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A studentized permutation test for the treatment effect in individual participant data meta-analysis

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MOTIVATION

- Meta-analysis can be performed on the basis of aggregate data or **individual participant data (IPD)**.
- For continuous outcome, assume a **linear mixed model (LMM)**.

EXAMPLE (KAMBIC ET AL., 2024)

- IPD MA on the safety and efficacy of exercise training on exercise capacity (e.g., six-minute walk test distance) and quality of life compared to standard care in left ventricular asssist device patients.
- 4 studies, each ranges from 14 to 54 patients.

→ Test and confidence intervals for the treatment effect based on the asymptotic normal distribution might not well control the Type I error rate.

…Satterthwaite's approach and Kenward-Roger's approach might be conservative.

→ Permutation tests might be useful.

MODEL (RILEY ET AL., 2013)

- Consider model:

stratified by study
random effect
treatment effect
residual variance

$$y_{ij} = \beta_{0i} + \beta_{1i} y_{0ij} + u_i z_{ij} + \varepsilon_{ij}, \; u_i \sim N(\theta, \tau^2), \qquad \varepsilon_{ij} \sim N(0, \sigma_i^2),$$

outcome
baseline value
group indicator (binary)
residual
between-study heterogeneity

- k: number of studies. study index: $i = 1, \dots, k$. study size: n_i. subject index: $j = 1, \dots, n_i$.
- β_{0i} and β_{1i} can be set random.

MODEL (MATRIX NOTATION)

$(y_{11}, \dots, y_{1n_1}, \dots, y_{k1}, \dots, y_{kn_k})^\top$ $\quad (u_1, \dots, u_k)^\top$ $\quad (\varepsilon_{11}, \dots, \varepsilon_{1n_1}, \dots, \varepsilon_{k1}, \dots, \varepsilon_{kn_k})^\top$ $\quad diag(\sigma_1^2, \dots, \sigma_1^2, \dots, \sigma_k^2, \dots, \sigma_k^2)$

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Zu} + \boldsymbol{\varepsilon},\ \boldsymbol{u} \sim N(\theta \mathbf{1}_k, \tau^2 \boldsymbol{I}_k), \boldsymbol{\varepsilon} \sim N(\mathbf{0}, \boldsymbol{R}), \tag{8}$$

$$\begin{pmatrix}
1 & 0 & \cdots & 0 & y_{011} & 0 & \cdots & 0 \\
\vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots \\
1 & 0 & & \vdots & y_{01n_1} & 0 & & \vdots \\
0 & 1 & & \vdots & 0 & y_{021} & & \vdots \\
\vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots \\
\vdots & 1 & & \vdots & \vdots & y_{02n_2} & & \vdots \\
\vdots & 0 & & \vdots & \vdots & 0 & & \vdots \\
\vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots \\
\vdots & \vdots & & 0 & \vdots & \vdots & & 0 \\
\vdots & \vdots & & 1 & \vdots & \vdots & & y_{0k1} \\
\vdots & \vdots & & \vdots & \vdots & \vdots & & \vdots \\
0 & 0 & \cdots & 1 & 0 & 0 & \cdots & y_{0kn_k}
\end{pmatrix}$$

$$(\beta_{01}, \dots, \beta_{0k}, \beta_{11}, \dots, \beta_{1k})^\top$$

$$\begin{pmatrix}
z_{011} & 0 & \cdots & 0 \\
\vdots & \vdots & & \vdots \\
z_{01n_1} & 0 & & \vdots \\
0 & z_{021} & & \vdots \\
\vdots & \vdots & & \vdots \\
\vdots & z_{02n_2} & & \vdots \\
\vdots & 0 & & \vdots \\
\vdots & \vdots & & \vdots \\
\vdots & \vdots & & 0 \\
\vdots & \vdots & & z_{0k1} \\
\vdots & \vdots & & \vdots \\
0 & 0 & \cdots & z_{0kn_k}
\end{pmatrix}$$

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ESTIMATION & INFERENCE

$$\rightarrow \boldsymbol{Y} \sim N(\boldsymbol{X\beta} + \theta \boldsymbol{Z1}_k, \tau^2 \boldsymbol{ZZ}^\top + \boldsymbol{R})$$

- Approach: maximum likelihood, **restricted maximum likelihood (REML)**.
- No closed-form expressions for estimators.
- Maximize the restricted likelihood function using iterative algorithms.
- **Interest in estimation and inference on the treatment effect $\boldsymbol{\theta}$ (testing $\boldsymbol{\theta = 0}$).**

