Non Clinical Statistics Conference 2018, Paris

Non-inferiority testing under generalized Poisson distribution

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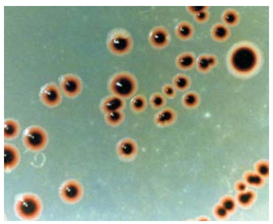
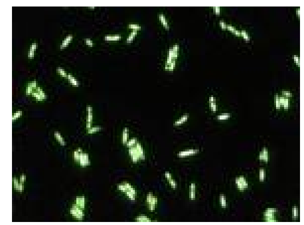
Introduction

- Alternative rapid microbiological methods (RMMs) are developed to replace conventional growth-based methods






  - Reduce time to result from ≥ 2 weeks to 0-5 days
  - In-process controls, Root cause investigations, Release
  - Improve lab efficiency
  - Cost savings (e.g. when batch can be saved)
    - Early detection of contaminations and reliable counting methods may save $millions/year

Definitions

Equality

Objective: To determine a clinically relevant difference between two interventions

Equivalence

Objective: To determine whether a (new) intervention is neither worse nor better than another (established) intervention

Non-inferiority

Objective: To determine whether a (new) intervention is not inferior to another (established) intervention

Standard setup

Interms of difference

Test for	Null hypothesis	Alternative hypothesis
Equality	$H_0: \mu_1 - \mu_2 = 0$	$H_1: \mu_1 - \mu_2 \neq 0$
Equivalence	$H_0: \|\mu_1 - \mu_2\| > \delta$	$H_1: \|\mu_1 - \mu_2\| \leq \delta$
Non-inferiority	$H_0: \mu_1 - \mu_2 \leq \delta$	$H_1: \mu_1 - \mu_2 > \delta$

Interms of ratio

Test for	Null hypothesis	Alternative hypothesis
Equality	$H_0: \mu_1/\mu_2 = 1$	$H_1: \mu_1/\mu_2 \neq 1$
Equivalence	$H_0: \mu_1/\mu_2 \notin [1/\phi, \phi]$	$H_1: \mu_1/\mu_2 \in [1/\phi, \phi]$
Non-inferiority	$H_0: \mu_1/\mu_2 \leq \phi$	$H_1: \mu_1/\mu_2 > \phi$

μ_1= expected outcome in the new treatment (or test method)
μ_2= expected outcome in the standard treatment (or test method)
δ or ϕ = equivalence or non-inferiority margins

Count type outcome

Common distributions count data

- **Poisson distribution** is commonly assumed for count data
- **Negative binomial** is also assumed to analyze over-dispersed count data

Less studied and well-known distributions

- **Generalized Poisson distribution**
- **Conway Maxwell Poisson**

Literature review non-inferiority

- Non-inferiority testing for count data[2-7]
- Distribution
  - **Poisson** and **Negative Binomial** distributions
- Hypothesis testing
  - Difference: $\mathrm{H}_0\!: \mu_1 - \mu_2 \leq \delta$ vs $\mathrm{H}_1\!: \mu_1 - \mu_2 > \delta$
  - Ratio: $\mathrm{H}_0\!: \mu_1/\mu_2 \leq \phi$ vs $\mathrm{H}_1\!: \mu_1/\mu_2 > \phi$
- Statistical tests
  - **Asymptotic likelihood ratio test (LRT)**
  - **Wald test** (based on asymptotic normality of the maximum likelihood estimators)
  - **Exact conditional test**
- Sample size caclculation

Asymptotic likelihood ratio test (LRT)

- Assume $X \sim Poi(\mu_1)$ and $Y \sim Poi(\mu_2)$
- iid observations from group or method 1 and 2 respectively
  - $X_1, X_2, \ldots, X_{n_1}$ and $Y_1, Y_2, \ldots, Y_{n_2}$
- **likelihood ratio**

$$l = \begin{cases} \dfrac{L(\tilde{\mu}_1, \tilde{\mu}_2)}{L(\hat{\mu}_1, \hat{\mu}_2)}, & \text{if } \dfrac{\hat{\mu}_1}{\hat{\mu}_2} > \phi \\ 1, & \text{if } \dfrac{\hat{\mu}_1}{\hat{\mu}_2} \leq \phi \end{cases}$$

where, $\hat{\mu}_1$ and $\hat{\mu}_2$ are the MLEs of μ_1 and μ_2 (no ristrictions)

$\tilde{\mu}_1$ and $\tilde{\mu}_2$ are the MLEs of μ_1 and μ_2 under H_0

- Asymptotically $-2 ln l \sim \frac{1}{2} + \frac{1}{2}\chi^2$, where χ^2 is a chi-square variate with 1 degree of freedom

Wald test

- Assume $X \sim Poi(\mu_1)$ and $Y \sim Poi(\mu_2)$
- iid observations from group or method 1 and 2 respectively
  - $X_1, X_2, \ldots, X_{n_1}$ and $Y_1, Y_2, \ldots, Y_{n_2}$
- **Wald test**

$$\mathrm{W} = \frac{\hat{\mu}_1 - \phi\hat{\mu}_2}{\sqrt{\mathrm{Var}(\hat{\mu}_1) + \phi^2\mathrm{Var}(\hat{\mu}_2) - 2\phi\mathrm{Cov}(\hat{\mu}_1, \hat{\mu}_2)}}$$

where, $\hat{\mu}_1$ and $\hat{\mu}_2$ are the MLEs of μ_1 and μ_2 (no restriction)

- Asymptotically $\mathrm{W} \xrightarrow{d} N(0,1)$

Exact conditional test

- Assume $X \sim Poi(\mu_1)$ and $Y \sim Poi(\mu_2)$
- iid observations from group or method 1 and 2 respectively
  - $X_1, X_2, \ldots, X_{n_1}$ and $Y_1, Y_2, \ldots, Y_{n_2}$
  - $S_x = \sum_{i=1}^{n_1} X_i \sim Poi(n_1\mu_1)$, $S_y = \sum_{j=1}^{n_2} Y_j \sim Poi(n_2\mu_2)$ and
  - $T = S_x + S_y \sim Poi(n_1\mu_1 + n_2\mu_2)$
  - $S_x | T = t \sim \text{Binomial (t, p)}$ with $p = \frac{n_1\phi_1}{n_1\phi_1 + n_2}$, $\phi_1 = \mu_1/\mu_2$
- **Exact conditional test**

$$\text{p-value} = \sup_{\phi_1 \leq \phi} P(S_x \geq k | T = t, p) \leq \alpha$$

where, α = level of significance

Non-inferiority testing under GPD

- We have extended all these approaches for non-inferiority testing under GPD
- **Why?**
  – In practice the data that we get are under-dispersed (mostly) or over-dispersed

