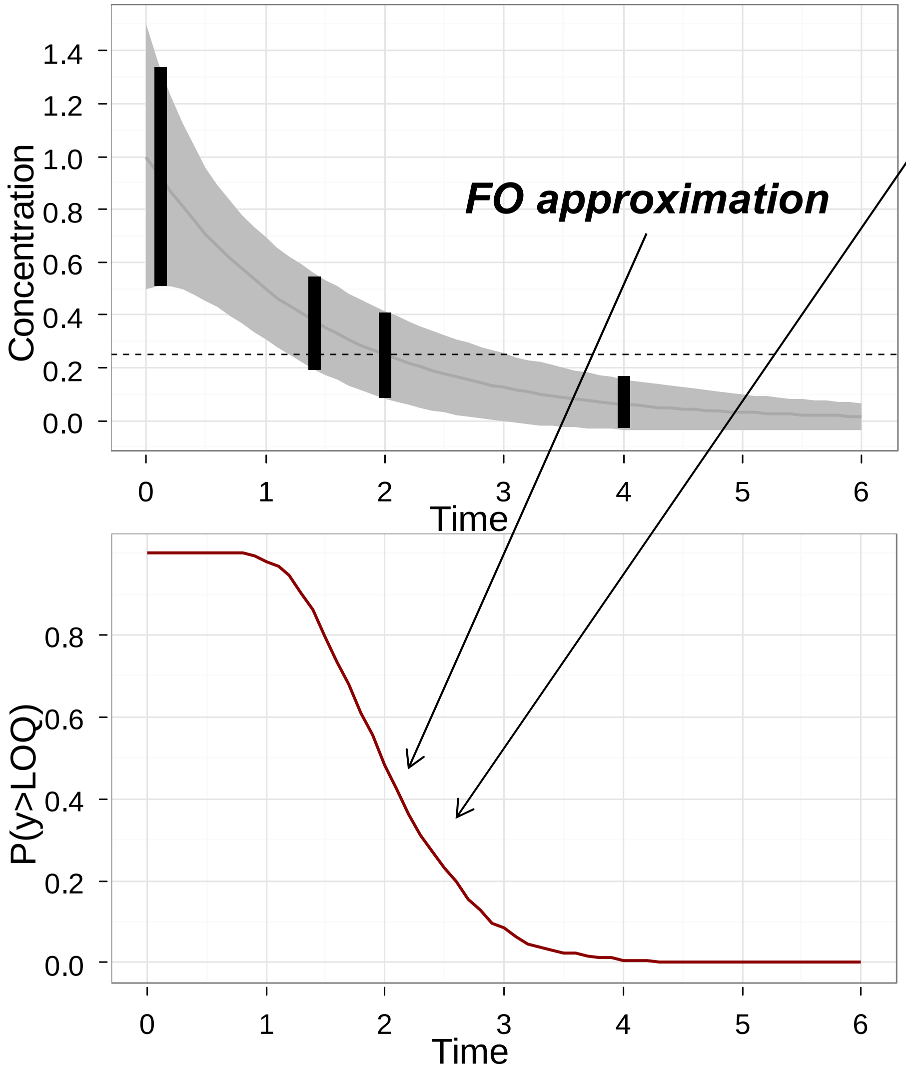
3%

...

LOQ data in Trial design

Alternative strategies

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation & FIM scaling*
- ***D6: Integration & FIM scaling***
- *D7: Laplace*



$$F = \sum_{r=1}^{N_S} \frac{N_S!}{r! \times (N_S - r)!}$$

Sampling times

0%	0	0	0	0
2%	0	0	0	1
1%	0	0	1	0
0%	0	0	1	1
1%	0	1	0	0
2%	0	1	0	1
0%	0	1	1	0
5%	0	1	1	1
11%	1	0	0	0
0%	1	0	0	1
0%	1	0	1	0
2%	1	0	1	1
18%	1	1	0	0
6%	1	1	0	1
35%	1	1	1	0
17%	1	1	1	1

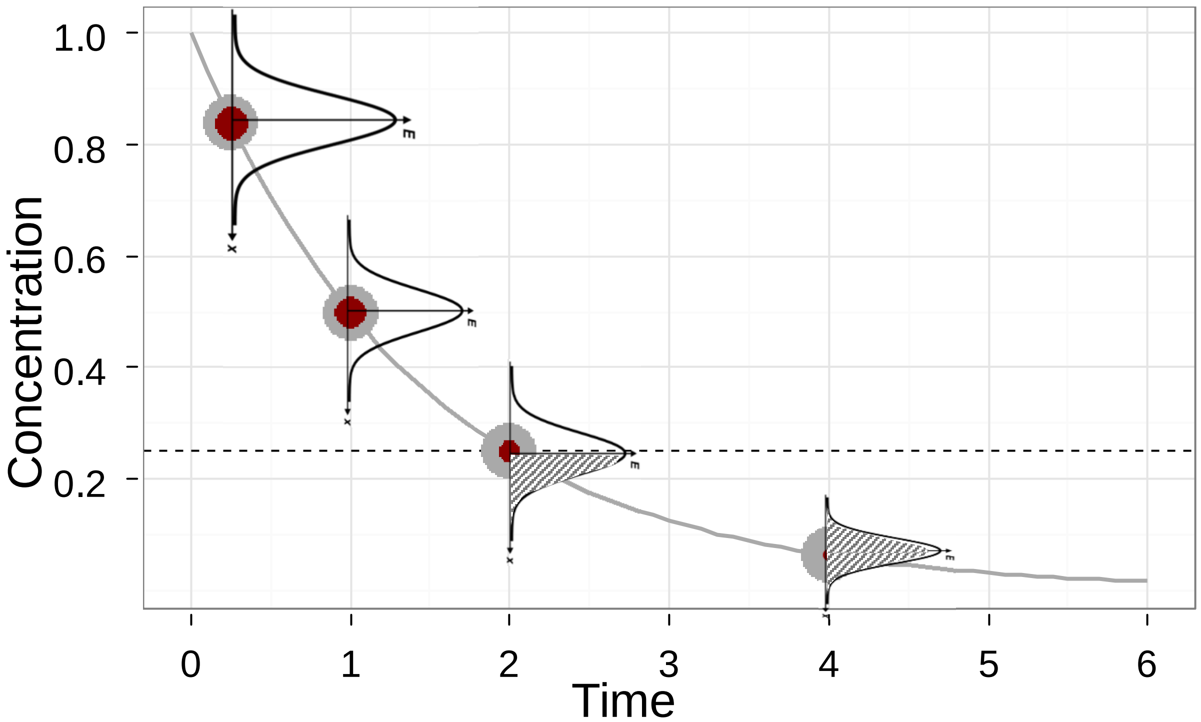
LOQ data in Trial design

Alternative strategies

BQL data treated as censored

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4**:** Additive error*
- *D5: Simulation & FIM scaling*
- *D6: Integration & FIM scaling*
- ***D7: Laplace***

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



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METHOD PERFORMANCE

INFORMATION CONTENT / RUNTIME

Evaluation

The model

Model *One-compartment IV Bolus*

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

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

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

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

Censoring levels

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

Fixed non-optimized design *0.25,1,2,4 hours post-dose*

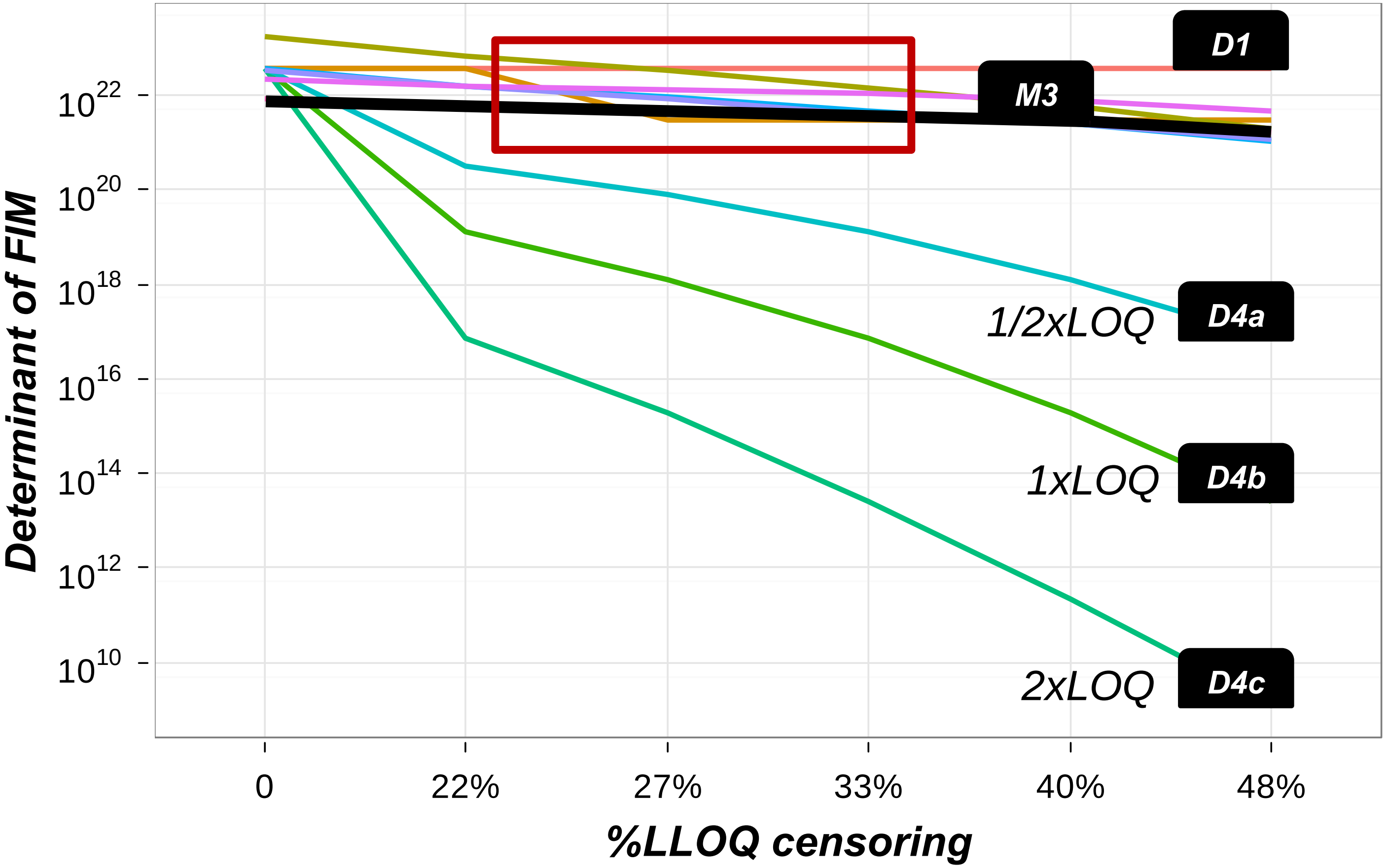
Method of reference *M3 method*

Evaluation

Design's information content comparison

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation & FIM scaling*
- *D6: Integration & FIM scaling*
- *D7: Laplace*

Adding an additive error is not recommended for expected parameter precision



Evaluation

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- *D4: Additive error*
- *D5: Simulation & FIM scaling*
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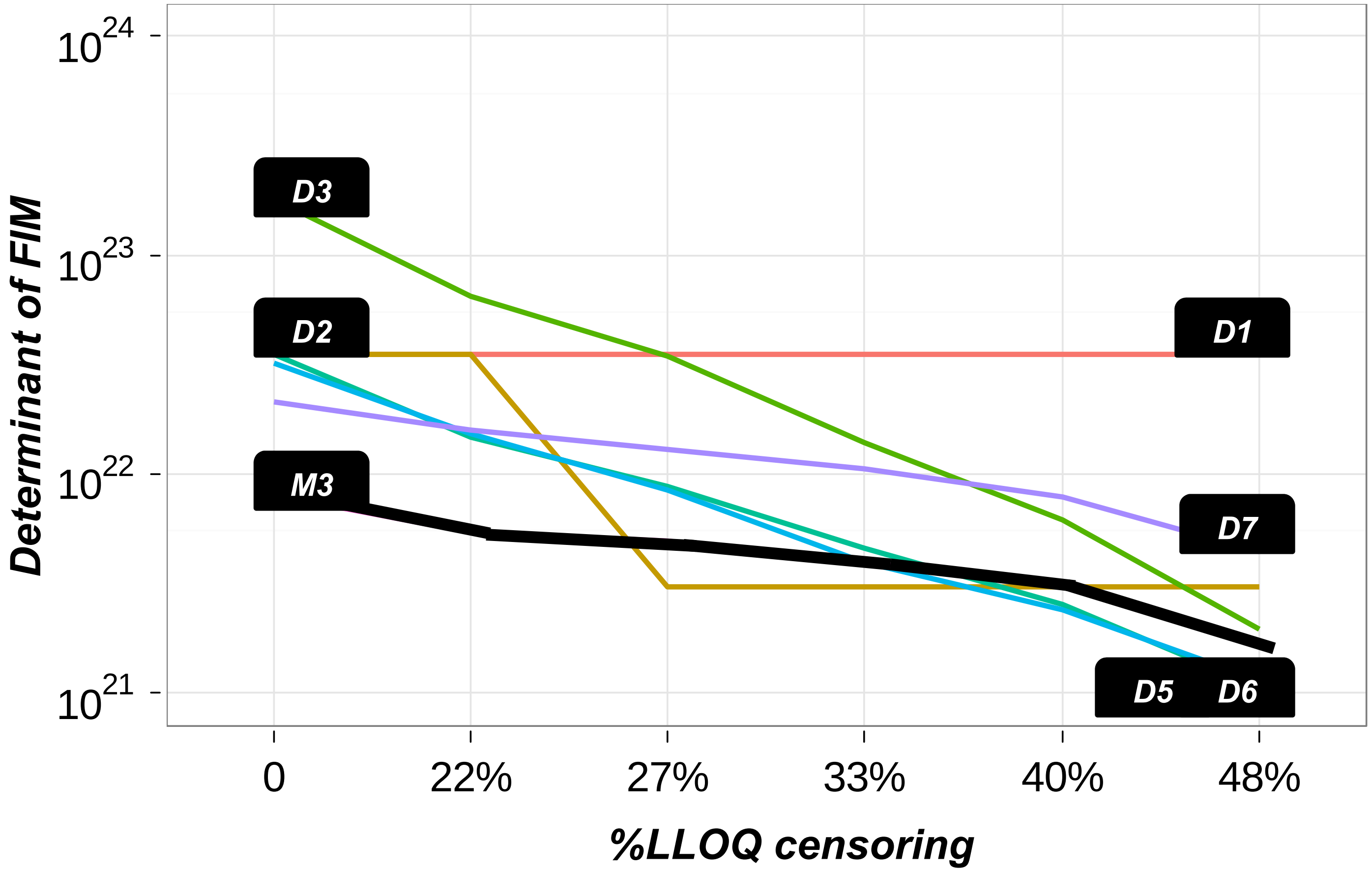
- *D7: Laplace*