STANDARD APPROACHES

- Asymptotic normal distribution:

$$t = \frac{\theta}{\widehat{se}(\hat{\theta})} \sim N(0,1), \qquad CI_N = \hat{\theta} \pm z_{1-\alpha/2}\,\widehat{se}(\hat{\theta})$$

- Student-t distribution:

degree of freedom

$$t \sim T_{df}, \qquad CI_T = \hat{\theta} \pm t_{1-\frac{\alpha}{2},df}\,\widehat{se}(\hat{\theta})$$

Pinheiro's method (Pinheiro, 2000): df = $\sum_i n_i - 2k$

Satterthwaite's method (Giesbrecht and Burns, 1985) and **Kenward & Roger's method** (Kenward and Roger, 1997): df = $2\left[\widehat{var}(\hat{\theta})\right]^2/\widehat{var}\left[\widehat{var}(\hat{\theta})\right]$

- **Kenward & Roger's method** modifies $\widehat{se}(\hat{\theta})$ to account for the biasness in $\widehat{cov}(\hat{\beta},\hat{\theta})$.

PROS & CONS

- Normal-based approach and Pinheiro's approach cannot control Type I error rate (Riley et al., 2021).
- Satterwaite's approach and Kenward & Roger's approach might be conservative in IPD MA (Legha et al., 2018).
- All the above approaches are with distributional assumption.
- **Resampling approaches and permutation approaches are well-known for controlling Type I error, even for small data. → Might be useful.**

PROPOSED METHODS - IDEA

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Zu} + \boldsymbol{\varepsilon},\ \boldsymbol{u} \sim N(\theta\mathbf{1}_k, \tau^2\boldsymbol{I}_k), \boldsymbol{\varepsilon} \sim N(\mathbf{0}, \boldsymbol{R})$$

center **u**

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Z}(\theta\mathbf{1}_k + \boldsymbol{u}_0) + \boldsymbol{\varepsilon},\ \boldsymbol{u}_0 \sim N(\mathbf{0}, \tau^2\boldsymbol{I}_k)$$

separate fix effects from random effects

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Z}\theta\mathbf{1}_k + (\boldsymbol{Zu}_0 + \boldsymbol{\varepsilon}\ )$$

define new residuals

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Z}\theta\mathbf{1}_k + \boldsymbol{\varepsilon}_0,$$

where $\boldsymbol{\varepsilon}_0 = \boldsymbol{Zu}_0 + \boldsymbol{\varepsilon}$ and $\sim N\left(\mathbf{0}, \boldsymbol{\Sigma}_{\boldsymbol{\varepsilon}_0} = \tau^2\boldsymbol{ZZ}^\top + \boldsymbol{R}\right)$.

PROPOSED METHODS – IDEA (CONT.)

Under H_0: $\theta = 0$,

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{\varepsilon}_0$$
$$\rightarrow \boldsymbol{\varepsilon}_0 = \boldsymbol{Y} - \boldsymbol{X\beta} \qquad (7)$$

Impossible to permute ε_{0ij}'s since they are not **exchangeable** as $\boldsymbol{\Sigma}_{\varepsilon_0}$.

Solution (standardization):

Let **W** is an upper triangle matrix such that $\boldsymbol{\Sigma}_{\varepsilon_0} = \boldsymbol{W}^\top \boldsymbol{W}$ (Cholesky's decomposition).

So

$$\tilde{\boldsymbol{\varepsilon}} = (\boldsymbol{W}^\top)^{-1} \boldsymbol{\varepsilon}_0 \sim N(\boldsymbol{0}, \boldsymbol{I})$$

$\rightarrow$ $\tilde{\varepsilon}_{ij}$'s (asymptotic) exchangeable $\rightarrow$ **permute** $\tilde{\varepsilon}_{ij}$'s, **not** ε_{0ij}'s (first proposed in Lee & Braun, 2012).

PROPOSED PERMUTATION TEST

Table 1: Pseudo code for the proposed studentized permutation test, generating a permutation distribution of t-statistic values.

