# 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 $j$th response of the $i$th individual ($i = 1, ..., N; j = 1, ..., J_i$)
- $\beta$: vector of fixed effects
- $x_{ij}$: known covariates
- $\Lambda$: 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):**

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

- $\Theta$: unrestricted parameter space
- $\Theta_0$: 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 ${\sigma^*_N}^2 = \hat{\sigma}^2_N$
**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 $\varepsilon^{*,b}_i \sim \mathcal{N}(0, {\sigma^*_N}^2 I_{J_i})$ and $\xi^{*,b}_i \sim \mathcal{N}(0, I_p)$
    build the $i$th value of the $b$th bootstrap sample $y^{*,b}_i = g(x_i, \beta^*_N, \Lambda^*_N\xi^{*,b}_i) + \varepsilon^{*,b}_i$
    compute the likelihood ratio statistic $\mathrm{lrt}(y^{*,b}_{1:N})$
  **end for**
**end for**
Compute the bootstrap $p$-value as $p_{boot} = \frac{1}{B}\sum_{b=1}^{B} \mathbb{1}\left(\mathrm{lrt}(y^{*,b}_{1:N}) > \mathrm{lrt}(y_{1:N})\right)$
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:**

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

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

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

## Theoretical results

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

$\lambda$ → tested parameters; $\delta$ → nuisance parameters; $\psi$ → remaining parameters

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

***Theorem:*** *Under regularity conditions, if $\theta^*_N$ 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*

$$pr^*\{\mathrm{lrt}(y^*_{1:N}) \le t\} \longrightarrow pr(\mathrm{lrt}_\infty \le t).$$

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 $\theta_0$.*

*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 $\theta^*_N$ 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 $\alpha$ | $N=10$ | | $N=20$ | | $N=30$ | | $N=40$ | | $N=100$ | | 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 $\alpha$ | 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

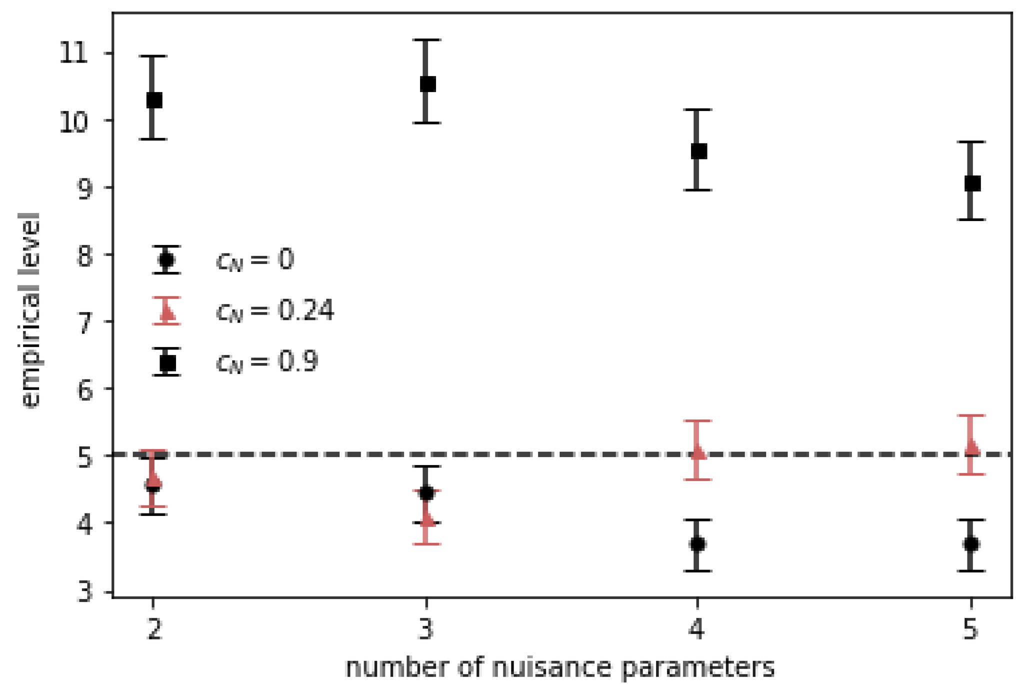


Figure 1. Empirical levels (in %) for $K = 2500$ datasets of size $N = 30$ and $B = 300$

## 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 $\mathrm{lrt}(y_{1:N})$

## References

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[3] G. Cavaliere, H. B. Nielsen, and A. Rahbek. On the consistency of bootstrap testing for a parameter on the boundary of the parameter space. *Journal of Time Series Analysis*, 38(4):513–534, 2017.