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Conditional weighted residuals

an improved model diagnostic for the FO/FOCE methods.

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Introduction

- Development and analysis of population PK/PD models has shifted from FO to FOCE
  - FOCE Allows for hypothesis testing during model development
  - FOCE gives less biased model parameter estimates

Medline search:

'NONMEM', in 2005

131 hits

Estimation method				
FO	FOCE	FOCE INTER	Combo	Not Provided
15%	21%	28%	16%	20%

50% specifically mentioned examining WRES during model diagnosis

Of those, 80% provided a plot of the WRES

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Introduction

- Weighted residuals (WRES)
  - Commonly used as a model diagnostic for evaluating model misspecification.
  - Calculated using FO approximation even when running FOCE
  - Possibility of misguided model development if WRES are wrong

- Conditional WRES (FOCE)
  - A new model diagnostic tool
  - Calculated based on FOCE approximation

Weighted residuals (WRES) – An example…

- Sigmoidal Emax model, exponential IIV, additive RE, Hill-coefficient = 4.5

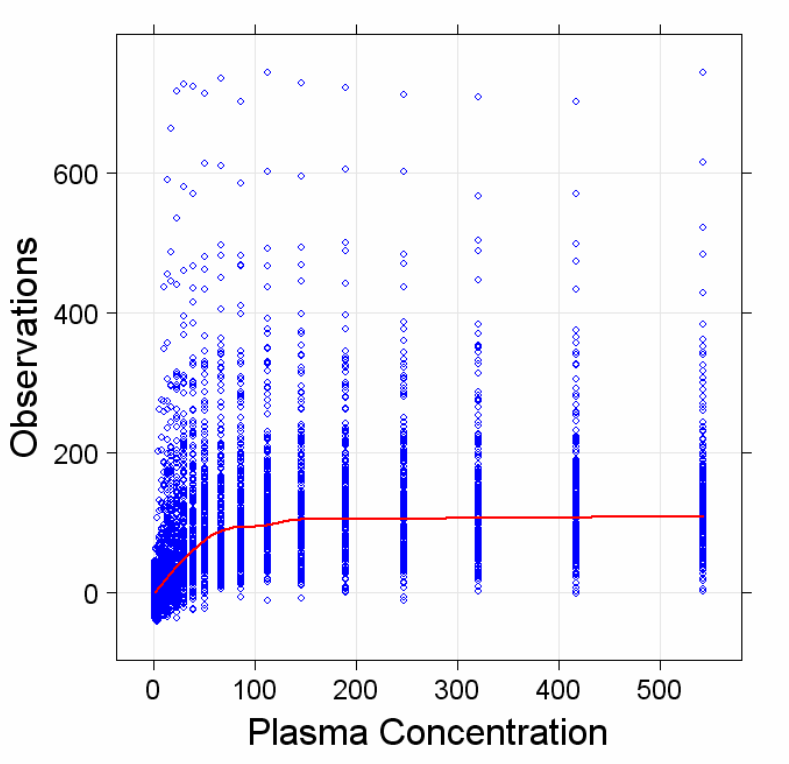
$$E = \frac{E_{\max} C^{\gamma}}{C^{\gamma} + C_{50}{}^{\gamma}} + \varepsilon$$

$$E_{\max} = \theta_1 e^{\eta_1}$$

$$C_{50} = \theta_2 e^{\eta_2}$$

$$\gamma = \theta_3$$

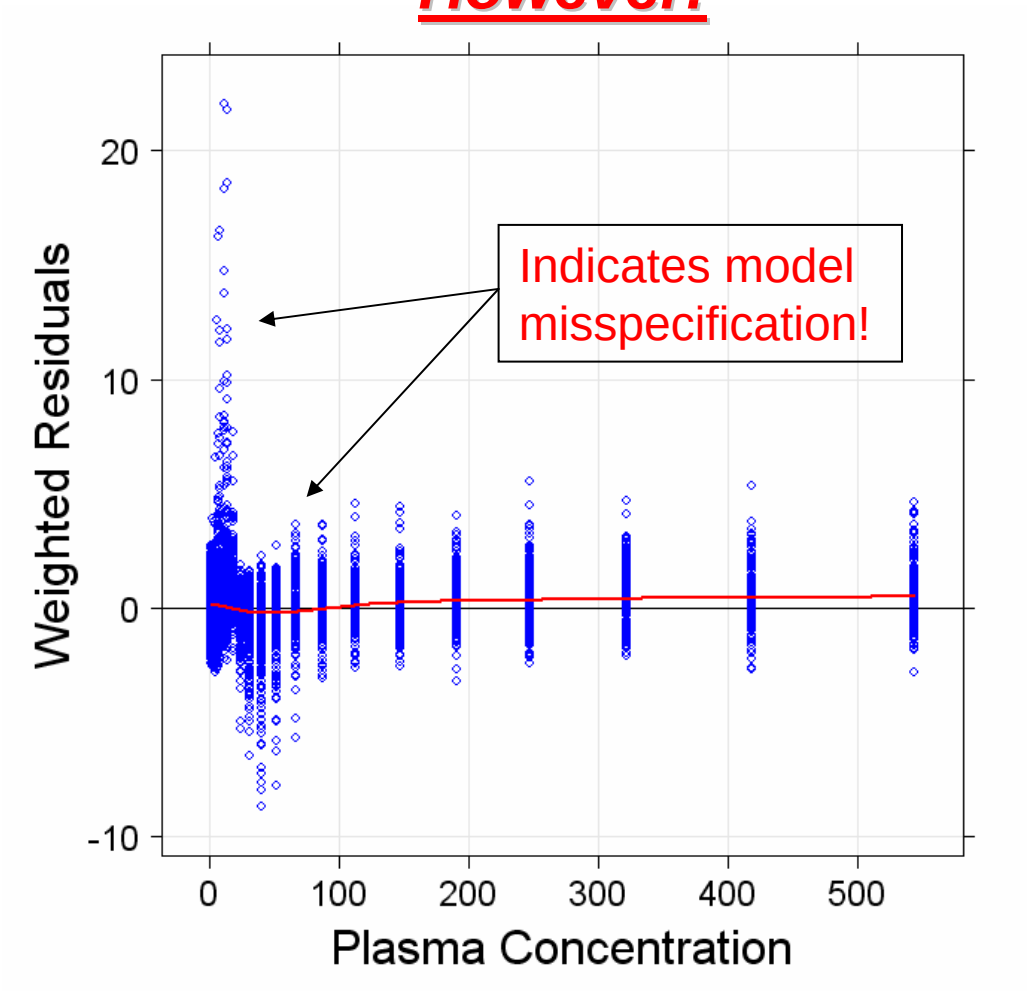
- Data simulated from model: 200 ind, 25 samps/ind.