1. Fit Model (7) to the response $\boldsymbol{Y}$ and compute t-statistic $t = \hat{\theta}/\widehat{\text{se}}(\hat{\theta})$.
2. Fit Model (8) to the response $\boldsymbol{Y}$ and compute the standardized error $\hat{\tilde{\varepsilon}} = (\hat{\boldsymbol{W}}^{\top})^{-1}(\boldsymbol{Y} - \boldsymbol{X}\hat{\beta})$, where $\hat{\boldsymbol{W}}$ is the Cholesky decomposition of $\hat{\boldsymbol{\Sigma}}_{\varepsilon_0} = \hat{\tau}^2\boldsymbol{Z}\boldsymbol{Z}^{\top} + \hat{\boldsymbol{R}}$.
3. For permutation $p = 1, \cdots, N$,
   - Permute $\hat{\tilde{\varepsilon}}$ as $\hat{\tilde{\varepsilon}}_{(p)}$ and compute the permuted response $\boldsymbol{Y}_{(p)} = \boldsymbol{X}\hat{\beta} + \hat{\boldsymbol{W}}^{\top}\hat{\tilde{\varepsilon}}_{(p)}$.
   - Refit Model (7) to $\boldsymbol{Y}_{(p)}$ and compute t-statistic $t_{(p)} = \hat{\theta}_{(p)}/\widehat{\text{se}}(\hat{\theta}_{(p)})$.

PROPOSED CONFIDENCE INTERVALS

- Quantile-based confidence interval:

$$CI_{p1} = \left[\hat{\theta} - t^*_{1-\frac{\alpha}{2}} se(\hat{\theta}); \hat{\theta} - t^*_{\frac{\alpha}{2}} se(\hat{\theta})\right]$$

- Simple but may not well control Type I error when $\theta \neq 0$.
- Search-based confidence interval:
  - Idea: confidence bounds are the closest values to $\hat{\theta}$ such that they are just significantly different from θ (Follmann & Proschan, 1999).

→ Search for values θ_0 closest to $\hat{\theta}$ and perform permutation test $H_0: \theta = \theta_0$ until the test significant.

  - Let $\tilde{\theta} = \theta - \theta_0$,

$$H_0: \theta = \theta_0 \Leftrightarrow H_0: \tilde{\theta} = 0,$$

PROPOSED CONFIDENCE INTERVALS

- Search-based confidence intervals:

$$CI_{p2} = [\theta_{lower}, \theta_{upper}]$$

- Idea: θ_{lower} and θ_{upper} are the closest values to $\hat{\theta}$ such that they are just significantly different from θ (Follmann & Proschan, 1999).

→ Search for values θ_0 closest to $\hat{\theta}$ and perform permutation test $H_0: \theta = \theta_0$ until the test significant.

- Let $\tilde{\theta} = \theta - \theta_0$,

$$H_0: \theta = \theta_0 \Leftrightarrow H_0: \tilde{\theta} = 0,$$

→ Analogous to Table (1).

- Better control Type I error rate, but computationally expensive!!!

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PROPOSED CONFIDENCE INTERVALS

Table 2: Pseudo code for constructing the upper bound of the search- and permutation-based $100\%(1-\alpha)$ confidence interval. Construction of the lower bound works analogously.

For $\theta_{0i} = i \times (b-a)/(M-1), i = 1, \cdots, M$, where M denotes the number of grid points in $[a;b], b \geq a \geq \hat{\theta}$,

1. Compute $\boldsymbol{Y}_{\theta_{0i}} = \boldsymbol{Y} - \theta_{0i}\boldsymbol{Z}\mathbf{1}_k$.
2. Replace $\boldsymbol{Y}$ with $\boldsymbol{Y}_{\theta_{0i}}$ and perform steps 1-3 in Table 1.
3. Compute p-value for the test $H_0 : \theta = \theta_0$ vs. $H_1 : \theta < \theta_0$,:
   p-value $= 1 - \sum_{p=1}^{N} \mathbb{1}(t_{(p)} \geq t)/N$.
4. If p-value $\leq \alpha/2$, stop and return $\theta_{upper} := \theta_{0i}$.

SIMULATION SETTING

1. Simulate data from Model (8)

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Zu} + \boldsymbol{\varepsilon},\ \boldsymbol{u} \sim N(\theta \mathbf{1}_k, \tau^2 \boldsymbol{I}_k), \boldsymbol{\varepsilon} \sim N(\mathbf{0}, \boldsymbol{R}),$$