Generalized Poisson distribution (GPD)

<u>Generalized Poisson distribution (GPD)</u>

A random variable *X* is said to have a GPD if its probability mass function is given by

$$\Pr(X = x; \gamma, \theta) = \begin{cases} \dfrac{\gamma(\gamma + x\theta)^{x-1}}{x!} \exp(-\gamma - x\theta) & \text{for } x = 0, 1, 2, \dots \\ 0 & \text{for } \theta < 0, x > m \end{cases}$$

with location parameter $\gamma > 0$ and dispersion parameter $\max(-1, -\gamma/m) < \theta < 1.$

Generalized Poisson distribution (GPD)

- Mean and variance:

$$Mean = \mathbf{E}(X) = \mu = \frac{\gamma}{(1-\theta)}$$

$$Variance = Var(X) = \tau^2 = \frac{\gamma}{(1-\theta)^3}$$

- For $\theta = 0$, GPD reduces to a Poisson distribution with

$$Mean = Variance = \gamma$$

- For $\theta > 0$, we get $\tau^2 > \mu$ (overdispersion)
- For $\theta < 0$, we get $\tau^2 < \mu$ (underdispersion)

Motivating example: Milliflex Quantum data

- Statistically evaluate the results of two microbiological method validation experiments for the Milliflex Quantum
- **Microbiological methods:**
  (i) Milliflex Quantum (ii) Compendial
- Experiment performed for two micro-organisms:
  - *S. aureus* and *A. brasiliensis*
- 6 dilution samples with expected numbers of CFUs
  - Dilution 1: 68.5 CFU, Dilution 2: 60 CFU
  - Dilution 3: 45 CFU, Dilution 4: 30 CFU
  - Dilution 5: 15 CFU, Dilution 6: 1.5 CFU

Milliflex Quantum data: *S. aureus*

Method 1: Milliflex Quantum							
Dilution	Data		Estimates of GPD parameters				
	Average	SD	$\hat{\gamma}_1$	$\hat{\theta}_1$	$\hat{\mu}_1$	$\hat{\tau}_1^2$	$\hat{\tau}_1$
1	58.2	5.53	82.60	-0.42	58.20	28.89	5.38
2	53.3	7.41	55.34	-0.04	53.30	49.44	7.03
3	40.1	6.71	39.91	0.00	40.10	40.49	6.36
4	25.0	3.30	39.70	-0.59	25.00	9.91	3.15
5	13.0	2.58	19.64	-0.51	13.00	5.69	2.39
6	1.30	1.25	1.22	0.06	1.30	1.48	1.22

Method 2: Compendial							
Dilution	Data		Estimates of GPD parameters				
	Average	SD	$\hat{\gamma}_2$	$\hat{\theta}_2$	$\hat{\mu}_2$	$\hat{\tau}_2^2$	$\hat{\tau}_2$
1	61.50	9.05	56.19	0.09	61.50	73.67	8.58
2	50.70	6.24	61.10	-0.21	50.70	34.91	5.91
3	38.00	5.12	48.50	-0.28	38.00	23.33	4.83
4	24.70	4.64	27.73	-0.12	24.70	19.59	4.43
5	13.00	2.58	18.76	-0.44	13.00	6.24	2.50
6	1.70	1.42	1.64	0.03	1.70	1.82	1.35

Milliflex Quantum data: *A. brasiliensis*

Method 1: Milliflex Quantum							
Dilution	Data		Estimates of GPD parameters				
	Average	SD	$\hat{\gamma}_1$	$\hat{\theta}_1$	$\hat{\mu}_1$	$\hat{\tau}_1^2$	$\hat{\tau}_1$
1	31.50	3.78	48.77	-0.55	31.50	13.14	3.63
2	27.40	5.76	26.26	0.04	27.40	29.84	5.46
3	21.10	2.85	36.01	-0.71	21.10	7.24	2.69
4	17.60	3.53	22.04	-0.25	17.60	11.22	3.35
5	9.10	2.60	11.44	-0.26	9.10	5.76	2.40
6	0.70	0.95	0.65	0.07	0.70	0.81	0.90

Method 2: Compendial							
Dilution	Data		Estimates of GPD parameters				
	Average	SD	$\hat{\gamma}_2$	$\hat{\theta}_2$	$\hat{\mu}_2$	$\hat{\tau}_2^2$	$\hat{\tau}_2$
1	32.60	3.06	65.10	-1.00	32.60	8.17	2.86
2	29.00	5.35	30.68	-0.06	29.00	25.92	5.09
3	23.20	4.13	28.71	-0.24	23.20	15.15	3.89
4	16.50	5.38	12.97	0.21	16.50	26.71	5.17
5	9.80	2.94	11.07	-0.13	9.80	7.68	2.77
6	0.60	0.70	0.71	-0.19	0.60	0.42	0.65

Non-inferiority testing under GPD

- Assume $X \sim \mathrm{GPD}(\gamma_1, \theta_1)$ and $Y \sim \mathrm{GPD}(\gamma_2, \theta_2)$
- Observations from group or method 1 and 2 iid
  - $X_1, X_2, \dots, X_{n_1}$ and $Y_1, Y_2, \dots, Y_{n_2}$
- **Case 1:** Both dispersion parameters (θ_1 & θ_2) are different and unknown ($\theta_1 \neq \theta_2$)
  - Likelihood ratio (LR) test
  - Wald test
- **Case 2:** Both dispersion parameters (θ_1 & θ_2) are the same but unknown ($\theta_1 = \theta_2 = \theta$)
  - Likelihood ratio (LR) test
  - Wald test
  - Exact condtional test

Simulations

- Scenarios considered

Factor	Range
Location parameters of GPD γ_1 and γ_2	5, 10 and 15
Dispersion parameter sof GPD θ_1 and θ_2	-0.15, 0, and 0.10
True ratio (ϕ_1)	0.8, 0.9 and 1.0
Non-inferiority margin (ϕ)	0.8
Significance level	0.05
Sample size per group	10, 25, 50, 75, 100, 125 and 150
Statistical power	0.80