No clear winner (D1 clear loser), Laplace follows M3's trend the best



Evaluation

Runtime comparison

Methods using FOCE and Laplace are impractical due to long run times

- *D1: Ignore*
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- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation & FIM scaling*
- *D6: Integration & FIM scaling*
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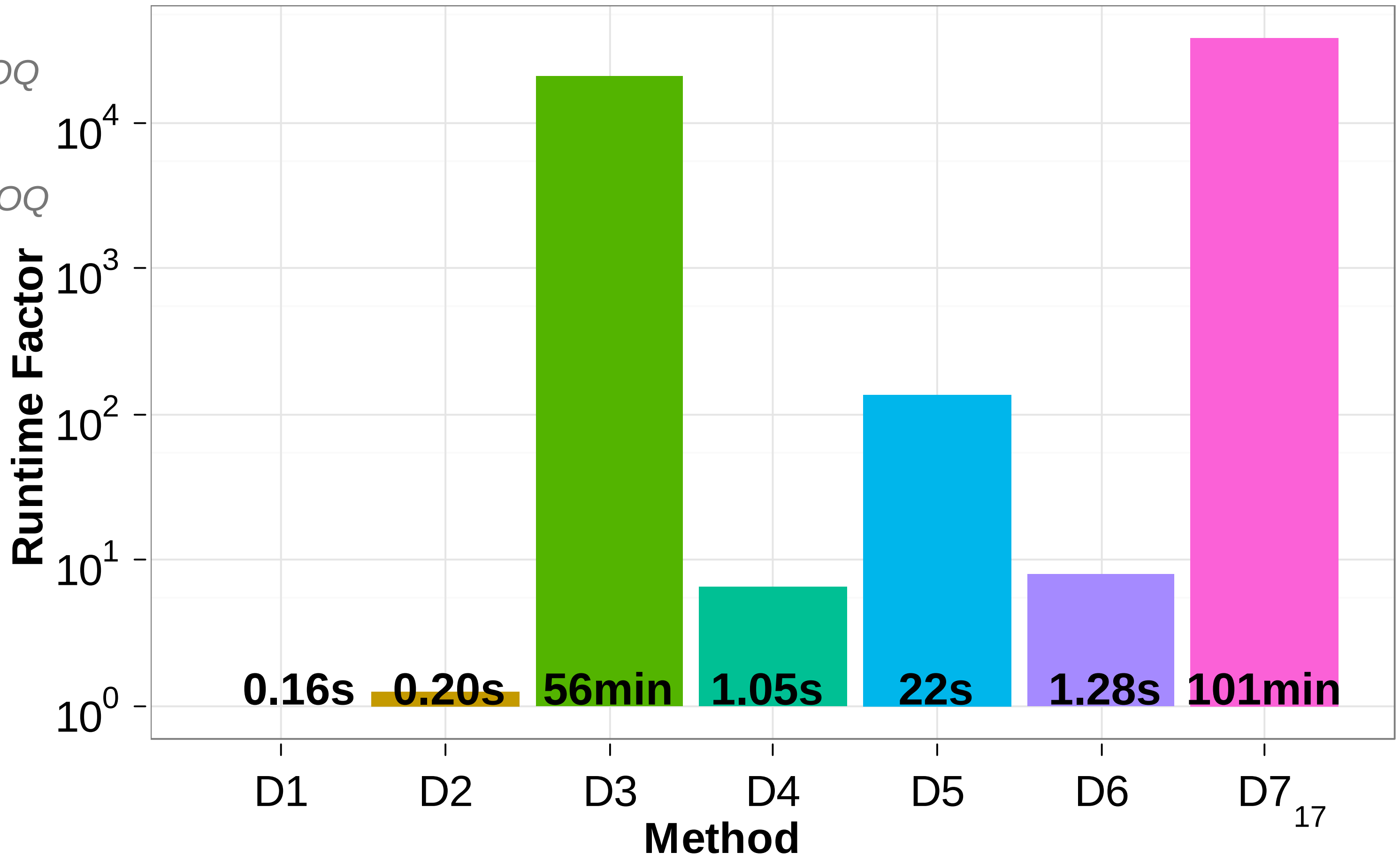

Evaluation

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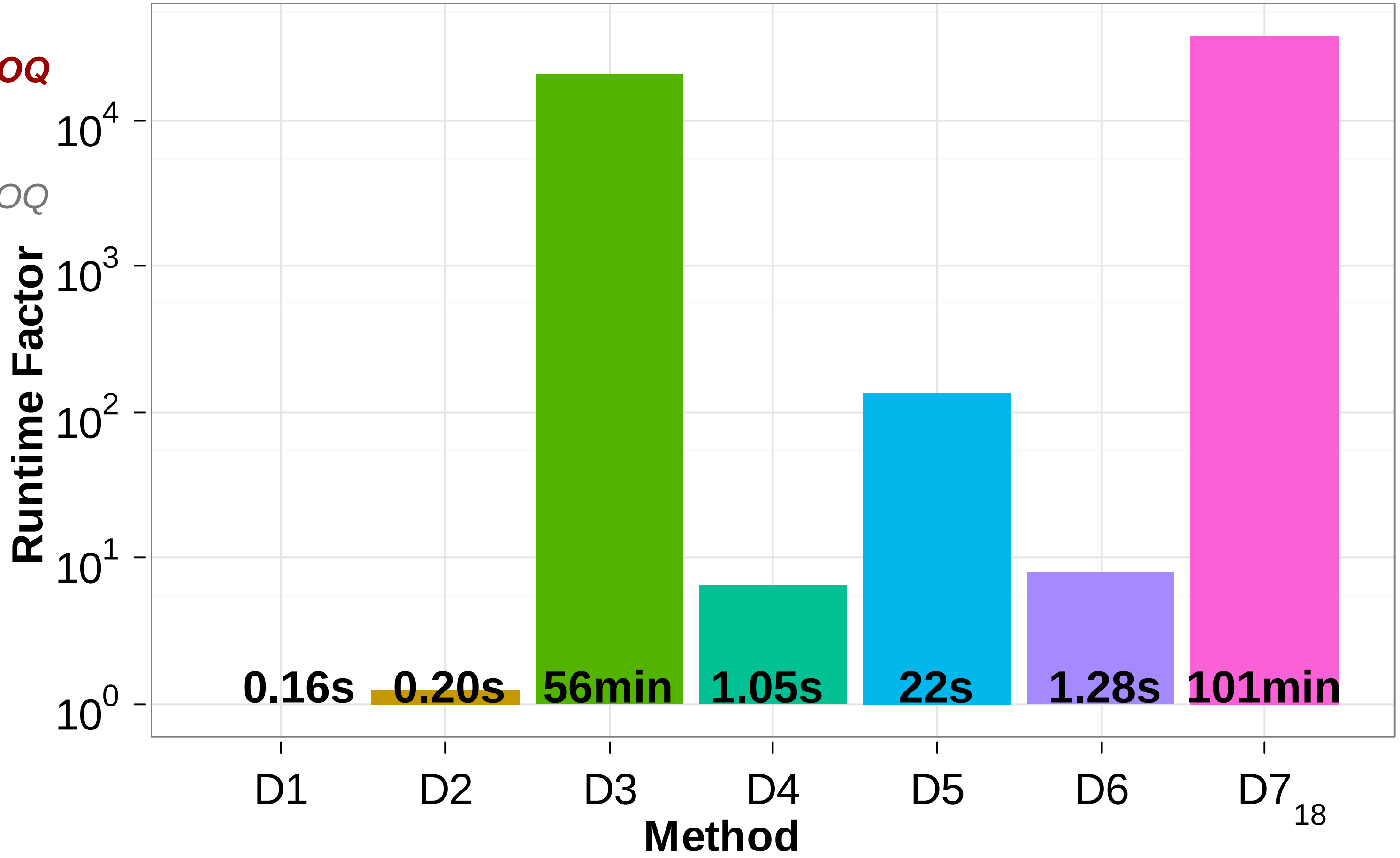

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DESIGN OPTIMIZATION

DESIGNS/ BIAS & IMPRECISION/ ROBUSTNESS/ PREDICTABILITY

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Optimization

Models and fixed non-opt. designs

Model	Data	Fixed Design	Censoring Levels	Type Of Censoring
2-cmp IV Bolus	PK	0, 0.25, 1, 12, 24 hours post-dose	20, 41, 57, 73%	Elimination phase (LLOQ)
1st order absorption	PK	0, 0.4, 1, 4, 20 hours post-dose	18, 22, 37, 59%	Absorption phase (LLOQ)
Sigmoid Emax	PD	0, 0.4, 1, 4, 20 hours post-dose	12, 19, 24, 31%	Upper linear to saturation (ULOQ)
Indirect response	PD	0, 10, 20, 30, 200 hours post-dose	16, 25, 45, 66%	Inhibition peak (LLOQ)

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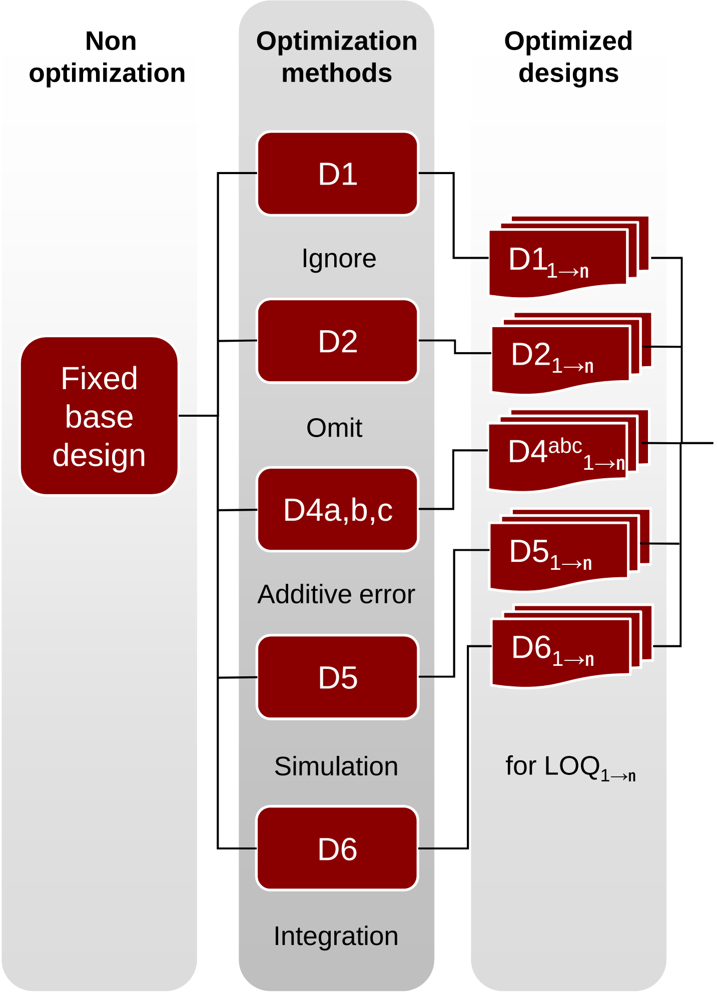
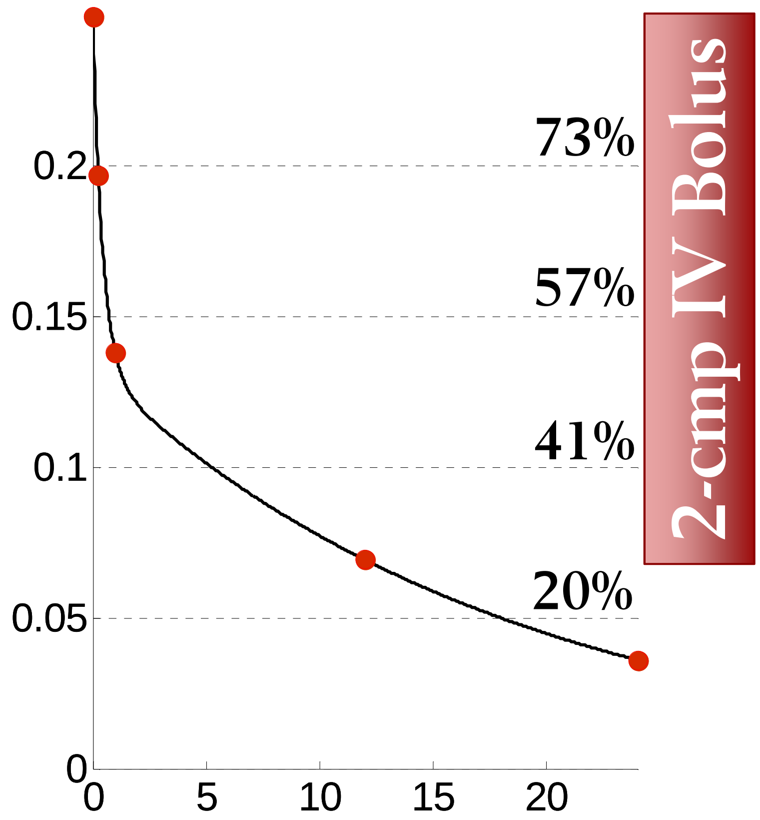
Optimization

