Validity of summary statistics-based mixed-effects group fMRI

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informatics mathematics

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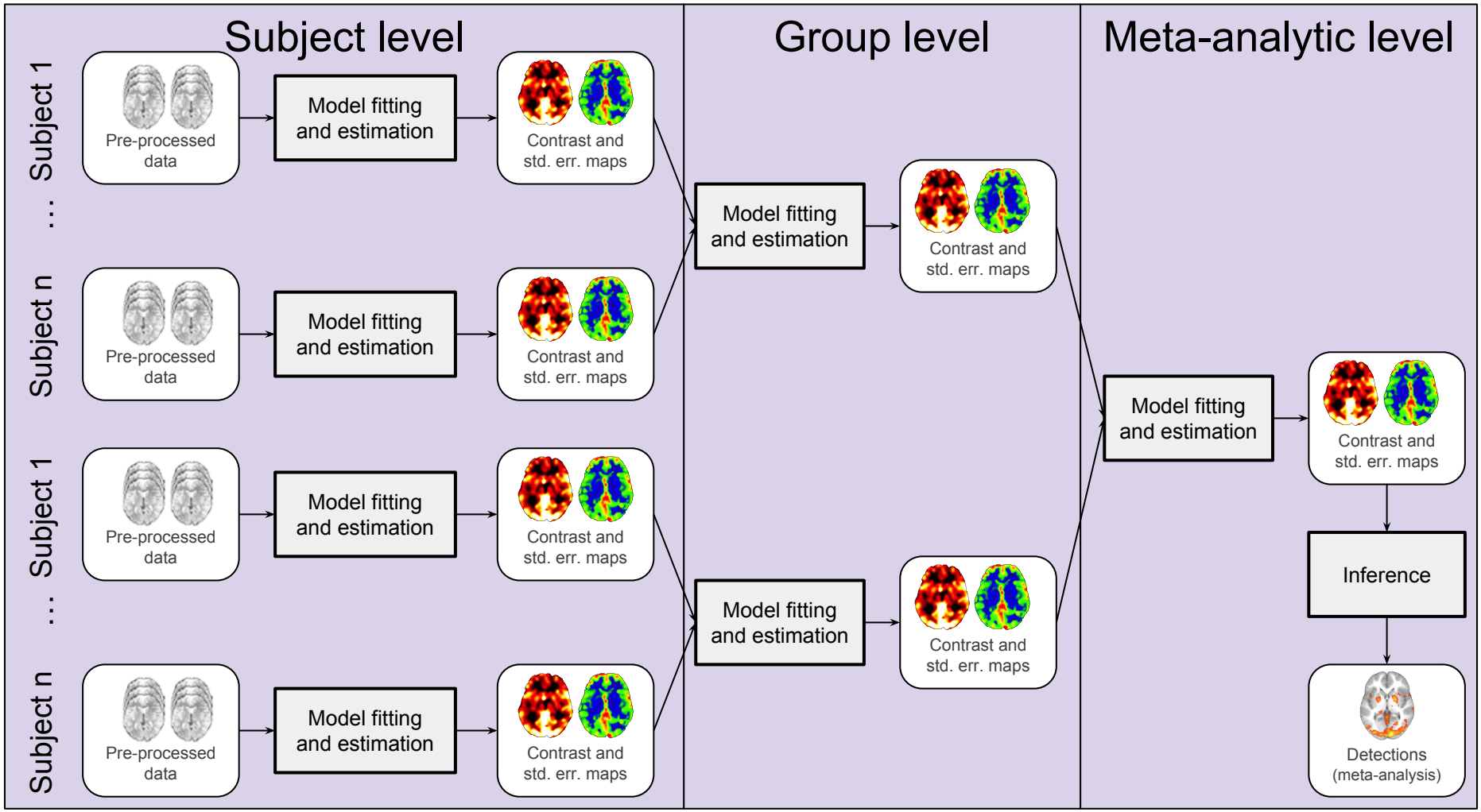
What is the link between meta-analysis and group fMRI?



