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Shrinkage in Empirical Bayes Estimates for Diagnostics and Estimation: Problems and Solutions

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Outline

- ✓ Empirical Bayes Estimates
- ✓ Use in Non-linear Mixed Effects Modelling
- ✓ Shrinkage phenomenon
- ✓ Shrinkage related problems:
  - Diagnostics
  - Estimation process (FOCE & NONP)
- ✓ Solutions & Recommendations

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Empirical Bayes Estimates

POSTHOC estimates – individual parameter estimates

Provide population PKPD modellers with:

- ✓ EBE - individual parameter estimate
- ✓ IPRED – individual predictions
- ✓ IWRES – individual weighted residuals

$$IWRES_{ij}=(DV_{ij}-IPRED_{ij})/SD(\varepsilon_{ij})$$

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Use of EBEs

- ✓ ***Diagnostics***
  - IPRED vs DV
  - IWRES vs IPRED
  - EBE vs EBE
  - EBE vs Covariate
  - GAM
- ✓ ***Estimation***
  - FOCE
  - Nonparametric estimation
- ✓ ***Predicition (TDM)***
- ✓ ***Simulation***

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Diagnostics based on EBEs

Increases resolution by separating variability components

<u>If data are uniformative</u>:

1. EBE distribution will shrink towards 0 (population mean)

   EBE → 0

2. Individual predictions **(IPRED)** will shrink towards the corresponding observation (DV)

   IPRED → DV

3. **IWRES,** residual components will shrink towards 0

   IWRES → 0

R.M. Savic, J.J. Wilkins and M.O. Karlsson.
(Un)informativeness of EBE-based diagnostics, AAPS J, Abstract T3360, 2006.

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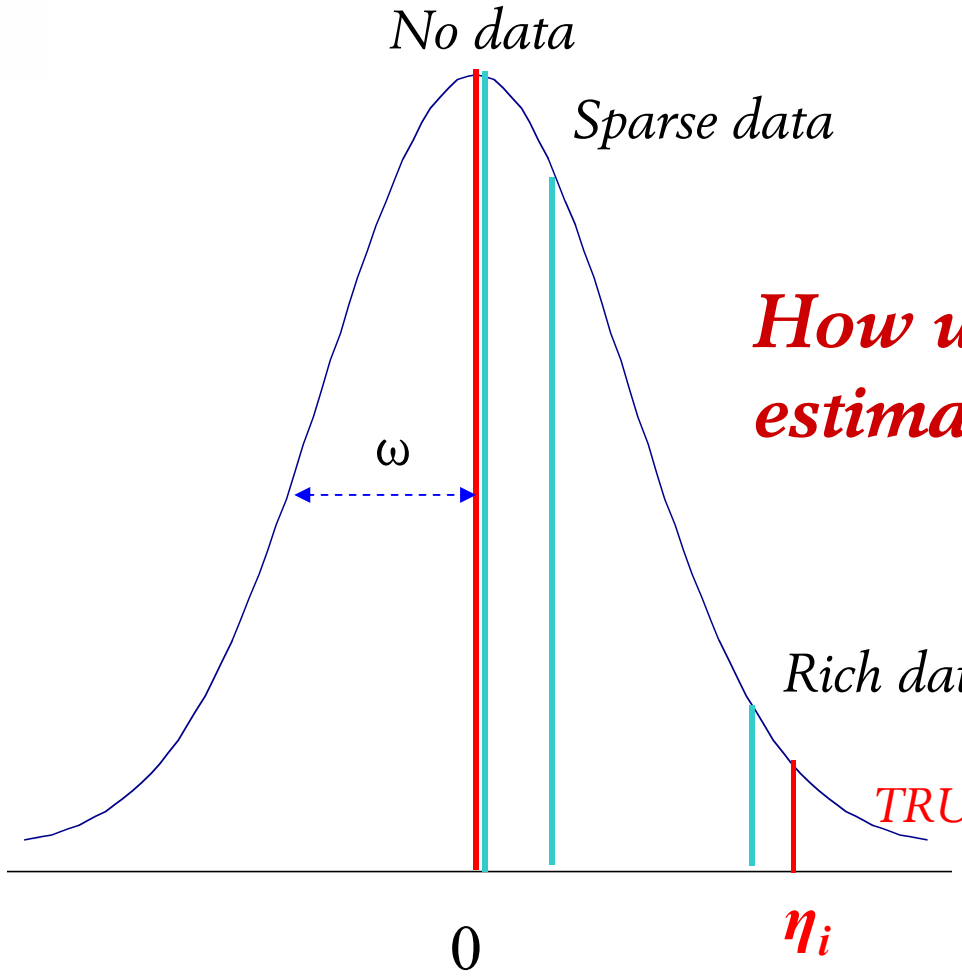
Concept of EBE shrinkage



How well can we estimate this parameter?

η distribution

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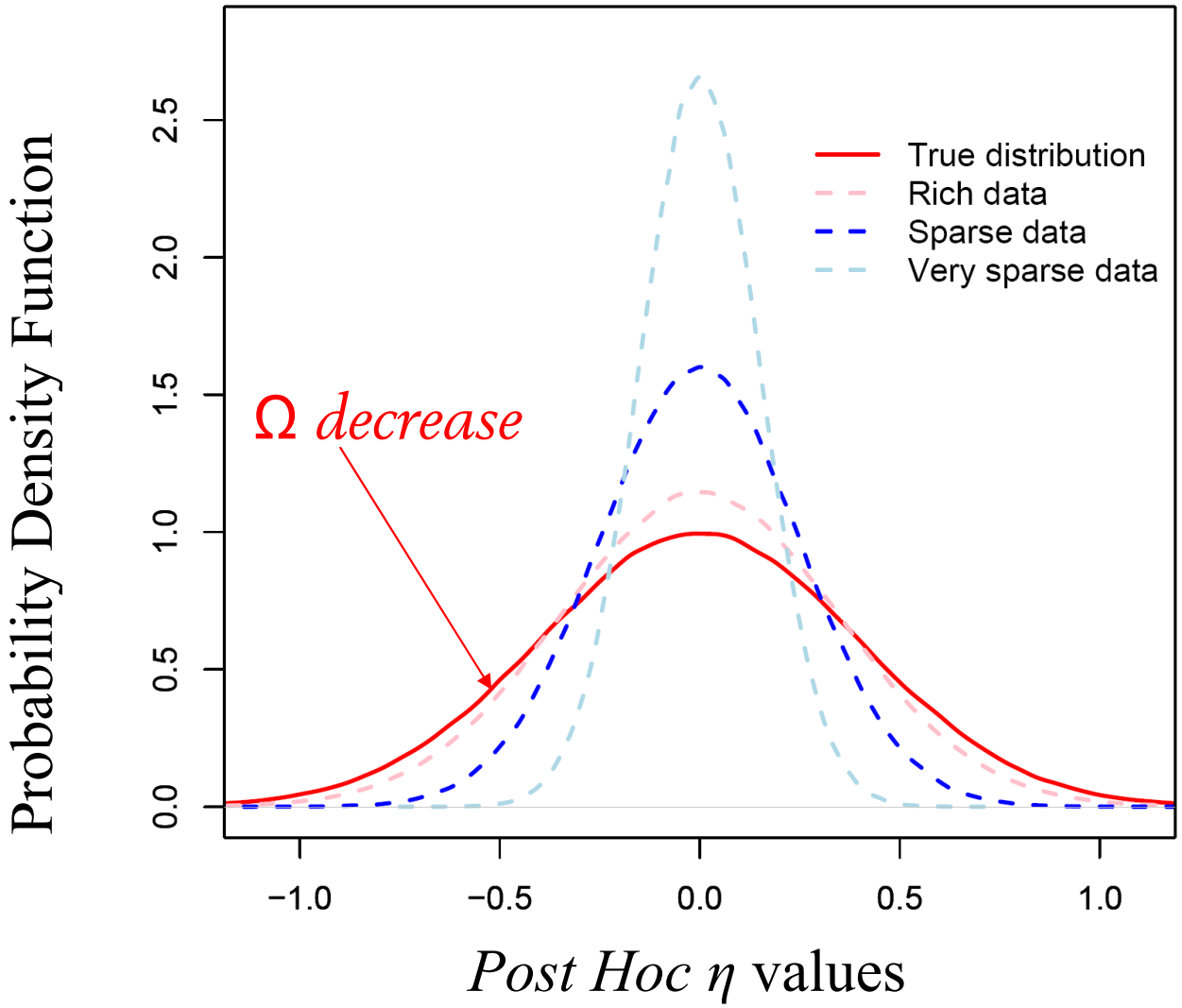
Shrinking EBE distribution towards 0