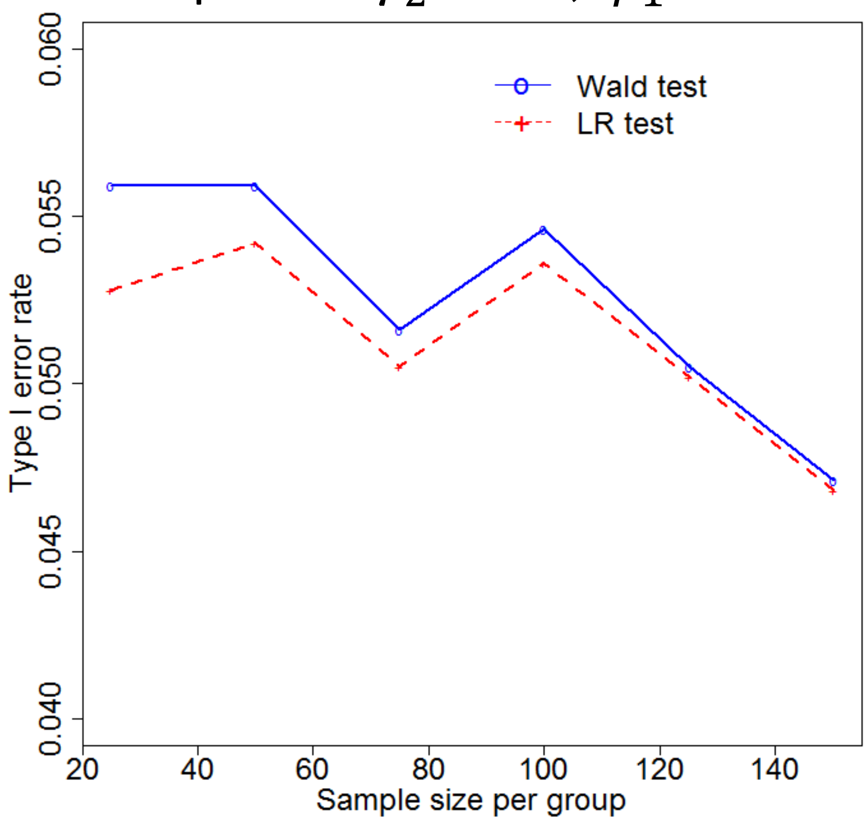
- Criteria: (i) Type I error rate (ii) Statistical power
- Number of simulations per scenario: 10,000

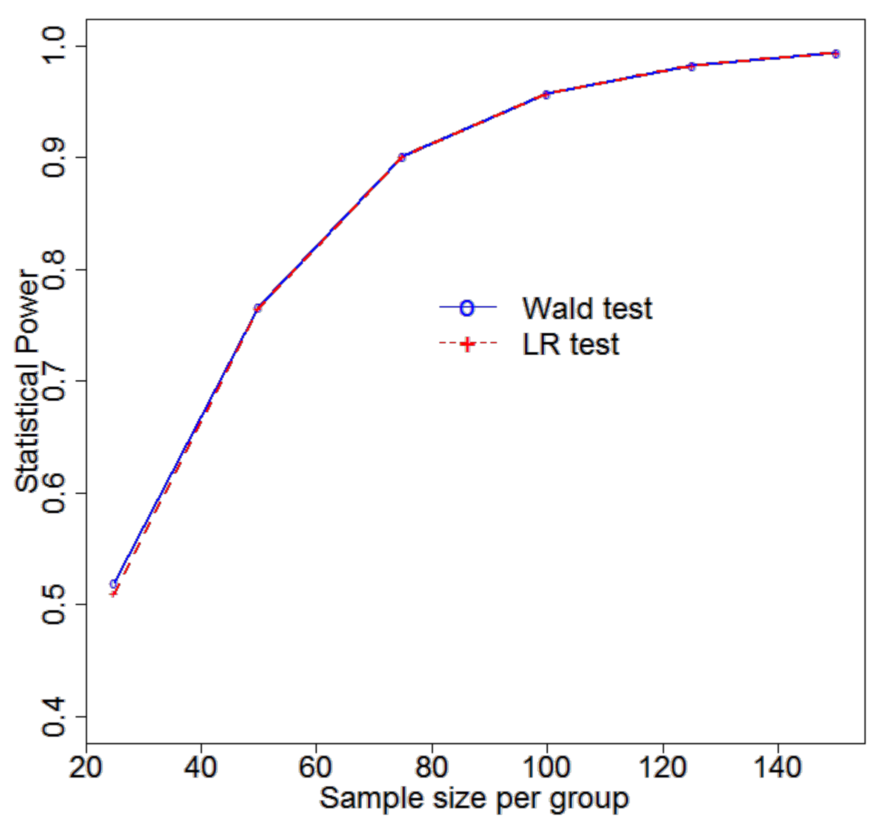
Case 1: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are different and unknown

- **Type I error rate and statistical power are plotted as a function of sample size per group**
- **Nominal level of type I error rate is 0.05**

Case 1: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are different and unknown

- Both groups under-dispersed: $\theta_1 = -0.15$, $\theta_2 = -0.10$
- For type I error rate: $\gamma_2 = 15$, $\phi_1 = \phi = 0.8$
- For power: $\gamma_2 = 15$, $\phi_1 = 0.9$





