Conditional weighted residuals
an improved model diagnostic for the FO/FOCE methods.

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• 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

<table>
<thead>
<tr>
<th>Estimation method</th>
<th>FO</th>
<th>FOCE</th>
<th>FOCE INTER</th>
<th>Combo</th>
<th>Not Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>percentage</td>
<td>15%</td>
<td>21%</td>
<td>28%</td>
<td>16%</td>
<td>20%</td>
</tr>
</tbody>
</table>

50% specifically mentioned examining WRES during model diagnosis
Of those, 80% provided a plot of the WRES
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

\[ E = \frac{E_{\text{max}} C^\gamma}{C^\gamma + C_{50}^\gamma} + \epsilon \]

\[ E_{\text{max}} = \theta_1 e^{n_1} \]

\[ C_{50} = \theta_2 e^{n_2} \]

\[ \gamma = \theta_3 \]

- 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.
Weighted residuals (WRES) – An example...

*Model Misspecification:*
Remove Hill-Coefficient from model and re-estimate

WRES indicate that misspecified model is a better model!
What is going on…

The FO perspective

The FO objective function

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

Expectation and covariance matrix based on FO approximation

\[ E_{FO,i}(f) = f(\tilde{\theta}, 0) \]
\[ \text{Cov}_{FO}(\tilde{y}_i) = \left. \frac{df}{d\tilde{\eta}} \right|_{\tilde{\eta}=0} \cdot \left. \Omega \cdot \frac{df'}{d\tilde{\eta}} \right|_{\tilde{\eta}=0} + \text{diag} \left( \left. \frac{dh}{d\tilde{\epsilon}_i} \right|_{\tilde{\epsilon}_i=0} \cdot \Sigma_i \cdot \left. \frac{dh'}{d\tilde{\epsilon}_i} \right|_{\tilde{\epsilon}_i=0} \right) \]

WRES always calculated this way (even with FOCE)

\[ WRES = \frac{\tilde{y}_i - E_{FO,i}(f)}{\sqrt{\text{Cov}_{FO}(\tilde{y}_i)}} \in N(0, 1) \]
What is going on…

The FOCE perspective

The FOCE objective function

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

Expectation and covariance matrix based on FOCE approximation

\[ E_{FOCE,i}(f) = f(\hat{\theta}, \hat{\eta}_i) - \frac{df}{d\hat{\eta}_i} \bigg|_{\hat{\eta}_i = \hat{\eta}_i} \cdot \hat{\eta}_i \]

\[ \text{Cov}_{FOCE}(\bar{y}_i) = \frac{df}{d\hat{\eta}_i} \bigg|_{\hat{\eta}_i = \hat{\eta}_i} \cdot \Omega \cdot \frac{df'}{d\hat{\eta}_i} \bigg|_{\hat{\eta}_i = \hat{\eta}_i} + \text{diag} \left( \frac{dh}{d\bar{e}_i} \bigg|_{\bar{e}_i = 0} \cdot \Sigma_i \cdot \frac{dh'}{d\bar{e}_i} \bigg|_{\bar{e}_i = 0} \right) \]

These values are NOT the WRES!

\[ \text{CWRES} = \frac{\bar{y}_i - E_{FOCE,i}(f)}{\sqrt{\text{Cov}_{FOCE}(\bar{y}_i)}} \in N(0, 1) \]
Investigating the CWRES: Model misspecification example

*Recall WRES –* misspecified model looks better than true model

<table>
<thead>
<tr>
<th></th>
<th>True Model</th>
<th>Misspecified Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.225</td>
<td>-0.0523</td>
</tr>
<tr>
<td>Var</td>
<td>2.75</td>
<td>1.02</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>31.2</td>
<td>9.12</td>
</tr>
</tbody>
</table>

![Graph showing weighted residuals vs plasma concentration for true model and misspecified model](image-url)
Investigating the CWRES: Model misspecification example

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

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<tr>
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<th>True Model</th>
<th>Misspecified Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-0.00762</td>
<td>-0.151</td>
</tr>
<tr>
<td>Var</td>
<td>1.00</td>
<td>0.978</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>2.95</td>
<td>6.78</td>
</tr>
</tbody>
</table>

Plasma Concentration
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
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

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

- CWRES tells us what is happening in FOCE

\[
OFV_{FOCE} = \sum_{i=1}^{m} \left[ \log|\text{Cov}_{FOCE}(\tilde{y}_i)| + \frac{\left(\tilde{y}_i - E_{FOCE,i}(f)\right)^2}{\text{Cov}_{FOCE}(\tilde{y}_i)} \right]
\]
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?
CWRES Properties:
 CWRES after FO estimation

CWRES and WRES using FO

+ ...
CWRES Properties:
CWRES after FO estimation

Percent difference in parameter values between FO and FOCE

Leads to …
CWRES Properties:
CWRES after FO estimation

Average % parameter difference

vs.

Difference between WRES and CWRES in FO

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.
CWRES Properties: Real Data – Moxonidine

- Transit compartment model (R. Savic, PAGE, 2004).
- CWRES indicate less model misspecification than previously thought from WRES.
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.
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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