Weighted residuals (WRES) – An example…

- Estimate using FOCE with true model.
  - Difference between estimated and true parameters is small (<10%)
  - FOCE does not have a problem with fit.

However!



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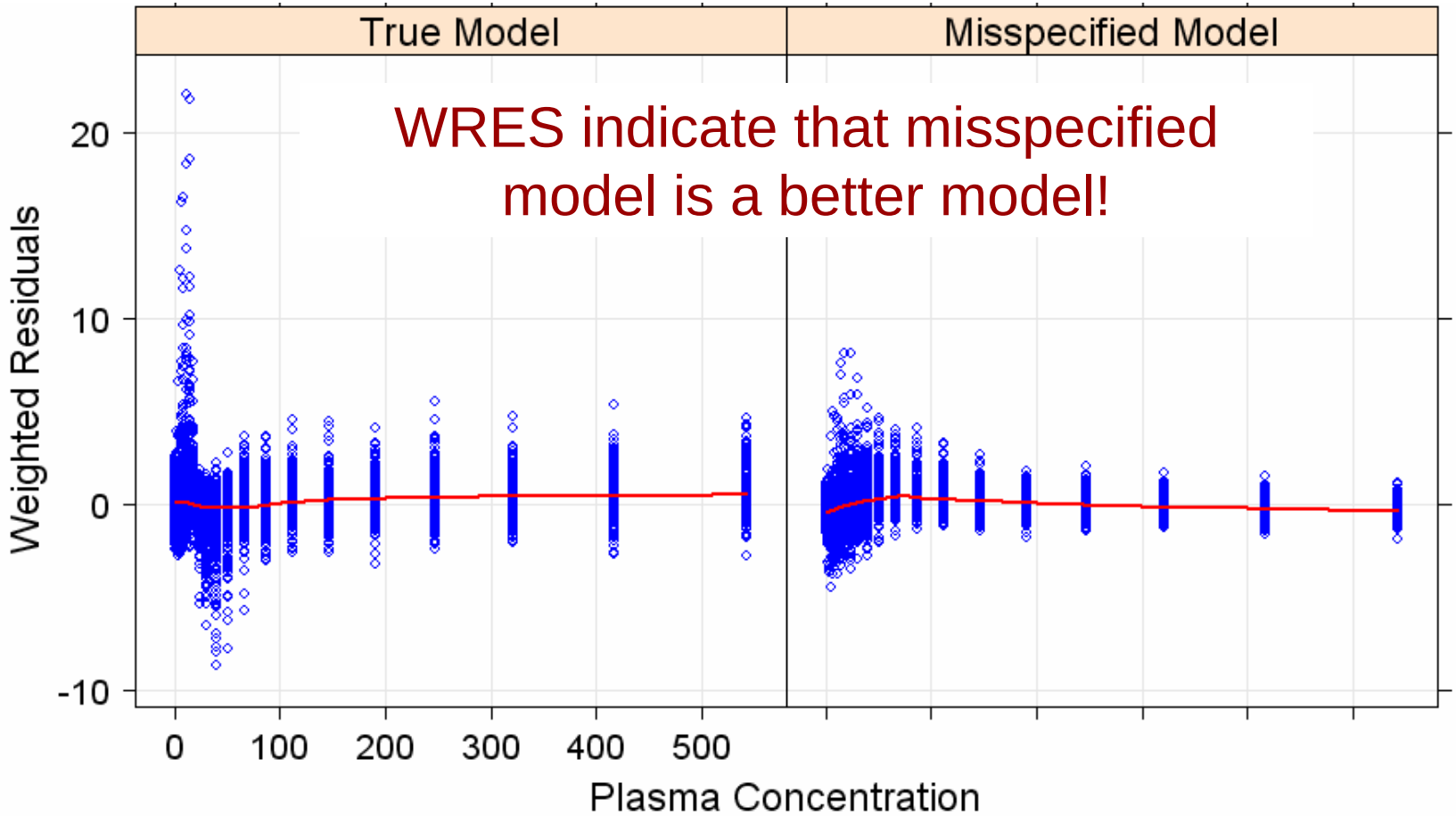
Weighted residuals (WRES) – An example…

Model Misspecification:

Remove Hill-Coefficient from model and re-estimate



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What is going on… The FO perspective

The FO objective function

$$\sum_{i=1}^{m}\left[\log\left|\mathbf{Cov}_{FO}(\vec{y}_i)\right| + \frac{\left(\vec{y}_i - E_{FO,i}(f)\right)^2}{\mathbf{Cov}_{FO}(\vec{y}_i)}\right]$$

Expectation and covariance matrix based on FO approximation

$$E_{FO,i}(f) = f(\vec{\theta}, 0)$$

$$Cov_{FO}(\vec{y}_i) = \left.\frac{df}{d\vec{\eta}}\right|_{\vec{\eta}=0} \cdot \Omega \cdot \left.\frac{df'}{d\vec{\eta}}\right|_{\vec{\eta}=0} + diag\left(\left.\frac{dh}{d\vec{\varepsilon}_i}\right|_{\vec{\varepsilon}_i=0} \cdot \Sigma_i \cdot \left.\frac{dh'}{d\vec{\varepsilon}_i}\right|_{\vec{\varepsilon}_i=0}\right)$$

WRES *always* calculated this way (even with FOCE)

$$WRES = \frac{\vec{y}_i - E_{FO,i}(f)}{\sqrt{\mathbf{Cov}_{FO}(\vec{y}_i)}} \in N(0,1)$$

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What is going on… The FOCE perspective

The FOCE objective function

$$\sum_{i=1}^{m}\left[\log\left|\mathbf{Cov}_{FOCE}(\vec{y}_i)\right| + \frac{\left(\vec{y}_i - E_{FOCE,i}(f)\right)^2}{\mathbf{Cov}_{FOCE}(\vec{y}_i)}\right]$$

Expectation and covariance matrix based on FOCE approximation

$$E_{FOCE,i}(f) = f(\vec{\theta}, \hat{\eta}_i) - \left.\frac{df}{d\vec{\eta}_i}\right|_{\vec{\eta}_i=\hat{\eta}_i} \cdot \hat{\eta}_i$$

$$Cov_{FOCE}(\vec{y}_i) = \left.\frac{df}{d\vec{\eta}_i}\right|_{\vec{\eta}_i=\hat{\eta}_i} \cdot \Omega \cdot \left.\frac{df'}{d\vec{\eta}}\right|_{\vec{\eta}_i=\hat{\eta}_i} + diag\left(\left.\frac{dh}{d\vec{\varepsilon}_i}\right|_{\vec{\varepsilon}_i=0} \cdot \Sigma_i \cdot \left.\frac{dh'}{d\vec{\varepsilon}_i}\right|_{\vec{\varepsilon}_i=0}\right)$$

These values are *NOT* the WRES!

$$\text{CWRES} = \frac{\vec{y}_i - E_{FOCE,i}(f)}{\sqrt{\mathbf{Cov}_{FOCE}(\vec{y}_i)}} \in N(0,1)$$

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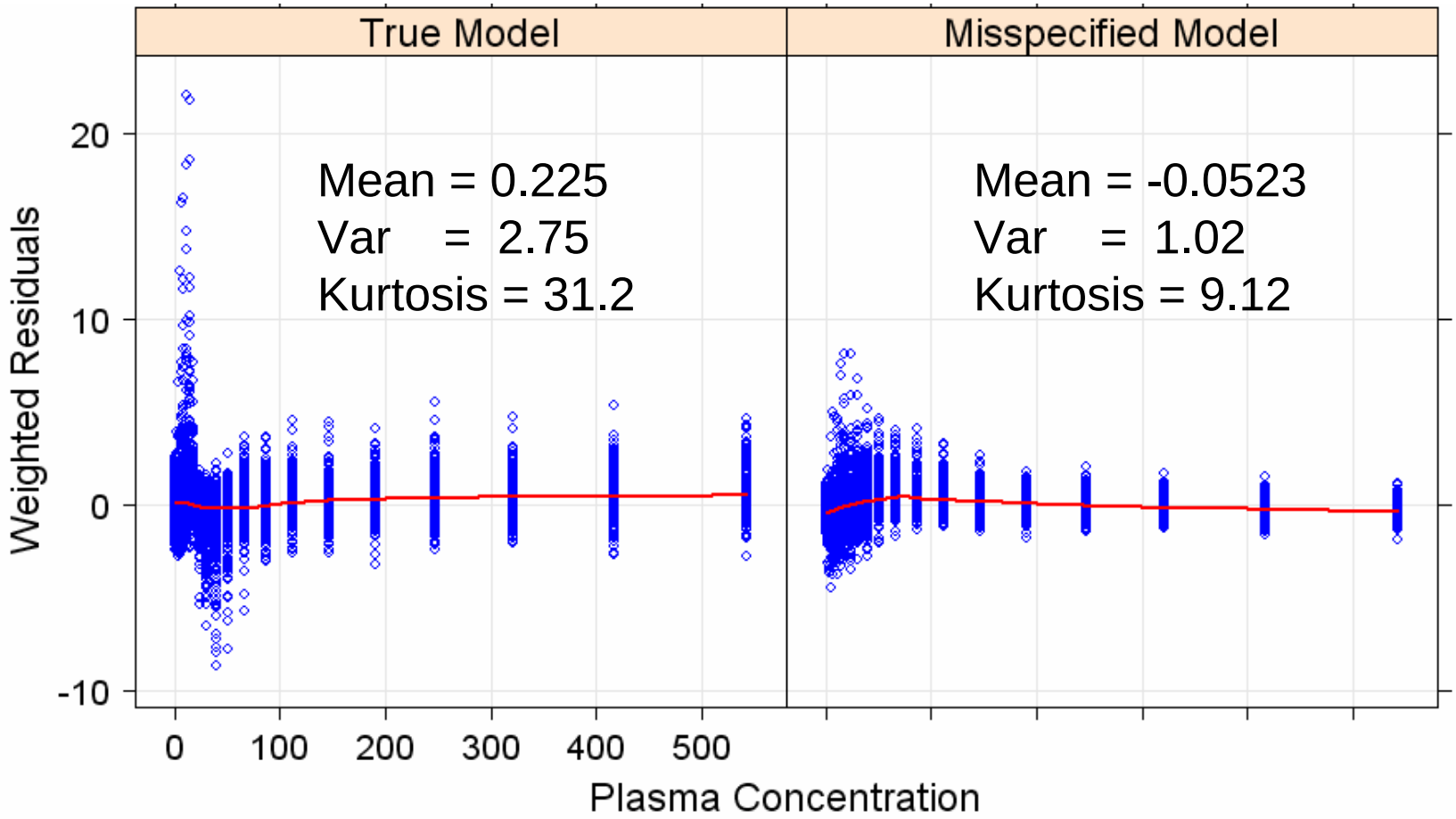
Investigating the CWRES: Model misspecification example