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- Both groups over-dispersed: $\theta_1 = 0.15$, $\theta_2 = 0.10$
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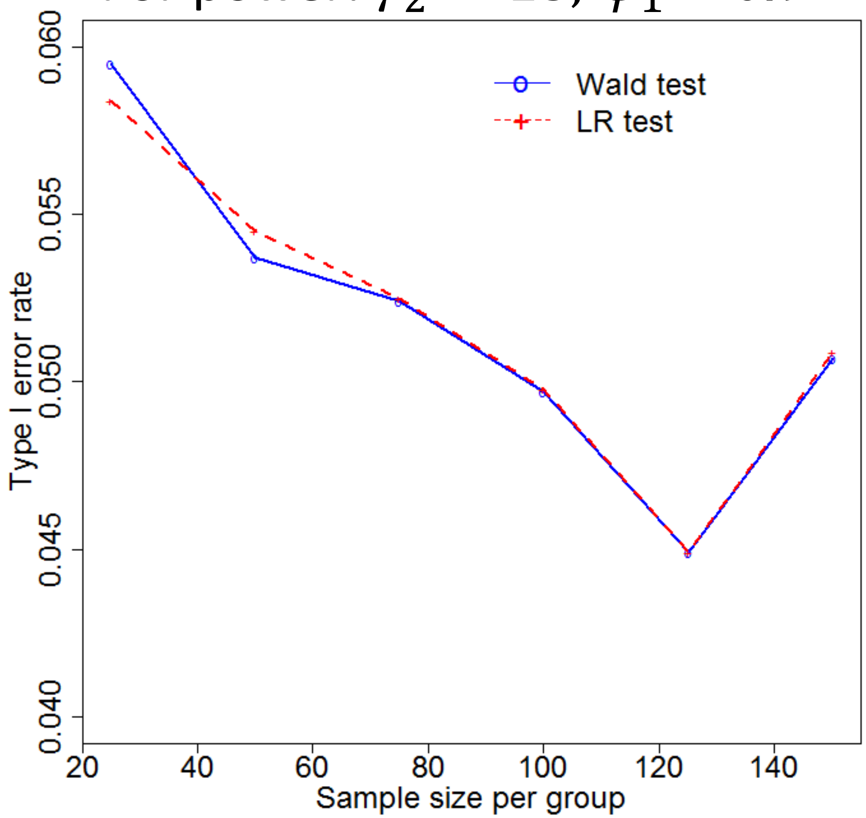
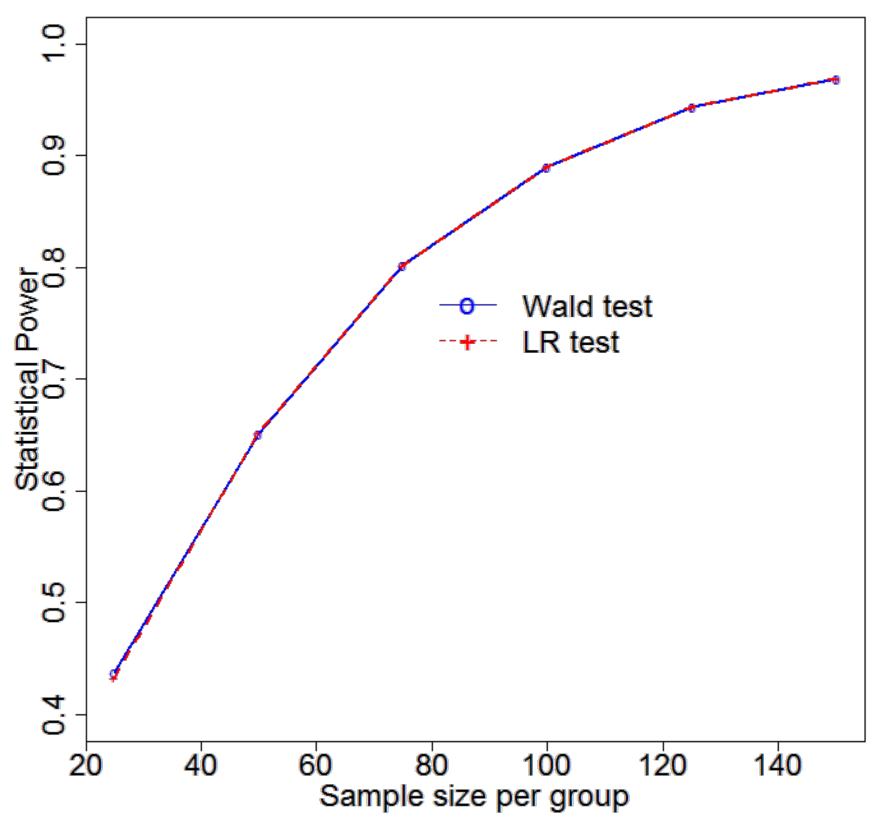


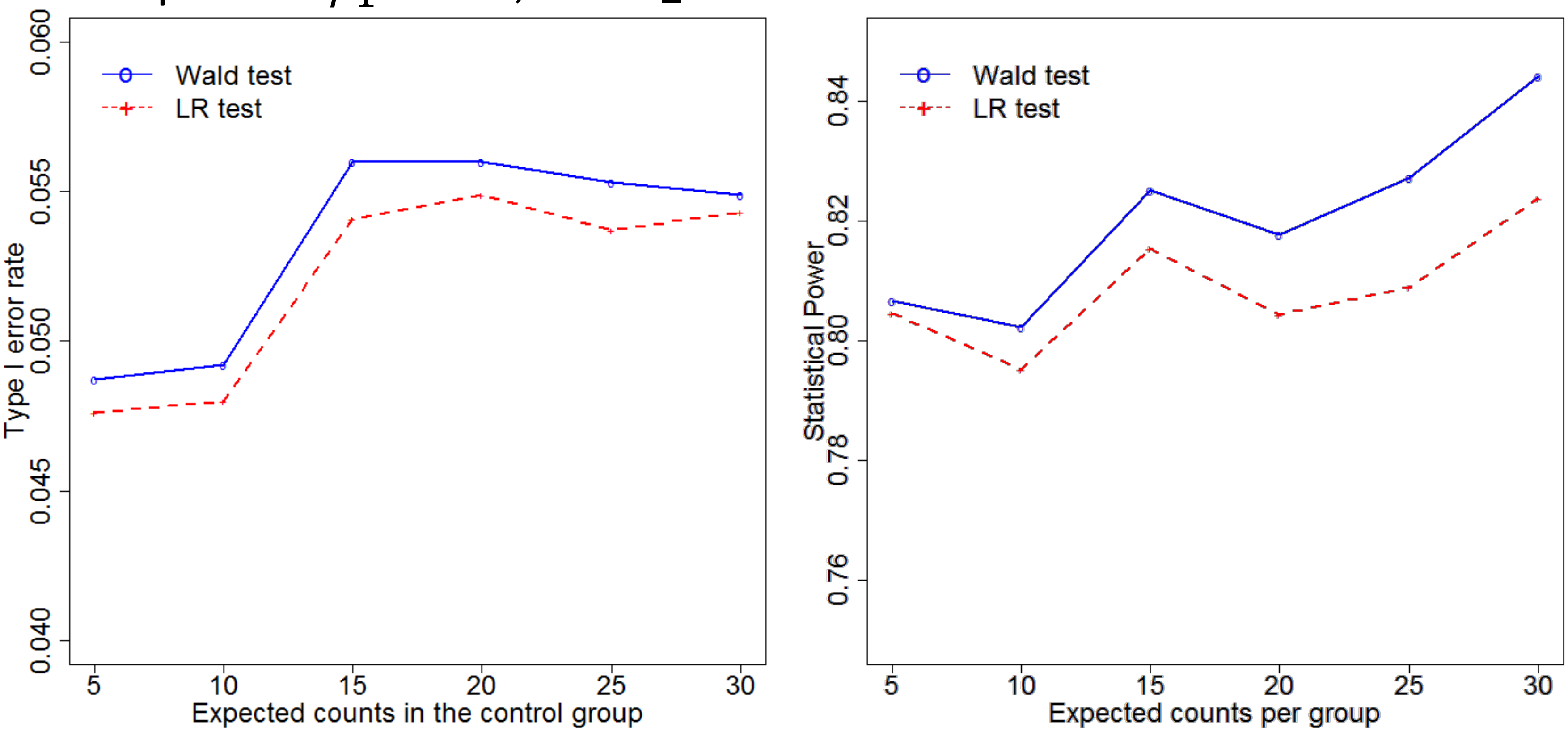


Case 1: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are different and unknown