Framework for optimized designs comparison

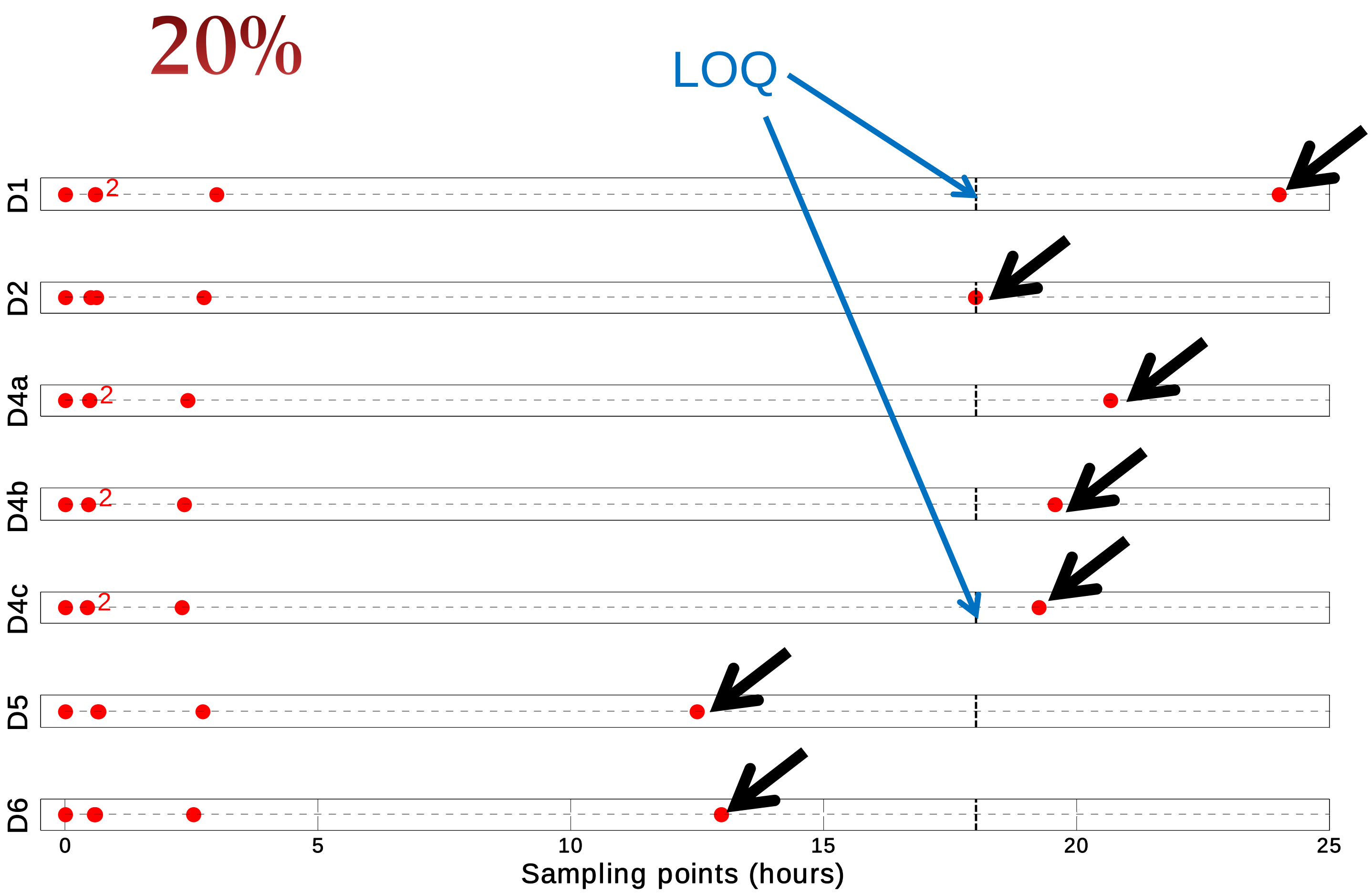




Optimization

Optimized designs for the 2-comp. IV Bolus

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation & FIM scaling*
- *D6: Integration & FIM scaling*
- *D7: Laplace*

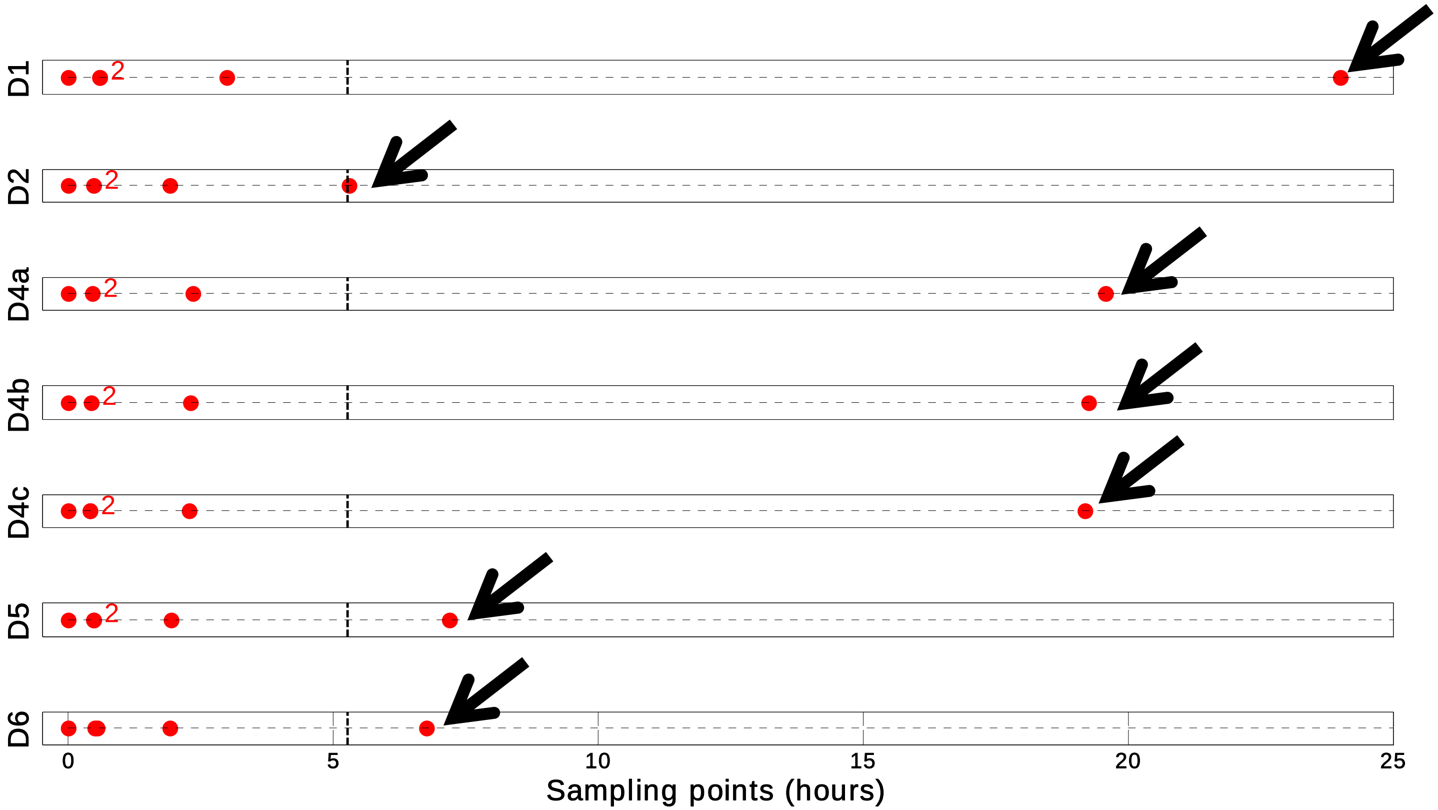


Optimization

Optimized designs for the 2-comp. IV Bolus

41%

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation & FIM scaling*
- *D6: Integration & FIM scaling*
- *D7: Laplace*



Optimization

Optimized designs for the 2-comp. IV Bolus

57%

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation & FIM scaling*
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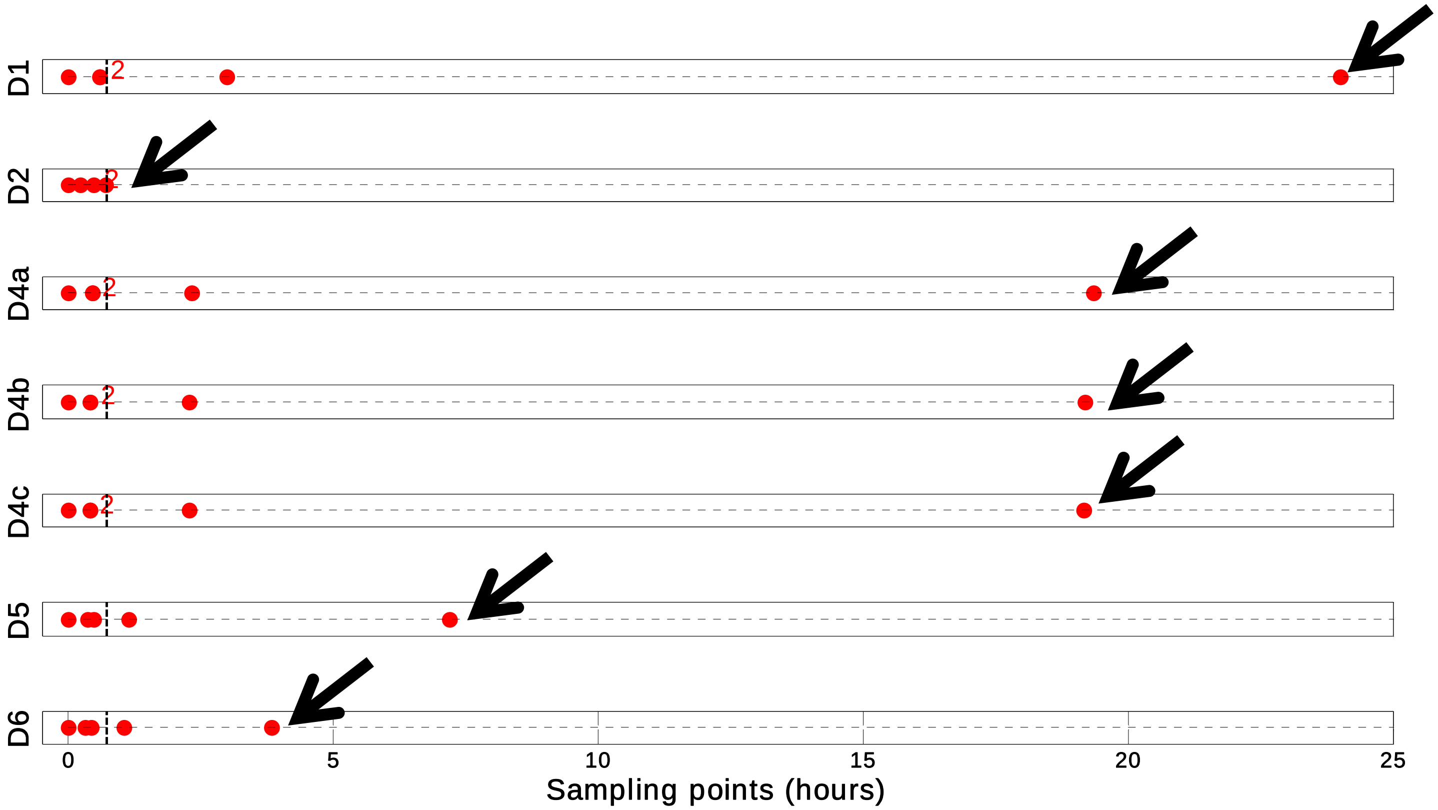
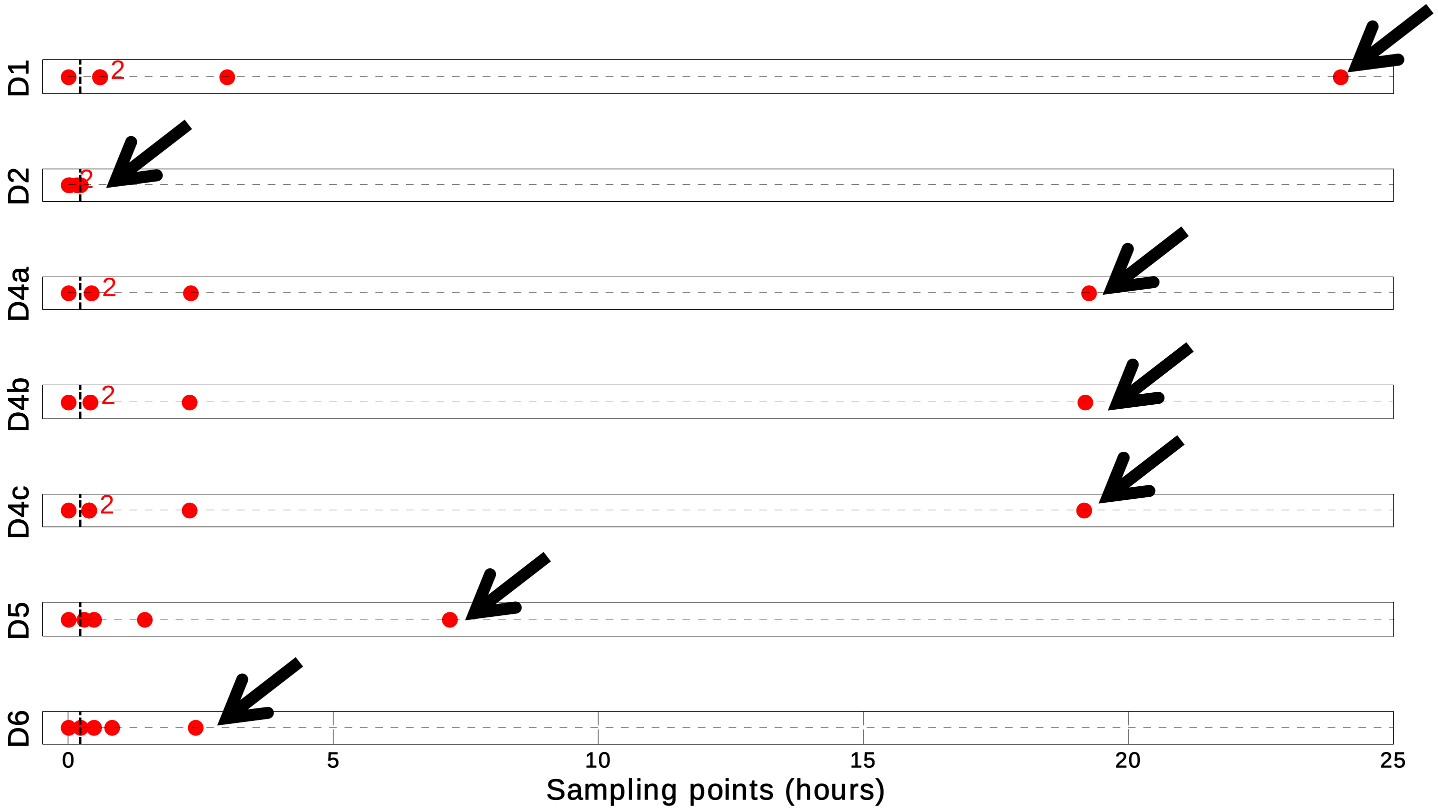