2. Fit Model (8) assuming σ_i are the equal.

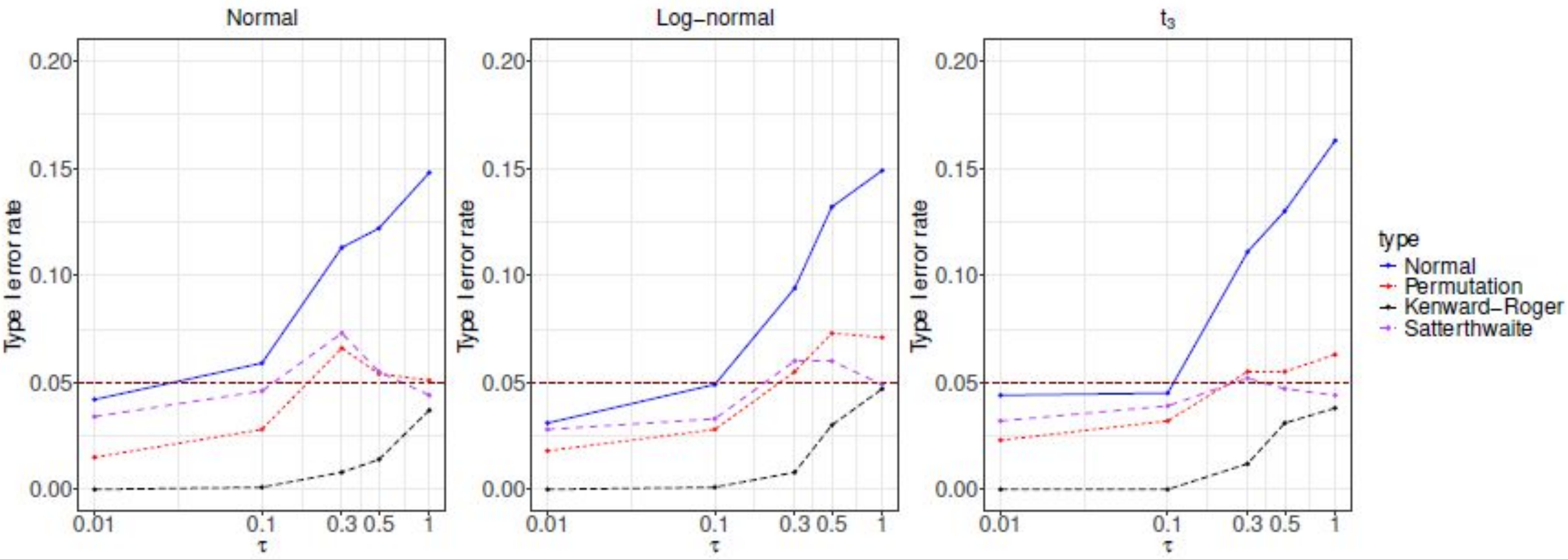
3. Compare tests and CIs based on: the proposed methods, Normal distribution, Satterthwaite‘s approach, and Kenward & Roger‘s approach.

SIMULATION SETTING

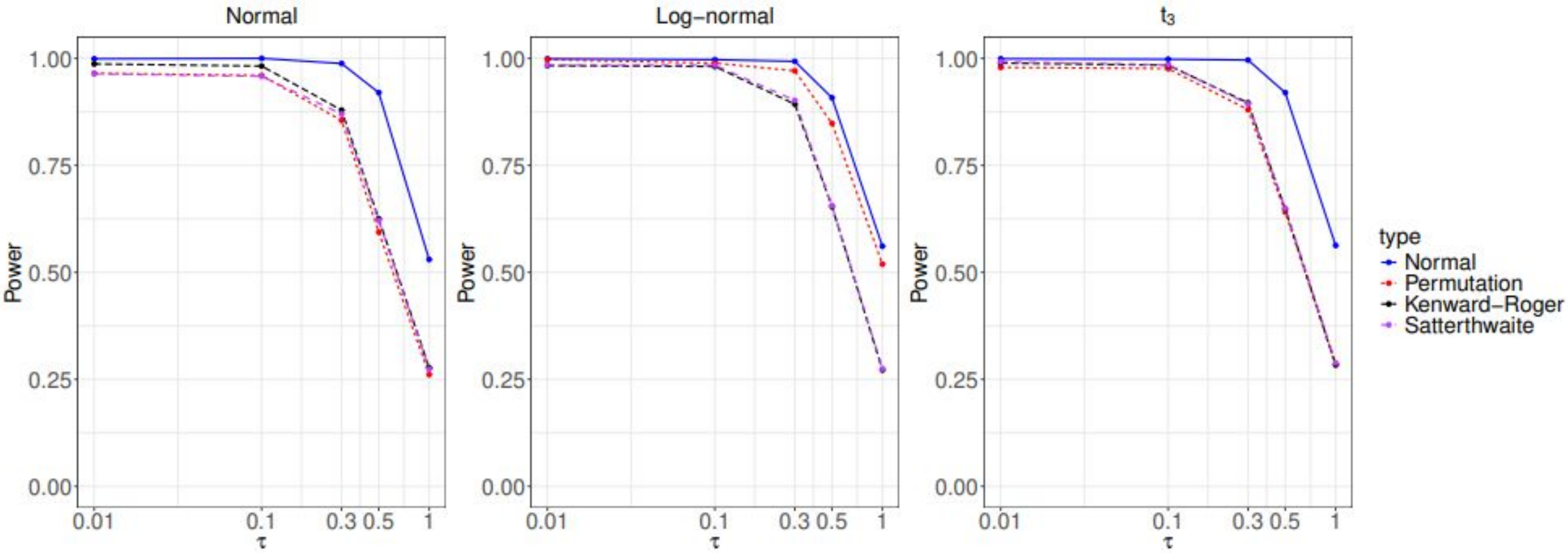
Table 3: Parameter settings for the simulations discussed in Section 4.