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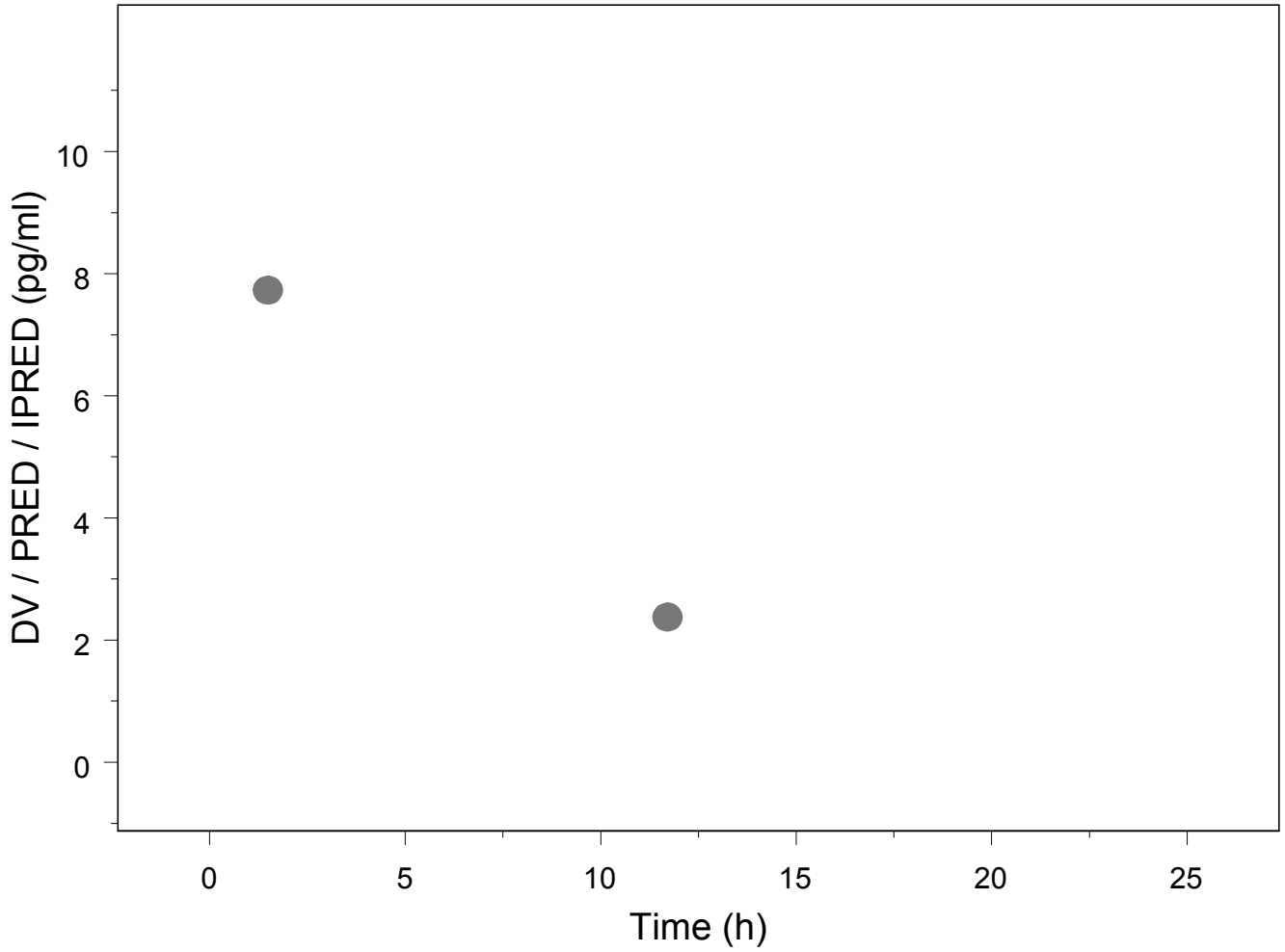
Shrinking IPRED towards DV



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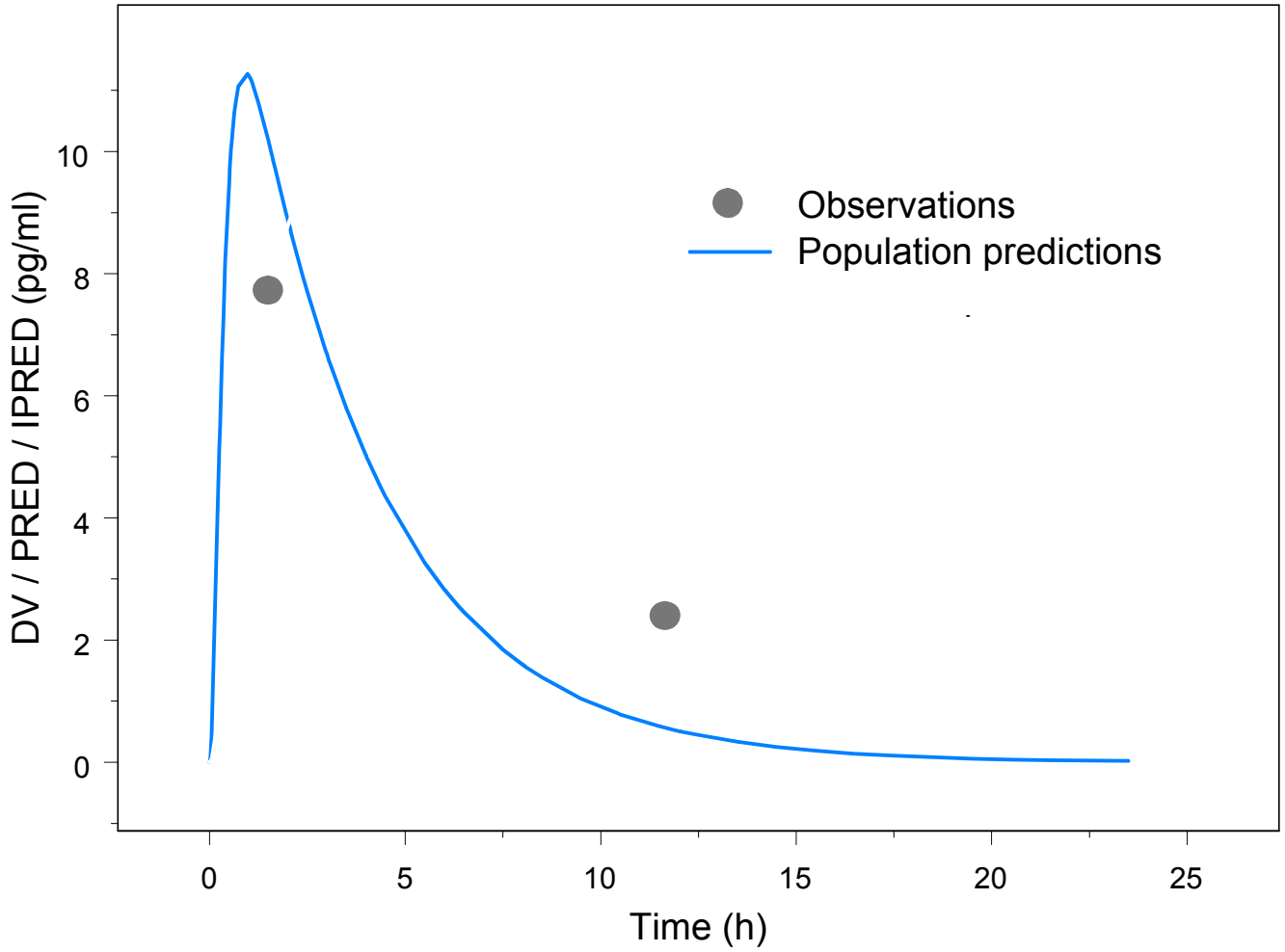
Shrinking IPRED towards DV



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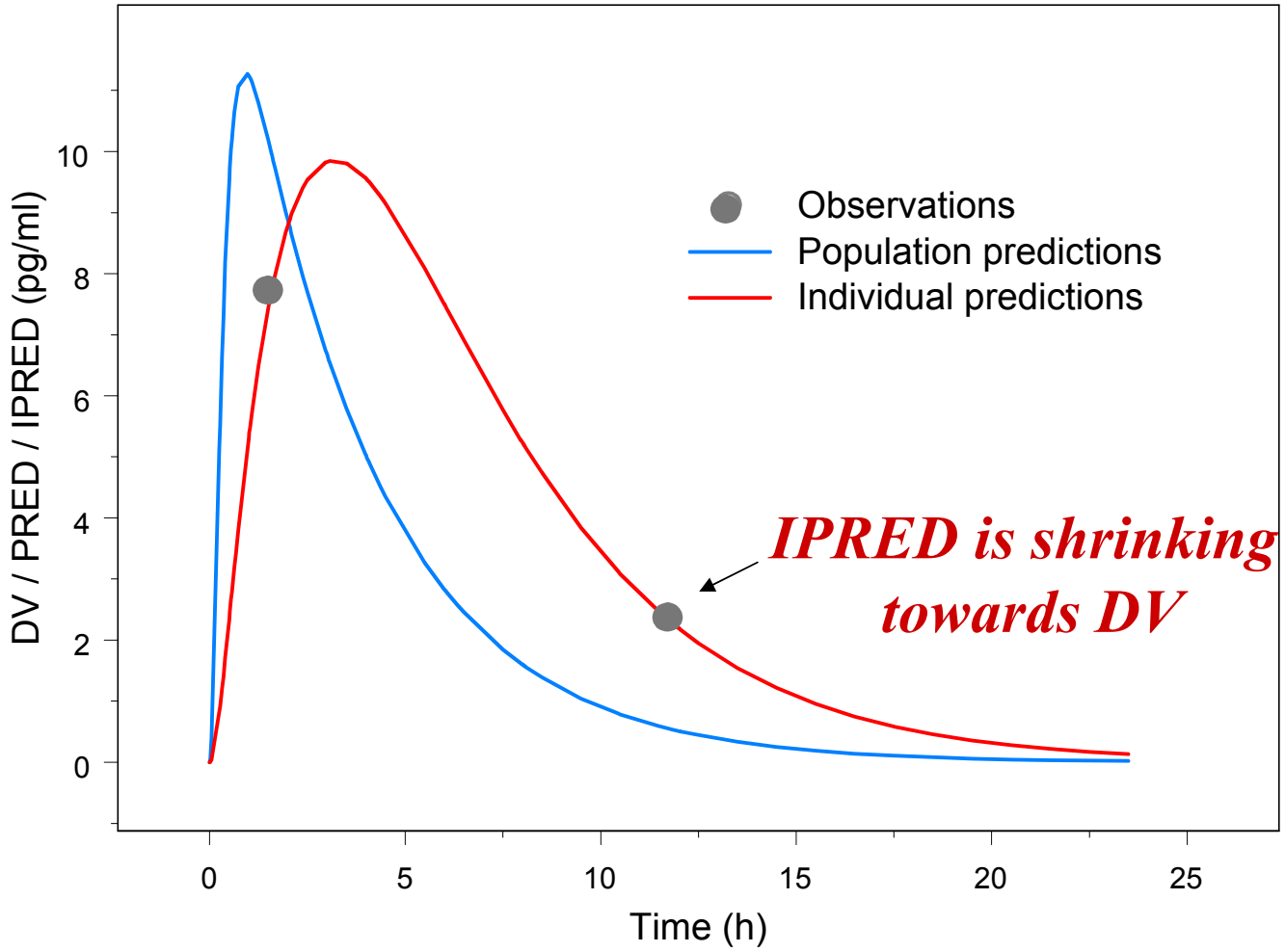
Shrinking IPRED towards DV