Methods

GLM for group fMRI

$$Y = X\beta + \varepsilon$$

N-vector of subject-level contrast estimates

Design matrix

Random error

$$\text{where } \varepsilon \sim N(0, \tau^2 + \sigma^2_i)$$

Between-subject variance

Variance of subject i's contrast

Solving the GLM: OLS vs. FGLS

$$Y = X\beta + \varepsilon, \quad \text{where } \varepsilon \sim N(0, \tau^2 + \sigma^2_i)$$

Assuming $\tau^2 + \sigma^2_i$ constant, **Ordinary Least Squares (OLS)** gives the following group statistic estimate:

$$T = \left(\sum_{i=1}^{N} \frac{Y_i}{\sqrt{N}} \right) \Big/ \widehat{\sigma^2_C}$$

where $\widehat{\sigma^2_C}$ is the usual one-sample variance.

Under H_0: $T \sim \mathcal{T}_{N-1}$

Solving the GLM: OLS vs. FGLS

$$Y = X\beta + \varepsilon, \quad \text{where } \varepsilon \sim N(0, \tau^2 + \sigma^2_i)$$

Feasible Generalised Least Squares (FGLS) gives the following group statistic estimate:

$$T = \left(\sum \kappa_i Y_i\right) \Big/ \sqrt{\sum_{i=1}^{N} \kappa_i} \quad \text{where } \kappa_i = 1/(\hat{\tau}^2 + s_i^2)$$

where s_i^2 is the study i's sampling variance.

In large samples, under H_0: $T \sim \mathcal{T}_{N-1}$

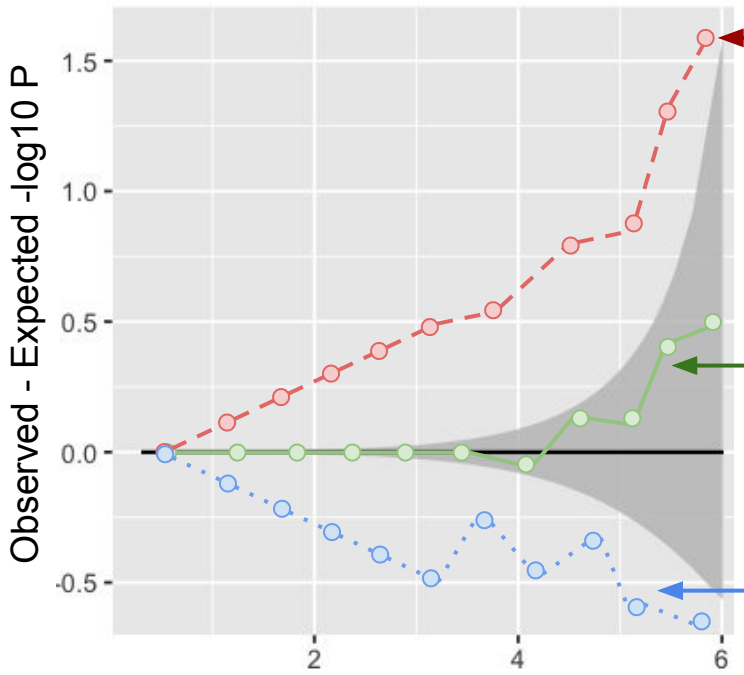
Solving the GLM: OLS vs. FGLS

	Statistic	Assumptions	Implementation
OLS	$T = \left(\sum_{i=1}^{N} \frac{Y_i}{\sqrt{N}}\right) \Big/ \widehat{\sigma_C^2}$	$\tau^2 + \sigma^2_i$ constant	SPM 'One-sample t-test' (default) FSL 'Mixed effects: Simple OLS' AFNI 3dttest++
FGLS	$T = \left(\sum \kappa_i Y_i\right) \Big/ \sqrt{\sum_{i=1}^{N} \kappa_i}$	Large samples	SPM 'Mixed-effects analysis' FSL 'Mixed effects: FLAME1' (default) AFNI 3dMEMA

Goal: assess the validity of OLS and FGLS under violation of their assumption

Method: Monte Carlo simulations

Difference between sorted observed P-values (computed by OLS or FGLS) and sorted expected -log10 P-values.