parameter		settings
number of studies	k	4
study size	n_i	medium: Unif(100, 200), small: Unif(30, 100), very small: 0.8 Unif(15, 30) + 0.2 Unif(30, 100)
treatment allocation	p_i	Unif(0.5, 0.7)
intercepts	β_{0i}	$(0.9, 2.3, 0.3, 0.1)^\top$
slopes	β_{1i}	$(0.8, 0.7, 0.9, 0.9)^\top$
treatment effect	θ	$\{0, 1\}$
heterogeneity	τ	$\{0.01, 0.1, 0.3, 0.5, 0.7, 1.0\}$
residual s.d.	σ_i	$1, (0.9, 0.9, 0.9, 1.4)^\top$
baseline value	y_{0ij}	Normal(4, 1)
residuals	ϵ_{ij}	Normal, Student-t_3, log-Normal
permutations	N	10 000 (permutation test, CI_{p1}), 2 000 (2nd permutation, CI_{p2})

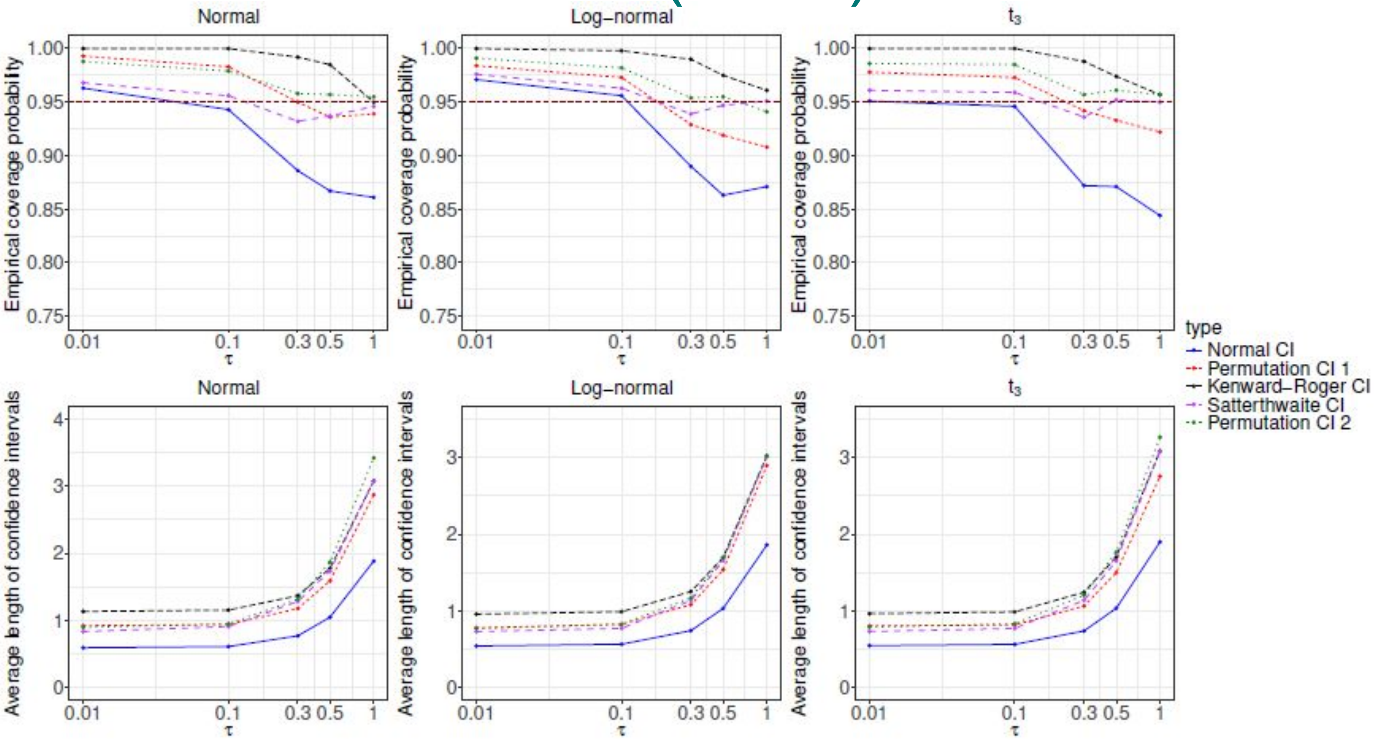
SIMULATION RESULTS



SIMULATION RESULTS (cont.)