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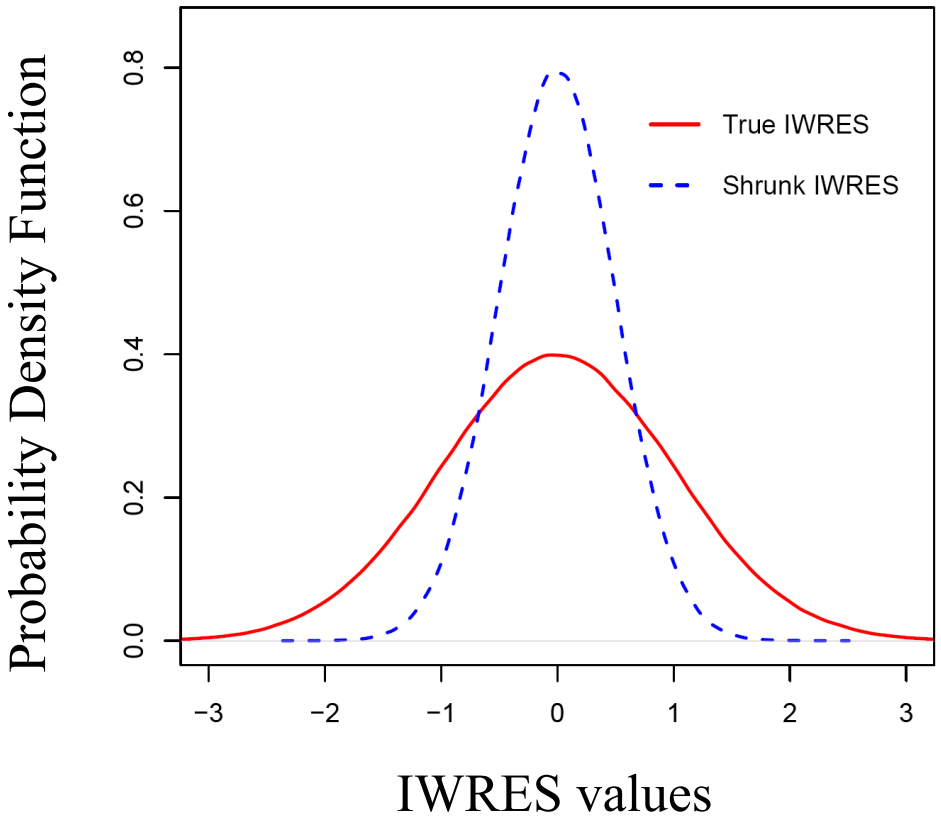
Shrinking IWRES towards 0

$$IWRES_{ij} = \frac{DV_{ij} - IPRED_{ij}}{SD(\varepsilon)}$$

If IPRED $\longrightarrow$ DV

IWRES $\longrightarrow$ 0



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Quantifying Shrinkage

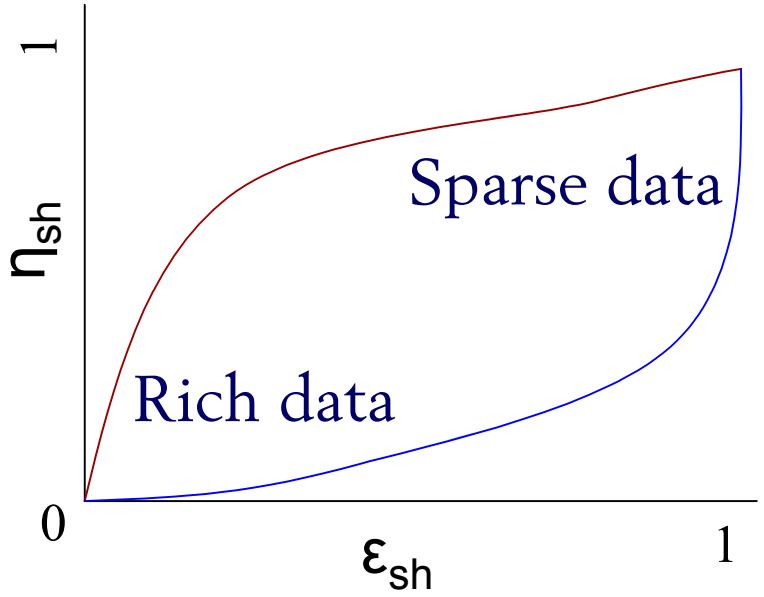
1. ETA shrinkage

$$\eta_{sh} = 1 - \frac{SD(\hat{\eta}_{ph})}{\omega}$$

2. EPSILON shrinkage

$$\varepsilon_{sh} = 1 - SD(IWRES)$$

How do these values change with information content?



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How shrinkage may influence diagnostics?

Diagnostics explored:

1. **EBE-related diagnostics (*η - shrinkage*)**
   - EBE distribution plots
   - EBE vs EBE plots
   - EBE vs Covariate plots

2. **IPRED / IWRES - related diagnostics (*ε - shrinkage*)**
   - IPRED vs DV plot
   - IWRES vs IPRED plot

Methods: MC simulations

✓ True model was fitted to data unless otherwise stated

✓ Graphical diagnostics showed on single simulation example to facilitate visualization

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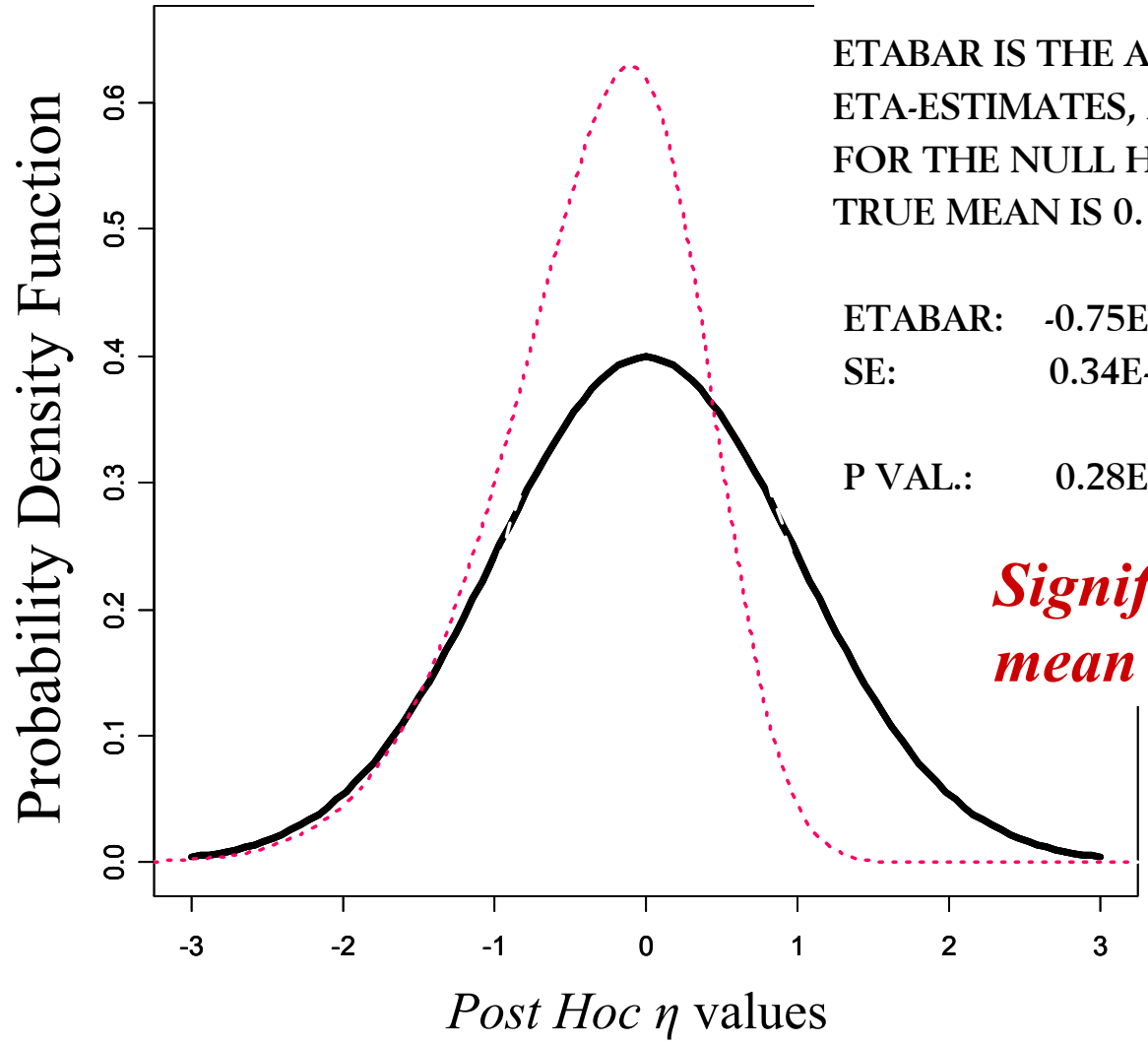
Consequences of η- shrinkage: (i) Change of distribution shape



ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES, AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.

ETABAR:	-0.75E-01	0.63E+00	-0.30E+00
SE:	0.34E-01	0.17E+00	0.17E+00
P VAL.:	0.28E-01	0.13E-03	0.71E-01

Significant change in mean value of ETAs!

