Bootstrap test for variance components in nonlinear mixed effects models

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Introduction

Context:

- hypothesis testing under nonstandard conditions
- usual MLE asymptotic theory not applicable

Motivations: build a procedure

- non asymptotic
- applicable to any type of mixed-effect models (linear, nonlinear)

Mixed effects models

We consider the following nonlinear mixed effects model

$$\begin{cases} y_{ij} = g(x_{ij}, \beta, \Lambda\xi_i) + \varepsilon_{ij} & \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2) \\ \xi_i \sim \mathcal{N}(0, I_p) \end{cases}, \qquad (1)$$

- y_{ij}: the jth response of the ith individual ($i = 1, ..., N; j = 1, ..., J_i$)
- β: vector of fixed effects
- x_{ij}: known covariates
- Λ: lower triangular matrix with nonnegative diagonal coefficients
- $(\xi_i)_i$ and $(\varepsilon_{ij})_{ij}$ are mutually independent
- $y_i = (y_{ij})_{j=1...J_i} \sim f_i(y_i; \theta)$, $y_i|\xi_i \sim f_i(y_i; \xi_i, \theta)$, $\xi_i \sim \pi(\xi_i)$

Variance components testing

Objective: Test the nullity of the last r variances of the scaled random effects $(\Lambda\xi_i)_i$.

$$H_0: \quad \Lambda = \begin{pmatrix} \Lambda_1 & 0 \\ 0 & 0 \end{pmatrix} \qquad H_1: \quad \Lambda = \begin{pmatrix} \Lambda_1 & 0 \\ \Lambda_{12} & \Lambda_2 \end{pmatrix}$$

Likelihood ratio test statistic (lrt):

$$\text{lrt}(y_{1:N}) = -2\left(\sup_{\theta\in\Theta} l(\theta; y_{1:N}) - \sup_{\theta\in\Theta_0} l(\theta; y_{1:N})\right).$$

- Θ: unrestricted parameter space
- Θ_0: restricted parameter space (under H_0)
- $l(\theta; y_{1:N})$: log marginal likelihood

$$l(\theta; y_{1:N}) = \sum_{i=1}^{N} \log\{f_i(y_i; \theta)\} = \sum_{i=1}^{N} \log\{\int f_i(y_i; \xi_i, \theta)\pi(\xi_i)d\xi_i\}$$

Proposed test procedure

Shrinked parametric bootstrap for variance components testing

Input: $c_N > 0$, $B \in \mathbb{N}^*$, $0 < \alpha < 1$
Set: $\beta_N^* = \hat{\beta}_N$, $\Lambda_N^* = \hat{\Lambda}_N$, and ${\sigma_N^*}^2 = \hat{\sigma}_N^2$
Set: $\Lambda_{2,N}^* = \Lambda_{12,N}^* = 0$
Set: $[\Lambda_{1,N}^*]_{mn} = [\hat{\Lambda}_{1,N}]_{mn}\mathbb{1}\left([\hat{\Lambda}_{1,N}]_{mn} > c_N\right)$
for $b = 1, \ldots, B$ **do**
  for $i = 1, \ldots, N$ **do**
    draw independently $\varepsilon_i^{*,b} \sim \mathcal{N}(0, {\sigma_N^*}^2 I_{J_i})$ and $\xi_i^{*,b} \sim \mathcal{N}(0, I_p)$
    build the ith value of the bth bootstrap sample $y_i^{*,b} = g(x_i, \beta_N^*, \Lambda_N^*\xi_i^{*,b}) + \varepsilon_i^{*,b}$
    compute the likelihood ratio statistic $\text{lrt}(y_{1:N}^{*,b})$
  end for
end for
Compute the bootstrap p-value as $p_{boot} = \frac{1}{B}\sum_{b=1}^{B} \mathbb{1}\left(\text{lrt}(y_{1:N}^{*,b}) > \text{lrt}(y_{1:N})\right)$
Reject H_0 if $p_{boot} < \alpha$

Theoretical issues

Boundary issue: $\Lambda_2 = 0 \notin \mathring{\Theta}$
Singularity issue: vanishing score

Example of a linear model with one random effect:

$$\begin{cases} y_{ij} = \lambda\xi_i + \varepsilon_{ij} & \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2) \\ \xi_i \sim \mathcal{N}(0, 1) \end{cases},$$

$$\frac{\partial l(\theta; y_{1:N})}{\partial\lambda}|_{\lambda=0} = \sum_{i=1}^{N} f_i(y_i; \theta)^{-1}\frac{\sum_{j=1}^{J} y_{ij}}{\sigma^2}\int \xi_i\pi(\xi_i)d\xi_i = 0$$

- singularity and boundary issues: sources of inconsistency of the bootstrap procedure
- nuisance parameters: issues cited above occurring at unknown locations

Theoretical results

Notations: $\theta = (\lambda, \delta, \psi)$

λ → tested parameters; δ → nuisance parameters; ψ → remaining parameters

True value: $\theta_0 = (0, 0, \psi_0)$

Theorem: *Under regularity conditions, if θ_N^* is chosen such that $\theta_N^* \in \Theta_0$, $\theta_N^* = \theta_0 + o_p(1)$ and $N^{1/4}\delta_N^* = o_p(1)$ then as $N \to +\infty$, it holds in probability that*

$$pr^*\{\text{lrt}(y_{1:N}^*) \leq t\} \longrightarrow pr(\text{lrt}_\infty \leq t).$$

How to choose the bootstrap parameter $\theta_N^* = (\lambda_N^*, \delta_N^*, \psi_N^*)$?

