Model-based diagnostics post-processing for fast automated model building; show-cased with residual error models and CWRES

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Objective

We propose a new diagnostic tool based on conditional weighted residuals CWRES [1], that scan extended residual variability RUV models and assess in a fast and robust way quantitively whether extensions are needed to implement

The extended RUV models evaluated were [2-4] :

1) Autocorrelated errors AR1 (Eq.2)
2) Dynamic transform both sides dTBS (Eq.3)
3) Interindividual variability IIV on RUV (Eq.4)
4) Power model (Eq.5)
5) T-distributed errors (Eq.6)
6) Time varying error magnitude (Eq.7)

Methods

CWRES are expected to be distributed $N(0,1)$ for a correct model.[1]

CWRES data outputted from the original model execution, were treated as dependent variable DV and modelled by a base model:

$$y_i = \Theta_1 + \eta_{1i} + \varepsilon_{1i} \quad \text{Eq.1}$$

The base model (Eq.1) was then extended with the different RUV models, and used to model CWRES:

$$\text{Corr}(\varepsilon_{1ij},\varepsilon_{1ik}) = \exp(\ (-0.693/\ \Theta_2)\ *(Time_j - Time_k)\ )$$
$$y_i = \Theta_1 + \eta_{1i} + \varepsilon_{1i} \quad \text{Eq.2}$$

$$y_i = \exp(y_i)$$
$$ln(y_i) = \ln(IPRED) + \varepsilon_{1i} * IPRED^{\zeta} \quad \text{if } \lambda=0$$
$$\frac{y_i^{\lambda}-1}{\lambda} = \frac{IPRED^{\lambda}-1}{\lambda} + \varepsilon_{1i} * IPRED^{\zeta} \quad \text{Otherwise} \quad \text{Eq.3}$$

$$y_i = \Theta_1 + \eta_{1i} + \varepsilon_{1i} * \exp(\eta_{2i}) \quad \text{Eq.4}$$

$$y_i = \Theta_1 + \eta_{1i} + \varepsilon_{1i} * IPRED^{\zeta} \quad \text{Eq.5}$$

$$L_{base} = \left(\sqrt{2\pi\sigma^2}\right) \exp(-\frac{IWRES^2}{2})$$
$$L_{t-dist} = \frac{\Gamma(\frac{\upsilon+1}{2})}{\Gamma(\frac{\upsilon}{2}\sqrt{\upsilon\pi\sigma^2})}(1+\frac{IWRES^2}{\upsilon})^{-(\frac{\upsilon+1}{2})} \quad \text{Eq.6}$$

$$y_i = \Theta_1 + \eta_{1i} + \varepsilon_{1i}$$
$$IF(\ Time > break\ point\ time)\ y_i = \Theta_1 + \eta_{1i} + \varepsilon_{2i} \quad \text{Eq.7}$$

Different base models were needed for different transformations (Eq.3 & 6).

ΔOFV_{CWRES} was calculated for each extended RUV model as the difference between CWRES base model (Eq.1) objective function value OFV and extended RUV model OFV.

$\Delta\text{OFV}_{original}$ was calculated by implementing these extended RUV models on the original model (conventional analysis).

The agreement between $\Delta\text{OFV}_{original}$ and ΔOFV_{CWRES} was evaluated in both simulated and real data examples.