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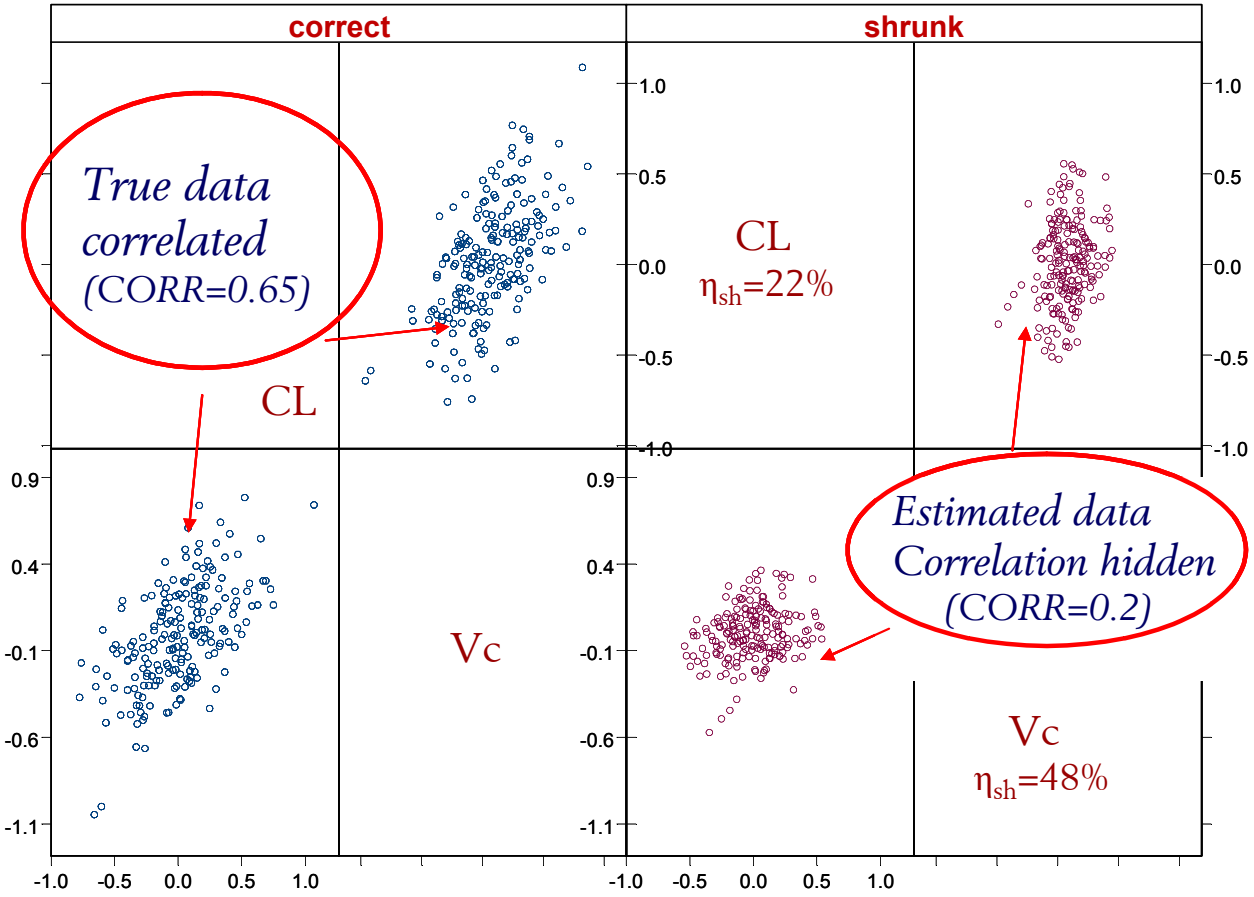
Consequences of η- shrinkage (iii) parameter correlation (hidden)



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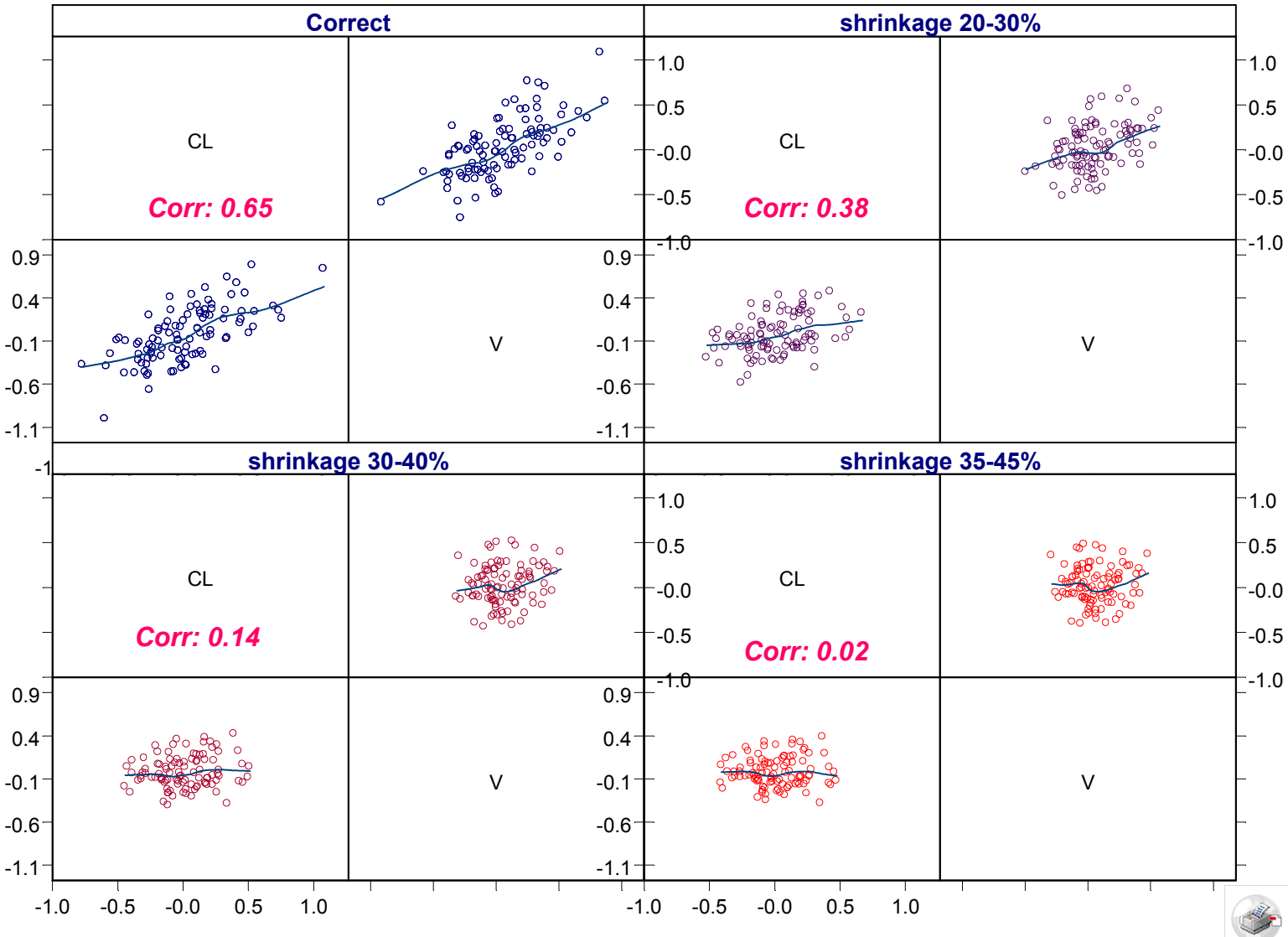
Consequences of η- shrinkage
(iii) parameter correlation (hidden)



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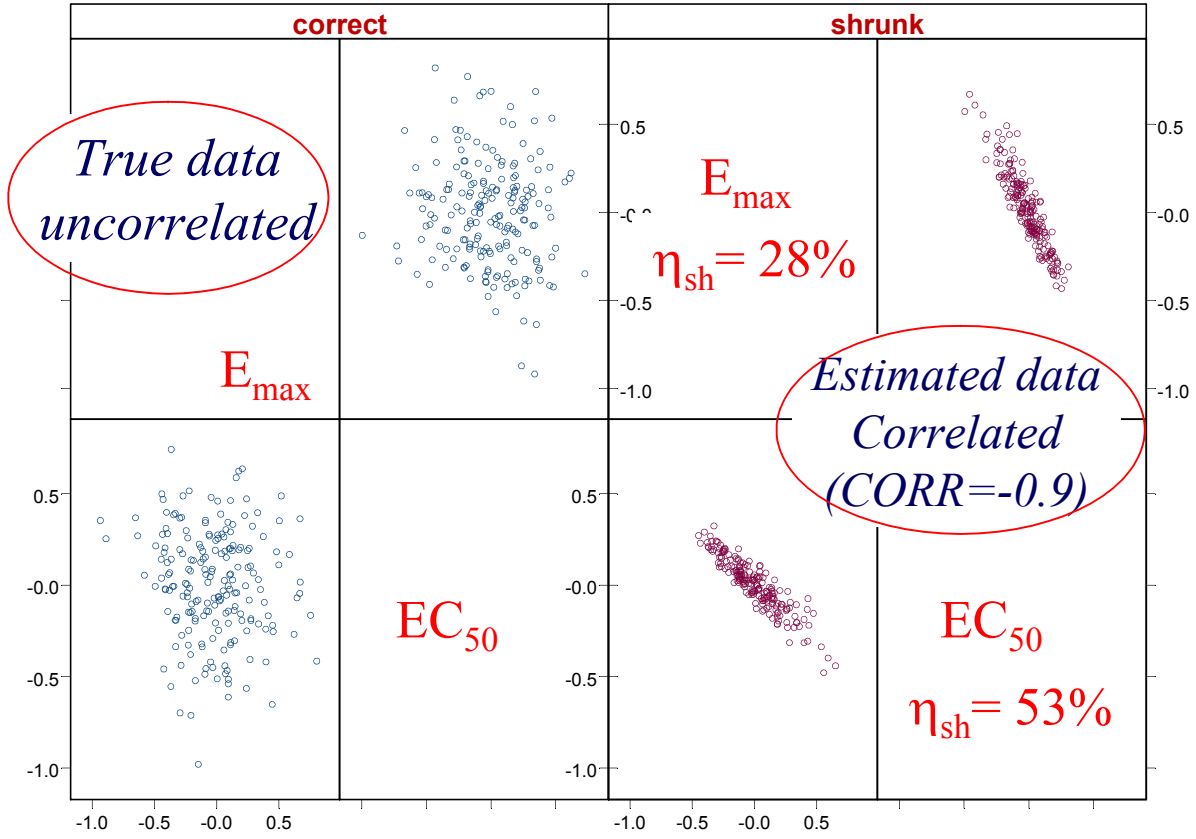
Consequences of η- shrinkage (iii) parameter correlation (induced)



Commonly induced correlations:

- ✓ ka ~ V
- ✓ EC_{50} ~ E_{max}
- ✓ EC_{50} ~ k_{out}

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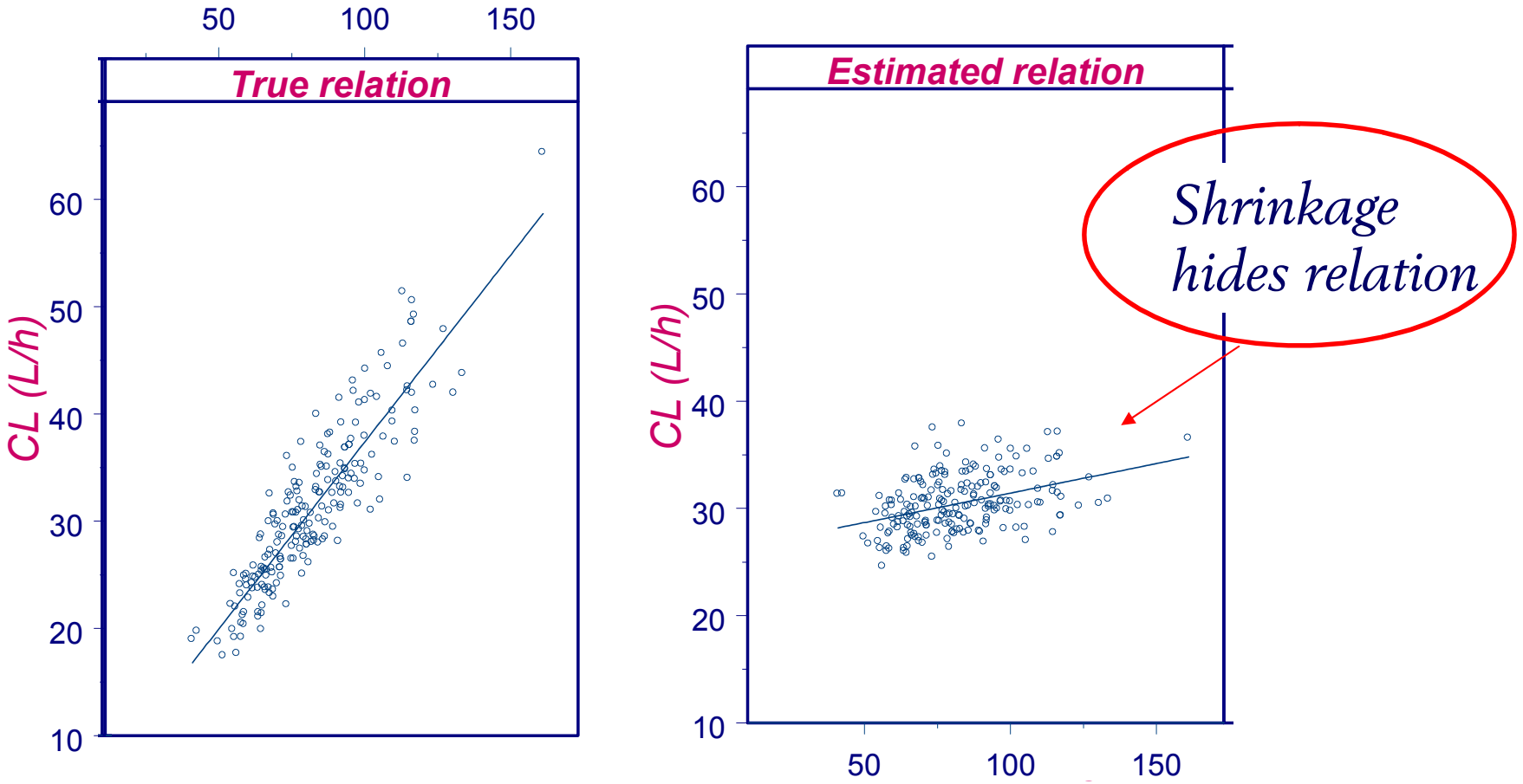
Consequences of η- shrinkage
(iv) parameters / η_s vs. Covariates



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Consequences of η- shrinkage - Summary

(i) EBEs may, in addition to shrinkage, show ***non-normal distribution*** *even when the underlying η distribution is normal*

*(ii) mean values of EBEs ("****ETABAR****") may be* ***significantly different from zero****, even for a correctly-specified model (a result of asymmetric η-shrinkage)*

(iii) EBE-EBE correlations *may be* ***hidden*** *or even* ***induced***

(iv) covariate relationships *may be* ***hidden, falsely induced****, or the shape of the true relationship* ***distorted***

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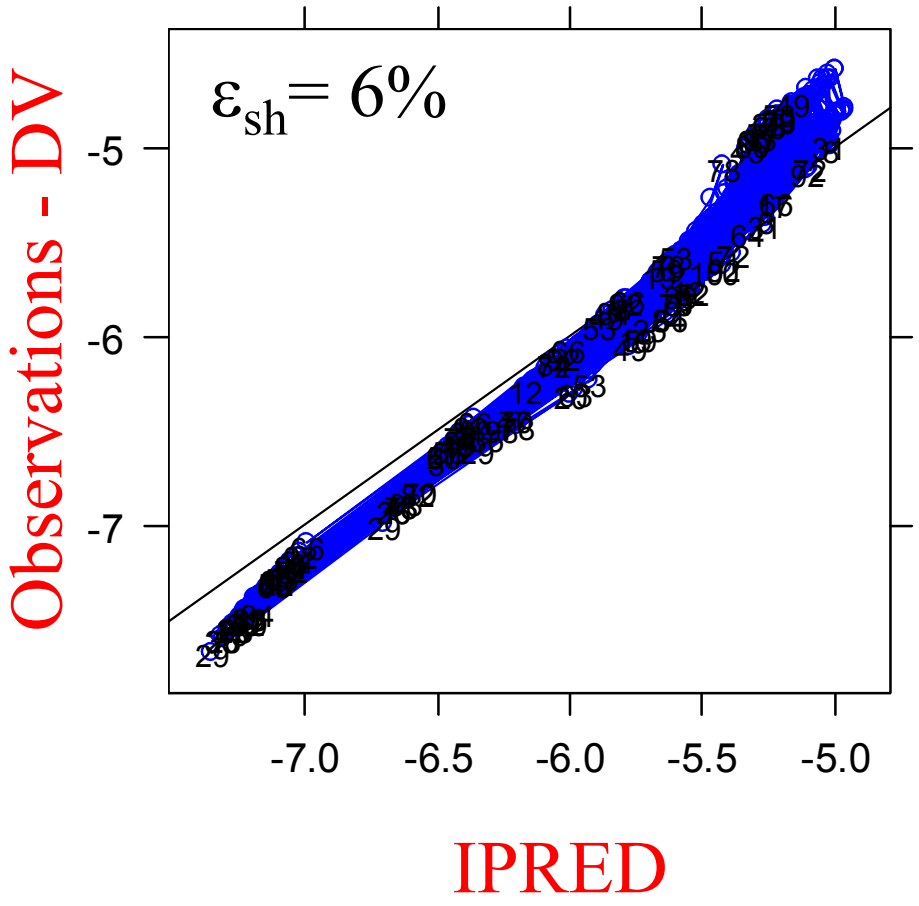
Consequences of ε- shrinkage

(i) Low power of IPRED to detect model misspecification



Plot is a clear indication of model misspecification

Fitted model:
first order absorption

True model:
zero-order absorption model

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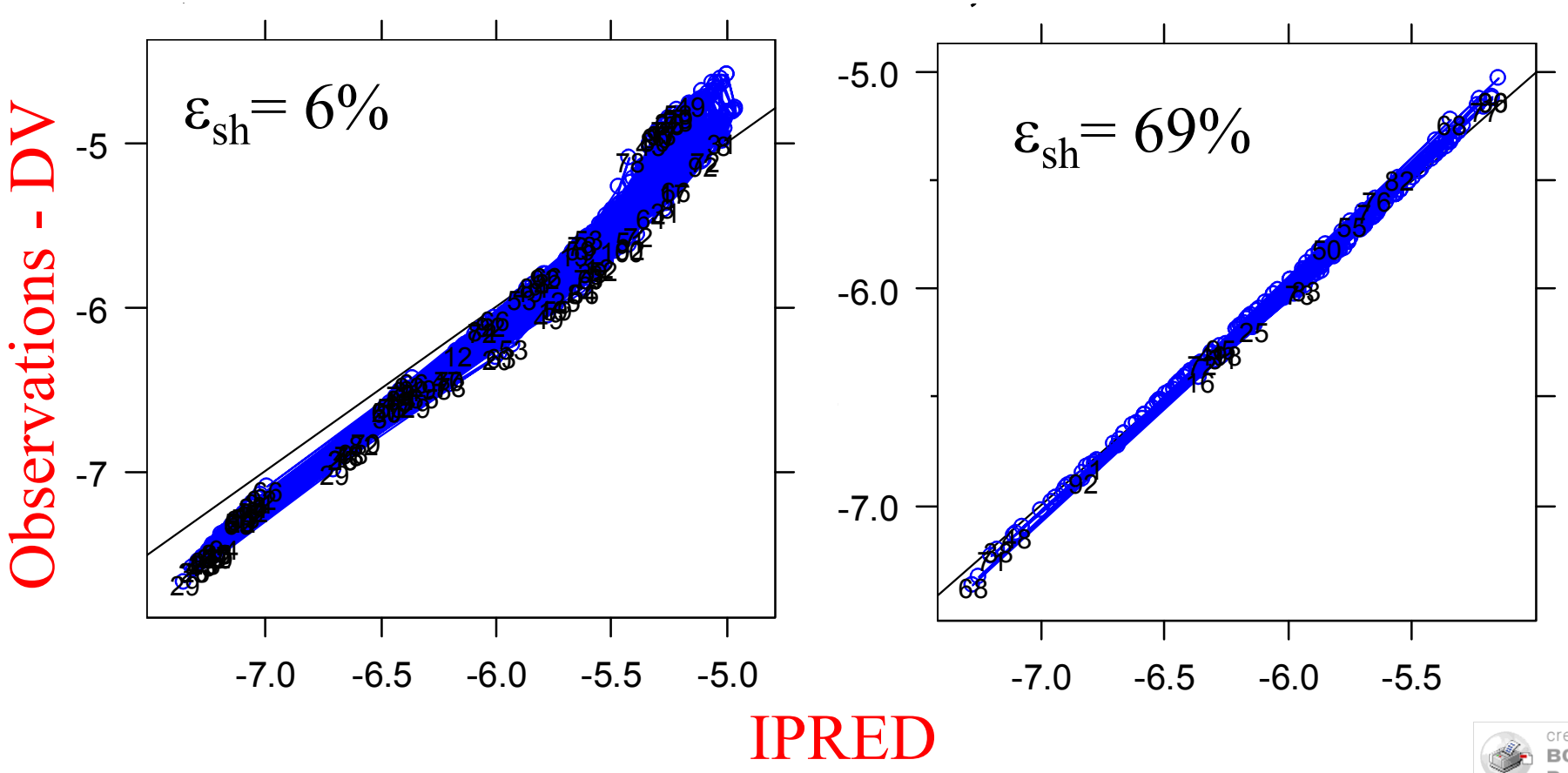
Consequences of ε- shrinkage