- **Type I error rate and statistical power are plotted as a function of expected counts in the control group**
- **Nominal level of type I error rate is 0.05**
- **Sample sizes are computed such that the power equals 0.8 based on Wald test**

Case 1: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are different and unknown

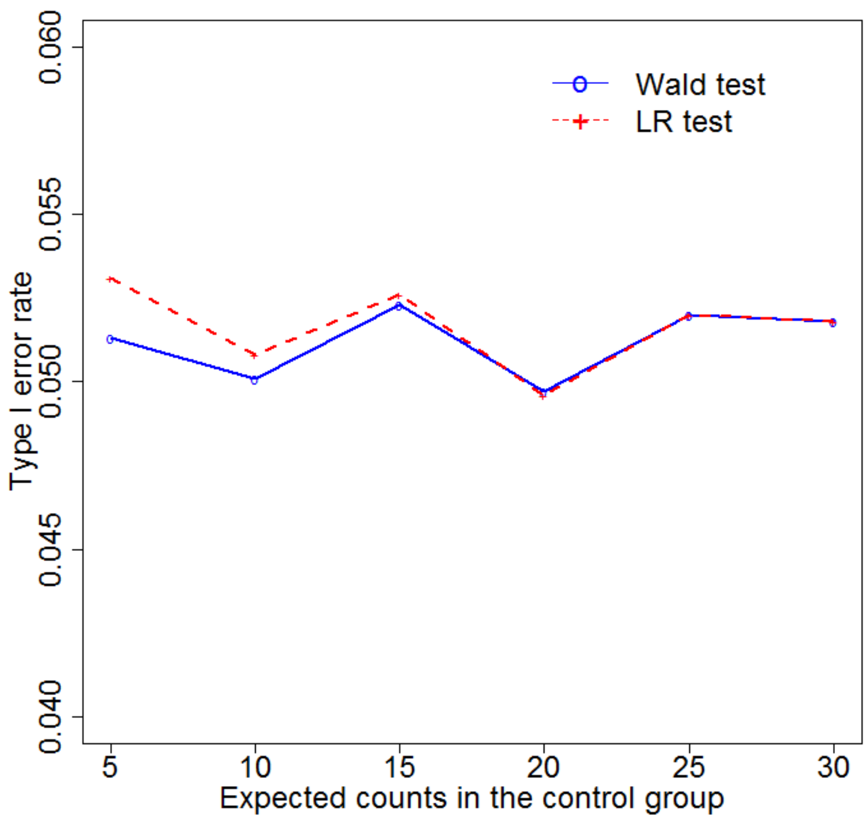
- Both groups are under-dispersed: $\theta_1 = -0.15$, $\theta_2 = -0.10$
- For type I error rate: $\phi_1 = \phi = 0.8, n_1 = n_2 = 50$
- For power: $\phi_1 = 1.0$, $\text{Pow\_0} = 0.80$

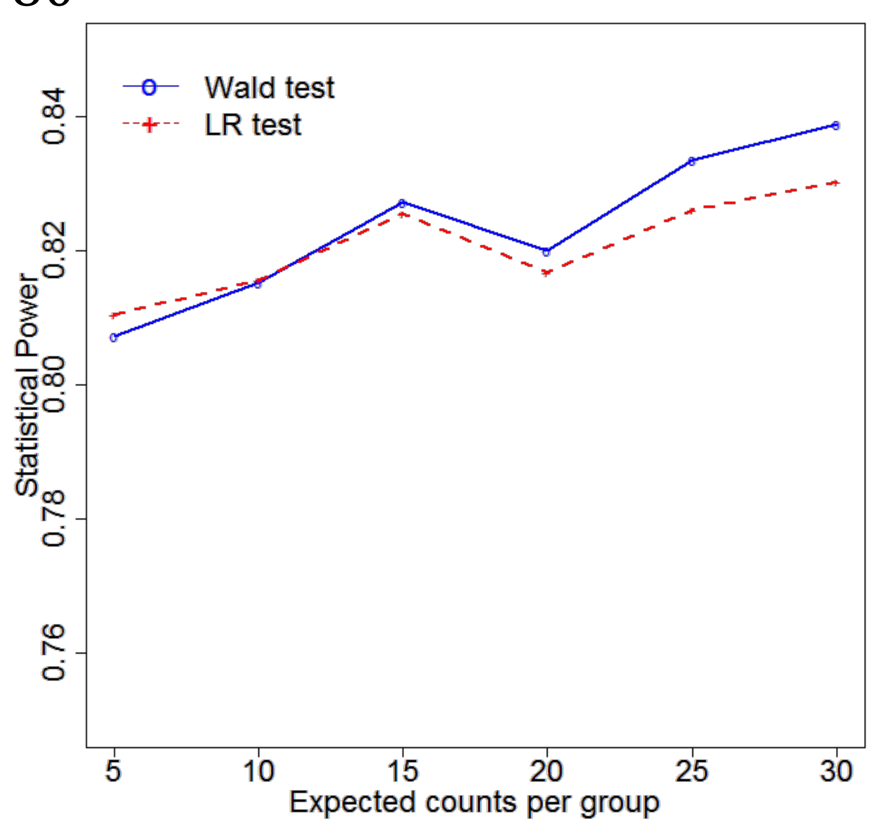


Case 1: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are different and unknown

- Both groups are over-dispersed: $\theta_1 = 0.15$, $\theta_2 = 0.10$
- For type I error rate: $\phi_1 = \phi = 0.8, n_1 = n_2 = 50$