Recall WRES – misspecified model looks better than true model



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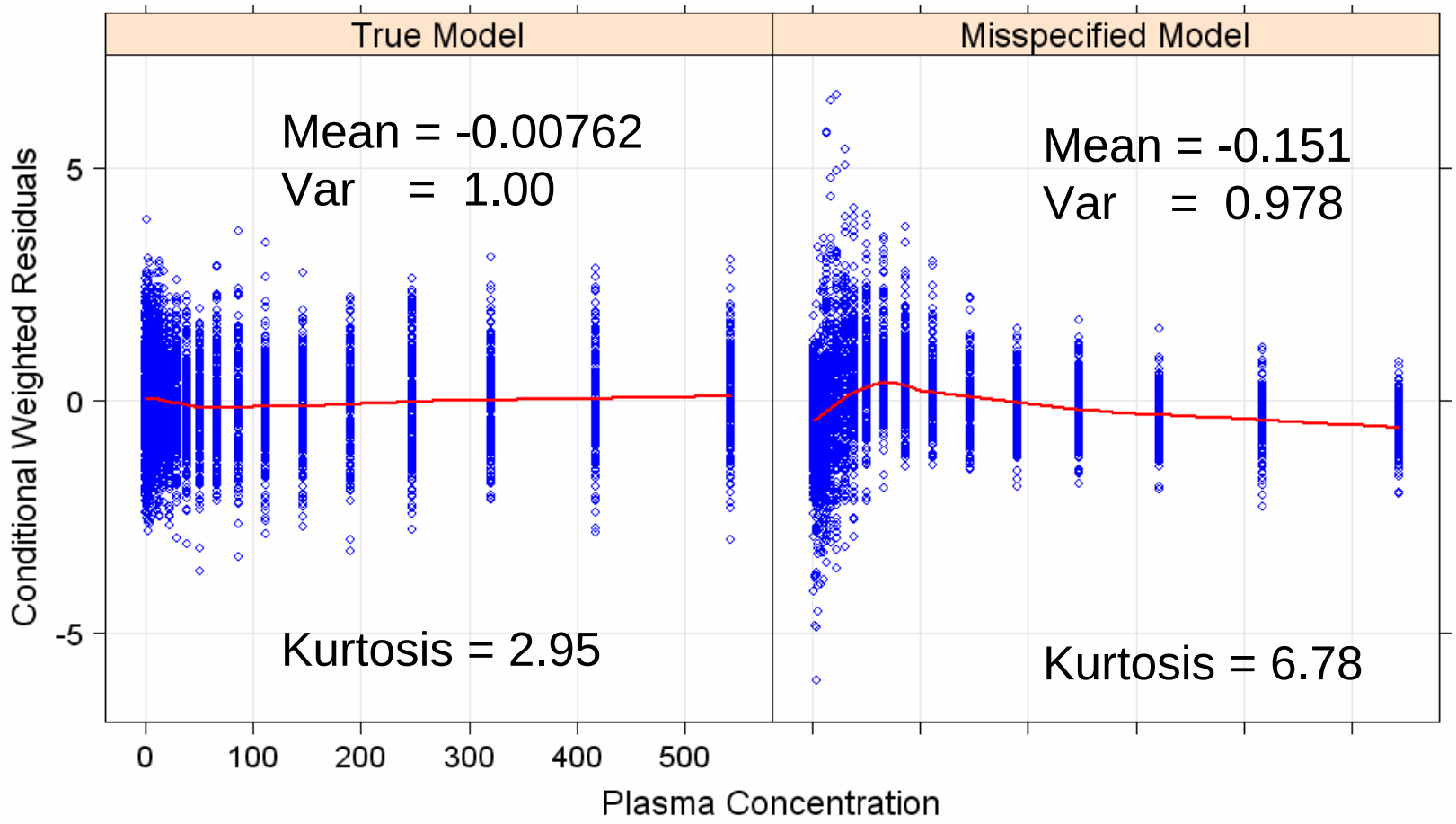
Investigating the CWRES: Model misspecification example

CWRES – indicates that correctly specified model is a better model.