Optimization

Optimized designs for the 2-comp. IV Bolus

73%

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation & FIM scaling*
- *D6: Integration & FIM scaling*
- *D7: Laplace*

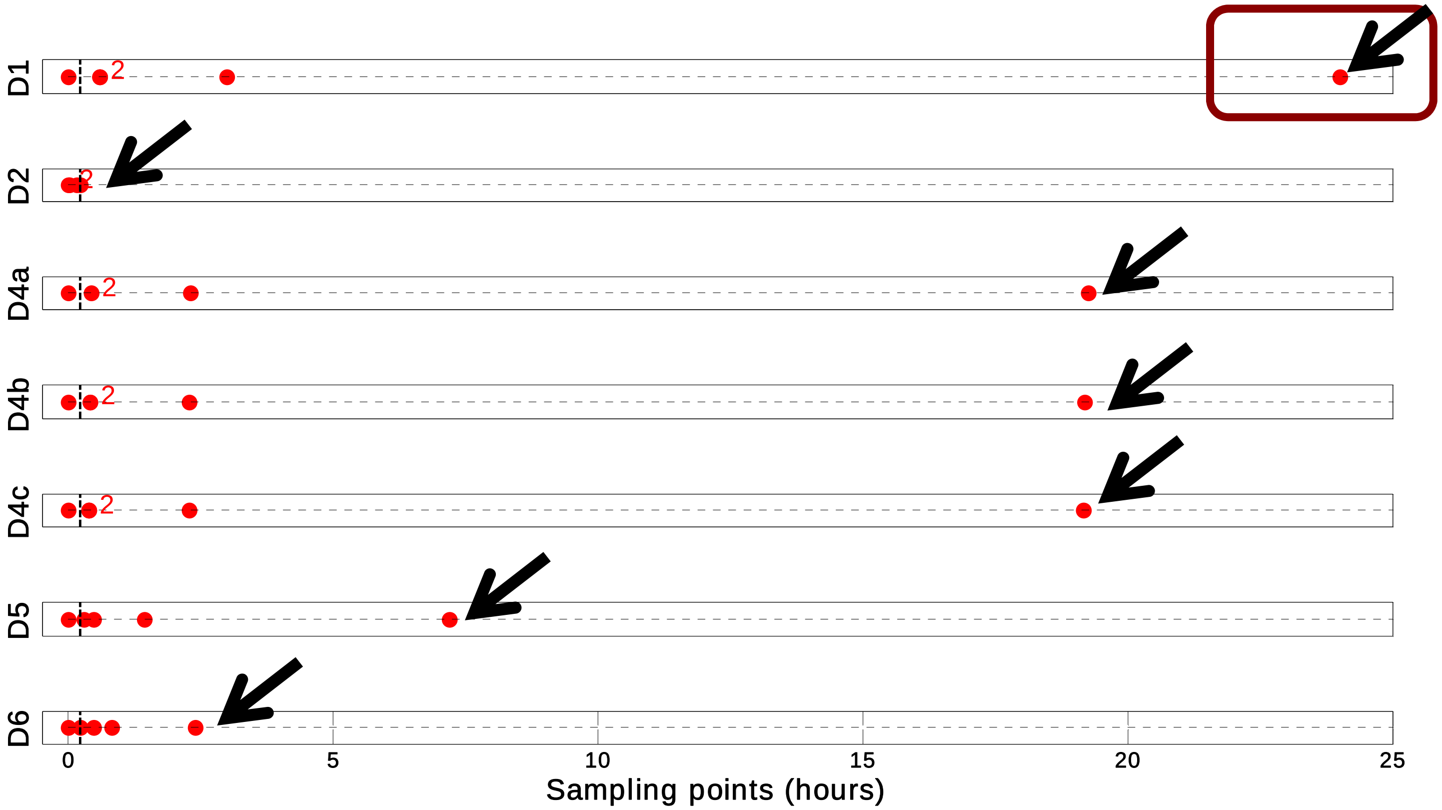


Optimization

Optimized designs for the 2-comp. IV Bolus

Method D1 → identical design for all LOQ levels

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation*
  & FIM scaling
- *D6: Integration*
  & FIM scaling
- *D7: Laplace*

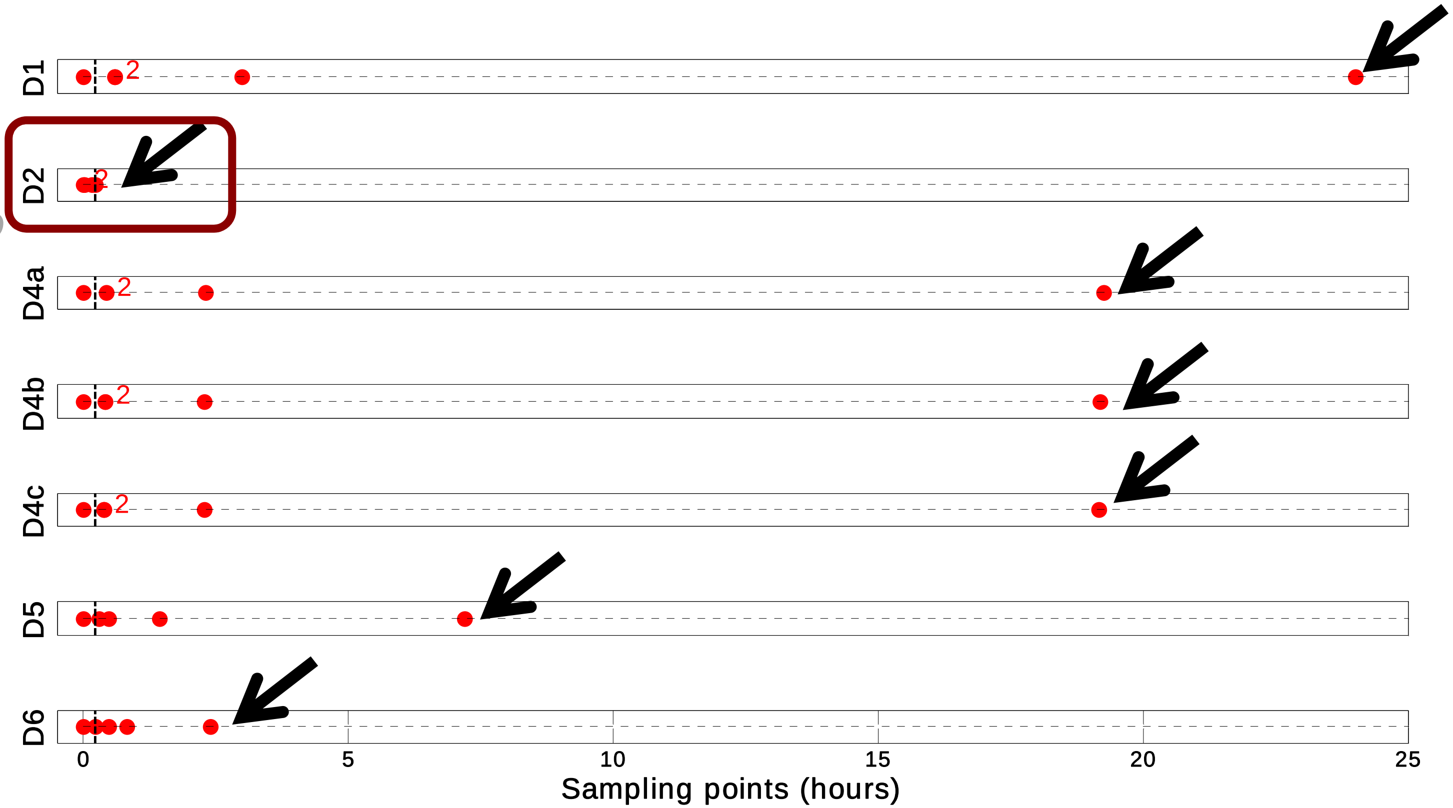


Optimization

Optimized designs for the 2-comp. IV Bolus

Method D2 → no point below LOQ

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation*
  & FIM scaling
- *D6: Integration*
  & FIM scaling
- *D7: Laplace*