80



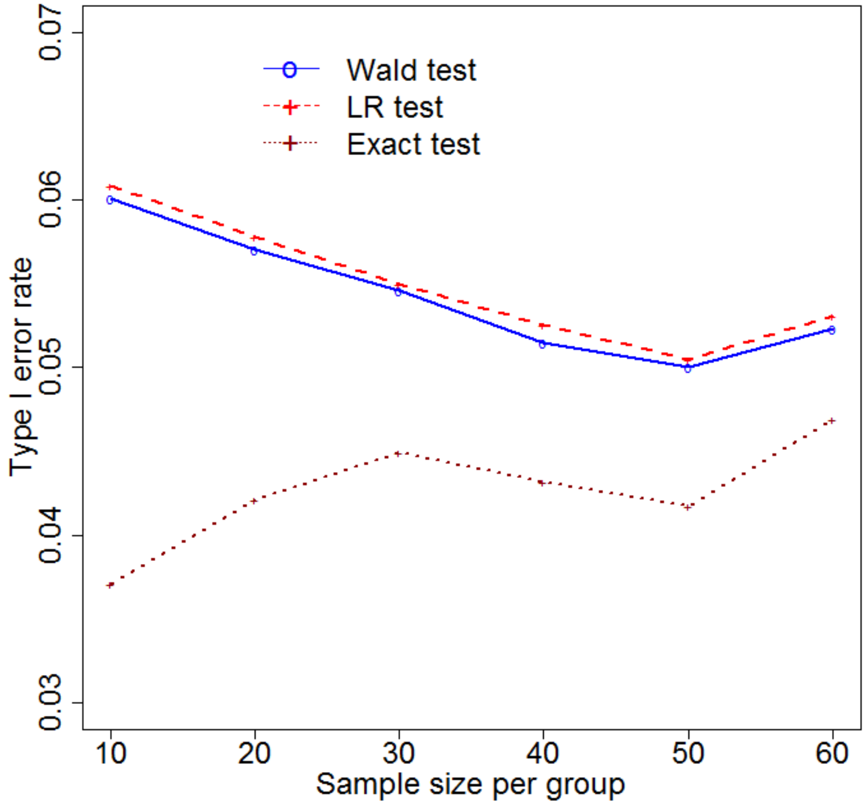


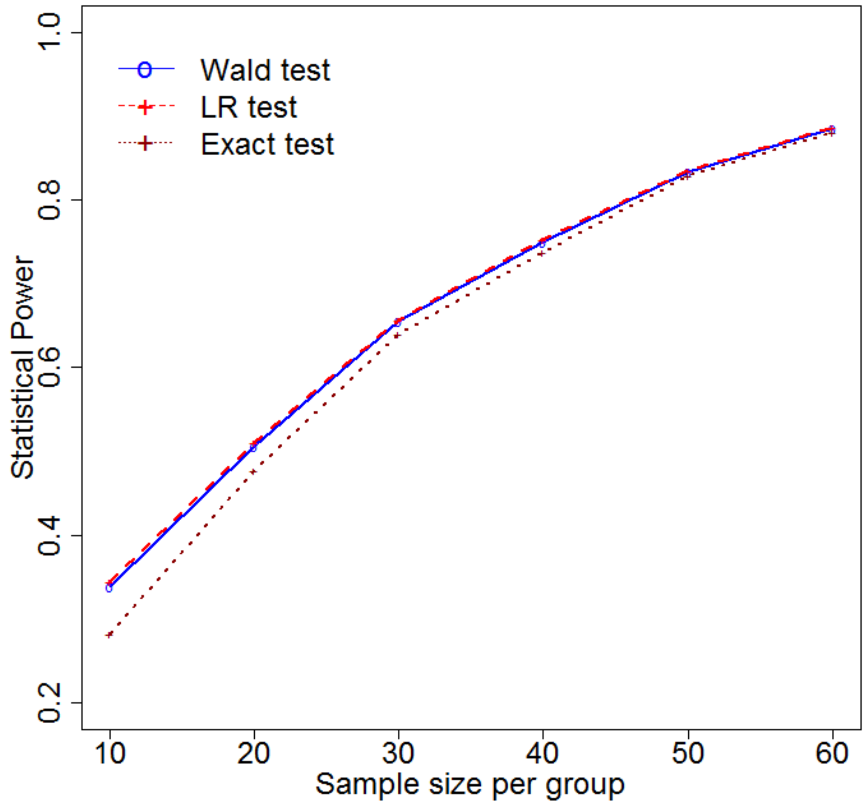
Case 2: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are same but unknown

- **Type I error rate and statistical power are plotted as a function of sample size per group**
- **Nominal level of type I error rate is 0.05**

Case 2: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are same but unknown

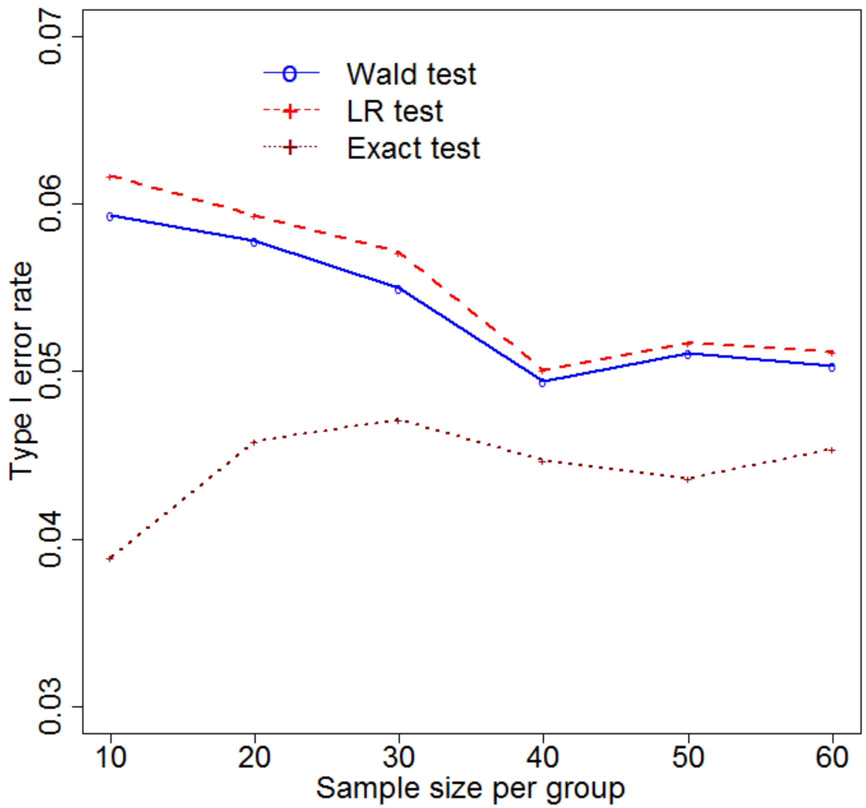
- Groups are under-dispersed: $\theta_1 = \theta_2 = \theta = -0.10$
- For type I error rate: $\gamma_2 = 5, \phi = 0.8$
- For power: $\gamma_2 = 5, \phi_1 = 1.0$