(i) Low power of IPRED to detect model misspecification

"Perfect fit" phenomenon



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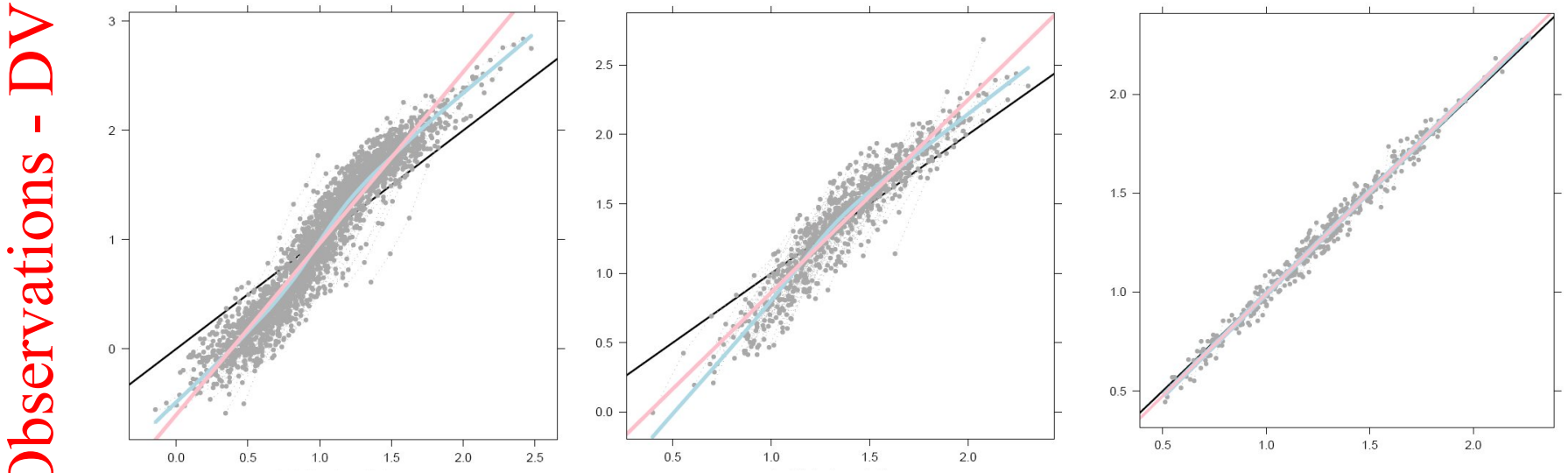
Emax model fitted to data simulated with a sigmoidal Emax model

ε_{sh} = 5%

ε_{sh} = 13%

ε_{sh} = 29%



Line of identity

Linear regression

Loess smooth

Karlsson MO & Savic RM, ***Diagnosing model diagnostics****, To appear in CPT, July 2007*

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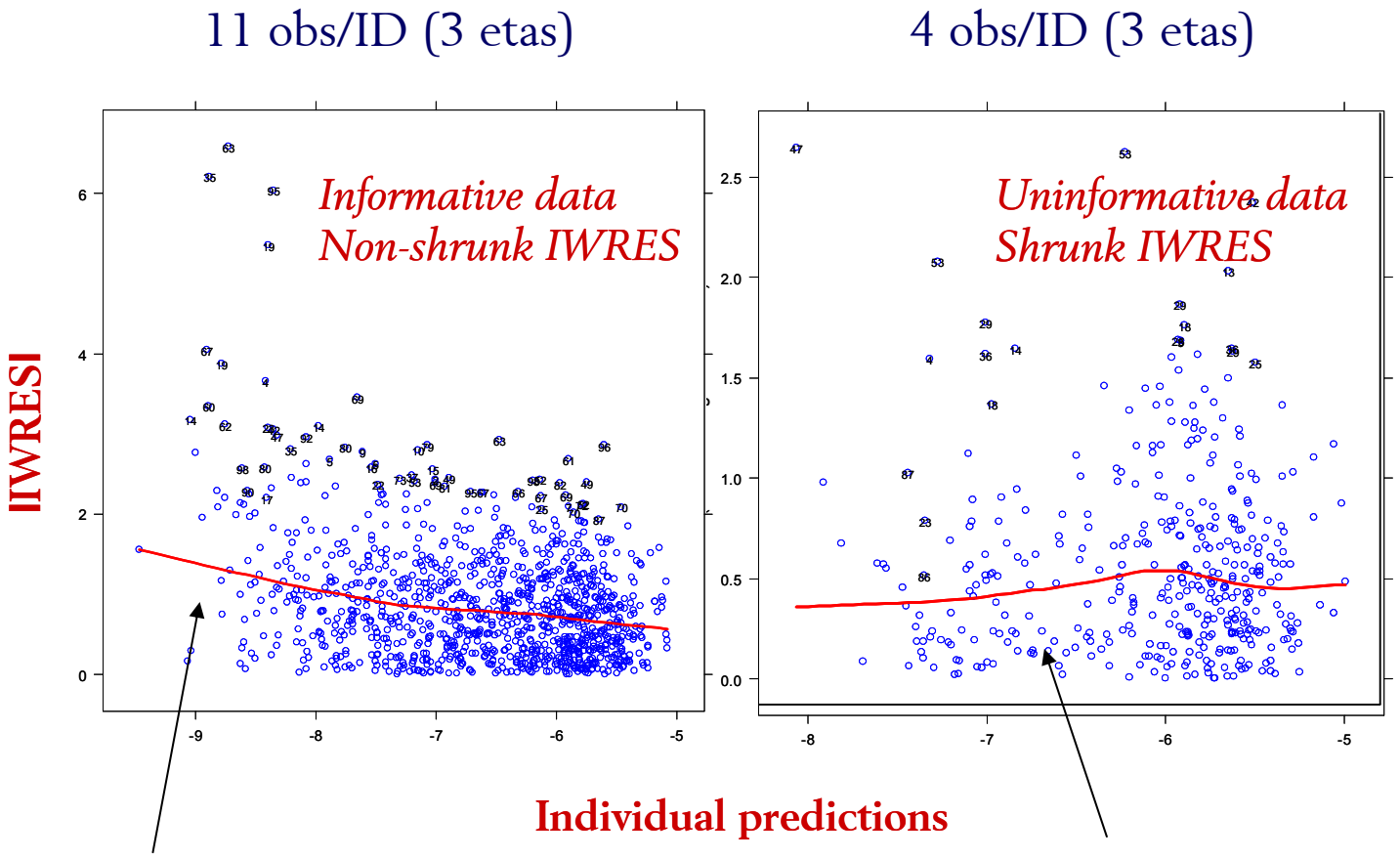
Consequences of ε- shrinkage

(ii) Low power of IWRES to diagnose residual error misspecification



Misspecification indicated

Misspecification NOT indicated

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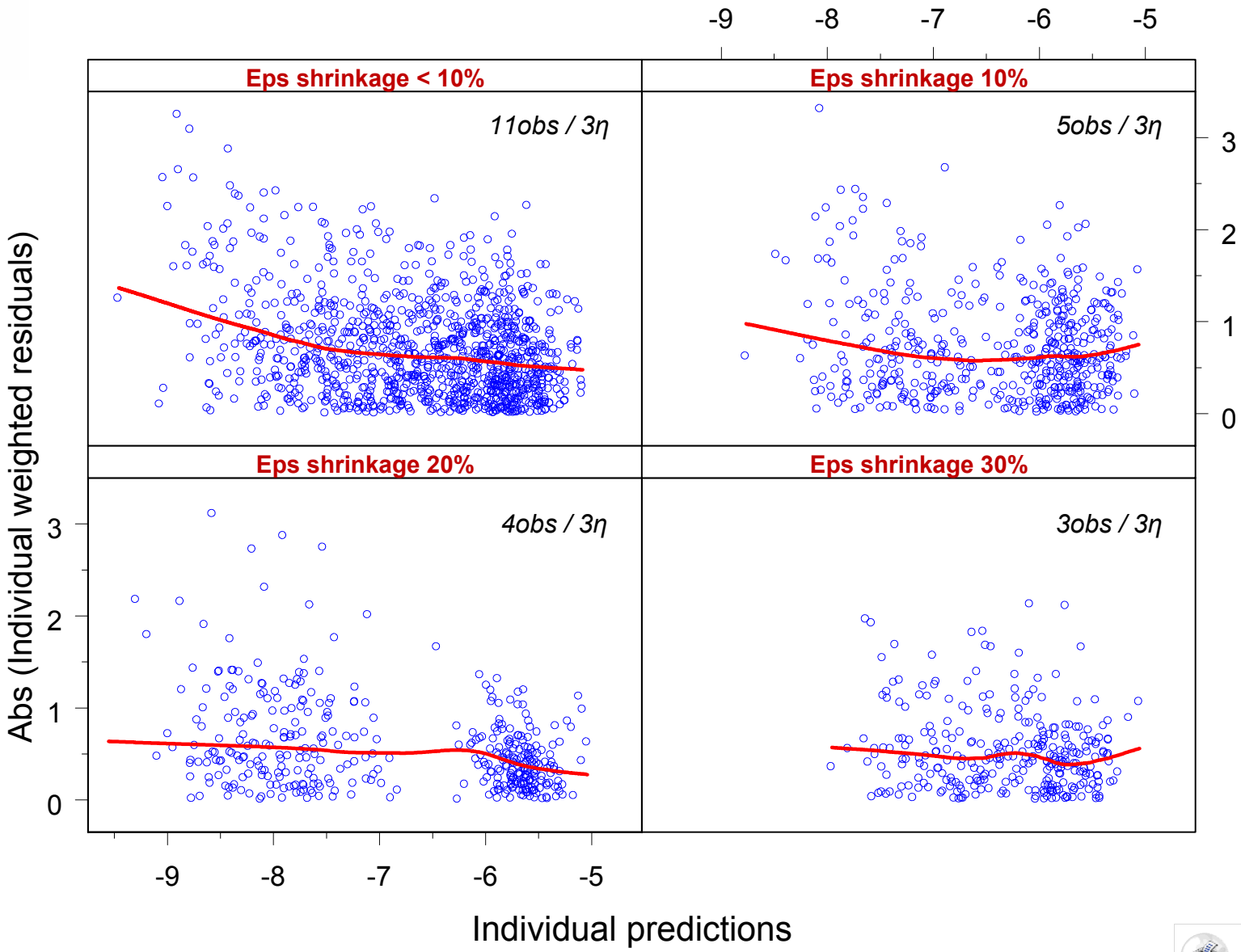
(ii) low power of IWRES to diagnose residual error model misspecification



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Consequences of ε- shrinkage - Summary

(i) low power of IPRED to diagnose structural model misspecification ("perfect fit" phenomenon)

(ii) low power of IWRES to diagnose residual error model misspecification

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Conclusions – part 1

✓Model diagnostics involving EBE, IPRED, IWRES is **misleading** in the presence of shrinkage

✓The problem of shrinkage in showed examples associated to the diagnostics solely. Estimation is not affected.