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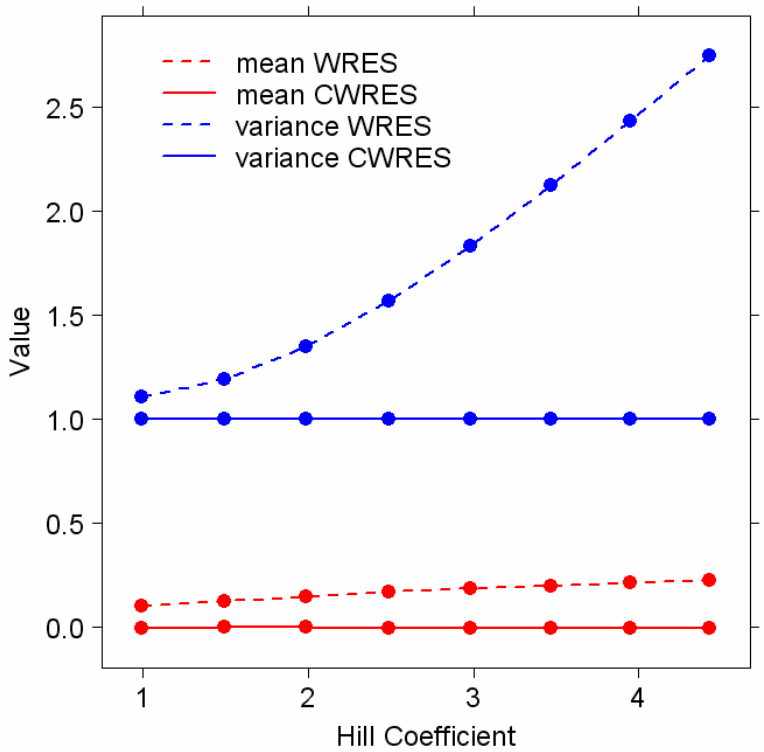
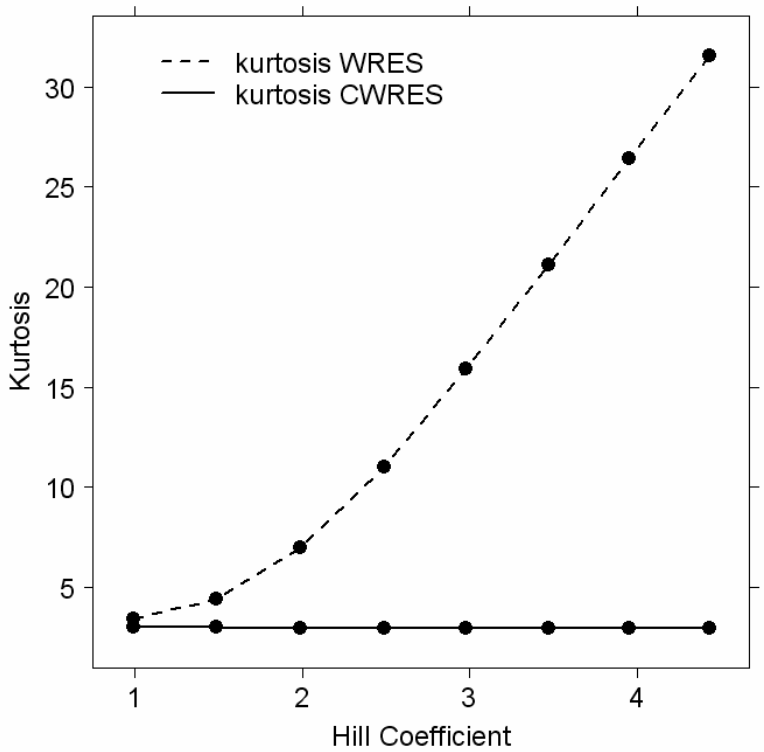
CWRES Properties: When the model is correct

- Simulate and estimate from Sigmoidal Emax model with changing Hill-coefficient.
  - Difference between estimated and true parameters is small (FOCE fit is good).
- CWRES are more normally distributed





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CWRES Properties: CWRES after FO estimation

- CWRES can be computed even in FO, using POSTHOC step in NONMEM
- WRES tells us what is happening in FO

$$OFV_{FO} = \sum_{i=1}^{m} \left[\log \left| \mathbf{Cov}_{FO}(\vec{y}_i) \right| + \frac{\left(\vec{y}_i - E_{FO,i}(f) \right)^2}{\mathbf{Cov}_{FO}(\vec{y}_i)} \right]$$

- CWRES tells us what is happening in FOCE

$$OFV_{FOCE} = \sum_{i=1}^{m} \left[\log \left| \mathbf{Cov}_{FOCE}(\vec{y}_i) \right| + \frac{\left(\vec{y}_i - E_{FOCE,i}(f) \right)^2}{\mathbf{Cov}_{FOCE}(\vec{y}_i)} \right]$$

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CWRES Properties: CWRES after FO estimation

- Many models don't run in FOCE
  - Remember: since 2005, 15% of models in the literature have estimated parameters using FO!

- Can the differences between WRES and CWRES in FO tell us something about the differences between FO and FOCE estimation?