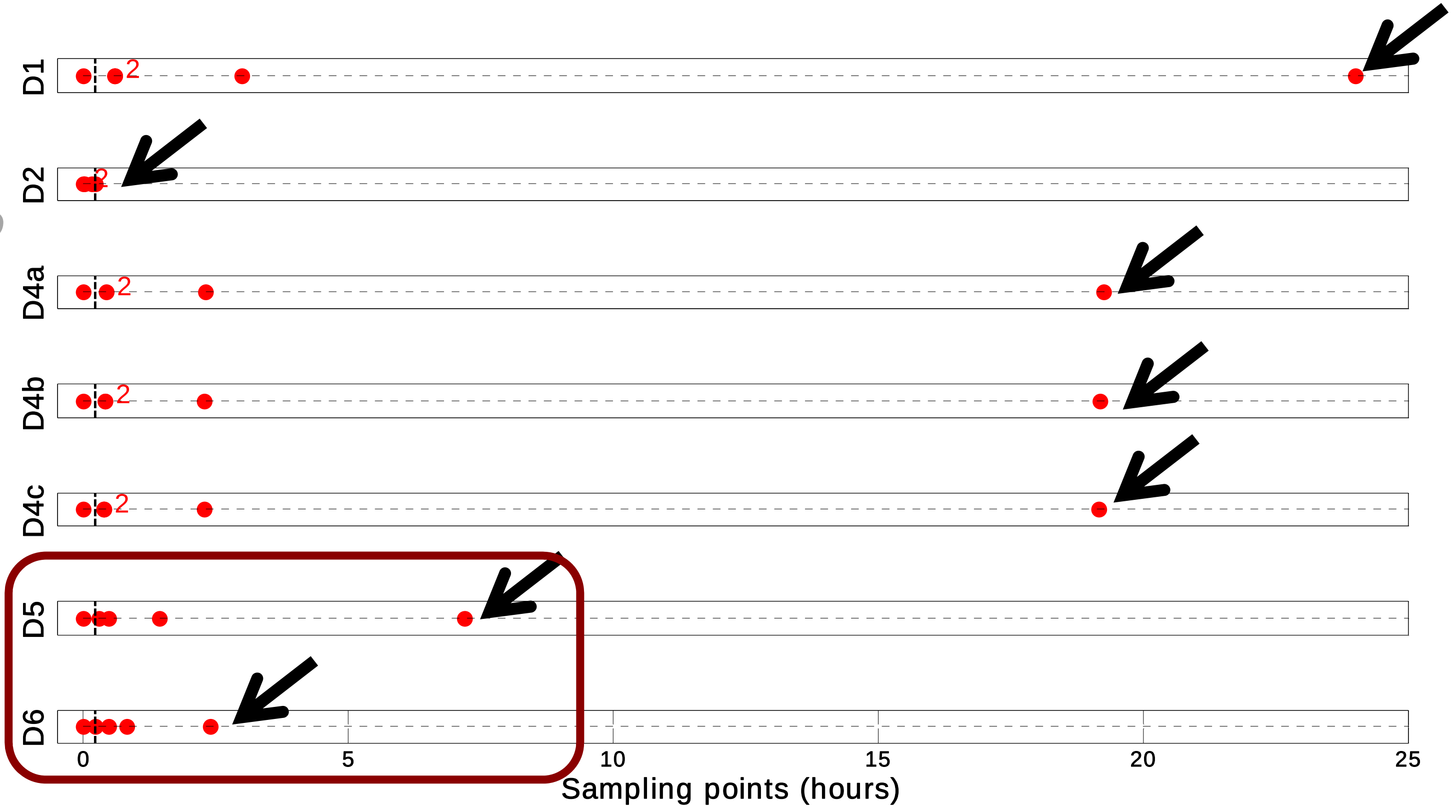


Optimization

Optimized designs for the 2-comp. IV Bolus

Method D2 → no point below LOQ
Method D5/D6 → allow BLQ data strategically

- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation & FIM scaling*
- *D6: Integration & FIM scaling*
- *D7: Laplace*



Optimization

Optimized designs for the 2-comp. IV Bolus

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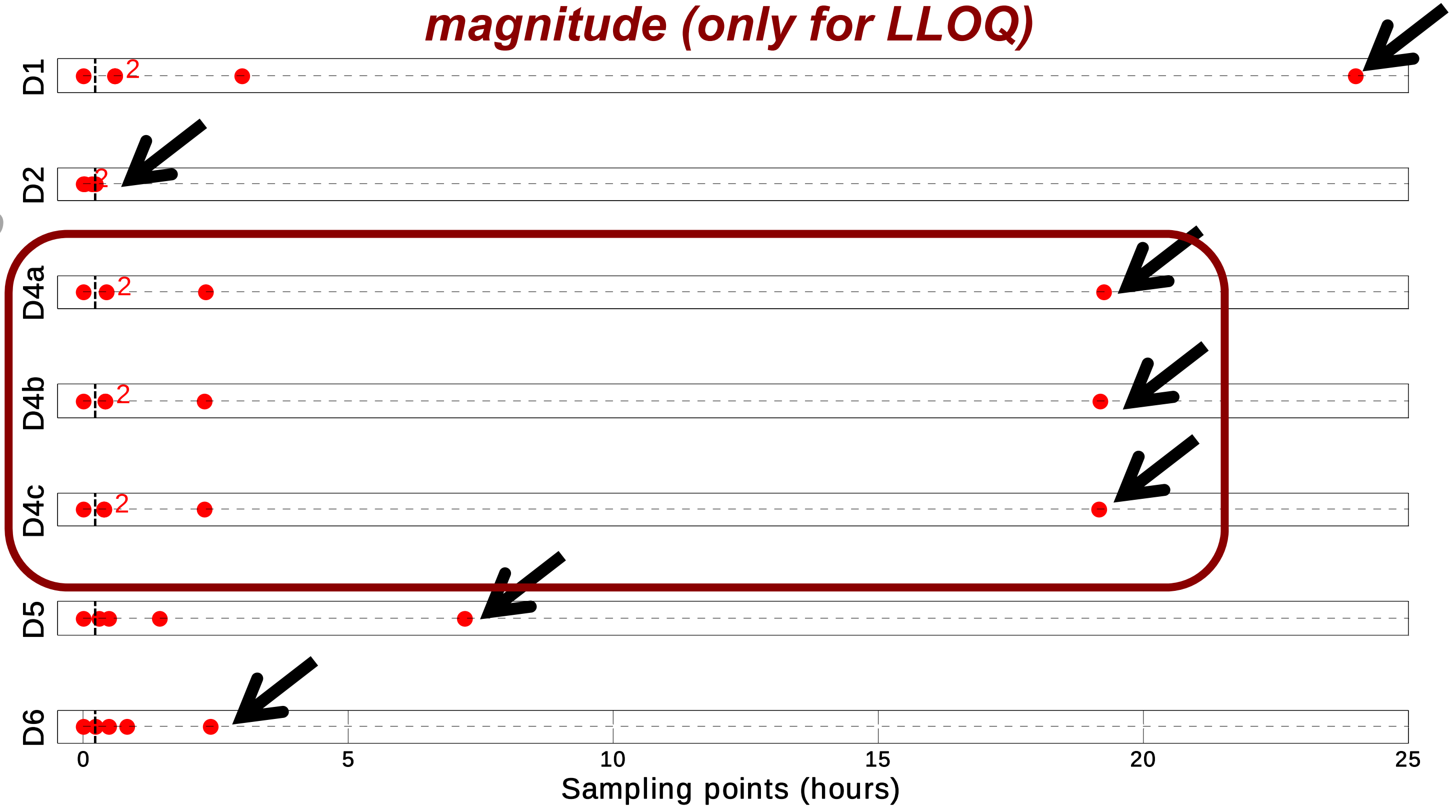
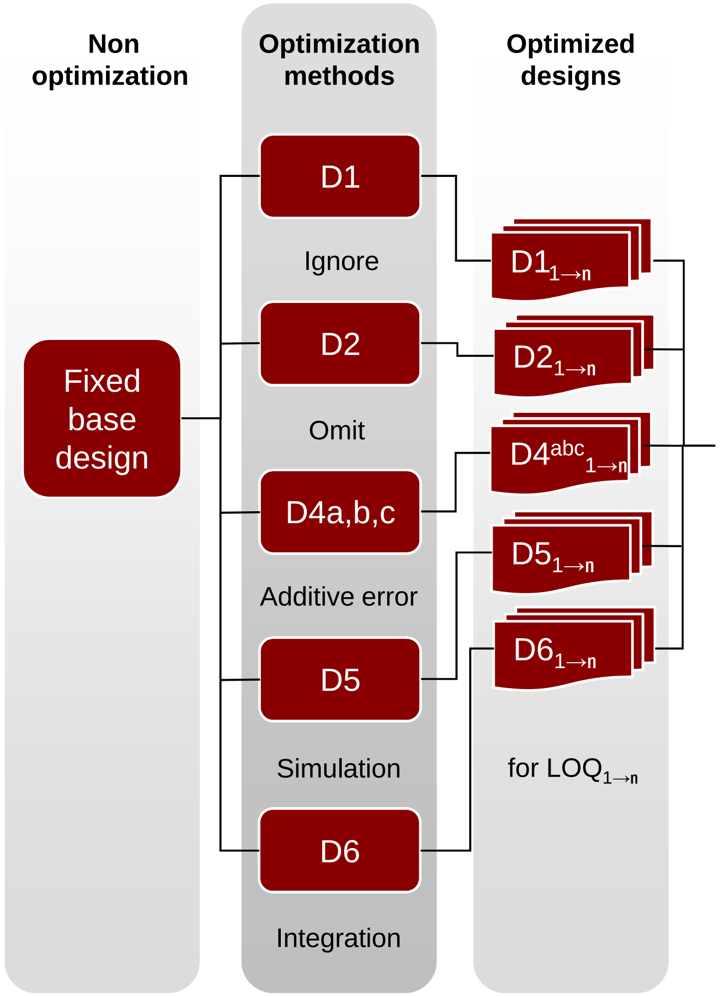
- *D1: Ignore*
- *D2: Omit PRED<LOQ*
- *D3: Omit IPRED<LOQ*
- *D4: Additive error*
- *D5: Simulation*
  & FIM scaling
- *D6: Integration*
  & FIM scaling
- *D7: Laplace*

Method D2 → no point below LOQ
Method D5/D6 → allow BLQ data strategically
Method D4 → allows BLQ data but insensitive to LOQ magnitude (only for LLOQ)