✓Consequences of shrinkage ignorance:

- wrong decisions
- increased time for data analysis
- wrong models

✓Shrinkage phenomenon is likely to affect other type of model diagnostics such as:

- GAM
- CWRES

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Solutions

1. *Report the shrinkage extent!*
   - *Inform modelers about relevance of the graphs*

2. *Estimate standard errors of ETAs*
   - *Refine EBEs and EBE-based diagnostics*

3. *Use other type of diagnostics*
   - *Simulation based diagnostics*

4. *Do more model testing inside NONMEM*

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EBE shrinkage & Estimation
FOCE

Background:

EBEs are computed at each iteration step

Question:

How shrinkage may affect FOCE method?

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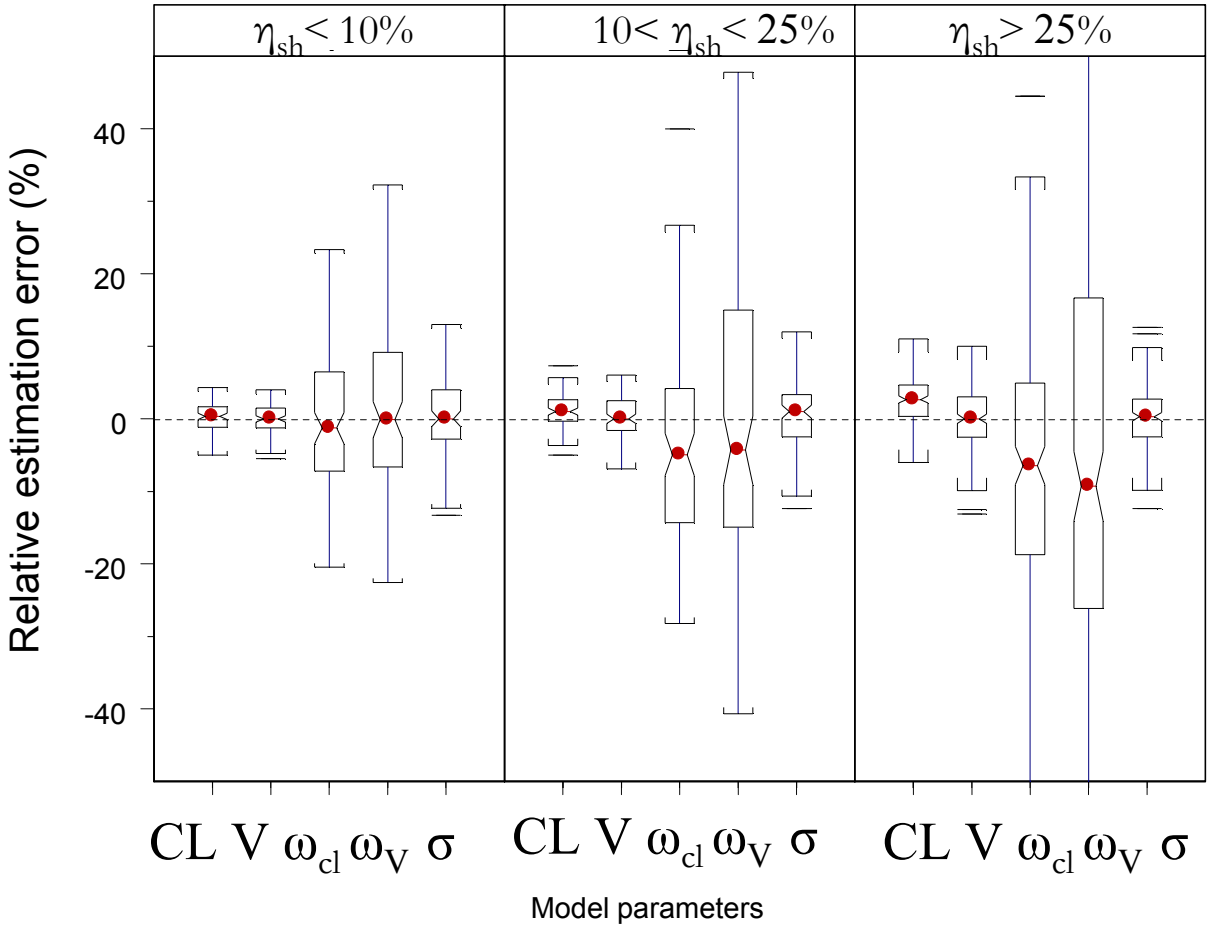
EBE shrinkage & FOCE

Bias in FOCE parameter estimates with EBE shrinkage



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Conclusions - part 2

1. *Increased bias & variance of FOCE parameter estimates in the presence of shrinkage*

→ *FOCE method is becoming more like FO method*

- Biased variance estimates

Solution

- ✓ new algorithms
- ✓ refine variance estimates (NONP)

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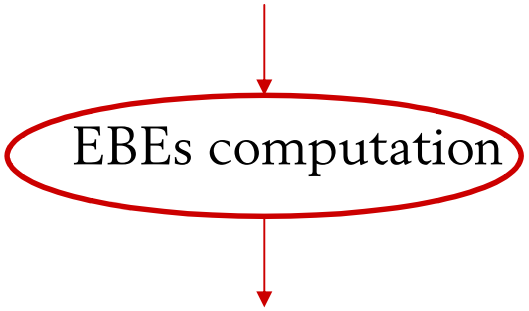
EBE shrinkage & $NONP

1. Search for support points

parametric step (FO/FOCE)



What if EBEs are shrunk?

Points of support

2. Probability estimation

- ✓ the joint probability
- ✓ the marginal cumulative probability

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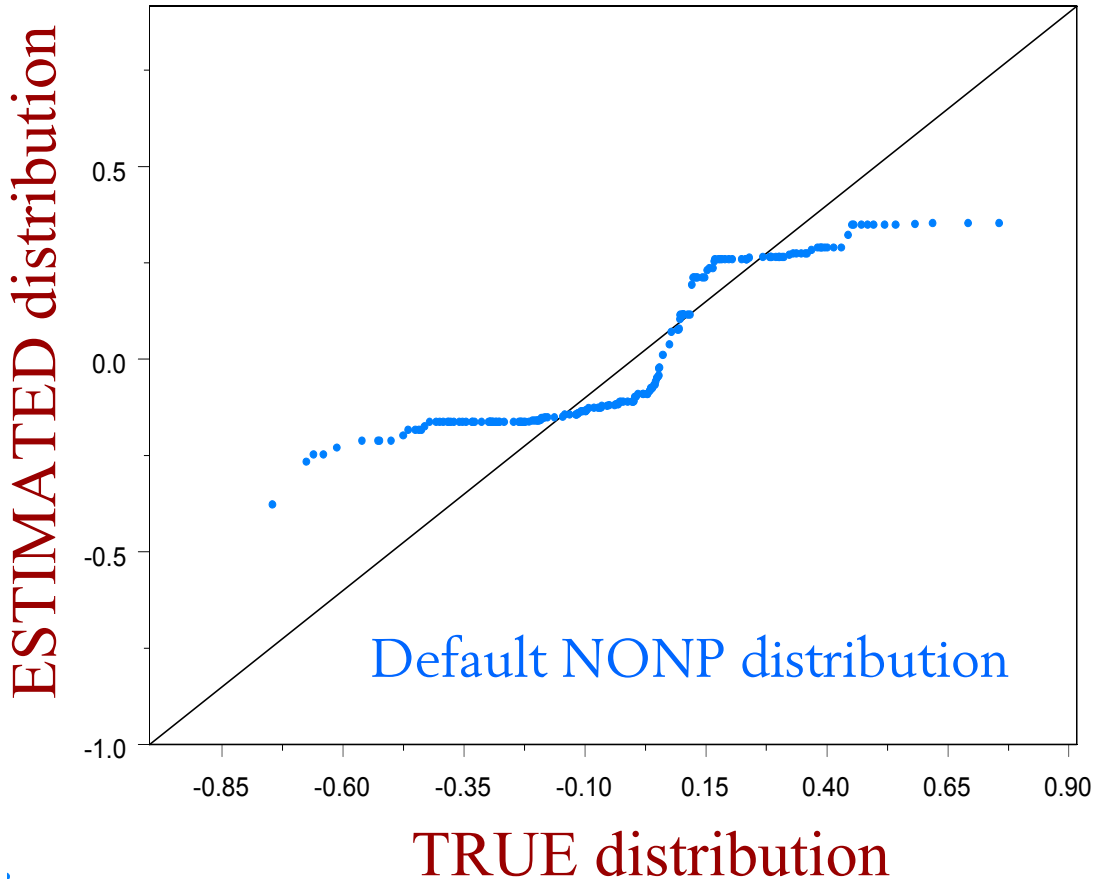
Consequences of EBE shrinkage

QQ plot: true versus estimated distribution



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NONP and EBE shrinkage How to proceed?