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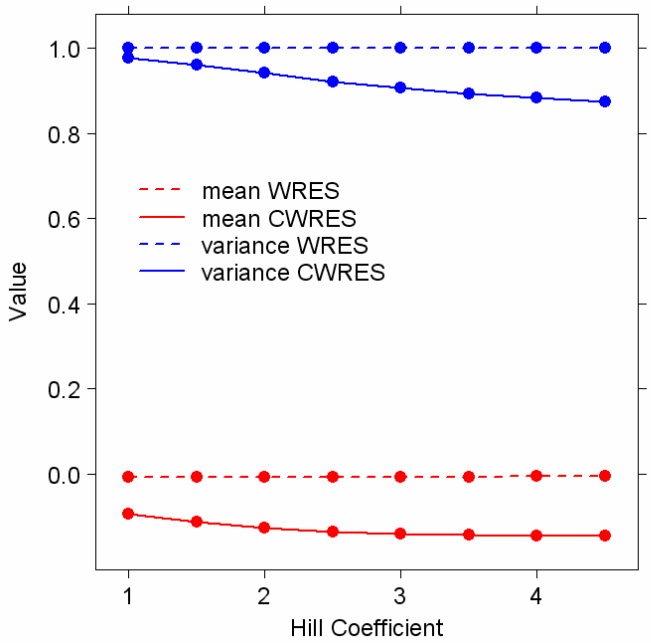
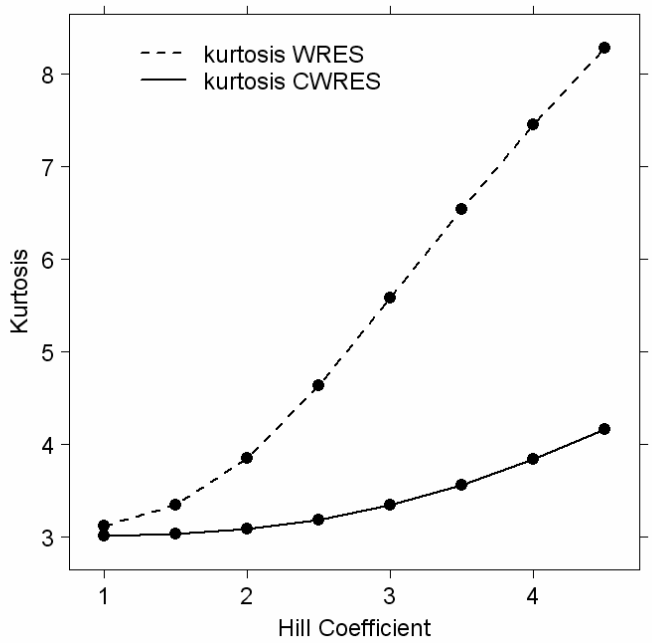
CWRES Properties: CWRES after FO estimation

CWRES and WRES using FO





+ ...

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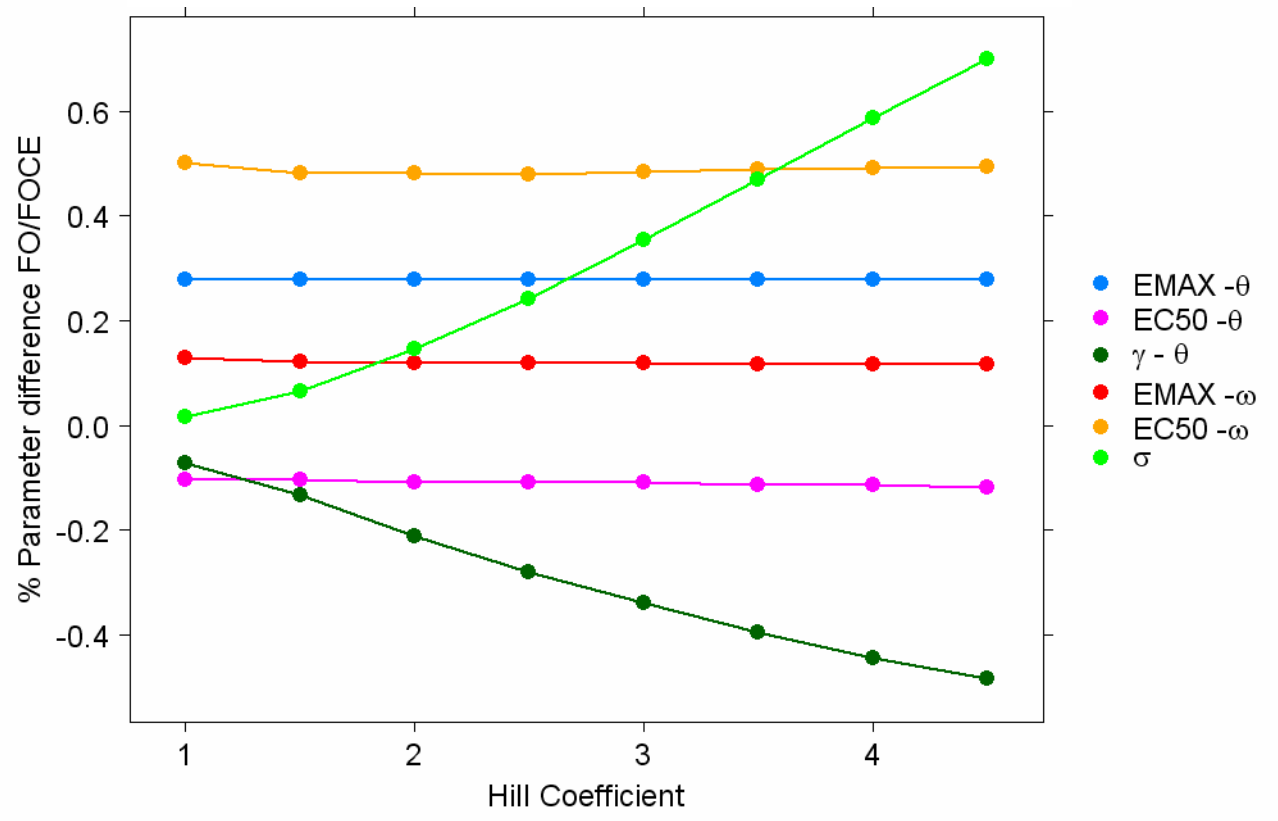
CWRES Properties: CWRES after FO estimation