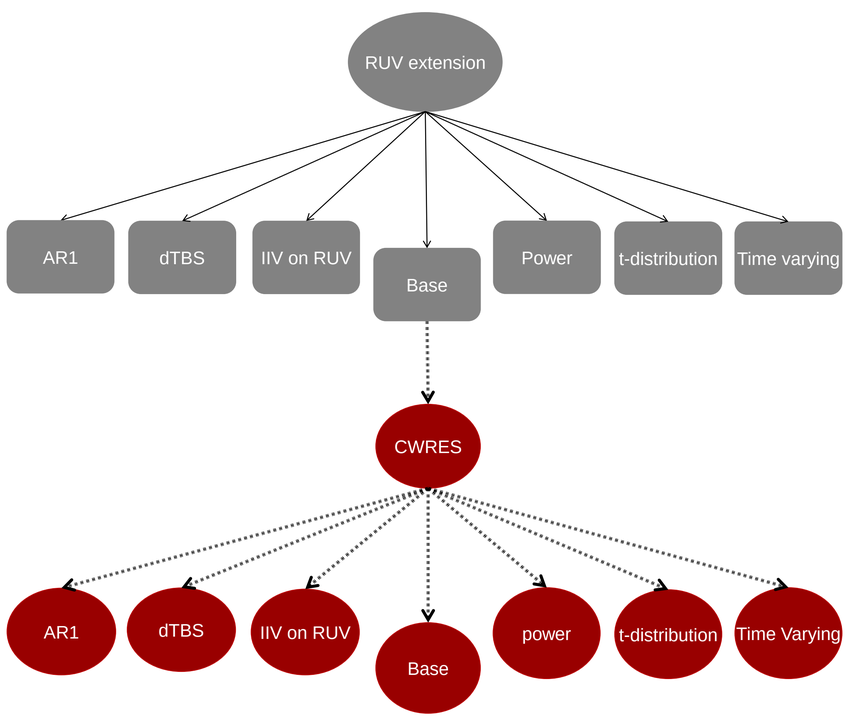

Figure 1: Setup for both simulated and real data examples

Results

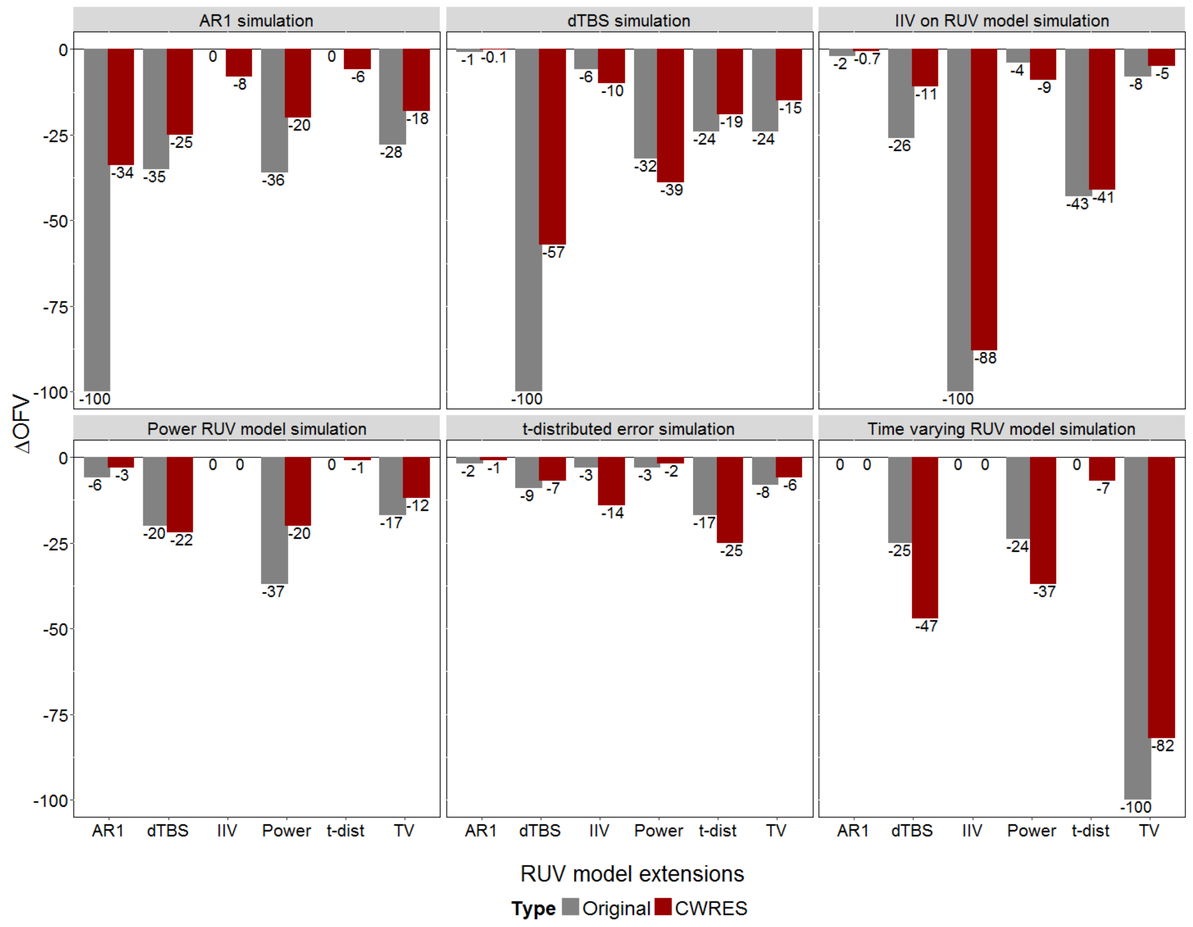

Figure 2:Simulations results

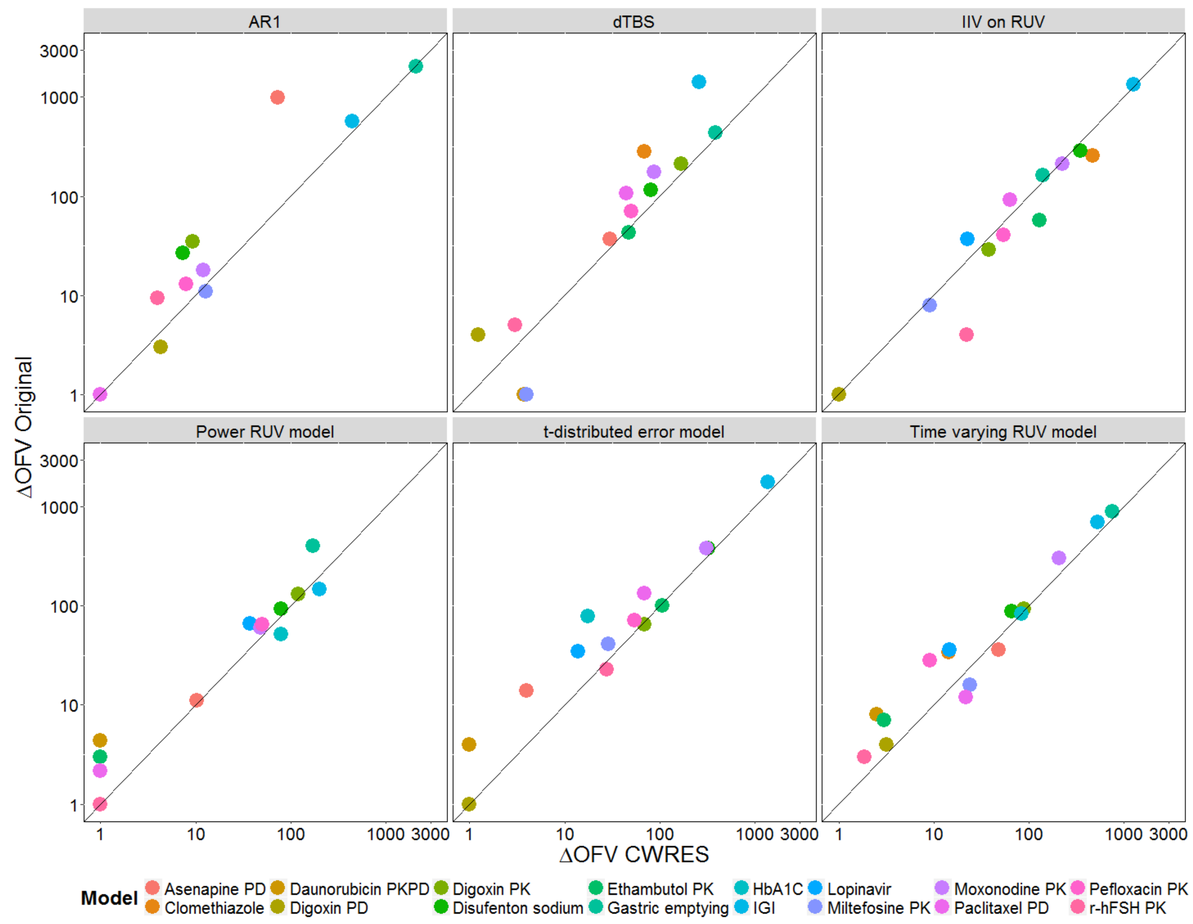

Figure 3: Real data results.

The agreement between $\Delta\text{OFV}_{original}$ and ΔOFV_{CWRES} was high for all 6 RUV extensions (r across all models = 0.88 with an average ratio of ΔOFVs of 0.92).

The typical improvement $\Delta\text{OFV}_{original}$ was substantial across all models with average of -220.

The parameters governing the extended RUV showed good concordance between the estimates obtained in the CWRES and original models, except for dTBS as they are on different scale.

When t-distribution was the most important improvement, IIV on RUV showed inflated ΔOFV_{CWRES}.

Conclusion

- CWRES modelling is a promising easily automated diagnostic tool for model development/evaluation process, as it provides guidance for the nature and magnitude of potential model misspecification/improvements.
- It is extremely fast compared to conventional analysis.
- It can be easily implemented in analysis software and is already implemented as **resmod** tool in **PsN**.

References

[1] Hooker, A. C., Staatz, C. E., & Karlsson, M. O. (2007). Conditional Weighted Residuals (CWRES): A Model Diagnostic for the FOCE Method. Pharmaceutical Research, 24(12), 2187-2197

[2] Karlsson, M. O., Beal, S. L., & Sheiner, L. B. (1995). Three new residual error models for population PK/PD analyses. Journal of Pharmacokinetics and Biopharmaceutics, 23(6), 651-672.

[3] Karlsson, M.O., Jonsson, E. N., Wiltse, C.G & Wade, J.R. (1998). Assumption Testing in Population Pharmacokinetic Models: Illustrated with an Analysis of Moxonidine Data from Congestive Heart Failure Patients. Journal of Pharmacokinetics and Biopharmaceutics, 26(2),207-246.

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