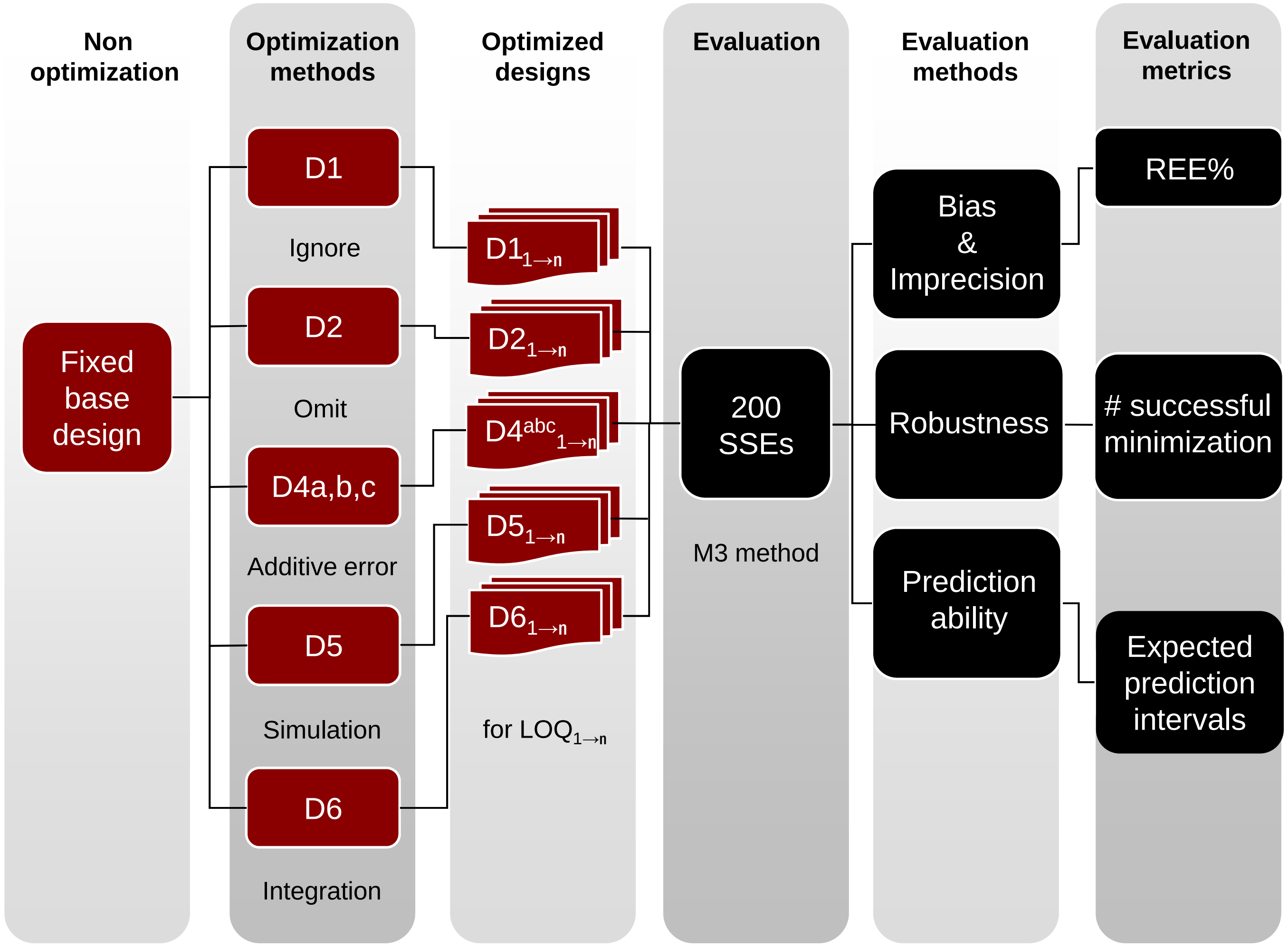
Optimization

Framework for optimized designs comparison



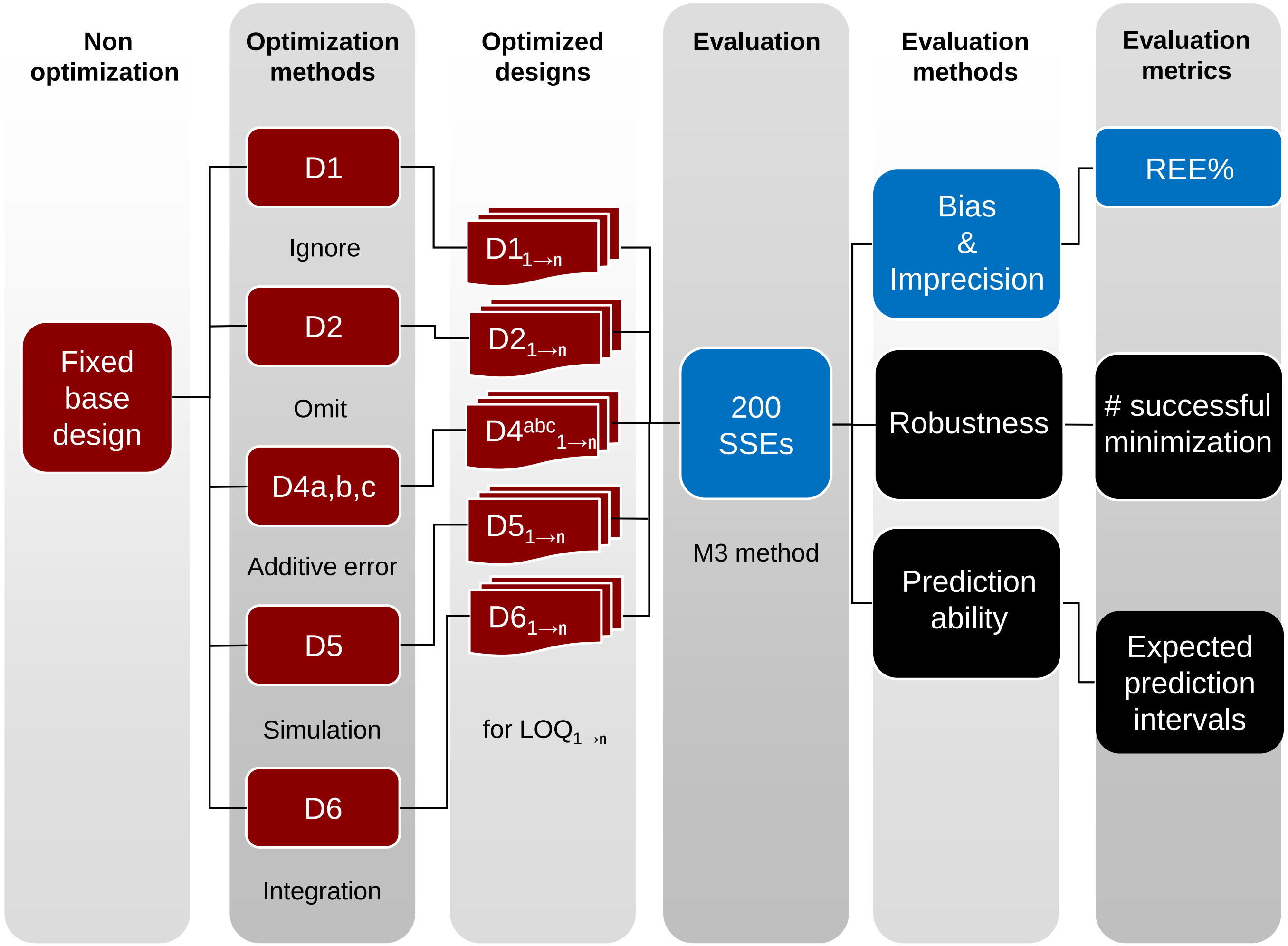
Optimization

Framework for optimized designs comparison



Optimization

Framework for optimized designs comparison



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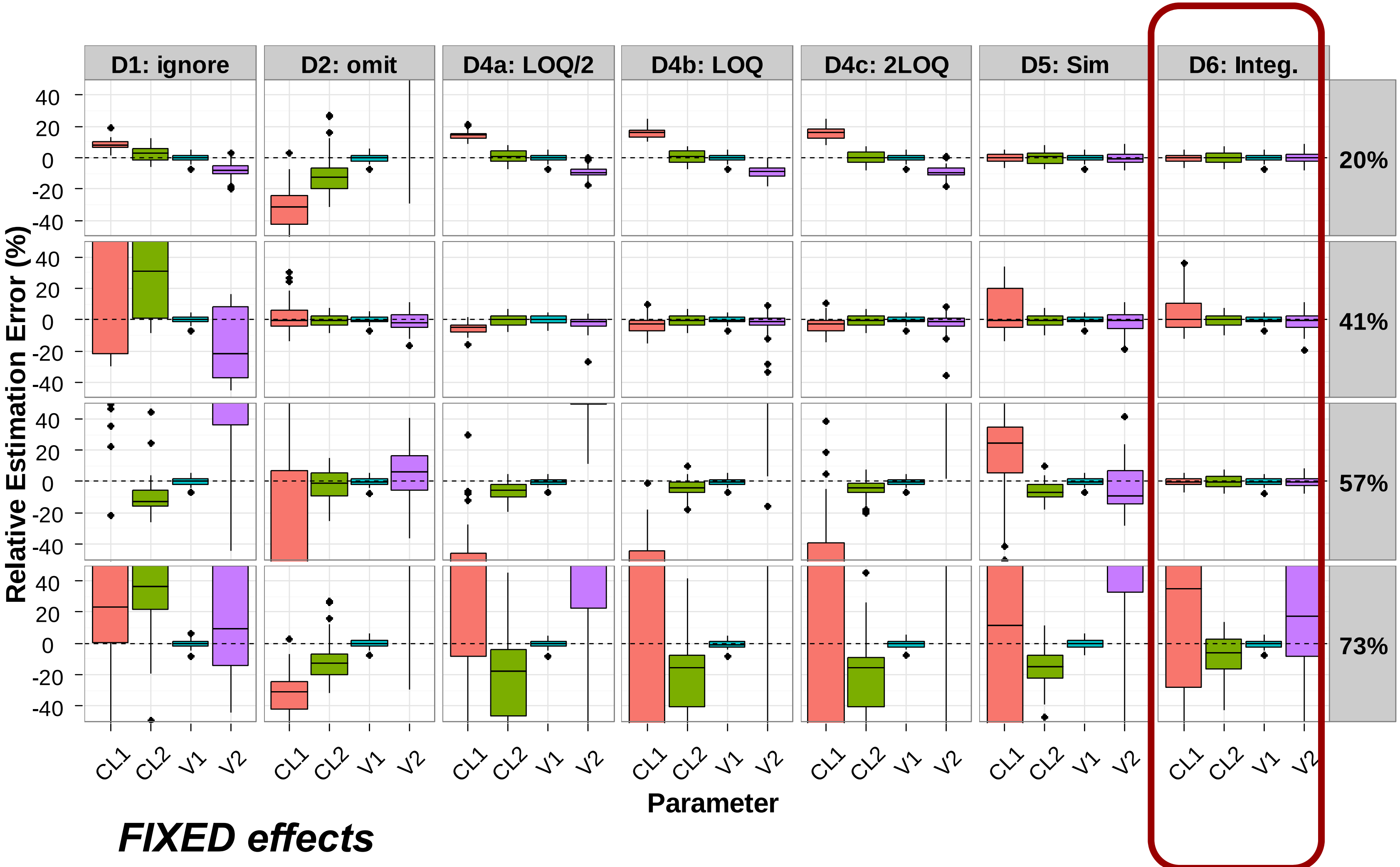
Optimization

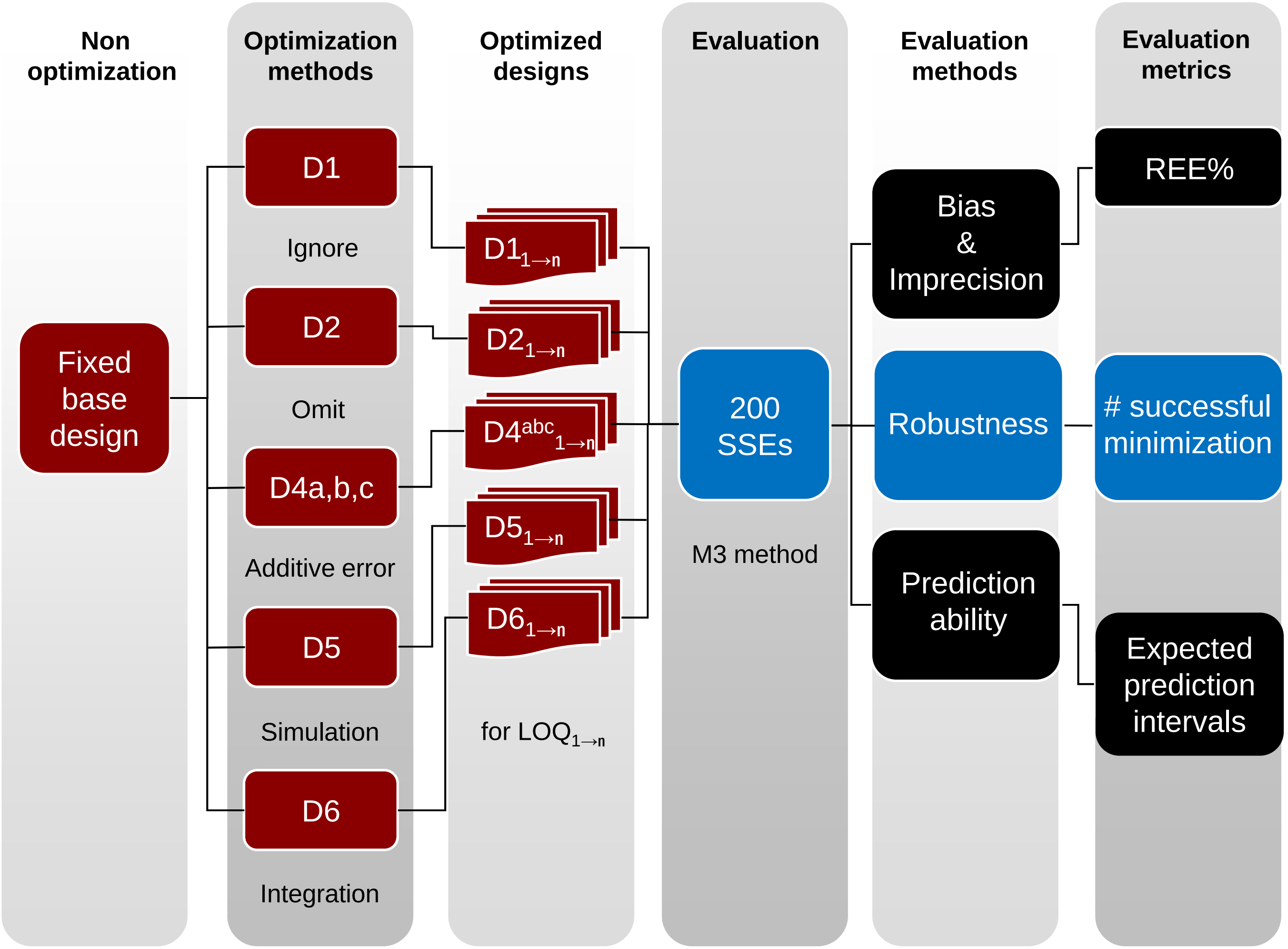
Bias & imprecision for the 2-comp. IV Bolus



FIXED effects

Optimization

Framework for optimized designs comparison



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Optimization

Robustness for the 2-comp IV Bolus

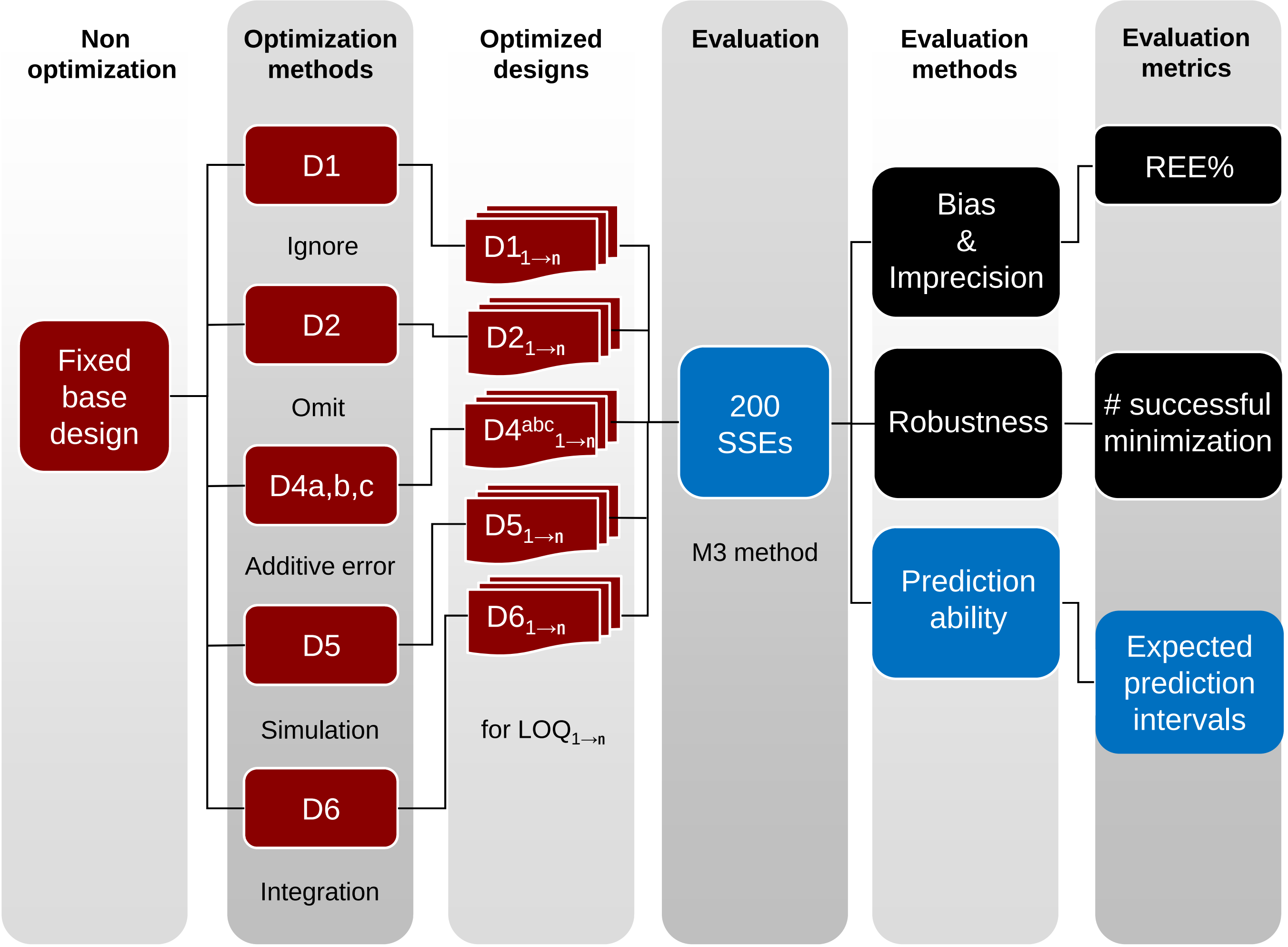
For <41%, all methods are robust, overall D6 performs the best