Percent difference in parameter values between FO and FOCE



Leads to …

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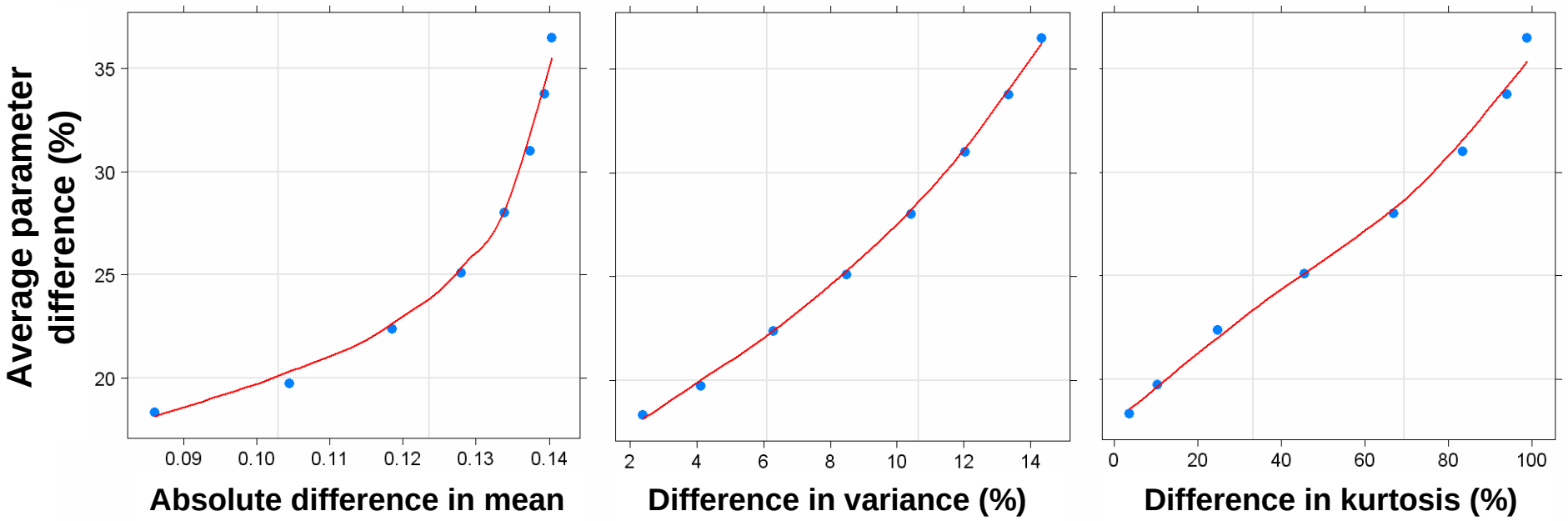
CWRES Properties: CWRES after FO estimation

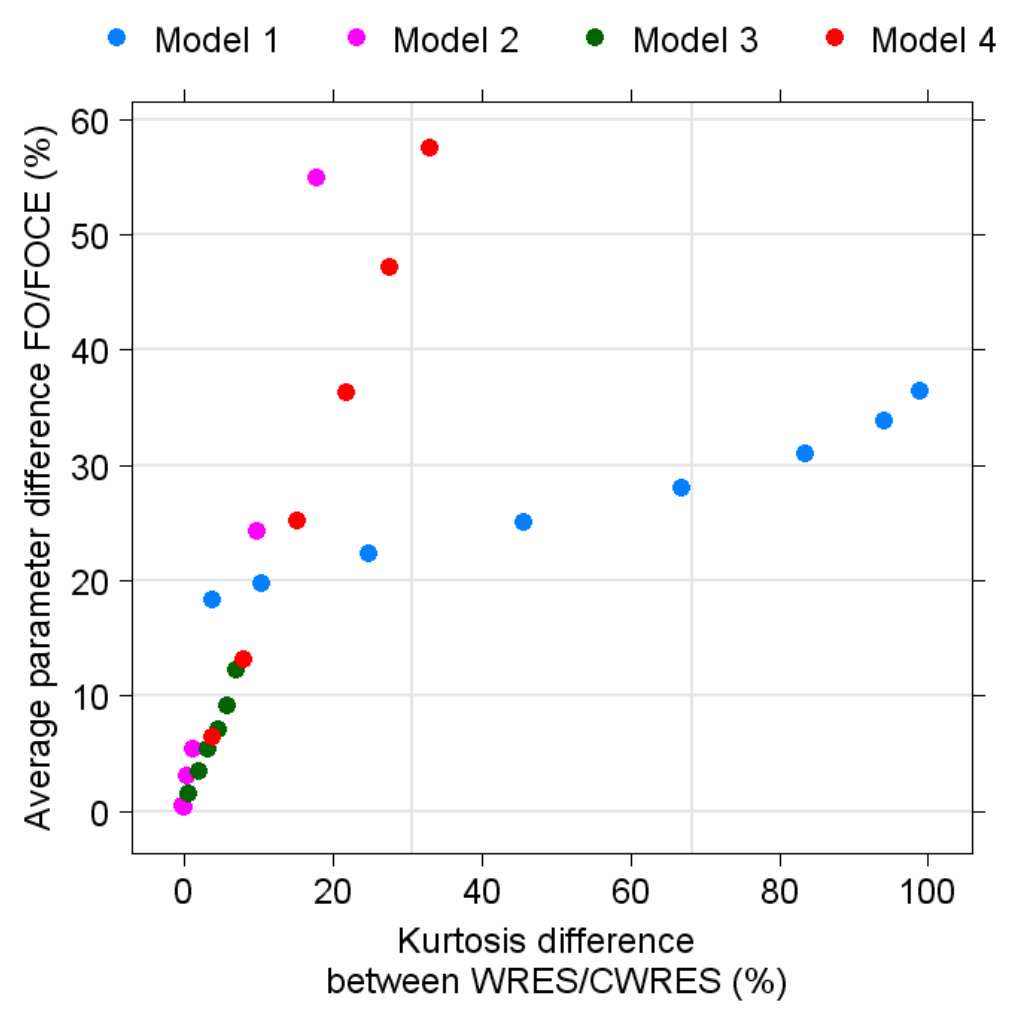
Average % parameter difference
vs.
Difference between WRES and CWRES in FO