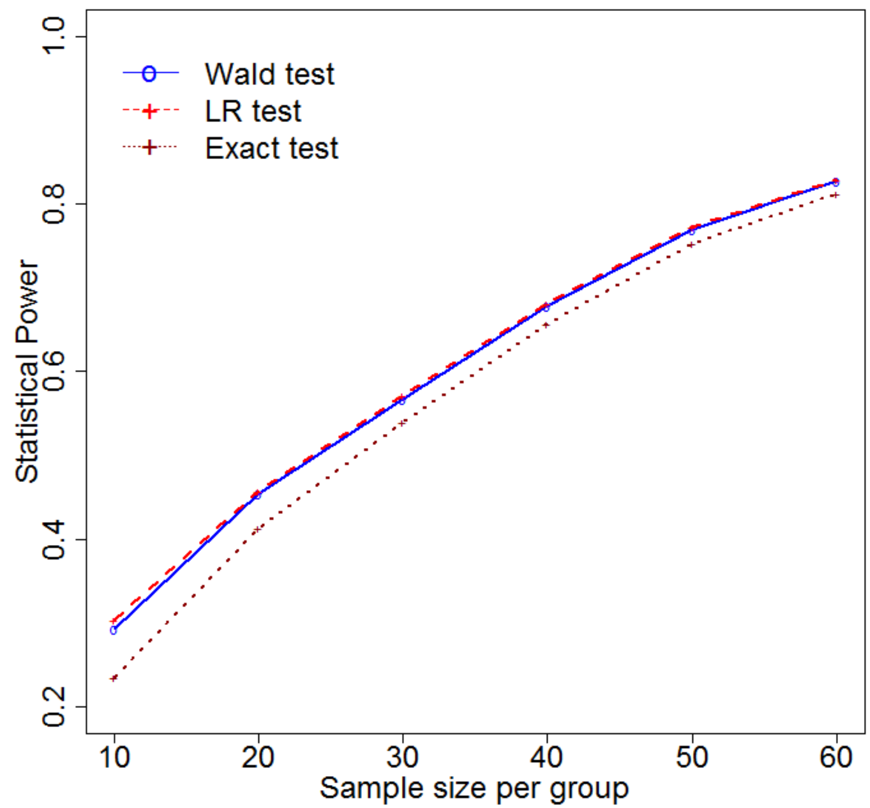




Case 2: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are same but unknown

- Groups are over-dispersed: $\theta_1 = \theta_2 = \theta = 0.10$
- For type I error rate: $\gamma_2 = 5, \phi = 0.8$
- For power: $\gamma_2 = 5, \phi_1 = 1.0$