LOQ	Minimization successful* (%)							
censoring	*Fixed base design*	D1	D2	D4a	D4b	D4c	D5	D6
0%	96.5	100	-	-	-	-	-	-
20%	85	98	99.5	100	99.5	99.5	100	100
41%	93.5	82	100	100	98.5	99	100	100
57%	78.5	77	77.5	88	92	90	100	100
73%	53	36	31.5	59.5	50.5	53.5	58	74

** As reported by NONMEM*

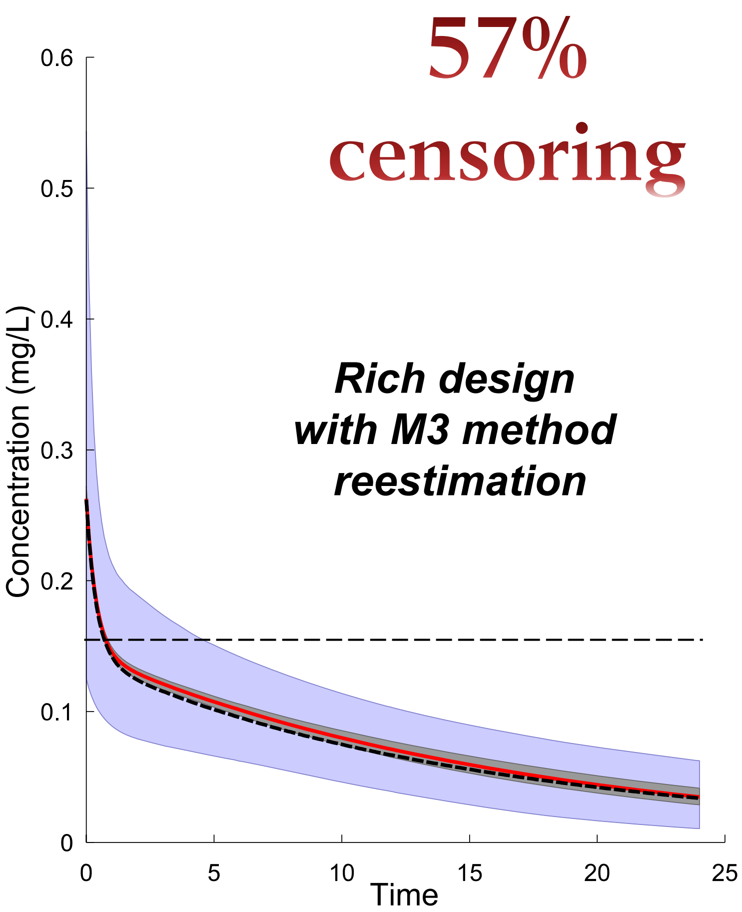
Optimization

Framework for optimized designs comparison

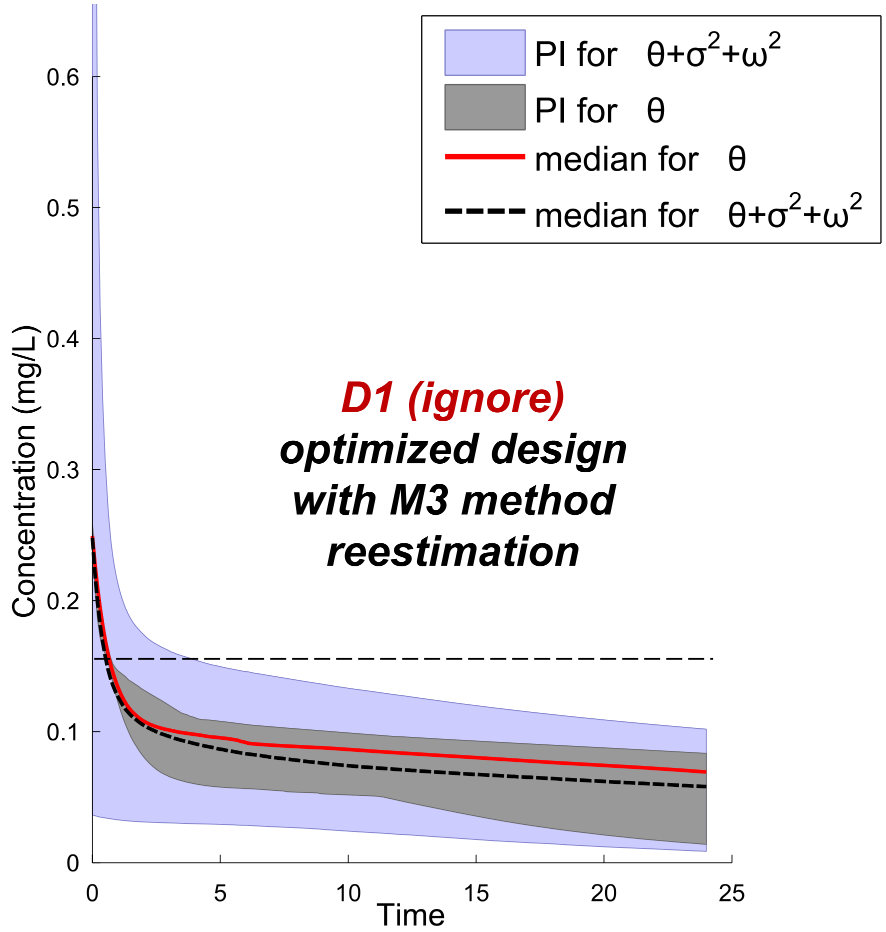


Optimization

Expected prediction intervals for the 2-comp IV Bolus



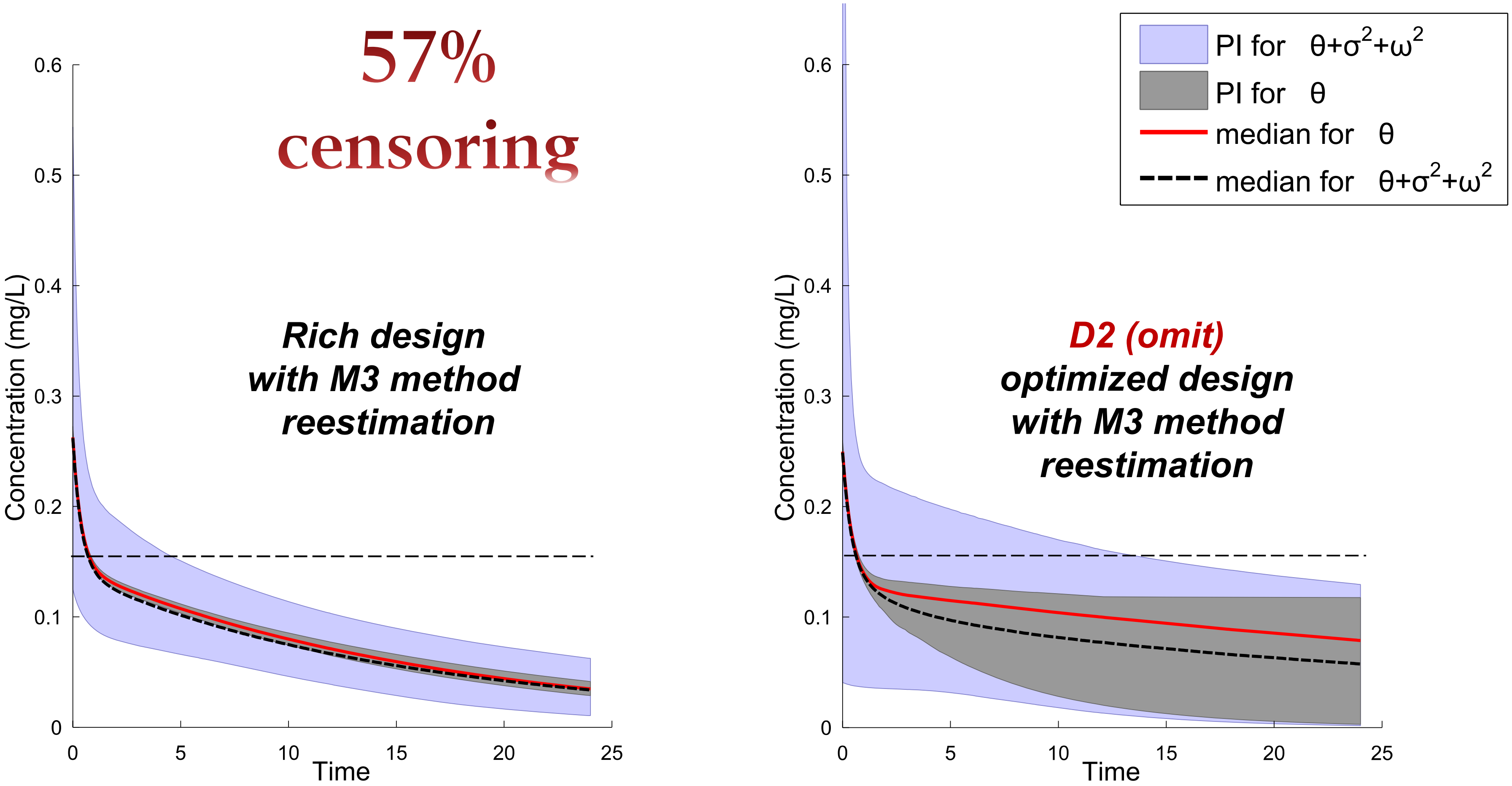
2400 sampling times



5 sampling times

Optimization

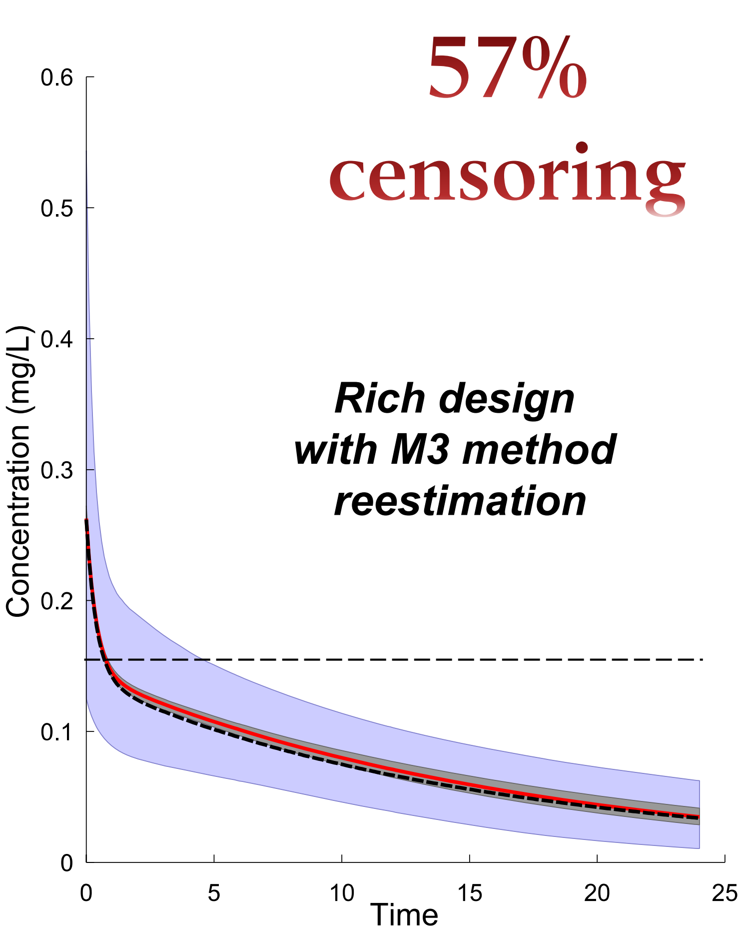
Expected prediction intervals for the 2-comp IV Bolus