Proposition: *Let $(c_N)_{N\in\mathbb{N}}$ be a sequence such that $\lim_{N\to+\infty} c_N = 0$ and $\lim_{N\to+\infty} N^{\frac{1}{4}}c_N = +\infty$. Let $\hat{\theta}_N = (\hat{\psi}_N, \hat{\delta}_N, \hat{\lambda}_N)$ be the MLE of θ_0.*

Under regularity conditions if

- $\forall k = 1, .., d_\psi$ $\psi_{N,k}^* = \hat{\psi}_{N,k}\,\mathbb{1}(\hat{\psi}_{N,k} > c_N)$
- $\forall k = 1, .., d_\delta$ $\delta_{N,k}^* = \hat{\delta}_{N,k}\,\mathbb{1}(\hat{\delta}_{N,k} > c_N)$
- $\lambda_N^* = 0_{d_\lambda}$

then θ_N^* verifies the hypothesis of the main theorem.

Simulations study

Small sample properties:

Test that one variance is null in a linear model with two random effects

Level α	$N=10$		$N=20$		$N=30$		$N=40$		$N=100$		max sd
	boot	asym	boot	asym	boot	asym	boot	asym	boot	asym	
1%	1.14	0.68	0.98	0.68	1.20	0.94	0.74	0.70	0.86	0.72	0.15
5%	5.20	3.64	5.22	3.82	5.74	4.30	4.86	3.94	5.26	4.50	0.33
10%	10.72	7.16	10.80	7.98	10.30	8.40	10.80	8.44	10.34	8.86	0.44

Table 1. Empirical levels (in %) for $K = 5000$ simulated datasets and $B = 500$

Test that one variance is null in a nonlinear model with three random effects (logistic model)

Level α	boot	asym	max sd
1%	0.80	0.80	0.28
5%	5.10	3.60	0.70
10%	10.30	7.00	0.96

Table 2. Empirical levels (in %) for $K = 1000$ datasets of size $N = 40$ and $B = 300$.

Effect of the shrinkage in presence of nuisance parameters:

Test that one variance is null in a linear model with 8 random effects

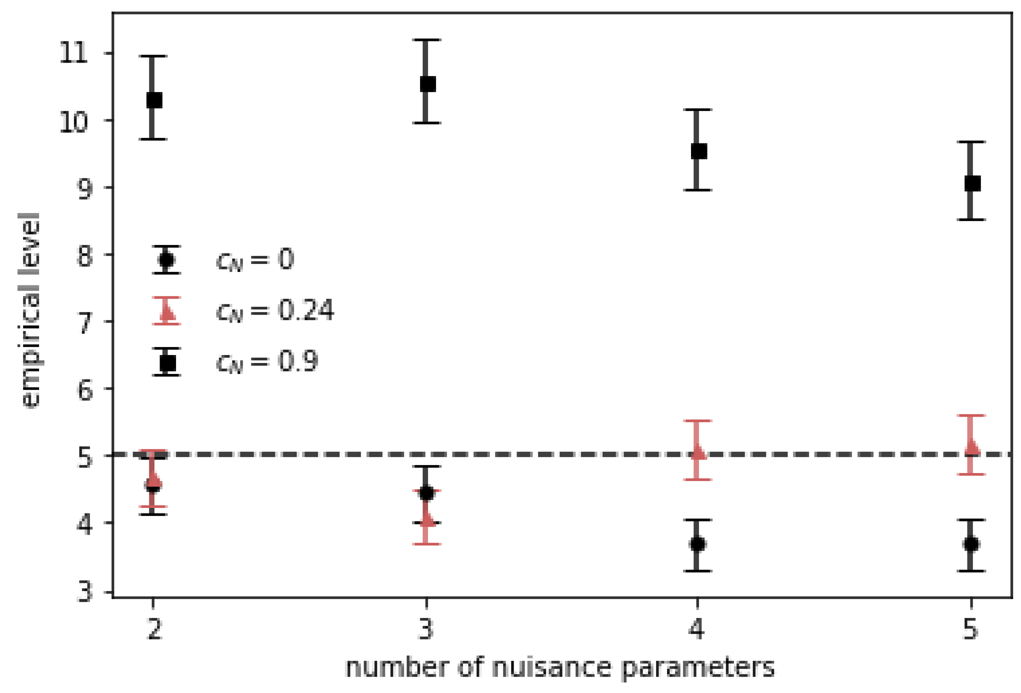

Figure 1. Empirical levels (in %) for $K = 2500$ datasets of size $N = 30$ and $B = 300$

Conclusion

Contributions: a test procedure

- with good small samples properties
- robust to nuisance parameters
- applicable to any type of mixed effects models

Perspectives:

- choice of c_N
- efficient computation of $\text{lrt}(y_{1:N})$

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