Confidence Intervals for Variability Estimates of Mixed-Effect Models

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OBJECTIVES

Confidence intervals (CIs) for the parameter estimates of mixed-effect models are often reported using the assumption of asymptotic normality. While this assumption is a reasonable approximation for the estimates of fixed effects and off-diagonal elements of the variance-covariance matrix, variances of the random effects are χ^2 distributed. We aim to introduce CIs for variances based on χ^2 distribution (χ^2 CIs), and compare them with the asymptotically normal CIs (nCIs) and CIs obtained by bootstrap (bCIs) and simulation-estimation (sseCIs) procedures on the example of a PK model with high variability and uncertainty of the parameter estimates.

METHODS

Concentrations of 50, 100, 300, or 1000 subjects were simulated from a two-compartment PK model with high inter-individual and moderate or high intra-individual variability (CV=55% for clearance (CL) and central volume (Vc), CV=100% for absorption rate constant (K_a), and CV=20% or 50% for proportional residual variability) for 2 sampling designs (4 or 6 post-dose samples) following a single oral dose. The parameters were estimated for all 16 data sets, and 95% χ2CIs and nCIs were computed for all variance parameters. 95% bCIs and sseCIs from 1000 bootstrap or simulation-estimation samples were also computed. For each estimated variance (ω^2_{CL}, ω^2_{Vc}, ω^2_{Ka}, σ^2), normalized CIs were plotted versus relative standard error (RSE) of the estimates for all datasets and CI methods. The normalized true values were also overlaid.

SIMULATIONS

- Single oral dose
- 2-compartment model, first-order absorption, proportional residual error

Parameter	Value	IIV (ω^2)
CL (L/h)	15	0.3
Vc (L)	60	0.3
Q (L/h)	30	-
Vp (L)	60	-
Ka (h^{-1})	0.5	1
σ^2_{prop}	a. 0.25 b. 0.04	-

- **N subjects:** 50 (only for b.), 100, 300, 1000
- **Sampling:**
  - Design 1: 0, 0.25, 1, 2, 4, 6, 8 h
  - Design 2: 0, 0.25, 1, 4, 8 h

χ^2 CONFIDENCE INTERVALS

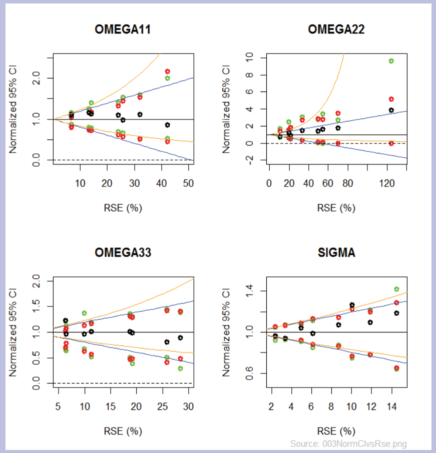
- The degrees of freedom (df) are computed as

$$df = 2/RSE^2$$

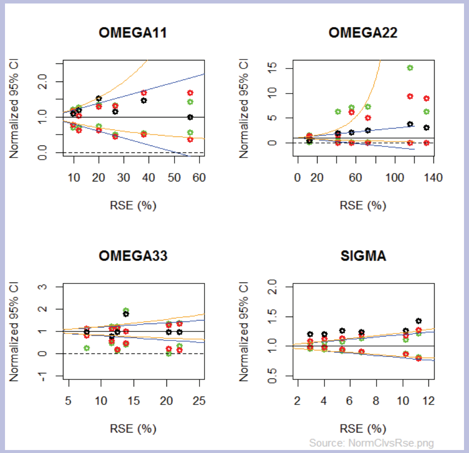
- 100*(1-α)% χ^2CIs for an estimated parameter (ω^2) are computed as

$$\chi^2CI = [\omega^2 * df/\chi^2_{1-\alpha/2},df \;;\; \omega^2 * df/\chi^2_{\alpha/2},df]$$

$\sigma^2 = 0.04$



$\sigma^2 = 0.25$



Points : black (•) – parameter estimates normalized to true values,
green (•) – normalized bootstrap CIs (bCIs),
red (•) – simulation-estimation CIs (sseCIs)

Lines: blue (-) - normalized normal CIs (nCIs)
orange (-) - normalized χ^2 CIs (χ^2 CIs)

RESULTS

χ^2CIs are always shifted up compared to nCIs, but for RSE<20%, the difference is small (<13%). For RSE>50%, the lower bound of nCIs becomes negative while it slowly approaches zero for χ^2CI. The upper bound of χ^2CIs increases steeply after RSE>60% and becomes very wide. bCIs and sseCIs were generally close to each other and were somewhere between nCIs and χ^2CIs, but both of them were sometimes inconsistently wide or narrow in relation to χ^2CIs, nCIs and each other.

CONCLUSIONS

Theoretically correct χ^2-based confidence intervals for estimates of the variance parameters were introduced. Practical applicability of these CIs needs further investigation.