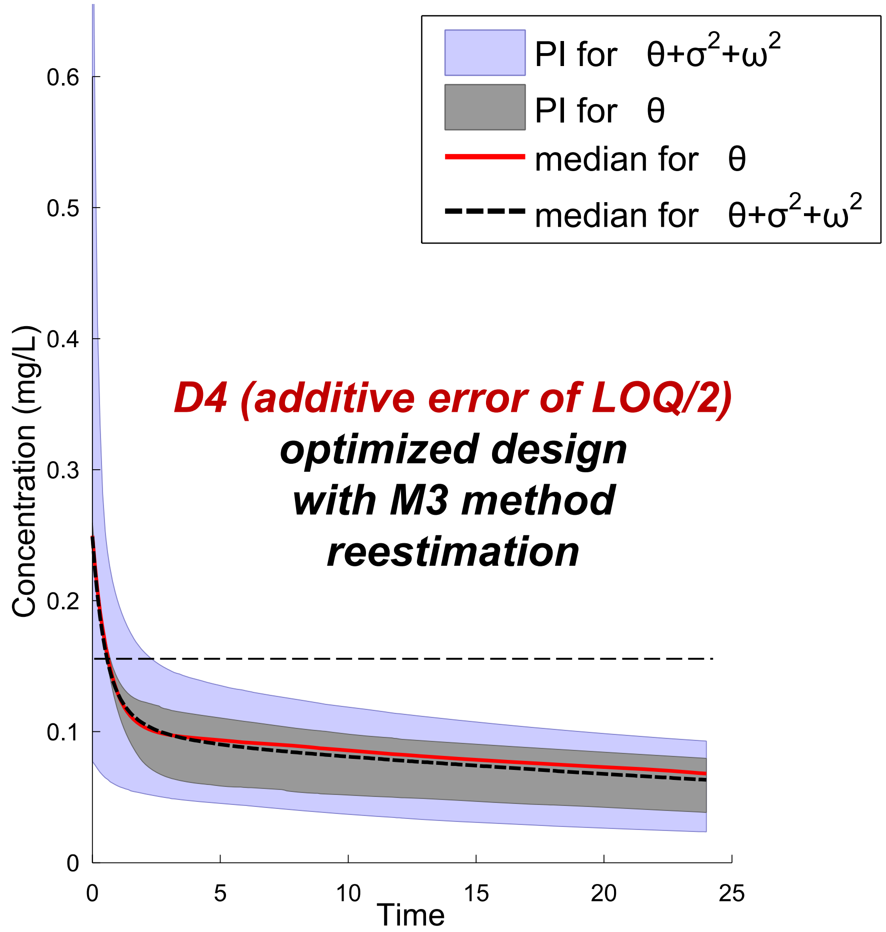
2400 sampling times ***5 sampling times***

Optimization

Expected prediction intervals for the 2-comp IV Bolus



2400 sampling times



5 sampling times

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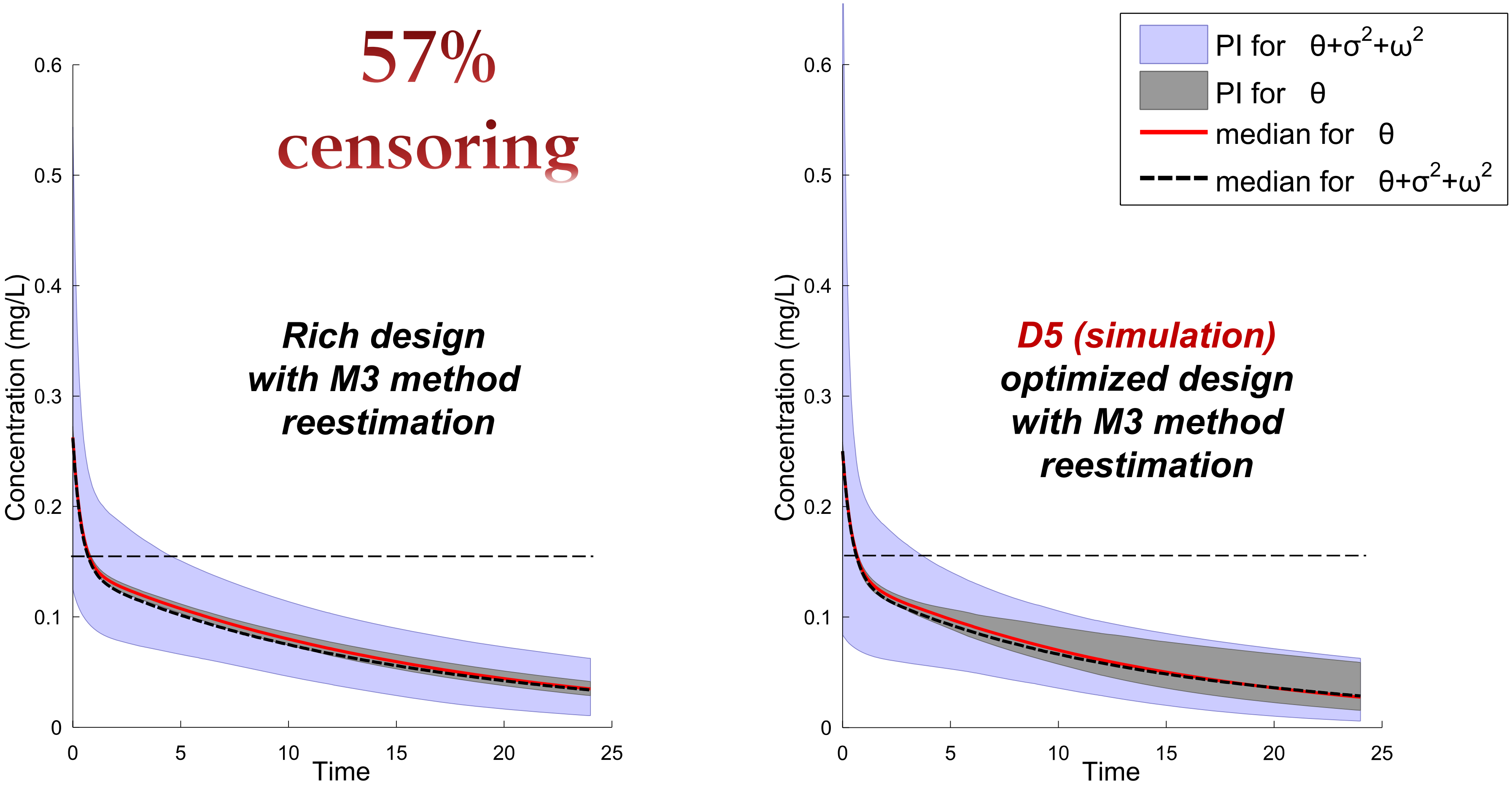
Optimization

Expected prediction intervals for the 2-comp IV Bolus



2400 sampling times ***5 sampling times***

Optimization

Expected prediction intervals for the 2-comp IV Bolus

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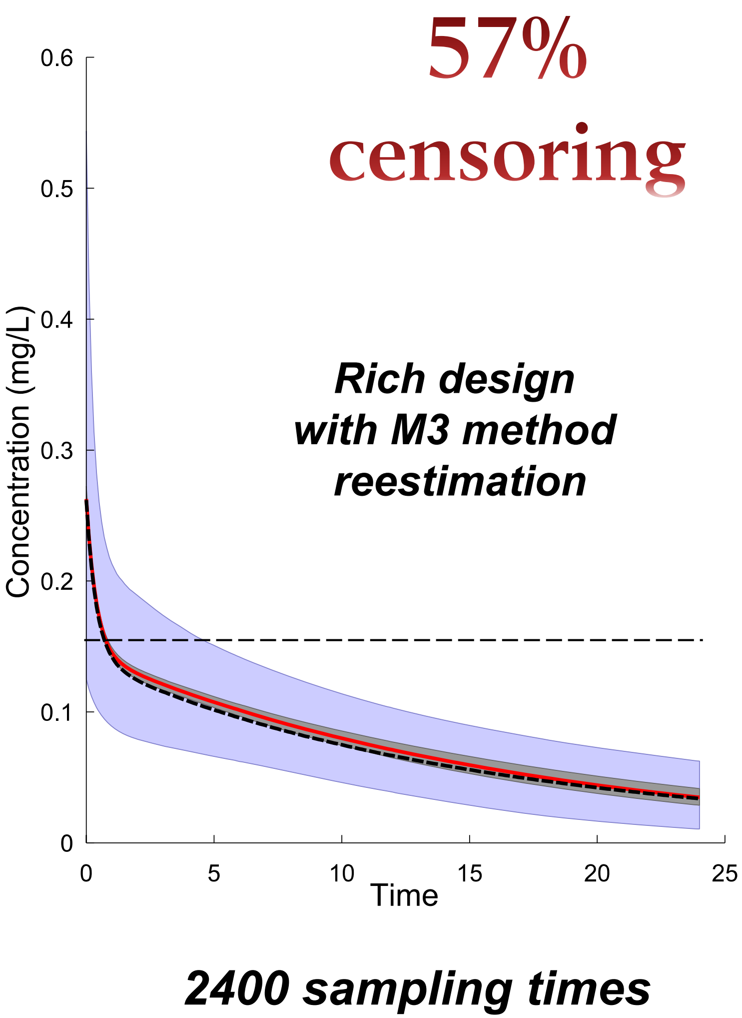

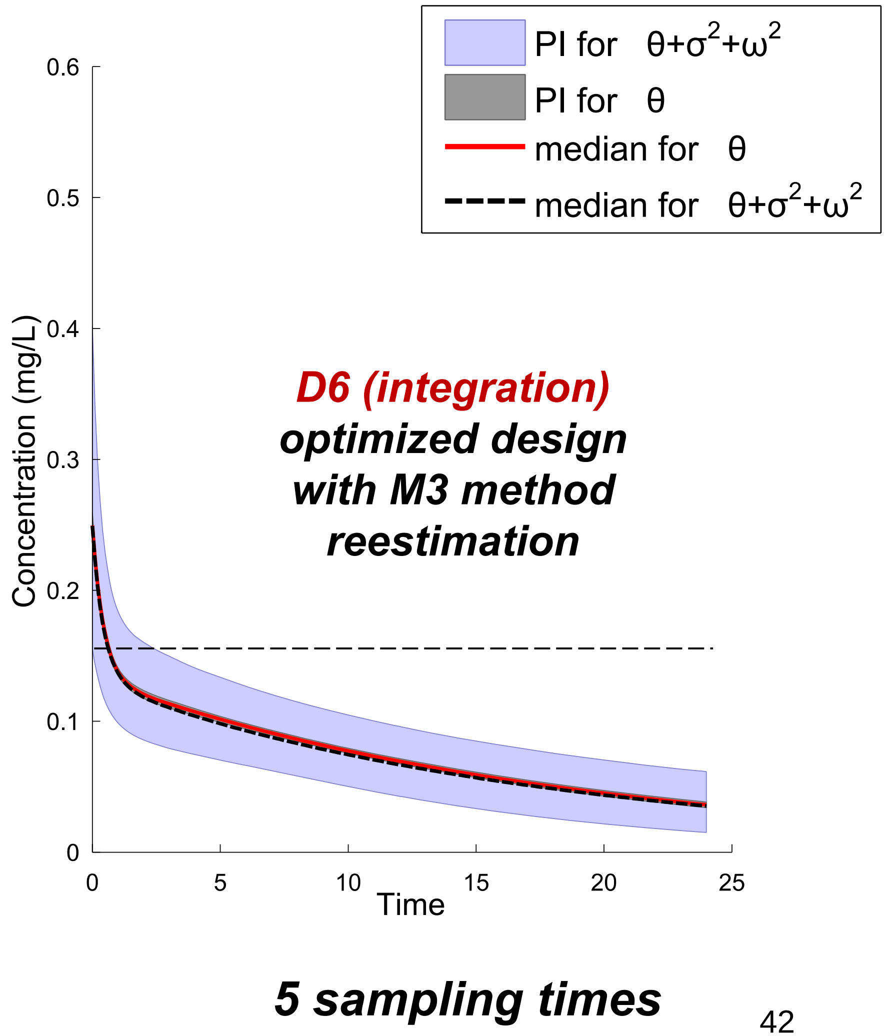

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Discussion

Summary

- ***Precision prediction:***
  - All methods, ***except method D1 (ignore) and D4 (additive error)*** fairly well described the loss in information with increasing LOQ levels.
- ***Optimization:***
  - Runtime renders Laplace & FOCE impractical
  - ***Method D4 (additive error) is insensitive to LOQ levels*** and has limitations (only LLOQ)
  - Designs obtained with all other methods ***performed better for BQL levels >20% (decreased %BQL data) than D1 (ignore)***
  - ***Method D6 (integration) performed the best***
  - BQL fractions/LOQ levels hence method's performance are ***model-dependent***

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Discussion

Take-home message

1. Pre-assess expected fraction of BQL data
2. Pre-assess BQL data's impact given your model

%BQL high Low impact	Integration Simulation	Integration Simulation	**%BQL high High impact**
% BQL low Low impact	Ignore Omit Additive Integration Simulation	Integration Simulation	**%BQL low High impact**

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Discussion

Take-home message

1. Pre-assess expected fraction of BQL data
2. Pre-assess BQL data's impact given your model

%BQL high Low impact	Integration Simulation	Integration Simulation	%BQL high High impact
% BQL low Low impact	Ignore Omit Additive Integration Simulation	Integration Simulation	%BQL low High impact

If you are not certain,

Use Integration/Simulation method

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Drug Disease Model Resources

Innovative Medicines Initiative

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