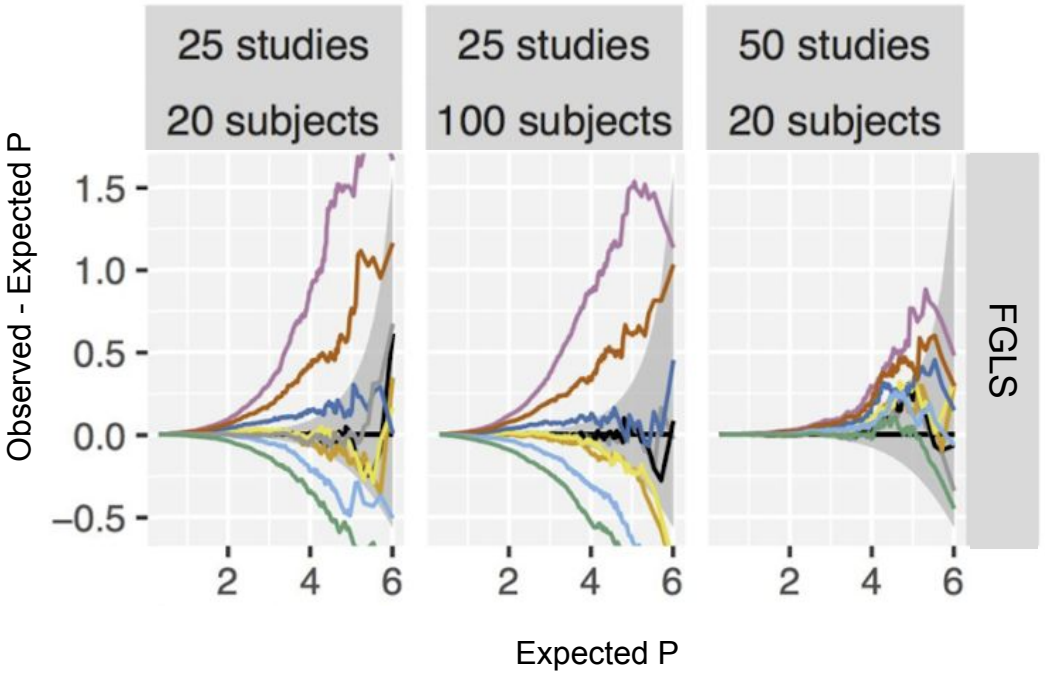
Invalid method

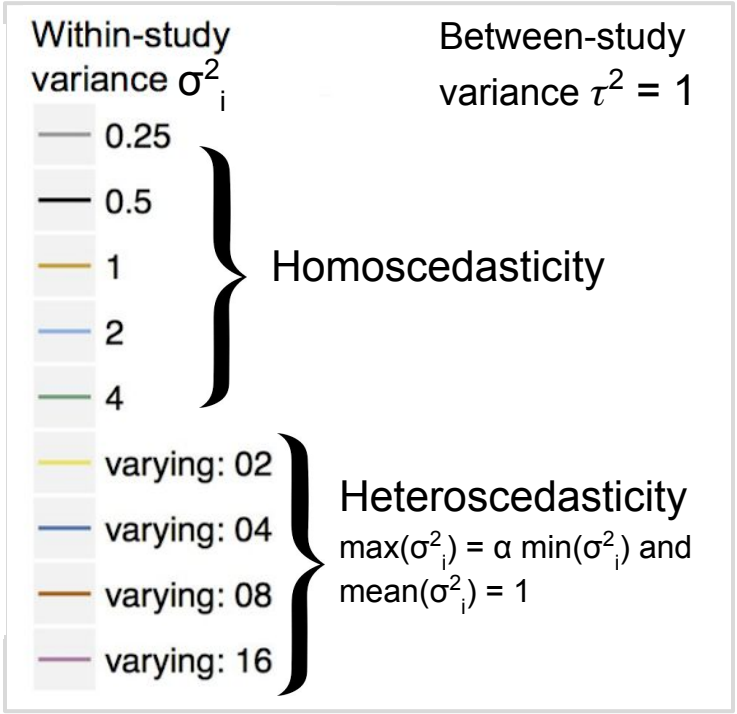
If the method is exact then the difference will lie in the 95% CI (**grey ribbon**) around zero (**black line**).

Conservative method

"True" -log10 P-values computed empirically by MC simulations

And in meta-analyses?





Question: Does this issue also affects group fMRI studies?