SIMULATION RESULTS (cont.)



SUMMARY

- Proposed a studentized permutation test and two permutation-based confidence intervals for the treatment effect in IPD MA of continuous outcomes, assuming the exchangeability of the standardized residuals.
- Future work:
  - ❖ Analytical proof due the lack of a closed-form expression for the effect estimator when variance components are unknown.
  - ❖ Reduce the computational expense of the search-based confidence interval method.
  - ❖ Straightforward to extend the proposed method to cases when there is more than one random effect. About extension of the proposed method to other types of outcomes.

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THANK YOU

Preprint:
http://arxiv.org/abs/2505.24774

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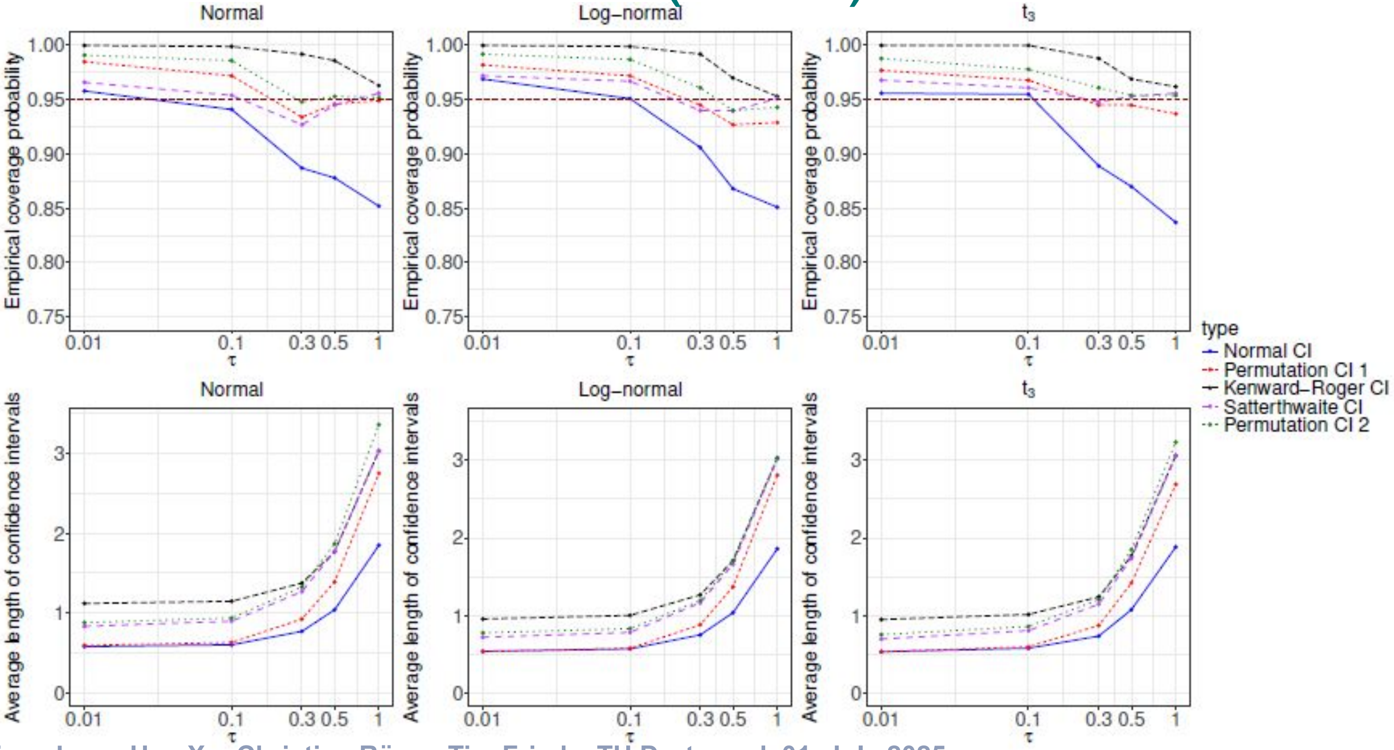
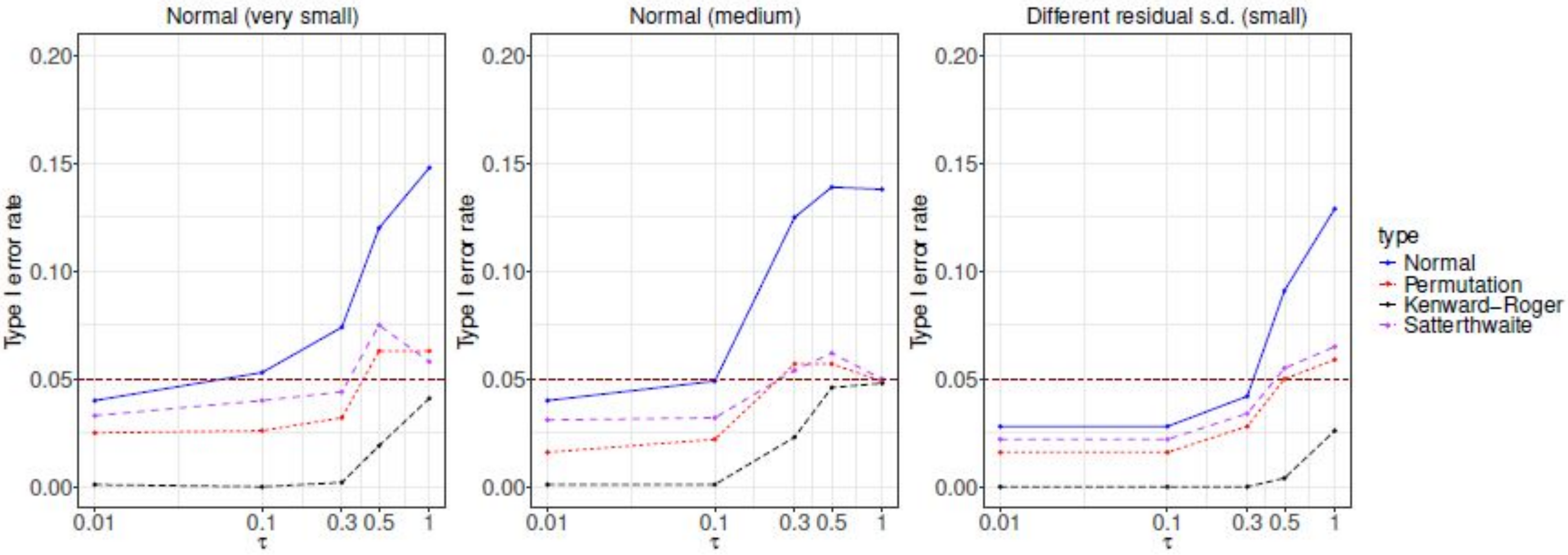
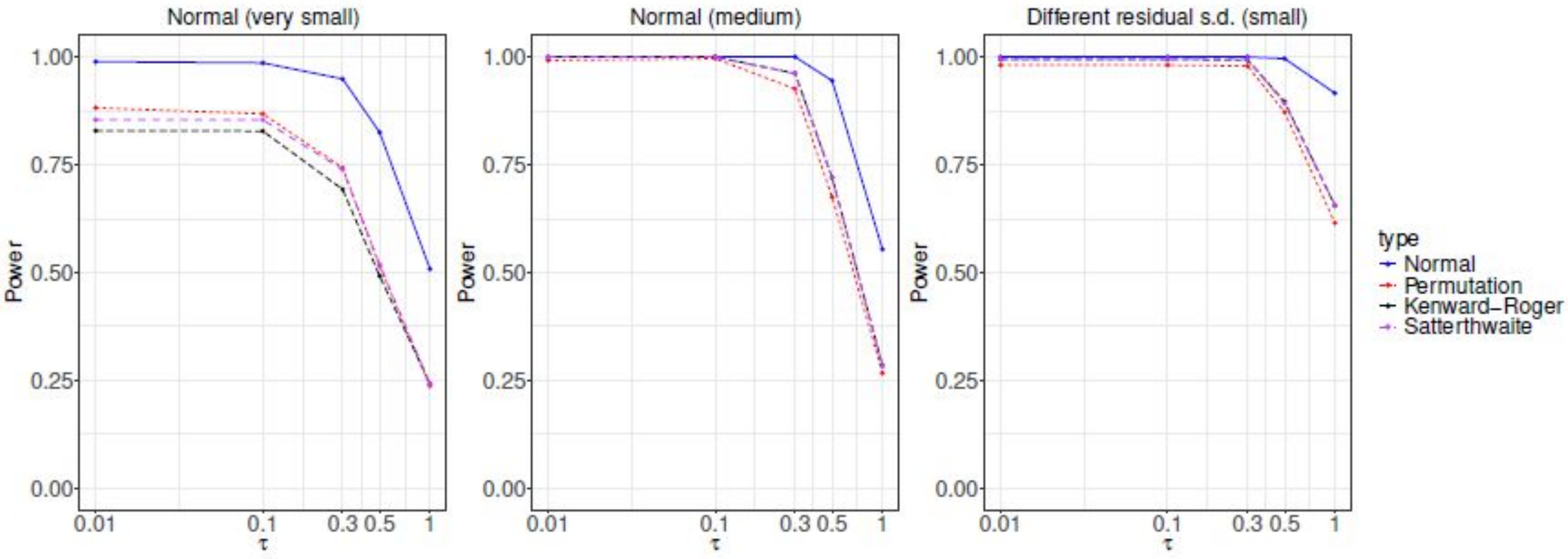
SIMULATION RESULTS (cont.)