1. *Keep using default NONMEM support points*

✓ range of available support points may be sufficient

✓ range of available support points lower than expected

-results still may be improved compared to the parametric outcome

2. *Inflate variances prior to EBE (POSTHOC) estimation*

(enough to inflate twice the variances)

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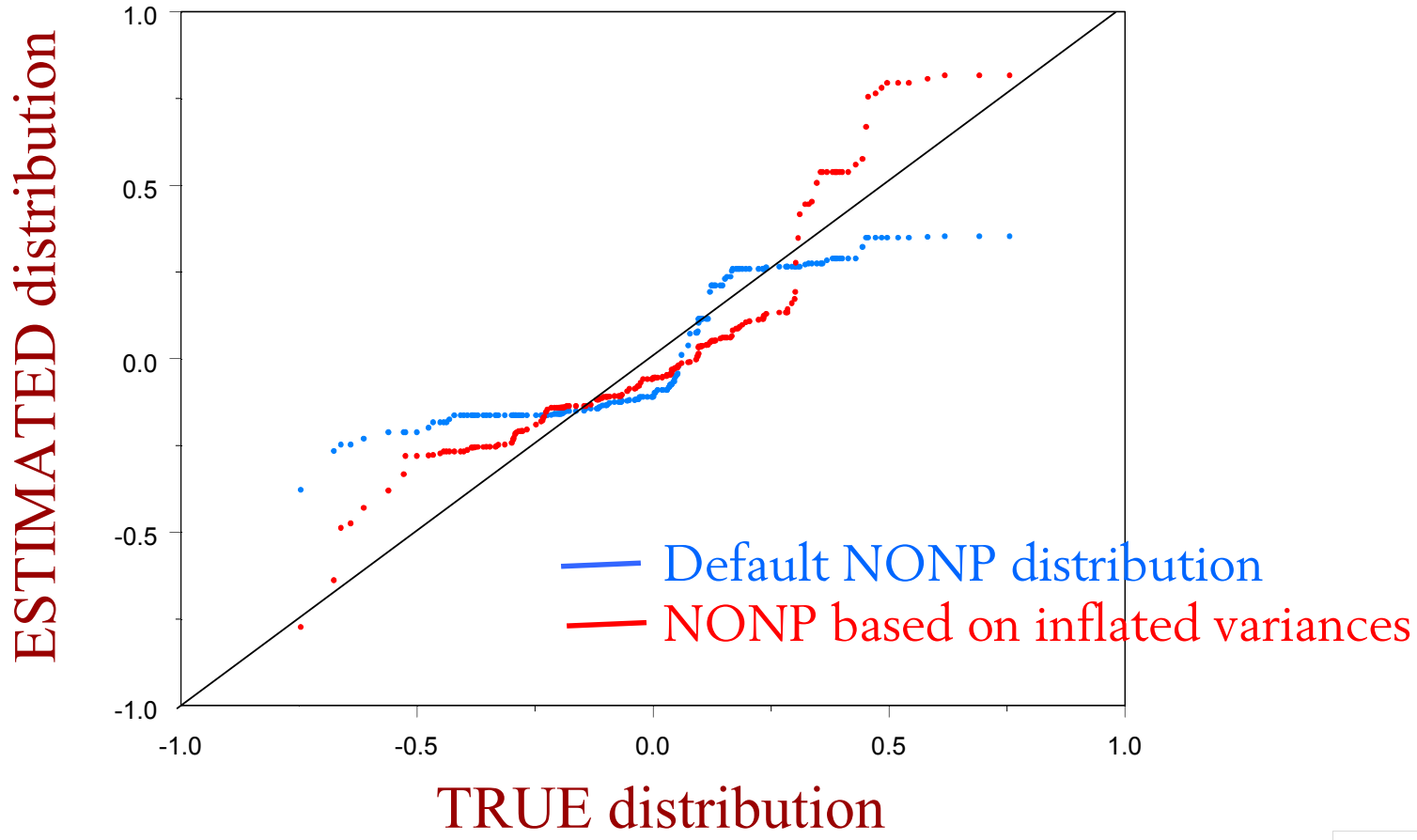
Improvement with the inflated variances method



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NONP & EBE shrinkage - How to proceed?

Enriched grid method

There is a way to enhance the NONP grid with additional points of support

Additional points of support are generated via simulations from final model

Practicaly it requrires:

- ✓ simulation from the final model
- ✓ computation of the individual contributions to the entire NONP density

A general routine that automizes this is under development

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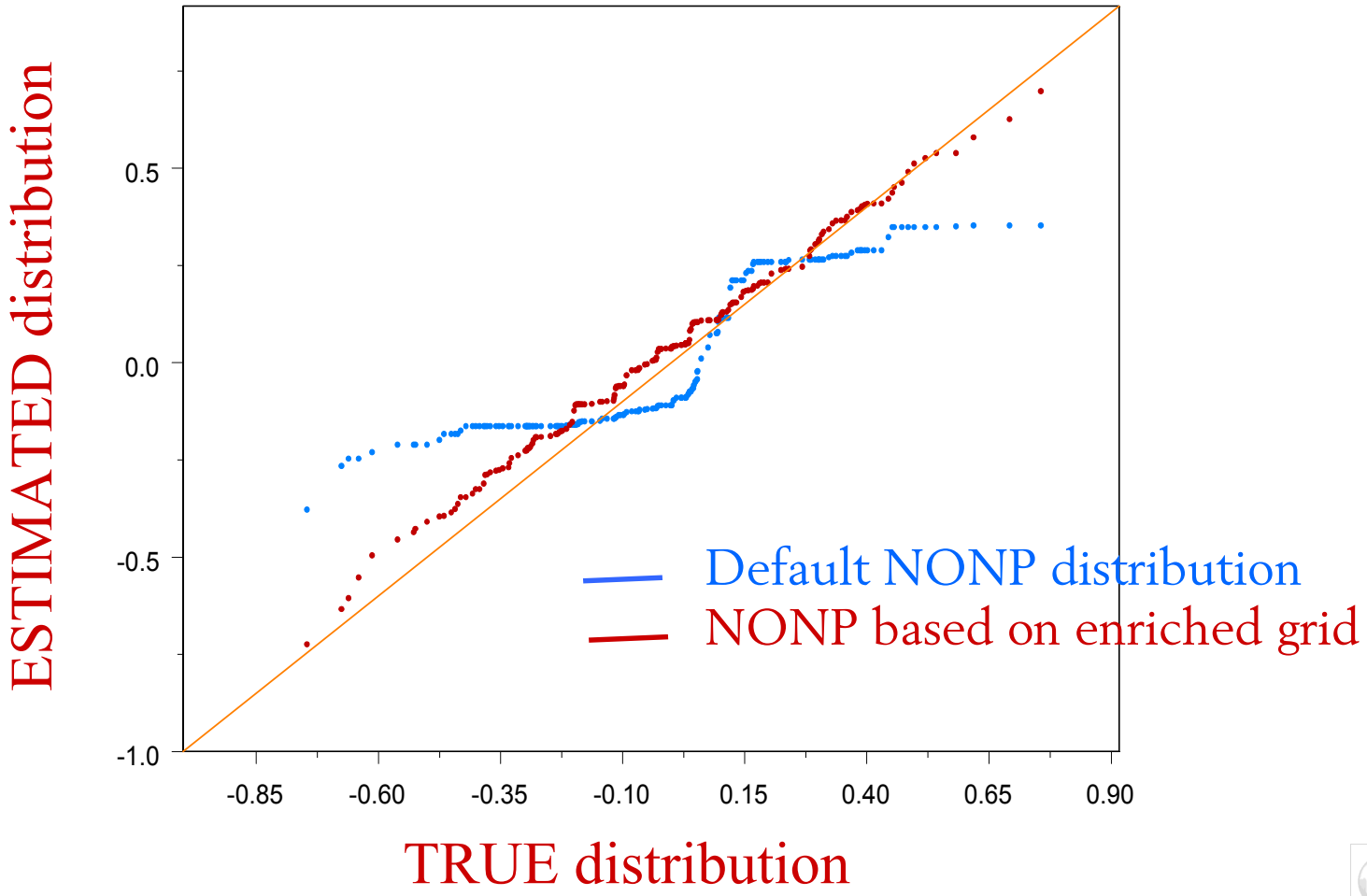
Improvement with the enriched grid method



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Conclusions

1. Model diagnostics involving EBE, IPRED, IWRES is misleading

Essential part of model building:

- wrong decisions
- increased time for data analysis
- wrong models

2. FOCE method is becoming more like FO method

Biased variance estimates

3. NONP method may be biased

At higher shrinkage extents

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Take-home message

Compute the shrinkage!

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Solutions

1. *Model diagnostics*

- ✓ Report the shrinkage extent!
- ✓ Compute standard errors of ETAs
- ✓ Use other type of diagnostics
- ✓ More testing directly in NONMEM

2. *FOCE*

- ✓ new algorithms
- ✓ refine variance estimates (NONP)

3. *NONP method*

- ✓ Inflate varainces prior to EBE estimation
- ✓ Use extended grid method (soon available in PsN)

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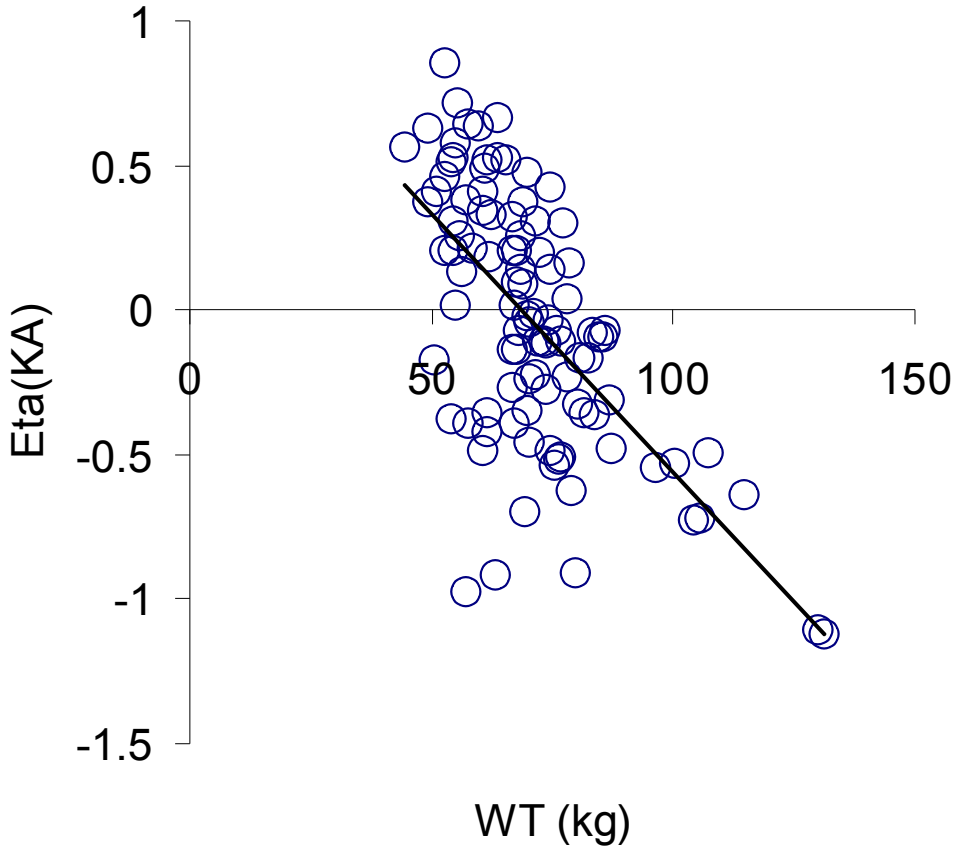
Falsely induced covariate relationships by EBE shrinkage



Simulations:

- ✓WT as covariate on V
- ✓no covariance V-Ka
- ✓no influence of WT on ka.