Simulations

Between- and within-subject variances in real fMRI data

21 studies investigating pain

Study	# subjects	# outliers	Mean τ^2	Mean σ^2_{in}	Max/Min σ^2_{in} ratio	Mean σ^2_{out}
01	25	2	354	100	4	282
02	25	1	680	100	5	317
03	20	2	800	100	5	281
04	20	3	886		9	347
05	9	0	1802		3	-
...	...	...	...	...	...	...
Summary		**0-15%**	**18-170**	**100**	**2-9**	**164-300**

Simulation setup

N $\in$ { 25, 50 } subjects

τ^2 = 1 and mean(σ^2_{in}) = 1

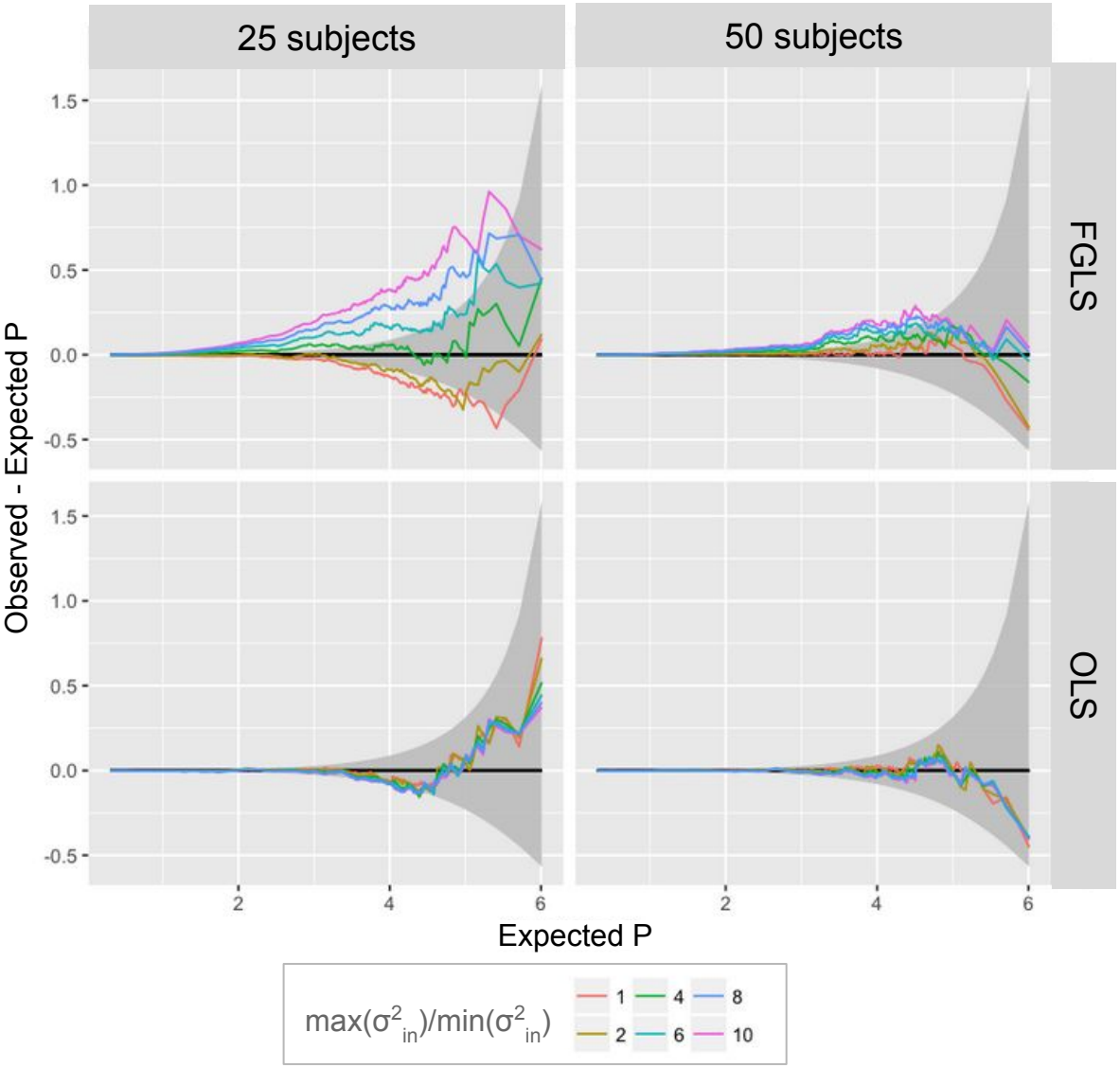
Two settings for the within-subject variance:

- max(σ^2_{in}) / min(σ^2_{in}) $\in$ { 1, 2, 4, 6, 8, 10 }
- 16% of outliers with $\sigma^2_{out} \in$ { 0.25, 0.5, 2, 4 }

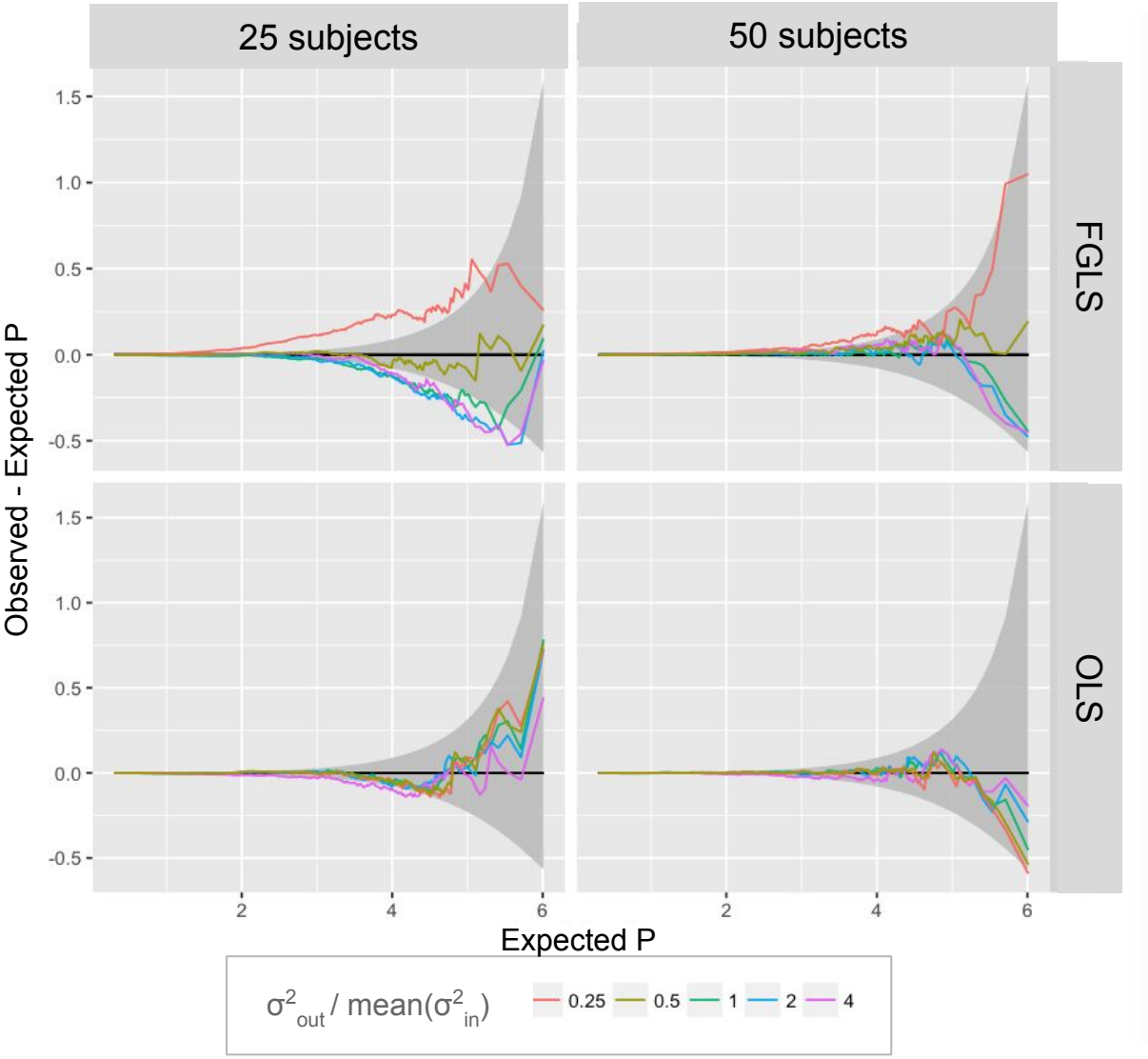
10^6 realisations

Results

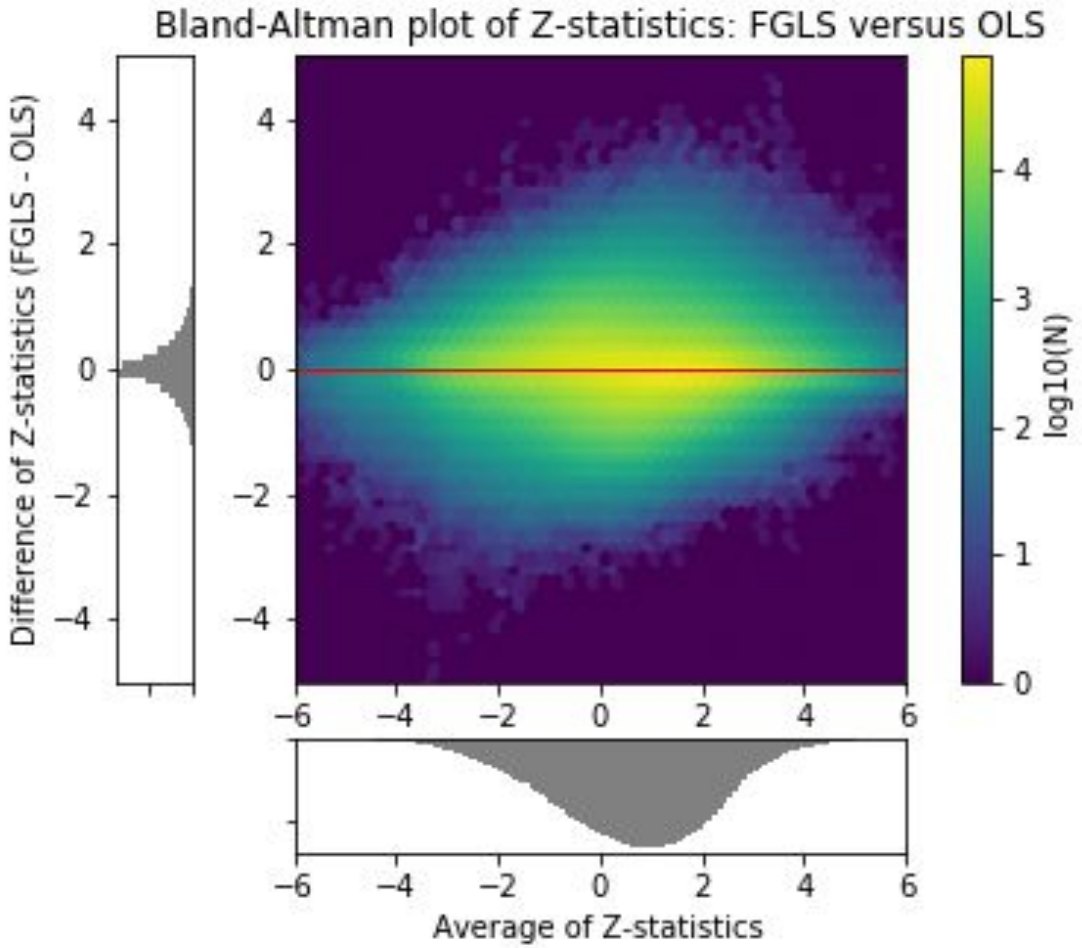
Varying levels of heteroscedasticity



In the presence of outliers



Real data


Bland-Altman plot of Z-statistics: FGLS versus OLS
Difference of Z-statistics (FGLS - OLS)
Average of Z-statistics
log10(N)
4
2
0
−2
−4
−6
3
1

Conclusions

FGLS can be invalid is small samples, especially in the presence of **strong heteroscedasticity** or **'low variance' outliers**.

RFX remained valid in all studied settings.

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