CWRES Properties: CWRES after FO estimation

With more models and datasets:

- With large differences between the kurtosis of the WRES and CWRES in FO, parameter values will differ between FO and FOCE.
- With small CWRES/WRES differences, FO/FOCE parameter estimates are similar.



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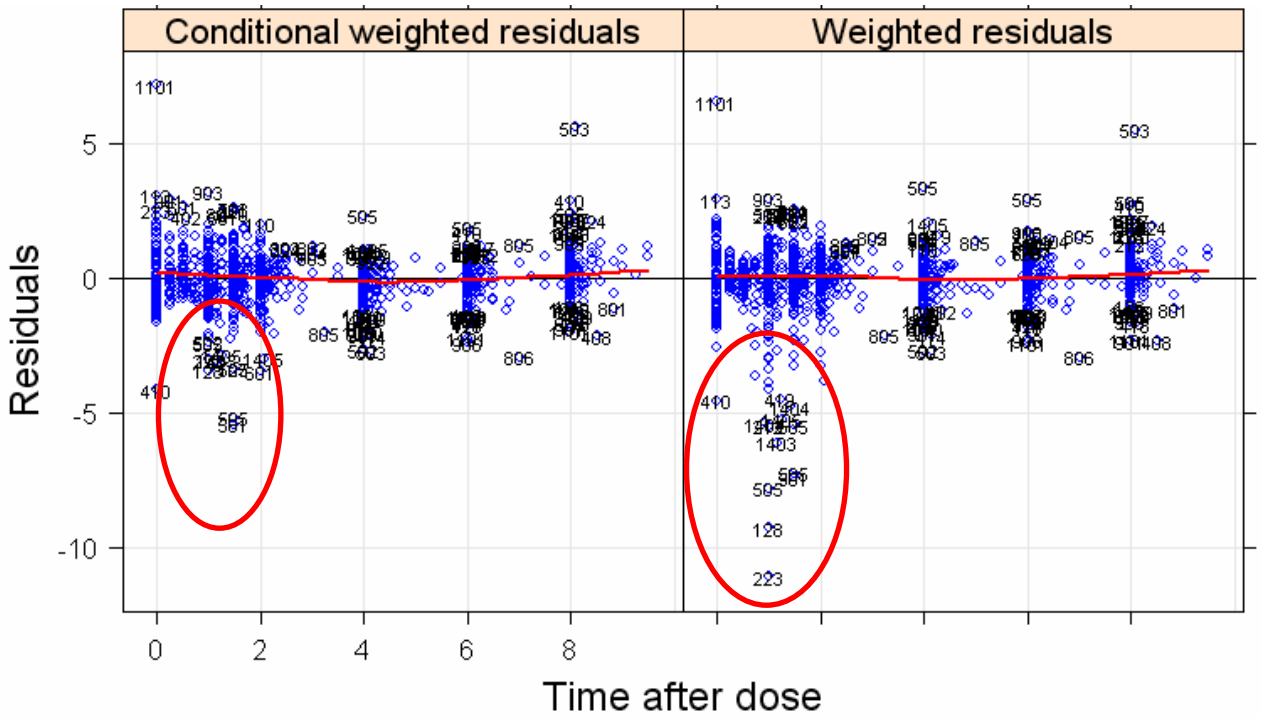
CWRES Properties: Real Data – Moxonidine

- Moxonidine PK data (Karlsson, Jonsson, Wiltse, Wade. J. Pharmacokinet. Biopharm. 1998).
- Transit compartment model (R. Savic, PAGE, 2004).
- CWRES indicate less model misspecification than previously thought from WRES.



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Conclusions

- Utilization of the CWRES could improve model development by giving a more accurate picture of if and when a model is misspecified when using the FOCE approximation.

- CWRES can also *indicate* if the FOCE estimation method will improve the results of an FO model fit to data or not.

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Compute the CWRES yourself!

- Computation of CWRES available in the latest version of Xpose 4
  - Available for free at xpose.sourceforge.net
  - Implemented in R (free from www.r-project.org)
  - Software demonstration at PAGE: www.page-meeting.org/?abstract=1031
- CWRES computation Also available in MATLAB by request

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