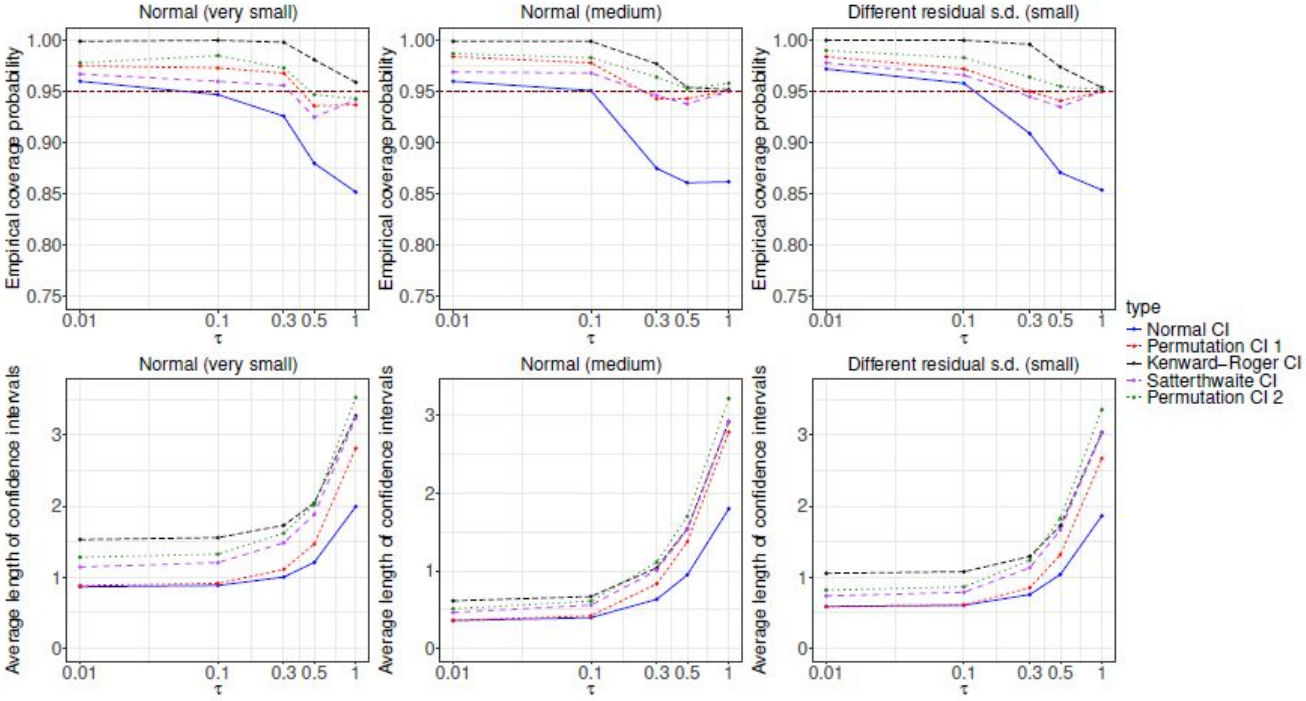
SIMULATION RESULTS (cont.)



SIMULATION RESULTS (cont.)



SIMULATION RESULTS (cont.)



SIMULATION RESULTS (cont.)