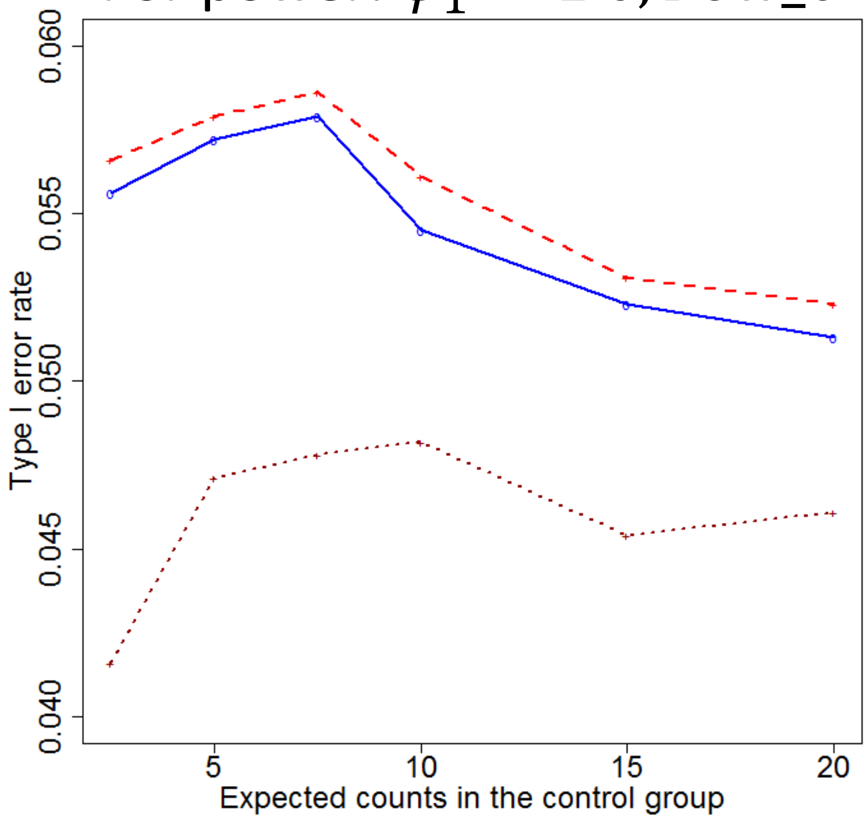


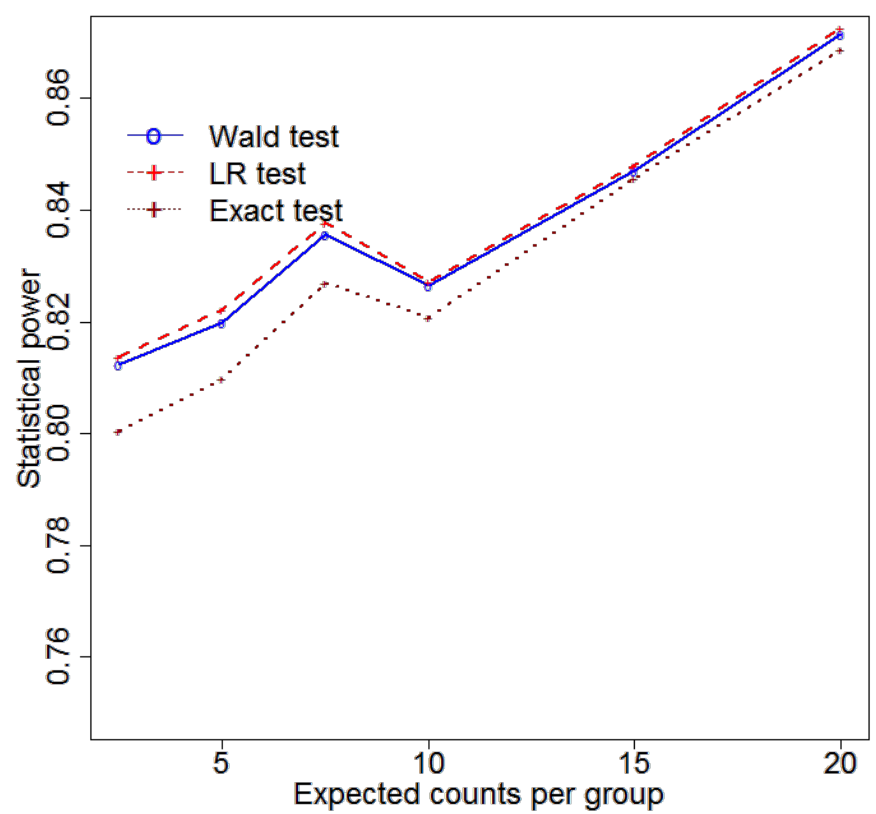
Case 2: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are same but unknown

- **Type I error rate and statistical power are plotted as a function of expected counts in the control group**
- **Nominal level of type I error rate is 0.05**
- **Sample sizes are computed such that the power equals 0.8 based on Wald test**

Case 2: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are same but unknown

- Groups are under-dispersed: $\theta_1 = \theta_2 = \theta = -0.10$
- For type I error rate: $\phi_1 = \phi = 0.8, n_1 = n_2 = 25$
- For power: $\phi_1 = 1.0, \mathrm{Pow\_0} = 0.80$





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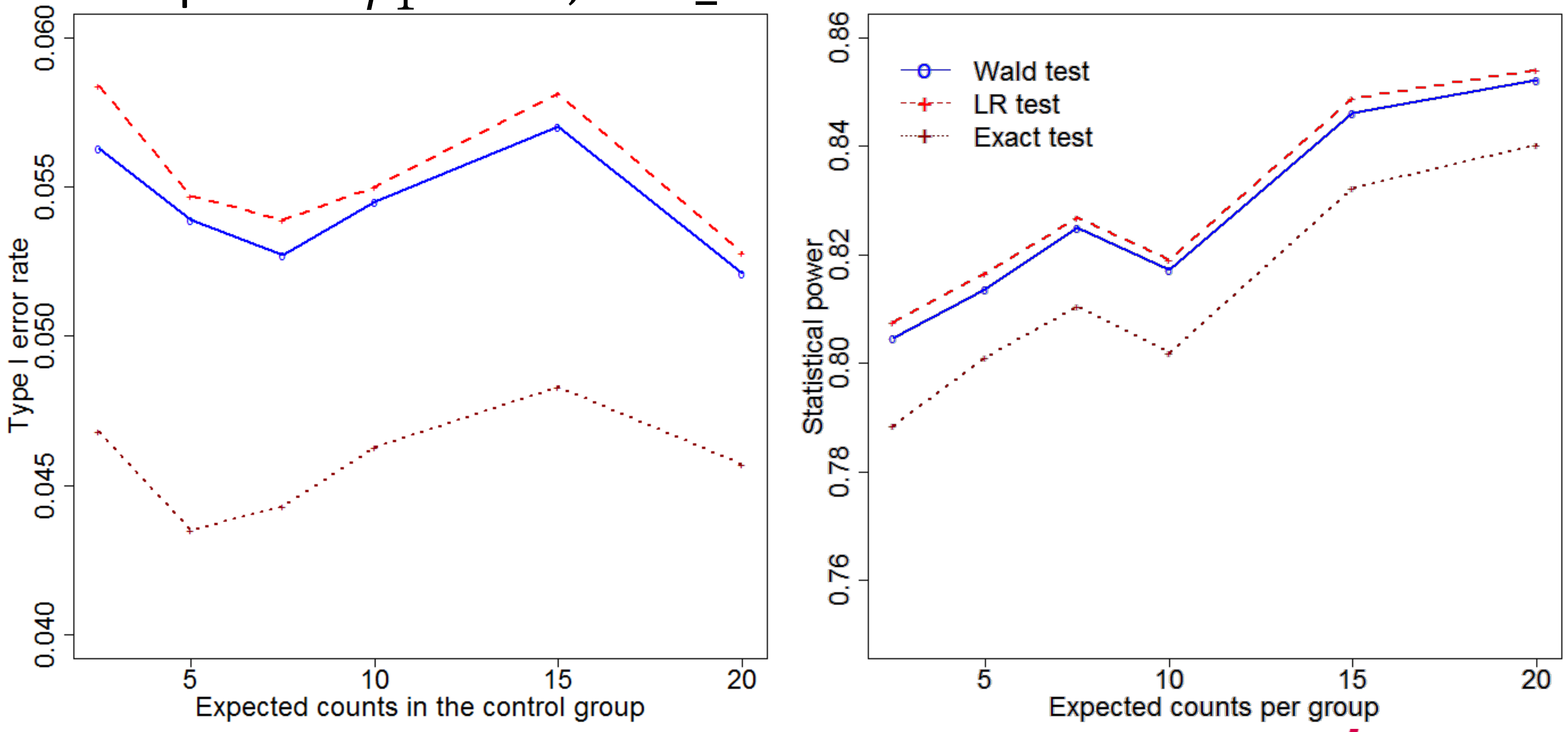
Case 2: $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are same but unknown

- Groups are over-dispersed: $\theta_1 = \theta_2 = \theta = 0.10$
- For type I error rate: $\phi_1 = \phi = 0.8, n_1 = n_2 = 25$
- For power: $\phi_1 = 1.0, \mathrm{Pow\_0} = 0.80$



Conclusions

- Methods extended from Poisson to GPD
- LRT and Wald test perform similarly
- Exact test is conservative and has less power than the LRT and Wald test

References

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Thank you !